

Acidity Study on 3-Substituted Pyridines

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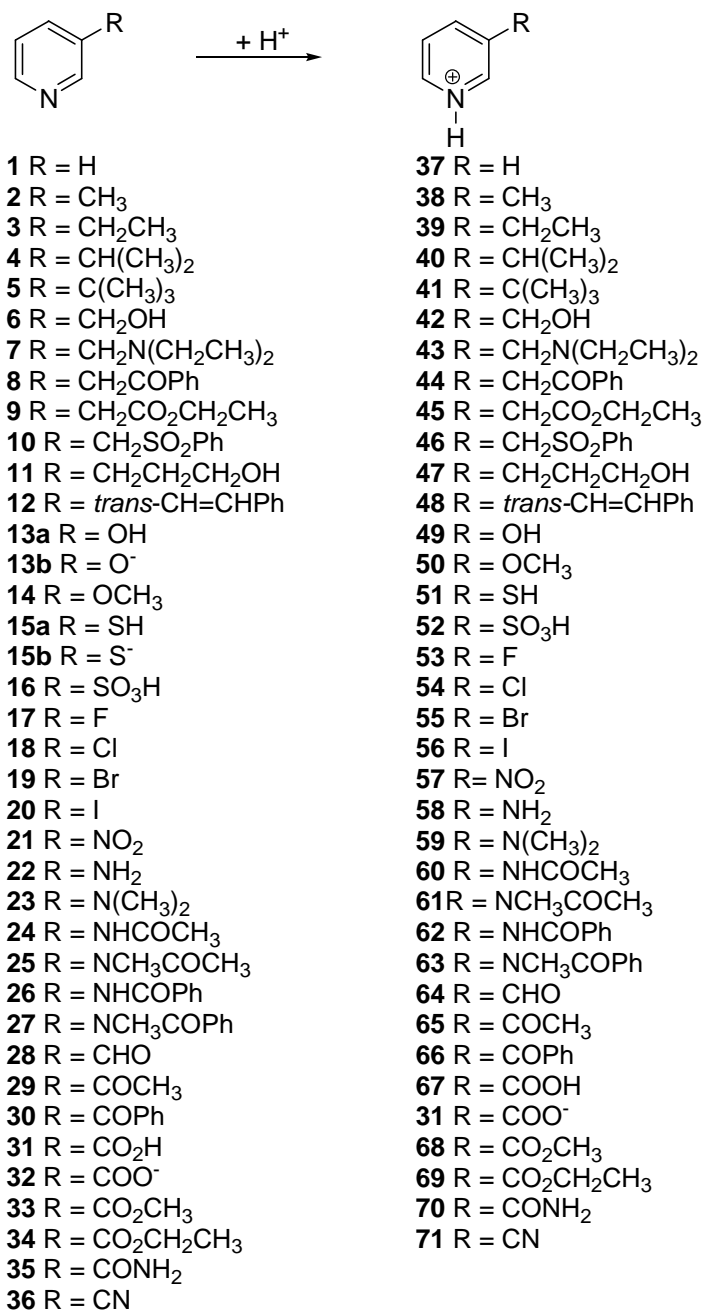
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Received: 24 June 2005 / Accepted: 21 October 2005 / Published: 1 November 2005

Abstract: A comprehensive theoretical study for the protonation of some 3-substituted pyridines has been carried out in aqueous solution ($\epsilon=78.4$) by semi empirical AM1 method in MOPAC2000 and PM5 method in MOPAC2002. Solvent effect was accounted for implicitly by means of the conductor like screening model (COSMO). The acidity constants of these pyridine derivatives have been calculated. The tautomeric and/or conformational equilibria for these compounds, where available, were also taken into account to find out the mol fractions of the species in aqueous media. The results obtained from the calculations were compared with the available experimental values, and the results indicate a considerable agreement with available experimental data.

Keywords: Pyridine, tautomeric equilibrium, conformation, acidity, basicity, pK_a , solvation, AM1, PM5, COSMO.



Scheme 1. The studied pyridines.

Introduction

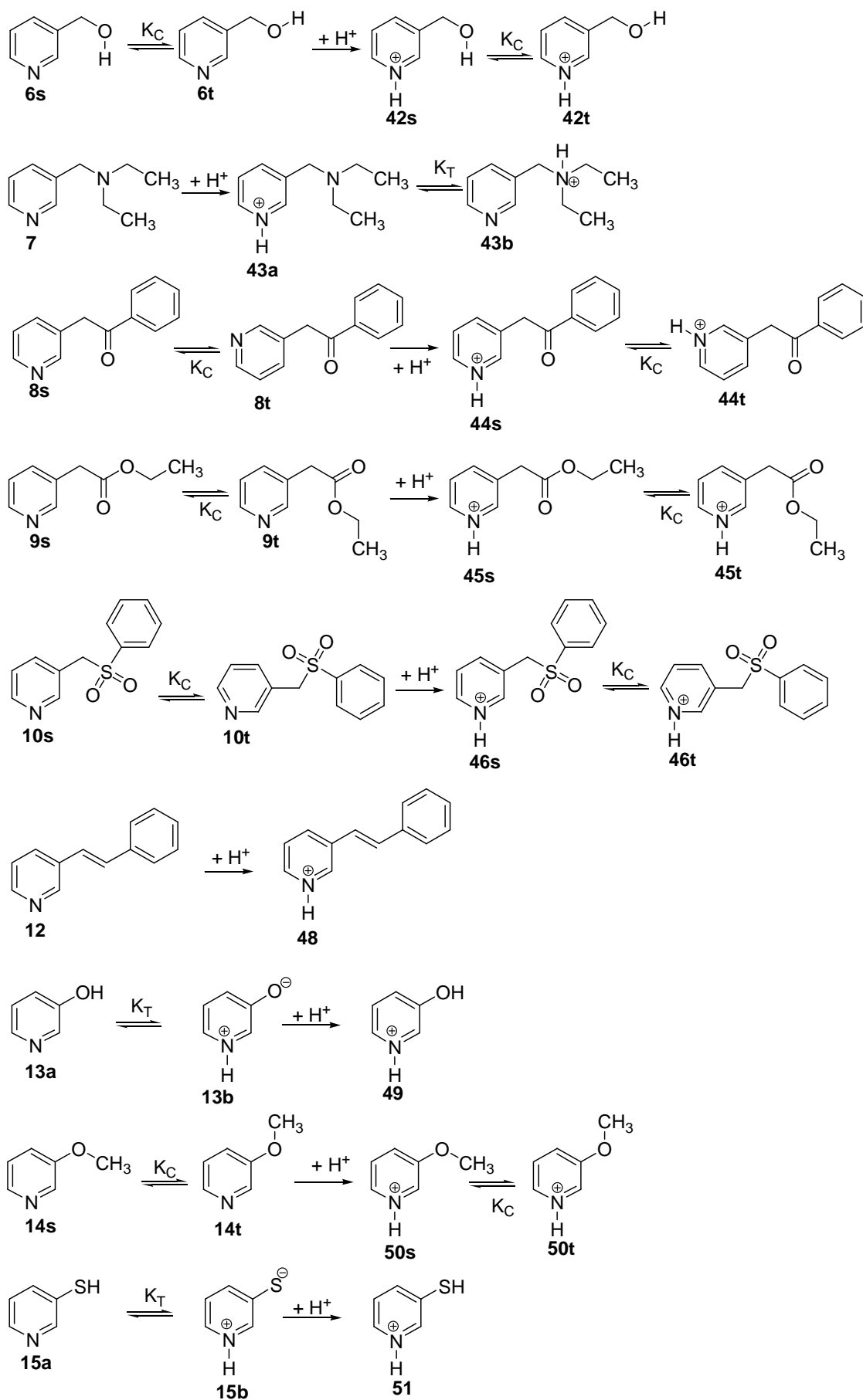
As a continuation of our previous studies [1-9] on tautomerism and acidity of biologically important heterocyclic molecules, I now report a study on acidity for some 3-substituted pyridine derivatives 1-36 (Scheme1). The tautomerism and basicity of heterocycles are great of importance in many areas of chemistry [10-11]. Therefore, the tautomeric and conformational equilibria for the studied molecules should be considered to be able to predict the more accurate pK_a values. In this study the possible tautomeric and conformational equilibria, where available, for 3-substituted pyridines (Scheme1-4), which can exist as different major tautomers according to the solvent and the mode of the substitution,

