Syntheses of Chelating Agents. I. Stability of the Metal Chelate of Benzylamine-N, N-diacetic Acid and its Nitro Derivatives[*]

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Although many papers[1-7] have been published concerning the stabilities of the metal chelates of iminodiacetic acid and its derivatives, no investigation has been undertaken of the stability of its benzyl derivatives.

During the course of our search for new chelating agents of the aminopolycarboxylic acid type, benzylamine-*N*, *N*-diacetic acid and two of its nitro derivatives have been synthesized.

This paper is to report on the syntheses of new ligands as well as on the stabilities of their metal chelates, with an attempt to correlate the structure of the ligand with the stability of the metal chelates.

The synthesis of benzylamine-*N*, *N*-diacetic acid (BADA) has been reported on in the literature[8]. The syntheses of the new ligands, *o*- and *p*-nitrobenzylamine-*N*, *N*-diacetic acid (*o*-NBADA and *p*-NBADA), has been carried out by the standard procedure[9] from the corresponding nitrobenzylamine and monochloroacetic acid.

The chelate stability measurements were carried out by the pH titration method on these ligands only for a 1 : 1 ratio of the ligand to the metal ion, and the first stability constants have been obtained.

For BADA, the chelate stability constants with copper(II), nickel(II), cobalt(II), lead(II), zinc(II), calcium(II) and magnesium(II) were obtained. The results indicate that the behavior of BADA in relation to metal ions is similar to that of iminodiacetic acid. The copper chelate is so stable that it exists even in a strongly acid solution where the undissociated form of the ligand predominates. It forms relatively stable chelates with nickel, zinc, lead and cobalt, and forms very unstable chelates with magnesium and calcium. It was also noted that the pH titration curves indicated the formation of hydrogen complexes with some metal ions in the low pH region.

For *o*- and *p*-nitrobenzylamine-*N*, *N*-diacetic acid, the stability constants of magnesium(II) and calcium(III) have been obtained, the results indicated that the nitro substitution on the benzene ring had an appreciable effect on the dissociation constant of the ligand as well as on the stability constant of the chelates.

Experimental

Syntheses of Ligands.—BADA, which had been prepared according to the method of Chase and Downer[8], was purified by repeated recrystallization from water. The pure product decomposed at 204°C.

Found: N, 6.17. Calcd. for $C_{11}H_{13}NO_4$: N, 6.28%.

Syntheses of *o*-NBADA and *p*-NBADA.—These were synthesized from *o*- and *p*-nitrobenzylchloride respectively, according to the following reaction scheme, in which both compounds were processed in the way otherwise mentioned:

$$C_6H_4(NO_2)CH_2Cl \xrightarrow[\text{in dimethylformamide}]{C_6H_4(CO)_2NK}$$

$$\underset{\text{(I)}}{C_6H_4(NO_2)CH_2N(CO)_2C_6H_4} \xrightarrow[\text{dil.HCl}]{H_2NNH_2}$$

$$\underset{\text{(II)}}{C_6H_4(NO_2)CH_2NH_2\cdot HCl} \xrightarrow{ClCH_2CO_2H}$$

$$\underset{\text{(III)}}{C_6H_4(NO_2)CH_2N(CH_2CO_2H)_2}$$

o- and p-Nitrobenzylphthalimide (I). — The corresponding nitrobenzylchloride (18 g.) and potassium phthalimide (18 g.) were suspended in dimethylformamide[**], and the mixture was heated while being stirred in an oil bath at 100~110°C. The temperature was kept below 120°C to prevent any side reaction. After two hours, the mixture was cooled; then it was poured into 500 ml. of water and stirred well. After the mixture had been left

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[*] Contribution No. 23 from the Department of Organic Synthesis, Faculty of Engineering, Kyushu University.

[1] S. Chaberek, Jr. and A. E. Martell, *J. Am. Chem. Soc.*, **74**, 5052 (1952).

[2] S. Chaberek, Jr., R. C. Courtney and A. E. Martell, ibid., **74**, 5057 (1952).

[3] G. Schwarzenbach, E. Kamplitsh and R. Steiner, *Helv. Chim. Acta*, **29**, 364 (1946).

