Quantum chemical studies on tautomerism, isomerism and deprotonation of some 5(6)-substituted benzimidazole-2-thiones

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Abstract

Acidity constants, pK_a values, tautomeric and isomeric equilibrium constants, K_T and $K_{eq.}$ values, of some 5(6)-substituted benzimidazole-2-thiones and related fixed models, in which the possibility of proton migration is eliminated by replacing the mobile proton with methyl group, were calculated using semi-empirically computed physical and thermodynamic parameters. Full geometry optimization was carried out using semi-empirical AM1, PM3 and PM5 methods. The theoretically calculated acidity constants were compared with the experimental values and a reasonable correlation was observed.

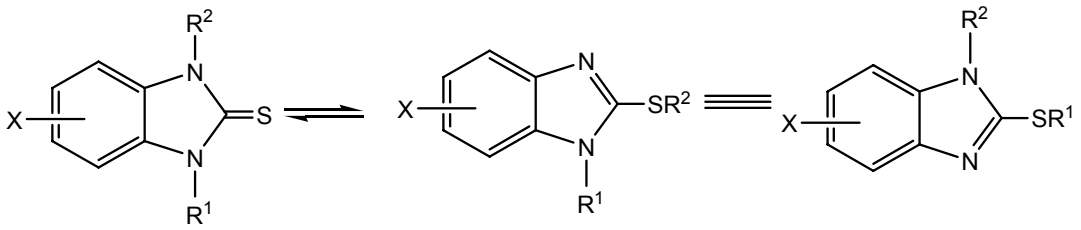
Keywords: Benzimidazole-2-thione; relative stability; acidity constant; proton affinity; tautomerism

Introduction

Due to the antagonist effect of benzimidazole derivatives towards purine compounds, the investigation of benzimidazole-2-thiones has been a matter of interest for a long time.[1,2] Wolley had observed that benzimidazole inhibits the growth of several kinds of yeasts and bacteria. He also proved that the inhibition could be completely eliminated by the addition of aminopurines.[3] Klotz and Mellody demonstrated that yeast nucleic acid reversed the inhibitory effect of benzimidazole on the growth of the bacterium, *Eschericha coli*.[4] Some benzimidazole and imidazole derivatives were investigated earlier both by experimental and theoretical method by our research group.[5-13]

An understanding of the tautomeric and isomeric equilibrium of heterocycles, especially thiol-thione, helps in understanding many areas of chemistry and biochemistry, such as rationalization of physical and chemical properties and quantitative reactivity of heterocycles,[14-20] the variation of intrinsic stabilities, solvent effects,[21-23] as a test of aromaticity,[24-26] and enzymatic catalysis and receptor interactions.[27] Therefore, we believe that 5(6)-substituted

benzimidazole-2-thione derivatives deserve a detailed theoretical study and four derivatives of 5(6)-substituted 2-mecapto benzimidazole along with their half model molecules, in which the migration of one proton was eliminated by replacing one of the mobile hydrogen atoms with a methyl group, were investigated in the present work. Since the protonation of these four compounds had been studied already[5,6] we have concentrated now on deprotonation. The nomenclature and formulation of the compounds studied are depicted in Table 1.



thione form thiol forms

parent molecules : R^1=R^2=H

model molecules: R^1=CH_3 R^2=H or R^1=H R^2=CH_3

Computational methods

Theoretical calculations were carried out at the restricted Hartree-Fock level (RHF) using AM1, PM3 and PM5 semi-empirical SCF-MO methods in the MOPAC 2002 program,[28] implemented on an Intel Pentium IV PC computer, using a relative permittivity of 78.4 corresponding to water. The solvent effect was included in the geometry optimizations following the 'COnductor-like Screening Model' (COSMO)[20] implemented in MOPAC 2002. All the structures were optimized to a gradient norm of <0.1 in the gas phase and 0.1-1.0 in the aqueous phase as commonly accepted, using the eigenvector method (EF). The absolute entropies of all structures were calculated from a complete vibration analysis. Enthalpies were corrected to free energies using calculated entropies. Initial estimates of the geometry of all the structures were obtained by a molecular mechanics program (CS ChemOffice Pro for Windows),[30] followed by full optimization of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, the semi-empirical AM1, PM3 and PM5 quantum chemical methods in the MOPAC 2002 programs.

Table 1. Nomenclature of molecules studied

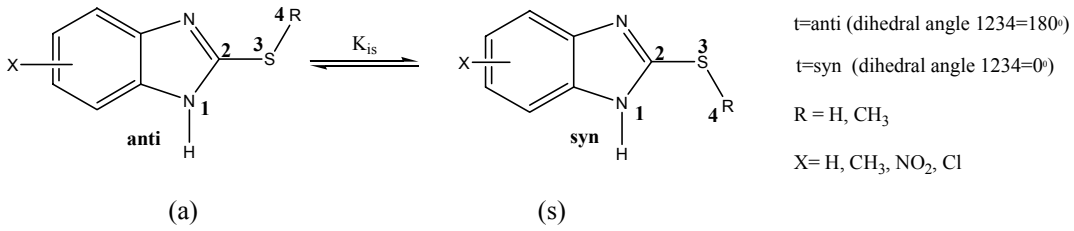
Compound Number	Form	name	X	R^1	R^2
I	**1b**	Benzimidazole-2-thione	H	H	H
1bm (model of **1b**)		1-Methylbenzimidazole-2-thione	H	CH_3	H
II	**2c**	2-Mercaptobenzimidazole	H	H	H
2cam(model of **2c**)		1-Methyl-2-mercaptobenzimidazole	H	CH_3	H
2cbm (model of **2c**)		2-Methylthiobenzimidazole	H	H	CH_3
III	**1c**	5(6)-Methylbenzimidazole-2-thione	CH_3	H	H
1cam (model of **1c**)		5(6)-Methyl-1-methylbenzimidazole-2-thione	CH_3	CH_3	H
1cbm (model of **1c**)		5(6)-Methyl-3-methylbenzimidazole-2-thione	CH_3	H	CH_3
III	**2c**	5(6)- Methyl-2-mercaptobenzimidazole	CH_3	H	H
2cam (model of **2c**)		5(6)-Methyl-2-methylthiobenzimidazole	CH_3	H	CH_3
2cbm (model of **2c**)		5(6)-Methyl-1-methylbenzimidazole-2-thione	CH_3	CH_3	H
III	**3c**	5(6)-Methyl-2-mercaptobenzimidazole	CH_3	H	H
3cam (model of **3c**)		5(6)-Methyl-2-methylthiobenzimidazole	CH_3	CH_3	H
3cbm (model of **3c**)		5(6)-Methyl-3-methylbenzimidazole-2-thione	CH_3	H	CH_3
IV	**1c**	5 (6)-Nitrobenzimidazole-2-thione	NO_2	H	H
1cam (model of **1c**)		5(6)-Nitro-1-methylbenzimidazole-2-thione	NO_2	CH_3	H
1cbm (model of **1c**)		5(6)-Nitro-3-methylbenzimidazole-2-thione	NO_2	H	CH_3
IV	**2c**	5 (6)- Nitro-2-mercaptobenzimidazole	NO_2	H	H
2cam (model of **2c**)		5(6)-Nitro-2-methylthiobenzimidazole	NO_2	H	CH_3
2cbm (model of **2c**)		5(6)-Nitro-1-methylbenzimidazole-2-thione	NO_2	CH_3	H
IV	**3c**	5(6)-Nitro-2-mercaptobenzimidazole	NO_2	H	H
3cam (model of **3c**)		5(6)-Nitro-2-methylthiobenzimidazole	NO_2	CH_3	H
3cbm (model of **3c**)		5(6)-Nitro-3-methylbenzimidazole-2-thione	NO_2	H	CH_3
V	**1c**	5(6)-Chlorobenzimidazole-2-thionee	Cl	H	H
1cam (model of **1c**)		5(6)-Chloro-1-methylbenzimidazole-2-thione	Cl	CH_3	H
1cbm (model of **1c**)		5(6)-Chloro-3-methylbenzimidazole-2-thione	Cl	H	CH_3
V	**2c**	5 (6)- Chloro-2-mercaptobenzimidazole	Cl	H	H
2cam (model of **2c**)		5(6)-Chloro-2-methyolthiobenzimidazole	Cl	H	CH_3
2cbm (model of **2c**)		5(6)-Chloro-1-methylbenzimidazole-2-thione	Cl	CH_3	H
V	**3c**	5(6)-Chloro-2-mercaptobenzimidazole	Cl	H	H
3cam (model of **3c**)		5(6)-Chloro-2-methylthiobenzimidazole	Cl	CH_3	H
3cbm (model of **3c**)		5(6)-Chloro-3-methylbenzimidazole-2-thione	Cl	H	CH_3

Result and Discussion

The nomenclature and computed physical and thermodynamic parameters for the studied compounds are depicted in Tables 2-8. We have attempted to evaluate the results obtained as follows.

Relative Stability, Tautomerism and Stereoisomerism

Among the other possible conformers of mercapto bezimidazoles, with the exception of molecule **I** in which R^1=R^2=H and X=H, the *syn* and *anti* forms are identical, only the *anti* (i.e. dihedral angle 1234=180º) and *syn* (dihedral angle 1234=0º) conformers (Scheme 1) were considered in the present work.

