

# 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

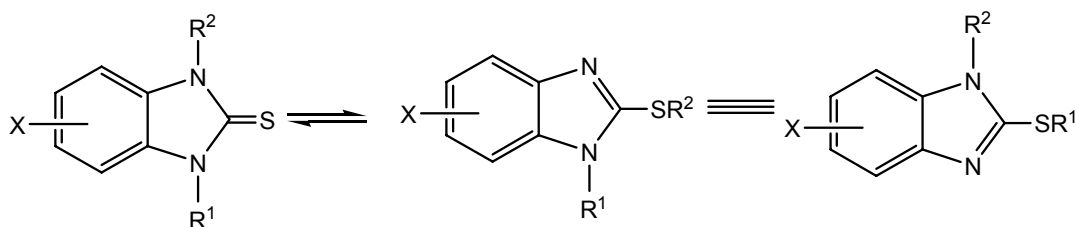
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## Introduction

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.<sup>1,2</sup> 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.<sup>3</sup> Klotz and Mellody demonstrated that yeast nucleic acid reversed the inhibitory effect of benzimidazole on the growth of the bacterium, *Escherichia coli*.<sup>4</sup> Some benzimidazole and imidazole derivatives were investigated earlier both by experimental and theoretical method by our research group.<sup>5-13</sup>

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,<sup>14-20</sup> the variation of intrinsic stabilities, solvent effects,<sup>21-23</sup> as a test of aromaticity,<sup>24-26</sup> and enzymatic catalysis and receptor interactions.<sup>27</sup> 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<sup>5,6</sup> 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,<sup>28</sup> 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)<sup>20</sup> 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),<sup>30</sup> 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

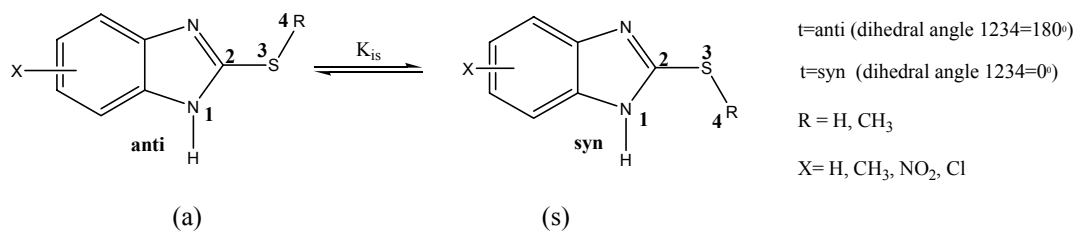
Compound Number	Form name	X	R <sup>1</sup>	R <sup>2</sup>
I	<b>1b</b> Benzimidazole-2-thione	H	H	H
	<b>1bm</b> (model of <b>1b</b> ) 1-Methylbenzimidazole-2-thione	H	CH <sub>3</sub>	H
II	<b>2c</b> 2-Mercaptobenzimidazole	H	H	H
	<b>2cam</b> (model of <b>2c</b> ) 1-Methyl-2-mercaptobenzimidazole	H	CH <sub>3</sub>	H
	<b>2cbm</b> (model of <b>2c</b> ) 2-Methylthiobenzimidazole	H	H	CH <sub>3</sub>
III	<b>1c</b> 5(6)-Methylbenzimidazole-2-thione	CH <sub>3</sub>	H	H
	<b>1cam</b> (model of <b>1c</b> ) 5(6)-Methyl-1-methylbenzimidazole-2-thione	CH <sub>3</sub>	CH <sub>3</sub>	H
	<b>1cbm</b> (model of <b>1c</b> ) 5(6)-Methyl-3-methylbenzimidazole-2-thione	CH <sub>3</sub>	H	CH <sub>3</sub>
III	<b>2c</b> 5(6)-Methyl-2-mercaptobenzimidazole	CH <sub>3</sub>	H	H
	<b>2cam</b> (model of <b>2c</b> ) 5(6)-Methyl-2-methylthiobenzimidazole	CH <sub>3</sub>	H	CH <sub>3</sub>
	<b>2cbm</b> (model of <b>2c</b> ) 5(6)-Methyl-1-methylbenzimidazole-2-thione	CH <sub>3</sub>	CH <sub>3</sub>	H
III	<b>3c</b> 5(6)-Methyl-2-mercaptobenzimidazole	CH <sub>3</sub>	H	H
	<b>3cam</b> (model of <b>3c</b> ) 5(6)-Methyl-2-methylthiobenzimidazole	CH <sub>3</sub>	CH <sub>3</sub>	H
	<b>3cbm</b> (model of <b>3c</b> ) 5(6)-Methyl-3-methylbenzimidazole-2-thione	CH <sub>3</sub>	H	CH <sub>3</sub>
IV	<b>1c</b> 5(6)-Nitrobenzimidazole-2-thione	NO <sub>2</sub>	H	H
	<b>1cam</b> (model of <b>1c</b> ) 5(6)-Nitro-1-methylbenzimidazole-2-thione	NO <sub>2</sub>	CH <sub>3</sub>	H
	<b>1cbm</b> (model of <b>1c</b> ) 5(6)-Nitro-3-methylbenzimidazole-2-thione	NO <sub>2</sub>	H	CH <sub>3</sub>
IV	<b>2c</b> 5(6)-Nitro-2-mercaptobenzimidazole	NO <sub>2</sub>	H	H
	<b>2cam</b> (model of <b>2c</b> ) 5(6)-Nitro-2-methylthiobenzimidazole	NO <sub>2</sub>	H	CH <sub>3</sub>
	<b>2cbm</b> (model of <b>2c</b> ) 5(6)-Nitro-1-methylbenzimidazole-2-thione	NO <sub>2</sub>	CH <sub>3</sub>	H
IV	<b>3c</b> 5(6)-Nitro-2-mercaptobenzimidazole	NO <sub>2</sub>	H	H
	<b>3cam</b> (model of <b>3c</b> ) 5(6)-Nitro-2-methylthiobenzimidazole	NO <sub>2</sub>	CH <sub>3</sub>	H
	<b>3cbm</b> (model of <b>3c</b> ) 5(6)-Nitro-3-methylbenzimidazole-2-thione	NO <sub>2</sub>	H	CH <sub>3</sub>
V	<b>1c</b> 5(6)-Chlorobenzimidazole-2-thione	Cl	H	H
	<b>1cam</b> (model of <b>1c</b> ) 5(6)-Chloro-1-methylbenzimidazole-2-thione	Cl	CH <sub>3</sub>	H
	<b>1cbm</b> (model of <b>1c</b> ) 5(6)-Chloro-3-methylbenzimidazole-2-thione	Cl	H	CH <sub>3</sub>
V	<b>2c</b> 5(6)-Chloro-2-mercaptobenzimidazole	Cl	H	H
	<b>2cam</b> (model of <b>2c</b> ) 5(6)-Chloro-2-methylthiobenzimidazole	Cl	H	CH <sub>3</sub>
	<b>2cbm</b> (model of <b>2c</b> ) 5(6)-Chloro-1-methylbenzimidazole-2-thione	Cl	CH <sub>3</sub>	H
V	<b>3c</b> 5(6)-Chloro-2-mercaptobenzimidazole	Cl	H	H
	<b>3cam</b> (model of <b>3c</b> ) 5(6)-Chloro-2-methylthiobenzimidazole	Cl	CH <sub>3</sub>	H
	<b>3cbm</b> (model of <b>3c</b> ) 5(6)-Chloro-3-methylbenzimidazole-2-thione	Cl	H	CH <sub>3</sub>

## 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=180°) and *syn* (dihedral angle 1234=0°) conformers (Scheme 1) were considered in the present work.

