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A THEORETICAL STUDY ON PROTON-GAIN BEHAVIORS OF SOME AZAINDOLE DERIVATIVES

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ABSTRACT

The acidities, relative stabilities (RS), nucleophilicities (η) and proton affinities (PA) of seven azaindole molecules were determined in both gas and liquid phases using semi-empirical AM1, PM3 and PM5 methods. The calculated pK_a values were compared with those of experimental pK_a values to search for a possible correlation. The protonation centers and protonation patterns were elucidated by taking into account of the best fitting results.

Keywords: Proton gain, Azaindole derivatives, Semi-empirical calculation.

BAZI AZAİNDOL TÜREVLERİNİN PROTON ALMA DAVRANIŞLARININ TEORİK OLARAK İNCELENMESİ

ÖZ

Yedi adet azaindol molekülünün asitlikleri, bağıl kararlılıkları (RS), nukleofilliği (η) ve proton ilgileri (PA) yarı-deneysel AM1, PM3 ve PM5 yöntemleriyle hem gaz hem de sıvı fazlarda belirlenmiştir. Hesaplanan pKa değerleri ile deneysel deneysel pKa değerleri arasındaki olası ilişki araştırılmıştır. Protonlanma merkezleri ve protonlanma mekanizmaları için en uygun sonuç dikkate alınarak aydınlatılmıştır.

Anahtar Kelimeler: Proton alma, Azaindol türevleri, Yarı-deneysel hesaplama.

1. INTRODUCTION

Azaindoles belonging to azole family of drug-like heteroaromatic structures have received an arisen interest recently because of their usage as anti-inflammatory agents, anti-psychotic agents in pharmacy; dying and photographic processes as well as in scientific studies (Yakhontov 1968; Katrizky 1984; Chi et al. 2000). There are some studies on biological activities of azaindole derivatives for animals and plants (Adler and Albert 1963; Ohshiro and Kikuta 2000; Jiang et al. 2011). Moreover, the variable position of the heteroatom existing in the azaindoles increases the chance of suitable binding in biological systems, increasing selectivity, as well as improving bioavailability (Fang et al. 2007). Pharmacological interest in the azaindoles stems from the possibility that they may serve as the parent nucleus of active or antagonistic analogs of naturally occurring indole derivatives such as the endogenously important serotonin. Furthermore, it seemed likely that unsubstantiated azaindoles would have pharmacological properties. It depresses smooth muscle and produces convulsions originating in the spinal cord and subthalamic areas of the brain. Because azaindoles have electron-

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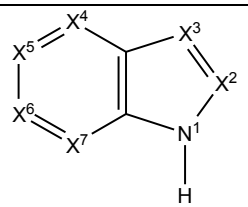
rich azole and electron-poor azine ring systems, they could be possible to selectively functionalize both rings in a controlled fashion. In that way, it is possible to have new opportunities for the site-selective functionalization of useful organic building blocks and may find application in the preparation of novel medicinal compounds (Huestis and Fagnou 2009).

Acid dissociation constants, K_a, of drug precursor molecules are very important and they have been used in activity searches and determination of certain physical parameters such as tautomeric equilibrium, K_T, and synthetic studies as well as the quantitative structure activity (QSAR) and quantitative structure property relations (QSPR) (Güven and Öğretir 1998; Açikkalp et al. 2001; Öğretir et al. 2001, 2003, 2006, 2007; Kanışkan and Öğretir 2002; Öğretir and Kaypak 2002; Öğretir and Tokay 2004; Güray et al. 2007; Yarlıgan et al. 2005).

To the best of our knowledge, we did not find any systematic theoretical study on azaindole derivatives in the literature. Therefore, we have attempted to calculate and evaluate the proton affinities (i.e. PA values), relative stabilities (i.e. RS values), acidity constants, pK_a, and tautomeric equilibrium constants, K_T, of seven azaindole molecules (Table 1) both in gas and liquid phases in the present work. The obtained results were compared with those of experimental results to search any possible correlation.

Table 1. Nomenclature of the studied molecules **(1-7)**.



