

Prototype of the Heteroaromatic Tautomers: 2-Pyridone / 2-Hydroxypyridine

Andre Ricardo Carvalho

Submitted date: 10/02/2019 • Posted date: 11/02/2019

Licence: CC BY-NC-ND 4.0

Citation information: Carvalho, Andre Ricardo (2019): Prototype of the Heteroaromatic Tautomers: 2-Pyridone / 2-Hydroxypyridine. ChemRxiv. Preprint.

In this work, we review the theoretical/experimental study progress in the classic case of a tautomeric equilibrium, 2-pyridone/2-hydroxypyridine (2-PY/2-HY), as well as original research on tautomerization reaction energetics. Our work sheds light on a matter of investigation which lasts more than a century, a challenge to the reliability of the quantum methods, especially to DFT. Our results reveal the responsible for the notable contrast between the relative stability order estimation by wavefunction (WF) and density functional (DFT) methods: The Koopmans' theorem. Among the results by Hartree-Fock, QCISD and 127 DFT functionals, our work extends on one LC functional. The estimation of the relative stability is in excellent agreement with experiments. The analogous approach for other tautomeric compounds corroborates the reliability of our description and its potential application, e.g., on the development of the molecular switches, computer-aided drug design, and new DFT functionals.

File list (2)

chemrxiv_ARCarvalho_Tautomers.pdf (582.72 KiB)

[view on ChemRxiv](#) • [download file](#)

support-information_chemrxiv_ARCarvalho_Tautomers... (150.29 KiB)

[view on ChemRxiv](#) • [download file](#)

Prototype of the heteroaromatic tautomers: 2-pyridone / 2-hydroxypyridine

A. R. Carvalho^{*,†,‡}

[†]*Available to postdoctoral position*

[‡]*Current address: Niterói, Brazil*

ORCID: 0000-0001-9756-9225

E-mail: andre_carvalho@id.uff.br

Abstract

The research on proton-transfer tautomerism has been explored over the past century due to its importance in the biological process, cheminformatics, and its potential applications, e.g., as molecular switches. Despite its apparent simplicity, an isomeric interconversion process, the theoretical calculations on the tautomeric equilibrium by ab initio and density functional theory (DFT) methods show that a quantitative agreement with the tautomerization energy is a challenge. In this work, we review the theoretical/experimental study progress in the classic case of a tautomeric equilibrium in the gas-phase, the 2-pyridone/2-hydroxypyridine (2-PY/2-HY) system, as well as we provide original research on tautomerization reaction energetics. Our results reveal Koopmans' theorem as responsible for the remarkable contrast between the relative stability order estimation by wavefunction (WF) and DFT methods. The long-range correction (LC) plays a role in the accurate description of the rotational constant ionization potential and tautomeric equilibrium of the 2-PY/2-HY system. Among the results by Hartree-Fock, QCISD and 127 DFT functionals, our work extends on the

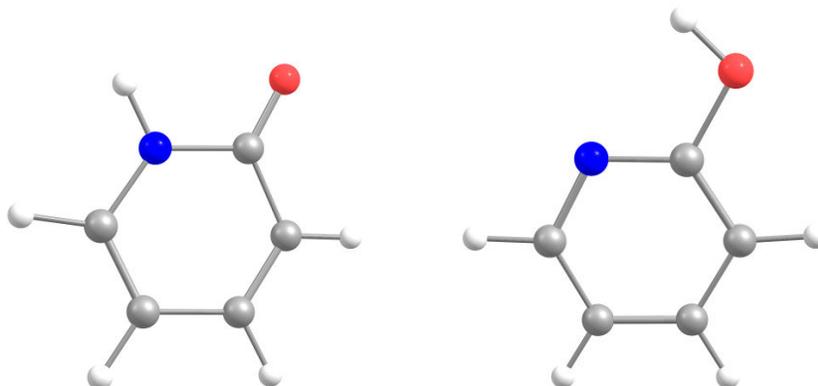
LC-TPSSP86 functional. The estimation of the relative stability is in excellent agreement with experiments. The analogous approach for other tautomeric compounds corroborates the reliability of our description and its potential application, e.g., on the development of the molecular switches, computer-aided drug design, and new DFT functionals.

1 Introduction

Tautomerism is the dynamic equilibrium between molecules with the same atomic composition, where there are a potential barrier and a relative energy small enough to allow interconversion.^{1,2} Research on tautomerism covers scientific fields ranging from chemistry, biochemistry to chemical physics. These studies are of fundamental importance in the interpretation of reaction mechanisms involving tautomers,¹ e.g., to stabilize covalent organic frameworks,³ in computer-aided drug design and their biological effects,^{4,5} as a possible factor of spontaneous mutagenesis due to the tautomeric forms of nucleic acid bases^{6,7} and as molecular switches for logic gates, diodes and transistors.^{8,9}

The 2-pyridone/2-hydroxypyridine (2-PY/2-HY) isomerization, see Scheme (1), is one of the simplest prototype systems for proton-transfer tautomerism and hydrogen bonding studies yet an important heteroaromatic system on account of: Analogous to hydrogen-bonded DNA base pairs,¹⁰ as a design element to catalysis¹¹ with a potential for self-assembly platform of bidentate ligands,¹² an emergent antitumor antiviral agent and building blocks in synthesis.¹³

A focus of investigation for more than a century,^{14,15} experimental studies of the relative stability on 2-PY/2-HY tautomerism include ultraviolet (UV),¹⁶ infrared,^{16,17} photoemission (PES)^{18,19} spectroscopies, to rotationally resolved laser induced fluorescence,²⁰ microwave²¹ spectroscopies and ion cyclotron resonance.²² The measurements of this keto-enol isomers in the gas-phase, Table (1), shows an electronic energy difference in favor of the 2-hydroxypyridine form.



Scheme 1: 2-pyridone (left) and 2-hydroxypyridine (right): Molecular structures of the prototypical model for heteroaromatic proton-transfer tautomerism. Molecular formula: C_5H_5NO .

Table 1: Experimental data: Tautomeric equilibrium of the 2-hydroxypyridine/2-pyridone in the gas-phase, argon and nitrogen matrices. The energy in kJ/mol, T in Kelvin, and [HY]:[PY] as the ratio of the concentration at equilibrium.

ΔE	ΔH	ΔG	[HY]:[PY]	T	Method	Ref.
gas ($\epsilon = 1.0$):						
-2.1(0.6)	-3.0(0.6)	-	2.2 : 1	473	Infrared	17
	1.3(1.3)	-3.3	2.5 : 1	405	UV	16
	-3.2(0.4)	-	3 : 1	356	Microwave	21
	-	5.4	-	298	Basicity	22
	-	-2.4(0.3)	2 : 1	403	X-ray PES	18
	-2.5(0.4)	-	4 : 1	323	PES	19
	-	-	2 : 1	503	Infrared	23
in Ar matrix:						
	-	-2.9(0.5)	2.80 : 1	340	Infrared	17
	-	-	3.03 : 1	303	Infrared	24
in N_2 matrix:						
	-	-	2.99 : 1	340	Infrared	17

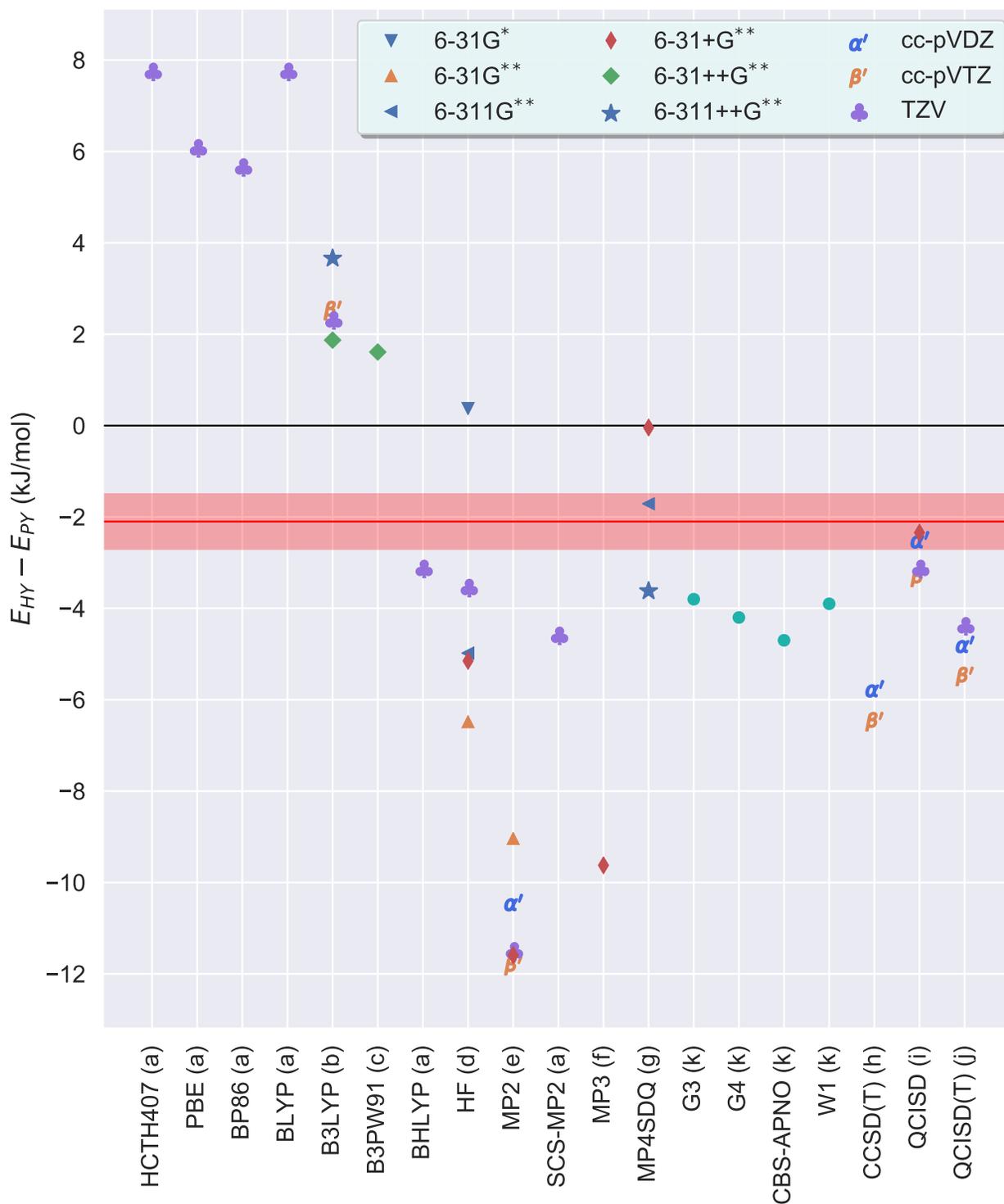
Theoretical studies performed at semiempirical, density functional theory (DFT) and ab initio level of theory have attempted to predict the relative stability of the 2-pyridone/2-hydroxypyridine system in the gas-phase.^{10,25,26} A coalescence of three decades of theoretical calculations on the tautomeric equilibrium by DFT and ab initio, Scheme (2), show that a quantitative agreement with the tautomerization energy is a challenge.

