Original Research Article

Tautomeric Equilibria of Substituted 2-Pyridone/2-Hydroxypyridine in the Gas and Aqueous Phases

Abstract

Heats of formation, entropies and Gibbs free energies for the twenty structures of substituted 2-pyridone and 2-hydroxypyridine were studied using semiempirical Austin Model (AM1) and Parametric Model 3 (PM3) calculations at the self-consistent field level, both in the gas and liquid phases, with full geometry optimization. 2-hydroxypyridine is predominant in the gas phase, while 2-pyridone in the liquid phase, agrees with the experimental and theoretical predictions. All substituents (F, Cl, OH, CH_3, NH_2, NO_2, CHO, CN, CF_3) stabilize the 2-pyridone in the gas and liquid phases except F, Cl and NH_2 in PM3 calculations in the gas phase. Substituents stabilization is more effective in the liquid phase. This was confirmed by thermodynamic calculations and isodesmic reactions.

Key words: 2-Pyridone; 2-Hydroxypyridine; Tautomerism; Substituents, AM1, PM3

1. Introduction

The tautomerism of 2-pyridone/2-hydroxypyridine plays a role in many areas of chemistry and biochemistry: e.g., the rationalization of structures, properties, and reactivities in heterocyclic chemistry [1,2]; concepts and probes of aromaticity [3]; measures of intrinsic stabilities verse solvent effect [4, 5]; mechanisms of enzymatic catalysis and receptor interactions [6]; and possibly even mutations during DNA replication [2, 7]. Investigations of tautomerism of 2-pyridone date from 1907 [8]. Most studies since then have dealt with the equilibrium in liquid media [1, 9]. X-ray crystallography shows that pyridone is also favored in the solid [10-12].

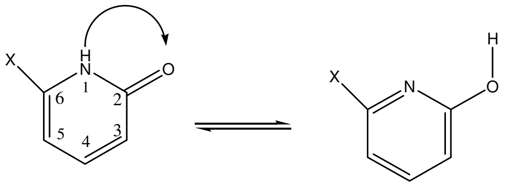
The dominance of the pyridone tautomer in solution neat liquid and solid has been shown to be the result of strong solvent effects, ion binding and self associations [1, 4, 5, 10-16]. In contrast, infra-red (IR) and ultraviolet (UV) measurements have established that the tautomers are nearly equal in energy when unassociated in the vapor [4, 17, 18]. IR spectroscopy in inert gas matrices [19], and microwave spectroscopy [20] have led to conclusion that the free energy differences between the hydroxy form and the oxy form is 0.478-0.717 kcal/mol in favor of the hydroxy form. Similar gas-phase tautomerizations have since been investigated for a number of lactam/lactim pairs by using IR [21], UV [22], photoelectron [23, 24], ion cyclotron resonance [25-27] and mass spectroscopy [28, 29]. All of these gas–phase equilibria show marked differences from solution data [1, 2, 9, 13-17, 30].

Numerous theoretical studies have attempted to reproduce the tautomerization energy for pyridone/hydroxypyridine and similar heterocyclic systems [31-38].

In solution state, the energy difference between the two tautomers seems to be very small and depending on the polarity of the solvent, polar solvents favor the 2-pyridone whereas in non-polar solvents both tautomers can co-exist [39, 40]. The experimental tautomerism free energy changes for 2-pyridone in the gas phase and acetonitrile are -0.81 and 2.96 kcal/mol respectively [40].

Electronegative substituents at the C-6 position have been shown [41] to have a considerable effect on the pyridone/hydroxypyridine equilibrium, both in the gas phase and in a variety of solvents. The studies of Beak *et al.* [4,42] have provided such experimental data on a number of chloro derivatives of 2-hydroxypyridine and 2-mercaptopyridine. Experimentally the equilibrium between 6-chloro-2-pyridone and 6-chloro-2-hydroxypyridine in the gas phase, in water and in carbon tetrachloride was found that, both in the gas phase and in carbon tetrachloride, the hydroxy-form is dominant whilst in an aqueous environment the 2-pyridone is preferred [43-46].

The main objective of this paper is to give more theoretical insight to the problem of the tautomerism of 2-pyridone/2-hydroxypyridine (Scheme 1) by studying the effect of substituents X (X= F, OH, NH_2, CH_3, CN, NO_2 and CF_3) at C-6 position in



Scheme 1.

the gas phase (ε =1) and liquid phase (ε =78.4) using the semiempirical methods AM1 [47] and PM3 [48].