Molecule No	Nomenclature		X^2	X^3	X^4	X^5	X^6	X^7
1	Indole	1H-Indole	*C*	*C*	*C*	*C*	*C*	*C*
2	2-Azaindole	1H-Indazole	**N**	*C*	*C*	*C*	*C*	*C*
3	3-Azaindole	1H-benzo[d]imidazole	*C*	**N**	*C*	*C*	*C*	*C*
4	4-Azaindole	1H-pyrrolo[3,2-b]pyridine	*C*	*C*	**N**	*C*	*C*	*C*
5	5-Azaindole	1H-pyrrolo[3,2-c]pyridine	*C*	*C*	*C*	**N**	*C*	*C*
6	6-Azaindole	1H-pyrrolo[2,3-c]pyridine	*C*	*C*	*C*	*C*	**N**	*C*
7	7-Azaindole	1H-pyrrolo[2,3-b]pyridine	*C*	*C*	*C*	*C*	C	**N**

2. CALCULATION METHOD

The theoretical calculations were carried out by the CAChe 6.1.12 packet program at Restricted Hartree-Fock level using AM1, PM3 and PM5 semi-empirical SCF-MO methods (CAChe Programme). An Intel Pentium Pro 400 MHz computer was used in all calculations. The initial data for geometry optimization (bond lengths, bond angles and dihedral angles) were estimated by molecular mechanic program (CS ChemOffice Pro for Microsoft Windows).

The gas phase protonation can be defined as in Eqn. 2.1 for a neutral base:

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O \qquad (2.1)$$

where B is the neutral base, H_3O^+ is the hydronium ion and BH^+ is the protonated base.

Since $-\Delta G^o_B = -[\Delta G^o_{BH^+}]$ for the gas phase protonation, the Eqn. 2.2 can be derived for the proton affinity (PA);

$$(PA) = [(\Delta H^{o}_{(H_3O^+)} - \Delta H^{o}_{(H_2O)}) - (\Delta H^{o}_{(B)} - \Delta H^{o}_{(BH^+)})] = -\Delta G^{o}_{B} \quad (2.2)$$

The basic equation for proton uptake of a base in aqueous medium can be expressed as follows;

$$B + AH^+ \rightleftharpoons BH^+ + A \quad (2.3)$$

where AH^+ is the hydronium ion, BH^+ is the protonated base molecule, A is the water molecule and B is the neutral base. The aqueous phase protonation of a neutral base then can be represented as in Eqn. 2.4.

$$\delta\Delta G_{f(BH^+)} = [\Delta G_{f(B)} + \Delta G_{f(AH^+)}] - [\Delta G_{f(BH^+)} + \Delta G_{f(A)}] \quad (2.4)$$

On the other hand from the thermodynamic free energy relationship;

$\Delta G = \Delta H - T\Delta S = -RT\ln K_a$ the Eqn. 2.5 can be derived;

$$pK_{af(BH^+)} = \delta\Delta G_{f(BH^+)} / (2.303RT) \quad (2.5)$$

The standard proton affinities (PA) for gas phase protonation can be calculated using the following equation (Speranza 1986):

$$PA = 367.2 + \Delta H_{f(\text{unprotonated species})} - \Delta H_{f(\text{protonated species})} \quad (2.6)$$

where ΔH_f indicates the heat of formation values. We can use the Eqn. 2.7 for relative stability (RS) calculations:

$$RS = \Delta H_{f(\text{tautomeric form } \mathbf{a})} - \Delta H_{f(\text{tautomeric form } \mathbf{b})} \quad (2.7)$$

The nucleophilicity values can be calculated using Eqn. 2.8 (Harris 1987; Açikkalp et al. 2001):

$$\eta = E_{HOMO} - E_{LUMO} \quad (2.8)$$

The tautomerism values can be calculated using Eqn. 2.9 (Katrizky et al. 1964; Elguero et al. 1976; Jaramillo et al. 2008):

$$\begin{aligned} &K_T=[A]/[B] \\ &\log K_T=\log A - \log B \\ &-\log K_T= -\log A + \log B \\ &pK_T = pK_A - pK_B \end{aligned} \quad (2.9)$$

The nomenclatura belonging to the calculated gas phase and liquid phase parameters along with the protonation pathways are given in Table 1 and Scheme 1, respectively. The termodynamic parameters both in gas and liquid phases, the calculated proton affinities (PA), relative stabilities (RS) along with nucleophilicities (η) for the gas phase and acidity constants, pK_a values, in liquid phase are given in Tables 2-8.

