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Synthesis of Chelating Agents. IV.*1 Synthesis and Chelating Behavior of 1-Phenyl-ethylenedinitrilo-*N*, *N*, *N'*, *N'*-tetraacetic Acid and 1, 2-Diphenyl-ethylenedinitrilo-*N*, *N*, *N'*, *N'*-tetraacetic Acid*2

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1-Phenylethylenedinitrilo-*N*, *N*, *N'*, *N'*-tetraacetic acid and *dl*-1, 2-diphenylethylenedinitrilo-*N*, *N*, *N'*, *N'*-tetraacetic acid have been synthesized by the carboxymethylation of the corresponding phenyl-substituted ethylenediamines. The chelate stability constants of the two ligands have been determined potentiometrically for alkaline earth and selected transition metal ions. The increase in the chelate stability as compared with EDTA was interpreted in terms of the steric effect of phenyl substitutions.

Many papers have been published on the relationship between the structure of the complexane-type chelating agents and their chelate stability constants. In our laboratories, two phenyl-substituted derivatives of ethylenedinitrilotetraacetic acid (EDTA) have been synthesized. These compounds, 1-phenylethylenedinitrilo-*N*, *N*, *N'*, *N'*-tetraacetic acid (PEDTA) and *dl*-1, 2-diphenylethylenedinitrilo-*N*, *N*, *N'*, *N'*-tetraacetic acid (*dl*-DPEDTA), were synthesized for the purpose of introducing these functional groups into a polymer matrix to obtain the chelating ion exchange resin. Although the syntheses of these two ligands have been reported in the literatures,[1,2] very little detailed information on the synthesis and on the chelating behavior has been reported. It is the purpose of this paper to report, in detail, on the syntheses, properties, and chelating behavior of PEDTA and *dl*-DPEDTA.

It is known that the introduction of a methyl group to the 1- or 1, 2-positions of EDTA results in an increase in the chelate stability constant. A similar effect may also be expected in the case of the phenyl substitution of EDTA.

In the case of diphenyl derivatives, two stereoisomeric forms are expected to exist, *i. e.*, *dl*- and *meso*-forms. If one considers the steric effect of the phenyl group on the chelate stability constant, it may be of great interest to compare the chelate stability constants of *dl*- and *meso*-DPEDTA. Although our efforts to synthesize *meso*-DPEDTA were unsuccessful, the cyclization products of reaction intermediates were obtained.

The chelate stability constants of PEDTA and *dl*-DPEDTA were measured by the direct titration method for alkaline-earth metal ions, and by competitive reactions with triaminotriethylamine for the transition metal ions, such as copper(II), zinc(II), cobalt(II), and nickel(II).

*1 Paper III: T. Ando and K. Ueno, *Inorg. Chem.*, **4**, 375 (1965).

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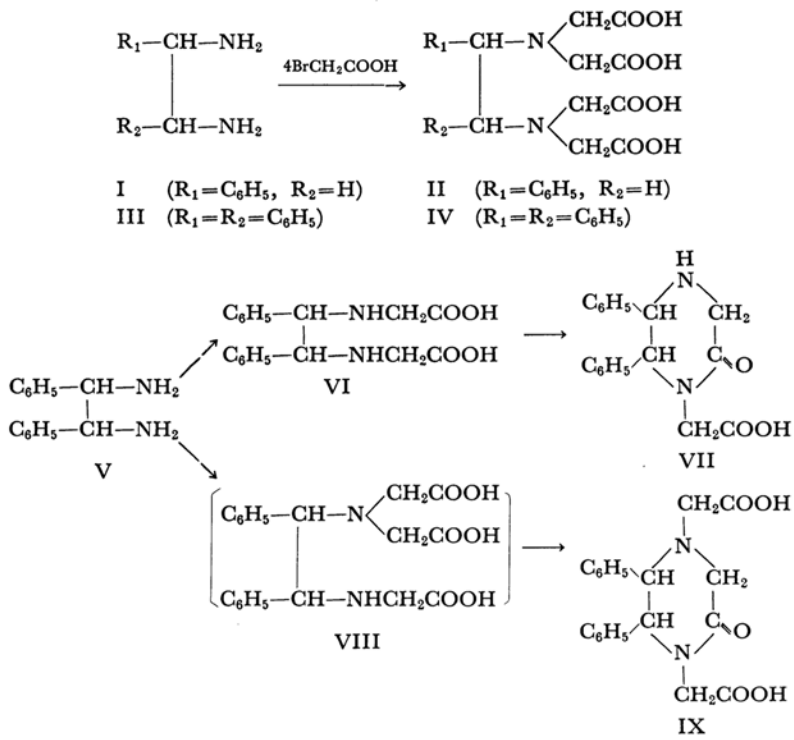
1) V. G. Yashunskii, V. F. Vasileva and L. I. Tikbobova, *Zhur. Obshichie Khim.*, **29**, 2709 (1959).