2. Materials and Methods

Materials are substituted 2-pyrydone.2-hydroxypyridine. Substituents are F, Cl, OH, CH_3, NH_2, NO_2 and CHO. Theoretical calculations were performed using well known AM1 and PM3 for calculation [47, 48].

3. Results and discussion

The present work first performed by AM1 method and then by PM3 method.

3.1 AM1 Method

Calculations were first performed in the gas phase and then in liquid phase.

3.1.1 AM1 Calculations in the Gas Phase (ε =1)

The calculated molecular structures of 20 compounds are given in Figure 1. Calculations were first performed on the parent compounds (2-pyridone and 2-hydroxypyridine without substitution), and then on the substituted parent compounds.

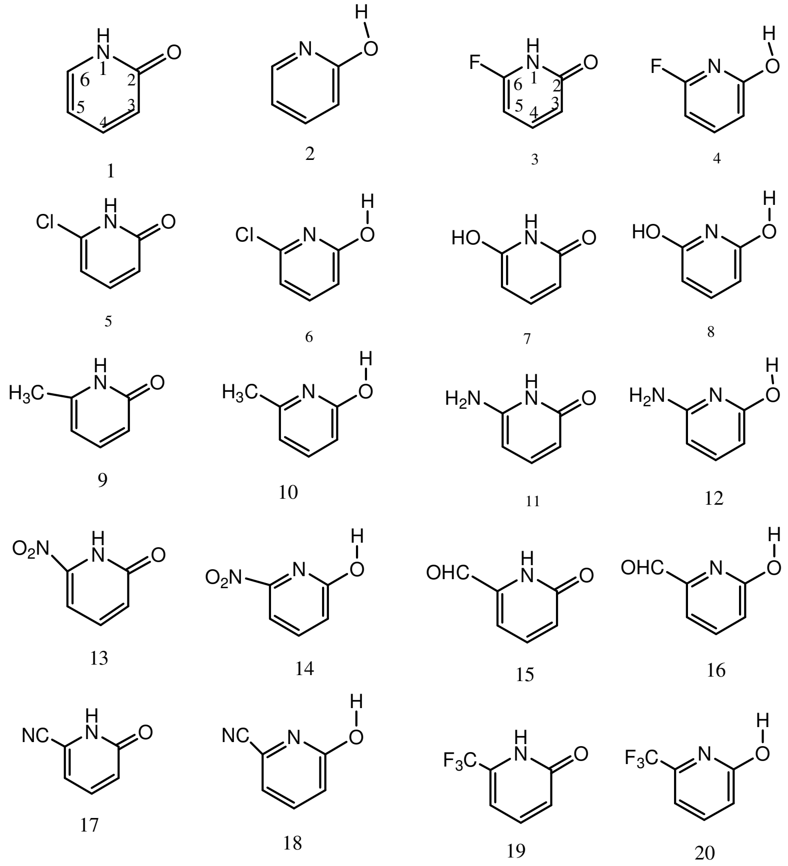
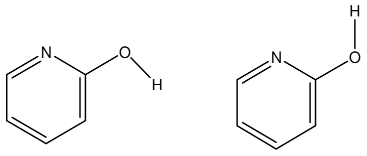


Figure 1. Molecular structures of the substituted 2-Pyridone and 2-Hydroxypyridine.

a) Parent Compounds (2-pyridone and 2-hydoxypyridine)

2- hydroxypyridine: Exists in two forms:

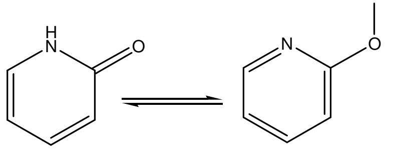


1B **2B**

Scheme 2.

The forms **1B** and **2B** (Scheme 2) differ in the orientation of OH group relative to the nitrogen atom. The calculated heat of formation of **2B** (-11.854 kcal/mol) is more negative than that of **1B** (-7.977 kcal/mol), suggesting that **2B** is preferred. This agrees with theoretical calculations [32, 34, 49].

Tautomerism:



2-pyridone (A) 2-hydroxypyridine (B)

Scheme 3.

Thermodynamic calculations of Gibbs free energies of 2-pyridone and 2-hydroxypyridine are given in Table 1.