Despite methods of different levels of theory predicts the planarity in the ground-state geometries of 2-PY/2-HY isomers, as measured,^{20,21} the choice of a reliable approach is still required for an accurate relative energetic description, and we show that modeling is sensitive to the level method used to determine the structures.

The tautomerism of the 2-pyridone/2-hydroxypyridine represented a reliability test of the DFT method for the prediction of the tautomeric stabilities. The density functional theory provides good agreement with the experimental vibrational frequencies and rotational constants, but considered inherently wrong with regard to the relative stability of different tautomers.^{10,27,32,33}

The accuracy of the tautomerism energy by DFT functionals, vide Scheme (2), can be ordered as B3PW91 > B3LYP > BP86 > PBE > HCTH407 = BLYP. The hybrid DFT methods, in which the functional contains an amount of Hartree-Fock (HF) exchange, prove to be superior to pure DFT functionals HCTH407, PBE, BP86 and BLYP. The B3LYP model gives a wrong sign for ΔE , even so, provides better results than the non-hybrid ones. The BHandLYP is the only one that predicts the correct tautomeric order, the 2-hydroxypyridine molecule as the most stable form in the gas-phase. Its similar performance with HF for the tautomers of pyridone and formamide¹⁰ state that the outcome for energetic stability is due the effects of the large percentage of HF exchange in the functional. Despite the reasonable estimate, the BHandLYP functional gives rotational constants in poor agreement with the experimental values.³³

Hartree-Fock (HF) calculation gives a modest estimation of tautomeric energy with TZV(2df,2dp) basis set, albeit inferior on molecular constants.^{10,27,30} The Hartree-Fock/6-



Scheme 2: Results of three decades: Relative electronic energies, without zero point correction, of the 2-hydroxypyridine with respect to 2-pyridone in the gas-phase calculated by quantum methods. The correspondent experimental, $\Delta E = -2.1(0.6)$ kJ/mol, in red.¹⁷ Data from: (a, b, d, e, i, j),¹⁰ (b, c),²⁷ (b, e, h, i, j),²⁸ (b, g),²⁹ (d, e, f, g, i),³⁰ (g),³¹ (k).³²

311G(d,p) calculation gives a $\Delta E_{HF} = -4.97$ kJ/mol using the optimal geometry of the same method,³⁰ and $\Delta E_{HF} = -7.13$ kJ/mol when the structure used is optimized by MP2,³¹ data not included in Scheme (2). The comparison reveals that HF grossly overestimates the tautomeric energy when employed geometric parameters closer of the experimental measurements. We should expect a similar behavior from BHandLYP functional.

The second-order Moller-Plesset perturbation (MP2) method with Pople basis set which includes p-polarization functions on hydrogens or TZV(2df,2dp) overestimates the predominance of 2-hydroxypyridine in the gas-phase.^{10,30} The spin-component-scaled Moller-Plesset theory (SCS-MP2) increased the energetic accuracy compared to standard MP2 and MP3. The fourth order (MP4) proved to be the most accurate among Moller-Plesset perturbation methods, see Scheme (2), although the dependence of the basis set size on the reliability of its results to represent a disadvantage due to computational cost.

Quantum chemistry composite methods G3, G4, CBS-APNO, and W1 were employed to explain the gas- and solution-phase tautomerization reaction energetics.³² Compound techniques, combined methods with different levels of theory and basis set, led to an improvement on the estimation of the 2-PY/2-HY relative stability when compared with other post-HF methods, e.g. MP2, MP3 and CCSD(T).

Quadratic configuration interaction with single and double excitations (QCISD) method accurately predicts the energy differences in the gas-phase with basis sets cc-pVDZ and 6-31+G(d,p),^{28,30} but deviates of the experimental measurements when the basis set is increased to cc-pVTZ and TZV. Despite its accuracy to be a reference for other methods presented in Scheme (2), the QCISD method is computationally very expensive.

In this work, our study sheds light on the structural features of tautomeric systems and suggests how to proceed to predict the most stable form. The long-range-corrected (LC) exchange plays a role in the accurate description of geometrical parameters, rotational constant, dipole moment, ionization potential, energy barrier and tautomeric equilibrium of the 2-pyridone/2-hydroxypyridone. We compare the DFT results with the reference wavefunc-

tion method QCISD/aug-cc-pVTZ. In the Section 2, we present the theoretical methods, the bond distances and angles, rotational constants and dipole momentum in comparative with experimental measurements are shown in the Section 3. Among the various DFT functionals, we emphasize the TPSSP86 in the study of the rotational constants, dipole moments and tautomeric energy. The Section 4 explain how the long-range correction fixes the relative stability prediction. In the end, Section 5, we address the tautomerization energy to the 2-PY/2-HY system by several functionals and others tautomers with focus given to the relative stabilities in the gas-phase, which offers unique opportunities to review the reliability of the density functional theory method. The DELTAGAUSS software, a tool developed for the calculation of relative energies, is shown in the supporting information.

2 Computational details

We perform the calculations with GAUSSIAN 09 (G09) suite of programs that enable the reproducibility of the results provided by the same functional specification and code. Our results are by QCISD method and long-range corrected DFT functionals. Since the exchange and correlation functionals are in principle independent, we use different combinations given by concatenating the acronym of the exchange [PKZB, O, BRX, G96, TPSS, B, S, XA, PBE, PW91] with correlation functionals [B95, P86, VP86, TPSS, PKZB, PW91, BRC, LYP, PL, VWN5, KCIS, PBE], as well as the standalone [M06L, M11L, B97D, HCTH407] and exchange-only functionals [HFB, HFS, XAlpha]. The basis sets vary in complexity from 6-31++G(d,p) to aug-cc-pVQZ.

The non-Coulomb part of the functionals generally dies off too fast, i.e., becomes inaccurate at large distances, and long-range correction fixes the asymptotic limit for the exchange interaction.³⁴ The correction supplements the long-range exchange effect by replacing the Hartree-Fock exchange integral with the long-range part of exchange functionals in Kohn-Sham density functional.³⁵ We add the prefix LC- to part of the exchange to apply the

long-range correction,³⁶ where we set the LC parameter as $\omega = 0.47$, the G09 default, and other amounts as $\omega = 0.04$ with the *iop*(3/107 = 0040000000, 3/108 = 0040000000) keyword.

Our calculations are in the gas-phase and we process the results through DELTGAUSS software. Except as otherwise indicated, we optimize all structures on internal coordinates for each functional and basis set.

3 Geometric and spectroscopic data

The experimental-theoretical geometrical parameters in the solid state of 2-pyridone and 6-chloro-2-hydroxypyridine are in Tables 2 and 3, respectively, together with theoretical calculation in the gas-phase of 2-PY, 6-chloro-2-HY, and 2-HY carried out with QCISD and TPSSP86 DFT functional with and without long-range correction (LC). A theoretical-experimental comparison to the substituted hydroxypyridine allows us to estimate the validity of 2-HY geometrical parameters since is not possible to find 2-hydroxypyridine in the crystal state. The X-ray crystal results belong to hydrogen-bonded dimers while the calculations, refer to gas-phase monomers, so a variation up to 0.02 Å is expected between theory and experiment.²⁵

Geometric predictions of the 2-pyridone and 6-chloro-2-hydroxypyridine shows a good agreement with experiments, an indicative of the reliability of 2-hydroxypyridine optimal geometry. The inclusion of long-range correction with $\omega = 0.04$ in the functionals does not have a significant impact on bond lengths and angles in comparison to pure ones, whereas with $\omega = 0.47$ tend to Hartree-Fock results. The 2-PY structure predicted by QCISD is closer to HF than our chosen meta-GGA functional.

The bond lengths of the transition state (TS), see Table (4), are intermediaries between the bond distances of the 2-PY (Table (2)) and 2-HY (Table (3)). Yet, as noted by Moreno et al.,³⁹ the TS bond angles are non-intermediaries values of the two minima, wherein is necessary a significant decrease of the angle $\angle OC_1N$ to allow the intramolecular tautomerism. This

Table 2: Experimental geometrical parameters of the 2-pyridone (2-PY) in the solid phase, first column, from ref. ³⁷ Our geometric optimization results of the 2-PY (gas-phase) by QCISD, Hartree-Fock and our TPSSP86 DFT functional with aug-cc-pVTZ basis set excepting for ω' , performed with cc-pVTZ. Pure functional is the case where the long-range correction parameter is $\omega = 0$. Units: Angles in Degrees and r in Å.

	2-PY		gas (theory) 2-pyridone				
	solid (exp.)	QCISD	Pure	$\omega(0.04)$	$\omega'(0.04)$	$\omega(0.47)$	HF
$r(\text{N}-\text{C}_1)$	1.379	1.393	1.419	1.415	1.417	1.377	1.379
$r(\text{C}_1-\text{C}_2)$	1.437	1.456	1.448	1.445	1.445	1.439	1.455
$r(\text{C}_2-\text{C}_3)$	1.370	1.357	1.369	1.368	1.367	1.338	1.339
$r(\text{C}_3-\text{C}_4)$	1.416	1.433	1.424	1.421	1.422	1.418	1.435
$r(\text{C}_4-\text{C}_5)$	1.366	1.353	1.366	1.365	1.365	1.336	1.335
$r(\text{C}_1-\text{O})$	1.250	1.223	1.233	1.232	1.230	1.211	1.199
$r(\text{N}-\text{H}_1)$	1.034	1.007	1.016	1.016	1.016	1.009	0.993
$r(\text{C}_2-\text{H}_2)$	1.088	1.080	1.085	1.085	1.085	1.079	1.071
$r(\text{C}_3-\text{H}_3)$	1.088	1.082	1.088	1.088	1.088	1.082	1.074
$r(\text{C}_4-\text{H}_4)$	1.087	1.078	1.083	1.083	1.083	1.077	1.069
$r(\text{C}_5-\text{H}_5)$	1.083	1.080	1.085	1.085	1.085	1.080	1.071
$\angle \text{NC}_1\text{C}_2$	114.97	113.52	112.90	112.95	112.78	113.69	113.86
$\angle \text{C}_1\text{C}_2\text{C}_3$	121.07	121.42	121.72	121.68	121.78	121.20	120.98
$\angle \text{C}_2\text{C}_3\text{C}_4$	120.97	121.31	121.58	121.57	121.58	121.55	121.52
$\angle \text{C}_3\text{C}_4\text{C}_5$	117.77	117.89	118.09	118.06	118.03	117.72	117.58
$\angle \text{OC}_1\text{N}$	120.23	120.46	119.63	119.58	119.63	120.08	120.48
$\angle \text{H}_1\text{NC}_1$	117.95	114.69	114.27	114.11	114.00	114.30	115.11
$\angle \text{H}_2\text{C}_2\text{C}_1$	120.25	116.24	116.34	116.31	116.23	116.30	116.49
$\angle \text{H}_3\text{C}_3\text{C}_2$	119.28	119.58	119.46	119.45	119.46	119.42	119.59
$\angle \text{H}_4\text{C}_4\text{C}_3$	122.24	121.66	121.64	121.68	121.67	121.69	121.54
$\angle \text{H}_5\text{C}_5\text{C}_4$	125.62	123.50	123.66	123.63	123.60	123.24	123.03

Table 3: Experimental data, from ref.,³⁸ and theoretical (DFT) geometrical parameters of the 6-chloro-2-hydroxypyridine (6-chloro-2-HY) in solid and gas-phase, first and second column, respectively. Our calculations for 2-HY by QCISD, Hartree-Fock and TPSSP86 DFT functional with aug-cc-pVTZ basis set excepting for ω' , performed with cc-pVTZ. Pure functional is the case where the long-range correction parameter is $\omega = 0$. Units: Angles in Degrees and r in Å.

