BASICITY AND STRUCTURE OF 5-HYDROXYBENZIMIDAZOLES IN NITROMETHANE

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Examination of the acid–base properties of 5-hydroxybenzimidazoles has shown them to exist in nitromethane as the 5-hydroxy-tautomers. Substituents in the 2-position have a predominantly inductive effect on the basicity of the 3-nitrogen, rationalized as in other nitrogen heterocycles by the proximity of the substituents to the reaction center.

Keywords: 5-hydroxybenzimidazole, its tautomers and derivatives; acid-base properties and the effect thereon of substituents; Taft and inductive constants.

Substituted 5-hydroxybenzimidazoles have received little attention, so that there is virtually no information on their acid–base properties [1].

Studies of electrophilic substitution in 5-hydroxybenzimidazoles [2-6], and reports of their potential value as synthetic antioxidants and plant growth regulants [7, 8], justify a study of the acid–base properties of these compounds.

The basicity of substituted 5-hydroxybenzimidazoles has been measured in nitromethane, in which the pK_{BH^+} values of many aliphatic, aromatic, and heterocyclic nitrogen bases are known [9-11].

It will be seen from Table 1 that in nitromethane imidazole (1) is quite a strong base, $pK_{BH^+}(MeNO_2)$ = 14.34 (see the values for pyridine, 11.95 [13], pyrimidine 8.04 [13], aliphatic amines 15-18 [14]), although the basicity of benzimidazole (2) is some 1.7 pK units lower as a result of the influence of the annelated benzene ring.

TABLE 1. Basicities in Nitromethane of Imidazole, Benzimidazole, and Substituted 5-Hydroxybenzimidazole

Compound	$pK_{BH^+}(MeNO_2)$	$pK_{BH^+}(H_2O)$
Imidazole (1)	14.64 *	7.00; 7.25 [1]
Benzimidazole (2)	12.92 *	5.53 [1]
5-Hydroxybenzimidazole (3)	12.96	–
2-Methyl-5-hydroxybenzimidazole (4)	14.02	–
1-Ethyl-2-methyl-5-hydroxybenzimidazole (5)	14.55	–
2-Phenyl-5-hydroxybenzimidazole (6)	12.52	–
2-Benzyl-5-hydroxybenzimidazole (7)	13.28	–

*After statistical correction for the presence of two identical deprotonation centers in the BH^+ cation [12]; the experimental $pK_{BH^+}(MeNO_2)$ values are 0.3 pK units smaller.

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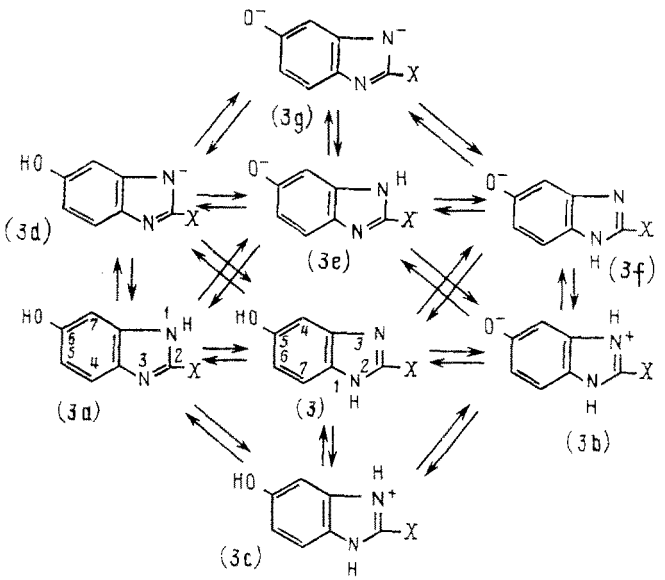
We now consider the possible existence of keto- (zwitterionic) forms (3b) of 5-hydroxybenzimidazoles in nitromethane (diagram 3 ⇄ 3a ⇄ 3b). The tautomeric composition of 5-hydroxybenzimidazoles is unknown, but it has been reported [1] that the isomeric 2-hydroxybenzimidazole exists in water as benzimidazol-2-one (the keto-form). The impossibility of hydrogen bonding with the C=O group in the keto-form results in a shift in the keto–enol equilibrium in azaheterocycles in nitromethane towards the hydroxy forms. For example, in the case of 3-hydroxypyridine the tautomeric constant K_t, the ratio [hydroxy form]/(zwitterionic form], is some four times greater in nitromethane than in water, the $K_t(MeNO_2)$ value being ∿4 [9].

