



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

**Aamer A. Alhatem<sup>1\*</sup>**

<sup>1</sup>Department of Chemistry, College of Education for Girls, University of Mosul, Mosul, Iraq.

### **Author's contribution**

The sole author designed, analyzed, interpreted and prepared the manuscript.

### **Article Information**

DOI: 10.9734/CSJI/2018/42946

#### Editor(s):

(1) Pradip K. Bhowmik, Professor, Department of Chemistry, University of Nevada Las Vegas, USA.

#### Reviewers:

(1) Nobuaki Tanaka, Shinshu University, Japan.

(2) Toluwase H. Fatoki, Federal University of Technology Akure, Nigeria.

(3) Max Majireck, Hamilton College, USA.

Complete Peer review History: <http://www.sciencedomain.org/review-history/25882>

**Original Research Article**

**Received 28<sup>th</sup> May 2018**  
**Accepted 2<sup>nd</sup> August 2018**  
**Published 14<sup>th</sup> August 2018**

### **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 Method 3 (PM3) calculations at the self-consistent field level, both in the gas and liquid phases, with full geometry optimization. It was revealed from the study that 2-hydroxypyridine is predominant in gas phase, while 2-pyridone in the liquid phase which agrees with the experimental and theoretical predictions. All substituents such as F, Cl, OH, CH<sub>3</sub>, NH<sub>2</sub>, NO<sub>2</sub>, CHO, CN, CF<sub>3</sub> stabilize the 2-pyridone in the gas and liquid phases except F, Cl and NH<sub>2</sub> in PM3 calculations in the gas phase. The substituents stabilization is more effective in liquid phase. This was also confirmed by thermodynamic calculations and isodesmic reactions.

**Keywords:** 2-pyridone; 2-hydroxypyridine; tautomerism; substituents; AM1; PM3.

### **1. INTRODUCTION**

The tautomerism of 2-pyridone/2-hydroxypyridine plays a significant role in many areas of chemistry and biochemistry, viz., 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

\*Corresponding author: E-mail: [aaalhatem@gmail.com](mailto:aaalhatem@gmail.com), [aaalhatim@yahoo.com](mailto:aaalhatim@yahoo.com);

interactions [6]; and possibly even mutations during DNA replication [2,7]. Early investigations of tautomerism of 2-pyridone were performed by Baker and Baely [8]. Since then, most studies have dealt with the equilibrium in liquid media [1,9]. X-ray crystallography has shown that pyridone is also favored in the solid [10-12].

The dominance of pyridone tautomer in solution neat liquid and solid has been shown to be the results of strong solvent effects, ion binding and self associations [1,4,5,10-16]. In contrast, IR and 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 hydroxy form and oxy form is 0.478-0.717 kcal/mol in favour of the hydroxy form. A similar gas-phase tautomerizations have 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 these gas-phase equilibria showed marked differences from solution data [1,2,9,13-17,30].

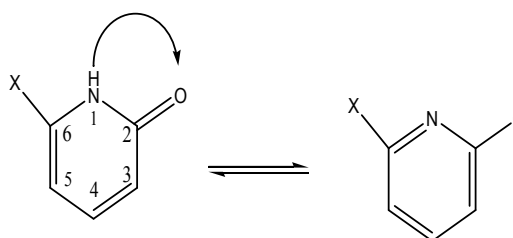
Numerous theoretical studies have attempted previously to reproduce the tautomerization energy for pyridone/hydroxypyridine and similar heterocyclic systems [31-38].

In solution state, the energy difference between two tautomers seems to be very small and depending on the polarity of the solvent, polar solvents favour 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 was -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 revealed such experimental data on several 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, water and carbon tetrachloride reported that, both in

the gas phase and in carbon tetrachloride, the hydroxy-form is dominant while 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<sub>2</sub>, CH<sub>3</sub>, CN, NO<sub>2</sub> and CF<sub>3</sub>) at C-6 position in the gas phase ( $\epsilon = 1$ ) and liquid phase ( $\epsilon = 78.4$ ) by using semiempirical methods AM1 [47] and PM3 [48].