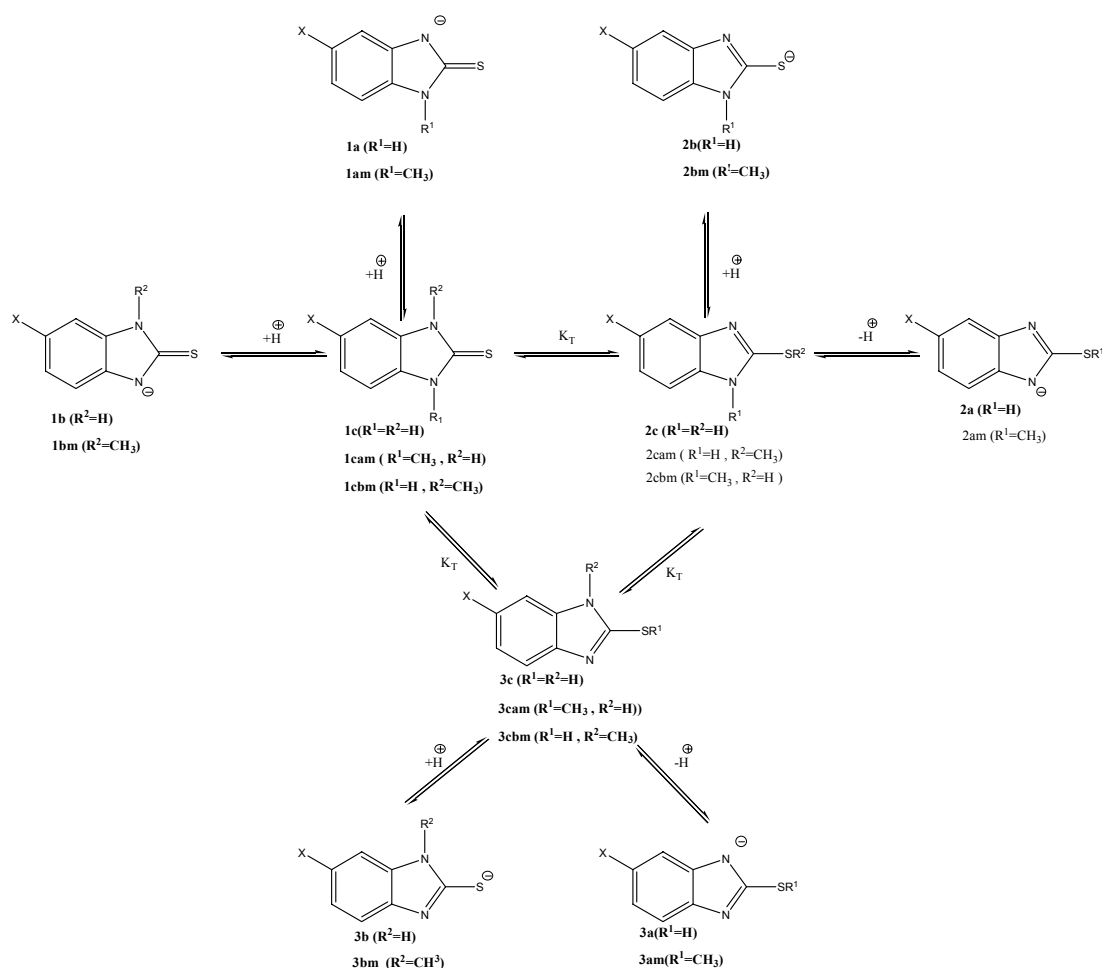


**Scheme 1.** The *anti* and *syn* form for studied molecules.

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 ( $\epsilon : 78.4$ )

Compound	$\Delta H_f$	$\Delta S$	$\Delta G_f$	Compou nd	$\Delta H_f$	$\Delta S$	$\Delta G_f$	Compou nd	$\Delta H_f$	$\Delta S$	$\Delta G_f$
	(kcal/m ol)	(cal/mol K)	(kcal/mo l) <sup>a</sup>		(kcal/m ol)	(cal/mol K)	(kcal/mo l) <sup>a</sup>		(kcal/m ol)	(cal/mol K)	(kcal/mo l) <sup>a</sup>
AM1											
<b>X= H</b>											
<b>1a</b>	-36.26	85.85	-61.84	<b>2c(a)</b>	61.49	88.30	35.18	<b>2cam(s)</b>	66.71	94.33	38.60
<b>1c</b>	53.37	85.69	27.83	<b>1am</b>	-29.59	91.04	-56.72	<b>2cam(a)</b>	68.08	94.30	39.98
<b>2a(s)</b>	-23.13	87.75	-49.28	<b>1cam</b>	59.80	97.92	30.62	<b>2cbm(s)</b>	55.94	97.68	26.83
<b>2a(a)</b>	-23.14	87.32	-49.16	<b>2am(s)</b>	-27.15	96.57	-55.93	<b>2cbm(a)</b>	56.41	98.07	27.19
<b>2b</b>	-36.26	85.84	-61.84	<b>2am(a)</b>	-27.15	96.35	-55.86				

<b>2c(s)</b>	60.86	89.16	34.29	<b>2bm</b>	-29.59	94.34	-57.70
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X= 5(6)-CH<sub>3</sub>