	6-chloro-2-HY		gas (theory) 2-hydroxypyridine					HF
	solid (exp.)	$\omega(0.04)$	QCISD	Pure	$\omega(0.04)$	$\omega'(0.04)$	$\omega(0.47)$	
$r(\text{N}-\text{C}_1)$	1.341	1.334	1.321	1.332	1.330	1.331	1.305	1.304
$r(\text{C}_1-\text{C}_2)$	1.393	1.398	1.400	1.402	1.400	1.400	1.383	1.394
$r(\text{C}_2-\text{C}_3)$	1.377	1.388	1.381	1.388	1.386	1.386	1.364	1.369
$r(\text{C}_3-\text{C}_4)$	1.382	1.396	1.399	1.401	1.398	1.399	1.382	1.391
$r(\text{C}_4-\text{C}_5)$	1.362	1.389	1.383	1.390	1.388	1.388	1.367	1.371
$r(\text{C}_1-\text{O})$	1.321	1.354	1.352	1.362	1.358	1.357	1.335	1.332
$r(\text{C}_5-\text{Cl})$	1.739	1.753	-	-	-	-	-	-
$r(\text{O}-\text{H}_1)$	1.009	0.977	0.964	0.977	0.977	0.977	0.965	0.944
$r(\text{C}_2-\text{H}_2)$	0.974	1.084	1.080	1.085	1.085	1.085	1.079	1.071
$r(\text{C}_3-\text{H}_3)$	0.925	1.086	1.082	1.087	1.087	1.087	1.082	1.074
$r(\text{C}_4-\text{H}_4)$	1.020	1.083	1.080	1.085	1.085	1.085	1.079	1.071
$r(\text{C}_5-\text{H}_5)$	-	-	1.083	1.088	1.088	1.088	1.083	1.074
$\angle \text{NC}_1\text{C}_2$	122.05	123.94	124.41	124.30	124.32	124.30	123.98	123.87
$\angle \text{C}_1\text{C}_2\text{C}_3$	118.44	117.10	117.35	117.26	117.26	117.28	117.31	117.26
$\angle \text{C}_2\text{C}_3\text{C}_4$	120.06	120.32	119.47	119.63	119.61	119.62	119.69	119.74
$\angle \text{C}_3\text{C}_4\text{C}_5$	116.94	116.63	117.96	118.09	118.11	118.07	117.91	117.51
$\angle \text{OC}_1\text{N}$	118.57	116.83	117.47	116.96	116.90	116.83	117.29	117.88
$\angle \text{H}_1\text{OC}_1$	116.14	106.09	106.17	105.61	105.40	105.00	106.72	108.56
$\angle \text{NC}_5\text{Cl}$	114.79	116.13	-	-	-	-	-	-
$\angle \text{H}_2\text{C}_2\text{C}_1$	117.50	120.32	119.97	120.26	120.19	120.14	119.85	120.06
$\angle \text{H}_3\text{C}_3\text{C}_2$	121.13	119.95	120.05	119.91	119.93	119.92	119.94	119.93
$\angle \text{H}_4\text{C}_4\text{C}_3$	125.23	122.45	121.51	121.37	121.39	121.39	121.55	121.67
$\angle \text{H}_5\text{C}_5\text{C}_4$	-	-	120.79	121.05	121.03	120.98	120.82	120.59

Table 4: Geometrical parameters of the 2-pyridone/2-hydroxypyridine transition state (TS) in the gas-phase. Our geometric optimizations by Hartree-Fock and TPSSP86 DFT functional with aug-cc-pVTZ basis set excepting for ω' , performed with cc-pVTZ. Pure functional is the case where the long-range correction parameter is $\omega = 0$. Units: Angles in Degrees and r in Å.

	gas (theory) transition state of 2-PY/2-HY				
	Pure	$\omega(0.04)$	$\omega'(0.04)$	$\omega(0.47)$	HF
$r(\text{N}-\text{C}_1)$	1.369	1.367	1.368	1.338	1.335
$r(\text{C}_1-\text{C}_2)$	1.410	1.407	1.408	1.393	1.403
$r(\text{C}_2-\text{C}_3)$	1.389	1.387	1.386	1.362	1.366
$r(\text{C}_3-\text{C}_4)$	1.410	1.407	1.407	1.395	1.407
$r(\text{C}_4-\text{C}_5)$	1.389	1.387	1.386	1.361	1.365
$r(\text{C}_1-\text{O})$	1.298	1.295	1.294	1.273	1.266
$r(\text{O}-\text{H}_1)$	1.383	1.382	1.382	1.353	1.330
$r(\text{N}-\text{H}_1)$	1.302	1.299	1.299	1.274	1.270
$r(\text{C}_2-\text{H}_2)$	1.084	1.084	1.084	1.078	1.069
$r(\text{C}_3-\text{H}_3)$	1.088	1.087	1.087	1.082	1.074
$r(\text{C}_4-\text{H}_4)$	1.084	1.084	1.084	1.078	1.070
$r(\text{C}_5-\text{H}_5)$	1.086	1.085	1.085	1.081	1.072
$\angle \text{NC}_1\text{C}_2$	120.19	120.17	120.05	120.38	120.75
$\angle \text{C}_1\text{C}_2\text{C}_3$	116.59	116.58	116.64	116.26	115.95
$\angle \text{C}_2\text{C}_3\text{C}_4$	122.09	122.12	122.13	122.32	122.32
$\angle \text{C}_3\text{C}_4\text{C}_5$	118.77	118.75	118.71	118.39	118.07
$\angle \text{OC}_1\text{N}$	105.34	105.40	105.50	105.58	105.16
$\angle \text{H}_1\text{OC}_1$	74.99	74.93	74.88	74.63	74.97
$\angle \text{H}_1\text{NC}_1$	75.34	75.32	75.23	75.11	74.65
$\angle \text{H}_2\text{C}_2\text{C}_1$	120.94	120.93	120.86	120.85	121.08
$\angle \text{H}_3\text{C}_3\text{C}_2$	119.02	119.00	118.99	118.93	119.00
$\angle \text{H}_4\text{C}_4\text{C}_3$	121.02	121.04	121.05	121.13	121.15
$\angle \text{H}_5\text{C}_5\text{C}_4$	123.39	123.37	123.36	123.09	122.72

profound change in the angles involved in the H-atom transfer explains the high energetic barrier of the tautomers, shown in Section 5.

Table 5: Rotational constants, in MHz, and dipole moments, in Debye, of the 2-hydroxypyridine (2-HY) and 2-pyridone (2-PY). ^(a)Exp. data from ref. ²⁷ Our theoretical results in the gas-phase by QCISD and TPSSP86 DFT functional with aug-cc-pVTZ basis set excepting for $\tilde{\omega}$ $\bar{\omega}$ and $\hat{\omega}$, performed respectively with aug-cc-pVDZ, 6-311++G(2d,2p) and aug-cc-pVQZ. The pure functional is with LC parameter $\omega = 0$.

	Exp. ^(a)	QCISD	TPSSP86						
			Pure	$\omega(0.04)$	$\omega(0.26)$	$\omega(0.47)$	$\tilde{\omega}(0.04)$	$\bar{\omega}(0.04)$	$\hat{\omega}(0.04)$
2-HY:									
<i>A</i>	5824.9459(44)	5860.42	5805.98	5822.59	5898.08	6000.60	5753.34	5813.79	5825.84
<i>B</i>	2767.5307(20)	2779.42	2752.14	2763.46	2801.38	2840.68	2741.46	2760.92	2765.35
<i>C</i>	1876.1647(17)	1885.29	1867.10	1874.03	1899.28	1927.98	1856.73	1871.95	1875.23
μ	1.39(3)	1.53	1.32	1.31	1.38	1.41	1.34	1.35	1.31
2-PY:									
<i>A</i>	5643.7585(15)	5677.58	5643.20	5664.30	5731.55	5799.52	5610.19	5654.57	5666.35
<i>B</i>	2793.47174(98)	2802.16	2767.36	2777.16	2818.72	2868.22	2751.12	2774.39	2779.48
<i>C</i>	1868.82345(99)	1876.18	1856.80	1863.50	1889.49	1919.10	1845.92	1861.20	1864.77
μ	4.26(24)	4.79	4.30	4.30	4.38	4.45	4.35	4.35	4.29

It is important to highlight the nonplanarity failures of MP2, MP3, CISD, and CCSD ab initio methods with popular basis sets on arenes,⁴⁰ which arise from an adverse intramolecular basis set incompleteness error (BSIE). Our calculations by post-HF methods with Pople basis set, of geometry by MP2/aug-cc-pVDZ, provides: 2-pyridone has at least one sizable imaginary vibrational frequency at MP2/6-311G ($225i$ cm⁻¹, A^{''}; $65i$ cm⁻¹, A^{''}), MP3/6-311++G ($798i$ cm⁻¹, A^{''}; $39i$ cm⁻¹, A^{''}), MP4/6-311++G ($838i$ cm⁻¹, A^{''}; $161i$ cm⁻¹, A^{''}); on 2-hydroxypyridine gives: MP2/6-311++G ($559i$ cm⁻¹, A^{''}), MP3/6-311++G ($471i$ cm⁻¹, A^{''}), MP4/6-311++G ($533i$ cm⁻¹, A^{''}). Independent of the method applied to 2-PY/2-HY system, the correlation-consistent (aug)-cc-pVXZ basis sets, that provide the necessary BSIE balance,⁴⁰ are good choices in this regard.