have been examined in water ($\epsilon=78.4$) by means of AM1 [12] method in MOPAC2000 [13] and newly PM5 [14] method in MOPAC2002 [15]. The pK_a values of these molecules have been calculated by using the obtained weighted average energy figures corresponding the tautomers and/or conformers.

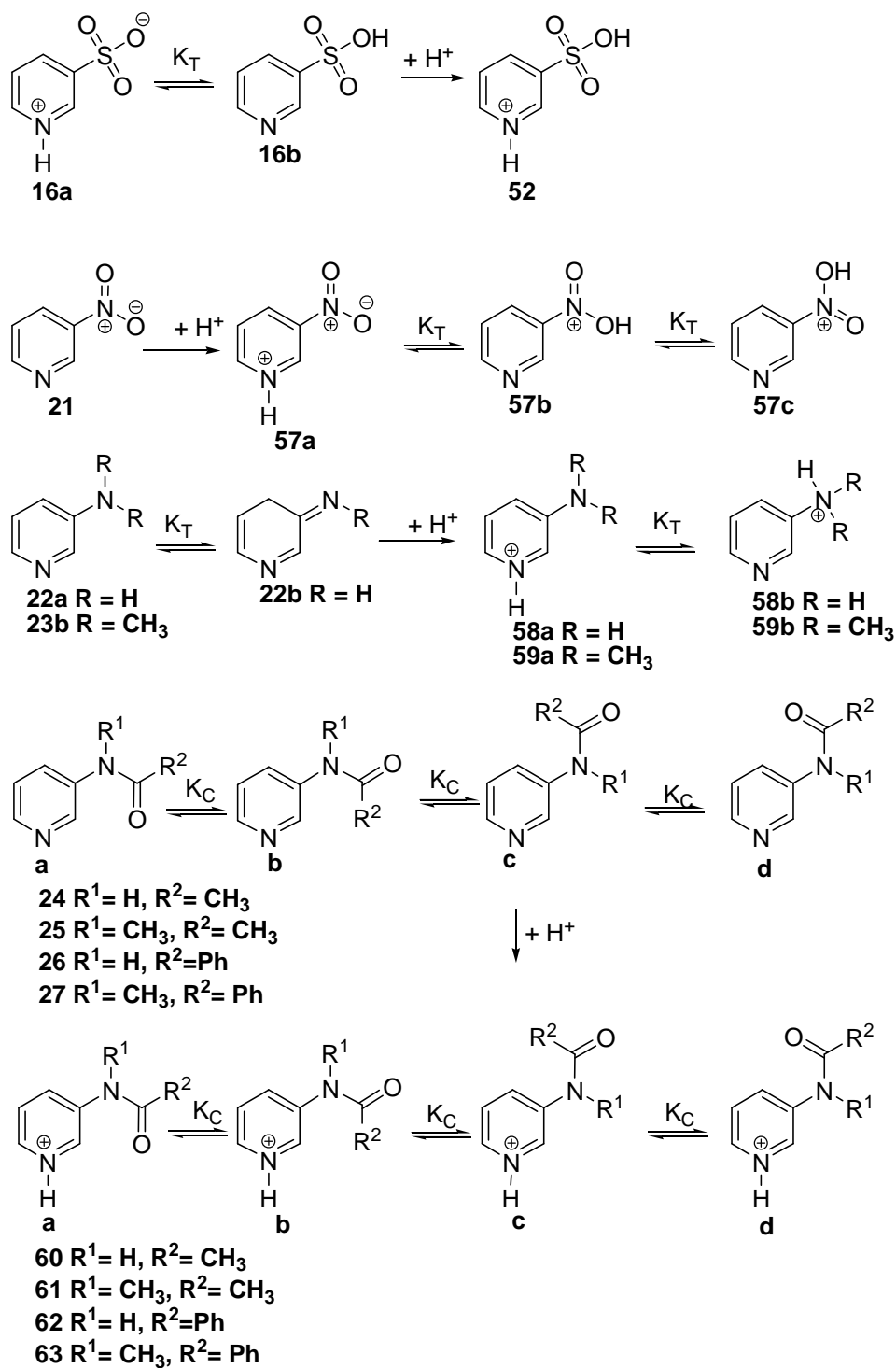
The aim of the present study is to search for correlations between the previously reported experimental data and the calculated results by means of semi empirical methods AM1 and PM5 and also to compare the AM1 results with those obtained by newly PM5 method.

