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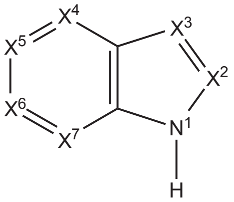
rich azole and electron-poor azine ring systems, they could be possible to selectively functionalize both rings in a controlled fashion. In that way, it is possible to have new opportunities for the site-selective functionalization of useful organic building blocks and may find application in the preparation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

$$B + H_3O^+ \rightleftharpoons \overset{+}{BH} + H_2O \tag{2.1}$$

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);

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

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

$$B + A\overset{+}{H} \rightleftharpoons B\overset{+}{H} + A \qquad (2.3)$$

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.

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

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;

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

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

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

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

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

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

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

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

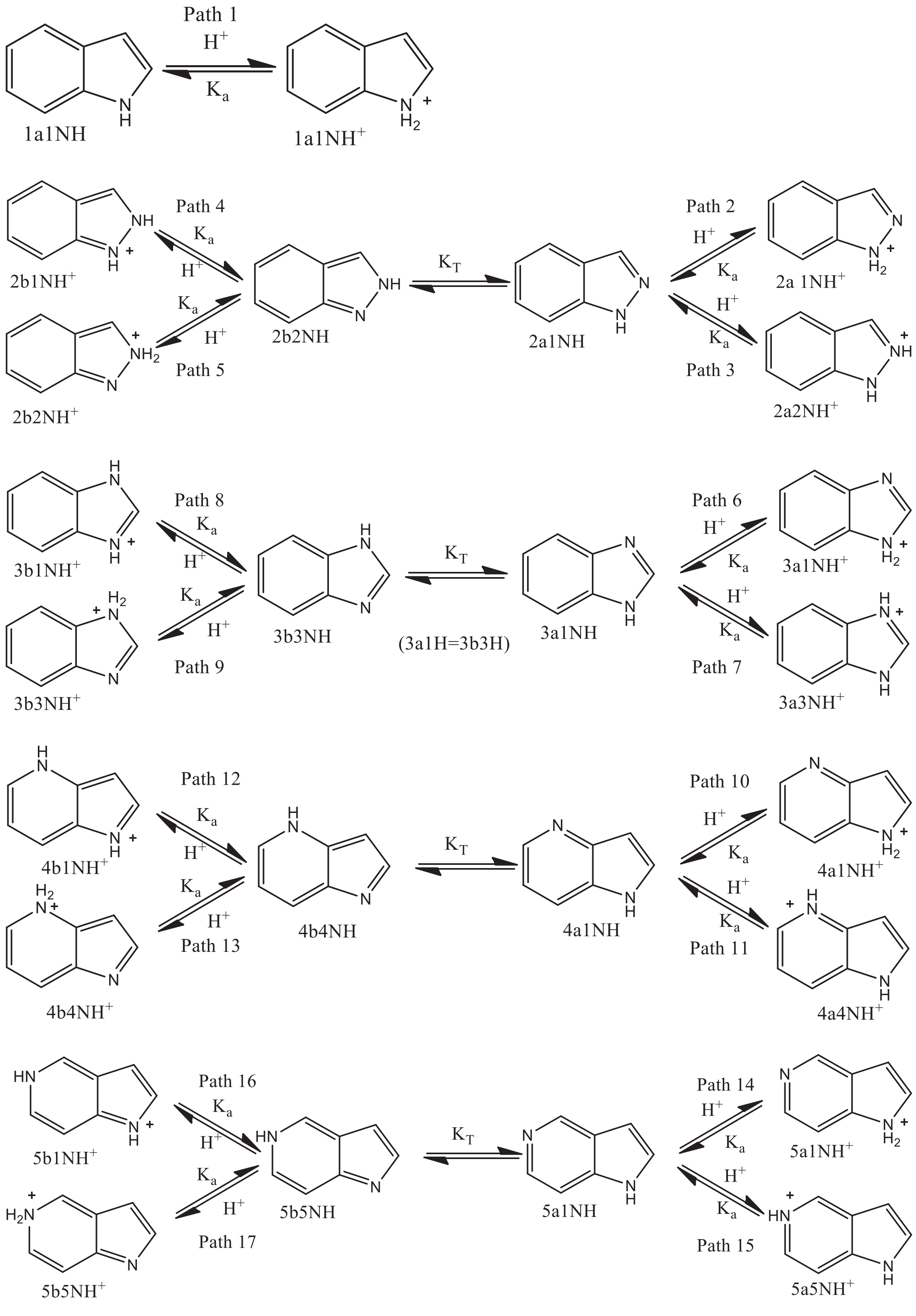
$$\begin{aligned} &K_T=[A]/[B] \\ &\log K_T=\log A - \log B \\ &-\log K_T= -\log A + \log B \\ &pK_T = pK_A - pK_B \end{aligned} \qquad (2.9)$$

