Chem. Pharm. Bull.
22(8)1923—1927(1974)

UDC 547.785.5.03 : 543.422.6

Acidic Properties of Benzimidazoles and Substituents Effects. I. Correlation between Acid Dissociations and Hydrogen Bondings of Some Benzimidazoles[1]

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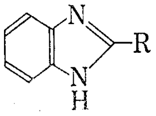
(Received February 4, 1974)

Studies on the degrees of ionization of carbon acids such as ketones and nitro compounds have contributed greatly to the understanding of proton transfer reactions. Considerably less work has however been done on heterocyclic compounds although such work could be of benefit in providing information of synthetic use and serving as substrates in enzymatic processes. We have previously published our findings for quinazolinones[3] and benzimidazoles.[4] In the present work acid dissociation constants and hydrogen bond equilibrium constants of 2-substitutedbenzimidazoles have been measured in relation to the reactivity at N-1 of the benzimidazole ring. Table I lists the compounds investigated, their mp's, and the analytical data.

TABLE I. Structures, mp's, and Analytical Data of the 2-Substitutedbenzimidazoles



Compd.	R	mp (lit.) (°C)	Appearance (recryst. solvent)	Analysis (%) Calcd. (Found) C	H	N
I	H	170(170)[5]				
II	CH_3	175(175)[a]				
III	phenyl	285(285)[b]				
IV	2-pyridyl	219—220 (216—218)[c]	colorless needles (benzene)	73.85 (74.17)	4.61 (4.63)	21.54 (21.33)
V	4-pyridyl	216 (217—218)[d,e]	colorless needles (H_2O)	73.85 (73.93)	4.61 (4.73)	21.54 (21.09)
VI	2-quinolyl	195	colorless needles (benzene)	78.37 (78.59)	4.49 (4.40)	17.14 (16.79)
VII	4-quinolyl	220	colorless needles (MeOH–H_2O)	78.37 (78.03)	4.49 (4.41)	17.14 (16.85)

a) K. Brand and E. Stohr, *Chem. Ber.*, **39**, 4062 (1906)
b) F.R. Japp and A.N. Meldrum, *J. Chem. Soc.*, **75**, 1043 (1899)
c) E.A. Steck, F.C. Nachod, G.W. Ewing, and N.H. Gorman, *J. Am. Chem. Soc.*, **70**, 3406 (1948)
d) J.L. Walter and H. Freiser, *Anal. Chem.*, **26**, 217 (1954)
e) D. Jerchel, M. Kracht, and K. Krucker, *Ann.*, **590**, 232 (1954)

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1) A part of this work was presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan, Kumamoto, December 1973.
2) Location: *Oe-hon-machi, Kumamoto.*
3) T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), 19, 2625 (1971); *idem, ibid.*, 20, 163 (1972).
4) T. Hisano and M. Ichikawa, *Yakugaku Zasshi*, 91, 1136 (1971).
5) H. Pauly and K. Gundermann, *Chem. Ber.*, 41, 4012 (1908)

Experimental

Synthesis of Compounds IV, V, VI, and VII——These products were prepared from condensation of 2-picoline, 4-picoline, quinaldine, and lepidine, which were employed as an active methyl compound, with *o*-phenylene diamine in the presence of sulfur, respectively; a mixture of the corresponding active methyl compound (0.1 mole), *o*-phenylene diamine (0.1 mole), and sulfur (0.3 mole) was heated at 170° for 10 hr. After the reaction, the reaction mixture was concentrated *in vacuo* to be made gummy. The residue was extracted with hot ethanol. The extract was evaporated *in vacuo*, and purified by recrystallization with an active charcoal in 60% yield.