Scheme 1

## 2. MATERIALS AND METHODS

Materials are substituted 2-pyridone/2-hydroxypyridine. Substituents are F, Cl, OH, CH<sub>3</sub>, NH<sub>2</sub>, NO<sub>2</sub> and CHO. Theoretical calculations were performed by using well known AM1 (47) and PM3 (48) for calculations.

## 3. RESULTS AND DISCUSSION

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

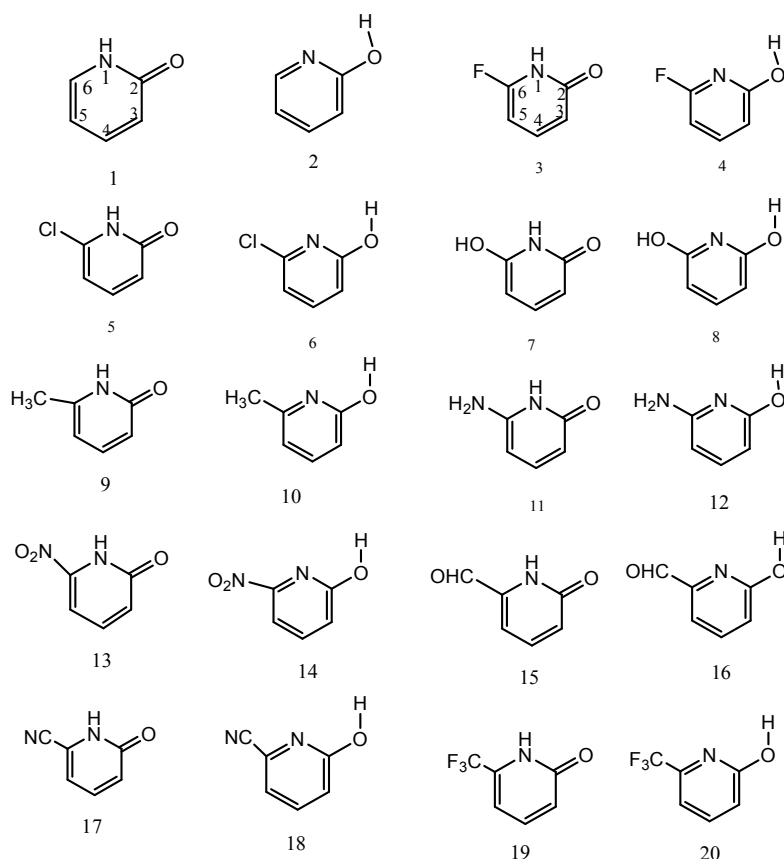
### 3.1 AM1 Method

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

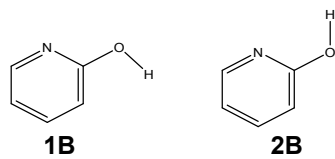
#### 3.1.1 AM1 calculations in the gas phase ( $\epsilon = 1$ )

The calculated molecular structures of 20 compounds are given in Fig. 1.

The calculations were first performed on a parent compounds (2-pyridone and 2-hydroxypyridine without substitution), and then on a substituted parent compounds.



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



**Scheme 2**

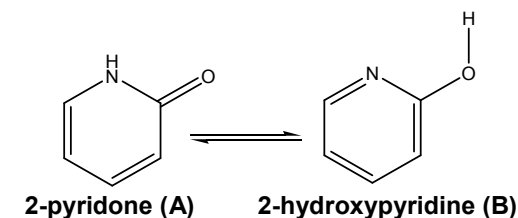
a) Parent Compounds (2-pyridone and 2-hydroxypyridine)

2- hydroxypyridine: Exists in two forms:

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 in compared to **1B** (-7.977 kcal/mol), suggesting that **2B** is preferred. This agrees with theoretical calculations done by other researchers [32,34, 49].

