Summary

As part of the systematic studies on imidazole derivatives as chelating agents, four azoimidazoles having an ortho-hydroxy group, a dimethylamino group, or both groups were prepared from 4(5)-amino-5(4)-methylimidazole as a diazo component and 2-naphthol, *p*-methoxyphenol, N,N-dimethylaniline, and N,N-dimethyl-*m*-aminophenol as coupling components: 1-[4(5)-methyl-5(4)-imidazolylazo]-2-naphthol; 2-[4(5)-methyl-5(4)-imidazolylazo]-4-methoxyphenol; 4(5)-methyl-5(4)-(*p*-dimethylaminophenylazo)imidazole; 3-dimethylamino-6-[4(5)-methyl-5(4)-imidazolylazo]phenol. The reactions of the azo derivatives with various metal ions were studied by spot tests in acid, neutral, and alkaline solutions. All the azo derivatives react with metal ions, such as Fe (III), Co (II), Ni (II), Cu (II), Zn (II), Pd (II) and Pb (II), to give intensely colored chelates which are usually extracted into chloroform or iso-amyl alcohol. These results indicate that the azoimidazoles can be used as metallochromic indicators or as extractants for determinations of metal ions by chelatometric titrations or by solvent extractions.

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129. Osamu Yamauchi, Hisashi Tanaka, and Toyozo Uno:

Studies on Imidazole Derivatives as Chelating Agents. II.[*1] Spectrophotometric and Potentiometric Investigations of Acid-base Equilibria of Azoimidazoles.

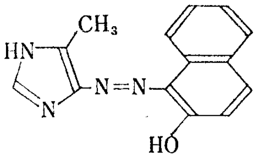
(*Faculty of Pharmaceutical Sciences, Kyoto University*[*2])

In the preceding paper[*1] the authors reported the syntheses of some azoimidazoles having an ortho-hydroxy group, a dimethylamino group, or both groups, along with their remarkable color formations with a number of metal ions. Most of their colored chelates are decomposed by EDTA, and the fact indicates the possibilities of their applications as metallochromic indicators in chelatometric titrations. Just as other azo compounds with a dimethylamino group or a hydroxy group generally exhibit color changes as the pH of the solution varies, these azoimidazoles show spectral changes owing to the equilibria that are dependent on the pH of the solution.

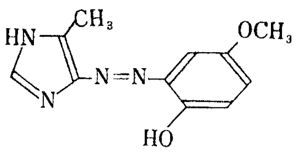
The groups contributing to the acid-base equilibria of the azoimidazoles concerned are the pyridine-like nitrogen and the pyrrole-like imino group of the imidazole nucleus, the hydroxy group, and the dimethylamino group, and protonation of the azo group does not occur in the usual pH range. As a basis of their applications to chelatometric titrations and calculations of the stability constants of their metal chelates, the authors investigated the pH dependence of the spectra and determined the acid dissociation constants by spectrophotometric and potentiometric methods.

[*1] Part I: This Bulletin, **14**, 948 (1966).

[*2] Yoshidashimoadachi-cho, Sakyo-ku, Kyoto (山内 脩, 田中 久, 宇野豊三).



I



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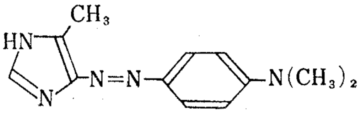

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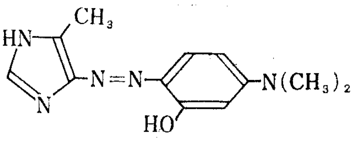

IV

Experimental

Materials——Syntheses of the azoimidazoles, 1-[4(5)-methyl-5(4)-imidazolylazo]-2-naphthol (I), 2-[4(5)-methyl-5(4)-imidazolylazo]-4-methoxyphenol (II), 4(5)-methyl-5(4)-(*p*-dimethylaminophenylazo)imidazole (III), and 3-dimethylamino-6-[4(5)-methyl-5(4)-imidazolylazo]phenol (IV), were described in the preceding paper.[*1] 2-Phenylazoimidazole and 2-methyl-4(5)-phenylazoimidazole were prepared by coupling of diazotized aniline with imidazole and 2-methylimidazole, respectively, according to the method of Fargher and Pyman.[1]

