Influence of Substituent on Tautomeric Equilibrium Constant in 5(6)-Substituted Benzimidazoles in the Gas Phase†

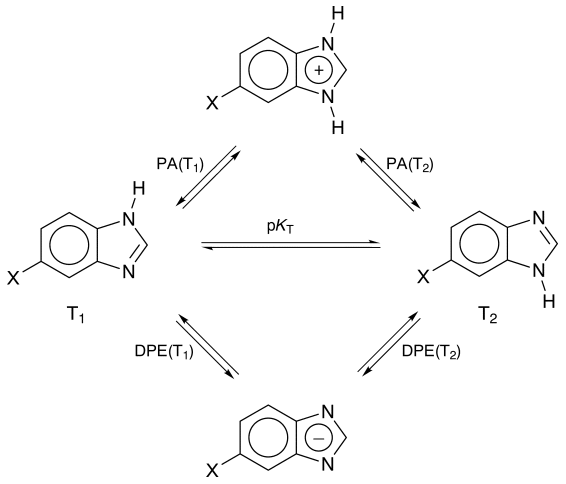
J. Chem. Research (S), 1998, 704–705†

Ewa D. Raczyńska

Institute of General Chemistry, Agricultural University, 02528 Warszawa, Poland

For 5(6)-substituted benzimidazoles, for which direct intramolecular interactions between the amidine moiety and substituent are absent, the pK_T values calculated by the AM1 method are well reproduced by differences in the transmission of substituent electronic effects: $pK_T = (5.08 \pm 0.22)\Delta\sigma + (0.00 \pm 0.01)$; these differences result mainly from different transmission of resonance effect: $pK_T = (0.04 \pm 0.12)\sigma_\alpha - (0.36 \pm 0.10)\sigma_F - (1.76 \pm 0.30)\sigma_R + (0.00 \pm 0.06)$.

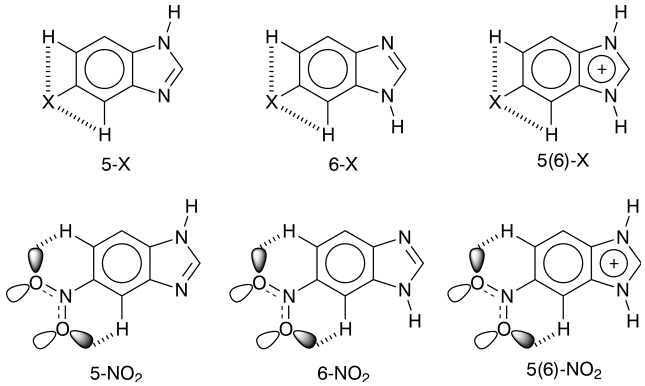
Although it is well known that compounds containing the amidine moiety (–NH–CR=N–) display prototropic tautomerism[1,2] investigations on the acid–base and tautomeric equilibria by experimental methods are exceptionally difficult, because tautomerisation is a very fast reaction.[3] Fortunately, theoretical methods permit us to study separately for each tautomer its structure and physicochemical properties. Recently, Austin Model 1 (AM1)[4] has successfully been applied to the prediction of tautomeric equilibrium constants (pK_T) in cyclic amidine systems.[5–8] Due to intramolecular interactions between the amidine moiety and substituent exceptionally high pK_T values have been observed for 4(5)-substituted imidazoles containing heteroatom(s) and/or π electrons in the substituent.[7]



Scheme 1

To eliminate these direct interactions, AM1 calculations have been performed for 5(6)-substituted benzimidazoles (Scheme 1). For our investigations, derivatives with X = H, Me, F, Cl, C≡CH, CN and NO_2 have been chosen, for which rotational isomerism is not possible or has no significant influence on the pK_T. Moreover the intramolecular interactions between substituent X and the CH group in the phenyl ring possible for derivatives with heteroatom(s) and/or π electrons are the same for the neutral (T_1 and T_2) and protonated forms even in the case of the nitro derivative, for which these interactions are considerably higher (Scheme 2). They have no direct effect on the tautomerizing amidine moiety in the imidazole ring. Therefore the influence of substituent electronic effects on the pK_T can be observed.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 2

Aci-nitro forms possible for nitro derivatives have not been considered in the general scheme of acid–base and tautomeric equilibria, because their ΔH_f° values are higher by 30–50 kcal mol^{-1} than those of tautomeric forms T_1 and T_2 given in Scheme 1. So large differences in the ΔH_f° values indicate that the percentage content of *aci*-nitro forms in the tautomeric mixture is less than 1×10^{-20}%.