The Gibbs free energy of the tautomerization (Δ*G*) (Scheme 3) at 298.15 K were predicated by adding the heat of formation (ΔH_f) and entropic (-TΔS) terms. The calculated Gibbs free energy for the tautomerization (Δ*G*) is - 0.540 kcal/mol, in favor of the product (2-hydroxypyridine). This result agrees with the experimental values [19, 20]~~. It also agrees with~~ and the theoretical calculations [33, 34, 40]. This Δ*G* was taken as reference for determining the relative stability of X-substituted 2-pyridone and 2- hydroxypyridine.

b) Effect of substituents:

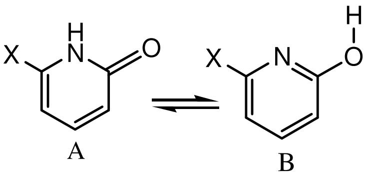
Effect of F

The thermodynamic calculation of compound **3** (Fig. 1) shows that Δ*G* = - 0.240 kcal/mol (Table 1) is slightly more positive than that of the parent (Δ*G* = - 0.540 kcal/mol) which suggests that F substituent slightly stabilizes the 2-pyridone.

The stabilization effect is also supported by isodesmic reactions [50-56]. A negative value for the reaction indicates a less stable, and a positive value a more stable product.

It was observed that ΔH_{rxn} value of the isodesmic reaction of compound **3** (Table 2) is positive (0.044 kcal /mol) and that of **4** is negative (-0.253 kcal/mol) which suggests that F slightly stabilizes the compound **3.** This agrees with the present thermodynamic calculation, which predicts a small shift in equilibrium to the 2-pyridone compared to parent.

Table 1. Calculated Gibbs free energies (kcal mol^{-1}) of the substituted 2- pyridine/ 2 –hydoxypyridine in the gas phase (ε =1) and liquid phase (ε =78.4) using AM1.

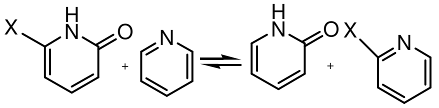
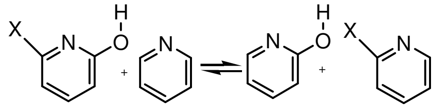


X	ΔG (ε = 1)	ΔG (ε = 78.4)
H	-0.540	7.140
F	-0.240	7.628
Cl	-0.390	7.315
OH	0.300	8.090
CH_3	0.264	7.534
NH_2	-0.080	8.433
NO_2	0.130	8.610
CHO	1.000	8.302
CN	-0.300	8.075
CF_3	0.130	18.127

Effect of Cl

Thermodynamic calculation of compound **5** (Fig. 1) shows that ΔG = - 0.390 kcal/mol (Table 1) is slightly greater than of the parent compounds (ΔG = - 0.540 kcal/mol), which suggests that Cl slightly stabilizes the 2-pyridone. This is confirmed by the isodesmic reaction of compound **5** (Table 2) where ΔH_{rxn} is negative (-0.276 kcal/mol) and that of **6** is also negative (- 0.348 kcal/mol), but that for **5** is more positive than **6** . This suggests that Cl slightly stabilizes the compound **5**. This agrees with the present thermodynamic calculation (ΔG = - 0.390 kcal/mol) which predicts a small shift in equilibrium to the 2-pyridone compared to the parent compounds (ΔG = - 0.540 kcal/mol). But ΔG is still negative, suggesting that 6-chloro-2-hydroxypyridine is dominant. This agrees with the experimental predictions [43- 46].

Table 2. Evaluation of substituent effects of the substituted 2-pyridone $\rightleftharpoons$ 2-hydroxypyridine tautomerism via isodesmic reactions (ΔH_{rxn} in kcal/mol), in the gas phase

	X								
Isodesmic Reactions	F	Cl	OH	CH_3	NH_2	NO_2	CHO	CN	CF_3
	0.044	-0.276	1.138	0.166	0.682	1.528	2.445	0.617	0.975
	-0.253	-0.348	0.243	-0.239	0.245	0.817	0.828	0.392	0.444

Effect of OH

Thermodynamic calculation of compound **7** (Fig. 1) shows that ΔG = 0.300 kcal /mol (Table 1) is greater than that of the parent (ΔG = - 0.540 kcal/mol) which suggests that OH stabilizes the 2-pyridone. This is confirmed by the isodesmic reactions of compound **7** (Table 2) where ΔH_{rxn} is 1.138 kcal/mol more positive than that for **8** (ΔH_{rxn} = 0.243 kcal/mol), which suggests that OH stabilizes compound **7.** This agrees with the present thermodynamic calculation (ΔG = 0.300 kcal/mol) which predicts a small shift in equilibrium to the 2-pyridone compared to the parent compounds (ΔG = - 0.540 kcal/mol).

