Quantum chemical studies on protonation of some substituted thiazole derivatives

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Abstract

The acidity constants, pK_a values for protonation of some substituted thiazole derivatives were calculated by using AM1 and PM3 basis sets of semi-empirical methods and B3LYP/6-31G(d) basis sets of density functional theory (DFT) calculated physical and thermodynamic parameters. Correlation search among the experimental and calculated acidity constants, pK_a values, revealed that the best correlation exist between the experimental and *ab initio* calculated pK_a values with a regression of $R^2 = 0.98$.
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1. Introduction

The acidity or basicity of a molecular site is very important to the chemical and biological processes that may take place at that site. The acidity plays an important role in the possible hydrogen ion catalysis of processes. The basicity, besides being related to the acidity, can easily be related to the nucleophilicity of the basic site. Whether, the application is polymers or pharmaceuticals, the understanding of the acidity or basicity of molecule is fundamental to molecular design and mechanistic understanding. If the acidity and basicity can be reliably and quickly estimated without the normal synthesis and experimental determination, the efficiency and productivity will greatly be enchanted. Recently several computational approaches have been applied in estimating acidities and basicities which are used in interpretation of structure reactivity relations safely [1,2].

Since thiazole moiety is present in the structure of many biologically active compounds such as thiamine, penicillin G, amphetamine drugs and used an analytical reagent in analysis of heavy metals such as cadmium, lead, copper and gold [3], as an active centre we believe that thiazole derivatives deserve a close theoretical investigation to study structure–reactivity relationships, and performed some quantum chemical calculation on some thiazole derivatives (Table 1) and we are now reporting on the obtained results and evaluation of them.

2. Methods of calculations

Ab inito Hartree-Fock and density functional geometry optimisations were performed with the Gaussian 98 program system [4]. The optimisations were done using HF/3-21G method. These results were re-optimised at the B3LYP type of Density Functional Theory by using the larger basis set 6-31G(d). The *ab initio* geometries were employed in calculating the solvation free energies carried out using at the B3LYP/6-31G(d). The total energies are given in hartree using the conversation factor 1 hartree = 627.5095 kcal mol^{-1}. The value of $\Delta G_s(H^+)$ was taken as -259.5 kcal mol^{-1} [5].

Semi-empiric theoretical calculations were carried out at the restricted Hartree-Fock level (RHF) using AM1 and PM3 [6] semi-empirical SCF-MO methods in MOPAC 7.0 program [7] implemented on an Intel Pentium Pro 133 MHz computer, using a relative permittivity of 78.4 corresponding to water, with up to 60 surface segments per atom for the COSMO model being used to construct a solvent accessible surface area based on van der Waals radii [8]. All structures were optimised to a gradient norm of <0.1 in the gas phase and 0.1–1.0 in the

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Table 1
Nomendate of the studied thiazole derivative
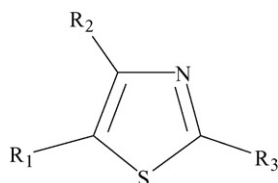
	R_1	R_2	R_3
1	–H	–H	–H
2	–H	–H	$-CH_3$
3	$-CH_3$	–H	–H
4	–H	$-CH_3$	–H
5	–H	–H	$-NO_2$
6	$-NO_2$	–H	–H
7	–H	$-NO_2$	–H
8	$-CH_3$	–H	$-CH_3$
9	–H	$-CH_3$	$-CH_3$
10	$-CH_3$	$-CH_3$	–H
11	$-CH_3$	–H	$-NO_2$
12	–H	$-CH_3$	$-NO_2$
13	$-NO_2$	–H	$-CH_3$
14	$-NO_2$	$-CH_3$	–H
15	$-CH_3$	$-NO_2$	–H
16	–H	$-NO_2$	$-CH_3$
17	$-CH_3$	$-CH_3$	$-NO_2$
18	$-NO_2$	$-CH_3$	$-CH_3$
19	$-CH_3$	$-NO_2$	$-CH_3$

aqueous phase. The absolute entropies of all structures were calculated from a complete vibrational analysis. Enthalpies were corrected to free energies using calculated enthalpies. Initial estimates of all the structures were obtained by a molecular mechanics program (CS Chem Office Pro for Windows) [9], followed by full optimisation of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, using the semi-empirical AM1 and PM3 quantum chemical methods in the MOPAC 7.0 program.

2.1. Absolute and relative pK_a calculations

The interrelationship between gas–liquid phase acidities can be seen in Scheme 1 and taking the general equilibrium (1) into account, where n can have negative, positive or zero value, the Eq. (2) can be driven for the free energy calculation. Eqs. (3) and (4) describe the absolute and relative pK_a values, respectively. In Eq. (3) ΔG_g and ΔG_a are the gas phase and solutions free energies of the ionisation, respectively. The

ΔG_s's are solvation free energies. For *ab initio* calculations ΔG_g is the differences between thermal and solvation energies of the protonated and unprotonated species. The appropriate $\Delta G_{s(H^+)}$ values were appointed by the program with a changing values from -240 to -270 kcal mol^{-1} for *ab initio* calculations.

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

$$\delta\Delta G_{(BH^+)} = [\Delta G_{(B)} + \Delta G_{(H_3O^+)}] - [\Delta G_{(BH^+)} + \Delta G_{(H_2O)}] \tag{2}$$

Absolute pK_a:

$$pK_a = [\Delta G_g + \Delta G_{s(B)} - \Delta G_{s(BH)} + \Delta G_{s(H^+)}]/2.303RT \tag{3}$$

Relative pK_a: $pK_{a(BH^+)} = \delta\Delta G_{(BH^+)}/2.303RT$ (4)

3. Results and discussion

A list of the studied thiazole derivatives and their protonation pattern are given in Table 1 and Scheme 2, respectively. Both semi-empirical and *ab initio* gas phase calculated physical parameters and aqueous phase calculated acidity constants are depicted in Tables 2–7.