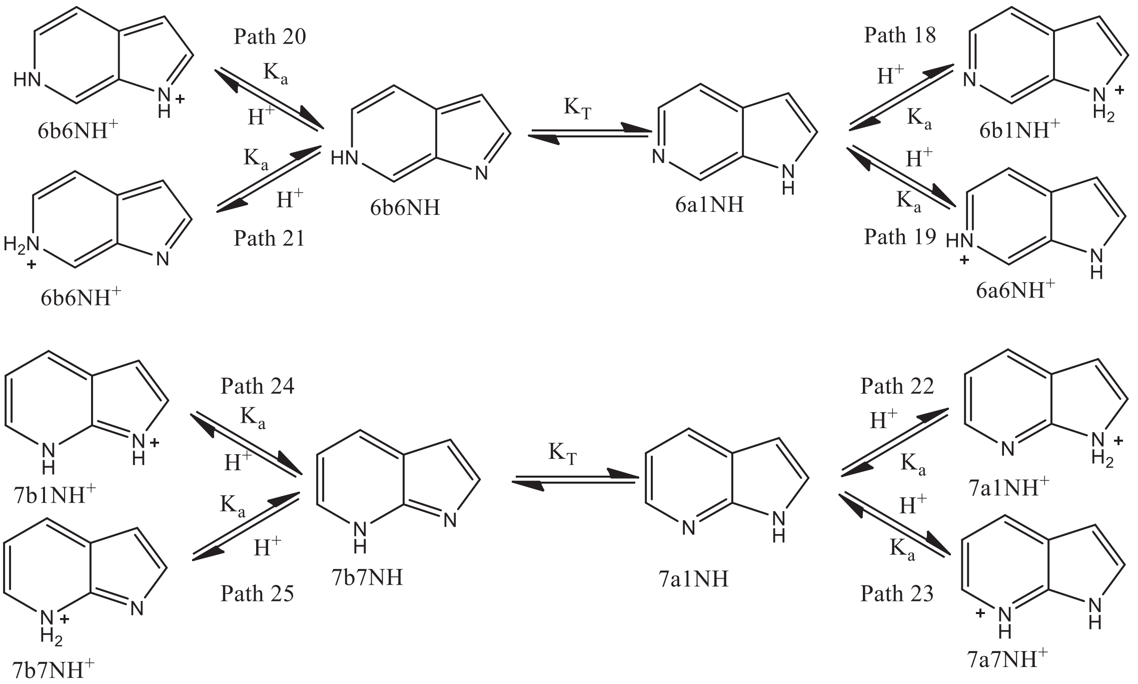
The nomenclatura belonging to the calculated gas phase and liquid phase parameters along with the protonation pathways are given in Table 1 and Scheme 1, respectively. The termodynamic parameters both in gas and liquid phases, the calculated proton affinities (PA), relative stabilities (RS) along with 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 attempted to determine the tautomeric forms of the studied compounds. These molecules were classified as **a** and **b** forms by taking into consideration of those protonation centers (Scheme 1).





Scheme 1. Possible protonation patterns for the studied molecules 1-7.

Table 2. The calculated thermodynamic parameters of the studied molecules by AM1, PM3 and PM5 in gas phase (T=298 K).

Molecule	ΔH_f kcal mol^{-1}	ΔH cal mol^{-1}	ΔS kcal mol^{-1}	ΔG_f^a kcal mol^{-1}	ΔG^b kcal mol^{-1}	HOMO (eV)	LUMO (eV)	η^c
				AM1				
1a1NH	55.042	4639.441	80.078	31.179	-19.224	-8.404	0.300	-8.704
2a1NH	82.207	4201.104	77.532	59.102	-18.903	-8.867	-0.043	-8.824
3a1NH	66.977	4475.055	79.022	43.428	-19.074	-8.996	0.058	-9.054
4a1NH	65.480	4514.760	79.378	41.825	-19.140	-8.879	0.033	-8.912
5a1NH	65.535	4481.007	79.104	41.962	-19.092	-8.675	-0.019	-8.656
6a1NH	65.214	4496.653	79.223	41.606	-19.112	-8.756	0.011	-8.767
7a1NH	65.863	4437.160	78.784	42.385	-19.040	-8.780	0.050	-8.830
H_2O	-59.251	2369.362	45.086	-72.687	-11.066	-	-	-
2b2NH	88.750	4356.036	78.305	65.415	-18.979	-8.467	-0.212	-8.255
4b4NH	80.530	4360.700	78.306	57.195	-18.974	-8.347	-0.621	-7.726
5b5NH	82.791	4392.995	78.532	59.388	-19.010	-8.269	-0.418	-7.851
6b6NH	82.382	4396.194	78.542	58.976	-19.009	-8.167	-0.351	-7.816
7b7NH	81.726	4347.981	78.248	58.408	-18.970	-8.392	-0.656	-7.736
1a1NH$^+$	217.474	4472.686	79.172	193.881	-19.121	-13.725	-4.983	-8.742
2a1NH$^+$	250.559	4364.026	78.589	227.139	-19.055	-14.392	-5.354	-9.038
2a2NH$^+$	210.125	4450.616	77.398	187.060	-18.614	-13.706	-5.087	-8.619