#### **Tautomerism:**

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



**Scheme 3**

The Gibbs free energy of the tautomerization ( $\Delta G$ ) (Scheme 3) at 298.15 K were predicated by adding the heat of formation  $\Delta H_f$  and entropic ( $-T\Delta S$ ) terms. The calculated Gibbs free energy for tautomerization  $\Delta G$  is - 0.540 kcal/mol, which is in favour of the product (2-hydroxypyridine). This result agrees with the experimental values recorded by other workers [19,20]. It also agrees with the theoretical calculations [33,34,40]. This  $\Delta G$  has been 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) showed that  $\Delta G = -0.240$  kcal/mol (Table 1) was more positive than that of the parent ( $\Delta G = -0.540$  kcal/mol) suggested that F substituent slightly stabilizes the 2-pyridone.

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

It was observed that  $\Delta H_{rxn}$  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 is in agreement 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<sup>-1</sup>) of the substituted 2- pyridine/ 2 – hydroxypyridine in the gas phase ( $\epsilon = 1$ ) and liquid phase ( $\epsilon = 78.4$ ) using AM1**

X	$\Delta G (\epsilon = 1)$	$\Delta G (\epsilon = 78.4)$
H	-0.540	7.140
F	-0.240	7.628
Cl	-0.390	7.315
OH	0.300	8.090
CH <sub>3</sub>	0.264	7.534
NH <sub>2</sub>	-0.080	8.433
NO <sub>2</sub>	0.130	8.610
CHO	1.000	8.302
CN	-0.300	8.075
CF <sub>3</sub>	0.130	18.127

**Effect of Cl:**

Thermodynamic calculation of compound **5** (Fig. 1) shows that  $\Delta G = -0.390$  kcal/mol (Table 1) is

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

**Effect of OH:**

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

**Effect of CH<sub>3</sub>:**

Thermodynamic calculation of compound **9** (Fig. 1) shows that  $\Delta G = 0.264$  kcal/mol (Table 1) is greater in compared to the parent ( $\Delta G = -0.540$  kcal/mol), which suggests that CH<sub>3</sub> slightly stabilizes the 2- pyridone.

This confirmed by the isodesmic reaction of compound **9** (Table 2) where  $\Delta H_{rxn}$  is positive ( $\Delta H_{rxn} = 0.166$  kcal/mol) and that of **10** is negative ( $\Delta H_{rxn} = -0.239$  kcal/mol), which suggests that CH<sub>3</sub> stabilizes compound **9**.

**Effect of NH<sub>2</sub> :**

Thermodynamic calculation of compound **11** (Fig. 1) shows that  $\Delta G = -0.080$  kcal/mol (Table 1) is greater in compared to the parent ( $\Delta G = -0.54$  kcal/mol) which suggests that NH<sub>2</sub> stabilizes the 2- pyridone.

This confirmed by the isodesmic reaction of compound **11** (Table 2) where  $\Delta H_{rxn}$  is positive

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

Isodesmic Reactions	X								
	F	Cl	OH	CH <sub>3</sub>	NH <sub>2</sub>	NO <sub>2</sub>	CHO	CN	CF <sub>3</sub>
	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

(0.682 kcal/mol) and that of **12** is also positive (0.245 kcal/mol), but that of **11** is more positive than **12**, which suggests that NH<sub>2</sub> stabilizes the compound **11**.

#### Effect of NO<sub>2</sub>:

Thermodynamic calculation of compound **13** (Fig. 1) shows that  $\Delta G = 0.130$  kcal/mol (Table 1) is greater in compared to the parent ( $\Delta G = -0.540$  kcal/mol) which suggests that NO<sub>2</sub> stabilizes the 2-pyridone.

This confirmed by the isodesmic reaction of compound **13** (Table 2) where  $\Delta H_{rxn}$  (1.528 kcal/mol) is greater than that of compound **14** ( $\Delta H_{rxn} = 0.817$  kcal/mol), which suggests that NO<sub>2</sub> stabilizes the compound **13**.

#### Effect of CHO:

Thermodynamic calculation of compound **15** (Fig. 1) shows that  $\Delta G = 1.000$  kcal/mol (Table 1) is greater than the parent ( $\Delta G = -0.540$  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  $\Delta H_{rxn}$  value of the isodesmic reaction of compound **15** is 2.445 kcal/mol is greater than that of compound **16** ( $\Delta H_{rxn} = 0.828$  kcal/mol), which suggests that CHO stabilizes the compound **15**.