Spectrophotometric Evaluation of Dissociation Constants——The acid dissociation constants of 2-substitutedbenzimidazoles were evaluated spectrophotometrically using a Hitachi ESP-3T at $25° \pm 1$. A solution of the benzimidazole in methanol was diluted with an aqueous buffer so that the final solution had a concentration in the range 1.65×10^{-5}—1.0×10^{-4}M, and did not contain more than 1% organic solvent. The benzimidazoles were dissolved in a buffered solution (pH 7.40) to ensure that all the solute were in the undissociated form and in a solution of 0.1N NaOH in order to give complete dissociation of the solute. Other solutions were made in buffers whose pH were near to the pK_a of the compound. By measuring the absorbance of the above solutions at the wavelength of maximum absorbance of either the dissociated or undissociated form, and taking into account that at this λ either the molar absorptivity of the dissociated form was in general small or negligible for that of the undissociated form or the reversed situation, the pK_a was calculated by use of the equation,[6,7]

$$pK_a = \mathrm{pH} - \mathrm{loq}(A - A_{HA})/(A_{A^-} - A) \qquad (1)$$

where A_{HA}, A_{A^-}, and A are the absorbance of the acid HA, the ion A^-, and the solution under investigation, all at the same concentration. Figures 1 and 2 show the collected spectra of compounds I and VI at different pH values as typical sets in this area. In the range 9 to 12, a mixture of 0.05M $Na_2B_4O_7$ and 0.1N NaOH was used, while for pH<9 a mixture of 0.05M $Na_2B_4O_7$ and 0.1N HCl was adapted as a buffer solution. The pK_a, λ_{max}, and log ε values of the benzimidazoles are listed in Table II.

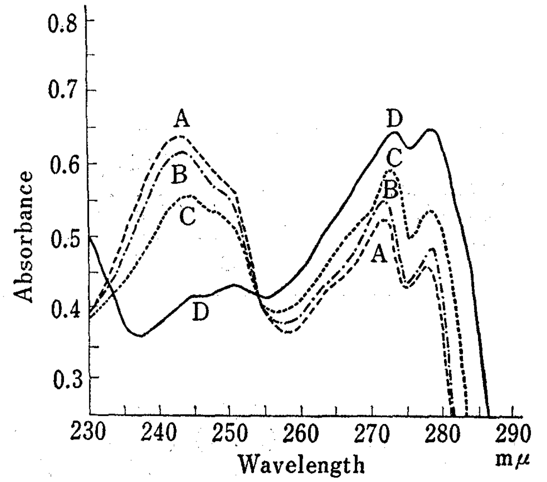

Fig. 1. Absorption Spectra of Compound (I)[a] at Different pH Values

[(I)] 1.0×10^{-4}M; 25°, pH: A, 9.91; B, 10.91; C, 12.25; D, 0.1N NaOH

[a] The absorption spectra of the several alkyl- and alkylamino-benzimidazoles have been determined in alcohol, 0.01N HCl, and 0.01N NaOH in an analogous manner.[5]

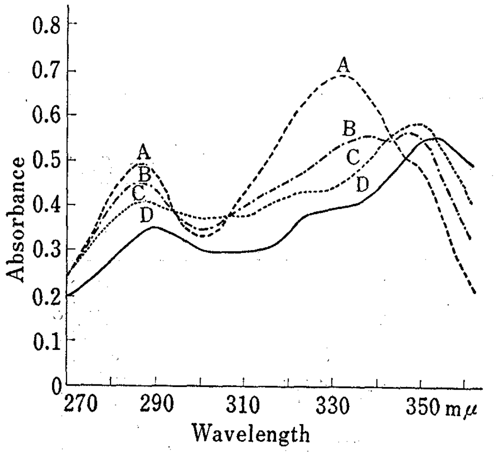

Fig. 2. Absorption Spectra of Compound (VI) at Different pH Values

[(VI)] 2.5×10^{-5}M; 25°. pH: A, 7.40; B, 9.24; C, 10.60; D, 0.1N NaOH

Hydrogen Bonding Equilibrium Constants——Measurements of near ultra violet absorption were made with ternary systems containing small amounts of the benzimidazoles as a proton donor and triethylamine (bp 89—90°) as a proton acceptor in *n*-heptane using a Hitachi EPS-3T at $25° \pm 1$. Figures 3 and 4 show the collected spectra of compounds I and VI as typical sets of the proton acceptor and the donor. Tri-

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6) E. Pelizzetti and C. Verdi, *J. Chem. Soc.* (Perkin II), 1973, 808.