<b>1a</b>	-43.81	90.72	-70.84	<b>3c(s)</b>	53.82	96.50	25.06	<b>2cbm(s)</b>	59.13	104.53	27.98
<b>1b</b>	-43.89	96.14	-72.54	<b>3c(a)</b>	53.16	93.98	25.15	<b>2cbm(a)</b>	60.51	108.67	28.13
<b>1c</b>	45.72	91.89	18.34	<b>1am</b>	-37.14	110.61	-70.10	<b>3am(s)</b>	-34.69	107.03	-66.58
<b>2a(s)</b>	-30.71	92.65	-58.32	<b>1bm</b>	-37.20	95.89	-65.78	<b>3am(a)</b>	-34.70	110.05	-67.49
<b>2a(a)</b>	-30.69	97.89	-59.86	<b>1cam</b>	52.19	100.54	22.23	<b>3bm</b>	-37.20	95.98	-65.80
<b>2b</b>	-43.81	96.44	-72.55	<b>1cbm</b>	52.20	96.93	23.31	<b>3cam(s)</b>	48.75	107.41	16.74
<b>2c(s)</b>	53.24	98.69	23.83	<b>2am(s)</b>	-34.69	106.73	-66.50	<b>3cam(a)</b>	48.29	109.64	15.62
<b>2c(a)</b>	53.92	93.36	26.10	<b>2am(a)</b>	-34.70	100.32	-64.60	<b>3cbm(s)</b>	60.43	104.20	29.38
<b>3a(s)</b>	-30.71	94.94	-59.00	<b>2bm</b>	-37.15	98.93	-66.63	<b>3cbm(a)</b>	59.17	97.78	30.03
<b>3a(a)</b>	-30.69	97.89	-59.86	<b>2cam(s)</b>	48.37	107.05	16.47				
<b>3b</b>	-43.89	94.55	-72.07	<b>2cam(a)</b>	48.83	107.96	16.66				

X= 5(6)-NO<sub>2</sub>

<b>1a</b>	-39.61	100.44	-69.54	<b>3c(s)</b>	60.01	103.78	29.08	<b>2cbm(s)</b>	65.03	113.32	31.26
<b>1b</b>	-39.67	100.54	-69.63	<b>3c(a)</b>	59.32	103.52	28.47	<b>2cbm(a)</b>	67.24	106.06	35.63
<b>1c</b>	53.27	102.09	22.85	<b>1am</b>	-32.99	105.72	-64.49	<b>3am(s)</b>	-34.01	106.87	-65.86
<b>2a(s)</b>	-29.77	101.06	-59.89	<b>1bm</b>	-32.97	105.81	-64.50	<b>3am(a)</b>	-33.94	110.97	-67.01
<b>2a(a)</b>	-29.70	101.61	-59.98	<b>1cam</b>	59.90	107.31	27.92	<b>3bm</b>	-32.99	106.09	-64.60
<b>2b</b>	-39.61	100.44	-69.54	<b>1cbm</b>	59.89	107.14	27.96	<b>3cam(s)</b>	54.79	111.57	21.54
<b>2c(s)</b>	58.83	103.45	28.00	<b>2am(s)</b>	-34.01	106.47	-65.74	<b>3cam(a)</b>	54.22	112.50	20.70
<b>2c(a)</b>	59.52	103.94	28.55	<b>2am(a)</b>	-33.94	110.28	-66.80	<b>3cbm(s)</b>	67.68	105.65	36.20
<b>3a(s)</b>	-29.77	101.06	-59.89	<b>2bm</b>	-32.99	108.29	-65.26	<b>3cbm(a)</b>	65.56	108.58	33.20
<b>3a(a)</b>	-29.70	101.61	-59.98	<b>2cam(s)</b>	53.75	111.76	20.45				
<b>3b</b>	-39.68	100.43	-69.61	<b>2cam(a)</b>	54.41	112.26	20.96				

## X= 5(6)-Cl

<b>1a</b>	-43.73	92.62	-71.33	<b>3c(s)</b>	54.68	96.52	25.92	<b>2cbm(s)</b>	59.84	105.62	28.37
<b>1b</b>	-43.66	92.67	-71.28	<b>3c(a)</b>	54.00	95.89	25.42	<b>2cbm(a)</b>	61.34	102.96	30.66
<b>1c</b>	47.13	93.95	19.13	<b>1am</b>	-37.07	97.99	-66.27	<b>3am(s)</b>	-35.77	103.36	-66.57
<b>2a(s)</b>	-31.65	94.37	-59.77	<b>1bm</b>	-37.02	97.86	-66.18	<b>3am(a)</b>	-35.76	103.61	-66.64
<b>2a(a)</b>	-31.65	94.42	-59.79	<b>1cam</b>	53.64	99.11	24.11	<b>3bm</b>	-37.02	97.85	-66.18
<b>2b</b>	-43.73	92.62	-71.33	<b>1cbm</b>	53.62	99.14	24.08	<b>3cam(s)</b>	49.55	104.44	18.43
<b>2c(s)</b>	53.89	95.60	25.40	<b>2am(s)</b>	-35.77	103.25	-66.54	<b>3cam(a)</b>	49.04	104.82	17.80
<b>2c(a)</b>	54.59	95.04	26.27	<b>2am(a)</b>	-35.76	103.64	-66.64	<b>3cbm(s)</b>	61.36	105.98	29.78
<b>3a(s)</b>	-31.65	94.37	-59.77	<b>2bm</b>	-37.07	100.06	-66.89	<b>3cbm(a)</b>	59.93	106.42	28.22
<b>3a(a)</b>	-31.65	94.50	-59.81	<b>2cam(s)</b>	48.93	104.14	17.90				
<b>3b</b>	-43.67	92.66	-71.28	<b>2cam(a)</b>	49.46	104.39	18.35				

## PM3

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

				X= 5(6)-CH <sub>3</sub>							
<b>1a</b>	-67.11	91.44	-94.36	<b>3c(s)</b>	33.72	99.23	4.15	<b>2cbm(s)</b>	33.48	104.25	2.41
<b>1b</b>	-67.14	95.81	-95.69	<b>3c(a)</b>	32.56	99.90	2.79	<b>2cbm(a)</b>	34.88	108.66	2.50
<b>1c</b>	27.52	97.01	-1.39	<b>1am</b>	-66.48	101.78	-96.81	<b>3am(s)</b>	-59.94	102.58	-90.51
<b>2a(s)</b>	-56.42	98.60	-85.80	<b>1bm</b>	-66.49	106.83	-98.33	<b>3am(a)</b>	-59.92	101.82	-90.26
<b>2a(a)</b>	-56.41	97.90	-85.58	<b>1cam</b>	28.49	103.96	-2.49	<b>3bm</b>	-66.49	107.62	-98.56
<b>2b</b>	-67.11	95.80	-95.66	<b>1cbm</b>	28.48	106.48	-3.25	<b>3cam(s)</b>	29.47	108.68	-2.92
<b>2c(s)</b>	32.57	99.40	2.95	<b>2am(s)</b>	-59.94	102.39	-90.45	<b>3cam(a)</b>	28.59	103.34	-2.21
<b>2c(a)</b>	33.94	97.95	4.75	<b>2am(a)</b>	-59.92	99.83	-89.67	<b>3cbm(s)</b>	34.88	106.88	3.03
<b>3a(s)</b>	-56.42	99.00	-85.92	<b>2bm</b>	-66.48	99.78	-96.21	<b>3cbm(a)</b>	33.47	112.03	0.09
<b>3a(a)</b>	-56.41	97.90	-85.58	<b>2cam(s)</b>	28.57	109.61	-4.09				
<b>3b</b>	-67.14	94.95	-95.44	<b>2cam(a)</b>	29.50	103.30	-1.28				

