Supporting Information

Empirical conversion of pK_A values between different solvents and interpretation of the parameters: application to water, acetonitrile, dimethyl sulfoxide and methanol.

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Table of content

Table S1: Comparison of experimental (exp) and with the empirical conversion method (ECM) predicted (JPM) pK_A values for the family of alcohols (A) and phenols (B) in acetonitrile (MeCN), dimethyl-sulfoxide (Me_2SO) and methanol (MeOH). The predicted pK_A values for water were obtained with the Jaguar pK_A prediction method (JPM)[1] except for phenols where for 2-nitro-p the results from Friesner et al. Ref. [2] were used. The predicted pK_A values for the other solvents were obtained by applying the ECM to the pK_A values in water predicted with the JPM pK_A predictor[1] and matching them with known experimental or ETM pK_A values in the corresponding organic solvents. The family specific parameters for prediction are adjusted to 17 measured pK_A values (3 for alcohols and 14 for phenols). pK_A values of ECM in the solvents MeCN, Me_2SO and MeOH that deviate by more than 1.5 pH units from the corresponding measured or with ETM computed pK_A values are considered as outliers and are marked by bold digits.

#	**family**	pK_A in water			pK_A in MeCN			pK_A in Me_2SO			pK_A in MeOH		
A	**alcohols**	exp	JPM	dev	exp	ECM	dev	exp	ECM	dev	exp	ECM	dev
1	methanol	15.50a	16.40	-0.90				29.00	29.60	0.60			
2	ethanol	15.90a	16.00	-0.10				29.80	29.20	-0.60			
3	i-propanol	17.10a	17.10	0.00				30.30	30.30	0.00			
	pK_A-RMSD			0.52						0.49			
B	**phenols (p)**	exp	JPM	dev	exp	ECM	dev	exp	ECM	dev	exp	ECM	dev
1	phenol	10.00a	9.80a	0.20	26.60a	26.10	0.50	18.00	17.70	0.30	14.32a	13.80	0.52
2	4-amino-p	10.46b	9.30a	1.16		25.60			17.20			13.30	
3	4-chloro-p [α]	9.90a	9.60a	0.30	25.44b	25.90	-0.46	16.70	17.50	-0.80		13.60	
4	4-fluoro-p	10.20a	10.40a	-0.20		26.70		18.00	18.30	-0.30		14.40	
5	4-methoxy-p	10.40a	10.30a	0.10		26.60		19.10	18.20	0.90		14.30	
6	4-methyl-p	10.50a	10.60a	-0.10	27.45b	26.90	0.55	18.90	18.50	0.40	14.52a	14.60	-0.05
7	4-nitro-p	7.20a	7.30a	-0.10	21.30c	**23.60**	**-2.30**		15.20		11.24a	11.30	-0.06
8	4-hydroxy-benzaldehyde-p	7.60a	7.60a	0.00		23.90			15.50			11.60	
9	2-nitro-p	7.17c	8.00	-0.83	22.85d	24.30	-1.45		15.90		11.52a	12.00	0.48
∑12	*pK_A-RMSD*			0.50			1.10			0.60			0.36

Water: a – value taken from Ref. [2], b – value taken from Ref. [3], c – value taken from Ref. [4]; MeCN:
a – value taken from Ref. [5], b – value taken from Ref. [6], c – value taken from Ref. [7],
d – value taken from Ref. [8]; Me_2SO: all the experimental values are taken from Ref. [9];
MeOH: a – value taken from Ref. [10]

Table S2: Comparison of experimental (exp) and with ECM predicted (ECM) pK_A values for the family of carboxylic acids (C) in acetonitrile (MeCN), dimethyl-sulfoxide (Me_2SO) and methanol (MeOH). The predicted pK_A values in water (JPM) were obtained with the JPM pK_A predictor[1]. The predicted pK_A values for the other solvents were obtained by applying the ECM to the pK_A values in water predicted with the JPM pK_A predictor[1] and matching them with known experimental or ETM pK_A values in the corresponding organic solvents. The pK_A values in blue digits were computed by the electrostatic transform method (ETM), which uses the measured pK_A values in water[11]. The ETM pK_A values were added in cases where only few experimental values are available and for demonstrating its validity. The family specific parameter for prediction is adjusted to 18 measured and 2 ETM pK_A values. pK_A values of ECM in the solvents MeCN, Me_2SO and MeOH that deviate by more than 1.5 pH units from the corresponding measured or with ETM computed pK_A values are considered as outliers and are marked by bold digits.

