Photometric Study of the Prototropic Constant of the Anion of 2-Hydroxymethylbenzimidazole[1]

Harold Walba, Wallace J. Murray,[2] Gaylen Knutson,[2] and Arthur Diaz[2]

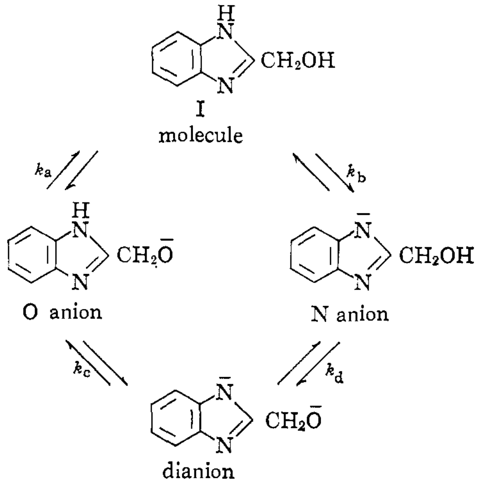
Contribution from the Department of Chemistry, San Diego State College, San Diego, California 92115. *Received November 8, 1965*

Abstract: Evidence is presented that the anion of 2-hydroxymethylbenzimidazole (I) is measurably prototropic with its N anion predominating over its O anion. The prototropic constant is 4.3 ± 0.5. The constant was obtained from ultraviolet spectra and independently from acidity–basicity constants, both experimental and estimated. Model compounds used in the study are benzimidazole and its 1-methyl, 2-methyl, and 2-methoxymethyl derivatives. Presented and in part interpreted are the ultraviolet spectra of the neutral molecules, cations, and anions of I and model compounds. Also given are the acidity constants of the cations and the hydrolysis constants of the anions of I and model compounds. The two dissociation constants of the diprotic compound I are found to overlap. Macroconstants are obtained by successive approximations. Microconstants are obtained from the macroconstants and the prototropic constant. The microhydrolysis constant of the O anion and the known ρ^* for the series RCH_2OH permit a secondary σ^* of 2.0 to be obtained for the strong electron-attracting 2-benzimidazolyl group. The spectrum of the neutral molecule of indole is found to give insight into the probable nature of the spectrum of the anion of benzimidazole and many of its derivatives.

While investigating acid–base equilibria of amphoteric 2-substituted benzimidazoles photometrically we became especially interested in 2-hydroxymethylbenzimidazole (I). Interest was engendered by previous work on the acidity of benzimidazole[3] and N-methyl-2-hydroxymethylbenzimidazole[4] (II). The earlier work showed that the acidity constants of these two compounds were not too far separated and that a quantitative measure of a novel type of tautomerism in the anion of compound I might be obtained. Although tautomeric measurements involving the shift of a proton between a cyclic nitrogen and a phenolic type oxygen, or oxygen attached to a sp^2-hybridized ring carbon, are known,[5] we know of no quantitative measure of prototropy between a ring nitrogen and an alcoholic oxygen, or oxygen attached to an sp^3-hybridized carbon. To obtain such a measure in the anion of compound I was the main goal of this work.

Since compound I is diprotic the proximity of its two stages of dissociation is of experimental concern. Pertinent relationships are shown in Scheme I. Reported values[4,6–8] for the acidity of compound I and related compounds assume that dianion formation may be neglected. Further it has been assumed that in the first stage of dissociation the O anion–N anion ratio is sufficiently high that equilibrium k_b may be neglected. In this paper it will be demonstrated that both of these assumptions are in error. However, neglect of the second stage of dissociation does not result in as serious an error as neglect of equilibrium k_b.

Scheme I. The Dissociation Scheme of 2-Hydroxymethylbenzimidazole



The prototropic constant of the anion of compound I is obtained from spectra and independently from acidity constant data.[9] As model compounds N-methylbenzimidazole (II), 2-methoxymethylbenzimidazole (III), and 2-methylbenzimidazole (IV) are utilized.

The spectra of the just mentioned compounds and their ions, positive and negative, as well as the spectra of benzimidazole and its ions are of theoretical interest. These spectra are reported and discussed. Of particular interest is the correlation of the spectrum of the anion of benzimidazole and the iso-π-electronic neutral molecule of indole. Also worthy of note is the effect of protonation and deprotonation on the spectra.

The prototropic constant coupled with the macroconstants determined for the first and second stages of dissociation allow the scheme in Scheme I to be unscrambled and the microconstants to be presented. One consequence is a Taft substituent constant (σ^*) for the 2-benzimidazolyl moiety.

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(2) Work performed as National Science Foundation Undergraduate Research Participants and in partial fulfillment of the requirements for the Bachelor of Science Degree in Chemistry.

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Experimental Section

Preparation of Compounds. All compounds were prepared by known methods and recrystallized to a constant melting point and constant ultraviolet spectrum. Compound I had mp 174–175° (lit[10] mp 171–172°). Compound II had mp 145–146° (lit[4,11] mp 143–144°). Compound III had mp 141–142° (lit[11] mp 136°). Compound IV had mp 180–181° (lit[12] mp 178.5–179.5°).

Spectral Data. All spectral curves reported were run in aqueous solution on a thermostated Cary Model 14 spectrophotometer. The temperature was controlled to 25.0 ± 0.2°. For compound I spectral data used for the composite basicity constants of the anion and dianion were obtained on a Cary Model 14. Data for the acidity constant of its cation were obtained on the Beckman Model DU. For compounds II, III, and IV, spectral data for all ionization constants were obtained on the Beckman DU as previously described.[3,13] Spectral curves of cations were run in 0.1 *N* HCl. Neutral molecules were run in pH 9 Borax buffer solution. Where alkaline solutions of total ionic strength 0.5 were used the additional electrolyte was NaCl.