Computational methods

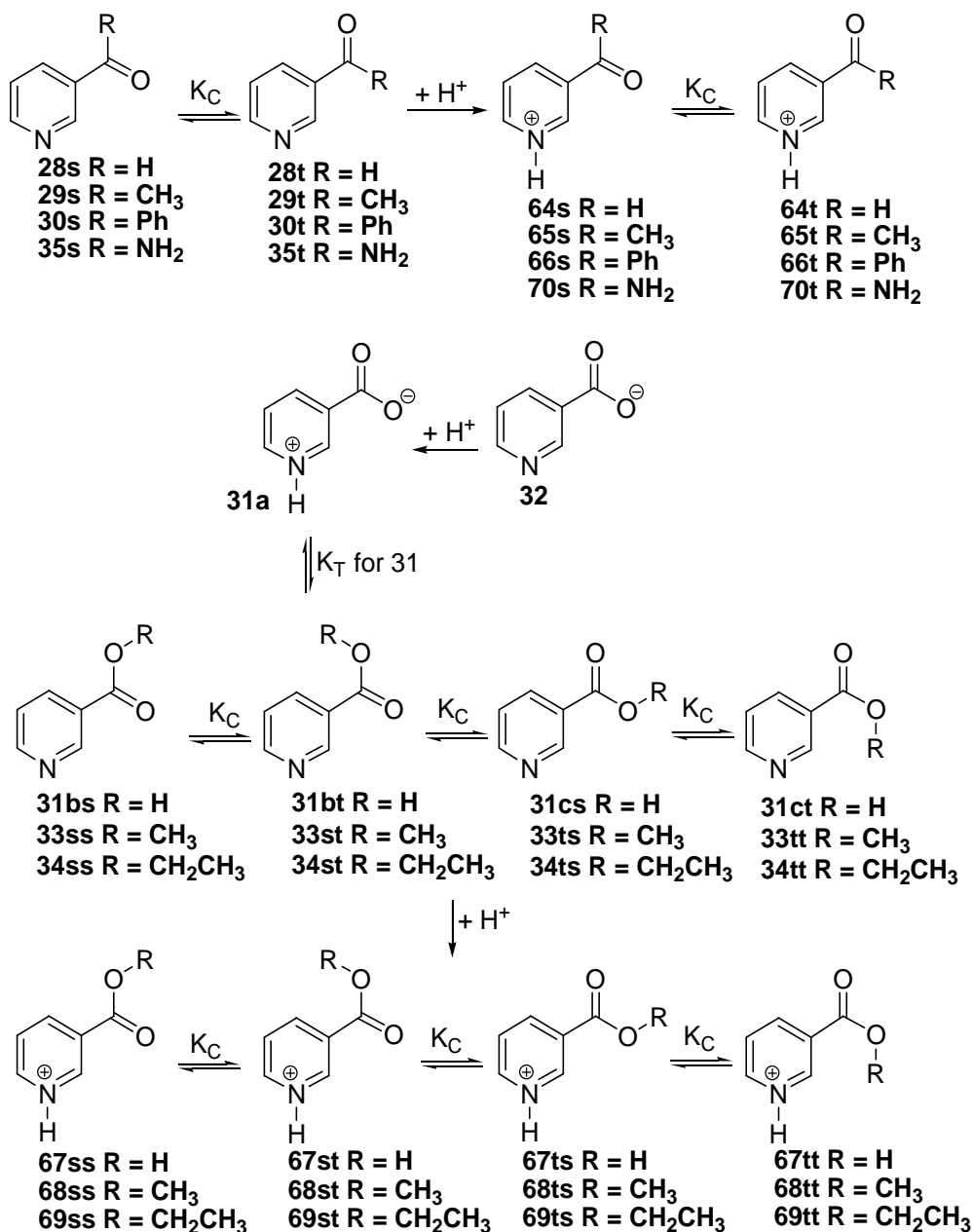
Theoretical calculations were carried out at the restricted Hartree-Fock level (RHF) by using AM1 semi empirical method in the MOPAC2000 and PM5 in the MOPAC2002 implemented on an Intel Pentium IV 3.2 GHz computer, using a relative permittivity of 78.4 corresponding to water, with up to 252, instead of default value 42, surface segment per atom (NSPA, which controls the number of segments) being able to get more accurate results for the COSMO [16] model being used to van der Waals radii. Initial estimates of the geometry of the all structures were obtained by Chem3D in ChemOffice [17] followed by full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles), without any symmetry constraint. All structures were optimized to a gradient norm 0.1-0.5, using the eigenvector following method (EF). The absolute entropies of all structures were calculated from a complete vibrational analysis. Enthalpies were corrected to free energies using the calculated entropies. According to MOPAC manual, the disex is in units of mean segment diameter, which is the distance up to which the interactions of two segments are calculated as the sum of the fine grid interactions. Disex controls the radius, up to which the segment-segment interactions are evaluated on the basis of the basic grid points. For accurate calculations larger values may be used. In this case the calculation time may increase as disex^2 . The Disex = 2, which is the default value, were implicitly used for conjugate bases 1-36 and explicitly for conjugate acids 37-71 in both AM1 and PM5 calculations. When the Disex=2 not used explicitly for conjugate acids 37-71 in both AM1 and PM5 calculations there are a little differences between the figures obtained explicitly and the ones found implicitly.



Scheme 2. The protonated forms of 3-substituted pyridines.



Scheme 3. The protonated forms of 3-substituted pyridines.



Scheme 4. The protonated forms of 3-substituted pyridines.

Results and discussion

Conformation and tautomerism

The AM1 and PM5 calculated heats of formation, absolute entropies, and the mole fractions for the individual tautomeric forms and conformers, where available, for the conjugate bases and conjugate acids (Scheme 2-4) are listed in Table 1-2 and 4-5. The estimation of the pK_a values for the conjugate bases 5, 7-10, 12, 26-27, and 30 failed by AM1 COSMO solvation since the absolute entropy values for the protonated species of the compounds 41, 43-46, 48, 62-63, and 66 could not be calculated by MOPAC2000 in ChemOffice.