#### Effect of CN:

Thermodynamic calculation of compound **17** (Fig. 1) shows that  $\Delta G = -0.300$  kcal/mol (Table

1) is slightly greater than that of the parent ( $\Delta G = -0.540$  kcal/mol) which suggests that CN slightly stabilizes the 2-pyridone. The stabilization effect is confirmed by the isodesmic reaction. It can be seen from Table 2 that  $\Delta H_{rxn}$  value of the isodesmic reaction of compound **17** is 0.617 kcal/mol greater in compared to the compound **18** ( $\Delta H_{rxn} = 0.392$  kcal/mol), suggested that CN stabilizes the compound **17**.

#### Effect of CF<sub>3</sub>:

Thermodynamic calculation of compound **19** (Fig. 1) shows that  $\Delta G = 0.130$  kcal/mol (Table 1) is greater than the parent ( $\Delta G = -0.540$  kcal/mol) which suggests that CF<sub>3</sub> stabilizes the 2-pyridone.

The stabilization effect confirmed by isodesmic reaction, it can be seen from Table 2 that  $\Delta H_{rxn}$  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<sub>3</sub> stabilizes the compound **19**.

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

#### 3.1.2 AM1 calculations in liquid phase ( $\epsilon = 78.4$ )

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-hydroxypyridine)

The calculated Gibbs free energies of 2-pyridone and 2-hydroxypyridine are shown in Table 1. The heat formation of 2-pyridone (A) ( $\Delta H_f = -31.480$  kcal/mol) is more negative in compared to 2-hydroxypyridine (B) ( $\Delta H_f = -24.204$  kcal/mol) suggesting that compound (A) is the more stable (Scheme 3). This agrees with the previous published works [1,4,5,10-16].

The calculated Gibbs free energy ( $\Delta G$ ) for the tautomerization (Scheme 3) is 7.140 kcal/mol, suggesting that 2-pyridone was predominant. This agrees with theoretical and experimental predictions [33,34,40]. This  $\Delta G$  was taken as a 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 ( $\Delta G$ ) (Table 1) in compared to the parents ( $\Delta G = 7.140$  kcal/mol), suggested that all the substituents stabilize the 2-pyridone thermodynamically. This confirmed by the isodesmic reactions in Table 3, where all  $\Delta H_{rxn}$  values of the 2-pyridone are more positive than that of 2-hydroxypyridine.

### 3.2 PM3 Calculations

PM3 calculations were primarily performed in the gas phase and then in the liquid phase.

#### 3.2.1 PM3 calculations in the gas phase ( $\epsilon = 1$ )

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-hydroxypyridine)

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

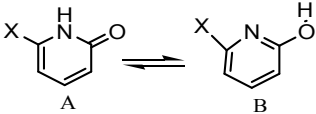
b) Effect of Substituents

The substituents F, Cl and  $\text{NH}_2$  showed a decrease in Gibbs energy values  $\Delta G$  (Table 4) in compared to the parent ( $\Delta G = -2.571$  kcal/mol), indicating that the substituents destabilize the 2-pyridone i.e., in favour of the product (2-hydroxypyridine). This is confirmed by the isodesmic reactions in Table 5, where the values of  $\Delta H_{rxn}$  of the substituents (F, Cl and  $\text{NH}_2$ ) in case of the 2-hydroxypyridine are more.

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

Isodesmic Reaction	X								
	F	Cl	OH	CH <sub>3</sub>	NH <sub>2</sub>	NO <sub>2</sub>	CHO	CN	CF <sub>3</sub>
	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

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

X		
	$\Delta G (\epsilon = 1)$	$\Delta G (\epsilon = 78.4)$
H	-2.571	7.199
F	-3.001	7.750
Cl	-2.798	8.567
OH	-2.414	7.533
CH <sub>3</sub>	-1.617	7.898
NH <sub>2</sub>	-4.049	7.439
NO <sub>2</sub>	-1.313	8.679
CHO	-1.397	7.485
CN	-2.313	8.136
CF <sub>3</sub>	-2.010	8.225

positive than that of 2-pyridone. It suggests a destabilization of 2-pyridone. The rest of the substituents (OH, CH<sub>3</sub>, NO<sub>2</sub>, CHO, CN and CF<sub>3</sub>) showed more positive  $\Delta H_{rxn}$  values for the 2-pyridone than that of the 2-hydroxypyridine, which suggests a more stabilization of the 2-pyridone.