[4] G. Schwarzenbach, A. Wili and R. O. Bach, ibid., **30**, 1303 (1947).

[5] G. Schwarzenbach and W. Biedermann, ibid., **38**, 1492 (1951).

[6] G. Anderegg and G. Schwarzenbach, ibid., **38**, 1940 (1951).

[7] G. Schwarzenbach, G. Anderegg, W. Schneider and H. Senn, ibid., **38**, 1147 (1955).

[8] B. H. Chase and A. M. Downer, *J. Chem. Soc.*, **1953**, 3874.

[9] G. Schwarzenbach and H. Ackermann, *Helv. Chim. Acta*, **31**, 1029 (148).

[**] The use of dimethylformamide, which was recently suggested by Sheehan and Bolhofer, has an advantage of a lower reaction temperature with an increased yield, while avoiding tar formation (*J. Am. Chem. Soc.*, **72**, 2786 (1950)).

standing for a while, the separated precipitate was filtered off and washed repeatedly. The crude product was purified by recrystallization from acetic acid. The melting point was 218°C for *o*-nitrobenzylphthalimide and 174°C for *p*-nitrobenzylphthalimide.

Found: *o*-isomer N, 9.91. *p*-isomer N, 9.92. Calcd. for $C_{15}H_{10}N_2O_6$: N, 9.91%.

o- and p-Nitrobenzylamine (II).—The corresponding phthalyl compounds I were decomposed with hydrazine hydrate and dilute hydrochloric acid in an ordinary manner[10]. The hydrochlorides thus obtained were recrystallized several times from 95% ethanol and were then used for the next step. *o*- and *p*-Nitrobenzylamine hydrochloride decomposed at 248 and 249°C respectively.

o- and p-NBADA. — The same general procedure was also followed in this step. To 70 ml. of a 2 M aqueous solution of monochloroacetic acid which had been carefully neutralized with sodium hydroxide, 10 g. of the corresponding nitrobenzylamine hydrochloride was added. The pH value of the mixture was adjusted to 10 by dropping in a 2 N sodium hydroxide solution. After the mixture had been stirred for three hours at 50°C, the temperature was raised to 70~80°C to complete the reaction, while the pH value of the reaction mixture was maintained between 7 and 10 by the intermittent addition of a sodium hydroxide solution. After it had cooled, the reaction mixture was filtered to remove some precipitates. The crude acid was precipitated as barium salt from the filtrate, and free acid was regenerated by treating barium salt with the theoretical amount of sulfuric acid.

The free acid was further purified by repeated recrystallization from 70% ethanol or methanol. Colorless crystls of *o*-NBADA, which decomposed at 189°C, were obtained in a 50% yield. Pale yellow crystals of *p*-NBADA, which decomposed at 201~202°C, were obtained in a 40% yield.

Found for *o*-NBADA: C, 49.31; H, 4.47; N, 10.65. Found for *p*-NBADA: C, 49.46; H, 4.41; N, 10.45. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.45%.

Both compounds were slightly soluble in water (about 1.8×10^{-2} mol./1000 ml. water) and were appreciably soluble in ethanol.

Measurement of Dissociation and Chelate Stability Constants.—The experimental method consisted of the potentiometric titration of the ligand in both the absence and the presence of the metal ion being investigated. The ionic strength was kept constant ($\mu=0.1$) by using potassium nitrate as a supporting electrolyte and by employing relatively low concentrations (about 2×10^{-3} mol.) of the metal ion and the ligand. The titrations were carried out on a solution of only a 1 : 1 ratio of the ligand to the metal ion concentration. All measurements were carried out at 25±0.1°C.

The titration assembly consisted of a Hitachi-Horiba model P pH meter with glass and calomel electrodes and of a jacketed glass titration cell 130 ml. in capacity. Instead of using the standard buffer, the calibration of the pH meter was carried out under a constant ionic strength ($\mu=0.1$) by referring to the hydrogen ion concentration calculated from the hydrochloric acid-sodium hydroxide titration system for the regions below pH 3 and above pH 7, and from the acetic acid-sodium hydroxide system for the region between pH 3~7.