Acidity Constants of the Cations. The acidity constants of the cations of compounds I, III, and IV were determined in the manner previously described,[13] except that a Beckman 1019 research pH meter was used for compounds I and III. The temperature of the solution was maintained at 25.0 ± 0.1° by measuring the pH of the solutions in a water-jacketed beaker.

Macroscopic Basicity Constants of the Anion and Dianion of Compound I. Let BH_2 represent compound I; BH^- then is the composite of the photometrically inseparable O anion and N anion and B^{2-} is the dianion. The equation for the concentration macrobasicity or macrohydrolysis constant, K_1, of the composite monoanion is

$$K_1 = [OH][BH_2]/[BH^-] \qquad (1)$$

and the macroconstant, K_2, for the hydrolysis of the dianion is

$$K_2 = [OH][BH^-]/[B^{2-}] \qquad (2)$$

It is readily shown that

$$1/K_1 = 1/k_a + 1/k_b \qquad (3)$$

where k_a = [OH][I]/[O anion] and k_b = [OH][I]/[N anion] and

$$K_2 = k_c + k_d \qquad (4)$$

where k_c = [OH][O anion]/[B^{2-}] and k_d = [OH][N anion]/[B^{2-}]. The equilibria tied to these relationships between macroconstants, K_i, and microconstants, k_i, are shown schematically in Scheme I with the omission of OH, the hydroxide ion. Since the O and N anions are not independently obtainable using the photometric method, microconstants may not be determined directly. The macroconstants may, however, be determined by simple procedures if the macroconstants are sufficiently separated ($K_2/K_1 > 1000$), and if, at a given wavelength, the molar absorptivities of the neutral molecule, the composite anion, and the dianion are adequately separated. Experiment shows that a region may be found where the separation of the curves is adequate. However, the macroconstants are not sufficiently separated. In Figure 1 we have a sampling of 26 curves spaced between pH 9 and 18.3 *M*. We note that between pH 9 and 0.5 *M* OH there is a sharp isosbestic point at 255 mμ due to the neutral molecule and the composite anion. However, the curve for the composite anion does not achieve constancy and between 0.5 and 4 *M* OH a new isosbestic point appears at 273.5 mμ. The second isosbestic point is due to the composite anion and the dianion. Above 4 *M* a lateral red shift attributable to a medium effect is observed for the spectral curves. From 4 to 18.3 *M* the curve shifts laterally about 3 mμ. If one adjusts the high [OH] curves to the isosbestic point at 273.5 it appears that the 18.3 *M* curve is close to the curve of the dianion though constancy has not quite been achieved. Thus, inability to obtain directly the molar absorptivities of the composite anion, because of overlap of macroconstants, and the dianion, because of its high base strength, requires that special procedures be used if we are to calculate the macroconstants.

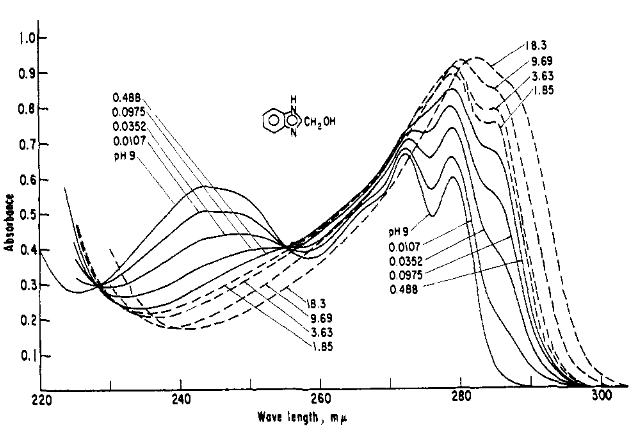

Figure 1. Variation of the spectrum of compound I with varying hydroxide ion concentration. Solid lines for solutions having [OH] < 0.5. Dashed lines for solutions having [OH] > 0.5. Numbers aside the curves indicate the molarity of the hydroxide ion.

In terms of absorbances eq 1 and 2 may be rewritten

$$K_1 = [OH]_a[A_t^- - A_a]/[A_a - A^0] \qquad (5)$$

$$K_2 = [OH]_c[A^{2-} - A_c]/[A_c - A_t^-] \qquad (6)$$

where A^0, A_t^-, and A^{2-} are the absorbances of the neutral molecule, the composite anion, and the dianion, respectively. Other absorbances are equilibrium values at the [OH] indicated by the subscripts. All absorbances are obtained at the same concentration of compound I or are adjusted by Beer's law. At low hydroxide ion concentrations the neutral molecule's spectrum is obtained virtually free of its cationic and anionic forms. Borax pH 9 buffer served to obtain A^0. However, because of overlap of the two stages of hydrolysis and incomplete ionization to the dianion at the highest hydroxide ion concentration practical, we are dealing with four unknowns. They are the two macroconstants, K_1 and K_2, and the absorbances of the composite anion and the dianion. Treatments of this type of problem in photometric determinations are known.[14–16]

For this case it was found convenient to calculate the macroconstants, K_1, K_2, and absorbances A_t^- and A^{2-} by successive approximations using as a starting point the method employed earlier by us for determining very weak acids in aqueous solution.[8,17] To employ this method four additional quantities are needed besides those shown in eq 5 and 6. They are two additional hydroxide ion concentrations and their accompanying absorbances, that is, $[OH]_b$, A_b, $[OH]_d$, and A_d. Thus, to solve for the four unknowns, a set of nine pieces of experimental information, the four [OH]'s and accompanying absorbances, and A^0 are necessary.