3. RESULTS AND DISCUSSION

Most indoles were reported to exist overwhelmingly in the indole form (Reinecke et al. 1971, 1972). It was also reported that the tendency for indolines to exist is considerably grater than that for pyrrolenines. Similarly isoindole was reported to exist as such rather than in the isoindolenin form (Veber and Lwowski 1964).

As it was stated earlier the knowledge of the tautomeric form of the studied compounds is very useful in structure-activity or structure-property studies. Therefore, in the present study we have at-

Table 5. Proton affinities (PA) in gas phase (T=298 K).

Process Protonation	PA[1]			pKa_{exp}[2]
	AM1	PM3	PM5	
1a1NH-1a1NH$^+$	365.144	374.003	345.650	-2.400
2a1NH-2a1NH$^+$	371.064	378.317	352.531	1.220
2a1NH-2a2NH$^+$	330.630	337.983	318.441	1.220
2b2NH-2b1NH$^+$	359.748	372.392	349.672	1.220
2b2NH-2b2NH$^+$	359.748	372.392	349.671	1.220
3a1NH-3a1NH$^+$	373.138	353.790	358.179	5.530
3a1NH-3a3NH$^+$	345.860	324.913	335.312	5.530
4a1NH-4a1NH$^+$	371.248	379.718	351.933	6.940
4a1NH-4a4NH$^+$	344.893	356.344	332.716	6.940
4b4NH-4b1NH$^+$	329.842	340.775	320.179	6.940
4b4NH-4b4NH$^+$	383.055	388.122	357.023	6.940
5a1NH-5a1NH$^+$	372.067	381.942	354.867	8.260
5a1NH-5a5NH$^+$	343.691	357.945	333.625	8.260
5b5NH-5b1NH$^+$	326.435	338.532	317.117	8.260
5b5NH-5b5NH$^+$	385.827	391.129	365.800	8.260
6a1NH-6a1NH$^+$	371.827	380.634	352.711	7.950
6a1NH-6a6NH$^+$	346.729	359.193	335.201	7.950
6b6NH-6b1NH$^+$	329.553	340.696	319.541	7.950
6b6NH-6b6NH$^+$	390.248	387.552	360.658	7.950
7a1NH-7a1NH$^+$	369.882	379.182	352.241	4.590
7a1NH-7a7NH$^+$	349.552	363.798	338.766	4.590
7b7NH-7b1NH$^+$	333.689	347.766	325.675	4.590
7b7NH-7b7NH$^+$	385.085	390.518	367.021	4.590

[1] $PA = 367.2 + \Delta H_{f(\text{unprotonated species})} - \Delta H_{f(\text{protonated species})}$,
[2]Experimental values taken from Ref. Harris 1987.

3.3 Acidity

The protonation calculations of all the molecules were done in aqueous phase (Table 6 and Figure 3). The theoretical pK_a calculations were fulfilled considering all protonation centers including possible tautomer forms. It is observed that Group1 and Group 4 showed the best correlation of those experimental and theoretical pK_a values. pK_a calculations supported that that **a** forms are most preferred (dominant) instead of **b** forms considering pK_a values likewise tautomer calculations. The correlation order between theoretical and experimental pK_a values taking into consideration of the molecule groups and calculation methods for the studied molecules is given in the following order: group4 (PM5>PM3>AM1) > group1 (PM5>AM1>PM3) >group3 (AM1, PM3, PM5) >group2 (AM1>PM3>PM5). It is found that the most successful protonation was for Group 4 and Group 1 with PM5 method. The protonation mechanisms were realized by via paths 3, 7, 11, 15, 19, 23 and 5, 9, 13, 17, 21, 25 for Group 4 and Group 1 molecules, respectively.