7) H.H. Jaffe and M. Orchin, "Theory and Applications of Ultra Violet Spectroscopy," John Wiley & Sons, Inc., New York, 1966, p. 560.

Table II. Dissociation Constants and Spectrophotometric Data of Compounds (I)—(VII) at 25°±1

Compound	λ_{max} (mμ)	$\log\varepsilon_{max}$	pK_a
I	243	3.79	11.26
II	243	3.71	11.65
III	241	4.21	11.41
IV	240	4.22	10.17
V	243	3.88	10.27
VI	287	4.28	11.01
VII	234	4.61	11.12

ethylamine, which was purified by fractional distillation, bp 89—90°, was used in the range 2.5×10^{-3} to 3.7×10^{-2}M for 1.0×10^{-4}M of the benzimidazoles and *n*-heptane used as an inert solvent was purified by repeating the distillation, bp 98°.

When the absorption band of the hydrogen bonded proton donor molecule is largely different from that of the free molecule, the equilibrium constant (K) between the proton acceptor and the proton donor in an inert solvent such as *n*-heptane can be determined by measuring absorbance values of three solutions which are equal in the concentration of the proton donor but different in that of the proton acceptor; namely whose proton acceptor concentrations are zero, C_a, and C_a'. Of course, absorbance measurements of these solutions should be made at a constant temperature and a constant wavelength. Then the equilibrium constant K can be determined by the equation,[7-9]

$$K = [C_a(K_0-K') + C_a'(K-K_0)]/C_aC_a'(K'-K) \qquad (2)$$

where K_0, K, and K' are absorbance values measured with solutions whose proton acceptor concentrations 0, C_a, and C_a', respectively. The above equation should be adaptable only when the following three conditions are fulfilled: first, the concentration of the hydrogen bonded proton-donating molecule is very much smaller than that of the proton acceptor; second, the absorption spectra of both the hydrogen bonded and the free proton donor molecules obey Beer's law; and third, the absorbance of the proton acceptor is negligibly small in the wavelength region used for the determination of K. The first and the second conditions are fulfilled in the present experiment where the concentration of the proton donor is about 10^{-4}M, and the third condition is also satisfied, because the absorbance measurements are made in the wavelength region longer than 2600 Å. The K, λ_{max}, and the concentrations of triethylamine, C_a and C_a', are listed in Table III.

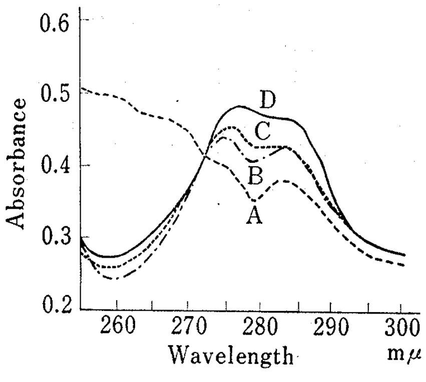

Fig. 3. Absorption Spectra of Compound (I) at 25°

curve A, in *n*-heptane; curve B, C, and D, in mixed solvents of *n*-heptane and triethyl amine

The concentrations of triethylamine are 3.30×10^{-3}M, 6.30×10^{-3}M, and 1.25×10^{-2}M, respectively. The concentration of compound (I) is 1.0×10^{-4}.