Therefore, all substituents stabilize the 2-pyridone, except F, Cl, and NH<sub>2</sub>.

### 3.2.2 PM3 calculations in liquid phase ( $\epsilon = 78.4$ )

Calculations were primarily 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-hydroxypyridine)

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

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

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

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

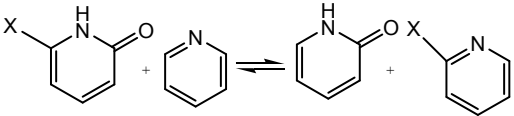
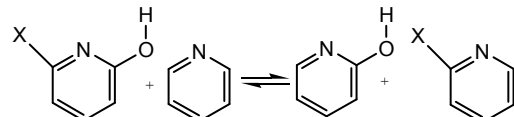
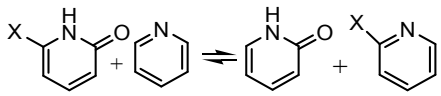
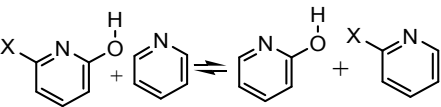
Isodesmic Reactions	X								
	F	Cl	OH	CH <sub>3</sub>	NH <sub>2</sub>	NO <sub>2</sub>	CHO	CN	CF <sub>3</sub>
	-0.363	-0.369	2.616	0.967	-1.497	2.763	2.096	0.659	1.287
	0.103	-0.116	2.469	-0.059	-0.162	1.437	0.809	0.411	0.695

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

Isodesmic Reactions	X								
	F	Cl	OH	CH <sub>3</sub>	NH <sub>2</sub>	NO <sub>2</sub>	CHO	CN	CF <sub>3</sub>
	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

#### b) Effect of substituents

All substituents showed an increase in the Gibbs free energy values ( $\Delta G$ ) (Table 4) as compared to the parents ( $\Delta G = 7.199$  kcal/mol), which suggested that all substituent stabilize the 2-pyridone thermodynamically. This is confirmed by the isodesmic reactions in Table 6, where all  $\Delta H_{rxn}$  values of 2-pyridone are more positive than that of 2-hydroxypyridine. Therefore, thermodynamically, all substituent showed an increase in the stability of 2-pyridone.

#### 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 substituent showed an increase in the stability of 2-pyridone in the gas and aqueous phases apart from the substituents F, Cl and NH<sub>2</sub> in PM3 calculations in the gas phase. These results were confirmed by Gibbs free energy calculations and isodesmic reactions.

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

#### REFERENCES

- Katritzky AR, Drum CA. Advances in heterocyclic chemistry: Prospect and retrospect. Adv. Heterocycl Chem. 1986; 40:1-24.
- Rasool N, Kanwal A, Rasheed T, Ain Q, Mahmood T, Ayub K, Zubair M, Khan K, Arshad M, Asiri MN, Zia-Ul-Haq M, Jaafar, HZE. One pot selective arylation of 2-bromo-5-chloro thiophene; molecular structure investigation via Density Functional Theory (DFT), X-ray Analysis. and Their Biological Activities Int. J. Mol. Sci. 2016;17(7):912-927.
- Cook MJ, Katritzky AR, Linda P, Tack RD. Aromaticity and tautomerism. part II. the 4-pyridone, 2-quinolone, and 1-isoquinolone series. J. Chem. Soc. Perkin Trans. 1973; 2:1080-1086.
- McCann BW, McFarland S, Acevedo O. Benchmarking continuum solvent models for Keto–Enol tautomerizations. J. Phys. Chem. A. 2015;119(32):8724–8733.
- Beak P. Energies and alkylations of tautomeric heterocyclic compounds: Old problems - New Answers. Acc. Chem. Res. 1977;10(5):186-192.
- Jiang H, Pritchard JR, Williams RT, Lauffenburger DA, Hemann MT. A mammalian functional-genetic approach to characterizing cancer the rapeutics. Nature Chemical Biology. 2011;7:92–100.
- Pullman B, Pullman A. Electronic aspects of purine tautomerism, Adv. Heterocycl. Chem. 1971;13:77-159.
- Baker F, Baley EC. The relation between absorption spectra and chemical constitution. Part VII. Pyridine and some of its derivatives, J. Chem. Soc. Trans. 1907;91:1122-1132.