The titrations were carried out by the usual procedure in an atmosphere of carbon-dioxide free nitrogen. The pH reading were taken until the pH value reached 10.5~11.0 for each titration. The concentrations of the ligand and the metal ion were about 2×10^{-3} mol. for BADA, and about 8×10^{-4} mol. for *o*- and *p*-NBADA because of their low solubilities. The concentrations of the metal ion stock solutions were determined by the EDTA titration.

All reagents used in this investigation were of the analytical grade.

Calculation

Calculation of Acid Dissociation Constants.—The acid dissociation constants were calculated from the titration curves of ligands in the absence of metal ions (Figs. 1, 2 and 3). The equilibria involved and the dissociation constants to be determined are:

$$H_2A \rightleftarrows HA^- + H^+ ; \quad k_1=(H^+)(HA^-)/(H_2A) \qquad (1)$$

$$HA^- \rightleftarrows A^{2-} + H^+ ; \quad k_2=(H^+)(A^{2-})/(HA^-) \qquad (2)$$

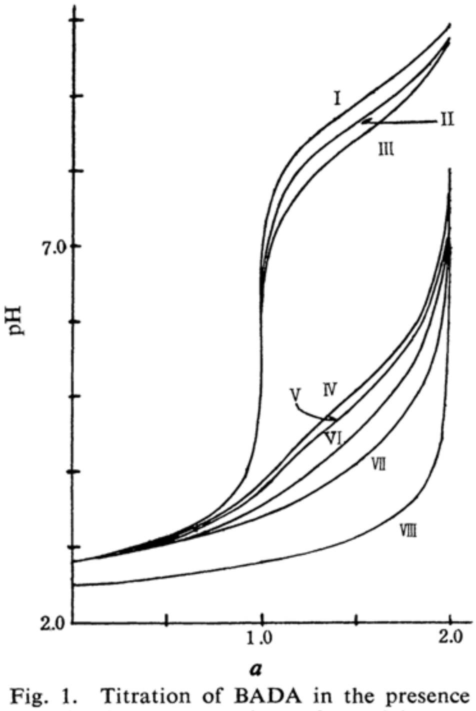

Fig. 1. Titration of BADA in the presence of equimolar concentrations of metal ions.
I, 2×10^{-3} M BADA with 0.1 N NaOH; II, Mg(II); III, Ca(II); IV, Co(II); V, Zn(II); VI, Pb(II); VII, Ni(II); VIII, Cu(II).
a, denotes moles of base added per mole of acid.

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[10] H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, **1926**, 2348.

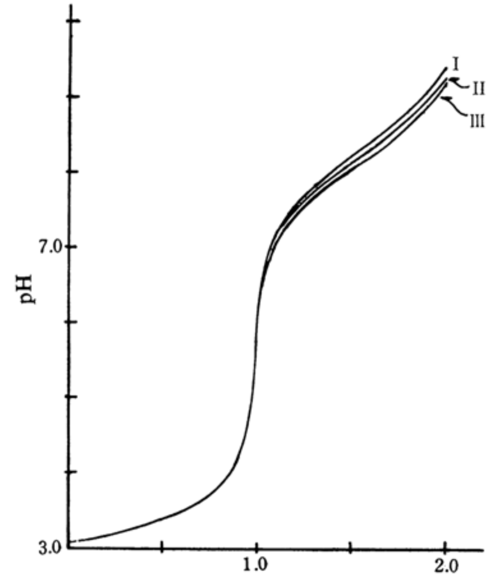


Fig. 2. Titration of *o*-NBADA in the presence of equimolar concentrations of Mg(II) and Ca(II) ions.
I, 8×10^{-4} M *o*-NBADA with 0.1 N NaOH; II, Mg(II); III, Ca(II).
a, denotes moles of base added per mole of acid.