The two equations used to calculate A_t^- and A^{2-} in the first approximation are

$$A_t^- = [Q_1(A_a - A^0)A_b - (A_b - A^0)A_a]/[Q_1(A_a - A^0) - (A_b - A^0)] \qquad (7)$$

and

$$A^{2-} = [Q_2(A_c - A_t^-)A_d - (A_d - A_t^-)A_c]/[Q_2(A_c - A_t^-) - (A_d - A_t^-)] \qquad (8)$$

where $Q_1 = [OH]_b/[OH]_a$ and $Q_2 = [OH]_d/[OH]_c$.

For accuracy in the method of successive approximations $[OH]_a$ values close to the value of K_1 were used. Desirable $[OH]_b$ values are those that give a large conversion to the composite anion but relatively little dianion. The isosbestic point at 255 mμ, mainly characteristic of the first stage of hydrolysis measured by K_1, serves as a guide to choice of $[OH]_b$ values. Suitable $[OH]_c$ values may

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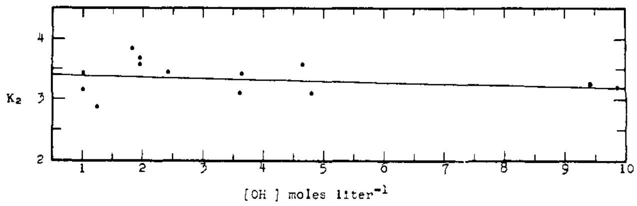

Figure 2. Plot of macroconstant K_2 *vs.* hydroxide ion concentration.

be obtained by trial. It is desirable to use the highest $[OH]_d$ practical.

In the ideal all measurements should be at constant ionic strength. This is not practical for all solutions but constant ionic strength of 0.5 was maintained for solutions having [OH] equal to or less than 0.5 *M*. At [OH] of 18.3 *M* compound I is not far from complete ionization to the dianion, and the method of successive approximations used does not lead to a serious error in A^{2-}. No serious error results since the accuracy of A^{2-} is dependent mainly on the accuracy of A_d and is not sensitive to the change in K_2 with change in ionic strength. For the sets of data used the calculation of K_2 on the other hand is sensitive to the ionic strength equal to $[OH]_c$. That, in the range of 2 to 5 *M* in hydroxide ion, K_2's are found to be within experimental error of one another may be a reflection in part of the small range; in part of the large experimental error, contributed to by small absorbance differences between the composite anion and the dianion curves; and in part of the not too great change in the activity coefficient factor relating K_2 to the thermodynamic constant for the hydrolysis of the dianion. The latter statement is illustrated by eq 12 given later in the Experimental Section. Errors are minimized by adjusting curves with the aid of the isosbestic point at 273.5 mμ, and by working in the 283- to 285-mμ region. For equilibrium solutions in this region readings are at a maximum or on a very shallow slope. Also in this region the accuracy of K_1 is aided by large absorbance differences between equilibrium solutions and solutions containing the neutral molecule.

Calculations. From A^0, $[OH]_a$, A_a, $[OH]_b$, A_b, and the use of eq 5 and 7 a first approximation for A_t^- and K_1 are calculated. Similarly, A_t^-, just obtained in the first approximation of this quantity, $[OH]_c$, A_c, $[OH]_d$, and A_d, are used with eq 6 and 8 to obtain the first approximation for A^{2-} and K_2. From K_1, K_2, and a given [OH], concentration fractions, N_i, may be calculated. If N_i is the concentration fraction at $[OH]_i$

$$N_i = Z/[K_1K_2 + K_2[OH]_i + [OH]_i^2] \tag{9}$$

To calculate N^0, $Z = K_1K_2$; to calculate N^-, $Z = K_1[OH]_i$; and to calculate N^{2-}, $Z = [OH]_i^2$. N^0, N^-, and N^{2-} are the concentration fractions of the neutral molecule, composite anion, and dianion, respectively. From the concentration fractions "corrected" absorbances for A_a and A_d are calculated. For example, the corrected absorbance "A_a," using appropriate concentration fractions, is

$$\text{“}A_a\text{”} = [A_a - N^{2-}A^{2-}]/[N^- + N^0] \tag{10}$$

where the A^{2-} used is the one obtained in the previous approximation. With the corrected A_a and A_b a new A_t^- and K_1 are calculated. Using the second approximation for K_1, A_c, and A_d, we obtain corrected absorbances at $[OH]_c$ and $[OH]_d$. For example, the corrected absorbance "A_c," using appropriate concentration fractions, is

$$\text{“}A_c\text{”} = [A_c - N^0A^0]/[N^- + N^{2-}] \tag{11}$$

Using A_t^- obtained from the preceding approximation and corrected absorbances A_c and A_d a new A^{2-} and K_2 is calculated. This makes one complete cycle. The iteration is continued until A_t^-, which has a slower rate of convergence than A^{2-}, converges to designated tolerances. Computations were carried out on an IBM 1620. Four to nine cycles were required for convergence to within 0.2% for A_t^-. Allowing A_t^- to converge to better than 0.2% gave no significant change in the results. A set of data obtained at 285 mμ and at a concentration of compound I of 10^{-4} *M* follows: A^0, 0.066; A_a, 0.423; $[OH]_a$, 0.0403; A_b, 0.631; $[OH]_b$, 0.1997; $[OH]_c$, 3.63; A_c 0.792; $[OH]_d$, 18.30; A_d 0.855. The calculated values are: K_1, 0.0331; A_t^-, 0.711; K_2, 3.92; A^{2-}, 0.886.

