

# The Prediction of Tautomer Preference in Aqueous Solution (Version 1.0)

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Peter Taylor (PJT) established and led the physical-organic chemistry group at ICI Pharmaceuticals in Cheshire. PJT read Chemistry at Oxford although he had been introduced to tautomerism at high school and continued to contribute to the field long after he ‘retired’ in 1988. He is also known to physical-organic chemists and drug discovery scientists for his work on lipophilicity, hydrogen bonding and reaction mechanisms. PJT passed away in 2012.

Photo (from Cathy Taylor): PJT in Alderley Edge, c 2010.



Peter Kenny (PWK) is a physical-organic chemist who dabbles in computational chemistry and cheminformatics. He studied chemistry at Reading and Oxford, joined ICI Pharmaceuticals in 1988 and retired from AstraZeneca in 2009.

Photo: PWK with djabs in Paramin, 2017

## VERSION NOTES

1.0	<p>PJT actually wrote <i>'The prediction of tautomer preference in aqueous solution'</i> over a decade ago. While the study has been shared informally with interested scientists for a number of years, the work was distributed over a number of document files and few people even knew of its existence. PJT was keen that the work be used and I believe that there are considerable benefits to assembling the study in its current form and making it publicly visible.</p> <p>Apart from making some minor changes to the introduction, I have not actually edited what was originally written by PJT other than assemble the individual files. However, I have re-formatted the references to include article titles and DOI links since this will make the study easier to use (especially by non-specialists whose primary interest may be specific projects rather than general aspects of tautomerism). I plan to review recent developments in the tautomerism field in the next version and make a start to converting the graphics. I'll also attempt to capture and summarize any discussion in the literature that the study may generate.</p> <p>The document can be used in number of ways. First it helps researchers find the primary literature for tautomerism that is directly relevant to specific projects on which they are working. Second, the study provides guidelines to predict (or even measure) tautomeric preferences even in cases where the specific system of interest has not been studied. Third, it unifies a vast and fragmented body of experimental measurements related to tautomerism. Fourth, the study provides insight into how PJT thought about physicochemical phenomena.</p> <p>PJT published on tautomerism after the original manuscript was written and material in those articles is likely to supersede material in the current document. I would recommend that anybody planning to use this version of the study (other than as a means to identify primary literature sources) read these articles.</p> <ul style="list-style-type: none"><li>• Chapters <a href="#">1</a> , <a href="#">11</a> and <a href="#">12</a> in 'Tautomerism: Methods and Theories' (Editor: L Antonov, Wiley 2013) <a href="#">DOI</a></li><li>• Chapters <a href="#">2</a> and <a href="#">5</a> in 'Tautomerism: Concepts and Applications in Science and Technology' (Editor: L Antonov, Wiley 2016) <a href="#">DOI</a></li></ul> <p>The encouragement of Yvonne Martin, Anthony Nicholls, Roger Sayle and (the late) David Weininger is gratefully acknowledged.</p> <p>Peter W Kenny, July 2019</p>
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# CONTENTS

INTRODUCTION	1
The Quantitative Measurement of Tautomeric Ratio	5
Topics Excluded from the Investigation	7
Ground Plan of this Treatise	9
Rationale and Apologia	11
SECTION A: 'C-TYPE' TAUTOMERISM	12
A.1 Annular and Related Tautomerism involving Carbon Atoms	12
A.1.1 Allylic Systems: Annular Tautomerism	14
A.1.2 Allylic Systems: <i>endo-exo</i> Tautomerism	16
A.1.3 Double Bond Stabilisation in Keto-Enol Tautomerism	20
A.1.4 Double Bond Stabilisation and Destabilisation in $\beta$ -Diketones and Related Compounds: Steric Compression and Steric Crowding	23
A.1.5 The Competitive Stabilisation of C=C vs. C=N	26
A.2 Ketones and Enols	27
A.2.1 $R^1COCH_2R^2$ : Monofunctional Substitution at $R^1$	28
A.2.2 $R^1COCH_2R^2$ : Monofunctional Substitution at $R^2$	29
A.2.3 Substitution in $R^1COCH_2R^2$ : Summary and Speculations	32
A.2.4 Carboxylic Acids, Esters, and Amides	34
A.2.5 Bifunctional Substituents $R^1$ : $\alpha$ -Diketones	34
A.2.6 Aromatisation in Carbocycles	37
A.2.7 Aromatisation vs. Conjugation in 5-Membered Ring Oxoheterocycles: One Heteroatom	40
A.2.8 Aromatisation vs. Conjugation in 5-Membered Ring Oxoheterocycles: Multiple Heteroatoms	43
A.3 Thioketones and Enethiols	46
A.3.1 $R^1CSCH_2R^2$ : Monofunctional Substitution at $R^1$	46
A.3.2 $R^1CSCH_2R^2$ : Monofunctional Substitution at $R^2$	47
A.3.4 Thiocarboxylic Acids, Esters, and Amides	47
A.3.5 Bifunctional Substitution at $R^1$ : $\alpha$ -Thioketones	47
A.3.6 Aromatisation in Carbocycles	48
A.3.7 Aromatisation vs. Conjugation in 5-Membered Ring Thionoheterocycles: One Heteroatom	48
A.3.8 Aromatisation vs. Conjugation in 5-Membered Ring Thionoheterocycles: Multiple Heteroatoms	50

A.4 Imines and Enamines	51
A.4.1 Open-Chain and Cyclic Compounds with R = H or Alkyl	52
A.4.2 Compounds in which R <sup>2</sup> = Aryl	55
A.4.3 Compounds in which R = Aryl	55
A.4.4 Compounds in which R = Acyl	57
A.4.5 Oximes and Hydrazones	57
A.4.6 N-Substitution: Summary and Conclusions	57
A.4.7 Aromatisation in 6-Membered Rings	58
A.4.8 Competitive Conjugation in 5-Membered Rings	62
A.4.9 'Anti-Aromaticity'	64
A.5 Other Simple Nitrogenous Systems	65
A.5.1 Azo-Compounds and Hydrazones	65
A.5.2 Nitroso-Compounds and Oximes	68
A.5.3 Nitro- and <i>aci</i> -Nitro Compounds	68
A.5.4 Nitro- and Nitroso-Amines	69
A.5.5 Nitriles and Ketenimines	69
A.5.6 Cyanamides and Carbodiimides	69
A.5.7 Triazenes	69
A.6 $\beta$ -Dicarbonyl Compounds	71
A.6.1 The Energetics of Scheme 10	72
A.6.2 Extended Conjugation in 6-Membered Rings	76
A.6.3 Conjugation, Aromatisation and Acylation in 6-Membered Rings	79
A.6.4 Extended Conjugation in 5-Membered Rings	82
A.6.5 C-Substitution in Conjugated 5-Membered Rings	83
A.6.6 C-Acylation in Aromatic 5-Membered Rings	88
A.6.7 Open-Chain $\beta$ -Dicarbonyl Compounds	91
A.6.8 $\beta$ -Acylation of Cyclic Ketones	96
A.6.9 Other Electronegative $\beta$ -Substituents	98
A.6.10 Potential Additivity in Unconjugated $\beta$ -Dicarbonyl Compounds	99
A.7 $\beta$ -Dithiones	99
A.8 $\beta$ -Thionoketones and Related Compounds	100
A.8.1 The Energetics of Enolisation and Thioenolisation	100
A.8.2 Extended $\beta$ -Thionoketones	102
A.8.3 Chelated $\beta$ -Thionoketones	103
A.8.4 The $\beta$ -Thionoketone Unit in Aromatic 5-Membered Rings	103
A.9 $\beta$ -Diimines and Vinylogous Amidines	105
A.9.1 Extended Structures	106

A.9.2 Heterocyclic <i>endo</i> -Diimines and Vinylogous Amidines	106
A.9.3 $\beta$ -( $\gamma$ )-Amino Derivatives of 5-Membered Ring Heterocycles	109
A.9.4 $\gamma$ -Amino Derivatives of 6-Membered Ring Heterocycles	110
A.9.5 Open-Chain $\beta$ -Diimines	116
A.9.6 'Nested' Vinylogous Amidines	117
A.9.7 Benzenoid Vinylogues and Divinylogues of $\beta$ -Diimines	117
A.10 $\beta$ -Iminoketones and Aminoenones	119
A.10.1 Energetics	120
A.10.2 Solvent Studies	122
A.10.3 Correction Factors for the 'Basicity Method'	126
A.10.4 Extended Structures: One Donor, One Acceptor	126
A.10.5 Extended Structures: Two Donors, One Acceptor	129
A.10.6 Aromatisation in Extended Structures: 4-Pyridones	132
A.10.7 Aromatisation in Extended Structures: Related Oxoheterocycles	139
A.10.8 Aromatisation in Extended Structures: The Effect of Intramolecular Hydrogen Bonding on Tautomeric Form	139
A.10.9 Aromatisation in Extended Structures: Nonchelated Heterocyclic Anhydro-Bases	141
A.10.10 Chelated Structures: One Donor, One Acceptor	145
A.10.11 Chelated Structures: One Donor, Two Acceptors	147
A.10.12 Chelated Structures: Two Donors, One Acceptor	149
A.10.13 Chelated Structures: Two Donors, Two Acceptors	150
A.10.14 Aromatic Chelates: One Donor, One Exocyclic Acceptor	151
A.10.15 Aromatic Chelates: One Donor, Two Exocyclic Acceptors	159
A.10.16 Aromatic Chelates: Two Donors, One Exocyclic Acceptor	162
A.10.17 Aromatic Chelates: Two Donors, Two Exocyclic Acceptors	164
A.10.18 Exocyclic Enamine Donor, Aromatic Acceptor	165
A.10.19 Exocyclic Hydrazo Donor, Aromatic or Non-aromatic Acceptor	169
A.10.20 Exocyclic Oximino Donor, Aromatic or Non-aromatic Acceptor	174
A.11 $\beta$ -Iminothioketones and Aminoenethiones	177
A.11.1 Energetics	178
A.11.2 Solvent Studies	179
A.11.3 Correction Factors for the 'Basicity Method'	180
A.11.4 Extended Structures: 4-Thiopyridone and Related Thionoheterocycles	181
A.11.5 Chelated Structures	182
A.12 Summary and Overview	183
A.12.1 Ketones, Thioketones and Imines	184

A.12.2 The Energetics of C=Z/C=Z Interaction	189
A.12.3 Modifying, Conflicting and Perturbing Factors	191
A.12.4 Competitive Conjugation	191
A.12.5 Aromatisation	197
A.12.6 Anti-Aromaticity	199
A.12.7 Aromatisation Revisited	200
A.12.8 Effects of Ring Size	209
A.12.9 $\pi$ -Acceptors other than C=Z: the Pecking Order	211
A.12.10 Intramolecular Hydrogen Bonding and Lone Pair Repulsion	212
 SECTION B: 'N-TYPE' TAUTOMERISM	 218
B.1 Annular Tautomerism at Nitrogen	218
B.1.1 Annular Tautomerism in 6-Membered Rings	219
B.1.2 Annular Tautomerism in 5-Membered Rings: <i>s</i> -Triazole	220
B.1.3 Annular Tautomerism in 5-Membered Rings: <i>v</i> -Triazole	224
B.1.4 Annular Tautomerism in 5-Membered Rings: Tetrazole	226
B.1.5 Indazole and other Fused Pyrazoles	227
B.1.6 Benzotriazoles and other Fused Triazoles	228
B.1.7 Benzimidazoles and other Fused Imidazoles	229
B.1.8 C-Substitution in Symmetrical Azoles: Pyrazole, Imidazole, Benzimidazole, Benzotriazole, and 1(3)- <i>H v</i> -Triazoles	232
B.1.9 5,5-Ring Fusions ('Azapentalenes')	235
 B.2 Amides, Imides, Ureas and Related Structures	 237
B.2.1 Correction Factors for the Basicity Method	238
B.2.2 Solvent Studies	240
B.2.3 Open-Chain and Alicyclic Amides (CONH)	242
B.2.4 Aromatic 6-Membered Ring Amides: 2-pyridones	245
B.2.5 Aromatic 6-Membered Ring Amides: Related Oxoheterocycles	249
B.2.6 Aromatic 6-Membered Ring Amides: N-Oxides	252
B.2.7 Cyclic pyruvamides (COCONH) and Oxamides (NHCOCONH)	252
B.2.8 Imides (CONHCO)	254
B.2.9 Ureas (NHCONH) and Acylureas (CONHCONH)	255
B.2.10 Hydrazides (CONHNH) and Related Compounds	259
B.2.11 Cyclic 3-Acylhydrazides (COCONHNH)	266
B.2.12 Diacylhydrazines (CONHNHCO)	266
 B.3 Thioamides, Thioureas and Related Structures	 273
B.3.1 Correction Factors for the Basicity Method	273
B.3.2 Solvent Studies	274
B.3.3 Aliphatic Thioamides	275
B.3.4 6-Membered Ring 2-Thionoheterocycles	277
B.3.5 Thioureas (NHCSNH) and Acylthioureas (CZNHCSNH)	278
B.3.6 Thiohydrazides (CSNHNH) and Related Compounds	282

B.3.7 Dithioacylhydrazines (CSNHNHCS) and Related Compounds	283
B.4 Amidines	285
B.4.1 Correction Factors for the Basicity Method	285
B.4.2 Tautomeric Balance in Symmetrical Amidines	286
B.4.3 Tautomeric Balance in Unsymmetrical Amidines	293
B.4.4 Unsymmetrical Amidines: 6-Membered Ring $\alpha$ -Amino-Heteroaromatics	294
B.4.5 Unsymmetrical Amidines: 5-Membered Ring $\alpha$ -Amino-Heteroaromatics	300
B.5 Acylamidines	307
B.5.1 Open-Chain Acylamidines	310
B.5.2 Alicyclic exo-Acyliminoguanidines	310
B.5.3 Other Alicyclic exo-Acyliminoamidines	310
B.5.4 2-Acylaminoheterocycles	311
B.5.5 Alicyclic Acylamidines: Correction Factors for the Basicity Method	314
B.5.6 Alicyclic Acylguanidines: Carbonyl in 6-Membered Ring	314
B.5.7 Alicyclic Acylguanidines: Carbonyl in 5-Membered Ring	317
B.5.8 Aromatised Bicyclic Acylamidines	319
B.5.9 Alicyclic Acylamidines: <i>endo-Z</i> , <i>exo-N</i>	319
B.5.10 Alicyclic Acylamidines: <i>endo-N</i> , <i>exo-Z</i>	323
B.5.11 Aromatic Acylamidines: Annular Tautomerism in 4-pyrimidones and 4-Quinazolones	326
B.5.12 Aromatic Acylamidines: Evidence concerning Iminol Forms	332
B.5.13 Triazinones related to 4-pyrimidone	337
B.5.14 2,3-Heterofused 2-Amino-4-Pyrimidones and their Aza-Analogues: <i>endo-endo</i> Tautomerism	338
B.5.15 2-Pyrimidones and Related Species	346
B.6 Thioacylamidines	353
B.6.1 Alicyclic Thioacylamidines	353
B.6.2 2- and 4-Pyrimidinethiones and Quinazolinethiones	353
B.6.3 2,3-Heterofused 2-Amino-4-Thiopyrimidones: <i>endo-endo</i> Tautomerism	355
B.7 Imidines	355
B.7.1 Alicyclic Imidines	356
B.7.2 Heteroaromatic Imidines: 2- and 4-Amino- Pyrimidines	358
B.8 Summary and Overview	362
TAUTOMERISM INVOLVING ONLY NITROGEN ATOMS	362

B.8.1 Annular Tautomerism in 5-Membered Ring Heterocycles and their Ring-Fused Derivatives lacking Bridgehead Nitrogen	362
B.8.2 Annular Tautomerism involving Contiguous Nitrogen Atoms: General	369
B.8.3 Amidines and Imidines: Open-Chain and Cyclic	372
B.8.4 Annular Tautomerism in Acylamidines: Open-Chain and Alicyclic	375
B.8.5 Annular Tautomerism in Aromatic Acylamidines	378
B.8.6 <i>endo-exo</i> Tautomerism in Alicyclic and Aromatic Amidines: General	380
B.8.7 <i>endo-exo</i> Tautomerism in 6-Membered Ring Heteroaromatics	382
B.8.8 <i>endo-exo</i> Tautomerism in 5-Membered Ring Heteroaromatics	385
B.8.9 Annular Tautomerism in Bicyclic Heterocycles possessing Bridgehead Nitrogen	389
 TAUTOMERISM INVOLVING IMINOL FORMATION	 395
B.8.10 Tautomerism in Amides and Related Structures containing Adjacent CO and NH but lacking contiguous NHZ (Z = O, S or NR) or COCO: - Aliphatic Compounds	395
B.8.11 - Unsaturated Compounds	397
B.8.12 - 6-Membered Ring Heteroaromatics	398
B.8.13 Contiguous NHZ (Z = O, S or NR) in 5-Membered Ring Heterocycles containing One Carbonyl Group	402
B.8.14 Contiguous NHZ (Z = O, S or NR) in 5-Membered Ring Heterocycles containing Two Carbonyl Groups	409
B.8.15 Contiguous NHZ (Z = O, S or NR) in 6-membered Ring Heterocycles containing Two Carbonyl Groups	411
B.8.16 Amides containing Contiguous Carbonyl Groups	412
B.8.17 Thioamides: General	413
B.8.18 Tautomerism in Open-Chain, Alicyclic and all 5-Membered Ring Thioamides lacking Contiguous NHZ (Z = O, S or NR)	415
B.8.19 Tautomerism in 6-Membered Ring Heteroaromatics lacking Contiguous NHZ (Z = O, S or NR)	416
B.8.20 Contiguous NHZ (Z = O, S or NR) in 5- and 6-Membered Ring Heterocycles containing One or Two Thiones	416
 SECTION C: QUALITATIVE RULES AND QUANTITATIVE PREDICTIONS; CORRELATIONS AND CROSS-CORRELATIONS	 418
C.1 Open-Chain Ketones with Unconjugated Enols	418
C.2 Open-Chain Thioketones with Unconjugated Enethiols	422
C.3 Enolisation and Aromatisation in Carbocyclic Ketones (Thioketones)	422
C.4 Open-Chain Ketones with Conjugated, Chelated Enols	423
C.5 Carbocyclic Ketones with <i>exo</i> -Conjugated, Chelated Enols	426
C.6 Carbocyclic Ketones with Conjugated <i>endo</i> -Enols	426
C.7 Alicyclic 6-Membered Ring Ketones (Thioketones) with Conjugated <i>endo</i> -Enols	429
C.8 $\beta$ -Iminoketones and Aminoenones: General Considerations	435

C.9 $\beta$ -Iminoketones and Aminoenones: Substitution Patterns	438
C.10 Enolisation and Aromatisation in 5-Membered Ring 2-Oxo(thiono)heterocycles with One Ring Heteroatom	446
C.11 Enolisation and Aromatisation in 5-Membered Ring 3-Oxo(thiono)heterocycles with One Ring Heteroatom	455
C.12 Enolisation and Aromatisation in 5-Membered Ring Oxo(thiono)- heterocycles with One Ring $\pi$ -Donor Heteroatom and One Potential Aza-nitrogen: Overview	458
C.13 2-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-nitrogen in a 1,3-Relationship: 139	460
C.14 2-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-nitrogen in a 1,4 Relationship: 138	463
C.15 2-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-nitrogen in a 1,5-Relationship: 137	466
C.16 3-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-nitrogen in a 1,2-Relationship: 142	470
C.17 3-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-nitrogen in a 1,4-Relationship: 141	472
C.18 3-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-nitrogen in a 1,5-Relationship: 140	475
C.19 5-Membered Ring Oxo(thiono)heterocycles containing Three Contiguous Heteroatoms	476
C.20 5-Membered Ring Oxo(thiono)heterocycles containing a 1,2,4-Distribution of Heteroatoms; Tetrazolone	477
C.21 6-Membered Ring Mono-oxo(thiono)heterocycles and their Benzofused Derivatives	480
C.22 6-Membered Ring Heterocycles and their Benzofused Derivatives with Two or More Potential Oxo(thiono)Substituents	487
C.23 Non-Benzenoid Ring Fusions to 6-Membered Ring Oxoheterocycles	494
C.24 Short Summary of Carbonyl Tautomerism	497
C.25 Open-Chain and Alicyclic Imines with Unconjugated Enamines: R = Alkyl	499
C.26 Open-Chain and Alicyclic Imines with Unconjugated Enamines: Substitution at R	501
C.27 Imine-Enamine Equilibria in Simple Heteroaromatic Structures	502
C.28 Open-Chain and Alicyclic Imines with Enamines Conjugated to C=N	504
C.29 Enamines Conjugated with C=N Embedded in Complex Hetero- aromatic Structures. Azo-Compounds and Hydrazones	507
C.30 Imine-Enamine Equilibria for <i>exo</i> -Nitrogen: Amino-substitution in $\pi$ -Excessive Heterocycles	508
C.31 Hammett Relationships in the Tautomerism of Amidines	511
C.32 2- and 4-Aminoazines	517
C.33 2-Aminoazoles	524
C.34 5,5-Heterocyclic Ring Fusions containing Bridgehead Nitrogen	525
C.35 6,5-Heterocyclic Ring Fusions containing Bridgehead Nitrogen	526
C.36 3- and 5-Aminoazoles containing Contiguous Aza-nitrogen and a Ring $\pi$ -Donor Heteroatom	528

C.37 <i>endo</i> -Amidines: Annular Tautomerism in 5-Membered Ring Monocyclic Heterocycles	529
C.38 Annular Tautomerism in Ring Fusions to 5-Membered Ring Monocyclic Heterocycles not involving Bridgehead Nitrogen	533
C.39 5-Membered Ring Alicyclic Acylamidines and Guanidines	537
C.40 Open-Chain and 6-Membered Ring Alicyclic Acylamidines and Guanidines	539
C.41 Aromatic <i>endo</i> -Acylamidines	540
C.42 Imidines	543
C.43 Short Summary: The Comparative Behaviour of C=S and C=O	544
C.44 Short Summary: Nitrones and N-Oxides	546
C.45 Short Summary: Other Nitrogenous Electron Acceptors	546
C.46 Short Summary: The Energetics of C=Z/C=Z Interaction	547
C.47 Short Summary: Perturbing Factors in C=N/C=O Interactions	551
C.48 Predictive Criteria for Tautomeric Preference	554
 APPENDIX 1: Correction Factors for the 'Basicity Method'	 560
(a) Simple Amidines: 818	565
(b) <i>endo</i> -Acylamidines, Aromatic: 821 and 822	565
(c) <i>endo</i> -Acylamidines, Alicyclic: 825 and 826	568
(d) Alicyclic Acylguanidines: 1130 and 1131	569
(e) Bicyclic Acylguanidines: 820	571
(f) Cyclic Vinylogous Amidines with Contiguous Nitrogen: 817	571
(g) Correction Factors for Amides: 812, 823 and 827 (828, 829)	573
(h) Correction Factors for Vinylogous Amides: 830a, 824 and 830	575
(i) $\Delta(\text{NR})$ Values for <i>N</i> -linked Amides, 815 and 815a, and Imides, 816	578
(j) $\Delta(\text{NR})$ Values for Conjugated NH adjacent to sp <sup>2</sup> -Nittrogen: 814	579
(k) Unresolved Problems: 3-Hydroxyisoxazoles	581
(l) Unresolved Problems: Oxo- and Thionopyrazines, 813 and 958	583
(m) $\Delta(\text{NR})$ Values for Thioamides: 957, 958, 959 and 960	586
(n) Unresolved Problems: $\Delta(\text{SR})$ ; 961 and 963	586
(o) Overview	590
 APPENDIX 2: Solvent Effects	 591
(a) Solvatochromic Parameters for Water	595
(b) Systematic Ground Plan	598
(c) Solvent Effects on Structure 13	602
(d) Solvent Effects on Structure 14: Amides	602
(e) Solvent Effects on Structure 14: Thioamides	605
(f) Solvent Effects on Annular Tautomerism	607
(g) Extended 3-Way Equilibria: $K_T$ in 260	608
(h) 3-Way Equilibria for Chelates: $K_T$ in (261, X = NR, Y = O)	610
(i) 3-Way Equilibria for Chelates: $K_T$ in (261, X = NR, Y = NR')	613
(j) 3-Way Equilibria for Chelates: $K_T$ in (261, X = S, Y = O)	613
(k) Extended 3-Way Equilibria: $K_E$ in 260	615

(l) Extended 3-Way Equilibria: $K_M$ in 260	622
(m) Chelated Enols 261: $K_E$ for $\beta$ -Dicarbonyl Compounds	622
(n) Chelated Enols 261: $K_E$ for $\beta$ -Iminoketones	627
(o) Chelated Enols 261: $K_M$ for $\beta$ -Iminoketones	629
(p) Overview	632
(q) Problems in the Extrapolation of LSER Equations to Water	633
 APPENDIX 3: Lone Pair and Dipolar Repulsion	 637
(a) Annular Lone Pair Repulsion in 6-Membered Ring Heterocycles	639
(b) Annular Lone Pair Repulsion in 5-Membered Ring Heterocycles	642
(c) Lone Pair <i>peri</i> -Interactions in Bicyclic Structures	643
(d) Lone Pair 1,4-Interactions: N,N-Type with NR...N Dipolar Attraction	646
(e) Lone Pair 1,4-Interactions: N,O-Type with OH...N Bonding	647
(f) Lone Pair 1,4-Interactions: O,O-Type with OH...O Bonding	647
(g) Lone Pair 1,5-Interactions: N,N-Type with NH...N Bonding	649
(h) Lone Pair 1,5-Interactions: N,O-Type with NH...O and OH...N Bonding	649
(i) Lone Pair 1,5-Interactions: O,O-Type with OH...O Bonding	650
(j) Lone Pair 1,6-Interactions: O,O-Type with OH...O Bonding	652
(k) Annular Dipolar Repulsion in 6-Membered Ring Heterocycles	652
(l) Annular Dipolar Repulsion in 5-Membered Ring Heterocycles	653
(m) Dipolar <i>peri</i> -Interactions in Bicyclic Structures	657
(n) Dipolar Interactions: NH,NH-Type with NH...N Hydrogen Bonding	660
(o) Summary and Overview	660
 APPENDIX 4: Intramolecular Hydrogen Bonding	 664
(a) 1,4-Interactions: NH...O Bonding	664
(b) 1,5-Interactions: NH...O Bonding	666
(c) 1,5-Interactions: OH...O Bonding	666
(d) Conjugation vs. Hydrogen Bonding in Chelated $\beta$ -Diketones	667
(e) Conjugation vs. Hydrogen Bonding in Other Chelates	669
(f) Summary and Overview	670
 APPENDIX 5: Aspects of Aromaticity	 671
(1) The Energetics of Aromatisation	671
(2) Anti-Aromaticity	678
(3) Benzofusion	680
(4) Quinonoid Forms	685
 NOTES AND REFERENCES	 689

*DEDICATION (P.J.T)*

*To the memory of G. Phillips Harris (1919-2004),*

*scientist, polymath and friend,*

*the inspired teacher who introduced me to tautomerism*

*while still at school,*

*this treatise is dedicated*

## INTRODUCTION

The phenomenon of *prototropic tautomerism*, defined by its discoverers as “the addition of a proton at one molecular site and its removal from another,” has continued to fascinate chemists ever since its first formulation just over a century ago.<sup>1</sup> There are several reasons for this, the first and foremost a simple matter of identity. Tautomers are the chameleons of chemistry, capable of changing by a simple change of phase from an apparently established structure to another not perhaps till then suspected, then back again when the original conditions are restored, and of doing this in an instant: intriguing, disconcerting, even perhaps at times exasperating. But the fascination, for some at least, goes deeper. Change of structure means change of properties also. A ketone does not in the least resemble its enol tautomer. The first is a stable, not unduly reactive proton acceptor; the second is a highly reactive proton donor, capable of adding halogens almost instantaneously, and responsible for whatever reactivity in that respect the parent ketone appears to possess. So it may become important to know, even in this very simple context, just how much enol is present.

More importantly, tautomerism alters molecular recognition characteristics. For example, tautomerism inverts polarity, transforming hydrogen bond donor to hydrogen bond acceptor and vice versa. Katritzky in particular has emphasised, writing in the context of heterocyclic chemistry, the failure of chemists themselves to appreciate which was the predominant tautomer of the various nucleic acid bases, and to pass this information even when they knew it to their biochemical and biological colleagues, materially hindered the research that led eventually to unravelling the structure of DNA.<sup>2a</sup> Speaking from our own experience, there are no good grounds for believing that such problems are at an end.

Recently however, a new and perhaps even more urgent reason for resolving these problems has appeared. In the era of classical synthetic chemistry that lasted till perhaps a decade ago it was possible to prepare a new compound, or a set of them, and then investigate the physical properties of at least some members of the set with a view to placing these in the context of chemistry at large. This was true not only in academia but in those major non-academic research institutions that exist, for example, in the pharmaceutical industry. With the advent of combinatorial chemistry this has become, in any commercial context, an almost unimaginable luxury. Only a tiny fraction of compounds prepared in this way (or in any other) can any longer be investigated beyond the point that is required to establish their chemical identity.

The result has inevitably been to throw the emphasis on calculational methods. The medicinal chemist requires swift, reliable, computer-based methodologies that will help to make up for this deficiency.

Algorithms now exist that will calculate, with varying degrees of reliability, such physical properties of a compound as its vapour pressure, partition coefficient, solubility or even  $pK_a$ , given only its chemical structure. And that has raised a new problem. If a compound is entered as the wrong tautomer, a whole range of properties is likely to be calculated incorrectly. And if those properties are then used to attempt some structure-property correlation for a series of compounds, some in the correct tautomeric form and some not, the result will be a nonsense. This problem is compounded by another. One of the aims of a *quantitative structure-activity relationship* (QSAR)<sup>3</sup> is to predict the physical or biological properties of a compound *before* it is synthesised, so that where some relationship is known or suspected the synthesis of compounds unlikely to show activity can be avoided. Such an approach depends critically on the medicinal chemist's ability to write an unambiguous structure for a compound he has not yet synthesised. Tautomerism is one potential source of structural ambiguity. The purpose of this document is, so far as lies within our power, to remove it.

Two simple illustrations of the way in which biologically important properties may relate to tautomer preference are provided by the pairs of compounds **1** and **2**. 4-Quinolone **1b** possesses<sup>4</sup>  $pK_a$  2.27; we shall later demonstrate that  $pK_a$  7.15 may be estimated for its tautomer 4-hydroxyquinoline **1a**. Angyal and Angyal<sup>5</sup> in 1952 were the first to point out that the tautomeric ratio as  $\log K_T$  is the simple difference between their  $pK_a$  values for any two tautomers that share a common cation, the favoured tautomer being *necessarily* the weaker base (and weaker acid). This is illustrated by the free energy diagram Fig. 1, where the tautomers **1a** and **1b** relate to their common cation **1H+** in such a way that the species **1a** which requires a smaller gain in energy in order to protonate is inevitably that of higher  $\Delta G$  (this conclusion applies equally to anions and is true regardless of what arbitrary  $\Delta G$  value is chosen for **1H+**, as inspection will reveal). Hence  $\log K_T$  is 4.88 in favour of the oxo-form. One biologically important property is the partition coefficient.<sup>6</sup> For **1b**,  $\log P$  in octanol-water is<sup>7</sup> 0.58; we may calculate from our published algorithm<sup>8</sup>  $\log P$  2.07 for **1a**, which makes it 30 times less hydrophilic. For the isomers **2a** and **2b**  $\log P$  is 1.12 and 1.90 respectively;<sup>9</sup> for benzotriazole itself the *1H* tautomer predominates in all solvents studied.<sup>10</sup>

In each case the favoured aqueous tautomer is that which partitions the more favourably towards water (lower  $\log P$ ), and in each case too the latter preference is less. This follows from the general principle that the less polar tautomer is favoured by less polar solvents (Fig. 1 again). A recent study<sup>11</sup> has demonstrated that, for one tautomeric equilibrium, not only overall  $K_T$  but the separate partitioning behaviour of each tautomer can be described in terms of the *linear solvation energy* (LSER)<sup>12</sup> approach to be detailed in Appendix 2. Perhaps this is just another consequence of the *reactivity-selectivity principle* (RSP);<sup>13</sup> that is, tautomer preference like reactivity is a driving force whose impact on related phenomena, here other equilibria, tends to be somewhat attenuated by countervailing forces. No general study has yet been made that may throw light on this.

In attempting our task we have first to decide on a *standard phase*. Some have argued that the gas phase is fundamental. Beak<sup>14</sup> points out that gas phase studies show much that has been regarded as intrinsic to be solvational in origin; he criticises aqueous studies of purines and pyrimidines, for example, as potentially irrelevant to “the structure and association of these bases in the nucleic acids either in ground states or during reactions.” We are forced to disagree. We shall have cause to remark later that the iminol forms of amides are much more favoured (or much less disfavoured) in nonpolar solvents and the gas phase than they are in polar solvents such as water, and in this respect the solid state effectively counts as a polar solvent, as Katritzky and co-workers have observed.<sup>15</sup> And  $K_T \sim 1$  is found for benzotriazole in the gas phase<sup>16</sup> despite the miniscule proportion of the 2H-form even in nonpolar solvents. Solvation is not an irrelevance; it is what biological systems are about. A tautomeric switch at the surface of the biological receptor is perfectly possible in marginal cases, but its likely direction given the receptor's hypothetical properties will often be predictable on the basis of the solvent studies set out in Appendix 2, and neither singly nor collectively can the myriad of potential receptors add up to the definition of a standard phase. Water or something approaching it is the medium in which almost every drug is administered, is that from which it approaches its site of action, and is in our opinion the only sensible standard to choose. Hence the aim and title of this treatise.

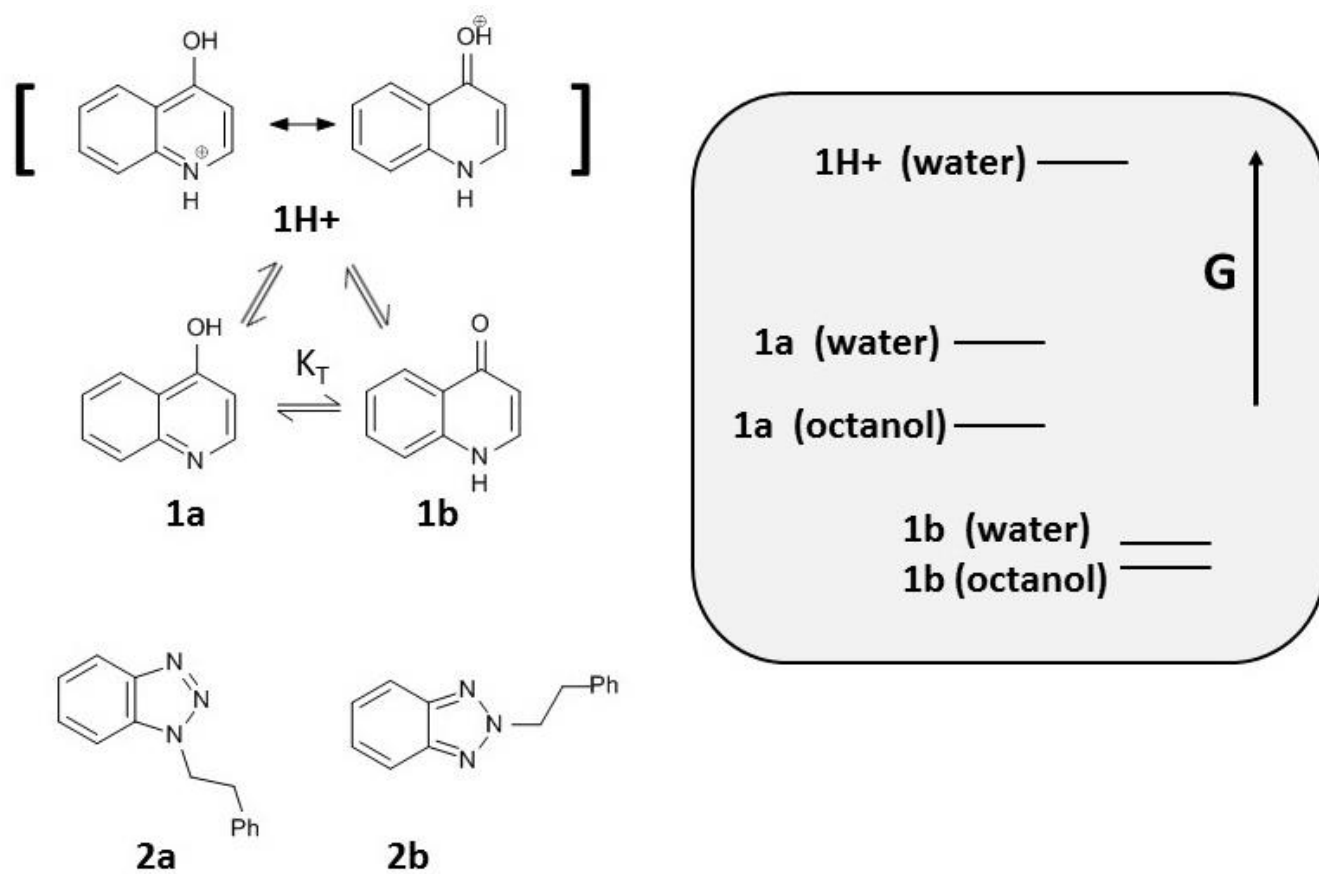


Figure 1

## THE QUANTITATIVE MEASUREMENT OF TAUTOMERIC RATIO

Direct observation cannot quantify tautomeric ratio  $K_T$  with any accuracy outside the range  $0.1 < K_T < 10$  or, at best,  $0.01 < K_T < 100$ .<sup>2b</sup> The one major exception to this concerns the recent work of Kresge and co-workers<sup>17</sup> in which, by generating *in situ* far more than equilibrium concentrations of enol, they have succeeded in estimating accurately tautomeric ratios well in excess of  $10^8$  (for some extreme examples, see section A.2.4). It is impossible to exaggerate the importance of this work in demonstrating that highly accurate determinations of very large quantities are possible and that anything less represents a second best. However the success of this technique depends on a degree of stability for the minor tautomer only possible for proton transfer to and from carbon, so unfortunately it cannot be generalised. Elsewhere two contrasting approaches have mostly been employed:

(i) Probably the majority of tautomeric systems have been studied in organic solvents where spectroscopic techniques, other than UV, are easier to use than in water. This has the advantage that the investigator can experiment with a range of solvents among which there may well be one or two which display both (all) tautomers in quantifiable amounts. Unfortunately however the results bear no necessary relation to what would have been observed in water; indeed, there are cases where even the form tautomerism takes in water is quite different. While there is no general or universal way of getting round this problem, LSER can help. Some LSER studies appear in the literature and we have found it possible to add to their number by making use of published solvent studies which have not previously been analysed in this way. With some trepidation, one may attempt to go further. Where insufficient solvents have been studied to allow the derivation of a viable LSER equation it is still sometimes possible to discern a pattern which closely corresponds to one already established for a compound of similar sort, and here we have occasionally felt justified in extrapolating the results to water by assuming a simple parallelism. While any such extrapolation is unlikely to be accurate, it may still be good enough for qualitative or even semi-quantitative use. We make it clear in the text where any such form of reasoning is employed; detailed justification is reserved to Appendix 2.

(ii) The second approach is to prepare fixed models for each tautomer, *e.g.* the O-methyl and N-methyl derivatives of **1a** and **1b** respectively, and compare these with the parent compound either qualitatively, *e.g.* in terms of their UV spectra, or in what is held to be a

quantitative manner by comparing their basicities (*cf.* Fig. 1).<sup>5</sup> As a quantitative approach, this as it stands requires one of two basic assumptions: either methylation affects neither basicity, or it affects both in equal measure.<sup>2c</sup> If the first, we may use Ebert's relation<sup>18</sup> (i)

$$\log (1 + K_T) = pK (\text{OMe}) - pK_t \quad (\text{i})$$

$$\log K_T = pK (\text{OMe}) - pK (\text{NMe}) \quad (\text{ii})$$

in which  $K_t$  is the  $pK_a$  of the tautomeric mixture; if either the first or the second, eqn. (ii) holds.<sup>19</sup> These equations, especially the second, have been widely used despite the fact that they were discovered quite early to be invalid.<sup>20</sup> Essentially this arises since  $\text{OH}^+$  and  $\text{NH}^+$ , especially the first, are much more strongly solvated than  $\text{OMe}^+$  and  $\text{NMe}^+$  respectively and therefore benefit much more from solvation,<sup>2c</sup> so that contrary to the usual experience, alkylation in this context is *base-weakening*. Recent years have seen a growing realisation of this problem and a start has been made to resolving it. Correction factors are required;<sup>21</sup> these appear at appropriate points in the text while Appendix 1 provides their detailed justification. From three a decade ago<sup>22</sup> we now have almost 30 (Scheme 123). Their effect is to strip out the assumptions that hitherto have had to be used and provide what we believe to be an accurate rendering of tautomeric ratio in aqueous solution. While most are relatively minor some are substantial, with factors ranging up to 10-fold, some compounds require multiple corrections, and in any case there is no point in searching for additive relationships unless the raw data on which they must be based are accurately known.

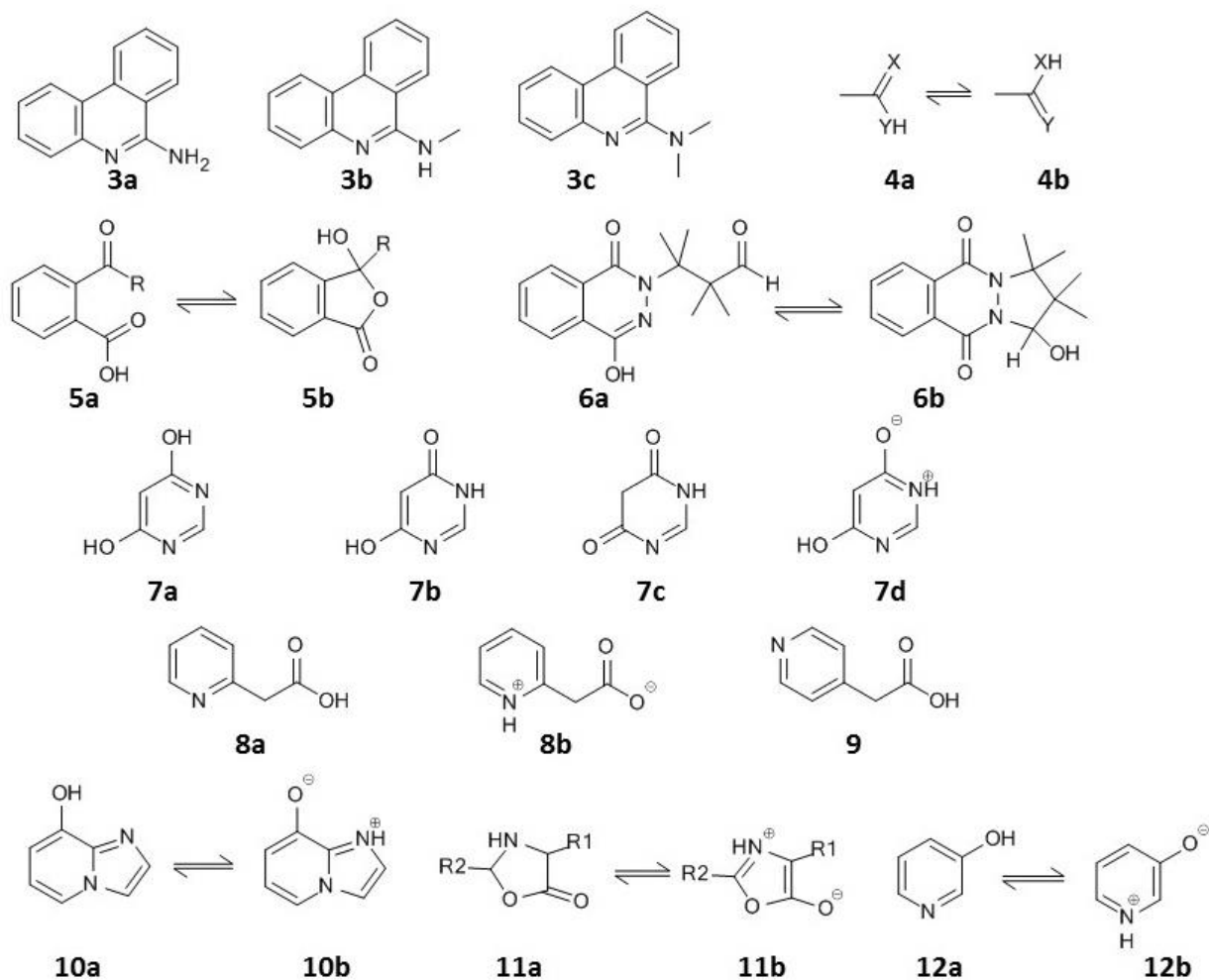
One fact we have discovered when studying model compounds is that crowded molecules are bad news: the simpler the model, the better. This is specially true for noncyclic compounds, where the response to overmuch crowding can go beyond lack of planarity, a serious enough matter where resonance interactions are involved, to changes in conformation or even in configuration that may have been thought not to matter but actually do. We shall deal with such cases as they occur. Where possible therefore we have based our estimates on cyclic molecules though even here there are traps; as is well known, systematic differences between the rules for 5- and 6-membered ring compounds frequently occur. Even in cyclic compounds, peripheral groups are specially vulnerable. To take a simple but fairly extreme example, the  $pK_a$  values (in 70% ethanol) are 4.91, 6.70 and 6.30 for **3a**, **3b** and **3c** respectively,<sup>23</sup> so that the first is no sort of model for the second or third.

This is clearly caused by a *peri*-interaction and illustrates one type of hazard of which one must beware. Of course there are some contexts, and again we shall encounter them, where such effects either probably cancel, or are integral to the type of tautomerism we are attempting to quantify, as sometimes occurs in competitive processes where two tautomeric ‘rules’ conflict. But generally speaking, the problem is best avoided.

## TOPICS EXCLUDED FROM THE INVESTIGATION

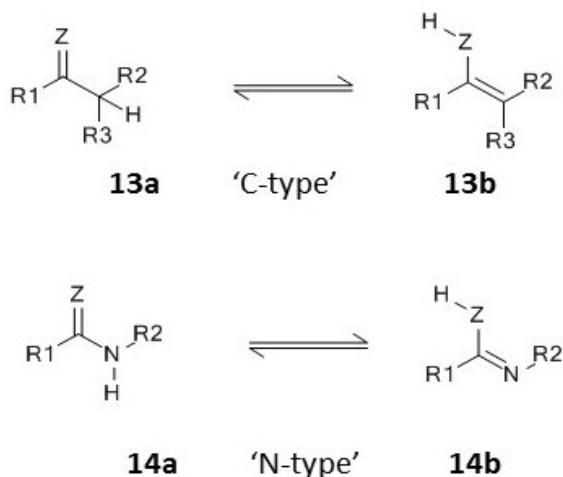
We are concerned here entirely with *functional group tautomerism* **4** (this becomes known as *annular tautomerism* when X and Y both form part of a ring). We exclude, for example, the treatment of metal chelation which is covered, alongside other forms, in the recent update by the Elguero-Katritzky team<sup>24</sup> of their original heterocyclic monograph.<sup>2</sup> We also exclude *ring-chain tautomerism*<sup>25</sup> here exemplified by **5** and **6**. The first depends on the proximity of nucleophile and electrophile; typically, for R = Ph,  $K_c$  lies in the range  $1 < K_c < 10$ , is mildly increased by electronegative substitution into R, and since the ring **5b** is the less polar species, falls as the solvent becomes more polar.<sup>26</sup> The driving force behind cyclisation to **6b**<sup>27</sup> probably combines steric compression resulting from *gem*-dialkylation<sup>28</sup> with the susceptibility of aldehydes to nucleophilic addition, but the well known tendency of water to break up associated species is likely to mean that **6b** too is disfavoured in aqueous solution. While the medicinal chemist must be aware of possibilities such as these, they need not in our opinion greatly concern him or her.

The other main complication is ionisation. There are a number of cases in which the favoured tautomer is not a neutral species but a zwitterion. To take one spectacular example, the dominant form in aqueous solution of the pyrimidine **7** is none of **7a** - **7c** but the betaine **7d**<sup>29</sup> (it is probably **7b** in the solid state<sup>30</sup>). Dominant zwitterion formation is inevitable for  $pK_a$  (acid) <  $pK_a$  (base) but is also liable to occur when the potentially ionising species are in close proximity and so able to influence one another's behaviour, which is essentially the case for **7**. As a non-tautomeric example,<sup>31</sup> while the neutral form **8a** of pyridine-2-acetic acid possesses acid and basic  $pK_a$  values of 4.26 and 4.15 respectively, these become 2.63 and 5.78 in the zwitterion **8b**, so that this instead of being roughly in balance with **8a** is in fact the dominant species (> 97%). In its position isomer **9** this enhancement has fallen<sup>31</sup> from  $\Delta pK_a$  1.63 to  $\Delta pK_a$  0.87, the result of its greater separation of charge. Compounds **10**<sup>32</sup> and **11**<sup>2e</sup> provide two further examples; while **10** can be seen as a 'disguised' imidazole, the rationale behind **11b** is harder to discern.



It is particularly favoured for  $\text{R}^1 = \text{Ph}$ , which is counter-intuitive in electronic terms but forms an example of the double bond stabilisation especially by phenyl to be discussed in section A.1.1. Probably the commonest context in which substantial unsuspected zwitterion formation in water is likely to be met is in 3-hydroxypyridine **12** and related hydroxyquinolines;<sup>33</sup> the corresponding diazines do not show this phenomenon since much weaker bases, but thiols, which are much stronger acids than their OH analogues (typically by  $\Delta \text{pK}_a \sim -3$ ), will show it much more. Again, this can be a problem for the medicinal chemist but its solution must lie in accurate  $\text{pK}_a$  estimation, a type of calculation quite different from that envisaged here.

## GROUND PLAN OF THIS TREATISE



Functional group tautomerism takes two basic forms: 'C-type' or 'N-type.' The first consists in some hetero double bond  $\text{C}=\text{Z}$  ( $\text{Z} = \text{O}, \text{S}$  or  $\text{NR}$ )<sup>34</sup> adjacent to a carbon atom with which it may perform a proton switch. In the second, the adjacent atom is nitrogen. The simplest exemplars of the first are ketones and their enols, thioketones and their thioenols, and imines and enamines. The simplest members of the second are amides, thioamides, amidines, and their respective tautomers; for an amidine with  $\text{R} = \text{R}^2$ ,  $K_{\text{T}} = 1$  necessarily. Each can then be further modified by suitable adjustment of  $\text{R}^1$  or  $\text{R}^2$ , and this process can continue till quite complex molecules, linear or cyclic, have been built up. Eventually, especially in the latter, the two series can merge or overlap.

We shall find that, while some attempt can be made to construct qualitative or even at times quantitative rules inside each series, there is little commonality between them.<sup>36</sup> For example, amides and thioamides have very similar values of  $K_{\text{T}}$ ; for ketones and thioketones, these are very different. Hence the starting point for each series is also different. Even more significantly, the *electronic* forces operating in C- and N-type tautomerism differ profoundly (see sections A.10.9 and B.4.4 for detailed discussion). If rules for computational algorithms are to be formulated, these crucial differences will have to be written in to them.

We shall deal below firstly with Series C (Section A), then with Series N (Section B), then merge these in the summary Section C. On the way we shall incorporate important subsidiary topics such as the effects of ring size, lone pair

repulsion, intramolecular hydrogen bonding, and aromatisation, as they occur. All these have been considered by others<sup>2</sup> but for one or two the emphasis is novel, as for instance that which we sometimes give to conformation. In some cases, as with solvent effects and the correction factors required for model compounds, detailed discussion will be reserved for an Appendix. In terms of past treatments of this subject, our emphasis on *functional group tautomerism* has one odd consequence. Explicitly, *we are not concerned with chemical classes*; as an example, 4-pyridones and 2-pyridones belong in the 'C-type' and 'N-type' series respectively, so are not considered together. The fact that both are pyridine derivatives and nearly equivalent in  $K_T$ , readily explicable in chemical terms as that turns out to be, is here an irrelevance.

*Conventions and Nomenclature.* — While  $K_T$  is a dimensionless quantity hence unambiguous *per se* there is no general agreement on the *direction* in which it is defined, and it is difficult to see how there could be. Most typically<sup>2</sup> it tends to be defined in favour of the major tautomer, which means that in the case of most 'hydroxy'- and aminoheterocycles for example, it is defined in chemically inconsistent directions. Because of the many and often conflicting types of tautomeric shift we have been forced to evolve some *specific* definitions; not only  $K_T$  (towards oxoforms) and  $K_E$  (towards enols) but  $K_M$  towards imino-forms, and sometimes others which are defined *in situ* when they occur. As a way of avoiding ambiguity we frequently use a *single-headed* arrow  $\rightarrow$  to indicate the defined direction. Tautomer ratios are usually given as  $\log K$  and, where these have been derived by introducing correction factors or by some other indirect means, will generally be estimated to the nearest 0.1 log unit. We place these correction factors on the same scale as  $\log K$  by casting them in the form  $\Delta \log K$ , generally shortened to  $\Delta(XR)$ , as for example  $\Delta(NMe)$  which stands for the correction factor to use in going from NMe to NH in a given context (see above, and Appendix 1). On another topic, we avoid encumbering the text with strict chemical nomenclature when a solvent is deuteriated, so that, for example,  $CHCl_3$  in an NMR context refers to  $CDCl_3$ .

*References.* — These are listed at the end. With so much material to reference we have adopted a dual policy. While key references are given individually, especially those involving quantitative data, useful minor work is frequently acknowledged via some review in which it has appeared. Results which are qualitative in nature and occasion no surprise will generally fall into the latter category. Much of the latter material comes from ref.2, to which we are particularly indebted.

## RATIONALE AND APOLOGIA

Inevitably this treatise is a compilation of data since these are the facts on which hypotheses must be built, but it aims to be much more than that. Essentially its goal is *prediction*, and this has consequences that set it apart. In the first place, it is deliberately discursive. Tautomerism is a multi-layered, multi-faceted, many-dimensional subject such that a compound or phenomenon crucial to one area can be of equally crucial importance to another, but in a quite different way. So the same compounds and phenomena keep cropping up, but in quite different contexts, and each time they do it is necessary to consider their import afresh. Some form a *leitmotiv* that keeps recurring across sections that at first sight have no connection with one another. We have tried to help the reader with extensive, almost obsessive cross-referencing, but this also requires that each time the compound appears there must be some recapitulation, of structures or facts or both; it is simply not possible to compartmentalise, to create neat compound sub-groups, in the way that most review texts do. Without these features its length might well have been halved, but with an immense loss in comprehensibility and the potential for new understanding.

We also indulge in a degree of speculation that goes to the limits of reasonable surmise and at places beyond. We make no apology for this. We are working in territory only in part explored, in which oases of orderly fact are separated by stretches of terrain where settlement is sparse and there are scarcely even paths, let alone highways, to form a link. Our reward has been to find, at the end of a long chain of reasoning any step of which might have proved disastrously wrong, that a sensible result has emerged. Rationalisation of the pattern formed by oxoheterocycle tautomerism (section C.21), and elucidation of the mutual interactions of C=O, C=S and C=N (section C.46), are two such topics. Our justification is the coherence, however partial, we believe we have achieved.

Parts A and B present the factual meat whereas C is an overview that recapitulates most of this material, but heavily condensed and with a different purpose: to collate, re-cast, cohere, establish links, and come to conclusions. It should probably be consulted first, on any topic; cross-referencing is comprehensive. Afterwards the Appendices present detail that would be too disruptive if in the main text; for those who do not wish to do so, they need not be consulted at all.

## A: 'C-TYPE' TAUTOMERISM

### A.1 Annular and Related Tautomerism involving Carbon Atoms

Proton switches involving carbon atoms only are generally classified as *isomerisations* but the distinction from tautomerism can be blurred. The stabilisation of one allylic double bond relative to another (section A.1.1) may possess tautomeric consequences, as may the effect of ring size (section A.1.2). Related to this is the effect of  $\alpha$ -substitution ( $R^3$ ) on the balance between  $C=C$  and  $C=Z$  in **13** (sections A.1.3 *et seq.*). Those substituents capable of through conjugation or intramolecular hydrogen bonding, where new factors enter, are considered later.

Unusually for tautomerism solvent effects are predicted to be slight, since solute polarity will rarely be much affected by the isomerisation process. Since this is borne out by work on one highly polar solute series,<sup>37</sup> we make no allowance for solvent variation below.

**Table 1. Carbon double bond stabilisation factors <sup>a</sup>**

R	$\Delta \log K^b$	$\sigma_e^c$	R	$\Delta \log K^b$	$\sigma_e^c$
-NMe <sub>2</sub>	5.5	-0.24	-NHCOMe		-0.088
-CH=CH <sub>2</sub>	4.3	-0.11	-OCOMe		-0.005
-OMe	3.6	-0.064	-SCOMe		-0.057
-Ph	3.3	-0.12	-Alkyl	2.2	-0.03
-CHO <sup>d,g</sup>	3.2	-0.10	-CN	2.1	-0.055
-OPh	2.8	-0.083	-Bu <sup>t</sup>	2.0	-0.036
-NO <sub>2</sub>	2.5	-0.077	-Pr <sup>i</sup>	2.0	-0.040
-COMe <sup>e,g</sup>	2.5	-0.095	-CH <sub>2</sub> OMe	1.8	-0.041
-F	2.5	0.041	-CH <sub>2</sub> CO <sub>2</sub> R	1.5	-0.020
-CONH <sub>2</sub>		-0.055	-Cl	0.9	-0.011
-CO <sub>2</sub> R <sup>f</sup>	2.3	-0.064	-Br	0.3	-0.018
-SMe	2.2	-0.13	-SO <sub>2</sub> Me	0.0	-0.052

<sup>a</sup> Ref. 38; at 25°C and incorporating cross-interaction terms. <sup>b</sup> Scaled from  $\Delta G$  to allow direct comparison with  $\log K$ . <sup>c</sup> Ref. 39. <sup>d</sup> *s-trans* alignment with  $C=C$ . <sup>e</sup> Probably *s-cis*. <sup>f</sup> Probably *s-trans*. <sup>g</sup> Ref. 40.

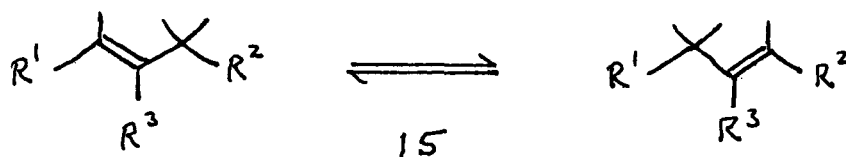
Table 2.  $\sigma$ -Values for some common substituents <sup>a,b</sup>

R	$\sigma_I$	$\sigma_m$	$\sigma_{R^-}$	$\sigma_{R^0}$	$\sigma_R$	$\sigma_{R^+}$
-CH <sub>2</sub> Ph	0.03	-0.01	-0.14 <sup>h</sup>		-0.13	
-Me <sup>c</sup>	-0.01	-0.06			-0.15	
-CH=CH <sub>2</sub>	0.11	0.06			-0.08	
-Ph	0.12	0.09			-0.11	-0.17
-CF <sub>3</sub>	0.40	0.46			0.11	0.15
-F	0.54	0.34	-0.58	-0.44	-0.48	-0.37
-Cl	0.47	0.37	-0.30		-0.28	-0.21
-Br	0.47	0.34	-0.28		-0.27	-0.19
-I	0.40	0.35	-0.18		-0.20	
-NH <sub>2</sub>	0.17	-0.21	-0.55	-0.42	-0.68	-1.10
-NHMe <sup>c</sup>	0.13	-0.16			-0.67	-1.16
-NMe <sub>2</sub> <sup>c</sup>	0.17	-0.16	-0.30	-0.44	-0.66	-1.22
-NHPh	0.20				-0.62	
-NHNH <sub>2</sub>	0.11				-0.64	
-NHCOMe <sup>c</sup>	0.28	0.16		-0.25	-0.35	-0.47
-NHCONH <sub>2</sub>	0.23	0.06		-0.33 <sup>d</sup>	-0.47	
-N=C(NH <sub>2</sub> ) <sub>2</sub> <sup>d</sup>	0.08			-0.37		
-NHC(NH <sub>2</sub> ) <sub>2</sub> <sup>+d</sup>	0.43			-0.14		
-OH	0.24	0.13	-0.45	-0.46	-0.57	-0.64
-OMe <sup>c</sup>	0.30	0.11		-0.44	-0.55	-0.66
-OPh	0.40	0.23		-0.42	-0.51	
-OCOMe <sup>c</sup>	0.38	0.30			-0.24	
-SH	0.27				-0.40	
-SMe <sup>c</sup>	0.30	0.17	-0.24	-0.31	-0.38	-0.55
-SCOMe <sup>c</sup>	0.39	0.39	-0.02		-0.08	
-CHO	0.30		0.53		0.27	
-COR <sup>c</sup>	0.30	0.38	0.41		0.25	0.06
-COCF <sub>3</sub>	0.52		0.45 <sup>e</sup>		0.33	
-CO <sub>2</sub> Me	0.32	0.38	0.30		0.18	
-CO <sub>2</sub> Et <sup>c</sup>	0.30	0.36	0.31		0.18	
-CONH <sub>2</sub>	0.28		0.23		0.12	
-SOMe	0.54		0.05		-0.09	
-SO <sub>2</sub> Me <sup>c</sup>	0.59	0.65	0.35		0.13	
-CN	0.57	0.61	0.26		0.12	
-NO <sup>e</sup>	0.49	0.62			0.42	
-NO <sub>2</sub>	0.67	0.74	0.37		0.18	
-N <sub>3</sub>	0.43	0.32			-0.27	
-N=NPh <sup>e</sup>	0.32	0.30			0.09	
-N= <sup>f,g</sup>	0.47	0.65			0.49	

<sup>a</sup> M. Charton, *Prog. Phys. Org. Chem.*, 1981, **13**, 119, with some corrections to  $\sigma_R$  from ref. 39. <sup>b</sup> Estimates are italicised. <sup>c</sup> Any alkyl. <sup>d</sup> Scaled from: A. Heesing and W. Schmaladt, *Chem. Ber.* 1978, **111**, 320. <sup>e</sup> C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165. <sup>f</sup> Values of  $\sigma_m = 0.65$  and  $\sigma_p = 0.96$  for aza-nitrogen (A. D. Campbell, S. Y. Chooi, L. W. Deady and R. W. Shanks, *Aust. J. Chem.*, 1970, **23**, 203), which have been shown to be additive for the hydrolysis of diazine carboxylate esters (L. W. Deady, D. J. Foskey and R. A. Shanks, *J. Chem. Soc., Perkin Trans. 2*, 1971, 1962), may be combined with  $\sigma_m = 1.07 \sigma_I + 0.30 \sigma_R$  (ref. <sup>e</sup> above) and the definition  $\sigma_p = \sigma_I + \sigma_R$  to give  $\sigma_I = 0.47$  and  $\sigma_R = 0.49$ . <sup>g</sup>  $\sigma_O = 0.75$ .

<sup>h</sup> For CH<sub>2</sub>CH=CH<sub>2</sub>.

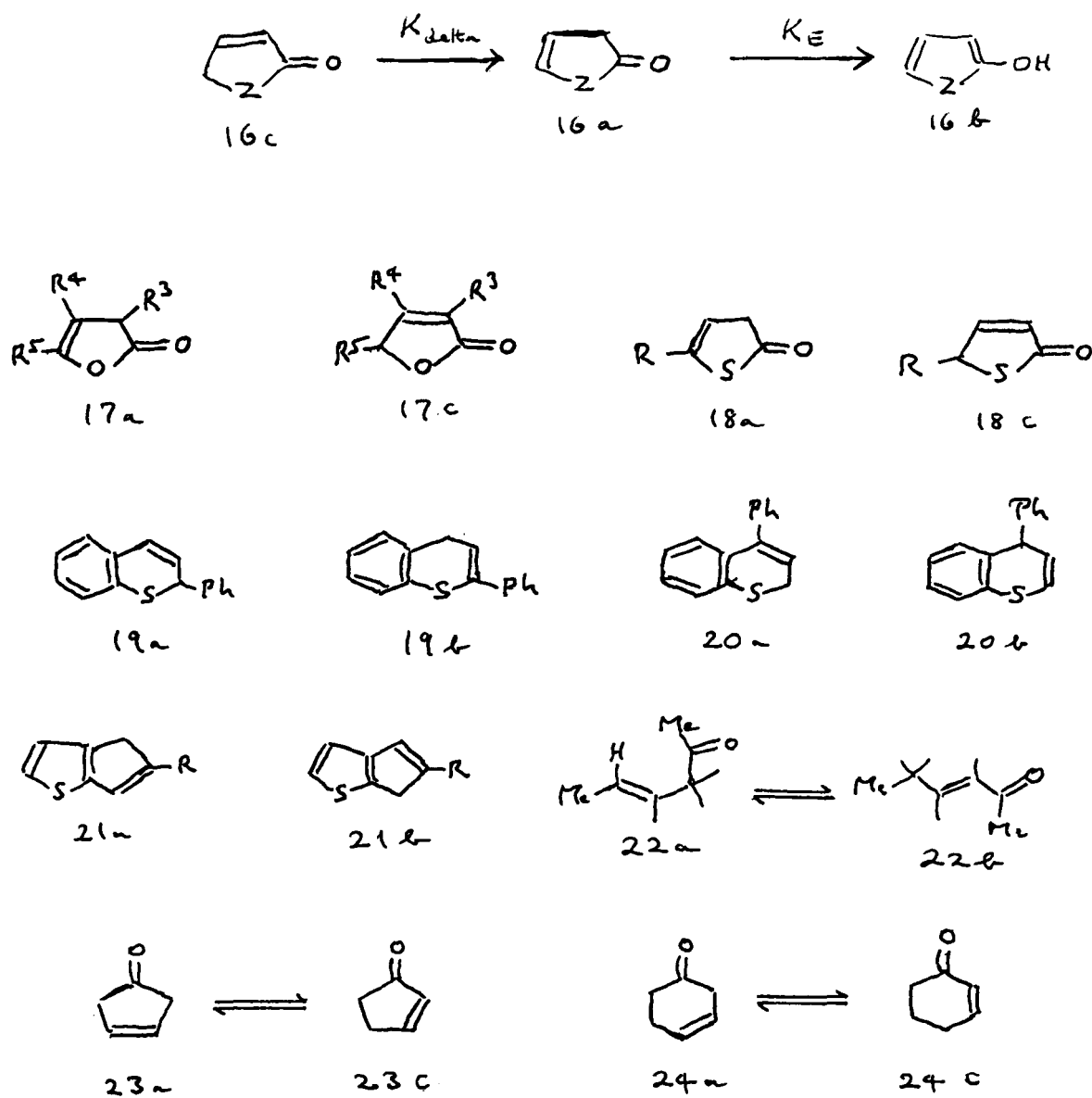
### A.1.1 Allylic Systems: Annular Tautomerism



Some of Hine's data<sup>38</sup> on the stabilisation of double bonds in allylic systems **15** ( $R^3 = H$ ) are listed in Table 1, re-expressed as  $\Delta \log K_T$  for ease of use and shown alongside Charton's resonance demand susceptibility parameter  $\sigma_e$ .<sup>39,41</sup> We may attempt to apply these data to the annular tautomerism of 2-oxofurans, thiophenes and pyrroles (**16**,  $Z = O, S,$  or  $NR$  respectively). Here the parent compounds possess the  $\Delta^3$ -form **16c** but 5-substitution can induce a switch to **16a**. In treating this as an allylic system we suppose that, for the parent compounds,  $K_{\text{delta}}$  will depend on the relative double bond stabilising ability of  $-\text{COZR}$  *vs.*  $-\text{ZCOR}$ . Most of the values required to decide this issue are missing from Table 1, but there are useful clues. Given  $\text{NMe}_2 > \text{OMe} > \text{SMe}$  we may anticipate a similar if less widely spaced order for  $-\text{ZCOR}$  while by contrast the values for  $-\text{COR}$  and  $-\text{CO}_2\text{R}$  are almost identical, and given a similar difference in pattern for the  $\sigma$ -values of these two substituent sets (Table 2),  $K_{\text{delta}}$  should be dominated by the influence of  $-\text{ZCOR}$ . Hence we predict  $Z = S > O > NR$  as the  $K_{\text{delta}}$  order of **16**.

For 2-oxopyrrole and -1-methylpyrrole,  $K_{\text{delta}} \sim 0.1$  in the liquid state<sup>42</sup> (an alternative value<sup>43</sup> of  $K_{\text{delta}} < 0.02$  appears to be based on a confusion between the kinetics and thermodynamics of deuteration). No such data for furan or thiophene exist but again we may utilise Table 1. For (**17**,  $R^3 = R^4 = R^5 = H$  or  $\text{Ph}$ ) **17a** is undetectable,<sup>44</sup> whereas for (**17**,  $R^3 = R^4 = H, R^5 = \text{Ph}$ ) it is formed exclusively.<sup>45</sup> Given that 100% of one form indicates  $\log K \geq 1.5$  in its favour, these data suggest  $\log K_{\text{delta}} \sim -2$  for 2-oxofuran itself. A calculated<sup>46</sup> (B3LYP/6-31G\*) gas phase value of  $\Delta H^\circ$  2.9 kcal mol<sup>-1</sup> ( $\equiv \Delta \log K_{\text{delta}} -2.1$ ) is of the same order and, unusually, its probable lack of solvent sensitivity<sup>37</sup> permits acceptance of this value. Data for **18** in  $\text{CCl}_4$ , while as for 2-oxofuran showing 100% **18a** for  $R = \text{Ph}$  and 100% **18c** for  $R = H$ , more helpfully give  $\log K_{\text{delta}} -0.6$  and  $-0.75$  for  $R = \text{Me}$  and  $\text{SMe}$  respectively.<sup>47</sup> Given  $\Delta \log K$  2.2 for both,  $\log K_{\text{delta}} -2.8$  or  $-3.0$  for 2-oxothiophene follows; we take the average. These parent values are given in Table 3. In fact the relation between  $\log K_{\text{delta}}$  and Hine's  $\log K$  is linear:

$$\log K_{\text{delta}} = 0.576 \Delta \log K - 4.17 \quad (r^2 > 0.999) \quad (\text{z})$$



**Table 3. Annular tautomerism in 2-oxofurans, -thiophenes, and -pyrroles**

	$\log K_{\delta}$
Pyrrole	-1.0 <sup>a</sup>
Furan	-2.1 <sup>b</sup>
Thiophene	-2.9 <sup>c</sup>

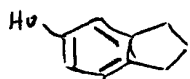
<sup>a</sup> Ref. 42. <sup>b</sup> Ref. 46. <sup>c</sup> See the text.

This less than unit slope plausibly results from the compensating effect of  $-\text{COZR}$  on  $K_{\text{delta}}$  and perhaps other factors such as perturbations due to the 5-membered ring. On additive assumptions it should now be possible to predict  $K_{\text{delta}}$  values as a function of  $R^3$ ,  $R^5$  or both together. Note however that 4-substitution has little effect on  $K_{\text{delta}}$ ; as the pivot of the allylic system ( $\equiv R^3$  in **15**), this is as expected.

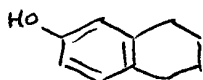
A handful of largely qualitative results follow. The tetrahydrothiazines **19** and **20** exist as **19b** but **20a**; from Table 1 on additive assumptions, these preferences may be estimated as *ca*  $10^2$  and  $> 10^4$  respectively.<sup>43</sup> For **21**, **21a** is only slightly preferred and this is not affected by the electronic nature of the substituent;<sup>43</sup> see remarks above. For **22**, the conjugated tautomer **22b** is preferred by a margin of only  $\log K$  0.66;<sup>40</sup> this at first sight surprising result is readily explained on the data of Table 1 (expected  $\log K$  0.3). However, the cyclic ketones **23** and **24** show a massive preference for the **b** forms, by  $> 10^4$  and  $10^{2.4}$  respectively,<sup>50</sup> which is thought to be due to a very large reduction in CH eclipsing interactions on conjugation; in larger rings, the differential is much less.

### A.1.2 Allylic Systems: *Endo-Exo* Tautomerism

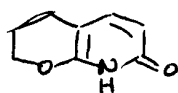
It was first suggested by H. C. Brown<sup>51</sup> that *exo* and *endo* double bonds are differently stabilised by 5- and 6-membered rings: “reactions will proceed in such a manner as to favour the formation or retention of an *exo* double bond in the 5-ring and to avoid the formation of the *exo* double bond in the 6-ring systems.” The thermodynamic basis for this kinetic phenomenon was seen as resulting from eclipsing interactions which are appreciable in cyclopentane but can be relieved by an *exo* double bond, whereas in cyclohexane its presence introduces them. This postulate was used to explain<sup>51</sup> the ‘Mills-Nixon effect’<sup>52</sup> partial double bond localisation as in **25** and **26**, the first showing two double bonds *exo* to the 5-membered ring, the second showing one double bond along the ring junction. Subsequently, Spinner and Yeoh<sup>20</sup> demonstrated the reality of this effect for the tautomerism of the pyridones **27** and **28**. In the former, where the ring junction double bond is favourably placed,  $\log K_T = 2.14$ ; in the latter, where it is not, iminol formation is relatively favoured, leading to  $\log K_T = 1.08$ .<sup>53</sup> More recently, Castro and Martinez<sup>54</sup> have found that **29** and **30** exist as shown in the solid state, and largely so in both  $\text{CHCl}_3$  and DMSO solution. These two observations are consistent with a roughly 10-fold stabilisation of the *exo* double bond in 5- relative to 6-membered rings as will be seen below.



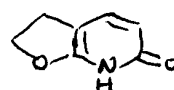
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26



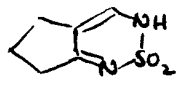
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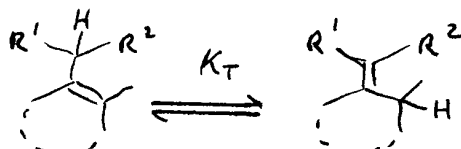
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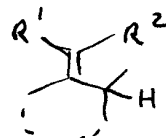
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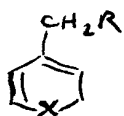
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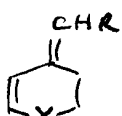
31a



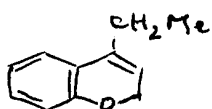
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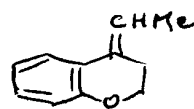
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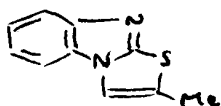
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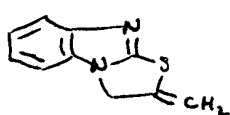
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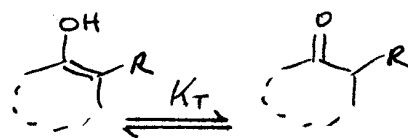
33b



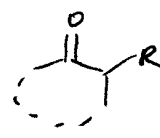
34a



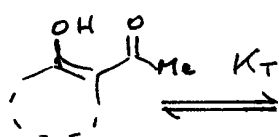
34b



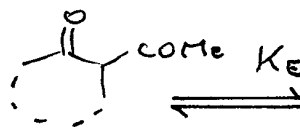
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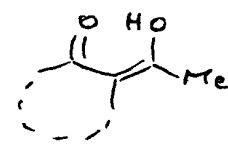
35b



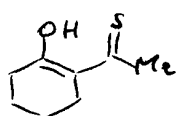
36a



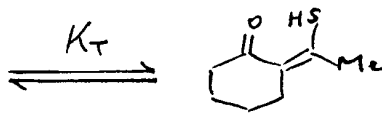
36b



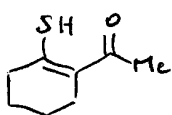
36c



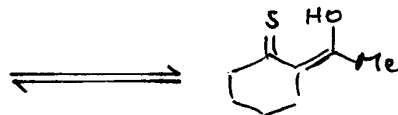
37a



37b



38a



38b

Brown and co-workers<sup>51</sup> studied the isomerisation of a range of compounds **31** for which  $R^1 = \text{H}$  or alkyl and  $R^2 = \text{COR}$ . Their results show internal inconsistencies for reasons which probably include steric crowding but may also reflect some failure, on occasion, to attain full equilibrium. For this reason we place more weight on the very careful work of Bigley and May<sup>55</sup> using purely hydrocarbon systems in which equilibrium was certainly attained. The latter results, and some of the former, appear in Table 4. Bigley's data<sup>55</sup> show the well known alternant effect of ring size and, for  $\Delta \log K_T$  ( $6 \rightarrow 5$ ), provide a value of 1.0 which is backed up by the *mean* of Brown's results (except for  $R^2 = \text{CO}_2\text{H}$ ):  $0.96 \pm 0.33$  ( $n = 5$ ). This value is close to that implied by **28** vs. **27** and to the 1.1 finally adopted (see below). Bigley<sup>55</sup> notes that his  $K_T$  values are proportional to those for  $R^1 = R^2 = \text{H}$  in 5- and 6-membered rings, being consistently about 100 times greater. This amplification for  $R^1 = R^2 = \text{Me}$  is about that expected for a single Me according to Table 1, so the shortfall is presumably the result of saturation. Other results are in accord with this; see A.1.3 below.

The few qualitative results show inconsistencies. It is perhaps surprising that, in the pyrans (**32**,  $X = \text{O}$ ) and thiapyrans (**32**,  $X = \text{S}$ ) and in the benzopyrans **33**, both *endo-a* and *exo-b* tautomers should coexist in solution,<sup>56,57</sup> since Bigley's data (Table 4) suggest that the former should predominate. Similarly, it is surprising that **34a** and **34b** should be of comparable stability.<sup>58</sup> In such conformationally constrained molecules, predictions based on simple alicyclic rings may be unsafe.

Similar but not identical preferences are found in the enolisation of cyclic ketones **35**. Some data appear in Table 4. Cyclopentanone in water is more favoured over its enol than cyclohexanone by  $\Delta \log K_T$  1.55; for its  $\alpha$ -CO<sub>2</sub>Et derivative (in CCl<sub>4</sub>) this margin is 1.66 while for  $\alpha$ -COMe in water it is 0.96.<sup>17</sup> It is also relevant to consider the overall process **36a**  $\rightarrow$  **36c** for which  $K = K_T K_E = 0.60$  or  $-0.56$  for the 5- and 6-membered rings respectively. The  $\beta$ -thionoketones **37** and **38**, which enolise completely (Section A.8), have been studied by Duus.<sup>58</sup> The oxo-form is disfavoured in both but by a larger margin ( $\Delta \log K_T$  0.77) when in the ring; for MeCSCH<sub>2</sub>COMe also in CCl<sub>4</sub>,  $\log K_T = 0.55$  in favour of the hydroxythiono tautomer.<sup>59</sup> With the proviso that varying strength for the intramolecular hydrogen bond may influence the results (SH---O bonding in  $\beta$ -thionoketones is probably negligible<sup>59</sup>), those of Table 4 taken together fit the hypothesis that

**Table 4.** *Exo-endo* preference ( $\log K_T$ ) as a function of ring size

Compound	R <sup>1</sup>	R <sup>2</sup>	Ring size:	5	6	7	8	Ref.
<b>31</b> <sup>a</sup>	Me	Me		0.18	-0.86	-0.21	-0.75	55
<b>31</b> <sup>b</sup>	Me	COMe		0.72	-0.36			51
<b>35</b> , R = H <sup>c</sup>				7.94	6.39	8.00		17
<b>35</b> , R = CO <sub>2</sub> Et <sup>d</sup>				0.89	-0.75			17
<b>35</b> , R = COMe <sup>c</sup>				1.45	0.49			17
<b>36</b> <sup>c,e</sup>				0.60	-0.56			17
<b>37</b> <sup>d</sup>					-1.12			59
<b>38</b> <sup>d</sup>					-0.35			59

<sup>a</sup> In HOAc. <sup>b</sup> Solvent unspecified. <sup>c</sup> In water. <sup>d</sup> In CCl<sub>4</sub>. <sup>e</sup>  $\log K$ :  $K = K_T K_E$ .

**Table 5.** Values of  $\log K_E$  in water for ketones R<sup>1</sup>COCHR<sup>2</sup>R<sup>3</sup> **42**<sup>a</sup>

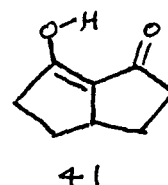
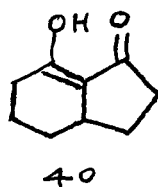
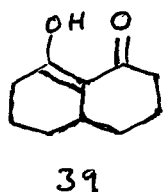
	R <sup>2</sup> =	H	Me	Me	Ph	Ph	OMe
R <sup>1</sup>	R <sup>3</sup> =	H	H	Me	H	Ph	H
H		-6.23		-3.86	-3.07	0.98	
Me		-8.63 <sup>b</sup>	-7.51 <sup>c</sup>	-7.33	-6.4		
Ph		-7.97		-6.48	-5.15		-6.47

<sup>a</sup> Ref. 17. <sup>b</sup> Statistically corrected. <sup>c</sup>  $\log K_E$  -8.76 for enolisation at methyl.

**Table 6.** Values of  $\log K_E$  for compounds of type Ar<sub>2</sub>C=C(OH)R

	R =	H	Me	Et	Pr <sup>i</sup>	Bu <sup>t</sup>	Ph	Mesyl
<b>47</b> <sup>a,b</sup>		1.30	-0.19	-0.51	-0.55	-2.23		1.88
<b>48</b> <sup>c</sup>		1.22	-2.28				-1.91	

<sup>a</sup> Ar = mesyl. <sup>b</sup> Ref. 64, in hexane. <sup>c</sup> Ref. 65, in water.



*endo*-C=C is relatively stabilised in 6-membered rings by  $\Delta \log K_T$  *ca.* 0.6; that *exo*-C=C is relatively stabilised in 5-membered rings by  $\Delta \log K_T$  *ca.* 0.5; and that replacement of C=C by C=O in the latter conveys an extra boost of about  $\Delta \log K_T$  0.4. This way of looking at the data is not quite in line with Brown's original hypothesis<sup>51</sup> but will serve as a rule of thumb.

The importance of intramolecular hydrogen bonding is emphasised by the sequence **39**  $\rightarrow$  **41** for which the enol content is 100, 80, and 1.4% respectively;<sup>17</sup> this compares with 75% for MeCOCH<sub>2</sub>COMe<sup>60</sup> (all values in MeOH). While enolisation of **41** must be disfavoured by 5-*endo*-C=C ( $\Delta \log K_E$  *ca.* -0.6 on the above analysis) the other major factors must be hydrogen bond strength and lone pair repulsion, both of which will be boosted in **39** by a compression effect and reduced as the oxygen atoms draw apart. Allowing for the first factor, the second and third together — here as so frequently it is virtually impossible to disentangle them — appear to reduce enolisation in **41** relative to **40** some 70-fold. (Note that the *direction* of enolisation in **40** is as expected). Other possible contexts for the use of this factor are explored elsewhere.

### A.1.3 Double Bond Stabilisation in Keto-Enol Tautomerism

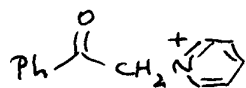
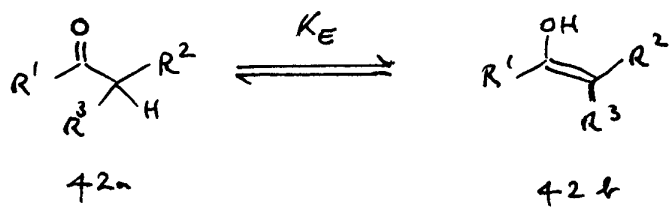
In allylic tautomerism **15**, the role of the substituent is confined to stabilising a carbon double bond. In keto-enol tautomerism **42** it may stabilise or destabilise carbonyl also, and if it stabilises both, the factors found for **15** are likely to be attenuated. Here we explore the situation for the type of substituent examined in section A.1.1; those capable of through-conjugation or intramolecular hydrogen bonding appear later.

Table 5 summarises the data that exist for R<sup>1</sup> = H, Me and Ph on alkyl and aryl substitution. For R<sup>1</sup> = Me a single methyl substituent R<sup>2</sup> has only half the C=C stabilising ability predicted on the basis of Table 1, and a second methyl increases this only slightly. For R<sup>1</sup> = Ph the situation is probably similar. Some of this attenuation may be due to the fact that OH as well as the substituent will stabilise C=C and the two are cross-conjugated; the latter factor has been invoked to explain the small effect of R<sup>2</sup> = OMe.<sup>17</sup>

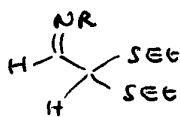
Hine's values (Table 1) are for  $R^3 = H$  and any substituent  $R^3$  may be expected to attenuate them. In the absence of conjugation there is no special effect due to electronegativity *per se*, as demonstrated by  $\log K_E = -6.12$  for **43**,<sup>17</sup> a lower value than for  $R^2 = Ph$ . However, when  $R^2 = Ph$  replaces Me the effect is much greater, and for  $R^1 = H$  it is barely attenuated below the 'predicted' value of Table 1 even when two aryls are present. Steric crowding in **44** has been invoked<sup>61</sup> to explain why **44b** is formed exclusively whereas the imine **44a** would normally be expected to predominate (section A.4) and a similar explanation may fit here. If so, other bulky, near-planar groups may have the same effect. Whatever the reason that Ph as substituent largely escapes attenuation the result can be spectacular: the effect of benzene ring annelation in **45** is to increase  $K_E$  by *ca.*  $10^4$ , to  $\log K_E -3.84$ ;<sup>62a</sup> for its position isomer **46**,  $\log K_E = -7.48$ ,<sup>62b</sup> both in water.

Although it has been claimed that enolisation is favoured by *any* substituent,<sup>63</sup> the equilibrium in **42** lies so far against **42b** that very few stable simple enols are known. As already foreshadowed in Table 5, all contain the unit  $Ar_2C=C$ . This area has been explored by Rappoport,<sup>64</sup> who for (**47**,  $Ar = R = mesyl$ ) finds  $\log K_E = 1.9$  in hexane. Alkyl groups however destabilise, as also found by Harcourt and More O'Ferrall<sup>66</sup> for some fluorenes **48**, and in the former case<sup>64</sup> the variation for *alkyl* substituents correlates with  $E_s$ , presumably through steric constraints on planarity. Some data for both series appear in Table 6. Elsewhere, aryl and (at any rate multiple) alkyl substitution can prove decisive when tautomeric form is finely balanced. Few quantitative studies exist, but one on **49**<sup>66</sup> shows that, in the absence of a steric clash between  $R^1$  and  $R^2$ ,  $\Delta \log K_E \geq 1.2$  for Ph whereas the effect of alkyl is small. Given  $\log K_E$  in water of  $-0.89$  and  $-0.74$  for (**49**,  $R^1 = R^2 = H$ ) and (**49**,  $R^1 = Me$ ,  $R^2 = H$ ) respectively,<sup>67a</sup> this presumably means that 2-alkyl derivatives will exist as **49a** in water but 2-aryl derivatives as **49b**. However, while the parent compound is present as its enol in DMSO,<sup>67b</sup> its 4,5-dimethyl derivative **50** exists in that solvent as written.<sup>68</sup> Given a differential for (**49**,  $R^1 = Bu^t$ ,  $R^2 = H$ ) of  $\Delta \log K_E$  *ca.*  $-2.3$  between DMSO and water<sup>66</sup> (Table 131, Appendix 2), this implies  $\log K_E < -3$  for **50**. Here of course substitution is not on the *tautomerisable*  $C=C$  and stabilisation of the oxo-form by  $> 10^2$  implies this to be the more polar, as is further discussed in section C.11.

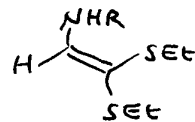
Substituents appear to be particularly good at promoting enolisation when the resulting compound may be considered 'aromatic.' Whereas the parent thiazolone (**51**,  $Z = S$ ,  $R = H$ ) exists in the solid state as such, all alkyl



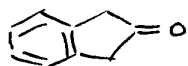
43a



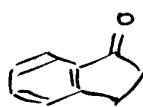
44a



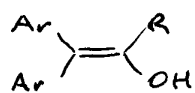
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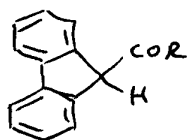
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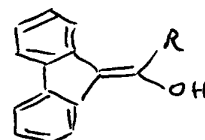
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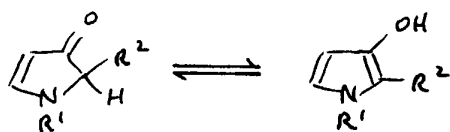
47b



48a

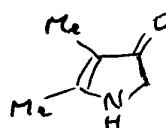


48b

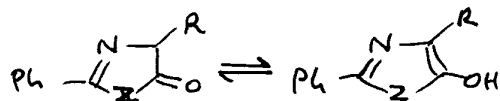


49a

49b

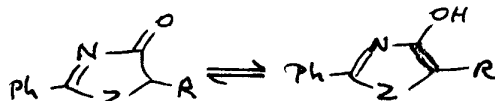


50



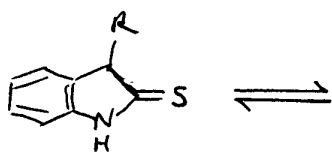
51a

51b

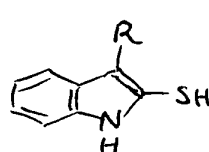


52a

52b



53a



53b

substituents examined ( $R = \text{Me}$ ,  $\text{CHMe}_2$ ,  $\text{CH}_2\text{Ph}$  *etc.*) convert it to the thiazole **51b**.<sup>69</sup> The situation in DMSO is more confusing, with  $R = \text{CHMe}_2$  giving the same result (75% enol) as the parent but others giving 100%.<sup>69</sup> A similar picture is found for its isomer (**52**,  $Z = \text{S}$ ).<sup>70</sup> In both cases (see below) the enol form will probably dominate in water. The corresponding oxazolones (**51** or **52**,  $Z = \text{O}$ ) enolise less,<sup>2g</sup> consistently with a lower degree of aromaticity for oxazole,<sup>2f</sup> so the position in water is less certain. And while (**53**,  $R = \text{H}$ ) predominates as **53a** in all solvents, the balance when  $R = \text{Ph}$  tips heavily towards **53b**.<sup>71</sup> While there seem to have been no solvent studies on simple thiones their very much poorer proton acceptor properties than carbonyl, and the negligible proton donor properties of  $\text{SH}$ ,<sup>72</sup> probably mean that **53** and similar compounds will be relatively solvent-insensitive; if so, these tautomeric preferences may extend to water. It will later be seen (sections C.10 and C.11) that these types of structure represent one of the commonest contexts for the predominance of enol forms, especially when, as here, thiocarbonyl is present.<sup>2f</sup> This is one of the borders at which ‘C-type’ and ‘N-type’ tautomerism most commonly meet; the nominal thioamide **53a** can behave as a simple thione (section A.3) whose intrinsic tautomeric bias is radically different.

#### A.1.4 Double Bond Stabilisation and Destabilisation in $\beta$ -Diketones and Related Compounds: Steric Compression and Steric Crowding

In  $\beta$ -diketones and related structures, further complications arise. Firstly, since the substituent affects two  $\text{C}=\text{Z}$  not one, its effect on  $\text{C}=\text{C}$  should be further attenuated. Secondly, since the stability of the enol form now depends in part on through-conjugation, *steric crowding* with loss of planarity is likely to be deleterious; the opposite effect to that shown by **44**. Barbiturates **54** show both effects (Table 7), with small alkyl groups mildly stabilising ( $\Delta \log K_E$  0.3 - 0.5) but large groups destabilising.<sup>73</sup> Nevertheless Ph retains the effect seen in simpler cases, with  $\Delta \log K_E$  1.8 not much below its value (2.2) in acetone (Table 5). In the cyclohexanediones **55** the effect of Me is slightly greater, with  $\Delta \log K_E \sim 0.8$ ;<sup>74</sup> in its fused analogue **56**, **56b** is the preferred tautomer in DMSO for  $R = \text{Ph}$  but **56a** for  $R = \text{alkyl}$ .<sup>75</sup> Given  $\Delta \log K_E$  (DMSO  $\rightarrow$  water) -0.8 for (**55**,  $R = \text{H}$ ,  $R' = \text{Me}$ ),<sup>60</sup> it is probable that these preferences are retained in water.

**Table 7.** The effect of 5-substitution on log  $K_E$  for  $\beta$ -diketones

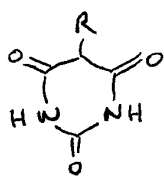
R =	H	Me	Et	Pr <sup>i</sup>	Ph	Cl	Br
<b>54</b> <sup>a,b</sup>	-1.7	-1.2	-1.4	-2.5	0.1		
<b>54</b> <sup>a,c</sup>	-1.3	-0.88				-0.76	-0.21
<b>55</b> <sup>a,d</sup>	1.3	2.1					

<sup>a</sup> In water. <sup>b</sup> Ref. 73. <sup>c</sup> Ref. 76. <sup>d</sup> Ref. 60.

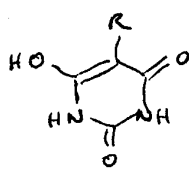
Enolisation in barbiturates is also promoted by halogen;<sup>76</sup> the authors correlate enol content (Table 7) with the acidity of the enol.<sup>77</sup> Since iminol formation in oxoheterocycles (sections B.2.4 and C.21) is also promoted by halogens, this may be a general phenomenon, but elsewhere it does not seem to have been quantitatively explored.

Open-chain (chelated)  $\beta$ -diketones **57** present in an acute form the conflict between steric compression and steric crowding. Emsley *et al.*<sup>79</sup> state that, for  $R^1 = R^2 = \text{Me}$ , almost any substituent  $R^3$  will strengthen the intramolecular hydrogen bond by a compression effect and hence increase enol content, regardless of its electronic nature; however, the same authors find that (**57**,  $R^1 = R^2 = R^3 = \text{Ph}$ ) does not enolise at all, in consequence of steric crowding. By contrast, enolisation is complete in all solvents for (**57**,  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{Ph}$ ). For (**57**,  $R^1 = \text{Me}$ ,  $R^2 = \text{OEt}$ )  $\Delta \log K_E$  is only 0.66 for  $R^3 = \text{Ph}$ ,<sup>17</sup> clearly the result of a balance between opposing forces. Toullec<sup>17</sup> indeed remarks that large substituents can increase the strength of the enolic hydrogen bond while simultaneously decreasing the actual proportion of enol. In consequence enolisation is generally less for a given substituent  $R^3$  in (**57**,  $R^1 = R^2 = \text{Ph}$ ) than in (**57**,  $R^1 = R^2 = \text{Me}$ )<sup>17</sup> even though, for the parent compounds, there is little difference.

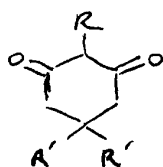
Chelated aminoenones **58b** are in general preferred to the unconjugated  $\beta$ -iminoketones **58a** (section A.10.1), but this too can be severely upset by steric factors. In the solid state, (**59**,  $R = \text{H}$ ) is present as **59b**, but  $\alpha$ -methylation to (**59**,  $R = \text{Me}$ ) is sufficient to convert it to **59a**.<sup>80</sup> The related compounds **60**,<sup>81</sup> **61**<sup>82</sup> and (**62**,  $R^1 = \text{alkyl}$ ,  $R^2 = \text{bulky alkyl}$ ) exist in  $\text{CHCl}_3$  as written to the extent of 5, 40 and 100% respectively. A particularly striking contrast is shown by **63** and **64**, both of which exist in  $\text{CHCl}_3$  as written.<sup>83</sup> Both are of a structural type in which the exomethylene tautomer is expected to predominate (section A.10.11), as it does for **65**,<sup>83</sup> but for **63** with its space-demanding structure that is impossible.



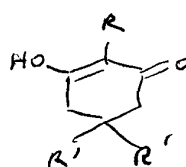
54a



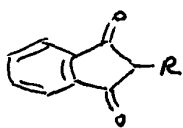
54b



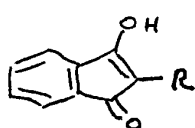
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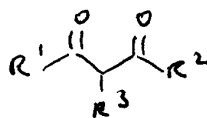
55b



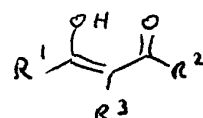
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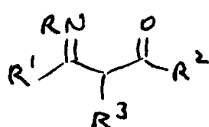
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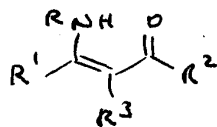
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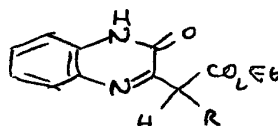
57b



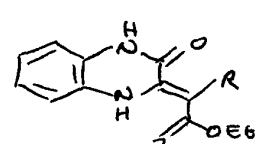
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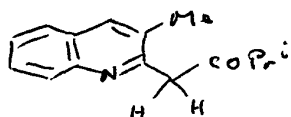
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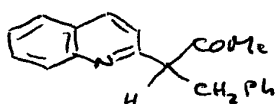
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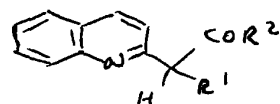
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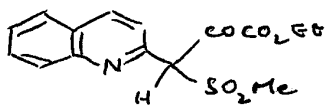
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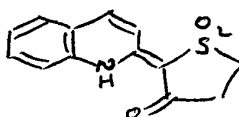
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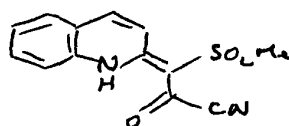
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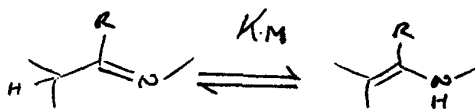
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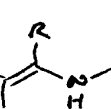
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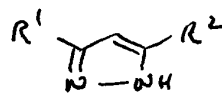
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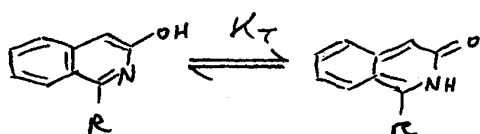
66a



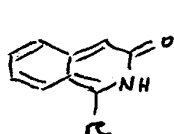
66b



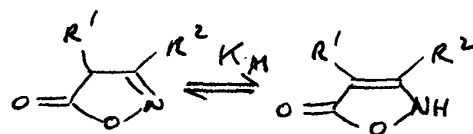
67



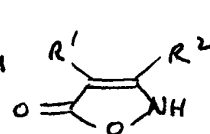
68a



68b



69a



69b

In no such case is it yet possible to quantify the steric factors involved, though as a general guide, two bulky nonplanar substituents in  $\text{-CHR}_2$  will prevent enolisation to  $\text{=CR}_2$  while one will still allow it to take place. If however the ring is  $\alpha$ -substituted, as in **59** and **60**, a single bulky substituent in  $\text{-CHR}_2$  may be enough to block enolisation. Cyclic structures as in **64** help to enforce planarity in the electron acceptor moiety so can overcome this in part. It should also be mentioned that solvent effects are a particular source of confusion. The NMR techniques used for most of this work employ solvents whose relevance to tautomeric preference in aqueous solution is chancy at best (Appendix 2), and nowhere more so than here. Where it is available, information as to the solid state is likely to prove the most reliable guide.<sup>15</sup>

### A.1.5 The Competitive Stabilisation of $\text{C}=\text{C}$ vs. $\text{C}=\text{N}$

Essentially this is an aspect of imine-enamine tautomerism **66**, with the proviso that either double bond or both may be further conjugated. Especially in the latter case, large effects would not be expected and on the scant information available, this is found. Elguero and co-workers<sup>37</sup> have studied annular tautomerism in the pyrazoles **67** and find  $\Delta \log K_M$  values, in terms of structure **66**, of  $\sim 0.1$  for  $\text{R} = \text{Me}$  and  $\sim -0.4$  for  $\text{R} = \text{Ph}$ . For 3-hydroxyisoquinoline **68** in water,<sup>84</sup> replacement of  $\text{R} = \text{H}$  by  $\text{R} = \text{Me}$  boosts  $\log K_T$  by *ca.* 0.4, in the same direction as for **67** but slightly more. It would seem that, in cases such as these, correction for  $\text{R}$  is barely worth attempting. Somewhat larger effects are found for **69**,<sup>88</sup> where several competing influences overlap. For (**69**,  $\text{R}^1 = \text{H}$ ) in water,  $\Delta \log K_M \sim -0.4$  for  $\text{R}^2 = \text{Me}$  or  $\text{Ph}$ , so consistently with expectation for **66**, the usual differential between these substituents is not found. As for  $\text{R}^3$  in **15** or in the 4-position of **16** they occupy a pivotal position, where they may influence the behaviour of substituents to either side of them but have little influence themselves. However, for (**69**,  $\text{R}^2 = \text{Me}$  or  $\text{Ph}$ ), replacement of  $\text{R}^1 = \text{H}$  by  $\text{Br}$  leads to  $\Delta \log K_M$  1.0, in line with its effect in barbituric acid **54** (Table 7) and greater than predicted for a simple allylic system (Table 1). Otherwise however these expectations<sup>38</sup> appear to be fulfilled;  $\text{R}^1 = \text{Me}$  and  $\text{CO}_2\text{Et}$  give 100% of **69b**<sup>85</sup> which implies  $\Delta \log K_M > 1.5$ , in line with predictions of 2.2 and 2.3 (Table 1) respectively. While some inconsistencies remain it seems likely therefore that, if sufficient care is employed in disentangling the competing factors, quantitative sense can be made even of quite complex systems such as these.

## A.2 Ketones and Enols

The effects of ring size on keto-enol tautomerism (section A.1.2) and of multiple substitution on C=C in stabilising the enol tautomer (section A.1.3) are treated above. Here we consider monosubstitution at  $R^1$  and  $R^2$  in  $R^1COCH_2R^2$ . The enol content of simple ketones is so small that, in the absence of major perturbations, predominance of the keto-form may be assumed. However, some types of perturbation are large and it is therefore worth knowing one's starting point in simple systems since this may help prediction in more complex cases. The types of compound for which enolisation leads to through-conjugation involving  $R^2$  are considered in later sections.

**Table 8. Log  $K_E$  in water for ketones of structure 70 and 71 <sup>a</sup>**

$R^1$	$\sigma_I^b$	$\sigma_R^b$	log $K_E$ (70)	log $K_E$ (71)
H	0.00	0.00	-6.23	-3.07
Me	-0.01	-0.16	-8.63 <sup>c</sup>	-6.4
Et	-0.01	-0.14	-8.76	
Pr <sup>i</sup>	0.01	-0.16	-8.61	
Bu <sup>t</sup>	-0.01	-0.18	-8.76	
Cyclohexanone			-6.69 <sup>c,d,e</sup>	
$\alpha$ -Tetralone			-7.31 <sup>f</sup>	
Cyclopentanone			-8.24 <sup>c,d</sup>	
<b>46</b>			-7.48 <sup>f</sup>	
<b>45</b>			-4.14 <sup>c,f</sup>	
Ph	0.12	-0.11	-7.97	-5.15
4-MeOC <sub>6</sub> H <sub>4</sub>	0.11	-0.19	-8.80	
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	0.23	0.03	-6.69	
2-Thienyl	0.19 <sup>g</sup>	-0.19 <sup>g</sup>		-6.45 <sup>h</sup>
2-Furyl	0.17 <sup>g</sup>	-0.19 <sup>g</sup>		-5.9 <sup>h</sup>
4-Pyridinyl				-3.1 <sup>i</sup>
3-Pyridinyl				-4.2 <sup>i</sup>
2-Pyridinyl	0.18 <sup>g</sup>			-3.35 <sup>i</sup>
2-Pyrazinyl	0.25 <sup>g</sup>			-2.9 <sup>h</sup>

<sup>a</sup> Ref. 17 for log  $K_E$  unless otherwise stated. <sup>b</sup> Ref. 39 unless otherwise stated.

<sup>c</sup> Statistically corrected. <sup>d</sup> For purposes of comparison. <sup>e</sup> Ref. 86. <sup>f</sup> Ref. 62. <sup>g</sup> Ref. 96.

<sup>h</sup> Ref. 89. <sup>i</sup> Ref. 90.

### A.2.1 R<sup>1</sup>COCH<sub>2</sub>R<sup>2</sup>: Monofunctional Substitution at R<sup>1</sup>

Here R<sup>1</sup> is peripheral, *i.e.* not in general part of a cyclic structure. For the series R<sup>1</sup>COMe **70** and R<sup>1</sup>COCH<sub>2</sub>Ph **71** (Table 8) there are enough data for trends to be apparent. Two stand out:

(a) Aldehydes (R<sup>1</sup> = H) possess  $K_E$  values much larger than would be expected from the difference in electronegativity between H and alkyl. The reason lies in hybridisation, which for CH is sp<sup>2</sup>-s by contrast with sp<sup>2</sup>-sp<sup>3</sup> for C-alkyl or sp<sup>2</sup>-sp<sup>2</sup> for C-aryl. This makes the carbon atom of C=O more electron deficient and is responsible for the much greater susceptibility of aldehydes to nucleophilic addition, *e.g.* to give hydrates in water, which typically occurs<sup>87</sup> to the extent of *ca.* 50% but can be more.  $\alpha$ -Dicarbonyl compounds also show this feature (section A.2.5).

(b) Excluding R<sup>1</sup> = H,  $K_E$  rises with the electronegativity of R<sup>1</sup>. Quantitatively, we obtain eqn. (iii) for those members of series **70** where  $\sigma_I$  and

$$\log K_E = -7.39(0.22) + 1.97(1.01) \sigma_I + 8.11(1.25) \sigma_R \quad (\text{iii})$$

$$(n = 7 \quad r^2 = 0.977 \quad s = 0.14 \quad F = 86)$$

$\sigma_R$  are known. The data set is unbalanced so these coefficients must be treated with caution, but nevertheless they show that enolisation is promoted by both field and resonance effects, particularly the latter. The intercept term is quite accurate and suggests that the hybridisation effect for aldehydes is responsible for  $\Delta \log K_E$  *ca.* 1.2. Data for series **71** are too few to correlate but, here as well, substituents more electronegative than Ph raise  $K_E$ . Consistently, Gawinecki and coworkers<sup>88</sup> have obtained an equation for the effect (in CHCl<sub>3</sub>) of *m*- and *p*-substitution in Ph on  $\log K_E$  for **72** which we have (slightly) recast to give (iv). By contrast, the *lower*  $K_E$

$$\log K_E = -0.20(0.03) + 1.53(0.06) \sigma \quad (\text{iv})$$

$$(n = 13 \quad r^2 = 0.982 \quad s = 0.09 \quad F = 602)$$

values for R<sup>1</sup> = 2-thienyl and 2-furyl (Table 8) have been attributed to vinylogous conjugation<sup>89</sup> as illustrated by **73**. Given the results in Table 8 for 2- and 4-pyridinyl,<sup>90</sup> intramolecular hydrogen bonding to R<sup>1</sup> as in **74b** does not appear to stabilise the enol. This is in sharp contrast to variation at R<sup>2</sup> as will be seen below. Presumably the much more favourable geometry of the bond in **72b**, a 6-membered ring as in chelated  $\beta$ -diketones, is responsible. This point is taken up in the next section.

While no other series of constant  $R^2$  is extensive enough for detailed analysis, some cross-comparisons are possible. Here compounds **75** are particularly valuable.<sup>91-93</sup> For  $R^1 = \text{alkyl, aryl, and 2-pyridinyl}$  in  $\text{CHCl}_3$  only **75a** is visible, but for  $R^1 = \text{CO}_2\text{R}$  **75b** predominates, with  $\log K_E \sim 1$  for  $R = \text{CO}_2\text{Et}$ .<sup>91</sup> More O'Ferrall and Murray<sup>92</sup> confirm **75a** for  $R^1 = \text{Ph}$  in  $\text{CHCl}_3$ , and in water this compound possesses<sup>93</sup>  $\log K_E -4.2$ . Since Greenhill *et al.*<sup>91</sup> find a minor amount of **75b** for  $R^1 = \text{CO}_2\text{Et}$  in ethanol and water, we may estimate for **75** a factor of at least  $\Delta \log K_E + 3$  for the effect of replacing  $R^1 = \text{Ph}$  with  $R^1 = \text{CO}_2\text{Et}$ . Consistently, in  $\text{CHCl}_3$ , **76a** for  $R^1 = \text{Me}$  and **76b** for  $R^1 = \text{CO}_2\text{Et}$  are the only detectable species. However,  $\beta$ -positions are less electronegative so enolisation here is less likely;  $K_E \sim 2$  for **79** in  $\text{DMSO}$ <sup>94</sup> probably implies mostly **79a** in water. This remarkable enhancement of enolisation for  $R^1 = \text{CO}_2\text{R}$  is a general feature of  $\alpha$ -diketones (section A.2.5) and also shows itself in the alternative conjugative process to give an aminoenone (sections A.10.14 and C.9). From other substituent variations it is possible to deduce roughly quantitative rankings for  $\text{CHCl}_3$  based on series **76**,<sup>92,93</sup> **77**<sup>92</sup> and **78**<sup>92</sup> which are contrasted in Table 9 with those of Table 8 for series **70** and **71** in water. Agreement is not good but, where there is overlap, at least the same ranking order is preserved.

### A.2.2 $R^1\text{COCH}_2R^2$ : Monofunctional Substitution at $R^2$

Data here are more scattered and, since most are for water, are readily summarised in the ranking orders of Table 10. The much larger  $\Delta \log K_E$  for Ph relative to Table 9 is artefactual, the result of the double bond stabilisation by aryl discussed in section A.1.3 and summarised in Table 5. Allowing for this, the effect of  $R^2$  differs in two important respects from that for  $R^1$ . Relative to Ph the effect of electronegativity on  $K_E$  is much less, probably because  $R^2$  is more remote from carbonyl than  $R^1$ ; evidence *inter alia* for the theory that stabilisation or destabilisation by substituents acts chiefly on the ketone.<sup>17</sup> Secondly however, the intramolecular hydrogen bond shown as **72b**, **76b** or **78b** is clearly far more important. It is particularly interesting that  $K_E$  for **76** and **78**<sup>95</sup> should be so little different. The reason is apparent if their  $\sigma_I$  values<sup>96</sup> are compared with their proton acceptor abilities expressed as  $\log K_\beta$ <sup>72</sup> (Table 11): the first, which should raise  $K_E$  for pyrazine, appears to cancel almost exactly against the likely drop in strength of its intramolecular hydrogen bond. We return to this subject in the following section.

**Table 9. Ranking Orders in log  $K_E$  relative to  $R^1 = \text{Me}$** 

$R^1$	$\Delta \log K_E$			
	$\text{CHCl}_3^a$	Water ( <b>70</b> )	Water ( <b>71</b> )	Water ( <b>71</b> ) <sup>b</sup>
2-Thienyl			0.0	
2-Furyl			0.5	
Ph	0.7	0.7	1.2	
2-Pyridinyl	1.2		3.0	1.8
4-Pyridinyl	1.9		3.3	2.1
2-Pyrazinyl			3.5	2.3
$\text{CO}_2\text{Et}$			> 4.2	> 3

<sup>a</sup> See the text. <sup>b</sup> Relative to  $R^1 = \text{Ph}$ .

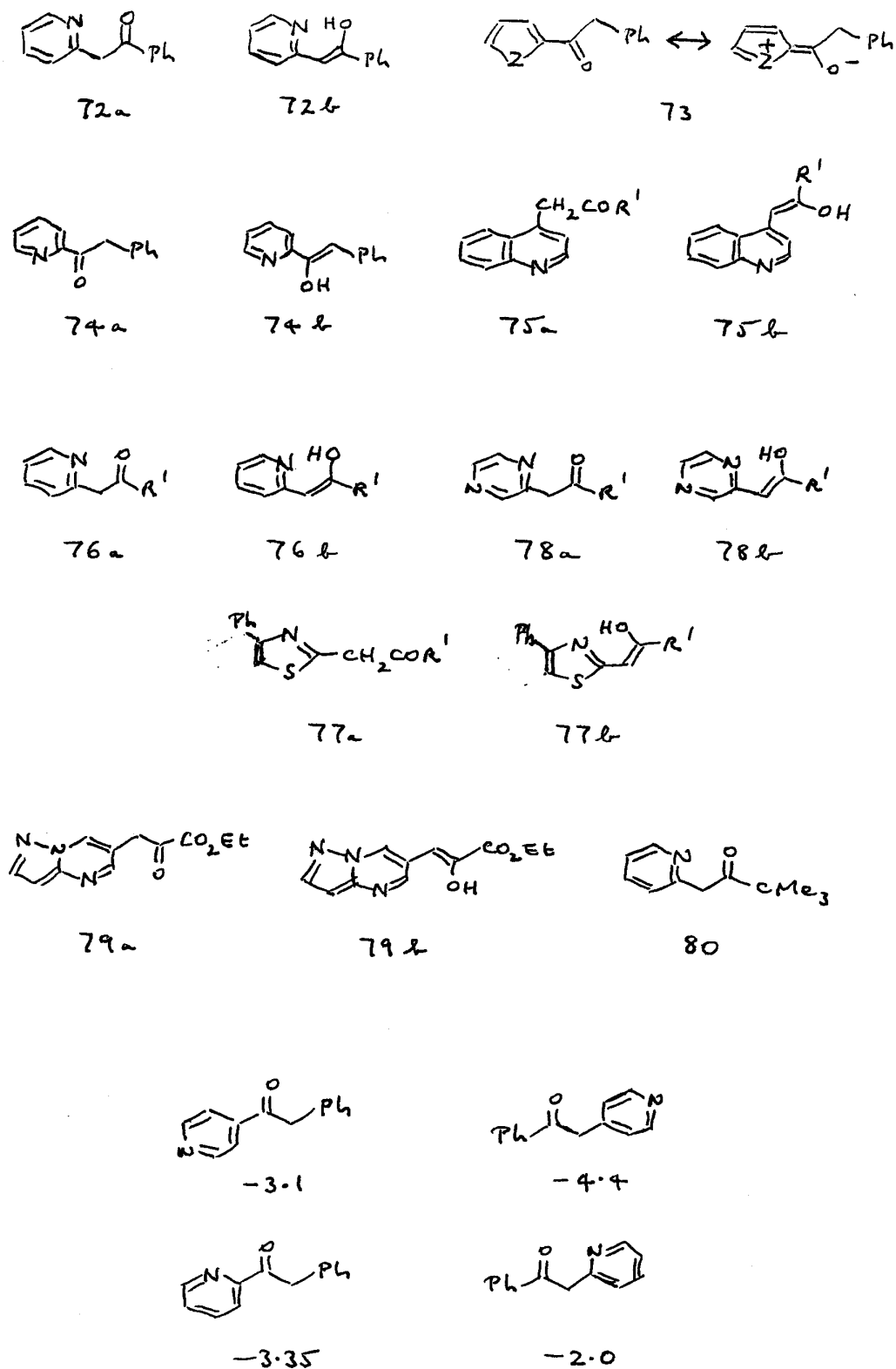
**Table 10. Ranking orders in log  $K_E$  for  $\text{PhCOCH}_2R^2$  relative to  $R^2 = \text{H}$** 

$R^2$	$\Delta \log K_E$			$\sigma_I^a$	$\log K_\beta^b$
	$\text{CHCl}_3^c$	Water	Water <sup>d</sup>		
Ph		2.8 <sup>e</sup>		0.12	
3-Pyridinyl		3.1 <sup>f</sup>	0.3		
4-Pyridinyl		3.6 <sup>f</sup>	0.8		
2-Pyridinyl		6.0 <sup>f</sup>	3.2	0.18	2.52
2-Pyrazinyl	(0)	5.9 <sup>g</sup>	3.1	0.25	1.16 <sup>h</sup>
2-Benzoxazolyl	0.4			0.41	1.67 <sup>i</sup>
2-Benzthiazolyl	0.6			0.37	1.90 <sup>j</sup>

<sup>a</sup> Ph from ref. 39, otherwise from ref. 96. <sup>b</sup>  $\log K_\beta$  for hydrogen bonding to 4-nitrophenol; ref. 72.

<sup>c</sup> Ref. 92. <sup>d</sup> Relative to  $R^2 = \text{Ph}$ . <sup>e</sup> Ref. 17. <sup>f</sup> Ref. 93. <sup>g</sup> Ref. 95. <sup>h</sup> Statistically corrected.

<sup>i</sup> For oxazole. <sup>j</sup> For thiazole.

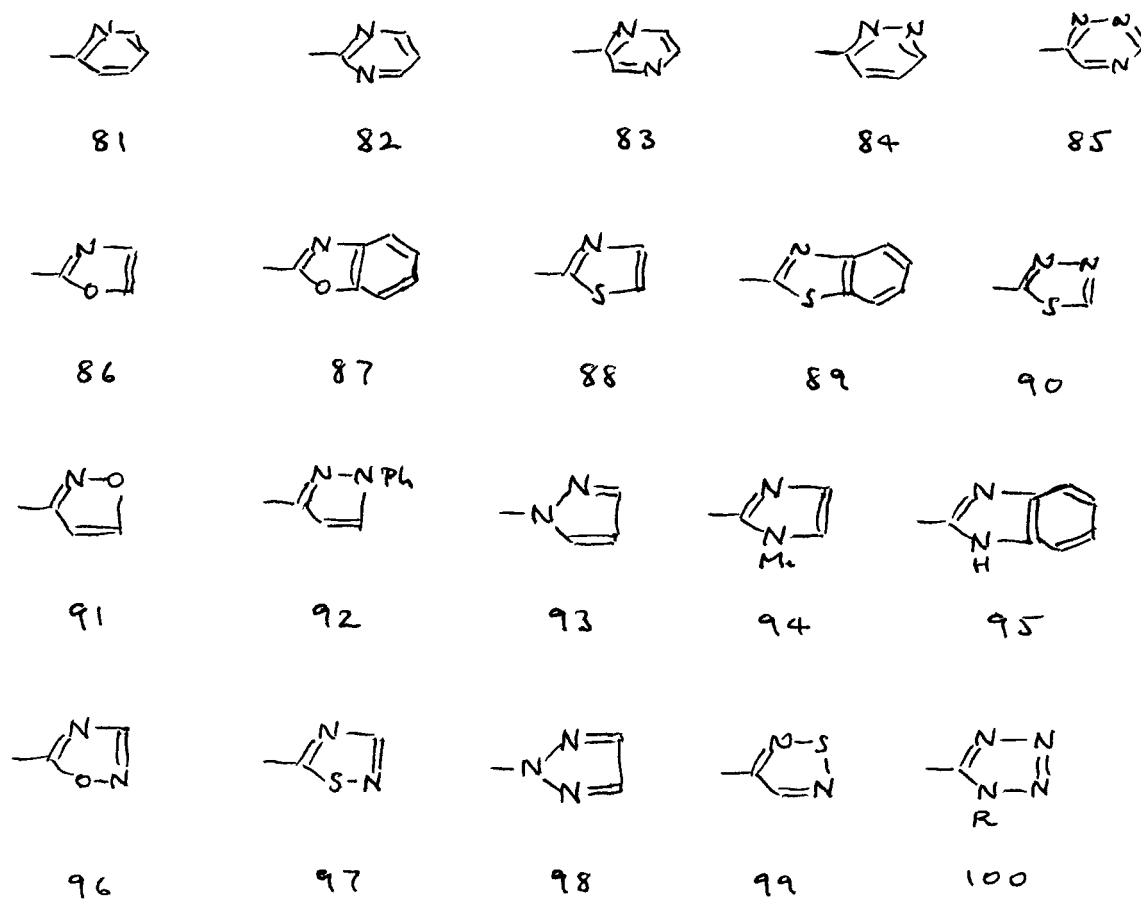


Scheme 1

The contrast in behaviour between  $R^1$  and  $R^2$  is illustrated by the quartet of compounds set out as Scheme 1. Substitution of 2-pyridinyl for 4-pyridinyl in  $R^1$  reduces enolisation by  $\Delta \log K_E -0.25$ , as is consistent with its lower  $\sigma$ -value (Table 2, footnotes *f* and *g*). As noted above, the intramolecular bond cannot be important here. By contrast, the same substitution in  $R^2$  raises it by  $\log K_E 2.4$ . We may regard this as the *minimum* contribution of its intramolecular hydrogen bond to the enolisation of **72**. A parallel estimate based on the corresponding quinolines<sup>93</sup> results in  $\Delta \log K_E 2.9$  (see further discussion in Appendix 4). Hence we arrive at a value approaching  $\Delta \log K_E 3$  for the contribution to enolisation of this OH---N bond; *i.e.*,  $-\Delta G$  *ca.* 4 kcal. mol<sup>-1</sup>. Note that this represents, not hydrogen bond strength *per se*, but its *differential* relative to solvent (water) bonding; for the corresponding OH---O bond in  $\beta$ -diketones, a value of  $-\Delta H_f$  in the range 10 – 20 kcal mol<sup>-1</sup> *in vacuo* has been estimated.<sup>97</sup> This  $\Delta \log K_E$  value is important in contexts where OH---N intramolecular bonding competes with some other type, as with NH---O in hydroxyimine-aminoenone tautomerism (section A.10.1).

### A.2.3 Substitution in $R^1COCH_2R^2$ : Summary and Speculations

Given  $K_E \leq 10^{-7}$  for most simple alkyl and aryl ketones the predominance of the keto-form is usually taken for granted, and mostly this is justified. Nevertheless in certain of these cases enol contents in water of 1% or more have been found,<sup>93</sup> and we have carried out LSER analyses (Appendix 2) which predict  $\log K_E$  values of -1.7 and -2.0 for **80**<sup>98</sup> and (**77**,  $R = Me$ )<sup>99</sup> *i.e.* about 2 and 1% respectively. On present evidence, high enol content should entail high electronegativity for both  $R^1$  and  $R^2$  combined with a strong proton acceptor in the  $\alpha$ -position of the latter. Table 11 sets out  $\sigma_I$  and  $\log K_\beta$  values for the heterocycles of Scheme 2. The twin requirements of high electronegativity and high proton acceptor ability are partially in conflict for  $R^2$ , hence the near-equivalence of  $\log K_E$  for **76** and **78** as noted above. However, this cancellation is not inevitable.<sup>96</sup> One heterocycle that breaks the correlation is 2-substituted imidazole **94**, for which both  $\sigma_I$  and  $K_\beta$  are higher than for 2-pyridyl **81**. It should however be noted that 4-imidazolyl possesses  $\sigma_I$  0.08,<sup>96</sup> so substituent position is critical. Inspection of Scheme 2 will reveal other examples which might possibly be exploited. We postpone to sections A.10.18-20 discussion of certain heterocyclic systems whose high enol content is only one aspect of a much more complex situation in which other factors, not so far discussed, play a part.



Scheme 2

Table 11.  $\sigma_I^a$  and  $\log K_\beta^b$  Values for Heterocycles

$\sigma_I$	$\log K_\beta$		$\sigma_I$	$\log K_\beta$		$\sigma_I$	$\log K_\beta$	
<b>81</b>	0.18	2.52	<b>88</b>	0.34	1.90	<b>95</b>	0.32	
<b>82</b>	0.23	1.37 <sup>c</sup>	<b>89</b>	0.37	1.76	<b>96</b>	0.49	0.57 <sup>e</sup>
<b>83</b>	0.25	1.16 <sup>c</sup>	<b>90</b>		2.51 <sup>d</sup>	<b>97</b>	0.41	
<b>84</b>	0.26	2.53 <sup>d</sup>	<b>91</b>		1.06	<b>98</b>	0.41	
<b>85</b>	0.37		<b>92</b>	0.21		<b>99</b>		0.40 <sup>c</sup>
<b>86</b>	0.38	1.67	<b>93</b>		2.22	<b>100</b>	0.49	1.99 <sup>e</sup>
<b>87</b>	0.41		<b>94</b>	0.26	3.68			

<sup>a</sup> At substituent position shown: ref. 96. <sup>b</sup> Ref. 72; note throughout that  $\pi$ -donor atoms are not proton acceptors. <sup>c</sup> Statistically corrected. <sup>d</sup> Not statistically corrected; bonding is probably bifurcated (ref. 72). <sup>e</sup> Summation over all positions but the 4-nitrogen atom probably dominates  $K_\beta$ ; see refs. 72 and 100.

### A.2.4 Carboxylic Acids, Esters, and Amides

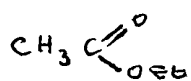
Any carbonyl adjacent to CH may in principle enolise, but the enolisation of a carboxylic acid, ester or amide involves disruption of an existing conjugated system so should be exceptionally disfavoured. The enolisation of ethyl acetate **101** has been studied in water by Amyes and Richard<sup>101</sup> who obtain  $\log K_E$  -18.6, a factor of  $10^{10}$  less favourable than for acetone. Previous MO calculation<sup>102</sup> had placed this factor at *ca.*  $10^{-7.5}$  while  $\log K_E$  *ca.* -17.6 was estimated similarly<sup>103</sup> for  $RCH_2CO_2H$ . Sklenak *et al.*<sup>104a</sup> calculate, at the B3LYP/6-31G\*\* level,  $\log K_E$  -21.3 for  $CH_3CONH_2$ ; more recently, Kresge and co-workers<sup>104b</sup> have estimated -21.7 for  $MeCONHMe$  from work on a related but more complex amide. In terms of loss of resonance the ordering of these results is as expected, with amide enolisation still more disfavoured than that for ester or acid.

Enolisation is less disfavoured if a new conjugated system results. Generation of **102b** gives  $\log K_E$  -15.4 for  $R = OH$  but -7.22 for  $R = CN$ .<sup>17</sup> The unsaturated acid **103a** enolises to the dihydroxyfulvene **103b** with  $\log K_E$  -8.4, whereas for **104**,  $\log K_E$  -9.3 results.<sup>17</sup> It is a general feature of tautomeric processes that the penalty for loss of aromaticity (**a**  $\rightarrow$  **b**), when this occurs, is less for bicyclic than for monocyclic systems since the effect is attenuated by the presence of one ring that suffers no such loss. The factor of *ca.* 10 between **103** and **104** is in line with that found elsewhere (Appendix 5).

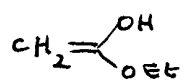
The practical importance of these results lies in their establishing a pecking order.  $\beta$ -Ketoesters **105a** enolise to give **105b** not **105c**; similarly the tetronic acids exist as **106b** not **106c** and ‘2,4-dihydroxypyridine’ as **107b** not **107c**, we estimate by a factor of *ca.* 50 for the latter (section C.7). Such examples are discussed from section A.6 onwards.

### A.2.5 Bifunctional Substituents R<sup>1</sup>: $\alpha$ -Diketones

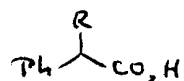
Bifunctional substitution, unlike that considered so far, enables the -COCH<sub>2</sub>- unit to be incorporated into a ring. The extra complications so entailed are considered in this and the following sections. In addition to the high electronegativity of carbonyl, greater than that of many heterocycles (compare Tables 2 and 11), adjacent carbonyls possess the potential for a lone pair clash that itself may promote enolisation.



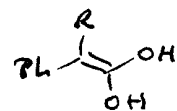
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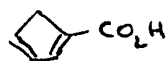
101b



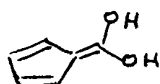
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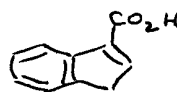
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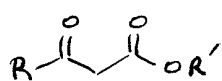
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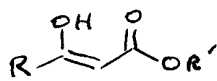
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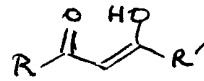
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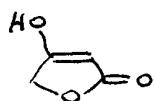
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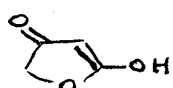
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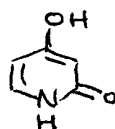
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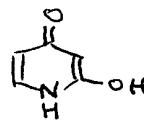
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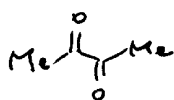
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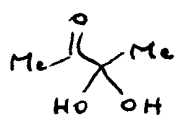
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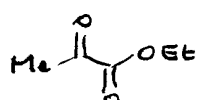
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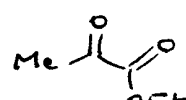
108E



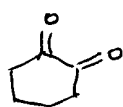
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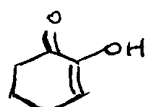
109E



109Z



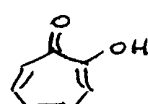
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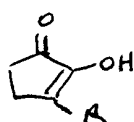
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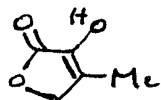
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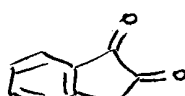
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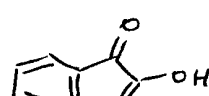
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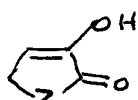
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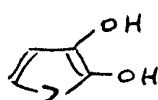
114a



114b



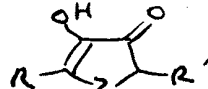
115b



115c



116a



116b

Biacetyl **108** exists in the gas phase exclusively as the planar all-*trans* conformation **108E**<sup>105</sup> and an IR study<sup>106</sup> has failed to find any trace of any other conformation, or of enol, in solvents that range from CCl<sub>4</sub> to DMSO. This must be due to lone pair repulsion so it is at first sight surprising that **109Z** is disfavoured (at the 6-31G level)<sup>107</sup> by only 2.5 kcal mol<sup>-1</sup>; 9% of this exists in CCl<sub>4</sub> and 20% in DMSO, with further stabilisation in amphiprotic solvents such as MeOH.<sup>107</sup> In fact lone pair repulsion is inevitable in *either* planar conformation of **109** (**109Z** is calculated to be partly twisted), which probably explains the high value of  $\Delta \log K_E$  for R<sup>1</sup> = -CO<sub>2</sub>Et (Table 9) as noted in section A.2.1 above. Another feature of  $\alpha$ -diketones is hydration, as for aldehydes;<sup>87</sup> **108** and **109** are both about 75% hydrated. Hydration very likely follows the same trend as enolisation, which eventually supercedes it, though whether there is any quantitative relation between them is unknown.

Biacetyl in water contains 77% of **108a**.<sup>108</sup> Its alkali-catalysed dehydration has been studied and its enol content stated to be < 1% but  $K_E$  *per se* was not determined.<sup>108</sup> An early value<sup>109b</sup> of  $\log K_E$  -4.25 must be discounted since in technique it predates the 'Kresge era' and several accompanying values are seriously in error. Use of eqn. (iii) would predict  $\log K_E$  *ca* -4.85 for **108** and, while this value is not reliable either, it could well be reasonable. Cyclic  $\alpha$ -diketones behave in a dramatically different manner. Cyclohexane-1,2-dione **110** in water is 40% hydrated with probably < 1% of **110a** present,<sup>110</sup> leading to  $K_E \geq 10^2$ . This represents a likely  $K_E$  ratio of  $10^8$  -  $10^9$  relative to cyclohexanone (Table 8) of which perhaps  $10^3$  -  $10^4$  is due to intrinsic electronegativity and the remainder, *ca*  $10^5$ , to lone pair repulsion (*cf.* Appendix 3). In view of the way that aromatisation may be expected to stabilise the known structure **111b** of tropolone (see next section), it is no surprise that the alternative  $\alpha$ -diketone tautomer **111a** has never been detected.<sup>17</sup>

In 5-membered rings the enol tautomer is still more dominant, with 100% in water reported for **112** (R = H or Me) and **113**.<sup>109a</sup> (Note however that **114** exists largely as **114a**,<sup>17</sup> possibly because ring fusion would give some degree of anti-aromaticity to **114b**. The inhibiting effect of this has parallels elsewhere; *cf.* sections A.2.6 and A.4.9). The behaviour of **113** is typical also of 2,3-dioxofurans (**115**, Z = O)<sup>2h</sup> and -thiophenes (**115**, Z = S),<sup>2i</sup> with enolisation remote from Z. The fully aromatic tautomer **115c** is never found. The same behaviour is generally encountered in their 3,4-dioxo isomers **116**,<sup>111</sup> except that the parent furan (**116**, Z = O, R = R' = H)

exists as **116a**. Enforced near-planarity of the diketo unit may explain this increased preference for the enol on the part of 5-membered rings, enhanced for **116** by through-conjugation in **116b**. This is likely to be less advantageous for furans than for thiophenes but, we speculate, more so for pyrroles; *cf.* section A.2.7.

### A.2.6 Aromatisation in Carbocycles

If the carbon double bond of an enol conjugates with another, one might expect some increase in  $K_E$ . A mild example of this is the replacement of Me in acetone by Ph, leading to  $\Delta \log K_E$  *ca.* 0.7. Turecek<sup>112</sup> has measured  $\Delta H_f$  in the gas phase for the enolisation of acetone and **117** and finds the enol form of the latter to be relatively favoured by  $\Delta H_f$  1.68 kcal mol<sup>-1</sup>. An identical effect on  $\Delta G$  would result in  $\Delta \log K_E$  1.2. A much greater effect is shown by the cyclic diene **118**, which enolises in DMSO<sup>113</sup> to the extent of 35%; using the nearest available model, this translates to  $\log K_E$  *ca.* -1 in water. Relative to cycloheptanone -8.00 (Table 4) this represents an enhancement of  $10^7$  in  $K_E$ . This is much greater than the corresponding enhancement of *ca.*  $10^4$  between cyclopentanone **119** and **45** (Table 8) in which conjugation extends to a unit that is already fully aromatic (see comments below). However, none of these enhancements in  $K_E$  approach that attainable when a partially conjugated system becomes fully aromatic. For generation of phenol **120b** from the dienones **120a** and **120c** Wirz and co-workers<sup>114</sup> obtain  $K_E$  *ca.*  $10^{13}$  and  $10^{10.98}$  respectively; given  $10^{-6.7}$  for cyclohexanone (Table 8) this represents a reversal in  $K_E$  of  $10^{18}$  -  $10^{20}$ , equivalent to  $-\Delta G$  24-27 kcal mol<sup>-1</sup>. These  $\Delta G$  values are of the right order to represent resonance energies, lying in the range derived for benzene of 36 to 20 kcal mol<sup>-1</sup> (Table 12). A recent group additivity approach<sup>115</sup> estimates the enthalpy of tautomerisation **120a**  $\rightarrow$  **120b** as  $-\Delta H$  *ca.* 24 kcal mol<sup>-1</sup> with **120c** as 1 - 2 kcal mol<sup>-1</sup> less stable than either.

Nevertheless, these remarkable enhancements are also remarkably easy to reverse. The 1-naphthol tautomers **121a** and **121c** possess  $\log K_E$  7.14 and 6.17 in water respectively,<sup>116</sup> a decrease for the former of *ca.*  $10^6$  relative to **120a** and of *ca.*  $10^5$  for the latter relative to **120c**. As noted above (section A.2.4), loss of aromaticity matters much less in bicyclic than in monocyclic systems, essentially because the ring junction bond preserves its aromaticity. Here the *p*-quinonoid structure of **121c** appears to suffer less loss than the *o*-quinonoid **121a**. Further ring fusions reduce the importance of aromatisation still further, to the extent that in water **122** exists predominantly as **122a** with  $\log K_E$  - 2.1,<sup>116</sup> a further fall of  $10^8$  -  $10^9$

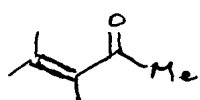
relative to the naphthols or of  $10^{13}$  relative to **120c**. Here the contribution to aromaticity of anthrone's central ring must be minimal. In  $\text{CHCl}_3$  it possesses  $\log K_E$  -2.6, a solvent in which the enol form of **123** is undetectable.<sup>117</sup> Rather more but still minor amounts of enol are found for isomers of **124** but not for **124** itself where again this is undetectable, the quinonoid structure of **124b** being highly disfavoured (*cf.* **132**, section A.2.7).<sup>117</sup> The rather startling transmogrification of the hydroquinone **125b** into the diketone **125a**<sup>2j</sup> is presumably connected with the status of the former as a disguised aminoenone (see section A.10, and immediately below).

Another example of a countervailing influence is shown by the diaminophenol **126**, for which  $\log K_E \sim -1$  in water,<sup>118</sup> a reversal relative to phenol **120b** of  $10^{14}$ . Greenhill<sup>119</sup> has demonstrated  $K_T \sim 10^{8.5}$  for aminoenones in the extended conformation **127**, but while **126a** should therefore be favoured *per se*, it is not related to **126b** through the same type of equilibrium. It is also improbable that the two amino-groups of **126a** possess equal effects. Malhotra and Whiting<sup>120</sup> have shown by UV that the molecular dipole of the merocyanines ceases to increase beyond a certain chain length, while similarly, we<sup>121</sup> have used IR criteria to demonstrate that the extended structure **128** is less well conjugated than **127**, suggesting a larger rôle for the amino-group closer to carbonyl. We cannot go further than this at the present time.

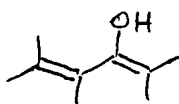
**Table 12. Resonance Energies for Monocyclic Heterocycles <sup>a</sup>**

	<i>b</i>	<i>c</i>		<i>c</i>
Benzene	36.0	20.0	Pyrrole	8.5
Pyridine	34.2	20.9	Thiophene	6.5
Pyrazine	32.0	14.6	Furan	1.6
Pyrimidine	32.6	20.2	Imidazole	15.4

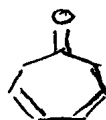
<sup>a</sup>  $\Delta H_f$ , kcal mol<sup>-1</sup>. <sup>b</sup> K. B. Wiberg, D. Nakaji and C. M. Brenemann, *J. Am. Chem. Soc.*, 1989, **111**, 4178. <sup>c</sup> 'Dewar resonance energies' relative to  $\Delta H_f$  for the nearest open-chain analogue (M. J. Cook, A. R. Katritzky and P. Linda, *Adv. Het. Chem.*, 1974, **17**, 255).



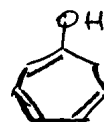
117a



117b



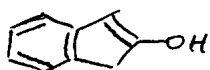
118a



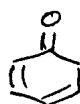
118b



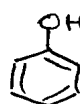
119b



45b



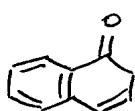
120a



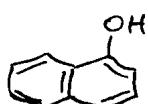
120b



120c



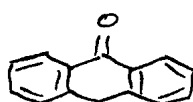
121a



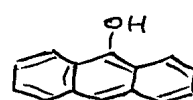
121b



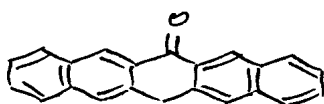
121c



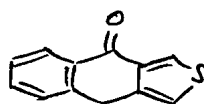
122a



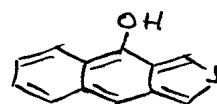
122b



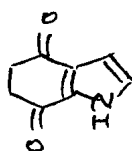
123



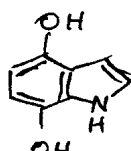
124a



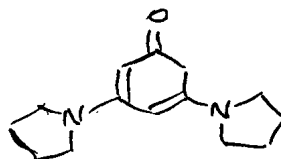
124b



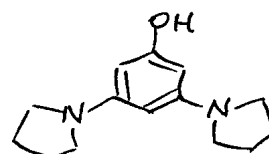
125a



125b



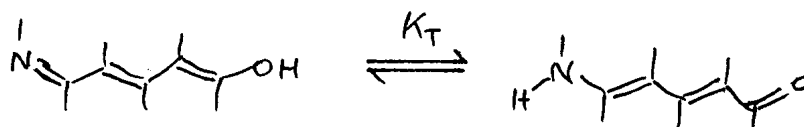
126a



126b



127



128

### A.2.7 Aromatisation vs. Conjugation in 5-Membered Ring Oxoheterocycles: One Heteroatom

The tautomerism of 6-membered ring oxoheterocycles is chiefly that of an amide (section B.2) or vinylogous amide (sections A.10.6-7) and does not involve structures analogous to **120a** or **120c**.<sup>2d</sup> By contrast, cyclopentadiene can be aromatised only if  $sp^3$  carbon is replaced by  $\pi$ -donor O, S or N. Introduction of OH in the 2- or 3-position then produces structures that can tautomerise to oxoheterocycles which are conjugated without being ‘aromatic.’ According to circumstances, either tautomer can dominate. Replacement of CH by aza-nitrogen adds further possibilities. We explore these options below, excluding, as throughout this section, any substituent with the potential to induce enolisation by some competing pathway; these are discussed in section A.6 onwards.

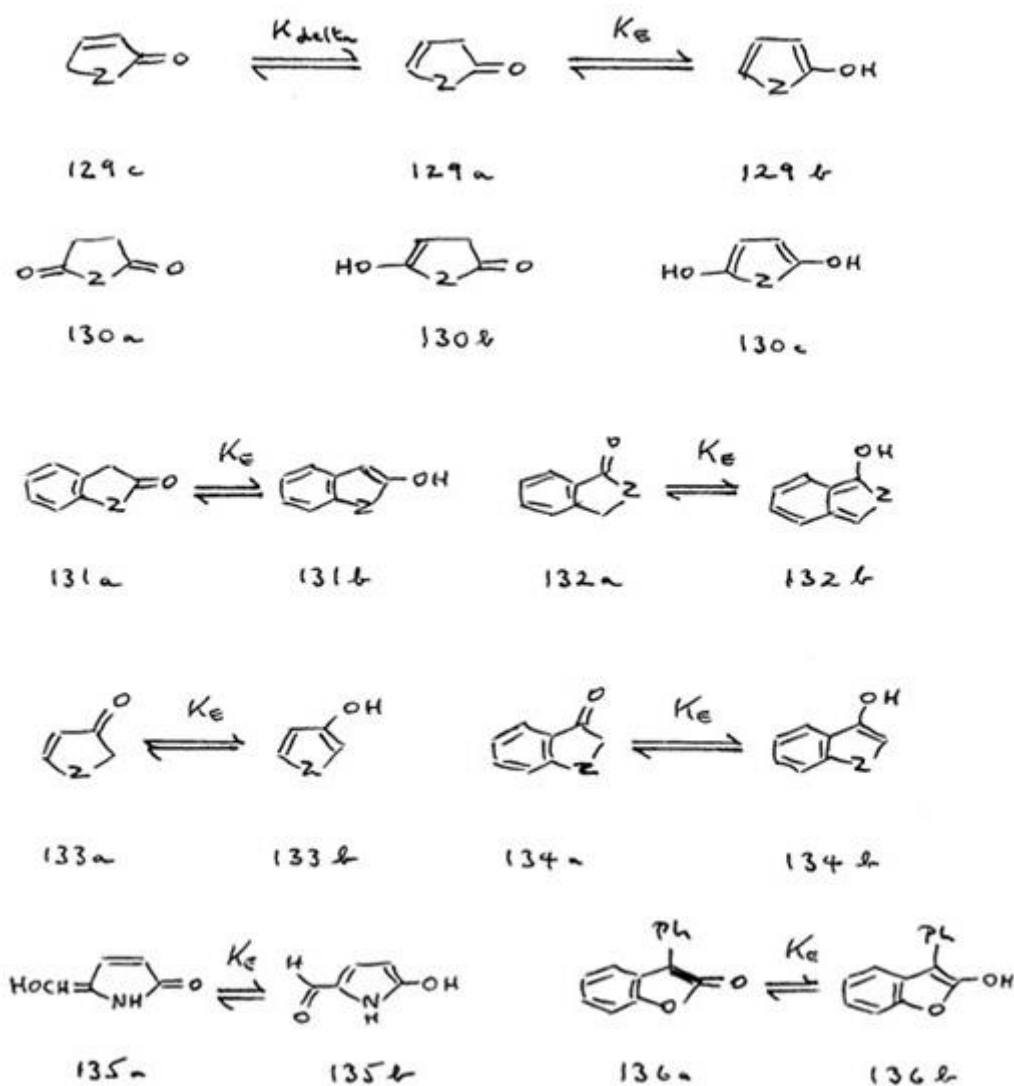
Most data in the literature are qualitative and few are for aqueous solution. In assessing this area we have had therefore to employ a mixture of empirical criteria. As a highly polar medium the solid state commonly gives the same tautomeric form as aqueous solution<sup>15</sup> (exceptions mostly entail strong intermolecular hydrogen bonds) and we have used this criterion whenever possible. (It is less remarked, and equally useful, that the liquid state tends to resemble a nonpolar solution). Evidence from organic solvents alone, especially those most commonly used in spectroscopy, is more equivocal. Our survey of solvent effects (Appendix 2) shows, unsurprisingly, that the enol form is strongly favoured by proton acceptor solvents but disfavoured by proton donors and solvents of high polarity. The ‘typical’ solvent ordering in  $K_E$  is DMSO > amphiprotics > weakly polar >  $CHCl_3$  > water with an overall spread of *ca.*  $10^2$ . Hence the oxo-form will tend to be much more important in water than work in most organic solvents would seem to imply, and appreciable corrections to the published data may be necessary. For example, (**133**,  $Z = NBU^t$ )<sup>66</sup> is 95% enolised in DMSO, 10% in  $CHCl_3$ , and according to our LSER treatment (Appendix 2), should be about 6% enolised in water.

Katritzky and co-workers<sup>2f</sup> have discussed the situations summarised in Scheme 3. Resonance energy for the aromatised ring **b** follows the order  $Z = NR > S \gg O$  (Table 12); for carbonyl when  $\alpha$ -substituted however — less certainly, in the  $\beta$ -position — the order is  $Z = NR \gg O > S$ . Qualitatively, the interplay between these forces will tend to favour the OH tautomer for thiophene and the oxo-form elsewhere. However, oxo-forms are also more strongly favoured in the 2- than in the 3-position, to the extent that **129b** has not been detected for the parent compound whatever

the nature of Z, in any solvent. This preference extends to **135**<sup>2k</sup> for which only **135a** is known. Dominance of the oxo-form may be helped by the double equilibrium as a result of which not only is **129a** favoured over **129b** but **129c** predominates over both (section A.1.1). In addition, while enolisation in **129** is partly determined by the equilibrium between **129a** and **129c** (Scheme 3) which depends on Z, this becomes irrelevant on benzofusion to give **131**. This rules out the possibility of constant relationships  $\Delta \log K_T$  for benzofusion such as those we have established (sections A.10.7 and B.2.5) for the 6-membered ring oxoheterocycles and which are summarised in section C.21. In series **132** the enol **132b** is hugely disfavoured through its quinonoid form (Appendix 5) and, even for thiones (section A.3), this tautomer is unknown. 5-Membered ring anhydrides **130** might in principle give either or both of the enols **130b** or **130c** but no trace of either has ever been detected.<sup>21</sup>

Quantitative data are lacking for any parent 2-oxoheterocycle and only two allow extrapolated estimates. For the benzofuranone **136**<sup>122</sup>  $\log K_E$  is -2.9; the three examples of simple enols in Table 5 which show the effect of replacing H by Ph provide a tentative estimate of  $\Delta \log K_E$   $2.7 \pm 0.4$  for the increment expected, leading to a predicted  $\log K_E$  in the range -5.2 to -6.0 for (**131**, Z = O). It is suggested in section A.1.3 that this attenuation in the effect of Ph is plausibly the result of replacing  $R^3 = H$  by  $R^3 = OH$  in **15** (section A.1.1). Oxindole (**131**, Z = NH) shows no trace of enol even in DMSO and even for its 5-nitro derivative<sup>2m</sup> which may place its enol content even lower. In section C.10 we present a framework for these and other data, *e.g.* those of Table 3 and for the related thiones of section A.3.7, which while far from watertight will both rationalise the known facts and allow plausible extrapolation from them.

Much more is known quantitatively concerning the  $\beta$ -carbonyl series **133** and **134**. Capon and co-workers<sup>67a</sup> have studied all the parent compounds in water and their results appear in Table 13. The furanones (Z = O) are much the most resistant to enolisation while, at the other extreme, 3-oxothiophene is 75% enolised as (**133b**, Z = S). This difference is in accord with what is known concerning the aromaticity of the parent heterocycles; the authors quote 'Dewar resonance energies' (*cf.* Table 12) but the correlation, if any, is qualitative. It is clear however, by comparison with  $K_E$  for **46** (Table 13), that the effect of aromatisation is considerable even for (**134**, Z = O). These  $\Delta \log K_E$  values, translated into  $-\Delta G$ , also appear in Table 13. Nevertheless the lack of any precise parallelism between **133** and **134** suggests that more than one factor is present. In section C.11 we re-examine  $\log K_E$  for **134** alongside our estimates for **131** (section C.10) to produce a quantitative analysis according to which aromaticity in **131b**, opposed by resonance energy in **131a**, will account for the results. A parallel treatment of



Scheme 3

Table 13. Log  $K_E$  in water for 133 and 134<sup>a</sup>

Z	CH <sub>2</sub>	O	S	NH	NMe
log $K_E$ , <b>133</b>	-	< -2.0	0.47	-0.89	-0.74
log $K_E$ , <b>134</b>	-7.48 <sup>b</sup>	-4.06	-1.1	-1.07	-0.52
-Δ <i>G</i> , <b>134</b> <sup>c</sup>		4.6	8.7	8.7	

<sup>a</sup> Ref. 67a. <sup>b</sup> Table 8, compound **46**. <sup>c</sup> In kcal mol<sup>-1</sup> relative to Z = CH<sub>2</sub>; see the text.

**133** has so far eluded us through paucity of data but we suspect the same factors, balanced differently, to be present.

2-Substitution in all these 3-oxo-heterocycles can have a profound effect on the tautomeric balance, usually by favouring the enol form. One driving force is stabilisation of enolic C=C by 'bland' substituents (section A.1.3) whereas formation of a new, often exocyclic conjugated system is the other, *e.g.* by an acyl group to give an enolised  $\beta$ -diketone. The 2-oxoheterocycles are much more resistant to enolisation (*cf.* section A.2.4) so that this, when it occurs as a result of 3-substitution, will sometimes involve the substituent. These forms of tautomerism receive extended treatment from section A.6 onwards.

#### A.2.8 Aromatisation vs. Conjugation in 5-Membered Ring Oxoheterocycles: Multiple Heteroatoms

There are three possible ways (Scheme 4) in which a single azanitrogen may be added to either **129** or **133**. Of these, **139** and **142** are 'N-type' while **137** behaves essentially as a vinylogue of **142** so all appear in sections B.2.9 and B.2.10, leaving **138**, **140** and **141** to be considered here. Extended treatment of all six will be found in sections C.13 - C.18, with **143** and **144** following in C.19.

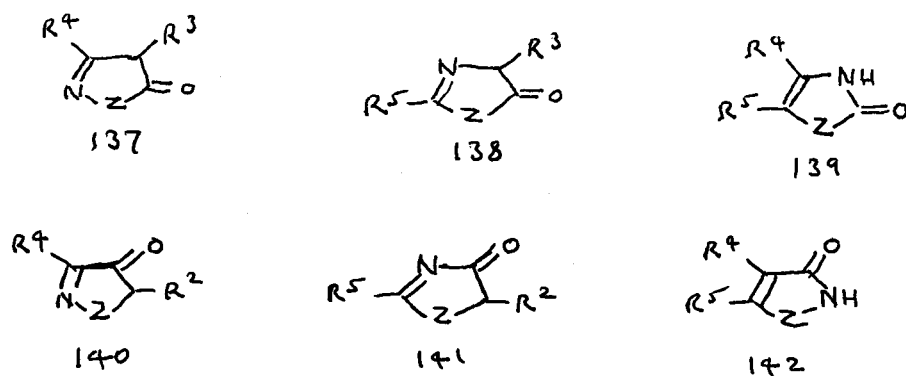
For carbonyl in the  $\alpha$ -position we have only **138**. It was noted in the Introduction that (**138**, Z = O) exists in water in equilibrium with the betaine **138z**,<sup>2e</sup> this species being preponderant for azlactone ( $R^3 = R^5 = \text{Ph}$ ). A solvent study<sup>123</sup> has shown that the proportion of **138z** rises with solvent polarity; *e.g.* 49% in DMF, <0.5% in  $\text{CHCl}_3$ . No trace of (unionised) enol was detected. By contrast, the enol predominates for (**138**, Z = S) except when  $R^3 = \text{H}$ , and no zwitterion was found.<sup>69</sup> The situation for (**138**, Z = NR) is more complex. For (**138**, Z = NMe) in the solid state, the oxo-form is found for  $R^3 = \text{H}$  or Me but the enol for  $R = \text{Ph}$ .<sup>124</sup> Again, little or no betaine is present. The situation for (**138**, Z = NH) is complicated by an annular tautomerism with **141** in which **138** is preferred; consistently, (**141**, Z = NMe) probably exists as the enol in the solid state whatever the nature of  $R^2$ .<sup>124</sup> The thiazole (**141**, Z = S,  $R^5 = \text{Ph}$ ,  $R^2 = \text{H}$ ) exists as the oxo-tautomer in the solid state but is 80% enolised in DMSO, while even  $R^2 = \text{Me}$  converts it to the enol form in the solid state.<sup>70</sup> The corresponding oxazole (**141**, Z = O,  $R^5 = \text{Ph}$ ) appears considerably more

resistant to enolisation, existing as the oxo-tautomer in the solid state even for  $R^2 = \text{Ph}$ ,<sup>125</sup> while AM1 calculation supports the oxo-form for (**138**,  $Z = \text{O}$ ) and (**141**,  $Z = \text{O}$ ) in water but the zwitterion for (**140**,  $Z = \text{NH}$ ).<sup>126</sup> Despite this evident confusion it seems probable that the order in  $Z$  found for **129** and **133** is largely preserved, with enolisation preferred in the order  $Z = \text{S} > \text{N} > \text{O}$ . Aqueous prediction is difficult, but we hazard the guess that aryl substitution at  $R^3$  for **138** or  $R^2$  for **141** will convert all or most compounds predominantly to enols (or zwitterions), with the oxazolone (**141**,  $Z = \text{O}$ ) likely to be the most resistant. Alkyl substitution is a grey area and would benefit from more investigation.

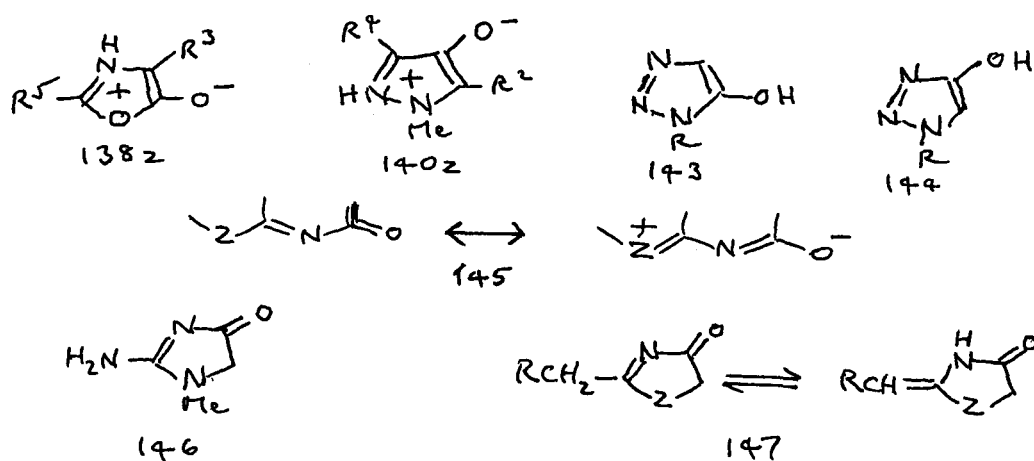
The remaining entries under this section are more straightforward. A definitive study of (**140**,  $Z = \text{O}$ ) by Katritzky and co-workers,<sup>127</sup> based on the spectra of fixed forms, assigned these unequivocally to the OH tautomer. While there is little evidence for (**140**,  $Z = \text{S}$ ), all of it supports the same conclusion.<sup>2n</sup> Nye and Tang<sup>128</sup> find similarly for (**140**,  $Z = \text{NR}$ ), and from model compounds estimate the fraction of zwitterion **140z** for  $Z = \text{NMe}$  as  $3.2 \times 10^{-5}$ . More aza-nitrogen carries the process further: **143** and **144**, related to **138** and **141** respectively, exist in water (**143**) and the solid state (**144**) as the OH tautomer shown.<sup>2n</sup> Nothing is known concerning the related oxadiazoles and thiadiazoles but it seems highly probable that the situation will be similar.

We may attempt a rationalisation. While hard data are lacking there appears to be a consensus<sup>129</sup> that oxazole, thiazole and imidazole follow the trend in resonance energy set by furan, thiophene and pyrrole (see above). Given the higher resonance energy of imidazole than of pyrrole (Table 12), this ought to mean that **138** and **141** will show a larger tendency to aromatise than **129** and **133** respectively. The above results bear out not only this trend but that which places the tendency to aromatise as a function of  $Z$  in the order  $\text{S} \gg \text{N} > \text{O}$ . Its net result is that, for most compounds discussed in this section, the enol tautomer is likely to be the major one in aqueous solution; if an exception exists, it might be (**141**,  $Z = \text{O}$ ).

However, two important caveats are necessary concerning structure **141**. It might be thought that the oxo-form as written should be stabilised through the through-conjugation shown as **145**, but this, while it must be present, appears insufficient to prevent enolisation. There are probably two reasons for this. Firstly, conjugation as in **145** appears to be inferior to that in



Scheme 4



**127** (as present in **133a** for example) probably because aza-nitrogen in the former tends to attenuate it.<sup>130</sup> Secondly, there is undoubtedly lone pair repulsion in **145** between N and O; open-chain compounds of this type adopt the *s-cis* conformation.<sup>130</sup> However, substitution of a  $\pi$ -donor at  $R^5$  in **141** can effect a transformation. No enol is detectable for creatinine **146**, whose CH protons exchange with  $k_{OD}^E = 36.3 \text{ l mol}^{-1} \text{ s}^{-1}$  in  $D_2O$ .<sup>131</sup> This rate compares with  $k_{OH}^E = 0.22 \text{ l mol}^{-1} \text{ s}^{-1}$  for acetone,<sup>132</sup>  $\log K_E -8.63$ , and  $225 \text{ l mol}^{-1} \text{ s}^{-1}$  for **45**,<sup>62a</sup>  $\log K_E -3.84$ , suggesting  $\log K_E \leq -5$  for **146**. We<sup>130</sup> have previously noted that, to balance out the extra electronegativity of  $=N$ - alongside  $=O$  in **145**, even two  $\pi$ -donor atoms are barely sufficient. As acylguanidines or their close relatives, further consideration of this class of compound is postponed to section B.5.

The second caveat concerns the substitution in **141** of  $R^5 = CH_2R$ . The resulting imine-enamine tautomerism **147** is competitive with that at carbonyl and generally takes precedence. According to the type of substituent R, these compounds are discussed in sections A.4 or A.10.

### A.3 Thioketones and Enethiols

Simple thiones hydrolyse readily to give ketones (thioamides are much more resistant) while thiols are notorious for the ease with which they oxidise to disulfides. These instabilities, which ultimately derive from low bond energies,<sup>20,36</sup> severely limit what is known about them and limit, even more seriously, their practical importance. More than anywhere else, therefore, this section provides the background needed to place the later ones in context.

In order to facilitate comparison with ketones, this section is organised exactly on the lines of the preceding one.

#### A.3.1 R<sup>1</sup>CSCH<sub>2</sub>R<sup>2</sup>: Monofunctional Substitution at R<sup>1</sup>

Until recently, this subject was confined to the neat liquid or non-aqueous solution and appeared to indicate a predominance of the thiol tautomer.<sup>133</sup> With the work of Kresge and Meng<sup>134</sup> on (**148**, Z = S) in water, these early studies become of only historic interest in the present context. For (**148**, Z = O and S) these authors find log  $K_E$  -6.92 and -0.94 respectively: a gap of 10<sup>6</sup>. The thione was chosen for its unusual stability,<sup>134</sup> and while this comparison is definitive, there are unlikely to be many more.

**Table 14. Solution and Gas Phase Comparisons for Ketones and Thioketones <sup>a</sup>**

	$\Delta G / \text{H}_2\text{O}^b$	$\Delta H / \text{calc.}^c$		$\Delta H / \text{calc.}^c$
(CH <sub>2</sub> ) <sub>4</sub> C=O	10.83	14.49	(CH <sub>2</sub> ) <sub>4</sub> C=S	3.96
Variation in R <sup>1</sup> :				
HCOMe	8.47	13.09	HCSMe	4.25
MeCOMe	11.32	14.93	MeCSMe	6.14
PhCOMe	10.84	16.15	PhCSMe	7.15
N≡CCOMe	(7.2) <sup>d</sup>	11.34	N≡CCSMe	3.56
Variation in R <sup>2</sup> :				
HCOMe	8.47	13.09	HCSMe	4.25
HCOCH <sub>2</sub> CF <sub>3</sub>		7.46	HCSCH <sub>2</sub> CF <sub>3</sub>	0.48
HCOCH <sub>2</sub> CH=CH <sub>2</sub>		4.63	HCSCH <sub>2</sub> CH=CH <sub>2</sub>	-5.58

<sup>a</sup> Keto → enol, kcal mol<sup>-1</sup>. <sup>b</sup> Scaled from data of Table 8. <sup>c</sup> Ref. 35: B3LYP/6-31G(d,p).

<sup>d</sup> Estimate based on eqn. (iii).

Earlier than this, Selzer and Rappoport<sup>135</sup> in a study of highly hindered enols (*cf.* **47b**, section A.1.3) had surmised a typical factor of  $10^6$  for the difference in  $K_E$  between ketones and thioketones. More recently, calculations have been performed on pairs of compounds containing C=O and C=S by Rappoport and co-workers<sup>35</sup> some of whose results appear in Table 14. For this series we have  $\Delta\Delta H$   $8.87 \pm 1.15$  kcal mol<sup>-1</sup> ( $n = 7$ ), equivalent, if this difference carries through to  $\Delta G$ , to  $\Delta \log K_E$   $6.5 \pm 0.8$ , with no perceptible effect on behaviour caused by substituent position. The trends of Table 14 are in line with those discussed for ketones in section A.2.3, and these for thioketones run consistently in parallel. Taken together, the evidence for a differential in  $K_E$  between simple ketones and thioketones on the order of  $10^6$  appears compelling.

### A.3.2 R<sup>1</sup>CSCH<sub>2</sub>R<sup>2</sup>: Monofunctional Substitution at R<sup>2</sup>

In MeOH, the thioketones **149** exist entirely as their enols **149b**.<sup>136</sup> This compares with *ca.* 25% enol for its ketone equivalent **76**<sup>93</sup> in the same solvent and, so far as it goes, supports the above scenario.

### A.3.4 Thiocarboxylic Acids, Esters, and Amides

For enolisation in water to give the species shown, Kresge and co-workers<sup>137</sup> find  $\log K_E$  -9.5 and -5.8 for **150** and **151** respectively. If the influence of OH on **150** and of OMe on **151** may be taken as broadly equivalent, this differential of only  $\Delta \log K_E$  3.7 must mean either (a) that it is attenuated specifically in dienols, or (b) that, in more complex molecules with greater opportunity for electron delocalisation, it is in any case expected to be less. Evidence presented in section A.3.6 onwards may indicate the latter explanation. Given a typical differential of  $\Delta \log K_T$  *ca.* 1 for thioamides relative to amides (section B.3), this implies a differential in the present context not far from the half-way point between thioamides (conjugated) and simple ketones (unconjugated); on the face of it, a not-unreasonable situation.

### A.3.5 Bifunctional Substitution at R<sup>1</sup>: $\alpha$ -Thioketones

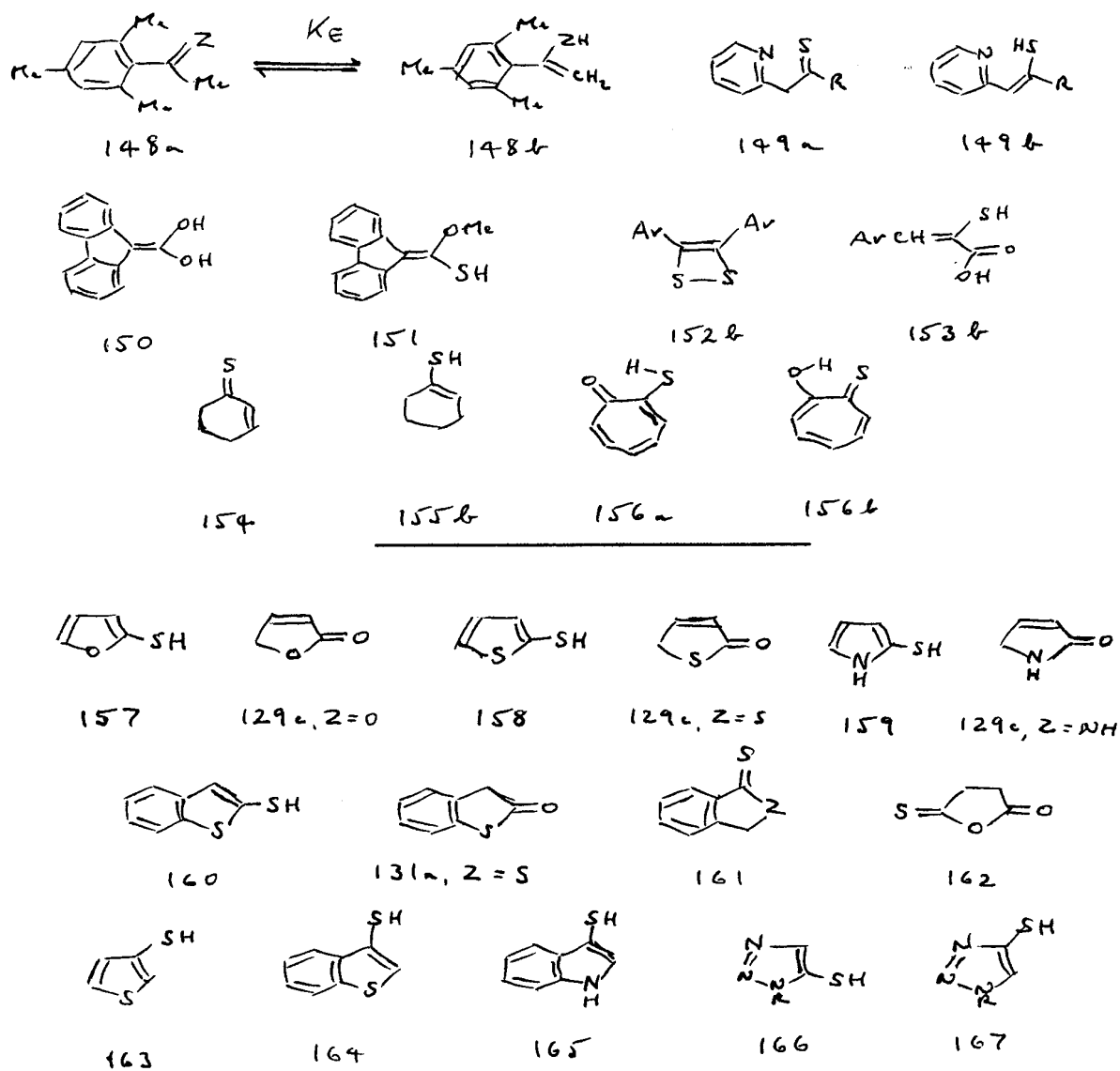
Dithiones of type ArCSCSAr **152** exist in the solid state as such but in solution as a mixture with **152b**,<sup>138</sup> behaviour of which benzoin PhCOCOPh is innocent. Thiopyruvic acids ArCH<sub>2</sub>CSCo<sub>2</sub>H **153** give the enethiol **153b** under all conditions;<sup>138</sup> this contrasts with **109** (section A.2.5) which hydrates<sup>87</sup> but does not appear to produce detectable enol.

### A.3.6 Aromatisation in Carbocycles

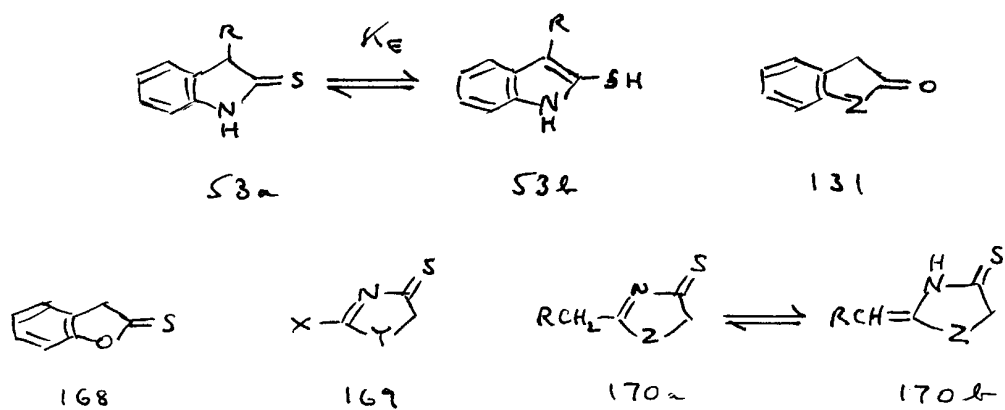
According to Metzner and Vialle,<sup>139</sup> cyclohexenethione **154** and cyclopentenethione do not enolise in CCl<sub>4</sub>, benzene, cyclohexane or MeCN. This result is severely out of line with the corresponding ketones, where conjugation (mildly) favours enolisation; *cf.* **117**, section A.2.6. Also quite inconsistent with it is the observation<sup>140</sup> that the thiol **155b** can be distilled out of its tautomeric mixture with the thione, clearly an example of the way in which the liquid state tends to resemble a nonpolar solution (*cf.* Katritzky's opposite observation concerning the solid state<sup>15</sup>). However, the identification of **156b** as the preferred tautomer of thiotropolone **156**<sup>141</sup> need not be doubted. There is evidence that chelated  $\beta$ -thionoketones also prefer this tautomer (section A.8.3) and we have traced the reason for this to two mutually reinforcing factors (section A.8.1). The first is a cross-interaction between C=O and C=S which has the effect of cancelling at least half the differential in  $\Delta G$  for enolisation between them, which in simple cases is otherwise worth  $\Delta \log K_E$  *ca.* 6 (see above). The second, applicable to chelates, lies in the much greater strength of OH---S=C than of SH---O=C hydrogen bonding; the latter is so weak as to be barely discernible. This second factor not merely cancels the remaining energetic deficit but actually reverses its sign, if not by a large margin, leading *inter alia* to a preference for **156b** over **156a**. There are no corresponding data for 6-membered aromatic molecules.

### A.3.7 Aromatisation vs. Conjugation in 5-Membered Ring Thiono-heterocycles: One Heteroatom

Much less is known than for the corresponding oxoheterocycles, but cross-comparison allows some generalisations to be made. Scheme 5 sets out those thiones for which tautomeric form has been established,<sup>2p</sup> in the solid state and/or solution, alongside their oxygen equivalents as previously discussed (section A.2.7). On this evidence the enethiol tautomer is almost universal, the only major (and predictable) exceptions being **161** and **162**, the first through the quinonoid structure of the thiol (*cf.* section A.2.7), the second through some degree of resonance energy in the thiono tautomer. Nevertheless, we query some of these results as relevant to aqueous solution. The thiol structures of **157** and **159** were established<sup>2p</sup> in the liquid state and that of **158** in benzene, all of which count as highly nonpolar media. Hence a C=O  $\rightarrow$  C=S differential of *ca.*  $10^{-3.7}$  in tautomeric ratio, as suggested above, might well be sufficient to reverse, for aqueous solution, the preferences reported for **157** - **159**. By contrast, the structure of **160** was determined in KBr, a polar medium, so should hold for water. We return to this subject in section C.10.



Scheme 5



Certain pairs of compounds provide a further clue as to what the  $\text{C=O} \rightarrow \text{C=S}$  factor may be. The thioindolone (**53**,  $\text{R} = \text{H}$ ) is borderline with mostly **53a** in polar solvents but **53b** elsewhere; its complete conversion to enethiol when  $\text{R} = \text{Ph}$ <sup>71</sup> has been noted (section A.1.3). Given the status of water as an ‘ultra-polar’ solvent, a value of  $\log K_E$  in the region of -2 might fit both observations. This may be compared with our suggestion (section A.2.7) of  $K_E < 10^{-5.5}$  for oxindole (**131**,  $\text{Z} = \text{NH}$ ), giving a likely factor  $\Delta \log K_E$  *ca.* 3 - 4. This is of the same order as  $\Delta \log K_E$  3.7 for **150**  $\rightarrow$  **151** where, again,  $\text{C=S}$  replaces  $\text{C=O}$ , but the adjacent  $\pi$ -donor is O not NH. Since these estimates are so similar it is tempting to postulate a factor of  $\Delta \log K_E$  *ca.* 3.5 for replacement of (nominal)  $\text{C=O}$  by  $\text{C=S}$ , independently of the  $\pi$ -donor atom. Such a factor would make qualitative and perhaps quantitative sense (section C.10) of any difference in tautomeric form between the oxo- and thiono-series. From the data of Table 13 this factor would be ample to account for the observed switch in tautomeric preference between the 3-oxo and 3-thiono series, as shown for **164** and **165** (that of **163** is unaltered).

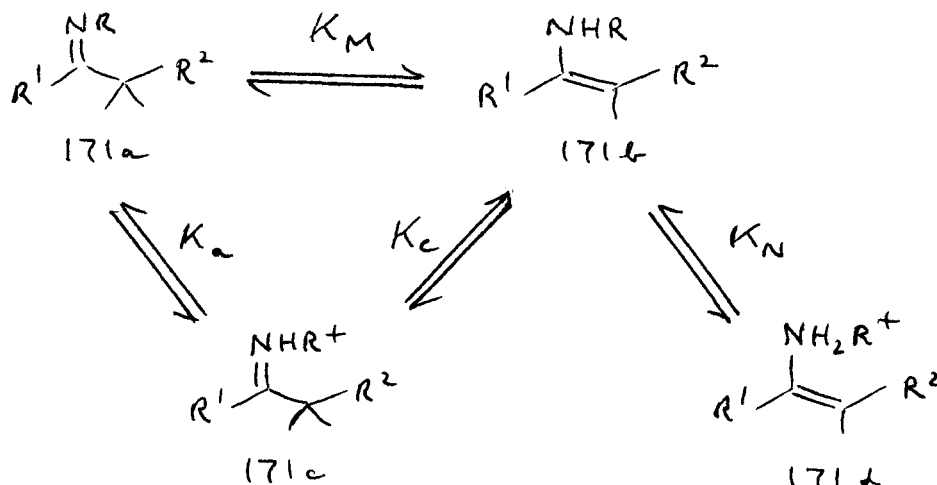
The compound least likely to exist as the thiol is probably **168**. However, it must be noted once again (*cf.* section A.2.7) that almost any substitution adjacent to thiocarbonyl will increase its tendency to enolise, especially when that substituent is aryl. Hence, in practice, true thiono-derivatives of these heterocycles are likely to be rare.

### A.3.8 Aromatisation *vs.* Conjugation in 5-Membered Ring Thiono-Heterocycles: Multiple Heteroatoms

Only two members of this class have been investigated, **166** and **167**, both of which take the enol form as written,<sup>2q</sup> as do their oxygen analogues **143** and **144** above. Bearing in mind the evidence rehearsed in section A.2.8, that aza-substitution appears throughout to increase the extent of enolisation, it is possible that no thiones *per se* of this type exist at all. Also, with SH so much more acidic than OH, zwitterion formation as in **138** may be more important. However, it is also just possible that strong  $\pi$ -donors X and Y in **169**, and putative thioamide formation in the enamine **170b** if formed, might exceptionally give rise to genuine thiones.

Since tetrazole and 1,2,4-triazole do not contain adjacent carbon atoms they are incapable of ‘C-type’ tautomerism so their oxo(thiono) derivatives do not appear in section A.2.8 or here; they are considered in sections B.2.9 and B.3.5 with a summary in section C.20.

## A.4 Imines and Enamines



Scheme 6

Imines and enamines (Scheme 6) differ in two important respects from the compound series so far considered. Nitrogen's extra valency means not only that an extra substituent position has to be considered, R in **171**, but also that C=N can be found in endocyclic contexts not open to C=O or C=S. Secondly, both are bases, so that, in principle, the 'basicity method'<sup>5</sup> is available to quantify tautomeric ratio.

In practice, there are problems. Both imines<sup>142</sup> and enamines<sup>143</sup> are subject to pH-dependent hydrolysis in such a way that  $pK_a$  measurement is often fraught with difficulty. Some indeed of the  $pK_a$  values reported here have been obtained from the rate-pH profile for hydrolysis, either directly or more indirectly from a quite complex kinetic analysis. For enamines the situation is further complicated by the existence of kinetic *N*-protonation ( $pK_N$ ) to give **171d** alongside thermodynamic *C*-protonation ( $pK_C$ ) to give the common cation **171c**. Since the first process is effectively instantaneous while the second takes time to establish there is scope for confusion, and because  $pK_N < pK_C$  necessarily, erroneous  $K_M$  values can result (*n.b.* use of  $K_M$ <sup>93</sup> for imine tautomerism avoids confusion with  $K_E$  for oxo-forms, especially when both occur together; see in particular section A.10). These problems are now resolved<sup>144</sup> and only authentic  $pK_C$  values are reported here. Cyclic compounds appear to have presented fewer problems than those that are open-chain, perhaps for the same reasons that stabilise lactones relative to esters.<sup>145</sup> Even so few  $pK_a$  values exist, so that our deductions below have to be considered as highly provisional.

### A.4.1 Open-Chain and Cyclic Compounds with R = H or Alkyl

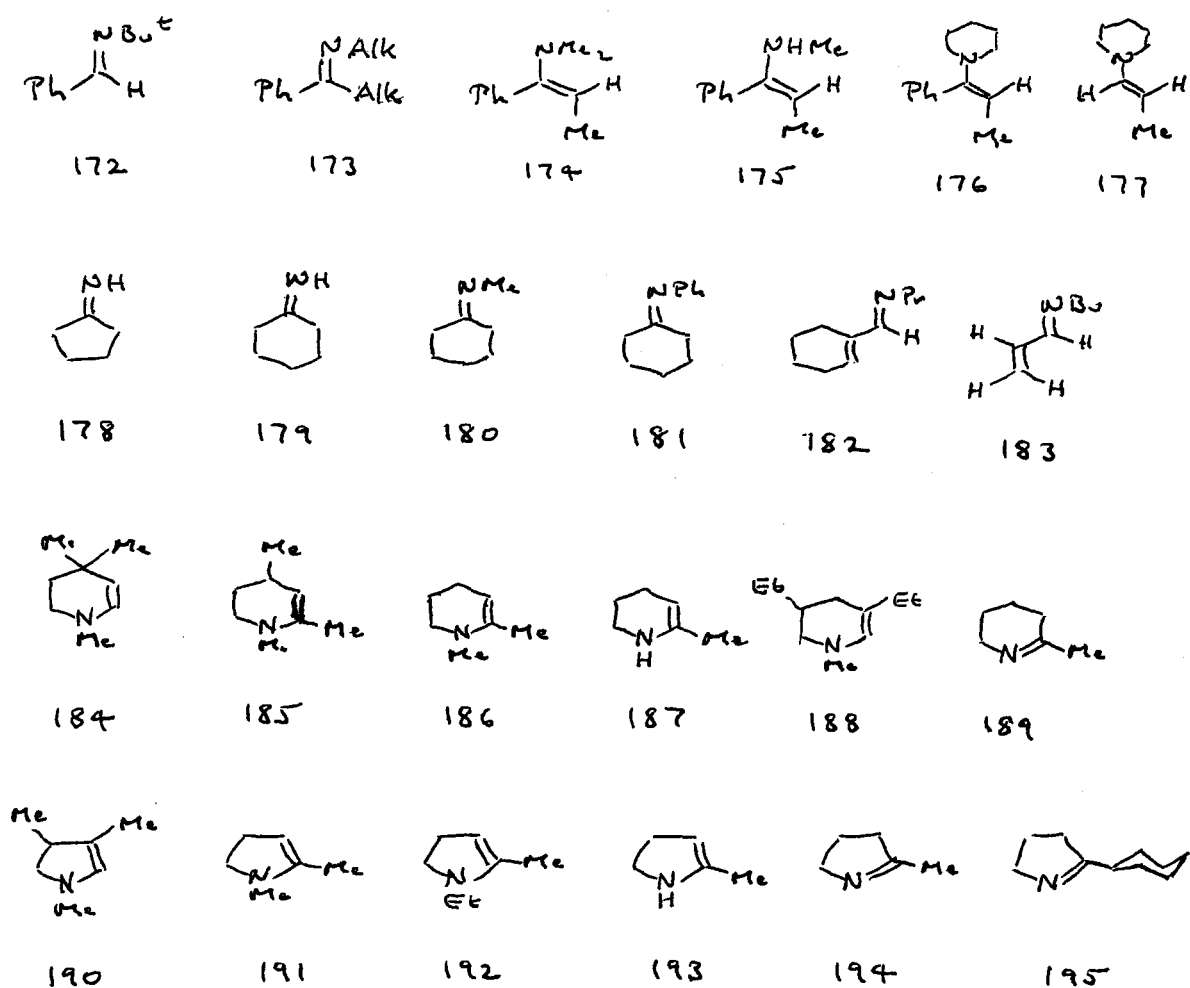
It is pertinent first to enquire what might be anticipated. While theoretical studies have been sparse so far, Rappoport, Lammertsma and their co-workers<sup>35,148</sup> have recently carried out high level MO calculations on the compounds of Table 15 that help to establish the requisite base-line. Despite the use of varying basis sets, the overall picture (Table 15) is clear:  $K_E$  is much more negative for C=O than for the remainder, with C=NH and C=S probably very similar. If for the sake of argument we equate  $\Delta G_E$  with  $\Delta H_E$  we arrive at log  $K_E$  values in the range -9.6 to -7.6 for Z = O, of -3.1 for Z = S, and of -2.9 to -1.7 for Z = NH. These are surprisingly close to typical values for aqueous solution (*vide infra*) and suggest the possibility that, at the least, internal enthalpy is the major driving force behind these tautomeric ratios. Our own calculations on simple C=Z compounds and those in which two such groups interact will be found in sections A.6 to A.11 and help to substantiate that conclusion.

Every  $pK_a$  value of relevance that we can find is set out in Table 16 and Scheme 7. In order to use the ‘basicity method’ correctly we require two correction factors. While imine  $pK_a$  values may be used unchanged, enamines must be prevented from switching to the imine tautomer by *N*-alkylation, so we require a correction  $\Delta(NR)$  for *N*-alkyl  $\rightarrow$  NH. From **180**  $\rightarrow$  **179** we obtain  $\Delta(NR)$  *ca.* -0.3 and this correction is legitimate since imine and enamine share the iminium cation **171c**. It is also in line with  $\Delta pK_a$  values found elsewhere (Appendix 1).<sup>156</sup> The  $pK_a$  values for **187** and **193** have been derived on this basis. For **175** we have had additionally to estimate for **174**, described<sup>143</sup> as possessing  $pK_a > 9.85$ . From inspection of the published rate-pH profile, and comparison with **176** and **177**, we believe  $pK_a$  *ca.* 10 to represent an upper limit for **174**, from which  $pK_a$  *ca.* 9.7 for **175** follows.

**Table 15.**  $\Delta H_E$  for the process  $\text{CH}_3\text{CH}=\text{Z} \leftrightarrow \text{CH}_2=\text{CH}-\text{ZH}$  <sup>a</sup>

	Z = O	Z = S	Z = NH
B3LYP/6-31G(d,p) <sup>b</sup>	13.08	4.25	
B3LYP/6-311G** <sup>c</sup>	10.4		2.3
G2MP2 <sup>b</sup>	11.1		4.0

<sup>a</sup> In kcal mol<sup>-1</sup>. <sup>b</sup> Ref. 35. <sup>c</sup> Ref. 148.



Scheme 7

Table 16.  $pK_a$  Values for Imines and Enamines<sup>a</sup>

$pK_a$	$pK_a$	$pK_a$	$pK_a$
<b>172</b> 6.70 <sup>b</sup>	<b>178</b> 8.95 <sup>f</sup>	<b>184</b> 10.45 <sup>i</sup>	<b>190</b> 9.6 <sup>d</sup>
<b>173</b> 8.3	<b>179</b> 9.15 <sup>f</sup>	<b>185</b> 11.03 <sup>j</sup>	<b>191</b> 11.90 <sup>l</sup>
<b>174</b> >9.85 <sup>c</sup>	<b>180</b> 9.43 <sup>f</sup>	<b>186</b> 11.43 <sup>k</sup>	<b>192</b> 11.84 <sup>l</sup>
<b>175</b> 9.7	<b>181</b> 5.8 <sup>g</sup>	<b>187</b> 11.1	<b>193</b> 11.6
<b>176</b> 9.76 <sup>c</sup>	<b>182</b> 8.34 <sup>h</sup>	<b>188</b> 9.47 <sup>d</sup>	<b>194</b> 7.87 <sup>l</sup>
<b>177</b> 10.66 <sup>d,e</sup>	<b>183</b> 8.7 <sup>i</sup>	<b>189</b> 9.55 <sup>k</sup>	<b>195</b> 7.91 <sup>l</sup>

<sup>a</sup> Estimates (for which see the text) are italicised. <sup>b</sup> Ref. 142. <sup>c</sup> Ref. 143. <sup>d</sup> Ref. 144.<sup>e</sup> The 2,2-dimethyl derivative possesses  $pK_N$  8.35: E. J. Stamhuis, W. Maas and H. Wynberg, *J. Org. Chem.*, 1965, **30**, 2156. <sup>f</sup> Ref. 149. <sup>g</sup> Ref. 150. <sup>h</sup> Ref. 151. <sup>i</sup> Ref. 152. <sup>j</sup> Ref. 153.<sup>k</sup> Ref. 154. <sup>l</sup> Ref. 155.

From **189**<sup>157</sup>  $\leftrightarrow$  **187** and **194**  $\leftrightarrow$  **193** we obtain  $\log K_M$  -1.6 and -3.7 for *endo*-imines with  $\alpha$ -alkyl in 6- and 5-membered rings respectively. These are the only unequivocal values available. This considerable difference may be factored, *via* the  $pK_a$  values of **194** and **189**, into *stabilisation* of *endo*-C=N by  $\Delta \log K$  *ca.* 1.6 on transfer from a 5- to a 6-membered ring, reinforced by  $\Delta \log K$  *ca.* 0.5 for a parallel *destabilisation* of *endo*-C=C, *via* the  $pK_a$  values of **191** and **186**. This value for C=N is consistent with  $\Delta pK_a$  *ca.* 1.8 for 6- and 5-membered cyclic amidines in a similar context<sup>159</sup> and is plausibly explained by their different steric requirements:<sup>159</sup> while the preferred internal bond angle at C=C—C is 120° that at C=N—C is 110°, so that the cation is disfavoured in 5-membered rings. The smaller differential for *endo*-C=C is close to  $\Delta \log K$  0.6 as deduced from simple hydrocarbons for its stabilisation in 6-membered rings (section A.1.2) and used elsewhere (*cf.* section B.2.3).

Despite the paucity of matching compound pairs,<sup>160</sup> some provisional estimates can be made. Given the essentially strain-free structures for **180** and **189**, and their similar carbon skeletons (see section C.25), their close similarity in  $pK_a$  (Table 16) suggests a parallel similarity in  $\log K_M$ . Also, they and their enamines all effectively contain  $\alpha$ -alkyl groups. The same should be true for the corresponding open-chain compounds with the slight caveat that, in these less rigid structures, the enamine tautomer may be more prone to twisting, leading to a slight fall in  $K_M$ . We suggest  $\log K_M$  -1.8 $\pm$ 0.2 as a baseline value for **171** with R, R<sup>1</sup> and R<sup>2</sup> all alkyl; the corresponding value for ketones is *ca.* -7.5 (Table 5).

$\alpha$ -Substitution has been little explored. For Ph in place of alkyl we have  $pK_a$  *ca.* 9.7 as deduced above for **175** but no value for **173**. However if **216D** (Scheme 9),  $pK_a$  8.3 (Table 17) may be used in its place then  $\log K_M$  -1.4 results. At  $\Delta \log K_M$  0.4 $\pm$ 0.2 this is a much smaller effect than that in  $K_E$  for ketones, 0.7 - 1.2 (Table 8). There is a large differential in  $K_E$  between aldehydes and ketones but most of this is probably due to special factors (section A.2.1) and may not be echoed here. No direct evidence exists for imines but other structural types (*cf.* **66**, section A.1.5) produce small effects for the replacement of  $\alpha$ -alkyl by  $\alpha$ -H which are inconsistent and average to zero. We postulate that, R<sup>1</sup> = H apart, the effect of substitution at R<sup>1</sup> will be about half as great for imines as it is for ketones, consistently with the smaller differential in electronegativity of C=C relative to C=N rather than to C=O (*cf.* section A.2.1).

#### A.4.2 Compounds in which $R^2 = \text{Aryl}$

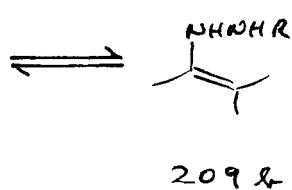
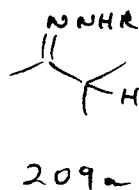
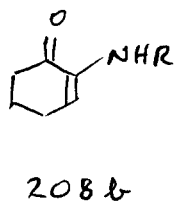
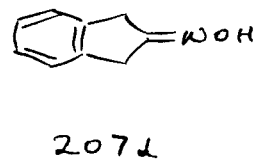
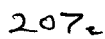
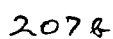
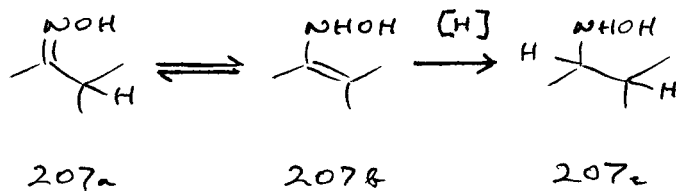
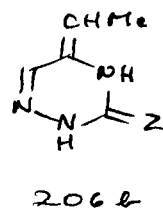
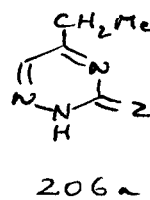
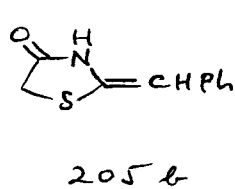
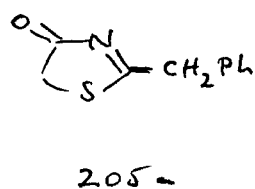
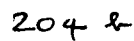
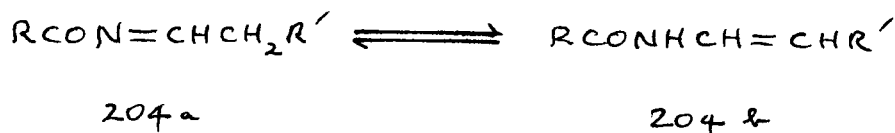
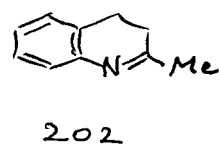
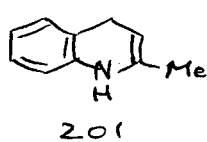
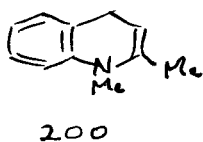
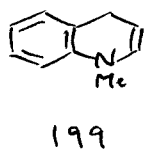
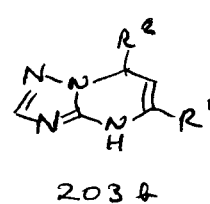
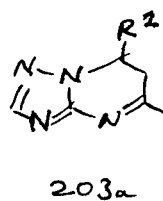
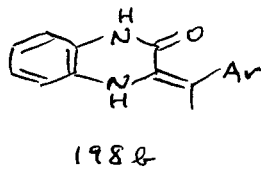
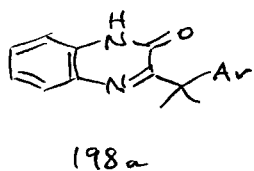
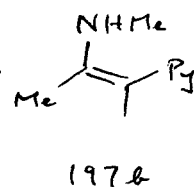
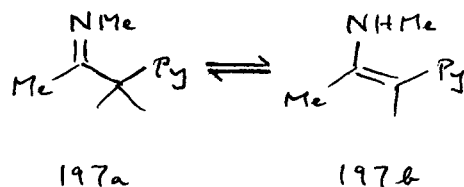
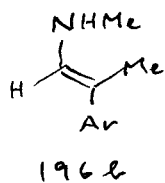
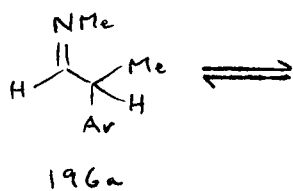
Albrecht and co-workers have investigated two series of compounds for which  $R^2 = \text{aryl}$ : **196** where  $R^2 = \text{substituted phenyl}$ <sup>161a</sup> and **197** in which  $R^2$ , in terms of **171**, is the three isomeric pyridinyls.<sup>161b</sup> In the first,  $K_M$  rises slowly as the substituent becomes electronegative and, in consequence, the ‘push-pull’ effect across  $C=C$  increases (*cf.* **145**). For  $R^2 = \text{Ph}$ ,  $K_M \sim 1$ . This is in  $\text{PhNO}_2$ , a proton acceptor solvent; **196a** might be expected to be the major tautomer in water, essentially a proton donor (Appendix 2). The isomers **197** were studied in benzene and DMSO; only **197b** was found for  $R^2 = 2\text{-pyridinyl}$  in either solvent, with **197b** still dominant, or the balance about even, for 4- and 3-pyridinyl respectively. Qualitatively this is the same trend as that for the corresponding ketones  $\text{PhCOCH}_2\text{Py}$  (Table 10), where however the enol is greatly disfavoured in water.<sup>93</sup> The predominance of **197b** in water for 2-pyridinyl but **197a** elsewhere would seem plausible here.

In reviewing their own work and that of others, Kurasawa and Takada<sup>162</sup> report on a number of compounds of type **198**. Here the aryl groups are 5-membered ring heteroaromatics, most of them quite strongly electronegative, and  $\log K_M$  in DMSO ranges from -0.17 to +0.95. Since DMSO should favour the enamine it is likely that, in water, **198a** will be preferred. Effectively  $R = \text{Alk}$  in **171** is here replaced by  $R = \text{Ph}$ , which favours the imine tautomer as will be seen below.

#### A.4.3 Compounds in which $R = \text{Aryl}$

Katritzky and co-workers<sup>150</sup> use **181**,  $pK_a$  5.8, as model for **202**, with which we concur, their carbon skeletons being similar. For **201** we start from  $pK_a$  7.9 for **199** and adjust to 8.5 for **200** from the  $pK_a$  difference between **184** and **185**; final adjustment using  $\Delta(\text{NR})$  results in  $pK_a$  8.2. This implies  $\log K_M$  *ca* -2.4, a value appreciably more negative than -1.6 for **189**. There are no other usable data but we anticipate the same trend elsewhere (*cf.* section A.4.6).

Rather a different situation is found for **203**.<sup>163</sup> For  $R = \text{Ph}^1$  and *p*-methoxyphenyl, **203b** is not only dominant in  $\text{CHCl}_3$  solution but the tautomer found in the solid state, generally a good predictor of that in aqueous solution.<sup>15</sup> For  $R = 2\text{-thienyl}$  the tautomers in  $\text{CHCl}_3$  are roughly in balance. There are also minor effects of substitution at  $R^2$ , in that increasing bulk favours **203a**, perhaps by reducing enamine planarity. This apparent discrepancy between **201/202** and **203b/203a** is taken up in A.4.6 below.



#### A.4.4 Compounds in which R = Acyl

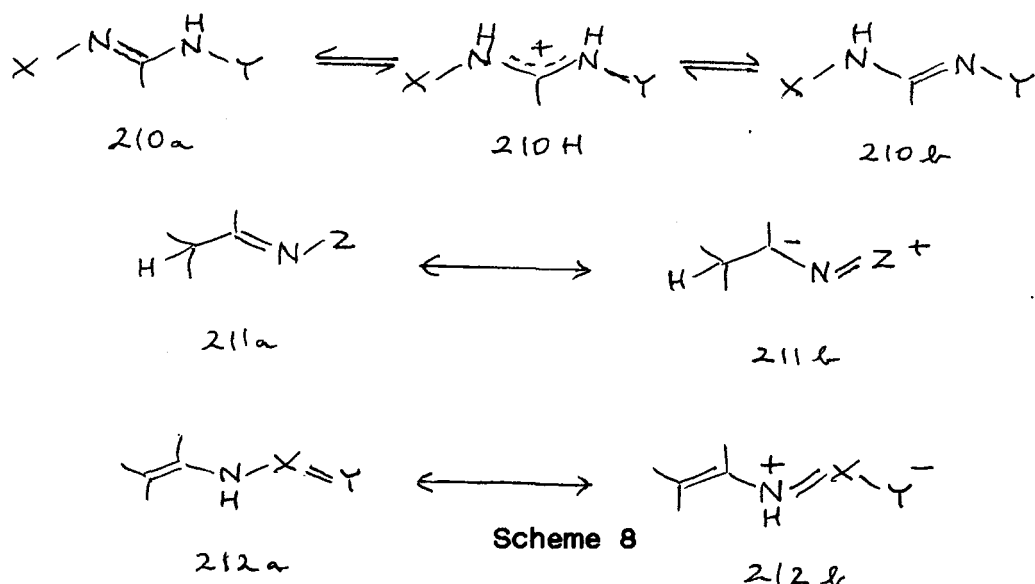
*N*-Acylation produces a decisive shift from the imine to the enamine tautomer; simple compounds of type **204** exist exclusively as **204b**.<sup>164</sup> The thiazolidinone **205** lies close to the borderline, existing as **205a** in the solid state but mostly as **205b** in CHCl<sub>3</sub> solution.<sup>165,166</sup> Even more intriguingly,<sup>167</sup> (**206**, Z = O or S) exists partly as **206b** in ethanol and DMSO (more in the latter) despite the loss of aromaticity which this might seem to entail. However, the ‘aromaticity’ of **206a** may be minimal; there is some evidence, so far not well recognised, that groupings of type X=C—C=Y where X and Y are hetero-atoms tend to be disfavoured when an alternative is available, perhaps because of the opposed dipoles of C=X and C=Y. It has been suggested<sup>211</sup> that the abnormal stability of **206b** may be related to the strong preference of **204b** over **204a**, possibly attenuated in **205** by competitive conjugation, in **205a**, of the acylamidine type (Z-C=N-C=O  $\leftrightarrow$  Z<sup>+</sup>=C-N=C-O<sup>-</sup>; see especially section B.5.9).

#### A.4.5 Oximes and Hydrazones

Although the enamine **207b** has never been detected, it is thought likely that the reduction of oximes **207a** to hydroxylamines **207c** goes *via* C-reduction of this species.<sup>168a</sup> A particularly facile reduction is that of the indanone oxime **207d**,<sup>168a</sup> whose parent ketone is notable for its relatively high enol content (**45**, Table 8). Consistently, while **208** exists as the enamine shown<sup>106</sup> (*cf.* **110**),  $\alpha$ -monoximes R<sup>1</sup>COC(=NOH)CH<sub>2</sub>R<sup>2</sup> possess that structure whether cyclic or open-chain.<sup>168f</sup> Enehydrazines **209b** have not been detected either.<sup>168b</sup> While all this evidence is qualitative, it strongly suggests that *N*-substitution by OH or NHR tips the balance further towards the imine tautomer.

#### A.4.6 N-Substitution: Summary and Conclusions

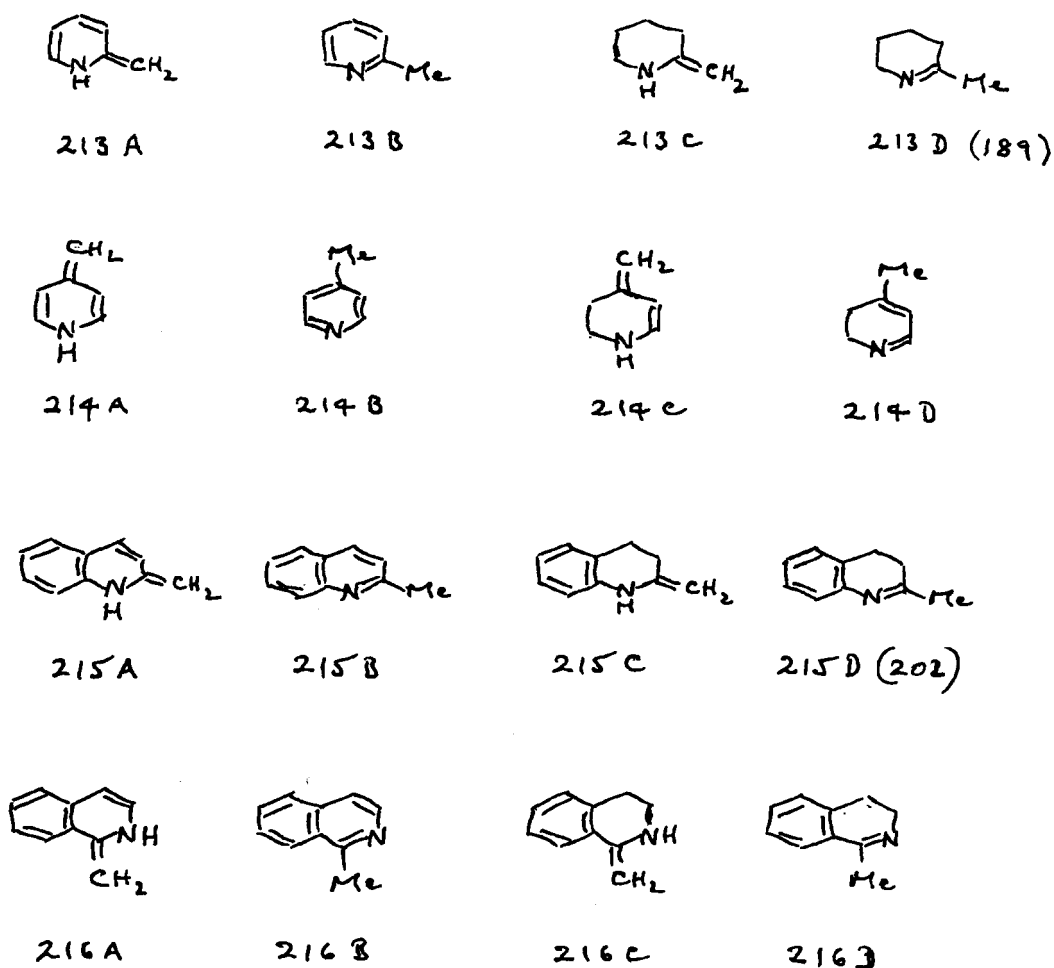
While the above examples are few and the information they provide is mostly qualitative, it adds up to a consistent picture. Resonance *donors* such as Ph, OH, and NHR stabilise the imine tautomer; resonance *acceptors* such as C=O, C=S, and triazolyl<sup>169</sup> stabilise the enamine. This is in sharp distinction to the behaviour of amidines, which we contrast in Scheme 8 with the present case. The former (section B.4.2) is quite straightforward: C=N is polarised towards whichever of X and Y in **210** is the more electronegative, so that the common cation **210H** should lose its proton most readily from this nitrogen atom.



It is found in fact that the basicity of monosubstituted amidines depends simply on  $\sigma_I$  for the substituent,<sup>96,170</sup> and we shall later show that this principle can be exploited to arrive at tautomeric ratios (section B.4.2). By contrast, for N-substituted imines and enamines we may plausibly write the resonance hybrids **211** and **212** as major factors in their stabilisation by  $\pi$ -donors and  $\pi$ -acceptors respectively. Nevertheless, since canonical form **211b** is likely to contribute much less to **211** than **212b** does to **212**, some other factor must contribute to the lack of stability shown by species such as **207b** and **209b**. We suggest this to be *dipolar repulsion* between contiguous  $\pi$ -donors in the enamine tautomer, a phenomenon capable of very large effects on tautomer stability (Appendix 3) and, unlike the equally important phenomenon of lone pair repulsion, evidently one which cannot be relieved by changing the bond angle between the hetero-atoms. Since it is also true, in those cases examined, that substituents with large  $\sigma_I$  values ( $\geq 0.30$ ) favour the enamine whereas those with lesser ones ( $\leq 0.24$ ) favour the imine, the importance of the field effect relative to resonance cannot presently be assessed, but its magnitude seems likely to be less. We pay further attention to these issues in section B.4.

#### A.4.7 Aromatisation in 6-Membered Rings

Our knowledge here is due entirely to the Katritzky team<sup>150</sup> and confined to the pyridines and quinolines of Scheme 9 (*n.b.* that  $pK_a$  values in the **A** and **C** series were necessarily measured for the ring *N*-methyl derivatives). This was work of ground-breaking significance and the detail given below, while more than strictly necessary in the present context, is justified by its importance.



Scheme 9

Table 17.  $pK_a$  and  $\log K_M$  Values for Pyridine and Quinoline Methides <sup>a</sup>

	A	B	$\log K_M$	C	D	$\log K_M$	$\Delta pK_a^b$	$(A_{py} - A_x)^c$	
<b>213</b> <sup>d</sup>	18.95 <sup>e</sup>	5.97	- 13.0	(11.73) <sup>f</sup>	(9.55)	- 2.2	10.8	13.5	(17.5) <sup>e</sup>
<b>214</b> <sup>e</sup>	19.26 <sup>g</sup>	6.02	- 13.2	(9.3) <sup>g</sup>	(8.7)	- 0.6	12.6	15.2	(19.5) <sup>e</sup>
<b>215</b> <sup>e</sup>	14.93	5.83	- 9.1	(8.2)	(5.8)	- 2.4	6.7	7.6	(7.9) <sup>e</sup>
<b>216</b> <sup>e</sup>	15.59	6.42	- 9.2	12.76	8.30	- 4.4	4.7	6.0	(7.4) <sup>e</sup>

<sup>a</sup> Bracketed values are estimates from refs. 150a and 150b; *italicised* estimates are ours (see the text); values bracketed as well as *italicised* are very provisional. <sup>b</sup> Eqn. (v). <sup>c</sup> Eqn. (viii). <sup>d</sup> Ref. 150b. <sup>e</sup> Ref. 150a.

<sup>f</sup> Minimum value (see the text). <sup>g</sup>  $\Delta(NR)$  - 0.2 (section A.10.9).

The imine  $\rightarrow$  enamine tautomeric ratio ( $K_M = [A]/[B]$ ) comes cleanly from the first two columns of Table 17, requiring only a trifling correction of  $\Delta pK_a$  - 0.3 for the **A**-series (-0.2 for **214A**; *vide* Table 17.) However, in pursuit of an estimate for the aromaticity lost in the process **B**  $\rightarrow$  **A** these authors also measured or estimated  $pK_a$  values for their non-aromatic equivalents **C** and **D**, and here there are problems, since only for **216** are all values experimental. For **213C** they take **186** (Table 16) as model, but these two compounds are themselves tautomerically related and if **186** is preferred, **213C** is *necessarily* a stronger base. Our tentative estimate starts from the known *endo*-preference of  $\log K$  0.6 for C=C in 6-membered rings (section A.1.2), giving  $pK_a \sim 12$  and, after correction for NMe ( $\Delta NH$ ), the value for **213C** in Table 17. There is a similar problem in their use of  $pK_a$  7.91 for **199** as model for **215C**, requiring the same corrections and resulting in  $pK_a$  9.2. Trivial corrections are also required to their estimates for **214C** and **216C** whereas those for **213D**, **214D** and **215D** may be accepted *faute de mieux*. There is a distinct peculiarity attaching to **216C** in the form of its remarkably high  $pK_a$ . We think this must be due to the strong *peri*-interaction between 8-CH and =CH<sub>2</sub> which protonation will help to relieve; if so this will also be present in **216A**, will arguably be of similar magnitude, and in that case will not appreciably affect the deductions concerning aromaticity that follow.

$$\Delta pK_a = pK_A - pK_B - pK_C + pK_D \quad (\text{v})$$

Equation (v) expresses the extent to which tautomeric preference in the aromatic compound pair, **A** and **B**, is already implicit in their non-aromatic equivalents **C** and **D**; the *difference* between these,  $\Delta pK_a$ , is then some measure of the aromaticity lost. Given however that 'resonance energy' is normally defined as an *enthalpic* quantity,  $\Delta pK_a$  does not measure this difference directly but requires translation into  $\Delta\Delta H$ .<sup>150b</sup> In attempting this translation, Katritzky<sup>150</sup> starts from Hepler's postulate<sup>171</sup> that, for solution processes, the required *internal* enthalpy  $\Delta H_{\text{int}}$  should be related to overall free energy  $\Delta G^\circ$  by eqn. (vi),

$$\Delta G^\circ = \Delta H_{\text{int}} (1 + \gamma) \quad (\text{vi})$$

$$\Delta H^\circ = a pK_a + c \quad (\text{vii})$$

$$(A_{\text{py}} - A_{\text{x}}) = 1.13 (pK_A - pK_C) - 1.48 (pK_B - pK_D) \quad (\text{viii})$$

where  $\gamma$  is an entropic term ultimately derived from the theory of *enthalpy-entropy compensation*.<sup>172</sup> In the present case,  $pK_a$  is a form of  $\Delta G^\circ$ ,  $\Delta H^\circ$  is its temperature coefficient, eqn. (vii) represents the relation between them,  $A_{py}$  and  $A_x$  are the resonance energies lost in the processes **B**  $\rightarrow$  **A** and **D**  $\rightarrow$  **C** respectively, and the final equation for *nett* loss of resonance energy is (viii).<sup>150b</sup> The two different coefficients for  $pK_a$  in (viii) derive from the fact that, empirically, pyridines **B** and (putatively) imines **D** possess inherently different values for  $a$  in eqn. (vii) from the other bases here considered.

Katritzky's original values<sup>150</sup> of  $(A_{py} - A_x)$  for the methides of Scheme 9 are given in Table 17 alongside those resulting from the above re-assessment. For pyridones and quinolones (sections A.10.7 and B.2.5), while this quantity is quite large it is less than amide resonance, so that **A** still predominates over **B** even though by a much smaller margin than that of **C** over **D**. For these methides, it is very large. Qualitatively,  $\Delta pK_a$  gives much the same result and is equally germane for present purposes. Three points may be stressed. Firstly, although the loss of aromaticity in **213A** and **214A** is severe, these  $\log K_M$  values do not compare with  $\log K_E$  for phenol **122b** vs. the dienone **122a** when similarly 'corrected' for the enol content of cyclohexanone (section A.2.6). In that case the dienone **122a** contains  $CH_2$  as a total 'conjugation-stopper' and the reversal in  $\log K_E$  approaches  $10^{20}$ . Secondly, the result of benzene ring annelation in **215** and **216** is greatly to reduce the energetic penalty involved in forming the enamine **A**. As we have noted previously (section A.2.6), loss of aromaticity matters much less in fused bicyclic than in monocyclic systems, essentially because the ring junction bond which is shared by both preserves its full aromaticity. Even so, the mean rise in  $K_M$  of *ca.*  $10^6$  between these compound pairs is much more than normal (Appendix 5) and perhaps reflects the miniscule value it starts from.

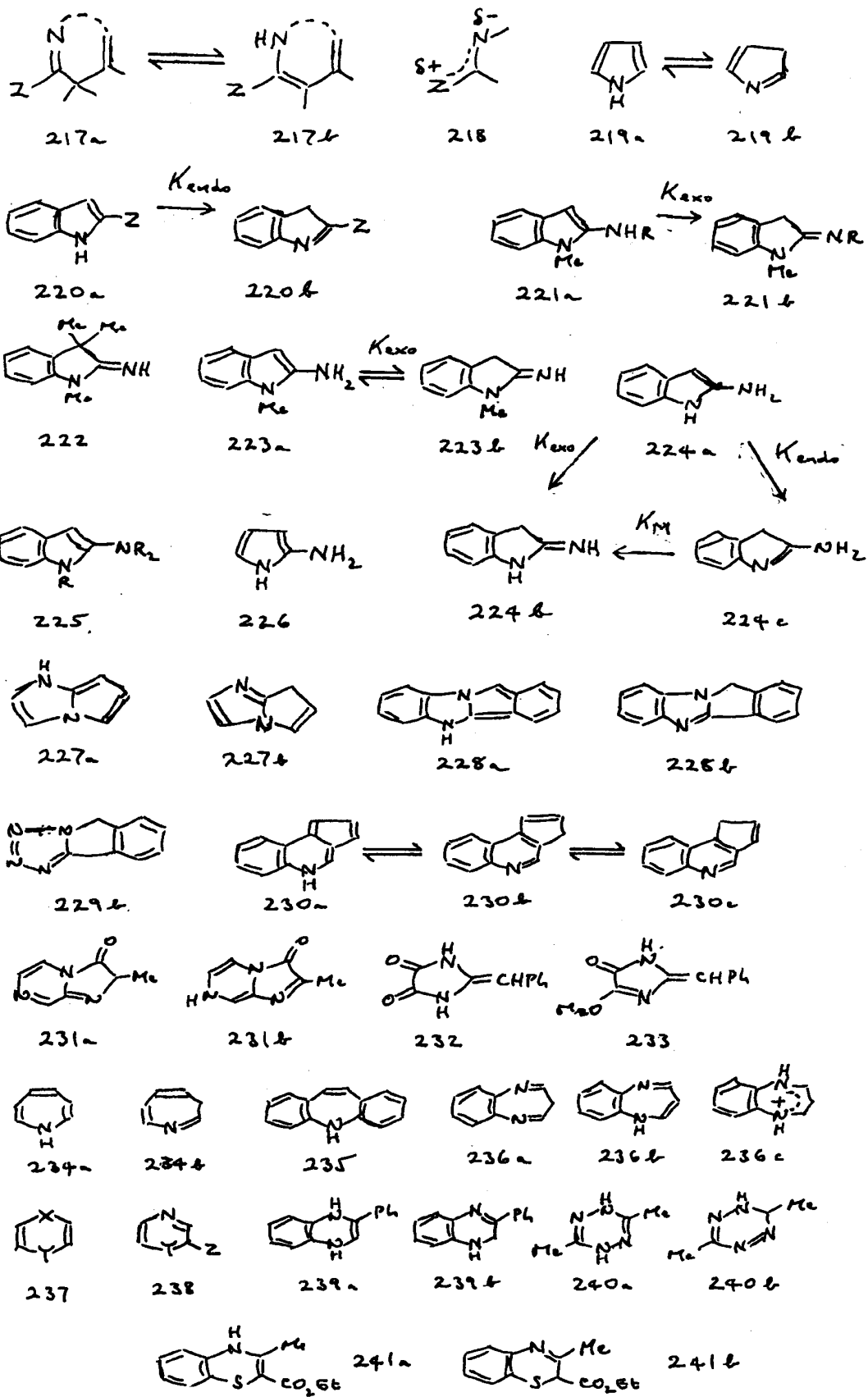
And thirdly: it is interesting that  $\log K_M$  for **213A/213B** and **214A/214B** should be essentially identical. Quinonoid structures are strongly disfavoured relative to their benzenoid alternatives (Appendix 5); on this evidence, there is little to choose in that respect between the *ortho*- and *para*-alignments. The same is found by calculation<sup>115</sup> for the dienones **120a** and **120b** (section A.2.6). Given that this close similarity in  $K_M$  extends to the corresponding pyridones and other compounds examined in these papers<sup>150</sup> there are clearly common factors at work that require careful examination and will receive this in due course.

#### A.4.8 Competitive Conjugation in 5-Membered Rings

If R and R<sup>2</sup> in **171** are linked in such a way that the enamine **217b** can form part of an aromatic structure whereas the imine **217a** cannot, then the position for simple imines is reversed and the enamine becomes the favoured tautomer. If in addition however R<sup>1</sup> in **171** becomes in **217** an electron donor Z, this will stabilise the imine by resonance (*vide* **218**) and *competitive conjugation* will result. Since the resonance energies of 5-membered ring heterocycles are in general far below those for their 6-membered ring counterparts (Table 12, and see preceding section), no *a priori* judgement is possible as to the outcome and these factors must be disentangled with care. This is a very common situation and numerous examples will follow in subsequent sections.

For pyrrole **219** the imine tautomer **219b** is unknown and the same is true for indole. Indole however readily loses its aromaticity when  $\pi$ -donor 2-substituents are added. For (**220**, Z = OEt) Harley-Mason and Leeney<sup>173</sup> obtained  $K_{\text{endo}} \sim 1.5$  in CCl<sub>4</sub>, while Nakagawa and co-workers<sup>174</sup> found mostly **220b** for Z = SEt and very predominantly **220b** for Z = NR<sub>2</sub>, both in CHCl<sub>3</sub>. Since CHCl<sub>3</sub> should favour the imine more than CCl<sub>4</sub>, then as the authors state, the order in  $K_{\text{endo}}$  is probably NR<sub>2</sub>  $\gg$  OEt > SEt, *i.e.* their  $\pi$ -donor order (Table 2). Given that water is an exceptional proton donor, it is likely that all these compounds will exist mostly as **220b** in aqueous solution.

The position for **221** is less certain.<sup>174b</sup> In CHCl<sub>3</sub>, **221** exists mostly as **221a** but there is more of **221b** in EtOH, so  $K_{\text{exo}} > 1$  in water seems probable. Kebarle and Hoffmann<sup>175</sup> have measured pK<sub>a</sub> values in water for **222** (9.25) and for whatever tautomeric mixture is represented by **223** (9.60) and **224** (8.15). Since only **224c** is inaccessible to **222** or **223** this is clearly the dominant tautomer, as inferred above, but nothing more can be stated with certainty. On UV grounds the authors believe **223b** to dominate, in which case  $\log K_M \sim -1.4$  (we make no attempt to correct for NMe since the position is so uncertain). An extrapolation based on phenylguanidine (section B.4.2) would suggest  $\log K_M \sim -1.7$  (see section B.4.4 for the use of  $K_M$  in this context). Extrapolation from **224** again supports  $K_{\text{endo}} > 1$  for Z = OEt and SEt in **220**. Unfortunately no pK<sub>a</sub> is available for a compound of type **225**, which might help to settle this issue. 2-Aminopyrrole **226** exists very predominantly or exclusively as shown,<sup>2r</sup> as expected for the greater importance of aromaticity in monocyclic heterocycles.



If alternatively Z and NH in **217** are linked, competition between rival aromatic structures can result. The fused heterocycle **227** exists as **227b**;<sup>2s</sup> this is found for all derivatives unless NH is blocked (comment by original reviewers). Here loss of the pyrrole unit in **227a** is amply compensated by imidazole resonance in **227b** (*cf.* Table 12). Tautomers **228b** and **229b** are similarly preferred. Elguero *et al.*<sup>176</sup> discuss these as examples of their ‘third rule’ (out of four; the rest appear in section B1) for deciding tautomeric preference in 5,5-fused ring heterocycles: the avoidance of quinonoid structures. This is certainly a major factor (*cf.* Appendix 5) but the analogy with **227** is also valid. Avoidance of the *p*-quinonoid structure **230a** present when **230** is first formed will explain why it tautomerises to a mixture of **230b** and **230c**.<sup>177</sup> It is more difficult to understand why **231** should exist as **231b**, proved by UV in MeOH by the use of fixed forms;<sup>178</sup> both tautomers here are quinonoid and **231b** in addition is ‘anti-aromatic’ (see below).

As seen in section A.4.4, *N*-acylation of imines produces a decisive switch to the enamine tautomer. Further examples are **232** and **233**, found in the solid state and all solutions as shown.<sup>2t</sup> Here imidazole conjugation is entirely lost in favour of amide resonance. That **205** exists in part as **205a** probably indicates that ring S is a better resonance donor than NHCO (*cf.* Table 2 for their  $\sigma_R^+$  values).

#### A.4.9 ‘Anti-Aromaticity’

Aromaticity usually entails six  $\pi$ -electrons; rings with more or less are ‘anti-aromatic,’ hence disfavoured.<sup>179</sup> This topic is broached here since most of its applications are to be found in the present context. Anti-aromaticity like aromaticity itself diminishes in importance as a structural determinant with ring fusion,<sup>180</sup> hence **234** gives **234b** but **235** is stable.<sup>2u</sup> Similarly **236** exists as **236a** but nevertheless its cation **236c** is derived from **236b**.<sup>2u</sup> However the more typical antiaromatic heterocycle is of type **237**, a  $8\pi$ -system in which X and Y are O, S, or NR. Its instability can lead to rearrangement<sup>181</sup> but if X is NH it will exist as **238**; hence **239a** gives **239b** and **240a** goes to **240b** despite the latter's lone pair clash (Appendix 3),<sup>2v</sup> some measure of the extent to which it is disfavoured (see full discussion in Appendix 5). The only important exception to this instability occurs when Z in **238** is an electron acceptor; **241a** not **241b** is now preferred.<sup>2v</sup> Here carbonyl taps off the excess electrons so that **241** becomes a simple aminoenone (section A.10). ‘Anti-aromaticity’ is not a common complication but a few more examples will appear in section A.6 and the topic is discussed in Appendix 5.

## A.5 Other Simple Nitrogenous Systems

This section brings together a number of potentially tautomeric nitrogenous systems that do not belong in Section A.4. Only the first two are of real importance and some will never feature in these pages again; most appear here simply to set the record straight.

Along with high level MO calculations for more familiar modes of tautomerisation, Lammertsma and co-workers have published results for some more obscure systems. All together are summarised in Table 18, taken from a recent publication.<sup>182</sup>

### A.5.1 Azo-Compounds and Hydrazones

On the basis of bond energetics, Karabatsos and Taller<sup>183</sup> calculate the unit **242a** to be less stable than its tautomer **242b** by 9 kcal mol<sup>-1</sup>; if the same gap exists in  $\Delta G$ , this implies  $K_T \sim 10^{6.6}$ . This may be an exaggeration. While azo-compounds of type **243** go totally and irreversibly to the hydrazones **244** in CHCl<sub>3</sub> and hexane,<sup>184</sup> **245a** in Bu<sup>t</sup>OH at 20°C does not go quantitatively to **245b**;  $K_T \sim 60$  and the authors<sup>185</sup> state that a trace of the hydrazine tautomer **245c** may also be present (*cf.* section A.4.5). Possibly therefore Ph on nitrogen stabilises **244** relative to both its rival tautomers. For PrN=NPri the preferred hydrazone product is PrNHN=CMe<sub>2</sub>,<sup>185</sup> in line with the usual effect of alkyl substitution in stabilising double bonds (*cf.* section A.1). A curious exception has been noted by Houssin *et al.*<sup>186</sup> according to whom **246a** (in DMSO) is preferred to **246b**; no obvious explanation suggests itself. However, **247a** goes to **247b** as expected.<sup>2w</sup>

All these results are for organic solvents and there are no solvent studies from which a guess at  $K_T$  in water is even remotely possible. However, some indirect evidence comes from octanol-water fragment values ('*f*-values').<sup>187</sup> These are a (logarithmic) measure of hydrophobicity, becoming more positive as this increases, and are listed in Table 19 for various molecular units A in compounds of general structure PhA<sup>188</sup> While the unit -CH=N- is very hydrophilic, more so even than carbonyl, the azo-linkage is *hydrophobic*. This is evidence for very poor proton acceptor ability and, given that solvent water is an exceptional proton donor (Appendix 2), probably means that  $K_T$  should be much greater in water than in any solvent reported above. While this is unlikely to raise log  $K_T$  to anywhere near the sort of value implied on bond energy arguments,<sup>183</sup> it could well be one or two orders of magnitude greater. Speculation on this point is hazardous at the present time.

**Table 18. Energetics of various Tautomeric Systems** <sup>a,b</sup>

$\Delta E$ , kcal mol <sup>-1</sup>			
CH <sub>3</sub> CH=NH	→	CH <sub>2</sub> =CHNH <sub>2</sub>	3.9
CH <sub>3</sub> CHO	→	CH <sub>2</sub> =CHOH	10.8
NH <sub>2</sub> CHO	→	HN=CHOH	11.5
CH <sub>3</sub> NO	→	CH <sub>2</sub> =NOH	- 12.0
CH <sub>2</sub> =N <sup>+</sup> (H)O <sup>-</sup>	→	CH <sub>2</sub> =NOH	- 11.1
CH <sub>3</sub> NO <sub>2</sub>	→	CH <sub>2</sub> =N <sup>+</sup> (OH)O <sup>-</sup>	14.1
NH <sub>2</sub> NO <sub>2</sub>	→	HN=N <sup>+</sup> (OH)O <sup>-</sup>	8.8

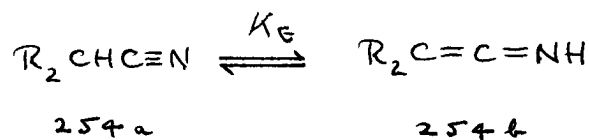
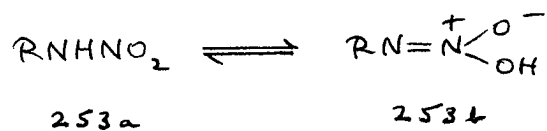
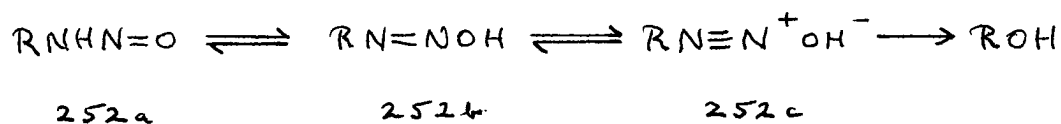
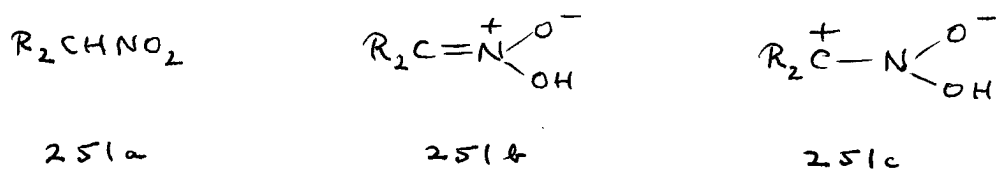
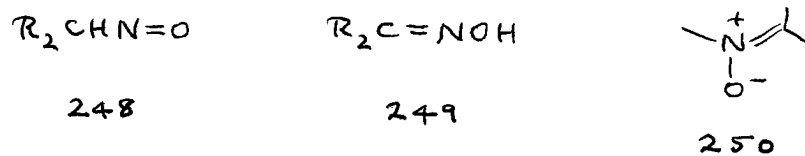
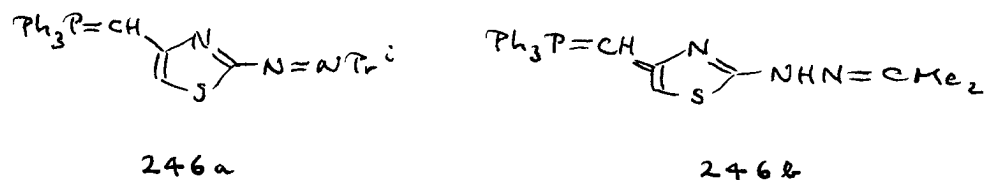
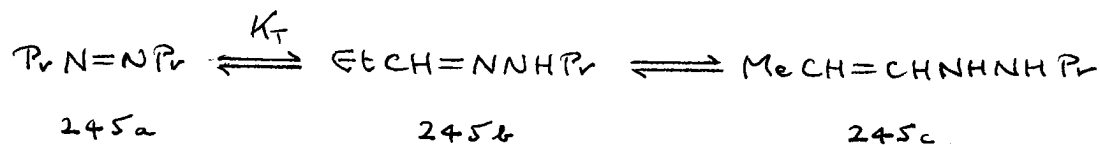
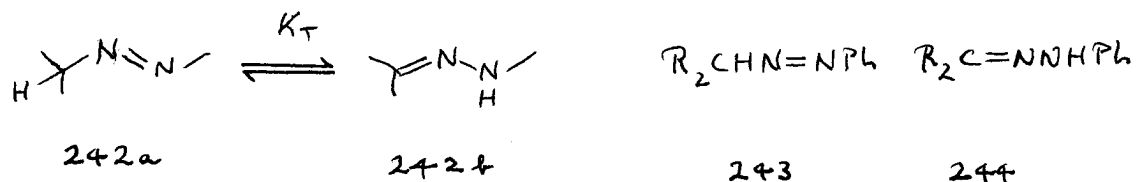
<sup>a</sup> Ref. 182. <sup>b</sup> MP2(full)/6-31G\***Table 19. Fragment Values for A in Compounds of Type PhAPh** <sup>a,b</sup>

A	-CH=CH-	-CH=N-	-N=N-	>C=O
<i>f</i> -value	1.08	- 0.86	0.14	-0.50

<sup>a</sup> For octanol-water. <sup>b</sup> Ref. 188.**Table 20. Tautomerism of Nitro-Compounds RCH<sub>2</sub>NO<sub>2</sub> → RCH=N<sup>+</sup>(OH)O<sup>-</sup> in Water** <sup>a</sup>

R	log <i>K</i> <sub>E</sub> , 25°C	Δ log <i>K</i> <sub>E</sub>	Δ log <i>K</i> <sub>E</sub> , RCOMe <sup>b</sup>
Me	- 6.9		
MeCH <sub>2</sub>	- 4.1	2.8	1.1
MeCH <sub>2</sub> CH <sub>2</sub>	- 4.4	2.5	
Me <sub>2</sub> CH	- 2.6	4.3	1.3
PhCH <sub>2</sub>	- 2.9	4.0	2.2
Cyclohexyl	- 1.9		

<sup>a</sup> Ref. 191. <sup>b</sup> *cf.* Table 5.



### A.5.2 Nitroso-Compounds and Oximes

Any synthetic method to give primary or secondary aliphatic nitroso-compounds **248** yields the tautomeric oxime **249** swiftly and irreversibly.<sup>189</sup> This is consistent with the calculations shown in Table 18 which suggest that  $\text{CH}_3\text{NO}$  is disfavoured relative to  $\text{CH}_2=\text{NOH}$  by about the same margin as is the iminol  $\text{NH}=\text{CHOH}$  relative to formamide<sup>148</sup> (*cf.* sections A.4.5 and A.10.20 for more on oximes). Qualitatively therefore the situation is very much as for azo-compounds, though there are indications from the more complex compounds later to be discussed (sections A.10.19 and A.10.20) that  $-\text{N}=\text{O}$  is still more ready to tautomerise than  $-\text{N}=\text{NPh}$ . This may result from the greater electronegativity of  $-\text{N}=\text{O}$ : this group and  $-\text{N}=\text{NPh}$  possess  $\sigma_{\text{I}} = 0.49$  and  $\sigma_{\text{R}} = 0.42$ , and  $\sigma_{\text{I}} = 0.32$  and  $\sigma_{\text{R}} = 0.09$ , respectively.<sup>190</sup> The need to shed excessive electronegativity as one major driving force in tautomeric preference is a *leitmotiv* which will be found to run the whole way through this subject.

Smith<sup>188c</sup> has pointed out that nitrones  $\text{R}_2\text{C}=\text{N}^+(\text{H})\text{O}^-$  as well as nitroso-compounds  $\text{R}_2\text{CHN}=\text{O}$  are formally related to oximes  $\text{R}_2\text{C}=\text{NOH}$ ; according to Lammertsma<sup>182</sup> (Table 18), each of these minor tautomers is disfavoured to about the same extent. These however are stable species since they can be ‘trapped’ by *N*-substitution (**250**). Nitrones are heteroaromatic *N*-oxides in embryo and the tautomerism of which these are capable is discussed in section B.2.6.

### A.5.3 Nitro- and *aci*-Nitro Compounds

Table 20 lists  $K_{\text{E}}$  values for the tautomerisation of nitro-compounds **251a** to the *aci*-form (nitronic acid) **251b** at 25°C in water.<sup>191</sup> While the *aci*-form even of  $\text{MeNO}_2$  is much less disfavoured than Table 18 would predict, this may in part be due to its formal charge which water will accommodate very much better than the gas phase (the relative stability of nitrones may be underestimated for the same reason). The effect of substituents in stabilising  $\text{C}=\text{N}$  is compared in Table 20 with that found for ketones. Not only is the effect much greater but, interestingly, it is relatively more pronounced for alkyl than for Ph. Since  $\sigma_{\text{R}}$  is greater for alkyl than for Ph, both features may be explained if canonical form **251c** is invoked: essentially, because the effect is on the charged species  $\text{C}=\text{N}^+$ , a species still more electronegative than  $\text{C}=\text{O}$ , rather than on  $\text{C}=\text{N}$  as such.

From the data of Table 20, it might be thought that appropriate substitution could tip the balance towards the *aci*-nitro tautomer. This is probably not the case. From the calculations of Lammertsma and Bharatam<sup>148</sup> it seems clear that the very electronegative -NO<sub>2</sub> is much better at promoting enolisation in other groups than *vice versa*, as will be seen in section A.6. Nielsen<sup>191</sup> indeed remarks that nitronic acids, while they may be generated *in situ* as fugitive species on acidifying an alkaline solution, have never been observed at equilibrium.

#### A.5.4 Nitro- and Nitroso-Amines

Primary nitrosamines **252a** are fugitive species on the way to the alcohol ROH and nitrogen, probably *via* the azo-tautomer **252b** and its cation **252c**, and have never been isolated.<sup>169c</sup> Nitroamides **253** are acids of pK<sub>a</sub> ~ 7 and somewhat more stable;<sup>168c</sup> fixed derivatives of both tautomers are known, if somewhat obscure.<sup>192</sup>

#### A.5.5 Nitriles and Ketenimines

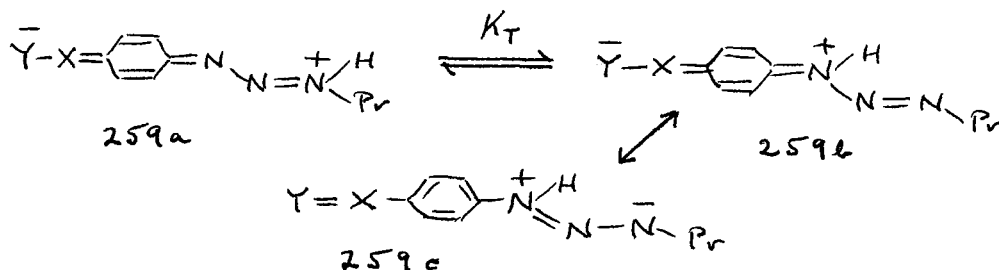
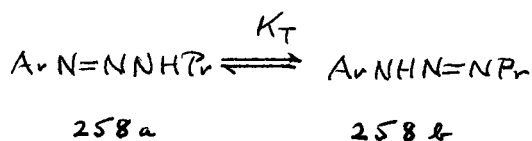
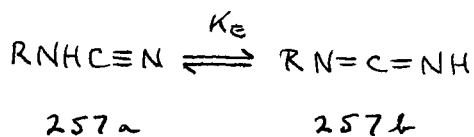
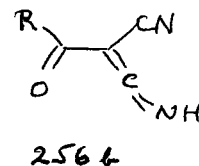
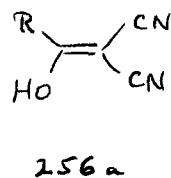
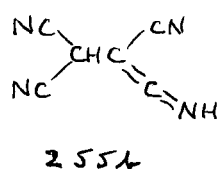
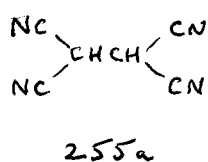
Ketenimines **254b** are tautomeric with nitriles **254a** but are normally of negligible importance. However, traces of the ketenimine tautomer are detectable in such cases as **255** and **256** in which nitrile is  $\alpha$ -substituted with another strongly electronegative group;<sup>193</sup> quantitative data however are lacking. Formally these cases belong with the  $\beta$ -diketones and related compounds of section A.6 onwards, but are included here because of their sparsity and the general kinship between nitrile, nitro, nitroso, azo, and suchlike highly electronegative substituents.

#### A.5.6 Cyanamides and Carbodiimides

These are nitrogenous analogues to the above. Again the nitrile tautomer **257a** is vastly preferred, according to Moffat<sup>194</sup> by 18 kcal mol<sup>-1</sup> on the basis of *ab initio* calculation. An alternative, empirical estimate based on aqueous solution data suggests the possibly more realistic figure of  $K_E \sim 10^{-6}$  (ref. 72, p.1372).

#### A.5.7 Triazenes

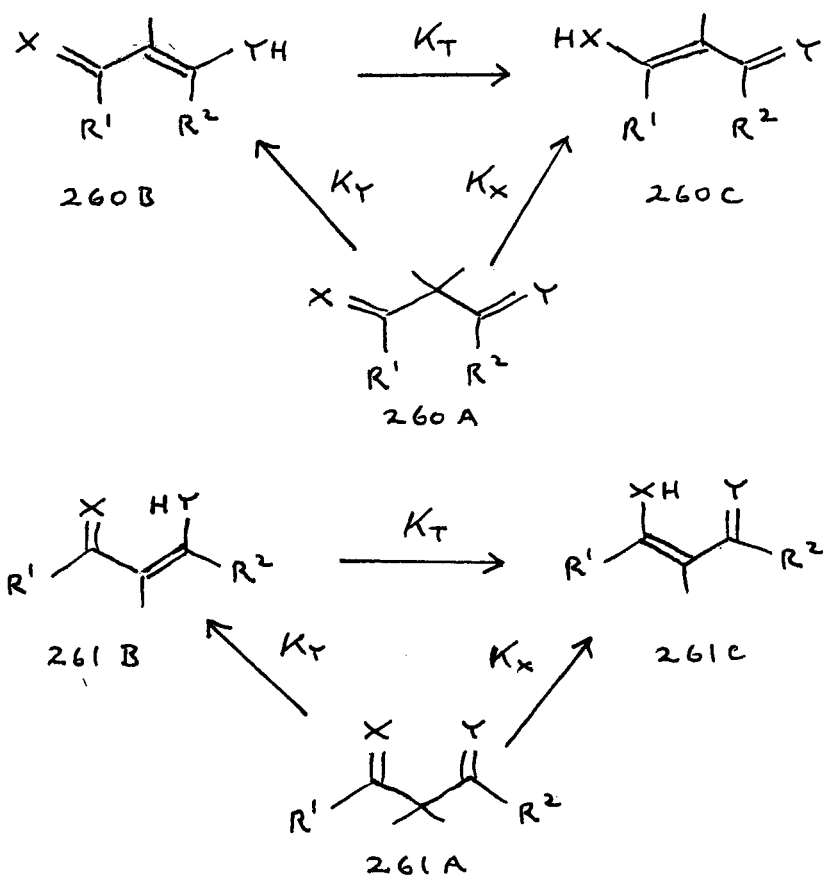
Formally these may be regarded as all-nitrogen analogues of either carbodiimides (above) or amidines (section B.4.2); they are included here on grounds of convenience. Sinnott and co-workers<sup>195</sup> have studied the tautomerism



of **258** in MeCN; since added water does not appreciably affect  $K_T$ , their results may be regarded as a reasonable approximation to those expected for aqueous solution. The equilibrium is quite evenly balanced, with  $\log K_T$  ca. -1.1, -0.7 and +0.4 for Ar = p-methoxy, p-methyl- and p-nitrophenyl respectively. Assuming, from the authors' correlation equation,  $\log K_T$  ca. -0.7 for Ph itself, this is the direction (but not nearly the magnitude) of  $K_T$  in the corresponding amidines, where it can be discussed in terms of *cation* stability (**210H**; cf. section A.4.6). However, the effect of *substitution* into Ph is then anomalous. Sinnott<sup>195</sup> discusses the electronic influences in terms of competitive conjugation in the *free base*, **259a** vs. **259b**, such that an electronegative substituent -X=Y will favour the latter. However, his predicted result is not at all what happens if the central nitrogen atom of the triazene unit is replaced by -CR= to give an amidine, and in the interests of consistency, a supplementary explanation is required. We suggest that **259c**, in which the azo-linkage acts as an alternative electron sink, may also help to stabilise tautomer **258b**. No equivalent canonical form can be important for an amidine since C=N will be much less able than N=N to support a negative charge. In addition the positive charge of **259a**, easily accommodated by C=N, will be heavily disfavoured when this is replaced by N=N, with similar consequences. This modification to Sinnott's analysis will explain both why Ph stabilises **258a** and why substitution appears to produce the 'wrong' result, so removing the apparent discrepancy.

## A.6 $\beta$ -Dicarbonyl Compounds

Compounds in which  $\text{CH}_2$  or  $\text{CHR}$  separates two groups of type  $\text{C}=\text{Z}$ , which may be the same or different, represent probably the most widespread and arguably the most important context for tautomerism, that of the 6-membered ring oxoheterocycles being their only possible rival in this respect. The combinations of  $\text{C}=\text{O}$ ,  $\text{C}=\text{S}$  and  $\text{C}=\text{N}$ , with themselves and one another, form the subject matter of the next six sections.



Scheme 10

(The nomenclature we shall use in these sections is indicated in outline above. Here  $K_T = K_X / K_Y$  and  $K_E = (K_X + K_Y)$  so that when  $X = Y$ ,  $R^1 = R^2$ , and therefore  $K_X = K_Y$ , then  $K_E = 2K_X$  and, for comparison outside the series, statistical correction is required. For unsymmetrical compounds we shall have cause in later sections to replace  $K_Y$  by  $K_E$  when  $Y = \text{O}$  and  $K_X$  by  $K_M$  when  $X = \text{NR}$ ; cf. section A.4).

Two contexts must be distinguished. The tautomeric unit may be *extended*, as **260**, or *chelated*, as **261** (Scheme 10), and there are major differences in the rules for each. In **260**, one at least of the enolised forms

**260B** and **260C** is likely to possess a larger dipole moment than **260A**, so that solvents of high polarity will tend to favour it. For the chelated enols **261B** and **261C** the reverse will generally be true: their ‘closed’ structure militates against solvent participation so that, despite conjugation, solvents of high polarity will disfavour them.<sup>196</sup> This is illustrated very clearly by the LSER equations for acetylacetone (**57**,  $R^1 = R^2 = \text{Me}$ ,  $R = \text{H}$ )<sup>60,197</sup> and dimedone (**55**,  $R = \text{H}$ )<sup>60</sup> of which our revamped versions (Appendix 2) are set out here as (ix) and (x) respectively.<sup>198</sup> In the former the  $\pi^*$  term is large and negative, *i.e.* less polar solvents stabilise the less polar chelate, with a small contribution of the same sign from solvent proton donor ability; there is no term in  $\beta$  since OH is inaccessible to solvent. By contrast, solvent proton *acceptor* ability hugely dominates the behaviour of dimedone, since its enol form contains an accessible, and exceptional, proton donor. These compounds possess, in water,  $\log K_E$  -0.83 and +1.28 respectively, *i.e.* enolisation is two orders of magnitude more favourable in the latter case.

$$\log K_E = 1.50(0.09) - 1.58(0.14)\pi^* - 0.18(0.10)\alpha \quad (\text{ix})$$

$$(n = 18 \quad r^2 = 0.905 \quad s = 0.16 \quad F = 71)$$

$$\log K_E = -1.78(0.24) + 0.54(0.33)\pi^* + 0.70(0.20)\alpha + 4.38(0.21)\beta \quad (\text{x})$$

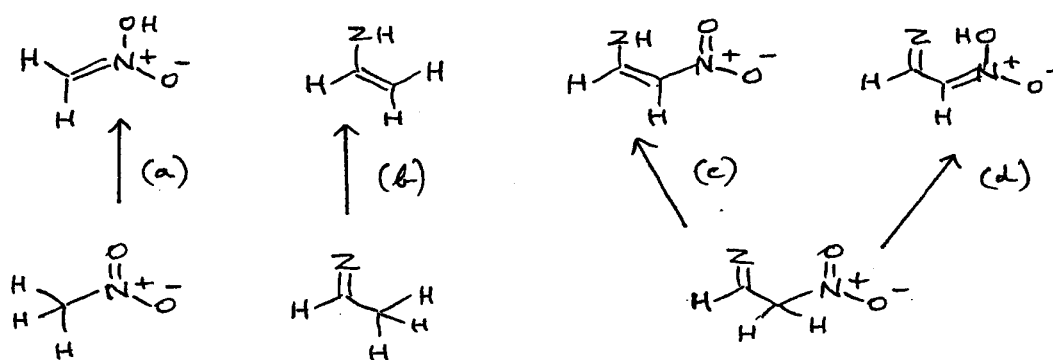
$$(n = 14 \quad r^2 = 0.981 \quad s = 0.21 \quad F = 171)$$

Since the extended structure **260** lacks the complication of an intramolecular hydrogen bond, then here and mostly elsewhere, we shall consider it first. Since chelates are always formed with however variable efficiency (*vide infra*) when the possibility exists, structure **260** is confined in practice to cyclic compounds. In addition to the simple categories **260** and **261** there is an intermediate type of structure in which enolisation is caused, or reinforced, by substitution into a ring; the substituent will generally be another carbonyl but may include such other electronegative groups as NO<sub>2</sub> or CN, and except for the latter, chelation will again result.

#### A.6.1 The Energetics of Scheme 10

Throughout these sections we shall be looking for *additive rules*, starting from the simpler compounds of sections A.1 to A.5 but extended by a number of complementary criteria. Some encouragement for the belief that such rules are possible is supplied by the high level MO (gas phase) calculations of Lammertsma and Bharatam.<sup>148</sup> These authors studied the energetics of tautomerism for the compounds of Scheme 11; their values (as  $-\Delta H$ , kcal mol<sup>-1</sup>) for the processes (a) – (d) are given in Table 11. For the

simple units involving C=O, C=N and NO<sub>2</sub> enolisation is disfavoured throughout, but to very varying extents and in an order NO<sub>2</sub> > C=O > C=NH which is clearly that of electronegativity. This same order is also found for the extent to which NO<sub>2</sub> can influence (**c** - **b**), and be influenced by (**d** - **a**), the tautomerisation of C=O and C=NH. Two points stand out. Firstly, the effect of NO<sub>2</sub> on C=O and C=NH is very nearly the same: - $\Delta\Delta H$  11.5(14.3) or 11.3(14.7) kcal mol<sup>-1</sup> respectively. Perhaps more surprisingly, so is the effect *on* NO<sub>2</sub>: -  $\Delta\Delta H$  9.9(13.9) by C=O, 9.2(13.5) by C=NH. If these  $\Delta\Delta H$  values were to carry over to the effect of C=O and C=NH on themselves and one another, this would lead to -  $\Delta H$  3.1(-1.9) for the enolisation of a chelated  $\beta$ -diketone; -  $\Delta H$  11.2(5.2) for the enolisation of a chelated  $\beta$ -diimine; and -  $\Delta H$  8.5(7.8) kcal mol<sup>-1</sup> for the formation of a chelated aminoenone from an iminoenol (*cf.* **127**). These are plausible values and have encouraged us to carry out parallel calculations for Scheme 10, concentrating on series **260** for which intramolecular hydrogen bonding is not a factor.

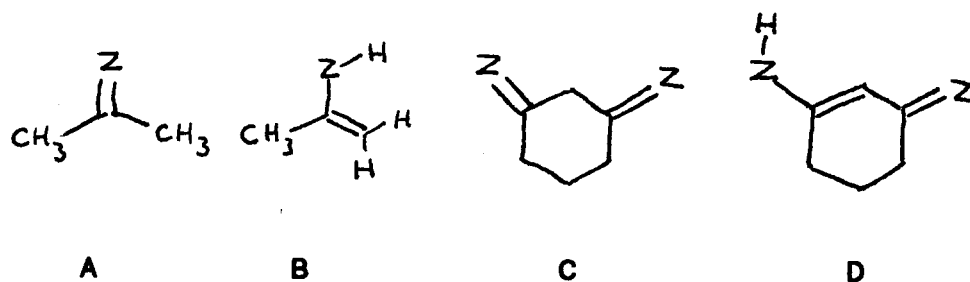


Scheme 11

Table 21. Energetics for the Tautomeric Processes of Scheme 11 <sup>a,b,c</sup>

Z	(a)	(b)	(c)	(c - b)	(d)	(d - a)
O	- 14.6 (- 14.1)	- 11.1 (- 10.4)	0.4 (3.9)	11.5 (14.3)	- 4.7 (- 0.2)	9.9 (13.9)
NH	- 14.6 (- 14.1)	- 4.0 (- 2.3)	7.3 (12.4)	11.3 (14.7)	- 5.4 (- 0.6)	9.2 (13.5)

<sup>a</sup> Ref. 148. <sup>b</sup> Energetics as -  $\Delta H$ , kcal mol<sup>-1</sup>. <sup>c</sup> Upper line: G2MP2; lower (bracketed) line: B3LYP/6-311G\*\*.



**Table 22. Energetics ( $\Delta H$ , kJ mol<sup>-1</sup>) for Structures A - D <sup>a</sup>**

		<b>A → B</b>		<b>C → D</b>		<b>B → D</b>	
		$\Delta H$	'log $K_E$ '	$\Delta H$	'log $K_E$ '	$\Delta H$	'Δ log $K_E$ '
Z = O	<i>b</i>	64.438	- 11.3	18.615	- 3.3	- 45.823	8.0
	<i>c</i>	65.941	- 11.6	21.025	- 3.7	- 44.916	7.9
	<i>d</i>	59.408	- 10.4	10.494	- 1.8	- 48.914	8.6
Z = S	<i>b</i>	26.667 <sup>e</sup>	- 4.7	- 21.041	3.7	- 47.708	8.4
	<i>c</i>	37.568	- 6.6	- 5.601	1.0	- 43.169	7.6
	<i>d</i>	31.774	- 5.6	- 25.454	4.4	- 57.228	10.0
Z = NH	<i>b</i>	27.207	- 4.8	- 10.639	1.8	- 37.846	6.6
	<i>c</i>	31.068	- 5.4	- 7.455	1.3	- 38.523	6.7
	<i>d</i>	23.689	- 4.2	- 22.282	3.9	- 45.971	8.1

<sup>a</sup> The quantities 'log  $K_E$ ' and 'Δ log  $K_E$ ' are hypothetical values for the case that  $\Delta G = \Delta H$  (see the text). <sup>b</sup> RHF/6-31G\*\*//RHF/6-31G\*\*. <sup>c</sup> MP2/6-31G\*\*//MP2/6-31G\*\*. <sup>d</sup> B3LYP/6-31G\*\*//B3LYP/6-31G\*\*. <sup>e</sup> The *E*-conformer is very slightly favoured (by  $\Delta\Delta H$  0.113 kJ mol<sup>-1</sup>).

Table 22 summarises our results at three levels of theory for the symmetrical cyclic structures **C** and **D** and their precursor molecules **A** and **B**. Given that our calculations have been carried out on 'ketone type' structures whereas those of Tables 15 and 21 employ those of 'aldehyde type,' it is unsurprising that smaller degrees of enolisation are predicted throughout; *cf.* Table 8. Nevertheless it is almost certain that the gas-phase stability of tautomer **A** is over-predicted by all calculations and for all structural types (*cf.* the solvent effects enumerated in section A.2.7, according to which the enol tautomer should be favoured in the gas phase relative to water). Either therefore there is some unidentified source of error, or a considerable countervailing entropy effect. Whatever its origin, however, there are hints

that this error may be systematic. While both ‘ $\log K_E$ ’ values of Table 22 may be quantitatively at fault there is some evidence that ‘ $\Delta \log K_E$ ’ is quite accurate: certainly for  $Z = O$  (see dimedone, section A.6.2) and plausibly elsewhere. And qualitatively at least, the results for  $C \rightarrow D$  appear to accord with expectation. From eqn. (x) we may predict  $\log K_E$  *ca.* -2.2 for dimedone in the gas phase (Appendix 2), not far from the values for  $Z = O$  in Table 22, while the positive values of ‘ $\log K_E$ ’ predicted for  $Z = S$  and  $Z = NH$  are almost certainly of the right sign and likely to be at least as positive in water. Evidence on both will be considered later (sections A.7 and A.9).

It should be stated here that a fuller treatment of these results, incorporating the calculations for (**260**,  $X \neq Y$ ), does not support the presumption of additivity, at least for ‘ $\Delta \log K_E$ .’ We find that the order of *enolising power* is  $C=S > C=O > C=NH$  whereas the order of *susceptibility to enolisation* is  $C=NH > C=O > C=S$ . Either order alone would allow additivity, but the two together cannot. At the extreme ends of the scale, the effect of  $C=S$  in promoting the enolisation of  $C=NH$  is much greater than *vice versa*, which given the near-equality of  $\Delta H$  for  $Z = S$  and  $Z = NH$  for the precursor processes  $A \rightarrow B$  (Table 22), means that this imbalance is responsible for most of the preference shown by  $\beta$ -iminothiones for the aminoenethione tautomer (section A.11). Nevertheless a sort of ‘pseudo-additivity’ prevails in the middle of the scale and can be used to help systematise the data. These, and possible rationalisations of the orders given above, will be discussed in the appropriate section.

Series **260** are semi-rigid molecules whose geometry is unlikely to vary much with phase. Despite the example of Lammertsma and Bharatam<sup>148</sup> we have carried out no parallel calculations for **261** since while its enols are of fixed geometry **261A** is not, and the conformation of this species is likely to depend so markedly on phase as to make parallel comparisons almost meaningless. This point is further emphasised by the radical differences between equations (ix) and (x). Instead, where  $X \neq Y$  we have carried out calculations on the relative stabilities of the two *enol* forms, and this can be used to throw light on the contribution of intramolecular hydrogen bonding to  $K_T$  as here defined (see sections A.8, A.10 and A.11). We shall have further reason to discuss these calculations in the Overview, section A.12.

### A.6.2 Extended Conjugation in 6-Membered Rings

Here dimedone (**55**, R = H) is the archetype, with  $\log K_E$  1.28 in water. This represents a reversal of  $\Delta \log K_E$  *ca.* 7.7 relative to cyclohexanone, not much less than the factor of  $10^8$  -  $10^9$  found for cyclohexane-1,2-dione **110** where the two carbonyls are proximate (section A.2.5), hence clear evidence that something more than electronegativity *per se* must be responsible. We suspect this to be the dihedral angle between them (*cf.* **265**), which as it widens will generate an increasing repulsion between the positive ends of the dipoles that can be relieved by enolisation. This interpretation will account for the greater degree of enolisation shown by 5-membered rings (section A.6.3). It has been seen (section A.1.4) that  $\Delta \log K_E \sim 0.8$  for (**55**, R = Me) and larger effects may be anticipated for R = Ph or any electronegative substituent, so that enolisation in aqueous solution will be essentially complete.

Tautomeric and  $pK_a$  data for **55** and some related compounds appear in Table 23. ‘Meldrum’s acid’ **263** presents a puzzle. Given that the enolisation of ethyl acetate **101**<sup>101</sup> (section A.2.4) is  $10^{10}$  times less favourable than that of acetone, its enol content should have been minute. We may attempt to quantify expectation from a cross-comparison between the first four compounds of Table 23, which in the absence of experimental data entails estimating  $\log K_E$  for diethyl malonate (**264**, R = OEt). If we suppose that  $pK_a^E$  (not  $pK_a^K$ ) will behave in a regular fashion since all four enols (and their anions) will form regular structures, we arrive at an estimate of  $pK_a^E$  *ca.*

**Table 23. Enol Content and  $pK_a$  for Alicyclic and Related Open-Chain  $\beta$ -Dicarbonyl Compounds**

Compound	$\log K_E$	$pK_a$	$pK_a^K$	$pK_a^E$
<b>264</b> , R = Me	- 0.69 <sup>a</sup>	9.03 <sup>b</sup>	8.93 <sup>a</sup>	8.24 <sup>a</sup>
<b>55</b> , R = H	1.28 <sup>c</sup>	5.25 <sup>d</sup>	3.95 <sup>e</sup>	5.23 <sup>e</sup>
<b>264</b> , R = OEt		12.9 <sup>f</sup>		
<b>263</b> , R = H	- 2.35 <sup>g</sup>		4.83 <sup>g</sup>	2.48 <sup>g</sup>
<b>54</b> , R = H	- 1.89 <sup>g</sup>		4.00 <sup>g</sup>	2.13 <sup>g</sup>

<sup>a</sup> J. Calman and P. Maroni, *Bull. Soc. Chim. Fr.*, 1965, 2565. This  $K_E$  value differs from that of Emsley and Freeman<sup>197</sup> but is retained here for internal consistency. <sup>b</sup> M. Laloi-Diard and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1961, 1645. <sup>c</sup> Ref. 60. <sup>d</sup> G. Schwartzenbach and K. Lutz, *Helv. Chim. Acta.*, 1940, **23**, 1162. <sup>e</sup> By calculation. <sup>f</sup> R. P. Bell, *Trans. Faraday Soc.*, 1943, **39**, 243. <sup>g</sup> Ref. 78.

5.5 from which  $\log K_E$  *ca.* -7.4 follows. This is not far from  $\log K_E$  -8.13 for malonic acid (**264**, R = OH)<sup>199</sup> though its closeness, while gratifying, does not guarantee accuracy. Allowing for a built-in factor (in water) of  $\Delta \log K_E$  *ca.* 2.1 on going from a chelated (**264**, R = Me) to an extended (**55**, R = H) structure, we arrive at a rough expectation of  $\log K_E$  *ca.* -5.3 for (**263**, R = H); still a deficit of *ca.*  $10^3$  as compared with the  $K_E$  value observed.

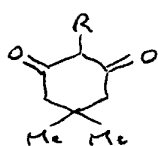
There may be similar problems with barbituric acid **54**, for which  $K_E$  is very similar (Table 23). Here there is a fall in  $K_E$  of only *ca.*  $10^3$  relative to dimedone (**55**, R = H), perhaps because imide not amide resonance is lost; *cf.* the comparative ease with which anhydrides such as **275** and **281** will enolise (see below). For substitution at R see Table 7 (section A.1.4).

We propose as important two factors not hitherto considered. The first is conformation. Lactones necessarily take up the *E*-conformation disfavoured for esters by  $\Delta G$  *ca.* 3 kcal mol<sup>-1</sup>;<sup>200</sup> if **263a** is destabilised by this amount (Table 24), a deficit in  $K_E$  of less than a factor of 10 remains to be accounted for. Lactams are similarly destabilised<sup>201</sup> (Table 24), a fact that becomes specially important in section B. The second is conjugative stabilisation of the enol tautomer as shown for **265**. This is not available to the simple monoacyl precursors and may be responsible not only for the remaining deficit, but also for the remarkably enhanced factor (statistically corrected) of  $\Delta \log K_E$  10.9 shown (by hypothesis) for the diester (**264**, R = OEt) relative to ethyl acetate, compared with  $\Delta \log K_E$  7.7 for dimedone relative to cyclohexanone and of  $\Delta \log K_E$  7.5 for acetylacetone relative to acetone itself.<sup>202</sup> We have noted for **102** (section A.2.4) a rather similar enhancement of  $\Delta \log K_E$  8.2 when R = OH is replaced by R = CN. For (**265**, Z = NH) as in the enol **54b** of barbituric acid, this conjugative stabilisation could be considerably greater; **54b** is in fact a hydroxyuracil, so highly conjugated if not quite ‘aromatic’ (section B.2.9). Both factors extend their

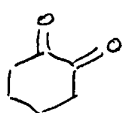
**Table 24. Conformational Preference ( $K_C = Z/E$ ) for RCOX**

X =	OH	OAlk	NHMe
$\log K_C$	1.5 <sup>a</sup>	2.2 <sup>b</sup>	1.5 <sup>c</sup>

<sup>a</sup> L. Eberson, in *The Chemistry of Carboxylic Acids and Esters*, ed. S. Patai, Interscience, 1969, p. 211. <sup>b</sup> Ref. 200. <sup>c</sup> Ref. 201.



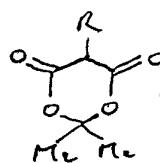
55



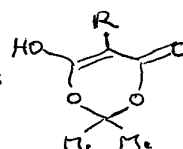
110



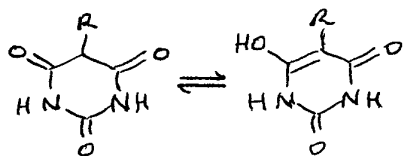
262



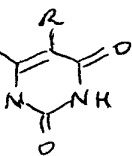
263a



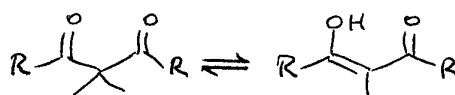
263b



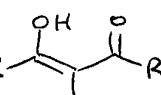
54a



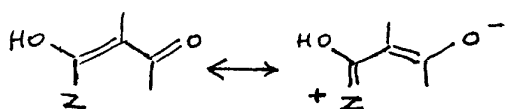
54b



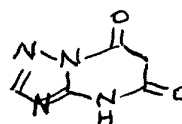
264a



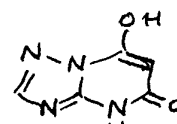
264b



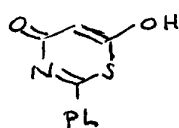
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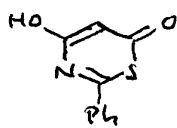
266a



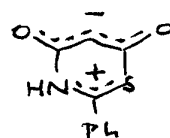
266b



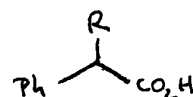
267a



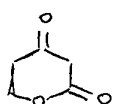
267b



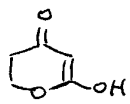
267c



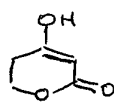
102a



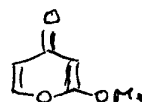
268a



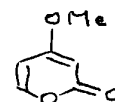
268b



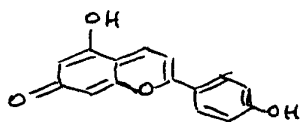
268c



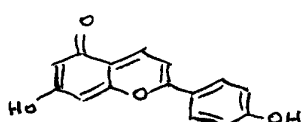
269



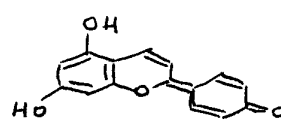
270



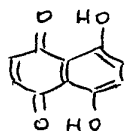
271a



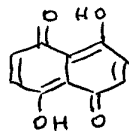
271b



271c



272a



272b

influence throughout the length and breadth of this investigation. Here the upshot is that, while in simple cases an ester or amide will enolise with far greater difficulty than a ketone, there are special cases in more complex molecules, some of which appear below, where that preference may be reversed.

The triazolopyrimidone **266** exists as the diketone **266a** in the solid state;<sup>203</sup> its  $pK_a$ , 2.9, does not decide the issue for aqueous solution since either  $pK_a^E$  or  $pK_a^K$  could be lower than this. Comparison with barbituric acid **54** (Table 23) shows that triazolyl must have a similar electronegativity to carbonyl (*cf.* section A.2.6). The thiazine **267** is fully enolised and variously described as **267a**<sup>204a</sup> or **267b**;<sup>204b</sup> its IR spectrum<sup>204a</sup> however clearly shows it to exist as the inner salt **267c**,<sup>205</sup> analogously to the pyrimidinedione **7**<sup>29</sup> which is mentioned in the Introduction as a 'trap for the unwary.'

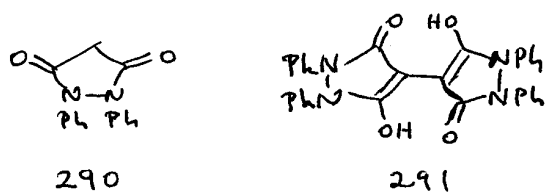
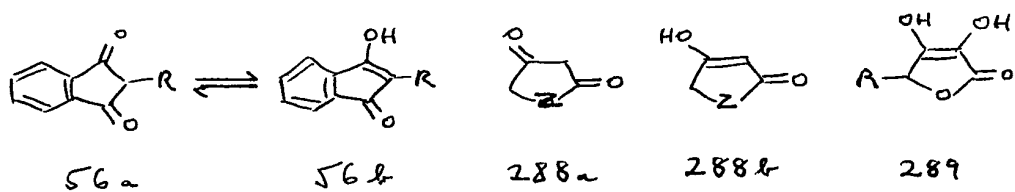
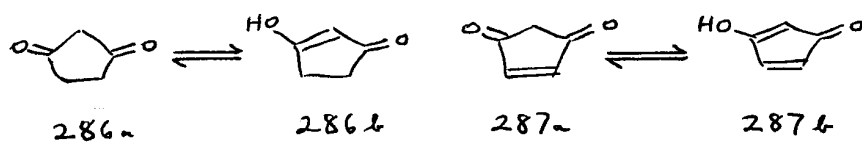
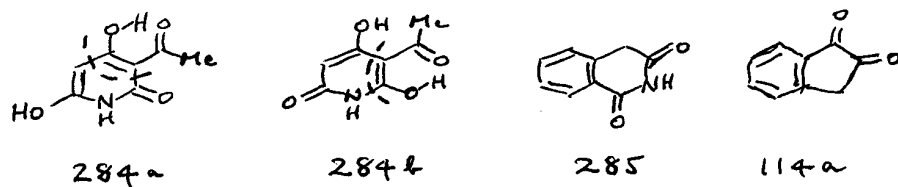
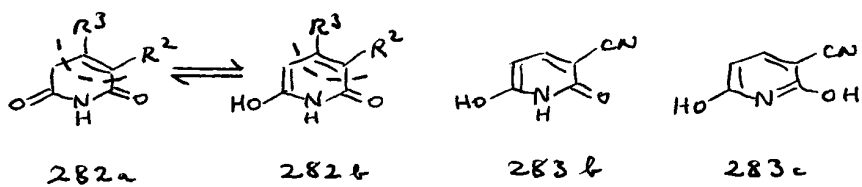
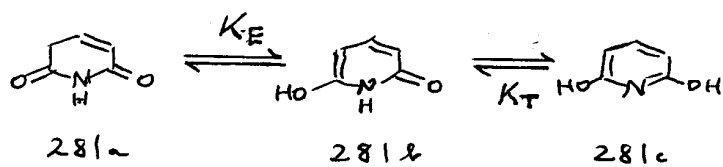
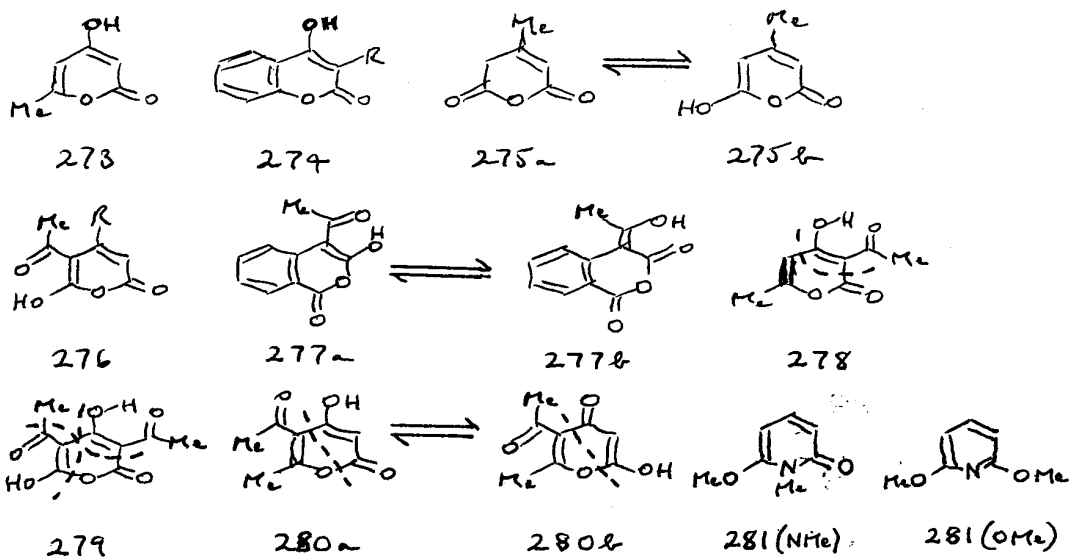
In fact, biologically the most important property of all compounds discussed in this section is not their tautomerism but their acidity: all will be largely ionised at physiological pH. Most forms of substitution, while increasing their enol content, will increase their acidity even more. This is a problem common to a great swathe of  $\beta$ -diketones and their sulfur analogues, especially in the extended configuration, and only really disappears when nitrogen is introduced (sections A.9 to A.11). It must sharply attenuate their rate of absorption and may make their tautomeric form in water of secondary importance. In addition, a sharp drop in  $K_E$  is to be expected in hydrophobic surroundings — for dimedone, by a factor of *ca.*  $10^3$  in hydrocarbon solvents; *cf.* eqn. (x) — so that the biologically active tautomer may not always be that predicted for aqueous conditions and a careful assessment of the evidence may be necessary.

### A.6.3 Conjugation, Aromatisation and Acylation in 6-Membered Rings

Tautomeric data are lacking for **268** but we may attempt an estimate. If the 'pull' of ester on ketone ( $\Delta \log K_E$ ) is equal to that of ketone on ester, then  $\log K_E$  for dimedone (**55**, R = H) and Meldrum's acid (**263**, R = H) can simply be transferred to **268c** and **268b** respectively: 1.28 and -2.35 for 4-carbonyl and 2-carbonyl respectively (Table 22). In fact, this is unlikely. If as we shall postulate  $\Delta \log K_E$  is some function of dipole moment for the group that *promotes* enolisation, ketone in **268b** and ester in **268c**, then  $\log K_T = [c]/[b]$  will be somewhat less than the value of 3.63 predicted on this simple argument:  $\mu = 3.6$ , 2.83 and 1.84 debyes for EtNO<sub>2</sub>, MeCOMe and MeCO<sub>2</sub>Et respectively<sup>207</sup> (*cf.* Table 23). A value of  $\log K_T$  *ca.* 3 might then

seem reasonable, with **268** a little less enolised overall than dimedone. Equilibration studies<sup>2x</sup> on **269** and **270** show the latter to be favoured by  $\Delta G > 3 \text{ kcal mol}^{-1}$  *i.e.*  $\log K_T > 2.2$ , a little below the above estimate for **268**, consistently with the expected effect of aromaticity in reducing this differential (*cf.* iminol formation in uracil, section B.2.9). Another implication must be that there is little to choose in point of stability between the *p*-quinonoid structure of **269** and the *o*-quinonoid structure of **270**, in line with what has been found for the carbonyl tautomers of phenol and 1-naphthol (section A.2.6: contradictory results but by small margins in each direction; and *cf.* section A.4.7). Pertinently in this context, Costantino *et al.*<sup>208</sup> have found, using an ingenious variant on the 'basicity method,' that the *p*-quinonoid **271a** is favoured over the *o*-quinonoid tautomer **271b**, but by less than a factor of five; **271c** is a minor component (<1%). Note in passing that **272** exists as **272a** not **272b** so as to avoid the latter's quinonoid form.<sup>2x</sup>

The pyrone **273**<sup>209a</sup> and the coumarinones **274**<sup>2x</sup> exist exclusively as shown in water, with no trace of any other tautomer. This is as expected; on the arguments presented above, the 4-OH should be preferred to the 2-OH tautomer by a factor of *ca.*  $10^2$  while loss of aromatic character in the diketo-form should ensure its absence. However, vinylogous conjugation in **275b** has to compete with anhydride resonance in **275a** and as a result **275b** dominates only in polar solvents, water included.<sup>209a</sup> 5-Acylation in **276** locks this molecule into the 6-OH tautomer shown.<sup>209a</sup> Similarly, the isocoumarinone **277** exists only as an enol, **277a** in water but **277b** in  $\text{CHCl}_3$  and MeOH.<sup>2x</sup> While enolisation in **277a** involves loss of anhydride conjugation, the *exo* double bond of **277b** is also in principle unfavourable (section A.1.2) and analogous tautomers are not found for pyrones since too much loss of aromaticity would result. As discussed in other contexts, in *e.g.* sections A.2.6, A.4.8, and for the fused oxoheterocycles of sections A.10.7 and B.2.5, this matters less in bicyclic structures. Unsurprisingly, the tautomeric preferences for **273** and **276** are reinforced by acylation in **278** and diacylation in **279**<sup>209a</sup> (here and throughout, the likeliest conformation is shown). It has been suggested<sup>209b</sup> on UV evidence that 5-acylation of **273** induces a partial shift to the 4-pyrone **280b** in polar solvents but the position is greatly complicated by intermolecular association, especially in KBr, and must be considered uncertain. These compounds like those of the preceding section will be largely ionised at physiological pH but, because of aromatisation, non-enolic forms are improbable however nonpolar their surroundings.



Glutaconimide **281** undergoes a 3-way equilibrium<sup>210,211</sup> in which, on UV evidence,<sup>211</sup> ca. 40% of **281a** is present ( $K_E = 1.5$ ), allowing an overall  $pK_a$  1.19<sup>210</sup> to be corrected to  $pK_a$  1.37 for (**281b** + **281c**). Correction factors (Appendix 1) applied to  $pK_a$  0.91 for **281(NMe)** and 1.60 for **281(OMe)**<sup>210</sup> then result in  $pK_a$  values for **281b** and **281c** of 1.36 and 2.60 respectively, *i.e.*  $K_T$  ca. 20, assuming that 6-OH and 6-OMe will have similar electronic effects. The proportion of **281a** rises with falling solvent polarity, reaching 99.8% in  $CHCl_3$  and dioxan,<sup>211</sup> a solvent shift comparable to that for dimedone [eqn. (x)] and in the same direction.

Substituted glutaconimides have been extensively studied. For (**282**,  $R^2 = H$ ) the substitution of electron donor groups at  $R^3$  does not much affect the tautomeric balance,<sup>212</sup> whereas (**282**,  $R^2 = H$ ,  $R^3 = CO_2Et$ ) exists as **282a** in nonpolar solvents but as **282b** in  $MeOH^{2y}$  and, presumably therefore, in water. 3-Substitution of **281** with CN abolishes the imide tautomer and gives rise to appreciable amounts of **283c**; if however the 2- and 3- positions are substituted with electron acceptors and donors respectively, **282b** becomes dominant, so that **284** exists as **284a**<sup>2y</sup> (or possibly as **284b**: see below). It is clear that tautomeric form in these compounds is finely balanced and may need individual assessment, though water will probably favour **282b** in general, if not by much. Again, these 6-OH compounds are quite strong acids.<sup>210</sup> Homophthalide **285** exists in the solid state as shown,<sup>2y</sup> demonstrating the usual effect of fused bicyclic structures in diminishing the importance of aromaticity. If the same factor for benzofusion were to be operative here as it is on  $K_T$  for amides (section B.8.3),  $\log K_E$  -1.6 for **285** would result.

Structures **278**, **279**, **280**, **282** and **284** exemplify a scarcely recognised phenomenon: the existence, inside the overall framework of extended conjugation, of some conjugated sub-unit which pursues its own semi-independent path. Here the self-cancelling effect of the units indicated by dashes is to leave the tautomeric balance very much as if neither substituent were there. It is a situation that will constantly recur in this and the following sections.