Measurements of Spectra——The ultraviolet and the visible region absorption spectra were measured in 50 v/v% EtOH-H_2O (I, II, and IV) and in 2 v/v% EtOH-H_2O (III) at the concentrations $5\times10^{-5}\sim2\times10^{-5}M$ by using a Hitachi Model EPS-2U recording spectrophotometer and a Shimadzu Model QV-50 spectrophotometer.

pH Titrations——As all the azoimidazoles investigated are insoluble or only slightly soluble in H_2O, pH titrations were carried out in 50 v/v% dioxane-H_2O. To a weighed amount of the azoimidazole (10～20 mg.) placed in a titration vessel were added 4 ml. of purified dioxane, 1 (or 2) ml. of $0.1N$ HNO_3, and 0.8 ml. of $1M$ KNO_3, and the total volume was adjusted to 8 ml. by addition of deionized H_2O, the concentration being $0.005\sim0.008\,M$. The temperature of the solution was maintained at 25±0.1° by circulating water from a thermostated bath. The solution was titrated with carbonate-free $0.1N$ KOH prepared by the method of Armstrong[2] and standardized against potassium hydrogen phthalate. Stirring was effected by a stirring motor, and CO_2-free nitrogen gas was maintained over the solution during the titration. The composition of the solvent was kept constant by adding equal volumes of $0.1N$ KOH and dioxane by a double syringe buret. Measurements of pH were made with a Radiometer Titrator TTT1 and Titrigraph equipped with a Radiometer G202B glass electrode and a K401 saturated calomel electrode. The pH meter was calibrated by a Toa Electronics buffer solution (pH 4.01). The meter readings in 50 v/v% dioxane-H_2O were calibrated by titrating a 50 v/v% dioxane-H_2O mixture containing $0.1M$ KNO_3 with $0.1N$ HNO_3 under the condition described above.[3] They were found to be 0.12 unit higher than the corresponding values of $-\log[H^+]$, where $[H^+]$ is the calculated stoichiometric concentration of hydrogen ion. The apparent ion product of H_2O (Kw′) was obtained by titrating a 50 v/v% dioxane-H_2O mixture containing $0.1M$ KNO_3 with $0.1N$ KOH under the same condition. The value of pKw′ was calculated to be 15.52 according to the following equation:

$$pKw' = pHm - \log[OH^-]$$

where pHm is the meter reading and $[OH^-]$ is the calculated stoichiometric concentration of hydroxyl ion. These values are in agreement with those reported recently by Takamoto, *et al.*[4]

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1) R.G. Fargher, F.L. Pyman: J. Chem. Soc., **115**, 236 (1919).

2) D.M.G. Armstrong: Chem. & Ind. (London), **1955**, 1405; A. Albert, E.P. Serjeant: "Ionization Constants of Acids and Bases," Methuen & Co., Ltd., London (1962) (Japanese Edition: "Ion Teisu," Maruzen Co., Ltd., Tokyo (1963)).

3) L.G. Van Uitert, C.G. Haas: J. Am. Chem. Soc., **75**, 451 (1953).

4) S. Takamoto, Q. Fernando, H. Freiser: Anal. Chem., **37**, 1249 (1965).

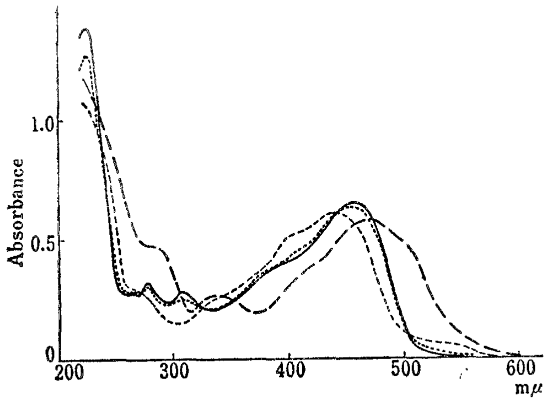

Fig. 1. Absorption Spectra of I at Various pH Values

I: $4\times10^{-5}M$ (50 v/v% EtOH-H$_2$O)
———— pH <1[*3] ·············· 3.1
- - - - - - 4.5~7.0 — — — — — 12.9