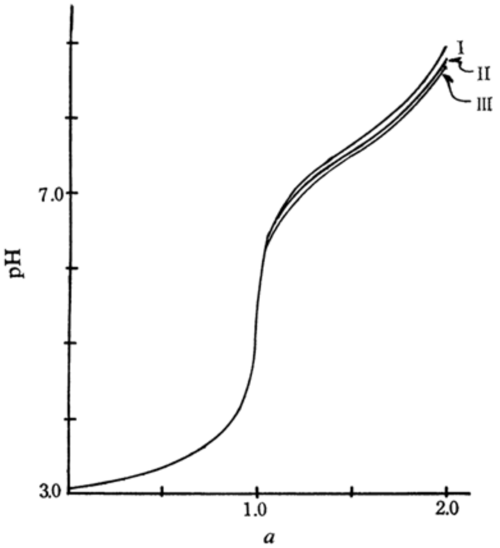


Fig. 3. Titration of *p*-NBADA in the presence of equimolar concentrations of Mg(II) and Ca(II) ions.
I, 8×10^{-4} M *p*-NBADA with 0.1 N NaOH; II, Mg(II); III, Ca(II).
a, denotes moles of base added per mole of acid.

where H_2A represents the undissociated ligand. As is shown in Figs. 1, 2 and 3, the two buffer regions are so clearly separated that each dissociation stage can be treated independently. If C_A represents the total concentraions of the ligand species and a represents the number of moles of the base added per mole of the ligands present, it follows that in the low pH buffer region

$$C_A=(H_2A)+(HA^-) \quad (3)$$

$$aC_A+(H^+)=(HA^-) \quad (4)$$

Also, the first dissociation constant may be calculated from the following equation:

$$k_1=\frac{(H^+)\,[aC_A+(H^+)]}{C_A-[aC_A+(H^+)]} \quad (5)$$

In the high pH buffer region, the concentration of the acid form (H_2A) of the ligand may be neglected, and Eqs. 3 and 4 can be rewritten as

$$C_A=(HA^-)+(A^{2-}) \quad (6)$$

$$(a-1)C_A-(H^+)/K_W=(A^{2-}) \quad (7)$$

Under these conditions, k_2 may be expressed as

$$k_2=\frac{(H^+)\,[(a-1)C_A-(H^+)/K_W]}{C_A-[(a-1)C_A-(H^+)/K_W]} \quad (8)$$

where $K_W=(H^+)(OH^-)$. Alternatively, the second dissociation constant could be obtained directly from the titration curve, if one preserved a relationship in which the value of pk_2 is equal to the pH value at $a=1.5$ on the titration curve of the ligand. In this investigation, the k_2 value of BADA was determined by both methods, while the k_2 value of *o*-NBADA and *p*-NBADA were obtained only by the graphical method.

Calculation of the Chelate Stability Constants.—It has been reported[1)] that, in the case of iminodiacetic acid and iminodipropionic acid, the formation of 1:2 chelate (MA_2) could be neglected in the region around $a=1.5$ in the titration curve of a 1:1 metal ligand mixture. Accordingly, it may be safe to assume for BADA chelates that in the pH range corresponding to *a* values of about 1.0∼1.8, the equilibria involved in the chelate formation may be expressed as follows:

$$M^{2+}+A^{2-}\rightleftarrows MA;$$

$$K_{MA}=(MA)/(M^{2+})(A^{2-}) \quad (9)$$

where M represents the divalent metal ion used. Therefore, K_{MA} can be calculated by the following equation, which was derived by Chaberek and Martell[1)]:

$$K_{MA}=\frac{C_A-\alpha(A^{2-})}{(A^{2-})\,[C_M+\alpha(A^{2-})-C_A]}=\frac{C_A-\alpha(A^{2-})}{\alpha(A^{2-})^2} \quad (10)$$

The last formula in Eq. 10 may be obtained because $C_A=C_M$ in this case. In this equation, (A^{2-}) and α are expressed as

$$(A^{2-})=\frac{(2-a)C_A-(H^+)+(OH^-)}{2(H^+)^2/k_1k_2+(H^+)k_2} \tag{11}$$

$$\alpha=(H^+)^2/k_1k_2+(H^+)/k_2+1 \tag{11'}$$

where C_M represents the total concentration of the metal ion species.