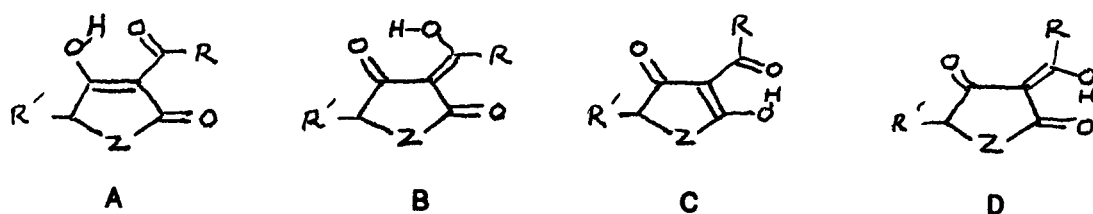
#### A.6.4 Extended Conjugation in 5-Membered Rings

We consider alicyclics first. Cyclopentane-1,3-dione **286** is stated<sup>17</sup> to be 100% enolised in the solid state, water, and most other solvents, so evidently more so than for dimedone; in the preceding section we suggest one possible reason for this. However, **287** is only 1.6% enolised in water<sup>17</sup> and the probable reason for this lies in the anti-aromaticity of **287b** (*cf.* section A.4.9). Similarly and perhaps for the same reason, (**56**,  $R = H$ ) is only about 1% enolised in water<sup>17</sup> with **56a** dominant even in DMSO.<sup>75</sup> There are parallels here with its isomer **114** (section A.2.5).

Tetronic acid **106** (or **288**,  $Z = O$ ) exists largely as **288a** in  $CCl_4$  but as **288b** in  $CHCl_3$ ; <sup>111</sup> given  $\log K_E$  -1.3 for dimedone in  $CHCl_3$  but +1.3 in water, <sup>60</sup> essentially complete enolisation in water may safely be assumed. An estimate based on these data and those of Table 131 (Appendix 2) predicts  $\log K_E \geq 2.5$ . The same is true in EtOH and DMSO for (**288**,  $Z = S$ ) <sup>111</sup> and, again, the enol should predominate in water. However, tetramic acids (**288**,  $Z = NR$ ) give a mixture of tautomers in DMSO but **288a** alone in  $CHCl_3$ , <sup>46b</sup> so the position for water is far from clear. Given  $\sigma_R^-$  0.31 for  $CO_2Et$  but 0.23 for  $CONH_2$  (Table 2) it is altogether possible that ‘resonance pull’ will operate less in the tetramic than the tetronic acids (though *cf.* the chelated analogues of the next section). Ascorbic acid **289** is a member of the latter class and its structure in solution is as shown. <sup>213</sup> The pyrazolonedione **290** exists as such but its dimer as **291**, <sup>2z</sup> so given the rather poor geometries of the hydrogen bonds in **291**, it seems likely that little difference in energy exists between the tautomers (*cf.* **308**, section A.6.5). This contrasts with the situation for barbituric acid (section A.6.3) which as a diimide might have been expected to enolise more readily than **290**, a diamide, but there is no quantitative evidence to decide this issue.

#### A.6.5 C-Substitution in Conjugated 5-Membered Rings

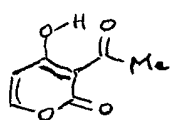
The position as to tautomeric balance in 3-acyltetronic acids and related compounds is confusing and confused. All investigators agree that the unenolised form is absent, and we may assume that this will be true for water, but that leaves four possible enols **292A-D** and different groups have provided radically different analyses (Table 25). Through hindered rotation there is no difficulty in using NMR to distinguish the pairs of ‘external tautomers’ **A,B** and **C,D** from one another, but rapid proton exchange inside each pair of ‘internal tautomers’ poses problems on account of time-averaging and only Yamaguchi *et al.* <sup>214</sup> claim to have overcome them. Unfortunately, while the technique they employ is ingenious and not obviously at fault, their results for **295** in the same solvent are entirely at variance with those of Jacobsen *et al.* <sup>215</sup> and, in the series **299** - **301**, substituent changes remote from the active site appear capable of large and inexplicable changes in tautomeric balance. It is particularly disturbing that **292C**, for any  $\pi$ -donor  $Z$  much the least likely tautomer, is assigned from 4 to 62% of the total present.

Table 25. Tautomer Percentages (CDCl<sub>3</sub>) for Compounds 292

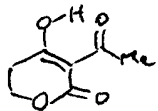
Cpd.	Ref.	Z	R	R'	A	B	C	D
<b>293</b>	216b	O	H	H	68	32	0	0
<b>294</b>	216a	O	Me	H	30	30	0	40
<b>294</b>	214	O	Me	H	19	17	34	30
<b>295</b>	214	O	Me	Me	22	28	21	28
<b>295</b>	215	O	Me	Me	41.5		58.5	
<b>296</b>	215	O	Ph	Me <sub>2</sub>	50		50	
<b>297</b>	215	O	OEt	Me	0	0	100	0
<b>298</b>	214	S	Me	H	20	4	62	14
<b>299</b>	214	NH	Me	H	12	65	4	19
<b>300</b>	214	NH	Me	CH <sub>2</sub> Ph	80	2	18	0
<b>301</b>	214	NH	Me	(CH <sub>2</sub> ) <sub>2</sub> SMe	85	2	17	0
<b>305</b>	217				100	0	0	0

Table 26. Selected <sup>13</sup>C-NMR Data (CDCl<sub>3</sub>, ppm from TMS) for 292-type Compounds

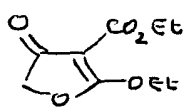
Compound	Ref.	C-2	C-4	<i>exo</i> -C
<b>302</b>	215	161.2	181.21	205.25
<b>303</b>	215	164.45	195.18	201.28
<b>294 A,B</b>	215	175.75	195.64	188.43
<b>294 C,D</b>	215	167.7	200.24	194.46
<b>304</b>	215	182.57	193.75	161.85
<b>297</b>	215	166.33	192.19	166.14
<b>300 A</b>	214	175.07	194.22	185.29
<b>300 C</b>	214	168.66	200.07	189.03
<b>305 (DMSO)</b>	217	166.45	187.57	—



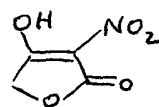
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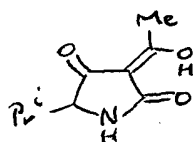
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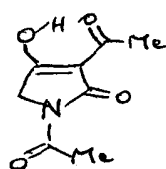
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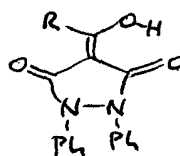
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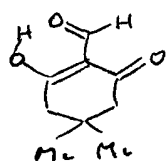
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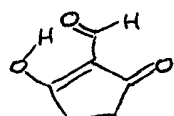
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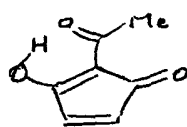
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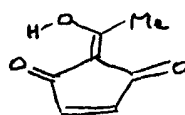
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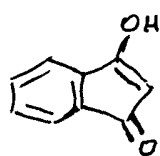
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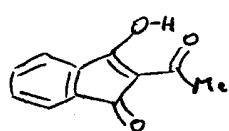
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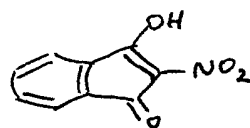
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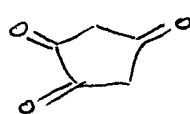
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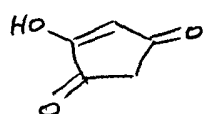
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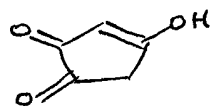
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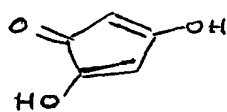
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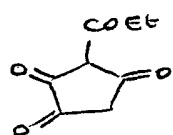
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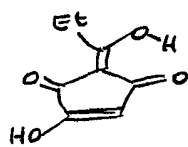
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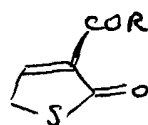
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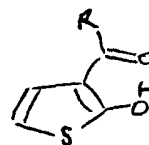
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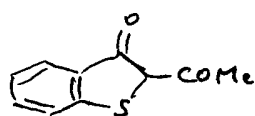
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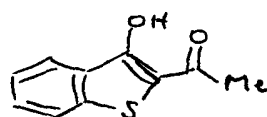
316a



316b



317a



317b

The  $^{13}\text{C}$ -NMR data of Table 26 are of some help here. There is no ambiguity concerning the single tautomer of **302**<sup>215</sup> (*cf.* **273**<sup>209a</sup>) or **303**,<sup>215</sup> which differs from the former at C-4 through aromatisation but very little at C-2 or *exo*-C. One would expect **294A,B** to resemble **303** but it does not and the obvious implication is that **294B** is dominant. Similarly, the C-2 signal of **294C,D** is clearly that of an ester, pointing to the great predominance of **294D**<sup>218a</sup> and not as given by Yamaguchi *et al.*<sup>214</sup> It is entirely reasonable that the switch from a 6-membered ring in **303** to a 5-membered ring in these compounds should favour the *exo*-tautomers **B** and **D**; *cf.* Table 4 and section A.1.2. The assignment of **297** to **297C** by Jacobsen *et al.*<sup>215</sup> is based on a putative  $^{13}\text{C}$ -NMR resemblance to the fixed tautomer **304** but this is highly disputable. In the writers' view the signals for **297** at 166.33 and 166.14 ppm are most plausibly due to two *unenolised* ester groups, pointing to **297A** as overwhelmingly dominant, as for the 3-nitro derivative **305** where this is unambiguous<sup>217</sup> and whose  $^{13}\text{C}$ -NMR data are included in Table 26 for comparison. A C-4 signal at very low field, almost as low as that for unconjugated carbonyl, appears characteristic of compounds in which two electronegative groups are conjugated with ring OH, the corresponding *exo*-C signal being at slightly higher field, as in **294B** and **D**. For similar reasons we re-assign the tetramic acid tautomers **300A** and **300C** to **300B** and **300D** respectively; their close resemblance to **294B** and **294D** will be noted (Table 26). Enolisation of an amide as required by **300C** is even less likely than that of an ester.

Two crystal structures help to elucidate this question. The acyltetramic acid **306** exists in the **D**-form shown,<sup>218</sup> in  $\text{CHCl}_3$  solution as well as in the solid state; the authors point to the superior proton acceptor ability of amide carbonyl as the explanation. In **307**, where this is lost through *N*-acylation, the more familiar **A**-form results.<sup>219</sup> The tautomeric form of **290** is retained in its 4-acyl derivatives **308**<sup>2z</sup> and is not lost as in **291** where there is no opportunity for *exo*-enolisation. These results throw further doubt on the analyses of Yamaguchi *et al.*<sup>214</sup> on the tetramic acids **299** - **301** (Table 25) and, by implication, the remainder.

While it is impossible to be certain, we therefore believe that, while the **A**-form is important (and exclusive where the 3-substituent does not enolise), there is a strong tendency for *exo*-enolisation to take place and possibly to predominate. As noted above this is the expected behaviour for a 5-membered ring and it fails only for  $\text{R} = \text{H}$  (**293**), presumably because *exo*-C=C then lacks

stabilisation by an alkyl group. Since this prediction is contrary to what is found for simple  $\beta$ -ketoaldehydes (section A.6.7) there must be some special reason for it, and this could lie in appreciable non-planarity for 3-CHO, as has been demonstrated for the nitro-group in **305**.<sup>217</sup> Formyl is more electronegative than most other forms of carbonyl<sup>39,190</sup> so may well be a poorer proton acceptor, though nothing is known. There is ample evidence from similar systems that a second acyl acceptor group contributes relatively little to overall conjugation; in aminodienones for example, one carbonyl or the other is usually to some extent twisted out of plane.<sup>220</sup> Any such tendency is likely to be exaggerated in strong hydrogen bonding solvents so that, in water, it is quite possible that tautomer **A** will be relatively much more favoured than it is in  $\text{CHCl}_3$ . Steric hindrance *per se* does not appear to matter; Jacobsen *et al.*<sup>215</sup> find only trivial changes in tautomeric balance to accompany quite wide variation in the size of R. But once again, we draw attention to the acidity of these compounds. Those studied by Yamaguchi *et al.*<sup>214</sup> have (in aqueous methanol)  $\text{p}K_{\text{a}}$  values in the range 0.5 - 2.94 and *gem*-tricarbonyl compounds generally may be expected to possess acidities of this order.

There has been limited work on acyl derivatives of cyclic  $\beta$ -diketones. Like **293**, the 2-formyl derivatives **309** and **310** exist in  $\text{CHCl}_3$  as shown.<sup>221</sup> 2-Acylation of **287** whose enol is anti-aromatic (section A.6.4) gives 100% enolisation and a mixture of **311a** and **311b**.<sup>222</sup> However 2-acetylation of **56**, where **56b** is also anti-aromatic, gives 100% of **312** (in  $\text{CS}_2$ )<sup>222</sup> so any *endo-exo* preference must be slight. The related triketone **313a** gives the enol **313b**, not its isomer **313c** in which (as in **313a** itself) the lone pair clash would be severe or **313d** which would be anti-aromatic.<sup>223</sup> Its 3-acyl derivative **314a** avoids both problems by *exo*-enolisation to **314b** (*cf.* **311b**).<sup>223</sup> It seems probable that all these compounds will be fully enolised in all solvents, including water, but once again we draw attention to their high acidity.

Among electronegative substituents other than carbonyl capable of forming an intramolecular hydrogen bond, only nitro seems to have been investigated, and that not much. There are no quantitative data for **305**<sup>217</sup> but **315** possesses  $K_{\text{E}} \sim 50$  in water;<sup>191</sup> set against *ca.* 1% for its parent compound,<sup>17</sup> this implies an enhancement in  $K_{\text{E}}$  approaching  $10^4$ . This is about half the effect found for that of one carbonyl on the other in dimedone (Table 22) and, judging from the results of Lammertsma and Bharatam,<sup>148</sup> probably more than may be expected for a third carbonyl group as in **312** (for

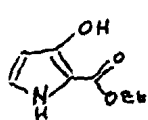
which no  $K_E$  value is available). It has been noted earlier (section A.6.1) that, as indicated by calculation,<sup>148</sup> the nitro-group is highly resistant to enolisation and does not enolise when any possible alternative is present.

#### A.6.6 C-Acylation in Aromatic 5-Membered Rings

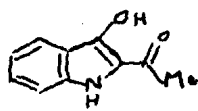
These compounds differ from those of the preceding section in two respects. Firstly,  $\beta$ -dicarbonyl not  $\beta$ -tricarbonyl compounds are formed on acylation, so the bias towards enolisation is correspondingly less. To counterbalance this, the parent compounds already have a built-in tendency to enolise since an aromatic structure will then result. However this is only the case for *endo*-enolisation, so that the bias towards *exo*-enols noted elsewhere for 5-membered rings is absent. The balance between these factors determines not only the presence or absence of enolisation but the form it takes, as will emerge.

Nearly all the available information is qualitative and none of it concerns aqueous solution, in which the tendency to give chelated enols is much less than in even the most polar organic solvent (Appendix 2). Much of it may therefore be misleading in the present context; for example, while **316**<sup>2aa</sup> and **317**<sup>2bb</sup> both give the **b**-forms in  $\text{CHCl}_3$  and  $\text{CCl}_4$ , it is uncertain whether **316a** or **316b** would be found in water. These compounds belong to the 2-oxo and 3-oxo series respectively, the latter being much more susceptible to enolisation (section A.2.7); data for some parent 3-oxoheterocycles in water appear in Table 13. Here values of  $\log K_E$  range from *ca* 0.5 to -4, and even the latter is probably capable of dominant enol formation in water on 2-acylation. In section C.10 we derive a factor  $\Delta \log K_E$  *ca.* 6.7 which we believe should quantify this effect (it may be greater for  $\text{CO}_2\text{R}$  than for  $\text{COR}$ ) in both the 3-oxo and the 2-oxo series. We consider these series in turn.

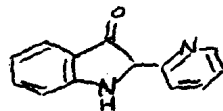
All available evidence is consistent with the proposition that 2-acyl-3-oxoheterocycles invariably exist as the enol. Straightforward examples include **318** and **319**, which give the **b**-form in the solid state,<sup>2cc</sup> while **332** and **334** behave likewise in chlorinated solvents.<sup>2dd</sup> Less straightforwardly, enolisation in **320**<sup>2m</sup> and **333**<sup>2dd</sup> is induced by a proton acceptor heterocycle; the former case is curious in that, while it exists as **320b** in  $\text{CHCl}_3$  and the solid state, some **320a** is found in dioxane. In **336**, **336b** is found for  $\text{R} = \text{H}$  in nonpolar solvents,<sup>224</sup> as is **332b**, but a switch occurs to **336c** when 4-OH is present. This surprising result may reflect either or both of (a) the resistance



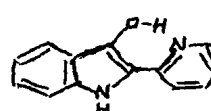
318b



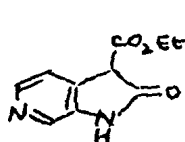
319b



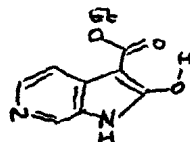
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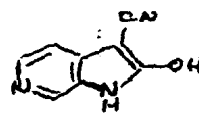
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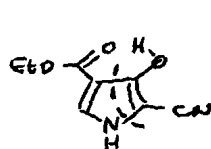
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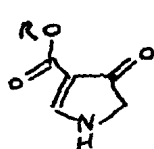
321b



322b



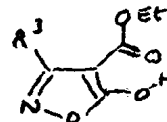
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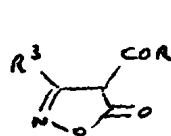
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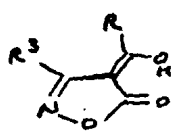
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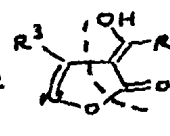
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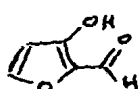
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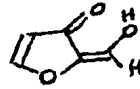
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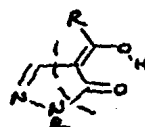
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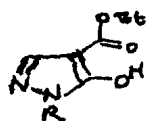
328a



328b



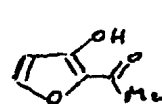
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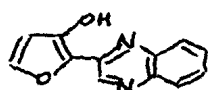
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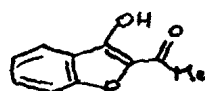
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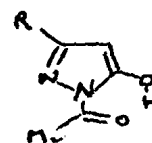
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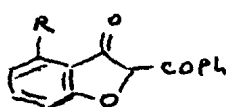
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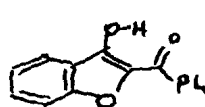
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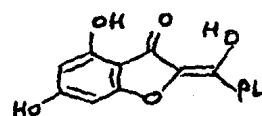
335b



336a



336b



336c

to enolisation of 3-C=O, now reinforced by hydrogen bonding, (b) stabilisation of C=C in **336c** by phenyl. Except for R = OH, however, it is unlikely that **336a** will be dominant in water even here. Formation of an intramolecular hydrogen bond is not always necessary for enolisation to occur; while insertion of CN in **324** gives the enol **323b**,<sup>2cc</sup> **324** itself,<sup>2cc</sup> and even **325** in CCl<sub>4</sub>,<sup>2dd</sup> do not enolise. Here, with a second acyl group reinforcing it, 'push-pull' conjugation as already present in the parent 3-oxoheterocycle appears as superior to 'aromaticity' in providing resonance stabilisation (further such examples appear in section A.10). Calculation<sup>46</sup> (B3LYP/6-31G\*) shows **328a** to be more stable than **328b** by -  $\Delta H$  4.2 kcal mol<sup>-1</sup>, a surprisingly small margin which emphasises how little aromaticity **328a** has to lose (*cf.* Table 12 for the resonance energies of parent heterocycles).

While no  $K_E$  value for a simple 2-oxoheterocycle is known, enol forms have never been detected (section A.2.7) and they are presumed to form much less readily. In section C.10 we derive certain estimates which, if valid, confirm this picture. Nevertheless, enols can be generated on 3-substitution. Given an estimated  $K_E \sim 10^{-6}$  for 2-indolone (section C.10), 3-acylation ( $\Delta \log K_E$  6.7), added to the electronegativity of the extra aza-nitrogen, will reasonably account for **321b** as found in KBr<sup>225,226</sup> and, very likely, in water, whereas the parallel formation of **322b** is more probably explained by the use of DMSO as solvent (*cf.* Appendix 2). Most reported examples, however, have concerned 5-aza derivatives for which enolisation is much more favourable; for (**326**, R<sup>3</sup> = Me)<sup>2ee</sup>  $\log K_E$  -1.2 is found in water, and the related pyrazolones behave similarly (section C.15). Nevertheless **329b**<sup>2ff</sup> and especially **327c**<sup>227</sup> as dominant structures, for compounds in which simple acyl replaces the unenolisable ester group, are quite surprising; here the *exo*-enolisation often found in alicyclic 5-membered rings (sections A.6.4 and A.6.5), but normally suppressed on aromatisation, appears to reassert itself. Plausibly this derives from a much reduced degree of aromaticity in the parent heterocycles, possibly induced by aza-substitution contiguous to a  $\pi$ -donor atom. This is quite different from the situation which results on their 1,3-disubstitution *e.g.* in imidazole (Table 12); here, instead of exerting their full effects, the  $\pi$ -donor characteristics of NR, O and (presumably) S are largely suppressed. Additionally, in cases such as **327** and **323** it is as if the molecule had split into two independent conjugated systems (*vide* the structures as written), a feature that frequently recurs *e.g.* in section A.10 (and *cf.* section A.6.3). However **330**<sup>2ff</sup> and **331**<sup>2cc</sup> behave more normally, enolising in such a way as to preserve ester conjugation. N-Acylation is another way of reducing  $\pi$ -donor properties and the enolisation of **335** to give **335b**<sup>2ff</sup> is therefore to be expected.

### A.6.7 Open-Chain $\beta$ -Dicarbonyl Compounds

These compounds, exemplified by acetylacetone, represent the commonest type of  $\beta$ -dicarbonyl structure, the most worked on, and in consequence, that category which tends to be regarded as the norm. What this perception hides is their atypical behaviour in water. Table 27 lists the correction factors ( $\Delta \log K_E$ ) required to translate  $K_E$  for a number of common organic solvents to water for acetylacetone itself.<sup>197</sup> All corrections are negative, some by very long margins; eqn. (ix) will make the point clear (see Appendix 2, and *cf.* ref. 196). Hence it cannot be assumed that the extensive and painstaking work on  $\beta$ -dicarbonyl tautomerism in organic solvents has any necessary relevance to aqueous solution. In fact, it may be stated that most open-chain  $\beta$ -dicarbonyl compounds probably exist largely as such in water, though there are exceptions, as will be seen. Some remarks on di ketone conformation are therefore in order. As Toullec<sup>17</sup> points out, **337a** is destabilised by polar interactions and probably the least likely, even in water, whereas **337b** and **337c** are subject to steric interactions so probably twisted. Some variant on **337b** may usually represent the best compromise, though one that may vary with solvent. We have adduced these uncertainties (section A.6.1) as our essential reason for not subjecting **261** (Scheme 10) to the same detailed computational analysis as **260**.

When however the  $\beta$ -dicarbonyl compound is asymmetrical ( $R^1 \neq R^2$  in Scheme 10), another question enters. Since both chelate forms **261B** and **261C** are locked away from the solvent, it is improbable that  $K_T$  will be much affected by a change of phase; indeed Floris<sup>223</sup> states this as experimental fact. Hence information on this point obtained even from very nonpolar solvents is likely to translate quite well to water and we shall examine this aspect first.

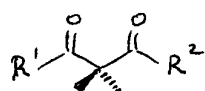
**Table 27. Correction Factors ( $\Delta \log K_E$ ) from Organic Solvents to Water for Acetylacetone (57,  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ )<sup>a</sup>**

Solvent	$\Delta \log K_E$	Solvent	$\Delta \log K_E$	Solvent	$\Delta \log K_E$
DMSO	- 0.71	EtOH	- 1.29	CCl <sub>4</sub>	-2.07
MeCN	- 0.88	Benzene	-1.40 <sup>b</sup>	C <sub>6</sub> H <sub>12</sub>	-2.34
CH <sub>2</sub> Cl <sub>2</sub>	- 0.94 <sup>b</sup>	Dioxan	-1.50	Alkane <sup>c</sup>	-2.51 <sup>b</sup>
MeOH	- 1.16	CHCl <sub>3</sub>	-1.51	Gas Phase	-4.42 <sup>b</sup>

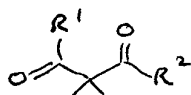
<sup>a</sup> Ref. 197. <sup>b</sup> Estimated using eqn. (ix). <sup>c</sup> Any non-cyclic.

In simple diketones of type **338**, the effect on  $K_T$  of varying  $R^1$  and  $R^2$  appears to be minimal. For  $R^1 = CF_3$ ,  $R^2 = Me$  for example,  $K_T \sim 2.5$  in several nonpolar solvents, whereas for  $R^1 = Ph$ ,  $R^2 = Me$  and  $R^1 = Ph$ ,  $R^2 = CF_3$  these values are close to 1.5 and 0.9 respectively.<sup>223</sup> Effectively this means that if enolisation possesses any biological significance, which it might at a nonpolar receptor, the energy barrier between the rival enols will be small. One probable reason for this insensitivity relates to the strength of the intramolecular hydrogen bond. If for example  $CF_3$  replaces  $CH_3$  at  $R^1$  in **338**, this should increase the proton donor strength of OH in **338b** while diminishing the acceptor ability of C=O in **338a**, hence on this account **338b** should be favoured. However, through-conjugation should lead to the *same* effect on OH in **338a** and C=O in **338b**, so leading to the near-cancellation observed. Consistently, for **339** in  $CHCl_3$   $\log K_T = 0.20$  for  $R = H$ , rising to 0.34 for  $R = NO_2$  and falling to 0.11 for  $R = OMe$ ,<sup>228</sup> an effect in the same direction but a small one. No data for any of these compounds have been reported in water, but it is unlikely that overall enolisation will differ much from acetylacetone's 13% though electronegative substituents at  $R^1$  or  $R^2$  may increase it slightly. The same goes for the extended triketone **340**, which in  $CHCl_3$  gives 7, 67 and 26% of **340a**, **340b** and **340c** respectively when  $R = Me$ , and 2, 37 and 61% when  $R = Ph$ .<sup>223</sup> There may be some use for this information in the context of nonpolar receptors, but again, **340a** may be expected to dominate in water.

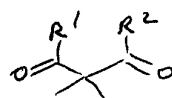
Some evidence on the relative importance of substituent electronegativity and the strength of the intramolecular hydrogen bond in determining the extent of enolisation comes from compound **341**. Data are known for several organic solvents from which, by extrapolation from Table 27 (see Appendix 2), we may roughly estimate  $\log K_E$  in water as -2.3. This is enormously less than any plausible value for  $PhCOCH_2COMe$  and, given that COMe is a much stronger proton acceptor than  $NO_2$ ,<sup>72</sup> settles the issue in favour of hydrogen bonding. The reverse conclusion might readily have been based on the calculations (for  $HCOCH_2NO_2$ ) of Lammertsma and Bharatam<sup>148</sup> (Table 21) but the present results apply to water and an important *qualitative* shift from the gas phase for chelates may be indicated.



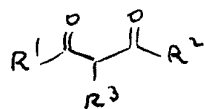
337a



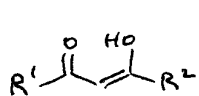
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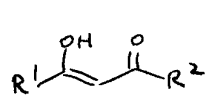
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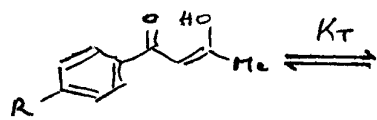
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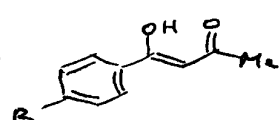
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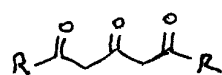
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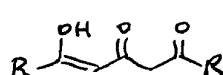
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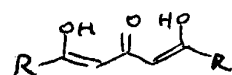
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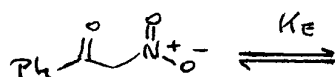
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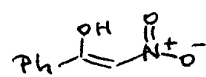
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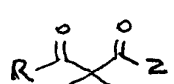
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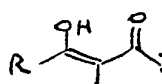
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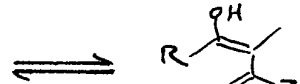
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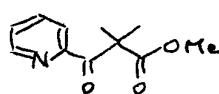
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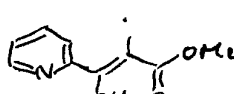
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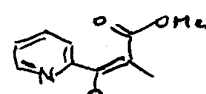
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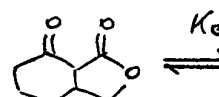
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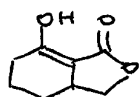
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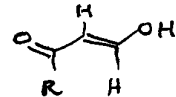
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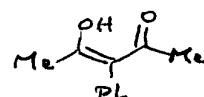
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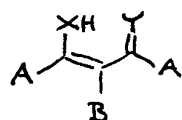
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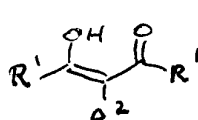
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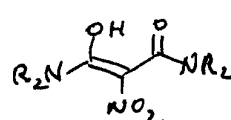
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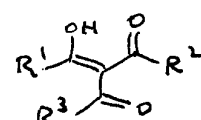
347



348



349



350

When carbonyl forms part of a unit that is conjugated in its own right, *e.g.* ester or amide, enolisation becomes extremely disfavoured (section A.2.4) and only the alternative enol is formed. (Exceptions occur when aromatisation can result: see examples in sections A.1.3, A.2.5, A.2.7, A.2.8 and *passim* from A.2.6). Beak<sup>60</sup> studied the enolisation of ethyl acetoacetate (**342**, R = Me, Z = OEt) in a number of solvents; his (slightly) amended LSER equation appears as (xi). Later, Bunting and Kanter<sup>229</sup> examined a number of  $\beta$ -ketoesters and  $\beta$ -ketoamides in water. For compounds **342** in which R = Me or Ph and Z = OR or NR<sub>2</sub>, log  $K_E$  is almost a constant:  $-1.07 \pm 0.06$  ( $n = 5$ ). For R = pyridinyl,  $K_E$  is larger; for **343** log  $K_E = -0.07$ , with the values for 3- and 4-pyridinyl in the range  $-0.8$  to  $-0.4$ . Given the behaviour of pyridinyl as shown for example in compounds of type RCOCH<sub>2</sub>Ph (Table 9) its effect here is quite small by comparison and helps to establish the point made above that, typically, varying R<sup>1</sup> and R<sup>2</sup> in structure **57** does not greatly influence the nature or extent of enolisation.

$$\log K_E = 0.11(0.10) - 1.33(0.20) \pi^* - 0.42(0.14) \alpha \quad (\text{xi})$$

$$(n = 14 \quad r^2 = 0.82 \quad s = 0.18 \quad F = 25)$$

$$\log K_E = 0.34(0.10) - 1.78(0.16) \pi^* - 0.30(0.13) \beta \quad (\text{xii})$$

$$(n = 13 \quad r^2 = 0.939 \quad s = 0.13 \quad F = 77)$$

Nevertheless, detailed consideration of these results reveals a feature that appears to have been overlooked. The  $\beta$ -diketone LSER eqn. (ix) and the  $\beta$ -ketoester eqn. (xi) are very similar in form, their chief difference lying in the intercept term which reveals the  $\beta$ -diketone as intrinsically much more enolised. This is reflected in the  $K_E$  values *calculated* for water but not in those observed (Table 28). For (**342**, R = Me, Z = OEt), the discrepancy lies

**Table 28. Observed and Calculated Aqueous log  $K_E$  Values for  $\beta$ -Dicarbonyl Compounds**

	log $K_E$ (obs)	log $K_E$ (calc)	Eqn.
( <b>57</b> , R <sup>1</sup> = R <sup>2</sup> = Me, R <sup>3</sup> = H)	- 0.83 <sup>a,b</sup>	- 0.43	(ix)
( <b>342</b> , R = Me, Z = OEt)	- 1.06 <sup>c,d</sup>	- 1.83	(xi)
( <b>344</b> )	- 1.62 <sup>e</sup>	- 1.72	(xii)

<sup>a</sup> Ref. 197. <sup>b</sup> Other values: - 0.64, - 0.74, - 0.77, - 0.80. <sup>c</sup> Ref. 229. <sup>d</sup> Other value: - 1.15 (ref.60). <sup>e</sup> Ref. 60.

far beyond the limits of error: much more enol is formed than should be. The only reasonable explanation must be that, in water if nowhere else, the chelate is substantially broken to give extended enols of type **342c** in which bonding to solvent has replaced the chelate bond. (The special effect of 2-pyridinyl in raising  $K_E$  may be due to additional species such as **343c**). By contrast, agreement between the observed aqueous value for the rigid  $\beta$ -ketoester **344**<sup>60</sup> and that calculated is excellent; here such complications are necessarily absent. We believe that the ability of water to break chelates that survive in other polar solvents is a common if barely recognised phenomenon. It is more difficult to pinpoint the cause. It may simply be that the enols of  $\beta$ -diketones form stronger intramolecular bonds; ketones are (marginally) stronger proton acceptors than esters.<sup>72</sup> On the other hand, it may be connected with hydrophobicity. Perhaps the hydrophobic surface that envelopes the polar centre of the chelate in  $\beta$ -diketones helps to compress this and prevent solvent from breaking into it, whereas when ketones are replaced by esters or amides, this feature is lost. It is known<sup>230</sup> that the completely enolised compounds (**345**, R = H or Me), which possess a minimal hydrophobic surface, exist in water as the extended enol shown.  $\beta$ -Diketone *anions* exist<sup>206</sup> in the conformation obtained by deprotonating **345**.

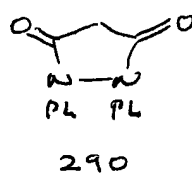
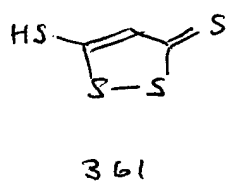
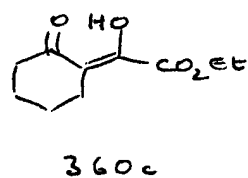
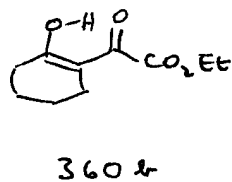
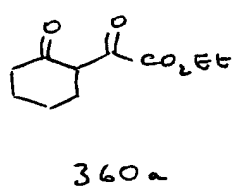
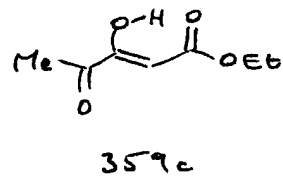
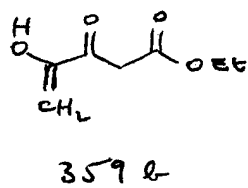
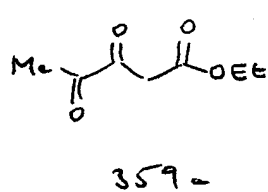
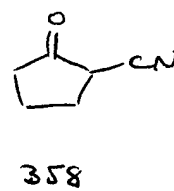
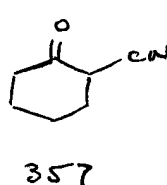
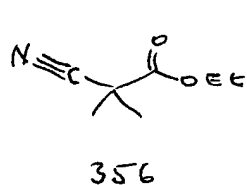
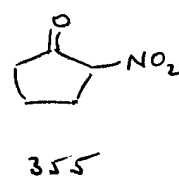
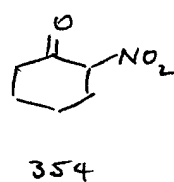
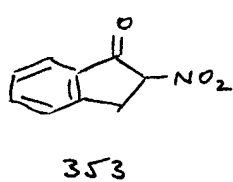
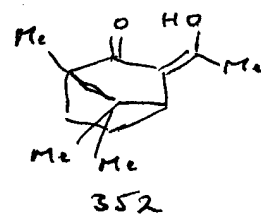
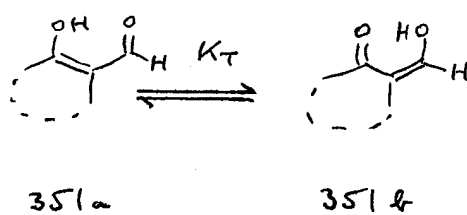
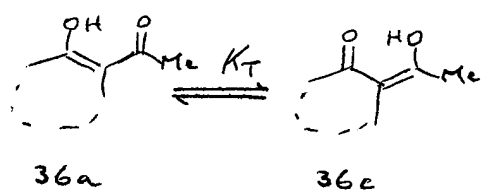
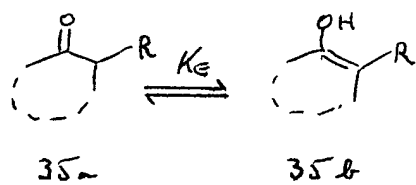
As previously noted (section A.1.4), almost any substituent  $R^3$  in **57** will tend to promote enolisation, up to the point that steric compression becomes excessive and leads to steric crowding.<sup>63</sup> For example, **346** is fully enolised in all solvents including water,<sup>223</sup> a result that may be interpreted indifferently as steric compression or the stabilisation by Ph of a carbon double bond. Haddon<sup>97</sup> has considered for **347** the effect of structure on the strength of the intramolecular hydrogen bond. According to his calculations this is maximised by increasing the energy gap between X and Y, which is said to require A and B to be electron donors and acceptors respectively. As applied to **348** this leads to predicted optimal structures, such as **349**, which are unlikely to enolise appreciably at all, but other guidelines may be more useful. For (**348**,  $R^1 = H$ ) the predicted order in bond strength is  $R^2 = NO_2$ , CHO > CN > H > NR<sub>2</sub> and there are indications of this order elsewhere. Where  $R^1$  is bland this will probably be the enolisation order as well so may prove valuable. To judge by the behaviour of tricarbonyl compounds, however, these effects may be quite modest. Triacetylmethane (**350**,  $R^1 = R^2 = R^3 = Me$ ) is 57% enolised in water,<sup>17</sup> but this represents only  $\Delta \log K_E \sim 1$  relative to acetylacetone. (This compound is also, of course, a strong acid). When  $R^3$  is Ph or OEt, enolisation is complete;<sup>17</sup> again, steric compression is probably the cause.

A little is known concerning directional preferences. Forsén and Nilsson,<sup>231</sup> working with asymmetrical  $\beta$ -triketones in  $\text{CCl}_4$ , find partitioning in one case to give 80% of (**350**,  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{H}$ ), *i.e.* CHO is preferentially excluded from the chelate. In another case involving CHO, COMe and  $\text{CO}_2\text{Et}$ , only 10% contains the latter in the chelate. These place the order of preference for chelation firmly in the order  $\text{COMe} > \text{CHO} \gg \text{CO}_2\text{Et}$ , which may have some relevance to the different behaviour in water of  $\beta$ -diketones and  $\beta$ -ketoesters as discussed above.

#### A.6.8 $\beta$ -Acylation of Cyclic Ketones

These compounds are basically similar to those of the preceding section but have been separated out because of features peculiar to cyclic structures, chiefly the effects of ring size. Data on this have been presented earlier (section A.1.2) and are listed in Table 4 for (**35**,  $\text{R} = \text{COMe}$  and  $\text{CO}_2\text{Et}$ ) and **36** in water. Garbisch<sup>232</sup> has studied  $K_T$  for **351** in  $\text{CCl}_4$  and gives data for ring sizes ranging from 5 to 12 which show the familiar alternant effect and in which  $\Delta \log K_T$  1.05 for switching from a 6- to a 5-membered ring is close to that found, 1.16, for the equivalent process involving **36** in water.<sup>17</sup> We have suggested above that  $K_T$  as defined by structure **261** (start of A.6) should be little affected by solvent. Seven- and eight-membered rings give intermediate results.<sup>232</sup> It is perhaps not surprising that, in  $\text{CCl}_4$ , the diketotautomer appears to be absent. However, none of these compounds is likely to be predominantly enolic in water; for the 6- and 5-membered compounds of type **36**, overall enolic content is 29 and 15% respectively<sup>17</sup> (*cf.* 13% for acetylacetone<sup>197</sup>). However the much more crowded **352**, an acetyl derivative of camphor, is fully enolised in water.<sup>17</sup> As a general rule, *exo*-enolisation is favoured (to the extent it happens at all) in 5-membered rings such as **352** but *endo*-enolisation in 6-membered rings and mostly elsewhere (section A.1.2).

The fused-ring  $\beta$ -diketones **39** - **41** are described in section A.1.2. If '100% enolisation' for **39** in  $\text{MeOH}$ <sup>17</sup> can be translated as  $\log K_E \geq 1.5$  and if this compound follows the acetylacetone eqn. (ix),  $\log K_E \geq 0.3$  in water results. If **40** follows eqn. (xii) through its similar geometry then  $\log K_E$  0.6 in  $\text{MeOH}$  translates to  $\log K_E \sim 0$  in water. Both represent  $\Delta \log K_E \geq 1$  relative to acetylacetone or  $\geq 0.5$  relative to the *endo*-enolisation of 2-acetylcyclohexanone. These are modest effects that presumably result from the 'entropic encouragement' of greater molecular rigidity. Without a good LSER model for **41** one cannot translate 1.4% enol in  $\text{MeOH}$  through to water



but since the solvent differential which is less for **40** than for **39** is unlikely to rise again for **41**,  $K_E$  must be much less and a value of  $\log K_E$  *ca.* -2.5 could be a reasonable estimate. As noted above (section A.1.2) about  $\Delta \log K_E$  -0.6 of this can be attributed to its disfavoured *endo*-C=C unit but the rest presumably results from non-optimal bond angles and distances in the intramolecular hydrogen bond. As expected therefore, large departures from the optimal geometry are not tolerated. In terms of ring fusion, enolisation is favoured in the order 6,6 > 6,5  $\gg$  5,5 with the position of unconstrained chelates lying between the last two but probably closer to **40** than to **41**. It is possible that this rule will be general, applying to any compound of type **261**.

### A.6.9 Other Electronegative $\beta$ -Substituents

Nearly all the fragmentary data on these come from cyclic compounds, so are conveniently slotted in here. All concern nitro- or cyano-substitution. For **353**,  $\log K_E = -0.37$  in EtOH;<sup>191</sup> given -1.25 for PhCOCH<sub>2</sub>NO<sub>2</sub> **341** in this solvent (section A.6.7) then parallel behaviour would give  $\log K_E$  *ca.* -1.7 in water. A similar parallelism between **353** and **354**<sup>191</sup> would result in  $\log K_E$  *ca.* -1.3 for the latter. It is stated by Toullec<sup>17</sup> that only the ketone form of **354** is visible in water and other polar solvents, with **355** still less prone to enolisation. Hence the above estimates are probably maximum values and that for **354** compares with  $\log K_E$  -0.49 for *endo*-enolisation in the equivalent 2-acetyl derivative (Table 4). Probably for NO<sub>2</sub> in general,  $\Delta \log K_E$  lies in the range -1 to -2 relative to COR. Nevertheless this still represents a factor of  $> 10^5$  relative to the parent ketone, compared with  $> 10^7$  for acyl substitution and our estimate above (section A.6.4) of up to  $10^4$  for the effect of 2-NO<sub>2</sub> in the extended  $\beta$ -diketone **315** where, as an extra electronegative substituent, its effect would be expected to be less.

Since CN cannot form an intramolecular hydrogen bond one might expect still lower  $K_E$  values for nitrile substitution. The value of  $\log K_E$  -9.6 for **356** in water<sup>233</sup> compares with -8.13 for malonic acid<sup>191</sup> and our tentative estimate (section A.6.2) of -7.4 for diethyl malonate (**264**, R = OEt), *i.e.*  $\Delta \log K_E$  *ca.* -2 relative to an acyl group. This is similar to, but perhaps a little more negative than, the ranking order suggested for NO<sub>2</sub> above. Toullec<sup>17</sup> states that **357** is 35% enolised in dioxane but **358** gives no enol at all; an estimate based on the difference in  $K_E$  between the parent ketones (Table 8) would give  $\log K_E$  -1.8 for the latter. No other relevant data appear to exist.

### A.6.10 Potential Additivity in Unconjugated $\beta$ -Dicarbonyl Compounds

It would be valuable to know how far the various factors we have discussed are additive. No hard facts are available, but qualitative observations exist for **359** and **360** and it is possible to extrapolate to quantitative estimates that appear plausible. Rejecting ester enolisation *a priori*, each gives two possible enols. Toullec<sup>17</sup> states that **359** is fully enolised in  $\text{CHCl}_3$  to give **359c**. The  $\beta$ -ketoester  $\text{MeCOCH}_2\text{CO}_2\text{Et}$  enolises in this sense with  $\log K_E$  *ca.* -1.1 in water, but this result must be modified through replacement of Me by MeCO. For MeCOCOMe we predict  $\Delta \log K_E$  *ca.* 3.1 relative to MeCOMe (section A.2.5) so, adding these estimates together, we reach  $K_E \sim 10^2$  in favour of **359c** in water. For **359b** we start from our estimate of  $\log K_E$  -5.2 for MeCOCOMe in water; though very tentative this is enough to rule out **359b** as a serious contender. We conclude that **359c** should predominate in all solvents. In the case of **360**, **360b** represents the normal direction for enolisation but Floris<sup>223</sup> states **360c** to be the preferred form in all solvents. For **360b**, we start from  $\log K_E$  -0.5 for *endo*-enolisation in 2-acetylcyclohexanone which will be somewhat increased, but probably not outstandingly, by the electronegativity of  $\text{CO}_2\text{Et}$ . For **360c** we start from the *exo*-enol **36c**,  $\log K_E$  -0.6 (Table 4), and estimate the result of replacing -Me by  $-\text{CO}_2\text{Et}$ . This has a likely value (Table 9) of  $\Delta \log K_E > 4.2$  which enables us to estimate  $K_E > 10^3$  for water, in agreement at least qualitatively with Floris.<sup>223</sup> More comparisons would be welcome but at least these appear to be successful so far as they go.

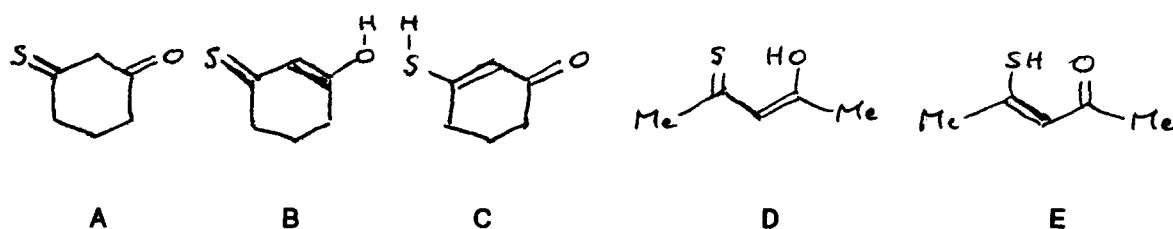
### A.7 $\beta$ -Dithiones

It will be seen from Table 22 that, while an extended  $\beta$ -diketone (**260**,  $\text{X} = \text{Y} = \text{O}$ ) is expected to be enthalpically the favoured species, for the corresponding  $\beta$ -dithione this preference is reversed: enolisation is expected to be dominant or complete. This is borne out by the only such example we have been able to find, **361**<sup>2gg</sup>, whose enolic form contrasts with that of the diamide **290**<sup>2z</sup> (section A.6.4). Any such compound should be very acidic. Parallel behaviour of chelated  $\beta$ -dithiones with the equivalent  $\beta$ -diketones would lead to the same result.

## A.8 $\beta$ -Thionoketones and Related Compounds

Since thioketones are much more readily enolised than ketones, in simple cases by *ca.*  $10^6$  (section A.3.1), it might be imagined that  $\beta$ -thionoketones would enolise to give exclusively the  $\beta$ -mercaptoenone tautomer. This is not the case. Before reviewing the rather sparse experimental evidence, we shall present the results of calculations which throw some light on this matter.

### A.8.1 The Energetics of Enolisation and Thioenolisation



**Table 29.** Energetics ( $\Delta H$ , kJ mol<sup>-1</sup>) for Structures A – E <sup>a</sup>

	<b>A <math>\rightarrow</math> B</b>		<b>A <math>\rightarrow</math> C</b>		<b>B <math>\rightarrow</math> C</b>		<b>D <math>\rightarrow</math> E</b>	
	$\Delta H$	'log $K_E$ '	$\Delta H$	'log $K_E$ '	$\Delta H$	'log $K_E$ '	$\Delta H$	' $\Delta$ log $K_E$ '
<i>b</i>	7.13	- 1.2	- 10.093	1.8	- 17.223	3.0	1.014	- 0.2
<i>c</i>	14.188	- 2.5	2.926	- 0.5	- 11.262	2.0	5.396	- 1.0
<i>d</i>	- 4.12	0.7	- 8.851	1.6	- 4.731	0.9	15.894	- 2.8
	<b>C=O <math>\rightarrow</math> OH <sup>e</sup></b>		<b>C=S <math>\rightarrow</math> SH <sup>f</sup></b>		<b><math>\Delta</math> C=O / C=S <sup>g</sup></b>		<b>(D <math>\rightarrow</math> E) – (B <math>\rightarrow</math> C) <sup>h</sup></b>	
<i>b</i>	64.438	- 11.3	26.667	- 4.7	- 37.771	6.6	18.227	- 3.2
<i>c</i>	65.941	- 11.6	37.968	- 6.6	- 28.373	5.0	16.658	- 3.0
<i>d</i>	59.408	- 10.4	31.774	- 5.6	- 27.634	4.8	20.625	- 3.7

<sup>a</sup> The quantities 'log  $K_E$ ' and ' $\Delta$  log  $K_E$ ' are hypothetical values for the circumstance that  $\Delta G = \Delta H$  (see the text). <sup>b</sup> RHF/6-31G\*\*//RHF/61-3G\*\*. <sup>c</sup> MP2/6-31G\*\*//MP2/6-31G\*\*.

<sup>d</sup> B3LYP/6-31G\*\*//B3LYP/6-31G\*\*. <sup>e</sup> Energetics for the enolisation of acetone (Table 22).

<sup>f</sup> Energetics for the enolisation of thioacetone (Table 22). <sup>g</sup> Energetics for the enolisation of thioacetone relative to that of acetone. <sup>h</sup> Energetics for the process  $K_T = [\mathbf{E}] / [\mathbf{D}]$  relative to that for the process  $K_T = [\mathbf{C}] / [\mathbf{B}]$ .

Table 29 presents data for the structures **A** - **E**, alongside those for the ‘parent compounds’ MeCOMe and MeCSMe (from Table 22). From these (lower data set) one might anticipate a differential in favour of **C** of  $\geq 10^5$ . While **C** is indeed favoured over **B**, the differential in its favour falls short of this by a factor of  $> 10^3$ , and even this effectively disappears in the chelate, where **D** is favoured over **E** by a margin which, according to the mode of calculation, varies from the slim to the substantial. There is total disagreement as to the status of **A** relative its enols **B** and **C**: according to MP2 it is the most stable tautomer, according to B3LYP the least, whereas RHF places it in the middle. However overall margins are not large at any level of theory and, if the analogous  $\beta$ -diketones **55** are any guide, the gas phase and very nonpolar solvents are the likeliest media to stabilise **A**. In water one would expect **B** and **C** to predominate over **A** by a large margin. The situation for **D** and **E** is less clear but, with the enol of acetylacetone disfavoured by less than one order of magnitude in water, very little of the unconjugated tautomer is expected here either. Duus<sup>138</sup> states that unenolised tautomers are never found, but this refers to organic solvents and the position for aqueous solution, where chelated  $\beta$ -diketones are at their least enolised, is less certain.

The sharp reversal of tautomer preference on chelation requires comment. On the basis of CNDO calculation Duus and Anthonsen<sup>234</sup> claim that  $>\text{C}=\text{S}---\text{HOR}$  forms a much stronger hydrogen bond than  $>\text{C}=\text{O}---\text{HOR}$ , at least in this intramolecular context. Given that thioamides and thioureas are much weaker proton acceptors than amides and ureas,<sup>72</sup> this seems unlikely. A much more probable explanation starts from the extremely low proton donor ability of SH.<sup>235</sup> Duus himself has demonstrated that, for **362** at low temperatures in  $\text{CS}_2$ , the unbonded rotamer **362c** is present alongside the expected chelate **362b**.<sup>236</sup> There are even cases in which **364b** has been detected as well as **364a**.<sup>138</sup> Employing the data given by Duus<sup>59</sup> for  $K_T = (\mathbf{362b} + \mathbf{362c}) / \mathbf{362a}$ , we can take this argument further. Its 2-parameter LSER equation is (xiii). This demonstrates an exceedingly shallow dependence on  $\pi^*$  and  $\beta$  and its most interesting feature is that there should be a  $\beta$ -term at all. The *positive* sign of this shows it to be associated with SH not OH: while OH is locked in the chelate **362a**, SH in **362c** is free to interact with the solvent. This coefficient of 0.3 for  $\beta$  contrasts with 4.4 when OH is generated in the enolisation of dimedone **55** (section A.6) and helps to emphasise just how poor a proton donor SH is. Equation (xiii) extrapolates

$$\log K_T = -0.63(0.03) + 0.41(0.05)\pi^* + 0.30(0.08)\beta \quad (\text{xiii})$$

$$(n = 6 \quad r^2 = 0.977 \quad s = 0.03 \quad F = 62)$$

to  $K \sim 1$  in water (see section A.8.3). For the gas phase it predicts  $\log K_E$  *ca.* -1.1, well inside the range indicated in Table 29. Note that this difference, for competition between enols, is far below that for acetylacetone ( $\Delta \log K_E$  *ca.* 4.2) and dimedone ( $\Delta \log K_E$  *ca.* 3.7) where competition is between an enol and an unconjugated tautomer.

Even for the extended series, however, the preference for the enethiol tautomer is much less than expected. In terms of the mutual effects of C=O and C=S on one another we find, from Tables 22 and 29, that at the RHF level for example, the effect of C=S on C=O *additional* to that contained in the enolisation of MeCOMe amounts to  $\Delta\Delta H$  -57.3 kJ mol<sup>-1</sup> whereas the corresponding effect of C=O on C=S, net of enolisation in MeCSMe, is only  $\Delta\Delta H$  -36.8 kJ mol<sup>-1</sup>. If  $\Delta G$  were precisely to reflect  $\Delta H$  this would amount to a ‘boost’ for **B** of  $\Delta \log K_T$  -3.6. This of course is precisely the quantity encoded in the third column of Table 29, as (‘ $\log K_E$ ’ **B**  $\rightarrow$  **C** minus  $\Delta$  C=O/C=S), which reveals its derivation but not its origin. We believe the latter to arise from a *greater electronegativity for C=S than for C=O* which might be encoded by its dipole moment if this were known, as it is for thioamides *vs.* amides and thioureas *vs.* ureas.<sup>207</sup> This built-in bias is less for aminoenones (favoured by an additional  $\Delta \log K_T$  *ca.* 3.2) but much greater for aminoenethiones (favoured by  $\Delta \log K_T$  *ca.* 8.3). The equivalent calculations at the MP2 and B3LYP levels of theory differ in quantitative terms but, qualitatively, show the same trends.

### A.8.2 Extended $\beta$ -Thionoketones

Only the dimedone analogue **365** has been studied, and that not in water. Dalgaard and Lawesson<sup>237</sup> report that the neat liquid and solutions in hexane and CHCl<sub>3</sub> contain **365b** exclusively and in Et<sub>2</sub>O and MeCN this is heavily predominant, but that in CCl<sub>4</sub> and DMSO there is a considerable, though not predominant, proportion of **365a**. The parent  $\beta$ -thionoketone was not detected. Leaving aside the puzzling datum for CCl<sub>4</sub> (H-bonded dimers?) these results would readily fit a hypothetical LSER equation constructed by combining the  $\pi^*$  coefficient from eqn. (xiii) with that of the  $\beta$ -term (with negative sign) for dimedone, eqn. (x). Such an equation would predict, for  $K_T$ , the order hexane, CCl<sub>4</sub>, CHCl<sub>3</sub> > gas phase > MeCN > Et<sub>2</sub>O > DMSO with the value for water slightly below that for MeCN. This is very much the order implicit in Table 29, with  $\log K_T$  for water less than that for the gas phase ( $\Delta \log K_T$  *ca.* - 0.8?) but probably still positive, if by no great margin.

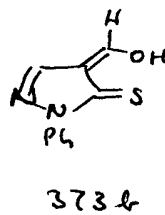
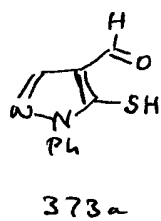
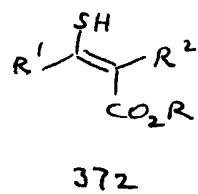
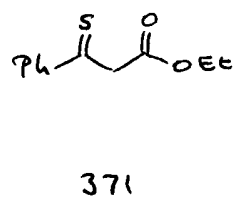
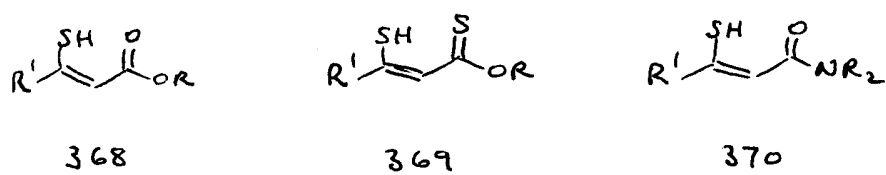
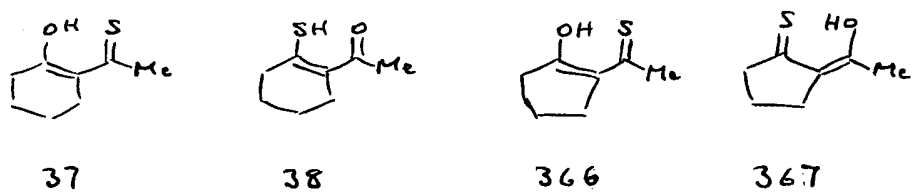
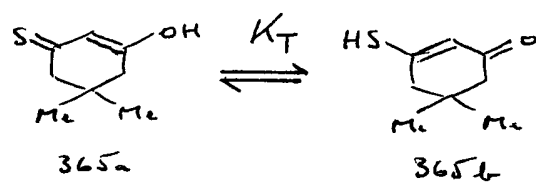
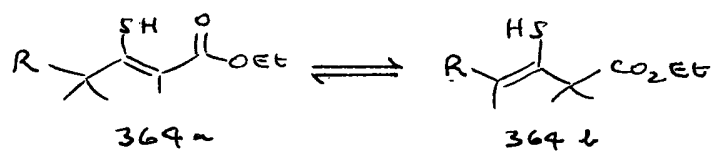
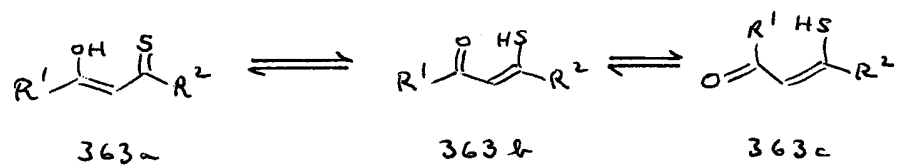
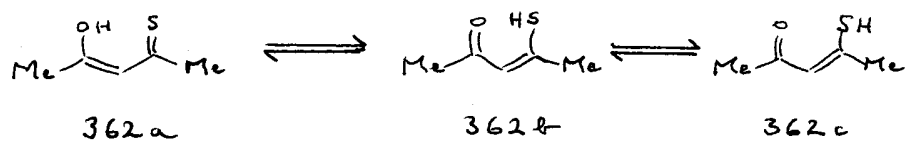
### A.8.3 Chelated $\beta$ -Thionoketones

In addition to **362**, Duus<sup>59</sup> has studied the solvent dependence of several further compounds **363** with varying alkyl groups and the differences are minute (*vide* Table 128, Appendix 2). Carlson and Duus<sup>238</sup> state that  $R^1 = \text{Ph}$  in place of  $R^1 = \text{Me}$  increases the proportion of **363a** but even this effect is not large. Duus<sup>59</sup> notes that the thione tautomer **363a** is always that found in the solid state and believes that, in solution, rotamer **363c** dominates the thiol tautomer. Again, the  $\beta$ -thionoketone tautomer is never observed. We have used data for **37** and **38**, also studied by Duus,<sup>59</sup> in a previous section (A.1.2) to help establish the extent of the preference for *endo*-C=C in 6-membered rings. From their 3-parameter LSER equations (Table 128) which closely resemble eqn. (xiii) we calculate  $\log K_T$  (defined as for **365**) *ca.* -0.4 and 1.1 respectively, so that the preferred aqueous tautomer in each case is as shown. As elsewhere therefore, there is little preference for one enol tautomer over the other so no great energetic penalty if one or the other is thought to be required at the biological receptor. In 5-membered rings the expected switch to *exo*-preference is sufficient to tip the balance for **367** but not for **366**,<sup>223</sup> perhaps an indication that, in these relatively rigid structures, the formation of species analogous to **363c** is less easy.

There is some minor dispute concerning  $\beta$ -thionoesters and related compounds. Duus<sup>138</sup> states **368** - **370** to exist exclusively as shown; Reyes and Silverstein<sup>239</sup> claim **371** to be only 87% enolised in 95% ethanol. Even if the latter are right in this instance, predominant enolisation is not in dispute. Steric crowding by a bulky  $R^2$  in **372**, enough in a  $\beta$ -diketone to inhibit enolisation (section A.1.4), here results simply in a switch to the configuration shown.<sup>138</sup>

### A.8.4 The $\beta$ -Thionoketone Unit in Aromatic 5-Membered Rings

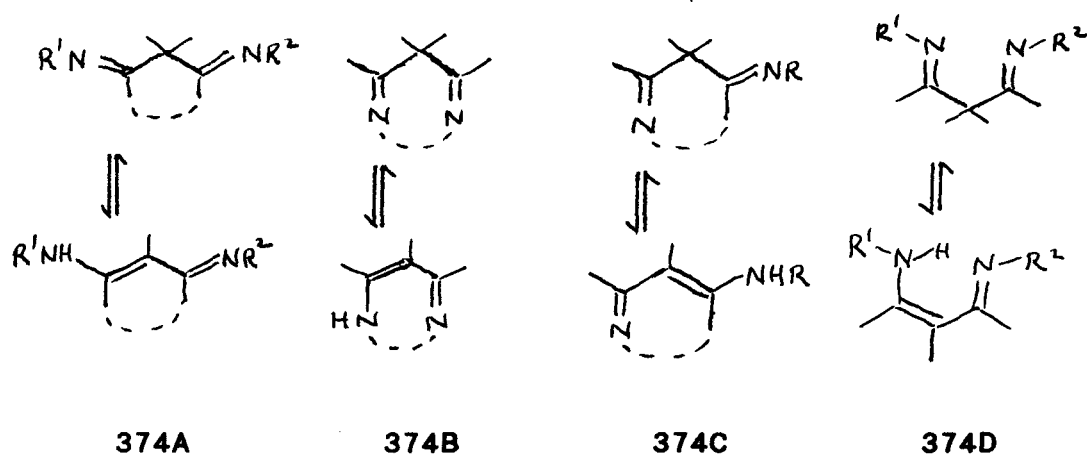
The pyrazole **373** exists as **373a** not **373b**,<sup>2hh</sup> as expected on the criteria previously sketched out (section A.6.6). Since enolisation in  $\beta$ -thionoketones is so closely in balance, it seems probable that no extra criteria are required.



## A.9 $\beta$ -Diimines and Vinylogous Amidines

As in the case of simple imines (section A.4), these compounds are distinguished from their C=O and C=S analogues by the endocyclic possibilities open to C=N, allowing four structural variants in place of two (Scheme 12; *cf.* Scheme 10). There are other important differences. In place of the acidity associated with enolised  $\beta$ -diketones and  $\beta$ -dithiones, enolised  $\beta$ -diimines as vinylogous amidines share, in principle, the high basicity of this class. Since however most common forms of substitution (aryl, halo, carbonyl *etc.*) are such as to reduce basicity (or increase acidity), this is a less persistent problem than for C=O or, in particular, for C=S.

The calculations of Table 22 might suggest that, as for  $\beta$ -dithiones, the unconjugated structure should be of little importance, and this is amply borne out in practice.



Scheme 12

Tautomerism as in **374D** has been little studied, and as in **374A** is scarcely known. However, some heterocycles classify as examples of **374B**, some aminoheterocycles as **374C**, and there is one extra category, not previously encountered, of some importance. We shall classify as 'nested' the type of molecule in which a  $\beta$ -diimine, or more usually a vinylogous amidine, forms a sub-unit inside some much more complex structure and is responsible for any tautomeric features that structure may possess. This situation, potentially a common one, reaches its apogee in the aminoenones of section A.10 where almost a majority of such structures are of the 'nested' type. In fact we shall use some of these to suggest possible types of vinylogous amidine, whose tautomerism has not so far been reported, but which might well be encountered in the future.

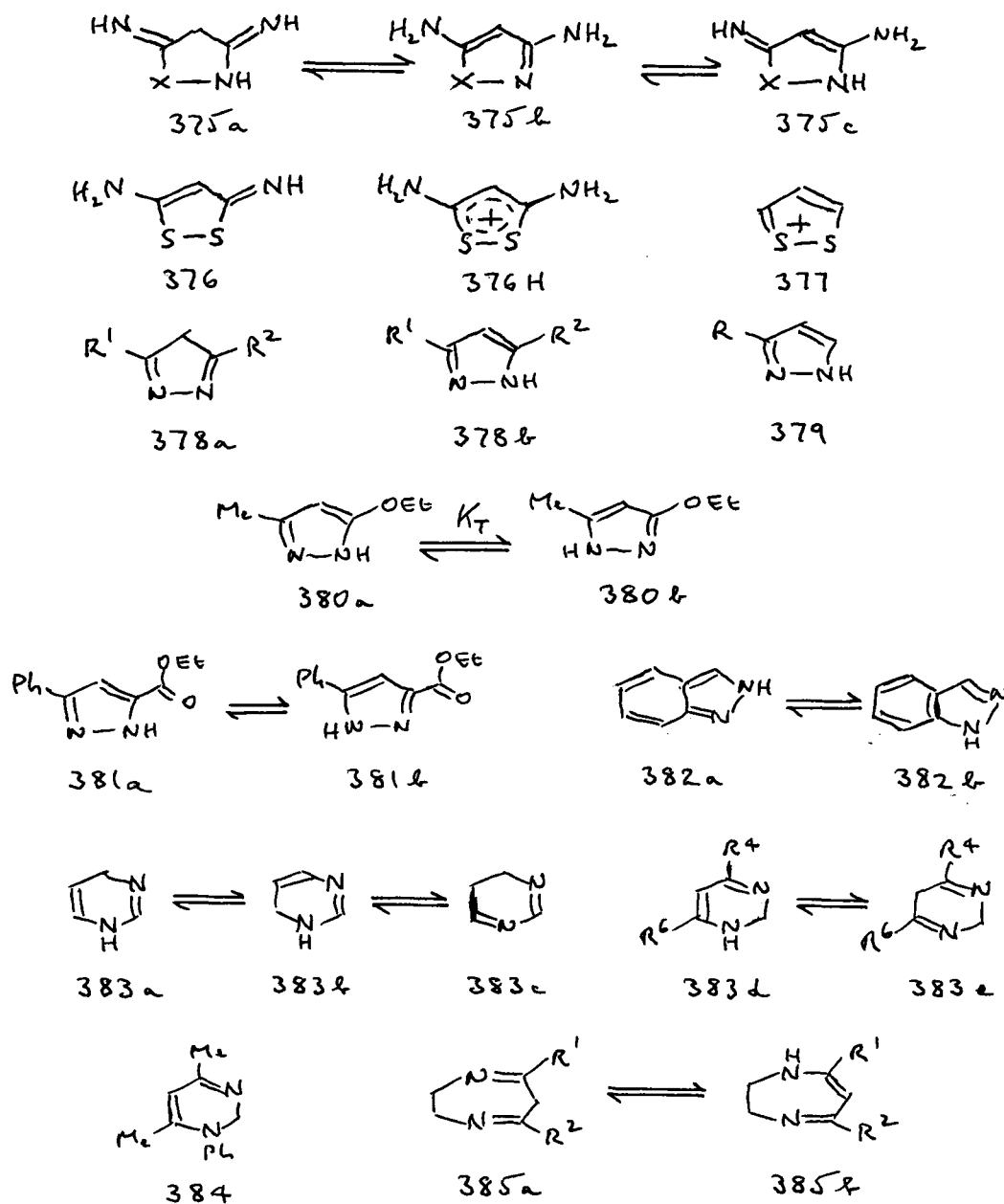
### A.9.1 Extended Structures (374A)

No simple examples appear to be known. Heterocycles of type **375** exist as **375b**,<sup>2ii</sup> and can be quite appreciably basic. The special case of **376**, a very strong base, depends on the ‘pseudo-quaternary’ properties of the parent dithiolium cation.<sup>240</sup> This cation **377** is ‘locked’ in the sense that it cannot lose a proton and any other heterocycle with this characteristic may be expected to behave in the same way.

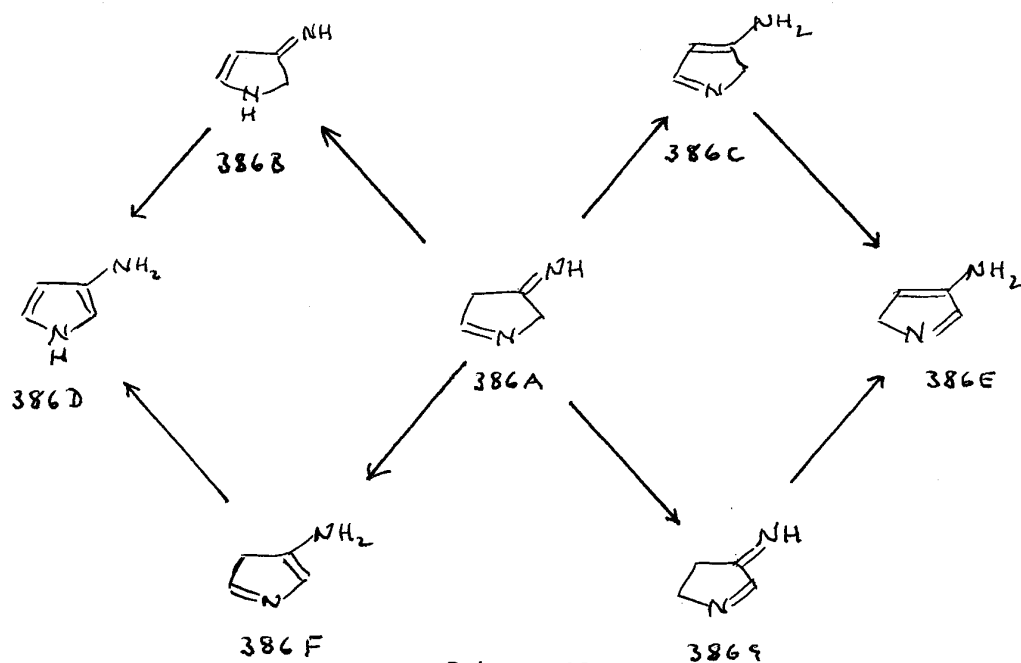
### A.9.2 Heterocyclic *endo*-Diimines and Vinylogous Amidines

The simplest structure for an *endo*-diimine is pyrazole **378**. In fact the diimine **378a** has not been detected and the vinylogous amidine structure **378b** results. Because of the mutual electronegativity of the linked nitrogen atoms this is an uncharacteristically weak base ( $pK_a = 2.52$ ). All monosubstituted pyrazoles favour the substituent as in **379** though if this is bland (Me, Ph)<sup>37</sup> or electronegative,<sup>241</sup> the effect is small ( $< 5$ -fold). Consistently, (**379**, R = Ph) exists as this tautomer in the solid state.<sup>37</sup> When R is a  $\pi$ -donor the effect is much greater; **380b** is favoured over **380a** by 30:1 in water,<sup>242</sup> no doubt through superior conjugation as shown (*cf.* **218**, section A.4.8, and the quantitative analysis of section B.8.1). It has been calculated<sup>241</sup> that (**379**, R = NH<sub>2</sub>) should be more stable than its tautomer by 1.95 kcal mol<sup>-1</sup>, equivalent to  $\Delta \log K$  1.4, a similar figure. The preference shown for **381a** over **381b** is intuitively to be expected ( $\pi$ -donor next to N, proton acceptor next to NH) and the only surprise is that the effect is so slight, about a factor of three<sup>2jj</sup> (again, see section B.8.1). In view of the quinonoid structure of **382a** it is to be expected that indazole should prefer **382b**, which it does by a factor of about 50 in water.<sup>243</sup> This is important evidence as to the margin by which quinonoid forms are disfavoured; *cf.* Appendix 5.

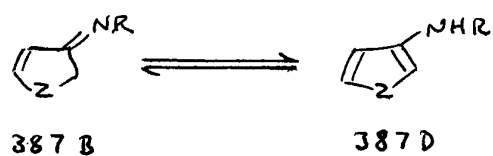
Dihydropyrimidines have been studied, mostly by Weis.<sup>244</sup> These form two non-interconvertible sets: **383a**, **b** and **c**; and **383d** and **e**. All are unstable through oxidation, polymerisation, or disproportionation. In the first set, **383a** is dominant in DMSO but exists in equal proportion in CHCl<sub>3</sub> with **383b**; **383c** is absent.<sup>244a</sup> The second set is more important, with **383e** relatively stable when R<sup>4</sup> and R<sup>6</sup> are  $\pi$ -donors *e.g.* OR,<sup>244b</sup> and **383d** similarly for R<sup>4</sup> = R<sup>6</sup> = alkyl or aryl;<sup>244b</sup> series **383d** is stabilised by the ‘push-pull’ system which makes them quite strong bases (*e.g.* **384**,  $pK_a$  9.66).<sup>244c</sup> Dihydroheterocycles have been reviewed.<sup>244d</sup>



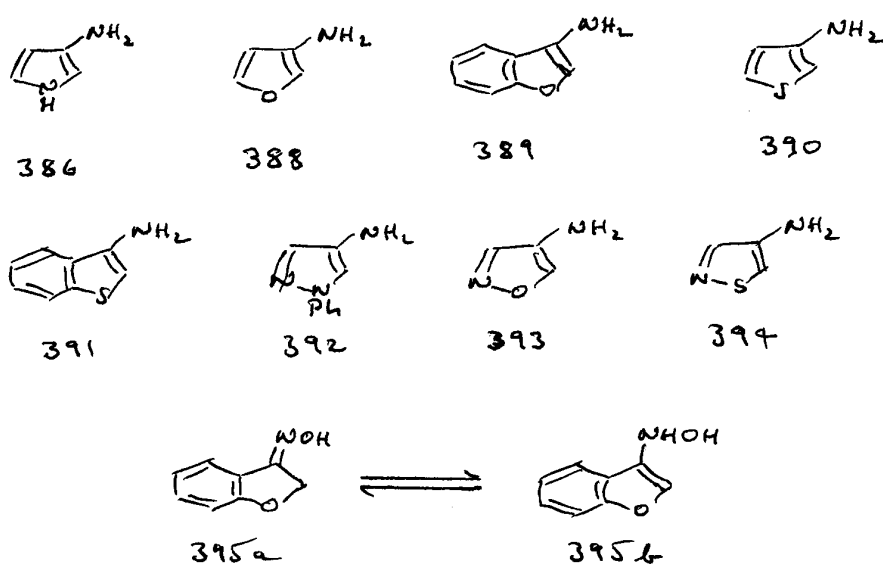
The similar interposition of two methylene units leads to the 1,4-diazepine structure **385**. For these as written the diimine tautomer **385a** is unknown<sup>245</sup> whereas **385b** forms a very stable cation and is a strong base: for (**385**,  $R^1 = R^2 = \text{Me}$ ),  $\text{p}K_a = 13.4$ .<sup>246</sup> However, as noted in section A.4.9, benzofusion across the 2,3-positions produces a compound **236** which if conjugated would be antiaromatic, so in this case the diimine tautomer is preferred. Larger ring vinylogous amidines are possible in principle and their properties should resemble those of **385**.



Scheme 13



Scheme 14



Scheme 15

### A.9.3 $\beta$ -( $\gamma$ -)Amino Derivatives of 5-Membered Ring Heterocycles

It is instructive to consider the possible tautomers of 3-aminopyrrole (Scheme 13). There are seven of these, forming two quadrilaterals linked by the common diimine **386A**, in each of which each tautomer is related to its immediate neighbours by a single proton switch. Of these seven, **386E** and **386F** are cross-conjugated so likely to be disfavoured relative to the through-conjugated tautomers **386B** and **386C**, while **386G** is not only cross-conjugated but its dipoles are opposed, making it in all probability less stable even than **386A** (*cf.* the  $\alpha$ -diketones of section A.2.5). This leaves only the diimine **386A** and the two vinylogous amidines **386B** and **386C**, all related in the usual manner (*cf.* Scheme 10), plus **386D**. On previous arguments (*cf.* Table 22) **386A** is likely to be unimportant relative to **386B** and **386C**, and the difference between these will probably be marginal. Aromatisation of **386B** or **386C** to **386D** will then be highly favourable, so that **386D** will be the only observable species, as is found.

If ring NH is replaced by O, S or NR then only two tautomers remain, **387B** and **387D** (Scheme 14). For Z = NR the energy of the **B**-tautomer will be much as for Z = NH, but since O and S are poorer  $\pi$ -donors, it is arguable that (**387B**, Z = O or S) should be disfavoured relative to (**387B**, Z = NR). In addition, and probably more important, there is the resonance energy imparted by aromatisation to **387D** and which goes in the order Z = NR > S > O (Table 12). It is therefore likely that, if **387B** is ever a viable species, this will be found in the furan series. Scheme 15 lists all relevant simple 3-aminoheterocycles (and one or two others) whose structure is firmly established according to ref. 2. The only doubtful case is **388**, where the position is uncertain and calculation suggests a mixture.<sup>2kk</sup> There is no information on **389**, the likeliest compound of this type to contain a substantial proportion of the imino-form; *cf.* its 3-oxo analogue (**134**, Z = O), the most resistant to enolisation in that series (Table 13).

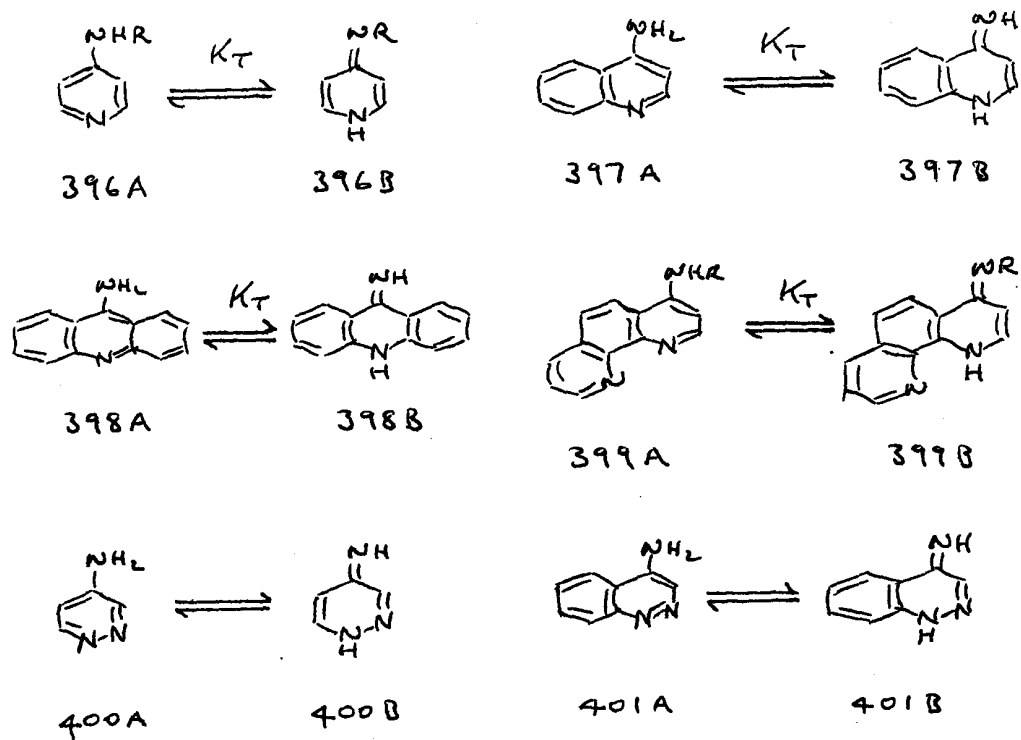
The tautomeric process **387B**  $\rightleftharpoons$  **387D** is also that of imine and enamine. It has been seen (section A.4.6) that, while resonance donor *N*-substituents somewhat favour the imine tautomer, resonance acceptors strongly favour the enamine. It is probable therefore that *N*-acylation, for example, will favour **387D** and may ensure its dominance in even the least favourable cases. Contrariwise, the corresponding hydroxylamines and hydrazines may well exist as oximes and hydrazones respectively, *e.g.* **395a** not **395b**, though there is no suggestion of this tautomer for **391**. Such cases do not seem to have attracted attention as yet.

#### A.9.4 $\gamma$ -Amino Derivatives of 6-Membered Ring Heterocycles

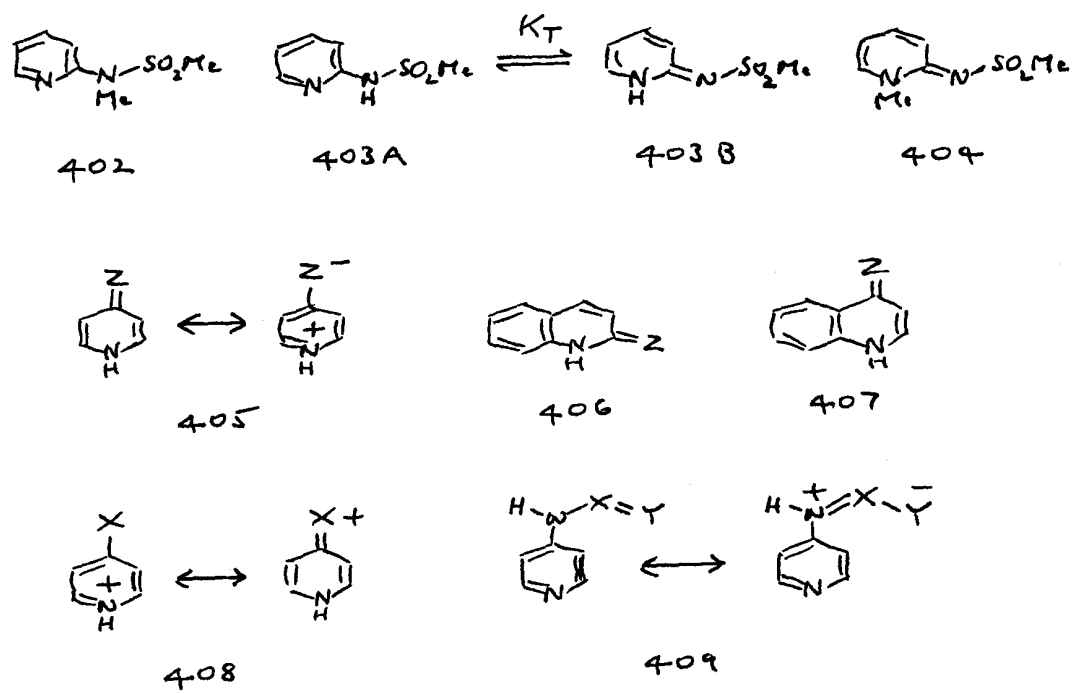
In the great majority of potentially tautomeric aminoheterocycles on which information exists (Table 30), 5- or 6-membered, the amino-group is  $\alpha$ -substituted with respect to a ring hetero-atom, and the probability of this inevitably increases with the number of hetero-atoms per ring. In the present context, the compounds of Scheme 16 cover almost all the relevant structural types there are. As emphasised in the Introduction we omit, here and elsewhere, discussion of compounds in which the second tautomeric species is a zwitterion, so that, *e.g.*, 3-substituted pyridines and 5-substituted pyrimidines are excluded.

Tautomerism has been studied in almost all cases by the 'basicity method,' which involves the use of some model compound for the minor species, and mostly by Katritzky and co-workers.<sup>150a,247-250</sup> We consider the requisite corrections in Appendix 1. Where the imino-tautomer is the minor species, correction is required for ring *N*-methylation:  $pK_a(\text{NH}) - pK_a(\text{NMe}) = \Delta(\text{NR})$ . For the equivalent oxo-compounds this correction is  $\Delta(\text{NR}) = -0.01 \pm 0.09$  ( $n = 9$ ), and since it is unlikely to be greater we assume  $\Delta(\text{NR}) = 0$  here also, so that  $pK_a(\text{B})$  in Table 30 is that of the original authors throughout, as is also true for  $pK_a(\text{A})$  except in the two cases where this is the minor species. For these we have not accepted the authors'  $pK_a$  values for the *exo-N*-methylated species as models since there is a very real risk of non-planarity with consequent effect on basicity. The reality of this threat is illustrated by the fact that *exo-N*-methylation of (**396A**, R = COMe) results in  $\Delta pK_a = -1.25$ .<sup>248</sup> We have preferred a different approach. Jones and Katritzky<sup>247</sup> report  $pK_a$  values of 1.73 and 1.10 for **402** and **403** respectively; it is clear from the UV spectra of these and **404** that **403B** is the dominant species, with up to 10% of **403A**.<sup>247</sup> This leads to  $pK_a$  2.1 for **403A**, *i.e.* a minimum correction of  $\Delta(\text{NR})$  0.4. We have applied this to  $pK_a(\text{A})$  for (**396**, R = SO<sub>2</sub>Me) in Table 30, bearing in mind that the correction for a 4-substituent is likely to be less and balancing this against a possibly low initial estimate. With rather less justification, we have assumed the same correction for (**396A**, R = NO<sub>2</sub>).<sup>251</sup> The much larger correction required for (**396A**, R = COMe), noted above, may result from an extra distortion caused by the need to preserve planarity in the amide group.

The methide **214** (Table 17) corresponding to (**396**, R = H) possesses  $\log K_T$  -12.8 after correction for the 'intrinsic' tautomeric ratio shown by its non-aromatic equivalent (*cf.* section A.4.7). As pointed out by Katritzky and co-



Scheme 16



workers<sup>150a</sup> any such correction must be negligible in the present case, so  $\log K_T$  -8.7 may be compared directly with this value. What the comparison shows is that **396B**, unlike **214**, still retains a considerable degree of aromaticity,<sup>150a</sup> as can be emphasised by writing charged canonical forms such as **405**; obviously this electronic interpretation will be much more favourable for  $Z = O$  or  $S$  than for  $Z = NR$ , but nevertheless not negligible as it must be for  $Z = CH_2$ . Related to this is the effect of benzofusion, best discussed here at the more naive level of simple  $\Delta \log K_T$  values. For  $Z = O$  in **406** and **407**, the effect on the pyridone of benzene ring annelation is to raise  $\log K_T$  in both cases by 1.0 (see summary section C.21); for  $Z = NH$ , the equivalent values are *ca.* 1.8 and (according to Table 30) 5.5. This last value is quite unreasonable and we suspect  $pK_a(B)$  for **397** to be a ‘mirage.’<sup>252</sup> It was measured<sup>5</sup> at a time when modern techniques for obtaining high  $pK_a$  values were not fully developed and, while other such values have been identified and corrected,<sup>150</sup> this one appears to have been overlooked. A value of  $\log K_T$  *ca.* -7 for **397** would be much more reasonable and we suggest its acceptance (Table 30). Katritzky and co-workers<sup>249</sup> report that **398B** is undetectable in  $CHCl_3$ ,  $CCl_4$ , THF, dioxane and pyridine, an unlikely result if  $\log K_T$  -3.2 were to be true for **397**; the parallel two-

**Table 30.**  $pK_a$  and  $\log K_T$  Values for the Compounds of Scheme 16

	R	$pK_a$ (A)	Ref.	$pK_a$ (B)	Ref.	$\log K_T$
<b>396</b>	H	9.17	255	17.87	150	- 8.7
<b>396</b>	NH <sub>2</sub>	9.25	252	12.7 <sup>a</sup>	252	- 3.5 <sup>b</sup>
<b>396</b>	COMe	5.87	248	11.03	248	- 5.2
<b>396</b>	COPh	5.32	248	9.89	248	- 4.6
<b>396</b>	SO <sub>2</sub> Me	5.54 <sup>c</sup>	247	3.64	247	1.9
<b>396</b>	NO <sub>2</sub>	4.4 <sup>c</sup>	251	1.99	251	2.4
<b>397</b>		9.17	255	12.4 <sup>d</sup>	5	- 3.2 <sup>b</sup>
<b>399</b>	Cyclohexyl	9.06	250	13.82	250	- 4.8
<b>399</b>	Ph	8.10	250	10.49	250	- 2.4
<b>400</b>		6.65	256	12.18	255	- 5.5
<b>401</b>		6.84	255	11.29	256	- 4.4

<sup>a</sup> Inaccurate, according to the authors. <sup>b</sup> Probably invalid (see the text). <sup>c</sup> Incorporates putative correction of  $\Delta \log K_T = 0.4$  (see the text). <sup>d</sup> Probably a ‘mirage;’ we suggest a corrected value of  $\log K_T$  *ca.* - 7 (see the text).

stage benzene ring annelation of phenol (section A.2.6) results in successive enhancements of  $10^6$  and  $10^9$  in the relative importance of the non-aromatic tautomer. It should be mentioned however that the **B**-form has been found to be the dominant tautomer in polar solvents for some derivatives of **398**,<sup>253</sup> so this compound may lie close to the borderline.

Two results throw some light on other correction factors. The effect of lone pair repulsion in (**399A**,  $R = H$ ), aided perhaps by some dipolar attraction in the **B**-form, is probably to raise  $K_T$  by  $\Delta \log K_T$  *ca.* 2 relative to **397**. Since the model for **399B** was (inevitably) *N*-methylated this value does not incorporate the effect of the intramolecular hydrogen bond, which would no doubt result in a considerably higher  $\Delta \log K_T$  value if this quantity were measurable. A comparison of  $\log K_T$  for (**396**,  $R = H$ ) and **400** results in  $\Delta \log K_T$  3.2 for the effect of the 2-aza substituent. Any such effect is composite of two factors: the electronegativity of aza-nitrogen which should lower  $K_T$ , and lone pair repulsion which should raise it,<sup>254</sup> both operating mainly on the **A**-form. Katritzky<sup>254</sup> points out that the former is usually more important; for the corresponding oxo-compounds,  $\Delta \log K_T \sim -0.7$ . So the above value appears to be anomalous. While the first factor might be greater in this case through the superior electron donor ability of  $NH_2$ , so for the same reason might the second, so this consideration does not resolve the problem. It is altogether possible, bearing in mind their date, that the  $pK_a$  values for **400B**<sup>257</sup> and **401B**<sup>258</sup> are further ‘mirages,’ despite the contra-indication that  $\Delta \log K_T$  for **401** *vs.* **400** appears quite normal. We have to leave this problem unresolved. Nevertheless, since all these compounds exist overwhelmingly as the **A**-tautomer, no confusion results in that respect. In addition, nearly all forms of substitution in oxoheterocycles result in a fall in  $K_T$  and a similar result here, which is probable, can only increase the dominance of the amino-tautomer.

It is otherwise for *N*-substitution, where the range of substituents from  $R = H$  to  $R = NO_2$  spans  $\Delta K_T > 10^{11}$  (Table 30). To these five values we can add a sixth if we assume that the  $pK_a$  and  $\log K_T$  shifts shown by (**399**,  $R = Ph$ ) relative to (**399**,  $R = cyclohexyl$ ) would be echoed by **396** if the data were available. Equations (xiv) and (xv) are the relations that result for the dependence on  $\sigma$  of  $pK_a(A)$  and  $pK_a(B)$ . Equation (xv) echoes the simple  $\sigma_I$  dependence already known for guanidines<sup>96,170</sup> and which we shall show (section B.4.2) is found for amidines in general (*cf.* **210**, Scheme 8, section A.4.6); even its  $\rho$ -value is almost identical,  $-23.5$  *vs.*  $-22.6$ .<sup>96</sup> However, for

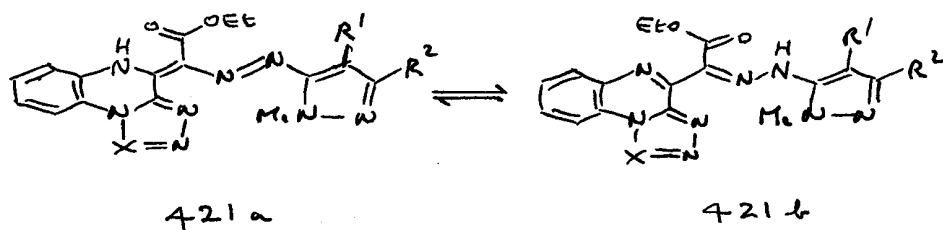
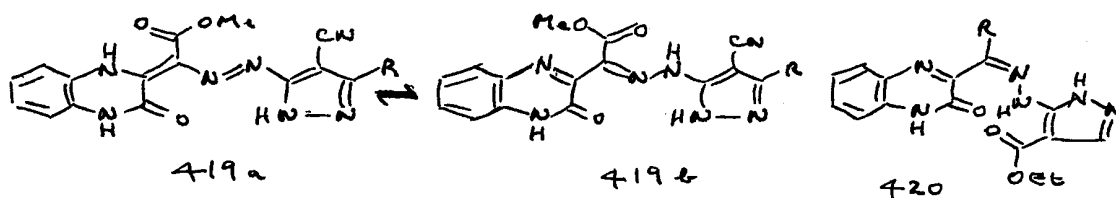
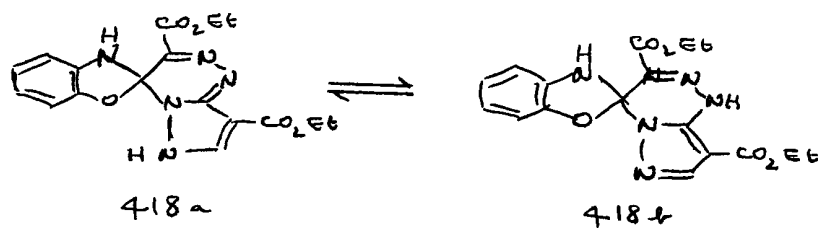
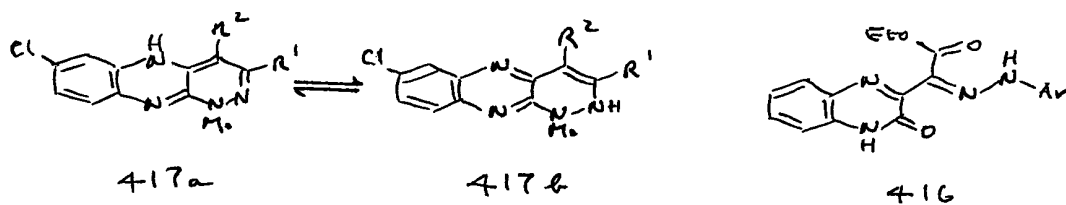
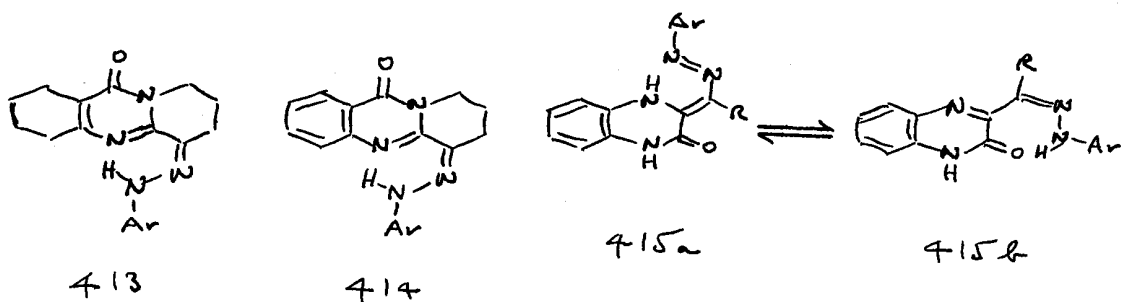
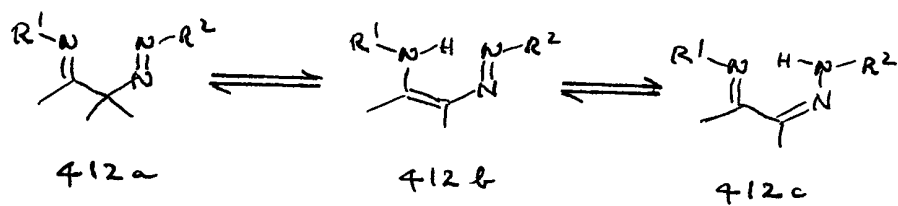
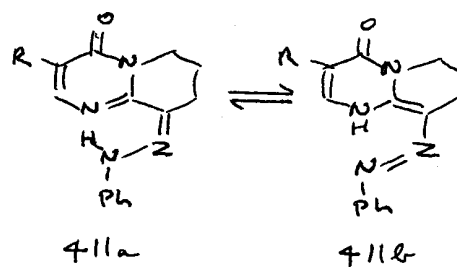
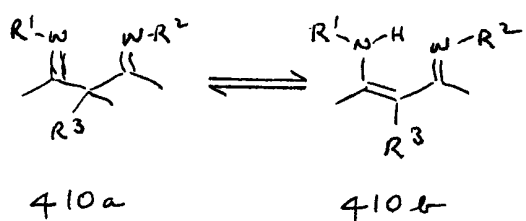
$$\begin{aligned} \text{p}K_{\text{a}}(\mathbf{A}) &= 8.68(0.36) - 4.53(1.04) \sigma_{\text{I}} - 6.23(1.87) \sigma_{\text{R}} & (\text{xiv}) \\ (n &= 6 \quad r^2 = 0.956 \quad s = 0.51 \quad F = 33) \end{aligned}$$

$$\begin{aligned} \text{p}K_{\text{a}}(\mathbf{B}) &= 17.59(0.37) - 23.5(0.78) \sigma_{\text{I}} & (\text{xv}) \\ (n &= 6 \quad r^2 = 0.996 \quad s = 0.45 \quad F = 912) \end{aligned}$$

$$\begin{aligned} \log K_{\text{T}} &= -8.94(0.31) + 19.1(0.9) \sigma_{\text{I}} - 6.43(0.16) \sigma_{\text{R}} & (\text{xvi}) \\ (n &= 6 \quad r^2 = 0.994 \quad s = 0.44 \quad F = 267) \end{aligned}$$

$\text{p}K_{\text{a}}(\mathbf{A})$ ,  $\sigma_{\text{R}}$  is also significant and indeed is more important than  $\sigma_{\text{I}}$ . For 4- (and 2)-substituted pyridines **408**, Taft and co-workers<sup>259</sup> found  $\text{p}K_{\text{a}}$  to follow a mixed  $\sigma_{\text{I}}/\sigma_{\text{R}}^+$  relation. In the present case,  $\sigma_{\text{R}}^+$  (and  $\sigma_{\text{R}}^-$ ) are markedly inferior to  $\sigma_{\text{R}}$ , indicating that through-conjugation as in **408** is not involved. In place of stabilisation of the cation by resonance donors as in **408**, we interpret eqn. (xiv) as involving stabilisation of the *free base* by resonance acceptors as in **409**. This is the same type of *localised* conjugation that we have used to interpret the parallel stabilisation of enamines *vs.* imines (*cf.* **212**, Scheme 8), giving some credence to the qualitative arguments of section A.4.6.

The resultant for  $\log K_{\text{T}}$  is eqn. (xvi), which is more or less identical, as it should be, to eqn. (xiv) minus eqn. (xv). This shows the imino-tautomer **396B** to be favoured by inductive (field effect) *acceptors* (which in practice means almost anything but alkyl) but resonance *donors*, hence *inter alia* by strong inductive acceptors with minimal resonance acceptor ability. Aside from  $-\text{SO}_2\text{R}$  (Table 30), promising candidates in this category include  $-\text{CN}$  by perhaps a factor of ten;  $-\text{CF}_3$  should fall short by a factor of about  $10^2$ . The field acceptor / resonance donor class is in general more promising in this respect, with **396B** predicted to be favoured quite strongly by  $-\text{OPh}$  and  $-\text{NHCN}$  and not greatly disfavoured by  $-\text{OH}$ ,  $-\text{NHCF}_3$ ,  $-\text{NHCOR}$  or  $-\text{NHPh}$ . (Halogens as a class, except for  $-\text{I}$ , should nominally favour **396B**, but such compounds are likely to be unstable). Additionally, benzofusion should elevate some marginal possibilities into strong probabilities. These compounds remain to be investigated.



### A.9.5 Open-Chain $\beta$ -Diimines

It might be expected by analogy with  $\beta$ -dithiones (Table 22) that open-chain  $\beta$ -diimines **410** would exist exclusively as the vinylogous amidine **410b**, but this is not always the case. Knorr and Ruff<sup>260</sup> find that bulky substituents  $R^3$  in (**410**,  $R^1 = R^2 = \text{Me}$ ) can result in up to 60% of the diimine **410a** in  $\text{CHCl}_3$  solution. This is not entirely a steric effect since, under the same constraints, (**410**,  $R^1 = R^2 = \text{Ph}$ ) remains fully enolised. Comparison with the equivalent  $\beta$ -diketones (section A.1.4) suggests that the latter are less affected. One probable reason for the greater susceptibility of **410** to steric crowding lies in the relative weakness of the  $\text{NH} \cdots \text{N}$  hydrogen bond;  $\text{OH} \cdots \text{O}$  bonds are in general much stronger.<sup>72</sup>

When  $R^1 \neq R^2$ , alternative enols become possible. Work on this topic is not extensive, but four trends emerge from what there is. (1) Aromatic structures, where present, will be preserved; (**411**,  $Z = \text{CH}$ ) exists as **411a** not **411b**.<sup>261</sup> (2) If one imine is replaced by the azo-linkage, the latter not the former will generally enolise; *i.e.* **412** will exist as **412c** not **412b**. This is consistent with the strong tautomeric preference for hydrazones over aliphatic azo-compounds (section A.5.1). (3) In no case is the diimine tautomer of any importance. These rules are for  $\text{CHCl}_3$  solution but, except where radically different hydrogen bonding can occur (see section A.9.6), are likely to apply to any solvent, including water. (4) The likely effect of differing  $R^1$  and  $R^2$  in general for structure **410b** is unclear: whether on the lines of eqn. (xvi), those of the  $\pi$ -donor/ $\pi$ -acceptor distinction for imines/enamines in section A.4.6, or different again.

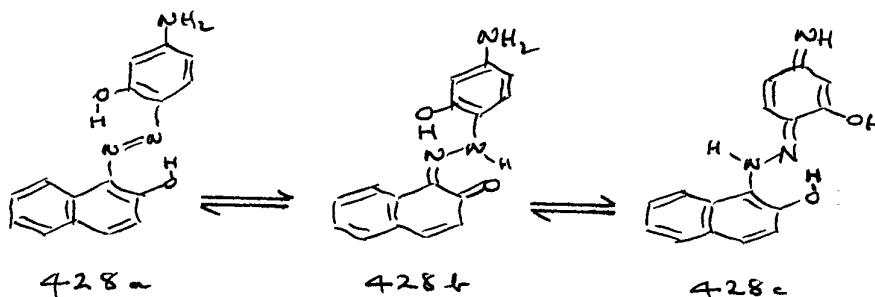
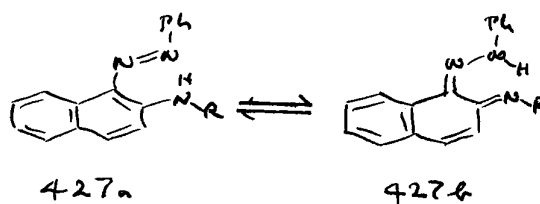
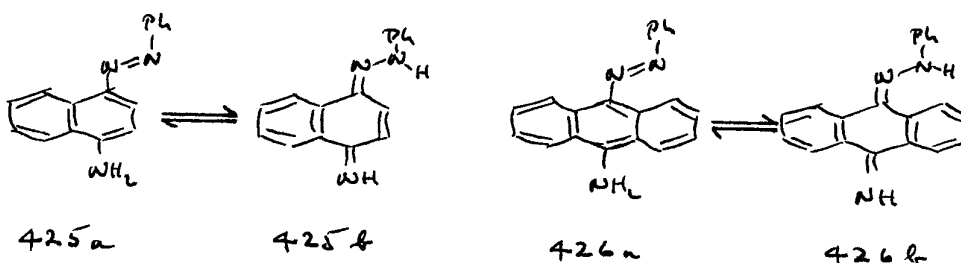
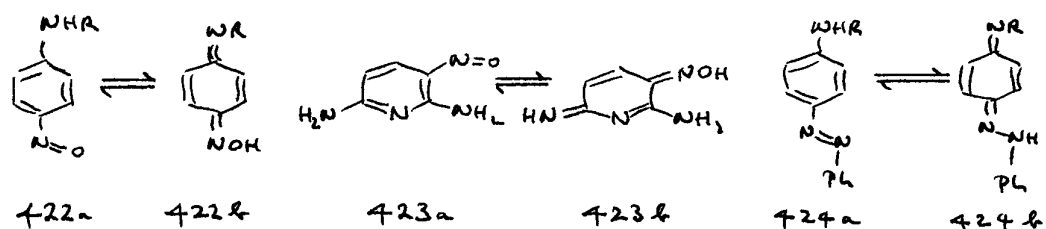
Compound (**411**,  $Z = \text{N}$ ) like (**411**,  $Z = \text{CH}$ ) exists as the **a**-form.<sup>261</sup> Both give a mixture of (mostly) *Z*- (as shown) and *E*-conformers in  $\text{CHCl}_3$  so the strength of the intramolecular hydrogen bond does not appear to influence tautomeric balance. Other such dominant or exclusive tautomers include **413** and **414** where, again, *E/Z* mixtures are found.<sup>262</sup> Compound **415** is out of line to the extent that **415a** is the dominant tautomer in TFA whereas, in DMSO, **415a** and **415b** are evenly balanced.<sup>263</sup> It is odd that **415a** should be favoured at all; however the azo-linkage is a poor proton acceptor (*vide* section A.5.1) so it is possible that solvents can break the intramolecular bond of **415a** but not that of **415b** and so favour the former. At all events, when  $R = \text{H}$  in **415** is replaced by  $R = \text{CO}_2\text{Et}$  to give **416**, this is the only tautomer visible in DMSO.<sup>263</sup>

### A.9.6 ‘Nested’ Vinylogous Amidines

These compounds lead on naturally from those immediately above and are again dominated by the work of Kurasawa *et al.* Some results are straightforward but others give rise to serious problems. On the above criteria it would be expected, as is found, that **417** should exist as **417a** not **417b**;<sup>264</sup> the hydrazone structure of the former is greatly preferred to the hydrazine unit of the latter (section A.5.1), a major and possibly dominant component in this being severe dipolar repulsion (Appendix 3). It is all the more surprising that **418** is said to exist as **418a** not **418b**<sup>265</sup> despite the two blatant intramolecular repulsions in the former both of which are absent in the latter, with the additional potential for an intramolecular hydrogen bond. And **419** does not behave at all like **416** despite its clear structural resemblance; the azo-compound **419a** is dominant (85% or 95%) in DMSO for R = H or Me,<sup>266</sup> and **419b** only becomes important (>50%) when water is added – which, however, could mean that expectation is fulfilled in aqueous solution, here and perhaps generally. Replacement of ester in **419** by R = H in **420** causes reversion to the same type of structure as present in **415b** but now to the extent of 100% (in DMSO).<sup>266</sup> When the amide group of **419** is replaced by triazolyl (**421**, R = CH) or tetrazoiyl (**421**, R = N) the results show a general parallelism to those above, with **421a** dominant in DMSO for (**421**, R<sup>1</sup> = CN, R<sup>2</sup> = Me) but **421b** even more dominant for (**421**, R<sup>1</sup> = CO<sub>2</sub>Et, R<sup>2</sup> = H).<sup>267</sup> Possibly **420** and **421b** are both stabilised by the bifurcated hydrogen bond we show speculatively for the former. Except when (R<sup>1</sup>)NH is an unusually powerful proton donor and/or (R<sup>2</sup>)N is an atypically powerful proton acceptor it is difficult to see why structures of type **412b** should ever be favoured, as appears to be the case at least for **415** and **419**. However, the extreme solvent sensitivity of the latter (see above) does suggest the nature of the solvent to be of unusual importance; with so many competing factors we may not always be comparing like with like. As guides to behaviour in aqueous solution, these results must be treated with great reserve.

### A.9.7 Benzenoid Vinylogues and Divinylogues of β-Diimines

Unlike its oxygen analogue (section A.10.20) this is a very fugitive category of compound, but is included here for completion. According to Coombes,<sup>268</sup> the tautomerisation of **422a** to **422b** has not been detected. Similarly,<sup>211</sup> **423a** gives no detectable amount of **423b** despite the ready formation of oximes from its oxygen analogues. Since nitroso-compounds tautomerise to oximes still more readily than azo-compounds do to hydrazones (sections A.5.1 and A.5.2) it is improbable, therefore, that any detectable amount of **424b** is present in **424a** despite some speculation to the

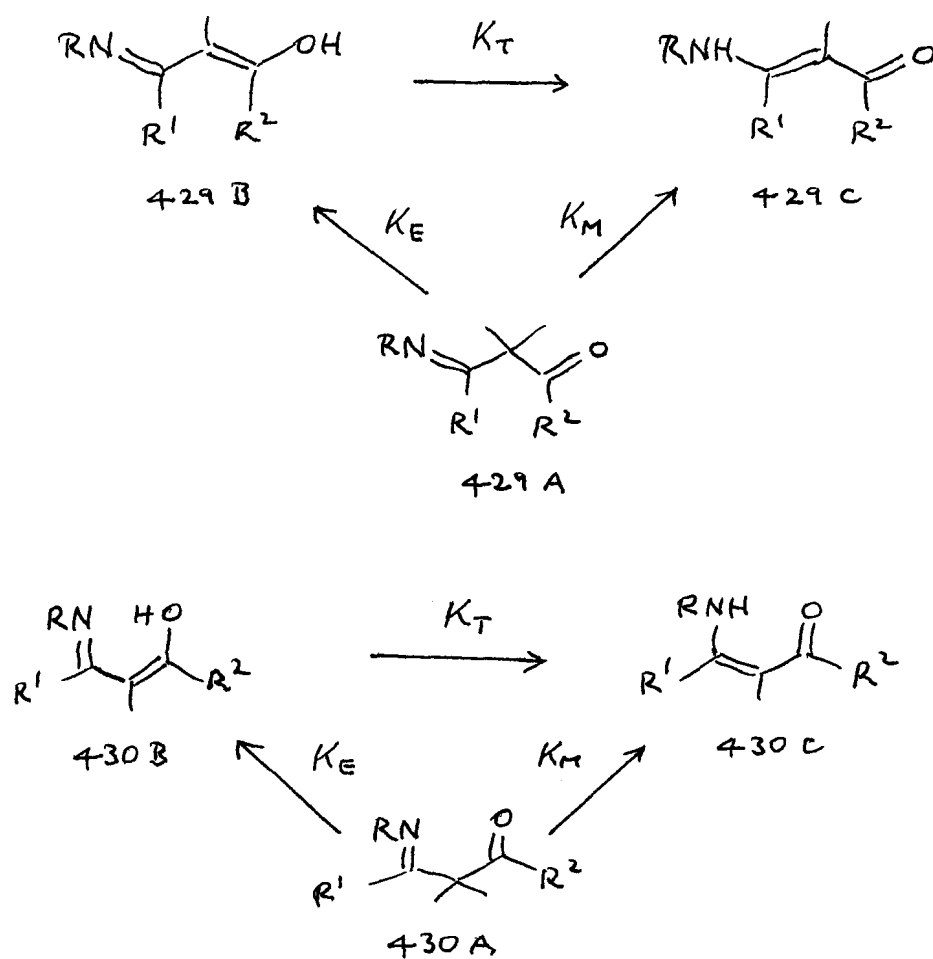


contrary.<sup>269</sup> Certainly no **425b** is detectable in **425a**,<sup>270</sup> though the presence of some **426b** in **426a** has been claimed.<sup>270</sup> By analogy with anthrone **122** (section A.2.6) and 9-aminoacridine **398** (section A.9.4), **426** is the likeliest of these compounds to show traces of the **b**-form.

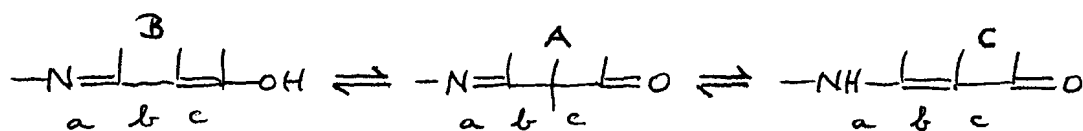
The above are divinylogues for which the hydrazone tautomer is likely to be exceptionally disfavoured. It is more likely in vinylogues such as **427** where there is a suggestion, but no more, that some of (**427b**, R = H or COMe) may be present.<sup>270</sup> The evidence seems firmer concerning **428**. Here it is probable that, alongside the expected vinylogous amide **428b**, some of its isomer **428c** may also be present.<sup>271</sup> (The authors do not consider a further structural variant in which the 1,3-iminoenol unit shown for **428c** becomes an aminoenone). This may be the only authentic example of the type; **428c** either as an aminoenone or as written would be stabilised by a much stronger intramolecular hydrogen bond than that of **428a**.<sup>106</sup>

### A.10 $\beta$ -Iminoketones and Aminoenones

Scheme 17, which is a special case of Scheme 10 (start of section A.6), sets out the three-way equilibrium between  $\beta$ -iminoketones **A**, enolamines **B** and aminoenones **C**, along with the nomenclature we shall use for the equilibrium constants that connect them. As previously we distinguish the *extended* **429** from the *chelated* structure **430** since, again as previously, relative stability follows different rules for each. Nevertheless in all simple cases the aminoenone tautomer is dominant, and perhaps our most important single task is to delineate the circumstances in which that no longer holds true. Aminoenones are vinylogous amides; it will be seen in section B.2 that  $K_T$  for amides parallels in many respects the pattern for  $K_T$  shown here.



Scheme 17

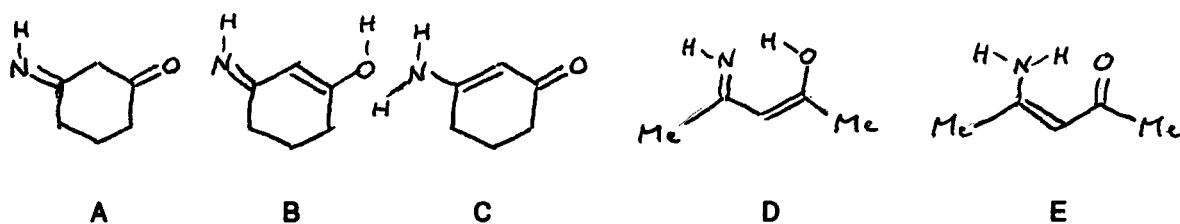


Scheme 18

A preliminary characterisation of perturbing factors can be made on the following lines. Scheme 18, set out deliberately in a conformationally ambiguous fashion, shows as (a), (b) and (c) three bonds each of which, if part of an aromatic unit, will tend to stabilise one tautomer at the expense of another. If (b) is part of such a unit the already dominant tautomer **C** will be stabilised still further, leading to compounds such as *o*- and *p*-aminoacetophenone which, with good reason, are not ordinarily thought of as capable of tautomerisation at all. Hence this case is trivial. However, aromatisation at (a) will stabilise **A** or **B** against **C**; some such cases have appeared in sections A.2.1 and A.2.2 but more will follow and some of these earlier examples now need placing in a broader context. Aromatisation at (c) will stabilise **B** against both **A** and **C** and becomes important, *inter alia*, for Schiff bases and some related compounds (sections A.10.18 and A.10.19). Substitution at the carbon end of C=N or C=O can also have an effect.  $\pi$ -Donors in the former case can help to stabilise **A** (just possibly, **B**); at C=O they will almost invariably prevent enolisation to **B** — compare section A.2.4 and the consequences that are manifested in A.6.5 - A.6.8. These issues are among those explored in the following sections.

### A.10.1 Energetics

Our calculations for the structures **A** - **E** are presented in Table 31, along with those for the 'parent compounds'  $\text{Me}_2\text{C}=\text{O}$  and its imine  $\text{Me}_2\text{C}=\text{NH}$  which form the first two entries in the lower group. It is instructive to compare these results with the equivalent calculations for acetone *vs.* thioacetone which appear in Table 29 (section A.8). The first three sets of entries of the lower group predict, on additivity assumptions, a similar margin in favour of structure **C** in both cases, an average value of 'log  $K_T$ ' *ca.* 6.3 here as against *ca.* 5.5 for  $\beta$ -thionoketones. There the resemblance ends. While the energetic advantage actually calculated for the thioloenone tautomer is less than half that predicted on additivity assumptions, that in favour of the aminoenone tautomer, averaging at 'log  $K_T$ ' *ca.* 8.6, is substantially greater. The reason for this difference, as previously discussed (section A.6.1), appears to lie in an electronegativity order such that *promotion of enolisation* is favoured in the order  $\text{C}=\text{S} > \text{C}=\text{O} > \text{C}=\text{NH}$  whereas *susceptibility to enolisation* follows the opposite order,  $\text{C}=\text{NH} > \text{C}=\text{O} > \text{C}=\text{S}$ . The different behaviour of  $\beta$ -thiono- and  $\beta$ -iminoketones follows simply from the fact that C=S lies above C=O in the pecking order whereas C=NH lies below it.

Table 31. Energetics ( $\Delta H$ , kJ mol<sup>-1</sup>) for Structures A – E <sup>a</sup>

	A → B		A → C		B → C		D → E	
	$\Delta H$	'log $K_E$ '	$\Delta H$	'log $K_M$ '	$\Delta H$	'log $K_T$ '	$\Delta H$	'log $K_T$ '
<i>b</i>	29.109	- 5.1	- 21.639	3.8	- 50.748	8.9	- 35.541	6.2
<i>c</i>	29.541 <sup>e</sup>	- 5.2	- 16.118	2.8	- 45.659	8.0	- 24.83	4.4
<i>d</i>	19.06	- 3.3	- 31.806	5.6	- 50.866	8.9	- 27.461	4.8
	C=O → OH <sup>f</sup>		C=NH → NH <sub>2</sub> <sup>g</sup>		$\Delta$ C=O / C=NH <sup>h</sup>		(D → E) – (B → C) <sup>i</sup>	
							' $\Delta$ log $K_T$ '	
<i>b</i>	64.438	- 11.3	27.207	- 4.8	- 37.231	6.5	15.207	- 2.7
<i>c</i>	65.941	- 11.6	31.068	- 5.4	- 34.873	6.2	20.829	- 3.6
<i>d</i>	59.408	- 10.4	23.689	- 4.1	- 35.719	6.3	23.405	- 4.1

<sup>a</sup> The quantities 'log  $K$ ' and ' $\Delta$  log  $K$ ' are hypothetical values for the circumstance that  $\Delta G = \Delta H$  (see the text). <sup>b</sup> RHF/6-31G\*\*//RHF/6-31G\*\*. <sup>c</sup> MP2/6-31G\*\*//MP2/6-31G\*\*. <sup>d</sup> B3LYP/6-31G\*\*//B3LYP/6-31G\*\*. <sup>e</sup> The *E*-conformer at NH for **B** is slightly favoured (by 0.208 kJ mol<sup>-1</sup>). <sup>f</sup> Energetics for the enolisation of acetone (Table 22). <sup>g</sup> Energetics for the enolisation of acetone imine (Table 22). <sup>h</sup> Energetics for the enolisation of acetone imine relative to that for acetone. <sup>i</sup> Energetics for the process  $K_T = [E] / [D]$  relative to that for the process  $K_T = [C] / [B]$ .

The calculations of Table 31 form a remarkably consistent set, with only minor differences of emphasis between the various computational methodologies. All predict the stability order **C** > **A** > **B**, with large energy gaps at each stage and a final result, of 'log  $K_T$ ' *ca.* 8.6, remarkably close to that observed for water (section A.10.4). In the absence of a similar experimental value for **D**  $\rightleftharpoons$  **E** it is interesting, and intuitively reasonable, that  $K_T$  should be less in this case: firstly because conjugation in the extended structure is expected to be better, secondly because the intramolecular OH---N bond of **D** should be stronger than the NH---O bond of **E**. There is insufficient evidence

to establish which, if either, factor predominates. Sensitive IR studies in a variety of solvents have established<sup>272,273</sup> that the *Z*-forms of tertiary aminoenones are undetectable, whereas substantial proportions of the unbonded *E*-form of secondary aminoenones can be found in polar solvents, and up to 5% even in nonpolar ones.<sup>274</sup> Another estimate<sup>275</sup> gives, for a different aminoenone, *ca* 28% of the *trans*- (unbonded) form even in heptane, rising to *ca.* 65% in ethanol. Taken together these observations must mean either that the intramolecular NH---O bond is very weak or that conjugative preference for the *E*-form is very strong, but does not allow of a decision. Other evidence tends to support the weakness of NH---O; in particular, the solution frequency of  $\nu\text{NH}$  in secondary aminoenones is not exceptionally low,<sup>272</sup> and where both chelated and unchelated isomers exist, there is no great difference in  $\nu\text{NH}$  between them.<sup>165</sup> For the isomer of **D** in which the intramolecular bonding pattern is switched from OH---N to NH---O our calculations show an energy deficit, relative to **D**, of 53-66 kJ mol<sup>-1</sup>, but this enormous effect is no doubt exaggerated by the gas phase relative to expectation in aqueous solution.

The overall picture is therefore one in which tautomeric preference is very clear for the extended structure **429** and high, but not quite so decisive, for the chelate **430**. The solvent studies described below tend to reinforce this difference, and aromatisation also tends to occur more frequently in the latter class, leading to some divergence between them.

### A.10.2 Solvent Studies

While  $\beta$ -diketones in the extended form enolise more as the solvent becomes more polar, the reverse is true when these are chelated, so that the latter show substantially less tendency to enolise in water [section A.6, eqns. (x) and (ix) respectively] and the same is true here.

$$\log K_E = -2.78(0.82) + 0.60(1.19)\pi^* + 0.05(0.56)\alpha + 3.61(1.06)\beta \quad (\text{xvii})$$

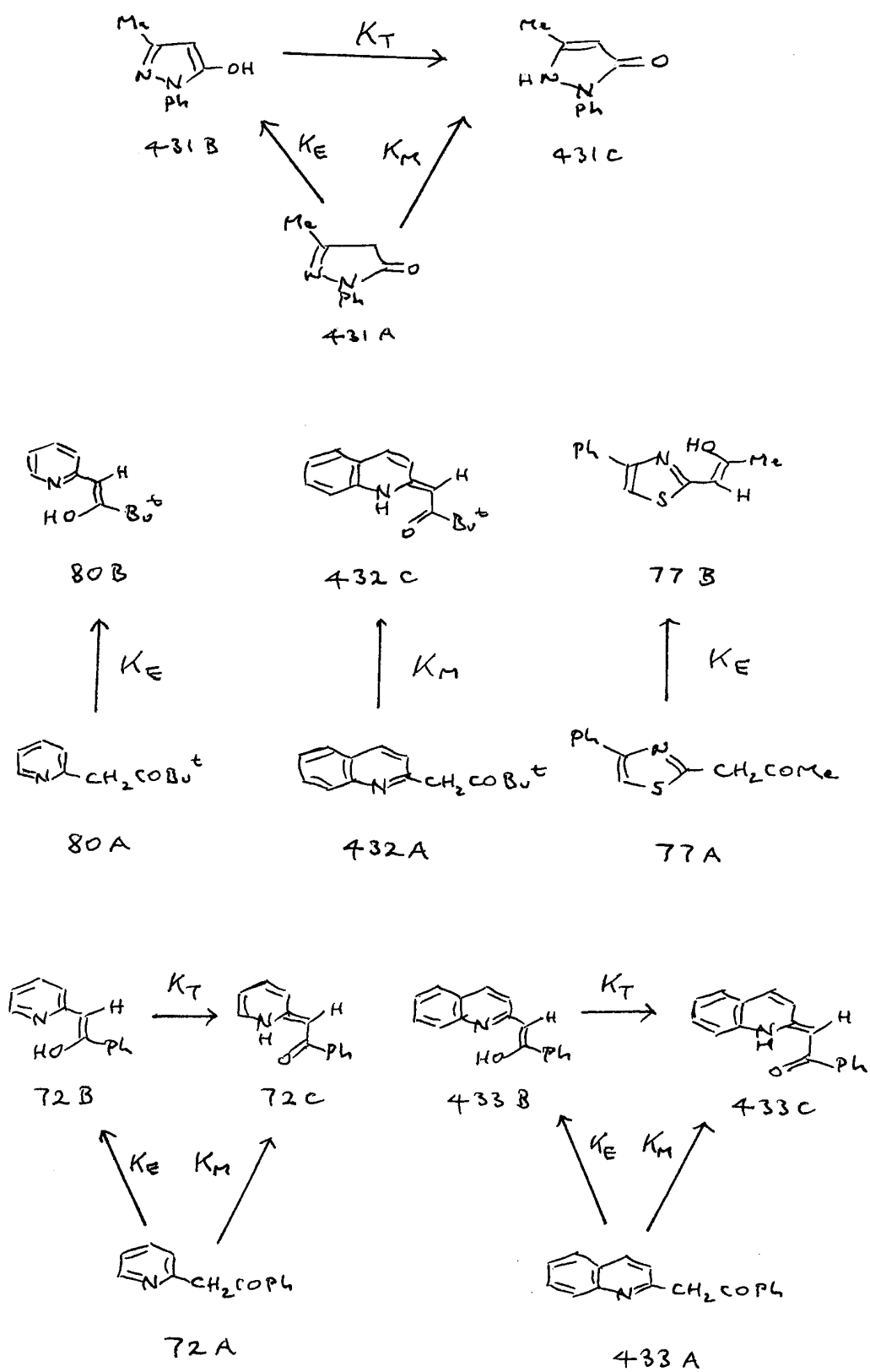
$$(n = 9 \quad r^2 = 0.80 \quad s = 0.42 \quad F = 6)$$

$$\log K_M = -3.78(0.52) + 1.79(0.54)\pi^* + 1.33(0.16)\alpha + 2.93(0.37)\beta \quad (\text{xviii})$$

$$(n = 9 \quad r^2 = 0.94 \quad s = 0.21 \quad F = 28)$$

$$\log K_T = -0.41(0.80) + 0.98(1.02)\pi^* + 1.29(0.44)\alpha - 1.42(0.58)\beta \quad (\text{xvix})$$

$$(n = 9 \quad r^2 = 0.76 \quad s = 0.32 \quad F = 5)$$



Scheme 19

Freyer *et al.*<sup>276</sup> have studied the solvent dependence of the 3-way equilibrium involving the pyrazolone **431** (Scheme 19) and our analysis of their data appears as equations (xvii) - (xix).<sup>277</sup> Since each has required a different selection of solvents these equations are not fully orthogonal, but nevertheless conclusions can be drawn. Table 32 gives the 'solvent factors'  $\Delta \log K$  (Appendix 2) calculated from the LSER equations to convert  $\log K$  in a range of common spectroscopic solvents to that, shown in the footnotes, expected for aqueous solution. As for dimedone **55** (section A.6) the unconjugated species **431A** dominates in nonpolar solvents, but here there are two conjugated tautomers **431B** and **431C**, favoured by dipolar aprotic and amphiprotic solvents respectively. Actual values range from 90% **431A** in dioxane, through 50% **431B** in DMSO, to 83% **431C** in  $\text{CF}_3\text{CH}_2\text{OH}$ ; that calculated for water is 87% **431C**, this increase being due to the positive  $\pi^*$  term which appears throughout. Note how misleading, with respect to water, the result for DMSO can be.

**Table 32. Solvent Dependence of Tautomerism for Scheme 19** <sup>a,b</sup>

Eqn.	MeOH	EtOH	DMSO	$\text{CHCl}_3$	Dioxane	Benzene	$\text{CCl}_4$	Alkane
(xvii) <sup>c</sup>	- 0.5	- 1.0	- 1.2	1.8	0.5	1.4	2.0	2.2
(xviii) <sup>d</sup>	0.5	0.3	0.7	3.0	2.6	3.3	4.2	4.8
(xix) <sup>e</sup>	1.1	1.5	2.1	0.9	2.0	1.6	1.7	2.1
(xx) <sup>f</sup>	- 0.6	- 0.7	- 1.1	- 1.0	- 1.4	- 1.4	- 1.7	- 2.0
(xxi) <sup>g</sup>	- 0.4	- 0.5	- 0.7	- 0.7	- 0.9	- 0.9	- 1.1	- 1.3

<sup>a</sup> Compound **77** omitted. <sup>b</sup> Values are  $\Delta \log K$  required for adjustment to aqueous value.

<sup>c</sup>  $K_E$  for **431**;  $\log K_E$  - 0.63 calculated for water. <sup>d</sup>  $K_M$  for **431**;  $\log K_M$  0.90 calculated for water. <sup>e</sup>  $K_T$  for **431**;  $\log K_T$  1.60 calculated for water. <sup>f</sup>  $K_E$  for **80**;  $\log K_E$  - 1.71 calculated for water. <sup>g</sup>  $K_M$  for **432**;  $\log K_M$  - 0.26 calculated for water.

$$\log K_E = 0.18(0.09) - 0.78(0.13)\pi^* - 0.89(0.11)\alpha \quad (\text{xx})$$

$$(n = 17 \quad r^2 = 0.90 \quad s = 0.14 \quad F = 63)$$

$$\log K_M = 1.06(0.11) - 0.62(0.16)\pi^* - 0.53(0.08)\alpha \quad (\text{xxi})$$

$$(n = 17 \quad r^2 = 0.79 \quad s = 0.15 \quad F = 27)$$

There is no one compound from which a similar picture for chelated aminoenones can be drawn, but Roussel *et al.*<sup>98</sup> have studied the related compounds **80** and **432** from which a composite picture can be built up. Our (slightly) revised versions of their equations in  $K_E$  for **80** and  $K_M$  for **432** appear as (xx)

and (xxi) respectively. For both there is a reversal in sign for the solvatochromic parameters  $\pi^*$  and  $\alpha$  relative to eqns. (xvii) - (xix); that is, the **A**-form is now favoured by polar solvents. Quantitatively, this trend appears alongside those for **431** in Table 32 and, as seen for  $\beta$ -diketones (section A.6), represents a characteristic difference in behaviour between chelated *vs.* extended structures (Appendix 2). [A very similar equation to (xx) is obtained for  $K_E$  in the case of **77**;<sup>99</sup> see Appendix 2.] The relation is slightly steeper for  $K_E$  than for  $K_M$ , implying that **C** should show only a slight gain over **B** with increasing solvent polarity, not the sharp rise shown by **431**.

The reason for the switch from **A**  $\rightleftharpoons$  **B** for the pyridines to **A**  $\rightleftharpoons$  **C** for the quinolines lies in benzofusion. Since **C** disrupts the aromatic structure whereas **B** does not, **C** is suppressed in pyridines relative to quinolines for which this factor matters much less. Table 33 presents the data of More O'Ferrall *et al.*<sup>93</sup> for the compounds at the foot of Scheme 19 and their 4-substituted isomers. For the former, the dominant species in water are **72A** (*ca.* 90%) and **433C** (*ca.* 92%) with **B** the least important in both cases. (The use by Roussel *et al.*<sup>98</sup> of -COBu<sup>t</sup> in place of -COPh scarcely affects  $K_E$  ( $\Delta \log K_E$  0.3) but sharply reduces  $K_M$  ( $\Delta \log K_M$  *ca.* - 1.4), allowing a clean but possibly exaggerated distinction between **80** and **432**. This effect is presumably steric, leading to a distortion in planarity specially unfavourable to the **C**-form). The result of benzofusion in **433** is to boost the **C**-form by  $\Delta \log K_M$  2.14, close to the upper limit found for this effect (Appendix 5). Its effect on  $K_E$  is relatively slight, that on  $K_T$  being simply their resultant. A curious feature of these results, not echoed *e.g.* by  $K_T$  for 4-pyridone and 4-quinolone (section A.10.7), is the negligible effect of benzofusion on  $K_M$  in the 4-substituted series (not much effect is expected on  $K_E$ ). Further but qualitative data, mostly for 2-substitution, appear in Section A.10.14.

**Table 33. Tautomeric Equilibria for 2- and 4-CH<sub>2</sub>COPh (2- and 4-X) Derivatives of Pyridine (P) and Quinoline (Q)**

	$\log K_E$		$\Delta \log K$	$\log K_M$		$\Delta \log K$	$\log K_T$		$\Delta \log K$
	P	Q		P	Q		P	Q	
2-X	- 2.0	- 1.3	0.7	- 1.05	1.09	2.14	0.95	2.4	1.45
4-X	- 4.4	- 4.2	0.2	- 2.42	- 2.30	0.12	2.0	1.9	- 0.1

### A.10.3 Correction Factors for the 'Basicity Method'

Only two of general applicability are needed here. One is for  $\Delta pK_a$  (NAlk  $\rightarrow$  NH), i.e.  $\Delta(NR)$ , while the other is for  $\Delta pK_a$  (OAlk  $\rightarrow$  OH), i.e.  $\Delta(OR)$ . For the whole class of vinylogous amides we have  $\Delta(NR) = 0.05 \pm 0.11$  ( $n = 12$ ), but inspection reveals that 6- and 5-membered rings show different behaviour:  $-0.01 \pm 0.09$  ( $n = 8$ ) and  $0.16 \pm 0.02$  ( $n = 4$ ) respectively. Hence we employ  $\Delta(NR)$  0.0 and 0.15 in these two contexts. The available pyridinols give  $\Delta(OR) 0.46 \pm 0.15$  ( $n = 5$ ) which becomes  $0.47 \pm 0.16$  for the four most reliable values. In addition, (**434**, R = H or alkyl)<sup>278</sup> gives, after statistical correction when R = H,  $\Delta(OR) = 0.56$ , suggesting that  $\Delta(OR)$  *ca.* 0.5 may apply generally to  $\gamma$ -OH; its incorporation gives  $\Delta(OR) 0.49 \pm 0.15$  ( $n = 5$ ). We accept  $\Delta(OR)$  0.5 for vinylogous bases of whatever sort (Appendix 1).

### A.10.4 Extended Structures: One Donor, One Acceptor

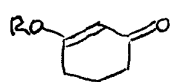
The definitive study is by Greenhill,<sup>119</sup> who measured  $pK_a$  values in water for (**435**, R = alkyl). Here (**435B**, R' = Me) and **435C** possess  $pK_a$   $11.20 \pm 0.07$  ( $n = 4$ ) and  $3.04 \pm 0.06$  ( $n = 4$ ) respectively, i.e.  $\Delta pK_a$  8.16 which, with the above correction for  $\Delta \log K_T$ , becomes  $\log K_T = 8.7$ . This is close to the value predicted by calculation (section A.10.1) and not far short of that we deduce for a simple aliphatic amide,  $\log K_T$  *ca.* 9.1 (section B.2.3). Greenhill notes that the UV spectra of **435C** and **435D** are essentially identical in water, EtOH and C<sub>6</sub>H<sub>12</sub>, hence **435A** and **435B** remain undetectable even in the least polar solvents.

Different  $\pi$ -donors may however give different results. For the equilibrium between **436A** and **436C**, Fatiadi<sup>279</sup> found 3% or 1% of the former to be present in DMSO for R = H and Me respectively, hence  $\log K_M$  probably lies in the range 1.5 - 2.0. If this equilibrium follows eqn. (xviii) we may predict  $\log K_M$  *ca.* 2.5 for aqueous solution. On any argument **436C** like **435C** will be overwhelmingly the dominant tautomer in water, but conceivably the A-form, which is undetectable for **435**, may be more important for **436**. We have postulated (section A.4.6) that  $\pi$ -donor substituents on nitrogen stabilise imines relative to enamines in simple cases. While the data for **436** do not allow that suggestion to be quantified, some related equilibria involving 4-amino-2-pyrimidones (section B.5.15) suggest that -NHNH<sub>2</sub> in place of -NH<sub>2</sub>, to give =NNH<sub>2</sub> not =NH, may produce a shift of  $\Delta \log K_M$  *ca.* 2.6. In that case  $\log K_M \geq 5$  follows for **435** (the mean value predicted in Table 31 is 4.1), leading to  $\log K_E$  *ca.*

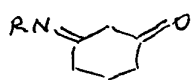
-3.5 and a stability order  $\mathbf{C} \gg \mathbf{A} \gg \mathbf{B}$  in line with the predictions of section A.10.1. The importance of this insight lies in the realisation that the overwhelming preponderance of  $\mathbf{C}$  over  $\mathbf{B}$  does not necessarily, even in simple cases, mean that no other tautomer can be present; there may be scope occasionally for  $\mathbf{A}$  to co-exist.

This point is emphasised by the results of Israel *et al.*<sup>280</sup> for the 1,4-diazepinones **438** - **443**. In  $\text{CHCl}_3$ , DMSO and MeOH, **438** ( $\text{R} = \text{Me}$  or  $\text{CF}_3$ ) exists exclusively in the  $\mathbf{A}$ -form shown; assuming that ‘exclusivity’ entails  $\log K_M \leq -2$ , eqn. (xviii) which we postulate as relevant since **431** and **438** possess similar geometries would predict  $\log K_M \leq -1$  in water. This on the face of it is highly anomalous given the picture for **431** above, but the core unit **437C** is formally anti-aromatic and, as for the corresponding benzofused diazepines (section A.9.2), the unconjugated tautomer **438A** is preferred. However,  $\log K_M = -0.3$  for **439** in pyridine, which again using eqn. (xviii), leads to a predicted value of *ca.* 0.9 in water. This difference of *ca.*  $10^2$  in  $K_M$  between **438** and **439** is consistent with the postulate (section A.4.6) that, while a  $\pi$ -donor on N will stabilise the imine, the enamine tautomer will be favoured by  $\pi$ -acceptors. Where lone pair repulsion in **440A** is replaced by a dipolar attraction in **440C**,  $\log K_M$  in pyridine rises to 0.5; where this is accompanied by extra electron withdrawal in **441**, only the  $\mathbf{C}$ -tautomer is visible. The much less aromatic (or less anti-aromatic) compound **443** exists entirely in the  $\mathbf{C}$ -form, but the dipolar clash (NR-NH) in its isomer **442C** is sufficient to lead to **442A** instead. We estimate this dipolar clash to be destabilising, in water, by  $> 10^3$  (Appendix 3). A similar repulsion is present in **443C** but this is insufficient to overwhelm amide resonance (section B.2). We may confidently predict that nonaromatic 1,4-diazepinones such as **444** will exist in the  $\mathbf{C}$ -form shown.

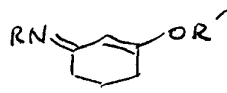
Several cases of ‘nested’ aminoenones (*cf.* section A.9.6) have been reported. In 90% EtOH, Seiffert *et al.*<sup>281</sup> state the  $\mathbf{B}$ - and  $\mathbf{C}$ -forms of the acridines **445** and **446** to co-exist, but this claim is based on calculated UV spectra, no model compounds were studied, and given the loss of aromaticity, the evidence must be considered doubtful. Tautomerisation to the  $\mathbf{C}$ -form is more likely for the less aromatic phenazines **447** where Corbett,<sup>282</sup> using model compounds, found **447B** but **448C** to predominate in water. Here methyl, an electron donor, as usual favours the more polar tautomer. However the predominant tautomer of **449** is **449b** not **449c**, presumably because of lone pair repulsion in the latter. Structures **449** in particular may be considered as split horizontally into two almost independent conjugated units, much as barbituric acid (section A.6.2) may be regarded as an imide



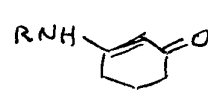
434



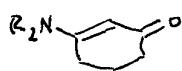
435A



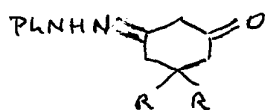
435B



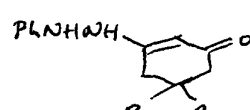
435C



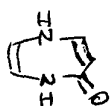
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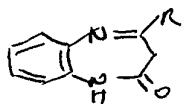
436A



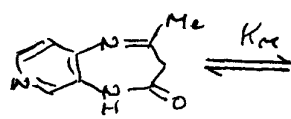
436C



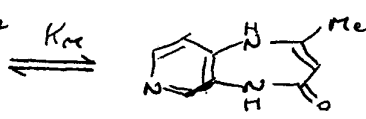
437C



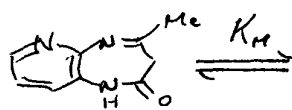
438A



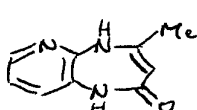
439A



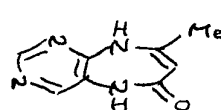
439C



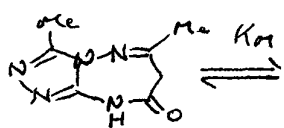
440A



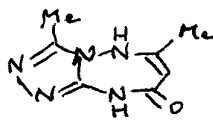
440C



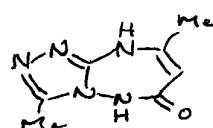
441C



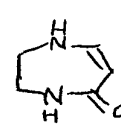
442A



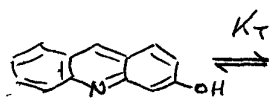
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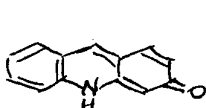
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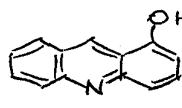
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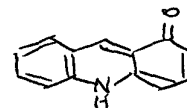
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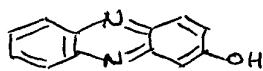
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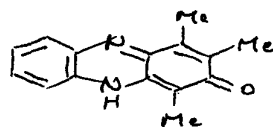
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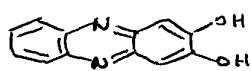
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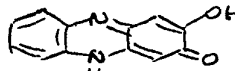
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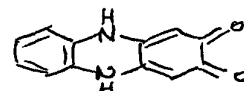
448C



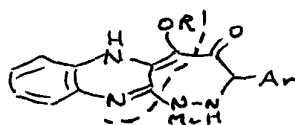
449a



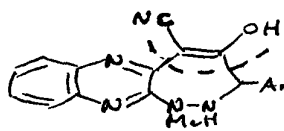
449b



449c



450



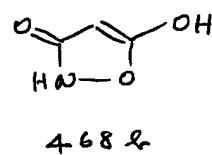
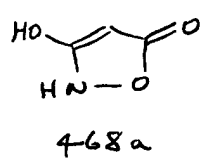
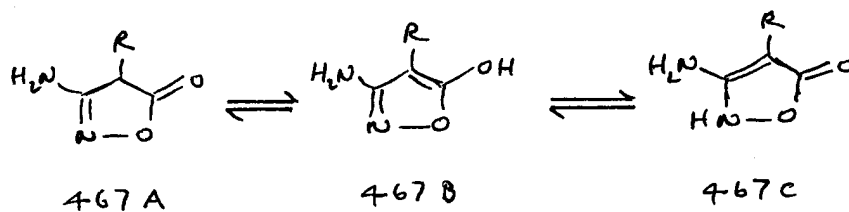
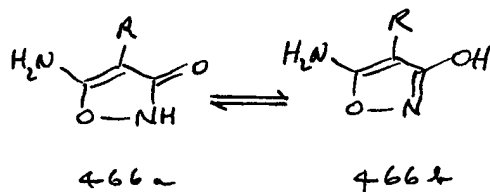
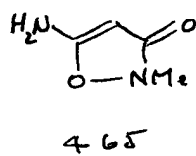
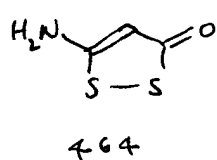
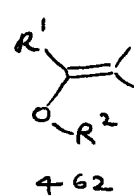
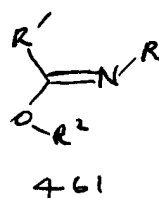
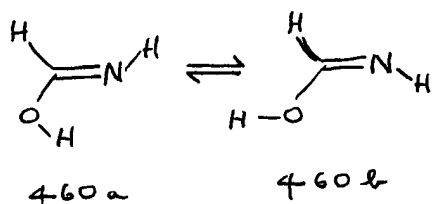
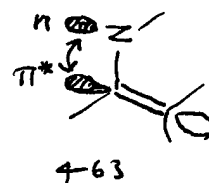
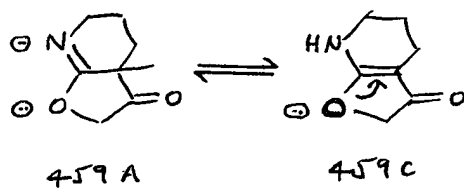
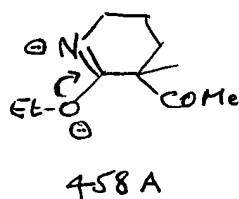
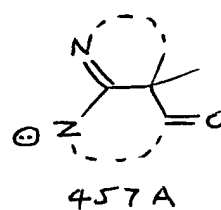
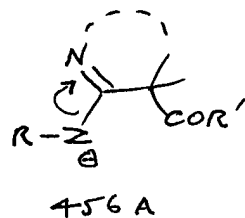
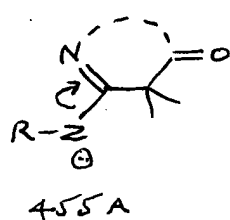
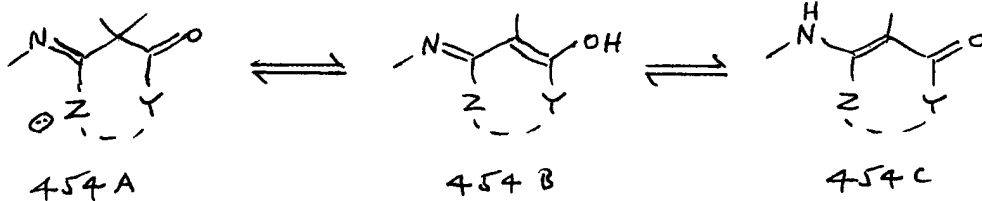
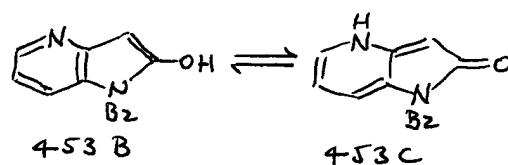
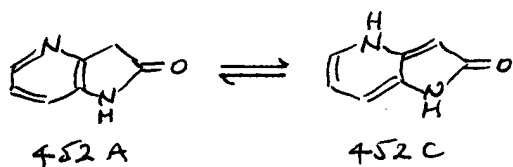
451

grafted on to a  $\beta$ -diketone. Compounds **450** and **451**, which in DMSO exist as shown,<sup>283</sup> are complex and instructive examples. The key to their difference in tautomeric form probably lies in the *localised conjugation* we have identified elsewhere (*cf.* section A.6.3). The aminoenone structure of **450** is reinforced by the  $\pi$ -donor OR which, rather as in **449b**, superimposes its own complementary conjugated system; in **451** this is opposed by the  $\pi$ -acceptor CN whose priorities are quite different. Clearly both compounds lie close to the tautomeric borderline and the position for water is uncertain, but quite plausibly both structures are maintained, with that of **450**, with two  $\pi$ -acceptors acting on NH, the more likely if both take the same form. Two ostensibly surprising examples are the related pyrrolopyridines **452** and **453**.<sup>284</sup> Here **452A** but **453C** are the tautomers present in the solid state, whereas both give the **C**-tautomer in MeOH. Possibly the lactam **452A** gives dimers whereas, this being denied to **453A**, **453B** achieves hydrogen bonding *via* its OH-group. A parallel situation in DMSO may explain why this solvent favours **452A** but **453C**. Given a probable  $\log K_M > 5$  for **435** (see above) but a likely penalty for loss of aromaticity on the same order (section A.10.6) it is a moot point whether the **A**- or **C**-tautomer will dominate in water, but **B** can probably be discounted. This is one example where the preference shown by the solid state cannot be trusted to extend to water.

### A.10.5 Extended Structures: Two Donors, One Acceptor

It has been noted in discussing Scheme 18 that a  $\pi$ -donor placed in conjugation with C=N may in principle stabilise the **A**- or **B**-tautomer in much the same way as when C=N is part of an aromatic ring. While there is a dearth of information on this type of compound — contrast that for chelates, section A.10.12 — it represents a potentially important class and informed speculation is in order.

The simplest situation is that depicted as **454** (*cf.* **429**), where Z is a  $\pi$ -donor and, if Y is one as well, **454B** may be eliminated *a priori* (*cf.* the  $\beta$ -ketoesters of section A.6.7). Here Z and Y are necessarily part of a ring, or a chelate would result, and if Y is also a hetero-atom they must not be linked, or the molecule would count as aromatic (but see below). Other possible alignments that avoid chelate formation include the monocycles **455** and **456** and the fused bicycle **457**, all shown as the **A**-form; it is always necessary for C=N or Z to form part of a ring, but both need not do so.



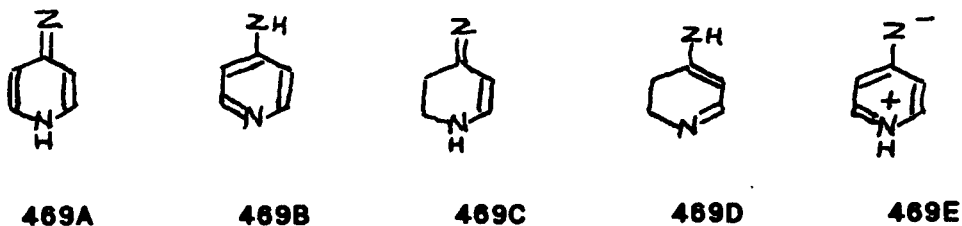
Sliwa and Delauney<sup>285</sup> showed **458** and **459** to exist as the **A**- and **C**-tautomers respectively, and attributed this to lone pair repulsion in **459A**. While this is certainly a major factor, a still more significant phenomenon is hiding behind it. In iminoethers **461**, the *syn*-conformation shown is overwhelmingly dominant;<sup>286</sup> in the iminol **460**, **460a** is calculated<sup>287</sup> (at the 4-31G level) to be preferred to its nearest rival **460b** by  $\Delta H$  3.77 kcal mol<sup>-1</sup>. This same *syn*-preference, by *ca.* 3 kcal mol<sup>-1</sup>, attaches to esters<sup>200</sup> (Table 24) and is also found for vinyl ethers **462**<sup>286</sup> in which lone pair repulsion cannot be a factor. The reason in all cases is that the  $n\text{-}\pi^*$  interaction shown as **463** is a function of the *syn*-conformation whereas in the *anti*-conformation it is impaired or destroyed. Its importance here is that the *syn*- and *anti*-conformations should stabilise C=N (in the **A**-) and C=C (in the **C**-tautomer) respectively. Hence while the normally dominant **C**-tautomer is expected for **454** and **457**, the **A**-tautomer may result in **455** and **456**. Lack of examples prevents us from being more specific, and prediction is anyway not so clearcut for Z = NH as for Z = O or S, but strong supporting evidence comes from the corresponding chelates (section A.10.12). Nevertheless, resonance stabilisation of the **A**-form by Z has to overcome  $K_M \geq 10^5$  which is a quite formidable obstacle, and it is much more likely that, in these extended structures, **454** and **457** will retain a preference for the **C**-tautomer than that this preference will be lost by **455** and **456**, at least in water. Experimental evidence is badly needed.

If Y and Z are linked hetero-atoms this generates a formally  $6\pi$  system, though the existence of a ring current is problematical and lone pair repulsion necessarily possesses a major rôle. When this cannot be relieved by tautomerisation, as in **464**<sup>2gg</sup> and **465**<sup>2mm</sup>, the **C**-tautomer continues to dominate (but note **290**, section A.6.4, as an exception). However, **466** consists in the mixture shown, though the proportions have not been established.<sup>2mm</sup> Similarly, while (**467**, R = Ph) exists entirely, and (**467**, R = Et) mostly, as **467C** in EtOH, both are found as **467A** in the solid state;<sup>2mm</sup> this time, the **B**-form is absent. In these cases, the otherwise favoured **C**-forms **466a** and **467C** are destabilised by dipolar repulsion. Some insight is provided by **468**, thought to exist as **468a** not **468b**.<sup>2nn</sup> Here the better donor (ring NH > O) is combined vinylogously in the dominant tautomer with the stronger acceptor (ester > amide) and similarly the amide group of **466** will tautomerise whereas the ester group of **467** will not. Pyrazolones and isoxazolones are considered more generally in section B.2.10 and summarised in sections C.15 and C.16.

### A.10.6 Aromatisation in Extended Structures: 4-Pyridones

Aromatisation at (a) in Scheme 18 will stabilise the **A**- or **B**-tautomer relative to **C**; at (c) it will stabilise **B** relative to **A** and **C**. These cases are dealt with in subsequent sections. Aromatisation at *both* (a) and (c) has the effect that **B** alone is fully aromatic and is strongly favoured relative to the normally dominant tautomer **C** whereas the unconjugated tautomer **A** is suppressed. 4-Pyridone (**469A**,  $Z = O$ ) exemplifies this class.

Katritzky and co-workers<sup>150a</sup> have discussed the effect of aromaticity here on the lines previously set out (section A.4.7) for the corresponding methide, (**469**,  $Z = CH_2$ ). Table 34 compares these compounds and the related pyridonimine (**469**,  $Z = NH$ ) from section A.9.4.<sup>289</sup> Here we follow these authors<sup>150a</sup> in using Greenhill's results<sup>119</sup> for **435** (section A.10.4) as models for **469C** and **469D**,  $Z = O$  and, similarly, use the symmetrical 1,4-diazepine (**385**,  $R^1 = R^2 = Me$ ) to supply  $pK_a$  estimates for **469C** and **469D**,  $Z = NH$ . In neither case is the geometry of the model compound identical to that which it models, but also in neither case is this likely to have serious consequences. Outstandingly, Table 34 reveals that the loss of aromaticity involved in **469A** vs. **469B** is vastly less for  $Z = O$  than for  $Z = CH_2$ , whether measured as free energy ( $\log K_T$ ) or as enthalpy ( $A_{py} - A_x$ ), with  $Z = NH$  occupying an intermediate position. The origin of this difference lies<sup>150a</sup> in the contribution of canonical form **469E** to the electronic structure of **469A**: where this is high, as for  $Z = O$  which readily accepts a negative charge, **469A** will retain a considerable degree of aromaticity. The overall result is that, while **469A** is strongly disfavoured relative to **469B** for  $Z = CH_2$  and  $Z = NH$ , it remains the favoured tautomer for  $Z = O$  even though much less dominant:  $\log K_T$  3.9 for **469** (Table 35) in place of  $\log K_T$  8.7 for **435**.

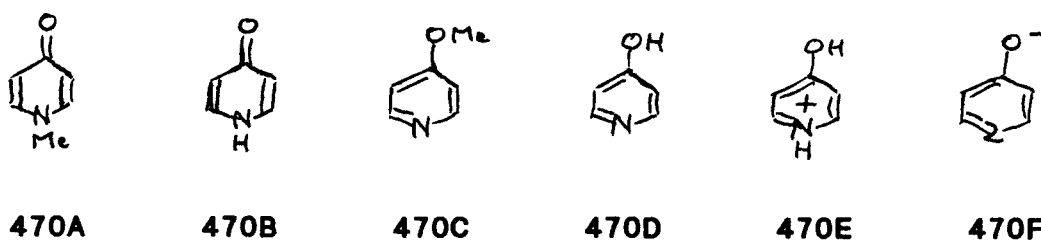


**Table 34. Thermodynamics of Tautomerisation for 469<sup>a</sup>**

Z	pK <sub>a</sub> (A)	pK <sub>a</sub> (B)	pK <sub>a</sub> (C)	pK <sub>a</sub> (D)	Δ log K <sub>T</sub> <sup>b</sup>	(A <sub>py</sub> - A <sub>x</sub> ) <sup>c</sup>
CH <sub>2</sub> <sup>d</sup>	19.46	6.02	9.2	8.7	12.9	15.6
NH	17.87 <sup>e</sup>	9.17 <sup>e</sup>	13.4 <sup>f</sup>	13.4 <sup>f</sup>	8.7 <sup>e</sup>	11.3
O	3.27 <sup>g</sup>	7.12 <sup>g</sup>	3.04 <sup>h</sup>	11.75 <sup>h</sup>	4.8	7.0 <sup>i</sup>

<sup>a</sup> Ref. 150a and section A.4.7. <sup>b</sup> Attenuation for **469B** → **469A** relative to **469D** → **469C**.

<sup>c</sup> Eqn. (viii). <sup>d</sup> Table 17 (section A.4.7). <sup>e</sup> Table 30 (section A.9.4). <sup>f</sup> For (**385**, R<sup>1</sup> = R<sup>2</sup> = Me); see the text. <sup>g</sup> Table 35. <sup>h</sup> For **435** (section A.10.4); see the text. <sup>i</sup> Ref. 150a; see the text.

**Table 35. pK<sub>a</sub> and log K<sub>T</sub> Values for Compounds 470 in Water<sup>a,b</sup>**

Substituent	pK <sub>a</sub> (A)	pK <sub>a</sub> (B)	pK <sub>a</sub> (C)	pK <sub>a</sub> (D)	log K <sub>T</sub>
-		3.27 <sup>c</sup>	6.62 <sup>c</sup>	7.12	3.9
2-NH <sub>2</sub> <sup>d</sup>		5.04 <sup>e</sup>	7.62 <sup>e</sup>	8.12	3.1
2,6-di-Me	4.12 <sup>f</sup>	4.12	7.86	8.36	4.2
2-Cl	2.27 <sup>g</sup>	2.27	1.93 <sup>g</sup>	2.43	0.2 <sup>h</sup>
2,6-di-CO <sub>2</sub> Et	1.29 <sup>f</sup>	1.29	0.18 <sup>f</sup>	0.68	-0.6 <sup>i</sup>
3-NH <sub>2</sub>	3.91 <sup>f</sup>	3.91	7.52 <sup>f</sup>	8.02	4.1
3-NO <sub>2</sub>	-0.80 <sup>f</sup>	-0.80	2.63 <sup>f</sup>	3.13	3.9
3,5-di-Cl	-1.22 <sup>f</sup>	-1.22	1.14 <sup>f</sup>	1.64	2.9

<sup>a</sup> log K<sub>T</sub> = pK<sub>a</sub>(D) - pK<sub>a</sub>(B). <sup>b</sup> Estimated values (section A.10.3) are *italicised*. <sup>c</sup> Ref. 4.

<sup>d</sup> Not used for deriving correlations (see the text). <sup>e</sup> Ref. 293. <sup>f</sup> From compilation in ref. 290.

<sup>g</sup> Ref. 294. <sup>h</sup> D%: calculated, 39; observed, 40. <sup>i</sup> D%: calculated, 80; observed, 72.

Katritzky<sup>200,290</sup> has analysed the effect of substituents on  $\log K_T$  for 4-pyridones **470** in the following way. The common cation **470E** can deprotonate from nitrogen to give **470D** or from oxygen to give **470B**. According to Clark and Perrin,<sup>291</sup> the  $\rho\sigma$  relation for substituted pyridines takes the form of eqn.

$$pK_a(\text{Py}) = 5.25 - 5.90 \sigma_s \quad (\text{xxii})$$

$$pK_a(\text{F}) = 10.0 - 2.11 \sigma_s \quad (\text{xxiii})$$

$$pK_a(\text{B}) = 3.3 - 2.11 \sigma_s \quad (\text{xxiv})$$

(xxii) where  $\sigma_s$  represents an experimentally derived ‘standard’ value for use in context; to give  $pK_a(\text{D})$  this must be adjusted by  $\Delta pK_a + 1.3$  to give a calculated value for the 4-hydroxypyridine. For **470B**, we start from Jaffé’s equation (xxiii)<sup>292</sup> for the deprotonation of substituted phenols to the anion (**470F**,  $Z = \text{CH}$ ) and, treating **470B** as its resonance form (**470F**,  $Z = \text{NH}^+$ ), convert this to eqn. (xxiv). Then  $\log K_T = pK_a(\text{D}) - pK_a(\text{B})$  follows. This approach should work but in fact the results, for the few usable data (Table 35), are rather unsatisfactory.

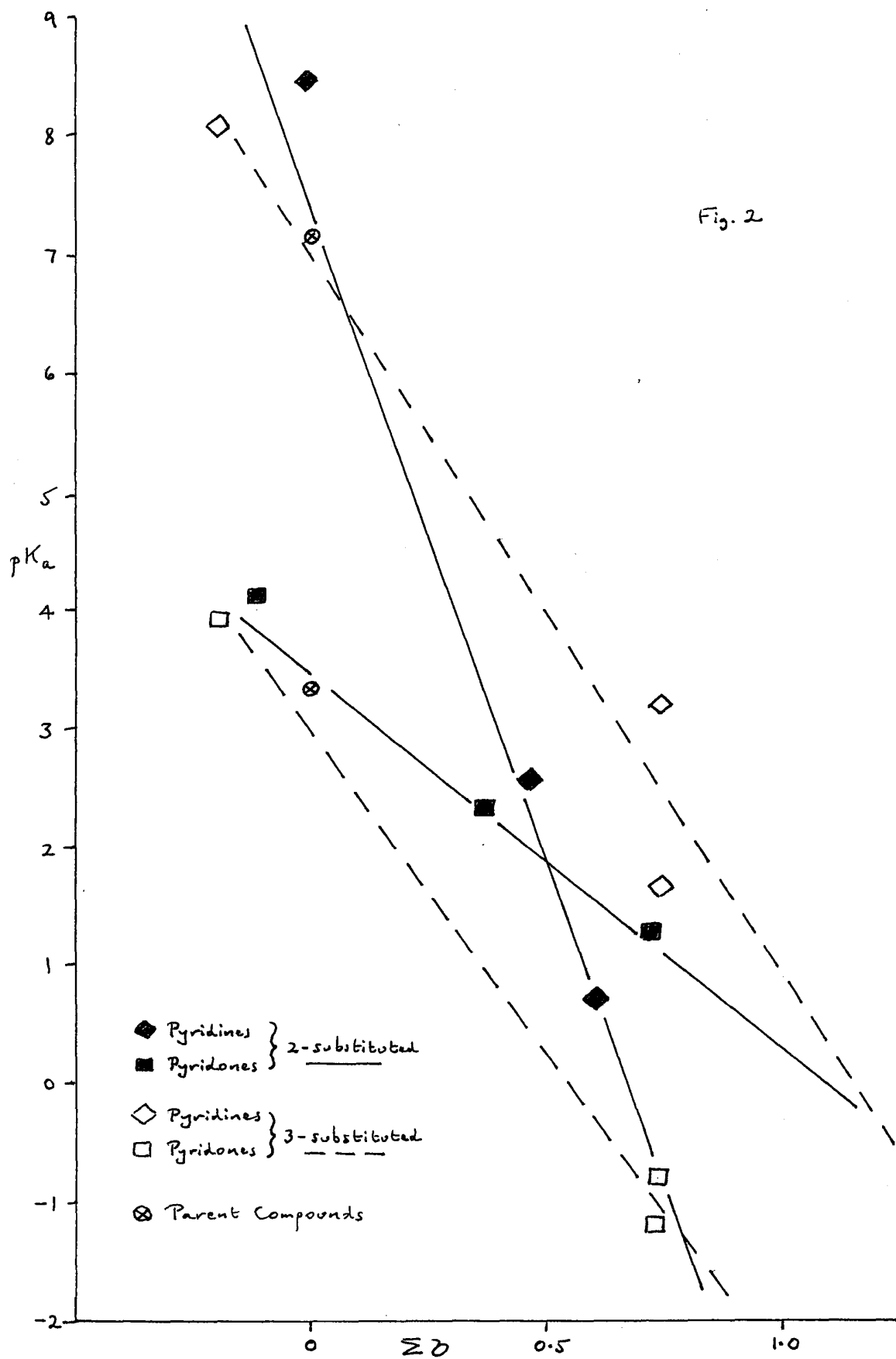
$$\Delta pK_a (2\text{-Py}) = -10.6\sigma_I - 1.39\sigma_R^+ \quad (\text{xxv})$$

$$\Delta pK_a (3\text{-Py}) = -6.02\sigma_I - 2.63\sigma_R^0 \quad (\text{xxvi})$$

$$\Delta pK_a (4\text{-Py}) = -5.15\sigma_I - 2.69\sigma_R^+ \quad (\text{xxvii})$$

We believe the problem to arise from the use by Katritzky, inevitable at that time, of ‘standard’  $\sigma$ -values derived for the most part from benzenoid compounds. Taft’s later results for 2-, 3- and 4-substituted pyridines<sup>259</sup> are given as eqns. (xxv) - (xxvii). Here the field-resonance balance  $\lambda = \rho_R/\rho_I$  is 0.13, 0.44 and 0.52 respectively, in sharp contrast to  $\lambda = 1$  (by definition) for  $\sigma_p$  and 0.28 for  $\sigma_m$ .<sup>259</sup> It is a general trend that the resonance term is relatively less important for LFER relationships in heteroaromatic than in benzenoid compounds;<sup>106</sup> this is specially true for 2-substituted pyridines, eqn. (xxv), where a simple  $\sigma_I$  relationship will tolerably well fit all but alkyl- and amino-substituents (see below).

With so few usable data, the DSP approach<sup>39,259</sup> is in any case infeasible here. We have tried the experiment of using  $\sigma_I$  for 2-substituted pyridines and  $\sigma_m$  elsewhere; while not a perfect solution,  $\sigma_m$  frequently gives acceptable LFER equations in heterocyclic contexts.<sup>106</sup> The results are plotted in Fig. 2 and the derived equations appear in Table 36. Statistical validation is not possible but we reproduce the wide variations in  $pK_a$  of the 2-substituted compounds and the shallow variation for 3-substituents, perceptively attributed by Katritzky<sup>290</sup> to the equidistant spacing



of the substituent from  $\text{OH}^+$  and  $\text{NH}^+$  in the cation, hence its equal influence on each. Tentatively, Table 37 sets out the results predicted by eqns. (xxx) and (xxxiii) for  $\Delta \log K_T$  for some common substituents relative to 4-pyridone itself. The very low sensitivity of  $K_T$  to 3-substitution is striking and indicates that only in rare circumstances is much of the OH-tautomer likely to be generated. For 2-substitution the crossover comes in the region occupied by most halogens, with only very electronegative substituents capable of reversing the normal preference for the pyridone tautomer. Even more tentatively, we postulate the same  $\Delta \log K_T$  values for 4-quinolone, though starting from a higher  $K_T$  value (see footnote to Table 37, and following section).

**Table 36. LFER Equations for 2- and 3-Substituted 4-Hydroxypyridine and 4-Pyridone  $\text{pK}_a$  Values in Water <sup>a</sup>**

	2-Substituents		3-Substituents
Pyridine $\text{pK}_a$ :	7.2 - 10.5 $\sigma_I$	(xxviii)	7.0 - 6.1 $\sigma_m$ (xxxi)
Pyridone $\text{pK}_a$ :	3.5 - 3.2 $\sigma_m$	(xxix)	3.0 - 5.4 $\sigma_m$ (xxxii)
$\log K_T$ :	3.7 + 3.2 $\sigma_m$ - 10.5 $\sigma_I$	(xxx)	4.0 - 0.7 $\sigma_m$ (xxxiii)

<sup>a</sup> See Fig. 2.

**Table 37. Predicted  $\Delta \log K_T$  for Selected Substituents <sup>a</sup>**

	2-Substs.	3-Substs.		2-Substs.	3-Substs.
Alk	<i>b</i>	<i>b</i>	OCOMe	- 3.0	- 0.2
NR <sub>2</sub>	- 0.8 <sup>d</sup>	0.1	I	- 3.1	- 0.2
Ph	- 1.0	<i>c</i>	OPh	- 3.4	- 0.1
COMe	- 1.9	- 0.3	Cl	- 3.7	- 0.2
CO <sub>2</sub> Me	- 2.0	- 0.3	Br	- 3.8	- 0.2
NHCOMe	- 2.4	- 0.1	CN	- 4.0	- 0.4
SMe	- 2.6	- 0.1	SO <sub>2</sub> Me	- 4.1	- 0.4
CF <sub>3</sub>	- 2.7	- 0.3	F	- 4.5	- 0.2
OMe	- 2.8	<i>c</i>	NO <sub>2</sub>	- 4.7	- 0.5

<sup>a</sup> Relative to  $\log K_T$  3.9 for 4-pyridone or 4.9 for 4-quinolone. <sup>b</sup> Probable increment *ca.* + 0.3 per alkyl group. <sup>c</sup> Negligible ( $< \pm 0.1$ ). <sup>d</sup> See the text.

It was noted above that 2-amino- and alkyl-substituent  $pK_a$  values are not expected to fit a simple  $\sigma_I$  or even  $\sigma_m$  relation. This is indicated by the data for the 2-amino substituent<sup>293</sup> in Table 35, whose  $\log K_T$  value is much higher than eqn. (xxx) would predict, since the effect of  $NH_2$  is dominated by the resonance term of eqn. (xxv) which eqn. (xxx) omits. Spinner<sup>20</sup> demonstrated that, while alkyl groups are base-strengthening towards both 2-pyridinols and 2-pyridones, their nett effect is to increase  $K_T$ , by *ca.* 5-fold for 4,5-disubstitution; more generally we suggest an increment, for 4-pyridones as well, on the order of  $\Delta \log K_T$  *ca.* +0.3 per alkyl group. No other common substituent should seriously misbehave. Multiple 2- or 2,3-substitution of other groups may of course result in a preference for the hydroxy tautomer; some known or suspected examples have been published.<sup>290,294</sup> In fact, the plot (Fig. 2) for 2-substituted pyridines *vs.*  $\sigma_I$  is linear despite containing two 2,6-disubstituted compounds, which argues strongly for  $\sigma$ -additivity. This is another area where more data are needed.

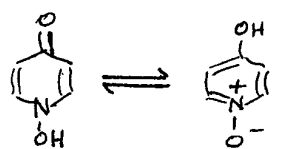
*N*-Oxides may be regarded as involving a special sort of highly electronegative substitution, that on ring nitrogen itself, and its consequences are much as seen for the 2-position above.<sup>295</sup> For the pyridone *N*-oxide **471**,  $K_T \sim 1$ ,<sup>296</sup> and a curious feature of these compounds is that benzofusion has almost no effect on tautomeric form:  $K_T \sim 1$  for **472** also.<sup>29</sup> Very often also there is no common cation so that the 'basicity method'<sup>5</sup> is inapplicable,<sup>295</sup> which has severely inhibited quantitative study. For these and other reasons our treatment of *N*-oxide tautomerism will be cursory.

**Table 38.  $pK_a$  and  $\log K_T$  Values for 2-Aza and Benzofused 4-Pyridones in Water** <sup>a,b,c</sup>

Compound	$pK_a$ (NH)	$pK_a$ (OMe)	$pK_a$ (OH)	$\log K_T$
<b>470</b>	3.27	6.62	<i>7.12</i>	3.9
<b>1</b>	2.27	6.65	<i>7.15</i>	4.9
<b>473</b>	-0.32	<i>ca.</i> 7	<i>ca.</i> 7.5	<i>ca.</i> 7.8
<b>474</b>	1.07	3.70	<i>4.2</i>	3.1
<b>475</b>	-0.35	3.21 <sup>d</sup>	<i>3.71</i>	4.1

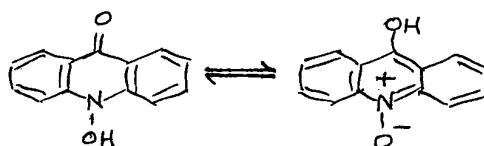
<sup>a</sup>  $\log K_T = pK_a(OH) - pK_a(NH)$ . <sup>b</sup> Estimated values (section A.10.3) are *italicised*.

<sup>c</sup> All  $pK_a$  values are from ref. 4 except where otherwise indicated. <sup>d</sup> A. Albert and A. Hampson, *J. Chem. Soc.*, 1954, 505.



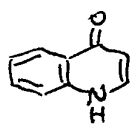
471a

471b

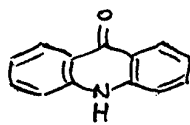


472a

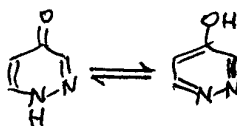
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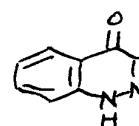
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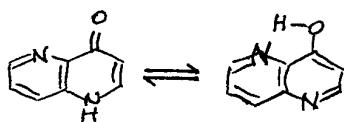
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474

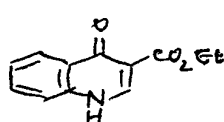


475

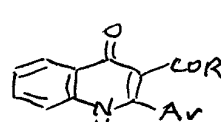


476a

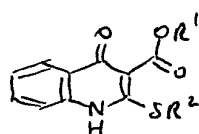
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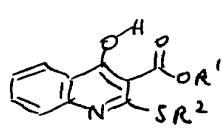
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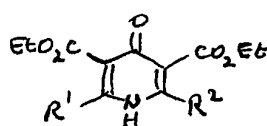
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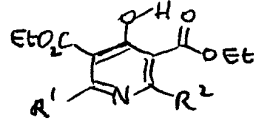
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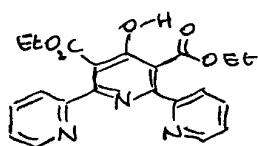
479b



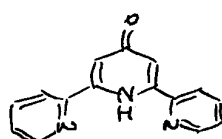
480a



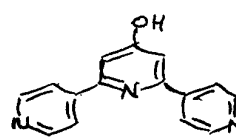
480b



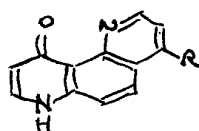
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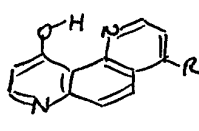
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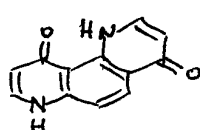
483



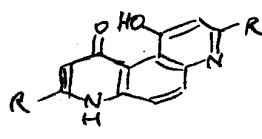
484a



484b



485



486

### A.10.7 Aromatisation in Extended Structures: Related Oxoheterocycles

Simple heterocycles related to 4-pyridone are confined to **1** and **473** - **475**, for each of which  $K_T$  is known (Table 38). Benzofusion of **470** to give **1** and of **474** to give **475** leads in each case to  $\Delta \log K_T$  *ca.* 1.0, consistently with the behaviour of the 4-cinnolonimine **400** and entirely out of line with that of 4-pyridonimine (**396**, R = H), somewhat supporting our view (section A.9.4) that the published information on **397** is at fault. This relatively slight effect of benzofusion appears characteristic of compounds in which tautomeric nitrogen is adjacent to the ring junction (Appendix 5). However, the very large rise in  $K_T$  for 5-acridone **473**, to a level little short of that for the non-aromatic **435**, is at first sight surprising. A possible explanation, suggested by Dr Roger Sayle, lies in the quinonoid nature of its *iminol* tautomer, which on evidence presented elsewhere (section B.2.5) should boost  $K_T$  by  $\Delta \log K_T$  *ca.* 1.9. If to this we add the expected effect of benzofusion in the oxo-tautomer (see above),  $\log K_T$  7.8 is predicted, identical with the estimate of Table 38.

The fall in  $\log K_T$  on 2-aza substitution, of 0.7 - 0.8 in **474** and **475** relative to **470** and **1** respectively, is at first sight surprisingly small. Given  $\sigma_m = 0.65$  for aza-nitrogen (Table 2), its effect on  $pK_a(\text{NH})$  for **474** is much as predicted. However, for  $\sigma_I = 0.47$  one expects  $\Delta pK_a(\text{OH})$  - 4.9 where - 2.9 is found. This value, which adjusts to  $\Delta \log K_T$  2.1 on more accurate calculation, is plausibly due to destabilisation of the OH tautomer by *N,N*-lone pair repulsion and is entirely in line with other estimates for this quantity (Appendix 3). For the 2-chloro substituent, also with  $\sigma_I = 0.47$ ,  $\Delta pK_a(\text{OH})$  - 4.7 is found (Table 35).

### A.10.8 Aromatisation in Extended Structures: The Effect of Intramolecular Hydrogen Bonding on Tautomeric Form

Intramolecular hydrogen bonding is an important factor in inducing tautomerisation to the OH form in solution (or *intermolecular* bonding in the solid state), but it frequently requires assistance in doing so. A simple example is **476**,<sup>297</sup> which tautomerises to **476b** but only in nonpolar solvents such as dioxan; it is wholly **476a** in water and 80-90% so in MeCN. Given  $\log K_T$  *ca.* 4.4 for **476** from eqn. (xxxiii), and allowing for the solvent shift expected for the vinylogous amide **431** in MeCN (Appendix 2), a value of  $\Delta \log K_T$  *ca.* -1.9 may be calculated for the combined effect of lone pair repulsion and an intramolecular bond (Appendix 3). Multiple substitution is often required to force the issue: thus while **477**<sup>299</sup> and **478**<sup>300</sup> exist as shown under all conditions studied, compounds **479** mostly give **479a** in MeOH but **479b** in CCl<sub>4</sub>.<sup>299</sup> An exception is (**479**, R<sup>1</sup> = Et, R<sup>2</sup> = Pr<sup>i</sup>) which does not

enolise, presumably because steric hindrance makes the intramolecular hydrogen bond impossible. If 4-pyridones and -quinolones possess similar  $\Delta \log K_T$  values as postulated above,  $\log K_T$  *ca.* 2.0 would be predicted for **479** in water in the absence of this bond. However, a calculation on the lines of that for **476** shows the effect of hydrogen bonding in (**479b**,  $R^1 = \text{Et}$ ,  $R^2$  various) to be quite small (Appendix 4). Given **479b** as the usual solid state tautomer, we presume that this bond is enforced by planarity. A parallel estimate for **478** as written predicts  $\log K_T$  3.6, hence its failure to enolise.

Multiple substitution in 4-pyridone leads to further cross-interactions. Whereas (**480**,  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) exists as **480a** in water, for  $R^1 = R^2 = \text{Ph}$  more of **480b** is present,<sup>301</sup> while **481** predominates as shown in all media investigated.<sup>302</sup> Removal of the ester groups from **481** to give **482** restores the oxo-tautomer even in  $\text{CHCl}_3$ <sup>303</sup> as a result of the intramolecular hydrogen bond which may be bifurcated as shown. However, **483** where this bond is no longer possible reverts to the OH tautomer even in DMSO; the authors<sup>303</sup> suggest that *peri*-interactions involving CH could force the pyridyl rings out of plane in the NH form, but an equally valid explanation might lie in the electronegativity of the 2-substituents (*cf.* Table 37) when no longer offset by hydrogen bonding. Steric factors are clearly important<sup>304</sup> and steric compression may well explain why (**480**,  $R^1 = R^2 = \text{Ph}$ ) enolises whereas (**480**,  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) does not; it can hardly result from the electronegativity of Ph (Table 37). Here the picture is greatly confused by the multiplicity of solvents employed and, while it is usually possible to find plausible explanations after the event, the various conflicting factors need disentangling with care.

The most detailed (and gratifyingly aqueous) study of any such system is due to Katritzky and co-workers.<sup>304</sup> This concerns the 1,7-phenanthrolines **484** and **485**. For (**484**,  $R = \text{Cl}$ ) which exists as **484b** in all media studied, they estimate  $\log K_T$  *ca.* -1.4 in water, a reversal of  $\Delta \log K_T$  *ca.* - 6.3 relative to 4-quinolone. They split this quantity into a 'push' from hydrogen bonding in **484b** and a 'pull' from lone pair repulsion in **484a** of which the second appears to be the more important (see Appendix 3). However, when  $R = \text{OH}$  the equilibrium shifts right over to the dipyridone **485**, with  $\log K_T$  *ca.* 6.4 which is significantly less than double that for 4-quinolone. They explain this shortfall as a difference term between NH---O bonding in the major tautomer and the OH---N bonding that would have existed in the minor one. (A more comprehensive discussion of this very complex case will be found in Appendix 3, sub-section **h**). An unusual, rather special case of 'tautomeric distortion' is found in the 1,4-phenanthrolines **486** where each ring exists as a different tautomer in the solid state (these compounds are extremely insoluble) as their IR spectra demonstrate.<sup>305</sup> Hence the intramolecular hydrogen bond, while very

strong ( $\nu\text{OH}$  at 2600 and 1850  $\text{cm}^{-1}$ ), possesses two potential minima not one, as in symmetrical chelated  $\beta$ -diketones where this is also the case.<sup>97</sup>

#### A.10.9 Aromatisation in Extended Structures: Nonchelated Heterocyclic Anhydro-Bases

Heterocyclic anhydro-bases form an important class of potentially tautomeric structure exemplified by **72C**, **432C** and **433C** in Scheme 19. Like these, most such compounds will be chelated as the aminoenone **C**-tautomer hence are considered later (section A.10.14). However, two series of 2-substituted compounds have been evaluated quantitatively using *N*-methylated **C**-tautomers such as (**487**, R = Me), which cannot chelate and which, therefore, do not give direct evidence on tautomeric ratio ( $K_M$ ) involving (**487**, R = H). Nevertheless these series provide basic information as to the electronic factors operating on  $K_M$  and on which any added effect of hydrogen bonding must be superimposed. There is some evidence moreover (section A.10.14) to suggest that such effects may be quite small. In addition, compounds of type **488** are free of intramolecular bonding so provide  $K_M$  directly. Since **488A** is the reference point for both (**488**, R = H) and (**488**, R = Me) the difference in  $K_M$  may be used to provide the correction factor  $\Delta(\text{NR})$  for the replacement of NMe by NH. For the pair in

**Table 39.  $\text{p}K_a$  and  $\log K_M$  Values for Formation of the Pyridine Anhydro-Bases **487** and **488****

X	<b>487</b>			<b>488</b>		
	$\text{p}K_a(\text{A})$	$\text{p}K_a(\text{C})^a$	$\log K_M$	$\text{p}K_a(\text{A})$	$\text{p}K_a(\text{C})^b$	$\log K_M$
H	5.97 <sup>c</sup>	18.95 <sup>c</sup>	- 13.0	6.02 <sup>d</sup>	19.46 <sup>d</sup>	- 13.3
Ph	5.13 <sup>e</sup>	16.71 <sup>e</sup>	- 11.6			
SO <sub>2</sub> Ph	2.54 <sup>f</sup>	10.15 <sup>f</sup>	- 7.6	3.75 <sup>f</sup>	11.37 <sup>f</sup>	- 7.6
CO <sub>2</sub> Et	4.02 <sup>g</sup>	10.04 <sup>g</sup>	- 6.0	4.86 <sup>g</sup>	10.18 <sup>g</sup>	- 5.3
	4.15 <sup>h</sup>	10.24 <sup>h</sup>	- 6.1			
COPh	5.05 <sup>i</sup>	7.08 <sup>i</sup>	- 2.03	4.93 <sup>i</sup>	7.58 <sup>i</sup>	- 2.65
COPh <sup>j</sup>	5.03 <sup>k</sup>	6.08 <sup>k</sup>	- 1.05	4.57 <sup>k</sup>	7.05 <sup>k</sup>	- 2.48

<sup>a</sup> For R = H after incorporating  $\Delta(\text{NR}) = - 0.3$ . <sup>b</sup> Assumes  $\Delta(\text{NR}) = 0$  (see the text). <sup>c</sup> Ref. 157.

<sup>d</sup> Ref. 150. <sup>e</sup> Ref. 307. <sup>f</sup> Ref. 308. <sup>g</sup> Ref. 309. <sup>h</sup> Ref. 310. <sup>i</sup> Ref. 306. <sup>j</sup> Direct observation.

<sup>k</sup> Ref. 93.

which  $X = \text{COPh}$ <sup>93,306</sup>  $\Delta(\text{NR})$  is  $< 0.2$  (Table 39) so, allowing for the fact that these authors used very different ionic strengths, we shall take  $\Delta(\text{NR})$  to be negligible for 4-substituted compounds of this type. However, in its isomer **72C** *i.e.* (**487**,  $R = \text{H}$ ,  $X = \text{COPh}$ ) in which an intramolecular hydrogen bond is possible,  $K_M$  is enhanced 10-fold (Table 39). This rather complex case, in which stereoelectronic factors are also present, is further discussed in Appendix 4.

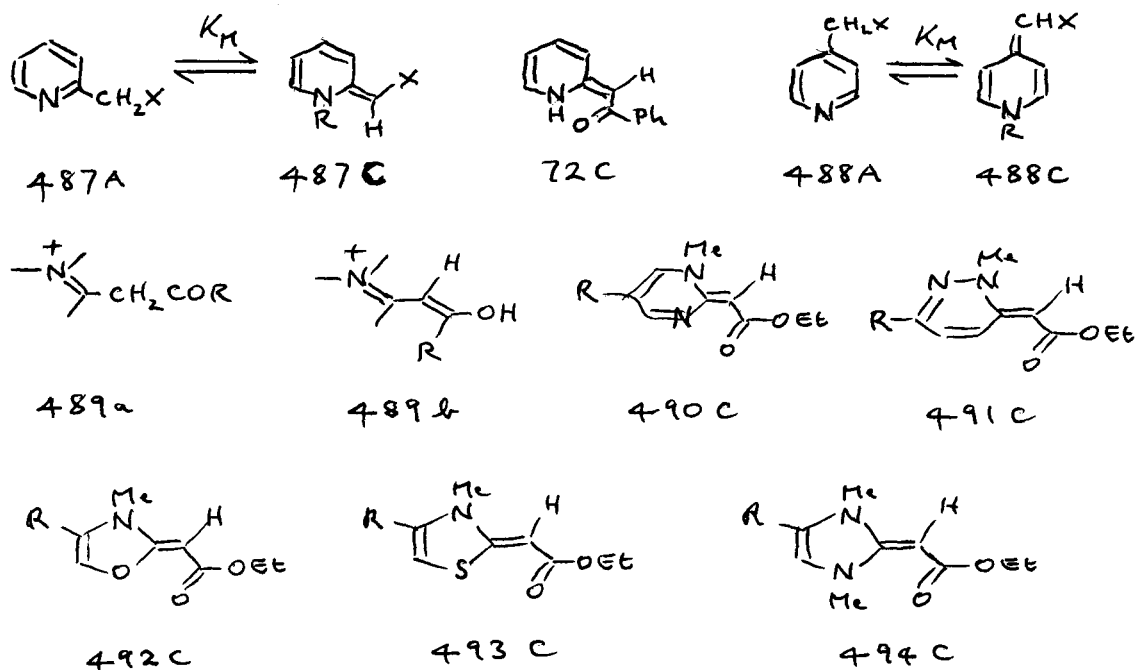
Unlike simple aminoenones such as **435C** these compounds C-protonate to give a common cation **489a** which is also that of the **A**-tautomer; for  $X = \text{COPh}$  this is preferred<sup>93</sup> to the O-protonated cation which we write as **489b** by a factor of  $10^{2.51}$ . This preference for C-protonation is presumably connected with the enhanced importance of the **A**-tautomer consequent on aromatisation but the explanation cannot be that simple since the C-protonated cation is still favoured by a factor of  $10^{1.73}$  in **433** despite the fact that **433C** (Scheme 19) is now the dominant tautomer.<sup>93</sup> The data required to resolve this puzzle are not available.

$$\begin{aligned} \text{p}K_a(\mathbf{487A}) &= 5.85(0.43) - 7.12(1.34)\sigma_1 + 2.76(1.90)\sigma_d - 4.45(5.19)\sigma_e \\ (n = 5 \quad r^2 = 0.971 \quad s = 0.44 \quad F = 11.2) \end{aligned} \quad (\text{xxxiv})$$

$$\begin{aligned} \text{p}K_a(\mathbf{487C}) &= 19.02(0.27) - 6.43(0.84)\sigma_1 - 25.5(1.2)\sigma_d - 38.76(3.27)\sigma_e \\ (n = 5 \quad r^2 = 0.999 \quad s = 0.28 \quad F = 428) \end{aligned} \quad (\text{xxxv})$$

$$\begin{aligned} \log K_M &= -13.2(0.5) + 27.9(2.0)\sigma_d - 42.3(5.8)\sigma_e \\ (n = 5 \quad r^2 = 0.992 \quad s = 0.56 \quad F = 125) \end{aligned} \quad (\text{xxxvi})$$

Available data for compound series **487** and **488** are summarised in Table 39. For **487** there are five usable data points which, through experimental consistency, have proved just enough to analyse using Charton's triparametric technique<sup>39</sup> (see ref. 41 for a definition of the parameters). Most remarkably,  $K_M$  is entirely dominated by the resonance  $\sigma_d$  and 'resonance susceptibility'  $\sigma_e$  parameters, the field parameter  $\sigma_1$  being absent. The reason for this becomes clear on inspection of the equations for **487A** and **487C**:  $\sigma_1$  appears in both and indeed is the most important term for  $\text{p}K_a(\mathbf{487A})$  but effectively cancels between them. In noting the surprising order of  $\text{COPh}$  and  $\text{SO}_2\text{Ph}$  in terms of  $K_M$  Katritzky<sup>306</sup> pointed out that  $\text{COR}$  is a much stronger resonance acceptor than  $\text{SO}_2\text{R}$  while the reverse is true inductively, but the present analysis goes further. Very large  $\rho$ -values as found here are, of course, a severe test for the  $\sigma$ -values employed, and the considerably enhanced effect of  $\text{COPh}$  over  $\text{COMe}$  which is found elsewhere (section A.10.14) is not reflected in Charton's parameter values.<sup>39</sup>



Nevertheless it is worth noting that *calculated*  $\log K_M$  values for **487** include -7.5 for  $X = \text{CN}$  and -4.9 for  $X = \text{NO}_2$ ; the first no more effective than for  $\text{SO}_2\text{Ph}$ , the second lying between  $\text{CO}_2\text{Et}$  and  $\text{COPh}$  in efficacy. Feuer and Lawrence<sup>311</sup> state (**487**,  $X = \text{NO}_2$ ) and (**488**,  $X = \text{NO}_2$ ) to possess  $\log K_M$  -1.05 and -0.3 respectively in DMSO, but these could only be extrapolated to water if their behaviour were to parallel **80** (Table 32) and this is improbable. None of these parameters is known for the strong resonance acceptor  $\text{COCF}_3$ , but the *calculated* enhancement, based on their parameter values,<sup>39</sup> of  $\text{SO}_2\text{CF}_3$  over  $\text{SO}_2\text{Ph}$  is  $\Delta \log K_M$  4.8 and probably less than this would be required to account both for some qualitative observations in section A.10.14 and for the well attested ability of  $\text{COCF}_3$  to polarise  $\text{C}=\text{N}$  in the corresponding amidines (section B.5.4).

It should be noted that, while the ratio  $\rho_e/\rho_d$  at -1.52 is close to that expected for  $\sigma_R^-$  at -1.4,<sup>39</sup> use of conventional  $\sigma_R^-$  values gives a rather poor equation ( $r^2 = 0.79$ ), probably because the derivation of  $\sigma_d$  and  $\sigma_e$  has effected a considerable refinement of resonance parameters in general. Use of a re-calculated  $\sigma_R^- = \sigma_d + 1.4\sigma_e$  leads to  $r^2 = 0.990$  on replacement of eqn. (xxxvi). However it is quite likely that the electron demand associated with  $K_M$  may exceed even that of  $\sigma_R^-$ , as  $\rho_e/\sigma_d = -1.52$  seems to imply.

Insufficient data for **488** are known for a similar approach, but there is clearly a general parallelism (Table 39). The differences for  $X = \text{CO}_2\text{Et}$  and  $\text{COPh}$  may indicate, if significant, slightly larger and smaller  $\rho$ -values for  $\sigma_d$  and  $\rho_e$  respectively in this case. The equivalent imine **396**  $K_T$  values (section A.9.4) are dominated by  $\sigma_I$  ( $\equiv \sigma_I$ ) like amidines (section B.4.2) but nevertheless contain a substantial  $\sigma_R$  component.

A set of miscellaneous heterocycles comprising (**487**,  $X = \text{CO}_2\text{Et}$ ) and **490** – **494**, shown as the **C**-tautomer in its most likely configuration, were investigated by Button and Taylor.<sup>310</sup> Like **487** and **488**, all **C**-protonate to give a common cation of type **489a**. In view of the uncertainty as to whether correction factors will be the same across this series, the data of Table 40 are presented raw. Only qualitative trends can be discussed but some are interesting. A second 2-aza substituent in the pyrimidine **490** scarcely affects  $K_M$ ; by contrast this drops very sharply in the pyridazine **491**, presumably because of  $N,N$ -lone pair repulsion in the **A**-form. (A contributory factor may be pyridazine's probably lesser aromaticity). The relative behaviour of **492** and **493**, which is difficult to understand on those grounds, may be influenced by ring size: the increased bond length of  $\text{C-S}$  relative to  $\text{C-O}$  is likely to attenuate, in **493**, the normal bias (section A.1.2) of 5-membered rings in favour of *exo*- $\text{C}=\text{C}$ . Planarity is another possible factor. While both **492C** and **493C** should be substantially planar, it is likely that **494C** will be severely twisted, in which case its destabilisation relative to the **C**-protonated cation may account for its very high basicity. Lone pair repulsion in **490C**, and even perhaps in **492C**, is another possible cause of twisting. In Appendix 1 (Table 98 and accompanying discussion) we assemble a number of molecules, related in structure to the above, whose abnormally high basicity we attribute to this cause. If so chelated analogues should behave normally, but the evidence required is lacking.

**Table 40.**  $\text{p}K_a$  and  $\log K_M$  for Some Heterocyclic Anhydro-Bases in Water <sup>a</sup>

Compound	$\text{p}K_a(\text{A})$	$\text{p}K_a(\text{C})$ <sup>b</sup>	$\log K_M$ <sup>c</sup>
<b>487</b> , $X = \text{CO}_2\text{Et}$	4.15	10.54	- 6.4
<b>490</b> <sup>d</sup>	0.29	7.02	- 6.7
<b>491</b> <sup>d</sup>	2.34	5.73	- 3.4
<b>492</b> <sup>d</sup>	0.20	6.64	- 6.4
<b>493</b> <sup>d</sup>	0.96	5.70	- 4.7
<b>494</b> <sup>d</sup>	5.12	> 17	< - 12

<sup>a</sup> Ref. 310. <sup>b</sup> Of NMe derivative illustrated. <sup>c</sup> No  $\Delta(\text{NR})$  correction applied.

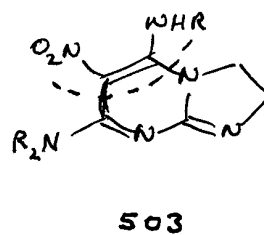
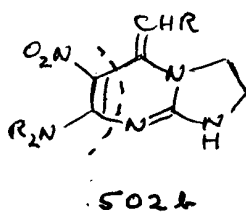
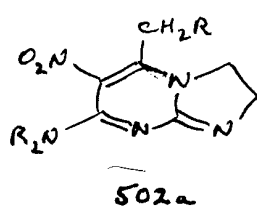
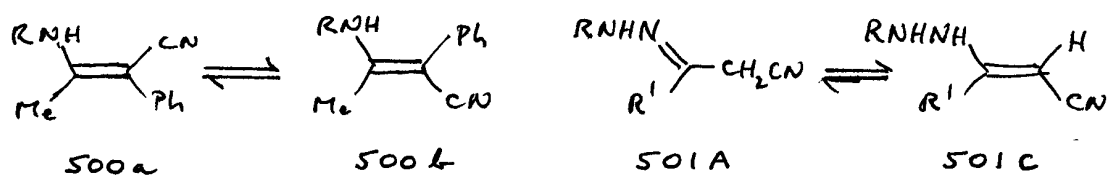
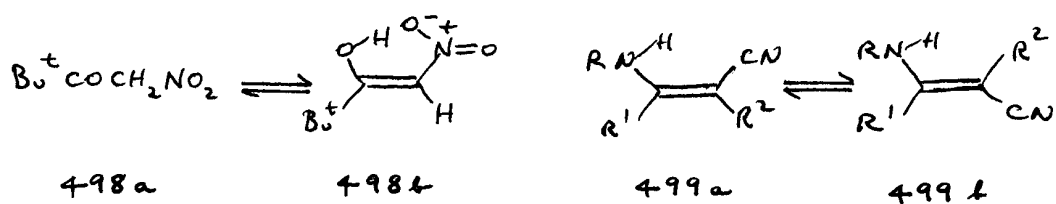
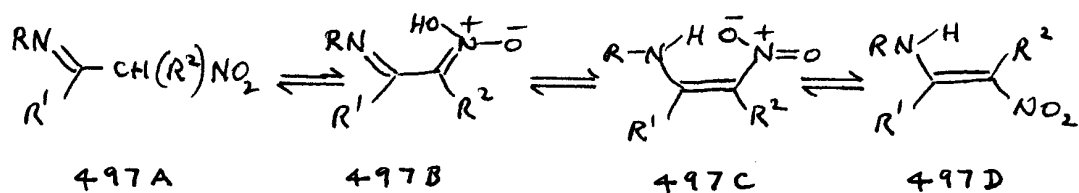
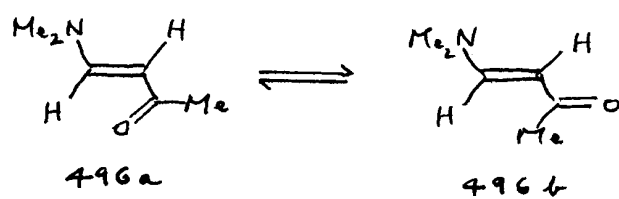
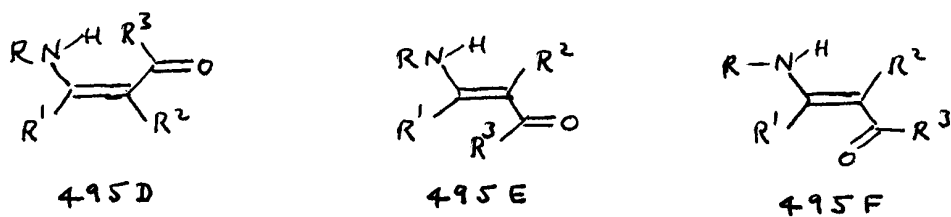
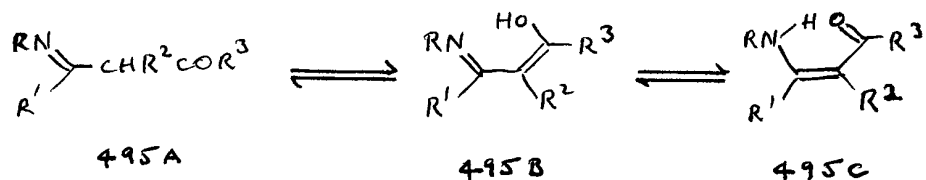
<sup>d</sup> R = 4-halophenyl.

### A.10.10 Chelated Structures: One Donor, One Acceptor

There have been no quantitative studies of the chelate **430** to parallel that of Greenhill<sup>119</sup> on the extended structure **429** so that our speculation in section A.10.1, that  $K_T$  should be less, is unsupported so far by experimental evidence. However, even 'log  $K_T$ ' *ca* 5.1 which represents the mean estimate for the process **D**  $\rightarrow$  **E** in Table 31 should be ample to ensure the overwhelming preponderance of **430C**, even allowing for a possible reduction in  $K_T$  for aqueous solution implied by the resultant of eqns. (xx) and (xxi). This prognosis appears to be borne out. While few really wide-ranging solvent studies have been carried out, and fewer still have been quantitative, none has revealed even traces of **495A** or **495B** and interest has centred on the alignments available to **495C**. A few words on this subject may be apposite.

It might be anticipated that primary and secondary open-chain aminoenones should exist overwhelmingly as **495C** but this is not always the case. For (**495**, R = Et, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H) Vey<sup>275</sup> found that the *sum* of **495C** and **495F** falls with increasing solvent polarity to about one-third of the total in EtOH and presumably less than that in water, **495E** being dominant. Tertiary aminoenones exist as a mixture of the **E**- and **F**-type isomers, the former in general predominating for ketones<sup>272</sup> (R<sup>3</sup> = alkyl) and the latter for esters<sup>272, 273</sup> (R<sup>3</sup> = OR'), and these preferences may be expected to carry over to the *trans* component of secondary aminoenones as well. On the evidence of  $\nu_{NH}$  the intramolecular NH---O bond of **495C** is not exceptionally strong,<sup>272</sup> certainly not for esters, and it is even quite likely that **495E** or **495F** may be preferred to **495C** in water. (Here and throughout one can presumably eliminate **495D** as unlikely to be important for any compound). In 1,1-dichloroethylene, **496a** is preferred to **496b** by about a factor of two, but loses ground in MeOH because its *s-cis* carbonyl is partially shielded from hydrogen bonding<sup>312</sup> and the same may be expected in water. None of these energy differentials appears sufficient to have important implications for receptor binding.

As well as COR, NO<sub>2</sub> and CN have been studied as  $\pi$ -acceptors. Rajappa<sup>313</sup> has reviewed nitroenamines **497**. As in the case of aminoenones **497B** has never been detected (*cf.* section A.5.3) but **497A** is said to be possible if the steric clash between R<sup>1</sup> and R<sup>2</sup> is severe enough,<sup>313</sup> though the only example quoted is not an aminoenone but **498**, enolised to the extent of only 10% in CCl<sub>4</sub>. However it is clear that steric hindrance will very readily force **497C** over into **497D**: for R<sup>1</sup> = Bu<sup>t</sup>, R<sup>2</sup> = Pr 98% exists in iso-octane as



**497D**, whereas only **497C** is visible for  $R^2 = H$ .<sup>314</sup> Compounds for which  $R = \text{alkyl}$ ,  $R^1 = R^2 = H$  exist exclusively as **497C** in a range of solvents<sup>315</sup> whereas tertiary nitroenamines always give **497D**.<sup>313</sup> Hence nitroenamines behave in a very similar fashion to aminoenones but are more sensitive to steric clashes, perhaps because the intramolecular hydrogen bond is weaker.

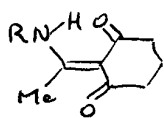
Simple cyanoenamines also exist in the fully conjugated form, but since intramolecular hydrogen bonding cannot take place, the *E*-isomer **499b** is now preferred in the absence of steric hindrance.<sup>316</sup> If  $R^2$  is large however, **499a** can become important, as in **500** where the isomers coexist.<sup>317</sup> It is interesting that, in DMSO, (**501**,  $R^1 = \text{Me}$ ) exists as **501A**. This compares with the result for **436** (section A.10.4) where the **A**-form is again a hydrazone and suggests that CN is intrinsically less good at promoting enolisation ( $K_M$ ) than COAlk. In section B.5.15 we present suggestive evidence that RNHNH- as in **501C** is destabilising in water, relative to RNHN= as in **501A**, by  $\Delta \log K_M \text{ ca. } -2.5$ . Further evidence follows in section A.10.14. Addition of water to DMSO promotes the more polar tautomer **501C** (25% - 45%).<sup>317</sup> In water the picture for all three  $\pi$ -acceptors – COR, NO<sub>2</sub>, CN – may well be indistinguishable.

The pyrimidine **502** provides an example of ‘nesting’ (section A.9.6). Here the imine tautomer **502a** which dominates in nonpolar solvents is displaced in polar ones towards **502b**,<sup>318</sup> in which the highly polar nitroenamine sub-unit indicated helps to stabilise its enamine structure. When  $-\text{CH}_2\text{R}$  in **502** is replaced by  $-\text{NHR}$  in **503** a new nitroenamine subunit appears;<sup>318</sup> the tautomers are now symmetrically related and the observed preference for **503** may reflect that of *endo*-C=N for 5-membered rings (section A.4.1). Both sub-units illustrate the high degree of bond fixation to be found in many complex heterocycles and which frequently override expectations based on naive interpretations of ‘aromaticity.’

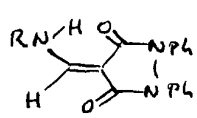
#### A.10.11 Chelated Structures: One Donor, Two Acceptors

If one  $\pi$ -acceptor will generally result in dominance of the aminoenone tautomer **430C**, one might expect that two should render this inevitable. Except in one special circumstance, this expectation is fulfilled.

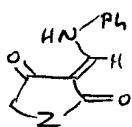
Compounds **504**<sup>319</sup> and **505**<sup>2z</sup> exist as shown. Slightly more interest attaches to **506**, where two configurations are possible. According to Saito and Yamaguchi<sup>214</sup> the balance is even for  $Z = \text{NH}$  but **506b** is preferred to the extent of *ca.* 75% when  $Z = \text{O}$  or  $\text{S}$ . Since the proton acceptor order is<sup>72</sup>  $\text{CONR}_2 \gg \text{COR} > \text{CO}_2\text{R}$ , COSR this is the reverse of expectation. We have had cause previously to query these authors’ evidence (section A.6.5) and



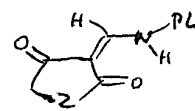
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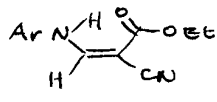
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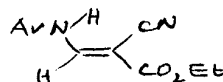
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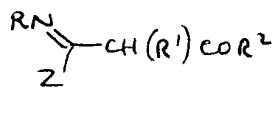
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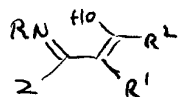
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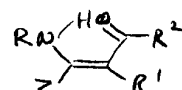
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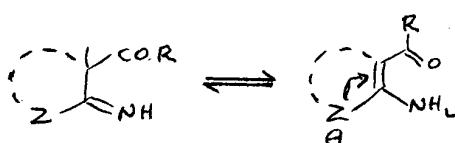
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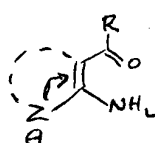
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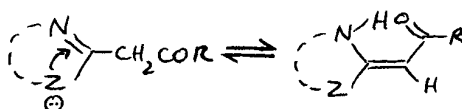
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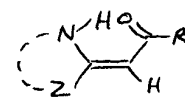
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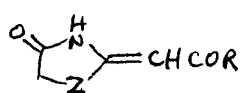
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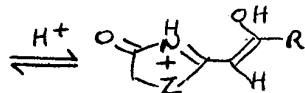
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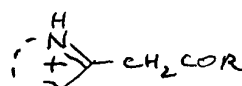
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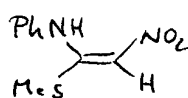
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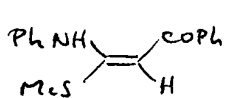
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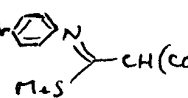
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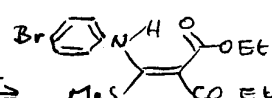
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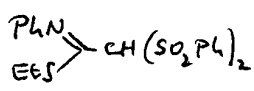
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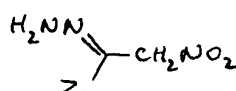
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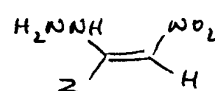
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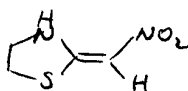
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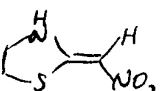
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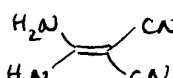
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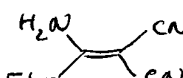
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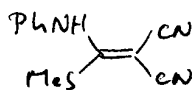
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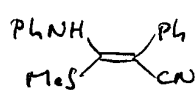
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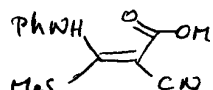
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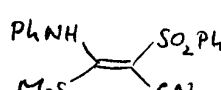
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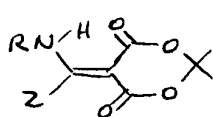
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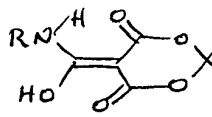
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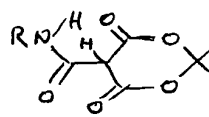
524



525



526a



526b

regard this result as dubious. Nishigaki *et al.*<sup>320</sup> and Cottam and Robins<sup>321</sup> have investigated compound series of type **507** in which Ar is some complex heterocycle; in general no strong preference is shown for either isomer but the situation is too much compromised by the nature of Ar to be readily interpretable. In neither **506** nor **507** is the energetic advantage of the major component such that it might not be overturned at a suitable biological receptor.

The only likely circumstance in which a second  $\pi$ -acceptor might diminish or destroy the expected preference for the **C**-form is when a severe steric interaction, leading to loss of planarity, would result. Almost all the cases known to us are listed in section A.1.4. In fact this is quite rare. In the event of its happening the likeliest culprit would be the very bulky SO<sub>2</sub>Ph and the least likely is CN. Even among compounds in which generation of the **C**-tautomer is strongly opposed by aromaticity (section A.10.15) we have encountered no example of a dicyanomethyl substituent which failed to ensure its preponderance.

#### A.10.12 Chelated Structures: Two Donors, One Acceptor

The presence of a second  $\pi$ -donor Z in **508** has the same effect here as for the extended structure (section A.10.5), in that its lone pair alignment appears to have a major influence on tautomeric preference. Whereas Wamhoff *et al.*<sup>322</sup> found a number of cyclic compounds (**509**, Z = O or S) to exist exclusively as **509C** in solvents ranging from CHCl<sub>3</sub> to MeOH, Wamhoff and Materne<sup>323</sup> and one of us<sup>106</sup> investigated a different series of esters **510** which, while like **509** they exist as the **C**-tautomer in the solid state, give mixtures in CHCl<sub>3</sub>. If eqn. (xxi) is any guide to the solvent dependence of **510**, then for Z = S, R = OEt log  $K_M$  *ca.* -0.3 is predicted for aqueous solution (Appendix 2) whereas, for **509**, we predict **509C** greatly to predominate. This difference in tautomeric preference is readily rationalised in terms of lone pair alignment as shown. Ring size (5- or 6-) does not appear to be a factor.<sup>106,322</sup> Only in (**511**, Z = S)<sup>165</sup> and (**511**, Z = NH)<sup>324</sup> is **510** firmly locked as the **C**-tautomer, existing as shown under all conditions examined, including aqueous solution,<sup>165</sup> the result of *N*-acylation which strongly favours the enamine alternative (section A.4.4). In these acylamino compounds, preference for the **C**-tautomer is so pronounced that protonation takes place on *exo*-carbonyl<sup>165</sup> to give **511H** as in a simple aminoenone,<sup>119</sup> in sharp contrast to the C-protonation normal elsewhere to give the cation **512**. Consistently, the **C**-tautomer remains the favoured form in (**511**, Z = S) when -COR is replaced by other  $\pi$ -acceptors such as -NO<sub>2</sub> or -CN.<sup>165</sup>

Not all results are at first sight consistent with this picture. A compilation by Walter and Meyer<sup>325a</sup> gives **513** and **514** as preferred tautomers despite the fact that **515** with its two acceptor groups is present as a mixture (all in CHCl<sub>3</sub>). It is possible that, in open-chain structures, the conformation of Z can ‘flip’ according to the steric requirements of R<sup>1</sup> in **508**, favouring the C-tautomer when R<sup>1</sup> is small but the A-tautomer when it is bulky. A plausible example of this is **516** which exists as shown.<sup>325</sup> These results may imply that open-chain compounds will typically resemble **509** rather than **510** in tautomeric preference, but more data are badly needed. A solvent study by these authors<sup>325b</sup> on **515** shows the decline in  $K_M$  with increasing solvent polarity expected on the basis of eqn. (xxi) but the effect is slight and no LSER analysis has proved possible.

Walter and Meyer<sup>325a</sup> have also studied the effect on  $K_M$  for **515** of varying the benzene ring substituent. In CHCl<sub>3</sub>, log  $K_M$  declines from 0.87 for 4-NMe<sub>2</sub> to 0.04 for 4-NO<sub>2</sub>, *i.e.* electron donors increase  $K_M$  with  $\rho \sim -0.6$ . It should follow that a better electron donor Z, replacing MeS, should also increase  $K_M$ . Hamberger *et al.*<sup>326</sup> find, in a CHCl<sub>3</sub>/DMSO mixture, that **517** gives 100% **517A** for Z = SMe but mostly **517C** for Z = NHAlk, with a roughly even balance for Z = NHPh, which is consistent with this postulate. (Note that, as a hydrazone, **517** should favour the A-tautomer much more than a simple imine would: *cf.* sections A.4.5 and A.10.4). Similarly, we<sup>106</sup> find **510C** to be favoured for Z = NH about 5-fold relative to Z = S on the basis of a semiquantitative study in CHCl<sub>3</sub>. Again, a stronger acceptor favours the C-tautomer: for example, **513** in MeOH exists entirely as shown,<sup>327</sup> and so does **518** but its configuration depends on the solvent, with **518a** in CHCl<sub>3</sub> but **518b** in DMSO.<sup>327</sup>

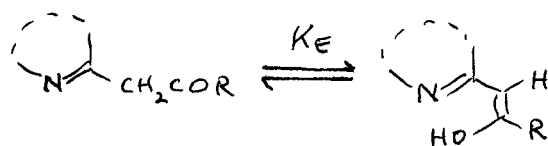
### A.10.13 Chelated Structures: Two Donors, Two Acceptors

It was noted in section A.10.7 that two acceptors should be better than one in favouring the C-tautomer, so that the extent of its formation should certainly not be less. As previously, this appears to be true except where severe steric hindrance would be present as in **516**, or where both acceptors are of only moderate strength, which covers **515** as well. Otherwise, expectation is fulfilled. Structures firmly established include **519** and **520** in MeOH, EtOH and water,<sup>316</sup> and **521** – **524** mostly in CHCl<sub>3</sub>,<sup>325a</sup> while **524** demonstrates that a single –SO<sub>2</sub>Ph is not bulky enough to displace the equilibrium far towards the A-form. A recent solid-state study<sup>328</sup> shows all the Meldrum’s acid derivatives (**525**, Z = OR, SR or NHR) to exist as shown, including even **526**, so that a quite enormous preference for the amide unit present in **526b** is overthrown by the combined electronegativity of its two *planar* ester groups. Sadly, this paper joins the legion<sup>2,24</sup> that still do not properly distinguish proton transfer (zwitterion formation) from electron transfer (charge-separated canonical forms), but its conclusions are clear cut.

#### A.10.14 Aromatic Chelates: One Donor, One Exocyclic Acceptor

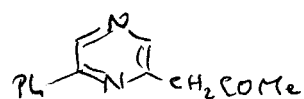
Almost all of the extensive work on this topic has been carried out in organic solvents, most commonly  $\text{CHCl}_3$  and DMSO, chosen to exhibit the phenomenon but, as previously discussed (section A.10.2), with results of no quantitative relevance to aqueous solution. Most of the aqueous data of which we are aware appear in Table 33. These<sup>93</sup> preview the most important distinction we are going to find: that, while  $K_E$  (enol formation) may or may not be significant for aromatic 6-membered ring heteroaromatics,  $K_M$  (enamine formation) scarcely ever dominates except among their benzofused derivatives. This distinction also holds in organic solvents and we have to attempt extrapolation. Such five membered ring heterocycles as oxazole and thiazole count as possessing two potential donor atoms as the enamine tautomer so appear in section A.10.16.

More O'Ferrall and Murray<sup>92</sup> have presented an important survey, mostly in  $\text{CHCl}_3$  and much of it quantitative, which highlights this distinction. As they point out, among the compounds they examine the **B**- or **C**-form may be detected, but never both. For pyridines and pyrazines, tautomerism if found at all is of type **527** (*cf.* **72** in Scheme 19). It is possible to discern a pattern as to the effect of R on  $K_E$ , with  $\text{R} = 4\text{-pyridyl} > 2\text{-pyridyl} > \text{Ph} \gg \text{Me}$  in order of efficacy. This ties in with the effect of substituents in  $\text{R} = \text{Ph}$  [eqn. (iv), section A.2.1] suggesting, in both cases, that a rise in  $K_E$  is associated with greater proton donor strength in the enol. For  $\text{R} = \text{Me}$  no enolisation is found when the heterocycle is pyridine or in **528** when pyrazine<sup>329</sup> (in  $\text{CCl}_4$  by NMR, in  $\text{CHCl}_3$  by IR). For the triazines **529** the **B**-form tends to dominate, in  $\text{C}_6\text{H}_{12}$ ,<sup>330</sup>  $\text{CCl}_4$ ,<sup>330</sup>  $\text{CHCl}_3$ <sup>330,331</sup> or  $\text{EtOH}$ ,<sup>331</sup> when  $\text{R}^1$  and  $\text{R}^2$  are bland or electronegative, but substitution by electron donors (amines,<sup>330</sup> vinylamines<sup>331</sup>) or multiple substitution by  $\text{CH}_2\text{CHO}$ <sup>330,331</sup> can switch the pattern to **529C**, the ultimate structure being **530C** which dominates in  $\text{CHCl}_3$ .<sup>331</sup> If any of these structures survives as such in water it will probably be **530C** which is wholly non-aromatic and possibly a few close analogues; given  $\Delta \log K_E -1.8$  for **72** in water relative to  $\text{CHCl}_3$ ,<sup>92,93</sup> it is unlikely that any other of these **B**-tautomers will survive the transition. Pyruvate ( $\text{R} = \text{COCO}_2\text{Alk}$ ) always tautomerises completely in organic solvents in one sense or the other (*cf.* sections A.2.1 and A.6.10); here **531** is listed by More O'Ferrall and Murray<sup>92</sup> as the only compound they studied to exist exclusively in the **B**-form (in  $\text{CHCl}_3$ ). Possibly **531** would preserve its identity in water; if strict additivity holds, extrapolation from data in Tables

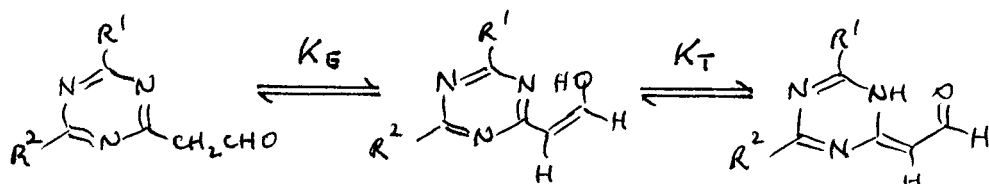


527 A

527 B



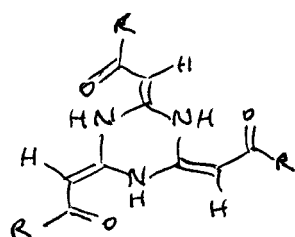
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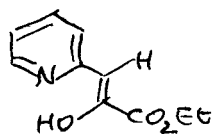
529 A

529 B

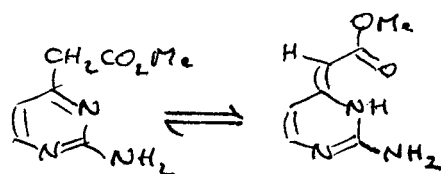
529 C



530 C

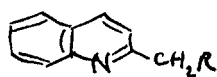


531 B

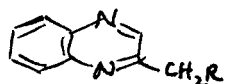


532 A

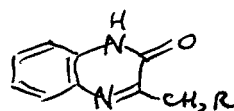
532 C



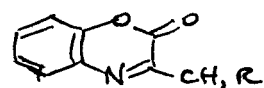
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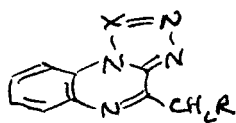
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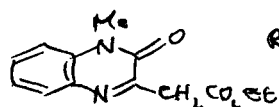
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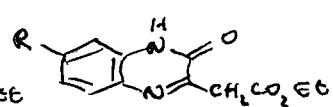
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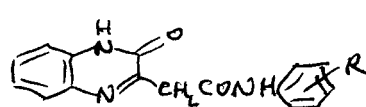
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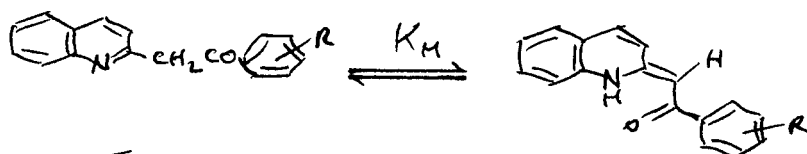
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539

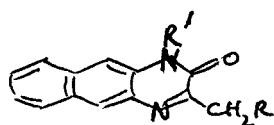


540

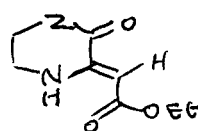


541 A

541 C



542



543

8 and 9 (section A.2.1) suggests  $K_E \sim 10^2$ . It is believed that **532** exists as **532C** in the solid state<sup>2pp</sup> but there are special reasons in this context for mistrusting solid state data as relevant to aqueous solution which we touch on below.

The most valuable studies on 6-membered ring benzofused heterocycles are those that have concentrated on varying the heterocycle, the exocyclic substituent, or both, preferably in the same solvent or range of solvents. Apart from the work of More O'Ferrall and Murray,<sup>92</sup> specially important contributions have come from Mondelli and Merlini,<sup>332</sup> Greenhill and co-workers,<sup>333</sup> Macheidek *et al.*,<sup>334</sup> and Kurasawa *et al.*<sup>335</sup> Nevertheless, while their results are coherent and (we shall show) internally consistent, they cover only a small fraction of the potentially relevant ground, with only two simple parent heterocycles, quinoline and quinoxaline, studied in any detail, while *inter alia* quinazoline, cinnoline and phthalazine remain almost virgin territory. Hence nothing beyond guide-lines can be given at this stage and extrapolation to other systems is all but impossible.

Available information in  $\text{CHCl}_3$  and DMSO for the most commonly encountered substituents in the most studied heterocycles is given in Table 41. All quantitative data appear and in addition we include, as 0% and 100% respectively, those cases in which the aminoenone tautomer was reported either as absent, or as the only detectable species. For clarity, Table 41 is arranged in such a way that the importance of this tautomer increases down the Table and to its right; it will be seen that, qualitatively, there are no important inconsistencies. If additivity is postulated, we may extend the argument further. Table 42 uses only those cases for which quantitative data exist to arrive at a grid relationship between them, built up sequentially and from both solvents, though without assuming any relation between these. Most points on this grid depend on a single sequence. Two of these points may be checked. Given  $\log K_M$  for **433** in water (section A.10.2, Scheme 19 and Table 33), a notional value of 2.8 for this compound in Table 42 (*i.e.* **533**,  $R = \text{COPh}$ ) entails a correction factor of  $\Delta \log K_M -1.7$ . We may also make a provisional estimate for (**535**,  $R = \text{CO}_2\text{Et}$ ). Solvent data<sup>334</sup> on **538** (Table 135, Appendix 2) result in eqn. (xxxvii):

$$\log K_M = 0.68(0.09) - 0.69(0.18)\pi^* - 0.80(0.11)\alpha \quad (\text{xxxvii})$$

$$(n = 5 \quad r^2 = 0.977 \quad s = 0.09 \quad F = 43)$$

**Table 41. Qualitative and Quantitative Evidence concerning  $K_M$  in Compounds of Type Het-2-CH<sub>2</sub>R <sup>a</sup>**

R =	CO <sub>2</sub> Et	CN	COMe	COPh	COCO <sub>2</sub> Et
<b>534</b>	0% <sup>c</sup> 0% <sup>c</sup>	0% <sup>c</sup> 0% <sup>c</sup>	0% <sup>c</sup> 0% <sup>c</sup>	- 0.6 <sup>d</sup>	100% <sup>c</sup> 100% <sup>c</sup>
<b>533</b>	- -	- -	0.27 <sup>c</sup> 0.48, <sup>c</sup> 0.60 <sup>e</sup>	- 1.32, <sup>d</sup> 1.51 <sup>e</sup>	- 100% <sup>e</sup>
<b>535</b>	0.24 <sup>f</sup> ?	0.5, <sup>c</sup> 0.4 <sup>f</sup> -	1.38 <sup>f</sup> 100% <sup>c</sup>	100% <sup>c</sup> 100% <sup>c</sup>	100% <sup>c</sup> 100% <sup>c</sup>
<b>537</b> <sup>b</sup>	0.95 <sup>g</sup> -	- -	- -	- -	- -
<b>536</b>	100% <sup>c</sup> 100% <sup>c</sup>	- -	100% <sup>c</sup> 100% <sup>c</sup>	- -	- -

<sup>a</sup> log  $K_M$  for DMSO (upper line) or CHCl<sub>3</sub> (lower line). Qualitative results are indicated as: 0%, no detectable aminoenone; 100%, no other species detected. <sup>b</sup> X = N or CH.

<sup>c</sup> Ref. 332. <sup>d</sup> Ref. 92. <sup>e</sup> Ref. 333. <sup>f</sup> Ref. 334. <sup>g</sup> Ref. 335.

**Table 42. Provisional Interaction Terms ( $\Delta \log K_M$ ) for Heterocycles (Het) and their Substituents (R) in Compounds of Type Het-2-CH<sub>2</sub>R <sup>a</sup>**

R =	CO <sub>2</sub> Et	CN	COMe	COPh
<b>534</b>	0.0	0.2	1.1	2.0
<b>533</b>	0.8	1.0	1.9	<b>2.8</b>
<b>535</b>	1.9	2.1	<b>3.0</b>	<b>3.9</b>
<b>537</b>	2.6	<b>2.8</b>	<b>3.7</b>	<b>4.6</b>

<sup>a</sup> Normal type: compounds likely to exist in water predominantly as the unconjugated A-tautomer. **Bold type:** compounds likely to exist in water predominantly as the aminoenone C-tautomer. *Italic type:* status of tautomerism in water uncertain.

which closely resembles eqn. (xxi) for the related **432** (section A.10.2 and Scheme 19) and leads to a predicted  $\log K_M$  -1.03 in water. The effect of *N*-methylation on **538** *vis-a-vis* (**535**, R = CO<sub>2</sub>Et) is to lower  $K_M$  (in DMSO) by  $\Delta \log K_M$  -0.35, leading to a postulated  $\log K_M$  -0.7 for the latter in water. Comparison with a notional value of 1.9 in Table 42 leads to an estimated correction factor of  $\Delta \log K_M$  -2.6. Because of the poor agreement between these estimates, -1.7 and -2.6, we indicate three broad categories in Table 42: **bold type** for those where the aminoenone tautomer will probably predominate in water; normal type where it is unlikely to be important; and *italics* where the outcome must be considered highly speculative. Despite the obvious caveats, and its extremely provisional nature, it is hoped that Tables 41 and 42 may act as a stimulus to thought and even, perhaps, to experiment.

The substituent sequence of Tables 41 and 42 should tie in with that of the 2-pyridyl anhydro-bases of section A.10.9 [Table 39 and eqn. (xxxvi)] and qualitatively it does, but not quantitatively: here the gap between CO<sub>2</sub>Et and CPh is less, 10<sup>2</sup> against 10<sup>4</sup>, and on one result, CN is possibly more effective than anticipated. These differences may relate to the presence, here, of intramolecular hydrogen bonding that varies in strength along the series. Otherwise, if the same factors are in play,  $K_M$  should be determined by *resonance* acceptor ability. This ties in with the probability (a) that pyruvate (R = COCO<sub>2</sub>R') with its extreme ability to effect enolisation will give some aminoenone with even the most resistant heterocycle, (b) that this characteristic may extend generally to groups, such as COCF<sub>3</sub>, COCCl<sub>3</sub> and COCN, of type (R = COR'), in which R' is highly electronegative.<sup>81</sup> Substituent effects have been studied in three cases: **539** in DMSO,<sup>334</sup> **540** in DMSO/TFA,<sup>336</sup> and **541** in CHCl<sub>3</sub>.<sup>337</sup> These give rise to the approximate LFER equations (xxxviii), (xxxix) and (xl) respectively:

$$\log K_M = 0.14 + 0.98 \sigma_p \quad (\text{xxxviii})$$

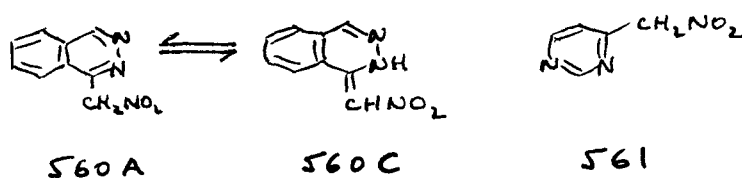
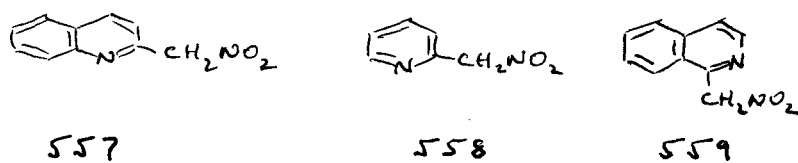
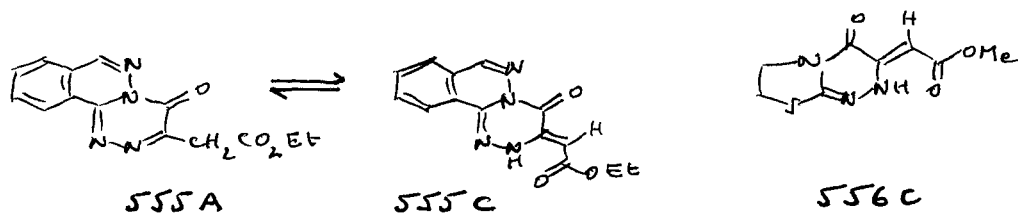
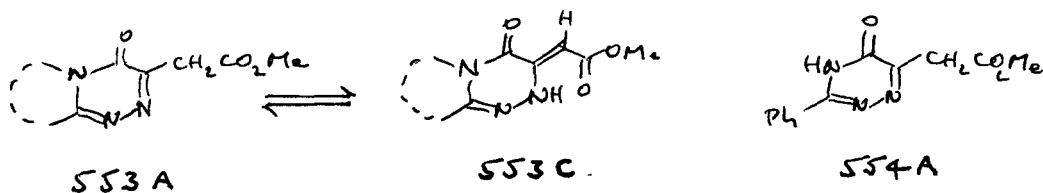
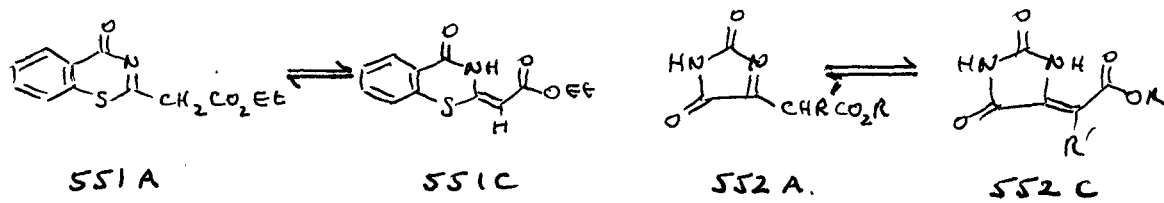
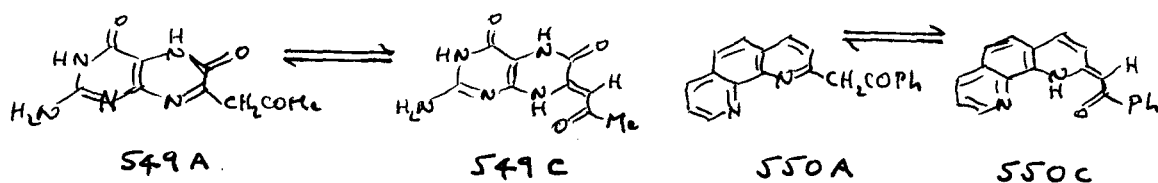
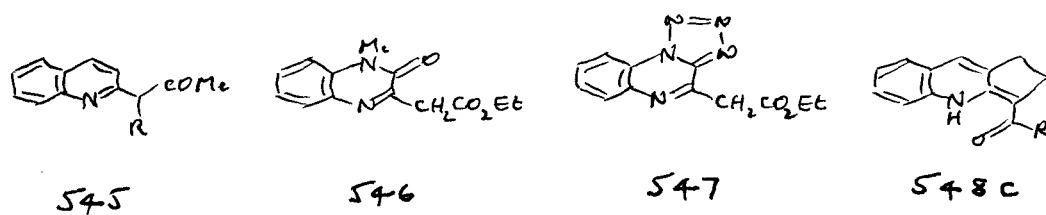
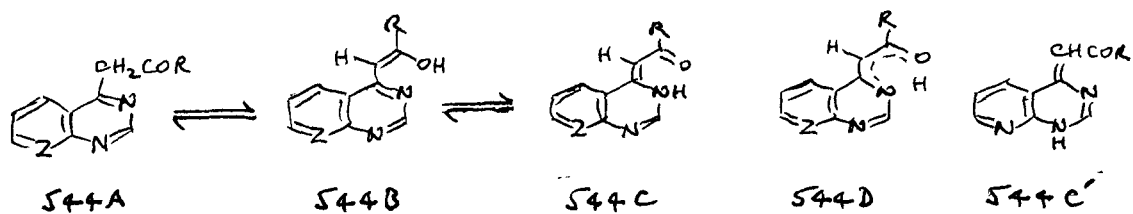
$$\log K_M = 0.23 + 0.4 \sigma \quad (\text{xxxix})$$

$$\log K_M = 1.32 + 1.38 \sigma \quad (\text{xl})$$

All have positive  $\rho$ -values the relative magnitude of which is a simple function of the distance between substituent and reaction centre: **541** > **539** > **540**; both features are as expected. The near-constancy of  $\delta\text{NH}$  in **541C**<sup>337</sup> suggests that resonance stabilisation is a more important factor in  $K_M$  than hydrogen bond strength, consistently with the above; for  $K_E$  as in **527B**, the reverse is found (section A.2.1).

Information concerning other ring systems is sparse. Data on (**542**, R = COMe or CO<sub>2</sub>Et, R' = H or Me) show this, unsurprisingly, to behave like **535** in DMSO or TFA.<sup>332</sup> However, (**542**, R = CO<sub>2</sub>Et) exists as the **C**-tautomer in the solid state; one of several cases (see below) in which this indicator of what to expect in polar solvents<sup>15</sup> may be misleading. It may simply be due to lone pair repulsion in the solid state which chelation avoids, a serious possibility which must sometimes be considered with care. Elsewhere, the data of Table 41 suggest that **536** is more susceptible to chelate formation than **535** and possibly on a level with **537**, but this impression cannot be quantified. Replacement of NH in **535** by O in **536** should lead to lower aromaticity so would be compatible with the difference observed, and certainly (**543**, Z = O or NH), which is not aromatic at all, exists as shown under all conditions.<sup>338</sup> However aromaticity cannot account for everything or **533** would be less susceptible than **534** instead of *vice versa*, so other factors must enter. We have previously noted (section A.2.2) that  $K_E$  in water for this same pair of compounds is very similar, and attributed this to a near-cancellation between the greater electronegativity of pyrazine but the greater proton acceptor ability of pyridine. Since these may not exhaust the relevant factors, no overall rationale is presently possible.

One puzzling case concerns (**544**, Z = CH) written by the authors<sup>339</sup> ambiguously as **544D** and later<sup>20</sup> misinterpreted as **544B**; the published spectra<sup>339a</sup> establish it as **544C**. For Z = N<sup>339b</sup> it is possible, though unlikely, that lone pair repulsion (*cf.* below) might lead to **544C'** but, for Z = CH, loss of the intramolecular hydrogen bond makes this highly improbable. Dominance of the **C**-tautomer as seen above for benzofused heterocycles of this type, even in aqueous solution (Table 42), makes it improbable that either of these compounds exists to any significant extent as the enolimine **544B**, as alleged by Kurasawa *et al.*<sup>331</sup> It is possible that the ready covalent hydration of quinazolines,<sup>341</sup> implying a facile loss of aromaticity at the 4-position, represents a further factor that helps to stabilise the chelate structure **544C**.



Perturbing factors include steric hindrance and lone pair repulsion. We consider the former first. If the heterocycle possesses no other substituents in close proximity, then even quite bulky  $\alpha$ -substituents may have little effect; substitution of  $R = \text{CH}_2\text{Ph}$  for  $R = \text{H}$  in **545** reduces  $\log K_M$  (in  $\text{CHCl}_3$ ) by only about a factor of two.<sup>82</sup> Further substitution however will rapidly inhibit chelate formation altogether<sup>81</sup> (see section A.1.4 for details). Ring  $\alpha$ -substitution by  $\text{C}=\text{O}$  or  $\text{C}=\text{N}$  seems particularly deleterious, as in **546**<sup>90</sup> and **547**,<sup>342</sup> perhaps because planarity for the chelate interferes with its solvation shell. At the other end of the scale, **548C** may owe its predominance<sup>20</sup> to enforced planarity; see section A.10.16 for other possible examples of this.

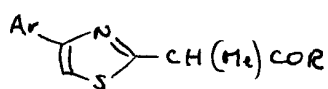
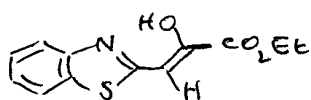
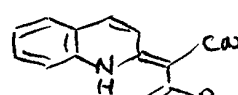
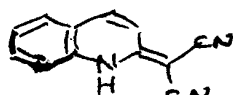
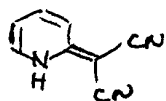
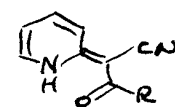
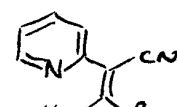
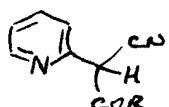
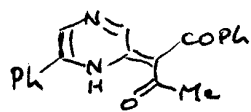
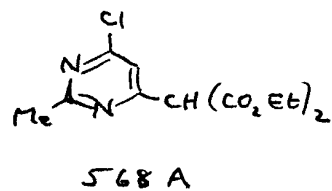
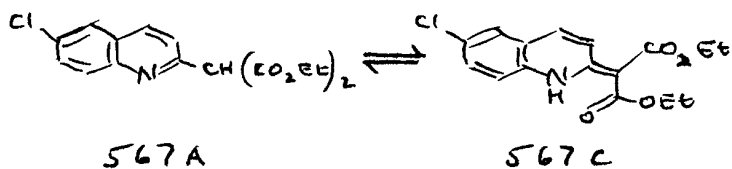
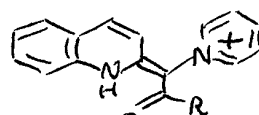
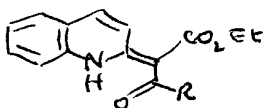
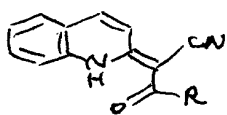
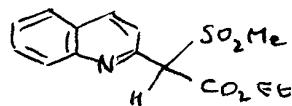
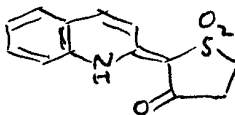
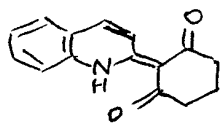
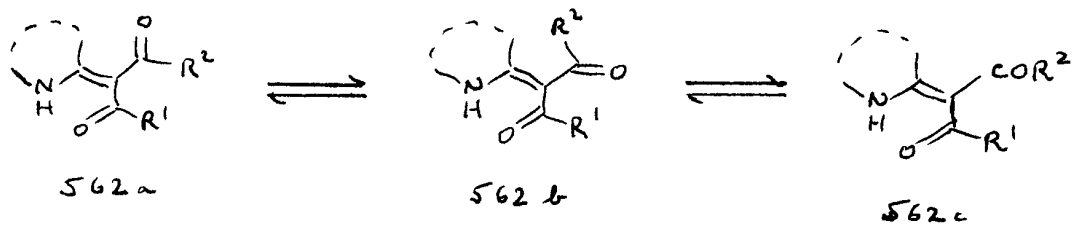
Lone pair repulsion more commonly acts in the opposite direction, as possibly for **549** (where an annular proton switch might cancel this effect) and certainly for **550**<sup>92</sup> (1,8- and 1,10-interactions in the **A**-tautomer respectively), resulting in the **C**-tautomer for both. Nevertheless, this factor is not always decisive. Wamhoff and co-workers<sup>344</sup> found the bicyclic compounds **553** to give mixtures in  $\text{CHCl}_3$  but the **A**-form only in  $\text{MeOH}$ , whereas **554** (or more probably its annular  $\text{NH}$  tautomer: *cf.* section B.5.15) gave mixtures in both; however, all exist as the **C**-tautomer in the solid state, another possible artefact of the type discussed for **532** above. (Surprisingly, the **A**-tautomer was found for a closely related compound in the solid state by Rashed *et al.*<sup>345</sup>). Le Count and Greer<sup>346</sup> also obtained mixed results, with some compounds forming only the **A**-tautomer but the balance for **555** so fine that both **555A** and **555C** could, under different conditions, be isolated from solution. In these last cases the process  $\text{A} \rightarrow \text{C}$  is probably driven mainly by lone pair repulsion in the former; the energy deficit to which this gives rise is typically equivalent to  $\Delta \log K$  *ca.* -2.2 (Appendix 3). It may be pertinent that, in discussing the IR spectroscopy of **556C**, Le Count and Taylor<sup>347</sup> noted that  $\nu(\text{C}=\text{O})$  and  $\nu(\text{C}=\text{C})$  are so close to those expected for the chelate unit in isolation as to suggest that, for this system, nominal loss of conjugation is not the major factor affecting its tautomeric preference. Nevertheless, while lone pair repulsion must help to destabilise **551A**<sup>106</sup> and **552**<sup>349</sup> in similar fashion, their existence as the **C**-tautomer is more probably due chiefly to the strong preference for acylenamine over acylimino structures discussed in section A.4.3; *cf.* **204b** *vs.* **204a**. In the absence of any reliable method for estimating the loss in ring aromaticity involved in forming the **C**-tautomer from such very varied heterocyclic structures, quantitative treatment of these interlinked phenomena has eluded us so far.

Some nitromethyl derivatives of heterocycles were studied by Feuer and Lawrence<sup>311</sup> but all bar one, unfortunately, bear no relation to any compound here considered so their results cannot be calibrated. The exception is **557** for which  $\log K_M = 0.2$  in DMSO, just a little below that for (**533**, R = COMe). For **558**,  $\log K_M = -1.05$ , hence  $\Delta \log K_M$  1.25 here (in DMSO) compares with 2.14 (in water) for their COPh equivalents<sup>93</sup> so any parallelism may be tenuous. Nevertheless, some results are interesting. Compounds **559** and **560** possess  $\log K_M$  0.55 and 1.03 respectively in DMSO; this difference is arguably related to lone pair repulsion in **560A**. The pyrimidine **561** possesses  $\log K_M$  -0.3, a surprisingly high value for a monocyclic heterocycle but one which may throw light on the behaviour of **532** and **544**. Bearing in mind the solvent dependence found elsewhere, none of these nitro-compounds is likely to give much of the nitroenamine tautomer in water. Except for **545**, **552**, **554**, perhaps **550**, and the compounds indicated by bold type in Table 42, the same is likely to be true for the acyl derivatives described in this section.

#### A.10.15 Aromatic Chelates: One Donor, Two Exocyclic Acceptors

It might be anticipated that replacement of one exocyclic acceptor (section A.10.14) by two should greatly increase formation of the aminoenone C-tautomer, and as for the analogous non-aromatic compounds (section A.10.11), this expectation is in general fulfilled.

Diacyl compounds present a problem in that any of the conformations **562a - c** is in principle possible and, when  $R^1 \neq R^2$ , further possibilities arise. It is likely that these conformations will differ sharply in the effect they have on aminoenone formation, with **562c** the least effective. In dimedone **55** which necessarily adopts the Z,Z-conformation **562a**,  $K_E$  is enhanced in water through its *second* carbonyl by *ca*  $10^{7.7}$  but the steric clash between  $R^1$  and  $R^2$  could render **562a** extremely unfavourable and, indeed, one of us<sup>220</sup> has demonstrated that, for aliphatic compounds of this general type, conformation **562b** is generally preferred, for steric and perhaps also for electronic reasons (its dipole gradient is less). It is not known what enhancement is expected for **562b** but it may well be less than for **562a**. The usual alternative to **562b** is **562c**,<sup>220</sup> when a bulky  $R^1$  forces lack of planarity on the second acyl group. It also follows that whichever of  $R^1$  and  $R^2$  is the less bulky should generally be attached to the carbonyl group which forms the intramolecular bond, though in few cases are the facts actually known.



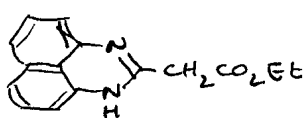
It is very surprising, therefore, that **563C** is favoured over the **A**-tautomer in  $\text{CHCl}_3$  by only a factor of four,<sup>349</sup> scarcely more than that for (**533**,  $\text{R} = \text{COMe}$ ) in the same solvent (Table 41). Possibly **563C** is more strained than appears and  $K_M$  would be much greater in its cyclopentane homologue. Certainly, in the same solvent, **63** which is severely strained (section A.1.4) and **64** exist entirely as shown,<sup>83</sup> while Greenhill and co-workers<sup>81</sup> demonstrated **564** and **565**, where  $\text{R}$  in both cases is strongly electronegative, to exist 100% as the **C**-tautomers. Similarly, **566** exists as shown in  $\text{EtOH}$  and the solid state.<sup>20</sup> Compound **567**, whose acyl groups are individually less effective than most (*cf.* Table 42), is present chiefly as **567C** in  $\text{CHCl}_3$  and  $\text{CH}_2\text{I}_2$  but the position is reversed for  $\text{DMSO}$  and  $\text{MeCN}$  with about 50% of each in  $\text{CH}_2\text{Cl}_2$ ;<sup>106</sup>  $\log K_M$  -1 to -0.5 is predicted for water (Appendix 2), contrasting with +1 for a single  $\text{COPh}$ .<sup>93</sup> As a monocyclic heterocycle (section A.10.14), **568** exists solely as **568A** in polar solvents but 50% as the **C**-form in  $\text{CCl}_4$ .<sup>106</sup> Note also that both **567** and **568** exist as the **C**-tautomer in the solid state,<sup>106</sup> yet another probable artefact, due to lone pair repulsion, of the sort discussed above.

Whereas **528** exists in  $\text{CCl}_4$  and  $\text{CHCl}_3$  exclusively in the **A**-form (section A.10.14), the insertion of  $\text{COPh}$  in **569** converts it entirely to the aminoenone **569C**.<sup>329</sup> The data of Table 42 would predict  $\Delta \log K_M$  0.9 for this change but the effect found must be much greater than this, perhaps through steric compression. (It is not generally established for asymmetrical acyl substitution *which* acyl group takes part in the intramolecular hydrogen bond, but  $\text{CN}$  in combination with acyl will always be found in the *E*-configuration<sup>106</sup>). A second acceptor group can also affect the type of tautomeric shift, replacing enolisation to the **B**-form by generation of the **C**-tautomer. A case in point is **570**, where **570B** is formed, as expected for either acceptor separately, in  $\text{CHCl}_3$ ,<sup>92</sup> but **570C** is the product in ethanolic or aqueous solution.<sup>331</sup> The effect of  $\text{CN}$  is therefore to increase  $K_M$  for water by  $\Delta \log K_M \geq 2$ . If this is generally true, with additional  $\text{CO}_2\text{R}$  giving  $\Delta \log K_M$  less than that but most other acyl groups more, then most diacyl and similar compounds are likely, if planar, to give the aminoenone tautomer, even in the case of monocyclic heterocycles. The likeliest exceptions are diesters, as for **568**, whereas at the other end of the scale, almost any acceptor if not too bulky in combination with  $\text{COCO}_2\text{R}$ ,  $\text{COCN}$ ,  $\text{COCF}_3$ ,  $\text{COCCl}_3$  and perhaps even  $\text{COPh}$ , is likely to lead to predominant aminoenone formation in water, especially when that acceptor is  $\text{CN}$ , since its effect on the overall planarity of the molecule is likely to be minimal. Compounds that bear this out include **571** – **573**, especially the first, but many electron acceptor combinations have yet to be examined.

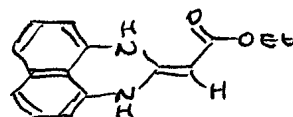
### A.10.16 Aromatic Chelates: Two Donors, One Exocyclic Acceptor

For the reasons discussed in section A.10.12, five-membered ring heteroaromatics in water never give the **C**-tautomer in appreciable quantity, whether monocyclic or benzofused. Even in an alicyclic context, the lone pair alignment shown in **510A** is inimical to formation of the aminoenone **510C**, and the extra factor of aromatisation suppresses this completely. Since benzofusion does not affect this, it has no significant effect. More O'Ferrall and Murray<sup>92</sup> list a number of benzoxazoles and benzothiazoles which show the **B**-tautomer to be important or dominant (in CHCl<sub>3</sub>) and, incidentally, reflect the same order for the effect of R (in COR) on  $K_E$  noted for pyridines and pyrazines above. Generally their  $K_E$  values are slightly higher. However, except for **574B**, we do not think that any of these **B**-forms will be important in water. A solitary estimate for  $K_M$  in this context<sup>350</sup> places that of (**575**, R = OH) in water at *ca.*  $10^{-5}$ . A rough guesstimate for (**575**, R = Ph) based on the approach sketched out below would place it at  $K_M \sim 10^{-3}$ , well below  $\log K_M -1.05$  for **72** let alone 1.09 for its benzofused analogue<sup>93</sup> (Scheme 19 and Table 33). The data of Table 40 add a further gloss on this. However approximate these estimates, they confirm the large intrinsic difference between benzofused 5- and 6-membered ring heteroaromatics in this respect.

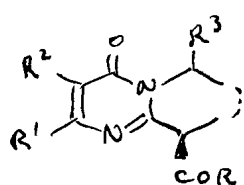
Some 6-membered ring heteroaromatics are capable of a similar tautomerism. One example is the barely aromatic **576A** which gives 55% of **576C** in DMSO, the latter also being the form found in the solid state.<sup>323</sup> However, aqueous solution should favour **576A**. An intriguing series of (mostly) fused ring pyrimidones was studied by Hungarian workers<sup>261,351-3</sup> with the results summarised in Table 43. A number of variables were tested but the only one that appears to matter is the size of the fused alicyclic ring. Qualitatively these results tie in with those of Bigley and May<sup>55</sup> for *exo-endo* tautomerism (section A.1.2), with the 5- and 6-membered ring compounds showing a marked tendency to give *exo*- and *endo*-C=C respectively. On the evidence of **578** - **580**, then as expected, open-chain compounds will exhibit the same tautomeric preference as those containing a 6-membered ring. Nevertheless the most intriguing feature of these compounds is how close to the **B/C** borderline this tautomeric preference falls; it argues for a remarkable lack of aromaticity in the parent pyrimidone ring (*cf.* section B.5.14). Except for **579** and **580**, however, these compounds will probably exist mostly as the **A**-tautomer in water. The strong preference (in CHCl<sub>3</sub>) for **577C** and **577A** by -CONHR and -CONR<sub>2</sub> respectively<sup>261</sup> is presumably due to the inability of the latter, for steric reasons, to adopt a planar configuration.



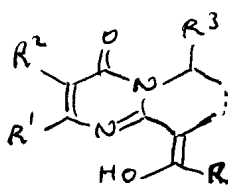
576 A



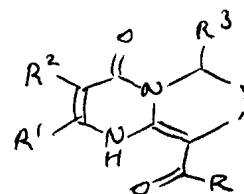
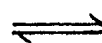
576 C



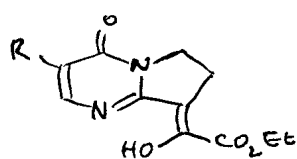
577 A



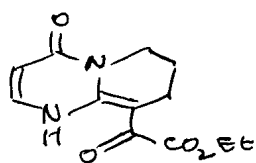
577 B



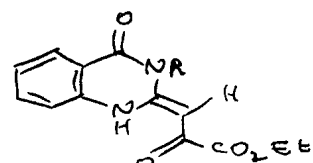
577 C



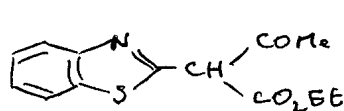
578



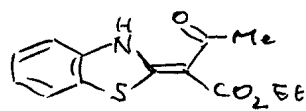
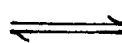
579



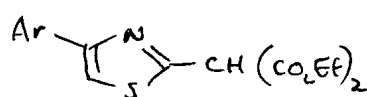
580



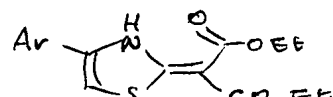
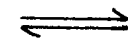
581 A



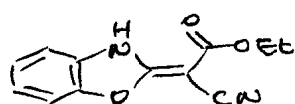
581 C



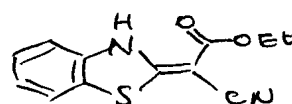
582 A



582 C



583



584

**Table 43. Dominant Tautomers for the Pyrimidones 577**

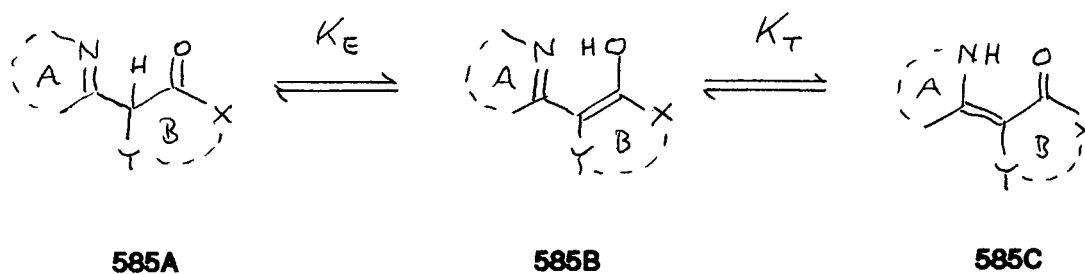
Solvent	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R	Ring Size <sup>a</sup>				
					5	6	7	8	
CHCl <sub>3</sub>	CO <sub>2</sub> Et	H	Me	H		<b>C</b>			<i>b</i>
“	H	CO <sub>2</sub> Et	H	H	<b>B</b>	<b>C</b>	<b>C</b>	<b>A</b>	<i>c</i>
“	— (CH <sub>2</sub> ) <sub>4</sub> —		H	H		<b>C</b>			<i>d</i>
“	H	H	H	NHR		<b>C</b>			<i>c</i>
“	CO <sub>2</sub> Et	H	H	NR <sub>2</sub>		<b>A</b>			<i>c</i>
96% EtOH	H	CO <sub>2</sub> Et	H	CO <sub>2</sub> Et	<b>B</b>	<b>C</b>			<i>e</i>

<sup>a</sup> Of alicyclic portion. <sup>b</sup> Ref. 351. <sup>c</sup> Ref. 261. <sup>c</sup> Ref. 352. <sup>d</sup> Ref. 353.

#### A.10.17 Aromatic Chelates: Two Donors, Two Exocyclic Acceptors

Almost nothing is known. An equilibrium has been alleged between **581A** and **581C**, but proof was not given.<sup>299</sup> However, **582** is present as **582A** in polar solvents and as **582C** in non-polar solvents and the solid state, a now-familiar dichotomy, and from solvent studies<sup>106</sup> we predict  $\log K_M$  *ca.* -1 in water (Appendix 2), while **583** and **584** exist as the **C**-tautomer shown under all conditions. These compounds illustrate, as noted in section A.10.15, the great propensity of CN for tipping the balance towards the **C**-tautomer when combined with other acceptors or itself, through its small bulk (thickness) and consequent lack of effect on the planarity of the chelate unit. In these cases, though probably not elsewhere, it is likely that the **C**-tautomer will dominate in aqueous solution. The surprisingly small difference in behaviour between **582** and **515** (section A.10.12), which may be thought of as its open-chain equivalent, is also noteworthy as possible evidence of a tendency for  $n, \pi^*$  interactions to favour the **C**- rather than the **A**-tautomer when given the choice.

## A.10.18 Exocyclic Enamine Donor, Aromatic Acceptor



Scheme 20

According to its nature and position, aromatisation in  $\beta$ -iminoketones (Scheme 18) affects the normal dominance of the aminoenone tautomer (section A.10.1) in one of several distinct ways. Aromatisation at A (Scheme 20) produces a decisive shift in favour of **585A**, with **585B** or **585C** often dominant in nonpolar solvents but their importance in aqueous solution largely confined to 6-membered ring heterocycles, where diminished loss of aromaticity on benzofusion and/or a strongly electronegative group R in COR can sometimes make **585C** the major tautomer. For chelates, this issue is explored in sections A.10.14 - 17. Aromatisation at B has contrasting effects which depend on the natures of X and Y. For  $X = Y = C=C$ , **585B** is a phenol; given  $K_E \sim 10^{13}$  for phenol itself relative to its 2-*H* tautomer (section A.2.6), **585A** loses its importance and **585B** will, in general, have the advantage over **585C**. If however  $X = C=C$  and Y is a heteroatom, or *vice versa*, replacement of a highly aromatic 6-membered carbocyclic ring by a much less aromatic 5-membered ring heterocycle will swing the tautomeric balance strongly back towards **585C**, with **585B** unimportant. These issues are explored in sections A.10.18 - 20 for compounds of the above types whether chelated or not.

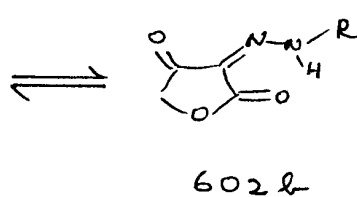
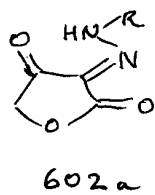
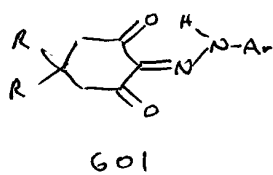
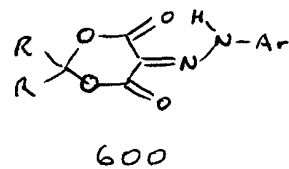
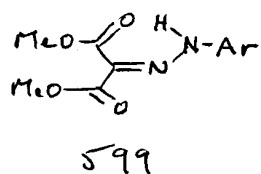
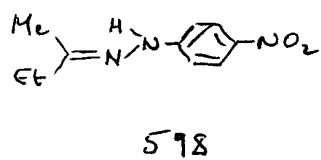
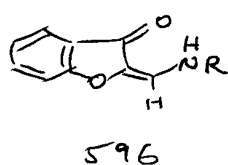
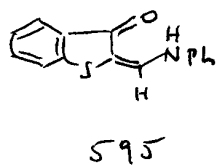
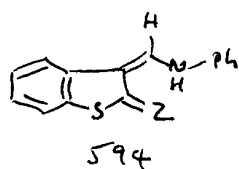
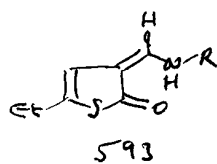
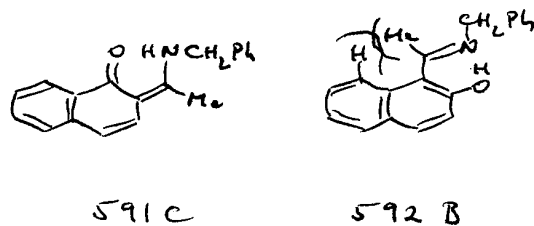
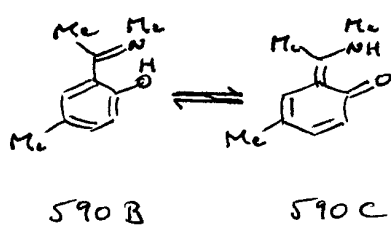
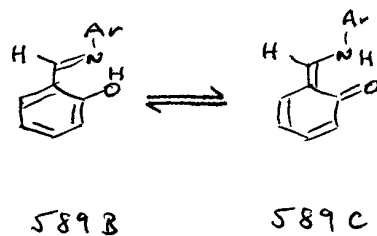
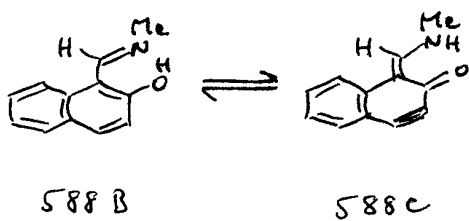
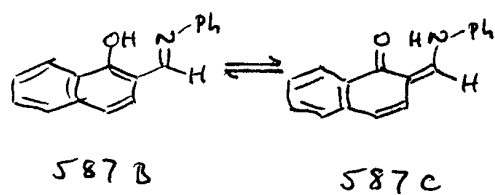
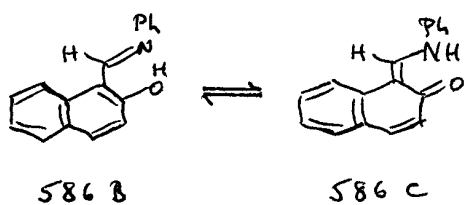
Schiff bases exemplify the compounds for which **585B** is a phenol. Antonov and co-workers have recently examined the solvent dependence of tautomerism in **586**<sup>354</sup> and **587**.<sup>355</sup> The resulting LSER equations, (xli) and (xlii) respectively,<sup>356</sup> show positive coefficients for  $\pi^*$  and  $\alpha$  but no term in  $\beta$ .

$$\log K_T = -1.05(0.04) + 0.85(0.07) \pi^* + 0.60(0.06) \alpha \quad (\text{xli})$$

$$(n = 10 \quad r^2 = 0.976 \quad s = 0.07 \quad F = 143)$$

$$\log K_T = -0.76(0.06) + 0.55(0.10) \pi^* + 0.63(0.07) \alpha \quad (\text{xlii})$$

$$(n = 12 \quad r^2 = 0.940 \quad s = 0.08 \quad F = 74)$$



This contrasts with eqn. (xix) for the pyrazolone **431** (section A.10.2) which shows a (negative) term in  $\beta$  since, with its extended structure, both NH and OH are accessible to the solvent. Here they are not,<sup>355</sup> as is generally the case for chelated  $\beta$ -diketones (section A.6.7) and for the same reason. The positive term in  $\alpha$  presumably derives from accessibility to the solvent of the *second* carbonyl lone pair of **586C** and **587C**. The coefficients of both  $\pi^*$  and  $\alpha$  in eqns. (xli) and (xlii) are much smaller than those of eqn. (xix), the former probably because extended structures like **431** allow a much larger electronic flux than is possible in chelates such as these Schiff bases, the latter because only one lone pair is here involved; we have evidence<sup>72</sup> that the second lone pair of carbonyl, when the first is already bound, adds only *ca.* 25% to the proton acceptor ability of the first one.

From the forms of eqns. (xli) and (xlii), an important distinction arises between these and other chelates. Where  $K_E$  or  $K_M$  is the dominant equilibrium, as for  $\beta$ -diketones or throughout sections A.10.14 – 17, the chelate form is disfavoured in water relative to all or most organic solvents. For  $K_T$  the situation is quite different: if the **C**-tautomer is already dominant in organic solvents, then because of its greater polarity, it will certainly dominate in water. This distinction spreads across to section A.10.19 and (probably) section A.10.20 also. Because solvent effects on  $K_T$  tend to be quite shallow (section A.10.2), work in organic solvents provides, in this instance, a reasonably good guide to the outcome in aqueous solution.

$$\log K_T = -0.87(0.12) + 1.25(0.16)\pi^* + 1.17(0.11)\alpha \quad (\text{xliii})$$

$$(n = 5 \quad r^2 = 0.987 \quad s = 0.09 \quad F = 74)$$

$$\log K_T = -1.23(0.03) - 0.674(0.082)\sigma_I - 0.238(0.060)\sigma_R \quad (\text{xliv})$$

$$(n = 7 \quad r^2 = 0.97 \quad s = 0.05 \quad F = 63)$$

Because of the aqueous insolubility of these Schiff bases their  $K_T$  values in water had to be obtained by attempting extrapolation from those in aqueous ethanolic mixtures, so cannot be considered reliable. However, at  $\log K_T$  0.43 and 0.49 respectively they are in fair agreement with the values of 0.58 for each that can be calculated from eqns. (xli) and (xlii). Just enough solvent information is provided by Dudek and Dudek<sup>319</sup> to allow a similar treatment of **588**. This yields eqn. (xliii) which extrapolates to  $\log K_T$  1.86 in water. This difference relative to **586** of about 20-fold is consistent with the greater resonance donor ability of NHMe relative to NHPh and, for

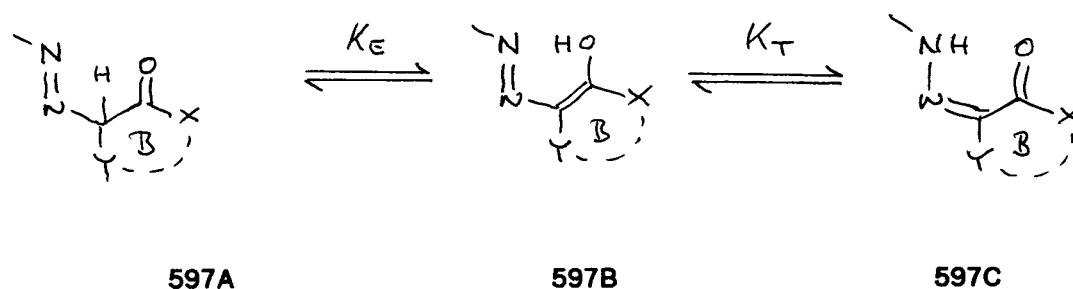
the same reason, should lead to the larger coefficients for  $\pi^*$  and  $\alpha$  that are actually observed. Vargas and Amigo<sup>357</sup> have studied the effect, in MeOH, of phenyl 4-substituents in **589** and demonstrate a relation with  $\sigma_p$ . In fact, the DSP eqn. (xliv) is rather better ( $F = 63$  in place of 32). Here  $\lambda = \rho_R/\rho_I = 0.35$  is closer to  $\sigma_m$  ( $\lambda$  0.28) than  $\sigma_p$  ( $\lambda$  1.0), as is commonly found for LFER equations involving 6-membered ring heterocycles (see section A.10.6 for one example) and may in both cases reflect poorer resonance transmission across C=N than C=C. Nevertheless, eqns. (xliii) and (xliv) agree in demonstrating that better electron donor groups favour the **C**-tautomer. Since strongly electronegative acceptors have the same effect (section A.10.14), the essentially ‘push-pull’ nature of resonance stabilisation in aminoenones<sup>358</sup> is once again confirmed.

Since aminoenone stabilisation in **585C** is balanced by phenol-type stabilisation in **585B**, both of them known quite accurately, it might have been hoped that additive rules could be applied. This does not appear to be the case. Given stabilisation of 1-naphthol **121a** relative to its 2-*H* tautomer by  $10^{7.14}$  (section A.2.6), stabilisation of a simple aliphatic aminoenone by *ca.*  $10^{8.7}$  (section A.10.3), and the near-equivalence of  $\log K_T$  for **586** and **587**,  $\log K_T$  *ca.* 1.6 for **588** in water may be estimated, a value gratifyingly close to  $\log K_T$  1.86 as deduced from eqn. (xliii). However, closer examination reveals severe flaws in this argument. In the first place, we do not know what value of  $K_T$  attaches to chelated aminoenones, but suspect that it may be less, perhaps as low as *ca.*  $10^5$  (section A.10.1). Secondly, it certainly will not work for monocyclic Schiff bases. Phenol **120a** is stabilised relative to its 2-*H* tautomer by *ca.*  $10^{13}$  (section A.2.6), which should imply, on simple additive assumptions, a rise of *ca.*  $10^6$  in the relative stability of **585B**. In fact,  $\Delta \log K_T$  in MeOH for **586** and **587** relative to (**589**, Ar = Ph)<sup>357</sup> is *ca.* 1.3, not greatly different from the effect of benzofusion on pyridones in water (Appendix 5), and while this factor may differ in water, the difference is unlikely to be great. We note elsewhere (section A.10.6) that, as clearly set out by Katritzky and co-workers,<sup>150</sup> ‘loss of aromaticity’ is a function of the overall structure and is not transferable from one type of structure to another. Here its behaviour seems roughly to echo that of 2-pyridone and its congeners, as if the nitrogen of the exocyclic unit were actually part of the ring; not in absolute value –  $K_T$  here is substantially lower – but in its sensitivity to structural factors.

Other results are more scattered. For **586**, Olivieri and co-workers<sup>359</sup> found  $\log K_T$  0.25 in  $\text{CHCl}_3$  (by  $^{13}\text{C}$  NMR) whereas Antonov *et al.*<sup>354</sup> reported  $\log K_T$  -0.28 (by UV); they also found no appreciable, or consistent, effect of phenyl ring substituents on  $K_T$ . Neither observation is in accord with that of others<sup>354,355,357</sup> and we are unable to resolve this discrepancy. From scattered solvent data on **590**<sup>319</sup> it is possible to deduce a mean  $\Delta \log K_T$  *ca* 0.85 which is lower than the estimate of 1.3 deduced above, but this may be due to some enhancement of  $K_T$  in **590** through the resonance donor properties of methyl. Steric effects have been little studied, but Dudek and Holm<sup>360</sup> find that, while **591** exists in  $\text{CHCl}_3$  entirely as the C-tautomer, its isomer **592** is present largely as **592B** (contrast **586** and **587**), most probably because the *peri*-interaction shown destroys the planarity of the exocyclic unit, an even more serious matter for **592C** than for **592B**.

All known examples of imine substitution in 5-membered ring oxoheterocycles give the aminoenone tautomer, whether as the 2- or 3-substituent.<sup>2dd,2rr</sup> Unequivocal examples include **593** - **596** and this applies even to the thione (**594**,  $\text{Z} = \text{S}$ ) which in the absence of such substitution exists as the thiol (section A.3.7). Except where some bulky substituent interferes with the planarity of the chelate as in **592**, it is highly probable that all compounds of this type will exist as **585C**, even in water.

#### A.10.19 Exocyclic Hydrazo Donor, Aromatic or Non-Aromatic Acceptor



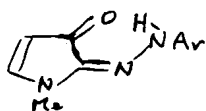
Scheme 21

Replacement of CH in **585** by N in **597** to give an azo-linkage in place of an imine, or a hydrazo-derivative in place of an enamine, leads to the situation of Scheme 21. The cases are not exactly similar since ring A cannot exist, but otherwise, the parallelism with Scheme 20 is complete. This case is important since azo-compounds are readily prepared by diazotisation at saturated or unsaturated carbon and there have been many more cases of the resulting tautomerism than for the Schiff bases of the preceding section.

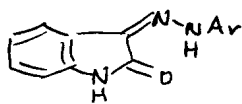
It has been noted in connection with the LFER treatment of **589** (section A.10.18) that C=N is a poorer resonance transmitter than C=C. It follows that RNHN=C should be a poorer resonance donor than RNHC=C. Since enhancing the resonance donor ability of the enamine moiety increases  $K_T$ , as has also been demonstrated for **589**, one might have predicted  $K_T$  to be lower for these azo-compounds than for the corresponding Schiff bases. At the same time, and operating in the reverse direction, azo-compounds are strongly disfavoured relative to their hydrazo tautomers (section A.5.1). In the event, these factors almost cancel.

It is convenient to start with non-aromatic compounds. Given that **598** exists as shown in the solid state,<sup>361a</sup> it is unsurprising that **599**,<sup>361a</sup> **600**,<sup>361b</sup> and **601**<sup>361c</sup> should do so also (all these are crystal structure determinations). The unsymmetrical dienone **602** exists in CHCl<sub>3</sub> as an almost equal mixture of **602a** and **602b**;<sup>217</sup> *cf.* the very similar results of Yamaguchi *et al.*<sup>214</sup> for the corresponding enamines **506** (section A.10.11). Five membered ring heterocycles may next be considered. As for the corresponding enamines of section A.10.18, tautomer **597C** is expected and generally found: examples include **603**,<sup>46b</sup> **604**<sup>46b</sup> and **605**;<sup>2ee</sup> **606C** which is exclusively present in CHCl<sub>3</sub><sup>362</sup> and in other chlorinated solvents<sup>363</sup> though some of **606B** is found alongside it in DMSO; and **607**<sup>364</sup> where a very similar situation prevails. These results in DMSO, a very strong proton acceptor, must be regarded with suspicion as guides elsewhere since the azo-linkage is a very poor proton acceptor (section A.5.1, and below) and DMSO is probably able to open the chelate.<sup>356</sup> Compound **608**, which can barely be considered aromatic (*cf.* **602**), exists in CHCl<sub>3</sub> and DMSO as shown.<sup>364</sup> Some results are not so straightforward. Compound **609** exists as the azo-compound in several solvents, perhaps through hydrogen bonding between ester and OH as shown,<sup>364</sup> whereas **610** gives the iminol **610B** not the amide **610C**<sup>364</sup> perhaps because the azo-linkage, which cannot here tautomerise, is acting simply as an electronegative substituent and having the usual effect of lowering  $K_T$  (*cf.* 4-pyridone, section A.10.6). Yoder *et al.*<sup>364</sup> indeed remark that azo-substitution does not in general much affect the tautomeric preference (OH  $\rightleftharpoons$  C=O) that would otherwise obtain, which allowing for the electronegativity effect noted above, means that this and the countervailing influence of replacing imine by hydrazone must more or less cancel, as expected.