9. Albert A, Phillips JN. Ionization constants of heterocyclic substances. Part II. hydroxy-derivatives of nitrogenous six-membered ring-compounds. *J. Chem. Soc.* 1956;1294-1304.
10. Penfold BR. The electron distribution in crystalline  $\alpha$ -pyridone, *Acta Cryst.* 1953;6: 591-600.
11. Almlöf J, Kvick Å, Olovsson I. Hydrogen bond studies. XLVII. The crystal structure of the intermolecular complex 2-pyridone:6-Chloro-2-Hydroxypyridine, *Acta Cryst. Sect. B.* 1971;27(6):1201-1208.
12. Rai SK, Khanam S, Khanna RS, Tewari, A. K. Polymorphic study and anti-inflammatory activity of 3-cyano-2-pyridone based flexible model, *cryst. Growth Des.* 2015;15(3):1430-1439.
13. Esfandiary R, Parupudi A, Casas- Finet J, Gadre D, Sathish H. Mechanism of reversible self-association of a monoclonal antibody: Role of electrostatic and hydrophobic interactions. *J. Pharm. Sci.* 2015; 104(2):577–586.
14. Beak P, Covington JB, Zeigler JM. Self-association and the protomeric equilibria of 4-hydroxypyridine-4-pyridone and related compounds. *J. Org. Chem.* 1978;43(1): 177-178.
15. Bensaude O, Chevrier M, DuBois JE. Lactim-lactam tautomeric equilibria of 2-hydroxypyridines. 1. cation binding, dimerization, and interconversion mechanism in aprotic solvents. A spectroscopic and temperature-jump kinetic study. *J. Am. Chem. Soc.* 1978;100(22):7055-7060.
16. Bensaude O, Chevrier M, Guillerez J, Du Bois JE. preferential anion binding to the lactim tautomers of 2-hydroxypyridines. *J. Am. Chem. Soc.* 1980;102(1):401-403.
17. Beak P, Fry Jr. FS, Lee J, Steele F. Equilibration studies. protomeric equilibria of 2- and 4-hydroxypyridines, 2- and 4-hydroxypyrimidines, 2- and 4-mercapto-pyridines, and structurally related compounds in the gas phase. *J. Am. Chem. Soc.* 1976;98(1):171-179.
18. Beak P, Fry Jr. FS. The equilibrium between 2-hydroxypyridine and 2-pyridone in the gas phase. *J. Am. Chem. Soc.* 1973; 95:1700-1710.
19. Flitcroft JM, Molinari M, Brincat NA, Williams NR, Storr MT, Allen GC, Parker SC. The critical role of hydrogen on the stability of oxyhydroxyl defect clusters in uranium oxide. *J. Mater. Chem. A.* 2018;6: 13162-11369.
20. Hatherley LD, Brown RD, Godfrey PD, Pierlot AP, Caminati W, Damiani D, Melandri S, Favero LB. Gas-phase tautomeric equilibrium of 2-pyridinone and 2-hydroxypyridine by microwave spectroscopy. *J. Phys. Chem.* 1993;97(1): 46-51.
21. Peng CS, Baiz CR, Tokmakoff A. Direct observation of ground-state lactam–lactim tautomerization using temperature-jump transient 2D IR spectroscopy. *P. Natl. Acad. Sci.* 2013;110:9243-9248.
22. Lin J, Yu C, Peng S, Akiyama L, Li K, Lee LK, LeBreton PR. Ultraviolet photoelectron studies of the ground-state electronic structure and gas-phase tautomerism of purine and adenine. *J. Am. Chem. Soc.* 1980;102(14):4627-4631.
23. Dkhissi A, Houben L, Smets J, Adamoicz L, Maes G. Density functional theory and ab initio computational study of the 2-hydroxypyridine/2-pyridone system: A comparison with FT-IR data matrix isolation experiments. *J. Mol. Strc.* 1999; 484(1-3):215-227.
24. Brown RS, Tse A, Vederas JC. Photoelectron-determined core binding energies and predicted gas phase basicities for the 2-hydroxypyridine/2-pyridone system. *J. Am. Chem. Soc.* 1980; 102(3):1174-1176.
25. Cook MJ, Katritzky AR, Taapgepera M, Singh TD, Taft RW. Application of ion cyclotron resonance spectroscopic gas-phase basicity: The study of tautomeric equilibrium. *J. Am. Chem. Soc.* 1976; 98(19):6048- 6049.
26. Schlegel HB, Gund P, Fluder EM. Tautomerization of formamide and 4-pyridone: An ab initio study. *J. Am. Chem. Soc.* 1982;104:5347-5351.
27. Aue DH, Betowski LD, Davidson, Bowers MT, Beak P, Lee J. Gas-phase basicities of amides and imidates. Estimation of protomeric equilibrium constants by the basicity method in the gas phase. *J. Am. Chem. Soc.* 1979;101(6):1361-1368.
28. Maquestiau A, van Haverbeke Y, de Meyer C, Katritzky AR, Cook JM, Page AD. Demonstration of the enolic tautomers of the hydroxypyridines in the source of the mass spectrometer. *Can. J. Chem.* 1975; 53(4):490-496.
29. Maquestiau A, van Haverbeke Y, Flammang R, Mispreveuve H, Katritzky AR,