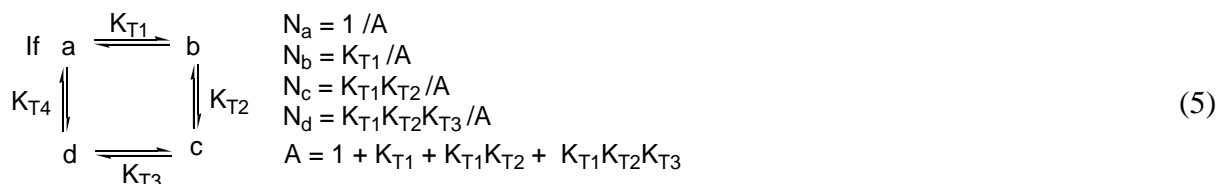
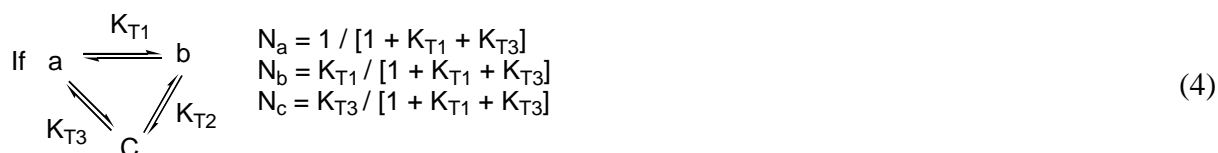
The tautomeric and/or conformational equilibria for the compounds under investigation, if available, were taken into account to find out the mol fractions of the species leading to the weighted average of ΔG_f for conformers and/or tautomers (Scheme 2-4).

The weighted averages of the free energies ($\Delta G_{f(wA)}$) for the tautomers and conformers have been estimated by using the following equations.

$$\Delta G_{f(wa)} = [N_a] [\Delta G_{f(a)}] + [N_b] [\Delta G_{f(b)}] + \dots \quad (1)$$



$$K_T = e^{-\delta\Delta G / RT} \quad R = 1.987 \times 10^{-3} \text{ kcal/mol} \quad \text{and} \quad T = 298 \text{ K}^\circ$$

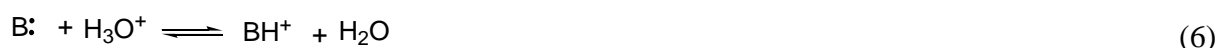


Where N_t , N_s , N_a , N_b , N_c , and N_d are the mole fractions of the individual conformers and/or tautomers. $\Delta G_{f(s)}$, $\Delta G_{f(t)}$, $\Delta G_{f(a)}$, $\Delta G_{f(b)}$, $\Delta G_{f(c)}$, and $\Delta G_{f(d)}$ are the free energies of the *syn* and *anti* conformers and tautomers. Regarding the values of the mole fractions in Table 1-2 and 4-5 for the conformers and/or tautomers of the molecules studied in Scheme1-4, it can be easily seen which molecule has more stable form than the other in AM1 and PM5 calculations. The PM5 COSMO in MOPAC2002 estimates that the 3-hydroxypyridine 13 exist entirely in zwitterion form 13b, whereas the AM1 COSMO in MOPAC2000 calculations gives the 3-hydroxypyridine 13 exist entirely in the hydroxy form 13a while the hydroxy form 13a experimentally is greatly dominant only in of low dielectric constant [18]. The comparison of the pKa value of the 3-hydroxypyridine 13a with those of methylated forms indicated that the two tautomeric forms 13a and 13b exist almost equally in aqueous solution [18]. Both AM1 and PM5 shows that 3-mercaptopyridine 15 exist predominantly in zwitterionic form 15b rather than the 3-mercaptopyridine 15a in aqueous solution, which is consistent

with the findings found by UV spectral comparisons and pKa measurements [19]. 3-Aminopyridine 22 has been also shown to exist predominantly in amino form 22a by infrared spectroscopy [20, 21], which is in good agreement with both AM1 and PM5 results. As expected both AM1 and PM5 estimated that the zwitterionic structure 31a of 3-pyridinecarboxylic acid 31 is much more stable than the 3-carboxypyridine structure 31b, which is consistent with the experimental finding [22].

Basicity

It is well known that it is impossible to measure the pKa values of the individual tautomers in the tautomeric equilibrium and it is usually difficult to prepare all the fixed model compounds of the individual tautomers in which the mobile H-atom replaced with a generally methyl group to eliminate the migration of H-atom. In aqueous solution the acidity of a given base B is the standard free energy change calculated by means of Eq. 7 for the reaction 6.



$$\delta\Delta G_{f(\text{BH}^+)} = [\Delta G_{f(\text{B})} + \Delta G_{f(\text{H}_3\text{O}^+)}] - [\delta\Delta G_{f(\text{BH}^+)} + \Delta G_{f(\text{H}_2\text{O})}] \quad (7)$$

AM1 and PM5 calculated heats of formation and absolute entropy values of H₃O⁺ and H₂O in aqueous solution are given in Table 1-2 and Table 3-4. These were converted to free energy by using AM1 and PM5 calculated absolute entropy values. In aqueous solution the pK_a values of the studied molecules were found by using the following equation

$$\text{pK}_{a(\text{BH}^+)} = \frac{\delta\Delta G_{f(\text{BH}^+)}}{2.303RT} \quad (8)$$

Where R= 1.987x10⁻³ kcal/mol °K and T= 298 °K. In this work pKa values of various 3-substituted pyridine derivatives were calculated in aqueous media by means of AM1 COSMO method in MOPAC2000 and PM5 COSMO method in MOPAC2002. All pKa values calculated by Eq. 8 are listed in Table 3 and Table 6. As can be seen from Table 3 and Table 6 the obtained pKa values from AM1 and PM5 calculations are generally in very good agreement with the experimental pKa values. The absolute error between experimental and calculated pKa values are within ± 0-1 kcal/mol range, exceptions of conjugate bases 15, 21-23, and 36, with AM1 calculations i.e., ± 0-2 kcal/mol, and conjugate bases 13, 15-16, 22, and 31 with PM5 calculations.

Both AM1 and PM5 overestimated the pK_a value of the 3-mercaptopyridine 15 approximately in 5 pK_a units giving the figures 10.58 and 10.90, respectively. Experimentally 3-aminopyridine 22 in aqueous solution undergoes predominant protonation at the ring nitrogen atom [11]. In both AM1 and PM5 calculations the protonation of 22 found to be predominantly takes place at exocyclic nitrogen atom giving cation 58b, which is not consistent with experimental data. However, the protonation of 23 occurs predominantly at the ring nitrogen atom in AM1 calculations and mostly at the exocyclic nitrogen atom in PM5 resulting in cation 59a. Due to these results, probably, the acidity constant of the 3-aminopyridine 22 was found to be 5 pK_a units less than the experimental value by both AM1 and PM5. While the PM5 could calculate the pK_a value for 3-cyanopyridine 36 which is very close to experimental value being approximately 1.35. However, the AM1 overestimated value of 4.21 was obtained by AM1. By AM1 method the pK_a value for the conjugate base 31 was found to be as 3.32, which is consistent with the experimental values 3.13 or 3.75, but PM5 predicted the molecule 31 as much more acidic compared to the experimental data. The acidity constants for the 3-nitropyridine 21 and 3-dimethylaminopyridine 23 predicted by means of AM1 COSMO method exceeds the acceptable limit $\pm 0.1 pK_a$ unit.