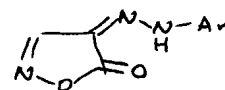
Antonov and co-workers have studied the solvent dependence of **611**<sup>365</sup> and **612**<sup>366</sup> in studies which parallel their work on the corresponding Schiff bases **586**<sup>354</sup> and **587**<sup>355</sup> (section A.10.18). Here eqns. (xlv) or (xlvi) for **611**



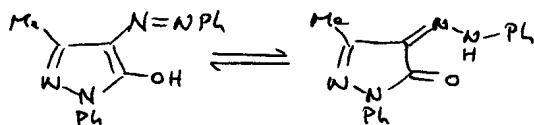
603



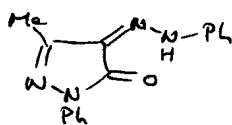
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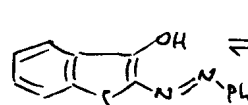
605



606 B



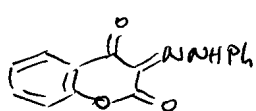
606 C



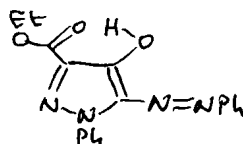
607 B



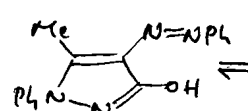
607 C



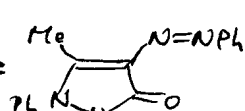
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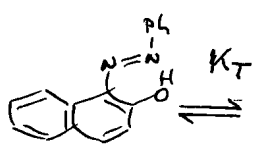
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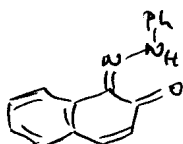
610 B



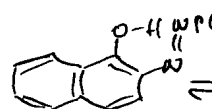
610 C



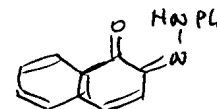
611 B



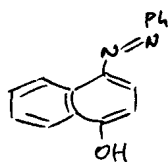
611 C



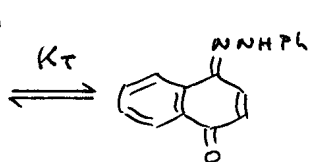
612 B



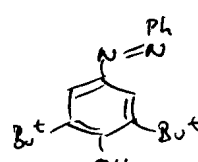
612 C



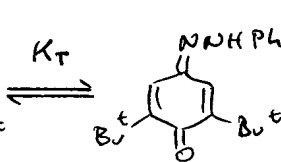
613 B



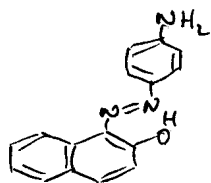
613 C



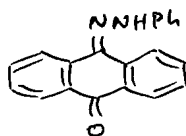
614 B



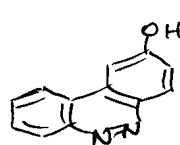
614 C



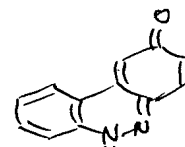
615



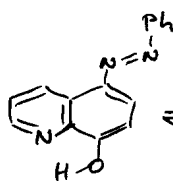
616



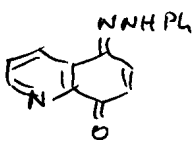
617 B



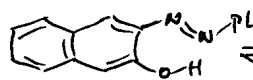
617 C



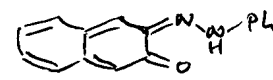
618 B



618 C



619 B



619 C

$$\log K_T = -0.35(0.14) + 0.35(0.26)\pi^* + 0.33(0.23)\alpha \quad (\text{xlv})$$

$$(n = 8 \quad r^2 = 0.61 \quad s = 0.19 \quad F = 4)$$

$$\log K_T = -0.29(0.10) + 0.11(0.19)\pi^* + 0.79(0.27)\alpha - 0.68(0.28)\beta$$

$$(n = 7 \quad r^2 = 0.81 \quad s = 0.12 \quad F = 4) \quad (\text{xlvii})$$

$$\log K_T = 0.23(0.02) + 0.17(0.04)\pi^* + 0.16(0.03)\alpha - 0.23(0.03)\beta$$

$$(n = 13 \quad r^2 = 0.87 \quad s = 0.03 \quad F = 20) \quad (\text{xlviii})$$

$$\log K_T = -0.81(0.17) + 1.17(0.26)\pi^* + 0.63(0.19)\alpha - 1.50(0.26)\beta$$

$$(n = 11 \quad r^2 = 0.86 \quad s = 0.21 \quad F = 14) \quad (\text{xlviii})$$

and (xlvii) for **612**<sup>356</sup> are to be compared with (xli) and (xiii) respectively. Two differences may be noted. Firstly, the solvent dependence of  $K_T$  is even shallower, especially for **612**. Secondly, for **612** and (equivocally) for **611**, a term in  $\beta$  is now present. This points to a breaking of the chelate by proton acceptor solvents with, as expected in consequence, stronger bonding to OH. This feature, which presumably results from the very poor proton acceptor properties of the azo-linkage<sup>354</sup> (see section A.5.1) may also be responsible for the poor statistics, since each tautomer must then incorporate a variable quantity of unchelated sub-species whose proportion varies with solvent in a way that may not reflect the behaviour of the chelates. A distantly related phenomenon is found for some open-chain  $\beta$ -ketoesters (section A.6.7).

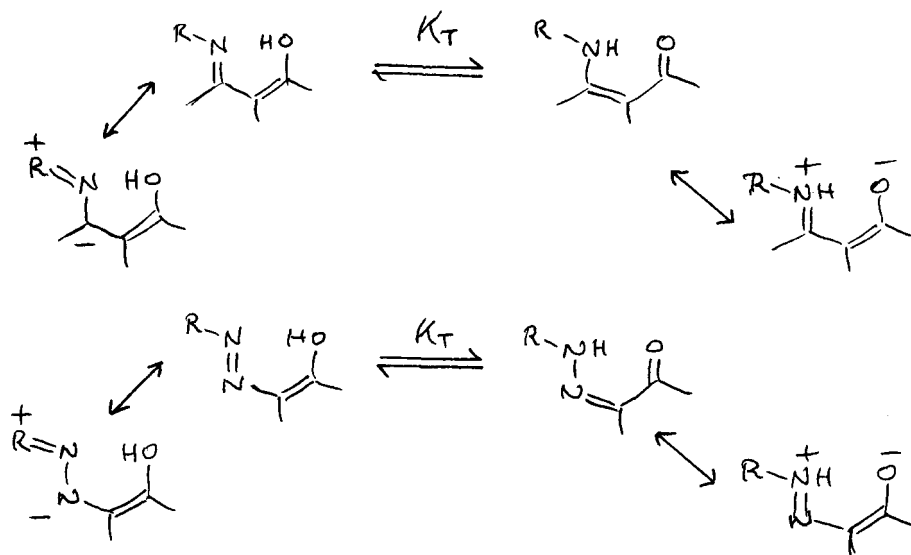
These compounds are even more water-insoluble than their Schiff base equivalents: for **611** a value of  $\log K_T$  ca. 0.07 was obtained by extrapolation from water-ethanol mixtures, whereas for **612** no value at all could be obtained. The values calculated for eqns. (xlv) - (xlvii) are  $\log K_T$  0.42, 0.59 and 0.51 respectively, very close to the value of 0.58 estimated similarly for both **586** and **587**. The solvent dependence of the 4-isomer **613** of **611** has also been investigated by Stoyanov and Antonov<sup>367</sup> with the results expressed in eqn. (xlviii)<sup>356</sup> which extrapolates to the very similar aqueous values of  $\log K_T$  0.61 (calculated) or  $> 0$  (observed). Here the  $\pi^*$  term is much larger, consistently with the longer (extended) conjugated system, while since there is no chelate, the term in  $\beta$  is now much more important; eqn. (xvix) for the tautomerisation of **431B** to **431C** (section A.10.2), where again a switch from OH to NH is involved, possesses a negative  $\beta$ -term of similar magnitude.

Earlier work is not entirely consistent either with that of Antonov *et al.* or, internally, always with itself; for example, Korewa and Urbanska<sup>368</sup> report  $K_T$  for **613** to be greater for its 4'-nitro derivative in Me<sub>2</sub>CO but much less in DMF, while relatively minor discrepancies for **611** appear in work by Saeva<sup>369</sup> and by Mathias and co-workers.<sup>370</sup> Antonov and Nedeltcheva<sup>371</sup> point out that there are serious difficulties in the quantitative resolution of overlapping UV bands which may have misled earlier workers but for which they have evolved a satisfactory technique. Their own work appears to be internally consistent and we shall accept it as definitive.

$$\log K_T = -0.35(0.05) + 1.04(0.12)\sigma_p \quad (\text{xlix})$$

$$(n = 6 \quad r^2 = 0.946 \quad s = 0.12 \quad F = 70)$$

Electronic effects on  $K_T$  are of some interest and have been examined for substituents in the phenyl moiety by a number of authors. Mathias and co-workers,<sup>370</sup> while unable to obtain a satisfactory LFER equation, showed that electronegative substituents in the phenyl ring increase  $K_T$  for **611** in CHCl<sub>3</sub>, while in CCl<sub>4</sub>, these push the equilibrium in **614** from mostly **614B** in the parent compound to mostly **614C**.<sup>372</sup> Skulski *et al.*<sup>269</sup> find **615** to exist overwhelmingly as shown in all solvents. A study of **613** in 50% EtOH by Stoyanov and Antonov<sup>367</sup> yields, for 4'-substitution, the LFER eqn. (xlix).<sup>356</sup> Confirming these qualitative results this shows a clear dependence of  $K_T$  on substituent electronegativity, in diametric opposition to the Schiff base **589** (section A.10.18). So some new factor must have entered. We suggest a plausible origin for it in Scheme 22, which compares the types of electronic stabilisation open to Schiff bases and their azo-analogues. If R is an electron donor then, in each case, the **C**-tautomer is stabilised by conjugation, though probably less so in the case of the hydrazone as discussed above. However a second, localised form of conjugation is open to the **B**-tautomer, as shown. It will probably be negligible for Schiff bases but could become important for azo-compounds through the much greater ability of nitrogen than of carbon to support a negative charge. This is not quite the same mechanism as the one we have invoked to explain stabilisation of the enamine *vs.* the imine tautomer by electronegative substituents on nitrogen (Scheme 8, section A.4.6) since  $\text{--N=}$  here replaces the very different  $\text{--CH=}$  in the earlier case, but it possesses formally similar consequences in stabilising the NH tautomer. In the event its importance for azo-compounds appears to outweigh the effect of through conjugation, so accounting for the reversed sign of  $\rho$  in eqn. (xlix) relative to (xliv). A similar factor appears to operate in triazenes

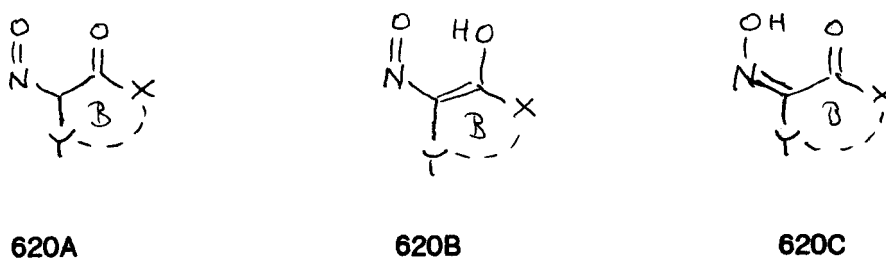


Scheme 22

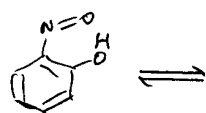
(section A.5.7) and we note other examples particularly in sections A.6.3 and A.6.6. The existence of localised effects within the general framework of through resonance is an established phenomenon and has been reviewed.<sup>373</sup>

Some further results are of interest. It is unsurprising (*cf.* **473**, section A.10.7) that **616** exists as such in all solvents.<sup>363</sup> Interestingly however, **617** shows the opposite preference and gives **617B** only;<sup>2ss</sup> here lone pair repulsion is not enough to overcome aromaticity, in addition to which, and perhaps of equal significance, **617C** like **614C** is both quinonoid and at least nominally anti-aromatic. Finally, two eminently predictable results: that **618** is locked as the **B**-tautomer by lone pair repulsion (in the **C**-form) and/or by its intramolecular hydrogen bond;<sup>270</sup> whereas the **C**-tautomer of **619** is not found because of the highly disfavoured quinonoid structure ( $\Delta \log K_T$  *ca.* -1.8; *cf.* Appendix 5) that its formation would entail.<sup>270</sup>

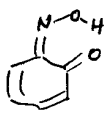
#### A.10.20 Exocyclic Oximino Donor, Aromatic or Non-Aromatic Acceptor



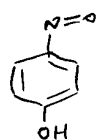
Scheme 23



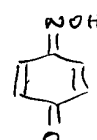
621 B



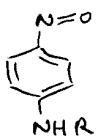
621 C



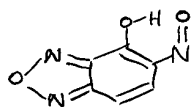
622 B



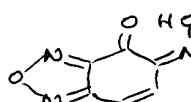
622 C



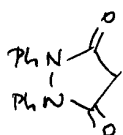
622 a



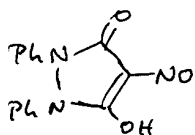
623 B



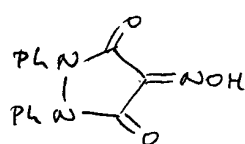
623 C



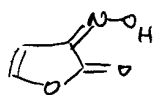
290



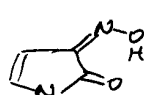
624 B



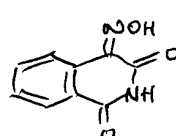
624 C



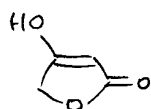
625



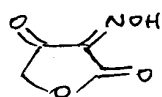
626



627



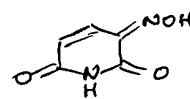
288 b



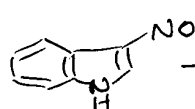
628



281 b



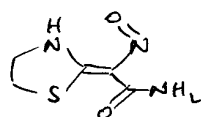
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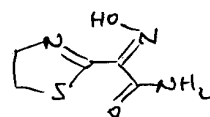
630 B



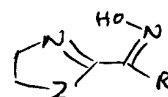
630 C



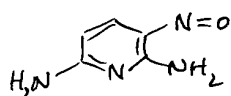
631 B



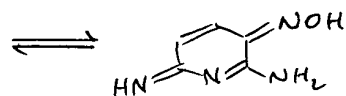
631 C



632 C



633 B



633 C

According to the calculations of Lammertsma and Bharatam,<sup>145</sup>  $\text{CH}_3\text{NO}$  is disfavoured relative to  $\text{CH}_2=\text{NOH}$  by about the same energetic margin as the iminol  $\text{NH}=\text{CHOH}$  relative to formamide (section A.5.2). That being so, it is scarcely surprising that the nitroso-structures **620A** and **620B** should prove both to be fugitive species relative to the oximino-tautomer **620C**.

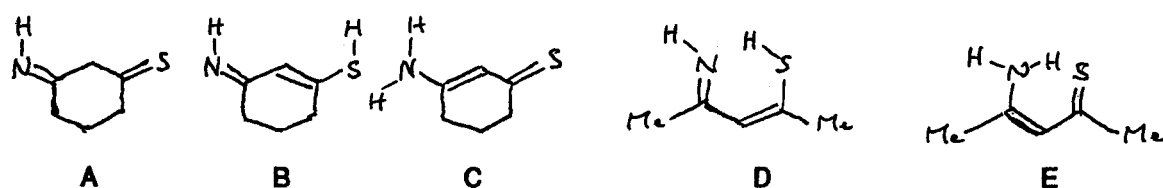
The best chance for **620B** would seem to exist in a benzenoid context, where phenol is favoured relative to its 2-*H* tautomer by *ca.*  $10^{13}$  (section A.2.6). Ershov and Nikiforov<sup>374</sup> state that 2-nitrosophenol **621B** is the exclusive species in nonpolar solvents and dominates in polar ones, whereas its 4-isomer **622**, while existing largely as **622B** in  $\text{Et}_2\text{O}$ , is present mostly as **622C** in  $\text{EtOH}$  and water. Boyer<sup>189</sup> states the balance for **622** in water to lie 85% in favour of the **C**-tautomer. This difference between the isomers may be caused in part by a strong intramolecular hydrogen bond in **621B**. Substitution in **622** has little effect unless on both sides of  $\text{OH}/\text{C}=\text{O}$  when it pushes the equilibrium back towards the **B**-tautomer.<sup>374</sup> This situation is to be contrasted with **422** which exists exclusively as shown (section A.9.7); here while both tautomers of **622** are ‘push-pull’ systems, and so is **422a**, the latter’s imino-tautomer is scarcely one at all, so no advantage would accrue from its formation.

The fused oxadiazole **623B** has less aromaticity to lose, being quinonoid already, so goes exclusively to **623C**.<sup>2tt</sup> As with azo-substitution (section A.10.19), compounds whose tautomeric form is unaffected when  $\text{CH}_2$  is replaced by  $\text{C}=\text{NOH}$  may be expected to give exclusively this product. One example is **290** (section A.6.4) which gives **624C** not **624B**;<sup>2z</sup> others include **625**,<sup>375</sup> **626**,<sup>375</sup> and **627**.<sup>376</sup> Slightly or moderately disfavoured tautomeric forms are also readily stabilised; for example, **288b** of which the  $\beta$ -ketoester is the disfavoured tautomer (section A.6.4) gives **628**,<sup>217</sup> whereas **281b** which is slightly favoured over the imide tautomer gives **629**.<sup>376</sup> *Contra* **422**, which possesses much more aromaticity, **630** in water goes entirely to **630C**.<sup>189</sup>

We have encountered only two reports of a heterocyclic nitroso-compound, in principle capable of tautomerisation to the oxime, in which this fails to go to completion. One is **631**, which in water exists as a mixture of **631B** and **631C**.<sup>377</sup> Here **631B** may be looked upon as a chelated structure with two donors and two acceptors (section A.10.13), and in that sense constitutes a special case. Where *R* is *not* an acceptor, **632C** results.<sup>377</sup> The other is **633B**, which does not tautomerise to the oxime **633C**;<sup>211</sup> the latter would involve a highly disfavoured *p*-quinonoid structure, at least some degree of anti-aromaticity, and also the formation of an imino- (not amino-) heterocycle (section B.4.4), so on all counts is disallowed.

### A.11 $\beta$ -Iminothiketones and Aminoenethiones

By contrast with the massive amount of information on aminoenones (section A.10), that on their sulfur equivalents is sparse. 4-Pyridithione and related thionoheterocycles have been well studied, but little is known concerning simpler chelated and nonchelated structures. There has been a presumption<sup>2uu</sup> that  $K_T$  for equivalent oxo- and thionoheterocycles will in general be similar, the chief exceptions being found among 5-membered rings where the enethiol tautomer is almost universal (sections A.3.7 and A.3.8). We shall find that the evidence for this is equivocal.



**Table 44.** Energetics ( $\Delta H$ , kJ mol<sup>-1</sup>) for Structures A – E <sup>a</sup>

	A $\rightarrow$ B		A $\rightarrow$ C		B $\rightarrow$ C		D $\rightarrow$ E	
	$\Delta H$	'log $K_E$ '	$\Delta H$	'log $K_M$ '	$\Delta H$	'log $K_T$ '	$\Delta H$	'log $K_T$ '
<i>b</i>	-3.404 <sup>e</sup>	0.6	-38.244	6.7	-34.820	6.1	-45.685	8.0
<i>c</i>	7.861 <sup>e</sup>	-1.4	-26.675	4.7	-34.098	6.0	-38.744	6.8
<i>d</i>	-4.156 <sup>e</sup>	0.7	-51.893	9.1	-47.709	8.4	-51.654	9.1
	C=S $\rightarrow$ SH <sup>f</sup>		C=NH $\rightarrow$ NH <sub>2</sub> <sup>g</sup>		$\Delta$ C=S / C=NH <sup>h</sup>		(D $\rightarrow$ E) – (B $\rightarrow$ C) <sup>i</sup>	
							' $\Delta$ log $K_T$ '	
<i>b</i>	26.667	-4.7	27.207	-4.8	0.540	-0.1	-10.865	1.9
<i>c</i>	37.568	-6.6	31.068	-5.4	-6.500	1.1	-4.676	0.8
<i>d</i>	31.774	-5.6	23.689	-4.1	-8.085	1.4	-3.945	0.7

<sup>a</sup> The quantities 'log  $K$ ' and ' $\Delta$  log  $K$ ' are hypothetical values for the circumstance that  $\Delta G = \Delta H$  (see the text). <sup>b</sup> RHF/6-31G\*\*//RHF/6-31G\*\*. <sup>c</sup> MP2/6-31G\*\*//MP2/6-31G\*\*.

<sup>d</sup> B3LYP/6-31G\*\*//B3LYP/6-31G\*\*. <sup>e</sup> The *E*-conformer at NH for **B** is slightly favoured (by 0.738, 0.438 and 0.028 kJ mol<sup>-1</sup> respectively). <sup>f</sup> Energetics for the enolisation of thioacetone (Table 22).

<sup>g</sup> Energetics for the enolisation of acetone imine (Table 22).

<sup>h</sup> Energetics for the enolisation of acetone imine relative to that for thioacetone. <sup>i</sup> Energetics for the process  $K_T = [E] / [D]$  relative to that for the process  $K_T = [C] / [B]$ .

### A.11.1 Energetics

Comparison of Table 44 with Table 31 will reveal that aminoenethiones, like aminoenones, are heavily favoured over their rival tautomers. Here however the resemblance ends. Firstly, in place of a stability order  $\mathbf{C} \gg \mathbf{A} \gg \mathbf{B}$  we now have  $\mathbf{C} \gg \mathbf{A}, \mathbf{B}$  with almost no differential between the latter tautomers. Secondly, and very strikingly, the reason for this preponderance is wholly different. Ketones enolise with difficulty, imines with ease, and this difference is responsible for most (not all) of the sign of  $\log K_T$ . However, there is almost no difference in the intrinsic tendency of imines and thiones to enolise; the third column of the lower set of data in Table 44 shows thiones as less liable by a margin somewhere in the region of 0 - 8 kJ mol<sup>-1</sup>. What is chiefly responsible for the overall difference is a combination of C=S as the most powerful *promoter* of enolisation (C=S > C=O > C=NH) with C=NH as that hetero-double bond most *susceptible* to it (C=NH > C=O > C=S). According to the method of calculation, this factor ( $\mathbf{B} \rightarrow \mathbf{C}$  vs.  $\Delta \text{C=S/C=NH}$ , Table 44) adds *ca.* 10<sup>6</sup>, 10<sup>5</sup> or 10<sup>7</sup> to that margin expected in favour of tautomer  $\mathbf{C}$  from the 'intrinsic' tendency of each group in isolation to enolise. The corresponding value for aminoenones (Table 31) averages at *ca.* 10<sup>2.3</sup> superimposed on an 'intrinsic' value averaging *ca.* 10<sup>6.3</sup>, an entirely different situation. This profound asymmetry in the relation between the two series may be expected to have other consequences, and probably does (*vide infra*).

The contrast in behaviour between the 'extended' ( $\mathbf{A} - \mathbf{C}$ ) and 'chelated' ( $\mathbf{D}$  and  $\mathbf{E}$ ) forms is, again, quite different from that found for the corresponding aminoenones (section A.10.1). Chelation in the latter leads to a drop in ' $\Delta \log K_T$ ' averaging 3.5 for the three computational methodologies, whereas here there is a (more modest) *rise* (lower right column of Table 44). This different result is most plausibly the result of a switch in the relative strengths of the rival intramolecular hydrogen bonds. For chelated aminoenones, OH---N=C > NH---O=C; here by contrast NH---S=C > SH---N=C, the effect being to *increase* the predominance of the  $\mathbf{C}$ -tautomer whereas, for aminoenones, chelate formation *decreases* it. A similar factor operates in  $\beta$ -thionoketones (section A.8.1), where the preferred tautomeric form is actually reversed by chelation. The extreme weakness of SH as a proton donor<sup>235,378</sup> has other consequences which we explore in the following two sub-sections.

### A.11.2 Solvent Studies

Beak and Covington<sup>379</sup> studied the solvent dependence of  $K_T$  in a set of pyridones including 4-thiopyridone **634**, for which they obtained eqn. (1). Replacing the Kirkwood function by  $\pi^*$  and using more recent values for  $\alpha$  and  $\beta$ , we obtain eqn. (li). Unfortunately, both equations are invalid.

$$\log K_T = -2.57 + 5.37(\epsilon - 1/2\epsilon + 1) + 4.26\alpha + 1.69\beta \quad (1)$$

$$\log K_T = -1.81(0.61) + 1.64(0.99)\pi^* + 2.14(0.78)\alpha + 1.69(0.84)\beta \quad (li)$$

( $n = 10$   $r^2 = 0.86$   $s = 0.71$   $F = 12$ )

$$\log K_T = -1.44(0.38) + 1.04(0.61)\pi^* + 0.72(0.62)\alpha + 2.00(0.50)\beta \quad (lii)$$

( $n = 9$   $r^2 = 0.85$   $s = 0.42$   $F = 9.5$ )

Nine of Beak's data points involve direct observation in organic solvents, with  $\log K_T$  values in the range  $0 \pm 1.5$ . The tenth, for water, was obtained by the 'basicity method' using eqn. (ii) and assuming the NMe and SMe derivatives **635** and **636** to be accurate models for **634C** and **634B** respectively. This point,  $\log K_T$  3.97, is so far away from the remainder as to turn eqns. (1) and (li) into two-point correlations and so essentially meaningless. If water is eliminated, eqn. (lii) results. This extrapolates to a value of  $\log K_T$  1.33 in water, several orders of magnitude below the commonly accepted value. Even allowing for only a moderate statistical fit, this gap is far too great to bridge.

We have found that the same problem attaches to 2-thiopyridone (section B.3.2) but not to 6-chloro-2-pyridone (section B.2.2), both reported in the same paper.<sup>379</sup> This is a major hiatus which we discuss further in Appendix 2 but cannot resolve. Nevertheless it adds to our suspicion, expounded in more detail below, that  $K_T$  for thioamides and related compounds may have been considerably overestimated.

The positive sign of  $\beta$  in all these equations contrasts with its negative sign in eqn. (xix) for an extended aminoenone (section A.10.2) and confirms the conclusion arrived at by calculation (section A.11.1) that, while  $\text{OH} > \text{NH}$  in strength as a hydrogen bond donor,  $\text{NH} > \text{SH}$ . This difference has further implications for the 'basicity method' (see the following section).

### A.11.3 Correction Factors for the 'Basicity Method'

For  $\Delta pK_a$  (NMe  $\rightarrow$  NH), *i.e.*  $\Delta(NR)$ , these differ slightly from those for the corresponding pyridones (see Appendix 1) but the point is immaterial here since  $pK_a$  (NH) is available in all cases where an estimate for  $K_T$  can be made. For (SR) there is no information and we have to attempt an indirect method, as follows.

The correction factor  $\Delta(XR)$  derives from the effect of increased solvation in increasing the basic strength of XH (Appendix 1) and it seems logical to suppose, therefore, that as  $XH^+$  becomes a stronger proton donor, so  $\Delta(XR)$  will increase; this will explain, for example, why it should be greater for oxygen than for nitrogen cations. We therefore require some *quantitative* way of ranking  $OH^+$ ,  $NH^+$  and  $SH^+$  as proton donors. If we postulate that the neutral species OH, NH and SH will have donor strengths proportional to that of their cations, then suitable model compounds of this type may provide the necessary data. Abraham *et al.*<sup>378</sup> report proton donor strengths ( $\alpha$ -values) for PhOH, PhNHMe and PhSH, and these three compounds possess not only a simple structural relation to one another but also the important feature of a hetero-atom linked to an aromatic system, **637**, very similar to that of the target molecules, **639** and **641**. The requisite data, available for  $X = O$  and  $X = NMe$ , may now be extrapolated to give  $\Delta pK_a$  values for  $X = S$ . The results, for the 2-substituted as well as the 4-substituted series, appear in Table 45.

The conclusion of Table 45, that  $\Delta pK_a$  for SMe  $\rightarrow$  SH may be *negative*, is unsurprising. The corollary of this, that *S*-alkylation must be *base-strengthening* or have no effect, is also true for *aliphatic* secondary amines which possess similar  $\alpha$ -values (typically  $\alpha \sim 0.08$ )<sup>378</sup> to PhSH. The values for  $\Delta(SR)$  in Table 45 must be regarded as highly provisional but at present we cannot go beyond them. More work is needed.

**Table 45. Cross-Comparison of Proton Donor Strengths (637) with XMe  $\rightarrow$  XH Correction Factors (for 638 – 641)**

	$\alpha$ ( <b>637</b> ) <sup>a</sup>	$\Delta pK_a$ ( <b>638</b> $\rightarrow$ <b>639</b> )	$\Delta pK_a$ ( <b>640</b> $\rightarrow$ <b>641</b> )
X = O	0.60	0.5 <sup>b</sup>	1.0 <sup>b</sup>
X = NMe	0.17	0.04 <sup>c</sup>	0.05 <sup>c</sup>
X = S	0.09	-0.05 <sup>d</sup>	-0.15 <sup>d</sup>

<sup>a</sup> Ref. 378. <sup>b</sup> Estimated (see Appendix 1). <sup>c</sup> Ref. 380. <sup>d</sup> By extrapolation (see the text). A mean value of -0.1 could be used for both without perceptible error.

#### A.11.4 Extended Structures: 4-Thiopyridone and Related Heterocycles

Quantitative work on this topic, none of it recent, is summarised in Table 46. The minimal corrections to  $\log K_T$  required on the basis of Table 45 still leave these compounds with  $K_T$  values greater than those for the corresponding oxoheterocycles, though by smaller margins than currently accepted, and by variable amounts. For **634**, **644** and **645** this margin is  $\Delta \log K_T$  0.6, 0.9 and 0.8 respectively, which is near enough a constant, but for **642** it is 0.1, which is out of line not only in this respect but also in leading to  $\Delta \log K_T$  0.5 for the effect of benzofusion in place of the value of *ca.* 1.0 found both for the corresponding oxoheterocycles and for **644** and **645** as well. Perhaps  $K_T$  for **642** should be checked. In addition to these quantitative data, Acheson *et al.*<sup>383</sup> established by comparison with model compounds that the thione **643** exists as such; *cf.*  $\log K_T$  7.8 for its oxygen analogue (section A.10.7, for which see further commentary). Nothing is known concerning substituent effects on  $K_T$ , but in the absence of other information, the 4-pyridones (section A.10.6) may provide a reasonable guide.

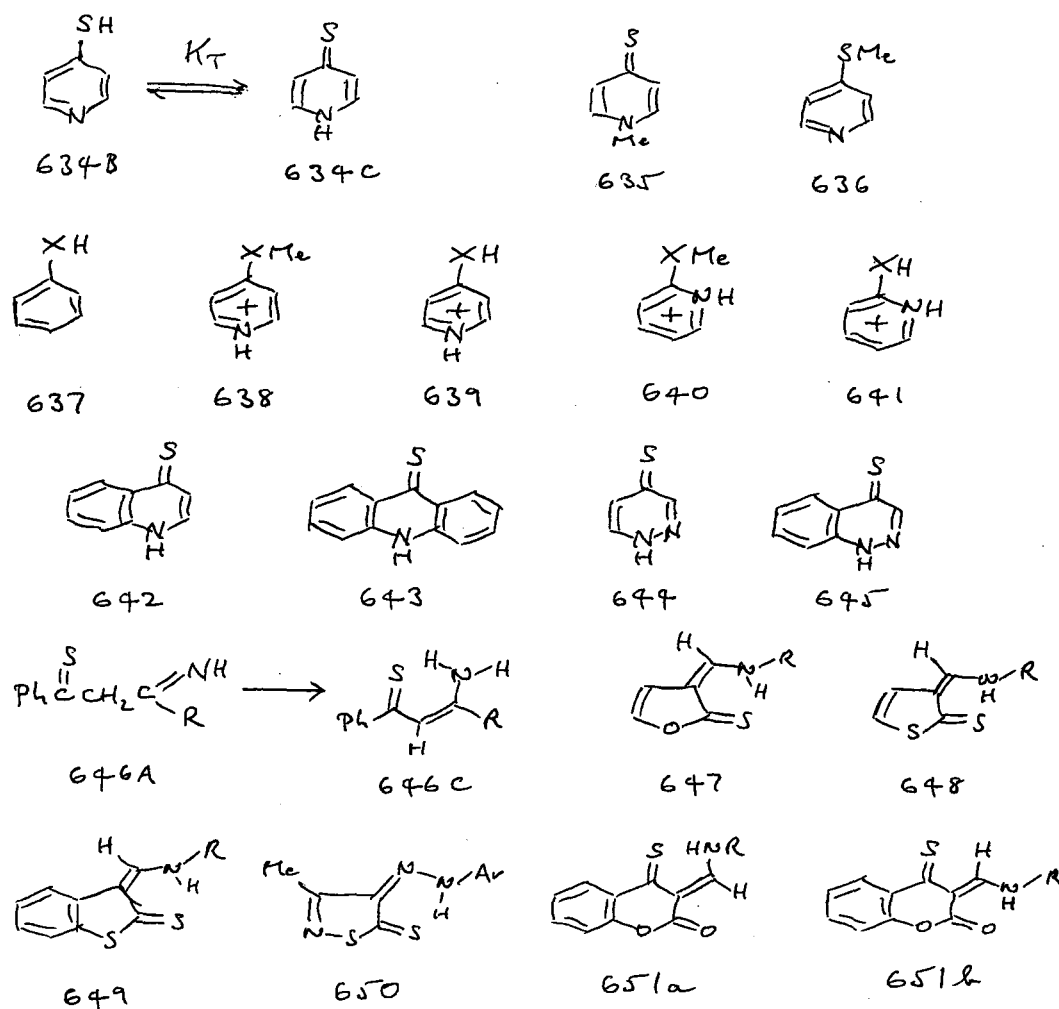
Whatever their true  $K_T$  values, it must be emphasised that in none of these compounds is the thiol tautomer likely to be important in water. In cases that are marginal for the corresponding oxoheterocycle that is less certain, and this might prove a profitable field for study.

**Table 46.  $pK_a$  and  $\log K_T$  Values for 4-Thiopyridone and some Related Thionoheterocycles in Water** <sup>a,b</sup>

Compound	$pK_a$ (NH)	$pK_a$ (SMe)	$pK_a$ (SH)	$\log K_T$	$\log K_T$ <sup>c</sup>
<b>634</b>	1.43 <sup>d</sup>	5.97 <sup>d</sup>	5.92	4.5	3.9
<b>642</b>	0.77 <sup>d</sup>	5.81 <sup>d</sup>	5.76	5.0	4.9
<b>644</b>	-0.75 <sup>e</sup>	3.26 <sup>e</sup>	3.21	4.0	3.1
<b>645</b>	-1.83 <sup>e</sup>	3.13 <sup>e</sup>	3.08	4.9	4.1

<sup>a</sup>  $\log K_T = pK_a$  (SH) -  $pK_a$  (SMe). <sup>b</sup> Calculated values (see section A.11.3) are *italicised*.

<sup>c</sup> For corresponding oxoheterocycle (Table 38, section A.10.7). <sup>d</sup> Ref. 381. <sup>e</sup> Ref. 382.

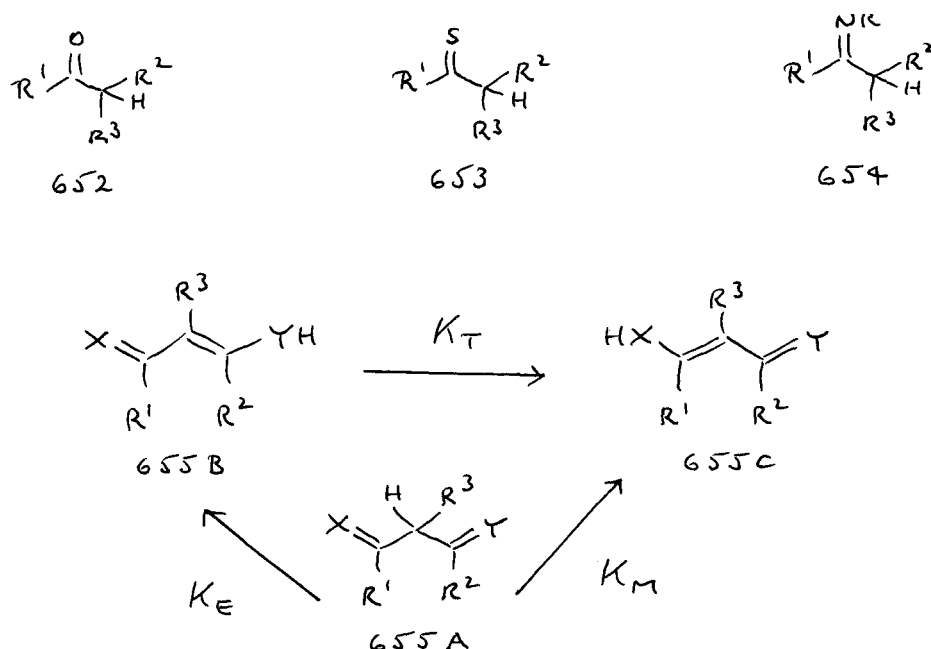


### A.11.5 Chelated Structures

There is extraordinarily little information on this topic. Goerdeler and Mittler<sup>384</sup> state, on the basis of solid-state IR, that the compounds they prepared as (**646A**,  $R = OR'$  or  $NH_2$ ) proved to have the structure **646C**. Like their oxo-analogues, the thiones **647** - **649** exist as shown,<sup>2p</sup> as does the hydrazone **650**, in EtOH,  $CHCl_3$ , and KBr.<sup>2vv</sup> The tautomeric form of **651**,<sup>385</sup> which reflects that of the hydrazone **608** (section A.10.18), is equally as expected. It is however interesting in that its preferred configuration (in  $CHCl_3$ ), **651a**, shows thione in this context to be a better proton acceptor than carbonyl. While esters are poorer acceptors than the corresponding ketones,<sup>72</sup>  $C=S$  is much inferior to the equivalent  $C=O$ ,<sup>72</sup> and a possible explanation is that, in such rigid structures, its greater bond length gives it the advantage. If so, this may be generally true of chelates and could help to explain some of the preference for  $OH---S=C$  over  $SH---O=C$  bonding which we have noted for  $\beta$ -thionoketones (sections A.8.1 and A.8.3), additionally to the major part undoubtedly played by the weakness of SH as a proton donor.

## A.12 Summary and Overview

The preceding sections concern tautomerisation brought about when a saturated carbon atom is adjacent to a hetero-double bond  $C=Z$ , where  $Z = O, S$  or  $NR$  (sections A.2 - A.4), or between two such bonds in any of their six possible combinations (sections A.6 - A.11). In addition, section A.1 considers *inter alia* the effect mostly on **652** of  $R^2$  and/or  $R^3$  (Scheme 24), when not also  $C=Z$ , in stabilising or destabilising the carbon double bond so generated. Here we attempt an Overview, listing the factors common to these situations but with equal emphasis on the ways they differ.



Scheme 24

Table 47. Qualitative Tautomeric Preferences for **655** as Calculated *in vacuo*<sup>a</sup>

X	Y	Extended	Chelated	Section
O	O	$A > B = C^b$	$(B = C > A)^b$	A.6, Table 22
S	S	$B = C > A$	$(B = C > A)^c$	A.6, Table 22
NH	NH	$B = C > A$	$(B = C > A)^c$	A.6, Table 22
S	O	$C > A > B$	$B > C$	A.8, Table 29
NH	O	$C \gg A \gg B$	$C > B$	A.10, Table 31
NH	S	$C \gg A, B$	$C \gg B$	A.11, Table 44

<sup>a</sup> Bracketed values are LSER-based extrapolations to the gas phase. <sup>b</sup> Reverse order is observed in water. <sup>c</sup> This order observed in water also.

Certain topics are excluded here. Section A.5 considers the extra possibilities available to nitrogen on account of its extra valency relative to O and S, some of little and most of no further importance, the chief exceptions being hydrazones (section A.10.19) and oximes (section A.10.20). It also needs to be emphasised that, while simple hetero-double bonds  $C=Z$  are highly electronegative, this does not seem to be a sufficient criterion for generating tautomers. For example,  $SO_2R$  appears to be incapable of promoting tautomerism either on its own or when combined with another promoter X as  $XCH_2SO_2R$ , and while CN and  $NO_2$  are promoters, they are generally less successful than their electronegativity might suggest; there are few cases (see sections A.5.3, A.5.5, A.6.7, A.6.9, A.10.4, A.10.10, A.10.12 and A.10.13) in which enols have been detected, and fewer still where they are likely to be important in water. The more characteristic behaviour of  $XCH_2Y$  in water, where both X and Y are electronegative but neither group is of type  $C=Z$ , is ionisation, which as noted in the text, is also true for many combinations of  $C=O$  and especially  $C=S$  with themselves or one another. And as also stated (section A.4), two  $C=NR$  in this context will often give rise to bases, at physiological pH.

In the sub-sections that follow data refer exclusively to aqueous solution, known or extrapolated, unless clearly stated to the contrary, with the obvious exception of computations the results of which are expressed as  $\Delta H$  in  $\text{kJ mol}^{-1}$ .

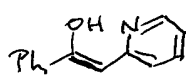
### A.12.1 Ketones, Thioketones and Imines

A very condensed, comparative survey of these three basic structures follows (Scheme 24).

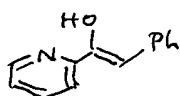
Acetone possesses  $K_E = 10^{-8.63}$  and this effectively sets a lower limit since *any* substituent  $R^2/R^3$  in **652** helps to stabilise  $C=C$  whereas  $R^1$ , if bland, has little effect, and otherwise will also generally raise  $K_E$ . Aldehydes typically possess  $\Delta \log K_E \geq 3$  relative to the nearest related ketone and this is a factor in some cases (Tables 5 and 6). Qualitatively, enol stabilisation by  $R^2/R^3$  follows very much the order found by Hine for allylic stabilisation (Table 1) but the effect is generally of lesser magnitude unless both substituents are bulky, when it may be greater and in extreme cases can lead to a dominant enol tautomer (Tables 5 and 6). Intramolecular hydrogen bonding can stabilise the enol tautomer, as in **72b** (section A.2.2) with  $\Delta \log K_E \geq 2.4$  relative to its 4-pyridinyl analogue whereas the effect in **74b** is negligible. Nevertheless, in all known cases the

keto-form remains dominant. The effect is much greater in rigid structures such as **656** where the enol **656b** is now favoured, for cyclohexane-1,2-dione **110** to give  $K_E \geq 10^2$ , hence  $\Delta \log K_E$  8 - 9 (section A.2.5). We estimate this value as comprising *ca.*  $10^{3.5}$  for the intrinsic electronegativity of  $R^1$  (*cf.*  $10^{3.3}$  for 4-pyridinyl) with *ca.*  $10^5$  for the combined effect of lone pair repulsion in **656a** and the hydrogen bond of **656b**. Presumably lone pair repulsion is dominant since nonrigid compounds of type **657**, which produce no detectable enol, prefer the *E*-conformation shown. A different type of electrostatic repulsion, not involving lone pairs, operates in extended  $\beta$ -diketones of type **655** and produces similar results (section A.6.2, and see below). Here the magnitude of the effect appears to depend on the dihedral angle  $\theta$  in **262** between the carbonyl groups so is greater in 5- than in 6-membered rings (section A.6.2) but the difference cannot yet be quantified. Chelated  $\beta$ -diketones are stabilised by their intramolecular hydrogen bonds, but while in nonpolar solvents the enol is dominant this is rarely the case for water through the levelling effect on hydrogen bonding that its high dipolarity exerts. This trend *reverses* that for extended  $\beta$ -diketones which are most enolised in the most polar solvents [section A.6, eqns. (ix) and (x)] and similar effects have been found for  $\beta$ -iminoketones (section A.10.2). It seems probable that this difference between *extended* structures **655** and the corresponding chelates would be found to be universal if the facts were known. For  $\beta$ -diketones, the archetypal compounds dimedone (**55**,  $R = H$ ) and acetylacetone (**264**,  $R = Me$ ) are separated by  $\Delta \log K_E$  *ca.* 2 in water, the former being predominantly enolised whereas the latter is not.

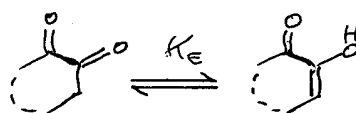
Much less is known concerning simple thioketones but various lines of evidence indicate  $\Delta \log K_E$  *ca.* 6 - 6.5 relative to the corresponding ketones (section A.3 *passim*). It seems probable however that the effect of substitution at  $R^1 - R^3$  in **653** should be qualitatively similar to **652** and should readily lead to a predominance of the thioenol. Simple thioketones and thioenols are both unstable and may be considered as marginal species but this does not apply to heterocycles of type (**658** and **659**,  $Z = S$ ). Here the **b**-form predominates for **659** but this is less certain for **658** (section A.3.7); the question is re-examined in sections C.10 and C.11. Tentatively, we suggest that a more or less constant factor of  $\Delta \log K_E$  *ca.* 3.5 for  $C=O \rightarrow C=S$  is consistent with observation. A smaller factor than for simple thioketones is reasonable here through the levelling effect of the  $\pi$ -donor heteroatom ( $X = O, S$  or  $NR$ ). For  $Z = O$  throughout, and for  $Z = S$  where known, enolisation is likeliest for  $X = S$  and least likely for  $X = O$  with  $X = NR$  closer to the latter.



72b

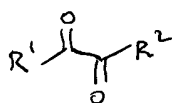


74b



656a

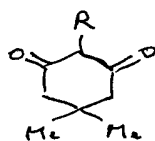
656b



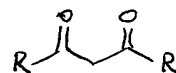
657



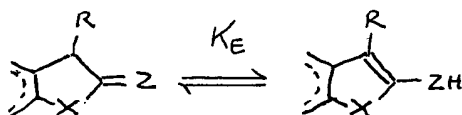
262



55a



264a



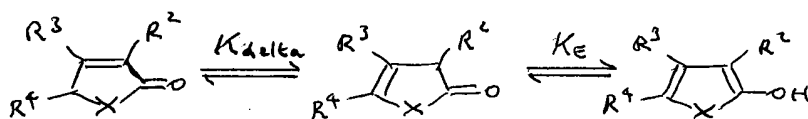
658a

658b



659a

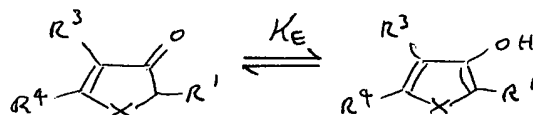
659b



129c

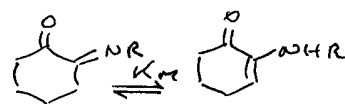
129a

129b



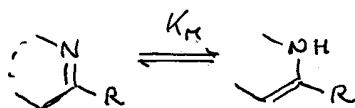
133a

133b



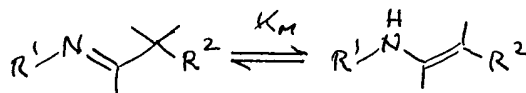
208a

208b



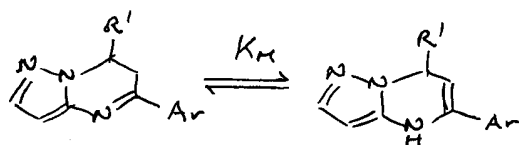
660a

660b



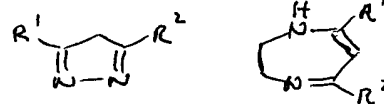
661a

661b



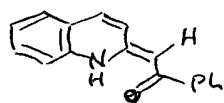
203a

203b

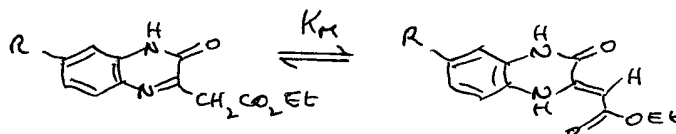


378a

385b



433c



539a

539c

Oxoheterocycles of type **129** or **658** are highly resistant to enolisation though no  $K_E$  value is known (but see section C.10). For the former most interest lies in the balance between **129a** and **129c**, which favours the latter according to the nature of X by a factor of  $10 - 10^3$  (Table 3). There is evidence (section A.1.1) that Hine's factors for allylic C=C bond stabilisation (Table 1) are close to quantitative here; thus alkyl and especially aryl substitution at R<sup>4</sup> can tip the balance towards **129a**, whereas substitution at R<sup>3</sup>, since pivotal, has little effect (*cf.* the slight effect of R in **660**, section A.1.5; except that when R here is a  $\pi$ -donor it will stabilise **660a**). Substitution at R in **658** favours **658b** but this becomes dominant only for R = acyl or other conjugating substituents. The corresponding 3-oxo derivatives **133** and **659** are much less resistant to enolisation, differing among themselves by a considerable margin (see Table 13, section A.2.7). Enolisation is most readily induced in both the 2-oxo and 3-oxo series by substitution at saturated carbon since aromatisation can then result, to give **129b** and **133b** respectively; in the 3-oxo series, it often requires no more than alkyl or aryl substitution to bring this about. The corresponding thiones are still more susceptible to enolisation, possibly by a factor of  $10^3 - 10^4$  (section A.3.7).

Imines differ from ketones and thioketones in two important respects. Firstly, endocyclic C=N is possible whereas endocyclic C=O or C=S is not. For the simplest structures, analogous to **652** or **653**, we estimate enamine content as  $\log K_M$  *ca.* -1.8 for **654** and close to -1.6 and -3.7 for (**660**, R = alkyl) where this is respectively part of a 6- or 5-membered ring (section A.4.1). This difference, of  $\Delta \log K_M$  *ca.* 2.1, is probably due to the differential stabilisation of endocyclic C=N as a function of ring size. Secondly, imines can be substituted on nitrogen as in **661**. While quantitative data are lacking, **661a** appears to be favoured by  $\pi$ -donors and **661b** by  $\pi$ -acceptors. Tentatively, we find  $\Delta \log K_M$  -0.8 for R<sup>1</sup> = Ph (section A.4.3), while **208b** for R = H, Alk or Ph becomes **208a** for R = OH or NPh (section A.4.5). By contrast, R<sup>1</sup> = COR leads to the preponderance of **661b**, and **203b** is favoured over **203a** (section A.4.3). This may typify the behaviour of ' $\pi$ -deficient' heterocycles; for 4-pyridinyl in a more complex context (section A.10.4),  $\Delta \log K_M$  is *ca.* 2 relative to phenyl. Similarly, R in **539** favours the enamine **539C** when electron-withdrawing ( $\rho = 0.98$ ; section A.10.14). This difference between  $\pi$ -donors and  $\pi$ -acceptors can be rationalised (section A.4.6) and further work might allow its quantification. Little is known concerning the effect of R<sup>2</sup> in **661** but, by analogy with **652** and **653**, it might in general be expected to stabilise **661b**, and if R<sup>2</sup> is a  $\pi$ -acceptor this will often be sufficient to overcome aromaticity as in **433C** (*vide* section A.10).

**Table 48.**  $\Delta H$ , kJ mol<sup>-1</sup> (RHF Methodology) for the Enolisation of **652**, **653**, **654** ( $R^1 = \text{Me}$ ,  $R = R^2 = R^3 = \text{H}$ ), and **655** ( $X = Y = \text{O}$ ,  $\text{S}$ , or  $\text{NH}$ ;  $R^1R^2 = [\text{CH}_2]_3$ ,  $R^3 = \text{H}$ )<sup>a</sup>

	<b>652</b>	<b>655</b> , $X = Y = \text{O}$	<b>653</b>	<b>655</b> , $X = Y = \text{S}$	<b>654</b>	<b>655</b> , $X = Y = \text{NH}$
$\Delta H_E$	64.4	18.6	26.7	- 21.0	27.2	- 10.6

<sup>a</sup> See Table 22, Section A.6.1.

**Table 49.**  $\Delta H$ , kJ mol<sup>-1</sup> (RHF Methodology) for the Tautomerisation of **655**,  $X \neq Y$ ,  $R^1R^2 = (\text{CH}_2)_3$ ,  $R^3 = \text{H}$ <sup>a</sup>

Equilibrium:		$K_E$	$K_M$	$K_T$	$K_T^b$
$X = \text{S}$	$Y = \text{O}$	7.1	- 10.1	- 17.2	1.0
$X = \text{NH}$	$Y = \text{O}$	29.1	- 21.6	- 50.7	- 35.5
$X = \text{NH}$	$Y = \text{S}$	- 3.4	- 38.2	- 34.8	- 45.7

<sup>a</sup> See Table 29, section A.8.1; Table 31, section A.10.1; Table 44, section A.11.1.

<sup>b</sup> For corresponding chelate (see Tables 29, 31 and 44).

**Table 50.** Mutual Interaction Terms ( $\Delta H$ , kJ mol<sup>-1</sup>, RHF Methodology) for **655**,  $\text{C}=\text{X}$  vs.  $\text{C}=\text{Y}$ ,  $R^1R^2 = (\text{CH}_2)_3$ ,  $R^3 = \text{H}$ <sup>a</sup>

	Effect on:	$\text{C}=\text{S}$	$\text{C}=\text{O}$	$\text{C}=\text{NH}$
Effect of:	$\text{C}=\text{S}$	- 47.7	- 57.3	- 64.9
	$\text{C}=\text{O}$	- 36.8	- 45.8	- 48.8
	$\text{C}=\text{NH}$	- 30.6	- 35.2	- 37.8

<sup>a</sup> Each value in this Table is the resultant of one value in Table 48 and one other value, in Table 48 or 49; *e.g.* the difference between  $\Delta H_E$  for **652** and for (**655**,  $X = Y = \text{O}$ ), both in Table 48, furnishes the entry of -45.8 that appears above, whereas the difference between  $\Delta H_E$  for **652** and  $\Delta H$  for ( $X = \text{S}$ ,  $Y = \text{O}$ ) in Table 49 gives rise to -57.3 above.

### A.12.2 The Energetics of C=Z/C=Z Interaction

This has been explored by high level *ab initio* calculation at various places which are listed, along with a qualitative summary of the results, in Table 47. Of the three techniques employed we select for present purposes the RHF methodology as the most internally consistent and possibly the most reliable, though analysis of any of the others would bring out the same salient points. The picture so revealed is unexpected and uncommonly interesting.

Table 48 reveals that ketones are expected to be very much more resistant to enolisation than thioketones or imines, which in that respect closely resemble one another. If the contribution of  $\Delta S$  is set arbitrarily to zero, these  $\Delta H$  values translate as 'log  $K_E$ ' -11.3, -4.7 and -4.8 for **652**, **653** and **654** respectively. These are notably more negative than the (aqueous) values detailed above, but differ from them by an almost constant factor: on the above naive assumption, imines and thioketones are both expected to enolise more readily than ketones by a factor of  $\Delta \log K_E$  *ca* 6.5. It might therefore have been anticipated that placing C=O in competition with C=S or C=NH should result overwhelmingly in enolisation of the latter, whereas for C=S in combination with C=NH the balance might be even. Neither expectation is fulfilled. In terms of  $\Delta H$ , the actual predictions for  $K_T$  appear in Table 49. Translated into 'log  $K_T$ ' as for 'log  $K_E$ ' above these become 3.0, 8.9 and 6.1 for  $\beta$ -thionoketones,  $\beta$ -iminoketones and  $\beta$ -iminothioketones respectively: greater in the second case, much greater in the third, and much less in the first. Furthermore, these predictions are qualitatively borne out by the data in sections A.8, A.10 and A.11 respectively.

The explanation for this apparent paradox is to be found in Table 50. It is possible to fillet these data in such a way as to reveal the effect of each C=Z on itself and on the others. It turns out that the order in which each C=Z *promotes* enolisation ("effect of") is consistent across the board and is *in the reverse order* to its *susceptibility* to this process ("effect on"). That is: promotion follows the order C=S > C=O > C=NH; susceptibility, the order C=NH > C=O > C=S. However, this simply replaces one puzzle by another. For C=O to be more electronegative than C=NH, as these results imply, fits with all that is known of their electronic properties. The still higher implied electronegativity of C=S comes as a surprise, and we do not think it has been suspected before. Thioketones are fugitive species and, understandably, little work has been carried out on them. There may be a clue in that thioamides and thioureas possess higher dipole moments than their oxygen equivalents, and in the well known ability of sulfur to stabilise a neighbouring carbanionic charge, though the origin of this phenomenon is disputed.<sup>386</sup> For the present, we have to leave this question open.

Information on the relative stability of the unconjugated tautomer **655A** may also be deduced from Tables 48 and 49. Only for  $\beta$ -diketones is this predicted as the dominant species, as is known to be true for dimedone (**55a**,  $R = H$ ) in nonpolar solvents. By contrast, extended  $\beta$ -diimines are expected to be predominantly enolised even in the gas phase, and most of the data are consistent with this (but see section A.9.5); pyrazoles and 1,4-diazepines for example exist wholly in extended conjugation as **378b** and **385b** respectively (section A.9.1), and while some of the first preference must be attributed to lone pair repulsion in **378a**, that of the second cannot be. There is very little known concerning  $\beta$ -dithiones but what there is points the same way (section A.7). Also, while aminoenones are greatly favoured over the iminoenol tautomer, these calculations suggest that the stability of the unconjugated **A**-tautomer may fall somewhere in between, which throws considerable light on the different conjugation patterns of pyridines to give **72b** *vs.* the corresponding quinolines to give **433C** (Scheme 19). Here a stability order  $A > C > B$  for the first is supplanted by  $C > A > B$  for the second, the result of sharply diminished loss of aromaticity in bicyclic relative to monocyclic heterocycles when the **C**-tautomer is formed (section A.10.2). No corresponding information exists for  $\beta$ -iminothiones but the calculations of Table 49 suggest that the chelated **C**-tautomer might be dominant in water even for monocyclic heterocycles. Only the position for  $\beta$ -thionoketones is uncertain; here the **A**-tautomer is rarely if ever found (section A.8.1) but nothing is known about aqueous solution where its occurrence is most likely.

Table 49 also contains our calculated  $\Delta H_T$  values for the three relevant corresponding chelates (necessarily,  $\Delta H_T = 0$  elsewhere). The predicted *reversal* of tautomeric preference between extended and chelated  $\beta$ -thionoketones is a known phenomenon and is discussed in section A.8.1. For aminoenones the facts are not established, but the 'extended' structure is expected to be better conjugated and  $OH\cdots N$  forms much stronger hydrogen bonds than  $NH\cdots O$ , both of them factors that should reduce  $K_T$  in chelates relative to extended forms. In fact, all these differences may be plausibly explained largely in terms of competitive hydrogen bonding. The order of proton donor ability is  $OH \gg NH > SH$  and this on its own will qualitatively account for the above trends. For the difference between  $OH\cdots N$  and  $NH\cdots O$  hydrogen bonding we provisionally estimate  $\Delta \log K$  *ca.* 1.9 (Appendix 4); the calculated difference in ' $\log K_T$ ' (Table 49) is *ca.* 2.7. We have no corresponding estimate for the difference in bond strength between  $SH\cdots N$  and  $NH\cdots S$  but the latter should be much the stronger, so accounting for the predicted *gain* in ' $\log K_T$ ' for aminoenethiones of *ca.* 1.9 on chelation. It would be valuable to have harder evidence, but in the meantime the above predictions appear plausible.

### A.12.3 Modifying, Conflicting and Perturbing Factors

The simple picture presented above may be modified, especially in cyclic structures, by a number of factors which can alter the balance between one tautomer and another. While some can be quantified most are qualitative and here it may be helpful to introduce a number of *rules* that can then be applied, though not slavishly, to resolve the balance of probabilities where the stated criteria appear to conflict. So far as is possible we shall progress from the clearest and least equivocal to the most complex and unstraightforward. Rules that apply only in Part B will, for the moment, be ignored.

### A.12.4 Competitive Conjugation

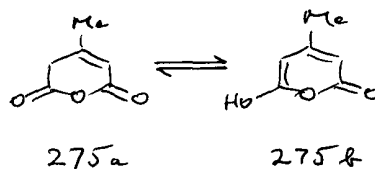
For  $X \neq Y$  in **655** there are clear preferences as to the **B**- and **C**-tautomers which are listed in Table 47 and may be rationalised as RULE 1:

*RULE 1: Where alternative conjugated systems can be created from an unconjugated unit (**655B** or **C** from **655A**), the preferred tautomer will be that which combines the stronger  $\pi$ -donor with the stronger  $\pi$ -acceptor.*

This is most obviously true of the preference for aminoenones and aminoenethiones over the corresponding iminols. It gives rise to a CODICIL:

*Any factor which increases the electron donor strength of the  $\pi$ -donor atom or electron acceptor ability of the  $\pi$ -acceptor group will further increase the bias towards this preferred tautomer, and vice versa. Conversely, electronegative substituents in aromatic rings and other conjugated systems will tend to diminish the preference for oxo- (or thiono-) tautomers by competing with them for any  $\pi$ -donor present.*

Quantitative information on the effect of  $\pi$ -donors is scarce. In **515** (section A.10.11),  $K_M$  rises when R is an electron donor with  $\rho \sim -0.6$ . Replacement of R = Ph in **586** by R = Me in **588** (section A.10.18) raises  $K_T$  about 20-fold. In **470** (section A.10.6), while the effect of 3-substituents is negligible, since they are sited midway between O and N and equally affect both, electronegative 2-substituents greatly reduce  $K_T$ , from  $10^{3.9}$  in the parent compound to a (calculated) predominance of **470B** when R = CN, SO<sub>2</sub>Me, or NO<sub>2</sub> (Table 37). More information, most of it qualitative however, attaches to the  $\pi$ -acceptor. In the type of heteroaromatic context here summarised as **662** and when possible chelated, the effect of X on  $K_M$  can be ordered semi-



quantitatively as  $\text{COPh} > \text{COMe}$ ,  $\text{NO}_2 > \text{CN} > \text{CO}_2\text{Et}$  (section A.10.14) spanning a factor of at least  $10^2$ . (Because  $K_M$  is strongly opposed by aromatisation – see later – which of **A** or **C** is or is likely to be dominant in water is a complex function of heterocycle and substituent; some limited guidance appears in Table 42. Any of these groups should ensure an overwhelming preponderance of the **C**-tautomer in a non-aromatic context). It is also clear on qualitative evidence that acceptors of type COR where R is an electronegative group such as CN or  $\text{CO}_2\text{R}'$  are specially effective in promoting the **C**-tautomer, which in such cases is probably dominant in aqueous solution even for most monocyclic heteroaromatics.

From the  $\text{p}K_a$  values of **487A** and (**487C**, R = Me) we have shown that  $K_M$  is entirely, and very steeply, a function of the *resonance acceptor* properties of X, with no field ( $\sigma_I$ ) component (section A.10.9). The same is probably true for 4-substitution. However most of the compounds listed in the previous paragraph are likely to be chelated, and it cannot be assumed that an identical equation will apply. There are some pointers, however. While (**487C**, R = Me, X = COPh) cannot be chelated whereas (**487C**, R = H, X = COPh) probably is,  $K_M$  for the latter is greater by only  $\Delta \log K_M$  1.0, which suggests the strength of the intramolecular hydrogen bond to be a relatively minor perturbation. This issue is not clear cut and receives further discussion in Appendix 4. However, it should still be possible to predict, if only qualitatively, what other  $\pi$ -acceptors should be effective at enhancing  $K_M$ ;  $\text{COCF}_3$  is one such obvious suggestion.

Other things being equal one would expect two  $\pi$ -acceptors to be better than one in generating the **C**-tautomer, and in general this is true (sections A.10.13, A.10.15, and A.10.17), the exceptions occurring when at least one of X and Y in **663** is bulky, so that planarity in **663C**, hence optimum conjugation, is difficult to attain. To take a few nonaromatic examples where the information is most extensive: **516** where steric hindrance must be severe does not enolise at all; for **515** (see above) enolisation is only partial; but for **523** and **524** which should be planar it is complete. Steric hindrance in this context is quite a complex phenomenon and is chiefly considered in section A.1.4. Where it is absent, the **C**-tautomer is so dominant for aliphatic aminoenones that it is quite difficult to demonstrate the effect of a second  $\pi$ -acceptor in boosting  $K_M$ . Recourse must be had to aromatic systems, where for example (**664**, R = H) possesses  $\log K_M$  -1.05 in water (section A.10.2) but, for (**664**, R = CN), only the **C**-tautomer is detectable. Indeed nitrile seems able to boost  $K_M$  very substantially in combination with

other acceptors, where we estimate its effect as  $\Delta \log K_M \text{ ca. } 10^2$  (section A.10.15). This is notably more than would be expected from its normal ranking (Table 42) and probably results from its minimal steric requirement, hence lack of effect on the planarity of the conjugated unit; note that **571** as written predominates in aqueous solution. Because of doubt concerning their effects on planarity it is difficult to guess how the various types of COR will rank as *second*  $\pi$ -acceptors, but it is possible that CPh, which ranks highly on its own, may be less effective in combination than a smaller group such as COCF<sub>3</sub> or even COMe. On the other hand, extrapolation from solvent studies indicates that -CH<sub>2</sub>CPh can induce much more enolisation than -CH(CO<sub>2</sub>Et)<sub>2</sub>, so the question remains open. Many possible acceptor combinations have yet to be studied.

These results may be summarised in RULE 2, which incorporates an important caveat:

*RULE 2: Whereas in the absence of steric hindrance a second  $\pi$ -acceptor will increase the extent of C-tautomer formation, a second  $\pi$ -donor may not, since conjugation with C=N when present is potentially competitive and may be preferred.*

Outstandingly, while cyclic compounds of type **665** give exclusively the C-tautomer, those of type **666** mostly do not; mixtures of **666A** and **666C** result (section A.10.12). We believe this difference to result from a crucial shift in lone pair alignment. In **665C**, the X lone pair is lined up to favour conjugation with C=C; in **666** it will similarly favour **666A**. This bar to the formation of the C-tautomer is not absolute, but it is likely to reduce  $K_M$  (hence  $K_T$ ; Scheme 24) quite sharply enough to account for the difference. The same is found among compounds that adopt the extended structure **655** (start of A.12; see section A.10.5). It is less clear what should happen in open-chain systems and the available information is not definitive. Since both favoured conformations **666A** and **665C** are in principle available, the result in many cases may be a compromise, as perhaps for **515** (drawn to show this possibility), **516** where interaction with C=N may be encouraged by steric hindrance, and **523** and **524**, considered in a different context above, where *lack* of steric hindrance by CN may have the opposite result. Nevertheless there is marginal evidence that a better electron donor X will increase  $K_M$ , even for **666** (section A.10.12). That **511** is locked as the C-form (section A.10.12) results from stabilisation of the enamine tautomer by *N*-acylation (section A.4.4).

As seen above, for the generalised structure (**655**,  $X = S$ ,  $Y = O$ ) of Scheme 24 the tautomeric balance appears to favour **655C** by an unknown but probably not enormous margin, whereas this is overturned in the chelate (section A.8.3) but not by much. For  $X = Y$  the situation is necessarily different. Most of the evidence comes from chelated  $\beta$ -diketones **57**, where the effect of changing  $R^1$  and/or  $R^2$  is in general quite small, probably due to the existence of largely self-cancelling factors to do with hydrogen bonding (section A.6.7). (It should be noted that enolisation of **57** is diminished by steric inhibition just as in **663**, notably if more than one of  $R^1 - R^3$  is bulky; see section A.1.4). However this ceases to be the case if  $R^1$  or  $R^2$  is a  $\pi$ -donor, which gives rise to RULE 3:

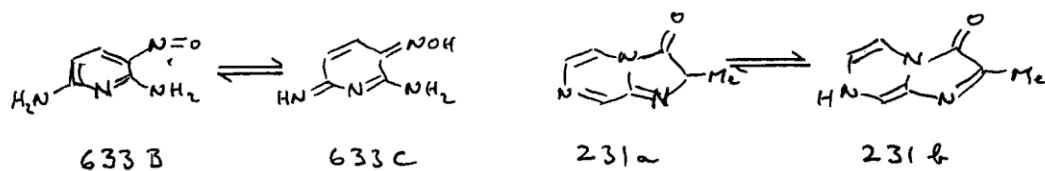
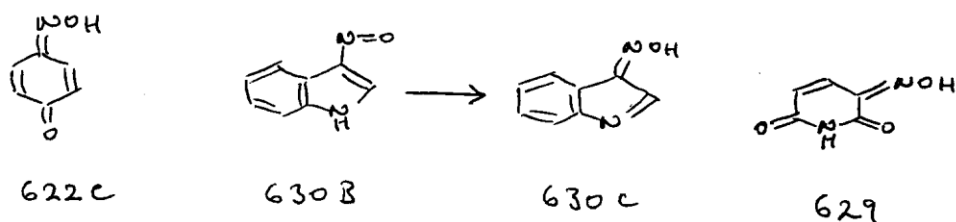
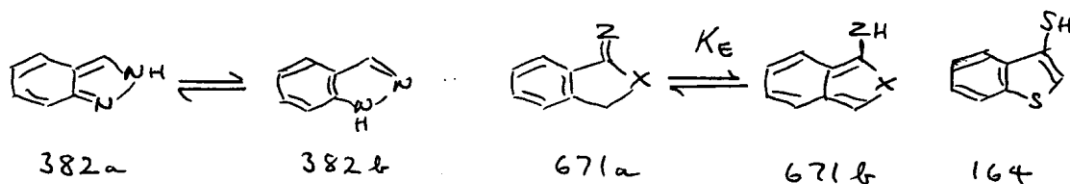
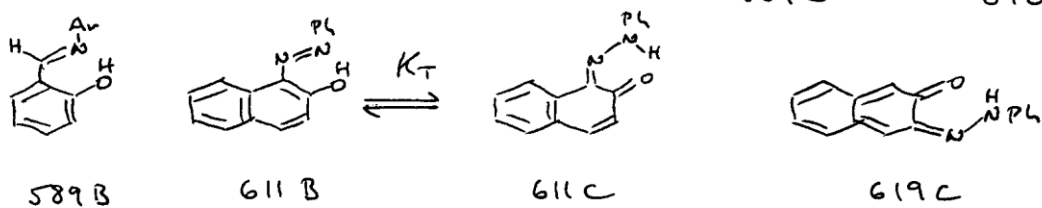
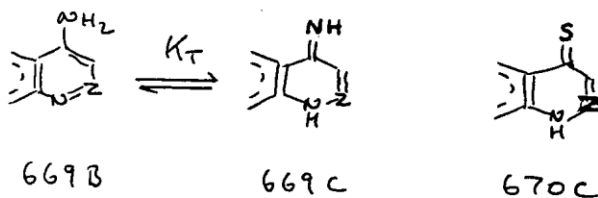
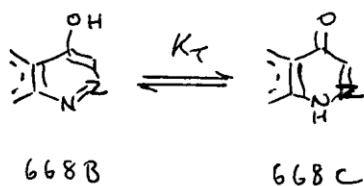
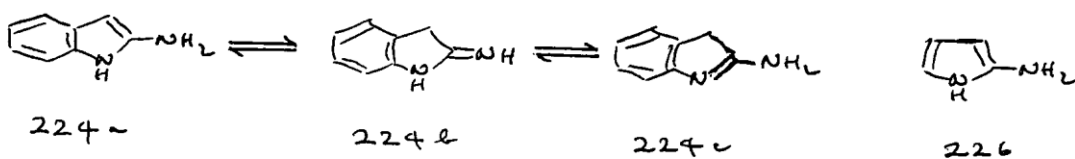
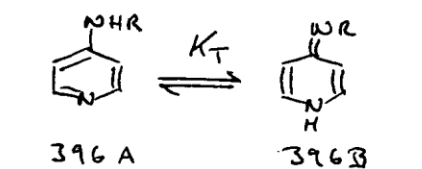
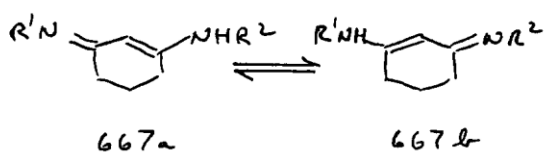
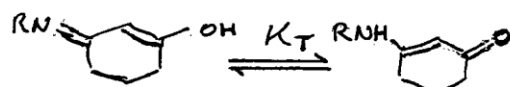
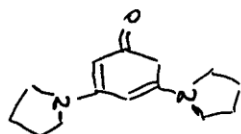
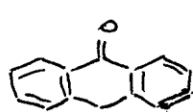
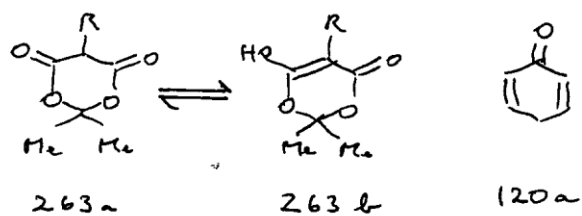
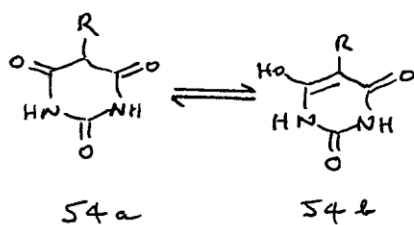
*RULE 3: If alternative modes of tautomerisation exist, enolisation will always take place in a direction that avoids disrupting prior conjugation.*

In the present case, the presence of an ester or an amide represents *prior conjugation* so this carbonyl group will not enolise. Thus  $\beta$ -ketoesters and  $\beta$ -ketoamides (**342**,  $Z = OR$  or  $NR_2$ ) enolise exclusively to **342b** (section A.6.7; note however that, in water, this does not imply any large proportion of the enol, which as for the related  $\beta$ -diketones, is typically about 10%). Other examples include **288b** ( $Z = O$ ,  $S$  and possibly  $NR$ ; section A.6.4) and it would appear possible to extrapolate this principle even to aromatic structures such as **273** and **107** to which one might have thought it need not apply. In fact, it has been shown on the basis of equilibration studies that **270** is more stable than **269** by a factor of  $\Delta G > 3 \text{ kcal mol}^{-1}$  (section A.6.3); a similar margin between **273** and its isomer would easily account for what is observed.

Note of course that conjugation of a  $\pi$ -donor with  $C=N$ , discussed above, also counts as ‘prior conjugation;’ this is a weaker effect than that operating in an ester or an amide but is nevertheless plausibly responsible for  $\log K_T$  ca. 1.5 in the case of **380** (section A.9.2, which also contains other, qualitative, examples).

A corollary to RULE 3 states that

*Enolisation may be prevented if the strength of prior conjugation is great enough, whereas in other cases some compromise can result, in particular when the enol form is aromatic.*



Examples of both kinds follow. Open-chain  $\beta$ -diesters and -diamides do not enolise to any appreciable extent (see discussion in A.6.2), and neither does **290** (section A.6.4), but glutaconimide **281** exists in water mostly as a mixture of **281a** and **281b**, whereas in **275**, **275b** predominates (both section A.6.3). Here imide and especially anhydride resonance is clearly insufficient to compete effectively with aromatisation; the second carbonyl group may even detract from the resonance energy associated with the first one. This postulate will help to explain why barbituric acid (**54a**,  $R = H$ ), a cyclic diacylurea, contains around 1% of its enol **54b**, the other part of the explanation probably being that **54b** is a hydroxyuracil and so possesses at least a marginal aromatic character (section A.6.2). No such easy explanation can be found for the low but not negligible proportion of enol **263b** in Meldrum's Acid **263**; here our treatment highlights the highly disfavoured conformation of **263a** (also in section A.6.2).

### A.12.5 Aromatisation

The effect of aromatisation is akin to prior conjugation but is often greater and can be complex. It may be summarised as RULE 4:

*RULE 4: In aromatic structures, aromaticity competes strongly and often decisively with other forms of conjugation.*

6-Membered cyclic dienones such as **120a** aromatised to phenols so readily that dominant oxo-tautomers are exceedingly rare; the exceptions include **122a**,  $\log K_E -2.1$ , and **126a**,  $\log K_E \text{ ca } -1$  (section A.2.6). For phenol **120b** the alternative is non-aromatic; insertion of NH in place of  $CH_2$ , a conjugation-stopper, changes the situation to the extent that  $K_E \sim 10^{13}$  in **120a** becomes  $10^{-3.9}$  in 4-pyridone. Another valid comparison is that of 4-pyridone with the conjugated but non-aromatic aminoenone **435** for which  $K_T = 10^{8.7}$  (section A.10.4). Nothing is known for the equivalent sulfur compounds but, at least qualitatively, similar behaviour would be expected. However, since  $K = 1$  necessarily for a symmetrical diimine such as (**667**,  $R^1 = R^2$ ), it is unsurprising that  $\gamma$ -aminoheterocycles should almost always exist as such; sections A.9.3 (Scheme 15) and A.9.4 (Scheme 16) collate most of the known facts for 5- and 6-membered heteroaromatics respectively. An interesting minor exception concerns **396**, where highly electronegative substituents can induce a switch to the 4-pyridonimine structure **396B**. This goes clean contrary to expectation for simple imines in which, as seen above,

resonance donors favour the imine but resonance acceptors the enamine (section A.4.6). Analysis of this case (section A.9.4) shows that while resonance acceptors continue to favour the enamine, the imine is now favoured by *field effect* acceptors, just as in amidines (section B.4.2). The second effect is larger, so dominates. The other exception is 2-aminoindole **224**, where the amidine **224c** appears to be the major tautomer (section A.4.8) although **226** exists very predominantly as shown. This difference exemplifies RULE 5:

*RULE 5: However, the influence of Rule 4 is somewhat attenuated on benzofusion, since all aromaticity is not then lost.*

Implicit examples already considered include **122** and the different tautomer stability orders of the pyridine **72** and the quinoline **433** (section A.10.2), **A** > **C** > **B** and **C** > **A** > **B** respectively. Quantitatively, the effect of benzofusion there is  $\Delta \log K_M$  *ca.* 2.1 (section A.10.2). The **C**-forms of these compounds may be regarded as *o*-quinonoid, and for *p*-quinonoid molecules  $\Delta \log K_M$  may be less: *ca.* 1 for the 4-oxoheterocycles **668**, where Z = CH or N (section A.10.7) and (probably) about the same for their imines **669** (section A.9.4). For benzofusion of (**589**, Ar = Ph),  $\Delta \log K_T$  is *ca.* 1.3. Appendix 5 contains a full discussion. There is some evidence (sections A.2.7 and A.10.16) that benzofusion has less effect on the attenuation of aromaticity, and hence presumably on aromaticity itself, in 5- than in 6-membered rings.

These 4-oxo and 4-aminoheterocycles exist overwhelmingly as **668C** and **669B** respectively, the only caveat being the effect of highly electronegative substituents in 2-substituted 4-pyridones (and probably 4-quinolones) as noted above (details in section A.10.6), and very probably their thione equivalents as well. For 4-thiopyridones and related compounds **670**,  $\log K_T$  is probably a little higher than for **668** (average difference *ca.* 0.6) and the effect of benzofusion appears much the same (section A.11.4). However we draw attention (section A.11.3) to serious and worrying problems in the necessary estimation of correction factors (sections A.11.2 and A.11.3) which point to the need for a radical re-investigation (see section B.3 and Appendix 1).

*RULE 6: Quinonoid tautomers are strongly disfavoured relative to a benzenoid structure if one is available.*

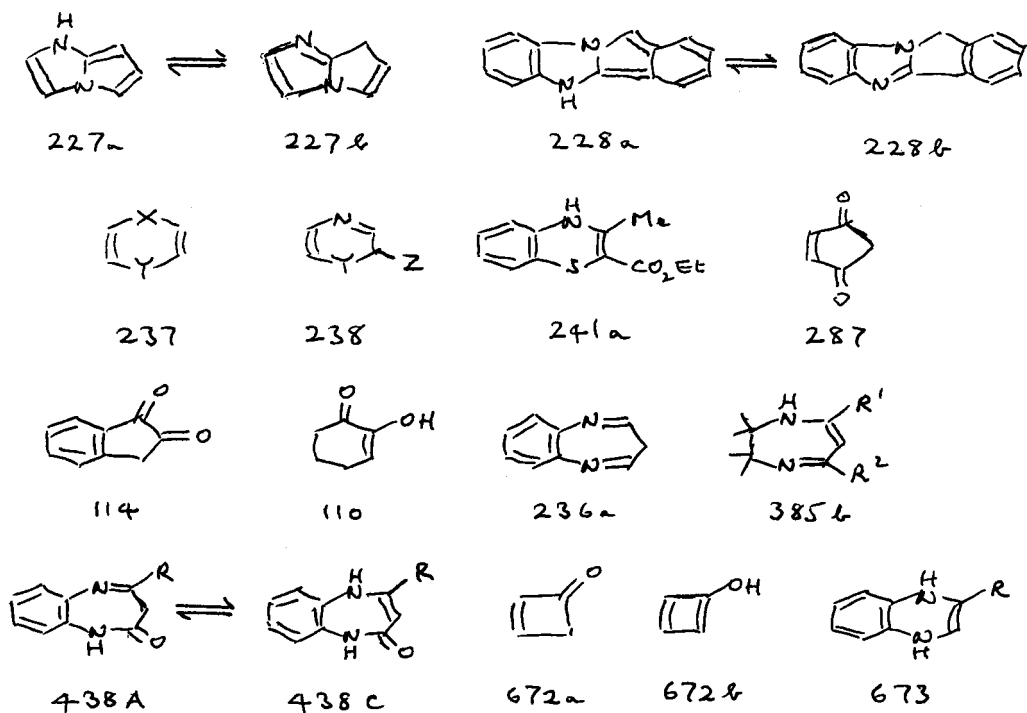
The conversion of a hydroxypyridine to a pyridone, for example, exchanges a benzenoid structure for one that may be regarded as quinonoid, and to that extent, Rule 6 is implicit already. However, we use the term here to cover structures in which *both* rings of a fused bicyclic compound are involved. A simple example is indazole **382**, for which  $K \sim 50$  in favour of **382b**. Other 6,5-fusions to which the same applies include, quite generally, structures of type **671**, where in all known examples **671b** is entirely suppressed. This is true not only for  $Z = O$  (section A.2.7) but for  $Z = S$  (section A.3.7) despite the strong tendency of  $C=S$  to enolise, as *e.g.* in **164**. Similarly, whereas  $K_T \sim 3$  for **611**, formation of **619C** is suppressed (section A.10.19). However, the driving force behind the formation of oximes from nitroso-compounds is so great (section A.5.2) that ‘4-nitrosophenol’ exists mostly as **622C** and **630B** goes to **630C** (section A.10.20). Nevertheless, while **629** exists as shown, **633** remains as **633B** (section A.10.20); here, the generation of a 2-iminopyridine (section B.4.4) would disfavour **633C** still further.

Competition between quinonoid alternatives is a more difficult area to rationalise; for example, it is not clear why **231b** should be preferred to **231a** (section A.4.8). Other cases listed in that section involve the superimposed effect of imine-enamine tautomerism, as for **227** and **228**, in both of which the **b**-tautomer is preferred. It is difficult to give general guidance for such compounds and recourse may be necessary to searching for plausible analogues.

#### A.12.6 ‘Anti-Aromaticity’

Antiaromatic structures are highly disfavoured and a simple example is **237** (section A.4.9), an  $8\pi$  system if  $X$  and  $Y$  are both  $\pi$ -donors. If  $X = NH$  this goes to **238**. However, if  $Z$  in **238** is a  $\pi$ -acceptor this can revert to a conjugated system such as **241a** which is still technically antiaromatic, even though otherwise highly favoured, so the prohibition is not absolute (all in section A.4.9). As in several cases below, benzofusion possibly attenuates the effect, much as it does for aromaticity itself.

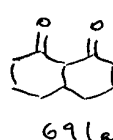
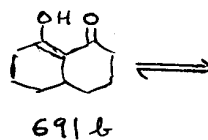
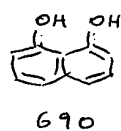
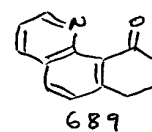
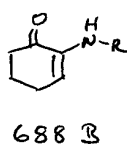
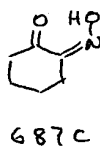
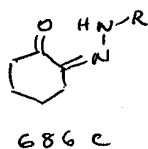
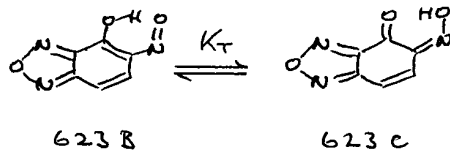
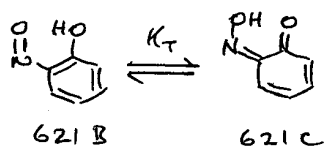
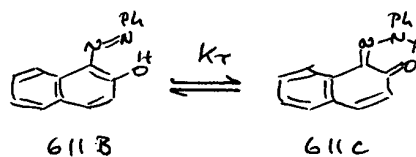
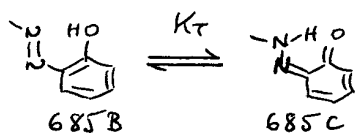
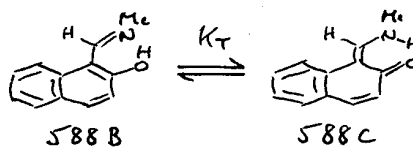
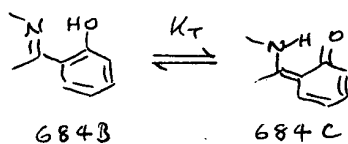
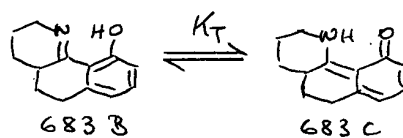
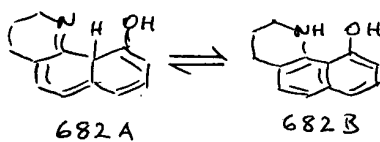
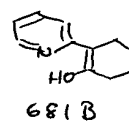
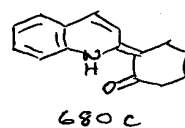
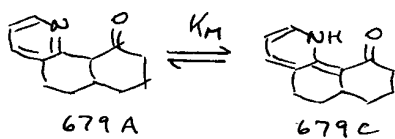
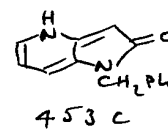
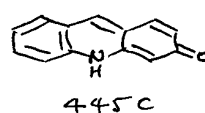
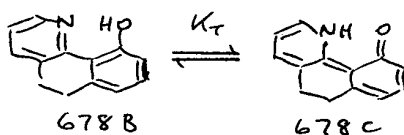
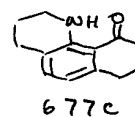
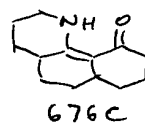
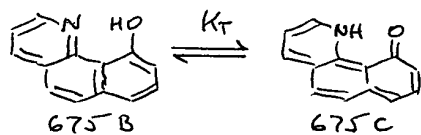
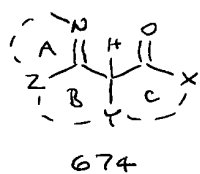
For reasons that will become evident, most cases of antiaromaticity involve 5- or 7-membered rings. For example, **287** as written or when benzofused (section A.6.4) does not enolise. Neither does **114** despite the contrary behaviour of **110** (section A.2.5). Another example is the benzofused diazepine **236** which exists as **236a** (section A.4.9) although none of this tautomer is detectable in **385b** (section A.9.2). Similarly, **438** gives a mixture containing (mostly) **438A** (section A.10.4), despite the normally overwhelming preponderance of the aminoenone tautomer in compounds of this type.



A feature common to many antiaromatic structures, and exemplified here by **287**, **114** and **438**, is the presence in the ring of a carbonyl or other group which does not contribute to the  $\pi$ -electron count and can distract attention from the nature of the molecule that would remain if it were deleted. For example, **287** then becomes **672a**, whose enol **672b** is plainly antiaromatic. Similarly, **438C** would become the antiaromatic **673**. This hazard is not common, but one needs to be on one's guard against it. Very tentative proposals for quantifying 'anti-aromaticity' appear in Appendix 5.

#### A.12.7 Aromatisation Revisited

This section is frankly speculative. Here we employ insights derived from the  $\beta$ -iminoketones of section A.10, the most complex and possibly the most extensive category of 'C-type' tautomer to have been investigated, to explore the likely effect of structural variations only some of which have so far been investigated, through variants on the generalised tricyclic structure **674** (Scheme 25). Here any or all of X, Y and Z may be CH or a hetero-atom, C=O may be replaced by C=S or C=NR, and any or all of the rings A, B and C may be aromatic. By freezing the stereochemistry in this way we eliminate most forms of structural ambiguity, especially configurational and conformational variation, and throw the emphasis on electronic factors, especially those involved in aromaticity. Inevitably chelate forms dominate but, since these tend to predominate, the emphasis is not unreasonable. As well as providing a framework into which many existing examples can fit, we hope to stimulate the synthetic chemist to explore new possibilities.



Scheme 25

We start with structures in which  $X = Y = Z = \text{CH}$  (or  $\text{CR}$ ). If all rings are aromatic we have **675**, for which tautomer **A** is inconceivable and the choice lies between **675B** and **675C**. This molecule has not been studied, but **675C** is so compromised by its quinonoid structure (Rule 6) that **675B** is certain to be preferred. Another factor is the intramolecular hydrogen bond. By contrast, **676** should give the **C**-tautomer, and this should be even more dominant if only ring B is aromatic; **677** is merely 2-aminoacetophenone in cyclic form. As emphasised at the start of section A.10, this case is trivial.

If rings A and C are aromatic but B is not we have **678**, where as for **675**, the **C**-tautomer is unlikely. The nearest exemplars in the text are **445C** and **453C**, the first of doubtful provenance and the second of limited relevance (section A.10.4). If as in **679** ring C is not aromatic, the **B**- or **C**-tautomer may be enforced by proximity. The first is more likely for monocyclic heterocycles as in **681B**, the second when benzofused as in **680C**, for which  $K_T = 4$  in  $\text{CHCl}_3$ ,<sup>333</sup> since aromaticity is then less important (Rule 5). Both however may be minor species in water (section A.10.2).

If rings B and C are aromatic **674** becomes **682**, of which **682B** is the only viable tautomer. This case like **677** is trivial. However, if only ring C is aromatic we have **683**, which is exemplified by Schiff bases such as **684**. Here as for other potential phenols (**675**, **678**, **682**) the **A**-tautomer will be unimportant and the choice lies between **683B** and **683C**. We have used a LSER equation (Appendix 2) to estimate  $\log K_T$  *ca.* 1.9 for the benzofused analogue **588**; our estimate for the effect of benzofusion (section A.10.18) would reduce  $\log K_T$  to *ca.* 0.6 for **684** with an alkyl group on nitrogen. Hence **683C** is marginally supported. It has been noted above (codicil to Rule 1) that replacement of NMe by NPh would also lower  $\log K_T$ , probably by  $\Delta \log K_T$  *ca.* 1.3.

Once ring A is severed we may replace the imine **684B** by the azo-compound **685B**, which is capable of the same type of tautomerism, here to give a hydrazone, and gives surprisingly similar  $K_T$  values. (We discuss possible reasons for this similarity, involving cancellation of factors, in section A.10.19). No quantitative data are available for compounds of type **685**, but  $K_T \sim 1$  is found for **611**, fractionally less than  $K_T \sim 2.5$  for **586** (*i.e.* **588** with NMe replaced by NPh). On additivity assumptions, these corrections taken together lead to a possible value of  $\log K_T$  *ca.* 0.2 for **685** (or *ca.* -1.1 if NPh replaces NMe). An unexpected feature of these azo-compounds is that electronegative, not electropositive, substituents in Ph increase  $K_T$ ; we attempt a rationalisation in section A.10.19.

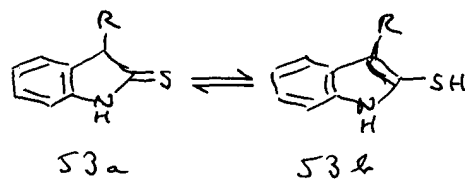
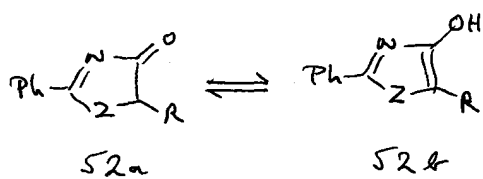
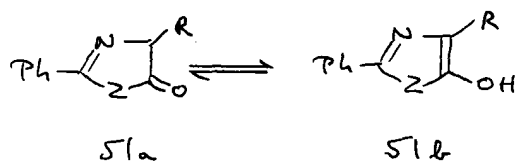
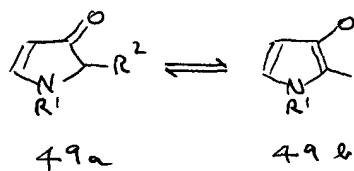
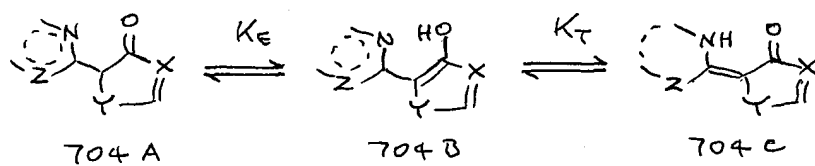
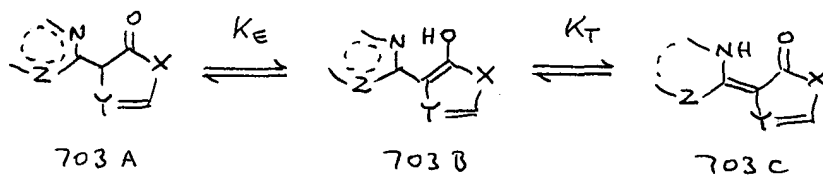
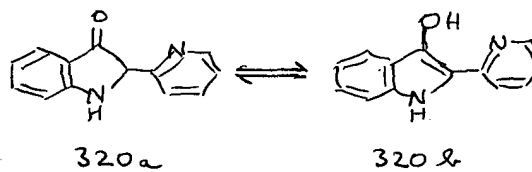
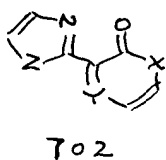
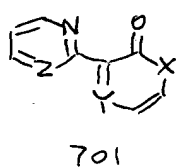
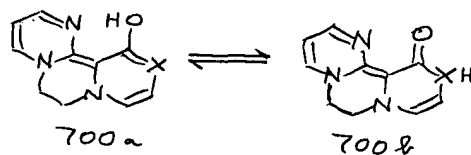
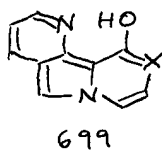
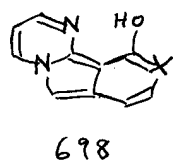
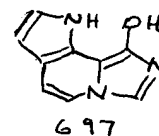
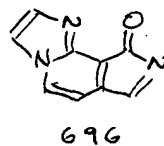
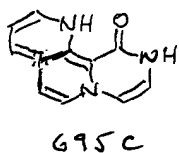
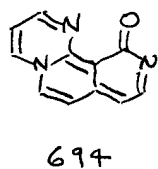
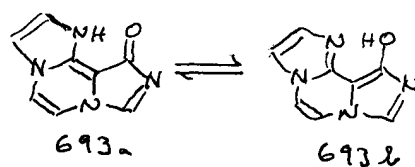
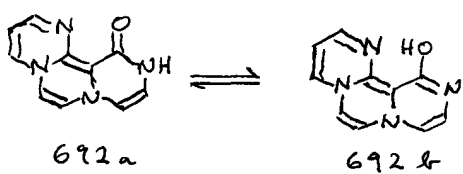
If  $\text{N}=\text{O}$  not  $\text{N}=\text{NR}$  replaces  $\text{C}=\text{NR}$  in **684**, we have **621**. Here **621B** is said to dominate in water (section A.10.20), but the fused oxadiazole **623** with less aromaticity to lose gives **623C** exclusively. Oximes are much poorer proton donors than phenols<sup>72</sup> which should favour **621B**, but their formation from nitroso-compounds is very highly exergonic (section A.5.2) and this factor appears to be crucial. Since  $-\text{N}=\text{O}$  is unique whereas the behaviour of  $-\text{N}=\text{NR}$  and  $-\text{CH}=\text{NR}$  depends on R there is no unambiguous way of comparing their tautomeric behaviour, but at the closest point of contact available we estimate (sections A.10.18-20) that  $K_{\text{T}}$  is probably about 10-fold greater for  $-\text{N}=\text{O}$  in this context than for  $-\text{N}=\text{NPh}$  with  $-\text{CH}=\text{NPh}$  in an intermediate position,  $\Delta \log K_{\text{T}}$  *ca.* 0.4 relative to  $-\text{N}=\text{NPh}$ . As might be expected (section A.4.6), monohydrazones such as **686** and monoximes such as **687** of aliphatic  $\alpha$ -diketones exist exclusively as shown; except for simple amines such as (**688**, R = Alk), the enamine tautomer is not important.<sup>168f</sup>

On their own an aromatic A-ring, an aromatic B-ring and an aromatic C-ring will generally result in dominance of the **A**, **C** and **B** tautomers respectively, but certain combinations of these also tend to have consequences. If in **674** rings A and B are aromatic but C is not, we have the **A**-form **689** which might undergo ‘forced’ enolisation because of lone pair repulsion to the **B**-tautomer, but not otherwise. If rings A and C are aromatic as in **678** the **C**-tautomer is again likely to be suppressed, while only the **B**-tautomer is possible if B and C are both aromatic, as in **682**. Most of these variants will tend to reduce the importance of the **C**-tautomer. However this will gain in importance and may regain its dominance on benzofusion: of ring A in **679**, ring C in **683**, or of either or both in **678**. In the absence of information on  $\text{C}=\text{S}$  in place of  $\text{C}=\text{O}$  we may assume that similar rules will apply, but with notably more bias towards the **B**-tautomer. Note also that thiophenols are likely to ionise, with the sulfur equivalents *inter alia* of **621** and **685** existing as their anions at physiological pH.

If  $\text{C}=\text{N}$  in **674** is replaced by  $\text{C}=\text{O}$  or  $\text{C}=\text{S}$  ring A is lost and the number of viable possibilities shrinks dramatically, with obligatory tautomers such as **690** in six cases out of eight and with **676** and **679** collapsing to give **691**. Here only ring size is a significant variable (section A.1.2) and even if  $\text{C}=\text{S}$  replaces one  $\text{C}=\text{O}$  this merely doubles the number of possible structures (section A.8.3) without affecting the outcome in any other way. The contrary replacement of  $\text{C}=\text{O}$  by  $\text{C}=\text{N}$  affects the initial tautomeric balance so profoundly as to make this topic an unprofitable one to pursue.

If any or all of X, Y and Z are hetero-atoms, the situation becomes more complex. When all are hetero-atoms, tricyclic aromatic structures are possible only if all are nitrogen, as in the hypothetical compound **692** which is the nearest possible equivalent to **675**. Here both tautomers are anti-aromatic and the severe lone pair clash in **692a** should lead to **692b** if, indeed, either can exist. If rings A and C are 5-membered, **693** results; here **693b** is an obligatory tautomer since rings A and C are then fully aromatic. Anti-aromaticity in ring B is a feature of these nitrogen-rich structures but can be circumvented in one of several ways. If Y = N or Z = N is replaced by CH, **692** becomes, respectively, the nontautomeric **694** and (probably) **695C**, while **693** becomes the nontautomeric **696** (with an anti-aromatic ring C) or the obligatory structure **697**. If ring B is 5-membered, **694** and **695** give **698** and **699**, respectively, as the only tautomers likely to be viable, even for X = N. If ring B is non-aromatic as in **700** the risk of anti-aromaticity is removed, but otherwise the situation is as for **698** and **699**, with **700b** likely to be disfavoured in similar fashion by the very strong lone pair repulsion that would result.

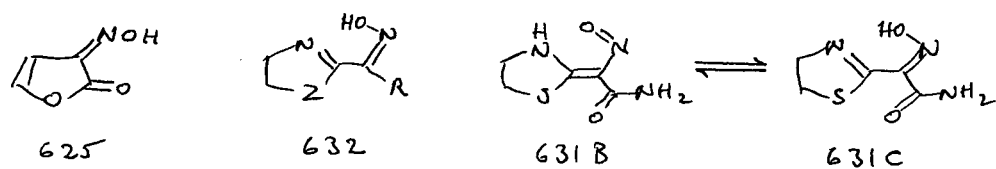
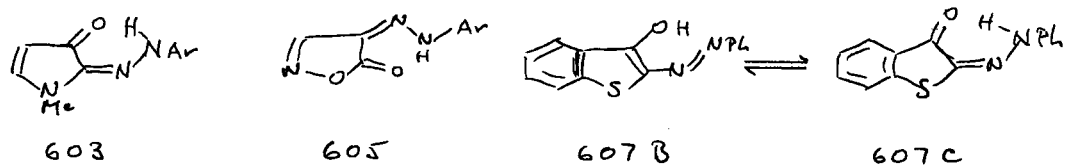
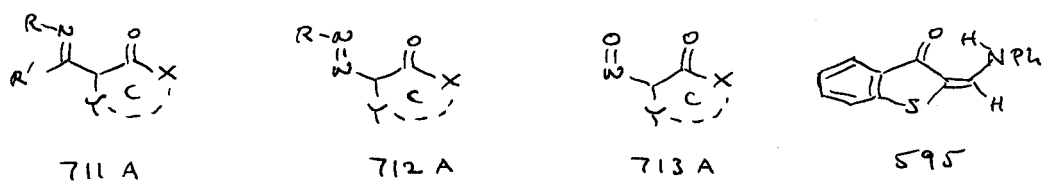
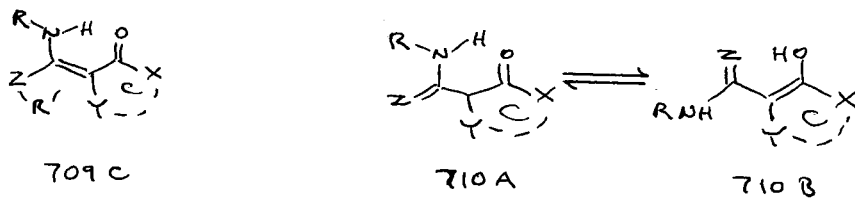
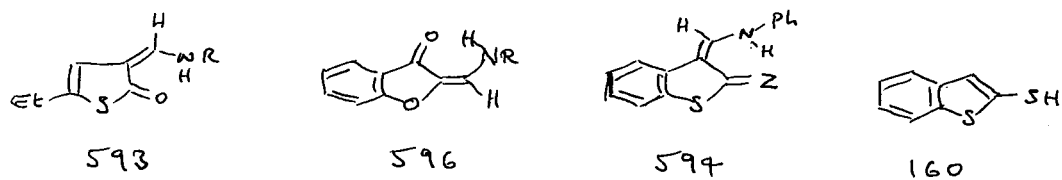
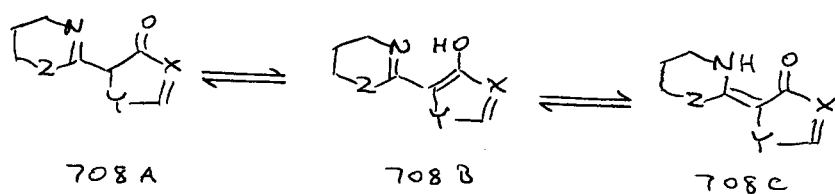
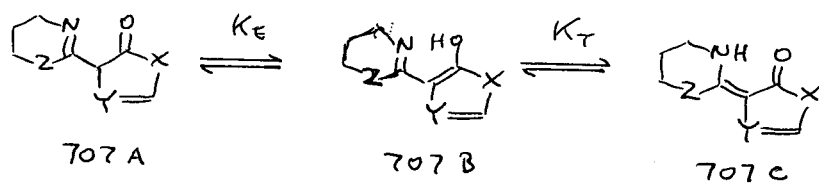
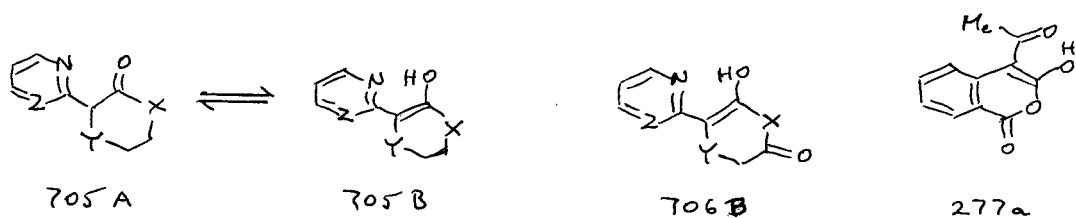
Fission of ring B releases **692** from the necessity that Y and Z are restricted to nitrogen and leads to most options of real importance. If A and C are both 6-membered heteroaromatic rings we have **701** (X = O, S or NR; Y and Z = N or CH) for which the **A**-tautomer shown is expected. The same will be true for **702** in which ring A is aromatic but 5-membered (Z = O, S or NR). In **703** and **704**, either option for ring A is combined with C as a heteroaromatic 5-membered ring. Here the **B**-tautomer is viable but the **C**-tautomer is not, since loss of aromaticity by *both* rings would be entailed. The balance of probabilities between the **A**- and **B**-tautomers will then depend on the precise composition of ring C. For **703** in which X = O, S or NR and Y = CH, ring C is strongly resistant to enolisation and **703A** should generally result. However, if Y = N the parent ring C is intrinsically more aromatic (*cf.* Table 12, section A.2.6) and **703B** is likely to be preferred. In **704** ring C is considerably less resistant to enolisation in any case (*cf.* Table 13, section A.2.7) so that (**704B**, Y = O, S or NR) is likely even for X = CH and overwhelmingly probable for X = N. An example for which X = CH, Y = NH is **320**, which can exist as either tautomer according to solvent (section A.6.5). It should be remembered that almost any substituent will stabilise C=C and aromatic substituents are particularly effective, resulting in a further bias towards the **B**-tautomer;  $\Delta \log K_E \geq 1.2$  for R<sup>2</sup> = Ph in **49** (section A.1.3). There may also be a substantial contribution to the stability of **320b** from its intramolecular hydrogen bond (see Table 33, section A.10.2). Note too that, in **51** and **52**, even R = alkyl in place of H can cause a switch to **51b** and **52b** (section A.1.3), further evidence for (**703B**, Y = N) and (**704B**, X = N) as the predominant tautomers.



In sum, therefore, the **A**-tautomer is likely in general for (**703**, Y = CH) but the **B**-tautomer is probable for (**704**, X = CH) and overwhelmingly probable for any azole. Even for (**703**, Y = CH) it may depend on the nature of X, with **703B** most likely for X = S and least likely for X = O (section A.2.7). In no case will the **C**-tautomer be important. (These preferences are largely echoed by the corresponding acyl derivatives, compounds that in which C=N in **674** is replaced by C=O and ring A is eliminated; see below). And if C=O is replaced by C=S it may safely be presumed that the **B**-tautomer will predominate in all cases; even **53a**, nominally a thioamide, goes to **53b** when R = Ph (section A.1.3).

If ring B is missing and A is aromatic but C is not we have essentially the same situation as discussed already for **681** above, and here generalised as **705** in which X, Y and Z have their previous connotations. As for **681** the **B**-tautomer will generally be a minor species with **705A** the major component. If Y is a hetero-atom its influence is likely to be minimal since in **705B** it is cross-conjugated. However, a hetero-atom at X would lock the structure as **705A** (Rule 3) though, on the precedent of **277a** (section A.6.3), it is possible that an imide (X = NR) or more probably an anhydride (X = O) in **706**, with less resonance energy to lose, might lead to **706B** in preference to **706A**. This area has yet to be explored.

The situation changes dramatically if the converse applies and ring C is aromatic but A is not. The important case in which C is a 5-membered heterocyclic ring is set out as **707** and **708** which allows direct comparison with **703** and **704**, X, Y and Z possessing the same significance. There are two contrasting circumstances, according as to whether Z is CH<sub>2</sub> or a hetero-atom. We first consider Z = CH<sub>2</sub>. Here the potential aromaticity of ring C which makes the **B**-tautomer so important for **703** and (especially) **704** is overtaken and supplanted by the rival claims of **C**-tautomer formation:  $K_T$  unknown but probably  $> 10^5$  for its aminoenone core (section A.10.10). The result is that every known compound of this type that can tautomerise to give the **C**-tautomer does so. As it happens, compounds in which A is alicyclic have not been studied and the actual exemplars of this class are Schiff bases such as **593** and **596** (section A.10.18); there are even cases such as (**594**, Z = S) which exists as the thione shown although its 'parent compound' **160** (section A.3.7) does not.



Schiff bases typically possess  $Z = \text{H}$  or alkyl and the situation in which  $Z$  in **707** and **708** is a hetero-atom is effectively undocumented. The interaction of  $Z$  with  $\text{C}=\text{N}$  represents *competitive conjugation* (Rule 2) and, where it happens will diminish the importance of the **C**-tautomer. It is most likely to be fatal in alicyclic rings as illustrated for **707** and **708** since this interaction is enforced by geometry (sections A.10.5 and A.10.11). Here it is plausible that the **A**-tautomer may dominate for (**707**,  $Y = \text{CH}$ ,  $Y = \text{heteroatom}$ ) and the **B**-tautomer for both azoles, (**707**,  $Y = \text{N}$ ) and (**708**,  $X = \text{N}$ ), *i.e.* as in the parent compounds, only (**708**,  $X = \text{CH}$ ,  $Y = \text{heteroatom}$ ) retaining a preference for the **C**-tautomer. The flexibility of open-chain structures makes the **C**-tautomer much more generally likely here, as illustrated for **709C** in which the crucial difference is the change of conformation for  $\text{ZR}'$ . This is very much a grey area deserving of investigation. If on breaking ring A the  $\text{Z}-\text{C}=\text{N}$  unit itself can tautomerise as in **710**, this will be 'locked' (Rule 3) and the choice then lies between **710A** and **710B**; if  $Z = \text{O}$  or  $\text{S}$  almost certainly the latter, except when  $X$  is a hetero-atom so that  $\text{COX}$  is locked as well.

The parallelism between Schiff bases, hydrazones and oximes (sections A.10.18, A.10.19 and A.10.20 respectively) discussed above for the compounds of Scheme 25 (**684**, **685**, **621** and their congeners) extends to the present series. (In those cases ring C is a phenol, so that the **C**-tautomer is much less favoured there than it is here). On limited evidence it seems probable that, in the former series,  $K_{\text{T}}$  may be slightly less for hydrazones and somewhat more for oximes than for the benchmark Schiff base series, but the differences do not appear to be overwhelming. One would expect the same for 711 - 713, and so far as it goes, that postulate is consistent with the evidence. For example, **603** and **605** exist exclusively as shown but at least a trace of **607B** is found alongside **607C** despite the absence of any equivalent report for **595**. Information on oximes is more scattered and throws no light on this question but **625** is a typical structure. One oddity is (**632**,  $Z = \text{O}$ ,  $\text{S}$  or  $\text{NR}$ ) which if  $\text{R}$  is bland is an oxime as written but for  $Z = \text{S}$ ,  $\text{R} = \text{CONH}_2$  exists in admixture with the nitroso-compound **631B**. Here we suggest that  $\text{NO}$  and  $\text{CONH}_2$  are to be seen as twin electronegative  $\pi$ -acceptors, a situation that commonly leads to an overwhelming preponderance of the **C**-tautomer which, in this context, **631B** is. Nothing is known to reveal whether Schiff bases or hydrazones are capable of similar behaviour.

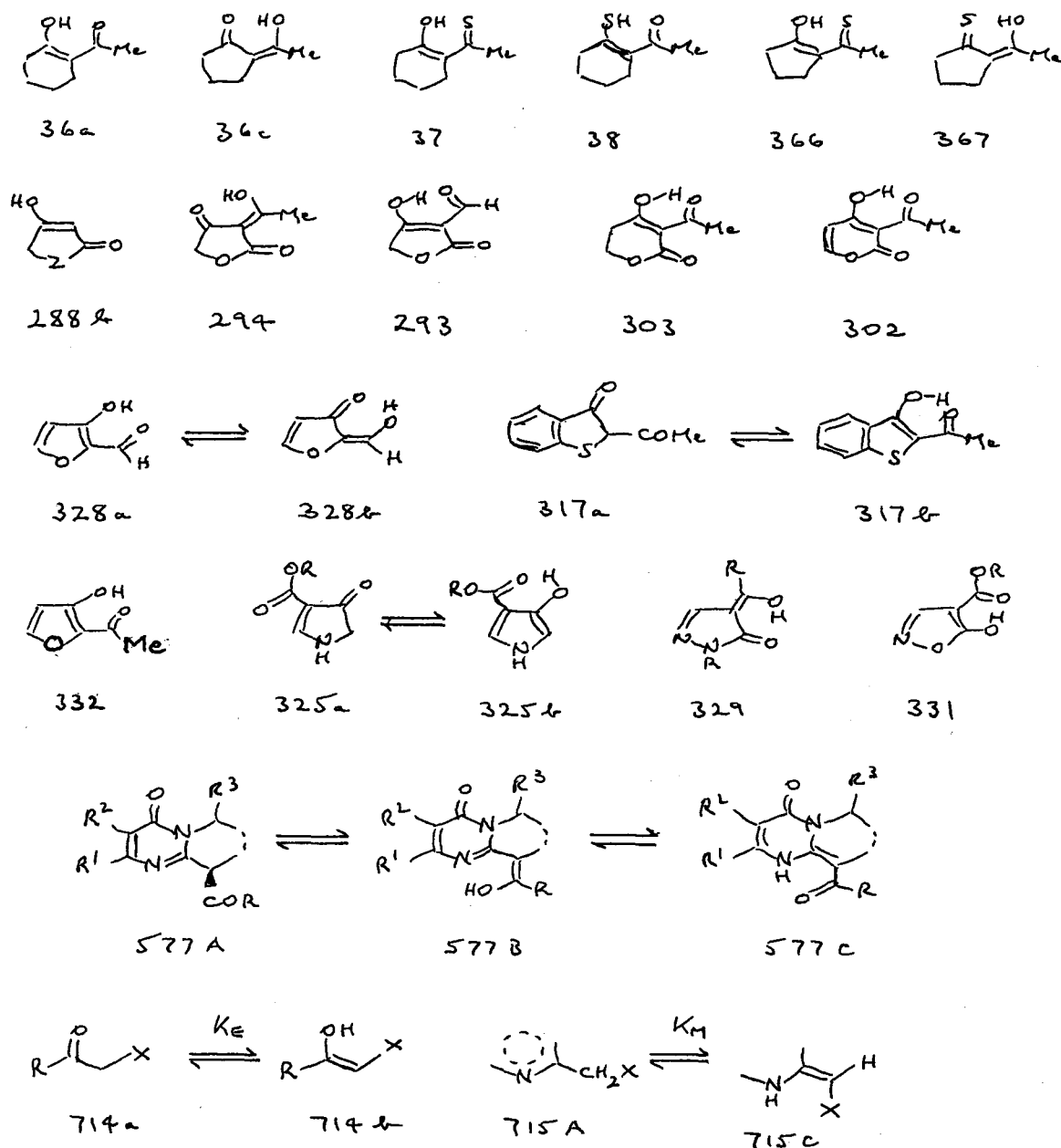
### A.12.8 Effects of Ring Size

We show (section A.1.2) that *endo*-C=C is stabilised in 6- relative to 5-membered rings by  $\Delta \log K$  ca. 0.6, whereas *exo*-C=C is stabilised in 5- relative to 6-membered rings by  $\Delta \log K$  ca. 0.5. Hence the overall effect of a switch from a 6- to a 5-membered ring, in contexts where both act together (which is not always the case) is to enhance  $\log K$  in favour of *exo*-C=C by ca. 1.1, this value rising to ca. 1.5 for *exo*-C=O. Rule 7 follows:

*RULE 7: If alternative enols are finely balanced and one is exo to a ring, endo-C=C will tend to be preferred for 6-membered and exo-C=C for 5-membered rings. This rule is countermanded by Rule 4, in that endo-C=C is required, and almost always found, when the ring is aromatic.*

A simple example (section A.1.2) is **36**, where **36a** is the preferred enol for 2-acetylcyclohexanone and **36c** for 2-acetylcyclopentanone, each to the extent of ca. 80%. It should be noted, however, that in this and similar cases, both are minor species in aqueous solution, the unconjugated tautomer predominating (see Table 4). Chelated  $\beta$ -thionoketones are fully enolised in water and the OH/C=S enol is slightly preferred (section A.8.1), hence **38** and **366** are borderline species, Rule 7 working for the first but not for the second (section A.8.3). A more general context is that of acylation in 5- and 6-membered alicyclic rings (section A.6.5). The furanone tetrone acid (**288b**, Z = O) gives mostly **294** or its geometric isomer on 2-acylation whereas the equivalent pyranone gives exclusively **303**; there is a suggestion here that *exo*-C=C is not quite so dominant in 5-membered rings as is *endo*-C=C in their 6-membered equivalents. In view of the greater ease of enolisation of simple aldehydes than of simple ketones (section A.2.1) it is at first sight surprising that formyl *exo* to a 5-membered ring, in **293** and other examples, appears reluctant to enolise. This may be some consequence of allylic stabilisation (section A.1.1) which, for simpler systems, is inapplicable; since almost any substituent stabilises C=C (Table 1), Me in **294** vs. H in **293** may tip the balance. If so, other types of *exo*-substitution (*e.g.* by Ph) might be still more effective, in other contexts as well as this one, but this possibility does not seem to have been explored.

Aromatisation of **303** leads to **302** in which the same direction of enolisation, as expected, is preserved, but for 5-membered rings it changes the picture. It has been calculated that **328a** is more stable than **328b** by 4.2 kcal mol<sup>-1</sup> and consistently with this **317** and **332**, among others, give the enols shown. (The above value is eloquent testimony to the low resonance energy of furan; *cf.* Table 12, section A.2.6). However, there are exceptions.



While 3-oxoheterocycles are readily enolised by 2-substituents to give **332** for example, 4-acylation as in **325** has no such effect, despite the hydrogen bond that can similarly be written for **325b**. Evidently conjugation as in **325a**, which may be considered as an aminoenedione (*cf.* section A.10.11), is much more important. This principle may be quite general – many examples follow in section B – and, if so, can be considered as an illustration of the codicil to Rule 1. The importance of localised conjugation within the framework of through-resonance, which **332** and **325a** both in their different ways illustrate, needs to be stressed (*cf.* sections A.6.6 and A.10.10).

Where the resonance energy of the aromatic ring is minimal, there are indications that the steric preference normal for its size can re-assert itself; this is the probable explanation for the preferred tautomer shown for **329** – though note its reversion in **331**, in consequence of Rule 3. In the case of **577**, the size of the alicyclic ring is reflected in the preference observed for **577B** or **577C** (section A.10.16). The ease with which the pyrimidone ring loses its aromaticity, in **577C**, is remarkable but has parallels elsewhere (section B.5.14). However, while the behaviour of (**577**, R = CO<sub>2</sub>Et) was charted in 96% ethanol, so is likely to apply to water, most data were obtained for R = H and only in CHCl<sub>3</sub>, for which that is much more dubious. This raises a point of general significance. Most work on these sorts of compound has been carried out in nonpolar solvents that will tend to exaggerate the proportion of enol likely to be found in water (Appendix 2), in which many may enolise very little; for R = H, **577A** is likely to dominate. Dominance of the **A**-tautomer in water is specially likely, among 5-membered ring heteroaromatics, for their 2-oxo derivatives since these mostly resist enolisation quite well. Unfortunately, to go further than that is speculation at the present time.

#### A.12.9 $\pi$ -Acceptors other than C=Z: the Pecking Order

Two of these are potentially important, NO<sub>2</sub> and CN; SO<sub>2</sub>R on its own, a very poor resonance acceptor (Table 2), seems not to promote enolisation (it may cause ionisation instead). Data are sparse. For **714** we estimate  $\Delta \log K_E$  *ca* -1.5 for NO<sub>2</sub> and < -2 for CN, both relative to COMe (sections A.6.7 and A.6.9). However, it is possible and even likely that  $K_M$  may be affected differently. Here our evidence (section A.10.14) is that  $K_M$  for **715C**, where **715A** incorporates a heteroaromatic ring, follows the order COCO<sub>2</sub>Et  $\gg$  CPh  $\gg$  COMe, NO<sub>2</sub> > CN > CO<sub>2</sub>R, but we cannot accurately estimate these differences (guesses for some appear in Table 42). Possibly these different rankings are influenced by the much greater strength of OH than of NH as a proton donor, so that intramolecular hydrogen bonding will count relatively for more with  $K_E$  than with  $K_M$ . Since almost any form of COR is a stronger proton acceptor than NO<sub>2</sub>,<sup>72</sup> while CN cannot form an intramolecular bond at all, these two acceptors will appear as less effective in processes to which intramolecular hydrogen bonding makes a major contribution. Among *carbonyl* acceptors, the ranking order shown above seems to be the same for  $K_E$  as for  $K_M$  (section A.6.8), though its spread may be somewhat different. Beyond these sketchy notes, it is presently impossible to go.

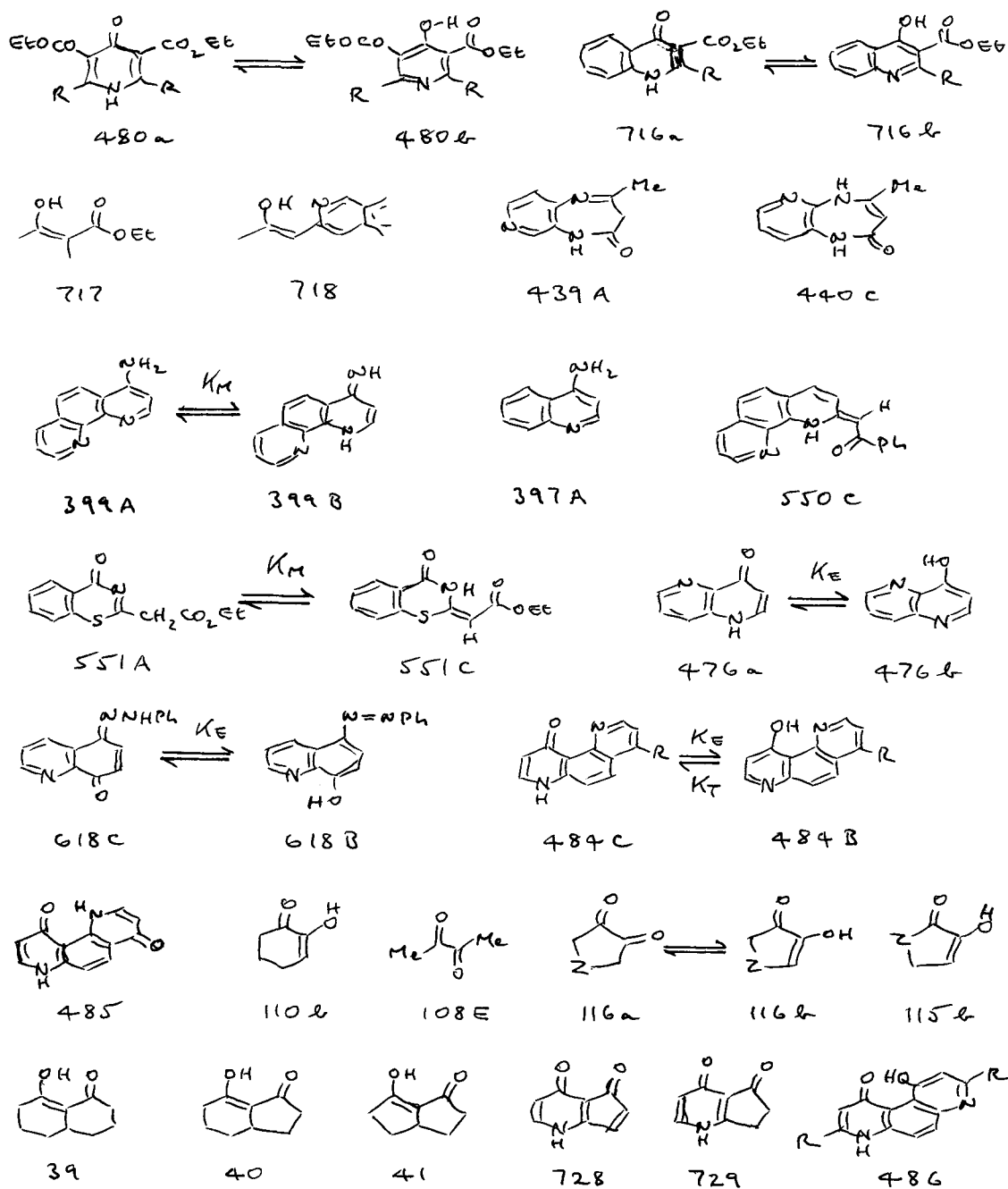
### A.12.10 Intramolecular Hydrogen Bonding and Lone Pair Repulsion

These may occur separately or together and, if the latter, their individual contributions can be difficult to disentangle. Rule 8 follows:

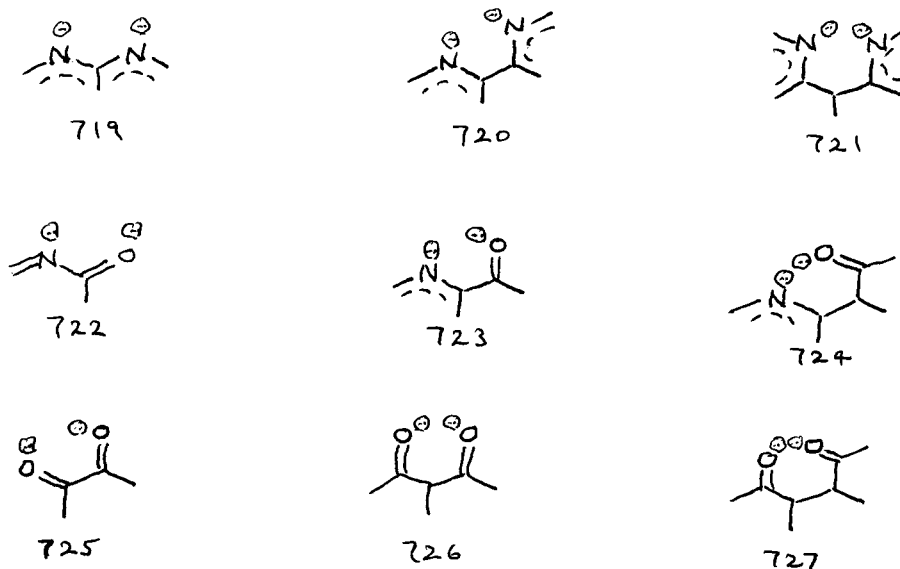
*RULE 8: Intramolecular hydrogen bonding can upset the tautomeric preference otherwise expected on the basis of competitive conjugation.*

Three key situations are discussed in previous sections. These are: reversal of the tautomeric balance in  $\beta$ -thionoketones on enolisation, both as known (section A.8.3) and as predicted (Tables 47 and 49); the predicted, but not so far confirmed, fall in  $K_T$  on chelation for aminoenones; and its predicted rise on chelation, again not yet confirmed, in aminoenethiones (all as set out in Scheme 24). Each of these observations may be rationalised in terms of the known proton donor order  $\text{OH} \gg \text{NH} > \text{SH}$  (section A.11.3) though other factors may enter and probably do. However, while intramolecular hydrogen bonding is undoubtedly a driving force in any form of chelation, *e.g.* in the formation of **317b** and **332** (above) from their parent oxoheterocycles, the actual *direction* of enolisation is more usually determined by the other factors listed above (ring size, aromaticity, competitive conjugation). We start by attempting to quantify the ability of intramolecular hydrogen bonding to bring about enolisation at all; that is, its effect on  $K_E$  (or  $K_M$ ) rather than  $K_T$ .

A characteristic of enolisation involving floppy molecules is that the rigidity of the chelate places it at an entropic disadvantage which, particularly in polar solvents, offsets much of the advantage attaching to its intramolecular hydrogen bond (see section A.6.7 for a more extended discussion). It follows that its effect is much easier to quantify in rigid structures. 3-Substitution in 4-pyridones has little effect on  $K_T$  (section A.10.6) so that (**480**, R = H or Me) and (**716**, R = Ph) exist in water as their oxo-tautomers (section A.10.8). However, (**480**, R = Ph) gives a mixture of tautomers in water, whereas (**716**, R = SR') exists as **716a** or **716b** according to the medium, the exception being R = SPr<sup>i</sup> in which planarity cannot be attained. We may approach the effect of intramolecular bonding by calculating  $K_T$  as a function of electronic factors alone (Table 37). For (**480**, R = H), (**480**, R = Ph) and (**716**, R = Ph) we estimate  $\log K_T$  on this basis as 3.3, 1.3 and 3.6 respectively. Hence, starting from 3.9, 3.9 and 4.9 for the parent compounds, a bond strength in **717** equivalent to  $\Delta \log K_T$  *ca.* -1.5 would account for all three results. For (**716**, R = SR') however it may be calculated (Appendix 4) that the intramolecular bond in **716b** contributes only  $\Delta \log K_T$  *ca.* -1, suggesting that (**480b**, R = Ph) may be abnormally affected by entropic factors. For **718** with its much better proton acceptor<sup>72</sup> we estimate  $\Delta \log K_E$  as 2.4 to 2.9 (section A.2.2 and Appendix 4).



*RULE 9: Where intramolecular hydrogen bonding can replace lone pair repulsion, any induced tautomeric change is likely to be exceptionally large. Many such effects supposedly due to hydrogen bonding are probably dominated in fact by this repulsive effect.*



Scheme 26

Lone pair repulsion is not a factor in any of the above examples since free rotation readily avoids it. Where however this is locked in by the rigidity of the structure, and can only be relieved by forming an alternative tautomer, the effect is often large. We may approach this subject in terms of geometry. Scheme 26 sets out various hypothetical examples involving carbonyl and imino-nitrogen in lone pair clashes with themselves and one another. Nothing in the available data corresponds to **721**, but there are examples of all the others:

(i) **719** is exemplified by **439** and **440** which exist in pyridine largely as shown (section A.10.4), with  $\Delta \log K_M$  *ca.* 0.8 chiefly (perhaps not entirely) the result of lone pair repulsion in **440A**. This type of 1,3-interaction between parallel nitrogen lone pairs is much more widespread among the compounds of Part B.

(ii) **720** is represented by **399** (section A.9.4). Here lone pair repulsion in **399A** can be relieved by hydrogen bonding in **399B**. Given  $\log K_M$  -4.9, comparison is required with **397**, for which we suggest (section A.9.4) a revised estimate of *ca.* -7 from which  $\Delta \log K_M$  *ca.* 2 follows. A value of this order will readily explain why **550** is locked as **550C** (section A.10.14). Since the  $pK_a$  value of **399B** is inevitably based on its 1-Me derivative it does not incorporate the reinforcing effect of the NH---N bond, though this, since involving a 1,4-interaction, may be quite small.

(iii) Evidence concerning **722** is equivocal since the dominant tautomer **551C**, and others like it (section A.10.14), should in any case be favoured by its *N*-acylenamine structure (section A.4.4). Better evidence comes from *N*-acylamidines (section B.5.6) and suggests that lone pair repulsion of this type amounts only to  $\Delta \log K \nless 1$ . Its geometry, that of a '3-membered ring,' is similar to that of **719** where, again, this repulsion is perceptible but rarely decisive (sections A.10.4, A.10.14 and B.1.7).

(iv) Evidence concerning **723**, whose '4-membered ring' leads to a sharper angle between the clashing lone pairs, is sparse. In **476**, **476b** is dominant in nonpolar solvents but undetectable in water, and solvent comparisons suggest  $\Delta \log K_E$  *ca.* 1.9 (Appendix 3). Consistently, the effect of aza-nitrogen in **618** is to replace  $\log K_T$  *ca.* 0.4 in the 'parent' naphthalene by a much lower value so that **618C** is now unobservable, from which  $\Delta \log K_E \geq 2$  follows. Certainly an effect greater than that for **722** would be expected.

(v) Unequivocal evidence concerning **724** comes from a careful and detailed study of **484** (section A.10.8). For  $R = Cl$ ,  $\log K_E = 1.4$ , which represents a tautomeric shift of  $\Delta \log K_T$  -6.3 relative to 4-quinolone. Hence the shift in tautomeric ratio for these three situations follows the order **722** < **723** < **724** and the same ordering may be expected for the N,N and O,O sequences (Scheme 26). The authors provide evidence that most of the shift for **484** derives from the relief of lone pair repulsion rather than from hydrogen bonding *per se*. For **485** (**484**,  $R = OH$ ) they find  $\log K_T$  6.4 which, given 8.2 (their estimate) for two 4-quinolone units, indicates a shortfall of  $\Delta \log K_T$  1.8, and attribute this to the *difference* between the strengths of OH---N and NH---O hydrogen bonding.<sup>304</sup> We correct  $\log K_T$  to 7.4 (Appendix 1) and think a fairer comparison to be with  $\Sigma \log K_T$  8.8 for 4-quinolone plus 4-pyridone, giving  $\Delta \log K_T$  -1.4. For OH---N and NH---O in this geometry, but unfortunately not with the same degree of molecular rigidity, we find  $\Delta \log K_T$  2.7 and 1.0 respectively; *vide* full account in Appendix 3.

(vi) **725** represents a '4-membered ring' like **723** but the effect of clashing carbonyls is far greater, perhaps the result of larger dipoles and (for oxygen) 'harder' lone pairs. For **110** we estimate the effect of lone pair repulsion/hydrogen bonding, leading to **110b**, as  $\Delta \log K_E \geq 5$  in a total shift of > 8.5, the rest being due to a carbonyl electronegativity which on its own, in **108E**, leads to no perceptible enolisation (section A.2.5). At first sight it is surprising that this effect should be even greater in 5-membered rings but perhaps the adjacent carbonyls are constrained to be more planar. Here it is rather surprising that (**116**,  $Z = O$ ) is said to exist as the diketo-tautomer despite the fact that **116b** is preferred for  $Z \neq O$ , and **115b** always.

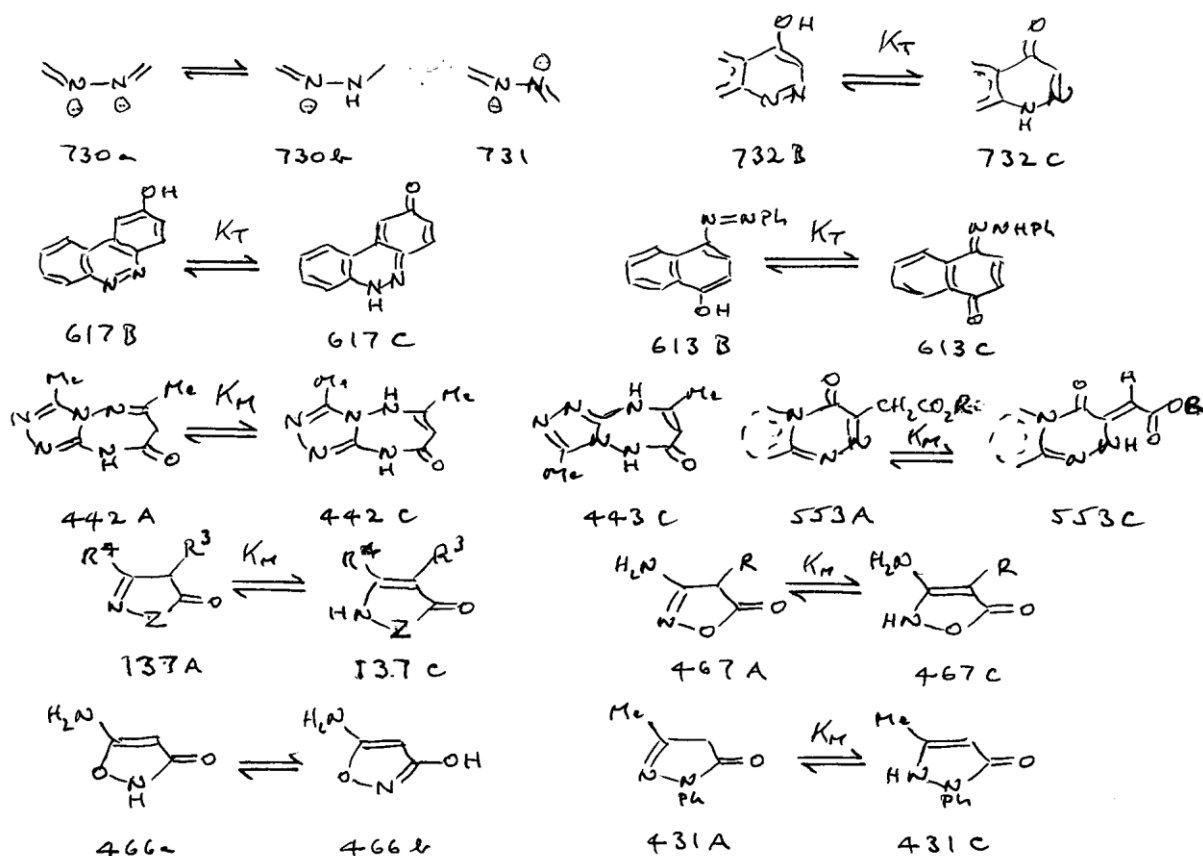
(vii) Compounds **39** - **41** (shown as their enols) exemplify **726** but  $\Delta \log K_E$  is clearly much smaller than for **725**: in MeOH, enol content is 100, 80 and 1.4% respectively (section A.1.2) and should be less in water. However, the observed trend is expected as the carbonyls move apart and the OH---O bond has to stretch. In these *trans*-fused alicyclics there is presumably considerable scope for lone pair repulsion to be relieved by twisting of the carbonyls relative to that in **110** and its analogues. Rigid molecules such as **728** or even **729** would be likely to show an effect equal to or greater than that of **724**, also a '5-membered ring,' but no such compound has been studied, and enolisation would probably in practice relieve the situation.

(viii) The degenerate tautomers of compound **486** form our only representative of **727**. This is not only locked as shown, but its intramolecular hydrogen bond is of quite exceptional strength though not symmetrical (section A.10.8). Here the lone pair repulsion present in its hypothetical dipyridone tautomer must be of gargantuan proportions. Planar structures of type **727** may be incapable of existence.

Lone pair repulsion on its own (any hydrogen bonding is to solvent) can be found in a context that becomes much more important in Section B:

*RULE 10: In cyclic structures, adjacent hetero-atoms of the same hybridisation type will be avoided if at all possible.*

There are two variants to consider. Adjacent imino-nitrogen atoms as shown for **730a** generate a lone pair clash which can be relieved by tautomerisation to **730b**. (This clash is absent in **731** hence in open-chain structures the *trans*-configuration will always be found where possible). In heteroaromatics of type **732** we estimate it as contributing  $\Delta \log K_T$  ca. 2.2 to enhancing the proportion of the C-tautomer (section A.10.7). However, **617** exists as **617B** not **617C** (section A.10.19); evidently the aromaticity of 9,10-phenanthroline more than compensates for the hydrazone part-structure of **617C**; and for **613**, the C-tautomer is only slightly preferred. Relief of lone pair repulsion in **553A** is partly offset by cross-conjugation in **553C**, so that the latter loses much of its advantage (contrast **732**) and either tautomer can dominate (section A.10.14).



The second concerns the clash between amino-nitrogen and itself, O, or S, which can be relieved by tautomerisation in the opposite sense to the above. There are a number of pertinent examples in the text. Dipolar repulsion involving bridgehead nitrogen will explain reversion of the expected **442C** to **442A**; it is not strong enough, however, to overcome the amide resonance present in **443C** (section A.10.14). It is also a besetting problem in such 5-membered ring heteroaromatics as (**137**, Z = O, R<sup>3</sup> = H, R<sup>4</sup> = Me) of which only 70% is present in water as **137C** (section C.15) despite the otherwise expected predominance of the aminoenone tautomer. Another example is **467**, which in EtOH exists mostly as **467C** when R = Et and overwhelmingly so for R = Ph, since both substituents stabilise C=C (section A.1.1) but, in both cases, becomes **467A** in the solid state (section A.10.5); here, even NH<sub>2</sub> does not provide a sufficient driving force to ensure the predominance of **467C** under all conditions. And in **466** the aminoenone stabilisation expected for NH<sub>2</sub> fails completely, the **B**-tautomer **466b** unusually existing in equilibrium with the **C**-tautomer **466a**. So far as the degree of dipolar repulsion is concerned, while it cannot be quantified from within these data (but must be large), there is evidence that it is worse for -N(R)O- (cf. **137**) than for adjacent nitrogen atoms (e.g. **431**). Quantitative data are assembled in section B.2.10 and receive a rationale, as eqn. (cxvi) in section C.15, which takes into account both dipolar repulsion and aromaticity. Further aspects of these topics are explored in section B.1.

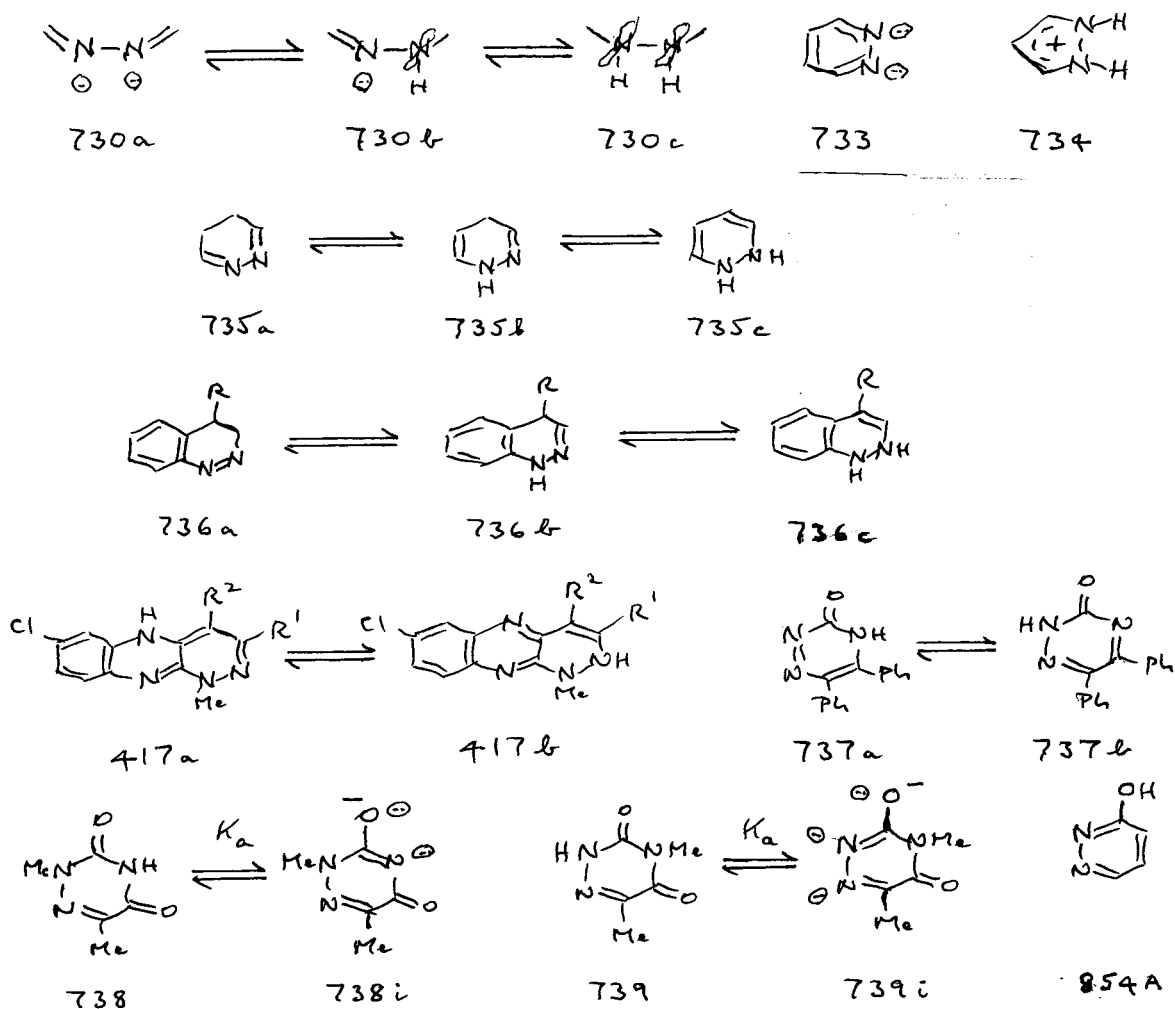
## B: 'N-TYPE' TAUTOMERISM

### B.1 Annular Tautomerism at Nitrogen

This is an extensive subject and not all examples of it are covered; others appear throughout this section, particularly in B.5 and B.6, and in the corresponding sub-sections of Part A, such as A.10.7 and A.11.4. Discussion here is confined to compounds in which the tautomerisation of any functional group that may be present is unaffected.

Two different though related contexts are to be found among present examples. When two or more nitrogen atoms are contiguous there is the potential for lone pair or dipolar repulsion; as discussed in the final part of section A.12, **730a** and **730c** which possess the first and second features respectively are greatly disfavoured relative to **730b**. (An enhanced repulsion is present if, in **730c**, NR replaces NH, and there is evidence, which we analyse quantitatively in section C.15, that replacing NR by O will increase it still further). Taft and co-workers<sup>387</sup> have attempted to quantify these effects in the gas phase and for aqueous solution. They were able to demonstrate that a value of 6.5 kcal mol<sup>-1</sup>, both for lone pair repulsion in **733** and for dipolar repulsion in **734**, will give self-consistent results for the energetics of isodesmic schemes involving gas phase protonation, falling to 2.5 kcal mol<sup>-1</sup> for both in aqueous solution. Taken in conjunction with *favourable* interactions in water of 0.5 kcal mol<sup>-1</sup> in **730b** and of 1.0 kcal mol<sup>-1</sup> when its NH carries a positive charge (*e.g.* in the monocation of **733**), this leads to a total energy, in water, of 3.0 kcal mol<sup>-1</sup> for the formation of **730b** from **730a** but does not allow an estimate for its formation from **730c**. Since dipolar repulsion in **730c** must be less than in **734** one might expect **730c** to be less disfavoured than **730a**, but the picture is more complicated than this; see Appendix 3.

The second context concerns the effect of C-substitution on annular tautomerism. This is chiefly important for those very few heterocycles in which the annular tautomers are degenerate, but where degeneracy can be lost on substitution: pyrazole (section A.9.2), imidazole, benzimidazole, benzotriazole, and in *v*-triazoles if strictly confined to the 1(3)-*H* tautomer. Such effects, where known, are mostly unspectacular; those due to contiguous nitrogen atoms are in general more significant and, for monocyclic heterocycles, are considered first.



### B.1.1 Annular Tautomerism in 6-Membered Rings

Leaving aside the oxo- and thionoheterocycles noted above, there are few of these, but all illustrate the expected consequences of lone pair or dipolar repulsion. The dihydropyridazine **735** exists as **735b** and the equivalent tautomer is found for **736**,<sup>388</sup> even  $R = Ph$  cannot sufficiently stabilise **736c**. (It should be noted, in passing, that both **c**-tautomers are anti-aromatic). Similarly, **417a** is the preferred tautomer of **417** (section A.9.6) despite the loss of aromaticity this entails, while **737** exists as **737b**, 100% in 95% EtOH according to Paudler and Lee.<sup>167</sup> The different  $pK_a$  values of **738** and **739**, 7.49 and 10.1 respectively, are readily explained by the  $N,N$  lone pair repulsion present in **739i**; corrected for the  $pK_a$  values of the corresponding  $N$ -methyl uracils,<sup>388</sup> 9.72 and 9.85 respectively, this becomes  $\Delta\Delta pK_a$  ca. 2.5. Even so, this margin is appreciably less than  $\Delta\Delta pK_a$  3.4 as estimated for the iminol **854A** of 3-pyridazinone and other factors may be present; see Appendix 3 for further discussion.

### B.1.2 Annular Tautomerism in 5-Membered Rings: *s*-Triazoles

This is a much studied subject with many ramifications but the overall conclusion is clear: while the substituents  $R^1$  and  $R^2$  can change the balance between the 1,2,4-tautomers **A** and **B** (Scheme 27), the 1,3,4-tautomer **C** is always a minor species.

$$K_a = K_1 K_{A^+} + K_2 + K' (K_{A^+} + 1) \quad (\text{liii})$$

$$K' = K_3 K_4 / (K_3 + K_4) \quad (\text{liv})$$

$$K_T = (K_1 K_{A^+} + K_2) / K' (K_{A^+} + 1) \quad (\text{lv})$$

In the most general case (Scheme 27), three neutral tautomers **A**, **B** and **C** are related to one another through two tautomeric monocations, **AH**<sup>+</sup> and **BH**<sup>+</sup>. This Scheme is soluble using the ‘basicity method’ (Appendix 1) if enough good models exist, which is rarely the case. The three key equations which may be derived from Scheme 27 are (liii) - (lv); here  $K_a$  represents the *macro*- $pK$  for the system as a whole, observed or calculated, whereas  $K'$  is a further *macro*- $pK$  which defines the summation of proton transfers involving tautomer **C**. In the special case of symmetrical substitution ( $R^1 = R^2$ ), which includes the parent triazole, we have **B** = **A**,  $K_1 = K_2$ ,  $K_3 = K_4$  and  $K_A = K_{A^+} = 1$ , whereupon equations (liii) - (lv) collapse to (lvi) - (lviii) with replacement of  $K'$  by the former *micro*-constant  $K_3$ .

$$K_a = 2K_1 + K_3 \quad (\text{lvi})$$

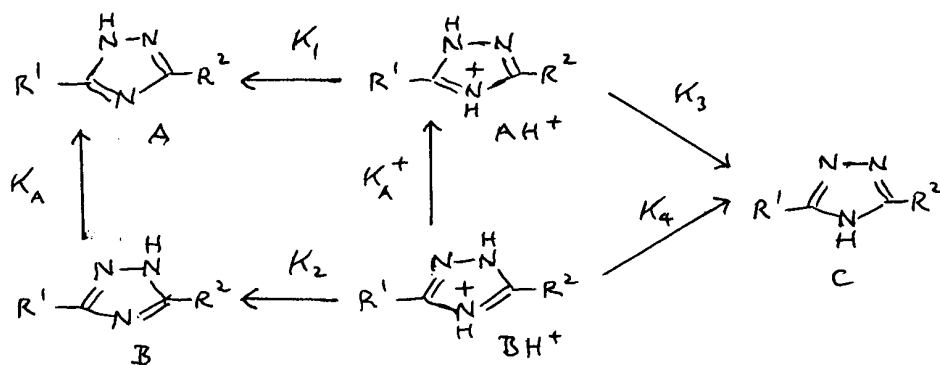
$$K_3 = 2K' \quad (\text{lvii})$$

$$K_T = 2K_1 / K_3 \quad (\text{lviii})$$

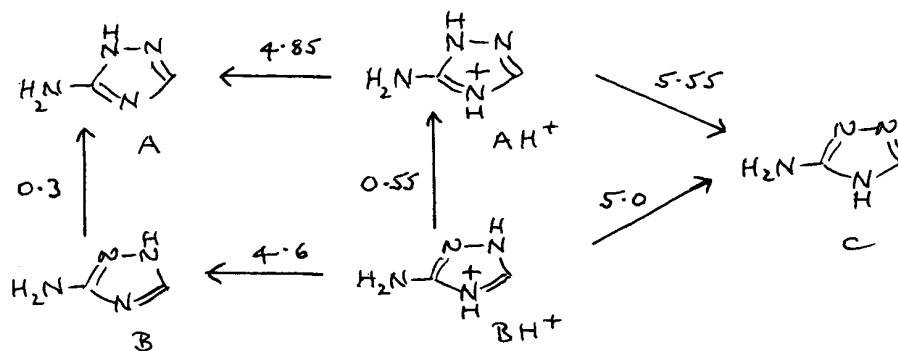
**Table 51.  $pK_a$  Data and Calculated  $K_T$  Values for Symmetrically Substituted *s*-Triazoles <sup>a</sup>**

$R^1 = R^2$	Ref.	$pK_{1Me}$	$pK_1$	$pK_{3Me}$	$pK_3$	$pK_a$ (calc.)	$pK_a$ (obs.)	$K_T$
H	390	2.05	2.60	2.64	2.94	2.21	2.21	4.3
H	391a	1.7	2.25	2.7	3.0	1.91	2.27	11.7
Me	390	3.69	4.24	4.34	4.64	3.86	3.97	5.0

<sup>a</sup>  $pK_1$  and  $pK_3$  are calculated from the observed values for  $pK_{1Me}$  and  $pK_{3Me}$  respectively; see the text.

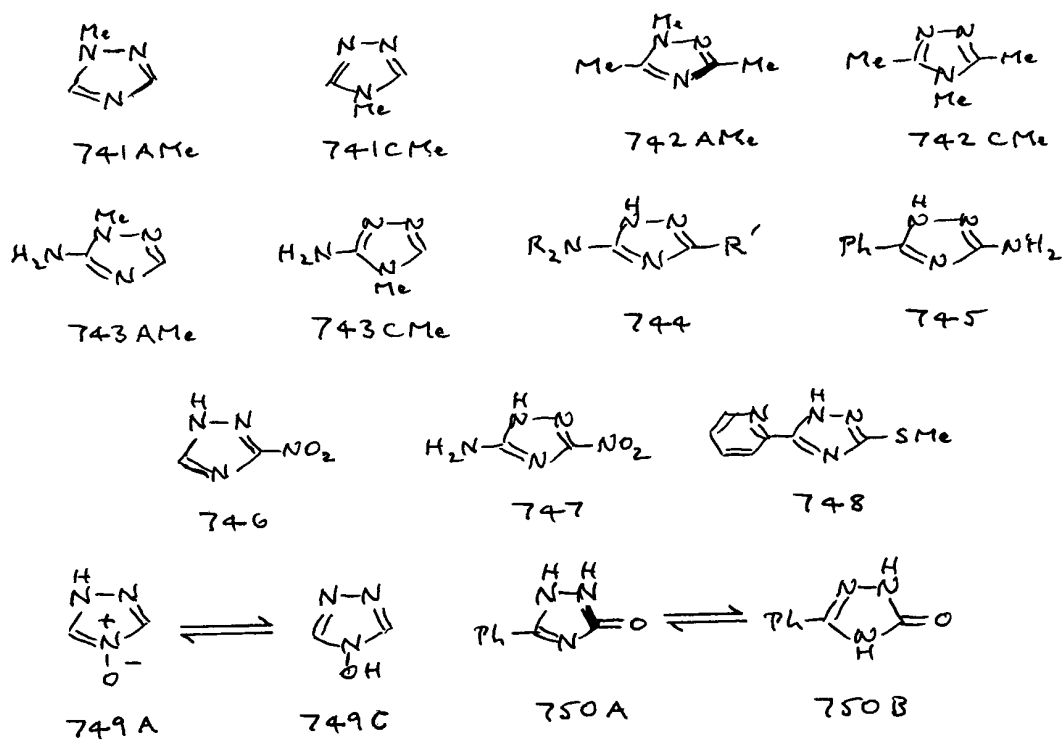


Scheme 27



Scheme 28

## Tautomeric Behaviour of 743



The tautomerism of s-triazole **741** has been studied in water by two groups.<sup>390,391a</sup> We may use the  $pK_a$  values for **741AMe** and **741CMe** as models for the **A** and **C** tautomers respectively if the required  $pK$  correction factors  $\Delta(NR)$  are known. For the second we estimate  $\Delta(NR) = 0.30$  using imidazole as model, whereas for the first we use  $\Delta(NR) = 0.55$  derived by trial and error from the observed  $pK_a$  values. This value lies close to  $\Delta(NR) 0.6$  for  $=NH^+NHC(=O)-$  which it somewhat resembles, and also fits within the pattern of  $\Delta(NR)$  values revealed by experiment (see Scheme 123, and discussion, in Appendix 1). Data are given in Table 51 along with those for its dimethyl derivative **742**.<sup>390</sup> A check on the accuracy of data *and* correction factors consists in the ability of these calculations to reproduce the observed global  $pK_a$ . Here one result for s-triazole is remarkably good, with that for **742**, by the same author,<sup>390</sup> not far behind. Only one asymmetrical compound, the monoamino derivative **743**, has been studied in comparable detail. Barlin<sup>392</sup> gives  $pK_a$  values of 4.29 and 5.38 for **743AMe** and **743CMe** respectively, which in the absence of a model for **743B** is insufficient to solve these equations by the 'basicity method' alone, but Fritz<sup>393</sup> has demonstrated a 2:1 ratio of **743A** to **743B** on good N-15 NMR evidence, and this enables simultaneous equations to be constructed (Appendix 1) which, along with the 'corrected'  $pK_a$  data, allow Scheme 28 to be solved as shown, where the values set out are for  $\log K_T$  or  $pK_a$  as appropriate. (Note that **743CMe** models  $pK'$ , not  $pK_3$  or  $pK_4$  separately). A plausible feature of Scheme 28 is that  $AH^+$  is favoured over  $BH^+$  by a margin which, while small, is greater than that of **A** over **B**; this is expected, since electron demand should be greater in the cation. The resulting value of  $K_T \sim 8$  is in the range found for the compounds of Table 51 which suggests that little variation is likely. For **743**, to within the limits of error, the **A**, **B** and **C** forms are present in water to the extent of 60, 30, and 10% respectively. Fritz<sup>393</sup> could not detect **743C**, but at this low concentration that is unsurprising. As this example has been solved using simultaneous equations the global  $pK_a$  of 4.04<sup>391b</sup> for **743** cannot be used as a check, since incorporated into the data.

There is scattered information of some value. Åkerblom and Sandberg<sup>394</sup> state that compounds of type **744**, with  $R = H$  and  $R' = \text{alkyl or 2-furyl}$ , exist exclusively as shown in EtOH (by UV) and in  $CHCl_3$  or the solid state (on IR evidence). In water, EtOH,  $Et_2O$  and THF, otherwise similar compounds with  $R = Me$  may exist as mixtures of the **A**- and **B**-tautomers but **A** is still dominant.<sup>394</sup> This fits in with the picture presented above. However, while Mazeika *et al.*<sup>395</sup> confirm the predominance of **743A** in dioxan by dipole moment measurement, they believe **745** to exist chiefly as shown. If **746** as claimed<sup>2ww</sup> exists in the **B**-form illustrated, this may signal a

shift to that structure when the (sole) substituent is electronegative, and such a postulate is supported by the demonstration<sup>396</sup> that **747** exists predominantly as written in polar solvents, *i.e.* as the structure expected for each substituent considered separately. These authors calculate this structure to possess a larger dipole moment than its isomer, the difference in energy being estimated for water at  $\Delta E$  6.84 kcal mol<sup>-1</sup>, equivalent (for  $\Delta\Delta S = 0$ ) to log  $K_T$  5.0 in its favour. Even allowing for synergism this margin seems excessive, but it may nevertheless help to indicate the forces which determine tautomeric balance. However, the preferred tautomer shown for **748**<sup>2ww</sup> is most probably the result of its intramolecular hydrogen bond, and while stereoelectronic factors of this sort have not been explored, they are likely to dominate when present.

Hillier and co-workers<sup>397</sup> have carried out high-level MO calculations on *s*-triazole **741** in the gas phase and in simulated aqueous solution. For the gas phase they obtain log  $K_T$  4.7, which agrees with experiment in that **741C** is undetectable. The corresponding value for aqueous solution is log  $K_T$  1.7, which implies about 2% of the **C**-tautomer (*cf.* Table 51). For other solvents, there are two reports. Wofford *et al.*<sup>398</sup> state up to 5% of the **C**-tautomer to be present in DMSO, on <sup>15</sup>N-NMR evidence, while Lunazzi *et al.*<sup>399</sup> find this to be undetectable in THF. The latter authors criticise the former result as a ‘discrepancy’ but in fact it is not; a steadily falling proportion of **741C** as solvent polarity falls is echoed by the calculations of Hillier *et al.*<sup>397</sup> and is a simple consequence of the expected increase in lone pair repulsion. More recently, Hillier and his team<sup>400</sup> have superimposed self-consistent reaction field (SCRF) and polarised continuum (PCM) models on MO calculations at the 6-31G\*\*//6-31G\*\* level in an attempt to elucidate the aqueous solution behaviour of **743**. Both methodologies predict **743C** to be a minor tautomer, but differ as to whether **743A** or **743B** should dominate, and the SCRF treatment which correctly assigns this dominance to **743A** also predicts **743B** to be the least stable tautomer. We believe the position for **743** in water to be given with as much accuracy by Scheme 28, which implies a 60:30:10 ratio of **A:B:C**, as is possible at the present time.

In sum, we believe that for *s*-triazoles in water the **C**-tautomer will always be a minor species, and that its importance will decline further as solvent polarity falls. There is suggestive evidence that its proportion, at 10 – 20%, may be almost independent of the substitution pattern. An interesting

exception is **749**, where **749C** is undetectable in any solvent.<sup>2y</sup> So far as the **A**- and **B**-forms are concerned, while the **A**-tautomer appears to be the more important in most cases so far investigated, the difference is not great and may reverse when the substituent is electronegative. The implication from **748** must also be that the balance is easily upset by intramolecular forces, *e.g.* hydrogen bonding. Overall it is highly improbable that, at a biological receptor, there will be any energetic barrier worth considering between the **A**- and **B**-tautomers, though unless the receptor is very polar, the **C**-tautomer should still be very much disfavoured.

While intramolecular repulsion exclusively in the sense of **730a** has been considered above, its rival form is possible on occasion. Dipolar repulsion as in **730c** will explain why the triazinone **750** exists as **750B** not **750A**,<sup>401</sup> and in this respect **750** makes an interesting contrast with its 6-membered ring analogue **737** considered earlier (section B.1.1).

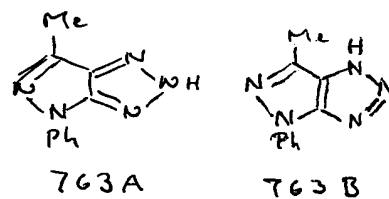
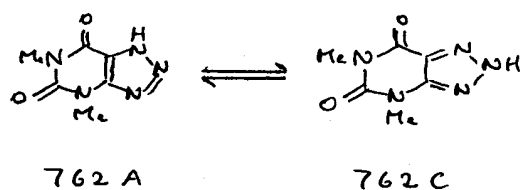
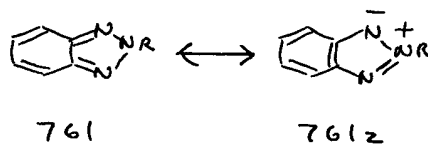
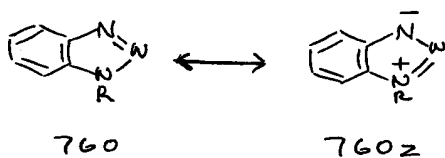
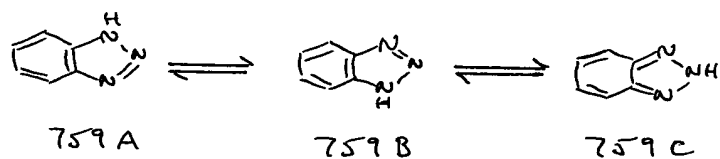
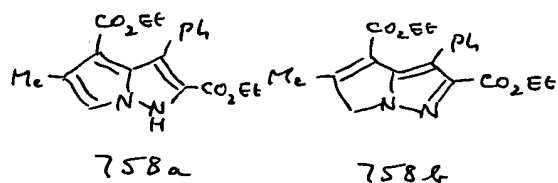
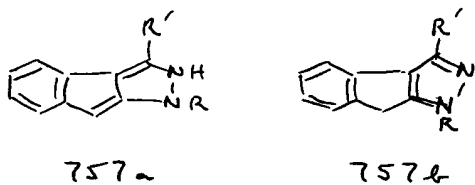
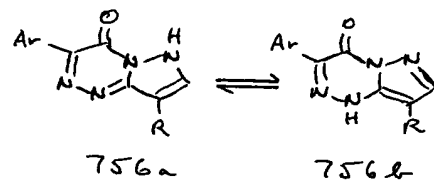
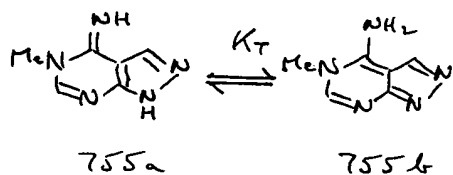
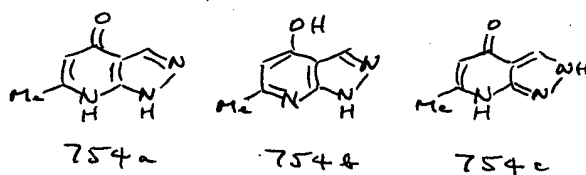
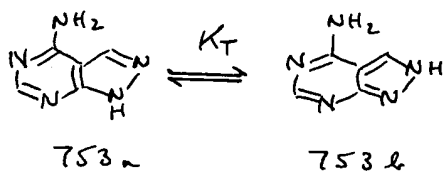
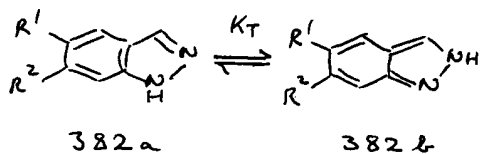
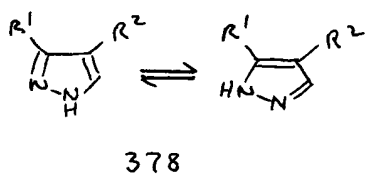
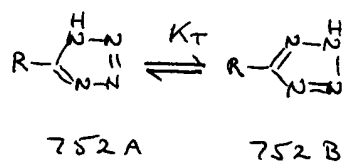
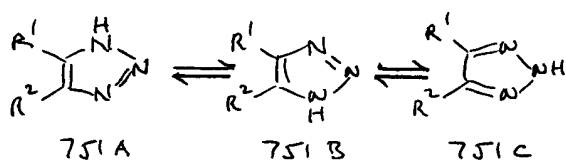
### B.1.3 Annular Tautomerism in 5-Membered Rings: *v*-Triazole

*v*-Triazoles **751** like *s*-triazoles **741** potentially possess three tautomeric forms, two of which, again as for *s*-triazoles, become degenerate if  $R^1 = R^2$ . This time however it is the non-degenerate tautomer that avoids lone pair repulsion, so that for consistency we define  $K_T$  by eqns. (lix) and (lx), according as to whether there is degeneracy or not.

$$K_T = [C]/[A] + [C]/[B] = [C]([A] + [B])/[A][B] \quad (\text{lix})$$

$$K_T = 2[C]/[A] \quad (\text{lx})$$

*v*-Triazole itself is an extremely weak base and this, taken in conjunction with the lack of a single cation common to all species, renders the ‘basicity method’ inapplicable<sup>2c</sup> and, historically, made its tautomeric balance the last of any simple heterocycle to be elucidated. However, two indirect and independent lines of argument converged on a 1:2 ratio of **751A** to **751C** in water,<sup>9</sup> which after statistical correction *via* eqn. (lx) leads to  $K_T = 4$ , a value remarkably close to that of its isomer (section B.1.2).



Solvent effects may be rationalised.<sup>9</sup> With the exception of  $\text{CHCl}_3$ , in which **751A/B** predominates,<sup>399,402</sup> and DMSO with 55% of **751C**,<sup>398</sup> all other solvents show a higher proportion of **751C** than water: 80% in  $\text{CH}_2\text{Cl}_2$ ,<sup>399</sup> 97% in toluene,<sup>399</sup> and > 70% or > 90% in MeOH according to the method of calculation,<sup>403</sup> while 92% can be estimated for 1-octanol.<sup>9</sup> In the gas phase, **751A** is undetectable.<sup>404</sup> As in the case of *s*-triazole, these variations clearly result from lone pair repulsion in **751A/B**. Hillier and co-workers<sup>397</sup> calculate the proportion of **751A/B** in the gas phase to be negligible, but about 10% is predicted for water. Elguero and his team<sup>405</sup> have carried out calculations which indicate that an overall margin of 4.7 kcal mol<sup>-1</sup> in favour of **751C** in the gas phase can be broken down into an *intrinsic* stability of 1.8 kcal mol<sup>-1</sup> in favour of **751A**, much more than offset by lone pair repulsion amounting to 6.5 kcal mol<sup>-1</sup>: a figure very close to that previously deduced for pyridazine **733**.<sup>397</sup> We may safely deduce that **751C** will be the predominant tautomer in any biological context, but this is an exceptionally malleable system and the occasional usefulness to the medicinal chemist of compounds containing it as a sub-unit may well be connected with this.

The influence of substituents on  $K_T$  has not been explored, but there is marginal information concerning their effect on the balance between **751A** and **751B** and this is contained in section B.1.8 below.

#### B.1.4 Annular Tautomerism in 5-Membered Rings: Tetrazole

Tetrazoles may exist as 1-*H* (**752A**) or 2-*H* (**752B**) tautomers. As bases they are far too weak for use of the 'basicity method' but fortunately the <sup>13</sup>C-NMR signals of these forms are very distinctive and allow unequivocal identification.<sup>406</sup> The parent compound (R = H) is **752A** in the solid state and, while no quantitative data are known, exists overwhelmingly as that tautomer in water, acetone, DMF and DMSO, with 80-95% present in dioxane.<sup>406</sup> However it is believed that **752B** dominates in the gas phase,<sup>407</sup> consistently with the lower dipole moment of the 2-*H* tautomer and its (presumed) reduction in lone pair repulsion: two adjacent aza-nitrogens in place of three.

$$\log K_T = -0.77(0.08) + 0.54(0.02) \sigma_p \quad (\text{Ixi})$$

$$(n = 7 \quad r^2 = 0.992 \quad s = 0.02 \quad F = 648)$$

$$\log K_T = -1.11(0.08) + 3.26(0.44)\sigma_I + 0.74(0.25)\sigma_R \quad (\text{Ixii})$$

$$(n = 6 \quad r^2 = 0.993 \quad s = 0.02 \quad F = 226)$$

The effect of substitution has been investigated in several solvents but not in water. Here we define  $K_T$  in the same direction as for the triazoles, *i.e.* in favour of what, in this case, is the minor tautomer. Butler and co-workers<sup>408</sup> examined a number of 4-substituted 5-phenyl tetrazoles in DMSO and summarised past results. They demonstrated an excellent relation between  $\log K_T$  and  $\sigma_p$  but did not give its equation, which is (lxi). This shows electron donors and acceptors to favour the 1-*H* and 2-*H* tautomers respectively, which the authors discuss in terms of their respective dipolar canonical forms. It is interesting also to note that, since **752A** and **752B** derive from the corresponding *s*-triazole tautomers by simple addition of aza-nitrogen, this represents parallel behaviour, if as we have postulated (section B.1.2) donor and acceptor substituents tend to favour **741A** and **741B** respectively (*cf.* 747).

It is also possible to re-analyse these data by replacing eqn. (lxi) by (lxii), in which  $\sigma_I$  and  $\sigma_R$  now refer to *the entire phenyl substituent* where the values for these are known.<sup>39</sup> Here the intercept term represents a prediction for  $R = H$ , *i.e.* tetrazole itself. Webb and co-workers<sup>409</sup> find a value of  $\log K_T$  for DMSO in the range -0.9 to -1.3, whereas scattered data collated by Minkin *et al.*<sup>377</sup> include  $\log K_T$  -1.12 in DMSO for  $R = NH_2$ , which may be calculated on the basis of eqn. (lxii) to possess much the same  $K_T$  value as the parent compound. (For what it is worth, a similar calculation for  $R = NO_2$  suggests an almost exact reversal of this preference). Since **752A** has a higher dipole moment than **752B**<sup>408</sup> a still greater predominance of the 1-*H* tautomer in water than in DMSO would be expected for tetrazole itself and most of its C-substituted derivatives.

### B.1.5 Indazole and other Fused Pyrazoles

Pyrazole (**378**,  $R^1 = R^2 = H$ ) comprises two identical tautomers but in indazoles **382** this degeneracy disappears (see section A.9.2). Hence  $\log K_T$  -1.7 for (**382**,  $R^1 = R^2 = H$ ) in water<sup>243</sup> may be attributed essentially to the disfavoured quinonoid form of **382b**, and this value is scarcely altered in (**382**,  $R^1 = NO_2$ ) or (**382**,  $R^2 = NO_2$ ).<sup>243b</sup> This strong tautomeric preference persists in the gas phase and in all media investigated.

Aromaticity, and hence resistance to the formation of quinonoid forms, is at a maximum for benzofusion. Elsewhere, resistance can be less. Dubois and co-workers,<sup>411</sup> in an investigation of proton loss rates from **753** in water by the T-jump technique, found  $\log K_T$  -1.0 for the formation of **753b** from **753a**, probably indicating a substantially smaller resonance energy for the aminopyrimidine moiety, partly offset by lone pair repulsion in the latter (but not by much; see discussion in section A.12). However, **754** in water

possesses the structure **754a** not **754b** or **754c**,<sup>2xx</sup> despite the relief of dipolar repulsion that either would provide. Here of course the 4-pyridone moiety represents a highly favoured structure, at log  $K_T$  3.9 (section A.10.6) well able to resist the formation of **754b** or, probably, of **754c**, though there is no precise model in the latter case. In **755** however the quinonoid structure **755b** is actually preferred ( $K_T = 10$ )<sup>411</sup> which is remarkable even though imino-heterocycles are very disfavoured (section B.4.4), and despite the lone pair repulsion this structure entails. However, it is very difficult to understand why **756a** with two repulsive clashes should be preferred to **756b**, as is claimed on the basis of NOE experiments in DMSO;<sup>266</sup> perhaps this work requires re-examination.

In certain cases, the quinonoid form is so disfavoured that even a partially non-aromatic structure is preferred: **757** and **758** both take the **b**-form. Even more to the point, these are cited by Elguero<sup>176</sup> as examples of his Rule 1: that NH-NR dipole clashes will be avoided where possible. In addition, and taken in conjunction with further examples (sections B.1.9 and B.2.10), they go some way to substantiate the view that this type of repulsion is still more endergonic than the more familiar *N,N*-lone pair clash.

### B.1.6 Benzotriazoles and other Fused Triazoles

Benzotriazole **759** like *v*-triazole **751** itself possesses three tautomeric forms, two of which are degenerate in the parent heterocycle. Elguero and co-workers<sup>410</sup> have instructively compared the cases of indazole **382** and **759**, with special reference to the influence of aromaticity.

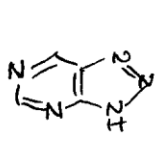
The calculated (MP2/6-31G\*\*) gas phase stability of indazole (**382a**,  $R^1 = R^2 = H$ ) is greater than that of its quinonoid isomer by 3.64 kcal mol<sup>-1</sup>, a result attributed almost entirely to the benzenoid-quinonoid difference.<sup>410</sup> The corresponding value for **759A/B** vs. **759C** is 2.5 kcal mol<sup>-1</sup>.<sup>410</sup> Set against an estimated 6.2 kcal mol<sup>-1</sup> for lone pair repulsion in **759A/B**<sup>410</sup> this should lead to an overwhelming preponderance of **759C** in the gas phase. In fact the proportions are almost even<sup>16</sup> but, even so, it is surprising that **759C** should be of marginal importance even in such a non-polar solvent as isooctane.<sup>16</sup> In fact, while quantitative data do not exist, there seems to be no doubt that **759A/B** is greatly predominant in every solvent examined. Webb and co-workers<sup>442</sup> go so far as to state that **759C** at a constant mole fraction of 0.05 is to be found in CHCl<sub>3</sub>, acetone, DMSO and EtOH, but this claim would be difficult to substantiate and seems unlikely *a priori*, given the expected rise in relative stability of **759A/B** with increasing solvent polarity. It seems more likely that this value represents a lower detection limit, as does the claim by Wofford *et al.*<sup>398</sup> that 2% of **759** is present in CHCl<sub>3</sub> and DMSO.

A naive estimate for water based on additivity assumptions, starting from  $\log K_T$  -1.7 for indazole **382** and superimposing on it the twofold preference for **751C** over **751A/B**,<sup>9</sup> would lead to 4% of **759C** in aqueous solution. This takes no account of aromaticity differences and is probably a considerable over-estimate. It may add to the confusion to note the conclusion of Giordano and Zagari,<sup>413</sup> based on their crystal structures for **760** and **761** ( $R = \text{CH}_2\text{CO}_2\text{H}$ ), that a large contribution from the dipolar canonical structures **760z** and **761z** would go a long way to explain their unexpected similarity in bond lengths and angles, largely abolishing as it does the difference between the ‘benzenoid’ and ‘quinonoid’ alternatives. Certainly, the importance of **760z** will explain why proton acceptor ability in some similar situations is confined to (the equivalent of) *N*-3,<sup>100</sup> which could be of some biological significance if true for  $-\text{NHN}=\text{N}-$  linkages generally.

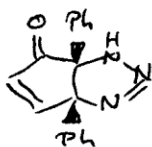
The fused  $\nu$ -triazoles **762** and **763** provide evidence that the large effect of benzofusion on tautomeric form may not extend to other forms of ring fusion. Compound **762** exists 80% in DMSO as **762C**,<sup>414</sup> as compared with 55% for  $\nu$ -triazole itself in that solvent,<sup>398</sup> while **763A** is similarly the major tautomer, by about a factor of two, for **763**.<sup>176</sup> The fused uracil **762** also introduces the subject of *peri*-interactions in such molecules. The dominance of **762C** seems to indicate that neither dipolar attraction in **762A** nor lone pair repulsion in **762C** is as important a determinant of tautomer preference as might have been supposed, while the second conclusion is reinforced by **766** (see below). Nevertheless, in **765** where there is no other *peri*-interaction to compete, the preferred tautomer (in  $\text{CHCl}_3$ ) is as expected, though only by a factor of four.<sup>415</sup> Appendix 3 deals with this subject in depth. We defer consideration of 8-azapurine **764** to the following section.

### B.1.7 Benzimidazole and other Fused Imidazoles

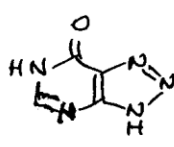
Benzimidazole like imidazole itself consists in two degenerate tautomers, leaving aside such improbable variants as **769b** (though see **788** and **789** below). Few simple substituted benzimidazoles have been studied and only for **770**, where 80% exists as shown, are quantitative results available.<sup>416</sup> This surprisingly small dominance may help to explain some other apparent anomalies, such as that purine **771**, while **771a** in the solid state, exists as an equimolar mixture with **771b** in aqueous solution, according to dipole moment<sup>417a</sup> and  $^{13}\text{C}$ -NMR<sup>417b</sup> studies (but *cf.* discussion in section B.8.1). However, if its imidazole moiety is replaced by the much stronger proton donor  $\nu$ -triazole in **764**, or pyrimidine by the much stronger proton acceptor pyridine in **772**, the structures shown result, according to calculation<sup>418a</sup> or dipole moment<sup>418b</sup> respectively (for donor and acceptor strengths, see Table 140 in Appendix 3). And while adenine **774** with its extra hydrogen bond does indeed exist mostly as **774a**, this is only by a factor of about 15 in water.<sup>417c</sup> None of the above interactions appears to be of decisive importance for tautomeric form.



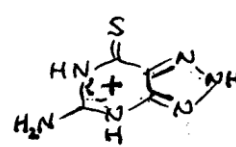
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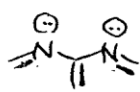
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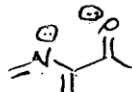
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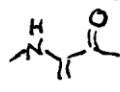
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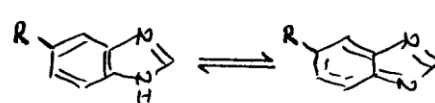
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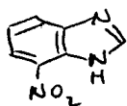


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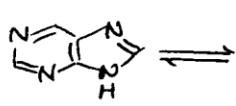


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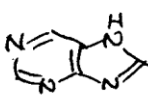
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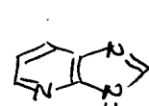
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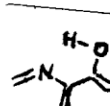
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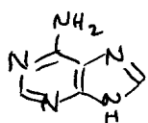
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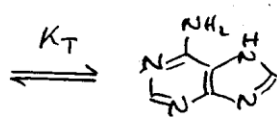
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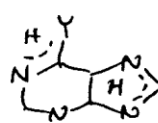
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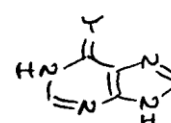
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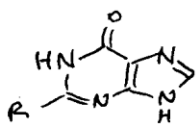
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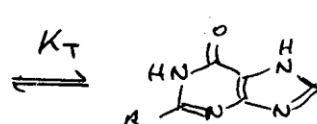
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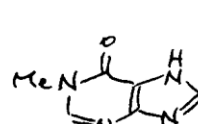
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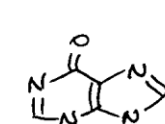
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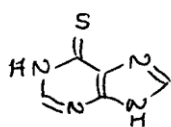
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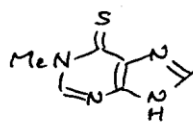
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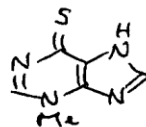
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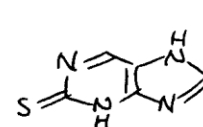
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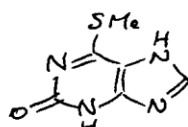
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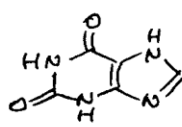
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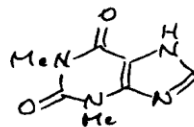
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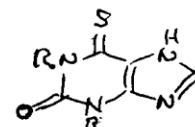
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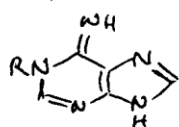
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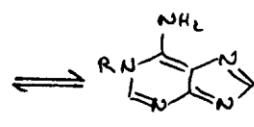
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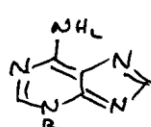
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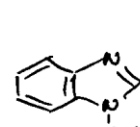
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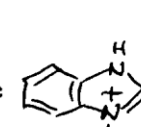
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789



790a



790b

The chief importance of these and other observations lies in predicting their likely effect when, as so often, competing *peri*-interactions are present, and which can take either positive or negative forms. In few such cases are the results easy to interpret. Grant and co-workers<sup>419</sup> have stated that, of the tautomeric structures available to **775**, those of type **776** are generally dominant, a result based on work in DMSO. However, the results for water are equivocal. A survey by Pullman and Pullman<sup>418a</sup> of the calculated, solution and solid state evidence on the annular tautomerism of oxopurines gives **777b** only a slight advantage over **777a** for the 6-oxopurines hypoxanthine (R = H) and guanine (R = NH<sub>2</sub>), while **766** mimics **777a**. Later work by Neimann and co-workers however showed, by UV comparison, that (**777**, R = SMe)<sup>420a</sup> and hypoxanthine<sup>421a</sup> probably exist in water mostly as **777b**, while the thiones **780**, **781** and **782** are predominantly as written,<sup>421a</sup> as is **779**;<sup>421a</sup> its isomer **778** has not been examined. (In compounds lacking 1-*Me* or 3-*Me* the near-unit ratio of 4-pyrimidone's annular tautomers (section B.5.11) imposes some ambiguity). Allowing for this, the difference in tautomeric form in the imidazole moiety between the thiones **780** and **781**, and the variants on **777b**, is instructive. Evidence from other sources<sup>72</sup> suggests that the difference in bond length between C=O and C=S has consequences for their *intramolecular* proton ability over and above that derived from their intrinsic difference in energetics. It seems probable therefore that both dipolar attraction between C=S and NH, and lone pair repulsion between C=S and aza-nitrogen, will be substantially less than for the corresponding interactions involving C=O, so accounting for the switch between these groups of compounds. This points to a qualitative 'pecking order' of NH/C=O dipolar attraction as in **768** > dipolar attraction of type NH/aza-N >> NH/C=S dipolar attraction, with lone pair repulsion of types **719** and **723** lying in energy somewhere between the first two of these factors, that between C=S and aza-nitrogen being negligible. (Note that, while the switch from **723** to **773** is stated in section A.12.10 to be worth  $\Delta \log K$  *ca.* 1.9 overall, where **768** results preferentially the effect appears to be far more modest; OH---N bonding is known to be much stronger than NH---O – see Appendix 3). At present the only one of these factors to which we can attach even an approximate value is the *peri*-interaction **719**, a repulsive force worth  $\Delta \log K$  *ca.* -0.8.

The one *peri*-interaction apparently capable of really large effects is dipolar repulsion between NH and NH or NR, which on various lines of evidence (Appendix 3) we estimate as  $\Delta \log K$  *ca.* -2.5. Plausibly this dictates the tautomeric form of the fused uracils xanthine **785** (by NMR in D<sub>2</sub>O and DMSO),<sup>420c</sup> theophylline **786** (by X-ray diffraction),<sup>420d</sup> and (**787**, R = H or Me) by UV in water,<sup>421b</sup> and others such as **783** and **784**<sup>421a</sup> in which amide NH is also involved. Additionally, while its N(8)H-tautomer (as in **762C**), is that least favoured for 8-azaguanine,<sup>418a</sup> its crystalline hydrochloride exists as **767**,<sup>421c</sup> presumably for the same reason. The one glaring exception is **779**,<sup>421a</sup> for which we can offer no explanation.

In an experiment parallel to their work on **755** (section B.1.5), Dubois and co-workers<sup>422</sup> demonstrated that, while the imino-tautomer **788a** of **788** is dominant in non-polar solvents, the quinonoid tautomer **788b** is preferred in polar ones, by a factor of up to  $10^2$ . (Its isomer **789** exists only as shown<sup>2zz</sup>). In an otherwise similar molecule this appears to indicate that imidazole-type resonance is easier to overcome than that of pyrazole, a surprising conclusion until it is noted that a contiguous NN-type lone pair clash is generated in **755b** whereas in **788b** it is not. We estimate this effect in 5-membered rings as  $\Delta \log K_T$  *ca.* -0.8 (Appendix 3) which roughly fits the difference in  $K_T$  between **755** and **788**, but this may be fortuitous in view of the concomitant loss in resonance energy, which should be greater for an imidazole (**788**) than for a pyrazole (**755**). As for **755** we reiterate the point that imino-heterocycles are extremely disfavoured. A rather special case in which tautomeric balance is also a function of solvent polarity concerns the *N*-oxide **790**; here **790a** is the dominant form in organic solvents but **790b** in water.<sup>2y</sup>

#### B.1.8 C-Substitution in Symmetrical Azoles: Pyrazole, Imidazole, Benzimidazole, Benzotriazole, and 1(3)-*H* $\nu$ -Triazoles

Leaving aside pyrazole these azoles exhibit *N1/N3* tautomerism, *i.e.* **791** *vs.* **792**, and the results of this survey may be summarised simply. Electron acceptors *X=Y*, presumably *via* canonical forms such as **791z**, support tautomer **791**. With rather less consistency, perhaps because the charged canonical form **792z** is not so favourable, electron donors *Z* tend to support tautomer **792**. While these effects vary in magnitude with the ring system they all conform to this pattern, except that either preference is readily overturned by intramolecular forces such as hydrogen bonding.

**Table 52. Tautomerism of Imidazoles 793 in Aqueous Solution**<sup>a</sup>

R <sup>1</sup>	R <sup>2</sup>	log $K_T$	R <sup>1</sup>	R <sup>2</sup>	log $K_T$
NO <sub>2</sub>	H	2.68 <sup>b</sup> (2.5 - 2.7)	Ph	H	1.3 <sup>c</sup> (1.0 - 1.6)
Br	H	(1.8 - 2.2)	NO <sub>2</sub>	Cl	2.07
Cl	H	1.65 <sup>b</sup>			

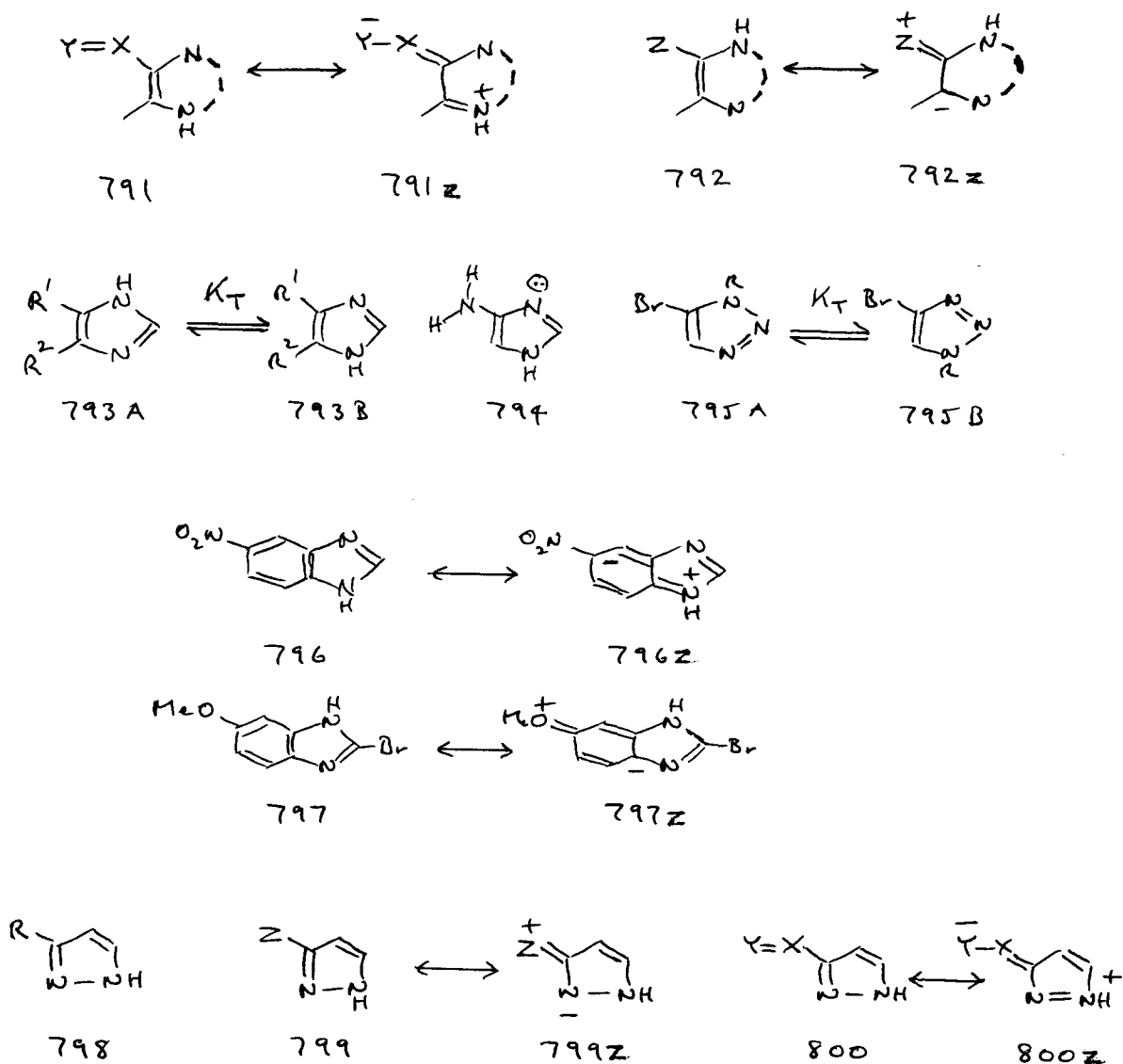
<sup>a</sup> Table 4-5, ref. 2. <sup>b</sup> Ref. 392. <sup>c</sup> Ref. 424.

The known information on imidazoles<sup>2aaa</sup> is summarised in Table 52. For (**793**,  $R^2 = H$ ) Charton<sup>423a</sup> proposed a relation for  $R^1$  of the form  $\log K_T = 3.2\sigma_m$ ; later, Elguero and Katritzky<sup>2aaa</sup> preferred  $\log K_T = 4\sigma_m$ . We find that the relationship  $\log K_T = 4\sigma_I$  fits the data for Cl, Br and  $NO_2$  almost exactly but underpredicts  $K_T$  for the remainder, suggesting dominance by the field effect but with some contribution from elsewhere for less polar substituents. (The result for **794**,<sup>2aaa</sup> which exists predominantly as shown, is probably influenced by hydrogen bonding). Elguero and co-workers<sup>424</sup> find for (**793**,  $R^1 = Ph$ ,  $R^2 = H$ ) that, while **793B** is favoured according to calculation in all media,  $K_T$  falls as solvent polarity decreases, presumably because this is the more polar tautomer.

The work of Ganellin and his collaborators on the activity of histamine (**793**,  $R^1 = CH_2CH_2NH_2$ ,  $R^2 = H$ ) is very relevant here in addition to its high biological importance. At pH 7.4 histamine exists in water predominantly as its monocation ( $R^1 = CH_2CH_2NH_3^+$ ) with the ring ‘ $\tau$ -tautomer’ corresponding to **793B** responsible for about 80% of the tautomeric mixture.<sup>423b</sup> By varying  $R^2$  it was possible to *calculate* the proportion of this tautomer, using the equation  $\log K_T = \rho_m(\sigma_m(R1) - \sigma_m(R2))$  with  $\sigma_m = 0.11$  for  $R^2 = CH_2CH_2NH_3^+$ ,  $\rho_m = 3.4$ , alongside corrections for the effect of  $R^2$  on histamine  $pK_a$ , and then show that this proportion tied in with the activity of each compound as an  $H_2$ -receptor agonist.<sup>423c</sup> Histamine free base should show much less tautomeric bias than its monocation, and this has been confirmed by calculation.<sup>423d</sup>

For the related  $\nu$ -triazole **795**, Barlin<sup>392</sup> established  $\log K_T$  1.2 from the  $pK_a$  values of the two  $N$ -methyl derivatives, in the same direction as for imidazole but a lesser effect, perhaps indicating an attenuated sensitivity. Given the predominance of the 2- $H$  tautomer however (section B.1.3), this result has limited importance.

The very little information on benzimidazole suggests the same electronic forces to be at work, but greatly attenuated. The 5- $NO_2$  tautomer **796** is favoured over its 6- $NO_2$  isomer, but by less than a factor of two, and even this small value is greater than for any other substituent.<sup>2bbb</sup> Similarly, **797** as written is marginally favoured in THF.<sup>2bbb</sup> These preferences can be rationalised in terms of the charged canonical forms **796z** and **797z**, but their consequences are slight. However, 4(7)-substitution may often have more effect through intramolecular interactions as in **770** (section B.1.7), and this is equally likely for benzotriazole, concerning which nothing is known.

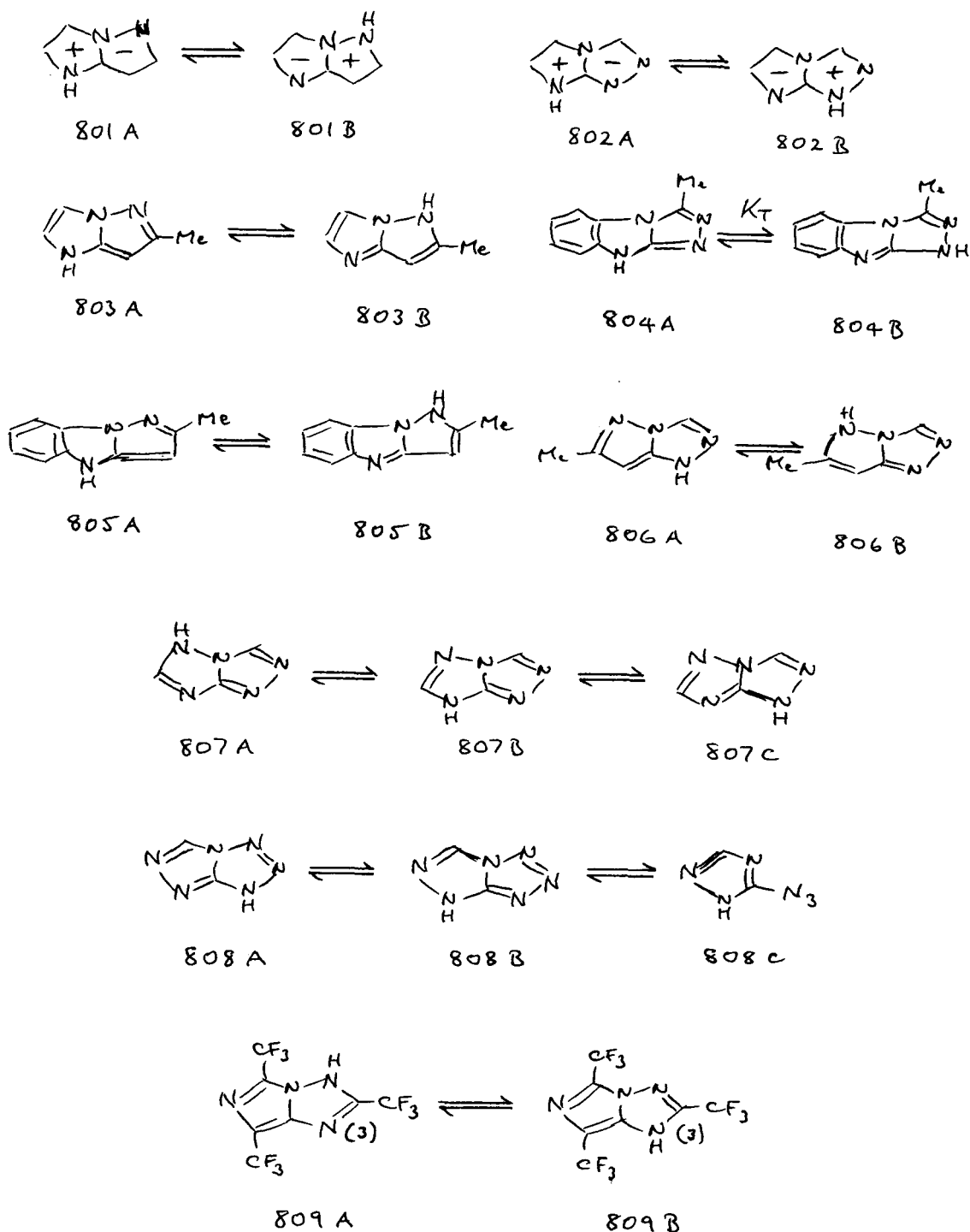


Pyrazoles have been discussed in section A.9.2, but a summary here will point up the differences. An apparent anomaly is that, in contrast to the above, *all* substituents appear to favour **798**. This may derive from the support for this tautomer conveyed by *both* the charged canonical forms, **799z** and **800z**, in sharp contrast to those for **791** vs. **792** and **796** vs. **797**. A gas-phase investigation by Elguero and co-workers<sup>425</sup> showed all substituents examined, ranging from  $NO_2$  ( $\log K_T$  0.51) to  $NH_2$  ( $\log K_T$  1.76), to support structure **798**, the lowest  $K_T$  values attaching to bland substituents, *e.g.*  $\log K_T$  0.30 and 0.36 for Me and Ph respectively (see section B.8.1 for a tentative quantification). The only exception was  $R = CO_2Et$  where intramolecular bonding to NH reverses the preference, as reported in section A.9.2 for **381**.<sup>2jj</sup> Nevertheless, perhaps excepting  $R = NH_2$  (and OMe: section A.9.2), these differences are not profound. As elsewhere in this section, it is easy to envisage their reversal under biological conditions.

### B.1.9 5,5-Ring Fusions ('Azapentalenes')

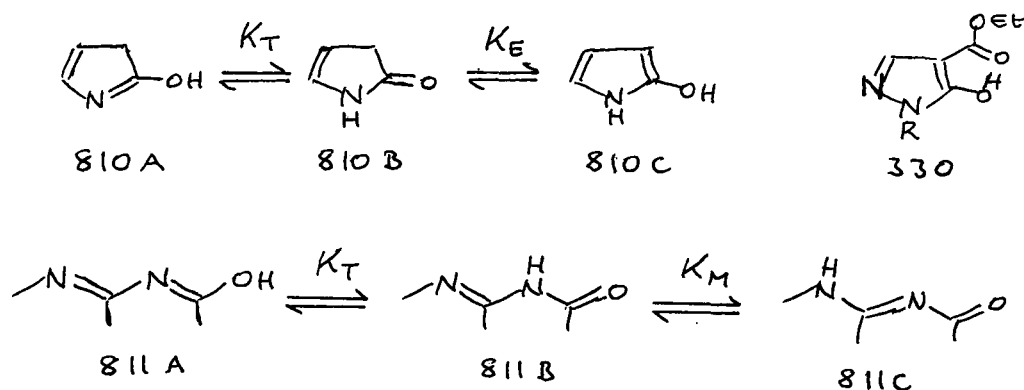
These compounds, many of which possess bridgehead nitrogen, are a test bed for theories concerning aromaticity and the influence on it of the interactions between contiguous nitrogen atoms. These matters have been discussed by Elguero who, in a seminal review,<sup>176</sup> set out four rules that define the criteria for tautomeric preference. Rule 3, concerning the avoidance of quinonoid forms, appears in section A.4.8; here the driving force can be so strong that actual loss of conjugation can be preferred (*cf.* compounds **228** and **229**). Two more, concerning dipolar (Rule 1) and lone pair (Rule 2) repulsion, form recurrent themes throughout this section and can also lead to loss of conjugation (*vide* **757** and **758**, section B.1.5) though, in the present context, they do not. The fourth Rule is specific to azapentalenes, and novel. It is suggested that the mobile proton will be found attached to whichever ring can better support a positive charge, which carries the implication that the other ring will be the more electron-deficient. Elguero illustrates Rule 4 with such schematic contrasts as those between **801A** and **801B** and between **802A** and **802B**. These translate as **803**, where **803A** is indeed the favoured tautomer,<sup>426</sup> and as **804**, whose behaviour is more equivocal. While Rules 2 and 4 point the same way for **803** they predict opposite tautomers for **804**;<sup>176</sup> in practice **804B**, which avoids a lone pair clash, is favoured in nonpolar solvents where this matters most (98% in dioxane),<sup>427</sup> but on UV evidence, **804A** is dominant in EtOH and water, and only 10% of EtOH in dioxane is required to effect this conversion.<sup>428</sup> Benzofusion of **803** results in **805** where, analogously, **805A** is overwhelmingly preferred.<sup>427</sup> In all these cases, Rule 4 effectively amounts to the choice of imidazole rather than triazole to carry the nominal positive charge, which is intuitively reasonable but does not allow prediction for combinations from which the imidazole unit is absent. Often, simple criteria work; **806A** in which lone pair *and* dipolar clashes are avoided is overwhelmingly preferred over **806B**,<sup>426</sup> while of its three possible tautomers, **807** exists as **807C**.<sup>429</sup> It should be noted that azapentalenes, if sufficiently packed with nitrogen, may behave in unusual ways; **808A**, instead of switching to its tautomer **808B**, dissociates reversibly to the azide **808C**<sup>430</sup> – a form of ring-chain tautomerism (see Introduction), so excluded from detailed consideration here. An examination of the repulsive forces that underlie these phenomena appears in sections B.8.9 and Appendix 3.

A potential way of combining and quantifying all but Rule 3, lacking only in comprehensive coverage of the data required to do so, is sketched in section C.35.



Middleton and Metzger<sup>431</sup> report an apparent exception to Elguero's Rules: **809** exists in acetone as **809A** not **809B**. The evidence is based on the *absence* of proton to nitrogen coupling in material labelled with N-15 at N(3), but **809** is a strong acid ( $pK_a \sim 2$ ) and rapid proton exchange *via* the anion is likely. In addition, its UV spectrum in EtOH appears to be that of the anion, while that of the 3-methylated fixed tautomer looks like **809** itself as the neutral form. We believe the authors' conclusions to be unsound.

## B.2 Amides, Imides, Ureas, and Related Structures



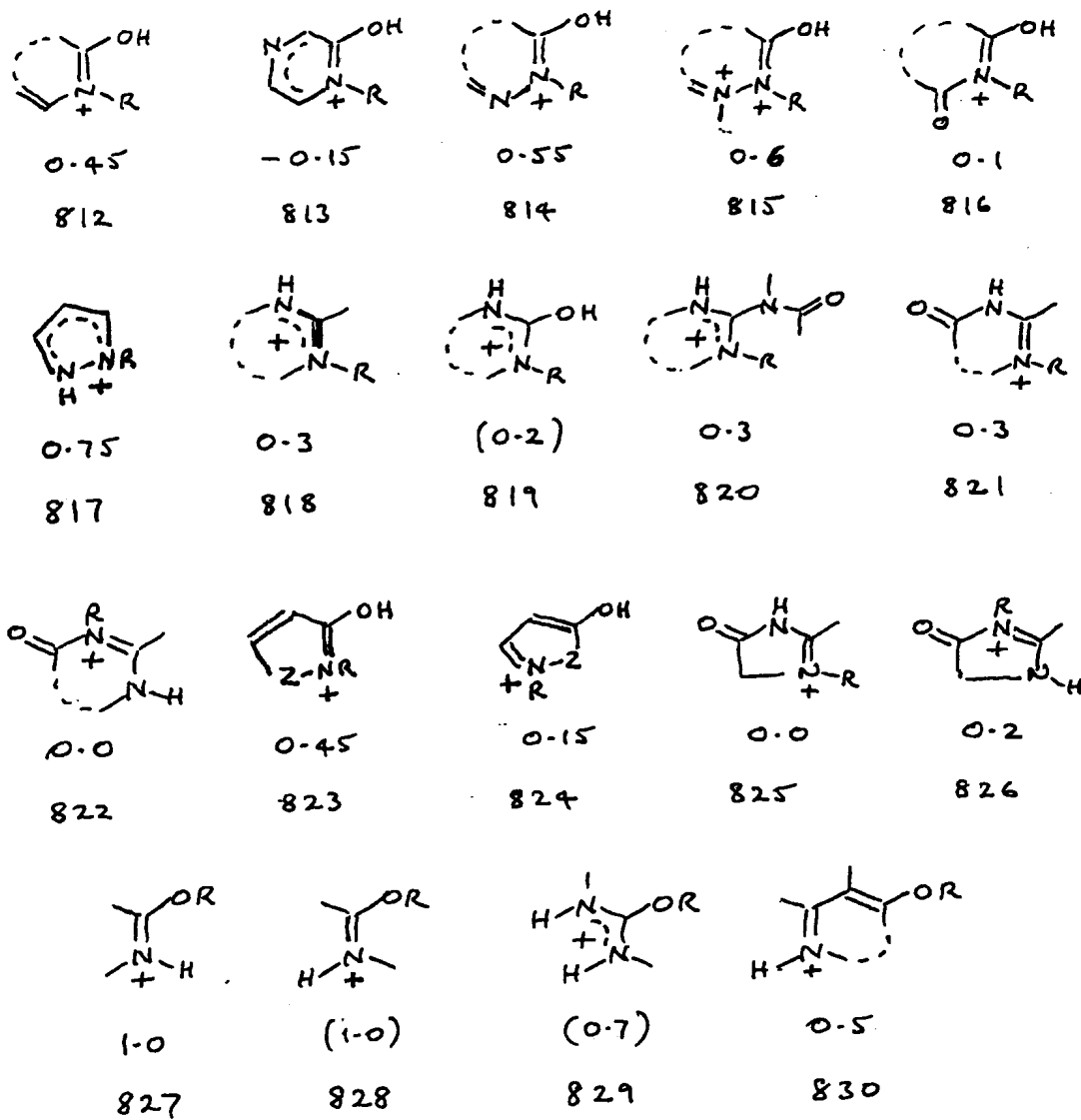
Scheme 29

This section comprises those structures in which C=O and NH are to be found contiguous with themselves and/or one another: amides, imides, ureas, and their extended analogues. It is confined to amide-iminol tautomerism (*e.g.* **810A**  $\rightleftharpoons$  **810B**, Scheme 29) and consequently excludes two other sorts. The first is 'C-type' tautomerism (*e.g.* **810B**  $\rightleftharpoons$  **810C**) for which the driving force is aromatisation (section A.2.7), augmented in **330** for example (section A.6.6) by electronegative substitution and the formation of an intramolecular hydrogen bond. No such driving force operates to favour **810A** and its enolisation in this sense is unknown (see section B.2.3 below). The second concerns structures of type **811**, some cyclic some not, in which a second potential NH stands in a 1,3 relation to the first. Such compounds whether aromatised or not are basically acylamidines and most of the interest in practice attaches to tautomerism involving solely their nitrogen atoms; iminol formation **811A**, while sometimes detected, is generally much less important. These compounds, which include for example the pyrimidones, are the subject of section B.5. Here we appropriate  $K_M$ , in 'C-type' tautomerism used to designate enamine formation from an imine (section A.4),<sup>93</sup> in the sense of Scheme 29. For both **810** and **811**,  $K_T$  is defined in the direction of amide formation from the iminol. Additionally, in sections B.2.10 and subsequently we use the composite term  $K_M K_T$  to designate the sequence  $N=CC=C-OH \rightarrow NHC=CC=O$ , the vinylogous equivalent to  $K_T$  for an amide and one that frequently occurs when 'C-type' and 'N-type' processes overlap.

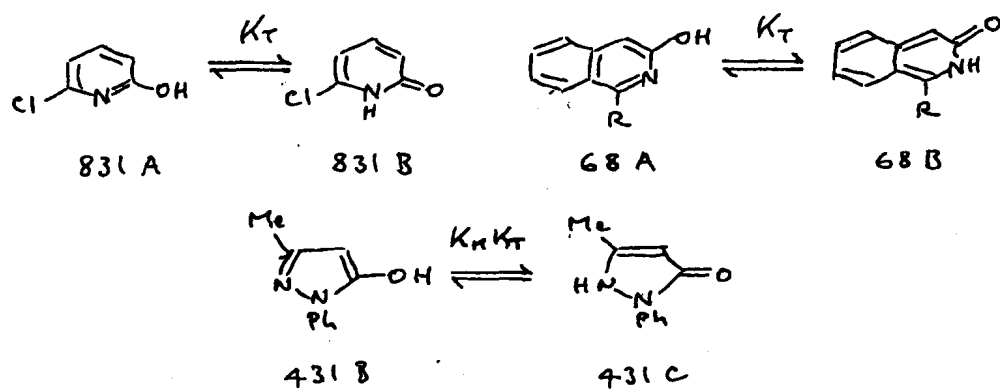
Because amides and iminols are both bases this is prime territory for use of the 'basicity method'<sup>5</sup> and, unusually, most results have been obtained for aqueous solution. Solvent studies are illuminating but much less common than in 'C-type' tautomerism, where results for aqueous solution are correspondingly fewer. These two aspects of the subject are explored first.

### B.2.1 Correction Factors for the ‘Basicity Method’

While only a single term in  $\Delta(\text{NR})$  and one in  $\Delta(\text{OR})$  is required to handle 4-pyridone and related compounds (section A.10.3), a multiplicity of correction factors is needed here. This comes about chiefly because the nature of X in CONHX helps to determine  $\Delta(\text{NR})$ , and furthermore, the contiguity of NH with C=O makes all such factors greater (they may simply be less visible in the former, more extended category). Scheme 30 sets out our conclusions, the detailed justification for which is reserved to Appendix 1. These values are given to the nearest 0.05 log unit and the derived  $\log K_T$  values, which appear later, to the nearest 0.1. Charges are generally shown, for **812** - **826**, as attached to the nitrogen atom bearing the substituent R (alkyl or hydrogen), to emphasise that this is where differential solvation has its impact. The strength of the evidence is very variable: whereas **812** [ $\Delta(\text{NR}) 0.453 \pm 0.154$ ,  $n = 19$ ] is well documented most are fragmentary, depending on a handful of examples. The complementary  $\Delta(\text{OR})$  for **827** has to be much more provisional, since there is so little evidence on compounds for which a significant proportion ( $\geq 10\%$ ) of the iminol tautomer can be quantified by spectroscopic means. Nevertheless a value of  $\Delta(\text{OR})$  1.0, unchanged from Spinner’s 1971 estimate,<sup>20</sup> appears to be that which best fits the available evidence (Appendix 1). It is not known whether the same correction applies to trans-amides **828** but there is no good reason to suppose otherwise, since the dominant factor in  $\Delta(\text{OR})$  is presumably the electronic ‘pull’ of  $=\text{N}^+$  on OR, and it is unlikely that this will be much affected by the geometry of bland substituents trigonally disposed at nitrogen. We shall therefore assume the same  $\Delta(\text{OR})$  value for **828** (*i.e.* trans-amides) as for **827** (lactams), and we also find that 5- and 6-membered oxoheterocycles require the same correction. The appropriate value of  $\Delta(\text{OR})$  for ureas **829** is presently unknown. It is plausible that the distribution of charge between two nitrogen donors will reduce their overall ‘electronic pull,’ in which case  $\Delta(\text{OR})$  should be less than for an amide, in much the way it is attenuated in **830** (*e.g.* in 4-pyridones) relative to **827**. We arbitrarily assign  $\Delta(\text{OR})$  0.7 to **829**, as representing, for two NH donors, a twofold attenuation in charge density on oxygen relative to **827**. It is equally plausible that the electron pull from an exceptionally electronegative nitrogen atom might enhance  $\Delta(\text{OR})$ , and while we have encountered no clear evidence for this —  $\Delta(\text{NR})$  for **812** which should also be affected does not appear to depend on basicity — there is one possible exception<sup>22</sup> involving  $\Delta(\text{NR})$  as well which we mention later (section B.2.10).



Scheme 30



Most variation lies in  $\Delta(\text{NR})$ . It is unsurprising that this should be greater for **814** and **815** than for **812**, since both  $\alpha$ -substituents will enhance the electronegativity of NR, but very surprising that this correction should actually be *negative* for **813**. However the scope of this correction is necessarily limited, while the same effect is found for the corresponding thiones (section B.3.1). Nevertheless there is some cause for concern; *vide* discussion in section B.8.19 and Appendix 1. It is also unclear why  $\Delta(\text{NR})$  should be so slight for **816**, unless because NH here is scarcely accessible to solvent. While they do not strictly belong in this section, results applicable to amidines and their acyl derivatives are also included for purposes of comparison. Here charge-spreading and the consequent lowering of charge density at nitrogen sharply lowers  $\Delta(\text{NR})$ ; it is 0.3 for simple amidines **818**, unchanged in **820**, and perhaps a little lower in ureas **819** (*cf.* **829** above). Six-membered cyclic acylamidines show the usual amidine correction in **821** but nil in **822**; presumably the latter differs so sharply from **812** because, here, most of the positive charge is on the nitrogen atom remote from carbonyl. It is therefore a puzzle that this position reverses for **825** and **826**; this may be some quirk of geometry connected with the difference in ring size, or due in some way to lack of aromatisation. Nevertheless, the general pattern of these results (Appendix 1) suggests that  $\Delta(\text{NR})$  is largely a function of the group NHX and is affected only marginally by the presence of OH. On this basis **823** is apparently anomalous by the side of **817** but the latter, with dipolar repulsion between adjacent NH's, will require more solvation, so accounting for the difference. A fortuitous equivalence to **812** results. By contrast  $\Delta(\text{NR})$  for **824** is greater than for the 4-pyridones, whose charge distribution it resembles, and for which  $\Delta(\text{NR}) = 0.00$  (section A.10.2). Here enhancement is presumably caused by a dipolar clash with the adjacent Z-atom, much as for **815** relative to **812**. There may be other minor variants in  $\Delta(\text{NR})$  which, through a paucity of examples, the present investigation has failed to pick up.

### B.2.2 Solvent Studies

There has been little systematic work in this area. Beak and Covington<sup>379</sup> examined **831** in a variety of solvents and obtained a triparametric equation in  $\alpha$ ,  $\beta$  and the Kirkwood function. We have re-derived their equation, which appears below as (lxiii) with  $\pi^*$  replacing  $(\epsilon - 1)/(2\epsilon + 1)$  and with more up-to-date values<sup>12</sup> of  $\alpha$  and  $\beta$ ; for full discussion, see Appendix 2. Smith and co-workers<sup>84</sup> have published solvent data on (**68**, R = H) from which eqn. (lxiv) can be derived. Unfortunately, this is the sum total of systematic information. In both cases, a positive term in  $\alpha$  and a negative term

$$\log K_T = -1.21(0.12) + 0.22(0.22) \pi^* + 1.53(0.15) \alpha - 0.88(0.15) \beta \quad (\text{lxiii})$$

$$(n = 16 \quad r^2 = 0.89 \quad s = 0.17 \quad F = 33)$$

$$\log K_T = -2.36(0.22) + 1.56(0.40) \pi^* + 2.22(0.22) \alpha - 0.70(0.26) \beta \quad (\text{lxiv})$$

$$(n = 6 \quad r^2 = 0.983 \quad s = 0.14 \quad F = 39)$$

in  $\beta$  is expected and found; it is also reasonable that the coefficient of  $\alpha$  should be greater for **68** than for **831**, since Cl is likely to diminish the proton acceptor ability of carbonyl. However, it is probable that *both* terms in  $\pi^*$  are atypical, being exaggerated in **68** by the quinonoid nature of the oxo-tautomer and suppressed in **831** by the opposed dipole of C-Cl. These points are emphasised by the severe discrepancies which appear in Table 53. Here we attempt to predict  $\Delta \log K_T$  for aqueous solution, using these rival equations, relative to the values calculated for a number of common probe solvents, in principle a useful exercise if data for water are lacking but some for organic solvents are available and the predictions are consistent. Plainly, they are not; both compounds show the expected rise in  $K_T$  with increasing solvent polarity, but the response of **831** is much the shallower and there are qualitative differences also. We also show, on the second line of Table 53, a much more fragmentary ‘consensus list’ gleaned from the papers of Spinner and Yeoh<sup>20,432</sup> which may well be more representative than either equation. Some roundabout evidence on this point comes from gas phase results. The iminol tautomer of 2-pyridone is slightly favoured,<sup>433</sup>  $\log K_T$  -0.4, a value backed by high-level (6-31G\*\*//6-31G\*\*) MO calculation.<sup>434</sup> Relative to  $\log K_T$  3.5 for water (section B.2.4), this results in  $\Delta$

**Table 53. Solvent Dependence of Tautomerism for 2-Pyridones** <sup>a</sup>

Correction ( $\Delta \log K_T$ ) to aqueous solution from data in:									
Cpd.	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane	Vacuum
<b>831</b>	0.7	1.0	2.1	0.9	1.9	1.6	1.6	1.7	2.5
<i>b</i>		1.4		1.6	2.7				
<b>68</b>	1.5	1.9	3.0	2.1	3.4	3.2	3.6	4.1	5.8
<b>431</b> <sup>c</sup>	1.1	1.5	2.1	0.9	2.0	1.6	1.7	2.1	3.0

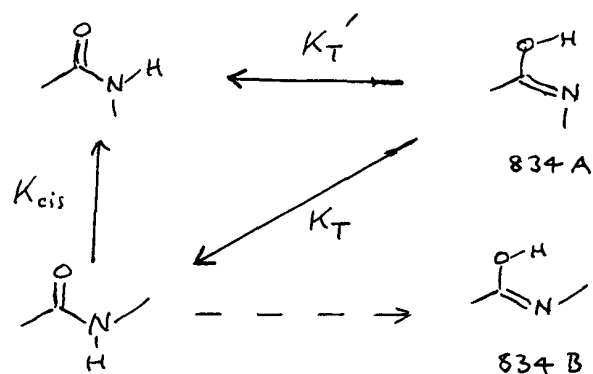
<sup>a</sup> Relative to aqueous values, using eqns. (lxiii), (lxiv) and (xix) for **831**, (**68**, R = H) and **431** respectively. <sup>b</sup> Experimental ‘consensus’ values; see the text. <sup>c</sup> For  $\Delta \log K_M K_T$  (see section B.2.10).

$\log K_T$  3.9, about half way between the (calculated) vacuum  $\Delta \log K_T$  values for **831** and **68** given in Table 53. The very large  $\pi^*$  term for **68**, probably as we note above exaggerated by its quinonoid structure, contributes  $\Delta \log K_T$  *ca.* 3.6 to its total shift; just half this quantity, combined with similar coefficients for  $\alpha$  and  $\beta$ , would reproduce the experimental results for 2-pyridone. In addition we add, for purposes of comparison, parallel data for the vinylogous amide **431** (Table 32, section A.10.2). The solvent dependence of this compound is different again, but more resembles **831** (see further discussion in section B.2.10). Even for **831** and **431** it is notable how even the most polar solvents fall well short of water in their support for the oxo-tautomer. In view of its popularity as an NMR solvent it should particularly be noted how misleading is DMSO in this respect, and other dipolar aprotic solvents are not much better.

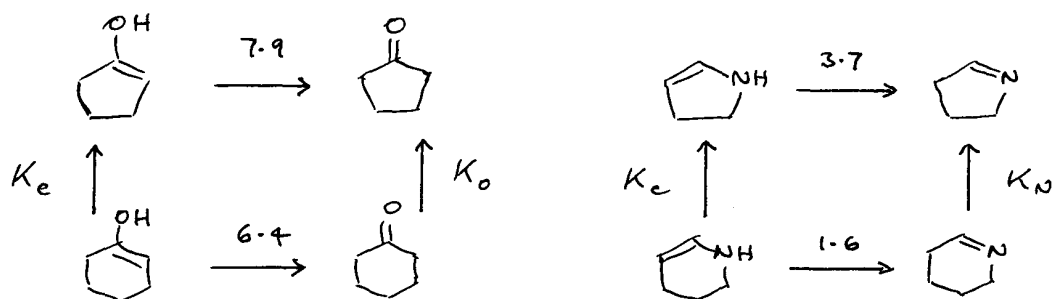
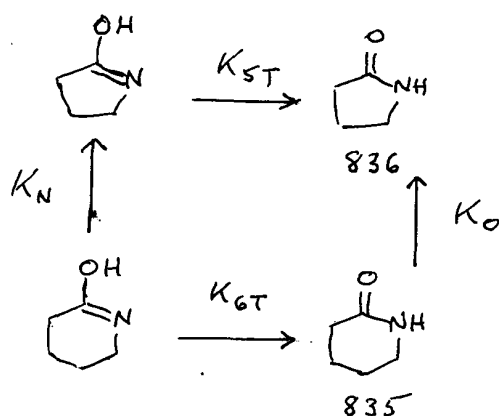
No aqueous  $K_T$  value is known for (**68**, R = H) but eqn. (lxiv) extrapolates to  $\log K_T$  1.66, and this fits reasonably into the pattern shown by other oxoheterocycles (section B.2.5). Disturbingly however, eqn. (lxiii) predicts a value for **831**,  $\log K_T$  0.47, substantially below that observed. (Note that we have followed our usual practice in leaving the point for water out of eqn. lxiii). However, since the 'basicity method' and direct observation by UV give different values for  $K_T$ , and the latter is peculiar in being almost identical with that for 6-methoxypyrid-2-one despite the different electronic nature of the substituent (section B.2.4), there is reason to suspect **831** of being a 'problem compound.' We cannot resolve this discrepancy. While paying tribute to this painstaking early work we can only observe that, as so often, more data are badly needed.

### B.2.3 Open-Chain and Alicyclic Amides (CONH)

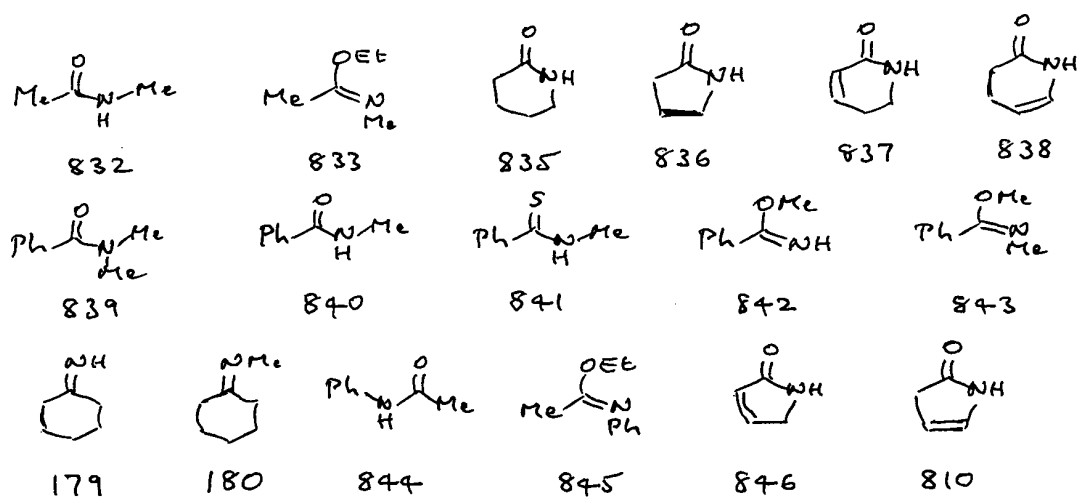
Information on this subject is sparse but, fortunately, of high quality. From  $pK_a$  values of -0.56 for **832**<sup>435</sup> and of 7.5 for **833**<sup>436</sup> then, applying correction **828** (Scheme 30), we obtain  $\log K_T$  9.1. We now attempt to estimate  $\log K_T$  for the corresponding *cis*-amide. Scheme 31 sets out the relevant equilibria. By the Principle of Least Motion<sup>437</sup> *cis*- and *trans*-amides must give, in the first instance, the iminols **834A** and **834B** respectively. However, as discussed in section A.10.5, the *cis*-iminol **834A** which is obligatory for small-ring lactams is overwhelmingly preferred, relative to **834B** and according to calculation (at the 6-31G level),<sup>287,438</sup> by > 10 kcal mol.<sup>-1</sup> Given  $\log K_{cis}$  -1.5 in water for the representative amide **832** (Table 24, section A.6.2) we have  $\log K'$  7.6. So far as we are aware, no such estimate has previously been attempted.



Scheme 31



Scheme 32



If we suppose  $\log K_T$  7.6 to be a good approximation to  $\log K_{6T}$  for piperidinone **835**, we may now attempt to estimate  $K_{5T}$  for pyrrolidinone **836** *via* the isodesmic processes of Scheme 32. For this we need data from cyclic ketones and endo-imines to provide  $K_O$  and  $K_N$  respectively. Data for ketones are given in section A.1.2 and supply  $\log K_C = -0.6$  and  $\log K_O = 0.9$ . The latter tautomeric processes come from section A.4.1 and, using the above value for  $\log K_C$ , give  $\log K_N = 1.5$ . From  $\log K_{6T}$ ,  $\log K_N$  and  $\log K_O$ , we now have  $\log K_{5T} = 7.0$ . The only assumptions involved in this derivation concern the very small bond length and angle changes as between the rival amides and iminols, in so far as these may not be entirely reflected by the various model processes. It is reasonable that the difference in  $K_T$  between **835** and **836**, while perceptible, should be quite small.

We may also attempt to estimate  $K_T$  for two sorts of unsaturated cyclic amide, **837** and **838**. In view of the close resemblance between phenyl and vinyl with respect to all  $\sigma$ -values (Table 2), it is legitimate to substitute the former. (This same equivalence, in the reverse direction, was commonly used in MO calculations till quite recently as a way of saving computer space). As a preliminary model for **837**, **839** is unsatisfactory since probably non-planar so we require an estimate for **840**. We obtain this from  $pK_a$  -2.61 for **841**<sup>150</sup> and the assumption that  $\Delta pK_a$  for  $\text{MeCONH}_2$  (-0.66)<sup>435</sup> and  $\text{MeCSNH}_2$  (-1.76)<sup>440</sup> may be transposed to give  $pK_a$  *ca* -1.5 for **840**. This is, in fact, not much different from  $pK_a$  -1.62 for **839**.<sup>441</sup> For the iminol we start from  $pK_a$  5.8 for **842**<sup>442</sup> and correct to  $pK_a$  6.1 for **843** by applying an increment of  $\Delta pK_a$  0.3 derived from the *exo*-iminol **179** and **180** (section A.4.1). Adding  $\Delta(\text{OR})$  this becomes  $pK_a$  7.1 for the iminol itself, leading to  $\log K_T$  8.6 which after correction for  $\log K_{\text{cis}}$  -1.5 becomes  $\log K_T$  7.1 for **837**, a little below the postulated value for **835** as is reasonable. More straightforwardly, from  $pK_a$  -1.42 for **844** and  $pK_a$  4.63 for **845**<sup>444</sup> and incorporating the  $\Delta(\text{OR})$  **828**,  $\log K_T$  7.0 results, leading after use of  $\log K_{\text{cis}}$  to  $\log K_T$  5.5 for **838**.

It is of interest to explore how nearly the  $\Delta \log K_T$  values for **837** and **838**, relative to **835**, sum to give the actual  $\log K_T$  value of 2-pyridone, which nominally contains both double bonds. The resulting estimate for  $\log K_T$  of 5.0 as compared with the actual value of 3.5 demonstrates, perhaps surprisingly, that most of this fall can be accounted for without invoking 'aromaticity' at all. For this reason, we do not here pursue the much more complex treatment of Katritzky and co-workers<sup>150</sup> which is largely aimed at unravelling its contribution (contrast the case of 4-pyridone, section A.10.6).

If we assume a constant value for  $\log K_{\text{cis}}$  we may also estimate  $\log K_{\text{T}}$  for **846** and **810** by a similar isodesmic approach to that of Scheme 32. The resulting values are 6.5 and 4.9 respectively. The latter has no relevance to the formation of **810C** (Scheme 29) which is driven by aromaticity, but will adequately explain why **810A** has never been observed. The values of  $\log K_{\text{T}}$  derived here appear in Table 54.

**Table 54. Estimated Values of  $\log K_{\text{T}}$  for Open-Chain and Alicyclic Amides <sup>a</sup>**

$\log K_{\text{T}}$		$\log K_{\text{T}}$		$\log K_{\text{T}}$	
<b>832</b>	9.1	<b>837</b>	7.1	<b>846</b>	6.5
<b>835</b>	7.6	<b>838</b>	5.5	<b>810</b>	4.9
<b>836</b>	7.0				

<sup>a</sup> For derivation see text.

#### B.2.4 Aromatic 6-Membered Ring Amides: 2-Pyridones

All available data for the  $\text{p}K_{\text{a}}$  values of monosubstituted 2-pyridones **847B** and 2-methoxypyridines **847C**, mostly due to Spinner,<sup>445</sup> are assembled in Table 55. With four distinct substituent positions in 2-pyridone as against only two in 4-pyridone these data are even less adequate than formerly (section A.10.6) to the task of discerning quantitative trends. We set out as eqns. (lxv) - (lxviii) the only respectable correlations we can find. With the addition of  $\Delta(\text{OR})$ , subtraction of eqn. (lxvi) from eqn. (lxv) should give  $\log K_{\text{T}(5)}$ , but in fact eqn. (lxviii) results from a direct correlation for  $\log K_{\text{T}}$  into which  $\Delta(\text{OR})$  has been incorporated, and a further slight improvement in fit is obtained by its modification to eqn. (lxix) which has been adjusted to possess the correct intercept term. In the same way, very rough correlations for  $\text{p}K_{\text{NH}(6)}$  and  $\text{p}K_{\text{OMe}(6)}$  have been used to derive an equation for  $\log K_{\text{T}(6)}$  which, on similar adjustment, gives eqn. (lxx). The use of  $\sigma_{\text{I}}$  to correlate  $\text{R}^6$  in **847C** only, with  $\sigma_{\text{m}}$  elsewhere, is consistent with its parallel use in 4-pyridones (section A.10.6) and for  $\alpha$ -substituted pyridines generally.<sup>259</sup>

**Table 55.  $pK_a$  and  $\log K_T$  Values for Substituted 2-Pyridones <sup>a</sup>**

$R^3$	$R^4$	$R^5$	$R^6$	$pK_a$ (847B)	$pK_a$ (847C)	$\log K_T$ : estd. <sup>b</sup>	calc.	eqn.
H	H	H	H	0.75 <sup>c</sup>	3.28 <sup>c</sup>	3.5		
Me	H	H	H	0.20				
H	Me	H	H	1.14				
H	H	Me	H	1.13	3.73	3.6	3.7	(lxix)
H	H	H	Me	1.12			3.6	(lxx)
H	H	H	OMe	1.14 <sup>d,e</sup>	1.60	1.46	1.4	(lxx)
OH	H	H	H	0.22	2.10	2.9		
H	H	H	OH	1.43 <sup>d,f</sup>		1.3 <sup>d,g</sup>	2.0	(lxx)
Br	H	H	H	-2.15				
H	H	Br	H	-0.06	1.14	2.2	2.5	(lxix)
Br	H	Br	H	-2.45	-1.50	1.95		
Cl	H	H	H	-2.03				
H	H	Cl	H	-0.07	1.18	2.25	2.4	(lxix)
Cl	H	Cl	H	-2.40	-1.40	2.1		
H	H	H	Cl	-0.18 <sup>e,h</sup>	-0.13 <sup>h</sup>	1.05	0.9	(lxx)
						1.3 <sup>g,h</sup>		
H	H	H	I	0.00	1.51	2.6	2.5	(lxix)
NO <sub>2</sub>	H	H	H	-4.00				
H	H	NO <sub>2</sub>	H	-2.45 <sup>i</sup>			1.3	(lxix)
H	NH <sub>2</sub>	H	H	2.65 <sup>j</sup>	7.05 <sup>j</sup>	5.4		
H	H	H	NH <sub>2</sub>	2.32 <sup>j</sup>	4.64 <sup>j</sup>	3.3 <sup>m</sup>	2.8	(lxx)

<sup>a</sup>  $pK_a$  values from ref. 445 unless otherwise stated. <sup>b</sup> By use of the 'basicity method' (see the text) adjusted by using  $\Delta(OR) = 1.0$  unless otherwise indicated. <sup>c</sup> Ref. 4. <sup>d</sup> Ref. 210.

<sup>e</sup>  $pK_a$  of dominant NH component. <sup>f</sup> Global  $pK_a$  adjusted for minor components (see the text).

<sup>g</sup> By direct observation of UV spectrum. <sup>h</sup> Ref. 294. <sup>i</sup> Outlier, omitted from eqn. (lxvi); see the text. <sup>j</sup> Ref. 293. <sup>k</sup> Not used in the derivation of eqn. (lxx).

$$\begin{aligned} \text{p}K_{\text{OMe}(5)} &= 3.3(0.1) - 6.1(0.3) \sigma_{\text{m}} & (\text{lxv}) \\ (n = 4 \quad r^2 = 0.99 \quad s = 0.12 \quad F = 393) \end{aligned}$$

$$\begin{aligned} \text{p}K_{\text{NH}(5)} &= 0.9(0.1) - 2.7(0.3) \sigma_{\text{m}} & (\text{lxvi}) \\ (n = 4 \quad r^2 = 0.97 \quad s = 0.12 \quad F = 78) \end{aligned}$$

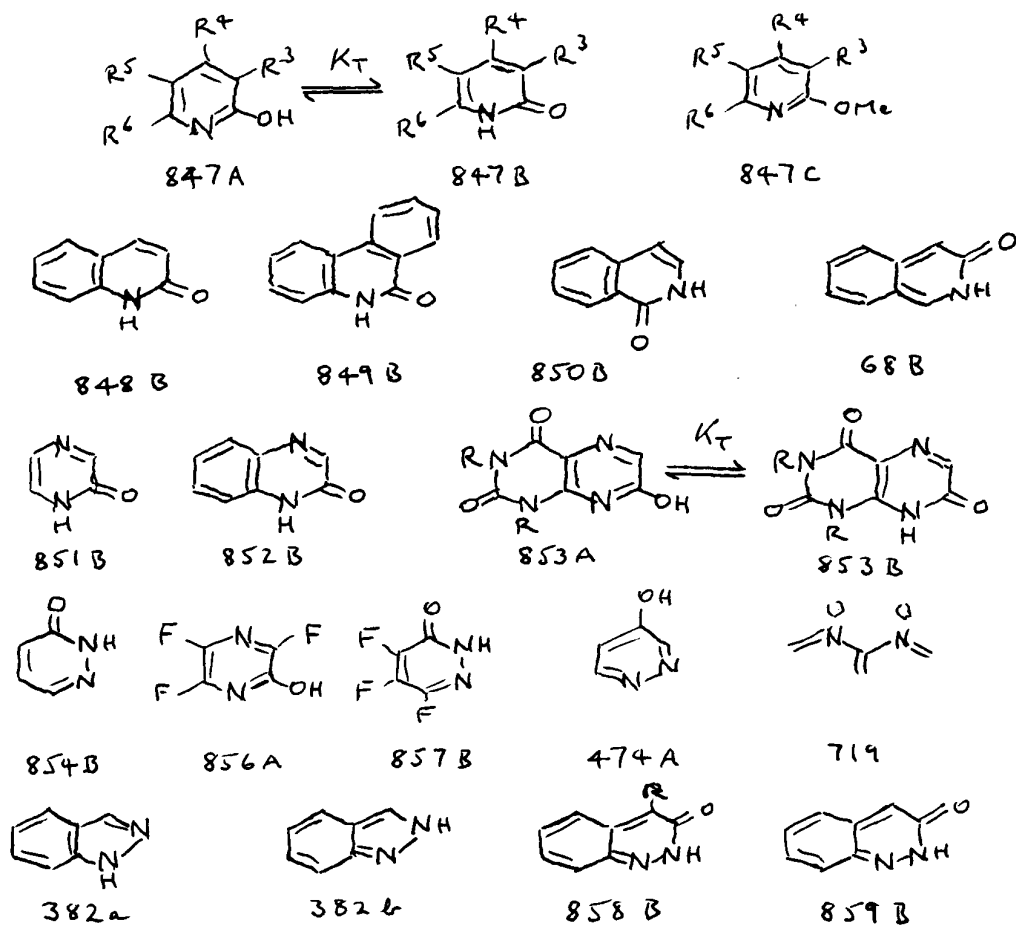
$$\begin{aligned} \text{p}K_{\text{NH}(3)} &= 0.4(0.3) - 6.1(0.8) \sigma_{\text{m}} & (\text{lxvii}) \\ (n = 6 \quad r^2 = 0.94 \quad s = 0.52 \quad F = 58) \end{aligned}$$

$$\begin{aligned} \log K_{\text{T}(5)} &= 3.45(0.07) - 3.44(0.27) \sigma_{\text{m}} & (\text{lxviii}) \\ (n = 4 \quad r^2 = 0.988 \quad s = 0.10 \quad F = 167) \end{aligned}$$

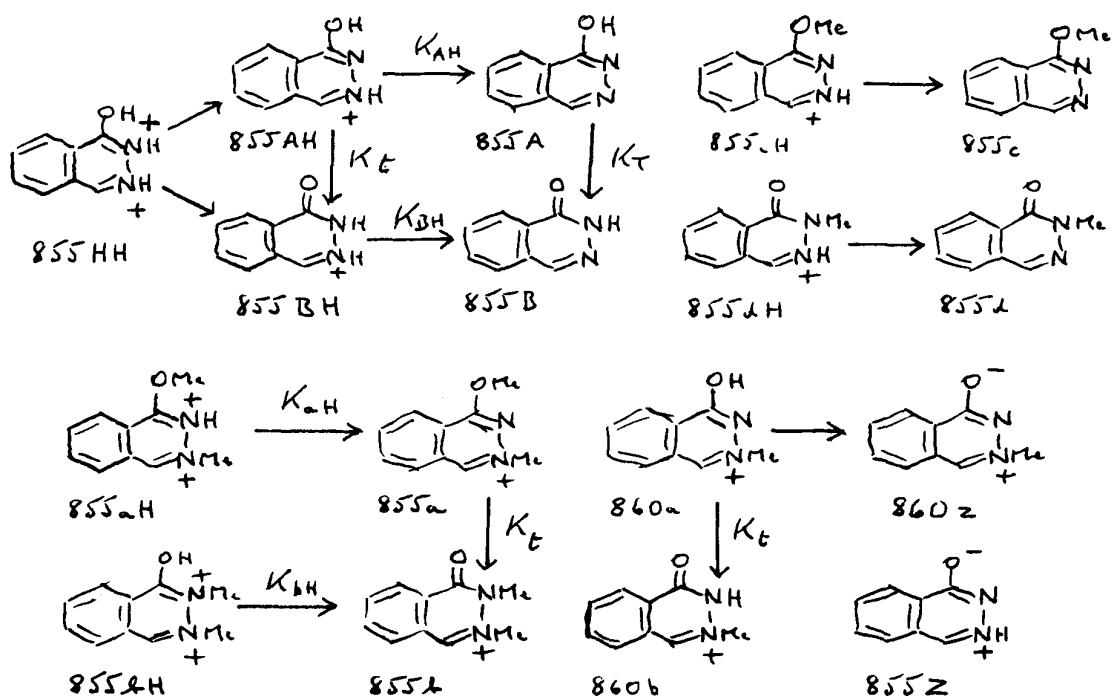
$$\log K_{\text{T}(5)} = 3.5 - 3 \sigma_{\text{m}} \quad (\text{lxix})$$

$$\log K_{\text{T}(6)} = 3.5 + 3 \sigma_{\text{m}} - 8 \sigma_{\text{I}} \quad (\text{lxx})$$

The predictions of eqns. (lxix) and (lxx) are compared against our estimates in Table 55. Those for  $\text{R}^5$  are generally satisfactory, though the narrow range of substituents must counsel caution. In addition,  $\text{p}K_{\text{NH}}$  for 5- $\text{NO}_2$  has had to be treated as an outlier since much lower than eqn. (lxvi) would predict. Equation (lxx) possesses no statistical backing and is simply the best we can find given the twin assumptions that (a) its iminol should follow a  $\sigma_{\text{I}}$  relation as for 2-substituted 4-pyridones (section A.10.7), (b)  $\sigma_{\text{m}}$  with  $\rho_{\text{m}} \sim 3$  is expected for the amide (see section C.21). Its predictions fit for  $\text{R}^6 = \text{OMe}$  but underpredict  $\text{R}^6 = \text{OH}$  where  $K_{\text{T}}$  was obtained by direct observation. Substituents that correspond to the lyate ion are notorious for bad behaviour<sup>259</sup> – that is, their  $\sigma$ -values can be unreliable – which may help to explain this discrepancy. More serious is the clash between direct observation of  $K_{\text{T}}$  and that obtained by the ‘basicity method’ for  $\text{R}^6 = \text{Cl}$  where, interestingly, eqn. (lxx) better supports the latter. We have noted in section B.2.2 that extrapolation from organic solvents to water *via* the LSER eqn. (lxiii), for **831**, quite seriously underpredicts the observed  $K_{\text{T}}$ . These problems are presently unresolved. We observe in section A.10.6 that the simplified  $\text{p}K_{\text{a}}$  equations we are forced to use through paucity of data are inapplicable, for substituents adjacent to ring nitrogen, when their  $\sigma$ -values are dominated by  $\sigma_{\text{R}}$  and an example is provided by  $K_{\text{T}}$  for  $\text{R}^6 = \text{NH}_2$ , which is badly fit by eqn. (lxx). Alkyl groups however, which are donors but not  $\pi$ -donors, appear to provide an exception, though one difficult to quantify; while Spinner and Yeoh<sup>20</sup> have suggested that a constant factor,  $\Delta \log K_{\text{T}}$  *ca.* 0.5, can be used for the effect of two alkyl substituents at any position in *any* pyridine, a rather smaller factor is suggested by the data of Table 55. At present we have to leave this matter *sub judice*.



Scheme 33



Scheme 34

Since use of  $\Sigma\sigma_m$  for  $R^3 = R^5 = \text{Br}$  and  $R^3 = R^5 = \text{Cl}$  gives points that lie precisely on the regression line for eqn. (lxv), we may postulate that  $R^3$  and  $R^5$  for  $pK_{\text{OMe}}$  will obey the same equation. This is plausible, since these positions are symmetrically placed with respect to the site of protonation in **847A/C**. (That is no longer true for **847B**). If so, eqns. (lxv) and (lxvii) should in principle yield  $\log K_T$  for  $R^3$ . In fact there are too few data points for this to be possible, but the near-equivalence of  $\rho_m$  for eqns. (lxv) and (lxvii) strongly suggests that the slope of  $\log K_{T(3)}$  must be small. Supporting evidence comes from the sharp contrast between  $pK_{\text{NH}}$  for 3-Br and 3-Cl *vs.* 5-Br and 5-Cl,  $\Delta pK_a$  relative to 2-pyridone itself being much less in the former series. There is virtually no information on  $R^4$  at all.

Leaving aside  $R^4$  concerning which nothing can be said, we may attempt an overview. Even  $\text{NO}_2$  at  $R^5$  should produce no appreciable fraction of the pyridinol, though caution is required in the light of  $pK_{\text{NH}}$  (see above). It seems likely that the 3-position will be still less sensitive. Prediction for  $R^6$  is more complicated since two  $\sigma$ -values have to be considered, but eqn. (lxx) predicts the tautomers to be roughly in balance for  $R^6 = \text{F}$  or  $\text{NO}_2$ , with **847B** still narrowly favoured by CN and  $\text{SO}_2\text{Me}$  and dominant elsewhere. Qualitatively, 6-substituted 2-pyridones should be less susceptible than the equivalent 4-pyridones (Table 37), chiefly because the term in  $\sigma_I$  appears to be smaller [compare equations (xxx) and (lxx)]. It should be remembered that 6-substituents that are strong proton acceptors may help to stabilise the pyridone tautomer by means of an intramolecular hydrogen bond even when strongly electronegative, *e.g.* some forms of COR.

Nothing quantitatively is known concerning the effect of substituents in other aromatic amides. Qualitatively similar trends may be anticipated, which probably means in practice that only oxoheterocycles with lower values of  $K_T$  than 2-pyridone itself (see following section) are appreciably at risk.

### B.2.5 Aromatic 6-Membered Ring Amides: Related Oxoheterocycles

Those oxoheterocycles for which  $K_T$  may be reliably estimated are set out in Scheme 33, mostly as the **B**-tautomer where dominant, along with others that provide useful qualitative information. The derivation of  $\log K_T$  (Table 56) is mostly straightforward, but that for **68** derives from an LSER equation (section B.2.2) and the very complex case of **855**<sup>448</sup> appears as Scheme 34. Here preferred protonation at *N*-1 forced Katritzky and co-workers<sup>448</sup> to start from the dication **855HH** and employ a multiplicity of model compounds. From  $pK_a$  3.77 and -4.3 for **855c** and **855d** respectively we

require values for **855A** and **855B**; the first probably needs no correction whereas  $\Delta(\text{NR})$  0.6 is estimated for the second (Appendix 3). However, because **855A** and **855B** do not share a common monocation and  $K_t \neq 1$  we have to correct for this difference. Katritzky used the difference between -8.19 for  $\text{p}K_{\text{aH}}$  and -8.52 for  $\text{p}K_{\text{bH}}$  to deduce  $\log K_t$  0.3. In fact,  $\log K_t$  0.7 results from direct observation of **860b** *vs.* **860a**;<sup>448</sup> on the assumption that any distortion of this ratio due to  $\text{NMe}^+$  *vs.*  $\text{NH}^+$  cancels between the **860a/b** and **855AH/BH** compound pairs, this value is to be preferred. From  $\Delta\text{p}K_{\text{a}} \sim 7.5$  for **855A** *vs.* **855B** and correcting for  $\log K_t$  0.7 in favour of the monocation **855BH**, we obtain  $\log K_T \sim 6.8$ , substantially lower than the published value<sup>448</sup> of 7.8. In addition, a zwitterionic tautomer **855Z** is present whose ratio *vs.* **855A** may be deduced from  $\text{p}K_{\text{a}}$  3.77 for **855a** (above) and  $\text{p}K_{\text{a}}$  1.95 as measured for **860a**  $\rightarrow$  **860z**;<sup>448</sup> assuming ‘remote’ effects due to NMe and OMe to be negligible,  $\log K_Z \sim 1.8$  (**855A**  $\rightarrow$  **855Z**) results.<sup>448</sup> Hence the tautomer stability order is **855B**  $\gg$  **855Z**  $>$  **855A** with **855Z** disfavoured globally by *ca.*  $10^5$ . Since in less polar solvents than water  $K_Z$  is likely to diminish, the biological importance of **855Z** must be negligible. These complications appear to be much less marked in **859** which was investigated<sup>254</sup> *via* its fixed NMe and OMe forms alone (Table 56). This prevents interference by species that parallel **855Z** and to avoid all doubt we have adopted this procedure for **854** as well, in both cases allowing  $\Delta \text{p}K_{\text{a}}$  0.55 for  $\text{NMe} \rightarrow \text{NH}$  (**814**, Scheme 30). Other misgivings, especially concerning

**Table 56.**  $\text{p}K_{\text{a}}$   $\log K_T$  Values for 2-Pyridone and Related Oxoheterocycles in Water <sup>a,b</sup>

Compound	$\text{p}K_{\text{a}}$ (NH)	$\text{p}K_{\text{a}}$ (OMe)	$\text{p}K_{\text{a}}$ (OH) <sup>c</sup>	$\log K_T$
<b>847</b> <sup>d</sup>	0.75	3.28	4.28	3.5
<b>848</b>	- 0.31	3.17	4.17	4.5
<b>849</b>	< - 1.5	2.38	3.38	> 4.9
<b>850</b>	- 1.2	3.05	4.05	5.3
<b>68</b>	0.21			1.7 <sup>e</sup>
<b>851</b>	- 0.1	0.75	1.75	1.9
<b>852</b>	- 1.38 <sup>f</sup>	0.28 <sup>f</sup>	1.28	2.7
<b>853</b>				- 0.75 <sup>g</sup>
<b>854</b>	- 1.6 <sup>h,i</sup>	2.52	3.52	5.1
<b>855</b>				6.8 <sup>h</sup>
<b>859</b>	- 0.1 <sup>h,j</sup>	1.97 <sup>k</sup>	2.97	3.1

<sup>a</sup>  $\log K_T = \text{p}K_{\text{a}}(\text{OH}) - \text{p}K_{\text{a}}(\text{NH})$ . <sup>b</sup>  $\text{p}K_{\text{a}}$  Values from ref. 4 unless otherwise stated.

<sup>c</sup> Calculated as  $\text{p}K_{\text{a}}(\text{OMe}) + 1.0$  (Scheme 30). <sup>d</sup>  $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{R}^6 = \text{H}$ . <sup>e</sup> From LSER eqn. (Ixiv), section B.2.2. <sup>f</sup> Ref. 446. <sup>g</sup> By direct observation of model compound UV spectra, ref. 449a. <sup>h</sup> See the text. <sup>i</sup> Estimated from  $\text{p}K_{\text{a}}(\text{NMe}) - 2.1$ , ref. 382a (see the text). <sup>j</sup> Estimated from  $\text{p}K_{\text{a}}(\text{NMe}) - 0.61$ , ref. 254 (see the text). <sup>k</sup> Ref. 254.

pyrazinones, are expressed in Appendix 1. Little is known about the effects of substitution. Given  $\log K_T$  1.9 and 5.1 for **851** and **854** respectively it is unsurprising that their perfluorinated derivatives **856** and **857** exist as shown,<sup>2ccc</sup> but of some interest that **858** does not give the **A**-tautomer for  $R = \text{CO}_2\text{Et}$ . In fact, when as here the ester group is capable of free rotation, we estimate the OH-ester hydrogen bond in water as likely to result in  $\Delta \log K_T$  *ca.* -1 (Appendix 4), so no detectable fraction of **858A** should result.

One advantage of such a complete set of reasonably reliable tautomeric ratios is that, for the first time, regularities become apparent. For example, the effect of benzofusion on  $K_T$  takes two distinct forms. If NH is adjacent to the ring junction,  $\Delta \log K_T$  close to 1.0 is found: this value is 1.0 for **847** → **848**, 0.8 for **851** → **852**. In 4-pyridone and 4-pyridazinone we similarly find  $\Delta \log K_T$  1.0 for both (section A.10.7); given the doubts attaching to **851** and **852** (Appendix 1), we accept  $\Delta \log K_T$  1.0 as the standard for this category. When NH is in the 2-position, however, this value almost doubles, to 1.8 for **847** → **848** and 1.7 for **854** → **855**. This difference is surprising and we cannot explain it. Electron donors are more sensitive than electron acceptors to conjugation with  $\text{C}=\text{C}$  – *cf.* our putative  $\log K_T$  values for **837** and **838**, section B.2.3 – hence compounds containing  $\alpha$ -NH should plausibly have been the more affected by benzofusion, not those with  $\beta$ -NH as found. To compound the problem,  $\Delta \log K_T$  2.14 is found for a 2-pyridone → 2-quinolone vinylogue (**72C** → **433C**, Table 33, section A.10.2). The replacement of benzenoid by quinonoid structures also produces consistent results: expressed as **847** → **68** and **854** → **859** this leads to shifts of  $\Delta \log K_T$  -1.8 and -2.0 respectively, in line with -1.7 for pyrazole → indazole (section B.1.5) which we take as the reference point for this process since other structural differences are absent. On present evidence therefore, just three correction factors, namely 1.0, 1.8 and -1.9, will cover benzofusion in all 6-membered ring oxoheterocycles. These extraordinarily pleasing symmetries depend for their validity on meticulous use of the very variable  $\Delta(\text{NR})$  values set out in Scheme 30 and go far to confirm the validity of those as well.

Two of these results throw light on the energetic penalties attaching to lone pair and dipolar repulsion. The 2-aza nitrogen of **854** stabilises the **B**-tautomer by  $\Delta \log K_T$  1.6 relative to **847**, while **850** → **855** results in  $\Delta \log K_T$  1.5. Given the general reduction in  $K_T$  resulting from electronegative substituents (section B.2.4), this on the face of it is remarkable. The effect turns out to lie largely in  $\text{pK}(\text{OMe})$ , which for **847** subtracting  $8 \times \sigma_I$  for  $\alpha$ -N (*vide* Table 2) calculates as  $\text{pK}_a$  -0.48 where 2.52 is found. Allowing for a small discrepancy ( $\Delta \text{pK}_a$  0.4) between the observed and calculated  $\text{pK}(\text{NH})$  values,  $\Delta \log K_T$  3.4 results (Appendix 3). This is much greater than the  $\Delta \log K_T$  2.1 found for its 4-oxo isomer **474** on similar reasoning and may result

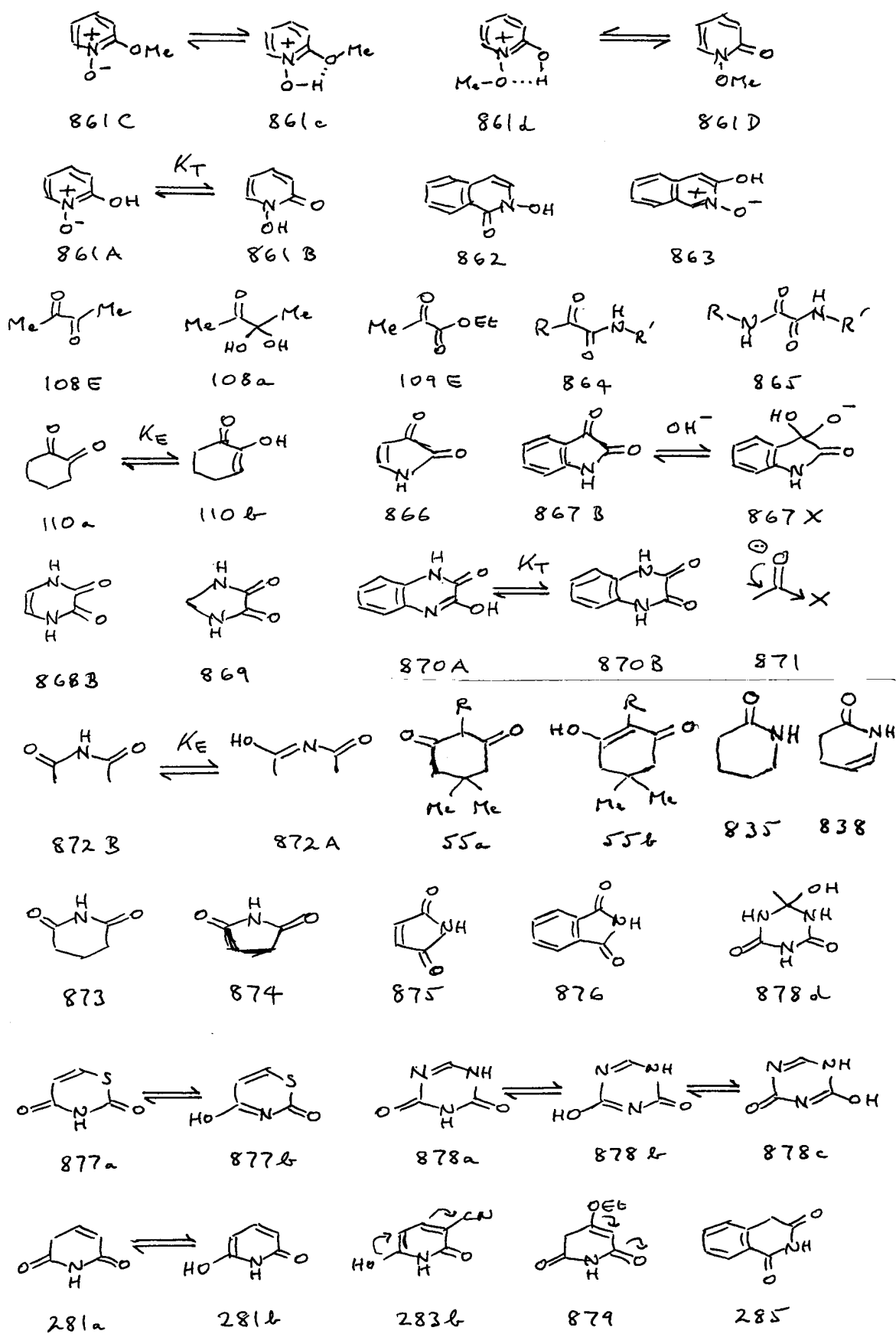
from the closer proximity here of OH (or OMe) as electron donor to aza-nitrogen, with consequent enhancement in its electron density. (This same factor may account for the preferential protonation at *N*-2 of **855**). An example of dipolar repulsion is provided by **853**, where for R = H,  $\log K_T$  -0.75 in water results,<sup>449a</sup> a reversal of 2.7 or 3.5 in  $\log K_T$  according as to whether **851** or **852** is chosen for comparison (evidence adduced in Appendix 3 indicates that the former is more appropriate). Since even in water these effects are formidably large, they should be of still greater importance in a less polar environment. It is instructive to note that, when *peri*-NH's as in **853B** are replaced by aza-nitrogens as in **719** (Scheme 26, section A.12),  $\Delta \log K_T$  is only *ca.* -0.8, evidence (*vide* Appendix 3) that, in this rather different context, dipolar interaction is a much greater destabilising force than lone pair repulsion; and see section B.1.7 for further examples that illustrate this point.

### B.2.6 Aromatic 6-Membered Ring Amides: N-Oxides

Quantitative information is hard to come by, chiefly because of problems concerning the structure of the supposedly 'common cation.' Gardner and Katritzky<sup>296</sup> point out that **861c** forms a much stronger intramolecular hydrogen bond than **861d**, so greatly increasing the basic strength of **861C** ( $pK_a$  1.23) and exaggerating that of **861A** if **861C** is used as a model for it. Similarly the cation of **861B** may have a structure closer to **861c** than **861d**. In terms of the 'basicity method' this will result in overestimating the importance of the oxo-tautomer **861B**, possibly by a large margin; given  $pK_a$  -1.3 for **861D**, the global  $pK_a$  -0.8 for **861** becomes incommensurable. However, there is extensive qualitative evidence that  $\log K_T$  for these *N*-oxides lies well below the value found for the corresponding oxoheterocycles, oxide ( $N^+-O^-$ ) acting essentially as an electronegative substituent. From the fact that **862** (in EtOH) certainly, and **863** probably, exist as shown,<sup>2y</sup> we may deduce from the parent oxoheterocycle tautomeric preferences (**850** and **68**, Table 56) that the ability of *N*-oxide formation to upset these probably lies in the range  $\Delta \log K_T$  -2 to -5. That, in this field, is as far as we can go.

### B.2.7 Cyclic Pyruvamides (COCONH) and Oxamides (NHCOCONH)

Biacetyl **108** (see section A.2.5) takes up the *E*-conformation shown to avoid lone pair repulsion, and the same may be anticipated for open-chain pyruvamides **864** and oxamides **865**, which possess the additional incentive of an intramolecular hydrogen bond. Neither has ever been suspected of iminol formation. Biacetyl **108** and pyruvate esters **109** are *ca.* 75% hydrated



in water and the same may be anticipated for RCO in **864**, but no enolisation has been detected for either. The situation on cyclisation is radically different. Cyclohexane-1,2-dione **110** hydrates to the extent of about 40% but very little of the diketo-form is present in the remainder; we estimate  $K_E \geq 10^2$  (section A.2.5). This represents a reversal relative to cyclohexanone of  $\Delta \log K_E \geq 8.5$  of which we attribute *ca.* 3.5 to the effect of adjacent carbonyl and  $\geq 5$  to lone pair repulsion. We may examine how far these factors operate here.

Pyrrole-2,3-dione **866** appears not to have been investigated. Its benzofused analogue isatin **867** ionises, most unusually, by hydroxide ion addition to give **867X**,  $pK_a$  10.89,<sup>451</sup> but does not appear to hydrate to any great extent, or form detectable amounts of iminol. (It should be noted that either iminol would be anti-aromatic, which may help to explain their absence). However the UV spectra of model compounds prove **870B** to dominate in water,<sup>2000</sup> **868B** has been assumed by analogy,<sup>2t</sup> and **869** was reported as such without comment.<sup>2000</sup> From an estimated  $\log K_T$  5.5 for **838** (section B.2.3) we may take this as a maximum value for each amide unit of **870B** in the absence of perturbation by the other. If subject to  $\Delta \log K_T$  *ca.* -8.5 as for **110**, **870** would certainly exist as the mono-iminol **870A**, for which there is no evidence. Carbonyl electronegativity must be present, even if not at the level of  $\Delta \log K_T$  *ca.* -3.5, as estimated for **108**, and it follows that lone pair repulsion must be very much attenuated. A possible explanation starts from the known inequality of the carbonyl lone pairs in species of type **871**. The interaction shown has considerable effect in making the *E*-lone pair less available for  $Z = OR$ ,<sup>452</sup> and the same phenomenon operates in amides.<sup>453</sup> (The presence of two such lone pairs in ureas will probably explain why ureas are poorer proton acceptors than amides,<sup>453</sup> not stronger ones as 'resonance' arguments might suggest). Since these *E*-lone pairs face one another in **867B** and **870B**, the evident absence of iminol formation may be explained, at least in part. Nevertheless, in the absence of data for aqueous solution this matter remains *sub judice*, and more work is needed.

### B.2.8 Imides (CONHCO)

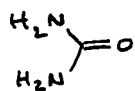
Cyclic imides **872** (open-chain imides more usually adopt the *E,Z*-conformation<sup>454</sup>) are formally analogous to extended  $\beta$ -diketones such as dimedone (**55**,  $R = H$ ) for which we estimate the effect of one carbonyl on the other as  $\Delta \log K_E$  *ca.* 7.7 (section A.6.2). Starting from **835** with  $\log K_T$  a presumed 7.6 this would make **873** a borderline case, but evidence for iminol formation is absent here and for **874**, **875** and **876**.<sup>21</sup> For **875** and **876** the iminol would be anti-aromatic, as for **866** and **867** above, but a more general explanation for this apparent discrepancy is that imides **872B** unlike  $\beta$ -diketones **55** are already conjugated structures. The former class therefore possesses much less incentive to enolise and, while this difference cannot be

quantified, aromatisation in the sense of **877b**,<sup>2ddd</sup> **878b** or **878c**<sup>2ccc</sup> is also unknown (but note the latter's susceptibility to covalent hydration, as **878d**). In fact the only clear case in which aromatisation has proved able to overcome imide resonance is that of glutaconimide **281** (section A.6.3), which in water exists about 60% as **281b**. This is a needle case, with electronegative substituents as in **283b** and electron donors as in **879**<sup>2y</sup> favouring the enol and imide structure respectively, for the obvious electronic reasons indicated. The related homophthalide **285** follows the usual trend on benzofusion by remaining firmly as the imide shown<sup>2y</sup> (section A.6.3). Unfortunately, while if **281b** were an iminol  $\log K_E -1.6$  for **285** could be predicted (section B.2.5), the enolisation processes shown for **281** ('C-type') and **872** ('N-type') cannot yet be related, and quantification of the former remains in abeyance.

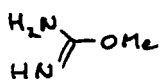
### B.2.9 Ureas (NHCONH) and Acylureas (CONHCONH)

From urea **880**,  $pK_a$  0.1,<sup>454</sup> and its methoxy-derivative **881**,  $pK_a$  9.72,<sup>455</sup> then incorporating  $\Delta(OR)$  0.7 for structure **829** (Scheme 30), we arrive at a provisional  $\log K_T$  *ca.* 10.3 for urea itself. Given  $\log K_T$  9.1 for *N*-methylacetamide **832** (section B.2.3) this makes ureas even less susceptible to enolisation than amides, a proposition supported by all that is known. Ureas and urea-like structures that unquestionably exist as such with no detectable trace of enolisation include **882**,<sup>2eee</sup> **883** and **884**.<sup>2fff</sup> It has been stated<sup>2ggg</sup> that all compounds of types **885** and **886**, where  $Z = O, S$  and  $NR$ , exist as such, and this probably extends in most such cases to the presence of potentially enolising substituents and even to very non-polar media, such is the resonance energy that attaches to ureas and urea-type structures.

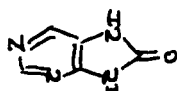
This immunity towards enolisation appears to extend to acylureas. Hydantoins (**887**,  $Z = NH$ ) and, more generally, (**887**,  $Z = O, S$  and  $NR$ ), do not appear to enolise appreciably,<sup>2z</sup> and neither do uracils **888B**<sup>2ddd</sup> or related compounds such as the imide **877**, here re-classified as a urea-type molecule (classification in this area is particularly ambiguous and has to depend on context). Other firmly established oxo-forms include **889**,<sup>2hhh</sup> **785** (section B.1.7), **890** and **891**<sup>2ddd</sup> which, confusingly, can also be classified as an anhydride. (Similarly **892**, the ultimate triamide,<sup>2jjj</sup> could be re-classified as imide plus urea). It has been stated<sup>2iii</sup> that all compounds of type (**893**,  $X$  or  $Y = O$  or  $S$ ) take the form shown; since its structure neatly avoids both lone pair and dipolar repulsion, this is to be expected (*cf.* **899** below). The only contrary report concerns **894**, stated by Roth<sup>456</sup> to form the hydrogen bonded enol **894A**. Inspection of their data suggests **894** to exist as the zwitterion **894Z**, an entirely reasonable proposition given  $pK_a \geq 10$  for a typical aliphatic amine and  $pK_{NH} < 8$  for a barbituric acid.<sup>457</sup> Dominant enol formation is therefore unproven, and we believe it to be unlikely, for any derivative of a simple urea.



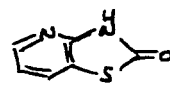
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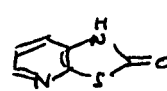
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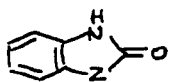
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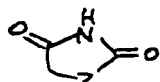
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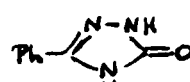
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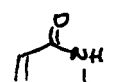
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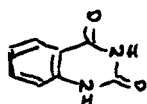
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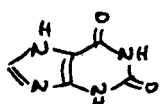
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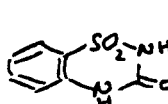
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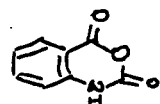
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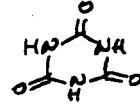
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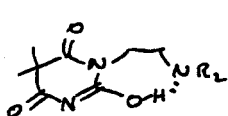
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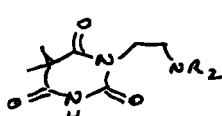
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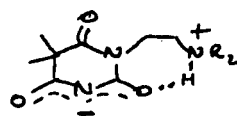
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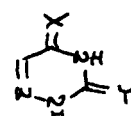
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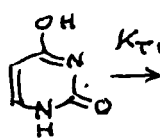
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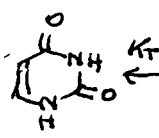
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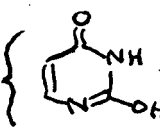
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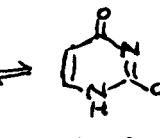
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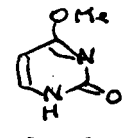
888 B



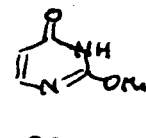
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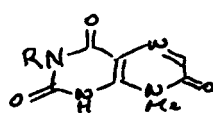
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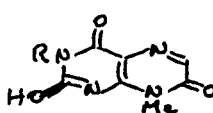
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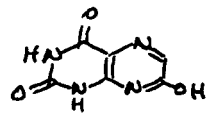
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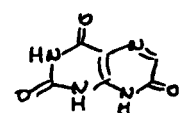
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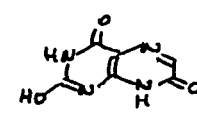
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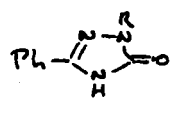
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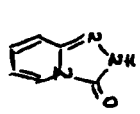
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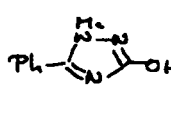
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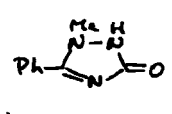
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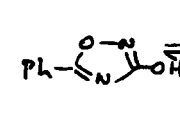
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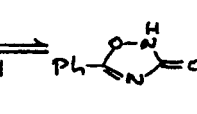
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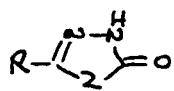
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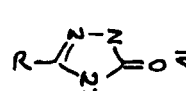
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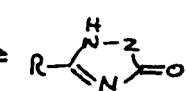
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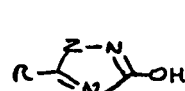
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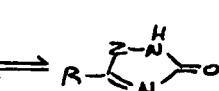
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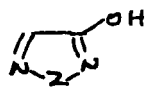
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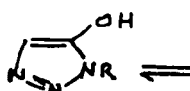
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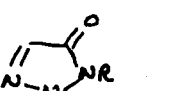
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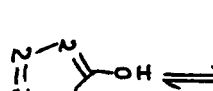
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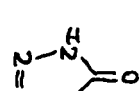
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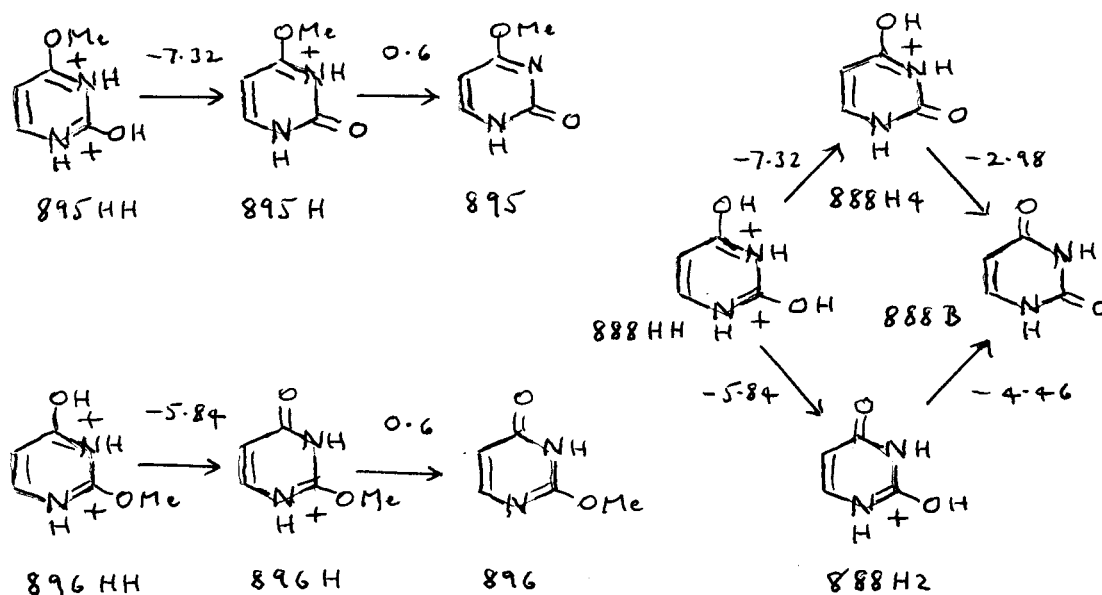
907 B



908 A



908 B



The tautomerisation of uracil **888B** has been studied by Katritzky and Waring<sup>458</sup> (in part) and by Poulter and Frederick.<sup>459</sup> The dicationic  $pK_a$  value of -7.32 for **888HH** compares with -7.32 and -5.84 for **895** and **896** respectively,<sup>459</sup> establishing **888H4** as on the dominant deprotonation pathway. No  $pK_a$  corrections are required for the latter pair since deprotonation of  $HN^+=COMe$  is not involved. Hence the measured<sup>459</sup> monocationic  $pK_a$  -2.98 also attaches to **888H4**, from which  $pK_a$  -4.46 follows by difference for **888H2**. These are the parent amide  $pK_a$  values and require those of the iminols to interpret them. As models for these, **895**<sup>458,459</sup> and **896**<sup>459</sup> possess identical  $pK_a$  values of 0.6, which become 1.6 and 1.3 respectively on applying  $\Delta(OR)$  from Scheme 30. The complication of **888C** and **888D** as alternatives for the 2-OH iminol can probably be ignored since the same applies to **896** and there is evidence (section B.5.11) that, in 4-pyrimidone, strong  $\pi$ -donors in the 2-position give near-unity 1-*H*/3-*H* ratios. Values of  $\log K_{T(2)}$  5.8 and  $\log K_{T(4)}$  4.6 follow. This difference is surprising only in not being greater, given that they involve nominally urea- and imide-like  $C=O$  respectively, but conjugation with  $C=C$  may contribute a levelling effect. High level *ab initio* calculations by Gould and Hillier<sup>460a</sup> predict **888B** as the major tautomer but by much larger margins than found above, while Beak and White<sup>460b</sup> earlier considered tautomerism only at 2- $C=O$ , with still more discrepant results. These however are gas phase predictions; no allowance for solvation was attempted.

The only type of urea that on present evidence is appreciably sensitive to enolisation is one seriously compromised by contiguous or *peri* NH-type dipolar interactions. Pfleiderer<sup>449b</sup> claims 35% of **897b** in (**897**, R = H) which is surprising in itself and difficult to reconcile with his observation<sup>449b</sup> that (**897**, R = Me) does not enolise. On the face of it, combining the former result with that for **898** (section B.2.5: **853**, R = H) should lead to a balance of *ca.* 85:15:5 for the **A**-, **B**- and **C**-tautomers respectively of **898**, but since dipolar repulsion in **898B** results in  $\Delta \log K_T$  *ca.* -2.5 which is enough to result in dominance for **898A** (section B.1.5) but not for **897b** (see uracil, above), it seems more likely that this area warrants re-investigation. Other results are less contentious. The unsubstituted triazolone **750** (section B.1.2) has the structure **750B** not **750A**; triazolones when 1-substituted as in (**899**, R = Me or Ph),<sup>401</sup> and more generally as **904B**<sup>461</sup> or 4-substituted as in **900**<sup>2111</sup> and **903**<sup>2111</sup>, are able to preserve this tautomeric form, but when that is prevented *e.g.* by 2-substitution, enolisation takes place, as in **901** which exists as **901D**.<sup>401</sup> Similarly, **902** is present in water as (probably) a 50:50 mixture of the **D**- and **C**-forms,<sup>461</sup> while more generally, **905D** predominates over **905C**.<sup>461</sup> Since dipolar repulsion in –NHO– relative to =NO– appears, in this context at least and perhaps generally (Appendix 3), to entail a penalty of  $\Delta \log K_T$  *ca.* -5, we may postulate much higher  $K_T$  values when this constraint is removed, as in (**904**, Z = O).<sup>2111</sup> Since –NHNR– dipolar repulsion is substantially less than for –NHO– a higher  $K_T$  value for **901** than for **902** might have been expected, but the former result<sup>401</sup> is for KBr and some organic solvents, not for water. As in the case of C-type tautomerism (section A.2.8), three contiguous hetero-atoms will generally force a predominance of the hydroxy-tautomer, as in **906** and **907**.<sup>2111</sup> The presence of cumulative lone pair repulsion in **908A** may help to explain why **908** prefers the oxo-structure **908B**<sup>2111</sup> against the trend of **906** and **907**; alternatively, **908B** can be considered a urea. Nevertheless, even though it may seem possible to rationalise these trends that is no substitute for quantitative results, and this is one of the many areas from which they are missing.