				X= 5(6)-NO <sub>2</sub>							
<b>1a</b>	-76.99	102.38	-107.50	<b>3c(s)</b>	24.61	100.22	-5.26	<b>2cbm(s)</b>	24.52	114.62	-9.64
<b>1b</b>	-77.19	105.13	-108.52	<b>3c(a)</b>	23.41	99.37	-6.20	<b>2cbm(a)</b>	25.90	105.70	-5.60
<b>1c</b>	20.27	96.89	-8.60	<b>1am</b>	-76.26	108.77	-108.67	<b>3am(s)</b>	-72.53	105.97	-104.11
<b>2a(s)</b>	-68.80	102.56	-99.36	<b>1bm</b>	-76.38	112.66	-109.95	<b>3am(a)</b>	-72.58	106.42	-104.29
<b>2a(a)</b>	-68.79	102.00	-99.19	<b>1cam</b>	21.44	102.55	-9.12	<b>3bm</b>	-76.38	111.66	-109.65
<b>2b</b>	-76.99	102.35	-107.49	<b>1cbm</b>	21.47	106.08	-10.14	<b>3cam(s)</b>	20.52	108.52	-11.82
<b>2c(s)</b>	23.41	99.59	-6.27	<b>2am(s)</b>	-72.52	106.43	-104.24	<b>3cam(a)</b>	19.37	102.93	-11.30
<b>2c(a)</b>	24.54	100.56	-5.43	<b>2am(a)</b>	-72.61	106.53	-104.36	<b>3cbm(s)</b>	26.26	107.17	-5.68
<b>3a(s)</b>	-68.80	102.55	-99.36	<b>2bm</b>	-76.26	114.14	-110.27	<b>3cbm(a)</b>	24.68	108.90	-7.77
<b>3a(a)</b>	-68.79	102.00	-99.19	<b>2cam(s)</b>	19.29	102.57	-11.28				
<b>3b</b>	-77.16	96.49	-105.91	<b>2cam(a)</b>	20.38	109.45	-12.24				

				X= 5(6)-Cl							
<b>1a</b>	-64.85	93.63	-92.75	<b>3c(s)</b>	36.41	97.80	7.27	<b>2cbm(s)</b>	36.14	102.86	5.49
<b>1b</b>	-64.78	94.00	-92.79	<b>3c(a)</b>	35.24	97.08	6.31	<b>2cbm(a)</b>	37.55	100.90	7.48
<b>1c</b>	30.85	94.73	2.62	<b>1am</b>	-64.20	99.49	-93.85	<b>3am(s)</b>	-58.58	100.3	-88.47
<b>2a(s)</b>	-55.01	95.75	-83.54	<b>1bm</b>	-64.13	105.82	-95.66	<b>3am(a)</b>	-58.52	99.49	-88.17

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

## PM5

## X=H

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

X= 5 (6)-CH<sub>3</sub>

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

X= 5(6)-NO<sub>2</sub>

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



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

<sup>a</sup> from  $\Delta G_f = \Delta H_f - T \cdot \Delta S$

**H<sub>2</sub>O** - **AM1:**  $\Delta H_f$  (kcal/mol) = -64.39,  $\Delta S$  (cal/molK) = 45.10,  $\Delta G_f$  (kcal/mol) = -77.83

**PM3:**  $\Delta H_f$  (kcal/mol) = -58.02,  $\Delta S$  (cal/molK) = 45.00,  $\Delta G_f$  (kcal/mol) = -71.43

**PM5:**  $\Delta H_f$  (kcal/mol) = -59.47,  $\Delta S$  (cal/molK) = 44.99,  $\Delta G_f$  (kcal/mol) = -72.88

**H<sub>3</sub>O<sup>+</sup>** - **AM1:**  $\Delta H_f$  (kcal/mol) = 50.61,  $\Delta S$  (cal/molK) = 46.15,  $\Delta G_f$  (kcal/mol) = 36.83

**PM3:**  $\Delta H_f$  (kcal/mol) = 67.33,  $\Delta S$  (cal/molK) = 46.01,  $\Delta G_f$  (kcal/mol) = 53.62

**PM5:**  $\Delta H_f$  (kcal/mol) = 46.51,  $\Delta S$  (cal/molK) = 45.88,  $\Delta G_f$  (kcal/mol) = 32.84

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

Substituen t (X)	Annular		$\delta\Delta G^a$		$\delta\Delta G^a$		$\delta\Delta G^a$		$\delta\Delta G^a$		
	Tautomer	Ring-chain tautomer	(kcal/m ol)	$K_T^b$	$pK_T^c$	(kcal/m ol)	$K_T^b$	$pK_T^c$	(kcal/m ol)	$K_T^b$	$pK_T^c$
				<b>PM3</b>		<b>PM5</b>		<b>AM1</b>			
	<i>Main</i>										
<b>H</b>	<i>tautomers</i>										
	...	<b>1c-2c(s)</b>	3.76	1.75 10 <sup>-3</sup>	2.758	15.15	7.73 10 <sup>-12</sup>	11.112	6.46	1.8210 <sup>-5</sup>	4.738
	...	<b>1c-2c(a)</b>	6.04	3.72 10 <sup>-5</sup>	4.430	17.27	2.15 10 <sup>-13</sup>	12.667	7.35	4.0610 <sup>-6</sup>	5.391
	<i>Fixed models</i>										
		<b>1cam-</b>									
	...	<b>2cam(s)</b>	...	6.03 10 <sup>-7</sup>	6.220	...	9.55 10 <sup>-7</sup>	6.020	...	4.37 10 <sup>-4</sup>	3.360

