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THEORETICAL STUDIES ON ACID- BASE BEHAVIOUR OF SOME ALKYL SUBSTITUTED PYRIDINE DERIVATIVES

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ABSTRACT : *The geometries, heat of formations (ΔH_f), entropies (ΔS), proton affinities (PA), atomic charges (q), nucleophilicities (n), substituted constants (σ) and local electrophilic sensitivities (s), were calculated for some alkylated pyridine derivatives after full geometry optimization using AM1, PM3 and PM5 methods in both aqueous and gas phases for studied molecules. The calculated acidity constants, pK_a values, were evaluated by means of searching the possible correlation between experimentally obtained results and the computed data.*

KEYWORDS : *Pyridine derivatives, acidity, basicity, substituted pyridines, quantum chemical calculations.*

BAZI ALKİL SÜBSTİTÜYE PİRİDİN TÜREVLERİNİN ASİT- BAZ DAVRANIŞLARI ÜZERİNE TEORİK ÇALIŞMALAR

ÖZET : *Bu çalışmada, bazı alkillenmiş piridin türevlerinin geometrik optimizasyonu yapıldıktan sonra, AM1, PM3 ve PM5 yöntemleri kullanılarak sıvı ve gaz fazında; geometrileri, oluşum ısıları (ΔH_f), entropileri (ΔS), proton afiniteleri (PA), atomik yükleri (q), nükleofillikleri (n), substituent sabitleri (σ) ve elektrofilik duyarlılıkları (s) hesaplanmıştır. Teorik asitlik sabitleri, deneysel olarak elde edilen pK_a değerleriyle, hesaplanan veriler arasındaki olası korelasyonlar değerlendirilerek incelenmiştir*

ANAHTAR KELİMELER: *Piridin türevleri, asitlik, bazlık, sübstitüye piridinler, kuantum kimyasal hesaplamalar.*

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I. INTRODUCTION

Too many biologically active compounds which contain pyridine ring like herbicides, pesticides, fungicides, cardiovascular drugs such as analgesics, sulfa drugs has been studied experimentally [1-25] and theoretically [26-33]. However, we believe that the potentially active pyridine derivatives deserve more detailed and systematic theoretical studies using updated computer programs and knowledge on structure activity relations (QSAR).

It has been well established that one of the versatile approach to have an idea on the structure and the activity of any molecules is learning about the knowledge of the acidity constants, pK_a values and tautomeric structure of ionisable molecules. They are of particular interest for elucidating reaction mechanisms, especially those having proton transfers and for interpreting binding of substrates or inhibitors to enzymes. The experimental determinations of individual pK_a values are difficult in complex systems and kinetic assignments of pK_a values are often concealed by uncertainties in interpreting the pH dependence of the measured parameters. It is useful, therefore, to have reliable and accurate means of calculating relative and / or absolute pK_a values and to have an understanding is essential for the measured effective pK_a values in complex polyions [33].

We had previously reported some studies on methoxy, methylthio and cyano substituted pyridine rings with DFT methods [31-33]. İn this study, on the acidity-basicity behaviour of some alkyl substituted pyridine derivatives using semi empirically methods was reported.

II. MATERIALS AND METHODS

Theoretical calculations were carried out at the restricted Hartre-Fock level (RHF) using AM1, PM3 and PM5 semi empirical SCF-MO methods in the MOPAC 2002 program. All structures were optimized to a gradient norm of < 0.1 in the gas phase and 0.1–1.0 in the aqueous phase at 298 K (e=78.4). The initial estimates of the geometry of all the structures were obtained by Augmented MM3 and MMFF molecular mechanic methods, followed by full optimization of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, using the semi-empirical AM1, PM3 and PM5 quantum chemical methods [34].

One of the commonly used methods to search for the effect of substituent on an equilibrium proces is the usage of the Hammett equation [35]. When an heteroatom of a heteroaromatic compound acts as reaction site as in the case of protonation or deprotonation process (Equation 1) in which **n** can have positive, negative or zero value. Hammett equation can be used in elucidation of reaction mechanisms.

$$BH^{n+} \rightleftharpoons BH^{(n-1)+} + H^{+} \qquad (1)$$

A general form of the Hammett equation can be written as in Equation 2;

$$\log K / K_o = \rho\ \sigma \qquad (2)$$

in which K and K_0 values are acid dissociation equilibrium constants of substituted and unsubstituted molecules respectively. The slope of the correlation line of   vs. log K/K_0 plot is a measure of the sensitivity of the reaction or equilibrium to electronic substituent effect and referred as   the *reaction constant*. A large   value for equilibrium implies the strong interaction between the substituent and positive heteroatom. The parameter   is referred as the *substituent constant* and it consists of inductive and mesomeric effects and they are mathematically addible (i.e. ${}_{T} = {}_{mesomeric} + {}_{inductive}$). So it can be used the ${}_{T}$ values in interpreting the obtained results.