The microwave spectroscopic study of the 2-PY/2-HY equilibrium in the gas-phase provided both the rotational constants and the dipole moments for the two isomers in question.²⁷ The spectroscopic data are presented in Table (5) along with the predicted quantities

Table 6: Spectroscopic data of the 2-hydroxypyridine (2-HY) and 2-pyridone (2-PY). A , B and C are rotational constants in megahertz; μ , dipole moment in Debye, ^(a)experimental data from ref. ²⁷ Our theoretical results in the gas-phase by TPSSP86 DFT functional with may-, jun-, jul-, aug- cc-pVTZ basis sets. The long-range correction parameter $\omega = 0.04$.

	Exp. ^(a)	LC-TPSSP86 $\omega(0.04)$				
		cc-	may-cc-	jun-cc-	jul-cc-	aug-cc-
2-HY:						
A (MHz)	5824.9459(44)	5822.26	5821.94	5822.00	5822.81	5822.59
B (MHz)	2767.5307(20)	2764.70	2763.14	2763.20	2763.49	2763.46
C (MHz)	1876.1647(17)	1874.57	1873.82	1873.85	1874.06	1874.03
μ (D)	1.39(3)	1.17	1.33	1.31	1.31	1.31
2-PY:						
A (MHz)	5643.7585(15)	5665.31	5663.78	5663.79	5664.40	5664.30
B (MHz)	2793.47174(98)	2775.89	2776.43	2776.81	2777.37	2777.16
C (MHz)	1868.82345(99)	1863.04	1863.12	1863.29	1863.61	1863.50
μ (D)	4.26(24)	4.15	4.35	4.30	4.30	4.30

at QCISD and DFT level. We note a better accordance between experiments and theory with the inclusion of the long-range correction with parameter $\omega = 0.04$. The root-mean-square errors (r.m.s) of the theoretical rotational constants in Table (5) for 2-hydroxypyridine are 22, 15, 3 and 114 MHz by QCISD, pure TPSSP86, LC-TPSSP86 with $\omega = 0.04$ and $\omega = 0.47$, respectively, while for 2-PY the r.m.s are 21, 17, 15 and 104 MHz.

Rotational constant results with $\omega = 0.04$ parameter long-range exchange exceed the accuracies of our computation by QCISD/aug-cc-pVTZ and MP2 approaches with Pople basis set, cf. MP2 results.^{27,31} As the parameter ω increases, the estimated constants tend to be closer to that predicted by HF²⁷ overestimating the rotational constants of the 2-PY/2-HY molecules. The inclusion of diffuse functions gives a significant improvement in the dipole moment of the 2-hydroxypyridine, see Table (6), and thereby plays a relevant role on solvation. Accurate calculations of electrical properties also need augmented basis sets for accurate calculations.⁴¹ The addition of the dispersion function in the basis set, especially aug-cc-pVTZ, provides reliable results with a small difference to the given by a bigger basis set, aug-cc-pVQZ, indicating a quick convergence to the same value of the complete basis set (CBS) limit with respect to geometric parameters, dipole moment and rotational constants.

Table 7: Theoretical results of the rotational constants and dipole moment of the 2-hydroxypyridine (2-HY) and 2-pyridone (2-PY) in the gas-phase. Our calculations by exchange-correlation (Exc-Cor) energy functionals in density functional theory (DFT) with aug-cc-pVTZ basis and long-range correction parameter $\omega = 0.04$.

Exchange:	TPSS			B		BRX	
Correlation:	PKZB	TPSS	PW91	KCIS	PW91	KCIS	PW91
2-HY:							
A (MHz)	5829.13	5830.77	5835.48	5825.15	5827.14	5820.53	5822.47
B (MHz)	2765.08	2766.05	2767.65	2759.97	2763.96	2754.71	2758.64
C (MHz)	1875.45	1876.07	1877.29	1872.69	1874.73	1869.79	1871.80
μ (D)	1.29	1.28	1.30	1.22	1.23	1.26	1.28
2-PY:							
A (MHz)	5671.02	5672.78	5676.32	5662.54	5666.71	5654.50	5658.34
B (MHz)	2778.75	2779.53	2781.76	2773.99	2777.22	2772.32	2775.40
C (MHz)	1864.95	1865.49	1866.87	1861.88	1863.79	1860.26	1862.06
μ (D)	4.28	4.27	4.29	4.21	4.27	4.34	4.36

Predictions by LC-TPSSP86 functional, $\omega = 0.04$, with aug-cc-pVDZ and 6-31++G(d,p) basis sets underestimates the rotational constants in comparative to experiments, Table (5). The results with 6-311++G(2d,2p) basis set, indicated by cost-effective for optical rotation calculations of two simple chiral molecules,^{42,43} agree to the aug-cc-pVTZ, but as will see in Section 5 the same augmented Pople basis to overestimate the tautomeric energy.

4 The Koopmans' theorem

The HOMO energy (ε_{HOMO}) and ionization potential (IP) are the most important quantities to explain why the pure DFT prediction, shown in Scheme (2), is inherently wrong with regard to the relative stability of the proton-transfer tautomerism. The energy difference between the neutral and radical species without the geometric relaxation upon electron subtraction defines the vertical ionization potential (vIP). The vIPs are determined to be 879.10 and 831.72 kJ/mol for 2-hydroxypyridine and 2-pyridone, respectively.⁴⁴

The vertical IPs of the 2-hydroxypyridine and 2-pyridone by TPSSP86 with several long-range correction parameters, shown in Table (8). The same functional with $\omega = 0.00$ (pure)

Table 8: Theoretical and experimental vertical ionization potentials (vIP) of the 2-hydroxypyridine (2-HY) and 2-pyridone (2-PY). Our results in the gas-phase by QCISD and TPSSP86 DFT functional with aug-cc-pVTZ basis sets. The calculations are in kJ/mol and from relaxed geometry, except for ω^* , wherein the long-range correction parameter $\omega = 0.04$ define the structures. The $\Delta(\text{vIP}_{\text{teo-exp}})$ is the accuracy of our results, cf. exp. data of the ref.,⁴⁴ and $\varepsilon_{\text{HOMO}}$ is the HOMO energy. When $\Delta K_{\text{teo}} = 0$, fulfill Koopmans’ theorem. $(E_{\text{HY}} - E_{\text{PY}})$ is the estimated tautomeric energy, cf. $\Delta E_{\text{exp}} = -2.1(6)$ kJ/mol. $\Delta\varepsilon_{\text{HOMO}}$ is the difference between the $-\varepsilon_{\text{HOMO}}$ of each tautomer.

	$-\varepsilon_{\text{HOMO}}$	vIP_{teo}	$\Delta(\text{vIP}_{\text{teo-exp}})$	ΔK_{teo}	$\parallel (E_{\text{HY}} - E_{\text{PY}})$	$\Delta\varepsilon_{\text{HOMO}}$
2-HY:						
$w(0.00)$	583.84	856.80	-22.30	272.96	5.70	42.79
$w(0.04)$	640.83	856.76	-22.34	215.93	4.69	42.83
$w(0.26)$	873.42	888.89	9.79	15.47	-1.30	48.43
$w(0.47)$	953.21	901.81	22.71	-51.40	-1.20	47.27
$w^*(0.25)$	867.06	887.17	8.06	20.11	-1.49	49.81
$w^*(0.26)$	873.31	888.32	9.20	15.01	-1.65	50.15
$w^*(0.47)$	951.51	899.16	20.06	-52.35	-2.66	52.50
QCISD	871.73	868.04	-11.06	-3.69	-1.50	36.47
HF	870.54	746.75	-132.35	123.79	-3.28	32.36
2-PY:						
$w(0.00)$	541.05	810.15	-21.57	269.10		
$w(0.04)$	598.00	810.08	-21.64	212.08		
$w(0.26)$	824.99	840.25	8.53	15.26		
$w(0.47)$	905.94	855.37	23.65	-50.57		
$w^*(0.25)$	817.25	836.73	5.01	19.48		
$w^*(0.26)$	823.16	837.70	5.98	14.54		
$w^*(0.47)$	899.01	846.26	14.54	-52.75		
QCISD	835.26	822.48	-9.24	-12.78		
HF	838.18	693.85	-137.87	144.33		

and $\omega = 0.04$ yields good structures (Section 3) but underestimates the vIP, while the predictions with relaxed structures by $\omega = 0.26$ and $\omega = 0.47$ overestimates the measurements. We achieve the smallest deviation in $\Delta(\text{vIP}_{\text{teo-exp}})$ by $\omega^* = 0.25$ and $\omega^* = 0.26$ where the asterisk means that we calculate from a reliable geometry, i.e., with $\omega = 0.04$. Koopmans’ theorem, which states $\text{IP} = -\varepsilon_{\text{HOMO}}$, allows us a comparison between the first ionization energy and the orbital energy of the highest occupied molecular orbital (HOMO). We define $\Delta K_{\text{teo}} = \text{IP} + \varepsilon_{\text{HOMO}}$, in which $\Delta K_{\text{teo}} = 0$ fulfill Koopmans’ theorem. The pure TPSSP86 functional or with a small long-range parameter, $\omega = 0.04$, presents the largest deviations of

the theorem, while the increment in ω , especially $\omega^* = 0.26$, tend to fulfill. The reason why long-range correction enhances the reproducibility of HOMO energy is due to the orbital energies almost constant for fractional occupied orbitals.^{35,45,46}

QCISD method results as well exhibits small ΔK_{teo} . Despite the large deviation of the ΔK_{teo} by Hartree-Fock calculation, in the account of wrong vIP prediction, the $-\varepsilon_{HOMO}$ is close to the experimental vIP what explains the correct order estimation on the relative stability of the 2-PY/2-HY tautomeric forms.

The difference between the $-\varepsilon_{HOMO}$ of each tautomer, $\Delta\varepsilon_{HOMO}$, reveals the other piece of the puzzle for a quantitative estimation of the relative stability. We highlight the robust correlation between $\Delta\varepsilon_{HOMO}$ and ΔE results by DFT in Table (8). Despite LC-TPSSP86 with $\omega^* = 47$ dissatisfy the Koopmans' theorem, the long-range exchange interaction pushes the orbitals up consistently, while the ΔE cancels the total energy error. The use of reliable structures becomes the key to this achievement. The same argument explains why $\Delta E_{\omega^*=25}$, calculation from a good structure ($\omega = 0.04$), is closer to experimental results than $\Delta E_{\omega=26}$, albeit the $\omega^* = 25$ to provide a bigger deviation in ΔK_{teo} .

