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A theoretical study of substituent effects on tautomerism of 2-hydroxybenzimidazoles

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Abstract The geometries, relative stabilities of some **4(7)** and **5(6)** substituted 2-hydroxybenzimidazole derivatives were calculated with full geometry optimization using AM1 and PM3 in aqueous phase. With the exception of molecules 4, 6 and 7 for all the **4(7)** and **5(6)** substituted 2-hydroxybenzimidazole derivatives the 3H and keto forms were found to be favored.

Keywords Substituted benzimidazoles · Aqueous phase · Semi-empirical calculations · Annular tautomerism · Chain tautomerism

Introduction

Taking into account the utilization of the benzimidazole derivatives in the synthesis of heat-resistant fibers, which are also used in the manufacture of parachutes, conveyer belts, heat-insulating material and asbestos replacements, they strongly influence progress in aerospace and aeronautics technology. Use of some benzimidazole molecules, such as 5-nitrobenzimidazole, as antifogging substances, photoemulsion stabilizers and as a fungicides significantly increase the importance of benzimidazole derivatives and led our research group to investigate their structure–reactivity relationships at both experimental and theoretical levels. [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]

We now report on the substituent effects on tautomerism of **4(7)** and **5(6)** substituted 2-hydroxybenzimidazole derivatives to fill the gap in the literature and hoping to give some clues to those researchers who will attempt to obtain alternatives in synthesis and use in the above mentioned applications. As one can immediately notice, there exist two kinds of prototautomerism in **4(7)** or **5(6)** substituted 2-hydroxybenzimidazole derivatives and these are annular and ring–chain tautomerisms (Scheme 1).

It was reported in the literature that the substitution in position 2 of the benzimidazole molecule has no influence on annular tautomerism (i.e. K_T) and the symmetry was C_s. [13] Substituents in position **4(7)** and **5(6)** exercise a relatively remote perturbation. Therefore K_T does not differ much from 1 unless an unusual (attractive or repulsive) interaction occurs between a subsituituent in the 7-position and the proton bound to the nitrogen atom (N1). Experimental studies on annular tautomerism of unsubstituted and **4(7)** and **5(6)** substituted benzimidazoles have been reported in the literature [13, 14] but we did not come across any detailed theoretical study on this subject. On the other hand, a few experimental [13] and theoretical [10, 11, 12, 13] results on ring–chain tautomerism for unsubstituted and for **4(7)** and **5(6)** substituted 2-hydroxybenzimidazoles have also been reported. However no systematic theoretical work exists yet.

Method

Theoretical calculations were carried out at the restricted Hartree–Fock level (RHF) using AM1 and PM3 semi-empirical SCF-MO methods in the MOPAC 7.0 program [14] implemented on an Intel Pentium Pro 200-MHz computer. All the structures were optimized to a gradient norm of <0.1 kcal mol^{-1} $Å^{-1}$ in the aqueous phase. The initial estimates of the geometries of all the structures were obtained by a molecular mechanics program of PCMODEL 3.1 from Serena Software.

Results and discussion

Relative stabilities and tautomerism

The aqueous phase semi-empirical AM1 and PM3 computed thermodynamic and stability data for **4(7)** and **5(6)** substituted 2-hydroxybenzimidazole derivatives are given Tables 1 and 2, respectively.

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Scheme 1 Annular and ring–chain prototautomerism for **4(7)** and **5(6)** substituted 2- hydroxy-benzimidazole derivatives

