A quantum chemical DFT/HF study on acidity constants of some benzothiazole and thiazole derivatives

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The acid dissociation (K_a) constants of some 4-and/or 6-substituted-2-aminobenzothiazole compounds have been investigated theoretically. The gas and aqueous phase geometries, thermal and solvation free energies have been calculated with full geometry optimization by using HF (6-31G(d)) and B3LYP (6-31G(d)) methods for 2-aminobenzothiazole, 2-aminothiazole derivatives and their fixed models. From the calculated acidity constants of investigated compounds, it has been detected that the protonation occurs at the the nitrogen atom of the amino group for 2-aminobenzothiazoles and at ring nitrogen atom for 2-aminothiazoles. Acceptable correlations have been observed between theoretically (HF and B3LYP) and experimental $p K_a$ values of the molecules with regression coefficients (R^2 = 0.98, 0.86) and (R^2= 0.98, 0.85) for the protonation of benzothiazole and thiazole molecules, respectively. Theoretical calculations also show that basicity of the studied compounds increase in the presence of electron donor substituents.

Keywords: 2-Aminobenzothiazole, 2-aminothiazole, $p K_a$ calculation, theoretical calculations, PCM

Determination of the acid-base properties of organic compounds benefits the chemical industry. Determination of acidity constants of organic compounds in various solvents is very important as they explain the reaction mechanisms in organic chemistry, clarify the role of substrates attaching to enzymes in biochemistry, and help to design new drugs in the pharmaceutical industry[1-14].
Benzothiazole derivatives are the members of "azoles" family and they are known for their high biological activities[15-23]. On the other hand, complex formation studies[24-26] and polymerization studies[27,28] of these compounds have also been performed.
Quantum chemical parameters are utilized to define the quantitative correlation between the physicochemical properties and chemical structures of organic compounds. Acidity constants can be obtained from the quantum chemically calculated Gibbs free energies of organic compounds. In literature, there have been many studies on the determination of acidity constants of organic compounds by semi-empirical and *ab-initio* methods in the gas and aqueous phase[29-35]. On the other hand, theoretical studies performed for 2-aminobenzothiazoles were related to tautomerism[36] and adsorption[37-40].
In this study, the acidity constant values were calculated theoretically in the gas and aqueous phase employing the *ab-initio* Hartree-Fock (HF) and density functional theory (DFT/B3LYP) methods for 4- and/or 6-substituted-2-aminobenzothiazole derivatives and their model compounds. Model forms of the studied molecules were created by replacing the mobile hydrogen atom with a methyl group, in order to eliminate proton migration.

Computational Methods

Nowadays, both microscopic and macroscopic theoretical methods are available for the estimation of solvation free energies. Therefore, in principle it is possible to determine relative or absolute acidity constants, $p K_a$ values, theoretically. Thermodynamic cycle given in **Figure 1**, explains the relation between the thermodynamic parameters of gas and solution phases.

The acidity constant, $p K_a$, can be calculated by using Equations 1-2. Equation 2 is rearranged form of Equation 1.

$$\Delta G = -RT \ln K_a \qquad (1)$$

$$p K_a = \Delta G_{(aq)}/2.303 RT \qquad (2)$$

$\Delta G_{(aq)}$ value in Equation 2 is determined from Equation 3 and $\Delta G^{\circ}_{(g)}$ value in Equation 3 is determined from Equation 4:
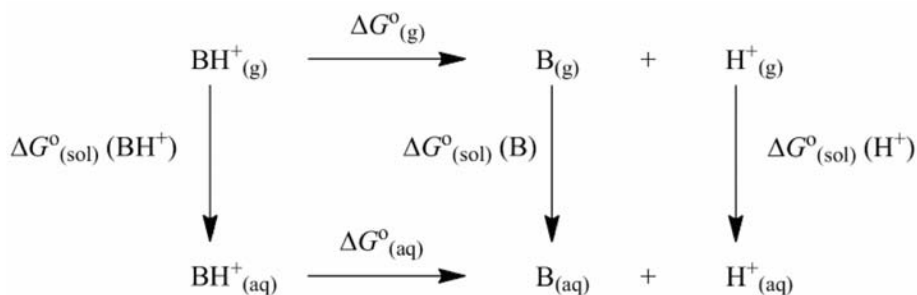
Figure 1 — Thermodynamic cycle illustrating the calculation of theoretical pK_a values

$$\Delta G°_{(aq)} = (\Delta G°_{(g)} + \Delta G°_{(sol)}(BH^+) - \Delta G°_{(sol)}(B) - \Delta G°_{(sol)}(H^+)) \tag{3}$$

$$\Delta G°_{(g)} = \Delta G°_{(g)}(BH^+) - \Delta G°_{(g)}(H^+) - \Delta G°_{(g)}(B) \tag{4}$$

Most of the values in these equations will be derived from our computations. The free energy of a proton in the gas phase $\Delta G°_{(g)}(H^+)$ is -4.40 kcal mol^{-1} and its solvation free energy $\Delta G°_{(sol)}(H^+)$ is -260 kcal mol^{-1}. These values have been used for all the pK_a calculations[41].