2) W. Zerweck and O. Trösken, German Pat. 828574 (1952); *Chem. Abstr.*, **47**, 6979 (1953).



The results of the acid dissociation constants and the chelate stability constants measurements indicate that both constants are undoubtedly influenced by the inductive and steric effects of phenyl groups, and that the increased stability constants as compared with EDTA may be attributed to the steric effect of phenyl groups.

Experimental

Synthesis of Ligands. *1-Phenylethylenediamine (I).* The diamine dihydrochloride was synthesized from benzaldehyde *via* 1-phenyl-1-aminoacetonitrile, 1-phenyl-1-acetoaminonitrile, and *N, N'*-diacetyl-1-phenylethylenediamine successively. The dihydrochloride was recrystallized from methanol to obtain white needles which decomposed above 270°C.[3]

Found: C, 45.65; H, 7.00; N, 12.85%; mol wt (Neut. equiv.), 214. Calcd for $C_8H_{12}N_2 \cdot 2HCl$: C, 45.95; H, 6.75; N, 13.39%; mol wt, 209.

1-Phenylethylenedinitrilo-N, N, N', N'-tetraacetic Acid (II). The tetraacetic acid (II) was synthesized by the alkaline condensation of bromoacetic acid with 1-phenylethylenediamine (I). Although the condensation of chloroacetic acid and the carboxymethylation of diamine were tried, the most satisfiable results were obtained in the condensation of bromoacetic acid.

The reaction of a typical run was as follows: in a 200-m*l* reaction flask, a solution of 17.4 g (0.125 mol) of bromoacetic acid in 30 m*l* of water was placed. The solution was neutralized to phenolphthalein with a 7 N sodium hydroxide solution below 10°C, after which another 10% excess of alkali was added. Into this solution, a solution of 5.07 g (0.024 mol) of 1-phenylethylenediamine dihydrochloride in 15 m*l* of water which had been previously neutralized with sodium hydroxide was added with stirring, and the temperature of the mixture was raised to 40—50°C. The pH of the mixture was maintained at 10—11 by adding a sodium hydroxide solution intermittently. The degree of condensation can be measured by the consumption of alkali. About 50% of the theoretical value was consumed within 30—60 min, and the reaction was stopped after 15 hr, when 110% of the alkali had been consumed.

The reaction mixture was acidified with 6 N HCl to pH 1.6—1.8 while cooling it with an ice-salt mixture. After the solution had been kept in an ice box overnight, 6.88 g of a white precipitate was separated by filtration. Another 0.2—0.3 g of the product was obtained from the filtrate after it had been left standing for a few days. Total yield, 75%. The crude product was purified by repeated crystallizations from hot water. The pure ligand is a white powder, very slightly soluble in water and soluble in methanol and hot ethanol. When it was dried in a vacuum over phosphorus pentoxide at 75—80°C for 5 hr, an anhydrous material was obtained as a white crystalline powder which decomposed at 142—143°C (reported decompt. pt. 127—150°C).

Found: C, 51.94; H, 5.21; N, 7.57%. Calcd for $C_{16}H_{20}N_2O_8$: C, 52.17; H, 5.47; N, 7.61%.

dl-1, 2-Diphenylethylenediamine (III). The diamine was synthesized from benzaldehyde *via* amaline and isoamaline according to the method of Lifschitz.[4] Free diamine was recrystallized from ligroin to obtain white

3) H. Reihlen, G. V. Hessling, W. Hühn and E. Weinbrenner, *Ann.*, **493**, 20 (1932).

4) I. Lifschitz and J. G. Bos, *Rec. Trav. Chim.*, **59**, 173 (1940).

crystals, which melted at 82—82.5°C (reported mp 83°C).

dl-1, 2 - Diphenylethylenedinitrilo - N, N, N', N' - tetraacetic Acid (IV). Of the three methods, the alkaline condensation of bromoacetic acid, that of chloroacetic acid, and the carboxymethylation with cyanide and formaldehyde, the first method gave the most satisfactory results, as in the case of the 1-phenyl derivative.