- Ellison J, Frank J, Meszaros ZJ. A novel mass-spectroscopic technique for the investigation of vapor-phase tautomeric Equilibria. *J. Chem. Soc. Chem. Commun.* 1979;888-888.
30. Cook MJ, Katritzky AR, Hepler LG, Matsu T. Heats of solution and tautomeric equilibrium constants. The 2-Pyridone: 2-Hydroxypyridine Equilibrium in Non-aqueous Media, *Tetrahedron Lett.* 1976; 17(31):2685-2688.
  31. Hejazi SA, Osman OI, Alyoubi AO, Aziz SG, Hilal RH. The thermodynamic and kinetic properties of 2-hydroxypyridine/2-pyridone tautomerization: A theoretical and computational revisit. *Int. J. Mol. Sci.* 2016; 17(11):1893-1910.
  32. Schlegel HB, Gund P, Fluder EM. Tautomerization of formamide, 2-pyridone and 4-pyridone :An AB initio study. *J. Am. Chem. Soc.* 1982;104:5347-5351.
  33. Katritzky AR, Szafran M, Stevens J. AM1 study of the tautomerism of 2- and 4-pyridones and their thio-analogs. *J. Mol. Struct. (Theochem).* 1989;184(1-2):179-192.
  34. Parchmen OGT, Burton NA, Hillier IH. Tautomeric equilibrium of 2-hydroxypyridine/2-pyridone: Does a theoretical—experimental discrepancy Exist, *Chem. Phys. Letters.* 1993;203(1):46-48.
  35. Chou PT, Wei CY, Hung FT. The conjugated dual hydrogen-bonds mediating 2-pyridone/2- hydroxypyridine tautomerism. *J. Phys. Chem. B.* 1997; 101(44):9119-912.
  36. Esboui M, Nsangou M, Jaidane N, Ben Kakhdar Z. DFT study of ground state proton transfer in 2-pyridone/2-hydroxypyridine—ammonia clusters. *Chem. Phys.* 2005;311(3):277-285.
  37. 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. *J. Mol. Struct.* 1999; 484(1-3):215-227.
  38. Todorov AR, Wirtanen T, Helaja J. Photo reductive removal of O-Benzyl groups from oxyarene N-heterocycles assisted by O-pyridine—pyridone tautomerism. *J. Org. Chem.* 2017;82(24):13756–13767.
  39. Nichol GS, Clegg W. Complexes of 6-methyl-2-pyridone with the alkaline earth metals magnesium, strontium and barium: Synthesis and structural characterization. *Inorg. Chim. Acta.* 2006;359:3474-3480.
  40. Wong MW, Wiberg KB, Frisch MJ. Solvent effects 3. tautomeric equilibria of formamide and 2-pyridone in the gas phase and solution: An Ab initio SCRF study. *J. Am. Chem. Soc.* 1992;114(5): 1645-1652.
  41. King SST, Dilling WL, Tefertille NB. An infrared study of the tautomerism of chlorinated 2-pyridinols isolated in an argon matrix. *Tetrahedron.* 1972;28(24): 5859-5863.