The semi empirical calculations that used in the present work are based on the following reaction (Eq. 3) and they do not consider the solvation;

$$B + H_3O^{+} \rightleftharpoons BH^{+} + H_2O \qquad (3)$$

In this reaction **B** is the base and BH^+ is the protonated base. The degree of solvations for **B** and BH^+ of course would be different. Semi empirical calculations were carried out using Equations 4 and 5.

$$G_{(BH^+)} = \Delta G_{(BH^+)} + \Delta G_{(H2O)} - \Delta G_{(B)} + \Delta G_{(H3O^+)} \qquad (4)$$

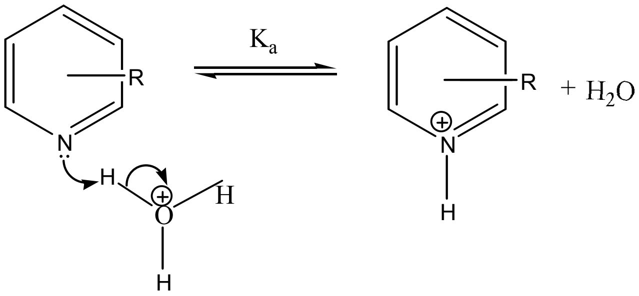
$$pK_a = G_{(BH^+)} / 2.303RT \qquad (5)$$

Frontier molecular orbital theory proposed by Fukui   is a versatile general approach to look at the chemical reactivity. Since the protonation is an electrophilic attack, the Fukui function (Eq. 6) may help to elucidate the mechanism of an electrophilic attack for an atom (p) in the molecule [36, 37].

$$SE(p) = 2 * \sum_{j=1,m} \sum_{\alpha=1,q} \left(c^2_{\alpha j} / \lambda_j \right) \qquad (6)$$

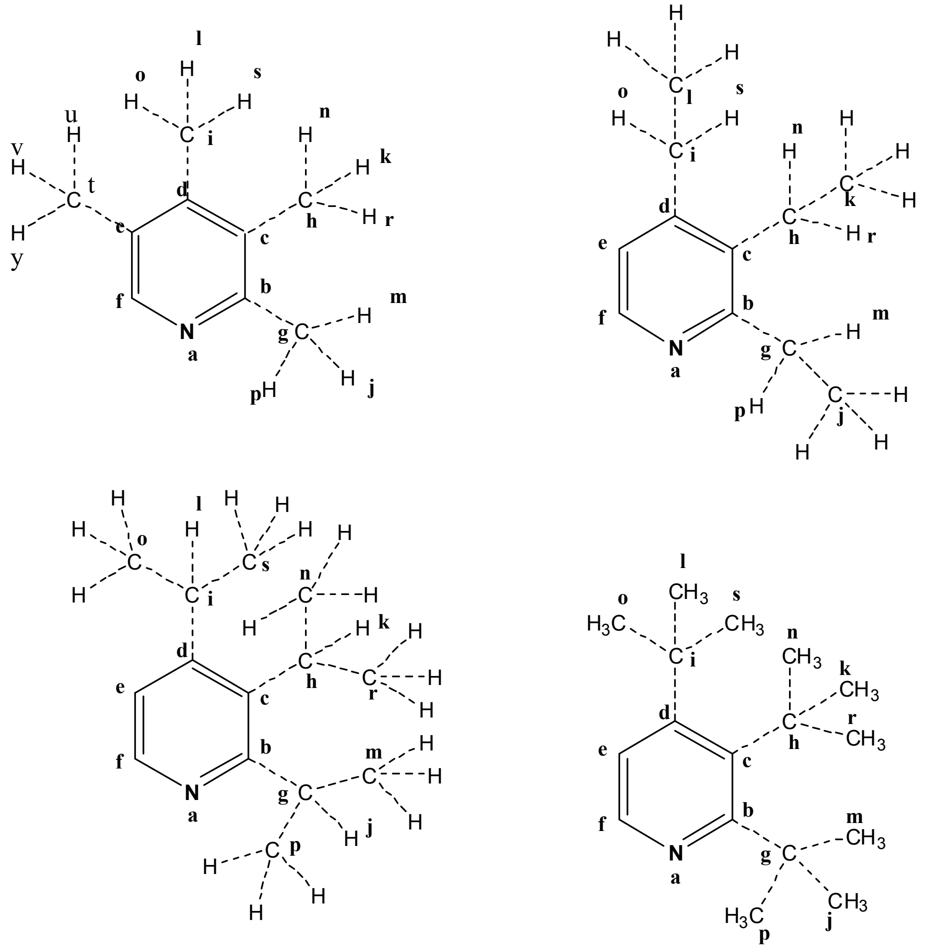
III. RESULTS AND DISCUSSION

The gas and liquid phase calculated thermodynamic data and physical parameters were depicted in Tables 1 and 2. The protonation pattern and the structural data were presented in Scheme 1 and 2 respectively. The evaluation of obtained data will be done with the following sequence;



R= CH_3, CH_2CH_3, *i*-C_3H_7, *t*-C_4H_9

Scheme 1: *Protanation pattern for pyridine derivatives.*



Scheme 2 : Representative formula of studied pyridine derivatives.