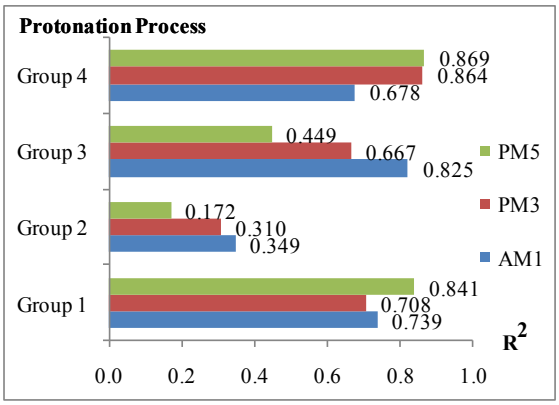


Figure 3. The correlations between theoretical and experimental pK_a values of the molecules, R^2: correlation coefficient.

Table 6. The acidity constants (pK_a) in liquid phase (T=298 K; ε=78.4).

Process Protonation	pKa_{calc}[1]						pKa_{exp}[2]
	AM1		PM3		PM5		
	$\delta\Delta G_{fBH+}$[3]	$pKa_{(f)(BH+)}$[4]	$\delta\Delta G_{fBH+}$[3]	$pKa_{(f)(BH+)}$[4]	$\delta\Delta G_{fBH+}$[3]	$pKa_{(f)(BH+)}$[4]	
1a1NH-1a1NH$^+$	4.204	3.083	16.122	11.823	3.537	2.594	-2.400
2a1NH-2a1NH$^+$	-0.345	-0.253	13.622	9.989	-2.244	-1.646	1.220
2a1NH-2a2NH$^+$	2.993	2.195	14.045	10.299	-4.895	-3.590	1.220
2b2NH-2b1NH$^+$	7.056	5.174	15.048	11.035	-3.498	-2.565	1.220
2b2NH-2b2NH$^+$	7.060	5.177	15.038	11.028	-3.543	-2.598	1.220
3a1NH-3a1NH$^+$	-1.425	-1.045	6.534	4.791	-8.618	-6.320	5.530
3a1NH-3a3NH$^+$	18.723	13.730	28.302	20.754	6.641	4.870	5.530
4a1NH-4a1NH$^+$	0.476	0.349	12.452	9.131	-0.508	-0.373	6.940
4a1NH-4a4NH$^+$	16.602	12.175	27.077	19.856	8.484	6.221	6.940
4b4NH-4b1NH$^+$	28.834	21.144	37.740	27.675	16.527	12.120	6.940
4b4NH-4b4NH$^+$	-11.810	-8.660	0.497	0.364	-14.156	-10.381	6.940
5a1NH-5a1NH$^+$	0.244	0.179	11.584	8.495	-2.131	-1.563	8.260
5a1NH-5a5NH$^+$	18.179	13.331	26.220	19.228	8.735	6.406	8.260
5b5NH-5b1NH$^+$	29.916	21.938	37.889	27.785	16.920	12.408	8.260
5b5NH-5b5NH$^+$	-16.104	-11.809	-3.611	-2.648	-17.261	-12.658	8.260
6a1NH-6a1NH$^+$	0.967	0.709	12.635	9.265	-0.344	-0.252	7.950
6a1NH-6a6NH$^+$	16.815	12.331	26.068	19.116	8.201	6.014	7.950
6b6NH-6b1NH$^+$	28.877	21.176	38.033	27.890	17.288	12.678	7.950
6b6NH-6b6NH$^+$	-12.394	-9.089	0.121	0.089	-13.771	-10.099	7.950
7a1NH-7a1NH$^+$	0.134	0.098	11.738	8.608	-2.879	-2.111	4.590
7a1NH-7a7NH$^+$	15.710	11.520	24.333	17.844	6.679	4.898	4.590
7b7NH-7b1NH$^+$	27.509	20.173	34.618	25.386	13.955	10.233	4.590
7b7NH-7b7NH$^+$	-15.915	-11.671	-3.088	-2.264	-19.775	-14.501	4.590

[1] Calculated pK_a values, [2]Experimental values taken from Ref. Harris 1987, [3]$\delta\Delta G_{f(BH^+)} = [\Delta G_{f(B)} + \Delta G_{f(AH^+)}] - [\Delta G_{f(BH^+)} + \Delta G_{f(A)}]$, [4]$pK_{a(f)(BH^+)} = \delta\Delta G_{(f)(BH^+)} / (2.303RT)$. $R=1.987\times10^{-3}$ kcal mol^{-1} K^{-1} and T=298 K.