2b1NH$^+$	245.786	4407.680	78.677	222.340	-19.038	-13.473	-5.482	-7.991
2b2NH$^+$	245.786	4409.644	78.690	222.336	-19.040	-13.473	-5.482	-7.991
3a1NH$^+$	237.403	4372.441	78.590	213.983	-19.047	-14.046	-5.312	-8.734
3a3NH$^+$	210.125	4450.616	77.398	187.060	-18.614	-13.706	-5.087	-8.619
4a1NH$^+$	234.016	4352.407	78.518	210.618	-19.046	-14.140	-5.298	-8.842
4a4NH$^+$	207.661	4429.757	78.687	184.212	-19.019	-13.509	-5.424	-8.085
4b1NH$^+$	207.660	4431.482	78.697	184.208	-19.020	-13.510	-5.425	-8.085
4b4NH$^+$	260.873	4513.785	79.879	237.069	-19.290	-14.003	-5.990	-8.013
5a1NH$^+$	234.890	4374.459	78.674	211.445	-19.070	-13.990	-5.329	-8.661
5a5NH$^+$	206.514	4425.384	78.705	183.060	-19.029	-13.256	-5.141	-8.115
5b1NH$^+$	206.514	4424.170	78.697	183.062	-19.028	-13.256	-5.141	-8.115
5b5NH$^+$	265.906	4552.928	80.052	242.051	-19.303	-13.653	-5.955	-7.698
6a1NH$^+$	234.329	4374.270	78.684	210.881	-19.074	-14.372	-5.327	-9.045
6a6NH$^+$	209.231	4456.733	78.866	185.729	-19.045	-13.280	-5.348	-7.932
6b1NH$^+$	209.223	4458.977	78.881	185.716	-19.048	-13.281	-5.348	-7.933
6b6NH$^+$	269.918	4541.835	79.968	246.088	-19.289	-13.944	-5.773	-8.171
7a1NH$^+$	233.033	4349.241	78.483	209.645	-19.039	-14.142	-5.328	-8.814
7a7NH$^+$	212.703	4491.939	79.047	189.147	-19.064	-13.498	-5.376	-8.122
7b1NH$^+$	212.703	4491.489	79.045	189.148	-19.064	-13.497	-5.376	-8.121
7b7NH$^+$	264.099	4524.483	79.937	240.278	-19.297	-13.819	-6.114	-7.705
H_3O^+	143.461	2379.122	46.193	129.695	-11.386	-	-	-
PM3								
1a1NH	42.496	4446.286	78.765	19.024	-19.026	-8.355	0.174	-8.529
2a1NH	65.597	4369.897	78.394	42.236	-18.991	-8.762	-0.254	-8.508
3a1NH	78.667	4369.999	78.362	55.315	-18.991	-8.889	-0.070	-8.819
4a1NH	50.176	4355.784	78.290	26.846	-18.991	-8.750	-0.140	-8.610
5a1NH	48.807	4369.497	78.379	25.450	-18.991	-8.718	-0.118	-8.600
6a1NH	49.199	4368.179	78.374	25.844	-18.991	-8.685	-0.125	-8.560
7a1NH	48.045	4762.038	81.036	23.896	-18.991	-8.761	-0.134	-8.627
H_2O	-53.433	2369.863	44.988	-66.839	-18.991	-	-	-
2b2NH	70.125	4484.920	78.939	46.601	-18.991	-8.631	-0.405	-8.226
4b4NH	65.748	4565.835	79.366	42.097	-18.991	-8.249	-0.867	-7.382
5b5NH	68.220	4628.560	79.781	44.445	-18.991	-8.290	-0.667	-7.623
6b6NH	67.696	4637.305	79.836	43.905	-18.991	-8.133	-0.641	-7.492
7b7NH	64.077	4536.206	79.195	40.477	-18.991	-8.359	-0.894	-7.465
1a1NH$^+$	204.000	4622.695	79.947	180.176	-18.991	-13.968	-5.326	-8.642
2a1NH$^+$	231.415	4595.117	79.783	207.640	-18.991	-14.576	-5.764	-8.812