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

<i>Main</i>											
<b>5(6)-NO<sub>2</sub></b>	<i>tautomers</i>										
...	<b>1c-2c(s)</b>	2.33	1.95 10 <sup>-2</sup>	1.709	12.81	4.02 10 <sup>-10</sup>	9.395	5.15	1.67 10 <sup>-4</sup>	3.777	
...	<b>1c-2c(a)</b>	3.17	4.71 10 <sup>-3</sup>	2.327	12.82	3.93 10 <sup>-10</sup>	9.406	5.70	6.64 10 <sup>-5</sup>	4.178	
...	<b>1c-3c(s)</b>	3.34	3.55 10 <sup>-3</sup>	2.450	13.89	6.49 10 <sup>-11</sup>	10.188	6.23	2.70 10 <sup>-5</sup>	4.569	
...	<b>1c-3c(a)</b>	2.40	1.74 10 <sup>-2</sup>	1.759	13.20	2.09 10 <sup>-10</sup>	9.679	5.62	7.54 10 <sup>-5</sup>	4.123	
	<b>2c(s)-3c(s)</b>	...	1.01	1.82 10 <sup>-1</sup>	0.741	1.08	1.61 10 <sup>-1</sup>	0.792	1.08	1.61 10 <sup>-1</sup>	0.792
	<b>2c(a)-3c(a)</b>	...	-0.78	3.70	-0.569	0.37	5.33 10 <sup>-1</sup>	0.273	-0.07	1.13	-0.055
	<i>Fixed models</i>										
	<b>1cam-</b>										-
...	<b>2cbm(s)</b>	...	6.17	-0.790	...	1.95 10 <sup>10</sup>	10.290	...	1.02 10 <sup>3</sup>	-3.010	
	<b>1cam-</b>										-
...	<b>2cmb(a)</b>	...	5.70 10 <sup>3</sup>	-3.756	...	2.85 10 <sup>11</sup>	11.455	...	1.65 10 <sup>6</sup>	-6.217	
	<b>1cam-</b>										-
...	<b>3cam(s)</b>	...	4.72 10 <sup>-6</sup>	5.326	...	2.52 10 <sup>-4</sup>	3.598	...	2.09 10 <sup>-4</sup>	3.679	
	<b>1cam-</b>										-
...	<b>3cam(a)</b>	...	1.54 10 <sup>-5</sup>	4.813	...	1.13 10 <sup>-2</sup>	1.946	...	3.51 10 <sup>-4</sup>	3.455	
	<b>2cbm(s)-</b>										-
	<b>3cbm(s)</b>	...	...	2.83 10 <sup>2</sup>	-2.452	...	1.58	-0.200	...	1.38 10 <sup>3</sup>	-3.139
	<b>2cbm(a)-</b>										-
	<b>3cbm(a)</b>	...	...	8.95 10 <sup>-3</sup>	2.048	...	2.44 10 <sup>-2</sup>	1.613	...	5.46 10 <sup>-3</sup>	2.263
	<b>1cbm-</b>										-
...	<b>3cbm(s)</b>	...	1.14 10 <sup>3</sup>	-3.056	...	4.24 10 <sup>12</sup>	12.627	...	1.30 10 <sup>6</sup>	-6.114	
	<b>1cbm-</b>										-
...	<b>3cbm(a)</b>	...	3.30 10 <sup>1</sup>	-1.519	...	9.51 10 <sup>11</sup>	11.978	...	8.30 10 <sup>3</sup>	-3.919	
	<b>1cbm-</b>										-
...	<b>2cam(s)</b>	...	9.46 10 <sup>-6</sup>	5.024	...	4.11 10 <sup>-1</sup>	0.386	...	2.48 10 <sup>-5</sup>	4.605	
	<b>1cbm-</b>										-
...	<b>2cam(a)</b>	...	2.29 10 <sup>-6</sup>	5.640	...	2.67 10 <sup>-1</sup>	0.573	...	3.56 10 <sup>-4</sup>	3.449	
	<b>2cam(s)-</b>										-
	<b>3cam(s)</b>	...	...	3.23 10 <sup>-1</sup>	0.491	...	8.39 10 <sup>-2</sup>	1.076	...	7.80	-0.892
	<b>2cam(a)-</b>										-
	<b>3cam(a)</b>	...	...	4.35	-0.638	...	5.79	-0.763	...	9.10 10 <sup>-1</sup>	0.041
	<i>Main</i>										
<b>5(6)-Cl</b>	<i>tautomers</i>										
...	<b>1c-2c(s)</b>	3.61	2.25 10 <sup>-3</sup>	2.648	14.96	1.07 10 <sup>-11</sup>	10.972	6.27	2.52 10 <sup>-5</sup>	4.599	
...	<b>1c-2c(a)</b>	4.73	3.39 10 <sup>-4</sup>	3.470	16.11	1.53 10 <sup>-12</sup>	11.815	7.14	5.82 10 <sup>-6</sup>	5.235	
...	<b>1c-3c(s)</b>	4.65	3.89 10 <sup>-4</sup>	3.411	15.02	9.63 10 <sup>-12</sup>	11.016	6.79	1.05 10 <sup>-5</sup>	4.980	
...	<b>1c-3c(a)</b>	3.69	1.97 10 <sup>-3</sup>	2.707	14.53	2.20 10 <sup>-11</sup>	10.658	6.29	2.42 10 <sup>-5</sup>	4.617	

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

$$^a \delta\Delta G = \Delta G_{(\text{product})} - \Delta G_{(\text{reactant})}$$

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

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

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

Substituent (X)	Isomers	$\delta\Delta G^a$ (kcal/mo)			$\delta\Delta G^a$ (kcal/mo)			$\delta\Delta G^a$ (kcal/mo)		
		l)	$K_{is}^b$	$pK_{is}^c$	l)	$K_{is}^b$	$pK_{is}^c$	l)	$K_{is}^b$	$pK_{is}^c$
		PM3			PM5			AM1		
<b>H</b>	<i>Main isomers</i>									
	2c(s)-2c(a)	2.28	$2.09 \cdot 10^{-2}$	1.680	2.12	$2.74 \cdot 10^{-2}$	1.562	0.89	$2.21 \cdot 10^{-1}$	0.656
	<i>Fixed models</i>									
	2cam(s)-2cam(a)		$2.09 \cdot 10^1$	-1.320		$2.19 \cdot 10^1$	-1.340	...	$1.02 \cdot 10^1$	-1.010
	2cbm(s)-2cbm(a)		$1.91 \cdot 10^2$	-2.280		$2.19 \cdot 10^1$	-1.340	...	1.62	-0.210
	<b>5(6)-CH<sub>3</sub></b>	<i>Main isomers</i>								
2c(s)-2c(a)	1.80	$4.72 \cdot 10^{-2}$	1.326	1.33	$1.05 \cdot 10^{-1}$	0.980	2.27	$2.13 \cdot 10^{-2}$	1.673	
3c(s)-3c(a)	-1.36	$1.00 \cdot 10^1$	-1.002	0.08	$8.73 \cdot 10^{-1}$	0.059	0.09	$8.58 \cdot 10^{-1}$	0.066	
	<i>Fixed models</i>									
	2cam(s)-2cam(a)		$3.02 \cdot 10^1$	-1.480		1.17	-0.070	...	$5.50 \cdot 10^{-2}$	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	...	$7.08 \cdot 10^{-1}$	0.150
	3cbm(s)-3cbm(a)		$6.92 \cdot 10^{-3}$	2.160		$4.17 \cdot 10^{-2}$	1.380	...	2.95	-0.470
<b>5(6)-NO<sub>2</sub></b>	<i>Main isomers</i>									
2c(s)-2c(a)	0.84	$2.40 \cdot 10^{-1}$	0.619	0.01	$9.83 \cdot 10^{-1}$	0.007	0.55	$3.93 \cdot 10^{-1}$	0.405	
3c(s)-3c(a)	-0.94	4.93	-0.693	-0.69	3.22	-0.508	-0.61	2.81	-0.449	
	<i>Fixed models</i>									
	2cam(s)-2cam(a)		$2.40 \cdot 10^{-1}$	0.620		$6.61 \cdot 10^{-1}$	0.180	...	$1.41 \cdot 10^1$	-1.150
	2cbm(s)-2cbm(a)		$9.12 \cdot 10^2$	-2.960		$1.45 \cdot 10^1$	-1.160	...	$1.62 \cdot 10^3$	-3.210
	3cam(s)-3cam(a)	3.24	-0.510		$4.47 \cdot 10^1$	-1.650	...	1.66	-0.220	
	3cbm(s)-3cbm(a)	$2.88 \cdot 10^{-2}$	1.540		$2.24 \cdot 10^{-1}$	0.650	...	$6.31 \cdot 10^{-3}$	2.200	
<b>5(6)-Cl</b>	<i>Main isomers</i>									
2c(s)-2c(a)	1.12	$1.50 \cdot 10^{-1}$	0.825	1.15	$1.42 \cdot 10^{-1}$	0.847	0.87	$2.29 \cdot 10^{-1}$	0.641	
3c(s)-3c(a)	-0.96	5.10	-0.707	-0.49	2.30	-0.361	-0.50	2.34	-0.368	
	<i>Fixed models</i>									
	2cam(s)-2cam(a)		2.51	-0.400		$1.91 \cdot 10^1$	-1.280	...	2.57	-0.410
	2cbm(s)-2cbm(a)		$2.88 \cdot 10^1$	-1.460		6.03	-0.780	...	$4.79 \cdot 10^1$	-1.680