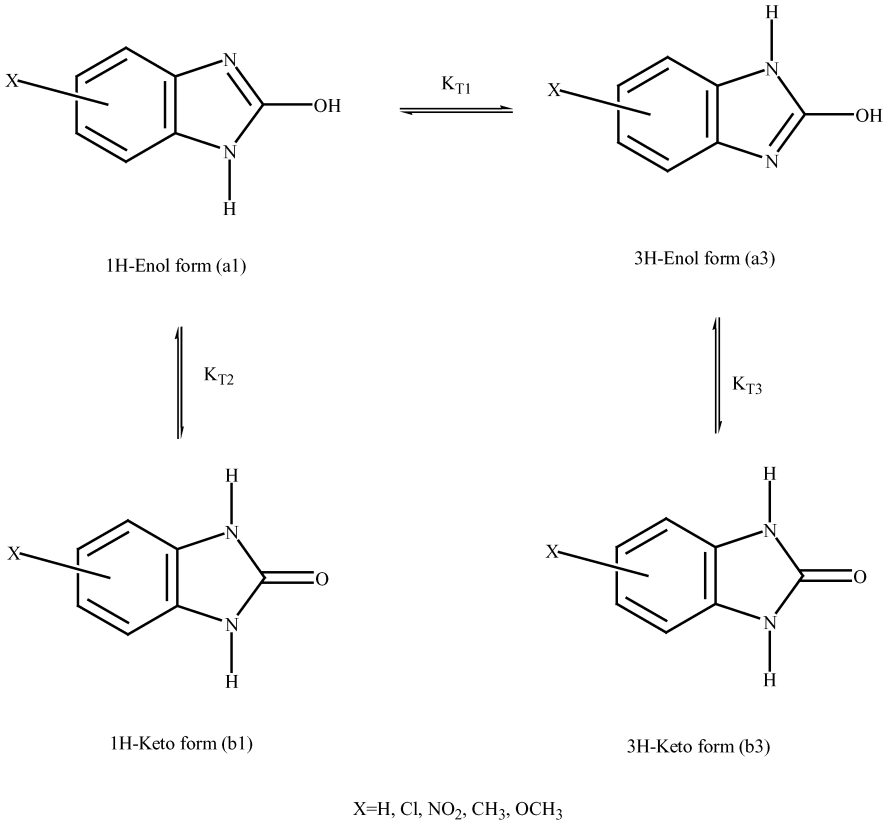


Table 1 Aqueous phase AM1 and PM3 calculated thermodynamic data (ε=78.4) for **4(7)** and **5(6)** substitued 2-hydroxy benzimidazole derivatives

Tautomeric form	X	ΔH_f (kcal mol^{-1})		ΔS (cal mol^{-1} K^{-1})		ΔG (kcal mol^{-1})	
		AM1	PM3	AM1	PM3	AM1	PM3
a1≡a3	H	10.939	–15.374	83.319	83.688	–13.891	–40.314
b1≡b3	H	–3.855	–27.316	86.776	83.042	–29.727	–52.070
a1	4(7)-Me	4.307	–22.982	91.157	92.338	–22.853	–50.500
a3	4(7)-Me	4.034	–23.468	91.457	93.593	–23.220	–51.360
b1	4(7)-Me	–10.802	–36.025	90.848	92.089	–37.870	–63.460
b3	4(7)-Me	–10.802	–36.025	90.848	92.089	–37.870	–63.460
a1	5(6)-Me	3.783	–24.206	91.570	93.584	–23.507	–52.096
a3	5(6)-Me	3.740	–24.083	93.894	91.705	–24.240	–51.410
b1	5(6)-Me	–11.318	–36.595	99.046	92.358	–40.849	–64.110
b3	5(6)-Me	–11.318	–36.595	99.046	92.358	–40.849	–64.110
a1	4(7)-NO_2	6.921	–39.063	100.437	99.853	–23.024	–68.834
a3	4(7)-NO_2	6.234	–40.215	101.114	102.289	–23.912	–70.712
b1	4(7)-NO_2	–7.963	–52.966	97.648	99.976	–37.077	–82.774
b3	4(7)-NO_2	–7.934	–53.008	95.142	95.727	–36.280	–80.540
a1	5(6)-NO_2	5.738	–42.774	93.550	101.196	–23.645	–72.946
a3	5(6)-NO_2	5.538	–43.188	101.190	97.725	–24.632	–72.310
b1	5(6)-NO_2	0.907	–45.831	127.040	123.304	–36.973	–82.594
b3	5(6)-NO_2	–4.893	–51.053	97.891	97.577	–34.060	–80.130
a1	4(7)-Cl	4.511	–21.253	89.897	90.619	–22.280	–48.250
a3	4(7)-Cl	5.119	–19.105	90.701	90.688	–21.910	–46.120
b1	4(7)-Cl	–9.512	–32.578	90.172	90.453	–36.380	–59.530
b3	4(7)-Cl	–9.512	–32.578	90.172	90.453	–36.380	–59.530
a1	5(6)-Cl	4.313	–21.884	90.413	90.568	–22.630	–48.870
a3	5(6)-Cl	4.059	–22.334	91.287	91.082	–23.140	–49.470
b1	5(6)-Cl	–10.309	–34.218	89.448	89.807	–36.960	–60.980
b3	5(6)-Cl	–10.309	–34.218	89.448	89.807	–36.960	–60.980
a1	4(7)-OCH_3	–24.882	–49.011	96.888	97.897	–53.750	–78.180
a3	4(7)-OCH_3	–22.297	–51.612	103.946	97.510	–53.280	–80.670
b1	4(7)-OCH_3	–40.029	–64.105	94.986	96.897	–68.750	–92.970
b3	4(7)-OCH_3	–40.029	–64.105	94.986	96.897	–68.340	–92.970
a1	5(6)-OCH_3	–29.893	–55.684	96.751	98.608	–58.220	–85.060
a3	5(6)-OCH_3	–29.545	–55.093	98.738	98.973	–58.970	–84.580
b1	5(6)-OCH_3	–43.761	–67.396	97.200	96.583	–72.750	–98.180
b3	5(6)-OCH_3	–43.761	–67.396	97.300	96.583	–72.750	–98.180