Comparing to semi-empirically calculated pK_a values the *ab initio* calculated pK_a values which were calculated using the computed parameters and were depicted in Tables 2–4, respectively are much closer to that of experimental ones (Table 5). The correlation search between calculated and experimental pK_a values indicate that the best correlation exists between the pK_a (*ab initio* calc.) and pK_a (experimental) values (Fig. 1) (i.e. $R^2 = 0.98$ and the slope is 1.18) with the exception of the pK_a value of thiazole molecule itself. The next best correlation was observed between the experimental, and PM3 calculated pK_a values for the increasing order of basicity.

As it can be seen in Scheme 2 the only potential protonation centre in the studied molecules is the azo nitrogen atom of the thiazole ring. The changes in strength of basicity or acidity inevitably arises from the different substituents at different positions which in turn may causes changes in geometries and perturbate the electronic configuration of molecules. So taking these points into account in discussion of basicity and/or acidity power is a necessity.

Expectedly, the basicity of a molecule increases when an electron-donating group such as methyl (i.e. donates electron to the ring inductively) is placed at 2C, 4C or 5C positions. The increasing order of basicity was found as follows:

1		**2**		**3**		**4**	
H	<	5-Me	<	4-Me	<	2-Me	by experimental pK_a values

1		**2**		**4**		**3**	
H	<	5-Me	<	2-Me	<	4-Me	by AM1 pK_a values

1		**2**		**3**		**4**	
H	<	5-Me	<	4-Me	<	2-Me	by PM3 pK_a values

3		**2**		**4**		**1**	
4-Me	<	5-Me	<	2-Me	<	H	by ab initio pK_a values

← decrease of basicity   increase of basicity →
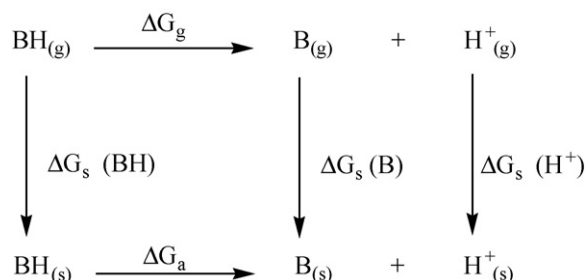
Scheme 1. Inter-relationship between the gas phase and solution thermodynamic parameters.

Scheme 2. Protonation pattern for 2,4,5-mono-, di- or tri-substituted thiazole derivatives.

Although the *ab initio* calculated pK_a values are closer to the experimental ones it seems that they do not keep the same trend of increase with experimental pK_a values. The best-fit to experimental increase come from PM3 method. It is obvious that the greatest substituent effect is observed when the methyl group placed at 2C of the thiazole molecule. Since the dihedral

angles of all three molecules (i.e. 2C-methyl, 4C-methyl and 5C-methyl derivatives) are almost the same (Table 6) the greater substituent influence in 2C methylated thiazole molecule can be attributed to the closeness of the methyl group to the protonation centre and being between two hetero atoms. Since in 5C methylated thiazole molecule the methyl group is located further away from protonation centre the

Table 2
Semi-empirical method gas-phase AM1 and PM3 calculated physical parameters for the studied molecules

Compound	AM1			PM3		
	ΔH_f (kcal mol^{-1})	ΔS (kcal mol^{-1} K^{-1})	ΔG_f^a (kcal mol^{-1})	ΔH_f (kcal mol^{-1})	ΔS (kcal mol^{-1} K^{-1})	ΔG_f^a (kcal mol^{-1})
1	38.580	0.0673	18.505	40.225	0.0678	20.289
2	31.566	0.0724	9.969	32.804	0.0792	9.238
3	30.806	0.0728	9.090	32.606	0.0784	9.219
4	30.983	0.0724	9.386	30.493	0.0774	7.405
5	51.411	0.0775	28.293	38.806	0.0848	13.510
6	44.956	0.0772	21.927	36.981	0.0836	12.222
7	47.889	0.0770	24.920	34.154	0.0872	8.202
8	23.740	0.0777	0.562	25.171	0.0900	−1.676
9	23.823	0.0797	0.049	23.067	0.0890	−3.482
10	24.211	0.0770	1.242	22.842	0.0839	−2.185
11	42.121	0.0839	17.094	30.969	0.0968	2.124
12	42.732	0.0851	17.347	28.930	0.0944	0.801
13	37.101	0.0848	11.805	28.909	0.0934	1.048
14	38.026	0.0846	12.790	28.786	0.0959	0.179
15	40.040	0.0838	15.043	26.669	0.0955	−1.818
16	40.395	0.0842	15.278	26.478	0.0979	−2.725
17	35.060	0.0902	8.154	21.367	0.1040	−9.626
18	29.461	0.0891	2.883	20.718	0.1020	−9.708
19	32.941	0.0914	5.677	19.035	0.1060	−12.585
20	190.098	0.0676	169.933	200.450	0.0682	188.106
21	179.709	0.0763	156.949	189.405	0.0783	166.138
22	180.739	0.0772	157.710	190.718	0.0779	167.749
23	179.556	0.0779	156.319	188.244	0.0804	164.261
24	215.098	0.0775	191.980	211.645	0.0839	186.647
25	212.478	0.0823	187.928	211.666	0.0845	186.459
26	214.699	0.0821	190.209	206.802	0.0833	181.953
27	170.211	0.0780	146.944	179.562	0.0893	153.013
28	168.742	0.0778	145.534	177.269	0.0912	90.064
29	170.413	0.0777	147.235	178.620	0.0862	152.907
30	205.092	0.0914	177.828	201.098	0.0841	176.041
31	203.948	0.0937	175.997	199.076	0.0941	171.006
32	200.855	0.0910	173.710	199.857	0.0840	174.800
33	200.562	0.0849	175.237	200.403	0.0969	171.498
34	204.182	0.0897	177.425	197.085	0.0910	169.939
35	203.521	0.0908	176.436	195.252	0.0932	167.451
36	194.319	0.0874	168.248	189.089	0.1001	159.229
37	189.208	0.0900	162.361	188.875	0.1053	157.554
38	194.286	0.0991	164.724	185.607	0.1022	155.121