3.4 Tautomerism

When tautomer behaviors in liquid phase for the studied molecules are investigated, it is thougth that **a** forms are most preferred form (dominant) instead of **b** forms considering calculated tautomeric constants (K_T) and pK_T values (Table 7 and Figure 4). It is determined that **a** form is predominant in the equilibria between **a** and **b** by evaluating the obtained K_T data. K_T values for the equilibria (**2a1NH ⇌ 2b2H)** were highest among all the protonation processes in Table 7 by all the calculation methods, AM1, PM3 and PM5.

Table 7. The calculated tautomeric constants (KT) in liquid phase.

Process Protonation	AM1		PM3		PM5	
	K_T[1]	pK_T[2]	K_T[1]	pK_T[2]	K_T[1]	pK_T[2]
2a1NH-2b2H	1.14×10^{-3}	2.945	1.63×10^{-1}	0.788	1.11×10^{-1}	0.955
4a1NH-4b4H	1.23×10^{-9}	8.911	1.14×10^{-8}	7.942	1.56×10^{-6}	5.807
5a1NH-5b5H	2.34×10^{-9}	8.631	3.02×10^{-9}	8.520	1.19×10^{-6}	5.924
6a1NH-6b6H	1.27×10^{-9}	8.897	1.45×10^{-9}	8.840	2.49×10^{-7}	6.603
7a1NH-7b7H	2.17×10^{-9}	8.663	3.56×10^{-8}	7.449	4.52×10^{-6}	5.345

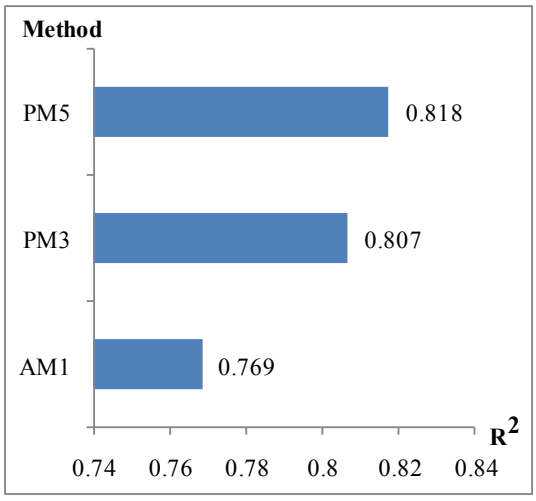


Figure 4. The correlations between tautomerism and experimental pK_a values of the molecules, R^2: correlation coefficient.

3.5.Relative Stabilities

The relative stabilities were calculated by mole fractions of tautomers **a** and **b**. The mole fractions of individual tautomeric forms **a** and **b** can be calculated by using the following equation;

$$\mathbf{a} \underset{}{\overset{K_T}{\rightleftharpoons}} \mathbf{b}$$

According to equilibrium given above for the following equation (Hür and Güven 2002),

$$K_T = N_b/N_a \text{ and } N_a + N_b = 1 \qquad (3.1)$$

where K_T is tautomeric equilibrium constant between **a** and **b** forms, N_a and N_b are mole fractions of **a** and **b** forms.