5 Tautomeric energies

Various levels of theory was applied to estimate the tautomeric energy of the 2-pyridone and 2-hydroxypyridine, but none of the methods shown a quantitative result of the relative stability, see Scheme (2). We report in Table (9) the relative energies at 298 K considering the effect of basis set and long-range exchange interaction on 2-PY/2-HY system. The total energies is in Table (10). The inclusion of the long-range parameter $\omega^* = 0.26$ ($\omega^* = 0.47$) in TPSSP86/aug-cc-pVTZ yields a relative energy $\Delta E_{\omega^*(0.26)} = -1.65$ kJ/mol ($\Delta E_{\omega^*(0.47)} = -2.66$) in excellent agreement with experimental measurements $\Delta E_{exp} = -2.1(0.6)$ kJ/mol, where the asterisk means the use of geometric data close to the empirical one, i.e., by the inclusion of $\omega = 0.04$. When we use structures by LC-parameter $\omega = 0.47$, the G09

Table 9: Relative energies in kJ/mol from the relaxed geometry of the 2-pyridone (2-PY) \rightarrow 2-hydroxypyridine (2-HY), except for ω^* , wherein we calculate the structures with long-range correction parameter $\omega = 0.04$. Experimental data from ^(a) ref. ¹⁷ and ^(b) ref. ²¹ Our theoretical results in gas-phase at room temperature (298.15 K) by QCISD, Hartree-Fock and TPSSP86 DFT functional with aug-cc-pVTZ basis set excepting for $\tilde{\omega}$ and $\bar{\omega}$, performed respectively with aug-cc-pVDZ and 6-311++G(2d,2p). Pure functional: $\omega = 0$.

	Exp.	QC	TPSSP86						HF
			Pure	$\omega^*(0.26)$	$\omega^*(0.47)$	$\omega(0.47)$	$\tilde{\omega}^*(0.47)$	$\bar{\omega}^*(0.47)$	
ΔE	-2.1(0.6) ^(a)	-1.5	5.70	-1.65	-2.66	-1.20	-4.07	-4.06	-3.28
ΔH	-3.2(0.4) ^(b)		4.97	-2.45	-3.65	-2.27	-4.98	-4.77	-4.38
ΔG	-2.9(0.5) ^(a)		5.49	-2.10	-3.34	-1.79	-4.66	-4.38	-3.84
Δzpc	-0.9 ^(a)		-0.57	-0.69	-0.86	-0.94	-0.77	-0.53	-0.94
ΔE^z			5.13	-2.34	-3.52	-2.14	-4.85	-4.60	-4.22
$-T\Delta S$			0.52	0.35	0.31	0.49	0.32	0.39	0.54
ΔE^\ddagger			138.81	130.83	151.17	151.18			210.05
ΔH^\ddagger			124.99	117.60	136.80	137.28			194.69
ΔG^\ddagger			126.20	118.75	137.82	138.54			195.94

Table 10: Total energies in Hartrees from the relaxed geometry of the 2-pyridone (2-PY) \rightarrow 2-hydroxypyridine (2-HY), except for ω^* , wherein we calculate the structures with long-range correction parameter $\omega = 0.04$. Our theoretical results in gas-phase by QCISD, Hartree-Fock and TPSSP86 DFT functional with aug-cc-pVTZ basis set. Pure functional: $\omega = 0$.

	QC	TPSSP86				HF
		Pure	$\omega^*(0.26)$	$\omega^*(0.47)$	$\omega(0.47)$	
E_{PY}	-322.93729	-323.84142	-323.33217	-323.22828	-323.23218	-321.68730
E_{HY}	-322.93786	-323.83924	-323.33280	-323.22930	-323.23263	-321.68855

default, we get a decline on the relative stability $\Delta E_{\omega(0.47)} = -1.20$ kJ/mol, a non-intuitive result, since we would expect a tendency of a larger ω to the Hartree-Fock/aug-cc-pVTZ estimation, $\Delta E_{HF} = -3.28$ kJ/mol. Another notable effect of the long-range correction is on energy barrier, without zero-point energy, where our calculations establish an interval $\Delta E^\ddagger = [130.83 - 151.17]$ kJ/mol by $\omega^* = 0.26$ and $\omega^* = 0.47$, both parameters within the experimental accuracy of tautomeric energy ΔE .

The deviation of the energy values in Table (11) for not full augmented basis sets, e.g. jul-cc-pVTZ, that remove the diffuse function from hydrogens from aug-cc-pVTZ, is small in respect to full one. These basis sets also give good concordance with aug-cc-pVTZ on rota-

Table 11: Relative energies in kJ/mol of the 2-hydroxypyridine (2-HY) and 2-pyridone (2-PY). Experimental data: $^{(a)}\Delta E$ from ref. ¹⁷ $^{(b)}\Delta H$ at 356 K from ref. ²¹ and $^{(a)}\Delta G$ at 340 K. Our theoretical results in the gas-phase at 356 Kelvin by TPSSP86 DFT functional with may-, jun-, jul-, aug- cc-pVTZ basis sets. The long-range correction parameter is $\omega^* = 0.47$ from the geometry with $\omega = 0.04$.

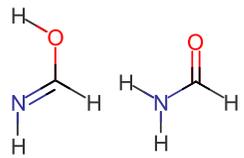
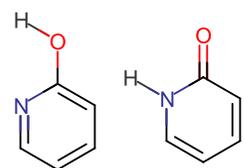
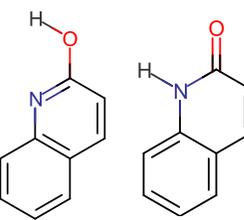
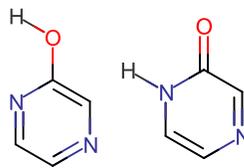
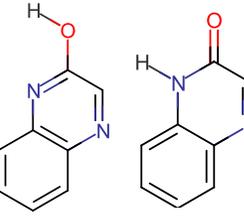
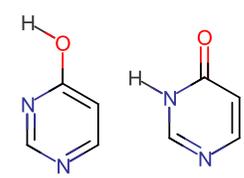
	Exp.	LC-TPSSP86 $\omega^*(0.47)$				
		cc-	may-cc-	jun-cc-	jul-cc-	aug-cc-
ΔE	$-2.1(0.6)^{(a)}$	-2.88	-3.09	-2.78	-2.72	-2.66
ΔH	$-3.2(0.4)^{(b)}$	-3.83	-4.00	-3.71	-3.68	-3.65
ΔG	$-2.9(0.5)^{(a)}$	-3.39	-3.59	-3.32	-3.30	-3.27
Δzpc	$-0.9^{(a)}$	-0.79	-0.76	-0.79	-0.83	-0.86
ΔE^z		-3.66	-3.85	-3.57	-3.55	-3.52
$-T\Delta S$		0.43	0.40	0.39	0.39	0.38

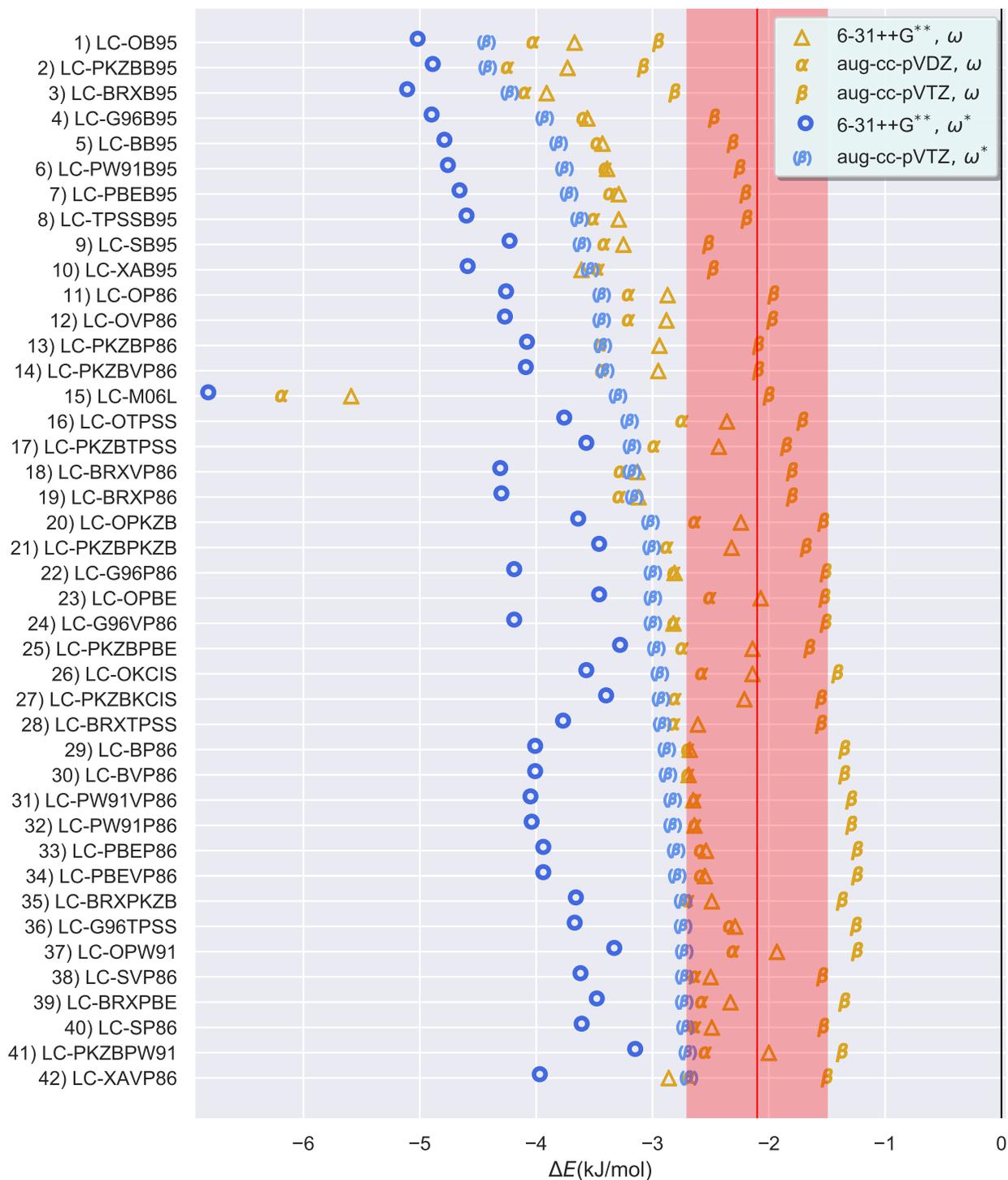
tional and dipole moments as shown in Table (6). We get a clear trend of the overestimation of the 2-HY stability in absence of diffuse functions of the basis set for $\omega^* = 0.47$.