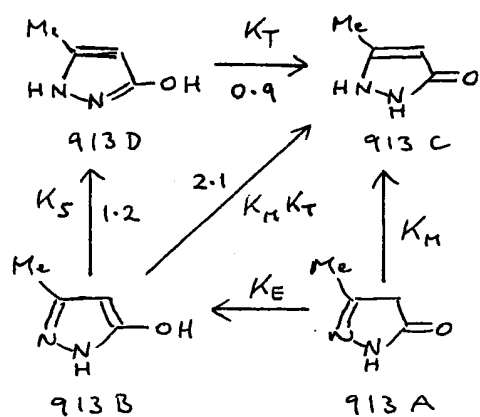
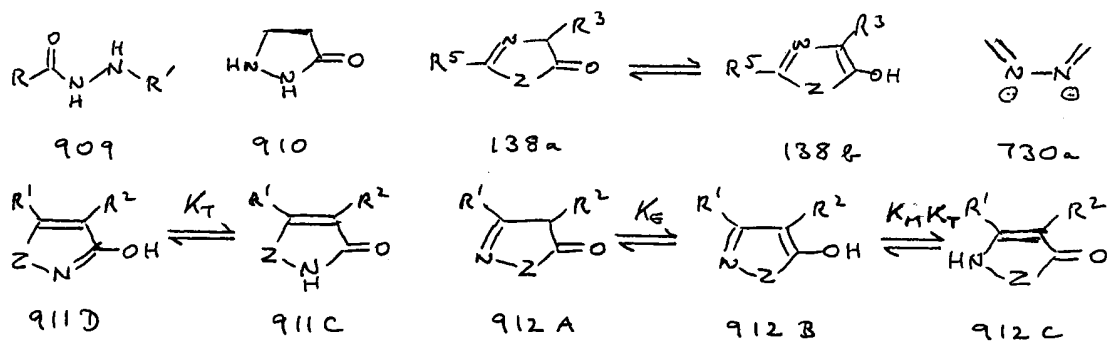
Dipolar repulsion as in **907B** appears to be much more destabilising than lone pair repulsion in **907A** and there is suggestive evidence, reviewed in Appendix 3, that at least in 5-membered rings this may be general. Elsewhere however lone pair repulsion is possible only for disfavoured iminol forms such as **903A** (not shown) and **908A**, and that double disadvantage ensures their absence from this class of compound. To summarise: urea-type structures of types **903B** and **904B** will always be the favoured tautomer when they can be formed, and probably by wide margins; it is only in those of type **905**, where formation of the oxo-tautomer **905C** entails severe dipolar repulsion, and in compounds which lack urea-type structures, that the iminol tautomer is likely to dominate. That, at present, is as far as we can go.

### B.2.10 Hydrazides (CONHNH) and Related Compounds

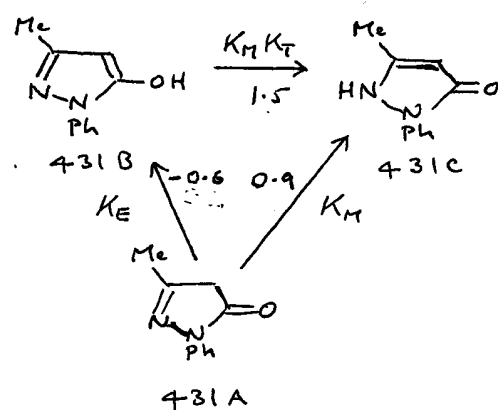
Section B.2.10 concerns the situation in which two NH's are contiguous, or alternatively NH is contiguous with O, S or NR, and carbonyl is adjacent to one or the other (not both; *cf.* section B.2.12). Its subject matter differs from that of B.2.9 in the absence of a third annular hetero-atom. While no information is available concerning open-chain acylhydrazines **909** there is no reason for supposing that these will differ greatly in tautomeric balance from the corresponding amides ( $-\text{NHNH}_2$  is only a slightly poorer electron donor than  $-\text{NH}_2$ : Table 2), and while there must be considerable dipolar repulsion in alicyclic analogues such as **910**, this is unlikely to be great enough, on the evidence presented below, to result in perceptible enolisation. In 5-membered ring heteroaromatics of this type, however, there is the potential for aromatisation as well, and this is a well worked field for tautomeric studies<sup>2</sup> as well as a complex and confusing one.

The compounds of this section relate in one instructive way to those of section B.2.9. In the general structure **903**,  $Z = \text{O}, \text{S}$  or  $\text{NR}$  converts **903B** into a compound that is stabilised by its urea-type part-structure, whereas **904B** with the same  $Z$  is stabilised in a similar way (these compound series are all but identical if  $Z = \text{NR}$  for both). If  $Z = \text{CHR}$  in either the molecule ceases to be a urea or pseudo-urea and, with loss of the resonance stabilisation due to that part-structure, becomes much more susceptible to enol formation. If  $Z = \text{CHR}$  in **904**, aromatisation readily occurs and the enol or (sometimes) the betaine generally predominates; compounds of this type (*e.g.* **138**) are treated in section A.2.8, along with their 4-hydroxy isomers which behave similarly. If  $Z = \text{CHR}$  in **905**, a further proton switch will generate the very stable urea-type structure **885**. If  $Z = \text{CHR}$  in **903**, we have the compounds that form the main subject matter of this section.

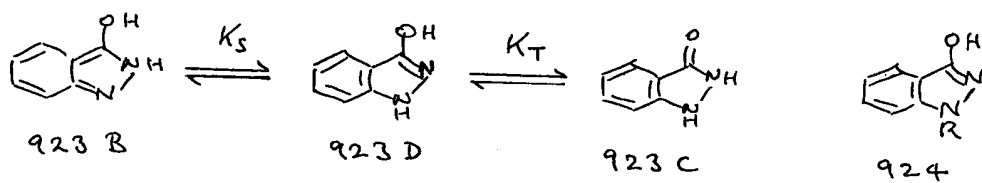
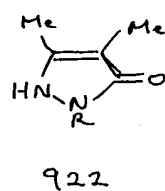
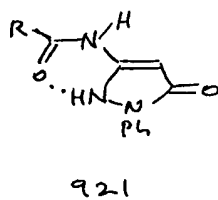
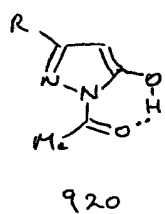
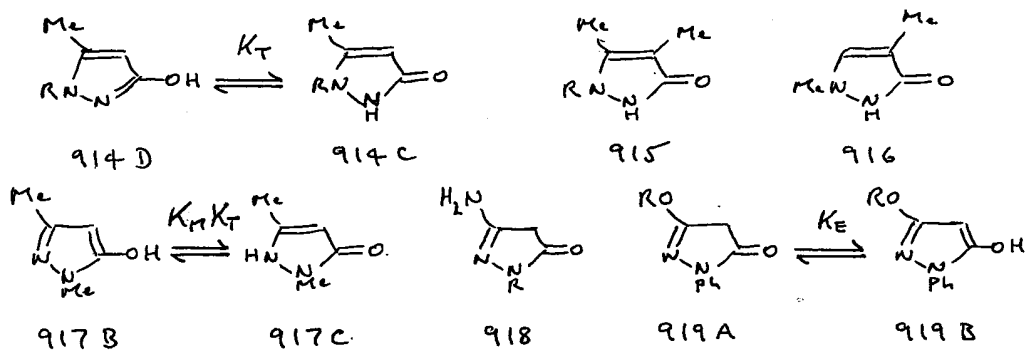
Dipolar repulsion involving the  $-\text{NHZ}-$  unit ( $Z = \text{O}, \text{S}$  or  $\text{NR}$ ), which acts as a driving force for generating  $=\text{NZ}-$  in its place, dominates the behaviour of the compounds in this section even more completely than in section B.2.9. Unlike the lone pair repulsion found for contiguous aza-nitrogens (*vide* **730a**), which is effectively abolished in open-chain structures by geometrical isomerism (*cf.* section A.12), dipolar repulsion does not appear to be cancelled in this way. The generation of imines from enamines is assisted by linking the nitrogen atom to a  $\pi$ -donor (section A.4.6) to give *e.g.* a hydrazone or oxime, and the subject may be approached from this direction.



Scheme 35



Scheme 19



Two general situations may be distinguished, **911** and **912**. Here the **C**-tautomers are related but the remainder are not; in particular, the unconjugated **A**-tautomer (*cf.* Scheme 17, section A.10) is unavailable to **911**. These situations overlap when  $Z = \text{NH}$  and this case has been examined in depth. One of us<sup>21</sup> has processed the original model compound data of Katritzky,<sup>462</sup> Elguero,<sup>463</sup> and their co-workers to give the three-way equilibrium of Scheme 35 (values are  $\log K$ ; **913A**<sup>462</sup> is known to be of negligible importance in water). Here **913C** dominates to the extent of 88% in water (estimated<sup>21</sup>) or 90% (observed<sup>463</sup>) with the fraction of **913B** estimated as *ca.*  $8 \times 10^{-3}$ . If  $Z = \text{NR}$  in **911** the equilibrium simplifies and we may consider the effect of  $R$ . From  $pK_a$  2.05 and 2.22 for the OEt and NMe derivatives of (**914**,  $R = \text{Me}$ ) we obtain,<sup>21</sup> after correction (Scheme 30),  $\log K_T$  0.4, *i.e.* a predicted 72% of **914C** where 70% is found by direct UV observation.<sup>462</sup> In similar fashion, from  $pK_a$  1.17 and 1.66 for the corresponding *N*-phenyl model compounds, we obtain  $\log K_T$  -0.1, a calculated 45% of (**914C**,  $R = \text{Ph}$ ) where the UV evidence is for *ca.* 50% of each.<sup>462</sup> This small drop in  $K_T$  reflects the usual effect of electron-withdrawing substituents (as indeed do the  $pK_a$  values). Conversely, 4-alkylation raises  $K_T$ ; while there are no firm quantitative data, (**915**,  $R = \text{H}$ ) and (**915**,  $R = \text{Me}$ ) are both overwhelmingly in the oxo-form on UV evidence.<sup>463</sup> Similarly, **916** on UV evidence contains about 60% of the oxo-tautomer compared with 70% for (**914**,  $R = \text{Me}$ ), *i.e.*  $\log K_T$  0.2, perhaps 95% for (**915**,  $R = \text{Me}$ ), *i.e.*  $\log K_T$  *ca.* 1.3, and a good deal less for its desmethyl analogue.<sup>2mmm</sup> These results may be construed to mean that alkylation at  $R^1$  and  $R^2$  (a) has about the same effect in each position, (b) that its effect is large, and (c) that it is not only cumulative, but quite possibly additive as well. This last possibility is explored in section B.8.13.

There is some quantitative information on the analogues of type **912**. For **913**,  $\log K_M K_T$  is  $\sim 2.1$  (Scheme 35);<sup>464</sup> from  $pK_a$  2.35 for **917C** and 3.51 for the OEt derivative of **917B** we obtain, after correction,  $\log K_M K_T$  *ca.* 1.7 for **917**, a slightly smaller value than for the *N*-desmethyl derivative as in the case of its isomer. (Here we use, in Scheme 19 and subsequently,  $K_M K_T$  rather than  $K_M/K_E$ , *via* the relation  $K_T = 1/K_E$ , in line with the acylamidine **811** convention employed at the start of this section). This effect while not large is found throughout and possesses no obvious electronic explanation; we attribute it to poorer solvation of  $-\text{NHNR}-$  than of  $-\text{NHNH}-$ , resulting in increased dipolar repulsion (*vide* section C.15). Electronic factors are certainly present; the **C**-tautomer in both compound series is successively disfavoured, relative to  $Z = \text{NH}$ , by  $Z = \text{NMe}$ ,  $\text{NPh}$  and  $\text{O}$ , *i.e.* as the electronegativity of  $Z$  increases. Quantitative data are rare, with the only 3-way analysis than that of Scheme 35 an investigation of **431** by LSER (section A.10.2). This resulted in estimates of -0.63, 0.90 and 1.60 for  $\log K_E$ ,  $K_M$  and  $K_M K_T$  respectively in aqueous solution. Since a different set of

solvent data<sup>276</sup> had to be employed for each (Appendix 2), these are independent estimates and their mutual consistency is gratifying. If we apply a  $\Delta(\text{OR})$  correction factor to the results of Katritzky and Maine<sup>462</sup> (none is required for NMe),  $\text{p}K_{\text{a}}$  2.34 becomes 2.84 for **431C** against 1.42 for **431B** and  $\log K_{\text{M}}K_{\text{T}}$  1.4 results. The average value for  $\log K_{\text{M}}K_{\text{T}}$  appears in Scheme 19 and the fit is exact. Since the **A**-tautomer possesses no (mono)-cation in common with any other,<sup>462</sup> LSER analysis is the only technique other than direct observation, definitive but rare, that can quantify  $K_{\text{E}}$  or  $K_{\text{M}}$ , and it is unfortunate that nowhere else has it been attempted.

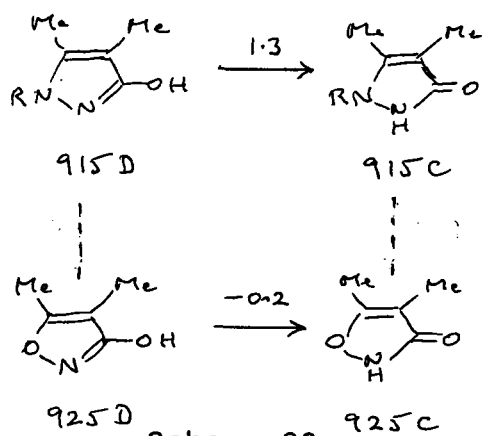
Some related compounds demonstrate the effect of substituents. Compounds (**918**, R = Me) and (**918**, R = Ph) both take the **A**-form shown in water, this being stabilised by amidine-type resonance, and OR has the same effect in **919**.<sup>2nnn</sup> With the tautomers so closely in balance, intramolecular hydrogen bonding can easily reverse it, as in **920**,<sup>2nnn</sup> and in **921** which, in DMSO, gives 70% of the **C**-form shown.<sup>2nnn</sup> Ring alkylation has a similar effect as in series **911**, with (**922**, R = Me) existing overwhelmingly as the **C**-tautomer while (**922**, R = Ph) gives  $\log K_{\text{M}}K_{\text{T}}$  1.7 using the 'revised basicity method' applied<sup>464</sup> to the original data.<sup>462</sup>

For the series **911** and **912** in which Z = O, quantitative evidence is more sparse. Qualitatively however it is clear that the oxo-tautomers are substantially less favoured, especially for (**911**, Z = O) where **911D** is generally dominant.<sup>2ooo</sup> The exact margin is more difficult to determine. Katritzky and co-workers<sup>465</sup> have examined the tautomerisation of **925**. From  $\text{p}K_{\text{a}}$  values of -2.08 and -1.36 for **925(OMe)** and **925(NMe)** respectively they deduced a 5:1 ratio of **925D** to **925C** but expressed the view that **925D** is probably much more dominant. That view was based essentially on the NMR demonstration that **925D** greatly predominates in  $\text{CCl}_4$  and DMSO, which on LSER evidence for other amides (*cf.* Table 53) could be misleading so far as aqueous solution is concerned (and see section A.10.2 for the example of **431**). It may be correct but is very difficult to check, especially since we<sup>22</sup> find  $\text{p}K_{\text{a}}$  -0.89 for **925** itself, which is incommensurate with the fixed NMe and OMe derivatives and can only mean that one or both of  $\Delta(\text{OR})$  and  $\Delta(\text{NR})$  must be exceptionally large. A rise in these to 1.4 and 0.9 respectively, parallel to the normal values of 1.0 for **827** and 0.45 for **823** (Scheme 30) but greater because of the much greater electron-deficiency of this system (as also adduced from its much lower  $\text{p}K_{\text{a}}$  values), would result in 63% of **925D** ( $\log K_{\text{T}}$  -0.2) and an overall  $\text{p}K_{\text{a}}$  -0.88, to fit that observed.<sup>22</sup> There is no doubt that **925** exists as **925D** in the solid state<sup>465</sup> but a close balance is also suggested by UV peaks at 224, 218 and 230 nm for **925**, **925(OMe)** and **925(NMe)** respectively.<sup>465</sup> Even so,  $\log K_{\text{T}}$  -0.2 for **925** reflects a shift of  $\Delta \log K_{\text{T}}$  *ca.* -1.5 relative to (**915**, R =

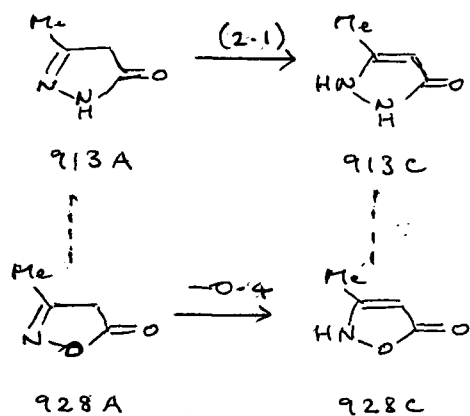
Me) with which it may be compared (Scheme 36). However, on IR evidence, **927** probably exists as shown;<sup>2nnn</sup> here, as in **918** and **919**, a  $\pi$ -donor (at R<sup>1</sup> in **911**) tips the balance.

The outstanding feature of (**912**, Z = O) is the much greater importance, in water, of **912A** as compared with (**912**, Z = NR). Katritzky and co-workers<sup>85</sup> have studied the effect of R<sup>1</sup> and R<sup>2</sup> on the equilibria of **928**. For R<sup>2</sup> = H, either R<sup>1</sup> = alkyl or R<sup>1</sup> = aryl leads to about 70% of **928A** and 30% of **928C**; as previously noted (section A.1.5), R<sup>1</sup> here occupies a pivotal position between alternative double bonds so is unlikely to have much influence. These compounds also exist as **928A** in the solid state. However, for R<sup>2</sup> = Br the proportion of **928C** rises to 80%, and for R<sup>2</sup> = alkyl or CO<sub>2</sub>Et, whether R<sup>1</sup> is alkyl or aryl, only the **C**-tautomer is visible. All these give **928C** in the solid state; however, **928B** while never visible in water is found in nonpolar solvents. These observations are backed by de Sarlo,<sup>466</sup> who states that **929(OMe)** and **929(NMe)** possess totally different UV spectra, that of the unsubstituted compound closely resembling **929(NMe)** in dioxan and hydroxylic solvents, with the **B**-tautomer important only in DMSO. Some of the **A**-tautomer is found in polar solvents. However, if R<sup>2</sup> = COR, this will induce a switch (for R<sup>1</sup> = alkyl or aryl) to **928B**.<sup>2ee</sup> In nonpolar solvents and the solid state, (**930**, R<sup>2</sup> = H) exists as **930A** as might be expected by analogy with **918**, but for R<sup>2</sup> = Et this is only a minor component in water and, for R<sup>2</sup> = Ph, only **930C** is visible. Presumably this results from carbon double bond stabilisation (*cf.* section A.1.1); substitution at R<sup>2</sup> is considered further in sections B.8.13 and C.15.

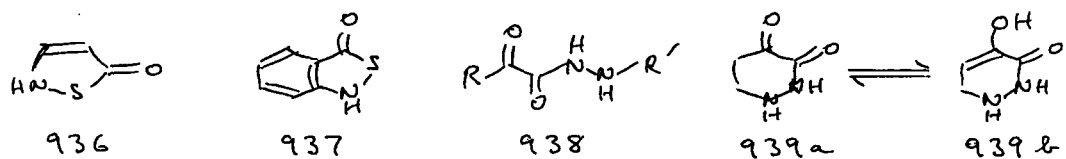
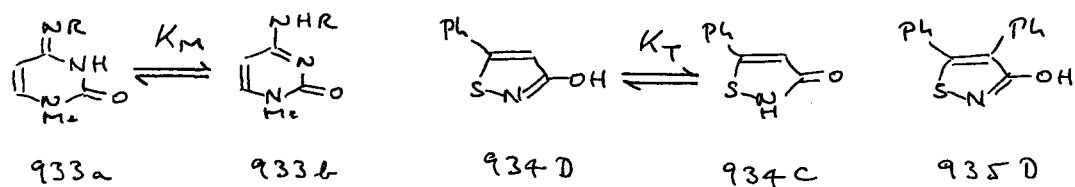
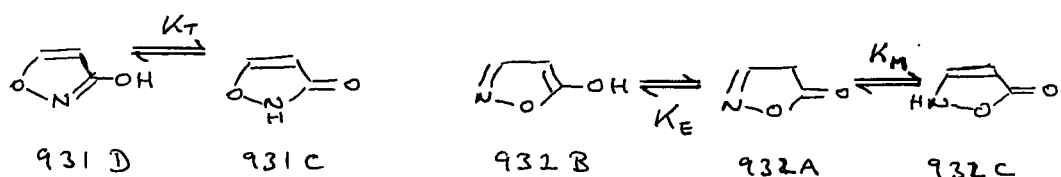
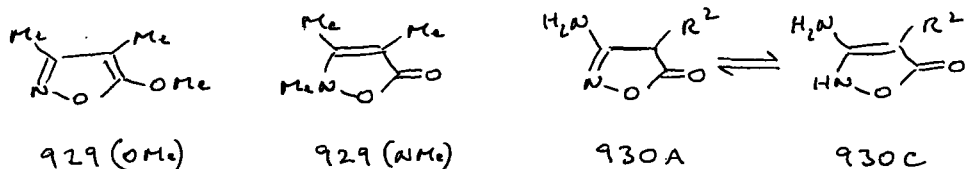
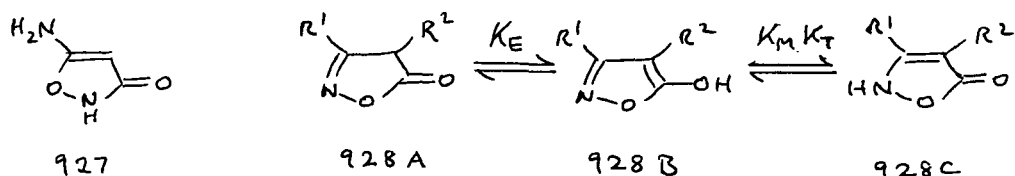
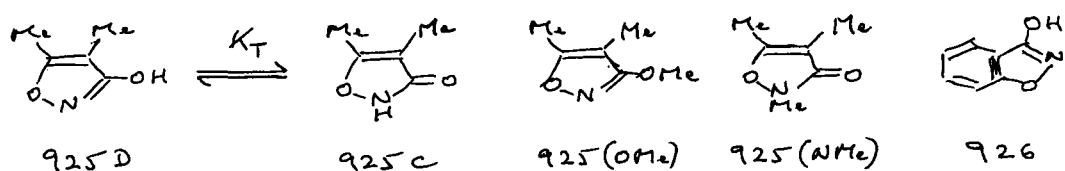
Calculations<sup>467a</sup> on **931** at the 6-31G\*\* level with the SCRF or PCM models superimposed to simulate aqueous solution predicted log  $K_T$  1.3 or -3.5 respectively, both well off target. Similarly, while **932B** was ruled out of court, log  $K_M$  is either 1.7 or -8.8 on these alternative methodologies. Later calculations on **932** by the same team<sup>467b</sup> suggested log  $K_M$  -5.4 using the SCRF simulation, which is not an improvement. An alternative approach is the following. In section B.5.15 we derive the true experimental aqueous values of log  $K_M$  for **933** where R = H, NH<sub>2</sub> and OH. These are 4.1, 1.5 and -1.1 respectively, so that the gap between R = H and R = NH<sub>2</sub> is already  $\Delta$  log  $K_M$  -2.6, and a further gap of equal size exists between R = NH<sub>2</sub> and R = OH. Qualitatively, these values already help to explain the preponderance of hydrazones (section A.5.1) and oximes (section A.5.2) over their tautomeric rivals, as further discussed in sections A.4.5, A.10.19, and A.10.20. Here they may be applied to  $K_T$  for **915** and **925** (Scheme 36), *i.e.* the difference, for **911**, between Z = NMe and Z = O. Our suggested  $\Delta$  log  $K_T$  *ca.* 1.5 (see



Scheme 36



Scheme 37



above) for this difference falls short of that for **933**, essentially because the **D**-forms are favoured here not only by dipolar repulsion but by aromaticity, and in that respect NH contributes more than O, so that the difference in overall effect between them is somewhat attenuated (see Appendix 3 for a quantitative treatment). In compounds of type **912**, however, where the  $K_M$  step is experimentally isolable (*vide* Scheme 19), an observed value of -0.4 for **928** is compared with an extrapolated value (Table 83, section B.8.13) of 2.1 for **913** to give a putative differential of  $\Delta \log K_M$  of 2.5, comparable to that noted above for **933**. By contrast the major contributor to  $K_E$  should be the aromaticity resulting from enolisation (NH > O); here a difference of  $\Delta \log K_E$  1.3 between **928** and **913** (Table 83) turns out to be twice as great as the resonance contribution differential (0.6) in  $\log K_T$  for O  $\rightarrow$  NH for the compound series represented by **925** and **915** (Scheme 36). Possibly this results from the longer conjugated system of series **912**. (Note that these effects are *opposed*:  $\Delta \log K_T$  -1.5 for **915**  $\rightarrow$  **925** is composite of increased lone pair repulsion,  $\Delta$  2.4 for the example analysed in Appendix 3, partially offset by a lesser gain in aromaticity,  $\Delta$  -0.6). One consequence is that the amount of **912A** will rise as Z becomes more electronegative, so accounting for its importance when Z = O, whereas in water, **912B** will never be important (see Table 84, section B.8.13).

Indazolone **923** has also been studied.<sup>22</sup> Here (*cf.* Scheme 35) the **A**-tautomer is absent, the **C**-tautomer is a little more favoured than for **913** ( $\log K_T$  *ca.* 1.3), a rather low margin for the effect of benzofusion but one which may be normal for 5-membered rings, and **923B** because quinonoid is very disfavoured ( $\log K_S$  3.0).<sup>484</sup> Relative to **913D** this gives  $\Delta \log K_S$  -1.8 for the quinonoid tautomer, almost exactly the value for indazole itself (section B.1.5), an encouragement to the proposition that a standard allowance can be made for this (Appendix 5). While 2-substituted indazolones are therefore effectively locked as the **C**-tautomer, a peculiarity of this system is that their 1-substituted isomers give the **D**-tautomer **924**, though by what margin is unknown. We<sup>22</sup> have suggested that enforced planarity may be the reason, by increasing dipolar repulsion; calculations<sup>22</sup> reveal that planarity would certainly have this effect, though what aspect of R might encourage planarity, unless simply its bulk, is unclear. No parallel phenomenon appears to attach to **913**, at least so far as NMe and NPh are concerned. This matter remains *sub judice*. Its analogue **926** exists predominantly as shown,<sup>2000</sup> which given  $\log K_T$  1.3 for **923**, is consistent with the value of  $\Delta \log K_T$  -2.0 we postulate for NH  $\rightarrow$  O in the monocyclic series **911** (Table 83, section B.8.13).

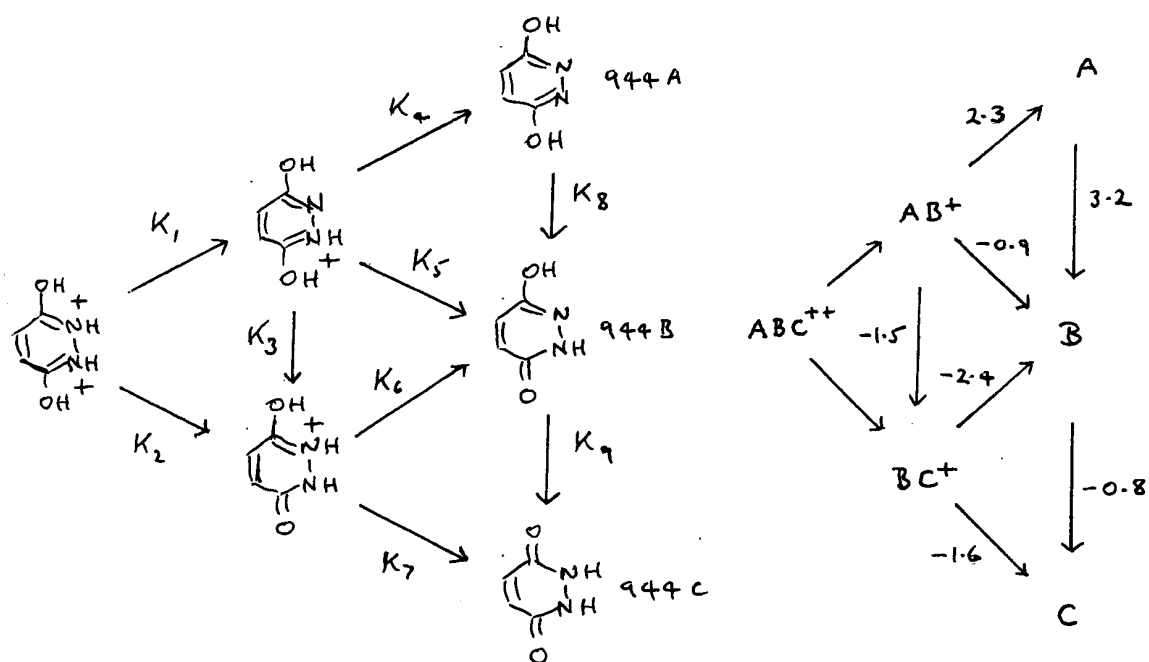
Information on isothiazolones is sparse. Chan *et al.*<sup>469</sup> give  $\log K_T$  0.5 for **934** in water; this falls to -0.6 in EtOH, a solvent effect typical of an amide (*cf.* section B.2.2). However, **935** with a second electron acceptor substituent exists as the enol shown, **936C** is probably dominant, and **937C** certainly so;<sup>2000</sup> here enolisation would give a quinonoid structure. These results suggest an order for  $K_T$  in **911** and probably **912** of  $Z = S > NR > O$ , *i.e.*  $K_T$  falls with rising electronegativity (see further in section C.15). However few of the structural types described in this section are incapable of generating, with suitable substituents or in nonpolar media, any of the possible tautomers, and more than with most chemical classes, individual compounds need to be considered on their merits.

### B.2.11 Cyclic 3-Acylhydrazides (COCONHNH)

As with pyruvamides **864** (section B.2.7) no perceptible enolisation is likely for open-chain 3-acylhydrazides **938**, though in principle this might occur in alicyclic molecules such as **939** (*cf.* **110**). No simple aromatic example has been reported but one of us<sup>106</sup> has investigated **940**, though only in  $\text{CHCl}_3$  solution, where its principal IR bands are at 1687s, 1625vs, and 1542ms  $\text{cm}^{-1}$ . This is enough to eliminate **940A**, and with the single  $\nu(\text{C}=\text{O})$  of **941** at 1656 vs  $\text{cm}^{-1}$ , **940D** may be discounted also. However, while the 1625 and 1542  $\text{cm}^{-1}$  bands of **940** are closely matched by 1622s and 1542ms  $\text{cm}^{-1}$  in **942**, its 1687  $\text{cm}^{-1}$  band is paralleled by  $\nu(\text{C}=\text{O})$  at 1678  $\text{cm}^{-1}$  in **854**,<sup>469</sup> so it is very probably a mixture of **940B** and **940C**. Despite the quinonoid nature of **940C** there is, in fact, no more difference between **475** (section A.10.7) and **859** (section B.2.5),  $\log K_T$  4.1 and 3.1 respectively, than substituent and effect of solvent might compensate for. We conclude, pending further investigation, that this compound probably exists as a mixture of **940B** and **940C**, with the former likely to be the major component but not by any great margin.

### B.2.12 Diacylhydrazines (CONHNHCO)<sup>470</sup>

Sandström<sup>471</sup> states that compounds of type (**943**,  $R^2 = \text{Me}$ ,  $Z = \text{S}$ ) show no sign of iminol formation to give either **943A** or **943C** and, as for simple hydrazides (section B.2.10), that conclusion may safely be assumed for all open-chain diacylhydrazines. Indeed **943B**, with its opposed dipoles and symmetrical intramolecular hydrogen bond, is a peculiarly stable structure and likely to be general. Problems arise on cyclisation, which gives scope for



945 (\*)                      945                      945 (+)                      947 (+)                      947

946 (++)                      946 (+)                      946                      948 (+)                      948

severe NH,NH-dipole clashes. Here the archetype is ‘maleic hydrazide’ **944**, the tautomeric pattern for which is set out as Scheme 38. This relates three neutral species through two monocations to a common dication, and is fundamentally insoluble since unequivocal models for the rival monocations are impossible.<sup>472</sup> (The contrast here is with uracil **888**, section B.2.9, whose deprotonation pattern follows that of Scheme 38 but with the difference that its two monocations are clearly distinguishable). It has been shown<sup>447</sup> on UV evidence that **945** protonates largely in the sense of **945**(+), not of **945**(\*), but since the ratio of these cations cannot be determined,  $K_3$  becomes incommensurable. Presumably this preference relates to the dipolar repulsion generated by protonation in the sense of **BC**+. In principle it should be possible to rescue the situation by working with models for  $pK_1$  and  $pK_2$ , but Barlin later<sup>473</sup> discounted his earlier results for  $pK_{10}$  and  $pK_{++}$  (Table 57) as probably artefacts due to drifting isosbestic induced by the changing composition of the solvent. Probably both true values lie at much lower  $pK_a$  values (*cf.* 4-phthalazinone **855**, section B.2.5). Values of around  $pK_a$  -2 or greater are likely to be reliable however,<sup>473</sup> and we base our analysis on these.

$$K^+ = \{(K_4 + K_5) + K_3 (K_6 + K_7)\} / 2 (K_3 + 1) \quad (\text{lxxi})$$

Our published analysis<sup>474</sup> has been modified in two minor ways. Firstly, we have taken **947** as a closer and therefore better model than **945** for  $pK_5$ . Here  $pK_{12}$  -1.32<sup>447</sup> becomes  $pK_5$  -0.9 (Table 57) after the usual correction. Secondly, we have applied the statistical corrections that should have been present previously but were not;  $pK_{11}$  -1.94<sup>447</sup> then becomes -2.24 and, on adding  $\Delta(\text{NR})$ , gives  $pK_7$  -1.6, whereas  $pK_{13}$  1.61<sup>447</sup> becomes 1.3, corrected to

**Table 57. Observed and ‘Corrected’  $pK_a$  Values for ‘Maleic Hydrazide’ **944** and Related Compounds<sup>a</sup>**

Compound	Model $pK_a$		‘Corrected’ $pK_a$	
<b>944</b> (++)			-3.28 <sup>b</sup>	$pK^{++}$
<b>944</b> (+)			-0.99 <sup>c</sup>	$pK^+$
<b>946</b> (++)	-3.96 <sup>b</sup>	( $pK_{10}$ )		
<b>946</b> (+)	-2.24 <sup>d</sup>	( $pK_{11}$ )	-1.6	$pK_7$
<b>947</b> (+)	-1.32	( $pK_{12}$ )	-0.9	$pK_5$
<b>948</b> (+)	1.31 <sup>d</sup>	( $pK_{13}$ )	2.3	$pK_4$

<sup>a</sup> Model  $pK_a$  data from ref. 447. <sup>b</sup> Value later discounted by author (ref. 447) as inauthentic.

<sup>c</sup> Experimental value. <sup>d</sup> Statistically corrected.

$pK_4$  2.3 by incorporating  $\Delta(\text{OR})$  for contiguous protonation (see Scheme 30). The value of  $K_3$  is unknown but from the UV evidence<sup>447</sup> concerning **945** it cannot be greater than 0.1, is probably less, and the value of 0.03 we have chosen<sup>474</sup> allows a very close fit of our calculated  $pK^+$  to the value observed, which is an important check on the validity of the analysis (Appendix 1). Solution of eqn. (1xxi) gives  $pK^+$  -0.92 where -0.99 is observed.<sup>447</sup> It will also be noticed that our estimated  $pK_5$ , which is expected to dominate over  $pK_4$ , lies close to the experimental value of  $pK^+$ . This probably takes the analysis as far as it can go at the present time.

Our prediction, for *ca.* 87% of **944B** and 13% of **944C** with a negligible fraction of **944A**, is in agreement with the consensus of opinion that **944B** is dominant but not overwhelmingly so. Other details are of interest. For **944A**  $\rightleftharpoons$  **944B**,  $\log K_8$  3.2 compares with a calculated 1.3 by use of eqns. (lxix) for OH and (lxx) for aza-nitrogen and indicates  $\Delta \log K_T$  1.9 as the consequence of lone pair repulsion in **944A**. A precisely parallel estimate for **944B**  $\rightleftharpoons$  **944C** is not possible, but we have attempted calculation in a more convoluted manner which results in an estimate of  $\Delta \log K_T$  -2.6 for *NH,NH*-dipolar repulsion (Appendix 3). This is the largest such value we have encountered and somewhat contradicts the proposition<sup>387</sup> (section B.1) that lone pair and dipolar repulsion at nitrogen typically show effects of similar magnitude. Calculations carried out at the 6-31G\*\*//6-31G\*\* level using molecular dynamics (MD) and two types of continuum model to simulate aqueous solution<sup>474</sup> also support **944B** as the dominant tautomer. Recasting  $\Delta G_{\text{tot}}$ <sup>474</sup> as  $\log K_8$ , these predict **944A** to be disfavoured by  $\log K_E$  *ca.* -3.5 in reasonable agreement with the empirical estimate above, but concerning **944C** the methodologies disagree. Here MD comes out as clearly superior, predicting  $\log K_9$  -1.4 whereas the continuum models give results ranging from -2.7 to -3.5. These calculations also predict the solvation order as **C** > **B** > **A**, but say nothing directly concerning intramolecular repulsive forces.

There is some information on benzofused species. The ease with which **6a** undergoes ring-chain tautomerism to **6b**<sup>27</sup> (Introduction) is suggestive evidence for a rather small energy gap between the **B**- and **C**-tautomers, and in complementary fashion, the predominance of **949B** over **949A**<sup>475</sup> despite the inducement of a potential intramolecular hydrogen bond helps to emphasise the latter's lack of importance. There is, however, some uncertainty concerning **950**. Elvidge and Redman<sup>476a</sup> demonstrate, from the IR spectra of **950**, **950(OMe)** and **950(NMe)**, that **950B** is that species present in the solid state, but their statement that the same is true for water is belied by their own UV spectrum, which shows **950** to resemble **950(NMe)** much more closely.<sup>476b</sup>

As seen elsewhere, it is nothing unusual for water to engender a switch in this direction. There is also another factor. We have noted (section B.2.5) that benzofusion of a 6-membered ring monocyclic oxoheterocycle appears to add  $\Delta \log K_T$  *ca.* 1.8 when the tautomeric nitrogen atom is in the  $\beta$ -position; that increment applied here would result in  $\log K_T$  1.0 for **950**, which is qualitatively and might be quantitatively correct.

Urazole **951** exists as shown in the solid state.<sup>2t</sup> With four neutral tautomers linked by three monocations its tautomeric pattern is still more complex than that of ‘maleic hydrazide’ **944** and, by abolishing some degeneracies, 1-substitution increases this still further. The tautomerism of 1-phenylurazole has been studied by Katritzky and co-workers<sup>477</sup> (Scheme 38a). Not all the possible model compounds were investigated, but the overall picture is reasonably clear. The fixed tautomers (**953**,  $R^2 = R^4 = \text{Me}$ ), **954**, and **955**, possess very different  $pK_a$  ranges, whose relative values demonstrate the dicarbonyl **C**-tautomer to dominate. Consistently, all compounds for which this is possible exist as that tautomer in the solid state.<sup>477</sup> The small  $pK_a$  variants shown by type **953** are not a contra-indication but have, in fact, provided two  $\Delta(\text{NR})$  values (**815a** and **816**, Appendix 1). Comparison of the  $pK_a$  values for **954** and **955** eliminates **956A** as an important contributor to the structure of **956** but does not certainly distinguish between **956B** and **956E**, though severe dipolar repulsion in **956E** (*vide* Appendix 3) makes **956B** much more probable. Since **952D** is similarly disadvantaged, it seems probable that the pathways from **A** to **C** *via* **D** or **E** in Scheme 38a may be eliminated from consideration. Hence, for **952** and probably for any urazole, **C** > **B** > **A** will be the order of tautomeric preference in water.

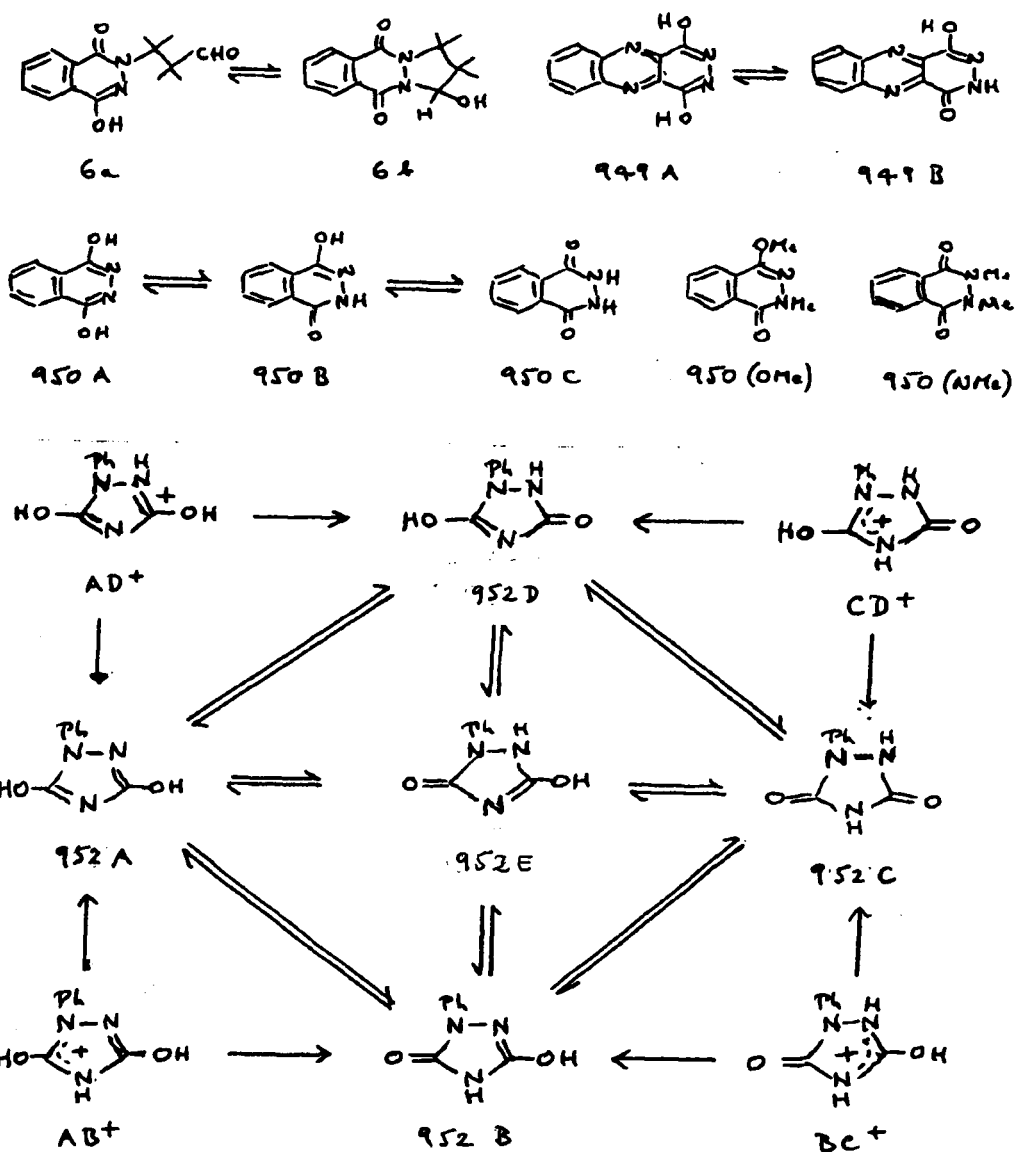
The actual tautomeric ratios are much more difficult to establish. Unfortunately, as noted by the authors, all neutral species possess similar UV spectra ( $\lambda_{\text{max}}$  239 – 248 nm) and so do all cations ( $\lambda_{\text{max}}$  238 – 243 nm), with the former always at the longer wavelength, making the spectra qualitatively valueless for present purposes. Hence it is impossible to establish, on this evidence, whether protonation of **952B** takes place predominantly to give **AB**<sup>+</sup>,

**Table 58.  $pK_a$  Values for 1-Phenylurazoles <sup>a</sup>**

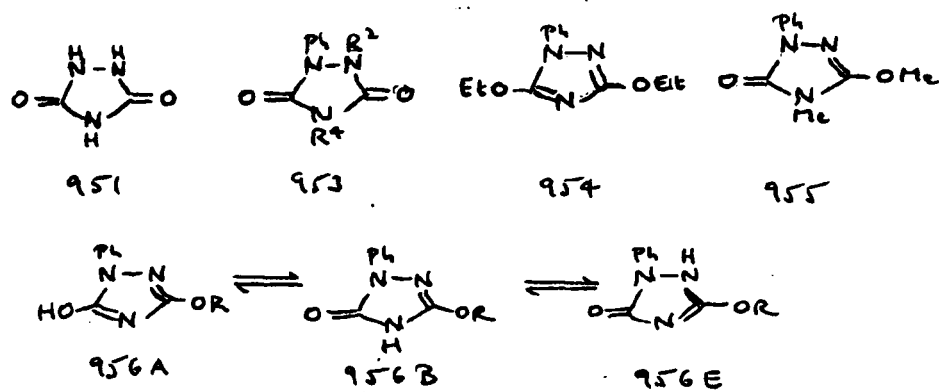
Compound	<b>953</b> <sup>b</sup>	<b>953</b> <sup>c</sup>	<b>953</b> <sup>d</sup>	<b>953</b> <sup>e</sup>	<b>954</b>	<b>955</b>	<b>956</b> <sup>g</sup>	<b>956</b> <sup>h</sup>
$pK_a$	-4.8	-4.7	-4.2	-4.1	-0.55	-3.1	-3.4	-2.9

<sup>a</sup> Ref. 477. <sup>b</sup>  $R^2 = R^4 = \text{Me}$ . <sup>c</sup>  $R^2 = \text{Me}$ ,  $R^4 = \text{H}$ . <sup>d</sup>  $R^2 = \text{H}$ ,  $R^4 = \text{Me}$ .

<sup>e</sup>  $R^2 = R^4 = \text{H}$ . <sup>f</sup>  $R = \text{Me}$ . <sup>h</sup>  $R = \text{Et}$ .



Scheme 38a



in which case  $K_{AB}$  is accessible but  $K_{BC}$  is not, or  $\mathbf{BC}^+$ , in which case the reverse applies. However, small but structurally significant differences in  $pK_a$  are found for **955** and **956**. 4-*N*-Methylation of (**956**, R = Me) to give **955** results in a rise in  $pK_a$ , from -3.4 to -3.1. In terms of *O*-protonation to  $\mathbf{AB}^+$  this would imply  $\Delta(\text{NR})$  -0.3, in the opposite direction to 0.45 for **812** for example (Scheme 30) and suggestive of the small but consistent base-strengthening effect found for *remote N*-methylation (Appendix 1). This supports the predominance of  $\mathbf{BC}^+$ . Too little is known concerning possible differences between  $\Delta(\text{OMe})$  and  $\Delta(\text{OEt})$  for the result for (**956**, R = Et) to be interpretable, but the relatively large effect of replacing OMe by OEt again suggests a direct rather than a remote effect. Both arguments point the same way, in which case **952B** and **952C** share a common cation. Correction of  $pK_a$  -3.4 for (**954**, R = H, R' = Me) to -2.4 for **952B** (*via* **812**, Scheme 30) yields  $\log K_T$  *ca.* 1.7 for the process **952B**  $\rightarrow$  **952C**. Unfortunately,  $\log K_T$  for the process **952A**  $\rightarrow$  **952B** then becomes inaccessible. However, an approximate estimate is possible. If  $\mathbf{BC}^+$  is the predominant cation of **952B** then  $pK_a < 2.4$  is required for the disfavoured cation  $\mathbf{AB}^+$  (*cf.*  $K_N$  and  $K_C$  for the kinetic and thermodynamic protonation of enamines, Scheme 6 in section A.4). This may be compared with a (presumed)  $pK_a > 0$  for **952A**, resulting from the (unknown)  $\Delta(\text{OR})$  correction for OEt, and leads to an estimate of  $\log K_T \geq 3$  for the process **952A** to **952B**.

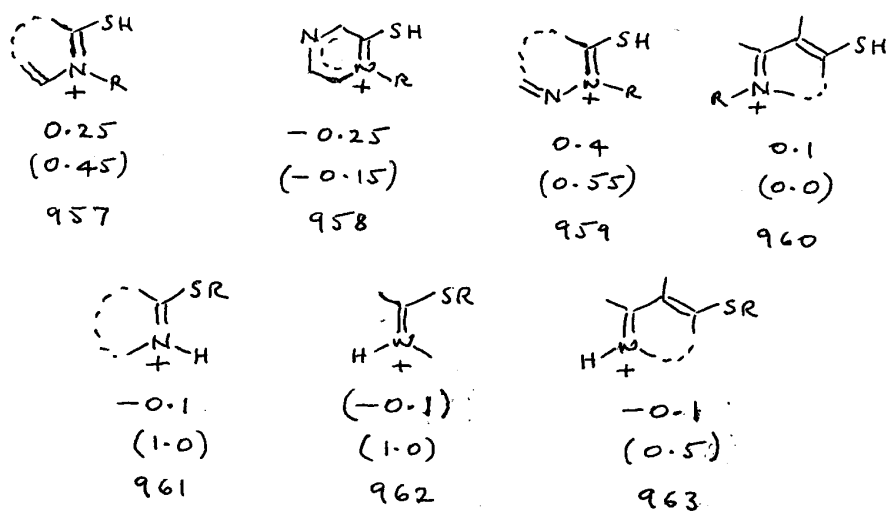
Successive  $\log K_T$  values of *ca.* 3 and 1.7 for **952** seem at first sight out of line with 3.2 and -0.8 for the formally similar tautomeric steps of 'maleic hydrazide.' However the first value, for **944A**  $\rightarrow$  **944B**, contains a contribution for lone pair repulsion in the former, estimated above as  $\Delta \log K_T$  *ca.* 1.9, which is absent from the parallel process for **952**. Correcting for this, the **A**  $\rightarrow$  **B** steps for **944** and **952** differ by  $\Delta \log K_T$  *ca.* 2, whereas the **B**  $\rightarrow$  **C** steps differ by the reasonably comparable margin of *ca.* 2.5, **952** possessing the higher value for each. Presumably this differential results from the replacement of C=C in **944**, an electron sink, by the strong electron donor NH in **952**; it is clear from other data on oxoheterocycles (sections A.10.6 and B.2.4) that electron-donor and -acceptor substituents tend to raise and lower  $K_T$  respectively. Or to put it another way: while **944** is an aromatic amide, **952** is expected to show some of the characteristics of an aliphatic urea. No more far-reaching conclusions can be drawn in this area at the present time.

### B.3 Thioamides, Thioureas and Related Structures

$$\log K_{T(S)} = 1.7 + 0.8 \log K_{T(O)} \quad (\text{lxxii})$$

The literature consensus is that tautomeric ratios in thioamides and related compounds so closely resemble those of their oxygen analogues that the latter may stand as surrogate for the former in the absence of precise information, and indeed Katritzky<sup>2uu</sup> suggests this as a guiding principle. So far as they differ, it is also supposed that  $K_T$  is still higher for the thiones; Katritzky<sup>2ppp</sup> suggests eqn. (lxxii), which implies  $K_{T(S)} > K_{T(O)}$  at any value of the latter but a slow decline in this differential as  $K_{T(O)}$  rises; in the important region of  $\log K_T$  3-4, about one unit difference would be expected. Use of  $\Delta(\text{OR})$  and  $\Delta(\text{SR})$  correction factors (Scheme 30, section B.2.1 and Scheme 39, below) narrows the gap appreciably but does not abolish it. Nevertheless doubts and hesitations, to be detailed below, must attach to the true  $K_T$  values of this class of compound, and these are exacerbated by an almost total failure to detect the SH tautomer in aqueous solution, so precluding the direct observation that has been so valuable in helping to establish the position for their oxygen analogues (section B.2.1). This contrasts with the behaviour of simple thiones, where enolisation of  $\text{C}=\text{S}$  is readier than that of  $\text{C}=\text{O}$  by a factor that ranges from  $\geq 10^6$  in simple cases (see section A.3.1 *et seq.*) to, possibly, *ca.*  $10^{3.5}$  in some more complex ones (section A.3.7), but this represents 'C-type' tautomerism whose driving force is entirely different (section A, *passim*).

#### B.3.1 Correction Factors for the Basicity Method



Scheme 39

Our very limited list of correction factors is displayed in Scheme 39, to which their oxygen equivalents from Scheme 30 are added in brackets. Here, with the exception of **960**, the values of  $\Delta(\text{NR})$  parallel those for their oxoheterocycle analogues but are less positive, and this parallelism extends even to those of the thiopyrazinones **958**, which are as anomalous here as for their oxygen analogues (*cf.* section B.2.1). The derivation of  $\Delta(\text{SR})$  for **961** and **963** has been explained (Table 45, section A.11.3); as before (section B.2.1), we have assumed that *cis-trans* isomerism will make no difference. Also as previously, it is the value of  $\Delta(\text{SR})$  that really counts. No other correction factors are accessible at the present time.

### B.3.2 Solvent Studies

$$\log K_T = -2.13 - 6.25(\varepsilon - 1)/(2\varepsilon + 1) + 2.87\alpha + 2.35\beta \quad (\text{lxxiii})$$

$$\log K_T = -0.95(0.10) + 1.74(0.18)\pi^* + 0.45(0.18)\alpha + 1.43(0.16)\beta$$

$$(n = 9 \quad r^2 = 0.979 \quad s = 0.13 \quad F = 77) \quad (\text{lxxiv})$$

$$\log K_T = -1.87(0.71) + 1.12(0.88)\pi^* + 1.09(0.37)\alpha + 0.33(0.30)\beta$$

$$(n = 11 \quad r^2 = 0.70 \quad s = 0.30 \quad F = 5.5) \quad (\text{lxxv})$$

The problems attaching to the LSER analysis of 4-thiopyridone **634** by Beak and Covington<sup>379</sup> are discussed in section A.11.2. They are equally prominent here. These authors studied 2-thiopyridone **964** and its 6-chloro derivative **965**, and their equation for the former, re-cast as  $\log K_T$ , is given as (lxxiii). As previously, an aqueous value for  $\log K_T$ , 4.3 of undisclosed origin, is set against values for organic solvents ranging from -0.9 to 1.5, making (lxxiii) a 'two-point correlation' hence statistically invalid. Removal of the point for water and the use of more up-to-date solvent parameters (Appendix 2) leads to eqn. (lxxiv). This equation, from which benzene and dioxane were excluded as outliers, predicts  $\log K_T$  2.06 for **964** in water, whereas use of the 'revised basicity method' (section B.3.4) gives  $\log K_T$  *ca.* 4.6. Inclusion of all organic solvents leads to much worse statistics ( $r^2 = 0.79$ ) but a very similar result:  $\log K_T$  2.14. Beak and Covington<sup>379</sup> give data, not including water, for **965**, but no equation. Use of all their data results in eqn. (lxxv) which predicts  $\log K_T$  0.76 for water, a believable value (*cf.* a predicted  $\log K_T$  *ca.* 0.3 for 6-chloro-2-pyridone **831**, section B.2.2), but the statistics are poor. It remains puzzling, and a worry, that both 2-thio- and 4-thiopyridone with their almost certainly very high  $K_T$  values should be so badly predicted by LSER when compounds for which this is much lower appear to give reasonable results.

Rejection of  $\text{CHCl}_3$  and DMA improves the statistics for **964** (to  $r^2 = 0.945$ ) but a still lower predicted  $\log K_T$  2.02 results. It is also disturbing that **964B** is much less disfavoured in an inert gas matrix ( $\log K_T -1.7$ )<sup>478</sup> than eqn. (1xxiv) would predict (*ca.* -3; and *cf.* ref. 434). We can only conclude that, at present, the LSER methodology is for some reason incapable of handling thioamides, and that the ‘revised basicity method’ is to be preferred.

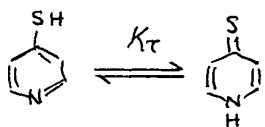
### B.3.3 Aliphatic Thioamides

From  $\text{p}K_a$  -1.9 and 7.71 for **966** and **967** respectively,<sup>479</sup> and after applying the  $\Delta(\text{SR})$  correction **962** (Scheme 39), we obtain  $\log K_T$  *ca.* 9.6 for a typical open-chain aliphatic thioamide. The only other available value is for **968**, where  $\text{p}K_a$  values of -2.5 and 6.42 for **968** and **969** respectively<sup>478</sup> lead similarly to  $\log K_T$  *ca.* 8.8. This difference of  $\Delta \log K_T$  -0.8 compares with our estimate of -0.5 for **840** *vs.* **832** (section B.2.3) and appears reasonable. Thioamides like amides are known to exist largely in the *trans*-conformation written for **966** and **968** but while there are indications that the *trans/cis* ratio may be greater for thioamides than for amides<sup>480</sup> none of the data are for aqueous solution so, in the absence of definitive information, we do not here attempt the isodesmic approach of section B.2.3 that has allowed tentative estimates of  $K_T$  for certain lactams (Table 54).

**Table 59. Comparative Data on Simple Thioamides, Thioureas, and their Oxygen Analogues**

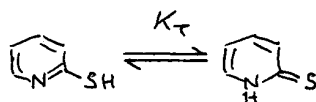
	$\text{R}^1\text{CZNHR}^2$			$\text{R}^1\text{NHCZNHR}^2$		
	$\log K_T$	$\mu^a$	$\log K_\beta^b$	$\log K_T$	$\mu^a$	$\log K_\beta^b$
Z = O	9.1 <sup>c</sup>	3.88 <sup>d</sup>	2.82 <sup>e</sup>	10.3 <sup>f</sup>	4.34 <sup>g</sup>	3.19 <sup>h</sup>
Z = S	9.6 <sup>c</sup>	4.64 <sup>i</sup>	1.76 <sup>j</sup>	11.0 <sup>k</sup>	5.50 <sup>l</sup>	1.96 <sup>m</sup>

<sup>a</sup> Permittivity in debyes at 25° in dioxane: A. L. McLellan, *Tables of Experimental Dipole Moments*, Vol. 1, W. H. Freeman, San Francisco, 1963; Vol. 2, Rahara Enterprises, El Cerrito, CA 94530, 1974. <sup>b</sup> For 1:1 association with 4-nitrophenol in 1,1,1-trichloroethane: ref. 72. <sup>c</sup>  $\text{R}^1 = \text{R}^2 = \text{Me}$ . <sup>d</sup> For  $\text{MeCONHPh}$ . <sup>e</sup> For  $\text{PhCONMe}_2$ . <sup>f</sup> For  $(\text{NH}_2)_2\text{C=O}$ . <sup>g</sup> For  $\text{MeNHCONH}_2$ . <sup>h</sup> For  $(\text{Me}_2\text{N})_2\text{C=O}$ . <sup>i</sup> For  $\text{MeCSNHPh}$ . <sup>j</sup> For  $\text{MeCSNMe}_2$ . <sup>k</sup> For  $(\text{NH}_2)_2\text{C=S}$ . <sup>l</sup> For  $\text{BuNHCSNH}_2$ . <sup>m</sup> For  $(\text{Me}_2\text{N})_2\text{C=S}$ .



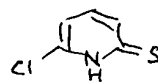
634 A

634 B

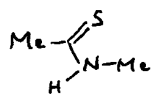


964 A

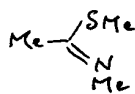
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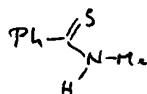
965 B



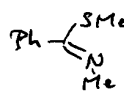
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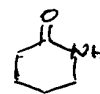
967



968



969



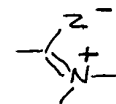
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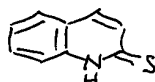
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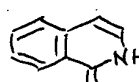
970a



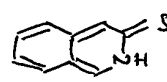
970b



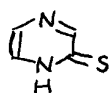
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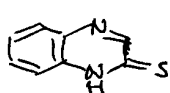
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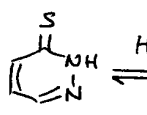
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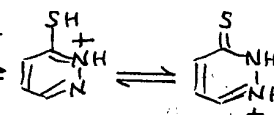
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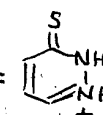
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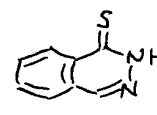
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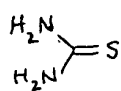
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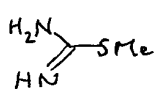
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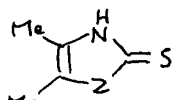
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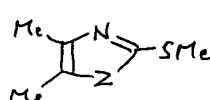
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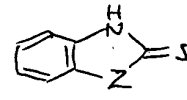
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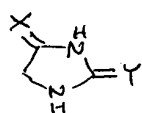
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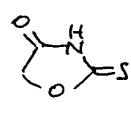
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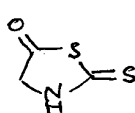
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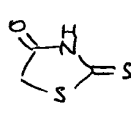
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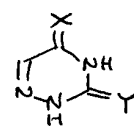
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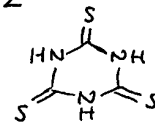
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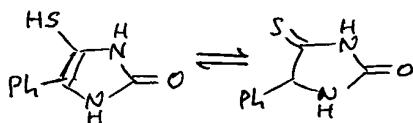
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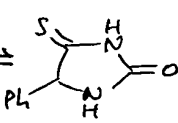
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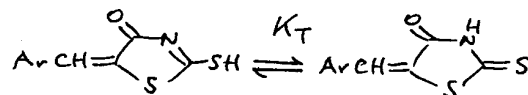
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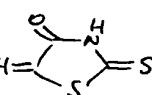
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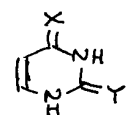
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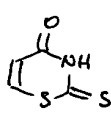
989 A



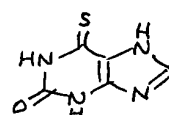
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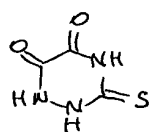
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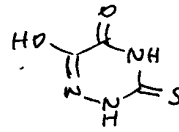
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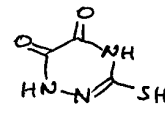
992



993 B



993 A



993 C

The higher value of  $K_T$  for thioamides and thioureas than their oxygen analogues, while quite slight, is difficult to reconcile with simple chemical theory. Their higher dipole moments are commonly discussed in terms of a presumed greater contribution of the dipolar canonical form **970b**, which if true would help to account for higher  $K_T$  values, since greater stabilisation of the thiono-tautomer is implied. Katritzky<sup>2qqq</sup> uses a variant of this argument in supposing that the greater acidity of C–SH compared with C–OH stabilises (**970b**, Z = S) in relative terms to a greater extent than the greater bond strength of C=O stabilises (**970a**, Z = O). However, an enhancement of their proton acceptor ability would also be expected (*cf.* its very high value for sulfoxides and phosphoryl compounds<sup>72</sup> with their largely dipolar structures<sup>481</sup>) whereas the reverse is found (contrast the data for  $\mu$  and  $\log K_\beta$  in Table 59). It seems possible to the authors that this dipole moment enhancement is due, not to resonance, but to a field effect, perhaps resulting in part from the longer dipole of C=S. This would fall into line with the much stronger electron withdrawing ability of simple thione C=S relative to ketonic C=O revealed by our *ab initio* calculations and which shows itself in their relative ‘promoting power’ towards enolisation in structures of type  $R^1C(=X)CH_2C(=Y)R^2$  (see summary discussion in section A.12). If so, it provides an unexpected point of contact between ‘C-type’ and ‘N-type’ tautomerism which has so far been overlooked.

#### B.3.4 6-Membered Ring 2-Thionoheterocycles

Aqueous solution data are assembled in Table 60. It will be seen that, according to the ‘revised basicity method,’ most  $K_T$  values are higher than for their oxygen analogues, and indeed eqn. (lxxii) is approximately obeyed (at 0.75, the exponent is fractionally lower). The surprising exceptions are **974** and **975** where  $K_T$  is much reduced, the second result being corroborated by two groups of workers. This result is inexplicable, but in that respect is in line with the equally puzzling values of  $\Delta(NR)$  found in both the oxygen and sulfur series (Schemes 30 and 39 respectively); see however section B.8.19. According to Barlin and Young,<sup>382b</sup> protonation of **976** is split more or less evenly between **976H** and **976X**, which given  $pK_a$  -2.68 overall implies  $pK_a$  *ca.* -3 for each, and it is on this basis that  $\log K_T$  has been calculated. Given the complications attaching to its oxygen analogue **855** (section B.2.5), it is altogether possible that our calculated  $K_T$  for **977** is in error, but at least there can be no doubt which tautomer is dominant.

Some unease must attach to the lack of consistency shown *e.g.* by the effect of benzofusion on  $K_T$ , in contrast to the simple and elegant regularities shown by their oxygen analogues (section B.2.5). It is unfortunately possible that some of this early work (1958-62), carried out without the knowledge since gained on protomeric complications (cf. **855**) and having to use slow-paced titrational techniques that may have contributed to compound breakdown, now requires revision. Nevertheless the central message is clear: the thiono-tautomer dominates, usually by a large margin, and in general probably larger than that for their oxygen analogues. No work appears to have been carried out to determine the effect of substitution but, as with their oxygen analogues, it is probable that only for the pyrazines is there much chance of forcing these compounds over to the SH tautomer, except with the most electronegative substituents.

**Table 60.  $pK_a$  and  $\log K_T$  Values for 2-Pyridithione and Related Thionoheterocycles in Aqueous Solution<sup>a</sup>**

Compound	$pK_a$ (NH)	$pK_a$ (SMe)	$pK_a$ (SH) <sup>b</sup>	$\log K_T$	$\log K_{T(O)}$ <sup>c</sup>
<b>964</b>	- 1.07 <sup>d</sup>	3.62 <sup>d</sup>	3.52	4.6	3.5
<b>971</b>	- 1.44 <sup>d</sup>	3.71 <sup>d</sup>	3.61	5.1	4.5
<b>972</b>	- 1.9 <sup>d</sup>	3.93 <sup>d</sup>	3.83	5.7	5.4
<b>973</b>	0.39 <sup>d</sup>	3.41 <sup>d</sup>	3.31	2.9	1.7
<b>974</b>	- 0.73 <sup>e</sup>	0.48 <sup>e</sup>	0.38	1.1	1.9
<b>975</b>	- 1.24 <sup>e</sup>	0.29 <sup>e</sup>	0.19	1.4	2.8
	- 1.11 <sup>f</sup>	0.26 <sup>f</sup>	0.16	1.3	2.8
<b>976</b>	<i>ca.</i> - 3 <sup>g</sup>	2.26 <sup>h</sup>	2.16	5.2	5.1
<b>977</b>	- 3.43 <sup>e</sup>	3.48 <sup>e</sup>	3.38	6.8 <sup>g</sup>	6.8

<sup>a</sup>  $\log K_T = pK_a(\text{SH}) - pK_a(\text{NH})$ . <sup>b</sup> Calculated as  $\Delta(\text{SMe}) = - 0.1$  (Scheme 39).

<sup>c</sup>  $\log K_T$  for oxygen analogue (section B.2.5). <sup>d</sup> Ref. 381. <sup>e</sup> Ref. 382a. <sup>f</sup> Ref. 446. <sup>g</sup> See the text. <sup>h</sup> Ref. 382b.

### B.3.5 Thioureas (NHCSNH) and Acylthioureas (CZNHCSNH)

For thiourea **978** as for urea (section B.2.9), the requisite data are available. From **978**,  $pK_a$  -1.28,<sup>452</sup> and **979**,  $pK_a$  9.83,<sup>255</sup> then applying a constant correction of  $\Delta(\text{SR}) = - 0.1$  as appears in Scheme 39, we obtain  $\log K_T$  *ca.* 11.0. This small enhancement is similar to that for thioamides (*cf.* Table 59) and appears reasonable.

**Table 61.  $pK_a$  and  $\log K_T$  Values for 5-Membered Cyclic Thioureas and Related Compounds<sup>a</sup>**

Z	$pK_a$ ( <b>980</b> )	$pK_a$ ( <b>981</b> )	$pK_a$ (SH) <sup>b</sup>	$\log K_T$
NH	- 1.2	6.85	6.75	8.0
NMe	- 1.4	6.68	6.58	8.0
O	- 3.9	2.5	2.4	6.3
S	- 2.8	3.3	3.2	6.0

<sup>a</sup> Ref. 483. <sup>b</sup> Assumes  $pK_a$  (SH) =  $pK_a$  (SMe) - 0.1 (Scheme 39).

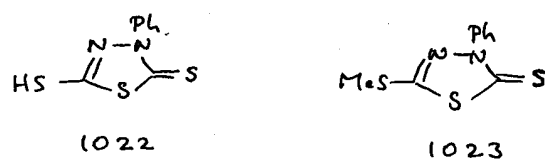
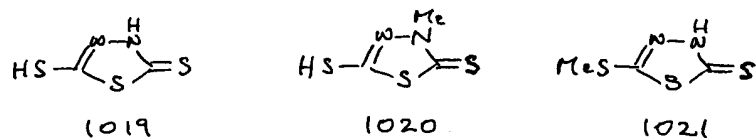
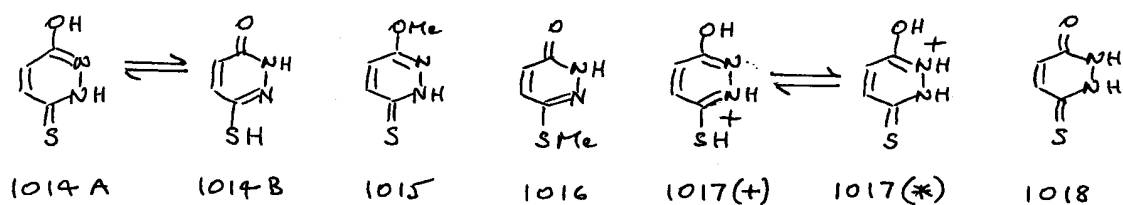
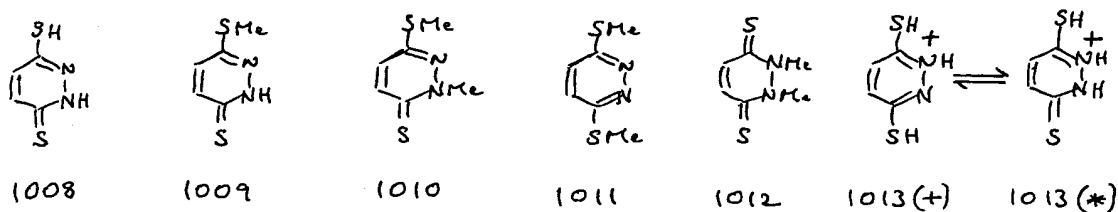
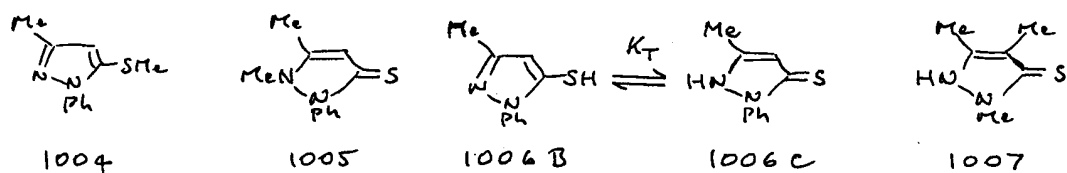
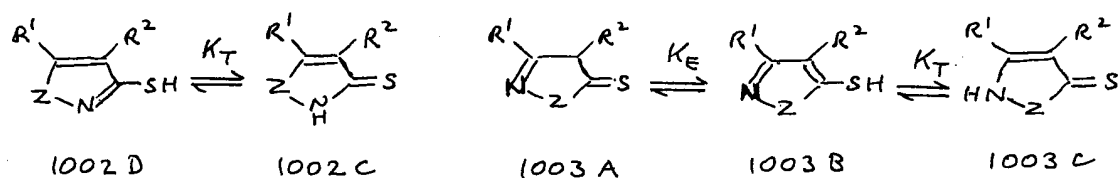
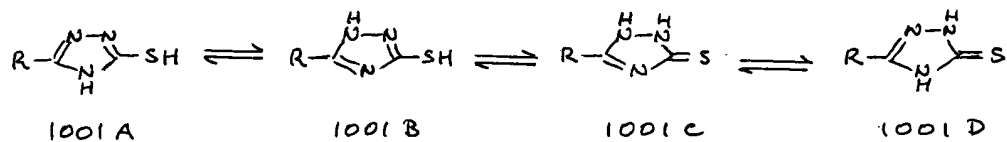
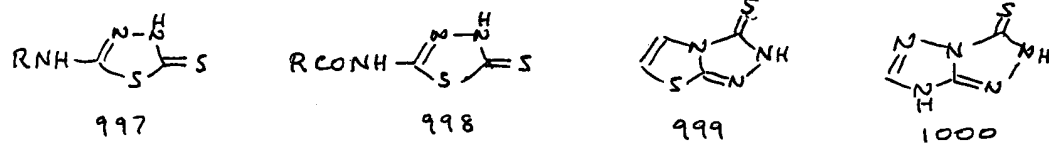
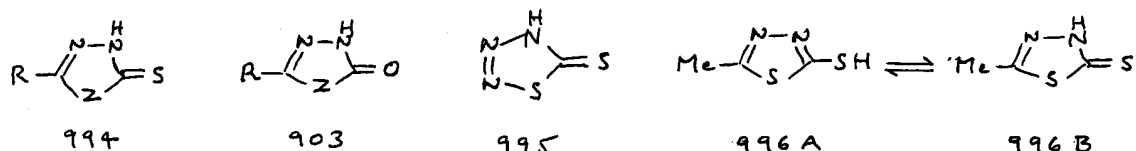
Kjellin and Sandström<sup>483</sup> have studied the cyclic ureas and urea-type compounds that appear in Table 61. Here the effect of aromaticity, partly counterbalanced by alkyl substitution, is to reduce  $K_T$  by a factor of *ca.*  $10^3$ , notably less than the (not entirely comparable) gap of *ca.*  $10^6$  between an open-chain thioamide **966** and pyrid-2-thione **964** (sections B.3.3 and B.3.4, above). This adds to the indications that benzofusion has much less effect on  $K_T$  in 5- than in 6-membered rings. The data for (**980**, Z = O and S) are also useful in confirming the classification of these as urea-type structures, with  $K_T$  not greatly inferior to those for the thioureas themselves, while lying in the direction expected on resonance considerations. They are also valuable in allowing an intelligent guess to be made concerning their oxo-analogues. Equation (lxxii) predicts  $\log K_T$  *ca.* 7.8 for Z = NH; a more likely empirical estimate, based on simple oxo-thiono comparisons, would suggest  $\Delta \log K_T \sim -0.5$  for the series. Neither estimate is likely to be far from the truth.

These authors also demonstrate  $\Delta \log K_T$  *ca.* -1.5 for compounds in which 4- or 5-Ph replaces 4,5-diMe substitution, and state that  $K_T$  increases on benzofusion, as expected, but probably not by much. It is all the more surprising, therefore, that Balastrero *et al.*,<sup>484</sup> who have investigated the parallel members of series **982** in DMSO, report 8% of the iminothiol for (**982**, Z = S), *i.e.*  $\log K_T$  *ca.* 1.1. Their evidence is based on the position of the <sup>15</sup>N signal, which is subject to time-averaging but shows a downfield shift of 90 - 120 ppm in the -SMe derivatives, which margin, as the authors say, should be ample for quantitative work. Nevertheless this method suffers from the same potential trap as 'naive basicity' in that equal <sup>15</sup>N shifts for SMe and SH have to be assumed, and we regard this result as unproven. It also requires a solvent shift, from DMSO to water, probably of  $\Delta \log K_T \geq 4$ . While such shifts can often be large, and should be in this direction (Appendix 2), there is no precedent involving these solvents for one of such magnitude.

Hydantoins in every possible permutation (**983**, X or Y = O or S) are known and exist as such, along with such variants as **984** - **986**;<sup>2mm</sup> one may compare (**893**, X or Y = O or S) for which the same is true (section B.2.9). Similarly, **987**<sup>2rrr</sup> may be compared with its oxo-analogue **892**. Nevertheless, there are two curious exceptions. Phenyl substitution into (**983**, X = S, Y = O) gives **988A** not **988B**;<sup>2mm</sup> this does not happen with hydantoins and highlights the far greater susceptibility of C=S than of C=O to ‘C-type’ tautomerism (*cf.* section A.3.7 for a provisional estimate of  $\Delta \log K_E$  *ca.* 3.5 for this difference). The other example, much more difficult (*i.e.* impossible) to explain, is **989**, for which  $K_T = 6$  in aqueous dioxane<sup>2mm</sup> though **986** shows no tendency to generate a thioiminol. Setting aside other potential examples of these types, however, it may otherwise be taken for granted that C=O and C=S are interchangeable as to tautomeric form throughout this series.

The same applies to uracils, and here there are no exceptions, though quantitatively, nothing is known. All variants on (**990**, X or Y = O or S) have been prepared and exist as such,<sup>2sss</sup> and similarly **991**, which may be compared to its oxo-analogue **877** (section B.2.9). The xanthine analogue **992** exists in the identical tautomeric form<sup>2yy</sup> (other variants involving thiones appear in sections B.1.6 and B.1.7). Lone pair and dipolar interactions ensure that **993** exists as **993A** rather than as either alternative possibility.<sup>2rrr</sup> Here as almost throughout this section, simple principles previously enunciated can act as definitive guides to structure.

We also include in this section compounds of type **994**, which may equally be classified as thionohydrazides (following section) and are placed in close proximity to these for that reason. (The same dichotomy arises with their oxo-analogues, placed on similar arguments in section B.2.9). Here, (**994**, Z = O and S) exist as shown<sup>2q</sup> as do their analogues **903**; the alternative SH-tautomer, here and for **995**, would entail severe lone pair repulsion. For **996**, Müller and co-workers<sup>485</sup> carried out *ab initio* calculations [B3LYP/6-311 + G(d,p)] which resulted in  $\Delta E_{\text{elec}}$  37.2 kJ mol<sup>-1</sup> in favour of **996B**; for  $\Delta\Delta S = 0$  this corresponds to  $\log K_T$  *ca.* 6.5. This is surprisingly close to the experimental result (Table 61) for (**982**, Z = S);<sup>483</sup> avoidance of lone pair repulsion in **996A** might well have resulted in a larger value. Kurasawa and Takada<sup>486</sup> demonstrated that, in DMSO, no forms of **997** or **998** other than those shown are detectable, whereas by UV in MeOH, Potts and co-workers did the same for **999**<sup>487a</sup> and **1000**.<sup>487b</sup> Annular tautomerism other than that involving thiol formation was not discussed, but the alternatives involving nitrogen alone that are open to **1000** would show severe dipolar repulsion (Appendix 3) and are highly improbable.



Compound **1001**<sup>488</sup> represents a more difficult case, since while **1001D** is expected to dominate, there are three other possibilities, not one. While **1001C** can certainly be eliminated on the grounds of severe dipolar repulsion (*vide* Appendix 3), it is not clear to which of **1001A** and **1001B** their reported  $\log K_T$  4.4 refers, since an S-methyl species could be derived from either. If from **1001B** as is perhaps more likely,  $K_T$  relative to **1001A** with which it directly compares and which is relevant to 4-substituted compounds must be higher, in line with its much higher values (Table 61) for (**980**, Z = NH or NMe). For (**994**, Z = O and S), it is therefore probable that  $K_T$  will also be quite high.

### B.3.6 Thiohydrazides (CSNHNH) and Related Compounds

As for their oxygen analogues, the chief interest of this section lies in 5-membered ring heterocycles containing contiguous hetero-atoms, for which lone pair or dipolar repulsion is likely to be important. As before, there are two distinct series, **1002** and **1003** (Z = O, S or NR) which parallel **911** and **912** respectively (section B.2.10). Much less is known, however. For series **1002** the only hard data are for (**1002**, R<sup>1</sup> = Ph, R<sup>2</sup> = H, Z = S) which, on UV evidence,<sup>489</sup> is 100% **1002D** in CCl<sub>4</sub> and still mostly this in EtOH. Given  $\log K_T$  -0.6 for its oxo-analogue **934** in EtOH,<sup>468</sup> this suggests little difference between them, in which case  $\log K_T$  0.5 in water for **934**<sup>468</sup> may not be far off the mark for both. There is more information on series **1003**, mostly due to Tanaka.<sup>490</sup> From  $pK_a$  values of 1.30 and -0.35 for **1004** and **1005** respectively, we deduce  $\log K_T \sim 1.6$  for **1006**;  $pK_a$  -0.30 for the latter<sup>490</sup> confirms both the identity of the major tautomer and the miniscule  $\Delta(NR)$  correction required (**963**, Scheme 39). The  $K_T$  value for (**1003**, R<sup>1</sup> = Me, R<sup>2</sup> = H, Z = NMe) is not quite so certain, but given  $\log K_T$  values of 0.18 and 0.41 in EtOH and MeOH respectively, as compared with values of -0.43 and -0.25 for **1006**,<sup>490</sup> we may fairly estimate  $\Delta \log K_T$  -0.6 relative to the latter, from which we deduce  $\log K_T$  2.2 for the former in aqueous solution. These deductions lie close enough to Tanaka's estimates<sup>490</sup> of 98% and 99% for the amount of C-tautomer in **1006** and this N-methyl analogue to pass muster (though 96% for **1007**, hence  $\log K_T$  *ca.* 1.4, does seem too low). These estimates, of  $\log K_T$  1.6 and 2.2 in water for **1006** and (**1003**, R<sup>1</sup> = Me, R<sup>2</sup> = H, Z = NMe) respectively, are just on the high side of 1.5 and 1.7 for their oxo-equivalents **431** and **917** (section B.2.10). Maquestiau *et al.*<sup>491</sup> have also investigated the latter thione and state the B-tautomer to be present to the extent of 100% in dioxane and 70% in DMSO, which approaches the factors for these solvents,  $\Delta \log K_T \sim -2$  relative to water in each case, found for the related **431** (Appendix 2). It is interesting that the A-tautomer (*cf.* section B.2.10) seems never to have been reported for this series, perhaps because of the susceptibility of C=S to 'C-type' tautomerism as noted above.

### B.3.7 Dithioacylhydrazines (CSNHNHCS) and Related Compounds<sup>492</sup>

Barlin<sup>447</sup> has measured the  $pK_a$  values of **1008**, the sulfur equivalent to ‘maleic hydrazide’ **944** (section B.2.12), and its derivatives **1009** - **1012**. The near-identity of the UV spectra for **1008**, **1009** and **1010**, along with a near-identity in their  $pK_a$  values (-2.55, -2.62 and -2.55), marks all as possessing the tautomeric form represented by **1010**,<sup>447</sup> as for ‘maleic hydrazide’ itself. (These  $pK_a$  values provide further evidence as to the very small  $\Delta(SR)$  and even  $\Delta(NR)$  values present in thioamides; *cf.* Scheme 39). Given a (statistically corrected)  $pK_a$  -4.4 for **1012**, which on further correction for  $\Delta(NR)$  becomes -3.9,<sup>493</sup> **1013(\*)** must be even more disfavoured relative to **1013(+)** than its equivalents in the former series; by  $10^{2.5}$  at the very least. No estimate for the proportion of the dithiono-tautomer **1018** can be made. However, given  $pK_a$  1.55 for **1011** (after statistical and  $\Delta(SR)$  corrections), and  $pK_a$  -2.55 for the *dominant* deprotonation pathway leading from **1013(+)** to **1008** (*cf.* Scheme 38), we arrive at  $\log K_T$  *ca.* 4.1 for formation of **1008** from the tautomeric dithiol, somewhat greater than that for ‘maleic hydrazide’ (3.2) in line with expectation.

For the ‘mixed species’ **1014** the chief interest lies in which of **1014A** and **1014B** dominates. Given typically higher  $K_T$  values for thioamides than for amides – see above – one expects **1014A** to predominate and this has been confirmed:<sup>494</sup> whereas **1016** in water has a single, very strong UV peak at 250 nm, **1014** and **1015** possess twin peaks at 245 and 280 nm. Other aspects are more puzzling. Precedent suggests that the major cation of **1014** should be **1017(+)** not **1017(\*)**, but  $pK_a$  -2.36 and -1.39 for **1015** and **1014** respectively strongly suggests the usual  $\Delta(OR)$  +1.0 correction for *O*-protonation of an amide, not the almost negligible effect normal for *S*-protonation (Scheme 39), implying the reverse. The alternative, a ‘remote’ effect of  $\Delta pK_a$  0.97 on the deprotonation of **1017(+)**, due to the replacement of OMe by OH, strains credulity. Preference for the monocation **1013(+)**, and the parallel species for ‘maleic hydrazide,’ is plausibly driven by severe dipolar repulsion in its rival, but while this must be present in **1017(\*)** as well, there is an extra factor, due to its asymmetry, to consider. Amides are stronger bases than thioamides, typically by  $\Delta pK_a$  *ca.* 2 or more, and this will stabilise **1017(\*)** relative to **1017(+)** to an extent that might prove decisive. Without more evidence, this issue cannot be decided.

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Compound <sup>a</sup>	<b>1019</b> <sup>b</sup>	<b>1020</b> <sup>b</sup>	<b>1021</b>	<b>1022</b> <sup>b</sup>	<b>1023</b>
acid $pK_a$	- 1.36, 7.53	- 1.40		- 1.59	
basic $pK_a$	- 5.40	- 5.30	- 4.85	- 6.50	- 5.44

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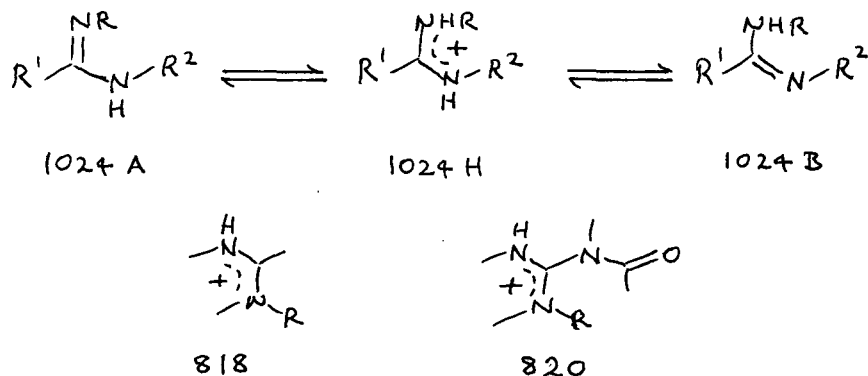
<sup>a</sup> Ref. 496. <sup>b</sup> These compounds possess v(SH).

The only other compound to be investigated in detail is the potential dithione **1019**. This exists as the ‘mixed’ ZH/C=Z tautomer displayed, in the crystal state<sup>495</sup> and in DMSO solution,<sup>487</sup> *i.e.* that form which also dominates for **1008**, **1014**, and ‘maleic hydrazide’ **944** itself. Calculations by Müller and co-workers<sup>485</sup> at the [B3LYP/6-311 + G(d,p)] level assign it as more stable than the dithione and dithiol by  $\Delta E_{\text{elec}}$  24.6 and 42.7 kJ mol<sup>-1</sup> respectively, *i.e.* qualitatively in the order found for ‘maleic hydrazide’ and, probably, elsewhere. Investigations of the series **1019** - **1023** by Stanovnik and Tišler<sup>496</sup> in aqueous solution show **1019**, **1020** and **1022** to possess  $pK_a$  values in the region of -1.5 which must be due to ionisation of SH since the basic  $pK_a$ ’s of all five compounds are much lower. The potential dithiol **1019** forms a dianion of  $pK_a$  7.53 in the region expected for a thioamide. All potential dithiols, but not **1021**, show  $\nu(\text{SH})$  though the medium is not stated. Taken together this evidence confirms that all exist as the above ‘mixed’ tautomer, but since no model for any other tautomer has been studied, no estimate of tautomeric ratio can be made.

Their site of protonation, whether C=S or C=N, is uncertain. The authors<sup>496</sup> assume dominant S-protonation and claim support from the basic  $pK_a$  values but this evidence is equivocal. Given  $pK_a$  -5.40 and -5.30 for **1019** and **1020** respectively we have, for the latter, either an anomalous  $\Delta(\text{NR})$  -0.1 for thione protonation where an appreciable positive value would be expected (*cf.* **959**),<sup>493</sup> or the slight base-strengthening effect on thioiminol  $pK_a$  expected for remote N-alkyl. From  $pK_a$  -5.40 and -4.85 for **1019** and **1021** respectively, we have, after statistical correction, either  $\Delta(\text{SR})$  -0.25 for protonation of a thioiminol, or an effect on thione protonation of  $\Delta pK_a$  0.25 caused by remote S-methylation. The situation worsens for **1022** *vs.* **1023**,  $pK_a$  -6.50 and -5.44 respectively, since even larger effects are implied, for which neither interpretation seems reasonable. Leaving aside the last example as seriously anomalous, we find the interpretation in terms of thioiminol protonation in each case more convincing; *cf.* the urazoles of section B.2.12, where we believe a similar situation to prevail. As for ‘maleic hydrazide’ and **1013** the countervailing argument is that of dipolar repulsion in the N-protonated cation, but in the present case, unfortunately, insufficient model compounds have been studied for all issues to be resolved.

If  $pK_a$  -0.25 for **1021**  $\rightarrow$  **1019** does indeed represent  $\Delta(\text{SR})$ , there results a small revision of our current estimate (Scheme 39). It is the kind of value associated with the effect of remote N-alkylation on the  $pK_a$  values of heterocycles (Appendix 1) and carries the implication that for C-SH, even when carrying a partial positive charge, solvation by water has negligible effects. Such a value for  $\Delta(\text{SR})$  would remove most of the remaining difference in  $K_T$  between amides and thioamides and, while this postulate cannot be proved, we think it plausible.

## B.4 Amidines



Of the six basic tautomeric systems – ketones, thioketones and imines; amides, thioamides and amidines – the last is unique. Since the same element, nitrogen, is common to both arms of the structure, tautomeric balance as in **1024** depends entirely on the nature of the substituents and not at all on the underlying system. Two distinct situations may be identified. In the first,  $\text{R}^1$  is symmetrical and tautomeric ratio depends entirely on  $\text{R}^2$  and  $\text{R}$ ; for  $\text{R} = \text{R}^2$ ,  $K = 1$  necessarily. If  $\text{R}^1$  is asymmetrical, however, there is scope for an intercept term: that is,  $K \neq 1$  even when  $\text{R}^2$  and  $\text{R}$  are identical. We shall examine the simpler situation first.

Amidines are bases and the ‘basicity method’ is central here to the derivation of tautomeric ratio. Correction factors are generally small and have been listed in Scheme 30 (section B.2.1) but are repeated in section B.4.1 below for convenience. Except for some acylamidines, which form a major category of their own (section B.5) and are here excluded except in passing, no solvent studies of any consequence have been carried out.

### B.4.1 Correction Factors for the Basicity Method

These appear in section B.2.1. For simple amidines **818** we find  $\Delta(\text{NR})$  0.3, essentially unchanged in 2(3)-substituted acylguanidines **820**. The first is derived from imidazole and benzimidazole (Appendix 1). The second may be derived from **1025**<sup>159</sup> if we suppose that the same  $\Delta(\text{NR})$  is applicable to both nitrogen atoms, given that their geometries are all but identical. In that case,  $\text{p}K_{\text{a}}$  8.14 and 8.56 for **1026** and **1027** respectively<sup>159</sup> sum to give  $\text{p}K_{\text{a}}$  8.00, which on comparison with  $\text{p}K_{\text{a}}$  8.36 for **1025**, gives  $\Delta(\text{NR})$  0.36. This is close enough to  $\Delta(\text{NR})$  for **818** to suggest identity with it, resulting in  $\Delta(\text{NR})$  0.3 for both.

### B.4.2 Tautomeric Balance in Symmetrical Amidines

Charton<sup>170</sup> has pointed out that the cation (**1024H**,  $R \neq R^2$ ) of any amidine may be expected to lose its proton from that nitrogen atom which carries the more electronegative substituent.<sup>497</sup> He also postulated,<sup>170</sup> and we have confirmed,<sup>96</sup> that the influence of substituents on the  $pK_a$  values of monosubstituted guanidines is governed solely by a field effect. We give our equation as (lxxvi); it was painstakingly demonstrated that no variant on  $\sigma_R$ , nor any variable intended to take into consideration the possible effect of an intramolecular hydrogen bond, is statistically significant.<sup>96</sup>

$$pK_a = 14.18(0.25) - 22.58(0.78) \sigma_I \quad (\text{lxxvi})$$

$$(n = 16 \quad r^2 = 0.984 \quad s = 0.51 \quad F = 835)$$

Since almost all substituents possess positive values of  $\sigma_I$  (Table 2), then presuming that all amidines behave in a parallel fashion, the major tautomer for almost any monosubstituted amidine must be that in which  $C=N$  carries the substituent. (Alkyl, for which  $\sigma_I \sim -0.01$ , is marginally an exception; here it is probable that no preference exists<sup>96</sup>). However, this fact does not on its own supply a tautomeric *ratio*. In principle, that information is accessible *via* the ‘basicity method,’ from the  $pK_a$  values of models for the rival tautomers. In practice, scarcely any such work has been carried out. Instead, and uniquely, a different approach is possible.

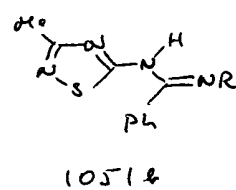
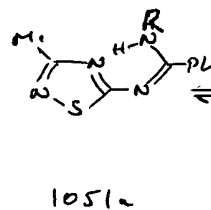
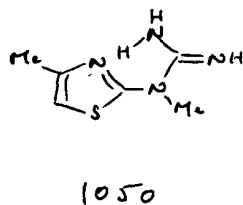
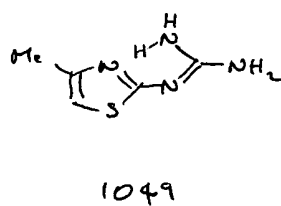
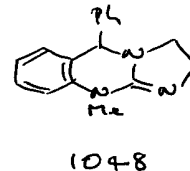
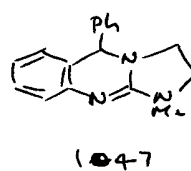
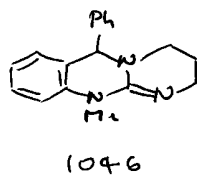
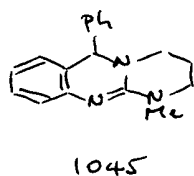
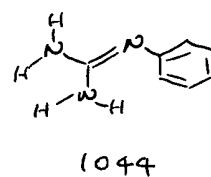
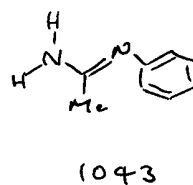
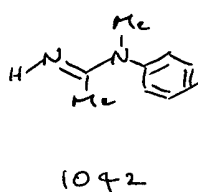
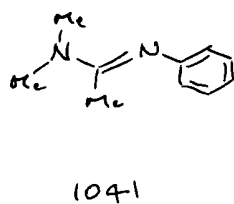
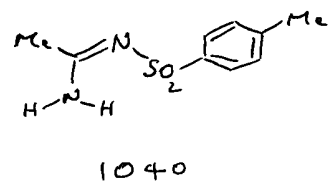
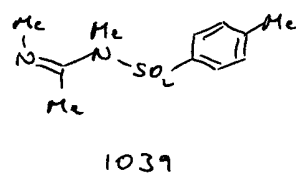
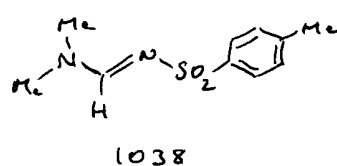
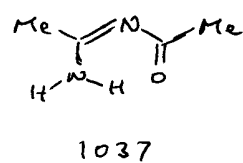
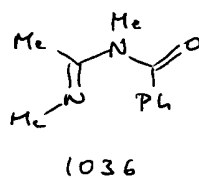
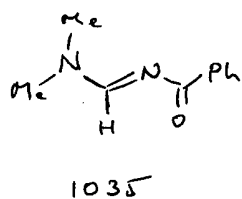
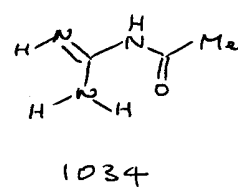
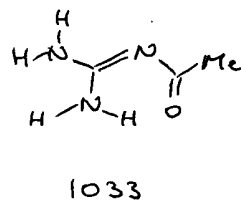
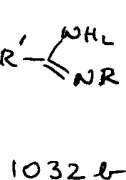
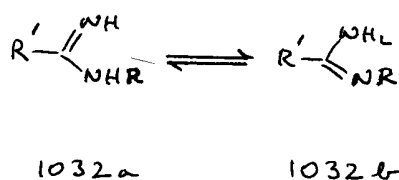
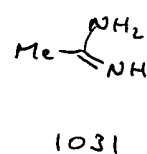
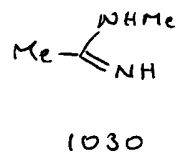
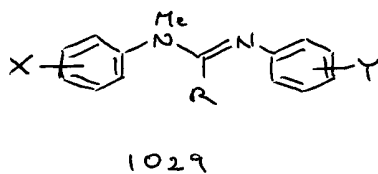
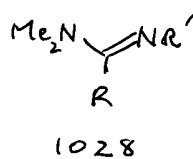
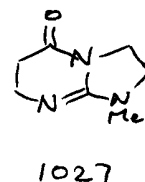
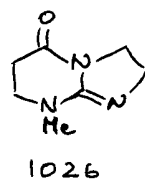
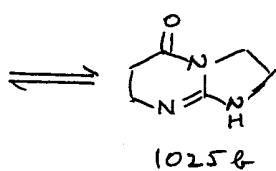
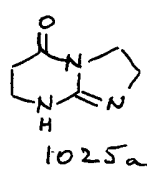
Oszczapowicz and co-workers<sup>498</sup> have published a set of papers on the  $pK_a$  values, in ‘azeotropic ethanol’ (95.6% EtOH), of a series of amidines whose structures may be summarised as **1028** and **1029**, where  $R = H$ , alkyl or aryl and  $R'$  in **1028** includes *inter alia* the whole group PhY. This work was aimed at establishing predictive rules for  $pK_a$  values in multi-substituted compounds of type **1029**. Its importance here is that it enables us to solve the problem of tautomeric ratio in simple amidines.

$$pK_a = 8.24(0.05) - 2.99(0.17) \sigma_Y \quad (\text{lxxvii})$$

$$(n = 12 \quad r^2 = 0.968 \quad s = 0.17 \quad F = 299)$$

$$pK_a = 10.09(0.06) - 3.57(0.14) \sigma_P \quad (\text{lxxviii})$$

$$(n = 7 \quad r^2 = 0.993 \quad s = 0.13 \quad F = 689)$$



For a series of compounds **1028** in which  $R = \text{Me}$  and  $R' = m\text{-}$  and  $p\text{-}$ substituted phenyl, we obtain eqn. (1xxvii) from their data.<sup>498a</sup> From a similar series in water, confined to  $p\text{-}$ substituted compounds but comprising a wider range of substituents,<sup>499</sup> we obtain eqn. (1xxviii). The intercept term, for  $R' = \text{Ph}$ , is as expected greater in water, but  $\rho$  is not much different. On the evidence that  $\sigma_p$  not  $\sigma_p^-$  is required in eqn. (xlvi), Katritzky<sup>499</sup> notes that  $\text{C}=\text{N}$  and phenyl must approach coplanarity rather than attain it, and also that the near-identity of  $pK_a$  for (**1028**,  $R = \text{Me}$ ,  $R' = \text{Ph}$ ) when  $\text{NMe}_2$  is replaced by  $\text{NH}_2$  argues against any major steric effect due to the former.

$$pK_{\text{PhX}} = 6.90(0.04) - 1.38(0.17) \sigma_X \quad (1\text{xxix})$$

$$(n = 5 \quad r^2 = 0.955 \quad s = 0.09 \quad F = 63)$$

$$pK_{\text{PhY}} = 6.86(0.04) - 2.76(0.19) \sigma_Y \quad (1\text{xxx})$$

$$(n = 6 \quad r^2 = 0.982 \quad s = 0.10 \quad F = 214)$$

From the data of Oszczapowicz and co-workers<sup>498b</sup> we may go on to construct similar equations, (1xxix) and (1xxx), for the *separate* effects of X and Y in (**1029**,  $R = \text{Me}$ ). Subsequently we shall designate these as  $pK_{\text{Am}}$  and  $pK_{\text{Im}}$  respectively. As expected the intercept terms are virtually identical but  $\rho_X$  and  $\rho_Y$  are very different. Also, since  $m\text{-}$  and  $p\text{-}$ substituents fit the same equation, implying that their  $\rho$ -values are near enough identical, we may presume that neither phenyl group of **1029** is sufficiently nonplanar to have any important effect on substituent conjugation with  $\text{C}=\text{N}$ . Furthermore,  $\rho_Y$  is almost identical in (1xxvii) and (1xxx), while  $\rho_p$  in (1xxviii) does not differ enough to suggest that Oszczapowicz's choice of solvent has had any seriously distorting effect on his results.

$$pK_a = 12.14(0.14) - 29.7(1.3) \sigma_{\text{I}(R')} \quad (1\text{xxxi})$$

$$(n = 14 \quad r^2 = 0.977 \quad s = 0.40 \quad F = 510)$$

Oszczapowicz's data for (**1028**,  $R = \text{Me}$ ),<sup>498a</sup> in which  $R' = \text{alkyl}$  as well as aryl, may be incorporated into this analysis if a suitable set of  $\sigma$ -values can be found. Here  $\sigma_{\text{I}}$  gives the best fit and the resulting equation is (1xxxi). The intercept term is predictive for **1030** and compares with  $pK_a$  12.41 for acetamidine **1031** in water. In its general form it resembles eqn. (1xxvi) for guanidines, and in this case as well  $pK_a$  is necessarily that of the major tautomer, i.e.  $pK_{\text{Im}}$ .

$$pK_{AmR} = pK_H - \rho_{Am} \sigma_{(R)} \quad (1xxxii)$$

$$pK_{ImR} = pK_H - \rho_{Im} \sigma_{(R)} \quad (1xxxiii)$$

$$pK_{ImR} = pK_{AmR} - \log K_{T(R)} \quad (1xxxiv)$$

$$\rho_r = \rho_{Im} / \rho_{Am} = (pK_H - pK_{ImR}) / (pK_H - pK_{AmR}) \quad (1xxxv)$$

$$\rho_r = (pK_H - pK_{ImR}) / (pK_H - pK_{ImR} - \log K_{T(R)}) \quad (1xxxvi)$$

$$\log K_{T(R)} = \{(\rho_r - 1) / \rho_r\} (pK_H - pK_{ImR}) \quad (1xxxvii)$$

$$\log K_{T(R)} = \{(\rho_r - 1) / \rho_r\} \rho_{Im} \sigma_R \quad (1xxxviii)$$

The importance of  $pK_{Am}$  and  $pK_{Im}$  lies in their application to the mobile tautomeric system **1032**. We may conduct the analysis as follows. From eqns. (1xxxii), (1xxxiii) and (1xxxiv), where  $pK_H$  is that of the parent compound we obtain eqn. (1xxxv), which may be re-cast as (1xxxvi) and further transformed to give (1xxxvii). The crucial quantity is that we define as  $\rho_r$ , the *ratio* of the slopes for the lines that define the two  $pK_a$  values; given that  $\sigma_{(R)}$  is always positive,  $\rho_r > 1$  necessarily. Hence, for any monosubstituted amidine, it is possible to estimate  $\log K_T$  *knowing only the  $pK_a$  of the parent compound and that of the major tautomer*, along with  $\rho_r$ . If  $pK_{ImR}$  is unknown but  $\rho_{Im}$  is established, eqn. (1xxxviii) may provide an acceptable alternative. Either method is readily adaptable to multi-substitution;  $\log K_T$  then becomes the difference of the values expected for each substituent separately.

For (**1029**,  $R = Me$ ) then, from eqns. (1xxix) and (1xxx),  $\rho_r = 2.0$ . It is reasonable that  $\rho_{Im} > \rho_{Am}$  since electronic effects are transmitted through a double and a single bond respectively, though no doubt a coincidence that the first  $\rho$ -value is exactly twice that of the second. A more extended series of compounds<sup>498e</sup> gave  $\rho_{Am}$  -1.44 and  $\rho_{Im}$  -3.08, again very close to  $\rho_r = 2$ . If it is supposed that  $\rho_r = 2$  can be assumed for **1032** wherever  $R$  is a freely rotating, centrosymmetric substituent and therefore unlikely to introduce a differential effect into  $K_T$ , we may attempt to use these equations in a predictive sense. We<sup>159</sup> have investigated a number of monosubstituted guanidines which included **1033**,  $pK_a$  8.20, while  $pK_a$  11.3 was estimated<sup>160</sup> for **1034**, resulting in  $\log K_T$  3.1. A calculation based on eqn. (1xxxvii), using  $pK_H$  14.4 for guanidine and 8.20 for **1033**, predicts  $\log K_T$  3.1; alternatively, given  $\rho_{Im}$  22.6 from eqn. (1xxvi) and  $\sigma_I$  0.30 for -COMe (Table 2), then from eqn. (1xxxviii) we may estimate  $\log K_T$  3.4. Katritzky and co-workers<sup>501</sup> measured the  $pK_a$  values for a number of model acyl- and sulfonyl-amidines. As acknowledged by the authors, these inevitably tended

to be crowded molecules and so severely at risk from loss of planarity and sometimes change in conformation, both capable of influencing  $pK_a$  in unpredictable and unwanted ways. In the acyl series they considered that **1035** and **1036**,  $pK_a$  4.36 and 5.88 respectively, might be the most reliable compounds to compare, in which case  $\log K_T$  *ca.* 1.5 results. A much simpler comparison, starting from  $pK_a$  12.41 for **1031** and  $pK_a$  6.87 for **1037**,<sup>501</sup> and then employing eqn. (lxxxvii), gives  $\log K_T$  *ca.* 2.8, not greatly different from that for **1033**. A slightly lower  $K_T$  value for **1037** than for **1033** might be expected since it contains one  $\pi$ -donor in place of two. (Some related alicyclic acyl-amidines and -guanidines are discussed in sections B.5.9 and B.5.10). In the sulfonyl series,  $pK_a$  -1.68 and 5.89 for **1038** and **1039** as favoured by the authors yields  $\log K_T$  *ca.* 7.6, whereas  $pK_a$  12.41 for **1031** and  $pK_a$  -0.23 for **1040**, again employing eqn. (lxxxvii), would predict  $\log K_T$  *ca.* 6.3. It is clear from inspection that **1035** is a poor model for **1037** and **1038** an even poorer one for **1040**, both of them lacking the crucial intramolecular hydrogen bond, and while there may be compensating deficiencies in **1036** and **1039**, it is impossible to know this. From  $pK_a$  9.85 and 12.25 for **1041** and **1042** respectively, Katritzky<sup>499</sup> deduced  $\log K_T$  2.4 for the effect of N-phenyl, whereas use of eqn. (lxxxvii) would predict *ca.* 1.2. Hydrogen bonding being absent **1041** is an excellent model for **1043**,  $pK_a$  9.95, but  $pK_a$  12.25 for **1042** is remarkably high for phenyl substitution even into the disfavoured tautomer; it is only 12.41 for acetamidine **1031** itself. Inspection of models suggests however that **1042** may be severely twisted, in which case loss of conjugation with phenyl might result in an abnormally high  $pK_a$  value. In the parallel guanidine case, given  $pK_a$  10.77 for **1044** and 14.4 for guanidine itself,<sup>96</sup> eqns. (lxxxvii) and (lxxxviii) predict  $\log K_T$  *ca.* 1.8 or 1.4, and further information comes from **1045** - **1048**. Their  $pK_a$  values were measured<sup>502</sup> in 83% methylcellosolve but it is unlikely that solvent will have a differential effect on this type of compound so we shall assume  $\Delta pK_a$  to be reliable. From  $pK_a$  8.80 and 10.24 for **1045** and **1046** respectively we deduce  $\log K_T$  1.44; similarly, from  $pK_a$  7.15 and 8.14 for **1047** and **1048**,  $\log K_T$  0.99 follows. These are rigid molecules and likely to be nearly planar, and leaving aside the second pair as subject to bond angle distortions,  $\log K_T$  1.44 is inside the range predicted and probably represents a near-definitive value for guanidine N-phenylation. A slightly lower value might be expected for an amidine; on a *pro rata* basis,  $\log K_T$  1.2 - 1.3 might be expected for **1043**. The thiazolylguanidine **1049** also provides a check. From  $pK_a$  values of 7.05 for **1049** and 10.67 for **1050**, the latter corrected to 10.97 by  $\Delta(NR)$ , we<sup>503</sup> arrive at  $\log K_T$  3.9; quite independently, the former  $pK_a$  has been used to deduce  $\sigma_I$  0.32 for the 4-methylthiazolyl unit. Either of eqns. (lxxxvii) or (lxxxviii) then leads to  $\log K_T$  3.6, further evidence that  $\rho_r \sim 2.0$  for guanidines is correct and that this approach to  $K_T$  can be made reasonably predictive.

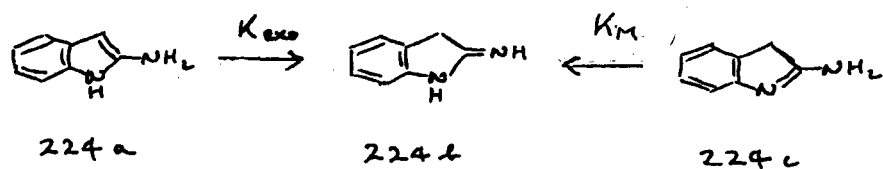
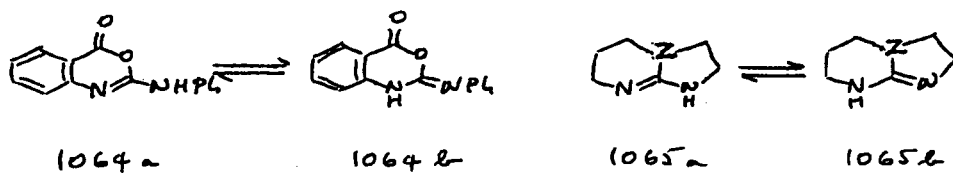
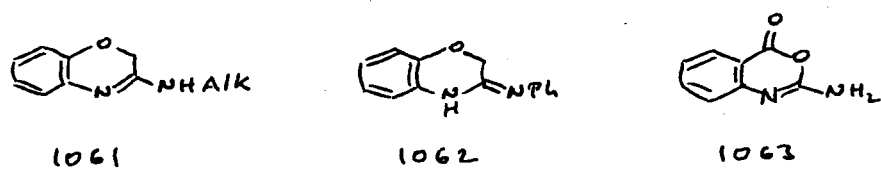
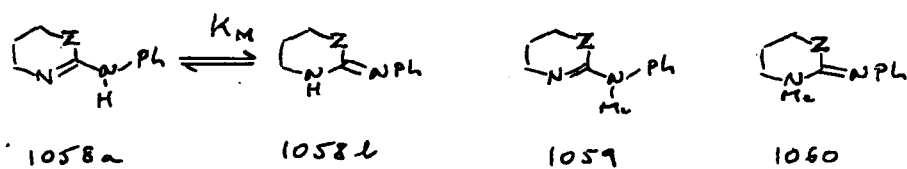
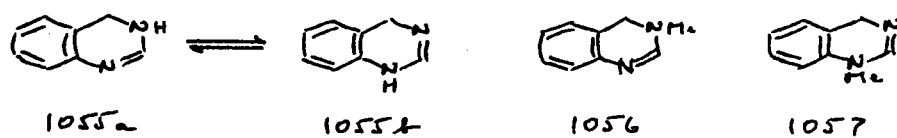
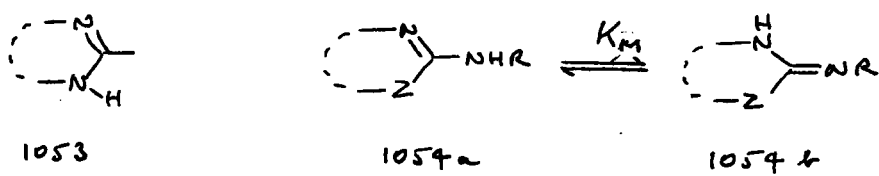
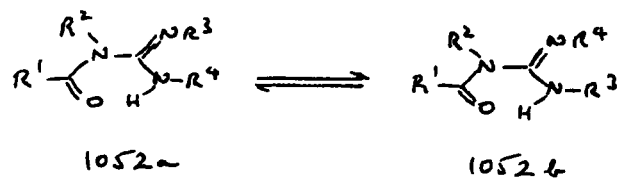
**Table 62. Tentative log  $K_T$  Values Calculated for Monosubstituted Guanidines (1032, R' = NH<sub>2</sub>)<sup>a</sup>**

R	log $K_T$ <sup>b</sup>	log $K_T$ <sup>c</sup>	R	log $K_T$ <sup>b</sup>	log $K_T$ <sup>c</sup>
Ph <sup>d</sup>	1.8	1.4	OMe	3.4	3.4
NH <sub>2</sub>	1.6	1.9	COPh	3.6	3.4
OH	3.1	2.7	CO <sub>2</sub> Et	3.6	3.4
CONH <sub>2</sub>	3.0	3.2	CSNH <sub>2</sub>	4.3	4.3
NHCOPh	3.1	3.2	SO <sub>2</sub> NH <sub>2</sub>	6.3	6.0
NHPh	3.0	3.4	CN	<sup>e</sup>	6.4
COMe <sup>f</sup>	3.1	3.4	NO <sub>2</sub>	7.6	7.6
and for 1049: <sup>g</sup>				3.6	3.6

<sup>a</sup> pK<sub>a</sub> data from ref. 96. <sup>b</sup> Eqn. (lxxxvii). <sup>c</sup> Eqn. (lxxxviii). <sup>d</sup> Other values: 1.4, 1.44 (see the text). <sup>e</sup> pK<sub>a</sub> abnormal so no valid calculation possible.<sup>96</sup> <sup>f</sup> 3.1 (exptl). <sup>g</sup> 3.9 (exptl).

Table 62 presents a tentative listing of log  $K_T$  values for monosubstituted guanidines, assuming  $\rho_r = 2.0$  and employing both methodologies. Their general agreement is inevitable given the way the two equations are related, but at least it is reassuring that no major discrepancies appear. We would expect simple amidines **1032** to follow the same trend, perhaps with slightly lower values of  $K_T$  overall. However it is important to note that these results, to the extent they are valid, apply only to a *sterically unconstrained* molecule, and cannot be expected to survive unchanged *e.g.* if this is locked in a disfavoured conformation, as for *trans*- in place of *cis*-carbonyl<sup>159</sup> (see section B.5).

A somewhat discordant note is struck by L'abbé and co-workers,<sup>504</sup> who for (**1051**, R = Me or CH<sub>2</sub>Ph) found a mixture of **1051a** and **1051b** in DMSO. Given  $\sigma_I$  0.41 for 1,2,4-thiadiazol-5-yl as substituent<sup>96</sup> one might have expected this compound to exist overwhelmingly as **1051a** in any solvent. Formation of **1051b** must certainly induce a conformational change (that shown is speculative) since it cannot form an intramolecular hydrogen bond, so this switch will be favoured by strong proton acceptor solvents. Nevertheless log  $K_T \sim 4.6$  would be predicted for the corresponding guanidine in water, and the switch required appears excessive. We consider this case *sub judice*.



### B.4.3 Tautomeric Balance in Unsymmetrical Amidines

While the evidence above for symmetrical amidines<sup>438</sup> and guanidines<sup>96</sup> is for  $p_r \sim 2$  and an absence of tautomeric bias in the parent molecule, neither can be generalised to unsymmetrical compounds. In the hypothetical situation of (**1052**,  $R \neq H$ ) for example, it is possible to imagine that the expected bias towards **1052a** when  $R^3$  is the sole or more electronegative amidine substituent might be partially or wholly cancelled by the greater strength of the intramolecular hydrogen bond expected for **1052b**. No evidence exists to test this hypothesis, either for open-chain or symmetrical cyclic compounds of type **1053**. The main contexts for asymmetry in practice are *endo-exo* tautomerism of type **1054** ( $Z = \text{carbon or a hetero-atom}$ ), and bicyclic compounds containing alternative sites for *endo*-C=N in rings of different sizes. We consider the former first.

Albert and co-workers<sup>505</sup> compared **1055** with **1056** and **1057** and from its close UV resemblance to **1056** concluded that it exists in the 3-*H* form (*cf.* **1043** and **1044** above). However, **1056** and **1057** possess  $pK_a$  9.23 and 9.43 respectively, suggesting only a minimal tautomeric preference, while  $pK_a$  9.19 for **1055** is that of a weaker base, making  $\Delta(NR)$  incommensurable. Najer *et al.*<sup>506</sup> reported (**1058**,  $Z = O$  or  $S$ ) to exist predominantly as **1058a** ( $pK_a$  9.38 or 8.49) by UV comparison with **1059** ( $pK_a$  10.71 or 9.86) and **1060** ( $pK_a$  9.08 or 7.86), despite their own basicity evidence to the contrary.<sup>507</sup> This misassignment, as also for the corresponding 5-membered rings,<sup>507</sup> probably derives from steric crowding in *both* model compounds, leading to abnormal UV spectra and  $pK_a$  values which, while qualitatively decisive, are probably not quantitatively reliable. No estimate for  $\log K_M$  is therefore possible. Mazharuddin and Thayagarajan<sup>508</sup> found tautomers **1061** and **1062** to be those preferred in DMSO, while Lempert and Doleschall<sup>509</sup> assigned **1063** on this and solid state IR evidence. Solvent bias is unlikely here in either case. For **1064** the latter authors could not decide the issue. It is possible that electron donor oxygen in **1062**, and electron acceptor carbonyl in **1064**, are the factors here which will decide the *endo-exo* balance; comparison suggests that, in the absence of either, there may be a marginal bias towards *exo*-C=N.

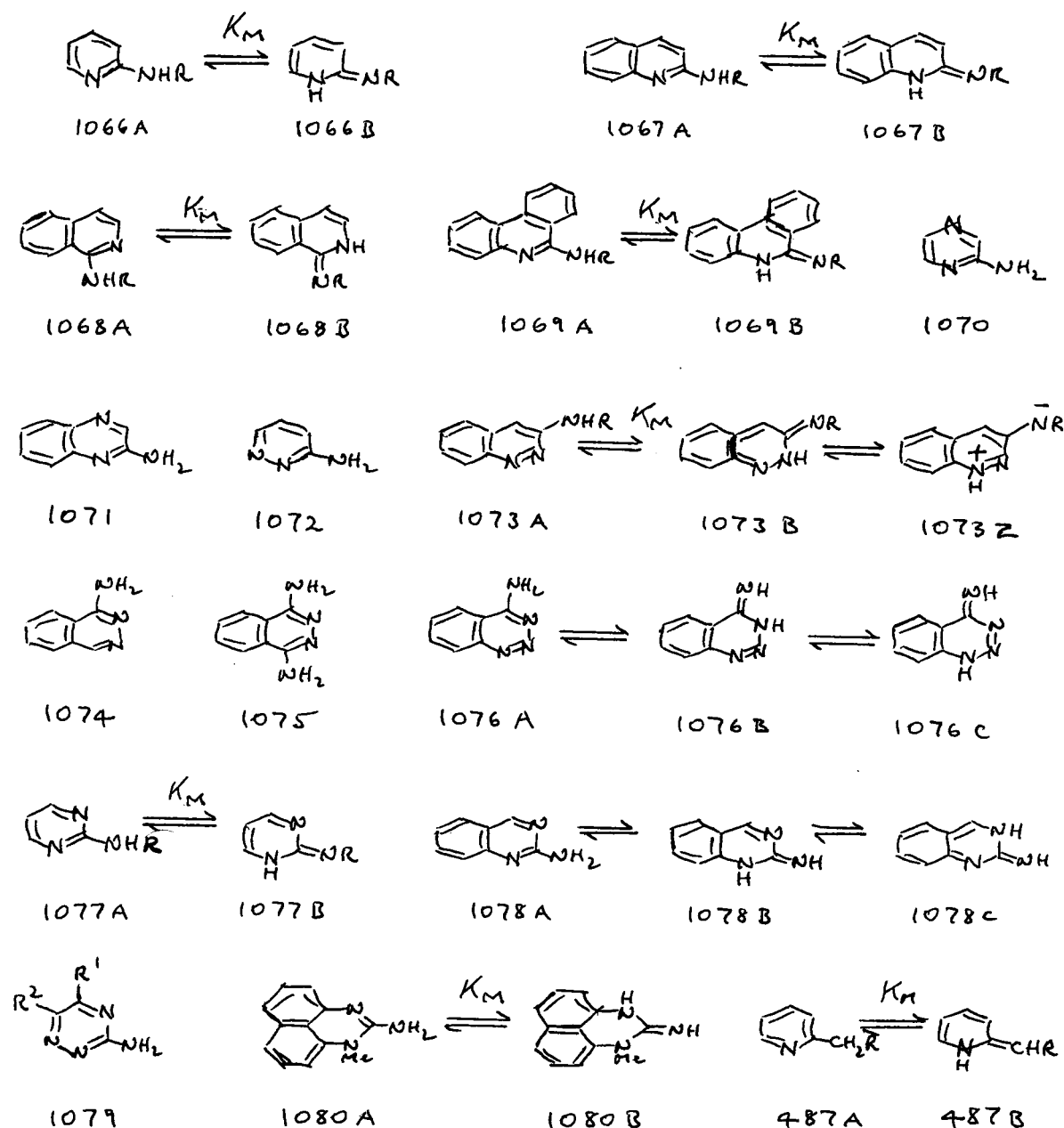
In structures of type **1065** ( $Z = CH$  or  $N$ ) the stabilisation of *endo*-C=N by 5-membered rings should lead to the **b**-form being favoured. Two results discussed above throw light on this. For **1025**,  $\log K_T$  is 0.42 in favour of **1025a** (section B.4.1), while the difference between  $\log K_T$  in favour of **1045** and **1047**, 1.44 and 0.99 respectively, indicates that C=N is stabilised by  $\Delta \log K_M$  0.45 in **1048** relative to **1046** (section B.4.2). This is much smaller than the factor,  $\log K_N$  1.5, which we have deduced in favour of 5-membered

ring C=N taken in isolation, but here it is offset by a corresponding destabilisation of C=N exocyclic to a 6-membered ring, on this evidence  $\Delta \log K_N$  *ca.* -1.1, close to the corresponding value for C=O ( $K_O$ ; for both see Scheme 32, section B.2.3). Hence a value of  $\Delta \log K_M \pm 0.4$  is expected for 6,5-ring fusions, and  $K_M$  should also be less for **224** than *e.g.* for **1044** or **1045**. It is less clear what is to be expected for competition between C=N *endo* and *exo* to an unfused 5-membered ring, but  $\log K_M$  *ca.* -1.4 for **224** (section A.4.8), essentially identical with that for **1045** *vs.* **1046** where C=N switches between rings of the same size, suggests that the differential here must also be negligible.

#### B.4.4 Unsymmetrical Amidines: 6-Membered Ring $\alpha$ -Amino-Heteroaromatics

An amidine **1054** in which N and Z are part of an aromatic ring may be considered as the ultimate in asymmetry, structural and electronic. Given the initial lack of tautomeric bias (*cf.* **1024**,  $R^2 = R$ ) the effect of aromatisation should be decisive, and this is found. In 6-membered rings, Z = CR or (sometimes) N; in 5-membered rings, Z is a heteroatom. Almost all such compounds exist predominantly as the *endo*-imino tautomer **1054a**, and in the great majority of cases, overwhelmingly so. Except in a very few special circumstances to be described, this structure may be assumed, and there is little realistic chance that the energetics of a biological interface will reverse it, especially since **1054a** is generally the less polar tautomer. It may also be noted that the dipolar repulsion which can destabilise oxo-forms in 5-membered rings (sections B.2.10 to B.2.12) will generally act here in the opposite manner, further stabilising **1054a** relative to **1054b**.

We draw attention to a point of nomenclature. The usual convention concerning the sign of  $K_T$  is to define it in favour of what is generally the major tautomer,<sup>2</sup> as we have done for such amides as **810**, and the general category of acylamidines **811** (Scheme 29, section B.2). Here however it seems more logical to define the equilibrium for  $K_M$  as in **1054**, *i.e.* in favour of *exo*-C=N, consistently with our usage of  $K_M$ <sup>93</sup> for acylamidines **811** above. This gives  $K_M$  for the generation of *exo*-C=N the same sign as  $K_T$  for the generation of *exo*-C=O and assists in making comparisons. Where the whole amidine unit is endocyclic, as *e.g.* in 4-pyrimidone, we extend this usage by defining  $K_M$  in the direction of conjugation between C=N and an electronegative unit such as carbonyl, as again shown for **811**. This convention was first used for **224** in section A.4.8 and has been employed throughout.



Scheme 41

Those  $\alpha$ -aminoheterocycles whose structures are firmly established are set out in Scheme 41, with quantitative data where known in Table 63.<sup>510</sup> Most results use the 'basicity method' but a handful were obtained by direct UV observation, using model fixed tautomers to calibrate the mobile species.<sup>511,512</sup> Except where R is extremely electronegative there is no case recorded of a compound for which the amino-tautomer does not predominate, usually by a very long margin.<sup>510</sup> It is particularly notable that this remains true even for compounds **1072** – **1075** and **1079**<sup>2ttt</sup> where the A-tautomer will

to some extent be destabilised by lone pair repulsion. The situation for **1076** is regarded as “doubtful”<sup>21tt</sup> but, on balance, **1076A** appears the most probable structure. Speculation is idle as to which imino-tautomer, **1076B** or **1076C**, might be the less disfavoured. (Note that compounds **1071**, **1074** and **1078** have not been investigated but the unequivocal results for **1070**,<sup>255</sup> **1075**<sup>255</sup> and **1077**<sup>257</sup> respectively render any other tautomer highly improbable). If an imino-structure were to be detected for **1078** or any derivative, one could presumably rule out **1078C** on account of its quinonoid structure; **1073B** is exceptionally disfavoured<sup>254</sup> (Table 63). The smallest quantitative margin given in Table 63 for a parent compound is that for **1080**<sup>513</sup> but this compound can barely be considered as aromatic; if it is regarded as a phenylguanidine, log  $K_M$  is quite normal (section B.4.2).

**Table 63.  $pK_a$  and log  $K_M$  Values for 6-Membered Ring  $\alpha$ -Aminoheterocycles in Water<sup>a</sup>**

Cpd.	R	$pK_a$ (A)	$pK_a$ (NMe) <sup>b</sup>	$pK_a$ (B) <sup>c</sup>	log $K_M$	log $K_T$ <sup>d</sup>
<b>1066</b>	H	6.86 <sup>e</sup>	13.02 <sup>f</sup>	13.32	- 6.5	3.5
“	Ph	5.84 <sup>g</sup>	10.17 <sup>g</sup>	10.47	- 4.6	
“	COMe	4.09 <sup>h</sup>	7.12 <sup>h</sup>	7.42	- 3.3	
“	COCHCl <sub>2</sub>				(- 1.9) <sup>ij</sup>	
“	COCCl <sub>3</sub>				- 1.0 <sup>i</sup>	
“	SO <sub>2</sub> Me				0.8 <sup>i</sup>	
“	SO <sub>2</sub> Me	2.03 <sup>k,l</sup>		1.10 <sup>k,l</sup>	0.9	
“	SO <sub>2</sub> Ph				(1.8) <sup>ij</sup>	
<b>1067</b>	H	7.34 <sup>e</sup>	11.68 <sup>m</sup>	11.98	- 4.6	4.5
“	COCCl <sub>3</sub>				- 0.5 <sup>i</sup>	
<b>1068</b>	H	7.62 <sup>e</sup>	11.38 <sup>m</sup>	11.68	- 4.1	5.4
<b>1069</b>	H	6.30 <sup>n</sup>	9.10 <sup>n</sup>	9.40	- 3.1	> 4.9
<b>1073</b>	H	3.76 <sup>o</sup>	12.19 <sup>p</sup>	12.74 <sup>l</sup>	- 9.0	3.0
<b>1077</b>	H	3.54 <sup>e</sup>	10.75 <sup>q</sup>	11.05	- 7.5	
<b>1080</b> <sup>r</sup>	H	7.94 <sup>s</sup>	9.15 <sup>s</sup>	9.45	- 1.5	

<sup>a</sup> Scheme 41. <sup>b</sup>  $pK_a$  Value of ring-*N*-methylated derivative. <sup>c</sup>  $\Delta(NR)$  0.3 assumed (section B.4.1) unless otherwise stated. <sup>d</sup> For equivalent oxoheterocycle (Table 56, section B.2.5).

<sup>e</sup> Ref. 255. <sup>f</sup> Ref. 150b. <sup>g</sup> Ref. 307. <sup>h</sup> Ref. 248. <sup>i</sup> Ref. 511. <sup>j</sup> Very approximate (see the text).

<sup>k</sup> Ref. 247. <sup>l</sup> See the text. <sup>m</sup> Ref. 150a. <sup>n</sup> Ref. 23. <sup>o</sup> A. R. Osborn, K. Schofield and L. N.

Short, *J. Chem. Soc.*, 1956, 4191. <sup>p</sup> Ref. 254. <sup>q</sup> Ref. 257. <sup>r</sup> In 10% EtOH. <sup>s</sup> Ref. 513.

The values of  $\log K_M$  in Table 63 have been obtained, in general, by subtracting  $pK_a(\mathbf{A})$  for the dominant tautomer from  $pK_a(\text{NMe})$  for its ring *N*-methyl derivative and applying  $\Delta(\text{NR})$  as above. There are two exceptions. For (**1066**,  $\text{R} = \text{SO}_2\text{Me}$ )<sup>247</sup> the *exo*-imine is the major tautomer by a sufficient margin to treat its  $pK_a$  value as  $pK_a(\mathbf{B})$  without significant error;  $pK_a(\mathbf{A})$  is then that of its *exo-N*-methyl derivative, after adding  $\Delta(\text{NR})$ . The resultant,  $\log K_M$  0.9, agrees with 0.8 as obtained by Scheinker *et al.*<sup>511</sup> by direct observation (Table 3). For (**1073**,  $\text{R} = \text{H}$ ) Katritzky and co-workers<sup>254</sup> used 3-dimethylaminocinnoline as model for **1073A** so as to avoid possible complications from the zwitterion **1073Z**. In retrospect this fear seems to have been exaggerated since the  $pK_a$  values for this and 3-aminocinnoline are very similar, so we have preferred to use the latter instead. 3-Dimethylaminocinnoline protonates at *N*-1 to the extent of about 20%<sup>254</sup> and a similar effect may be presumed for **1073A** but the correction required for this is negligible. Estimation of  $pK_a(\mathbf{B})$  makes use of the somewhat larger  $\Delta(\text{NR})$  correction required here (see **812**, Scheme 30). It has been demonstrated<sup>257</sup> that (**1077B**,  $\text{R} = \text{H}$ ) *exo*-protonates, hence **1077A** and **1077B** share a common cation; this contrasts with the related 2-pyrimidone where they do not (see section B.5), so rendering the 'basicity method' inapplicable.<sup>244</sup>

$$\log K_M = 2.2 \log K_T - 14.7 \quad (\text{lxxxix})$$

For five of these parent compounds,  $\log K_M$  is related to  $\log K_T$  for the corresponding oxoheterocycles (section B.2.5) by eqn. (lxxxix). This relation is very rough ( $r^2 = 0.84$ ,  $s = 1.0$ ) but, qualitatively, carries the implication that the same structural factors operate in both series. Quantitatively, the coefficient of  $\log K_T$  demonstrates that  $\text{C}=\text{N}$  is much more sensitive to these factors than  $\text{C}=\text{O}$ , as might be expected on general grounds and is consistent with our demonstration (see summary in section A.12) that, in the context of  $\beta$ -diketones and related compounds,  $\text{C}=\text{O} > \text{C}=\text{N}$  as a *promoter* of enolisation whereas its *susceptibility* to enolisation is less. It is also interesting that eqn. (lxxxix) may be used to predict  $\log K_T > 3$  for 2-pyrimidone, a value very similar to that for 2-pyridone itself, of which it may be considered an 'iminologue.' This reasoning is followed up in section B.5.

$$pK_a(\mathbf{A}) = 6.78(0.04) - 8.24(0.42) \sigma_I \quad (\text{xc})$$

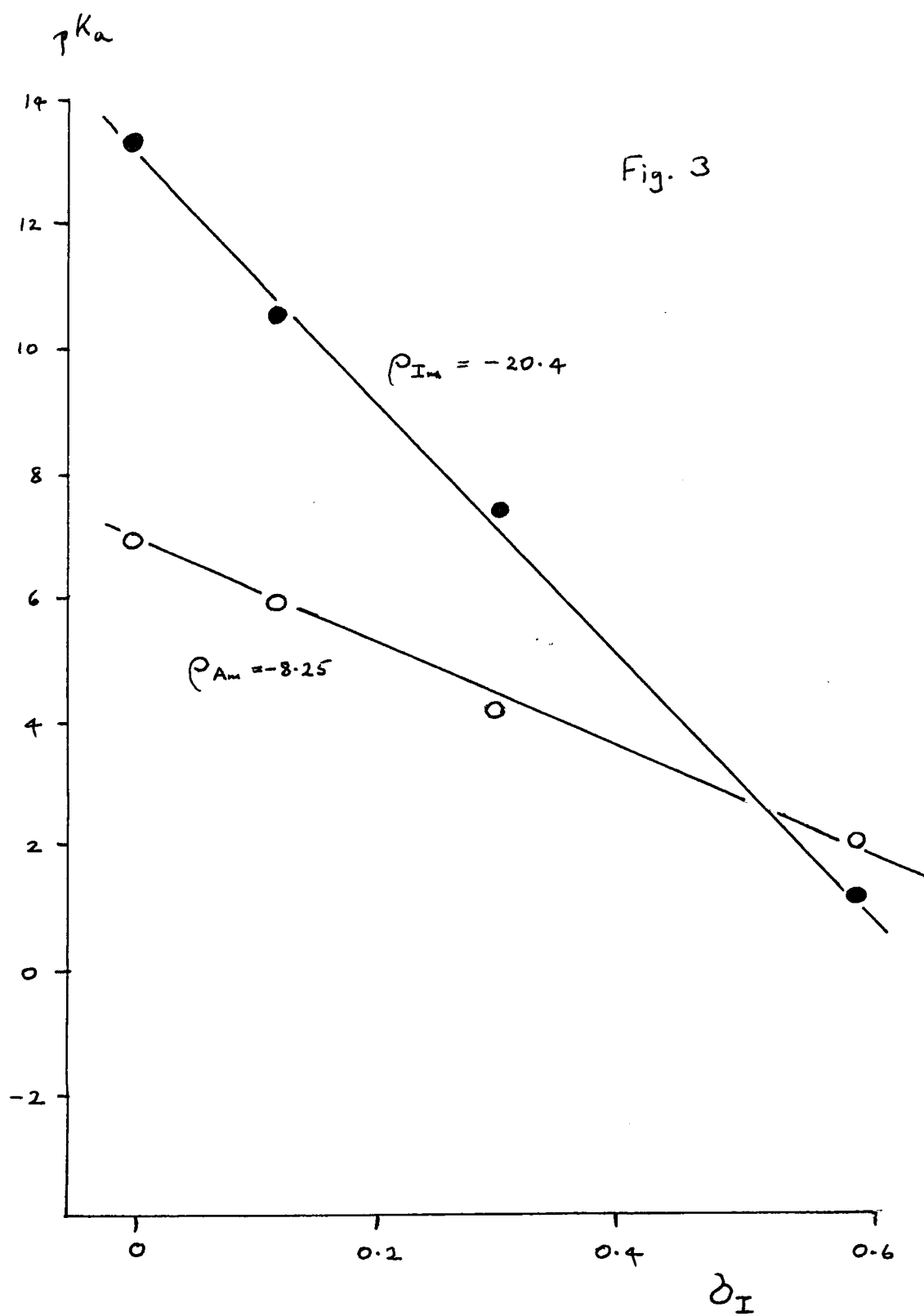
$(n = 4 \quad r^2 = 0.995 \quad s = 0.19 \quad F = 390)$

$$pK_a(\mathbf{B}) = 13.23(0.25) - 20.39(0.73) \sigma_I \quad (\text{xc i})$$

$(n = 4 \quad r^2 = 0.997 \quad s = 0.32 \quad F = 780)$

$$\log K_M = 12.14(1.05) \sigma_I - 6.44(0.35) \quad (\text{xc ii})$$

$(n = 4 \quad r^2 = 0.985 \quad s = 0.47 \quad F = 134)$



On Fig. 3 we plot the four results for (**1066**, R = various) obtained by Katritzky and co-workers (all in Table 63). This demonstrates a clean relation with  $\sigma_I$  for both  $pK_a(\mathbf{A})$  and  $pK_a(\mathbf{B})$ , *i.e.*  $pK_{Am}$  and  $pK_{Im}$  respectively, as expected from our treatment of simple amidines above (section B.4.2). There are two important differences. Firstly, the intercept term is non-zero; the **A**-tautomer is stabilised by aromaticity whereas the **B**-tautomer is not. Secondly,  $\rho_r = \rho_{Im} / \rho_{Am} \sim 2.5$  is considerably larger than  $\rho_r \sim 2.0$  as found for symmetrical amidines, probably a consequence of asymmetry *per se*; the direction of the molecular dipole must differ considerably for these two tautomers. Unfortunately therefore, the relation  $\rho_r \sim 2.0$  is likely to be inapplicable in a heteroaromatic context. Equation (xcii) solves to give a crossover in tautomeric form at  $\sigma_I \sim 0.53$  and invites predictions. No  $\sigma_I$  value is known for  $\text{COCHCl}_2$  or  $\text{COCCl}_3$  but for  $\text{COCF}_3$ , which is somewhat more electronegative, eqn. (xcii) predicts  $\log K_M$  *ca* 0.1. From  $\sigma_I$  0.67 for  $\text{NO}_2$  one expects  $\log K_M$  *ca* 1.7; Scheinker *et al.*<sup>511</sup> state this compound to exist 100% as (**1066B**, R =  $\text{NO}_2$ ). Qualitatively at least, eqn. (xcii) appears to be predictive.

**Table 64. Comparative Values of  $\Delta \log K_M$  for 1066 and 487 <sup>a</sup>**

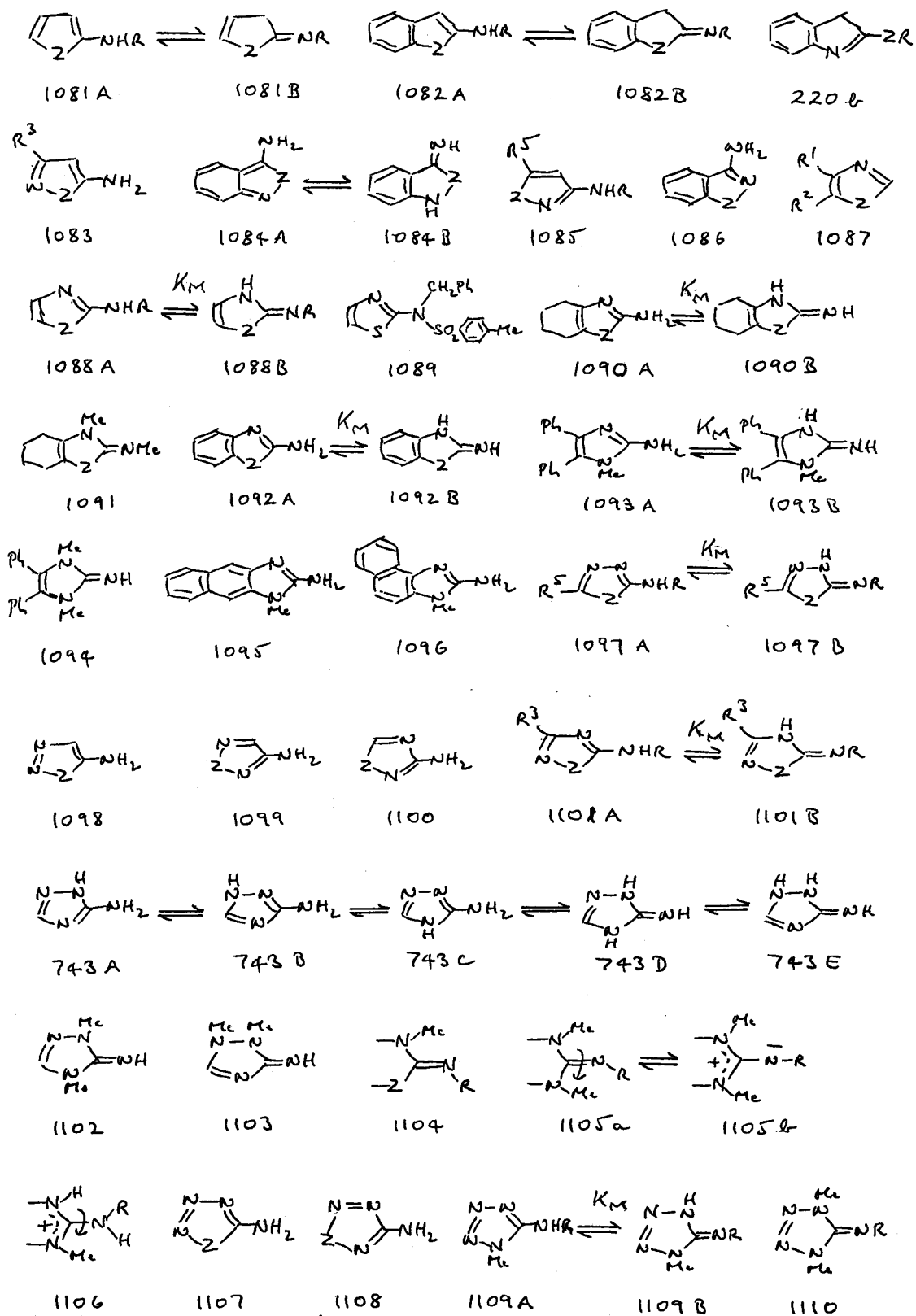
R	$\sigma_I$	<b>1066</b> <sup>b</sup>	<b>487</b> <sup>c</sup>
Ph	0.12	1.9	1.4
CO <sub>2</sub> Et	0.30		7.0
COMe	0.30	3.2	
COPh	0.30		10.9
COCHCl <sub>2</sub>		4.6 <sup>d</sup>	
COCCl <sub>3</sub>		5.5	
COCF <sub>3</sub>	0.54	(6.5) <sup>e</sup>	
SO <sub>2</sub> Ph	0.56 <sup>f</sup>	8.3 <sup>d</sup>	5.4
CN	0.57	(6.9) <sup>e</sup>	(5.5) <sup>g</sup>
SO <sub>2</sub> Me	0.59 <sup>f</sup>	7.4	
NO <sub>2</sub>	0.67	(8.2) <sup>e</sup>	(8.1) <sup>g</sup>

<sup>a</sup> Relative to R = H. <sup>b</sup> From data in Table 63. <sup>c</sup> From data in Table 39. <sup>d</sup> Very approximate (see text). <sup>e</sup> Calculated using eqn. (xcii). <sup>f</sup> Some doubt attaches to the relative ordering of these  $\sigma$ -values. <sup>g</sup> Calculated using eqn. (xxxvi).

There is a startling contrast between the behaviour of **1066** and its ‘C-type’ analogue **487** (Table 39, section A.10.9) with respect to the effect of the substituent R. For the former  $K_M$  is controlled entirely by field effects [eqn. (xcii)], whereas for the latter, the dominance of resonance effects is equally complete. Table 64, which includes predictions for certain key electronegative substituents, sets out this contrast. Katritzky<sup>307</sup> explains the sharply contrasting behaviour of COR and SO<sub>2</sub>R as ‘predominantly mesomeric’ in the first case but ‘inductive’ in the second. More accurately it is the *systems* that show this distinction, in addition to which, **487** shows much larger substituent effects overall than **1066**. We may explain both differences quite simply. Whereas both **1066A** and **487A** are aromatic molecules, and both **1066B** and **487B** possess long through-conjugated systems, the side-chain of **1066A** is conjugated to the aromatic ring whereas that of **487A** is not. Hence, while resonance effects should at least partially cancel between **1066A** and **1066B**, and in practice appear to cancel completely, for **487** they exist in the **B**-tautomer alone, and are consequently enormous. Put simply: CH<sub>2</sub> is a ‘conjugation-stopper’ whereas NH is not. Analysis of  $pK_a(\mathbf{A})$  and  $pK_a(\mathbf{B})$  for **487** shows that both contain a term in  $\sigma_1$  (section A.10.9), but this is nearly the same for both and is swamped out in  $K_M$  by the resonance parameters. If there is any puzzle here, it is why  $\rho_1$  does not similarly cancel between **1066A** and **1066B**. The most probable explanation is that the field effect of R is in practice modified by the hybridisation state of the nitrogen atom to which it is linked, and that, for reasons which are not entirely clear, a proportionality results which is independent of the substituent involved. Hence this analysis raises as many questions as it solves. We return to it in section B.5.

#### B.4.5 Unsymmetrical Amidines: 5-Membered Ring $\alpha$ -Amino-Heteroaromatics

Scheme 42 sets out those compounds for which tautomeric preference is known, with quantitative data where available in Table 65. 5-Membered ring heteroaromatics encompass a much wider range of structures than their 6-membered ring analogues, and this leads to a less straightforward picture. Two new factors are of particular importance. The lower resonance energies of simple ‘ $\pi$ -excessive’ heteroaromatics lead, for **1081** and **1082**, to situations in which the **A**-tautomer may not necessarily predominate. While (**1081**, Z = S, R = H) exists as **1081A**, the position for (**1081**, Z = O, R = H) is uncertain, and when R = Ph, (**1081**, Z = NH) prefers the **B**-tautomer.<sup>2kk</sup> The process **1081B**  $\rightarrow$  **1081A** is formally analogous to enolisation of the corresponding oxoheterocycle; on independent but fragmentary evidence we speculate, in



Scheme 42

**Table 65.**  $pK_a$  and  $\log K_M$  Values for 5-Membered Ring  $\alpha$ -Aminoheterocycles in Water <sup>a</sup>

Cpd.	Z	R	$pK_a$ (A)	$pK_a$ (NMe) <sup>b</sup>	$pK_a$ (B) <sup>c</sup>	$\log K_M$
<b>1088</b> <sup>d</sup>	S	H	5.32	9.50	9.80	- 4.5
"	"	CH <sub>2</sub> Ph	5.15	8.98	9.28	- 4.1
"	"	Ph	4.33	6.30	6.60	- 2.3
"	"	Tosyl	0.3 <sup>e</sup>		- 1.33 <sup>f</sup>	1.6
<b>1090</b> <sup>g</sup>	O		5.78	10.27 <sup>h</sup>	10.07 <sup>i</sup>	- 4.3
" <sup>g</sup>	S		6.11	10.00 <sup>j</sup>	9.80 <sup>i</sup>	- 3.7
<b>1092</b> <sup>d</sup>	S		4.23	7.96	8.26	- 4.0
" <sup>k,l</sup>	NMe		7.21	9.49	9.79	- 2.6
<b>1093</b> <sup>k,m</sup>			7.29	10.52 <sup>n</sup>	10.82	- 3.5
<b>1095</b> <sup>k,l</sup>			7.15	9.05	9.35	- 2.2
<b>1096</b> <sup>k,l</sup>			7.25	9.76	10.06	- 2.8
<b>1097</b> <sup>o,p</sup>	O	Ph	0.63	4.12	4.67 <sup>q</sup>	- 4.0
" <sup>o,r</sup>	"	H	1.88	6.84	7.39 <sup>q</sup>	- 5.5
" <sup>o,r</sup>	"	Me	1.98	7.48	8.03 <sup>q</sup>	- 6.0
" <sup>g,r</sup>	"	Ph	1.00	4.08	4.63 <sup>q</sup>	- 3.6
" <sup>p,s</sup>	S	Ph	1.76	4.56	5.11 <sup>q</sup>	- 3.4
" <sup>r,t</sup>	"	H	2.9	7.9	8.45 <sup>q</sup>	- 5.5
" <sup>r,s</sup>	"	Ph	1.79	4.14	4.69 <sup>q</sup>	- 2.9
<b>1101</b> <sup>u,v</sup>	O	H	- 0.25	5.95	6.25	- 6.5
" <sup>u,v</sup>	"	Me	- 0.21	6.43	6.73	- 6.9
<b>743</b> <sup>w</sup>			?		?	- 6.5 <sup>x</sup>
<b>1109</b> <sup>y</sup>		H	1.81	8.68	9.23 <sup>q</sup>	- 7.4
" <sup>z</sup>		Me	0.55	9.57	10.12 <sup>q</sup>	- 9.6

<sup>a</sup> Scheme 42. <sup>b</sup>  $pK_a$  value of ring *N*-methyl species. <sup>c</sup>  $\Delta(NR)$  0.3 except where stated otherwise.<sup>d</sup> Ref. 521. <sup>e</sup>  $pK_a$  (**1089**), ref.521, with  $\Delta(NR)$  0.8 as required for *N*-benzyl, ref. 22. <sup>f</sup>  $pK_a$  of 2-tosyl-aminothiazole (see the text). <sup>g</sup> Ref. 507. <sup>h</sup>  $pK_a$  (**1091**, Z = O). <sup>i</sup> Incorporates  $\Delta(NR)$  0.3 plus a correction of  $\Delta pK_a$  - 0.5 based on (**1101**, Z = O); see the text. <sup>j</sup>  $pK_a$  (**1091**, Z = S). <sup>k</sup> Ref. 513.<sup>l</sup> In 10% EtOH. <sup>m</sup> In 50% EtOH. <sup>n</sup>  $pK_a$  (**1094**). <sup>o</sup> Ref. 515. <sup>p</sup> R<sup>5</sup> = H. <sup>q</sup>  $\Delta(NR)$  0.55 (**814**, Scheme 30). <sup>r</sup> R<sup>5</sup> = Ph. <sup>s</sup> Ref. 516. <sup>t</sup> Ref. 517. <sup>u</sup> Ref. 518. <sup>v</sup> R<sup>3</sup> = Ph. <sup>w</sup> Ref. 488. <sup>x</sup> See the text.<sup>y</sup> Ref. 519. <sup>z</sup> Ref. 520;  $pK_a$  (NMe) is that for (**1110**, R = Me).

section C.10, a susceptibility order  $S > O > NR$  for enolisation which parallels this behaviour. Benzofusion leads to further possibilities. While **1082A** is preferred for  $Z = O$  or  $S$ , as also for  $Z = S$ ,  $R = COMe$ ,<sup>2kk</sup> when  $Z = NH$  a third tautomer **220b** is possible, and for (**220**,  $Z = O$ ,  $S$  or  $NR$ ) this tends to predominate, the fused pyrrole ring losing all its aromaticity. The compound (**1082**,  $Z = NH$ ,  $R = tosyl$ ) exists as an equal mixture of **1082B** and **220b** in DMSO.<sup>514</sup> There are no reports of *endo*-C=N in pyrroles.

The second factor, which acts in the opposite direction, is ring electronegativity. The  $\sigma_I$  values *as substituents* for those 5-membered ring heteroaromatics that contain aza-nitrogen tend to be substantially higher than those of their 6-membered ring analogues, which we<sup>96</sup> have postulated as due to a compression effect related to their smaller size and resulting in increased intramolecular electrostatic repulsion and a steeper dipole gradient. In Table 66 we align some  $\log K_M$  values from Tables 63 and 65 with the nearest available heteroaromatic  $\sigma_I$  value.<sup>96</sup> With one exception to be discussed,  $\log K_M$  among the 5-membered rings becomes more negative as  $\sigma_I$  increases, a trend consistent with the form of eqn. (xcii). For 6-membered rings,  $\log K_M$  is much more negative than this comparison would suggest, but that results from their much greater aromaticity, the missing (and mostly unquantifiable) contributor to the overall picture.

**Table 66. Comparison of  $\log K_M$  (Tables 63 and 65) with  $\sigma_I$  Values<sup>a</sup> for the Nearest Available Heterocycle at the Site of Amino-Substitution**

Compound	$\sigma_I$	Compound	$\log K_M$
Pyridin-2-yl	0.18	<b>1066</b>	- 6.5
4,6-Dimethylpyrimidin-2-yl	0.21	<b>1077</b>	- 7.5
Thiazol-2-yl	0.34	<b>1088</b> , $Z = S$ , $R = H$	- 4.5
4,5-Dimethyloxazol-2-yl	0.35	<b>1090</b> , $Z = O$	- 4.3
4,5-Dimethylthiazolyl-2-yl	0.31	<b>1090</b> , $Z = S$	- 3.7
Benzimidazol-2-yl	0.32	<b>1092</b> , $Z = NMe$	- 2.6
Benzothiazol-2-yl	0.37	<b>1092</b> , $Z = S$	- 4.0
3-Methyl-1,2,4-oxadiazol-2-yl	0.48	<b>1101</b> , $Z = O$	- 6.5
Tetrazol-2-yl	0.49	<b>1109</b>	- 7.4

<sup>a</sup> Ref. 96.

Elsewhere, the presence of aza-nitrogen in the ring with the accompanying rise in its resonance energy is a sufficient guarantee that, unless R is very electronegative, the amino-tautomer will be overwhelmingly predominant. Qualitatively, this is found for (**1083**, Z = O, S or NR, R<sup>3</sup> various); for **1085**, similarly; and for (**1085**, Z = O) even when R = COR or SO<sub>2</sub>R.<sup>2uuu</sup> It might have been anticipated for (**1086**, Z = O, S, SO<sub>2</sub> or NR) as is the case, but remarkably it is also true for anthranil (**1084**, Z = O) and its congeners with Z = S or NR despite their quinonoid structure.<sup>2uuu</sup> (The evidence points to  $\Delta \log K$  ca. -1.7 for the 'quinonoid penalty' in a similar context: section B.1.5.) Note however that (**1083**, Z = NH) reverts to its isomer (**1085**, Z = NH), and similarly for **1084** and **1086**.<sup>2uuu</sup> Compounds (**1087**, Z = O or NR, R<sup>1</sup> or R<sup>2</sup> = NH<sub>2</sub>) exist, as expected, as the amino-tautomer.<sup>2vvv</sup>

Quantitative data are available for some compounds of type **1088**, **1097** and **1101**, in all of which a ring  $\pi$ -donor is conjugated with a ring  $\pi$ -acceptor. [In the estimates of Table 65 we have allowed for the effect of *exo-N*-methylation in **1090B**<sup>507</sup> to give **1091** by incorporating a correction of  $\Delta pK_a$  -0.5 based on the difference between the sterically similar compounds (**1101**, Z = O, R = H) and (**1101**, Z = O, R = Me).<sup>518</sup> This difference is one example of a phenomenon noted below and described in Appendix 1]. There is a trend among these data for  $\log K_M$  to become more negative in the order NR  $\ll$  S < O which, as we shall elaborate in section B.8.8, correlates with  $\sigma_I$  for the parent heterocycle<sup>96</sup> at the point of attachment for the amino-group. Unfortunately many potentially valuable data are missing; for example, Z = O and S are available for **1090** but Z = NR is not, whereas for **1092**, Z = O is the missing species. And since the relation between  $\sigma_I$  and  $\log K_M$  is different for monocycles and their benzofused derivatives (*vide* Table 66) it cannot be assumed that the missing data can be interpolated. (There are other hazards: Katritzky<sup>2uuu</sup> has drawn attention to features in the UV spectroscopy of **1093** that cast doubt on  $K_M$  in this case; **1093A** and **1094** may not give a truly common cation). The 'carbonyl equivalents' to these compounds (C=O in place of C=NH) are ureas if Z = NR and we have characterised their analogues in which Z = O or S as 'pseudo-ureas' (section B.2.9) with similar but less extreme properties. Ureas are exceptionally resistant to iminol formation (section B.2.9) and this feature might be expected to make  $\log K_M$  less negative for Z = NR than for Z = O or S (*cf.* Table 61 for some related thiones). Contrast the more negative values that accompany the drop in basicity as the ring becomes more electronegative, especially where contiguous hetero-atoms are present (*vide* Table 66):  $\log K_M$  becomes generally more negative in the sequence **1090** to **1097** to **1101** and is most negative of all for the tetrazoles **1109**.<sup>519,520</sup> Qualitatively similar behaviour is found for **1098**, **1099** or **1100** (Z = O, S or NR) and **1107** or **1108** (Z = S or NR);<sup>2vvv</sup> and *cf.* section A.2.8 for the absence of oxo-tautomers when OH replaces NH<sub>2</sub> in **1098** and **1099**, Z = NMe.

The position for amino-*s*-triazole is unclear. A very short preliminary communication<sup>489</sup> reports  $\log K_M$  -6.5 but contains no structural formulae and no full report has followed. Dimethylation, to give **1102** or **1103**, is required to fix the structure of the *exo*-imino tautomer. The two relevant comparisons are **743E** with **743B**, or **743D** with either **743A** (60% of the total) or **743C** (10%). We adduce evidence (section B.2.10) that, when N and Z are contiguous as in **1083**, the electron donor order changes from  $Z = NR > S > O$  as in **1088** to  $Z = S \geq NR > O$ , i.e. the reverse order of electronegativity. This places  $\log K_M$  -6.5 in the region expected for  $(\mathbf{743A} + \mathbf{743C}) \rightarrow \mathbf{743D}$  and not the formation of **743E** which should be exceptionally disfavoured (B.8.8).

A further problem is raised here for the same reason. While replacement of  $R = H$  by  $R = Ph$  always leads to a rise in  $\log K_M$ , as expected, its replacement by  $R = Me$  leads to an anomalous fall. For **1097** and **1101** where  $Z = O$  this fall is quite modest, but for **1109** where  $Z = NMe$  it is large, and in all cases is driven by a rise in  $pK_a(\mathbf{B})$ . We suspect this phenomenon to have a stereoelectronic origin. In the **B**-tautomer (**1104**,  $R \neq H$ ) there must be some twisting, but this may not be severe for  $Z = O$  or  $S$ . For  $Z = NMe$ , however, such twisting might be enough, in **1105**, to result in a free base form approaching in structure the orthogonal zwitterion **1105b**, with a consequent rise in basicity. Twisting in the **A**-tautomer, as **1106**, would have the opposite effect of reducing basicity, hence the fall in  $pK_a(\mathbf{A})$  observed for (**1109A**,  $R = Me$ ). We consider that (**1110**,  $R = Me$ ) is simply too crowded a molecule to act as a valid model for (**1109B**,  $R = H$ ) and the earlier result,<sup>519</sup> for (**1109A**,  $R = H$ ) *vs.* (**1110**,  $R = H$ ) is to be preferred.

$$pK_a(\mathbf{A}) = 5.38(0.04) - 9.06(0.13) \sigma_I \quad (\text{xciii})$$

$$(n = 4 \quad r^2 = 0.999 \quad s = 0.05 \quad F = 4947)$$

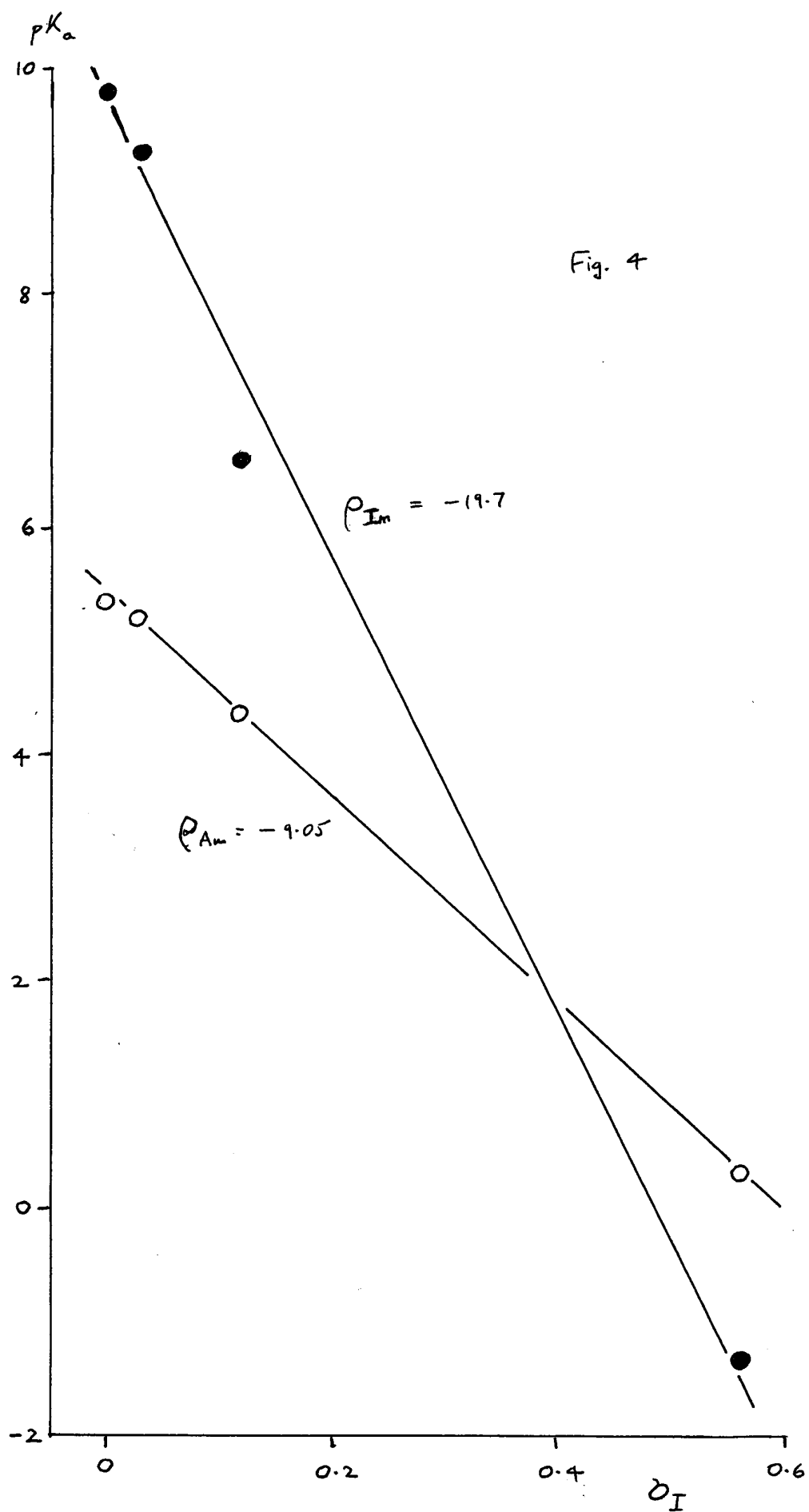
$$pK_a(\mathbf{B}) = 9.58(0.33) - 19.70(1.14) \sigma_I \quad (\text{xciv})$$

$$(n = 4 \quad r^2 = 0.993 \quad s = 0.51 \quad F = 298)$$

$$\log K_M = 10.59(1.16) \sigma_I - 4.20(0.33) \quad (\text{xcv})$$

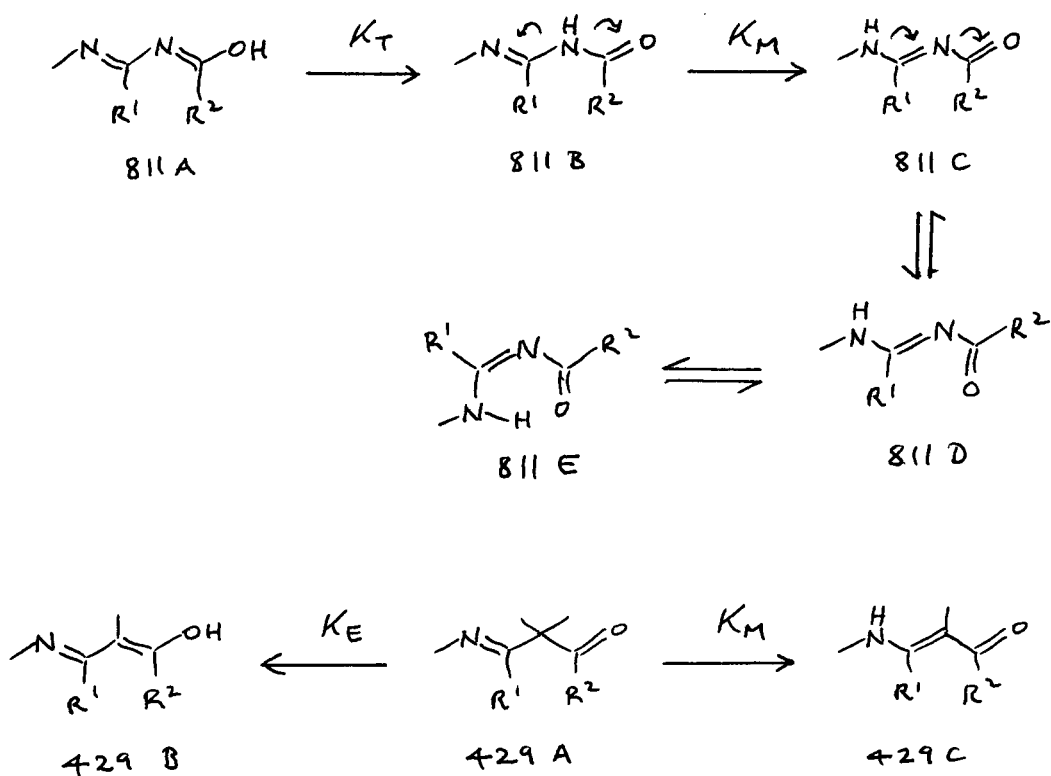
$$(n = 4 \quad r^2 = 0.976 \quad s = 0.52 \quad F = 82)$$

Forlani and De Maria<sup>521</sup> have measured  $pK_a(\mathbf{A})$  and  $pK_a(\mathbf{B})$  for variation in  $R$  for a series of thiazoles (**1088**,  $Z = S$ ), with results which appear in Table 65 and Figure 4. As for **1066** all parameters are linear in  $\sigma_I$  and the governing equations are (xciii) - (xcv). Here the intercept term is less negative than for **1066** (thiazole possesses less resonance energy than pyridine) and  $\rho_r = \rho_{Im} / \rho_{Am}$  is also smaller, *ca.* 2.2 in place of *ca.* 2.5. It is tempting to suppose that these factors are connected but they probably are not;  $\rho_r$  most probably depends on molecular geometry. Data for other series are badly needed.



## B.5 Acylamidines

Acylamidines form an important class of mostly cyclic compounds with special tautomeric problems of their own. These derive from the three-way nature of the tautomeric equilibrium involving **811** (Scheme 29, section B.2) which may be compared and contrasted with that of the  $\beta$ -iminoketones **429** (Scheme 17) considered in section A.10. Scheme 43 compares these cases schematically and summarises the nomenclature that we shall use.



Scheme 43

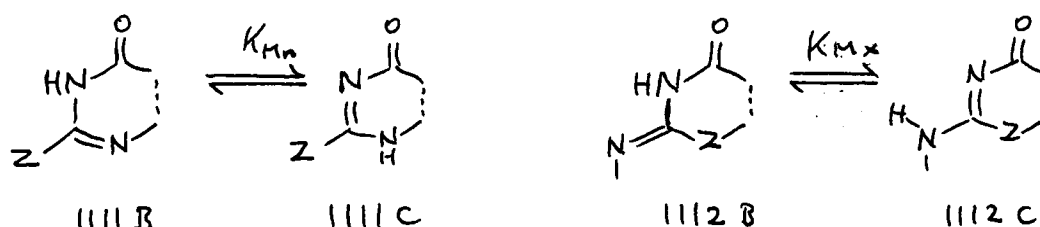
The most striking and obvious difference between these chemical classes is that **811B** is conjugated whereas **429A** is not. Hence the very large, substituent-related variations in  $K_M$  found for **429** and explored in section A.10 are expected to be absent in **811**, and this is found. Similarly, while **429B** can compete effectively with **429A** when N is part of an aromatic ring (sections A.10.2, A.10.14 and A.10.16), there is no parallel example in which  $K_T < 1$  for **811**. Another difference is that the *competitive* effect of  $\text{R}^1$  vs.  $\text{R}^2$  which is such a feature of **429** is largely absent here; whereas  $\pi$ -donors at  $\text{R}^1$  will tend to stabilise **429A** and (sometimes) **429B** at the expense of **429C**, and at  $\text{R}^2$  contrariwise will tend to stabilise **429A** or **429C**, then while such effects persist (at least for  $\text{R}^1$ ) in **811**, they appear to be more muted (section B.5.3). A fourth distinction, unique to **811**, involves conformation. Whereas

open-chain compounds will tend to form chelates such as **811E**, much in the manner of their analogues **429C** or **429B**, this preference for the *Z*-conformer extends to **811D** where intramolecular hydrogen bonding is absent.<sup>130</sup> The reason for this lies in the lone pair repulsion present in **811C**; we shall find that in cyclic compounds, where the *E*-conformation is enforced, the resulting effect on  $K_M$ , while not enormous, is perceptible.

$$K_{\text{tot}} = K_T K_M \quad (\text{xcvi})$$

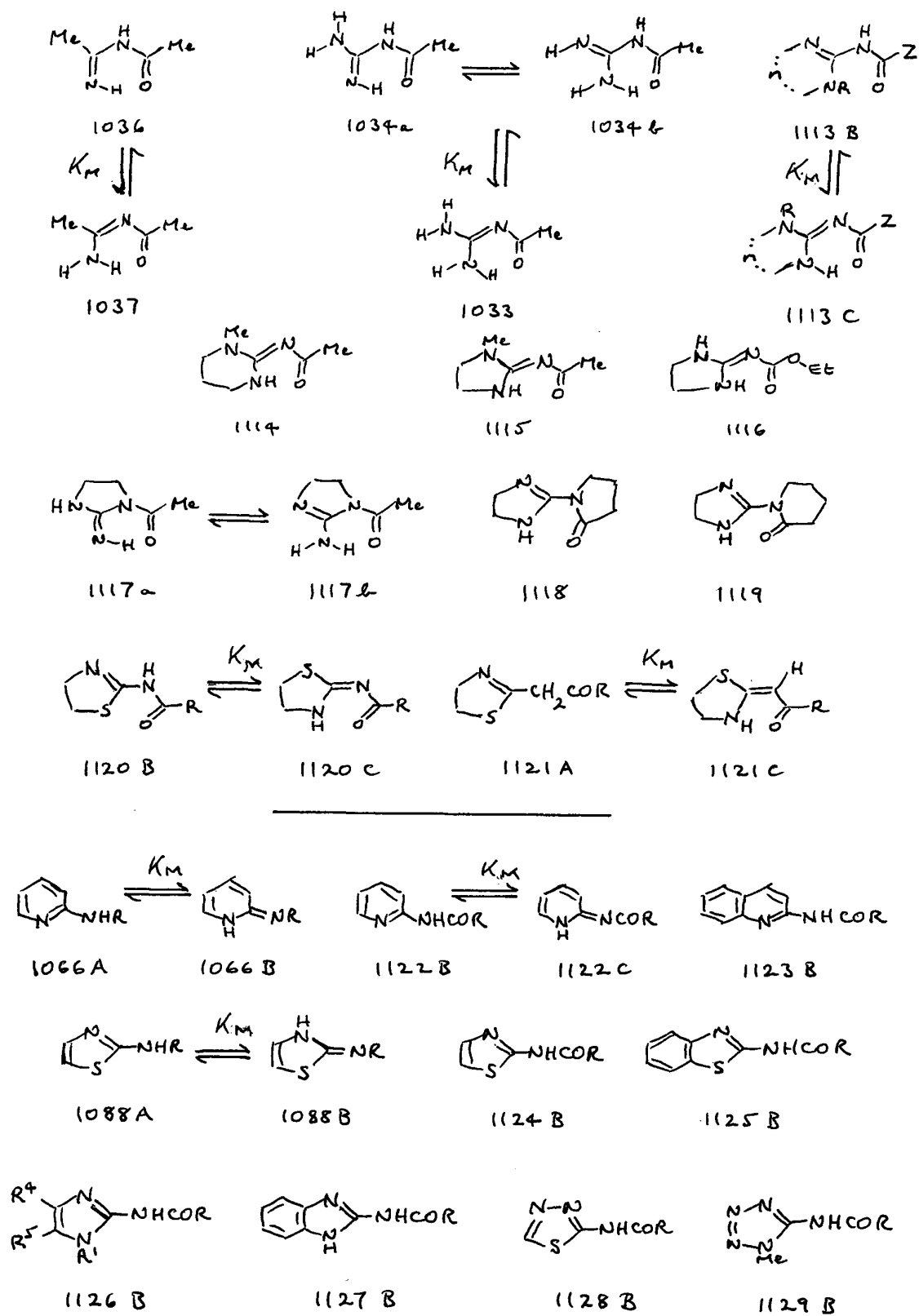
$$K_T = K_M / K_E \quad (\text{xcvii})$$

The overall equilibrium involving **811** is given by eqn. (xcvi), where  $K_{\text{tot}} = [\mathbf{811C}]/[\mathbf{811A}]$ . This nomenclature is clumsy and takes a different form from that of eqn. (xcvii) for **429**, but it is difficult to think of a less unsatisfactory alternative. There is an obvious logic in accepting **429A** as the unconjugated 'primaeval tautomer' from which alternative conjugated systems can result, but **811B** is still conjugated if nominally less so than **811C** (it would commonly be described as 'cross-conjugated') and a similar distinction cannot be maintained.



Scheme 44

In the case of  $\beta$ -diketones,  $\beta$ -iminoketones *etc.* we have considered 'extended' structures, *i.e.* those corresponding to **429**, ahead of chelated structures in which intramolecular hydrogen bonding appears as an additional complication. Here we reverse the order, for two reasons. The first is that intramolecular bonding is commonly found in both tautomers or neither, so that any effect on  $K_M$  is likely to be marginal.<sup>96</sup> The second is that most complications here attach to cyclic structures; not only because of their potential for aromatisation, but through a unique conformational problem. In cyclic structures the **B**-tautomer can possess either *endo*- or *exo*-C=N (Scheme 44); only for  $Z = \text{NHR}$  is choice between these possible. (Note here the special nomenclature, with  $K_{Mn}$  and  $K_{Mx}$  designating a shift from *endo*- or *exo*-C=N where the choice is open). Furthermore, if  $Z$  is a  $\pi$ -donor **1111** and **1112** are essentially different structures, in principle with different tautomeric ratios. This complication is explored in sections B.5.9 and B.5.10. For noncyclic compounds whether chelated or not the situation is simpler; these are therefore treated first.



### B.5.1 Open-Chain Acylamidines

Quantitative information exists only for **1037** and **1033** (section B.4.2), for which we respectively estimate  $\log K_M$  2.8, and 3.1 - 3.4, in aqueous solution. For the latter, the balance between **1034a** and **1034b** is unknown. Replacement of Me by  $\text{NH}_2$  evidently enhances  $K_M$  and other  $\pi$ -donors may show similar behaviour, but nothing is known.

### B.5.2 Alicyclic *exo*-Acyliminoguanidines

In all media examined, compounds of type (**1113**,  $n = 0$  or 1,  $\text{R} = \text{H}$  or alkyl,  $\text{Z} = \text{alkyl}$ ) exist overwhelmingly in the **C**-form; **1114**,<sup>106,130</sup> **1115**<sup>106,130</sup> and **1116**<sup>106</sup> are among those comprehensively examined by IR, in solution and the solid state. However, the difficulties in finding adequate models for the disfavoured tautomer have seriously hindered quantitative evaluation. Matsumoto and Rappoport<sup>522</sup> and Greenhill *et al.*<sup>159</sup> have synthesised **1117** and **1118** respectively,  $\text{p}K_a$  9.06 and 9.43. Given  $\text{p}K_a$  6.72 for **1115**<sup>159</sup> this leads to  $\log K_M$  2.3 or 2.7 according to the model chosen. We prefer the latter since **1117** is tautomerically ambiguous (*cf.* **1034**) whereas **1118** is more analogous geometrically and the two tautomers are then *N*-alkylated to the same extent. Its homologue **1119** might have been a better model still, but any difference in  $\text{p}K_a$  is likely to be marginal since most of the positive charge in either cation will be carried by the imidazoline ring. This fall in  $K_M$  when the acylimino unit is *exo* to a 5-membered ring, while small, is echoed by other compounds that contain this feature (section B.5.6) and is discussed in that context.

### B.5.3 Other Alicyclic *exo*-Acyliminoamidines

No results are known for aqueous solution. The thiazoline (**1120**,  $\text{R} = \text{Me}$ ) on IR evidence exists as **1120B** in  $\text{CHCl}_3$  and the solid state, whereas (**1120**,  $\text{R} = \text{OEt}$ ) takes the **C**-form as the solid and to the extent of *ca.* 90% in  $\text{CHCl}_3$ .<sup>106</sup> Hence preference for the **C**-form is much more muted even though, in water, it is likely that both will exist mostly as **1120C** since this is highly favoured in polar solvents (*cf.* the case of 4-pyrimidone, section B.5.11). Fortuitously, since the same situation is improbable for water (**1121C** will be *disfavoured* in solvents of high polarity: section A.10.2), the analogous ‘**C**-type’ molecule **1121** enolises in  $\text{CHCl}_3$  to a similar extent (75%) as **1120**. In discussing this and similar cases we draw attention (section A.10.12) to the preferential stabilisation of **1121A** over **1121B** caused by lone pair alignment at sulfur, and it is possible that the same factor operates in **1120**.

If so, it should apply equally to the corresponding oxazolines, but the situation may be quite different, as it is in the 'C-type' series, when a different alignment is enforced or the SR or OR substituent is free to rotate.

#### B.5.4 2-Acylaminoheterocycles

This is a large and important class of potentially tautomeric compounds, some of which have appeared in passing previously (section B.4.4). Here, *contra* the usage in that section, we are constrained to modify our nomenclature in line with Scheme 43; for example **1122B** and **1122C** are the equivalents, in this context, of **1066A** and **1066B** – **1122A** would represent the hypothetical iminol tautomer. Scheme 45 lists the series for which data are available (Table 67); except for **1122**, only the **B**-tautomer is illustrated.

Only a few of these compounds have been investigated quantitatively, and fewer still in water. Nevertheless, Table 67 exhibits trends which are regular enough to provide a reasonably consistent picture. Firstly, the **C**-tautomer is increasingly favoured as solvent polarity rises, as would be expected (*vide* Scheme 43) and is noted above for **1120C**. Hence, in sharp contrast to the corresponding aminoenones (section A.10.2; *cf.* discussion in section B.4.4), the **C**-tautomer achieves its maximum prominence in water. Secondly, the relative effect of various COR is qualitatively and perhaps even semi-quantitatively consistent. In terms of promoting the **C**-tautomer, we obtain from **1122** the order  $\text{COCCl}_3 > \text{COCHCl}_2 > \text{COMe}$ ; from **1129** the order  $\text{COCF}_3 > \text{COCCl}_3$ ; and (probably) from **1126**, the order  $\text{COPh} > \text{CO}_2\text{Et}$ . Except for the last, this represents the order known or expected for  $\sigma_I$ ; the exception is difficult to explain except in terms of proton acceptor ability.<sup>72,493</sup> Taken together these lead to the overall sequence  $\text{COCF}_3 > \text{COCCl}_3 > \text{COCHCl}_2 \gg \text{COPh}, \text{COMe} > \text{CO}_2\text{Et}$ , with a separation between  $\text{COCHCl}_2$  and  $\text{COCCl}_3$  in the range  $\Delta \log K_M$  1.3 - 1.5. Qualitatively this is the order found among COR groups for heterocyclic aminoenones (section A.10.14) and probably reflects the general parallelism between field and resonance forces among substituents of similar type.<sup>39</sup> Since  $\rho_I$  is unlikely to be constant, then as between various heterocycles these  $\Delta \log K_M$  values will not be constant either, but nevertheless their differences may not be great; for  $\text{COMe} \rightarrow \text{COCF}_3$ , for example, they *calculate* as 2.9 and 2.6 for **1066** and **1088** respectively [eqns. (xcii) and (xcv), sections B.4.4 and B.4.5; *n.b.* (**1122**, R = Me), Table 67, *calculates* as  $\log K_M - 2.8$ ].

**Table 67. Tautomeric Preference (B, C or log  $K_M$ ) for some 2-Acylamino-Heterocycles <sup>a,b</sup>**

Compound	R	Water	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	CCl <sub>4</sub>	Solid
<b>1122</b>	Me	- 3.3 <sup>c</sup>						
"	Ph	- 3.3 <sup>d</sup>						
"	CHCl <sub>2</sub>	(- 1.9) <sup>e</sup>	(- 3.5) <sup>e</sup>			(- 3.8) <sup>e</sup>		
"	CCl <sub>3</sub>	- 1.0 <sup>e</sup>	(- 2.2) <sup>e</sup>			(- 2.7) <sup>e</sup>		
"	CF <sub>3</sub>	0.1 <sup>d</sup>						
<b>1123</b>	CCl <sub>3</sub>	- 0.5 <sup>e</sup>	- 1.1 <sup>e</sup>			- 1.4 <sup>e</sup>		
<b>1124</b>	Me	- 1.0 <sup>f</sup>		<b>B</b> <sup>g</sup>			<b>B</b> <sup>g</sup>	
"	CHCl <sub>2</sub>	- 0.3 <sup>e</sup>	- 0.7 <sup>e</sup>	<b>B</b> <sup>g</sup>		- 1.1 <sup>e</sup>	<b>B</b> <sup>g</sup>	
"	CCl <sub>3</sub>		0.7 <sup>e</sup>	<b>C</b> <sup>g</sup>		0.2 <sup>e</sup>	<b>B</b> <sup>g</sup>	
"	CF <sub>3</sub>	1.3 <sup>f</sup>		<b>C</b> <sup>g</sup>			<b>B</b> <sup>g</sup>	
<b>1125</b>	CHCl <sub>2</sub>		- 0.6 <sup>e</sup>	<b>B</b> <sup>g</sup>		- 1.0 <sup>e</sup>	<b>B</b> <sup>g</sup>	
"	CCl <sub>3</sub>		0.9 <sup>e</sup>	<b>C</b> <sup>g</sup>		0.3 <sup>e</sup>	<b>B</b> <sup>g</sup>	
<b>1126</b>	OMe <sup>h</sup>			<b>B</b> <sup>i</sup>				<b>B</b> <sup>i</sup>
"	OEt <sup>j</sup>							<b>B</b> <sup>i</sup>
"	Ph <sup>k</sup>							<b>B</b> <sup>i</sup>
"	Ph <sup>j</sup>				<b>C</b> <sup>i</sup>			
"	Ph <sup>l</sup>				<b>C</b> <sup>i</sup>			<b>C</b> <sup>i</sup>
<b>1127</b>	OMe			<b>B</b> <sup>i</sup>				<b>B</b> <sup>i</sup>
<b>1128</b>	CHCl <sub>2</sub>	0.2 <sup>e</sup>	- 0.4 <sup>e</sup>			- 0.7 <sup>e</sup>		
"	CCl <sub>3</sub>					0.8 <sup>e</sup>		
<b>1129</b>	Me				<b>B</b> <sup>m</sup>			<b>B</b> <sup>n</sup>
"	Ph							<b>B</b> <sup>n</sup>
"	CCl <sub>3</sub>				<b>B</b> <sup>m,o</sup>			<b>B</b> <sup>m</sup>
"	CF <sub>3</sub>				<b>C</b> <sup>m,o</sup>			

<sup>a</sup> Preference (**B** or **C**) according to authors where log  $K_M$  is unavailable. <sup>b</sup> Bracketed values are highly approximate, *calculated* values are italicised. <sup>c</sup> Ref. 248. <sup>d</sup> Eqn. (xcii), section B.4.4.

<sup>e</sup> Ref. 511. <sup>f</sup> Eqn. (xcv), section B.4.5. <sup>g</sup> Ref. 523. <sup>h</sup> R<sup>4</sup> = Ph, R<sup>1</sup> = R<sup>5</sup> = H. <sup>i</sup> Ref. 106.

<sup>j</sup> R<sup>1</sup> = Bu, R<sup>4</sup> = H, R<sup>5</sup> = CO<sub>2</sub>Et. <sup>k</sup> R<sup>1</sup> = R<sup>4</sup> = H, R<sup>5</sup> = CO<sub>2</sub>Et. <sup>l</sup> R<sup>1</sup> = Bu, R<sup>4</sup> = CH<sub>2</sub>OH, R<sup>5</sup> = Me.

<sup>m</sup> Ref. 524(a). <sup>n</sup> Ref. 524(b). <sup>o</sup> Predominant but not exclusive tautomer.

On limited evidence there also appears to be a reasonable degree of consistency as to the magnitude of the solvent effect, at least concerning EtOH and water and for the most accurate data. If  $\Delta \log K_M$  *ca.* 0.6 for this quantity is combined with the ordering quoted above, we arrive at the provisional picture of Table 68 for the best attested case, that in which the acyl group is COCCl<sub>3</sub>. The large difference between 6- and 5-membered ring heteroaromatics is consistent with the much higher resonance energy of the former group (Table 12, section A.2.6). Among the latter, while **1124**, **1125** and **1128** come out as very similar, the presumed higher value of  $K_M$  for **1126** and probable lower one for **1129** deserve comment. It is noted in section B.4.5 that imidazoles appear to show much less resistance to *exo*-imine formation than the corresponding oxazoles and thiazoles, whereas the resistance of tetrazoles is exceptional (Table 66), and the present results are consistent with this.

It is possible to go further and to compare, instructively, the effect of aromatisation in an acylamidine with that in the parent amidine itself. For **1037**, we estimate  $\log K_M$  *ca.* 2.8 (section B.5.1); for (**1122**, R = Me) we have  $\log K_M$  -3.3, hence  $\Delta \log K$  is *ca.* 6.1. For (**1066**, R = H) relative to a simple cyclic amidine with zero tautomeric preference<sup>157</sup> (section B.4.4),  $\Delta \log K$  is 6.5 (Table 66). Bearing in mind that we have no idea what effect replacement of Me by SR would have on  $\log K_M$  for **1037** (but probably not much) we may compare  $\log K_M$  2.8 with a calculated value [eqn. (xcv)] of -1.0 for (**1124**, R = Me; Table 67) to obtain  $\Delta \log K_M$  -3.8; this compares with  $\Delta \log K_M$  -4.5 for (**1088**, R = H; Table 65) relative to its hypothetical parent thiazoline. Given that heterocycles possess very differing degrees of aromaticity, this resemblance is striking. It suggests that, at least for some acylaminoheterocycles, tautomeric ratio may parallel that of the parent aminoheterocycle closely enough for either to be used as a reasonably predictive tool for the other.

**Table 68. Predicted  $\log K_M$  Values in Water for 2-Trichloroacetyl amino Derivatives of Some Heterocycles (Scheme 45) <sup>a</sup>**

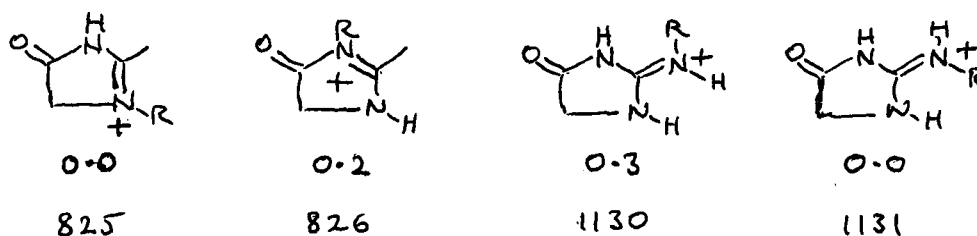
Compound	$\log K_M$	Compound	$\log K_M$
<b>1122</b>	- 1.0	<b>1126</b>	$\gg 0$
<b>1123</b>	- 0.5	<b>1128</b>	1.6
<b>1124</b>	1.3	<b>1129</b>	$\sim 0$ <sup>b</sup>
<b>1125</b>	1.5		

<sup>a</sup> See the text. <sup>b</sup> May be appreciably below zero.

The overall picture is that while COAlk may never be electron-withdrawing enough to compel dominance of the C-tautomer in any reasonably aromatic heterocycle, COCF<sub>3</sub> is probably capable of doing so in all but exceptionally resistant cases and even COCCl<sub>3</sub> may be electronegative enough to tip the balance in most 5-membered ring heteroaromatics. Among the latter class, imidazole is more susceptible than the norm to this process, and tetrazole less so. But fine detail is largely lacking, and as so often, more work is needed.

### B.5.5 Alicyclic Acylamidines: Correction Factors for the Basicity Method

The required  $\Delta(\text{NR})$  values are summarised in Scheme 46. Those for **825** and **826** are taken from Scheme 30 whereas the conformationally-dependent

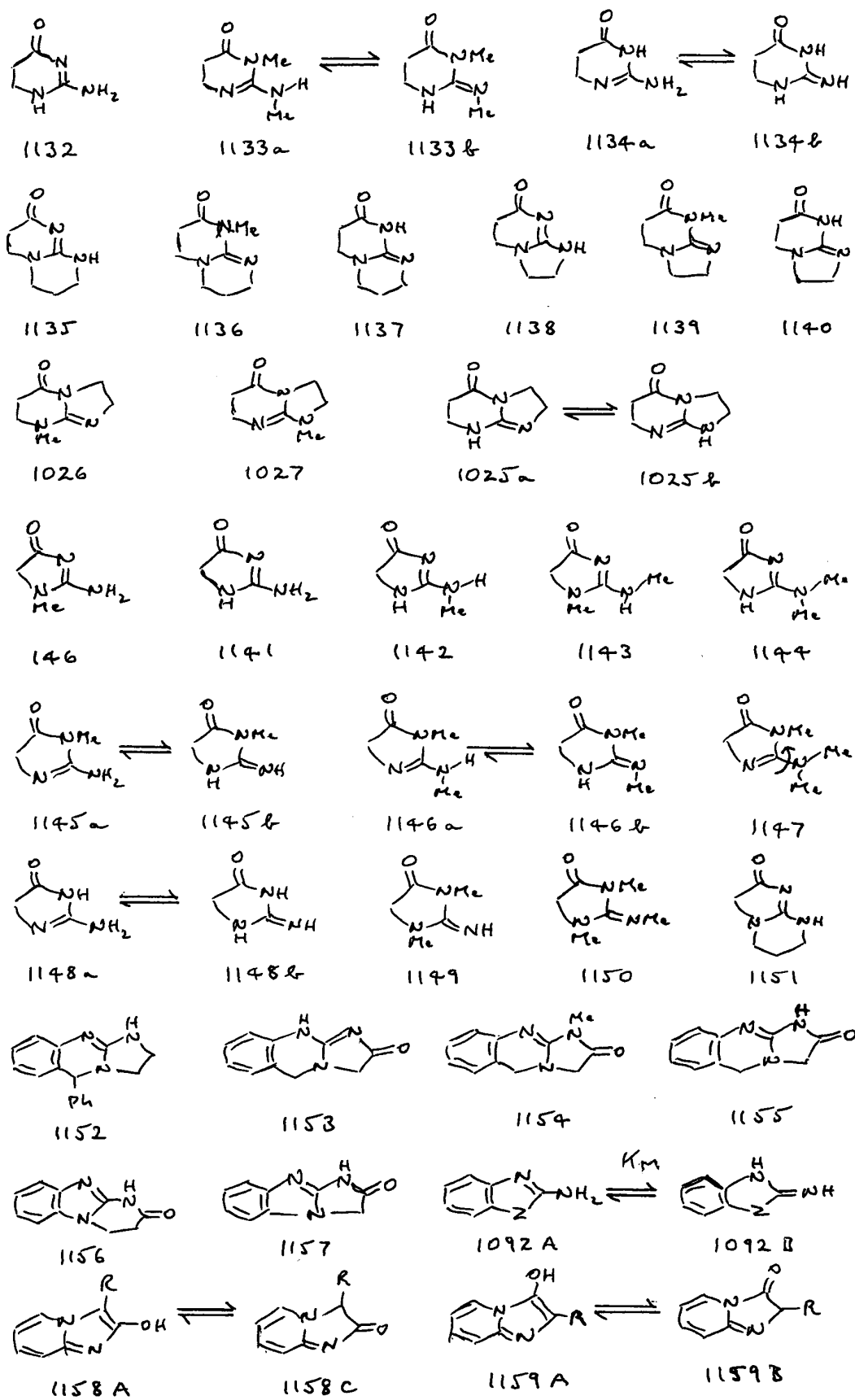


Scheme 46

exocyclic corrections for **1130** and **1131** are derived from the present study. There is one perceived inconsistency, in that the work<sup>159</sup> we have reported in section B.4.1 on **1025** - **1027** might have led to the expectation of  $\Delta(\text{NR})$  *ca.* 0.3 for **825** and **1131** whereas in neither case does any correction appear to be needed. Possibly for **825** this is a ring size effect, or for **1131**, caused in some way by the more flexible nature of the molecules here examined. These corrections, while small, lead to a remarkably consistent picture (see sections B.5.6 - B.5.10 below). All are based on 5-membered ring acylguanidines; with some trepidation we have assumed the same correction for 6-membered rings in the one context,  $\Delta(\text{NR})$  for **826**, where this is required.

### B.5.6 Alicyclic Acylguanidines: Carbonyl in 6-Membered Ring

The compounds discussed in this and the following section appear in Scheme 47. Most of the data were determined by Matsumoto and Rappoport,<sup>522</sup> Kenyon and Rowley,<sup>525</sup> or ourselves.<sup>159</sup> We<sup>159</sup> have discussed the tautomerism of **1132** and suggested  $\log K_M$  *ca.* 2.8 in its favour. Detailed



Scheme 47

**Table 69. Observed and Estimated <sup>a</sup> pK<sub>a</sub> Values, and the log K<sub>M</sub> Values Resulting, for Some Alicyclic Acylguanidines**

Compound	Observed pK <sub>a</sub>	Compound	Estimated pK <sub>a</sub>	log K <sub>M</sub>
<b>1132</b>	7.05 <sup>b</sup>			
<b>1133</b>	9.48 <sup>c</sup>	<b>1134a</b>	10.0	2.9 <sup>d</sup>
		<b>1134b</b>	10.0	2.9 <sup>d</sup>
<b>1135</b>	6.79 <sup>e</sup>			
<b>1136</b>	9.49 <sup>e</sup>	<b>1137</b>	9.7	2.9 <sup>f</sup>
<b>1138</b>	5.80 <sup>e</sup>			
<b>1139</b>	7.98 <sup>e</sup>	<b>1140</b>	8.2	2.4 <sup>g</sup>
<b>1026</b>	8.14 <sup>e</sup>			
<b>1027</b>	8.56 <sup>e</sup>			
<b>1025</b>	8.36 <sup>e</sup>	<b>1025a</b>	8.5	2.7 <sup>g</sup>
		<b>1025b</b>	8.9	3.1 <sup>g</sup>
<b>146</b>	4.83 <sup>h</sup>			
<b>1141</b>	4.80 <sup>i</sup>			
<b>1142</b>	4.84 <sup>c</sup>			
<b>1143</b>	4.55 <sup>j</sup>			
<b>1144</b>	4.48 <sup>c</sup>			
<b>1145</b>	7.91 <sup>j</sup>	<b>1148</b>	7.9 <sup>l</sup>	
<b>1146</b>	7.96 <sup>c</sup>			
<b>1147</b>	7.57 <sup>j</sup>	<b>1148a</b>	8.1	3.3 <sup>k</sup>
<b>1149</b>	8.07 <sup>j</sup>	<b>1148b</b>	8.3	3.5 <sup>k</sup>
<b>1150</b>	9.01 <sup>j</sup>			
<b>1151</b>	4.75 <sup>j</sup>			
<b>1152</b>				1.0 <sup>a</sup>
<b>1153</b>	3.39 <sup>m</sup>			
<b>1154</b>	5.01 <sup>m</sup>	<b>1155</b>	5.2	1.8 <sup>n</sup>

<sup>a</sup> See the text. <sup>b</sup> P. Goursot and I. Wadso, *Acta Chem. Scand.*, 1966, **20**, 1314. <sup>c</sup> Ref. 522.

<sup>d</sup> In favour of **1132**. <sup>e</sup> Ref. 159. <sup>f</sup> In favour of **1135**. <sup>g</sup> In favour of **1138**. <sup>h</sup> A. K. Grzybowski and S. P. Datta, *J. Chem. Soc.*, 1964, 187. <sup>i</sup> C. F. Failey and C. Brand, *J. Biol. Chem.*, 1933, **102**, 767. <sup>j</sup> Ref. 525. <sup>k</sup> In favour of **1141**. <sup>l</sup> Summation of estimates for **1148a** and **1148b**.

<sup>m</sup> Ref. 106. <sup>n</sup> In favour of **1153**.

analysis now confirms this figure. From pK<sub>a</sub> 9.48 for **1133** (Table 69) we obtain pK<sub>a</sub> ca. 9.7 for **1134**, which becomes pK<sub>a</sub> 10.0 for each of **1134a** and **1134b** if we assume<sup>159</sup> that there is no energetic difference between them. A similar treatment

of the 6,6-fused bicyclic system **1135**  $\rightleftharpoons$  **1137** leads to  $\log K$  2.9 in favour of **1135** (Table 69). This identical value is consistent with the common experience that there is commonly no appreciable difference in behaviour between open-chain compounds and their 6-membered ring analogues. By contrast, the 6,5-fused bicyclic system **1138**  $\rightleftharpoons$  **1140** shows a drop in  $\log K$  to *ca.* 2.4. This difference is echoed by the  $pK_a$  values of **1026** and **1027** which demonstrate a relative stabilisation of  $\Delta \log K$  *ca.* 0.4 in favour of **1026** since C=N is here incorporated into a 5-membered ring. If  $\Delta(NR)$  for **1026** and **1027** are assumed identical (section B.4.1) we may calculate  $pK_a$  values for **1025a** and **1025b** of *ca.* 8.5 and 8.9 respectively, leading to the notional  $\log K$  values, relative to **1138**, given for these in Table 69. Both appear to be somewhat more disfavoured than **1140**, perhaps because of small differences in bond angle or lone pair alignment that are difficult to chart accurately.

Overall therefore, a value close to  $\log K_M$  2.9 appears normal for this class of compound but, in bicyclic systems, can be modified by hybridisation effects. This value is slightly but significantly lower than *ca.* 3.1 – 3.4 for acetylguanidine itself (section B.4.2) as is consistent with the lone pair repulsion which must exist in *trans*-acylimines such as **1132** but is relieved in amides such as **1134**. Nevertheless, at a likely factor of *ca.* 2 it is clearly far less in aqueous solution than in organic solvents such as  $\text{CHCl}_3$  or DMSO where the *s-trans* conformer is commonly undetectable,<sup>106,130</sup> the result presumably of their much poorer proton donor ability.<sup>72</sup>

### B.5.7 Alicyclic Acylguanidines: Carbonyl in 5-Membered Ring

Much of this work<sup>522,525</sup> was sparked by an interest in the tautomerism of creatinine **146**. The near-identity in  $pK_a$  between this and its parent compound glycyamidine **1141**, as also its isomer **1142**, provide evidence for  $\Delta(NR) \sim 0$  in the case of both **825** and **1131** (Scheme 46). Taken with this,  $A(NR)$  *ca.* 0.3 follows for **1130** from the difference between **1141** and **1143** plus its isomer **1144**, in both of which the second Me contributes about the same, near-zero amount to overall  $\Delta(NR)$ . For **1142** and **1143** we have assumed that conformation which appears most reasonable in avoiding steric hindrance; it will be seen that consistent results are obtained.

The  $pK_a$  values of 7.91 and 7.96 for **1145** and **1146** respectively, while confirming a near-zero  $\Delta(NR)$  for **1131**, do not permit of partitioning between the **a**- and **b**-forms. We proceed as follows. Starting from  $pK_a$  7.57 for **1147** we have to correct for  $-\text{NMe}_2 \rightarrow -\text{NH}_2$  and for ring NMe. The first derives from **1144**  $\rightarrow$  **1141**,  $\Delta pK_a$  0.32, and the second from  $\Delta(NR)$  0.2 for **826**; if we

can assume additivity,  $pK_a$  *ca.* 8.1 for **1148a** results. More straightforwardly,  $pK_a$  8.07 for **1149** plus the  $\Delta(NR)$  values for **825** and **826** gives  $pK_a$  *ca.* 8.3 for **1148b**. This small degree of asymmetry, relative to none in **1134**, seems reasonable. In fact **1147** will probably be twisted, leading to some loss of conjugation by  $NMe_2$ , so the value for **1148a** at least is likely to be an underestimate. (We discount  $pK_a$  9.01 for **1150** for the reason discussed in section B.4.5; *cf.* structure **1105**). In addition, the summation  $pK_a$  calculated for **1148** equals that found for **1145** whereas it should be slightly greater, which again suggests that these  $pK_a$  values are underestimated, so that the latter, hence the  $\log K_M$  values for **1141** *vs.* **1148a** and **1148b** (Table 69) represent minima. Hence the difference between  $\log K$  2.9 in favour of **1132**, and 3.3 or 3.5 in favour of **1141**, is probably real. Its origin is not entirely clear. While *endo*-C=N is stabilised in 5- *vs.* 6-membered rings (*cf.* section A.4.1) the effect of a switch between two sorts of *endo*-C=N, in **1132** *vs.* **1133a** and **1141** *vs.* **1148a**, should be independent of ring size; nevertheless, the parallel bias towards carbonyl *vs.* its enol may form part of the explanation. It is also possible that lone pair repulsion between C=O and aza-nitrogen is less in 5- than in 6-membered rings; *cf.* the effect of ring size on that between adjacent aza-nitrogens (Appendix 3).

According to the treatment we give in section B.4.2, a symmetrical 1,2-disubstituted amidine should possess a tautomeric balance which is the *ratio* of those expected for its substituents (*i.e.* their *difference* in  $\log K$ ). There are no cases that put this principle unequivocally to the test, but an approximation is provided by **1153**  $\rightleftharpoons$  **1155**, for which  $\log K_M$  *ca.* 1.8 in favour of **1153** may be calculated from the  $pK_a$  data (Table 69) using  $\Delta(NR)$  0.2 for **826**. This molecule may be viewed as a combination of **1152**, for which we calculate  $\log K_M$  1.0 in the direction shown (section B.4.2), with **1151**, for which  $\log K_M$  is unknown but may tentatively be estimated. The fusion of a 6-membered alicyclic ring to **1132** to give **1135** does not affect  $K_M$ , and if this is also true for **1141**, then  $\log K_M$  *ca.* 3.5 follows for **1151**. The difference,  $\Delta \log K_M$  *ca.* 2.5, therefore overpredicts  $\log K_M$  for **1153**. A possible explanation lies in the difference between (alk)NH in **1151** and (ar)NH in **1153** as  $\pi$ -donors, given that aromatic NH is a poorer  $\pi$ -donor (Table 2) than aliphatic NH as present in the model compounds considered above. A reduction of  $\Delta \log K_M$  -0.7 in **1153** from this cause does not seem unreasonable. Curiously, calculations derived from the simple mono-substituted guanidines of Table 62 give much better results:  $\Delta \log K_M$  1.3 if based on the  $pK_a$  values of phenyl- and acetyl-guanidine, or 2.0 if based on the  $\sigma_I$  values of -Ph and -COMe. More good examples would be helpful.

### B.5.8 Aromatised Bicyclic Acylamidines

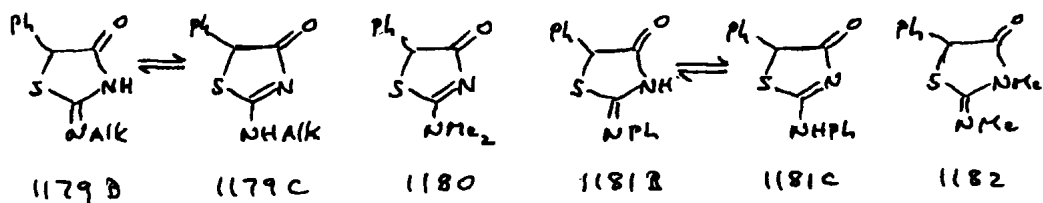
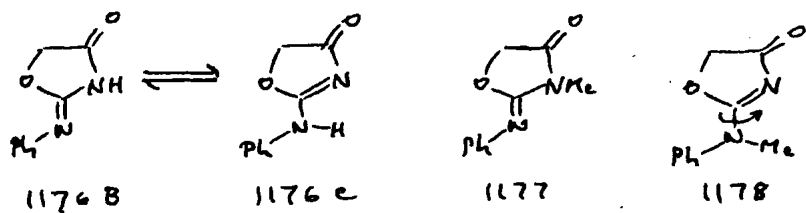
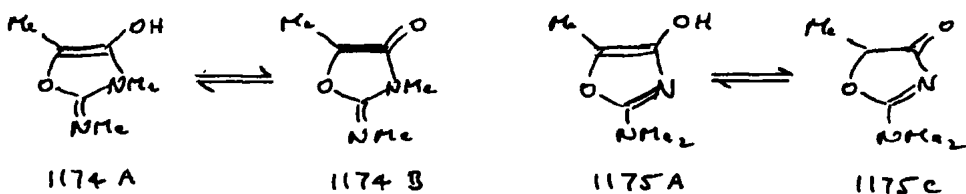
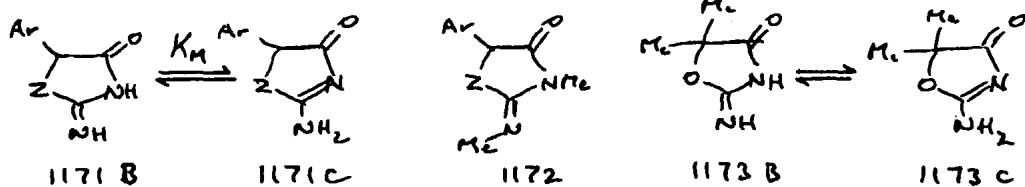
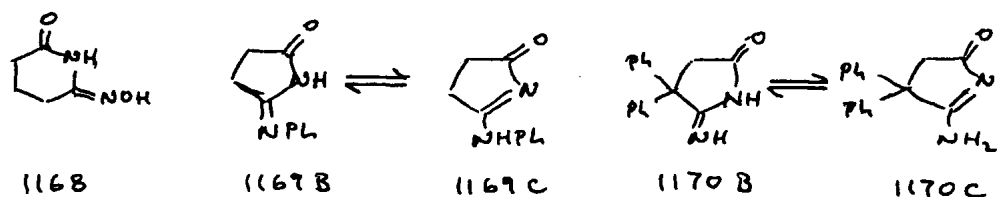
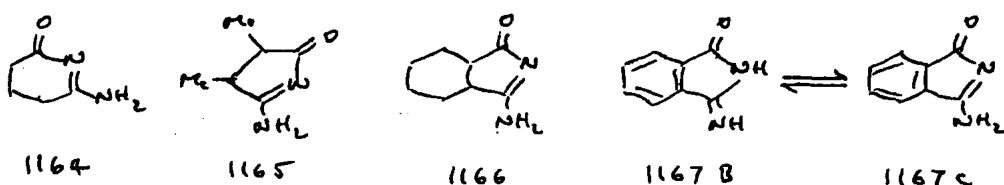
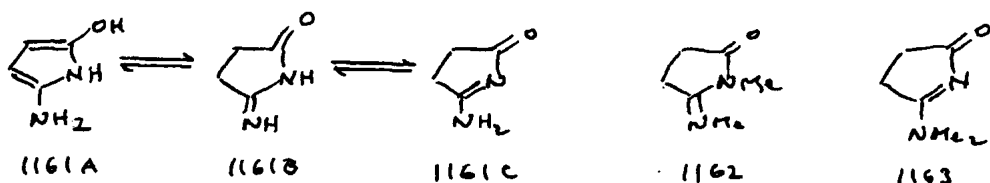
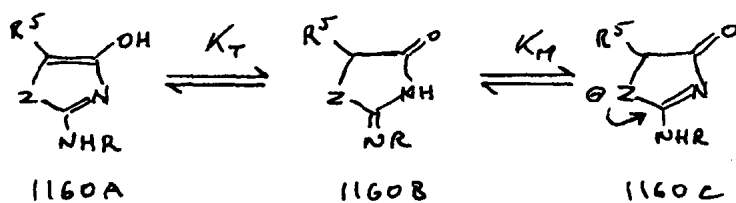
This is a rare category, included for the sake of completion. While as noted above **1153** is the dominant tautomer, in water probably by about  $\log K_M$  1.8 over **1155**, in **1156** and **1157** this preference is reversed as shown, on IR evidence for the solid state.<sup>106</sup> We note (section B.4.5) that (**1092**, Z = NMe) is disfavoured in water by only  $\log K_M$  -3.1 so these may be borderline cases. There are also rare cases in which aromatisation can give rise to the OH tautomer. While Paolini and Robins<sup>526</sup> found (**1158**, R = H) to exist exclusively as **1158C** in DMSO, Sigiura and co-workers<sup>527</sup> found the replacement of R = H by R = Me to provide a mixture of tautomers. Inspection of Hine's double bond stabilisation factors (Table 1) suggests that for R = Ph, **1158A** should be very dominant, whereas if R = Me produces a mixture, then for R = H, **1158C** will be the only detectable tautomer. Aromatisation in such cases is a strong driving force; in the isomer **1159**, where **1159B** lacks the through-conjugation of **1158C**, **1159A** dominates (in DMSO) even for R = H,<sup>527</sup> and a similar preference is possible for water. Note that **1158** and **1159** may also be regarded as benzofused derivatives of **141** and **138**, for which enolisation is facile; see sections C.17 and C.14 respectively.

### B.5.9 Alicyclic Acylamidines: *endo-Z*, *exo-N*

In these compounds, one ring  $\pi$ -donor nitrogen atom is replaced by a nontautomeric unit which may be C, O, S or NR: *i.e.* **1112** in Scheme 44. The alternative series **1111**, in which a cyclic acylamidine possesses a nontautomeric *exo*-substituent, is the subject of section B.5.10.

With one exception, no 6-membered cyclic compounds have been studied in either series. In 5-membered rings aromatisation becomes a possibility except for Z = carbon, leading here to species **1160A**. This possibility has been explored for creatinine **146** (Scheme 47), whose rate of deuterium exchange suggests  $K_E \leq 10^{-5}$  (section A.2.8). It is unlikely, therefore, that enolisation will be important for any alicyclic acylguanidine, but there is scattered evidence for its existence in some of the compounds to be considered in this and the following section.

Spiessens and Anteunis,<sup>528</sup> using **1162** and **1163** as model compounds, demonstrated by NMR that **1161** exists in CHCl<sub>3</sub> and DMSO as **1161C**; they state that no trace of **1161A** is detectable. Their IR data (KBr), which they do



not quote, provide further confirmation. The UV spectrum of **1161** in EtOH is also stated by them to be so similar to those for **1164**, **1165** and **1166** as to establish the **C**-tautomer for these as well. We note (section B.5.1) that the chelated acylamidine **1037** possesses a  $K_M$  value not much less than that of its acylguanidine equivalent **1033**. According to Elvidge and co-workers,<sup>529</sup> however, on IR (Nujol) evidence, **1161** and **1164** both take up the **B**-form in the solid state. We have re-examined their data and conclude that this is true for **1164** but not for **1161**; however, in EtOH their UV spectra are identical. It is not unusual to find that imides give rise to tight dimers in the solid state and that could be the explanation here; nevertheless, it may indicate that preference for the **C**-form is not overwhelming. Consistently with this, there appears to be good evidence that **1168** takes up the **B**-form shown,<sup>529</sup> while we<sup>106</sup> find **1169C** to be the major (75%) but not exclusive tautomer of **1169** in DMSO. We note elsewhere (section A.4.6; see also B.5.15) that Ph mildly, and NH<sub>2</sub> and OH strongly, stabilise the imino-tautomer when attached to nitrogen. Interestingly in view of the above, **1169** gives **1169B** in the solid state.<sup>106</sup> Again on solid state (Nujol) evidence, Foucard<sup>530</sup> claims **1170B** as the structure for this compound, whereas his data point to **1170C** [strong  $\nu(\text{C}=\text{O})$  and  $\nu(\text{C}=\text{N})$  at 1673 and 1523 cm<sup>-1</sup> respectively]. However, the claimed<sup>531</sup> existence of **1167** as **1167B** is confirmed by Spiessens and Anteunis,<sup>528</sup> who estimate a 70:30 ratio of **B**- to **C**-forms in EtOH. Katritzky and Lagowski<sup>532</sup> attribute this difference to interactions between *both* C=Z and the benzene ring, an interesting idea with other possible applications.

Najer *et al.*<sup>507,533</sup> have provided quantitative data, summarised in Table 70, on compounds of type **1171** where Z = O or S. Here we assume that **1172** unlike **1150** (*vide* section B.5.7) should be able to take up a near-planar conformation, so that standard  $\Delta(\text{NR})$  values remain applicable. The log  $K_M$

**Table 70.  $pK_a$  and log  $K_M$  Values for Compounds of Type 1171**

Ar	Z	Cpd.	Observed $pK_a$	Cpd.	Estimated $pK_a$	log $K_M$
Ph	S	<b>1171C</b>	1.55			
Ph	S	<b>1172</b>	4.07	<b>1171B</b>	4.27	2.7
Ph	O	<b>1171C</b>	0.90			
Ph	O	<b>1172</b>	3.80	<b>1171B</b>	4.00	3.1
<i>a</i>	O	<b>1171C</b>	0.67			
<i>a</i>	O	<b>1172</b>	4.36	<b>1171B</b>	4.56	3.9
H	NMe	<b>146</b>				$\sim 3.5^b$

<sup>a</sup> Ar = 3,4-dimethoxyphenyl. <sup>b</sup> Assumed equal to that for **1148b**  $\rightarrow$  **1141** (Table 69).

values of Table 70 follow. We are uneasy concerning the compound in which 3,4-dimethoxyphenyl replaces Ph as 5-substituent since its  $pK_a$  values change in opposite directions, and prefer to discount this result. The remaining sequence for  $\log K_M$  follows the order  $NR > O > S$  which is that of  $\sigma_R$  (Table 2) though the fit is not quantitative. The implication however is that  $K_M$  should be increased by any  $\pi$ -donor relative to  $Z = \text{carbon}$ , as is consistent with the lone pair interaction indicated for **1160C**. A similar and probably greater effect has been demonstrated to operate in some aminoenones (section A.10.5); and see the section that follows.

There is some useful qualitative work. By spectroscopic means, Rapi *et al.*<sup>534</sup> demonstrated that **1173** exists exclusively as **1173C** in the solid state (KBr) and in MeOH, MeCN, DMSO and dioxane. This comprehensive range is indicative of a probably high  $K_M$  value in water and fits with the data of Table 70. Importantly, they also demonstrate that neither **1174A** nor **1175A** is detectable in any of these solvents. Similar evidence is provided by Howell *et al.*<sup>535</sup> These authors claim **1176B** on UV evidence as the dominant tautomer of **1176** in MeOH, since  $\lambda_{\max}$  254 nm is common to **1176** and **1177** but that for **1178** is different (233 nm). However the model compound **1178** must be very crowded and the anomalously low UV intensity of **1177** is also disquieting. Nevertheless Najer *et al.*<sup>536</sup> claim **1179** to exist in EtOH as **1179C** but **1181** as **1181B** on the basis of close UV resemblances to **1180** and **1182** respectively, and this seems sound, so the case of **1176** is open. Some caution is necessary. Whereas Ph as substituent is expected to have a considerable effect on  $K_M$ , then if the picture for guanidine is any guide (section B.4.2), it should not be able to outdo the ‘pull’ of carbonyl in aqueous solution. Its opposing  $\log K_M$  value (Table 62) of 1.4 - 1.7 has to be compared with  $\log K_M$  2.6 - 3.4 as listed in Table 70, so that **1176**, **1181** *etc.* in water should still give predominantly the C-tautomer. However these results are for EtOH, and while this solvent is a much better match for water than, for example,  $\text{CHCl}_3$  or DMSO, there are a surprising number of LSER studies (Appendix 2) which demonstrate an appreciable drop of  $\log K$  in EtOH relative to water (and *cf.* Table 72). Here **1160C** is much more polar than **1160B** so is likely to be strongly favoured in aqueous solution.

One apparent anomaly requires mention. In examining the crystal structure of **1183**, Amirthalingam and Muralidharan<sup>537</sup> assigned it to **1183B** on the apparently reasonable grounds that *exo*-C=N is shorter than *endo*-C=N. However, that is also a feature *inter alia* of **1184**, whose recent X-ray determination by Mingos and co-workers<sup>538</sup> included accurate location of all protons. This is a hybridisation effect: it results from the  $sp^2$ -s nature of the N-H bond – it is not found where alkyl replaces H – and has caused some confusion. The mis-assignment of **1183** may not be unique.

### B.5.10 Alicyclic Acylamidines: *endo*-N, *exo*-Z

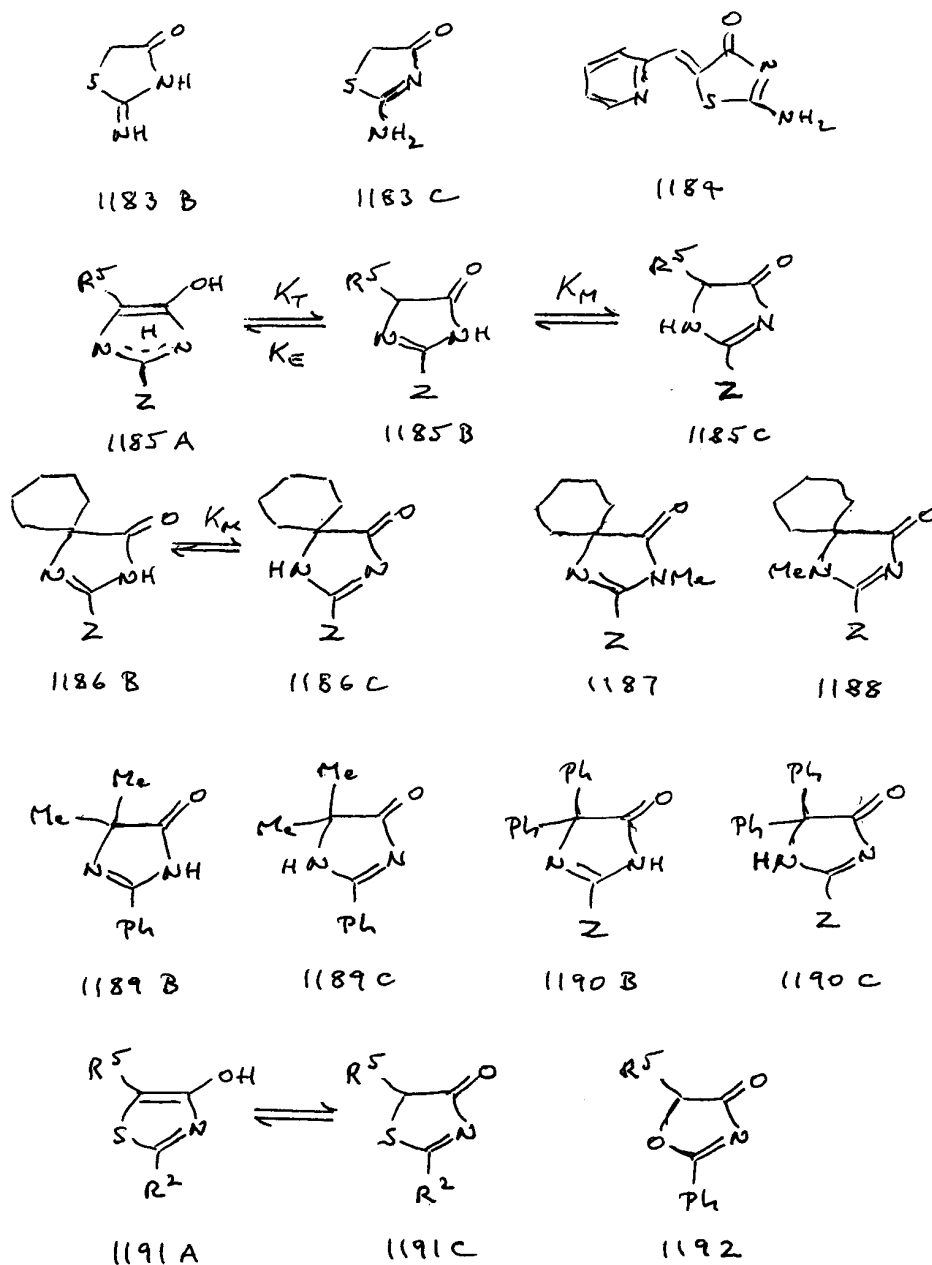
These compounds (**1185**) exemplify series **1111** and show two significant differences from those of section B.5.9. Firstly, all are necessarily imidazolines. Secondly, the exocyclic nature of Z allows a much greater variety of substituents, which are no longer confined to alkyl or a  $\pi$ -donor atom. Again there are no 6-membered ring examples.

Quantitative data in water are confined to two papers by Edward and co-workers<sup>539,540</sup> the results of which are summarised in Table 71. Two of the three compounds are based on the spiro-structure of **1186** – **1188**; in the third, 5,5-diphenyl replaces this. The effect of this switch on  $K_M$  is inappreciable. We also add, from Table 69, our estimated  $\log K_M$  value for Z = NH<sub>2</sub>. These results are strikingly different from those for **1171** (Table 70) in that a much greater range in  $K_M$  is covered; the two series more or less converge for Z = NR, but for Z = S,  $\log K_M$  2.6 has become 1.0. Plausibly, the much greater range in  $\log K$  for **1171** results from *trans*-conjugation in that case, contrasting with *cis*-conjugation here. The case of Z = H is particularly interesting. Here, uniquely, the **B**-tautomer is favoured in water, and by almost exactly the margin found for 4-pyrimidone (section B.5.11). There may, therefore, be no special explanation needed for the latter's apparently anomalous tautomeric balance; it may simply be a conformational effect (but see the following section for a contrary view).

**Table 71.  $pK_a$  and  $\log K_M$  Values for Compounds of Type 1186**

Z	Cpd.	Observed $pK_a$	Cpd.	Estimated $pK_a$ <sup>a</sup>	$\log K_M$	%C (est.)
H <sup>b</sup>	<b>1187</b>	3.72	<b>1186B</b>	3.92		
H <sup>b</sup>	<b>1188</b>	4.21	<b>1186C</b>	4.21	- 0.3	35 <sup>f</sup>
H <sup>b,c</sup>	<b>1187</b>	1.72	<b>1186B</b>	1.92		
H <sup>b,c</sup>	<b>1188</b>	2.32	<b>1186C</b>	2.32	- 0.4	28
SMe <sup>d</sup>	<b>1187</b>	3.78	<b>1186B</b>	3.98		
SMe <sup>d</sup>	<b>1188</b>	3.00	<b>1186C</b>	3.00	1.0	91
NH <sub>2</sub>	<b>1141</b>				3.3 <sup>e</sup>	

<sup>a</sup> For  $\Delta$ (NR) estimation see Appendix 1, section (c). <sup>b</sup> Ref. 539. <sup>c</sup> Of compound in which CPh<sub>2</sub> replaces the *spiro*-cyclohexyl unit. <sup>d</sup> Ref. 540. <sup>e</sup> Table 69. <sup>f</sup> Authors' estimate (UV spectrum).

Table 72. Solvent Dependence of Tautomer Balance for Compounds of Type 1186<sup>a</sup>

Z	Solvent:	C <sub>6</sub> H <sub>12</sub>	CHCl <sub>3</sub>	DMSO	EtOH	Water
H <sup>b</sup>			0	25	10	35
SMe <sup>c</sup>		0	0	60	70	91 <sup>d</sup>

<sup>a</sup> % C-tautomer. <sup>b</sup> Ref. 539. <sup>c</sup> Ref. 540. <sup>d</sup> Calculated (Table 71).

There is limited qualitative evidence that bears especially on the latter point. The tautomers **1189B** and **1189C** co-exist in the solid state,<sup>124</sup> and so do those of (**1190**, Z = Me) whereas (**1190B**, Z = Ph) and (**1190C**, Z = Ph) are separately isolable.<sup>541</sup> This suggests strongly that, where Z is not a  $\pi$ -donor, the energetic gap between the **B**- and **C**-forms is slight. In the case of (**1190**, Z = SMe), **1190C** which is the stable form in the solid state gives the metastable species **1190B** on sublimation or on recrystallisation from nonpolar solvents.<sup>542</sup> Edward and co-workers<sup>539,540</sup> have published limited solvent data on (**1186**, Z = H and SMe) which is also relevant here. It will be seen (Table 72) that tautomer balance shifts considerably with solvent polarity, with the C-tautomer notably more favoured in water than elsewhere.

It is clear from the above that  $K_M$  is close to unity even in water unless Z is a  $\pi$ -donor, and while we have no information for Z = OR,  $K_M$  is likely to approach the values for the rival series **1160** only when Z = NR<sub>2</sub>. However, this switch has another consequence: if Z is not a  $\pi$ -donor, enolisation to give **1185A** is greatly promoted. (It is of course suppressed in **1186** – **1190**). This has been investigated by Jacquier and co-workers<sup>124</sup> who have studied the effects of Me and Ph at Z and R<sup>5</sup> in the solid state and a number of organic solvents. If R<sup>5</sup> = H and Z = Me or Ph, **1185B** alone is found in the solid state and all solvents studied (CHCl<sub>3</sub>, DMSO, pyridine); if Z = R<sup>5</sup> = Me, the **B**-form is still dominant; if R<sup>5</sup> = Me and Z = Ph or *vice versa*, considerable enolisation is found; whereas if Z = R<sup>5</sup> = Ph, **1185A** now dominates. There are puzzling aspects here: while effects at R<sup>5</sup> are consistent with ‘Hine’s Rules’ (Table 1, section A.1), it is difficult to see why they should be so precisely matched at R<sup>2</sup> (= Z). Nevertheless, these are consistent trends. It is possible that Ph at R<sup>5</sup> and R<sup>2</sup> favours enolisation for different reasons: as stabilising C=C in the first case, but through the field effect in the second. Nevertheless these last compounds link up with some discussed elsewhere, notably in section A.2.8. Without too much recapitulation, one may note that (**1191**, R<sup>2</sup> = Ph) exists in the solid state as **1191C** when R<sup>5</sup> = H but as **1191A** when R<sup>5</sup> = Me, whereas even the former is 80% enolised in DMSO.<sup>70</sup> By contrast, **1192** exists as shown in the solid state even for R<sup>5</sup> = Ph.<sup>70</sup> While there are complications in some cases such as zwitterion formation (section A.2.8) it is clear that, as a general rule, oxazolidinones are the most resistant to enolisation and thiazolidinones the least, with imidazolidinones somewhere in between but closer to the latter category. A rationalisation is attempted in section A.2.8 to which the reader is referred.

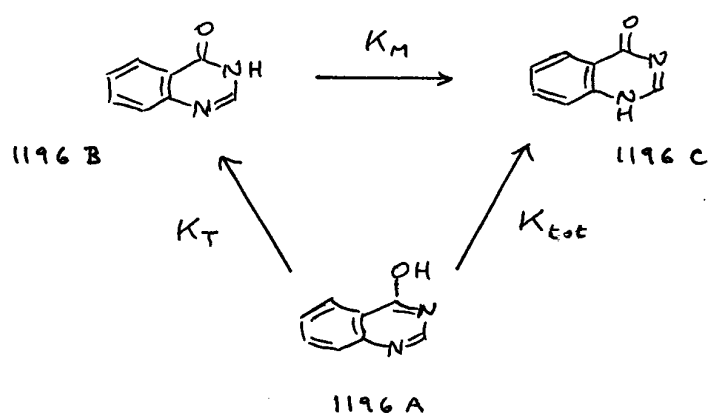
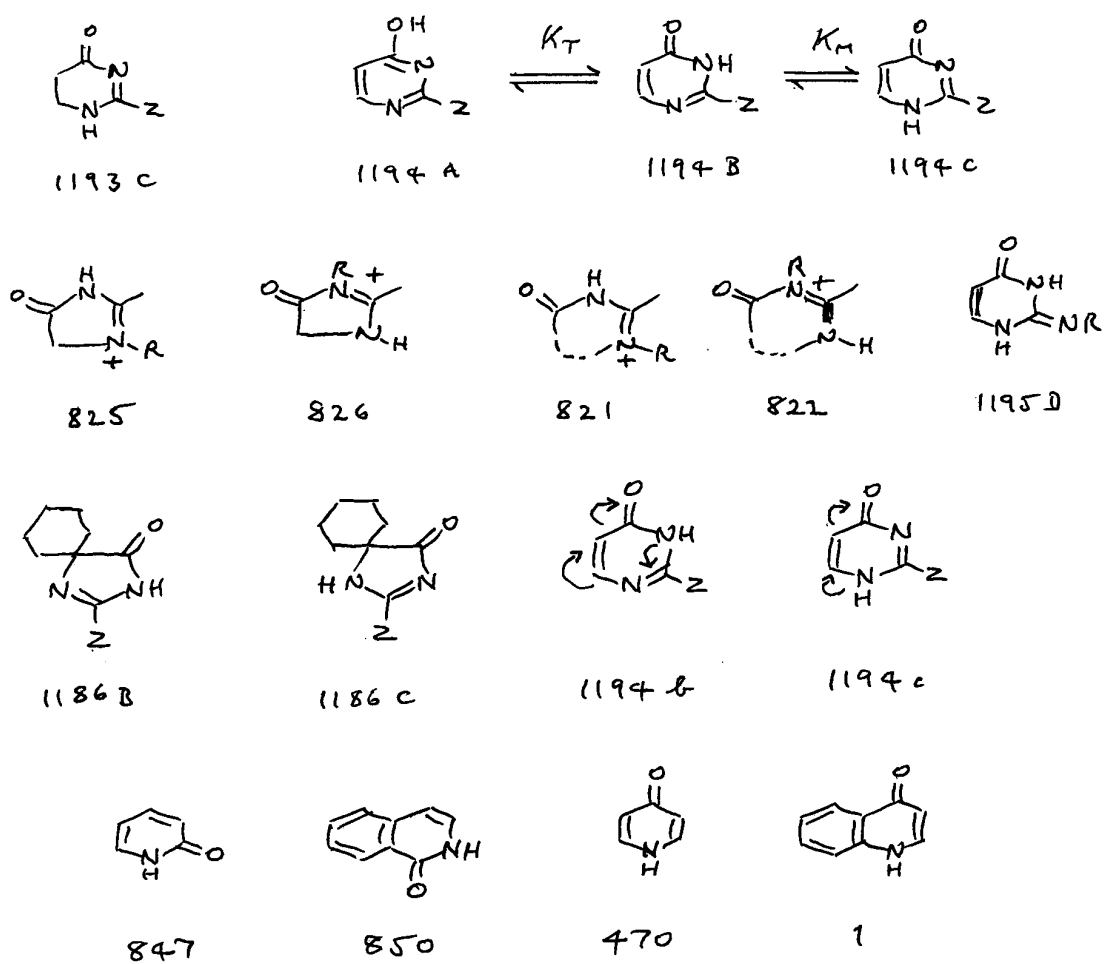
Overall there appears to be a hierarchy. Alicyclic acylguanidines are the most resistant to enolisation; we have estimated  $K_E$  for creatinine as on the order of  $10^{-5}$  (section A.2.8). Replacement of one  $\pi$ -donor nitrogen by a different (weaker)  $\pi$ -donor increases susceptibility, to a probably smaller extent where this is endocyclic in **1160** than when an *exo*-substituent as in **1185** – a reflection of the greater importance of *exo*-substitution itself (see above). If Z in **1185** is not a  $\pi$ -donor at all, there occurs a step jump in susceptibility which is powerfully reinforced when the 5-position is substituted, especially by phenyl. (This is probably a general effect but may be invisible elsewhere). Also, in such cases  $K_M \sim 1$ . There remains the question of aqueous solution behaviour. Relative to other solvents the balance for water will certainly follow the trend **C** > **B** > **A** and it seems likely that, except for the last category listed above, enolisation will be largely suppressed. Further than this it is not possible to go.

#### B.5.11 Aromatic Acylamidines: Annular Tautomerism in 4-Pyrimidones and 4-Quinazolones

If the *endo*-N, *exo*-Z unit of the preceding section is incorporated into a 6-membered ring, the result is **1193** or, on aromatisation, **1194**. While nothing is known concerning tautomerism for  $Z \neq \text{NH}_2$  in the former, the 4-pyrimidones **1194** have been the subject of extensive studies.

One effect of aromatisation should be to increase the importance of the **A**-tautomer, which has been conspicuous by its absence till now. This, for which the evidence is fugitive, is discussed in section B.5.12. Much more important in practice is the resulting near-equivalence in importance of the **B**- and **C**-forms. That is the subject of this section.

Available data for (**1194**, Z = H) are listed in Table 73. For close tautomeric ratios the classical UV methodology is probably the most accurate, and a very careful study<sup>543</sup> summarised by Mason<sup>18</sup> finds a 70:30 ratio of **1194B** to **1194C** with no detectable trace of **1194A**, the spectrum of the fixed OMe derivative being very different from any other. Other estimates<sup>544-548</sup> do not differ significantly from this. It is important to note that, as will be further discussed, the **B/C** ratio is very sensitive to solvent dielectric; in water-ethanol mixtures this ratio rises, and in pure EtOH the **C**-tautomer is undetectable.<sup>546</sup> Similarly, Lardenois *et al.*<sup>547</sup> find (**1194B**, Z = H) to predominate in EtOH and DMSO, while a dipole moment study by Mussetta *et al.*<sup>548</sup> in benzene and dioxan claims 82% of **1194B** in these solvents on the assumption that **1194A** is absent (the fixed methyl derivatives of **1194A**, **B** and **C** possess  $\mu = 1.82, 2.24$  and  $7.50$  debyes respectively<sup>548</sup>).



Scheme 48

It is of interest to check this result ( $\log K_M -0.4$ ) against the ‘basicity method,’ using the data of Table 73. If no  $\Delta(\text{NR})$  correction is required, the rival values of  $\text{p}K(1\text{-NMe})$  lead to estimates of *ca.* 50% and 60% respectively for **1194B** where 70% is required, with overall  $\text{p}K_a$  1.52 or 1.65 as against measured values of 1.69 or 1.85. If we apply  $\Delta(\text{NR})$  corrections based on **825** and **826** (section B.5.5) the situation worsens: the predicted fraction of **1194B** falls to 42 and 55% respectively, with overall  $\text{p}K_a$  predicted as 1.56 or 1.68. However, corrections of  $\Delta(\text{NR})$  0.3 and 0.0 for 1-NMe and 3-NMe respectively lead to predictions of 65 or 75% respectively for **1194B**, with overall  $\text{p}K_a$  values of 1.65 or 1.71. These compare closely with  $\text{p}K_a$  1.69 as found by Brown and Short;<sup>544</sup> the rival value<sup>4</sup> of 1.85 is too close for comfort to that for  $\text{p}K(3\text{-NMe})$  so less likely. These values for  $\Delta(\text{NR})$  appear to represent the best compromise and appear in Scheme 30 as **821** and **822**. Their rationale is discussed elsewhere (section B.2.1).

A handful of compounds for which  $Z \neq \text{H}$  have been studied. For  $Z = \text{Ph}$ , the dipole moment study of Mussetta *et al.*<sup>548</sup> finds a slightly increased proportion of **1194B** relative to  $Z = \text{H}$ , 93% *vs.* 82%, equivalent to  $\Delta\Delta \log K_M$  *ca.* - 0.5. Lardenois *et al.*<sup>547</sup> find similar behaviour for  $Z = \text{H}$ , Me and Ph in that **1194B** predominates in EtOH and DMSO; in the latter solvent, however, they claim some admixture with **1194A** for  $Z = \text{Ph}$ . Pitha<sup>549</sup> found on UV evidence that, for  $Z = \text{OEt}$ , **1194B** and **1194C** in water co-exist in comparable amounts, but that **1194B** greatly predominates in  $\text{CHCl}_3$ ; its predominance in

**Table 73.**  $\text{p}K_a$  Values for 4-Pyrimidone (**1194**,  $Z = \text{H}$ ), 4-Quinazolone (**1196**,  $Z = \text{H}$ ), and their Fixed OMe and NMe Forms in Water

Compound	$\text{p}K(\text{OMe})$	$\text{p}K(3\text{-NMe})$	$\text{p}K(1\text{-NMe})$	$\text{p}K_a^a$	% <b>B</b> <sup>b</sup>
<b>1194</b>	2.50 <sup>c</sup>	1.84 <sup>d,e</sup>	1.8 <sup>d</sup> 2.02 <sup>e</sup>	1.69 <sup>c</sup> 1.85 <sup>f</sup>	70 <sup>e</sup>
<b>1196</b>	3.13 <sup>g</sup>	2.18 <sup>h</sup>	3.19 <sup>h</sup>	2.12 <sup>f</sup>	> 90 <sup>h</sup>

<sup>a</sup> Of parent compound. <sup>b</sup> Of **B**-tautomer on UV evidence. <sup>c</sup> Ref. 543. <sup>d</sup> Ref. 544. <sup>e</sup> Ref. 18.

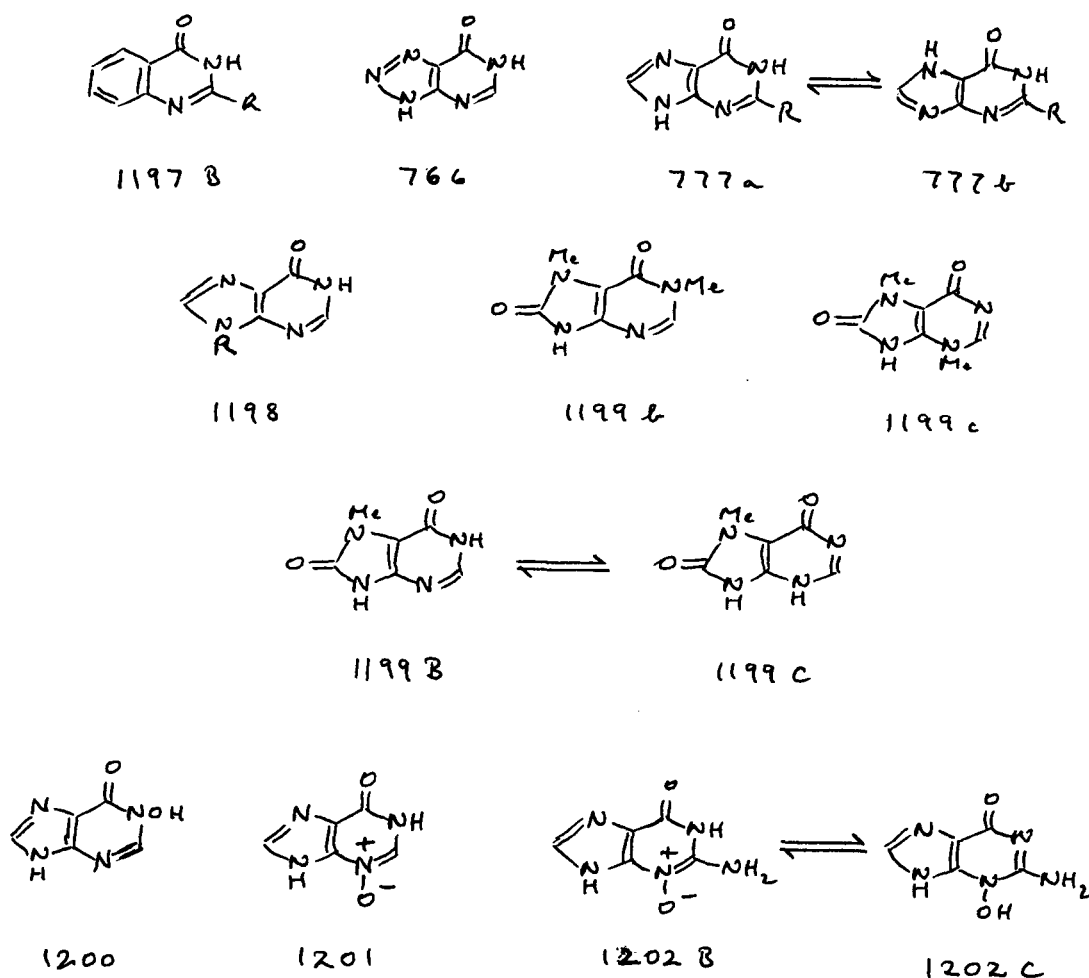
<sup>f</sup> Ref. 4. <sup>g</sup> A. Albert and A. Hampton, *J. Chem. Soc.*, 1954, 505. <sup>h</sup> Ref. 382a.

$\text{CHCl}_3$  and  $\text{CCl}_4$  is confirmed by Katritzky and Waring.<sup>458</sup> For isocytosine (**1194**,  $\text{Z} = \text{NH}_2$ ) Brown and Teitei<sup>550</sup> state the UV spectrum in water exactly to split the difference between those of the fixed 1-*N*Me and 3-*N*Me derivatives, while Hélène and Douzot<sup>551</sup> found similarly for water but showed a 90% predominance of the B-form in EtOH and were unable to detect the C-tautomer in a mixture of this with 90% of Et<sub>2</sub>O. These authors also found its 1-ribosyl derivative isocytidine to possess exactly the UV spectrum expected for the C-tautomer, which helps to demonstrate the absence of *exo*-imino tautomers of type **1195D**, as explicitly stated<sup>547</sup> for (**1195**,  $\text{R} = \text{H}$ , Me and COMe). It is also of interest that (**1194**,  $\text{Z} = \text{NH}_2$ ) gives a 1:1 complex of the B- and C-tautomers in the solid state,<sup>552</sup> consistently with their close equivalence in energetic terms.

This shift in tautomeric balance towards the C-form appears to be associated with  $\pi$ -donors: OEt,  $\text{NH}_2$ , and possibly others.<sup>553</sup> However it is far less than that encountered with **1186**, where with a different substitution pattern at C-5, replacement of  $\text{Z} = \text{H}$  by  $\text{Z} = \text{NH}_2$  leads to  $\Delta \log K_M > 3$  (Table 71). Hence the near-equivalence of  $\log K_M$  for (**1186**,  $\text{Z} = \text{H}$ ) and (**1194**,  $\text{Z} = \text{H}$ ), which might be connected with a lesser ability of *endo*-donors to stabilise the C-tautomer, may be fortuitous. A possibly more fruitful approach is to consider the likely effect of inserted  $\text{C}=\text{C}$  on the resonance stabilisation present in each tautomer. Whereas **1186B** may be described as ‘cross-conjugated,’ the additional vinylogous conjugation shown for **1194b** may help to stabilise **1194B**; similarly, the rival ‘through-conjugation’ indicated in **1194c** may help to destabilise that derived from **1186C**. Both the near-zero value of  $\log K_M$  typically found for **1194**, and its insensitivity to the nature of  $\text{Z}$ , suggest that broadly the same factors operate in both directions. Hélène and Douzot<sup>551</sup> note that the C-tautomer of (**1194**,  $\text{Z} = \text{NH}_2$ ) falls in importance with rising temperature, so must enthalpically be the favoured one. An attempt to predict  $K_T$  for the B- and C-tautomers of 4-pyrimidone by treating aza-nitrogen as an electronegative substituent in 2-pyridone and 4-pyridone respectively, using the algorithms of sections B.2.4 and A.10.6, failed, greatly exaggerating the importance of the C-tautomer. This is most likely due to the inability of this approach to treat the amidine moiety as a single conjugated unit, but a contributory factor may lie in the extreme sensitivity of the B/C ratio to solvent dielectric, a sensitivity which reflects that of solute molecular dipole. For the 1-Me and 3-Me derivatives of (**1194**,  $\text{Z} = \text{H}$ ) these are 7.50 and 2.24 debyes respectively,<sup>548</sup> a much greater difference than for the corresponding pyridones **470** and **847** which serve as implicit reference points for the above comparison.

Albert and Barlin<sup>382a</sup> studied the tautomerism of 4-quinazolone **1196** by the  $pK_a$  methodology (Table 73) and deduced  $\geq 90\%$  of the **B**-form to be present in water. Mason<sup>18</sup> estimated  $\log K_M$  -0.85 or about 88% of **1196B** from UV cross-comparisons. (An earlier study by Hearn *et al.*<sup>554</sup> in 95% EtOH which resulted in a widely quoted ratio of 20:70:10 for the **A**-, **B**- and **C**-forms must be discounted not only because of the solvent employed but since in it, fortuitously, the UV spectra of its fixed OMe and 3-NMe derivatives are very similar). Alternatively we may attempt to estimate  $K_M$  by the following, essentially isodesmic procedure. Benzofusion of 4-pyridone **470** to 4-quinolone **1** results in  $\Delta \log K_T$  1.0 (section A.10.7) and that of 2-pyridone **847** to isoquinolone **850** results in  $\Delta \log K_T$  1.8 (section B.2.5), values typical of the situations in which NH is in the  $\alpha$ - or the  $\beta$ -position, respectively, relative to the fused benzene ring<sup>555</sup> (for discussion see section B.2.5). While  $K_T$  for 4-pyrimidone is unknown (section B.5.12), then given  $\log K_M$  -0.4 and the relation  $K_{tot} = K_T K_M$  [eqn. (xcvi); start of section B.5], it follows that  $\log K_{tot} = \log K_T - 0.4$ . (We shall use  $K_{tot}$  and  $K_T K_M$  from here as interchangeable equivalents, according to context). The equivalent process for 4-quinazolone is set out in Scheme 48. If we suppose that  $\Delta \log K_T$  for **1196B** and **1196C** relative to the equivalent 4-pyrimidones mimics those of **850** and **1** respectively, the resultant for Scheme 48 is  $\log K_M$  -1.2. This implies about 95% of **1196B** and is almost identical to the estimate,  $\log K_M$  -1.3, which results from applying  $\Delta(NR)$  as given by **822** and **821** to the  $pK_a$  data of Albert and Barlin<sup>382a</sup> (Table 73). These results reinforce one another; their close agreement suggests not only that these  $\Delta(NR)$  values are reasonably reliable, but also that the tautomeric behaviour of 4-pyrimidones on benzofusion falls in line with that for other aromatic amides and related compounds.

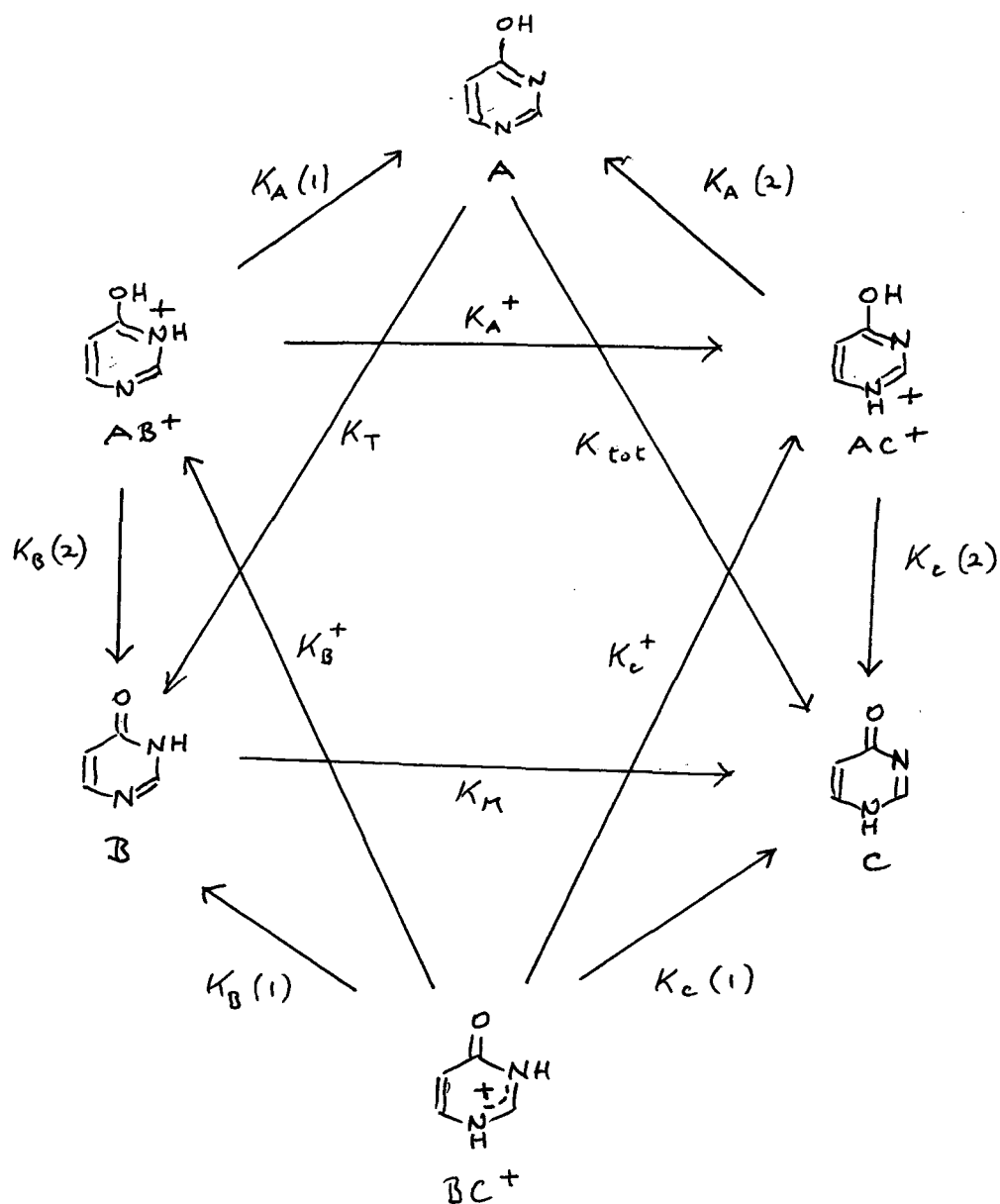
Evidence concerning 2-substituted 4-quinazolones is limited. Hagiwara *et al.*<sup>558</sup> showed by comparison with fixed derivatives that **1197B** is that form present in the solid state (KBr), and the only or predominant species in EtOH, for R = Me or Ph; the same tautomer predominates in DMSO for R = Ph or CH<sub>2</sub>Ph. A parallel predominance is known, or (probably with good reason) assumed, for **766**, section B.1.6, for hypoxanthine (**777**, R = H) and guanine (**777**, R = NH<sub>2</sub>), both section B.1.7, and the closely related inosine (**1198**, R = ribose).<sup>557</sup> It cannot of course be assumed that ring fusions other than with benzene will result in the same  $K_M$  value, and one set of results bears on this point. Rahat *et al.*<sup>558</sup> measured the *acid*  $pK_a$  values of **1199b** and **1199c** as 8.5 and 6.0 respectively, from which  $\log K_M$  *ca.* -2.5 results for



**1199** itself. The probable reason for this shift lies in repulsion between the adjacent NH dipoles of **1199C**, on this evidence deleterious to the extent of  $\Delta \log K_M$  *ca.* -2.1. The corresponding effect of lone pair repulsion in similarly aligned aza-nitrogen atoms is only *ca.* -0.8 (section A.12), helping to indicate that dipolar repulsion tends to be a much more powerful determinant of tautomeric form in water than lone pair repulsion (*vide* Appendix 3 for full exemplification of these and other variants on both).

There is some information on *N*-oxides. On IR evidence (KBr) and that qualitatively of  $pK_a$  values in water, both **1200** and **1201** exist as the normally dominant **B**-tautomers shown.<sup>559</sup> However, **1202** is present in water as a mixture of **1202B** and **1202C** with the latter predominating.<sup>559</sup> Nevertheless it should be noted that the tautomeric form of the imidazole ring has not certainly been established – reversing this from that shown for **1202C** might lead to an exceptionally powerful intramolecular hydrogen bond – so these conclusions must be provisional.

## B.5.12 Aromatic Acylamidines: Evidence concerning Iminol Forms



Scheme 49

$$1/K_A^1 = 1/K_A(1) + 1/K_A(2) \quad (\text{xcviii})$$

$$K_T = K_B(1)/K_A^1(K_B^+ + K_C^+) \quad (\text{xcix})$$

$$K_{\text{tot}} = K_C(1)/K_A^1(K_B^+ + K_C^+) \quad (\text{c})$$

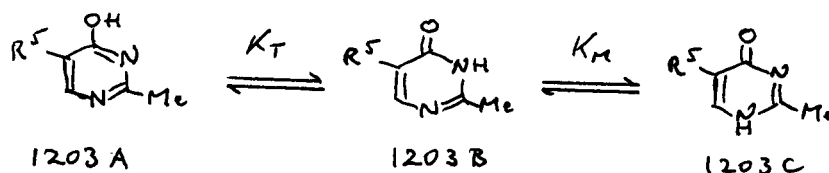
$$K_a = \{ K_A^1(K_B^+ + K_C^+) + K_B(1) + K_C(1) \} / (1 + K_B^+ + K_C^+) \quad (\text{ci})$$

$$(K_B^+ + K_C^+) = \{ K_B(1) + K_C(1) - K_a \} / (K_a - K_A^1) \quad (\text{cii})$$

There is some dispute as to whether iminol forms of the pyrimidones have ever been detected in aqueous solution. The most comprehensive attack on this problem was carried out by Kitagawa *et al.*,<sup>553</sup> who studied a series of 2-methyl-4-pyrimidones with various substituents in the 5-position. We have re-cast their 'Chart 2' as Scheme 49 and changed its nomenclature in what follows. The neutral annular tautomers **B** and **C** share a common cation **BC**<sup>+</sup> with  $K_M = [C]/[B]$  as previously, while two annular cations **AB**<sup>+</sup> and **AC**<sup>+</sup> deprotonate to give the common neutral iminol **A**. Whereas *N*-methyl derivatives can be used to model **B** and **C**, as seen above, no such model is possible for **AB**<sup>+</sup> or **AC**<sup>+</sup> separately, so that the measured  $pK_a$  of the iminol **A** or its methoxy-derivative is the composite term  $pK_A^1$ , defined by eqn. (xcviii).

The key equations are (xcix) - (cii). All are unusual in form, and require comment. While the  $pK_a$  values of the separate tautomers are simply defined, and those of their models are readily measurable,  $K_T$  and  $K_{tot}$  are not, as mostly elsewhere, simple ratios. Each is modified by a term ( $K_B^+ + K_C^+$ ) which defines the ratios of the iminol cations **AB**<sup>+</sup> and **AC**<sup>+</sup> to **BC**<sup>+</sup> so that neither  $K_T$  nor  $K_{tot}$  is accessible without knowing its magnitude. In principle this can be obtained from eqn. (cii), rearranged from eqn. (ci) which defines overall  $pK_a$ , but in practice things are not so straightforward, as will appear below.

Kitagawa *et al.*<sup>553</sup> derived ( $K_B^+ + K_C^+$ ) as above, and used this quantity along with the measured model  $pK_a$  values to calculate  $K_T$  and  $K_{tot}$  as given by eqns. (xcix) and (c); the results for their six compounds are in Table 74. This procedure assumes no  $\Delta(NR)$  or  $\Delta(OR)$  corrections to be required and cannot be accurate even though the trend expected is there; intuitively, one expects  $K_T$  and  $K_{tot}$  to fall as  $R^5$  becomes more electronegative, as is found. In particular, whereas Table 74 shows the proportion of the OH cations **AB**<sup>+</sup> and **AC**<sup>+</sup> varying from 19 to 32% across the series, Mason<sup>18,543</sup> is adamant that no appreciable fraction of these is visible in the cation of 4-pyrimidone itself, certainly not if that of 4-methoxypyrimidine is any guide. In fact, these authors<sup>553</sup> confirm this: the UV spectra of the *N*-methylated cations derived from **1203B** and **1203C** closely resemble the quaternary cations **1204**, the spectra of the 4-methoxypyrimidine cations closely resemble the cations **1205**, and there is little UV resemblance between the series. It is difficult to be certain what proportion of the latter cation might pass undetected in the former, but 10% is probably a generous upper limit.



**Table 74.  $pK_a$  Data and Calculated Tautomeric Ratios for some 5-Substituted 2-Methyl-4-Hydroxypyrimidines 1203 <sup>a</sup>**

$R^5 =$	Me	H	OMe	CONH <sub>2</sub>	CO <sub>2</sub> Et	CN
$pK_a^b$	3.23	2.51	2.58	1.32	1.27	-0.18
$pK_a(\text{OMe})^c$	4.79	3.99	4.11	2.49	2.36	0.80
$pK_a(3\text{-NMe})^c$	3.42	2.74	2.72	1.48	1.38	-0.06
$pK_a(1\text{-NMe})^c$	3.46	2.69	2.79	1.44	1.50	-0.01
$K_A^1 / (K_B^+ + K_C^+)$	0.24	0.24	0.35	0.48	0.40	0.48
$\log K_T$	2.00	1.86	1.83	1.34	1.37	1.18
$\log K_{\text{tot}}$	1.96	1.92	1.76	1.37	1.25	1.13
$\log K_M$	-0.04	0.05	-0.07	0.03	-0.12	-0.05
% <b>A</b>	0.5	0.6	0.8	2.2	2.4	4.0

<sup>a</sup>  $pK_a$  data from ref. 553. <sup>b</sup> Measured overall  $pK_a$  value. <sup>c</sup> For purposes of calculation,  $pK_a(\text{OMe})$ ,  $pK_a(3\text{-NMe})$  and  $pK_a(1\text{-NMe})$  are assumed equal in value to  $pK_A^1$ ,  $pK_B(1)$  and  $pK_C(1)$  respectively.

**Table 75. Tentative  $pK_a$  Values for 1203 after Correction for  $\Delta(\text{OR})$  and  $\Delta(\text{NR})$ , with Calculated Tautomeric Ratios <sup>a,b</sup>**

$R =$	OMe	CONH <sub>2</sub>	CO <sub>2</sub> Et	CN
$pK_a^c$	2.58	1.32	1.27	-0.18
$pK_1^d$	4.71	3.09	2.96	1.40
$pK_B(1)$	2.72	1.48	1.38	-0.06
$pK_C(1)^e$	3.09	1.74	1.80	0.29
$K_A^1 / (K_B^+ + K_C^+)$	0.034	0.072	0.072	0.099
$\log K_T$	3.45	2.76	2.72	1.99
$\log K_{\text{tot}}$	3.08	2.50	2.30	1.64
$\log K_M$	-0.37	-0.26	-0.42	-0.35
% <b>A</b>	0.025	0.112	0.138	0.714

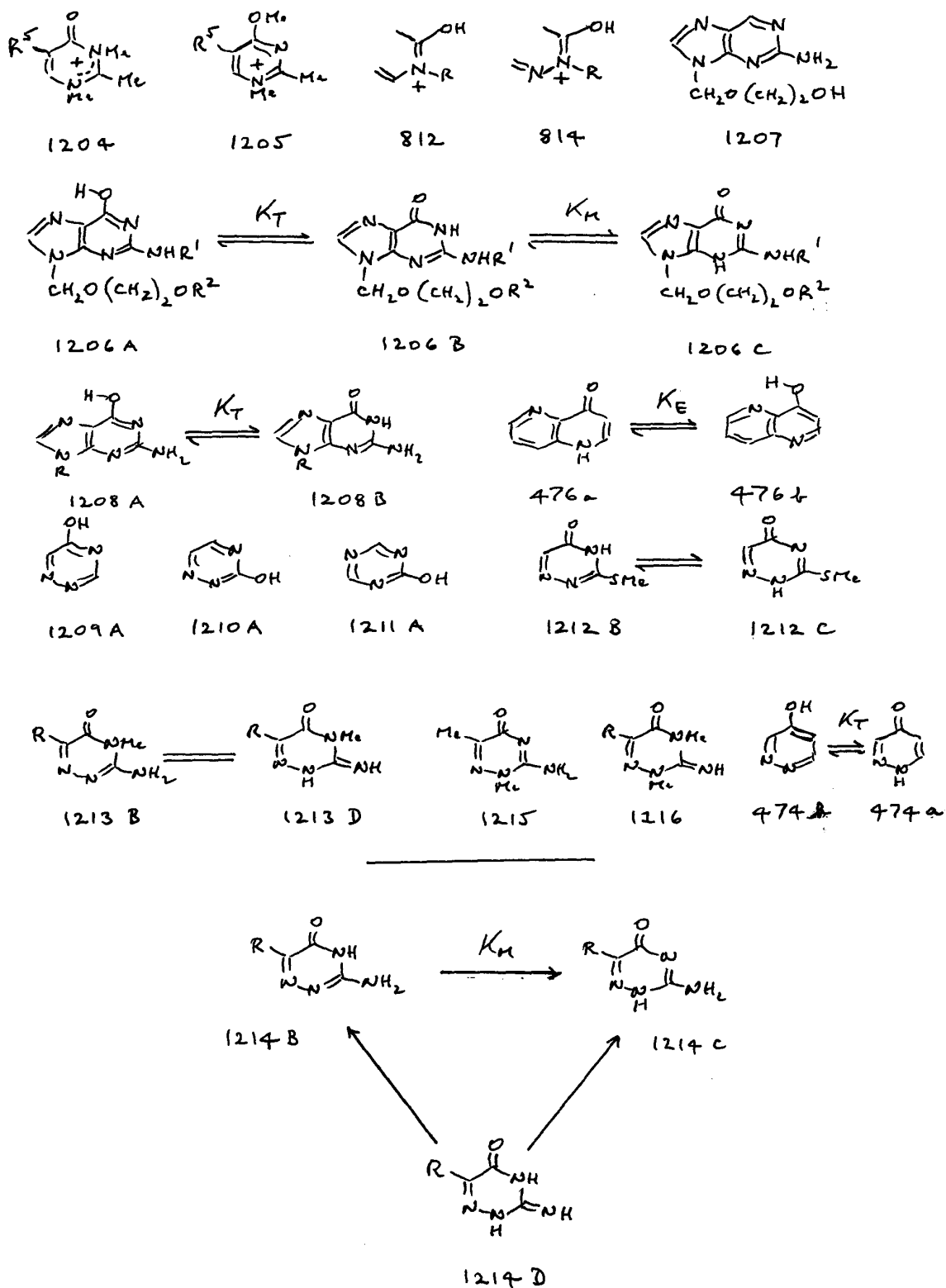
<sup>a</sup> Compounds as for Table 74. <sup>b</sup> See the text. <sup>c</sup> Overall  $pK_a$  value. <sup>d</sup> Incorporates  $\Delta(\text{OR}) = 0.6$ .

<sup>e</sup> Incorporates  $\Delta(\text{NR}) = 0.3$ .

We have accordingly attempted to apply  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  corrections to the compounds of Table 74. For 3-NMe and 1-NMe we have  $\Delta(\text{NR})$  0.0 and 0.3 respectively, but no exact model exists for  $\Delta(\text{OR})$ . The evidence of these authors<sup>553</sup> and that outlined in section B.7.2 (from which we may calculate  $\log K_{\text{A}^+}$  ca. 2.8) identifies  $\text{AC}^+$  as overwhelmingly more important than  $\text{AB}^+$ , which simplifies the problem. Formally this resembles the cation of 4-pyridone but with aza-nitrogen in the 3-position. Structures **812** and **814** (Scheme 30) provide a distant analogy: here replacement of CH by N elevates  $\Delta(\text{NR})$  from 0.45 in the former to 0.55 in the latter. It is therefore unlikely that  $\Delta(\text{OR})$  for  $\text{AC}^+$  will have less than the 4-pyridone value of 0.5, and we employ 0.6 here as a ‘rounded-off’ provisional value. For four of these six compounds, estimates for  $\text{p}K_{\text{A}}^1$ ,  $\text{p}K_{\text{B}}(1)$  and  $\text{p}K_{\text{C}}(1)$  appear in Table 75, along with the revised calculations based on them.

For (**1203**,  $\text{R}^5 = \text{H}$  and Me) the calculation is incommensurate, since in eqn. (cii),  $K_{\text{a}} > \{K_{\text{B}}(1) + K_{\text{C}}(1)\}$ . Even for the remainder it is a rather small positive quantity, so that accuracy is out of the question and, while deliberately not rounded off, the results of Table 75 must at best be highly approximate. Nevertheless, they are consistent and make sense. The same trends as in Table 74 are apparent, but with the proportion of iminol cation down to a believable 3 - 9% in place of the 26 - 32% required by the uncorrected model compound data. Parallel changes occur in the estimates for  $K_{\text{T}}$  and  $K_{\text{tot}}$  and in the proportion of **1203A**, down by factors of 6 to 30 according to the nature of  $\text{R}^5$ . These differences are greatest for the least electron-deficient compounds; for the ‘parent’ compound (**1203**,  $\text{R} = \text{H}$ ) we may tentatively estimate  $\log K_{\text{T}}$  and  $\log K_{\text{tot}}$ , if Table 75 is not too badly misleading, as probably about 3.5 and 3.1 respectively. Katritzky<sup>2www</sup> has suggested that aza-nitrogen electronegativity may cancel against amidine resonance to give roughly equal tautomeric ratios for pyridones and pyrimidones; these calculations appear to provide some vindication.

There are two contrary reports. In investigating a series of compounds **1206**, Plass *et al.*<sup>561</sup> claim to show that acyclovir (**1206**,  $\text{R}^1 = \text{R}^2 = \text{H}$ ) exists in saturated aqueous solution as a 50:50 mixture of **1206A** and **1206B**. This evidence is based on two distinct 8H singlets in its proton NMR spectrum; a single signal, corresponding to the **B**-form, is found in MeCN. There are many problems with this evidence, one being that neither (**1206**,  $\text{R}^1 = \text{COMe}$ ,  $\text{R}^2 = \text{H}$ ) nor (**1206**,  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{COMe}$ ), both of which are much more water-soluble, shows this phenomenon. Another is that acyclovir and (**1206**,  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{COMe}$ ) possess, except for the addition of ester carbonyl in the latter, very similar IR spectra in water, with strong  $\nu(\text{C}=\text{O})$



Scheme 50

bands at 1665 and 1674  $\text{cm}^{-1}$  respectively. Also, while the signals of acyclovir at  $\delta$  5.506 and  $\delta$  7.817 are assigned to the **A**- and **B**-forms since these are their approximate positions in **1207** and (**1206**,  $R^1 = \text{H}$ ,  $R^2 = \text{COMe}$ ) respectively, the corresponding singlets of (**1206**,  $R^1 = \text{COMe}$ ,  $R^2 = \text{H}$ ) and (**1206**,  $R^1 = R^2 = \text{COMe}$ ), which indisputably exist as the **B**-tautomer, appear at the position expected on this evidence for the iminol **1206A**. Furthermore, it would be extraordinary on our evidence as to solvent effects (section B.5.11) for water to contain more of the iminol than MeCN – unsurprisingly, (**1206A**,  $R^1 = R^2 = \text{H}$ ) dominates in  $\text{CH}_2\text{Cl}_2$ .<sup>561</sup> In fact, their UV spectra in water show no evidence for any detectable quantity of the iminol. Consistently, the fused pyridone **476** gives **476b** in dioxane but shows no perceptible iminol formation in water (section A.10.8); we estimate (Appendix 3)  $\Delta \log K_E \gtrsim 2$  in aqueous solution for this type of intramolecular bond. It is possible that, in saturated solution, some kind of slow exchange phenomenon involving different sorts of aggregation can occur. Whatever the true explanation, tautomerism is unlikely to play any part in it. The authors' failure to detect the **C**-tautomer is consistent with the quinazolone results, and that for **1199**, described above (section B.5.11).

Earlier, Lee and Chan<sup>562</sup> had claimed to detect 16% of **1208A** for guanosine (**1208**,  $R = \text{ribose}$ ) in water. This claim, again based on proton NMR evidence, was demolished by two sets of workers<sup>563</sup> who found its origin to lie in line-broadening brought about by paramagnetic ions. Dewar and co-workers<sup>564</sup> have postulated the iminol form of guanosine to be important, but this is based on MO calculation for the gas phase at the SCF level of theory. While iminol forms of pyrimidones and related compounds may be prominent in nonpolar solvents, we believe that there is no evidence for their detection, let alone for their importance, in aqueous or near-aqueous solution.

### B.5.13 Triazinones related to 4-Pyrimidone

There are four series of nominal hydroxytriazines of which **1209** is relevant here; **1210** and **1211** follow in section B.5.15. Compound **1212** exists as **1212C**.<sup>2ccc</sup> Piřha *et al.*<sup>565</sup> have studied compounds **1213** - **1215**, with results some of which are quantitative. For **1213** they find  $\text{p}K_a$  3.95 and 4.53 for  $R = \text{H}$  or  $\text{Me}$  respectively, the corresponding values for **1214** itself being 1.55 and 2.19, with  $\text{p}K_a$  1.90 for **1215** and ' $\text{p}K_a < 7$ ' for (**1216**,  $R$  not specified). Compounds **1213**, **1214/1215** and **1216** on UV evidence share a common cation while the free base spectra are very different; hence their tautomeric stability order has to be **1215** > **1213** > **1216** with **1214C** > **1214B**

by a margin of  $\log K_M$  2.40 (R = H) or 2.34 (R = Me). As suggested by the authors,<sup>565</sup> the probable reason for this striking difference from 4-pyrimidone (section B.5.11) lies in *N,N*-lone pair repulsion. The corresponding value for this effect in **474** is  $\Delta \log K_T$  *ca.* 2.1 (section A.10.7), but it may be boosted here by the electron-donor amino-group (*vide* Appendix 3). The *exo*-imino tautomer **1214D** is the least stable but by a margin that is presently impossible to estimate. If we interpret ' $pK_a < 7$ ' for **1216** as  $pK_a \sim 6$  and correct this, using  $\Delta(NR)$  0.3 for 1-*N* and perhaps the same for 3-*N*, we obtain  $pK_a$  *ca.* 6.6 for **1214D**. According as to whether R = H or Me, this results in  $\Delta pK_a$  2.65 or 2.07 relative to **1213**, hence  $\log K$  *ca.* - 2.65 or - 2.07 for the process **1214B**  $\rightarrow$  **1214D**. For the parallel process involving 2-amino-4-pyrimidone we estimate, in the following section,  $\log K$  *ca.* - 4.7; if true this would result in an effect of the extra nitrogen atom, plausibly due to lone pair repulsion, of  $\Delta \log K$  2.0 – 2.6 for **1214B**  $\rightarrow$  **1214D** in place of *ca.* 2.4 for **1214B**  $\rightarrow$  **1214C**, *i.e.* in the same direction and of comparable magnitude. It is possible that, to within the limits of error, these are the same value.

#### B.5.14 2,3-Heterofused 2-Amino-4-Pyrimidones and their Aza-Analogues: *Endo-Exo* Tautomerism

This important form of tautomerism, while widespread and well exemplified, has been little discussed and so far lacks a rationale. It is summarised in structure **1217**. Here the **C**-tautomer is ruled out by 3-substitution and, with the **A**-tautomer sometimes impossible and never detected, tautomerism is confined in practice to that between the **B**- and **D**-forms. Some cases may be decided by inspection. If in **1217** only one ring is aromatic, then since *exo*-C=N reduces aromaticity, *endo*-C=N will be found in the aromatic ring. If neither ring or both is aromatic, the situation is more complex. In **1025**, **1025a** is preferred by  $\log K$  *ca.* 0.4; that is the margin expected for *endo*-C=N in a 5- vs. 6-membered cyclic amidine (section B.4.3), and evidently ring carbonyl does not alter this. When both rings are aromatic, we believe the outcome to depend on relative aromaticity. This concept, much easier to define than to prove, is the main subject of this subsection.

Nomenclature is a problem. The quantity  $K_M$ , defined above as  $K_M = [C]/[B]$ , has been applied in section B.4.4 to *endo-exo* tautomerism involving C=N, but *endo-endo* tautomerism as in **1217** has not so far been encountered. The usage of Scheme 44 (start of B.5) is equally inapplicable. However, since iminol formation is blocked in any compound of this type we may safely use  $K_T$  without causing confusion. Any decision as to its forward direction being arbitrary, we have chosen this as 6-membered ring  $\rightarrow$  5-membered or acyclic, which as in the simpler *endo-exo* case, tends to lie in the direction of the less aromatic tautomer.



Ample qualitative evidence exists concerning alicyclic 5-membered ring fusions and their open-chain analogues. The fixed forms **1218**<sup>566</sup> and **1219**<sup>567</sup> possess very different UV spectra, enabling Lempert and co-workers<sup>567</sup> to eliminate **1220D** as contributing appreciably, in EtOH, to the structure of **1220**. On IR grounds, in the solid state and a variety of organic solvents, we<sup>106</sup> have established **1221B** as the structure of **1221**, while by comparison with fixed forms, Sohár *et al.*<sup>568</sup> have confirmed the structures of **1222** and **1223** as **1222B** and **1223C** respectively by NMR in CHCl<sub>3</sub> and water. Consistently, Lardenois *et al.*<sup>547</sup> claim that, in DMSO and EtOH, the tautomer **1195D** is absent from **1195** for R = Me and COMe as well as for R = H (section B.5.11). This last case is important since COMe is expected to polarise C=N strongly in its direction (see section B.5.1). Similarly, and again using fixed forms, Lempert and co-workers<sup>567</sup> have demonstrated that **1224** exists in EtOH as **1224C** and **1225** as **1225B**. They note concerning the latter that its UV spectrum is scarcely affected by removal of carbonyl to give **1221B**, evidence that this group does not much affect the conjugated system, as it would if **1225D** were the dominant tautomer.

The compounds for which tautomerism of type **1217** is in practice most important include the linear 6,6,5-fused quinazolones **1226**, **1227**, **1228** and **1231**, and their bicyclic (pyrimidone) congeners. In only one case is there quantitative information. We<sup>106</sup> have measured p*K*<sub>a</sub> values in water for **1229** (0.47: λ<sub>max</sub> 229, 321 nm) and **1230** (-1.10: λ<sub>max</sub> 231, 313 nm); they possess on UV evidence (λ<sub>max</sub> 232, 334 nm) a common cation which must, therefore, involve protonation at C=N. On the reasonable assumption that Δ(NR) will be the same for each and therefore cancel (*cf.* **1025**, section B.4.1), we obtain log *K*<sub>T</sub> *ca.* 1.6 for **1228**. Here and elsewhere, overall *K*<sub>T</sub> is likely to be dominated by the individual *K*<sub>M</sub> values for the heterocycles *N*-fused together, each when aromatic attempting to avoid *exo*-C=N as tautomerically disfavoured. In practice it cannot be so simple since other factors must be present, such as acylation at bridgehead nitrogen (though no such effect is shown by **1025**: see discussion in section B.4.2) and overall resonance energy, but it is worth pursuing this argument to see how far it will go.