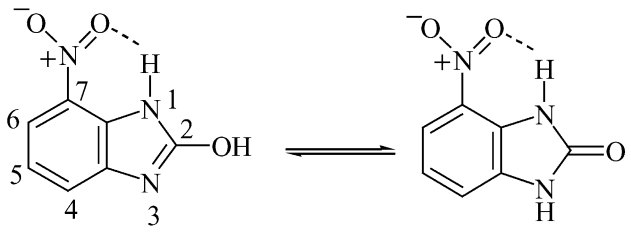
Table 2 Comparision of AM1 and PM3 calculated stabilities (RS) of benzimidazole molecules

Molecule	Tautomeric equilibria	RS[a] (kcal mol^{-1}) AM1	PM3	Stable form
1	X=H			
	$a1 \rightleftharpoons a3$	0.00	0.00	1H≡3H
	$b1 \rightleftharpoons a1$	−14.79	−11.94	1H-keto
	$b3 \rightleftharpoons a3$	−14.79	−11.94	1H-keto
2	X=4(7)-CH_3			
	$a1 \rightleftharpoons a3$	0.27	0.49	3H
	$b1 \rightleftharpoons a1$	−15.80	−13.04	1H-keto
	$b3 \rightleftharpoons a3$	−14.84	−12.56	3H-keto
3	X=5(6)-CH_3			
	$a1 \rightleftharpoons a3$	0.04	−0.12	1H, 3H
	$b1 \rightleftharpoons a1$	−15.10	−12.39	1H-keto
	$b3 \rightleftharpoons a3$	−15.06	−12.51	3H-keto
4	X=4(7)-NO_2			
	$a1 \rightleftharpoons a3$	0.69	−1.15	1H, 3H
	$b1 \rightleftharpoons a1$	−14.88	−13.90	1H-keto
	$b3 \rightleftharpoons a3$	−14.17	−12.79	3H-keto
5	X=5(6)-NO_2			
	$a1 \rightleftharpoons a3$	0.20	0.41	3H
	$b1 \rightleftharpoons a1$	−4.83	−3.06	1H-keto
	$b3 \rightleftharpoons a3$	−10.43	−7.87	3H-keto
6	X=4(7)-Cl			
	$a1 \rightleftharpoons a3$	−0.61	−2.15	1H
	$b1 \rightleftharpoons a1$	−14.02	−11.33	1H-keto
	$b3 \rightleftharpoons a3$	−14.63	−13.47	3H-keto
7	X=5(6)-Cl			
	$a1 \rightleftharpoons a3$	0.26	0.45	3H
	$b1 \rightleftharpoons a1$	−14.62	−12.33	1H-keto
	$b3 \rightleftharpoons a3$	−14.37	−11.88	3H-keto
8	X=4(7)-OCH_3			
	$a1 \rightleftharpoons a3$	−2.59	−2.60	1H
	$b1 \rightleftharpoons a1$	−15.15	−15.09	1H-keto
	$b3 \rightleftharpoons a3$	−17.73	−12.49	3H-keto
9	X=5(6)-OCH_3			
	$a1 \rightleftharpoons a3$	−0.35	−0.59	1H
	$b1 \rightleftharpoons a1$	−13.87	−11.72	1H-keto
	$b3 \rightleftharpoons a3$	−14.22	−12.30	3H-keto