Eight such sets at two wavelengths were used to obtain the macroconstants for compound I. Used were $[OH]_a$'s between 0.03 and 0.04, $[OH]_b$'s from 0.2 to 0.5, $[OH]_c$'s between 2 and 5, and $[OH]_d$ of 18.3. Using the average A^{2-} and A_t^- from the preceding eight sets, 13 equilibrium absorbances from solutions ranging from 1 to 10 *M* in OH, and eq 6, a plot of K_2 *vs.* [OH] was made. Absorbances of the equilibrium solutions were corrected according to eq 11. Concentration fractions were obtained from eq 9 using the average K_1 and K_2 obtained from the eight sets of data mentioned at the beginning of this paragraph. Adjustments were made for lateral shifts at the high [OH]'s. The results of this plot are shown in Figure 2. Using an average A_t^- assumes that the activity coefficient ratio for the tautomeric equilibrium, K_t, does not change. The deviation in constancy of K_t is probably buried in the error in K_2 and should not seriously affect our extrapolation to ionic strength 0.5. This is the ionic strength at which our macroconstants are compared with the hydrolysis constants of model compounds. The precision in K_2 is poor, a 1% error in A_c, giving from 17 to 25% error in K_2. Within the precision of the measurements the points fall on a straight line whose equation by a least-squares treatment is

$$K_2 = -0.02[OH] + 3.41 \tag{12}$$

At ionic strength 0.5, K_2 from eq 12 is 3.4. The average value for K_2 obtained from the eight sets mentioned above is 3.3. Further refinement in the treatment such as extrapolating to ionic strength 0.5 and correcting absorbances further are not called for here. From the data in Figure 2 it appears that K_2 is not very sensitive to ionic strength effects in the range 1 to 10 *M* in hydroxide ion. This unpredictable circumstance greatly simplifies our problem.

For the eight sets of data used we find a mean deviation of 3% in A_t^-, of 0.6% in A^{2-}, of 10% in K_1, and 35% in K_2. The spread, that is, the difference between the mean and the greatest deviation from the mean, is 6% for A_t^-, 17% for A^{2-}, 20% for K_1, and 60% for K_2. Absorbances are for solutions 10^{-4} *M* in compound I. See sample set of data above for magnitudes of absorbances in question.

Calculated Spectra. The spectra of the anions of compounds II, III, and IV, and of benzimidazole, because of their weakness as acids,[3] are calculated from spectra taken in solutions whose total ionic strength is 0.5. At a given wavelength the molar absorptivity, ϵ^-, of the anion is given by the equation

$$\epsilon^- = [K_h(\epsilon_m - \epsilon^0)/[OH]_m] + \epsilon_m \tag{13}$$

where K_h is the hydrolysis constant of the anion, ϵ_m is the molar absorptivity of an equilibrium mixture of nonanion and anion at a given [OH] of molarity *m*, and ϵ^0 is molar absorptivity of the molecule. Spectral data given are the average of three equilibrium solutions.

The spectrum of the composite anion of compound I is the average of three curves measured between 0.1 and 0.5 [OH] with the total ionic strength being 0.5. The equation used is

$$\epsilon_t^- = (\epsilon_i - [N^0\epsilon^0 + N^{2-}\epsilon^{2-}])/N^- \tag{14}$$

where ϵ_i is an equilibrium mixture of neutral molecule, composite anion, and dianion and N_i, the concentration fraction at $[OH]_i$, is calculated from eq 9 using an appropriate *Z*.

For the dianion of compound I the reported spectral data are the averages obtained from three curves obtained at hydroxide ion concentrations from 4 to 10 *M*. To calculate the curve the following equation was used

$$\epsilon^{2-} = (\epsilon_i - (N^0\epsilon^0 + N^-\epsilon_t^-))/N^{2-} \tag{15}$$

where ϵ_i is the molar absorptivity of a solution containing a mixture of neutral molecule, composite anion, and dianion. N_i is calculated from eq 9 with an appropriate *Z*. Spectral data are corrected for lateral shifts at high [OH]. These calculated curves are in good agreement with the curve calculated from 18.3 *M* solutions. Equation 12 was assumed to hold at 18.3 *M*.

Reversibility of Ionization in Strong Alkali. Though equilibria and spectral observations do not indicate we are dealing with an irreversible change in very strong alkaline solutions, we have as a precautionary measure acidified the 18 *M* solution containing compound I. On acidification the spectra of the neutral molecule and that of the positive ion were unchanged. Thus we are dealing in strong alkaline solutions with a reversible ionization.

Table I. Ultraviolet Spectra in Aqueous Solution

Compound	Species[a]	λ_{max}, mμ	ϵ_{max} $\times 10^{-3}$	λ_{max}, mμ	ϵ_{max} $\times 10^{-3}$	λ_{max} or λ_{min}, mμ	ϵ_{max} or ϵ_{min} $\times 10^{-3}$
Benzimidazole	N	278	4.65	271	4.96	243	5.36
	C	274	6.25	262.5	6.68	241	3.88
	A[c]	282	5.8	276.5	6.9	233.5[b]	1.6[b]
Indole	N	286	4.00	277	5.40	270	5.49
2-Hydroxymethylbenzimidazole (I)	N	279	6.03	272.5	6.70	243.5	5.78
	C	274	8.72	268	8.38	237.5	3.90
	Composite anion[f]	285	6.9[g]	279	8.6	235[b]	2.3
	N anion[d]	285	8.4	278.5	9.3	237.5[b]	1.9[b]
	Dianion[e]	285	8.9	279	9.4	238.5[b]	1.7[b]
N-Methyl-2-hydroxymethylbenzimidazole (II)	N	282	5.18	275	6.55	254	6.43
	C	275	8.12	269	8.17	242	4.38
	A	283	6.9	276	7.1	254	6.5
2-Methoxymethylbenzimidazole (III)	N	279	6.06	273	6.90	244	5.81
	C	275	8.54	268	8.83	240	3.87
	A	285	8.6	278.5	9.6	235.5[b]	1.8[b]
2-Methylbenzimidazole (IV)	N	278	6.50	271.5	6.20	242	5.72
	C	274	9.62	267.5	8.40	234.5	4.71
	A	283.5	7.1	278.5	8.4	235[b]	2.5

[a] N, neutral molecule; C, cation; A, anion. [b] Values are at minima. [c] Anions with an A designation are calculated from eq 13. [d] Formed on N deprotonation and calculated from eq 23. [e] Calculated from eq 15. [f] Calculated from eq 14. [g] Plateau.