Effect of CH_3

Thermodynamic calculation of compound **9** (Fig. 1) shows that ΔG = 0.264 kcal/mol (Table 1) is greater than of the parent (ΔG = - 0.540 kcal/mol), which suggests that CH_3 slightly stabilizes the 2- pyridone.

This was confirmed by the isodesmic reaction of compound **9** (Table 2) where ΔH_{rxn} is positive (ΔH_{rxn} = 0.166 kcal/mol) and that of **10** is negative (ΔH_{rxn} = - 0.239 kcal/mol), which suggests that CH_3 stabilizes compound **9.**

Effect of NH_2

Thermodynamic calculation of compound **11** (Fig. 1) shows that ΔG = - 0.080 kcal/mol (Table 1) is greater than that of the parent (ΔG = - 0.54 kcal/mol) which suggests that NH_2 stabilizes the 2- pyridone.

This was confirmed by the isodesmic reaction of compound **11** (Table 2) where ΔH_{rxn} is positive (0.682 kcal/mol) and that of **12** also is positive (0.245 kcal/mol), but that of **11** is more positive than **12,** which suggests that NH_2 stabilizes the compound **11**.

Effect of NO_2

Thermodynamic calculation of compound **13** (Fig. 1) shows that ΔG = 0.130 kcal/mol (Table 1) is greater than of the parent (ΔG = - 0.540 kcal/mol) which suggest that NO_2 stabilizes the 2- pyridone.

This was confirmed by the isodesmic reaction of compound **13** (Table 2) where ΔH_{rxn} (1.528 kcal/mol) is greater than that of compound **14** (ΔH_{rxn} = 0. 817 kcal/mol), which suggests that NO_2 stabilizes the compound **13.**

Effect of CHO

Thermodynamic calculation of compound **15** (Fig. 1) shows that ΔG = 1.000 kcal/mol (Table 1) is greater than of the parent (ΔG = - 0.540 kcal/mol) which suggests that CHO stabilizes the 2-pyridone.

The stabilization effect is confirmed by the isodesmic reaction, it can be seen from Table 2 that ΔH_{rxn} value of the isodesmic reaction of compound **15** is 2.445 kcal/mol greater than that of compound **16** (ΔH_{rxn} = 0.828 kcal/mol), which suggests that CHO stabilizes the compound **15.**

Effect of CN

Thermodynamic calculation of compound **17** (Fig. 1) shows that ΔG = - 0.300 kcal/mol (Table 1) is slightly greater than that of the parent (ΔG = - 0.540 kcal/mol) which suggests that CN slightly stabilizes the 2-pyridone. The stabilization effect is confirmed by the isodesmic reaction. It can be see from Table 2 that ΔH_{rxn} value of the isodesmic reaction of compound **17** is 0.617 kcal/mol greater than that of compound **18** (ΔH_{rxn} = 0.392 kcal/mol), which suggests that CN stabilizes the compound **17.**

Effect of CF_3

Thermodynamic calculation of compound **19** (Fig. 1) shows that ΔG = 0.130 kcal/mol (Table 1) is greater than of the parent (ΔG = - 0.540 kcal/mol) which suggests that CF_3 stabilizes the 2-pyridone.

The stabilization effect was confirmed by isodesmic reaction, it can be seen from Table 2 that ΔH_{rxn} value of the isodesmic reaction of compound **19** is 0.975 kcal/mol greater than that of compound **20** (0.444 kcal/mol), which suggests that CF_3 stabilizes the compound **19**.

Therefore, all substituents show an increase in the stability of 2-pyridone.

3.1.2 AM1 Calculations in Liquid Phase (ε = 78.4)

Calculations first performed on the parent compounds (2-pyridone and 2-hydroxypyridine without substitution), and then on the substituted parent compounds.

a) Parent Compounds (2-pyridone and 2-hydoxypyridine)

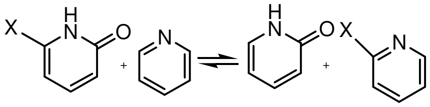
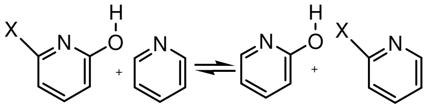
The calculated Gibbs free energies of 2-pyridone and 2-hydroxypyridine are given in Table 1 The heat of formation of 2-pyridone (A) (ΔH_f = - 31.480 kcal/mol) is more negative than that of 2-hydroxypyridine (B) (ΔH_f = - 24.204 kcal/mol) which suggests that compound (A) is the more stable (Scheme 3). This agrees with the published work [1, 4, 5, 10-16].