In the present work, DFT (B3LYP/6-31G(d)) and (HF/6-31G(d)) geometry optimizations and frequency calculations were performed *via* the Gaussian 03W program[42]. All the structures were fully optimized and characterized as true minima by the absence of imaginary frequencies. The calculation of the solvation free energies was carried out by using the B3LYP/6-31G(d) method in the aqueous phase with HF (Hartree Fock) atomic radii with PCM (Polarizable Continuum Model)[43,44]. The total energies are given in Hartree unit, using the conversion factor of 1 Hartree = 627.5095 kcal mol^{-1}. The thermodynamic parameters of 4- and/or 6-substituted 2-aminobenzothiazole derivatives were calculated by employing the *ab-initio* HF/6-31G(d) and DFT B3LYP/6-31G(d) methods.

The Hammett equation is widely used to find out the effect of a substituent on a process in equilibrium[45]. When a heteroatom of a heteroaromatic compound acts as reaction site in the case of the protonation process (**Figure 2** and Equation 5), "n" can be a positive, negative, or zero value:

$$BH^{n+} \rightleftharpoons B^{(n-1)+} + H^+ \tag{5}$$

The Hammett equation can be written as follows in Equation 6 and 7:

$$\log K / \log K_\circ = \rho\sigma \tag{6}$$

$$\log K = \rho\sigma + \log K_\circ \tag{7}$$

where the K and $K_\circ$ values are acid dissociation equilibrium constants of substituted and unsubstituted molecules, respectively. The ρ parameter is the reaction constant. It is a measure of the sensitivity of the reaction or equilibrium to the electronic substituent effect. The parameter σ is referred to the substituent constant and it consists of inductive and mesomeric effects, and they are mathematically addable (*i.e.* $\sigma_T = \sigma_{mesomeric} + \sigma_{inductive}$).

Result and Discussion

The HF and DFT/B3LYP calculated gas and solvation free energy (ΔG_g and ΔG_{sol}) values for neutral molecules and their protonated cations, are given in **Tables I** and **II**. By utilizing the thermodynamic parameters, protonation acidity constants were calculated and results given in **Figure 2** and **Tables I** and **II**.

An attempt was made to evaluate the results as follows:

Basicity

The change in solvation free energy values of the investigated compounds for both HF/6-31G(d) and B3LYP/6-31G(d) calculation methods revealed that increase of total free energies indicates amino groups protonation for benzothiazole derivatives (**Tables I** and **II**, **Figure 2a**). The same trend was observed in nucleophilicity increase of the compounds. The compound **19** was found to be the most powerful nucleophile among the studied benzothiazole compounds in aqueous phase for both HF/6-31G(d) and B3LYP/6-31G(d) calculation methods (**Table III**).