#	**family**	pK_A in water			pK_A in MeCN			pK_A in Me_2SO			pK_A in MeOH		
C	**carbox acids**	exp	JPM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev
1	benzoic ac	4.20a	3.90	0.30	20.10a	19.40	0.70	11.00	11.10	-0.10	9.30a	8.90	0.40
2	3,4Me2-benzoic	4.44b	3.70	0.74	19.44	19.20	0.24	11.40 10.54	10.90	0.50	9.09	8.70	0.39
3	3OH benzoic	4.08a	3.50	0.58		19.00		11.10	10.70	0.40		8.50	
4	4Br benzoic	3.96a	3.50	0.46		19.00		10.90	10.70	0.20		8.50	
5	4Cl benzoic	4.00a	3.40	0.60		18.90		10.10	10.60	-0.50		8.40	
6	glutaric ac	4.32a	4.30	0.02	19.20b	19.80	-0.60	10.90	11.50	-0.60		9.30	
7	fumaric ac	3.02a	3.00	0.02	18.60c	18.50	0.10		10.20		8.01b	8.00	0.01
8	propionic ac	4.85c	4.80	0.05		20.30			12.00		9.71b	9.80	-0.09
9	adipic ac	4.41a	4.40	0.01	20.40c	19.90	0.40	11.90	11.60	0.30		9.40	
10	succinic ac	4.21d	4.10	0.11	17.60b	**19.60**	**-2.00**		11.30		9.14b	9.10	0.04
11	malic ac	3.50a	2.70	0.80		18.20			9.90		8.35b	7.70	0.65
12	malonic ac	2.90a	3.40	-0.50		18.90			10.60		7.66b	8.40	-0.74
∑12	*pK_A-RMSD*			0.45			0.93			0.41			0.43

Water: a - value taken from Ref. [12], b - value taken from Ref. [13], c – value taken from Ref. [14], d – value taken from Ref. [15]; MeCN: a – value taken from Ref. [16], b – value taken from Ref. [17], c – value taken from Ref. [18]; Me_2SO: all the experimental values are taken from Ref. [9]; MeOH: a – value taken from Ref. [19], b – value taken from Ref. [20]

Table S3: Comparison of experimental (exp) and with ECM predicted (ECM) pK_A values for the families of thiols (D) and hydroxamic acids (E), in acetonitrile (MeCN), dimethyl-sulfoxide (Me_2SO) and methanol (MeOH). The predicted pK_A values for water were obtained with the JPM pK_A predictor[1]. The predicted pK_A values for the other solvents were obtained by applying the ECM to the pK_A values in water predicted with the JPM pK_A predictor[1] and matching them with known experimental or ETM pK_A values in the corresponding organic solvents. The pK_A values in blue digits were computed by the electrostatic transform method (ETM), which uses the measured pK_A values in water[11]. They were added in cases where only few experimental values were available and to demonstrate its validity. The family specific parameter for prediction is adjusted to 11 measured and 3 with the electrostatic transform obtained[11] pK_A values.

#	**family**	pK_A in water			pK_A in MeCN			pK_A in Me_2SO			pK_A in MeOH		
D	**thiols (t)**	exp	JPM	dev	ETM	ECM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev
1	thiophenol	6.62a	6.60	0.02	18.89	19.30	-0.41	10.28 10.18	10.30	-0.02	8.65a 9.31	8.80	-0.15
2	4CH3-t	6.82b	6.60	0.22	19.32	19.30	-0.02	10.82 10.95	10.30	0.52	8.96**a** 8.63	8.80	0.16
3	3CH3-t	6.66c	6.50	0.16	19.51	19.20	0.31	10.55 11.33	10.20	0.35	8.44	8.70	-0.26
4	M-toluidine	6.78	6.60	0.18		19.30		11.19	10.30	0.89	8.95**a**	8.80	0.15
5	2-chloro-t	5.90	5.50	0.40		18.20		8.55	9.20	-0.65		7.70	
6	2OMe-benz-t	6.89d	6.80	0.09		19.50		11.35	10.50	0.85		9.00	
7	2Me-benz-t	6.64e	6.50	0.14		19.20		10.70	10.20	0.50		8.70	
8	4Br-benz-t	6.02e	6.20	-0.18		18.90		8.98	9.90	-0.92		8.40	
∑8	*pK_A-RMSD*			0.20			0.30			0.65			0.19
E	**hydroxamic acids**	exp	JPM	dev	ETM	ECM	dev	exp ETM	ECM	dev	ETM	ECM	dev
1	benz-hyd-ac	8.80a	8.50	0.30	22.34	23.50	-1.16	13.70 14.26	15.10	-1.40	13.25	13.50	-0.25
2	methyl-hyd-ac	8.70b	8.10	0.60	24.27	23.10	1.17	16.00 15.02	14.70	1.30	13.41	13.10	0.31
3	capryl-hyd-ac	9.00c	8.50	0.50	24.55	23.50	1.05	15.58	15.10	0.48	13.48	13.50	-0.02
	pK_A-RMSD			0.48			1.13			1.14			0.23

Water: a – value taken from Ref. [17], b – value taken from Ref. [3], c – value taken from Ref. [3,11], d – value taken from Ref. [21], e – value taken from Ref. [22]; Me_2SO: all the experimental values are taken from Ref. [9]; MeOH: a - value taken from Ref. [23]

Table S4: Comparison of experimental (exp) and ECM predicted (ECM) pK_A values for the following three families: barbituric acids (F), sulfonamides (G) and imides (H) in acetonitrile (MeCN), dimethyl-sulfoxide (Me_2SO) and methanol (MeOH). The predicted pK_A values for water were obtained with the Jaguar pK_A predictor (JPM)[1]. The predicted pK_A values for the other solvents were obtained by applying the ECM to the pK_A values in water predicted with the Jaguar pK_A predictor[1] and matching them with known experimental or ETM pK_A values in the corresponding organic solvents. The pK_A values in blue digits were computed by the electrostatic transform method (ETM), which uses the measured pK_A values in water[11]. They were added in cases where only few experimental values were available and to demonstrate its validity. The family specific parameters for prediction are adjusted to 7 measured and 23 with the electrostatic transform obtained [11] pK_A values. pK_A values of ECM in the solvents MeCN, Me_2SO and MeOH that deviate by more than 1.5 pH units from the corresponding measured or with ETM computed pK_A values are considered as outliers and are marked by bold digits.