Table 1. The AM1 calculated thermodynamic properties of pyridine derivatives in aqueous solution ($\epsilon=78.4$).

Compound	ΔH_f (kcal/mol)	ΔS (cal/mol K)	ΔG_f^a (kcal/mol)	Mol fractions of conformers or tautomers ^b	Weighted average ΔG_f^c (kcal/mol)
1	23.81	67.41	3.72		
2	15.82	75.27	-6.61		
3	9.99	84.08	-15.07		
4	5.94	90.20	-20.94		
6s	-35.14	78.17	-58.43	N6s = 0.08	-59.74
6t	-35.12	83.00	-59.85	N6t = 0.92	
11	-48.81	101.49	-79.05		
13a	-24.83	74.70	-47.10	N13a = 1.00	-47.10
13b	-21.69	73.35	-43.55	N13b = 0.00	
14s	-17.00	81.44	-41.27	N14s = 0.49	-41.28
14t	-16.82	82.11	-41.29	N14t = 0.51	
15a	23.47	79.34	-0.17	N15a = 0.00	-9.62
15b	13.15	76.40	-9.62	N15b = 1.00	
16a	-138.95	90.49	-165.92	N16a = 0.99	-165.89
16b	-135.16	94.22	-163.24	N16b = 0.01	
17	-21.00	73.05	-42.77		
18	16.94	75.78	-5.64		
19	27.89	78.72	4.43		
20	39.32	80.62	15.30		
21	17.16	84.73	-8.09		

Table 1 continued

22a	15.58	74.66	-6.67	N22a = 1.00	-6.67
22b	39.53	76.79	16.65	N22b = 0.00	
23	28.09	90.57	1.10		
24a	-25.52	88.95	-52.03	N24a = 0.10	-52.72
24b	-24.92	91.95	-51.60	N24b = 0.05	
24c	-25.04	93.73	-52.97	N24c = 0.52	
24d	-25.35	91.78	-52.70	N24d = 0.33	
25a	-16.06	100.30	-45.95	N25a = 0.32	-45.82
25b	-15.62	100.88	-45.68	N25b = 0.20	
25c	-15.67	100.63	-45.66	N25c = 0.20	
25d	-16.00	100.25	-45.87	N25d = 0.28	
28s	-14.56	80.42	-38.53	N28s = 0.51	-38.52
28t	-14.58	80.26	-38.50	N28t = 0.49	
29s	-20.40	91.34	-47.62	N29s = 0.82	-47.46
29t	-20.34	88.53	-46.73	N29t = 0.18	
31a	-77.03	86.63	-102.84	N31a = 0.84	-102.62
31bs	-75.82	85.56	-101.32	N31b = 0.05	
31bt	-74.81	85.85	-100.39	N31c = 0.11	
31cs	-75.84	86.97	-101.76		
31ct	-74.62	86.45	-100.38		
32	-173.27	86.39	-199.01		
33ss	-66.86	98.59	-96.24	N33ss = 0.98	-96.21
33st	-64.15	93.94	-92.14	N33st = 0.00	
33ts	-66.89	90.99	-94.01	N33ts = 0.02	
33tt	-64.07	94.50	-92.23	N33tt = 0.00	
34ss	-72.52	103.66	-103.41	N34ss = 0.68	-103.22
34st	-69.89	105.79	-101.42	N34st = 0.02	
34ts	-72.56	101.89	-102.92	N34ts = 0.30	
34tt	-69.84	102.97	-100.53	N34tt = 0.00	
35s	-28.56	85.54	-54.06	N35s = 0.54	-54.01
35t	-28.50	85.45	-53.96	N35t = 0.46	
36	52.35	77.61	29.22		
H ₂ O	-68.89	45.11	-82.31		

^a from $\Delta G_f = \Delta H_f - T\Delta S$

^b from Eq. 2-5

^c from Eq. 7

Table 2. The AM1 calculated thermodynamic properties of protonated pyridine derivatives in aqueous solution ($\epsilon=78.4$).

Compound	ΔH_f (kcal/mol)	ΔS (cal/mol K)	ΔG_f^a (kcal/mol)	Mol fractions of conformers or tautomers ^b	Weighted average ΔG_f^c (kcal/mol)
37	118.38	67.77	98.18		
38	111.04	80.48	87.06		
39	105.20	85.55	79.71		
40	101.20	92.26	73.71		
42s	60.17	78.45	36.81	N42s = 0.04	35.07
42t	60.09	84.19	35.00	N42t = 0.96	
47	44.81	100.39	14.89		
49	71.25	75.35	48.80		