According to **Table I**, the aqueous phase acidity constants (pK_a) values of studied molecules indicated that molecule **16** has the most basicity for HF/6-31G(d) method. The presence of fluorine atom at the 6-position of molecule **16** causes a decrease in
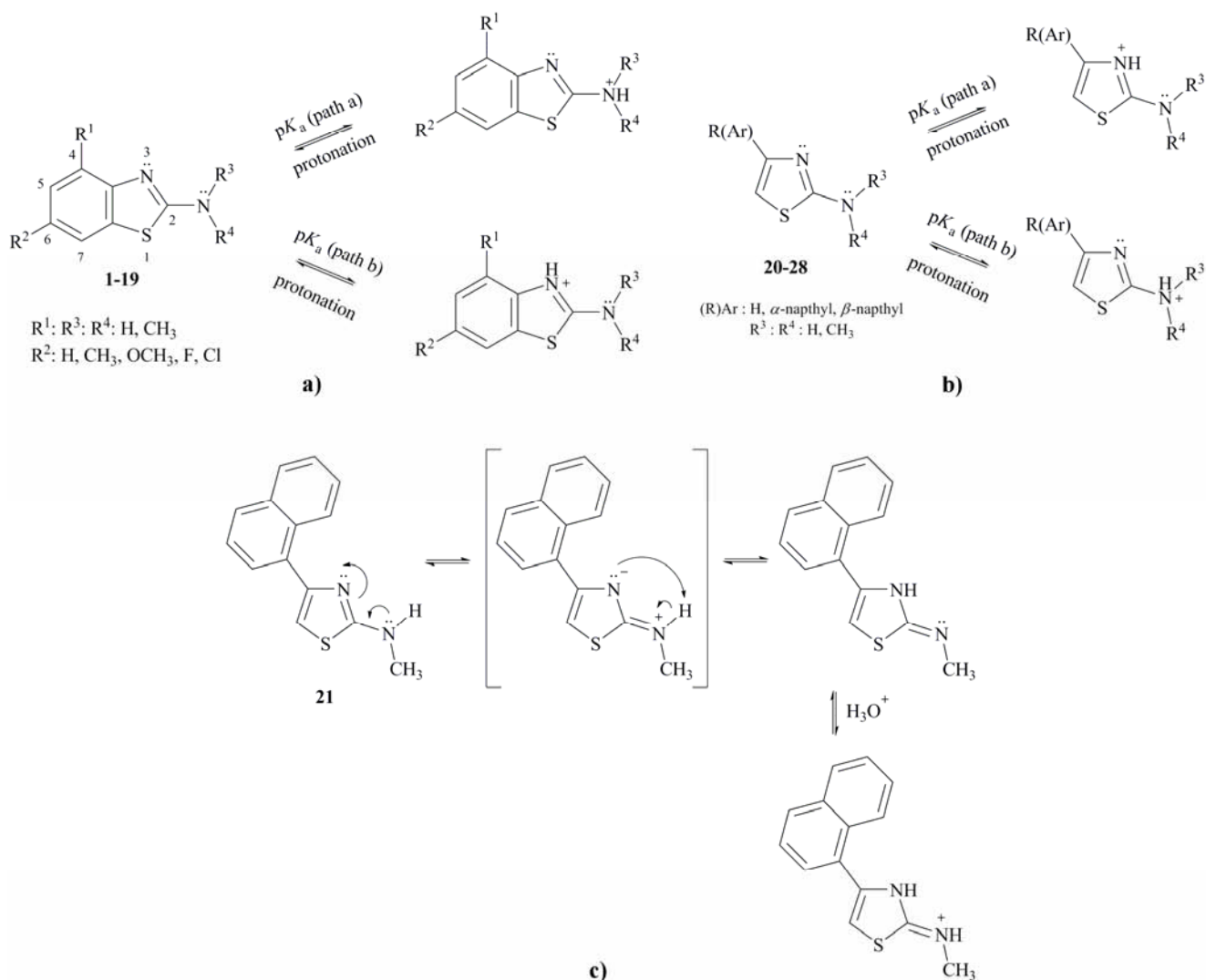
Figure 2 — Protonation pattern of studied (a) 2-aminobenzothiazole, (b) 2-aminothiazole derivatives and possible protonation pattern for molecule 21 (c)

electron density of amino group due to withdrawing of electrons inductively from the ring. On the other hand, it can be seen from the **Table II**, B3LYP/6-31G(d) method revealed that the molecule **19** has the most basicity. Due to the presence of methyl in their amino groups, it is expected that the molecules **2**, **5**, **8**, **11**, **14**, **17** and **19** to be more basic than the molecules of **1**, **4**, **7**, **10**, **13** and **16**; but methyl groups prevent their protonation because of steric hindrance. If the pK_a values given in **Tables I** and **II** are considered, it can be said that, the hydrogen substituted compounds (**1**, **4**, **7**, **10**, **13** and **16**) have more basic character than the methyl substituted (**2**, **5**, **8**, **11**, **14**, **17**) benzothiazole derivatives, for both calculation methods. Furthermore, molecules **3**, **6**, **9**, **12**, **15** and **18** have more steric hindrance due to the presence of

two methyl groups on their amino groups. Therefore, these compounds have the lowest basicity, than the one methyl substituted and unsubstituted benzothiazoles.

As can be seen from the **Table IV**, the aqueous phase calculations indicated that the Mulliken charge (q) of amino nitrogen atom is the lowest in molecule **18** and is the highest in molecule **16** for HF/6-31G(d) and B3LYP/6-31G(d) methods.

The possible protonation paths were shown in **Figure 2**. It can be clearly seen from the structure of studied compounds that there are two potential protonation centers in each molecule. From the calculated acidity constants of 2-aminobenzothiazoles, it was detected that the protonation occurs at the nitrogen atom of the amino group rather than ring

Table I — HF (6-31G(d)) calculated free energies in gas and aqueous phase ($G_{(g)}$, $G_{(aq)}$) and pK_a values for neutral and protonated forms of studied compounds at 298 K