  42. Beak P, Covington JB. Solvent effects on protomeric equilibria: Quantitative correlation with an electrostatic hydrogen-bonding model. *J. Am. Chem. Soc.* 1978; 100(12):3961-3963.
  43. Katritzky AR, Rowe JD, Roy SK. Potentially tautomeric pyridines. Part IX. The effect of chlorine substituents on pyridone—hydroxypyridine tautomerism. *J. Chem. Soc. B.* 1967;758-760.
  44. Marino VM, Gill MJ. Modeling of tautomerism of pyridine-2(1H) thione from vapor to solution, *J. Chem. Soc., Perkins Trans.* 1999;2:801-806.
  45. Moreno M, Miller WH. On the tautomerization reaction 2-pyridone/2-hydroxypyridine: An ab initio study. *Chem. Phys. Letters.* 1990;171(5):475-479.
  46. Gordon A, Katritzky AR. A quantitative relation between heteroaromatic tautomeric equilibrium constants and solvent polarity. *Tetrahedron Lett.* 1968;9(23): 2767-2770.
  47. Dewar MJS, Zebisch EG, Healy EF, Stewart JJP. Development and use of quantum mechanical molecular models. 76. AM1: A new general-purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* 1985;107(13):3902-3909.
  48. Stewart JJP. Optimization of parameters for semiempirical methods I. Method, *J. Comput. Chem.* 1989;10(2):209-220.
  49. Scanlan MJ, Hillier IH, Mac Dowel AA. Theoretical studies of the tautomeric equilibria and isomer energetics of 2-, 3-, and 4-Hydroxypyridine. *J. Am. Chem. Soc.* 1983;105(11):3568-3571.
  50. Khalil SM. DFT study on the stepwise fluorinated methylenecyclopropane and 1-methylcyclopropene system *Z. Naturforsch.* 2008;63a:42- 48.
  51. Al-Halasa WF, Mahasnah A, Khalil SM. MINDO-forces study on the substituted

- effect in the Keto-Enol tautomerism of acetyl derivatives, Z. Naturforsch. 2004; 59a:299-303.
52. Sway MI, Al-Shawabkeh ID, Khalil SM. Z. Naturforsch. 2004;59a:838.
53. Jarjis HM, Khalil SM. MINDO-forces calculations of allyl and crotyl systems. J. Chem. Soc. Perkin Trans. 1986;2:1701-1704.
54. Al-Noeemat MS, Al-Ma'ani RA, Khalil SM. A theoretical study of substituted cyclopentanones and their enols Z. Naturforsch. 2003;58a:738-748.
55. El-Alali A, Marashdeh AA, Khalil SM. A theoretical study of substituted stepwise fluorinated cyclopropanone Keto-Enol system. Z. Naturforsch. 2003;58a:749-755.
56. Lien MH, Hopkinson AC. A theoretical study of monosubstituted allyl cations. J. Phys. Chem. 1984;88(8):1513-1517.

© 2018 Alhateem; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*  
*The peer review history for this paper can be accessed here:*  
<http://www.sciencedomain.org/review-history/25882>