To test if the reproduction of the experimental data on 2-PY/2-HY system by our model is only a particular case, we carry out an analogous approach for other proton-transfer tautomeric compounds. In Table (12) we compare the results of such computations with experimental measurements. There is an excellent concordance on relative stability prediction in the gas-phase for formamide, 2-pyridone, 2-quinolinone, 2-pyrazinone, 2-quinoxalinone and 4-pyrimidinone at their respective temperatures by LC-TPSSP86/aug-cc-pVTZ with long-range parameter $\omega^* = 0.26$ and $\omega^* = 0.47$, where the asterisk means the use of a structure close to the pure DFT functional evaluation, i.e., $\omega = 0.04$. These excellent results corroborate the reliability of our model.

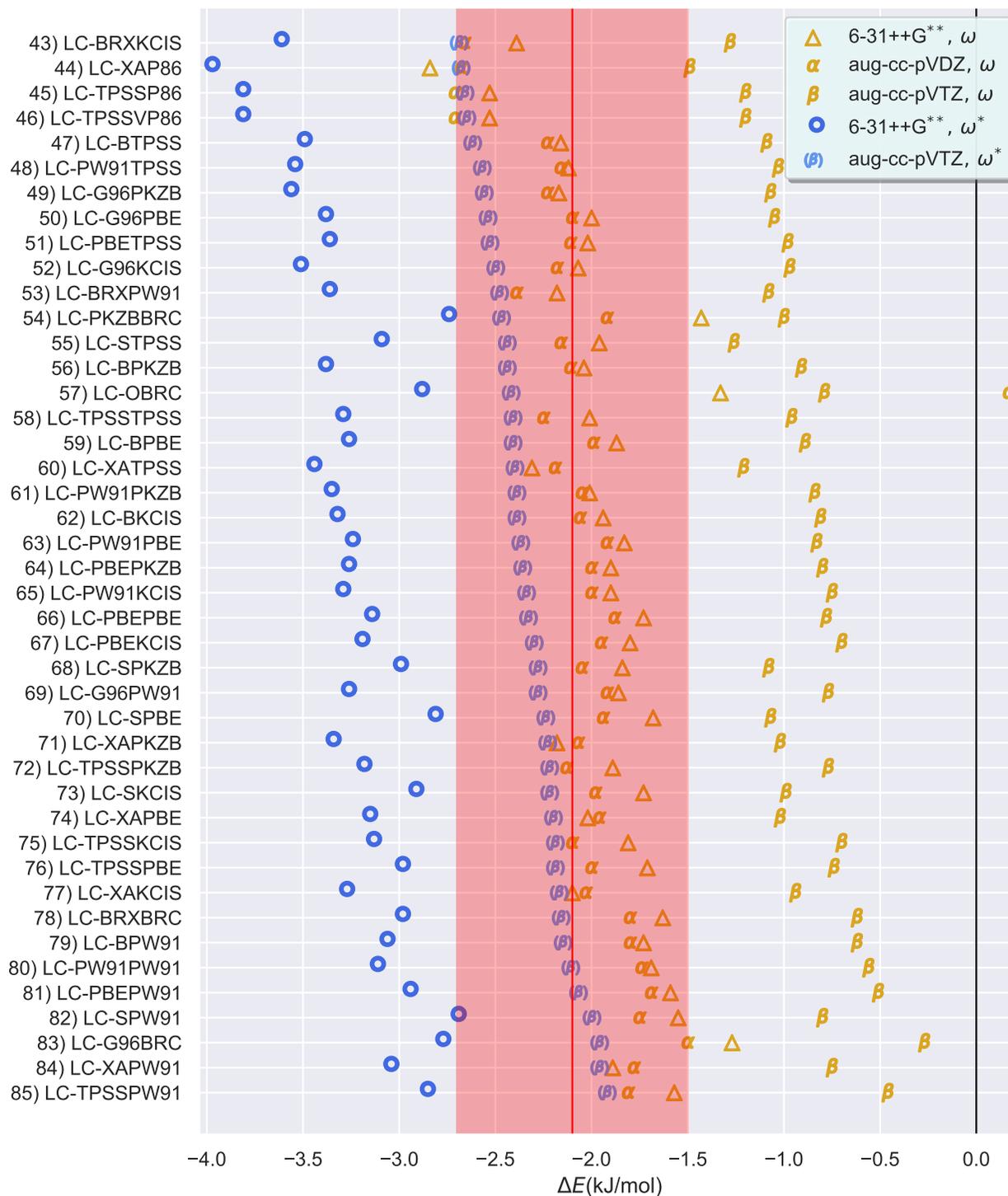
The Schemes 3, 4 and 5 coalesce the estimation of the relative energy by our list of functionals in Section 2. We highlight in Table (13) the excellent agreement of the ΔE by some LC functionals with $\omega^* = 0.47$, in which the asterisk means the use of structures with $\omega^* = 0.04$ that shows a good concordance to the measured rotational constant, see Table (7).

Table 12: Theoretical and experimental tautomeric equilibrium of the hydroxy (left) and oxo (right) forms at the respective temperature, in Kelvin. Our results by LC-TPSSP86/aug-cc-pVTZ with $\omega^* = 0.26$ at the top and $\omega^* = 0.47$ in brackets, see text. Experimental data of the formamide from ref.,²⁵ 2-pyridone from ref.,¹⁷ and from ref.²⁸ for the 2-quinolinone, 2-pyrazinone, 2-quinoxalinone and 4-pyrimidinone. Energies in kJ/mol.

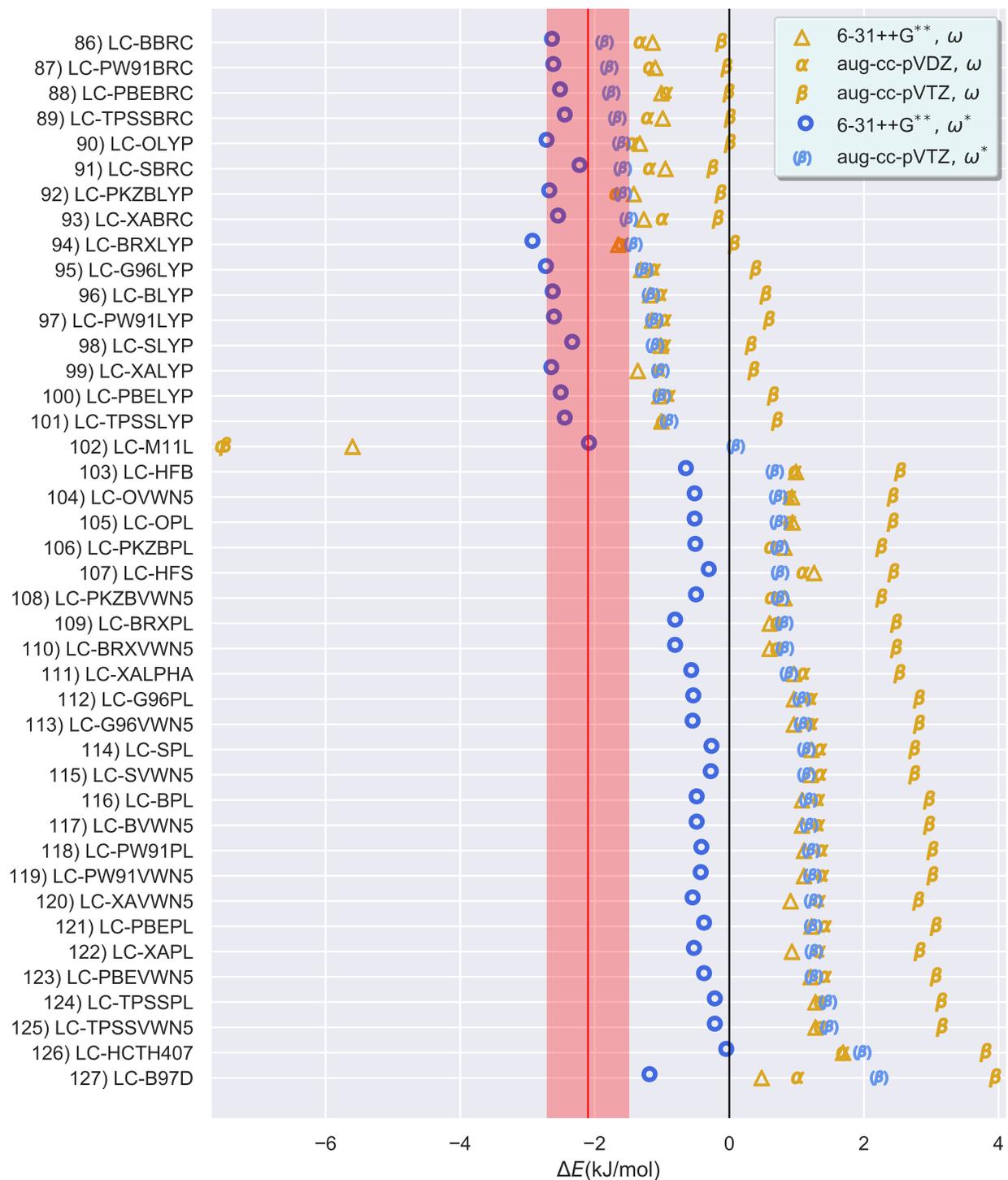
Tautomers	Theoretical			T	Experimental		
	ΔE	ΔG	[hy]:[oxo]		ΔE	ΔG	[hy]:[oxo]
	48.52 [51.79]	50.73 [53.40]	$1 : 77 \cdot 10^7$ $[1 : 23 \cdot 10^8]$	298	46.0(16.7)	—	—
	-1.65 [-2.66]	-2.05 [-3.29]	2.1 : 1 [3.2 : 1]	340	-2.1(0.6)	-2.9(0.5)	2.8 : 1
	16.19 [18.43]	15.77 [17.89]	1 : 68 [1 : 120]	450	—	17(1.5)	1 : 95
	-6.49 [-7.64]	-6.79 [-8.38]	9.7 : 1 [16 : 1]	360	—	-8.0(1.0)	14 : 1
	13.49 [16.17]	13.18 [15.61]	1 : 34 [1 : 65]	450	—	14(1.0)	1 : 40
	2.93 [2.80]	2.76 [2.29]	1 : 2.3 [1 : 2.0]	400	—	2.4(0.3)	1 : 2.1



Scheme 3: Our benchmark: Relative electronic energies, without zero point correction, of the 2-hydroxypyridine with respect to 2-pyridone in the gas-phase calculated by LC- functionals with $\omega = 0.47$, basis set in the legend. The asterisk on the ω^* means the calculation over geometric optimizations with long-range parameter $\omega = 0.04$. The correspondent experimental $\Delta E = -2.1(0.6)$ kJ/mol in red.¹⁷