Compd	R^1	R^2	R^3	R^4	$G_{(g)}(B)^a$	$\Delta G_{(sol)}(B)^b$	$G_{(g)}(BH^+)$	$\Delta G_{(sol)}(BH^+)$	$\Delta G°_{(aq)}{}^c$	$pK_{a(calc.)}{}^d$	$pK_{a(calc.)}{}^e$	$pK_{a1(exp.)}{}^f$	$pK_{a2(exp.)}{}^g$
1	H	H	H	H	-774.905977	-6.949668	-775.325328	-70.404683	1.25	0.92	-	-	4.51
							-775.364522	-65.164979	-8.34	-	-6.11		
2	H	H	CH_3	H	-813.914333	-11.072405	-814.360697	-84.442698	-15.70	-11.51	-	-	2.17
							-814.362788	-59.960415	-2.01	-	-1.47		
3	H	H	CH_3	CH_3	-852.906391	-7.159256	-853.321280	-54.019783	4.05	2.97	-	-	-1.75
							-853.352815	-51.536728	-0.74	-	-0.54		
4	CH_3	H	H	H	-813.924109	-11.630261	-814.320162	-59.391892	15.87	11.63	-	7.28	-0.98
							-814.371034	-61.703637	-1.05	-	-0.77		
5	CH_3	H	CH_3	H	-852.922615	-10.614951	-853.336301	-61.480871	4.81	3.52	-	5.33	-
							-853.369340	-56.647793	-15.92	-	-11.67		
6	CH_3	H	CH_3	CH_3	-891.914587	-5.643820	-892.333072	-53.859140	1.80	1.32	-	-	2.32
							-892.354980	-45.562210	3.05	-	2.23		
7	H	CH_3	H	H	-813.924504	-12.216982	-814.320313	-59.317846	16.03	11.75	-	2.28	-
							-814.353884	-50.543380	-5.04	-	-3.69		
8	H	CH_3	CH_3	H	-852.919658	-9.154109	-853.323550	-53.326385	10.95	8.03	-	-	2.59
							-853.355439	-73.337035	5.94	-	4.36		
9	H	CH_3	CH_3	CH_3	-891.913258	-5.181346	-892.324719	-48.449381	6.20	4.55	-	-	-
							-892.353974	-44.509876	-12.15	-	-8.91		
10	CH_3	CH_3	H	H	-852.933206	-11.017184	-853.331379	-58.515261	14.54	10.66	-	-	4.46
							-853.364091	-49.460926	9.02	-	6.61		
11	CH_3	CH_3	CH_3	H	-891.930551	-9.363697	-892.334261	-52.403318	11.07	8.11	-	2.36	-1.05
							-892.365953	-46.775186	-3.82	-	-2.80		
12	CH_3	CH_3	CH_3	CH_3	-930.923802	-5.178208	-931.335716	-47.799909	5.92	4.34	-	-	-
							-931.363191	-43.032091	-11.32	-	-8.30		
13	H	CH_3O	H	H	-888.762399	-13.409251	-889.160130	-60.437322	14.82	10.86	-	-	0.31
							-889.144715	-21.917652	24.49	-	17.95		
14	H	CH_3O	CH_3	H	-927.742660	-1.103789	-928.161946	-53.645787	1.29	0.95	-	-	1.83
							-928.193121	-48.407338	-3.27	-	-2.40		
15	H	CH_3O	CH_3	CH_3	-966.754005	-8.175821	-967.163575	-48.961429	7.39	5.42	-	-	-
							-967.190692	-45.851492	-9.63	-	-7.05		
16	H	F	H	H	-873.774807	-12.907870	-874.168843	-62.956773	17.14	12.56	-	7.80	-
							-874.200099	-54.078769	-2.47	-	-1.81		
17	H	F	CH_3	H	-912.772152	-11.125743	-913.172142	-56.772039	13.40	9.82	-	-	2.17
							-913.201879	-50.966949	-5.26	-	-3.85		
18	H	F	CH_3	CH_3	-951.765814	-7.164276	-952.173186	-51.617676	8.77	6.43	-	-	-
							-952.200282	-47.649306	-3.23	-	-2.37		
19	H	Cl	CH_3	CH_3	-1311.818264	-7.341861	-1312.223084	-51.827892	10.37	7.60	-	6.40	-
							-1312.251192	-48.006987	-7.27	-	-5.33		
20	α-naphthyl	H	H	H	-1004.374189	-15.456186	-1004.768769	-61.706147	16.80	12.31	-	2.58	
							-1004.803476	-50.468707	10.02	-	7.34		
21	α-naphthyl	CH_3	H	H	-1043.361695	-7.334959	-1043.803052	-46.282591	-12.56	-9.20	-	-	-
							-1043.772018	-55.552789	6.92	-	5.07		
22	α-naphthyl	CH_3	CH_3		-1082.365389	-9.727025	-1082.774088	-51.317099	7.94	5.82	-	1.00	-
							-1082.801282	-43.124335	5.87	-	4.30		
23	β-naphthyl	H	H	H	-1004.381286	-15.571648	-1004.775184	-61.743170	17.23	12.62	-	3.80	-
							-1004.755440	-18.409874	29.61	-	21.71		
24	β-naphthyl	CH_3	H	H	-1043.378957	-13.820897	-1043.778336	-55.540238	13.79	10.10	-	-	-
							-1043.808158	-47.532590	-4.93	-	-3.61		
25	β-naphthyl	CH_3	CH_3		-1082.372335	-9.764675	-1082.780511	-51.325257	8.27	6.06	-	0.51	-
							-1082.807031	38.200268	6.62	-	4.85		
26		H	H	H	-622.285700	-6.314001	-622.692768	-62.429038	8.96	6.57	-	5.39	-
							-622.726064	-55.167498	-11.93	-	-8.75		
27		H	CH_3	H	-661.284837	-5.277982	-661.695197	-55.500078	6.90	5.05	-	-	-
							-661.727176	-51.473349	-13.17	-	-9.65		
28		H	CH_3	CH_3	-700.283124	-4.284007	-700.699012	-52.122822	3.43	2.51	-	-	-
							-700.683695	-21.187858	13.04	-	9.56		