2a2NH$^+$	191.081	4629.980	78.347	167.734	-18.991	-13.634	-5.318	-8.316
2b1NH$^+$	230.018	4598.675	79.666	206.278	-18.991	-13.489	-5.764	-7.725
2b2NH$^+$	230.018	4598.664	79.666	206.278	-18.991	-13.489	-5.764	-7.725
3a1NH$^+$	219.958	4556.355	79.553	196.251	-18.991	-14.286	-5.598	-8.688
3a3NH$^+$	191.081	4629.980	78.347	167.734	-18.991	-13.634	-5.318	-8.316
4a1NH$^+$	217.395	4593.236	79.687	193.648	-18.991	-14.428	-5.619	-8.809
4a4NH$^+$	194.021	4608.900	79.631	170.291	-18.991	-13.437	-5.594	-7.843
4b1NH$^+$	194.024	4608.834	79.631	170.294	-18.991	-13.437	-5.594	-7.843
4b4NH$^+$	241.371	4684.153	80.814	217.288	-18.991	-14.331	-6.341	-7.990
5a1NH$^+$	218.250	4611.352	79.795	194.471	-18.991	-14.276	-5.660	-8.616
5a5NH$^+$	194.253	4618.230	79.701	170.502	-18.991	-13.323	-5.378	-7.945
5b1NH$^+$	194.253	4618.095	79.700	170.502	-18.991	-13.323	-5.378	-7.945
5b5NH$^+$	246.850	4724.557	80.955	222.725	-18.991	-14.012	-6.233	-7.779
6a1NH$^+$	217.334	4611.241	79.809	193.551	-18.991	-14.399	-5.669	-8.730
6a6NH$^+$	195.893	4643.321	79.846	172.099	-18.991	-13.249	-5.542	-7.707
6b1NH$^+$	195.893	4643.182	79.846	172.099	-18.991	-13.249	-5.542	-7.707
6b6NH$^+$	242.749	4708.347	80.837	218.660	-18.991	-14.175	-6.153	-8.022
7a1NH$^+$	214.728	4533.789	79.440	191.055	-18.991	-14.422	-5.625	-8.797
7a7NH$^+$	199.344	4745.312	80.462	175.366	-18.991	-13.477	-5.602	-7.875
7b1NH$^+$	199.344	4747.105	80.460	175.367	-18.991	-13.477	-5.601	-7.876
7b7NH$^+$	242.096	4696.660	80.823	218.011	-18.991	-14.183	-6.413	-7.770
H_3O^+	159.066	2378.690	46.036	145.347	-18.991	-	-	-
PM5								
1a1NH	46.347	4539.127	79.182	22.751	-19.057	-8.242	0.439	-8.681
2a1NH	66.274	4429.154	78.673	42.829	-19.015	-8.674	-0.068	-8.606
3a1NH	49.403	4861.096	81.728	25.048	-19.494	-8.901	0.085	-8.986
4a1NH	54.628	4432.227	78.632	31.196	-19.000	-8.750	-0.027	-8.723
5a1NH	52.155	4437.353	78.698	28.703	-19.015	-8.639	0.078	-8.717
6a1NH	53.100	4440.098	78.724	29.640	-19.020	-8.601	-0.001	-8.600
7a1NH	52.354	4418.185	78.506	28.959	-18.977	-8.749	-0.023	-8.726
H_2O	-53.696	2371.272	44.949	-67.091	-11.024	-	-	-
2b2NH	70.595	4635.042	79.737	46.833	-19.127	-8.498	-0.193	-8.305
4b4NH	67.165	4674.618	79.912	43.351	-19.139	-8.286	-0.568	-7.718
5b5NH	68.663	4739.776	80.373	44.712	-19.211	-8.318	-0.358	-7.960
6b6NH	68.759	4738.896	80.357	44.813	-19.207	-8.121	-0.371	-7.750
7b7NH	65.223	4646.071	79.750	41.458	-19.119	-8.413	-0.559	-7.854
1a1NH$^+$	200.235	4724.909	80.436	176.265	-19.245	-13.583	-4.811	-8.772

2a1NH$^+$	227.043	4608.364	79.840	203.251	-19.184	-14.236	-5.367	-8.869
2a2NH$^+$	192.953	4773.469	79.057	169.394	-18.786	-13.478	-4.969	-8.509
2b1NH$^+$	228.505	4708.328	80.263	204.587	-19.210	-13.253	-5.491	-7.762
2b2NH$^+$	228.504	4708.639	80.266	204.585	-19.210	-13.253	-5.491	-7.762
3a1NH$^+$	215.820	4629.567	79.892	192.012	-19.178	-13.912	-5.310	-8.601
3a3NH$^+$	192.953	4773.469	79.057	169.394	-18.786	-13.478	-4.969	-8.509
4a1NH$^+$	214.799	4620.017	79.893	190.991	-19.188	-14.073	-5.178	-8.895
4a4NH$^+$	195.582	4791.319	80.596	171.564	-19.226	-13.304	-5.252	-8.052
4b1NH$^+$	195.582	4792.064	80.600	171.563	-19.227	-13.304	-5.252	-8.052
4b4NH$^+$	232.426	4789.911	81.405	208.167	-19.469	-13.948	-5.825	-8.123
5a1NH$^+$	215.260	4638.619	80.035	191.410	-19.212	-13.920	-5.210	-8.710
5a5NH$^+$	194.018	4762.073	80.433	170.049	-19.207	-13.156	-4.984	-8.172
5b1NH$^+$	194.018	4763.124	80.438	170.047	-19.207	-13.157	-4.984	-8.173
5b5NH$^+$	242.701	4832.421	81.618	218.379	-19.490	-13.692	-5.813	-7.879
6a1NH$^+$	214.049	4634.313	80.033	190.199	-19.216	-14.275	-5.238	-9.037
6a6NH$^+$	196.539	4822.043	80.822	172.454	-19.263	-13.078	-5.192	-7.886
6b1NH$^+$	196.538	4824.665	80.840	172.448	-19.266	-13.078	-5.192	-7.886
6b6NH$^+$	237.655	4812.646	81.485	213.372	-19.470	-13.958	-5.660	-8.298
7a1NH$^+$	212.833	4616.124	79.837	189.042	-19.175	-14.085	-5.176	-8.909
7a7NH$^+$	199.358	4949.833	81.761	174.993	-19.415	-13.376	-5.200	-8.176
7b1NH$^+$	199.136	4947.757	81.742	174.777	-19.411	-13.376	-5.199	-8.177
7b7NH$^+$	240.482	4799.904	81.394	216.227	-19.456	-13.836	-5.985	-7.851
H_3O^+	138.066	2451.652	46.161	124.310	-11.304	-	-	-