Table 1. *AM1, PM3 and PM5 calculated thermodynamic data of the studied molecules in gas phase.*

Compound	**Substituent**	**AM1** **ΔH_f (kcal/mol)**	**PM3** **ΔH_f (kcal/mol)**	**PM5** **ΔH_f(kcal/mol)**
1	H	31.97	30.30	29.20
2	2-methyl	25.61	21.07	21.09
3	3-methyl	24.00	20.77	20.89
4	4 methyl	24.08	20.70	20.51
5	2-ethyl	19.83	17.71	16.84
6	3-ethyl	18.54	17.10	16.39
7	4-ethyl	18.63	17.02	16.06
8	2-isopropyl	15.26	12.36	11.33
9	3-isopropyl	14.21	11.31	10.24
10	4-isopropyl	14.31	11.33	10.09
11	2-tert-butyl	14.19	8.24	5.97
12	3-tert-butyl	12.84	5.49	5.49
13	4-tert-butyl	12.98	7.83	5.42
1p	H	184.09	187.19	179.85
2p	2-methyl	173.80	174.65	167.91
3p	3-methyl	174.54	175.71	169.50
4p	4 methyl	171.41	175.00	168.07
5p	2-ethyl	166.32	169.72	162.14
6p	3-ethyl	168.43	171.41	164.27
7p	4-ethyl	167.04	170.59	162.76
8p	2-isopropyl	161.46	163.90	155.63
9p	3-isopropyl	163.84	165.83	157.80
10p	4-isopropyl	162.78	165.26	156.78
11p	2-tert-butyl	159.35	159.54	149.93
12p	3-tert-butyl	161.66	161.51	152.06
13p	4-tert-butyl	160.65	161.02	151.15

Table 2. *AM1, PM3 and PM5 calculated thermodynamic data of the studied molecules in aqueous phase.*

Molecule	ΔH_f (kcal/mol)	ΔS (cal/molK)	ΔG_f (kcal/mol)[a]	Molecule	ΔH_f (kcal/mol)	ΔS (cal/molK)	ΔG_f (kcal/mol)[a]
				AM1			
1	27.73	67.36	7.66	**1p**	126.91	67.90	106.68
2	21.35	79.60	-2.37	**2p**	119.94	74.16	97.84
3	19.72	79.41	-3.94	**3p**	119.31	78.24	96.00
4	19.71	78.24	-3.60	**4p**	118.45	74.22	96.33
5	15.88	79.27	-7.74	**5p**	114.38	79.71	90.63
6	14.24	79.24	-9.37	**6p**	113.91	79.64	90.18
7	14.24	79.17	-9.36	**7p**	112.98	79.90	89.17
8	11.49	92.48	-16.07	**8p**	110.44	87.55	84.35
9	9.93	90.80	-17.13	**9p**	109.61	90.60	82.61
10	9.97	92.05	-17.46	**10p**	109.04	91.67	81.72
11	10.45	95.90	-18.13	**11p**	109.22	96.40	80.49
12	8.63	96.05	-20.00	**12p**	108.47	95.94	79.88
13	8.65	95.42	-19.78	**13p**	107.66	96.25	78.98
				PM3			
1	26.78	69.31	6.12	**1p**	128.61	68.38	108.23
2	17.58	78.56	-5.83	**2p**	119.27	74.76	96.99
3	17.24	74.33	-4.91	**3p**	119.00	75.88	96.39
4	19.71	78.24	-3.60	**4p**	118.65	74.74	96.38
5	11.07	81.08	-13.10	**5p**	116.24	80.08	92.37
6	13.53	79.90	-10.28	**6p**	115.37	79.99	91.53
7	13.33	79.93	-10.49	**7p**	114.95	80.33	91.01
8	9.37	93.12	-18.38	**8p**	111.33	93.89	83.35
9	7.78	91.61	-19.52	**9p**	109.89	93.96	81.89
10	7.74	91.08	-19.40	**10p**	109.66	91.91	82.27
11	5.36	98.77	-24.07	**11p**	107.71	91.96	80.30
12	4.34	92.40	-23.20	**12p**	105.36	90.85	78.29
13	4.25	92.57	-23.34	**13p**	106.19	91.60	78.90
				PM5			
1	22.99	68.11	2.69	**1p**	121.93	68.69	101.46
2	14.82	78.39	-8.54	**2p**	113.64	80.54	89.64
3	14.66	74.59	-7.57	**3p**	113.81	75.04	91.45
4	14.04	74.56	-8.18	**4p**	112.70	79.56	88.99
5	11.03	80.72	-13.03	**5p**	110.00	80.42	86.03
6	10.13	80.11	-13.75	**6p**	109.33	88.08	83.08
7	9.55	80.09	-14.32	**7p**	108.20	80.04	84.34
8	5.83	87.26	-20.18	**8p**	104.40	91.04	77.26
9	4.03	90.92	-23.06	**9p**	103.35	93.94	75.35
10	3.74	88.31	-22.58	**10p**	102.60	89.84	75.82
11	0.57	97.18	-28.39	**11p**	99.66	100.09	69.83
12	-0.69	97.47	-29.74	**12p**	98.57	92.35	71.05
13	-0.98	97.14	-29.92	**13p**	97.76	91.73	70.42