Conditions similar to those described in the synthesis of the 1-phenyl derivative were employed, but the diamine (III) was dissolved into methanol. As the reaction proceeded, sodium salt of tetraacetic acid precipitated from the methanolic solution, but it could be redissolved by adding a small amount of water. After the reaction, the reaction mixture was acidified with hydrochloric acid to pH 1.8—2, and then kept in an ice box overnight. The white crystalline product which was separated by filtration was dried in a vacuum at 50°C. Starting from 4.59 g of diamine (III), 9.1 g of monohydrate of monosodium salt of tetraacetic acid (IV) were obtained (87%). Free acid was prepared by dissolving monosodium salt into hot water, followed by the readjustment of the pH of the solution to 1.8—2. The crude free acid was recrystallized from hot water to obtain a pure sample, which was then dried in a vacuum over phosphorus pentoxide at 60—65°C for 5 hr. It contained one mole of water and decomposed at 189°C.

Found: C, 57.32; H, 5.72; N, 6.08%. Calcd for $C_{22}H_{24}N_2O_8 \cdot H_2O$: C, 57.13; H, 5.67; N, 6.05%.

During the course of the recrystallization of free tetraacetic acid (IV), it was noticed that the infrared spectrum of the sample from an earlier stage of recrystallization was quite different from that of the sample from a later stage (later than the fourth crystallization) of recrystallization. These two isomeric samples were named the α form and the β form respectively. Infrared spectra of these two isomers are shown in Fig. 1. It is interesting to note that similar observations have been made in the case of iminodiacetic acid.[5]

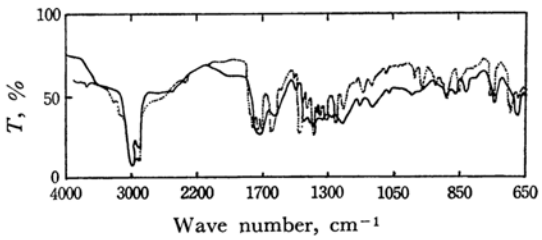


Fig. 1. Infrared spectra of *dl*-DPEDTA.
—— α form (earlier stage of recrystallization)
····· β form (later stage of recrystallization)
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Meso-1, 2-Diphenylethylenediamine (V). The diamine was synthesized from benzaldehyde either *via meso-N*-benzoyl-*N'*-benzylidene-1, 2-diphenylethylenediamine[6] or *via* amaline[7]. Free diamine was recrystallized from ligroin or water to obtain white crystals which melted at 118°C (reported mp 120.5—121.5°C).

Attempted Synthesis of meso-1, 2-Diphenylethylenedinitrilo-N, N, N', N'-tetraacetic Acid. With the purpose of obtaining the *meso* isomer of tetraacetic acid, various reactions, such as the alkaline condensation of bromoacetic acid with diamine (V), the alkaline condensation of ethyl bromoacetate with diamine in methanol, or the carboxymethylation using cyanide and formaldehyde, were tried. However, instead of obtaining the tetraacetic acid, keto piperazine derivatives, the cyclization products of the reaction intermediates, were obtained.

When the reaction mixture of bromoacetic acid and diamine (V) was acidified to pH 5—6, a white precipitate was obtained (P_1). After the precipitate had been separated, the filtrate was acidified to pH 1—2 to precipitate another white material (P_2).

The P_1 product is a white powder which is hardly soluble at all in water or in most organic solvents, but which is easily soluble in hot acetic acid, 1 N hydrochloric acid, and 5% sodium carbonate solution. It decomposed at 170—180°C. From the observation of the infrared spectra and from the neutralization value, this material was assumed to be *meso*-1, 2-diphenylethylenedinitrilo-*N, N'*-diacetic acid (VI).

When P_1 was dissolved in hot 2 N hydrochloric acid and the solution was cooled, the hydrochloride of 2-keto-5, 6-diphenylpiperazine-1-acetic acid was obtained as a white precipitate. It was recrystallized from 50% methanol. Mp 233—250°C (with decomposition).

Found: C, 62.52; H, 5.15; N, 8.14%. Calcd for $C_{18}H_{18}N_2O_3 \cdot HCl$: C 62.33; H, 5.52; N, 8.07%.

When the hydrochloride was neutralized, 2-keto-5, 6-diphenylpiperazine-1-acetic acid (VII) was obtained as a white crystalline powder. Mp 113—119°C (with decomposition).

Mol wt (Neut. equiv.) 315. Calcd for $C_{18}H_{18}N_2O_3$: 310.36. It is easily soluble in methanol, ethanol, and acetone.