#	**families**	pK_A in water			pK_A in MeCN			pK_A in Me_2SO			pK_A in MeOH		
F	**barbit-acids**	exp	JPM	dev	ETM	ECM	dev	ETM	ECM	dev	ETM	ECM	dev
1	55dimeth-bar-ac	8.00a	8.10	-0.10	23.74	23.50	0.24	14.79	14.60	0.19	12.71	12.80	-0.09
2	55meth-phen-bar-ac	7.40a	7.50	-0.10	22.58	22.90	-0.32	13.70	14.00	-0.30	11.77	12.20	-0.43
3	hexobarbital	8.20a	8.20	0.00	23.90	23.60	0.30	14.97	14.70	0.27	13.21	12.90	0.31
	pK_A-RMSD			0.10			0.29			0.26			0.26
G	**sulfonamides**	exp	JPM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev	ETM	ECM	dev
1	saccharin	1.80d	3.00	-1.40	14.57a 15.91	15.80	-1.23	6.64	7.50	-0.86	6.07	7.20	-1.13
2	piloty's acid	9.29e	9.80	-0.51	23.78	22.60	1.13	15.40	14.30	1.10	13.25	14.00	-0.75
3	phenyl-SA	10.10f	10.20	-0.10	24.61b 24.60	**23.00**	**1.56**	16.10 15.91	14.70	1.40	15.70	14.40	1.30
4	methyl-SA	10.87g	12.00	-1.13	25.76	24.80	0.91	17.50 17.70	16.50	1.00	15.00	16.20	-1.20
∑10	*pK_A-RMSD*			0.94			1.26			1.11			1.11
H	**imides**	exp	JPM	dev	ETM	ECM	dev	exp ETM	ECM	dev	ETM	ECM	dev
1	succinimide	9.60a	8.70	0.90	24.32	23.70	0.62	14.70 14.11	14.40	0.30	13.76	12.80	0.96
2	dimethadione	6.10a	7.60	-1.50	21.79	22.60	-0.81	13.47	13.30	0.17	10.78	11.70	-0.92
3	phenytoin	8.30a	8.00	0.30	22.38	23.00	-0.62	13.42	13.70	-0.28	12.08	12.10	-0.02
	pK_A-RMSD			1.02			0.69			0.26			0.85

Water: a – value taken from Ref. [2], b – value taken from Ref. [11], c – value taken from Ref. [24], d – value taken from Ref. [25], e – value taken from Ref. [26], f – value taken from Ref. [27], g – value taken from Ref. [28]; MeCN: a – value taken from Ref. [29], b – value taken from Ref. [8]; Me_2SO: all the experimental values are taken from Ref. [9]

Table S5: Comparison of experimental (exp) and with ECM predicted (ECM) pK_A values for the following four families: indoles&pyrroles (I), primary amines (J), secondary amines (K), and tertiary amines (L) in acetonitrile (MeCN), dimethyl-sulfoxide (Me_2SO) and methanol (MeOH). The predicted pK_A values for water were obtained with the Jaguar pK_A predictor (JPM)[1]. The predicted pK_A values for the other solvents were obtained by applying the ECM to the pK_A values in water predicted with the JPM pK_A predictor[1] and matching them with known experimental or ETM pK_A values in the corresponding organic solvents. The pK_A values in blue digits were computed by the electrostatic transform method (ETM), which uses the measured pK_A values in water[11]. They were added in cases where only few experimental values were available and to demonstrate its validity. The family specific parameters for prediction are adjusted to 16 measured and 26 with the electrostatic transform obtained[11] pK_A values.