ᵃGas phase Gibbs Energy (Hartree), ᵇAqueous phase Gibbs Energy (Hartree), ᶜ Solvation Free Energy (kcal·mol⁻¹),
ᵈProtonation at the 2-amino group (path a), ᵉProtonation at the ring nitrogen (path b), ᶠ·ᵍExperimental pK_a taken from Ref. 46

Table II — DFT (B3LYP/6-31G(d))calculated free energies in gas and aqueous phase ($G_{(g)}$, $G_{(aq)}$) and pK_a values for neutral and protonated forms of studied compounds at 298 K

Compd	R^1	R^2	R^3	R^4	$G_{(g)}(B)$[a]	$\Delta G_{(sol)}(B)$[b]	$G_{(g)}(BH^+)$	$\Delta G_{(sol)}(BH^+)$	$\Delta G°_{(aq)}$[c]	$pK_{a(calc)}$[d]	$pK_{a(calc.)}$[e]	$pK_{a1(exp.)}$[f]	$pK_{a2(exp)}$[g]
1	H	H	H	H	-777.983907	-6.027856	-778.388760	-57.925402	10.35	7.59	-	-	4.51
							-778.418457	-50.851487	-8.28	-	-6.07		
2	H	H	CH$_3$	H	-817.266775	-5.131145	-817.673551	-52.497445	9.14	6.70	-	-	2.17
							-817.702843	-47.791751	5.76	-	4.22		
3	H	H	CH$_3$	CH$_3$	-856.549011	-4.513676	-856.956226	-47.698252	8.87	6.50	-	-	-1.75
							-856.984326	-44.278325	-3.76	-	-2.76		
4	CH$_3$	H	H	H	-817.277109	-5.744222	-817.682857	-56.728741	9.79	7.17	-	7.28	-0.98
							-817.712150	-49.808567	-3.59	-	-2.63		
5	CH$_3$	H	CH$_3$	H	-856.559793	-5.235312	-856.967506	-51.588811	8.56	6.27	-	5.33	-
							-856.996981	-47.128473	-9.94	-	-7.28		
6	CH$_3$	H	CH$_3$	CH$_3$	-895.842197	-4.311618	-896.250143	-46.998579	8.41	6.16	-	-	2.32
							-896.278178	-43.600615	5.82	-	4.26		
7	H	CH$_3$	H	H	-817.276915	-5.992716	-817.683162	-57.026181	6.56	4.81	-	2.28	-
							-817.711699	-49.165997	-8.43	-	-6.18		
8	H	CH$_3$	CH$_3$	H	-856.559783	-5.405367	-856.966728	-50.952516	9.04	6.62	-	-	2.59
							-856.997350	-46.900688	4.82	-	3.53		
9	H	CH$_3$	CH$_3$	CH$_3$	-895.841871	-4.471005	-896.250299	-46.671647	8.11	5.94	-	-	-
							-896.278926	-43.723607	-9.86	-	-7.22		
10	CH$_3$	CH$_3$	H	H	-856.570122	-5.717239	-856.977065	-56.017146	9.04	6.63	-	-	4.46
							-857.003377	-46.887510	7.53	-	5.52		
11	CH$_3$	CH$_3$	CH$_3$	H	-895.852739	-5.315633	-896.261522	-50.557813	7.88	5.78	-	2.36	-1.05
							-896.290263	-45.901692	-5.15	-	-3.77		
12	CH$_3$	CH$_3$	CH$_3$	CH$_3$	-935.134908	-4.249494	-935.544073	-45.483144	7.65	5.60	-	-	-
							-935.570982	-42.032469	-9.24	-	-6.77		
13	H	CH$_3$O	H	H	-892.476897	-6.972886	-892.885223	-57.154193	8.17	5.99	-	-	0.31
							-892.912016	-49.177920	6.36	-	4.66		
14	H	CH$_3$O	CH$_3$	H	-931.759281	-6.392439	-932.167746	-50.636879	8.08	5.93	-	-	1.83
							-932.197630	-47.405833	4.33	-	3.17		
15	H	CH$_3$O	CH$_3$	CH$_3$	-971.041928	-5.624995	-971.452298	-47.373202	6.89	5.05	-	-	-
							-971.479001	-43.788868	-9.87	-	-7.23		
16	H	F	H	H	-877.225417	-6.147711	-877.630688	-60.072739	10.09	7.39	-	7.80	-
							-877.657470	-52.250206	-6.72	-	-4.92		
17	H	F	CH$_3$	H	-916.507924	-5.345126	-916.913615	-53.465064	9.83	7.20	-	-	2.17
							-916.943129	-49.942226	6.30	-	4.62		
18	H	F	CH$_3$	CH$_3$	-955.790292	-4.376251	-956.196897	-49.003472	9.25	6.78	-	-	-
							-956.224573	-46.308946	-8.12	-	-5.95		
19	H	Cl	CH$_3$	CH$_3$	-1316.156672	-4.678711	-1316.561184	-49.636629	10.56	7.74	-	6.40	-
							-1316.590267	-47.365045	-7.68	-	-5.63		
20	α-naphthyl	H	H	-1008.954569	-6.665406	-1009.362351	-58.391642	8.51	6.24	-	2.58	-
							-1009.390603	-48.519662	-9.22	-	-6.75		
21	α-naphthyl	CH$_3$	H	-1048.238318	-6.319021	-1048.674877	-45.616176	-9.54	-7.00	-	-	-
							-1048.646819	-27.626106	8.06	-	5.91		
22	α-naphthyl	CH$_3$	CH$_3$	-1087.519967	-5.251627	-1087.930979	-49.139641	6.49	4.75	-	1.00	-
							-1087.956813	-42.460430	-9.73	-	-7.13		
23	β-naphthyl	H	H	-1008.961277	-6.578182	-1009.369418	-58.721084	8.29	6.07	-	3.80	-
							-1009.395950	-48.950761	-8.36	-	-6.13		
24	β-naphthyl	CH$_3$	H	-1048.244298	-6.116963	-1048.653396	-52.803669	7.69	5.63	-	-	-
							-1048.679804	-45.808821	-8.88	-	-6.51		
25	β-naphthyl	CH$_3$	CH$_3$	-1087.526361	-5.129263	-1087.936880	-48.756233	6.80	4.98	-	0.51	-
							-1087.961258	-42.599110	-8.50	-	-6.23		
26	H		H	H	-624.370007	-5.490081	-624.779507	-60.806298	7.43	5.45	-	5.39	-
							-624.807628	-54.354245	-10.21	-	-7.48		
27	H		CH$_3$	H	-663.653033	-4.647963	-664.062502	-53.888006	7.45	5.46	-	-	-
							-664.091779	-50.874705	-10.92	-	-8.00		
28	H		CH$_3$	CH$_3$	-702.935410	-3.716739	-703.348496	-51.179675	5.18	3.80	-	-	-
							-703.373273	-47.791751	-10.36	-	-7.60		