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

$$^a \delta\Delta G = \Delta G_{(\text{product})} - \Delta G_{(\text{reactant})}$$

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

$^c pK_{is} = -\log K_s$  (for main isomers)  $pK_{is} = pK_{a(\text{product})} - pK_{a(\text{reactant})}$  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 AM1 calculated relative stabilities for tautomers, RS, of studied molecules

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

	...	<b>1cbm-2cam(a)</b>	2.33	-7.60	3.59
	<b>2cam(s)-3cam(s)</b>	...	-4.06	-3.13	-2.72
	<b>2cam(a)-3cam(a)</b>	...	4.19	3.39	2.94
<b>5(6)-NO<sub>2</sub></b>	<i>Main tautomers</i>				
	...	<b>1c-2c(s)</b>	4.86	-8.62	-2.02
	...	<b>1c-2c(a)</b>	0.29	-12.50	-5.53
	...	<b>1c-3c(s)</b>	0.08	-8.84	-5.71
	...	<b>1c-3c(a)</b>	4.63	-8.86	-2.30
	<b>2c(s)-3c(s)</b>	...	-4.78	-0.22	-3.69
	<b>2c(a)-3c(a)</b>	...	4.34	3.64	3.23
	<i>Fixed models</i>				
	...	<b>1cam-2cbm(s)</b>	4.55	-8.79	-1.98
	...	<b>1cam-2cmba</b>	0.19	-13.39	-6.60
	...	<b>1cam-3cam(s)</b>	4.21	-1.85	5.23
	...	<b>1cam-3cam(a)</b>	8.46	-1.87	8.09
	<b>2cbm(s)-3cbm(s)</b>	...	-4.59	0.01	-4.63
	<b>2cbm(a)-3cbm(a)</b>	...	4.20	4.56	4.44
	...	<b>1cbm-3cbm(s)</b>	-0.12	-8.93	-6.69
	...	<b>1cbm-3cbm(a)</b>	4.31	-8.98	-2.24
	...	<b>1cbm-2cam(s)</b>	8.63	-1.78	8.27
	...	<b>1cbm-2cam(a)</b>	4.32	-5.19	5.24
	<b>2cam(s)-3cam(s)</b>	...	-4.50	-0.22	-3.12
	<b>2cam(a)-3cam(a)</b>	...	4.06	3.17	2.77
<b>5(6)-Cl</b>	<i>Main tautomers</i>				
	...	<b>1c-2c(s)</b>	3.30	-10.28	-3.20
	...	<b>1c-2c(a)</b>	3.30	-14.16	-6.64
	...	<b>1c-3c(s)</b>	-0.91	-13.96	-6.48
	...	<b>1c-3c(a)</b>	3.40	-10.15	-3.11
	<b>2c(s)-3c(s)</b>	...	-4.21	-3.68	-3.28
	<b>2c(a)-3c(a)</b>	...	0.10	4.01	3.53
	<i>Fixed models</i>				
	...	<b>1cam-2cbm(s)</b>	2.97	-10.46	-3.19
<b>Table 5 cont.</b>	...	<b>1cam-2cmba</b>	-1.33	-15.02	-7.68
	...	<b>1cam-3cam(s)</b>	3.00	-6.53	4.28
	...	<b>1cam-3cam(a)</b>	7.14	-3.29	7.11
	<b>2cbm(s)-3cbm(s)</b>	...	-4.13	-4.33	-4.32
	<b>2cbm(a)-3cbm(a)</b>	...	4.41	4.72	4.60

...	<b>1cbm-3cbm(s)</b>	-1.18	-14.82	-7.52
...	<b>1cbm-3cbm(a)</b>	3.06	-10.33	-3.09
...	<b>1cbm-2cam(s)</b>	7.03	-3.43	7.02
...	<b>1cbm-2cam(a)</b>	2.83	-6.75	4.12
<b>2cam(s)-3cam(s)</b>	...	-4.05	-3.13	-2.75
<b>2cam(a)-3cam(a)</b>	...	4.29	3.43	2.98

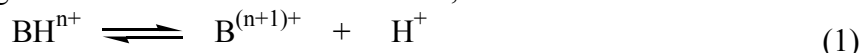
$$^a \text{RS} = \Delta H_{\text{f(reactant)}} - \Delta H_{\text{f(product)}}$$

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<sub>3</sub>, NO<sub>2</sub> 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 the 3 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.<sup>31-33</sup>

### Acidity

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



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

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<sup>+</sup> are neutral and protonated species of base B, and A and AH<sup>+</sup> are H<sub>2</sub>O and H<sub>3</sub>O<sup>+</sup> 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 AM1 method) 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<sub>3</sub>- > H- > Cl- > NO<sub>2</sub>-**