[a] $\Delta G_f = \Delta H_f - T\Delta S$

III.1. Basicity

III.1.1. Proton Affinities

There is no doubt that availability of lone pair electrons on nitrogen atom of the pyridine ring will determine the extent of basic power. So the proton affinities in gas phase can be a measure of basicity. The biggest proton affinity values (**PA**) were obtained with all methods for compound **11** (i.e **11** $\rightleftharpoons$ **11p** equilibrium) (Table 3). This is not an unusual situation because of the steric hindrance of t-butyl group has been avoided by sticking it out of the pyridine ring. The gas phase calculated dihedral angles of **a-b-g-j** and **a-b-g-p** were found as 120.28; 120.31; 120.34 and -120.25; -120.31; -120.31 degree with AM1, PM3 and PM5 respectively (Scheme 2). So these two methyl group cannot be fully effective in electron donation. But lone pair electrons of nitrogen atoms can be free to approach which means that proton affinity becomes bigger. The smallest **PA** values were obtained for the simple pyridine molecule as expected and no substituent in the ring and no electron donation exists. Furthermore, it seems that *ortho*-alkyl-substituted derivatives have bigger **PA** values than *para*-alkyl-substitutents within the series. In turn *meta*-alkyl-substituted derivatives were found to be smallest. The dipole moment values of gas and aqueous phase AM1, PM3 and PM5 calculations indicate the *para*-substituted derivatives have bigger values than that of *meta*-substituted derivatives and in turn the meta substituted derivatives have bigger values than that of *ortho*-substituted derivatives (Table 4).

Table 3. *AM1, PM3 and PM5 calculated proton affinities in gas phase.*

Protonation	**AM1**	**PM3**	**PM5**
1-1p	215.08	210.31	216.55
2-2p	219.01	213.63	220.38
3-3p	216.66	212.27	218.59
4-4p	219.87	212.90	219.64
5-5p	220.70	215.20	221.90
6-6p	217.32	212.90	219.32
7-7p	218.78	213.63	220.50
8-8p	221.00	215.66	222.89
9-9p	217.57	212.68	219.64
10-10p	218.73	213.27	220.51
11-11p	222.04	215.90	223.24
12-12p	218.38	211.18	220.63
13-13p	219.52	214.01	221.47

[a]PA. = $367.2 + [\Delta H_f(B) - \Delta H_f(BH^+)]$ [38]

Table 4. *AM1, PM3 and PM5 calculated nucleophilicity (n) charge on nitrogen atom, qN dipole moment (D) values of investigated molecules in gas and aqueous phases.*

Compound	**AM1**			**PM3**			**PM5**		
	n[a]	**qN**[b]	**(D)**[c]	**n**[a]	**qN**[b]	**(D)**[c]	**n**[a]	**qN**[b]	**(D)**[c]
				Gas Phase					
1	-10.07	-0.14	1.97	-10.05	-0.08	1.94	-10.02	-0.23	2.28
2	-9.78	-0.14	1.78	-9.80	-0.08	1.75	-9.75	-0.25	2.02
3	-9.76	-0.14	2.10	-9.79	-0.07	2.06	-9.72	-0.22	2.44
4	-10.09	-0.14	2.32	-10.06	-0.09	2.28	-9.99	-0.24	2.75
5	-9.76	-0.14	1.69	-9.77	-0.07	1.68	-9.73	-0.25	1.89
6	-9.73	-0.14	2.18	-9.74	-0.07	2.14	-9.70	-0.22	2.54
7	-10.09	-0.14	2.40	-10.06	-0.09	2.37	-9.99	-0.24	2.84
8	-9.85	-0.14	1.58	-9.89	-0.07	1.63	-9.83	-0.24	1.79
9	-9.84	-0.14	2.17	-9.89	-0.08	2.10	-9.82	-0.23	2.51
10	-10.09	-0.14	2.35	-10.06	-0.08	2.26	-9.99	-0.24	2.75
11	-9.83	-0.14	1.65	-9.88	-0.07	1.67	-9.82	-0.24	1.86
12	-9.81	-0.14	2.16	-9.80	-0.23	2.51	-9.80	-0.23	2.51
13	-10.09	-0.14	2.43	-10.05	-0.08	2.35	-9.98	-0.24	2.86
				Aqueous Phase					
1	-10.08	-0.21	2.71	-10.02	-0.16	2.67	-9.93	-0.34	3.32
2	-9.77	-0.21	2.56	-9.76	-0.16	2.51	-9.64	-0.36	3.11
3	-9.74	-0.20	2.85	-9.74	-0.15	2.81	-9.59	-0.32	3.49
4	-10.09	-0.21	3.10	-10.09	-0.21	3.10	-9.92	-0.35	3.89
5	-9.75	-0.20	2.47	-9.63	-0.34	2.97	-9.63	-0.34	2.97
6	-9.71	-0.20	2.89	-9.71	-0.15	2.86	-9.56	-0.32	3.55
7	-10.09	-0.21	3.18	-9.97	-0.17	3.16	-9.91	-0.35	3.97
8	-9.85	-0.20	2.37	-9.87	-0.13	2.38	-9.76	-0.33	2.85
9	-9.83	-0.21	2.93	-9.85	-0.16	2.85	-9.72	-0.33	3.58
10	-10.09	-0.21	3.11	-9.96	-0.16	3.00	-9.90	-0.35	3.84
11	-9.83	-0.20	2.43	-9.87	-0.13	2.42	-9.75	-0.33	2.95
12	-9.81	-0.21	2.91	-9.83	-0.16	2.83	-9.70	-0.33	3.57
13	-10.09	-0.21	3.20	-9.96	-0.17	3.10	-9.89	-0.34	3.96