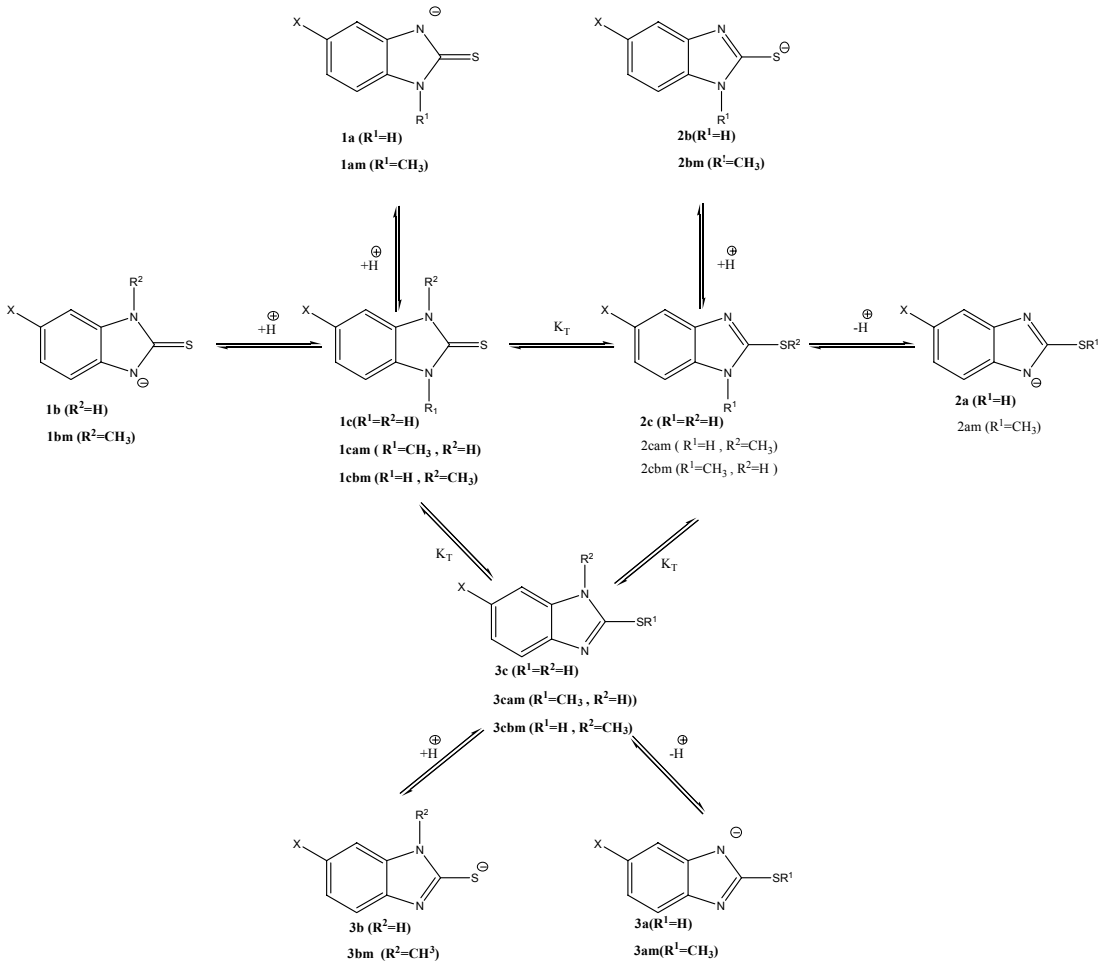


Scheme 1. The *anti* and *syn* form for studied molecules.

Using the aqueous phase, AM1, PM3 and PM5 calculated physical and thermodynamic parameters (Table 2) semi-empirical isomerisation and tautomerisation equilibrium constants for 5(6)-substituted benzimidazole-2-thione derivatives along with their fixed models are given Table 3 and Table 4 respectively.

The gas-phase semi-empirical calculated relative stability data for tautomers and isomers along with their fixed models are given Table 5.

As can be seen from Table 3 and Scheme 2, when a potential mercapto group is located at C-2 of benzimidazole and its two half models (i.e. one of the mobile hydrogen atoms replaced by a methyl group) the tautomeric equilibrium constants indicate that thione forms I **1c, I 1cam** and **I 1cbm** are predominant over thiol forms **I 2c**, **I 2cam** and **I 2cbm** with all methods.



Scheme 2. The deprotonation process and tautomeric forms for 5(6)-substituted benzimidazole-2-thione derivatives (X = H, CH_3, NO_2, Cl).

Table 2. Aqueous phase AM1, PM3 and PM5 calculated thermodynamic data of the studied molecules (ε : 78.4)

Compound	ΔH_f (kcal/mol)	ΔS (cal/mol K)	ΔG_f (kcal/mol)[a]	Compound	ΔH_f (kcal/mol)	ΔS (cal/mol K)	ΔG_f (kcal/mol)[a]	Compound	ΔH_f (kcal/mol)	ΔS (cal/mol K)	ΔG_f (kcal/mol)[a]
AM1											
					X= H						
1a	-36.26	85.85	-61.84	**2c(a)**	61.49	88.30	35.18	**2cam(s)**	66.71	94.33	38.60
1c	53.37	85.69	27.83	**1am**	-29.59	91.04	-56.72	**2cam(a)**	68.08	94.30	39.98
2a(s)	-23.13	87.75	-49.28	**1cam**	59.80	97.92	30.62	**2cbm(s)**	55.94	97.68	26.83
2a(a)	-23.14	87.32	-49.16	**2am(s)**	-27.15	96.57	-55.93	**2cbm(a)**	56.41	98.07	27.19
2b	-36.26	85.84	-61.84	**2am(a)**	-27.15	96.35	-55.86				

2c(s)	60.86	89.16	34.29	**2bm**	-29.59	94.34	-57.70				
					X= 5(6)-CH_3						
1a	-43.81	90.72	-70.84	**3c(s)**	53.82	96.50	25.06	**2cbm(s)**	59.13	104.53	27.98
1b	-43.89	96.14	-72.54	**3c(a)**	53.16	93.98	25.15	**2cbm(a)**	60.51	108.67	28.13
1c	45.72	91.89	18.34	**1am**	-37.14	110.61	-70.10	**3am(s)**	-34.69	107.03	-66.58
2a(s)	-30.71	92.65	-58.32	**1bm**	-37.20	95.89	-65.78	**3am(a)**	-34.70	110.05	-67.49
2a(a)	-30.69	97.89	-59.86	**1cam**	52.19	100.54	22.23	**3bm**	-37.20	95.98	-65.80
2b	-43.81	96.44	-72.55	**1cbm**	52.20	96.93	23.31	**3cam(s)**	48.75	107.41	16.74
2c(s)	53.24	98.69	23.83	**2am(s)**	-34.69	106.73	-66.50	**3cam(a)**	48.29	109.64	15.62
2c(a)	53.92	93.36	26.10	**2am(a)**	-34.70	100.32	-64.60	**3cbm(s)**	60.43	104.20	29.38
3a(s)	-30.71	94.94	-59.00	**2bm**	-37.15	98.93	-66.63	**3cbm(a)**	59.17	97.78	30.03
3a(a)	-30.69	97.89	-59.86	**2cam(s)**	48.37	107.05	16.47				
3b	-43.89	94.55	-72.07	**2cam(a)**	48.83	107.96	16.66				
					X= 5(6)-NO_2						
1a	-39.61	100.44	-69.54	**3c(s)**	60.01	103.78	29.08	**2cbm(s)**	65.03	113.32	31.26
1b	-39.67	100.54	-69.63	**3c(a)**	59.32	103.52	28.47	**2cbm(a)**	67.24	106.06	35.63
1c	53.27	102.09	22.85	**1am**	-32.99	105.72	-64.49	**3am(s)**	-34.01	106.87	-65.86
2a(s)	-29.77	101.06	-59.89	**1bm**	-32.97	105.81	-64.50	**3am(a)**	-33.94	110.97	-67.01
2a(a)	-29.70	101.61	-59.98	**1cam**	59.90	107.31	27.92	**3bm**	-32.99	106.09	-64.60
2b	-39.61	100.44	-69.54	**1cbm**	59.89	107.14	27.96	**3cam(s)**	54.79	111.57	21.54
2c(s)	58.83	103.45	28.00	**2am(s)**	-34.01	106.47	-65.74	**3cam(a)**	54.22	112.50	20.70
2c(a)	59.52	103.94	28.55	**2am(a)**	-33.94	110.28	-66.80	**3cbm(s)**	67.68	105.65	36.20
3a(s)	-29.77	101.06	-59.89	**2bm**	-32.99	108.29	-65.26	**3cbm(a)**	65.56	108.58	33.20
3a(a)	-29.70	101.61	-59.98	**2cam(s)**	53.75	111.76	20.45				
3b	-39.68	100.43	-69.61	**2cam(a)**	54.41	112.26	20.96				
					X= 5(6)-Cl						
1a	-43.73	92.62	-71.33	**3c(s)**	54.68	96.52	25.92	**2cbm(s)**	59.84	105.62	28.37
1b	-43.66	92.67	-71.28	**3c(a)**	54.00	95.89	25.42	**2cbm(a)**	61.34	102.96	30.66
1c	47.13	93.95	19.13	**1am**	-37.07	97.99	-66.27	**3am(s)**	-35.77	103.36	-66.57
2a(s)	-31.65	94.37	-59.77	**1bm**	-37.02	97.86	-66.18	**3am(a)**	-35.76	103.61	-66.64
2a(a)	-31.65	94.42	-59.79	**1cam**	53.64	99.11	24.11	**3bm**	-37.02	97.85	-66.18
2b	-43.73	92.62	-71.33	**1cbm**	53.62	99.14	24.08	**3cam(s)**	49.55	104.44	18.43
2c(s)	53.89	95.60	25.40	**2am(s)**	-35.77	103.25	-66.54	**3cam(a)**	49.04	104.82	17.80
2c(a)	54.59	95.04	26.27	**2am(a)**	-35.76	103.64	-66.64	**3cbm(s)**	61.36	105.98	29.78
3a(s)	-31.65	94.37	-59.77	**2bm**	-37.07	100.06	-66.89	**3cbm(a)**	59.93	106.42	28.22
3a(a)	-31.65	94.50	-59.81	**2cam(s)**	48.93	104.14	17.90				
3b	-43.67	92.66	-71.28	**2cam(a)**	49.46	104.39	18.35				