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

Table 3
Semi-empirical method aqueous-phase AM1 and PM3 calculated physical parameters for the studied molecules

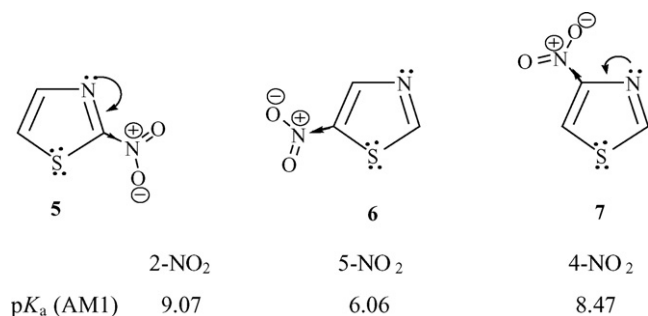| Compound	AM1			PM3		
	ΔH_f (kcal mol^{-1})	ΔS (kcal mol^{-1} K^{-1})	ΔG_f^{a} (kcal mol^{-1})	ΔH_f (kcal mol^{-1})	ΔS (kcal mol^{-1} K^{-1})	ΔG_f^{a} (kcal mol^{-1})
1	29.269	0.0673	9.194	32.704	0.0680	12.419
2	23.131	0.0724	1.534	25.735	0.0785	2.319
3	21.941	0.0727	0.255	25.282	0.0785	1.866
4	22.167	0.0724	0.570	23.459	0.0759	0.818
5	31.101	0.0794	7.416	16.945	0.0835	−7.963
6	23.805	0.0771	0.806	9.591	0.0831	−15.197
7	26.280	0.0769	3.341	6.009	0.0854	−19.346
8	15.734	0.0777	−7.444	18.359	0.0888	−8.130
9	15.742	0.0826	−8.897	16.504	0.0881	−9.746
10	15.827	0.0804	−8.156	15.899	0.0840	−9.128
11	22.006	0.0839	−3.021	9.972	0.0942	−18.068
12	21.224	0.0815	−3.087	7.868	0.0943	−20.261
13	18.153	0.0847	−7.113	2.846	0.0932	−24.955
14	18.734	0.0842	−6.383	3.236	0.0937	−24.715
15	20.586	0.0838	4.411	5.207	0.0925	−22.386
16	20.222	0.0837	−4.746	−0.781	0.0980	−28.433
17	15.504	0.0865	−10.299	1.010	0.1027	−29.625
18	12.083	0.0895	−14.615	−3.706	0.0984	−33.058
19	14.927	0.0913	−12.308	−1.333	0.1031	−32.057
20	125.785	0.0678	105.560	135.128	0.0683	114.754
21	120.275	0.0765	97.455	128.652	0.0881	104.490
22	119.412	0.0776	96.264	127.994	0.0790	104.428
23	118.544	0.0776	95.396	126.313	0.0779	103.076
24	131.140	0.0772	108.110	120.229	0.0835	95.351
25	125.144	0.0820	100.684	115.198	0.0849	89.872
26	132.295	0.0837	107.327	112.822	0.0824	88.242
27	113.646	0.0813	89.394	121.875	0.0897	95.118
28	112.284	0.0778	89.076	119.854	0.0895	93.156
29	112.328	0.0813	88.076	118.994	0.0827	94.325
30	126.450	0.0932	98.649	113.579	0.0833	88.820
31	124.516	0.0928	96.834	112.121	0.0933	84.290
32	120.374	0.0904	93.408	109.882	0.0864	84.109
33	119.073	0.0837	94.105	109.620	0.0898	82.833
34	127.058	0.0898	100.271	108.579	0.0890	82.030
35	126.770	0.0913	99.535	107.184	0.0940	79.144
36	119.700	0.0900	92.853	105.974	0.0981	76.741
37	114.310	0.0869	88.388	104.378	0.1028	73.713
38	123.849	0.0971	94.884	103.053	0.1005	73.551

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

former reason can also explain the greater influence of the methyl group which is located at 4C than that 5C of thiazole ring.

literature, we now have to rely on semi-empirical AM1 and PM3 calculated pK_a values in this argument. The decreasing order of basicity was found as follows:

	1		**2**		**4**		**3**	
	H	>	5-Me	>	2-Me	>	4-Me	by AM1 method
pK_a	11.10		9.07		8.47		6.06	
	1		**2**		**3**		**4**	
	H	>	5-Me	>	4-Me	>	2-Me	by PM3 method
pK_a	14.94		14.22		12.94		11.09	

← increase of basicity   decrease of basicity →

When a strong electron-withdrawing group such as nitro group is placed at 2C, 4C and 5C position of the thiazole molecule, however, the reverse of the methyl group effect should be observed. In another words the basicity of the molecule decreases as well as the nucleophilicity. Since we did not come across with the experimental pK_a values in the

Both AM1 and PM3 methods suggest the biggest decrease of basicity occurs in 4-NO$_2$ derivative. This effect can be explained by thinking the electron withdrawing power of the nitro group both inductively and mesomerically. The electron density on the azo nitrogen atom decreases greatly in molecule **7** because the nitro group is located next to azo nitrogen

	5	6	7
	2-NO$_2$	5-NO$_2$	4-NO$_2$
pK_a (AM1)	9.07	6.06	8.47

Fig. 1. The correlation graph of semi-empirical AM1 (Δ), PM3 (□) calculated and *ab initio* calculated (●), and the experimentally observed pK_a values of substituted thiazole.