Tautomeric Equilibrium of 5-Hydroxybenzimidazole in Various States of Protonation (the tautomeric forms which predominate in nitromethane are underlined).



It may be assumed that 5-hydroxybenzimidazoles exist in nitromethane predominantly in the hydroxy-form (3, 3a). The normal shape of the titration plots for these 5-hydroxybenzimidazoles, indicating protonation at nitrogen,† confirms this assumption.

As for tautomerism due to shift of a proton between N^1 and N^3, it is believed [1] that the value of K_t in substituted benzimidazoles must be close to unity. However, the 5-hydroxybenzimidazoles 3 ⇄ 3a probably exist as the 5-hydroxy tautomers (3), since in the anion (which according to the information given above must exist in the hydroxy form (3a) rather than the zwitterionic forms (3f, 3g)), the electron donor hydroxy group is conjugated with the para-nitorgen atom which on adding a proton gives tautomer (3). This conclusion is in agreement with the absence of an electron donor effect of the 5-hydroxy group in benzimidazol (Table 1, compounds (2) and (3); cf. the effects of the hydroxy group on the basicity of the –N= atom in the 6- and 5-hydroxy tautomers (3a) and (3)). The postulated existence of 5-hydroxybenzimidazoles as the 5-hydroxy tautomers (3) is supported by the small (0.5 pK units) increase in basicity (as a result of the effects of the ethyl group) on passing from the potentially tautomeric 2-methyl-5-hydroxybenzimidazole (3 ⇄ 3a, X = Me) to its fixed 5-hydroxy tautomer, 1-ethyl-2-methyl-5-hydroxybenzimidazole (5).

†In the zwitterionic form of 5-hydroxybenzimidazoles (3b), the oxygen atom is protonated, resulting in distortion of the shape of the titration plots (see [9]).

The effects of substituents in the 2-position on the basicity of 5-hydroxybenzimidazole (3) are as expected (Table 1), the methyl group (4) considerably increasing, and the phenyl group slightly decreasing, the basicity of N6, the benzyl group (7) having an intermediate effect.

When constructing plots of the basicity of 2-substituted 5-hydroxybenzimidazoles (3), where X = Me, Ph, or Bzl against the inductive substituents, the best correlations were obtained using the Taft constant σ* [15], $pK_{BH^+}(MeNO_2) = 13.94 - 2.27\sigma^*$, r 0.976, s 0.17.

The predominant inductive effects of 2-substituents in 5-hydroxybenzimidazole are due to their steric proximity to the reaction center (the heterocyclic N); 2-substituents in pyridine and sym-triazine have similar effects [10].

EXPERIMENTAL

The acid–base properties of imidazole and benzimidazoles in nitromethane were determined by potentiometric titration using glass and calomel electrodes [10].

The PMR spectra of the compounds were obtained on a Varian T-60 spectrometer, the chemical shifts being given from TMS.