[a]Nucleophilicity (n =E_{HOMO}-E_{LUMO}). [b]q_N =Charge on nitrogen atom. [c] (D) =Dipol moment

III.2. Acidity constants, pK_a values

The closer values of acidity constants (pK_a values) to experimental values were obtained using PM5 calculations (Table 5). The experimental acidity constant reflects the geometry dependence more successfully than that of calculated. The ortho alkyl substituted molecules have the following sequences;

Molecule: **1** **11** **8** **5** **2**
pK_a (exp.): 5.17 < 5.76 < 5.83 < 5.97 ≡ 5.97
Increasing basicity →

The *ortho* electron–donation effect of methyl group and ethyl group were found to be the biggest and equal. The effect of isopropyl group in Molecule 8 however is smaller. This basicity drop can only be explained by dihedral angle difference and steric effect of the isopropyl group. As expected *ortho* effect in Molecule 11 is the smallest so the basicity of molecule 11 is the smallest because of the drastic changes in dihedral angle as well as the drastic steric effect.

With the same analogy the *meta*-alkyl-substituted molecules have the following sequence;

Molecule**:** **3** **6** **9** **12**
pK_a(exp.): 5.68 < 5.70 < 5.72 < 5.82
Increasing basicity →

Since alkyl groups are *ortho* and *para* effective an electron-donating group at *meta* position the effect of donation is not as great as at *ortho* and *para* positions. This situation is reflected in above trend. The difference between the minimum and maximum effect is 5.82-5.68=0.14 unit where as in *ortho* position trend the difference was 5.97-5.76=0.21 pK_a unit. As we can see that *ortho* effect is more pronounced. When we take the *para* effect into account we have the following trend;

Molecule**:** **13** **10** **7** **4**
pK_a(exp.): 5.99 < 6.02 ≡ 6.02 ≡ 6.02
Increasing basicity →

In this case PM5 calculated pK_a values provide better and acceptable results;

Molecule**:** **13** **7** **10** **4**
pK_a(PM5 calc.): 3.81 < 5.05 < 5.24 < 6.14
Increasing basicity →

Table 5. *AM1, PM3 and PM5 calculated and experimental pK_a values for the investigated molecules in aqueous phase.*

	AM1		PM3		PM5		
Protonation process	**$\delta\Delta G_{(BH+)}$ (kcal/mol)[a]**	**pKa[b]**	**$\delta\Delta G_{(BH+)}$ (kcal/mol)[a]**	**pKa[b]**	**$\delta\Delta G_{(BH+)}$ (kcal/mol)[a]**	**pKa[b]**	**pKa(exp.)[c]**
1-1p	15.71	11.52	23.01	16.87	6.77	4.96	5.17
2-2p	14.52	10.65	22.30	16.35	7.36	5.40	5.97
3-3p	14.79	10.85	23.82	17.47	6.52	4.78	5.68
4-4p	14.80	10.85	25.14	18.44	8.37	6.14	6.02
5-5p	16.36	12.00	19.65	14.41	6.48	4.75	5.97
6-6p	15.18	11.13	23.31	17.09	8.71	6.39	5.70
7-7p	16.20	11.88	23.62	17.32	6.88	5.05	6.02
8-8p	14.31	10.49	23.39	17.15	8.10	5.94	5.83
9-9p	14.99	10.99	23.71	17.39	7.13	5.23	5.72
10-10p	15.55	11.40	23.45	17.20	7.14	5.24	6.02
11-11p	16.11	11.81	20.75	15.22	7.32	5.37	5.76
12-12p	14.85	10.89	23.63	17.33	4.75	3.48	5.82
13-13p	15.97	11.71	22.88	16.78	5.20	3.81	5.99

[a] $\delta\Delta G_{(BH+)} = [\Delta G_{(B)} + \Delta G_{(H3O+)}] - [\Delta G_{(BH+)} + \Delta G_{(H2O)}]$, [b] $pK_a = \delta\Delta G_{(BH+)} / (2.303RT)$, [c] $pK_{a\,(expt.)}$ were taken from ref [39]

Para effect can be observed better in this sequence. The difference between the minimum and the maximum is 6.14-3.81=2.33 pK_a unit. Electron donating effect of *p*-methyl group is much bigger than t-butyl group.This situation well explains the electron-donation effect of alkyl groups [38].