#	**families**	pK_A in water			pK_A in MeCN			pK_A in Me_2SO			pK_A in MeOH		
I	**indoles & pyrroles N**	exp	JPM	dev	ETM	ECM	dev	exp ETM	ECM	dev	ETM	ECM	dev
1	indole	16.20a	15.50	0.70	28.61	29.70	-1.09	21.00 22.35	21.30	-0.30	20.69	20.90	-0.21
2	pyrrole	16.50b	16.80	-0.30	32.04	31.00	1.04	23.00 23.81	22.60	0.40	22.46	22.20	0.26
	pK_A-RMSD			0.54			1.06			0.35			0.23
J	**prim-amin**	exp	JPM	dev	exp ETM	ECM	dev	ETM	ECM	dev	exp ETM	ECM	dev
1	methylamin	10.60c	10.50	0.10	18.37b 17.53	18.20	0.17	10.97	10.00	0.97	11.00a 10.06	10.80	0.20
2	ethylamin	10.87d	11.00	-0.13	18.40c 18.73	18.70	-0.30	10.38	10.50	-0.12	11.00a 11.01	11.30	-0.30
3	butylamin	10.78d	10.70	0.08	18.68	18.40	0.28	10.35	10.20	0.15	11.47b 10.89	11.00	0.47
	pK_A-RMSD			0.11			0.26			0.57			0.34
K	**secon-amin**	exp	JPM	dev	exp ETM	ECM	dev	ETM	ECM	dev	exp ETM	ECM	dev
1	dimethamin	10.73d	10.90	-0.17	18.70c 18.50	18.80	-0.10	10.30	11.10	-0.80	11.20a 10.68	11.10	0.10
2	diethamin	11.09d	11.10	-0.01	18.80c 18.09	19.00	-0.20	12.15	11.30	0.85	11.04	11.30	-0.26
3	dipropylamin	11.00d	10.60	0.40	18.81	18.50	0.31	10.73	10.80	-0.07	11.08	10.80	0.28
4	ethylpropylamin	11.00e	10.40	0.60	18.47	18.30	0.17	10.41	10.60	-0.19	10.89	10.60	0.29
	pK_A-RMSD			0.37			0.21			0.59			0.21
L	**tert-amin**	exp	JPM	dev	exp ETM	ECM	dev	ETM	ECM	dev	exp ETM	ECM	dev
1	trimeth-amin	9.80f	10.10	0.30	17.60c 16.69	18.40	-0.80	8.89	9.70	-0.81	9.80a 9.32	10.30	-0.50
2	triethyl-amin	10.78g	10.60	0.18	18.50c 18.08	18.90	-0.40	9.66	10.20	-0.54	10.78a 10.15	10.80	0.02
3	tripropyl-amin	10.65d	9.20	1.45	17.92	17.50	0.70	9.59	8.80	0.79	10.01	9.40	0.61
∑13	*pK_A-RMSD*			0.86			0.66			0.72			0.46

Water: a – value taken from Ref. [30], b – value taken from Ref. [31], c – value taken from Ref. [32], d – value taken from Ref. [33], e – value taken from Ref. [34], f – value taken from Ref. [35], g – value taken from Ref. [36]; MeCN: a – value taken from Ref. [37], b – value taken from Ref. [11], c – value taken from Ref. [17]; Me_2SO: all the experimental values are taken from Ref. [9]; MeOH: a – value taken from Ref. [38], b – value taken from Ref. [20]

Table S6: Comparison of experimental (exp) and with ECM predicted (JPM) pK_A values for the following three families: anilines (M), heterocycles (N), and amidines (O) in water, acetonitrile (MeCN), dimethyl-sulfoxide (Me_2SO) and methanol (MeOH). The predicted pK_A values for water were obtained with the JPM pK_A predictor[1]. The predicted pK_A values for the other solvents were obtained by applying the ECM to the pK_A values in water predicted with the JPM pK_A predictor[1] and matching them with known experimental or ETM pK_A values in the corresponding organic solvents. The pK_A values in blue digits were computed by the electrostatic transform method (ETM), which uses the measured pK_A values in water[11]. They were added in cases where only few experimental values were available and to demonstrate its validity. The family specific parameters for prediction are adjusted to 20 measured and 13 with the electrostatic transform obtained[11] pK_A values.

#	**families**	pK_A in water			pK_A in MeCN			pK_A in Me_2SO			pK_A in MeOH		
M	**anilines**	exp	JPM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev
1	aniline	4.60a	4.70	-0.10	10.56a 11.48	11.50	-0.94	3.82 3.68	4.00	-0.18	6.05a 3.97	5.50	0.55
2	2-chloro-a [α]	2.66a	2.60	0.06	9.66	9.40	0.26	1.94	1.90	0.04	3.71a	3.40	0.31
3	M-toluidine	4.69b	4.60	0.09		11.40			3.90		5.95a	5.40	0.55
4	4-chloro-a [α]	4.00c	4.00	0.00		10.80			3.30		4.95a	4.80	0.15
5	3-chloro-a [α]	3.52a	3.70	-0.18	10.94	10.50	0.44	2.98 2.38	3.00	-0.02	3.61	4.50	-0.89
6	4-methyl-a	5.10b	4.90	0.20	12.52	11.70	0.82	4.48 4.56	4.20	0.28	6.57a 5.11	5.70	-0.87
	pK_A-RMSD			0.13			0.67			0.17			0.62
N	**hetero-cycles**	exp	JPM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev	exp ETM	ECM	dev
1	imidazole	7.05d	6.80	0,25	15.05d 14.72	14.50	0.55	6.40 6.55	5.80	0.60	7.02	7.10	-0.08
2	piperidine	11.10e	11.10	0.00	18.92b	18.80	0.12	10.42	11.10	0.32	10.76a	11.40	-0.64
3	quinoline	4.90f	5.00	-0.10	11.96d	12.70	0.74		4.00		5.91a	5.30	0.61
4	pyridine	5.23g	5.20	0.03	12.53a	12.90	-0.37	3.50	4.20	-0.70	5.44a	5.50	-0.06
	pK_A-RMSD			0.14			0.30			0.65			0.36
O	**amidines**	exp	JPM	dev	ETM	ECM	dev	ETM	ECM	dev	ETM	ECM	dev
1	benzamidine	11.53h	11.40	0.13	21.81	21.30	0.56	13.59	13.20	0.39	12.98	12.60	0.38
2	acetamidine	10.25i	10.60	-0.35	19.98	20.50	-0.52	11.98	12.40	-0.42	11.44	11.80	-0.36
∑14	*pK_A-RMSD*			0.26			0.54			0.41			0.37