For the aminoquinazolone component we may start by comparing **1155** and **1225**, the latter being 'aromatic' by virtue of quinazolone carbonyl. Here the former possesses log *K* 1.8 in favour of **1153** (section B.5.7) but this preference is reversed in **1225**, where **1225B** predominates.<sup>567</sup> If the latter's predominance implies a maximum value of *ca.* -1.3 for log *K*<sub>T</sub>, then the effect

then the effect of ‘aromaticity’ here is to reduce  $K_T$  by a factor of  $\geq 10^3$ . A similar factor, applied to **1046** for which **1046D** possesses  $\log K_T -1.0$  (section B.4.2), would predict a maximum value of  $10^{-4}$  for  $K_T$  in **1221**. This tentative isodesmic relation has to assume that differential effects of 5-membered ring carbonyl on the tautomers of **1155** and **1225** cancel, so a check is desirable, and follows. A value of  $\log K_M -6.5$  is claimed for tautomerism in 2-amino-*s*-triazole **743** (section B.4.5), but it is unclear from the short report that contains all the available information which of **743D** or **743E** this refers to, *i.e.* what model compound was used; if this value refers to the latter, the result is irrelevant in this context. On the hopeful supposition that **743D** was concerned, the unit present in **1227B** and **1228B**, we may factor the reported  $K_M$ , necessarily without allowance for  $\Delta(\text{NR})$ , into  $\log K_M -6.3$  and  $-5.5$  with respect to **743A** and **743C** respectively, given that these species comprise *ca.* 60% and 10% of the total (section B.1.2). The overall value of  $\log K_T 1.6$  for **1228** then leads to a deduced  $\log K_M -4.7$  for the latter’s aminoquinazolone unit, remarkably close to the above estimate. This is notably less negative than  $\log K_M -7.5$  for 2-aminopyrimidine (section B.4.4); as emphasised by Katritzky and co-workers,<sup>150</sup> oxoheterocycles are substantially less aromatic than their parents, so have less to lose from any further deleterious structural modification. The alternative imine **743E** will be very disfavoured by dipolar repulsion and if this not **743D** is concerned in the measured tautomeric equilibrium,<sup>488</sup>  $\log K_M$  for *both* contributing heterocycles could be substantially less negative.

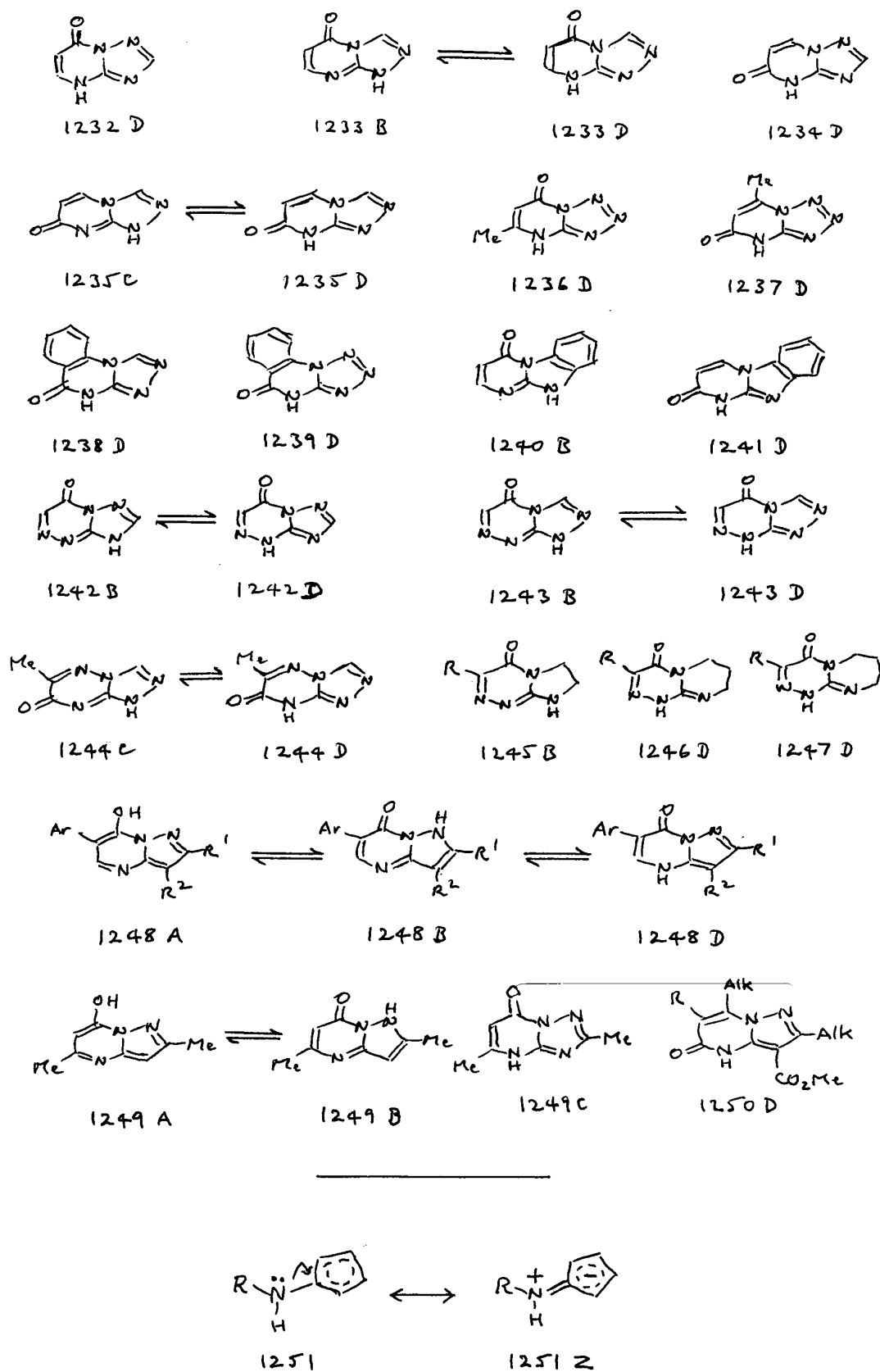
Evidence has been given (section B.4.5) that (**1092**, Z = NMe) possesses  $\log K_M -2.6$ . The corresponding imidazole value is required here, and we estimate it as follows. For (**1088**, Z = S, R = H) and (**1092**, Z = S) we have  $\log K_M -4.5$  and  $-4.0$  respectively. This difference is typical of the rather small effect of benzofusion on 5-membered rings (loss of aromaticity on benzofusion of 6-membered rings is generally much greater; see Appendix 5). A similar effect for Z = NR would result in  $\log K_M -3.1$  for imidazole. At the other end of the scale we obtain, from **1109**,  $\log K_M -7.4$  for tetrazole (all section B.4.5). Putative values of  $\log K_M -6.3$  and  $-5.5$  for the *s*-triazole isomers fall within this range. The resulting estimated ‘ $\Sigma \log K_M$ ’ (*i.e.*  $\log K_T$ ) values appear, along with that for **1228**, in Table 76. Here the value of  $\Sigma \log K_M$  for **1221** assumes the usual stabilising factor of  $\Delta \log K 0.4$  for *endo*-C=N to be operative in **1221D**. The unexpected feature of Table 76 is the prediction that **1226** should reverse the tautomeric preference mostly found elsewhere; unfortunately, there are no experimental data against which this can be checked.

So far as it goes, the available evidence in general confirms this picture. Comparison of IR data in DMSO and the solid state with those of NMe fixed forms confirms the **D**-tautomer for **1227** and **1228**;<sup>106</sup> the above calculations predict, for the former,  $\log K_T$  *ca.* 0.8 in water. Replacement of the 4-quinazolone by a 4-pyrimidone moiety leaves the situation more or less unchanged; Beckett *et al.*<sup>569</sup> on UV evidence find the **D**-forms shown for **1232** and **1233** in water. On identical evidence,<sup>569</sup> the ‘angular’ isomers **1234** and **1235** behave in the same way. These authors note that the ‘pyrimidine NH’ tautomer is always preferred which effectively summarises, without explaining, the known facts. A recent crystal structure determination<sup>570</sup> confirms **1232D** and **1234D** as those forms present in the solid state, while earlier, IR evidence in DMSO had established **1236D** and **1237D** as the structures preferred for the analogous fused tetrazoles.<sup>571</sup> Similarly, **1238** and **1239** exist as the **D**-tautomer in DMSO and the solid state.<sup>106</sup> Since **C**-are in general less favoured than **B**-tautomers, especially in quinazolones (section B.5.11), ‘angular’ compounds such as **1234** are likely to show a still greater preference for the **D**-tautomer than their ‘linear’ equivalents such as **1232** (see below). It is less certain what the effect of benzofusion should be, but by analogy *e.g.* with the oxoheterocycles (Appendix 5) one would expect (**1195D**, R = alkyl) to be more disfavoured than **1220D**, though the effect may not be large.

Unusually for amides, solvent-insensitivity appears to be a feature of tautomerism in these compounds, presumably because the rival tautomers are both aromatic and do not differ greatly in polarity. In this context the results for **1240** and **1241**, benzofused in the opposite sense to **1238** and **1239**, are specially significant. On UV evidence in MeOH and IR evidence for the solid state (νC=O only), and probably but not certainly on NMR evidence in CHCl<sub>3</sub>, these are borderline cases, with **1240** and **1241** giving the **B**- and **D**-tautomers respectively.<sup>572</sup> Given a predicted  $\log K_T$  -1.9 for **1226** (see above) the result for **1240** is expected, but there are conflicting requirements: **1241** is more likely than **1240** to give the **D**-form, but benzofusion on to imidazole should make  $\Sigma \log K_M$  (Table 76) more negative for both. Quantitative work in water is required to resolve this dilemma.

$$\log K_M = 2.38(0.42) - 19.83(1.16) \sigma_I \quad (\text{ciiii})$$

$$(n = 5 \quad r^2 = 0.990 \quad s = 0.19 \quad F = 293)$$



Scheme 51

Qualitatively, a simple rationale for these variations in  $K_M$  lies in the electronegativity of the azole ring (Scheme 51), which rises with nitrogen content,<sup>96</sup> so stabilising the amino-form. Quantitatively, for the five monocyclic azoles where comparative data are available, this relation obeys eqn. (ciii). Certain approximations have had to be introduced. We have assumed that  $\sigma_I$  for (**1090**, Z = O and S) should be substantially identical to those for 4,5-dimethyloxazol-2-yl and its thiazolyl analogue, respectively, since all are dialkyl derivatives, while  $\sigma_I$  0.27 for (**1088**, Z = NH) is further supported by  $\sigma_I$  0.26 for both 1-methyl- and 4-methylimidazol-2-yl.<sup>96</sup> As with  $K_T$  for oxoheterocycles (sections A.10.7 and B.2.5) we expect a more positive (less negative) value for log  $K_M$  on benzofusion, and for (**1092**, Z = S) *vs.* (**1088**, Z = S) this is found; as noted above, a similar factor applied to (**1092**, Z = NMe) leads to an estimated log  $K_M$  -3.1 for (**1088**, Z = NH). Benzofusion of 3-pyrazolone **913** to give indazolone **923C** (section B.2.10) results in  $\Delta$  log  $K_T$  0.4, a similar increment. The rival values of log  $K_M$  for **1109** have been discussed (section B.4.5).

**Table 76. Log  $K_M$  and  $\Sigma$  log  $K_M$  Values**

Compound	Z	R	$\sigma_I^a$	log $K_M^b$	Compound	log $K_T \equiv \Sigma$ log $K_M^c$
<b>1195</b>		H		- 4.7 <sup>d</sup>		
<b>1054<sup>e</sup></b>	NH	H		- 0.4 <sup>d</sup>	<b>1221</b>	- 4.3 <sup>d</sup>
<b>1092</b>	O		0.41			
<b>1092</b>	S		0.37	- 4.0		
<b>1092</b>	NMe		0.32 <sup>f</sup>	- 2.6		
<b>1090</b>	O		0.35 <sup>d</sup>	- 4.3		
<b>1090</b>	S		0.31 <sup>d</sup>	- 3.7		
<b>1088</b>	O		0.38 <sup>d</sup>	- 5.1 <sup>d</sup>		
<b>1088</b>	S		0.34	- 4.5		
<b>1088</b>	NH		0.27 <sup>d</sup>	- 3.1	<b>1226</b>	- 1.6 <sup>d</sup>
<b>1101<sup>g</sup></b>	O	H	0.48			
<b>1101<sup>h</sup></b>	O	H		- 6.5		
<b>1101<sup>g</sup></b>	S	H	0.40			
<b>743D</b>				- 5.5 <sup>d,i</sup>	<b>1227</b>	0.8 <sup>d</sup>
<b>743D</b>				- 6.3 <sup>d,j</sup>	<b>1228</b>	1.6
<b>1109A</b>			0.49	- 7.4	<b>1231</b>	2.7 <sup>d</sup>

<sup>a</sup> For attachment at the 2-position; ref. 96. <sup>b</sup> For the aminoheterocycle (section B.4); except for estimates, from Table 65. <sup>c</sup> See definition of  $K_T$  in this context earlier in this section.

<sup>d</sup> Estimate; see text. <sup>e</sup> As 2-aminoimidazoline. <sup>f</sup> Z = NH. <sup>g</sup> R<sup>3</sup> = Me. <sup>h</sup> R<sup>3</sup> = Ph.

<sup>i</sup> Relative to **743C**. <sup>j</sup> Relative to **743A**.

A relation between  $\log K_M$  and  $\sigma_I$  is unsurprising, since these heterocyclic  $\sigma_I$  values themselves derive, *inter alia*, from  $pK_a$  data for substituted guanidines<sup>96</sup> (section B.5.1). Nevertheless, eqn. (ciii) despite good statistics must be regarded as highly approximate, since a value of  $\rho_I \sim 20$  results in a predictive ability enormously susceptible to the value chosen for  $\sigma_I$ . It is also clear that benzofused azoles do not obey the same relationship, since benzofusion influences  $\sigma_I$  and  $K_M$  in opposite directions, and it is improbable that 6-membered rings will follow it either. Within these limitations, it may prove useful as more  $\sigma_I$  values become available. It also demonstrates the underlying factors very clearly; a parallel relationship for the corresponding oxoheterocycles, and in the same direction (*cf.* section B.4.4), would be entirely plausible.

Marzin and co-workers<sup>573</sup> studied the triazinones **1242** – **1244** by  $^{13}\text{C}$ -NMR in DMSO and, using fixed NMe forms as reference points, assigned their structures as **1242D**, **1243D** but **1244C** respectively. Care is needed. Lone pair repulsion as is present in the triazinone ring of **1242B**, the triazole ring of **1244D**, and one ring or the other of **1243** according to its tautomer, is bound to be much more important in DMSO than in water and may be influencing these results. In **1242** it will reinforce the dominance of **1242D** and the countervailing effect of the triazole ring in **1243D** is unlikely to be enough to reverse a preference for this tautomer (*cf.* **1233** above) but the preference for **1244C** is at first sight surprising. We believe its chief cause to lie in a change in relative stability from  $\text{B} \sim \text{C} \gg \text{D}$  for **1195**, or  $\text{B} > \text{C} \gg \text{D}$  for the quinazolones, both in water, to  $\text{C} > \text{B} \sim \text{D}$  for these triazinones in proton acceptor solvents or those of low polarity. Further light comes from a study of **1245** – **1247** ( $\text{R} = \text{Me}$  or  $\text{Ph}$ ) in  $\text{CHCl}_3$ <sup>348</sup> where their dominant forms are as shown. Small effects of ring size are expected but the observed variations show these compounds to lie on the tautomeric borderline. This matter is pursued in section B.8.9.

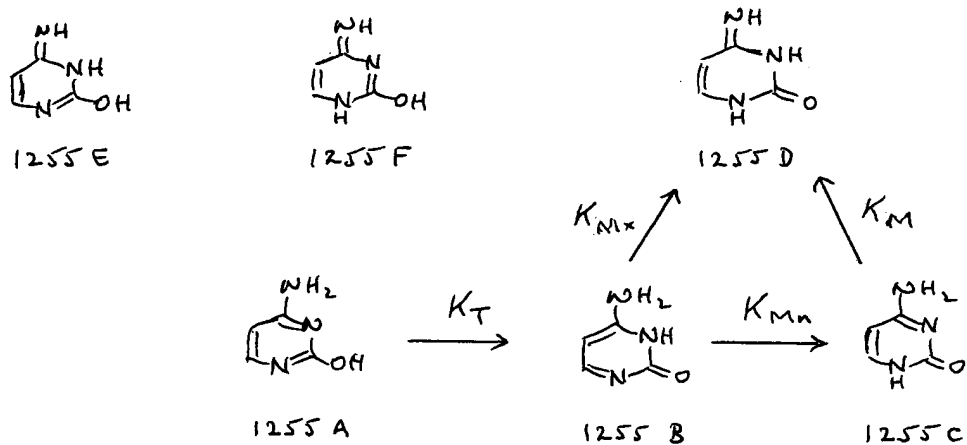
Although the central guanidine unit is missing from (**1248**,  $\text{R}^1 = \text{alkyl}$  or  $\text{NH}_2$ ,  $\text{R}^2 = \text{H}$ ,  $\text{CO}_2\text{R}$  or  $\text{CN}$ ), its tautomeric preference must still depend on the energetic balance between rival amino-forms, but nothing is known. Kurasawa *et al.*<sup>674</sup> state on NOE evidence that **1248D** dominates in DMSO, which is reasonable since the **A**-tautomer should be exceptionally disfavoured (it is not aromatic) while **1248B** contains a severe NR-NH dipole clash which is relieved in **1248D**. However, while Hori *et al.*<sup>575</sup> claim **1249** to exist as a mixture of **1249A** and **1249B** even in the solid state, which seems improbable, they do not consider **1249C** which relieves dipolar repulsion and is arguably more likely than either. More reasonably, they assign **1250** to the **D**-tautomer on solid-state evidence. This area is poorly researched and more work would be highly desirable.

### B.5.15 2-Pyrimidones and Related Species

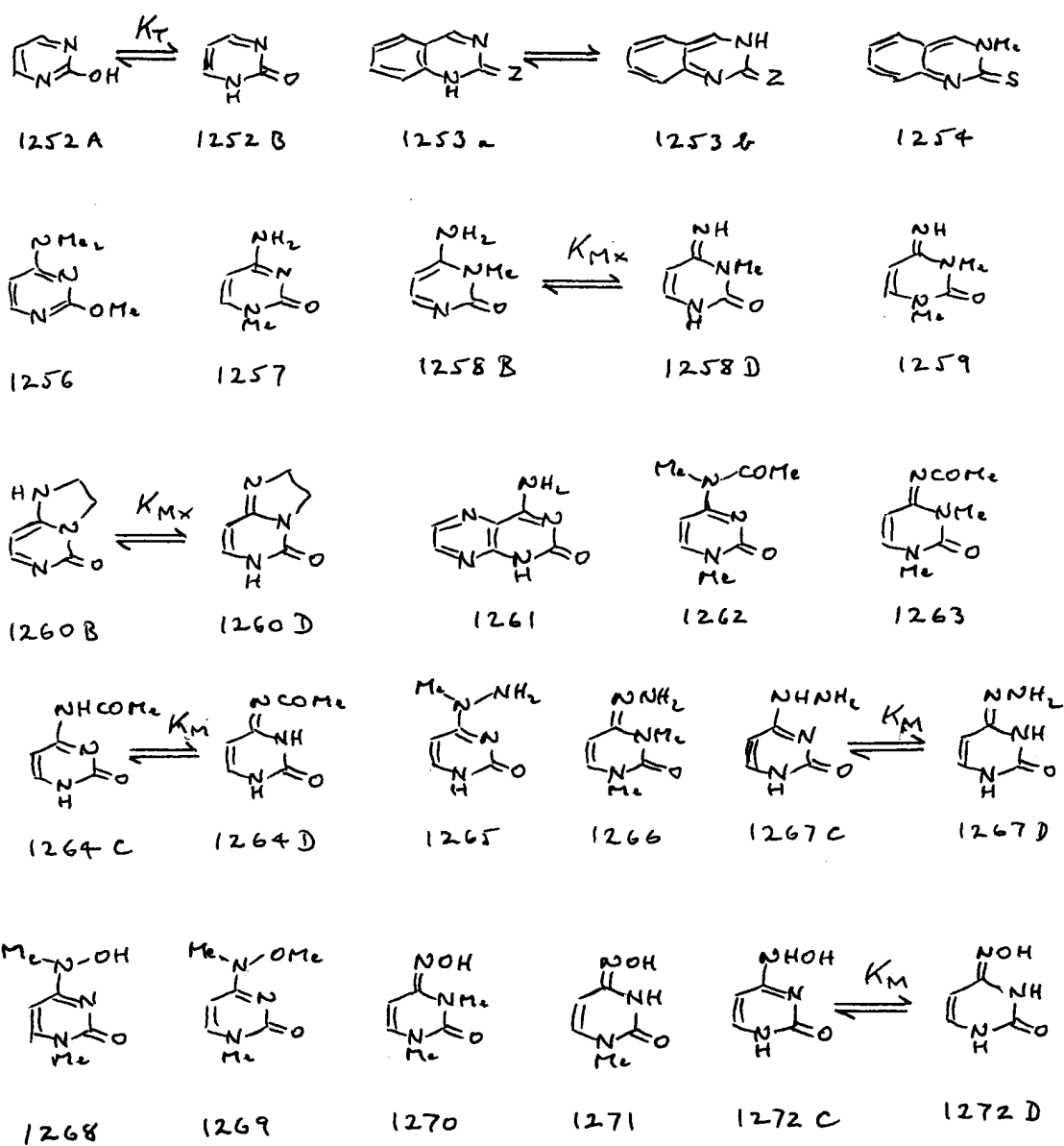
The tautomeric ratio  $K_T$  for 2-pyrimidone **1252** is unknown since, as for 4-pyrimidone, **1252B** protonates on nitrogen so that there is no common cation with **1252A**. Kollman and co-workers<sup>576</sup> calculate  $\Delta E_T$  2.48 kcal mol<sup>-1</sup> in favour of **1252A** in the gas phase at the HF/6-31G\* level of theory, which on adding  $\Delta\Delta G_{\text{solv}}$  for water changes sign to become  $\log K_T$  2.2, and their parallel calculations for its 4-amino derivative (see below) are reasonably accurate; however, see section B.8.12 for a major re-assessment.

The oxo-form **1252B** consists in two degenerate tautomers, but this degeneracy disappears for other than 5-substitution. 2-Quinazolone could exist predominantly as **1253a** or **1253b** ( $Z = \text{O}$ ); the latter is quinonoid so certainly disfavoured, but by what margin is unknown. However, there are  $pK_a$  data for the corresponding thione (**1253**,  $Z = \text{S}$ ). Barlin<sup>577</sup> measured  $pK_a$  0.26 and 2.15 for (**1253**,  $Z = \text{S}$ ) and **1254** respectively; use for **1254** of  $\Delta(\text{NR})$  0.25 for thioamides (section B.3.1), which may be an overestimate, gives  $\log K$  ca. -2.1 for the energetic penalty imposed by the latter's quinonoid structure. This is slightly more than  $\Delta \log K$  ca. -1.9 for the effect of quinonoid ring formation on 6-membered ring oxoheterocycles (section B.2.5) or -1.7 in the case of indazole (section B.1.5). Nevertheless, it lies within the range  $\Delta \log K$  -1.9 $\pm$ 0.2 found for the five quantifiable examples of quinonoid structure (Appendix 5). At all events, there is no doubt that 2-quinazolone exists predominantly as (**1253a**,  $Z = \text{O}$ ). It should be noted that its 4-position, when unsubstituted, is susceptible to covalent hydration.<sup>341</sup>

Interest in this field has centred on the effect of 4-substitution (5-substituents should not, and do not, affect the picture), especially as concerns its 4-amino derivative, cytosine **1255**, whose six possible tautomers are set out on Scheme 52. Scanlan and Hillier<sup>578</sup> have carried out calculations at the 3-21G level of theory for the gas phase, and combined this with a solvation model to predict results for water. Both sets of calculations give **1255C** as the dominant tautomer, in agreement with the experimental evidence for aqueous solution.<sup>2xxx</sup> However, whereas results for the gas phase show **C** ~ **D** > **A** > **B** as the stability order, **1255B** comes closest to **1255C** in aqueous solution with the imine **1255D** in third place (Table 77). Interestingly, the **A**-tautomer appears as quite disfavoured even in the gas phase (contrast both pyridones) and enormously so in water,<sup>578</sup> by ca.  $10^{10}$ . Tautomers **1255E** and **1255F** are of negligible importance anywhere. Kollmann and co-workers<sup>576</sup> calculate **1255D** to be disfavoured in water relative to **1255C** by  $\log K_M$  -3.1 but discuss no other tautomer.



Scheme 52



Definitive results for cytosine in aqueous solution were obtained by Dubois and co-workers,<sup>579</sup> using the T-jump methodology on two sets of equilibria. The first, on **1255** itself, revealed the annular tautomer **1255B** to be the chief rival to **1255C**, with  $\log K_{\text{Mn}}$  2.6 (Scheme 52). The second, starting from **1258** as model for **1255B**, showed **1258D** to be disfavoured by a further margin of  $\log K_{\text{Mx}}$  1.5. If this model is valid, **1255D** is disfavoured relative to **1255C** by  $\log K_{\text{M}}$  -4.1, almost the same margin as that we deduce above (section B.5.14) for its isomer isocytosine (**1195**, R = H). Brown and Lyall<sup>580</sup> had earlier noted that the UV spectrum of **1256** is very different from that of **1255**, again helping to eliminate **1255A** from consideration, while the similarity between **1255** and **1257** helps to eliminate **1255B**. There are minor discrepancies in  $\log K$  between the  $\text{p}K_{\text{a}}$  and T-jump methodologies, such as that the  $\text{p}K_{\text{a}}$  for **1258** (*i.e.* of **1258B**) is above that calculated from the T-jump results for **1255B**. [Note however that the rise in  $\text{p}K_{\text{a}}$  on 3-methylation shown by comparing **1259** with **1258D** (Table 77) is due to the *normal* base-strengthening effect of alkylation at a nitrogen atom that does not share the positive charge; *cf.* examples in Appendix 1]. Since obtained without the need for correction factors, we shall assume the T-jump results to be the more reliable.

**Table 77. Tautomerism in Cytosine 1255**

Compound	$\text{p}K_{\text{a}}$ <sup>a</sup>	Compound	$\text{p}K_{\text{a}}$ <sup>b</sup>	$\log K$ <sup>c</sup>	$\log K$ <sup>d</sup>
<b>1255</b>	4.58 <sup>e</sup> 4.45 <sup>f</sup>	<b>1255C</b>	4.6 <sup>h</sup>		
<b>1257</b>	4.57 <sup>f</sup>				
		<b>1255B</b>	7.2 <sup>h</sup>	2.6 ( $K_{\text{Mn}}$ )	0.8
<b>1258</b>	7.43 <sup>e</sup>	<b>1258D</b>	8.9 <sup>i</sup>	- 1.5 ( $K_{\text{Mx}}$ )	- 4.3
<b>1259</b>	9.23 <sup>e</sup> 9.29 <sup>g</sup>	<b>1255D</b>	8.7 <sup>h</sup>	- 4.1 ( $K_{\text{M}}$ )	- 5.1 <sup>j</sup>

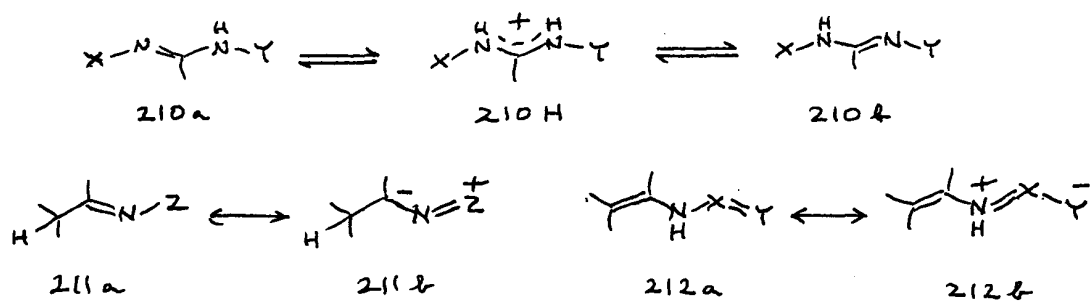
<sup>a</sup> Experimental. <sup>b</sup> Deduced from T-jump results; see the text. <sup>c</sup> Ref. 579. <sup>d</sup> Ref. 578; results calculated (3-21G) for water. <sup>e</sup> Ref. 580b. <sup>f</sup> Ref. 580a. <sup>g</sup> Ref. 581. <sup>h</sup> Based on T-jump results for **1255** (ref. 579). <sup>i</sup> Based on T-jump results for **1258** (ref. 579). <sup>j</sup> Or - 3.1 (ref. 576).

Dubois and co-workers<sup>579</sup> also studied solvent effects. The disfavoured fixed tautomer **1258** exists as **1258B** in water, alcohols and MeCN, but goes over to **1258D** in dioxane, CHCl<sub>3</sub> and EtOAc. Similarly, **1260** is present as **1260B** in water but as **1260D** in dioxane.<sup>579</sup> This is consistent with UV evidence that the **D**-type aminotriazinone **1216** is less well conjugated than its **B**- and **C**-type isomers (section B.5.13) so that **D**-tautomers in general (except possibly for 6,5-aromatic ring fusions: section B.5.14) are likely to be the least polar. No such work has been carried out on **1255** itself, but Hillier's calculations (Table 76) give the same qualitative ordering for tautomers **B**, **C** and **D** as the T-jump results and suggest that **1255D** will, under all circumstances, remain the least important of these three. That in its turn suggests a very high value for  $K_T$ , perhaps an example of the general principle that  $\pi$ -donors, here NH<sub>2</sub>, stabilise the more polar tautomer (*cf.* sections A.10.6 and B.2.4). There is also some circumstantial evidence which suggests that electronegative substituents – contrast the pyridones – do not generate hydroxy-forms: Brown and Teitei<sup>550</sup> state that 6-halo substituents generate **1255B**, not **1255A**, from **1255C**; and the tautomeric form of the cytosine moiety remains unchanged in **1261**<sup>2xxx</sup> (though intramolecular hydrogen bonding may be a factor here).

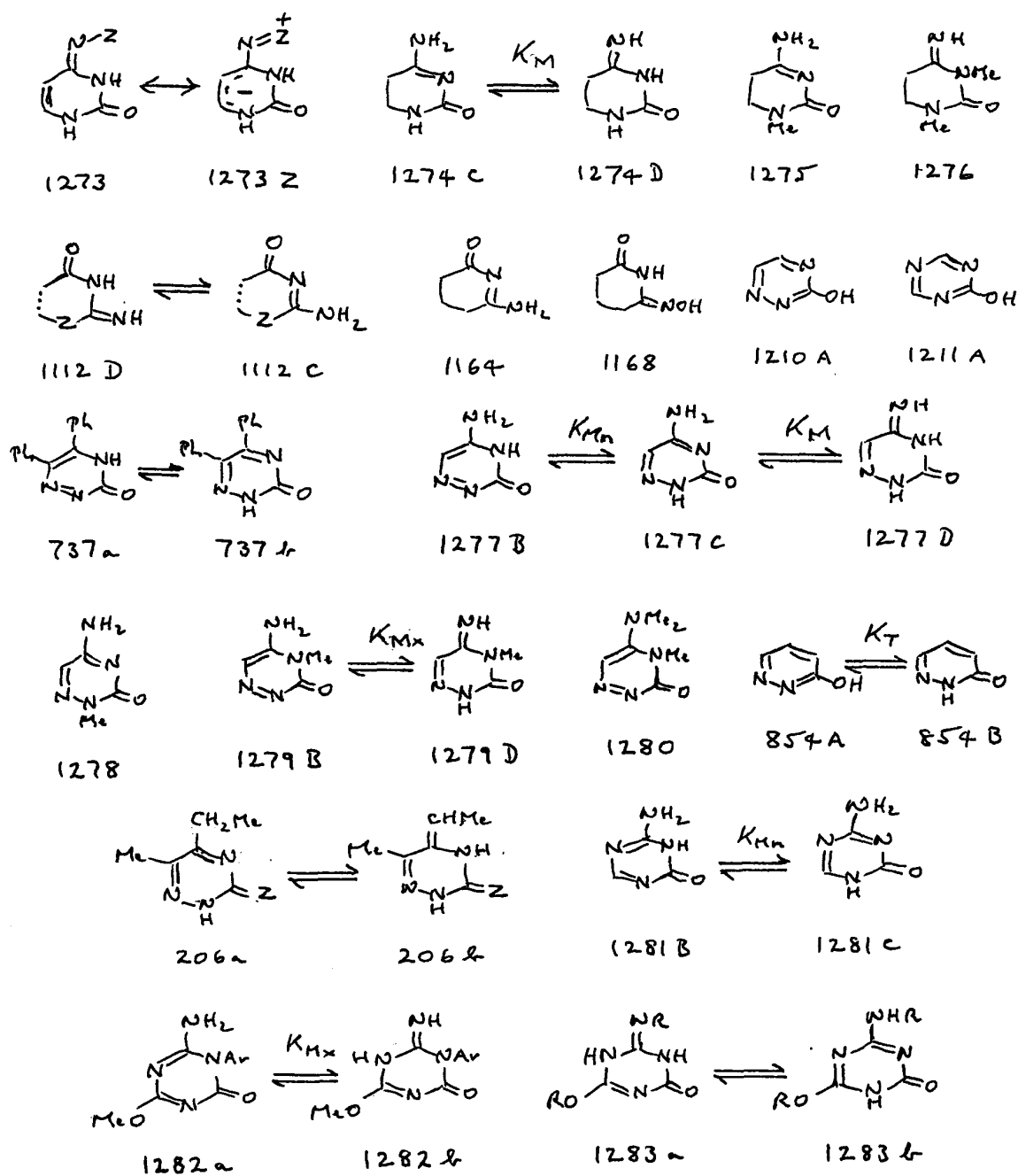
Some results on cytosines substituted in the amino-group are, in detail, unexpected and illuminating. Kenner *et al.*<sup>581</sup> used **1262** and **1263** to demonstrate, by UV, that **1264** exists as **1264C** not **1264D**. This is entirely consistent with the view (section B.5.2) that  $\Delta \log K_M$  *ca.* 2.7 is probably an upper limit for the enhancement brought about by acylation of the *exo*-amino moiety, so that, here, it should be insufficient to overturn  $\log K_M$  -4.1 (Table 77). By the same token, R = NH<sub>2</sub> or R = OH in *exo*-NHR should not produce a switch to the **D**-tautomer either: the shift brought about in guanidine, for which we have quantitative data,<sup>96</sup> is around  $\Delta \log K$  1.7 and 2.9 respectively, with that for R = COMe *ca.* 3.2 (Table 62, section B.4.2). There is no certainty, of course, that the same *quantitative* shifts in tautomer balance should be followed here, but any 'N-type' system should give the same *qualitative* order, one based on  $\sigma_I$  (see below). Brown *et al.*<sup>582</sup> used the 'basicity method' to elucidate the tautomerism of **1267** and **1272** (previously lumped together as **933**, R = NH<sub>2</sub> and OH; section B.2.10). Given pK<sub>a</sub> 5.00, 6.30 and 4.85 for **1265**, **1266** and **1267** respectively, **1267** clearly exists mostly as **1267C** and, using pK<sub>a</sub> values of 2.70 and 2.88 for **1270** and **1271** as guides to the effect of 3-methylation,  $\log K_M$  *ca.* -1.5 results. Similarly, pK<sub>a</sub> values of 3.80 and 3.85 for **1268** and **1269** respectively, set against 2.72 and 2.80 for **1270** and **1272**, shows the latter to exist mostly as **1272D**. Severe twisting in **1268** could result in an underestimate for the pK<sub>a</sub> of **1272C**, but since there appears to be no such effect in **1265** *vs.* **1267** we can probably discount this, leading to  $\log K_M$  1.1 for **1272**.

For **1267** and **1272**, therefore,  $\Delta \log K_M$  is 2.6 and 5.2 respectively, far larger effects than those found for guanidine. While these shifts are not quite proportional to those listed above,  $R = \text{COMe}$  would have been expected, on the same basis, to exist very firmly as the **D**-tautomer, which does not appear to be the case.<sup>581</sup> One possibility, which nevertheless strains credulity, is that these compounds follow the rules expected for ‘C-type,’ not ‘N-type,’ tautomerism. From section A.4.6 we reproduce Scheme 8, on which these are contrasted. Tautomer preference in the latter depends on relative ease of deprotonation, from **210H**, to give **210a** or **210b**; empirically this is controlled by the electronegativity of X vs. Y solely in terms of their *field effect*, so that the substituent towards which  $\text{C}=\text{N}$  is polarised is that with the higher  $\sigma_I$  value. By contrast, tautomer preference in ‘C-type’ tautomerism, while it cannot yet be quantified, appears empirically to depend on *resonance* effects: donors attached to nitrogen favour the imine as in **211**, whereas acceptors give the enamine tautomer **212**. The empirical ordering as to tautomeric preference of the above N-substituted cytosine derivatives suggests the ‘C-type’ pattern, but with an exceptional degree of imine stabilisation when the substituent is a resonance donor. It is just possible that this may be due to an enhanced p-value in **1273**, relative to **211**, due to the charge-spreading present in **1273Z**, a type of allylic anion. Existing information<sup>581</sup> does not allow the effect of  $-\text{COMe}$ , a resonance acceptor, to be quantified. This is one of the most puzzling anomalies we have encountered and it seems unlikely that much progress will be made without quantitative work on a few key substituents (Z in **1273**) of contrasting type which may help to elucidate the electronic factors at work here.

Brown and Hewlins<sup>583</sup> studied **1274** and some related compounds. They found  $\text{p}K_a$  6.62 and 8.05 for **1275** and **1276** respectively, hence **1274C** is the dominant tautomer. These require empirical adjustment to give the corrected values for **1274**. Since **1275** and **1276** both contain a 1-methyl substituent, which on the evidence of **1259** (Table 77) is base-strengthening, this factor can be ignored, but 3-methylation in **1276** cannot. In fact **1258B**  $\rightarrow$  **1255B** and **1258D**  $\rightarrow$  **1255D** both entail  $\Delta \text{p}K_a$  -0.2 so  $\Delta \text{p}K_a$  1.43 for **1275**  $\rightarrow$  **1276** becomes -1.2 for  $\log K_M$ . This compares with -4.1 for **1255**; since **1274C** has no aromaticity to lose, the difference between these values is a measure of the loss of aromaticity entailed when **1255C** is replaced by **1255D**. It also supports the postulate (section B.5.9) that compounds of type **1112** (Scheme 44), such as **1164**, may possess a smaller preference for the **C**-form when Z in **1112** is not a hetero-atom; and in the light of **1272**, it may also be significant that **1168** (section B.5.9) exists as the oxime shown.



Scheme 8



We note in section B.5.13 that there are four possible series of nominal hydroxytriazines, of which **1210A** and **1211A** are 2-pyrimidone ‘azalogues’ and require mention here. The triazinone **737** exists in 95% EtOH exclusively as **737b** (section 8.1.1). The cytosine ‘azalogue’ **1277** has been studied by Piřha and co-workers.<sup>584</sup> They assign this as **1277C** on three pieces of evidence. The first is that **1277** closely resembles **1278** according to IR in DMSO and the solid state and UV in water. The second is that **1279** exists as **1279D** not **1279B** on the evidence of its IR spectrum in CHCl<sub>3</sub>, an observation confirmed by Katritzky and co-workers.<sup>249</sup> Since in addition  $pK_a(\mathbf{1279}) > pK_a(\mathbf{1278})$ ,<sup>584</sup> the stability order is **1277C** > **1277D** with **1277B** presumably the least favoured tautomer. Unfortunately neither  $pK_a$  is recorded and it is uncertain whether **1280** could possess a common cation with either since this would entail protonation on what is nominally an azo-linkage *i.e.* –N=N–, not normally a favoured process, so while the stability order is probably **C** > **D** > **B**, this cannot be quantified.

However, we may speculate. For **1255** the stability order is **C** > **B** > **D** (Table 77) and for an *exo*-imino species to be favoured over any other is rare. Clearly **1277B** will be disfavoured relative to **1255B** by lone pair repulsion, which in **854A** is worth  $\Delta \log K_T$  *ca.* 3 (section B.2.5). While the present case is not precisely parallel, a similar value superimposed on  $\log K_{Mx}$  -1.5 for **1255** (Scheme 52) would be enough to produce the observed reversal in stability order. (A different factor, the stability of acylenamines, may explain the apparently similar case of **206**: section A.4.4). It is less clear whether  $K_M$  should be affected. If the extra aza-nitrogen were to act on the system as an electronegative substituent, its effect could be to stabilise **1277D** as less polar than its rivals, especially in nonpolar solvents; **1277B** and **206a** may well be more stable in water than in most organic solvents – *cf.* the case of **1260**, above. This is another system that deserves re-investigation.

Species **1211A** is symmetrical about its added aza-nitrogen, so little effect from this is expected. The preferred tautomer of **1281** has not been certainly established but **1281C** results, as expected, when NMe replaces ring NH.<sup>2ttt</sup> Surprisingly, on the basis of partial deuteration studies **1282** is reported to give **1282b** not **1282a**.<sup>2ttt</sup> Here **1282b** is the analogue of **1255D** and, with **1282a** lacking any special disability such as the lone pair repulsion present in **1277B**, it is difficult to see **1282b** as the more stable. This compound too might benefit from re-examination. Where all NH's are mobile, as in the hypothetical structure **1283**, **1283b** with its superior conjugated sub-unit (NHR rather than OR through-conjugated to carbonyl) should be strongly favoured over any rival. No information on this general point exists.

## B.6 Thioacylamidines

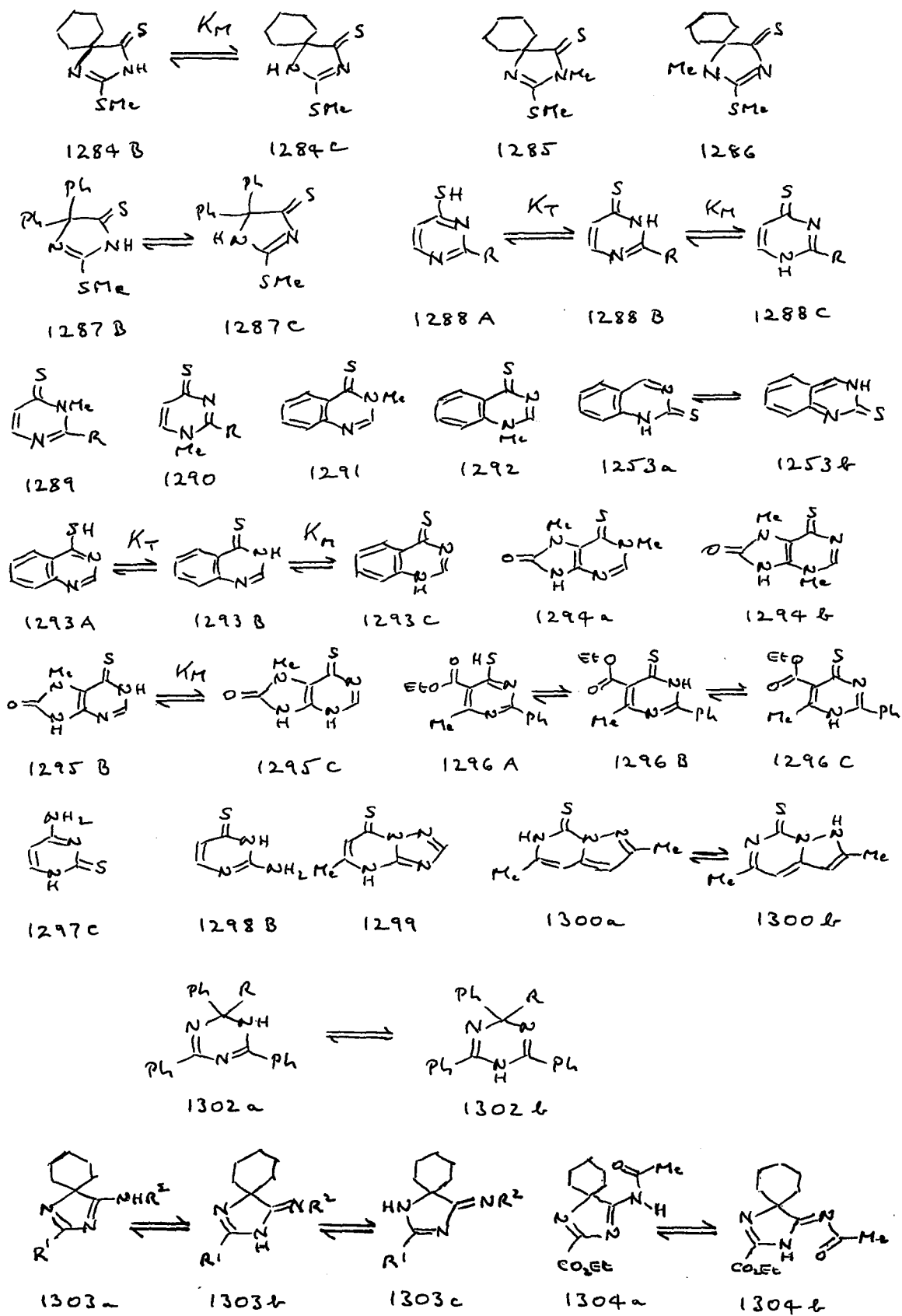
Information on this topic is fragmentary, but there are enough points of contact with the acylamidines of section B.5 to suggest that the general situation is not materially different. However, small differences of detail do appear, and these are highlighted below.

### B.6.1 Alicyclic Thioacylamidines

Edward and Liu<sup>540</sup> investigated the tautomerism of **1284** in water alongside that of its oxygen analogue (section B.5.10) and with almost identical results. From  $pK_a$  3.06 for **1285** and 2.48 for **1286**, corrected in the former case to 3.26 by using  $\Delta(NR)$  0.2 as before, we obtain  $\log K_M$  0.8, as compared with 1.0 in the former case. The calculated  $pK_a$  for **1284**, 2.40, is identical with that found. Similarly, the related **1287** converts between tautomers by sublimation (to **1287B**) or recrystallisation in a manner identical to that of its oxygen analogue<sup>542</sup> (section B.5.10). No other work on aliphatic thioacylamidines seems to have been reported.

### B.6.2 2-and 4-Pyrimidinethiones and Quinazolinethiones

While the picture is otherwise similar, all the evidence points to a greater dominance of the **B**-tautomer among these thiones than is found for their oxygen analogues. If the same  $\Delta(NR)$  values as for the 4-pyrimidones are assumed for **1288B** and **1288C**, Albert and Barlin's values<sup>382a</sup> of  $pK_a$  0.56 and 1.16 for **1289** and **1290** ( $R = H$ ) translate into  $\log K_M$  -0.9; similarly,  $pK_a$  1.22 and 3.00 for **1291** and **1292** respectively<sup>382a</sup> give  $\log K_M$  -2.1 for **1293**. These compare with  $\log K_M$  -0.4 and -1.3 for their oxygen analogues, and while the difference is not large, there is supporting, more qualitative evidence concerning its direction. Mussetta *et al.*<sup>548</sup> found, in their dipole moment study, 97% of (**1288B**,  $R = H$ ) to be present whereas for 4-pyrimidone this value was 88%, implying a similar margin ( $\Delta \log K_M$  *ca.* -0.8). Similarly, Lardenois *et al.*<sup>847</sup> ran the oxygen and sulfur series in parallel and found that, while for  $R = H$  or Me the **B**-tautomer greatly predominates in EtOH, for (**1288**,  $R = Ph$ ) but not for the corresponding 4-pyrimidone, a considerable admixture of **1288A** is present. Either therefore  $K_T$  as well as  $K_M$  is lower for the thiones, or their solvent-sensitivity is greater (it remains unlikely that **1288A** will ever be important in water). If the former option is correct, this would help to confirm other indications (section A.11.1) that  $C=S$ , while more *electronegative* than  $C=O$ , is a poorer



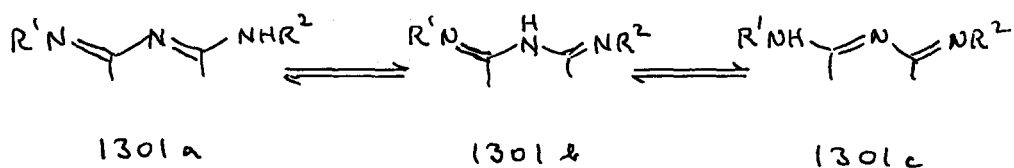
*resonance* acceptor. Supporting evidence comes from a more complex case. Acid  $pK_a$  values of 8.2 and 4.8 are found for **1294a** and **1294b** respectively,<sup>558</sup> giving  $\log K$  *ca.* 3.4 in favour of **1294a** and by implication in favour of **1295B**; for the oxygen analogue **1199** (section B.5.11), this value is  $\log K$  *ca.* 2.5. If ring fusion as in **1295** confers a negligible increase in aromaticity, for which there is other evidence (Appendix 3),  $\Delta \log K_M$  for **1295** relative to (**1288**, R = H), and that in the equivalent 4-pyrimidone case, implies contributions of -2.5 and -2.1 respectively from dipolar repulsion to the effect observed. Thioamides possess larger dipole moments than amides (Table 59, section B.3.3) and if that distinction carries over to the extended dipole of **1293C**, an enhancement of this order seems quite feasible.

There is evidence<sup>2sss</sup> that **1296B** and **1296C** co-exist but **1296A** has not been detected despite the potential for an intramolecular hydrogen bond, which underlines the unimportance of SH-forms; also, SH is a negligible proton donor (Appendix 1). The sulfur analogues **1297** of cytosine and **1298** of isocytosine exist as shown,<sup>550</sup> but unfortunately the available  $pK_a$  values are in neither case sufficiently comprehensive to allow calculation of tautomeric ratio. It is clear however from their UV spectra, and those of models, that the thiol form is undetectable, as is the equivalent **A**-form for the pyrimidones. In **1253**, the quinonoid tautomer **1253b** is disfavoured by  $\log K$  -2.1, in line with some simpler cases (section B.5.15).

### B.6.3 2,3-Heterofused 2-Amino-4-Thiopyrimidones: *endo-exo* Tautomerism

Compound **1299** exists as shown and **1300** as **1300a**,<sup>2yyy</sup> where the latter avoids the dipolar repulsion and loss of thioamide resonance that would be entailed in **1300b**. Both therefore take up the tautomeric forms known or expected for their oxo-analogues, as in all cases above. It is improbable that, among these thiones, this will ever fail to be the case.

### B.7 Imidines



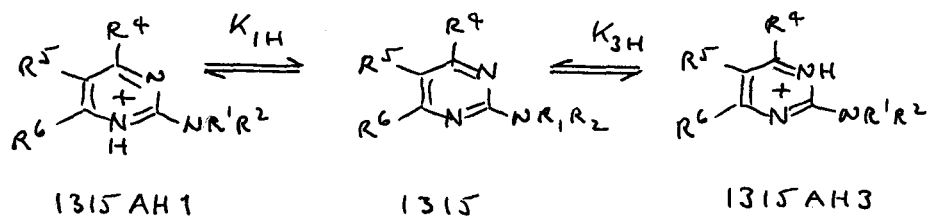
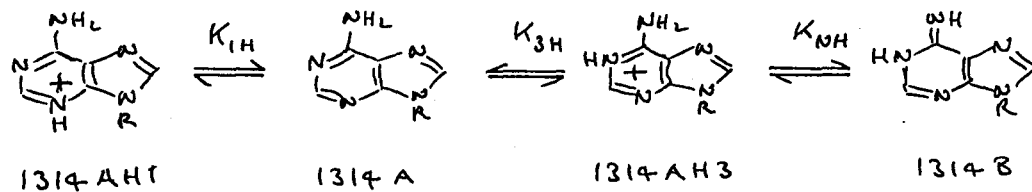
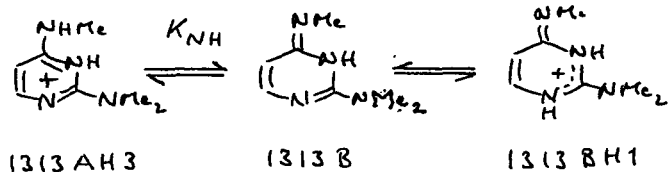
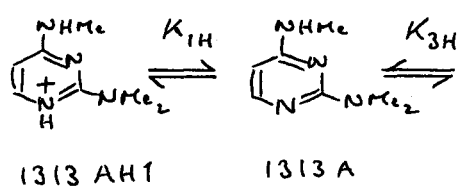
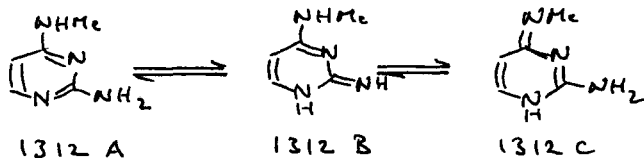
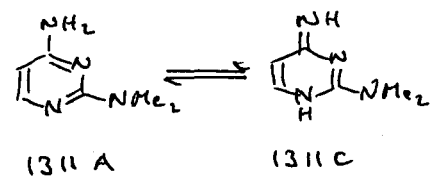
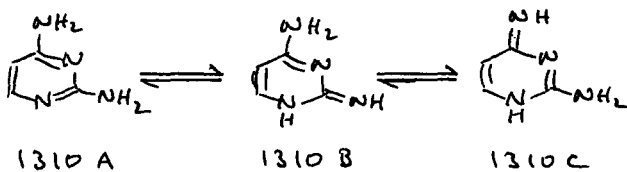
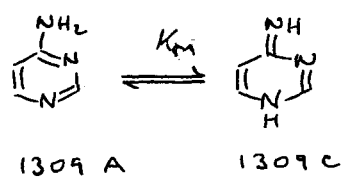
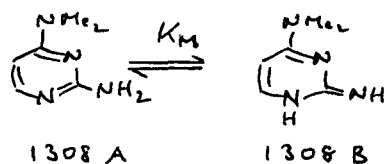
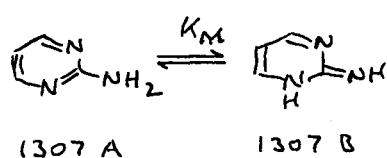
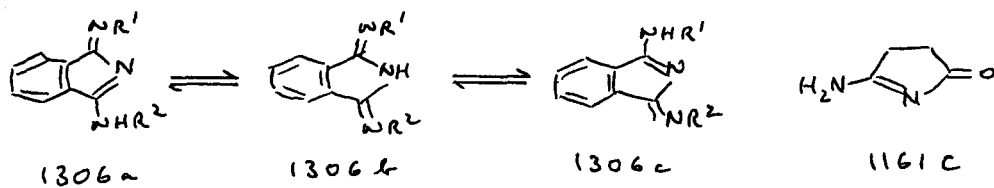
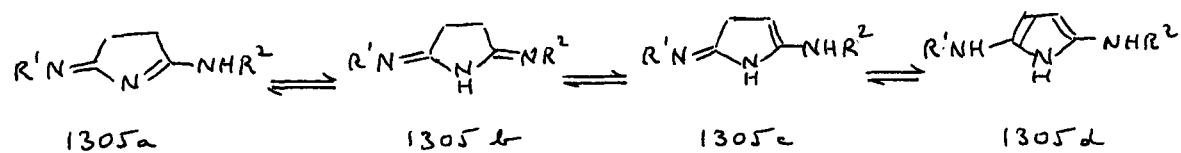
Scheme 53

Imidines possess three tautomeric forms **1301a** – **c** (Scheme 53), of which the first and third are potentially degenerate. There are formal similarities between these compounds and both imides (section B.2.8), which are symmetrical, and acylamidines (section B.5, Scheme 43) which are not, but a closer resemblance than either is to the  $\beta$ -diimines (section A.9), of which they may be regarded as the ‘N-type’ equivalents. As in that case, it is the substituents at the terminal nitrogen atoms that tend to dominate their tautomeric behaviour. And as in the parallel contrast between  $\beta$ -iminoketones **429** and acylamidines **811** (Scheme 43) there is no unconjugated tautomer here, which once again leads to a considerable levelling effect on the stability of the rival tautomers.

### B.7.1 Alicyclic Imidines

The dihydrotriazine (**1302**, R = H, alkyl or Ph) exists in CHCl<sub>3</sub> as a mixture of **1302a** and **1302b** with the former more important, but only for R = Ph by (marginally) more than a factor of two.<sup>586</sup> Curiously, similar mixtures are alleged for the solid state (KBr).<sup>586</sup> Since **1302a** is more polar than **1302b** it is probable that, in more polar solvents, the **a**-tautomer (**1301a** or **1301c** in Scheme 53) will dominate. Bellanato *et al.*<sup>587</sup> studied a series of imidines **1303** in which R<sup>1</sup> and R<sup>2</sup> were some combination of H, alkyl, 2-pyridyl or acyl (COMe or CO<sub>2</sub>Et). In CHCl<sub>3</sub>, the tautomeric balance appears to be dominated by whichever of **1303a** and **1303b** allows the presence of an intramolecular hydrogen bond; in the solid state, the choice appears to be modified by the possibility of intermolecular bonding instead. An example is **1304**, where **1304a** in the solid state goes over to **1304b** in CHCl<sub>3</sub> solution. Interestingly, even for (**1303**, R<sup>1</sup> = CO<sub>2</sub>Et, R<sup>2</sup> = H) **1303b** is the species present in CHCl<sub>3</sub> and **1303c** does not appear to have been detected, possibly because of the preference for *endo*-C=N in 5-membered rings (section A.4.1); **1303a** where only intermolecular bonding is possible is found in the solid state. In view of the relative unimportance of intramolecular hydrogen bonding in determining tautomeric form (Appendix 4), these results point to quite a small intrinsic tautomeric preference among the above compounds.

If **1302** and **1303** may be characterised as *endo-endo* and *endo-exo* compounds respectively, succinimidine (**1305**, R<sup>1</sup> = R<sup>2</sup> = H) allows for the *exo-exo* type. This compound, on NMR evidence, contains no trace of the pyrrole **1305d** or pyrrolenine **1305c** tautomers,<sup>588</sup> so exists as **1305a** or **1305b**, and the same choice must apply to its benzofused derivative **1306**, for which any other possibility is out of the question. Examples of both series have been studied, with results that are inconsistent and occasionally confusing. Early investigators<sup>531,588</sup> tended to favour the symmetrical **b**-tautomer in most cases, but some of their evidence<sup>588</sup> was based on NMR



arguments that took insufficient account of time-averaging. A more recent re-assessment<sup>528</sup> suggests that the **a**-tautomer is more generally favoured. It is possible that some of this evidence does not compare like with like. As seen for **1302** the **b**-form is the less polar and its importance may be exaggerated, relative to water, in other solvents, while the substitution pattern at terminal nitrogen may be even more important. Since almost any substituent in a simple amidine will tend to polarise C=N in its direction (section B.4.2), the effect of symmetric substitution  $R^1 = R^2$  in **1305** or **1306** should be to shift the balance towards the **b**-tautomer, and this effect should increase with electronegativity. This may explain why Elvidge and co-workers<sup>531</sup> found (**1306**,  $R^1 = R^2 = \text{Ph}$ ) to exist as **1306b**, whereas Spiessens and Anteunis<sup>528b</sup> believe on UV evidence that (**1306a**,  $R^1 = R^2 = \text{H}$ ) predominates in DMSO,  $\text{CHCl}_3$ , MeOH and water, but the **b**-form in less polar solvents. Similarly, while Spiessens and Anteunis<sup>528a</sup> argue from the close UV resemblance between **1161C** (section B.5.9) and (**1305**,  $R^1 = R^2 = \text{H}$ ) that this compound in water exists as **1305a**, Armand *et al.*<sup>588</sup> on NMR evidence in DMSO believe the same compound, for  $R^1 = R^2 = \text{H}$ , OH or Ph, to be present as **1305b**. While the discrepancy for  $R = \text{H}$  is most probably a solvent effect, the **b**-form in aqueous solution seems entirely plausible for the others. It would be interesting to study compounds, in either series or both, for which  $R^1 \neq R^2$  and one substituent, say  $R^1$ , was notably more electronegative than the other. We postulate that **1301a** should then be more important than **1301c**, and that, as the gap in electronegativity increases, **1301b** will become progressively less important. However, that is speculation at the present time.

### B.7.2 Heteroaromatic Imidines: 2- and 4-Aminopyrimidines

These compounds and the related quinazolines could exist as the amino-tautomer, **1307A** and **1309A**, or as one of the imino-tautomers **1307B** (for **1307**) and **1309C** (for **1309**). All the evidence concerning imino-forms of other 6-membered ring heteroaromatics (sections A.9.4 and B.4.4) is that these are extremely disfavoured and that is equally true here, but the situation is more complex and requires analysis.

Most of the evidence comes from the work of Brown and Teitei,<sup>589</sup> whose key  $\text{p}K_{\text{a}}$  values appear in Table 78. Of their seven compound pairs only **1307** allows of a totally unambiguous solution, with an annular proton switch between *N*-1 and *N*-3 possible in principle in every other case. This is accompanied by a corresponding ambiguity concerning the **A**-tautomer *cation*, both features precisely paralleling the similar ambiguities present in the 4-pyrimidones (section B.5.12). Here we are forced to ignore the first of these ambiguities and confine our attention to that imino-tautomer which corresponds to the position of ring *N*-methylation found in the model fixed

tautomers prepared by Brown and Teitei.<sup>589</sup> Our solution to the second, which also encompasses **1313** and **1314** where 3-methylation was carried out,<sup>557</sup> appears below. Scheme 54, which incorporates all allowable imino-tautomers, summarises the tautomeric systems we shall consider.

$$\Delta pK_a (2\text{-Py}) = -10.60 \sigma_I - 1.39 \sigma_R^+ \quad (\text{xxv})$$

$$\Delta pK_a (3\text{-Py}) = -6.02 \sigma_I - 2.63 \sigma_R^0 \quad (\text{xxvi})$$

$$\Delta pK_a (4\text{-Py}) = -5.15 \sigma_I - 2.69 \sigma_R^+ \quad (\text{xxvii})$$

A common cation between the **A**- and **B/C**-tautomers requires, for **1308** - **1312**, protonation at *N*-1 in the former case. This rather than at *N*-3 is the universal literature assumption, supported by UV evidence<sup>589</sup> and, obliquely, by eqns. (xxv) - (xxvii), derived by Taft and co-workers<sup>259</sup> for the  $pK_a$  values of substituted pyridines and discussed in section A.10.6. These equations reveal that electron donors are much more effective at increasing basicity in the 4- than in the 2-position, where (except for alkyl and amino) they generally *lower* it since the field effect is so dominant. These substituent positions of pyridine correspond, in terms of cation structure, to *N*-1 and *N*-3 protonation, respectively, of 4-substituted pyrimidines; and since protonation at rival sites in the same neutral species is *necessarily* dominated by that of the stronger base, 1-protonation is expected to be strongly preferred.

$$\begin{aligned} pK_a = & 3.94(0.09) - 3.64(0.39)\sigma_I(4) - 3.70(0.09)\sigma_R^+(4) \\ & - 5.47(0.16)\sigma_I(5) - 3.34(0.24)\sigma_R^0(5) - 7.78(0.30)\sigma_I(6) \\ & - 0.83(0.12)\sigma_R^+(6) + 0.44(6\text{-Me}) \quad (\text{civ}) \\ & (n = 61 \quad r^2 = 0.986 \quad s = 0.26 \quad F = 549) \end{aligned}$$

Morris and Taylor<sup>560</sup> have attempted to quantify the *cationic* tautomerism of 61 compounds of type **1315** which comprise all the available data. They proceeded as follows. (1) While most 2-NR<sup>1</sup>R<sup>2</sup> groups are NHMe, some are not. It would have been possible to handle these by using indicator variables, but this is statistically wasteful so a different procedure was followed. Inspection showed that each such compound differed from another, identical except in its possession of 2-NHMe, by a  $\Delta pK_a$  value which was near enough constant for a given 2-substituent, so that adjustment of  $pK_a$  by the appropriate amount would allow its incorporation into the main series. The adjustments required relative to 2-NHMe were these:

2-NH <sub>2</sub> :	$\Delta pK_a + 0.2$
2-NHEt:	$\Delta pK_a - 0.10$
2-NMe <sub>2</sub> :	$\Delta pK_a - 0.15$

(2) Test runs on compounds otherwise substituted only at the 4- or 5-position led to equations with  $\Delta pK_a$  values quite close to predictions based on (xxvii) and (xxvi) respectively, demonstrating that very similar relationships must hold. (3) It was also found by inspection that 4,6-disubstituted compounds incorporating a  $\pi$ -donor 4-substituent invariably possessed  $pK_a$  values *less* than that calculated for the 4-substituent alone, showing that the poorer electron donor (or better acceptor) must always be regarded as a 6-substituent (*i.e.* as a 2-substituent in terms of pyridine). The only exception to this was methyl, for which, when it is the poorer electron donor (and for  $R^4 = R^6 = \text{Me}$ ), an indicator variable is required.

The final equation was (civ), which uses all members of the set and whose predictions appear as  $pK_a(\text{calc})$  in Table 78. These are close enough to those observed for the **A**-tautomer to confirm dominant 1-protonation. (This equation is used in section B.5.12 to confirm that postulate for the cation of 4-hydroxypyrimidine). Its outstanding virtue, however, is that it allows calculation of the  $pK_a$  value for the *disfavoured* cation. For example, for (**1315**,  $\text{NR}^1\text{R}^2 = \text{NHMe}$ ,  $R^4 = \text{NH}_2$ ,  $R^6 = \text{Cl}$ ), a member of the set, a predicted  $pK_a$  3.96 results. If however  $R^4$  and  $R^6$  are exchanged, which amounts to postulating 3-protonation,  $pK_a$  2.66 is obtained; the observed value is 3.79. 3-Methylation of compound **1313A**<sup>589</sup> leads to **1313B** as the tautomeric imino-derivative we have to consider since this shares a common cation **1313AH3** with **1313A**; however, the  $pK_a$  actually observed for **1313A** involves 1-protonation to give **1313AH1** ( $pK_{1H}$ ). Instead we require  $pK_{3H}$ , which would result from 3-protonation. This may be calculated from eqn. (civ) as 3.89, leading to  $\log K_M$  -7.0. We may similarly analyse adenosine (**1314A**,  $R = \text{ribose}$ ) investigated by Wolfenden,<sup>557</sup> in which the 3-methyl derivative of (**1314B**,  $R = \text{Me}$ ),  $pK_a$  8.25, was used as model. The structure of **1314A** is not that of **1315** but the problem may still be addressed if we suppose that  $\Delta pK_a$  for 1- and 3-protonation in (**1315**,  $R^4 = \text{NH}_2$ ,  $R^5 = R^6 = \text{H}$ ) can be used as a surrogate for that in **1314**. Given an observed  $pK_{1H}$  3.65 for **1314A**,<sup>557</sup> we may calculate  $pK_{3H}$  as -0.15 on this assumption and, after  $\Delta(\text{NR})$  correction for (**1314B**,  $R = \text{Me}$ ),  $\log K_M$  -8.7 results. This very negative value may be exaggerated by the assumptions employed, but at least it confirms that **1314** is in line with the other compounds considered here.

The resulting  $\log K_M$  values are all negative (Table 78), and for **1307** and **1309** even more so than for the corresponding pyridonimines (sections A.9.4 and B.4.4). The effect of a second amino-substituent in **1308** and **1311** is to make  $\log K_M$  less negative, and incidentally more or less to destroy the difference in this respect between 2- and 4-pyrimidonimines which **1307** and **1309** might have suggested. In consequence, for **1310** and **1312** where either the **B**- or the **C**-type imine could be generated, it is impossible to be sure which would be the more likely to result. As noted above, we have had to neglect the possibility of 3-NH imine formation, but the case of **1313** where this is enforced, with its exceptionally negative  $\log K_M$  value, suggests that any such imine structure will be even more disfavoured than those which dominate Scheme 54. In practical terms, the free base forms of all these imines are so heavily disfavoured at any physiologically attainable pH that the question may be dismissed as academic. That is not of course true for the **A**-type tautomers, many of which possess  $pK_a$  values close to physiological pH, and for these, the information that eqn. (civ) can provide on *cation* tautomerism may prove useful.

**Table 78.  $pK_a$  and  $\log K_M$  Values for Aminopyrimidines <sup>a</sup>**

Compound	$pK_a$ (obs)	$pK_a$ (calc) <sup>b</sup>	Compound	$pK_a$ (NMe) <sup>c</sup>	$pK_a$ (NH) <sup>d</sup>	$\log K_M$
<b>1307A</b>	3.54	3.93	<b>1307B</b>	10.75	11.05	- 7.5
<b>1308A</b>	7.96	7.83	<b>1308B</b>	13.66	13.96	- 6.0
<b>1309A</b>	5.71		<b>1309C</b>	12.22	12.22	- 6.5
<b>1310A</b>	7.26	7.39	<b>1310B/C</b>	12.9	13.2 ( <b>B</b> )	- 5.9
					12.9 ( <b>C</b> )	- 5.6
<b>1311A</b>	7.64	7.38	<b>1311B</b>	13.51	13.51	- 5.9
<b>1312A</b>	7.77	7.76	<b>1312B/C</b>	13.14	13.44 ( <b>B</b> )	- 5.7
					13.14 ( <b>C</b> )	- 5.4
<b>1313A</b>	8.10	7.76 <sup>e</sup>	<b>1313B</b>	10.6 <sup>f</sup>	10.9	<sup>g</sup>
<b>1314A</b>	3.65	<sup>h</sup>	<b>1314B</b>	8.25 <sup>f</sup>	8.55	<sup>i</sup>

<sup>a</sup> See the text. <sup>b</sup> From eqn. (civ) assuming 1-protonation and incorporating  $\Delta pK_a$  for 2-NH<sub>2</sub> or 2-NMe<sub>2</sub> (see the text). <sup>c</sup> For 1-NMe or 3-NMe derivative as appropriate. <sup>d</sup> After applying  $\Delta(NR)$  corrections where necessary to  $pK_a$  (NMe). <sup>e</sup> For 3-protonation this becomes  $pK_a$  3.89. <sup>f</sup> For methylation at 3-NH. <sup>g</sup> Calculated as -7.0 (see the text). <sup>h</sup> For 3-protonation this becomes  $pK_a$  -0.15 (see the text). <sup>i</sup> Calculated as -8.7 (see the text).

## B.8 Summary and Overview

In this section we summarise the results discussed in sections B.1 – B.7 in the nearest approach we can find to a logical order. This is in some ways easier than for C-type tautomerism since, here, there are no unconjugated tautomers. In the interests of flow and to avoid overmuch repetition we have omitted the statistics for the equations we recapitulate and, similarly, all but the most serious of our caveats concerning correlations and our predictions based on them; for these see the original sub-sections, which are indicated throughout.

Two forms of tautomerism dominate. One involves only nitrogen atoms: contiguous, of amidine type, or as an important sub-section of the latter which consists in the *endo-exo* relationship *e.g.* of the  $\alpha$ -aminoheterocycles. These categories frequently overlap, so that a clean separation is not possible. Again, while all forms of annular tautomerism belong in one or another, this is not their only context and it has proved unproductive to consider annular tautomerism on its own. The other consists in amide-iminol tautomerism and its sulfur equivalent; in many ways this is simpler, not least because oxo-(thiono)-forms are so generally dominant, but again overlap is inevitable in such cases as the pyrimidones, where amidine tautomerism also enters.

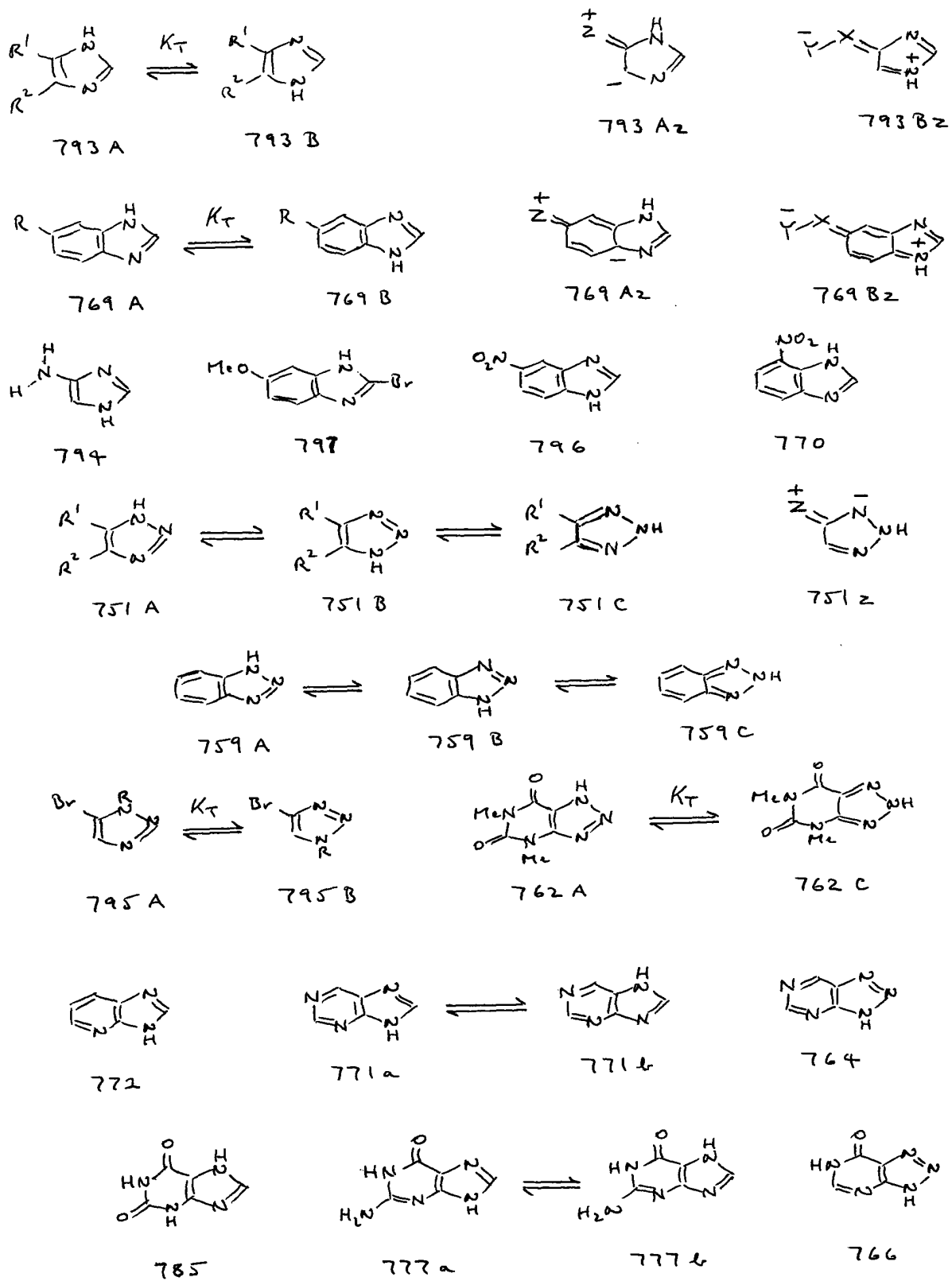
Tautomerism involving nitrogen alone is more complex, more wide-ranging and in practice more important, so is considered first. We start with the parent heterocycles and their substitution patterns, since the rules derived for use elsewhere do not apply reliably to these eight compounds and they will probably need incorporation *de novo* into any computer algorithm created for the purpose of prediction.

### TAUTOMERISM INVOLVING ONLY NITROGEN ATOMS

#### B.8.1 Annular Tautomerism in 5-Membered Ring Heterocycles and their Ring-Fused Derivatives lacking Bridgehead Nitrogen. Substituent Effects

We split these into (a) the imidazole (symmetric) and (b) the pyrazole (asymmetric) categories and consider the former first (Scheme 55).

(a) Imidazole (**793**,  $R^1 = R^2 = H$ ) and benzimidazole (**769**,  $R = H$ ) each possess two degenerate tautomers;  $\nu$ -triazole (**751**,  $R^1 = R^2 = H$ ) and benzotriazole (**759**) possess three, of which two are degenerate but the third is not (Scheme 55). Here, while **751C** is dominant (*ca.* 68%) in water and still more so in most other solvents, **759C** is effectively suppressed in all but



Scheme 55

the gas phase (sections B.1.3, B.1.6). Its quinonoid form is presumably the reason for this but the exact margin, while probably very large, is unknown.

$$\log K_T = 4 \sigma_I \quad (\text{cv})$$

Substitution in all cases removes degeneracy unless symmetrical. For (**793**,  $R^2 = \text{H}$ ) substitution at  $R^1$  follows eqn. (cv) for very electronegative substituents (section B.1.8) but  $K_T$  is more than predicted otherwise; it is still considerable ( $K_T > 10$ ) for  $R^1 = \text{Ph}$  or  $\text{NH}_2$ . That is: monosubstitution at  $R^1$  *always* gives **793B** as the dominant tautomer. This bias is plausibly rationalised by structure **793Bz** to the extent that  $\sigma_I$  and  $\sigma_R$  change roughly in parallel. The  $\pi$ -inductive interaction shown as **793Az** is clearly unimportant for **794** (where hydrogen bonding may dominate) and may be too weak to count.

The effect of R in benzimidazoles **769** is greatly attenuated, with even **796** possessing  $K_T < 2$  (section B.1.8) in favour of the structure as written, as compared with  $\log K_T$  *ca.* 2.6 for (**793**,  $R^1 = \text{NO}_2$ ,  $R^2 = \text{H}$ ). Similarly, the margin in favour of **797** is slight. Presumably structures **769Bz** and especially **769Az** are of limited importance. However, 4(7)-substitution of **769** is likely to influence tautomeric form if the substituent possesses proton donor or acceptor properties; **770** exists 80% as shown in water (section B.1.7). Note however that  $\text{NO}_2$  is a poor proton acceptor<sup>72</sup> and other acceptors (or donors) may have much more effect.

On the evidence of **795** for which  $K_T \sim 16$  is found (section B.1.8),  $\nu$ -triazole shows (for **751A/B**) a substituent effect similar to that of imidazole but probably less;  $\log K_T$  *ca.* 1.2 here compares with 2.0 for (**793**,  $R^1 = \text{Br}$ ,  $R^2 = \text{H}$ ). The relative importance of **751C** for this compound is unknown. Nothing is known for benzotriazole **759A/B** but behaviour similar to benzimidazole would be expected. For  $\nu$ -triazole, stabilisation of **751C** by electron donors (*vide* **751z**) is plausible but nothing is known here either. Parallel behaviour by **759** can be discounted since **759C** is so disfavoured. This may not be true for other forms of ring fusion; **762C** is preferred (in DMSO) by  $\log K_T$  *ca.* 0.6 (section B.1.6 and Appendix 5). Here the uracil moiety appears to possess minimal aromaticity (contrast **764** and **766** below, for which C-forms are unimportant).

Other ring fusions have been studied. Xanthine **785** exists as shown, and its tautomeric form is typical of those cases in which the fused 6-membered ring possesses a proton acceptor and donor so placed as to interact with NH and aza-nitrogen respectively (section B.1.7). Some examples lack one type of interaction or the other, and here the sequence **772**  $\rightarrow$  **771**  $\rightarrow$  **764** is instructive: whereas **772** and **764** exist as such in water, purine **771** is present as the 50:50 mixture shown. This can be rationalised with respect to the proton donor and acceptor values<sup>72</sup> of Table 79, since the relative strength of hydrogen bonds varies with the *product* (not the *sum*)<sup>590</sup> of these donor and acceptor quantities.<sup>591</sup> Pyridine is a strong acceptor and *v*-triazole a strong donor, but pyrimidine and imidazole are much weaker in these respects. There result ‘product values’ (*ex* Table 79) of 4.5 for **772** and 5.1 for **764** but only 2.7 for purine **771**, which value appears on this evidence to be borderline. (Nevertheless, with  $\Delta \log K$  -0.8 expected for the effect of lone pair repulsion in **771b**, section A.12 and Appendix 3, some countervailing factor must be present, and this may be dipole moment, if also greater for **771b** as seems likely). For **770**, with  $\log K_T \sim 0.6$  but bond alignment close to optimal, the ‘product value’ calculation yields 1.6 so the borderline as expected lies lower.

**Table 79. Proton Donor ( $K_\alpha$ ) and Acceptor ( $K_\beta$ ) Strengths ( $\log K$ ) for 1:1 Association**<sup>a,b</sup>

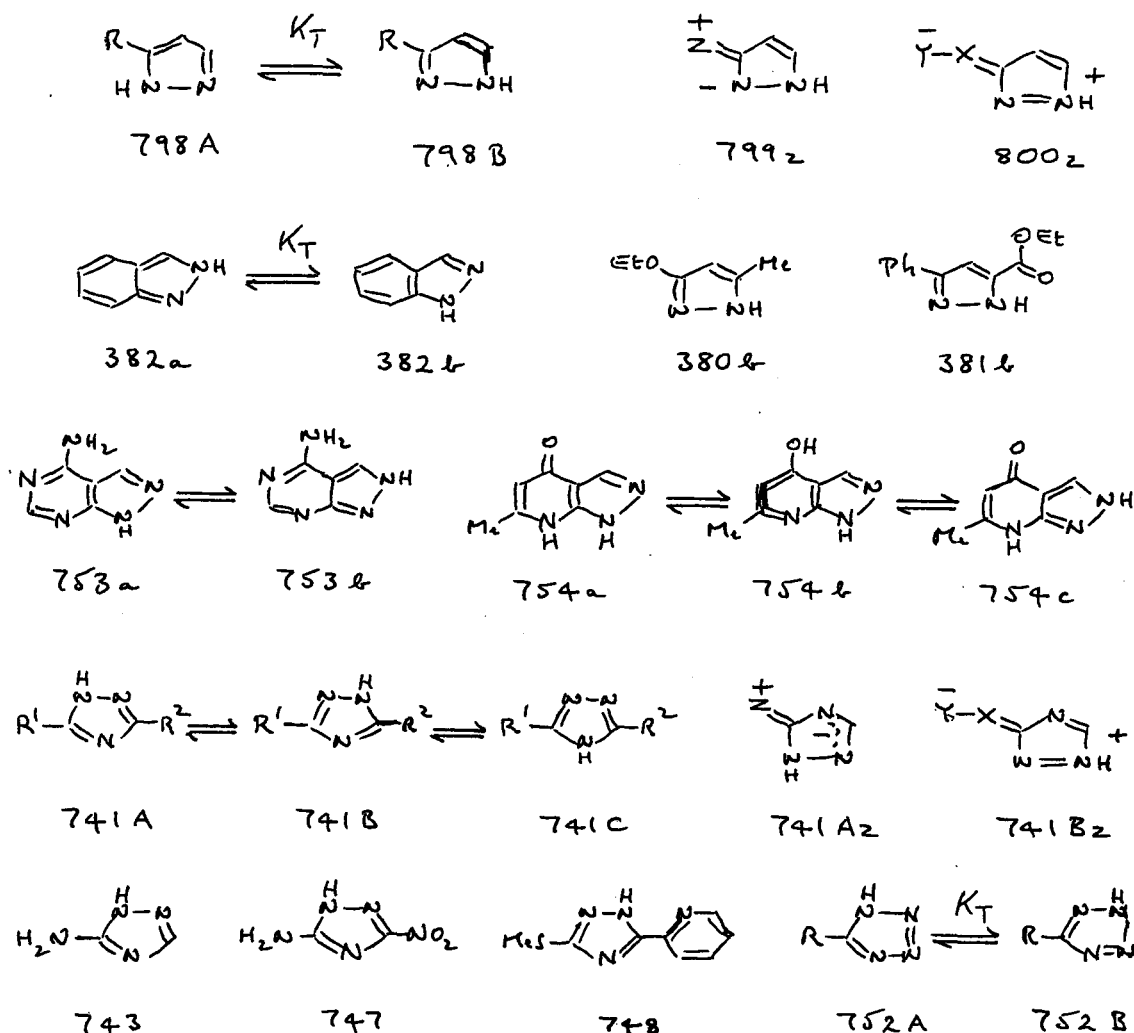
Functional Group <sup>c</sup>	$\log K_\alpha$	$\log K_\beta$
(Ar)NO <sub>2</sub>		0.7
Amide	0.7	3.1 <sup>f</sup>
Imidazole	1.2	3.7
Pyrazole		2.2
1 <i>H</i> - <i>s</i> -Triazole	2.0	2.4
1 <i>H</i> - <i>v</i> -Triazole		2.6
2 <i>H</i> - <i>v</i> -Triazole	2.4	
Tetrazole	3.6	2.0
Pyridine		2.5
Pyrimidine		1.4 <sup>g</sup>
4-Quinolone		$\geq 4$

<sup>a</sup> Ref. 72. <sup>b</sup> Here the ‘product value’  $\log K = (\log K_\alpha + 0.4)(\log K_\beta + 0.3)$  for any combination of proton donor and acceptor (see section C.37). <sup>c</sup> Heterocycles appear under this heading. For 1*H*-*s*-triazole, 1*H*-*v*-triazole, and tetrazole, proton donors probably interact with that aza-nitrogen atom most remote from NH (ref. 100). <sup>d</sup> With *N*-methylpyrrolidinone as standard acceptor in CH<sub>3</sub>Cl<sub>3</sub>.

<sup>e</sup> With 4-nitrophenol as standard donor in CH<sub>3</sub>Cl<sub>3</sub>. <sup>f</sup> Lactam. <sup>g</sup> Statistically corrected.

Where the fused moiety contains rival acceptors, some inconsistencies appear. In guanine **777** lone pair repulsion in **777a** is predicted to be at least 10 times greater than in **777b** (section A.12.9) while hydrogen bonding in the latter should be stronger, so **777b** is expected to dominate, as is found (section B.1.7). However **766** which should behave the same way exists mostly as shown (section B.1.6); perhaps its probably lower  $K_{\beta}$  value (Table 79) implies less lone pair repulsion than for imidazole as well. It is probable however that none of these preferences is very decisive and the energetic penalty for an unfavourable switch at the receptor may in most cases be quite small, perhaps no more than 1 - 2 kcal mol<sup>-1</sup> in the typical case. The interesting possibility arises that, in certain natural biomolecules such as purine **771** and guanine **777**, easy tautomer interchange may possess some biological value. Further bicyclic compounds in which similar balancing factors operate appear in B.8.5 below (Scheme 61).

(b) Pyrazole (**798**, R = H), *s*-triazole (**741**) and tetrazole (**752**) form a sequence in which aza-nitrogen is added at each stage (Scheme 56). All contain contiguous nitrogen atoms and all but **752** possess, as the parent compound, two degenerate tautomers (*s*-triazole **741** also possesses one other). Pyrazole gives a benzofused product, indazole **382**, for which  $K_T \sim 50$ ; the quinonoid structure of **382a** may be the main driving force for tautomer preference here (section A.9.2). If this effect were to be transferred quantitatively to benzotriazole **759**, **759C** would be disfavoured by a factor of *ca.* 25 but this margin is almost certainly much too low, so that the 'quinonoid penalty' (Appendix 5) is not here additive. No substituent is likely to reverse the preference for **382b** since 3-substitution will probably increase the stability of this tautomer (*cf.* **798B**, below) and substitution elsewhere, if benzimidazole is any guide, is too remote to matter. This preference can be challenged when fusion takes place to a unit of doubtful aromaticity, though in no known case is the major tautomer quinonoid. For **753** in water, **753b** is disfavoured only to the extent of  $\Delta \log K -1.0$  (section B.1.5), which given a putative value of  $\Delta \log K$  *ca.* -0.8 for lone pair repulsion in **753b** (Appendix 3), means that almost no aromatic stabilisation can attach to the 4-aminopyrimidine moiety. However **754** exists as **754a** despite dipolar repulsion equivalent to  $\Delta \log K$  *ca.* -1.2 (Appendix 3), which is consistent both with the high resistance of 4-pyridone to enolisation ( $\log K_T$  3.9) as required for **754b**, and to the quinonoid structure required for **754c** ( $\Delta \log K -1.7$  for indazole itself). Tetrazole and *s*-triazole can form fused derivatives only *via* bridgehead nitrogen.



Scheme 56

$$\log K_T = 2.6 \sqrt{(\sigma_R)^2}$$

(cvi)

Monosubstitution in pyrazole **798** results in  $K_T > 1$  whatever the electronic nature of R. This may be understood in terms of the charge-separated structures **799z** and **800z**, both of which stabilise **798B**. This effect is largest for substituents with strong electronic characteristics and is probably more pronounced for donors than for acceptors. For **798**,  $\log K_T$  in the gas phase is 0.51 and 1.76 for  $R = \text{NO}_2$  and  $\text{NH}_2$  respectively (section B.1.8); in water,  $\log K_T = 1.5$  in favour of **380b** (section A.9.2) so the same bias holds. Equation (cvi) roughly fits the gas-phase results; for **380** it would have predicted  $\log K_T$  1.04, so surprisingly,  $\rho_R$  in water may be larger. Note the difference between  $\sigma_I$ -dependence for the electron-rich imidazole, eqn. (cv), and  $\sigma_R$ -dependence here for the electron-deficient pyrazole, complementary behaviour of some interest. For **381**, eqn. (cvi) would predict  $\log K_T$  ca. 0.2 in favour of **381a**; the apparent contradiction that **381b** is preferred by about a factor of three in water probably results from its intramolecular hydrogen bond. Even allowing for some doubt concerning  $\rho_R$ , a value of ca.  $\Delta \log K$  0.7 for this bond appears reasonable (Appendix 4).

The degenerate **A/B** tautomers of *s*-triazole (**741**,  $R^1 = R^2 = H$ ) parallel those of pyrazole **798** but substitution has different consequences, in that monosubstitution at  $R^1$  by electron donors and acceptors favours the **A**- and **B**-tautomers respectively. This may be rationalised in terms of **741Az** and **741Bz**, where the latter parallels **800z** but the former takes advantage of an extended conjugation not available to **798**. However, the effect is slight, with  $A/B \sim 2$  for **743** and with the opposite bias, not quantitatively known, for  $R^1 = NO_2$  (section B.1.2). Unsurprisingly therefore **747** exists predominantly as shown, but the bias is easily reversed by hydrogen bonding, as in **748**. The amount of **C**-tautomer in aqueous solution has been elucidated in a handful of cases: about 20% in *s*-triazole itself, 16% in (**741**,  $R^1 = R^2 = Me$ ), and 10% in **743** (section B.1.2). In the light of its lone pair repulsion it is surprising that the proportion of **741C** should be so high, but it may possess a countervailing advantage due to its *bis*-amidine structure. Its importance however declines as solvent polarity falls, and it is unlikely ever to be a major species (*cf.* *v*-triazole **751**, above).

$$\log K_T = -1.11 + 3.26 \sigma_I + 0.74 \sigma_R \quad (1xii)$$

Tetrazole (**752**,  $R = H$ ) exists overwhelmingly as the more polar **752A** in water but the less polar **752B** becomes more important in less polar solvents. The **A**- and **B**-tautomers are also favoured by electron donor and acceptor substituents respectively (section B.1.4) and, for DMSO, this can be quantified by eqn. (1xii), which predicts a value for  $R = NH_2$  close to that for tetrazole itself, as is found, while for  $R = NO_2$ ,  $\log K_T$  *ca.* 1.2 is predicted. Much more negative values would be expected for water (*i.e.* **752A** should be still more dominant) but the same qualitative order may be assumed. It is interesting that charged resonance forms which parallel **741Az** and **741Bz** can be written for **752** as well, adding to the presumption that *s*-triazole will show the same trends, though probably in a much more muted manner.

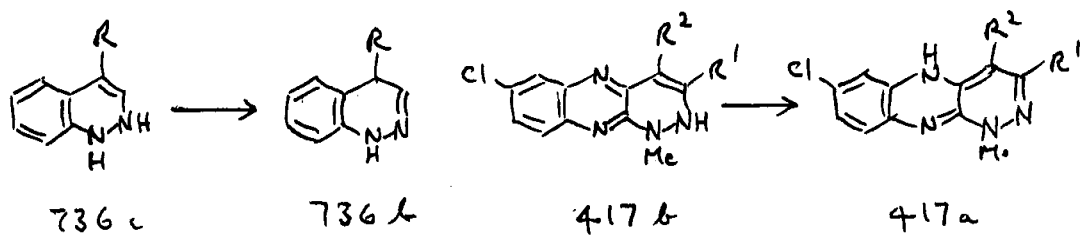
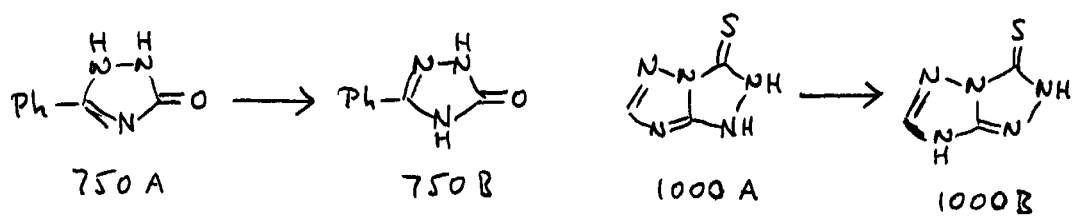
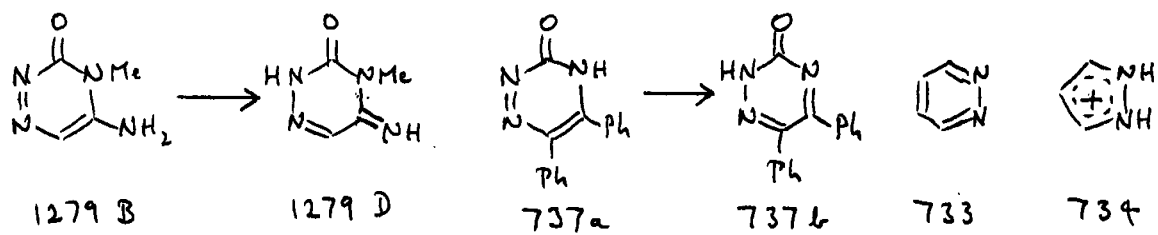
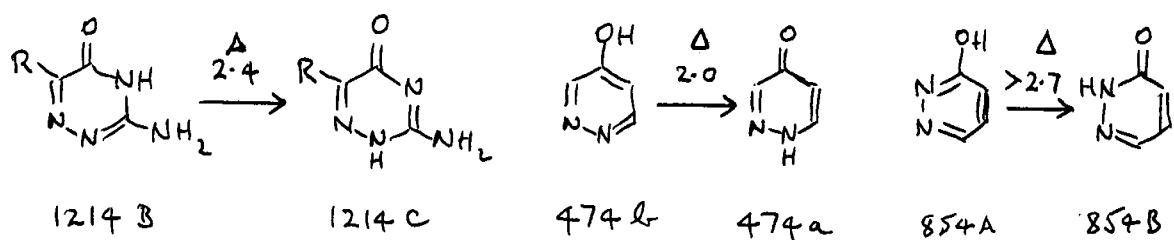
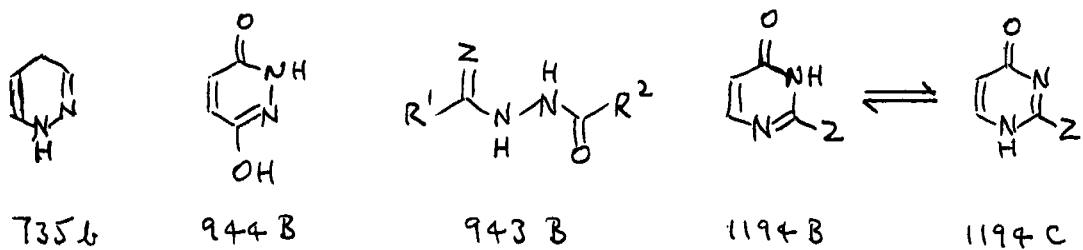
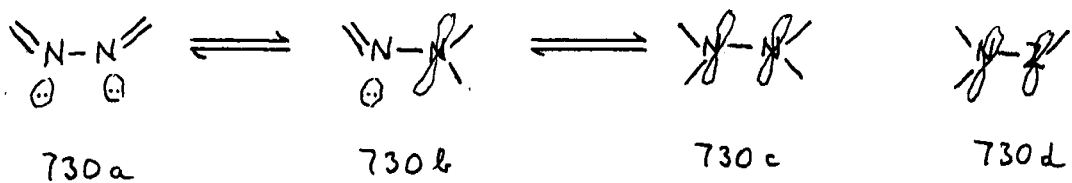
*Summary.* — Tautomerism in these seven crucial heterocycles may be summarised as follows. In imidazole and pyrazole, whose tautomers are degenerate, substituents that remove this degeneracy tend to have large effects: chiefly electron acceptors in the more basic imidazole, both types but with donors more dominant in the less basic pyrazole. The dominant tautomers are then (**793B**,  $R^1 \neq H$ ) and **798B**. Benzimidazole shows the same effects as for imidazole, but attenuated to the point that they are barely worth considering, and it seems likely that benzotriazole **759** will behave similarly. Nothing is known for indazole, but with **382b** greatly favoured it is improbable that any substituent could reverse this, let alone stabilise the equivalent tautomer **759C** of benzotriazole.

Tetrazole **752** possesses nondegenerate tautomers of which **752A** is strongly favoured in water and is also, probably, stabilised by electron donor substituents R. The equivalent tautomer (**741A**,  $R \neq H$ ) of *s*-triazole is stabilised similarly, but by a vastly smaller margin. Similarly, (**741B**,  $R \neq H$ ) is marginally stabilised by electron acceptors, and it is probable that these have a much larger effect in stabilising **752B**, but whether this can ever be the dominant tautomer in water is unknown. For *s*-triazole, **741C** is always a minor tautomer whose importance lessens as solvent polarity falls and may also diminish on any form of substitution. For *v*-triazole the same bias against contiguous aza-nitrogen atoms renders **751C** its most important tautomer but the effects of substitution have not been charted.

Substituents close enough to tautomeric nitrogen for intramolecular hydrogen bond formation may upset expectations based on any of these guidelines; examples include **770** (Scheme 55) and **381b** and **748** (Scheme 56). This is particularly important when considering fusions other than benzofusion, as in some nucleic acid bases and related compounds. While *e.g.* **785** as the preferred tautomer is the obvious choice, it is not at first sight obvious why **777b** should be preferred to **777a** and close reasoning is required (see above). However, while **766** remains anomalous, nearly all these variations appear to possess a chemical rationale and further work may help to resolve those anomalies that remain.

### B.8.2 Annual Tautomerism involving Contiguous Nitrogen Atoms: General

Lone pair repulsion in **730a** or dipolar repulsion in **730c** (Scheme 57) leaves **730b** as the optimal arrangement for contiguous nitrogen atoms in cyclic structures (section A.12). The unfavourable interaction in **730d** is still more severe for  $Z = O$  (but probably not  $Z = S$ ) than for  $Z = NR$  (section B.2.10) and may roughly be quantified (section C.15 and Appendix 3). *Note that lone pair repulsion is a problem only in cyclic structures*, or perhaps more generally, if it cannot be relieved by twisting of the molecule about the N–Z linkage. This is one reason why azo-compounds  $RN=NR$  exist exclusively as the *trans*-isomer, while **735b** is the preferred tautomer, out of three, for **735** (section B.1.1). Similarly, while **944B** is the dominant (*ca.* 90%) tautomer of ‘maleic hydrazide’ (section B.2.12), no trace of iminol has ever been detected in an open-chain diacylhydrazine (**943**,  $Z = O$  or  $S$ ). The latter contrast illustrates, as will be discussed below, how amide-iminol tautomerism is also subject to stereoelectronic constraints; it is indeed the commonest cause of substantial or predominant iminol formation. There is however evidence that dipolar repulsion (**730c**, **730d**) is *not* relieved in open-chain structures (Appendix 3).



Scheme 57

Sometimes these factors can be quantified. While the **B**- and **C**-tautomers of **1194** are quite evenly balanced, especially when Z is a  $\pi$ -donor (section B.5.11), for **1214**  $\log K_M$  *ca.* 2.4 is found (section B.5.13). Similar estimates apply to the case of **474** (Appendix 3) and in other related contexts. The effect is still greater in **854**, with  $\Delta \log K_T \geq 2.7$  (section B.2.5), perhaps through an increase in lone pair electron density resulting from the close proximity of OH in **854A**. A similar effect due to NH<sub>2</sub> probably helps to account for the existence of **1279** in the normally disfavoured **D**-form (section B.5.15, *cf.* **412**, section C.29); in **1194**, the **D**-tautomer (for Z = NH<sub>2</sub>) is disfavoured relative to **1194B** by  $> 10^4$  (section B.5.14). When no annular nitrogen atom is blocked, the simpler transformation *e.g.* of **737a** to **737b** is quantitative (section B.1.1).

According to a semi-empirical approach<sup>387</sup> (section B.1), lone pair repulsion in **733** and dipolar repulsion in **734** carry almost equal weight, in water equivalent to  $\Delta \log K$  *ca.* 2.2. Values of this order are regularly found for annular lone pair and dipolar repulsion in 5- and 6-membered rings, but both show considerable variation (Appendix 3). There is also suggestive evidence that dipolar repulsion may be, at least in water, the more severe. Whereas the preference of **750B** over **750A** (section B.1.2) requires no special explanation, that for **1000B** over **1000A** (section B.3.5) involves overcoming an energetic deficit in its 2-imino-*s*-triazole moiety which is probably  $> 10^6$  (section B.5.14, and see further discussion in section B.8.9; in the absence of dipolar repulsion, it is unlikely that the balancing deficit in **1000A** would be so great). Two other examples are more equivocal. In **736** (section B.1.1), **736b** is preferred even for R = Ph, which in allylic systems can stabilise C=C by a factor of  $\Delta \log K$  *ca.* 3.3 (section A.1.1). Similarly, **417a** is preferred to **417b** despite partial loss of aromaticity. However, the disfavoured alternatives **736c** and **417b** must both possess some antiaromatic character, and this complication may be crucial. ‘Anti-aromaticity’ is discussed at length in section A.4.9 and Appendix 5; note that 6-membered aromatic rings containing more than one annular  $\pi$ -donor atom, or 5-membered aromatic rings containing carbonyl but no  $\pi$ -donor, will generally possess it.

The avoidance of lone pair and dipolar repulsion form two of Elguero's four ‘rules’<sup>176</sup> for tautomeric preference in 5,5-ringfused heterocycles containing bridgehead nitrogen (the ‘azapentalenes:’ section B.1.9), and also more generally. Their use in that context is postponed to a more general treatment in B.8.9 below.

### B.8.3 Amidines and Imidines: Open-Chain and Alicyclic

This is the simplest category of amidine, as **1024**. Here a common cation **1024H** deprotonates to give a mixture of **1024A** ( $pK_{a1}$ ) and **1024B** ( $pK_{a2}$ ). For a monosubstituted amidine ( $R = H$ ,  $R^2 \neq H$ ) these  $pK_a$  values become  $pK_{Am}$  and  $pK_{Im}$ , respectively. For guanidines ( $R^1 = NH_2$ )  $pK_{Im}$  is a simple function of  $\sigma_{I(X)}$  where  $X = R^2$  and there is evidence that this  $\sigma_I$  relation holds generally for amidines, with respect to  $pK_{Am}$  as well as  $pK_{Im}$  (*vide* sections B.4.4 and B.4.5 for examples). The following formalism then holds (section B.4.2):

$$pK_{Am} = pK_H - \rho_{Am} \sigma_X \quad (lxxxii)$$

$$pK_{Am} = pK_H - \rho_{Im} \sigma_X \quad (lxxxiii)$$

$$\log K_T = \{ (\rho_r - 1) / \rho_r \} (pK_H - pK_{Im}) \quad (lxxxvii)$$

$$\log K_T = \{ (\rho_r - 1) / \rho_r \} \rho_{Im} \sigma_{I(X)} \quad (lxxxviii)$$

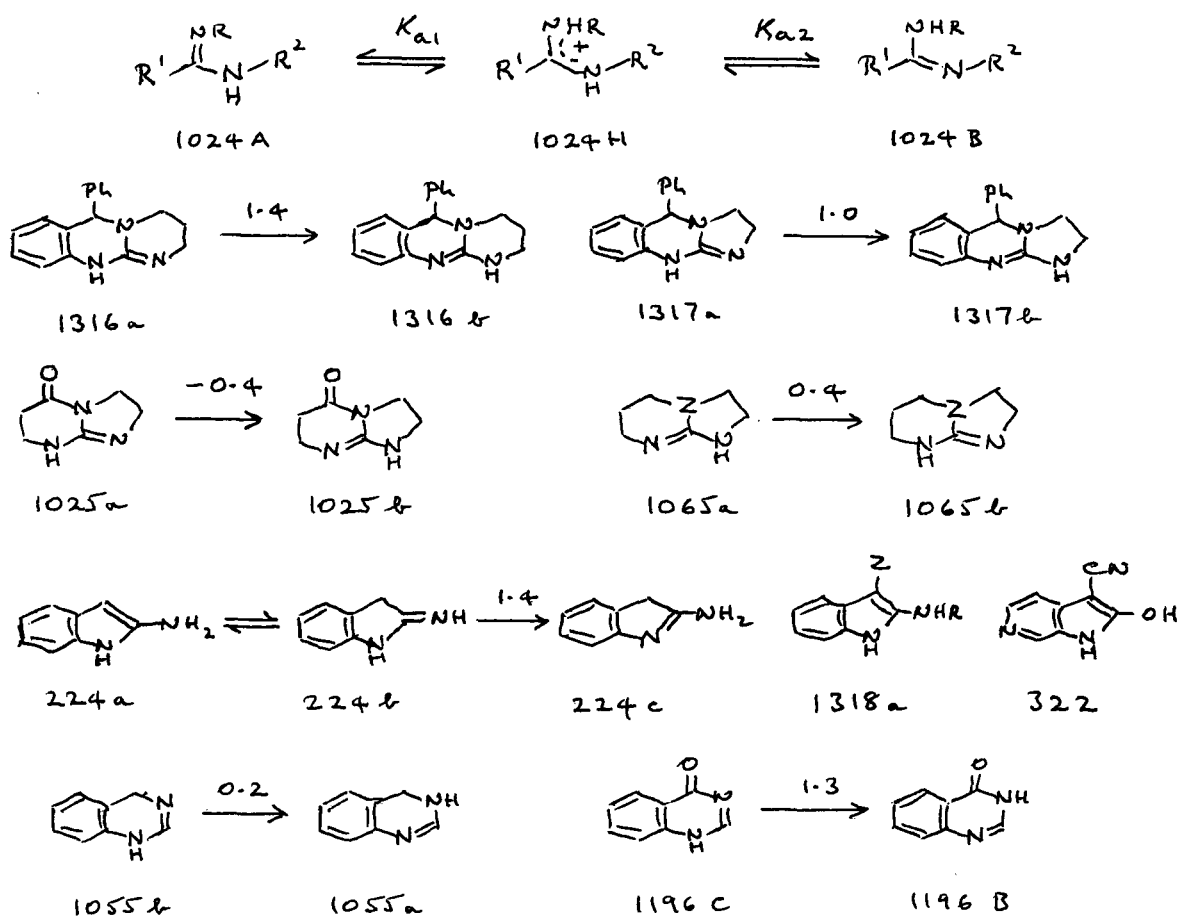
where  $pK_H$  is that of the ‘parent’ (unsubstituted) amidine,  $\sigma_{I(X)}$  is that for the substituent  $X = R^2$ , and we define  $\rho_r = \rho_{Im}/\rho_{Am}$ . Equations (lxxxvii) and (lxxxviii) are then alternative ways of calculating  $K_T$  *when only data for the major tautomer are known*, according to the information available.

$$\log K_T = 0.5 \rho_{Im} \sigma_{I(X)} \quad (cvii)$$

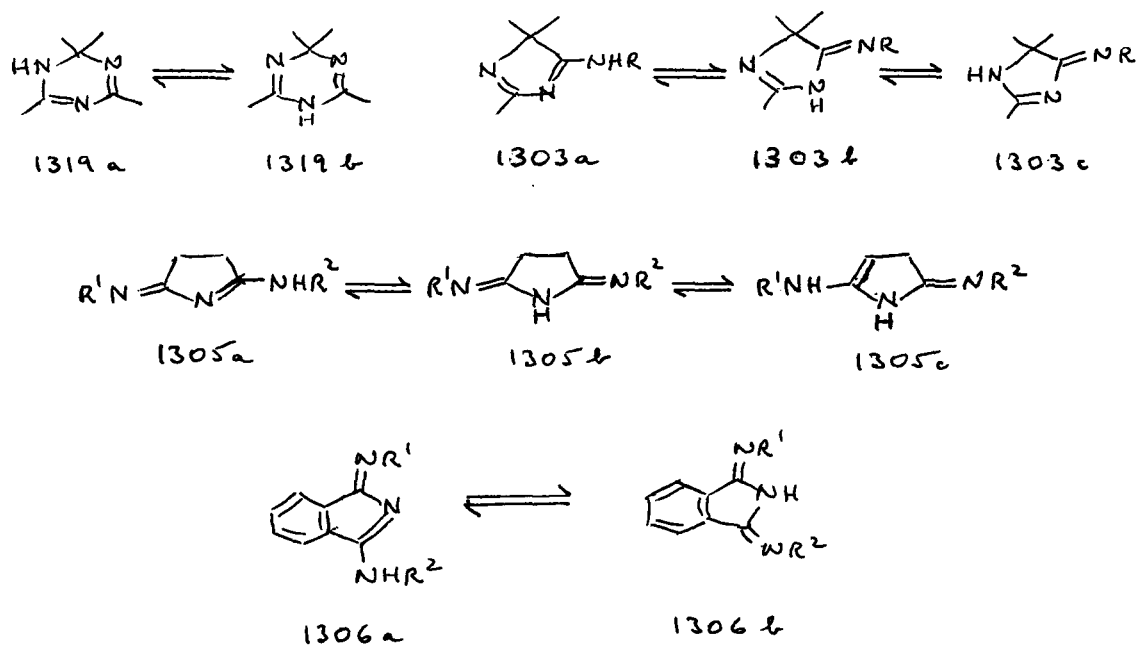
$$\log K_T = 11.3 \sigma_{I(X)} \quad (cviii)$$

Here  $\rho_r$  is the crucial quantity. For open-chain guanidines ( $R^1 = NH_2$ ),  $\rho_r = 2.0$  and we postulate, on limited but solid literature evidence, that this value will also apply to any amidine for which  $R^1$  is freely rotating and centrosymmetric. If so,  $\log K_T$  is then represented by *half* the difference between  $pK_H$  and the measured  $pK_a$  of the major tautomer,  $pK_{Im}$ , or *half*  $\rho_{Im}\sigma_{I(X)}$  if  $\rho_{Im}$  is known; eqn. (cvii). For the specific case of monosubstituted guanidines in aqueous solution, this becomes eqn. (cviii). In this case (Table 62, section B.4.2) there is reasonable agreement between the predictions as to  $K_T$  made by both routes, while the directly measured  $K_T$  values for  $R^2 = COMe$  and 4-methylthiazol-2-yl, the only ones that allow an unequivocal check, agree quite closely with those predicted for  $\rho_r = 2.0$ .

Qualitatively, an important consequence of these equations is that  $C=N$  for monosubstituted amidines should almost invariably be polarised towards the substituent. The only important exception is alkyl, for which  $\sigma_I \sim 0$  and in which case there is probably no preference. For 1,3-disubstituted amidines (**1024**,  $R = R^2 \neq H$ ) the overall  $K_T$  should be such as to favour the more electronegative substituent to an extent defined by the *difference* between their



Scheme 58



Scheme 59

$\sigma_1$  values. Allowing for possible conformational or ring size effects, this relation should apply in any context. Through present lack of evidence it is untestable for open-chain compounds, and is quantitatively inaccurate in the one known alicyclic case where special problems may be present (section B.8.4), but qualitatively at least, it can reasonably be accepted as a *de facto* guiding principle. We have established that no extra term is required for an intramolecular hydrogen bond in the case of eqn. (1xxxiii) for guanidines, possibly because any such effect cancels between neutral form and cation, in which case it is likely to cancel between the neutral tautomers as well.

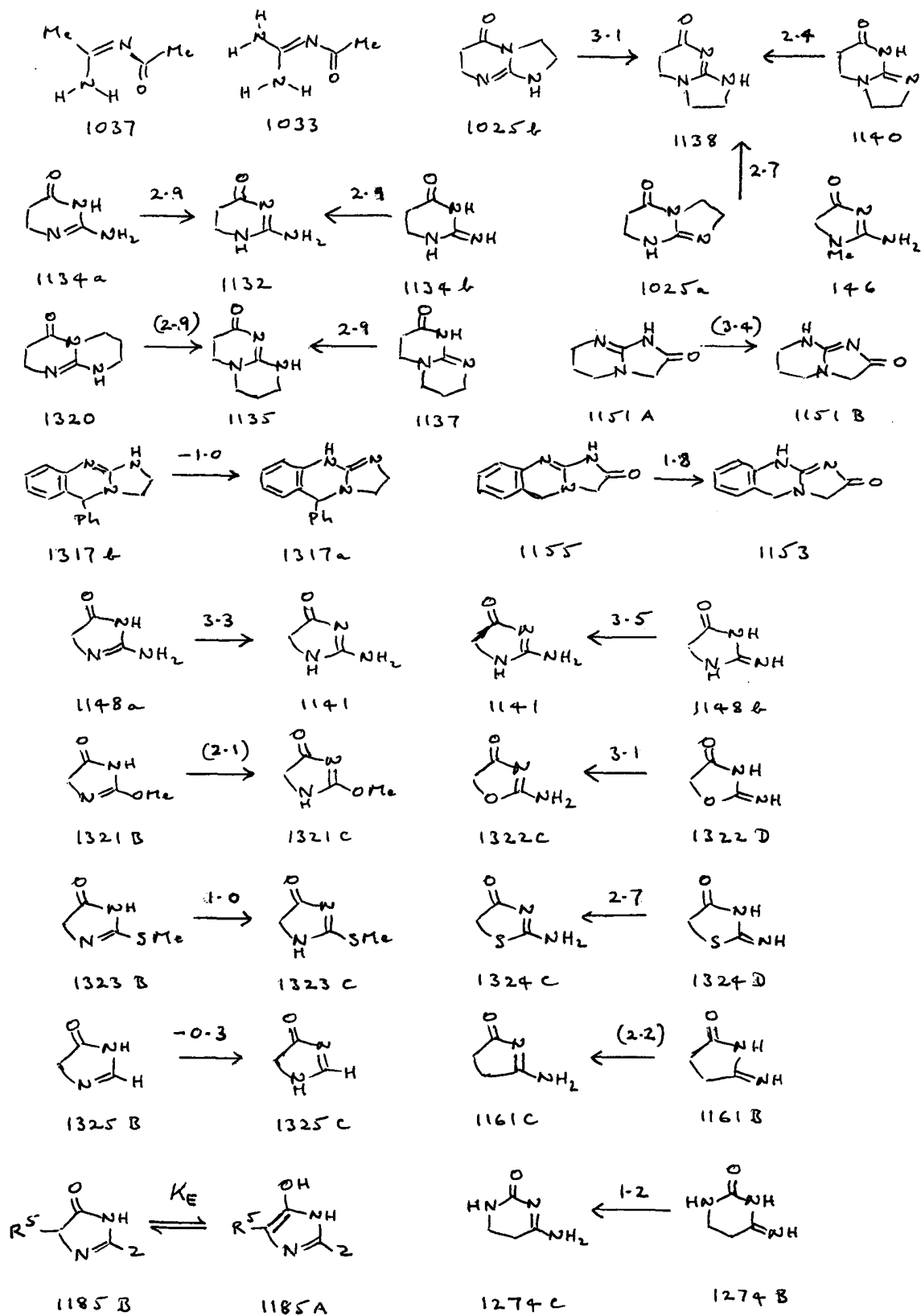
For alicyclic compounds most available quantitative evidence is based on phenyl (benzofusion) or (ring) carbonyl as substituents. For the former, we start from the prediction of  $\log K_T$  1.4 - 1.7 for phenylguanidine in Table 62 (section B.4.2) and consider the bicyclic ringfused guanidines of Scheme 58, on which  $\log K$  values appear where known. The above value is echoed by  $\log K$  1.44 for **1316a**  $\rightarrow$  **1316b** but for **1317a**  $\rightarrow$  **1317b** it is less,  $\log K$  0.99. We attribute this difference (section B.4.2) to the preference of *endo*-C=N for 5- vs. 6-membered rings, precisely echoed by  $\log K$  -0.42 for **1025a**  $\rightarrow$  **1025b** (section B.4.1). Taken together these results suggest, both that  $\log K$  *ca.* 1.4 is correct for amidines with phenyl as substituent, and that this effect of ring size is independent of  $R^1$  in **1024** so quite general;  $\log K$  *ca.* 0.4 is then expected for **1065** (section B.4.3) whatever the nature of Z. Perhaps more surprisingly, the same value is also found for the amidine **224**, whose 'aromatic' tautomer **224a** is unimportant, at least in water (sections A.4.8 and B.8.8). Note here, however, that an electronegative 3-substituent, Z in **1318**, is likely to stabilise this tautomer to the extent of making it the major species; *cf.* **322**, section A.6.6. With allowance for such special contexts,  $\Delta \log K$  1.4 for benzofusion to an alicyclic amidine is likely to be general.

Compound **1055** (section B.4.3) is anomalous, with  $\log K$  unexpectedly low, and the problem is compounded by  $\log K$  1.3 (as here defined) for **1196**, so that insertion of carbonyl appears to *reduce* the proportion of 'through-conjugated' tautomer. There may be special problems (section B.8.4) with the endocyclic nature of both nitrogen atoms (and these are not guanidines), and the latter result is predictable on isodesmic grounds (section B.5.11), but nevertheless, no obvious explanation is forthcoming.

Since C=N like C=O is an electronegative substituent, the imidines of Scheme 59 form a bridge between amidines generally and the acylamidines considered below. There are three series (section B.7.1), all of which have been studied: *endo-endo* **1319**, *endo-exo* **1303**, and *exo-exo* combined with *endo-exo*, **1305** and **1306**. By the above analogy the ‘through-conjugated’ **a**-tautomers ought to be preferred and this is probably true for **1319** in polar solvents. Structure **1303** allows of two such forms and in general **1303a** appears to be more favoured than **1303c** as possessing two *endo*-C=N units, but **1303b** is important when R is electronegative, as for R = COMe. In none of these cases, even the last, is any one tautomer very dominant. For the potential *exo-exo* case, the situation is somewhat different. In **1305**, **1305b** is generally favoured when  $R^1 = R^2$  and this preference increases as the substituent becomes more electronegative; however for  $R^1 = R^2 = H$ , the **a**-tautomer dominates, and for bland substituents such as alkyl or aryl, there is very little difference in their stability. (The pyrrolenine **1305c** and pyrrole tautomers are never found). When  $R^1 \neq R^2$  the more electronegative substituent will polarise C=N in its direction, so that the **b**-tautomer is suppressed. Benzofusion in **1306** makes little difference, with **1306a** favoured for  $R^1 = R^2 = Ph$  in water but by a narrow margin, and **1306b** dominant in nonpolar solvents. All this forms a rational pattern but preferences are nowhere very great.

#### B.8.4 Annular Tautomerism in Acylamidines: Open-Chain and Alicyclic

For the acylguanidines **1037** and **1033**  $\log K_M$  in favour of the through-conjugated tautomer illustrated is 2.8 and 3.1 respectively (section B.4.2), or up to 3.4 after correction for non-equivalent precursors (*cf.* **1132** *vs.* **1134a/1134b**) in the latter case. There is extensive information on related alicyclic acylguanidines (sections B.5.6 and B.5.7) and this is set out in Scheme 60. Almost all  $K$  values are high, so that the through-conjugated tautomer is very dominant wherever this structure is possible. Creatinine **146** (section B.5.7) is the ring NMe derivative of **1141** and possesses the same  $K_M$  value. The fractional lowering of  $K_M$  in **1140**  $\rightarrow$  **1138** relative to **1137**  $\rightarrow$  **1135** is consistent with the preference for *endo*-C=N in 5- *vs.* 6-membered rings ( $\Delta \log K$  0.4) noted above, and this may be one factor that increases  $K_M$  for **1141** *vs.* **1132**. By contrast, fusion with a 6-membered alicyclic ring has no effect on  $K_M$  for **1137** *vs.* **1134b** and we presume below the same to be true for **1151** (see Table 69, section B.5.6). The mean of all eight experimental values,  $\log K_M$   $2.9 \pm 0.3$ , is slightly below  $\log K_M$  for acetylguanidine **1033**, consistently with the avoidance of lone pair repulsion in the latter. With the exception of *N*-oxide formation, it is difficult to think of any form of substitution that could seriously upset these tautomeric preferences while retaining a stable structure.



Scheme 60

Additivity may be tested for **1155**  $\rightarrow$  **1153** (section B.5.7). Given  $\log K$  -1.0 for **1317b**  $\rightarrow$  **1317a** (section B.4.2), and assuming  $\log K$  3.4 for **1151** as indicated above,  $\log K$  2.4 may be estimated in favour of **1153** where 1.8 is found. However, while the above correction should handle any effect of ring size on  $\Delta \log K_M$  for C=N it does not necessarily allow for the difference between the electron donor properties of aliphatic NH in **1151B** and aromatic NH in **1153** towards carbonyl, which would be expected to act in this direction (Table 2). It is possible that unconsidered changes in bond length or angle also contribute. A resulting fall in  $K_M$  by  $\Delta \log K$  0.6 does not seem unreasonable.

With the exception of **1274** all results for other than guanidines involve carbonyl in a 5-membered ring, and here a clear distinction between the effect of *endo*- and *exo*-substitution appears. Whereas the order of effectiveness in promoting  $K_M$  is NR > O > S > C (or H) in either case, as is consistent with their  $\pi$ -donor order, *exo*-substitution has a far more variable effect, ranging from  $\log K_M$  -0.3 for H to 3.3 for NH<sub>2</sub>. If a parallelism is postulated between these series, and the  $K_M$  values for **1141**, and for **1324** vs. **1323**, are used to derive a 'two-point correlation,' the values deduced for **1321** (using **1322**) and **1161** (using **1315**) result. There is no check on the first, but  $\log K_M$  1.2 is found for **1274** (section B.5.15) and a higher value than this is expected for **1161** since (a) its ring is 5-membered, (b) its carbonyl group should be more electron-withdrawing ( $\sigma_R$  is 0.12 and 0.25 for CONH<sub>2</sub> and COMe respectively). Here (a) probably accounts for  $\Delta \log K_M$  *ca.* 0.4 and it is not unreasonable to suppose that (b) could account for the remainder. (These comparisons *assume* that the values displayed in Scheme 60 will not be affected appreciably by 5,5-dialkyl or 5,5-diaryl substitution, for which there is some evidence: sections B.5.9 and B.5.10). If the values deduced are correct, NH (or NR) on its own is a better  $\pi$ -donor *exo* than *endo* by *ca.* 2.5 log units, while any  $\pi$ -donor is three times more effective in this position (*vide* Tables 70 and 71, sections B.5.9 and B.5.10). It is generally accepted that *trans*-conjugation is superior to the *cis* variety, and these results provide striking confirmation. Whether the same applies to 6-membered rings is unknown, but on the evidence of **1037** and **1033** it may be that chelates, as generally preferred when possible for open-chain structures, follow different rules. It is tempting to suppose that these results throw light on the near-equal stability of the annular tautomers in 4-pyrimidone (see below) but other explanations are possible (section B.5.11). There are puzzles here that are yet to be resolved.

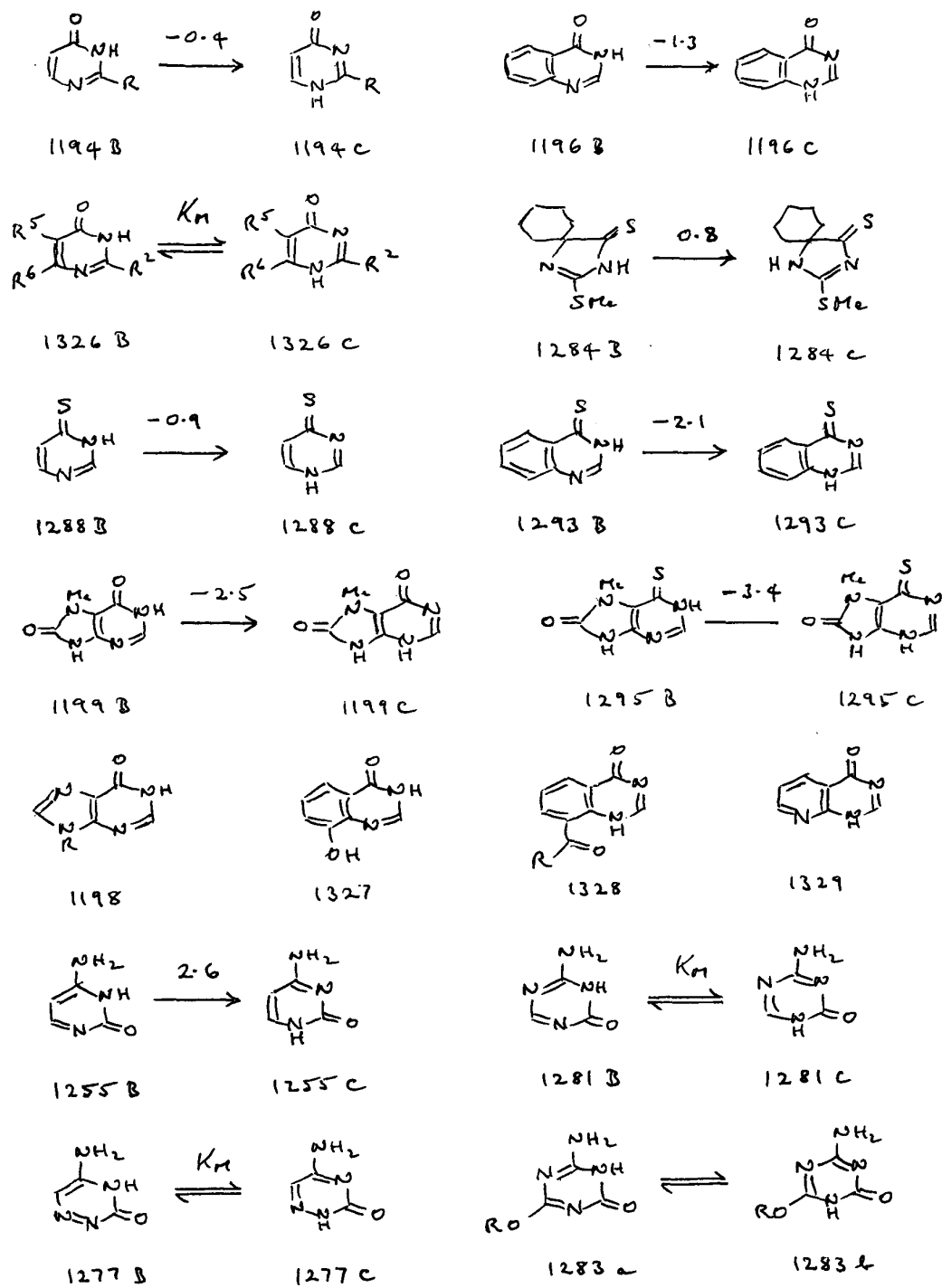
There is another problem with some of these 5-membered ring oxoheterocycles which properly belongs elsewhere, and indeed is discussed in section A.2.8 (with a summary in section B.5.10). This is enolisation as shown for **1185**. Its importance depends on two main factors: the aromaticity of the

resulting heteroaromatic, probably falling in the *endo*-substituent order  $S > N \gg O$ ; and the  $\pi$ -donor strength of both *endo*- and *exo*-substituents, which as it rises, will stabilise the oxo-form(s). The resultant of these conflicting tendencies appears to be that acylguanidines are never at risk of enolisation (the proportion of enol in creatinine **146** probably does not exceed  $10^{-5}$ ), whereas the replacement of nitrogen by a poorer  $\pi$ -donor increases that likelihood more for *exo*- than for *endo*-substitution. In practice it will probably be a serious possibility, in water, only when the *exo*-substituent is not a  $\pi$ -donor at all and there is a 5-substituent capable of stabilising  $C=C$ : *e.g.* **1185A**,  $R^5 = Z = Ph$  which is one likely example. However, there is a third factor which has not been explored, and that is the replacement of  $C=O$  by  $C=S$ . We have provisionally estimated this, in the context of 5-membered ring heterocycles, as likely to promote enolisation by a factor of *ca*  $10^{3.5}$  (section A.3.7), and a shift in tautomeric balance of this order might put far more structures than those suggested above at risk.

#### B.8.5 Annular Tautomerism in Aromatic Acylamidines

Results for 4-pyrimidone, its fused derivatives and its thiono-equivalents, are summarised where known in Scheme 61. Aromatisation would be expected sharply to reduce the difference in stability between the **B**- and **C**-tautomers, since aza-nitrogen *e.g.* in **1194B** may now be regarded as part of a vinylogous conjugated system comparable in stability to that of **1194C** (section B.5.11), though it is perhaps surprising that their relative stability should actually be reversed. Again qualitatively, the further increase in relative stability of **1196B** vs. **1196C** may be understood in terms of increased ease of deprotonation of their common cation at *N*-1 through juxtaposition of what is effectively a *N*-phenyl substituent, and can also be justified quantitatively by an isodesmic argument (section B.5.11).

Substituents at  $R^2$  in **1326** scarcely affect the value of  $\log K_M$ , which where known ranges from *ca.* -0.5 for  $R = Ph$  to *ca.* 0.0 where  $R^2$  is a  $\pi$ -donor (section B.5.11). For  $R^2 = Me$ ,  $K_M$  is virtually unchanged for a set of 5-substituents ranging from Me to CN (section B.5.12). This can be explained by the fact that  $R^2$  and  $R^5$  both lie on the axis of the two nitrogen atoms (*cf.* Katritzky's explanation<sup>290</sup> for the insensitivity of  $K_T$  to 3-substitution in 4-pyridone: section A.10.6). The effect of variation at  $R^6$  is unknown but, from the very much steeper response of  $pK_a$  to substituents in 2- than in 4-substituted pyridines, almost any substituent should stabilise the **B**-tautomer, and perhaps quite strongly so if electronegative.



Scheme 61

The replacement of C=O by C=S produces a further shift in favour of the **B**-tautomer which on the evidence of **1284** (section B.6.1) is only slight in alicyclic compounds (there  $\Delta \log K_M$  -0.2) but is more pronounced in heteroaromatic contexts. For these it lies in the range  $\Delta \log K_M$  -0.5 to -0.8 on present evidence. Despite the greater electronegativity of C=S than of C=O (Tables 48 to 50, section A.12), this points to a lesser conjugative ability of particular importance in extended structures (see subsequent discussion).

Another factor likely to affect the **B/C**-tautomer balance is intramolecular bonding and/or repulsive forces. This is seen in **1196**  $\rightarrow$  **1199** (section B.5.11) and **1288**  $\rightarrow$  **1295** (section B.6.2), where  $\Delta \log K_M$  -2.1 and -2.5 respectively can be attributed to dipolar repulsion in the **C**-tautomer (Appendix 3, which also see for evidence that non-benzenoid ring fusion has little or no effect in heteroaromatics). A similar, unquantified effect is found, *inter alia*, for inosine (**1198**, R = ribose). It is quite easy to write structures which might enhance the predominance of the **B**-tautomer, *e.g.* **1327**, or reduce or even reverse it, *e.g.* **1328** and **1329**, and these are included for their possible interest.

2-Pyrimidone (section B.5.15, *passim*) possesses degenerate tautomers but degeneracy disappears on other than 5-substitution. The only quantitative information concerns cytosine **1255**,  $\log K_M$  2.6. This strong preference clearly results from the through-conjugated part-structure of **1255C** which illustrates, as has been noted for its **C**-type aminoenone equivalent (section A.10), the strong tendency for localised conjugation to influence tautomeric form from within a more extended conjugated system. It is surprising, therefore, that **1281** is said to exist as **1281B**; perhaps this case should be re-investigated. Unequivocally, **1277** exists as **1277C**; an 'additivity postulate' prediction would result in an estimate of  $\log K_M$  *ca.* 5.5. As a final speculation we note that **1283** should most plausibly prefer the structure **1283b**, in which the stronger  $\pi$ -donor conjugates with C=O, the stronger  $\pi$ -acceptor, *via* the same localised unit as in cytosine **1255**, as seen above.

#### **B.8.6. *Endo-Exo* Tautomerism in Alicyclic and Aromatic Amidines: General**

If in **1024** (section B.4) R and R<sup>1</sup> form part of a ring, we have **1054** (section B.4.3 and Scheme 62) where one amidine nitrogen atom is *endo*, one is *exo*, and Z, which replaces R<sup>1</sup>, may be carbon or a hetero-atom. If Z is N, Z and R can be linked to form a second ring and there results a bicyclic guanidine with bridgehead nitrogen, in each of which C=N is *endo* to one ring



and simultaneously *exo* to the other. (If  $Z \neq N$  any bicyclic structure must involve two *endo* nitrogen atoms as for many of the compounds in Scheme 60). Either ring or both may be aromatic. All these situations are of practical importance and will unfold in the sub-sections that follow.

For monocyclic compounds the alicyclic case is relatively trivial since these differ from open-chain compounds only to the extent that ring size effects may enter. The evidence (section B.4.3) is that, in compounds of type **1065** (Scheme 58), **1065b** is preferred over **1065a** by  $\log K$  ca 0.4 (see section B.8.3). This implies either  $\log K_M$  0.0 and -0.4 to give **1330D** and **1331D** respectively, or two other values to give this difference. The first postulate is simpler, fits with the belief<sup>150</sup> that there should be no tautomeric preference in 6-membered ring alicyclic amidines, and in the absence of experimental evidence, we shall assume it in the following.

Evidence as to the effect of R in **1054** is limited. If R = Ph, *exo*-C=N should predominate; (**1058**, Z = O or S) exists mostly as **1058b** and so does its 5-membered ring analogue, *pace* a misleading interpretation by the authors (section B.4.3). Consistently, **224c** is the predominant tautomer of **224** (section B.8.3). The investigators of **1064** were unable to decide on tautomeric preference and postulated a mixture, which would not be surprising given that both nitrogen atoms effectively carry a phenyl substituent (section B.4.3). The acylguanidine **1115** is preferred as this tautomer by  $\log K_M$  ca. 2.7 (section B.5.2), less than that for acetylguanidine itself (B.8.4) by about the margin expected for the effect of losing *endo*-C=N as present in the rival tautomer. Interestingly, **1080B** is disfavoured by only  $\log K_M$  ca. -1.5 (section B.4.4), much less than expected for a truly aromatic ring (*vide* section B.8.7); it more resembles **224** for example,  $\log K_M$  -1.4, where neither **224b** nor **224c** is aromatic.

When the ring in **1054** is aromatic, then to a greater or lesser extent, aromaticity is lost in generating **1054b** and this becomes strongly disfavoured. Even a highly electronegative *exo*-substituent R may be unable to convert **1054b** into the predominant tautomer. Sections B.8.7 and B.8.8 explore this situation.

### B.8.7 *Endo-Exo* Tautomerism in 6-Membered Ring $\alpha$ -Amino-Heteroaromatics

Compounds for which tautomeric preference is known (as R = H; section B.4.4) are shown as the dominant tautomer in Scheme 62, with in addition the

**B**-forms of **1066**, **1073** and **1333**, in the last two cases to emphasise their disfavoured quinonoid form. This Scheme covers almost all possible monoamino-heterocycles plus **1075**, though for **1074** and **1078** the dominant form is unknown, while for **1076** the evidence has been judged equivocal. Some trends are apparent, such as more positive values of  $\log K_M$  on benzofusion and the contrary effect for the quinonoid tautomers of **1073** and **1333**, both familiar from the parallel oxoheterocycles (section B.2.5). An overwhelming preference for the amino-tautomer (**A**), long known, is the outstanding feature of these results. On the evidence of **1310** (section B.7.2; see Scheme 62) the imino-derivatives of diaminoheterocycles will be disfavoured only a little less than those of the related monoamines; cf. **1077** and **1309**, Table 80.

**Table 80. Tautomeric Preference in Water for 6-Membered Ring  $\alpha$ -Amino-Heterocycles**<sup>a</sup>

Compound	$\log K_M$ <sup>b</sup>	$\log K_M$ <sup>c</sup>	Tautomer <sup>d</sup>	Notes
<b>1066</b>	- 6.5	- 7.0	<b>A</b>	
<b>1067</b>	- 4.6	- 4.8	<b>A</b>	
<b>1068</b>	- 4.1	- 2.8	<b>A</b>	
<b>1069</b>	- 3.1	> - 3.9	<b>A</b>	
<b>1070</b>		- 10.5	<b>A</b>	
<b>1071</b>		- 8.5		Not investigated
<b>1072</b>		- 4.1	<b>A</b>	
<b>1073</b>	- 9.0	- 8.1	<b>A</b>	
<b>1074</b>		0.5		Not investigated
<b>1075</b>			<b>A</b>	
<b>1076</b>				Uncertain
<b>1077</b> <sup>e,f</sup>	- 7.5		<b>A</b>	
<b>1078</b> <sup>e</sup>				Not investigated
<b>1079</b>			<b>A</b>	
<b>1309</b> <sup>e</sup>	- 6.5		<b>A</b>	
<b>1332</b> <sup>e</sup>				?
<b>1333</b>		- 10.7		?

<sup>a</sup> Scheme 62. <sup>b</sup> Measured values (sections B.4.4 and B.7.2). <sup>c</sup> Calculated from eqn. (lxxxix); see the text. <sup>d</sup> Reported qualitative structure. <sup>e</sup> There is no common cation for the tautomers of the corresponding oxoheterocycles, so that eqn. (lxxxix) cannot be used in these cases (but see section B.5.12). <sup>f</sup> Also **1307**.

In **1073** the **B**-tautomer is strongly disfavoured despite relief of lone pair repulsion because of its quinonoid structure, and where the latter is not present the balance is likely to come much closer to parity, as for **1074** (Table 80). In less aromatic systems, predominance of the imino-tautomer may then result; see section B.8.2 for **1279** (Scheme 57) which provides an instructive example.

$$\log K_M = 2.2 \log K_T - 14.7 \quad (\text{lxxxix})$$

$$\log K_M = 1.8 \log K_T - 13.2 \quad (\text{cix})$$

The very rough ( $r^2 = 0.84$ ) relation of eqn. (lxxxix) for five of these heterocycles (see Table 80) may be used to predict  $\log K_M$  for an imino-heterocycle when  $\log K_T$  for the corresponding oxoheterocycle is known, and these calculations are included in the Table. With  $s \pm 1.0$  the results can only be suggestive, but are nevertheless of interest. Among the 'unknowns' the most negative values are anticipated for **1070** and **1071**, in which an electronegative aza-nitrogen makes the oxo-tautomer less than usually dominant, and the least negative for **1072** and **1074**, in which lone pair repulsion in both series provides the driving force. In fact the most intriguing prediction here is that for **1074**, with the additional factor of benzofusion in play, the amino- and imino-tautomers may be roughly in balance. Evidence on this point is lacking. A parallel equation to (lxxxix), eqn. (cvix), in which we have used presumed values of  $\log K_T$  7.6 for 2-pyrrolidinone (section B.2.3) and  $\log K_M$  0.0 for (**1330**,  $Z = \text{CH}_2$ ) to provide an additional point, gives generally similar results but with  $\log K_M$  -0.8 for **1074** (much the largest difference, since its  $K_T$  value is the largest for any simple oxoheterocycle). Whichever tautomeric form **1074** takes, it seems extremely probable that any reasonably electronegative *exo*-substituent should convert it to the *exo*-imino tautomer. And while no calculation is possible for **1076**, the equivocal nature of the evidence in this case, noted in Table 80, may indicate that this too represents a borderline case, if so plausibly through operation of the same structural factors.

$$\log K_M = 12.15 \sigma_I - 6.4 \quad (\text{xcii})$$

The effect of substituents **R** in **1066** has been studied quantitatively (section B.4.4) and leads to eqn. (xcii). As (almost) always for amidines, this is a clean relation in  $\sigma_I$ . It predicts a crossover between major tautomers corresponding roughly to  $R = \text{SO}_2\text{Me}$  (where both are visible) or  $\text{COCF}_3$ , with only  $\text{CN}$  and  $\text{NO}_2$  among common substituents giving predominantly **1066B**.

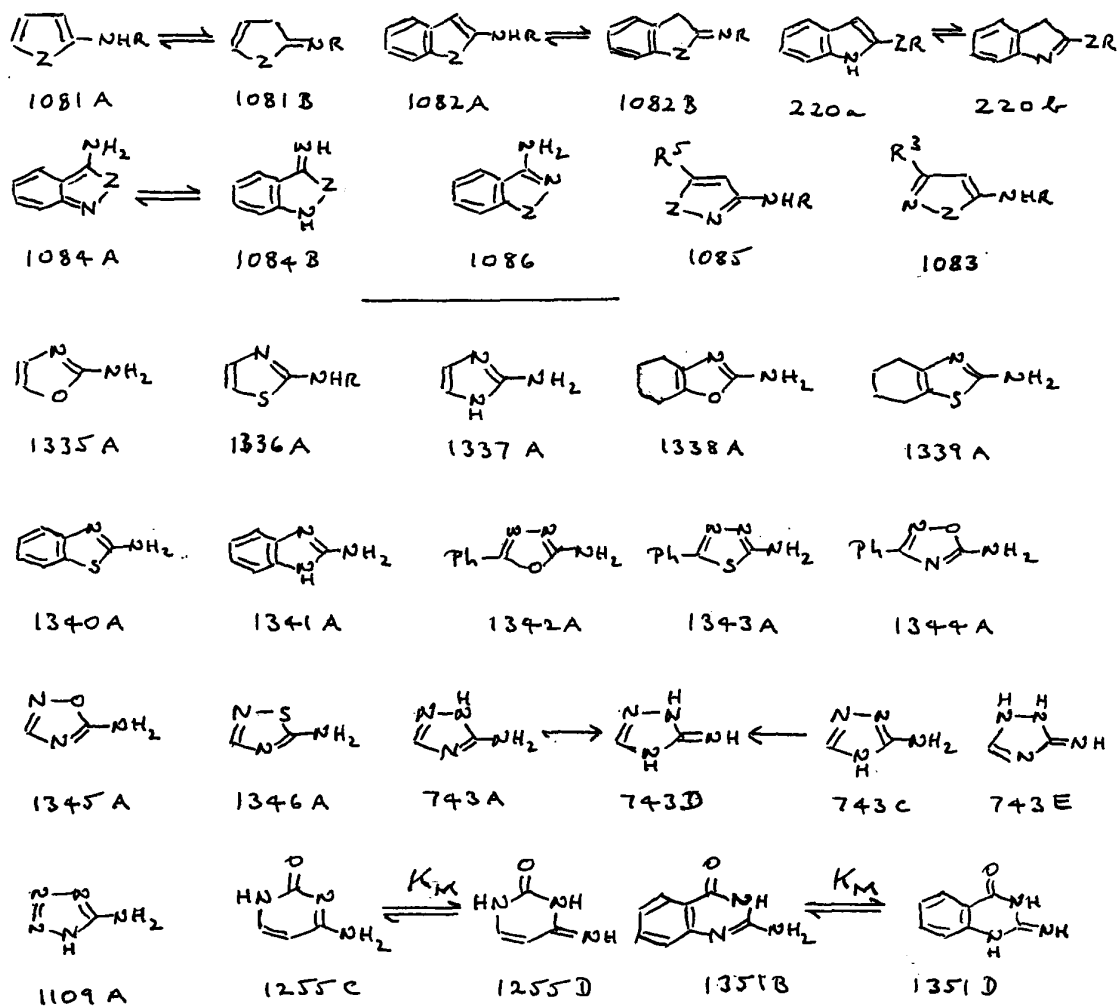
In the absence of other equations it is impossible to predict the outcome for other heterocycles, and the task is made no easier by  $\rho_r \sim 2.5$ , notably greater than 2.0 for simple amidines and plausibly a consequence of molecular asymmetry. However, heterocycles with less negative  $\log K_M$  values for the parent amino-derivative (in principle the equation's intercept term) will clearly be more likely to give the **B**-tautomer, examples including benzofused heterocycles such as **1068** and **1069** or, according to calculation, **1072** and **1074**, and possibly **1076**. The very high  $\rho_I$  value of eqn. (xcii) is close to that for open-chain guanidines (section B.4.2), and in conjunction with the results summarised in section B.8.8 below, suggests that  $\rho_I > 10$  may be the norm for this type of tautomerism.

Another set of data concerns those reported for **1334** (section B.5.15) in which  $\log K_M$  values of -4.1, -1.5 and 1.1 were obtained for  $R = H$ ,  $NH_2$  and  $OH$  respectively. These  $\Delta \log K_M$  values of 2.6 for  $R = NH_2$  and 5.2 for  $R = OH$  compare with 2.1 and 2.9 as calculated from eqn. (xcii) and imply a much larger  $\rho_I$  value for **1334**. Given  $\sigma_I$  values of 0.17, 0.24 and 0.30 for  $R = NH_2$ ,  $OH$  and  $COMe$ , the last should exist as **1334D** yet apparently it does not. No explanation is forthcoming. These results are disquieting in that they do not fit the pattern, so far found elsewhere, of straightforward  $\sigma_I$  dependence for amidines, and quantitative data for (**1334**,  $R = COMe$ ) would be desirable.

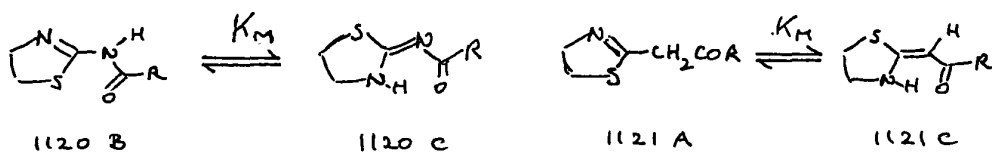
Some other results are equally difficult to understand. For **788** and **755**,  $\log K$  -2.0 and -1.0 is found (sections B.1.7 and B.1.6 respectively), so that **788b** and **755b** are preferred in water despite their quinonoid structure and the additional factor of lone pair repulsion in the latter case. Since the **a**- and **b**-tautomers are both in some sense iminoquinazolines (*cf.* **7**, Introduction, for a distant analogy), there is probably less energetic difference between them than at first sight might appear, but it is nevertheless surprising that the preferred tautomers are the ones in which, *prima facie*, greater aromaticity has been lost.

#### B.8.8 *Endo-Exo* Tautomerism in 5-Membered Ring $\alpha$ -Amino-Heteroaromatics

As a class these differ from B.8.7 above in that resonance energies are lower and, for the simple  $\pi$ -excessives, can be so low as to offer little resistance to *exo*-imine **1054b** formation, especially when benzofused. For example, (**1081**,  $Z = S$ ,  $R = H$ ) exists as the **A**-tautomer but the position for (**1081**,  $Z = O$ ,  $R = H$ ) is equivocal, and while (**1081**,  $Z = NH$ ) gives **1081A** when  $R = H$ , it switches to **1081B** when  $R = Ph$ . These results are consistent



Scheme 63



Scheme 51

with the known resonance energy order, for the parent heterocycles, of pyrrole > thiophene >> furan (Table 12, section A.2.6). On benzofusion, if as in **1082**  $Z \neq \text{NH}$  the **A**-tautomer is generally preferred, but if  $Z = \text{NH}$  a third tautomer becomes possible and for **220** when  $Z$  is a  $\pi$ -donor, the dominant tautomer is **220b**. This type of structure is unknown for **1081**; it is important for **220** because conjugation of  $\text{C}=\text{N}$  with the benzene ring over-rides residual aromaticity. Inevitably, all these are examples of C-type tautomerism but are considered here for the sake of completion.

If aza-nitrogen is present, resonance energy increases sharply; for pyrrole and imidazole, it is 8.5 and 15.4 kcal mol<sup>-1</sup> respectively (Table 12; *cf.* 34.2 kcal mol<sup>-1</sup> for pyridine). A further consequence is that the replacement of  $\text{CH}_2$  by N makes C-type tautomerism redundant. Dipole-dipole repulsion is another important factor: when  $Z$  and N are contiguous, even the quinonoid structure of **1084A** appears to be preferred. This is reasonable. Given a penalty of  $\Delta \log K$  2.5 – 3 from this cause for  $Z = \text{NR}$  in  $-\text{NHZ}-$ , (Appendix 3), an opposing penalty of  $\Delta \log K$  *ca.* 1.7 for its quinonoid structure should still leave **1084A** with a net advantage, as is found. However, if  $Z = \text{NH}$  in **1084** a switch can take place, and does, to (**1086**,  $Z = \text{NH}$ ) which avoids the need for a quinonoid structure. It is extremely probable that compounds of types **1085** and **1083** will exist exclusively as the amino-tautomer shown almost regardless of the nature of R, less the result of preserving resonance energy than of dipolar repulsion as in **1084B**. Consistently, the corresponding oxoheterocycles are the most likely of any category to exist largely or predominantly as the hydroxy-tautomer (section B.2.10).

$$\log K_M = 2.38(0.42) - 19.83(1.16) \sigma_I \quad (\text{ciii})$$

$$(n = 5 \quad r^2 = 0.990 \quad s = 0.19 \quad F = 293)$$

If  $Z$  and N are not contiguous and the *endo* and *exo* aza-nitrogen atoms form an amidine-type arrangement, we have the compounds (except **1255** and **1351**) of Scheme 63. As in **1054** (Scheme 62),  $Z$  may be O, S or NR and a number of  $K_M$  values are available. Qualitatively, these form sets in which, generally,  $\log K_M$  becomes more negative in the sequence  $\text{NR} < \text{S} < \text{O}$ , though there is some evidence that, when  $Z$  is contiguous to one aza-nitrogen, this sequence changes to  $\text{S} < \text{NR} < \text{O}$ , *i.e.* the electronegativity order. Quantitatively, five of these compounds – **1336** - **1339**, and **1109** – give eqn. (ciii). This confirms that *exo*-imine formation is steadily more disfavoured as

ring electronegativity increases, a trend also discernible, though it cannot similarly be quantified, in the 6-membered ring heterocycles of Table 80. We express its rationale in terms of Scheme 51 (section B.5.14): as the ring becomes more electronegative it increasingly benefits from the presence of  $\pi$ -donor substituents, which C-NHR is but C=NR is not. It is tempting to use equation (ciii) to derive ‘missing’  $\sigma_I$  or  $\log K_M$  values for some of the compounds in Table 81. It is important to note that this relation breaks down for benzofused species such as **1340** and **1341**, for which benzofusion acts as an independent influence on  $K_M$ , and is unlikely to apply to heterocycles such as **1083** in which no amidine unit is present; it may also fail for compounds such as **1085** in which Z is not part of the conjugated unit. With these caveats, it may be useful for predicting  $K_M$  as more  $\sigma_I$  values become available. Equation (ciii) can be re-expressed as Figure 5; its intercept at  $\log K_M = 0$ , corresponding to  $\sigma_I \sim 0.12$ , refers nominally to substitution at the carbon atom of unconjugated C=N in a 5-membered alicyclic ring, but unfortunately no values for simple C=N exist with which it can be compared.

$$\log K_M = 10.65 \sigma_I - 4.2 \quad (\text{xcv})$$

**Table 81. Log  $K_M$  Values for Amidine- and Guanidine-type 5-Membered Ring  $\alpha$ -Aminoheterocycles<sup>a,b</sup>**

Compound	$\sigma_I^c$	$\log K_M^{d,e}$	Compound	$\sigma_I^c$	$\log K_M^{d,e}$
<b>1335A</b>	0.38	(- 5.2)	<b>1344A</b>	(0.45)	- 6.5
<b>1336A</b>	0.34	- 4.5	<b>1345A</b>	0.49	(- 7.4)
<b>1337A</b>	0.27	- 3.1 <sup>g</sup>	<b>1346A</b>	0.41	(- 5.7)
<b>1338A</b>	0.35 <sup>h</sup>	- 4.3	<b>743A</b>	(0.44)	- 6.3 <sup>i</sup>
<b>1339A</b>	0.31 <sup>h</sup>	- 3.7	<b>743C</b>	(0.40)	- 5.5 <sup>i</sup>
<b>1340A</b>	0.37	- 4.0	<b>1109A</b>	0.49	- 7.4
<b>1341A</b>	0.32	- 2.3	<b>1255C</b>		- 4.1 <sup>j</sup>
<b>1342A</b>	(0.40)	- 5.5	<b>1351B</b>		- 4.7 <sup>k</sup>
<b>1343A</b>	(0.40)	- 5.5			

<sup>a</sup> Scheme 63. <sup>b</sup> Bracketed values are obtained by calculation, in either direction, from eqn. (ciii).

<sup>c</sup> For heterocycle at point of amino-substitution; ref. 96. <sup>d</sup> For *exo*-imino formation from species listed. <sup>e</sup> From sections B.4.5 and B.5.14. <sup>f</sup> R = H. <sup>g</sup> Assumes  $\Delta \log K_M$  - 0.5 relative to **1341** as is found for **1336** vs. **1340**. <sup>h</sup> Assumed equal to that for the 4,5-dimethylated heterocycle (ref. 96). <sup>i</sup> Speculative; see discussion in section B.4.5. <sup>j</sup> Experimental (section B.5.14).

<sup>k</sup> Provisional deduction (section B.5.11).

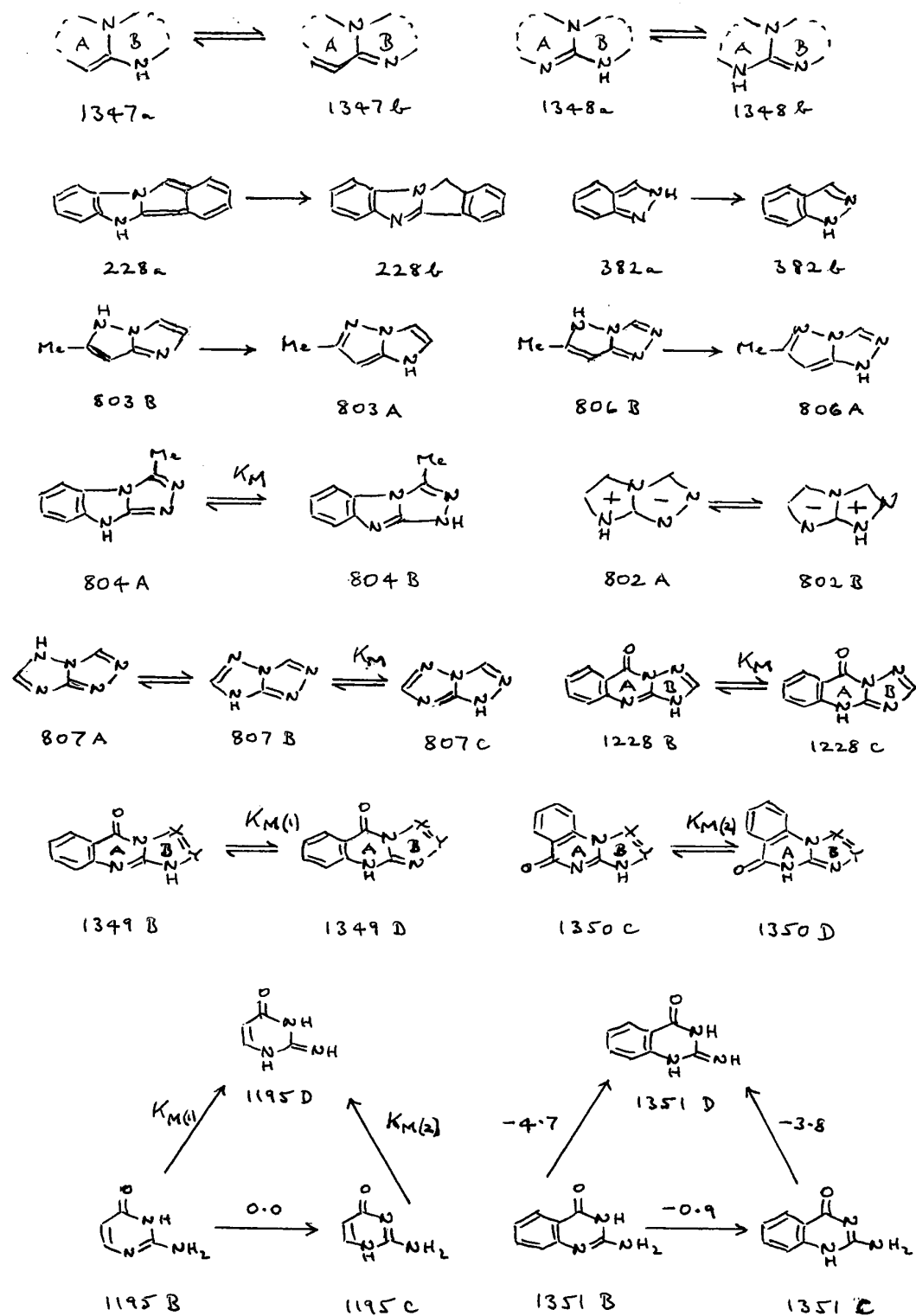
Only **1336** has been investigated for the effect on  $K_M$  of *exo*-amino substituents, and this resulted in eqn. (xcv). As for the 2-aminopyridines (section B.8.7) this is a clean relation in  $\sigma_I$  and its  $\rho_I$  value is not greatly different. Because the intercept term is less negative its crossover point is lower, at  $\sigma_I$  *ca.* 0.39, so that not only will CN, NO<sub>2</sub>, SO<sub>2</sub>R and COCF<sub>3</sub> be electronegative enough to generate a large or predominant fraction of the *exo*-imino tautomer, but CF<sub>3</sub>, NO and OPh should also be capable of this, though OMe, SMe and simple acyl groups should not. Again note that  $\rho_r = 2.2$  is greater than the 'basal' value (2.0).

These quantitative studies are complemented by a qualitative survey of the relative electron-withdrawing ability, in this context, of various acyl derivatives -COR (section B.5.4). Most -COR groups cover a relatively narrow range of  $\sigma_I$  values but, when  $\rho_I$  is large, these small differences become important and can reveal subtleties which otherwise would remain undetected. By extensive cross-comparison we find a consistent sequence, in terms of raising  $K_M$ , of COCF<sub>3</sub> > COCCl<sub>3</sub> > COCHCl<sub>2</sub> > CPh, COMe > CO<sub>2</sub>R. A gap typically of  $\Delta \log K_M$  1.3 - 1.5 lies between COCCl<sub>3</sub> and COCHCl<sub>2</sub>, with probably  $\Delta \log K_M$  2.5 - 3.1, depending on  $\rho_I$ , between COCF<sub>3</sub> and COMe. A further fall of around  $\Delta \log K_M$  0.5 lies between COAlk and CO<sub>2</sub>Alk. This is very much the same sequence as that for the equivalent aminoenones – compare *e.g.* **1120** and **1121**, section B.5.3 – and provides an important point of contact between 'C-type' and 'N-type' tautomerism. However this parallelism does not extend to other sorts of electronegative substituent, such as CN and NO<sub>2</sub>. We shall develop this theme further in Section C.

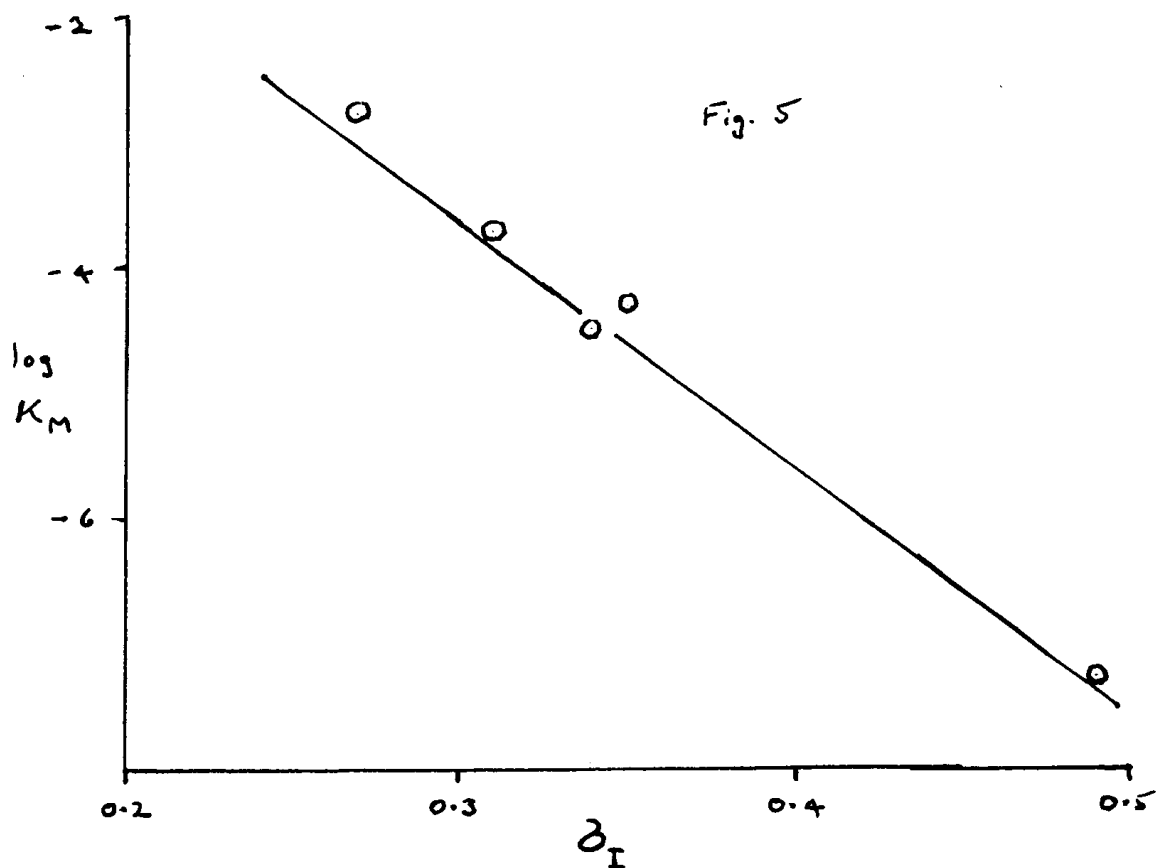
### B.8.9 Annular Tautomerism in Bicyclic Heterocycles possessing Bridgehead Nitrogen

Bridgehead nitrogen has been encountered in the bis-alicyclic guanidines and acylguanidines of sections B.8.3 and B.8.4 (Schemes 58 and 60 respectively), but here one ring or (usually) both is aromatic. There are two main categories, amidines **1347** and guanidines **1348**, whose tautomerism we define as shown.

Elguero<sup>176</sup> has enunciated four qualitative 'rules' for establishing the direction of tautomeric preference, primarily in 'azapentalenes' (5,5-ringfused heterocycles: section B.1.9) but with application elsewhere. One of these, concerning the avoidance of quinonoid forms, usually results in partial loss of conjugation as in **228b** (section A.4.8) when bridgehead nitrogen is involved, though otherwise this is not a necessary consequence; *cf.* **382**, sections A.9.2 and B.8.1 above. Tautomerism as in **228** is 'C-type' (imine-enamine) and will not be considered further here.



Scheme 64



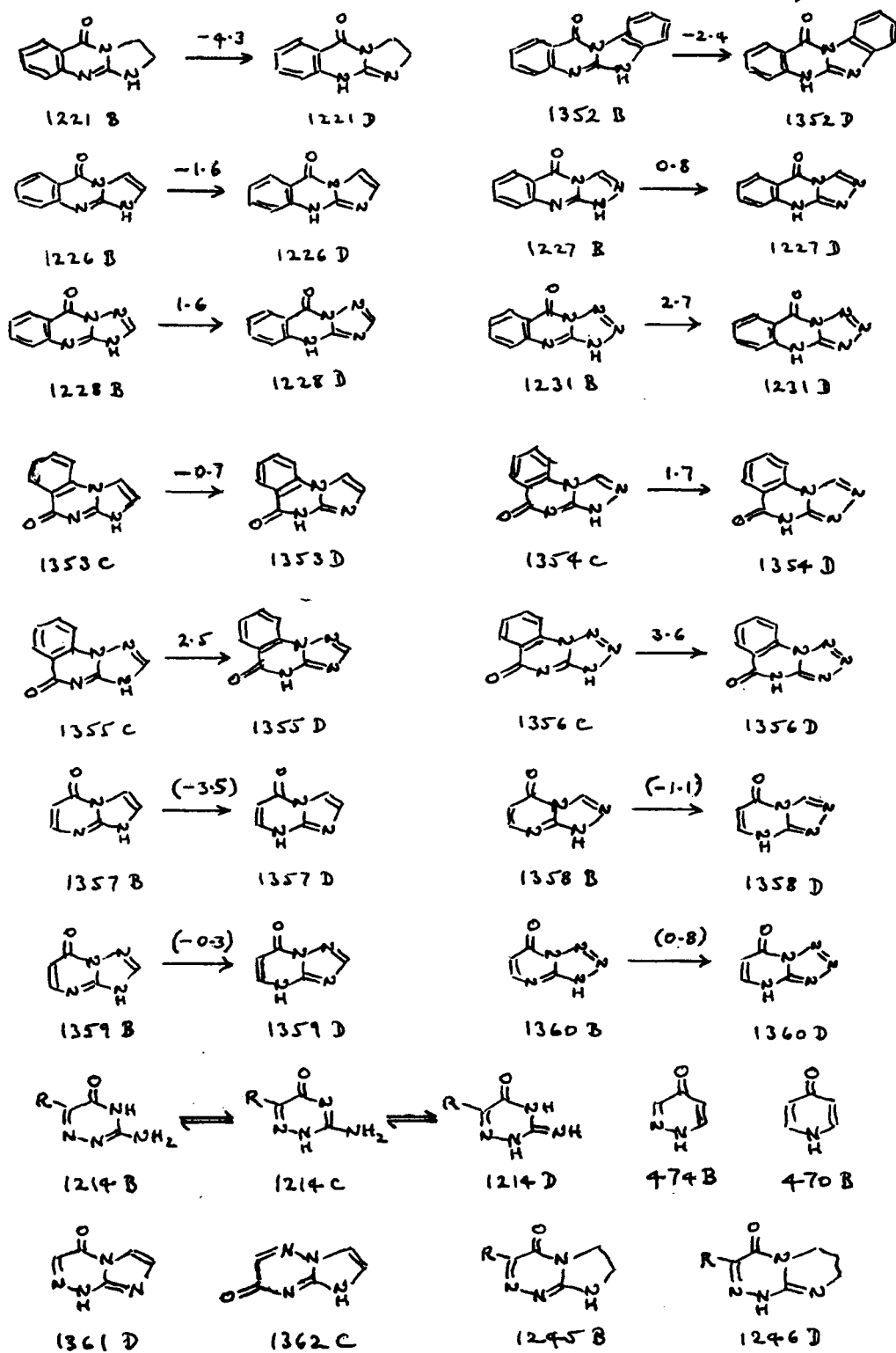
For bicyclic guanidines, it should be possible to replace Elguero's remaining 'rules' by an approach based on eqn. (ciii). In **1348** (Scheme 64), each alternative combines the favoured amino-tautomer for one ring with the disfavoured imino-tautomer of the other. Qualitatively, the more electronegative ring should in all cases dictate tautomeric form, leading to **1348a** if this is ring A and *vice versa*. Since the 'basicity' criterion (e.g. **802A** > **802B**) is in part determined by lone pair and dipolar repulsion this effectively combines all three 'rules' and we are inhibited from its quantitative application only by ignorance of the rival  $K_M$  values. If these are supposed to be approximated by the  $K_M$  values of each unit in isolation (Table 81), we may attempt a semi-quantitative approach. In **804** for example, employing **1341** and **743** as models we may regard **804A** and **804B** as disfavoured by  $\Delta \log K_M$  -2.3 and -5.5 respectively, leading to a putative  $\log K_M$  -3.2 overall, *i.e.* a strong preference for **804A**. It is important to note that repulsive forces *in water* are built into the  $K_M$  values of Table 81; in dioxane, where lone pair repulsion is plausibly much more important, **804** exists 98% as **804B** (section B.1.9). And even in water **807C**, the dominant tautomer of **807**, should be favoured over **807B** only by  $\log K_M$  *ca.* 0.8 (*cf.* **1227** and **1228** below). However there are presently two main gaps in this approach. Data on the quantitative aspects of dipole-dipole repulsion are very much lacking; **743D** (Scheme 63) will certainly be disfavoured relative to **743E**, hence **807A**

relative to **807B**, but by what margin (we suspect a large one) is unknown. Secondly, nothing is known concerning tautomeric preference for the B-ring in bicyclic amidines of type **1347**, which places, *e.g.*, **803** and **806** out of range. So far, therefore, the application of this simple but comprehensive approach to the above class of compound is limited.

However, it has immediate potential elsewhere. Compounds such as **1228** are not simple fused heterocycles but should obey the same rules. For **1228** we have measured  $\log K_M$  as 1.6 in water (section B.5.14) and, if  $\log K_M$  for its B-ring is presumed equal to our tentative value for **743A** (Table 81),  $\log K_M$  -4.7 for the A-ring results. We can then go on to estimate, in the case of any compound of type **1349** for which B-ring  $\log K_M$  data exist, its overall tautomeric preference  $\Sigma \log K_M$  (*cf.* Table 76, section B.5.14). For each such aminoheterocycle a better model would have been its ring *N*-acylated derivative, so that the validity of this approach depends on the assumption that any perturbation deriving from this source will roughly cancel across the series. No data exist that can be used to check this assumption but it does not have to be more than approximately correct to give at least the right preference, and we shall accept it *faute de mieux*. Given the firm value of  $\log K_M$  for **1228** it should be noted that any inaccuracy in the estimate for one ring must cancel with an equal inaccuracy in that of the other.

Given  $\log K_{M(1)}$  -4.7 for **1351** (Scheme 64) we may estimate  $\log K_{M(2)}$  as shown. This assumes the same differential in  $\log K_M$ , -0.9, as exists for the parent oxoheterocycles **1194**  $\rightarrow$  **1196**. Here  $\log K_{M(1)}$  and  $\log K_{M(2)}$  are the appropriate quantities to use for the 'linear' **1349** and 'angular' **1350** fused quinazolones respectively (Scheme 64), so that the latter should show more tendency than the former to give the **D**-tautomer. For the fused pyrimidones we have  $K_{M(2)} \sim K_{M(1)}$  (Scheme 64) but no information on either. In the distantly relevant case of  $K_T$  for the 6-membered ring oxoheterocycles we have  $\Delta \log K_T$  in the range 1 - 2 on benzofusion (sections A.10.7 and B.2.5), since benzofusion reduces the advantages of aromaticity, and a qualitatively similar result is expected in favour of the **D**-tautomer. An effect of similar magnitude here would result in  $K_{M(1)} \sim K_{M(2)} \sim 10^{-6}$  for **1195**; on closer reasoning we propose  $10^{-6.6}$  in section C.32. Whatever value obtains there should be no appreciable difference in tautomer ratio here between the 'linear' and 'angular' series.

Predictions for  $\Sigma \log K_M$  in both series of fused quinazolones in water appear in Scheme 65, along with much more tentative ones for the corresponding pyrimidones. (Predictions for 'angular' fused pyrimidones are, on the above reasoning, omitted as redundant). Only the value for **1228**



Scheme 65

is experimental but several of these predictions are supported by qualitative evidence, as for most of **1221** – **1231** and several in the ‘angular’ series **1353** – **1356** and the fused pyrimidones **1357** – **1360** (Table 76, section B.5.14). Certain needle cases could be used as quantitative checks. For example, **1226** is predicted to be out of line with the corresponding triazoles and tetrazole, and this is also true for **1357**, whereas for **1353**, and **1358** – **1360**, the tautomers may be quite closely in balance. (Note that the small difference predicted between **1227** and **1228** goes back to the tautomer ratio for **743A** to **743C**: section B.1.2). It should be possible to extend this approach to other types of bicyclic fused guanidines possessing bridgehead nitrogen (*i.e.* of structure **1348**, Scheme 64) if these become of interest.

The aminotriazinone **1214** ( $R = H$  or  $Me$ ) possesses  $\log K_M$  *ca.* 2.4 in water but the only information concerning **1214D** is that a model for it is essentially the free base at pH 7 (section B.5.13). Given  $pK_a$  values of *ca.* 4.5 and 2 for **1214B** and **1214C** this leads to estimates for the formation of **1214D** from each of these that cannot be much more negative than *ca.* -1.5 and -4 respectively. As a distant parallel to these shifts relative to **1195**,  $\Delta \log K_T$  *ca.* -3 can be estimated for **470B**  $\rightarrow$  **474B** if the effect of lone pair repulsion is neglected (Appendix 3); in each case, as is usual, an electronegative substituent stabilises the less polar tautomer. Given  $\log K_M$  *ca.* -3.1 for 2-aminoimidazole (Table 76, section B.5.14) we tentatively predict **1361D** but **1362C** as the dominant tautomers in water on ‘linear’ and ‘angular’ ring fusion respectively, their difference in tautomeric behaviour deriving from the strong preference for **1214C** over **1214B** (section B.5.13). Elsewhere this combination of lone pair repulsion (on  $K_M$ ) and ring electronegativity (on  $K_{M(2)}$ ; *cf.* Scheme 64) is expected to result in the **D**-tautomer, in the sense of **1349** and **1350** (Scheme 64), for all heteroaromatic ring fusions involving **1214**. Since  $K_{M(1)} = K_M K_{M(2)}$  and the last two terms will be affected in the same direction by solvent and most structural factors, the consequences for  $K_{M(1)}$  are cumulative and could become enormous. Even compounds resulting from alicyclic ring fusion can become borderline cases in nonpolar solvents; **1245B** but **1246D** are major but not exclusive tautomers in  $CHCl_3$  (section B.5.14). Variation in ring size can only in part account for this difference. Other such heteroaromatic ring fusions may show similar complexities but these are yet to be explored.

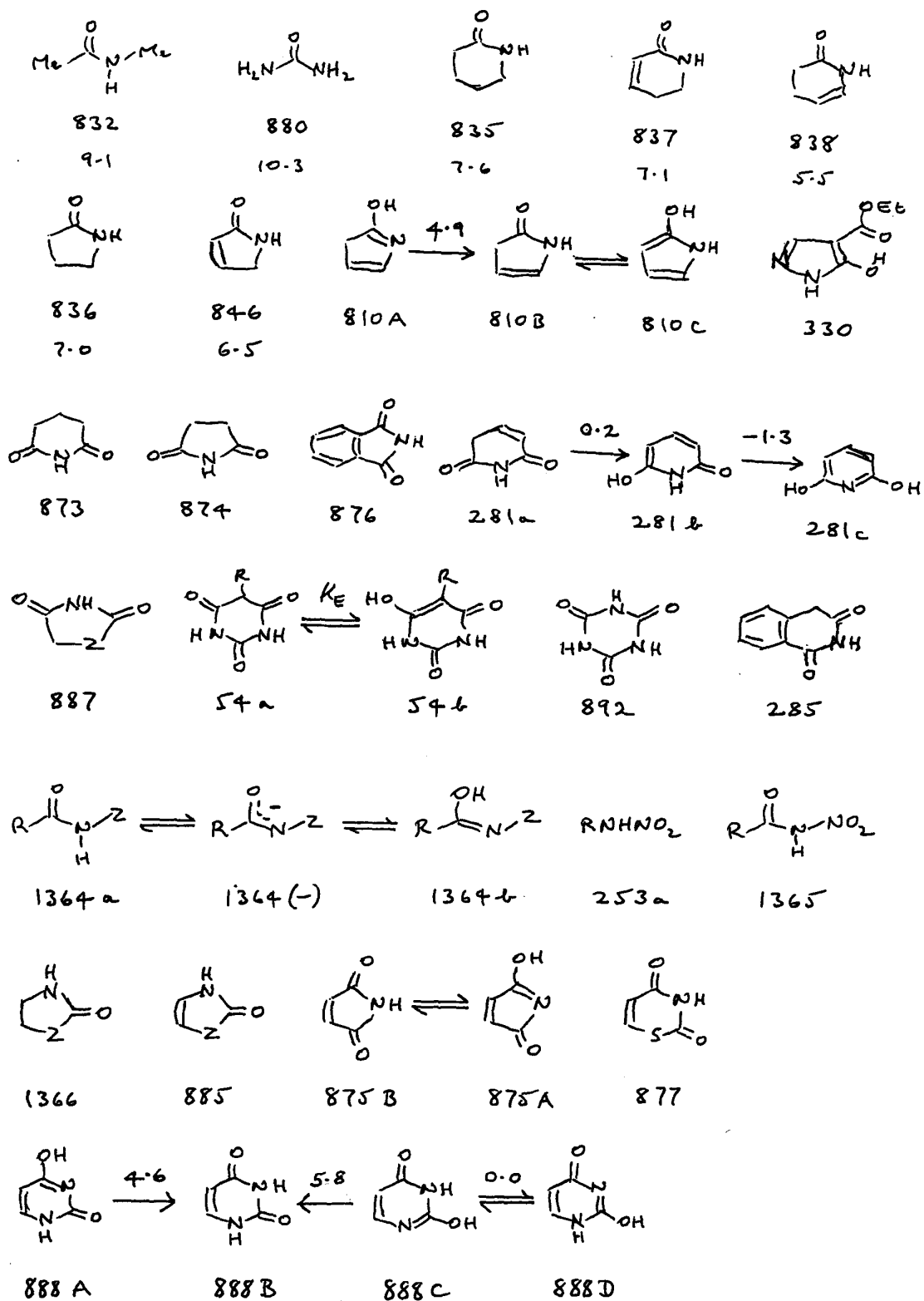
It is clear from the above that lone pair repulsion is a more serious matter for 6- than for 5-membered heteroaromatic rings. Curiously, little effect of ring size or conformation appears to be found for dipolar repulsion; *cf.* sections B.8.13 – B.8.15 below. Appendix 3 elaborates and discusses this apparent paradox.

## TAUTOMERISM INVOLVING IMINOL FORMATION

**B.8.10 The Tautomerism of Amides and Related Structures involving Contiguous NH and C=O but lacking Contiguous NHZ (Z = O, S or NR) or C=OC=O. Aliphatic Compounds**

We estimate  $\log K_T$  9.1 for *N*-methylacetamide **832** (section B.2.3) and anticipate similar values for other open-chain secondary amides. For urea **880** this preference, at  $\log K_T$  10.3, is greater but by only a small margin, probably diminished by 'resonance saturation' (a rather similar situation obtains for  $K_M$  in acylguanidines; *cf.* the two parallel series of Scheme 60). Because they necessarily exist in a disfavoured conformation (section B.2.3) lactams are expected to possess lower values of  $K_T$  (this may not be true for ureas) and isodesmic arguments can be used to estimate the values (as  $\log K_T$ ) incorporated for alicyclic compounds into Scheme 66. The estimate of  $\log K_T$  4.9 for **810** (section B.2.3) will sufficiently explain why the enolisation of 2-pyrrolidinone in this sense is unknown. However formation of **810C** involves generation of an aromatic structure and, with suitable ring substituents, this then becomes possible (section A.2.7) as in the case of **330** (section A.6.6).

Imides and acylureas come into this category. There has never been any suspicion of detectable iminol formation in open-chain imides, nor in their alicyclic analogues such as **873**, **874** or **876** (section B.2.8). However glutaconimide **281a** can partially aromatise to **281b** and by a small margin this tautomer is preferred (section A.6.3) though full aromatisation to **281c** is not; here the behaviour of OH is in line with that of other 6-substituents into 2-pyridone (section B.2.4). Since **281a** and **281b** possess different reference iminols it is unfortunately not possible to assess the relative importance of imide resonance in the first case and aromaticity in the second. Homophthalide **285** (section A.6.3) exhibits the usual effect of benzofusion in reducing the latter's importance, in that enolisation does not appear to occur. Compounds of type (**887**, Z = S or NR), which when Z = NR are hydantoins, also give no detectable enol (section B.2.9). Barbituric acids **54a** can give the enol **54b**; for R = H  $\log K_E$  is *ca.* -1.7 in water but this rises on substitution (section A.1.4), essentially through allylic stabilisation (section A.1.1). However this is 'C-type' enolisation as for **810C** and **281b** and, even for this diacylurea, iminol formation does not occur; this is also absent from its near-relative **892** (section B.2.9). It should be noted that **54b** may be regarded as a substituted uracil (see below).



Scheme 66

Like carbonyl, any other strongly electronegative substituent Z in **1364** might in principle promote enolisation to **1364b**, but this area has been little studied. In practice, however, it is probable that ionisation to **1364(-)** would take place, in water, at or below physiological pH before that point was reached, in which case the question of tautomeric form becomes irrelevant in the present context. There are few published data but EtOCONHNO<sub>2</sub> possesses  $pK_a$  3.32<sup>592</sup> whereas those for compounds of type R<sup>1</sup>CONHSO<sub>2</sub>R<sup>2</sup> are typically found in the region of  $pK_a$  5.5,<sup>106</sup> so that very little of the unionised compound is likely to be present.

### B.5.11 Unsaturated Compounds

We use ‘unsaturated’ in this context to denote compounds on the borderline of aromaticity, in which C=C links the ends of an amide-type sequence but the resulting compound cannot be considered as fully ‘aromatic.’ It has two chief contexts. The first consists in the replacement of -CHRCHR- in urea-type structures **1366** by -CR=CR- to give, in this case, **885**; in neither of these has the enol form been detected (section B.2.9). A sub-class here consists in the corresponding imide **874**, giving **875B** which should no doubt be more prone to enolisation except that the resulting enol **875A** (section B.2.8) would be anti-aromatic. In the second, a 5-membered ring expands by one carbon atom, replacing -CHR- by -CR=CR-; as an example, (**887**, Z = S) becomes **877** (section B.2.8). Detectable enolisation does not occur for either.

Imides as more electron-deficient than ureas should form iminols more readily, hence the 4-carbonyl group of an acylurea should possess a lower  $K_T$  value than the 2-carbonyl. Data are available only for uracil **888**, for which the position (section B.2.9) is set out in Scheme 66 (for **888C**  $\rightleftharpoons$  **888D**, cf. section B.5.11). The stability difference between **888A** and **888C/888D**, while in the expected direction, is surprisingly small, suggesting that different degrees of stabilisation conveyed by aromaticity may be responsible. Tentatively, we may take this argument further. Replacement of -CH<sub>2</sub>CH<sub>2</sub>- in **838** by -NHCO- to give **888B** gives an estimated  $\Delta \log K_T$  0.3 (5.5  $\rightarrow$  5.8); a similar replacement in **837** gives an estimated  $\Delta \log K_T$  -2.5 (7.1  $\rightarrow$  4.6). These correspond to iminol formation in uracil by the 2- and 4-carbonyls respectively, suggesting that if the effect of C=C is allowed for, the latter is more susceptible to iminol formation by  $\Delta \log K_T$  ca. -3. A factor of this order for the fall in  $K_T$  of an imide vs. an amide, or of the acyl group of an acylurea as in this case, does not seem unreasonable, but firm experimental evidence would be required for its acceptance.

### B.8.12 6-Membered Ring Heteroaromatics

Results for parent heterocycles ( $R = H$  throughout) and other pertinent data are set out in Scheme 67. Some of these results are based on surmises which are discussed below.

$$\begin{array}{lll} \mathbf{847}: & \log K_T(4) = 3.5 - 2.5 \sigma_m & (\text{cxi}) \\ \text{"} & \log K_T(5) = 3.5 - 3 \sigma_m & (\text{lxix}) \\ \text{"} & \log K_T(6) = 3.5 + 3 \sigma_m - 8 \sigma_I & (\text{lxx}) \end{array}$$

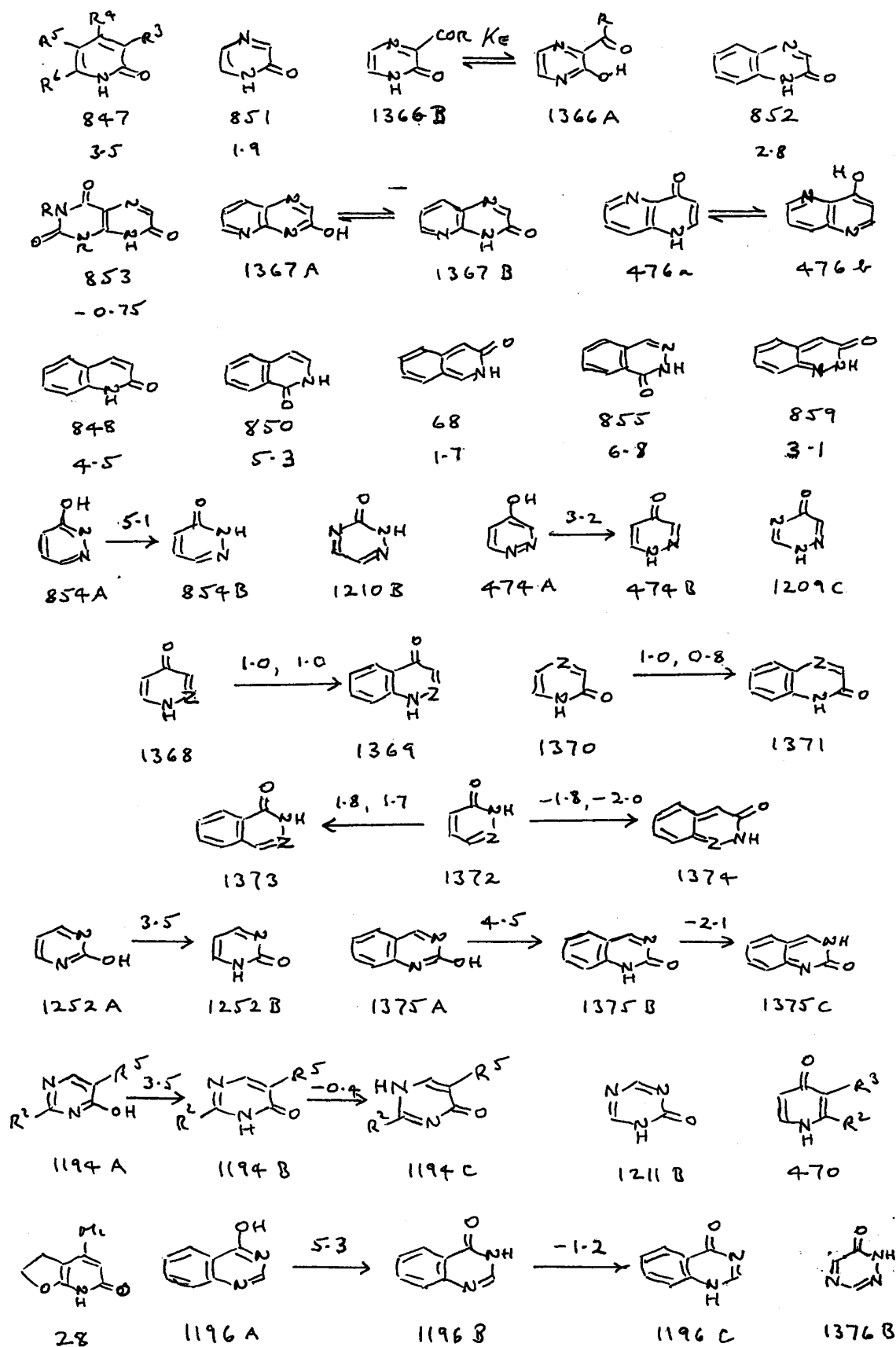
**1194** ( $R^2 = \text{Me}$ ):

$$\log K_T(5) = 3.77(0.01) - 2.92(0.02) \sigma_m \quad (\text{cxii})$$

$$(n = 4 \quad r^2 = 0.99 \quad s = 0.01 \quad F = 8400)$$

(a) *Substitution Patterns.* — Equations (lxix) and (lxx) represent tentative relations for 5- and 6-substitution into 2-pyridone (**847**, all  $R = H$ ). The first is reasonably satisfactory, the second less so, but the number of points is insufficient in either case for much weight to be placed on it (section 8.2.4). We note elsewhere (section A.10.6) the general applicability of  $\sigma_m$  in LFER equations for substituted 4-pyridones, the exception being that the  $pK_a$  values for 2-substituted 4-pyridinols are better correlated by  $\sigma_I$ , as is the case for 6-substituted 2-pyridinols in eqn. (lxx). Their common feature is a substituent in the  $\alpha$ -position to imino-nitrogen, and dominant  $\sigma_I$  dependence may always attach to this circumstance as it does in pyridine itself, but the evidence is lacking. Here  $\rho_I$  is less than in the former case hence  $K_T$  is less sensitive to the substituent; the calculated value of  $\Delta \log K_T$  for 6- $\text{NO}_2$  in 2-pyridone is -3.1 as against -4.7 for 2- $\text{NO}_2$  in 4-pyridone. The greater sensitivity of 4-pyridone may be due to its more extended so more polarised structure. Hence even  $\text{NO}_2$  is probably insufficient to convert 2-pyridone to 2-pyridinol and it would require two strongly electronegative substituents to do so. Equation (cxi) derives from a single-point correlation based on  $\log K_T$  for pyrazinone **851** assuming a relation with  $\sigma_m$ . It is interesting in so closely resembling eqn. (lxix). There are no data for  $R^3$  but  $\rho_m = 0.7$  for the corresponding, 3-position of 4-pyridone (section A.10.6) and a similar insensitivity to substitution may apply here (but see 4-pyrimidone, below). Note also that fusion of a 5-membered ring as in **28** can substantially lower  $\log K_T$  through operation of the ‘Mills-Nixon effect’ (section A.1.2).

The only other equation we have been able to derive is (cxii) for 5-substituted 2-methyl-4-pyrimidones **1194B** (section B.5.12) which, despite only four points, appears to be soundly based. Its intercept term defines  $\log K_T$  for (**1194B**,  $R^2 = \text{Me}$ ,  $R^5 = H$ ). It has been suggested (section B.2.4) that  $\Delta \log K_T$  ca. 0.5 for two alkyl groups is generally applicable to the pyridones,



Scheme 67

and on this basis we postulate  $\log K_T$  3.5 for the **B**-tautomer of 4-pyrimidone itself. Given  $\log K_M$  -0.4 (section B.5.11), this translates as  $\log K_{\text{total}}$  3.1 for **1194C**. Substitution at  $R^2$  scarcely affects  $K_M$  (section B.5.11) but, since neither does that at  $R^5$ , it may be dangerous to extrapolate this conclusion to  $K_T$ . Both  $R^2$  and  $R^5$  lie on the axis of the amidine moiety and this may explain their minimal effect on  $K_M$ . The consequence for 4-pyrimidone **1194**, and very likely for 4-quinazolone **1196** as well, is that  $K_T$  and  $K_{\text{total}}$  will be similarly affected. This may not apply to 6-substitution, where on the evidence sketched above, a preference for **1194C** should be much more diminished by electronegative substituents than that for **1194B**, so leading to a drop in  $K_M$ . Equation (cxii) is also of interest through possessing almost the same  $\rho_m$  value as appears in all those for 2-pyridone, suggesting some degree of generality where  $\alpha$ -NH is not involved, but there is no other evidence to support any such hypothesis at the present time.

(b) *Monocyclic Heterocycles.* — The monocyclic parent compounds of Scheme 67 possess an intelligible pattern for  $\log K_T$ . As seen above, the effect of 4-aza substitution in **851** is sharply to reduce  $K_T$  relative to **847**; however that is not true for the pyrimidones **1194** and **1252**, presumably because this nitrogen atom is part of a conjugated (amidine or vinylogous amidine) unit which has the effect of blunting its impact. We obtain the tentative value for **1252** by applying eqn. (cx) to  $\log K_M$  for the related imino-derivative **1077** (section B.4.4). It has been noted that **854** (section B.2.5) like **474** (section A.10.7) possesses a much larger  $K_T$  value than would have been expected from the incursion of aza-nitrogen (contrast **847**  $\rightarrow$  **851**), the result in each case of lone pair repulsion in the **A**-tautomer.

It is possible, using an isodesmic approach, to make an informed guess at  $\log K_T$  for the triazinones **1209** - **1211**. For this we suppose that **470B**, **474B** and **1194C** form a sort of box equilibrium such that, starting from **470B**,  $\Delta \log K_T$  -0.8 for its transformation into the amidine structure of **1194C** and -0.7 for the addition of aza-nitrogen to give **474B** are additive, in which case  $\log K_T$  2.4 for **1209C** results. A similar treatment of **847B**, **851B** and **854B** leads to an estimated  $\log K_T$  3.5 for the unreported triazinone **1376**, while for **1210**, use of **847B**, **854B** and **1252B** results in an estimate of  $\log K_T$  5.1. More simply, **1211B** differs from **1194B** through incorporation of 5-aza nitrogen; if this obeys eqn. (cxii),  $\log K_T$  1.6 results. While none of these predictions is likely to be accurate, the postulated values are large enough to ensure that all should exist predominantly as the oxo-form in water. This appears to be true for those derivatives that have been studied, though the interest here has lain in other forms of tautomerism (sections B.5.13 for **1209** and B.5.15 for **1210** and **1211**, and *cf.* section B.8.5 above).

(c) *Benzofusion*. — The effects of benzofusion are summarised by the structural types **1368** - **1374**. Here Z = CH or N, the  $\Delta \log K_T$  values shown over each arrow corresponding to each variant in turn. Consistency is remarkable, the more so since more than one methodology has been used for deriving the data on which they are based. For example,  $\log K_T$  1.7 for **68** came out of an LSER study from which water was absent (Appendix 2), so did not involve the ‘basicity method,’ whereas while this was used for **855**, the resulting value of  $\log K_T$  involved a re-analysis of the literature data which, atypically, led to an appreciable lowering of the reported value (section B.2.5). It appears from these results that  $\Delta \log K_T$  is either *ca.* 1.0 or *ca.* 1.8 according as to whether NH occupies a position  $\alpha$ - or  $\beta$ - to the fused benzene ring. The source of this difference appears to lie in a much greater drop in *amide*  $pK_a$  in the latter case, iminol  $pK_a$  remaining relatively unaffected. The sign of this difference is counter-intuitive and we have no explanation for it. If the resulting molecule is quinonoid, however,  $\log K_T$  falls; this is unsurprising in itself, but in precisely reflecting the tautomeric preference of pyrazole on benzofusion (sections A.9.2 and B.8.1), which can have no other source but this, it suggests yet another gratifying quantitative consistency. The slightly more negative value shown for **1375C** is based on the behaviour of the corresponding thione (section B.5.15) and, given some doubt (Appendix 1) concerning the true value of  $\Delta(SR)$ , may not be valid in the present context.

Use of these consistencies has allowed us, provisionally, to add some missing  $K_T$  values. Benzofusion of **1252B** to **1375B** and of **1194C** to **1196C** should result in  $\Delta \log K_T$  *ca.* 1.0, and that of **1194B** to **1196B** in  $\Delta \log K_T$  *ca.* 1.8, leading to  $\log K_T$  values of 4.5 for **1375B**, 5.3 for **1196B** and 4.1 for **1196C**. While no check is possible on the first, the extrapolated values for **1196** allow  $\log K_M$  -1.2 to be predicted whereas -1.3 was determined experimentally. This is not a severe test of the isodesmic approach but at least a consistent picture is maintained.

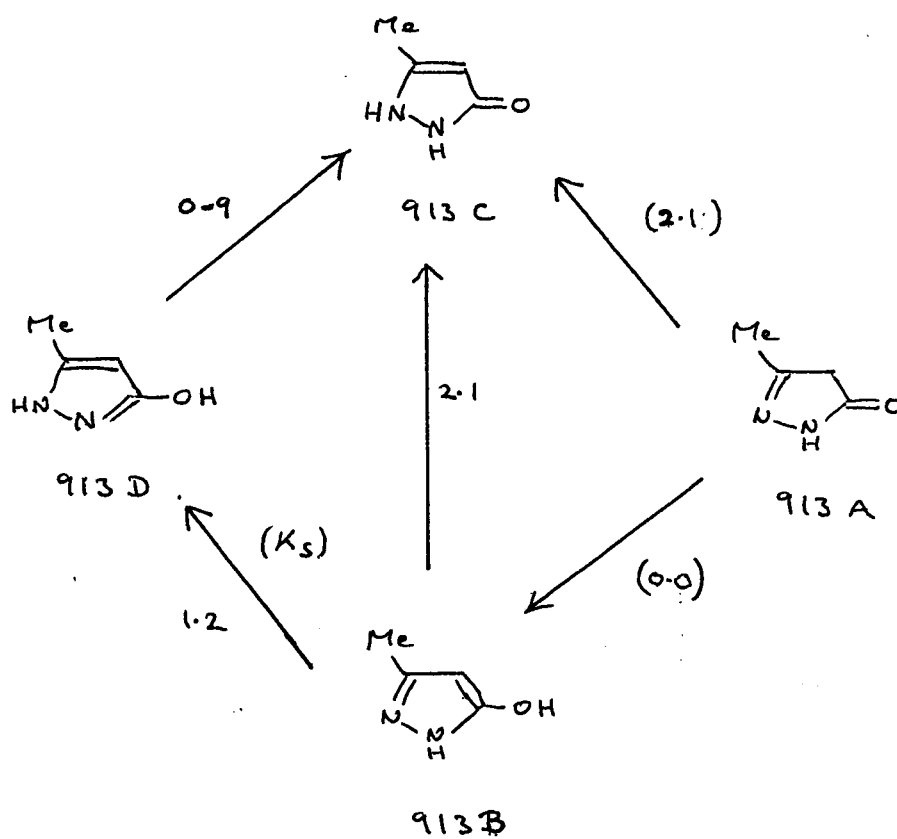
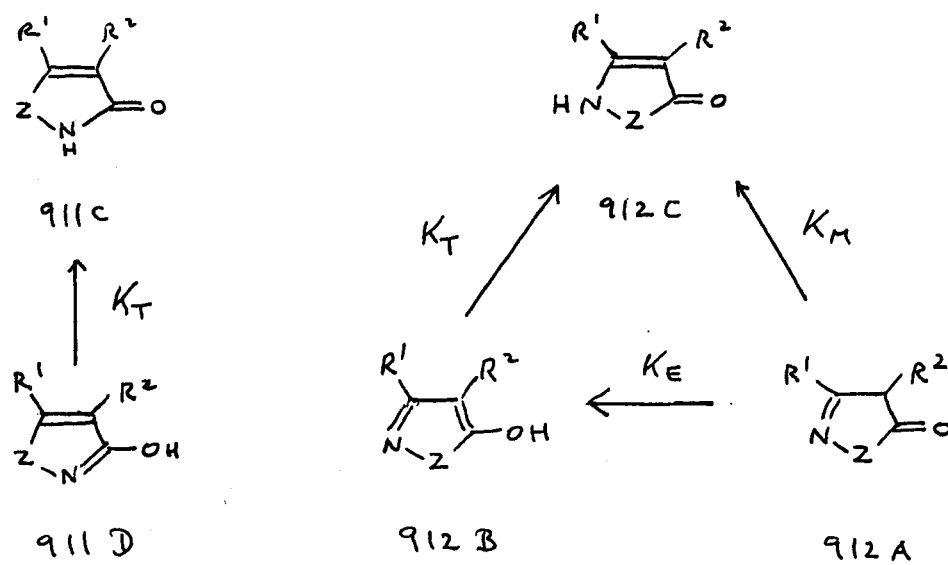
(d) *Implications*. — Preference for the oxo-tautomer is sufficiently overwhelming in most cases as to confirm that, in water, it is unchallengeable except by the most extremely electronegative substituents, and in some cases not even then. The likeliest parent heterocycles to be susceptible to a switch are pyrazinone **851**, 3-isoquinolone **68** and (according to our estimate) the triazinone **1211**, and the likeliest ways of inducing this involve intramolecular hydrogen bonding where lone pair repulsion is otherwise enforced (*e.g.* **476**), or dipolar repulsion (*e.g.* **853**). On their own,

lone pair repulsion and intramolecular bonding will often be relatively ineffective, as in the hypothetical example of **1367** where the former is likely to contribute only  $\Delta \log K_T$  *ca.* 0.8 (Appendix 3) to enhancing the proportion of **1367B**, while the intramolecular bond in such structures as **1366A** is likely to be of marginal importance ( $\Delta \log K_T \nrightarrow -1$ ) since free rotation enables bonding with solvent water to take place with equal facility (Appendix 4). There is some reason to suspect that  $\pi$ -donors may raise  $K_T$ , especially at the fulcrum of the amidine moieties that become increasingly important as aza-nitrogen is progressively added to the ring, and this may help to explain why hydroxy tautomers have not been detected even among the highly electron-deficient triazinones. Lone pair repulsion between contiguous aza-nitrogens is also, as has been seen above, a factor that pulls in the same direction. However dipolar repulsion involving contiguous atoms, a factor rarely encountered in 6-membered rings, is foremost among those which, in their 5-membered ring analogues, operates to reduce or reverse  $K_T$ . This subject dominates the remaining sub-sections.

### B.8.13 Contiguous NHZ (Z = O, S and NR) in 5-Membered Ring Heterocycles containing One Carbonyl Group

This is probably the most complex field for 'N-type' tautomerism, and perhaps anywhere, with four viable tautomers any of which might be dominant. We attempt here to summarise as much as possible of the known information in near-quantitative manner. By making liberal use of extrapolation and a few key additive assumptions, we have been able to produce a coherent picture for the compounds of Scheme 68 in aqueous solution in which few of the predicted values can be substantiated on present evidence but none of which seriously conflict with what is known.

Essentially there are two compound series, according as to whether NH is adjacent to carbonyl (**911**) or not (**912**). The former consists in a single equilibrium but the second is three-way, with a tautomer **912A** in which conjugation is broken as well as the usual iminol **D** and amidic **C** species. The equilibria involving **912A** are 'C-type' and a number of similar type but found in other contexts are discussed in section A.10; a solvent study on (**912**, Z = NPh, R<sup>1</sup> = Me, R<sup>2</sup> = H), there designated **431**, is reported in section A.10.2 and the resulting log  $K$  values are included in Table 83. It is necessary to incorporate 'C-type' equilibria at this point if the full picture for **912** is to be obtained.



Scheme 68

**Table 82. Known and (Extrapolated) log  $K_T$  Values for 911<sup>a</sup>**

R <sup>1</sup>	R <sup>2</sup>	Z =	NH	NMe	NPh	O
H	H		(0.0)	(- 0.5)	(- 1.0)	(- 2.0)
Me	H					
	}		0.9	0.4	- 0.1	(- 1.1)
H	Me					
Me	Me		(1.8)	(1.3)	(0.8)	- 0.2

<sup>a</sup> Section B.2.10.**Table 83. Known and (Extrapolated) Values for 911 and 912, R<sup>1</sup> = Me, R<sup>2</sup> = H**

	Z =	NH	NMe	NPh	O
log $K_T$ , <b>911</b>		0.9	0.4	- 0.1	(- 1.1)
log $K_T$ , <b>912</b>		2.1	1.8 <sup>a</sup>	1.5 <sup>c</sup>	( 0.9)
log $K_M$ , <b>912</b>		(2.1)	(1.5)	0.9 <sup>c</sup>	- 0.4 <sup>b</sup>
log $K_E$ , <b>912</b>		(0.0)	(- 0.3)	- 0.6 <sup>c</sup>	(- 1.2)

<sup>a</sup> Adjusted from 1.7 (section B.2.10) for internal consistency. <sup>b</sup> 'Predicted' as -0.3 (see the text).<sup>c</sup> By LFER (section A.10.2); see the text.**Table 84. Calculated Mole Fractions for Tautomers of (912, R<sup>1</sup> = Me, R<sup>2</sup> = H)<sup>a</sup>**

Tautomer	Z =	NH	NMe	NPh	O
<b>A</b>		7 x 10 <sup>-3</sup>	0.03	0.11	0.64
<b>B</b>		7 x 10 <sup>-3</sup>	0.01	0.03	0.04
<b>C</b>		0.88	0.96	0.86	0.32
<b>D</b>		0.11	—	—	—

<sup>a</sup> To the nearest 1% except when very small.

When  $Z = \text{NH}$  then, uniquely, the two series merge, and the complete picture for the case that  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ , appears as **913** in Scheme 68. We shall adopt this substitution pattern as standard for the following analysis since by far the largest amount of quantitative data attaches to it. Data are drawn from section B.2.10. Here and in Tables 82 and 83 bracketed values are extrapolations carried out on the lines to be discussed. The quantity designated as  $K_s$  for **913** is meaningless elsewhere since **911C** and **912C** are no longer identical.

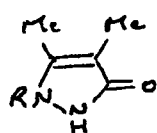
The data for (**911**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) indicate that  $\log K_T$  falls in the order  $Z = \text{NH} > \text{NMe} > \text{NPh}$  with  $\Delta \log K_T$  *ca.* -0.5 at each stage (Table 83). For (**912**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) the corresponding values of  $\log K_T$  are 2.1, 1.7 and 1.5, an overall range of  $\Delta \log K_T$  -0.6 which becomes exactly parallel, with  $\Delta \log K_T$  -0.3 at each stage, if  $\log K_T$  for  $Z = \text{NMe}$  is adjusted to 1.8 for the sake of internal consistency. For (**911** and **912**,  $Z = \text{O}$ ) no value of  $K_T$  exists in this substitution pattern, but we believe  $\log K_T$  -0.2 to represent the likeliest value for (**911**,  $R^1 = R^2 = \text{Me}$ ,  $Z = \text{O}$ ; **925** in section B.2.10) and the value for  $R^2 = \text{H}$  should be appreciably lower. We have no precise estimate of the adjustment required but, given  $\log K_T$  *ca.* 1.3 for (**911**,  $R^1 = R^2 = \text{Me}$ ,  $Z = \text{NMe}$ ; **915**,  $R = \text{NMe}$  in section B.2.10),  $\Delta \log K_T$  *ca.* -1.5 follows for  $Z = \text{NMe} \rightarrow \text{O}$ . Given  $\log K_T$  0.4 for (**911**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $Z = \text{NMe}$ ) the effect of ring alkylation is unusually large, and if  $\Delta \log K_T \pm 0.9$  per methyl is used as a constant factor, the values of Table 82 follow. The resulting spread in  $K_T$  values for **911** is such that  $Z = \text{NPh}$  lies about half-way between  $Z = \text{NH}$  and  $Z = \text{O}$ , with  $Z = \text{NMe}$  about half-way between  $Z = \text{NH}$  and  $Z = \text{NPh}$ . The parallelism in terms of  $K_T$  between **911** and **912**, noted above, may be extended to  $Z = \text{O}$  as shown in Table 83; here we have entered the firm experimental value of  $\log K_M$  -0.4 for (**912**,  $Z = \text{O}$ ) in place of the 'predicted' -0.3, but use of the latter alongside the experimental 0.9 for (**912**,  $Z = \text{NPh}$ ) allows further isodesmic 'predictions' for  $Z = \text{NH}$  and  $Z = \text{NMe}$  on which there are no quantitative data.

Despite the extremely provisional nature of these estimates, existing data are incompatible with any smaller gap in  $\log K$  between  $Z = \text{NPh}$  and  $Z = \text{O}$  in either series, while a much larger gap also leads to difficulties, in that the **A**-tautomer for (**912**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $Z = \text{NMe}$ ) and even for **913** might then become detectable in aqueous solution (*cf.* Table 84), which does not appear to be the case. There is also an argument that might be held to add weight to the present analysis. For the total range in  $Z$  of  $\text{NH} \rightarrow \text{O}$ ,  $\Delta \log K$  for (**912**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) is 'predicted' as 1.2, 2.4 and 1.2 for  $K_E$ ,  $K_M$  and  $K_T$  respectively (Scheme 68); for **431**, *i.e.* for (**912**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $Z = \text{NPh}$ ), the *calculated range* from water to alkane in  $\log K$  (section A.2.10) is  $\Delta \log K$  2.2, 4.8 and 2.1 in the same order. This correspondence fits with the dictum of Leffler and Grunwald<sup>172</sup> that a solvent may be regarded, in many respects, as a kind of loosely attached substituent; that is, solvent and substituent effects should run

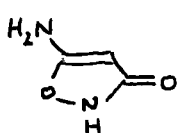
in parallel, as here they do. In the case of **911** the corresponding estimate for  $\Delta \log K_T$  over the range in Z of  $\text{NH} \rightarrow \text{O}$  is 2.0; there are no solvent data here but  $\Delta \log K_T$  as a function of solvent is typically greater for an amide than for its most nearly corresponding vinylogue (Appendix 2), which again is consistent so far as it goes.

The much greater sensitivity of  $K_M$  than of  $K_T$  to the nature of Z is the essential reason why, for  $Z = \text{O}$ , the **A**-tautomer appears quite suddenly to appear as important in aqueous solution despite its lack of importance elsewhere (Table 84). We attempt in section C.15 to split the effect of Z into its component parts and so take the argument further.

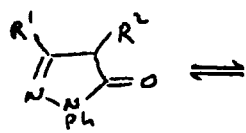
Since  $K_M$  involves a switch in the position and nature of the endocyclic double bond, this marks a major difference between **911** and **912** and the effects of  $R^1$  and  $R^2$  on the equilibria present in **912** are notably different in nature. Alkylation of **911** at  $R^1$  or  $R^2$  has a large effect in stabilising **911C** (Table 82) but other information is sparse; **927** probably exists as shown and other  $\pi$ -donors at  $R^1$  may behave similarly (*cf.* **912**, below) but data are lacking. Stabilisation by  $R^1$  of **1377A** relative to **1377C** follows the order  $R^1 = \text{NH}_2 > \text{OEt} > \text{Me} > \text{Ph} > \text{H} > \text{CO}_2\text{Et}$  whereas the stabilisation of **1377C** by  $R^2$  follows the order  $R^2 = \text{NO}_2, \text{CN}, \text{CO}_2\text{Et}, \text{Ph} \gg \text{Me}, \text{Br} > \text{H}$ .<sup>2zzz</sup> These largely represent  $\pi$ -donor and  $\pi$ -acceptor orders respectively but with Ph more prominent for  $R^2$  than expected, perhaps due to some contribution from Hine's allylic double bond stabilisation order (section A.1.1). They may be rationalised as the stabilisation of imine and enamine respectively, which appears to follow similar rules (*cf.* section A.4.8). However most of these results are not for water and differences are suggested by some others. In water, the **A**-tautomer dominates for (**912**,  $Z = \text{O}$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ), Table 84, and the same is true when  $\text{NH}_2$  replaces Me to give (**930**,  $R^2 = \text{H}$ ), but for  $R^2 = \text{Et}$  **930A** is only a minor component and for  $R^2 = \text{Ph}$  only **930C** is visible. Allylic stabilisation may therefore be more important in water than elsewhere. Note also that **912B** can become the dominant tautomer given a proton acceptor at  $R^2$ , as in (**928**,  $R^1 = \text{alkyl}$ ). According to Table 84 this would involve a reversal of the tautomeric preference in (**912**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) by  $\Delta \log K > 1.2$ , a margin comfortably within the expected range for an intramolecular hydrogen bond involving COR (Appendix 4). It is curious however that the **C**-tautomer appears to be favoured for (**928**,  $R^1 = \text{H}$ ); either the **B**-tautomer is favoured by a compression effect when  $R^1 \neq \text{H}$ , or perhaps more probably, **928C** can be stabilised by a greater degree of aminoenone resonance when  $R^2 = \text{COR}$  is able to lie in the plane of the ring (section A.10). Complications of that sort illustrate the considerable difficulties attaching to prediction in this area.



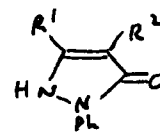
915



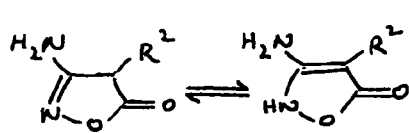
927



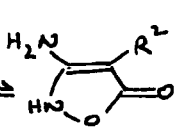
1377A



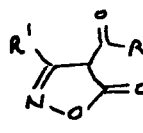
1377C



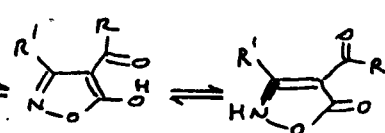
930A



930C

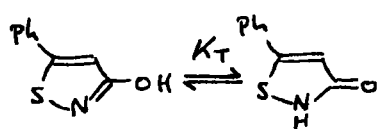


928A

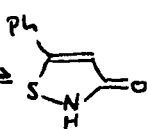


928B

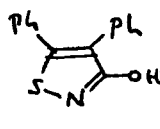
928C



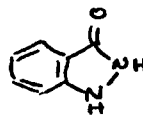
934D



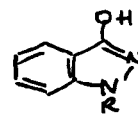
934C



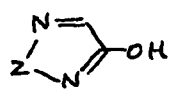
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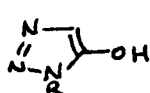
923



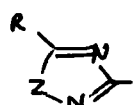
924



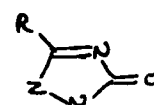
906A



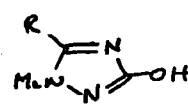
907A



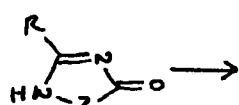
905D



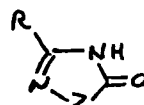
905C



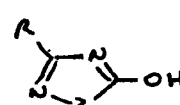
901D



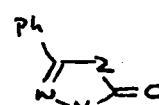
904C



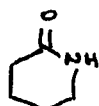
904B



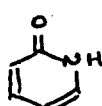
904A



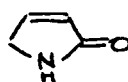
903B



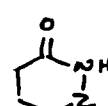
835



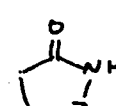
847



846



1379



1380

The position of  $Z = S$  in the tautomeric sequences for **911** and **912** has not been charted, but there is some tangential evidence. While **935** exists as shown,  $\log K_T = 0.5$  in water for **934**, a difference which is presumably electronic in origin. Given the status of Me as a better electron donor than Ph (Table 2) it is probable therefore that (**911**,  $Z = S$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) should possess a value of  $\log K_T$  equal to or greater than that for **913**. This is reasonable on the grounds both of lesser electronegativity and less dipolar repulsion (but see section C.15 for contrary arguments).

Aromatisation as in **923** has little effect except in suppressing the quinonoid **B**-tautomer. The curious fact that 1-substitution generates a switch to **924D**, which we<sup>22</sup> have attributed to a ponderal effect, may be further explained as due in part to the increased dipolar repulsion that appears (see above) to be present when alkyl replaces  $R = \text{H}$ .

Aza-nitrogen is a strongly electronegative substituent (section B.8.12) and it is therefore unsurprising that it typically engenders a decisive switch to the hydroxy-tautomer. This is always the case when the added nitrogen atom is contiguous with the hetero-atoms already present; thus **911D** becomes **906A** while **912B** becomes **907A**, and both predominate over the oxo-tautomer. There is one significant difference when added nitrogen is not contiguous. While **911** becomes **905** and **901D** for example results, the ability of **904C** to switch to **904B** when the same substitution of  $=\text{N}-$  for  $=\text{CH}-$  takes place in **912** guarantees that this tautomer will be dominant whatever the nature of  $Z$  or  $R$ . Similarly, if  $Z = \text{NH}$  in **912** while  $\text{CHR}^2$  is replaced by  $Z = \text{O}$ ,  $\text{S}$  or  $\text{NR}$  instead of by aza-nitrogen, **903B** exemplifies the structure that results. Effectively **903B** and **904B** replace the broken conjugation of **912A** with the very high degree of conjugation which attaches to ureas and urea-like structures. While no quantitative data have been reported, all these preferences are coherent and appear to be overwhelming.

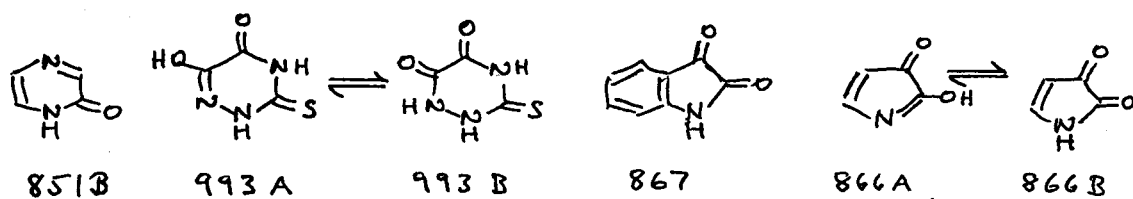
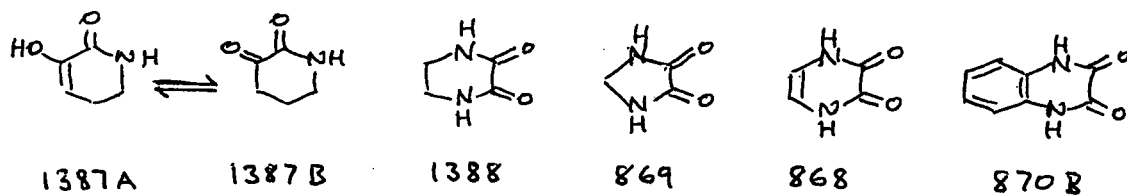
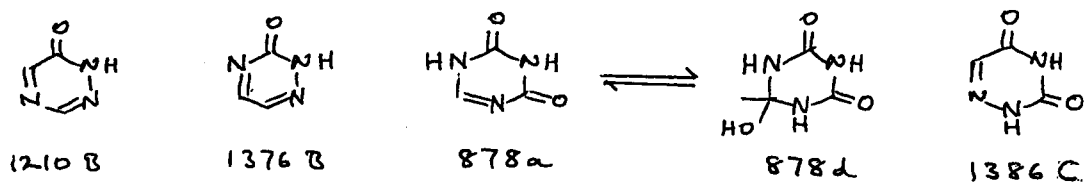
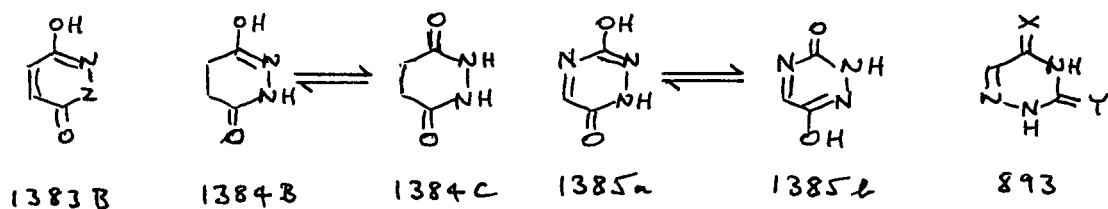
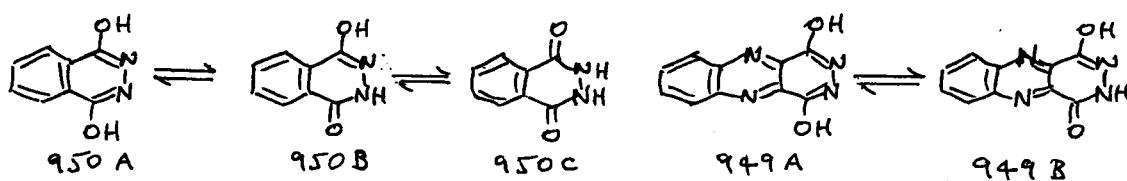
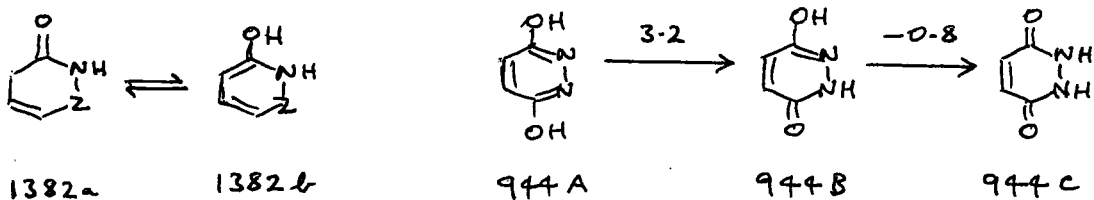
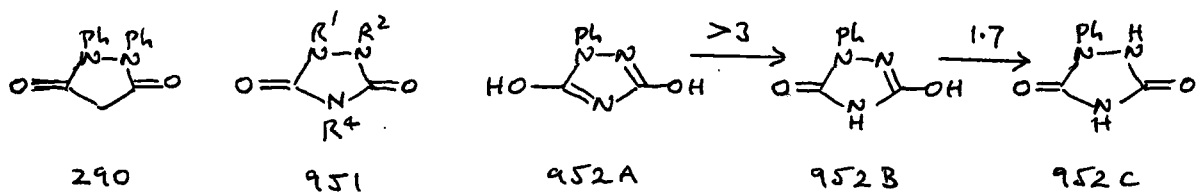
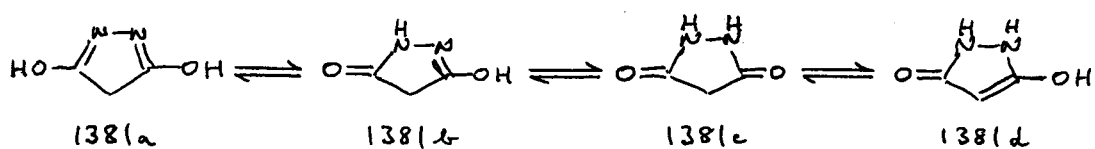
We may attempt to place these  $K_T$  values in perspective. While the effect of aromaticity in **847** relative to our estimated value for **835** (Scheme 66) is to lower  $K_T$  by  $\Delta \log K_T$  *ca.* -4.1, the decline from the  $K_T$  value estimated for **846** to that for (**911**,  $Z = \text{NH}$ ,  $R^1 = R^2 = \text{H}$ ) is, at  $\Delta \log K_T$  -6.5, much greater. Given that the gain in aromaticity for **911** must be much less than that for **847**, it seems probable that the contribution of dipolar repulsion in **911** to this value must equal or exceed  $10^3$ . This matter is taken further in Appendix 3.

These observations allow us to comment on a related question that, so far as we are aware, has not been discussed. While dipolar repulsion may partly be avoided in open-chain compounds  $R^1ZNHCOR^2$  **1378** by free rotation, this is not likely to be the case for alicyclic structures given the limited amount of twisting available to them (*cf.* Appendix 3). We may attempt to estimate the chance of iminol formation in **1379** and **1380**. For  $Z = CH_2$  we estimate  $\log K_T$  7.6 and 7.0 respectively (section B.2.3), on which the effect of  $Z$  when this is a hetero-atom has to be superimposed. In Appendix 3 we attempt to factor  $\Delta \log K_T$  for pyrazolones and isoxazolones into two factors: one due to aromaticity, the other due to dipolar repulsion. Only the latter is applicable here; for dipolar repulsion with NH contiguous to  $Z = NH$  and  $Z = O$ , we estimate  $\Delta \log K_T$  as -2.5 and -4.9 respectively. Independent evidence for closely similar values (-2.6 and -5.2) comes from an entirely unrelated set of compounds (section B.5.15). Hence dominant iminol formation for **1379** and even **1380** is improbable, but in compounds of this type it may need to be borne in mind.

#### B.8.14 Contiguous NHZ ( $Z = O, S$ or $NR$ ) in 5-Membered Ring Heterocycles containing Two Carbonyl Groups

A 5-membered ring containing four functional groups can become aromatic only through enolisation, in the case of the (hypothetical) compound **1381** to give **1381d**. (The same is true for a 6-membered ring containing five functional groups, *e.g.* barbituric acid **54**). In fact the dione **290** exists as the diamide shown, though this preference is probably not overwhelming (section A.6.4). This evidence indicates that **1381c** is preferred to **1381d**. However, it says nothing as to **1381b**, which may rival **1381c** in importance (see **1383** below). Relative to **1381b** the diol **1381a** has lost resonance energy and gained lone pair repulsion so is not expected to be important.

Replacement of  $CH_2$  in **1381** by  $NH$  in urazole (**951**,  $R^1 = R^2 = R^4 = H$ ) might be expected to have the same effect in stabilising the amide tautomer as its presence in **904B** or that of  $Z$  in **903B** conveys (section B.8.13), and this is found; urazole exists as shown (section B.2.12). Its ring consists entirely in functional groups so there is no 'aromatic' structure to compete with amide (or urea) resonance and the sole competing factor here is dipolar repulsion. Its 1-phenyl derivative **952** has been studied in water with results as shown (section B.2.12). Here **952C** dominates to the extent of *ca.* 98% and its dominance would probably be still greater for  $R^1 = H$  or alkyl (*cf.* section B.8.13). We may compare **951** and **1381**. Since dipolar repulsion in  $NHNPh$  is substantially greater than in  $NHNH$  (section C.15), the dominance of **952C** over its iminol **952B** suggests a preference for **1381c** over **1381b** of



much the same order. However, as effectively an aromatised form of **1381**, iminol formation might be expected for **944** and this is found (see below). It is possible to postulate related structural classes which may behave in a similar way, *e.g.* that in which 4-NH in **951** is replaced by a different  $\pi$ -donor, but nothing concerning their tautomerism is known.

#### B.8.15 Contiguous NHZ (Z = O, S or NR) in 6-Membered Ring Heterocycles containing Two Carbonyl Groups

An alicyclic 6-membered ring of type **1379** (section B.8.13) is even less likely to enolise than to form a stable iminol, and if unsaturation is added as in **1382a** the hypothetical enol **1382b** would be anti-aromatic so heavily disfavoured. However, when two carbonyl groups are present, aromatisation becomes possible. The tautomeric equilibria of 'maleic hydrazide' **944** have been investigated in water, with results as shown.

Qualitatively, the 'mixed tautomer' **944B** is favoured essentially because **944A** and **944C** are destabilised by lone pair and dipolar repulsion respectively, and this preference is found for almost all *aromatic* molecules of this type, though not necessarily elsewhere. Quantitative analysis is more difficult. That of Appendix 3, sections (a) and (k), based on a Hammett-type approach, results in tentative values of  $\Delta \log K_T$  *ca.* 1.9 and (possibly) -2.6 respectively for **944A**  $\rightarrow$  **944B** and **944B**  $\rightarrow$  **944C**, which contradicts the suggestion<sup>387</sup> that these two factors tend to be of roughly equal magnitude in water. Both in fact are very variable (Appendix 3). We may anticipate that any compound of type **1383**, where Z is a hetero-atom, will effectively be 'locked' as **1383B**.

Benzofusion generally increases the importance of oxo-tautomers (section B.2.5) and, on qualitative UV evidence, **950C** appears to be the dominant tautomer of **950** in water. If the regularities noted in section B.8.12 apply here, **950C** should indeed be preferred and perhaps by  $\log K_T$  *ca.* 1. With **944B** and **944C** so closely in balance it should be quite easy to shift the equilibrium decisively in either direction, and **949** is such a compound; here the diamide is unimportant and **949A** competes with **949B** which is still the major tautomer. Accessible proton donors should have the opposite effect when C-substituted into **944**, though note that *two* substituents will be required, as present in **949**, since the **B**-form is degenerate and with only one substituent OH and C=O can switch, with the inevitable result of reinforcing the previously existing dominance. Degeneracy is destroyed by *N*-substitution and a proton acceptor introduced in this way could in principle, by hydrogen bonding to NH, engender a switch to **944C**.

If **950** exists largely as the C-tautomer then **1384** must certainly do so, though it is difficult to predict by what margin. The iminol **944B** is better conjugated than **1384B** to an extent that is plainly much greater than that of the corresponding diamides, but it is difficult to quantify this difference. Starting from a predicted  $\log K_T$  7.6 for **835** and a presumed  $\Delta \log K_T$  of *ca.* -2.5 for dipolar repulsion, and assuming a fairly small effect otherwise of NHCO as substituent,  $\log K_T$  4–5 may represent a reasonable guess for **1384**. Similar considerations may apply to **1381** (section B.8.14) though for a 5-membered ring  $K_T$  is likely to be less and aromatisation is a possibility here not open to **1384**.

Nitrogen substitution into **944** to give a triazinedione also leads to nondegenerate tautomers, as **1385**. There is no information on this so we proceed as follows. On isodesmic reasoning we tentatively predict  $\log K_T$  3.2 and 4.8 in favour of **1210B** and **1376B** respectively (section B.8.12) and, while neither may be remotely accurate, this order is unlikely to be reversed. If the effect of OH substitution in **1385a** and **1385b** is not enormously dissimilar, then **1385b** should be preferred. The other triazinediones are both known and their structures are established. The 2,4-dione **878** takes the form **878a**; here the only problem is its readiness to give covalent hydrates, as **878d** (section B.2.8). Similarly **1386** is an azalogue of uracil and exists firmly as **1386C** in which the lone pair or dipolar repulsion which is present in most alternative tautomers are both avoided; it has been noted (section B.2.9) that all compounds of type (**893**, Z or Y = O or S) take this form. Here **878a** and **1386C**, unlike either tautomer of **1385**, benefit from the urea-type resonance also found in **903B** and **904B** (section B.8.13) and which always seems to guarantee an overwhelming dominance for the oxo-form.

### B.8.16 Amides containing Contiguous Carbonyl Groups

There is little information on this and many potential types of structure remain unexplored, so that a good deal of speculation is necessary. When two carbonyls are adjacent and unconjugated it is normal to find that one is partially hydrated in water, as for biacetyl MeCOCOMe **108**, whereas in alicyclic structures this is accompanied by extensive enolisation as in cyclohexanedione **110** (section A.2.5). Enolisation in the latter case represents a gain in  $K_E$  of  $> 10^8$  relative to cyclohexanone itself, the result of a lone pair repulsion which is avoided in open-chain structures by free rotation. When one carbonyl is conjugated both phenomena are normally confined to the other. For **1387** one might expect **1387A** to be the dominant tautomer, but this compound has not been studied. Iminol formation will also

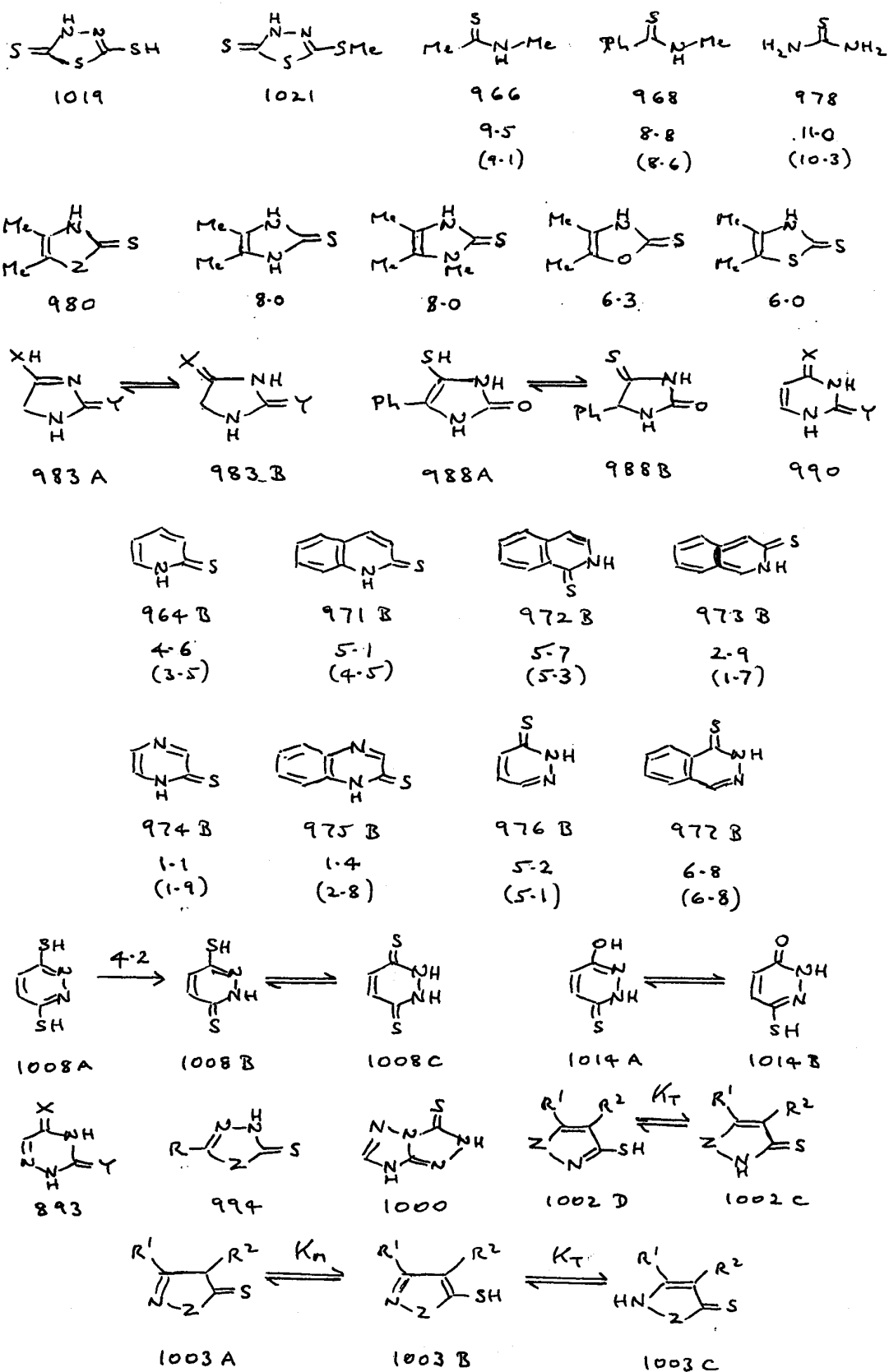
relieve lone pair repulsion and is indeed the only such possibility for compounds such as **1388**. These and their aromatised derivatives are the compounds that concern us here.

There is no evidence concerning **1388** but **869** is reported without comment as possessing the structure shown (section B.2.7). That of **868** has simply been assumed, a particularly surprising assumption given the quite low  $K_T$  value of **851** (section B.2.12; but see section B.8.19 also). However, the UV spectra of model compounds have shown decisively that **870** exists in water mostly as **870B**, while the only known case in which iminol formation operates to relieve lone pair repulsion in a compound of this type is **993**, in which the preferential formation of **993A** removes dipolar repulsion as well. A possible reason why lone pair repulsion may not be so severe in cyclic oxamides as in the equivalent diketones has been sketched in section B.2.7. Iminol formation has not been reported for their 5-membered ring equivalents such as isatin **867** either. Here however a different explanation can be invoked: in the (hypothetical) case of **866** the iminol **866A** would be anti-aromatic, and the same applies to isatin as well. For 6-membered and alicyclic rings the problems remain unresolved, and more work is clearly needed on this topic.

### B.8.17 Thioamides: General

The common perception is that amides and thioamides possess closely similar  $K_T$  values, and while this may be correct, is uncommonly difficult to prove. We assemble a number of  $\Delta(\text{NR})$  values appropriate to thioamides in Scheme 39 (section B.3.1) but no corresponding thioiminol has been found that will allow  $\Delta(\text{SR})$  to be estimated in the manner established for  $\Delta(\text{OR})$ . This situation is exacerbated by the extraordinary discrepancies thrown up by solvent studies (sections A.11.2 and B.3.2), which typically extrapolate to aqueous values of  $K_T$  much lower than those resulting from use of the 'basicity method.' Even if these results are set aside as uncertain or unreliable, major problems remain.

The effect of using  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  together is generally to increase the accepted value of  $K_T$ , often by  $\Delta \log K_T$  0.5 or more. The overall effect here is the reverse. While  $\Delta(\text{NR})$  is less for thioamides than for amides,  $\Delta(\text{SR})$  is certainly very much less than  $\Delta(\text{OR})$  and in all probability is *negative*. Rationalisation of this goes back to the reason why these corrections are necessary at all: replacement of ZH by ZMe, where Z = N or O, reduces cation solvation and with it  $\text{p}K_a$ , so that the reverse process as is involved in extrapolating from fixed models requires a positive correction. A



Scheme 69

negative  $\Delta(\text{SR})$  must mean that, whether for SH or SMe, cation solvation is negligible. Given the extraordinarily poor proton donor ability of SH, this is altogether possible. The problem is to estimate its magnitude.

We have used a simple LFER approach to suggest a value of  $\Delta(\text{SR})$  close to -0.1 and more or less independent of context (section B.3.1). It may be lower. The thiadiazole **1019** represents the only iminothiol whose  $\text{p}K_{\text{a}}$  has been reliably measured, alongside its SMe derivative **1021**. Given  $\text{p}K_{\text{a}}$  -5.40 and -4.85 for **1019** and **1021** respectively, and applying a statistical correction to the first,  $\Delta(\text{SR})$  -0.25 results. This is close to the value of  $\Delta(\text{NR})$  typically obtained for *remote* *N*-methylation, *i.e.* for a nitrogen atom that does not share the cationic charge (Appendix 1): that is, where the result is due to a simple electron donor effect by alkyl. This deduction is valid only if *N*-protonation dominates; the authors assume *S*-protonation, but we have given reasons in section B.3.7 for doubting this. We shall continue to use  $\Delta(\text{SR})$  -0.1 in the following sections, but it is probable that this represents a maximum value.

#### B.8.18 Tautomerism in Aliphatic, Alicyclic and all 5-Membered Ring Thioamides lacking Contiguous NHZ (Z = O, S or NR)

Results for three open-chain amides (sections B.3.3 and B.3.5) appear in Scheme 69. The bracketed values are for their oxo-analogues, giving a mean  $\Delta \log K_{\text{T}}$  0.4 in favour of the thione results. We employ a similar approach to the unsaturated thioureas and ‘pseudo-thioureas’ of type **980**, but here no data exist for the corresponding ureas. Replacement of both ring methyls by Ph in either position lowers  $K_{\text{T}}$  for **980** on average by  $\Delta \log K_{\text{T}}$  -1.5. Benzofusion raises  $K_{\text{T}}$  but not by much,<sup>483</sup> adding to the evidence that this small effect is normal in fused 5-membered rings. A fall of  $\Delta \log K_{\text{T}}$  *ca.* -3 between **978** and **980** for partial aromatisation appears reasonable. We may presume that  $\log K_{\text{T}}$  for the corresponding oxoheterocycles will be slightly lower. However, some doubt must be cast on all quantitative data by the fact that these thiones, while protonating on C=S, are not Hammett bases.<sup>483</sup>

All variants on (**983**, X or Y = O or S) exist as the **B**-tautomer shown, and this is equally true in all cases investigated in which either NH is replaced by O or S. However, while 5-phenylation does not affect the tautomeric form of hydantoin (**983B**, X = Y = O), it converts **988** to **988A**. Given  $\Delta \log K_{\text{T}}$  -3.3 for allylic stabilisation by Ph (Table 1) this suggests a minimum value of  $\log K_{\text{E}}$  -2 for the parent compound (**983**, X = S, Y = O).

We have suggested in section A.12.1 that C=S in 5-membered ring heterocycles may be more susceptible to C-type enolisation than C=O by a factor of  $\Delta \log K_E$  *ca.* 3.5, in which case  $\log K_E < -5$  results for hydantoin itself. Presently it is not known how this compares with iminol formation to give **983A**, but for both X = O and X = S the proportion of this must be negligible. For uracil (**990**, X = Y = O) the reverse of  $\log K_T$  for this process is -4.3 (section B.8.11) but the comparison may be invalid since both iminols of uracil must be stabilised to some extent by partial aromatisation, which is absent from **983** and should make iminol formation in that case less favourable.

#### B.8.19 Tautomerism in Aromatic 6-Membered Ring Thioamides lacking Contiguous NHZ (Z = O, S or NR)

Results for these compounds also appear in Scheme 69 with the values for their oxo-analogues in brackets. There are fewer results and, even disregarding the atypical behaviour of **974** and **975** for which thione  $\log K_T$  is much less, there is notably less consistency as to the effects of structural change. For the shift from C=O to C=S we have  $\Delta \log K_T$   $0.5 \pm 0.4$  ( $n = 6$ ) whereas for the *difference* in the effect of benzofusion, including that to quinonoid forms,  $\Delta \log K_T$   $-0.4 \pm 0.2$  ( $n = 3$ ) results. Neither is large but, more importantly, neither is consistent enough for predictive purposes. Most of this work on thiones is very early and, while painstaking, may have been subject to inaccuracies due to compound instability compounded by the necessarily slower techniques in use at that time.

The reversal in relative  $\log K_T$  shown by **974** and **975** is not their only peculiarity; both pairs of compound possess *negative*  $\Delta(\text{NR})$  values (sections B.2.1 and B.3.1). An outside possibility, not considered in the literature, is that the  $\text{p}K_a$  values attributed to C=O and C=S protonation of the amidic forms are actually due, at least in part, to protonation of ring C=N. If so, these negative  $\Delta(\text{NR})$  values become understandable as those expected for 'remote' alkylation, hence the true  $K_T$  values, which are *necessarily* larger, were not obtained. This point cannot be checked without experimental re-investigation. Whatever its result however there is no doubt, on UV evidence alone, that the thiono tautomer dominates in all cases even though by what margin may be unknown.

#### B.8.20 Contiguous NHZ (Z = O, S or NR) in 5- and 6-Membered Ring Heterocycles containing One or Two Thiocarbonyl Groups

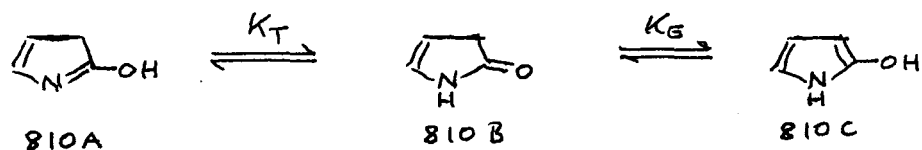
The sulfur equivalent **1008** to 'maleic hydrazide' **944** possesses the same dominant **B**-tautomer in water, as demonstrated by UV, and the available  $\text{p}K_a$

values enable its predominance over the dithiol **1008A** to be established, but they are insufficient in number and nature to establish quantitatively the proportion of **1008C**. The 'mixed species' **1014** also exists in this form and its UV spectrum, along with those of model compounds, shows **1014** to exist chiefly as **1014A**. This preference is in line with the generally larger  $K_T$  values for amidic C=S than for C=O, as appears above. This tautomeric preference extends to **1019** though, since only the  $pK_a$  values of **B**-forms were measured, no estimate of tautomeric ratio here is possible. It is highly probable that all *aromatic* compounds of this general type will show the same tautomeric preference. However this does not necessarily extend to their alicyclic analogues (*cf.* **1384**, section B.8.15) and, for these, the question has to be left open.

As noted previously all possible compounds (**893**, X or Y = O or S) exist as the tautomer shown, but that is inevitable if annular lone pair and dipolar repulsion are to be avoided and this is what dictates the form of **994** as well. The case of **1000** is more complex in that iminotriazoles are highly disfavoured but we do not know the position as to the thione-containing ring for which this may also be true; clearly competing factors operate (*cf.* discussion in section B.8.9).

Compound series **1002** and **1003** find their oxo-analogues in **911** and **912** as discussed in section B.8.13 and, where the data are known, the outcome is very similar; in the case of (**1002**, Z = S,  $R^1$  = Ph)  $\log K_T$  may even be identical (section B.3.6). For (**1003**, Z = NPh,  $R^1$  = Me,  $R^2$  = H) and (**1003**, Z = NMe,  $R^1$  = Me,  $R^2$  = H) we obtain  $\log K_T$  1.6 and 2.2 respectively, greater by 0.1 and 0.4 relative to their oxo-analogues (*cf.* Table 83). Again, this small shift of  $K_T$  in favour of the thiones conforms to the usual pattern. It may be adequate to assume identity of  $K_T$  between the oxo- and thiono-series for these compounds in the absence of precise information. However, there is an interesting exception: no thione **A**-tautomer has been reported. This may be due to the much greater susceptibility of thiones to C-type enolisation, which we have tentatively estimated (section A.12.1) as  $\Delta \log K_E$  *ca* 3.5. This factor applied to the data of Table 84 would reduce the mole fraction of **1003A** in (**1003**, Z = O,  $R^1$  = Me,  $R^2$  = H) from 0.64 in **912A** to *ca*  $6.3 \times 10^{-4}$ , with *ca.* 90%, rather than 32%, of **1003C**. Hence the **A**-tautomer should be invisible in these thiones for almost any conceivable variation in structure. Charting the interaction between 'C-type' and 'N-type' tautomerism becomes a major preoccupation in Section C.

**C: QUALITATIVE RULES AND QUANTITATIVE PREDICTIONS:  
CORRELATIONS AND CROSS-CORRELATIONS**



Section C attempts to draw the threads together, with (semi-)quantitative analyses where possible and qualitative rules where not. While the distinction between ‘C-type’ tautomerism (Section A) and ‘N-type’ tautomerism (Section B) is retained *de facto*, since these follow different rules, it is abandoned *de jure*, since a major remit of Section C is to examine those situations in which the two overlap. Hence, while the usual desideratum of examining simple cases before complex ones continues to be followed where possible, it is treated as subservient to the much more important aim of reaching a verdict on alternative modes of tautomerism, and their relative likelihood, where these co-exist. A classic example concerns **810** (Scheme 29, section B.2), where either ‘C-type’ (**810C**) or ‘N-type’ (**810A**) enolisation might in principle occur. We also attempt extrapolation to uninvestigated tautomeric possibilities where this seems appropriate. Of course not all examples can be recapitulated, and some of the rarer situations are omitted in the interests of coherence. Schemes are used in abundance and the values of  $\log K$  that appear in them, their direction indicated by single-headed arrows, are those known or estimated for water unless this is clearly stated to the contrary. Tables are sometimes reproduced from earlier sections, in whole or in part, but otherwise generally consist in data assembled from several sources in the preceding text, their intention being either to summarise, or to draw attention to aspects of the subject that have not been emphasised before. Equations are reproduced without the statistical justifications that will originally have accompanied them. Literature references are given only when new; otherwise they may be traced through the original subsection in which the compound or phenomenon was discussed, and which is always specified.

**C.1 Open-Chain Ketones with Unconjugated Enols**

The compounds here discussed are summarised as **42** (section A.1.3), where  $R^2$  and  $R^3$  when not H are bland or non-conjugated substituents; this allows aromatic as well as aliphatic moieties but excludes  $\pi$ -acceptors such as  $\text{NO}_2$  or carbonyl. Key aspects are the following:

(a) Substitution at R<sup>1</sup>: If R<sup>2</sup> = R<sup>3</sup> = H we have series **70** (Table 8, section A.2.1, and Scheme 70 below). For these we find eqn. (iii) which demonstrates that enolisation is promoted if R<sup>1</sup> is a field or resonance acceptor, especially the latter. Observed and calculated values of log K<sub>E</sub> appear in Table 85. All exist overwhelmingly as the keto-tautomer and differences between alkyl groups are slight; any steric effect is minimal (contrast R<sup>2</sup>, below). In the parallel series **71**, which behaves in a generally similar fashion, electron acceptor heterocycles such as pyridyl (all isomers) increase enolisation by  $\Delta \log K_E \geq 3$ , i.e. by about the same margin as calculated for R<sup>1</sup> = CN or COMe in Table 85, but still not sufficiently to generate an appreciable fraction of enol.

$$\log K_E = -7.39 + 1.97 \sigma_I + 8.11 \sigma_R \quad (\text{iii})$$

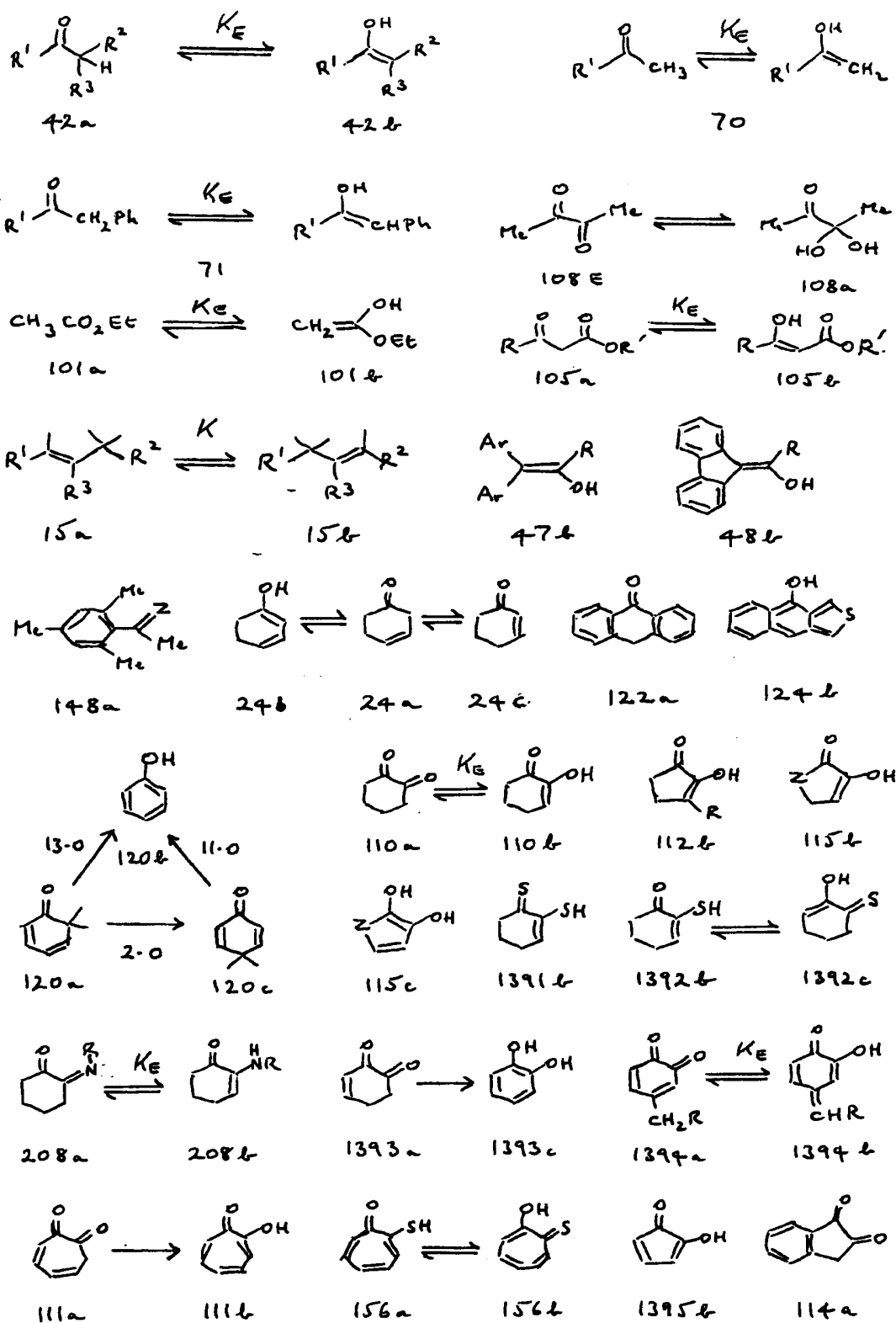
*Aldehydes* (R<sup>1</sup> = H; section A.2.1) are much more prone to enolisation than ketones ( $\Delta \log K_E$  2 - 3 typically) but only half this difference is predicted by eqn. (iii). The rest probably results from the replacement of sp<sup>2</sup>-sp<sup>3</sup> by sp<sup>2</sup>-s bonding, so making C=O more electron-deficient. Consistently, aliphatic aldehydes readily hydrate to give *ca.* 50% of the diol; this is a feature of electron-deficient ketones as well, such as biacetyl **108** which in water is *ca.* 75% hydrated to **108a**. In all such compounds, hydration is much more important than enolisation.

If R<sup>1</sup> is a  $\pi$ -donor as in **101**, enolisation is very severely disfavoured (Table 85) and this effect extends *e.g.* to  $\beta$ -ketoesters **105** which enolise only to **105b**. This exemplifies RULE 3 (section A.12.3): *If alternative modes of tautomerisation exist, enolisation will always take place in a direction that AVOIDS DISRUPTING PRIOR CONJUGATION.*

**Table 85. Observed and Calculated log K<sub>E</sub> Values for **70**<sup>a</sup>**

R <sup>1</sup>	log K <sub>E</sub> (obs)	log K <sub>E</sub> (calc) <sup>b</sup>	R <sup>1</sup>	log K <sub>E</sub> (obs)	log K <sub>E</sub> (calc) <sup>b</sup>
Me	- 8.63 <sup>c</sup>	- 8.63	CN		- 5.3
Bu <sup>t</sup>	- 8.76		COMe		- 4.8
Ph	- 7.97	- 8.04	OEt	- 18.6	
CH=CH <sub>2</sub>		- 7.8			

<sup>a</sup> More values in Table 8, section A.2.1. <sup>b</sup> Eqn. (iii). <sup>c</sup> Statistically corrected.



Scheme 70

(b) Substitution at R<sup>2</sup>: Substituents at R<sup>1</sup> or R<sup>2</sup> in allylic systems **15** will affect the direction of isomerisation (tautomerisation) according to their ability to stabilise a carbon double bond, and for R<sup>3</sup> = H this has been quantified (Table 1, section A.1.1). In **42b**, the position equivalent to R<sup>3</sup> in **15** is occupied by OH. Hence R<sup>2</sup> if a resonance donor will give rise to a cross-conjugated system and this is probably the principal reason why such substituents do not stabilise C=C to the extent expected from Table 1. Table 86 compares the effect of R<sup>2</sup> = Me, Ph and OMe for R<sup>1</sup> = H, Me or Ph (Table 5) with Hine's  $\Delta \log K$  values. A very tentative analysis suggests eqn. (cxiii), in which the first term derives from Table 1 while the second implies a degree of attenuation in proportion to the substituent's resonance donor properties. With so few data no truly quantitative approach is possible but those for R<sup>1</sup> = Me and Ph would roughly fit  $\rho_R = 8$  and 3.5 respectively. There is no way that this approach can be taken further at the present time.

$$\Delta \log K_E = \Delta \log K + \rho_R \sigma_R \quad (\text{cxiii})$$

(c) Disubstitution at R<sup>2</sup> and R<sup>3</sup>: This results in apparent inconsistencies which most probably derive from *steric compression* (section A.1.4): **42b** is less crowded than **42a**, so if R<sup>2</sup> and R<sup>3</sup> are both bulky, the enol may be favoured. For (**42**, R<sup>1</sup> = H, R<sup>2</sup> = R<sup>3</sup> = Ph)  $\log K_E$  0.98 is found, *i.e.*  $\Delta \log K_E$  7.2 or more than double the effect expected for a single Ph in **15**. By contrast,  $\Delta \log K_E$  is 2.4, 1.3 or 1.5 for R<sup>2</sup> = R<sup>3</sup> = Me when R<sup>1</sup> = H, Me or Ph respectively, *i.e.* little greater than for R<sup>2</sup> alone. Another variant is provided by **47**, where R<sup>2</sup> = R<sup>3</sup> = Ar = mesyl. If R = H then  $\log K_E = 1.3$  and this rises to 1.88 when R also is mesyl, but for R = Me and Bu<sup>t</sup>,  $\log K_E$  falls to -0.19 and -2.23 respectively. This suggests the opposite effect, of *steric crowding*: alkyl groups are more '3-dimensional' than simple aryl moieties, which can also benefit from charge transfer when they overlap. Another such context is **48**, where the enol is again

**Table 86.**  $\Delta \log K_E$  for Substitution relative to R<sup>2</sup> = H in **15** and **42**<sup>a</sup>

	R <sup>1</sup> <sup>b</sup>	R <sup>2</sup> =	Me	Ph	OMe
$\Delta \log K$ <sup>c</sup>	H			3.16	
	Me		1.12	2.23	
	Ph			2.82	1.50
			2.2	3.3	3.6

<sup>a</sup> See the text. <sup>b</sup> Structure **42**. <sup>c</sup> In terms of structure **15** (Table 1).

favoured when  $R = H$  but any substituent reverses this, presumably because of a steric clash with the rigid tricyclic structure. Table 6 (section A.1.3) summarises the data for both. Steric compression is the only factor that can lead to dominant enol formation in other than cyclic structures. Steric crowding with reduction in enol content is also found in conjugated open-chain enols and examples appear in sections C.4, C.5 and C.6.

## C.2 Open-Chain Thioketones with Unconjugated Enethiols

The only available data concern **148**, for which  $\log K_E$  is -6.92 and -0.94 for  $Z = O$  and  $Z = S$  respectively (section A.3.1). However, high level MO calculation and a qualitative survey of related structural types also support a  $K_E$  ratio relative to ketones of *ca*  $10^6$ . Given that twisting in **148** must preclude any large effect due to conjugation this is likely to make it a reasonably representative molecule and we suggest a constant factor of  $\Delta \log K_E \sim 6$  to be adequate for predictive purposes in these and the related alicyclic compounds. Different factors apply to thioamides and are likely in other sorts of conjugated structure; *vide* sections C.7, C.10 and C.13.

## C.3 Enolisation and Aromatisation in Carbocyclic Ketones (Thioketones)

One  $C=C$  adjacent to  $C=O$  as in **24b** will probably have little effect on  $K_E$  (*cf.*  $R^1 = CH=CH_2$  in Table 85) and while *e.g.* **24a** might in principle tautomerise to **24c**, in fact it goes to **24b** instead ( $\log K_T$  2.4; section A.1.1). However, two  $C=C$  in one ring generate the possibility of aromatisation; the position for phenol **120b** (section A.2.6) is shown as Scheme 70. The shift in ratio relative to cyclohexanone is enormous ( $\Delta \log K_E \sim 18$ ) but quite readily reversible;  $\log K_E$  is only half as great in the corresponding naphthols, and in **122** the ketone is the favoured tautomer,  $\log K_E$  -2.1. Further benzofusion renders the phenol tautomer unobservable in any solvent, as for **124b**, presumably in this case through its partially quinonoid structure (typical  $\Delta \log K_E$  *ca.* -1.8; Appendix 5).

$\alpha$ -Diketones *etc.* — For biacetyl **108** using eqn. (iii) we estimate  $\log K_E$  *ca.* -4.8 (Table 85), a rise of  $\Delta \log K_E \sim 3.8$  relative to acetone; the enol has not been observed. In cyclic structures however lone pair repulsion induces enolisation, as in **110** for which  $K_E \geq 10^2$  is a plausible estimate (section A.2.5). This represents an overall rise in  $K_E$  of *ca.*  $10^9$  relative to cyclohexanone, which we provisionally interpret as *ca.*  $10^5$  due to lone pair

repulsion superimposed on much the same electronic factors [*cf.* eqn. (iii)] as operate in **108**. Other saturated rings behave similarly, as *e.g.* **112b** where almost any substituent R will support this tautomer, and **115b** in which the hetero-atom Z will dictate which carbonyl enolises (the aromatised diol **115c** is not found: section A.2.5). The dithione **1391** should behave similarly, while the mixed species **1392** is expected to prefer **1392b** since thioketones enolise so much more readily (see C.2 above). The case of C=NR in **208** is more complex, but in general terms, the outcome depends on the nature of R, plus the ease with which lone pair repulsion can be avoided if **208a** adopts the conformation shown. Here strong  $\pi$ -donors (OH, NH<sub>2</sub>) stabilise **208a** whereas ‘bland’ substituents (H, Alk, Ph) generally favour **208b** (section A.4.5) and it is probable that  $\pi$ -acceptors such as COMe will also favour this tautomer (section A.4.3). These are aspects of imine-enamine tautomerism which is considered further below (section C.2.6). The effect of substituents on C=C in promoting enolisation, noted in section C.1.(b), should be particularly important in such borderline cases.

*Prior unsaturation* induces effects which depend on ring size:

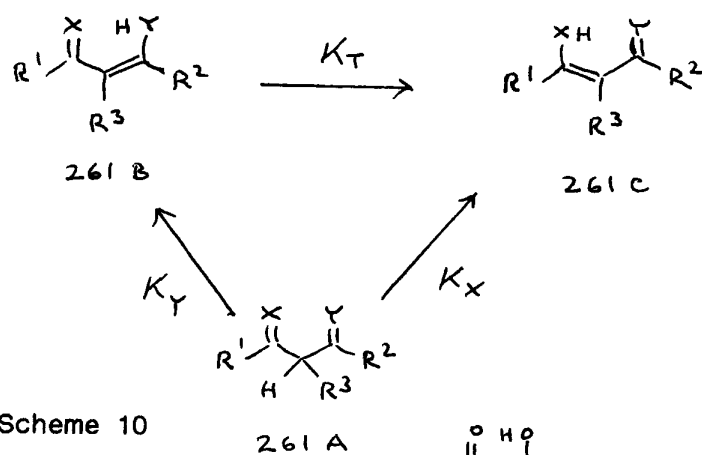
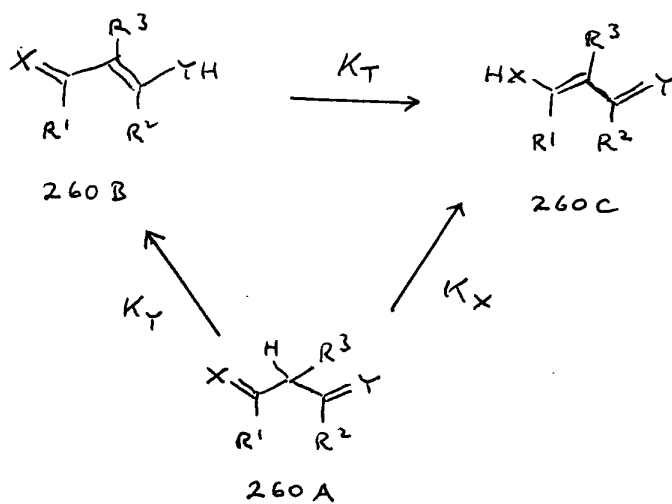
(a) 6-Membered: The hypothetical dione **1393a** would aromatise to the diol **1393c**. At the next stage of oxidation, simple *o*-quinones are devoid of tautomeric possibilities, but **1394a** can go to **1394b** if R is electronegative, as *e.g.* R = CN.<sup>593</sup>

(b) 7-Membered: Double unsaturation in **111a** induces enolisation to the fully aromatic tropolone, **111b**. Its mixed derivative exists mostly as **156b** (section A.3.6), as for conjugated  $\beta$ -thionoketones when chelated (section A.8), in sharp contrast with prediction for the (unconjugated) molecule **1392**.

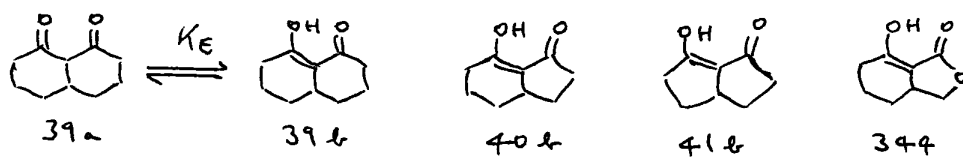
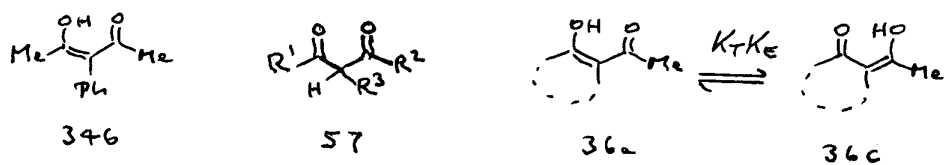
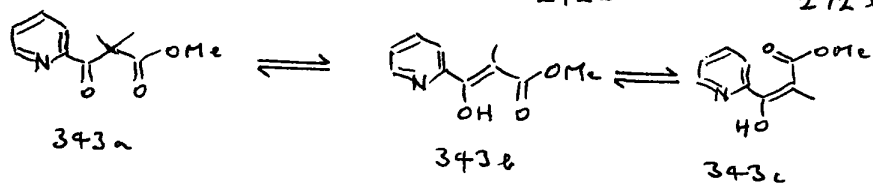
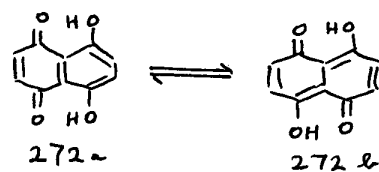
(c) 5-Membered: Here **1395b** differs from **111b** in being ‘anti-aromatic.’ While **1395** has not been studied, **114a** is preferred to **114b**, a large even though unquantifiable reversal relative to **112**.

#### C.4 Open-Chain Ketones with Conjugated, Chelated Enols

Conjugation to  $\beta$ -carbonyl is summarised in Scheme 10 (X = Y = O,  $K_E = K_X + K_Y$ ; section A.10). The extended conformation **260** is confined to cyclic compounds since chelation as in **261** is preferred when sterically possible. For R<sup>1</sup> and R<sup>2</sup> = alkyl or aryl, enolisation in **261** takes place preferentially at



Scheme 10



the more electronegative carbonyl but the margin is small,  $K_T \not\gg 10$ , and its overall extent in water does not exceed 20% (section A.6.7). Nevertheless this represents a shift of approaching  $\Delta \log K$  *ca.* 8 relative to the equivalent simple ketone. The enolisation of chelates is always greater in nonpolar solvents (Appendix 2). These special features require mention:

(a) If  $R^2$  is a  $\pi$ -donor (*cf.* **105**, Scheme 70),  $K_Y$  is suppressed so that  $K_E = K_X$ . The known examples, for which  $R^1 = \text{Me}$  or  $\text{Ph}$  and  $R^2 = \text{OR}$  or  $\text{NR}_2$ , are all about 10% enolised in water (section A.6.7). Even when  $R^1$  is electronegative  $K_E$  is not much affected; for example, if  $R^1 = \text{pyridyl}$  enolisation does not exceed 30%, rising to 50% only for **343** where **343c** as well as **343b** may be important. If  $R^1$  and  $R^2$  are both  $\pi$ -donors, no appreciable enolisation will take place.

(b) Almost any substituent  $R^3$  should in principle raise  $K_E$  especially in **261** since *steric compression* acting on the enol will strengthen its intramolecular hydrogen bond, but if in addition  $R^1$  and  $R^2$  are bulky this gives rise to *steric crowding* which inhibits planarity and can lead to the opposite effect. For example, while **346** is fully enolised in all solvents, (**57**,  $R^1 = R^2 = R^3 = \text{Ph}$ ) does not perceptibly enolise at all. These opposing forces are equally important for the corresponding aminoenones ( $X = \text{NR}$ ,  $Y = \text{O}$ ) and are probably found in all variants on **261**. Cyclic compounds tend to be more rigid which may be why both phenomena are less important for **260**. Steric effects give rise to a maze of competing factors which are explored, in so far as the data are available, in sections A.1.3 and A.1.4.

(c) Variations on  $\text{C}=\text{X}/\text{C}=\text{Y}$ : If one  $\text{C}=\text{O}$  is replaced by  $\text{C}=\text{S}$  the result is to suppress **261A** and confer parity on **261B** and **261C**;  $K_T \sim 1$  for  $R^1 = R^2 = \text{Me}$  (section A.8.3). Given that thiones enolise much more readily than simple ketones this is *prima facie* surprising but is documented and explained in section A.8.1. Virtually nothing is known when  $\text{C}=\text{S}$  replaces both  $\text{C}=\text{O}$  moieties (section A.7) but again the A-tautomer is suppressed. Replacement of  $X = \text{O}$  by  $X = \text{NR}$  results in compounds where the aminoenone tautomer **261C** is overwhelmingly predominant for  $R = \text{alkyl}$  but otherwise many variants are possible as detailed in section A.10 and charted in sub-sections C.8 and C.9 below.

(d) Other  $\pi$ -acceptors such as  $\text{NO}_2$  may replace  $\text{C}=\text{O}$ . For  $\text{PhCOCH}_2\text{NO}_2$  **341** we estimate  $\log K_E$  *ca.* -2.5 in water (section A.6.7), *i.e.*  $\Delta \log K_E$  *ca.* -1.5 relative to  $\text{PhCOCH}_2\text{CO}_2\text{R}$ . The nitro-group is more electronegative than any

carbonyl but a much weaker proton acceptor; for CN, which cannot form an intramolecular bond, we tentatively propose  $\Delta \log K_E$  -2 at least, relative to COMe. See section A.2.2 for other examples, *e.g.* 4-pyridinyl. While  $\text{RCH}(\text{NO}_2)_2$  and  $\text{RCH}(\text{CN})_2$  ionise, their enolisation is unknown.

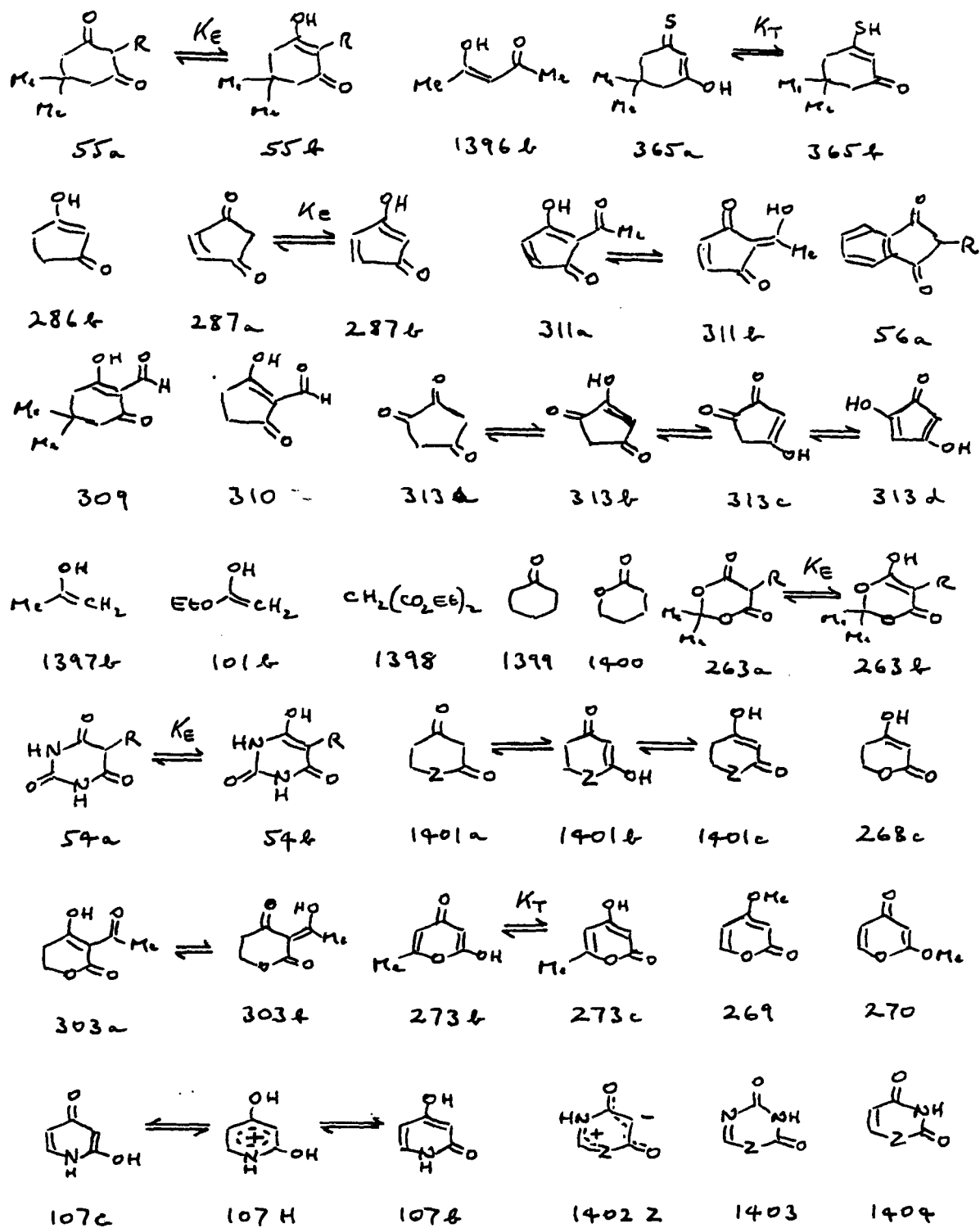
(e) Additivity in  $\beta$ -dicarbonyl enolisation is probably good enough to allow at least the confident prediction of the dominant tautomer in quite complex cases; see examples in section A.6.10.

## C.5 Carbocyclic Ketones with *exo*-Conjugated, Chelated Enols

$\beta$ -Acyl derivatives of cyclic ketones show the preferred direction of enolisation that would be expected on ring size considerations (section A.1.2), though the effect is small. For **36** for example, **36a** is preferred in 6-membered and **36c** in 5-membered rings, but by only a margin of 4:1 in either case, and the unconjugated tautomer **36b** dominates in both. The bicyclic  $\beta$ -diketones **39** - **41** have been studied but only in MeOH (section A.1.2). Enolisation is important in the ring fusion order  $6,6 > 6,5 \gg 5,5$ ; its direction for **40**, as expected, is as shown. Lone pair repulsion is likely to be severe in **39a** and here enolisation (in MeOH) is complete, while  $K_E$  is probably still elevated in **40** on account of molecular rigidity. However enolisation is appreciably reduced ( $\Delta \log K_E$  *ca.* -1) in **41**, presumably because of its non-optimal hydrogen bond. The behaviour of **344**,  $\log K_E$  -1.6 (section A.6.7), is correctly predicted by LSER (Appendix 2); the (typically fourfold) enhancement of  $K_E$  found for open-chain  $\beta$ -ketoesters, which is *not* as predicted, is plausibly due to the presence of *non-chelated* as well as chelated enols in these compounds (*cf.* **343**). The semiquinone **272** avoids the doubly enolised  $\beta$ -diketone structure **272b** and gives **272a** instead (section A.6.2), presumably since **272b** is formally quinonoid (Appendix 5).

## C.6 Carbocyclic Ketones with Conjugated *endo*-Enols

Cyclic  $\beta$ -dicarbonyl and related structures necessarily take up conformation **260** (Scheme 10), leading to major differences from their open-chain analogues **261**. The enol **260B/C** forms an extended conjugated system of much higher dipolarity than the A-tautomer, so that in contrast to that of **261** it is favoured by polar solvents. There results  $\log K_E$  1.3 for (**55**, R = H) in water (section A.6.2), *i.e.* the enol is now the favoured species, by contrast *e.g.* with **1396**,  $\log K_E$  -0.8 (section A.6.7; both values without statistical correction). If one C=O is replaced by C=S the enethiol **365b** predominates



Scheme 71

over **365a** but the margin in water, while probably substantial, is unknown (section A.8.2). This contrasts with the corresponding chelates for which  $K_T \sim 1$  (section A.8.3), probably through the far greater strength of OH---S=C over SH---O=C as a hydrogen bond. In both cases however the unconjugated tautomer is of negligible importance.

The enol **286b** predominates in most solvents (section A.6.4) which, given the solvent dependence (Appendix 2) of (**55**, R = H), probably implies  $\log K_E \geq 3$  in water. This rise relative to (**55**, R = H) contrasts with a fall in  $K_E$  for the parent monoketone ( $\Delta \log K_E$  ca. -1.5) and may result from the difference in dihedral angle between the two carbonyls, leading to enhanced electrostatic repulsion. However  $\log K_E$  ca. -1.8 is found for **287** since **287b** is anti-aromatic, a penalty of approaching  $\Delta \log K_E$  -5 from this cause. The interesting possibility arises that this may be a typical value (Appendix 5). 2-Acylation to give **311b** avoids this problem; it is more surprising that **311a** is also present (but see below). Similarly  $\log K_E$  ca. -2 is found for (**56**, R = H) but 1.7 for (**56**, R = NO<sub>2</sub>). Given  $\Delta \log K_E$  ca. -1.5 for NO<sub>2</sub> as  $\pi$ -acceptor in place of COMe in simpler cases [section C.4.(d)], this extrapolates to  $\Delta \log K_E > 5$  for the expected effect of 2-acylation, consistently with a reported 100% enol for (**56**, R = COMe) and reasonable in that a second acyl group in conjugation with OH (to give a nominal triacylmethane) should add a smaller factor than the first. On the evidence of **286** and **287** a factor of this order should also be sufficient at least to balance out the effect of anti-aromaticity, hence plausibly explaining the existence of **311a** in equilibrium with **311b**.