atom via a single (C–N) bond. The nitro group also makes the approach of hydronium ion sterically difficult. However, this situation does not arise in molecule **6** because the nitro group is located further away from protonation centre and since it is located next to the sulphur atom it may obtain electron from that heteroatom easily. In molecule **5**, however, both of the above effects are operative. The nitro group is located next to protonation centre via a double (N=C) bond and both azo nitrogen and sulphur atoms are electron rich heteroatoms. As for as the geometry is concerned (Table 6), they all have a very similar structure. The AM1 and PM3 calculated dihedral angles were found to be equal for each molecule. The comparison of the nucleophilicities of the related molecules reveals out the following trend:
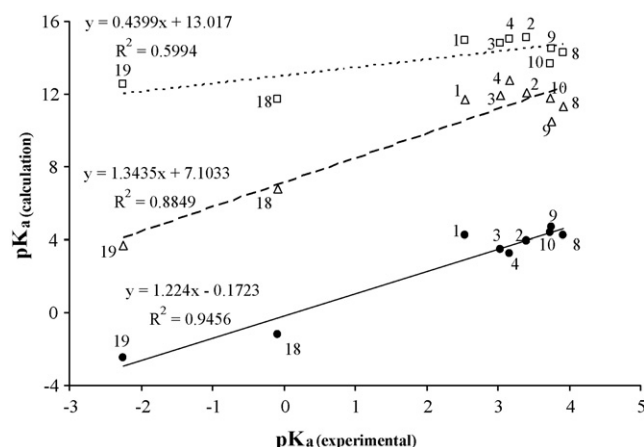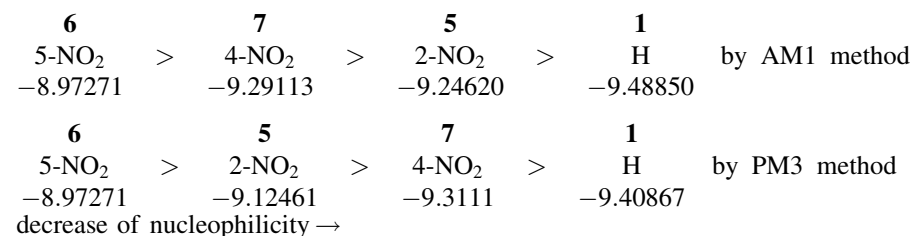
Both AM1 and PM3 methods are indicating that the previous discussion of decrease in basicity is correct and the nucleophilicity as well as the basicity of molecule **6** is not effected by nitro group very much because of its location which is far away from the reaction centre. Whereas, the nucleophilicity of molecules **5** and **7** influenced more and consequently they have

	6		**7**		**5**		**1**	
	5-NO$_2$	>	4-NO$_2$	>	2-NO$_2$	>	H	by AM1 method
	−8.97271		−9.29113		−9.24620		−9.48850	

	6		**5**		**7**		**1**	
	5-NO$_2$	>	2-NO$_2$	>	4-NO$_2$	>	H	by PM3 method
	−8.97271		−9.12461		−9.3111		−9.40867	

decrease of nucleophilicity →

Table 4
Ab initio calculated thermal and free energies, ΔG_a and ΔG_s values, experimental and calculated acidity constants pK_a values

Molecules	Thermal free energy $\Delta G_{g(B)}$ (kcal mol^{-1})	Solvation free energy $\Delta G_{s(B)}$ (kcal mol^{-1})	Thermal free energy $\Delta G_{g(BH^+)}$ (kcal mol^{-1})	Solvation free energy $\Delta G_{s(BH^+)}$ (kcal mol^{-1})	pK_a[a]	pK_a[b] (experimental)
1	−357053.86	−4.61	–	–	4.22[c]	2.55
20	–	–	−357283.09	−59.71		
2	−381730.21	−3.84	–	–	3.94	3.40
21	–	–	−381947.73	−55.70		
3	−381726.78	−3.97	–	–	3.48	3.03
22	–	–	−381943.85	−55.64		
4	−381729.93	−3.69	–	–	3.27	3.16
23	–	–	−381946.21	−55.86		
8	−406387.13	−3.12	–	–	4.21	3.91
27	–	–	−406608.27	−51.73		
9	−406389.10	−3.07	–	–	4.66	3.76
28	–	–	−406610.29	−52.24		
10	−406385.85	−3.26	–	–	4.38	3.73
29	–	–	−406607.71	−52.38		
18	−534717.27	−4.22	–	–	−1.23	−0.09
37	–	–	−534923.70	−58.12		
19	−534718.86	6.47	–	–	−2.52	−2.24
38	–	–	−534927.60	−56.30		

[a] p$K_a = [\Delta G_g + \Delta G_{s(B)} - \Delta G_{s(BH)} + \Delta G_{s(H^+)}]/2.303RT$.
[b] pK_a = Taken from Ref. [10].
[c] Reported as 17.12 in our earlier paper by mistake [2].

Table 5
Aqueous phase semi-empirical, *ab initio* (BLY3P/6-31G) calculated acidity constants, pK_a, values, for protonation of studied molecules

	AM1		PM3		*Ab initio* pK_a[c]	pK_a[d] (experimental)
	$\delta\Delta G^a$ (kcal mol^{-1})	pK_a[b](BH$^+$) (semi-empirical)	$\delta\Delta G^a$ (kcal mol^{-1})	pK_a[b](BH$^+$) (semi-empirical)		
1 → 20	15.952	11.69	20.396	14.942	4.22[e]	2.55
2 → 21	16.337	11.97	20.560	15.062	3.94	3.40
3 → 22	16.249	11.90	20.169	14.776	3.48	3.03
4 → 23	17.432	12.77	20.473	14.999	3.27	3.16
5 → 24	11.564	8.47	19.417	14.224	–	–
6 → 25	12.380	9.07	17.662	12.939	–	–
7 → 26	8.272	6.06	15.143	11.094	–	–
8 → 27	15.420	11.30	19.483	14.273	4.21	3.91
9 → 28	14.285	10.47	19.829	14.527	4.66	3.76
10 → 29	16.026	11.74	18.660	13.670	4.38	3.73
11 → 30	10.588	7.76	15.843	11.607	–	–
12 → 31	18.511	13.56	18.180	13.319	–	–
13 → 32	11.737	8.60	13.667	10.012	–	–
14 → 33	11.770	8.62	15.183	11.122	–	–
15 → 34	16.398	12.01	18.315	13.418	–	–
16 → 35	7.977	5.84	15.154	11.102	–	–
17 → 36	9.106	6.67	16.365	11.989	–	–
18 → 37	9.255	6.78	15.960	11.692	−1.23	−0.09
19 → 38	5.066	3.71	17.123	12.544	−2.52	−2.24