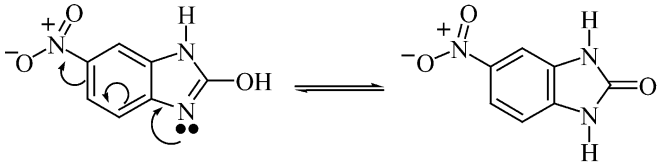
[a] $RS=\Delta H_{f(keto)}-\Delta H_{f(enol)}$ or $\Delta H_{f(3H)}-\Delta H_{f(1H)}$. The minus sign indicate the greater stability of keto and 1H-forms

Annular tautomerism

When the annular tautomerism of 2-hydroxybenzimidazole derivatives is considered, it seems that the presence of potentially tautomeric hydroxyl group at 2C of the benzimidazole molecule has no influence on relative stability values, RS, and the value of tautomeric equilibria constants, K_T, is about unity as indicated in the literature [13] (Tables 2 and 3). The calculated RS and K_{T1} values for $a1 \rightleftharpoons a3$ equilibria, which represent the annular 1H 3H for 2-hydroxbenzimidazole derivatives, were found to be close to zero and unity, respectively, in most cases (Scheme 1). This result fits the literature reports very nicely. [13] In same cases, however, considerable deviations were obtained from the zero value of RS and unity of K_{T1}. These deviations were presumably due to the unusual interactions between the substituent and the proton bound to the nitrogen atom as in the 7-nitro-2-hydroxybenzimidazole molecule and indicates the effect of chain tautomerism on annular tautomerism (Scheme 2).



Scheme 2 Annular $(1H \rightleftharpoons 3H)$ and ring–chain $(keto \rightleftharpoons enol)$ tautomerism for 7-nitro-2-hydroxybenzimidazole



Scheme 3 Annular $(1H \rightleftharpoons 3H)$ and ring-chain $(keto \rightleftharpoons enol)$ tautomerism for **5(6)**-nitro-2-hydroxybenzimidazole

The RS values for 7-nitro-2-hydroxybenzimidazole were found to be 0.69 and −1.15 kcal mol^{-1} for $a1 \rightleftharpoons a3$ equilibrium with the AM1 and PM3 methods, respectively. These are very small but contradictory values; the first value indicates that the 3H form is favored over 1H weakly for this molecule. From these values, which are close to the zero, we can say that 1H≡3H forms as for the other **4(7)** substituted 2-hydroxybenzimidazole molecules. RS results for the $a1 \rightleftharpoons a3$ equilibrium, which are 0.2 and 0.41 kcal mol^{-1} with the AM1 and PM3 methods, respectively, might well indicative that the 3H form is favored due to full the conjugative effect of NO_2, which is an electron-withdrawing group, by withdrawing electrons from the imidazole ring and rendering the formation of 3H keto form more favorable (Scheme 3).

This conclusion can be justified by looking at the K_{T2} and K_{T3} values of **5(6)**-nitro-2-hydroxybenzimidazole, which are smaller than the K_{T2} and K_{T3} values of **4(7)**-nitro-2-hydroxybenzimidazoles molecules (Table 3).