In general, Eqs. 10, 11 and 11′ can be used for the calculation of the stability constants of divalent metal chelates. However, in the case of calcium and magnesium chelates, they can be simplified, as will be discussed below. It can be seen from the titration curves (Figs. 1, 2 and 3) of these chelates that the chelate formations occur in approximately the region of $a=1.0\sim2.0$, where the first dissociation step of the ligand can be neglected. Therefore, the following stoichiometric relationships can be written for ligand ion species, metal ion species and the titrable hydrogen ion respectively:

$$C_A=(HA^-)+(A^{2-})+(MA) \tag{12}$$

$$C_M=(M^{2+})+(MA) \tag{13}$$

$$(2-a)C_A=(H^+)-(OH^-)+(HA^-) \tag{14}$$

Since $C_A=C_M$, as defined in the experimental conditions, Eqs. 2, 12 and 13 may be combined to give

$$K'_{MA}=\frac{C_A-\alpha'(A^{2-})}{(A^{2-})^2} \tag{15}$$

Here K'_{MA} represents the stability constants for magnesium and calcium chelates, while α' and (A^{2-}) can be given in the more simplified form:

$$(A^{2-})=\frac{(2-a)C_A+(OH^-)-(H^+)}{(H^+)/k_2} \tag{16}$$

$$\alpha'=(H^+)/k_2+1 \tag{16'}$$

with the aid of Eqs. 15, 16 and 16′, the stability constants of magnesium and calcium chelates of BADA, *o*-NBADA and *p*-NBADA were calculated.

Finally, as there is an indication of the formation of a hydrogen complex in the relatively low pH region in certain ions, the stability constants of the hydrogen complex were calculated. If one assume that, in a low pH region, only the formation of the hydrogen complex is predominant, the other reactions being negligible, the equilibria involved in this pH range can be given as follows:

$$H_2A \rightleftarrows H^+ + HA^-;$$

$$k_1=(H^+)(HA^-)/(H_2A) \tag{17}$$

$$M^{2+}+HA^- \rightleftarrows MHA^+;$$

$$K_{MHA}=(MAH^+)/(M^{2+})(HA^-) \tag{18}$$

Also the total concentration of the ligands, metal ions and titrable hydrogen ions are given respectively by;

$$C_A=(H_2A)+(HA^-)+(MHA^+) \tag{19}$$

$$C_M=(M^{2+})+(MHA^+) \tag{20}$$

$$(2-a)C_A=(H^+)-(OH^-)+(MHA^+)+(HA^-)+2(H_2A) \tag{21}$$

On the basis of these equations, K_{MHA} is expressed as

$$K_{MHA}=\frac{aC_A+(H^+)-\beta k_1/(H^+)}{\beta^2 k_1/(H^+)\,[1+k_1/(H^+)]} \tag{22}$$

where $\beta=(H_2A)=C_A(1-a)-(H^+)$. Calculations were carried out with the aid of the above equations, employing the data taken from the $a=0.5\sim0.8$ region of the titration curves (Fig. 1)

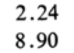
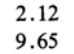
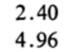
Results and Discussion

The acid dissociation constants of BADA and its chelate stability constants are listed in Table I. If one consider the basicity of the donor nitrogen, the value of the second dissociation constant and the chelate stability constants of BADA may be expected in between those of aniline-*N*, *N*-diacetic acid⁽⁷⁾ and of methylamine-*N*, *N*-diacetic acid⁽⁷⁾. The data obtained are in good accordance with our estimates, as is shown in Table I.

The other of the decreasing stability of the metal chelate is Cu(II)>Ni(II)>Pb(II)>Zn(II)>Co(II)>Ca(II)>Mg(II), as is listed in Table I. These values were calculated using Eqs. 15 and 16 for calcium and magnesium, and 10 and 11 for the rest of the metal ions, employing the data obtained from nine points on the titration curve in the $a=1.1\sim1.8$ range for each metal ion. The calculated values on each metal ion are found to be in good agreement within the range of experimental error, thus indicating the reasonableness of the assumption. The order of chelate stability for

TABLE I. THE STABILITY CONSTANTS OF CHELATES OF BADA AND RELATED LIGANDS

$\mu=0.1$ (KNO$_3$)

Ligand		 $CH_3-N(CH_2COOH)_2$ [7]	 [7]
	25°C	20°C	20°C
pk_1	2.24	2.12	2.40
pk_2	8.90	9.65	4.96
log K_{MA} for			
Cu(II)	10.51	10.09	6.57
Ni(II)	7.98	8.73	3.53
Pb(II)	7.39	—	3.49
Zn(II)	6.97	7.66	3.22
Co(II)	6.88	7.62	2.90
Ca(II)	3.13	3.75	1.50
Mg(II)	2.63	3.44	1.15

these ions is quite similar to that of methylamine-*N*, *N*-diacetic acid, as is shown in Table I. Moreover, the decreased values for the BADA chelates may be due to the electronegative effect of the phenyl group through $-CH_2-$ linkage.

