Spectrophotometric Study of the Acid Strength of Imidazole

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Alkali salts of imidazole have been found to be unstable in the presence of water being hydrolyzed to the acid and the metallic hydroxide.[1] In his monograph Hofmann refers without definition to the pseudo-acidic nature of the imino hydrogen of imidazole.[2] From the acid strength of 2-phenylimidazole and the observed additive effect of a 2-phenyl group on the acid strengths of both benzimidazole and 4(or 5)-phenylimidazole we were able to estimate a pK_a° of 14.2 for the thermodynamic acidity constant of imidazole.[3] This estimated value indicated that the general spectrophotometric method described previously[3] might prove fruitful when applied to the determination of the acid strength of imidazole.

Experimentally we have measured at ionic strength 0.5 the equilibrium

$$\text{Im}^- + \text{HOH} \rightleftharpoons \text{ImH} + \text{OH}^- \qquad \text{(A)}$$

where ImH refers to imidazole. The hydrolysis constant obtained experimentally is the classical one

$$K_h = C_{\text{OH}^-}(C_{\text{ImH}}/C_{\text{Im}^-}) \qquad \text{(B)}$$

where C is the concentration in moles per liter of the species indicated by the subscripts.

By use of the relationship between K_h and the thermodynamic constant, K_h°, observed emipirically for compounds closely related to imidazole, and by use of the thermodynamic ionization product of water, K_w°, the thermodynamic acidity or dissociation constant, K_a°, of imidazole may be calculated from the equation

$$K_a^\circ = K_w^\circ/K_h^\circ \qquad \text{(C)}$$

EXPERIMENTAL

Imidazole. Eastman Grade imidazole was used in this work. The commercial product was not purified further. It agreed spectrally with a sample prepared and purified in this laboratory.

Spectral Data. All spectral measurements were made with a model DU Beckman Spectrophotometer. A matched pair of 1-cm. cells was used. The temperature in the cell compartment was maintained at 25 ± 0.2° with Beckman thermospacers. Readings were corrected for any differences in the absorbancies of the two cells when filled with water.

Calculations. The reported K_h values were calculated from the known equation[4]

$$K_h = C_{\text{OH}}\ (A^- - A)/(A - A^0) \qquad \text{(D)}$$

where C_{OH} is the equilibrium hydroxide ion concentration in moles per liter, A^- is the absorbancy of the negative ion of imidazole, A is the absorbancy of the solution containing un-ionized imidazole and its negative ion in equilibrium, and A^0 is the absorbancy of the un-ionized imidazole. Absorbancy is equal to log (I^0/I) where

$$\log\ (I^0/I) = \epsilon cd \qquad \text{(E)}$$

ϵ is the molecular extinction coefficient, c is the stoichiometric concentration of imidazole, and d is the cell length. The absorbancy values in equation (D) are for a constant c.

Relatively high concentrations of imidazole, as high as 0.1 mole per liter, were used in the equilibrium measurements. These concentrations allowed for greater precision since wave lengths then could be selected at which the absorbancies of un-ionized imidazole and its negative ion were widely separated.

Where high concentrations of imidazole are used, the stoichiometric concentration of hydroxide ion calculated directly from known dilutions of standard sodium hydroxide solutions may differ significantly from the equilibrium hydroxide ion concentration, C_{OH}. In such case the laws of stoichiometry tell us that

$$C_{\text{OH}} = M_{\text{OH}} - C_{\text{Im}^-} \qquad \text{(F)}$$

where M_{OH} is the stoichiometric concentration of hydroxide ion and C_{Im^-} is the equilibrium concentration of the negative ion of imidazole. In this study a sufficiently close approximation to C_{Im^-} *for use in equation (F)* may be calculated from the quadratic equation (G)

$$0 = (C_{\text{Im}^-})^2 - C_{\text{Im}^-}(K_h^* + M_{\text{OH}} + m) + M_{\text{OH}}m \qquad \text{(G)}$$

where m is the stoichiometric concentration of imidazole defined by

$$m = C_{\text{Im}^-} + C_{\text{ImH}} \qquad \text{(H)}$$

and K_h^* is the approximate hydrolysis constant obtained by substituting M_{OH} for C_{OH} in equation (D).