Ring–chain tautomerism

The AM1 and PM3 aqueous phase calculated ring–chain tautomeric equilibrium constants, K_T values, are collected in Table 3. As one can easily see the K_{T2} and K_{T3} values suggest the oxo forms for all studied compounds are overwhelmingly favored, as stated in the literature. A small drop in K_{T2} values is observed when a strong electron-withdrawing (like NO_2) or electron-donating (like OCH_3) substituent moves from **4(7)** C to **5(6)** C, which obviously leads stronger interactions as mentioned earlier between the hydrogen atom of the imidazole ring and the substituent by causing a longer through conjuga-

Table 3 The aqueous phase AM1 and PM3 calculated tautomeric equlibrium constants, K_T[a], for the studied molecules

Tautomeric equlibrium	Type of process	$\partial\Delta G$		K_{T1}		K_{T2}		K_{T3}	
		AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
X=H									
*a*1 ⇌ *a*3	Annular (1H≡3H)	0.00	0.00	1	1				
*b*1 ⇌ *a*1	Ring chain (keto–enol)	−15.84	−11.76	4.51×10^{11}	4.48×10^{8}				
*b*3 ⇌ *a*3	Ring chain (keto–enol)	−15.84	−11.76	4.51×10^{11}	4.48×10^{8}				
X=**4(7)** Me									
*a*1 ⇌ *a*3	1H≡3H	−0.37	−0.64	1.86	0.233				
*b*1 ⇌ *a*1	keto–enol	−15.02	−9.54			9.18×10^{10}	2.90×10^{10}		
*b*3 ⇌ *a*3	keto–enol	−14.65	−12.10					6.04×10^{10}	8.08×10^{8}
X=**5(6)** Me									
*a*1 ⇌ *a*3	1H≡3H	−0.73	0.69	3.46	0.313				
*b*1 ⇌ *a*1	keto–enol	−17.34	−12.70			5.78×10^{12}	2.22×10^{9}		
*b*3 ⇌ *a*3	keto–enol	−16.61	−9.35					1.67×10^{12}	7.55×10^{6}
X=**4(7)** NO_2									
*a*1 ⇌ *a*3	1H≡3H	−0.89	−1.88	4.503	24.100				
*b*1 ⇌ *a*1	keto–enol	−14.05	−13.94			2.20×10^{10}	1.81×10^{10}		
*b*3 ⇌ *a*3	keto–enol	−12.37	−9.83					1.26×10^{9}	1.71×10^{7}
X=**5(6)** NO_2									
*a*1 ⇌ *a*3	1H≡3H	−0.99	0.64	5.325	0.340				
*b*1 ⇌ *a*1	keto–enol	−13.33	−9.65			6.43×10^{9}	1.26×10^{7}		
*b*3 ⇌ *a*3	keto–enol	−9.43	−7.82					8.67×10^{6}	5.69×10^{5}
X=**4(7)** Cl									
*a*1 ⇌ *a*3	1H≡3H	0.37	2.13	0.534	2.71×10^{-2}				
*b*1 ⇌ *a*1	keto–enol	−14.38	−11.28			3.82×10^{10}	2.00×10^{8}		
*b*3 ⇌ *a*3	keto–enol	−14.47	−13.41					4.45×10^{10}	7.39×10^{9}
X=**5(6)** Cl									
*a*1 ⇌ *a*3	1H≡3H	−0.51	−0.60	0.421	0.362				
*b*1 ⇌ *a*1	keto–enol	−14.33	−12.11			3.51×10^{10}	8.16×10^{8}		
*b*3 ⇌ *a*3	keto–enol							1.48×10^{10}	2.95×10^{8}
X=**4(7)** OCH_3									
*a*1 ⇌ *a*3	1H≡3H	0.47	−2.49	2.22	6.80				
*b*1 ⇌ *a*1	keto–enol	−15.00	−14.79			1.09×10^{11}	7.66×10^{10}		
*b*3 ⇌ *a*3	keto–enol							1.21×10^{11}	1.13×10^{8}
X=**5(6)** OCH_3									
*a*1 ⇌ *a*3	1H≡3H	−0.75	0.48	0.28	2.26				
*b*1 ⇌ *a*1	keto–enol	−14.53	−13.12			4.93×10^{10}	4.52×10^{9}		
*b*3 ⇌ *a*3	keto–enol							1.38×10^{10}	1.02×10^{10}