PM3

X=H

1a	-57.72	86.75	-83.57	**2c(a)**	43.35	86.91	17.45	**2cam(s)**	42.91	95.12	14.56
1c	37.04	85.99	11.41	**1am**	-57.09	92.33	-84.60	**2cam(a)**	44.32	93.81	16.36
2a(s)	-47.12	88.27	-73.42	**1cam**	37.99	92.81	10.33	**2cbm(s)**	38.01	100.21	8.15
2a(a)	-47.10	88.34	-73.43	**2am(s)**	-50.64	92.84	-78.31	**2cbm(a)**	38.92	100.02	9.11
2b	-57.72	86.75	-83.57	**2am(a)**	-50.62	100.09	-80.45				
2c(s)	42.00	90.03	15.17	**2bm**	-57.09	96.35	-85.80				

X= 5(6)-CH_3

1a	-67.11	91.44	-94.36	**3c(s)**	33.72	99.23	4.15	**2cbm(s)**	33.48	104.25	2.41
1b	-67.14	95.81	-95.69	**3c(a)**	32.56	99.90	2.79	**2cbm(a)**	34.88	108.66	2.50
1c	27.52	97.01	-1.39	**1am**	-66.48	101.78	-96.81	**3am(s)**	-59.94	102.58	-90.51
2a(s)	-56.42	98.60	-85.80	**1bm**	-66.49	106.83	-98.33	**3am(a)**	-59.92	101.82	-90.26
2a(a)	-56.41	97.90	-85.58	**1cam**	28.49	103.96	-2.49	**3bm**	-66.49	107.62	-98.56
2b	-67.11	95.80	-95.66	**1cbm**	28.48	106.48	-3.25	**3cam(s)**	29.47	108.68	-2.92
2c(s)	32.57	99.40	2.95	**2am(s)**	-59.94	102.39	-90.45	**3cam(a)**	28.59	103.34	-2.21
2c(a)	33.94	97.95	4.75	**2am(a)**	-59.92	99.83	-89.67	**3cbm(s)**	34.88	106.88	3.03
3a(s)	-56.42	99.00	-85.92	**2bm**	-66.48	99.78	-96.21	**3cbm(a)**	33.47	112.03	0.09
3a(a)	-56.41	97.90	-85.58	**2cam(s)**	28.57	109.61	-4.09				
3b	-67.14	94.95	-95.44	**2cam(a)**	29.50	103.30	-1.28				

X= 5(6)-NO_2

1a	-76.99	102.38	-107.50	**3c(s)**	24.61	100.22	-5.26	**2cbm(s)**	24.52	114.62	-9.64
1b	-77.19	105.13	-108.52	**3c(a)**	23.41	99.37	-6.20	**2cbm(a)**	25.90	105.70	-5.60
1c	20.27	96.89	-8.60	**1am**	-76.26	108.77	-108.67	**3am(s)**	-72.53	105.97	-104.11
2a(s)	-68.80	102.56	-99.36	**1bm**	-76.38	112.66	-109.95	**3am(a)**	-72.58	106.42	-104.29
2a(a)	-68.79	102.00	-99.19	**1cam**	21.44	102.55	-9.12	**3bm**	-76.38	111.66	-109.65
2b	-76.99	102.35	-107.49	**1cbm**	21.47	106.08	-10.14	**3cam(s)**	20.52	108.52	-11.82
2c(s)	23.41	99.59	-6.27	**2am(s)**	-72.52	106.43	-104.24	**3cam(a)**	19.37	102.93	-11.30
2c(a)	24.54	100.56	-5.43	**2am(a)**	-72.61	106.53	-104.36	**3cbm(s)**	26.26	107.17	-5.68
3a(s)	-68.80	102.55	-99.36	**2bm**	-76.26	114.14	-110.27	**3cbm(a)**	24.68	108.90	-7.77
3a(a)	-68.79	102.00	-99.19	**2cam(s)**	19.29	102.57	-11.28				
3b	-77.16	96.49	-105.91	**2cam(a)**	20.38	109.45	-12.24				

X= 5(6)-Cl

1a	-64.85	93.63	-92.75	**3c(s)**	36.41	97.80	7.27	**2cbm(s)**	36.14	102.86	5.49
1b	-64.78	94.00	-92.79	**3c(a)**	35.24	97.08	6.31	**2cbm(a)**	37.55	100.90	7.48
1c	30.85	94.73	2.62	**1am**	-64.20	99.49	-93.85	**3am(s)**	-58.58	100.3	-88.47
2a(s)	-55.01	95.75	-83.54	**1bm**	-64.13	105.82	-95.66	**3am(a)**	-58.52	99.49	-88.17

2a(a)	-54.98	95.58	-83.46	**1cam**	31.88	107.53	-0.16	**3bm**	-64.13	105.66	-95.62
2b	-64.85	93.63	-92.75	**1cbm**	31.86	104.06	0.85	**3cam(s)**	32.16	106.01	0.57
2c(s)	35.14	97.03	6.23	**2am(s)**	-58.58	100.35	-88.48	**3cam(a)**	31.21	100.78	1.18
2c(a)	36.32	97.21	7.35	**2am(a)**	-58.52	105.58	-89.98	**3cbm(s)**	37.65	104.41	6.54
3a(s)	-55.01	95.75	-83.54	**2bm**	-64.20	99.47	-93.84	**3cbm(a)**	36.2	102.69	5.60
3a(a)	-54.98	95.59	-83.47	**2cam(s)**	31.13	100.93	1.05				
3b	-64.78	94.00	-92.79	**2cam(a)**	32.09	107.33	0.11				

PM5

X=H

1a	-72.75	87.62	-98.86	**2c(a)**	43.54	87.63	17.43	**2cam(s)**	48.48	93.39	20.65
1c	26.26	87.59	0.16	**1am**	-66.64	99.56	-96.31	**2cam(a)**	50.20	93.05	22.47
2a(s)	-50.05	88.44	-76.41	**1cam**	32.22	98.01	3.01	**2cbm(s)**	40.95	94.58	12.77
2a(a)	-50.06	88.45	-76.42	**2am(s)**	-50.70	92.77	-78.35	**2cbm(a)**	41.13	94.30	13.03
2b	-72.75	87.62	-98.86	**2am(a)**	-50.70	98.05	-79.92				
2c(s)	42.77	92.14	15.31	**2bm**	-66.64	97.96	-95.83				

X= 5 (6)-CH_3

1a	-80.79	92.62	-108.39	**3c(s)**	35.37	100.18	5.52	**2cbm(s)**	40.40	106.57	8.64
1b	-80.83	97.23	-109.80	**3c(a)**	34.63	97.43	5.60	**2cbm(a)**	41.50	108.37	9.21
1c	18.06	98.28	-11.23	**1am**	-74.69	107.22	-106.64	**3am(s)**	-58.68	104.96	-89.96
2a(s)	-58.05	99.32	-87.65	**1bm**	-74.73	101.05	-104.84	**3am(a)**	-58.70	108.20	-90.94
2a(a)	-58.04	99.35	-87.65	**1cam**	24.09	108.88	-8.36	**3bm**	-74.72	100.35	-104.62
2b	-80.79	97.33	-109.79	**1cbm**	24.10	107.69	-7.99	**3cam(s)**	33.04	103.16	2.30
2c(s)	34.65	101.53	4.39	**2am(s)**	-58.64	110.60	-91.60	**3cam(a)**	32.87	105.12	1.54
2c(a)	35.46	99.79	5.72	**2am(a)**	-58.70	109.21	-91.24	**3cbm(s)**	41.30	102.50	10.76
3a(s)	-58.04	99.24	-87.61	**2bm**	-74.69	107.29	-106.66	**3cbm(a)**	40.38	105.76	8.86
3a(a)	-58.04	99.35	-87.65	**2cam(s)**	32.89	103.50	2.05				
3b	-80.83	96.11	-109.47	**2cam(a)**	33.06	102.52	2.51				

X= 5(6)-NO_2

1a	-83.55	96.95	-112.44	**3c(s)**	34.08	100.36	4.17	**2cbm(s)**	38.97	105.69	7.47
1b	-83.49	97.06	-112.41	**3c(a)**	33.45	100.58	3.48	**2cbm(a)**	40.81	106.55	9.06
1c	19.57	98.29	-9.72	**1am**	-77.50	106.07	-109.11	**3am(s)**	-65.72	111.66	-98.99
2a(s)	-64.44	105.20	-95.79	**1bm**	-77.48	106.43	-109.20	**3am(a)**	-65.79	110.59	-98.75
2a(a)	-64.47	105.10	-95.79	**1cam**	25.60	108.19	-6.64	**3bm**	-77.48	106.05	-109.08
2b	-83.56	96.95	-112.45	**1cbm**	25.38	117.52	-9.64	**3cam(s)**	31.61	110.88	-1.43
2c(s)	33.15	100.87	3.09	**2am(s)**	-65.72	111.21	-98.86	**3cam(a)**	31.31	101.48	1.07
2c(a)	33.84	103.14	3.10	**2am(a)**	-65.78	108.40	-98.08	**3cbm(s)**	40.73	110.87	7.69
3a(s)	-64.44	105.23	-95.80	**2bm**	-77.50	105.81	-109.03	**3cbm(a)**	39.25	108.87	6.81

3a(a)	-64.47	105.10	-95.79	**2cam(s)**	30.97	103.36	0.17				
3b	-83.52	103.07	-114.23	**2cam(a)**	31.51	103.42	0.69				
					X= 5(6)-Cl						
1a	-80.58	94.76	-108.82	**3c(s)**	36.11	100.63	6.12	**2cbm(s)**	40.98	103.64	10.10
1b	-80.45	94.78	-108.69	**3c(a)**	35.36	99.76	5.63	**2cbm(a)**	42.10	103.82	11.16
1c	19.70	95.97	-8.90	**1am**	-74.51	105.51	-105.95	**3am(s)**	-59.75	107.29	-91.72
2a(s)	-58.95	95.77	-87.49	**1bm**	-74.42	99.92	-104.20	**3am(a)**	-59.74	103.59	-90.61
2a(a)	-58.95	95.78	-87.49	**1cam**	25.72	104.84	-5.52	**3bm**	-74.42	99.91	-104.19
2b	-80.58	94.76	-108.82	**1cbm**	25.71	105.29	-5.67	**3cam(s)**	33.73	101.18	3.58
2c(s)	35.25	97.94	6.06	**2am(s)**	-59.75	99.01	-89.25	**3cam(a)**	33.48	103.35	2.68
2c(a)	36.04	96.75	7.21	**2am(a)**	-59.74	103.60	-90.61	**3cbm(s)**	42.23	103.88	11.27
3a(s)	-58.95	95.77	-87.49	**2bm**	-74.51	104.80	-105.74	**3cbm(a)**	41.11	103.37	10.31
3a(a)	-58.95	95.75	-87.48	**2cam(s)**	33.33	101.42	3.11				
3b	-80.45	94.78	-108.69	**2cam(a)**	33.59	101.00	3.49				

