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Studies on Benzothiazole Derivatives as Chelating Agents. III.[1] Acid-base Equilibria and Chelate Formation with Metal Ions

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The acid dissociation constants of 2-, 4- and 7-substituted benzothiazole derivatives and the formation constants of the complexes formed by these ligands with Mg^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Mn^{2+} and Cd^{2+} were determined potentiometrically at 25° in 2/1 (v/v) dioxane/water solution. The order of the basicity of the ligands is 4-substituted>7-substituted>2-substituted benzothiazole derivatives. Also the basicity of the benzothiazole derivatives, substituted at the same position, is in the order: aminomethyl> azomethine>azo compounds. Except for the azonaphthol derivatives, a linear relationship exists between the basicity and the π electron density of the hydroxyl group of the ligands, which may suggest that hydrazone form is predominant in the azo-hydrazone tautomerism of the benzothiazolylazonaphthol derivatives. The stability of the metal complexes corresponds to the basicity of the ligands and the log K_{ML} values approximately follow the Mellor–Maley stability sequence. It is expected that the benzothiazolylazo derivatives would be good metallochromic indicators in chelatometric titrations with ethylenediaminetetraacetic acid as titrant.

Keywords——benzothiazole derivatives; chelating agent; acid–base equilibrium; chelate formation; potentiometric titration

For the purpose of the development of new chelating agents, the benzothiazole derivatives were synthesized and their applications as analytical reagents have been investigated.[1,3] All of these ligands possesses a pyridine-like nitrogen and a hydroxyl group. In the present study, in order to obtain fundamental informations for the benzothiazole derivatives as chelating agents, their acid-base equilibria and their chelate formations with metal ions were investigated potentiometrically.

Experimental

Reagents——The benzothiazole derivatives shown in Table I were used. The syntheses of these ligands were described in the previous paper.[3]

Standard Metal Solution, 0.01 M——Prepared by dissolving $CuCl_2$, $NiCl_2$, $CoCl_2$, $MnCl_2$, $Zn(ClO_4)_2$, $CdCl_2$ and $MgCl_2$ in water, respectively, and determined by titration with ethylenediaminetetraacetic acid (EDTA), which was standardized with zinc (99.99% pure).

Carbonate-free 0.1 N Potassium Hydroxide——Prepared by the method of Armstrong[4] and standardized against potassium hydrogenphthalate.

Potentiometric Titration——Since all of the benzothiazole derivatives and their metal complexes investigated is insoluble in water, the potentiometric titration was carried out in 2/1 (v/v) dioxane/water. A 2/1 (v/v) dioxane/water solution containing a ligand (10^{-3} M), KCl (10^{-1} M) and if necessary, hydrochloric acid (10^{-3} M) and metal chloride or perchlorate (from 10^{-2} to 10^{-4} M) was titrated with 0.1 N KOH solution. During the course of titration, the temperature was maintained at 25±0.1° and carbonate–free nitrogen was passed through the titration vessel. The composition of the solvent was kept constant by adding simultaneously twice as much dioxane as 0.1 N KOH by volume using a double syringe buret. Measurement of pH were made with a Radiometer Titrater TTT2 and a Titrigraph SBR2 equipped with a Radiometer G2302C combined glass electrode. The instrument was standardized at pH 4.01 and 6.86 using a Toa Electronics buffer solu-

1) Part II: N. Shimidzu and T. Uno, *Chem. Pharm. Bull.* (Tokyo), **21**, 762 (1973).
2) Location: *Yoshidashimoadachi-cho, Sakyo-ku, Kyoto.*
3) N. Shimidzu and T. Uno, *Chem. Pharm. Bull.* (Tokyo), **21**, 184 (1973).
4) D.M.G. Armstrong, *Chem. Ind.* (London), **1955**, 1405.

tion. The pH meter correction and ion products of water for the solution of 2/1 (v/v) dioxane/water were determined to be 0.12 and 16.12 (at 25±0.1°), respectively, by the method of Van Uitert.[5]

Simple Linear Combination of Atomic Orbitals Molecular Orbital (LCAO-MO) Method——Parameters of hetero atoms and substituent groups, summarized by Yonezawa, *et al.*,[6] were used in the calculation.

