Determination of Thermodynamic Aqueous Acid–Base Stability Constants for Several Benzimidazole Derivatives

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In conjunction with a study of compounds for laboratory instruction in nonaqueous quantitative analysis, we became interested in using a series of substituted benzimidazoles as weak bases for titration by perchloric acid in glacial acetic acid. For this purpose the acid–base stability constants of several commercially available derivatives were needed. Acid dissociation constants for several protonated benzimidazoles have been reported, some measured in water and others in 50% by volume aqueous ethanol, by Davies and co-workers (*1*), but the data were incomplete. We report here the determination of thermodynamic pK_b values in water for benzimidazole and its 2-phenyl, 5-nitro, 2-methyl, and 5,6-dimethyl derivatives.

Experimental Section

Reagents. Benzimidazole, 2-phenylbenzimidazole, 5-nitrobenzimidazole, 2-methylbenzimidazole, and 5,6-dimethylbenzimidazole (Aldrich Chemical) were recrystallized three or more times from 1:1 by volume methanol/water. Purity was tested by melting point determination and by duplicate potentiometric titrations with perchloric acid in glacial acetic acid as solvent. The potentiometric titrations were performed on a computer-controlled automatic gravimetric titrator incorporating a Fisher Model 825MP Accumet pH meter, a Mettler AE 160 balance reading to the nearest 0.1 mg, and an Apple II+ microcomputer. The aqueous KCl filling solution in the calomel reference electrode was replaced by a solution of glacial acetic acid saturated with NaCl and $NaClO_4$ as described by Kolthoff and Bruckenstein (*2*). The precision of the titrator in standardization titrations against potassium hydrogen phthalate was ±0.1 to ±0.2% relative; the precision for titrations of the substituted benzimidazoles was ±0.1 to ±0.4% relative. Results of the purity studies were the following (all percentages reported as mass fractions × 100): benzimidazole, mp found 170 °C, lit. 170–172 °C (*3*); purity by titration 98.9%; 2-phenylbenzimidazole, mp found 291, lit. 290 (*3*), purity by titration 99.1%; 2-methylbenzimidazole, mp found 175–177, lit. 178.5 (*4*), purity by titration 99.7%; 5-nitrobenzimidazole, mp found 206–208, lit. 204–206 (*5*), purity by titration 98.8%; 5,6-dimethylbenzimidazole, mp found 203–204, lit. 204–205 (*3*), purity by titration 99.3%. All other chemicals used were reagent grade or better. Demineralized distilled water was used throughout.

Apparatus. For the pK measurements all pH values were obtained with a Fisher Model 825MP pH meter using a glass–calomel electrode pair calibrated prior to each experiment against two standard buffers, 0.05 M potassium hydrogen phthalate (pH 4.00 at 25 °C) and 0.05 M potassium hydrogen phosphate–sodium hydroxide (pH 7.00 at 25 °C). Spectra were recorded on a Hewlett-Packard 8451A diode array spectrophotometer in 1-cm silica cells thermostated at 25 ± 0.2 °C with a Lauda/Brinkmann Model K4R circulator.

Procedure. For each compound two sets of four solutions were prepared, one set to determine the pK at an ionic strength of 0.1 M and the other at an ionic strength of 0.05 M. For ionic strength 0.1 M the set of four solutions comprised (a) 0.1 g of benzimidazole or derivative dissolved in 30 mL of glacial acetic acid and diluted to 500 mL with water, (b) 1 M perchloric acid in water, (c) 1 M sodium perchlorate in water, and (d) 1 M ammonia in water. For ionic strength 0.05 M the set consisted of (a) 0.1 g of benzimidazole or derivative dissolved in 15 mL of glacial acetic acid and diluted to 500 mL with water, (b) 0.5 M perchloric acid in water, (c) 0.5 M sodium perchlorate in water, and (d) 0.5 M ammonia in water. For each ionic strength a series of solutions ranging in pH from 1 to 10 were prepared by combinations of the four solutions. The sodium perchlorate solution was used to adjust the ionic strength to the value required on dilution to 100 mL with water. The amount of acetic acid used was the minimum required for dissolution of the benzimidazole compounds. The quantity of acetic acid/acetate present in each of the solutions used for the measurements was of the order of 1% or less by volume in all cases. A few measurements were also made at an ionic strength of 0.02 M by dilution of the solutions prepared for set 2.