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

H_2O - **AM1:** ΔH_f (kcal/mol) = -64.39, ΔS (cal/molK) = 45.10, ΔG_f (kcal/mol) = -77.83
PM3: ΔH_f (kcal/mol) = -58.02, ΔS (cal/molK) = 45.00, ΔG_f (kcal/mol) = -71.43
PM5: ΔH_f (kcal/mol) = -59.47, ΔS (cal/molK) = 44.99, ΔG_f (kcal/mol) = -72.88

H_3O^+ - **AM1:** ΔH_f (kcal/mol) = 50.61, ΔS (cal/molK) = 46.15, ΔG_f (kcal/mol)= 36.83
PM3: ΔH_f (kcal/mol) = 67.33, ΔS (cal/molK) = 46.01, ΔG_f (kcal/mol) = 53.62
PM5: ΔH_f (kcal/mol) = 46.51, ΔS (cal/molK) = 45.88, ΔG_f (kcal/mol) = 32.84

Table 3. Aqueous phase PM3 , PM5 and AM1 calculated tautomeric equilibrium constants K_T of studied molecules

Substituent (X)	Annular Tautomer	Ring-chain tautomer	δΔG[a] (kcal/mol)	K_T[b]	pK_T[c]	δΔG[a] (kcal/mol)	K_T[b]	pK_T[c]	δΔG[a] (kcal/mol)	K_T[b]	pK_T[c]
				PM3			**PM5**			**AM1**	
	Main										
H	***tautomers***										
	…	**1c-2c(s)**	3.76	$1.75\ 10^{-3}$	2.758	15.15	$7.73\ 10^{-12}$	11.112	6.46	1.8210^{-5}	4.738
	…	**1c-2c(a)**	6.04	$3.72\ 10^{-5}$	4.430	17.27	$2.15\ 10^{-13}$	12.667	7.35	4.0610^{-6}	5.391
	Fixed models										
	…	**1cam-2cam(s)**	…	$6.03\ 10^{-7}$	6.220	…	$9.55\ 10^{-7}$	6.020	…	$4.37\ 10^{-4}$	3.360

		1cam-									
	…	**2cam(a)**	…	$1.14\ 10^{-4}$	3.942	…	$2.12\ 10^{-5}$	4.674	…	$7.11\ 10^{-4}$	3.148
		1cam-						-			
	…	**2cbm(s)**	…	$9.59\ 10^{3}$	-3.982	…	$3.84\ 10^{12}$	12.584	…	$3.74\ 10^{6}$	-6.573
		1cam-						-			
	…	**2cbm(a)**	…	$2.00\ 10^{5}$	-5.302	…	$8.30\ 10^{13}$	13.919	…	$3.84\ 10^{7}$	-7.584
	Main										
5(6)-CH_3	***tautomers***										
	…	**1c-2c(s)**	4.34	$6.56\ 10^{4}$	3.183	15.62	$3.50\ 10^{-12}$	11.456	5.49	$9.41\ 10^{-5}$	4.027
	…	**1c-2c(a)**	6.14	$3.13\ 10^{5}$	4.504	16.95	$3.68\ 10^{-13}$	12.434	7.76	$2.04\ 10^{-6}$	5.691
	…	**1c-3c(s)**	5.54	$8.64\ 10^{5}$	4.063	16.75	$5.18\ 10^{-13}$	12.285	6.72	$1.18\ 10^{-5}$	4.929
	…	**1c-3c(a)**	4.18	$8.60\ 10^{-4}$	3.066	16.83	$4.56\ 10^{-13}$	12.341	6.81	$1.01\ 10^{-5}$	4.998
	2c(s)-3c(s)	**…**	1.20	$1.32\ 10^{-1}$	0.880	1.13	$1.48\ 10^{-1}$	0.829	1.23	$1.25\ 10^{-1}$	0.902
	2c(a)-3c(a)	**…**	-1.96	$2.74\ 10^{1}$	-1.438	-0.13	1.24	-0.093	-0.94	4.93	-0.693
	Fixed models										
		1cam-						-			
	…	**2cbm(s)**	…	$1.45\ 10^{3}$	-3.160	…	$3.02\ 10^{12}$	12.480	…	$4.68\ 10^{1}$	-1.670
		1cam-						-			
	…	**2cmb(a)**	…	$1.67\ 10^{3}$	-3.222	…	$7.83\ 10^{12}$	12.894	…	$6.01\ 10^{1}$	-1.779
		1cam-									
	…	**3cam(s)**	…	$1.16\ 10^{5}$	4.934	…	$3.79\ 10^{-5}$	4.421	…	$2.49\ 10^{-7}$	6.603
		1cam-									
	…	**3cam(a)**	…	$2.55\ 10^{-5}$	4.593	…	$5.61\ 10^{-5}$	4.251	…	$1.74\ 10^{-7}$	6.760
	2cbm(s)-										
	3cbm(s)	**…**	…	$1.50\ 10^{2}$	-2.175	…	1.14	-0.056	…	2.61	-0.417
	2cbm(a)-										
	3cbm(a)	**…**	…	$8.91\ 10^{-1}$	0.050	…	$1.79\ 10^{-2}$	1.746	…	6.15	-0.789
		1cbm-						-			
	…	**3cbm(s)**	…	$6.00\ 10^{4}$	-4.778	…	$3.86\ 10^{13}$	13.587	…	$2.92\ 10^{4}$	-4.466
		1cbm-						-			
	…	**3cbm(a)**	…	$4.16\ 10^{2}$	-2.619	…	$1.58\ 10^{12}$	12.200	…	$8.81\ 10^{4}$	-4.945
		1cbm-									
	…	**2cam(s)**	…	$4.06\ 10^{-7}$	6.391	…	$4.46\ 10^{-3}$	2.351	…	$3.22\ 10^{-5}$	4.492
		1cbm-									
	…	**2cam(a)**	…	$1.24\ 10^{-5}$	4.905	…	$5.35\ 10^{-3}$	2.272	…	$1.79\ 10^{-6}$	5.747
	2cam(s)-										
	3cam(s)	**…**	…	8.04	-0.905	…	$9.57\ 10^{-2}$	1.019	…	1.85	-0.266
	2cam(a)-										
	3cam(a)	**…**	…	$5.74\ 10^{-1}$	0.241	…	$1.18\ 10^{-1}$	0.928	…	$2.31\ 10^{1}$	-1.363

	Main										
5(6)-NO_2	***tautomers***										
	…	**1c-2c(s)**	2.33	$1.95\ 10^{-2}$	1.709	12.81	$4.02\ 10^{-10}$	9.395	5.15	$1.67\ 10^{-4}$	3.777
	…	**1c-2c(a)**	3.17	$4.71\ 10^{-3}$	2.327	12.82	$3.93\ 10^{-10}$	9.406	5.70	$6.64\ 10^{-5}$	4.178
	…	**1c-3c(s)**	3.34	$3.55\ 10^{-3}$	2.450	13.89	$6.49\ 10^{-11}$	10.188	6.23	$2.70\ 10^{-5}$	4.569
	…	**1c-3c(a)**	2.40	$1.74\ 10^{-2}$	1.759	13.20	$2.09\ 10^{-10}$	9.679	5.62	$7.54\ 10^{-5}$	4.123
	2c(s)-3c(s)	**…**	1.01	$1.82\ 10^{-1}$	0.741	1.08	$1.61\ 10^{-1}$	0.792	1.08	$1.61\ 10^{-1}$	0.792
	2c(a)-3c(a)	**…**	-0.78	3.70	-0.569	0.37	$5.33\ 10^{-1}$	0.273	-0.07	1.13	-0.055
	Fixed models										
		1cam-						-			
	…	**2cbm(s)**	…	6.17	-0.790	…	$1.95\ 10^{10}$	10.290	…	$1.02\ 10^{3}$	-3.010
		1cam-						-			
	…	**2cmb(a)**	…	$5.70\ 10^{3}$	-3.756	…	$2.85\ 10^{11}$	11.455	…	$1.65\ 10^{6}$	-6.217
		1cam-									
	…	**3cam(s)**	…	$4.72\ 10^{-6}$	5.326	…	$2.52\ 10^{-4}$	3.598	…	$2.09\ 10^{-4}$	3.679
		1cam-									
	…	**3cam(a)**	…	$1.54\ 10^{-5}$	4.813	…	$1.13\ 10^{-2}$	1.946	…	$3.51\text{-}10^{4}$	3.455
	2cbm(s)-										
	3cbm(s)	**…**	…	$2.83\ 10^{2}$	-2.452	…	1.58	-0.200	…	$1.38\ 10^{3}$	-3.139
	2cbm(a)-										
	3cbm(a)	**…**	…	$8.95\ 10^{-3}$	2.048	…	$2.44\ 10^{-2}$	1.613	…	$5.46\ 10^{-3}$	2.263
		1cbm-						-			
	…	**3cbm(s)**	…	$1.14\ 10^{3}$	-3.056	…	$4.24\ 10^{12}$	12.627	…	$1.30\ 10^{6}$	-6.114
		1cbm-						-			
	…	**3cbm(a)**	…	$3.30\ 10^{1}$	-1.519	…	$9.51\ 10^{11}$	11.978	…	$8.30\ 10^{3}$	-3.919
		1cbm-									
	…	**2cam(s)**	…	$9.46\ 10^{-6}$	5.024	…	$4.11\ 10^{-1}$	0.386	…	$2.48\ 10^{-5}$	4.605
		1cbm-									
	…	**2cam(a)**	…	$2.29\ 10^{-6}$	5.640	…	$2.67\ 10^{-1}$	0.573	…	$3.56\ 10^{-4}$	3.449
	2cam(s)-										
	3cam(s)	**…**	…	$3.23\ 10^{-1}$	0.491	…	$8.39\ 10^{-2}$	1.076	…	7.80	-0.892
	2cam(a)-										
	3cam(a)	**…**	…	4.35	-0.638	…	5.79	-0.763	…	$9.10\ 10^{-1}$	0.041
	Main										
5(6)-Cl	***tautomers***										
	…	**1c-2c(s)**	3.61	$2.25\ 10^{-3}$	2.648	14.96	$1.07\ 10^{-11}$	10.972	6.27	2.5210^{-5}	4.599
	…	**1c-2c(a)**	4.73	$3.39\ 10^{-4}$	3.470	16.11	$1.53\ 10^{-12}$	11.815	7.14	$5.82\ 10^{-6}$	5.235
	…	**1c-3c(s)**	4.65	$3.89\ 10^{-4}$	3.411	15.02	$9.63\ 10^{-12}$	11.016	6.79	$1.05\ 10^{-5}$	4.980
	…	**1c-3c(a)**	3.69	$1.97\ 10^{-3}$	2.707	14.53	$2.20\ 10^{-11}$	10.658	6.29	$2.42\ 10^{-5}$	4.617