$N_a=1/(1+K_T)$ and $N_b=K_T/(1+K_T)$ (3.2)

Thermokinetic calculation;

$\Delta G_f(wa)=[N_a][\Delta G_{f(a)}]+)=[N_b][\Delta G_{f(b)}]$ (3.3)

Relative stability (f) **a** form: $\Delta G_f(wa)- \Delta G_{f(a)}$ (3.4)

Relative stability (f) **b** form: $\Delta G_f(wa)- \Delta G_{f(b)}$ (3.5)

Thermodynamic calculation;

$\Delta G(wa)=[N_a][\Delta G_{(a)}]+)=[N_b][\Delta G_{(b)}]$ (3.6)

Relative stability **a** form: $\Delta G(wa)- \Delta G_{(a)}$ (3.7)

Relative stability **b** form: $\Delta G(wa)- \Delta G_{(b)}$ (3.8)

AM1, PM3 and PM5 methods in liquid phase. The results are given in Table 8. In the calculations, the relative stabilities of **a** and **b** forms were investigated. The results show that **a** form is more stable than those of **b** form. The calculated relative stability values of -4.251 (AM1), -1.217 (PM3) and -1.570 (PM5) for these equilibria (i.e. **2a** ⇌ **2b** and **3a** ⇌ **3b**) also indicate the predominance of **2b2NH** form for compound **2a** and equivalent amount for **3a1NH** and **3b3NH** (i.e. with all three methods) (Table 8).

Table 8. The relative stabilities by AM1, PM3 and PM5 methods in liquid phase.

Molecule	**ΔG_f[a]** kcal mol^{-1}	**ΔG[b]** kcal mol^{-1}	**Mol fractions of tautomers[c]**		**The weighted average of the free energies of tautomeric forms**		**Relative stability$_{(f)}$[f]** kcal mol^{-1}	**Relative stability[g]** kcal mol^{-1}
					$\Delta G_f(wa)$[d] kcal mol^{-1}	**$\Delta G(wa)$[e]** kcal mol^{-1}		
AM1								
2a1NH	52.97	-18.914	**Na$_{(f)}$**=0.0185	**Na**=0.0558	56.9837	-21.1054	4.0137	-2.1914
2b2NH	56.985	-18.994	**Nb$_{(f)}$**=0.9828	**Nb**=1.0556			-0.0013	-2.1114
3a1NH	34.028	-19.125	**Na$_{(f)}$**=0.0285	**Na**=0.0552	34.0280	-21.2353	0.0000	-2.1103
3b1NH	34.028	-19.125	**Nb$_{(f)}$**=0.9715	**Nb**=1.0552			0.0000	-2.1103
4a1NH	32.909	-19.143	**Na$_{(f)}$**=0.0295	**Na**=0.0551	45.0512	-21.0738	12.1422	-1.9308
4b4NH	45.059	-18.963	**Nb$_{(f)}$**=0.9783	**Nb**=1.0557			-0.0078	-2.1108
5a1NH	32.572	-19.099	**Na$_{(f)}$**=0.0298	**Na**=0.0553	44.3323	-21.0988	11.7603	-1.9998
5b5NH	44.34	-18.988	**Nb$_{(f)}$**=0.9779	**Nb**=1.0556			-0.0077	-2.1108
6a1NH	33.23	-19.129	**Na$_{(f)}$**=0.0292	**Na**=0.0552	45.3534	-21.1017	12.1234	-1.9727
6b6NH	45.361	-18.991	**Nb$_{(f)}$**=0.9784	**Nb**=1.0556			-0.0076	-2.1107
7a1NH	35.157	-19.112	**Na$_{(f)}$**=0.0277	**Na**=0.0552	46.9622	-21.0819	11.8052	-1.9699
7b7NH	46.969	-18.971	**Nb$_{(f)}$**=0.9792	**Nb**=1.0556			-0.0068	-2.1109
PM3								
2a1NH	36.473	-18.99	**Na$_{(f)}$**=0.0267	**Na**=0.0556	37.5463	-21.1530	1.0733	-2.1630
2b2NH	37.547	-19.042	**Nb$_{(f)}$**=0.9741	**Nb**=1.0554			-0.0007	-2.1110
3a1NH	14.897	-19.108	**Na$_{(f)}$**=0.0629	**Na**=0.0552	14.8970	-21.2184	0.0000	-2.1104
3b1NH	14.897	-19.108	**Nb$_{(f)}$**=0.9371	**Nb**=1.0552			0.0000	-2.1104