Results and Discussion

The benzothiazole derivatives, investigated potentiometrically, are shown in Table I with their abbreviations. As shown in Fig. 1, the structure of the ligands consists of two major portions, benzothiazole and phenol or naphthol, which are bound with azo, azomethine or aminomethyl group.[3] The substituted position of the benzothiazole is 2, 4 or 7. The acid dissociation constants were calculated using the following equation.

$$pK_a = pH + \log \frac{C-[KOH]-[H^+]+[OH^-]}{[KOH]+[H^+]-[OH^-]} \quad (1)$$

where C is the total concentration of a ligand. Azomethine compounds are generally inclined to hydrolyze in aqueous solutions. Some of the azomethine compounds of the benzothiazole derivatives hydrolyzed in titration.

Table I. Benzothiazole Derivatives and Their Abbreviations

Number[a]	Compound	Abbreviation	X[b]	Y[b]
I	N-Salicylidene-2-aminobenzothiazole	NS2ABT	–N=CH–	C_6H_5OH
III	2-(*o*-Hydroxybenzyl)-aminobenzothiazole	2(HB)ABT	$-NHCH_2-$	C_6H_5OH
IV	Salicylaldehyde-2-benzothiazolylhydrazone	SA2BTH	–NHN=CH–	C_6H_5OH
V	2-(2-Benzothiazolylazo)-4-methoxyphenol	2(2BTA)4MePh	–N=N–	$C_6H_4OHOCH_3$
VI	2-(2-Benzothiazolylazo)-4-chlorophenol	2(2BTA)4ChPh	–N=N–	C_6H_4OHCl
VII	1-(2-Benzothiazolylazo)-2-naphthol	1(2BTA)2NT	–N=N–	$C_{10}H_6OH$
VIII	2-(*o*-Hydroxyphenylimino)-methylbenzothiazole	2(HPI)MBT	–CH=N–	C_6H_5OH
IX	2-(*o*-Hydroxyanilino)-methylbenzothiazole	2(HA)MBT	$-CH_2NH-$	C_6H_5OH
X	N-Salicylidene-4-aminobenzothiazole	NS4ABT	–N=CH–	C_6H_5OH
XII	4-(*o*-Hydroxybenzyl)-aminobenzothiazole	4(HB)ABT	$-NHCH_2-$	C_6H_5OH
XIII	2-(4-Benzothiazolylazo)-4-methoxyphenol	2(4BTA)4MePh	–N=N–	$C_6H_4OHOCH_3$
XIV	1-(4-Benzothiazolylazo)-2-naphthol	1(4BTA)2NT	–N=N–	$C_{10}H_6OH$
XV	2-(7-Benzothiazolylazo)-4-methoxyphenol	2(7BTA)4MePh	–N=N–	$C_6H_4OHOCH_3$
XVI	1-(7-Benzothiazolylazo)-2-naphthol	1(7BTA)2NT	–N=N–	$C_{10}H_6OH$
XVII	N-Salicylidene-7-aminobenzothiazole	NS7ABT	–N=CH–	C_6H_5OH

a) See ref. 3. *b*) See Fig. 1.

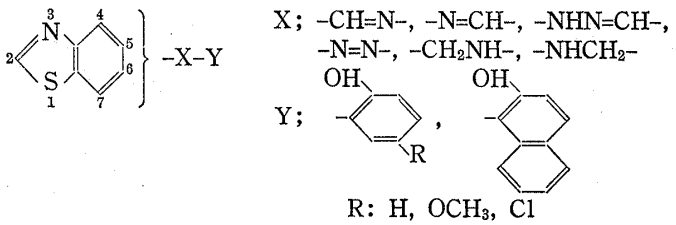

Fig. 1. Structures of Benzothiazole Derivatives

The acid dissociation constants of the benzothiazole derivatives are summarized in Table II. The order of the basicity of the ligands is 4-substituted>7-substituted>2-substituted benzothiazole derivatives. Also, the basicity of the benzothiazole derivatives, substituted at the same position, is in the order: aminomethyl>azomethine>azo compounds. These

5) L.G. Van Uitert and C.G. Haas, *J. Am. Chem. Soc.*, **75**, 451 (1953).
6) T. Yonezawa, T. Nagata, H. Kato, S. Imamura, and K. Morokuma, "Introduction to Quantum Chemistry," Vol. 1, Kagakudojin, Kyoto, 1963, p. 55.