2c(s)-3c(s)	**…**	1.04	$1.73\ 10^{-1}$	0.763	0.06	$9.04\ 10^{-1}$	0.044	0.52	$4.16\ 10^{-1}$	0.381
2c(a)-3c(a)	**…**	-1.04	5.80	-0.764	-1.58	$1.43\ 10^{1}$	-1.157	-0.84	4.15	-0.619
Fixed models										
	1cam-						-			
…	**2cbm(s)**	…	$1.38\ 10^{4}$	-4.140	…	$2.00\ 10^{11}$	11.300	…	$3.80\ 10^{3}$	-3.580
	1cam-						-			
…	**2cmb(a)**	…	$4.00\ 10^{5}$	-5.602	…	$1.20\ 10^{12}$	12.079	…	$1.81\ 10^{5}$	-5.258
	1cam-									
…	**3cam(s)**	…	$3.92\ 10^{-4}$	3.407	…	$1.73\ 10^{-4}$	3.761	…	$1.14\ 10^{-4}$	3.944
	1cam-									
…	**3cam(a)**	…	$6.59\ 10^{-4}$	3.181	…	$5.82\ 10^{-6}$	5.235	…	$4.43\ 10^{-5}$	4.354
2cbm(s)-										
3cbm(s)	**…**	…	$1.17\ 10^{2}$	-2.068	…	$5.32\ 10^{-1}$	0.274	…	3.26	-0.513
2cbm(a)-										
3cbm(a)	**…**	…	$8.32\ 10^{-1}$	0.080	…	$1.73\ 10^{-2}$	1.762	…	$4.90\ 10^{-3}$	2.310
	1cbm-						-			
…	**3cbm(s)**	…	$1.36\ 10^{4}$	-4.134	…	$2.63\ 10^{12}$	12.420	…	$1.51\ 10^{4}$	-4.179
	1cbm-						-			
…	**3cbm(a)**	…	$2.80\ 10^{3}$	-3.447	…	$5.13\ 10^{11}$	11.710	…	$1.08\ 10^{3}$	-3.034
	1cbm-									
…	**2cam(s)**	…	$7.64\ 10^{-6}$	5.117	…	$3.00\ 10^{-5}$	4.523	…	$5.36\ 10^{-5}$	4.271
	1cbm-									
…	**2cam(a)**	…	$1.94\ 10^{-5}$	4.712	…	$5.69\ 10^{-4}$	3.245	…	$1.38\ 10^{-4}$	3.859
2cam(s)-										
3cam(s)	**…**	…	$4.31\ 10^{-1}$	0.366	…	$1.43\ 10^{2}$	-2.155	…	2.59	-0.413
2cam(a)-										
3cam(a)	**…**	…	$2.85\ 10^{-1}$	0.545	…	$2.54\ 10^{-1}$	0.596	…	$3.90\ 10^{-1}$	0.409

[a] $\delta\Delta G = \Delta G_{(product)} - \Delta G_{(reactant)}$

[b] $K_T = e^{-(\delta\Delta G/RT)}$ (for Main tautomers). $K_T = 10^{-pK_T}$ (for Fixed models).

[c] $pK_T = -\log K_T$ (for Main tautomer) $pK_T = pK_{a(product)} - pK_{a(reactant)}$ Charton's equaton [29]. The minus sign indicate a shift to right side of equilbrium (for Fixed models).

Table 4. The aqueous phase PM3 ,PM5 and AM1 calculated some isomeric equilibrium constants K_{is}, of studied molecules

Substituent (X)	İsomers	δΔG[a] (kcal/mol)	K_{is}[b]	pK_{is}[c]	δΔG[a] (kcal/mol)	K_{is}[b]	pK_{is}[c]	δΔG[a] (kcal/mol)	K_{is}[b]	pK_{is}[c]
			PM3			**PM5**			**AM1**	
H	***Main isomers***									
	2c(s)-2c(a)	2.28	$2.09\ 10^{-2}$	1.680	2.12	$2.74\ 10^{-2}$	1.562	0.89	$2.21\ 10^{-1}$	0.656
	Fixed models									
	2cam(s)-2cam(a)		$2.09\ 10^{1}$	-1.320		$2.19\ 10^{1}$	-1.340	…	$1.02\ 10^{1}$	-1.010
	2cbm(s)-2cbm(a)		$1.91\ 10^{2}$	-2.280		$2.19\ 10^{1}$	-1.340	…	1.62	-0.210
5(6)-CH_3	***Main isomers***									
	2c(s)-2c(a)	1.80	$4.72\ 10^{-2}$	1.326	1.33	$1.05\ 10^{-1}$	0.980	2.27	$2.13\ 10^{-2}$	1.673
	3c(s)-3c(a)	-1.36	$1.00\ 10^{1}$	-1.002	0.08	$8.73\ 10^{-1}$	0.059	0.09	$8.58\ 10^{-1}$	0.066
	Fixed models									
	2cam(s)-2cam(a)		$3.02\ 10^{1}$	-1.480		1.17	-0.070	…	$5.50\ 10^{-2}$	1.260
	2cbm(s)-2cbm(a)		1.17	-0.070		2.57	-0.410	…	1.29	-0.110
	3cam(s)-3cam(a)		2.19	-0.340		1.48	-0.170	…	$7.08\ 10^{-1}$	0.150
	3cbm(s)-3cbm(a)		$6.92\ 10^{-3}$	2.160		$4.17\ 10^{-2}$	1.380	…	2.95	-0.470
5(6)-NO_2	***Main isomers***									
	2c(s)-2c(a)	0.84	$2.40\ 10^{-1}$	0.619	0.01	$9.83\ 10^{-1}$	0.007	0.55	$3.93\ 10^{-1}$	0.405
	3c(s)-3c(a)	-0.94	4.93	-0.693	-0.69	3.22	-0.508	-0.61	2.81	-0.449
	Fixed models									
	2cam(s)-2cam(a)		$2.40\ 10^{-1}$	0.620		$6.61\ 10^{-1}$	0.180	…	$1.41\ 10^{1}$	-1.150
	2cbm(s)-2cbm(a)		$9.12\ 10^{2}$	-2.960		$1.45\ 10^{1}$	-1.160	…	$1.62\ 10^{3}$	-3.210
	3cam(s)-3cam(a)	3.24	-0.510		$4.47\ 10^{1}$	-1.650		…	1.66	-0.220
	3cbm(s)-3cbm(a)	$2.88\ 10^{-2}$	1.540		$2.24\ 10^{-1}$	0.650		…	$6.31\ 10^{-3}$	2.200
	Main isomers									
5(6)-Cl										
	2c(s)-2c(a)	1.12	$1.50\ 10^{-1}$	0.825	1.15	$1.42\ 10^{-1}$	0.847	0.87	$2.29\ 10^{-1}$	0.641
	3c(s)-3c(a)	-0.96	5.10	-0.707	-0.49	2.30	-0.361	-0.50	2.34	-0.368
	Fixed models									
	2cam(s)-2cam(a)		2.51	-0.400		$1.91\ 10^{1}$	-1.280	…	2.57	-0.410
	2cbm(s)-2cbm(a)		$2.88\ 10^{1}$	-1.460		6.03	-0.780	…	$4.79\ 10^{1}$	-1.680

3cam(s)-3cam(a)	1.70	-0.230	$3.39\ 10^{-2}$	1.470	…	$3.89\ 10^{-1}$	0.410
3cbm(s)-3cbm(a)	$2.04\ 10^{-1}$	0.690	$1.95\ 10^{-1}$	0.710	…	$7.24\ 10^{-2}$	1.140

[a] $\delta\Delta G = \Delta G_{(product)} - \Delta G_{(reactant)}$

[b] $K_{is} = e^{-(\delta\Delta G/RT)}$ (for main isomers). $K_T = 10^{-pK_i}s$ (for half models).

[c] $pK_{is} = -\log K_s$ (for main isomers) $pK_{is} = pK_{a(product)} - pK_{a(reactant)}$ Charton's equation [29]. The minus sign indicate a shift to right side of equilibrium (for Fixed models).