[a] $\delta\Delta G_{(BH^+)} = [\Delta G_{(B)} + \Delta G_{(H_3O^+)}] - [\Delta G_{(BH^+)} + \Delta G_{(H_2O)}]$.
[b] p$K_{a(BH^+)} = \delta\Delta G_{(BH^+)}/2.303RT$.
[c] p$K_a = [\Delta G_g + \Delta G_{s(B)} - \Delta G_{s(BH)} + \Delta G_{s(H^+)}]/2.303RT$.
[d] pK_a = Taken from Ref. [10].
[e] Reported as 17.12 in our earlier paper by mistake [2].

smaller nucleophilic power than that of molecule **6**, respectively. These results also indicate that the nucleophilicity of an organic molecule changes parallel with basicity (i.e. molecule **7** is the least basic one but the softest nucleophile among the three nitro derivatives). The higher dipole moment values of molecule **7** both with AM1 and PM3 methods than that of molecule **1**, **5** and **6** are also a further support to the above conclusion (Table 6).

When two positions of the thiazole molecule occupied by two electron donating group such as methyl group increase in the basicity is found as follows:

The trend of increase in basicity of molecules **9–10** is a chaos by different methods and not conclusive at all. The experimental and *ab initio* calculations conflict badly. There seems no clue to explain this discrepancy by geometrical approach also (Table 6). The dihedral angles of the substituted methyl groups seem to be the same both with AM1 and PM3 methods. The dipole values of AM1 and PM3 methods indicate the equivalence of the dipole moments of 2,5-Me to the 4,5-Me derivative. Both dipole moments are, however, bigger than that of 2,4-derivative and it might indicate the occurrence of bigger electronic perturbation in molecules **8** and **10** than that of

	1		**10**		**9**		**8**	
	H	<	4, 5-Me	<	2, 4-Me	<	2, 5-Me	
pK_a	2.55		3.73		3.76		3.91	by experimental pK_a values
	9		**8**		**1**		**10**	
	2, 4-Me	<	2, 5-Me	<	H	<	4, 5-Me	
pK_a	10.47		11.30		11.69		11.74	by AM1 pK_a values
	10		**8**		**9**		**1**	
	4, 5-Me	<	2, 5-Me	<	2, 4-Me	<	H	
pK_a	13.67		14.27		14.53		14.94	by PM3 pK_a values
	8		**1**		**10**		**9**	
	2, 5-Me	<	H	<	4, 5-Me	<	2, 4-Me	
pK_a	4.21		4.22		4.38		4.66	by *ab initio* pK_a values

increase of basicity →

Table 6
The aqueous phase semi-empirical AM1 and PM3 computed dihedral angles of the studied compounds
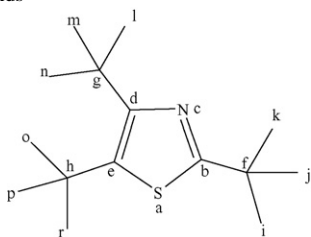
Compound	Dihedral angles	
	AM1	PM3
2		
2-Met		
a–b–f–i	−59.882	59.797
a–b–f–j	59.261	59.236
a–b–f–k	179.693	179.720
c–b–f–i	120.197	120.244
c–b–f–j	−120.660	−120.723
c–b–f–k	−0.228	−0.239
3		
5-Met		
a–e–h–r	179.842	179.883
a–e–h–p	−60.071	−60.195
a–e–h–o	59.749	59.835
d–e–h–r	−0.107	−0.138
d–e–h–p	119.979	119.835
d–e–h–o	−120.201	−120136
4		
4-Met		
c–d–g–l	−179.930	−179.877
c–d–g–m	60.135	60.166
c–d–g–n	−59.968	−59.910
e–d–g–l	0.107	0.133
e–d–g–m	−119.828	−119.824
e–d–g–n	120.069	120.099
5		
2-NO$_2$		
a–b–f–i	2.161	7.143
a–b–f–j	−177.741	−172.357
c–b–f–i	−177.971	−172.971
c–b–f–j	2.127	7.529
6		
5-NO$_2$		
a–e–h–o	179.980	−178.895
a–e–h–p	0.111	1.374
d–e–h–o	0.076	0.878
d–e–h–p	−179.792	−178.853
7		
4-NO$_2$		
c–d–g–l	1.140	1.707
c–d–g–m	−178.850	−178.590
e–d–g–l	−178.693	−178.224
e–d–g–m	1.317	1.479
8		
2-Met		
a–b–f–i	−59.803	−59.622

Table 6 (*Continued*)

Compound	Dihedral angles	
	AM1	PM3
a–b–f–j	179.762	179.896
a–b–f–k	59.337	59.412
c–b–f–i	120.246	120.315
c–b–f–j	−0.189	−0.167
c–b–f–k	−120.614	−120.652
5-Met		
a–e–h–r	−60.109	−60.215
a–e–h–p	179.811	179.828
a–e–h–o	59.712	59.843
d–e–h–r	119.987	119.837
d–e–h–p	−0.093	−0.120
d–e–h–o	−120.192	−120.105
9		
2-Met		
a–b–f–i	−59.866	−59.793
a–b–f–j	179.701	179.710
a–b–f–k	59.251	59.204
c–b–f–i	120.176	120.254
c–b–f–j	−0.257	−0.242
c–b–f–k	−120.707	−120.749
4-Met		
c–d–g–l	179.900	−179.866
c–d–g–m	60.165	60.181
c–d–g–n	−59.965	−59.904
e–d–g–l	0.227	0.154
e–d–g–m	−119.707	−119.799
e–d–g–n	120.162	120.116
10		
5-Met		
a–e–h–r	−59.954	−60.451
a–e–h–p	179.756	179.876
a–e–h–o	59.483	60.166
d–e–h–r	120.178	119.548
d–e–h–p	−0.111	−0.126
d–e–h–o	−120.384	−119.835
4-Met		
c–d–g–l	−179.940	−179.898
c–d–g–m	59.944	60.462
c–d–g–n	−59.805	−60.233
e–d–g–l	0.164	0.125
e–d–g–m	−119.952	−119.515
e–d–g–n	120.299	119.790
11		
2-NO$_2$		
a–b–f–i	2.973	6.910
a–b–f–j	−176.921	−172.980
c–b–f–i	−177.160	−173.315
c–b–f–j	2.945	6.796
5-Met		
a–e–h–r	−60.932	−61.207
a–e–h–p	179.023	178.842
a–e–h–o	58.918	58.809
d–e–h–r	119.208	119.009
d–e–h–p	−0.837	−0.943
d–e–h–o	−120.943	−120.976
12		
2-NO$_2$		
a–b–f–i	2.292	7.038