Compounds **309** and **310** exist as shown in CHCl<sub>3</sub> so predominance of an enol tautomer in water is assured. The latter does not give the *exo*-enol despite the tendency for this to occur in 5-membered rings (*cf.* section C.7); formyl groups in  $\beta$ -diketones do not enolise readily – contrast the behaviour of simple aldehydes *vs.* ketones [section C.1.(a)]. The nominal 1,2,4-triketone **313** illustrates several rules set out above. The 1,2-lone pair clash of **313a** and **313c** rules out these structures while **313d** is anti-aromatic; **313b** as is observed avoids both problems.

2-Substitution except as above has been little studied. For (**55**, R = Me)  $\Delta \log K_E = 0.8$  (section A.1.1); this is less than is found for simple ketones and much less than the full ‘allylic stabilisation’ effect (Table 86). In barbituric acid **54**  $\Delta \log K_E$  is typically ca 0.5 for R = small alkyl but reverses, through steric crowding, when these are large; as in -0.8 for R = Pr<sup>i</sup>. It is 1.8 for R = Ph. Also in **54**, small electron-withdrawing substituents that are not  $\pi$ -acceptors raise  $\log K_E$ , by 0.9 and 1.5 respectively for R = Cl

and Br. We conjecture that effects of this order may be general in cyclic systems. Steric crowding is likely to be important but there are too few data for predictive purposes. It might be reasonable to suppose that an already quite rigid cyclic structure should be less susceptible to steric distortion than its open-chain analogue, but again, the evidence is lacking.

### C.7 Alicyclic 6-Membered Ring Ketones (Thiones) with Conjugated *endo*-Enols

2.4-Dioxo Substitution. — The mutual effect of two ketonic  $\beta$ -carbonyls issues in  $\Delta \log K_E$  7.5 for **1397**  $\rightarrow$  **1396** and 7.7 for **1399**  $\rightarrow$  (**55**, R = H). To within the limits of error these values are identical which suggests the possibility of additivity. For ester C=O, this effect may be different;  $K_E$  for **1398** is unknown but for malonic acid is -8.4 after statistical correction, a factor of  $\Delta \log K_E$  10.2 relative to **101** (section A.2.4). This becomes 10.9 if our tentative estimate for **1398** (section A.2.4) is used, or 11.1 if we add in the (possibly spurious) difference between the two  $\Delta \log K_E$  values above. We now need an estimate of  $\log K_E$  for **1400**. Starting from  $\log K_E$  -6.7 for **1399**, adding  $\Delta \log K_E$  -10.0 for the difference between **1397** and **101** and correcting for the effect of its disfavoured conformation ( $\Delta \log K_E$  +2.2; cf. Table 24, section A.6.2), we obtain an estimate of  $\log K_E$  -14.5 for **1400**. This procedure is set out in Table 87. Adding estimates for mutual interaction that range from  $\Delta \log K_E$  10.2 to 11.1 leads to values of  $\log K_E$  for **263** that range from -4.3 to -3.4. We can therefore get quite close to the observed value of -2.65 (Table 23, section A.6.2). Interaction between the alkoxy groups in **263** should increase ester electronegativity and may account for the remaining difference. This result is probably as close to additivity as could reasonably be expected.

**Table 87. Factors ( $\Delta \log K_E$ ) applicable to Enol Conjugation in Open-Chain and 6-Membered Ring Structures**

Compound	$\log K_E$	Compound	$\log K_E$	$\Delta \log K_E$
<b>1397</b> <sup>a</sup>	-8.6 <sup>b</sup>	<b>1396</b> <sup>c</sup>	-1.1 <sup>b</sup>	7.5
<b>101</b> <sup>d</sup>	-18.6	<b>1398</b> <sup>e</sup>	-7.7 <sup>b,f</sup>	10.9
		Malonic Acid <sup>e</sup>	-8.4 <sup>b</sup>	10.2
<b>1399</b> <sup>a</sup>	-6.7 <sup>b</sup>	<b>55</b> , R = H <sup>e</sup>	1.0 <sup>b</sup>	7.7
<b>1400</b>	-14.5 <sup>g</sup>	<b>263</b> , R = H <sup>e</sup>	-3.7 <sup>b,g</sup>	11.1

<sup>a</sup> Section A.2.1. <sup>b</sup> Statistically corrected. <sup>c</sup> Section A.6.7. <sup>d</sup> Section A.2.4. <sup>e</sup> Section A.6.2.

<sup>f</sup> Estimate, section A.6.2. <sup>g</sup> See the text.

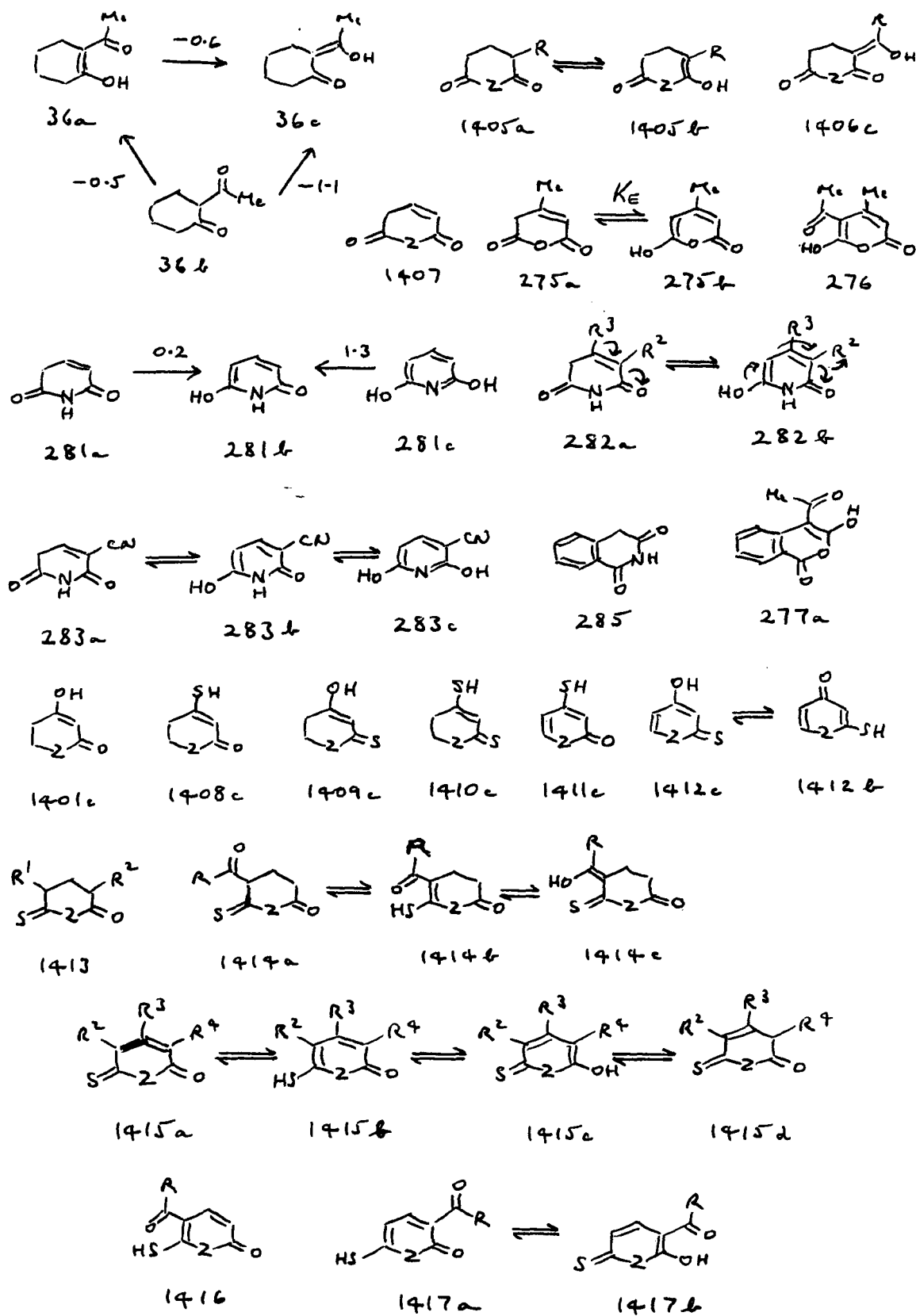
The compound class **1401** where Z is a hetero-atom may be regarded as, in some respects, a cross between the structural types **55** and **263**. Based on additivity assumptions for Z = O, extrapolation from the data of Table 87 would predict an enormous preference for **1401c** over **1401b** with  $\log K_E$  *ca.* 4.4 for formation of **268c** from the unconjugated tautomer. This is the only visible tautomer both for **268** and for its aromatised derivative **273** (section A.6.3). In the isomerisation process between **269** and **270** the former is favoured by  $\Delta G > 3 \text{ kcal mol}^{-1}$ ; if the same is true for **273**,  $\log K_T > 2.2$  results. It is reasonable that  $K_T$  should be somewhat attenuated on aromatisation since **273b** and **273c** are both, and perhaps to a comparable extent, aromatic structures.

2-Acylation of **268** will still further disfavour the unconjugated tautomer (i.e. **1401a**) but should leave the balance between the enol tautomers essentially unchanged. The same, perhaps to a lesser extent, is likely to be true for bland or other types of electronegative substituent; *cf.* **55** (section A.6.2). The 2-acetylation product is **303a** not **303b**, in line with the general preference for *endo*- and *exo*-C=C in 6- and 5-membered rings respectively (but note that formyl is anomalous: section C.6). This *endo*-preference is obligatory for any size of ring when aromatic; **311b** is an apparent exception since **311a** is anti-aromatic (section C.6).

$$\text{p}K_a(2\text{-X}) = 3.5 - 3.2 \sigma_m(\text{X}) \quad (\text{xxix})$$

The 2,4-dihydroxypyridinium cation **107H** (Scheme 71),  $\text{p}K_a$  1.37,<sup>4</sup> deprotonates to a mixture of **107b** and **107c** which the former is known to dominate (section A.6.3). We may use eqn. (xxix), section A.10.6, to estimate  $\text{p}K_a$  *ca.* 3.1 for the minor tautomer **107c**, leading to  $\log K_T$  *ca.* 1.7; compare *ca.* 2.2 for the corresponding pyrones (section A.6.3). Compounds of type (**1401**, Z = S or NR) have not been studied but a comparable dominance of tautomer **1401c** may be anticipated.

If aza-nitrogen is inserted to give compounds of type **1402** (*i.e.* containing an amidine or similar unit) these show a strong tendency to form the tautomeric zwitterion **1402Z** (Introduction, **7** and section A.6.2, for Z = NH and S respectively). This is overturned by the further insertion of nitrogen at the 5-position, to give **1403** where unless Z = NH, tautomerism is effectively locked (if Z = NH there are degenerate tautomers). This remains true if aza-nitrogen is removed to give **1404**, a uracil if Z = NR and a class of compound very resistant to iminol formation (section B.2.9).



Scheme 72

2.6-Dioxo Substitution. — Enolisation has not been reported for any compound of type (**1405**, R = H, Z = O, S or NR). For **1400** (Scheme 71) we estimate  $\log K_E$  *ca.* -14.5 and, while the second acyl group of **1405** should make enolisation much more favourable, it is unlikely that even R = Ph among 'bland' substituents could give any perceptible amount of **1405b**. The position could be different if R is a  $\pi$ -acceptor, but even here, on the analogy *e.g.* of **105** (Scheme 70), **1405b** remains unlikely as the major tautomer. The position for **36** (6-membered ring; Table 4, section A.1.2) is pertinent and is set out in Scheme 72. Here the processes **36b**  $\rightarrow$  **36a** and **36b**  $\rightarrow$  **36c** entail  $\Delta \log K_E$  6.2 and 6.4 respectively using the nearest relevant models, a little below the values for **1397**  $\rightarrow$  **1396** and **1399**  $\rightarrow$  (**55**, R = H) in Table 87, plausibly because of strain in both enols resulting from their enforced planarity. However, the 'pull' of lactone ( $\Delta \log K_E$ , Table 87) is considerably greater than that of ketone, and with its larger dipole that of a cyclic anhydride should be greater still, so **1406c** is likely to be the dominant tautomer, certainly for Z = O. This is perhaps less likely for Z = NR or S since their dipoles should be less and imides at least are less electron-deficient than anhydrides. Some of the results below throw light on this possibility.

If unsaturation is introduced as in **1407**, enolisation will lead to an aromatic structure, as in **275b** or **281b**. The energetic advantage of this has to be balanced against the loss of anhydride or imide resonance, respectively, both factors probably being greater in the latter case. In practice it turns out that, for both **275** and **281**, these factors almost cancel: the position for **281** is shown on Scheme 72, with about 60% of **281b**, whereas **275b** is stated to be the major but not dominant tautomer of **275** (section A.6.3). For both, the unconjugated **a**-tautomer dominates in nonpolar solvents. The proportion of dienol **281c** is in line with the known electronic effect of 6-substituents in 2-pyridone (section B.2.4). There is no information on (**1407**, Z = S) but in 5-membered ring oxoheterocycles (*q.v.*) the aromaticity order NR > S  $\gg$  O is balanced by a resonance energy sequence CONR  $\gg$  COO > COS which, if it applies here, should result in a somewhat greater bias towards the **b**-form.

This close similarity between Z = O and Z = NR plausibly means that we may discuss substituent effects for either as pertaining to both.  $\beta$ -Acylation of **275** locks it in the **b**-form shown for **276** and this is likely to be general. Other strongly electronegative substituents adjacent to carbonyl are likely to have the same effect; CN in **283** not only extinguishes **283a** but generates a substantial proportion of **283c** (only if Z = NH of course is a dienol possible).

Conversely, while  $R^2$  in **282** when electronegative will favour **282b**, there is marginal evidence that  $\pi$ -donors at  $R^3$  may favour **282a**. These trends can be rationalised, as shown, in terms of contrasting electron drifts; a feature of this compound series is the presence of ‘localised conjugation’ operating inside a nominally aromatic framework. This is discussed in section A.6.3 and possesses parallels elsewhere.

By contrast, the benzofused derivative **285** does not perceptibly enolise. In the distantly parallel case of the 6-membered ring mono-oxoheterocycles, those possessing  $\beta$ -NH relative to the position of benzofusion form iminols less readily than the parent monocycle by a factor of *ca.*  $10^2$  (section B.8.12). A similar factor here would account for this result. However C-acylation should encourage enol formation, and does; **277** in water exists exclusively as **277a** (section A.6.3), as is compatible with  $\Delta \log K_E$  6.2 for **36b**  $\rightarrow$  **36a** as discussed above. (This in fact is a minimal estimate; *cf.* Table 87).

Replacement of C=O by C=S. — Nothing is known but we may speculate. The crucial factor is that C=S is much more susceptible to C-type enolisation than C=O, by a factor of  $\Delta \log K_E$  *ca.* 6 in simple cases which should include 4-C=O  $\rightarrow$  4-C=S in **1401** (Scheme 71) and by possibly *ca.* 3.5 when adjacent to a hetero-atom as elsewhere. Its ability to enolise  $\beta$ -carbonyl relative to another C=O group is also greater, by  $\Delta \log K_E$  *ca.* 2 in **260** and therefore, plausibly, in **1408**; this differential is not likely to be less when placed adjacent to a hetero-atom as in **1409**. Hence **1408c** and **1409c** should be the dominant tautomers to an even greater extent than **1401c**. However, their behaviour on 2-acylation may be different. Whereas 2-acylation of **1409** should lead to a dominant structure similar in type to **303a** (Scheme 71), the corresponding species derived from **1408** contains a chelated  $\beta$ -thionoketone unit whose two possible enols, 4-SH and *exo*-C=C(R)OH, are of comparable importance (section A.8.3), so that a tautomeric mixture containing structures of both types may result.

By removing the special susceptibility of C=S to C-type enolisation, aromatisation of **1408** to **1411** and of **1409** to **1412** should result in much the same position as for **273** (Scheme 71). The slightly greater  $K_T$  values for thioamides *vs.* amides (typically  $\Delta \log K_T$  *ca.* 0.5; section C.21) should reduce the dominance of **1411c** and increase that of **1412c**, but not decisively so. The nature of Z is unlikely to have much effect on tautomeric balance.

While (**1413**,  $R^1 = R^2 = H$ ) will certainly not enolise, the effect of substituents  $R^1$  and  $R^2$  must be considered. The latter should behave as R in **1405**, leading probably if  $R^2 = COR$  to *exo*-enolisation as in **1406C**. Since *chelated*  $\beta$ -thionoketones show an almost even balance between the enol and thioenol tautomers, but  $C=S$  is less easy to enolise than a simple thione, possibly by a factor of *ca.*  $10^{2.5}$ , **1414c** like **406c** should be the dominant tautomer of **1414**, and perhaps by a greater margin. Also, while for  $R^2 = CO_2R$  in **1413** it is uncertain whether enolisation will be important – a structure analogous to **1405b** is the only viable option – for  $R^1 = CO_2R$  the likely result should be to replace **1414c** by **1414b** as the major tautomer, **1414a** remaining unimportant.

Aromatisation is likely to cause complications. For **1415** there are four viable tautomers, of which **1415c** and **1415d** should be roughly in balance (as for **275** and **281**), but since  $ZC=S$  C-enolises much more readily than  $ZC=O$ , **1415b** should be greatly preferred to **1415a**. Unless **1415d** is much more stable than **1415a**, therefore, **1415b** should be the major tautomer. 5-Acylation or similar should lock this as **1416** on the lines of **276**. The outcome for **1417** is more problematical, since the  $OH\cdots O=C$  bond of **1417b** might be strong enough to overcome the otherwise expected bias, due to through-conjugation, in favour of **1417a**. More probably it will not, since this is the only factor in its favour; conjugation *inside* the ring should be little affected by hydrogen bonding, and this bond *per se* is worth  $\Delta \log K_E < 2$  (Appendix 4). If NH replaces CHR to give **1403** or **1404** (Scheme 71) any compound in which  $C=S$  replaces  $C=O$  is now a thioamide, and with thioiminol at least as disfavoured as iminol formation, the tautomeric position for these two structures should be little affected. The exception is **1402**, where the greater acidity of SH *vs.* OH should make the zwitterion still more dominant.

Short Summary. — All compounds of type **1401** exist predominantly as **1401c**, **1401a** being marginally competitive. 2-Substitution and aromatisation both effectively abolish the unconjugated tautomer, but the second sharply reduces the dominance of the **c**-tautomer though this still remains the major one. Substitution of  $C=S$  for one or both  $C=O$  is unlikely to affect any of these conclusions. The parent 2,6-dicarbonyl compounds **1405** (Scheme 72) do not enolise, though  $\pi$ -acceptors in the  $\beta$ -position may induce enolisation in the sense of **1406c** (though not if R in **1406** is a  $\pi$ -donor, and not in any case for *both*  $C=O$ ). Unsaturation to give **1407** induces enolisation but not (for  $Z = O$  or NR) to any very dominant extent unless the enol is ‘locked’ by a neighbouring  $\pi$ -acceptor, as in **276**.  $\pi$ -Donors at the 4-position ( $R^3$  in **282**) tend to stabilise the **a**-tautomer and  $\pi$ -acceptors elsewhere (*e.g.*  $R^2$  in **282**) the **b**-tautomer; for  $Z = NH$  this trend is continued by the dienol **283c**. Substitution of  $C=S$  for  $C=O$  as in **1413** is predicted to give mostly **1415b**, **1415c** and any unaromatised tautomer being now of much less importance.

## C.8 $\beta$ -Iminoketones and Aminoenones: General Considerations

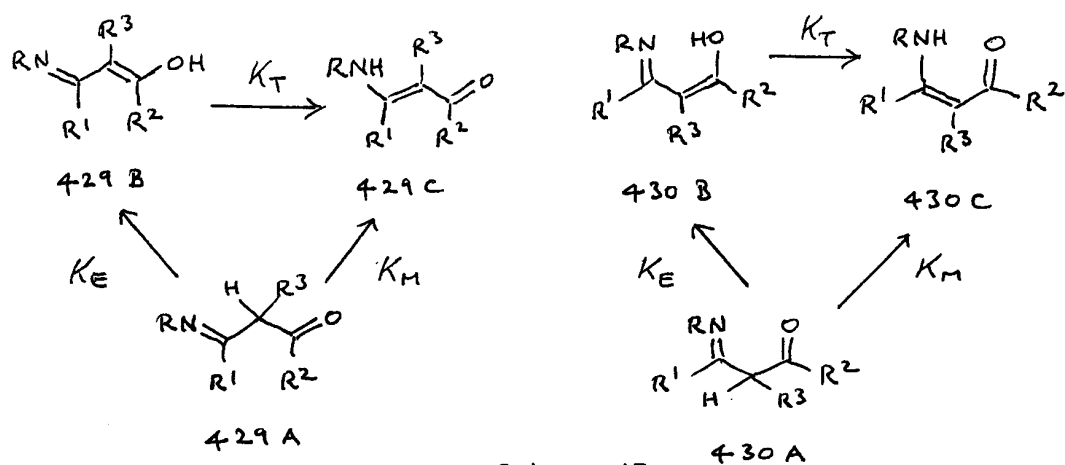
Enol conjugation with another C=O (Scheme 10) is considered in sections C.4 and C.5 for chelated **261** and in C.6 and C.7 for unchelated *endo*-enols **260**. More generally, one or both of X = O and Y = O in either may be replaced by S or NR, giving six possible combinations of X and Y (**655**, Scheme 24, section A.12). Of these, two are specially important: the  $\beta$ -diketones considered above, and those in which X = NR, Y = R. The option in which X = NR, Y = S appears generally similar to the latter so far as is known, though an important difference according to our calculations (section A.11.1) is that, here,  $K_T$  is predicted as *greater* for the chelate instead of as less. Scheme 17 (from section A.10) summarises the chelated **430** and unchelated **429** possibilities.

While these are among the most widespread of potentially tautomeric structures, the dominance of the aminoenone C-tautomer is so great in most contexts that the major tautomer, as for the corresponding amides of which they are vinylogues, is rarely in doubt. For example, (**435**, R = alkyl) (section A.10.4) and **832** (section B.2.3) possess log  $K_T$  values in water of *ca* 8.7 and 9.1 respectively. However, certain caveats are necessary:

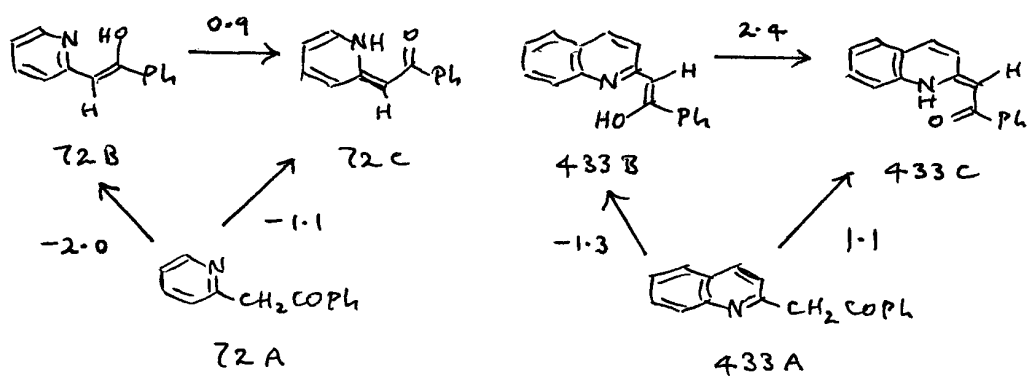
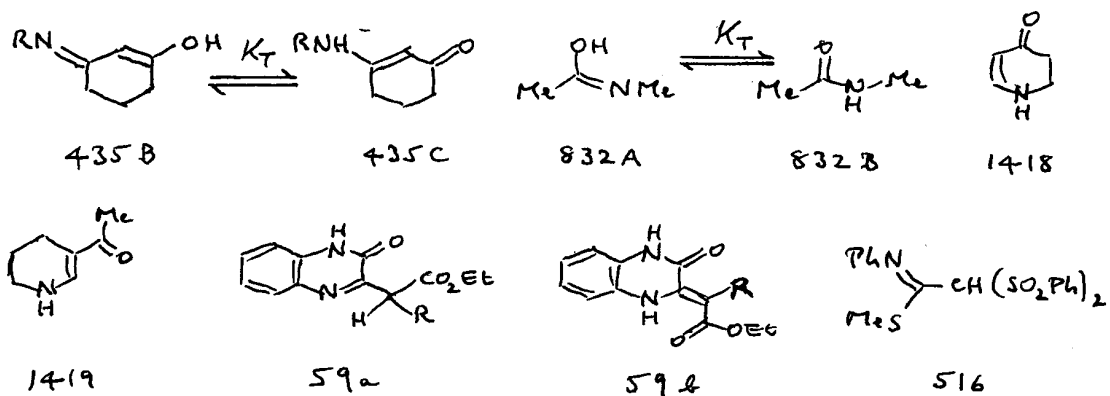
(i) There is no information on  $K_T$  for chelated structures but a strong suspicion, backed by calculation (section A.10.1), that it may be substantially less, possibly as low as  $10^5$ . Two factors could help to bring this about: the greater strength of OH---N than of NH---O hydrogen bonding; and the probability that resonance energy will be a function of dipole separation, and likely to be less than when this is less extended than in **429C**. The *reverse* prediction for chelated aminothiones, noted above, largely results from the extreme weakness of hydrogen bonding to SH.

(ii) It is possible therefore that compounds such as **1418** and **1419** will also be less overwhelmingly in the aminoenone form than **435**. A plausible order in  $K_T$  is **429** > **1419** > **1418** > **430** but nothing is known.

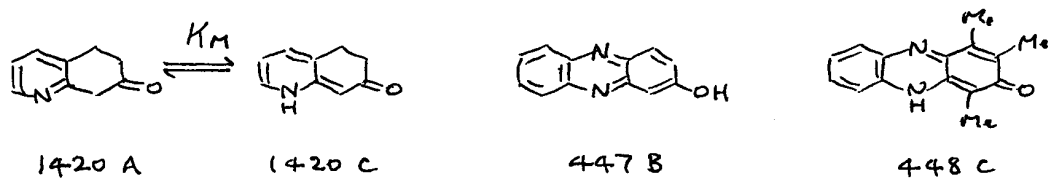
(iii) While R<sup>1</sup> and R<sup>2</sup> if without pronounced electronic character are unlikely to affect tautomeric balance very much, R<sup>3</sup> in **430B** and/or **430C** if bulky enough can cause distortion away from planarity sufficient to prevent conjugation in either form. For example, (**59**, R = H) exists as the aminoenone **59b** but even for R = Me it reverts to **59a**. Molecular mechanics is likely to be better than empirical rules at making viable predictions. This



Scheme 17



Scheme 73



is equally a hazard for  $\beta$ -diketones [see section C.4.(b)] and several examples for each compound class are listed in section A.1.4. Related structures also have this problem; **516**, for example, does not enolise at all (section A.10.12).

(iv) If C=N is part of an aromatic structure then formation of the **C**-tautomer is greatly inhibited and may be suppressed. Most such cases involve chelates. Typically the **A**-tautomer will dominate but any reduction in ring aromaticity, as brought about *e.g.* by benzofusion, will partially and may wholly restore the importance of the **C**-form. An example is given as Scheme 73 (*ex* Section A.10.2); here **72A** but **433C** are the dominant tautomers. It is possible to gain the impression from the literature that the **B**- and **C**-tautomers are favoured for monocyclic and benzofused heterocycles but here this is misleading. For transfer of **430** from an alkane to water we typically find  $\Delta \log K$  to be *ca.* -2.5 for  $K_E$ , -1 to -1.5 for  $K_M$  and 1.5 to 1 for  $K_T$  (Appendix 2), so as with other chelates such as the  $\beta$ -diketones, in water both these tautomers are relatively disfavoured and the **B**-form is never important. Nonchelated aromatic aminoenones such as **1420C** are formally possible but none have been reported. However, **B/C** tautomerism is known for several polycyclic heterocycles whose aromaticity has been lowered by benzofusion, examples including **447** and **448** which exist in water predominantly as shown and for which  $K_T$  therefore probably lies close to unity.

(v) When  $R^2$  and  $R^3$  in **430B** constitute part of an aromatic ring, the **A**-tautomer is suppressed and the **B**-tautomer greatly enhanced. While polycyclic structures incorporating this feature are in principle possible (Scheme 25, section A.12.7), their commonest exemplars are Schiff bases: **588** in water (section A.10.18) possesses  $\log K_T$  *ca.* 1.9 by extrapolation from other solvents. This probably represents an attenuation of  $10^3 - 10^4$  in  $K_T$  relative to an uncomplicated structure of type **430** (Scheme 17), quite similar to the  $10^{4.1}$  we estimate as the difference, in the same direction, between 2-piperidinone **835** (section B.2.3) and 2-pyridone **847** (section B.2.4). It is difficult to write a plausible structure incorporating these features and based on **429**, and indeed all known examples are chelates.

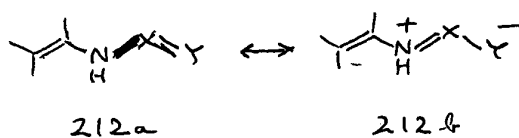
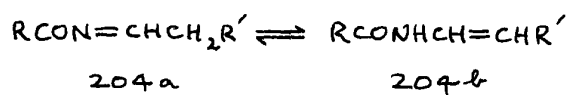
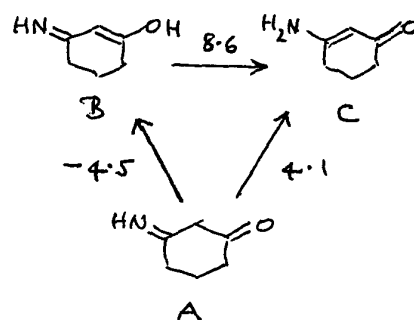
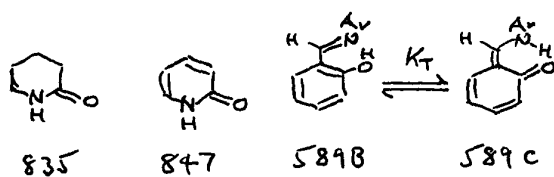
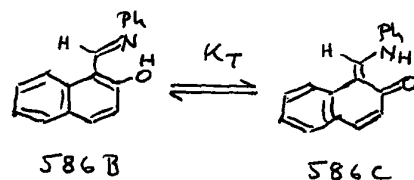
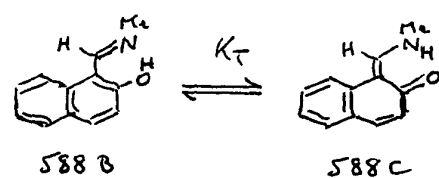
In sum: aromaticity at  $R/R^1$  or at  $R^2/R^3$  makes tautomers **A** and **B**, respectively, competitive with the otherwise dominant tautomer **C** and often more important. Chelates dominate both categories.

## C.9 $\beta$ -Iminoketones and Aminoenones: Substitution Patterns

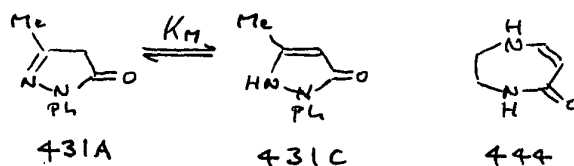
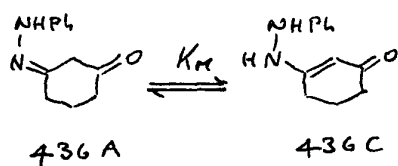
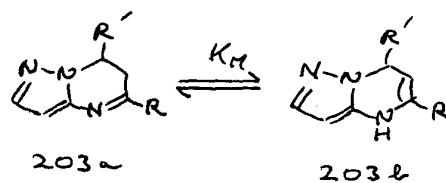
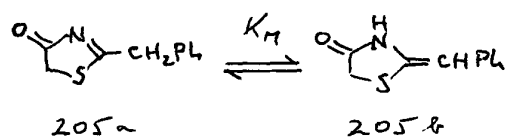
It might be expected that substituents R in **429** or **430** that enhance the  $\pi$ -donor ability of NH, and/or substituents R<sup>2</sup> that enhance the  $\pi$ -acceptor ability of carbonyl, should increase the dominance of the aminoenone tautomer and *vice versa*. With rare exceptions, this principle is fulfilled. We also consider substitution at R<sup>1</sup> and the effect of replacing the entire COR<sup>2</sup> unit by other  $\pi$ -acceptors, such as NO<sub>2</sub>, SO<sub>2</sub>R and CN. Data are drawn from a wide variety of compound types in the interests of generality.

N-substituents R. — The only hard evidence on  $K_T$  comes from **588** and **586**, leading to  $\Delta \log K_T$  ca. -1.3 for NMe  $\rightarrow$  NPh (section A.10.18). Consistently, a LFER study on (**589**, Ar = substituted phenyl) shows small negative  $\rho$  values leading to a quite narrow spread: only  $\Delta \log K_T$  -0.5 between 4-NMe<sub>2</sub> and 4-NO<sub>2</sub>. Different rules apply to  $K_M$  (Scheme 17). Simple imines are preferred over their enamine tautomers (section A.4 *passim*) but the latter are stabilised by  $\pi$ -acceptors; **204** gives **204b** not **204a** (section A.4.4) probably through resonance of type **212** (section A.4.6).  $\pi$ -Donors stabilise the imine but the effect is much weaker. The apparently paradoxical outcome is that electron acceptors stabilise **B** over **C** when tautomer **A** is unimportant, as found for oxoheterocycles (sections A.10.7 and B.2.5), but **C** over **A** when **B** is negligible or absent, as in **203** and **205**. The opposite situation necessarily applies when the substituent on nitrogen is an electron donor. In asymmetrical, 3-way equilibria such as those of Schemes 17 and 74, for which  $K_M = K_E K_T$ , it is also required that their *solvent sensitivity* shall obey the relation  $K_M \sim K_E + K_T$  as is found empirically (Appendix 2) for solvent effects. In **203** however a  $\pi$ -donor at R will reverse this preference; *cf.* effects at R<sup>1</sup>, below.

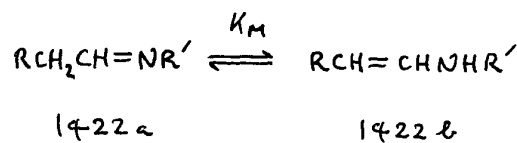
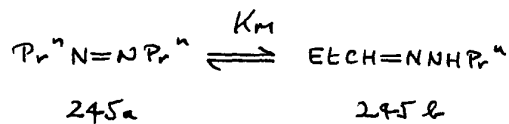
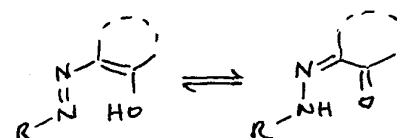
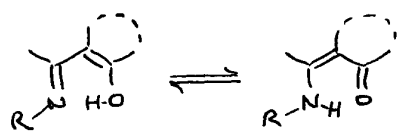
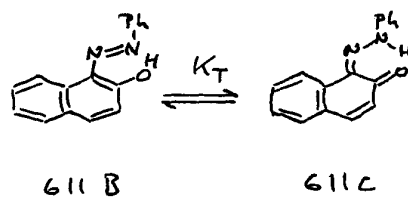
Scheme 74 presents as (log)  $K$  values the mean of our calculations by three methodologies (section A.10.1). Though calculated for the gas phase,  $K_T$  is indistinguishable from that found for **435** in water and this analysis also suggests **A** > **B** in such a case. Traces of **436A** have been observed in DMSO, which if its solvent dependence resembles that of **431** (section A.10.2) could imply  $\log K_M$  3.0 - 3.5 for **436** in water. A range of similar compounds for which the **C**-tautomer is antiaromatic, discussed in section A.10.4, include **1421**; here **1421A** and **1421C** result since the substituent on tautomeric nitrogen is effectively phenyl ( $\sigma_R$  -0.11) and 4-pyridyl ( $\sigma_R$  0.96) respectively (see Table 2). Compound **444** would be expected to exist as shown.



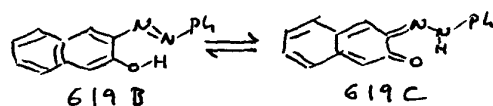
Scheme 74



444



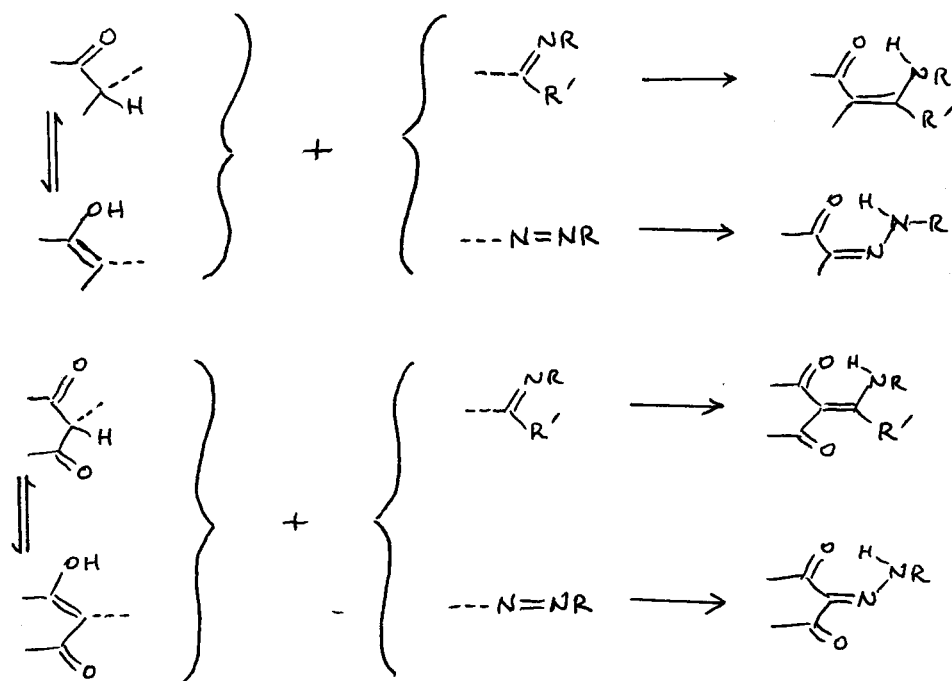
Scheme 75



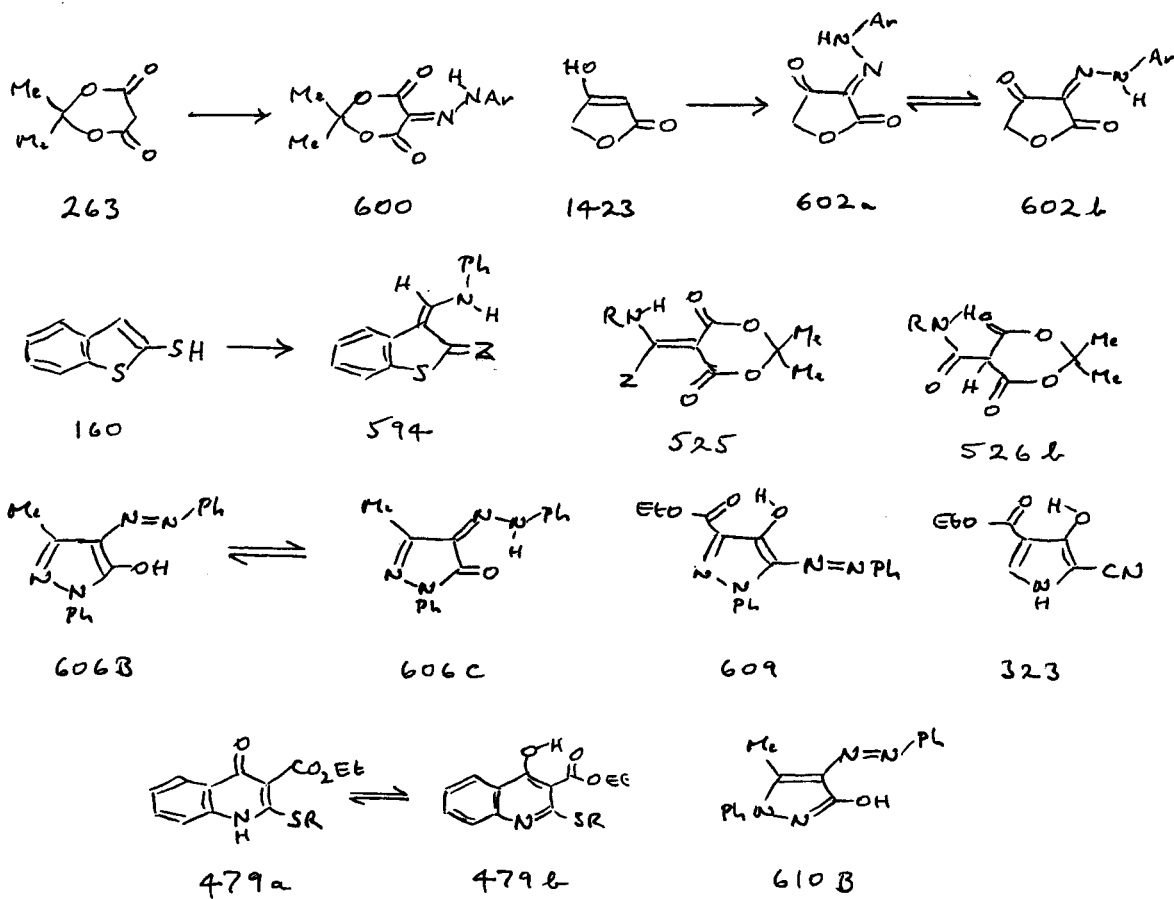
Quantitative data are also available for some azo/hydrazo equilibria. With  $\log K_T$  values in water close to 0.4 and 0.0 respectively the tautomeric behaviour of **586** and **611** (section A.10.19) is surprisingly similar, given that the extra aza-nitrogen atom of **611** counts as a strongly electronegative substituent. The probable reasons are twofold. The first (Scheme 75) is hydrogen bonding. For an aminoenone, the stronger OH---N bond of the **B**-tautomer attenuates  $K_T$  (section A.10.1), but in the corresponding azo/hydrazo equilibrium the position is reversed: NH will now be a stronger donor, whereas the azo-linkage is a very poor proton acceptor. Secondly, while imines **1422a** are favoured in water over enamines **1422b**, in this simple case by almost  $10^2$  (section A.4.1), the position is reversed in the corresponding azo/hydrazo case: **245a** goes to **245b** in Bu<sup>t</sup>OH with  $K_M$  ca. 60 (section A.5.1), an overall shift of ca.  $10^{3.5}$  to set against the extra electronegativity attaching to azo-compounds vs. Schiff bases.

On very limited evidence (section A.10.19), benzofusion in Schiff bases enhances  $K_T$  by  $\Delta \log K_T$  ca. 1.0, and by contrast with the corresponding oxoheterocycles this effect is not positionally sensitive. No such data exist on the analogous azo-compounds, but given the typical  $\Delta \log K_T$  ca. -1.8 when a quinonoid structure results (Appendix 5), the existence of **619** as **619B** is as expected.

The outcome, for imine or azo-compound as *substituent* into CH<sub>2</sub> adjacent to C=O (or the corresponding enol), is summarised as Scheme 76. Aminoenone resonance is so dominant as to override any other sort of tautomeric preference, even aromaticity. A handful of examples is shown. The same tautomeric form results from ketones (**263** → **600**) and their enols (**1423** → **602**); parent compound thiols are converted to the thione (**160** → **594**, Z=S). Where alternative configurations are possible, as for **602**, any preference is likely to be slight. While quantitative evidence is lacking, it seems probable that the tautomeric ‘pull’ of β-dicarbonyl compounds will generally exceed that of their monocyclic analogues, at least in cyclic structures (see substitution at R<sup>2</sup>, below); in **525** this effect is so pronounced that (**525**, Z = OH) exists as such, despite loss of the amide resonance that would have attached to its tautomer **526b** (section A.10.13). Exceptions are few and, in aqueous terms, can be misleading, as for **606** where **606B** is found in DMSO but not elsewhere (section A.10.19). The only relevant exception we have encountered is **609** whose hydrogen bond, as shown, should not be sufficient to tip the balance (Appendix 4). However all parent compounds of this type (**140**: section C.18) exist exclusively as the enol even in water and whatever the ring π-donor (section A.2.8) so the oxo-tautomer may just be extremely disfavoured. In **610**, where -N=NPh itself cannot tautomerise, it acts simply as an electronegative substituent, like CN in **323** which in structure somewhat resembles **609**.



Scheme 76

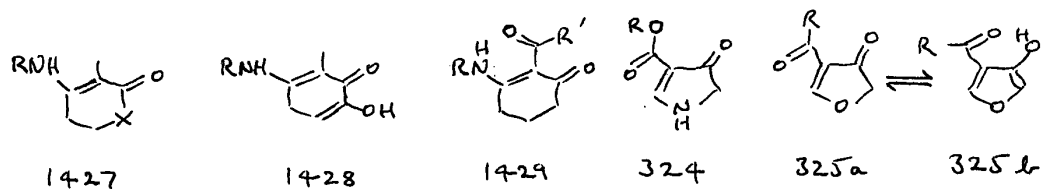
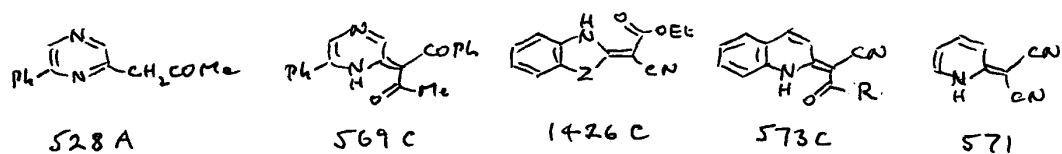
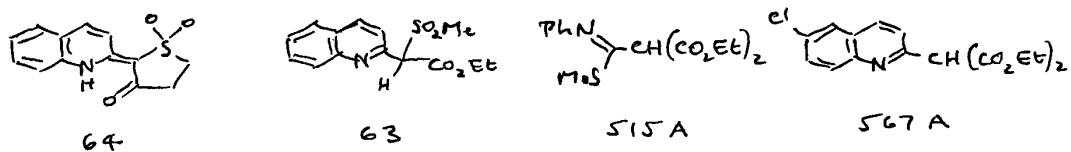
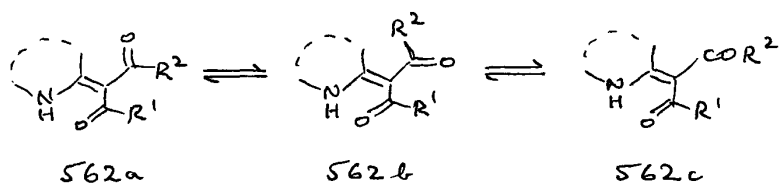
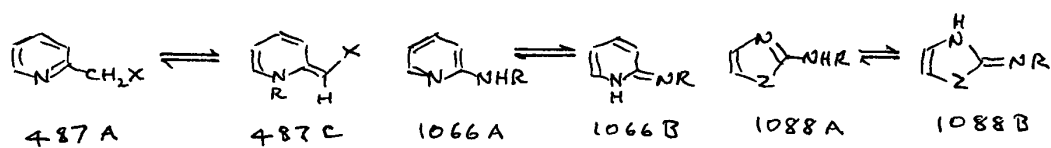
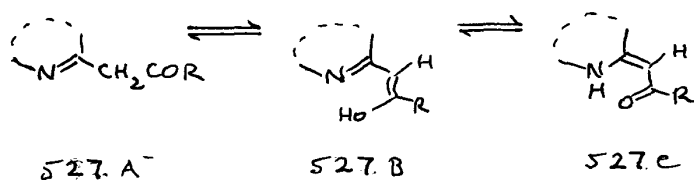
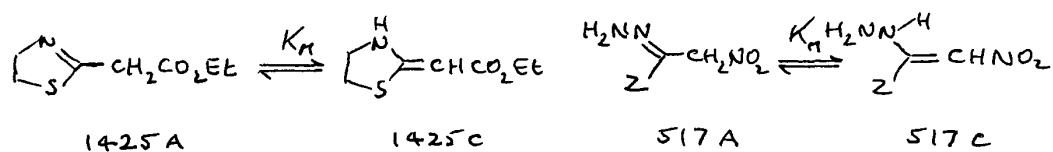
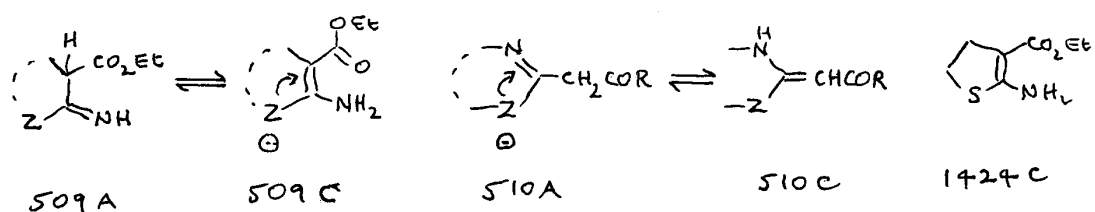


*Substitution at R<sup>1</sup>.* – A  $\pi$ -donor at R<sup>1</sup> or R<sup>2</sup> in **429** or **430** provides a rival source of conjugation for C=N and C=O respectively so may tend to lock the structure in this form. While this effect at R<sup>2</sup> is trivial when the **C**-tautomer is anyway favoured, a  $\pi$ -donor at R<sup>1</sup> sets up the **A**-tautomer as a serious rival and the outcome will depend on circumstances. [Aromatisation at R/R<sup>1</sup> has a similar effect: see C.8.(iv)]. We draw attention to the crucial importance, when R<sup>1</sup> is a  $\pi$ -donor Z, of *lone pair alignment* in the latter. In structures of types **509** and **510** (section A.10.12) the Z lone pair will interact preferentially with C=C and C=N respectively, so favouring **509C** but **510A**. For example, while **1424** appears to exist only as **1424C** in all solvents examined, we estimate  $\log K_M$  *ca.* -0.3 in water for **1425**. However, if Z = S in this compound is replaced by Z = NH then (in CHCl<sub>3</sub>)  $\Delta \log K_M$  *ca.* 0.7 results, so it is possible that the lone pair directionality shown by Z = O and S does not apply to NH. This topic might benefit from calculation. It is also uncertain which alignment, if either, is preferred in open-chain structures; there is marginal evidence in favour of greater support for the **C**-tautomer, such as a shift in balance from **517A** towards **517C** in the sequence Z = S < NHPH < NHMe, *i.e.* the  $\pi$ -donor order (section A.10.12). In other cases the balance may depend on a stereochemical preference based on different factors. The effect of a  $\pi$ -acceptor at R<sup>1</sup> has not been explored, but since this would be cross-conjugated with RNH, its effect is likely to be minimal.

*Substitution at R<sup>2</sup>.* – Cyclic and open-chain compounds have to be considered separately. Most of our information concerns the former. We have cross-compared (section A.10.14) available data for heterocycles of type **527** in a variety of organic solvents as to the equilibrium between **527A** and **527C** (all solvent studies suggest that **527B** however important in nonpolar solvents will be of negligible importance in water relative to **527C**). This leads to a predicted order in  $K_M$  of CPh > COMe > CO<sub>2</sub>Et with about a factor of 10 between each and CN about level with CO<sub>2</sub>Et. In addition, COCO<sub>2</sub>Et appears to be capable of generating a large preponderance of the **C**-tautomer in every case examined. These trends suggest *resonance acceptor ability* as the key factor in enhancing  $K_M$ ; if so, COCF<sub>3</sub> and COCN should have an effect similar to COCO<sub>2</sub>Et.

$$\log K_M = -13.2 + 27.9 \sigma_d - 42.3 \sigma_e \quad (\text{xxxvi})$$

Work on some 2-pyridyl anhydrobases **487** where R = Me (section A.10.9) is also relevant and in part contradictory. For five examples including X = H we derive eqn. (xxxvi). This demonstrates resonance factors



Scheme 77

alone to be operative:  $\sigma_d \equiv \sigma_R$ , plus Charton's  $\sigma_e$  which is a measure of *resonance susceptibility* under conditions of electron demand. Table 88 summarises the results in terms of  $\Delta \log K_M$  and includes predictions. These results necessarily neglect any contribution from the intramolecular hydrogen bond of (**487C**, R = H) when present, but since that of **72C** (Scheme 73) adds only  $\Delta \log K_M$  1.0 to the value for X = CPh in Table 88, and there is no better proton acceptor in the list, serious distortion from this cause is unlikely. There are problems: the observed  $K_M$  for CPh is  $10^4$  that for CO<sub>2</sub>Et, not  $10^2$  as implied for **527** above, and there is no basis in prediction for any appreciable difference between CPh and COMe. Both discrepancies may be genuine. The enhanced  $\rho$  values which are implied could be due to change in solvent, substrate specificity, or both, while steric effects may enter into the second comparison. However, many of these estimations are highly suggestive, with the sequence COR > NO<sub>2</sub> > CO<sub>2</sub>Et  $\geq$  CN receiving widespread empirical support. The very large predicted difference between SO<sub>2</sub>Me and SO<sub>2</sub>CF<sub>3</sub> may also be significant in view of the above suggestion that COCF<sub>3</sub> should be exceptionally effective in generating the **C**-tautomer. Provisionally, we suggest that the predictions of Table 88 may be suitable at any rate for qualitative use. They may be better than that; while the equations for **1066** (section B.4.4) and (**1088**, Z = S) (section B.4.5) show very different intercept terms, their  $\rho$ -values are quite similar. These equations by contrast to that for **487** are field-effect ( $\sigma_I$ ) relationships and their substituent ordering is both very different and not so extreme (section C.31 below).

**Table 88. Observed <sup>a</sup> and Estimated <sup>b</sup>  $\Delta \log K_M$  Values relative to X = H for 2-Pyridyl Anhydrobases **487** in Water**

X	$\Delta \log K_M$	X	$\Delta \log K_M$	X	$\Delta \log K_M$
Ph	1.4	CONH <sub>2</sub>	( 5.7 )	SO <sub>2</sub> CF <sub>3</sub>	( 10.4 )
CF <sub>3</sub>	( 4.7 )	SO <sub>2</sub> Me	( 5.8 )	CPh	10.9
SO <sub>2</sub> Ph	5.4	CO <sub>2</sub> Et	7.0	COMe	( 11.0 )
CN	( 5.7 )	NO <sub>2</sub>	( 8.3 )	HCO	( 11.7 )

<sup>a</sup> Relative to  $\log K_M$  -13.0 for X = H (section A.4.7) <sup>b</sup> Bracketed: eqn. (xxxvi).

In principle two acceptors should be more effective than one but this is not always the case. Two constraints operate: lack of planarity will diminish conjugation, whereas steric crowding can abolish it. Both may be analysed, for two acyl groups, in terms of **562**. Where planarity is possible, **562b** will be preferred with  $R^1$  the less bulky of  $R^1$  and  $R^2$ ; if  $R^2$  is too bulky for  $COR^2$  to lie planar, partial planarity as **562c** is still likely but its effect will be reduced. The Z,Z-conformation **562a** is disfavoured on both steric ( $R^1/R^2$  clash) and electronic ( $\pi$ -repulsive) grounds so is only likely if  $R^1$  and  $R^2$  form part of a ring, when it becomes exceptionally effective; see (**625**,  $Z = OH$ ) above. Related compound pairs which illustrate the ends of the scale include **64**, which is fully enolised, and **63**, which is too crowded to enolise at all (section A.10.15). The least effective as diacyls of common acyl groups are diesters, both through crowding and because  $\Delta \log K_M$  is relatively small (Table 88): **515** (section A.10.12) and **567** (section A.10.15) exist as shown in polar solvents. Diketones fare better: insertion of  $COPh$  into **528** (section A.10.12) transforms **528A** entirely into **569C** (section A.10.15). The most effective  $\pi$ -acceptor at this level is  $CN$ ; planar itself with  $C=C$ , it does not disrupt the planarity of other groups. In such a combination it will nearly always generate the **C**-tautomer. Examples include (**1426**,  $Z = O$  or  $S$ ) and **573**; we estimate the likely contribution of  $CN$  in such cases as  $\Delta \log K_M \geq 2$  (section A.10.15: the configuration of each is known and may be noted). And in every known case, even for such aromatic species as **571** (section A.10.15),  $\beta$ -dinitriles appear to give exclusively the **C**-tautomer. Quantification of this effect is difficult but may be roughly attempted for **571** in the following way. The precursor molecule 2-cyanomethylpyridine is known to exist in the **A**-form and, employing a factor of  $\Delta \log K_M -1.8$  for  $X = COPh \rightarrow X = CN$  (Table 42, section A.10.14) added to  $K_M -1.05$  for **72** (section A.10.2), we obtain a rough estimate of  $\log K_M \sim -3$ ; a notional value of  $\log K_M \geq 2$  for **571** would lead to  $\Delta \log K_M \geq 5$  for the second nitrile group. Such a value, if only approached, presumably results from the unit's absolute planarity.

If  $R^2$  is part of a ring there is much less scope for variation. This has not been explored but we may speculate. If  $R^2$  is a  $\pi$ -donor  $X$  (**1427**) the  $\pi$ -acceptor ability of  $C=O$  should be enhanced, as in **263** (Scheme 71, section C.7), where it probably has a conformational explanation:  $MeCO_2Me$  and  $\gamma$ -butyrolactone possess  $\mu = 1.72$  and  $4.27$  debyes respectively. Few other options are possible:  $Z = CF_2$  might have some effect, but  $Z = C=O$  would give **1428** (*cf.* **110**, Scheme 70). However a  $\pi$ -acceptor at  $R^3$  in **429** would probably reinforce the preponderance of the **C**-tautomer and, if acyl, should lead to **1429**, essentially a variant on **562b**. The nearest known exemplars are **324** which exists as such in  $KBr$ , and **325** which shows no trace of **325b** even in  $CCl_4$  (both section A.6.6). The possible outcomes if  $R^1$  and  $R^2$  were both  $\pi$ -donors and  $R^3$  a  $\pi$ -acceptor lie beyond the bounds of speculation.

### C.10 Enolisation and Aromatisation in 5-Membered Ring 2-Oxo(thiono)-heterocycles with One Ring Hetero-atom

We estimate  $\log K_E$  ca. -14.5 for **1400** (Scheme 72 and Table 87) and unsaturation as in **1430** is unlikely to make enolisation much more favourable. However, the equivalent process in a 5-membered ring generates an enol **129b** (Scheme 78) which is also aromatic so that this becomes a viable species (section A.2.7). Each of the two keto-tautomers **129a** and **129c** possesses a benzofused form, **131a** and **132a** respectively, the enol **b** of which is also aromatic. Replacement of any CH or all in any of these enol forms by aza-nitrogen leaves the above analysis, but not the tautomeric balance, essentially unchanged. Hence the possible variants are considerable in number and will form the subject matter of the next several sections. In terms of continuity with section C.7, note that **288b** (section A.6.4) is overwhelmingly the favoured tautomer of **288**, just as is **1401c** (Scheme 72) for its 6-membered ring homologue.

*The Influence of Z on Tautomeric Form.* — The balance between **129a** and **129c** is known for Z = NH and NMe and may be estimated for Z = O and S (Table 3, section A.1.1):

Z	=	NH/NMe	O	S
$\log K_{\text{delta}}$	=	1.0	2.1	2.9

By contrast, while oxo-forms appear to predominate for all the parent compounds of Scheme 78, no  $K_E$  value is known.

Katritzky and co-workers (section A.2.7) have discussed the expected effect of Z in **129**. The gain in energy resulting from aromatisation should favour the enol **129b**, in the order Z = NR > S >> O (Table 12); however loss of the resonance energy contained in Z(C=O) will counter this, in the order Z = NR >> O > S. This leads to an expected order S > NR ~ O for the ease of enol formation, which is consistent with the evidence. However all results are qualitative and the great majority, for both parent compounds and their derivatives, have been obtained in organic and often nonpolar solvents which, relative to water, are likely to favour enol forms. Hence the task of extrapolation to aqueous solution is, here, exceptionally difficult. In attempting it below we are forced to use additive and other assumptions of doubtful validity whose predictive ability cannot be adequately tested by the known facts.

**Table 89. Estimated  $K_{\text{delta}}$  and  $K_{\text{E}}$  Values (Scheme 78) for Parent and Benzofused 5-Membered Ring 2-Oxo(thiono)heterocycles containing One Heteroatom<sup>a,b,c</sup>**

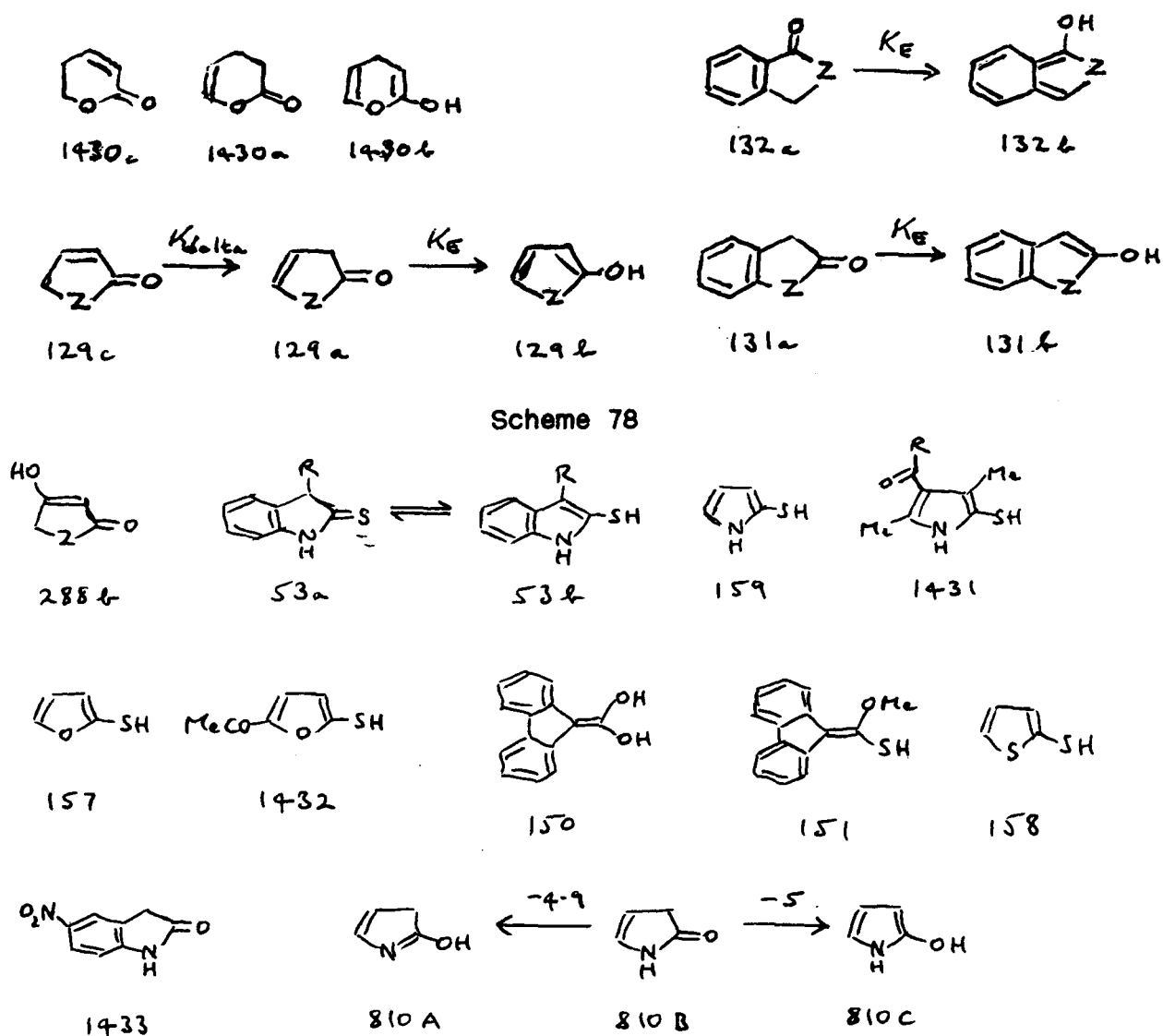
Z(C=O)	129c →	129a →	129b	131a → 131b	132a → 132b
	log $K_{\text{delta}}$	log $K_{\text{E}}$	log ( $K_{\text{delta}}K_{\text{E}}$ )	log $K_{\text{E}}$	log $K_{\text{E}}$
NH	- 1	- 6	- 7	- 6.5 <sup>d</sup>	- 9
			C=O	C=O	C=O
O	- 2	- 5	- 7	- 5.5 <sup>d</sup>	- 9
			C=O	C=O	C=O
S	- 3	- 1.5	- 4.5	- 2	- 6
			C=O	C=O	C=O
Z(C=S)	129c →	129a →	129b	131a → 131b	132a → 132b
	log $K_{\text{delta}}$	log $K_{\text{E}}$	log ( $K_{\text{delta}}K_{\text{E}}$ )	log $K_{\text{E}}$	log $K_{\text{E}}$
NH	-1 <sup>e</sup>	- 2.5	- 3.5	- 3 <sup>d</sup>	- 5.5
			SH <sup>e</sup>	C=S	
O	- 2 <sup>e</sup>	- 1.5	- 3.5	- 2	- 5.5
			SH <sup>e</sup>		C=S
S	- 3 <sup>e</sup>	2	- 1	1.5	- 3
			SH <sup>e</sup>	SH <sup>e</sup>	C=S

<sup>a</sup> Predictions to nearest 0.5. <sup>b</sup> Observed major tautomer, not in water, is indicated. <sup>c</sup> For **129**, only the composite term  $K_{\text{delta}}K_{\text{E}}$  is visible. <sup>d</sup> Estimates (see the text). <sup>e</sup> For commentary see text.

Table 89 is perhaps best described as “structured guesswork.” Here we use additional assumptions to construct an interlocking grid of log  $K$  values which do less injustice to the known facts than any other we have been able to devise. The following guidelines have gone into it:

(i) Estimates are made to the nearest 0.5 in log  $K$ .

(ii) Under the heading Z(C=O), log  $K_{\text{delta}}$  is approximated as shown. The extension of these values to Z(C=S) is unlikely to be valid and is intended solely as a temporary measure in the interests of symmetry.



(iii) For **129**, only the composite term  $K_{\text{delta}}K_E$  is visible. Nevertheless  $K_E$  possesses a potential use which is described in (iv) below.

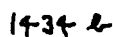
(iv) Benzofusion of **129a** gives **131a** which should be marginally less susceptible to enolisation. There is no direct evidence on this topic and scarcely any even on 'N-type' tautomerism, where however the two known examples (sections B.2.4 and B.4.5) agree on  $\Delta \log K_T$  ca. 0.5. We have adopted this estimate *faut de mieux* with no justification other than convenience.

(v) Benzofusion of **129c** gives **132** whose enol is quinonoid. All present evidence (Appendix 5) points to a penalty of  $\Delta \log K$  ca. -1.8 which we round off to -2 for present purposes. Again, this is assumed to apply, with rather more justification, to both compound series.

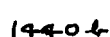
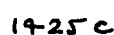
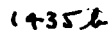
(vi) Values of  $\log K_E$  -9.5 and -5.8 for **150** and **151** (section A.3.4), which structurally parallel  $O(C=O)$  and  $O(C=S)$  respectively, lead to  $\Delta \log K_E$  3.7 for this difference which, in Table 89, we round off to 3.5 and assume to be applicable here and independent of  $Z$ . There is no empirical or theoretical justification for the second assumption but *faut de mieux* again applies.

A handful of compounds provide relevant data. For (**131**,  $Z = O$ ) substituted by Ph in the 3-position,  $\log K_E$  is -2.9 (section A.2.7); a mean value of  $\Delta \log K_E$  *ca.* 2.7 for the effect of  $R^2 = Ph$  in compounds of type  $R^1COCH_2R^2$  (Table 86) extrapolates to  $\log K_E$  *ca.* -5.6 for the parent compound which appears as -5.5 in Table 89. A similar treatment applied to (**53**,  $R = Ph$ ), which exists mostly as **53b** in MeOH,  $CHCl_3$  and benzene but as a mixture of tautomers in aqueous EtOH, implies  $\log K_E \geq 0$  in water, leading to a likely value of  $\log K_E$  *ca.* -3 for the parent thione. While no trace of enol is detectable for (**131**,  $Z = S$ ) even in  $CCl_4$ , its thione equivalent is present as the thiol in KBr, a polar medium, so will certainly be the dominant tautomer in water. The ‘guesstimates’ of Table 89 for these two compounds have been chosen to be compatible with this evidence. Extrapolation to the thione equivalent of (**132**,  $Z = S$ ) also gives, qualitatively, the correct result. Similarly, given the expected effects of substituent and solvent in promoting the enol, its absence from **1433** even in DMSO implies  $\log K_E < -5$ , which is compatible with an estimate for the parent compound, employing  $C=S \rightarrow C=O$ , of  $\log K_E$  *ca.* -6.5 but of course does not prove it. Some qualitative results are apparently incompatible: we predict the thione structures for **157**, **158** and **159** where all have been identified as the thiol. However **158** was examined in benzene and **157** and **159** in the liquid state, which effectively counts as nonpolar (the *opposite* phase bias from that of the solid, which generally behaves as if polar). Equally ambiguous is the evidence of **1431** and **1432**, which with their electronegative substituents might be expected to exist as the thiols in any solvent. The two likeliest causes of these discrepancies if genuine *and* systematic are either or both of (a)  $K_{\Delta}$  is less negative for thiones, (b) the difference in  $K_E$  between the oxo- and thiono-series is greater than we have assumed. It is unfortunate that more of these compounds were not examined in polar media. Despite serious doubts, therefore, we submit these estimates as a possible basis for calculation till better values come along (see however section C.11 below).

If this approach is valid we are now in a position to answer our self-imposed conundrum (section B.2): the enol **810C** and the iminol **810A** (section B.2.3) may well be disfavoured in water to much the same extent.



**Scheme 79**



The Influence of Substituents on Tautomeric Form. — For the monocycles **1434** we adopt the nomenclature shown in Scheme 79 (*cf.* section A.1.1). Our treatment differs according as to whether the substituents are  $\pi$ -donor/acceptor in character or may be considered as ‘bland.’ Here and elsewhere we define ‘bland,’ *i.e.* not capable of through-conjugation, by its context as well as its nature.  $\pi$ -Donors and  $\pi$ -acceptors show their distinctive properties only by through-conjugation, in the absence of which option they too are ‘bland.’

‘Bland’ Substituents. — Starting from  $\log K_{\text{delta}} 1 - 3$  in the absence of substitution (see start of section), the balance between **1434c** and **1434a** is controlled by  $R^3$  and  $R^5$ . While any substituent at  $R^3$  will increase the bias towards **1434c**, substitution at  $R^5$  will reduce and may reverse it. Thus while (**17**,  $R^3 = R^4 = R^5 = \text{H}$ ) and (**17**,  $R^3 = R^4 = R^5 = \text{Ph}$ ) exist as **17b**, (**17**,  $R^3 = R^4 = \text{H}$ ,  $R^5 = \text{Ph}$ ) and (**18**,  $R = \text{Ph}$ ) are converted to the **a**-form (section A.1.1). We postulate that, at least for  $R^4 = \text{H}$ , the outcome is quantitatively predictable according to Hine's carbon double bond stabilisation factors (Table 1); these include  $\Delta \log K$  *ca.* 2.2 for alkyl and 3.3 for Ph. ‘Bland’ substituents at  $R^4$  should not affect  $K_T$  *per se* (there are no data) but some evidence suggests that they may attenuate the effects of  $R^3$  and  $R^5$ .

Since the normally minor tautomer **1434a** is the necessary precursor to **1434b**, substitution at  $R^5$  may indirectly promote enol formation (Scheme 79). Given **1434a** as dominant even for  $Z = \text{S}$  when  $R^5 = \text{Ph}$ , 30% enol for **1435** in  $\text{MeOH}^{47}$  can be roughly estimated as  $\log K_E \sim -1$  in water. This is compatible with  $\log K_E -1.5$  for the parent compound if we suppose that Ph in **1435b** has only a marginal effect on  $K_E$  *per se*, which seems reasonable. The corresponding thiones should be much more vulnerable, and here a similar switch might also result for  $Z = \text{O}$ . However an automatic brake is applied to this process at  $R^3$  through the likelihood that electronegative substituents, by simultaneously increasing  $K_E$  and decreasing  $K_{\text{delta}}$ , could leave **1434c** as the dominant tautomer. This limitation is removed in **131a** where R will behave as  $R^3$  in the monocycle but allylic tautomerism is absent, resulting in a pattern in which enolisation becomes relatively more likely in the sequence  $Z = \text{NH} < \text{O} < \text{S}$ . The mean value of  $\Delta \log K_E$  *ca.* 2.7 for  $R = \text{Ph}$  we postulate above would therefore lead to dominant enol formation in (**131**,  $Z = \text{S}$ ) and for all the related thiones. The effect of  $R = \text{alkyl}$  should be about half as great. There are no data for **132** or its thione equivalent but enolisation here should be considerably more difficult to promote.

$\pi$ -Donors. – When these cannot themselves tautomerise they behave as bland substituents; R = SMe in **18** for example results in a mixture of **18a** and **18b** (section A.1.1). However, other options arise when R = XH, in particular the generation of *exo*-C=X. Only at R<sup>5</sup> is the resulting species dominant however; **130b** is unknown for Z = O or S and this remains true when either C=O or both is replaced by C=S (section A.2.7). The same may be surmised generally for parallel species such as (**1436**, Z = O, S and NR). However, for Z = NH *endo*-C=N becomes possible, as in acylamidines **1161** and imidines **1305**. For **1161** the through-conjugated species **1161C** tends to dominate (section B.5.9) and this effect is (qualitatively) independent of ring size. It does however depend on the *N*-substituent; **1169B** is important for **1169** though probably not the dominant tautomer. For imidines the balance depends on the nature of R<sup>1</sup> and R<sup>2</sup>; for R<sup>1</sup> = R<sup>2</sup> **1305b** tends to be favoured but a single substituent R<sup>2</sup> favours **1305a**. When R<sup>1</sup> ≠ R<sup>2</sup> **1305a** is favoured if R<sup>2</sup> is the more electronegative substituent, its dominance increasing with the gap in electronegativity (section B.7.1).

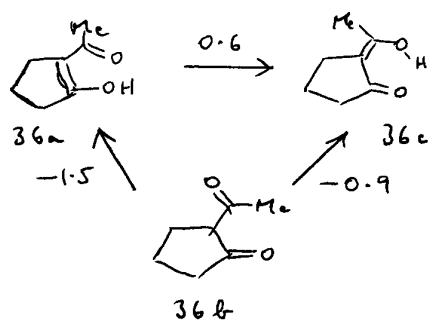
The same options for R = XH exist at R<sup>3</sup> and R<sup>4</sup>, but here for different reasons *exo*-C=X is disfavoured, in **115a** through lone pair repulsion (section A.2.5) and in **288a** because **288b** is through-conjugated (section A.6.4). The corresponding thiones presumably behave similarly, and very likely to much the same extent. For both there is probably no important difference from the corresponding carbocycles (*vide* section C.3). Effectively **1434a** and **1434c** containing  $\pi$ -donor substituents are non-aromatic molecules, a point further emphasised by the failure to detect **115c** (section A.2.5) or indeed any other variant on **1434b** when only these substituents are present. Electronegative substituents are required for **1434b** to become important (see below) though the same is not true for the corresponding thiones (*cf.* Table 89).

Nothing is known for R = NHR but, on the above evidence, the corresponding carbocycles probably form a reliable guide. While **110b** is very much the dominant tautomer for **110** (section A.2.5), the behaviour of **208** depends on the nature of R:  $\pi$ -donors or bland moieties give **208a** (section A.4.5), whereas  $\pi$ -acceptor moieties result in **208b** (section A.4.3). We discuss this difference in terms of rival resonance structures in section A.4.6 (and note that lone pair repulsion in **208a** can be avoided by adoption of the conformation shown). These distinctions are based in the first place on the behaviour of open-chain compounds (sections A.4.3 - A.4.5) but are supported by alicyclic data where known. There are also indications relevant to the (unexplored) case of **1437**. While (**435C**, R = alkyl) is overwhelmingly the dominant tautomer of **435** under all circumstances, there

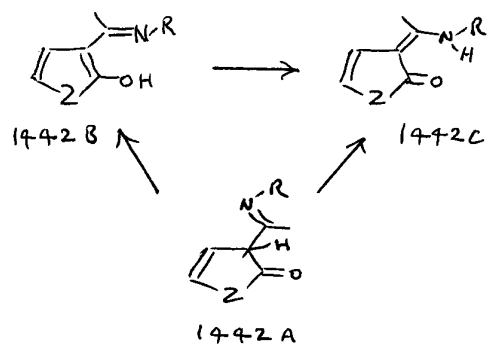
is evidence for a small but detectable fraction of **436A** in **436** (section A.10.4), whereas by contrast the balanced equilibrium found for **1425** (section C.9) is replaced on 4-acylation by the overwhelming predominance of **511C** (sections A.10.12 and A.12.4). Based on these considerations we predict, for example, **1438** and **1439** as dominant tautomers, the nature of Z being largely irrelevant, and the same should be true for the corresponding thiones. It is less certain what effect  $R^5$  might have on the position of equilibrium in **1440**; while even Ph among 'bland' substituents would probably not generate very much **1440b**, a  $\pi$ -acceptor would have the potential to generate an alternative through-conjugated system and the outcome is in doubt.

$\pi$ -Acceptors at  $R^3$ . — Most of what is known concerns  $R^3 = \text{acyl}$ . In attempting to predict its likely effect, we start in Scheme 80 from the related carbocycle, as for Scheme 72 (section C.7). On similar lines we derive  $\Delta \log K_E$  6.7 and 6.6 for **36b**  $\rightarrow$  **36a** and **36b**  $\rightarrow$  **36c** relative to acetone and cyclopentanone respectively as the precursor ketone. Of these only the first is relevant to **1434** but their near-equality provides reassuring support for the additivity postulate. Assuming that postulate,  $\Delta \log K_E$  6.7 follows for the process **1434a**  $\rightarrow$  **1434b**. However, there is also the process **1434c**  $\rightarrow$  **1434a** to consider. For  $R^4 = R^5 = H$ , the effect of  $R^3 = \text{COMe}$  is predicted as  $\Delta \log K_{\text{delta}}$  -2.5, leading to  $\Delta \log (K_{\text{delta}}K_E)$  4.2. This overall factor for the effect of  $R^3 = \text{COMe}$ , results in predictions of *ca.* -3, -3 and roughly zero for (**1434**, Z = NH, O and S) respectively. (All their thione equivalents should be enolised). Hard information is confined to **316** which exists as **316b** in  $\text{CHCl}_3$ ,  $\text{CCl}_4$  or the liquid state (section A.6.6), but since these are all non-polar media and the effect of  $-\text{CO}_2\text{Et}$  may be greater than that of  $-\text{COMe}$  (*cf.* **263**, section C.7), this evidence is equivocal. A similar problem attaches to **131**. Here only  $\log K_E$  (Table 89) and  $\Delta \log K_E$  6.7 require to be considered, leading to the conclusion that all 3-acyl derivatives should exist as the enol, but while several compounds of type **1441**, plus the nitrile **321b**, exist as shown in the solid state, their highly electronegative substitution pattern renders any simple analysis impossible. No work seems to have been carried out on substitution into **132**. It is constantly a problem that the importance of  $K_{\text{delta}}$  for **129** but not for **131** (or **132**) destroys any regular effect of benzofusion on  $K_E$  ( $K_T$ ) such as exists for the 6-membered ring oxoheterocycles (section C.21).

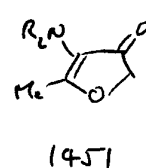
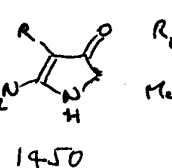
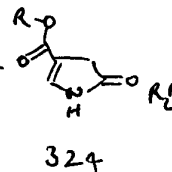
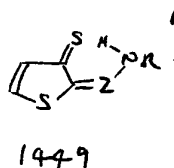
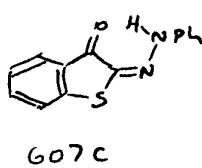
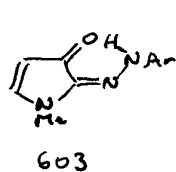
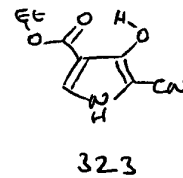
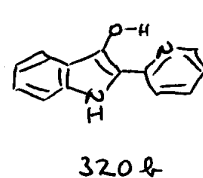
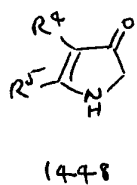
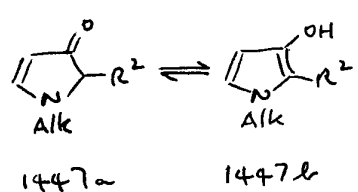
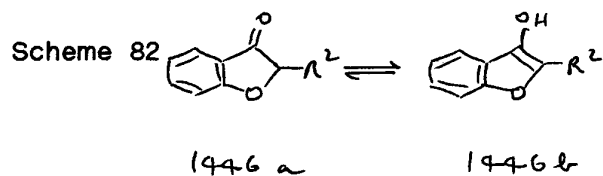
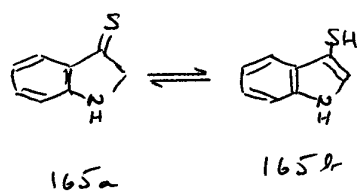
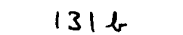
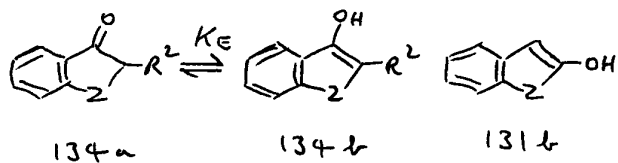
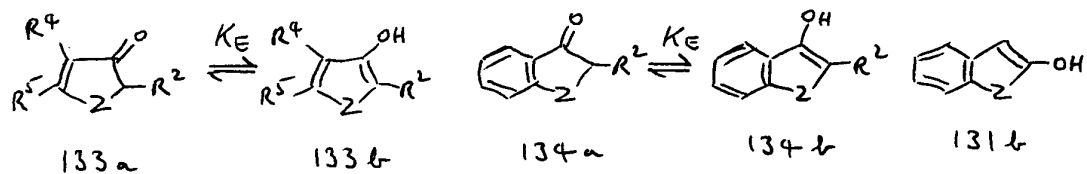
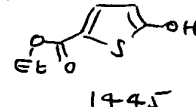
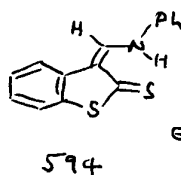
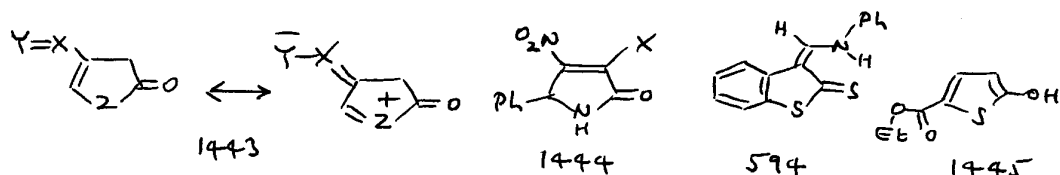
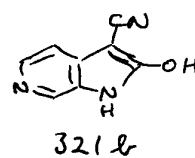
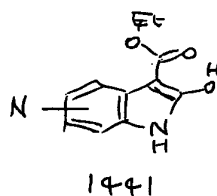
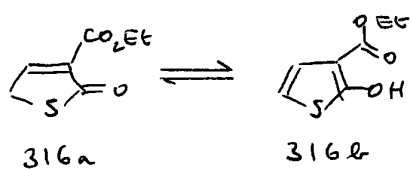
Substitution of imines  $-\text{C}=\text{NR}$  or azo-compounds  $-\text{N}=\text{NR}$  into saturated carbon (Scheme 81) is analogous to that of  $-\text{COR}$  in Scheme 80 and has been treated in Scheme 76, section C.9. Here the preference for the aminoenone structure **1442C** over-rides the usual prohibition of *exo*- $\text{C}=\text{C}$  (or *exo*- $\text{C}=\text{N}$ ) in



Scheme 80



Scheme 81



aromatic rings and can even reverse a preference for the enol tautomer (**160** → **594**; *cf.* section C.9). There is no way at present of quantifying Scheme 81 but this driving force appears to be overwhelming.

$\pi$ -Acceptors at  $R^4$ . — Just as  $\pi$ -donors stabilise **1434c** by conjugation with carbonyl (see above),  $\pi$ -acceptors should stabilise **1434a** by conjugation with Z (**1443**). Neither should stabilise **1434b**. The only known potential example is **1444**, where however the status of X as a  $\pi$ -donor (X = OH, OMe or NHR) compromises the issue. It is possible to regard (NHCO) and (XC=CNO<sub>2</sub>) in **1444** as independent ‘push-pull’ systems, and this situation when it occurs will tend to dominate (*cf.* section A.6.3 in a more general context).

$\pi$ -Acceptors at  $R^5$ . — Almost nothing is known. The 5-ester **1445** is 85% enolised as shown in CCl<sub>4</sub>, so its effect is probably little greater than that of 5-Ph in **1435** (*q.v.* above). If so its structure can be attributed mostly to the switch in dominant oxo-tautomer and through-conjugation is not a major factor. Analogous furans and pyrroles in water, therefore, should remain largely as **1434a**.

### C.11 Enolisation and Aromatisation in 5-Membered Ring 3-Oxo(thiono)-heterocycles with One Ring Hetero-Atom

The tautomeric pattern is simpler here than in C.10, with only one equilibrium and no rival oxo-tautomers, in addition to which much more is known, notably for the parent compounds **133** and **134** (section A.2.7). These and our estimates for **131** (Table 89) appear in Table 90. There is clearly no parallelism between **134** and **131** and we now attempt to analyse what is responsible for this difference.

$$\Delta\Delta \log K_E = \Delta \log K_E (\mathbf{131}) - \Delta \log K_E (\mathbf{134}) \quad (\text{cxiv})$$

$$\Delta\Delta \log K_E = 0.01 + 7.6 \sigma_R^+ \quad (\text{cxv})$$

We require three assumptions. The first is that  $\Delta \log K_E$  for Z = O, S or NH in **131**, relative to Z = CH<sub>2</sub>, represents the gain in aromaticity on enol formation offset by loss of resonance energy in Z(C=O). This is uncontroversial. The second is that through-conjugation of Z with C=O *via* phenyl in **134a** is, by contrast, substantially absent; it matters only for **131**. And the third postulates that, since the *skeletal* structures of **131b** and **134b** are effectively identical, differing only by the different position of the same

non-conjugating substituent, the gain in aromaticity  $\Delta \log K_E$  is, for a given hetero-atom Z, essentially the same for both. To the extent that these approximations are valid we may now use eqn. (cxiv) to deduce a quantity  $\Delta \log K_E$  which represents the effect of resonance energy in  $Z(C=O)$  in offsetting the otherwise expected gain in aromatisation when **131b** is formed. Given the dipolar nature of  $Z(C=O)$  one expects the appropriate resonance parameter to be  $\sigma_R^+$  as in eqn. (cxv). Not only is this relation linear ( $r^2 > 0.99$ ) but its intercept is effectively zero, neither of which should be possible if our basic assumptions were seriously in error. Indirectly, this helps to suggest that the estimates of Table 89 may prove reasonably accurate.

We postulate  $\Delta \log K_E$  ( $C=O \rightarrow C=S$ ) *ca.* 3.5 for the 2-thiono-heterocycles of section C.10 (see above) and, since  $C=S$  for **134** like  $C=O$  is evidently less conjugated with Z, this must represent a minimum value. For simple thiones it is *ca.* 6 (section A.3.7). Even  $\Delta \log K_E$  3.5 would, however, ensure dominant thiol formation, in water, for every parent heterocycle but (**134**,  $Z = O$ ) on replacing  $C=O$  by  $C=S$  (Table 90); in fact **165** is known to exist as **165b** as is the analogous benzothiazole (section A.3.7). Since almost any substituent  $R^2$  will help to induce enol formation then, with one exception noted below (**1449**), all such thiones will exist as thiols, probably in every solvent, and discussion of their tautomerism becomes superfluous.

**Table 90. Log  $K_E$  in Water for some 5-Membered Ring 3-Oxoheterocycles with One Ring Hetero-atom, and Related Compounds<sup>a</sup>**

Z =	CH <sub>2</sub>	O	S	NH
$\log K_E$ , <b>133</b> <sup>b</sup>	-	< - 2	0.5	- 0.9
$\log K_E$ , <b>134</b> <sup>b</sup>	- 7.5 <sup>c</sup>	- 4.1	- 1.1	- 1.1
$\log K_E$ , <b>131</b> <sup>d</sup>	- 4.1 <sup>ef</sup>	- 5.5	- 2	- 6.5
$\Delta \log K_E$ , <b>134</b> <sup>g</sup>		3.4	6.4	6.4
$\Delta \log K_E$ , <b>131</b> <sup>g</sup>		- 1.4	2.1	- 2.4
$\Delta \log K_E$ <sup>h</sup>		- 4.8	- 4.3	- 8.8
		OMe	SMe	NHMe
$\sigma_R^+$ <sup>i</sup>		- 0.66	- 0.55	- 1.16

<sup>a</sup> Approximated to  $\pm 0.1$ . <sup>b</sup> Values from Table 13, section A.2.7. <sup>c</sup> Cpd. **46**, section A.1.3.

<sup>d</sup> Estimates from Table 89, section C.10. <sup>e</sup> Cpd. **45**, section A.1.3. <sup>f</sup> Statistically corrected.

<sup>g</sup> Relative to  $Z = CH_2$ . <sup>h</sup> Eqn. (cxiv). <sup>i</sup> Table 2.

The Influence of Substituents. – We continue to employ the substituent classification set out in section C.10. Here  $R^2$  (Scheme 82) parallels the behaviour of  $R^3$  previously but  $R^4$  and  $R^5$ , since  $C=C$  is 'locked,' only in part parallel those at these positions in **1434**.

'Bland' Substituents. – With  $R^2 = \text{Ph, Me or OMe}$ , **1446** exists as **1446a**. Given  $\Delta \log K_E$  3.3, 2.2 and 3.6 for these respectively (Table 1), and  $\log K_E$  -4.1 for  $R^2 = \text{H}$  (Table 90), this result is gratifying, though  $R^3 = \text{OH}$  may in any case reduce the impact of these substituents. A similar attenuation in **1447**, or possibly steric hindrance, may explain why  $R^2 = \text{Alk}$  is insufficient to make **1447b** the dominant tautomer; it dominates for  $R^2 = \text{Ph}$  however (both section A.1.3). However,  $R^4 = R^5 = \text{Me}$  in **1448** produces a degree of stabilisation relative to  $R^4 = R^5 = \text{H}$  which may approach  $10^2$  (section A.1.3). Clearly Me is not 'bland' In this context. This may, in fact, be an electronic effect; **1448** or more generally **133a** with a  $\pi$ -donor at  $R^5$  (section C.10) becomes a strongly conjugated system, and further examples appear below.

$\pi$ -Donor/Acceptor Substituents at  $R^2$ . – A  $\pi$ -donor at  $R^2$  cannot conjugate or tautomerise and, in addition, would create a molecule of acetal (if XR) or hemiacetal (if XH) type which is likely to be unstable.  $\pi$ -Acceptors give rise to the enol form in every known case, even for (**1446**,  $R^2 = \text{COR}$ ), as is consistent with  $\Delta \log K_E$  6.7 (Scheme 80) here superimposed on  $\log K_E$  -4.1; contrast the behaviour of  $R^2 = \text{Ph}$ , above. Unusual variants include **320b** and **323** in which the  $\pi$ -acceptor is not carbonyl and further examples appear in section A.6.6. The pattern of substitution in **323** effectively splits the molecule into two independent conjugated units, OH to CN and NH to C=O, a situation which when present tends to dictate tautomeric form; sections A.6.3 and A.6.6 discuss this phenomenon further.

As previously (section C.10) a  $\pi$ -donor that can interact with a ring  $\pi$ -acceptor to give an aminoenone tautomer, as **1442C** in Scheme 81, leads invariably to this, as in **603** and **607C** (section A.10.19). Here *exo*- $C=C$  or  $C=N$  is preferred relative to the enol **1442B** despite the resulting loss of aromaticity. Since aminoenethiones are similarly favoured structures (section A.11.1) we predict that even (**1449**,  $Z = \text{CH or N}$ ), the least likely case, should exist as shown.

$\pi$ -Donors/Acceptors at  $R^4$  and  $R^5$ . — It has been noted above that the aminoenone structure of **133a** (or similar) is stabilised by substituents at  $R^4$  and  $R^5$  and this is specially true when these are  $\pi$ -acceptors and  $\pi$ -donors respectively. Examples include **324** and **1450** respectively; it is improbable

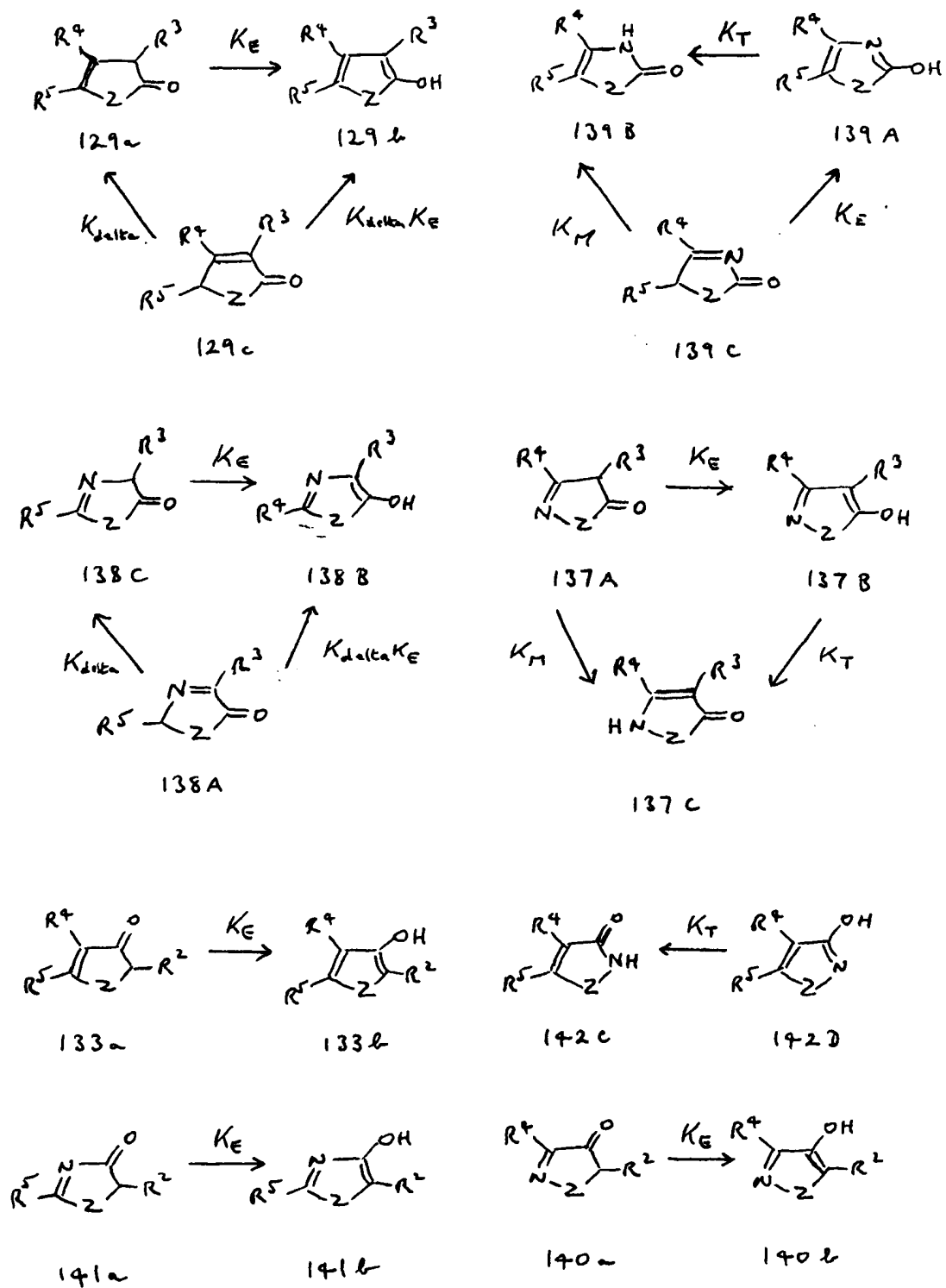
that even  $R^2 = \text{COR}$  could reverse these preferences. For **1451** the situation is less clear since  $\text{NR}_2$  is cross-conjugated and may not confer much extra stability. Replacement of  $R^4 = R^5 = \text{H}$  by benzofusion produces changes in  $\log K_E$  whose irregularity is discussed above; what effect benzene ring substituents might have is unknown.

### C.12 Enolisation and Aromatisation in 5-Membered Ring Oxo(thiono)-heterocycles with One Ring $\pi$ -Donor Hetero-atom and One Potential Aza-nitrogen: Overview

There are six such compound series, three formally derived from each of those considered in sections C.10 and C.11 (see Scheme 83). Those derived from the 2-oxo- and 3-oxo-heterocycles **129** and **133** possess, like their parents, three and two potential tautomers respectively. Two major consequences result from the addition of aza-nitrogen. As an electronegative substituent it tends to promote enol forms, and this effect is reinforced, to a variable extent, by an increase in the resonance energy of the aromatic ring (*cf.* Table 12). There are further important consequences when Z and aza-nitrogen are contiguous. Whereas  $=\text{NZ}-$  represents a favourable interaction –  $\text{NHZ}-$  is highly disfavoured at least in cyclic structures (Appendix 3) and the result in two cases, **142C** and **137C**, is again to disfavour the oxo-form. With certain exceptions therefore, enol forms are more important than formerly.

In constructing Scheme 83 we attempt to reconcile the nomenclature we have adopted in sections A and B with the desirability of employing a common format, but with limited success. For the 2-oxo series we use the same double bond pattern throughout but while **138** can be forced into the pattern of equilibria given to **129** this is inapplicable to **137** and **139**, as it is for **142**, where  $K_T = [\text{amide}]/[\text{iminol}]$  is given priority. The major infelicity we have generated concerns **139C**  $\rightarrow$  **139A**, a composite step whose designation as  $K_E$  is inappropriate but unavoidable. Fortunately, **139C** if  $R^4$  is bland is unlikely to be important (section C.13). A common numbering of substituent positions is used throughout to facilitate cross-comparison; sometimes this differs from that of sections A and B.

Tautomerism in these compound series is a complex and confusing subject. Nevertheless the above analysis will reveal regularities which, for both parent compounds and their substituents, we explore below.



Scheme 83

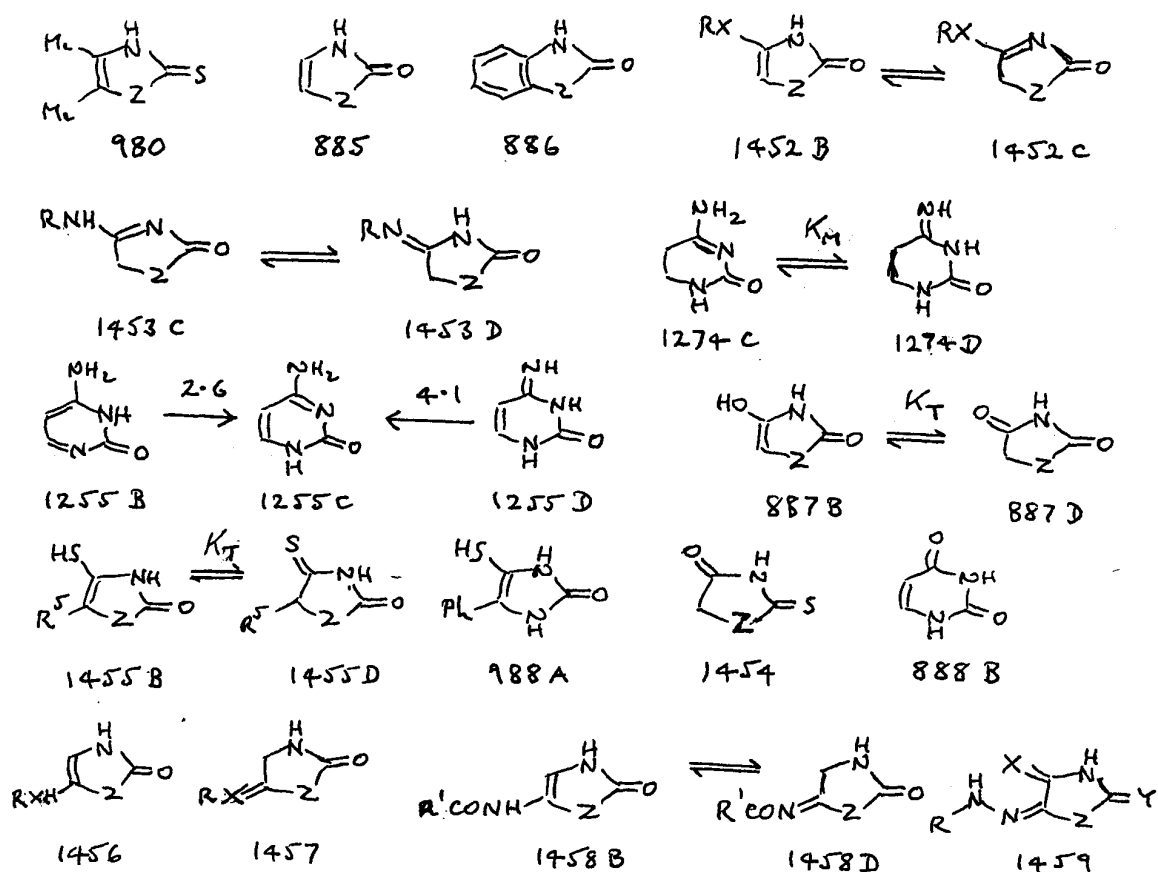
### C.13 2-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-Nitrogen in a 1,3-Relationship: **139**

In simple cases imines are preferred over enamines by a factor of about  $10^2$  (section A.4.1) but *N*-acylation decisively reverses this (section A.4.4); hence **139C** will be disfavoured relative to **139B** ( $K_M \ll 1$ ). If  $Z = \text{NR}$  in **139B** this compound is a urea, for which a very large value of  $K_T$  (Scheme 83) is expected (section B.2.9). No quantitative data exist for **139** as such but, for **980**,  $\log K_T$  in water is 8.0, 6.3 and 6.0 respectively for  $Z = \text{NH/NMe}$ , O and S (section B.3.5) and similar values would be expected here. All compounds of types **885** and **886** exist as shown and similar results have been found for other sorts of ring fusion (section B.2.9).

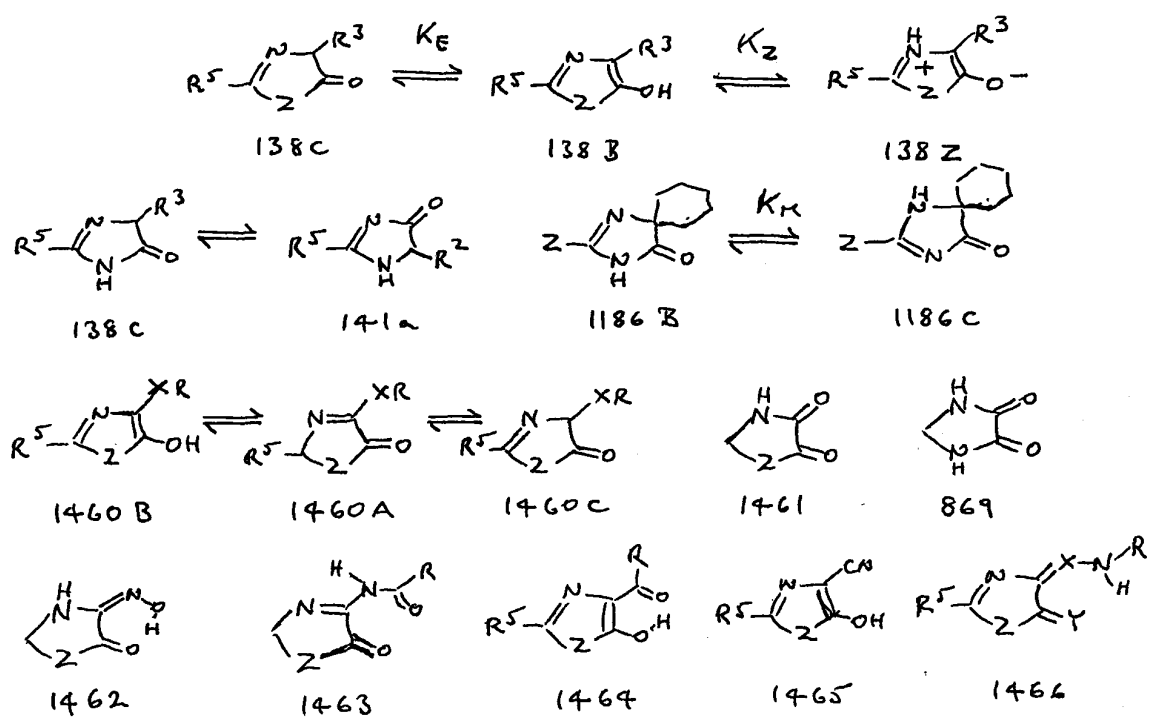
Bland Substituents at  $R^4$  and  $R^5$ . — Replacement of either Me by Ph in **980** (Scheme 84) reduces  $\log K_T$  by *ca.* 1.5. Since annular tautomerism is absent (contrast **129**, section C.10) this is clearly an electronic effect and should be echoed by other substituents. However, while a greater drop in  $K_T$  might be expected *e.g.* for  $\text{CF}_3$ , it is unlikely that any non-conjugating substituent could make **139A** the major tautomer.

$\pi$ -Donors at  $R^4$ . — A  $\pi$ -donor RX has the potential to generate through-conjugation by inducing a switch to **1452C**; cross-conjugation should disfavour **1452B**. For  $X = \text{NH}$ , further tautomerisation between **1453C** and **1453D** then becomes possible. There is no direct evidence on this point but its 6-membered ring analogue **1274** exists in water as a mixture of **1274C** and **1274D** with  $\log K_M$  -1.2 and a similar balance is possible here. On aromatisation **1274** becomes cytosine **1255** for which the tautomeric balance (section B.5.15) is set out in Scheme 84. For  $X = \text{O}$ , S or NR, **1452C** is likely to be the predominant tautomer throughout.

A  $\pi$ -donor HX at  $R^4$  in **139** can itself tautomerise and here the situation is different. Where  $X = \text{NR}$  the position is as described above. However **887B** can ketonise to **887D**. Relative to imines *vs.* enamines, ketones *vs.* enols are favoured by factors of up to  $10^6$  (sections A.2 and A.4 *passim*) so this is reasonable. All compounds of type **887** exist exclusively as **887D** (section B.2.9). As with **1453** there is an aromatised 6-membered ring analogue; uracils **888B** and all related structures, including their benzofused derivatives (and presumably their alicyclic analogues), exist exclusively in this tautomeric form (section B.2.9).



**Scheme 84**



Scheme 85

Compounds in which  $X = S$  occupy an intermediate position. While thioamides and thioureas are even more resistant to iminol formation than the corresponding amides and ureas (section B.3.3), so that (**1454**,  $Z = O$ , S or NR) is expected to exist as shown,  $C=S$  is much more susceptible than  $C=O$  to C-enolisation so that species of type **1455B** become viable; a known example is **988A** (section B.3.5). Given a maximum effect on carbon double bond formation of  $\Delta \log K$  3.3 for Ph (section A.1.1) we may provisionally estimate  $\log K_T \gtrsim 2$  for (**1455**,  $R^5 = H$ ). We estimate (section A.3.7)  $\Delta \log K_T$  ca. 3.5 for  $C=S \rightarrow C=O$  in this context, from which  $\log K_T \gtrsim 5.5$  is expected for **887**. If  $Z(C=O)$  in **887** is replaced by  $C=C$  we have (**129a**,  $Z = NH$ ), for which (section C.10) we estimate  $\log K_E$  ca. -6 (Scheme 78 and Table 89); the inverse of this is  $\log K_T$  as here defined. The close similarity of these estimates is, at the least, interesting.

$\pi$ -Donors at  $R^5$ . — Donors of type RX will give rise to the cross-conjugated species **1456** but no alternative tautomer avoids this situation so **1456** will presumably exist as shown. However HX can generate compounds **1457** whose structure parallels that of **1454** (and is identical, for  $RX = O$  and when  $Z = NH$ ). This structure is always found for  $RX = O$  or S. For  $X = N$  however there is a potential problem concerning **1458**.  $\pi$ -Acceptor substituents on nitrogen favour enamines over imines (section A.4.4) but if Z is a  $\pi$ -donor **1458B** becomes cross-conjugated and **1458D**, which has the same tautomeric form as **1274D**, will be preferred. If  $Z = NH$  however a further tautomeric switch is likely, to give a tautomer corresponding to **1274C**; in this respect, **1452** and **1458** are parallel cases.

$\pi$ -Acceptors at  $R^4$  and  $R^5$ . — Nothing concerning tautomerism appears to be known, but since a  $\pi$ -acceptor at  $R^4$  or  $R^5$  is capable of through-conjugation with Z or NH respectively, it seems unlikely that **139B** will cease to be the dominant tautomer. This is specially true for substitution at  $R^5$ , since conversion of **139B** to **139A** would turn  $\pi$ -donor NH into a  $\pi$ -acceptor and so destroy through-conjugation. Another untapped subject, in terms of tautomerism, is C-substitution by imines or azo-compounds to give structures which, in the present case, could include, *e.g.*, (**1459**, X and Y = O or S,  $Z = O$ , S or NR), and whose dominant tautomeric form may be confidently predicted to be that shown. Similar compounds appear above in sections C.10 and C.11 and more again in sections A.10.18 - A.10.20, some of which are listed in sections C.14 - C.18 below.

### C.14 2-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-Nitrogen in a 1,4-Relationship: **138**

Since **138A** contains opposed C=N and C=O dipoles – another sort of cross-conjugation – and stands to gain enormously in resonance energy by a switch to **138C**, it is unsurprising that this switch occurs and **138A** has never been detected. There is still a 3-way equilibrium however (Scheme 85), consisting in **138C**, its enol **138B**, and a zwitterion **138Z** formally derived from the latter. As a function of Z, its balance changes as follows (section A.2.8):

(i) For Z = O and  $R^3 = R^5 = H$ , **138** exists in water as a mixture of **138C** with **138Z**. For azlactone,  $R^3 = R^5 = Ph$ , **138Z** predominates. The enol **138B** does not appear ever to be present in appreciable quantity.

(ii) For Z = NMe,  $R^3 = H$  or Me, it consists mostly in **138C**, whereas for  $R^3 = Ph$ , **138B** predominates. The zwitterion is largely absent.

(iii) For Z = S, **138C** is found only for  $R^3 = H$ ; any other substituent, including  $R^3 = Me$ , converts it mostly to **138B**. This can be seen as a straightforward effect of  $R^3$  on enol stability (section A.2.2). The zwitterion is absent.

These differences demonstrate that aromatisation to give **138B** is important in the order Z = S > NMe > O, *i.e.* much the same as that for the ‘parent’  $\pi$ -donor heterocycles thiophene, pyrrole and furan (Table 12). The gaps between these cannot be accurately quantified but something on the order of  $10^2$  would fit that between S and NMe. The importance of **138Z** for Z = O is presumably connected with (a) its reluctance to enolise, (b) the impossibility, given the 1,4-separation of N and O, of formulating a neutral through-conjugated tautomer in which the cross-conjugation implicit in the **C**-form may nevertheless be relieved. The second factor, at least, seems to operate in the somewhat parallel case of **140** (section C.18).

As an extra complication, for Z = NH an equilibrium exists between **138C** and **141a** (also Scheme 85) in which, for  $R^5 = H$ , the former predominates. This relates to what is known for the (non-aromatisable) tautomerism of **1186** in water (section B.5.10). For (**1186**, Z = H),  $\log K_M$  -0.4 is found (Table 71); *i.e.* in the same direction as the preference for **138C** over **141a**. However, if Z in **1186** is a  $\pi$ -donor  $K_M$  rises sharply, to  $\log K_M$  1.0 for SMe and 3.3 for NH<sub>2</sub>. There are further implications of this; see below.

There is no information on the corresponding thiones but, given a putative  $\Delta \log K_E$  ca. 3.5 for  $C=O \rightarrow C=S$ , all parent compounds should exist as the thiol (or quite probably its zwitterion) and it is difficult to think of any possible substituent that might reverse this trend.

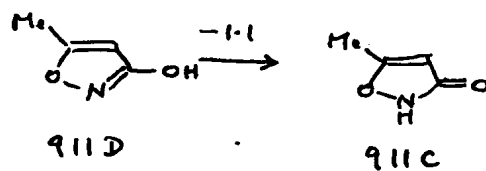
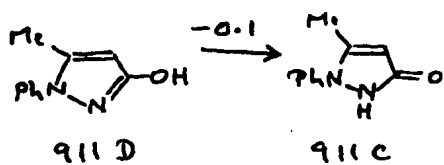
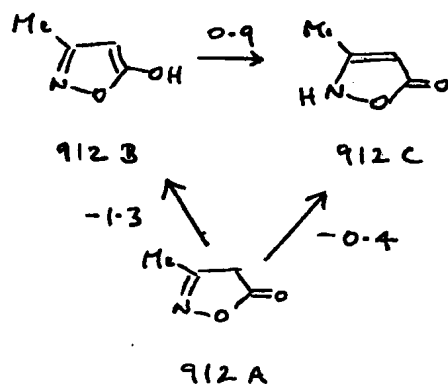
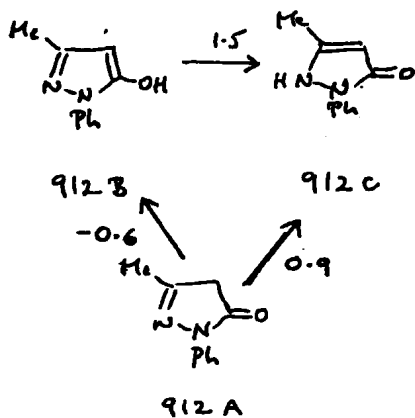
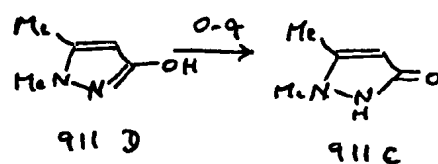
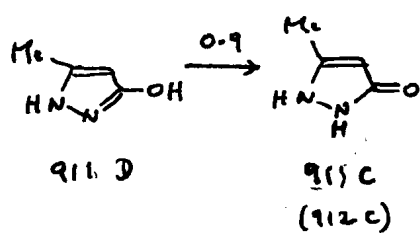
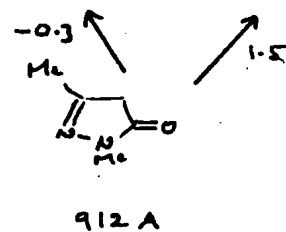
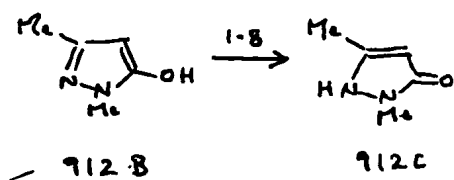
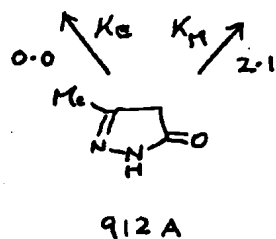
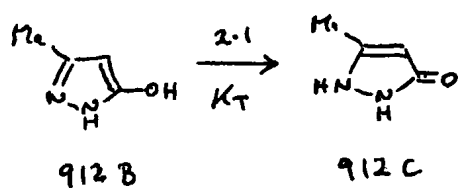
Bland Substituents. – The equilibrium between **138C** and **138B** or **138Z** lies so close to parity even for  $R^3 = H$  that almost any substituent  $R^3$  must give one of the latter. By contrast  $R^5$ , which operates at the fulcrum of a conjugated unit, is likely to have a disproportionately large effect in either direction. In the parallel case of **141** (section C.17; see Scheme 83),  $R^5 = Ph$  increases  $K_E$  ca. 10-fold relative to  $R^5 = Me$ , whereas  $\pi$ -donors will probably reduce this (see below).

$\pi$ -Donors at  $R^3$ . – A  $\pi$ -donor, whether  $RX$  or  $HX$ , may influence  $K_E$  like a ‘bland’ substituent (see Table 1) but the resulting species **1460B** would be cross-conjugated so its viability is uncertain. Otherwise it might influence structure by re-activating **138A**. For  $RX$  the required species **1460A** is unlikely to compete successfully with **1460C** but for  $HX$  it is another matter. By further tautomerisation (*cf.* **887**, Scheme 84)  $R^3 = OH$  could give **1461**, and since **869** has been reported as such (section B.2.7), **1461** is presumably a viable species. For  $R^3 = NHR$  the outcome is uncertain, but **1462** is likely to be a stable tautomer and the same may be true of **1463**, though an enol tautomer analogous to **1460B** is another possibility.

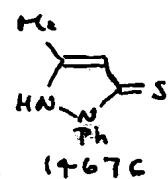
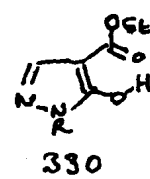
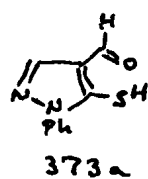
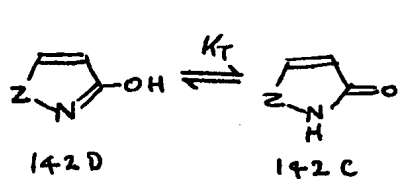
$\pi$ -Donors at  $R^5$ . – These will increase the electron-richness of the  $ZC=N$  unit. In **1186** their effect is greatly to enhance through-conjugation and, by a parallel mechanism, they may stabilise **138C**, but to the extent that they increase basicity they may, paradoxically, stabilise **138Z** even more. This area has yet to be explored.

$\pi$ -Acceptors at  $R^3$ . – Given the extreme ease with which **138C** may be converted to **138B** by substitution at  $R^3$ , any electronegative substituent should do this. Obvious possibilities include **1464** and **1465** but the potential variants are legion. Once again, however, imine or azo-compound substitution should lead to compounds of type (**1466**,  $X = CH$  or  $N$ ) and here it should make no difference whether  $Y = O$  or  $S$ .

$\pi$ -Acceptors at  $R^5$ . – Effectively these are cross-conjugated with the  $ZC=N$  unit and cannot directly influence tautomeric form. They may have some limited effect in increasing  $K_E$  but nothing is known.



Scheme 86



### C.15 2-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-Nitrogen in a 1,5-Relationship: 137

With a sometimes bewildering overlap between C-type and N-type tautomerism, and three tautomers closely enough in balance that each can dominate as the result of quite minor changes in ring  $\pi$ -donor and/or substituent, this is perhaps the most complex and confusing of any field that has been studied. As a first step towards its rationalisation we set out for the related series **142** and **137**, in sub-section B.8.13, a cross-comparison of the data for compounds in which Z = NH, NMe, NPh and O, and based on the ring substituents  $R^5 = \text{Me}$  and  $R^4 = \text{Me}$  respectively. Data for  $\log K$  appear in Table 83. These compound sub-sets have been categorised in Scheme 68 as **911** and **912** respectively, with **913** for the special case of Z = NH since here, uniquely, **911** and **912** overlap. In Scheme 86 we retain this nomenclature except that **913** appears only in disguised form, as **911D**  $\rightarrow$  **911C** (**912C**).

$$\log K_T = 6.45(0.74) - 21.5(7.2)\sigma_I + 5.25(2.31)\sigma_R \quad (\text{cxvi})$$

$$(n = 5 \quad r^2 = 0.976 \quad s = 0.75 \quad F = 40)$$

In both series, replacement of Z = NH successively by Z = NMe, NPh and O leads to a steadily falling dominance of the C-tautomer resulting, for Z = O, in **912A** as the major component. We may rationalise this trend *via* the simpler case of **911** (Scheme 86). Estimated  $\log K_T$  values for (**142**,  $R^4 = R^5 = \text{H}$ ), extrapolated from those for **911** in Table 83, appear in Table 91. Relative to Z = CH<sub>2</sub> (**846**, section B.2.3) the large drop in  $K_T$  when Z is a  $\pi$ -donor may be understood qualitatively in terms of two factors, both of which favour the iminol **142D**: aromaticity, and dipolar repulsion between Z and NH in **142C** (Appendix 3). These data may be analysed by eqn. (cxvi), according to which the iminol is favoured by field *acceptors* but resonance *donors*. These contributions are readily interpretable as due, respectively, to the varying effects of Z on dipolar repulsion in **142C**, and on aromaticity in **142D**. From eqn. (cxvi), that of Z on dipolar repulsion ranges from a fall in

**Table 91.** Estimated  $\log K_T$  Values for (**142**,  $R^4 = R^5 = \text{H}$ ) <sup>a</sup>

Z =	CH <sub>2</sub>	NH	NMe	NPh	O
$\log K_T$	6.5 <sup>b</sup>	0.0	-0.5	-1.0	-2.0
$\sigma_I$ <sup>c</sup>	0 <sup>d</sup>	0.17	0.13	0.20	0.24
$\sigma_R$ <sup>c</sup>	0 <sup>d</sup>	-0.68	-0.67	-0.62	-0.57

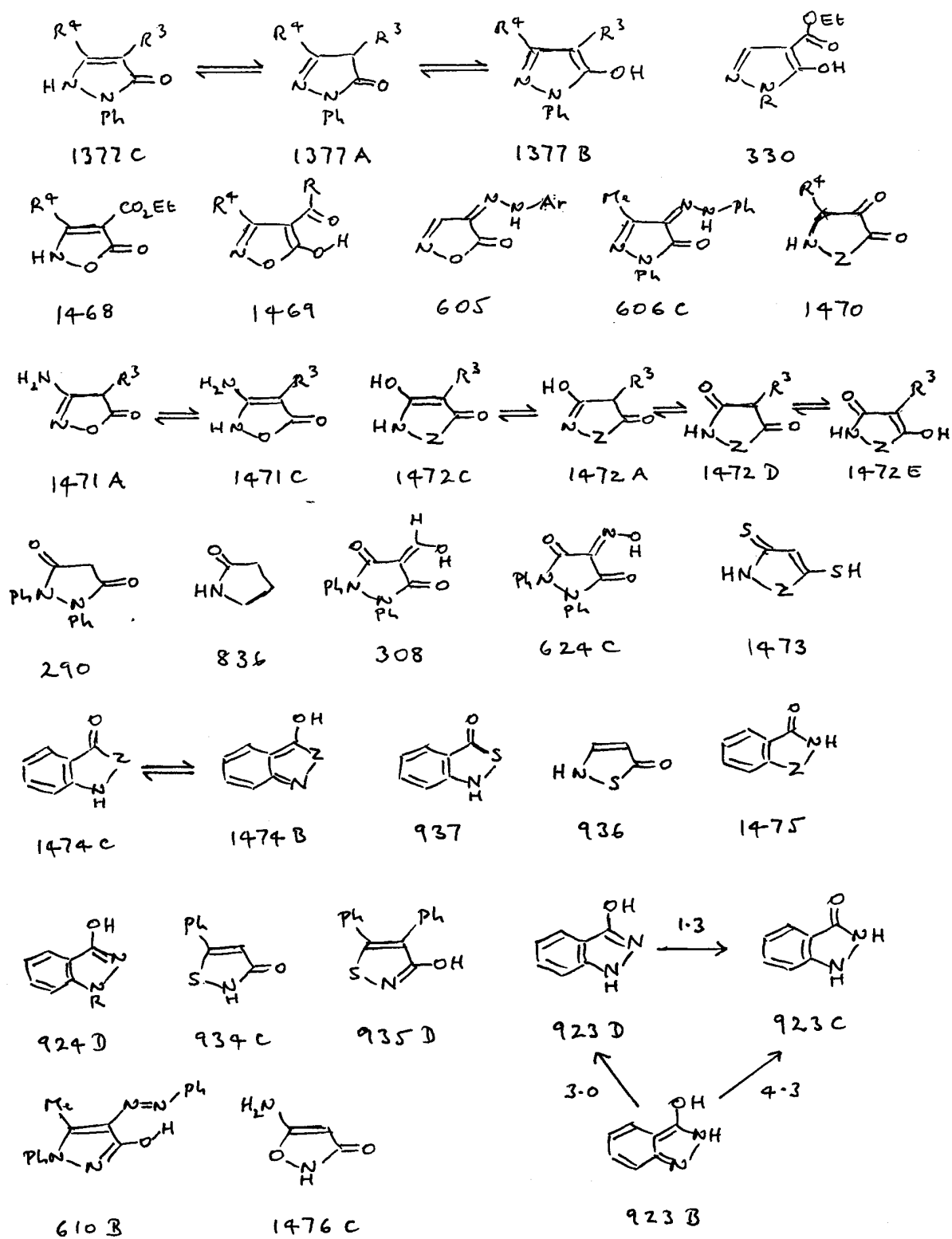
<sup>a</sup> Estimates except for Z = CH<sub>2</sub> corrected for removal of  $R^1 = \text{Me}$  by subtracting  $\Delta \log K_T$  0.9 from the values of Scheme 86 (see text). <sup>b</sup> Compound **846** (section B.2.3). <sup>c</sup> For ZH. <sup>d</sup> No contribution to either quantity possible in this context.

$\log K_T$  of 3 - 3.5 for  $Z = \text{NH}$  or  $\text{NMe}$  to *ca.* 5.5 for  $Z = \text{O}$ . A revised estimate [eqn. (cxlvii)] in Appendix 3, resulting from a more detailed but more problematic dissection of these results, leads to an estimate of  $\Delta \log K_T$  *ca.* -2.5 for  $\text{NHNH}$  in this context, close to the value adduced for maleic anhydride and pointing to little effect of ring size, in contrast to that found for lone pair repulsion. (The difference observed between  $\text{NH}$  and  $\text{NMe}$  is probably not a classical electronic effect but reflects the poorer solvation of  $\text{NHNMe}$  *vs.*  $\text{NHNH}$ ; this may also be a factor in the value of  $\log K_T$  for  $Z = \text{NPh}$ ). Our provisional estimates for the dipolar repulsion effect in this context, expressed as  $\Delta \log K_T$ , then become -2.5, -3, -4 and -5 respectively as rounded-off values for  $\text{NH}$ ,  $\text{NMe}$ ,  $\text{NPh}$  and  $\text{O}$ , and there is tantalising evidence that the first and last may remain the same in open-chain structures.

The  $\log K$  sequences of Scheme 86 repay study, even though taken from the idealised, isodesmic approach of Table 83 (section B.8.13); qualitatively the trend is certainly as given, even if quantitatively the data are incomplete. For **912**, while all three equilibrium constants decrease in the sequence  $\text{NH} > \text{NMe} > \text{NPh} > \text{O}$ , their *rates* of decline are very different. The easiest to interpret is  $K_E$ : this change involves only aromatisation, on which the positive influence of  $Z$  falls steadily with overall  $\Delta \log K_E$  *ca.* -1.3. The effect of  $K_M$  is more complex: **912C** is conjugated rather than aromatic, so the resonance component of the change is presumably less, but dipolar repulsion becomes much more severe, resulting in its formation becoming rapidly less favourable;  $\Delta \log K_M$  *ca.* -2.5 results. Since  $K_T = K_M / K_E$  this is necessarily a difference term, with  $\Delta \log K_T = \text{ca.}$  -1.2; it represents amide formation from the iminol offset by an increasing dipolar repulsion term, and is still positive even for  $Z = \text{O}$ , but by now **912A** is the dominant tautomer since  $\log K_E$  and  $\log K_M$  are both negative. The same two factors acting on  $K_T$  for **911**, whose blend may be quite different, shows a steeper decline because the electronic charge is less diffuse. Without more experimental evidence we can go no further.

There are too few hard data for  $Z = \text{S}$ , in either series, for even a rough analysis to be attempted, but the few comparisons that can be made suggest that  $K_T$  for **911** and **912** will both be higher than those for  $Z = \text{NH}$ . Contrariwise, eqn. (cxvi) predicts  $\log K_T$  *ca.* -1.5 for  $Z = \text{S}$ . The former estimate if valid is probably due to reduced dipolar repulsion, caused by the greater size of sulfur hence its lower electron density.

The corresponding thiones are almost unknown. Compound **373** exists as **373a** (section A.8.4), but since **330** is also enolised, this is scarcely evidence. One may anticipate greatly enhanced values of  $K_E$  resulting in the effective extinction of **912A** and this has been confirmed for **1467**, which exists 98% as **1467C** in water with no trace of **1467A**.<sup>2hh</sup> Series **911** should behave similarly, and for both series the sequence in  $Z$  should be the same.



Scheme 87

Benzofusion of **137** (Scheme 83) gives **1474**. For (**137**,  $Z = O$ ,  $R^3 = R^4 = H$ ) we expect a near-zero value of  $\log K_T$  (cf. Scheme 86, **912B**  $\rightarrow$  **912C**), but the enol **1474B** is quinonoid which entails a ‘penalty’ of  $\Delta \log K$  ca. -1.8 (Appendix 5). Hence **1474C** should be dominant even in this least favourable case, though hydrogen bonding 4- or 7-substituents might upset that conclusion. The only available datum is that **937** exists as shown, not a severe test when so does **936** (section B.2.10). The special case of (**1474**,  $Z = NH$ ) is considered in section C.16.

*Substituent Effects.* – Substitution in **137** (Scheme 83) at  $R^3$  and  $R^4$  has mostly been studied for  $Z = O$  and NPh, and largely in nonpolar solvents where the results often seem contradictory and are very difficult to extrapolate to water. In particular, one must beware of DMSO, whose penchant for exaggerating the importance of **137B** is a potent source of confusion. What appears to dominate, however, is the role of straightforward electronic effects, rather as in **133** (section C.12), in stabilising or destabilising the through-conjugated oxo-tautomer **137C**. We attempt below a consensus summary applicable to aqueous solution:

*Substitution at  $R^3$ .* – Most substituents stabilise **1377C** vs. **1377A** and stabilisation of **1377B** is uncommon. Stabilisation of **1377C** takes place in the order  $R^3 = NO_2$ , CN,  $CO_2Et$ , Ph, Me,  $Br > H$  (section B.8.13). Note that, in this series,  $R^3 = Ph$  does not generate **1377B** despite a deficit of only  $\log K$  1.5 in the parent compound. In all these cases  $R^4$  is also substituted, usually by alkyl, which may have the double effect of stabilising **1377C** and restricting the planarity of a bulky group, so that *e.g.* the strength of the hydrogen bond that might be formed to OH by  $CO_2Et$  will be severely affected. ‘Normal’ behaviour reasserts itself in **330** where  $R^4 = H$  (section A.6.6). Further evidence of borderline status is provided by **1468** and **1469**, where for  $R^4 = Me$  or Ph, acyl induces enol formation but ester does not (section B.2.10). This resistance to enolisation contrasts sharply *e.g.* with the behaviour of **129** (section C.10) and its probable reason is that **1377C** is a through-conjugated structure to which a  $\pi$ -acceptor at  $R^3$  can contribute, resulting in a further enhancement of its stability (and note the parallel case of  $\pi$ -donors at  $R^4$ , below). This results in **1377C** being competitive with **1377B** where on precedent that might not have been expected, making the outcome difficult to predict. However azo-substitution gives the expected product, such as **605** and **606C** (section A.10.19), and Schiff bases (section A.10.18) should show similar behaviour. For  $R^3 = OH$  there are no extra tautomeric options; as for **115** (quoted in section C.10), ketonisation to **1470** is in the highest degree improbable.

Substitution at  $R^4$ . – There are similar complications here. In the general case of **1377** the **A**-tautomer is stabilised by  $\pi$ -donors in the order  $R^4 = \text{NH}_2 > \text{OEt} > \text{Ph} > \text{H} > \text{CO}_2\text{Et}$ , the last therefore, a  $\pi$ -acceptor, being destabilising. However, since a  $\pi$ -donor will also stabilise the **C**-tautomer, these effects are competitive and the outcome is very sensitive to substitution at  $R^3$ : while (**1471**,  $R^3 = \text{H}$ ) exists as **1471A**,  $R^3 = \text{Et}$  converts it mostly and  $R^3 = \text{Ph}$  entirely to **1471C**. Note again that  $R^3 = \text{Ph}$  does *not* generate the enol, since through-conjugation between  $\text{NH}_2$  and carbonyl is of much greater importance energetically.

For  $R^4 = \text{OH}$  there is a range of possible tautomers **1472**. Since **290** exists as the diamide shown (section A.6.3), **1472C** may be eliminated but, for  $Z = \text{O}$ , **1472E** remains possible. We estimate  $\log K_T$  7.0 for **836** (section B.2.3) and, given a maximum value of  $\Delta \log K_T$  *ca.* -5.5 for  $Z = \text{O}$  (see above, this section), the iminol **1472A** may also be eliminated, leaving **1472D** and **1472E** as contenders, the second likely only for  $Z = \text{S}$  since  $\text{SC}=\text{O}$  is the most susceptible to *C*-enolisation of the three possibilities (section C.10, *passim*). The resistance of **290** to iminol formation is emphasised by the existence of **308** (section A.6.3) and **624C** (section A.10.20) as shown. We conclude that **1472D** is probably the major tautomer, with **1472E** as a possible rival for  $Z = \text{S}$ , with acylation at  $R^3$  likely to lead to *exo*-enolisation as in **308**. However, substitution of  $\text{C}=\text{S}$  for  $\text{C}=\text{O}$  would probably lead to thiol formation, *i.e.* **1472C** or **E** with  $\text{SH}$  in place of  $\text{OH}$ , **1473** being the likelier structure if both were to be replaced.

### C.16 3-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-Nitrogen in a 1,2-Relationship: **142**

As discussed in section C.15, Table 91 contains our estimates of  $\log K_T$ , some known some predicted, for (**142**,  $R^4 = R^5 = \text{H}$ ). These are based on values of  $\Delta \log K_T = 0.9$  for each substitution of Me for H along with the assumption of their additivity, all of which has been demonstrated for  $Z = \text{O}$  (section B.8.13) and is assumed *faut de mieux* elsewhere. The benzofused derivative **923** (Scheme 87) of **913** (Scheme 86) possesses  $\log K_T$  1.3 (section B.2.10), which is greater than that for **913** by a notably smaller margin ( $\Delta \log K_T$  0.4) than is found for benzofused 6-membered ring oxoheterocycles (section C.21). The quinonoid enol **923B** is disfavoured relative to **923D** by a margin which is greater by  $\Delta \log K$  1.8 than that between the equivalent monocyclic process involving **913B** and **913D** (Scheme 86), in line with the ‘quinonoid penalty’ (Appendix 5). There is evidence that any substitution at

*N*-1 results in the iminol **924D**; this represents a larger effect than would be predicted from Table 91 and may possess a steric origin (section B.2.10). If the effect of *Z* in **1475** is similar to that in **142**, the enol should be preferred for *Z* = O but the oxo-form more probably for *Z* = S.

The corresponding thiones do not appear to have been studied but, since the **C**-forms are thioamides, very similar  $K_T$  values are expected.

Substituent Effects. — Since the oxo-forms **142C** and **137C** so closely resemble one another (Scheme 83), it might be expected that much the same factors should stabilise both, even though their enols **142D** and **137B** (Scheme 83) while similar are isomeric, which argues for caution. In practice most differences concern  $R^5$  in **142** vs.  $R^4$  in **137**, since the latter can stabilise **137A** to which **142** has no equivalent.

Substitution at  $R^4$ . — The effect of Me in (**142**, *Z* = O) is described above. The existence of **934** and **935** as written (section B.10) suggests that, whereas alkyl acts as an electron donor, Ph behaves as if electronegative. This seems to contradict its effect in stabilising **1377C** (section C.15) until it is noticed that this operates *contra* the **A**-tautomer so the question remains open. The azo-compound **610**, in which the azo-group cannot tautomerise, exists as **610B** (section A.10.19), more probably through its electronegativity than because of an intramolecular hydrogen bond, which is expected to be weak. (The *des*-azo compound should possess  $K_T \sim 1$ ). Nothing else is known. More powerful proton acceptors *e.g.* acyl should favour **142D**, aided where possible by hydrogen bonding to OH, whereas  $\pi$ -donors are more likely to increase  $K_T$ , especially when, as for  $R^4$  = OH or NHR, hydrogen bonding to C=O is likely. Ketonisation of the former to give a structure similar to **1470** (Scheme 87) is, as in that case, highly unlikely.

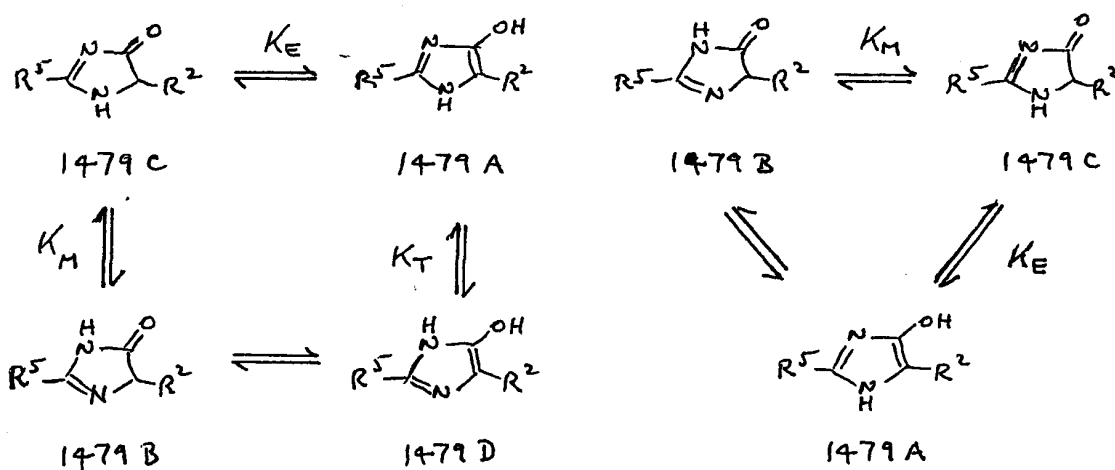
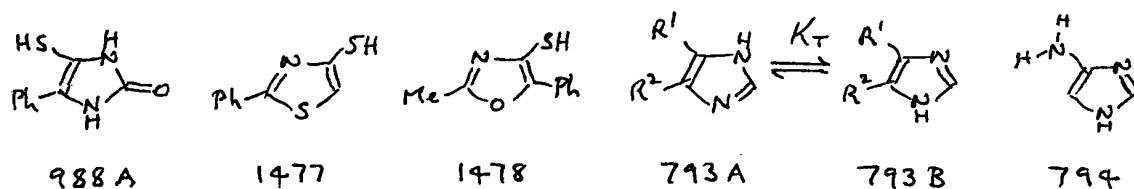
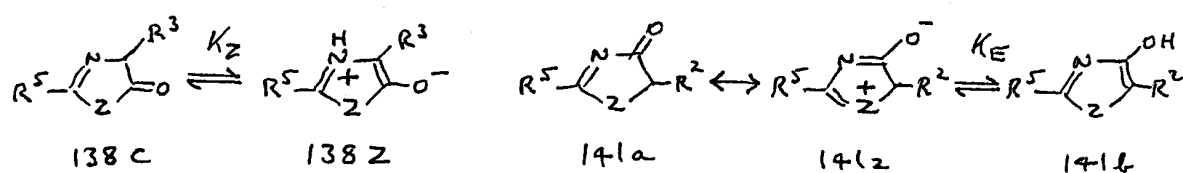
Substitution at  $R^5$ . — Methyl behaves as at  $R^4$ . Given the ‘push-pull’ nature of **142C** and the absence of competition from an **A**-form,  $\pi$ -donors should unequivocally stabilise the **C**-tautomer and indeed **1476** exists as **1476C**, which implies  $\Delta \log K_T \nless 3$  for  $R^5$  = NH<sub>2</sub>. A  $\pi$ -donor order similar to that for  $R^4$  in **137** (section C.15) seems likely, but probably more pronounced, with  $\pi$ -acceptors cross-conjugated so probably having little effect. The special case of  $R^5$  = OH (or SH) is covered above, as **1472E** in section C.15.

### C.17 3-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-Nitrogen in a 1,4-Relationship: **141**

These compounds are isomeric with series **138** (section C.14) but behave differently. Whereas aromatisation provides the driving force for enolisation in both, cross-conjugation in **138C** sets up a tension between competing electronegativities which is frequently resolved by formation of the zwitterion **138Z**. This problem is short-circuited in **141** by its through-conjugated structure (**141a**  $\leftrightarrow$  **141z**) which for  $Z = \text{NR}$  is that of an aminoenone and makes it less prone to enolisation than **138**. Another crucial distinction lies in the effect of  $R^5$ , which if a  $\pi$ -donor can undergo through-conjugation with carbonyl and so contribute profoundly to the resonance stabilisation of **141a**. Hence the interaction between effects due to  $R^2$  and  $R^5$  is complex and is explored below.

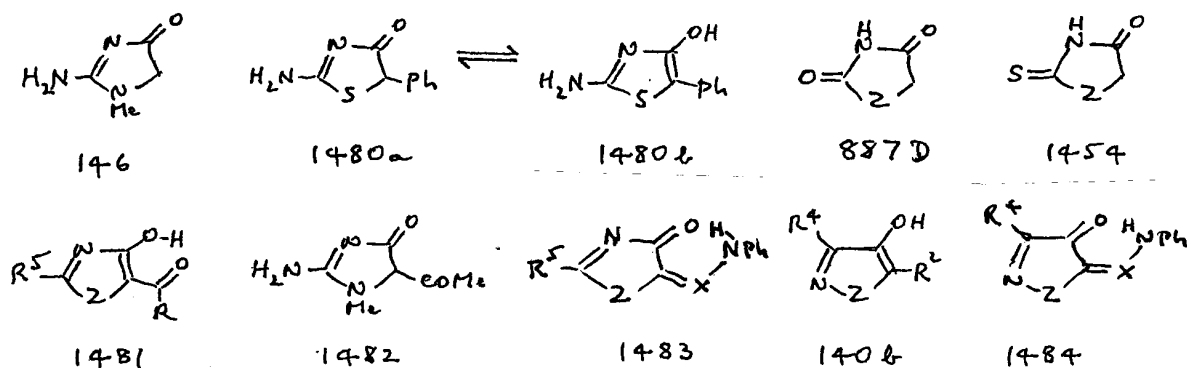
It is probable that, in water, all parent compounds except for  $Z = \text{NH}$  exist predominantly as **141a**, the dominance of this tautomer increasing in the order  $Z = \text{S} < \text{NR} \ll \text{O}$ ; *cf.* its 'parent' **133** (Table 90, section C.14) which behaves similarly. The exception occurs because (**138C**,  $Z = \text{NH}$ ) is preferred to its isomer (**141a**,  $Z = \text{NH}$ ) but the margin (for  $R^5 = \text{H}$ ) is not large and is reversed by  $\pi$ -donors (see below). Nothing is known concerning the corresponding thiones but the distant analogy of **988** (section C.13) suggests that  $K_E$  should be substantially greater; a factor of  $\Delta \log K_E$  *ca.* 3.5 (section A.3.7) should be sufficient to generate the thiol in compounds such as **1477** and **1478** (*vide* Table 92) but when  $R^5$  is a  $\pi$ -donor the position is likely to be very different (see below).

Bland Substituents at  $R^2$  and  $R^5$ . – Sufficient is known to construct Table 92. Here we have chosen tentative values of  $\log K_E$  which qualitatively reflect the observed tautomeric preferences for aqueous solution and the solid state (section B.5.10). From the cross-comparisons of Table 86 we have assumed constant factors of  $\Delta \log K_E$  2.7 and 1.6 for  $R^2 = \text{Ph}$  and  $\text{Me}$  respectively. These are less than the values (3.3 and 2.2; Table 1) given by Hine for simple allylic systems, plausibly because replacement of H by OH on the adjacent carbon atom attenuates their effect. For  $R^2 = \text{H}$  and  $R^5 = \text{Ph}$  these lead to predictions on the order of  $\log K_E$  *ca.* -4, -1 and -2 for  $Z = \text{O}$ ,  $\text{S}$  and  $\text{NR}$  respectively, qualitatively in the order found for **133** as noted above. The difference between  $R^5 = \text{Me}$  and  $\text{Ph}$  may entirely be due to electronic effects; there may be no truly 'bland' substituents at  $R^5$ .



Scheme 88

Scheme 89



$\pi$ -Donors at  $R^5$ . — We approach this subject *via* (141, Z = NH). Here a 4-way equilibrium obtains, with two oxo and two enol forms (Scheme 88). We may simplify as follows. For 4(5)-substituted imidazoles 793,  $\log K_T =$

$4\sigma_1$  fits highly electronegative substituents but underestimates others; for example,  $K_T > 10$  for **794** where  $K_T \sim 5$  would be predicted (section B.8.1). For (**1479**,  $R^2 = R^5 = H$ ),  $K_T \sim 10$  is predicted so this probably represents a minimum value. If the propensity of  $R^2$  to induce enolisation is similar in **1479B** and **1479C**, **1479A** will always be substantially preferred over **1479D** and Scheme 88 collapses to Scheme 89. The question now becomes how species **1479A** - **C** are related.

Annular tautomerism ( $K_M$ ) in **1479** as a function of  $R^5$  is charted, for  $R^2 = H$ , in Table 60 (section B.8.4). The dominance of **1479C** rises with the  $\pi$ -donor ability of  $R^5$ , from  $\log K_M -0.4$  for  $R^5 = H$  to 3.3 for  $R^5 = NH_2$ . Creatinine **146** also possesses  $\log K_M 3.3$  and for this we have estimated  $K_E \leq 10^{-5}$  (section A.2.8). This compares with an estimate of  $K_E \sim 10^{-3}$  in Table 92 for (**1479**,  $R^2 = H$ ,  $R^5 = Me$ ). If  $K_M$  is not greatly different for  $R^5 = H$  and  $R^5 = Me$ , which seems plausible,  $\Delta \log K_M ca. 3$  is accompanied by a fall of  $\geq -2$  in  $\log K_E$ . Qualitatively this is reasonable since stabilisation of the **C**-tautomer by  $\pi$ -donors should be accompanied by a lesser susceptibility of carbonyl to enolisation. It is even possible that these effects are of equal magnitude; that is, the equilibrium between **1479A** and **1479B** is unaffected.

In the more general case of (**141**,  $Z \neq NH$ ) one may similarly anticipate that  $K_E$  will fall as the  $\pi$ -donor ability of  $R^5$  increases. If its effect for  $Z = O$  and  $S$  were to parallel precisely that for  $Z = NH/NR$ , then even **1480** should exist in water as the oxo-form, as has been shown for this and some related compounds in EtOH and the solid state.<sup>538</sup>

**Table 92. The Effect of  $R^2$  and  $R^5$  on Enol Formation in **141** <sup>a</sup>**

Z	$R^5$	$R^2 =$	Dominant Tautomer: <sup>b</sup>			$\log K_E : ^c$		
			H	Me	Ph	H	Me	Ph
NR	Me		<b>a</b> <sup>d</sup>	<b>a</b>	<b>a</b> <sup>e</sup>	-3.0	-1.4	-0.3
NR	Ph		<b>a</b> <sup>d</sup>	<b>a</b> <sup>e</sup>	<b>b</b>	-2.0	-0.4	0.7
S	Ph		<b>a</b> <sup>f</sup>	<b>b</b> <sup>f</sup>		-1.0	0.6	1.7
O	Ph				<b>a</b> <sup>f</sup>	-4.0	-2.4	-1.3

<sup>a</sup> Scheme 83. <sup>b</sup> Observed for aqueous solution (section B.5.10). <sup>c</sup> Tentative estimate for aqueous solution (see text). <sup>d</sup> No trace of enol visible. <sup>e</sup> Tautomer major but not dominant. <sup>f</sup> Solid state.

For  $R^5 = \text{OH}$  or  $\text{SH}$  the product is an iminol which will ketonise to **887D** and **1454** respectively. These compounds can also be generated from **139** under which heading they have been discussed (section C.13).

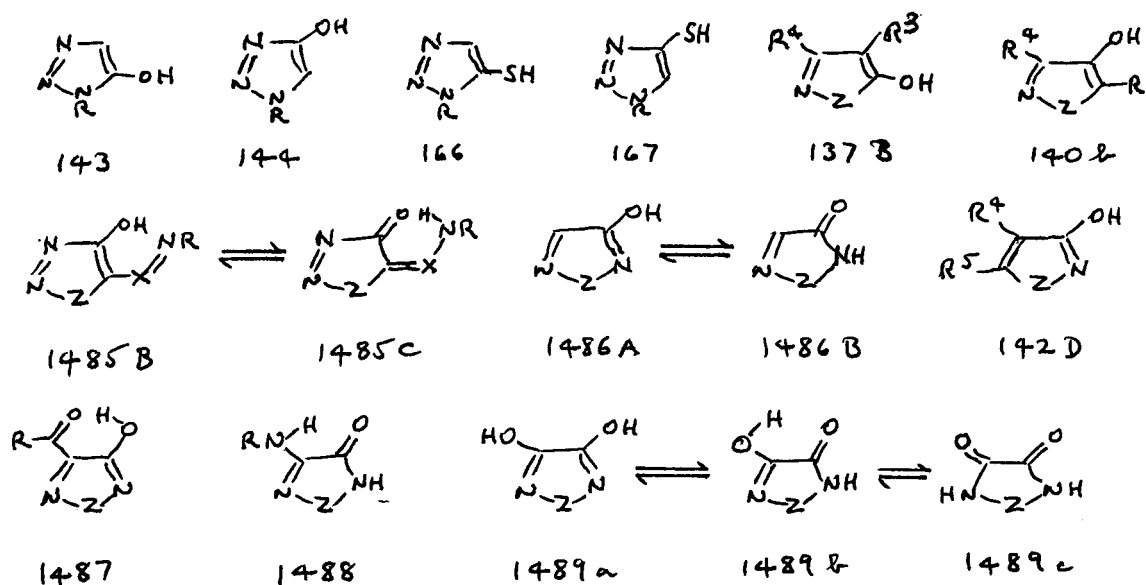
*$\pi$ -Acceptors at  $R^5$ .* – Nothing is known and there are no data from elsewhere to aid quantitative prediction. However, since  $\pi$ -donors reduce  $K_E$ , it seems probable that  $\pi$ -acceptors will increase it.

*$\pi$ -Donor/Acceptor Substituents at  $R^2$ .* – A  $\pi$ -donor at  $R^2$  cannot tautomerise and, additionally, would be cross-conjugated in the enol **141b** (Scheme 83), so is unlikely to affect  $K_E$  much if at all. (This feature is found whenever  $\text{CH}_2$  is placed between  $\text{C}=\text{O}$  and a hetero-atom:  $R^3$  in **138** and **137**,  $R^2$  in **133** and probably in **140** as well as here. Allylic tautomerism prevents it from happening at  $R^3$  or  $R^5$  in **129**).  $\pi$ -Acceptors possess the potential to induce enolisation, as suggested for structure **1481**, but no such compound appears to have been studied. Given a potential  $\Delta \log K_E$  ca. 6.7 in such a case (Scheme 80, section C.10) any of the compounds listed in Table 92 could ostensibly enolise in this fashion, but two caveats are necessary. Firstly, as seen above, a  $\pi$ -donor at  $R^5$  must make this shift more difficult. Secondly,  $\Delta \log K_E$  6.7 was derived for the mutual effect of unconjugated carbonyls, and the lower charge density at carbon of through-conjugated carbonyl is likely to result in a lower value of  $\Delta \log K_E$  being appropriate here. If so it may be that **1482**, for example, will exist as shown. A similar problem may exist for **133** (section C.11) but there is insufficient evidence to decide the issue. However, while tautomerism in imino- and azo-substituted compounds does not appear to have been examined, one can be reasonably confident that compounds of type **1483** ( $X = \text{N}$  or  $\text{CR}$ ) will exist as shown.

### C.18 3-Oxo(thiono)heterocycles with One $\pi$ -Donor Heteroatom and Aza-Nitrogen in a 1,5-Relationship: **140**

All variants Z on **140** exist as the enol **140b** (Scheme 83), even as the parent compounds (section A.2.8), so it follows that the thiones must behave similarly. Since substitution at  $R^4$  is unlikely to have much effect while that at  $R^2$  can only increase its proportion, **140b** must always dominate. The only plausible exception is shown as **1484**, analogous to **1483** and arising in the same way. It appears that **140b** is exceptionally electron-deficient, on the lines of **144** below.

### C.19 5-Membered Ring Oxo(thiono)heterocycles containing Three Contiguous Heteroatoms



Only four such compounds have been studied: **143** and **144** (section A.2.8) and **166** and **167** (section A.3.8). All exist as the enols shown. Of these, **143** and **144** may be regarded as 'azalogues' respectively of **137**, which enolises readily (section C.15), and **140** (section C.18), which gives exclusively the enol. Since aza-nitrogen counts as an electronegative substituent, these tautomeric preferences are unsurprising.

The only kind of substituent that might generate the oxo-form is that of the azo-compound or Schiff base type, as seen in previous sections, to give (**1485**, X = N or CR) or its isomer. Even so, a preference for **1485C** cannot be guaranteed. For the equivalent thiols **166** and **167** there is probably no way of generating the thione.

The isomeric series **1486** has not been investigated. This is an 'azalogue' of **142** and, since **142** tends to enolise still more readily than **137** (section C.16), it seems probable that **1486A** will be the preferred tautomer. While a  $\pi$ -acceptor as in **1487** can only enhance this preference, a  $\pi$ -donor as in **1488** might possibly reverse it, conjugation with NHR sharply reducing the electronegativity of C=N. A similar preference may be postulated for **1489**, with **1489c** severely disfavoured by both lone pair and dipolar repulsion, and a strong intramolecular hydrogen bond adding to the factors favouring **1489b**. Since in this series any thione is a thioamide, then by contrast with series **143** and **144**, the behaviour of C=O and C=S should run in parallel.

## C.20 5-Membered Ring Oxo(thiono)heterocycles containing a 1,2,4-Distribution of Hetroatoms; Tetrazolone

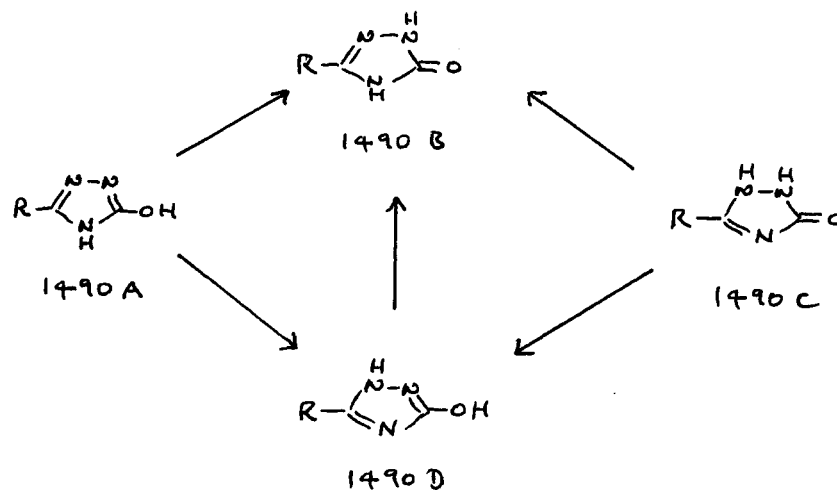
With no potential methylene groups these compounds are incapable of 'C-type' tautomerism so all enols are of the iminol type. For  $Z = \text{NH}$  we have the 4-way equilibrium shown for **1490** in Scheme 90. Here lone pair repulsion in **1490A** and dipolar repulsion in **1490C** severely destabilises both relative to **1490B** and the iminol **1490D**, with the former on account of its urea-like structure expected to be overwhelmingly preferred, as found *e.g.* for **750B** which exists as shown.

For  $Z \neq \text{NH}$  the resulting restriction on annular proton mobility splits Scheme 90 into the three simple, non-interconverting equilibria of Scheme 91. For **903** the result, exemplified by **900**, is that expected from Scheme 90. For **904** the same is expected and is found for **899** but **904C** though generally disfavoured is not unknown (section B.2.9); possibly the extended conjugation present in  $\text{NH}-\text{C}=\text{N}-\text{C}=\text{O}$  can sometimes compete successfully with the cross-conjugation present in **904B** (and *cf.* **902C**, below). However **904B** is almost always the dominant tautomer with **903B** similarly that of **903**, in each case avoiding a severe intramolecular repulsion. As exemplified by **901D**, dipolar repulsion in **905C** as in **904C** leads generally to dominance of the iminol. There are puzzles: although dipolar repulsion in the C-form should be greater for **902** than for **901**, **902** is said to be present in water as an equimolar mixture of the tautomers; **901** however was not examined in water (section B.2.9). This class of compound requires more attention than it has received so far.

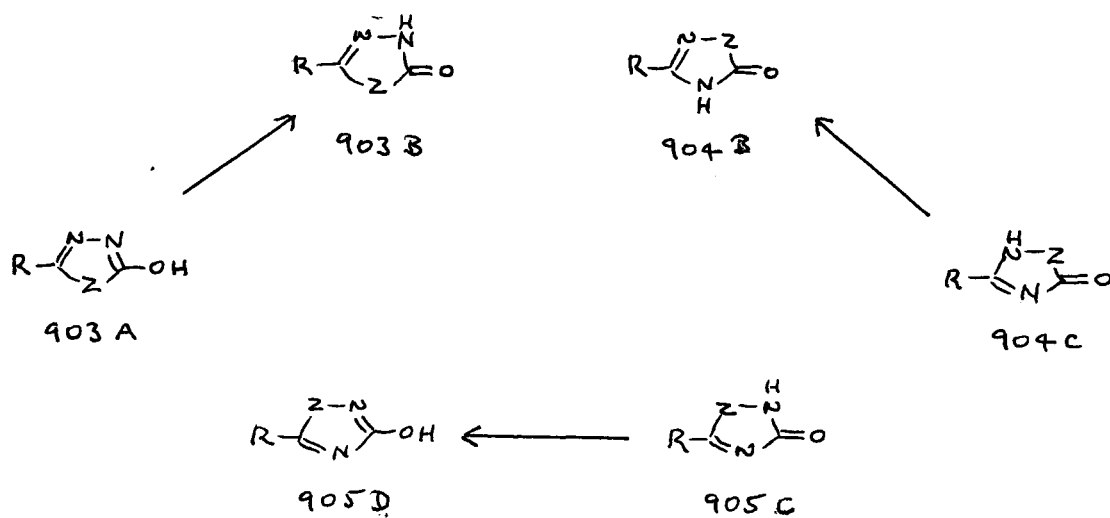
$$\log K_T = 6.4 + 0.39 \log K_M \quad (\text{cx})$$

Against the trend of those compounds discussed in section C.19, tetrazolone **908** exists as the oxo-tautomer **908B**. This may be due to its urea-type structure, to the increase in lone pair repulsion expected for the iminol, or to some contribution from each. Use of eqn. (cx), derived for 6-membered ring heterocycles (section B.8.11), would predict  $\log K_T$  *ca* 3.5, a plausible result. We anticipate that substitution of  $Z = \text{O}, \text{S}$  or  $\text{NR}$  for  $Z = \text{NH}$  would lead to qualitatively similar results, if rather lower values of  $K_T$ .

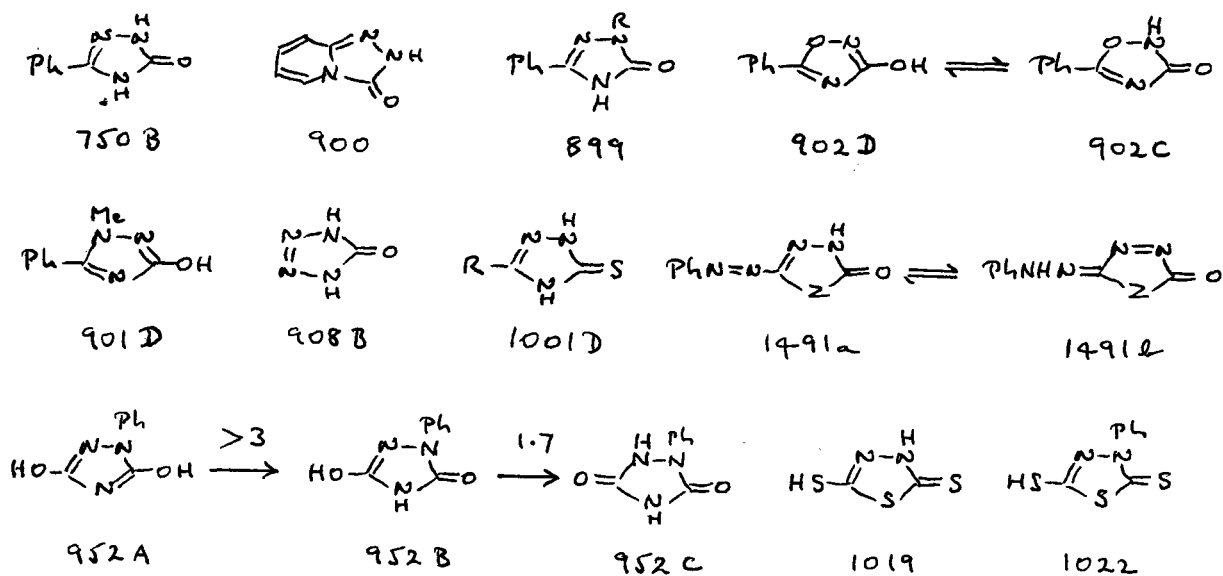
Only the last estimate is (semi-)quantitative, but for (**1001**,  $R = \text{H}$ ) the thione **1001D** is alleged to be favoured by  $\log K_T$  4.4, though this deeply unsatisfactory account (section B.3.5) does not even make clear which is the reference iminothiol. If relative stability here echoes that of Scheme 90, and



Scheme 90



Scheme 91



oxo-forms are in general disfavoured by  $\Delta \log K_T$  *ca.* -0.5 relative to the corresponding thiones (section B.3, *passim*), then  $\log K_T$  *ca.* 3.9 is implied for **1490D**  $\rightarrow$  **1490B**, R = H. Since its extra aza-nitrogen is an electronegative substituent, the further fall to  $\log K_T$  3.5 suggested above for **908** is reasonable; in fact this may be mitigated by increased lone pair repulsion in the iminol. Removal of both would lead to the simple unsaturated urea (**885**, Z = NH; section B.2.9) for which  $\log K_T \sim 6$  may roughly be estimated from the related thiourea (**980**, Z = NH; section B.3.5); a reasonable sequence in  $K_T$  then results.

Substitution at R. – Most published results are based on R = aryl and very little else is known. Annular tautomerism in amidines is in general little affected by substitution at the pivotal carbon atom (section B.1, *passim*) so, except for **905**, the nature of R is not likely to have much effect on it. It is possible that  $\pi$ -donors in **905** might stabilise **905C**, but this has not been investigated. Again, and in contrast to some other types of structure listed from C.13 onwards, it is unlikely that imino- or azo-substitution would have tautomeric consequences; **1491b** is an improbable alternative to **1491a**.

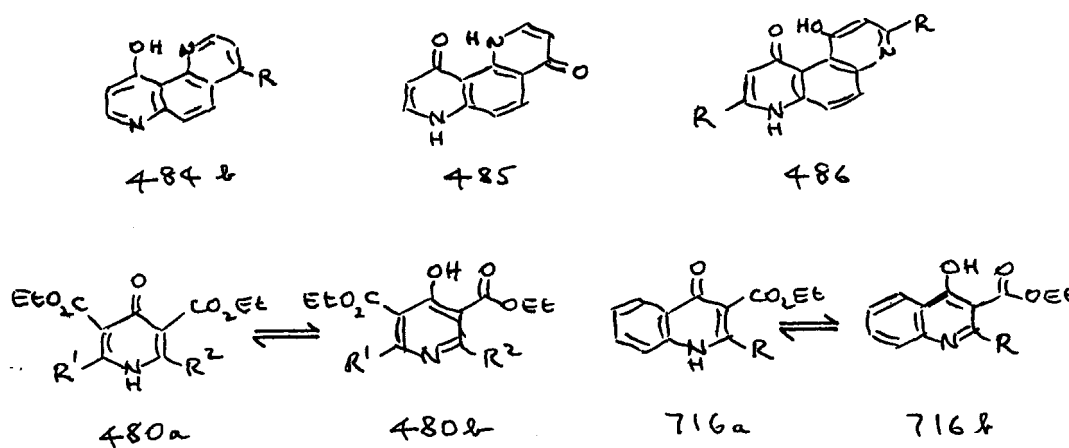
The only important exceptions are R = OH and SH, through their own tendency to tautomerise, and here some results are quantitative. The dioxo-tautomer **952C** of the urazole **952** is favoured over **952B** by  $\log K_T$  1.7; an accurate value cannot be determined for the first ketonisation step, but  $\log K_T > 3$  is probable (section B.2.12). This compares with  $\log K_T$  *ca.* 3.9 as deduced above for the formation of **1490B** from **1490D** but these two processes start from isomeric iminols (and R = OH and Ph respectively) so their quantitative similarity is, if anything, greater than expected. In view of the dipolar repulsion present in **952C** it may seem anomalous that **952B** should not be preferred but the explanation probably lies, once again, in the (*bis*-)urea nature of the former. Imides (section C.7) enolise very much less readily than alicyclic  $\beta$ -diketones (section C.6) so the presence of 4-NH appears likely to stabilise **952C**. This effect cannot yet be quantified but appears to be general; as another example, the cyclic  $\beta$ -diketone barbituric acid **54** will enolise (sections A.1.4 and A.6.2) but the corresponding cyclic triamide 892 (section B.2.9) does not. The roughly corresponding thiones **1019** and **1023** exist as the half-way tautomer shown (section B.3.7) but, in terms of **903**, a substantially lower  $K_T$  value would be expected for Z = S than for Z = NH (on isodesmic assumptions by *ca.*  $10^2$ ; *cf.* section B.3.5) so this result is not unreasonable.

## C.21 6-Membered Ring Mono-oxo(thiono)heterocycles and their Benzofused Derivatives

This large and important category is nevertheless straightforward enough in outline to be capable of description in a single section. Two important factors account for most of the difference between these and their 5-membered ring analogues of sections C.10 - C.20:

(a) Since one amidic plus two C=C groupings add up to a 6-membered ring, there is no scope for C-type tautomerism here (5- or 7-membered unsaturated ring fusions might in principle vitiate this conclusion).

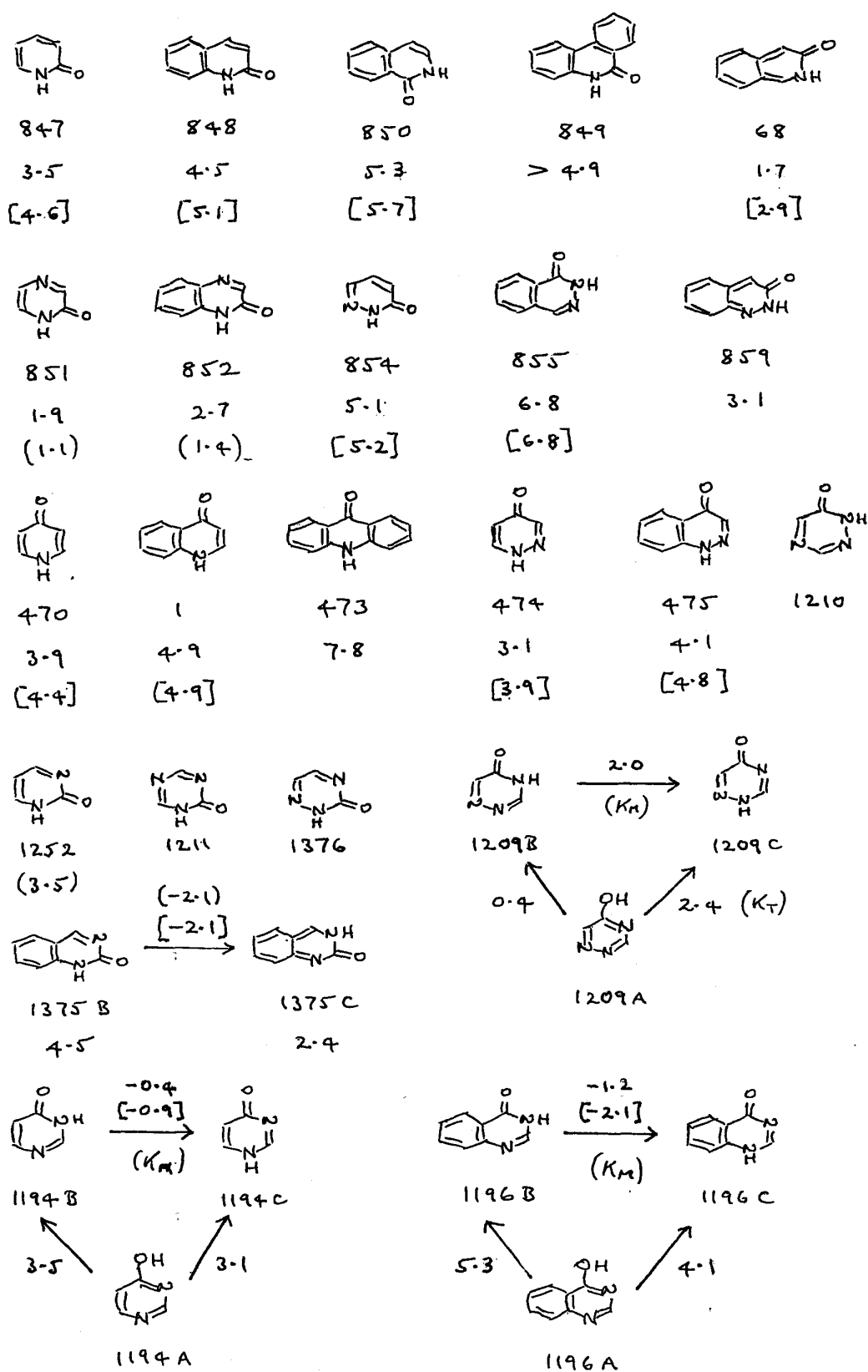
(b) The effect of substituents on tautomeric ratio, where charted, follows simple Hammett rules; the distinction between 'bland,'  $\pi$ -donor and  $\pi$ -acceptor substituents which we have found useful in sections C.10 - C.20 fades away, to be subsumed in the above. A major reason for this, if not the only one, probably lies in the strong tendency of 'N-type' and 'C-type' tautomerism to be primarily affected by field and resonance forces respectively; section A.10.9 deals with the latter and B.4.4 with the former, while a comparison of the very different results to which they give rise is presented in Table 64. It is significant that we find  $\sigma_m$  to correlate data in situations where, for benzenoid chemistry,  $\sigma_p$  might have been considered appropriate, helping to demonstrate the much greater importance of field effects in this area of heteroaromatic chemistry. Examples appear below.



Scheme 92

A major complication, mentioned here to be dismissed, concerns substituent groups capable of forming strong hydrogen bonds to NH, OH or carbonyl. Intramolecular bonds of other origins can sometimes be generated in polycyclic, mostly angular ring systems, and these can cause major distortions to the otherwise expected pattern; section A.10.8 is devoted *inter alia* to this subject. Examples appear in Scheme 92. Species **484b**, **485** and **486** represent extreme examples of this type, in **484b** and **486** leading to normally disfavoured tautomers whereas in **485** the normally dominant one is reinforced;  $\log K_T$  6.4 (section A.10.8) by contrast with 3.9 for 4-pyridone itself. A less extreme example is **480**, in which **480a** dominates as expected for  $R^1 = R^2 = H$  but steric compression when  $R^1 = R^2 = Ph$  forces conversion to the iminol **480b**. Similarly, **716** can generate **716b** as the major tautomer in certain solvents (though probably not in water) for  $R = SR$  but not for  $R = H$ , though this intramolecular bond probably contributes only  $\Delta \log K_T$  ca. -1 (in water) to the observed result. These factors are treated at length in Appendices 3 and 4 and will not receive further discussion here.

Scheme 93 has been compiled from the results given in Table 38 (section A.10.7), Table 56 (section B.2.5), and Scheme 67 (section B.8.12). It displays all known results as  $\log K_T$ , obtained by correcting the experimental data by use of the 'revised basicity method' (Appendix 1) along with estimates of varying reliability, to be described. Results for thionoheterocycles, where known, appear in square brackets below those for the corresponding oxoheterocycles. These include two, for **974** (*vide* **851**) and **975** (*vide* **852**), which we believe to be inauthentic (for full discussion see section B.8.19). The result for **68** is based on our LSER analysis (Appendix 2) and is consistent with those for related compounds (see below). The analysis of section B.5.12 for 2-methyl-4-quinazolone was combined in section B.8.12 with that of section B.5.11 for the effect of 2-substitution to give the pattern shown for the parent compound **1194**, whereas our estimate for **1252**, also from section B.8.12, is based on the use of eqn. (cx); *cf.* section C.20. Use of the benzofusion factors to be described below, separately for **1196B** and **1196C**, leads to an estimated  $\log K_M$  -1.2 almost identical with the value observed: -1.3 (Table 73, section B.5.11). By contrast, combining  $\log K_M$  -0.4 for **1194** with  $\Delta \log K_M$  2.4 for the effect of lone pair repulsion in **1209A** (section B.5.13) with an isodesmic estimate of  $\log K_T$  for **1209A**  $\rightarrow$  **1209C** (section B.8.12) yields a value for **1209A**  $\rightarrow$  **1209B** which does not look reasonable at all. Consequently we do not quote our isodesmic estimates for **1210**, **1211** or **1376** but nevertheless there can be little doubt that these compounds, in common with all others listed in Scheme 93, will exist firmly in the oxo-form.



Scheme 93

Regularities abound. If NH is in the  $\alpha$ -position to the ring junction,  $\Delta \log K_T$  on benzofusion is 0.8 for **851**  $\rightarrow$  **852** and 1.0 elsewhere ( $n = 4$ ); if in the  $\beta$ -position, it is 1.9 or 1.7. The effect of benzofusion to give a quinonoid structure is  $\Delta \log K_T$  -1.8 or -2.0, values echoed by some quite dissimilar compound series (Appendix 5). On the evidence of the equations discussed below, electronegative substituents reduce  $K_T$ ; consistently, aza-nitrogen in the 4-position leads to  $\Delta \log K_T$  -1.6 or -1.8. (This does not happen for the corresponding 1,3-relation as in **1194**, presumably because amidine resonance over-rides it). When the nitrogen atoms are contiguous, this effect is either much less ( $\Delta \log K_T$  -0.8 in the 4-oxo series) or it actually reverses ( $\Delta \log K_T$  1.5 or 1.4 for the 2-oxo set); we demonstrate in Appendix 3 that the reason lies in lone pair repulsion, its effect on the order of that found unambiguously for  $K_M$  in **1194**  $\rightarrow$  **1209** ( $\Delta \log K_M$  2.4; section B.5.13). As a set these regularities are extraordinarily comprehensive; as seen above, we regard them as firm enough to predict the behaviour of **1196** from that of **1194**, and there are other, more qualitative examples. It is also interesting that **1194B** and **1252** should, on our analysis, conform to expectation<sup>2www</sup> in possessing a  $K_T$  value similar to that for 2-pyridone **847** itself. The only anomaly is **473**, whose  $K_T$  value seems excessive. However there may be an explanation even here: it has been pointed out (Dr Roger Sayle) that its iminol tautomer, like acridine itself, may be regarded as having considerable quinonoid character, and the full allowance for this added to  $\log K_T$  for 4-quinolone would result in  $\log K_T$  7.7, almost exactly the value found. There are two possible approaches to the asymmetrical **849**: as **848** with a  $\beta$ -NH or as **850** with a  $\alpha$ -NH ring fusion, resulting in predictions of  $\log K_T$  6.7 or 6.3 respectively. Unluckily with a measured value listed as  $> 4.9$ , the result of an indeterminate  $pK_a(\text{NH}) < -1.5$  (section B.2.5), no decision is possible.

$$\log K_T(\text{S}) = 1.7 + 0.8 \log K_T(\text{O}) \quad (\text{1xxii})$$

Unfortunately, while the qualitative trends remain present, no such regularity attaches to the thiones. Katritzky<sup>2ppp</sup> has suggested eqn. (1xxii) for the relation between the two series, and using the 10 valid comparisons available from Scheme 93, which differ in detail from his set, we obtain an equation indistinguishable from his. Nevertheless we doubt its validity. There is simply too much inconsistency:  $\Delta \log K_T$  on benzofusion is 0.5, 0.3, 0.5 or 0.9 for  $\alpha$ -NH, 1.1 or 1.6 for  $\beta$ -NH, and a solitary -1.7 for quinonoid ring fusion which is contradicted by -2.1 for the thione equivalent (section B.5.15) to **1375** (note that the value suggested for **1375** itself *assumes* the validity of this figure; *cf.* section B.3.4). It has to be realised that much of this work, especially on thiones, is quite old, and that while the UV distinctions between tautomers on which most analyses rest tend to be greater for thiones, these compounds are relatively unstable and questions of purity

arise, unavoidably exacerbated by the rather slow experimental techniques obtaining at that time. A further complication, addressed inconclusively in sections A.11.3 and B.3.1, is that the correction factors we use for  $\Delta(\text{SR})$  are problematical, though it should be noted that errors from this source will be systematic rather than random so of little relevance to the above inconsistencies. A definitive study of these thiones is yet to come. In the meantime we have, as a simple approach,  $\Delta \log K_{\text{T(O} \rightarrow \text{S)}} 0.55 \pm 0.35$  ( $n = 10$ ), which is clearly imprecise but will have to do for now.

*Substituent Effects.* – Our LFER equations appear in Table 93. Those for **470** and **1194** appear to be quite reliable; from its derivation, the latter essentially references the major tautomer **1194B**. We therefore provisionally suggest its use as an approximation to the otherwise unavailable equations for 3-substituted 2-pyridones **847** and similar substituent positions elsewhere. Those for 5- and 6-substituted 2-pyridones are very much more tentative. Interestingly, those that contain no term in  $\sigma_{\text{I}}$  possess a value of  $\rho_{\text{m}}$  *ca.* -3,

**Table 93. Equations for Substituent Effects in the 6-Membered Ring Oxoheterocycles of Scheme 93<sup>a</sup>**

Compd.	Substituent position	Equation	Other potential applications <sup>b</sup>
<b>470</b>	2	$3.7 + 3.2 \sigma_{\text{m}} - 10.5 \sigma_{\text{I}}^{\text{c}}$	<b>1</b> (2), <b>474</b> (6), <b>1194C</b> (6)
<b>470</b>	3	$4.0 - 0.7 \sigma_{\text{m}}^{\text{d}}$	<b>1</b> (3), <b>474</b> (5), <b>1194C</b> (5)
<b>847</b>	3		
<b>847</b>	4	$\rho_{\text{m}}$ possibly <i>ca.</i> - 2.5 <sup>e,f</sup>	<b>848</b> (4), <b>854</b> (4), <b>1194B</b> (4)
<b>847</b>	5	$3.5 - 3 \sigma_{\text{m}}^{\text{g}}$	<b>850</b> (4), <b>851</b> (5), <b>854</b> (3), <b>1252</b> (5)
<b>847</b>	6	$3.5 + 3 \sigma_{\text{m}} - 8 \sigma_{\text{I}}^{\text{f,h}}$	<b>850</b> (3), <b>68</b> (1), <b>851</b> (6), <b>1252</b> (6)
<b>1194</b>	5	$3.5 - 2.9 \sigma_{\text{m}}^{\text{i,j}}$	<b>847</b> (3), <b>848</b> (3), <b>68</b> (4), <b>854</b> (5), <b>859</b> (4), <b>851</b> (5)

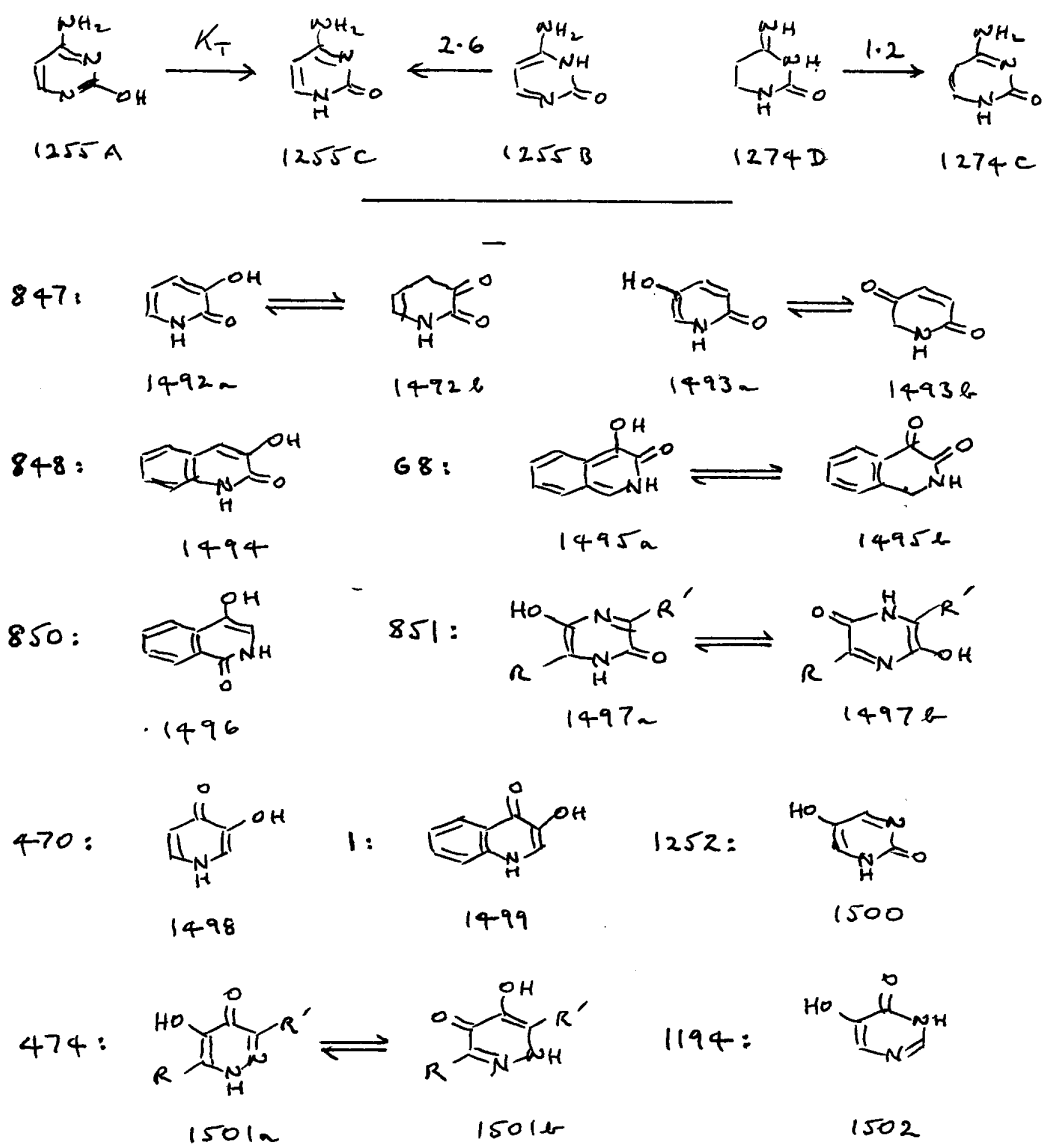
<sup>a</sup> Effect on  $\log K_{\text{T}}$ . <sup>b</sup> Compound and (substituent position). <sup>c</sup> Eqn. (xxx), section A.10.6.

<sup>d</sup> Eqn. (xxxiii), section A.10.6. <sup>e</sup> Section B.2.4. <sup>f</sup> Highly provisional. <sup>g</sup> Eqn. (lxix), section B.2.4. <sup>h</sup> Eqn. (lxx), section B.2.4. <sup>i</sup> Section B.8.12. <sup>j</sup> Adapted from eqn. (cxii) for 2-Me derivative.

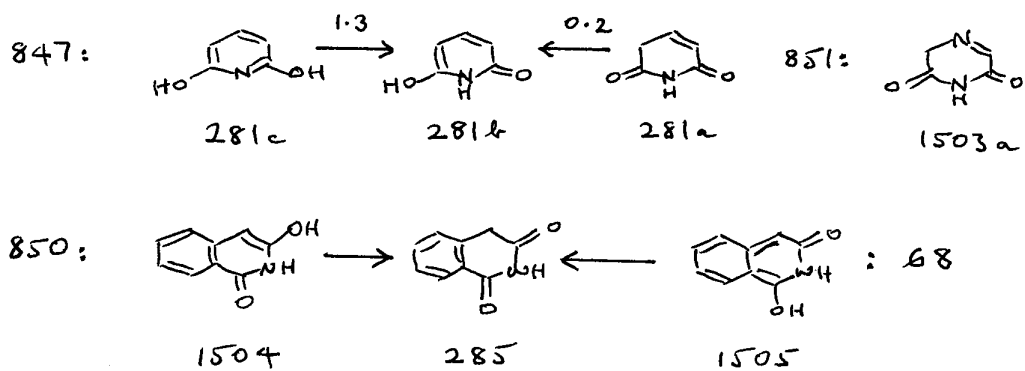
all except that for 3-substituted 4-pyridones which, as Katritzky<sup>290</sup> has pointed out, represents a pivotal position between the two protonation sites not found elsewhere. A single term implies that the two sets of  $pK_a$  values show parallel electronic behaviour. Only for substitution adjacent to NH is two terms found, that in  $\sigma_I$  due to iminol  $pK_a$  and responsible for a much steeper dependence of  $K_T$  on electronic factors than is found elsewhere. In fact  $\rho_I$  in the 2-position of **470** is virtually identical to that for pyridine itself, and it should be noted that  $\rho$  for its 3- and 4-substituent positions is much closer in blend to  $\rho_m$  than to  $\rho_p$  (section A.10.6).

Table 93 also lists substituent positions for the other oxoheterocycles of Scheme 93 which may sufficiently resemble those for which equations exist to behave in a similar manner. We do not list the resulting predictions since these are easily generated with the aid of Table 2, but some illustrations follow. In any substituent position for which  $\rho_m \sim -3$  is valid,  $\Delta \log K_T -2.2$  follows for the nitro-group; for substitution adjacent to NH this becomes -3.1 and -4.7 for 2- and 4-pyridone analogues respectively. Dominant iminol formation should result for **68** and **851** from any form of nitro-substitution (except benzenoid), but elsewhere only **852** (3-substitution) and **474** (6-substitution) should behave in a similar manner, with borderline behaviour from **1** (2-substitution) and **1252** (6-substitution). We choose  $\text{NO}_2$  as substituent for this comparison since if this cannot enforce iminol formation there is little else that can. At the other extreme, there is probably no 3-substituent in **1** or **470**, nor 5-substituent in **474**, capable on its own of enforcing iminol formation. However multiple substitution can lead quite easily to the iminol, and there is some evidence (see especially section A.10.6) that such effects are additive. Note in passing that, where rival oxo-tautomers are possible, a substituent which depresses one  $pK_a$  notably more than the other will have the effect of making the one most affected less important; in **1194** for example, a 6- $\text{NO}_2$  substituent should result in less **1194B** but also a negligible fraction of **1194C**. The tantalising possibility arises that a value of  $\rho_m$  close to -3 may be found to apply to almost all substituent positions not adjacent to NH, but presently this is sheer speculation.

These equations concern only substitution at a carbon double bond. For substitution at  $\text{C}=\text{N}$  quite different rules may apply, but the evidence is fragmentary. Substitution at the amidine carbon atom of **1194** has only a minor effect on  $K_M$  (section B.5.11; it is however very solvent-sensitive) and its effect on  $K_T$  is unknown; **1196** should behave similarly but evidence is lacking. Elsewhere the only data are for cytosine **1255** (section B.5.15), where **1255C** is preferred over **1255B** in water by  $\log K$  2.6. A similar situation is possible for **1211**. This preference for the through-conjugated C-



Scheme 94



Scheme 95

tautomer is already found in **1274** (section B.5.15) where the tautomeric process is different. None of this relates to iminol formation, however. Nevertheless, with **1255A** enormously disfavoured by MO calculation even in the gas phase, it seems probable that  $\pi$ -donors will have their usual effect of increasing the importance of the oxo-tautomer. What effect a  $\pi$ -acceptor might have is presently beyond conjecture. The special case of OH and SH as substituent is considered below.

## C.22 6-Membered Ring Heterocycles and their Benzofused Derivatives with Two or More Potential Oxo(thiono)-Substituents

Starting with the compounds of Scheme 93, simple rules can be formulated for tautomeric preference when a further OH or SH is inserted. These rules depend in large measure on its position of substitution relative to the molecular features already present, and fall broadly into the categories described below. While the following account largely concerns OH, its replacement by SH would involve little difference except where indicated. The consequence of adding a third OH or SH is explored only for certain cases of practical importance.

*(a) Insertion meta to NH.* — Scheme 94 sets out the compounds in question, referenced to those of Scheme 93 and mostly in the same order. Not all examples require comment. Ketonisation would, in every case, destroy aromaticity without conferring any compensating advantage, as in **1493b**, exacerbated in some cases, such as **1492b**, by the severe lone pair repulsion characteristic of cyclic  $\beta$ -diketones (*cf.* section C.3). So it is not expected and, where investigated, has not been found. We discount its likelihood even for **1495**, where removal of quinonoid character is a countervailing force that elsewhere often proves decisive. Here the ‘quinonoid penalty’ in **1495a** ( $\Delta \log K$  *ca.* -1.8) is unlikely to circumvent lone pair repulsion in **1495b**, which could be as great as  $\Delta \log K \sim -5$  (Appendix 3).

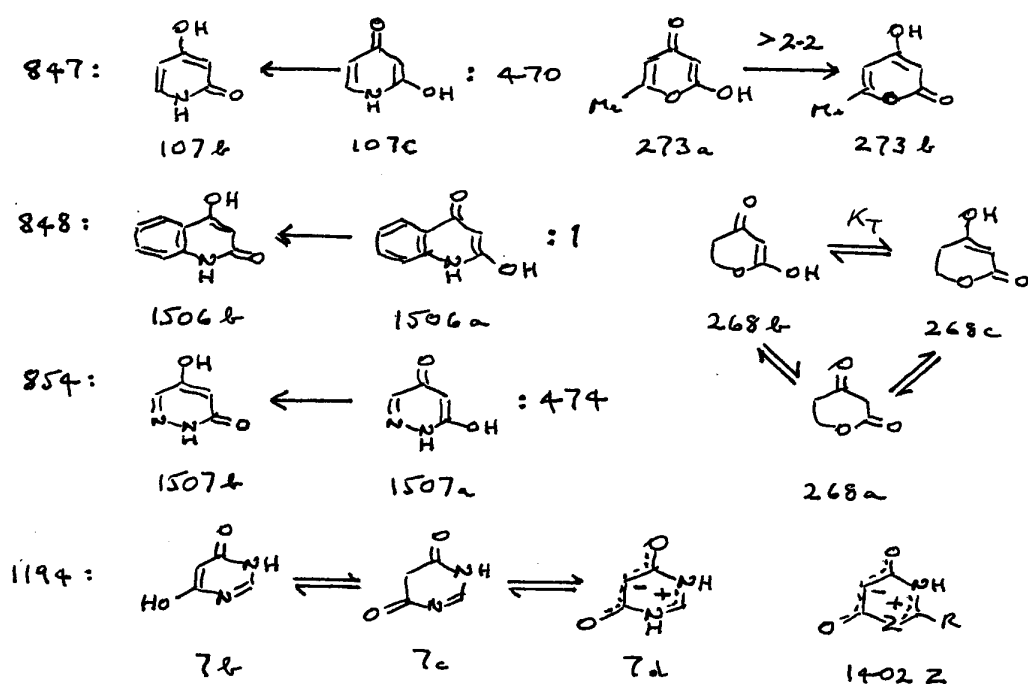
Compounds **1497** and **1501** exist as degenerate tautomers whose degeneracy disappears when  $R' \neq R$ . Here isomer choice will presumably depend on the electronic and hydrogen bonding potentialities of the substituents; for example, **1497a** and **1501a** are likely to be favoured by proton acceptors R, and the **b**-tautomers by proton donors. In principle the 5-OH of **1502** might affect its annular tautomerism, but in practice other 5-substituents appear to have virtually no effect (section B.5.12), perhaps because these lie equidistant from each nitrogen atom.

*(b) Insertion Adjacent to NH.* – Scheme 95 follows similar lines to Scheme 94. Again loss of aromaticity will accompany ketonisation, but is balanced this time by imide resonance which, for **281a** and **285**, results in its preponderance for the latter and, in water, an almost equal balance for the former (section A.6.3; see also section C.7). This difference is in line with that expected for benzofusion (section C.21). Here and elsewhere, note that if the tautomeric process does not involve NH this can be replaced by O, S or NR with similar results; for this and for the effects of other substituents in these and related compounds, see section C.7. In principle **1503** could behave in a similar way, but with  $K_T$  for **851** sharply reduced by its aza-nitrogen atom (section C.21) it seems likely that **1503a** will be a very minor species. Formal generation of the same compound, **285**, by hydroxylation of two distinct mono-oxoheterocycles, is the first of several examples we shall meet.

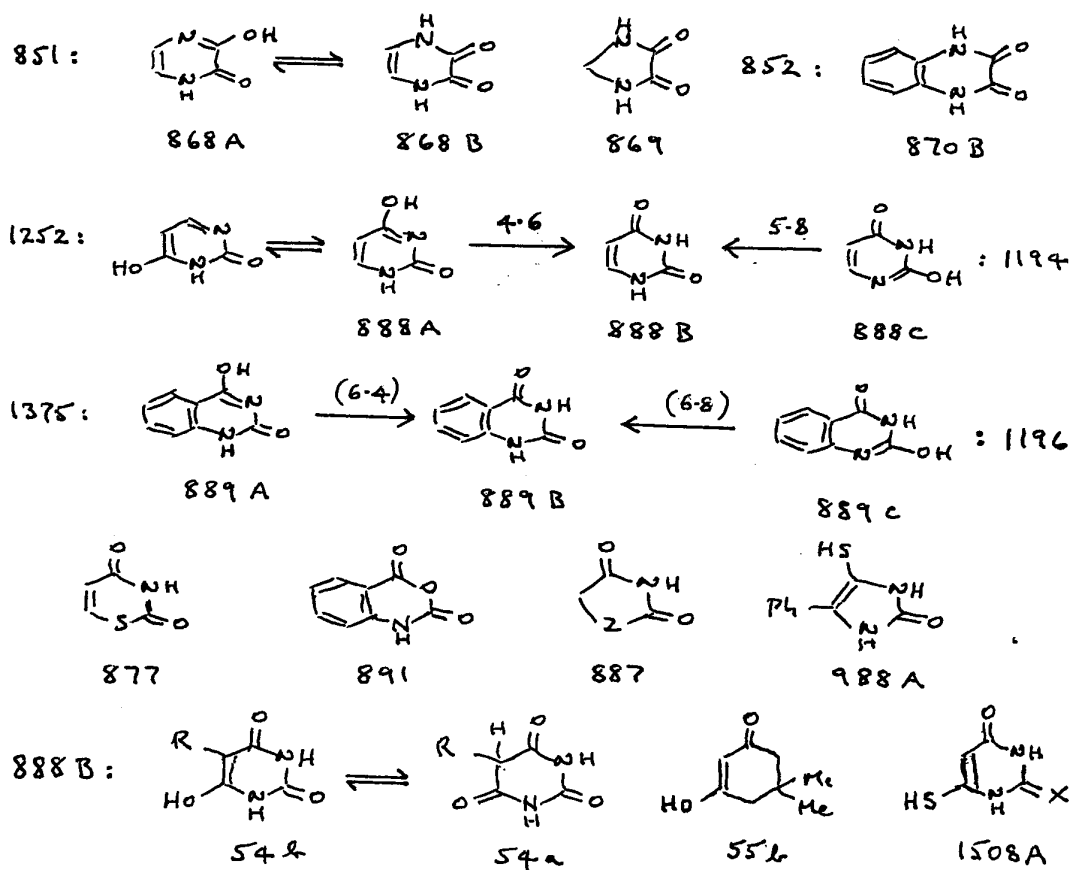
*(c) Insertion meta to Carbonyl.* — This situation (Scheme 96) generates an enolised  $\beta$ -diketone which is extremely stable and, in a heteroaromatic context, shows no tendency to revert to the dicarbonyl structure. Two isomers are possible and, in all known cases, the issue is resolved in the same direction, *i.e.* to that in which carbonyl is adjacent to the hetero-atom. Thus **847** and **470** give the same dominant tautomer **107b** on insertion of OH (section A.6.3) whereas **848** and **1** should give **1506b**. In the case of **854** and **474** the outcome is unknown but, again, the **b**-tautomer should predominate.

If  $Z = O, S$  or  $NR$  is substituted for  $Z = NH$ , the situation is essentially unchanged. Equilibration studies on model compounds imply  $\log K_T > 2.2$  for pyrones such as **273** whereas a simple Hammett approach suggests  $\log K_T \sim 3$  in favour of **107b** (both section A.6.3). For non-aromatic molecules a trace of di-oxo tautomer such as **268a** is sometimes detectable, but  $K_T$  is probably greater than *e.g.* for **273**; among aromatic compounds of this sort, a levelling effect due to comparable through-conjugation in both tautomers may be present.

In **7**, a combination of  $\beta$ -diketone acidity with amidine basicity leads, in aqueous solution, not to **7b**, its isomer, or **7c** but chiefly to the zwitterion **7d**. We have re-interpreted the solid-state IR spectrum of (**1402**,  $Z = S$ ,  $R = Ph$ ) as indicating a similar zwitterion, as **1402Z**, and this may be general (section C.7). However, further aza-nitrogen in either remaining substituent position will abolish acidity or basicity as the case may be, so there is limited scope for this phenomenon.



Scheme 96



Scheme 97

*(d) Insertion on C=N: Diazines lacking Contiguous Nitrogen Atoms.* –

These compounds are displayed on Scheme 97. They are iminols so can tautomerise to the amide and this mostly happens but sometimes it does not. Despite the lone pair repulsion that must be present in **870B** this structure has been proved for aqueous solution (section B.2.7, where we attempt an explanation) but that of **868B** was assumed by analogy and must be considered uncertain, since less likely than for **870** by  $\Delta \log K_T$  ca. 1 (section C.21). The structure of **869** is established but, since this is alicyclic, that fact is irrelevant since a much higher  $K_T$  would in any case be expected. The acylurea uracil **888B** can result from three pathways involving **1194** and **1252**, and a similar genesis follows for quinazolinedione **889B**. For uracil both  $\log K_T$  values are known (section B.2.9) and appear in Scheme 97. The higher value of  $K_T$  is as expected for an acylurea vs. an imide (section B.2.9) and indeed we argue elsewhere (section B.8.11) for the likelihood of a larger differential in saturated structures such as hydantoin (**887**, Z = NH) for which very tentative values of  $\log K_T$  ca. 7 and 4 are proposed. Structures such as **877** and (**887**, Z  $\neq$  NR) which contain poorer electron donors than NR are likely to possess lower  $K_T$  values for 2-carbonyl, but nevertheless in none of these, nor in compounds such as **891**, is any detectable proportion of the iminol tautomer present, nor is it likely on the above arguments. An isodesmic treatment of **889** vs. **888** similar to those of Scheme 93 would lead to the predictions set out in Scheme 97; both  $K_T$  values are large and their putative convergence is intriguing. In fact no case is known of detectable iminol formation in any urea (section B.2.9) and even among acylureas only C-type enolisation has been found, as for **54** and **988** below.

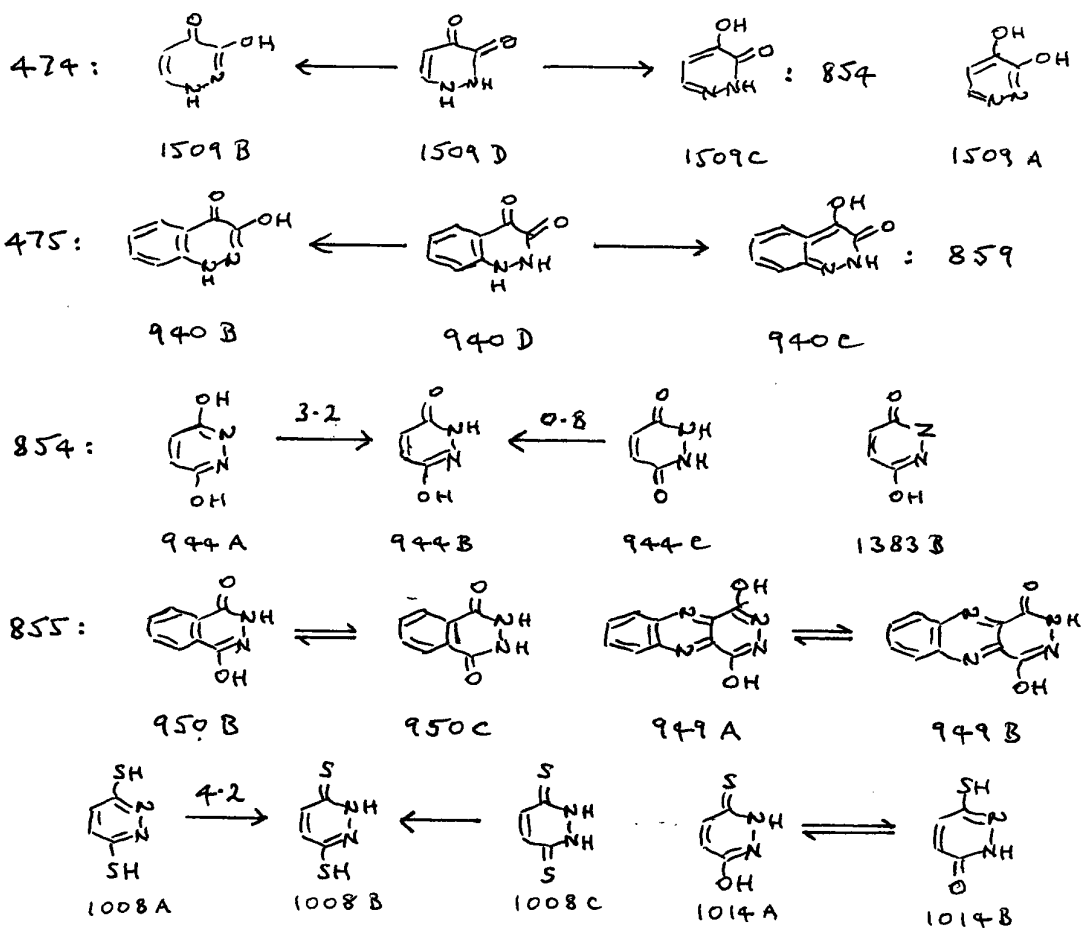
The insertion of 5-OH into uracil leads to barbituric acid **54**. The resulting structure **54a** is that of a  $\beta$ -diketone and, while this tautomer predominates by about 100-fold in water, almost any substituent R will enhance enolisation to **54b** (section A.6.2). The imidic character of the 4- and 6-carbonyl groups restricts enolisation by not much more than a factor of  $10^3$  relative to dimedone **55** (section C.6), probably since **54b** possesses some aromatic character (see full discussion in section A.6.2). If 4-C=O in **887** is replaced by C=S, which is much more susceptible than C=O to C-type enolisation (section A.3), aromatisation becomes possible (section C.13); an example is **988** which exists largely as **988A** (section B.3.5). Similarly it is probable that 4(6)-thiobarbituric acid will exist as the enethiol (**1508A**, X = O) and the same structure is to be expected for X = S.

*(e) Insertion on C=N: Diazines possessing Contiguous Nitrogen Atoms.*

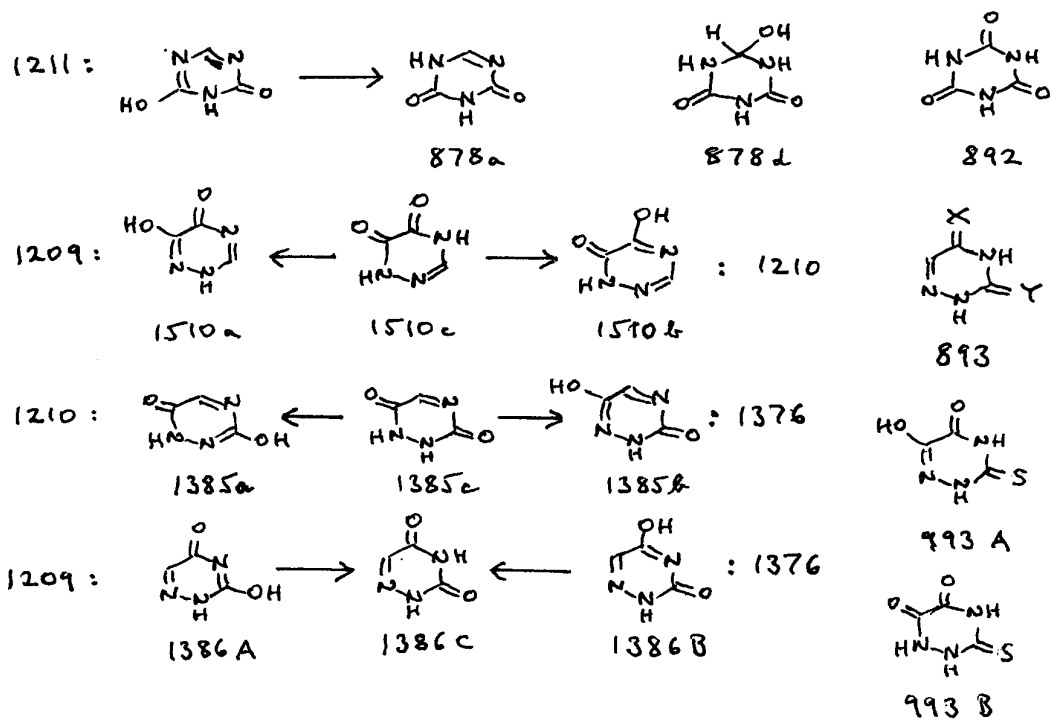
– These compounds comprise two series (Scheme 98). As to the first there is some information on **940**, but only in  $\text{CHCl}_3$ , where it appears to exist as a mixture of **940B** and **940C** with the former more important but not by much (section B.2.11). With large values of  $K_T$  for both **475** and **859** (Scheme 93) no appreciable proportion of **940A**, the dihydroxy-form, is likely while its combination of severe lone pair *and* dipolar repulsion rules out **940D**. There are no data for **1509** but we may attempt an estimate. With  $\log K_T$  3.2 and 4.8 for **474** and **854** respectively (Scheme 93), and fairly similar  $\Delta \log K_T$  values likely for the insertion of OH since both substituent positions flank carbonyl (section C.21), **1509C** is expected to be the major tautomer. The quinonoid nature of **940C** presumably accounts for **940B** as, probably, the major tautomer in that case.

The second and more important series consists in ‘maleic hydrazide’ **944** and compounds of similar type. Here the half-amide **944B** is the major tautomer but not overwhelmingly so, to the extent in water of *ca.* 90% (section B.2.12). The dihydroxy **944A** and diamide **944C** tautomers are disfavoured by lone pair and dipolar repulsion respectively, the margin for **944A**  $\rightarrow$  **944B** being coincidentally quite close to that for 2-pyridone **847** itself (Scheme 93) through a near-cancellation between the effects of lone pair repulsion (favourable) and ring electronegativity (unfavourable). The diamide **944C** is doubly disadvantaged since it combines the latter factor with dipolar repulsion; it can be shown (Appendix 3) that the two forms of *N,N* repulsion here carry similar weight. It also follows (*cf.* section C.16) that if one NH is replaced by Z = O, S or NR, the preferred tautomer will be **1383B** (section B.8.15).

There is some dispute as to the preferred tautomer of **950**. While **950B** is undoubtedly that present in the solid state, **950C** is more probably that which predominates in aqueous solution (section B.8.15). An expected  $\Delta \log K_T$  *ca.* 1.8 for NH in the  $\beta$ -position to benzofusion (section C.2.1) would transform  $\log K_T$  -0.8 in the case of **944C** to *ca.* 1.0 for **950C**, consistently with this result. While the solid state and aqueous tautomers are often identical, such a switch is not unusual; it could be caused here by formation of an iminol dimer in the crystal. In both **944** and **950** the margin is slim and it would only require appropriate 4,5-disubstitution to convert between tautomers (a *single* substituent would remove degeneracy but have no other effect). A known example is **949** where the **B**-tautomer is still dominant but **949A** is now its rival; proton donors in place of aza-nitrogens might stabilise the **C**-tautomer instead.



Scheme 98



Scheme 99

The sulfur analogue **1008** possesses the same dominant tautomer **1008B** (section B.3.7) but there are no data from which the fraction of **1008C** may be calculated. The somewhat greater margin by which the **B**-tautomer appears to be preferred, relative to **944**, is consistent with the known predominance of **1014A** over **1014B** but neither preference can be quantified. Suitable substituents should again be able to tip the balance.

Compounds of type **944** are exceptionally malleable in tautomeric terms, exhibiting behaviour more akin to that of the degenerate annular tautomerism common in nitrogen heterocycles than that found among their closer analogues. Such ease of interconversion may have biological merit and could be true for both. Many such examples appear in subsequent sections.

*(f) Insertion on C=N: Triazines.* — All substitution in oxotriazines is on C=N so all can be accommodated in a single sub-section. The structures of the four parent oxoheterocycles (Scheme 93) are assigned in sections B.5.13 (**1209**), B.5.15 (**1210** and **1211**) and B.8.12 (**1376**) while those that might result from insertion of OH are set out in Scheme 99. The symmetrical triazinone **1211** is the easiest to consider: one such insertion leads to **878a** and two to the symmetrical triazinetrione **892** (section B.2.8). A peculiarity is the ease with which the former gives covalent hydrates such as **878d**.

The remaining compounds relate to one another as shown, *i.e.* through three independent tautomeric pathways each involving two parent oxoheterocycles. Insertion of aza-nitrogen into **868** (Scheme 97), itself on the tautomeric borderline, should be sufficient to render **1510c** a minor tautomer, leaving **1510b** or **1510a** to dominate the mixture. Here the choice lies between an amide and a vinylogous amide respectively; in competitive situations the former is usually preferred but here the likely outcome is far from clear. For **1385**, with **944C** (Scheme 98) a disfavoured tautomer even before insertion of aza-nitrogen to give **1385c**, the choice must lie between **1385a** and **1385b** and we have given arguments (section B.8.15) that favour the latter. For **1386** the position is unequivocal: the azauracil structure **1386C** avoids iminol forms without entailing either lone pair repulsion as in **1510c** or dipolar repulsion as in **1385c** and it has furthermore been stated (section B.2.9) that all compounds of type (**893**, X and Y = O or S) exist in this tautomeric form.

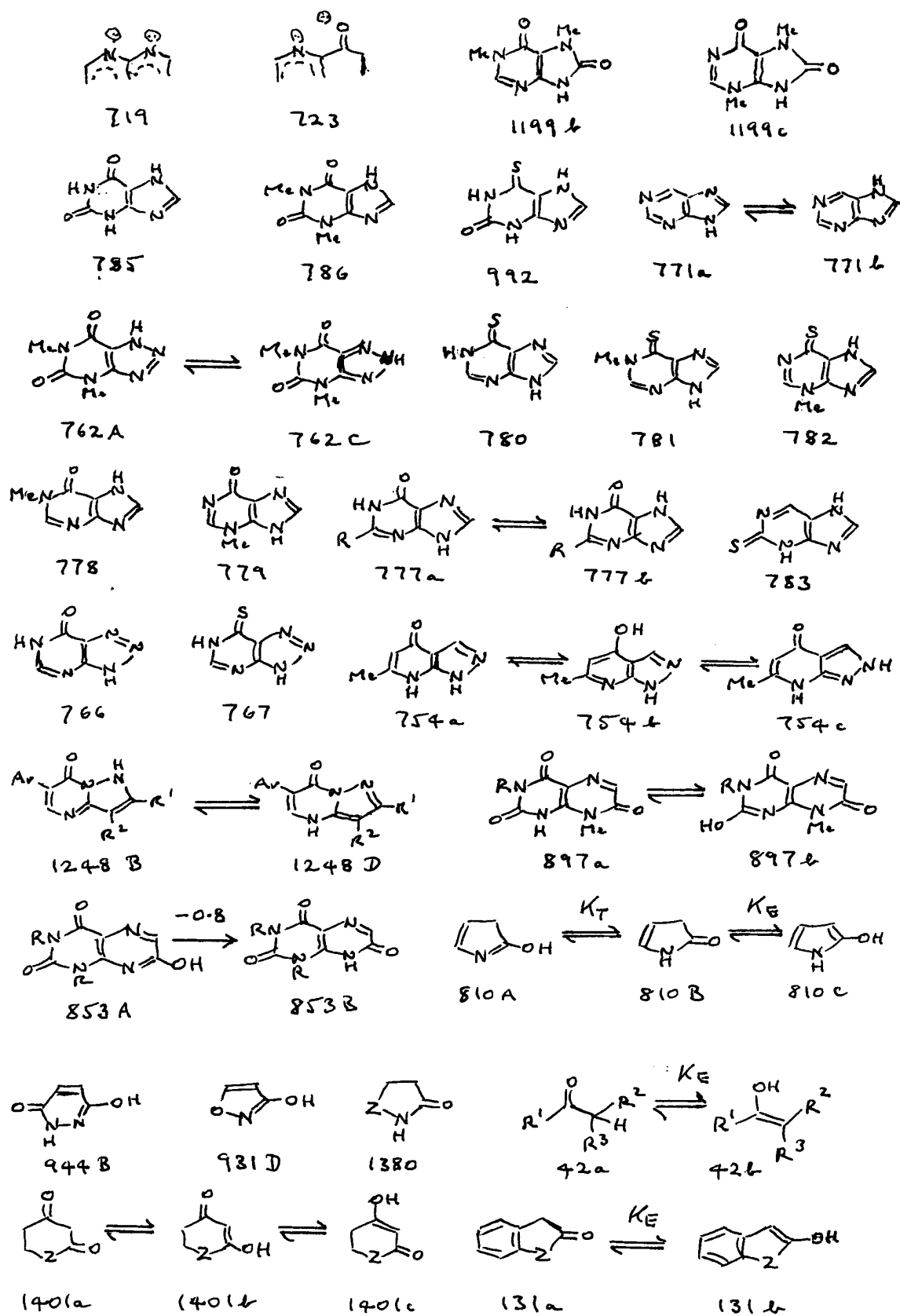
On the evidence of **993** (section B.3.5), the trione common to all three triazines exists as **993A**. This is reasonable, since the trione structure **993B** would contain all the intramolecular repulsions that eliminate **940D** from consideration (Scheme 98; and contrast **892**). It may be assumed throughout this series that compounds that can possess C=S/SH, C=O/OH or similar tautomers will exist in such forms.

### C.23 Non-Benzenoid Ring Fusions to 6-Membered Ring Oxoheterocycles

This is not a large category but it encompasses some compounds of biological importance. Since intramolecular repulsions or attractions, *e.g.* hydrogen bonding, may occur across the ring junction, such ring fusions possess the potential to influence tautomeric form. In practice most observable effects concern annual tautomerism, benzofusion (section C.21) being almost alone in its importance; other fusions, *e.g.* to cyclic ureas, appear to have almost no effect (*vide infra*). This topic is considered more specifically in sections B.1.5 - B.1.7, B.5.11, B.8.1 and B.8.5; here we attempt an overview.

Most of the following analysis centres on fused imidazoles. The *peri*-interactions that dominate tautomeric preference for most such compounds, some re-assembled in Scheme 100, are of two types: attractive and repulsive. What makes their disentangling particularly difficult is that each is so often accompanied by the other. In the dominant tautomer represented by **778**, for example, NH/C=O is clearly an attractive force and N/N a repulsive one; in a similar way, N/NH in the minor tautomer will be balanced by N/C=O. We have only a sketchy notion of the magnitude of each in isolation. While  $\Delta \log K$  *ca.*  $\pm 0.8$  for **719** incorporates the whole process N/N  $\rightarrow$  N/NH (section A.12), that of  $\leq 2$  for **723** (Appendix 3) involves the enolisation process N/C=O  $\rightarrow$  N/OH, whereas that entailed here is N/C=O  $\rightarrow$  NH/C=O instead. The evidence of **778** suggests that the process leading to the NH/C=O interaction is more important than that to give N/NH, and this is backed up by the results for hypoxanthine (**777**, R = H) and guanine (**777**, R = NH<sub>2</sub>) in both of which (less so for the second) the **b**-tautomer predominates. Note in this context that in purine **771**, where admittedly lone pair repulsion is likely to be less, water displays almost no tautomeric preference. However if C=S replaces C=O as in **780** and **781** tautomeric preference reverses, presumably because the C=S lone pair is too remote to interact with NH (or N). The tautomeric contrast between **778** and **781** should be noted. In the absence of a *peri*-interaction involving C=O the shift N/N  $\rightarrow$  N/NH will generally determine tautomeric form; the dominant tautomer shown for **783** (and some related compounds: section B.1.7) is then as expected.  $\nu$ -Triazole is a stronger proton donor but weaker acceptor than imidazole and, perhaps surprisingly, since these effects could have cancelled, the pattern reverses for **766**; its similar pattern in **767** is in line with expectation for C=O  $\rightarrow$  C=S.

When both *peri*-interactions are favourable (and their alternatives both unfavourable) one expects tautomeric form to be locked and, with only one exception, this is found; **782**, xanthine **785**, theophylline **786**, and **992**, all



Scheme 100

exemplify this situation. There is evidence in fact that, in sharp contrast to the relatively mild attractive and repulsive forces so far considered, *peri*-dipolar repulsion of the NR/NR type is so severe that it can dictate tautomeric form on its own. Direct evidence for xanthine **785**, from the basic  $pK_a$  values of its 7-NMe and 9-NMe fixed tautomers, has yet to be obtained, but several partial approaches point this way. If the *acid*  $pK_a$  (for uracil deprotonation) of these fixed tautomers is measured, and ionisation is assumed to take place (or predominate) at *peri*-NH, the 9-NMe derivative is the stronger acid by  $\Delta pK_a$  2.5, plausibly the result of relieving dipolar repulsion in the free base. This result is of course valid only to the extent that (differential) deprotonation of uracil is energetically similar to that of imidazole, and does not substitute for the basicity experiment outlined above. Similarly, **1199c** is a stronger acid than **1199b** by  $\Delta pK_a$  2.5 also, though it should be noted (a) that imidazolone is not necessarily a valid substitute for imidazole, (b) that, in contrast to the xanthine experiment above, the N/NR switch adjacent to carbonyl in xanthine is not reproduced. A third suggestive experiment involved **853**. In this compound the pyrazinone moiety possesses  $\log K_T$  -0.8, a switch of  $\Delta \log K_T$  2.7 relative to 2-pyrazinone itself (section C.21); of course, while this is indeed a tautomeric shift, it is not of the type it purports to model, and as for the second case, the N/NR switch adjacent to carbonyl is absent. Nevertheless their agreement is impressive and there can be little doubt that the structures written here for xanthine and its analogues are heavily favoured. It is all the more surprising that **779** appears to buck the trend. Perhaps the evidence requires re-examination, especially since its sulfur analogue **782** behaves normally. It is true that **754** in which dipolar repulsion should be considerable exists as **754a**, not **754b** or **754c** (section B.1.5), but given  $\log K_T$  3.9 for 4-pyridone (section C.21) as against a possible penalty of  $\Delta \log K$  *ca.* 2.5 for dipolar repulsion, this can be understood. [It is also known that 4-pyridone NH is an exceptionally poor NH donor; as one consequence, it requires *no*  $\Delta(NR)$  correction - Appendix 1]. The preference shown for **1248D** over **1248B** (section B.5.14) despite loss of pyrimidone resonance helps to re-emphasise the formidable nature of dipolar repulsion in another context. And while there must be some residual reservations concerning the potential effects of ring fusion, the case of **762** shows clearly how small these can be: the balance of tautomers between **762A** and **762B** (in DMSO) is almost exactly that of *v*-triazole itself, and other examples exist *e.g.* in section B.1.6.

There is some lack of consistency that requires mention. The uracil **897** is stated (section B.2.9) to give 35% of the iminol **897b** when R = H but none if R = Me, a difference so extraordinary as to suggest some misinterpretation of the evidence, the more so given  $\log K_T$  5.8 for the parent uracil (Scheme 97). The anomalous case of **779** is noted above. Despite all the experimental work that has been carried out, serious deficiencies remain.

Perhaps more than anywhere else, the compounds considered in this section reveal the limitations of attempting to apply simple empirical chemical rules to complex, densely structured organic molecules. A sophisticated computational assault is very much overdue.

## C.24 Short Summary of Carbonyl Tautomerism

Open-chain aliphatic amides possess  $\log K_T$  *ca.* 9. It is likely that the conformational switch forced by cyclisation will reduce this value and ring size affect it, while unsaturation certainly does (section B.2.3), but nevertheless our lowest estimate for any such simple compound is  $\log K_T$  4.9 for **810** (Table 54).

There are two structural modifications that will encourage iminol formation. One is aromatisation, since the iminol tautomer is always the more aromatic in 6-membered rings and usually but not always in 5-membered rings as well. For example,  $\log K_T$  3.5 for 2-pyridone **847** (Scheme 93) contrasts with an estimated 7.6 for 2-piperidinone **835** (Table 54). Electronegative substituents will then reduce  $K_T$  and, in extreme cases, result in the iminol as major tautomer (section C.21). The second process is the insertion of  $Z = O, S$  or  $NR$  contiguous to  $NH$ . In cyclic structures this results in a degree of dipolar repulsion that, on present evidence, can result in  $\Delta \log K_T$  values which range from *ca.* -2 to -5 according to context and the electronegativity of the hetero-atom (*vide* in particular sections C.15, C.16 and C.19). Their magnitude is such that, as the combined result of dipolar repulsion and aromaticity, the nominal amide **931** exists even in water as **931D**. It is not yet clear whether their magnitude depends on ring size, as it does for lone pair repulsion (Appendix 3), but detailed calculation on 'maleic hydrazide' **944** whose major tautomer is **944B** (section B.2.10) suggests otherwise. Its presence almost unchanged in one crucial open-chain series of compounds (section B.5.15) even prompts speculation that, with more evidence, it may come to be recognised as a conformationally independent property. If so, while similar in effect to lone pair repulsion, its genesis will turn out to be entirely different. So far, experimental evidence on alicyclic compounds is lacking; however extrapolation from the present mixture of speculation and experiment suggests that **1380** should retain, even for  $Z = O$ , the amide structure shown.

Ketones **42a** can give rise to enols **42b** but as for simple amides the proportion is negligible ( $K_E < 10^{-7}$ ) for open-chain ( $R^1 = R^2 = \text{alkyl}$ ) or most alicyclic molecules. However almost any substituent  $R^2$  or  $R^3$  will increase enol formation and the two together, if bulky, can sometimes give rise to a dominant enol. Again there are two processes that readily lead to enol formation. The first is when  $R^2$  and/or  $R^3$  is a  $\pi$ -acceptor, most commonly acyl (but *e.g.*  $\text{NO}_2$  and CN are also effective). This results in a  $\beta$ -diketone or similar which on enolisation becomes a conjugated system. It can give rise to  $\Delta \log K_E$  values on the order of  $10^7$ , resulting in borderline enol dominance which is *greater* in aqueous solution, other things being equal, for the extended (unchelated) than for the chelated conformation. (The reason for this counter-intuitive situation is connected with solvent dependence:  $K_E$  *rises* for the extended but *falls* for the chelated conformer as solvent polarity rises; see Appendix 2 for a full treatment of this subject). An example of the former is **1401**, which if Z is a hetero-atom will always enolise to give **1401c** not **1401b** since formation of the latter would disrupt prior conjugation. Lone pair repulsion in cyclic  $\alpha$ -diketones and similar compounds is another potent source of enol formation (section A.2.5); typically this is probably responsible for around  $\Delta \log K_E 10^5$  (Appendix 3), hence the absence of any reported enolisation in equivalent open-chain structures.

‘C-type’ enolisation of an amide is extremely unfavourable for any open-chain structure (section A.2.4) but can occur in cyclic compounds if certain conditions are satisfied. Here aromatisation is a major driving force especially in 5-membered rings; the enol **810C** is a viable alternative, since aromatic, to the iminol **810A**. An important difference between **810A** and **810C** is that, in the latter, any other  $\pi$ -donor Z, in practice O, S or NR, may replace NH, allowing a much wider variety of structures than is possible for an iminol; in a compound such as **131** for example, the magnitude of  $K_E$  depends on Z (section C.10). An enol such as **810C** or **131b** will be stabilised by the same factors that act on simpler enols like **42b**, such as aromatisation or conjugation *e.g.* to give a  $\beta$ -diketone, and very likely to a similar extent, in contrast to the Hammett-type electronic factors that chiefly influence such ‘N-type’ processes as amide formation in aromatic amides (section C.21) or the behaviour of amidines (section C.31). These distinctions are real and, in our opinion, lack of this understanding has been a major factor in holding the development of a theoretical framework for tautomerism back.

While  $K_T$  is slightly greater for thioamides than for amides the position for ‘C-type’ tautomerism is very different, with simple thioketones relatively disfavoured by a factor of *ca.*  $10^6$  (section A.3.1). For aromatic contexts such as **810** we have tentatively derived a factor of  $\Delta \log K_E 3.5$  relative to C=O which appears to give plausible results (sections C.10 and C.11). This topic is taken up again in section C.43. The interaction of ‘C-type’ and ‘N-type’ tautomerism, important as it is for carbonyl compounds, is still more important here.

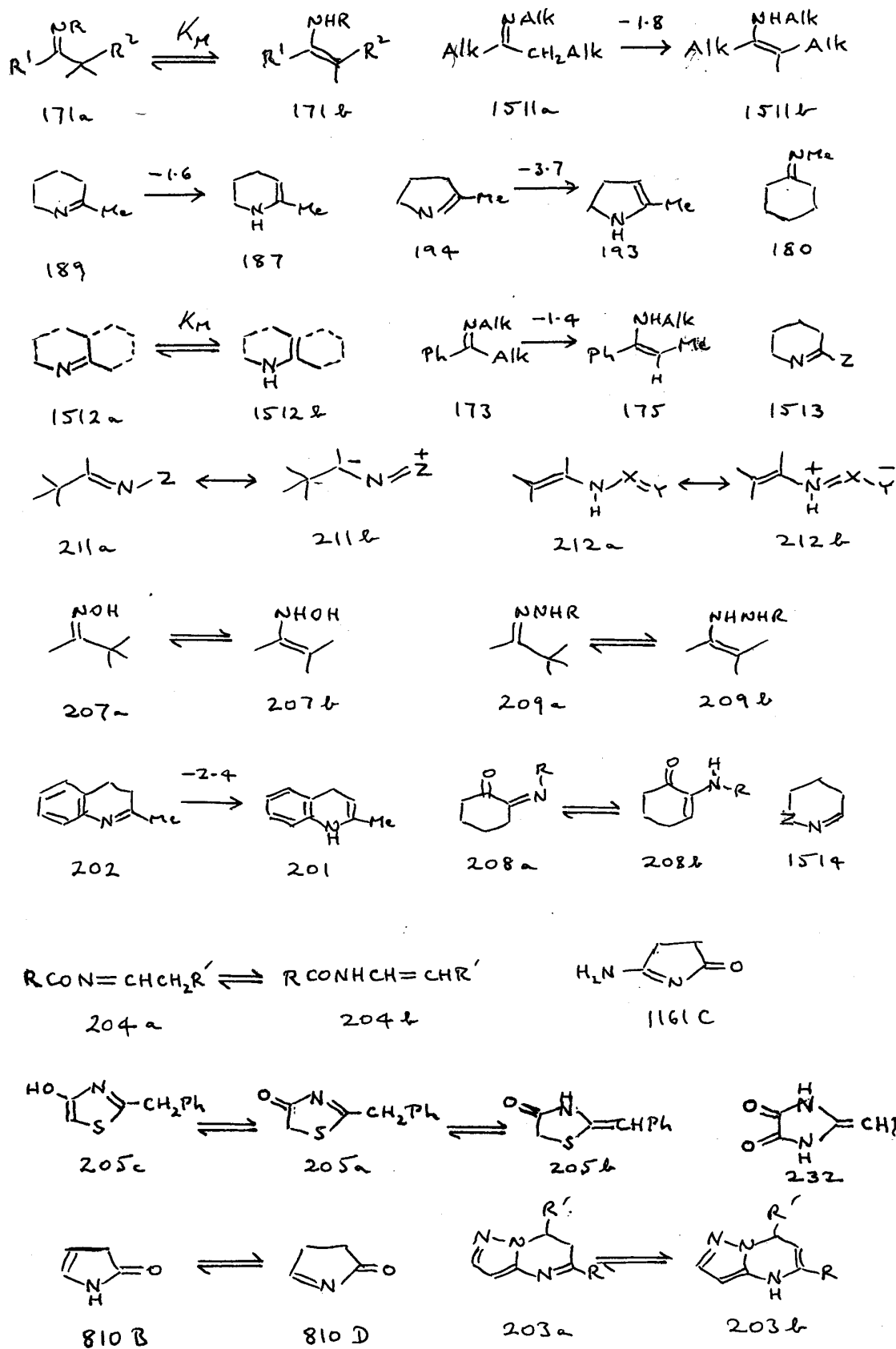
## C.25 Open-Chain and Alicyclic Imines with Unconjugated Enamines: R = Alkyl

This class of compound (Scheme 101) complements those of C.1, C.2 and C.3 with the important difference that C=NH, unlike C=O or C=S, can be substituted on the hetero-atom. Two crucial distinctions follow. Firstly the extra substituent, designated R in **171**, adds a further structural variant which is frequently more important than any other. For the compounds in this section, R is always alkyl so that variation is confined to R<sup>1</sup> and R<sup>2</sup>. Secondly, C=N unlike C=O or C=S can be *endo*- as well as *exo*-cyclic. Both factors have consequences that are explored below.

The following survey, unless stated otherwise, derives from section A.4.1. We note first that a correction factor  $\Delta(\text{NR})$  -0.3 applies to pK<sub>a</sub> values for NHR. Its negative sign, in contrast to those *e.g.* for amides and amidines (*cf.* Appendix 1), indicates that cation solvation is not here specially important, so that normal electronic trends apply.

For **189** → **187** and **194** → **193** we find the log K<sub>M</sub> values of Scheme 101. (The *exo*-enamines corresponding *e.g.* to **187** and **193** appear not to compete, presumably through lack of further substitution on =CH<sub>2</sub>R<sup>2</sup> in **171b**, and see **1515** in Scheme 102 – as is necessarily present in cyclic compounds). The imines **180** and **189** are closely similar in pK<sub>a</sub> and since these and their respective enamines share the carbon skeleton of **1512** we think it probable that there will be little difference in K<sub>M</sub> for imines whether *endo* or *exo* to 6-membered rings. Since **1511** shares that part of the same carbon skeleton indicated by full lines we postulate that the same will be true here, with the proviso that lesser rigidity especially in the enamine may give rise to twisting whose net effect should be to lower K<sub>M</sub>. Hence for open-chain compounds **1511** we postulate log K<sub>M</sub> -1.6 to possibly -2, and typically -1.8. The much more negative log K<sub>M</sub> value for **194** → **193** is a C=N– bond angle effect (sections A.4.1 and B.2.3) which should be general for 5-membered rings but is unlikely to be found elsewhere.

The above data are essentially for R<sup>1</sup> = alkyl. For R<sup>1</sup> = H the difference in cyclic compounds appears to be inappreciable (section A.1.5) but there are no data for open-chain compounds and the difference in K<sub>E</sub> for aldehydes and ketones (section A.2.1) counsels caution. For R<sup>1</sup> = Ph, from **173** and **175** we estimate log K<sub>M</sub> *ca.* -1.4. The difference from R<sup>1</sup> = alkyl is small but in cyclic contexts which involve Ph *vs.* H at the pivotal position between C=C and C=N we find  $\Delta \log K_M$  0.4 (section A.1.5) so a value of this order is probably genuine. A  $\pi$ -donor Z at R<sup>1</sup> will lock the structure as the imine, *e.g.*



Scheme 101

in **1513**. The effect of  $\pi$ -acceptors is unknown. It is possible that proton donors and acceptors at  $R^1$ , whether  $\pi$ -donor or  $\pi$ -acceptor in character, might respectively reduce or increase  $K_M$  but the outcome is known only for amidines ( $R^1 = \text{NHR}$ ; section C.31 *et seq.*)

## C.26 Open-Chain and Alicyclic Imines with Unconjugated Enamines: Substitution at R

Variation in this respect is most usually to be found in open-chain structures, since only certain *N*-substituents can form part of a ring. Two such exceptions are **202** and **205**, and others will be found in section C.29. As for the 5-membered ring oxoheterocycles of sections C.13 - C.19 it is useful to classify *N*-substituents R as bland,  $\pi$ -donor, or  $\pi$ -acceptor.

Bland Substituents. — If benzofusion is a reasonable model for  $R = \text{Ph}$ , **202**  $\rightarrow$  **201** provides the required information giving  $\Delta \log K_M$  *ca.* -0.8 (section A.4.3) relative to  $R = \text{alkyl}$  (**201** *vs.* **187**). In the stabilisation of  $\text{C}=\text{CR}$  (Table 1) the same order is followed, with  $\Delta \log K$  2.2 and 3.3 for alkyl and Ph respectively, relative to  $R = \text{H}$ . (Note that the situation here differs from that for  $R^1$ , which is placed on the pivotal carbon atom between  $\text{C}=\text{C}$  and  $\text{C}=\text{N}$  so that the equilibrium is subject to competitive forces). In the present context  $R = \text{H}$  is possible only for open-chain compounds or rings with *exo*- $\text{C}=\text{N}$  and no information exists on which to hazard a guess. If the sequence for  $\text{C}=\text{NR}$  were to be followed in proportion to that for  $\text{C}=\text{CR}$  then  $\log K_M \sim -0.4$  is expected for (**171**,  $R = \text{H}$ ,  $R^1 = R^2 = \text{alkyl}$ ) but there are no satisfactory grounds for supposing this.

$\pi$ -Donors and  $\pi$ -Acceptors. — These stabilise the imine and enamine tautomers respectively, often by wide margins, so are considered together. A rationalisation of this distinction (section A.4.6) is set out in the contrast between the resonance structures **211** and **212**.

The enamine tautomers **207b** and **209b** of simple oximes **207** and hydrazones **209** have never been detected (section A.4.5), whereas **204a** has proved equally fugitive as a contributor to **204**. In **208**, **208b** predominates for  $R = \text{H}$ , Alk or Ph (except when a 3-substituent stabilises  $\text{C}=\text{C}$ ) whereas for  $R = \text{OH}$  this tautomer is undetectable. An intramolecular bond may be a factor in both cases, and indeed the stereochemistry of (**208a**,  $R = \text{OH}$ ) persists in open-chain analogues, but this basic distinction holds for all. Hence, for  $Z = \text{O}$ , S or NR, all compounds of type **1514** as well as type **1513**

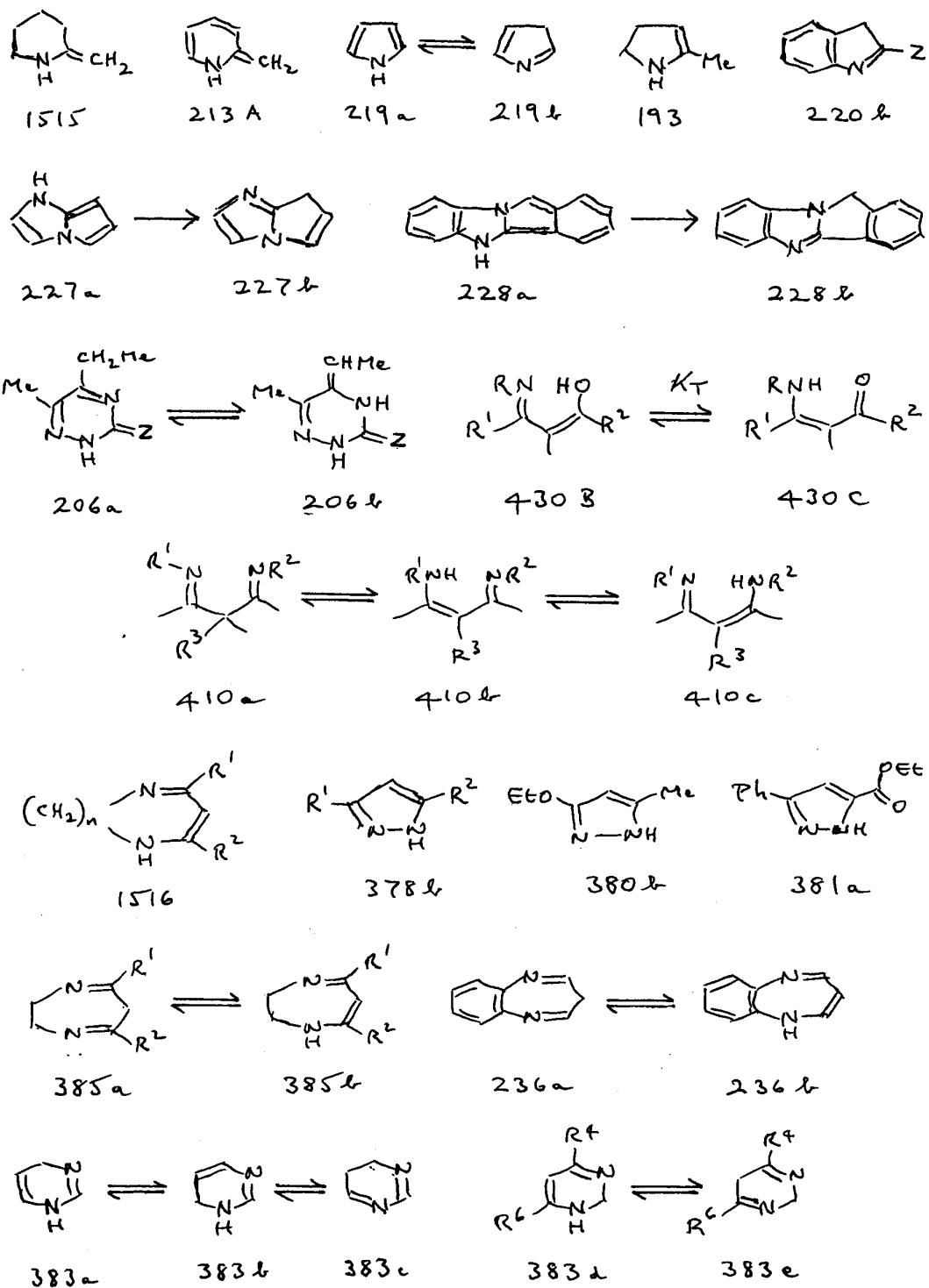
may confidently be assigned to the tautomer shown. An interesting case is provided by 2-oxopyrrole **810**, whose minor oxo-tautomer **810B** (section C.10) exists in this form and not as **810D**. However, as for **1513**, a  $\pi$ -donor on C=N transforms the situation; for **1161** the dominant tautomer is **1161C** (section B.2.9).

Enolisation of 4-oxothiazolines is promoted by 5-substituents (section C.17) but, by extrapolation from the data of Table 92, is unlikely to generate much **205c**. However, while **205a** is the solid-state tautomer of **205**, it exists mostly as **205b** in  $\text{CHCl}_3$  (section A.4.4). This tautomer is probably promoted by Ph in the 2-substituent and may not be the major tautomer in polar solvents whereas **205a** will be stabilised by through-conjugation; removal of S from the ring would almost certainly result in dominance of the **b**-tautomer under all circumstances. The case of **205** helps to illustrate how complex these cases can be. In general the effect of  $\pi$ -donors as in **205a** and **1161C** will probably be more important, at least in polar solvents, than that of C=C stabilisers such as Ph, but much uncertainty surrounds this topic and some computational help would be welcome. The closely related **232** exists as shown under all circumstances, indicating that -NHCO in this context is too poor a  $\pi$ -donor relative to -SAlk to force conversion to the **a**-form.

For the fused aminopyrazole **203** with R = Ph the enamine tautomer **203b** dominates in  $\text{CHCl}_3$  by contrast with  $\log K_M$  -1.6 for **189** in water and a putative -2.0 for its 2-Ph analogue (see section C.25 above). While the solvent dependence of this equilibrium is unknown it seems probable that *N*-pyrazolyl considerably stabilises the enamine tautomer. All heteroaromatic rings containing aza-nitrogen are  $\pi$ -acceptors so this result is expected. For R = 2-thienyl, a mild  $\pi$ -donor like phenyl,  $K_M \sim 1$  is found in  $\text{CHCl}_3$ , which helps to substantiate this distinction.

## C.27 Imine-Enamine Equilibria in Simple Heteroaromatic Structures

The disfavoured enamine tautomer **1515** (**213C** in section A.4.7) is there assigned  $\log K_M$  -2.2 as compared to -13.0 for **213A**. Most of this difference must be credited to the aromaticity lost by the latter and such tautomers are indeed of negligible importance for any simple 6-membered ring heterocycle. The position for 5-membered ring heterocycles is different, for two reasons. Firstly, they have less aromaticity to lose (*cf.* Table 12, section A.2.6). Secondly, here the aromatic tautomer is the *enamine*, as *e.g.* **219a**; **219b** has not been detected. Given  $\log K_M$  -3.7 for **193** however, it becomes less surprising that aromaticity can be lost quite readily in some related structures.



Scheme 102

For example, benzofusion is expected to reduce the energetic advantage of aromaticity and, in line with this, **220b** is the dominant indole tautomer for some  $\pi$ -donors Z. We explore in section C.30 the converse situation in which Z is present in the ring while the substituent is of type NHR. Some of these compounds possess amidine in place of imine tautomers, leading to complex and sometimes confusing interactions. In this section we consider a number of types of structure in which the highly malleable tautomerism of the pyrrole, indole and related rings results in unusual and sometimes surprising structural variation.

Related to **219a**  $\rightleftharpoons$  **219b** are a number of cases (section A.4.8) in which the imine-enamine balance in fused 5-membered ring heterocycles depends on the aromaticity of the rival tautomers. Typically, and in contrast to **219**, the enamine tautomer loses out in favour of the imine. Examples include **227** and **228**. In the first, the apparent loss of conjugation in **227b** is more than compensated by the imidazole aromaticity it gains, much greater than that of pyrrole which it loses (*cf.* Table 12). This is equally true of **228b** and an additional factor here is the highly disfavoured quinonoid structure of **228a** (Appendix 5). The latter exemplifies one of Elguero's four criteria for use in predicting the tautomeric preferences of 'azapentalenes' (section B.1.9); the others, all of them aspects of annular tautomerism involving nitrogen alone, are reviewed in section C.34.

A very few complex heterocycles are known in which exomethylene tautomers are detectable. Most are triazinones of which (**206**, Z = O or S) is an extreme example; this exists partly as **206b** in DMSO and EtOH (section A.4.4; its behaviour in water is unknown). It is difficult to rationalise this except in terms of an electronic structure which is close to being non-aromatic, leading to a tautomeric preference on the lines of **204b**. There is some evidence from this and some related structures that the part-structure N=C—C=N tends to be avoided if possible (opposed dipoles?) and this may be a phenomenon that warrants study.

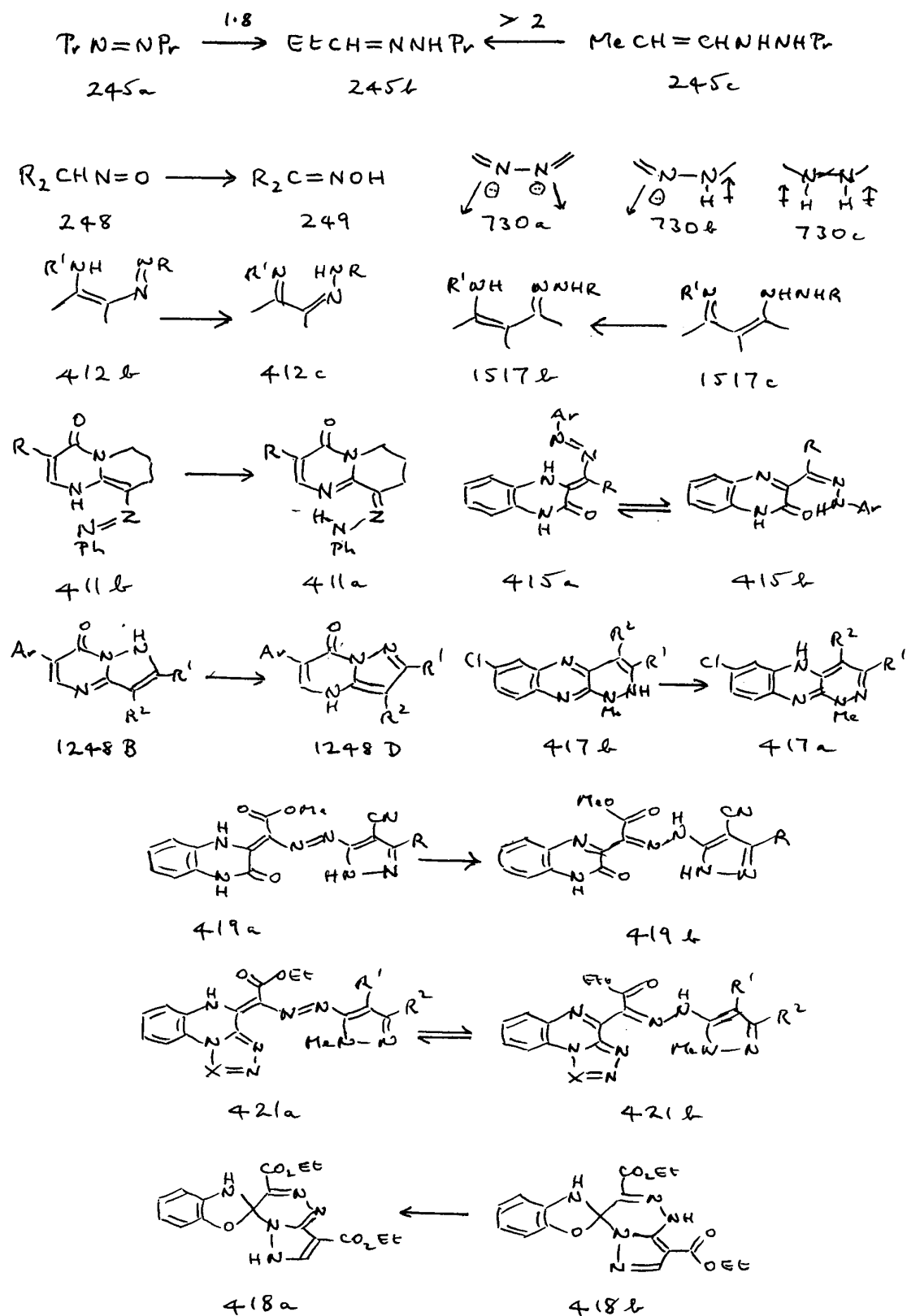
## C.28 Open-Chain and Alicyclic Imines with Enamines Conjugated to C=N

These are vinylogous amidines (*vide* section C.31 *et seq.*) but for convenience appear here. In an open-chain or alicyclic context the parallel equilibria involving C=O or C=S greatly favour conjugation as in **430C** (Scheme 102), for which we postulate  $K_T \geq 10^5$  (section C.8). By contrast, for  $R^1 = R^2$  in **410** the tautomers **410b** and **410c** are identical so the position of equilibrium must depend mostly on these substituents.

In general the  $\beta$ -diimine tautomer **410a** is of little importance; these compounds resemble  $\beta$ -dithiones (section A.7) in that respect rather than  $\beta$ -diketones (section A.6), for reasons that are summarised at the start of section A.12. There are two contra-indications. If  $R^3$  is bulky it may distort the planarity of the conjugated tautomers and so favour **410a**; on limited evidence **410** is more susceptible to this than the corresponding  $\beta$ -diketones (section A.1.4). A possible reason lies in the relative weakness of NH---N *vs.* OH---O hydrogen bonding (Appendix 4). This effect of  $R^3$  is weak or absent in cyclic structures. The second constraint involves 'anti-aromaticity' which is sometimes a problem for **410b** or **410c** in cyclic structures but can be resolved by reversion to **410a**. An example is given below.

$$\log K_T = 2.6 \sqrt{(\sigma_R)^2} \quad (\text{cvi})$$

The general formula for a conjugated cyclic  $\beta$ -diimine is **1516**, the most important types being those for which  $n = 0$  and  $n = 2$  (section A.9.2). For  $n = 0$  we have the pyrazoles **378**. Here a single substituent invariably takes up the  $R^1$  position in **378b** [eqn. (cvi), section B.8.1] though the margin may be small ( $< 10$ ) while, if  $R^2$  is also occupied,  $R^1$  will be the better  $\pi$ -donor or poorer  $\pi$ -acceptor of the pair (section B.1.8). For example, **380b** but **381a** are favoured tautomers, the former by a factor of 30, while eqn. (cvi) predicts the observed structure of the latter even without invoking its intramolecular hydrogen bond (Appendix 4). The diazepines (**1516**,  $n = 2$ ) are strong bases ( $pK_a > 13$ ) and stable as the cation; the free base exists as **385b** except on benzofusion, which makes **236b** anti-aromatic so that **236a** is preferred. Nevertheless it remains a strong base (section A.4.9) and its cation structure is unchanged. Higher homologues of **1516** will probably behave like **385**. The dihydropyrimidines (**1516**,  $n = 1$ ) are much less important since readily oxidised to pyrimidines. There are two non-interconverting sets of tautomers, **383a**  $\rightleftharpoons$  **383b**  $\rightleftharpoons$  **383c** and **383d**  $\rightleftharpoons$  **383e** of which the latter is the more important. Here **383e** is stabilised by  $\pi$ -donors at  $R^4$  and  $R^6$  but **383d** is the major species otherwise; **383d** like **385** is a fairly strong base ( $pK_a > 9$ ) as indeed is typical for unsymmetrical bases, such as those of type **1516**, that give symmetrical cations (pyrazole is the exception because of dipolar repulsion in its cation). In neither **383** nor **385** is the effect of substituents known except as stated; one might expect any resulting tautomeric asymmetry to resemble that shown by pyrazole **378** though one effect of their high basicity may be to make this question irrelevant under physiological conditions.



Scheme 103

### C.29 Enamines Conjugated with C=N Embedded in Complex Heteroaromatic Structures. Azo-Compounds and Hydrazones

The equilibrium **245a**  $\rightleftharpoons$  **245b** (Scheme 103) gives a preponderance of the hydrazone in Bu<sup>t</sup>OH (section A.5.1) while barely a trace of **245c** is detectable, and replacement of -N=NAlk by -N=NPh probably makes both margins even more overwhelming. (The corresponding process **248**  $\rightarrow$  **249** is total, swift, and irreversible: section A.5.2). Hence, in the equilibria involving **412** and **1517** which are special cases of **410** (Scheme 102), **412c** and **1517b** will be the favoured tautomers, both probably by long margins. In addition, **730b** is strongly favoured over **730a** and **730c** in cyclic structures since it avoids lone pair repulsion in the first and dipolar repulsion in the second (Appendix 3 and start of section B.1). These trends lie in the same direction as those of **245** so in heterocycles will reinforce them. We apply them here to the elucidation of tautomeric preference in a number of heterocyclic compounds containing embedded structures of these types.

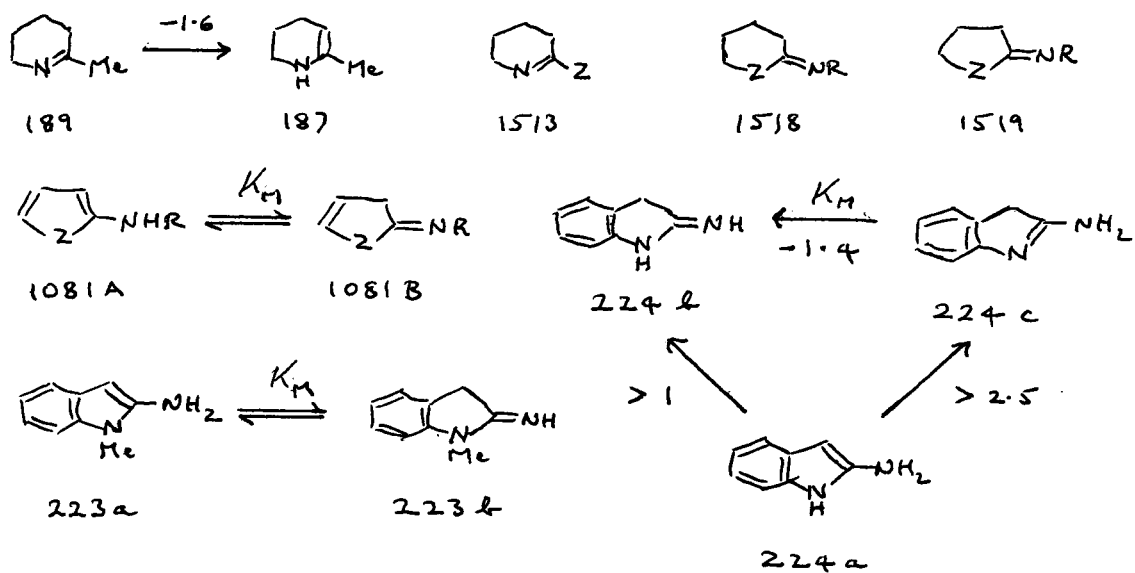
A number of compounds containing embedded units of types **412** (section A.9.6) or **1517** are set out in Scheme 103. A major problem with these studies is that nearly all have been carried out only in DMSO, a very strong proton acceptor which water is not (Appendix 2) and a particularly poor model for it when competitive intramolecular hydrogen bonds of varying strength are possible, due to its propensity for breaking some but not others. With this proviso, we discuss the results. For (**411**, Z = CH or N) aromatisation should favour **411a**; no **411b** is found in either DMSO or CHCl<sub>3</sub>. However the rather similar **415** gives an equimolar mixture of tautomers in DMSO; here the azo-linkage in **415a** will be a very poor proton acceptor. For **1248** (section B.5.14) and **417** the driving force is avoidance of dipolar repulsion, which we assess (section C.15) as  $\Delta \log K$  3 - 4 for the former. This appears enough to overcome any improvement in aromaticity attaching to **1248B** or **417b** (contrast **411a** above). Hence the claim (section B.1.5) that **756** with one less alkyl group than **1248** exists as the **B**-tautomer needs to be questioned. For **419**, perhaps significantly, the dominance of **419a** in DMSO is reversed on adding water. For **421** the position of equilibrium appears to depend on R<sup>1</sup>: for R<sup>1</sup> = CN and CO<sub>2</sub>Et, it is **421a** and **421b** respectively. Here and in **419** the hydrogen bonding possibilities are legion and the scope for solvent distortion correspondingly great. For **418** in DMSO **418a** is claimed, despite the triple disadvantage of lone pair and dipolar repulsion and no hydrogen bond. It is difficult to believe this result in any solvent. Overall therefore the picture is confused, but there is a powerful case for suspecting severe solvent distortion and, even so, most equilibria show the expected direction (that to the right in Scheme 103) and only the last permits of no explanation.

### C.30 Imine-Enamine Equilibria for *exo*-Nitrogen: Amino-Substitution in $\pi$ -Excessive Heterocycles

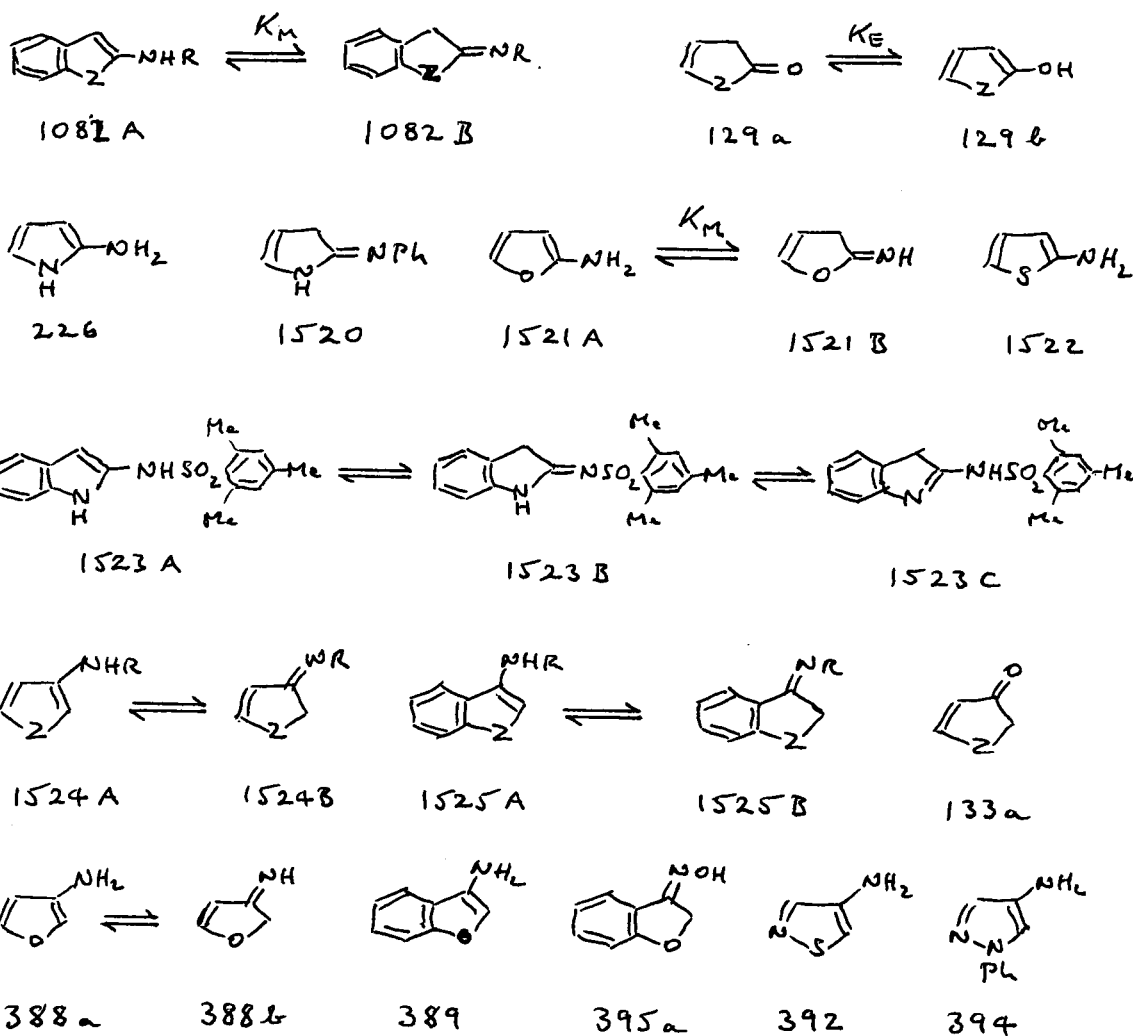
If in **189**  $\rightleftharpoons$  **187** (section C.25) Me is replaced by a  $\pi$ -donor Z we obtain **1513**, which is a conjugated system hence overwhelmingly preferred to its cross-conjugated enamine tautomer, and the same must be true for the *exo*-imines **1518** and **1519**. If however a  $\Delta^4$ -carbon double bond is present in the latter the result is **1081**, whose enamine tautomer **1081A** is aromatic so able to compete with the conjugated imine **1081B** (section B.4.5). Such compounds, except where Z = NH, are not capable of the amidine or vinylogous amidine tautomerism found for other aminoheterocycles and set out in section C.32, so that their properties are different and they are best considered separately.

2-Aminoindole **224** undergoes the 3-way tautomerism of Scheme 104. Here only  $K_M$  is known but since **223** exists on UV evidence in water largely as **223b** the other log  $K$  values shown are probably minima (section A.4.8). The aromatic **A**-tautomer is likely to be favoured more in **1081** than in **1082** though on other evidence the effect of benzofusion is likely to be less in 5- than in 6-membered rings, which leaves open its magnitude. For the parallel oxoheterocycles **129** we believe  $K_E$  to follow the order Z = S  $\gg$  O > NH (section C.10) which, if followed here, implies that **1081B** is likely to be favoured more for Z = NR than for Z = O and much more than for Z = S. This is consistent with the evidence that **226** but **1520** are the major tautomers and not badly inconsistent with some ambiguity concerning the structure of **1521** (section B.4.5); there is no doubt concerning **1522**, the most likely member of this series to resist *exo*-imine formation. The least likely to do so, as found for **223**, is (**1082**, Z = NR). In DMSO, **1523** consists in a roughly equimolar mixture of the **A**- and **B**-tautomers,<sup>514</sup> on the face of it a curious result, since this is an amidine for which the latter should dominate over **1523C** (section C.31). Nevertheless **1523A** would be strongly preferred if **1523** were a simple enamine, so unless this is a solvent effect, it may result from competition between two radically different patterns of behaviour: **B** > **C** but **A** > **C** also. In more orthodox fashion, (**1082**, Z = O, R = H), (**1082**, Z = S, R = H) and (**1082**, Z = S, R = COMe) all exist, as expected, as **1082A**.

All known compounds of types **1524** and **1525** exist exclusively as the **A**-tautomer, a fact consistent with the much greater susceptibility of **133a** than **129a** to enolisation (Table 89 section C.10; Table 90 section C.11). The only possible exception is **388**, where the position is uncertain; here the corresponding oxoheterocycle (**133**, Z = O) possesses log  $K_E$  < -2, which compares with -0.9 and 0.5 for Z = NH and S (Table 2, section A.2.7). As



Scheme 104



$$\log K_M = 2.2 \log K_T - 14.7 \quad (1xxxix)$$

between **129** *vs.* **133** the order in  $K_E$  differs and, qualitatively at least, the same distinction should apply to  $K_M$  for **1081** *vs.* **1524**. For 6-membered ring oxoheterocycles and the corresponding imines eqn. (1xxxix) is roughly followed (section B.4.4), and while the intercept term is irrelevant here, a greater susceptibility of  $K_M$  than of  $K_T$  is quite plausible since C=N is more polarisable than C=O. There is however evidence from a very few 5-membered ring oxoheterocycles and *exo*-imines (sections B.2.10 and B.4.5) which suggests that these are less susceptible to benzofusion, perhaps half as much as their 6-membered ring equivalents, so any parallel equation to (1xxxix) is likely to have a lower slope. Hence while it is probably safe to predict an order in  $K_M$  for Z of O > NH > S with fairly even spacings for **1524**, and one of O ~ NH >> S for **1525** with one wide gap, we can go no further. Since even **389** exists as written the A-form is expected for (**1525**, Z = NR or S) almost without regard to the nature of R. We speculate (section A.9.3) that **395** will exist as the oxime shown, but correspondingly, this is much less likely for its indole and benzothiophene analogues. In the absence of hard information on  $K_E$  for **129** predictions for **1081** and **1082** must be even more tentative, but on the basis of our speculations (section C.10) the order in  $\log K_M$  for both should be NH  $\geq$  O >> S with a possibly comparable spread in  $K_M$  values for **1081** but a wider one for **1082** (*cf.* Table 89). This very wide spread probably eliminates (**1081B**, Z = S) and (**1082B**, Z = S) as likely structures for almost any substituent R, with R = OH as plausibly the only exception. For Z = NR however, as seen above, the B-tautomer is likely for all but  $\pi$ -acceptors, for which **1523** suggests that mixtures may be found, whereas Z = O should occupy a position between Z = S and NR but show behaviour closer to the latter.

The likely effects of substitution may be summarised as follows. Since the amino-tautomer is an enamine, the position of equilibrium when this is substituted depends not on substituent electronegativity, as for the amidines that form the majority of aminoheterocycles (section C.32), but on *resonance donor* ability which favours conversion to the imine, *vs.* *resonance acceptor* ability which will reinforce its dominance. Certain prediction of compound behaviour is presently impossible but on limited data some guide-lines are still apparent. Among these it seems probable that the amino-tautomer will be much more dominant in the 3- than in the 2-substituted series, and that in either series it will be much more so for Z = S than for Z = O or NR, where sometimes the imine is found. And while the structures shown for **392** and **394** are in any case those expected, it seems likely that aza-nitrogen, as an electronegative substituent, will make the observed amino-tautomer more dominant still.

### C.31 Hammett Relationships in the Tautomerism of Amidines

$$\log K_T (\mathbf{1024B}/\mathbf{1024A}) = pK_a (\mathbf{1024A}) - pK_a (\mathbf{1024B}) \quad (\text{cxvii})$$

Amidines unlike *e.g.* amides or imines possess no intrinsic tautomeric bias, which is entirely a function here of the substitution pattern. As bases,  $K_T$  is accessible *via* eqn. (cxvii) if the individual  $pK_a$  values or good models for them are available. And since proton loss is expected preferentially from whichever nitrogen atom carries the more electron-withdrawing substituent, the prediction of  $K_T$  is an eminently suitable target for the Hammett approach. There have been several such studies and this section summarises the most relevant of them. Their importance lies not just in themselves but in their potential for prediction elsewhere.

$$pK_{(\text{PhX})} = 6.90 - 1.38 \sigma_X \quad (\text{lxxix})$$

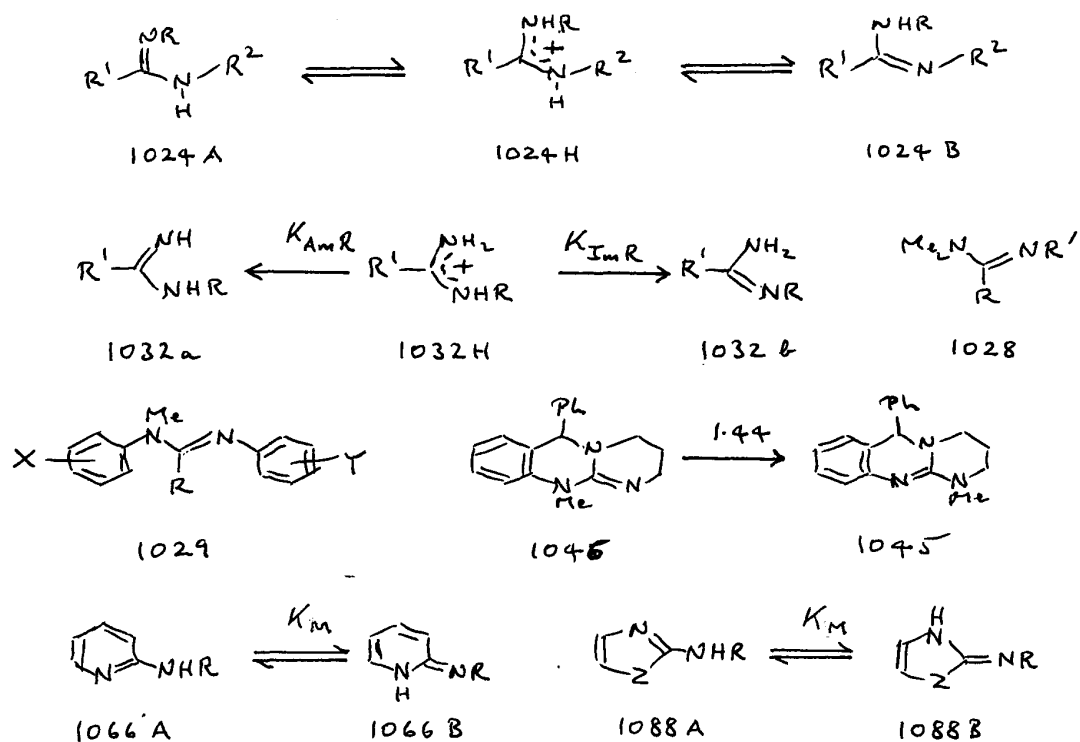
$$pK_{(\text{PhY})} = 6.86 - 2.76 \sigma_Y \quad (\text{lxxx})$$

The  $pK_a$  values for several series of general formula **1029** (Scheme 105) have been measured in 95.6% ('azeotropic') ethanol. All give basically similar results and, in the most comprehensive set,  $R = \text{Me}$  (section B.4.2). Here a variety of *m*- and *p*-substituents appeared in both rings. It is possible to analyse the data for the compounds with  $Y = \text{H}$  to give eqn. (lxxix), and those with  $X = \text{H}$  to give eqn. (lxxx). Since protonation always occurs at imino-nitrogen, the latter therefore registers the effect of proximate variation on  $pK_a$ , and the former the result of remote variation. In each the points for *m*- and *p*-substituents fall on the same line in terms of effect on  $pK_a$ , showing that the degree of conjugation is the same in both rings. This is important in demonstrating the absence of that factor as a perturbing influence on  $\rho$ . The intercept term for both equations is the common origin for the compound set, (**1029**,  $X = Y = \text{H}$ ).

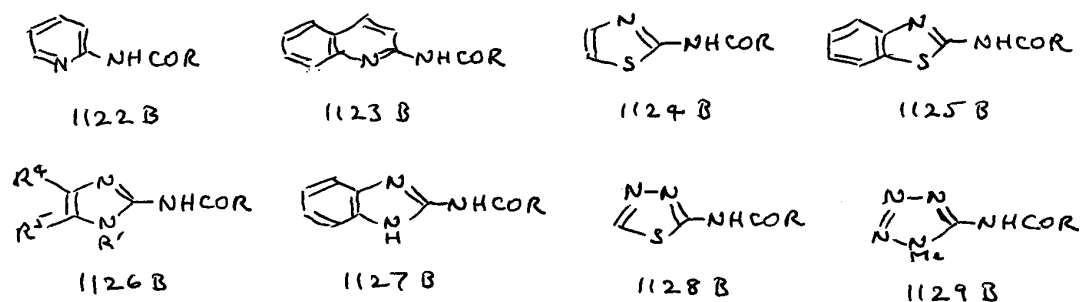
$$pK_a = 8.24 - 2.99 \sigma_Y \quad (\text{lxxvii})$$

$$pK_a = 12.14 - 29.7 \sigma_I(R') \quad (\text{lxxxi})$$

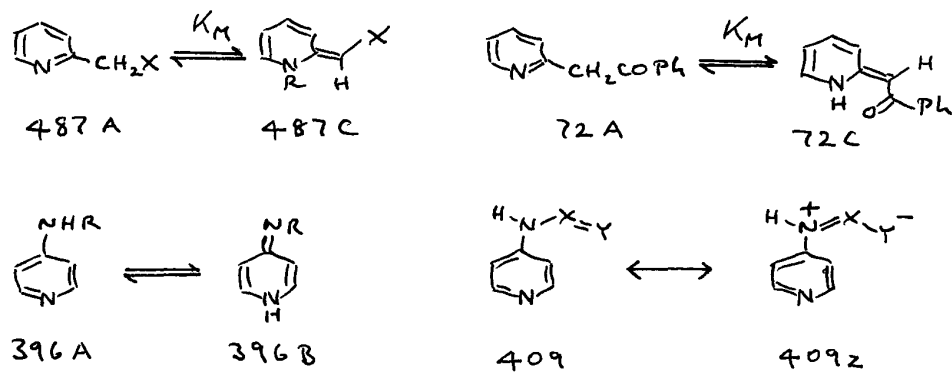
A further series of compounds (**1028**,  $R = \text{Me}$ ) for which  $R' = m$ - and *p*-substituted phenyl gave eqn. (lxxvii). Here the intercept term is necessarily different but its  $\rho$ -value is close to that of eqn. (lxxx). Among these data were some for  $R' = \text{H}$  and various alkyls which can also be incorporated into



Scheme 105



Scheme 106



the analysis by employing  $\sigma$ -values including those for the whole PhY unit. Much the most successful parameter was  $\sigma_I$ . The intercept term of eqn. (lxxxi) is different again since its reference point is  $R' = H$  not  $R' = Ph$  and its much greater slope reflects the compression produced by the narrower spread in  $\sigma_I$ .

$$pK_a = 14.18 - 22.58 \sigma_I \quad (\text{lxxvi})$$

For a monosubstituted amidine we re-cast the problem in terms of **1032** (Scheme 105). For any substituent R except H or alkyl **1032a** is the minor tautomer, hence  $pK_{Am(R)} > pK_{Im(R)}$  necessarily. These quantities possess the same significance as  $pK_{(PhX)}$  and  $pK_{(PhY)}$  respectively in eqns. (lxxix) and (lxxx). Hence in any mobile system the measured  $pK_a$  is always dominated by  $pK_{Im(R)}$ . Another such equation is (lxxvi), derived for a wide range ( $> 15$   $pK_a$  units) of *N*-substituted guanidines (**1032**,  $R^1 = NH_2$ ) in water, and again the appropriate parameter was found to be  $\sigma_I$  (section B.4.2). The larger intercept term and lower slope both probably derive from the difference in solvent.

$$pK_{Am(R)} = pK_H - \rho_{Am}\sigma_{I(R)} \quad (\text{lxxxii})$$

$$pK_{Im(R)} = pK_H - \rho_{Im}\sigma_{I(R)} \quad (\text{lxxxiii})$$

$$\rho_r = \rho_{Im} / \rho_{Am} \quad (\text{cxviii})$$

$$\log K_T = \{(\rho_r - 1) / \rho_r\} (pK_H - pK_{Im(R)}) \quad (\text{lxxxvii})$$

$$\log K_T = \{(p_r - 1) / \rho_r\} \rho_{Im}\sigma_{I(R)} \quad (\text{ixxxviii})$$

We may attempt the following formalism for a monosubstituted amidine (section B.4.2; subscript R = value for substituent R). From eqns. (lxxii) and (lxxiii) and employing our definition (section B.4.2) of the ratio  $\rho_r$ , eqn. (cxviii), we may derive eqns. (lxxxvii) and (lxxxviii) as alternative routes for calculating  $K_T$  for a compound containing the substituent R. The first requires knowledge of the parent compound  $pK_a$  value and that of the compound in question; the second requires  $\rho_{Im}$  for the set and the  $\sigma$  value of the substituent; both require  $\rho_r$ . On the above evidence,  $pK_{Im(R)}$  is a function of  $\sigma_I$ . We shall later present evidence that  $pK_{Am(R)}$  is a function of  $\sigma_I$  as well.