[a]Gas phase Gibbs Energy (Hartree), [b]Aqueous phase Gibbs Energy (Hartree), [c]Solvation Free Energy (kcal·mol^{-1}),
[d]Protonation at the 2-amino group (path a), [e]Protonation at the ring nitrogen (path b), [f,g]Experimental pK_a taken from Ref. 46

Table III — The aqueous phase HF/6-31G(d) and B3LYP/6-31G(d) calculated nucleophilicity, *n* (eV), values of investigated molecules

Compd	2-NH$_2$		Compd	2-*N*-methyl		Compd	2-*N,N*-dimethyl	
	HF	B3BYLP		HF	B3BYLP		HF	B3BYLP
1	-3.37	-3.38	**2**	-3.24	-3.24	**3**	-3.19	-3.15
4	-3.43	-3.44	**5**	-3.39	-3.34	**6**	-3.26	-3.20
7	-3.43	-3.41	**8**	-3.29	-3.31	**9**	-3.15	-3.17
10	-3.52	-3.48	**11**	-3.42	-3.37	**12**	-3.29	-3.23
13	-3.44	-3.39	**14**	-3.26	-3.24	**15**	-3.21	-3.10
16	-3.37	-3.32	**17**	-3.30	-3.25	**18**	-3.18	-3.12
-	-	-	**-**	-	-	**19**	-3.16	-3.10
20	-2.22	-2.07	**21**	-2.08	-1.96	**22**	-1.96	-1.80
23	-2.19	-2.04	**24**	-2.05	-1.90	**25**	-1.94	-1.77
26	-4.44	-4.21	**27**	-4.33	-4.17	**28**	-4.15	-4.00

$n=E_{HOMO}-E_{LUMO}$[47]