[α] For the electrostatic transform ETM [11] a chloride radius of 1.92 Å was used.
Water: a – values taken from Ref. [39], b – values taken from Ref. [33], c – values taken from Ref. [2], d – values taken from Ref. [40], e – values taken from Ref. [41], f – values taken from Ref. [42], g – values taken from Ref. [43], h – values taken from Ref. [44], i – values taken from Ref. [45]; MeCN: a – values taken from Ref. [46], b – values taken from Ref. [47], c – values taken from Ref. [37]; d - values taken from Ref. [48]; Me_2SO: all the experimental values are taken from Ref. [9]; MeOH: a – values taken from Ref. [38]

Table S7: Comparison of experimental (exp) and with ECM predicted (ECM) pK_A values for the following four families: guanidines (P), benzodiazepines (Q), pyrroles C2 (R), and indoles C3 (S) in acetonitrile (MeCN), dimethyl-sulfoxide (Me_2SO) and methanol (MeOH). The predicted pK_A values for water were obtained with the JPM pK_A predictor (JPM)[1]. The predicted pK_A values for the other solvents were obtained by applying the ECM to the pK_A values in water predicted with the JPM pK_A predictor[1] and matching them with known experimental or ETM pK_A values in the corresponding organic solvents. The pK_A values in blue digits were computed by the electrostatic transform method (ETM), which uses the measured pK_A values in water[11]. They were added in cases where only few experimental values were available and to demonstrate its validity. The family specific parameters for prediction are adjusted to 36 with the electrostatic transform obtained[11] pK_A values.

#	**families**	pK_A in water			pK_A in MeCN			pK_A in Me_2SO			pK_A in methanol		
P	**guanidines**	exp	JPM	dev	ETM	ECM	dev	ETM	ECM	dev	ETM	ECM	dev
1	guanidine	13.80a	12.50	1.30	22.91	22.00	0.91	14.85	13.90	0.95	13.67	13.10	0.57
2	methylguanidine	13.40a	13.40	0.00	23.43	22.90	0.53	15.78	14.80	0.98	14.18	14.00	0.18
3	debrisoquine	11.90a	13.00	-1.10	21.59	22.50	-0.91	13.36	14.40	-1.04	13.00	13.60	-0.60
	pK_A-RMSD			0.98			0.80			0.99			0.36
Q	**benzodiaz**	exp	JPM	dev	ETM	ECM	dev	ETM	ECM	dev	ETM	ECM	dev
1	1,3-dihydro-1-methyl-5phenyl-1,4-bzodiaz-2-one	3.30a	3.80	-0.50	10.83	11.10	-0.27	2.95	3.20	-0.25	3.29	3.50	-0.21
2	1,3-dihydro-3-hydro-5phen-1,4-bzodiaz-2-one	1.70a	1.90	-0.20	9.41	9.20	0.21	1.54	1.30	0.24	1.94	1.60	0.34
3	1,3-dihydro-5phenyl-1,4-bzodiaz-2-one	3.50a	4.00	-0.50	11.07	11.30	-0.23	3.20	3.40	-0.20	3.52	3.70	-0.18
	pK_A-RMSD			0.42			0.24			0.23			0.25
R	**pyrroles C2**	exp	JPM	dev	ETM	ECM	dev	ETM	ECM	dev	ETM	ECM	dev
1	pyrrole	-3.80a	-4.10	0.30	2.74	2.50	0.24	-5.23	-5.60	0.37	-4.16	-4.40	0.24
2	1methylpyrrole	-2.90a	-2.30	0.60	3.81	4.30	-0.49	-4.21	-3.80	-0.41	-3.36	-2.60	-0.76
3	3methylpyrrole	-1.00a	-0.90	-0.10	6.05	5.70	0.35	-2.02	-2.40	0.38	-1.28	-1.20	-0.08
	pK_A-RMSD			0.39			0.37			0.39			0.46
S	**indoles C3**	exp	JPM	dev	ETM	ECM	dev	ETM	ECM	dev	ETM	ECM	dev
1	indole	-3.60a	-3.70	0.10	3.42	3.20	0.22	-4.64	-4.80	0.16	-3.89	-4.00	0.11
2	1methylindole	-2.30a	-2.00	-0.30	4.80	4.90	-0.10	-3.25	-3.10	-0.15	-2.58	-2.30	-0.28
3	3methylindole	-4.60a	-4.60	0.00	2.42	2.30	0.12	-5.65	-5.70	0.05	-4.96	-5.20	0.24
∑12	pK_A-RMSD			0.18			0.16			0.13			0.19

a – pK_A values taken from Ref. [2]

Table S8: Empirical pK_A estimates in water for 17 species of the molecular family of squaramids using measured pK_A values in DMSO [a]. The results for water are compared with the ETM [b] and the pK_A prediction tool of Jaguar (JPM)[c]. In case there are two nearly equivalent protons the electrostatic transform method yields two different pK_A values. pK_A values of ECM in water that deviate by more than 1.5pH units from the corresponding pK_A values they are based on (which are ETM or JPM pK_A values in water) are considered as outliers and are marked by bold digits. The pK_A-RMSD between the predicted pK_A values in water from Jaguar and the ETM is 1.62. For the prediction with Jaguar the atomic radii with pbf radii=0 are used.