The P_2 product was obtained as scaly white crystals when recrystallized from water. It is easily soluble in methanol, ethanol, and acetone, and melted at 159—163°C with decomposition. From the results of elementary analysis, the neutralization equivalent value, and the infrared spectra, the P_2 product was concluded to be 2-keto-5, 6-diphenylpiperazine-1, 4-diacetic acid (IX), which is a cyclization product of *meso*-1, 2 - diphenylethylenedinitrilo - *N, N, N'* - triacetic acid (VIII).

Found: C, 65.06; H, 5.48; N, 7.95%; mol wt (Neut. equiv.) 373. Calcd for $C_{20}H_{20}N_2O_5$: 65.02; H, 5.47; N, 7.60%; mol wt, 368.4.

Determination of Acid Dissociation Constants and Chelate Stability Constants. The apparatus described in a previous paper[8] was employed. Measurements were carried out at 25.0±0.1°C in an aqueous solution with the ionic strength of μ=0.1 with KCl or KNO_3. For the determination of the acid dissociation constants, 100 m*l* of a 1×10^{-3} M solution of the ligands was titrated with a 1×10^{-1} M KOH solution.

For the determination of chelate stability constants with alkaline earth metals, the direct pH titration method was employed on 100 m*l* of a solution 5×10^{-4}

5) Y. Tomita, T. Ando and K. Ueno, This Bulletin, **38**, 138 (1965).
6) S. Tripett, *J. Chem. Soc.*, **1957**, 4407.
7) W. H. Mills and T. H. H. Quibell, *ibid.*, **1935**, 839.
8) T. Ando, This Bulletin, **36**, 1593 (1963).

M in ligand and in metal ions. In the case of transition metal ions, the chelate stability constants were determined by a competitive reaction using triaminotriethylamine and the calcium ion as the auxiliary ligand and the metal ion respectively.[9] As the competitive reaction came to equilibrium very slowly, the pH measurements were carried out on separate solutions, which were both 5×10^{-4} M in ligand, metal ion, and triaminotriethylamine, and 5×10^{-3} M in calcium, but which contained different amounts of KOH.

In the case of *dl*-DPEDTA, the chelate stability constants for zinc (II) and cobalt(II) could be determined after three weeks equilibration. The equilibria with other metal ions, such as copper(II) and nickel(II), were so slow that no reliable data could be obtained even after several weeks equilibration. In the case of PEDTA, the reaction came to equilibrium in three days for copper(II) and zinc(II), in five days for cobalt(II), and in two weeks for nickel(II).

Calculations

Calculations of the Acid Dissociation Constants. The titration curves of PEDTA and *dl*-DPEDTA are shown in Figs. 2 and 3 respectively. The acid dissociation scheme of these ligands can be expressed as follows:

$$H_4Y \rightleftharpoons H_3Y^- + H^+$$
$$K_1 = [H_3Y^-][H^+]/[H_4Y]$$
$$H_3Y^- \rightleftharpoons H_2Y^{2-} + H^+$$
$$K_2 = [H_2Y^{2-}][H^+]/[H_3Y^-]$$
$$H_2Y^{2-} \rightleftharpoons HY^{3-} + H^+$$
$$K_3 = [HY^{3-}][H^+]/[H_2Y^{2-}]$$
$$HY^{3-} \rightleftharpoons Y^{4-} + H^+$$
$$K_4 = [Y^{4-}][H^+]/[HY^{3-}]$$

As it was noticed from the titration curves that the

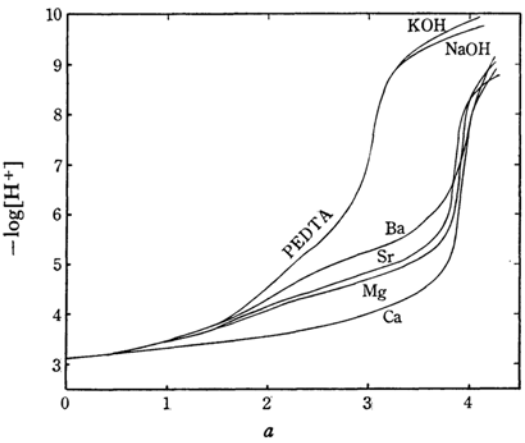


Fig. 2. Titration curves of PEDTA.
Concn. of ligand and metal ions: 5×10^{-4} M
For the titration of ligand only: 1×10^{-3} M