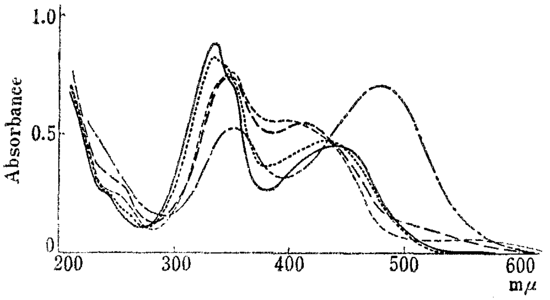

Fig. 2. Absorption Spectra of II at Various pH Values

II: $5\times10^{-5}M$ (50 v/v% EtOH-H$_2$O)
———— pH 1.3 ·············· 3.7
- - - - - - 6.4 — — — — — 10.5
—·—·— >13

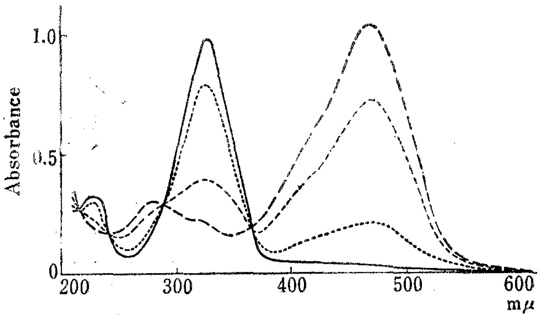

Fig. 3a. Absorption Spectra of III at pH Values lower than 3.5

III: $4\times10^{-5}M$ (2 v/v% EtOH-H$_2$O)
———— pH <1 ·············· 1.7
- - - - - - 2.5 — — — — — 3.3

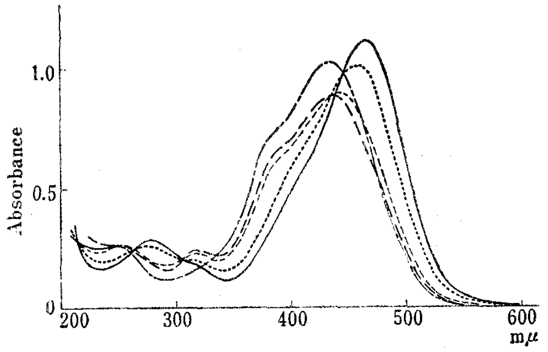

Fig. 3b. Absorption Spectra of III at pH Values higher than 3.5

III: $4\times10^{-5}M$ (2 v/v% EtOH-H$_2$O)
———— pH 3.9 ·············· 4.8
- - - - - - 5.8 — — — — — 7.2~9.5
—·—·— 12.9

Results and Discussion

The ultraviolet and the visible region absorption spectra of I, II, and IV in 50 v/v % EtOH-H$_2$O and those of III in 2 v/v% EtOH-H$_2$O at various pH values are shown in Figs. 1~4. The spectra of I and II are dependent on pH in acid and alkaline solutions, whereas in neutral solution they vary only slightly. It can be seen from the spectra of III in 2 v/v% EtOH-H$_2$O (Figs. 3a and 3b) that there exist three different equilibria according to the pH ranges 1~4, 4~10, and 10~13. The stepwise dissociations of the two protons attached to IV in acid solution are not obvious, indicating

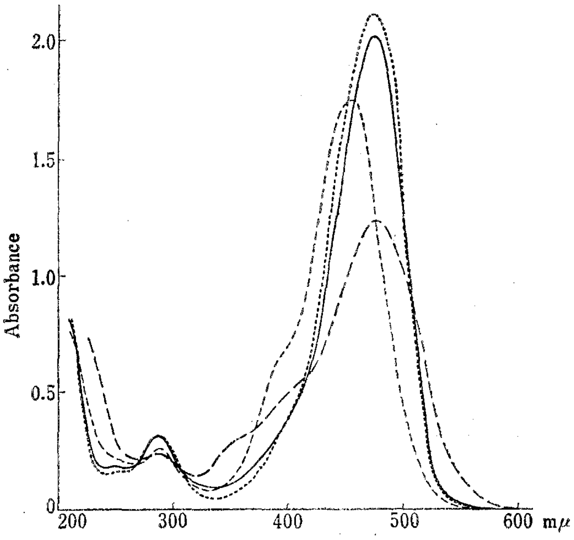

Fig. 4. Absorption Spectra of IV at Various pH Values

IV: $5\times10^{-5}M$ (50 v/v% EtOH-H$_2$C)
———— pH 1.3 ·············· 3.7
- - - - - - 6~10 — — — — — >13

[*3] All the pH values in the Figs. 1~6 are the pH meter readings.

that one of the protons probably dissociates to a considerable extent in the pH range 1.3～3.7. All the azoimidazoles, especially Ⅲ and Ⅳ, have strong absorptions between 400～500 mμ.