Table 5. The gas phase PM3, PM5 and AM1calculated relative stabilities for tautomers, RS, of studied molecules

			RS[a] (kcal/mol)		
Substiuent (X)	**Annular Tautomer**	**Ring-chain tautomer**	**PM3**	**PM5**	**AM1**
H	***Main tautomers***				
	…	**1c-2c(s)**	2.87	-10.97	-3.65
	…	**1c-2c(a)**	2.87	-14.80	-3.65
	Fixed models				
	…	**1cam-2cam(s)**	6.57	-4.15	6.52
	…	**1cam-2cam(a)**	6.57	-7.41	3.68
	…	**1cam-2cbm(s)**	2.53	-11.19	-3.64
	…	**1cam-2cbm(a)**	-1.71	-15.66	-8.08
5(6)-CH_3	***Main tautomers***				
	…	**1c-2c(s)**	2.76	-11.16	-3.74
	…	**1c-2c(a)**	2.76	-15.00	-3.74
	…	**1c-3c(s)**	-1.40	-14.84	-3.63
	…	**1c-3c(a)**	2.82	-11.02	-3.63
	2c(s)-3c(s)	**…**	-4.16	-3.68	0.11
	2c(a)-3c(a)	**…**	0.06	3.98	0.11
	Fixed				
	…	**1cam-2cbm(s)**	-12.21	-11.34	-3.74
	…	**1cam-2cmb(a)**	-16.45	-15.85	-8.17
	…	**1cam-3cam(s)**	-12.23	-7.47	3.70
	…	**1cam-3cam(a)**	-8.11	-4.22	6.52
	2cbm(s)-3cbm(s)	**…**	-4.16	-4.36	-4.31
	2cbm(a)-3cbm(a)	**…**	4.29	4.63	4.54
	…	**1cbm-3cbm(s)**	-1.74	-15.69	-8.04
	…	**1cbm-3cbm(a)**	2.47	-11.21	-3.62
	…	**1cbm-2cam(s)**	6.46	-4.33	6.43

	…	**1cbm-2cam(a)**	2.33	-7.60	3.59
	2cam(s)-3cam(s)	**…**	-4.06	-3.13	-2.72
	2cam(a)-3cam(a)	**…**	4.19	3.39	2.94
5(6)-NO_2	***Main tautomers***				
	…	**1c-2c(s)**	4.86	-8.62	-2.02
	…	**1c-2c(a)**	0.29	-12.50	-5.53
	…	**1c-3c(s)**	0.08	-8.84	-5.71
	…	**1c-3c(a)**	4.63	-8.86	-2.30
	2c(s)-3c(s)	**…**	-4.78	-0.22	-3.69
	2c(a)-3c(a)	**…**	4.34	3.64	3.23
	Fixed models				
	…	**1cam-2cbm(s)**	4.55	-8.79	-1.98
	…	**1cam-2cmba**	0.19	-13.39	-6.60
	…	**1cam-3cam(s)**	4.21	-1.85	5.23
	…	**1cam-3cam(a)**	8.46	-1.87	8.09
	2cbm(s)-3cbm(s)	**…**	-4.59	0.01	-4.63
	2cbm(a)-3cbm(a)	**…**	4.20	4.56	4.44
	…	**1cbm-3cbm(s)**	-0.12	-8.93	-6.69
	…	**1cbm-3cbm(a)**	4.31	-8.98	-2.24
	…	**1cbm-2cam(s)**	8.63	-1.78	8.27
	…	**1cbm-2cam(a)**	4.32	-5.19	5.24
	2cam(s)-3cam(s)	**…**	-4.50	-0.22	-3.12
	2cam(a)-3cam(a)	**…**	4.06	3.17	2.77
5(6)-Cl	***Main tautomers***				
	…	**1c-2c(s)**	3.30	-10.28	-3.20
	…	**1c-2c(a)**	3.30	-14.16	-6.64
	…	**1c-3c(s)**	-0.91	-13.96	-6.48
	…	**1c-3c(a)**	3.40	-10.15	-3.11
	2c(s)-3c(s)	**…**	-4.21	-3.68	-3.28
	2c(a)-3c(a)	**…**	0.10	4.01	3.53
	Fixed models				
	…	**1cam-2cbm(s)**	2.97	-10.46	-3.19
Table 5 cont.					
	…	**1cam-2cmba**	-1.33	-15.02	-7.68
	…	**1cam-3cam(s)**	3.00	-6.53	4.28
	…	**1cam-3cam(a)**	7.14	-3.29	7.11
	2cbm(s)-3cbm(s)	**…**	-4.13	-4.33	-4.32
	2cbm(a)-3cbm(a)	**…**	4.41	4.72	4.60

…	**1cbm-3cbm(s)**	-1.18	-14.82	-7.52
…	**1cbm-3cbm(a)**	3.06	-10.33	-3.09
…	**1cbm-2cam(s)**	7.03	-3.43	7.02
…	**1cbm-2cam(a)**	2.83	-6.75	4.12
2cam(s)-3cam(s)	**…**	-4.05	-3.13	-2.75
2cam(a)-3cam(a)	**…**	4.29	3.43	2.98

[a] $RS = \Delta H_{f(reactant)} - \Delta H_{f(product)}$

For 5(6)-substituted benzimidazole derivatives (i.e. molecules II-IV) the tautomeric equilibrium constants indicate that the thione form **1c** is predominant over the thiol forms **2c** and **3c** with all methods. For the model compounds 5(6)-methylbenzimidazole III and 5(6)-chlorobenzimidazole V derivatives the tautomeric equilibrium constants indicate the predominance of thiol forms **2cam and 2cbm** over the thione forms **1cam** and **1cbm** with all methods. For the model compounds of 5(6)-nitro benzimidazole IV, the tautomeric equilibrium constants indicate that thiol form **2cam** and **2cbm** is predominant over the thione form **1cam** and **1cbm** with AM1, PM3 and PM5 methods.

When a potential mercapto group is located at C-2 for benzimidazole, the relative stability data indicate that the thione form I **1b** predominates over the thiol form I **2c** AM1 and PM5 calculations, whereas PM3 data indicate the reverse. PM5 calculation for the model compounds suggest that the predominance of thione form **1bm** over the thiol forms **2cam** and **2cbm**. However the AM1 and PM3 methods suggest the reverse. For 5(6)-substituted benzimidazole derivatives (substituents; CH_3, NO_2 and Cl) the relative stability data of AM1 and PM5 methods indicate that thione form **1c** is predominant over the thiol forms **2c** and **3c**. However, the PM3 method indicates the reverse. For the model compounds of 5(6)-methylbenzimidazole the relative stability data indicate the predominance of thione forms **1cam** and **1cbm** over the thiol forms **2cam** and **2cbm** and **3cam** and **3cbm** with AM1, PM3 and PM5 methods. Similarly for the model compounds of 5(6)-nitrobenzimidazole and 5(6)-chlorobenzimidazole the relative stability data indicate that the3 thione forms **1cam** and **1cbm** are predominant over the thiol forms **2cam** and **2cbm** and **3cam** and **3cbm** with AM1 and PM5 methods. Whereas with PM3 methods the reverse is true. In the literature, the thione structure was shown to be the stable form of benzimidazole-2-thione derivatives.[31-33]

Acidity

The protonation reaction of a given base can be shown as follows;

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

$$\delta\Delta G_{(BH+)} = [\,\Delta G_{(B)} + \Delta G_{(AH+)}\,] - [\,\Delta G_{(BH+)} + \Delta G_{(A)}] \quad (2)$$

in which n can have a negative, positive or zero value. The acidity of a given base, B, for the protonation reaction can be calculated using Eq.2. in which B and BH^+ are neutral and protonated species of base B, and A and AH^+ are H_2O and H_3O^+ respectively. The computed

thermodynamic data were used in predicting the acidity constants, pK_a values, of various species, using Eq. 3, in which the $\delta\Delta G_{(BH+)}$ is the standard free energy change for the protonation reaction (Eq. 1) (Table 6).

$$pK_{a(BH+)} = \delta\Delta G_{(BH+)}/2.303RT \quad (3)$$

Possible deprotonation patterns for the studied molecules are shown in Schemes 1 and 2. Aqueous phase calculated acidity constant pK_a values are given in Table 3. From these data the deprotonation pK_a values of 5(6)-methylbenzimidazole-2-thiol was found to be the highest (i.e. 13.41 by the AM1method) and the deprotonation pK_a values of 5(6)-nitrobenzimidazole-2-thiol was found to be the lowest (i.e. 11.71 by the AM1 method).

Experimental pK_a : CH_3- > H- > Cl- > NO_2-

11.65 >10.24 >9.06>7.98

AM1 method pK_a : CH_3- > H- > Cl- > NO_2-

13.41 >12.94 >12.51>11.71

decreasing acidity ⟶

We have attempted to correlate the experimental pK_a values[34,35] with calculated pK_a values and we observed that the best fit occurred with the AM1 method (Fig. 1).

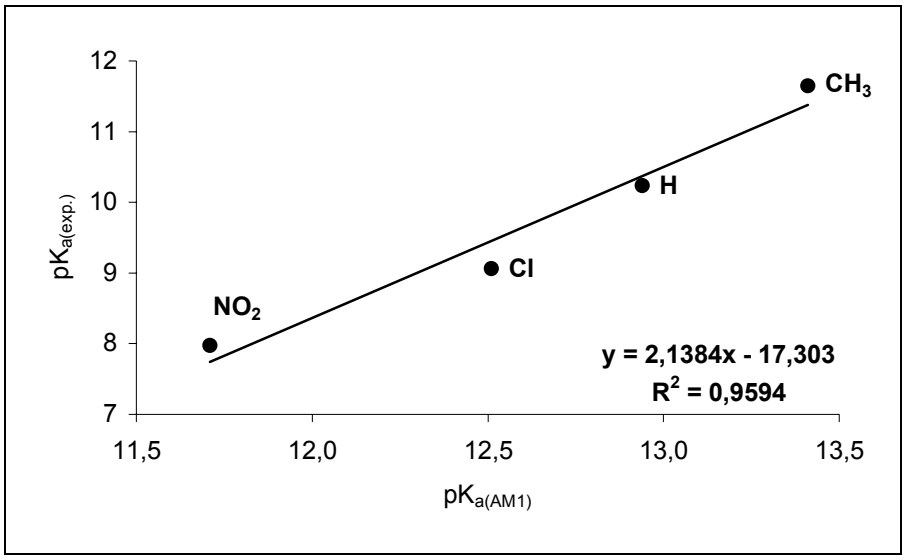


Figure 1. Plot of the aqueous phase AM1 calculated acidity constants, pK_a(calc.), and experimental acidity constants, pK_a(exp.), for the studied molecules.