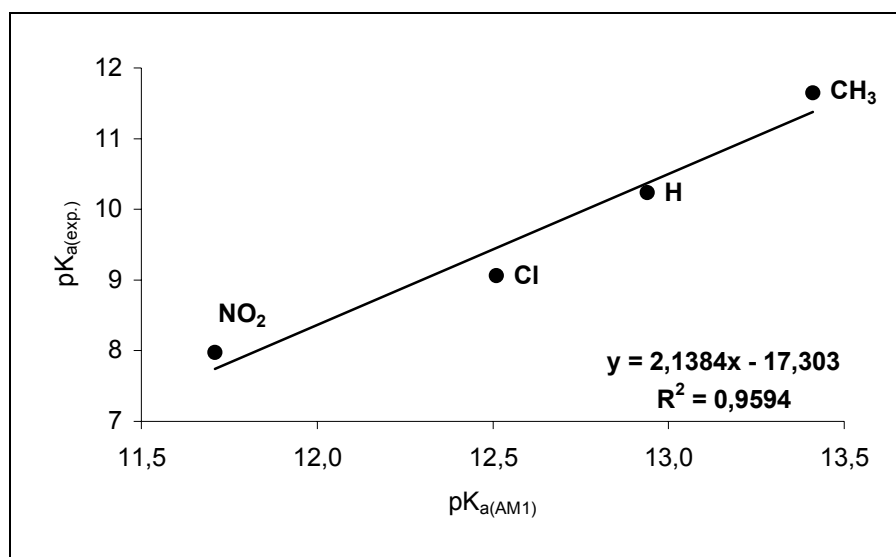
**11.65 > 10.24 > 9.06 > 7.98**

**AM1 method  $pK_a$  : CH<sub>3</sub>- > H- > Cl- > NO<sub>2</sub>-**

**13.41 > 12.94 > 12.51 > 11.71**

**decreasing acidity  $\longrightarrow$**

We have attempted to correlate the experimental  $pK_a$  values<sup>34,35</sup> 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,  $pK_a(\text{calc.})$ , and experimental acidity constants,  $pK_a(\text{exp.})$ , for the studied molecules.

**Table 6.** Aqueous phase PM3, PM5 and AM1 calculated pK<sub>a</sub> values for the investigated molecules

Substituent (X)	Anion (B)	PM3		PM5		AM1		pK <sub>a</sub> <sup>b</sup>	pK <sub>a</sub> (exp.) <sup>c</sup>
		Neutral (BH)	ΔΔG <sub>(BH<sup>+</sup>)</sub> (kcal/mol) <sup>a</sup>	ΔΔG <sub>(BH<sup>+</sup>)</sub> (kcal/mol) <sup>a</sup>	ΔΔG <sub>(BH<sup>+</sup>)</sub> (kcal/mol) <sup>a</sup>	pK <sub>a</sub> <sup>b</sup>	pK <sub>a</sub> <sup>b</sup>		
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 <sub>3</sub>	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 <sub>2</sub>	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	

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

$$^a \delta\Delta G_{(\text{BH}^+)} = [\Delta G_{(\text{B})} + \Delta G_{(\text{H}_3\text{O}^+)}] - [\Delta G_{(\text{BH})} + \Delta G_{(\text{H}_2\text{O})}]$$

$$^b \text{p}K_{\text{a}} = \delta\Delta G_{(\text{BH})} / (2.303RT)$$

<sup>c</sup>  $\text{p}K_{\text{a}}(\text{expt.})$  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*.<sup>36</sup>

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 AM1 calculated nucleophilicity ( $n$ ) values for studied molecules

Compnd	X	$E_{\text{HOMO}}$	$E_{\text{LUMO}}$	$n^a$	$E_{\text{HOMO}}$	$E_{\text{LUMO}}$	$n^a$	$E_{\text{HOMO}}$	$E_{\text{LUMO}}$	$n^a$
		PM3			PM5			AM1		
<b>H</b>										
<b>1c</b>		-8.858	-0.849	-8.009	-9.035	-0.765	-8.270	-8.761	-0.557	-8.204
<b>2c(a)</b>		-8.999	-0.494	-8.505	-8.982	-0.849	-8.133	-8.687	-0.339	-8.348
<b>2c(s)</b>		-8.961	-0.479	-8.482	-8.899	-0.879	-8.020	-8.691	-0.333	-8.358
<b>1cam</b>		-8.876	-0.892	-7.984	-9.010	-0.819	-8.191	-8.747	-0.58	-8.167
<b>2cam(s)</b>		-9.004	-0.530	-8.474	-8.902	-0.900	-8.002	-8.715	-0.369	-8.346
<b>2cam(a)</b>		-9.026	-0.582	-8.444	-8.912	-0.944	-7.968	-8.744	-0.404	-8.340
<b>2cbm(s)</b>		-8.874	-0.478	-8.396	-8.742	-0.757	-7.985	-8.503	-0.291	-8.212
<b>2cbm(a)</b>		-8.909	-0.558	-8.351	-8.765	-0.784	-7.981	-8.523	-0.325	-8.198
<b>5(6)-CH<sub>3</sub></b>										
<b>1c</b>		-8.815	-0.842	-7.973	-8.938	-0.765	-8.173	-8.700	-0.560	-8.140
<b>2c(a)</b>		-8.965	-0.488	-8.477	-8.868	-0.848	-8.020	-8.648	-0.332	-8.316
<b>2c(s)</b>		-8.914	-0.473	-8.441	-8.803	-0.873	-7.930	-8.648	-0.324	-8.324
<b>3c(a)</b>		-8.859	-0.474	-8.385	-8.762	-0.872	-7.890	-8.601	-0.347	-8.254
<b>3c(s)</b>		-8.854	-0.498	-8.356	-8.770	-0.866	-7.904	-8.598	-0.355	-8.243
<b>1cam</b>		-8.834	-0.885	-7.949	-8.907	-0.815	-8.092	-8.683	-0.579	-8.104
<b>1cbm</b>		-8.834	-0.887	-7.947	-8.921	-0.815	-8.106	-8.687	-0.582	-8.105
<b>2cam(s)</b>		-8.830	-0.472	-8.358	-8.668	-0.753	-7.915	-8.471	-0.282	-8.189
<b>2cam(a)</b>		-8.879	-0.553	-8.326	-8.701	-0.781	-7.920	-8.496	-0.316	-8.180
<b>2cbm(s)</b>		-8.951	-0.524	-8.427	-8.792	-0.896	-7.896	-8.670	-0.360	-8.310
<b>2cbm(a)</b>		-8.977	-0.578	-8.399	-8.929	-0.853	-8.076	-8.703	-0.396	-8.307
<b>3cam(s)</b>		-8.818	-0.552	-8.266	-8.651	-0.778	-7.873	-8.452	-0.339	-8.113
<b>3cam(a)</b>		-8.789	-0.472	-8.317	-8.635	-0.752	-7.883	-8.434	-0.305	-8.129
<b>3cbm(s)</b>		-8.918	-0.577	-8.341	-8.998	-0.825	-8.173	-8.654	-0.420	-8.234
<b>3cbm(a)</b>		-8.897	-0.523	-8.374	-8.771	-0.895	-7.876	-8.621	-0.383	-8.238
<b>5(6)-NO<sub>2</sub></b>										
<b>1c</b>		-8.990	-1.429	-7.561	-9.304	-2.153	-7.151	-9.004	-1.403	-7.601
<b>2c(a)</b>		-9.146	-1.132	-8.014	-9.235	-2.068	-7.167	-8.935	-1.201	-7.734
<b>2c(s)</b>		-9.154	-1.140	-8.014	-9.244	-2.07	-7.174	-8.944	-1.202	-7.742
<b>3c(a)</b>		-9.204	-1.235	-7.969	-9.265	-2.092	-7.173	-8.969	-1.358	-7.611
<b>3c(s)</b>		-9.199	-1.243	-7.956	-9.253	-2.092	-7.161	-8.960	-1.363	-7.597
<b>1cam</b>		-9.011	-1.435	-7.576	-9.275	-2.156	-7.119	-8.985	-1.412	-7.573