For each solution the pH was measured, and then a spectrum was recorded over the wavelength region 240–300 nm. This region included the wavelengths of maximum absorption for the benzimidazole derivatives but did not include any measurable absorption by either acetic acid or acetate ion. Wavelengths of maximum absorption for the protonated and unprotonated forms of each benzimidazole derivative were determined from spectra of solutions at pH 1 and 10, where it had been previously shown by a set of pH vs absorbance studies that the derivatives were all completely converted to their respective protonated or unprotonated forms. Absorbances at the wavelengths of maximum absorption were then determined for a series of solutions of intermediate pH.

Since the total absorbance (A_t) at each wavelength is equal to the sum of the absorbances of the acidic (A_a) and basic (A_b) forms, then

$$A_t = A_a + A_b = \epsilon_a b c_a + \epsilon_b b c_b \quad (1)$$

where ϵ, b, and c represent molar absorptivity, solution path length, and concentration. Also, the total concentration (c_t) of the compound is equal to the sum of the concentrations of the acidic (c_a) and basic (c_b) forms:

$$c_t = c_a + c_b \quad (2)$$

With knowledge of the total absorbance and molar absorptivity at each wavelength, and the total concentration of the compound, eqs 1 and 2 can be solved simultaneously to give c_a and c_b. Then

$$pK_a = pH + \log(c_a/c_b) \quad (3)$$

In all cases the experiments were repeated on independent solutions on separate days.

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Table I. pK_a Values for Substituted Benzimidazoles as a Function of Ionic Strength I at 25 ± 0.2 °C As Determined by UV Spectrophotometry: Replicate Values Obtained from Measurements on Independent Solutions on Separate Days

	I = 0.02 M	I = 0.05 M	I = 0.10 M
benzimidazole	5.47 ± 0.09 (7)[a]	5.55 ± 0.14 (5)	5.69 ± 0.17 (4)
	5.45 ± 0.09 (9)	5.52 ± 0.17 (9)	5.62 ± 0.12 (10)
2-methylbenz-imidazole	6.13 ± 0.20 (8)	6.16 ± 0.02 (6)	6.21 ± 0.04 (8)
	6.14 ± 0.11 (8)	6.16 ± 0.13 (6)	6.26 ± 0.12 (9)
5,6-dimethyl-benzimidazole	5.93 ± 0.07 (9)	5.97 ± 0.13 (9)	6.03 ± 0.14 (8)
	5.92 ± 0.10 (8)	5.99 ± 0.21 (9)	6.10 ± 0.08 (8)
5-nitrobenz-imidazole		4.27 ± 0.18 (8)	4.30 ± 0.18 (8)
		4.24 ± 0.21 (10)	4.39 ± 0.20 (11)
2-phenylbenz-imidazole		5.14 ± 0.26 (6)	5.36 ± 0.07 (4)
		5.12 ± 0.10 (9)	5.20 ± 0.25 (9)

[a] Uncertainties are standard deviations based on the number of spectral points (given in parentheses) used in eq 3 for a given solution series.

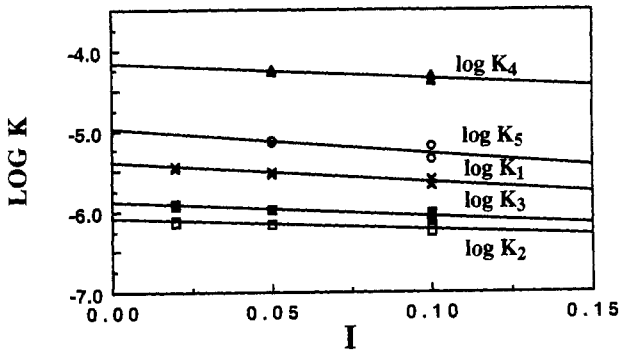

Figure 1. log K against ionic strength for benzimidazole and derivatives: log K_1, benzimidazole; log K_2, 2-methylbenzimidazole; log K_3, 5,6-dimethylbenzimidazole; log K_4, 5-nitrobenzimidazole; log K_5, 2-phenylbenzimidazole.