Results and Discussion

Spectra. Table I gives photometric data for the neutral molecules, the anions, and the cations of compounds I, II, III, and IV in aqueous solution. Also shown for purposes of comparison are spectral data for benzimidazole and indole. Ultraviolet spectra of benzimidazole in alcohol, in NaOH, and 1 *N* HCl,[18] of compound IV in alcohol and 1 *N* HCl,[18] and of indole in alcohol[19] have been reported.

Following Mason[20] we will designate the $\pi \rightarrow \pi^*$ transition in the 280-mμ region as the x band (seemingly resolved into two vibrational subbands) and the $\pi \rightarrow \pi^*$ transition in the 243-mμ region as the y band. These bands have also been correlated with the α and p bands of aromatic hydrocarbons[20] using Clar's classification.[21] The longest wavelength band has been correlated with the $A_{1g} \rightarrow B_{2u}$ band of benzene.[18,20,22] The 243-mμ band has been correlated with the electronic excitation of the amidine moiety[18] $-\ddot{N}{=}CH{-}\ddot{N}H-$ and with the $A_{1g} \rightarrow B_{1u}$ band of benzene.[22]

Benzimidazole and compounds I, III, and IV, being amphoteric, are capable of forming an anion by loss and a cation by gain of a proton. Since these compounds are π-isoelectronic and differ only in the nature of the *saturated* groups at the 2 position we would expect all to be similarly affected by loss or gain of a proton. This expectation is realized. In every case on deprotonation the broad y band with a maximum at about 245 mμ in the neutral molecule is replaced in the anion by a broad minimum at about 235 mμ. In addition the long wavelength band in the 280-mμ region is red shifted, increased in intensity, and markedly broadened. Protonation of the neutral molecule causes a blue shift of both the x and y bands. The x band increases in intensity but undergoes little change in shape, and the y band is attenuated.

On the basis of the theoretical indenyl anion model and empirical correlations presented by Mason,[20] we might expect the x and y bands of benzimidazole and its 1- and 2-substituted derivatives, shown in Table I, to blue shift as the 1 and 3 positions increase and red shift as they decrease in electronegativity. On protonation the nitrogen atoms in benzimidazoles increase in electronegativity and the x and y bands do shift as predicted. Anion formation is accompanied by a decrease in the electronegativity of the nitrogen atoms and the bands again shift as predicted. See Table I and Figure 3.

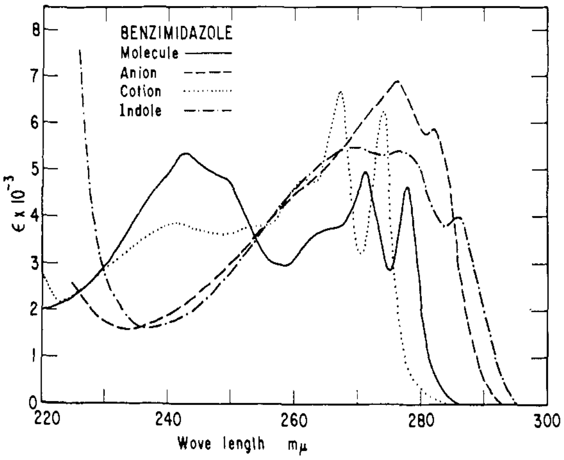

Figure 3. Ultraviolet spectra of benzimidazole, its ions, and indole in aqueous solution.

It appears, however, that in the anion the x and y bands are merged under the same band envelope. This merging would result were the y band to red shift to a greater extent than the x band. That such is the case is suggested by the anion's band envelope being broader and more intense than the band envelope of the x band of the neutral molecule. In addition, over the range 220 to

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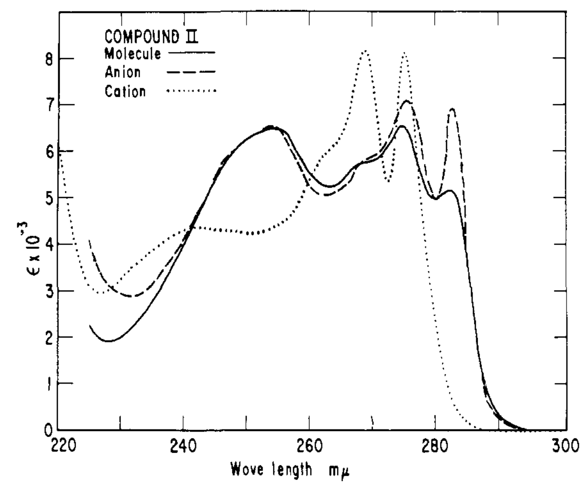

Figure 4. Ultraviolet spectra of compound II and its ions in aqueous solution.

300 mμ the ratio of the integrated intensity of the neutral molecule spectrum of benzimidazole to that of the anion spectrum is only about 1.1. That the x and y bands in the anion of benzimidazole are probably merged under the same band envelope is supported further by a consideration of the spectrum of the iso-π-electronic molecule indole. Just as the anion of benzimidazole is intermediate, on the basis of relative electronegativities, between benzimidazole and the indenyl anion, so is the neutral molecule of indole intermediate between benzimidazole and the indenyl anion. Since both occupy intermediate positions, it would not be surprising to find that their spectra are similar. In Figure 3 and Table I we note that the two are indeed very similar in both position and intensity with indole, however, manifesting three peaks where the anion of benzimidazole shows two peaks. It appears that the substitution of a 3-C for a 3-N in benzimidazole causes the y band at 243 mμ to shift to about 270 mμ. In this region the y band of indole has almost but not quite merged with the higher energy vibrational transition of the x band and three peaks are observed whose positions are 286, 277, and 270 mμ. It is not unlikely that the 286- and 277-mμ peaks originate from subbands of the x band and that the 270 mμ peak originates from the y band. In the anion of benzimidazole it seems that the y band has shifted in the same manner but to a greater extent than the y band of indole so that the y band merges with the higher energy x-vibrational subband—the result is two peaks instead of three. It is also noteworthy that, in support of the indenyl anion model, substitution of a 3-C for a 3-N in going from benzimidazole to indole causes a red shift of the x and y bands.