Although dissociations of the pyrrole-like NH group and the OH group are expected to occur above pH 10, detailed investigations in this pH range were not attempted owing to small spectral changes and labilities of the compounds.

As the presence of the isosbestic points in the spectra indicates the occurrence of only one dissociation step in the pH range being considered, the absorbances of I at 225 mμ (50 v/v% EtOH-H_2O) and of Ⅲ at 331, 445, and 470 mμ (2 v/v% EtOH-H_2O) were measured as a function of pH and plotted against pH (Figs. 5 and 6). The maximum or minimum values at the ends of a dissociation step were estimated graphically. From Fig. 5, one of the acid dissociation constants (pKa) of I was determined to be 3.8, and from Fig. 6, the pKa values of Ⅲ were determined to be 2.3 and 5.3 (ionic strength ≒ 0.01),*3 because at the midpoints of the curves pH = pKa.

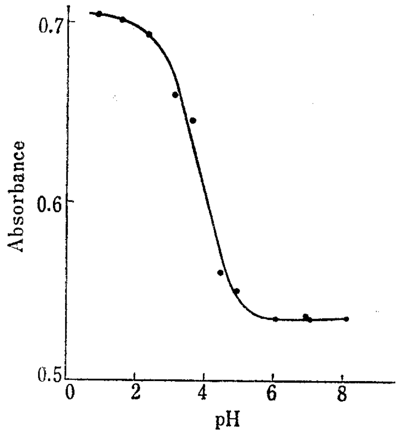

Fig. 5. Absorbance of I in 50 v/v% EtOH-H_2O at 225 mμ plotted against pH

concentration : 2×10^{-5} *M*

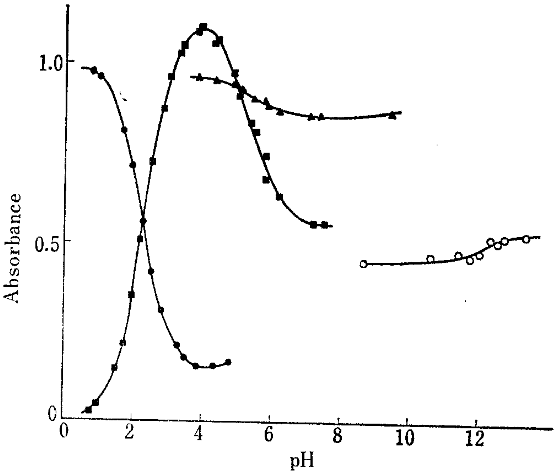

Fig. 6. Absorbance of Ⅲ in 2 v/v% EtOH-H_2O at 331, 445, and 470 mμ plotted against pH

—●—●— at 331 mμ (concentration : 4×10^{-5} *M*)
—▲—▲— at 445 mμ (concentration : 4×10^{-5} *M*)
—○—○— at 445 mμ (concentration : 2×10^{-5} *M*)
—■—■— at 470 mμ (concentration : 4×10^{-5} *M*)

The pKa values were also obtained potentiometrically according to the equations (1) (for pyridine-like nitrogens and amino groups) and (2) (for OH and NH groups) :

$$\mathrm{pKa}=-\log[\mathrm{H^+}]+\log\frac{[\mathrm{HNO_3}]-[\mathrm{KOH}]-[\mathrm{H^+}]+[\mathrm{OH^-}]}{\mathrm{C}-([\mathrm{HNO_3}]-[\mathrm{KOH}]-[\mathrm{H^+}]+[\mathrm{OH^-}])} \qquad (1)$$

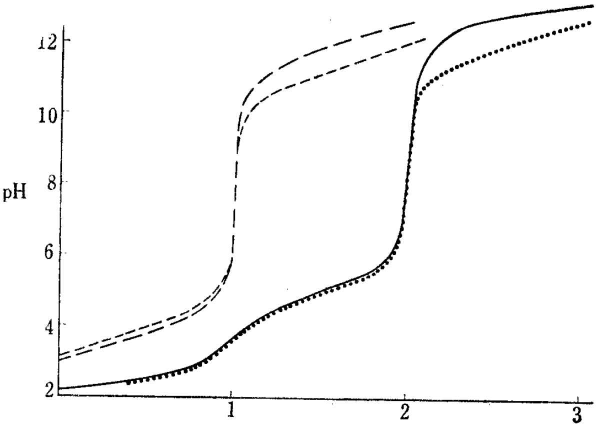

Fig. 7. pH Titrations of Azoimidazoles in 50 v/v% dioxane-H_2O at 25±0.1°

a : moles of KOH added per mole of azoimidazole
- - - - - Ⅰ - - - - - - Ⅱ
———— Ⅲ .... Ⅳ