Table 6. Aqueous phase PM3, PM5 and AM1calculated pK_a values for the investigated molecules

			PM3		PM5		AM1		
Substituent (X)	Anion (B^-)	Neutral (BH)	$\delta\Delta G_{(BH+)}$ (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]
H	**1a**	**1b**	30.07	22.05	6.70	4.91	24.99	18.33	10.24
	2a(s)	**2c(s)**	36.45	26.73	14.00	10.27	31.09	22.80	
	2a(a)	**2c(a)**	34.17	25.06	11.87	8.71	30.32	22.23	
	2b	**2c(s)**	26.31	19.29	-8.45	-6.20	18.53	13.59	
	2b	**2c(a)**	24.03	17.62	-10.57	-7.75	17.64	12.94	
	1am	**1bm**	30.11	22.08	6.40	4.69	27.32	20.03	
	2am(s)	**2cam(s)**	38.59	28.30	14.60	10.71	31.90	23.39	
	2am(a)	**2cam(a)**	35.49	26.02	12.77	9.37	31.61	23.18	
	2bm	**2cbm(s)**	24.68	18.10	-10.76	-7.89	18.36	13.46	
	2bm	**2cbm(a)**	22.88	16.78	-12.58	-9.23	16.98	12.45	
5(6)-CH_3	**1a**	**1c**	32.08	23.52	8.56	6.28	25.48	18.68	11.65
	1b	**1c**	30.75	22.55	7.14	5.24	23.78	17.44	
	2a(s)	**2c(s)**	36.30	26.62	13.68	10.03	32.51	23.84	
	2a(a)	**2c(a)**	34.71	25.46	12.35	9.06	28.70	21.05	
	2b	**2c(s)**	26.44	19.39	-8.47	-6.21	18.28	13.41	
	2b	**2c(a)**	24.64	18.07	-9.80	-7.18	16.01	11.74	
	3a(s)	**3c(s)**	34.98	25.65	12.59	9.23	30.60	22.44	
	3a(a)	**3c(a)**	36.68	26.90	12.48	9.15	29.64	21.74	
	3b	**3c(s)**	25.46	18.67	-9.27	-6.80	17.53	12.86	
	3b	**3c(a)**	26.83	19.67	-9.35	-6.85	17.44	12.79	
	1am	**1cam**	30.73	22.53	7.43	5.45	22.33	16.37	
	1bm	**1cbm**	29.98	21.98	8.87	6.50	25.57	18.75	
	2am(s)	**2cam(s)**	38.69	28.37	12.07	8.85	31.70	23.24	
	2am(a)	**2cam(a)**	36.66	26.89	11.97	8.78	33.41	24.50	
	2bm	**2cbm(s)**	26.43	19.38	-9.58	-7.03	20.05	14.70	
	2bm	**2cbm(a)**	26.34	19.31	-10.15	-7.44	19.90	14.59	
	3am(s)	**3cam(s)**	37.46	27.47	13.46	9.87	31.33	22.98	
	3am(a)	**3cam(a)**	36.99	27.13	13.23	9.70	31.55	23.13	
	3bm	**3cbm(s)**	23.46	17.20	-9.66	-7.08	19.48	14.28	
	3bm	**3cbm(a)**	26.40	19.36	-7.77	-5.70	18.83	13.81	
5(6)-NO_2	**1a**	**1c**	26.15	19.18	3.00	2.20	22.27	16.33	7.98
	1b	**1c**	25.13	18.43	3.03	2.22	22.18	16.27	
	2a(s)	**2c(s)**	31.95	23.43	6.84	5.02	26.77	19.63	

	2a(a)	**2c(a)**	31.29	22.95	6.83	5.01	26.13	19.16	
	2b	**2c(s)**	23.83	17.47	-9.82	-7.20	17.12	12.55	
	2b	**2c(a)**	22.99	16.86	-9.84	-7.21	16.57	12.15	
	3a(s)	**3c(s)**	30.95	22.70	5.75	4.22	25.69	18.84	
	3a(a)	**3c(a)**	32.07	23.51	6.45	4.73	26.21	19.22	
	3b	**3c(s)**	24.40	17.89	-12.68	-9.30	15.97	11.71	
	3b	**3c(a)**	25.34	18.58	-11.99	-8.79	16.58	12.16	
	1am	**1cam**	25.50	18.70	3.25	2.38	22.24	16.31	
	1bm	**1cbm**	25.24	18.51	6.16	4.52	22.20	16.28	
	2am(s)	**2cam(s)**	32.09	23.53	6.69	4.91	28.48	20.88	
	2am(a)	**2cam(a)**	32.93	24.15	6.95	5.09	26.90	19.73	
	2bm	**2cbm(s)**	24.42	17.90	-10.78	-7.91	18.14	13.30	
	2bm	**2cbm(a)**	20.37	14.94	-12.37	-9.07	13.77	10.09	
	3am(s)	**3cam(s)**	32.76	24.02	8.16	5.98	27.26	19.99	
	3am(a)	**3cam(a)**	32.06	23.51	5.91	4.33	26.96	19.77	
	3bm	**3cbm(s)**	21.07	15.45	-11.05	-8.11	13.86	10.16	
	3bm	**3cbm(a)**	23.17	16.99	-10.17	-7.46	16.85	12.36	
5(6)-Cl	**1a**	**1c**	29.68	21.76	5.80	4.25	24.20	17.75	9.06
	1b	**1c**	29.64	21.73	5.92	4.34	24.25	17.78	
	2a(s)	**2c(s)**	35.28	25.87	12.17	8.92	29.49	21.62	
	2a(a)	**2c(a)**	34.24	25.11	11.02	8.08	28.60	20.98	
	2b	**2c(s)**	26.07	19.12	-9.16	-6.72	17.93	13.15	
	2b	**2c(a)**	24.95	18.29	-10.31	-7.56	17.06	12.51	
	3a(s)	**3c(s)**	34.24	25.11	12.11	8.88	28.97	21.24	
	3a(a)	**3c(a)**	35.27	25.87	12.60	9.24	29.42	21.58	
	3b	**3c(s)**	24.99	18.32	-9.09	-6.67	17.46	12.80	
	3b	**3c(a)**	25.95	19.03	-8.61	-6.31	17.95	13.16	
	1am	**1cam**	31.37	23.00	5.29	3.88	24.28	17.81	
	1bm	**1cbm**	28.54	20.93	7.19	5.27	24.40	17.89	
	2am(s)	**2cam(s)**	35.51	26.04	13.36	9.80	30.23	22.16	
	2am(a)	**2cam(a)**	34.96	25.64	11.62	8.52	29.66	21.75	
	2bm	**2cbm(s)**	25.72	18.86	-10.12	-7.42	19.40	14.23	
	2bm	**2cbm(a)**	23.73	17.40	-11.18	-8.20	17.11	12.55	
	3am(s)	**3cam(s)**	36.01	26.41	10.42	7.64	29.66	21.75	
	3am(a)	**3cam(a)**	35.70	26.18	12.43	9.11	30.22	22.16	
	3bm	**3cbm(s)**	22.90	16.79	-9.75	-7.15	18.70	13.72	
	3bm	**3cbm(a)**	23.83	17.48	-8.78	-6.44	20.26	14.86	

[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.[6]

Nucleophilicity Criteria

The principle of hard and soft bases has been applied to kinetic phenomena for a long time. In this connection, organic chemistry has provided most of the examples, because organic reactions are often slow enough for their rates to be easily measured. In organic chemistry, we are generally interested in the reactions of electrophiles and nucleophiles. These reactions are a particular kind of the general acid-with-base type of reaction, and so the principle of hard and soft acids and bases applies equally to the reactions of electrophiles and nucleophiles. So acidity and basicity can be related to the theoretical interpretation of hard-soft acids and bases stating the following principles:

i. *Hard acids* have high-energy LUMOs and the *hard bases* have low-energy HOMOs.

ii. The lower the energy of the HOMO of a base the *harder* it is as a base.

iii. A *hard acid* bonds strongly to a *hard base* because the orbitals involved are far apart in energy.

iv. A *soft acid* bonds strongly to a *soft base* because the orbitals involved are close in energy.

Since it was observed that the rates with which nucleophiles attack one kind of electrophile are not necessarily a good guide to the rates with which the same nucleophile will attack other electrophiles, so it is a good idea to categorize nucleophiles as being hard or soft, and electrophiles as being soft or hard. The theoretical interpretation of them are as follows;

i. Hard nucleophiles have relatively low-energy HOMOs.

ii. Soft nucleophiles have high- energy HOMOs.

The solvated proton is a *hard electrophile* and little affected by frontier orbital interactions. For this reason, the pK_a of the conjugated acid of a nucleophile is a good measure of the rate at which that a *nucleophile* will attack another *hard electrophile*.[36]

Taking all those above mentioned points into account, we have attempted to find possible correlations between the experimental or computed *acidity* constants, pK_a values, and computed *nucleophilicity* of the studied molecules.

The *nucleophilicity*, $n = E_{HOMO} - E_{LUMO}$ [37], of the studied molecules was calculated and the aqueous phase calculated n values of the studied neutral molecules are depicted in Table 7.