The calculated Gibbs free energy (ΔG) for the tautomerization (Scheme 3) is 7.140 kcal/mol, suggesting that 2-pyridone is predominant. This agrees with theoretical and experimental predictions [33, 34, 40]. This ΔG taken as reference for determining the relative stability of X-substituted 2-pyridone and 2-hydroxypyridine.

b) Effect of substituents

All substituents show an increase in the Gibbs free energy values (ΔG) (Table 1) as compared to the parents (ΔG = 7.140 kcal/mol), which suggests that all the substituents stabilize the 2-pyrididone thermodynamically. This was confirmed by the isodesmic reactions in Table 3, where all ΔH_{rxn} values of the 2-pyridone are more positive than that of 2-hdroxypyridine.

Table 3 .Evaluation of substituent effects of the X-substituted 2-pyridone $\rightleftharpoons$ 2-hydroxypyridine tautomerism via isodesmic reaction ns (ΔH_{rxn} in kcal/mol), in liquid phase

	X								
Isodesmic Reaction	F	Cl	OH	CH_3	NH_2	NO_2	CHO	CN	CF_3
	0.213	-0.222	0.937	0.093	0.659	2.60	2.162	1.505	1.283
	-0.378	-0.460	-0.046	-0.144	0.094	1.180	0.922	0.666	0.609

3.2 PM3 Calculations

PM3 calculations are first performed in the gas phase and then in the liquid phase.

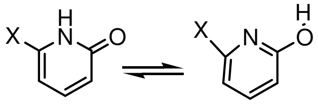
3.2.1 PM3 Calculations in the Gas Phase (ε =1)

Calculations were first performed on the parent compounds (2-pyridone and 2-hydroxypyridine without substitution), and then on the substituted parent compounds.

a) Parent Compounds (2-pyridone and 2-hydoxypyridine)

The calculated Gibbs free energies of 2-pyridone and 2-hydroxypyridine are given in Table 4. The heat of formation of 2-hydroxypyridine (B) (ΔH_f = - 18.150 kcal /mol) is more negative than that of 2-pyridone (A) (ΔH_f = - 15.658 kcal/mol), which suggests that compound (B) is the more stable (Scheme 3). i.e 2-hydroxypyridine is predominant in the gas phase, agrees with the theoretical and experimental predictions [4, 17-20, 33, 34, 40]. The calculated Gibbs free energy for the tautomerization (ΔG) (Scheme 3) is - 2.571 kcal /mol (Table 4), which is not closed to the experimental value (- 0.81 kcal/mol) [40] as that calculated by the present AM1. i.e. the present AM1 calculation gives better result in regard to the Gibbs free energy in the gas phase. This ΔG was used as reference for determining the relative stability of X-substituted 2-pyridone and 2- hydroxypyridine.

Table 4. Gibbs free energies (kcal/mol) of the X- substituted 2-pyridone/2-hydroxypyridine in the gas phase (ε =1) and liquid phase (ε =78.4) using PM3.



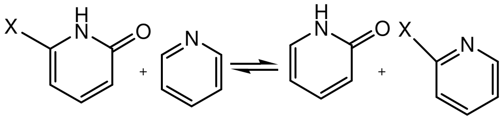
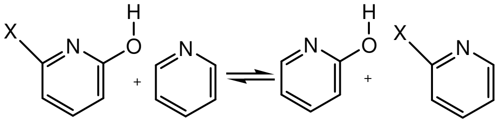
A B

X	ΔG (ε = 1)	ΔG (ε = 78.4)
H	-2.571	7.199
F	-3.001	7.750
Cl	-2.798	8.567
OH	-2.414	7.533
CH_3	-1.617	7.898
NH_2	-4.049	7.439
NO_2	-1.313	8.679
CHO	-1.397	7.485
CN	-2.313	8.136
CF_3	-2.010	8.225

b) Effect of Substituents

The substituents F, Cl and NH_2 show a decrease in Gibbs energy values ΔG (Table 4) as compared to the parent (ΔG = - 2.571 kcal /mol), indicating that the substituents destabilize the 2-pyrdone. i.e in favor of the product (2-hydroxypyridine). This was confirmed by the isodesmic reactions in Table 5, where the values of ΔH_{rxn} of the substituents (F, Cl and NH_2) in the case of the 2-hydroxypyridine are more