$$\mathrm{pKa}=-\log[\mathrm{H^+}]+\log\frac{\mathrm{C}-[\mathrm{KOH}]-[\mathrm{H^+}]+[\mathrm{OH^-}]}{[\mathrm{KOH}]+[\mathrm{H^+}]-[\mathrm{OH^-}]} \qquad (2)$$

where C is the total concentration of the azoimidazole. The pH titration curves of the azoimidazoles are shown in Fig. 7. Separations of the first and second dissociation steps of I and Ⅱ are indicated by the pH jumps at $a \doteq 1$ (a is the moles of potassium hydroxide added per mole of the azoimidazole). The titration curves of Ⅲ and Ⅳ show two pH jumps corresponding to the points $a=1$ and 2. However, pH jumps between the dissociation steps of the OH and NH groups in alkaline solution were observed in no case. All the data obtained spectrophotometrically and potentiometrically are shown in Table I.

Table I. Acid Dissociation Constants (pKa) of Azoimidazoles

Compound	$\mathrm{pK}_{\underset{\mathrm{H}}{\mathrm{N}^+}(\mathrm{CH}_3)_2}$	$\mathrm{pK}_{\mathrm{NH}^+}$	$\mathrm{pK}_{\mathrm{OH}}$	$\mathrm{pK}_{\mathrm{NH}}$
I	—	3.8a)	11.8a)	
		3.8b)	11.6c)	
Ⅱ	—	3.9a)	11.0a)	
Ⅲ	<2a)	5.1a)	—	>12a)
	2.3d)	5.3d)	—	11.9d)
Ⅳ	<2a)	4.9a)	11.8a)	
2-Phenylazoimidazole	—	3.2a)	—	
2-Methyl-4(5)-phenylazoimidazole	—	4.5a)	—	

Methods:
- *a*) Potentiometry in 50 v/v% dioxane-H_2O at 25±0.1°
- *b*) Spectrophotometry in 50 v/v% EtOH-H_2O at 25±2° with no corrections of the pH meter readings.
- *c*) Method *a*) and calculation according to Noyes and Britton2).
- *d*) Spectrophotometry in 2 v/v% EtOH-H_2O at 25±2° with no corrections of the pH meter readings.

The pKa values between 3.8 and 5.1 can be assigned to those of the pyridine nitrogens ($\mathrm{pK}_{\mathrm{NH}^+}$), because 2-phenylazoimidazole and 2-methyl-4(5)-phenylazoimidazole, where no other basic groups than the pyridine nitrogen are present, have the values 3.2 and 4.5, respectively. Accordingly the pKa values below 2 obtained by the pH titrations of Ⅲ and Ⅳ, and 2.3 of Ⅲ obtained spectrophotometrically are attributed to the dimethylamino groups ($\mathrm{pK}_{\underset{\mathrm{H}}{\mathrm{N}^+}(\mathrm{CH}_3)_2}$). The dissociations of protons from the OH and NH groups are considered to occur in alkaline solution at pH values greater than 10. The pKa values of the hydroxy groups ($\mathrm{pK}_{\mathrm{OH}}$) of I, Ⅱ, and Ⅳ were calculated to be 11.8, 11.0, and 11.8, respectively, by using the value of Kw′ described in the experimental part, with the assumption that the dissociation of the NH group is negligible in the pH range used for the calculations, since the pKa of the NH group ($\mathrm{pK}_{\mathrm{NH}}$) of imidazole itself is reported to be 14.2.5) However, introduction of the electron-attracting azo group may facilitate the ionization of the NH group considerably, resulting in the overlapping of $\mathrm{pK}_{\mathrm{NH}}$ and $\mathrm{pK}_{\mathrm{OH}}$, and it seems preferable to calculate the two constants separately. The authors therefore attempted to calculate the constants of I according to Noyes and Britton.2) When the terms X, Y, and Z are defined by the equations