It seems that the basicity and nucleophilicity of compound IV is reduced as expected from the strong electron-withdrawing effect of the nitro group. Whereas the weaker electron-withdrawing effect of chlorine reduces the basicity and nucleophilicity to a lower extent. On the other hand, the electron-donating methyl group seems to increase the basicity power of molecule II but not its nucleophilicity (Figs. 2-3)

Table 7. The aqueous phase PM3, PM5 and AM1calculated nucleophilicity (n) values for studied molecules

Compnd	X	E_{HOMO}	E_{LUMO}	n[a]	E_{HOMO}	E_{LUMO}	n[a]	E_{HOMO}	E_{LUMO}	n[a]
			PM3			**PM5**			**AM1**	
	H									
1c		-8.858	-0.849	-8.009	-9.035	-0.765	-8.270	-8.761	-0.557	-8.204
2c(a)		-8.999	-0.494	-8.505	-8.982	-0.849	-8.133	-8.687	-0.339	-8.348
2c(s)		-8.961	-0.479	-8.482	-8.899	-0.879	-8.020	-8.691	-0.333	-8.358
1cam		-8.876	-0.892	-7.984	-9.010	-0.819	-8.191	-8.747	-0.58	-8.167
2cam(s)		-9.004	-0.530	-8.474	-8.902	-0.900	-8.002	-8.715	-0.369	-8.346
2cam(a)		-9.026	-0.582	-8.444	-8.912	-0.944	-7.968	-8.744	-0.404	-8.340
2cbm(s)		-8.874	-0.478	-8.396	-8.742	-0.757	-7.985	-8.503	-0.291	-8.212
2cbm(a)		-8.909	-0.558	-8.351	-8.765	-0.784	-7.981	-8.523	-0.325	-8.198
	5(6)-CH_3									
1c		-8.815	-0.842	-7.973	-8.938	-0.765	-8.173	-8.700	-0.560	-8.140
2c(a)		-8.965	-0.488	-8.477	-8.868	-0.848	-8.020	-8.648	-0.332	-8.316
2c(s)		-8.914	-0.473	-8.441	-8.803	-0.873	-7.930	-8.648	-0.324	-8.324
3c(a)		-8.859	-0.474	-8.385	-8.762	-0.872	-7.890	-8.601	-0.347	-8.254
3c(s)		-8.854	-0.498	-8.356	-8.770	-0.866	-7.904	-8.598	-0.355	-8.243
1cam		-8.834	-0.885	-7.949	-8.907	-0.815	-8.092	-8.683	-0.579	-8.104
1cbm		-8.834	-0.887	-7.947	-8.921	-0.815	-8.106	-8.687	-0.582	-8.105
2cam(s)		-8.830	-0.472	-8.358	-8.668	-0.753	-7.915	-8.471	-0.282	-8.189
2cam(a)		-8.879	-0.553	-8.326	-8.701	-0.781	-7.920	-8.496	-0.316	-8.180
2cbm(s)		-8.951	-0.524	-8.427	-8.792	-0.896	-7.896	-8.670	-0.360	-8.310
2cbm(a)		-8.977	-0.578	-8.399	-8.929	-0.853	-8.076	-8.703	-0.396	-8.307
3cam(s)		-8.818	-0.552	-8.266	-8.651	-0.778	-7.873	-8.452	-0.339	-8.113
3cam(a)		-8.789	-0.472	-8.317	-8.635	-0.752	-7.883	-8.434	-0.305	-8.129
3cbm(s)		-8.918	-0.577	-8.341	-8.998	-0.825	-8.173	-8.654	-0.420	-8.234
3cbm(a)		-8.897	-0.523	-8.374	-8.771	-0.895	-7.876	-8.621	-0.383	-8.238
	5(6)-NO_2									
1c		-8.990	-1.429	-7.561	-9.304	-2.153	-7.151	-9.004	-1.403	-7.601
2c(a)		-9.146	-1.132	-8.014	-9.235	-2.068	-7.167	-8.935	-1.201	-7.734
2c(s)		-9.154	-1.140	-8.014	-9.244	-2.07	-7.174	-8.944	-1.202	-7.742
3c(a)		-9.204	-1.235	-7.969	-9.265	-2.092	-7.173	-8.969	-1.358	-7.611
3c(s)		-9.199	-1.243	-7.956	-9.253	-2.092	-7.161	-8.960	-1.363	-7.597
1cam		-9.011	-1.435	-7.576	-9.275	-2.156	-7.119	-8.985	-1.412	-7.573

1cbm	-9.015	-1.481	-7.534	-9.262	-2.111	-7.151	-8.980	-1.423	-7.557
2cam(s)	-9.047	-1.127	-7.920	-9.029	-2.060	-6.969	-8.713	-1.186	-7.527
2cam(a)	-9.082	-1.138	-7.944	-9.048	-2.066	-6.982	-8.733	-1.198	-7.535
2cbm(s)	-9.201	-1.153	-8.048	-9.252	-2.074	-7.178	-8.969	-1.216	-7.753
2cbm(a)	-9.222	-1.149	-8.073	-9.259	-2.075	-7.184	-8.965	-1.220	-7.745
3cam(s)	-9.132	-1.254	-7.878	-9.068	-2.088	-6.980	-8.757	-1.357	-7.400
3cam(a)	-9.082	-1.224	-7.858	-9.042	-2.083	-6.959	-8.734	-1.338	-7.396
3cbm(s)	-9.284	-1.316	-7.968	-9.562	-2.080	-7.482	-8.990	-1.399	-7.591
3cbm(a)	-9.255	-1.292	-7.963	-9.268	-2.101	-7.167	-8.993	-1.387	-7.606
	5(6)-Cl								
1c	-8.849	-0.967	-7.882	-9.063	-0.839	-8.224	-8.802	-0.717	-8.085
2c(a)	-8.974	-0.600	-8.374	-9.030	-0.903	-8.127	-8.758	-0.501	-8.257
Table 7 continued									
2c(s)	-8.967	-0.598	-8.369	-8.960	-0.926	-8.034	-8.759	-0.495	-8.264
3c(a)	-8.902	-0.623	-8.279	-8.927	-0.941	-7.986	-8.718	-0.554	-8.164
3c(s)	-8.895	-0.627	-8.268	-8.918	-0.935	-7.983	-8.714	-0.561	-8.153
1cam	-8.869	-1.005	-7.864	-9.031	-0.890	-8.141	-8.784	-0.734	-8.050
1cbm	-8.868	-1.013	-7.855	-9.041	-0.898	-8.143	-8.787	-0.740	-8.047
2cam(s)	-8.885	-0.568	-8.317	-8.80	-0.806	-7.994	-8.564	-0.456	-8.108
2cam(a)	-8.937	-0.606	-8.331	-8.83	-0.833	-7.997	-8.588	-0.487	-8.101
2cbm(s)	-8.998	-0.646	-8.352	-8.953	-0.955	-7.998	-8.782	-0.526	-8.256
2cbm(a)	-9.022	-0.663	-8.359	-9.142	-0.907	-8.235	-8.838	-0.570	-8.268
3cam(s)	-8.861	-0.635	-8.226	-8.795	-0.840	-7.955	-8.553	-0.548	-8.005
3cam(a)	-8.834	-0.595	-8.239	-8.777	-0.825	-7.952	-8.534	-0.515	-8.019
3cbm(s)	-8.958	-0.701	-8.257	-9.191	-0.908	-8.283	-8.763	-0.619	-8.144
3cbm(a)	-8.938	-0.678	-8.260	-8.935	-0.968	-7.967	-8.742	-0.590	-8.152

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

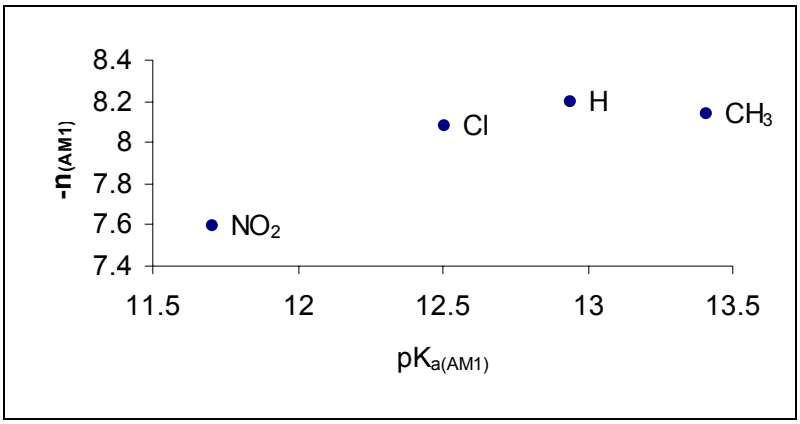


Figure 2. Plot of the aqueous phase AM1 calculated acidity constants, pK_a(calc.), and nucleophilicity values $n_{(AM1)}$, for studied molecules.

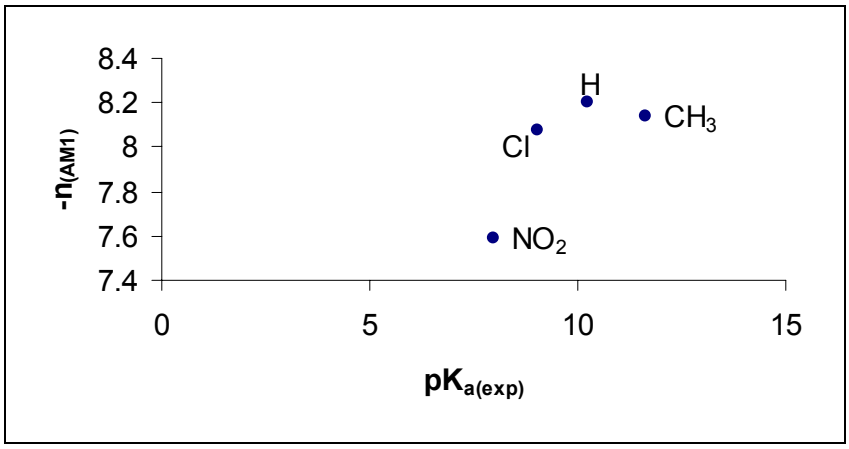


Figure 3. The plot of the aqueous phase experimental acidity constants, pK_a(calc.), and nucleophilicity values $n_{(AM1)}$, for studied molecules.

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