Table IV — The aqueous phase HF/6-31G(d) and B3LYP/6-31G(d) calculated Mulliken charges (*q*) of nitrogen atom investigated molecules

| Compd	q 2-amino		Compd	q 2-*N*-methylamino		Compd	q 2-*N,N*-dimethylamino	
	amino nitrogen	ring nitrogen		amino Nitrogen	ring nitrogen		amino nitrogen	ring nitrogen
				HF/6-31G(d)				
1	-0.928	-0.651	**2**	-0.814	-0.681	**3**	-0.653	-0.679
4	-0.949	-0.668	**5**	-0.787	-0.672	**6**	-0.653	-0.663
7	-0.924	-0.653	**8**	-0.804	-0.684	**9**	-0.668	-0.689
10	-0.924	-0.646	**11**	-0.794	-0.670	**12**	-0.653	-0.662
13	-0.924	-0.649	**14**	-0.805	-0.681	**15**	-0.653	-0.678
16	-0.948	-0.670	**17**	-0.796	-0.675	**18**	-0.645	-0.676
-	-	-	**-**	-	-	**19**	-0.654	-0.679
				B3LYP/6-31G				
1	-0.763	-0.545	**2**	-0.610	-0.567	**3**	-0.429	-0.580
4	-0.764	-0.543	**5**	-0.603	-0.570	**6**	-0.430	-0.579
7	-0.764	-0.545	**8**	-0.602	-0.571	**9**	-0.430	-0.581
10	-0.765	-0.544	**11**	-0.603	-0.570	**12**	-0.431	-0.581
13	-0.764	-0.545	**14**	-0.603	-0.571	**15**	-0.431	-0.582
16	-0.777	-0.559	**17**	-0.602	-0.570	**18**	-0.429	-0.581
-	-	-	**-**	-	-	**19**	-0.428	-0.579

nitrogen atom (**Table I** and **II**). The theoretical acidity constants values obtained by protonation of the amino nitrogen are consistent with the experimental acidity constant values (**Figure 3**).

The protonation of the studied thiazole molecules (except molecule **21**) occurs at the nitrogen atom of the ring (**Figure 2b**). Methyl group of molecule **27** and two methyl groups on the nitrogen atom of amino group in molecule **28** prevent easy protonation of the nitrogen atoms from 3-position because of steric hindrance. Therefore, they are less basic than the molecule **26**, which has no substituent on the nitrogen atom of amino group. The α-naphthyl and β-naphthyl groups are substituted in molecules **20** and **23**, respectively. While the molecule **20** is protonated from the thiazole ring, molecule **21** is protonated from amino/imino group (**Figure 2c**).

The molecule **23** is naphthyl group substituted at β-position and the molecule **20** includes the naphthyl group its α-position. Calculated *p*K$_a$ of the compound **23** shows the compound **23** does not have full conjugation compared to the molecule **20**. Thus, the electron density of the nitrogen atom on the thiazole ring for β-naphthyl substituted compound increases. This leads to an increase in basicity of the molecule **23**. Two methyl group substituted molecules (**22** and **25**) prevent protonation of thiazole ring nitrogen, due to the steric hindrance.