Correlation Attempts

The correlation attempts will be discussed in following order;

pK_a (calc.) and pK_a (exp.)-PA

Correlation attempts to search between the calculated and experimental acidity constants has revealed that the calculation methods had failed to produce close values to the experimental ones (Table 6). A correlation attempt between proton affinities and calculated or experimental acidity constants revealed that the best regression accuse between **PA** and pK_a (exp.) at AM1 and PM5 methods (Table 6). We used these regression equations to find calculated acidity constants.

Electronic sensitivity-pK_a

The calculated local electronic sensitivity values on **N** atoms are depicted in Table 7. The extrapolated pK_a values and calculated electrophilic sensitivity values are given in Table 8. A search for electronic sensitivity and pK_a values has revealed that the best correlation comes from AM1 method (Table 6).

pK_a – Nucleophilicity

The best correlation between experimental pK_a values and the calculated nucleophilicity values (Table 9) comes from PM5 calculations (Table 6).

$\underline{\sigma_{calc.} - \sigma_{exp.}}$

The Hammett substituent constants, which were obtained by using pK_a values, were depicted in Table 10. We must regret that the calculation methods had failed to produce close values to the experimental ones. PM5 Method however was quite successful for Compound 8.

The extrapolated acidity constants evaluated using best regression equations. As it can be seen from the Table 8, 11 and 12, extrapolated values are very close to experimental acidity constants.

Table 6. *The correlation studies between experimental pK_a and electrophilic sensitivity, experimental pK_a and nucleophilicty, experimental pK_a and proton affinities (PA) (equation and regression values).*

	AM1(gas)	**AM1(aq)**	**PM3 (gas)**	**PM3 (aq.)**	**PM5(gas)**	**PM5(aq.)**
			Electrophilic sensitivity			
Full series	$y = 10.661x - 4.3935$ **$R^2 = 0.4996$**	$y = 6.7387x - 0.1533$ **$R^2 = 0.1706$**	$y = 14.924x - 12.182$ **$R^2 = 0.7267$**	$y = 5.0062x + 0.4884$ **$R^2 = 0.1223$**	$y = 7.1951x - 2.4431$ **$R^2 = 0.4985$**	$y = 4.2411x + 1.5578$ **$R^2 = 0.1381$**
	$y = 20.4x - 13.6$ **$R^2 = 0.8719$** (except 2,5,8,11)	$y = 18.073x - 10.019$ **$R^2 = 0.9492$** (except 1,2,5,8,11)	$y = 17.563x - 15.338$ **$R^2 = 0.8879$** (except 11)	$y = 16.903x - 11.995$ **$R^2 = 0.8211$** (except 1,2,5,8,11)	$y = 13.015x - 9.0232$ **$R^2 = 0.8667$** (except 2,5,8,11)	$y = 13.517x - 7.58$ **$R^2 = 0.9278$** (except 1,2,5,8,11)
			Nucleophilicty			
Full series	$y = -0.1693x + 4.1437$ **$R^2 = 0.0118$**	$y = -0.1448x + 4.3871$ **$R^2 = 0.0094$**	$y = -0.1335x + 4.498$ **$R^2 = 0.0052$**	$y = 0.0628x + 6.4405$ **$R^2 = 0.0013$**	$y = -0.0193x + 5.6304$ **$R^2 = 1E-04$**	$y = -0.0753x + 5.0859$ **$R^2 = 0.0019$**
Except 1,2,5	$y = -0.9078x - 3.1479$ **$R^2 = 0.9369$**	$y = -0.8786x - 2.8536$ **$R^2 = 0.945$**	$y = -1.1237x - 5.2514$ **$R^2 = 0.8614$**	$y = -0.715x - 5.698$ **$R^2 = 0.8034$**	$y = -1.2038x - 6.0186$ **$R^2 = 0.93$**	$y = -1.0196x - 4.1059$ **$R^2 = 0.8934$**
			PA			
Full series	$y = 0.081x - 11.91$ **$R^2 = 0.4247$**		$y = 0.0785x - 10.936$ **$R^2 = 0.2957$**		$y = 0.0815x - 12.143$ **$R^2 = 0.3817$**	
	$y = 0.1739x - 32.123$ **$R^2 = 0.9021$** Except 5,8,11		$y = 0.1901x - 34.628$ **$R^2 = 0.684$** Except 5,8,11		$y = 0.1741x - 32.44$ **$R^2 = 0.8114$** Except 5,8,11	
			pKa			
Full series		$y = 0.0185x + 5.6125$ **$R^2 = 0.0016$**		$y = -0.0041x + 5.8902$ $R^2 = 0.0003$		$y = -0.005x + 5.8463$ **$R^2 = 0.0003$**