The absorbancy of the negative ion of imidazole, which in water cannot be directly measured in experimentally attainable concentrations of base, was calculated from equation (I). Equation (I) has been derived[3] but is here rearranged in a more convenient form.

$$A^- = [C_{\text{OH}}1/C_{\text{OH}}2(A_2 - A^0)\,A_1 - (A_1 - A^0)A_2]/[C_{\text{OH}}1/C_{\text{OH}}2(A_2 - A^0) - (A_1 - A^0)] \qquad \text{(I)}$$

Here $C_{\text{OH}}1$ and $C_{\text{OH}}2$ are the equilibrium concentrations of hydroxide ion and A_1 and A_2 are the corresponding absorbancies. Other terms have already been defined. For a fixed error in absorbancy, when $C_{\text{OH}}1 > C_{\text{OH}}2$, the higher the $C_{\text{OH}}1/C_{\text{OH}}2$ ratio the greater the precision with which A^- may be calculated. In this study $C_{\text{OH}}1/C_{\text{OH}}2$ ratios of from 2/1 to 5/1 were found suitable.

For the highest concentration of imidazole used (0.1 mole per liter) the A^- calculated from equation (I) using $M_{\text{OH}}1/M_{\text{OH}}2$ instead of $C_{\text{OH}}1/C_{\text{OH}}2$ leads to an error of the same magnitude as pipetting or dilution errors. It will be shown in the sample calculation which follows, where m is equal to 0.1M, that the difference between $M_{\text{OH}}1/M_{\text{OH}}2$ and $C_{\text{OH}}1/C_{\text{OH}}2$ is 0.2%. On the other hand the difference between M_{OH} and C_{OH} is as high as 3%.

For the sample calculation we will use the following set of experimentally obtained data: wave length, 255 mμ; for all measured absorbancy values, stoichiometric concentration of imidazole, m, 0.1000 mole per liter; A^0, 0.067, $M_{\text{OH}}1$, 0.3033 mole per liter; $M_{\text{OH}}2$, 0.1011 mole per liter; A_1, 0.850; and A_2, 0.344. All absorbancies were obtained in solutions of ionic strength 0.5 using NaCl as the neutral salt. We first solve for A^- by equation (I) using the stoichiometric concentrations of base $M_{\text{OH}}1$ and $M_{\text{OH}}2$ instead of the equilibrium concentrations $C_{\text{OH}}1$ and $C_{\text{OH}}2$. We thus obtain for A^- the value 9.104. We now solve for K_h^* using

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(1) Strain, *J. Am. Chem. Soc.*, **49**, 1995 (1927).

(2) Hofmann, *Imidazole and Its Derivatives*, Interscience Publishers, Inc., New York, N. Y., 1953, p. 19.

(3) Walba and Isensee, *J. Am. Chem. Soc.*, **77**, 5488 (1955).

(4) For discussions of the relationship between spectral data and the concentrations of the un-ionized acid and its ion see references (3) and (5).

(5) Stenstrom and Goldsmith, *J. Phys. Chem.*, **30**, 1683 (1926).

TABLE I

THE HYDROLYSIS CONSTANTS OF THE NEGATIVE ION OF IMIDAZOLE AT 25° AND IONIC STRENGTH[a] 0.5

Wave Length Range, mμ	m^b	$M_1{}^c$	$M_1/M_2{}^c$	$K_h{}^d$	Mean Dev.[e]	Dev.[f]
230-233	3.54×10^{-3}	0.455	5	3.58	0.22	0.31
240-246	1.698×10^{-2}	.500	2	4.26	.23	.37
247-252	3.57×10^{-2}	.493	2	3.70	.32	.19
253-257	5.00×10^{-2}	.500	2.5	4.18	.16	.29
252-257	1.000×10^{-1}	.3033	3	3.75	.34	.14
			Mean	3.89		.26

[a] NaCl used as neutral salt. [b] Stoichiometric concentration in moles/l. of imidazole. [c] M_1 and M_2 are stoichiometric concentrations of NaOH in moles/l. [d] Values are averages obtained from data at 7 to 9 different wave lengths. [e] Unweighted mean deviations from values in preceding column. [f] Deviations from mean value of 3.89.

either $M_{OH}1$ or $M_{OH}2$ and their corresponding absorbancy values. This yields a value of 3.20 for K_h^*. Using first $M_{OH}1$ and then $M_{OH}2$ in equation (G) we get the approximate values for C_{Im^-} of 0.0084 and 0.0030 respectively. Using equation (F) we obtain for $C_{OH}1$ and $C_{OH}2$ the values 0.2949 and 0.0981 respectively. Thus, whereas $M_{OH}1/M_{OH}2$ is 3/1, $C_{OH}1/C_{OH}2$ differs slightly having the value 3.006/1. Using $C_{OH}1/C_{OH}2$ in equation (I) we now get a calculated A^- value[6] of 8.828. Using this value for A^- and either $C_{OH}1$ or $C_{OH}2$ and their corresponding absorbancy values and substituting in equation (D) we get a K_h of 3.00. It should be noted that the entire treatment presented here may be greatly simplified or further refined as warranted by the data.