Table 6 (*Continued*)

Compound	Dihedral angles	
	AM1	PM3
a–b–f—j	−177.619	−172.694
c–b–f–i	−177.854	−172.992
c–b–f–j	2.235	7.275
4-Met		
c–d–g–l	−179.209	−179.119
c–d–g–m	60.921	61.075
c–d–g–n	−59.271	−59.197
e–d–g–l	0.760	1.036
e–d–g–m	−119.111	−118.769
e–d–g–n	120.698	120.959
13		
2-Met		
a–b–f–i	−59.706	−59.241
a–b–f–j	179.882	−179.788
a–b–f–k	59.483	59.645
c–b–f–i	120.406	120.558
c–b–f–j	−0.006	0.010
c–b–f–k	−120.405	−120.557
5-NO₂		
a–e–h–o	179.935	−179.707
a–e–h–p	0.047	0.485
d–e–h–o	0.135	0.565
d–e–h–p	−179.935	−179.243
14		
5-NO₂		
a–e–h–o	−179.935	179.290
a–e–h–p	0.233	0.018
d–e–h–o	0.235	0.426
d–e–h–p	−179.598	−178.847
4-Met		
c–d–g–l	−179.899	179.981
c–d–g–m	59.652	59.393
c–d–g–n	−59.442	−59.282
e–d–g–l	0.088	−0.131
e–d–g–m	−120.360	−120.719
e–d–g–n	120.546	120.606
15		
2-Met		
a–e–h–r	−179.968	−179.935
a–e–h–p	59.415	59.457
a–e–h–o	−59.379	−59.401
d–e–h–r	0.043	0.152
d–e–h–p	−120.574	−120.456
d–e–h–o	120.631	120.685
4-NO₂		
c–d–g–l	0.454	0.443
c–d–g–m	−179.636	−179.740
e–d–g–l	−179.241	179.975
e–d–g–m	0.669	−0.209
16		
2-Met		
a–b–f–i	59.131	59.138
a–b–f–j	−59.918	−59.901
a–b–f–k	179.603	179.627
c–b–f–i	−120.840	−120.857
c–b–f–j	120.112	120.105
c–b–f–k	−0.367	−0.368

Table 6 (*Continued*)

Compound	Dihedral angles	
	AM1	PM3
5-NO₂		
c–d–g–l	1.025	1.709
c–d–g–m	−178.969	−178.557
e–d–g–l	−178.789	−178.187
e–d–g–m	1.217	1.547
17		
2-NO₂		
a–b–f–i	28.665	29.381
a–b–f–j	−151.005	−150.696
c–b–f–i	−150.495	−150.568
c–b–f–j	29.835	29.356
4-Met		
a–e–h–r	179.889	179.909
a–e–h–p	59.441	60.222
a–e–h–o	−59.622	−60.277
d–e–h–r	0.162	0.238
d–e–h–p	−120.286	−119.448
d–e–h–o	120.651	120.052
5-Met		
c–d–g–l	−179.979	−179.973
c–d–g–m	59.881	60.426
c–d–g–n	−59.775	−60.387
e–d–g–l	−0.081	−0.030
e–d–g–m	−120.221	−119.631
e–d–g–n	120.123	119.556
18		
2-Met		
a–b–f–i	58.250	58.841
a–b–f–j	−60.900	−60.098
a–b–f–k	178.875	179.510
c–b–f–i	−120.656	−120.759
c–b–f–j	120.193	120.309
c–b–f–k	−0.032	−0.083
4-Met		
c–d–g–l	−179.770	−179.765
c–d–g–m	59.784	59.749
c–d–g—n	−59.317	−59.291
e–d–g–l	−0201	−0.446
e–d–g–m	−120.647	−120.932
e–d–g–n	120.252	120.028
5-NO₂		
a–e–h–o	−179.849	−179.763
a–e–h–p	0.222	0.553
d–e–h–o	1.402	1.387
d–e–h–p	−178.527	−178.297
19		
2-Met		
a–b–f–i	58.048	58.019
a–b–f–j	−60.895	−61.019
a–b–f–k	178.544	178.535
c–b–f–i	−121.858	121.830
c–b–f–j	119.198	119.132
c–b–f–k	−1.362	−1.314
5-Met		
a–e–h–r	−172.246	−171.054
a–e–h–p	66.955	68.332

Table 6 (*Continued*)