$$X=[\mathrm{H}^+](B-C+[\mathrm{H}^+])$$

$$Y=2C-(B+[\mathrm{H}^+])$$

$$Z=[\mathrm{H}^+]^2(B+[\mathrm{H}^+])$$

where B and C represent the concentration of alkali added and the total concentration of the all species of the acid being titrated, respectively, overlapping constants Ka_1 and Ka_2 can be calculated by the equations (3):

$$Ka_1=\frac{Y_1Z_2-Y_2Z_1}{X_1Y_2-X_2Y_1} \quad \text{and} \quad Ka_2=\frac{X_1Z_2-X_2Z_1}{Y_1Z_2-Y_2Z_1} \qquad (3)$$

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5) H. Walba, R.W. Isensee: J. Org. Chem., **21**, 702 (1956).

X_1, Y_1, and Z_1, refer to readings obtained with less than one equivalent of titrant and X_2, Y_2, and Z_2, refer to readings obtained with more than one equivalent of titrant. The equations need no knowledge of [OH^-]. By this method, pKa_1, which is presumed to correspond to pK_{OH}, was determined to be 11.6, which is not greatly different from the value obtained by neglecting the dissociation of the NH group. The value of pKa_2 (pK_{NH}) could not be calculated as a reasonable value. The approximate pK_{NH} of Ⅲ was found to be 11.9 (2 v/v% EtOH-H_2O) spectrophotometrically (Fig. 6). In any case these values may be subject to serious errors owing to low measuring accuracy in the high pH region in