<b>1cbm</b>	-9.015	-1.481	-7.534	-9.262	-2.111	-7.151	-8.980	-1.423	-7.557
<b>2cam(s)</b>	-9.047	-1.127	-7.920	-9.029	-2.060	-6.969	-8.713	-1.186	-7.527
<b>2cam(a)</b>	-9.082	-1.138	-7.944	-9.048	-2.066	-6.982	-8.733	-1.198	-7.535
<b>2cbm(s)</b>	-9.201	-1.153	-8.048	-9.252	-2.074	-7.178	-8.969	-1.216	-7.753
<b>2cbm(a)</b>	-9.222	-1.149	-8.073	-9.259	-2.075	-7.184	-8.965	-1.220	-7.745
<b>3cam(s)</b>	-9.132	-1.254	-7.878	-9.068	-2.088	-6.980	-8.757	-1.357	-7.400
<b>3cam(a)</b>	-9.082	-1.224	-7.858	-9.042	-2.083	-6.959	-8.734	-1.338	-7.396
<b>3cbm(s)</b>	-9.284	-1.316	-7.968	-9.562	-2.080	-7.482	-8.990	-1.399	-7.591
<b>3cbm(a)</b>	-9.255	-1.292	-7.963	-9.268	-2.101	-7.167	-8.993	-1.387	-7.606

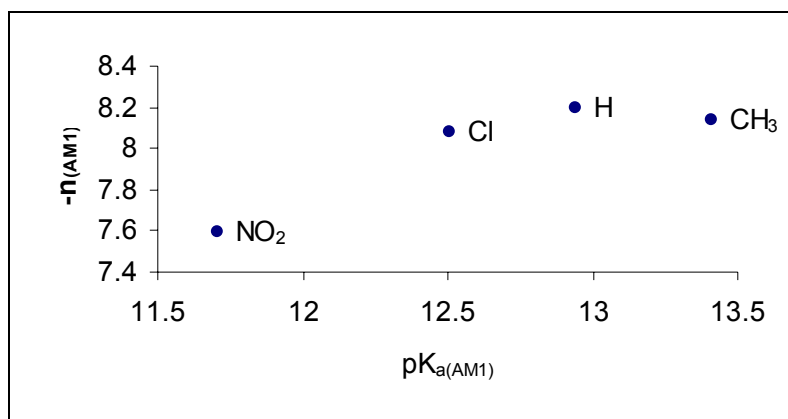
**5(6)-Cl**

<b>1c</b>	-8.849	-0.967	-7.882	-9.063	-0.839	-8.224	-8.802	-0.717	-8.085
<b>2c(a)</b>	-8.974	-0.600	-8.374	-9.030	-0.903	-8.127	-8.758	-0.501	-8.257

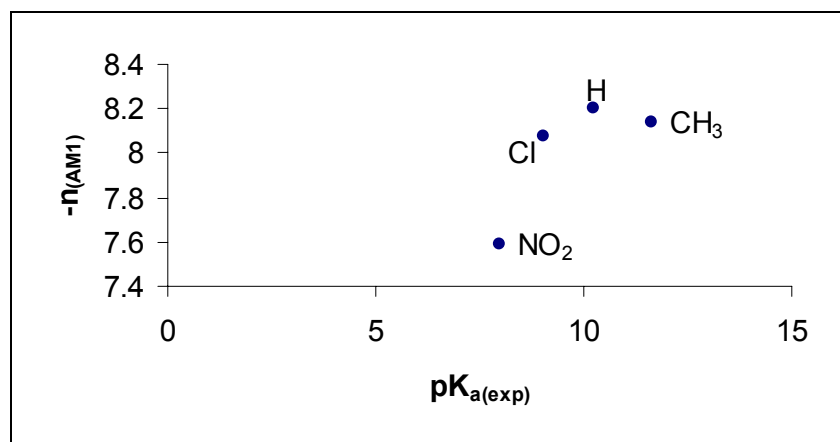
**Table 7**  
**continued**

<b>2c(s)</b>	-8.967	-0.598	-8.369	-8.960	-0.926	-8.034	-8.759	-0.495	-8.264
<b>3c(a)</b>	-8.902	-0.623	-8.279	-8.927	-0.941	-7.986	-8.718	-0.554	-8.164
<b>3c(s)</b>	-8.895	-0.627	-8.268	-8.918	-0.935	-7.983	-8.714	-0.561	-8.153
<b>1cam</b>	-8.869	-1.005	-7.864	-9.031	-0.890	-8.141	-8.784	-0.734	-8.050
<b>1cbm</b>	-8.868	-1.013	-7.855	-9.041	-0.898	-8.143	-8.787	-0.740	-8.047
<b>2cam(s)</b>	-8.885	-0.568	-8.317	-8.80	-0.806	-7.994	-8.564	-0.456	-8.108
<b>2cam(a)</b>	-8.937	-0.606	-8.331	-8.83	-0.833	-7.997	-8.588	-0.487	-8.101
<b>2cbm(s)</b>	-8.998	-0.646	-8.352	-8.953	-0.955	-7.998	-8.782	-0.526	-8.256
<b>2cbm(a)</b>	-9.022	-0.663	-8.359	-9.142	-0.907	-8.235	-8.838	-0.570	-8.268
<b>3cam(s)</b>	-8.861	-0.635	-8.226	-8.795	-0.840	-7.955	-8.553	-0.548	-8.005
<b>3cam(a)</b>	-8.834	-0.595	-8.239	-8.777	-0.825	-7.952	-8.534	-0.515	-8.019
<b>3cbm(s)</b>	-8.958	-0.701	-8.257	-9.191	-0.908	-8.283	-8.763	-0.619	-8.144
<b>3cbm(a)</b>	-8.938	-0.678	-8.260	-8.935	-0.968	-7.967	-8.742	-0.590	-8.152

$$^a n = E_{\text{HOMO}} - E_{\text{LUMO}}$$



**Figure 2.** Plot of the aqueous phase AM1 calculated acidity constants,  $pK_{a(AM1)}$ , 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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