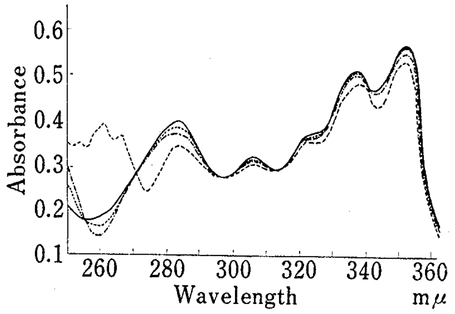

Fig. 4. Absorption Spectra of Compound (VI) at 25°

curve A, in *n*-heptane; curve B, C, and D, in mixed solvents of *n*-heptane and triethylamine

The concentration of triethylamine are 2.5×10^{-3}M, 4.6×10^{-3}M, and 9.3×10^{-3}M, respectively. The concentration of compound (VI) is 1.0×10^{-4}M.

curve A: ------- curve B: —·—·—
curve C: ┄┄┄┄ curve D: ———

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[7] G.J. Brealey and M. Kasha, *J. Am. Chem. Soc.*, 77, 4462 (1955).

[8] S. Nagakura, *J. Am. Chem. Soc.*, 76, 3070 (1954).

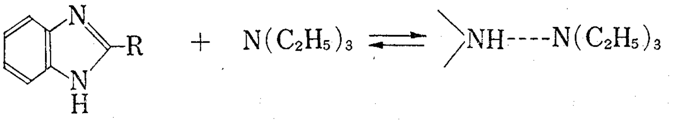
[9] S. Nagakura and J. Tanaka, "Jikken Kagaku Koza," Maruzen, Tokyo, 1970, p. 469.

Table III. Values of Equilibrium Constants (K) between Proton Acceptors and Proton Donors at 25° ±1

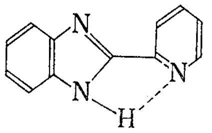
Compound	Concentration of triethylamine (mole/l) C_a	$C_{a'}$	K	λ_{max} (mμ)
I	2.5×10^{-3}	4.6×10^{-3}	147.8	274
II	2.5×10^{-3}	4.6×10^{-3}	111.3	279
III	9.3×10^{-3}	3.7×10^{-2}	134.0	304
IV	4.6×10^{-3}	9.3×10^{-3}	185.4	312
V	4.6×10^{-3}	9.3×10^{-3}	177.6	309
VI	3.3×10^{-3}	1.2×10^{-2}	176.5	285
VII	4.6×10^{-3}	1.7×10^{-2}	167.7	323

Result and Discussion

In the pK_a data for the benzimidazoles substituted at the second position, the pK_a value of compound IV is the heighest as expected from taking into account only a charge density of the pyridine nucleus,[10] while that of compound II is the lowest from an inductive effect of the methyl group. On the other hand, by measuring the effects of the substitution on the proton-donating powers of the benzimidazoles it was found consequently that all the absorption bands due to the hydrogen bonded molecules appear distinctly in the longer wavelength side than those due to the free molecule. Therefore, it seems reasonable to consider that the hydrogen bonding such as



can be formed in this field. It is seen from Table III that the proton-donating power decreases in the order of 2->4-pyridyl>2->4-quinolyl>H>phenyl>methyl, although 2-(2-pyridyl)benzimidazole may be expected to have the tendency forming the intramolecular hydrogen bonding such as



to weaken its proton-donating power for other molecules. Furthermore, to express the effects of substituents log (K_R/K_H) was plotted against the pK_a values in Fig. 5.