To obtain the spectral data for the neutral amphiprotic molecule, NaOH was added so that the *p*H as measured on a Beckman model G *p*H meter was between 9.7 and 10.0. Negligible amounts of the ionic species of imidazole are present in this *p*H range. For all wave lengths used Beer's law was obeyed for the neutral molecule. In most cases this check on Beer's law was made in the range from 0.01 to 0.35 *molar* with respect to imidazole. One-cm. cells were used in these checks. Greater reproducibility was attainable in the calculation of the A^- values when low A^0 values, (A^0 values ran as low as 0.014) were calculated by Beer's law, equation (E), from absorbancies of the neutral molecule having values between 0.2 and 0.8.

Before readings were made on the more alkaline solutions it was found desirable to allow the freshly poured solutions to stand for about 20 minutes. This procedure helped to minimize erratic results that might be obtained due to the initially high bubble formation generally observed on pouring the alkaline solutions into the absorption cells.

RESULTS AND DISCUSSION

In Table I are given the data for the hydrolysis constants obtained at different imidazole concentrations and at different ratios of hydroxide ion concentrations. The mean deviation in the K_h values at a given imidazole concentration and for a given pair of hydroxide ion concentrations is given in the sixth column. The mean deviations shown here are primarily attributable to the precision obtainable with the spectrophotometer. In the last column are shown the deviations from the average K_h value of 3.89. These deviations reflect spectrophotometer as well as dilution and other errors. The deviations shown in Table I are large compared with those obtained with somewhat stronger acids.[3] These relatively large deviations are in the main the result of the high sensitivity of the calculated A^- values to experimental error.[6] It will be noted that there is no trend over the range of concentrations used. This lack of trend indicates that the molar activity coefficient function[7] for equilibrium (A) does not undergo any appreciable change with the changing concentrations nor is there any appreciable dimerization or higher polymerization of imidazole in water at the relatively high concentrations of imidazole used. The absence of polymerization is to be expected since molecular weight determinations in water show that imidazole exhibits a normal molecular weight up to concentrations of 0.4 *molal*.[8]

We have shown empirically[3] that for 2-phenylbenzimidazole the thermodynamic hydrolysis constant may be obtained from the classical constant by the equation

$$pK_h^\circ = pK_h + 0.10 I_c{}^{1/2} \qquad \text{(J)}$$

where I_c is the ionic strength and pK_h and pK_h° are the negative logarithms of their respective hydrolysis constants. We have also found that this

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(6) Note how sensitive the calculated A^- value is to small experimental errors. Here we see that a difference of 0.2% in $C_{OH}1/C_{OH}2$ causes a 3% difference in the A^- value. This is due to the circumstance that imidazole is so weak an acid in water that it is approaching the condition where the equilibrium absorbancy values are coming close to being directly proportional to the hydroxide ion concentration. Thus for a given $A°$, A_1, $C_{OH}1$, and $C_{OH}1/C_{OH}2$ ratio the weaker the acid the smaller is the magnitude of the difference in the denominator of equation (I) and the greater will be the percent error in the calculated value for A^-. It will be appreciated that with the very weak acid imidazole we are close to the limit of applicability of the general method discussed here.

(7) The molar activity coefficient, F_h, for equilibrium (A) is defined as $F_h = f_{ImH}f_{OH^-}/a_{HOH}f_{Im^-}$ where f is the molar activity coefficient and a denotes activity of the species indicated by the subscripts. The thermodynamic hydrolysis constant is defined by $K_h^\circ = F_hK_h$.