Table II. Acid Dissociation Constants in 2/1(v/v) Dioxane/Water Solution at 25°, μ=0.1(KCl)

2-Substituted deriv.		4-Substituted deriv.		7-Substituted deriv.	
Compound	pK_a	Compound	pK_a	Compound	pK_a
2(HPI)MBT	11.4				
2(HA)MBT	12.1				
NS2ABT	10.57	NS4ABT	12.2	NS7ABT	11.93
2(HB)ABT	12.10	4(HB)ABT	12.22		
SA2BTH	10.53				
1(2BTA)2NT	9.27	1(4BTA)2NT	12.2	1(7BTA)2NT	11.85
2(2BTA)4MePh	9.31	2(4BTA)4MePh	11.69	2(7BTA)4MePh	11.10
2(2BTA)4ChPh	8.24				

pK_a values may be assigned to hydroxyl group. Generally, however, the possibility of an azo-hydrazone tautomerism is present with *o*-hydroxyazo compounds.[7]

It is expected that pK_a values are closely related to the total π electron density of the atom which donates or accepts a proton. In fact this relationship was found by Longuet-Higgins[8] and Albert, *et al.*[9] The π electron densities of the benzothiazole derivatives were calculated by simple LCAO-MO method and the results are shown in Fig. 2. The numbers on the abscissa in Fig. 2 indicate the total π electron density of oxygen of the hydroxyl group. The π electron density of the benzothiazolylazo derivatives are calculated by assuming the

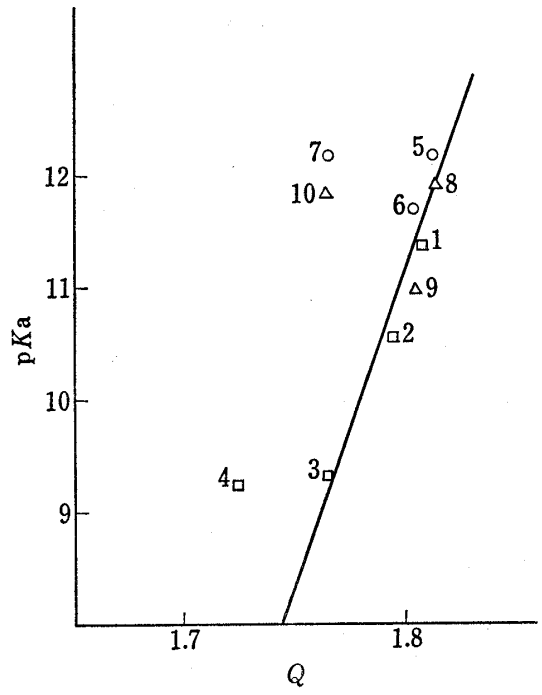

Fig. 2. Relationship between pK_a and π Electron Density

1, VIII; 2, I; 3, V; 4, VII; 5, X; 6, XIII; 7, XIV; 8, XVII; 9, XV; 10, XVI (See Table I).

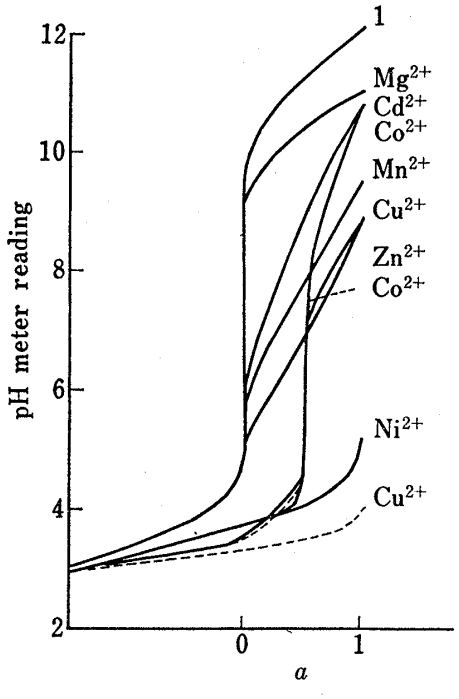

Fig. 3. Potentiometric Titration Curves of Molar Ratio of 2(4BTA)4MePh to Metal Ion 2: 1 and 1: 1; Solid Line and Broken Line represent the Curves of Molar Ratio 2: 1 and 1: 1, respectively; Curve 1, Ligand