For (**1029**, R = Me) and on the evidence of eqns. (lxxix) and (lxxx),  $\rho_r = 2.0$  in this series. While  $\rho_{Am}$  and  $\rho_{Im}$  will be solvent-sensitive there is no good reason why  $\rho_r$  must be, and indeed we shall postulate that  $\rho_r \sim 2$  for any amidine **1032** in which R is centrosymmetric. (This assumption does not imply solvent-insensitivity for  $K_T$ , which would be manifestly untrue, since  $\rho_{Im}$  hence  $pK_H - pK_{Im(R)}$  vary with solvent). Very little evidence is available but the three monosubstituted guanidines (**1032**,  $R^1 = NH_2$ ) for which the requisite data exist are compared in Table 94. The value of R = Ph derives from **1046**  $\rightarrow$  **1045** for which the correction factors cancel, and those of R = COMe and R = 4-methyl-2-thiazolyl from a more detailed analysis in which these factors have been taken fully into consideration. (Some literature estimations for amidines **1032**, which include  $\log K_T$  2.4 and 1.5 for R = Ph and R = CPh respectively, are vitiated by a variety of perturbations which centre on overcrowding in model compounds, leading to a variable lack of planarity, and in one case, the use of  $R^1 = H$  for one tautomer and  $R^1 = Me$  for the other; section B.4.2). The results here for R = Ph were obtained in methylcellosolve so that any effect of solvent on  $K_T$ , while likely to be small, may lead to a higher value in water since **1045** is slightly more polar than **1046**. Given s.e.  $\pm 0.51$  for eqn. (lxxvi) all three observed values lie within the error bars for  $\rho_r = 2.0$ . We believe therefore that this value may reasonably be assumed for open-chain, centrosymmetric amidines. For the guanidines studied, the resulting estimates for  $\log K_T$  range from that above for R = Ph to 7.6 for R =  $NO_2$ .

$$\log K_M = 12.15 \sigma_I - 6.4 \quad (\text{xcii})$$

$$\log K_M = 10.65 \sigma_I - 4.2 \quad (\text{xcv})$$

**Table 94. Observed and Predicted ( $\rho_r = 2.0$ )  $\log K_T$  Values for Monosubstituted Guanidines (**1032**,  $R^1 = NH_2$ ) <sup>a, b</sup>**

R	eqn. (lxxxvii)	eqn. (lxxxviii)	Observed
Ph	1.7	1.4	1.4
COMe	3.1	3.4	3.1
4-Methyl-2-thiazolyl	3.6	3.6	3.9

<sup>a</sup> Data from section B.4.2. <sup>b</sup> See the text.

2-Aminoazines and -azoles represent a special class of amidine and form the subject of sections C.32 and C.33 respectively. The effect of *exo-amino* substitution on tautomerism has been studied for some heterocycles and, in the cases of **1066** and (**1088**, Z = S) the results are both quantitative and cover a sufficient range in  $K_M$  to allow of LFER analysis. Here  $pK_{Am(R)}$  and  $pK_{Im(R)}$  are in each case unequivocally a function of  $\sigma_I$  and the resulting equations which define  $K_M$  are (xcii) and (xcv) respectively (sections B.4.4 and B.4.5). Two differences from the symmetric cases are apparent. Firstly, the intercept terms are not zero; their large negative values reflect the aromaticity of the ring and lie close, as they should, to the value for R = H. The crossover points at which  $K_M = 1$  are represented by  $\sigma_I$  ca. 0.53 and 0.39 respectively. Secondly,  $\rho_r = 2.0$  is not found;  $\rho_r \sim 2.5$  and 2.2 result for (xcii) and (xcv). Here by contrast with the previous series  $R^1$  in **1032** is not centrosymmetric but highly skewed with respect to the molecular dipole and this may be the factor responsible. Unfortunately the resulting variability in  $\rho_r$  makes it difficult to predict what to expect for substituent effects on  $K_M$  elsewhere even when its value for R = H is known. Nevertheless, there are positive features. The  $\rho_I$  values for  $\log K_M$  in **1066**, (**1088**, Z = S) and that deduced for monosubstituted guanidines (**1032**,  $R^1 = NH_2$ ) cover a quite narrow range, 10.6 - 12.2, over which the predicted  $\Delta \log K_M$  values for a given substituent are not vastly different; *vide* Table 95. Secondly, there is semi-quantitative evidence on the 2-acylamino derivatives for the compounds of Scheme 106 in some organic solvents (section B.5.4). This not only allows the order  $COCF_3 > COCCl_3 > COCHCl_2 \gg CPh$ ,  $COMe > CO_2R$  to be deduced, but tentatively suggests the following approximate  $\Delta \log K_M$  values: 1.3 to 1.5 for the gap between  $COCCl_3$  and  $COCHCl_2$ ; 0.5 for that between  $COR$  and  $CO_2R$ ; and 2.5 - 3.1 for that between  $COCF_3$  and  $COMe$ . If  $\Delta \sigma_I$  0.22 between  $COMe$  and  $COCF_3$  (Table 2) corresponds to  $\Delta \log K_M$  3.0 - 3.6, the required  $\rho_I$  value lies in the range 13.6 - 16.4. This is notably larger than the range given above but the difference is very likely a solvent effect; *cf.* eqns. (lxxxi) and (lxxvi), the former as expected possessing the larger  $\rho_I$  value. (In fact, both quantities are elevated in the organic solvent by about 30%.) Given the disparate nature of these heterocycles the implications for prediction among such compounds are moderately encouraging. It is also possible to cross-analyse these data to yield tentative predictions across the set for R =  $CCl_3$  in water; these range from  $\log K_M \sim -1$  for **1122**, its actual value, to ca. 1.6 for **1128** (Scheme 106, and see Table 68, section B.5.4). Lone pair repulsion in the latter must clearly help in facilitating *exo*-imine formation; in **1129** however this will be at least partly offset by the ring's extra electronegativity (see section C.33 for a full treatment of this subject).

It should be noted that, while the use of model compounds in deriving eqns. (xcii) and (xcv) entailed that one or other tautomer could not form an intramolecular hydrogen bond, those of Scheme 106 were involved in mobile equilibria such that both could do so, and the question arises as to whether and by how much this will have affected the equilibrium. There is no evidence on this point but the partially parallel case of **72** vs. **487** is illuminating. Here, while for (**487**, X = CPh) the species **72A** and **487A** are identical, **72C** can form an intramolecular hydrogen bond whereas **487C** cannot. This results in  $\log K_M$  -1.05 for **72** (section A.10.2) but -2.05 (section A.10.9) for **487**. The difference is appreciable but not overwhelming and is likely to be compensated in part, for **1066**, by the ability of both mobile tautomers to form intramolecular bonds. In addition, the linearity of  $pK_a$  vs.  $\sigma_I$  for **1066** (and **1088**) is unaffected by the varying ability of R to form hydrogen bonds and the same applies (section B.4.2) to the very mixed selection of substituents used in deriving eqn. (lxxvi) for guanidines (**1032**,  $R^1 = NH_2$ ). It is likely therefore that this factor, while not negligible, may be less important than the change of configuration that accompanies it.

$$\log K_M = 19.1 \sigma_I - 6.4 \sigma_R - 8.9 \quad (\text{xvi})$$

$$\log K_M = 27.9 \sigma_d - 42.3 \sigma_e - 13.2 \quad (\text{xxxvi})$$

**Table 95. Predicted  $\Delta \log K_M$  for *exo*-Imino Aromatic Compound Series**

R or X	Series:	<b>1066</b> <sup>a</sup>	<b>1088</b> <sup>b,c</sup>	<b>396</b> <sup>d</sup>	<b>487</b> <sup>e</sup>
Ph		1.5	1.3	3.1	1.7
CONH <sub>2</sub>		3.4	3.0	4.6	5.7
CO <sub>2</sub> Et		3.6	3.2	4.6	7.7
COMe		3.6	3.2	4.1	11.0
COPh		3.6	3.2	4.3	10.8
COCF <sub>3</sub>		6.6	5.8	8.5	$\geq 11.3$ <sup>g</sup>
SOMe		6.6	5.8	10.6	1.7
CN		6.9 <sup>f</sup>	6.1 <sup>f</sup>	10.1 <sup>f</sup>	5.7
SO <sub>2</sub> Me		7.2	6.3	10.4	5.8
NO <sub>2</sub>		8.1	7.1	11.6	8.3

<sup>a</sup> Eqn. (xcii). <sup>b</sup> Z = S. <sup>c</sup> Eqn. (xcv). <sup>d</sup> Eqn. (xvi). <sup>e</sup> Eqn. (xxxvi). <sup>f</sup> Prediction based on  $pK_{Im}$  probably more reliable than that based on  $\sigma_I$  (see the text). <sup>g</sup> Values for  $\sigma_d$  and  $\sigma_e$ : M. Charton, in *The Chemistry of Double-Bonded Functional Groups*, ed. S. Patai, Wiley, New York, 1989.

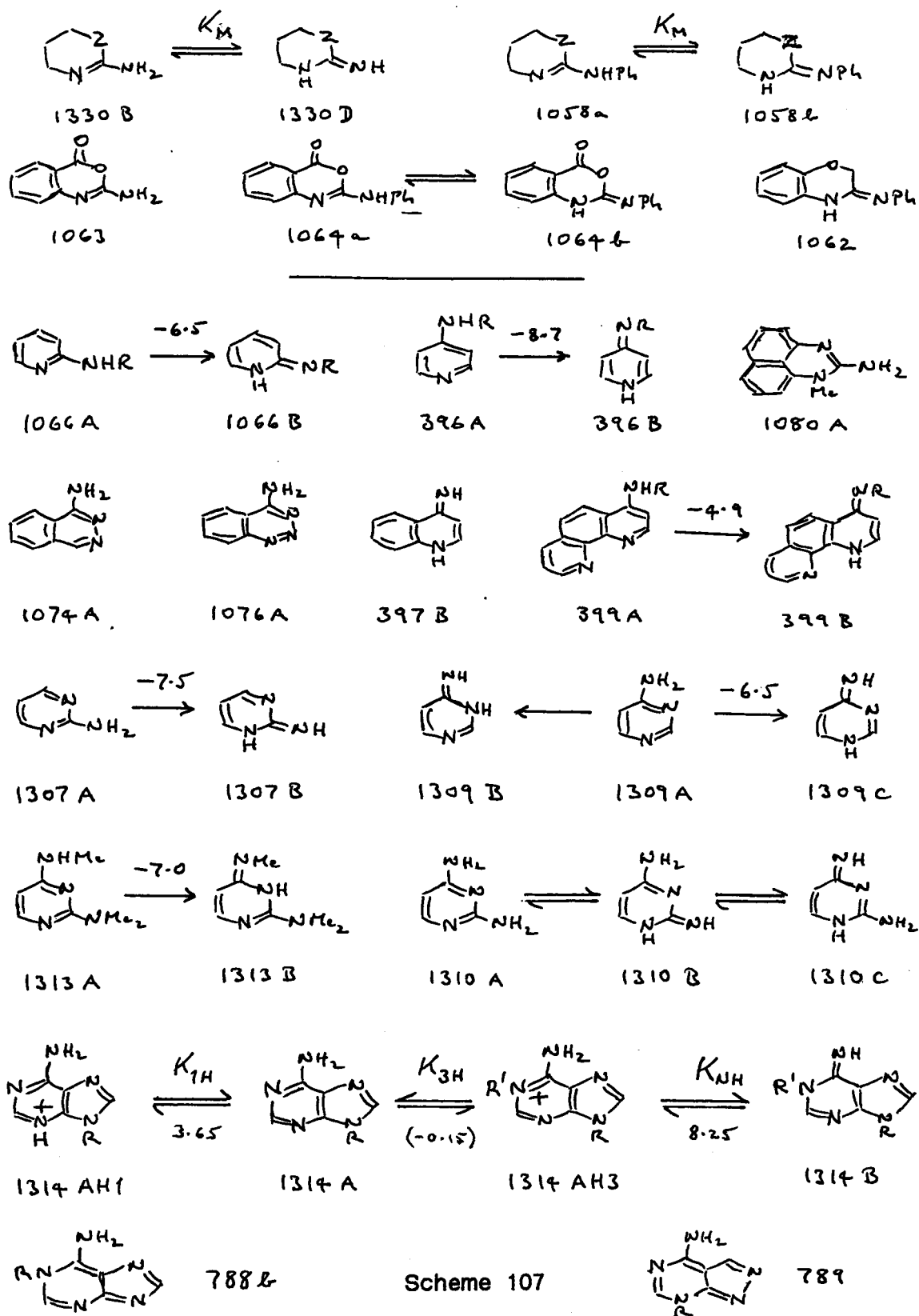
It is instructive to compare eqns. (xcii) for **1066** and (xcv) for (**1088**, Z = S) with eqns. (xvi) and (xxxvi) for **396** (section A.9.4) and **487** (section A.10.9) respectively. Inspection of the  $pK_a$  equations from which eqn. (xvi) derives shows that its  $\sigma_I$  component is the difference between a small term for  $pK_{Am(R)}$  and a large term for  $pK_{Am(R)}$ , whereas the  $\sigma_R$  term is associated with  $pK_{Am(R)}$  alone. While therefore both modes of deprotonation are controlled by  $\sigma_I$ , as for other amidines but with  $\rho_r \sim 5.2$ , the free base **396A** is specifically *stabilised* by resonance acceptors, presumably by the process **409**  $\leftrightarrow$  **409Z**. This atypical incursion of a resonance term suggests that vinylogous amidines may behave differently as a class from simple amidines, but there is no other evidence against which this postulate may be checked.

A much greater contrast, as noted in section C.9, is provided by eqn. (xcii) for **1066** vs. eqn. (xxxvi) for **487**, in which the position of equilibrium is controlled entirely by field and resonance forces respectively. The dominance of the ‘resonance susceptibility’ parameter  $\sigma_e$  for **487** represents a degree of charge transfer beyond even that present in  $\sigma_R^-$ , with consequences that appear in Table 95 where the predictions for each system are compared. It will be seen that, for **487**, the powerful resonance acceptor properties of carbonyl compounds upset the usual electronegativity order by giving these the edge over groups more commonly expected to show extreme behaviour such as CN, SO<sub>2</sub>R and NO<sub>2</sub>. Similar properties may be expected for -N=O and such heterocyclic  $\pi$ -acceptors as 4-pyridyl. These different consequences for ‘C-type’ (**487**) and ‘N-type’ (**1066**) tautomerism possess ramifications, as yet largely unexplored, that run through the entire subject.

### C.32 2- and 4-Aminoazines

Species **1330** will probably show no tautomeric preference whatever the nature of Z (contrast **1331**, section C.35) but *exo*-substitution will in general favour the **D**-tautomer. Thus (**1058**, Z = O or S) exists mostly as **1058b** (twisting may affect this) and **1063** as shown, whereas the issue for **1064**, which effectively balances two phenyl substituents, was left undecided. The observed preponderance of **1062** as written may result from O-substitution leading to a less electronegative fused ring.

Aromatisation leads, in almost all cases, to an overwhelming predominance of the *endo*-imine (*exo*-amino) structure, as seen for **1066** and (**1088**, Z = S) above. The few exceptions will be detailed. In addition, just as almost any substituent will increase the iminol content of an oxoheterocycle, so the same factors will increase the proportion of the already dominant amino-form, making the discussion of substituent effects largely redundant.

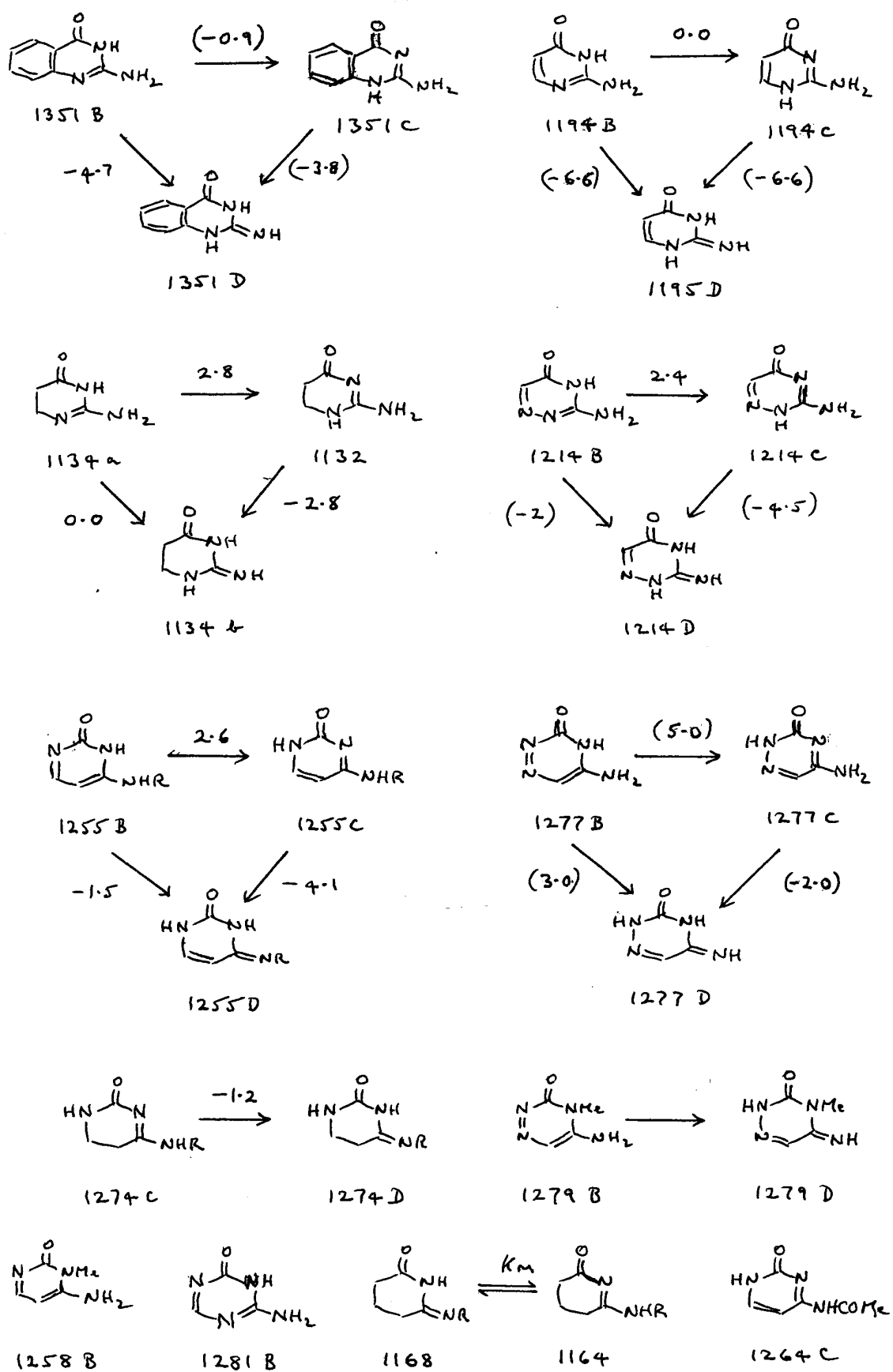


We choose **1066** and **396** to illustrate two of the three major classes of aminoazine, their  $\log K_M$  values corresponding to  $R = H$  (Scheme 107). All known  $K_M$  values for parent 2-aminoazines are contained in Table 63 (section B.4.4) and for their 4-aminoazine equivalents in Table 30 (section A.9.4). The nominally aromatic **1080** is included to emphasise its actual lack of aromaticity;  $\log K_M -1.5$  is close to that for phenylguanidine (section C.31).

$$\log K_M = 2.2 \log K_T - 14.7 \quad (1xxxix)$$

The very rough (*s.d.*  $\pm 1$ ) relation of eqn. (1xxxix) between  $\log K_M$  for azines and  $\log K_T$  for the corresponding oxoheterocycle (section B.4.4), applied to **1074** for which  $K_M$  is unknown, suggests that this compound may lie close to the tautomeric borderline (section B.8.7); it is certainly the closest for which calculation is possible. Perhaps significantly, the position for the related **1076** is uncertain experimentally (section B.4.4). Application of eqn. (1xxxix) also suggests that the published value for **397**,  $\log K_M -3.2$ , may be seriously at fault. The calculated value is  $-6.9$ . We suspect that the problem lies in the reported  $pK_a$  12.4 for **397B**, which is plausibly a ‘mirage’ *i.e.* should be much higher (section A.9.4). This revised value may be compared with  $\log K_M -4.9$  for (**399**,  $R = H$ ), which indicates  $\Delta \log K_M$  2.0 for the effect of lone pair repulsion in **399A** (Appendix 3). The existing value for **397** would turn this into an attraction!

The third major class of aminoazine consists in aminopyrimidines and related series for which, with rare exceptions such as **1307**, the site of protonation is equivocal. It is generally supposed that 1-protonation takes place in **1309** so that **1309C** not **1309A** is the relevant imino-form for  $pK_a$  comparison, in which case  $\log K_M -6.5$  as shown is correct. From literature data for substituted aminopyrimidines we have generated an algorithm (section B.7.2) which allows the  $pK_a$  values for the rival 1- and 3-protonated compounds to be generated. In all cases we find close agreement between the values calculated for 1-protonation and those observed, which confirms the common belief, but importantly, it also allows the  $pK_a$  value for the *unobservable* 3-protonated cation to be calculated (it is always lower) and compared with that of an imino-form obtained by 3-substitution. To illustrate its applicability the calculated values for **1313** and adenosine (**1314**,  $R = \text{ribose}$ ) are shown. The  $pK_a$  values observed for adenosine are  $pK_{NH}$  and  $pK_{1H}$  but this does not allow the fraction of imine (**1314B**,  $R' = H$ ) to be estimated;  $pK_{3H}$  for the minor cation is required. Our algorithm calculates  $-0.15$  for  $pK_{3H}$ , which after incorporation of  $\Delta(NR)$  0.3 for  $pK_{NH}$ , results in  $-8.7$  for  $\log K_M$ . In fact **1314B** is so disfavoured that removal of ribose leads to **788b** as the product, or when pyrazole ring fusion is involved to **789** (section B.1.7).



Scheme 108

Diaminopyrimidines possess the extra complication, in some cases, of alternative imino-forms even if 1-protonation is assumed, but again the algorithm allows this calculation to be carried out. For the formation of **1310B** and **1310C** from **1310A** we obtain  $\log K_M$  -5.9 and -5.6 respectively, so the latter is slightly favoured but, in general, little preference probably exists, and interestingly, the predicted  $K_M$  values are not greatly different from those for the corresponding mono-amines.

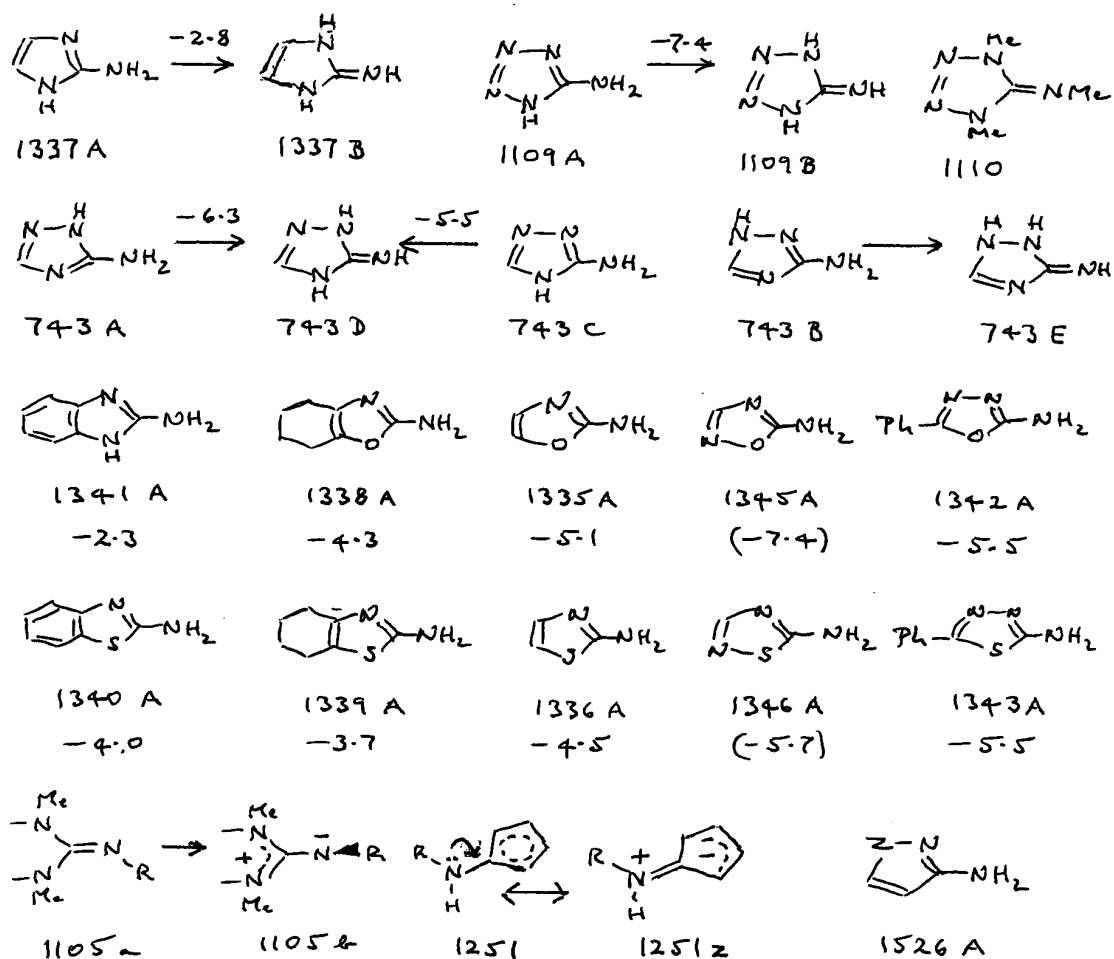
Aminopyrimidones and related compounds comprise another and rather different category. Because of their superimposed annular tautomerism these give rise to the 3-way equilibria set out in Scheme 108. For only two of these six series, **1134/1132** (section B.5.6) and (**1255**, R = H) (section B.5.15) are all  $K$  values known, but reasonable estimates may be made for some others. The  $pK_a$  values of **1214B** and **1214C** allow  $\log K_M$  2.4 for **1214** to be deduced (section B.5.13); evidence from the same source that suggests  $pK_a \sim 6$  for **1214D** leads to the picture provisionally adopted. Given  $\Delta \log K_M$  -0.9 on benzofusion of 4-pyrimidone to 4-quinazolone and  $\log K_M$  0.0 for **1194** (section B.5.11), we postulate  $\log K_M$  -0.9 for **1351**. In section B.5.14 we derive a tentative value of -4.7 for **1351B**  $\rightarrow$  **1351D**, from which an even more tentative value of  $\log K$  -3.8 for **1351C**  $\rightarrow$  **1351D** follows. The most serious missing quantity is the relative stability of **1195D**. A possible clue lies in the  $\log K_M$  values of -6.5 and -4.6 for 2-aminopyridine **1066** and 2-aminoquinoline **1067** respectively (section B.4.4). The second is very close to  $\log K_{M(1)}$  for **1351**, and given the close resemblance in tautomer ratio for pyridines and pyrimidines,<sup>2www</sup> suggests a similar differential here. Use of  $\log K_{M(2)}$  -3.8 for **1351** in place of  $\log K_{M(1)}$  would adjust -6.6 to -5.7 for **1195D**. Some possible implications of these values follow.

Aromatisation is the chief of these. Aromatisation conflicts with other forms of conjugation (Appendix 3) and here its expected effect is to reduce the stability of the **D**-tautomer, always the least aromatic, relative to the others. There are two pairs of compounds, one alicyclic one heteroaromatic, for which the comparison can be carried out. We choose to compare **C**  $\rightarrow$  **D** values since **C** is generally the dominant tautomer. For **1274** and **1255**  $\log K$  for this process changes from -1.2 to -4.1,  $\Delta \log K$  -2.9. More doubtfully,  $\log K$  -2.8 for **1332**  $\rightarrow$  **1334b** becomes  $\Delta \log K$  -3.8 or -2.9 relative to **1195D** according to which of the above values is chosen. For comparison, an (estimated) fall of  $\Delta \log K_T$  4.1 occurs when 2-piperidinone aromatises to 2-pyridone (Appendix 5). While none of these values may represent an effect due purely to 'aromaticity,' their general similarity is of some interest. In contrast to these cases, the (calculated) effect of benzofusion in **1194**  $\rightarrow$  **1351** incorporates positional effects concerning NH (section C.21) that muddy the picture and are not well understood at the present time.

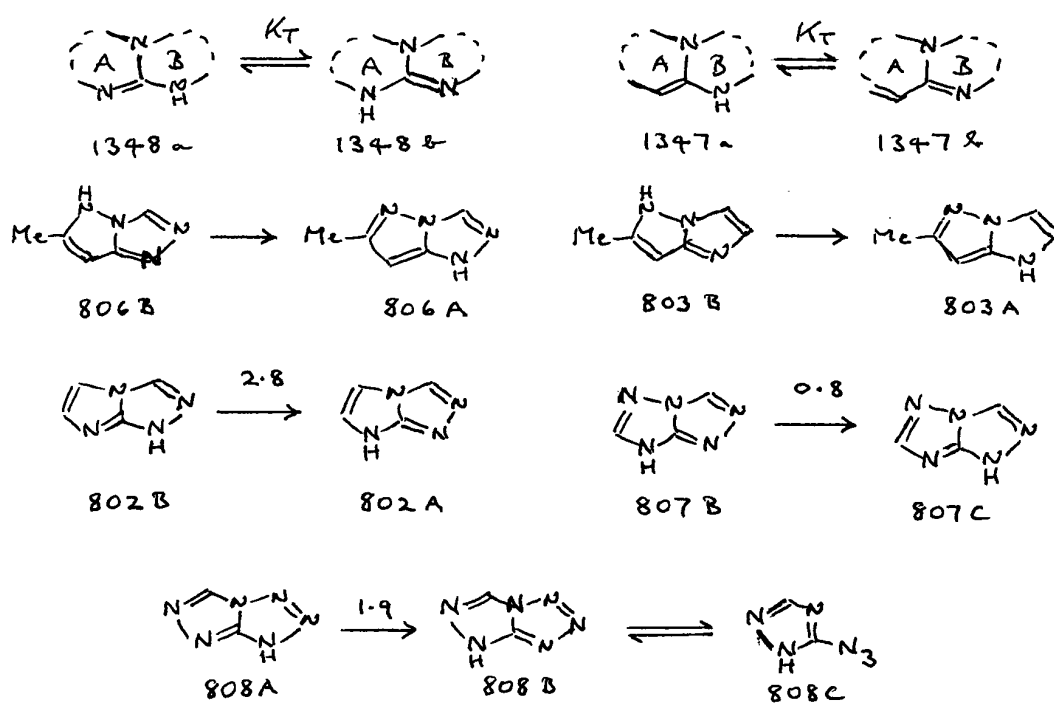
While the dominant tautomer of **1277** is **1277C**, in line with all members of this set but **1351**, it has one peculiarity: its derivative **1279** exists as **1279D**, the only known example of a simple heteroaromatic amine to prefer the *exo*-imino structure. Here we attempt a highly speculative rationalisation. Moving the aza-nitrogen atom of **1195** to **1255** leads to  $\Delta \log K_M$  2.6, while similarly introducing lone pair repulsion as in **1214** results in  $\Delta \log K_M$  2.4; both features are present in **1277** and, if additive,  $\log K_M$  5.0 might result. (The former shift may also involve a lone pair repulsion, between N and O, which if greater in **1277B**, could result in a greater than additive effect). Even more speculatively, **1214** and **1255** each show a sharp reduction in the very large margin by which **1195D** is disfavoured relative to **1194C**, and if this continues for **1277** in a similarly additive manner, we obtain a corresponding margin reduced to  $\log K$  *ca.* -2. Completion of the box equilibrium for **1277** would then result in a stability order of **1277C** > **1277D** > **1277B**, in agreement with observation. While it is highly improbable that these  $\log K$  values can be even remotely correct, as a *qualitative* picture they may help to elucidate the driving forces behind the, so far, anomalous and extremely puzzling phenomenon involved.

There is limited further information. That **1258B** exists as shown confirms the preference for **1255B** over **1255D**; again, contrast **1277** above. There is no obvious reason why **1281B** should be preferred to the C-tautomer, as is reported, and perhaps this should be re-examined. Given  $\log K_M < 2.1$  for **1164** (R = H) it is still a little surprising that **1168** (R = OH) exists as the oxime (section B.5.9), but some light on this apparent anomaly is shed by **1255**, for which  $\log K_M$  -4.1 for R = H (Scheme 108) becomes -1.5 for R = NH<sub>2</sub> and 1.1 for R = OH (section B.5.15), or an overall  $\Delta \log K_M$  5.2 for both. This effect of R = OH (and R = NH<sub>2</sub>) is enormously greater than that expected for a guanidine, overall  $\Delta \log K_T$  2.9 (section B.4.2), and no obvious explanation exists. The anomaly is compounded by the 'normal' behaviour shown by (**1255**, R = COMe) which exists as **1264C** (section B.5.15); given  $\Delta \log K_M$  3.1 - 3.4 for COAlk (section B.4.2), this result is reasonable.

These  $\log K_M$  values possess a further utility in the context of 6,5-heterocyclic ring fusions (sections B.5.14 and B.8.9) to be further discussed, and summarised, in section C.35.



Scheme 109



Scheme 110

### C.33 2-Aminoazoles

This is a more homogeneous compound set than that of the preceding section. Experimental values of  $\log K_M$  are given in Scheme 109 either above the arrows where both tautomers are shown, or below the formula number where only one is given. Full data including  $\sigma_I$  values where known appear in Table 81, section B.8.8. Difficulties attach to two compounds. An overall  $\log K_M$  -6.5 is quoted for **743** in a preliminary communication which does not make clear which of **743D** and **743E** was the imine in question, let alone what model compounds were employed (section B.4.5), and we have been unable to locate a follow-up. With its contiguous NHNH moiety **743E** will be an exceptionally disfavoured species (Appendix 3) and we think it more likely that the equilibria pertaining to **743D** were involved (note that **743E** is accessible only from **743B**). On this assumption, since **743A** and **743C** comprise 60% and 10% respectively of **743** (section B.1.2), the derived  $K_M$  values follow (and their *ratio* is independent of the values themselves). Of necessity they do not include correction factors but these will probably be small. It is reasonable that these estimates should lie between those for **1337** and **1109** but closer to the latter; if pertaining to **743E** they might well have been the most negative of all. The other problem concerns **1109**, where there are rival values for  $\log K_M$  of -7.4 and -9.6 (Table 65, section B.4.5), the second being based on **1110**. We have encountered a number of compounds of type **1105** whose  $pK_a$  values are substantially higher for R = alkyl than for R = H and we believe this to be caused (section B.4.5) by severe twisting for R = alkyl as a result of which its structure approximates to the inner salt **1105b**, leading to 'enforced protonation.' Hence we regard such models as unreliable. This effect is much less pronounced when one ring NR is replaced by O or S and will be suppressed, or nearly so, when NR is incorporated as *endo*-C=N into a cyclic structure, so it is not a general phenomenon but in this context is crucial (see section B.4.5 and Appendix 1 for further discussion).

$$\log K_M = 2.38(0.42) - 19.83(1.16) \sigma_I \quad (\text{ciii})$$

$$(n = 5 \quad r^2 = 0.990 \quad s = 0.19 \quad F = 566)$$

The five compounds of Scheme 109 for which we possess reliable  $K_M$  and  $\sigma_I$  values give rise to eqn. (ciii). Its rationale is expressed by **1251** (section B.5.14): the more electron-deficient the ring, the more it benefits from the amino-group as electron donor. It seems probable, though at present unprovable, that  $K_T$  for the corresponding oxoheterocycles will follow the same order. This equation is accurate enough to allow reliable prediction of either  $\log K_M$  from  $\sigma_I$ , or the reverse, and the two bracketed values of  $\log K_M$  in Scheme 109 have been derived this way. However its

limitations must be noted: it does not apply to benzofused compounds such as **1340** or **1341**, or to anything other than 5-membered rings. It may also not apply – we have no evidence on this – to compounds of type **1526** which do not possess the guanidine-like skeleton of those in Scheme 109. Within those limitations, however, it may prove useful for the prediction of  $\log K_M$  as more heterocyclic  $\sigma_I$ -values become available.

### C.34 5,5-Heterocyclic Ring Fusions containing Bridgehead Nitrogen

This subject is reviewed in sections A.4.8 and B.1.9 and summarised in section B.8.9. Elguero has enunciated four ‘rules’ as a help in predicting tautomeric preference, one of which concerns the need to avoid quinonoid structures; this is discussed elsewhere and summarised in section C.27. The others, which overlap, concern the avoidance of lone pair and dipolar repulsion, and the relative basicities of the two fused rings: the more basic of A and B in **1347** and **1348** (Scheme 110) will preferentially carry the mobile proton (section B.8.9). Applied to **806**, the first two of these criteria agree in predicting **806A** as the preferred structure and this is correct. Applied to **803**, imidazole is the more basic ring and **803B** is disfavoured by dipolar repulsion, both of which favour **803A** and this also is correct. In **802** however, while the greater basicity of imidazole than pyrazole favours **802A** this is disfavoured by lone pair repulsion, leaving the issue open. In fact, **802A** is preferred.

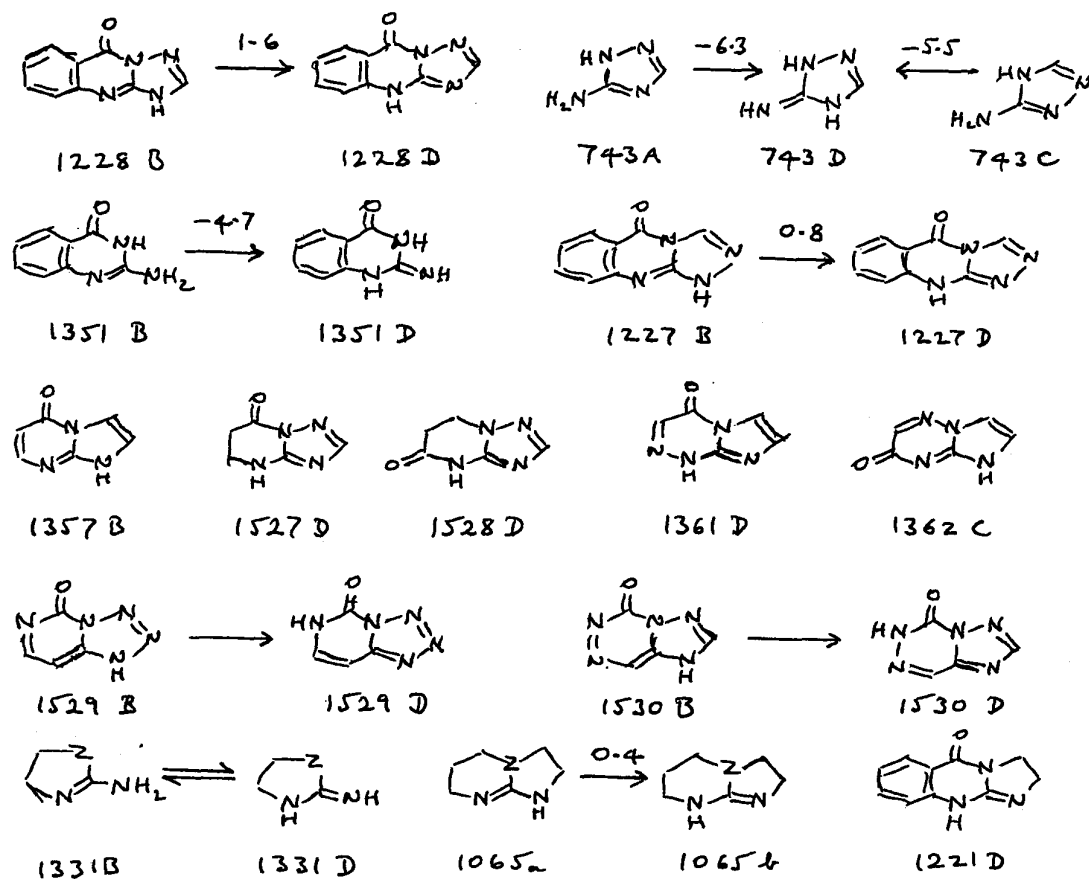
It will be evident that eqn. (ciii) provides an alternative approach which is not only potentially quantitative for aqueous solution, but incorporates the first and second criteria automatically along with the third. At present its utility is limited by the paucity of  $K_M$  values; it is inapplicable to **803** or **806**, for example, because  $K_M$  for 2-aminopyrazole is not yet known. For **802** it predicts a preference for **802A** of  $\log K_T$  2.8. Interestingly however, while eqn. (ciii) agrees with the qualitative prediction that **807C** should be preferred because of lone pair repulsion in **807B**, the margin calculated *for water* on this basis is only  $\log K_T$  0.8, a contrast with **802** not revealed by existing criteria. Because partial dissociation to the azide **808C** takes place in organic solvents (section B.1.9) – a reminder that this can happen – the identity of the major tautomer of **808** is unclear, but for **808A**  $\rightarrow$  **808B** we calculate  $\log K_T$  1.9 and the latter must in any case be the azide’s immediate precursor. Other predictions agree in principle with the known facts, none has so far failed, and from Scheme 109, the scope for further prediction based on this methodology is considerable. Its chief limitation lies in the paucity of known  $K_M$  and/or  $\sigma_I$  values, which would not be difficult to obtain, and other classes of fused heterocycle would also become available for study (for one example see section B.5.14) if more were known.

### C.35 6,5-Heterocyclic Ring Fusions containing Bridgehead Nitrogen

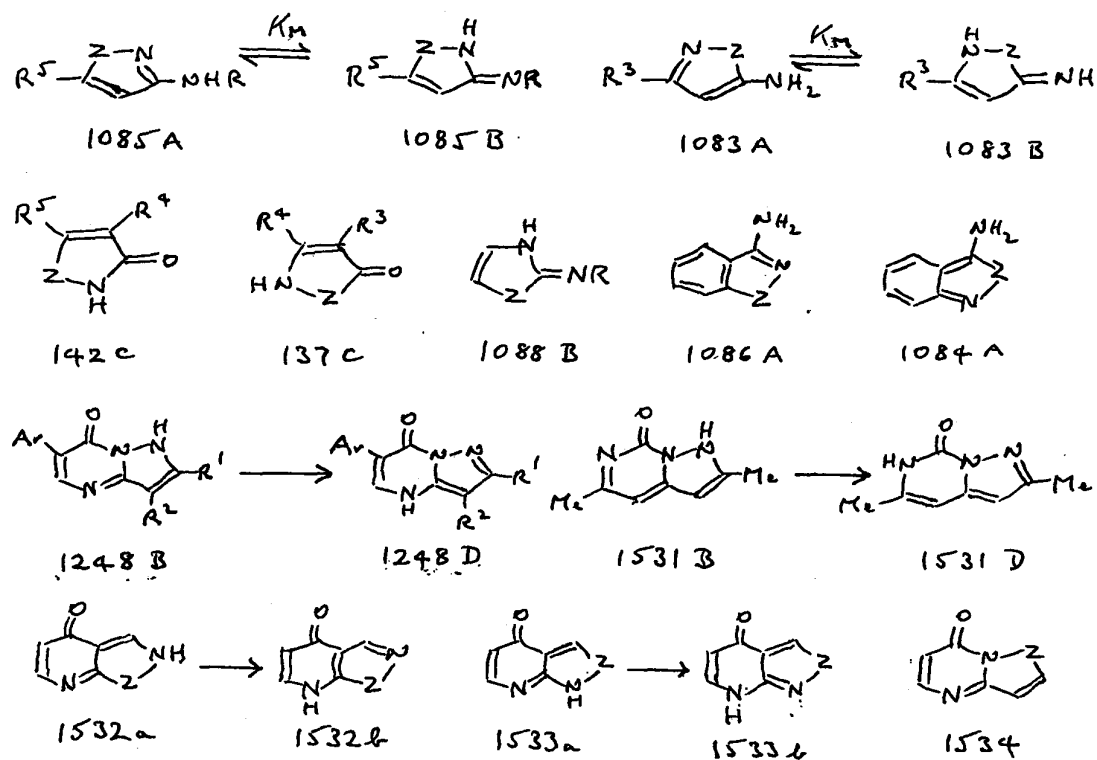
Expansion from a 5,5- to a 6,5-fused heterocyclic system with similar tautomeric characteristics becomes possible if the 6-membered ring is an oxoheterocycle. There is no reason in principle why the procedure of section C.34 should not be applied in such cases, and the data available for the compounds of Scheme 108 allow this to be carried out (section B.5.14). From an estimated  $\log K_M$  -6.3 for the process **743A**  $\rightarrow$  **743D** (section B.4.5) and the experimental value (section B.5.14) of  $\log K_T$  1.6 for **1228** (Scheme 111) we deduce, on additive principles,  $\log K_M$  -4.7 for **1351** as appears in Scheme 108. This value in its turn can be combined with any of those for 2-aminoazoles (Scheme 109) to arrive at tentative  $\log K_T$  values (defined in section B.5.14 as *e.g.* **1227B**  $\rightarrow$  **1227D**) for other possible combinations. (We *define* the forward direction for  $K_T$  as 6-*endo*-C=N  $\rightarrow$  5-*endo*-C=N and as either of these  $\rightarrow$  *exo*-C=NR where R  $\neq$  H). Such worked examples comprise Scheme 65 (section B.8.9). It is impossible to know how far this assumption may be valid, but it is plausible that any errors which attach to  $\log K_M$  for **1351** will, at least approximately, cancel when this is employed elsewhere. Hence the *difference* in  $\log K_T$  proposed for **1228** and **1227** simply reflects those between **743A** and **743C**, and while most  $K_M$  values of Scheme 108 are just as tentative as that for **1351**, it is not unreasonable to hope that they can be used in most cases to predict at least the right *qualitative* result. Where the predictions of Scheme 65 can be checked, all for which the evidence is available do indeed succeed in this respect.

These calculations whether valid or not are easy to perform, and we confine comment to a few salient features. On the basis of  $\log K_M$  -2.8 fused imidazoles are much the likeliest species to reverse the general trend and indeed **1357** is predicted to exist as **1357B** (Scheme 111), with  $\log K_T$  *ca.* -3.8 (*cf.* Scheme 108, section C.32). Secondly, while the difference in  $\log K_T$  between the 4-oxo and 6-oxo series will be small for 4-quinazolones and probably nil for 4-pyrimidones, it should be more pronounced elsewhere; for example, the predicted  $\log K_T$  values for **1527** and **1528** are 6.3 and 3.5 respectively. Sometimes this difference is enough to reverse the otherwise predicted direction; for **1361** and **1362** we estimate  $\log K_T$  as *ca.* -0.8 and 1.7 respectively, resulting in the different types of tautomer shown.

The situation encapsulated by **1347** (Scheme 110) represents a grey area. Employing the same procedure we obtain  $\log K_T \sim 6$  and  $> 8$  for **1529** and **1530** respectively, and while qualitatively these preferences can scarcely be wrong, the **D**-forms do not incorporate an aminoazole moiety and it is unclear whether this mode of calculation is any longer valid. Work, whether computational or otherwise, would be desirable.



Scheme 111



Scheme 112

In contrast to its 6-membered ring homologue **1330** (Scheme 108), **1331** (Scheme 111) should show a slight bias towards the **D**-form, and indeed several systems of type **1065** possess  $\log K_T$  *ca.* 0.4 (section B.4.3). We may reasonably predict, therefore,  $\log K_T$  -4.3 (*cf.* **1351**) for **1221** (section B.8.9). This factor will not be important except in needle cases but is mentioned for the sake of completion.

### C.36 3- and 5-Aminoazoles containing Contiguous Aza-Nitrogen and a Ring $\pi$ -Donor Heteroatom

These isomeric series, **1085** and **1083** respectively (section B.4.5), are shown in Scheme 112 and may be considered together. No  $\log K_M$  values are known, but all are likely to be extremely negative. The analogous species **142** (section C.16) and **137** (section C.15) are among the most readily enolised of any oxoheterocycle, through a degree of dipolar repulsion which, for the former, we estimate (section C.15) as responsible for  $\Delta \log K_E$  in the range 2.5 - 3 for  $Z = \text{NH}$  and  $\text{NMe}$  and *ca.* 5 for  $Z = \text{O}$ . It is probably less than this for **137**, but not by much. Not only therefore do all parent compounds of either type exist as the **A**-tautomer, but (**1085**,  $Z = \text{O}$ ,  $R = \text{COR}$ ) and even (**1085**,  $Z = \text{O}$ ,  $R = \text{SO}_2\text{R}$ ) do so too, in contrast *e.g.* to (**1088**,  $Z = \text{S}$ ,  $R = \text{tosyl}$ ) for which  $\log K_M$  1.6 is found for aqueous solution (Table 65, section B.4.5).

The full force of this difference shows itself on benzofusion. While **1086** as expected gives **1086A**, **1084** can give the amino-tautomer only by adopting the disfavoured quinonoid structure **1084A** (Appendix 5), which it does (section B.4.5). No *exo*-imine is detectable, for any form of  $Z$ .

Ring fusions involving **1085B** are likely therefore to be dominated by the avoidance of *exo*-imine formation to a greater extent than for any compound in sections C.34 or C.35. Two examples are **1248** and **1531** (section B.4.5), both of which give the **D**-tautomer. In the former, the doubly disfavoured imino-tautomer (*cf.* **1083B**) present in **1248B**, doubly disfavoured because it is also destabilised by dipolar repulsion, easily overcomes the aromaticity of the pyrimidone ring; as with **1529** (Scheme 111), a proton switch inside a vinylogous amidine unit is involved. In **1531** this switch is divinylogous; there is not even the driving force of imine  $\rightarrow$  amine conversion, dipolar repulsion apparently being wholly responsible. Conceivably this factor here and in **1248** is enhanced by the neighbouring carbonyl group, but there are no quantitative exemplars on which any such conclusion can be based.

With little hard evidence we are forced to rely, for the rest, largely on speculation. Examples of fairly obvious preferences are those likely for **1532b** and **1533b**, especially for the latter when  $Z = O$ . It is also possible to write structures whose topology does not allow of tautomerism at all, as in the case of **1534**, where for  $Z = NH$  however one may anticipate rearrangement to a species on the lines of **1248D**. Dipolar repulsion is probably more dominant in the tautomerism of these types of compound than in any other.

### C.37 *endo*-Amidines: Annular Tautomerism in 5-Membered Ring Monocyclic Heterocycles

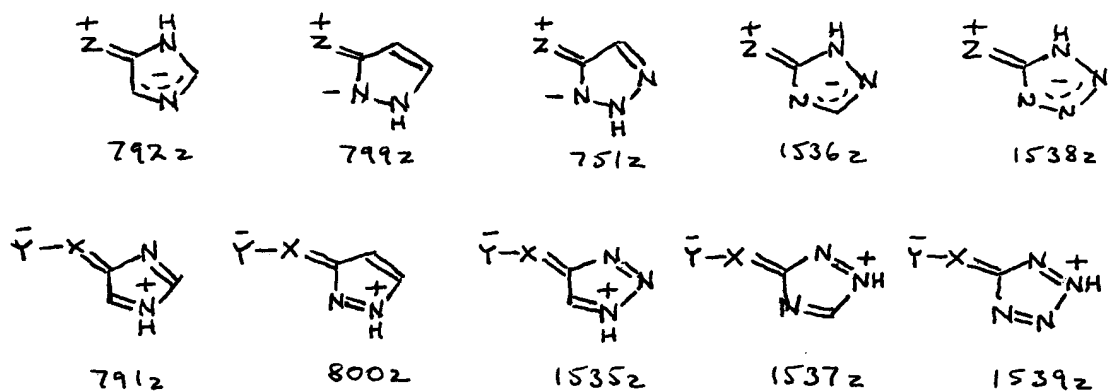
Imidazole is an aromatic cyclic amidine and most other members of this series, in most (not all) of their tautomers, may be considered as amidines in some sense. The exception is pyrazole, which is included for the sake of completeness and because, in terms of electronic effects, it contrasts significantly with the remainder. Accordingly we list these rings in electronic order, from the most electron-rich heterocycle to the most electron-deficient. Their ring-fused derivatives appear separately, in section C.38.

The difference between electron donor and acceptor substituents in their effects on annular tautomerism pervades this series. As a general rule donor substituents show their greatest effect on electron-deficient rings, and *vice versa*, but substituent position is also important. We discuss their effects in terms of Scheme 113, which sets out the canonical forms which appear to dominate substituent behaviour. Here  $-Z$  and  $-X=Y$  are  $\pi$ -donors and  $\pi$ -acceptors respectively so that parallel species result. When  $\sigma_I$  not  $\sigma_R$  is the appropriate parameter it may be better to think of its effect in terms of 'dipole enhancement' but that, in this context, is a distinction without a difference. The overall picture, while incomplete, is compatible with the available evidence.

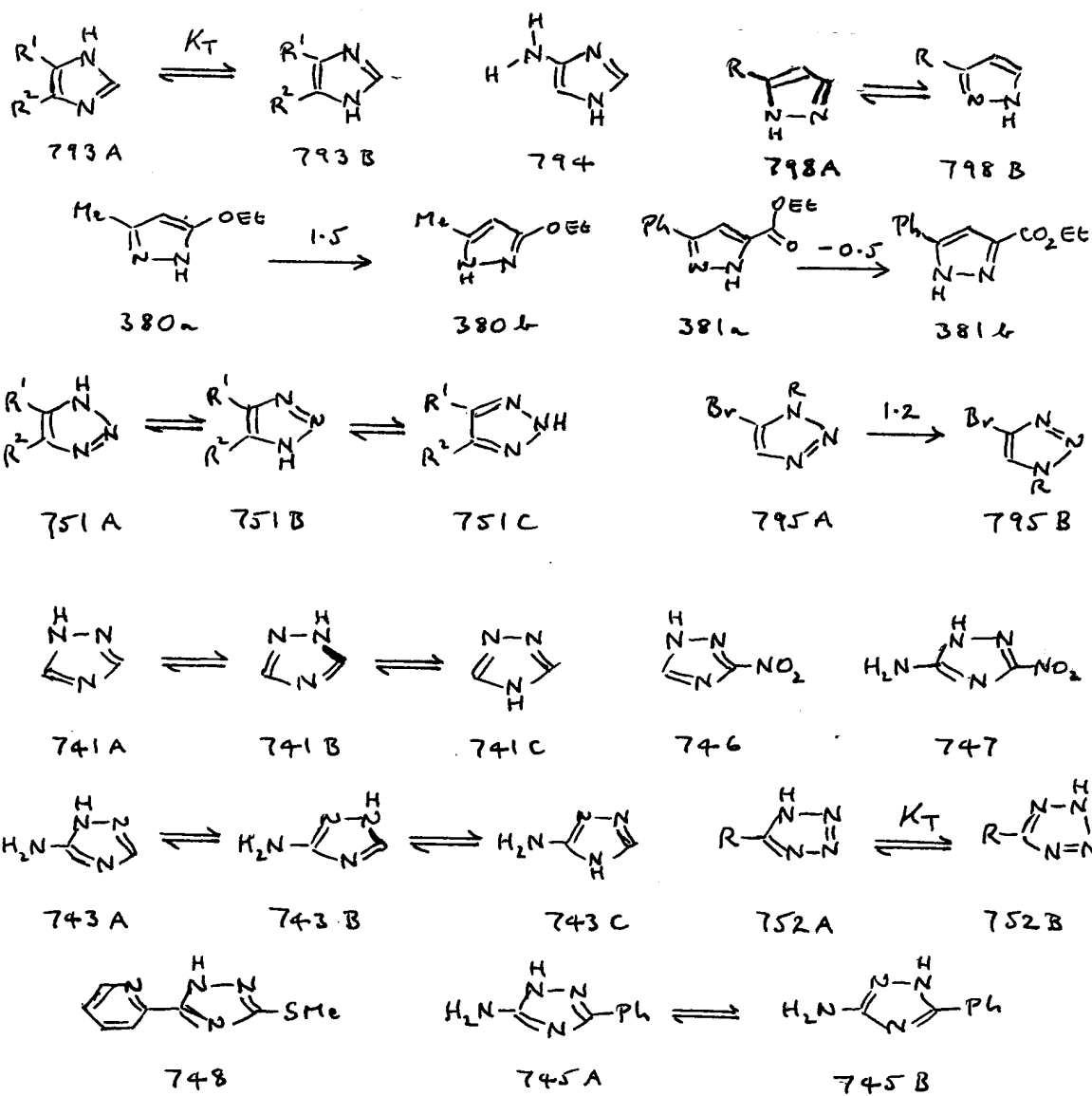
#### IMIDAZOLE

$$\log K_T = 4 \sigma_I \quad (cv)$$

2-Substitution is not expected to affect tautomeric form. For **793** we define  $K_T$  in terms of  $R^2 = H$ . Strong acceptors follow eqn. (cv):  $\log K_T$  is 2.68 and 1.8 - 2.2 for  $R^1 = NO_2$  and Br respectively (Table 52, section B.1.8) where eqn. (cv) predicts 2.7 and 1.9. This may be rationalised by canonical



Scheme 113



form **791z** (Scheme 113). However, all substituents favour 4-substitution to some extent, and  $\log K_T = 1.3$  is found in water for  $R^1 = \text{Ph}$  where 0.5 would be predicted. Imidazole is electron-rich and it is unsurprising, therefore, that its properties are dominated by the field effect of the substituent. The polarisation represented by **792z** may be too weak to be effective. The existence of **794** overwhelmingly as shown may be due to hydrogen bonding (or dipolar attraction, often almost synonymous); eqn. (cv) would predict  $\log K_T$  0.7. On the evidence of  $\log K_T = 2.07$  in favour of (**793B**,  $R^1 = \text{NO}_2$ ,  $R^2 = \text{Cl}$ ) (Table 52, section B.1.8), tautomeric form is dominated by the stronger  $\pi$ -acceptor, and perhaps more so than eqn. (cv) would predict. Taken together, these data suggest that some extra factor may enhance  $K_T$  for other than  $\pi$ -acceptors, so that predictions based on eqn. (cv) represent minima in such cases, but it is not at present clear what this factor may be.

## PYRAZOLE

$$\log K_T = 2.6 \sqrt{(\sigma_R)^2} \quad (\text{cvi})$$

Pyrazole like imidazole possesses degenerate tautomers and one substituent position, 4, that is not expected to influence tautomeric form. It differs however in being electron-deficient so that annular tautomerism depends on  $\sigma_R$  not  $\sigma_I$ . Uniquely, **799z** and **800z** stabilise the same tautomer, so that all 3(5)-monosubstitution results in **798B** (section B.1.8). Results in the gas phase follow eqn. (cvi); that is, the *magnitude* of  $\sigma_R$  matters but not its sign. Because this is usually greater for electron donors, these tend to give larger values of  $K_T$ ; for (**798**,  $R = \text{NH}_2$ ) and (**798**,  $R = \text{NO}_2$ ), which have been used to calibrate eqn. (cvi) (section B.8.1),  $\log K_T$  is 1.8 and 0.5 respectively. It then follows that  $\Delta\sigma_R$  should be used in eqn. (cvi) for 3,5-disubstituted compounds, but  $\log K_T$  1.04 is predicted for **380** in water where 1.5 is found (section A.9.2). Its negative value for **381**, where  $\log K_T$  0.2 is similarly predicted, is presumably due to the intramolecular hydrogen bond. It is possible that eqn. (cvi) under-predicts for water;  $\rho \sim 4$  would reproduce the result for **380** and leave a deficit of  $\Delta \log K_T$  *ca.* -0.8 for **381**. (For sterically unenforced hydrogen bonding of this type, a rather small effect is predicted: Appendix 4). It seems unlikely that progress will be made without more measurements in aqueous solution, but there is no doubt concerning the overall trend.

*v*-TRIAZOLE

The parent compound (**751**,  $R^1 = R^2 = H$ ) possesses an imidazole-like degeneracy as to **751A** and **751B** but **751C** is unique in structure and, indeed, the dominant tautomer in water (*ca.* 67%) and generally even more so elsewhere (section B.1.3). For  $R^2 = H$  the prediction of Scheme 113 is that **751C** should be stabilised by electron donors (*vide* **751z**) and **751A/B**, as for imidazole, by electron acceptors (*vide* **1535z**). The first is plausible but nothing is known. Concerning the second there is one piece of evidence: for  $R^1 = Me$ ,  $\log K_T$  1.2 is found for **795** (section B.1.8). This compares with  $\log K_T$  *ca.* 2 for (**793**,  $R^1 = Br$ ,  $R^2 = H$ ) and suggests a parallel trend but one less sensitive to the substituent; perhaps a similar equation to (cv) but with a lower  $\rho$ -value. However **1535z** also implies that  $\pi$ -acceptors may tend to suppress the normally dominant tautomer **751C**. This and the complementary suggestion (*vide* **751z**) that **751C** should be stabilised by electron donors is highly speculative however at the present time.

*s*-TRIAZOLE

The parent compound **741**, like *v*-triazole **751**, possesses degenerate tautomers and a third that is not, but which in this case is also an amidine. In water about 20% exists as **741C** and this proportion appears to diminish on substitution, falling to *ca.* 10% for **743C**. However the most notable feature of tautomerism in *s*-triazoles is its comparative insensitivity to the substitution pattern: amino-substitution leads to 60 and 30% for **743A** and **743B** respectively (section B.1.2), a small margin by the side of  $R = NH_2$  in pyrazole **798B** or the imidazole **794**, where no alternative tautomer is visible. Consistently with expectation based on **1536z** and **1537z**, however, **746** and **747** exist mostly as shown, and the apparently anomalous structure of **748** is plausibly due to an intramolecular hydrogen bond. Neither **1536z** nor **1537z** stabilises the **C**-tautomer and, so far as it goes, this is consistent with the latter's failure to be reported in any of these cases. It should also be noted that the **C**-tautomer, as the most polar, is likely to be even less important in solvents other than water. For **745** the major tautomer in dioxane is **745B** which is anomalous but again this may be a solvent effect, since the **A**-tautomer will probably be more polar. On balance, therefore, the evidence suggests that the major tautomer is correctly predicted by Scheme 113, but that margins are quite small and could readily be overturned by solvent or by intramolecular hydrogen bonding.

## TETRAZOLE

$$\log K_T = -1.11 + 3.26 \sigma_I + 0.74 \sigma_R \quad (\text{lxii})$$

Tetrazole **752** exists overwhelmingly, but by an unknown margin, as **752A** in water (section B.1.4). Equation (lxii), which is consistent with  $\sigma_R$ -dependence for donors (**1538z**) and  $\sigma_I$ -dependence for acceptors (**1539z**), the latter being more important, governs its behaviour in DMSO; values calculated for  $\log K_T$  in this solvent include -1.06 for  $\text{NH}_2$  (-1.12 is found) and 1.20 for  $\text{NO}_2$ . It is probable that **752A** as the more polar tautomer will be even more favoured in water than in DMSO, but it is nevertheless possible that strong  $\pi$ -acceptors may give rise to a predominance of **752B**. From the resemblance in their canonical forms it is possible that the effect of substitution in *s*-triazole may follow a similar relationship to (lxii), but with much lower  $\rho$ -values.

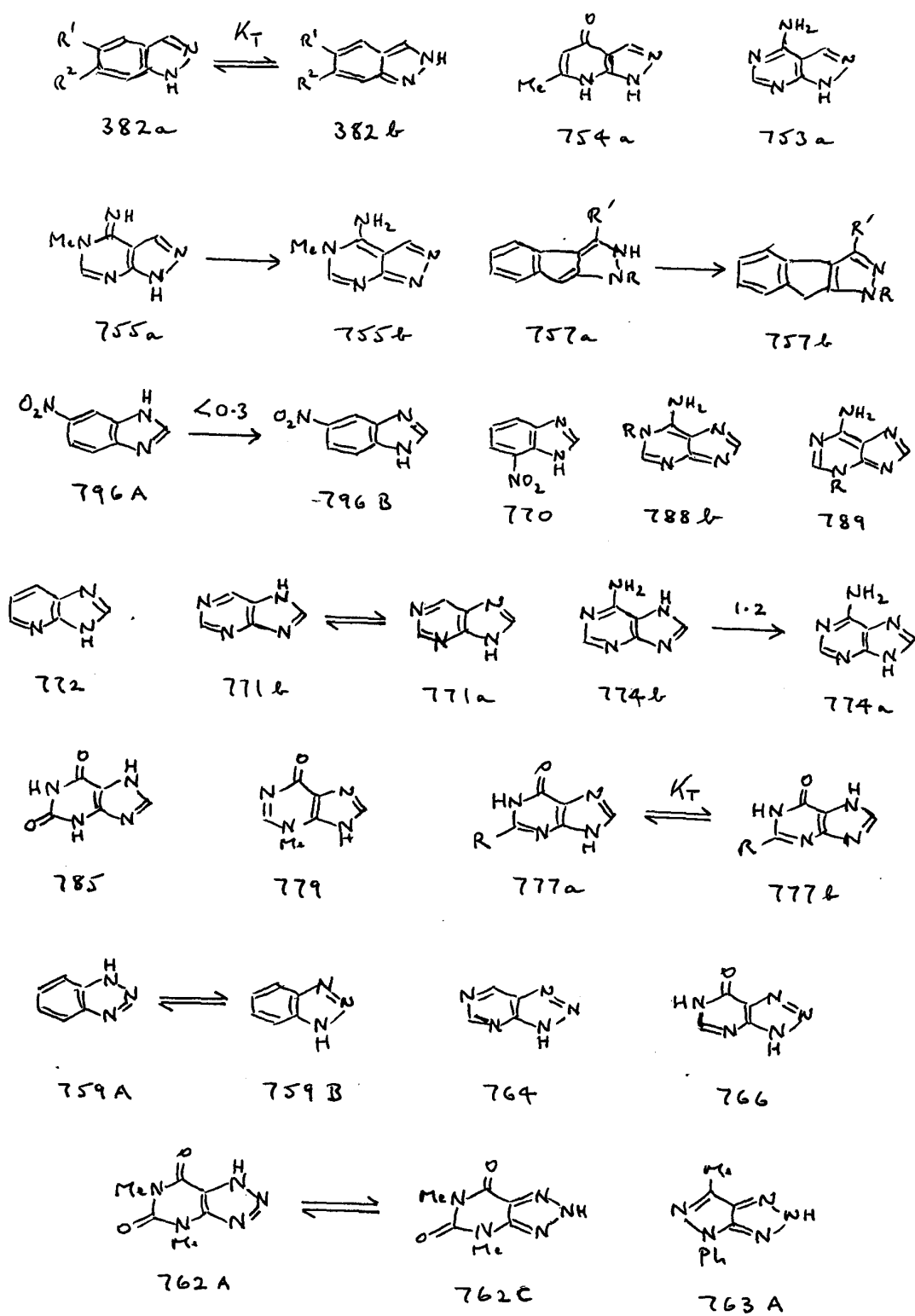
*Overview.* – In general tautomeric preferences for these five compounds are not pronounced, being greatest at the electronic extremes of the scale, imidazole and tetrazole, and probably least for *s*-triazole. So far as they go the data fit the predictions of Scheme 113 but these have the potential to be upset rather readily by intramolecular hydrogen bonding and the evidence, *e.g.* concerning **381** and **748**, appears to confirm this.

### C.38 Annular Tautomerism in Ring Fusions to 5-Membered Monocyclic Heterocycles not involving Bridgehead Nitrogen

Only three among the five heterocycles of section C.37 are capable of nonquinonoid benzofusion, but other sorts of aromatic ring fusion are also possible and these are included where known. They are classified separately since extra factors such as intramolecular attractions or repulsions often enter. This inevitably leads to overlap since it can mean approaching the same compound from different directions.

## INDAZOLE

Benzofusion of pyrazole **798** leads to indazole **382**. The quinonoid form of **382b** disfavors it by  $\Delta \log K$  -1.7, in line with other such structures (Appendix 5), and this value is scarcely affected even when  $\text{R}^1$  or  $\text{R}^2 = \text{NO}_2$  (section B.1.5). Hence indazole is locked as **382a** and no substituent is likely to affect this conclusion.



Scheme 114

## OTHER FUSED PYRAZOLES

The outcome here depends on the aromaticity of both fused rings, with dipolar repulsion involving NH a further potential source of trouble. The fused pyridone **754** exists as **754a** (Scheme 114) despite dipolar repulsion but surprisingly **753a** where this is absent is preferred to its quinonoid alternative by only a factor of 10 (section B.1.5). In **755** the pyrimidonimine tautomer **755a** is so enormously disfavoured (section C.32) that the equilibrium is forced over to give **755b**, despite the resulting lone pair repulsion and loss of aromaticity. Such cases are rare (but see fused imidazoles, below). However a preference for **757b** over **757a** is easy to understand since any nominal loss of conjugation in **757a** will be more than compensated by removal of dipolar repulsion; other examples appear in section B.1.5.

## BENZIMIDAZOLES

Since the tautomers of both are degenerate, benzofusion of imidazole alters the situation only in that sensitivity to substituents is greatly diminished;  $\log K_T < 0.3$  for **796** (Scheme 114) compares with  $\log K_T 2.7$  for 4(5)-nitroimidazole (section C.37). There is much more likelihood of dictating tautomeric form with 4(7)-substitution, but even **770** exists only *ca.* 80% as the tautomer written (section B.1.7). Stronger proton acceptors (or donors) however do not appear to have been studied, and these, especially if rigid, should offer greater scope.

## OTHER FUSED IMIDAZOLES

$$\log K = (\log K_\alpha + 0.4)(\log K_\beta + 0.3) \quad (\text{cxvii})$$

Because fused imidazoles unlike fused pyrazoles still possess mobile tautomers there is much less scope for loss of aromaticity, though **788b** and **789** (section B.1.7) should be noted in passing as parallel cases to **755** above. This subject has been reviewed in sections B.1.7 and B.8.1, while section C.23 comprehensively treats the subject of intramolecular interactions, and only a summary is given here. With easily switched proton donor (NH) and acceptor (=N-) groups in *peri*-positions the scope for attractive and repulsive intramolecular interactions is very great, but in practice the obvious predictions are not always fulfilled. For example, whereas **772** exists as shown in water, purine **771** is present as an equimolar mixture, and **774a** is preferred to **774b** for adenine **774** by a surprisingly small margin. While the

structure of xanthine **785** is as expected (and is echoed by other compounds of similar type: section C.23), it is not clear why **779** should exist as a tautomer from which hydrogen bonding is absent and in which intramolecular repulsions would appear to be maximised. If this structure is genuine, neglected factors may include solvation and molecular dipole. It is sometimes useful to employ a calculation based on eqn. (cxvii) for 1:1 hydrogen bond strength in water under optimum conditions<sup>595</sup> to predict *relative* bond strengths for alternative tautomers (section B.8.1); this reveals, for example, that hydrogen bonding (or dipolar attraction) is likely to be much stronger in **772** than in **771a** (and stronger again in **764**: see below). Prediction is most difficult when attractive *and* repulsive forces are both present in each tautomer, as in guanine (**777**, R = NH<sub>2</sub>) where **777b** is preferred. In this case our estimates (Appendix 3) when summed give the right result (section B.8.1), but at present these are pragmatic and would greatly benefit from theoretical underpinning.

## BENZOTRIAZOLE

One result of benzofusion on  $\nu$ -triazole **751** (section C.37) is to suppress its 2-*H* tautomer completely, leaving only the degenerate tautomers **759A** and **759B**. These parallel those of benzimidazole and, while evidence is lacking, it seems likely that the insensitivity of its tautomeric form to 5(6)- and perhaps even 4(7)-substitution will be paralleled here as well. As a much stronger proton donor but much weaker proton acceptor than benzimidazole, its annular tautomerism is likely to be more readily lockable by substituent proton acceptors (*vide* **764**) than by proton donors; the reverse should be true of benzimidazole.

## OTHER FUSED $\nu$ -TRIAZOLES

Generation of the triazole 2-*H* tautomer on fusion is relatively easy; **762B** (contrast **785**) and **763A** are both major though not dominant tautomers (section B.1.6). The former result is for DMSO, in which the proportion of 2-*H* tautomer is much the same as for  $\nu$ -triazole itself. On fusion with more aromatic rings the behaviour of  $\nu$ -triazole often but not always mimics that of imidazole: while **764** and **772** take the same form, **766** parallels that of the disfavoured tautomer **777a**, perhaps as a result of the lesser lone pair repulsion which is likely to accompany its poorer proton acceptor ability (section B.1.6). There are difficulties here which, again, computation might usefully address.

### C.39 5-Membered Ring Alicyclic Acylamidines and Guanidines

In their most general formulation these species may be characterised as **1112** or **1111** (Scheme 44, section B.5). In most cases of interest Z is a  $\pi$ -donor and, when Z = NH in **1112** and Z = NHR in **1111**, **1112C** and **1111C** are identical and form the link between the two series. For Z = CH<sub>2</sub> or H, S or SMe, O or OMe and NH or NH<sub>2</sub>, log  $K_M$  values are shown as parallel series in Scheme 60, section B.8.4, for the compounds of this section.

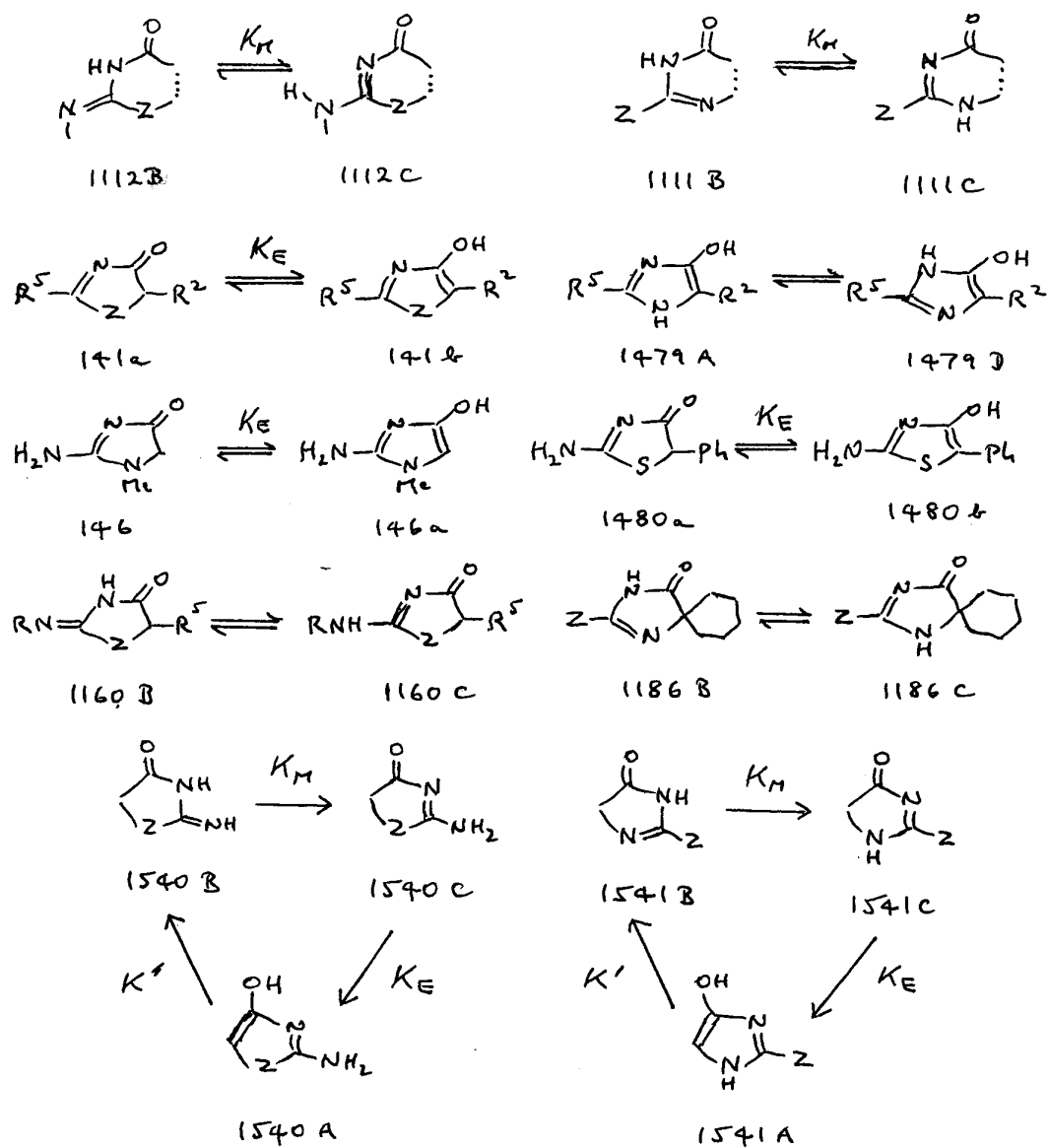
For 5-membered exemplars of **1112** and **1111** (Scheme 115) there is also the possibility of enolisation as shown for **141** (Scheme 82, section C.12) and this has to be considered. We present evidence (section C.17) that **1479D** will always be a minor species (probably < 10%) relative to **1479A**, so that even for (**141**, Z = NH), **141b** will remain the structure of the enol. We now attempt to estimate  $K_E$ . Table 92 (section C.17) contains rough estimates of log  $K_E$  for (**141**, R<sup>2</sup> = H, Me or Ph), where Z = O, S or NR and R<sup>5</sup> = Me or Ph, which can be used to rationalise the tautomeric preferences for these compounds in water. The grid is not complete but contains enough information to establish trends in a semi-quantitative fashion. We also estimate  $K_E < 10^{-5}$  for creatinine **146** (section A.2.8) which bridges the gap between R<sup>5</sup> = Me and R<sup>5</sup> = NH<sub>2</sub>. On isodesmic principles this leads to further estimates of log  $K_E$  ca. -7 and -4 for Z = O and S respectively in (**141**, R<sup>2</sup> = H, R<sup>5</sup> = NH<sub>2</sub>). Some indirect evidence comes from **1480**, which despite being potentially vulnerable to enolisation through possessing Z = S and R<sup>2</sup> = Ph, exists as **1480a** in EtOH and the solid state (section C.17); based on Table 96,

**Table 96. Tautomeric Ratios for 1540 and 1541** <sup>a,b</sup>

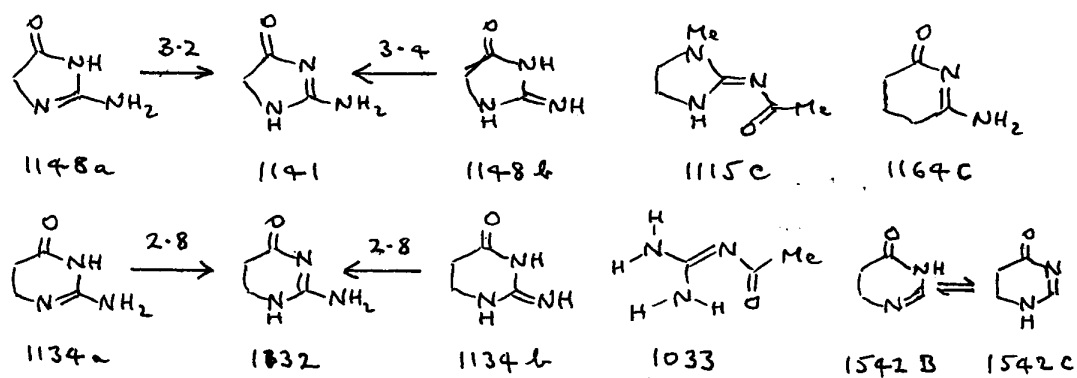
<b>1540:</b>				<b>1541:</b>			
Z	log $K_M$	log $K_E$	log $K'$	Z	log $K_M$	log $K_E$	log $K'$
CH <sub>2</sub>	(2.1) <sup>c</sup>			H	-0.3	(-3) <sup>d</sup>	(3.5)
S	2.6	(-4) <sup>e</sup>	(1.5)	SMe	1.0		
O	3.0	(-7) <sup>e</sup>	(4)	OMe	(2.1) <sup>c</sup>		
NR <sup>f</sup>	3.4	(-5) <sup>e</sup>	(1.5)	NH <sub>2</sub>	3.2	(-5) <sup>g</sup>	(1.5)

<sup>a</sup> Estimates are bracketed. <sup>b</sup> log  $K_M$  from Scheme 60, section B.8.4; log  $K'$  is a difference term and necessarily > 0. <sup>c</sup> Deduced on isodesmic assumptions (section B.4.4).

<sup>d</sup> For (**141**, Z = NR, R<sup>2</sup> = H, R<sup>5</sup> = Me): Table 92. <sup>e</sup> See the text. <sup>f</sup> R = H or alkyl. <sup>g</sup> Assumes equivalence between (**1541C**, Z = NH<sub>2</sub>) and (**1540C**, Z = NMe), *i.e.* **146**, in this respect.



Scheme 115



Scheme 116

we calculate  $\log K_E$  *ca.* -1.7. Note however that, if  $\Delta \log K_E$  *ca.* 3.5 applies to  $C=O \rightarrow C=S$  as we postulate, not only the thione corresponding to **1480** but many others in these two series are likely to exist as the thiol tautomer.

These estimates for  $K_E$  may now be combined with reliable  $K_M$  values for (**1160**,  $R = R^5 = H$ ) and **1186** from sections B.5.9 and B.5.10 respectively to solve parts of the 3-way tautomeric patterns of **1540** and **1541** as set out in Scheme 115 and Table 96. We note elsewhere (section B.8.4) that the effect on  $K_M$  of a  $\pi$ -donor Z is very much greater *exo* than *endo* to the ring, consistently with the expected superiority of *trans*-conjugation with carbonyl and a striking exemplification of that principle. Indeed for (**1541**,  $Z = H$ ) *i.e.* with no *exo*  $\pi$ -donor the **B**-tautomer is marginally preferred, and we anticipate that 'bland' substituents Z such as alkyl and aryl will behave in a similar way. There is no way of predicting from these data what the effect of a  $\pi$ -acceptor Z on  $K_E$  for **1541** might be, but an increase in its value would not be a surprise. (Replacement of a  $\pi$ -donor Z in **1540** by a  $\pi$ -acceptor such as carbonyl would probably leave the major tautomer as **1540C** since there are no obvious advantages in **1540B** and **1540A**, in this instance, would be anti-aromatic).

Since replacement of  $C=O$  by  $C=S$  in (**1186**,  $Z = SMe$ ) merely reduces  $\log K_M$  from 1.0 to 0.8 (section B.6.1), the effect of this change appears to be negligible; but see section C.41 below.

#### C.40 Open-Chain and 6-Membered Ring Alicyclic Amidines and Guanidines

Acylamidines in 6-membered rings are either wholly alicyclic or fully aromatic, and in neither case is enolisation likely. Hence interest is confined to  $K_M$ . We include here their open-chain analogues since major differences are neither expected nor found.

Five and 6-membered *endo*-cyclic guanidines (sections B.5.6 and B.5.7) are compared with related compounds in Scheme 116. Differences are slight and the marginal rise of  $K_M$  in **1141** *vs.* **1132** is probably due to the energetic advantage of *endo*- $C=N$  in 5-membered rings (*cf.* section C.35). The same factor may be partly responsible for the fall in  $K_M$  for **1115**, to  $\log K_M$  2.7 in favour of **1115C**. There are irregularities in some bicyclic systems (section B.5.6) that are not fully understood (again, they may involve bond angle distortion), but no change in the dominant tautomer results. Acetylguanidine

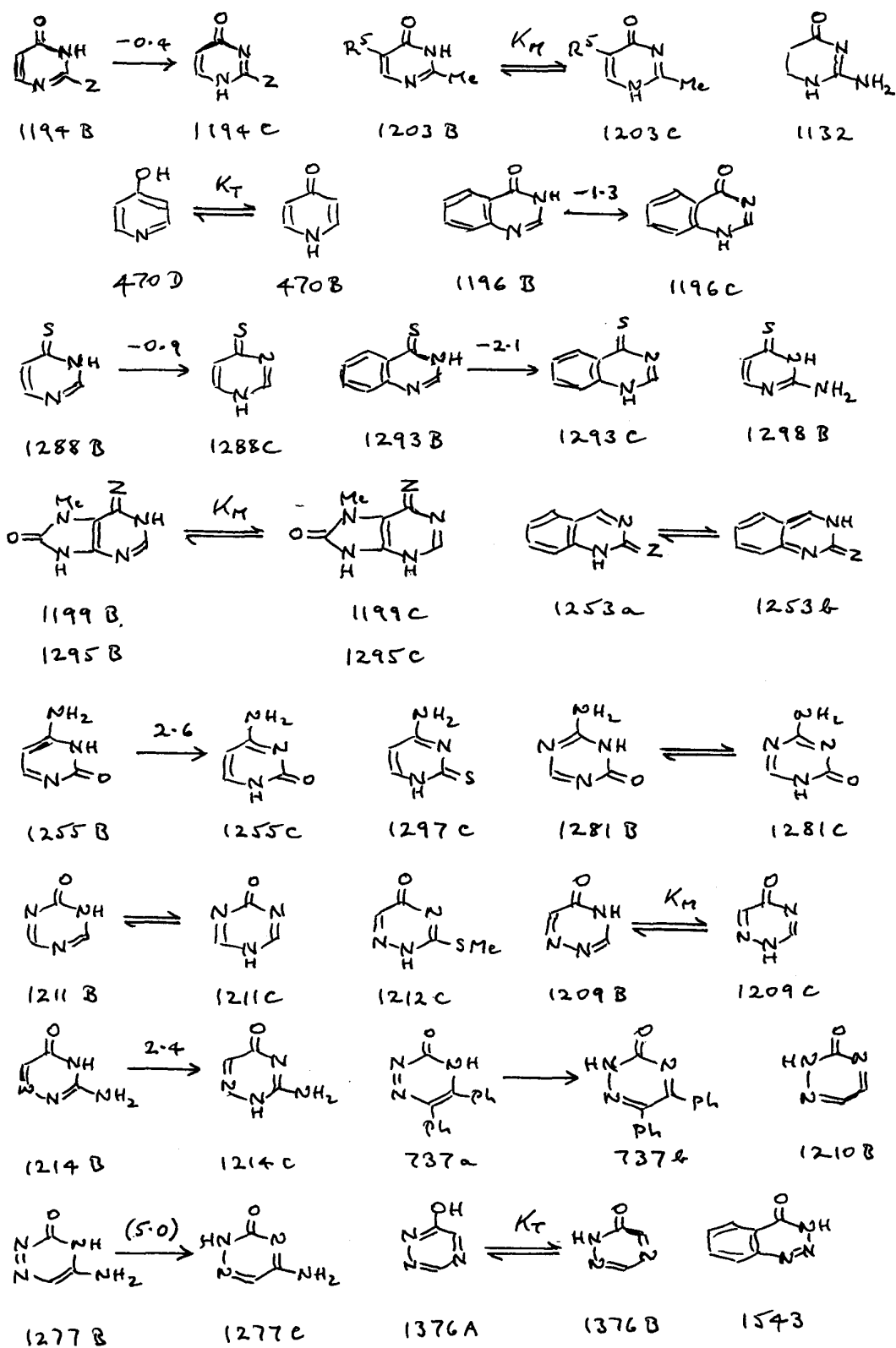
**1033** like **1115** adopts the *cis*-conformation shown so as to avoid the lone pair repulsion in the **C**-tautomer which is unavoidable for alicyclic structures; intramolecular hydrogen bonding may contribute but cannot be the major cause since this conformer is invariably found even when no such bond is possible (*cf.* Scheme 43, start of section B.5). It is possible that lone pair repulsion may also account for the slightly enhanced value of  $\log K_M$  3.1 for **1033** (section B.4.2) relative to 2.8 for **1132** where this cannot be avoided. If so the *cis*-conformer, while overwhelmingly dominant *e.g.* in  $\text{CHCl}_3$ , may be favoured in water by as little as  $\Delta \log K$  0.3; see discussion in section B.5.6.

There is little information otherwise on cyclic acylamidines but **1164**, while existing as shown in EtOH, takes up the **B**-form in the solid state. This may be a quirk of *intermolecular* hydrogen bonding, *e.g.* to give a dimeric lactam structure, but it may also imply an appreciable drop in  $K_M$  relative to (**1540**,  $Z = \text{CH}_2$ ). However its open-chain analogue, acetylacetamidine **1037**, at  $\log K_M$  2.8 shows only a slight drop in  $K_M$  relative to **1033** (section B.4.2). It would be interesting to know the position for **1542** (*cf.* **1186**,  $Z = \text{H}$ ), but this has not been examined.

#### C.41 Aromatic *endo*-Acylamidines

Much of the present subject matter has been summarised in sections C.21 and C.32, but it is brought together here along with other material since their collation allows for further perspectives. Scheme 117 sets out the compounds to be discussed.

4-Pyrimidones and related compounds are the most important members of this class (sections B.5.11 and B.5.12). In (**1194**,  $Z = \text{H}$ ) the 3-*H* tautomer **1194B** is marginally preferred and known values of  $\log K_M$  range from -0.5 for  $Z = \text{Ph}$  to approximately zero for the strong  $\pi$ -donors  $\text{NH}_2$  and  $\text{OEt}$  (section B.5.11). This tautomer balance (but not  $K_T$ : section B.5.12) is also insensitive to substitution at  $\text{R}^5$  in **1203**, being effectively constant at  $\log K_M$  -0.4 over a range extending from  $\text{OMe}$  to  $\text{CN}$ . This is understandable since both  $Z$  and  $\text{R}^5$  lie on the axis of the amidine unit; Katritzky has explained on similar lines the relative insensitivity of  $\log K_T$  for 4-pyridone **470B** to 3-substituents (section A.10.6). By contrast the solvent sensitivity of (**1194**,  $\text{R} = \text{H}$ ) is extreme, with its **C**-tautomer already invisible in EtOH, the result of a very large dipole. However even the lowest of these  $\log K_M$  values is wholly out of line with that for **1132** (section C.40), readily explained as resulting from through-conjugation, and we tentatively advance an explanation for this anomaly in terms of rival conjugation patterns, amidic *vs.* vinylogously amidic, whose effects fortuitously cancel (section B.5.11).



Scheme 117

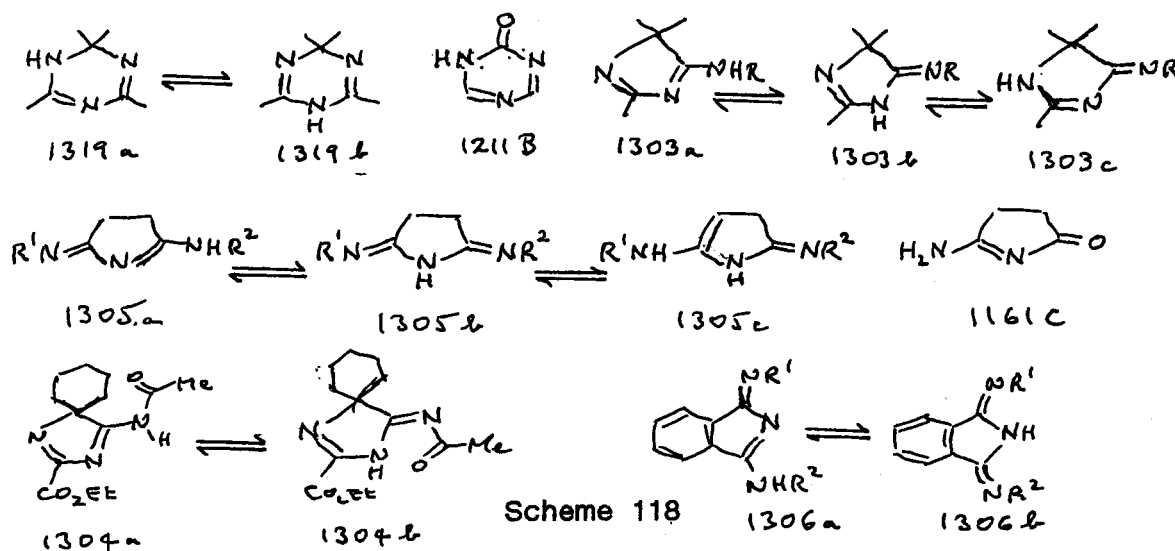
The effect of benzofusion in **1196** is to stabilise the **B**-tautomer by  $\Delta \log K_M$  0.9 (section B.5.11). This difference is predictable on an isodesmic argument which also allows reasonable estimates for  $K_T$  to be made (section C.21).

The corresponding thiones **1288** and **1293** (section B.6.2) show a greater bias throughout towards the **B**-tautomer, which may indicate a somewhat lesser tendency of C=S than C=O to support vinylogous (*i.e.* through)-conjugation. The difference between **1196** and **1293** is precisely echoed by **1199** (Z = O) and **1295** (Z = S) for which  $\log K_M$  is -2.5 and -3.4 respectively. The resulting shifts,  $\Delta \log K_M$  *ca.* -2.1 and -2.5, may plausibly be accepted as an estimate of the dipolar repulsion present in the **C**-tautomer (Appendix 3). Predictably, **1298** exists mostly as **1298B**.

The degeneracy of 2-pyrimidones and 2-pyrimidinethiones is broken by benzofusion and **1253b** as quinonoid should be strongly disfavoured. In most other contexts (Appendix 5)  $\Delta \log K$  *ca.* -1.8 results from this and, for (**1253**, Z = S),  $\log K_M$  -2.1 is found. The corresponding value for (**1253**, Z = O) is unknown but can safely be assumed to lie in the same region. Both **1255** and **1297** take the **C**-form shown.

Triazinones also show annular tautomerism. The triazinone **1211** (section B.5.15) like 2-pyrimidone **1252** possesses degenerate tautomers **1211B** (**1211C** may probably be discounted) and, since the through-conjugated tautomer **1255C** of cytosine **1255** is strongly favoured (*cf.* section C.32), **1281C** is expected for **1281**. Surprisingly, **1281B** is claimed to be its structure but this perhaps should be re-examined. In the other triazinones, all of which contain contiguous nitrogen atoms, the relief of lone pair repulsion is a major driving force in dictating tautomeric form. There can be no doubt that **1209C** is the major tautomer of **1209** since **1212C** is the structure of **1212** (section B.5.13) and for **1214** the results are quantitative (see also Scheme 108); the difference relative to (**1194**, Z = NH<sub>2</sub>) provides one good estimate of  $\Delta \log K$  for lone pair repulsion (Appendix 3). Similarly, since **737** exists as **737b** (section B.1.1), the parent triazinone **1210** (section B.5.13) will almost certainly possess structure **1210B** while, for its amino-derivative **1277**, we estimate the very large value shown for  $\log K_M$  (section C.32). Other than **1376B** (section B.8.12) the only tautomer available to **1376** is the iminol **1376A** and the oxo-form will certainly be preferred. Almost nothing is known concerning vicinal triazinones but we show compound **1543** as its likeliest tautomer.

## C.42 Imidines



Imidines possess some resemblance to acylamidines in the importance of a through-conjugated tautomer, though not nearly such a strong one, the decisive factor being the terminal substituent. There are three series: *endo-endo* **1319**, *endo-exo* **1303** and *endo-exo* plus *exo-exo* **1305** (section B.7.1). Those that can be described as heteroaromatic (section B.7.2) are covered in section C.32. However these are alicyclic; open-chain forms are possible (most will probably be chelated) but have not been studied.

For these compounds we reproduce, as Scheme 118, Scheme 59 (section B.8.3) with additions. In **1319** the terminal atom can only be alkyl, and here tautomeric bias is at its weakest; the resemblance to **1211** (Scheme 117) will be noted. Series **1303** and **1305** possess, respectively, one and two nitrogen atoms capable of carrying more electronegative substituents which, as for any other amidine (section C.31), will tend to bias C=N in their direction. In **1305** this leads to a situation in which **1305b** is favoured for  $R^1 = R^2$  as this becomes more electronegative, but **1305a** for  $R^1 \neq R^2$  with the more electronegative substituent on terminal C=N; the pyrrolenine tautomer **1305c** has never been detected. A complicating factor is that solvents of low polarity tend to favour the less polar **b**-tautomer, while **1305a** can be preferred in water even for  $R^1 = R^2$ ; for (**1306**,  $R^1 = R^2 = \text{Ph}$ ) **1306a** is the more important species in water but **1306b** dominates in less polar solvents. The situation concerning **1303** is uncertain, with a preference for *endo*-C=N which will favour **1303a** and the importance of chelate bonding in nonpolar solvents (Appendix 2) as complicating factors; **1304** exists as **1304b** in  $\text{CHCl}_3$  but as **1304a** in the solid state. The **c**-tautomer (*i.e.* **1303c**) is absent but as for **1305a** is likely to be much more important in water, analogously to **1161C** (Table 96, section C.39: **1540**,  $Z = \text{CH}_2$ ).

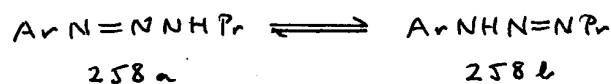
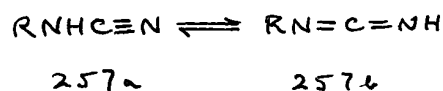
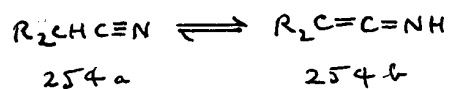
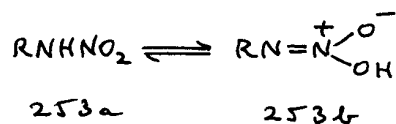
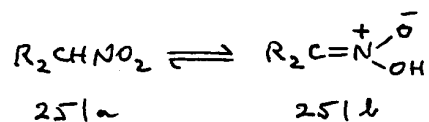
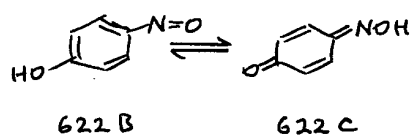
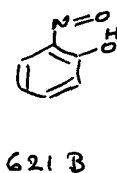
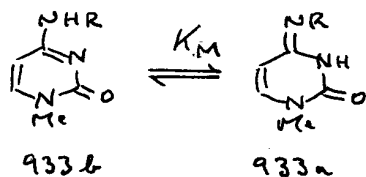
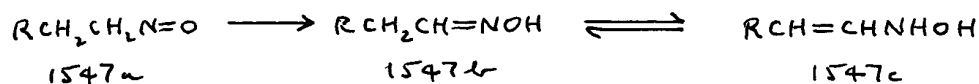
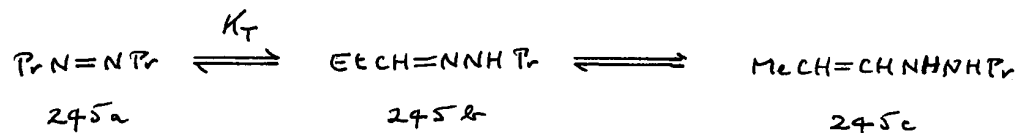
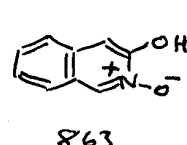
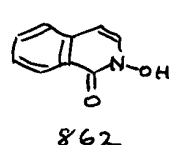
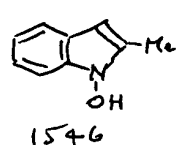
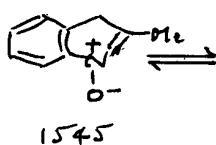
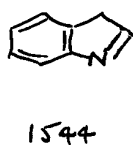
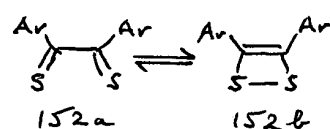
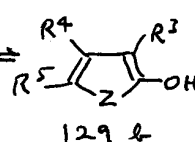
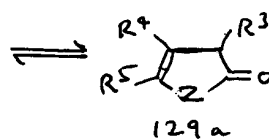
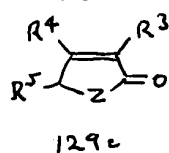
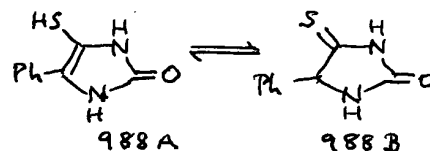
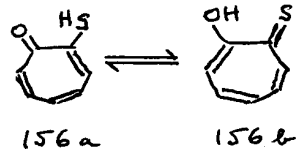
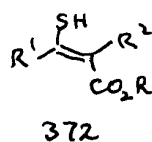
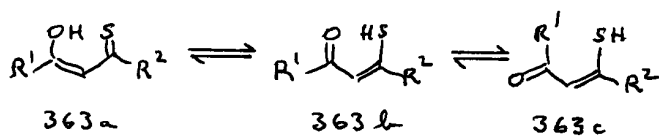
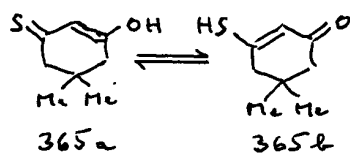
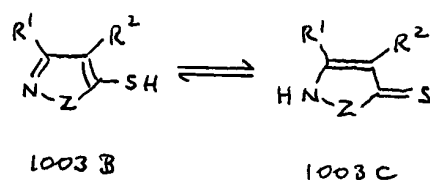
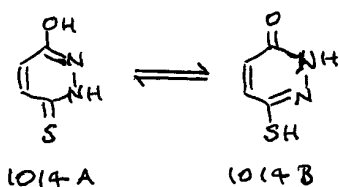
### C.43 Short Summary: The Comparative Behaviour of C=S and C=O

Simple thioketones  $R^1CSCH_2R^2$  (section A.3.1) enolise very much more readily than the corresponding ketones (section A.2.1) and the balance of the evidence suggests a reasonably constant factor of *ca*  $10^6$  (*vide* section C.2). It is very different elsewhere. Thioamides give the iminol tautomer less readily than amides, probably on average by  $\Delta \log K_E$  *ca.* -0.5 (sections B.3.3 and C.21), a much smaller margin than commonly supposed though still in the same direction (*vide* Appendix 1). Qualitatively this is supported by the known preference for **1014A** over **1014B** as the structure of **1014** and some similar examples (section B.3.7). It is important to note that vinylogous thioamides such as **1003C** (section B.3.6) closely resemble thioamides in their lack of susceptibility to thioiminol formation.

$\beta$ -Thionoketones behave differently. While **365** exists predominantly as **365b** in most solvents other than DMSO (section A.8.2), the tautomers of **363** and other chelates are closely in balance and there is some evidence that the thiol tautomer may exist largely as **363c** (section A.8.3). This may be traced, at least in part, to the extreme weakness of SH as a proton donor which destabilises **363b** and so favours **363a** by default. This helps to explain two other phenomena: the enhanced preference for **365a** in DMSO, which binds to OH, and the fact that bulky substituents  $R^2$  in **372** do not suppress enolisation as in the corresponding ketones but lead to the configuration shown. It may also contribute to the preference for **156b** over **156a** (section A.3.6) and even perhaps, through the relative strength of *intermolecular* hydrogen bonding, to that of **1014A** over **1014B**. It is just possible however, at least for **363**, that some effect due to the change in configuration also enters.

While thioiminol formation is greatly disfavoured, C-type enolisation of  $NH(C=S)$  is very much more facile than that of  $NH(C=O)$ : **988** exists as the thioenol **988A** (section B.3.5) whereas the corresponding hydantoin does not perceptibly enolise. We estimate  $\Delta \log K_E$  *ca.* 3.5 for  $C=O \rightarrow C=S$  in such cases; this estimate is based on  $Z(C=O) \rightarrow Z(C=S)$  where  $Z = O$  (section A.3.7) but in the absence of other evidence we have assumed it for  $Z = S$  and NR also. Its use leads to a reasonably consistent picture of tautomer preference in compounds of type **129** and their thione analogues (section C.10) and is also compatible with the result for **988**.

Uniquely,  $\alpha$ -dithiones of type **152** can tautomerise as shown (section A.3.5), an option not open to the corresponding  $\alpha$ -diketones.



#### C.44 Short Summary: Nitrones and N-Oxides

Whereas the indolenine tautomer **1544** of indole is unknown (*vide* **224**, section C.30) the nitrone **1545** and hydroxylamine **1546** predominate respectively in proton donor and proton acceptor solvents<sup>596</sup> so these tautomers are roughly in balance. Stabilisation of *endo*-C=N *vs.* C–N by the highly electronegative oxygen substituent should logically imply the stabilisation of iminols relative to their amide tautomers and this is found. For technical reasons related to the differing strengths of the hydrogen bonds the rival tautomers can form it is difficult if not impossible to quantify this process but there is no doubt concerning the trend. Perhaps the most relevant observation is that **862** and **863** exist respectively as the amide and *N*-oxide tautomers shown (section B.2.6), whereas  $\log K_T$  5.4 and 1.7 is found in water for the corresponding oxoheterocycles **850** and **68** (sections B.2.5 and C.21). This suggests a shift of  $\Delta \log K_T$  in the range -2 to -5 for the effect of *N*-oxide formation in such cases, and no closer estimate is presently possible.

#### C.45 Short Summary: Other Nitrogenous Electron Acceptors

Imines are electronegative groups and are stable relative to the enamine tautomer typically by a factor of *ca.*  $10^2$  (section C.25) in simple aliphatic structures. This survey, which draws almost entirely on section A.5, summarises the results for a number of simple tautomeric structures in which nitrogen is more electron-withdrawing than in C=N.

(a) The azo-compound **245a** goes to the hydrazone **245b** with  $K_T \sim 60$  in Bu<sup>t</sup>OH and this behaviour appears to be typical (section A.5.1). The hydrazine **245c** is only just detectable and may be even more disfavoured than **245a**. The consequences of the former equilibrium for more complex molecules are explored in section C.9 and of the latter in sections C.26 and C.29. When incorporated into cyclic structures this preference for adjacent nitrogen atoms in different hybridisation states is at least as strongly pronounced; see especially section C.15 and Appendix 3.

(b) A similar situation obtains for aliphatic nitroso-compounds **1547a**, which go totally and irreversibly to the oxime **1547b** (section A.5.2). This process can extend to their aromatic analogues when a suitable proton source (*i.e.* from OH) is present; **622** gives about 85% of **622C** in water but **621** remains largely as **621B**, so the balance is quite fine. Amines are less effective proton sources since *exo*-C=NR to an aromatic ring are so much less

favoured than carbonyl (section C.32). These and other examples are discussed in section A.10.20. Any such tautomerisation entails the formation of a heavily disfavoured quinonoid form (Appendix 5; *cf.* section C.3) and the fact that it can happen at all indicates a very strong driving force for oxime formation.

Again, the equilibrium between **1547b** and **1547c** is heavily biased towards the former. Compounds **933** possess  $\log K_M$  -4.1, -1.5 and 1.1 respectively for R = H, NH<sub>2</sub> and OH (section B.5.15); qualitatively at least, this ties in with the above observations and may throw some light on the energetics involved in the processes **245c** → **245b** and **1547c** → **1547b** (see discussion in section B.2.10).

(c) Aliphatic nitro-compounds **251a** are in equilibrium with the *aci*-nitro tautomer **251b** but the latter is greatly disfavoured, typically by 10<sup>3</sup> - 10<sup>4</sup>. The corresponding nitramines **253** behave in a somewhat similar manner but detail is lacking (section A.5.4).

(d) Aliphatic nitriles **254a** can in principle tautomerise to ketenimines **254b** but in practice this is only detectable in certain special cases (section A.5.5). The analogous cyanamides **257a** can similarly tautomerise to carbodiimides **257b** which are again disfavoured, probably by a factor of 10<sup>6</sup> or more (section A.5.6).

(e) Triazenes such as **258** are in a sense ‘azalogues’ of amidines and, as in that case (section C.31), tautomeric preference is quite evenly balanced. In **258** there is about a five-fold preference for **258a** (section A.5.7) which lies in the same direction as that expected for the corresponding amidine but is probably less than it would show (for Ar = Ph, a factor of *ca.* 25).

#### C.46 Short Summary: The Energetics of C=Z/C=Z Interaction

This section shares its title with A.12.2 and reworks more concisely the information to be found there. Of the three computational methodologies we have employed in the original Tables (see footnotes) one has been selected as representing a position roughly intermediate between the others and as generally the most internally self-consistent. The results appear in Tables 48 - 50, taken from section A.12.2, while Scheme 119 is built round Scheme 24 from the same source but adds from Scheme 10 (section A.6) the potential chelate **261**. Here only the process **261B** ⇌ **261C** was assessed since in our opinion too much ambiguity attaches to the unconjugated **A**-tautomer for the calculation of its energetics to be meaningful.

**Table 48.**  $\Delta H$ , kJ mol<sup>-1</sup> (RHF Methodology) for Enolisation of **652**, **653**, **654** ( $R^1 = \text{Me}$ ,  $R = R^2 = R^3 = \text{H}$ ), and (**655**,  $X = Y = \text{O}$ ,  $\text{S}$  or  $\text{NH}$ ;  $R^1 R^2 = [\text{CH}_2]_3$ ,  $R^3 = \text{H}$ )<sup>a</sup>

	<b>652</b>	<b>655</b> , $X = Y = \text{O}$	<b>653</b>	<b>655</b> , $X = Y = \text{S}$	<b>654</b>	<b>655</b> , $X = Y = \text{NH}$
$\Delta H_E$	64.4	18.6	26.7	- 21.0	27.2	-10.6

<sup>a</sup> See Table 22, section A.6.1.

**Table 49.**  $\Delta H$ , kJ mol<sup>-1</sup> (RHF Methodology) for **655**,  $X \neq Y$ ,  $R^1 R^2 = (\text{CH}_2)_3$ ,  $R = \text{H}$ <sup>a</sup>

Equilibrium:	$K_E$	$K_M$	$K_T$	$K_T$ <sup>b</sup>
$X = \text{S} \quad Y = \text{O}$	7.1	-10.1	-17.2	1.0
$X = \text{NH} \quad Y = \text{O}$	29.1	-21.6	-50.7	-35.5
$X = \text{NH} \quad Y = \text{S}$	- 3.4	-38.2	-34.8	-45.7

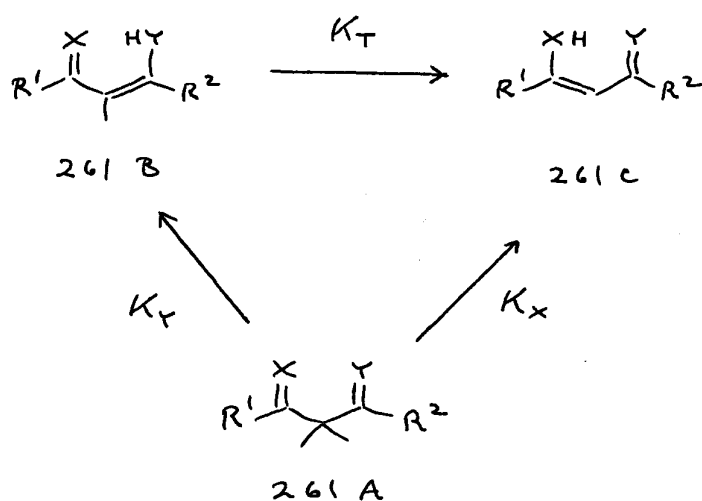
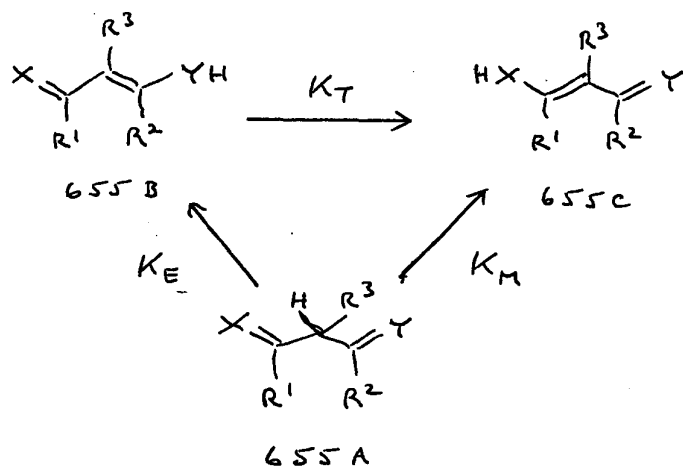
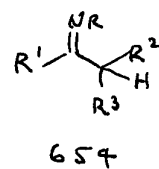
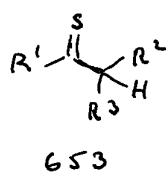
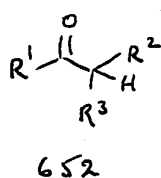
<sup>a</sup> See Table 29, section A.8.1; Table 31, section A.10.1; Table 44, section A.11.1.

<sup>b</sup> For corresponding chelate **261** (see Tables 29, 31 and 44).

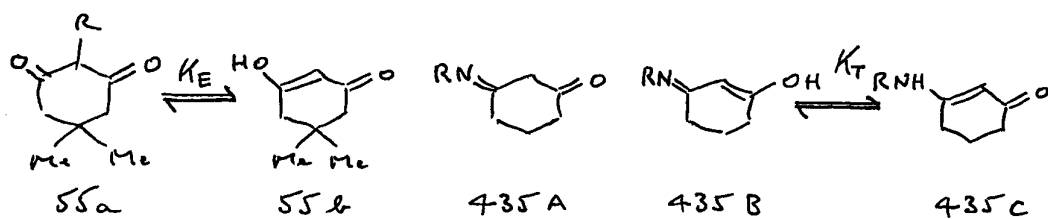
**Table 50.** Mutual Interaction Terms ( $\Delta H$ , kJ mol<sup>-1</sup>, RHF Methodology) for **655**,  $X \neq Y$ ,  $R^1 R^2 = (\text{CH}_2)_3$ ,  $R^3 = \text{H}$ <sup>a</sup>

	Effect on:	C=S	C=O	C=NH
Effect of:	C=S	-47.7	-57.3	-64.9
:	C=O	-36.8	-45.8	-48.8
:	C=NH	-30.6	-35.2	-37.8

<sup>a</sup> Each value in this Table is the resultant of one value in Table 48 and one other value, in Table 48 or 49; thus the difference between  $\Delta H_E$  for **652** and (**655**,  $X = Y = \text{O}$ ), both in Table 48, furnishes the entry of -45.8 for C=O/C=O, whereas the difference between  $\Delta H_E$  for **652** and  $\Delta H_E$  for (**655**,  $X = \text{S}$ ,  $Y = \text{O}$ ) in Table 49 gives rise to -57.3 for C=S/C=O.



Scheme 119



If we equate  $\Delta G$  with  $\Delta H$  we can recast these results as  $\log K$ . Given the rigidity of all species this postulate, while strictly invalid, may not be far from the truth, and the resulting  $\log K$  values are instructive. For  $R^1 = \text{Me}$ ,  $R^2 = R^3 = \text{H}$  the experimental value for **652** of  $\log K_E$  in water is -8.6 (section C.1), while the expected values for **653** and (**654**,  $R = \text{Me}$ ) are close to -2.5 (section C.2) and -1.8 (section C.25) respectively. At -11.3, -4.7 and -4.8 (*ex* Table 48; note that the third refers to  $R = \text{H}$ ) their predicted gas-phase values are more negative than this but by quite similar margins. The next significant comparison concerns (**655**,  $X = Y$ ). For  $X = Y = \text{O}$   $\log K_E$  -3.3 is predicted whereas for dimedone (**55**,  $R = \text{H}$ ) 1.3 is found, a somewhat greater discrepancy but in the same direction. However, estimates for the mutual effects of two carbonyl groups differ considerably less; from Table 50 this value is  $\Delta \log K_E$  8.0 by calculation whereas for dimedone (**55**,  $R = \text{H}$ ) *vs.* acetone **1397** it is 9.6 (Table 87, section C.7). The calculated  $\log K_E$  values for  $X = Y = \text{S}$  and  $X = Y = \text{NH}$  are 3.7 and 1.8 respectively, leading to  $\Delta \log K_E$  values of 8.4 and 6.6. Quantitative data are unavailable but these  $\log K_E$  values correctly predict the unimportance of the **A**-tautomer except for (**655**,  $X = Y = \text{O}$ ).

However, the most significant cross-comparisons concern those species for which  $X \neq Y$  (Table 49). From the great difficulty of enolising **652** relative to **653** and **654** it would have been logical to predict that  $K_T$  for (**655**,  $X = \text{S}$ ,  $Y = \text{O}$ ) and (**655**,  $X = \text{NH}$ ,  $Y = \text{O}$ ) should be large whereas for (**655**,  $X = \text{NH}$ ,  $Y = \text{S}$ ) it would probably be small. Only the second of these three predictions is even qualitatively correct. For (**655**,  $X = \text{NH}$ ,  $Y = \text{O}$ ) calculation predicts  $\log K_T$  8.9 where additive assumptions would have led to  $\log K_T$  6.5; for (**435**,  $R = \text{alkyl}$ )  $\log K_T$  8.7 is found in water (section A.10.4). For (**655**,  $X = \text{S}$ ,  $Y = \text{O}$ ) and (**655**,  $X = \text{NH}$ ,  $Y = \text{S}$ ) the calculated  $\log K_T$  values are 3.0 and 6.1 respectively; consistently with this, **365** exists in water predominantly as **365b** (section C.43) while the very little available information on aliphatic  $\beta$ -iminothiones suggests that **655C** will always be the major tautomer. However  $\log K_T$  6.5 and 0.1 would have been predicted for (**655**,  $X = \text{S}$ ,  $Y = \text{O}$ ) and (**655**,  $X = \text{NH}$ ,  $Y = \text{S}$ ) respectively, so that the calculated values are more than half for the first, and almost entirely for the second, due to some factor that does not obey additive assumptions.

The nature of that factor becomes clear from Table 50, in which we tabulate the mutual interactions of  $\text{C}=\text{O}$ ,  $\text{C}=\text{S}$  and  $\text{C}=\text{NH}$  in grid form. Here, consistently,  $\text{C}=\text{S} > \text{C}=\text{O} > \text{C}=\text{NH}$  in terms of their *promotion of enolisation* in interacting with themselves and one another whereas, with equal consistency, their *susceptibility to enolisation* follows the opposite order. Hence while dominance of the aminoenone tautomer (**655C**,  $X = \text{NH}$ ,  $Y = \text{O}$ )

is somewhat enhanced by the mutual interactions of C=NH and C=O, the equivalent aminoenethione owes its dominance almost entirely to those between C=NH and C=S. The order C=O > C=NH is unsurprising but, so far as we are aware, the greater electronegativity of C=S than C=O as revealed by Table 50 has not been suspected before. There may be other contexts in which this insight is important.

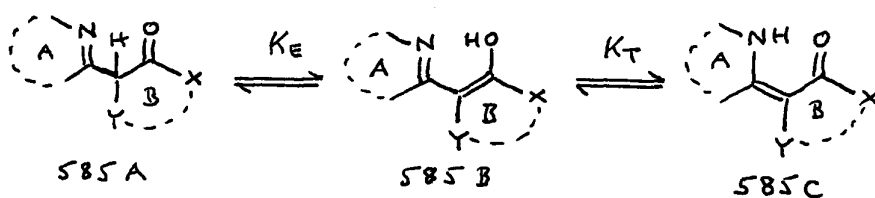
A comparison of  $K_T$  for the extended **655** and chelated **261** structures also appears in Table 49. For X = S, Y = O this predicts a switch, on chelation, from the dominance of **655C** to a close balance between **261B** and **261C** as is indeed found in organic solvents and, by extrapolation, in water (Appendix 2). Both (**261**, X = NH, Y = O) and (**261**, X = NH, Y = S) are expected to remain overwhelmingly as the **C**-tautomer, but for the former its predominance is sharply reduced whereas for the latter it is quite sharply increased. Neither prediction is experimentally verifiable and the first is a particularly widespread compound class (sections A.10.10 - A.10.20) for which this information could be important. In terms of the known sequences OH  $\gg$  NH > SH and C=O > C=NH  $\sim$  C=S for proton donor and acceptor strength respectively all three results make sense, with a particularly large effect expected for (**261**, X = S, Y = O) in agreement with these estimates. Even if somewhat exaggerated by gas phase calculation these shifts as a result of chelation remain significant.

The comparative resistance of C=O to enolisation has the consequence that only for (**655**, X = NH, Y = O) is **A**  $\gg$  **B** likely. From Table 49, the values calculated of log  $K_E$  and  $K_M$  for **435** are -5.1 and 3.8 respectively. For **436** (**435**, R = NHPh) the **A**-tautomer may have been detected in DMSO; this and other examples are discussed in section A.10.4. In some more complex structures this is accompanied by C-protonation, so that **A** and **C** not **B** and **C** share a common cation; some examples appear in the next section.

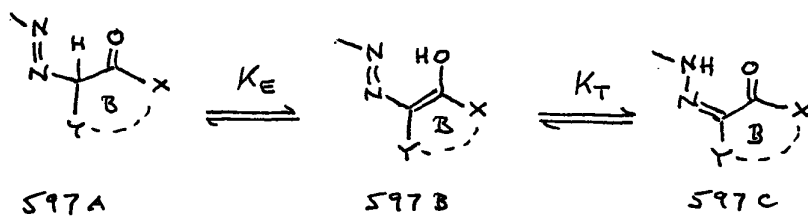
These calculations appear to rationalise, in a predictive and at least a semiquantitative manner, a major field of tautomerism for which a comprehensive rationale has been lacking so far. Some of the perturbations that can occur in practice for the particularly important class of the aminoenones are considered below.

#### C.47 Short Summary: Perturbing Factors in C=N/C=O Interactions

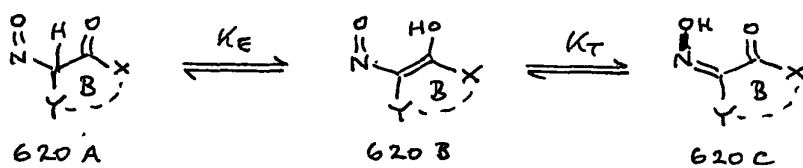
While in the typical aliphatic or alicyclic  $\beta$ -iminoketone such as **435** (sections C.8, C.9, C.46) the aminoenone tautomer is overwhelmingly dominant, various types of perturbation can upset this situation and the chief among these is aromaticity. We analyse the problem *via* Scheme 20 (section A.10.18). Here either or both of **A** or **B** may be cyclic structures, and if cyclic, then aromatic. We examine the options in turn.



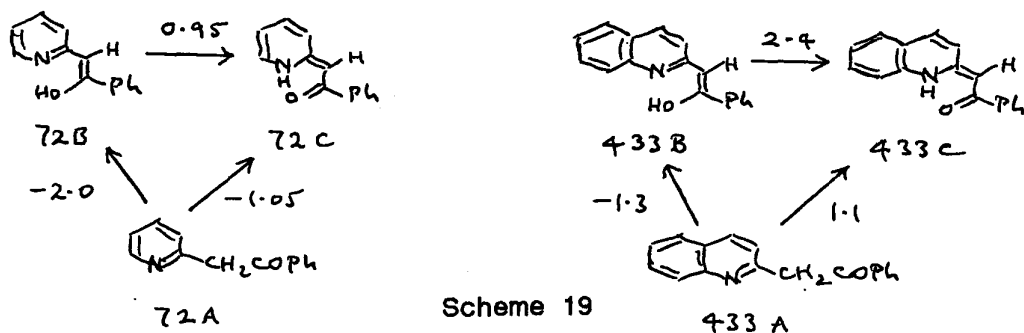
Scheme 20



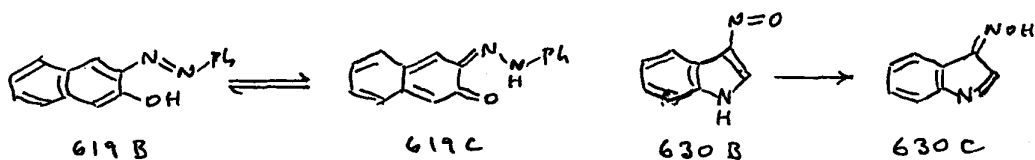
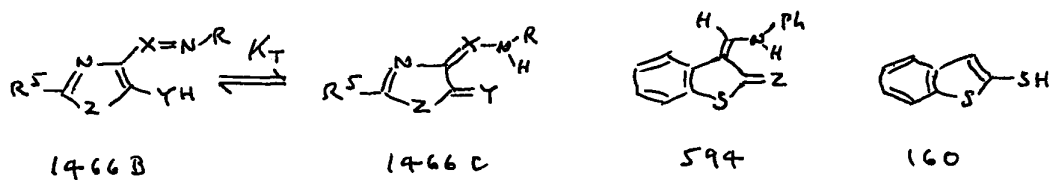
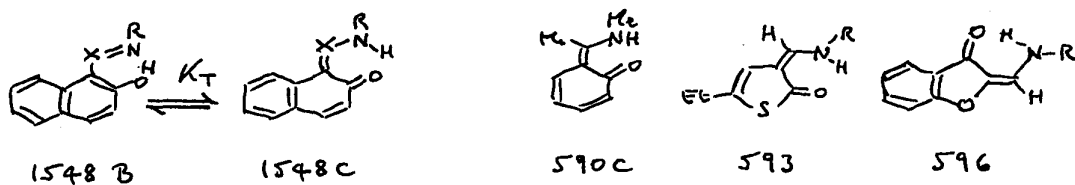
Scheme 21



Scheme 23



Scheme 19



If A is an aromatic ring the result is to make **585A** far more important and, in most cases, the dominant tautomer, as for **72A** (Scheme 19, section A.10.2). Important variants include the following: (a) Generally, the **B**- and **C**-tautomers will both be more important in nonpolar solvents than in water, **585B** overtaking **585C** as solvent polarity falls and sometimes becoming dominant (Appendix 2). (b) If X is a  $\pi$ -donor however **585B** will be totally suppressed; if Y is very bulky both the **B**- and **C**-tautomers may be suppressed. (c) If as well as X(C=O), Y is a  $\pi$ -acceptor, any tendency to give **585C** will be reinforced, but not necessarily by a large margin since planarity may be reduced; this caution applies to aliphatic (sections A.10.11 and A.10.13) as well as aromatic (sections A.10.15 and A.10.17) structures. If Y and X(C=O) are both  $\pi$ -acceptors and form part of a ring, planarity can be restored and this penalty avoided (see sections quoted above). (d) Benzofusion favours **B** and **C** over **A** but especially the **C**-tautomer, as in the case of **433** where **433C** (Scheme 19) is now the chief component; in this case but not always, the **B**-tautomer remains the least important. Anything else that weakens the aromaticity of ring A will have a similar effect.

If rings A and B are both aromatic **585B** should be the dominant tautomer. We consider various possibilities in section A.1.7 but nothing is known.

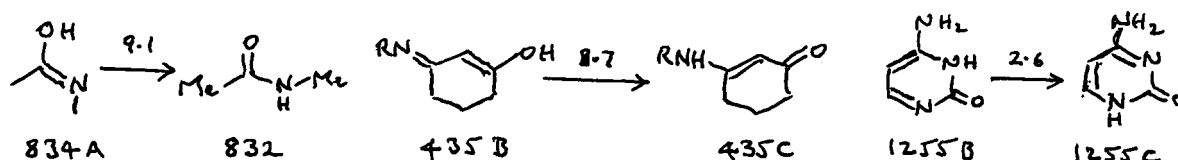
When ring B is aromatic but A is not the **A**-tautomer is wholly suppressed and the compound is typically a Schiff base (section A.10.18) in which the **B**- and **C**-tautomers are finely balanced, the outcome depending chiefly on the nature of X and Y and the substituent on nitrogen. Major trends include the following: (a) Predominance of the **C**-tautomer is strongly influenced by the  $\pi$ -donor ability of the amine moiety; any reduction in this will reduce  $K_T$ . For example, replacement of R = Me in (**1548**, X = CH) by R = Ph reduces  $\log K_T$  *ca.* 1.9 to *ca.* 0.6 (section A.10.18), *i.e.*  $\Delta \log K_T$  -1.3. (b) Benzofusion in such cases has its usual effect of increasing  $K_T$ ; for **590** we estimate  $\log K_T$  *ca.* 0.8 (Appendix 2), *i.e.*  $\Delta \log K_T \pm 1.1$ , close to the value for the nearest related oxoheterocycle. (c) If X = Y = C=C, *i.e.* ring B is benzenoid, **585B** can be dominant or nearly so as seen above. If however X or Y is a heteroatom and ring B is 5-membered, the reduction in aromaticity means that **585B** is rarely of any importance and **585C** will be the dominant and usually exclusive tautomer, as for **593** and **596** (section A.10.18; also see section C.9). The position if X and Y are both heteroatoms, *e.g.* (**1466**, X = CH, Y = O), is unknown. While the aromaticity of **1466B** should lie between those of **593** and **1548**, even that of the latter seems only marginally effective when competing with **1548C**, so probably **1466C** (section C.13) will be preferred. In such compounds (see section C.9)

the driving force for aminoenone formation can be very great; for example, (**594**, Z = S) takes the thione structure shown despite the existence of **160** as the thiol (sections A.3.7 and C.10). So far however it has not proved possible to quantify the general situation covered by Scheme 76 in section C.9, except in terms of the very rough guidelines set out here and below.

Two special variants on **585** are contained in Schemes 21 (section A.10.19) and 23 (section A.10.20). Here ring A does not exist and these situations parallel that of the Schiff bases described above. Since through its additional aza-nitrogen atom, replacing C=N by N=N or N=O, the substituent is now much more electronegative, it might be expected that **597B** and **620B** would be the dominant tautomers. However, azo- and nitroso-compounds have a very strong tendency to give the hydrazone and oxime tautomers respectively (section C.45), and in practice this leads to a near-cancellation of factors. Typically the order in  $K_T$  appears to be **620C** > **585C** > **597C** though the latter pair show little difference; for example, replacement of X = CH by X = N in (**1548**, R = Ph) reduces  $\log K_T$  from *ca.* 0.6 to *ca.* 0.1. Other structural factors have predictable effects, with **619** existing as **619B** since **619C** is quinonoid and typically disfavoured by  $\Delta \log K$  -1.8 (Appendix 5). In all known cases the behaviour of the compound series **585** and **597** is so closely parallel that a tautomeric preference known for one can plausibly be assumed for the other. It is possible that  $K_T$  for **620** is appreciably greater, given that **630** exists as **630C** for example, but the available evidence is insufficient to establish even a tentative quantitative ranking. However the oxime tautomer can almost always be assumed; the few known exceptions, all atypical in structure, are listed in section A.10.20.

#### C.48 Predictive Criteria for Tautomeric Preference

This final section builds on and extends the ‘rules’ set out in section A.12, now extended to part B as well, which attempt to provide a rapid way of assessing the relative probability of rival tautomers *in water* when the position is unknown. They will not always work and are sometimes in conflict, in which case the best course is to find out, *via* the Tautomer Compound Index, what is known concerning compounds of similar structure. Examples, usually simple ones, are given to illustrate each ‘rule’ along with warnings, where necessary, concerning hidden traps. References are omitted in the interests of concision but are readily located in the main text.

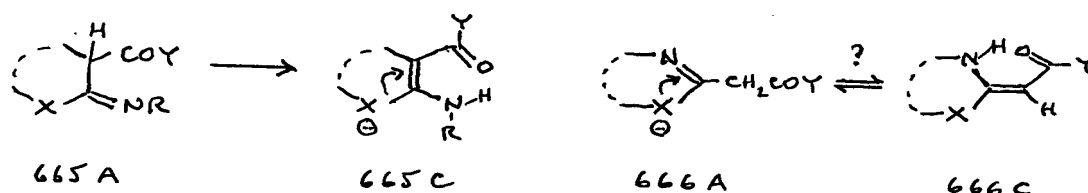


**RULE 1:** Where alternative conjugated systems are possible, the preferred tautomer will be that which combines the better  $\pi$ -donor with the stronger  $\pi$ -acceptor (in general  $\text{NH} > \text{OH}$  and  $\text{C=O} > \text{C=N}$  respectively).

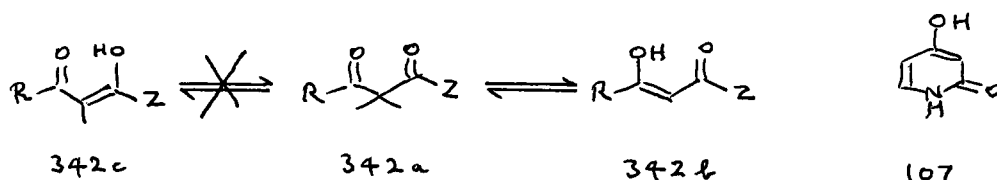
**CODICIL 1:** Any factor which increases the electron donor strength of the first or acceptor ability of the second will increase the bias towards this preferred tautomer, and vice versa. Similarly, electronegative substituents in aromatic rings and other conjugated systems will tend to diminish the preference for oxo- (or thiono-) tautomers.

**CODICIL 2:** There is a strong though not invariable tendency for tautomerically favoured part-structures to be preserved inside a larger conjugated system (e.g. the predominant tautomer of cytosine **1255** is not **1255B** but **1255C**, which preserves the part-structure of **435C**).

**CAVEAT:** See rules 4 and 10 for further considerations that can modify or even reverse the above conclusions.

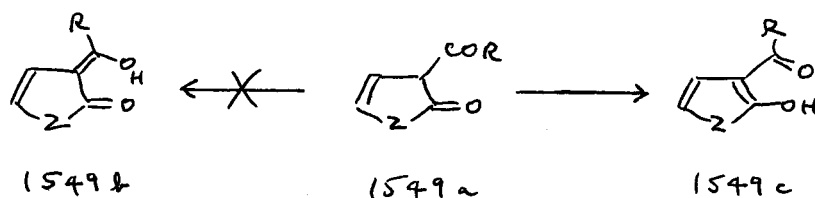


**RULE 2:** Whereas in the absence of steric hindrance a second  $\pi$ -acceptor will increase the tautomeric bias as set out in Rule 1, a second  $\pi$ -donor may not, since conjugation with  $\text{C=N}$  when present is potentially competitive and may be preferred (e.g. in **665** and **666** the  $\pi$ -donor X will mostly stabilise the C- and A-tautomers respectively, with an outcome that is uncertain in the latter case).

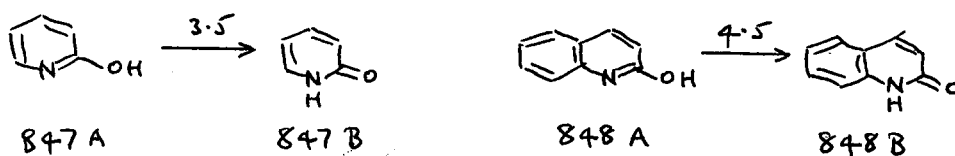


**RULE 3:** *If alternative modes of tautomerisation exist, enolisation will always take place in a direction that avoids disrupting prior conjugation (e.g. **342c** is disallowed if Z is a  $\pi$ -donor. Furthermore this conclusion mostly extends to aromatic systems for which it is not self-evident, e.g. in the preference for **107** over its 2-OH tautomer).*

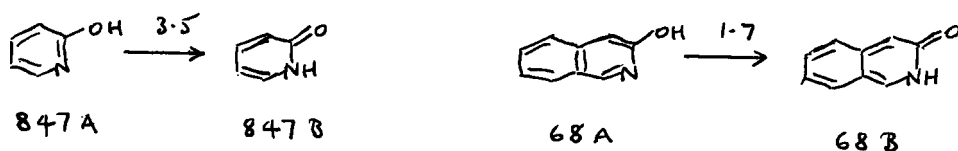
**CODICIL:** *Enolisation may be suppressed if the strength of prior conjugation is great enough (e.g. if R as well as Z is a  $\pi$ -donor, perceptible enolisation of **342a** will not take place).*



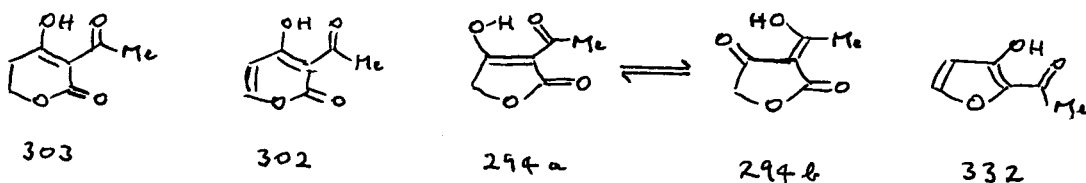
**RULE 4:** *In aromatic structures such as (**1549**, Z = O, S or NR), aromaticity competes strongly and often decisively with other forms of conjugation. (If **1549a** enolises, it will give **1549c** not **1549b** since **1549c** is aromatic).*



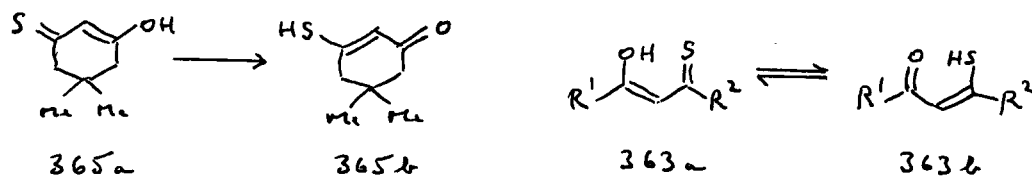
**RULE 5:** *However, the effect of Rule 4 is somewhat attenuated on benzofusion, since all aromaticity is not then lost (compare e.g.  $\log K_T$  for **847** and **848**).*



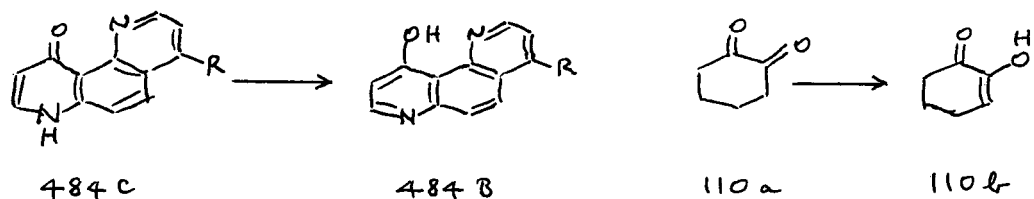
RULE 6: *Quinonoid tautomers are strongly disfavoured relative to a benzenoid tautomer if available (a penalty of  $\Delta \log K$  ca. 1.8 relative to benzenoid ring fusion appears to be nearly a constant; vide Appendix 5).*



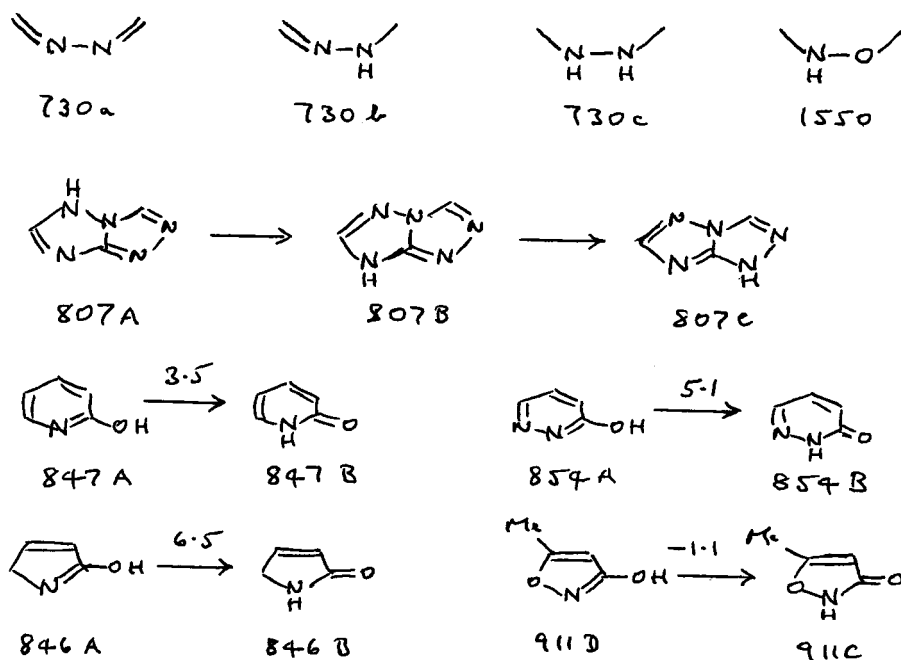
RULE 7: *If alternative enols are finely balanced and one is exo- to a ring, endo-C=C will tend to be preferred for 6-membered and exo-C=C for 5-membered rings. This rule is countermanded by Rule 4, in that endo-C=C is required, and almost always found, when the ring is aromatic. (The upshot is e.g. that 294b is the major tautomer of 294 whereas 303 exists predominantly and the others exclusively as shown).*



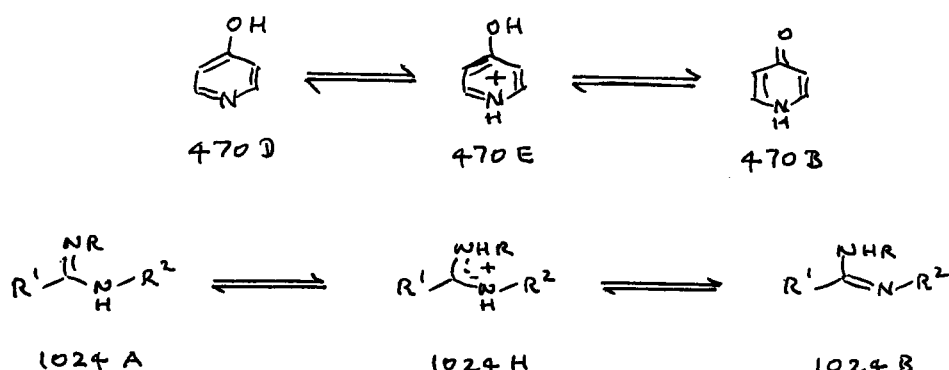
RULE 8: *Intramolecular hydrogen bonding can upset the tautomeric preference otherwise expected on the basis of competitive conjugation (as e.g. in replacing a strong preference for 365b by the even balance shown by 363. A parallel phenomenon is suspected for the corresponding aminoenones, NR in place of S, though if so this is only the attenuation of a very large effect – cf. Rule 1). Note however that aromaticity not an intramolecular bond is the major driving force in cases such as 1549a  $\rightarrow$  1549c (Rule 4), and that *unenforced* bonding on its own is rarely decisive (Appendix 4).*



RULE 9: Where intramolecular hydrogen bonding can replace lone pair repulsion, any induced tautomeric change is likely to be exceptionally large. Many such phenomena supposedly due to hydrogen bonding are probably dominated by this repulsive effect. (This Rule covers rigid structures and its consequences vary with ring size whereas Rule 8 applies to freely rotating compounds in which neither bonding nor repulsion is enforced. In **484**, R = Cl) and **110** the overall shift is estimated as  $\Delta \log K_E$  6.3 and  $> 5$  respectively. Geometry is critical; *vide* Appendix 3).

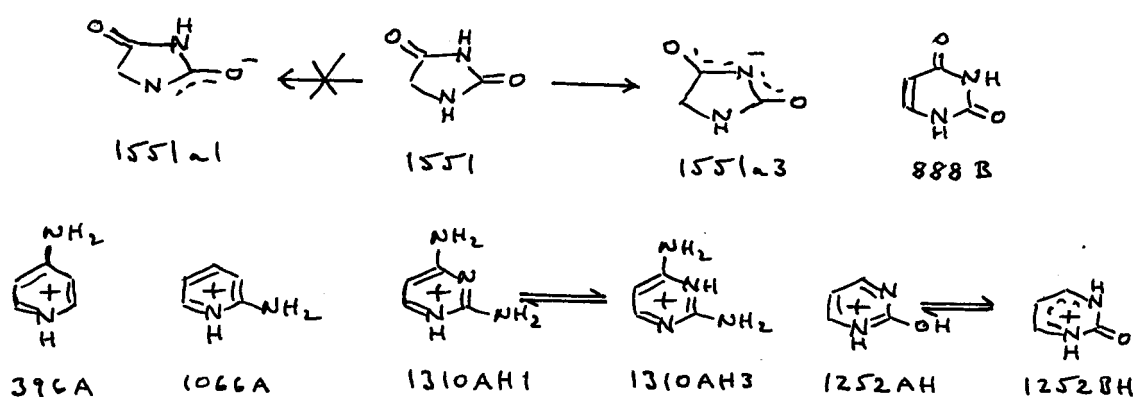


RULE 10: In cyclic structures, adjacent hetero-atoms of the same hybridisation type will be avoided if possible (i.e. **730b** is greatly preferred to **730a** (lone pair repulsion) or **730c** (dipolar repulsion) while **1550** is still more disfavoured than the latter. Lone pair repulsion is present in **807B** and both forms in **807A** so **807C** is preferred, and *e.g.* in **854** where it greatly enhances  $K_T$ . Dipolar repulsion as in **807A**, and *e.g.* in **911** where it is probably responsible for  $\Delta \log K_T$  *ca.* -5 relative to **846** (estimate), can be even more important especially in water and may be positionally independent. Along with Rule 9 it is the subject of Appendix 3.



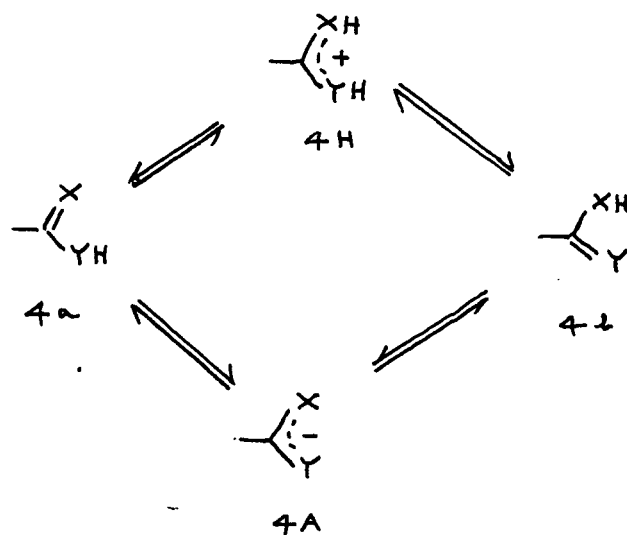
RULE 11: Given a common cation, the favoured tautomer is necessarily the weakest base (or acid) and this can be made quantitative if good models are available. (Note that correction factors may be needed: Appendix 1).

CODICIL: It is frequently possible to make an informed guess as to tautomeric preference by writing the structure of the cation and then removing a proton from the most electronegative hetero-atom. (For **470** and most amides this is clearly O not N; exception: **911** (Rule 10). Amidine cations **1024H** will lose a proton to give **1024A** if R is more electronegative than R<sup>2</sup> or **1024B** if the reverse).



RULE 12: Protonation and deprotonation commonly take place in such a way as to maximise conjugation in the ionised species. (Hydantoin **1551** preferentially deprotonates to give **1551a3** not **1551a1**; for uracil **888B** there is virtually no difference between its two pK<sub>a</sub> values since both anions are conjugated. The cations of **396A** and (**1066A**, R = H) possess pK<sub>a</sub> values of 9.17 and 6.86 respectively so the former is better conjugated and **1310AH1** not **1310AH3** is the cation structure expected for **1310** as is found. 2-Pyrimidone **1252B** protonates to give **1252BH** which is a vinylogous amidine not **1252AH** where the charge is shared with oxygen resulting in a weaker base, so it does not possess a cation in common with the iminol **1252A**).

## APPENDIX 1: Correction Factors for the 'Basicity Method'



If two tautomers **4a** and **4b** share a common cation **4H** or anion **4A**, where in general  $X = \text{NR}$  and  $Y = \text{NR}$ , O or S, the favoured tautomer is *necessarily* the weaker base or weaker acid and  $\log K_T$  may be quantified as the difference between their  $\text{p}K_a$  values (Fig. 1, Introduction). But since neither tautomer is separately isolable, it is generally necessary to seek fixed models for one or both.

$$\log (1 + K_T) = \text{p}K(\text{OMe}) - \text{p}K_t \quad (\text{i})$$

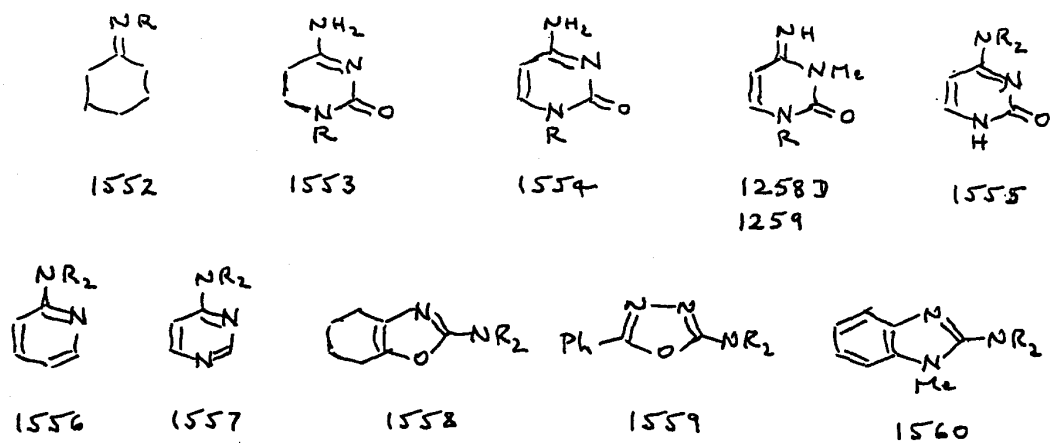
$$\log K_T = \text{p}K(\text{OMe}) - \text{p}K(\text{NMe}) \quad (\text{ii})$$

While unambiguous model anions are rare, fixed model cations are comparatively easy to generate by N-, O- or S-alkylation, generally to give methyl or ethyl derivatives. Use of model compounds for the quantitative estimation of  $K_T$  entails one of two assumptions: either substitution of H by alkyl does not affect  $\text{p}K_a$ , or it affects both  $\text{p}K_a$  values equally. Equations (i) and (ii) represent these two options respectively as they apply to amides and are chosen for illustration ( $K_t$  is  $K_a$  for the tautomeric mixture). Almost all reported quantitative estimations involving model compounds have employed one equation or the other. Yet this approach, which we<sup>22</sup> have designated the 'naive basicity' hypothesis, has been known to be invalid for more than 30 years.<sup>20</sup> The reason lies in cation solvation.

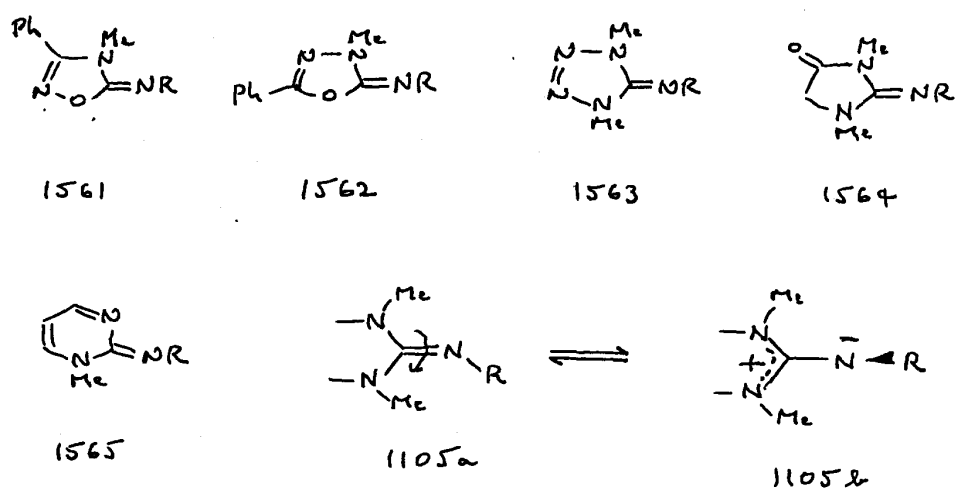
$$\Delta(\text{XR}) = \text{p}K(\text{XH}) - \text{p}K(\text{XR}) \quad (\text{cxviii})$$

We define the correction factor  $\Delta(XR)$  according to eqn. (cxviii). Here  $X = O, S,$  or  $N$  whereas  $R$  is the substituent, always alkyl and usually methyl, which is used to block the tautomeric process. Three main factors determine its sign and magnitude. Since alkyl groups are electron donors,  $\Delta(XR)$  from this cause alone is expected to be negative. Secondly however, since  $XH$  will generally be better solvated than  $XR$ , especially as its cation, a rise in  $pK(XH)$  is expected from this cause which will oppose and may overturn simple electronic expectation. It is important to note, therefore, that a positive  $\Delta(XR)$  must necessarily underestimate the total solvational effect, on the evidence detailed below by perhaps  $\Delta(XR)$  0.1 - 0.3 in the case of  $\Delta(NMe)$ . And thirdly,  $XR$  especially if a ring substituent may undergo steric clashes which, to the extent they occur, are bound to be greater than those for  $XH$ , with an effect on their relative  $pK_a$  values which may be unpredictable.

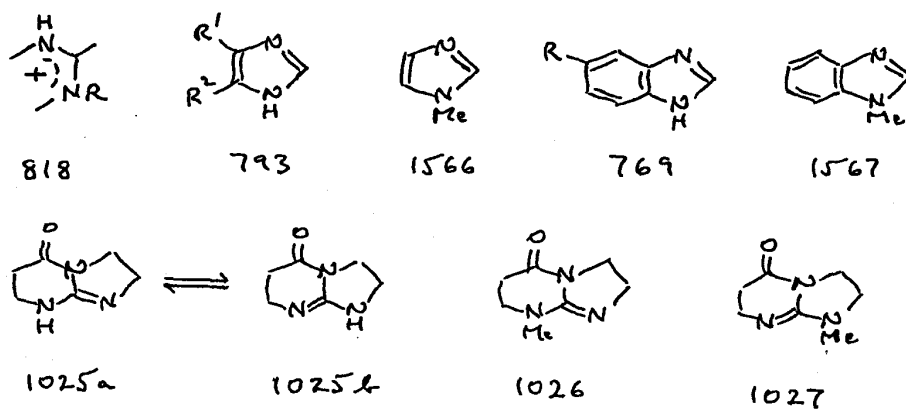
The compounds of Scheme 120 and Table 97 have been chosen to illustrate these points. Simple amines are extremely poor proton donors<sup>72,453</sup> and probably not impressive even as their cations; it is unsurprising that  $\Delta(NMe)$  for (**1552**,  $R = H$  or  $Me$ ) should be negative. The same is true for **1553**, **1554** and **1258D/1259** where  $NR$ , while amidic, does not share the cationic charge and can contribute only indirectly to it. In **1555** however the substituent  $NR_2$  is part of an acylamidine unit which is likely, if  $NH_2$ , to be a strong proton donor, and here  $\Delta(NMe)$  is positive. The remainder are aminoheterocycles in which high electron demand on the substituent  $NR_2$  is likely to be balanced, in its effect on  $\Delta(NMe)$ , by an intermediate degree of proton donor ability:<sup>72</sup> for most the result is a small negative value of  $\Delta(NMe)$  though in **1557**, where two aza-nitrogen atoms are present in the ring, electron demand appears to be exceptionally high. The very different behaviour of **1560** relative to **1558**, **1559** and similar compounds (see listed references) is probably a steric effect: ring  $NMe$  destroys planarity for (**1560**,  $R = Me$ ) so that  $pK(NMe)$  is differentially lowered. We also note here an important steric phenomenon that has hitherto escaped attention. Scheme 121 and Table 98 set out five pairs of compounds for which *N*-methylation produces a remarkable *rise* in  $pK_a$ . All are *exo*-imino species and we suspect the cause to lie in severe loss of planarity, as indicated by **1105** (section B.4.5) where in **1105b** the  $NR$  substituent is effectively decoupled, leading to an abnormal ease of protonation (we use the equilibrium sign here since the extent of decoupling is undefined and clearly very variable). It follows that the use of such compounds in estimating  $\log K_T$  is unsound.



Scheme 120



Scheme 121



Scheme 122

**Table 97.  $\Delta(\text{NMe})$  for some Nontautomeric Amines <sup>a</sup>**

Compound <sup>b</sup>	Ref.	p <i>K</i> (NH)	p <i>K</i> (NMe)	$\Delta(\text{NMe})$
<b>1552</b>	149	9.15	9.43	-0.28
<b>1553</b>	583	6.3	6.62	-0.30
<b>1554</b>	580a	4.45	4.57	-0.12
<b>1258D/1259</b>	579	8.93	9.23	-0.30
<b>1555</b>	580a	4.45	4.25	0.20
<b>1556</b>	380	6.86	6.99	-0.13
<b>1557</b>	257	5.71	6.35	-0.64
<b>1558</b>	507	5.78	5.90	-0.12
<b>1559</b>	515	1.88	2.02	-0.14
<b>1560</b> <sup>c</sup>	513	7.21	6.76	0.45

<sup>a</sup> Scheme 120. <sup>b</sup> R = H or Me (Scheme 120). <sup>c</sup> In 10% EtOH.

**Table 98.  $\Delta(\text{NMe})$  Values for the Compounds of Scheme 121**

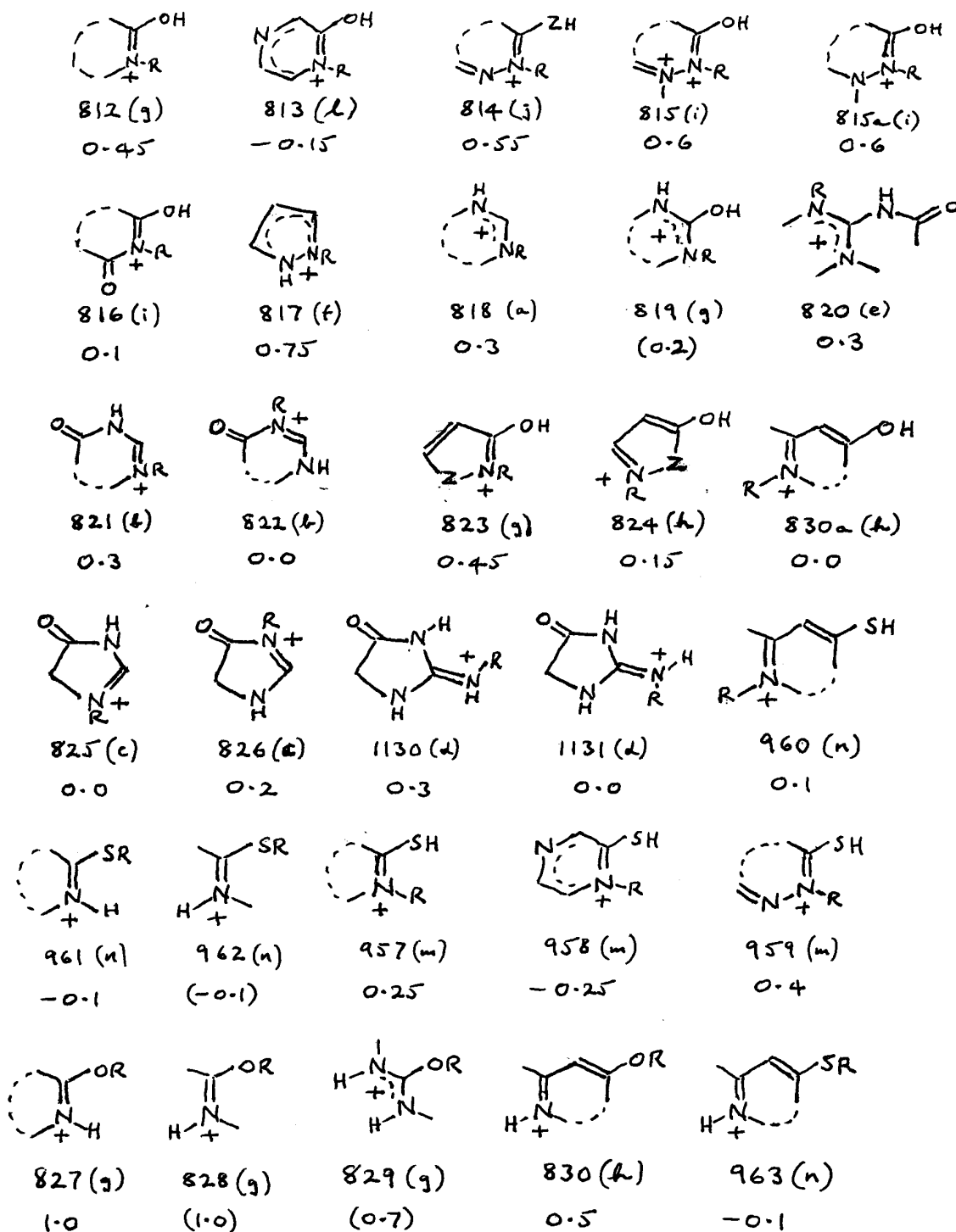
Compound	Ref.	p <i>K</i> (NH)	p <i>K</i> (NMe)	$\Delta(\text{NMe})$
<b>1561</b>	518	5.95	6.43	-0.48
<b>1562</b>	515	6.84	7.48	-0.64
<b>1563</b>	513	8.68	9.57 <sup>a</sup>	-0.89
<b>1564</b>	525	8.07	9.01	-0.94
<b>1565</b>	257	10.75	11.69 <sup>b</sup>	-0.94

<sup>a</sup> Ref. 520. <sup>b</sup> Ref. 598.

**Table 99.  $\Delta(\text{NMe})$  Values for Simple Amidines (818, Scheme 123)**

Compound	p <i>K</i> (NH)	Ref.	p <i>K</i> (NMe)	Ref.	$\Delta(\text{NMe})$
<b>793</b> , R <sup>1</sup> = R <sup>2</sup> = H	7.38 <sup>a,b,c</sup>	380	7.05 <sup>c,d,e</sup>	380	0.33
<b>769</b> , R = H	5.83 <sup>a,c</sup>	500	5.54 <sup>c,f</sup>	380	0.29
<b>1025</b>	8.36	158	8.14 <sup>g</sup>	158	0.36 <sup>i</sup>
			8.56 <sup>h</sup>	158	“ <sup>i</sup>

<sup>a</sup> Statistically corrected. <sup>b</sup> Mean of two values. <sup>c</sup> At 25°C. <sup>d</sup> Cpd. **1566**. <sup>e</sup> Mean of three values. <sup>f</sup> Cpd. **1567**. <sup>g</sup> Cpd. **1026**. <sup>h</sup> Cpd. **1027**. <sup>i</sup> These provide a *single* value (see the text).



Scheme 123

$\Delta pK_a$  values ( $XR \rightarrow XH$ ) to  $\pm 0.05$  for compounds in which  $X = N, O$  or  $S$ . Here  $R$  is a small alkyl group, generally methyl, and  $Z = O, S$  or  $NR$ . Values appear below the structure number, e.g. **812**, and letters in brackets refer to the sub-section in which this value is discussed.

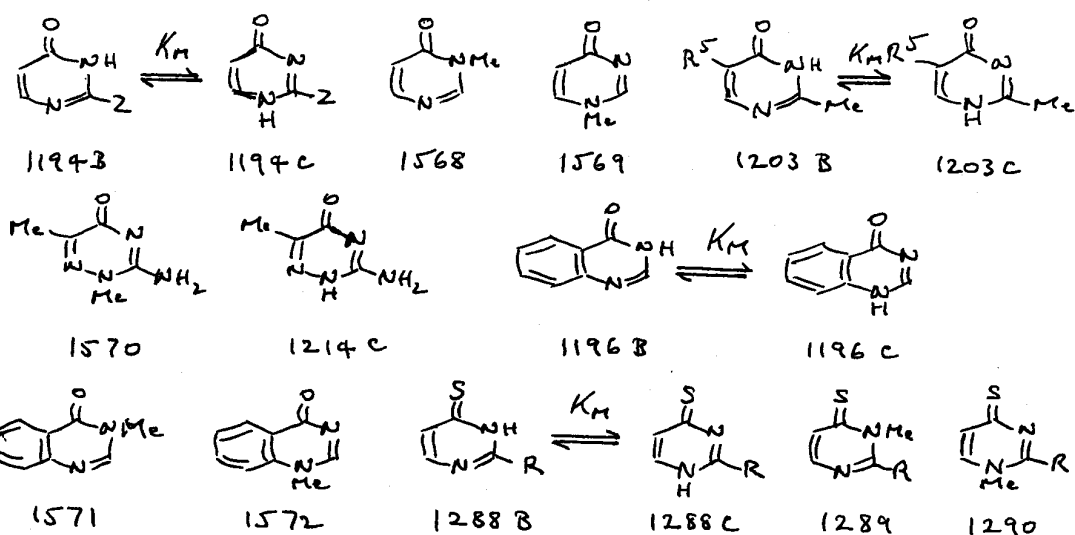
Scheme 123 summarises the correction factors we have derived. They are collated from Scheme 30, section B.2.1; Scheme 39, section B.3.1; Scheme 46, section B.5.5; with some further data from sections B.4.1 and A.10.3. These factors vary greatly in the weight that can be attached to them, sometimes depending on a single piece of information, but taken together they are chemically coherent and all have proved useful, leading to results that appear consistent internally and with one another. They are worth applying even when quite small for the extra coherence, and sometimes elegance, which they bring. We discuss them below in the nearest approach we can find to a logical order.

#### (a) Simple Amidines: 818

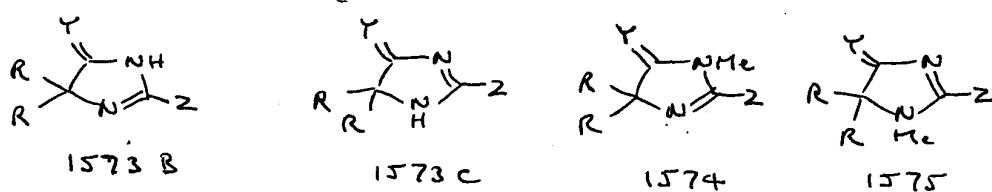
Structures appear in Scheme 122 and data in Table 99. These are sparse but consistent. The results for imidazole (**793**,  $R^1 = R^2 = H$ ) and benzimidazole (**769**,  $R = H$ ) are self-explanatory, those for **1025** (section B.4.1) a little less so. The  $pK_a$  data for the model compounds **1026** and **1027** combine to predict an overall  $pK_a$  8.00 for **1025** where 8.36 is found. (The same data lead to  $\log K_M$  0.4 for **1025b**  $\rightarrow$  **1025a**: section B.4.1). It is not established that **1025a** and **1025b** possess equal  $\Delta(NR)$  values but with their similar geometry there seems no reason to doubt this and this caveat is in any case much less important than the suggestive evidence that  $\Delta(NR)$  may be independent of amidine conformation. From these results we obtain  $\Delta(NR) = 0.33 \pm 0.03$ ,  $n = 3$  (**1025a** and **1025b** cannot be considered as independent entities). Consequently we adopt  $\Delta(NR)$  0.3 for **818** (Scheme 123).

#### (b) *endo*-Acylamidines, Aromatic: 821 and 822

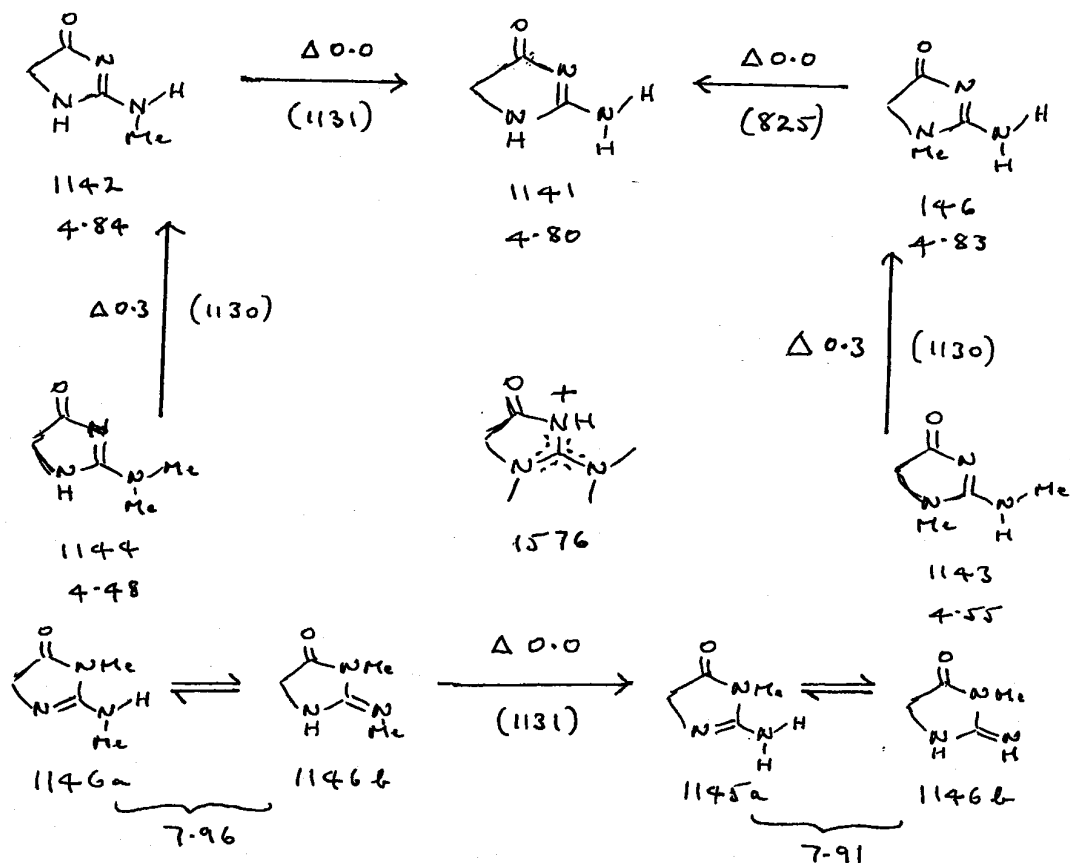
This class (Scheme 124) consists chiefly in 4-pyrimidones and related compounds (sections 13.5.11-13). Annular tautomerism dominates and, for the parent compound (**1194**,  $R = H$ ), Mason<sup>18</sup> collated the results of several teams to arrive at an estimate of 70:30 for the balance between **1194B** and **1194C** in water ( $\log K_M$  *ca.* -0.4; section B.5.11). Table 100 contains all relevant  $pK_a$  data along with calculations of overall  $pK_a$  and tautomeric balance based on putative correction factors. Without these, no calculation is found to be viable. Three give acceptable results; all require  $\Delta(NR)$  0.3 at *N*-1, as for simple amidines **818**, but either  $\Delta(NR)$  0.0 or 0.1 will fit for *N*-3 according to the set of  $pK_a$  values chosen. Further evidence comes from analysis of the  $pK_a$  values chosen by Hirai and co-workers<sup>553</sup> for six pyrimidones of structure **1203** and their *N*- and *O*-methylated models (section



Scheme 124



Scheme 125



Scheme 126

**Table 100. Experimental and Corrected pK<sub>a</sub> Data for the Compounds of Scheme 124**

Cpd.	pK <sub>a</sub>	Cpd.	pK <sub>a</sub>	Cpd.	pK <sub>a</sub>	pK <sub>a</sub> (calc.) <sup>a</sup>	%B
<b>1194</b> , R = H	1.69 <sup>b</sup>	<b>1568</b>	1.84 <sup>c</sup> 1.84 <sup>d</sup> 1.94 <sup>f</sup>	<b>1569</b>	1.8 <sup>c</sup> 2.1 <sup>e</sup> 2.1 <sup>e</sup>	1.52 1.65 1.71	48 65 59
<b>1194</b> , R = H	1.85 <sup>g</sup>	<b>1568</b>	1.84 <sup>c</sup> 1.84 <sup>d</sup> 1.94 <sup>f</sup>	<b>1569</b>	2.02 <sup>h</sup> 2.32 <sup>e</sup> 2.32 <sup>e</sup>	1.62 1.72 1.79	60 75 71
<b>1196</b>	2.12 <sup>g</sup>	<b>1571</b>	2.18 <sup>i</sup>	<b>1572</b>	3.19 <sup>i</sup> 3.49 <sup>e</sup>	2.14 2.17	90 95
<b>1288</b> , R = H	0.68 <sup>i</sup>	<b>1289</b>	0.56 <sup>i</sup>	<b>1290</b>	1.16 <sup>i</sup> 1.46 <sup>e</sup>	0.46 0.51	80 89

<sup>a</sup> Of tautomeric mixture. <sup>b</sup> Ref. 544. <sup>c</sup> Ref. 543. <sup>d</sup> Δ(NR) = 0.0. <sup>e</sup> Δ(NR) = 0.3. <sup>f</sup> Δ(NR) = 0.1. <sup>g</sup> Ref. 4. <sup>h</sup> Ref. 18. <sup>i</sup> Ref. 382a.

**Table 101. Tautomeric Balance and pK<sub>a</sub> Values for the Compounds of Scheme 125**

R	Y	Z	pK <sub>a</sub> ( <b>1573</b> ) <sup>a</sup>	pK <sub>a</sub> ( <b>1574</b> ) <sup>b</sup>	pK <sub>a</sub> ( <b>1575</b> )	pK <sub>a</sub> (calc.) <sup>a</sup>	%B	
							obs.	calc.
<i>c,d</i>	O	H	3.65	3.92	4.21	3.74	65	66
Ph	O	H	2.13	1.92	2.32	1.78		72
<i>c,d</i>	O	SMe	3.04	3.98	3.00	2.96	11 <sup>e</sup>	10
<i>c,f</i>	S	SMe	2.40	3.26	2.48	2.41		14

<sup>a</sup> Of tautomeric mixture. <sup>b</sup> Incorporating Δ(NR) = 0.2 (see the text). <sup>c</sup> *spiro*-cyclohexyl.

<sup>d</sup> Section B.5.10; see Tables 71 and 72. <sup>e</sup> See the text. <sup>f</sup> Section B.6.1

**Table 102. pK<sub>a</sub> Data for Bicyclic Acylguanidines: Scheme 127**

Compound	pK <sub>a</sub> (NH)	pK <sub>a</sub> (NMe)	Δ(NR)	Ref.
<b>1153</b>	3.39	3.16	0.23	106
<b>1135</b>	6.79	6.72	0.07	159
<b>1138</b>	5.80	5.21	0.59	159

B.5.12). If  $\Delta(\text{NR})$  0.3 and 0.0 are employed as above, the observed  $\text{p}K_{\text{a}}$  of the tautomeric mixture is reproduced with an accuracy of  $\Delta\text{p}K_{\text{a}} = 0.00 \pm 0.03$  ( $n = 6$ ) with  $\log K_{\text{M}} -0.33 \pm 0.06$  ( $n = 6$ ), *i.e.*  $68 \pm 3\%$  as the **B**-tautomer (*cf.* 70% for **1194**,  $\text{R} = \text{H}$ ).<sup>18</sup> Other results are sparse but broadly supportive. The triazinone (**1214**,  $\text{R} = \text{Me}$ ) which exists overwhelmingly as the **C**-tautomer (section B.5.13) possesses  $\text{p}K_{\text{a}}$  2.19 as against 1.90 for **1570**, consistently with  $\Delta(\text{NR})$  0.3 for this position. [Note that protonation takes place on the *non-adjacent* imino-nitrogen; contrast the very different  $\Delta(\text{NR})$  value for **817**, case (f) below]. However, there is conflicting evidence concerning N-3. 4-Quinazolone **1196** (section B.5.11) and 4-pyrimidinethione (**1288**,  $\text{R} = \text{H}$ ; section B.6.2) both exist predominantly in the 3*H* form, but while for the first overall  $\text{p}K_{\text{a}} < \text{p}K_{\text{a}}$  **1571** so that  $\Delta(\text{NR})$  appears slightly negative, that for the second is consistent with  $\Delta(\text{NR})$  0.1 (Table 100). Possibly the rules differ for thiones. Leaving aside this caveat (which we ignore for convenience in section B.6.2) we therefore adopt  $\Delta(\text{NR})$  0.3 and 0.0 for **821** and **822** respectively. A possible rationale for such a difference starts from charge asymmetry in the cation: if N-1 which does not possess an electronegative substituent also carries most of the positive charge, its need for solvation will be greater than at N-3. An alternative explanation, which may better fit the results for the following section, is that the lone pair repulsion which must exist in the **C**-tautomer and leads to its preferred Z-conformation whenever free rotation is possible (*cf.* Scheme 43, section B.5) is also relieved by protonation, and acts in this way as a form of internal solvation. Other possible examples of this phenomenon appear elsewhere.

### (c) *endo*-Acylamidines, Alicyclic: **825** and **826**

Data are in practice confined to 5-membered rings and two papers by Edward and co-workers<sup>539,540</sup> (sections B.5.10 and B.6.1). All compounds may be subsumed under structure **1573** (Scheme 125) while data appear in Table 101. Only the first compound allows correction factors to be deduced directly from the data and these comprise  $\Delta(\text{NR})$  0.2 and 0.0 at N-1 and N-3 respectively. However, the remaining results are compatible with these assignments. When the 5-*spiro*cyclohexyl moiety is replaced by diphenyl  $\log K_{\text{M}}$  is scarcely affected: -0.4 in place of -0.3 (the observed  $\text{p}K_{\text{a}}$  value for its tautomeric mixture is irreconcilable on any basis with that calculated from **1574** and **1575**). No UV estimate of tautomeric ratio in water is provided for (**1573**,  $\text{Y} = \text{O}$ ,  $\text{Z} = \text{SMe}$ ) but it is reported as 70% of **1573C** in EtOH, *i.e.*  $\log K_{\text{M}}$  0.4; given  $\Delta \log K_{\text{M}}$  *ca.* 0.65

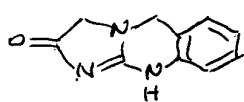
between EtOH and water for the first compound in the set (Table 72), and assuming parallel behaviour, this extrapolates to  $\log K_M$  *ca.* 1.05 where the above values of  $\Delta(\text{NR})$  lead to a predicted value of 1.0. The corresponding thione gives reasonable results on the same basis. These results have helped to build up a coherent picture for the effects of Z in compounds of this type (Scheme 60, section B.8.4) but it must be emphasised that extrapolation to 6-membered rings is hazardous and may be unwarranted.

For **825** and **826** we therefore propose  $\Delta(\text{NR})$  values of 0.0 and 0.2 respectively. Both values differ from those of the preceding section and this calls for rationalisation. As to the second, the greater angle subtended by 3-NH<sup>+</sup> relative to the carbonyl lone pair in 5- than in 6-membered rings may make its solvation less efficient, raising  $\Delta(\text{NR})$  towards that for a simple amidine. Explaining the former difference is much more difficult and we can only propose, rather lamely, that this too is connected with the difference in ring size. Nevertheless, whatever its explanation, it is reflected in the compounds next to be discussed.

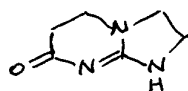
#### (d) Alicyclic Acylguanidines: **1130** and **1131**

These compounds, all of which like the above possess 5-membered rings, are comprehensively discussed in section B.5.7 and the relevant data, from Table 69, are set out schematically in Scheme 126, which gives compound numbers, observed correction factors ( $\Delta$ ), the category (Scheme 123) in brackets to which each NMe  $\rightarrow$  NH change in structure belongs, and our suggested conformation for each. The latter assume (i) that NH will preferentially eclipse C=N because of dipolar attraction, (ii) that this criterion will be over-ridden if a NMe/NMe steric clash would result.

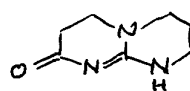
If NH/NMe eclipsing is replaced by NH/NH,  $\Delta(\text{NR})$  is close to zero: category **1131**. This is reflected by  $\Delta(\text{NR})$  0.0 for **825** to which this is symmetrically related (Scheme 126). However, when C=N is eclipsed by NMe  $\rightarrow$  NH the results are at first sight contradictory, with  $\Delta(\text{NR})$  0.3 if this is linked to carbonyl but zero otherwise. The explanation can probably be found in the structure of the *cation* **1576**, in which C=N has become C=NH<sup>+</sup>; as for **826** strong solvation is required when this is adjacent to carbonyl (**1143**  $\rightarrow$  **146**; **1144**  $\rightarrow$  **1142**) but, as in the case of **825**, not otherwise (**1146a**  $\rightarrow$  **1145a**). Hence while both tautomers of **1145** and **1146** behave in a similar way, **1143** and **1144** form a different category.



1153

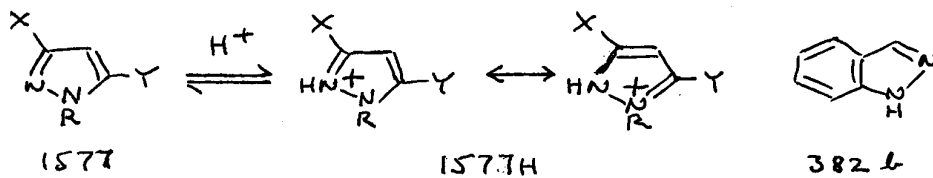


1138

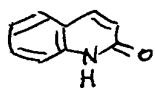
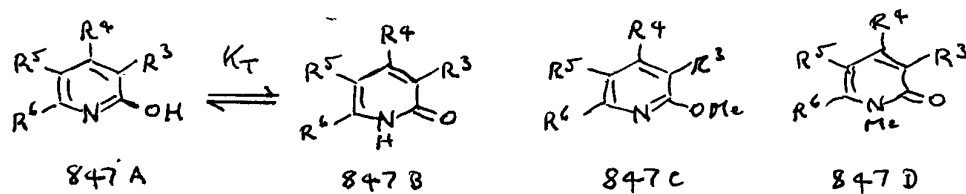


1135

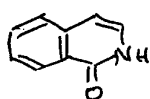
Scheme 127



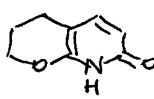
Scheme 128



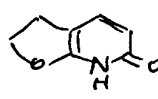
848B



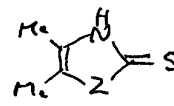
850B



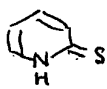
27



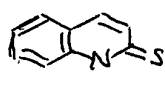
28



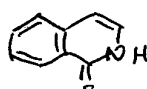
980



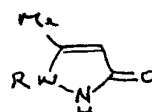
964B



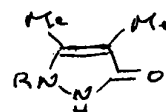
971



972

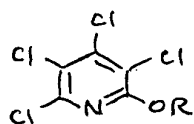


914C

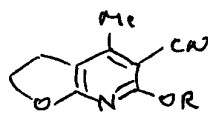


915

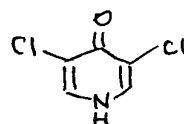
Scheme 129



1578



1579



1580

Scheme 130

**(e) Bicyclic Acylguanidines: 820**

The three compounds of Scheme 127 and their *N*-methyl derivatives (sections B.5.6 and 8.5.7) represent bicyclic equivalents to structure **1130** for which  $\Delta(\text{NR})$  *ca* 0.3 is found (Scheme 126), except that only the acylamidine unit of **1153** is 5-membered. The contrasting behaviour of **1135** and **1138** (Table 102) where this is 6-membered may result in some way from equal and opposite perturbations brought about by 6,6- and 6,5-ring fusion which average out to that of the monocyclic guanidine. For all three combined there results  $\Delta(\text{NR})$   $0.30 \pm 0.22$  which despite its severe scatter is, perhaps fortuitously, as expected. Provisionally we accept this value for **820** but further data would be valuable.

**(f) Cyclic Vinylogous Amidines with Contiguous Nitrogen: 817**

Protonation of these compounds (section A.9.2) leads to symmetrical cations **1577H** in which NH and NR share the positive charge (Scheme 128). Because of this, and the strong dipolar repulsion it generates, solvational requirements are exceptionally large and a high value of  $\Delta(\text{NR})$  is to be expected. Replacement of dipolar *attraction* in the free base by repulsion can only exacerbate this situation. Pyrazole (**1577**, R = X = Y = H) and indazole **382b** are the archetypes. The structure of pyrazole is degenerate so that  $\text{p}K_{\text{a}}$  2.52 requires statistical correction to 2.82 before comparison with  $\text{p}K_{\text{a}}$  2.09 which results from *N*-methylation,<sup>2c</sup> whereas  $\text{p}K_{\text{a}}$  1.04 for indazole may be compared directly with  $\text{p}K_{\text{a}}$  0.30 for its 1-methyl derivative.<sup>243</sup> These comparisons lead to  $\Delta(\text{NR})$  0.73 and 0.74 respectively which we round off to  $\Delta(\text{NR})$  0.75 for **817**.

The same type of cation is formed by compounds such as (**1577**, R = Y = Me, X = OEt) and (**1577**, R = X = Me, Y = OEt) for which we have used this value of  $\Delta(\text{NR})$  to estimate the  $\text{p}K_{\text{a}}$  of their desmethyl derivatives,<sup>21</sup> later extending this to the equivalent indazolones,<sup>22</sup> with results that agree with experiment and have allowed their tautomeric balance to be rationalised (section B.2.10). We therefore believe that this correction is general for compounds of this type. However there is no certainty that it will still apply when *N*-alkyl is replaced by a different heterocyclic substituent and a good deal to suggest it will not; see **(k)** below. It is also inapplicable if nitrogen adjacent to NR either does not share its positive charge, or is quaternary, when  $\Delta(\text{NR})$  is slightly less; *cf.* **815** and **815a**, **(i)** below.

**Table 103.  $\Delta(\text{NMe})$  Corrections for Amides containing Negligible Amounts of the OH Tautomer**

Cpd.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	pK(NH)	pK(NMe)	Ref.	$\Delta(\text{NMe})^a$
<b>847B</b>		H	H	H	H	0.75	0.32	4	0.43
"		H	H	H	OMe	1.14	0.91	210	0.23
"		H	Me	Me	OMe	1.87	1.64	20	0.23
"		H	H	CH <sub>2</sub> SMe	CH <sub>2</sub> SMe	0.76	0.24	432	0.52
"		H	H	CO <sub>2</sub> Et	CO <sub>2</sub> Et	- 1.53	- 2.27	432	0.74
"		H	H		CH <sub>2</sub> OCH <sub>2</sub>	0.50	0.01	432	0.49
"		H	H		CH <sub>2</sub> SCH <sub>2</sub>	0.69	0.26	432	0.43
"		H	H		CH <sub>2</sub> SO <sub>2</sub> CH <sub>2</sub>	- 0.40	- 0.94	432	0.54
"		H	Me		CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> O	1.94	1.65	20	0.29
" <sup>b</sup>		CN	Me		CH <sub>2</sub> CH <sub>2</sub> O	- 1.88	- 2.66	432	0.78
<b>848B</b>						- 0.31	- 0.71	4	0.40
<b>850B</b>						- 1.2	- 1.8	4	0.6
<b>914</b>	H					2.70	2.31	463	0.39
<b>915</b>	H					2.67	2.38	463	0.44
<b>915</b>	Me					2.52	2.05	463	0.47

<sup>a</sup> Mean value  $0.465 \pm 0.154$  ( $n = 15$ ). <sup>b</sup> Contains 4% of OH tautomer.

**Table 104.  $\Delta(\text{NMe})$  Corrections for Thioamides containing Negligible Amounts of the OH Tautomer**

Compound	Z	pK(NH)	pK(NMe)	$\Delta(\text{NMe})^a$
<b>964B</b> <sup>b</sup>		- 1.07	- 1.22	0.15
<b>971</b> <sup>b</sup>		- 1.44	- 1.60	0.16
<b>972</b> <sup>b</sup>		- 1.9	- 2.13	0.23
<b>980</b> <sup>c</sup>	O	- 3.9	- 4.3	0.4
"	S	- 2.8	- 3.0	0.2
"	NH	- 1.2	- 1.4	0.2
"	NMe	- 1.4	- 1.6	0.2

<sup>a</sup> Mean value  $0.22 \pm 0.08$  ( $n = 7$ ). <sup>b</sup> Ref. 381. <sup>c</sup> Ref. 483.

**(g) Correction Factors for Amides: 812, 823 and 827 (828, 829)**

Amides form one of the largest classes of potential tautomer but, since most exist overwhelmingly in the oxo-form, information concerning iminol is hard to come by. Furthermore almost all the data that exist are for aromatic amides (Scheme 128), hence confined to *cis*-amides (lactams); correction factors for open-chain compounds (*trans*-amides) are lacking and inferential arguments have to be employed.

In attempting to derive  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  simultaneously from the limited data at our disposal, we proceed as follows. Firstly, we set a lower limit to the allowable proportion of minor tautomer; with two exceptions to be detailed, we have chosen 5%. Secondly we require some criterion, independent of basicity, by which this proportion may be estimated. In fact UV spectroscopy was used as the method of choice and here we must pay tribute to the meticulous accuracy of these, mostly early, investigators. Their observations establish all  $\text{p}K_{\text{a}}$  values, UV criteria and the 'raw'  $K_{\text{T}}$ . Thirdly we assume that all  $\text{p}K_{\text{a}}$  determinations, whether of model compounds or the tautomeric mixture, are error-free. Clearly there are inherent dangers in this approach but with so few duplicate determinations these can only in part be avoided by treating the results as a statistical assemblage in which outliers are inevitable; nevertheless this is the best we can do.

$$K_{\text{a}} = x_{\text{NH}} K_{\text{NH}} + x_{\text{OH}} K_{\text{OH}} \quad (\text{cxix})$$

Table 103 contains data on 2-pyridones and related compounds from which  $\Delta(\text{NR})$  but not  $\Delta(\text{OR})$  may be deduced, while equivalent data for the thiones of (**m**) below appear in Table 104. These data are useful in that they indicate the range of  $\Delta(\text{NR})$  value likely to be found in tautomeric mixtures. Where sufficient amounts of the minor tautomer is present tautomeric composition as established by UV spectroscopy may be used to factor overall  $K_{\text{a}}$  into  $K_{\text{NH}}$  and  $K_{\text{OH}}$  according to eqn. (cxix), where  $x_{\text{NH}}$  and  $x_{\text{OH}}$  are mole fractions ( $x_{\text{NH}} + x_{\text{OH}} = 1.0$ ); comparison of  $\text{p}K(\text{NH})$  with  $\text{p}K(\text{NMe})$  and of  $\text{p}K(\text{OH})$  with  $\text{p}K(\text{OMe})$  gives  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  respectively (Table 105). The five results for  $\Delta(\text{NR})$  average at  $0.38 \pm 0.14$  compared to  $0.465 \pm 0.154$  ( $n = 15$ ) for the compounds of Table 103; all combined give  $\Delta(\text{NR})$   $0.453 \pm 0.154$  ( $n = 19$ ); *n.b.* that **27** belongs to each set. We therefore accept  $\Delta(\text{NR})$  0.45 for **812** and **823**, *i.e.* 5-membered as well as 6-membered rings. Because of the difference in geometry it is impossible to say whether this value should apply to *trans*-amides as well;  $\text{p}K_{\text{a}}$  values of -0.56 and -0.21 for *N*-methyl- and *N,N*-dimethyl acetamide<sup>435</sup> do not settle the issue since the latter may be distorted by a Me/Me eclipsing steric clash.

**Table 105. Simultaneous Estimation of  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  for Amides**

Cpd.	R	R <sup>6</sup>	%[OH] <sup>a</sup>	pK <sub>a</sub>	pK(NMe)	pK(NH) <sup>b</sup>	$\Delta(\text{NMe})^c$	pK(OMe)	pK(OH) <sup>d</sup>	$\Delta(\text{OMe})^e$
<b>847B</b> <sup>f,g</sup>		Cl	5	- 0.18	- 0.33	- 0.16	0.17	- 0.13	1.22	1.25
“ <sup>h</sup>		OMe	5	1.14		1.16		1.60	2.44	0.84
“ <sup>i,j</sup>		OMe	1.67 <sup>k</sup>	1.87		1.88		2.85	3.63	0.78
<b>27</b> <sup>i</sup>			0.71 <sup>l</sup>	1.94	1.65	1.94	0.29	3.04	4.09	1.05
<b>28</b> <sup>i</sup>			12	1.95	1.52	2.01	0.49	1.85	2.87	1.02
<b>914</b> <sup>m</sup>	Me		30	2.60	2.22	2.76	0.54	2.05	3.12	1.07
<b>914</b> <sup>m</sup>	Ph		50	1.79	1.66	2.09	0.43	1.17	2.09	0.92

<sup>a</sup> UV estimate. <sup>b</sup> Factored from pK<sub>a</sub> and %[NH]. <sup>c</sup> Incorporation of the results from Table 97 leads to  $\Delta(\text{NMe}) = 0.453 \pm 0.154$  ( $n = 19$ ). <sup>d</sup> Factored from pK<sub>a</sub> and %[OH].

<sup>e</sup>  $\Delta(\text{OMe}) = 0.99 \pm 0.15$  ( $n = 7$ ) or  $1.02 \pm 0.14$  ( $n = 5$ ); see the text. <sup>f</sup> Also listed as **831B**. <sup>g</sup> Ref. 294.

<sup>h</sup> Ref. 210. <sup>i</sup> Ref. 20. <sup>j</sup> 4,5-Dimethyl derivative. <sup>k</sup> Based on authors' estimate that  $K_T$  increases by a factor of 3 on dimethylation (ref. 20). <sup>l</sup> Authors estimate  $K_T = 140 \pm 30$  (ref. 20). <sup>m</sup> Ref. 462.

**Table 106. Simultaneous Estimation of  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  for Vinylogous Amides**

Cpd.	%[OH] <sup>a</sup>	pK <sub>a</sub>	pK(NMe)	pK(NH) <sup>b</sup>	$\Delta(\text{NMe})$	pK(OMe)	pK(OH) <sup>c</sup>	$\Delta(\text{OMe})^d$
<b>470</b> <sup>e,f</sup>	40	2.07	2.27	2.29	0.02	1.93	2.47	0.54
<b>470</b> <sup>f,g</sup>	100	- 1.15				- 1.36	- 1.15	0.21
<b>470</b> <sup>h,i</sup>	20	- 2.11	- 2.06	- 2.01	0.05	- 2.06	- 1.41	0.65
<b>470</b> <sup>f,j</sup>	100	- 4.1				- 4.5 <sup>k</sup>	- 4.1	0.4 <sup>d</sup>
<b>470</b> <sup>i,l</sup>	72	0.50	1.29	1.06	- 0.23 <sup>m</sup>	0.18	0.64	0.48
<b>434</b> <sup>n</sup>	> 95 <sup>o</sup>	- 0.45				- 0.71 <sup>p</sup>	- 0.15 <sup>q</sup>	0.56

<sup>a</sup> UV estimate. <sup>b</sup> Factored from pK<sub>a</sub> and %[NH]. <sup>c</sup> Factored from pK<sub>a</sub> and %[OH].

<sup>d</sup> See the text. <sup>e</sup> R<sup>3</sup> = R<sup>5</sup> = R<sup>6</sup> = H, R<sup>2</sup> = Cl. <sup>f</sup> Ref. 294. <sup>g</sup> R<sup>3</sup> = R<sup>5</sup> = H, R<sup>2</sup> = R<sup>6</sup> = Cl.

<sup>h</sup> R<sup>6</sup> = H, R<sup>2</sup> = R<sup>3</sup> = R<sup>5</sup> = Cl. <sup>i</sup> Ref. 290. <sup>j</sup> R<sup>2</sup> = R<sup>3</sup> = R<sup>5</sup> = R<sup>6</sup> = Cl. <sup>k</sup> R = Et.

<sup>l</sup> R<sup>3</sup> = R<sup>5</sup> = H, R<sup>2</sup> = R<sup>6</sup> = CO<sub>2</sub>Me. <sup>m</sup> Possibly distorted by intramolecular hydrogen bonding.

<sup>n</sup> Ref. 278. <sup>o</sup> Above 95% enolised as the neutral species, the rest as the 1,3-diketone tautomer.

<sup>p</sup> Mean of R = Me, pK<sub>a</sub> -0.73, and R = Et, pK<sub>a</sub> -0.69. <sup>q</sup> After statistical correction.

Those compounds that meet the criterion of  $x_{\text{OH}} \geq 0.05$  average to give  $\Delta(\text{OR}) 1.02 \pm 0.14$  ( $n = 5$ ). Two others, for one of which (**27**)  $\Delta(\text{NR})$  also appears in Table 103, possess much less iminol than this but its proportion was deduced by the authors<sup>20</sup> on what appears good evidence; added in, these result in  $\Delta(\text{OR}) 0.99 \pm 0.15$  ( $n = 7$ ). Either value is indistinguishable from that suggested by Spinner and Yeoh<sup>20</sup> in 1971. We accept  $\Delta(\text{OR}) 1.0$  at least for lactams **827**. In fact there is no good reason why this or a very similar value should not apply to *trans*-amides, since by concentrating the charge on nitrogen, protonation at carbonyl will help to blur the difference in geometry; compare **828** with **827** (Scheme 123). Carbonyl protonation of open-chain ureas gives **829** on whose  $\Delta(\text{OR})$  value we have no evidence but with the positive charge effectively spread across an amidine unit it seems likely that  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  will both be reduced; our guesses for **819** and **829** appear in Scheme 123. The unchanged values of  $\Delta(\text{NR})$  and  $\Delta(\text{OR})$  found for **914** and **915** despite the switch from carbon to NR as nearest neighbour to amide nitrogen suggests that these correction factors are quite robust and not easily perturbed by structural change. While certain of these do affect  $\Delta(\text{NR})$  – see (i) and (j) below in particular – we think that the relative remoteness of carbonyl from the point at which these happen (with the possible exception of **829**, above) means that  $\Delta(\text{OR})$  is less likely to be affected. In the absence of information on 6-membered oxoheterocycles other than the pyridones, this assumption has had to be adopted *faute de mieux* (cf. section B.2.5).

We have left out of consideration the  $\Delta(\text{OR})$  values of 0.52 for **1578**<sup>294</sup> and 1.89 for **1579**<sup>432</sup> (Scheme 130). These molecules are very crowded and distortions from planarity of OR or OH, especially if they differ, may plausibly explain such highly abnormal results. Since NH and (in general) NR cannot rotate out of plane it should be much more difficult to distort  $\Delta(\text{NR})$  in this way but the abnormally low  $\Delta(\text{NMe})$  value for 6-chloropyrid-2-one (**847**,  $\text{R}^6 = \text{Cl}$ ; Table 105) may arise from this cause. Similar problems can occur with 4-pyridones, cf. (h) below.

#### (h) Correction Factors for Vinylogous Amides: **830a**, **824**, and **830**

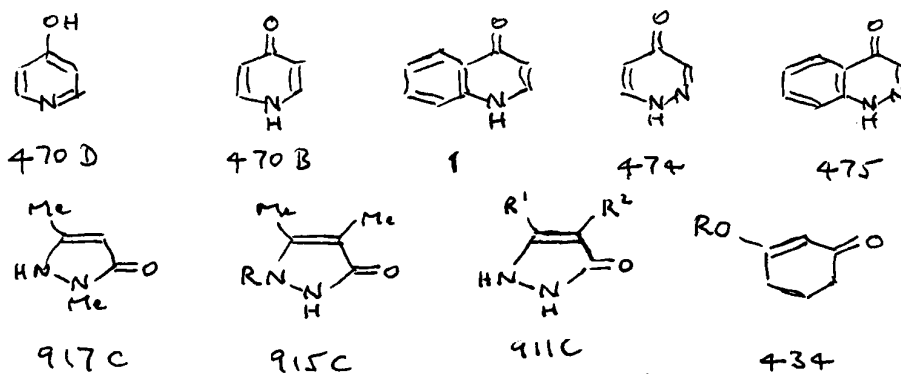
Correction factors for vinylogous amides may be derived in the same way as those for amides, (g) above. With a much smaller data base there are fewer compounds to work with but the quality of the data largely compensates for this; the five such compounds from which we derive  $\Delta(\text{OR})$  contain 20 - 100% of the OH tautomer (Table 106; contrast Table 105). The

relevant compounds appear in Scheme 131 and have been collated from sections A.10.3 (**434**), A.10.7 (**1**, **474**, **475**) and B.2.10 (**917C**, **915C**, **911C**:  $R^1 = R^2 = \text{Me}$ ) with the remainder, all 4-pyridones **470**, from section A.10.6.

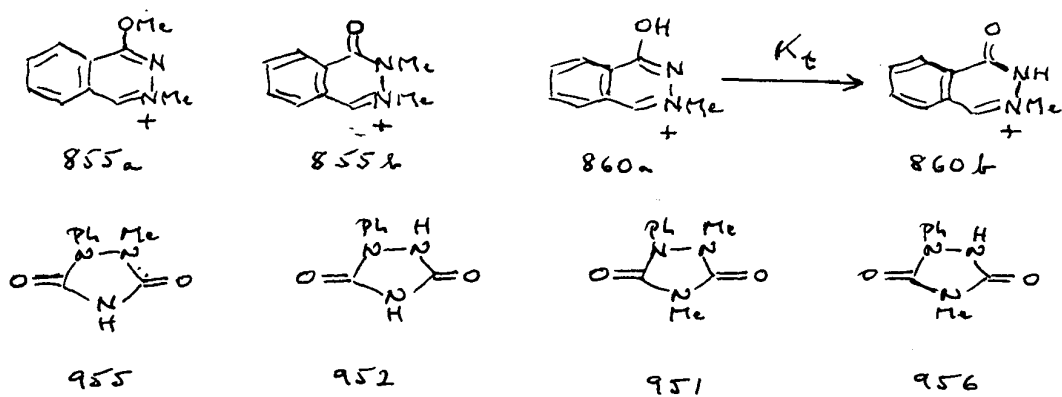
The first six  $\Delta(\text{NMe})$  values of Table 107, and two of the three in Table 106, average to give  $\Delta(\text{NR}) -0.01 \pm 0.09$  ( $n = 8$ ). The exception is  $-0.23$  for a compound in which NH is flanked by two ester groups so that an intramolecular hydrogen bond is more or less inevitable. By contrast,  $\Delta(\text{OR})$  for this compound is normal (Table 106). Accordingly we accept  $\Delta(\text{NR}) 0.0$  for **830a**. This very low value implies poor proton donor abilities for typical NH in vinylogous amides, as is consistent with other evidence (section A.10.10).

The last three compounds (four entries) of Table 107 clearly possess a different  $\Delta(\text{NMe})$  value to match the difference in structure:  $0.16 \pm 0.02$  ( $n = 4$ ). These are still vinylogous amides but contain NR flanked by amide nitrogen, and in a 5-membered ring. Either difference or both may be responsible. We propose  $\Delta(\text{NR}) 0.15$  for **824**. By contrast  $\Delta(\text{NR})$  for **823**, whose *amide* nitrogen is linked to *amine*, the complementary situation, is indistinguishable from that of a simple lactam **812**, *cf.* (**g**) above.

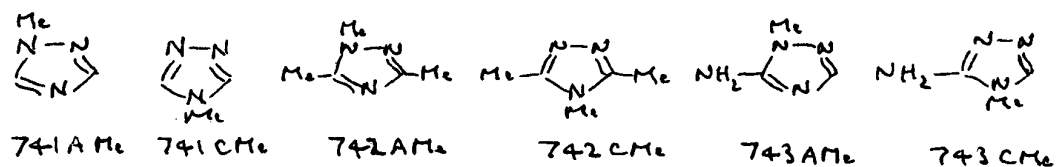
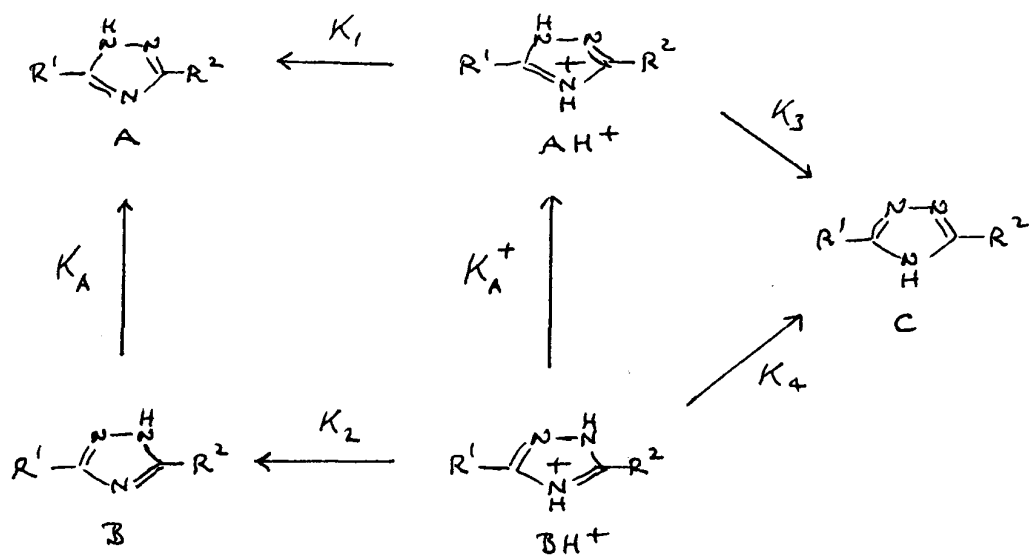
As well as pyridones we incorporate into Table 106 the enolised  $\beta$ -diketone **434** (section A.10.3), which possesses a  $\Delta(\text{OR})$  value within their range. Without it, we have  $0.46 \pm 0.16$  ( $n = 5$ ); with its incorporation, this becomes  $0.47 \pm 0.14$  ( $n = 6$ ); if the data involving  $\text{p}K_a < -4$  are eliminated as too coarse for use in this context, there results  $0.49 \pm 0.15$  ( $n = 5$ ). We accept the last estimate as most probably correct, *i.e.*  $\Delta(\text{OR}) 0.5$ . The result for **434**, a compound containing no nitrogen, helps to provide a rationale for the difference of this value from that for an amide, as essentially a function of *distance*: the charge is much better spread when a longer chain of atoms is involved, resulting in a sharp drop in charge density. The nature of the atoms bearing the charge appears to be of secondary importance. We therefore suspect that, except perhaps for ureas **829**, only these two values of  $\Delta(\text{OR})$  will turn out to be necessary. Ring nitrogen possesses many more structural variants than a carbonyl group so the way in which Scheme 123 is dominated by  $\Delta(\text{NR})$  is unsurprising.



Scheme 131



Scheme 132



Scheme 27

A 12% enol content is claimed on UV evidence<sup>294</sup> for **1580** (Scheme 130) and if so this compound would valuably add to the data of Table 106. However, given  $pK_a$  1.14 for its 4-methoxy derivative alongside an overall  $pK_a$  -1.07<sup>294</sup> this would imply  $\Delta(OR)$  -1.29, an impossible value; accordingly **1580** (as **470B**,  $R^3 = R^5 = Cl$ ) appears instead as an entry in Table 107. In fact **1580** is one of the compounds we have used in deriving an equation for  $\log K_T$  in 3-substituted 4-pyridones (section A.10.6), a very shallow relationship<sup>290</sup> which predicts  $\log K_T$  *ca.* 2.9 for this compound, *i.e.* a negligible OH content.

**(i)  $\Delta(NR)$  Values for *N*-linked Amides, **815** and **815a**, and Imides, **816****

4-Phthalazinone **855** (Scheme 132 and section B.2.5) protonates preferentially on aza-nitrogen, not carbonyl, so that determination of its  $K_T$  value requires a two-stage process starting from the dication.<sup>449</sup> Alternative deprotonation pathways from its 1-methyl cation lead to **860a** and **860b** (Scheme 132) with  $\log K_t$  *ca.* 0.7 on UV evidence.<sup>449</sup> However the *O*-methyl and *N*-methyl models for this process, **855a** and **855b**, possess  $pK_a$  values of -8.19 and -8.52 respectively,<sup>392a</sup> so correction factors are needed. If the usual amidic  $\Delta(OR)$  correction **827** applies to **855a**,  $pK_a$  *ca.* -7.2 is predicted for **860a**, so that  $pK_a$  *ca.* -7.9 is then required for **860b** to result in  $\log K_t = 0.7$ . On this evidence we require  $\Delta(NR)$  *ca.* 0.6 for **815**, amide nitrogen adjacent to a pre-existing positive charge. No other evidence presently exists to check this, but its half-way position between 0.45 for a simple amide (**812**) and 0.75 for (**817**) with its extreme solvational requirements is reassuring.

A similar value of  $\Delta(NR)$  is found when two amide groups are attached *via* nitrogen. Here there is just one set of examples, two pairs of triazolediones studied by Katritzky and Popp<sup>477</sup> (Scheme 132). These take the tautomeric form shown and protonate preferentially on the more basic carbonyl, *i.e.* that next to NMe. From  $pK_a$  -4.7 and -4.1 for **955** and **952** respectively, and -4.8 and -4.2 for **951** and **956**, there follows  $\Delta(NR)$  0.6 as a crude but useful estimate for **815a** (contrast **823**). These apparently identical values of  $\Delta(NR)$  for **815** and **815a** lie half way between **812** for a simple lactam and **817** for the pyrazole cation with its exceptional solvational requirements, not an unreasonable situation.

The same set of data suggests  $\Delta(NR)$  *ca.* 0.1 for imide NH, **816**. Such a small value may result from the repulsion of water's oxygen atoms by both carbonyl groups, resulting in much reduced solvation of NH so only a slight penalty for its replacement by NR. Again, we have not encountered other examples.

(j)  $\Delta(\text{NR})$  Values for Conjugated NH Adjacent to  $\text{sp}^2$ -Nitrogen: **814**

Because of the complications which attach to the tautomeric behaviour of 4-phthalazinone **855** (section B.2.5), one of which appears in (i) above, we think it unsafe to use the related 3-pyridazinone **854** or 3-cinnolinone **859** to deduce a  $\Delta(\text{NR})$  value (Scheme 123) for (**814**,  $\text{Z} = \text{OH}$ ). Bearing in mind however the relatively narrow range in  $\Delta(\text{NR})$  for other types of amide, 0.45 - 0.6, it seems unlikely that the above class would fall outside it. We find in fact that  $\Delta(\text{NR})$  for another sort of conjugated NH adjacent to  $\text{sp}^2$ -nitrogen, the 1(3)*H*-tautomer **741A/B** of *s*-triazole **741**, is quite closely fitted as demonstrated below. Interestingly, the *mean*  $\Delta(\text{NR})$  for **855** and **856**, despite our reservations, gives this same value (Table 109).

$$K_a = K_1 K_{\text{A}^+} + K_2 + K' (K_{\text{A}^+} + 1) \quad (\text{liii})$$

$$K' = K_3 K_4 / (K_3 + K_4) \quad (\text{liv})$$

$$K_{\text{T}} = (K_1 K_{\text{A}^+} + K_2) / K' (K_{\text{A}^+} + 1) \quad (\text{lv})$$

$$K_a = 2K_1 + K_3 \quad (\text{lvi})$$

$$K_3 = 2K' \quad (\text{lvii})$$

$$K_{\text{T}} = 2K_1 / K_3 \quad (\text{lviii})$$

Scheme 27, which we reproduce from section B.1.2, describes the form which this tautomerism takes. The key equations are (liii) - (lv); if  $\text{R}^1 = \text{R}^2$  these collapse to eqns. (lvi) - (lviii). In the latter case the  $\text{p}K_{\text{a}}$  values of **741AMe** and **741CMe**, and of **742AMe** and **742CMe**, provide in principle sufficient information to solve the equations for **741** and **742** respectively. From section B.1.2 we reproduce Table 51 which contains the requisite  $\text{p}K_{\text{a}}$  data and calculated  $K_{\text{T}}$  values. Here we find that if  $\Delta(\text{NR})$  0.3 is employed for the **C**-tautomer, *i.e.* the standard amidine value [(a) above], an enhanced value is required for the **A**-tautomer, *i.e.* the process  $\text{p}K_{1\text{Me}} \rightarrow \text{p}K_1$  (Table 51). Here  $\text{NR}(\text{NH})$  is positioned between  $\text{N}=\text{C}$  and  $\text{C}=\text{N}$ , somewhat as in **815** derived from **855** (above) in which  $\text{C}=\text{O}$  takes the place of  $\text{C}=\text{N}$ , and resulting in a similar enhancement in  $\Delta(\text{NR})$ . For **742** and one set of data for **741** agreement is highly satisfactory; in the other, an anomalously low value for  $\text{p}K_{1\text{Me}}$  results in a failure to reproduce the observed  $\text{p}K_{\text{a}}$ . Use of the uncorrected model  $\text{p}K_{\text{a}}$  data leads to predicted  $K_{\text{T}}$  values of 7.8 and 8.9 respectively, with predicted overall  $\text{p}K_{\text{a}}$  values of 1.70 and 3.34. For *s*-triazole itself, a split between **741A** and **741C** of 80:20 is generally accepted.

**Table 107.  $\Delta(\text{NMe})$  Corrections for Vinylogous Amides containing Negligible Amounts of the OH Tautomer**

Cpd.	R	R <sup>2</sup>	R <sup>3</sup>	R <sup>5</sup>	R <sup>6</sup>	p <i>K</i> (NH)	p <i>K</i> (NMe)	$\Delta(\text{NMe})$	Ref.
<b>470B</b>		H	H	H	H	3.27	3.33	- 0.06	4
“		H	Cl	Cl	H	- 1.07	- 1.22	0.15	4
“		H	NO <sub>2</sub>	NO <sub>2</sub>	H	- 5.27	- 5.25	- 0.02	294
<b>1</b>						2.27	2.46	- 0.19	4
<b>474</b>						1.07	1.02 <sup>a</sup>	0.05	4
<b>475</b>						- 0.35	- 0.29 <sup>b</sup>	- 0.06	4
<b>917C</b> <sup>c</sup>						2.35	2.22	0.13	462
						2.31	2.14	0.17	463
<b>915C</b> <sup>c</sup>	Me					2.23	2.05	0.18	463
<b>911C</b> <sup>c, d</sup>						2.67	2.52	0.15	463

<sup>a</sup> Ref. 382a. <sup>b</sup> Ref. 597. <sup>c</sup> p*K*(NMe) is that of the 1-methylated species. <sup>d</sup> R<sup>1</sup> = R<sup>2</sup> = Me.

**Table 51. p*K*<sub>a</sub> Data and Calculated *K*<sub>T</sub> Values for Symmetrically Substituted *s*-Triazoles <sup>a</sup>**

Cpd.	Ref.	p <i>K</i> <sub>1Me</sub>	p <i>K</i> <sub>1</sub>	p <i>K</i> <sub>3Me</sub>	p <i>K</i> <sub>3</sub>	p <i>K</i> <sub>a</sub> (calc.)	p <i>K</i> <sub>a</sub> (obs.)	<i>K</i> <sub>T</sub>
<b>741</b>	390	2.05	2.60	2.64	2.94	2.21	2.21	4.3
<b>741</b>	391a	1.7	2.25	2.7	3.0	1.91	2.27	11.7
<b>742</b>	390	3.69	4.24	4.34	4.64	3.86	3.97	5.0

<sup>a</sup> p*K*<sub>1</sub> and p*K*<sub>3</sub> are calculated from the observed values for p*K*<sub>1Me</sub> and p*K*<sub>3Me</sub> respectively; see the text.

**Table 108. p*K*<sub>a</sub> and Speculative Calculations for **925** and Derivatives in Water <sup>a</sup>**

<b>925</b>			<b>925(OMe)</b>			<b>925(NMe)</b>		
p <i>K</i> <sub>a</sub>	$\lambda_{\text{max}}$ <sup>b</sup>	%OH <sup>c</sup>	p <i>K</i> <sub>a</sub>	$\lambda_{\text{max}}$ <sup>b</sup>	$\Delta(\text{OR})$ <sup>c</sup>	p <i>K</i> <sub>a</sub>	$\lambda_{\text{max}}$ <sup>b</sup>	$\Delta(\text{NR})$ <sup>c</sup>
- 0.89 <sup>d</sup>	224 <sup>e</sup>	60	- 2.08 <sup>e</sup>	218 <sup>e</sup>	1.41	- 1.36 <sup>e</sup>	230 <sup>e</sup>	0.87
		95			1.21			1.75
		5			2.49			0.49

<sup>a</sup> Scheme 133. <sup>b</sup> In nm. <sup>c</sup> See the text. <sup>d</sup> Ref. 22. <sup>e</sup> Ref. 465.

$$K_1 K_A^+ = 2 K_2 \quad (\text{cxx})$$

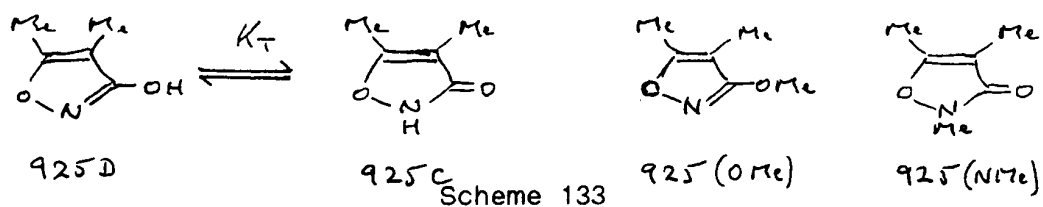
In the case of 2-amino-*s*-triazole **743**  $pK_a$  values of 4.29 and 5.38 are reported for **743AMe** and **743CMe** by Barlin<sup>392</sup> which on correction become 4.84 and 5.68 respectively. In the absence of a model for the **B**-form this information is insufficient to calculate tautomer composition on its own, but the situation can be remedied by using the observation by Fritz,<sup>393</sup> on good N-15 NMR evidence, of an accurately 2:1 ratio between the **A**- and **B**-tautomers. Expressed as eqn. (cxx), this relation and eqn. (liii) may be treated as simultaneous equations to yield  $K_A^+$  3.73 and  $pK_2$  4.57 from which  $K_T$  8.2 may be calculated (section B.1.2). If this is smoothed to  $K_T = 9$  a tautomeric composition **A**:**B**:**C** of 60:30:10 results, which is probably close enough to the truth for practical purposes. There is no independent check on the proportion of **C** but a  $\pi$ -donor substituent, by increasing electron density on aza-nitrogen and hence lone pair repulsion, might be expected to reduce this. Incorporation of the observed  $pK_a$  into these simultaneous equations means that no check on this is possible.

Accordingly we propose  $\Delta(\text{NR})$  0.55 for **814**. There should be other applications for this quantity but we have not so far encountered one.

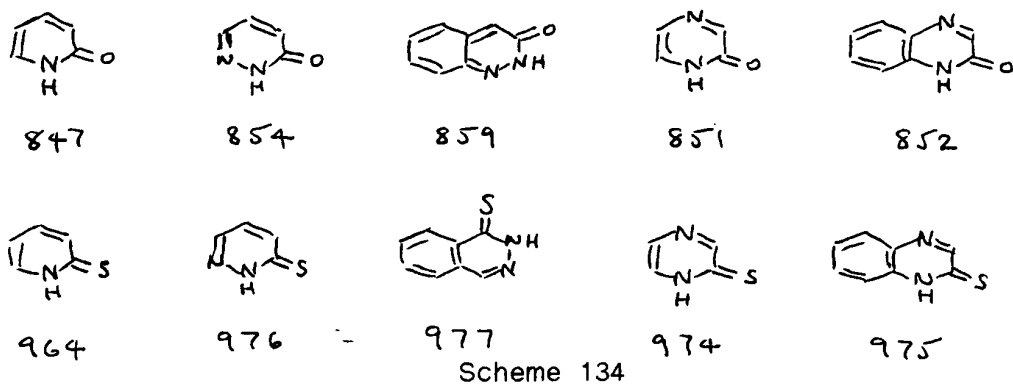
#### (k) Unresolved Problems: 3-Hydroxyisoxazoles

Katritzky and co-workers<sup>465</sup> estimated a 5:1 ratio of iminol **925D** to amide **925C** for the 3-hydroxyisoxazole **925** (Scheme 133) in water on the basis of the  $pK_a$  values<sup>465</sup> for the fixed derivatives **925(OMe)** and **925(NMe)** (Table 108); they also suggested that the proportion of iminol might be much higher than this, since **925D** is found overwhelmingly in  $\text{CCl}_4$  and DMSO and exclusively in the solid state.<sup>465</sup> However, as we<sup>22</sup> have indicated, the true position is uncertain.

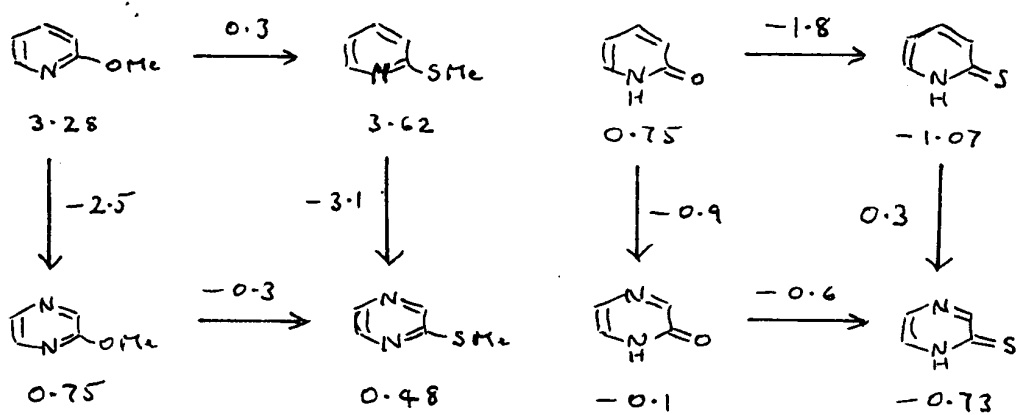
Nonpolar solvents such as  $\text{CCl}_4$  and proton acceptors such as DMSO strongly favour iminol forms (*vide* Appendix 2), while the typically much greater strength of OH---N than of NH---O hydrogen bonding (*cf.* section A.10.1) could well tip the balance in the solid state. Hence evidence from these sources is equivocal. The aqueous UV spectrum of **925** (Table 108) shows  $\lambda_{\text{max}}$  at 224 nm, just half-way between those of the two fixed forms, which suggests a fairly even balance, while our additive (isodesmic) treatment of these and related compounds (section B.8.13) leads to a predicted  $\log K_T$  ca. -0.2 for **925**; that is, about 60% iminol. However, the 'basicity method' gives equivocal results as well.



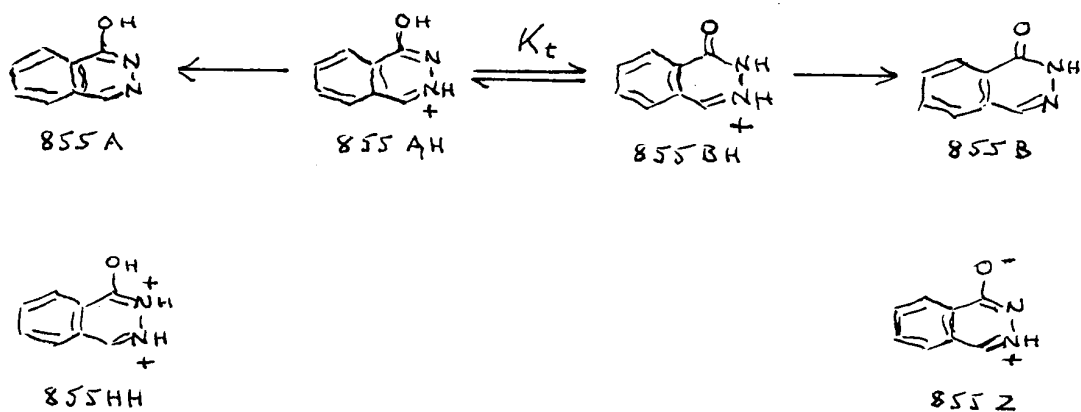
Scheme 133



Scheme 134



Scheme 135



Scheme 136

In Table 108 we analyse the published  $pK_a$  data along the lines of (g) and (h) above. Assuming a 60% iminol content, as would result from applying 'standard'  $\Delta(XR)$  values, leads by back-calculation to  $\Delta(OR)$  and  $\Delta(NR)$  values of 1.41 and 0.87 respectively. Given the much greater dipolar repulsion present in -ONH- relative to -NRNH- (section C.15) such a value for  $\Delta(NR)$  is not implausible, but it is difficult to think of any good reason for a comparable rise in  $\Delta(OR)$ . Values of 1.0 and 0.87 for  $\Delta(OR)$  and  $\Delta(NR)$  respectively, superimposed on the  $pK_a$  values of Table 108, would predict 80% of the iminol, not far from the 84% calculated on 'naïve basicity' assumptions, but the parallel prediction of an overall  $pK_a$  -1.18 is still some way from that observed ('naïve basicity' would predict  $pK_a$  -2.15, 60% iminol -1.30). We have to leave this question open. Calculations based on equal and opposite predominances of iminol and amide (Table 108) lead, in both cases, to extreme and unacceptable  $\Delta(XR)$  values. There seems no way of advancing beyond this point without more evidence.

#### (l) Unresolved Problems: Oxo- and Thionopyrazines, 813 and 958

Data for 3-oxo(thiono)pyridazines and oxo(thiono)pyrazines appear in Table 109. The 3-oxopyridazines are considered in (j) above; the related thiones (Scheme 134) continue the trend towards lower  $\Delta(NR)$  values present in the corresponding monoazines of Table 104 (*cf.* Table 103) and discussed in (m) below. However, while the oxo- and thionopyrazines show a similar trend, disquieting features attach to both.

The relevant data are contained in Table 110 and displayed in Scheme 135, in which the behaviour of the parent oxo- and thionoheterocycles is contrasted with that of their OMe and SMe derivatives. The latter pair behave in a reasonably regular fashion; replacement of OMe by SMe has a relatively small effect on  $pK_a$ , whereas the insertion of aza-nitrogen has a very large effect for both in reducing basicity. This relative regularity disappears in the parent amides. There is a very large fall in  $pK_a$  between 2-pyridone and 2-pyridithione, as is also found for their aliphatic analogues (section B.3.3), and quite a large fall on aza-substitution into 2-pyridone, but on its insertion into the thione,  $pK_a$  rises. On electronic grounds this is wildly improbable and the only reasonable explanation is that protonation of **974** takes place, preferentially and perhaps predominantly, on aza-nitrogen. Hence there is no common monocation on which the calculation of tautomeric ratio can be based.

This situation has precedents. It can only occur when the *microscopic*  $pK_a$  of the amide lies below that of its rival basic centre, here aza-nitrogen, in which case the usual formulae for calculating  $K_T$ , such as eqns. (i) and (ii), will *necessarily* underestimate its value. We illustrate this with a further consideration of 4-phthalazinone **855**. The problem this poses (not its solution: *cf.* Scheme 34) is set out in Scheme 136. The tautomers **855A** and **855B** possess different monocations, **855AH** and **855BH**, tautomers linked by the quantity  $K_t$  which has to be factored out before the value of  $K_T$  attaching to the neutral species can be calculated. These monocations result from rival deprotonation pathways of the dication **855HH** and their ratio has to be obtained from model fixed dications corresponding to each. This is a difficult process and is described in section B.2.5 for **855**, for which the existence of a zwitterionic tautomer **855Z** provided an extra complication. The correct choice of model compound requires some care and deciding even whether the phenomenon exists is not always straightforward.

There can be no doubt of this, however, in the case of **974**. With normal correction factors applied, the calculated  $\log K_T$  values for **851**, **852**, **974** and **975** (Scheme 134) become 1.9, 2.8, 1.1 and 1.4 respectively (sections B.2.5 and B.3.4): the only known cases in which a thioamide appears to possess a lower  $K_T$  value than the corresponding amide. In addition, benzofusion appears to have an abnormally small effect on  $\log K_T$  for **974**. If the effect of the 4-aza substituent on the microscopic amide  $pK_a$  of **964** in fact parallels its effect on **847**,  $\log K_T > 2$  for **975** results, which would restore the usual differential. The true distortion of  $K_T$  in **974** and **975** resulting from aza-nitrogen protonation may be greater still if it is already present in **851** and **852**. There is suggestive evidence for this in the *negative*  $\Delta(NR)$  values for all four compounds (Table 109), a phenomenon normally associated with *remote* protonation (see start of this Appendix). It may be that all four  $K_T$  values are invalid, though the 'normal'  $\Delta \log K_T$  value on benzofusion of **851** may argue for a considerably smaller effect in the oxygen series, perhaps involving comparable degrees of protonation. By contrast the amide cross-comparison set out in Scheme 135 suggests that  $K_T$  for **974** may have been underestimated by *at least* a factor of 10, and for **975** by probably more than that. Simply because of their lower basicity, thioamides are likely to be much more susceptible than amides to this source of error; see further below.

This phenomenon cannot occur if the two nitrogen atoms form part of an amidine unit, so thiopyrimidones for example should not be at risk from it. The possibility of its occurrence in more complex structures, such as triazinones, has yet to be explored, but their very low basicity might in practice place the investigation out of reach.

**Table 109.  $\Delta(\text{NMe})$  Values for 3-Oxo(thiono)pyridazines and Oxo(thiono)pyrazines**

Compound	$\text{p}K(\text{NH})$	Ref.	$\text{p}K(\text{NMe})$	Ref.	$\Delta(\text{NMe})$
<b>854</b>	- 1.8	382a	- 2.1	4	0.3
<b>855</b>					<sup>a</sup>
<b>859</b>	0.21	4	- 0.61	254	0.82
<b>976</b>	- 2.68	382a	- 2.95	382a	0.27
<b>977</b>	- 3.43	382a	- 3.98	382a	0.55
<b>851</b>	- 0.1	4	- 0.04	4	- 0.06
<b>852</b>	- 1.38	446	- 1.15	446	- 0.23
<b>974</b>	- 0.73	382a	- 0.45	382a	- 0.28
<b>975</b>	- 1.24	382a	- 1.01	382a	- 0.23

<sup>a</sup> Cation formed largely by protonation on imino-nitrogen, so no meaningful  $\Delta(\text{NMe})$  value exists.

**Table 110.  $\text{p}K_{\text{a}}$  Data on 2-Oxo, -Thiono, -OMe and SMe Derivatives of Pyridine and Pyrazine <sup>a</sup>**

Compound	$\text{p}K(\text{NH})$	Ref.	$\text{p}K(\text{OMe})$	Ref.	$\text{p}K(\text{SMe})$	Ref.
<b>847</b>	0.75	4	3.28	4	3.62	381
<b>851</b>	- 0.1	4	0.75	4	0.48	382a
<b>964</b>	- 1.07	381				
<b>974</b>	- 0.73	382a				

<sup>a</sup> Scheme 135.

**Table 111.  $\Delta(\text{NMe})$  Corrections for Vinylogous Thioamides <sup>a</sup>**

Cpd.	$\text{p}K(\text{NH})$	Ref.	$\text{p}K(\text{NMe})$	Ref.	$\Delta(\text{NMe})$
<b>634</b>	1.43	381	1.30	255	0.13
<b>642</b>	0.77	381	0.56	381	0.21
<b>644</b>	- 0.75	382a	- 0.83	382a	0.08
<b>645</b> <sup>b</sup>	- 1.83	382a	- 1.29	597	- 0.56

<sup>a</sup> Scheme 138. <sup>b</sup> See the text.

There is a further implication. The major site of protonation for maleic hydrazide **944B** (Scheme 38, section B.2.12) is on carbonyl to give **944AB**<sup>+</sup> not on aza-nitrogen to give **944BC**<sup>+</sup> (Scheme 137), and this seems to have led to a general assumption, in these and other cases, that their thione equivalents will follow suit. This may not necessarily be true. A major driving force in the preference for **944AB**<sup>+</sup> over **944BC**<sup>+</sup> is the very strong dipolar repulsion to be found in the latter (Appendix 3), but the much lower *pK<sub>a</sub>* values of thioamides than of amides constitute a competing factor with the potential to tip the balance. We return to this subject in (n) below.

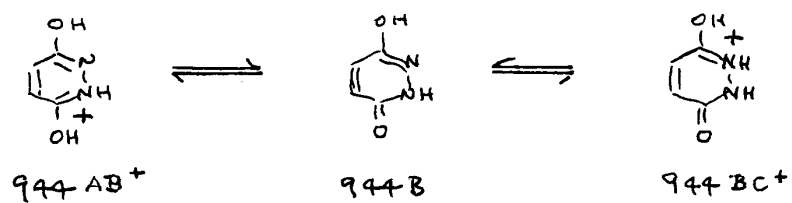
**(m)  $\Delta(\text{NR})$  Values for Thioamides: 957, 958, 959 and 960**

Tables 104, 109 and 111 summarise the data on which the  $\Delta(\text{NMe})$  values for these four compound classes are based. The last is for vinylogous thioamides, not so far discussed. Three of these (Scheme 138) point to a small positive value,  $0.14 \pm 0.05$ , but the fourth, **645**, to a large negative one. However, as a thionodiazine some results for this compound may be suspect; we note in (l) above that negative  $\Delta(\text{NMe})$  values may indicate protonation at some site other than amide (thio)carbonyl. We therefore think it best to discount this result. For the other three compounds the results (Table 111) do not indicate a degree of precision great enough to merit a value for **960** (Scheme 123) significantly different from  $\Delta(\text{NMe})$  0.1; it may indeed be indistinguishable from that for **830a**.

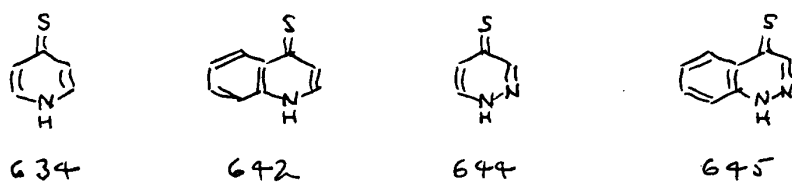
Table 112 cross-compares the  $\Delta(\text{NMe})$  values of oxo- and thiono-azines across the four series for which this is possible. Despite the above caveats, and provisionally setting aside **960** vs. **830a**,  $\Delta(\text{NMe})$  is consistently less for the thioamides. This is entirely in line with their greater size and therefore, presumably, the lower charge density of their cations, hence we believe it to be genuine if only qualitatively so.

**(n) Unresolved Problems:  $\Delta(\text{SR})$ ; 961 and 963**

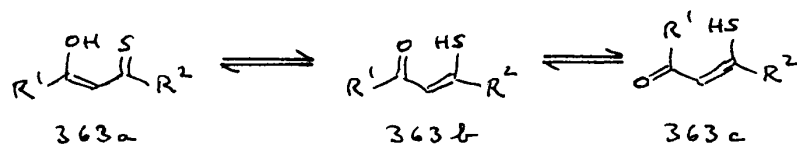
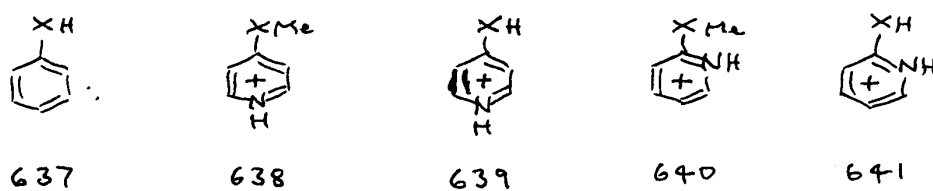
In the absence of any case in which the thiol tautomer has been observed in aqueous solution and its proportion quantified, there is no way of determining  $\Delta(\text{SR})$  experimentally and indirect arguments have to be employed.



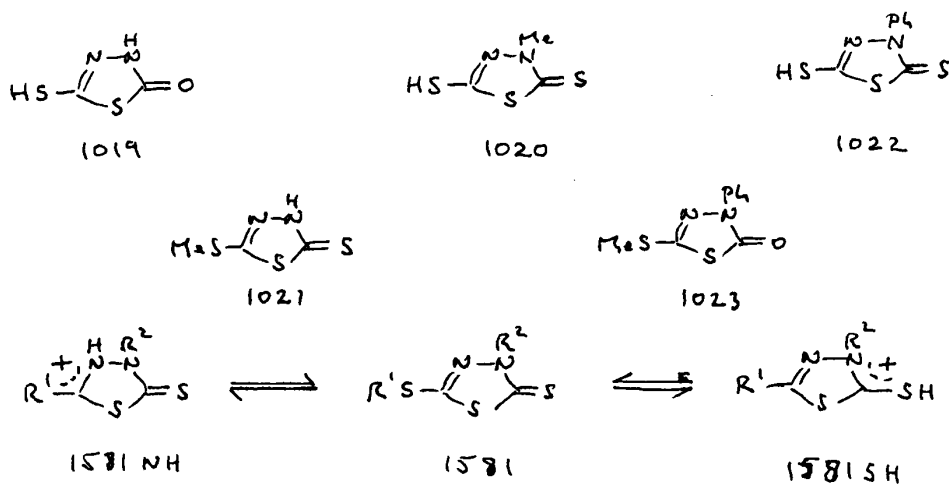
Scheme 137



Scheme 138



Scheme 139



Scheme 140

**Table 112. Summary of Apparent  $\Delta(\text{NR})$  Values for Aromatic Amides and Thioamides**

$\Delta(\text{NR})$ Structural Type <sup>a</sup>			$\Delta(\text{NR})$ Structural Type <sup>a</sup>		
2-Pyridones <sup>b</sup>	0.45	<b>812</b>	2-Pyridinethiones <sup>b</sup>	0.2	<b>957</b>
3-Pyridazinones <sup>c,d</sup>	0.55	<b>814</b>	3-Pyridazinethiones <sup>c</sup>	0.4	<b>959</b>
2-Pyrazinones <sup>c</sup>	- 0.15	<b>813</b>	2-Pyrazinethiones <sup>c</sup>	- 0.25	<b>958</b>
4-Pyridones <sup>e</sup>	0.0	<b>830a</b>	4-Pyridinethiones <sup>e</sup>	0.1	<b>960</b>

<sup>a</sup> Scheme 123. <sup>b</sup> Comprises all known 6-membered ring (thio)amides of monoazines (Tables 103 and 104). <sup>c</sup> Very provisional: Table 109. <sup>d</sup> Also applies if ZH is absent, as in -NHN=C- unit of *s*-triazoles. <sup>e</sup> Comprises all known 6-membered ring vinylogous (thio)amides (Tables 107 and 111).

**Table 45. Cross-Comparison of Proton Donor Strengths (637) with XMe  $\rightarrow$  XH Correction Factors (for 638 - 641) <sup>a</sup>**

	$\alpha$ (637) <sup>b</sup>	$\Delta \text{p}K_{\text{a}}$ (638 $\rightarrow$ 639)	$\Delta \text{p}K_{\text{a}}$ (640 $\rightarrow$ 641)
X = O	0.60	0.5 <sup>c</sup>	1.0 <sup>c</sup>
X = NMe	0.17	0.04 <sup>d</sup>	0.05 <sup>d</sup>
X = S	0.09	- 0.05 <sup>e</sup>	- 0.15 <sup>e</sup>

<sup>a</sup> Scheme 139. <sup>b</sup> Ref. 378. <sup>c</sup> Appendix 1. <sup>d</sup> Ref. 380. <sup>e</sup> By extrapolation (see the text).

**Table 113.  $\text{p}K_{\text{a}}$  Values for the Compounds of Scheme 140 <sup>a</sup>**

Compound	<b>1019</b>	<b>1020</b>	<b>1022</b>	<b>1021</b>	<b>1023</b>
$\text{p}K_{\text{a}}$	- 5.40	- 5.30	- 6.50	- 4.85	- 5.44
	- 1.36	- 1.40	- 1.59		
	7.23 <sup>b</sup>				

<sup>a</sup> Ref. 496. <sup>b</sup> Statistically corrected.

We proceed by analogy (Scheme 139). Structures **638** - **641** where X = O exemplify the types of compound from which  $\Delta(\text{OR})$  has been deduced for aromatic amides (**640**  $\rightarrow$  **641**) and vinylogous amides (**638**  $\rightarrow$  **639**) respectively, while for X = NMe this is the major tautomer and the required  $pK_a$  data are readily available.<sup>380</sup> The much larger value in each series of  $\Delta(\text{OMe})$  than of  $\Delta(\text{NMe})$  plausibly reflects the much greater solvational requirements of  $\text{OH}^+$  than of  $\text{NH}^+$  cations.<sup>2c</sup> We now introduce three postulates. The first relates this solvational requirement to proton donor ability; in comparable compounds, OH is a stronger proton donor than NH.<sup>72,235</sup> The second supposes a LFER relationship to exist between the proton donor abilities of XH and  $\text{XH}^+$  in compound series for which X is variable but the structures are otherwise comparable. And the third supposes that, in these terms, the proton donor ability of the neutral species **637**, which is known,<sup>378</sup> may be regarded as a surrogate for that of its cations **639** and **641**, which is unknown. This allows a two-point correlation between Abraham's proton donor parameter  $\alpha$ , for X = O and X = NMe,<sup>378</sup> and the corresponding  $\Delta(\text{XR})$  values, from which those for  $\Delta(\text{SMe})$  may be derived (section A.11.3). The results appear in Table 45.

Outstandingly, the two values for SMe are negative and virtually coincident; within the limits of error,  $\Delta(\text{SMe})$  is -0.1 for both **961** and **963** (Scheme 123). This negative value implies that the solvational requirements of SH even as its cation are negligible in water [see (**I**) above]. The relations for **639** and **641** extrapolate to  $\Delta(\text{XR})$  values of -0.15 or -0.3 respectively at  $\alpha = 0$ ; that is, the sort of value we find for the 'remote' base-strengthening effect of alkyl on nitrogen which is visible only because neutral aliphatic amines are such poor proton donors (see start of this Appendix). It appears that SH continues to act as a negligible proton donor even when it carries a positive charge.

Oblique supporting evidence derives from  $\beta$ -thionoketones of type **363** (Scheme 139). Here the major component of the thiol tautomer is **363c** not **363b** *even in nonpolar solvents* where chelation should be favoured (section A.8.3). Even though this result is for neutral species not cation, it demonstrates the extraordinary weakness as a proton donor even of 'activated' SH and reinforces the thesis presented above.

There is also one piece of evidence which may provide  $\Delta(\text{SMe})$  directly. Table 113 displays  $pK_a$  data for the compounds of Scheme 140, all of which exist in the same tautomeric form (section B.3.7);  $\nu(\text{SH})$  is present wherever

SH is indicated, for example. Here the site of protonation is uncertain. The authors<sup>496</sup> assume *S*-protonation to give the cation **1581SH** throughout; they do not present supporting evidence and presumably base their opinion on the known behaviour of **944B** (Scheme 137) and other compounds of similar type, where the main driving force is dipolar repulsion in the cation **944BC**<sup>+</sup> (section B.2.12). This is a powerful argument but thioamides are much weaker bases than amides and this factor renders the outcome problematical; *cf.* (**1**) above. It is apparently supported by the basicity order **1019**  $\gg$  **1022** though even here **1020** is anomalous in not also being a weaker base than **1019**:  $\Delta(\text{NR})$  *ca.* 0.6 is expected. However far less difference in basicity exists between **1021** and **1023** and the  $pK_a$  of **1022** is so far out of line with the remainder as to represent an anomaly. If *N*-protonation obtains,  $pK_a$  0.1 for **1019**  $\rightarrow$  **1020** and -0.59 for **1021**  $\rightarrow$  **1023** appear as reasonable estimates for the ‘remote’ effects of NMe and NPh *vs.* NH, while  $\Delta pK_a$  -0.55 for **1021**  $\rightarrow$  **1019** becomes  $\Delta(\text{SMe})$ . This is a much more negative value than that suggested above but  $\Delta pK_a$  0.55 for the ‘remote’ effect of SMe on the *S*-protonated cation makes even less sense. Possibly all or most of these cations are mixtures of **1581NH** and **1581SH** in which case the situation becomes uninterpretable. We cannot take our analysis beyond this point.

#### (o) Overview

Given the greater solvational requirements of OH<sup>+</sup> than of NH<sup>+</sup>, the larger values of  $\Delta(\text{OR})$  than of  $\Delta(\text{NR})$  when both refer to the *same* conjugated system (*cf.* Table 45) make good chemical sense. The multiplicity of  $\Delta(\text{NR})$  values follow the same pattern, with  $\Delta(\text{NMe})$  0.45 for amides, taken as a reference point, falling to 0.3 or less when the charge is well spread as in amidines and rising when adjacent electronegative substitution takes place, ultimately reaching  $\Delta(\text{NMe})$  0.75 when two adjacent NH groups share the positive charge. The fewer distinct types of  $\Delta(\text{OR})$  – there may only be two – ultimately reflects the fewer contexts open to carbonyl. There may be situations we have missed but we would expect these guidelines still to be followed.

We also believe that  $\Delta(\text{SR})$  is effectively zero. This again makes chemical sense as reflecting the minimal proton donor ability of SH, so miniscule that even SH<sup>+</sup> requires almost no solvation.

## APPENDIX 2: Solvent Effects

Like other chemical processes, both rates and equilibria, tautomerism is greatly influenced by change of phase. The quantitative study of solvent effects has a long history but in recent years has become concentrated into the *solvatochromic approach* initiated by Taft and co-workers<sup>12</sup> and further developed by Abraham and his collaborators.<sup>599</sup> This methodology is essentially empirical: spectroscopic shifts, UV mostly but sometimes of other sorts, are used to generate values for each parameter by comparison with a standard nonpolar solvent, namely cyclohexane.<sup>12</sup> The thermodynamic status of these shifts is uncertain; they were originally supposed to be free energy-related but they are certainly not free energies *per se* and some have been demonstrated<sup>600</sup> to represent blends of  $\Delta G$  with  $\Delta H$ . As used in linear solvation energy (LSER) equations, however, the values themselves are unimportant provided that they are proportional to the energy of the molecular property they purport to measure, and even their precise thermodynamic status is of muted importance if they are mutually orthogonal.

$$\log Q = c + s\pi^* + a\alpha + b\beta \quad (\text{cxxi})$$

Three crucial quantities were identified by Taft and co-workers<sup>12</sup> which have ever since dominated the solvatochromic approach. These are  $\alpha$ , a measure of solvent proton donor ability;  $\beta$ , a measure of its ability as a proton acceptor; and  $\pi^*$ , a less readily definable quantity which appears to consist in some blend of dipolarity with polarisability. How these quantities were derived and their orthogonality established, for 216 organic solvents (with some gaps in the parameter values) and water, has been fully documented.<sup>12</sup> Some further parameters have been found useful in special contexts, such as solvent-water partitioning and others in which the solvent's cohesive energy density is involved,<sup>599</sup> but none of these was required for the one example of tautomeric preference analysed in that Review,<sup>599</sup> which fact was noted by its authors. Differences between phases that give rise to such perturbations are likely to cancel when the equilibrium between species takes place in a single phase, so accounting for this observation. Nevertheless it is possible that *intrasolvent* perturbations may exist of types yet to be identified. One of these, for which sporadic evidence will be presented, concerns a potential difference between the behaviour of rigid structures and those which allow a facile free rotation inside the functional group concerned, a difference especially likely to be important in water with its

**Table 114. Solvatochromic Parameters** <sup>a,b,c</sup>

	Solvent	$\pi^*$	$\alpha$	$\beta$
1	Water	1.09	1.17	0.4 <sup>d</sup>
2	<b>MeOH</b>	0.60	0.93	0.62
3	<b>EtOH</b>	0.54	0.83	0.77
4	PrOH	0.52	0.78	0.82
5	Pr <sup>i</sup> OH	0.48	0.76	0.95
6	BuOH	0.47	0.79	0.88
7	Bu <sup>t</sup> OH	0.41	0.68	1.01
8	HOCH <sub>2</sub> CH <sub>2</sub> OH	0.92	0.90	0.52
9	CF <sub>3</sub> CH <sub>2</sub> OH	0.73	1.51	0
10	(CF <sub>3</sub> ) <sub>2</sub> CHOH	0.65	1.98	0
11	MeCO <sub>2</sub> H	0.64	1.12	(0.4)
12	Et <sub>2</sub> O	0.27	0	0.47
13	THF	0.58	0	0.55
14	<b>Dioxane</b>	0.55	0	0.37
15	MeOCH <sub>2</sub> CH <sub>2</sub> OMe	0.53	0	0.41
16	Acetone	0.71	0.08	0.48
17	EtOAc	0.55	0	0.45
18	Ethylene carbonate	0.83	0	0.40
19	MeNO <sub>2</sub>	0.85	0.22	0.39
20	MeCN	0.75	0.19	0.31
21	HCONH <sub>2</sub>	0.97	0.71	(0.6)
22	DMF	0.88	0	0.69
23	DMA	0.88	0	0.76
24	N-Methylpyrrolidinone	0.92	0	0.77
25	<b>DMSO</b>	1.00	0	0.76
26	HMPT	0.87	0	1.05
27	Et <sub>3</sub> N	0.14	0	0.71
28	Pyridine	0.87	0	0.64
29	<b>Benzene</b>	0.59	0	0.10
30	Toluene	0.54	0	0.11
31	ClCH <sub>2</sub> CH <sub>2</sub> Cl	0.81	0	0
32	CH <sub>2</sub> Cl <sub>2</sub>	0.82	0.30	0
33	<b>CHCl<sub>3</sub></b>	0.58	0.44	0
34	<b>CCl<sub>4</sub></b>	0.28	0	0
35	C <sub>6</sub> H <sub>12</sub>	0	0	0
36	<b>Alkane</b>	- 0.08 <sup>e</sup>	0	0
37	Gas phase <sup>f</sup>	- 1.23	0	0

<sup>a</sup> Ref. 12. <sup>b</sup> Bracketed values are provisional, values in **bold type** denote 'selected solvents' (see the text). <sup>c</sup> Solvents occasionally used in tautomerism studies but with unknown or incomplete and unestimable parameter values include: CS<sub>2</sub>, methyl pivalate, MeCONHMe, BuCN, and sulfolane. <sup>d</sup> Value derived in this study: see the text. <sup>e</sup> If alicyclic, use value for C<sub>6</sub>H<sub>12</sub>. <sup>f</sup> Ref. 601.

exceptionally high internal pressure and aptitude for many and varied patterns of solute-solvent hydrogen bonding. Nevertheless this is a fugitive phenomenon and the typical LSER equation may be summarised as (cxxi), where  $Q$  here is the tautomeric equilibrium constant under study and not all quantities are necessarily significant.

Other partial compilations have appeared since 1983 but for our purposes we have chosen to ignore them. Among these Laurence *et al.*<sup>601</sup> have conducted a searching re-examination of  $\pi^*$ , while Rosés and co-workers<sup>602</sup> have studied various alkanol-water mixtures and deduced values of  $\pi^*$ ,  $\alpha$  and  $\beta$  for them. However the second results in values for the pure solvents that differ from those of Taft *et al.*<sup>12</sup> and to use either set of results without adjusting the remaining parameters in line with it, a procedure presently impossible, would risk destroying the orthogonality that is one of the latter's great virtues. The one exception we have made is to include in Table 114, which summarises the parameter values we shall employ, one for  $\pi^*$  in the gas phase; and this is not for more than occasional use in this Appendix but to emphasise the fallacy, still to be found among some computational chemists, that calculation on an isolated molecule in the gas phase can be used to mimic that molecule's behaviour in a highly nonpolar, typically an alkane solvent. It cannot.

The use of eqn. (cxxi) can lead to fundamental insights into the nature of solute-solvent interactions in any given case and many of the studies described below perform this function. However, their chief importance in the present context is quite different: to provide some way of extrapolating from organic solvents to water. Most experiments on tautomerism have been carried out in organic solvents, chosen not to establish solvent dependence but simply so as to be able to observe the phenomenon at all. Extrapolation to water was not the aim of the original investigators but it has to be ours. For that reason we need not only to establish how well aqueous equilibria can be predicted where the facts are known, but also how reliable prediction is likely to be where they are not. Consequently we introduce an important innovation. It has been customary in past LSER studies to include in the analysis  $K$  for water, where known, along with its values in organic solvents. We *never* do this. We shall find that the result of this omission, while generally reassuring, has been to unearth some anomalies whose existence had not been suspected. While some remain a puzzle, others have proved illuminating and have helped to rationalise the differing behaviour of different compound classes, as will appear below.

**Table 115. LSER Data for some  $\beta$ -Diketones <sup>a</sup>**

Solvent <sup>b</sup>	55 <sup>c</sup>	55 <sup>d</sup>	57 <sup>e</sup>	57 <sup>e,f</sup>	344	342 <sup>g</sup>
2	2.17		0.46	0.33	- 1.05	- 1.15
3	2.23		0.76	0.46	- 0.72	- 0.85
5			0.83			- 0.77
11				0.44		
12	0.51	1.28		1.00		
13	0.65	1.48	0.86	0.85	- 0.85	- 0.40
14	0.38	1.11	0.68	0.67	- 0.74	- 0.89
15				0.59		
16	0.62				- 1.31	- 0.89
18				0.01		
19				0.07		
20	0.36	0.40	0.08 <sup>h</sup>	0.05	- 1.57 <sup>h</sup>	
21				- 0.32		
22	1.93	0.11		0.26	- 1.28	
23				0.28		
25	1.97		0.30	- 0.12	- 0.85 <sup>h</sup>	- 1.30
27				1.05		
28			0.57		- 0.60 <sup>h</sup>	- 1.00
29	- 0.92		1.17		- 0.66	- 0.59
30	- 1.10		1.10		- 0.66	- 0.41
31	- 1.40	- 0.41			- 1.10	
32	- 1.15	- 0.34	0.62		- 1.13	- 1.05
33	- 1.30	- 0.70	0.77	0.68	- 0.70	- 1.05
34			1.46	1.24	- 0.01	- 0.54
35			1.62	1.51	0.27	0.22
Water	1.28	ca. 2.1 <sup>i</sup>	- 0.64	- 0.83	- 1.62	- 1.06 <sup>j</sup>
Water <sup>k</sup>			- 0.28 <sup>l</sup>	- 0.43 <sup>m</sup>	- 1.72 <sup>n</sup>	- 1.82 <sup>o</sup>

<sup>a</sup> Log  $K_E$ ; from ref. 60 unless otherwise stated. <sup>b</sup> Solvent number code from Table 114.

<sup>c</sup> R = H. <sup>d</sup> R = Me. <sup>e</sup> R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = H. <sup>f</sup> Ref. 197. <sup>g</sup> R = Me, Z = OEt. <sup>h</sup> Outlier (see the text). <sup>i</sup> See section A.1.4. <sup>j</sup> Ref. 229 (also -1.15, ref. 60). <sup>k</sup> Calculated values: see the text.

<sup>l</sup> Eqn. (cx1), Table 133. <sup>m</sup> Eqn. (ix), ditto. <sup>n</sup> Eqn. (xii), ditto. <sup>o</sup> Eqn. (xi), ditto.

Behind this relatively hard-edged objective there lurks another and vaguer one. If patterns can be established, for classes of compound and between different structural types, it may be possible, based on work in a very few organic solvents, to predict at least qualitatively a compound's likely tautomeric form if transferred to water. These aims are pursued in parallel in the sections that follow.

#### (a) Solvatochromic Parameters for Water

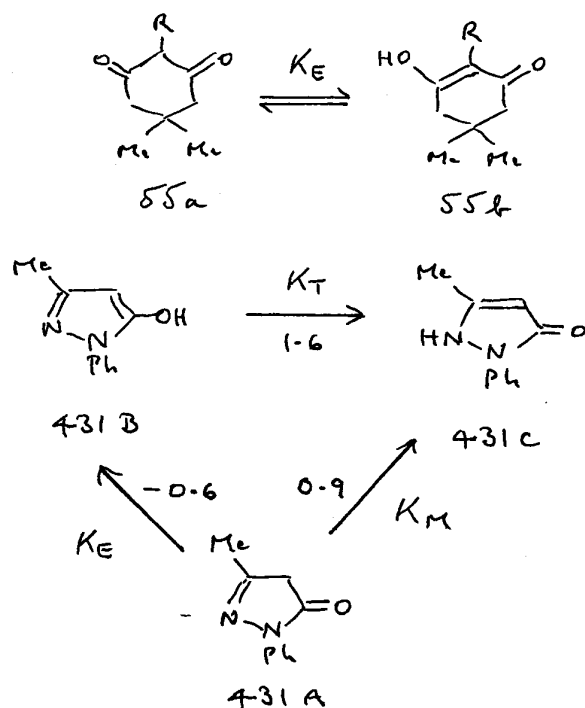
Water is an extreme and frequently misbehaved solvent whose LSER parameters must be accurately known if our objectives are to have any chance of success. Its  $\pi^*$  and  $\alpha$  values are well established (Table 114) but that of  $\beta$  is disputed and this problem we need to resolve.

The Taft-Kamlet<sup>12</sup> value of  $\beta = 0.18$  for water has been criticised more recently as much too low, with alternatives suggested<sup>603</sup> that span the range 0.14 - 0.58. Rosés and co-workers<sup>602</sup> give 0.49 or 0.50 as alternatives but their values of  $\pi^*$  and  $\alpha$  are also higher. It will be seen in Table 114 that  $\alpha$  rises and  $\beta$  falls as alkanol chain length decreases, and there are good reasons why  $\beta$  for water should be considerably smaller than that for methanol. With two OH groups per molecule water is predominantly a proton donor solvent, to the extent that other donors must find it difficult to compete.<sup>604</sup> The crystal structure of ice is enforced by crystal packing requirements<sup>605</sup> which visibly cause it to collapse as it melts to give a smaller volume containing a proportion, perhaps 15%, of only partially bonded water,<sup>606</sup> essentially because its second lone pair is so reluctant to interact with proton donors. This situation calls for a re-assessment.

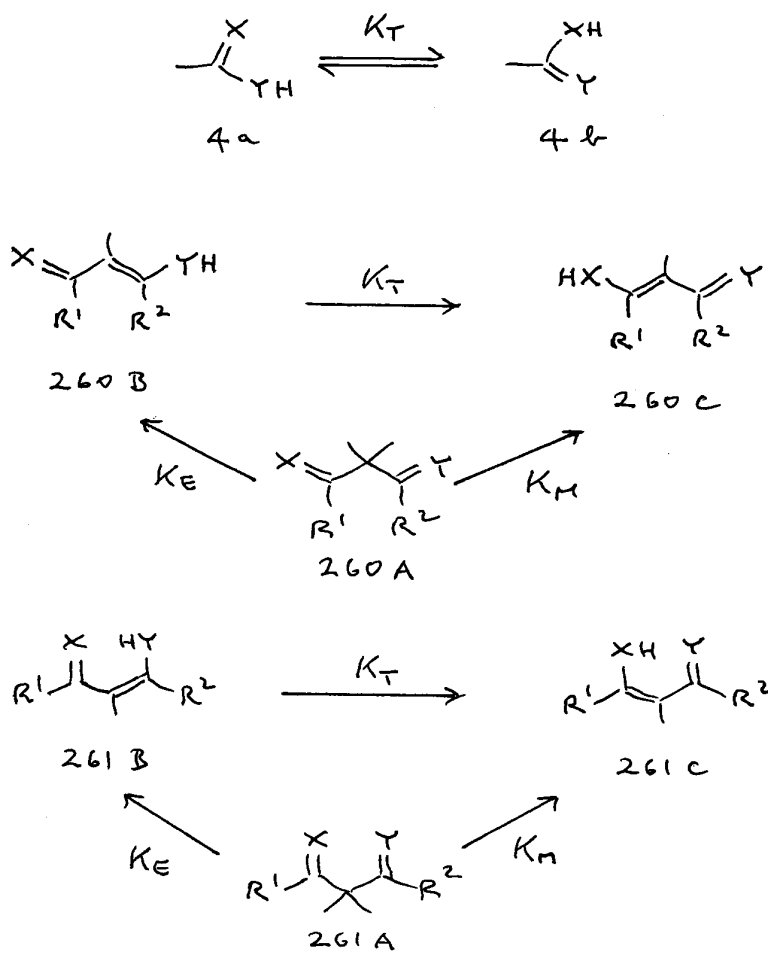
$$\log K_E = -1.78(0.24) + 0.54(0.33)\pi^* + 0.70(0.19)\alpha + 4.38(0.21)\beta \quad (x)$$

$$(n = 14 \quad r^2 = 0.981 \quad s = 0.21 \quad F = 171)$$

As a probe to help establish a  $\beta$ -value for water, we require a rigid molecule devoid of steric hindrance, whose LSER equation is dominated by  $\beta$  and whose  $K$  value in water is known. Few candidates exist and the best of these is dimedone (**55**, R = H), as studied by Mills and Beak<sup>60</sup> (Table 115). We have re-analysed their data using the parameters of Table 114 and the results (section A.6) appear as eqn. (x); there were no outliers. By back-calculation using the value of  $\log K_E$  for water we arrive at  $\beta = 0.38$  which we round to  $\beta = 0.4$  since no greater accuracy can be claimed. Use of  $\beta = 0.4$



Scheme 141



Scheme 142

**Table 116. Data Matrix for the 3-way Equilibrium of Compound 431** <sup>a,b,c</sup>

Solvent	log $K_E$	log $K_M$	log $K_T$
2	0.19	0.57	0.37
4	0.24	0.35	0.11
9		0.69	
10		0.00 <sup>d</sup>	
13	- 0.31	- 1.02	- 0.71
14	- 0.95		
16	- 1.16	- 1.03	0.12
20	- 1.37	- 1.49	- 0.12
22	0.25	- 0.10	- 0.36
25	0.36	0.10	- 0.25
26			- 1.28
28	0.59	- 0.18	- 0.77

<sup>a</sup> Scheme 141. <sup>b</sup> Data from ref. 276; cf. section A.10.2. <sup>c</sup> Solvents excluded from analysis on account of missing parameters: BuCN, sulfolane. <sup>d</sup> Outlier (see the text).

LSER analysis of **431**:

$$\log K_E = - 2.78(0.82) + 0.60(1.19) \pi^* + 0.05(0.56) \alpha + 3.61(1.06) \beta \quad (\text{xvii})$$

$$(n = 9 \quad r^2 = 0.80 \quad s = 0.42 \quad F = 6)$$

$$\log K_M = - 3.78(0.52) + 1.79(0.54) \pi^* + 1.33(0.16) \alpha + 2.93(0.37) \beta \quad (\text{xviii})$$

$$(n = 9 \quad r^2 = 0.94 \quad s = 0.21 \quad F = 28)$$

$$\log K_T = - 0.41(0.80) + 0.98(1.02) \pi^* + 1.29(0.44) \alpha - 1.42(0.58) \beta \quad (\text{xix})$$

$$(n = 9 \quad r^2 = 0.76 \quad s = 0.32 \quad F = 5)$$

Data matrix, % each component:<sup>276</sup>

	2	4	9	10	13	14	16	20	22	25	26	28
<b>A</b>	16	20	17	50	63	90	86	93	28	22	0	18
<b>B</b>	25	35	0	0	31	10	6	4	50	50	95	70
<b>C</b>	59	45	83	50	6	0	8	3	22	28	5	12

in eqn. (x) would result in  $\log K_E$   $1.38 \pm 0.21$ , placing the proposed  $\log K_E$  1.28 well within the error bars. Other published values consist in 1.30 according to Schwartzenbach and Wittwer,<sup>109a</sup> and -0.63 as reported by Toullec<sup>17</sup> which is plainly in error. A value of  $\beta$  for water about two-thirds that for methanol is entirely consistent with expectation.

Few possible checks exist but the 3-way equilibrium of **431** provides quite a rigorous one (Scheme 141). The results for this compound were analysed by the authors<sup>276</sup> using a different parameter set so we have again carried out a re-analysis. Two solvents, BuCN and sulfolane, had to be excluded for want of the necessary parameters, but the remainder appear in Table 116 and otherwise the only point we have dropped is that for  $(CF_3)_2CHOH$  (solvent 10), whose omission raised  $r^2$  for  $\log K_M$  from 0.80 to 0.94 and reduced  $s$  from 0.40 to 0.21. (Note that blank spaces in Table 116 are inevitable whenever 0% of one component is reported by the authors). The resulting LSER equations (xvii), (xviii) and (xix) are quoted from section A.10.2. Here and subsequently we retain all terms even when very small or statistically insignificant since in the worst-case scenario their removal would make no difference to the result predicted for water and there is the risk of losing information.

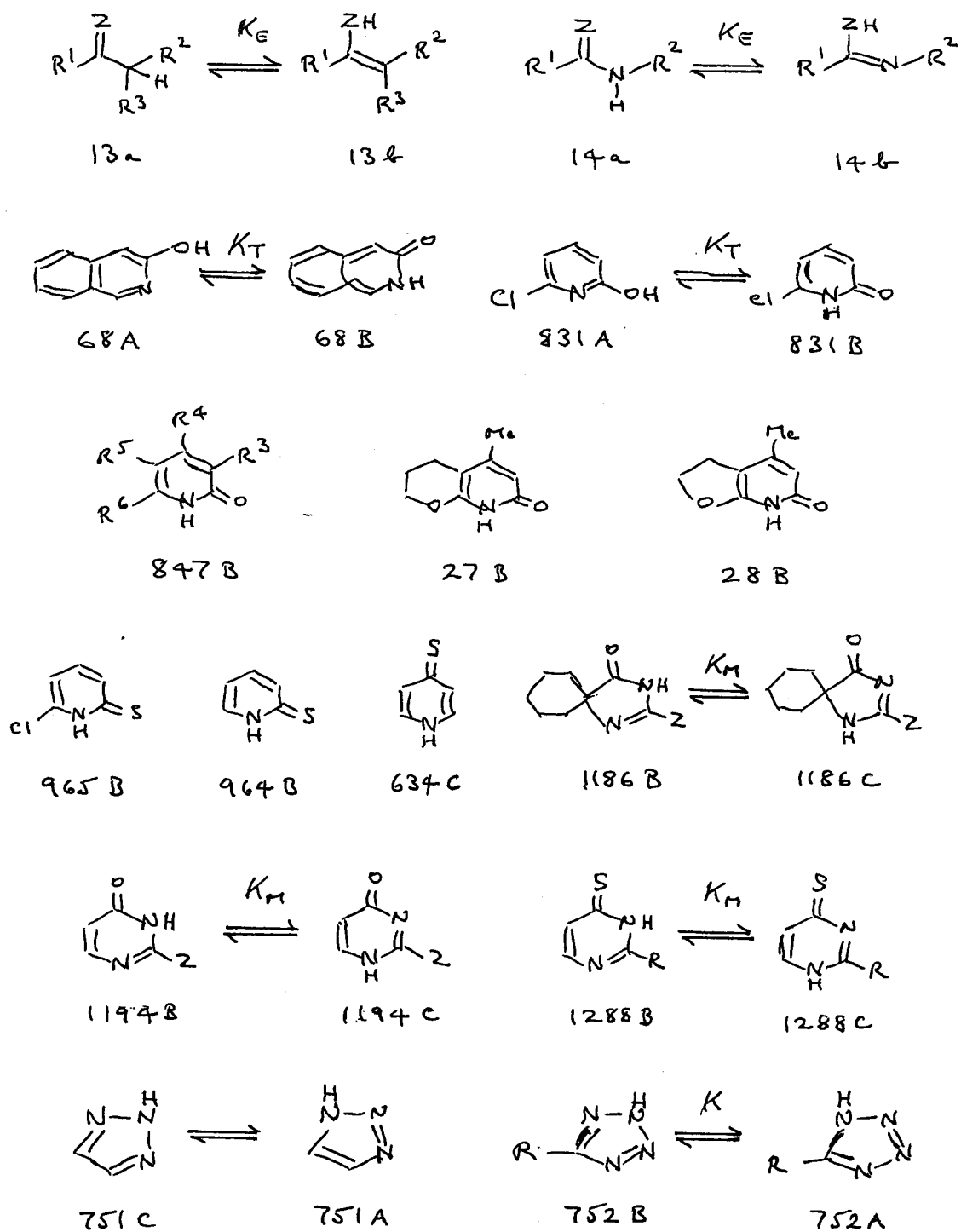
The processes that give rise to **431B** and **431C** generate strong proton donors from nothing and in eqns. (xvii) and (xviii) the coefficients of  $\beta$  are very large, almost rivalling that for (**55**, R = H) in eqn. (x). Extrapolation to water gives  $\log K_E$ ,  $\log K_M$  and  $\log K_T$  values of -0.63, 0.90 and 1.60 respectively, shown to the nearest 0.1 in Scheme 141. For the whole cycle these sum almost exactly to zero, with a cumulative error of  $\Delta \log K < 0.1$  across it. Given calculated contributions by the  $\beta$ -term to  $\log K$  in water of 1.44, 1.17 and -0.57 respectively, it is difficult to see how this result can be fortuitous. We are reasonably confident therefore that a value for water close to  $\beta = 0.4$  must be correct. There is always the possibility that different kinds of probe will introduce their own kind of bias to a particular type of investigation<sup>603</sup> and if so a different value may be required in other contexts, but we think it must apply in this one.

## (b) Systematic Ground Plan

This is set out in Scheme 142, adapted from Scheme 10 at the start of section A.6. The simplest situation is that of **4a**  $\rightleftharpoons$  **4b**, elaborated as **13a**  $\rightleftharpoons$  **13b** or **14a**  $\rightleftharpoons$  **14b** in Scheme 143 according as to whether C-type or N-type

tautomerism is involved. These cases, which may be categorised as simple or contiguous tautomerism, are considered first; they include, *via* **14** (Scheme 143), most examples of the annular type. Much more general in scope is the tautomeric pattern of **260** and **261** (Scheme 142) which we categorise respectively as 'extended' or 'chelated;' these will be found to follow very different rules, necessitating a sequential treatment. Here if  $X = Y$  then  $K_E = K_M$  while  $K_T = 1$  so is redundant and the system is reduced to a single equilibrium formally analogous to **13** of which it is a vinylogue; **55** above is one such example. However if  $X \neq Y$  a variety of possibilities arise. If  $K_E$  and  $K_M$  are both large then only  $K_T$  is important and, where  $X$  and  $Y$  have the same meaning as for **14**, **260** and **261** become their vinylogues. If all three equilibria are accessible we have the situation exemplified by **431**, where  $K_T$  is that for a vinylogous amide whereas  $K_E$  and  $K_M$  differ from  $K_E$  for **13**, but resemble the case in which  $K_E = K_M$ , in that each product forms a new, and rival, conjugated system, with consequences very different from that of the simpler system it supplants. It is important to note in such cases that a monocation common to all three tautomers is a formal impossibility so that, in the typical case, only  $K_T$  is accessible by the 'basicity method;' in such cases a common *dication* is required (see, *e.g.*, sections B.2.5 and B.2.12). If  $K_E \gg K_M$  or *vice versa* there again results a single equilibrium and a common cation is formally possible but is not guaranteed; a common monocation for **431A** and **431C**, for example, would only be possible if **431C** were to prefer C-protonation to protonation on carbonyl. Such cases do exist but here the incentive is usually aromatisation, as in (**o**) below. A common cation where  $X \neq N$  and  $Y \neq N$ , or at least one that is experimentally accessible, is even less likely and there are no examples of it. The vital importance of LSER to the elucidation of  $K_E$  and  $K_M$  in aqueous solution for such cases requires no further emphasis.

In so far as the observed trends can be quantified we shall attempt to *calculate* from the LSER equations the factor,  $\Delta \log K$ , by which  $K$  as observed in certain organic solvents would have to be adjusted to give the aqueous value. The eight 'selected solvents' (Table 114) have chiefly been chosen as those most commonly employed in spectroscopic studies but sometimes for ancillary reasons, *e.g.* benzene and dioxane for dipole moment measurement. Our hope is to establish patterns that differ from one compound class to another but may stay relatively constant for processes of a similar type, since if so, it may be possible to extrapolate the results, qualitatively at least, to compounds for which only minimal information presently exists.



Scheme 143

**Table 117. Log  $K_T$  for Amides and Thioamides <sup>a</sup>**

Solvent	<b>68</b> <sup>b</sup>	<b>831</b>	<b>965</b>	<b>964</b>	<b>634</b>
2		- 0.44	0.00		
3	- 0.2	- 0.59	- 0.10	1.47	
4		- 0.60	- 0.13		
5		- 0.70	- 0.15		1.47
6		- 0.59	- 0.13		
7		- 0.74	- 0.21		
12		(< -1.69) <sup>c</sup>		0.22	0.26
13		- 1.69 <sup>c</sup>		0.81	0.39
14		- 1.69 <sup>c</sup>		- 0.42 <sup>d</sup>	- 0.71 <sup>d</sup>
17		- 1.54	- 1.10	0.66	
23		- 1.69 <sup>c</sup>	- 0.96		
24	- 1.6	(< -1.69) <sup>c</sup>			
25	- 1.2	(< -1.69) <sup>c</sup>			
29	- 1.5	- 1.10		- 0.42	- 1.03
31		- 0.68	- 0.52	0.62	- 0.23
32		- 0.66	- 0.49	0.46	- 0.26
33	- 0.5	- 0.37	- 1.25	- 0.35	- 0.53
34	- 1.9	- 1.18		- 0.62	
35		- 1.18		- 0.88	- 1.47
1 <sup>e</sup>	1.66	0.47 <sup>f</sup>	0.76	g	g

<sup>a</sup> Data from ref. 379 unless otherwise stated. <sup>b</sup> Data from ref. 84. <sup>c</sup> Not used in eqn. (cxxii), bracketed values not used in either equation; see the text. <sup>d</sup> Outlier; see the text.

<sup>e</sup> Calculated from regression equation. <sup>f</sup> Eqn. (lxiii). <sup>g</sup> See the text.

$$\mathbf{68:} \quad \log K_T = - 2.36(0.22) + 1.56(0.40) \pi^* + 2.22(0.22) \alpha - 0.70(0.26) \beta \quad (\text{lxiv})$$

( $n = 6 \quad r^2 = 0.983 \quad s = 0.14 \quad F = 39$ )

$$\mathbf{831:} \quad \log K_T = - 1.21(0.12) + 0.22(0.22) \pi^* + 1.53(0.15) \alpha - 0.88(0.15) \beta \quad (\text{lxiii})$$

( $n = 16 \quad r^2 = 0.89 \quad s = 0.17 \quad F = 33$ )

$$\mathbf{831:} \quad \log K_T = - 1.21(0.12) + 0.35(0.22) \pi^* + 1.21(0.20) \alpha - 0.65(0.18) \beta \quad (\text{cxxii})$$

( $n = 13 \quad r^2 = 0.855 \quad s = 0.15 \quad F = 18$ )

$$\mathbf{965:} \quad \log K_T = - 1.87(0.71) + 1.12(0.88) \pi^* + 1.09(0.37) \alpha + 0.33(0.30) \beta \quad (\text{lxv})$$

( $n = 11 \quad r^2 = 0.70 \quad s = 0.30 \quad F = 5$ )

### (c) Solvent Effects on Structure 13

Not even qualitative information exists on simple ketones (**13**, Z = O; Scheme 143) which is scarcely surprising given their miniscule enol content (section A.2.3). Bulky groups at R<sup>2</sup> and R<sup>3</sup> greatly increase the proportion of enol (section A.1.3) and work with these might be possible but has not been attempted. The corresponding thiones (**13**, Z = S) have received some qualitative attention however; **13b** predominates in the liquid state and in organic solvents whereas **13a** is favoured in water, perhaps by a factor of *ca.* 10<sup>2</sup> (sections A.3.1 and A.3.2). These suggest the thione tautomer to be the more polar species and the same would be expected for ketones, but quantitative extrapolation could be hazardous; see however (**k**) below. While it is reasonably certain that ketones and enols should be favoured by proton donor and acceptor solvents respectively, at least in relative terms, even 'activated' thiols such as PhSH are such abysmal proton donors<sup>378</sup> that any close parallelism is improbable. The even more limited data for (**13**, Z = NR) are confined to compounds in which R<sup>2</sup> is a  $\pi$ -acceptor, (**l**) below, and there has been no work on simpler cases at all.