Experimental *p*K$_a$ values of the studied molecules were plotted *versus* theoretically calculated *p*K$_a$ values and these graphs were given in **Figures 3**. Acceptable correlations were observed between theoretically (HF and B3LYP) and experimental *p*K$_a$ values of the molecules with regression coefficients
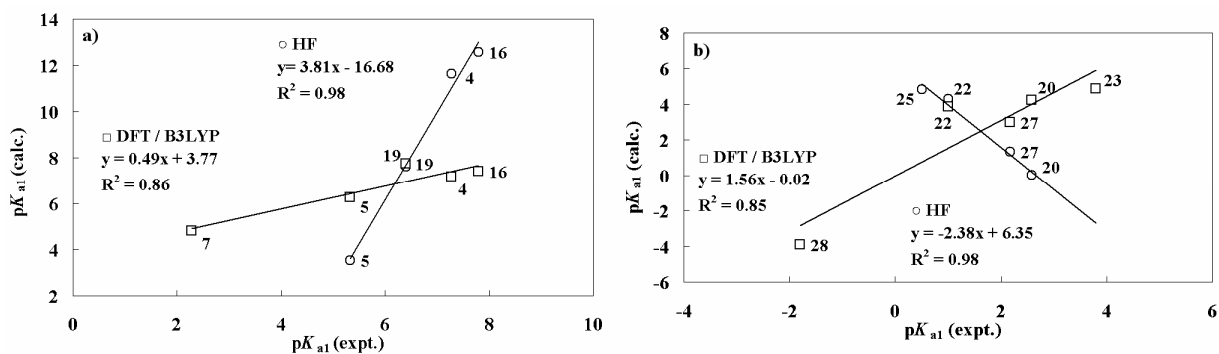
Figure 3 — Plot of first acidity constant values ($pK_{a1(calc.)}$) calculated by (○)HF and (□)DFT/B3LYP methods in aqueous phase *versus* the experimental acidity constants ($pK_{a(expt.)}$) for studied (a) 2-aminobenzothiazole, (b) 2-aminothiazole derivatives
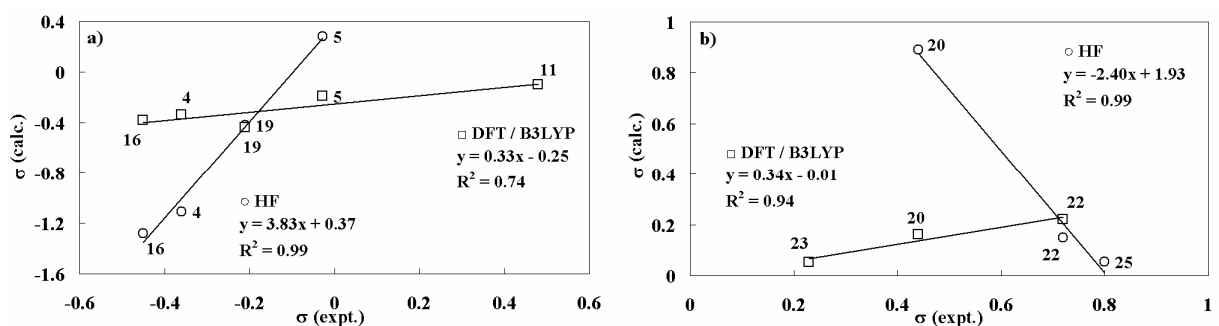
Figure 4 — The plot of (○)HF and (□)DFT/B3LYP aqueous phase calculated substituent constant σ $_{(calc.)}$ values, and experimental substituent constant, σ $_{(expt.)}$, for studied (a) 2-aminobenzothiazole, (b) 2-aminothiazole derivatives

(R^2 = 0.98, 0.86) and (R^2= 0.98, 0.85) for the protonation of benzothiazole and thiazole molecules, respectively. Calculated pK_a values in **Table I** and **II** supports that protonation of aminothiazoles occurs at the ring nitrogen atoms (**Figure 3**). As it can be seen from the obtained regression coefficients, the HF method gave better results as compared to the DFT method.

It is now possible to discuss that the position and the size of substituent effects on the basicities of studied molecules can be evaluated from the calculated σ values (**Table V**).

Substituent effects

The application of the Hammett equation to heterocyclic systems was described in section 2. The Hammett equation can be used to elucidate the reaction pathways and to ascertain the effect of substituent. In the present work, the substituent constant (σ) values for some benzothiazoles and thiazoles can be calculated by using Equation 7.

When the experimental σ values are taken into consideration, it is observed that molecules **4**, **5**, **16**, **19** have negative charges and the methyl groups on

Table V — The aqueous phase HF/6-31G(d) and DFT/B3LYP/6-31G(d) calculated substituent constants, σ values[a] for the investigated molecules

Compd	σ $_{(expt)}$	σ $_{(calc.)}$ B3LYP	σ $_{(calc.)}$ HF
4	-0.360	-0.340	-1.110
5	-0.027	-0.190	0.280
6	-	-0.170	-
7	-	-0.300	-1.140
8	-	-0.250	-0.490
9	-	-0.130	0.100
10	-	-0.250	-0.950
11	0.480	-0.100	-0.500
12	-	-0.074	0.140
13	-	-0.140	-0.980
14	-	-0.130	0.730
15	-	0.020	-0.043
16	-0.450	-0.380	-1.280
17	-	-0.350	-0.800
18	-	-0.270	-0.220
19	-0.210	-0.440	-0.420
20	0.440	0.160	0.890
21	-	0.200	0.580
22	0.720	0.220	0.150
23	0.230	0.052	-
24	-	0.120	-0.380
25	0.800	0.071	0.055

[a]Calculated using pK_a=-5.77σ + 5.17 equation. This equation was taken from Ref. 48

4-and/or 6-positions have electron donating effect. It was also observed that, connection of the α-naphthyl and β-naphthyl groups to the thiazole ring cause electron withdrawing effect due to the σ values of molecules **20**, **22**, **23** and **25** being positive. It was seen that the *ab-initio* and DFT methods give concordant results with the experimentally determined σ values (except for molecule **5** calculated by HF method).

A graph of the experimental σ values plotted against the calculated σ values can be seen in **Figure 4**. Acceptable correlations were observed between theoretical (HF and DFT/B3LYP) and experimental substituent constants, with the regression coefficients of R^2 = 0.99, 0.99, 0.74, 0.94 for benzothiazole and thiazole derivatives, respectively.

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