7) D. Hadzi, *J. Chem. Soc.*, **1956**, 2143; J.W. Dudek and E.P. Dudek, *J. Am. Chem. Soc.*, **88**, 2407 (1966); J.E. Kuder, *Tetrahedron*, **28**, 1973 (1972); *etc.*
8) H.C. Longuet-Higgins, *J. Chem. Phys.*, **18**, 275 (1950).
9) A. Albert, R. Goldacre and J. Phylips, *J. Chem. Soc.*, **1948**, 2240.

azo form in their structures. It is recognized that a linear relationship exists between the pKa values and the total π electron density of the hydroxyl group of the ligands except for the azonaphthol derivatives. In case that the calculation is made by assuming the hydrazone form, the benzothiazolylazo derivatives deviate from the linear relationship, but a linear relationship seems to be recognized between the pK_a values and the total π electron density of –NH– of the hydrazone group in the benzothiazolylazonaphthol derivatives. These results may suggest that hydrazone form is predominant in the azo-hydrazone tautomerism of the benzothiazolylazonaphthol derivatives. The basicity of the nitrogen of the thiazole ring in all of the investigated benzothiazole derivatives is very weak and their dissociation constants could not be obtained.

The titration curves of 2(4BTA)4MePh in the presence and the absence of metal ions are shown in Fig. 3, as a typical example. The titration curves of 2(4BTA)4MePh with metal ions except Cu^{2+} and Co^{2+} in the molar ratio of both 1:1 and 2:1 ligand-to-metal show an inflection at $a=1$, where a represents moles of KOH added per mole of the ligand. And in the curve of the 1:1 molar ratio, the hydrolysis of metal ions is recognized at a high pH. Accordingly, it is supposed that 2(4BTA)4MePh reacts with metal ions except Cu^{2+} and Co^{2+} to form 2:1 ligand-to-metal chelates. With Cu^{2+}, the curve of the 2:1 molar ratio gives an inflection at $a=0.5$ and shows the liberation of a proton at the region of higher pH, while the curve of the 1:1 molar ratio gives an inflection at $a=1$. The titration curves for the Cu^{2+} suggest the following reaction process. In the 2:1 molar ratio solution the formation reaction of the 1:1 chelate CuL^+ occur between $a=0$ and $a=0.5$, and this chelate reacts with the second ligand to form the 2:1 chelate CuL_2. On the other hand, in the 1:1 solution, the ligand reacts with the Cu^{2+} to form the 1:1 chelate in one step.

$$Cu^{2+} + L^- \rightleftarrows CuL^+ \qquad K_{ML} = \frac{[CuL^+]}{[Cu^{2+}][L^-]} \tag{2}$$

$$CuL^+ + L^- \rightleftarrows CuL_2 \qquad K_{ML_2} = \frac{[CuL_2]}{[CuL^+][L^-]} \tag{3}$$

The reactions of the other ligands are analogous to those of 2(4BTA)4MePh with metal ions except Co^{2+}. With Co^{2+}, the titration curves of the 2:1 and 1:1 molar ratios are identical between $a=0$ and $a=0.5$, but the hydrolysis of Co^{2+} occurs at about $a=0.5$ in the 1:1 solution. And the curve of 4:1 molar ratio gives an inflection at $a=0.25$. From these facts, it is considered that 2(4BTA)4MePh reacts with Co^{2+} to form a protonated chelate $Co.HL.L^+$ and then one proton is released to form a deprotonated 2:1 chelate CoL_2.