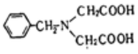
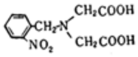
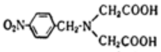
Although we tried to apply this calculation to the range below $a=1.0$ for copper, nickel, zinc, lead and cobalt, it was only successful in the case of copper and nickel, failing for the rest of metal ions. For copper and nickel, the consistent values were obtained even in this earlier part of the titration curve, and their mean values were identical with those obtained from the later part of the curve.

If one carefully examines the titration curves for zinc, lead and cobalt, a slight inflection will be noticed at a point near $a=1.0$. This inflection may indicates that the chelate formation reaction proceeds in two steps. The first step involves the formation of a hydrogen complex which predominates at the first buffer region of $a=0.8$, while the second step involves the formation of a neutral complex which predominates at the second buffer region of $a=1.3$. In the $a=0.8\sim1.3$ region, both reactions proceed simultaneously. Proceeding from this assumption, the stability constants of the hydrogen complex (K_{MHA}) with three metal ions were calculated in the first buffer region of $a=0.5\sim0.8$, the points used for the calculation being only five. The calculated values were found to be fairly consistent for the hydrogen complexes of cobalt and zinc, but not for lead. The values for cobalt and zinc thus determined are found to be $\log K_{\mathrm{CoHA}}=2.7$ and $\log K_{\mathrm{ZnHA}}=3.0$.

As the data used for the calculation were obtained from a relatively narrow range, these values may not be accurate enough. However, the formation of a hydrogen complex will be quite probable for zinc and cobalt. Although the calculation of the stability constant of a hydrogen complex for lead did not give satisfactory results, the formation of the hydrogen complex may also occur to some extent in this case.

The acid dissociation constants of *o*- and *p*-NBADA, as well as their chelate stability constants for calcium and magnesium, are listed in Table I. The first and second dissociation constants of both compounds indicate that these are more acidic than BADA. The higher acidity can be attributed to the electron inductive effect of the nitro group, which decreases the basicity of the donor nitrogen through $-CH_2-$ linkage. In the case of the *o*-isomer, the coplanarity of the nitro group is so hindered by the neighboring bis-(carboxymethyl)-iminomethylene group that the resonance of nitro group is decreased, which in turn reduces the inductive effect of the nitro group. Thus, the *o*-isomer is less acidic than the *p*-isomer, whose nitro group does not suffer from steric hindrance.

TABLE II. ALKALINE EARTH CHELATING TENDENCIES OF BADA AND ITS NITRO DERIVATIVES
$t=25°\mathrm{C}$, $\mu=0.1$ (KNO_3)

Ligand			
pk_1	2.24	1.99	1.80
pk_2	8.90	8.29	7.65
log K_{MA} for			
Ca(II)	3.13	2.93	2.53
Mg(II)	2.63	2.65	1.6

The stability constants of these two ligands with calcium and magnesium are found to be reasonable in comparison with those of BADA, and their stabilities decrease with the decreasing pk_2 values. The accuracy of the stability constant of magnesium chelate of *p*-NBADA is attained only to one decimal place on account of its low stability.

Summary

1. The acid dissociation constants of benzylamine-*N*, *N*-diacetic acid, and the stability constants of its chelates with Cu(II), Ni(II), Pb(II), Zn(II), Co(II), Ca(II) and Mg(II) at 25°C and 0.1 ionic strength, have been determined by the pH titration method.

2. *o*- and *p*-Nitrobenzylamine-*N*, *N*-diacetic acid have been newly synthesized from the corresponding benzylamine.

3. The acid dissociation constants of the above two ligands, and the stability constants of its chelates with Ca(II) and Mg(II), have been determined at 25°C and 0.1 ionic strength.

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