(8) Huckel, Datow, and Simmersbach, *Z. physik. Chem.*, **186A**, 129 (1940).

relationship holds for benzimidazole.[9] It is not unreasonable to assume that this relationship is also applicable to imidazole any error arising from this assumption being smaller than the uncertainty in the K_h of imidazole at ionic strength 0.5. Using the average value of 3.89 obtained at ionic strength 0.5 we obtain a pK_h° of -0.52. Using a pK_w° of 14 for water we obtain a thermodynamic acidity constant, pK_a°, of 14.52. This value is greater than the value previously estimated[3] by 0.3 pK units which difference shows that a 2-phenyl group is more effective in increasing the acid strength of imidazole than of benzimidazole or 4 (or 5)-phenylimidazole. The experimentally based value though differing from the estimated one is nevertheless in harmony with the qualitative theoretical arguments presented previously[3] relative to the acid strengths of imidazole and its derivatives.

The observed acid strength of imidazole readily explains the aforementioned instability of alkali salts of imidazole in water. However, our experiments show no justification for referring to imidazole as pseudoacidic.

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[9] Details of this determination will be reported as part of a separate communication.

Bromination of β-Phenylglutaric Acid

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β-Phenylglutaric acid might be expected to undergo bromination in either the *alpha* position of the glutaric acid or in the phenyl ring, depending on the conditions of the bromination. We have found that even under conditions which should favor bromination in the *alpha* position (*e.g.*, in the presence of phosphorus trichloride) the only product isolated is β-(*p*-bromophenyl)glutaric acid. The bromination of the aromatic portion of the molecule even in the absence of the usual catalysts is surprising. The yield is only 18% when the bromination is carried out in the presence of phosphorus trichloride but a 60–65% yield can be obtained by simply mixing β-phenylglutaric acid with bromine and allowing the mixture to stand until no more hydrogen bromide is given off. Efforts to effect side chain halogenation by exposing the reaction mixture to ultraviolet light did not affect the yield of *para*-substituted product.

The low yields under some conditions may be the result of attack at the benzylic or *beta* position as well as at the *alpha* and *para* positions to give a mixture from which no definite product could be isolated. The failure to form any appreciable amount of *alpha* substituted product may possibly be due to failure of phosphorus trichloride to convert the acid to its acid chloride. This point has not been investigated.

The great ease with which bromine enters the ring of β-phenylglutaric acid prompted us to look for other examples of facile ring substitution by bromine. Both side chain and nuclear bromination of cumene is reported to take place in sunlight.[2] Qvist[3] reports the preparation of *p*-bromocumene by the action of bromine alone on cumene.

The nuclear bromination described here can perhaps be explained by an ionic mechanism in which the aromatic system exhibits basic characteristics and complexes with the bromine to form intermediates of the type $A\ Br^+\ Br^-$. Such an explanation has been suggested by Buckles. Hausman, and Wheeler[4] for the formation of *p,p'*-dibromobiphenyl from biphenyl and bromine vapor.

EXPERIMENTAL

β-(p-Bromophenyl) glutaric acid. To 5 g. (0.024 mole) of β-phenylglutaric acid[5] in an open beaker was added 5.7 g. (1.8 ml., 0.036 mole) of bromine. The mixture was stirred with a glass rod so that all of the acid came in contact with the bromine. Evolution of hydrogen bromide started immediately and ceased after 7 to 8 hours. The mixture was washed repeatedly with cold water, dried, and recrystallized from acetone to give 4.1 to 4.5 g. (60–65%) of β-(*p*-bromophenyl) glutaric acid, m.p. 177–178°.

Anal. Calc'd for $C_{11}H_{11}BrO_4$: C, 46.0; H, 3.86. Found: C, 46.2; H, 3.81. Neut. equiv., Calc'd: 143.5. Found: 142.5.

When a sample of the product was heated with alkali, the resulting solution upon acidification gave a negative test with silver nitrate. Oxidation with permanganate gave *p*-bromobenzoic acid, m.p. 245–246°. Neut. equiv., Calc'd: 201. Found: 203.

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[1] Guest Scholar, 1954–1955.

[2] Varma and Arinivasan, *J. Indian Chem. Soc.*, **13**, 187–188 (1936).

[3] Qvist, *Acta Acad. Aboensis, Math. et Phys.*, **10**, No. 5 (1937).

[4] Buckles, Hausman, and Wheeler, *J. Am. Chem. Soc.*, **72**, 2494 (1950).

[5] Smith and Kort, *J. Am. Chem. Soc.*, **72**, 1877 (1950).