No	number of atoms[d]	abbreviated name	exp. pK_A in DMSO	JPM pK_A in DMSO [e]	ETM pK_A in H_2O	ECM pK_A in H_2O based on ETM	JPM pK_A in H_2O	ECM pK_A in H_2O based on JPM
		squaramids						
1	32	sq1	12.48		7.60	7.88	9.17	7.98
2	38	sq2_H34 sq2_H35	10.55		6.77 6.57	5.95	7.02	6.05
3	44	sq3	8.37		5.22	3.77	6.94	3.87
4	70	sq4_H47	12.17		**9.64**	**7.57**	**5.89**	**7.67**
5	73	sq5_H49 sq5_H50	10.54		7.24 5.11	5.94	6.43	6.04
6	76	sq6_H50 sq6_H51	14.99		11.01 9.50	10.39	10.87	10.49
7	66	sq7_H44 sq7_H45	12.18		7.40 6.83	7.58	5.68	7.68
8	69	sq8_H47 sq8_H48	11.03		7.91 6.18	6.43	5.93	6.53
9	72	sq9_H48 sq9_H49	15.13		9.89 9.52	10.53	9.83	10.63
10	49	sq10_H32 sq10_H33	13.10		9.21 7.61	8.50	8.7	8.60
11	52	sq11_H35	11.83		7.41	7.23	7.52	7.33
12	55	sq12_H36 sq12_H37	16.28		12.09 **9.94**	**11.68**	10.69	11.78
13	56	sq13_H35 sq13_H36	13.30		9.28 8.10	8.70	8.33	8.80
14	59	sq14_H38 sq14_H39	11.87		7.65 7.05	7.27	8.24	7.37
15	62	sq15_H39 sq15_H40	16.46		11.88 10.39	11.86	9.18	11.96
16	70	sq16_H66 sq16_H67	10.78		**9.58** **8.53**	**6.18**	5.85	6.28
17	62	sq17_H43 sq17_H44	11.42		7.00 6.06	6.82	**8.67**	**6.92**
		pK_A-RMSD relative to values without outliers in brackets				ETM in H_2O 1.18 (0.61)		JPM in H_2O 1.48 (0.71)
∑17		shift parameter ΔpK_A				4.60		4.50

[a] pK_A values taken from Ref. [49]
[b] pK_A values computed with ETM [11]
[c] pK_A values computed with the Jaguar prediction scheme. [50]
[d] number of atoms refer to the protonated state.
[e] JPM pK_A values in DMSO are not available yet for these compounds (work in progress).

Table S9: Empirical pK_A estimates in water for 13 species of the molecular family of thiourea using measured pK_A values in DMSO[a]. The results for water are compared with the electrostatic transform method [b] and the pK_A prediction tool of Jaguar (JPM)[c]. In case there are two nearly equivalent protons the electrostatic transform method yields two different pK_A values. pK_A values of ECM in water that deviate by more than 1.5pH units from the corresponding pK_A values they are based on (which are ETM or JPM pK_A values in water) are considered as outliers and are marked by bold digits. The pK_A-RMSD between the predicted pK_A values in water from Jaguar and ETM is 2.75. For the prediction with Jaguar the atomic radii with pbf radii=0 are used.

No	number of atoms [d]	abbreviated name	exp. pK_A in DMSO	JPM pK_A in DMSO [e]	ETM pK_A in H_2O	ECM pK_A in H_2O based on ETM	JPM pK_A in H_2O	ECM pK_A in H_2O based on JPM
		thiourea						
1	28	thiourea19_OL8	13.40		9.96	9.60	11.34	12.00
2	62	thiourea22_OL2_H58 thiourea22_OL2_H59	11.98		9.09 8.35	8.16	11.16	10.56
3	69	thiourea23_OL4_H44 thiourea23_OL4_H45	12.39		7.81 7.80	8.59	11.02	10.99
4	48	thiourea25_OL3_H28 thiourea25_OL3_H29	13.65		10.06 9.97	9.85	11.26	12.25
5	34	thiourea_OL11_H28 thiourea_OL11_H29	10.70		6.90 6.15	6.90	**10.91**	**9.30**
6	34	thiourea_OL12	10.90		6.72	7.10	10.56	9.50
7	64	thiourea_OL14_H44 thiourea_OL14_H45	10.72		7.51 6.65	6.92	10.06	9.32
8	57	thiourea_OL15_H36 thiourea_OL15_H37	12.54		6.90 9.75	8.74	10.39	11.14
9	59	thiourea_OL16_H35 thiourea_OL16_H36	12.57		10.25 9.32	8.77	10.68	11.17
10	42	thiourea_OL17_H29	12.98		10.12	9.18	11.14	11.58
11	39	thiourea_OL18_H25 thiourea_OL18_H26	13.38		9.79 9.44	9.58	11.25	11.98
12	93	thiourea_OL20_H41 thiourea_OL20_H42	18.30		**12.40** **16.52**	**14.50**	15.16	16.90
13	69	thiourea_OL21_H30 thiourea_OL21_H31	19.60		16.40 16.24	15.80	18.38	18.20
14	31	thiourea_OL9_H25 thiourea_OL9_H26	12.10		7.48 7.07	8.30	11.49	10.70
		pK_A-RMSD relative to values without outliers in brackets			ETM in H_2O 0.82 (0.66)			JPM in H_2O 0.90 (0.68)
∑14		shift parameter ΔpK_A			3.70			1.40