$$Co^{2+} + HL + L^- \rightleftarrows Co\cdot HL\cdot L^+ \qquad K_{Co\cdot HL\cdot L} = \frac{[Co\cdot HL\cdot L^+]}{[Co^{2+}][HL][L^-]} \tag{4}$$

$$Co\cdot HL\cdot L^+ \rightleftarrows CoL_2 + H^+ \qquad K_C = \frac{[CoL_2][H^+]}{[Co\cdot HL\cdot L^+]} \tag{5}$$

This reaction with Co^{2+} was only observed for 2(4BTA)4MePh and the other ligands react with Co^{2+} to form the 2:1 chelate in one step. 7-Substituted benzothiazole derivatives are poor in the reactivity with metal ions.[3] This is explained by a larger distance of sulfur—other coordinate atom, compared with that of nitrogen—other coordinate atom in 4-substituted benzothiazole derivatives; the 7-substituted benzothiazole derivatives do not behave as terdentate ligands.

The stability constant of the 2:1 ligand-to-metal chelate was calculated by Bjerrum's method,[10] as modified by Irving and Rossotti,[11] from the following equations:

$$[L] = \frac{C_L + [HCL] + [OH^-] - [KOH] - [H^+]}{P} \tag{6}$$

10) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Sons, Copenhagen, 1941.
11) G. Irving and H.S. Rossoti, *J. Chem. Soc.*, **1953**, 3397.

$$\bar{n} = \frac{C_L - Q\cdot[L]}{C_M} \quad (7)$$

where $P=[H^+]/K_a$ and $Q=1+[H^+]/K_a$; $\bar{n}$ is the average number of ligands bound per metal ion, C_L and C_M are the total ligand concentration and the total metal concentration, respectively, and K_a is acid dissociation constant. The values of $\bar{n}$ and [L] at each point of the titration curves were calculated from Eqs. (**6**) and (**7**). From these data, formation curves were plotted.

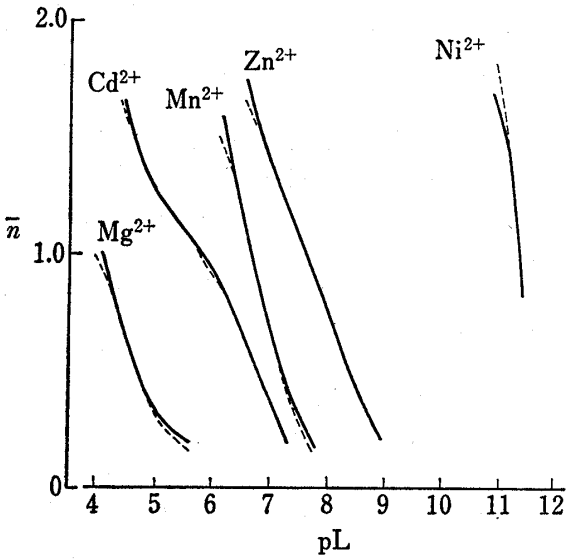

Fig. 4. Formation Curves of Metal Chelates of 2(4 BTA)4MePh; Solid Line and Broken Line represent Experimental and Theoretical Formation Curves, respectively

The stepwise stability constants, K_{ML} and K_{ML_2}, were calculated by the least-squares method by the use of Eq. (**8**):

$$\frac{\bar{n}}{(\bar{n}-1)\cdot[L]} = \frac{(2-\bar{n})\cdot[L]}{(\bar{n}-1)}\cdot K_{ML}\cdot K_{ML_2} - K_{ML} \quad (8)$$

When the precipitation was observed in the course of titration, the stability constants were estimated from the data obtained before the precipitation occurred. From the values of K_{ML}, K_{ML_2} and [L], $\bar{n}$ was recalculated by Eq. (**9**) and theoretical formation curves were plotted:

$$\bar{n} = \frac{K_{ML}\cdot[L] + 2K_{ML}\cdot K_{ML_2}\cdot[L]^2}{1 + K_{ML}\cdot[L] + K_{ML}\cdot K_{ML_2}\cdot[L]^2} \quad (9)$$

The theoretical and experimental formation curves of 2(4BTA)4MePh are shown in Fig. 4, as an example. The theoretical curve is in good agreement with the experimental. The formation constants of the copper chelates