### (c) Solvent Effects on Structure 14: Amides

There are some scattered data on pyridones, which we consider later, but the only published compilation comprehensive enough for LSER analysis is that of Beak and Covington,<sup>379</sup> plus a solvent study of **68**<sup>84</sup> which we analyse here (Table 117). The latter appears as eqn. (lxiv) in section B.2.2. The use of three parameters for six data points is scarcely good statistical practice but appears to be justified by the results: only  $\alpha$  is significant on its own ( $r^2 = 0.85$ ) and there is no improvement on adding  $\beta$ , but ( $\alpha + \pi^*$ ) results in  $r^2 = 0.92$  and all three parameters raise this to  $> 0.98$  with a steady fall in  $s$  from 0.33 through 0.24 to 0.14 and a corresponding rise in  $F$ . Equation (lxiv) is also remarkably stable to the 'leave-one-out' procedure and extrapolation to water yields  $\log K_T \sim 1.7$  (Table 117), in line with other estimates (Appendix 5) for the effect on  $K_T$  of quinonoid benzofusion. We therefore consider it reliable.

The only aromatic amide in the set for which Beak and Covington<sup>379</sup> were able to construct a viable LSER equation was 6-chloro-2-pyridone **831** (Scheme 143); they could make no sense of their data for 2-chloro-4-pyridone and neither can we, so this compound has had to be omitted. The remaining compounds are thiopyridones and will be considered later, in (e) below.

**Table 118. Solvent Data (log  $K_T$ ) for some Pyridones**

Compound	Water	EtOH	CHCl <sub>3</sub>	Dioxane	Alkane
<b>847</b> <sup>a, b, c</sup>	1.3	- 0.04	- 0.32 <sup>d</sup>	- 1.3	- 1.5
<b>847</b> <sup>e, f</sup>		0.8		- 0.03	
<b>847</b> <sup>f, g</sup>		0.7		- 0.04	
<b>27</b> <sup>b, c</sup>	2.15	0.76	0.83	- 0.34	- 0.43
<b>28</b> <sup>b, c</sup>	0.85	- 0.48	- 0.66	- 1.78	- 1.85

<sup>a</sup>  $R^3 = R^4 = R^5 = H$ ,  $R^6 = OMe$ . <sup>b</sup> Ref. 20. <sup>c</sup> Aqueous value from Table 105. <sup>d</sup> Value given as 0.32 in ref. 20 but this is clearly out of line and we postulate that its *sign* is a misprint.

<sup>e</sup>  $R^3 = R^4 = H$ ,  $R^5 + R^6 = CH_2OCH_2$ . <sup>f</sup> Ref. 432. <sup>g</sup>  $R^3 = R^4 = H$ ,  $R^5 + R^6 = CH_2SO_2CH_2$ .

**Table 119. ‘Solvent Factors’  $\Delta \log K_T$  for Amides and Thioamides <sup>a</sup>**

Cpd.	Eqn.	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane
<b>68</b>	(lxiv)	1.5	1.9	3.0	2.1	3.4	3.2	3.6	4.1
<b>831</b>	(lxiii)	0.7	1.0	2.1	0.9	1.9	1.6	1.6	1.7
<b>965</b>	(lxxv)	0.8	0.9	1.3	1.5	1.9	1.9	2.3	2.7
<i>b</i>	(cxxiii)	0.9	1.3	2.5	1.5	2.6	2.4	2.5	2.7

<sup>a</sup> The margin by which  $\log K_T$  in a given organic solvent should require adjustment to reproduce that in water. <sup>b</sup> Putative value for a ‘typical’ aromatic amide (see the text).

Beak and Covington<sup>379</sup> employed the Kirkwood function in their LSER treatment of **831** so we have carried out a re-analysis using  $\pi^*$  but certain problems remain. Their results are reported as  $\Delta G^\circ$ , among which several values of 2.3 and  $\geq 2.3$  are to be found. It is clear that the latter represent limiting values and must therefore be discarded as insufficiently defined, but the status of the former is uncertain, so we have conducted the analysis with and without them, to give eqn. (lxiii) which uses all but the bracketed data in Table 117, and (cxxii) from which solvents 13, 14 and 23 have also been omitted. These equations are similar in form and possess very similar consequences but

we prefer (lxiii) since calculations based on it correctly predict that the iminol tautomer should be undetectable in solvents 12, 25 and 26 (*i.e.*  $\log K_T \leq -1.7$ ) whereas using (cxxii) the results are equivocal. However eqn. (lxiii) predicts  $\log K_T$  0.47 for **831** in water whereas direct UV observation gives 1.25 and this value is not only well attested but has been used to calculate  $\Delta(\text{NMe})$  and  $\Delta(\text{OMe})$  values in line with those of other 2-pyridones and related amides (Table 105, Appendix 1). This discrepancy is disturbing and we return to it in (q) below. Still more to the point, it seems probable that neither eqn. (lxiii) nor (lxiv) will be typical of amides, aromatic or otherwise. The chief problem concerns  $\pi^*$ , whose magnitude in eqn. (lxiv) is likely to have been exaggerated by an abnormally large dipole for **68B** resulting from its quinonoid structure, and sharply diminished in eqn. (lxiii) by the opposed dipoles present in **831B**. While the  $\alpha$ - and  $\beta$ -terms are also affected, and in the expected directions, these effects appear as relatively small.

$$\Delta \log K_T = 2.7 - 0.7\pi^* - 1.9\alpha + 0.7\beta \quad (\text{cxxiii})$$

We have accordingly looked for evidence from aromatic amides with less extreme structures. Scattered data are to be found in the work of Spinner and Yeoh<sup>20,432</sup> which have proved suitable for our purposes. Table 118 summarises the data for compounds studied quantitatively in two or more organic solvents (structures in Scheme 143). Some regularity is observable and it is possible, by a rough and ready averaging procedure, to construct the very approximate eqn. (cxxiii). Interestingly, the coefficients of this equation fall almost halfway between those for **68** and **831** (note that, for  $\Delta \log K_T$ , signs of coefficients are necessarily reversed relative to  $\log K_T$  itself). Table 119 sets out the 'solvent factors'  $\Delta \log K_T$  by which  $\log K_T$  should require adjustment to give the aqueous value for each 'selected solvent' as defined in (b) above, according to each equation. All correction factors are positive, *i.e.* maximum values of  $K_T$  are attained in water, and there are important regularities. Most notably, proton acceptor (dipolar aprotic) are as effective as nonpolar solvents in reducing  $K_T$ ; the rôle of DMSO in this respect, while readily explicable, may come as a surprise but is backed by plentiful evidence. There is no direct check on eqn. (cxxiii) from other solvent data but one interesting prediction can be made. For the gas phase, eqn. (cxxiii) calculates as  $\Delta \log K_T$  3.6; this leads to a predicted  $\log K_T$  -0.1 for 2-pyridone itself whereas -0.4 is found.<sup>433</sup> For such an extreme extrapolation this is a tolerably good result and, in the absence of better evidence, we suggest eqn. (cxxiii) as a useful basis for exploratory calculation. We are unaware of any other relevant gas phase data.

### (e) Solvent Effects on Structure 14: Thioamides

Comparison of eqn. (lxiii) for **831** with (lxxv) for **965** reveals one important point of difference: a change in sign for the coefficient of  $\beta$ , from negative to positive. That is: while  $\text{OH} > \text{NH}$  in proton donor strength,  $\text{NH} > \text{SH}$ , in agreement with the results of Abraham *et al.*<sup>378</sup> (Table 45) and as foreshadowed by the near-zero value we have deduced for  $\Delta(\text{SR})$  in Appendix 1. One consequence, visible in Table 119, is the more ‘normal’ positioning of DMSO in the solvent sequence, since its high dipolarity now overshadows its proton acceptor ability and not *vice versa*. The value calculated for water is  $\log K_T$  0.76, a little above that for **831** as is normal for amide-thioamide comparisons (section C.21). In the light of the following paragraphs, however, we can attach no weight to this.

Beak and Covington<sup>373</sup> included the parent compounds 2-pyridithione **964** and 4-pyridithione **634** (the latter included here for convenience) in their LSER analyses; the data appear in Table 117. In their paper they again use the Kirkwood function rather than  $\pi^*$  and give no equation for **634**, so we have re-derived the appropriate LSER equations (Table 120) inclusive of the point for water, in accordance with their practice. As a minor puzzle the aqueous  $\log K_T$  values they incorporate, 4.26 and 3.97 for **964** and **634** respectively, agree neither with those of 4.84<sup>180b</sup> and 4.67<sup>381</sup> derived on ‘naive basicity’ assumptions<sup>21</sup> nor with the corresponding values, of *ca.* 4.6 (section B.3.4) and 4.4 (section A.11.4) which we have deduced by applying the correction factors of Appendix 1. These equations appear in Table 120 as (cxxiv) and (cxxvi) respectively and, while rather coarse, suggest nothing untoward. However, deletion of the point for water, eqns. (cxxv) and (lii), in both cases alters their character profoundly, with a sharp drop in the importance of the  $\pi^*$  term, a very sharp drop in that for  $\alpha$ , and a considerable rise in the  $\beta$ -term. The consequence for both is a spectacular drop in  $\log K_T$  as *calculated* for water: from 3.51 to 2.13 in the case of **964**, and from 3.16 to 1.33 in the case of **634**. Dioxane is a severe outlier in both equations and its removal leads to eqns. (lxxiv) and (cxxvii), in both cases to give much better statistics but with little change in the projected aqueous value.

There is no way of reconciling these projections with either the results of the ‘basicity method’ nor, in all probability, with the facts of the case. While the magnitude of  $\Delta(\text{SMe})$  remains in dispute, this is a matter of fine tuning and neither thione can possibly possess a  $K_T$  value remotely resembling that which these studies suggest. We remain in ignorance as to the

**Table 120. Correlation Equations (log  $K_T$ ) for 2- and 4-Pyridithione, 964 and 634 <sup>a</sup>**

Cpd.	Eqn.	<i>c</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>n</i>	<i>r</i> <sup>2</sup>	<i>s</i>	<i>F</i>
<b>964</b>	(cxxiv) <sup>b</sup>	- 1.26 (0.44)	1.97 (0.75)	1.86 (0.57)	1.10 (0.68)	12	0.87	0.58	17
	(cxxv) <sup>c</sup>	- 0.97 (0.31)	1.46 (0.53)	0.86 (0.49)	1.26 (0.46)	11	0.79	0.39	9
	(lxxiv) <sup>d</sup>	- 0.95 (0.10)	1.74 (0.18)	0.45 (0.18)	1.43 (0.16)	9	0.979	0.13	77
<b>634</b>	(cxxvi) <sup>e</sup>	- 1.81 (0.61)	1.64 (0.99)	2.14 (0.78)	1.69 (0.84)	10	0.86	0.71	12
	(lii) <sup>f</sup>	- 1.44 (0.38)	1.04 (0.61)	0.72 (0.62)	2.00 (0.50)	9	0.85	0.42	10
	(cxxvii) <sup>g</sup>	- 1.43 (0.30)	1.18 (0.49)	0.38 (0.52)	2.21 (0.42)	8	0.92	0.34	15

<sup>a</sup> For discussion see the text. <sup>b</sup> All data points; predicted log  $K_T$  = 3.51 for water. <sup>c</sup> Water omitted; predicted log  $K_T$  = 2.13 for water. <sup>d</sup> Water, benzene and dioxane omitted; predicted log  $K_T$  = 2.06 for water. <sup>e</sup> All data points; predicted log  $K_T$  = 3.16 for water. <sup>f</sup> Water omitted; predicted log  $K_T$  = 1.33 for water. <sup>g</sup> Water and dioxane omitted; predicted log  $K_T$  = 1.18 for water.

**Table 121. Annular Tautomerism in Acylamidines <sup>a</sup>**

Cpd.	Z, R <sup>b</sup>	log $K_T$ : Water	EtOH	DMSO	Dioxane/Benzene <sup>c</sup>	Others
<b>1186</b>	H	- 0.3 <sup>d</sup>	- 0.95 <sup>d</sup>	- 0.5 <sup>d</sup>		(low) <sup>d,e</sup>
<b>1186</b>	SMe	0.9 <sup>f</sup>	0.4 <sup>f</sup>	0.2 <sup>f</sup>		(low) <sup>f,g</sup>
<b>1194</b>	H	- 0.4 <sup>h</sup>	(low) <sup>i</sup>		- 0.65 <sup>j</sup>	
	“ OEt	ca. 0 <sup>k</sup>				(low) <sup>e,k</sup>
	“ NH <sub>2</sub>	ca. 0 <sup>l</sup>	ca. - 1 <sup>l</sup>			(low) <sup>e,l</sup>
<b>1288</b>	H	- 0.9 <sup>m</sup>			- 1.5 <sup>j</sup>	

<sup>a</sup> “(low)” implies undetectable by the method used, probably log  $K_T$  ≤ -1.5. <sup>b</sup> As appropriate; cf. Scheme 143. <sup>c</sup> Used indifferently for dipole moment measurement. <sup>d</sup> Ref. 539. <sup>e</sup> CHCl<sub>3</sub>. <sup>f</sup> Ref. 540. <sup>g</sup> Alkane and CHCl<sub>3</sub>. <sup>h</sup> Ref. 18. <sup>i</sup> Ref. 547. <sup>j</sup> Ref. 548. <sup>k</sup> Ref. 549. <sup>l</sup> Ref. 550. <sup>m</sup> Employing the ‘basicity method’ (section B.6.2).

nature of the phenomenon we have unearthed; there are no mitigating circumstances such as, for example, the lack of rigidity that may plausibly be adduced as a perturbing factor in some other cases. At the very least, these results emphasise the necessity of excluding the datum for water from any LSER treatment one of whose purposes is to rationalise its value. Essentially, eqns. (cxxiv) and (cxxvi) consist in two-point correlations: the point for water is out on its own, at  $\log K_T$  *ca.* 4, whereas the rest form essentially a cluster over a comparatively narrow, and quite distant, range (*vide* Table 117). This is as far as we can take the subject at the present time. The whole quantitative aspect of thioamide tautomerism is in urgent need of re-investigation.

#### (f) Solvent Effects on Annular Tautomerism

Scattered information exists on two kinds of structure: the cyclic acylamidines of type **1186**, **1194** and **1288**, and the 5-membered ring monocyclic heterocycles  $\nu$ -triazole **751** (section B.1.3) and tetrazole **752** (section B.1.4). There are insufficient data in either case for LSER analysis but the trends observed are suggestive. Data for the former class (Scheme 143) appear in Table 121. Here the solvent order in  $\pi^*$  is water > DMSO > EtOH  $\sim$  benzene > dioxane >  $\text{CHCl}_3$  > alkane, and allowing for minor discrepancies, this is the order in  $\log K_T$  as well. Given that the amidine unit is common to both tautomers, so that effects due to solvent hydrogen bonding are likely to cancel between them, it is reasonable that the dominant solvent property should be dipolarity/polarisability, and this may be general for amidines. The 1-methyl and 3-methyl derivatives of (**1194**, R = H) possess dipole moments of 7.50 and 2.24 debyes respectively,<sup>548</sup> consistently with the trend on  $K_M$  observed.

The data for  $\nu$ -triazole do not fit this pattern and are at first sight contradictory. However, while there are insufficient results for LSER analysis, it is possible to understand its solvent behaviour in terms of two opposed trends. While the more polar **751C** (Scheme 143) is the major tautomer in water (67%) and MeOH (70 - 90%), and on a par with **751A** in DMSO (55%), it is also increasingly favoured as solvent polarity falls, to the extent of 80% in  $\text{CH}_2\text{Cl}_2$  and 97% in toluene, while **751A** is undetectable in the gas phase (section B.1.3). The missing factor is presumably the severe lone pair repulsion present in **751A** which is mitigated by proton donor solvents and, to a limited extent, by those of exceptionally high polarity. In partial confirmation it is found that, on benzofusion which for **751C** leads to

a quinonoid structure, this tautomer is observed only in the gas phase (about 50%) where lone pair repulsion will be maximised (section B.1.6). Tetrazole (**752**, R = H) behaves quite differently: it exists overwhelmingly as the more polar tautomer **752A** in water, acetone, DMF and DMSO, with 80 - 95% still present in dioxane, whereas **752B** is dominant only in the gas phase. While **752B** has the lower dipole moment both tautomers possess the potential for lone pair repulsion, and it is presumably the near-cancellation of this factor that makes the difference. The only quantitative data are for (**752**, R = Ph) in DMSO and dioxane, giving  $\log K$  1.1 and 0.4 respectively in favour of **752A**, in line with the qualitative picture for tetrazole itself.

#### (g) Extended 3-Way Equilibria: $K_T$ in **260**

In principle,  $K_T$  for (**260**, X = Y) need not be unity if R<sup>1</sup> and R<sup>2</sup> differ enough, but no such compound has been investigated and the two known examples are aminoenones: X = NR, Y = O. The ideal exemplar would be a vinylogous amide of type **435** (Scheme 144) but, as with their amidic equivalents,  $K_T$  is so large as to render this impractical, and unfortunately the structural modifications that have allowed **431** and **613** to be studied have also rendered them atypical. Nevertheless the results are presented here for comparison both with the corresponding chelates and with amides themselves, since parallelisms do in fact occur.

An LSER treatment of  $K_T$  in **431** (Scheme 141) leads to eqn. (xix), show below Table 116, whereas eqn. (xlviii) for **613** appears below Table 122 which contains the relevant data. Calculated 'solvent factors' for both appear in Table 123; as for amides (Table 119) all are positive, *i.e.* the C-tautomer is favoured most in water. While solvent variation is less for **613** than for **431**, perhaps because the tautomeric unit is still more extended, and less for either than for an amide, there are also substantial resemblances; in particular, eqns. (lxii) for **831** and (xix) for **431** possess closely similar consequences. The smallest correction factor required for either is that from CHCl<sub>3</sub>, and this solvent also gives one of the better matches for amides *per se*; DMSO by contrast more resembles a solvent of low or intermediate polarity, such as the last four in the 'selected series.' These differences are readily explicable but may still generate surprise. Even MeOH however falls well short of reproducing water, typically for both by an order of magnitude in  $K_T$ , an effect already one-third to two-thirds of the whole solvent range. This behaviour will be contrasted with that for the corresponding chelates in (h) below.

**Table 122. Log  $K_T$  Values for Aromatic Schiff Bases and Related Azo-Compounds<sup>a</sup>**

Solvent	<b>613</b>	<b>588</b>	<b>586</b>	<b>587</b>	<b>611</b>	<b>612</b>
2	- 0.59	0.95	- 0.02	0.06	0.19	0.31
3	- 0.85		- 0.03	0.17	- 0.21	0.30
5				0.00		
12			- 0.87	- 0.62		
16	- 0.43		- 0.48	- 0.35		0.25
17	- 0.59			- 0.46		0.26
20	- 0.24		- 0.25		- 0.18	0.35
21	0.17				0.45 <sup>b</sup>	
22	- 1.06			- 0.31		0.20
25	- 0.90	0.30 <sup>c</sup>	- 0.12	- 0.08		0.22
28		0.30				
30				- 0.52		
31						0.36
32	0.20		- 0.23	- 0.19	- 0.08	0.40
33	0.13	0.40	- 0.28		0.17	0.40
34		- 0.55	- 0.83	- 0.66	- 0.25	0.33
35				- 0.70		0.21
36			- 1.06			
37 <sup>d</sup>	- 0.94				- 0.31	0.18
1 <sup>e</sup>	> 0 <sup>f</sup>		0.43	0.49	0.07	
1 <sup>g</sup>	0.61	1.86	0.58	0.58	0.48 <sup>h</sup>	0.51

<sup>a</sup> Data from ref. 356. <sup>b</sup> Outlier (see the text). <sup>c</sup> Estimated from value for **590** using the close parallelism between other values for **588** and **590** (see the text). <sup>d</sup> Iso-octane.

<sup>e</sup> Experimental, by extrapolation from EtOH-water mixtures. <sup>f</sup> The relationship between log  $K_T$  and solvent composition in EtOH- water is too non-linear to permit of extrapolation.

<sup>g</sup> Calculated from appropriate LSER equation in Table 123 (see the text). <sup>h</sup> This becomes 0.46 if the  $\pi^*$  term in eqn. (xliv) is omitted.

For **613**:

$$\log K_T = -0.81(0.17) + 1.17(0.26) \pi^* + 0.63(0.19) \alpha - 1.50(0.26) \beta \quad (\text{xlviii})$$

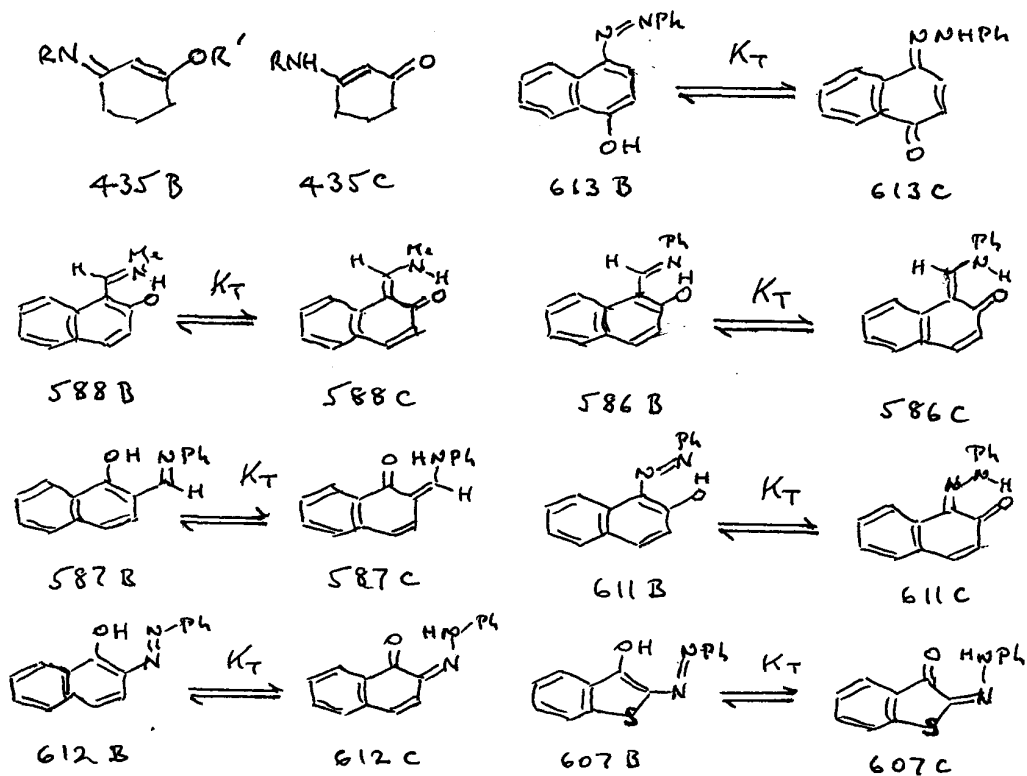
( $n = 11$   $r^2 = 0.86$   $s = 0.21$   $F = 14$ )

### (h) 3-Way Equilibria for Chelates: $K_T$ in (261, X = NR, Y = O)

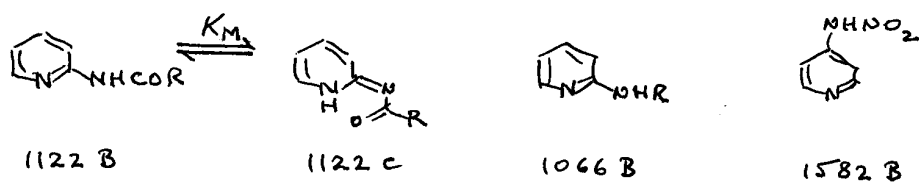
Compounds appear in Scheme 144 along with those for the preceding section. As noted in (b) above, the only compounds of this type for which  $K_T$  is likely to be accessible are those in which the **B**-tautomer is stabilised by aromatisation, so that quantitative data are confined in practice to the aromatic Schiff bases (section A.10.18) and related azo-compounds (section A.10.19) whose LSER analyses we have published.<sup>356</sup> The data appear in Table 122, the correlation equations in Table 123, and the ‘solvent factors’ deduced in Table 125, for comparison with those for **431** and **613** in Table 124 and for amides in Table 119.

Outstandingly, solvent sensitivity is highly variable. Among Schiff bases **588** covers twice the range in  $\Delta \log K_T$  as **587**, with an even further drop for the azo-compounds **611** and **612**. While all coefficients contribute, the central driving force appears to be the varying electron donor ability of NHR, which is less for NHPH than for NHMe and so leads to a 20-fold drop in  $K_T$  for water. This result carries the clear implication that, as  $K_T$  declines, solvent sensitivity will decline with it, a conclusion which may extend much further. If so we may have to abandon any notion of ‘typical’ behaviour inside a class, as was suggested above for eqn. (cxxiii). In fact, the evidence concerning amides is equivocal. While **68** possesses a greater solvent sensitivity than **831** (Table 119) as well as a higher  $K_T$ , this is mostly the result of a very large  $\pi^*$  term consequent on the quinonoid structure which actually *reduces* its  $K_T$  value relative to benzofused structures that do not possess it, and whereas the same parallelism exists (Table 124) for **431** and **613**, these are too different in structure to enable firm conclusions to be drawn. More evidence is needed.

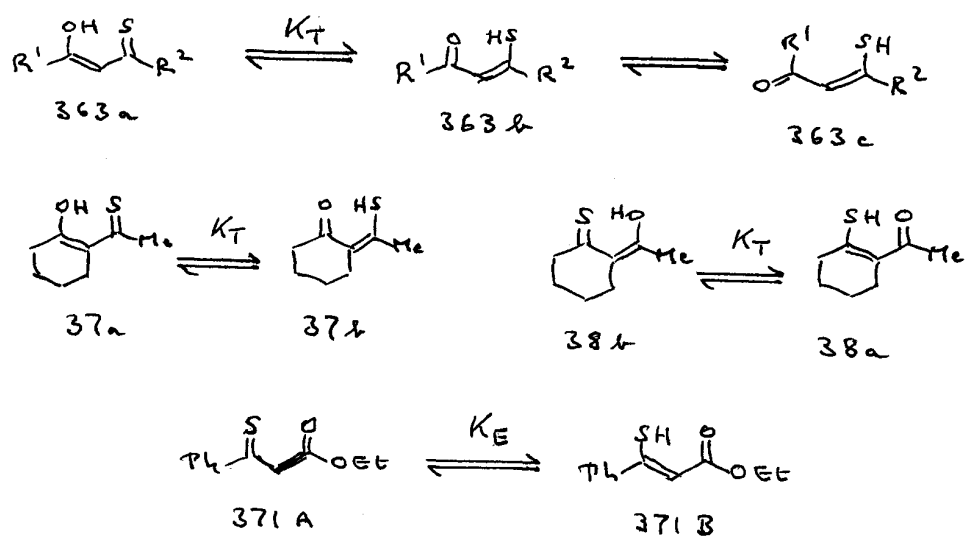
The azo-compounds **611** and **612** differ from the Schiff bases **586** – **588** in two important respects. Firstly, their LSER equations contain a term in  $\beta$ ; this indicates some breakage of the chelate bond and its sign implies a greater importance of this for the **B**-tautomer, the result of very poor proton acceptor properties for the azo-linkage.<sup>356</sup> One result is that while Schiff bases lose the extreme sensitivity to strong proton acceptor solvents that is noted above for amides, this returns in the azo-compounds. The other is a solvent sensitivity for the latter class that is quite abnormally low. This decline mostly results from a near-zero  $\pi^*$  term which must imply little difference in



Scheme 144



Scheme 145



Scheme 146

**Table 123. Correlation Equations in log  $K_T$  for Chelates (261, X = NR, Y = O) <sup>a</sup>**

Cpd.	Eqn.	<i>c</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>n</i>	<i>r</i> <sup>2</sup>	<i>s</i>	<i>F</i>
<b>588</b>	(xlili)	- 0.87 (0.12)	1.25 (0.16)	1.17 (0.11)		5	0.987	0.09	74
<b>586</b>	(xli)	- 1.05 (0.04)	0.85 (0.07)	0.60 (0.06)		10	0.976	0.07	143
<b>587</b>	(xlili)	- 0.76 (0.06)	0.55 (0.10)	0.63 (0.07)		12	0.94	0.08	74
<b>611</b>	(xlvi)	- 0.29 (0.10)	0.11 (0.19)	0.79 (0.27)	- 0.68 (0.28)	7	0.81	0.12	4
<b>612</b>	(xlvii)	0.23 (0.02)	0.17 (0.04)	0.16 (0.03)	- 0.23 (0.03)	13	0.87	0.03	20

<sup>a</sup> Data in Table 122.**Table 124. 'Solvent Factors'  $\Delta \log K_T$  for Extended Species 260**

Cpd.	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane
<b>431</b> <sup>a,b</sup>	1.1	1.5	2.1	0.9	2.0	1.6	1.7	2.1
<b>613</b> <sup>a,c</sup>	1.1	1.4	1.4	0.5	1.0	0.8	1.1	1.5

<sup>a</sup> See the text. <sup>b</sup> Employing eqn. (xix). <sup>c</sup> Employing eqn. (xlviii).**Table 125. 'Solvent Factors'  $\Delta \log K_T$  for Chelates (261, X = NR, Y = O) <sup>a, b</sup>**

Cpd.	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane
<b>588</b>	0.9	1.1	1.5	1.5	2.0	2.0	2.4	2.8
<b>586</b>	0.6	0.7	0.8	0.9	1.2	1.1	1.4	1.7
<b>587</b>	0.4	0.5	0.8	0.7	1.0	1.0	1.2	1.4
<b>611</b>	0.4	0.6	1.2	0.4	1.0	0.8	0.8	0.9
<b>612</b>	0.2	0.3	0.3	0.1	0.1	0.2	0.2	0.3

<sup>a</sup> See the text. <sup>b</sup> Employing relevant equation in Table 123.

tautomer polarity, despite which **611** and **612** possess almost identical aqueous  $K_T$  values to **586** and **587** (Table 122). However, factors other than tautomer polarity can affect  $K_T$ . Enamines (*e.g.* **586C**) are disfavoured relative to imines except when joined to electron acceptors (section A.4.1) whereas azo-compounds go predominantly to hydrazones (*e.g.* **611C**) whenever possible whatever the nature of the terminal nitrogen substituent, *e.g.* Ph or Me in Scheme 144 (section A.5.1); hence a fortuitous cancellation of properties probably explains this apparent paradox.<sup>356</sup>

The only qualitative evidence we have encountered concerns **607** and a handful of related compounds (section A.10.19). This exists as **607B** in DMSO but as an unspecified mixture of tautomers in  $\text{CHCl}_3$ . That is the *direction* expected from Table 125 and the difference between  $\log K_T$  in DMSO and  $\text{CHCl}_3$  shown by **611** would be sufficient to explain the result for **607** and, incidentally, to predict **607C** as the major tautomer in water, though probably not by much. It should be possible to extend this type of argument as data on other compounds become available.

**(i) 3-Way Equilibria for Chelates:  $K_T$  in (261, X = NR, Y = NR')**

All published data are for the *exo*-substituted aminopyridines of Scheme 145 (Table 126). Their surprising feature is the considerably larger gap in  $K_T$  between water and ethanol than between ethanol and dioxane, a feature that  $K_T$  shows in no other context. So far as is discernible their overall range is greater than that found for chelated aminoenones (Table 125) and more like that of an amide (Table 119). The overall range of **1582** is probably greater than that of (**1066**, R =  $\text{NO}_2$ ), plausibly because of its longer conjugated system. However there is insufficient information to disentangle the effect of intramolecular hydrogen bonding in **1066** which may also contribute to this difference.

**(j) 3-Way Equilibria for Chelates:  $K_T$  in (261, X = S, Y = O)**

The enolised tautomers of  $\beta$ -thionoketones (section A.8.3) are closely in balance, an apparent paradox since  $K_E$  for thioketones is very much larger than that for ketones (section A.3), and only to be explained by a detailed consideration of the energetics (section A.8.1). Since in addition the unconjugated tautomer is never visible (there is one contrary claim that **371A** is present as a minor species in ethanol), the only equilibrium to be studied is  $K_T$ , here to be defined as leading to the oxo-form.

**Table 126. Solvent Data for Acyl- and Nitroamidines<sup>a</sup>**

Compound	R	log $K_M$ in:	Water	EtOH	Dioxane	Alkane
<b>1122</b> <sup>b</sup>	CHCl <sub>2</sub>		- 1.9	- 3.3	- 3.8	
<b>1122</b> <sup>b</sup>	CCl <sub>3</sub>		- 1.0	- 2.2	- 2.7	- 3.6
<b>1066</b> <sup>c</sup>	NO <sub>2</sub>		1.7 <sup>d</sup>	0.2	- 0.8	
<b>1582</b> <sup>c</sup>			2.0		- 1.2	

<sup>a</sup> See section (i). <sup>b</sup> Ref. 511. <sup>c</sup> Ref. 251. <sup>d</sup> Calculated from eqn. (xcii), section B.4.4.

**Table 127. Log  $K_T$  for  $\beta$ -Thionoketones<sup>a</sup>**

Cpd.	R <sup>1</sup>	R <sup>2</sup>	MeCN	Dioxane	CH <sub>2</sub> Cl <sub>2</sub>	CHCl <sub>3</sub>	CCl <sub>4</sub>	C <sub>6</sub> H <sub>12</sub>	Water <sup>b</sup>
<b>363</b>	Me	Me	- 0.21	- 0.31	- 0.29	- 0.29	- 0.55	- 0.60	0.32
<b>363</b>	Me	Pr <sup>i</sup>	- 0.10	- 0.27	- 0.29	- 0.27	- 0.55	- 0.60	0.52
<b>363</b>	Me	Bu <sup>t</sup>	- 0.07	- 0.25	- 0.27	- 0.27	- 0.60	- 0.63	0.63
<b>37</b>			- 0.66	- 0.75	- 0.72	- 0.69	- 1.12	- 1.28	0.26
<b>38</b>			0.87	0.79	0.83	0.79	0.35	0.29	1.73

<sup>a</sup> Data from ref. 59. <sup>b</sup> Extrapolated from regression eqns. of Table 128.

**Table 128. Correlation Equations for Chelates (261, X = S, Y = O)<sup>a</sup>**

Cpd.	R <sup>1</sup>	R <sup>2</sup>	Eqn.	$c$	$s$	$a$	$b$	$n$	$r^2$	$s$	$F$
<b>363</b>	Me	Me	(cxxxviii)	- 0.61 (0.01)	0.22 (0.02)	0.43 (0.03)	0.47 (0.03)	6	0.999	0.01	830
<b>363</b>	Me	Pr <sup>i</sup>	(cxxxix)	- 0.61 (0.03)	0.20 (0.10)	0.54 (0.16)	0.71 (0.14)	6	0.985	0.04	43
<b>363</b>	Me	Bu <sup>t</sup>	(cxxxv)	- 0.65 (0.03)	0.24 (0.11)	0.60 (0.18)	0.81 (0.16)	6	0.986	0.04	46
<b>37</b>			(cxxxix)	- 1.25 (0.04)	0.41 (0.14)	0.68 (0.22)	0.65 (0.20)	6	0.985	0.05	43
<b>38</b>			(cxxxii)	0.27 (0.05)	0.41 (0.15)	0.63 (0.22)	0.68 (0.21)	6	0.982	0.05	37

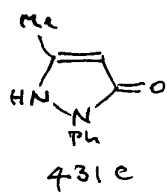
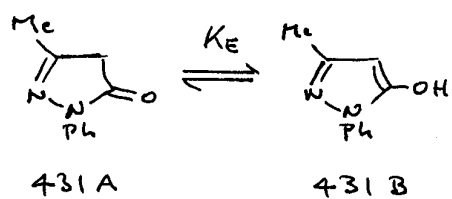
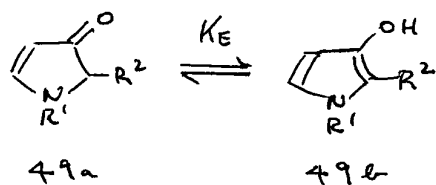
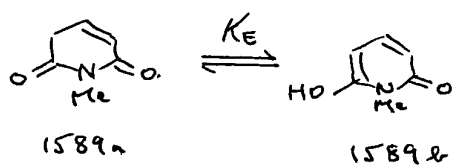
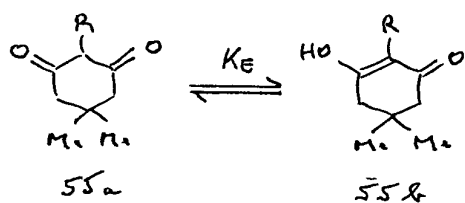
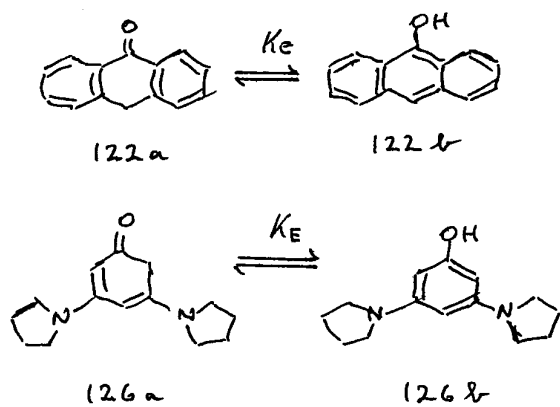
<sup>a</sup> Log  $K_T$ ; data in Table 127.

All the available quantitative material is due to Duus<sup>59</sup> and is set out in Table 127. The correlation equations (Table 128) are all very similar, with rather small terms in  $\pi^*$  (probably reflecting a nearly equal degree of conjugation for each tautomer) and still quite modest ones in  $\alpha$  and  $\beta$ . There is good spectroscopic evidence (section A.8.3) that the dominant thioenol form of **363** (Scheme 146) is **363c** not **363b**, even in nonaqueous solution, and the *positive* sign of the  $\beta$ -term throughout gives this strong support – the *opposite* situation to that which occurs in the azo-compounds of Table 123. (This phenomenon has not been reported for **37** or **38** so is not shown on Scheme 146, but Table 128 provides clear evidence for its presence). If we assume that the OH---S bond of the thione tautomer is too strong for any solvent to break, the  $\beta$ -term becomes a measure of the pure proton donor ability of SH; comparison with eqns. (x) and (xvii), giving  $\beta$  a range of 3.6 – 4.4 in contrast to 0.5 – 0.8 for the compounds of Table 128, helps to emphasise how far SH falls short of OH as a proton donor even when each is conjugated with a powerful electron acceptor. Because of this, and given the absence of amphiprotic solvents among those employed, it may be unwise to put too much weight on the calculated aqueous values of Table 127; if **363c** is a still more dominant thiol species in water than elsewhere,  $K_T$  in aqueous solution could be quite seriously underpredicted – *cf.* (m) below. Leaving this aside, however, the solute sensitivity shown by these compounds,  $\Delta \log K_T$  *ca.* 1 – 1.4, is sufficiently modest to provide some support for the hypothesis that low values may tend to be associated with a rather small energetic difference between the tautomers.

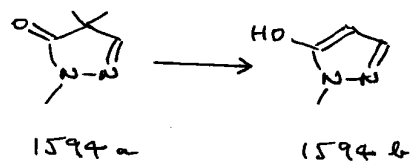
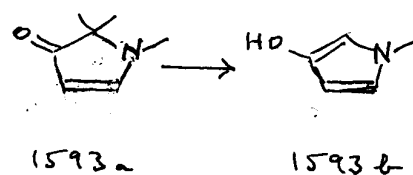
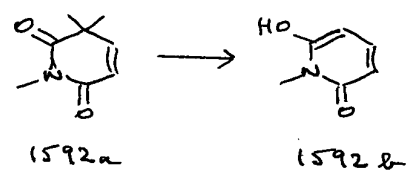
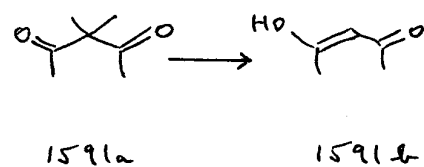
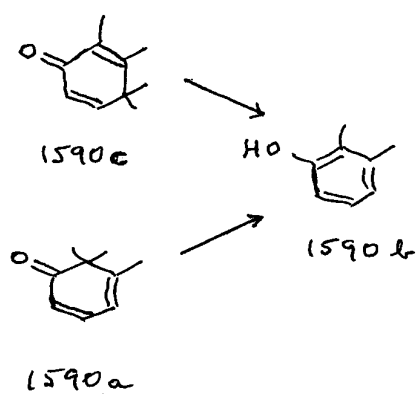
The difference between **37** and **38** is contained almost entirely in the intercept term, and scarcely changes across the solvent range, hence some extraneous factor must be present. This factor is presumably the preference for *endo*- over *exo*-(C=C) in 6-membered rings, as discussed in section A.1.2. Here it should destabilise **37b** and **38b**, with opposite effects on  $K_T$  relative to those for **363**. For nonpolar solvents this is found, with  $\Delta \log K_T$  *ca.* -0.7 and +0.9 in C<sub>6</sub>H<sub>12</sub> for **37** and **38** respectively, but in water most of this, while overall similar, is found in  $\log K_T$  for **38**. There seems no obvious explanation for this but it tends to reinforce the impression that LSER is not good at extrapolating to water the behaviour of thiones in organic solvents; *cf.* (e) above.

### (k) Extended 3-Way Equilibria: $K_E$ in 260

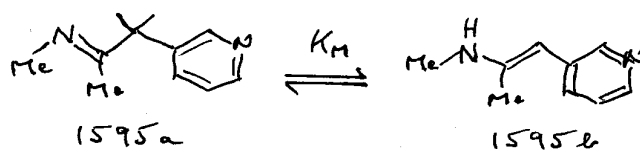
Two independent criteria help to dictate the pattern of solvent effects: extended *vs.* chelated structures, and  $K_T$  *vs.*  $K_E$  (or sometimes  $K_M$ ) where we employ the first to indicate tautomerism between two sorts of conjugated structure, and the second to designate either the generation of conjugation *de*



Scheme 147



Scheme 148



Scheme 149

*novo* or its enhancement *e.g.* by aromatisation. Scheme 142 sets out the ways in which these criteria can interweave. Sub-sections (c) – (j) are concerned with  $K_T$ ; this and the following sub-sections concern  $K_E$  and/or  $K_M$ .

Quantitative data are available in two or more solvents for six compounds that belong in this category. These are: dimedone (**55**,  $R = H$ ), Table 115; compound **431** (Table 116), for which  $K_E$  is relevant here; anthrone **122**, Table 129; and (**49**,  $R^1 = Bu^t$ ,  $R^2 = H$ ), **126**, and **1589**, assembled in Table 130. There are enough data to generate LSER equations for four of these six, the exceptions being **1589**, for which there are only two firm and two approximate data points, and **126**, whose published LSER equation is statistically invalid.

On the basis of their data set (Table 130) Highet and Chou<sup>118</sup> derived an LSER equation for **126** in ( $\alpha - \beta$ ). Leaving out water we obtain eqn. (cxxxv), which with  $r^2 = 0.979$  appears to be highly significant. However if  $\alpha$  and  $\beta$  are used as separate parameters, eqn. (cxxxvi), the statistics are still better, yet instead of comparable coefficients as expected from ( $\alpha - \beta$ ) these are totally out of balance, an apparent paradox, and eqn. (cxxxvii) for  $\beta$  alone is the best of all. The key fact here is that every solvent except water is an alkanol, for which  $\pi^*$ ,  $\alpha$  and  $\beta$  are colinear variables; if any one of these gives satisfactory results it is *inevitable* that any other, or any combination of them, must also do so. But this is entirely misleading. Even water is badly predicted: these equations solve to give  $\log K_E$  0.01, 0.28 or 0.28 respectively where the experimental value is -0.95. No equation based on homologues can be valid outside the series from which it is derived.

Anthrone **122** also presents problems. This was studied by Mills and Beak;<sup>80</sup> as with **831** in (d) above, it is not always clear whether very low values of  $K_E$  are approximations, crude but usable, or upper limits, in which case they have to be excluded from the analysis. So we have carried this out in two ways. For eqn. (cxxxiii) we have used all their data except those in triethylamine (27) and benzene (29), so covering a range of 0.26 to -1.22 in  $\log K_E$  (Table 129). For eqn. (cxxxiv) benzene was restored and two were added which they quote from other sources, acetone (16) and toluene (30) while -0.89, for (33), was rejected as an outlier; this extends the range in  $\log K_E$  to -2.6. While the latter equation is statistically poorer it gives a much better fit to the data at low  $K_E$ , at least in justifying values predicted as  $\leq 10^{-3}$  as probably too low to be measurable, and we therefore consider it the better one. The outstanding difference between eqns. (cxxxiii) and (cxxxiv) lies in the coefficient of  $\beta$ , whose much larger value for the second is more in accord with what is found elsewhere for generation of OH *de novo* (see below). Their predictions for  $\log K_E$  water are -0.50 and -1.64 respectively;

**Table 129. Log  $K_E$  for the Enolisation of Anthrone 122a <sup>a</sup>**

Solvent	log $K_E$ , obs.	eqn. (cxxxiii), calc.	eqn. (cxxxiv), calc.
2	- 1.00 <sup>b, c</sup>	- 1.06	- 1.47
3	- 0.82 <sup>b, c</sup>	- 0.95	- 1.01
5	- 0.96 <sup>b, c</sup>	- 0.80	- 0.47
6	- 1.00 <sup>b, c</sup>	- 0.77	- 0.37
12	- 1.22 <sup>b, c</sup>	- 1.44	- 1.53
13	- 0.70 <sup>b, c</sup>	- 0.73	- 0.82
14	- 1.15 <sup>b, c</sup>	- 1.02	- 1.41
16	(- 0.66) <sup>c</sup>	- 0.60	- 0.92
17	- 1.22 <sup>b, c</sup>	- 0.92	- 1.17
22	0.11 <sup>b, c</sup>	0.05	0.05
23	0.26 <sup>b, c</sup>	0.14	0.27
25	0.20 <sup>b, c</sup>	0.38	0.45
27	0.04 <sup>d, e</sup>	- 1.40	- 0.98
28	0.15 <sup>b, c</sup>	- 0.04	- 0.11
29	- 2.52 <sup>c, d</sup>	- 1.18	- 2.17
30	(- 2.60) <sup>c</sup>	- 1.37	- 2.22
31	( $\leq$ - 3)	- 1.04	- 2.15
32	( $\leq$ - 3)	- 1.10	- 2.43
33	( $\leq$ - 3) (- 0.89) <sup>d, e</sup>	- 1.65	- 2.92
34	( $\leq$ - 3)	- 2.02	- 2.94
35	( $\geq$ - 3)	- 2.58	- 3.36
1	(- 2.1 <sup>f</sup> )	- 0.50	- 1.64

<sup>a</sup>Data from ref. 60 except where bracketed. <sup>b</sup>Data point used in eqn. (cxxxiii). <sup>c</sup>Data point used in eqn. (cxxxiv). <sup>d</sup>Outlier from eqn. (cxxxiii). <sup>e</sup>Outlier from eqn. (cxxxiv). <sup>f</sup>Ref. 116.

For **122**:

$$\log K_E = - 2.58(0.26) + 1.99(0.35) \pi^* - 0.51(0.22) \alpha + 1.27(0.48) \beta \quad (\text{cxxxiii})$$

( $n = 12$   $r^2 = 0.926$   $s = 0.19$   $F = 33$ )

$$\log K_E = - 3.36(0.34) + 1.49(0.56) \pi^* - 0.96(0.34) \alpha + 3.05(0.50) \beta \quad (\text{cxxxiv})$$

( $n = 15$   $r^2 = 0.89$   $s = 0.33$   $F = 29$ )

**Table 130. Log  $K_E$  Values for some Variants on 260, Y = O <sup>a</sup>**

Solvent	Compound:	<b>126</b> <sup>b</sup>	<b>49</b> , R <sup>1</sup> = Bu <sup>t</sup> , R <sup>2</sup> = H <sup>c</sup>	<b>1589</b> <sup>d</sup>
2		0.74	- 0.45	
3		1.23		0.75
5		1.59		
6		1.37		
7		1.68		
8		0.57		
13			0.69	
16			0.48	
22			0.72	
25			1.28	0.25
33			- 0.95	< - 2.7
1		- 0.95 <sup>e</sup>		≥ 0.2
1 <sup>f</sup>			- 1.06 <sup>g</sup> - 1.19 <sup>h</sup>	

<sup>a</sup> Scheme 147. <sup>b</sup> Ref. 118. <sup>c</sup> Ref. 66. <sup>d</sup> Ref. 211. <sup>e</sup> Not used in eqns. (cxxxv), (cxxxvi) or (cxxxvii). <sup>f</sup> Calculated from regression equation. <sup>g</sup> Eqn. (cxxxviii). <sup>h</sup> Eqn. (cxxxix).

Regression equations in log  $K_E$  for **126**:

$$\log K_E = 1.23(0.03) - 1.59(0.12) (\alpha - \beta) \quad (\text{cxxxv})$$

$$(n = 6 \quad r^2 = 0.979 \quad s = 0.07 \quad F = 190)$$

$$\log K_E = - 0.38(0.11) - 0.23(0.94) + 2.33(0.45) \beta \quad (\text{cxxxvi})$$

$$(n = 6 \quad r^2 = 0.988 \quad s = 0.06 \quad F = 123)$$

$$\log K_E = - 0.66(0.11) + 2.34(0.13) \beta \quad (\text{cxxxvii})$$

$$(n = 6 \quad r^2 = 0.988 \quad s = 0.06 \quad F = 321)$$

Regression equations in log  $K_E$  for (**49**, R<sup>1</sup> = Bu<sup>t</sup>, R<sup>2</sup> = H)

$$\log K_E = - 0.49(0.52) + 0.22(0.79) \pi^* - 1.32(0.30) \alpha + 1.83(0.45) \beta \quad (\text{cxxxviii})$$

$$(n = 6 \quad r^2 = 0.974 \quad s = 0.21 \quad F = 25)$$

$$\log K_E = - 0.36(0.19) + 1.36(0.22) \alpha + 1.91(0.30) \beta \quad (\text{cxxxix})$$

$$(n = 6 \quad r^2 = 0.973 \quad s = 0.18 \quad F = 54)$$

the experimental value is -2.1 (section A.2.6). For (**49**,  $R^1 = \text{Bu}^t$ ,  $R^2 = \text{H}$ ), data in Table 130, there are again two possible equations, (cxxxviii) and (cxxxix), which differ in retaining or removing the nonsignificant  $\pi^*$  term; the only appreciable difference this makes is in the value predicted for water,  $\log K_E$  -1.06 or -1.19, both a little more negative than -0.89 and -0.74 as reported for their NH and NMe homologues (section A.2.7). We leave this question open. There are no problems for the other compounds, **55** and **431** (Schemes 141 and 147), whose LSER equations appear in (a) above.

'Solvent factors' appear in Table 131; if positive these indicate more enolisation than in water, and *vice versa*. While it is clear that no universal pattern of behaviour exists, we may seek to rationalise the trends. As a general guide, the largest solvent variations appear to correlate with enolisation to give 'activated' OH, *i.e.* when this is conjugated with a strong electron acceptor. The largest electronic flux in this set is probably that due to enolisation of the archetypal  $\beta$ -diketone **1591** (Scheme 148), exemplified here (Scheme 147) by dimedone (**55**,  $R = \text{H}$ ), whose (calculated) shift of  $\Delta \log K_E$  3.2 between water and alkane is largely due to a coefficient  $b$  for  $\beta$  (eqn. cxxi) of 4.4 (eqn. x), the largest for any of these parameters so far identified. One might expect the next largest to attach either to the  $\gamma$ -diketone structure **1592**, exemplified by **1589**, or the  $\beta$ -iminoketone structure **1594**, exemplified by **431**. Too few data points exist for **1589** to allow any meaningful estimate, though its very high 'solvent factor' for  $\text{CHCl}_3$  is suggestive, but **431** with  $\Delta \log K_E$  2.2 and  $b = 3.6$  (eqn. xvii) is second only to dimedone in either respect. Generation of aromatic OH as in **1590** comes next in line; here anthrone **122** is our only, rather atypical exemplar, and as discussed above, neither equation is very satisfactory. However eqn. (cxxxiv) which we believe to be the more predictive possesses  $b \sim 3.0$  and both point to  $\Delta \log K_E \leq 2$ . Last in terms of solvent sensitivity comes (**49**,  $R^1 = \text{Bu}^t$ ,  $R^2 = \text{H}$ ), with DMSO as elsewhere a strong promoter of enolisation but, for the rest, an unusually flat response. This comes about since the influence of  $b \sim 1.9$  is largely offset by a *negative* term in  $\pi^*$ , which is not found elsewhere in this series and presumably results from loss of the aminoenone conjugation present in **49a**. Note also that **49b** is effectively cross-conjugated; *cf.* **1594b** *vs.* **1594a** in Scheme 148. It may be that LSER analysis of **126** with a more varied solvent set would reveal a similar situation.

However tentative this picture, since the evidence is so fragmentary, it does suggest a pattern that makes sense. For enol formation in the *extended* structure **260**, increasing solvent sensitivity seems to be associated with increasing proton donor ability of OH as encapsulated in the  $\beta$ -term. It will be seen below that the behaviour of the *chelated* structure **261** is different.

**Table 131. ‘Solvent Factors’  $\Delta \log K_E$  for Compounds of Type 260, Y = O**

Compound	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane
<b>55</b> <sup>a, b</sup>	- 0.5	- 1.0	- 0.7	2.6	1.3	2.4	3.0	3.2
<b>126</b> <sup>c</sup>	- 1.7	- 2.2						
<b>122</b> <sup>d</sup>	0.6	0.5	- 0.9	1.2	0.5	0.8	1.5	1.9
“ <sup>e</sup>	- 0.2	- 0.6	- 2.1	1.3	- 0.2	0.5	1.3	1.8
<b>49</b> <sup>f, g</sup>	- 0.7	- 1.2	- 2.3	- 0.2	- 1.5	- 1.0	- 0.8	- 0.8
<b>1589</b> <sup>h</sup>		- 0.5	0.0	(3)				
<b>431</b> <sup>i</sup>	- 0.5	- 1.0	- 1.2	1.8	0.5	1.4	2.0	2.2

<sup>a</sup> R = H. <sup>b</sup> Eqn. (x). <sup>c</sup> No viable correlation equation (see the text); these are log  $K_E$  values relative to those in water. <sup>d</sup> Eqn. (cxxxiii). <sup>e</sup> Eqn. (cxxxiv). <sup>f</sup> R<sup>1</sup> = Bu<sup>t</sup>, R<sup>2</sup> = H. <sup>g</sup> Eqn. (cxxxix). <sup>h</sup> Log  $K_E$ , ref. 211. <sup>i</sup> Eqn. (xvii).

**Table 132. ‘Solvent Factors’  $\Delta \log K_M$  for Compounds of Type 261, Y = NR**

Compound	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane
<b>431</b> <sup>a</sup>	0.5	0.3	0.7	3.0	2.6	3.3	4.2	4.8
<b>1595</b> <sup>b, c</sup>			0.2			- 0.4		

<sup>a</sup> Eqn. (xviii). <sup>b</sup> Scheme 149. <sup>c</sup> No known aqueous value, so these are log  $K_M$ .

As noted in (c) above, nothing is known concerning solvent effects on simple aliphatic or alicyclic keto-enol tautomerism. Since enols and phenols possess very similar  $pK_a$  values<sup>17</sup> it may be that  $a \sim -1$  as for anthrone **122** can be predicted in such cases, while on the same grounds  $b \sim 3$  is also plausible. However, the positive value of  $s \sim 1.5$  for anthrone probably results from the formation, on enolisation, of a much more extended conjugated system and this will not be a feature in simple cases, for which the oxo-tautomer should in general be the more polar. Hence a negative value of  $s$  is expected, but its magnitude is not easy to guess. Given, on the above postulate,  $\Delta a\alpha$  and  $\Delta b\beta$  values of ca. -1.1 and 1.2 respectively for transfer from water to alkane, it seems likely that the *sign* of  $\Delta \log K_E$  on the transfer of a simple ketone from water to a nonpolar solvent will depend almost entirely on that of the  $\pi^*$  term. Further than that we cannot go at the present time.

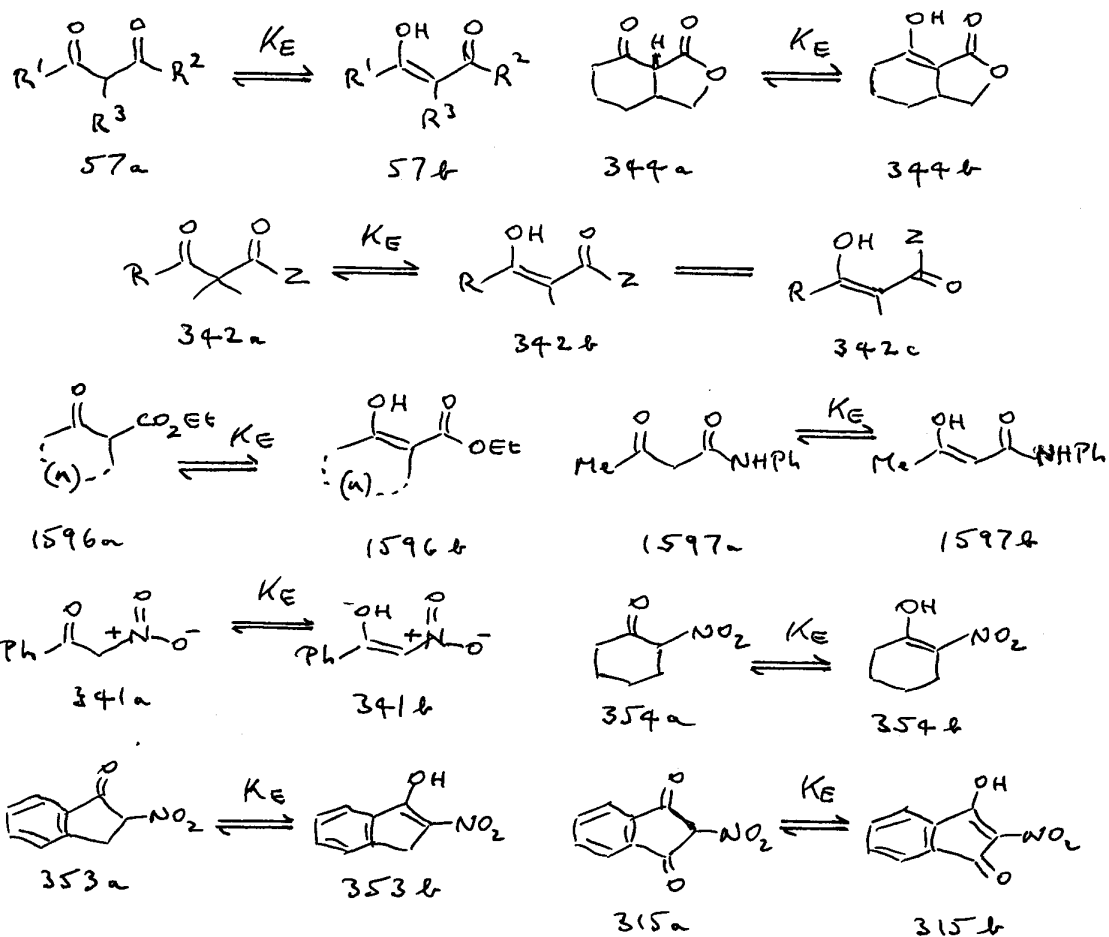
### (l) Extended 3-Way Equilibria: $K_M$ in 260

The only information available is that for the formation of **431C**, section (a) above, plus marginal data for **1595** (Scheme 149). The former shows the greatest degree of solvent sensitivity we have encountered (Table 132), more than twice that for formation of **431B** (Table 131), and all terms are positive, even those for alkanols;  $K_M$  here resembles  $K_T$  for amides (Table 119) in the latter respect, though the details differ. While the driving force mostly responsible for both features is a large  $\pi^*$  contribution,  $s = 1.79$ , that of  $\alpha$  as well as  $\beta$  is also positive, in contrast to what is found for  $K_E$ . This positive  $\alpha$ -value results not only from the continued presence of carbonyl, the stronger proton acceptor, but its actual enhancement by further conjugation, and since this tends to be characteristic of the process we have defined as  $K_M$  (Scheme 141), it is likely that this feature of **431A**  $\rightarrow$  **431C** will be general for this type of process. With  $b = 2.93$  the contribution of  $\beta$  is still very large, even though less than  $b = 3.61$  as found for **431A**  $\rightarrow$  **431B** since the latter generates OH which is a stronger proton donor than NH (see LSER analysis below Table 116). Unfortunately there is nothing with which to compare eqn. (xviii); on these fragmentary data **1595** does not in the least appear to resemble **431** in its behaviour, and any hope of generating a pattern like that of Scheme 148 lies in the future.

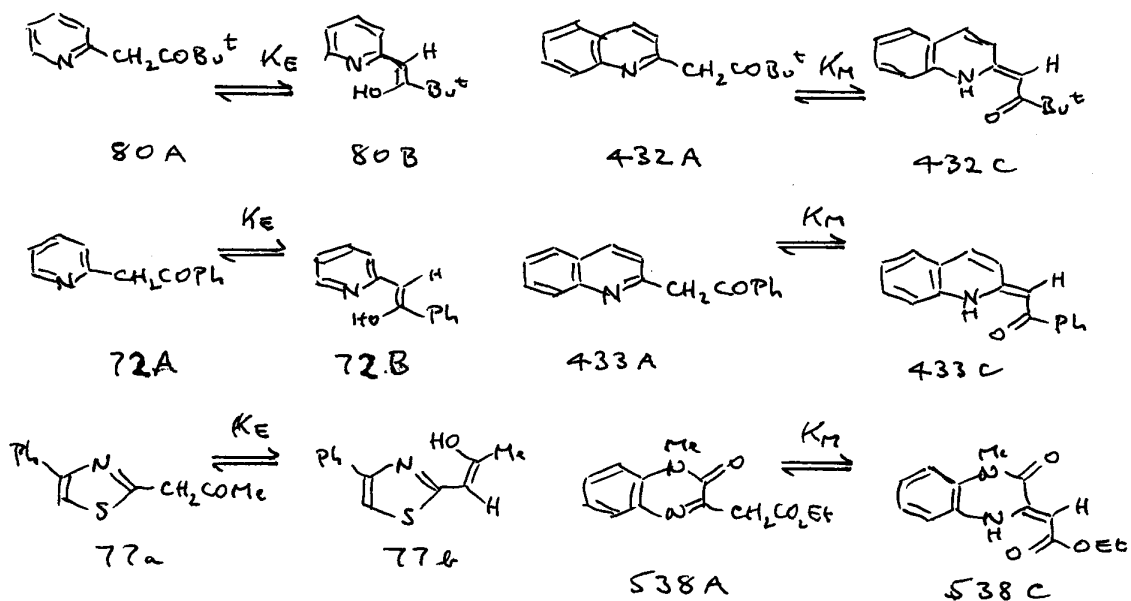
### (m) Chelated Enols 261: $K_E$ for $\beta$ -Dicarbonyl Compounds

This compound type, which centres round the  $\beta$ -diketones, forms perhaps the largest class whose tautomerism has been extensively studied, though mostly in organic solvents and only infrequently in water. Despite all this work there are enough data for LSER analysis only on three: acetylacetone (**57**,  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ ), which has twice been studied,<sup>60,197</sup> and the  $\beta$ -ketoesters (**342**,  $R = \text{Me}$ ,  $Z = \text{OEt}$ )<sup>60</sup> and **344**<sup>60</sup> (Scheme 150). Data appear in Table 115, the derived LSER equations in Table 133, and their 'solvent factors,' along with scattered data for related compounds, in Table 134.

In analysing their data for acetylacetone Mills and Beak<sup>60</sup> split their data into three sets of solvent in order to obtain satisfactory correlations. We have found this unnecessary and our analysis, using all but one of their solvents but excluding water, appears as eqn. (cx1) in Table 133. This predicts  $\log K_E -0.28$  for aqueous solution; their experimental value is  $-0.64$ . Acetonitrile (20) was rejected as an outlier. No outliers were found among the



Scheme 150



Scheme 151

18 organic solvents studied by Emsley and Freeman,<sup>197a</sup> from which we derive eqn. (ix);<sup>356</sup> as for eqn. (cx1), the  $\beta$ -term is non-significant. Water is predicted to possess  $\log K_E$  -0.43 whereas -0.83 was found.<sup>197a</sup> It is interesting that the error margins for these two independent data sets should be so similar, suggesting the possibility of a 'bench constant.' We discuss the nature of this error in (q) below. Abraham *et al.*<sup>197b</sup> quote eqn. (cxli) for this data set but statistics are not given and the datum for water was presumably included.

Acetoacetic ester (**342**, R = Me, Z = OEt) gave eqn. (xi) with no outliers.<sup>356</sup> The equation of Mills and Beak,<sup>60</sup> which is inclusive of water, possesses a small positive  $\beta$ -term,  $b = 0.19$ , but otherwise differs little. It is remarkable that, while eqn. (xi) predicts  $\log K_E$  -1.82 for water, -1.15<sup>60</sup> or -1.06<sup>229</sup> is found. This very large discrepancy lies far beyond the limits of error and we think it may indicate the three-way equilibrium shown for **342** (Scheme 150), prediction of  $K_E$  being based on **342a**  $\rightleftharpoons$  **342b** whereas nonchelated species such as **342c**, spectroscopically indistinguishable from **342b**, may also be present. We have invoked a similar phenomenon to account for the presence of a *negative*  $\beta$ -term in the ketonisation of some aromatic 2-hydroxy azo-compounds;<sup>356</sup> cf. (g) above. Since the  $\beta$ -term is small or absent here this phenomenon must be largely confined to water, which however with its very high dipolarity and exceptional amphiprotic character is the likeliest of any solvent to provoke it. Some light is thrown on this by the bicyclic  $\beta$ -ketoester **344**, which is incapable of such behaviour. Mills and Beak<sup>60</sup> were unable to obtain a satisfactory correlation if they included the data for DMSO (25) and pyridine (28), which were found to contain water; eliminating these we obtained eqn. (cxlii),<sup>356</sup> which is not very different from theirs with water included. However a great improvement in the statistics with minimal effect on the equation itself is obtained by eliminating MeCN (20) as well, to give eqn. (xii) which we now prefer. (A curious feature of all equations is the negative  $\beta$ -term, on which Mills and Beak do not comment but which can only result from solvent bonding to the 'activated' methine proton of **344a**; *vide* Scheme 150). The important result of this analysis is that, at  $\log K_E$  -1.62<sup>60</sup> and -1.72 for the observed and predicted aqueous values respectively, the discrepancy unearthed for (**342**, R = Me, Z = OEt), and possible for other compounds of this type,<sup>229</sup> has disappeared. If **342c** possesses the geometry shown (Scheme 150) a weak hydrogen bond involving Z may be possible, which could help to explain the *opposite* signs of this discrepancy in **342** and acetylacetone. It is possible that overprediction and underprediction of  $\log K_E$  by LSER may turn out, for these reasons, to be characteristic of  $\beta$ -diketones and  $\beta$ -ketoesters (plus probably  $\beta$ -ketoamides) respectively.

**Table 133. Correlation Equations ( $\log K_E$ ) for Chelated  $\beta$ -Diacyl Compounds<sup>a</sup>**

Cpd.	Eqn.	<i>c</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>n</i>	<i>r</i> <sup>2</sup>	<i>s</i>	<i>F</i>
<b>57</b> <sup>b, c</sup>	(cxl)	1.70 (0.11)	- 1.31 (0.17)	- 0.36 (0.12)		13	0.87	0.15	34
“ <sup>b, d</sup>	(ix)	1.50 (0.09)	- 1.58 (0.14)	- 0.18 (0.10)		18	0.905	0.16	71
“ <sup>b, e, f</sup>	(cxli)	1.65	- 1.76	- 0.24					
<b>342</b> <sup>c, d, g</sup>	(xi)	0.11 (0.13)	- 1.33 (0.20)	- 0.42 (0.14)		14	0.82	0.18	25
<b>344</b> <sup>c, d</sup>	(cxlii)	0.38 (0.14)	- 1.90 (0.23)		- 0.28 (0.18)	14	0.89	0.18	42
“ <sup>c, h</sup>	(xii)	0.34 (0.10)	- 1.78 (0.16)		- 0.30 (0.13)	13	0.939	0.13	77

<sup>a</sup> Data in Table 115, ‘solvent factors’ in Table 134. <sup>b</sup>  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ . <sup>c</sup> Data from ref. 60.

<sup>d</sup> Ref. 356. <sup>e</sup> Data from ref. 197a. <sup>f</sup> Analysis from ref. 197b. <sup>g</sup>  $R = \text{Me}$ ,  $Z = \text{OEt}$ . <sup>h</sup> This work.

Tautomerism of this type possesses a pattern of solvent dependence (Table 134) not seen elsewhere. With the  $\beta$ -term small or absent and the  $\alpha$ -term dependent on the balance, in proton acceptor ability, between two unconjugated carbonyl groups and one that is conjugated – it even disappears in **344** – tautomerism becomes largely a function of relative dipolarity. And since this is much diminished in chelates while still relatively high in **261A** (Scheme 142), a *negative*  $\pi^*$  term (Table 133) now reverses previous trends. There results the apparent paradox that generation of a conjugated system leads to a diminishing proportion of this as solvent polarity rises, the opposite behaviour to that of their nonchelated analogues **260**. The  $\Delta \log K_E$  values of Table 134 are universally negative, and gratifyingly, display a strong internal consistency in this regard.

This consistency is sufficient for some cautious prediction. The solvent factors of Table 134 give, for EtOH and  $\text{CCl}_4$  vs. water,  $\Delta \log K_E$   $1.03 \pm 0.16$  and  $1.68 \pm 0.13$  ( $n = 4$ ) respectively; if the  $\log K_E$  values for **1596** are added to these and the results for the two solvents are averaged, we obtain  $-2.3 \pm 0.1$ ,  $-0.9 \pm 0.1$  and  $-1.9 \pm 0.1$  as the predicted values in aqueous solution for  $n = 2, 3$

**Table 134. ‘Solvent Factors’  $\Delta \log K_E$  for the Compounds of Table 133, with  $\log K_E$  Values for other Compounds contained in Scheme 150**

Cpd.	Eqn.	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane
<b>57</b> <sup>a</sup> (cxl)		- 0.9	- 1.0	- 0.7	- 1.1	- 1.3	- 1.2	- 1.6	- 2.1
<b>57</b> <sup>a</sup> (ix)		- 1.2	- 1.3	- 0.7	- 1.4	- 1.5	- 1.4	- 1.9	- 2.5
<b>342</b> <sup>b</sup> (xi)		- 0.5	- 0.9	- 0.6	- 1.0	- 1.2	- 1.2	- 1.6	- 2.0
<b>344</b> (xii)		- 0.8	- 0.9	- 0.1	- 1.0	- 1.0	- 1.0	- 1.6	- 2.2
<b>1596</b> <sup>c,d</sup>			- 1.28 <sup>g</sup>					- 0.89	
“ <sup>c,e</sup>			0.12 <sup>g</sup>					0.75	
“ <sup>c,f</sup>			- 0.87 <sup>g</sup>					- 0.35	
<b>1597</b> <sup>h</sup>		- 0.9			- 0.6			- 0.5	
<b>341</b> <sup>i,j</sup>		- 1.54	- 1.25				- 0.94 <sup>m</sup>		
<b>354</b> <sup>i,k</sup>					- 0.35			0.0	
<b>353</b> <sup>i,k</sup>			- 0.37					- 0.37	- 0.95
<b>315</b> <sup>i,l</sup>			0.8			1.9 <sup>n</sup>	2.7		

<sup>a</sup> R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = H. <sup>b</sup> R = Me, Z = OEt. <sup>c</sup> **1596** is **34**, Table 4 (section A.1.2) with R = CO<sub>2</sub>Et and the sign of log  $K_T$  reversed to give log  $K_E$ . <sup>d</sup>  $n = 2$ . <sup>e</sup>  $n = 3$ . <sup>f</sup>  $n = 4$ . <sup>g</sup> 95% EtOH. <sup>h</sup> Ref. 17.

<sup>i</sup> Ref. 191. <sup>j</sup> *cf.* section A.6.7. <sup>k</sup> *cf.* section A.6.9. <sup>l</sup>  $\Delta \log K_E$  values based on log  $K_E$  1.7 for water.

<sup>m</sup> Toluene. <sup>n</sup> Et<sub>2</sub>O.

and 4 respectively. However, it is clear that **1597** does not behave in a quantitatively similar fashion to (**342**, R = Me, Z = OEt); the trend is in the same direction, but much shallower. Amide carbonyl is less electron-withdrawing than that of ester (*cf.* Table 2) and this difference in solvent dependence may result from that. Perhaps surprisingly, the nitro-compound **341** fits the diacyl pattern quite closely, log  $K_E$  -2.3±0.1 resulting for its predicted value in water (section A.6.7); however **353** and **354** (section A.6.9) show no sort of resemblance while the latter may even reverse the trend. Compound **315** certainly does (section A.6.5): this becomes more enolised with increasing solvent polarity so is to be considered an extended  $\beta$ -diketone rather than a chelate like **341**. Its exceptional solvent sensitivity is likely to be due to the (presumed) very high polarity of its enol. Here the nitro-group, a much poorer proton acceptor than carbonyl, behaves only as an electronegative substituent. Despite some irregularities, which are easy to detect, we believe that this approach may be useful, in the absence of either an aqueous  $K_E$  value or sufficient material for an LSER equation, for predicting at least qualitatively what the dominant tautomer in water should be.

### (n) Chelated Enols 261: $K_E$ for $\beta$ -Iminoketones

What little information exists is given in Table 135. The only data set sufficiently comprehensive for LSER analysis is that of Roussel *et al.*<sup>98</sup> on **80**, who also carried out that on **432** discussed in (o) below. Both regression equations appear under Table 135; their  $\Delta \log K$  values are contained in Table 136. Scheme 151 incorporates these and all other compounds mentioned here; all but **432** originate in section A.2.3, whereas section A.10.2 discusses in greater detail the more general aspects of their behaviour.

Roussel's paper is a searching re-examination of the LSER parameters available at that time (1982), which incidentally comes down in favour of  $\pi^*$  over its rivals, but as with Beak's papers<sup>60,379</sup> some of its parameter values are out of date, so we have carried out a re-analysis. Two solvents have had to be omitted since some values are not available, MeCONHMe and methyl pivalate, but otherwise our analyses incorporate all Roussel's data and there are no outliers.

Our results for **80** appear as eqn. (xx). As seen in Table 136 all  $\Delta \log K_E$  values are once again negative, but although the overall range is similar to that of the  $\beta$ -diacyl compounds of Table 134, there is no proportionality and no real parallelism. The reason for this lies in the very different magnitudes of their  $\pi^*$  and  $\alpha$  terms. While the  $\pi^*$  term dominates the behaviour of the  $\beta$ -diacyl compounds it is much smaller here, plausibly because the overall molecular dipole is much less affected by enolisation in **80B** than, for example, in **57b** (Scheme 150). One result is the quite different position of DMSO in the sequence: whereas for the  $\beta$ -diacyl compounds this is mostly dictated by its very high dipolarity, its position for **80** also reflects its lack of the proton donor properties that specially disadvantage water as a promoter of enolisation. Other strong and highly polar proton acceptor solvents, such as pyridine and DMA, will presumably behave in the same way. These much larger negative  $\alpha$ -terms as compared *e.g.* with **57** and **342** (Table 133 *vs.* foot of Table 135) probably stem from the considerably larger fall in proton acceptor ability on formation of the chelate that takes place in this type of compound. A similar situation, for  $K_T$  in Schiff bases, has been noted in (h) above.

Few data exist for which eqn. (xx) for **80** may be compared; those for its analogue **72** are too sparse to be useful. However, the data for **77**<sup>99</sup> (Table 135) so closely parallel those for **80**,  $\Delta \log K_E -0.32 \pm 0.01$  ( $n = 4$ ), as

**Table 135. LSER Data for some Chelated  $\beta$ -Iminoketones**

Solvent	<b>72</b> <sup>a,b</sup>	<b>80</b> <sup>a,c</sup>	<b>77</b> <sup>a,d</sup>	<b>432</b> <sup>c,e</sup>	<b>538</b> <sup>e,f</sup>
2	- 0.5	- 1.28		0.05	- 0.48
3				0.20	
7		- 0.58		0.48	
8		- 1.30			
9				- 0.15	
14		- 0.25		0.69	
15		- 0.27			
16		- 0.48		0.55	
17				0.69	
18		- 0.68		0.25	
19				0.27	
20		- 0.72		0.33	
21		- 1.34			
22		- 0.52			
25		- 0.58	- 0.88	0.49	- 0.08
26				0.64	
27				0.89	
28		- 0.36		0.64	
29		- 0.15		0.83	
30					0.40
32		- 0.47	- 0.80		
33	- 0.2 <sup>g</sup>	- 0.46	- 0.78	0.75	- 0.11
34		- 0.05	- 0.38	0.89	
35					0.62
36 <sup>h</sup>		0.16			
Water <sup>i</sup>	- 2.00 <sup>b</sup>	- 1.71	(- 2.0) <sup>j</sup>	- 0.26	- 1.02

<sup>a</sup> log  $K_E$ . <sup>b</sup> Ref. 93. <sup>c</sup> Ref. 98. <sup>d</sup> Ref. 99. <sup>e</sup> log  $K_M$ . <sup>f</sup> Ref. 334. <sup>g</sup> Ref. 92. <sup>h</sup> Hexane.

<sup>i</sup> Calculated from regression equation. <sup>j</sup> See the text.

$$\log K_E(\mathbf{80}) = 0.18(0.09) - 0.78(0.13) \pi^* - 0.89(0.11) \alpha \quad (\text{xx})$$

( $n = 17$   $r^2 = 0.90$   $s = 0.14$   $F = 63$ )

$$\log K_M(\mathbf{432}) = 1.04(0.11) - 0.63(0.16) \pi^* - 0.53(0.08) \alpha \quad (\text{xxi})$$

( $n = 17$   $r^2 = 0.79$   $s = 0.15$   $F = 27$ )

$$\log K_M(\mathbf{538}) = 0.67(0.09) - 0.69(0.18) \pi^* - 0.80(0.11) \alpha \quad (\text{xxxvii})$$

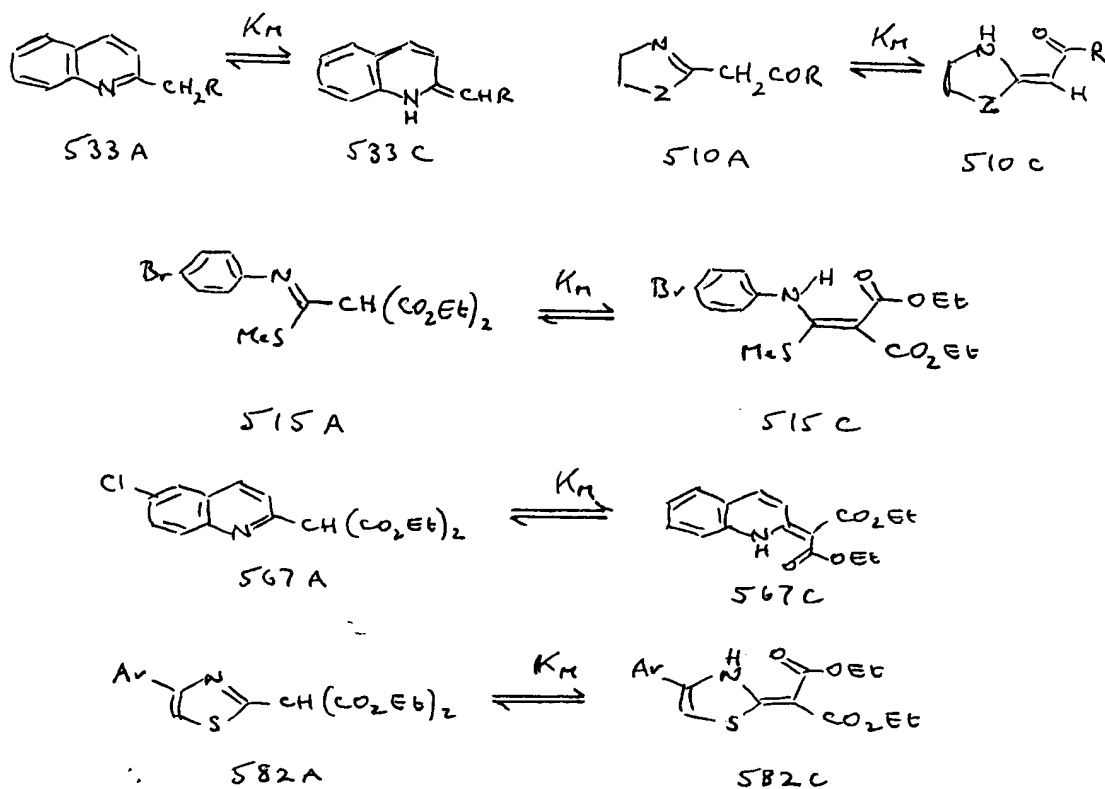
( $n = 5$   $r^2 = 0.977$   $s = 0.09$   $F = 43$ )

to permit reasonably accurate extrapolation to  $\log K_E$  *ca.* -2.0 in water. This difference may reflect weaker intramolecular bonding resulting from the change in hydrogen bonding geometry, the lower proton acceptor ability of thiazole than of pyridine, or both. It raises the possibility that a similar parallelism among these compounds to those of Table 134 might be found if more were known.

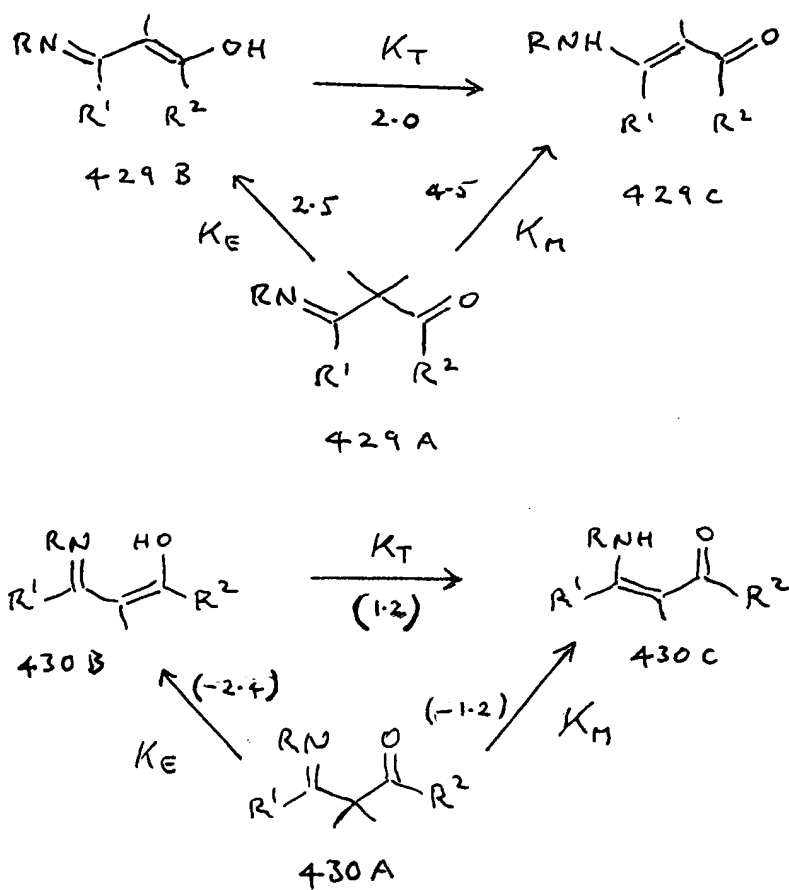
It is possible that the difference in magnitude of the  $\pi^*$  terms in  $\log K_E$  for  $\beta$ -diacyl compounds and for **80** is partly a consequence of the latter's unchanged aromaticity and an aliphatic analogue, if one could be examined, would not show it. However there is a contra-indication in the comparative values of  $K_E$  and  $K_M$  for **72** and **432** in aqueous solution<sup>93</sup> (Table 33, section A.10.2). Whereas  $\log K_M$  rises by *ca.* 2 in this sequence, through the usual effect of benzofusion in reducing the advantages of aromaticity (Appendix 5),  $\log K_E$  is only *ca.* 0.7, since this form of tautomerisation has much less effect on underlying molecular structure. Similarly, the  $\log K_M$  value for **433** in water differs much more from that calculated for **432**, 1.09 and -0.26 respectively, than the  $\log K_E$  values for **80** and **72**, -1.71 and -2.00. It is plausible therefore that structural effects on  $K_E$  for  $\beta$ -iminoketones should be comparatively minor, and that parallelisms among  $\Delta \log K_E$  values for varying categories will consequently result.

#### (o) Chelated Enols 261: $K_M$ for $\beta$ -Iminoketones

The situation for  $K_M$  is slightly better than that for  $K_E$ , (n) above, but not by much: two LSER analyses are possible and there are scattered data, incorporated into Table 136 along with the 'solvent factors' for **80**, **432** and **538** (*cf.* data of Table 135 and the LSER equations below it). Structures not in Scheme 151 appear in Scheme 152. The data of Roussel *et al.*<sup>99</sup> for **432** again give a satisfactory equation, and there are no outliers. It is interesting that the predicted  $\log K_M$  value for water, at *ca.* -0.3, is very much below that of **433** in which COPh replaces COBu<sup>t</sup> but is probably close to that of (**533**, R = COMe); see below. This is consistent with the qualitative picture we have generated (section A.10.14) according to which the order of increasing  $K_M$  for heterocycles 2-substituted with CH<sub>2</sub>X follows in water the sequence X = CO<sub>2</sub>R < CN  $\ll$  COMe  $\ll$  COPh, with  $\Delta \log K_E$  *ca.* 1 at each of the latter stages (Table 42). As we have noted this is not a simple electronegativity order and may require invocation of Charton's *resonance susceptibility* parameter  $\sigma_e$  (see under ref. 41 for a summary discussion).



Scheme 152



Scheme 153

**Table 136. ‘Solvent Factors’ for **80** ( $\Delta \log K_E$ ), **432** and **538** ( $\Delta \log K_M$ ), with  $\log K_M$  for the Compounds of Scheme 152**

Cpd.	Eqn.	MeOH	EtOH	DMSO	CHCl <sub>3</sub>	Dioxane	Benzene	CCl <sub>4</sub>	Alkane
<b>80</b>	(xx) <sup>a</sup>	- 0.6	- 0.7	- 1.1	- 1.0	- 1.4	- 1.4	- 1.7	- 2.0
<b>432</b>	(xxi) <sup>a</sup>	- 0.4	- 0.5	- 0.7	- 0.7	- 0.9	- 0.9	- 1.1	- 1.3
<b>538</b>	(xxxvii) <sup>a</sup>	- 0.5	- 0.6	- 1.0	- 0.9	- 1.3	- 1.3	- 0.15	- 1.5
<b>533</b>	<sup>b, c</sup>			0.3	0.5			0.8	
<b>510</b>	<sup>b, d</sup>			0.6	0.0				
<b>515</b>	<sup>b, e</sup>	0.31		0.23	0.39		0.39	0.39	
<b>567</b>	<sup>b</sup>			< 0 <sup>g</sup>			> 0		
<b>582</b>	<sup>b, f</sup>			< 0 <sup>h</sup>	> 0		> 0		

<sup>a</sup> Foot of Table 135. <sup>b</sup>  $\log K_M$ . <sup>c</sup> R = COMe. <sup>d</sup> Z = S, R = OEt. <sup>e</sup> Other solvents employed: MeCN, MeNO<sub>2</sub>, PhNO<sub>2</sub>, acetone, and pyridine. <sup>f</sup> Ar = *p*-bromophenyl. <sup>g</sup> Also MeCN. <sup>h</sup> Also MeCN and pyridine.

The LSER eqn. (xxxvii) for **538**<sup>334</sup> (section A.10.14) is based on only five points but appears to be sound: no single parameter exceeds  $r^2$  -0.65 for  $\alpha$ ; the only significant improvement on this results from adding  $\pi^*$ ; and  $F = 43$  for eqn. (xxxvii), below Table 135, compares with  $F < 6$  for any single parameter or other combination of parameters. It is of interest to compare the coefficients of  $\pi^*$  and  $\alpha$  for all three equations. For **432** relative to **80** both are lower, especially that of  $\alpha$ , with a consequent reduction in solvent sensitivity, but for **538** both rise again, to give almost the same range in  $\Delta \log K_M$ . The less negative  $\alpha$ -term for **432** is expected since, from almost the same starting point, while **80B** has lost its carbonyl group and has no unchelated proton acceptor, one carbonyl lone pair remains in **432C** for bonding to a proton donor solvent. (A similar end-point, though not from the same starting position, is found for the Schiff bases of section (h); here however, with its starting point an impenetrable chelate, the  $\alpha$ -term is positive). Hence **538** appears anomalous. Its ester group will be a poorer proton acceptor than the acyl groups of **80** and **432** but a more important factor, whose impact is difficult to gauge, may lie in tautomerism's effect on the proton acceptor properties of the ring amide group. However the overall difference between **80**, **432** and **538** revealed by Table 136 is not enormous, and may provide some guide to the behaviour of compounds of these types for which only scattered data are available.

A handful of such examples are listed in Table 136. Comparison of the three data points for (**533**, R = COMe)<sup>332</sup> with  $\Delta \log K_M$  for eqn. (xxi) leads to estimates of -0.4, -0.2 and -0.3 for  $\log K_M$  in aqueous solution; as noted above, this is substantially identical with the value extrapolated for **432** itself (Table 135). Unfortunately the data for (**510**, Z = S, R = OEt)<sup>323</sup> are too fragmentary to use, while those for **515**<sup>325b</sup> (both section A.10.12) are incapable of rationalisation by any LSER treatment; we return to the latter in (q) below. Compounds **567** (section A.10.15) and **582** (section A.10.17) exist mostly as the **A**-tautomer in polar and the **C**-tautomer in nonpolar solvents, as expected, with about 50% of each in CH<sub>2</sub>Cl<sub>2</sub>.<sup>106</sup> The calculated  $\Delta \log K_M$  value for CH<sub>2</sub>Cl<sub>2</sub> is ca. -0.6 for eqn. (xxi) and -0.9 for eqn. (xxxvii);  $\log K_M$  for water in the range -1 to -0.5 for both seems plausible. Sections A.10.10 to A.10.17 contain further information but of an entirely qualitative sort.

#### (p) Overview

We may attempt to rationalise the disparate facts presented above. Since for X = Y in structures **4**, **260** and **261** (Scheme 142) the options are limited it seems more relevant, if also more difficult, to examine the picture for X = NR and Y = O, *i.e.* for amides and aminoenones, the last as extended **429** or chelated **430** species (Scheme 17, section A.10).

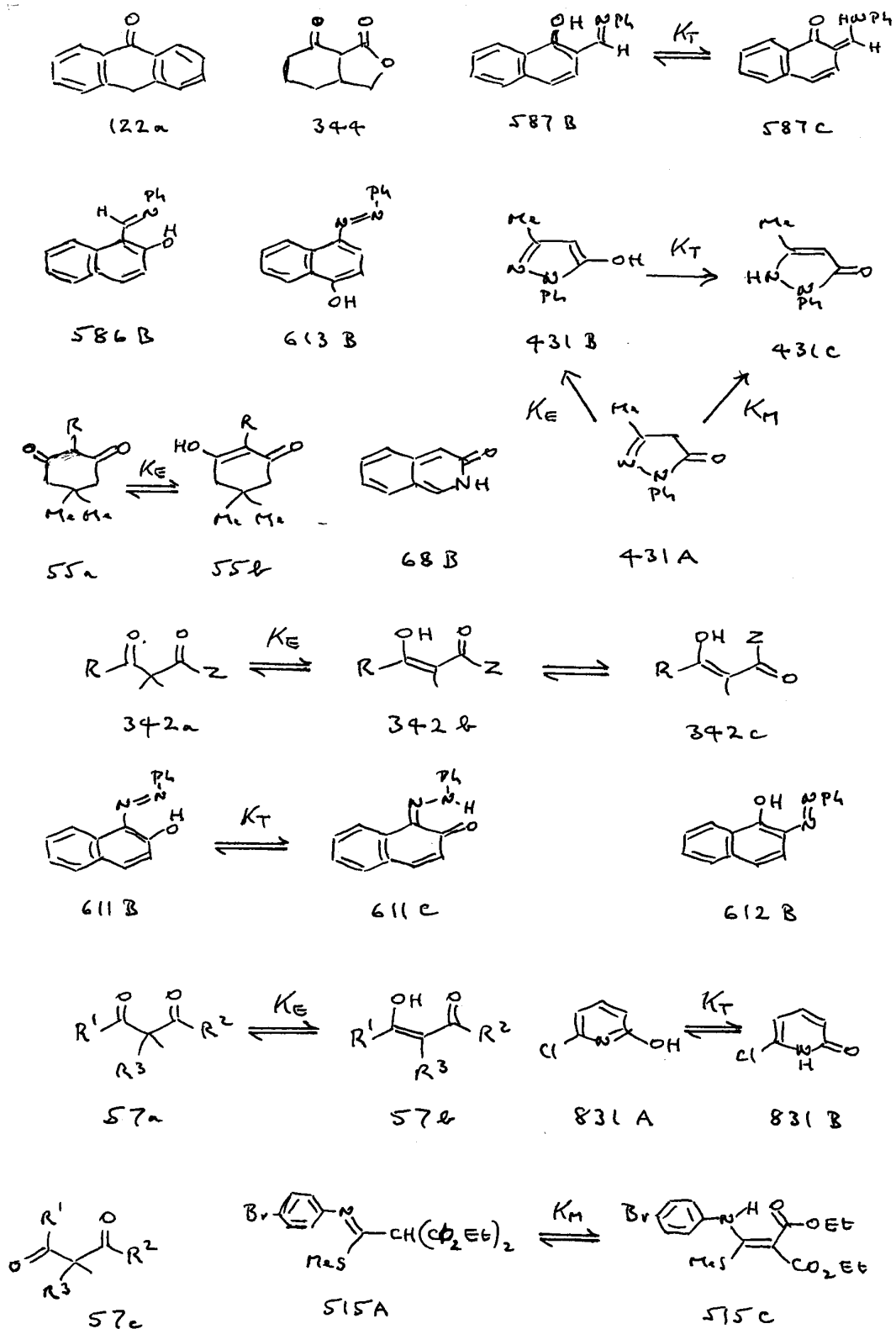
Given  $K_M = K_E K_T$  by definition, the three  $\Delta \log K$  values for these 3-way equilibria are required to be additive in the same way as the  $\log K$  values themselves. This objective is not precisely achieved in the one case where all the above have been measured, namely **431** (Scheme 141), with  $\Delta \log K_E$ ,  $K_M$  and  $K_T$  values of 2.2 (Table 131), 4.8 (Table 132) and 2.1 (Table 124) respectively. However a mean  $\Delta \log K_E$  2.4 results if the values (Table 131) for **122** and **55** (Scheme 147) are incorporated, leading, with some 'smoothing,' to the highly provisional suggestions shown for **429** in Scheme 153. Here  $\Delta \log K_T$  2.0 may be compared with  $\Delta \log K_T$  2.7 as deduced from our suggested eqn. (cxxiii) for a 'typical' amide (Table 119). A larger  $\Delta \log K_T$  for an amide than for an aminoenone would be expected in view of its steeper dipole gradient. While little weight can be placed on these values themselves, an order  $K_M \gg K_E > K_T$  seems probable as a general rule.

It is much more difficult with chelated aminoenones to compare like with like. Values of  $\Delta \log K_E$  are -2.0 or -2.5 and of  $\Delta \log K_M$  -1.3 or -1.8, whereas some very variable  $\Delta \log K_T$  values average at 1.4 (Table 125). The

compounds from which they are derived are very disparate and we are forced to guess. Some guiding principles are possible however. While the process  $\mathbf{B} \rightarrow \mathbf{C}$  leads to a more polar tautomer in both situations, so that  $\Delta \log K_T$  should be positive in either case, less advantage is expected for the more compressed chelate, leading to a lesser magnitude as is found. However, since **430A** is the most polar tautomer of the three, not the least polar tautomer as is **429A**,  $\Delta \log K_E$  and  $\Delta \log K_M$  both change signs on chelation, but since  $\Delta \log K_T$  remains positive,  $\Delta \log K_E$  is *necessarily* larger than  $\Delta \log K_M$  numerically. The compromise values shown for **430** on Scheme 153 are intended to convey the type of result to be expected, at least *vis-à-vis* **429**, without necessarily fitting the facts in any given case. While equal and opposite values for  $K_M$  and  $K_T$  are inherently improbable, the greater variability of  $K_E$  is likely to constitute a general rule. One major difficulty attaches to the conformational ambiguity concerning **430A**, which in so far as it distorts  $K_E$  and  $K_M$  must have the same effect on both, but cannot be predicted in advance unless some computational method can render it correctly. This is as far as we can take the analysis at the present time. An important further consequence of this ambiguity is considered below.

#### (q) Problems in the Extrapolation of LSER Equations to Water

Directly or indirectly, we can check on the ability of an LSER equation to predict correctly the aqueous value in about a dozen cases. The bicyclic keto-ester **344** and the Schiff's base **587** are correctly predicted to around one s.e., while results for the Schiff's base **586** and, probably, 4-phenylazo-1-naphthol **613** (Scheme 154) are almost equally satisfactory. The 3-way equilibrium for **431**, in which equations have been derived independently for  $K_E$ ,  $K_M$  and  $K_T$ , sums to a combined error of  $\Sigma \log K$  *ca.* 0.1 so also comes into this category. Here the equations for  $K_E$  and  $K_M$  contain very large  $\beta$ -terms and this close agreement helps to vindicate the  $\beta$ -value for water derived from the LSER equation for (**55**, R = H), which in turn is based on the assumption that the latter's aqueous value is accurately predicted and helps to confirm both hypotheses. There is no independent check on  $\log K_T$  *ca.* 1.7 for the lactam **68** but this implies an effect of quinonoid benzofusion, relative to 2-pyridone, in line with those found elsewhere (Appendix 5) and to that extent is also vindicated. These may all be regarded as successful predictions. Notably, all are probably rigid structures; other chelates may fail the test of rigidity – see below – but the Schiff bases **586** and **587** are evidently locked to an extent that makes them rigid *de facto* if not *de jure*.

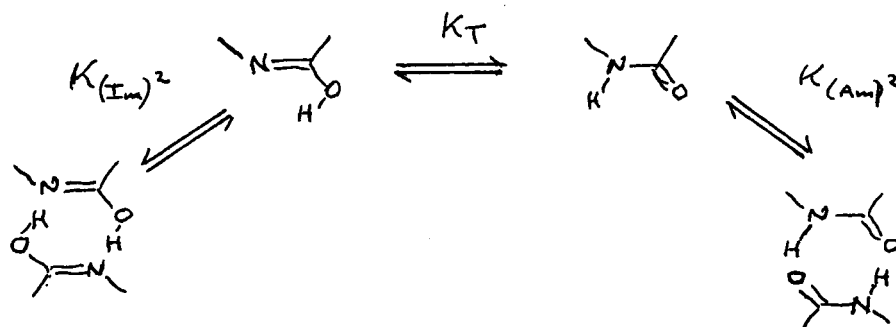


Scheme 154

There are also failures however, some of them spectacular. The most serious concerns the open-chain  $\beta$ -ketoester (**342**,  $R = \text{Me}$ ,  $Z = \text{OEt}$ ) for which  $K_E$  is grossly underpredicted:  $\log K_E$  -1.82 compares with -1.15 or -1.06 observed. We have suggested<sup>356</sup> in (**m**) above that, as well as **342a** and **342b** on which calculation is based, nonchelated enols such as **342c** or some *trans*-isomer may also be present, and to a much greater extent in water than elsewhere, the result of co-operative bonding due to its extreme amphiprotic nature. For **611**, where an equilibrium between two chelates is involved, the *overprediction* of  $K_T$  almost certainly involves a partial ring-opening of **611B**, already indicated for organic solvents by the *negative*  $\beta$ -term in its LSER equation and likely to be much more pronounced in water. A similar negative  $\beta$ -term is found for its isomer **612** but the aqueous solution value has not been determined. For both the overall statistics are much worse than for **586** and **587**, plausible evidence for solvent variations from some source independent of the parameters employed.<sup>356</sup>

A rather more subtle effect may be operating in acetylacetone (**57**,  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ ). On either of two analyses in (**m**) above  $\log K_E$  is overpredicted by  $\Delta \log K_E$  *ca.* 0.4, and this must imply that more of the diacyl form is present in water than expected. This may arise from a lack of structural integrity in **57a**. For any such structure there is a variety of conformational possibilities, *e.g.* **57c** (section A.6.7), precisely the reason why, in our M.O. treatment of **430** and related asymmetric species (section C.46), we have confined our calculations to  $K_T$  even though  $K_E$ ,  $K_M$  and  $K_T$  are all calculated for **429** (Table 49, section A.12.2). If the major conformer in water differs from that elsewhere, or even if a larger range of conformers is present, a sort of entropic effect, it is possible that the importance of **57a** will be exaggerated. By contrast, if the chelate is tight, **57b** will be a single species. More evidence is needed as to how serious and widespread this phenomenon may be.

There is fugitive evidence among the reported results for situations still more serious. For the  $\beta$ -iminoester **515**  $K_M$  has been measured in solvents that range from MeOH to CCl<sub>4</sub>;<sup>325b</sup> not only is the range in  $\log K_M$  quite narrow, 0.39 to -0.12, but the distribution of these results as a function of polarity has the appearance of a random walk. Here the conformational options are so extensive, and for both tautomers, with the added possibility that conformer energetics could vary more than that between the tautomers, that neither may possess any real integrity, so that intersolvent variation between them seems the likeliest explanation.

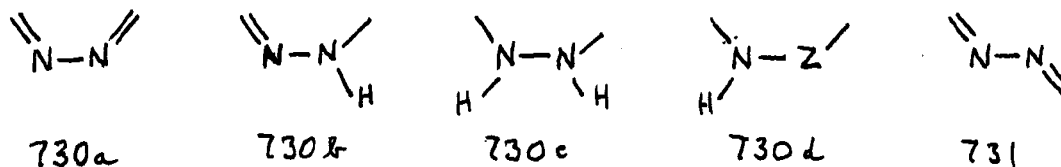


Scheme 155

While rigid compounds are in general well predicted we have encountered two exceptions. The dominant tautomer of anthrone **122** in water, **122a**, is underpredicted by  $\Delta \log K_T$  -1.6 or -0.46 according as to which of two unsatisfactory equations is employed; see (**k**) above. No good explanation can be suggested. The other is **831** whose LSER equation predicts  $\log K_T$  0.47 whereas there is clear UV evidence for  $\log K_T \geq 1.2$  and this fits much better with various sorts of expectation (section B.2.4). Lactams are known to dimerise in solution and Beak and co-workers<sup>608</sup> went to considerable trouble to establish the conditions required to avoid this, but curiously, the possibility of *lactim* dimerisation does not appear to have been considered. In fact, since OH---N is generally so much stronger than NH---O hydrogen bonding, this is potentially a much more serious threat. The cases are compared in Scheme 155. The relative importance of  $K_{(\text{Im})}^2$  and  $K_{(\text{Am})}^2$  will depend on three factors:  $K_T$ ;  $K_{(\text{Im})}^2$  vs.  $K_{(\text{Am})}^2$ ; and solute concentration; and while all three may vary independently the third, while also influenced by  $K_T$ , is likely to be crucial. While lactam dimerisation is avoidable<sup>608</sup> and lactim dimerisation unlikely to be important at high  $K_T$  values, then as  $K_T$  falls towards unity the latter will rapidly increase in magnitude and may come to influence the results. The under-prediction of  $K_T$  in organic solvents, where it is invariably lower than in water, will then lead to a false extrapolation whose effect is likely to be exacerbated by the absence of dimerisation in water itself. This effect does not have to be large in order for its results to be perceptible;  $K_T$  for **831** in water is underpredicted by perhaps no more than a factor of six. We think this to be the likeliest explanation for our observation, and if so it is a phenomenon, not necessarily confined to lactams, to which some attention may need to be paid.

Unfortunately this is not a plausible explanation for the behaviour of 2- and 4-pyridthione, (**e**) above, not only because the effects are so enormous but also because thioiminols are unlikely to form strong dimers since SH is such a poor proton donor. Here we are forced to await inspiration, experiment, or both.

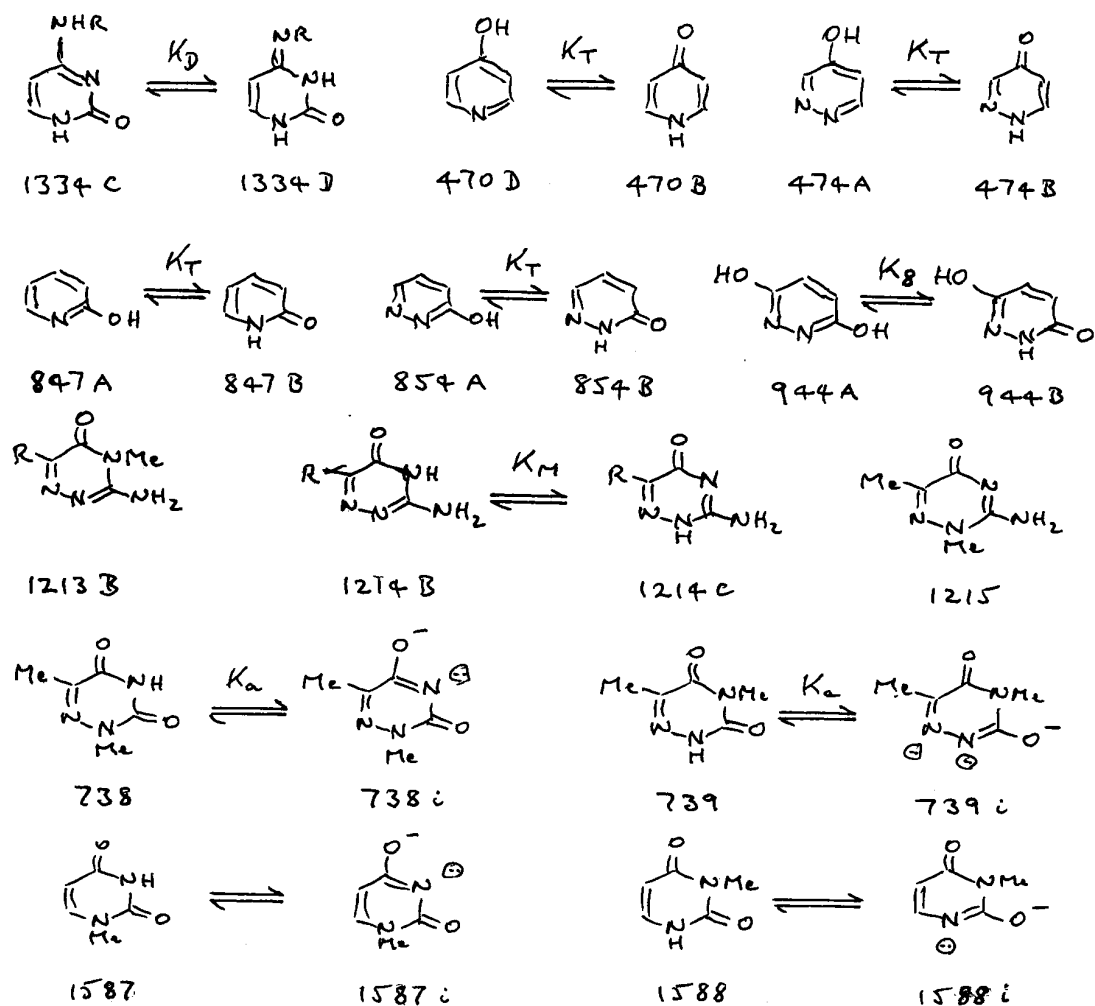
## APPENDIX 3: Lone Pair and Dipolar Repulsion



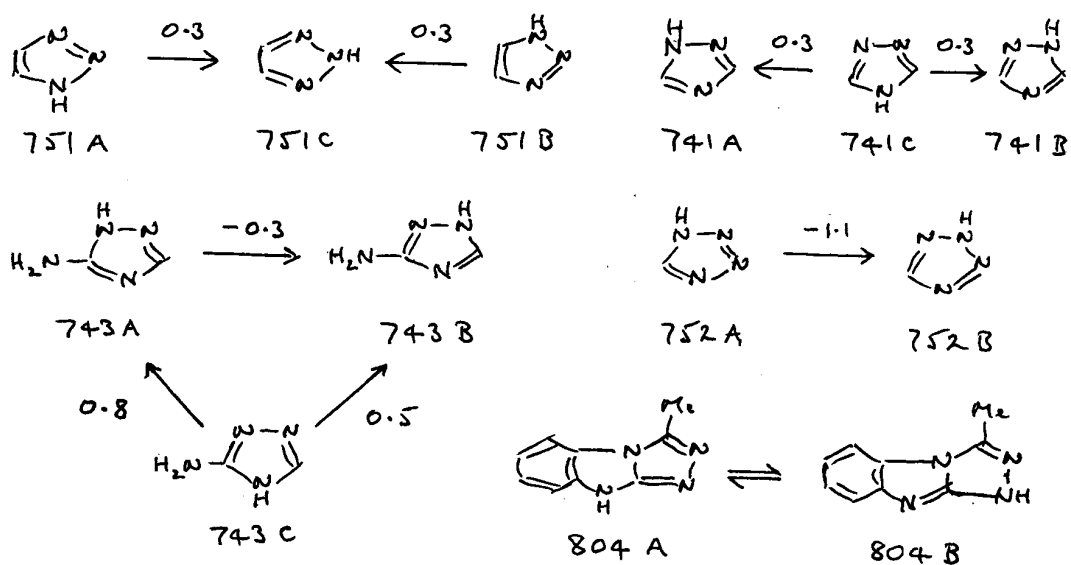
Lone pair and dipolar repulsion are perhaps the two most important factors that can act to upset expectation as to tautomeric preference, frequently over-riding any other form of electronic effect. Partly for this reason, and partly because their relative magnitudes in different situations form a reasonably coherent pattern, it is convenient to gather the information on this subject in one place.

For contiguous nitrogen atoms, the situation is summarised by structure **730** (section B.8.2). In cyclic structures, **730b** will always be preferred to **730a** (lone pair repulsion) or **730c** (dipolar repulsion); if one N in the last is replaced by the hetero-atom Z, to give **730d**, dipolar repulsion is still present and, for Z = O at least, is more severe. In noncyclic structures lone pair repulsion will be relieved by inversion, as *e.g.* in *trans*-azobenzene, but steric hindrance must also be important in such cases and no molecule containing precisely the required unit **731** has so far been studied in either respect. There is some evidence, however, that dipolar repulsion is not relieved so readily; **730c** and **730d** remain disfavoured structures relative to those of type **730b** even in compounds of flexible geometry, *e.g.* hydrazones (section A.5.1) and oximes (section A.5.2) while **1334** shows quantitative shifts in  $\log K_M$  for R = NH<sub>2</sub> and OH relative to R = H consistent with this picture; see (I) below. For cyclic compounds there appear to be large electronic effects on tautomeric ratio, monitored by  $\sigma_I$  for Z (section C.15), which are qualitatively and perhaps quantitatively paralleled by those in open-chain structures. This subject is not well understood at the present time.

In certain structures, mostly bicyclic, relief of lone pair repulsion is accompanied by a sterically enforced intramolecular hydrogen bond; see sections (d) – (j) below. In such cases the overall  $\Delta \log K$  incorporates both phenomena and there is generally no way of disentangling their separate effects. It is interesting to note that intramolecular hydrogen bonding gives rise to much smaller effects when unenforced, *i.e.* when due to a substituent capable of free rotation (Appendix 4). Presumably the reason lies in bonding to solvent, which at least in water may be highly competitive or even preferred. No case in which relief of dipolar repulsion gives rise to an intramolecular hydrogen bond is known.



Scheme 156



Scheme 157

## (a) Annular Lone Pair Repulsion in 6-Membered Ring Heterocycles

The five structural types for which quantitative data exist are displayed in Scheme 156. These comprise: 4-oxopyridazine **474** (Table 137), two types of 3-oxopyridazine, **854** and **944** (Table 138), and two types of 1,2,4-triazinone, **1214** and **738/739** (Table 139). All appear in earlier sections but not in the detail considered here.

$$pK_{\text{NH}(2)} = 3.5 - 3.2 \sigma_{\text{m}} \quad (\text{xxviii})$$

$$pK_{\text{OH}(2)} = 7.2 - 10.5 \sigma_{\text{I}} \quad (\text{xxix})$$

$$\log K_{\text{T}(2)} = 3.7 + 3.2 \sigma_{\text{m}} - 10.5 \sigma_{\text{I}} \quad (\text{xxx})$$

We approach  $K_{\text{T}}$  for **474** by treating this as a 2-aza-substituted 4-pyridone **470**. The key equations (section A.10.6) are (xxviii), (xxix) and (xxx), and their solution for **474** requires  $\sigma_{\text{m}} = 0.65$  and  $\sigma_{\text{I}} = 0.47$  for ring aza-nitrogen (Table 2) if this behaves as a normal substituent. The results are given in Table 137 along with a parallel treatment of (**470**,  $R^2 = \text{Cl}$ ). While  $pK_{\text{NH}(2)}$ ,  $pK_{\text{OH}(2)}$  and  $\log K_{\text{T}(2)}$  are reasonably well predicted for the latter, only  $pK_{\text{NH}(2)}$  for **474** gives the expected result;  $pK_{\text{OH}(2)}$  is underestimated by  $\Delta pK_{\text{a}}$  ca. 2, leading to  $\Delta \log K_{\text{T}} \sim 2.1$ . It seems reasonable to attribute this enhancement to lone pair repulsion in the iminol.

$$pK_{\text{NH}(6)} = 0.75 - 3 \sigma_{\text{m}} \quad (\text{cxliii})$$

$$pK_{\text{OMe}(6)} = 3.28 - 8 \sigma_{\text{I}} \quad (\text{cxliv})$$

$$\log K_{\text{T}(6)} = 3.5 + 3 \sigma_{\text{m}} - 8 \sigma_{\text{I}} \quad (\text{lxx})$$

A parallel treatment for **854** is more difficult since it starts from 2-pyridone **847** for which  $pK_{\text{a}}$  values at any substituent position are much more sparse (section B.2.4). The corresponding equations (cxliii), (cxliv) and (lxx) make no pretence at statistical validity but merely represent the best internally consistent set we can find that give acceptable results where they can be tested. We start by *assuming* eqn. (cxliii) since equations for  $pK_{\text{NH}}$  and  $pK_{\text{OMe}}$  in 2-pyridones and related oxoheterocycles, where known, appear to contain a term in  $\sigma_{\text{m}}$ , generally with  $\rho_{\text{m}} \sim -3$ , in all ring positions except that for the iminol adjacent to the tautomeric nitrogen atom, where  $\sigma_{\text{I}}$  is required instead, as for pyridine itself.<sup>259</sup> The best (rough) fit is obtained with  $\rho_{\text{I}} \sim 8$ , a lower value than in eqn. (xxix) perhaps because 2-pyridone possesses a lower dipole gradient. Table 138 contains data and calculations for **854**, along with those for (**847**,  $R^6 = \text{Cl}$ ) to parallel the above.

**Table 137. Observed and Calculated  $pK_a$  and  $\log K_T$  Values for 4-Pyridones <sup>a</sup>**

Cpd.	R <sup>6</sup>	$pK_a$ (NH)		$pK_a$ (OMe) + 0.5 <sup>b</sup>		$\log K_T$ <sup>c</sup>	
		Obs.	eqn. (xxviii)	Obs.	eqn. (xxix)	Obs.	eqn. (xxx)
<b>470</b>	H	3.27 <sup>d</sup>		7.12 <sup>d</sup>		3.85	3.7 <sup>e</sup>
<b>470</b>	Cl	2.29 <sup>f</sup>	2.09 <sup>e</sup>	2.47 <sup>f</sup>	2.18 <sup>e</sup>	0.18	0.09 <sup>e</sup>
<b>474</b>		1.07 <sup>g</sup>	1.19 <sup>e</sup>	4.20 <sup>g</sup>	2.18 <sup>e</sup>	3.13	0.99 <sup>e</sup>

<sup>a</sup> Data from section A.10.6. <sup>b</sup> As estimated for  $pK_a$  (OH), Appendix 1. <sup>c</sup>  $\log K_T = pK_a$  (OMe) + 0.5 -  $pK_a$  (NH). <sup>d</sup> Table 35. <sup>e</sup> Table 36. <sup>f</sup> Based on direct observation of tautomer ratio: Table 106, Appendix 1. <sup>g</sup> Table 38.

**Table 138. Observed and Calculated  $pK_a$  and  $\log K_T$  Values for 6-Aza-Substituted 2-Pyridones**

Cpd.	R <sup>6</sup>	$pK_{NH}$		$pK_{OMe}$		$\log K_T$ <sup>a</sup>	
		Obs.	eqn. (cxliii)	Obs.	eqn. (cxliv)	Obs.	eqn. (lxx)
<b>847</b> <sup>b</sup>	H	0.75 <sup>b</sup>		3.28 <sup>b</sup>		3.5	
<b>847</b> <sup>b</sup>	Cl	-0.18 <sup>b</sup>	-0.36	-0.13 <sup>b</sup>	-0.48	1.3 <sup>b,c</sup>	0.9
<b>854</b>		-1.6 <sup>d</sup>	-1.2	2.52 <sup>d</sup>	-0.48	5.1 <sup>d</sup>	1.7
<b>944</b>		-0.9 <sup>e</sup>	-1.6 <sup>f</sup>	2.3 <sup>g</sup>	-0.3 <sup>f</sup>	3.2 <sup>h</sup>	1.3 <sup>i</sup>

<sup>a</sup>  $\log K_T = (pK_{OMe} + 1) - pK_{NH}$ . <sup>b</sup> Table 55, section B.2.4. <sup>c</sup> Direct UV observation. <sup>d</sup> Table 56, section B.2.5. <sup>e</sup> Section B.2.12, Scheme 38:  $pK_5$ . <sup>f</sup> See the text. <sup>g</sup> Section B.2.12, Scheme 38:  $pK_4$ . <sup>h</sup> Section B.2.12, Scheme 38:  $\log K_8$ . <sup>i</sup> Eqn. (cxlv).

The calculated  $pK_{NH}$  and  $pK_{OMe}$  values for (**847**, R = Cl), while not good, are perhaps acceptable in the circumstances. However, while  $pK_{NH}$  for **854** is not well fit,  $pK_{OH}$  is underpredicted by  $\Delta pK_a$  ca. 3, the largest margin found for this category. Despite the sketchy nature of eqns. (cxliii) and (cxliv) it is scarcely possible that the resulting effect on  $K_T$  can be much less, if at all, than  $\Delta \log K_T$  3. Perhaps this extra enhancement is connected with increased lone pair repulsion as a result of electron donation from OH in very close proximity. If so, it has to be considered as a special circumstance.

**Table 139.  $pK_a$  Values for Triazinones**

Cpd.	R	$pK_a$	Cpd.	R	$pK_a$	$\Delta pK_a^a$
<b>1213B</b> <sup>b</sup>	H	3.95	<b>1214</b> <sup>b</sup>	H	1.55	- 2.40
“	Me	4.53	“	Me	2.19	- 2.34
<b>1587</b> <sup>c</sup>		9.43 <sup>d</sup>	<b>738</b> <sup>c,e</sup>		7.49 <sup>d</sup>	- 1.94
<b>1588</b> <sup>c</sup>		9.85 <sup>d</sup>	<b>739</b> <sup>c,e</sup>		10.1 <sup>d</sup>	0.25

<sup>a</sup> See the text. <sup>b</sup> Data from section B.5.13. <sup>c</sup> Data from ref. 389. <sup>d</sup> Acid  $pK_a$  value.

<sup>e</sup> Section B.1.1.

$$pK_{NH(5)} = 0.9 - 2.7\sigma_m \quad (\text{lxvi})$$

$$pK_{OMe(5)} = 3.3 - 6.1\sigma_m \quad (\text{lxv})$$

$$\log K_{T(5)} = 3.4 - 3.4\sigma_m \quad (\text{lxix})$$

$$\log K_8 = 3.5 - 3.4\sigma_m(5\text{-OH}) + 3\sigma_m(6\text{-N}) - 8\sigma_I(6\text{-N}) \quad (\text{cxlv})$$

Lone pair repulsion in  $K_8$  for ‘maleic hydrazide’ **944** (Scheme 56) may be addressed if we postulate, in the absence of  $\sigma$ -values for iminol or imino-ether, that the effects of 5-OH and 6-aza-nitrogen can be treated as additive, in which case eqns. (lxx) and (lxix) may be combined to give (cxlv) [but see sub-section (k) for a contrary treatment of  $K_9$ ]. At least it helps that (lxix) and its precursor equations (lxvi) and (lxv), unlike (lxx), are supported statistically (section B.2.4). The resulting analysis is given in Table 138. Neither  $pK_{NH}$  nor  $pK_{OMe}$  is calculated accurately, both being underpredicted, but this is very much greater for  $pK_{OMe}$  where any evidence for lone pair repulsion is expected to appear. By transferring electron density to nitrogen, resonance in the iminol moiety is likely to enhance either  $pK_a$  or both, so accounting plausibly for their underprediction, and if this is the same in extent or nearly so for each tautomer,  $\Delta \log K_T$  1.9 (Table 138) should provide at least an approximation to the effect of lone pair repulsion in  $K_8$ .

The triazinones **1214** exist predominantly as **1214C**, as is shown by the substantially higher  $pK_a$  values of **1213** (section B.5.13). Data for both appear in Table 139 and demonstrate  $\log K_M$  ca. 2.4. Since  $\log K_M \sim 0$  for 2-amino and 2-ethoxy-4-pyrimidones (*cf.* isocytosine, section B.5.11) that value would be expected for **1214** in the absence of lone pair repulsion, which plausibly it therefore monitors. For 4-pyrimidone  $\Delta(NR) = 0.3$  and 0.0 for 1-*N* and 3-*N* respectively, and since for **1214**  $\Delta(NR) = 0.3$  for 1-*N* similarly follows from  $pK_a$  1.90 for **1215** (section B.5.13), then by further

analogy, we assume that no correction factor is required for **1213B**. The triazinediones **738** and **739** provide a rare example of *acid*  $pK_a$  values relevant to tautomeric ratio (Table 139). Anion formation to give **738i** and **739i** must in both cases generate lone pair repulsion between aza-nitrogen and oxygen, as indicated in Scheme 156, but in **739i** there is additional repulsion between the two aza-nitrogen atoms, leading to a greater reluctance to ionise which appears in its relative  $pK_a$  value. We calibrate this effect by incorporating into Table 139 the corresponding microscopic  $pK_a$  values for uracil from which this extra lone pair repulsion is absent, using **1587** and **1588**. The resulting  $\Delta\Delta pK_a$  2.2 compares closely with  $\Delta \log K_M$  2.4 as deduced above for **1214**. Note that no correction factor is required for *any* anion since the blocked position cannot share the charge.

These five estimates for  $\Delta \log K$  comprise, in order, 2.1,  $\geq 3$ , (possibly) 1.9, 2.4, and 2.2. If 3-oxopyridazine is deleted as an (unexplained) outlier for which some special factor (see above) may be required,  $2.15 \pm 0.18$  ( $n = 4$ ) results. We shall employ  $2.2 \pm 0.2$  as an acceptable standard value.

#### (b) Annular Lone Pair Repulsion in 5-Membered Ring Heterocycles

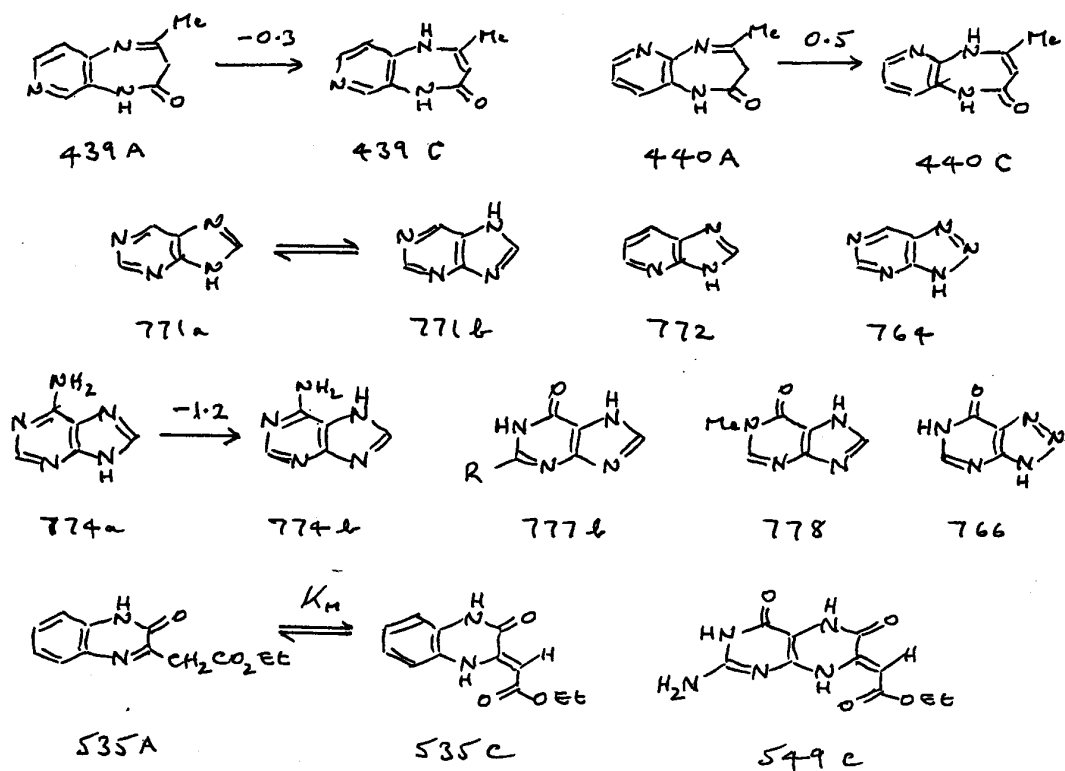
Quantitative information is sparse, being effectively confined to simple triazoles (Scheme 157). After statistical correction, contiguous aza-nitrogen is disfavoured by  $\Delta \log 0.3$  in both *v*-triazole **751** (section B.1.3) and *s*-triazole **741** (section B.1.2). Such a margin cannot be unequivocally assigned to lone pair repulsion since it is small enough to be the chance resultant of opposing factors. In 2-amino-*s*-triazole **743** however the margin is greater, and there is some evidence (section B.1.2) that 10-20% of **743C** is the usual range for other substituents also. Here the equilibrium between **743A** and **743C** is particularly important in the context of bicyclic species such as **804** (Scheme 157). This case is instructive. While **804B** is the dominant tautomer in nonpolar solvents where lone pair repulsion is likely to be specially pronounced, *e.g.* dioxane where 98% is present, **804A** dominates in EtOH and water and only 10% of EtOH in dioxane is required to effect the conversion (section B.1.9). This compound is a bicyclic guanidine and its key feature is that each tautomer combines a *favoured* aminoheterocycle part-structure for one ring with a *disfavoured* iminoheterocycle part-structure for the other. It should be possible to combine these (opposed) tautomeric ratios, if known, in order to arrive at least at a qualitative prediction of tautomeric form. On the basis of very provisional estimates, summarised in section C.33, we arrive at a tentative  $\log K$  3.2 in favour of **804A** in water, so accounting for the above observation.

Tetrazole **752**, uniquely for a monocycle, possesses lone pair repulsion in both tautomers. Beyond the certainty that **752A** dominates no data exist for water, but we have derived (section B.1.4) an LFER equation for DMSO from which the  $\log K$  value of Scheme 157 may be deduced. This compares with -0.2 for **751A**  $\rightarrow$  **751B** in the same solvent (section B.1.3) and indicates that the extra nitrogen further stabilises that tautomer which possesses the larger expected lone pair clash. There are two possible explanations. The first is that three contiguous aza-nitrogen atoms may in practice give rise to no more of a clash than two; certainly, **752A** is a much poorer proton acceptor than (a model for) **741C**.<sup>72</sup> Secondly, the amidine-type resonance possible for **752A**, but necessarily absent from **752B** or any tautomer of **751**, may considerably stabilise **752A**. At all events, **752** has to be regarded as a ‘one-off’ in this context.

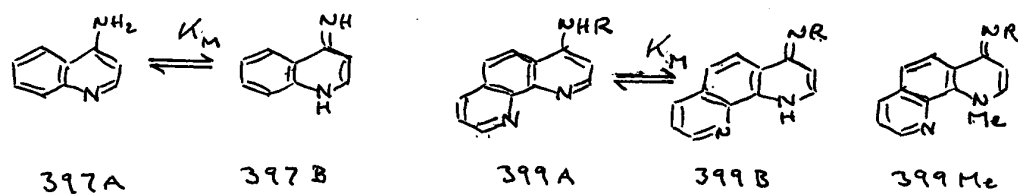
If the typical  $\Delta \log K$  for lone pair repulsion in 6-membered ring heterocycles is *ca* 2.2, whereas for 5-membered rings it is most relevantly *ca*. 0.8, this suggests it to be much less important in the latter. Part of this effect may be artefact: all examples of the first class are oxoheterocycles, a type of compound with no analogy in the second, and this feature may in some way enhance it. However, a perfectly rational geometric explanation is also possible. The angle subtended by contiguous lone pairs in a 5-membered ring is necessarily greater, ideally 72° against 60°, plausibly resulting in a lesser interaction. This consideration is also relevant to the *per/-*interactions considered below.

### (c) Lone Pair *peri*-Interactions in Bicyclic Structures

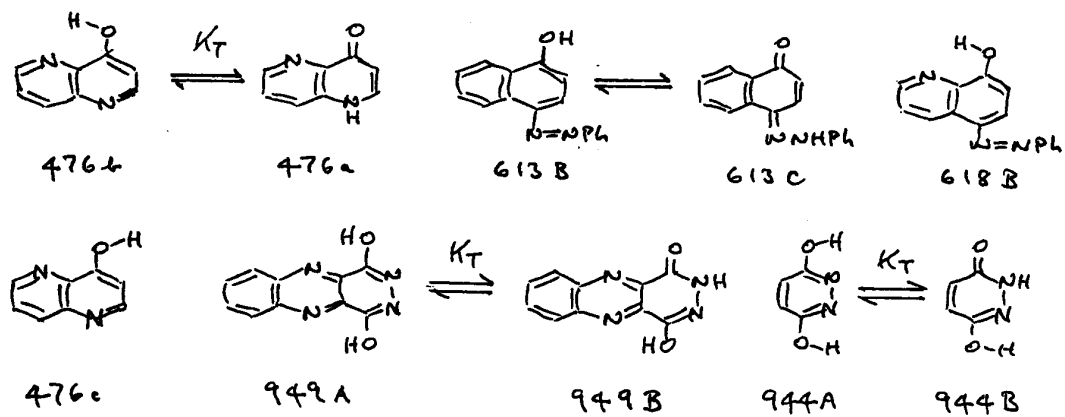
The 6,7-fused bicyclic heterocycles **439** and **440** (section A.10.4) provide quantitative information. The results for pyridine as solvent are shown in Scheme 158;  $\Delta \log K$  0.8 lies in the direction expected for a *peri*-interaction and the only caveat is that some part of the difference may relate to the different electronic effects of 2- and 4-pyridyl, on which there is little information. (Aminoenone tautomers are in general strongly favoured but the **C**-forms here are anti-aromatic). Most other examples concern 6,5-ring fusions. It is claimed (section B.1.7) that the tautomers of purine **771** are evenly balanced in water, despite the expected preference for **771a**; however **772** (section B.1.7) whose aza-nitrogen is a stronger acceptor and **764** (section B.1.6) where NH is a stronger donor both exist unequivocally as shown. This comparison suggests that any interaction may be marginal and dependent on circumstances – contrast (**m**) below. It may be significant, in the light of the discussion above, that the angle subtended by the lone pairs of **440A** will be appreciably smaller than those *e.g.* of **771b**.



Scheme 158



Scheme 159



Scheme 160

**Table 140. Proton Donor and Acceptor Strengths (log  $K_p$ ) for 1:1 Association** <sup>a,b</sup>

Functional Group <sup>c</sup>	log $K_\alpha$ <sup>d</sup>	log $K_\beta$ <sup>e</sup>
(Ar)NO <sub>2</sub>		0.7
(Ar)CN		1.0
Alkanol	1.2	1.4
Phenol	2.1	0.2 <sup>f</sup>
Amide	0.7	3.1 <sup>g</sup>
Imidazole	1.2	3.7
Pyrazole		2.2
1 <i>H</i> -1,2,4-Triazole	2.0	
1 <i>H</i> -1,3,4-Triazole		3.4
1 <i>H</i> - $\nu$ -Triazole	(2.7)	2.6
2 <i>H</i> - $\nu$ -Triazole	(2.2)	
Tetrazole	3.6	2.0
Oxazole		1.7 <sup>h</sup>
Pyridine		2.5
Pyrazine		1.5 <sup>i</sup>
Pyrimidine		1.7 <sup>i</sup>
Pyridazine		2.5 <sup>j</sup>
4-Quinolone		> 4

<sup>a</sup> Ref. 72. <sup>b</sup> For log  $K_p$  see eqn. (cxvii). <sup>c</sup> Also heterocyclic rings. For 1*H*-*s*-triazole, 1*H*- $\nu$ -triazole and tetrazole, proton donors probably interact with the aza-nitrogen atom most remote from NH.<sup>100</sup>

<sup>d</sup> With *N*-methylpyrrolidinone as acceptor in CH<sub>3</sub>Cl<sub>3</sub>. <sup>e</sup> With 4-nitrophenol as donor in CH<sub>3</sub>Cl<sub>3</sub>, using alkyl derivatives to block OH or NH. <sup>f</sup> Estimate, based on anisole. <sup>g</sup> Lactam. <sup>h</sup> For nitrogen atom. <sup>i</sup> Statistically corrected. <sup>j</sup> Bond may be bifurcated, so statistical correction not applied.

$$\log K_p = (\log K_\alpha + 0.4) (\log K_\beta + 0.3) \quad (\text{cxvii})$$

We suggest, in sections B.8.1 and C.38, that since hydrogen bond strength varies with the *product* of the separate donor and acceptor terms,<sup>590</sup> an equation of type (cxvii) might prove useful for assessing the relative magnitude of the *peri*-interactions  $K_p$  (it is more difficult to estimate the repulsive terms). The constants in eqn. (cxvii) relate the measured  $K_\alpha$  and  $K_\beta$  values to an empirical ‘scale zero’ for water; Table 140 contains some potentially useful log  $K_\alpha$  and log  $K_\beta$  values. For **771a**, **772** and **764** the ‘product value’ log  $K_p$  calculates as 3.2, 4.5 and 6.2 on the assumption that neither ring substantially affects the other. This might suggest a threshold value for affecting the tautomeric balance, in this context, of log  $K_p \geq 4$ . A good deal of work may be needed to calibrate this scale in order to make it predictive.

All other examples involve extra interactions and some of the results are puzzling. For adenine, **774a** is favoured by  $\log K$  1.2 in water where a much larger margin might have been anticipated. Very often the choice lies between alternative combinations of attractive and repulsive interactions so that the likely outcome is not obvious. For example, hypoxanthine (section B.1.7) exists predominantly as (**777b**,  $R = H$ ), suggesting that NH-carbonyl is more important than NH-N attraction and/or that N-carbonyl is more important than N-N repulsion. Consistently, **778** and guanine (**777**,  $R = NH_2$ ) behave in a similar manner. However, the structure preferred by **766** and the corresponding thione (section B.1.6) suggests the reverse, unless lone pair repulsion from its  $\nu$ -triazole unit is less than that from imidazole, which the data of Table 140 might suggest. (In addition, the dominant tautomeric form of the pyrimidone unit in **766**, unlike that of **778**, is not firmly established; unfortunately, this type of ambiguity is common). There is some evidence that N-N repulsion can be greater in other solvents than these results imply; for example, while  $\log K_M = 0.24$  for (**535**,  $R = CO_2Et$ ) in DMSO,<sup>334</sup> only **549C** is visible in DMSO or EtOH.<sup>343</sup> This probably implies  $\Delta \log K \geq 1.5$  but such a value is likely to be compatible with  $\Delta \log K < 1$  in water which appears to be implied for most cases of this type. Some re-investigation of this field, preferably quantitative, might be desirable.

#### (d) Lone Pair 1,4-Interactions: N,N-Type with NR---N Dipolar Attraction

Sections (e) - (j) comprise lone pair interactions to which the alternative is an intramolecular hydrogen bond, as distinct from the situation of (c) in which NH and the neighbouring nitrogen lone pair are roughly parallel so that dipolar attraction but no true hydrogen bond can result. A similar constraint obtains in the only case whose geometry assigns it to the present category. Note that we define the class of interaction in terms of heavy atom spacing.

The 1,10-phenanthroline (**399**,  $R = \text{cyclohexyl}$ ; section A.9.4) possesses  $\log K_M -4.8$  on the basis that **399Me** is employed as model for **399B** (Scheme 159). There are two problems with this result. The first is that 4-aminoquinoline **397** is reported as possessing  $\log K_M -3.5$ , so that lone pair repulsion appears to *stabilise* **399A**. We give reasons in section A.9.4 for believing the latter value to be inauthentic; we estimate  $\log K_M$  *ca.* -7 as the least negative likely value for **397**. The second is that NMe in **399NMe**, while certainly capable of dipolar attraction towards aza-nitrogen, cannot form a hydrogen bond. Hence  $\Delta \log K \geq 2$  as resulting from the above comparison represents a *minimum* value for the equivalent interaction to give an intramolecular hydrogen bond. There is no way round this problem at the present time.

**(e) Lone Pair 1,4-Interactions: N,O-Type with OH---N Bonding**

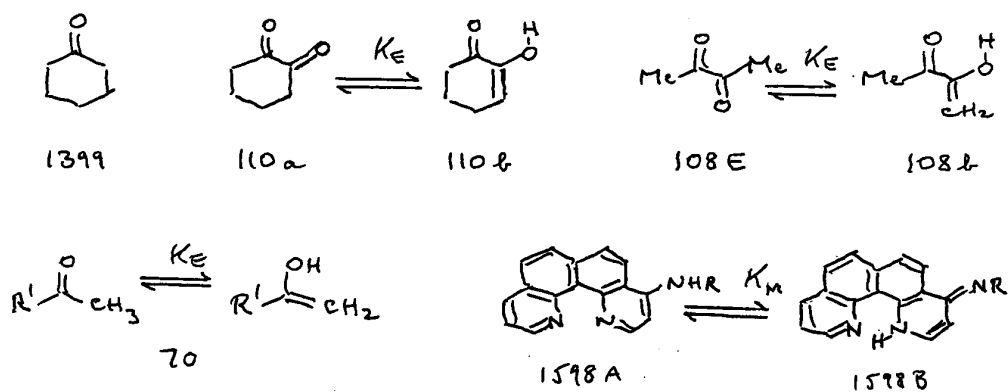
For **476** in water (Scheme 160), then starting from  $\log K_T$  4.9 for 4-quinolone (section A.10.7) and assuming that the effect of *peri*-nitrogen in the absence of a lone pair clash will not exceed that calculated for a 3-nitro group (section A.10.6), we arrive at a baseline value of  $\log K_T$  *ca.* 4.4. In MeCN, 80-90% of **476** is present as the iminol, *i.e.*  $\log K_T$  *ca.* 0.8 (section A.10.7). Using the solvent correction expected for an 'extended' vinylogous amide of  $\Delta \log K_T$  1.7 for MeCN  $\rightarrow$  water (Appendix 2), this results in a predicted  $\log K_T$  *ca.* 2.5 for **476** in aqueous solution. Hence the overall effect of replacing a lone pair interaction, still present in **476c**, with an intramolecular OH---N bond is probably  $\Delta \log K$  *ca.* 2. This calculation has to assume hydrogen bond strength to be unaffected by the change of solvent; since it is almost certain to be stronger in MeCN, the above must be taken as a maximum value.

Two qualitative pieces of information are consistent with an estimate of this order. Whereas  $\log K_T$  for **613** lies in the range 0 - 0.5, only **618B** is detectable for **618** (section A.10.19). For **949**, the **B**-tautomer is dominant as for **944** but the **A**-tautomer is detectable, whereas for **944** with  $\log K_T$  3.2 (section B.2.12) it is not. While  $\Delta \log K_T$  for **949** cannot precisely be calculated, a value approaching -2 would be compatible with this result. The agreement could be partly fortuitous: since pyrazine is a poorer proton acceptor than pyridine (Table 140) a weaker hydrogen bond would be expected, but this may be partly offset by the ring's greater electronegativity. Nevertheless it seems likely that  $\Delta \log K$  *ca.* 2 is a reasonable estimate for the process overall.

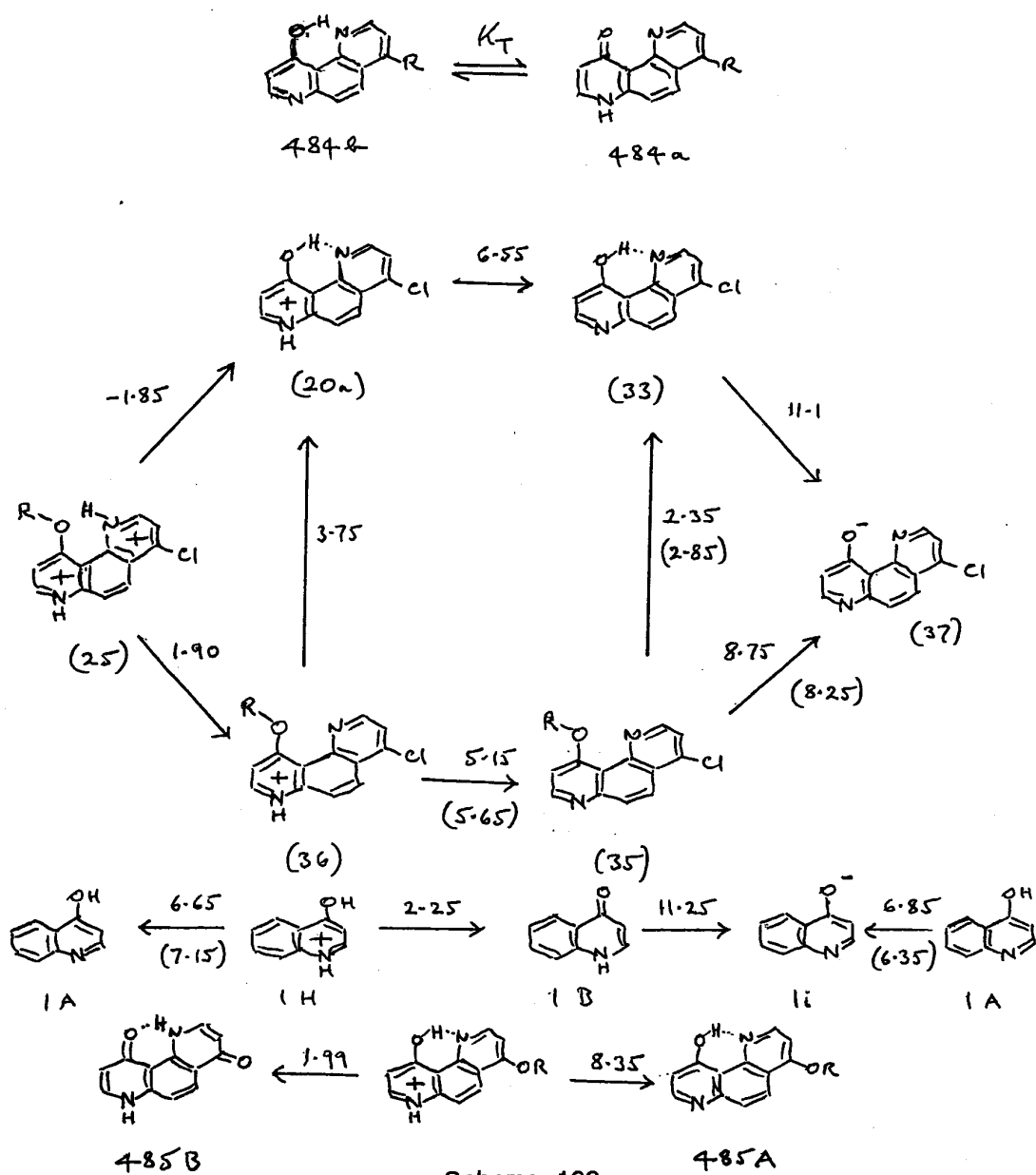
**(f) Lone Pair 1,4-Interactions: O,O-Type with OH---O Bonding**

$$\log K_E = -7.39 + 1.97\sigma_I + 8.11\sigma_R \quad (\text{iii})$$

The insertion of  $\alpha$ -carbonyl into cyclohexanone **1399** (Scheme 161) increases  $\log K_E$  from -6.7 (statistically corrected) to perhaps *ca.* 2 (section A.2.5), *i.e.*  $\Delta \log K_E$  for **110** is probably in the region 8 - 9. No enol can be detected in its open-chain analogue biacetyl **108**, which exists as **108E** (section A.2.5) so avoiding lone pair repulsion. Nevertheless one component in the behaviour of **110** must be the mutual electronegativity of the carbonyl groups, which should be roughly equal for **108** and **110** and may be calculable *via* eqn. (iii) for compounds of type **70** (section A.2.1). If so we predict  $\log K_E$  *ca.* 4.9 for **108** which, by comparison with 8.6 (statistically corrected) for acetone, gives  $\Delta \log K$  *ca.* 3.7 for the effect of electronegativity *alone*, *i.e.* it



Scheme 161



Scheme 162

does not allow for the hydrogen bond of **108b** so that, if this estimate is correct, the *difference* between it and the experimental value of  $\Delta \log K_E$  for **110** gives the required quantity. Very roughly, we therefore estimate  $\Delta \log K$  ca. 5 for the combined effect of lone pair repulsion and the intramolecular hydrogen bond in **110**. No information exists on the relative magnitude of this interaction as a function of ring size.

**(g) Lone Pair 1,5-Interactions: N,N-Type with NH---N Bonding**

There are no entries in this section. It would be no surprise if, in the hypothetical compound **1598** (Scheme 161), the amino-tautomer **1598A** proved impossible to detect. If an attempt were made to measure  $K_M$  it would certainly be worth trying to dispense, on this occasion, with the use of model compounds.

**(h) Lone Pair 1,5-Interactions: N,O-Type with NH---O and OH---N Bonding**

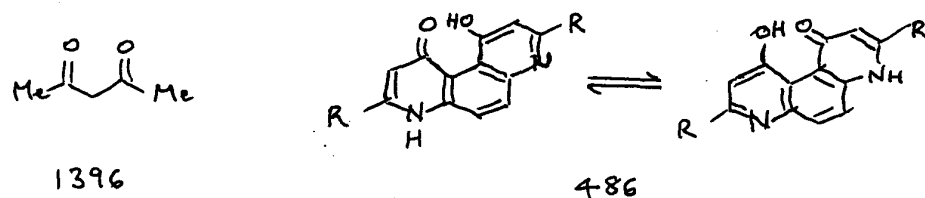
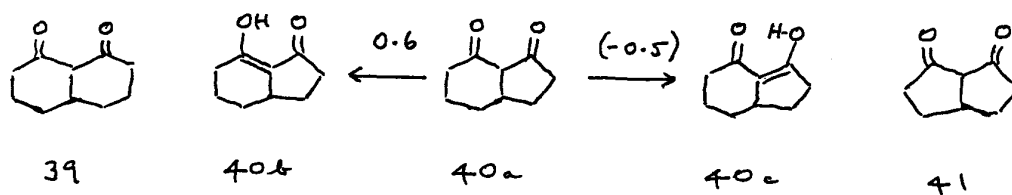
Just one paper bears on this point, an extremely ingenious study in which Katritzky and co-workers<sup>304</sup> investigated tautomerism in the 1,7-phenanthrolines **484** and **485** (section A.10.8). All compounds of type **484** exist predominantly as **484b**, except when R = OH which results in the dioxo-tautomer **485**. Scheme 162 shows all relevant compounds and the layout for (**484**, R = Cl) preserves for convenience the authors' numbering system. Here R = H or Me according as to whether the upper or lower branch is followed. The essential difference between them is the presence or absence of an intramolecular OH---N bond, to which  $\Delta pK_a$  3.75 and 2.35 is attributed by the authors for the cationic and neutral species respectively. Use of  $\Delta(OR)$  0.5 changes  $pK_a$  5.15 to 5.65 with corresponding changes elsewhere; the revised values are bracketed. The anionic  $pK_a$  values are also important because these can be used to estimate the effect of lone pair repulsion. The authors note that the successive deprotonation steps (**1H**)  $\rightarrow$  (**1A**)  $\rightarrow$  (**1i**) which may be calculated for 4-hydroxyquinoline give  $pK_a$  values that are very similar, while those of the sequence (36)  $\rightarrow$  (35)  $\rightarrow$  (37) are very different, anion formation being notably disfavoured. (In the values quoted for 4-quinolone **1** we take the opportunity to correct some minor arithmetical errors). By cross-comparison of these two sequences they arrive at  $\Delta pK_a$  3.4 (corrected from 3.15) for the effect of lone pair repulsion in (37); use of our revised values, by a cancellation of factors, leads to the *same* result. Adding in  $\Delta pK_a$  for hydrogen bonding, the total effect becomes  $\Delta \log K_T$  ca. -6.3. If **484** is considered a modified 4-quinolone,  $\log K_T$  -1.4 may then be calculated for (**484**, R = Cl), as estimated by the authors and qualitatively in agreement with observation.

The  $pK_a$  values shown for (**485**, R = H or Et) allow  $\log K_T$  6.4 to be calculated for the overall tautomeric shift from the dihydroxy to the dioxo species. The authors<sup>304</sup> calculate the shortfall in  $\log K_T$  in terms of two 4-quinolone molecules, but this involves counting the benzenoid moiety twice, with the result of adding  $\Delta \log K_T$  *ca.* 1 to each pyridone moiety, and we regard it as fairer to calculate in terms of 4-quinolone plus 4-pyridone, in which case  $\Delta \log K_T$  -2.4 results. As the authors point out, this quantity whatever its precise numerical value represents the *difference* in the strength of the intramolecular hydrogen bonds of **485A** and **485B**, the OH---N bond of **485A** being the stronger. On either calculation  $\Delta \log K$  *ca.* 0.5 results for the strength of NH---O bonding in **485B** (if the corrected  $\log K_T$  value of 4.9 for **1** is used to give  $\Sigma \log K_T$  as twice this value, this calculation becomes incommensurable). While 4-quinolone is a very strong proton acceptor (Table 140) its NH moiety is a poor proton donor –  $\Delta(NR) = 0$  for vinylogous amides (Appendix 1) – so this proposition is not difficult to accept; echoes of it appear in (**m**) below and Appendix 4.

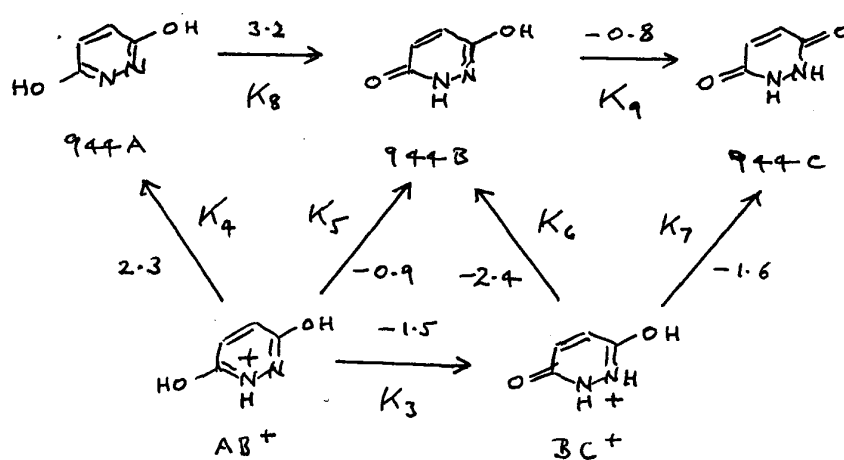
Combining the effects of lone pair repulsion and hydrogen bonding we arrive at  $\Delta \log K$  3.9 or 6.3 according as to whether the latter is of NH---O or OH---N type. The latter is enormously greater than  $\Delta \log K$  as proposed in (**e**) above and this is clearly due to the much more compressed geometry. No relevant comparison involving the former can be made at the present time. In view of frequent misunderstandings on this point it should perhaps be emphasised that lone pair repulsion *on its own*, necessarily the same in each case, at  $\Delta \log K$  3.4 is responsible for the larger part of the overall process; hydrogen bonding alone, and unenforced, does not compare in its influence on tautomeric form (Appendix 4). A minor caveat lies in the fact that, for the crucial process (35)  $\rightarrow$  (37), lone pair repulsion involves an anionic species, which may enhance its effect. Katritzky<sup>304</sup> addresses this point, but not very convincingly, and we prefer to leave it open.

#### (i) Lone Pair 1,5-Interactions: O,O-Type with OH---O Bonding

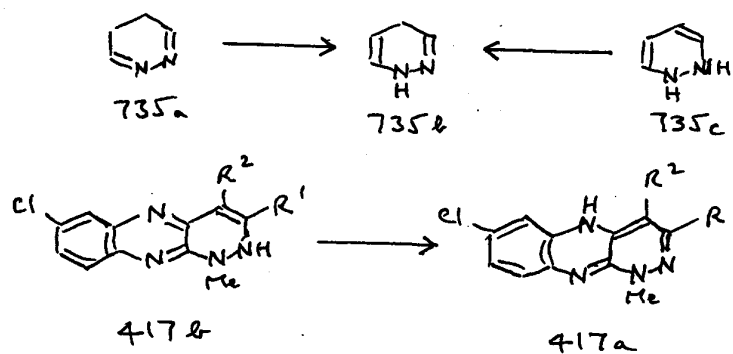
Our only information derives from the bicyclic  $\beta$ -diketones **39** – **41** (Scheme 163). For these, enolisation in MeOH gives 100, 80 and 1.4% of enol respectively, a sequence that clearly relates to a compression effect, greatest in **39**, which should increase both lone pair repulsion and the strength of the hydrogen bond. (Note that **40b** is the dominant enol of **40**, as expected on stereoelectronic grounds; *vide* section A.1.2). Acetylacetone **1396** as the nearest open-chain, nonrigid analogue possesses  $\log K_E$  *ca.* 0.4 in MeOH (Table 115, Appendix 2) *i.e.* quite comparable to **40**. The value for **39** implies not less than  $\Delta \log K_E \sim 1$  relative to **40** and the actual increment may



Scheme 163



Scheme 38



Scheme 164

be much greater than this. Allowing for statistical correction even the postulate of an equal spacing in  $K_E$  between each pair of compounds, for which there seems no good justification, would result in only  $\Delta \log K_E$  *ca.* 3, very much below the level found for **484** and **485** above. However **39** and **40** are only ‘pseudo-rigid’ and one carbonyl group may be able to twist out of plane with the other to an extent that greatly decreases the lone pair repulsion present, while the ‘butterfly’ shape of **41** even though quite rigid may have similar consequences. We conclude that while  $\Delta \log K$  if it were known would be relevant in context, any cross-comparison involving (f), (h) and (i) fails to compare like with like.

#### (j) Lone Pair 1,6-Interactions: O,O-Type with OH---O Bonding

The 1,4-phenanthrolines (**486**, R = CO<sub>2</sub>R') also of Scheme 163 represent the only members of the present class to have been studied. They comprise a single degenerate tautomer and are so insoluble that only solid state investigation was possible (section A.10.8). Their IR spectra show bands characteristic of both pyridone and pyridinol moieties and, in particular, ‘B’- and ‘C’-type  $\nu(\text{OH})$  vibrations centred on 2600 and 1860 cm<sup>-1</sup> respectively. These are not at low enough frequency to suggest a single potential minimum as is sometimes found<sup>609</sup> for cations and anions of type [BHB]<sup>+</sup> and [AHA]<sup>-</sup> but not so far, except for (**486**, R = CO<sub>2</sub>H) where they involve CO<sub>2</sub>H and aza-nitrogen, in any other context. There is no information on dipyridone or dipyridinol species and it is quite likely that their synthesis would prove impossible. This type of structure represents an extreme for which  $K_T$  will probably remain inaccessible.

#### (k) Annular Dipolar Repulsion in 6-Membered Ring Heterocycles

$$\log K_T = 3.5 + 3\sigma_m - 8\sigma_I \quad (1xx)$$

There are few reported cases of this type and only the second ketonisation step of maleic hydrazide ( $K_9$  in Scheme 38) provides quantitative data (section B.2.12). We examine the first step in (a) above on which Table 138 contains the required information. For  $K_8$  we treat 5-OH and 6-N *faute de mieux* as independent substituents, with moderate success, but here it is even less clear what the term ‘substituent’ can mean. For this reason we have chosen the experiment of treating -NHCO- as a single entity encompassing the 5- as well as the 6-position and acting essentially as a 6-substituent in the 2-pyridinol/2-pyridone tautomeric system, eqn. (1xx), corresponding to **944B**  $\rightleftharpoons$  **944C**, and with the electronic properties expected for -NHCOMe (Table 2).

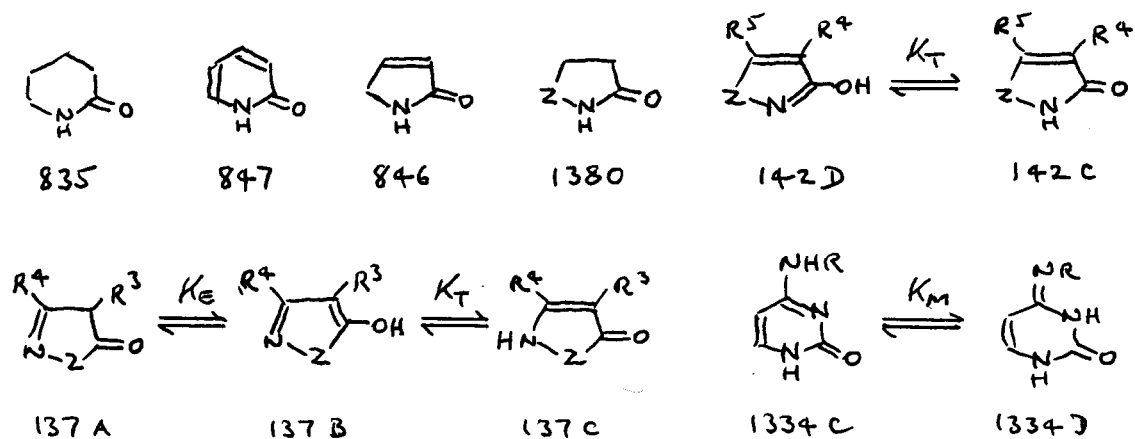
This leads to an estimate of 1.7 for  $\log K_9$ , whose actual value of -0.8 therefore represents a shortfall of  $\Delta \log K_T$  -2.5. We postulate that most or all of this shortfall is caused by dipolar repulsion in **944C**. A very similar estimate for dipolar repulsion in contiguous NH groups, but here attaching to 5-membered rings, appears in the following sub-section.

A more doubtful approach, but on parallel lines, attempts to predict  $pK_6$  and  $pK_7$  starting from  $pK_4$  and  $pK_5$  respectively. While  $K_5$  and  $K_7$  involve proton loss from oxygen to give an amide,  $K_4$  and  $K_6$  entail its loss from nitrogen to give an iminol. We postulate therefore that  $\Delta pK_a$  for  $pK_5 \rightarrow pK_7$  should show the  $-3\sigma_m$  dependence of a 2-pyridone, and that for  $pK_4 \rightarrow pK_6$  the  $-8\sigma_m$  dependence of a 2-pyridinol, the two strands that combine to give eqn. (lxx). This predicts  $pK_7$  -1.4 and  $pK_6$  0.1, leading to  $pK_9$  1.5 where -0.8 is found, a result nearly equal to the above. It will be noticed that the two 'anomalous' protonation steps are those in which one nitrogen atom changes its hybridisation state, the direction of this being favourable for **944A**  $\rightarrow$  **AB**<sup>+</sup> but detrimental for **944B**  $\rightarrow$  **BC**<sup>+</sup>. It is also interesting to note that the effect of dipolar repulsion,  $\Delta \log K_9$  -2.5, is greater than that of lone pair repulsion,  $\Delta \log K_8$  +1.9, under what are essentially isogeometric circumstances; this may reflect the greater solvation provided by water as proton donor than as proton acceptor, as shown for example by its  $\alpha$ - and  $\beta$ -values (Appendix 2).

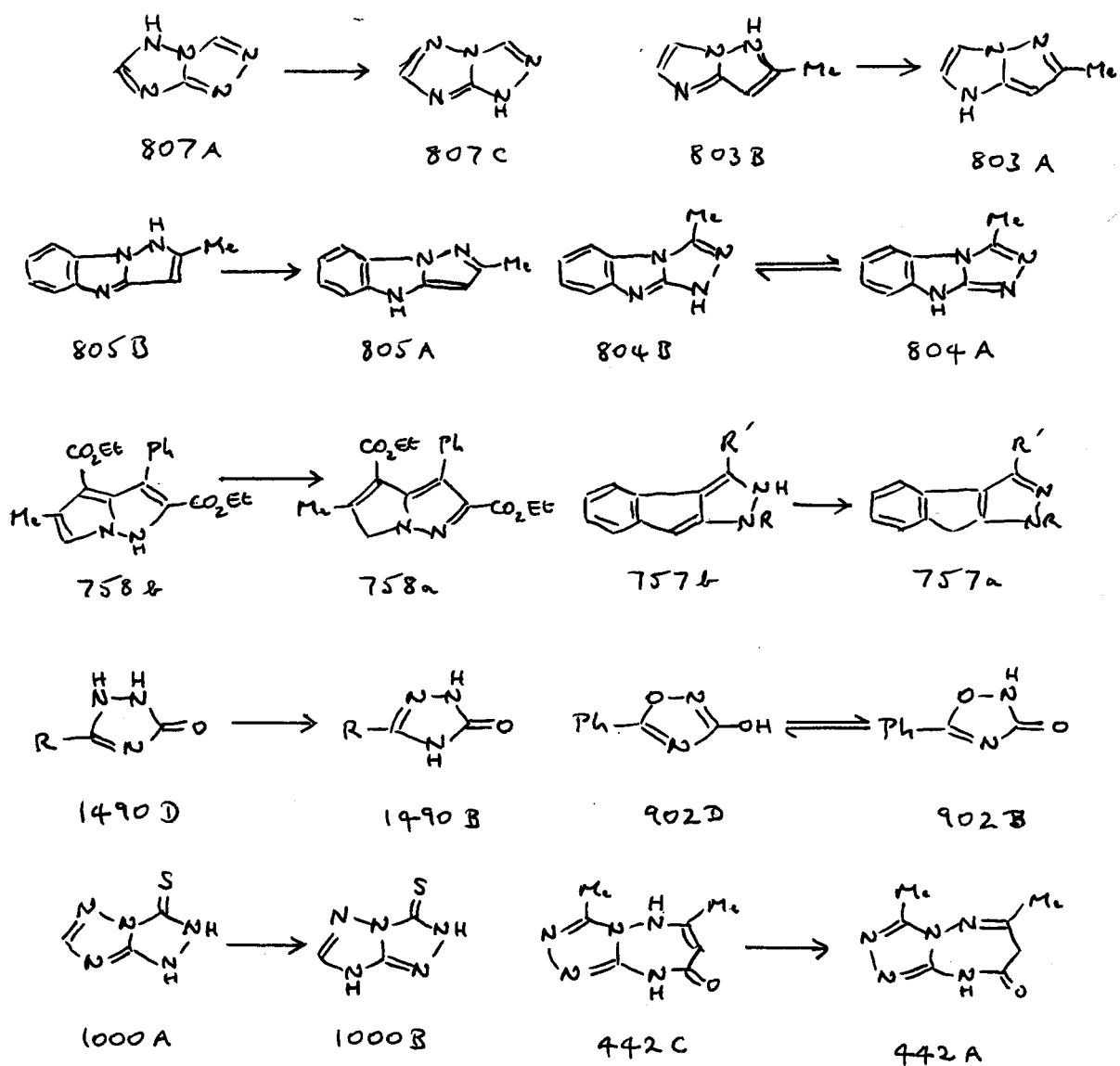
The existence of **735** as **735b** (Scheme 164), and similarly in other examples of this type (section B.1.1), reflects the same preferred structure **730b** but has not been quantified. It should also be noted that **735c** would be anti-aromatic (Appendix 5). A much more significant exemplar is **417** (section A.9.6) where dipolar repulsion in **417b** is strong enough to over-ride a significant degree of aromaticity. However some other compounds discussed in this section give contrary results and some are so anomalous as to warrant re-investigation. We cannot be sure at present, therefore, that  $\Delta \log K$  2.5 represents a constant factor.

### (I) Annular Dipolar Repulsion in 5-Membered Ring Heterocycles

For piperidinone **835** (Scheme 165) we estimate  $\log K_T$  ca. 7.6 (section B.2.3) whereas for 2-pyridone **847** 3.5 is found (section B.2.4), a drop due to aromatisation of ca.  $10^4$ . Similarly for **846** we estimate  $\log K_T$  ca. 6.5 (section B.2.3) whereas for compounds of type (**142**, Z = O, S or NR)  $\log K_T$  is frequently small and sometimes negative (section B.2.10). It seems improbable that this much greater effect can be wholly due to aromatisation and dipolar repulsion between Z and NH is the obvious additional factor. No information is available for compounds of type **1380** so we have to rely for elucidation on some form of dual-parameter analysis.



Scheme 165



Scheme 166

**Table 141. Quantitative Breakdown of  $\Delta \log K_T$  for **142**<sup>a</sup>**

	NH	NMe	NPh	O
$\sigma_R$ contribution (eqn. cxlvii)	- 3.9	- 3.9	- 3.6	- 3.3
$\sigma_I$ contribution (eqn. cxlvii)	- 2.5 <sup>b</sup>	- 3.0	- 4.1	- 4.9
$\Delta \log K_T$ (sum of contributions)	- 6.4	- 6.9	- 7.7	- 8.2
$\Delta \log K_T$ (estimated) <sup>c</sup>	- 6.5	- 7.0	- 7.5	- 8.5

<sup>a</sup> See the text. <sup>b</sup> Adjusted from NMe value as used in eqn. (cxlii) by adding  $\Delta \log K_T$  0.5.

<sup>c</sup> Section C.15; see the text.

$$\log K_T = 6.45(0.74) - 21.5(7.2) \sigma_I + 5.25(2.31) \sigma_R \quad (\text{cxlvi})$$

$$(n = 5 \quad r^2 = 0.976 \quad s = 0.75 \quad F = 40)$$

$$\log K_T = 6.47(0.50) - 20.4(4.8) \sigma_I + 5.8(1.5) \sigma_R \quad (\text{cxlvii})$$

$$(n = 5 \quad r^2 = 0.989 \quad s = 0.50 \quad F = 92)$$

For **142** with  $R^4 = R^5 = H$  and for  $Z = CH_2, NH, NMe, NPh$  and  $O$  (section C.15) we have attempted to quantify this situation by means of eqn. (cxvi). Here the term in  $\sigma_R$  plausibly represents the drive for aromatisation (note that the contribution of  $\sigma_R$  to  $K_T$  is always negative) whereas  $\sigma_I$  attempts to parameterise the effect of dipolar repulsion. However, this equation is not adequately predictive. Most of the reason lies in the dichotomy between near-identical  $\sigma$ -values for  $>NH$  and  $>NMe$ , and  $\log K_T$  values consistently less for the latter, in several compound series, by  $\Delta \log K_T$  ca. -0.5. We believe this difference to reflect the poorer solvation of  $NHNMe$  vs.  $NHNH$  (section C.15), a parallel consequence being  $\Delta(NMe)$  0.45 for amides (Appendix 1). By subtracting 0.5 from  $\log K_T$  for  $Z = NH$  to equalise the values for  $Z = NH$  and  $Z = NMe$  we obtain the much improved eqn. (cxlvii), which may be used to calculate the  $\sigma_I$  and  $\sigma_R$  contributions to  $\Delta \log K_T$  that appear in Table 141; the  $\sigma_I$  contribution to  $Z = NH$  is then re-adjusted in line with its original  $\log K_T$  value, so restoring the difference between them. As the series  $NH \rightarrow O$  is ascended, aromatisation becomes less important but dipolar repulsion much more so. The resulting agreement is almost exact; there may be a case for a slightly higher  $\sigma_I$  contribution to  $Z = O$ , but any such effect is minimal. To within the limits of error, we propose  $\Delta \log K$  values due to dipolar repulsion of 2.5, 3, 4 and 5 for  $Z = NH, NMe, NPh$  and  $O$  respectively. That for  $Z = NH$  appears to be identical to the value deduced in (**k**) above for maleic hydrazide **944**. No estimate can be hazarded for  $Z = S$  at the present time.

These values do not necessarily apply to all systems but differences may not be great. It is known that variation in  $K_T$  with  $Z$  is less for **137** than for **142**, and there is suggestive evidence for a proportionality that extends to  $K_E$  and  $K_M$  (Scheme 86; see sections C.15 and C.16), but since two factors are present any such differences could be due to one but not the other. However, important evidence comes from the open-chain compound series **1334** (section B.8.6; data in section B.2.15). For  $R = H, NH_2$  and  $OH$ ,  $\log K_M$  is -4.1, -1.5 and 1.1; that is,  $\Delta \log K_M$  is 2.6 and 5.2 for  $R = NH_2$  and  $OH$  respectively. These values are almost identical with the  $\sigma_I$  contribution to  $Z = NH$  and  $O$  in **142** and not only suggest the possibility of a universal applicability but demonstrate, in sharp contrast to the situation for lone pair repulsion, that dipolar repulsion is found, and may be present almost unchanged, in other than cyclic structures.

While quantitative data are absent, 5,5-ring fused heterocycles possessing bridgehead nitrogen ('azapentalenes,' section B.1.9) contain potent evidence of tautomeric preference dictated by lone pair or dipolar repulsion (Scheme 166). Whereas in cases such as **807** the choice of tautomer is dictated by both, others possess one or the other and in **803** and **805** only dipolar repulsion is present. The latter is specially instructive through its contrast with the effect of lone pair repulsion in **804**; cf. (b) above. While **805B** has not been detected, the tautomeric form of **804** is dictated by solvent: **804A** is found in EtOH and water whereas in non-hydroxylic solvents, **804B** dominates. Given postulated penalties of  $\Delta \log K$  0.8 and 2.5 disfavouring **804A** (lone pair repulsion) and **805B** (dipolar repulsion) respectively this difference in behaviour seems reasonable, but it also provides a clue as to why, at least in water, dipolar repulsion appears to be so much the more important. (In addition, **804A** should be favoured over **804B** in terms of the distribution of bonds around its central guanidine unit; see section B.8.9. The position concerning **805** is at present unpredictable). As noted in (k) above, water is predominantly a proton donor solvent and therefore much better able to solvate lone pairs than dipoles whose positive end faces the solvent. This rather than any intrinsic difference in free energy probably accounts for the larger, and often much larger,  $\Delta \log K$  values we find for dipolar repulsion in geometrically similar circumstances; see particularly (m) below.

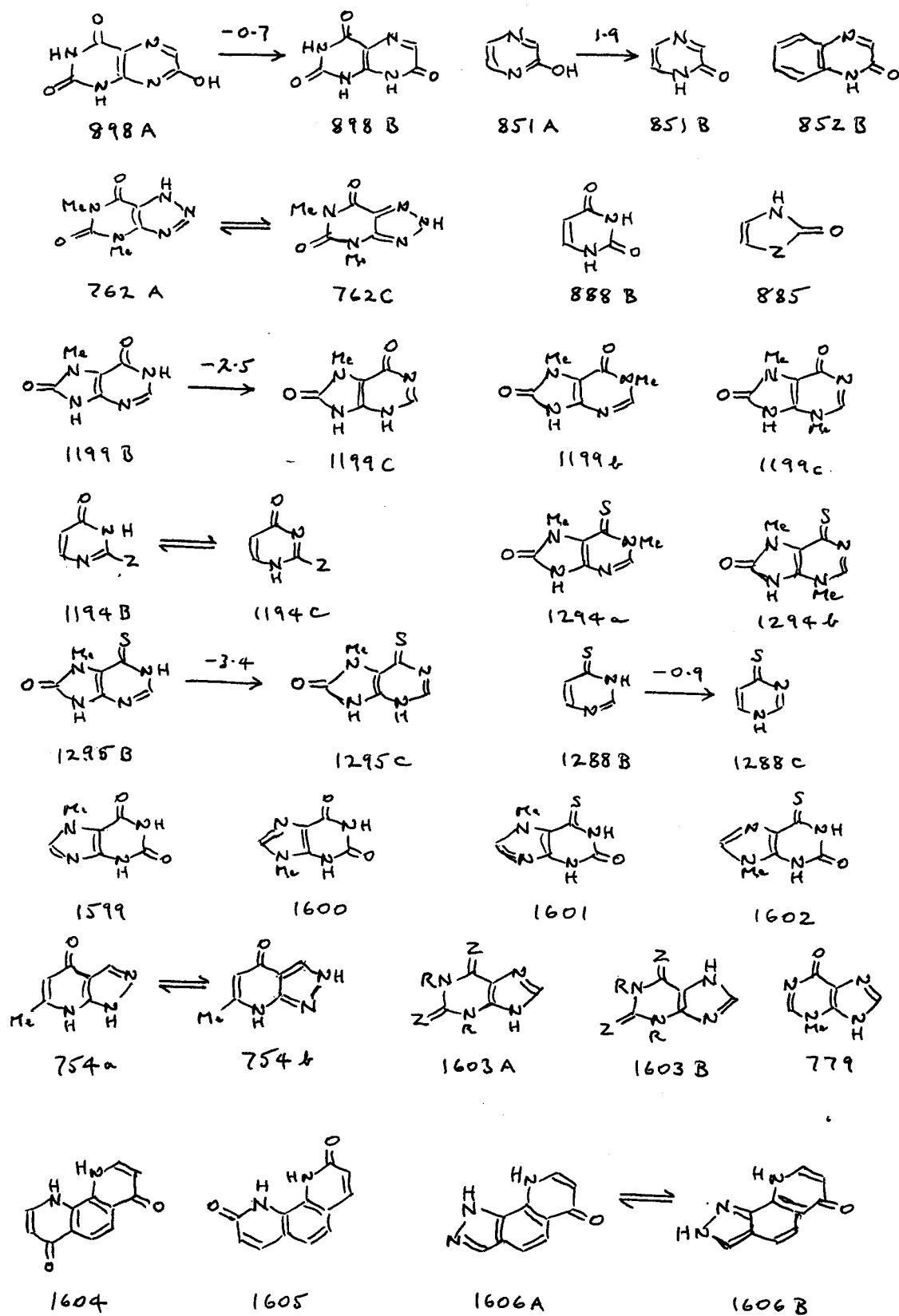
Dipolar repulsion can be so severe as to over-ride aromaticity, as in the preferred tautomer **758a** where that of pyrrole is lost, or in **757** where conjugation is severed to give **757a** (section B.1.5). Nevertheless, puzzles remain. Whereas **1490B** is found as expected for **1490**, the inability of **902** to undergo a similar proton switch leaves **902A** and **902B** roughly in balance in

water (section C.20) where, given  $\Delta \log K$  *ca.* 5 for NHO, the dominance of **902A** might have been expected. One possibility is that, combining two conjugated structures that converge on carbonyl, **902B** possesses enough resonance energy to balance out the challenge, but there are no obvious models on which to base the most tentative calculation. The same goes for **1000** (section B.3.5), which may appear a simple case of avoiding dipolar repulsion until it is noted that **1000B** contains an iminotriazole part-structure disfavoured possibly by a margin of  $> 10^6$  (section B.8.9) leaving, on the above evidence, a factor of  $> 10^4$  to be found in its favour from some other structural feature. Similarly, relief of dipolar repulsion through replacing **442B** by the preferred tautomer **442A** (section A.10.4) is obtained at the cost of aminoenone resonance, which on all available evidence is worth much more than the  $\Delta \log K$  *ca.* 2.5 expected in its favour. It is noted in (c) above, concerning the related compounds **439** and **440** (Scheme 158), that the crucial factor is antiaromaticity in the aminoenone tautomer, but it seems doubtful that this case can be explained quite so simply. There are still many problems to be resolved in this area.

#### (m) Dipolar *peri*-Interactions in Bicyclic Structures

Several cases exist which allow quantitative evaluation. In the pteridine **898**, the iminol is dominant:  $\log K_T$  -0.7 (section B.2.9). This compares with  $\log K_T$  1.9 for **851** or 2.8 for its benzofused derivative **852** (section B.2.5); *n.b.* that both values may be higher (Appendix 1). However benzofusion invariably raises  $K_T$  (Appendix 5) and the same could be true for other forms of ring fusion, we need to evaluate this factor. Since **762** in DMSO exists 80% as **762C** (section B.1.6) whereas the corresponding value for *v*-triazole **751** itself is 55% (section B.1.3), and as a quinonoid structure **762B** should be disfavoured by  $\Delta \log K$  *ca.* 1.8, we may conclude that ring fusion with uracil **888** does not affect aromaticity either way;  $\Delta \log K_T \sim -2.6$  follows for the effect of dipolar repulsion in **898B**.

If fusion with uracil does not affect the aromaticity of the fused heterocycle, the still less aromatic urea (**885**, Z = NH or NMe; section B.2.9) is unlikely to affect it either. This is relevant in several cases which concern the effect of *peri*-interactions on *acid* p*K<sub>a</sub>* values. Those of **1199b** and **1199c** are 8.5 and 6.0 respectively (section B.5.11). Proton loss from **1199b** is inhibited by a lone pair clash between the anion so formed and aza-nitrogen, whereas it is helped in **1199c** by the relief of dipolar repulsion. We deduce  $\log K_M$  -2.5 for **1199**; comparison with  $\log K_M$  -0.4 for (**1194**, Z = H) leads to  $\Delta \log K$  -2.1 as the resultant factor. A parallel treatment of the related thione



Scheme 167

**1295**, based on acid  $pK_a$  values of 8.2 and 4.8 for **1294a** and **1294b** respectively, gives  $\log K_M$  -3.4 which, corrected for -0.9 in 4-pyrimidinethione **1288**, leads to  $\Delta \log K$  -2.5 (section B.6.2). Strictly speaking, **1199** and **1295** both monitor NH,NMe not NH,NH clashes, but on the above arguments, the difference is not expected to be great. More equivocal evidence derives from the pairs of xanthines **1599** - **1602** investigated by Lichtenberg *et al.*<sup>610</sup> Here no correction is required for the imidazole moiety since its tautomers are degenerate but there is a potential ambiguity concerning the site(s) of proton loss from uracil and thiouracil. The *N*-methyl xanthines **1599** and **1600** possess  $pK_a$  values of 8.4 and 5.9 respectively, the corresponding values for **1601** and **1602** being 6.8 and 4.9, giving tentative  $\Delta \log K$  values of 2.5 and 1.9. (It is unfortunate that their *basic*  $pK_a$  values were not measured, since these would have given  $\Delta \log K$  directly without even the need for a correction factor). Outstandingly, all these values and that for **898** above are large, close to those of the contiguous interactions analysed in (I) above and out of the class of any related *peri*-interaction, attractive or repulsive, a very different situation from that found for lone pair repulsion.

An apparent exception is provided by **754**, which exists as **754a** in water (section B.1.5) despite the relief of dipolar repulsion that **754b** would provide. Formation of **754b** would involve substantial loss of aromaticity but this is unlikely to exceed the 'quinonoid penalty' of  $\Delta \log K$  -1.7 found for indazole (Appendix 5), so that as small a margin as  $K = 10$  in favour of **754a** sets an upper limit of  $\Delta \log K$  *ca.* 0.7 for the effect of dipolar repulsion, while  $K > 50$  would actually make it favourable. However, there is a possible explanation that would also help to rationalise the variability encountered above. In (c) we attempt to explain *qualitatively* the variable importance of NH,N *peri*-interactions in terms of eqn. (cxvii), which measures *inter alia* the strength of linear NH---N hydrogen bonds and so, by analogy, should show some parallelism to the *attractive* but non-linear forces present in the former case. The much larger effects demonstrated here suggest that, for dipolar interactions, it is the *repulsion* that dominates, so that in terms of Table 140, only the  $\log K_a$  values are relevant. Unfortunately too many of these are missing for our purposes, but another, more tentative approach is possible. The  $\Delta(NR)$  values of Appendix 1 reflect solvational differences between NR and NH which in turn must relate to the latter's proton donor ability and, by implication, to its dipole gradient. For amides, amidines and vinylogous amides, all of which figure as sources of dipolar repulsion in the compounds of Scheme 167, the appropriate  $\Delta(NR)$  values are 0.45, 0.3 and 0.0 respectively (Scheme 123), which could mean that the 4-pyridone moiety of **754** will induce much less dipolar repulsion than is present elsewhere. If so, its behaviour may not in fact be anomalous. This is one of the areas in which computation could be of real value.

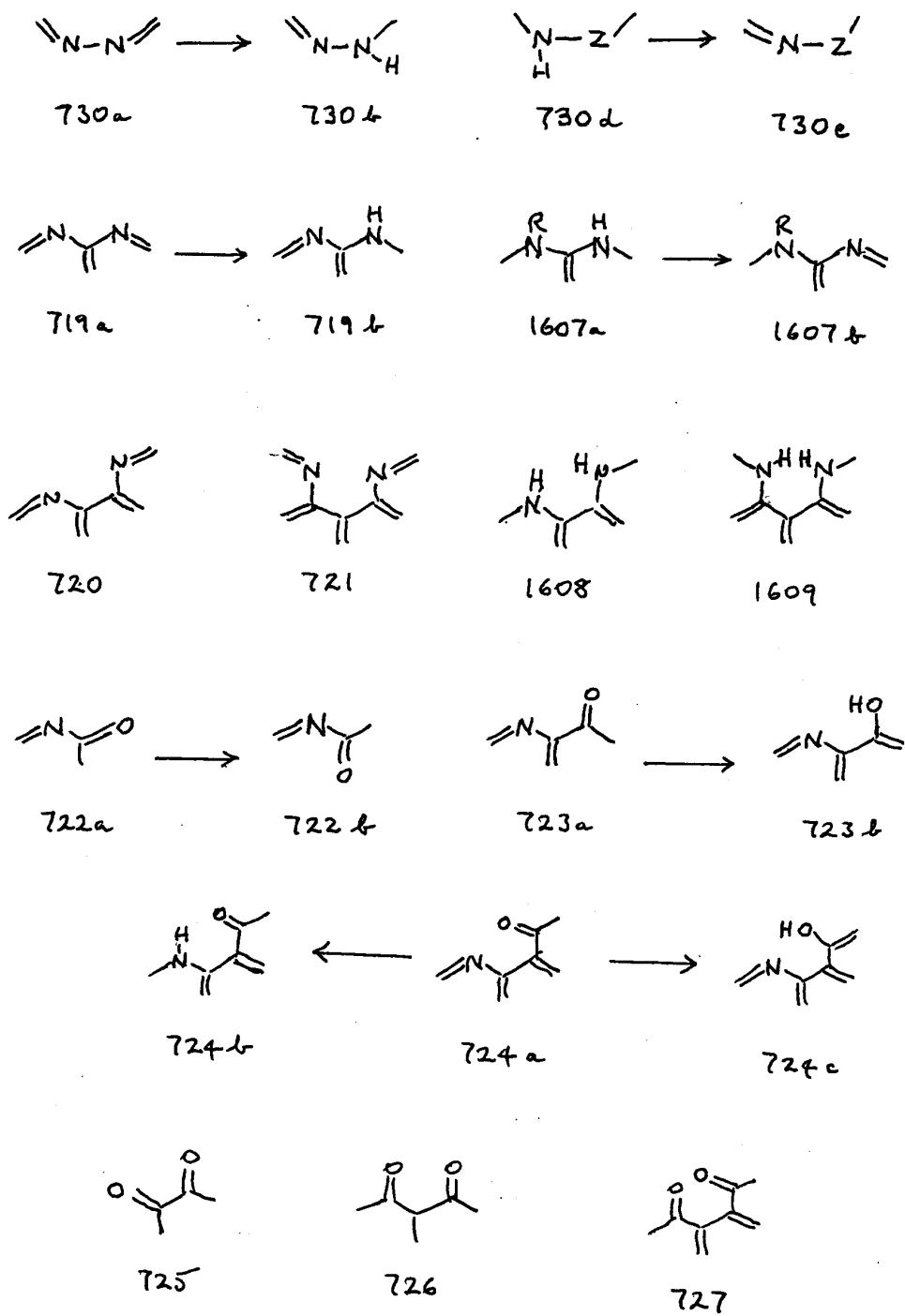
Where one tautomer contains both lone pair and *peri*-dipolar repulsion whereas the other contains neither, the latter will almost invariably be preferred; it has been stated for example (section B.1.7) that **1603** exists invariably as **1603B**. Compounds that fulfil this expectation include xanthine **785** (**1603**, R = H, Z = O), its sulfur analogue **787**, and theophylline **786** (**1603**, R = Me, Z = O). In such cases the avoidance of dipolar repulsion, at any rate in water, will generally be more important than any attractive force. One reason for this is that the relief of N/C=O *peri*-repulsion with formation of an OH---N bond, sub-section (e), is possible only when not precluded by a high log  $K_T$  value, as likely *e.g.* for **785**, or decisively for any compound of type **1603** or similar for which R  $\neq$  H. Among favourable *peri*-interactions there are indications, tentatively discussed in sub-section (c), that NH/C=O may be stronger than NH/N, but neither appears remotely to rival NH/NH in its effect on tautomeric form. For every reason it remains anomalous that **779** is said to exist as shown,<sup>421a</sup> and this compound appears ripe for re-examination.

#### (n) Dipolar Interactions: NH,NH-Type with NH---N Hydrogen Bonding

In total contrast to the position concerning lone pair repulsion, sub-sections (d) - (j), no such case appears to have been investigated. In Scheme 167 we incorporate a few hypothetical examples to emphasise the gaps in our knowledge, in all of which the relief of dipolar repulsion will be opposed by some balancing factor such that  $\Delta \log K$  should be calculable. (Note that, since only nitrogen can take part, the variety of possible situations is necessarily restricted). The phenanthroline **1604** complements **484** (Scheme 162) and **486** (Scheme 163); on the evidence of **754** above  $\Delta \log K$  might well be less than for either, but replacement of the 4-pyridone by 2-pyridone moieties as in **1605** should increase dipolar repulsion very considerably. Compound **1606** is another needle case, in which dipole repulsion in **1606A** is set against the 'quinonoid penalty' in **1606B**, and here again the balance could be quite fine. All these are 1,4-interactions but their 1,5-equivalents are also possible and, as for lone pair repulsion, further relevant information could result.

#### (o) Summary and Overview

The types of structure we have considered, with one or two additions, appear in Scheme 168 while the data pertaining to them are assembled in Table 142. A previous treatment of lone pair repulsion in section A.12.9, concerning **719** - **727** alone, is incorporated into the following account. Here we recapitulate our findings and attempt a rationale. Contiguous heteroatoms



Scheme 168

**Table 142. Characteristic  $\Delta \log K$  Values for Lone Pair and Dipolar Repulsion <sup>a</sup>**

Structure	Sub-section	Ring Size	Interaction Type	$\Delta \log K$
<b>730a/b</b>	<b>(a)</b>	6	N,N	$2.2 \pm 0.2$
<b>730a/b</b>	<b>(b)</b>	5	N,N	<i>ca.</i> 0.8
<b>719a/b</b>	<b>(c)</b>		1,3-N,N <sup>b</sup>	<i>ca.</i> 0.8
<b>720</b>	<b>(d)</b>		1,4-N,N <sup>c</sup>	$\geq 2$
<b>721</b>	<b>(g)</b>		1,5-N,N <sup>c</sup>	-
<b>722a/b</b>			1,3-N,O <sup>d</sup>	?
<b>723a/b</b>	<b>(e)</b>		1,4-N,O <sup>e</sup>	$\leq 2$
<b>724a/b</b>	<b>(h)</b>		1,5-N,O <sup>f</sup>	<i>ca.</i> 4
<b>724a/c</b>	"		1,5-N,O <sup>e</sup>	<i>ca.</i> 6
<b>725</b>	<b>(f)</b>	6	1,4-O,O <sup>g</sup>	<i>ca.</i> 5 ?
<b>726</b>	<b>(i)</b>	<i>h</i>	1,5-O,O <sup>g</sup>	<i>h</i>
<b>727</b>	<b>(j)</b>		1,6-O,O <sup>g</sup>	<i>i</i>
<b>730d/e</b>	<b>(k)</b>	6 <sup>j</sup>	NH,NH	2.5
<b>730d/e</b>	<b>(l)</b>	5 <sup>j</sup>	NH,NH	<i>ca.</i> 2.5
"	"	" <sup>j</sup>	NH,NHMe	<i>ca.</i> 3
"	"	" <sup>j</sup>	NH,NPh	<i>ca.</i> 4
"	"	" <sup>j</sup>	NH,O	<i>ca.</i> 5
<b>1607a/b</b>	<b>(m)</b>		1,3-NH,NH <sup>b</sup> (1,3-NH,NMe)	<i>ca.</i> 2.5 <sup>j</sup>
<b>1608</b>	<b>(n)</b>		1,4-NH,NH	-
<b>1609</b>	<b>(n)</b>		1,5-NH,NH	-

<sup>a</sup> Structures in Scheme 168. <sup>b</sup> *peri*-Interaction or of similar geometry. <sup>c</sup> Results in NH---N intramolecular bond. <sup>d</sup> Solvent-sensitive; may be as low as 0.3 in water but much higher in organic solvents. See discussion in section B.5.6. <sup>e</sup> Results in OH---N intramolecular bond. <sup>f</sup> Results in NH---O intramolecular bond. <sup>g</sup> Results in OH---O intramolecular bond. <sup>h</sup> Bicyclic fused-ring systems; results vary (see the text). <sup>i</sup> Value unknown but certainly large, with OH---O bonding of exceptional strength. <sup>j</sup> Values may be independent of context (see the text).

of similar hybridisation type lead to lone pair repulsion in **730a** or dipolar repulsion in **730d** which is relieved when one of each is present, as in **730b** or **730e**. The effect of lone pair repulsion is very much greater in 6- than in 5-membered rings, possibly because the angle subtended by the lone pairs is greater in the latter so they do not interact so strongly, but in dipolar repulsion no similar effect is found. Here for Z = NH the effect appears independent of ring size, but nothing is known in any other context. Otherwise the nature of Z appears to be the chief determinant of its magnitude,  $\Delta \log K$  increasing with its electronegativity (see sub-section ). In another sharp contrast with the behaviour

of lone pairs, dipolar repulsion appears still to operate in open-chain structures; in fact on the evidence of **1334** (Scheme 165),  $\Delta \log K$  may be much the same for  $R = \text{NH}_2$  and  $\text{OH}$  in that context as appears for  $Z = \text{NH}$  and  $\text{O}$  in Table 142.

Surprisingly, the *peri*-interactions of **719** and **1607** appear to mimic quite closely the behaviour (in 5-membered rings) of the same atoms when contiguous, with  $\Delta \log K$  *ca* 0.8 and about 2.5 respectively. There is suggestive evidence that the considerable variation attaching to the latter depends on dipole gradient, so that while commonly large, it may be much less when, for one or both of  $\text{NR}$  and  $\text{NH}$ , this is small. The same may be true for **719** but its much smaller magnitude makes it difficult to distinguish any but qualitative trends in the data.

Since the 1,4- and 1,5-interactions shown as **1608** and **1609** have yet to be studied, the remaining information is confined to lone pair repulsion. Encompassing  $\text{N,N}$ ,  $\text{N,O}$  and  $\text{O,O}$  interactions, these are much more varied in structure than those of the dipolar type. It might be anticipated that lone pair repulsion would increase, other things being equal, in the above order, but in practice it is difficult to compare like with like. Notably, while lone pair repulsion in **725** is already very large, and in **727** may be so great that this structure as written cannot exist, enolisation in **726** does not appear to be greatly enhanced, perhaps because those examples so far studied are readily twisted out of plane. However **720** shows a much larger effect than **719**, and **724** than **723**, as is consistent with their rigid structures throughout.

One special case, **722**, has not been discussed. This unit represents part of an acylamidine structure, and is so favoured tautomerically that the dominance of **722a** is never challenged, but in open-chain structures it switches to **722b** (section B.4.6). Most work has been carried out in organic solvents and there is suggestive evidence that **722b** may be less dominant in water; for example, the difference in  $\log K_M$  for otherwise equivalent acylguanidines is quite small, with **722a** only slightly disadvantaged (section B.5.6). This *conformational* preference does however fit the sequence **722**  $\rightarrow$  **723**  $\rightarrow$  **724** expected on grounds of lone pair proximity and elsewhere shown as a *tautomeric* preference, an interesting example of an unfavourable situation that resolves itself in any way it can. No doubt in rigid planar molecules the  $\Delta \log K$  sequences **1607a**  $\rightarrow$  **1608**  $\rightarrow$  **1609** and **725**  $\rightarrow$  **726**  $\rightarrow$  **727** would also be found, but at present the requisite data are missing and we have to take this postulate on trust.

## APPENDIX 4: Intramolecular Hydrogen Bonding

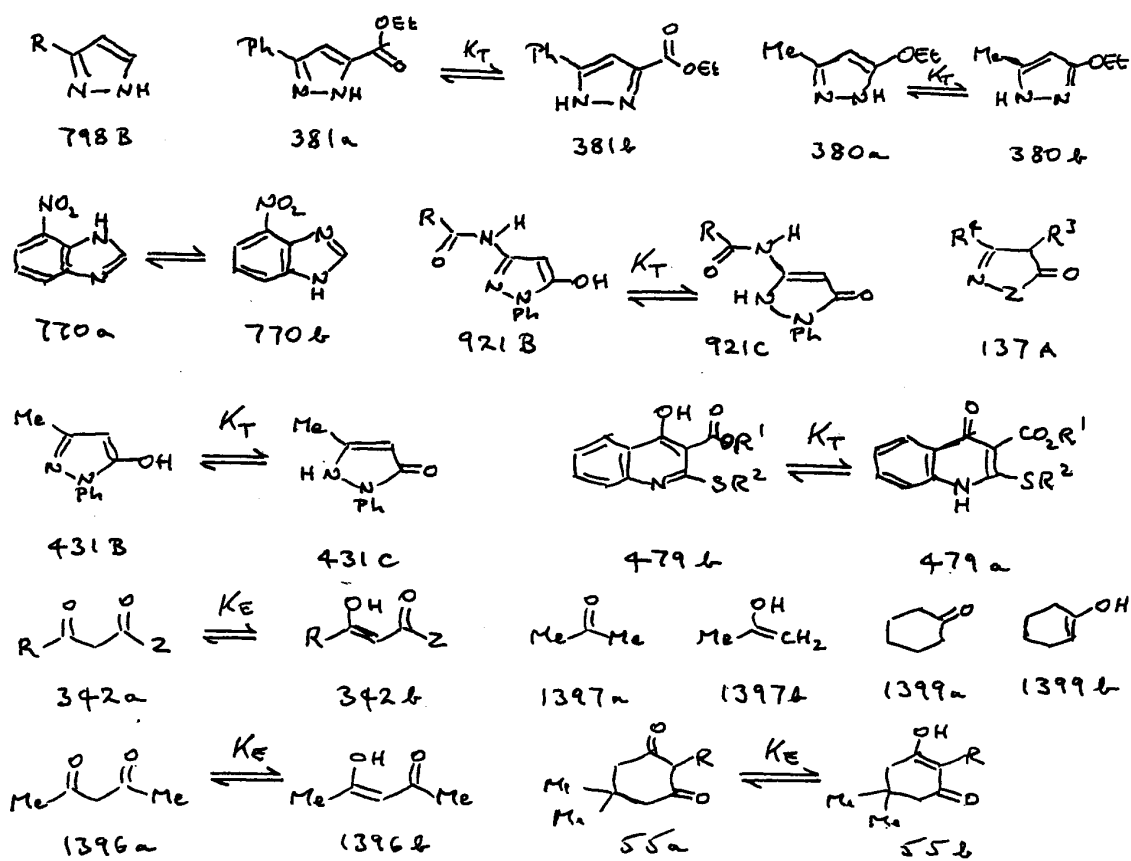
Intramolecular hydrogen bonding may influence tautomeric balance in three main ways. As the sterically enforced result of relieving lone pair or dipolar repulsion it will reinforce this factor and can lead to very large overall effects; such cases are included in Appendix 3. Hydrogen bonding due to freely rotating substituents as described here, however, is another matter. Neither the intramolecular bond nor the repulsive force (if any) that might otherwise occur is enforced, and our finding will be that *in water* such effects are generally quite small. It is otherwise in the solvents of lower and often much lower polarity in which intramolecular hydrogen bonding has commonly been studied, but while some such cases are analysed below as a means of extrapolation to water, they are not otherwise germane to our purpose.

A third category exists, in which an intramolecular hydrogen bond is both consequence and part cause of (further) conjugation. Here the main driving force is formation of the conjugated system itself and there is evidence, some of which we review (more is scattered through the text), that the intramolecular bond *per se* is often of marginal importance, at least in water. Except in these cases, reviewed in (d) and (e), the examples described below therefore concern an equilibrium between two already conjugated systems.

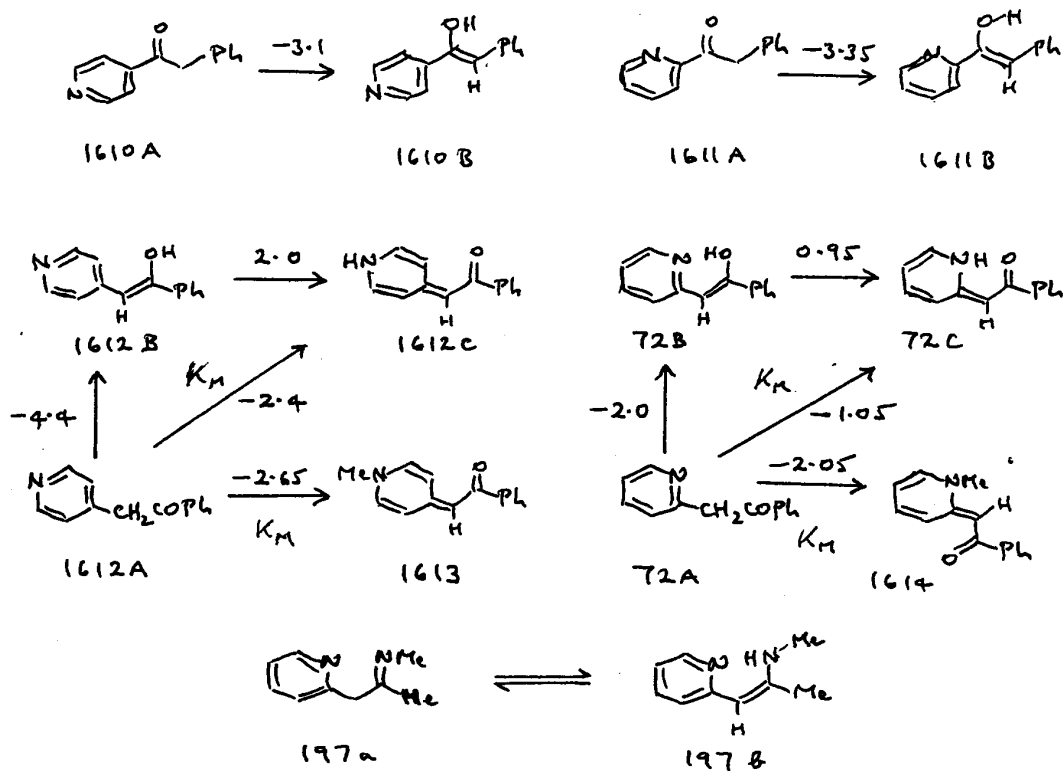
### (a) 1,4-Interactions: NH---O Bonding

$$\log K_T = 2.6 \sqrt{(\sigma_R)^2} \quad (\text{cvi})$$

The only quantitative information concerns **381** (section A.9.2). All 3(5)-monosubstituted pyrazoles prefer structure **798B** and eqn. (cvi) fits their behaviour in the gas phase (section B.8.1), the only medium for which sufficient data are available. If eqn. (cvi) is used to predict for each substituent separately,  $\log K_T$  0.2 is predicted whereas -0.5 is found. This gives  $\Delta \log K$  0.7 for the effect of the intramolecular hydrogen bond in shifting the balance towards **381a**, but this result is for the gas phase. A similar calculation for **380** where no hydrogen bond can be formed predicts  $\log K_T$  1.04 where 1.5 is found for water (section A.9.2). If the coefficient of eqn. (cvi) is altered to fit this result the predicted  $\log K_T$  for **381** increases only to 0.3, while  $\Delta \log K$  *ca.* 1 results. On any basis, therefore,  $\Delta \log K$  for NH---O bonding is likely to be small.



Scheme 169



Scheme 170

**(b) 1,5-Interactions: NH---O Bonding**

4(7)-Nitrobenzimidazole **770** exists 80% as **770a** in water (section B.1.7). Since even 5(6)-nitrobenzimidazole shows virtually no tautomeric preference, this result may be attributed wholly or mainly to the intramolecular bond, hence  $\Delta \log K$  0.6. However the nitro-group is a relatively poor proton acceptor (Table 140, Appendix 3) and the effect of acyl would be of interest.

The pyrazolone **921** possesses  $\log K_T$  0.2 in DMSO whereas for the corresponding methyl derivative **431** in the same solvent,  $\log K_T$  -0.3 is found. To calibrate this result we need to know the expected effect of the substituent in the absence of an intramolecular bond. Unfortunately nothing quantitative is known, but  $\pi$ -donors at  $R^4$  in **137** (section C.12) stabilise **137A** in the order  $\text{NH}_2 > \text{OEt} > \text{Ph} > \text{H}$  (section C.15). Since  $\pi$ -donors in this position do not stabilise the **B**-tautomer (section C.15) and their effects on the **A**- and **B**-forms tends to cancel, while **921A** has not been detected, it seems improbable that -NHCOR should differ much from -Me in its otherwise expected effect on  $K_T$ , so  $\Delta \log K < 1$  seems probable here as well.

**(c) 1,5-Interactions: OH---O Bonding**

$$\log K_T = 4.9 + 3.2 \sigma_{m(2)} - 10.5 \sigma_{I(2)} - 0.7 \sigma_{m(3)} \quad (\text{cxlvi})$$

The quinolones **479** exist mostly as **479a** in MeOH but mostly as **479b** in  $\text{CCl}_4$  (section A.10.8). Their  $\log K_T$  values in water should therefore lie between those which would be predicted for the appropriate  $\Delta \log K_T$  values from MeOH and  $\text{CCl}_4$  to water. Possible models for assessing these are **431** if **479** is regarded for this purpose as a vinylogous amide, or (**342**,  $R = \text{Me}$ ,  $Z = \text{OEt}$ ) if as a  $\beta$ -ketoester, though neither model is ideal. For the first,  $\Delta \log K_T$  values of 1.1 for MeOH and 1.7 for  $\text{CCl}_4$  are required to adjust from these solvents to water, the corresponding values for the second being 0.5 and 1.6 (Appendix 2). The 'best fit' available if **431** is the model then becomes  $\log K_T$  *ca.* 0.3 for **479** in MeOH and *ca.* -0.3 in  $\text{CCl}_4$ , or alternatively *ca.* 0.5 and *ca.* -0.5 respectively. In the light of the experimental observations (above) the latter set appears more realistic, leading to an estimated  $\log K_T$  *ca.* 1 for **479** as written in water. We may estimate its value in the absence of an intramolecular bond by combining the expected effects of 2- and 3-substitution on 4-pyridones, eqns. (xxx) and (xxxiii) from Table 36 in section A.10.6, and correcting for the effect of benzofusion (Appendix 5), to

to give eqn. (cxlviii). For  $R^2 = \text{SMe}$ ,  $R^3 = \text{CO}_2\text{Et}$  this calculates as  $\log K_T$  *ca.* 2.0, resulting in  $\Delta \log K$  *ca.* 1 for the effect of the intramolecular bond. A larger effect is expected for OH---O than for NH---O bonding, but this if present appears to be marginal.

#### (d) Conjugation vs. Hydrogen Bonding in Chelated $\beta$ -Diketones

Any  $\beta$ -diketone that can do so will form a chelate, though there is evidence that not all give chelates exclusively in water (section A.6.7 and Appendix 2). However, since the various unenolised  $\beta$ -diketone alignments may vary considerably in energy, it is difficult even to hazard a guess at the relative importance of these factors.

$$\log K_E = 1.50(0.09) - 1.58(0.14) \pi^* - 0.18(0.10) \alpha \quad (\text{ix})$$

$$(n = 18 \quad r^2 = 0.905 \quad s = 0.16 \quad F = 71)$$

$$\log K_E = -1.78(0.24) + 0.54(0.33) \pi^* + 0.70(0.20) \alpha + 4.38(0.21) \beta \quad (\text{x})$$

$$(n = 14 \quad r^2 = 0.981 \quad s = 0.21 \quad F = 171)$$

**Table 143. Log  $K_E$  Values for some Ketones and  $\beta$ -Diketones <sup>a</sup>**

Ketone	Solvent	$\log K_E$	$\beta$ -Diketone	Solvent	$\log K_E$	$\Delta \log K_E$
<b>1397</b>	Water	- 8.33 <sup>b</sup>	<b>1396</b>	Water	- 0.83 <sup>c</sup>	7.50
"	C <sub>6</sub> H <sub>12</sub>		"	C <sub>6</sub> H <sub>12</sub>	1.50 <sup>d</sup>	
"	Gas phase		"	Gas phase	3.44 <sup>d</sup>	
"	"	<sup>e</sup> - 11.1 <sup>f,g</sup>	"	"	—	<i>ca.</i> 14.5 <sup>h</sup>
<b>1399</b>	Water	- 6.39 <sup>b</sup>	( <b>55</b> , R = H)	Water	1.28 <sup>i</sup>	7.67
			"	C <sub>6</sub> H <sub>12</sub>	- 1.78 <sup>j</sup>	
			"	Gas phase	- 2.44 <sup>j</sup>	
"	Gas phase	(- 9.2) <sup>k</sup>	"	"	<sup>e,l</sup> - 2.93 <sup>g,l</sup>	(6.3) <sup>k</sup>

<sup>a</sup> Since all compounds are symmetrical, statistical corrections are not applied. <sup>b</sup> Table 8, section A.2. <sup>c</sup> Table 28, section A.6.7. <sup>d</sup> Eqn. (ix), section A.6. <sup>e</sup> M. O. calculation, Table 22 section A.6.1. <sup>f</sup> Mean of all three methodologies. <sup>g</sup> Assumes  $\Delta G_T \sim \Delta H_T$  (see section A.6.1). <sup>h</sup> Compares calculation for **1397** with eqn. (ix) for **1396**. <sup>i</sup> Table 23, section A.6.2. <sup>j</sup> Eqn. (x), section A.6. <sup>k</sup> Assumes the same shift from water to the gas phase as estimated above for **1397** (see the text). <sup>l</sup> Cyclohexane-1,3-dione used for M. O. calculation. <sup>m</sup> Gas phase value calculated for (**55**, R = H) relative to estimate for **1399**.

The best evidence we have (Table 142) comes from a comparison of  $K_E$  for acetylacetone **1396** and dimedone (**55**,  $R = H$ ) with their respective nominal precursors, acetone **1397** and cyclohexanone **1399** (Scheme 169). A full comparison is possible only for aqueous solution, where for the effect of the second acyl group,  $\Delta \log K_E$  values of ca 7.5 and 7.7 are found. This might seem to indicate a negligible strength for the chelate bond of **1396b**, but that indication is probably misleading. The extended conformation of **55b** almost certainly possesses a substantially greater resonance energy than that of **1396b**, and a near-cancellation of factors *in water* provides a much more plausible explanation. This suggestion is reinforced by the very different solvent effects operating on chelated and extended  $\beta$ -diketones, and summarised for **1396** and (**55**,  $R = H$ ) by eqns. (ix) and (x) respectively. While enolisation increases for the latter with increasing solvent polarity, for any sort of chelate it falls (Appendix 2), most obviously because the strength of the chelate bond is maximised by nonpolar surroundings. Unfortunately, a more revealing comparison is hampered by our present ignorance as to even the direction of the solvent effect on  $K_E$  for simple ketones. If  $\log K_E$  -8.3 for acetone in water may fairly be compared with -11.1 by M.O. calculation on the isolated molecule, then the direction of the effect parallels that for an extended  $\beta$ -diketone, firmly identifying the chelate as the species out of line. It is also quite gratifying that extrapolation of eqn. (x) to the gas phase leads to a  $K_E$  value not greatly different, given the shift relative to water, from that predicted for (**55**,  $R = H$ ) by high level M.O. calculation. For **1397**, (**55**,  $R = H$ ) and **1396** we then have estimated shifts in  $\log K_E$  from water to the gas phase of -2.8, -3.7 or -4.2, and 4.3 respectively. Given that the resonance energy of a chelated as well as an extended  $\beta$ -hydroxyenone should fall with solvent polarity, it is clear that the intramolecular bond of **1396b** must enormously boost enolisation in nonpolar solvents. If the extrapolated value of  $\log K_E$  ca 3.4 in the gas phase is realistic for **1396**, and may legitimately be compared with the M.O. result for **1397**,  $\Delta \log K_E$  7.5 for these compounds in water has become ca 14.5 in the gas phase (Table 143), and the extra strength of the intramolecular hydrogen bond may be responsible for  $\Delta \Delta \log K_E$  ca. 7. Similarly, if the difference in  $K_E$  estimated for the ketone **1397** between water and the gas phase were to be mirrored by the ketone **1399**, to give a gas phase  $\log K_E$  ca. -9.2 for the latter, we obtain  $\Delta \log K_E$  ca. 6 - 6.5 for **1399**  $\rightarrow$  (**55**,  $R = H$ ), a *smaller* shift than in water as might reasonably be expected if this value is dominated by resonance. This is as far as or further than legitimate speculation can go at the present time, but it serves to suggest some interesting possibilities.

### (e) Conjugation vs. Hydrogen Bonding in Other Chelates

There is some information for the pyridines of Scheme 170 but this, even where quantitative, suffers from difficulties to do with calibration. Here the data for **1610** and **1611** come from Table 8, section A.2.2; for **72** and **1612** from Table 33, section A.10.2; for **1613** (**488**, R = Me, Z = COPh) and **1614** (**487**, R = Me, Z = COPh) from Table 39, section A.10.9; and for **197**, from section A.4.2. The 3-way equilibria shown for **72** and **1612** are supplemented by tautomeric ratios involving the anhydro-bases **1614** and **1613** respectively. In the absence of intramolecular hydrogen bonding or a change in the configuration of the substituent each pair of tautomeric ratios should be identical, conditions satisfied by the processes **1612A**  $\rightarrow$  **1612C** and **1612A**  $\rightarrow$  **1613** if the enone moiety takes up the alignment shown for both, and resulting in near-identical values of  $\log K_M$ . Unfortunately, it is probable that neither condition obtains for **72A**  $\rightarrow$  **72C** vs. **72A**  $\rightarrow$  **1614**, since the obligatory *cis-s-cis* alignment of **72C** is most likely replaced, to avoid a steric clash, by the *trans-s-cis* alignment shown for **1614**. Since **1614** is probably better conjugated than **72C**, the observed differential of  $\Delta \log K_M$  ca. 1 in favour of **72C** probably represents a *minimum* for the contribution of hydrogen bonding to its stability; cf. the similar position for **55b** vs. **1396b** discussed in (d) above. Nevertheless, the small difference in  $\nu(\text{NH})$  commonly found between the chelated and unchelated isomers of aminoenones where these coexist in solution<sup>165</sup> does not argue for a strong intramolecular bond in the former, and this contra-indication is of some importance. Qualitatively, the superior conjugation of *E*- vs. *Z*-aminoenones has been clearly established,<sup>272</sup> but only for the *trans-s-trans* alignment is the actual  $K_T$  value presently known (section A.10.1). In this context we also draw attention to the evidence (section B.8.4) that, in 5-membered ring alicyclic amidines, *exo*- is much more effective than *endo*-substitution with  $\pi$ -donors in stabilising the C-tautomer.

It is possible however that, echoing the distinction between OH---N and NH---O hydrogen bond strength discussed in Appendix 3, something similar happens here. For **72A**  $\rightarrow$  **72B** which leads to OH---N bonding  $\log K_E$  -2.0 is found, whereas  $\log K_E$  -4.4 results for **1612A**  $\rightarrow$  **1612B** where it does not. The resulting  $\Delta \log K_E$  2.4 may underestimate the strength of this bond. Azanitrogen is more electron-withdrawing in the 4- than in the 2-position, as is demonstrated by the difference in  $\log K_E$  between **1610** and **1611** (and cf. the footnotes to Table 2); if this difference is used to 'calibrate' that between **1612** and **72**, which involves the arbitrary assumption of equal  $p$ -values for both processes,  $\Delta \log K_E$  may be as high as 2.7. This value is very close to  $\Delta \log K$  2.9 as estimated for the OH---N bonding component in iminol formation

for the phenanthroline-dione **485** [Appendix 3(h)]. It is interesting that, again in **485**, the alternative NH---O bond scores only  $\Delta \log K$  0.5, so helping to account for the very small values reported in (b) above. Note that **485** and (b) above as well as **72B** involve 1,5-interactions (between heavy atoms), *i.e.* they possess similar geometries so may legitimately be compared in this way. It may also be worth pointing out that both interactions involve what is essentially phenol (or even 'super-phenol') OH, and that much of their exceptional strength may derive from this source.

(The slightly puzzling lack of hydrogen bonding in **1611B** may possess a simple stereoelectronic explanation. The preferred Z-alignment of OR linked to a carbon double bond (*cf.* discussion in section A.10.5) requires the stereochemistry illustrated for **1611B** and the weak hydrogen bond which could result from the *E*-conformation is evidently unable to overcome this. No such conflict of interest occurs for **72B**).

The imine **197a** goes exclusively to the hydrogen bonded enamine **197b** in benzene and DMSO whereas its 3- and 4-pyridyl analogues give mixtures (section A.4.2). Clearly the intramolecular bond has some effect on the tautomeric equilibrium but this cannot be quantified and may not be great. A much lesser strength is expected for NH---N than for OH---N bonding and it is possible that **197b** would be undetectable in aqueous solution.

## (f) Summary and Overview

Too few quantitative data exist for any definitive pronouncement, especially since calibration problems are present in nearly every case. On the basis of these examples it seems highly probable that OH---N bonding has the potential to be much more effective in influencing tautomeric form than that of the NH---O or (probably) the NH---N type; the first may be capable of  $\Delta \log K > 2.5$ , whereas the second is commonly limited to  $\Delta \log K < 1$  and, with one hypothetical exception, a 1,5-interaction in which the donor properties of NH and acceptor properties of C=O have been carefully maximised, may never greatly exceed this. On the face of it this gap is surprisingly large, and though a possible rationalisation exists, as noted in (e) above, more evidence is needed. And while for lack of definitive evidence we have to leave the question open, it seems probable that for  $\beta$ -diketones and related structures intramolecular hydrogen bonding contributes relatively little to the energetics of chelate formation in aqueous solution, despite its importance elsewhere.

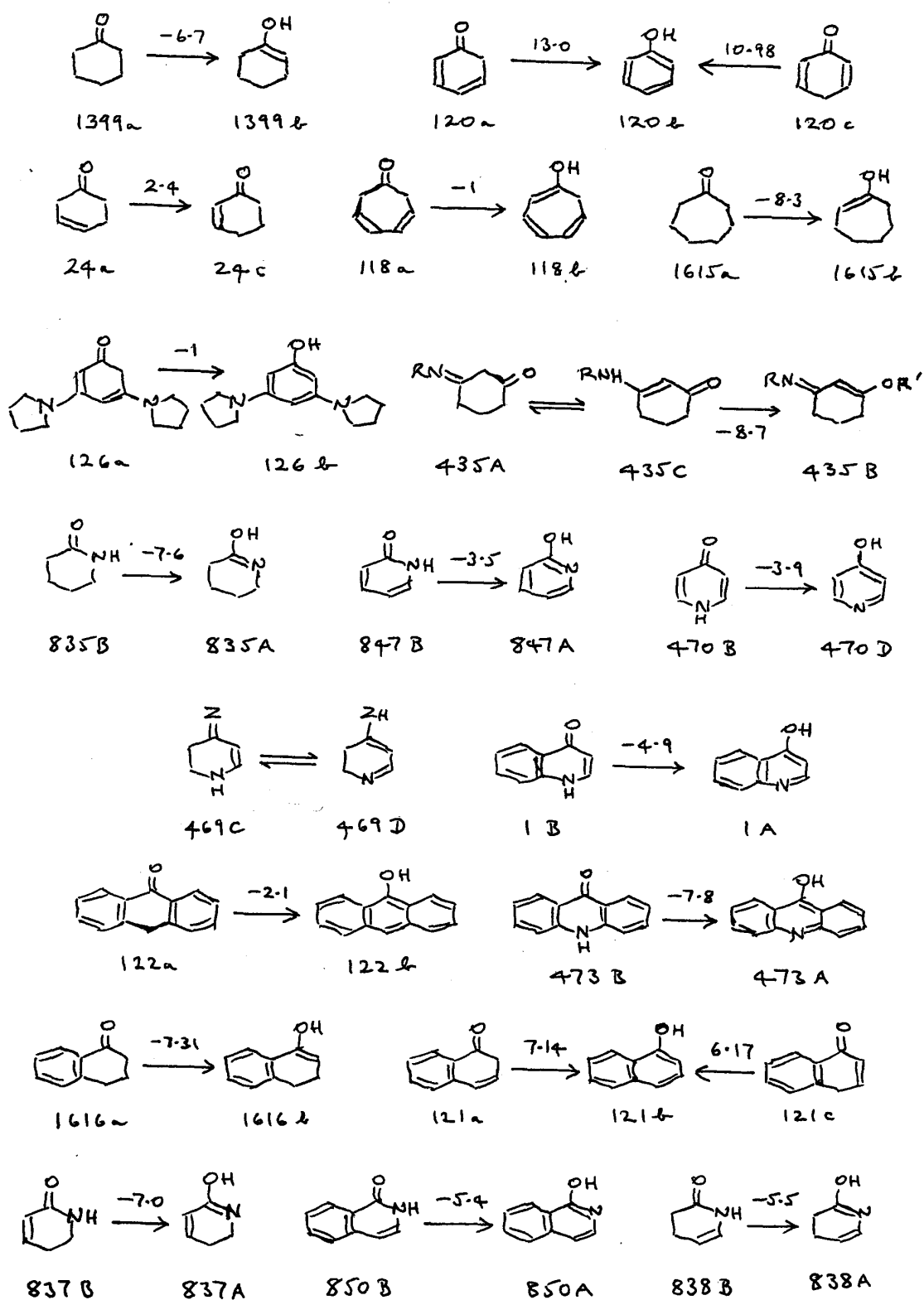
## APPENDIX 5: Aspects of Aromaticity

This is a more polyglot subject than those of the preceding Appendices, with less connection between its parts. While many of the data are quantitative and the trends to be described are coherent, the types of additive relationship present in other areas, and so valuable for predictive purposes, are not so common here. The probable reason for this lies in the enormous energetic span of the varying processes covered; it is not to be expected that  $\Delta \log K$  values that range from 2 to 20 can be expressed by a single relationship. A rather similar situation has been revealed by high level *ab initio* calculation on systems of type  $X=CCH_2C=Y$  (section C.46) where the picture obtained is coherent but nonlinear, hence non-additive. Here as in that case most examples involve 'C-type' tautomerism; those of the 'N-type' variety as in (3) below are notably better behaved.

### (1) THE ENERGETICS OF AROMATISATION

The resonance energy of benzene is  $36 \text{ kcal mol}^{-1}$  (Table 12, section A.2.6) relative to a nominally equivalent molecule possessing alternant single and double bonds and no ring current. If the aromatisation of this hypothetical species is regarded as a form of tautomerism, one may therefore deduce  $\log K_T$  *ca.* 26.5 in its favour at ambient temperature. We may describe this value as the 'theoretical limit.' However, this process as it stands is not realistic. The precursor to any act of aromatisation will itself be a conjugated system with a resonance energy that may rival and will sometimes exceed that of the fully aromatic molecule it can become. The effect of 'aromatisation' as a tautomeric driving force is therefore likely to be highly variable. Here we chart those processes for which quantitative data are known.

A number of relevant processes are set out in Scheme 171. The dienones **120a** and **120c** which require only a single proton transfer to give phenol **120b** possess  $\log K_E$  13.0 and 10.98 respectively (section A.2.6). This represents a shift of approaching  $10^{20}$  and  $10^{18}$  respectively, relative to the (statistically corrected) value for cyclohexanone **1399** (Table 8, section A.2). Even so these values fall well short of the theoretical limit, by  $10^7$  -  $10^9$  if benzene and phenol possess equal resonance energies. Most of this shortfall is presumably due to the resonance energies of the precursor dienones; there is no direct evidence on what value to expect, but **24c** is stabilised relative to **24a** by  $\log K$  2.4 (section A.1.1) and the stabilisation due to conjugation of **120a** and **120c** should presumably be greater. (Interestingly,  $\log K$  2.4 here



Scheme 171

compares with  $\Delta \log K$  2.5 for the allylic stabilisation of C=C by COMe: Table 1, section A.1.1). It may also be relevant that, relative to cycloheptanone **1615** (Table 8, section A.2, plus statistical correction), the dienone unit of **118a** (section A.2.6) stabilises enol formation by  $\Delta \log K_E$  *ca.* 7, even though the product **118b** is non-aromatic. While **118b** and **120a** are structurally dissimilar, each represents an extended conjugated system whose formation in the case of **118b** clearly supplies it with a considerable resonance energy; it is therefore plausible that **120a** and **120c** will possess this feature also.

Despite these enormous margins in favour of enolisation, there is scattered evidence that, in the right context, they are quite easy to reverse. For the diaminophenol **126** the oxo-tautomer **126a** is marginally favoured in water (section A.2.6), a reversal of  $10^{14}$  relative to  $K_E$  for **120a**. Unfortunately, there is no other datum with which this can be compared: while there is some analogy between **126a** and **435C**, they possess no equilibria in common. There seems no way of advancing beyond this point.

It is instructive to contrast ‘C-type’ enolisation here with iminol formation for some ‘N-type’ analogues. If CH<sub>2</sub> in **120a** and **120c** is replaced by NH we obtain 2-pyridone **847** (section B.2.4) and 4-pyridone **470** (section A.10.6) respectively. The former may be referenced to 2-piperidinone **835**, for which we estimate  $\log K_E$  -7.6 (section B.2.3). If this is correct, aromatisation of **847B** to **847A** involves a shift in  $K_E$  of *ca.*  $10^4$ , enormously less than the gain of *ca.*  $10^{20}$  shown by **120a**  $\rightarrow$  **120b** relative to **1399b** (above). It is much more difficult to find a true model for the alicyclic precursor to **470**. Katritzky and co-workers<sup>150</sup> employed the aminoenone **435**, resulting in  $\log K_E$  -8.7 for the process **435C**  $\rightarrow$  (**435B**, R' = H), but this possesses a different configuration from the required species (**469C**, Z = O), and already contains one of the two double bonds to be found in the product whereas **847**, as is required for an accurate comparison, contains neither. Even though  $\Delta \log K_E$  4.8 for the process **435**  $\rightarrow$  **470** is quite similar to  $\Delta \log K_E$  *ca.* 4.1 for **835**(estimate)  $\rightarrow$  **847**, this comparison is dubious. The former process cannot be extrapolated to some compound containing a single benzofusion – contrast **837**(estimate)  $\rightarrow$  **850** – but it becomes uniquely possible when both double bonds are incorporated into benzene rings, those of **120c** into **122a** (section A.2.6) and those of **470B** into **473B** (section A.10.7) respectively. However the ‘C-type’ sequence **120c**  $\rightarrow$  **121c**  $\rightarrow$  **122a** with  $\log K_E$  10.98  $\rightarrow$  6.17  $\rightarrow$  -2.1, and the ‘N-type’ sequence **470B**  $\rightarrow$  **1B**  $\rightarrow$  **473B** with  $\log K_E$  -3.9  $\rightarrow$  -4.9  $\rightarrow$  -7.8, may be compared directly. Even though the relation between them is some way short of linear, its slope of *ca.*

0.3 for the 'N-type' vs. the 'C-type' sequence clearly demonstrates the much greater sensitivity towards structural change of the latter: CH<sub>2</sub> is a 'conjugation-stopper' whereas NH is not.

Perhaps surprisingly, fewer relevant comparisons can be drawn between amides and their ketonic analogues, CH<sub>2</sub> in place of NH. In the simplest such example, **835** vs. **1399**, the oxo-tautomer is only a little more stable for the amide than for the ketone, but aromatisation greatly increases the differential, as previously. The only two solid comparisons are those for **847** vs. **120a** → **120b**, log *K<sub>E</sub>* -3.5 vs. 13.0, and **850** vs. **121a** → **121b**, log *K<sub>E</sub>* -5.4 vs. 7.14 (Scheme 171). Here, for what it is worth, a similar difference in sensitivity between 'N-type' and 'C-type' tautomerism as seen above appears to be present. There is a curious anomaly in that our tentative value of log *K<sub>E</sub>* (-log *K<sub>T</sub>*) -5.5 for **838**, based on the assumption that vinyl and phenyl contiguous to NH will carry equal weight (section B.2.3), lies so close to the authentic value for **850** as to imply a negligible effect of benzofusion in this context. A further, slightly disturbing fact lies in the *opposite* effect on *K<sub>E</sub>* of benzofusion in **1399**, to give **1616**, and on phenyl substitution into acetone. One possibility is that, while benzofusion should have a reasonably constant effect, phenyl substitution with its potential for geometrical imprecision may not. These questions await experimental elucidation.

In order to give rise to a neutral aromatic species, a 5-membered ring must incorporate a  $\pi$ -donor heteroatom to complete its quota of  $\pi$ -electrons. Such molecules lack the electronic homogeneity of their 6-membered ring analogues so their resonance energies are generally less, and because several hetero-atoms of differing electronic nature (including variants on NR) are available, they are much more disparate in structure and behaviour. With a single hetero-atom in the ring only 'C-type' tautomerism as in **810B** → **810C** can result in aromatisation (Scheme 172); iminol formation (when possible) *e.g.* to give **810A** does not, and is consequently of little importance. The replacement of CH by N leads to a maze of possibilities. With one aza-nitrogen there are six (*cf.* Scheme 83, section C.12) and with two there are six more; so far as they have been explored the consequences are charted in sections C.12 – C.20 and will not be recapitulated here. As a broad general guide, enol formation (aromatisation) increases with hetero-atom content but is negated when urea-like structures can result; a 1,3-spacing of  $\pi$ -donor atom and carbonyl is much more susceptible to enolisation than a 1,2-spacing (see below); and nitrogen contiguous to the  $\pi$ -donor hetero-atom (*cf.* Appendix 3) is another potent force making for enolic or (sometimes) even unconjugated forms.

**Table 90. Log  $K_E$  in Water for some 5-Membered Ring 3-Oxoheterocycles with One Ring Hetero-atom, and Related Compounds <sup>a</sup>**

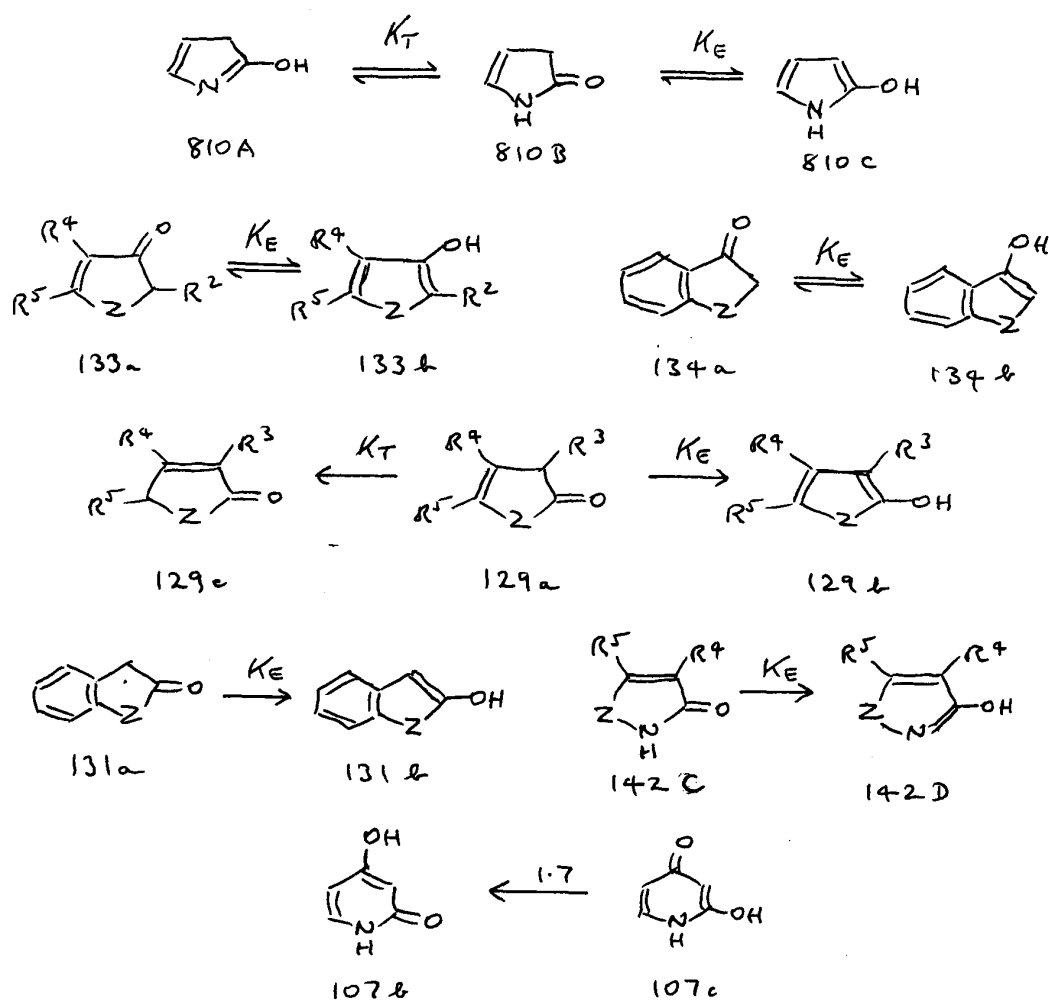
Z =	CH <sub>2</sub>	O	S	NH
log $K_E$ , <b>133</b> <sup>b</sup>	-	< - 2	0.5	- 0.9
log $K_E$ , <b>134</b> <sup>b</sup>	- 7.5 <sup>c</sup>	- 4.1	- 1.1	- 1.1
log $K_E$ , <b>131</b> <sup>d</sup>	- 4.1 <sup>e,f</sup>	- 5.5	- 2	- 6.5
$\Delta$ log $K_E$ , <b>134</b> <sup>g</sup>		3.4	6.4	6.4
$\Delta$ log $K_E$ , <b>131</b> <sup>g</sup>		- 1.4	2.1	- 2.4
$\Delta\Delta$ log $K_E$ <sup>h</sup>		- 4.8	- 4.3	- 8.8
		OMe	SMe	NHMe
$\sigma_R^+$ <sup>i</sup>		- 0.66	- 0.55	- 1.16

<sup>a</sup> Approximated to  $\pm 0.1$ . <sup>b</sup> Values from Table 13, section A.2.7. <sup>c</sup> Cpd. **46**, section A.1.3.

<sup>d</sup> Estimates from Table 89, section C.10. <sup>e</sup> Cpd. **45**, section A.1.3. <sup>f</sup> Statistically corrected.

<sup>g</sup> Relative to Z = CH<sub>2</sub>. <sup>h</sup> Eqn. (cxiv). <sup>i</sup> Table 2.

The only series for which log  $K_E$  has unequivocally been established are the parent 3-oxoheterocycles **133** and **134** (section C.11; *vide* Scheme 172). Because log  $K_E$  has been determined for (**134**, Z = CH<sub>2</sub>) it is possible to calculate the effect of Z = O, S and NH in promoting enolisation (see Table 90). These  $\Delta$  log  $K_E$  values, which show roughly equal effects for Z = S and NH but a much reduced one for Z = O, are qualitatively but not quantitatively in line with the Dewar resonance energies of thiophene, pyrrole and furan (Table 12, section A.2.6). It is also notable that the log  $K_E$  values themselves do not show the regular effect of benzofusion found for 6-membered ring oxoheterocycles in (3) below. Aromatisation is opposed by through-conjugation in the oxo-form, and if this is affected by benzofusion in an irregular manner, that parallelism will be lost. Here conjugation between NH and carbonyl will plausibly be much poorer for **134a** than for **133a** and may even be absent (see below) whereas the 2-oxo series should behave much more regularly and, in the absence of experimental evidence, we explore that hypothesis in section C.10.



Scheme 172

Table 144. Estimates of  $\Delta \log K$  in favour of Enolisation<sup>a</sup>

Structure	Z =	NH	NMe	NPh	O	S
<b>134b</b> <sup>b,c</sup>		6.4			3.4	6.4
<b>142d</b> <sup>d,e</sup>		-3.9	-3.9	-3.6	-3.3	

<sup>a</sup> All values ignore any electronic contribution from the OH substituent. <sup>b</sup> Values from Table 90 (section C.11). <sup>c</sup> By hypothesis valid for **131b** as well (see the text). <sup>d</sup> The  $\sigma_R$  contribution to  $\Delta \log K_T$  in Table 141 (Appendix 3). <sup>e</sup> For the whole  $-ZN=$  unit but ignoring the contribution due to  $\sigma_I$  (Table 141).

There are no experimental data on  $K_E$  for the parent compounds of the 2-oxoheterocycles **129** and **131** though it is clear qualitatively that they resist enolisation much more strongly than the parallel 3-oxo series. On various scraps of evidence we have derived the tentative estimates of  $\log K_E$  for series **131** (Scheme 172) that appear in Table 90. To take the analysis further we require certain assumptions, discussed in section C.11. The first is that the resonance energies of **131b** and **134b** are substantially equal; that is, they effectively act as a common enol for the oxo-tautomers of both series. The second is that, while enolisation (aromatisation) of **131** is opposed by the resonance energy of the  $ZC=O$  unit in **131a**, the corresponding factor in **134a** is inappreciable (see above). Hence the *difference* in  $\log K_E$  between **131** and **134** should relate to the resonance energy of  $ZC=O$ . Dissection of the data to give  $\Delta\Delta \log K_E$  (Table 90) yields a linear relation with  $\sigma_R^+$  for  $Z$  (section C.11), as expected on this hypothesis. While this evidence is too fragmentary to count as proof, it is suggestive and plausibly indicates the right line of argument. In the absence of  $\log K_E$  for (**129a**,  $Z = CH_2$ ) no parallel treatment of **129** is possible.

In passing it may be noted that the greater stability of **129a** than **133a** appears to be one aspect of a more general phenomenon. The pyridone **107** exists in water chiefly as **107b**, plausibly by  $\log K_T$  *ca.* 1.7 (section A.2.4), and other such compounds behave similarly. It therefore seems surprising that **120c** is more stable than **120a** and **121c** than **121a**. We have no explanation for this discrepancy.

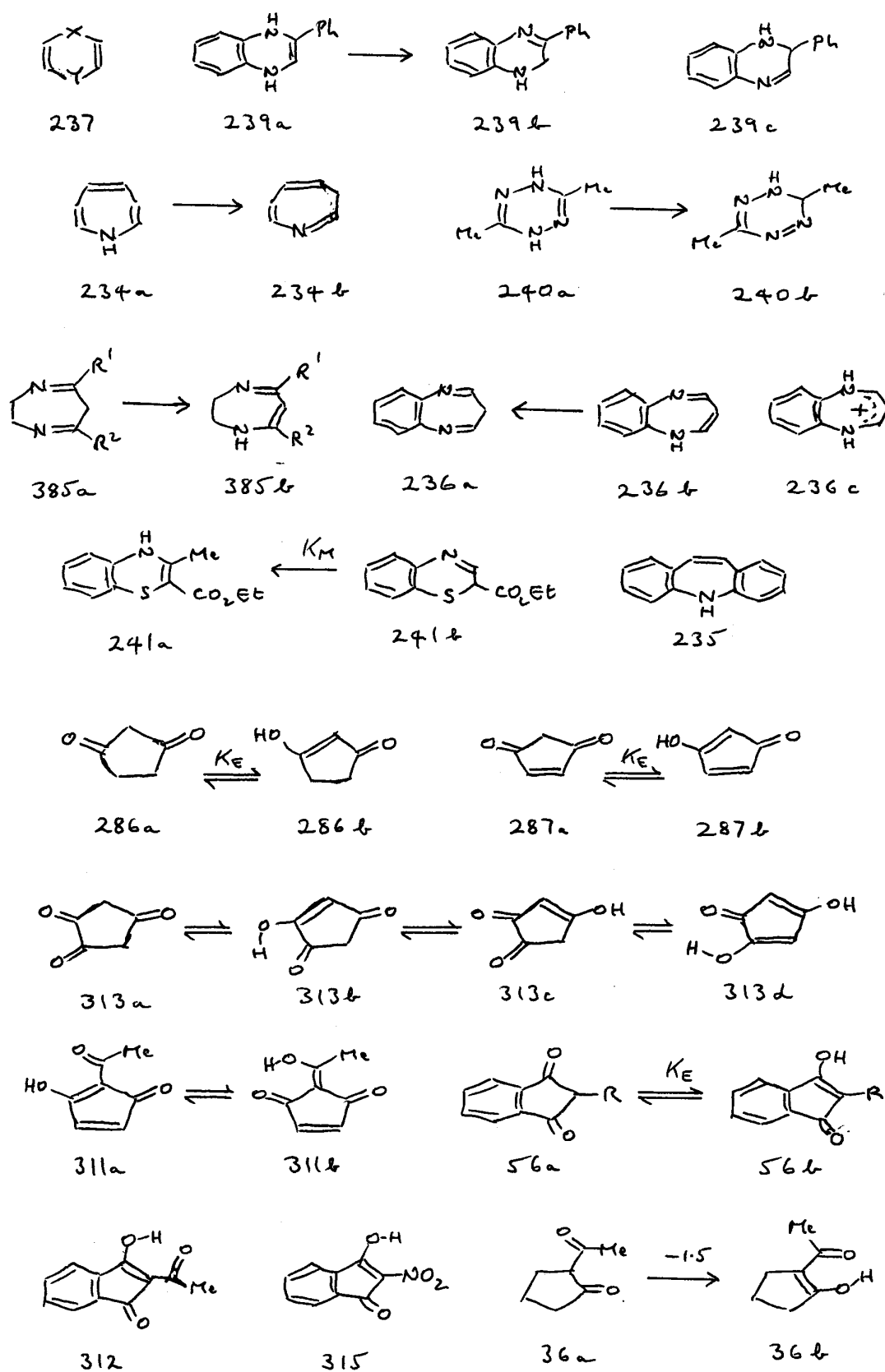
A partial analysis of  $K_E$  for **142** is also possible. Here again the effect of  $Z$  is twofold. As a resonance donor it increases the proportion of the aromatic tautomer **142D**; as a field effect acceptor it acts in the same direction, by dipolar repulsion in **142C** between  $Z$  and  $NH$ . We have dissected the overall effect into its components (Table 141 of Appendix 3). The  $\pi$ -donor ( $\sigma_R$ ) component appears in Table 144. Its variation with  $Z$  is much less than in series **129** and **134**, but this is simply because the effect is due to the whole  $-ZN=$  unit and not to  $Z$  alone. Qualitatively however it shows the same trends, with  $Z = NH$  a more powerful donor than  $Z = O$ .

It is clear even from these few analyses that the aromaticity of 5-membered ring heterocycles is highly variable and, while consistent results of varying  $Z$  are visible as trends, they do not carry over in any quantitative manner. A piecemeal approach is the only one possible at the present time.

## (2) ANTI-AROMATICITY

In order to qualify as 'aromatic' a cyclic molecule requires an unbroken conjugated system containing  $4n + 2$   $\pi$ -electrons, which in practice means 6 or 10 for monocyclic and bicyclic systems respectively. More  $\pi$ -electrons than this, or less, entails 'anti-aromaticity.' Such molecules are endergonic relative to most alternatives and if any tautomeric pathway can abolish this feature it becomes a likely option even when loss of conjugation will result. In the absence of any other escape route anti-aromatic molecules will frequently rearrange in some radical manner that does not concern us here.

There are two common patterns of anti-aromaticity, the  $8\pi$  and  $4\pi$  alternatives. The first, which is caused by an excess of  $\pi$ -electrons, is exemplified by **237** (Scheme 173). Where one or both of X and Y is NH anti-aromaticity may be eliminated by rearrangement as in **239a**  $\rightarrow$  **239b**; note that **239b** is preferred to **239c** since it preserves a greater element of conjugation. Two other examples are **234a** which goes to **234b** and **240** which exists as **240b** despite the presence here of the highly endergonic azo-linkage (section A.5.1). Benzofusion can sometimes introduce anti-aromaticity, as in **236**. While diazepines **385** exist in the vinylogous amidine structure **385b** and like amidines are strong bases (section A.9.2), benzofusion gives **236a** so as to avoid the anti-aromaticity implicit in **236b**. Nevertheless its cation **236c** takes the same form as that of **385**, perhaps because protonation effectively lowers the electron count by one lone pair. It should be noted however that the prohibition on anti-aromaticity is not absolute: by contrast with **239**, **241** exists as **241a** not **241b**. Here the aminoenone unit of **241a** is highly favoured over its unconjugated alternative, and while there is no direct experimental evidence on the point, *ab initio* calculation (section A.10.1) suggests  $K_M > 10^4$  for a simpler process of this type. The addition of benzofusion, which *pace* **236** as a special case generally reduces the energy gap between tautomers [see (3) below], may be another important factor; **235** exists as shown. This compound is one example, **122** and **473** in Scheme 171 being others, of a strong tendency for *bis*-benzofusion to result in compounds whose central ring is barely aromatic at all. All but the last two compounds are drawn from section A.4.9.

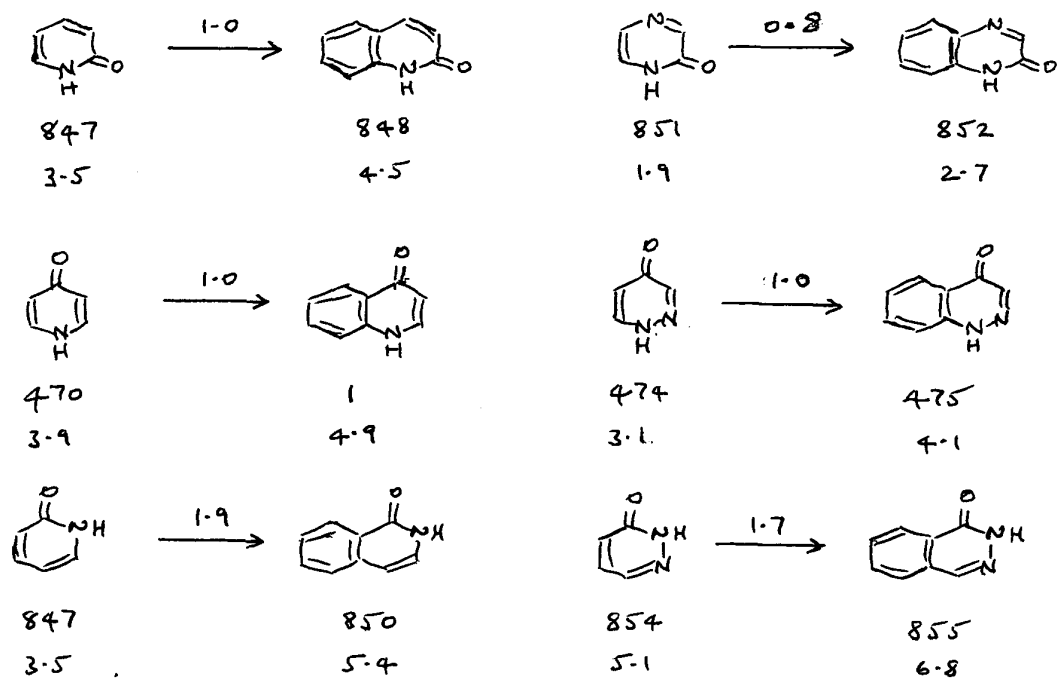


Scheme 173

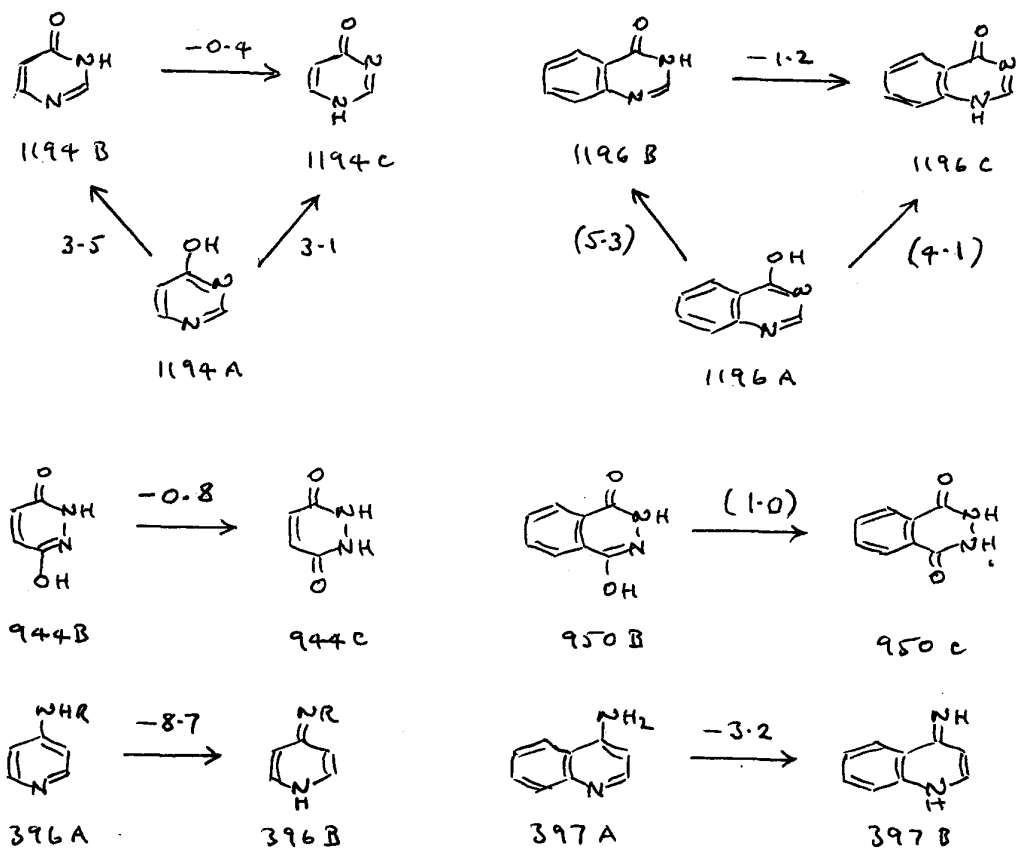
Most compounds of the  $4\pi$  type formally derive from the expansion of cyclobutadiene, itself anti-aromatic, by one or more conjugating groups which cannot donate  $\pi$ -electrons to give an aromatic sextet. For example, while **286** is overwhelmingly enolised to **286b** in water, **287** gives only 1.6% of **287b**. Here **287b** is a derivative of cyclopentadienone and shares its anti-aromaticity. In section C.6 we suggest  $\log K_E$  *ca* 3 as a plausible value for **286**, in which case the penalty for anti-aromaticity here is  $\Delta \log K$  *ca* 5; a similar value can be deduced for (**56**, R = H) which in water is about 1% enolised. Compound **313** exemplifies this and other prohibitions. It exists exclusively as **313b**; **313d** is ruled out by anti-aromaticity and **313a** and **313c** by lone pair repulsion (Appendix 3). Once again, however, the balance can be tipped by extra conjugation: **311** is 100% enolised to a mixture of **311a** and **311b**, the former still technically anti-aromatic, and **312** exists as shown in CS<sub>2</sub>. Comparisons between NO<sub>2</sub> and acyl groups as promoters of enolisation (section A.6.9) enable us to translate  $\log K_E$  1.7 for **315** in water into *ca* 3 for **312**, giving a probable factor of *ca.* 10<sup>5</sup> for the effect of 2-COMe (section C.6). Relative to cyclopentanone, ring acylation in **36** increases enolisation by  $\Delta \log K_E$  6.7 (section C.10) but a smaller effect seems reasonable for the third potential acyl group. All these examples but the last come from sections A.6.4 and A.6.5. In sum our best estimate of the penalty for anti-aromaticity is  $\Delta \log K$  *ca.* 5, possibly reduced on benzofusion as in **241** to *ca.* 4, but balancing factors can reduce or negate this value to an extent that is quantitatively reasonable. However much more evidence is required before these estimates can be considered reliable.

### (3) BENZOFUSION

If a ring current encompasses two or more fused aromatic rings, any loss of aromaticity in one ring will have less impact on the overall energetics than would result from the same modification to a monocycle. Hence benzofusion is expected to result in an increased proportion of the non-aromatic or less aromatic tautomer. This effect has been observed for the carbocycles of Scheme 171 where it is very large but the trends, while consistent, are not incremental. For oxoheterocycles however, where effects are much smaller, the increments due to benzofusion are sufficiently regular to possess predictive ability. Most of this section is devoted to that and related topics.

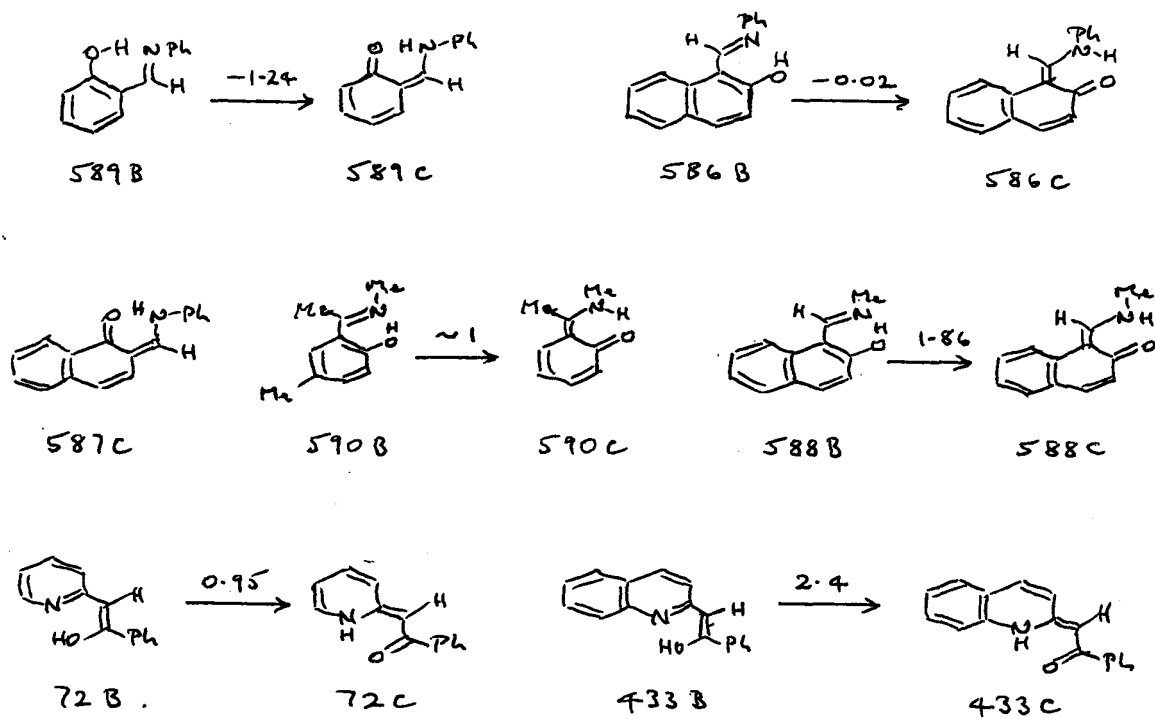


Scheme 174

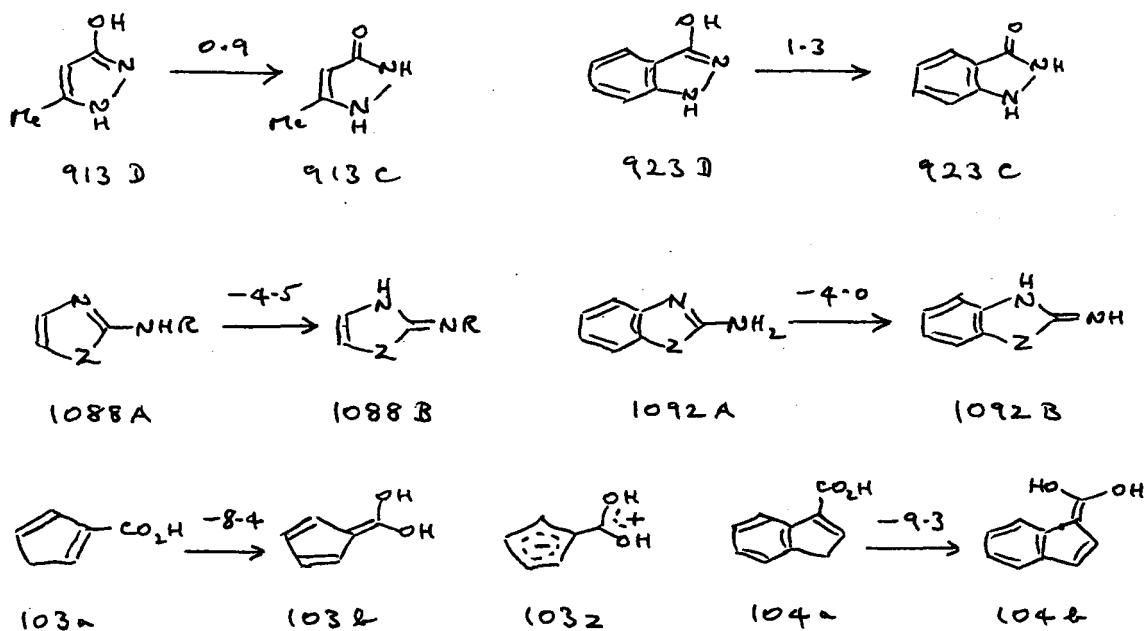


Scheme 175

Regular increments in  $K$  that depend on the position of benzofusion are particularly marked for the 6-membered ring oxoheterocycles, all known data for which (from sections A.10.7 and B.2.5), except where resulting in quinonoid structures, are set out in Scheme 174. Here  $\log K_T$  for each compound is shown below its serial number. If the tautomeric nitrogen atom is adjacent to the fused benzene ring, an increment of 0.8 (one doubtful case) or 1.0 is found; if in the  $\beta$ -position,  $\Delta \log K_T$  is 1.9 or 1.7. It is difficult to understand the origin of this difference and, indeed, a plausible case could be made for expecting this increment to be greater in the  $\alpha$ - rather than the  $\beta$ -position, but the facts brook no dispute. In Scheme 175 we list three resulting predictions which, while there is insufficient evidence to prove them, appear plausible. All  $\log K$  values for **1194** are known experimentally (section B.5.12); those shown bracketed for **1196** result from *assuming*  $\Delta \log K_T$  1.0 and 1.8 for  $\alpha$ -NH and  $\beta$ -NH (of the oxo-tautomer) respectively. The difference between them,  $\log K_M$  -1.2, compares with the experimental value of -1.3 (section B.5.11). For maleic hydrazide **944** the major tautomer is **944B** (section B.2.12), as shown; addition of  $\Delta \log K$  1.8 would result in  $\log K_T$  1.0 for **950**. Here the situation is confused; **950** undoubtedly exists as **950B** in the solid state, but despite the authors' similar claim for aqueous solution, their UV spectra for fixed model compounds show that **950C** predominates, though not overwhelmingly so (section B.2.12). We also believe this relation good enough to highlight probable errors in the literature. One of these concerns **397**, whose published  $\log K_M$  -3.2 is shown alongside that for (**396**, R = H). Inspection reveals that imino-heterocycles (sections A.9.4 and B.4.4) vary more widely in tautomeric ratio than oxoheterocycles, but nevertheless  $\Delta \log K_M$  5.5 for **396**  $\rightarrow$  **397** is out of the question; one or both values must be wrong. Almost certainly **397** is at fault, and for a plausible reason. The  $pK_a$  value of its 1-methyl derivative as model for **397B** was measured at a time (1952) before reliable techniques existed for determining very high pH values, and  $pK_a$  12.4 as reported for this compound is almost certainly far too low. By contrast,  $pK_a$  17.87 as measured by Katritzky and co-workers<sup>150</sup> for (**396**, R = H) in 1972 employed the necessary techniques and itself superseded the previous 'mirage' value for this compound. It will not surprise the authors if the failure of the corresponding imino- and thiono-heterocycles to show a degree of consistency anywhere near to that of Scheme 174 will ultimately be traced to problems of an experimental nature. One whose origin is certainly this is elaborated in section (I) of Appendix 1. For that reason, we do not discuss these compounds here.



Scheme 176



Scheme 177

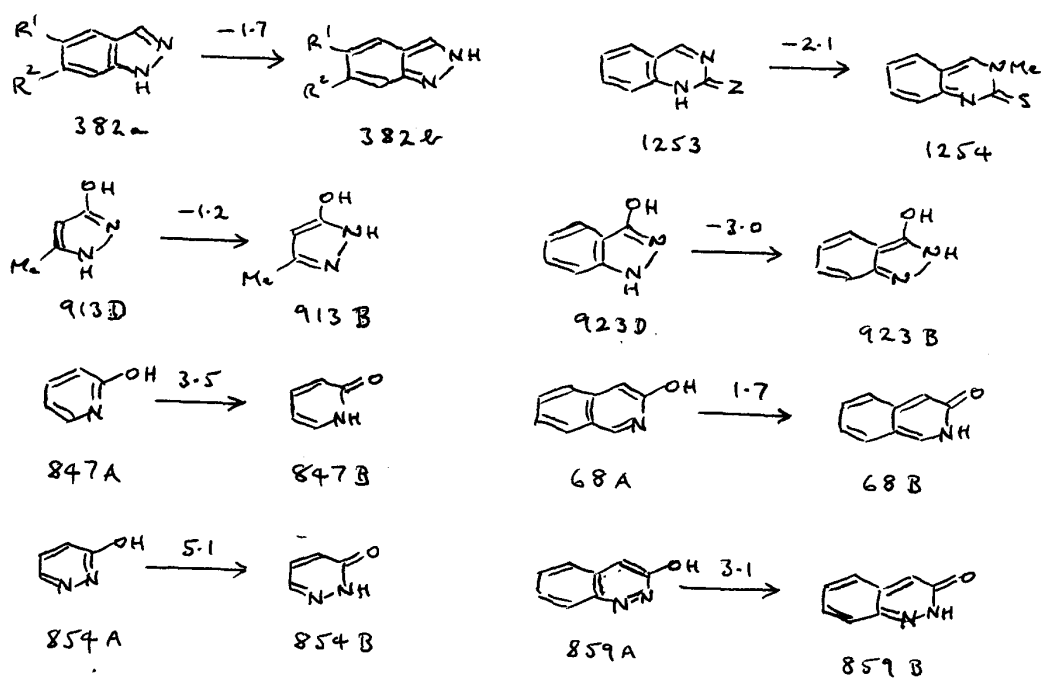
There is a handful of data concerning the effects of benzofusion on other than oxoheterocycles. Formation of **586C** is favoured over that of **589C** (Scheme 176) in MeOH by  $\Delta \log K_T$  *ca.* 1.2, only slightly greater than that for the nearest oxoheterocycle analogues in water, **848** *vs.* **847** (Scheme 174), but this parallelism is spoilt by  $\log K_T$  0.06 for **587**, almost identical to that for **586**; both values are for water. Aqueous values of  $\log K_T$  1.86 for **588** and *ca.* 1.0 for **590C** are apparently in line but potentially equivocal through the unknown effect of  $\alpha$ -Me in the latter (all section A.10.18). Another class of amide vinylogue, **433** *vs.* **72** with *exo*-C=O in place of carbonyl in the ring (section A.10.2) yields  $\Delta \log K$  *ca.* 1.5, intermediate between the two distinct values of Scheme 174. All these compounds possess, in both tautomers, intramolecular hydrogen bonds, and quite small variations in the strength especially of OH---N bonding, perhaps caused by varying departures from planarity, might be sufficient to affect  $\Delta \log K$  in some unpredictable manner. We have to conclude that any attempt to generalise the regularities of Scheme 174 to other compound classes requires caution at the present time.

Even less is known concerning the parallel consequences of benzofusion for 5-membered rings. The only quantitative comparison between a pair of oxoheterocycles involves **923** *vs.* **913** (Scheme 177) from which  $\Delta \log K$  0.4 results (section B.2.10). However, an effect of similar magnitude is found for *exo*-imine formation by **1092** *vs.* **1088**, and there is unquantifiable evidence from several unrelated compound series that any consequence of benzofusion, and not only to tautomerism, appears to be small. The only other quantitative information we can find concerns enol formation in **104** *vs.* **103**. These remarkably facile processes (section A.2.4) are presumably driven, for **103**, by incipient formation of the cyclopentadienyl inner salt **103z**, but relatively disfavoured on benzofusion by dilution of the charge. The opposite direction of the change in  $K_E$  on benzofusion, as compared with any other example of this, is sufficient evidence that the phenomenon has a different origin.

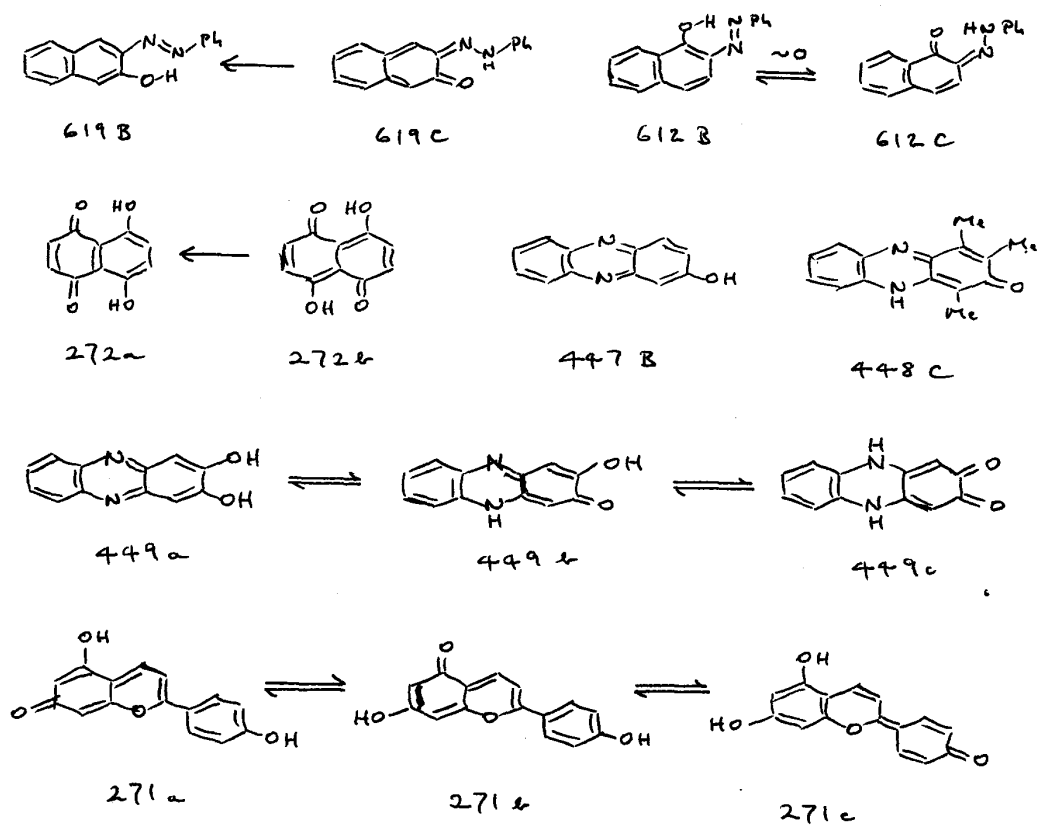
#### (4) QUINONOID FORMS

It is well established that quinonoid forms are metastable relative to benzenoid alternatives, sometimes even to the extent that unconjugated tautomers result when no benzenoid structure is possible (see below). Five sets of compounds exist that enable the benzenoid-quinonoid energy gap, in water, to be quantified (Scheme 178). Pyrazole possesses two degenerate tautomers which, when fused to benzene, give rise to the benzenoid tautomer **382a** or the quinonoid tautomer **382b** (both  $R^1 = R^2 = H$ ). The former has been shown by the basicity method to be preferred by a margin of  $\Delta \log K$  1.7 (section A.9.2). The tautomers **913D** and **913B**, both minor forms (the oxo-tautomer is dominant), are related as shown; on benzofusion the **B**-tautomer becomes quinonoid, and is disfavoured by a further margin of  $\Delta \log K$  -1.8 (all section B.2.10). 2-Pyrimidone like pyrazole possesses degenerate tautomers; again on benzofusion one becomes quinonoid, and  $pK_a$  comparison of (**1253**,  $Z = S$ ) and **1254**, after correction for  $\Delta(NR)$ , gives  $\Delta \log K$  *ca* -2.1 (section B.5.15). The other two comparisons involve 6-membered ring oxoheterocycles, **68** *vs.* **847** and **859** *vs.* **854**, to give  $\Delta \log K_T$  values of -1.8 and -2.0 respectively (section B.2.5). For five examples this results in  $\Delta \log K$  -1.9 $\pm$ 0.15, a larger spread than that for benzenoid ring fusion (Scheme 174) but quite good enough for most predictive purposes and apparently unaffected by the ring size of the heterocyclic moiety, a particularly valuable feature.

Qualitative exemplifications follow (Scheme 179). For **619** only **619B** is detectable in water, in line with expectation given  $\log K_T$  *ca.* 0 for **612** (section A.10.9), its nearest measured analogue. Another simple example concerns **272**, which exists exclusively as **272a** (section A.6.3); **272b** might be described as doubly half-quinonoid. For the phenazines **447** and **448** their tautomers must be closely in balance, since **447B** but **448C** predominate in water. Here while aromaticity should oppose formation of the *p*-quinonoid **C**-tautomer, aminoenone resonance should favour it, and with a limiting value in its favour of  $\log K_T$  8.7 (section A.10.4) the only surprise is that **447C** should not predominate as well. However carbonyl in the **C**-tautomer is linked to the electronegative aza-nitrogen atom as well as  $\pi$ -donor NH and no simple additive relationship is likely to cope; *ab initio* calculation may be a better prospect. For **449** structure **449c** avoids this problem but only at the cost of severe lone pair repulsion, and the preference observed for **449b** (section A.10.4) most likely results from the severe lone pair repulsion present in **449c**, possibly on the order of  $\Delta \log K > -5$  (Appendix 1). Sometimes the choice can lie *between* two quinonoid forms, and here the *p*-quinonoid alternative appears to possess advantages: **271a** predominates over



Scheme 178



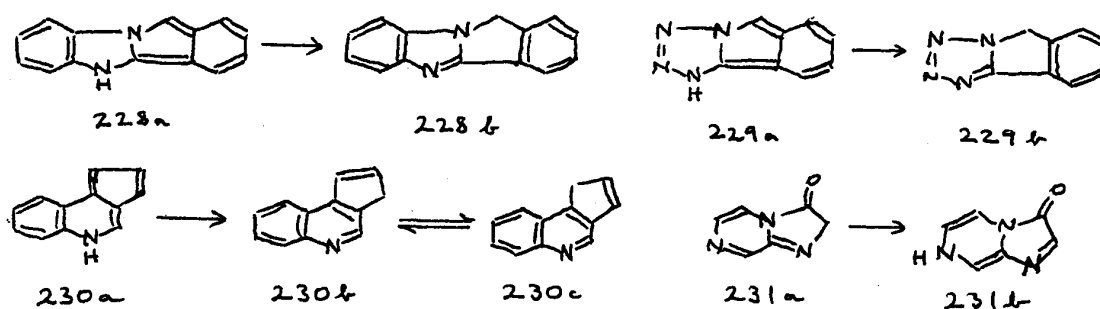
Scheme 179

**271b** by a 5-fold margin while the proportion of **271c** is negligible (section A.6.3). This is reminiscent of the relative stabilities of **120c** > **120a** and **121c** > **121a** in some simpler cases of aromatisation (Scheme 171) except that, for **271**, only the common cation is benzenoid.

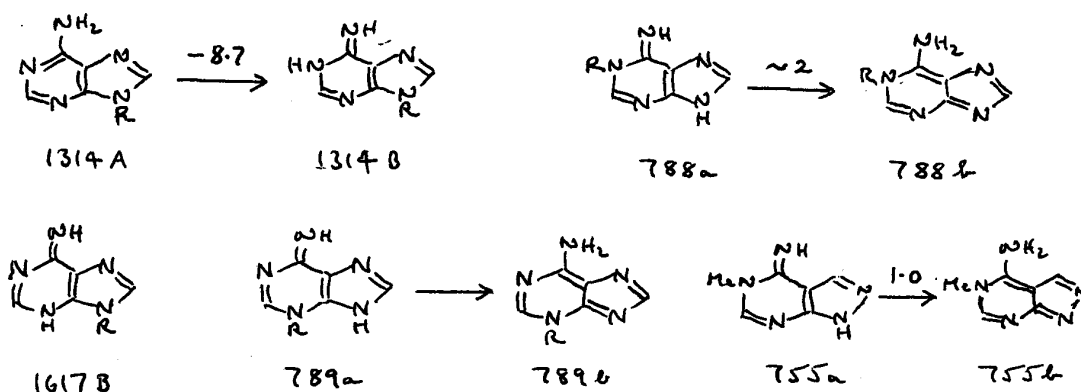
Examples of compounds that exist as the unconjugated tautomer (Scheme 180) include **228**, **229** and **230** (section A.4.8). None however is simple: **228b** restores imidazole as well as benzenoid resonance, a similar situation exists for **229**, and **230a** has lost its  $10\pi$  system. The first two of these exemplify one of Elguero's four 'rules' for predicting the tautomeric form of azapentalenes (section B.1.9). A very surprising case is that of **231**, which on the evidence of fixed forms exists as **231b** in MeOH even though this is not only quinonoid but anti-aromatic; it is difficult to believe that its nominally more extended conjugation can sufficiently compensate for this.

The fused aminopyrimidines **755**, **788** and **789** of Scheme 181 give rise to an involved and unusual pattern of tautomerism. All exist as quinonoid tautomers in which the aromaticity of the fused 5-membered ring is entirely destroyed. The key may lie in the extremely disfavoured formation of **1314B** from **1314A**, both with R = alkyl, for which we calculate  $\log K_M$  -8.7 (section B.7.2). If (**1314B**, R = alkyl) and (**788**, R = Me) are energetically equivalent, there results a 3-way equilibrium by which (**788b**, R = H) is disfavoured relative to (**1314A**, R = H) by  $\log K$  ca -6.7; that is, **788b** is formed only because **788a** is even more disfavoured. Since **788a** is dominant in nonpolar solvents but **789a** has not been detected in any, **1617B** is presumably still more disfavoured than **1314B**. It is also interesting that  $\log K$  in favour of **755b** is less than that for **788b** by almost the exact margin expected to result from lone pair repulsion in the former (Appendix 3), implying that the loss of resonance energy entailed in their formation may be almost identical.

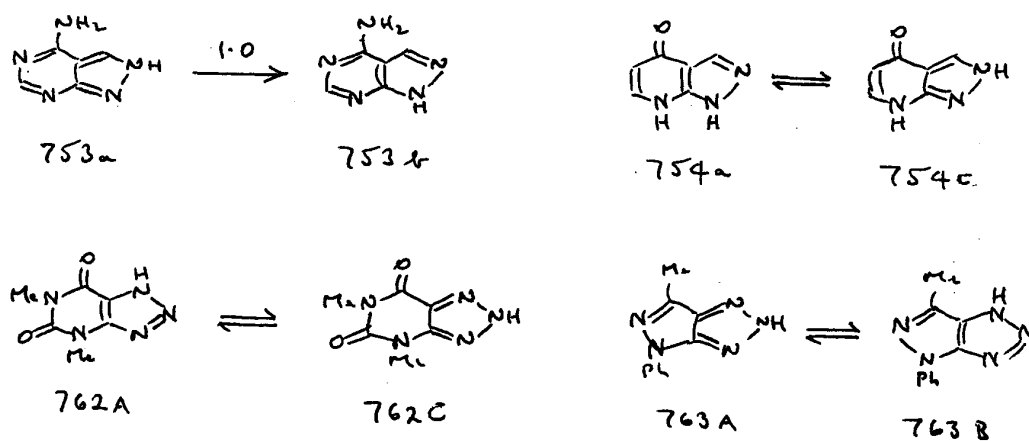
There is a handful of results from which it is possible to deduce how far the 'quinonoid penalty' on benzofusion applies to ring fusions of certain other sorts. In **753** (Scheme 182) the benzenoid tautomer **753b** is favoured (section B.1.5) by a margin small enough to be almost entirely explained by the *peri*-lone pair interaction present in **753a** (Appendix 3). We note in Appendix 3 that the tautomeric ratios in **762** and **763** (section B.1.6) are little different from that found in the relevant solvent for *v*-triazole itself, suggesting a minimal degree of interaction with the fused uracil and pyrazole units respectively. The one apparent exception is **754**, which exists in water



Scheme 180



Scheme 181



Scheme 182

exclusively as the benzenoid tautomer **754a** (section B.1.5) despite the apparent dipolar repulsion. However we analyse this case in Appendix 3, sub-section (**m**), and conclude that 4-pyridone NH is such a poor proton donor that dipolar repulsion will be minimal. At present therefore there is no evidence that, at least for 6,5-ring fusions, a 'quinonoid penalty' applies to anything other than benzofusion itself.

## NOTES AND REFERENCES

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there is an ongoing dispute concerning its  $\beta$ -value; and (c) that, in the special case of chelation, a severe disagreement between the calculated and (where known) observed  $\log K_T$  value for aqueous solution may help to establish the extent to which, in water, the chelate is actually formed.

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595. The intercept terms inside brackets each represent an 'effective scale zero' (cf. ref. 591) below which hydrogen bonding in water merges into a nonspecific polar attraction. The  $K_\alpha$  and  $K_\beta$  values are for 1:1 association in  $\text{CH}_2\text{Cl}_2$  (ref 72) whereas the 'scale zeros' are applicable to four oil-water partitioning systems in which the zero term for  $K_\beta$  is constant whereas that for  $K_\alpha$  is not, hence a mean value is taken for the latter.
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