[a] pK_A values taken from Ref. [51]
[b] pK_A values computed with ETM [11]
[c] pK_A values computed with the Jaguar prediction scheme [50]
[d] number of atoms refer to the protonated state.
[e] JPM pK_A values in DMSO are not available yet for these compounds (work in progress).

Table S10: Empirical pK_A estimates in water for 10 species of the molecular family cyano compounds using measured pK_A values in DMSO [a]. The results for water are compared with the electrostatic transform method [b] and the pK_A prediction tool of Jaguar (JPM)[c]. pK_A values of ECM in water that deviate by more than 1.5pH units from the corresponding pK_A values they are based on (which are ETM or JPM pK_A values in water) are considered as outliers and are marked by bold digits. The pK_A-RMSD between the predicted pK_A values in water from Jaguar and the ETM is 3.53. For the prediction with Jaguar the atomic radii with pbf radii=0 are used.

No.	number of atoms [d]	name	exp. pK_A in DMSO	JPM pK_A in DMSO [e]	ETM pK_A in H_2O (exp)	ECM pK_A in H_2O based on ETM	JPM pK_A in H_2O	ECM pK_A in H_2O based on JPM
	cyano compounds							
1	28	10-cyano-9-methylanthracene	20.00	21.87	14.37	13.60	14.97	14.00
2	27	9-cyano-dihydroanthracene	14.30	16.43	8.72	7.90	11.94	**8.30**
3	27	9-cyano-dihydrophenanthrene	21.90	22.68	16.41	15.50	15.95	15.90
4	7	$CH_2(CN)_2$	11.00	11.19	4.25 (11.2[f])	4.60	7.96	**5.00**
5	6	CH_3CN	31.30	29.33	20.89 (25.0[g])	**24.90**	19.23	**25.30**
6	16	p-cyanotoluene	30.80	29.63	23.39	24.40	19.74	**24.80**
7	16	$PhCH_2CN$	21.90	21.77	14.45	15.50	14,86	15.90
8	19	$PhCHCH_3CN$	23.00	23.18	16.95	16.60	16.05	17.00
		pK_A-RMSD relative to values without outliers in brackets		exp. in DMSO: 1.32		ETM in H_2O 1.57 (0.81)		JPM in H_2O 3.30 (0.85)
$\sum 8$		shift parameter ΔpK_A				6.40		6.00

[a] pK_A values taken from Ref. [52]
[b] pK_A values computed with ETM [11]
[c] pK_A values computed with the Jaguar prediction scheme [50]
[d] number of atoms refer to the protonated state.
[e] JPM pK_A values in DMSO are not available yet for these compounds (work in progress).
[f] pK_A values taken from Ref. [53]
[g] pK_A values taken from Ref. [54]

Table S11: Empirical pK_A estimates in water for 23 species of the molecular family keto using measured pK_A values in DMSO. The results for water are compared with the electrostatic transform method [a] and the pK_A prediction tool of Jaguar (JPM)[b]. pK_A values of ECM in water that deviate by more than 1.5pH units from the corresponding pK_A values they are based on (which are ETM or JPM pK_A values in water) are considered as outliers and are marked by bold digits. The pK_A-RMSD between the predicted pK_A values in water from Jaguar and the ETM is 2.50. For the prediction with Jaguar the atomic radii with pbf radii=0 are used.