***Table** 7. Local electrophilic sensitivity on N atom in the studied molecules.*

Compound	AM1[a]	AM1[b]	PM3[a]	PM3[b]	PM5[a]	PM5[b]
1	0.929	0.874	1.175	1.051	1.104	0.987
2	0.973	0.902	1.218	1.081	1.164	1.022
3	0.939	0.870	1.191	1.050	1.119	0.983
4	0.958	0.888	1.212	1.068	1.149	1.007
5	0.973	0.899	1.214	1.077	1.167	1.020
6	0.942	0.870	1.197	1.049	1.126	0.983
7	0.964	0.889	1.220	1.069	1.159	1.009
8	0.973	0.901	1.210	1.079	1.168	1.025
9	0.946	0.873	1.196	1.050	1.132	0.987
10	0.961	0.885	1.208	1.060	1.153	1.001
11	0.980	0.915	1.222	1.103	1.186	1.052
12	0.951	0.873	1.204	1.050	1.141	0.987
13	0.966	0.886	1.215	1.060	1.163	1.004

[a]Gas phase; [b]Aqueous phase

***Table 8**. Extrapolated pK_a values using semi empirically calculated electrophilic sensitivity values.*

Compound	pKa[a] AM1 (gas phase)	pKa[b] AM1 (aq. phase)	pKa[c] PM3 (gas phase)	pKa[d] PM3 (gas phase)	pKa[e] PM3 (aq. phase)	pKa[f] PM5 (gas phase)	pKa[g] PM5 (aq. phase)	pKa exp.
1	5.35	**5.78***	*5.35*	5.30	**5.77***	5.35	**5.76***	5.17
2	**6.25***	**6.28***	*6.00*	6.05	**6.28***	**6.13***	**6.23***	5.97
3	5.56	5.70	*5.59*	5.58	5.75	5.54	5.71	5.68
4	5.94	6.03	*5.91*	5.95	6.06	5.93	6.03	6.02
5	**6.25***	**6.23***	*5.94*	5.98	**6.21***	**6.17***	**6.21***	5.97
6	5.62	5.70	*5.68*	5.68	5.74	5.63	5.71	5.7
7	6.07	6.05	*6.03*	6.09	6.07	6.06	6.06	6.02
8	**6.25***	**6.26***	*5.88*	5.91	**6.24***	**6.18***	**6.27***	5.83
9	5.70	5.76	*5.67*	5.67	5.75	5.71	5.76	5.72
10	6.00	5.98	*5.85*	5.88	5.92	5.98	5.95	6.02
11	**6.39***	**6.52***	*6.06*	**6.12***	**6.65***	**6.41***	**6.64***	5.76
12	5.80	5.76	*5.79*	5.81	5.75	5.83	5.76	5.82
13	6.11	5.99	*5.95*	6.00	5.92	6.11	5.99	5.99

[a]Calculated using $y = 20.4x - 13.6$ **($R^2 = 0.8719$)** x=electrophilic sensitivity on **N** atom, [b] calculated using $y = 18.073x - 10.019$ **($R^2 = 0.9492$)** x=electrophilic sensitivity on N atom, [c] calculated using $y = 14.924x - 12.182$ **($R^2 = 0.7267$)** x=electrophilic sensitivity on N atom, [d] calculated using $y = 17.563x - 15.338$ **($R^2 = 0.8879$)** x=electrophilic sensitivity on N atom, [e] calculated using $y = 16.903x - 11.995$ **($R^2 = 0.8211$)** x=electrophilic sensitivity on N atom, [f] calculated using $y = 13.015x - 9.0232$ **($R^2 = 0.8667$)** x=electrophilic sensitivity on N atom, .[g] calculated using $y = 13.517x - 7.58$ **($R^2 = 0.9278$)** x=electrophilic sensitivity on N atom, * Extrapolated pKa values using the equations which is derivated without their x values.

Table 9. *AM1, PM3 and PM5 calculated HOMO-LUMO values of investigated molecules in gas and aqueous phases.*

Compound	**AM1**		**PM3**		**PM5**	
	HOMO	**LUMO**	**HOMO**	**LUMO**	**HOMO**	**LUMO**
			Gas Phase			
1	-9.93	0.14	-10.10	-0.05	-9.86	0.15
2	-9.63	0.15	-9.80	0.00	-9.52	0.23
3	-9.63	0.13	-9.80	-0.01	-9.51	0.21
4	-9.89	0.21	-10.06	0.00	-9.81	0.18
5	-9.59	0.16	-9.76	0.01	-9.47	0.26
6	-9.59	0.15	-9.75	-0.01	-9.46	0.25
7	-9.87	0.22	-10.03	0.02	-9.79	0.21
8	-9.67	0.18	-9.89	0.01	-9.58	0.26
9	-9.68	0.16	-9.89	0.00	-9.59	0.24
10	-9.86	0.22	-10.05	0.01	-9.77	0.21
11	-9.63	0.20	-9.86	0.03	-9.53	0.29
12	-9.63	0.18	-9.53	0.27	-9.53	0.27
13	-9.84	0.25	-10.02	0.03	-9.74	0.24
			Aqueous Phase			
1	-10.00	0.07	-10.15	-0.14	-9.98	-0.05
2	-9.74	0.03	-9.89	-0.13	-9.68	-0.04
3	-9.73	0.01	-9.88	-0.14	-9.64	-0.06
4	-10.02	0.07	-10.02	0.07	-10.00	-0.09
5	-9.70	0.05	-9.62	0.01	-9.62	0.01
6	-9.70	0.02	-9.84	-0.13	-9.60	-0.04
7	-10.01	0.08	-10.15	-0.18	-9.99	-0.08
8	-9.79	0.06	-9.98	-0.11	-9.75	0.01
9	-9.80	0.03	-10.00	-0.15	-9.76	-0.05
10	-10.00	0.09	-10.16	-0.19	-9.98	-0.08
11	-9.76	0.07	-9.96	-0.09	-9.72	0.03
12	-9.77	0.03	-9.97	-0.14	-9.73	-0.03
13	-9.99	0.09	-10.15	-0.19	-9.96	-0.07