1-Ethyl-2-methyl-5-hydroxybenzimidazole (5). A solution of 120 g (0.54 mole) of 2-nitro-4-ethoxyacetanilide (8) in 400 ml of conc. HCl was boiled for 2 h, cooled, poured into 1.5 liters of ice and water, and the precipitate washed with water, dried, and dissolved in 300 ml of pyridine. Toluene-p-sulfonyl chloride (104.86 g, 0.55 mole) was added portionwise, and the mixture stirred for 2.5 h at 100°C. The cooled solution was acidified with 2N HCl, and the solid separated, washed with water, dried, and added to a solution of 20 g of sodium in 500 ml of alcohol, followed by the dropwise addition of 200 ml (2.48 mole) of ethyl iodide. The mixture was boiled for 4 h, cooled, and the solid which separated filtered off, washed with alcohol, dried, and gradually added to 250 ml of sulfuric acid (d = 1.84). After stirring for 2 h at 100°C, the cooled solution was poured on to ice, and the solid filtered off, washed with water, dried, dissolved in one liter of alcohol, and 120 ml of aqueous hydrazine hydrate added. Raney nickel (7-8 g) was then added over 2 h at 70-80°C, the solution filtered, evaporated to dryness, and the residue added to a mixture of 300 ml of water, 200 ml of conc. HCl, and 150 ml of acetic acid. After boiling for 2 h, the solvent was removed to dryness, the residue dissolved in 150 ml of water, boiled with charcoal, filtered, and treated with aqueous ammonia to pH 7.5-8.0. The solid which separated was filtered off, washed with water, dried, and boiled for 10 h in 250 ml of hydrobromic acid, the solvent removed by distillation, and the residue recrystallized from water with charcoal.

Yield of (5), 21.65 g (22.75%), mp 260-261°C. PMR spectrum (CD_3OD, δ, ppm): 7.11 d (1H, H^7), 6.58 d.d (1H, H^6), 6.42 d (1H, H^4), 4.25 q (2H, CH_2(Et)), 2.85 s (3H, CH_3), 1.46 t (3H, CH_3(Et)). Found: C 68.35; H 6.76%. $C_{10}H_{12}N_2O$. Calculated: C 68.15; H 6.88%.

2-Phenyl-5-hydroxybenzimidazole (6). A solution of 50 g (0.22 mole) of (8) in 200 ml of conc. HCl was boiled for 2 h, cooled, poured into 0.75 liter of water and ice, the solid which separated washed with water, dried, and dissolved in 200 ml of alcohol. The solution was treated with 50 ml of hydrazine hydrate, followed by 8-10 g of Raney nickel over 5 h at 60-70°C. The solution was filtered, the residue was dissolved by heating in 150 ml of conc. HCl and cooled, the solid was isolated, dried, dissoved in 100 ml of water, boiled with charcoal, filtered, and neutralized with NaOH solution to pH 6.0-6.5. The solid which separated was filtered off, washed with water, dried, and fused with 21.8 g (0.17 mole) of benzoic acid in a sealed ampul with shaking for 6 h at 175-180°C. The resulting material was dissolved in 350 ml of alcohol, 200 ml of conc. HCl added, boiled, and the solid which separated on cooling was isolated, washed with water, dried, boiled with 250 ml of hydrobromic acid for 20 h, the solvent removed to dryness, the residue boiled in one liter of water with charcoal, and filtered. The cooled mother liquors were neutralized with NaOH solution to pH 5.5-6.0, and the solid which separated filtered off washed with water, dried, and recrystallized from aqueous alcohol to give 5.66 g (12.23%) of (6), mp 261-263°C. PMR spectrum (DMSO-d_6, δ, ppm): 8.18 m (2H, Ph), 7.52 m (3H, Ph), 7.47 d (1H, H^7), 7.04 d (1H, H^4), 6.82 d.d (1H, H^6). Found: C 74.52; H 6.22%. $C_{13}H_{10}N_2O$. Calculated: C 74.26; H 6.45%.

2-Benzyl-5-hydroxybenzimidazole (7). Obtained as for (6), from 50 g (0.22 mole) of (8), reduced to 2-amino-4-ethoxyacetanilide, followed by fusion in vacuo with 23.14 g (0.17 mole) of phenylacetic acid. Yield of (7) 12.25 g (24.82%), mp 184-184.5°C. PMR spectrum

(DMSO-d_6, δ, ppm): 7.10-7.40 m (5H, Bzl), 7.30 d (1H, H^7), 6.79 d (1H, H^4), 6.59 d.d (1H, H^6, 4.10 s (2H, Bzl). Found: C 74.76; H 5.28%. $C_{14}H_{12}N_2O$. Calculated: C 74.97; H 5.40%.

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