The slope of the linear plot corresponds to 3.0. From the results, it seems reasonable

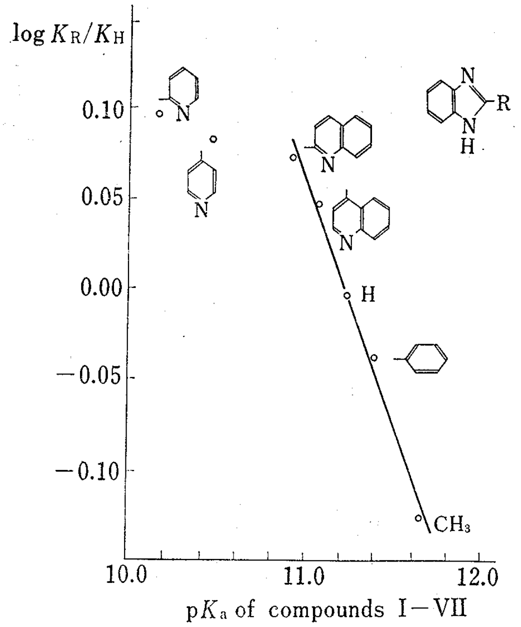


Fig. 5. log K_R/K_H vs. the pK_a Values of the 2-Substituted-benzimidazoles

K_H, hydrogen bond equilibrium constant of I; K_R, hydrogen bond equilibrium constants of the benzimidazoles substituted at the second position as given in Table I

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[10] H.C. Brown, D.H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," Vol. 1, Academic Press, New York, 1955, p. 597.

to point out that the hydrogen bonding can be considerably more reactive than the acid dissociation for basic media. Both compounds IV and V were however far below the line plotted in Fig. 5, in spite of the stronger acids of them. This fact suggests that the proton-donating abilities level off at about 11 of the pK_a values in this selected area.

Acknowledgement The authors express their deep gratitude to Mr. M. Nakatomi, President of Hisamitsu Pharmaceutical Co., Inc., for the supply of several chemicals. The microanalyses were performed by Mrs. K. Shiraki of the Central Analysis Room of this Faculty ot whom they are also grateful.

[Chem. Pharm. Bull.
22(8)1927—1929(1974)]

UDC 547.571.04 : 547.556.7.04

Mechanism of the Color Reaction between Aldehyde and Diazotized Aromatic Amine. II.[1] Color Reaction Product of Benzaldehyde with Diazotized Sulfanilamide

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(Received February 14, 1974)

In the previous paper,[1] the main coloring matters produced in the color reaction of formaldehyde with diazotized sulfanilamide and with diazotized *p*-aminobenzoic acid were isolated in crystalline forms and their chemical structures were characterized as 1,3,5-tri- and 1,5-diphenylformazan derivatives. This paper extends the study to the color reaction of benzaldehyde with diazotized sulfanilamide.

Isolation of Color Reaction Product

The color reaction of aldehyde, especially aromatic one, with diazotized aromatic amine in an alkaline medium, which has been utilized for its detection, usually required sodium amalgam as a reducing agent.[3] Recently, sodium hydrosulfite was found in our laboratories to be substituted for the amalgam, which was more conveniently used for the present purpose and gave more intense color.[4]

Benzaldehyde gave a reddish violet color when treated with diazotized sulfanilamide in the presence of sodium hydrosulfite at moderately high temperature. In the reaction, the maximum color intensity was observed in the molar ratio of the aldehyde to the diazotized amine approximately 1: 2. Therefore, this ratio was adopted to isolate the reaction product.

The reaction mixture thus obtained was neutralized. The resulting precipitate was collected and extracted with acetone. The extract was subjected to the column chromatographic separation on an alumina with acetone as developing solvent to give three fractions. The first and third fractions, which showed a yellow and violet colors on the alumina, respectively, were so small that they could not be treated successfully. The second and main fraction showed a red-brown color on the alumina and gave dark red needles of mp 236.5—237.5° (I).

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[1] Part I: M. Nakamura, K. Mihashi, and K. Egami, *Chem. Pharm. Bull.* (Tokyo), **20**, 35 (1972).
[2] Location: *a*) *Nanakuma, Nishi-ku, Fukuoka*; *b*) *Katakasu Higashi-ku, Fukuoka.*
[3] F. Penzolt and E. Fischer, *Ber.*, **16**, 657 (1883).
[4] Details of this study will be published elsewhere in the near future.