Compound	Dihedral angles	
	AM1	PM3
a–e–h–o	−51.878	−50.634
d–e–h–r	7.122	9.497
d–e–h–p	−113.676	−111.116
d–e–h–o	127.491	129.917
2-NO$_2$		
c–d–g–l	8.200	9.634
c–d–g–m	−171.416	−169.666
e–d–g–l	−171.851	−170.256
e–d–g–m	8.533	10.444
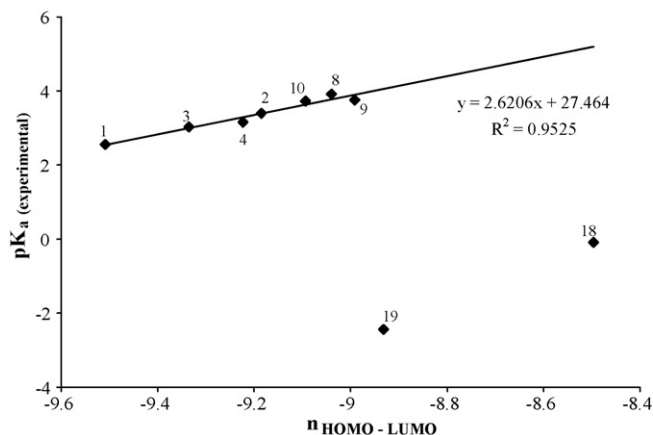
Fig. 2. The correlation plot for aqueous phase (AM1) calculated nucleophilicities, *n*, and experimental acidity constant, pK_a, of studied molecules.

molecule **9** (Table 7). When the nucleophilicity values of those three molecules were considered the following trends were obtained:

1		**10**		**8**		**9**	
H	<	4, 5-Me	<	2, 5-Me	<	2, 4-Me	by Am1 method
−9.48850		−9.09449		−9.05821		9.02897	
1		**8**		**10**		**9**	
H	<	2, 5-Me	≤	4, 5-Me	<	2, 4-Me	by PM3 method
−9.40867		−9.10382		−9.06807		−9.01547	
1		**10**		**9**		**8**	
H	<	4, 5-Me	≤	2, 4-Me	<	2, 5-Me	by *ab initio* method
−0.22089		−0.20936		−0.20876		−0.20751	

increase of nucleophilicity →

This trend indicates that the basicity values by *ab initio* increases parallel with AM1 and PM3 calculated nucleophilicities.

An interesting approach to search the degree of electronic perturbation within the thiazole ring upon substitution of course will be inserting the substituents of opposite electronic character (i.e. one will be electron donating and the other will be electron withdrawing) such as methyl and nitro groups. Molecules **11–16** have these two groups in the thiazole ring as subtituent with different combination. Since there is no experimental acidity constants available in the literature it's an obligation to rely on AM1 and PM3 calculated pK_a values and therein. The order of the increase in basicity was found as follows:

Although there seems a contradiction for the place of a compound within series there is a general argument that supported by both methods that is the nitro group acts more effectively when its located at 4C and the methyl group is located at 2C of the thiazole ring simultaneously. The NO$_2$ group behaves as it were alone in the ring as it does in compound **7** (i.e. 4-NO$_2$ thiazole). It also seems that the nitro group is least effective when its located at 2C and the methyl group is located at 4C. The planar structure of the NO$_2$ group in compound **16** (i.e. 2-Me 4-NO$_2$ derivative) let the full conjugation with the thiazole ring (Table 6). The dihedral angles of NO$_2$ group in molecule **16** are different from the other NO$_2$ groups which are located at different positions. This difference of geometry is also reflected in geometry of methyl

Compound	**16**	<	**11**	<	**13**	<	**14**	<	**15**	<	**12**	by AM1 calculation
	2-Me		5-Me		2-Me		4-Me		5-Me		4-Me	
	4-NO$_2$		2-NO$_2$		5-NO$_2$		5-NO$_2$		4-NO$_2$		2-NO$_2$	
	5.84		7.76		8.60		8.62		12.01		13.56	
Compound	**13**	<	**16**	<	**14**	<	**11**	<	**12**	<	**15**	by PM3 calculation
	2-Me		2-Me		4-Me		5-Me		4-Me		5-Me	
	5-NO$_2$		4-NO$_2$		5-NO$_2$		2-NO$_2$		2-NO$_2$		4-NO$_2$	
	10.01		11.10		11.12		11.61		13.32		13.42	

increase of basicity →

Table 7

Aqueous-phase AM1, PM3 and *ab initio* (BLY3P/6-31G) calculated frontier orbital energies and nucleophilicities n values of studied molecules

Molecule	AM1				PM3				*Ab initio*		
	HOMO	LUMO	n^a (nucleophilicity)	μ^b (D)	HOMO	LUMO	n^a (nucleophilicity)	μ^b (D)	HOMO	LUMO	n^a (nucleophilicity)
1	−9.69825	−0.20975	−9.48850	4.224	−10.01394	−0.60527	−9.40867	2.058	−0.26210	−0.04121	−0.22089
2	−9.42021	−0.19929	−9.22092	3.824	−9.80115	−0.57925	−9.22190	1.789	−0.24885	−0.03505	−0.21382
3	−9.55438	−0.23193	−9.32245	4.087	−9.92217	−0.59529	−9.32688	2.161	−0.24854	−0.03456	−0.21398
4	−9.35687	−0.13824	−9.21863	3.825	−9.68750	−0.52552	−9.16198	1.610	−0.24970	−0.03540	−0.21430
5	−10.53892	−1.29272	−9.24620	9.846	−10.81548	−1.69087	−9.12461	8.521	–	–	–
6	−10.73096	−1.75825	−8.97271	7.477	−10.92136	−1.99622	−8.92514	6.578	–	–	–
7	−10.68199	−1.39086	−9.29113	11.627	−11.04483	−1.73372	−9.31111	8.956	–	–	–
8	−9.27712	−0.21891	−9.05821	3.637	−9.67373	−0.56991	−9.10382	1.893	−0.23677	−0.02926	−0.20751
9	−9.14670	−0.11773	−9.02897	3.383	−9.51656	−0.50109	−9.01547	1.316	−0.23816	−0.02940	−0.20876
10	−9.25288	−0.15839	−9.09449	3.608	−9.58874	−0.52067	−9.06807	1.826	−0.23807	−0.02871	−0.20936
11	−10.35579	−1.64520	−8.71059	11.105	−10.71325	−1.65534	−9.05791	8.730	–	–	–
12	−10.16393	−1.58435	−8.57958	11.181	−10.44114	−1.59226	−8.84888	8.410	–	–	–
13	−10.41144	−1.69609	−8.71535	7.693	−10.70222	−1.94260	−8.75962	6.980	–	–	–
14	−10.32282	−1.64379	−8.67903	6.590	−10.55346	−1.87792	−8.67554	6.149	–	–	–
15	−10.49408	−1.34246	−9.15162	11.280	−10.97775	−1.67839	−9.29936	8.436	–	–	–
16	−10.37266	−1.31699	−9.05567	11.527	−10.78839	−1.67481	−9.11358	8.972	–	–	–
17	−10.02520	−1.56143	−8.46377	10.937	−10.33248	−1.56256	−8.76992	8.341	–	–	–
18	−10.08125	−1.59146	−8.48979	6.705	−10.38643	−1.82713	−8.55930	6.377	−0.27681	−0.11239	−0.16442
19	−10.18211	−1.27285	−8.90926	10.143	−10.57732	−1.45658	−9.12074	8.302	−0.27449	−0.09754	−0.17695