We find 2 substitution by methyl, hydroxymethyl, and methoxymethyl is either ineffectual on or red shifts slightly the position of the x band of the neutral molecule, the anion, and the cation of benzimidazole. Such 2 substitution, however, increases the intensity of the x band up to about 50%. The above substituents in the two position cause the y band of the neutral molecule of benzimidazole to shift slightly, the direction of shift varying; they cause the y band of the cation to blue shift from 1 to 6 mμ. Effects on the broad y band may be due in part to changes in the relative intensities of vibrational subbands.

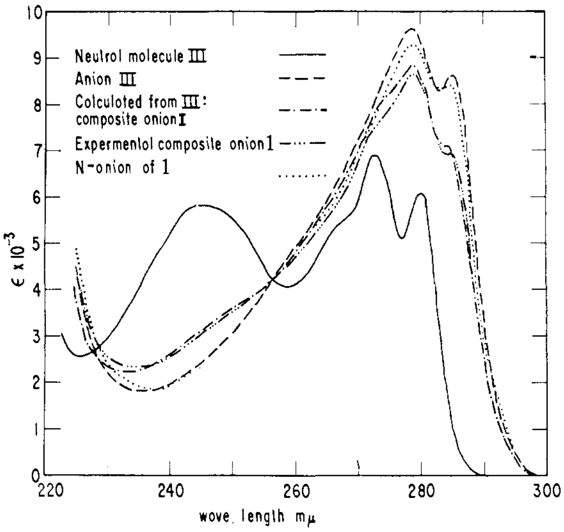

Figure 5. Ultraviolet spectra of compound III, its anion, the composite anion of compound I synthesized from the neutral molecule and the anion spectra of compound III, the experimental composite anion of compound I, and the N anion of compound I.

We note on comparing benzimidazole and compound IV that the conjugative effect of the methyl group manifested in benzene and naphthalene[23] is not paralleled. On the other hand, on comparing compounds I and II, we see that 1-methylation red shifts the x band by 3 mμ and the y band by 10 mμ. It is of interest that the methyl in the 1 position affects the presumably transversely polarized y band more than the longitudinally polarized x band.[23]

Prototropic Constant from Ultraviolet Spectra. When compound I's N anion, formed from N deprotonation, and O anion, formed from O deprotonation, are in equilibrium, one obtains photometrically a composite curve whose ordinates are given by

$$\epsilon_{t}^{-} = N_{\mathrm{O\ anion}}\epsilon_{\mathrm{O\ anion}} + N_{\mathrm{N\ anion}}\epsilon_{\mathrm{N\ anion}} \qquad (16)$$

where ϵ_{t}^{-}, $\epsilon_{\mathrm{O\ anion}}$, and $\epsilon_{\mathrm{N\ anion}}$ are the molar absorptivities of the composite anion, the O anion, and the N anion, respectively, and where N is the concentration fraction of the species indicated by subscripts. If the molar absorptivities of the two tautomers differ sufficiently and suitable model compounds can be found whose spectra are similar to those of the N anion and O anion the shape of the composite curve when compared with those of the model compounds can give information as to the ratio of the two tautomers. A simple test of the chosen models, leastwise in terms of consistency, is to synthesize composite curves from eq 16 using the molar absorptivities of the model anions and seeing whether some concentration fraction may be found that gives a synthesized composite anion that agrees with the one obtained experimentally.

A comparison of the spectra of the neutral molecule and anion of compound II shown in Figure 4 illustrates the near optical equivalence of the O-hydrogen and the O$^-$ group especially in the region of the y band. The spectrum of the neutral molecule of I

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[23] H. H. Jaffé and Milton Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp 257, 307.

shown in Figure 1 at pH 9 and the spectrum of the neutral molecule of compound III shown in Figure 5 demonstrate the near optical equivalence of the O hydrogen and the O methyl through the entire spectrum. Also see Table I. Since O hydrogen, O methyl, and O^- show near optical equivalence especially in the region of the y band, the neutral molecules of compounds I and III are indicated as suitable models for the O anion. Because of the nonoptical equivalence of the N hydrogen and N methyl discussed earlier, compound II is rejected as a model. For the N anion of compound I the anion of compound III might well prove suitable. Finding that the composite anion of compound I passes through the isosbestic point formed by the neutral molecule and anion of compound III, as shown in Figure 5, lends confidence to our choice of model compounds. We can now qualitatively conclude by inspection of Figure 5, contrary to the assumption in the literature,[4] that the N anion is unequivocally the main tautomer. Also shown in Figure 5 is the curve synthesized by replacing in eq 16 the O-anion and the N-anion spectra of compound I by the model neutral molecule (for O-anion) and anion (for N-anion) spectra of compound III. The shown curve was synthesized using a concentration fraction of the "O anion" of 0.2. The good agreement observed between the experimental curve for the composite anion and the synthesized curve further supports our choice of model spectra. In addition, defining the prototropic constant, K_t, as

$$K_t = [\text{N anion}]/[\text{O anion}] \qquad (17)$$

we obtain by visual superimposition a prototropic constant of 4. Alternatively we have calculated K_t from eq 18 derived from eq 16 and 17 with ϵ^0_{III} in place of $\epsilon_{\text{O anion}}$ and ϵ^-_{III} in place of $\epsilon_{\text{N anion}}$, that is

$$K_t = (\epsilon^0_{\text{III}} - \epsilon_t^-)/(\epsilon_t^- - \epsilon^-_{\text{III}}) \qquad (18)$$