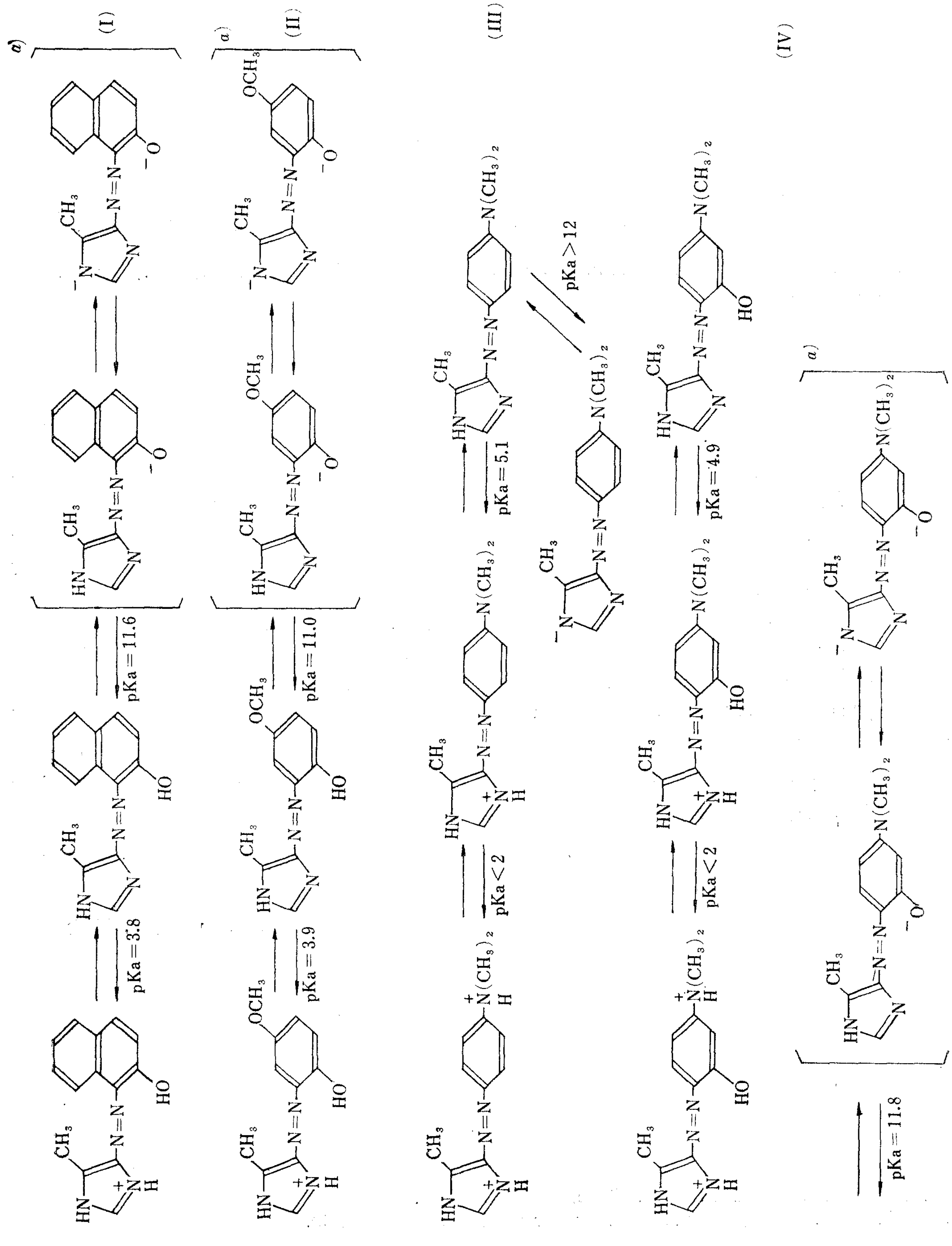

Chart 1.

a) The dissociation steps expressed in [ ] are not clearly determined.

50 v/v% dioxane-H_2O.

The pK_{OH} of Ⅳ (11.8) indicates the existence of an intramolecular hydrogen bond, and it is understandable that the hydroxy group is in the ortho-position to the azo group. This fact and the information of the infrared spectra[*1] are properly explained by the structure Ⅳ. The pKa values of 1-(2-pyridylazo)-2-naphthol (PAN), which is structurally related to I, were determined to be 1.9 and 12.2 (20 v/v% dioxane-H_2O) by Pease and Williams,[6] and <2 and 12.3 (50 v/v% dioxane-H_2O) by Corsini *et al.*[7] It is interesting that the pK_{NH^+} of I is about 2 units higher than the corresponding value of PAN.

The equilibria involving the dimethylamino groups and the pyridine-like nitrogens in aqueous media can be expressed in the way shown in Chart 1. The dissociation steps of the OH and NH groups are not completely clarified, but, from the above considerations, they may possibly be described as shown in the chart. Although the cation of Ⅲ may exist in the azonium form, the investigation of the equilibrium of the tautomers was not attempted.

The stability constants of the metal chelates of the azoimidazoles and the applications to analytical determinations of metals will be the subjects of later papers.

The authors are grateful to Dr. N. Sawa, Research Laboratory of Toho Rayon Co., Ltd., for his kind supply of 2-methylimidazole.

Summary

Spectrophotometric and potentiometric investigations of the acid-base equilibria of the following azoimidazoles in aqueous media were carried out with a view to get some basic knowledge for their applications to chelatometric titrations as metallochromic indicators and for the calculations of the stability constants of their metal chelates: 1-[4(5)-methyl-5(4)-imidazolylazo]-2-naphthol; 2-[4(5)-methyl-5(4)-imidazolylazo]-4-methoxyphenol; 4(5)-methyl-5(4)-(*p*-dimethylaminophenylazo)imidazole; 3-dimethylamino-6-[4(5)-methyl-5(4)-imidazolylazo]phenol.

pH Titrations of these azoimidazoles in 50 v/v% dioxane-H_2O at 25±0.1° afforded their acid dissociation constants (pKa). By comparing with the pKa values of 2-phenylazoimidazole (3.2) and 2-methyl-4(5)-phenylazoimidazole (4.5), assignments of the pKa values, $pK_{\underset{H}{N}^{+}(CH_3)_2}$, pK_{NH^+}, pK_{OH}, and pK_{NH}, which refer to the pKa values of dimethylamino group, pyridine nitrogen, hydroxy group, and imino group, respectively, were attempted: $pK_{\underset{H}{N}^{+}(CH_3)_2}<2$; $pK_{NH^+}=3.8\sim5.1$; $pK_{OH}=11.0\sim11.8$; $pK_{NH}>12$. The pK_{NH^+} of I and the $pK_{\underset{H}{N}^{+}(CH_3)_2}$, pK_{NH^+}, an dpK_{NH} of Ⅲ were also obtained spectrophotometrically by plotting the absorbances of I (50 v/v% EtOH-H_2O) and Ⅲ (2 v/v% EtOH-H_2O) against pH.

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6) B. F. Pease, M. B. Williams: Anal. Chem., **31**, 1044 (1959).
7) A. Corsini, I. M. Yih, Q. Fernando, H. Freiser: *Ibid.*, **34**, 1090 (1962).