4a1NH	18.636	-19.124	$\mathbf{Na_{(f)}}$=0.0509	**Na**=0.0552	29.3210	-21.1406	10.6850	-2.0166
4b4NH	29.339	-19.03	$\mathbf{Nb_{(f)}}$=0.9670	**Nb**=1.0555			-0.0180	-2.1106
5a1NH	17.63	-19.117	$\mathbf{Na_{(f)}}$=0.0537	**Na**=0.0552	29.2254	-21.1726	11.5954	-2.0556
5b5NH	29.246	-19.062	$\mathbf{Nb_{(f)}}$=0.9669	**Nb**=1.0554			-0.0206	-2.1106
6a1NH	18.125	-19.115	$\mathbf{Na_{(f)}}$=0.0523	**Na**=0.0552	30.1578	-21.1815	12.0328	-2.0665
6b6NH	30.178	-19.071	$\mathbf{Nb_{(f)}}$=0.9679	**Nb**=1.0553			-0.0202	-2.1105
7a1NH	18.622	-19.128	$\mathbf{Na_{(f)}}$=0.0510	**Na**=0.0552	28.7606	-21.0938	10.1386	-1.9658
7b7NH	28.778	-18.983	$\mathbf{Nb_{(f)}}$=0.9664	**Nb**=1.0556			-0.0174	-2.1108
PM5								
2a1NH	34.039	-19.047	$\mathbf{Na_{(f)}}$=0.0285	**Na**=0.0554	35.3400	-21.2475	1.3010	-2.2005
2b2NH	35.341	-19.137	$\mathbf{Nb_{(f)}}$=0.9725	**Nb**=1.0551			-0.0010	-2.1105
3a1NH	12.354	-19.588	$\mathbf{Na_{(f)}}$=0.0749	**Na**=0.0538	12.3540	-21.6956	0.0000	-2.1076
3b1NH	12.354	-19.588	$\mathbf{Nb_{(f)}}$=0.9251	**Nb**=1.0538			0.0000	-2.1076
4a1NH	19.393	-19.016	$\mathbf{Na_{(f)}}$=0.0490	**Na**=0.0555	27.2963	-21.2347	7.9033	-2.2187
4b4NH	27.31	-19.124	$\mathbf{Nb_{(f)}}$=0.9647	**Nb**=1.0552			-0.0137	-2.1107
5a1NH	17.539	-19.051	$\mathbf{Na_{(f)}}$=0.0539	**Na**=0.0554	25.5996	-21.2525	8.0606	-2.2015
5b5NH	25.616	-19.142	$\mathbf{Nb_{(f)}}$=0.9624	**Nb**=1.0551			-0.0164	-2.1105
6a1NH	18.495	-19.051	$\mathbf{Na_{(f)}}$=0.0513	**Na**=0.0554	27.4818	-21.2695	8.9868	-2.2185
6b6NH	27.498	-19.159	$\mathbf{Nb_{(f)}}$=0.9649	**Nb**=1.0551			-0.0162	-2.1105
7a1NH	19.218	-19.04	$\mathbf{Na_{(f)}}$=0.0495	**Na**=0.0554	26.4929	-21.2236	7.2749	-2.1836
7b7NH	26.506	-19.113	$\mathbf{Nb_{(f)}}$=0.9636	**Nb**=1.0552			-0.0131	-2.1106

[a]$\Delta G_f = \Delta H_f - T\Delta S$; [b]$\Delta G = \Delta H - T\Delta S$; [c]Equation (3.2); [d] Equation (3.3); [e] Equation (3.6); [f]Equation 3.4 and 3.5; [g] Equation 3.7 and 3.8.

4. CONCLUSIONS

The acidities, mole fractions, nucleophilicities (η) and proton affinities (PA) of seven azaindole molecules were determined in both gas and liquid phases using semi-empirical AM1, PM3 and PM5 methods. The calculated pK_a values were compared with those of experimental pK_a values. The best correlation between experimental pK_a values and nucleophilicity, proton affinity (PA), tautomerism and acidity of the whole molecules was for PM5 calculation method. The more stable form was form **b** for all the molcules by taking into account of the relative stability.

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