For use in eq 18 wavelengths in the region 235 to 248 mμ were chosen. In this region the slopes of the absorption curves are zero or shallow thus minimizing errors from any lateral differences between the model anions and true anions. Also, wavelengths were chosen at which the model anions were favorably separated. In addition, we chose points in the 284- to 286-mμ region where, because of the large difference $\epsilon^0_{\text{III}} - \epsilon_t^-$, error in choice of model for the O anion is small. Solving eq 18 gives for eight points in the region 235 to 248 mμ a value for K_t of 4.2 ± 0.3 (mean deviation) with a spread of 0.7. In the region 284 to 286 mμ, from four points we get a K_t of 3.8 ± 0.5 with a spread of 1. Thus, from the indicated spectral data we obtain a K_t of 4.

Acidity–Basicity Constants. In Table II are given the thermodynamic acidity constants, $\mathrm{p}K_+^0$, of the cations of compounds I, III, and IV; the basicity constants of the anions of I, II, III, and IV, obtained at ionic strength $I_c = 0.5$; and the macrobasicity constants of the composite anion of I at $I_c = 0.5$. Shown also are previously obtained constants for the parent compound, benzimidazole.[13] In the last column are the thermodynamic acidity constants of the neutral molecules obtained from the empirical equation[13]

$$\mathrm{p}K_A^0 = 13.93 - \mathrm{p}K_h^{I_c = 0.5} \qquad (19)$$

In Table II eq 19 is applied to all of the NH acids and with greater uncertainty to the neutral OH acid of compound I. Probable errors are indicated for experimental constants in Table II.

Table II. Acidity–Basicity Constants at 25.0°

Compound	$\mathrm{p}K_+^0$	$\mathrm{p}K_h^{I_c = 0.5}$	$\mathrm{p}K_A^{I_c = 0.5a}$	$\mathrm{p}K_A^0$
I	5.32 ± 0.02[b]	1.51 ± 0.03[c]	12.21[i]	...
		−0.5 ± 0.2[d]	14.2	...
Neutral OH acid		0.8 ± 0.1[e]	12.9	13.1
Neutral NH acid		1.42 ± 0.04[f]	12.30	12.51
Anionic NH acid		0.20 ± 0.15[g]	13.5	...
Anionic OH acid		−0.4 ± 0.2[h]	14.1	...
II	(5.55)[j]	0.62 ± 0.02	13.10[k]	...
III	4.94 ± 0.01	1.68 ± 0.01	12.04	12.25
IV	6.27 ± 0.02[l]	0.73 ± 0.01	12.99	13.20
Benzimidazole[m]	5.55 ± 0.02	1.15 ± 0.01	12.57	12.78

[a] Using $\mathrm{p}K_w = 13.72$: H. S. Harned and G. E. Mannweiler, *J. Am. Chem. Soc.*, **57**, 1873 (1935). [b] Reported as 5.40, $I_c = 0.16$.[4] [c,d] Macrohydrolysis constants K_1 and K_2, respectively. [e–h] Microhydrolysis constants k_a, k_b, k_c, and k_d respectively. [i] Reported as 11.55, $I_c = 0.16$.[4] [j] $I_c = 0.16$.[4] [k] Reported as 11.45, $I_c = 0.16$.[4] [l] Reported as 6.19.[24a] [m] From ref 13.

The acidity constants of the cations, $\mathrm{p}K_+^0$ values, obtained photometrically by us are in reasonable agreement with values obtained potentiometrically by others. However, the constants of the neutral acids of compounds I and II are in poor agreement with the values reported in ref 4. Since the potentiometric results for the neutral acids of compounds I and II, obtained with a stated reproducibility of ±0.02,[4] are not consistent with the N anion of compound I being the main tautomer, unequivocally demonstrated by spectra, we conclude that the potentiometric results have an uncertainty greater than indicated by the stated precision.

In Table II we note that 2-methylation and N-methylation are acid weakening. The question of cationic N-methylation has been discussed.[24] O methylation is found to be acid strengthening. The acid-strengthening effect of the methoxy relative to the hydroxy group in aqueous solution has been widely observed.[25–27] We note without comment that the hydroxymethyl group is acid strengthening relative to hydrogen, unlike the corresponding situation in the carboxylic acids.[28]

Estimation of the Prototropic Constant from pK Data. It is readily shown that the prototropic constant as defined in eq 17 is given by

$$K_t = k_a/k_b \qquad (20)$$

If as a first approximation we assume that the effects of the methyl group in compounds II and III cancel, then substituting K_h of compound II for K_a and K_h of compound III for k_b gives $K_t = 11$. This value, we can readily appreciate, would be an upper limit if the N methyl is acid weakening and the O methyl is acid

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(24) (a) M T. Davies, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, **3**, 420 (1951); (b) A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1352 (1960).

(25) E. J. King, *J. Am. Chem. Soc.*, **82**, 3575 (1960).

(26) T. C. Bissot, R. W. Parry, and D. H. Campbell, *ibid.*, **79**, 796 (1957).

(27) A. Bryson, N. R. Davies, and E. P. Serjeant, *ibid.*, **85**, 1933 (1963).

(28) H. C. Brown, D. H. McDaniel, and O. Häfleger, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press Inc., New York, N. Y., 1955, p 577.

strengthening. Spectral results, and results to follow, suggest that this value is an upper limit.