No.	number of atoms [d]	abbreviated name	exp. pK_A in DMSO [c]	JPM pK_A in DMSO [e]	ETM pK_A in H_2O (exp)	ECM pK_A in H_2O based on ETM	JPM pK_A in H_2O	ECM pK_A in H_2O based on JPM
	keto compounds							
1	10	acetone	26.50	24.70	**18.17** (19.3[h])	**20.20**	17.55	**20.30**
2	22	N-acetyl-2-oxindole	13.80	13.00	8.32	7.20	9.47	**7.30**
3	21	2,2,5-trimethyl-1,3-dioxane-4,6-dione	7.40	6.95	**2.84**	**1.10**	4.89	**1.20**
4	27	camphor	30.40	30.95	24.27	24.10	21.96	**24.20**
5	23	$CH_2(COOC_2H_5)_2$	16.40	14.72	10.80	10.10	6.95	**10.20**
6	20	$CH_2(COCH_3)_2$	13.30	10.48	6.54	7.00	5.59	**7.10**
7	15	$CH_2CH(COCH_3)_2$	15.05	11.79	9.88	8.70	6.89	**8.80**
8	20	CH_3COCH_2Ph	19.90	19.25	13.37	13.60	15.66	**13.70**
9	17	CH_3COPh	24.70	24.59	**16.56**	**18.40**	18.05	18.50
10	23	$CH(COOCH_3)_3$	10.81 [f]	12.80	5.00	4.50	5.91	4.60
11	20	$CH(COCH_3)_3$	8.60	5.74	3.77	2.30	3.82	2.40
12	11	cyclobutanone	25.05	25.70	17.72 (20.0[i])	18.70	18.53	18.80
13	14	cyclopentanone	25.80	23.08	18.66 (18.5[j])	19.50	18.82	19.60
14	17	cyclohexanone	26.40	23.49	19.03	20.10	18.96	20.20
15	20	cycloheptanone	27.80	24.49	20.59	21.50	19.53	**21.60**
16	15	delta-valerolactone	25.20	24.49	18.72	18.90	20.11	19.00
17	22	$((CH_3)_2CH)_2C=O$	28.20	28.53	22.45	21.90	21.06	22.00
18	22	1,3-cyclopentanedione	11.20	8.77	4.93 (5,23[k])	4.90	4.71	5.00
19	20	$CH_3CH(COOCH_3)_2$	18.04 [f]	19.15	12.74	11.70	8.05	**11.80**
20	20	$CH_3COCH2CON(CH_3)_2$	18.20 [g]	16.63	12.02	11.90	7.65	**12.00**
21	20	N-methyloxindole	18.50	18.75	12.19	12.20	11.77	12.30
22	25	$PhCH_2CON(CH_3)_2$	26.60 [g]	25.80	21.26	20.30	20.09	20.40
23	18	$PhCOCH_2CN$	10.20	11.59	3.63	3.90	10.78	**4.00**
		pK_A-RMSD relative to values without outliers in brackets		exp. in DMSO: 1.85		ETM in H_2O 0.98 (0.77)		JPM in H_2O 2.68 (0.89)
∑23		shift parameter ΔpK_A				6.30		6.20

[a] pK_A values computed with ETM [11] [b] pK_A values computed with the Jaguar prediction scheme [50] [c] If not otherwise noted experimental pK_A values can be found in Ref. [52] [d] number of atoms refer to the protonated state. [e] JPM pK_A values in DMSO are not available yet for these compounds (work in progress). [f] pK_A values taken from Ref. [55] [g] value taken from Ref. [h] pK_A values taken from Ref. [56] [i] pK_A values taken from Ref. [57] [j] pK_A values taken from Ref. [58] [k] pK_A values taken from Ref. [59]

Table S12: Empirical pK_A estimates in water for 14 species of the molecular family BINOL using measured pK_A values in DMSO [a]. The results for water are compared with the electrostatic transform method [b] and the pK_A prediction tool of Jaguar (JPM)[c]. pK_A values of ECM in water that deviate by more than 1.5pH units from the corresponding pK_A values they are based on (which are ETM or JPM pK_A values in water) are considered as outliers and are marked by bold digits. The pK_A-RMSD between the predicted pK_A values in water from Jaguar and the ETM is 1.12. For the prediction with Jaguar the atomic radii with pbf radii=0 are used.

No [d]	number of atoms [e]	abbreviated name	exp. pK_A in DMSO	JPM pK_A in DMSO [f]	ETM pK_A in H_2O	ECM pK_A in H_2O based on ETM	JPM pK_A in H_2O	ECM pK_A in H_2O based on JPM
	BINOL compounds							
1	24	Binol-H_2	12.98		9.44	10.58	8.51	**10.38**
2	30	Binol-$(CH_3)_2$	11.95		8.55	9.55	8.93	11.00
3	24	Binol-F_2	10.39		7.78	7.99	7.45	9.60
4	24	Binol-Cl_2	9.78		6.61	7.38	7.15	9.30
5	24	Binol-Br_2	9.44		7.57	7.04	7.03	9.00
6	24	Binol-I_2	9.30		8.26	6.90	7.05	8.70
7	44	Binol-Ph_2	10.93		8.43	8.53	8.88	11.30
8	64	Binol(4phenyl-$Ph)_2$	10.89		8.25	8.49	8.76	11.20
9	48	Binol(4-NO_2-$Ph)_2$	9.99		8.28	7.59	7.98	10.20
10	56	Binol(3,5$(CF_3)_2$$Ph)_2$	9.68		7.70	7.28	7.75	9.40
11	56	Binol(2naphthyl$)_2$	10.73		**5.72**	**8.33**	6.68	11.20
13	77	diBinol	11.92		10.26	9.52	8.90	12.40
14	57	Vanol	10.45		6.72	8.05	8.00	11.50
		pK_A-RMSD relative to values without outliers in brackets				ETM in H_2O 1.07 (0.82)		JPM in H_2O 0.76 (0.25)
∑13		shift parameter ΔpK_A				2.40		2.60

[a] pK_A values taken from Ref. [60]
[b] pK_A values computed with ETM [11]
[c] pK_A values computed with the Jaguar prediction scheme [50]
[d] Numbers refer to the notation in Ref. [60]
[e] number of atoms refer to the protonated state.
[f] JPM pK_A values in DMSO are not available yet for these compounds (work in progress).

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