Results and Discussion

Preliminary experiments were carried out on compounds of similar basicity but sufficiently soluble in water that their pK_a values could be determined without the addition of acetic acid. The results of these measurements showed that solutions containing acetic acid at the level of 1% by volume gave results that fell within experimental error of those obtained without acetic acid present. Therefore, we conclude that the small amount of acetic acid or acetate present in these solutions had a negligible effect on the pK determinations. However, since acetic acid and acetate absorb in the wavelength region of 200–230 nm, all absorbance data used here were obtained in the wavelength range of 240–300 nm. This did not present any difficulties.

Results of the experimental measurements are presented as pK_a values in Table I.

Calculation of Thermodynamic Equilibration Constants. A number of techniques for extrapolation to zero ionic strength to yield thermodynamic acid dissociation constants have been suggested over the years. In this study we compared values obtained by plots of log K against ionic strength I with those obtained by log K against the square root of ionic strength. The plots, shown in Figures 1 and 2,are more nearly linear when I is used instead of $\sqrt{I}$, and the values obtained agree more closely with literature values where available. The thermodynamic values obtained from extrapolation of these plots to zero ionic strength are given in Table II. Note the larger uncertainties in the plots using $\sqrt{I}$.

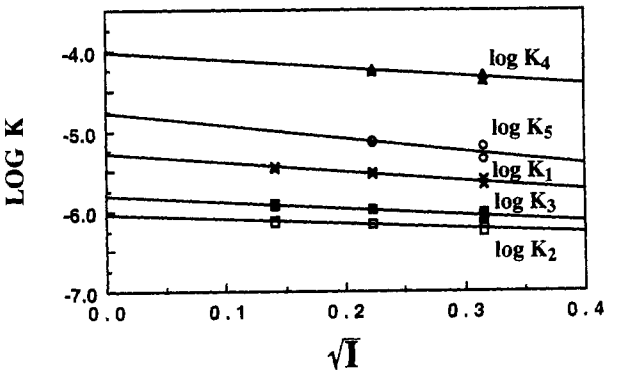

Figure 2. log K against the square root of ionic strength for benzimidazole and derivatives: log K_1, benzimidazole; log K_2, 2-methylbenzimidazole; log K_3, 5,6-dimethylbenzimidazole; log K_4, 5-nitrobenzimidazole; log K_5, 2-phenylbenzimidazole.

Table II. Thermodynamic pK_a Values for Benzimidazole and Substituted Benzimidazoles As Determined Spectrophotometrically in Aqueous Acetic Acid at 25 °C by Extrapolation from Figures 1 and 2[a]

	pK_a value	
	log K_a ($I \rightarrow 0$)	log K_a ($\sqrt{I} \rightarrow 0$)
benzimidazole	5.41 ± 0.02	5.30 ± 0.04
2-methylbenzimidazole	6.10 ± 0.02	6.05 ± 0.03
5,6-dimethylbenzimidazole	5.89 ± 0.02	5.81 ± 0.04
5-nitrobenzimidazole	4.17 ± 0.07	4.04 ± 0.14
2-phenylbenzimidazole	4.98 ± 0.12	4.77 ± 0.24

[a] Uncertainties are 1 Standard Error of the Mean (standard deviation/$\sqrt{n}$).

Summary. Thermodynamic acid dissociation constants were determined for several substituted benzimidazoles. It was shown that use of up to 1% by volume glacial acetic acid to aid in dissolution did not produce concentrations of acetic acid or acetate sufficient to affect to a detectable degree the accuracy or precision of the results. When extrapolating data at differing ionic strengths to $I = 0$ to obtain thermodynamic constants, plots of log K against I were found to give better precision and accuracy than plots of log K against $\sqrt{I}$.

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