[a] K_T values calculated from $\delta\Delta G = -RT \ln K_T$

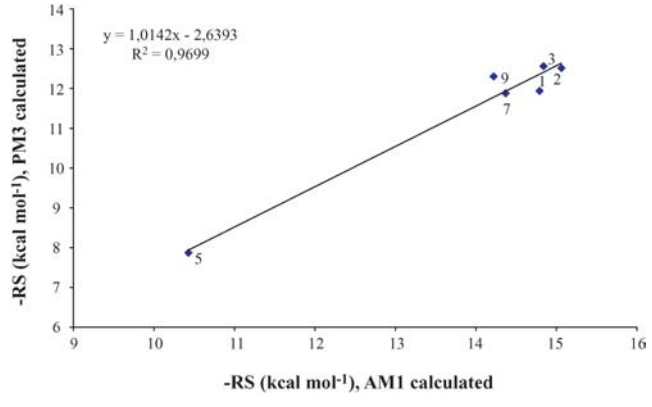


Fig. 1 The plot of AM1 calculated relative stabilities against PM3 calculated relative stabilities for *b*3 ⇌ *a*3 process for the studied molecules **(1–9)**

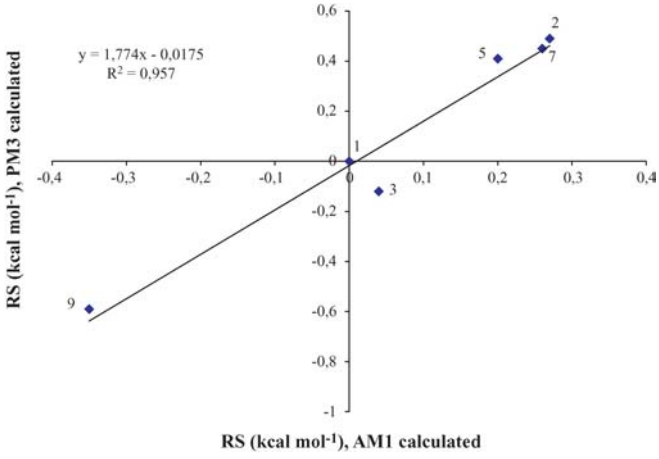


Fig. 2 The plot of AM1 calculated relative stabilities against PM3 calculated relative stabilities for *a*1 ⇌ *a*3 process for the studied molecules (**1–9**)

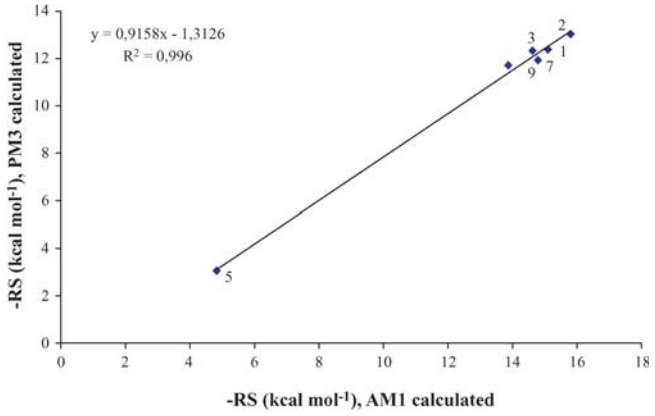


Fig. 3 The plot of AM1 calculated relative stabilities against PM3 calculated relative stabilities for $b1 \rightleftharpoons a1$ process for the studied molecules **(1–9)**

tion over the whole ring. All these observations fit well with the literature. [13]

Conclusion

It seems that the AM1 and PM3 aqueous phase calculations may let us predict the possible tautomeric form in neutral solutions, which may provide invaluable knowledge about the structure and activity of the substituted benzimidazoles for planning syntheses to use for a specific purpose. An attempt to compare the success of the two methods by searching a correlation between the AM1 and PM3 data revealed that in most cases there exists a perfect correlation with a regression of around unity (i.e. $R^2 \cong 1$) (see Figs. 1, 2, 3), which in turn indicates that only one of the methods of AM1 or PM3 can safely be used in such research, and the molecules that deviate (such as **4**, **6** and **8**) behave abnormally due to the substituents.

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