$^a\Delta G_f = \Delta H_f - T\Delta S$. $^b\Delta G = \Delta H - T\Delta S$. $^c\eta = E_{HOMO} - E_{LUMO}$

Table 3. The calculated thermodynamic parameters of the studied molecules by AM1, PM3 and PM5 in liquid phase (T=298 K; ε=78.4).

Molecule	**ΔH_f** kcal mol^{-1}	**ΔH** cal mol^{-1}	**ΔS** kcal mol^{-1}	**ΔG_f^a** kcal mol^{-1}	**ΔG^b** kcal mol^{-1}
AM1					
1a1NH	49.215	4718.518	80.764	25.147	-19.349
2a1NH	76.106	4222.305	77.637	52.970	-18.914
3a1NH	57.677	4523.676	79.358	34.028	-19.125
4a1NH	56.579	4526.604	79.429	32.909	-19.143
5a1NH	56.167	4495.582	79.178	32.572	-19.099
6a1NH	56.879	4520.776	79.360	33.230	-19.129
7a1NH	58.776	4506.772	79.259	35.157	-19.112
H_2O	-64.412	2369.439	45.086	-77.848	-11.066

2b2NH	80.357	4378.011	78.428	56.985	-18.994
4b4NH	68.375	4352.842	78.242	45.059	-18.963
5b5NH	67.688	4360.161	78.349	44.340	-18.988
6b6NH	68.719	4366.892	78.383	45.361	-18.991
7b7NH	70.297	4356.797	78.282	46.969	-18.971
1a1NH$^+$	159.806	4521.289	79.598	136.086	-19.199
2a1NH$^+$	191.852	4351.677	78.502	168.458	-19.042
2a2NH$^+$	188.553	4406.463	78.633	165.120	-19.026
2b1NH$^+$	188.498	4402.115	78.610	165.072	-19.024
2b2NH$^+$	188.498	4404.520	78.623	165.068	-19.025
3a1NH$^+$	173.946	4344.991	78.357	150.596	-19.005
3a3NH$^+$	153.630	4533.142	77.791	130.448	-18.649
4a1NH$^+$	170.970	4353.741	78.502	147.576	-19.040
4a4NH$^+$	154.960	4474.367	78.894	131.450	-19.036
4b1NH$^+$	154.932	4507.116	79.074	131.368	-19.057
4b4NH$^+$	195.928	4540.245	80.255	172.012	-19.376
5a1NH$^+$	171.026	4418.974	79.045	147.471	-19.136
5a5NH$^+$	153.028	4456.958	78.831	129.536	-19.035
5b1NH$^+$	153.022	4437.257	78.708	129.567	-19.018
5b5NH$^+$	198.596	4139.511	77.211	175.587	-18.869
6a1NH$^+$	170.944	4413.795	78.985	147.406	-19.124
6a6NH$^+$	155.124	4499.779	79.080	131.558	-19.066
6b1NH$^+$	155.109	4155.301	78.797	131.627	-19.326
6b6NH$^+$	196.756	4549.500	80.059	172.898	-19.308
7a1NH$^+$	173.504	4328.979	78.317	150.166	-19.009
7a7NH$^+$	158.200	4531.550	79.229	134.590	-19.079
7b1NH$^+$	158.180	4513.530	79.118	134.603	-19.064
7b7NH$^+$	200.949	4101.088	76.920	178.027	-18.821
H_3O^+	51.054	2373.137	46.170	37.295	-11.386
PM3					
1a1NH	37.951	4769.760	80.629	13.924	-19.258
2a1NH	59.843	4380.619	78.424	36.473	-18.990
3a1NH	38.606	4600.107	79.559	14.897	-19.108
4a1NH	42.373	4613.799	79.656	18.636	-19.124
5a1NH	41.351	4603.209	79.599	17.630	-19.117
6a1NH	41.843	4603.038	79.592	18.125	-19.115
7a1NH	42.371	4620.497	79.694	18.622	-19.128