A standard approach[9] to a value of K_t from equilibrium data is the easily derived expression

$$K_t = [k_a - K_1]/K_1 \tag{21}$$

The macrohydrolysis constant K_1 we have measured experimentally. A speculated value for the microhydrolysis constant k_a may be obtained by estimating the effect of the N methyl in compound II on the acidity of the methylol group. To obtain our estimate we have considered the change from acrylic acid to *cis*-crotonic acid. This structural change decreases the acidity of acrylic acid 0.19 pK unit.[28] Taft's ρ^* for the ionization of carboxylic acids,[29] RCOOH, is 1.72 and ρ^* for alcohols, RCH_2OH,[30] is 1.42. Thus we estimate 0.15 unit as the acid-weakening effect of the methyl group relative to hydrogen in *cis*-2-butan-1-ol. The effect of going from the unsaturated chain *cis*-$CH_3CH{=}CHCH_2OH$ to the similar chain *cis*-$CH_3N{=}CCH_2OH$, a pertinent though not unattached part of compound II, cannot be large in absolute magnitude since the effect of the methyl in the reference alkenol chain is small. Assuming no effect in going from the alkenol chain to compound II, we get an 0.15 pK unit acid-weakening effect of the methyl group. This gives us a speculated pK_a of 0.77 ($k_a = 0.17$). This estimate is probably within 0.1 pK unit of the true value. Using the experimentally observed K_1 value of 0.031 yields on substitution into eq 21 a K_t of 4.5 ± 1.

The equation corresponding to eq 21 but involving the microconstant k_b is

$$K_t = K_1/[k_b - K_1] \tag{22}$$

The microconstant k_b can be obtained by the following empirical approach which assumes a linear free-energy relationship between the structurally akin cationic and anionic equilibria of the amphoteric series R_BCH_2X where R_B is the 2-benzimidazolyl moiety. It is noteworthy that these equilibria differ only by a proton. Confidence in this empirical approach comes from a plot of the pK_A's[28] of acetic acid, methoxyacetic acid, and glycolic acid *vs.* the p$K_+{}^0$ of the corresponding benzimidazoles IV, III, and I, respectively. The pK_A values are fitted within 0.03 pK unit by the least-squares equation $pK_{RCOOH} = 0.95pK_+ - 1.18$. Because of the long-observed anomalous behavior of the first member of a series in free-energy relationships,[31] benzimidazole and formic acid have not been used in the plot. Since structurally the cationic and anionic equilibria of the amphoteric 2-substituted benzimidazoles are closer one to another than to the carboxylic acid equilibrium, we can expect a good linear relationship between p$K_+{}^0$ and $pK_h{}^{I_c = 0.5}$ in the amphoteric series R_BCH_2X. Assuming a linear relationship the p$K_+{}^0$'s of compounds I, III, and IV and the $pK_h{}^{I_c = 0.5}$'s of compounds III and IV yield by interpolation a pK_b value of 1.41($k_b = 0.039$). Substituting in eq 22 we obtain a K_t of 3.9. Since the difference $k_b - K_1$ is very small the agreement with the previous calculations may be somewhat fortuitous. However, assuming a 10% error in both K_1 and k_b brackets K_t between 2 and 9.

Finally we may obtain a value for K_t independent of any measurements on compound I by use of our above estimates of k_a and k_b. Substituting into eq 20 gives a value of 4.4.

Giving the greatest weight to values of K_t obtained from spectra, eq 20 (using estimated microconstants), and eq 21, we favor 4.3 ± 0.5 for the prototropic constant.

The Microhydrolysis Constants. With a knowledge of K_t, K_1, and K_2 we may unscramble the microconstants shown in Scheme I. We do so by rearranging eq 21 and 22 to obtain k_a and k_b and by deriving analogous equations for k_c and k_d.[32] The results are given in Table II.

The utility of σ^* values requires no comment. The microconstant k_a, converted to log K_A, when used with Ballinger and Long's equation, log $K_{A_i} = 1.426\sigma_i^* - 15.9$, obtained for the series RCH_2OH,[30] allows us to obtain a secondary σ^* value of 2.0 for the 2-benzimidazolyl group. This high σ^* value is largely attributable to the combined inductive effects of the two sp^2 nitrogens in the benzimidazole ring. If one considers water as the parent acid of compound I, the observed acid-strengthening effect of the 2-benzimidazolylmethyl group is 2.9 pK units using a statistically corrected pK_A for water of 16. Assuming that the interposed methylene group has an attenuation factor of 2.8[33] then the acid-strengthening effect on water of the 2-benzimidazolyl group is 8 pK units. Interestingly 8 pK units is twice the effect of the nitrogen atom in the 3 position of the pyridinium cation.[34]

The Spectrum of the N Anion of Compound I. The spectrum of the N anion, shown in Figure 5 and Table I, was calculated from eq 23 after making the substitutions indicated.

$$\epsilon_{N\ anion} = [\epsilon_t{}^- - N_{O\ anion}\epsilon_{O\ anion}]/N_{N\ anion} \tag{23}$$

The concentration fractions are obtained from our value of 4.3 for K_t. In place of $\epsilon_{O\ anion}$ the molar absorptivity of the model neutral molecule of III is inserted. Inserting the neutral molecule of I for $\epsilon_{O\ anion}$ gives virtually the same results since the spectrum of the neutral molecules of compounds I and III are so close. We note, as speculated earlier, that the N anion of compound I and the anion of compound III are very similar. Finally we note in Table I the similarity between the spectra of the N anion and the dianion of compound I. Such similarity illustrates the near optical equivalence of $-CH_2O^-$ and $-CH_2OH$ in the 2 position.

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(29) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 556.

(30) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, 82, 795 (1960).

(31) R. M. Hixon and I. B. Johns, *ibid.*, 49, 1786 (1927).

(32) $k_a = K_1[1 + K_t]$, $k_b = K_1[1 + 1/K_t]$, $k_c = K_2/[1 + K_t]$, and $k_d = K_2/[1 + 1/K_t]$.

(33) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p 204.

(34) A. Albert, R. S. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).