Table III. Stability Constants of the Metal Chelates of 2-Substituted Derivatives in 2/1(v/v) Dioxane/Water Solution at 25°, μ=0.1(KCl)

Ligand	Metal ion	log K_{ML}	log K_{ML_2}	log β
2(HPI)MBT	Cu^{2+}	9.9	4.7	14.6
	Co^{2+}	7.5	8.3	15.8
	Ni^{2+}	7.4	6.7	14.1
	Zn^{2+}	5.9	6.1	12.0
	Cd^{2+}	5.8	3.6	9.4
2(HA)MBT	Cu^{2+}	11.7	4.1	15.8
	Ni^{2+}	7.7	6.5	14.2
1(2BTA)2NT	Co^{2+}	8.3	(7.5)	15.8
	Ni^{2+}	7.5	7.7	15.2
	Zn^{2+}	6.2	(6.7)	12.8
	Cd^{+2}	5.4	(4.3)	9.7
2(2BTA)4MePh	Cu^{2+}	10.4	6.8	17.2
	Co^{2+}	7.9	8.5	16.4
	Ni^{2+}	7.8	7.1	14.9
	Zn^{2+}	5.6	5.9	11.5
	Cd^{2+}	5.4	3.9	9.3
	Mn^{2+}	4.3	4.9	9.1
2(2BTA)4ChPh	Cu^{2+}	8.3	4.9	13.2
	Ni^{2+}	6.5	7.0	13.5
	Zn^{2+}	3.6	4.3	7.9
	Cd^{2+}	3.9	3.2	7.1

Table IV. Stability Constants of the Metal Chelates of 4-Substituted Derivatives in 2/1(v/v) Dioxane/Water Solution at 25°, μ=0.1(KCl)

Ligand	Metal ion	log K_{ML}	log K_{ML_2}	log β
NS4ABT	Zn^{2+}	7.7	6.7	14.4
	Cd^{2+}	6.4	5.0	11.4
1(4BTA)2NT	Co^{2+}	10.8	10.9	21.7
	Ni^{2+}	11.5	(9.2)	20.7
	Zn^{2+}	8.1	(7.6)	15.7
	Cd^{2+}	6.6	6.0	12.6
	Mn^{2+}	7.3	(7.5)	14.8
2(4BTA)4MePh	Ni^{2+}	11.1	11.5	22.6
	Zn^{2+}	8.4	6.9	15.3
	Cd^{2+}	6.8	4.6	11.4
	Mn^{2+}	7.0	6.3	13.3
	Mg^{2+}	4.7	3.2	7.9
	Co^{2+}	log $K_{Co.HL.L}$=15.0, pK_C=10.8		

and the protonated chelate were estimated on bases of the law of the electroneutrality and material balance in solution.

The stability constants are summarized in Tables III and IV. The stability constants K_{ML_2} is designated in parentheses when the data of $\bar{n}>1$ was insufficient as the precipitaion occurred in the course of titration. Tables III and IV indicate that the stability of the metal chelate increases with the increase of the basicity of the ligand and that the log K_{ML} values approximately follow the Mellor–Maley stability sequence.[12] The stability constants of the metal chelates of the benzothiazolylazo derivatives are somewhat lower than those[13] of 1-(2-pyridylazo)-2-naphthol(PAN) and 4-(2-pyridylazo)-resorcinol(PAR), though the conditions in their measurements differ from those of PAN and PAR. However, they are sufficiently stable but not as stable as those of EDTA. Therefore, it is expected from the stability that the benzothiazolylazo derivatives would be good metallochromic indicators in chelatometric titrations with EDTA as titrant. The stability constant $K_{Co.HL.L}$ of the protonated chelate of 2(4BTA)4MePh with Co^{2+} is 15.0. Its dissociation constant pK_C is 10.8 and is lower than that of 2(4BTA)4MePh which does not coordinate to Co^{2+}. This should be predictable from the electron-withdrawing effect of the metal ion.

12) D.P. Mellor and L.E. Maley, *Nature* (London), **159**, 370 (1947); **161**, 436 (1948).
13) R.G. Anderson and G. Nickless, *Analyst*, **92**, 207 (1967).