H_2O	-58.046	2369.901	44.988	-71.452	-11.037
2b2NH	61.060	4470.849	78.902	37.547	-19.042
4b4NH	52.849	4479.179	78.891	29.339	-19.030
5b5NH	52.810	4501.845	79.074	29.246	-19.062
6b6NH	53.764	4514.915	79.148	30.178	-19.071
7b7NH	52.260	4499.003	78.798	28.778	-18.983
1a1NH$^+$	146.964	4616.840	79.906	123.152	-19.195
2a1NH$^+$	171.997	4605.018	79.853	148.201	-19.191
2a2NH$^+$	171.353	4514.692	79.111	147.778	-19.060
2b1NH$^+$	171.417	4506.923	79.086	147.849	-19.061
2b2NH$^+$	171.415	4501.163	79.049	147.859	-19.055
3a1NH$^+$	157.013	4367.884	78.189	133.713	-18.932
3a3NH$^+$	135.195	4576.815	78.019	111.945	-18.673
4a1NH$^+$	155.260	4547.104	79.616	131.534	-19.178
4a4NH$^+$	140.627	4599.681	79.590	116.909	-19.118
4b1NH$^+$	140.587	4458.329	79.322	116.949	-19.180
4b4NH$^+$	178.001	4597.762	79.895	154.192	-19.211
5a1NH$^+$	155.105	4545.950	79.561	131.396	-19.163
5a5NH$^+$	140.469	4591.186	79.559	116.760	-19.117
5b1NH$^+$	140.405	4585.117	79.525	116.707	-19.113
5b5NH$^+$	182.510	4753.371	81.554	158.207	-19.550
6a1NH$^+$	154.561	4555.307	79.601	130.840	-19.166
6a6NH$^+$	141.212	4643.721	79.882	117.407	-19.161
6b1NH$^+$	141.135	4564.864	79.329	117.495	-19.075
6b6NH$^+$	180.131	4806.825	82.966	155.407	-19.917
7a1NH$^+$	156.043	4588.818	79.896	132.234	-19.220
7a7NH$^+$	143.348	4602.350	79.560	119.639	-19.107
7b1NH$^+$	143.344	4661.658	79.980	119.510	-19.172
7b7NH$^+$	181.552	4751.895	81.664	157.216	-19.584
H_3O^+	67.613	2375.529	46.024	53.898	-11.340
PM5					
1a1NH	38.861	4580.905	79.399	15.200	-19.080
2a1NH	57.562	4475.375	78.935	34.039	-19.047
3a1NH	36.866	4924.481	82.256	12.354	-19.588
4a1NH	42.876	4467.039	78.801	19.393	-19.016
5a1NH	41.082	4491.657	79.003	17.539	-19.051
6a1NH	42.033	4487.260	78.987	18.495	-19.051

7a1NH	42.739	4481.297	78.929	19.218	-19.040
H_2O	-59.444	2372.330	44.953	-72.840	-11.024
2b2NH	59.132	4653.681	79.835	35.341	-19.137
4b4NH	51.098	4664.229	79.825	27.310	-19.124
5b5NH	49.425	4667.048	79.895	25.616	-19.142
6b6NH	51.342	4684.871	80.013	27.498	-19.159
7b7NH	50.271	4651.767	79.748	26.506	-19.113
1a1NH$^+$	142.010	4693.889	80.139	118.129	-19.188
2a1NH$^+$	167.148	4790.922	81.877	142.749	-19.608
2a2NH$^+$	169.232	4665.135	79.973	145.400	-19.167
2b1NH$^+$	169.167	4689.004	80.074	145.305	-19.173
2b2NH$^+$	169.165	4664.871	79.916	145.350	-19.150
3a1NH$^+$	151.416	4694.823	80.462	127.438	-19.283
3a3NH$^+$	135.779	4805.856	79.195	112.179	-18.794
4a1NH$^+$	150.306	4676.581	80.332	126.367	-19.262
4a4NH$^+$	141.422	4814.526	80.693	117.375	-19.232
4b1NH$^+$	141.382	4855.182	80.982	117.249	-19.277
4b4NH$^+$	172.072	4776.723	81.007	147.932	-19.363
5a1NH$^+$	149.955	4624.703	79.930	126.136	-19.194
5a5NH$^+$	139.302	4807.860	80.645	115.270	-19.224
5b1NH$^+$	139.234	4829.167	80.778	115.162	-19.243
5b5NH$^+$	173.648	4829.985	81.559	149.343	-19.475
6a1NH$^+$	149.239	4669.904	80.315	125.305	-19.264
6a6NH$^+$	140.944	4880.226	81.153	116.760	-19.303
6b1NH$^+$	140.863	4879.694	81.165	116.676	-19.307
6b6NH$^+$	172.008	4814.269	81.452	147.735	-19.458
7a1NH$^+$	152.321	4608.983	79.725	128.563	-19.149
7a7NH$^+$	143.654	5048.530	82.714	119.005	-19.600
7b1NH$^+$	143.610	5015.880	82.526	119.017	-19.577
7b7NH$^+$	176.223	4448.434	78.780	152.747	-19.028
H_3O^+	47.397	2462.174	46.212	33.626	-11.309

[a] $\Delta G_f = \Delta H_f - T\Delta S$. [b] $\Delta G = \Delta H - T\Delta S$.

3.1 Nucleophilicity

Possible correlations between the nucleophilicities (η) of the molecules in gas phase and those of experimental pK_a values are investigated. Concerning η -pK_a graphs by PM5, PM3 and AM1 are given in Figure 1 for **a** and **b** forms of the molecules. Although there are good meaningful correlation between those for both **a** (**1a1H, 2a1H, 3a1H, 4a1H, 5a1H, 6a1H, 7a1H**) and **b** forms (**2b2H, 4b4H, 5b5H, 6b6H, 7b7H**) could not be observed, corelations for **b** forms are better than those of **a** forms. It is observed that the most succesfull method is PM5, following by PM3 and AM1, successively for the molecules in the **b** form.