[a] $n = E_{HOMO} - E_{LUMO}$.
[b] μ (D) = dipole moment.

groups by having different dihedral angles from the others and getting a non-planer structure and in this way may not exercise a full effect to the ring in giving electrons inductively.

The nucleophilicity criteria however points out a different situation and the following nucleophilicity trend was observed:

Compound	**15**	<	**16**	<	**14**	<	**13**	<	**11**	<	**12**	by AM1 calculation
	5-Me		2-Me		4-Me		2-Me		5-Me		2-Me	
	4-NO_2		4-NO_2		5-NO_2		5-NO_2		2-NO_2		2-NO_2	
	−9.15162		−9.05567		−8.67903		−8.71535		−8.71059		−8.57958	
Compound	**15**	<	**16**	<	**11**	<	**13**	<	**12**	<	**14**	by PM3 calculation
	5-Me		2-Me		5-Me		2-Me		5-Me		4-Me	
	4-NO_2		4-NO_2		2-NO_2		5-NO_2		2-NO_2		5-NO_2	
	−9.29936		−9.11358		−9.05791		−8.75962		−8.84888		−8.67554	

It seems that the power of nucleophilicity do not change in parallel with the basicity. The compound **15**, for example, found to be the strongest base (i.e. pK_a values of 12.01 and 13.42 by AM1 and PM3 methods, respectively) whereas it was found as the weakest nucleophile with both AM1 and PM3 methods within the series of compounds **11–16**. This discrepancy can be explained by the differences in geometries of the studied molecules.

When all three available positions of thiazole ring have the substituents the following trend of increase in basicity was obtained:

As one immediately can realise that although the pK_a values differs from each other numerically they all indicate that the most basic one is the compound **18** among the three molecules under study. The geometric criteria reflects the same results indicating the possibility of full inductive and/or mesomeric effects of the substituents (i.e. inductive electron donating effect of Me and inductive and mesomeric electron-withdrawing effect of NO_2 group) which in closely related to the planarity of the molecule and the substituents (Table 6). It seems again that NO_2 group is fully effective in molecule **19** in which the NO_2 group is located at 4C and it is easy to see this effect if we take into account the decrease of electron density on azo nitrogen by mesomeric and inductive electron withdrawing effect of NO_2 group. Since the position of NO_2 group is different in molecule **19** the electron withdrawing effect is different at this position which there is no steric effect sulphur
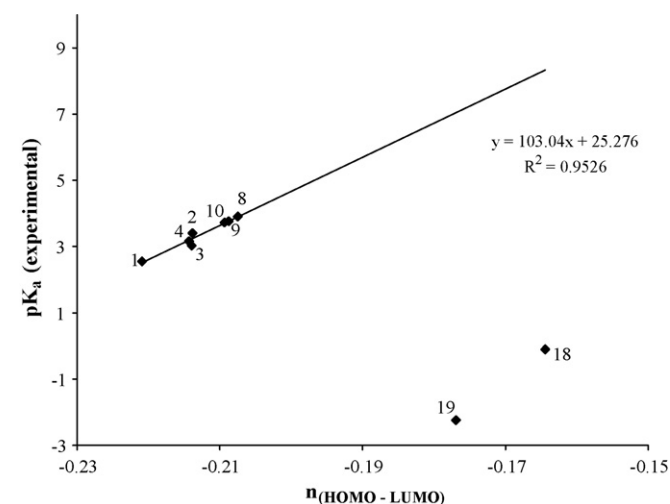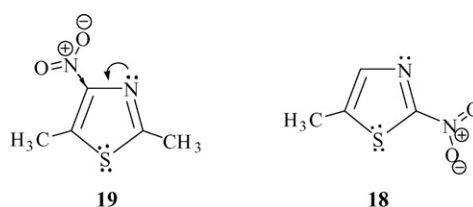
Compound :	**19**	<	**18**		
pK_a :	−2.24		−0.09		experimental
pK_a :	−2.52		−1.23		*ab inito* calculated
Compound :	**18**	<	**17**	<	**19**
pK_a :	11.69		11.99		12.54 PM3 calculated
Compund :	**19**	<	**17**	<	**18**
pK_a :	3.71		6.67		6.78 AM1 calculated

increase of basicity →

atom on it (Table 6, Fig. 1).

The nucleophilicity criteria has provided the following sequence of increase in the nucleophilic power of the molecules under study:

	19	<	**18**	<	**17**	by AM1 method
	−8.90926		−8.48979		−8.46377	
	19	<	**17**	<	**18**	by PM3 method
	−9.12074		−8.76992		−8.55930	

increasing nucleophilicity →

Fig. 3. The correlation plot for *ab initio* calculated nucleophilicities, n, and experimental acidity constant, pK_a, of studied molecules.

The PM3 results of nucleophilicity is contradicting with the basicity results but coincide with the basicity trend which were obtained by AM1 and *ab initio* methods. The experimental values indicate that the nucleophilicity of molecules **17–19** increases parallel with the basicity ([Figs. 2 and 3](#)). Both AM1 and PM3 methods indicates the lower nucleophilicity of compound **19** in which nitro group at 4C position of the nucleus is full operative and decreases the electron density on nitrogen of the thiazole ring.

Acknowledgement

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