Table 2 continued

50s	79.85	83.70	54.91	N50s = 0.25	54.43
50t	80.03	86.45	54.27	N50t = 0.75	
51	119.55	80.48	95.57		
52	-40.25	96.02	-68.86		
53	75.96	73.50	54.06		
54	113.65	76.24	90.93		
55	124.49	79.15	100.90		
56	135.60	81.00	111.46		
57a	115.06	84.23	89.96	N57a = 1.00	89.96
57b	141.24	84.66	116.01	N57b = 0.00	
57c	141.23	83.44	116.36	N57c = 0.00	
58a	112.39	75.87	89.79	N58a = 0.00	80.59
58b	103.51	76.92	80.59	N58b = 1.00	
59a	124.79	92.13	97.34	N59a = 1.00	97.34
59b	128.49	90.59	101.49	N59b = 0.00	
60a	71.08	88.65	44.68	N60a = 0.01	42.39
60b	71.27	94.16	43.21	N60b = 0.13	
60c	70.99	92.11	43.54	N60c = 0.07	
60d	70.76	96.12	42.12	N60d = 0.79	
61a	80.63	96.86	51.77	N61a = 0.08	50.84
61b	80.77	101.54	50.51	N61b = 0.70	
61c	80.58	97.09	51.65	N61c = 0.10	
61d	80.46	96.54	51.69	N61d = 0.11	
64s	81.23	80.93	57.11	N64s = 0.41	56.99
64t	80.96	80.74	56.90	N64t = 0.59	
65s	75.63	89.30	49.02	N65s = 0.56	49.08
65t	75.60	88.73	49.16	N65t = 0.44	
67ss	20.19	86.90	-5.71	N67ss = 0.50	-5.47
67st	21.06	86.73	-4.79	N67st = 0.11	
67ts	20.05	85.75	-5.50	N67ts = 0.35	
67tt	21.00	84.54	-4.19	N67tt = 0.04	
68ss	29.32	95.36	0.90	N68ss = 0.82	1.06
68st	32.03	94.92	3.74	N68st = 0.00	
68ts	29.13	91.75	1.79	N68ts = 0.18	
68tt	32.03	95.30	3.63	N68tt = 0.01	
69ss	23.79	96.89	-5.08	N69ss = 0.03	-6.80
69st	26.93	97.75	-2.20	N69st = 0.00	
69ts	23.58	102.34	-6.92	N69ts = 0.96	
69tt	26.25	103.35	-4.55	N69tt = 0.01	
70s	67.66	85.71	42.12	N70s = 0.49	42.10
70t	67.38	85.73	42.09	N70t = 0.51	
71	148.47	78.16	125.18		
H ₃ O+	33.13	46.13	19.38		

^a from $\Delta G_f = \Delta H_f - T\Delta S$

^b from Eq. 2-5

^c from Eq. 7

Table 3. The AM1 calculated pK_a values for pyridines in aqueous solution ($\epsilon=78.4$).

Conjugate base (B)	ΔG_f Kcal/mol	Conjugate acid (BH ⁺)	ΔG_f Kcal/mol	$\delta\Delta G_f^a$ Kcal/mol	pK _a (BH ⁺) ^b	Exp. pK _a (BH ⁺) ^c	Absolute error between pK _a (calc.) and pK _a (exp.)	References ^c
1	3.72	37	98.18	7.23	5.30	5.27, 5.28	0.03, 0.02	23, 24, 25
2	-6.61	38	87.06	8.02	5.88	5.67, 5.70, 5.75	0.21, 0.18, 0.13	26, 27, 28, 29
3	-15.07	39	79.71	6.91	5.07	5.70	0.63	30
4	-20.94	40	73.71	7.04	5.16	5.72	-0.56	30
6	-59.74	42	35.07	6.88	5.05	4.90, 4.95	0.15, 0.10	31, 32
11	-79.05	47	14.89	7.75	5.68	5.47	0.21	31
13	-47.10	49	48.80	5.79	4.25	4.80, 4.86	-0.55, -0.61	27, 38, 39, 40
14	-41.28	50	54.43	5.98	4.39	4.78, 4.88, 4.90	-0.39, -0.49, -0.51	26, 40, 38, 27
15	-9.62	51	95.57	-3.5	-2.57	2.28	-4.85	19
16	-165.89	52	-68.86	4.66	3.42	3.22	0.20	41
17	-42.77	53	54.06	4.86	3.56	2.97, 3.10	0.59, 0.46	30, 42
18	-5.64	54	90.93	5.12	3.75	2.81, 2.84, 2.98	0.94, 0.91, 0.77	26, 42, 27
19	4.43	55	100.90	5.22	3.83	2.80, 2.84, 2.85	1.03, 0.99, 0.98	27, 42, 26
20	15.30	56	111.46	5.53	4.05	3.25	0.85	30
21	-8.09	57	89.96	3.64	2.67	0.81, 1.18	1.86, 1.49	43, 26
22	-6.67	58	80.59	14.43	10.58	5.80, 5.98, 6.04	4.78, 4.60, 4.54	30, 44, 26, 27
23	1.10	59	97.34	5.38	3.95	6.45	-2.50	45
24	-52.72	60	42.39	6.58	4.83	4.46	0.37	46
25	-45.82	61	50.84	5.03	3.69	3.52	0.17	46
28	-38.52	64	56.99	6.18	4.53	3.70, 3.75	0.83, 0.78	47, 48
29	-47.46	65	49.08	5.15	3.78	3.18, 3.26	0.60, 0.52	30, 49
31	-102.62	67	-5.47	4.53	3.32	3.13, 3.75	0.19, -0.43	43, 50
32	-199.01	31	-102.62	5.30	3.89	4.77	-0.88	51
33	-96.21	68	1.06	4.42	3.24	3.09	0.15	26
34	-103.22	69	-6.80	5.27	3.86	3.35	0.51	42
35	-54.01	70	42.10	5.58	4.09	3.40	0.69	51
36	29.22	71	125.18	5.74	4.21	1.30, 1.36, 1.45	2.91, 2.85, 2.76	27, 26, 52, 51
H2O	-82.31	H3O+	19.38					

^a from Eq. 7^b from Eq. 8^c See references

Table 4. The PM5 calculated thermodynamic properties of pyridine derivatives in aqueous solution ($\epsilon=78.4$).