Scheme 4: Our benchmark: Relative electronic energies, without zero point correction, of the 2-hydroxypyridine with respect to 2-pyridone in the gas-phase calculated by LC- functionals with $\omega = 0.47$, basis set in the legend. The asterisk on the ω^* means the calculation over geometric optimizations with long-range parameter $\omega = 0.04$. The correspondent experimental $\Delta E = -2.1(0.6)$ kJ/mol in red.¹⁷



Scheme 5: Our benchmark: Relative electronic energies, without zero point correction, of the 2-hydroxypyridine with respect to 2-pyridone in the gas-phase calculated by LC- functionals with $\omega = 0.47$, basis set in the legend. The asterisk on the ω^* means the calculation over geometric optimizations with long-range parameter $\omega = 0.04$. The correspondent experimental $\Delta E = -2.1(0.6)$ kJ/mol in red.¹⁷

Table 13: Relative energies in kJ/mol from geometry, with LC parameter $\omega = 0.04$, of the 2-hydroxypyridine and 2-pyridone in the gas-phase. Our calculations by exchange-correlation (Exc-Cor) energy functionals in density functional theory (DFT) with an aug-cc-pVTZ basis set and a long-range correction parameter $\omega^* = 0.47$. ^(a)Experimental data from ref. ¹⁷

	Exp. ^(a)	Exc: Cor:	TPSS			B		BRX	
			PKZB	TPSS	PW91	KCIS	PW91	KCIS	PW91
ΔE	-2.1(0.6)		-2.22	-2.41	-1.92	-2.39	-2.15	-2.69	-2.48

6 Summary and outlook

In this work, we review the theoretical/experimental study progress in the classic case of a tautomeric equilibrium, 2-pyridone/2-hydroxypyridine (2-PY/2-HY), as well as original research on tautomerization reaction energetics. Our work sheds light on a matter of investigation which lasts more than a century, a challenge to the reliability of the quantum methods, especially to DFT. In our literary review, the QCISD method yielded the most accurate result, while the other wavefunction methods, including CCSD, tended to overestimate the predominance of the hydroxy form in the gas-phase. On the other hand, the pure density functional methods estimated the oxo form as the most stable, contradictory to the experimental measurements. Our results reveal the responsible for the notable contrast between the relative stability order estimation by wavefunction (WF) and density functional (DFT) methods: The Koopmans’ theorem. The WF methods, especially post-Hartree-Fock with large bases sets, reach a satisfactory level of reproducibility on the calculation of ionization potential (IP) and orbital energies (ε), i.e., tend to fulfill the theorem, while pure DFT calculations provide poor ε .

A well-known failure in DFT calculation is the band gap underestimation in insulating materials and semiconductors, known as the "band-gap problem". The inclusion of the long-range correction (LC) in some DFT functionals gives the orbital energies close to the minus IPs, where in our case it leads to an improvement on the estimation of the 2-PY/2-HY relative stability. But, our calculations with LC functionals shows the significant impact

on bond lengths and angles in comparison to pure ones, especially for long-range parameter $\omega = 0.47$, wherein tend to Hartree-Fock geometry computation. In contrast to what we find in the literature for 2-PY/2-HY tautomerism, the relative energy is sensitive to geometry which in turn is susceptible to the theoretical method. Among the results of 127 functionals, our work extends on the LC-TPSSP86. The inclusion of the long-range parameter $\omega = 0.04$ gives excellent geometric parameters and the smaller root-mean-square errors on rotational constants in the comparison between pure DFT, MP2 and QCISD methods. The estimation of the relative stability by LC-TPSSP86 with $\omega = 0.26$ to $\omega = 0.47$ on such good geometries, i.e., $\omega = 0.04$, yields excellent agreement with experiments. Despite the computation with $\omega = 0.47$ does not satisfy the Koopmans' theorem, the long-range exchange interaction pushes the orbitals up consistently, while the ΔE cancels the total energy error. Besides the reproduction of the experimental data on 2-PY/2-HY case, our computations also show excellent concordance on relative stability assess in gas-phase of the formamide, 2-quinolinone, 2-pyrazinone, 2-quinoxalinone and 4-pyrimidinone at their respective temperatures. The analogous approach for other proton-transfer tautomeric compounds corroborates the reliability of our description and its potential application. We hope this review and original research can collaborate in the development of the molecular switches, computer-aided drug design, and new DFT functionals.

Acknowledgement

The author is thankful to professor J. W. D. Cordeiro for his financial support and permission to use of the computer cluster.

References

- (1) Elguero, J.; Katritzky, A. R.; Denisko, O. Prototropic Tautomerism of Heterocycles: Heteroaromatic Tautomerism - General Overview and Methodology. *Advances in Het-*

- erocyclic Chemistry* **2000**, *76*, 1–84.
- (2) Raczyńska, E. D.; Kosińska, W.; Ośmiałowski, B.; Gawinecki, R. Tautomeric Equilibria in Relation to Pi-Electron Delocalization. **2005**,
 - (3) Xu, H.; Gao, J.; Jiang, D. Stable, crystalline, porous, covalent organic frameworks as a platform for chiral organocatalysts. *Nature Chemistry* **2015**, *7*, 905–912.
 - (4) Pospisil, P.; Ballmer, P.; Scapozza, L.; Folkers, G. Tautomerism in ComputerAided Drug Design. *Journal of Receptors and Signal Transduction* **2003**, *23*, 361–371.
 - (5) Martin, Y. C. Let's not forget tautomers. *Journal of computer-aided molecular design* **2009**, *23*, 693–704.
 - (6) Wang, W.; Hellinga, H. W.; Beese, L. S. Structural evidence for the rare tautomer hypothesis of spontaneous mutagenesis. *Proceedings of the National Academy of Sciences of the United States of America* **2011**, *108*, 17644–8.
 - (7) Florián, J.; Leszczyński, J. Spontaneous DNA Mutations Induced by Proton Transfer in the Guanine·Cytosine Base Pairs: An Energetic Perspective. *Journal of the American Chemical Society* **1996**, *118*, 3010–3017.
 - (8) Liljeroth, P.; Repp, J.; Meyer, G. Current-Induced Hydrogen Tautomerization and Conductance Switching of Naphthalocyanine Molecules. *Science* **2007**, *317*, 1203–1206.
 - (9) Zhang, J. L.; Zhong, J. Q.; Lin, J. D.; Hu, W. P.; Wu, K.; Xu, G. Q.; Wee, A. T. S.; Chen, W. Towards single molecule switches. *Chemical Society Reviews* **2015**, *44*, 2998–3022.
 - (10) Piacenza, M.; Grimme, S. Systematic quantum chemical study of DNA-base tautomers. *Journal of Computational Chemistry* **2004**, *25*, 83–99.

- (11) Moore, C. M.; Dahl, E. W.; Szymczak, N. K. Beyond H₂: exploiting 2-hydroxypyridine as a design element from [Fe]-hydrogenase for energy-relevant catalysis. *Current Opinion in Chemical Biology* **2015**, *25*, 9–17.
- (12) Reetz, M. T. Combinatorial Transition-Metal Catalysis: Mixing Monodentate Ligands to Control Enantio-, Diastereo-, and Regioselectivity. *Angewandte Chemie International Edition* **2008**, *47*, 2556–2588.
- (13) Torres, M.; Gil, S.; Parra, M. New Synthetic Methods to 2-Pyridone Rings. *Current Organic Chemistry* **2005**, *9*, 1757–1779.
- (14) Baker, F.; Baly, E. C. C. C. VI. The relation between absorption spectra and chemical constitution. Part VII. Pyridine and some of its derivatives. *J. Chem. Soc., Trans.* **1907**, *91*, 1122–1132.
- (15) Meyer, H. Über reziproke sterische Beeinflussungen. *Monatshefte für Chemie* **1905**, *26*, 1303–1310.
- (16) Beak, P.; Fry, F. S.; Lee, J.; Steele, F. Equilibration studies. Protomeric equilibria of 2- and 4-hydroxypyridines, 2- and 4-hydroxypyrimidines, 2- and 4-mercaptopyridines, and structurally related compounds in the gas phase. *Journal of the American Chemical Society* **1976**, *98*, 171.
- (17) Nowak, M. J.; Lapinski, L.; Fulara, J.; Les, A.; Adamowicz, L. Matrix isolation IR spectroscopy of tautomeric systems and its theoretical interpretation: 2-hydroxypyridine/2(1H)-pyridinone. *The Journal of Physical Chemistry* **1992**, *96*, 1562–1569.
- (18) Brown, R. S.; Tse, A.; Vederas, J. C. Photoelectron-determined core binding energies and predicted gas-phase basicities for the 2-hydroxypyridine .dblarw. 2-pyridone system. *Journal of the American Chemical Society* **1980**, *102*, 1174–1176.

- (19) Guimon, C.; Garrabe, G.; Pfister-Guillouzo, G. Spectroscopie photoelectronique a temperature variable equilibre prototropique des hydroxy-2 et mercapto-2 pyridines (1). *Tetrahedron Letters* **1979**, *20*, 2585–2588.
- (20) Held, A.; Champagne, B. B.; Pratt, D. W. Inertial axis reorientation in the S1 S0 electronic transition of 2pyridone. A rotational Duschinsky effect. Structural and dynamical consequences. *The Journal of Chemical Physics* **1991**, *95*, 8732–8743.
- (21) Hatherley, L. D.; Brown, R. D.; Godfrey, P. D.; Pierlot, A. P.; Caminati, W.; Damiani, D.; Melandri, S.; Favero, L. B. Gas-phase tautomeric equilibrium of 2-pyridinone and 2-hydroxypyridine by microwave spectroscopy. *Journal of Physical Chemistry* **1993**, *97*, 46–51.
- (22) Aue, D. H.; Betowski, L. D.; Davidson, W. R.; Bowers, M. T.; Beak, P.; Lee, J. Gas-phase basicities of amides and imidates. Estimation of protomeric equilibrium constants by the basicity method in the gas phase. *Journal of the American Chemical Society* **1979**, *101*, 1361–1368.
- (23) Levin, E. S.; Rodionova, G. N. Tautomeric studies on lactams in the vapour state by infrared spectroscopy. *Dokls Akad. Nauk* **1965**, *164*, 910.
- (24) Smets, J.; Maes, G. Matrix-isolation FT-IR study on the protomeric tautomerism 2-hydroxypyridine2-pyridone. *Chemical Physics Letters* **1991**, *187*, 532–536.
- (25) Schlegel, H. B.; Gund, P.; Fluder, E. M. Tautomerization of formamide, 2-pyridone, and 4-pyridone: an ab initio study. *Journal of the American Chemical Society* **1982**, *104*, 5347.
- (26) Fabian, W. M. F. Tautomeric equilibria of heterocyclic molecules. A test of the semiempirical AM1 and MNDO-PM3 methods. *Journal of Computational Chemistry* **1991**, *12*, 17–35.