Table 10. *Calculated substituent constants values for the investigated compounds AM1, PM3 and PM5.*

Molecule	**Substituent**	**$_{(calc.)}{}^{a}$ using calculated pK$_a$ values**			**$_{(exp.)}{}^{a}$ calculated exp. pK$_a$ values**
		AM1	**PM3**	**PM5**	
1	H	-	-	-	-
2	2-methyl	0.157	0.094	-0.079	-0.145
3	3-methyl	0.121	-0.108	0.032	-0.092
4	4 methyl	0.121	-0.283	-0.214	-0.153
5	2-ethyl	-0.086	0.444	0.037	-0.145
6	3-ethyl	0.071	-0.040	-0.258	-0.096
7	4-ethyl	-0.065	-0.081	-0.017	-0.153
8	2-isopropyl	0.186	-0.051	-0.177	-0.119
9	3-isopropyl	0.096	-0.094	-0.049	-0.099
10	4-isopropyl	0.022	-0.059	-0.051	-0.153
11	2-tert-butyl	-0.052	0.298	-0.074	-0.106
12	3-tert-butyl	0.114	-0.083	0.267	-0.118
13	4-tert-butyl	-0.034	0.017	0.207	-0.148

*$pK_{a(pyridine)}$-$pK_{a(subst.pyridine)}$= . ; $_{(for\ pyridine\ protanation)}$= -5.77.

[a]The minus sign (< 0) incidates the electron donation

***Table 11**. Extrapolated pK_a values using semiemprically calculated nucleophilicity values.*

Compound	pKa[a] AM1 (gas phase)	pKa[b] AM1 (aq.phase)	pKa[c] PM3 (gas phase)	pKa[d] PM3 (aq. phase)	pKa[e] PM5 (gas.phase)	pKa[f] PM5 (aq phase)	pKa Experimental
1	**5.99***	**6.00***	**5.99***	**6.01***	**6.04***	**6.02***	5.17
2	**5.73***	**5.73***	**5.73***	**5.72***	**5.72***	**5.72***	5.97
3	5.71	5.70	5.72	5.69	5.68	5.67	5.68
4	6.01	6.01	6.00	6.09	6.01	6.01	6.02
5	**5.71***	**5.71***	**5.70***	**5.57***	**5.69***	**5.71***	5.97
6	5.68	5.68	5.66	5.66	5.66	5.64	5.7
7	6.01	6.01	6.00	5.95	6.01	6.00	6.02
8	5.79	5.80	5.82	5.84	5.81	5.85	5.83
9	5.78	5.78	5.82	5.82	5.80	5.80	5.72
10	6.01	6.01	6.00	5.94	6.01	5.99	6.02
11	5.78	5.78	5.81	5.84	5.80	5.84	5.76
12	5.76	5.77	5.73	5.79	5.78	5.78	5.82
13	6.01	6.01	5.99	5.94	6.00	5.98	5.99

[a] calculated using y = -0.9078x – 3.1479 (R^2 = 0.9369) x=nucleophilicity (n),[b] calculated using y = -0.8786x – 2.8536 (**R^2 = 0.945)** x=nucleophilicity (n), [c] calculated using y = -1.1237x – 5.2514 (**R^2 = 0.8614)** x=nucleophilicity (n), [d] calculated using y = -0.715x – 5.698 (**R^2 = 0.8034)** x=nucleophilicity (n), [e] calculated using y = -1.2038x – 6.0186 (**R^2 = 0.93)** x=nucleophilicity (n), [f] calculated using y = -1.0196x – 4.1059 (**R^2 = 0.8934)** x=nucleophilicity (n),

* Extrapolated pKa values using the equations which is derivated without their x values.

***Table 12.** Extrapolated pK_a values of using best PA-pK_a(exp.) regressions in gas phase.*

Compound	pK_a(calc.) AM1	pK_a(calc.) PM5	pK_a(exp.)
1	5.28	5.26	5.17
2	5.96	5.93	5.97
3	5.55	5.62	5.68
4	6.11	5.80	6.02
5	**6.26***	**6.19***	5.97
6	5.67	5.74	5.7
7	5.92	5.95	6.02
8	**6.31***	**6.37***	5.83
9	5.71	5.80	5.72
10	5.91	5.95	6.02
11	**6.49***	**6.43***	5.76
12	5.85	5.97	5.82
13	6.05	6.12	5.99

* Extrapolated pK_a values using the equations which is derivated without their x values

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