Compound	ΔH_f (Kcal/mol)	ΔS (cal/mol K)	ΔG_f^a (Kcal/mol)	Mol fractions of conformers or tautomers ^b	Weighted average ΔG_f^c (Kcal/mol)
1	23.20	68.11	2.90		
2	14.89	76.07	-7.78		
3	9.86	86.55	-15.93		
4	4.38	93.33	-23.48		
5	-0.41	97.49	-29.46		
6s	-25.82	86.73	-51.67	N6s = 0.09	-52.93
6t	-27.77	84.82	-53.05	N6t = 0.91	
7	16.47	112.82	-17.15		
8s	-1.02	115.97	-35.58	N8a = 0.57	-35.51
8t	-0.97	115.61	-35.42	N8b = 0.43	
9s	-80.34	109.42	-112.95	N9a = 0.44	-113.03
9t	-79.82	111.68	-113.10	N9b = 0.56	
10s	-40.59	121.95	-76.93	N10a = 0.00	-82.08
10t	-45.00	124.42	-82.08	N10b = 1.00	
11	-39.97	101.01	-70.07		
12	57.30	110.02	24.51		
13a	-23.18	75.95	-45.81	N13a = 0.00	-50.34
13b	-28.23	74.19	-50.34	N13b = 1.00	
14s	-14.94	83.20	-39.74	N14s = 0.28	-40.14
14t	-15.09	84.59	-40.3	N14t = 0.72	
15a	26.92	81.95	2.50	N15a = 0.00	-5.68
15b	17.32	77.17	-5.68	N15b = 1.00	
16a	-126.62	92.81	-154.28	N16a = 1.00	-154.28
16b	-112.87	93.42	-140.71	N16b = 0.00	
17	-21.66	73.79	-43.65		
18	16.33	76.76	-6.54		
19	27.51	79.75	3.74		
20	40.88	82.31	16.35		
21	14.89	84.82	-10.39		
22a	16.69	76.03	-5.96	N22a = 1.00	-5.96
22b	37.36	78.10	14.09	N22b = 0.00	
23	27.40	91.44	0.15		
24a	-32.65	93.58	-60.54	N24a = 0.41	-60.32
24b	-31.30	94.64	-59.50	N24b = 0.08	
24c	-31.37	96.57	-60.15	N24c = 0.21	
24d	-32.49	93.49	-60.35	N24d = 0.30	
25a	-26.49	102.59	-57.06	N25a = 0.18	-57.31
25b	-25.71	107.07	-57.62	N25b = 0.47	
25c	-25.70	104.98	-56.98	N25c = 0.17	
25d	-26.36	103.04	-57.06	N25d = 0.18	
26a	-2.11	113.23	-35.85	N26a = 0.60	-35.62
26b	-0.69	111.98	-34.06	N26b = 0.03	
26c	-0.64	112.57	-34.19	N26c = 0.04	
26d	-1.97	112.55	-35.51	N26d = 0.33	
27a	4.50	125.10	-32.78	N27a = 0.54	-32.56
27b	4.95	121.27	-31.19	N27b = 0.04	
27c	5.02	121.98	-31.33	N27c = 0.05	
27d	4.68	124.97	-32.56	N27d = 0.37	
28s	-12.90	80.90	-37.01	N28s = 0.50	-37.01

Table 4 continued

28t	-12.81	81.17	-37.00	N28t = 0.50	
29s	-23.98	88.93	-50.48	N29s = 0.59	-50.39
29t	-23.88	88.52	-50.26	N29t = 0.41	
30s	6.57	105.44	-24.85	N30s = 0.47	-24.89
30t	6.46	105.33	-24.93	N30t = 0.53	
31a	-84.13	85.45	-109.59	N31a = 1.00	-109.59
31bs	-72.64	86.22	-98.33	N31b = 0.00	
31bt	-71.99	86.04	-97.62	N31c = 0.00	
31cs	-72.63	85.32	-98.06		
31ct	-70.93	81.13	-95.11		
32	-186.31	79.52	-210.13		
33ss	-65.43	94.48	-93.59	N33ss = 0.48	-93.52
33st	-63.30	95.82	-91.85	N33st = 0.03	
33ts	-65.43	94.52	-93.60	N33ts = 0.48	
33tt	-63.16	95.20	-91.53	N33tt = 0.01	
34ss	-71.88	103.55	-102.74	N34ss = 0.65	-102.49
34st	-70.05	103.73	-100.96	N34st = 0.03	
34ts	-71.86	102.01	-102.26	N34ts = 0.29	
34tt	-69.86	104.01	-100.85	N34tt = 0.03	
35s	-34.15	86.57	-59.95	N35s = 0.61	-59.85
35t	-34.02	86.13	-59.69	N35t = 0.39	
36	52.32	78.49	28.93		
H ₂ O	-59.44	44.99	-72.85		

^a from $\Delta G_f = \Delta H_f - T\Delta S$

^b from Eq. 2-5

^c from Eq. 7

Table 5. The PM5 calculated thermodynamic properties of protonated pyridine derivatives in aqueous solution ($\epsilon=78.4$).

Compound	ΔH_f (Kcal/mol)	ΔS (cal/mol K)	ΔG_f^a (Kcal/mol)	Mol fractions of conformers or tautomers ^b	Weighted average ΔG_f^c (Kcal/mol)
37	121.80	68.59	101.36		
38	113.73	79.14	90.15		
39	109.00	86.50	83.22		
40	103.32	93.27	75.53		
41	98.58	96.84	69.72		
42s	72.67	86.97	46.75	N42s = 0.53	46.78
42t	72.66	86.73	46.81	N42t = 0.47	
43a	115.66	113.65	81.79	N43a = 0.00	1.00
43b	109.85	112.55	76.31	N43b = 1.00	
44s	99.68	116.00	65.11	N44s = 0.26	64.64
44t	99.60	117.86	64.48	N44t = 0.74	
45s	20.63	113.10	-13.07	N45s = 0.71	-12.92
45t	20.69	111.56	-12.55	N45t = 0.29	
46s	61.58	122.15	25.18	N46s = 0.00	
46t	56.29	122.48	19.79	N46t = 1.00	
47	59.29	101.27	29.11		