For our calculations the same program and procedure as previously described[6,7,9] were used. ΔH_f°, PA and DPE values obtained are the summarised in Table 1. The PA calculated for unsubstituted derivative (224.1 kcal mol^{-1}) is close to the experimental one[10] (227 kcal mol^{-1}) with an error (2.9 kcal mol^{-1}) smaller than the average error of the AM1 method for nitrogen bases ($\pm$5.8 kcal mol^{-1}).[9]

The pK_T values resulting from the difference between the basicity or acidity parameters of T_1 and T_2 were calculated from eqn. (1) in which it was assumed that the $T\Delta S$ term for the proton-transfer reactions is the same for T_1 and T_2 and thus can be neglected.[7]

$$1.3643pK_T = \Delta H_f^\circ(T_1) - \Delta H_f^\circ(T_2) \quad (1)$$

The calculated pK_T values are given in Table 2. For the nitro derivative MINDO/3 calculations[11] give almost the same results ($pK_T = -0.26$, 65% of 5- and 35% of 6-isomer) as AM1. Calculations show that for 5(6)-substituted benzimidazoles both tautomers are present in the tautomeric mixture in quantities which may be detected experimentally. Unfortunately, there are no experimental data in the literature for tautomerizing benzimidazoles in the gas phase, and no comparison can be made. Only gas-phase basicities were measured for unsubstituted and non-tautomerizing 1- and 2-substituted benzimidazoles.[10,12]

In solution, the pK_T values estimated by direct (NMR) and indirect (basicity measurements) methods for Me, Cl and NO_2 derivatives are close to zero.[1,13–16] The thermodynamic stability of tautomer T_1 is almost the same as T_2, similarly to what has been found in the gas phase. This

Table 1 Heats of formation (ΔH_f°), proton affinities (PA) and deprotonation enthalpies (DPE) calculated at the AM1 level in the gas phase for 5(6)-substituted benzimidazoles and their ions given in Scheme 1 (in kcal mol^{-1}, 1 cal = 4.184 J)

	ΔH_f°/kcal mol^{-1}				PA/kcal mol^{-1}		DPE/kcal mol^{-1}	
X	T_1	T_2	Cation	Anion	T_1	T_2	T_1	T_2
H	66.9		210.0	39.4	224.1		340.0	
Me	59.4	59.3	201.2	31.9	225.4	225.3	339.7	339.8
F	22.3	21.8	169.1	−10.4	220.3	219.9	334.6	335.0
Cl	60.1	60.0	206.4	27.1	221.5	221.4	334.2	334.3
C≡CH	121.5	121.6	265.1	89.6	223.6	223.7	335.2	335.2
CN	98.2	98.5	248.6	60.4	216.9	217.1	329.4	329.1
NO_2	70.1	70.5	226.2	25.1	211.1	211.5	322.2	321.8

Table 2 Tautomeric equilibrium constants (pK_T) and percentage contents of each tautomer for 5(6)-substituted benzimidazoles

X	pK_T	% (T_1)	% (T_2)
H	0	50	50
Me	0.08	46	54
F	0.33	32	68
Cl	0.08	46	54
C≡CH	−0.04	52	48
CN	−0.21	62	38
NO_2	−0.29	66	34

suggests that the solvation of the amidine group and substituent has no important influence on the pK_T values. To confirm this suggestion the respective analysis of substituent and solvation effects should be performed. However there are not enough data to perform this kind of analysis.

The calculated pK_T values reproduce well the general rule of the basicity/acidity method. The tautomer which has smaller basicity (smaller PA value) and smaller acidity (higher DPE value) predominates in the tautomeric mixture. The T_1 with substituent X in the 5-position (*meta*-position to the site of protonation and *para*-position to the site of deprotonation) is preferred for C≡CH, CN and NO_2 derivatives, and the T_2 with substituent in the 6-position (*para*-position to the site of protonation and *meta*-position to the site of deprotonation) is slightly favoured for Me and halogen derivatives. This is in good agreement with the differences between the gas-phase substituent constants σ_m and σ_p proposed by Taft and co-workers.[17] The $\Delta\sigma$ values ($\Delta\sigma = \sigma_m - \sigma_p$) are positive for the resonance electron donating groups: Me (0.02), F (0.06) and Cl (0.02), and they are negative for the resonance electron accepting groups: CN (−0.04) and NO_2 (−0.06). The calculated pK_T values correlate well with the $\Delta\sigma$ values. The following regression line is found ($n = 6$, $r = 0.996$, $s = 0.02$):