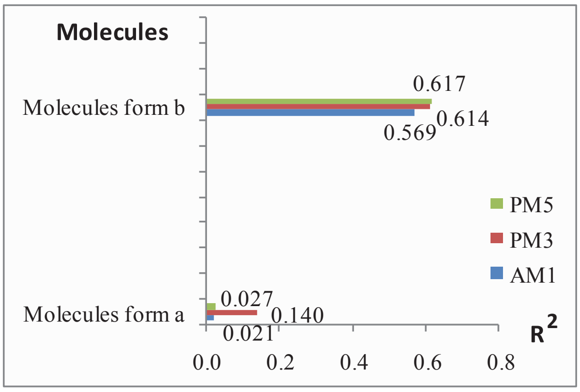


Figure 1. The correlations between nucleophilicity and experimental pK_a values of the molecules, R^2: correlation coefficient.

3.2 Proton Affinities

The proton affinities (PA) of all molecules in gas phase were calculated. The correlation between the proton affinities and both experimental and theoretical pK_a were investigated (Table 4-6 and Figure 2).

The correlation order between PA and experimental pK_a values for the studied molecules is given in the following order: Group4 > Group3 > Group2 > Group1. The success order of the calculated method for each group is PM3, PM5 and AM1; AM1, PM3 and PM5; AM1, PM5 and PM3; PM5, AM1 and PM3 for Group 4, 3, 2 and 1, respectively.

Table 4. Molecule groups considering protonation pathways.

Group 1	Group 2	Group 3	Group 4
2a1NH-2a2NH$^+$	1a1NH-1a1NH$^+$	2b2NH-2b1NH$^+$	2b2NH-2b2NH$^+$
3a3NH-3a3NH$^+$	2a1NH-2a1NH$^+$	4b4NH-4b1NH$^+$	4b4NH-4b4NH$^+$
4a1NH-4a4NH$^+$	3a3NH-3a1NH$^+$	5b5NH-5b1NH$^+$	5b5NH-5b5NH$^+$
5a1NH-5a5NH$^+$	4a1NH-4a1NH$^+$	6b6NH-6b1NH$^+$	6b6NH-6b6NH$^+$
6a1NH-6a6NH$^+$	5a1NH-5a1NH$^+$	7b7NH-7b1NH$^+$	7b7NH-7b7NH$^+$
7a1NH-7a7NH$^+$	6a1NH-6a1NH$^+$		
	7a1NH-7a1NH$^+$		

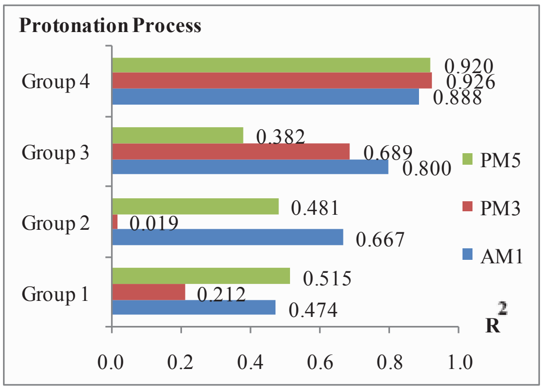


Figure 2. The correlations between proton affinity (PA) and experimental pK_a values of the molecules, R^2: correlation coefficient.

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.

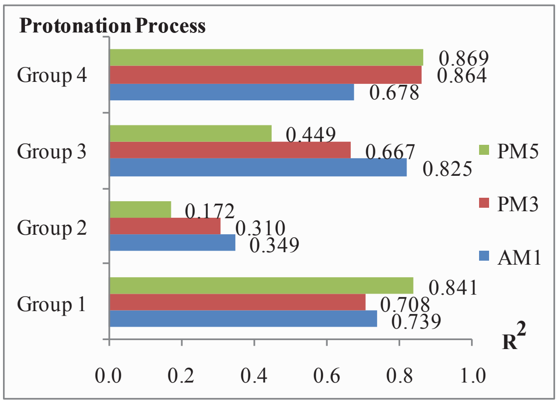


Figure 3. The correlations between theoretical and experimental pK$_a$ values of the molecules, R^2: correlation coefficient.