- (27) Dkhissi, A.; Houben, L.; Smets, J.; Adamowicz, L.; Maes, G. Density functional theory and ab-initio computational study of the 2-hydroxypyridine/2-pyridone system: a comparison with FT-IR data from matrix isolation experiments. *Journal of Molecular Structure* **1999**, *484*, 215.
- (28) Gerega, A.; Lapinski, L.; Nowak, M. J.; Furmanchuk, A.; Leszczynski, J. Systematic Effect of Benzo-Annellation on OxoHydroxy Tautomerism of Heterocyclic Compounds. Experimental Matrix-Isolation and Theoretical Study. *J. Phys. Chem. A* **2007**, *111*, 4934.
- (29) Maris, A.; Ottaviani, P.; Caminati, W. Pure rotational spectrum of 2-pyridone?water and quantum chemical calculations on the tautomeric equilibrium 2-pyridone...water/2-hydroxypyridine...water. *Chemical Physics Letters* **2002**, *360*, 155–160.
- (30) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. Solvent effects. 3. Tautomeric equilibria of formamide and 2-pyridone in the gas phase and solution: an ab initio SCRF study. *Journal of the American Chemical Society* **1992**, *114*, 1645.
- (31) Kwiatkowski, J. S.; Leszczynski, J. Ab initio post-Hartree-Fock calculations of the 2-hydroxypyridine/2(1H)-pyridinone system: molecular structures, vibrational IR spectra and tautomeric stability. *Journal of Molecular Structure: THEOCHEM* **1994**, *312*, 201–213.
- (32) Sonnenberg, J. L.; Wong, K. F.; Voth, G. A.; Schlegel, H. B. Distributed Gaussian Valence Bond Surface Derived from Ab Initio Calculations. *Journal of Chemical Theory and Computation* **2009**, *5*, 949.
- (33) Fu, A.; Li, H.; Du, D.; Zhou, Z. Density Functional Study on the Reaction Mechanism of Proton Transfer in 2-Pyridone: Effect of Hydration and Self-Association. *J. Phys. Chem. A* **2005**, *109*, 1468.

- (34) Voth, G. A. *Computational approaches for studying enzyme mechanism. Part A*, pag 397, 1st ed.; Academic Press, 2016; Vol. 577.
- (35) Tsuneda, T.; Hirao, K. Long-range correction for density functional theory. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2014**, *4*, 375–390.
- (36) Iikura, H.; Tsuneda, T.; Yanai, T.; Hirao, K. A long-range correction scheme for generalized-gradient-approximation exchange functionals. *The Journal of Chemical Physics* **2001**, *115*, 3540–3544.
- (37) Yang, H. W.; Craven, B. M.; IUCr, Charge Density Study of 2-Pyridone. *Acta Crystallographica Section B Structural Science* **1998**, *54*, 912.
- (38) Kvick, A.; Olovsson, I. No Title. *Arkiv fur Kemi* **1969**, *30*, 71.
- (39) Moreno, M.; Miller, W. H. On the tautomerization reaction 2-pyridone 2-hydroxypyridine: an ab initio study. *Chemical Physics Letters* **1990**, *171*, 475.
- (40) Moran, D.; Simmonett, A. C.; Leach, F. E.; Allen, W. D.; Schleyer, P. v. R.; Schaefer, H. F. Popular Theoretical Methods Predict Benzene and Arenes To Be Nonplanar. **2006**,
- (41) Papajak, E.; Zheng, J.; Xu, X.; Leverentz, H. R.; Truhlar, D. G. Perspectives on Basis Sets Beautiful: Seasonal Plantings of Diffuse Basis Functions. *Journal of Chemical Theory and Computation* **2011**, *7*, 3027–3034.
- (42) And, J. R. C.; Frisch, M. J.; And, F. J. D.; Stephens, P. J. Hartree-Fock and Density Functional Theory ab Initio Calculation of Optical Rotation Using GIAOs: Basis Set Dependence. **2000**,
- (43) P. J. Stephens, .; F. J. Devlin, .; ; J. R. Cheeseman, .; Frisch, M. J. Calculation of Optical Rotation Using Density Functional Theory. **2001**,

- (44) Cook, M. J.; El-Abbady, S.; Katritzky, A. R.; Guimon, C.; Pfister-Guillouzo, G. Photoelectron spectra of hydroxy- and mercapto-pyridines and models of fixed structure. *Journal of the Chemical Society, Perkin Transactions 2* **1977**, *0*, 1652.
- (45) Tsuneda, T.; Song, J.-W.; Suzuki, S.; Hirao, K. On Koopmans' theorem in density functional theory. *The Journal of Chemical Physics* **2010**, *133*, 174101.
- (46) Kar, R.; Song, J.-W.; Hirao, K. Long-range corrected functionals satisfy Koopmans' theorem: Calculation of correlation and relaxation energies. *Journal of Computational Chemistry* **2013**, *34*, 958–964.

chemrxiv_ARCarvalho_Tautomers.pdf (582.72 KiB)

[view on ChemRxiv](#) • [download file](#)

Supporting Material of the work Prototype of the heteroaromatic tautomers: 2-pyridone / 2-hydroxypyridine

A. R. Carvalho^{*,†,‡}

[†]*Available to postdoctoral position*

[‡]*Current address: Niterói, Brazil*

ORCID: 0000-0001-9756-9225

E-mail: andre_carvalho@id.uff.br

Supporting Information Available

DELTA GAUSS (DG) is easy-to-use software tool for working with quantum chemistry calculations. Version 1.0 provides the integration of the output files, containing thermochemical data by GAUSSIAN software (G09) calculations, in a unified reporting about the chemical reaction. DG is available for WINDOWS 10 and UBUNTU 16 operating systems at ref. ¹ Suggestions for improvements can be made by email, and donations by [paypal.me/deltagauss](https://www.paypal.me/deltagauss).

The step-by-step for DELTA GAUSS computing: We select a single or many G09 output files by the *add product* and *reactant* buttons, see Scheme (1). The names of the selected files are displayed below each respective button. When we click on *calculate* the software performs the computation in which a dialog allows us to choose the DG output name, the default is a concatenation of the reactant and product filenames. The DG output is a standard text (*.txt*) format and accessible by the *open results* button.

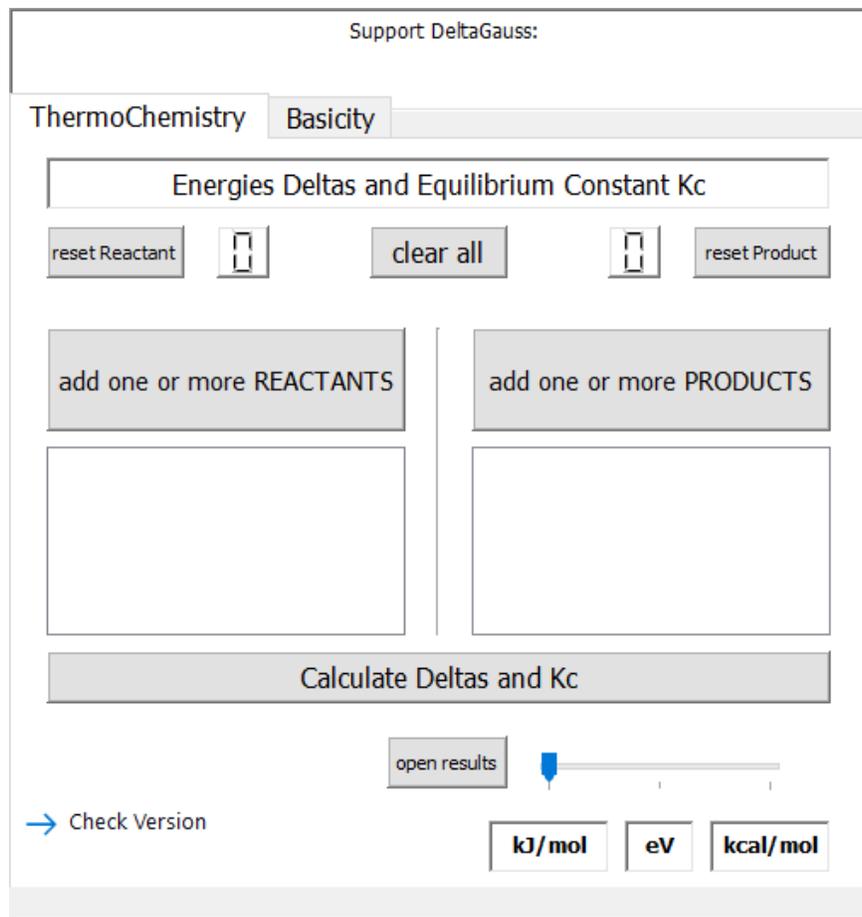


Figure 1: DELTAGAUSS 1.0, a free software tool developed to compute the equilibrium constant and energy changes in chemical reactions from the output file by GAUSSIAN 09 (G09) computation. Available for download at our ORCID page,¹ it works for WINDOWS 10 and UBUNTU 16 platforms.

DELTAGAUSS provides a pragmatic and inexpensive way to study reaction paths and the relative stability of molecules. We find the energy barrier of a system when we perform the DG calculation with the transition state data (intermediate configuration) instead of the product file. DG reports the Δ , i.e., the change in, energies are kJ/mol, eV or kcal/mol, which the slide bar allows us to switch the units. The output includes data about:

1. Δ_{zpc} , the variation in the zero-point correction (delta...Zpc)
2. Δ thermal correction to energy (delta...tcE)
3. Δ thermal correction to enthalpy (delta...tcH)

4. Δ thermal correction to Gibbs free energy ($\Delta_{tc}G$)
5. ΔE^z , sum of electronic and zero-point energies ($\Delta_{Zpc}E$)
6. Δ sum of electronic and thermal energies ($\Delta_{tc}E$)
7. ΔH , the change in the sum of electronic and thermal enthalpies ($\Delta_{tc}H$)
8. ΔG , the variation in the sum of electronic and thermal free energies ($\Delta_{tc}G$)
9. ΔE , sum of electronic energy (ΔE_{elec})
10. $(-T\Delta S)$ is entropy change.
11. Lastly, the equilibrium constant as $K_c = [P]/[R]$ calculated by the standard formula

$$\Delta G = -RT \ln K_c$$

References

- (1) Carvalho, A. R. The DeltaGauss program. 2017; <https://orcid.org/0000-0001-9756-9225>.

support-information_chemrxiv_ARCarvalho_Tautomers... (150.29 KiB)

[view on ChemRxiv](#) • [download file](#)