Table 5. Evaluation of substituent effects of the X- substituted 2-Pyridone $\rightleftharpoons$ 2-Hydroxy pyridine tautomerism via isodesmic reactions (ΔH_{rxn} in kcal/mol)in the gas phase.

	X								
Isodesmic Reactions	F	Cl	OH	CH_3	NH_2	NO_2	CHO	CN	CF_3
	-0.363	-0.369	2.616	0.967	-1.497	2.763	2.096	0.659	1.287
	0.103	-0.116	2.469	-0.059	-0.162	1.437	0.809	0.411	0.695

positive than that of 2-pyridone, which suggests a destabilization of 2-pyridone. The rest of the substituents (OH, CH_3, NO_2, CHO, CN and CF_3) show more positive ΔH_{rxn} values for the 2-pyridone than that of the 2-hydroxypyridine, which suggests a more stabilization of the 2-pyridone.

Thus, all substituents stabilize the 2-pyridone, except F, Cl, NH_2.

3.2.2 PM3 Calculations in Liquid Phase (ε = 78.4)

Calculations were first performed on the parent compounds (2-pyridone and 2-hydroxypyridine without substitution), and then on the substituted parent compounds.

a) Parent Compounds (2-pyridone and 2-hydoxypyridine)

The calculated Gibbs free energies of 2-pyridone and 2-hydroxypyridine are given in Table 4.

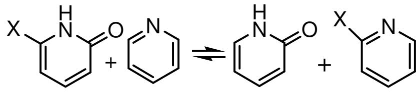
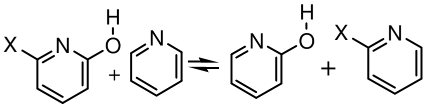
The heat of formation of 2-pyridone (A) ΔH_f (- 36.426 kcal/mol) is more negative than that of 2-hydroxypyridine (B)(ΔH_f = - 28.749 kcal/mol) which suggests that compound (A) is the more stable (Scheme 3). This agrees with the published work [1, 4, 5, 10-16].

The calculated Gibbs free energy (ΔG) for the tautomerization (Scheme 3) is 7.199 kcal/mol, suggesting that 2-pyridone is predominant in the liquid phase, which agrees with theoretical and experimental predictions [33,34,40]. This ΔG agrees also with the present AM1 calculation (ΔG = 7.140 kcal/mol) in the liquid phase. This ΔG will be taken as reference for determining the relative stability of X-substituted 2-pyridone and 2-hydroxypyridine.

b) *Effect of substituents*

All substituents showed an increase in the Gibbs free energy values (ΔG) (Table 4) as compared to the parents (ΔG = 7.199 kcal/mol), which suggests that all substituents stabilizes the 2-pyrididone thermodynamically. This was confirmed by the isodesmic reactions in Table 6, where all ΔH_{rxn} values of the 2-pyridone were more positive than that of 2-hdroxypyridine. Therefore, thermodynamically, all substituents showed an increase in the stability of 2-pyridone.

Table 6. Evaluation of substituent effects on the X- substituted 2-Pyridone $\rightleftharpoons$ 2-Hydroxypyridine tautomerism via isodesmic reactions (ΔH_{rxn} in kcal/mol), in liquid phase.

	X								
Isodesmic Reactions	F	Cl	OH	CH_3	NH_2	NO_2	CHO	CN	CF_3
	0.596	0.389	0.725	0.189	-0.310	3.535	1.141	1.771	1.737
	0.025	-0.447	0.341	-0.033	-1.360	1.470	0.924	0.839	0.836

4. Conclusion

It can be concluded that 2-hydroxypyridine is dominant in the gas phase, while 2-pyridone in the aqueous phase, which agrees with the theoretical and experimental predictions. Thermodynamically, all substituents show an increase in the stability of the 2-pyridone in the gas and aqueous phases apart from the substituents F, Cl and NH_2 in PM3 calculations in the gas phase. These results were confirmed by Gibbs free energy calculations and isodesmic reactions.

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