Table 5 continued

48	156.51	109.33	123.93		
49	77.90	75.96	55.26		
50s	86.40	87.29	60.39	N50s = 0.98	60.44
50t	86.71	80.44	62.74	N50t = 0.02	
51	127.96	81.08	103.80		
52	-6.43	94.86	-34.70		
53	81.79	74.22	59.67		
54	118.24	77.23	95.23		
55	129.46	80.21	105.56		
56	141.60	82.75	116.95		
57a	122.34	85.33	96.91	N57a = 1.00	96.91
57b	152.00	85.62	126.49	N57b = 0.00	
57c	151.94	86.06	126.29	N57c = 0.00	
58a	115.72	76.66	92.88	N58a = 0.00	85.14
58b	108.61	78.75	85.14	N58b = 1.00	
59a	127.09	92.35	99.57	N59a = 0.71	99.72
59b	127.52	92.01	100.10	N59b = 0.29	
60a	69.61	96.97	40.71	N60a = 0.58	40.79
60b	71.11	94.92	42.82	N60b = 0.00	
60c	70.92	94.36	42.80	N60c = 0.00	
60d	69.46	95.86	40.89	N60d = 0.42	
61a	76.06	103.79	45.13	N61a = 0.47	45.33
61b	76.84	99.34	47.24	N61b = 0.01	
61c	76.75	104.25	45.68	N61c = 0.19	
61d	75.93	102.62	45.35	N61d = 0.33	
62a	100.67	115.08	66.37	N62a = 0.71	66.59
62b	102.48	112.86	68.85	N62b = 0.01	
62c	101.96	112.37	68.47	N62c = 0.02	
62d	100.51	112.60	66.97	N62d = 0.26	
63a	107.58	122.27	71.14	N63a = 0.15	70.46
63b	108.32	122.08	71.94	N63b = 0.04	
63c	107.81	121.03	71.74	N63c = 0.05	
63d	107.41	124.95	70.17	N63d = 0.76	
64s	90.19	81.96	65.76	N64s = 0.46	65.71
64t	90.14	82.15	65.66	N64t = 0.54	
65s	78.97	89.14	52.41	N65s = 0.38	52.23
65t	78.90	89.85	52.12	N65t = 0.62	
66s	110.11	109.01	77.63	N66s = 0.64	77.75
66t	109.97	107.36	77.97	N66t = 0.36	
67ss	31.76	86.71	5.92	N67ss = 0.35	5.95
67st	32.52	86.50	6.74	N67st = 0.09	
67ts	31.65	87.04	5.71	N67ts = 0.50	
67tt	32.66	86.12	7.00	N67tt = 0.06	
68ss	39.09	95.33	10.68	N68ss = 0.40	10.77
68st	41.15	97.48	12.10	N68st = 0.04	
68ts	39.01	95.71	10.49	N68ts = 0.55	
68tt	41.17	96.63	12.37	N68tt = 0.02	
69ss	31.32	105.80	-0.21	N69ss = 0.97	-0.15
69st	34.51	98.56	5.14	N69st = 0.00	
69ts	33.75	106.83	1.91	N69ts = 0.03	
69tt	34.56	103.65	3.67	N69tt = 0.00	
70s	68.87	87.07	42.92	N70s = 0.53	42.95
70t	68.85	86.82	42.98	N70t = 0.47	
71	155.79	78.92	132.27		133.05
H ₃ O ⁺	46.81	45.91	33.13		

^a from $\Delta G_f = \Delta H_f - T\Delta S$ ^b from Eq. 2-5^c from Eq. 7**Table 6.** The PM5 calculated pK_a values for pyridines in aqueous solution ($\epsilon=78.4$).

Conjugate base (B)	ΔG_f kcal/mol	Conjugate acid (BH ⁺)	ΔG_f kcal/mol	$\delta\Delta G_f^a$ kcal/mol	pK _a (BH ⁺) ^b	Exp. pK _a (BH ⁺) ^c	Absolute error between pK _a (calc.) and pK _a (exp.)	References ^c
1	2.90	37	101.36	7.52	5.51	5.27, 5.28	0.24, 0.23	23, 24, 25
2	-7.78	38	90.15	8.05	5.90	5.67, 5.70, 5.75	0.23, 0.20, 0.15	26, 27, 28, 29
3	-15.93	39	83.22	6.83	5.01	5.70	-0.69	30
4	-23.48	40	75.53	6.97	5.11	5.72	-0.61	30
5	-29.46	41	69.72	6.80	4.99	5.82	-0.83	30
6	-52.93	42	46.78	6.27	4.59	4.90, 4.95	-0.31, -0.36	31, 32
7	-17.15	43	76.31	12.52	9.18	8.55	0.63	33
8	-35.51	44	64.64	5.83	4.28	4.87	-0.59	34
9	-113.03	45	-12.92	5.87	4.30	4.67	-0.37	35
10	-82.08	46	19.79	4.11	3.01	3.67	-0.66	36
11	-70.07	47	29.11	6.80	4.98	5.47	-0.49	31
12	24.51	48	123.93	6.56	4.81	4.75	0.06	37
13	-50.34	49	55.26	0.38	0.28	4.80, 4.86	-4.52, -4.58	27, 38, 39, 40
14	-40.14	50	60.44	5.40	3.96	4.78, 4.88, 4.90	-0.82, -0.92, -0.94	26, 40, 38, 27
15	-5.68	51	103.80	-3.50	-2.56	2.28	-4.84	19
16	-154.28	52	-34.70	-13.60	-9.97	3.22	-13.19	41
17	-43.65	53	59.67	2.66	1.95	2.97, 3.10	-1.14	30, 42
18	-6.54	54	95.23	4.21	3.08	2.81, 2.84, 2.98	0.27, 0.24, 0.10	26, 42, 27
19	3.74	55	105.56	4.16	3.05	2.80, 2.84, 2.85	0.15, 0.21, 0.20	27, 42, 26
20	16.35	56	116.95	5.38	3.94	3.25	0.69	30
21	-10.39	57	96.91	-1.32	-0.97	0.81, 1.18	-1.78, -2.15	43, 26
22	-5.96	58	85.14	14.88	10.90	5.80, 5.98, 6.04	5.10, 4.92, 4.86	30, 44, 26, 27
23	0.15	59	99.72	6.41	4.70	6.45	-1.75	45
24	-60.32	60	40.79	4.87	3.57	4.46	-0.89	46
25	-57.31	61	45.33	3.34	2.45	3.52	-1.07	46
26	-35.62	62	66.59	3.77	2.76	3.80	-1.04	46
27	-32.56	63	70.46	2.96	2.17	3.66	-1.49	46
28	-37.01	64	65.71	3.26	2.39	3.70, 3.75	-1.31, -1.36	47, 48
29	-50.39	65	52.23	3.36	2.46	3.18, 3.26	-0.72, -0.80	30, 49
30	-24.89	66	77.75	3.34	2.45	3.18	-0.73	26
31	-109.59	67	5.95	-9.56	-7.00	3.13, 3.75	-10.13, -10.75	43, 50
32	-210.13	31	-109.59	5.44	3.99	4.77	-0.78	51
33	-93.52	68	10.77	1.69	1.24	3.09	-1.85	26
34	-102.49	69	-0.15	3.64	2.67	3.35	-0.68	42
35	-59.85	70	42.95	3.18	2.33	3.40	-1.07	51
36	28.93	71	133.05	1.86	1.36	1.30, 1.36, 1.45	0.06, 0.00, -0.09	27, 26, 52, 51
H ₂ O	-72.85	H ₃ O ⁺	33.13					

^a from Eq. 7

^b from Eq. 8

^c See references

Conclusion

Regarding the pK_a values obtained by AM1 COSMO method in aqueous solution in MOPAC2000 and PM5 COSMO method in MOPAC2002 it can be said that AM1 COSMO method in MOPAC2000 seems to be still more suitable to predict the pK_a values for pyridine-like heterocyclic compounds than its rival PM5 COSMO method in MOPAC2002.

Acknowledgements

I thank Anadolu University Research Fund for supporting this study (AÜAF project number: 01 1066, 2001).

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