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 $\rightleftharpoons$ 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	$1.63\ x10^{-1}$	0.788	$1.11\ x10^{-1}$	0.955
4a1NH-4b4H	$1.23\ x10^{-9}$	8.911	$1.14\ x10^{-8}$	7.942	$1.56\ x10^{-6}$	5.807
5a1NH-5b5H	$2.34\ x10^{-9}$	8.631	$3.02\ x10^{-9}$	8.520	$1.19\ x10^{-6}$	5.924
6a1NH-6b6H	$1.27\ x10^{-9}$	8.897	$1.45\ x10^{-9}$	8.840	$2.49\ x10^{-7}$	6.603
7a1NH-7b7H	$2.17\ x10^{-9}$	8.663	$3.56\ x10^{-8}$	7.449	$4.52\ x10^{-6}$	5.345

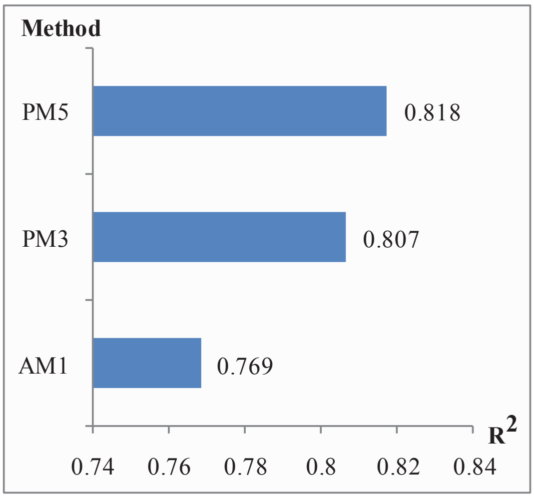


Figure 4. The correlations between tautomerism and experimental pK_a values of the molecules, R^2: correlation coefficient.

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;

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

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

$$K_T = N_b/N_a \text{ and } N_a + N_b = 1 \tag{3.1}$$

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.

$N_{\mathbf{a}}=1/(1+K_T)$ and $N_{\mathbf{b}}=K_T/(1+K_T)$ (3.2)

Thermokinetic calculation;

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

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

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

Thermodynamic calculation;

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

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

Relative stability **b** form: $\Delta G(wa)-\Delta G_{(\mathbf{b})}$ (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. $\mathbf{2a} \rightleftharpoons \mathbf{2b}$ and $\mathbf{3a} \rightleftharpoons \mathbf{3b}$) 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	$\mathbf{\Delta G_f}^a$ kcal mol^{-1}	$\mathbf{\Delta G}^b$ 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}
					$\mathbf{\Delta G_f(wa)}^d$ kcal mol^{-1}	$\mathbf{\Delta G(wa)}^e$ 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	**Na**$_{(f)}$=0.0509	**Na**=0.0552	29.3210	-21.1406	10.6850	-2.0166
4b4NH	29.339	-19.03	**Nb**$_{(f)}$=0.9670	**Nb**=1.0555			-0.0180	-2.1106
5a1NH	17.63	-19.117	**Na**$_{(f)}$=0.0537	**Na**=0.0552	29.2254	-21.1726	11.5954	-2.0556
5b5NH	29.246	-19.062	**Nb**$_{(f)}$=0.9669	**Nb**=1.0554			-0.0206	-2.1106
6a1NH	18.125	-19.115	**Na**$_{(f)}$=0.0523	**Na**=0.0552	30.1578	-21.1815	12.0328	-2.0665
6b6NH	30.178	-19.071	**Nb**$_{(f)}$=0.9679	**Nb**=1.0553			-0.0202	-2.1105
7a1NH	18.622	-19.128	**Na**$_{(f)}$=0.0510	**Na**=0.0552	28.7606	-21.0938	10.1386	-1.9658
7b7NH	28.778	-18.983	**Nb**$_{(f)}$=0.9664	**Nb**=1.0556			-0.0174	-2.1108
PM5								
2a1NH	34.039	-19.047	**Na**$_{(f)}$=0.0285	**Na**=0.0554	35.3400	-21.2475	1.3010	-2.2005
2b2NH	35.341	-19.137	**Nb**$_{(f)}$=0.9725	**Nb**=1.0551			-0.0010	-2.1105
3a1NH	12.354	-19.588	**Na**$_{(f)}$=0.0749	**Na**=0.0538	12.3540	-21.6956	0.0000	-2.1076
3b1NH	12.354	-19.588	**Nb**$_{(f)}$=0.9251	**Nb**=1.0538			0.0000	-2.1076
4a1NH	19.393	-19.016	**Na**$_{(f)}$=0.0490	**Na**=0.0555	27.2963	-21.2347	7.9033	-2.2187
4b4NH	27.31	-19.124	**Nb**$_{(f)}$=0.9647	**Nb**=1.0552			-0.0137	-2.1107
5a1NH	17.539	-19.051	**Na**$_{(f)}$=0.0539	**Na**=0.0554	25.5996	-21.2525	8.0606	-2.2015
5b5NH	25.616	-19.142	**Nb**$_{(f)}$=0.9624	**Nb**=1.0551			-0.0164	-2.1105
6a1NH	18.495	-19.051	**Na**$_{(f)}$=0.0513	**Na**=0.0554	27.4818	-21.2695	8.9868	-2.2185
6b6NH	27.498	-19.159	**Nb**$_{(f)}$=0.9649	**Nb**=1.0551			-0.0162	-2.1105
7a1NH	19.218	-19.04	**Na**$_{(f)}$=0.0495	**Na**=0.0554	26.4929	-21.2236	7.2749	-2.1836
7b7NH	26.506	-19.113	**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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