$$pK_T = (5.08 \pm 0.22)\Delta\sigma + (0.00 \pm 0.01) \quad (2)$$

This means that for 5(6)-substituted benzimidazoles, in which extra intramolecular interactions with the tautomerizing amidine moiety are absent, the pK_T values are well reproduced by the differences in the transmission of electronic effects of the substituent in the 5- and 6-position. To find which partial substituent effects, polarizability, field/inductive and/or resonance effect, is more important, quantitative analysis based on the equation proposed by Taft and Topsom[18] has been performed. The following regression line is found ($n = 7$, $r = 0.974$, $s = 0.065$):

$$pK_T = (0.04 \pm 0.12)\sigma_\alpha - (0.36 \pm 0.10)\sigma_F - (1.76 \pm 0.30)\sigma_R + (0.00 \pm 0.06) \quad (3)$$

The pK_T values result mainly from the different transmission of the substituent resonance effect from 5- and 6-position. The calculated ρ_R (1.76) is about five times higher than the ρ_F (0.36). The transmission of the substituent polarizability effect is the same for both positions and has no influence on the pK_T values. The ρ_α (0.04) is close to zero and thus can be neglected in eqn. (3).

In the case of 4(5)-substituted imidazoles containing substituents in the '*ortho*-position' to the site of protonation (4-substituted derivatives) or in the '*ortho*-position' to the site of deprotonation (5-substituted derivatives) the substituent field/inductive effect is found to be a very important contribution to pK_T.[7] For derivatives without extra intramolecular interactions the pK_T values depend mainly on the substituent polarizability and field/inductive effects [see eqn. (9)(a) in ref. 7]. This means that for substituents in the '*ortho*-position' to the site of protonation or deprotonation in imidazoles the transmission of the substituent resonance effect is almost the same and has only a slight influence on the pK_T values.

Received, 6th April 1998; Accepted, 9th July 1998
Paper E/8/02613K

References

1 J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, *The Tautomerism of Heterocycles*, Academic Press, New York, 1975.
2 G. Häfelinger and F. K. H. Kuske, in *The Chemistry of Amidines and Imidates*, ed. S. Patai and Z. Rappoport, Wiley, London, 1991, vol. 2, ch. 1.
3 R. Anulewicz, I. Wawer, T. M. Krygowski, F. Männle and H.-H. Limbach, *J. Am. Chem. Soc.*, 1997, **119**, 12223; and ref. 2–4 and 12–15 cited therein.
4 M. J. S. Dewar, E. G. Zoebish, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
5 M. M. Karelson, A. R. Katritzky, M. Szafran and M. C. Zerner, *J. Chem. Soc., Perkin Trans. 2*, 1990, 195.
6 E. D. Raczyńska, *Pol. J. Chem.*, 1996, **70**, 795.
7 E. D. Raczyńska, *Anal. Chim. Acta*, 1997, **348**, 431.
8 R. Gawinecki, E. D. Raczyńska, D. Rasala and S. Styrcz, *Tetrahedron*, 1997, **53**, 17211.
9 M. J. S. Dewar and K. M. Dieter, *J. Am. Chem. Soc.*, 1986, **108**, 8075.
10 S. G. Lias, J. E. Bartmess, J. L. Holmes, R. D. Levin, J. F. Liebman and W. G. Mallard, *J. Phys. Chem. Ref. Data*, 1988, **17**, suppl. 1.
11 V. A. Lopyrev, V. A. Bolotin, L. I. Larina and T. I. Vakul'skaya, *Zh. Strukt. Khim.*, 1984, **25**, 163.
12 J. Catalán, J. L. G. de Paz, M. Yáñez, R. M. Claramunt, C. López, J. Elguero, F. Anvia, J. H. Quian, M. Taagepera and R. W. Taft, *J. Am. Chem. Soc.*, 1990, **112**, 1303.
13 J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1960, 1363.
14 H. Walba, D. H. Stiggal and S. M. Coutts, *J. Org. Chem.*, 1967, **32**, 1954.
15 A. Fruchier, L. Pappalando and J. Elguero, *An. Quim., Ser. C*, 1980, **76**, 79.
16 J. W. Wiench, W. Bocian, L. Stefaniak and G. A. Webb, *Bull. Pol. Acad. Sci. Chem.*, 1995, **43**, 287.
17 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
18 R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, 1987, **16**, 1.