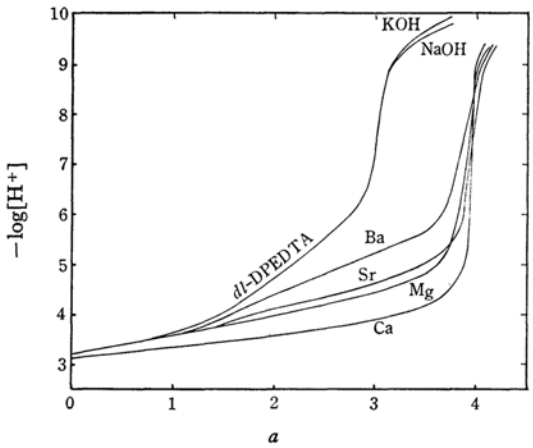


Fig. 3. Titration curves of *dl*-DPEDTA.
Concn. of ligand and metal ions: 5×10^{-4} M
For the titration of ligand only: 1×10^{-3} M

dissociations of the first three steps are clearly separated from the fourth step, the calculation of the dissociation constants of the first three steps and of the last step were conducted separately.

The calculations were based on the Bjerrum method as modified by McIntyre.[10] The final equations for the first three dissociation steps are:

$$\bar{n} = J_1/K_3 + J_2/K_2\cdot K_3 + J_3/K_1\cdot K_2\cdot K_3 \quad (1)$$
$$\bar{n}' = J'_1/K_3 + J'_2/K_2\cdot K_3 + J'_3/K_1\cdot K_2\cdot K_3 \quad (2)$$
$$\bar{n}'' = J''_1/K_3 + J''_2/K_2\cdot K_3 + J''_3/K_1\cdot K_2\cdot K_3 \quad (3)$$

where $\bar{n}$ represents the mean number of protons attached to the ligand, and where

$$J_n = (n-\bar{n})[H^+]^n \quad (4)$$

Equations (1), (2) and (3) were manipulated by five sets of experimental data at $a=0.5\pm0.3$, 1.5 ± 0.3, and 2.5 ± 0.3 respectively, where a represents the moles of alkali added per mole of ligand.

For the calculation of K_4, the following equation was used:

$$K_4 = \{[H^+](a-3)C_Y - K_W\}/\{[OH^-] + (4-a)C_Y\} \quad (5)$$

where C_Y represents the total ligand concentration, and K_W, the ionic product of water. Equation (5) was manipulated with the five experimental data at $a=3.5\pm0.3$. The results of the calculations, which represent the mean values, are summarized in Table 1.

Calculation of the Chelate Stability Constants. *A) By the Direct pH Titration Method for Alkaline Earth Metal Ions.* By analogy with EDTA, PEDTA and *dl*-DPEDTA will form the

9) G. Schwarzenbach and E. Freitag, *Helv. Chim. Acta*, **34**, 1503 (1951).

10) B. P. Block and G. H. McIntyre, Jr., *J. Am. Chem. Soc.*, **75**, 5667 (1953); G. H. McIntyre, Jr., B. P. Block and W. C. Fernelius, *ibid.*, **81**, 529 (1959).

Table 1. Acid dissociation constants of PEDTA and *dl*-DPEDTA
25±0.1°C; μ=0.1 (KCl)

Ligand	pK_1	pK_2	pK_3	pK_4
PEDTA	1.87±0.05	3.21±0.01	5.42±0.02	9.60±0.02
dl-DPEDTA	2.18±0.06	3.73±0.02	5.42±0.03	9.91±0.01
EDTA[12]	2.00	2.67	6.16	10.26

1 : 1 chelate with multivalent metal ions almost exclusively.

$$M + Y \rightleftharpoons MY$$

$$K_{MY} = [MY]/]M][Y] \quad (6)$$

The calculation of the chelate stability constant, K_{MY}, can be carried out according to Bjerrum's standard procedure.[11] The final equation can be written as follows:

$$K_{MY} = \{C_Y - \alpha[Y^{4-}]\}/\{C_M - C_Y + \alpha[Y^{4-}]\}[Y^{4-}] \quad (7)$$

where C_Y and C_M represent the total concentrations of the ligand and the metal ion respectively, and where;

$$\alpha = [H^+]^4/K_1 \cdot K_2 \cdot K_3 \cdot K_4 + [H^+]^3/K_2 \cdot K_3 \cdot K_4 + [H^+]^2/K_3 \cdot K_4 + [H^+]/K_4 + 1 \quad (8)$$

$$[Y^{4-}] = \{(4-a)C_Y - [H^+] + [OH^-]\}/\{4[H^+]^4/K_1 \cdot K_2 \cdot K_3 \cdot K_4 + 3[H^+]^3/K_2 \cdot K_3 \cdot K_4 + 2[H^+]^2/K_3 \cdot K_4 + [H^+]/K_4\} \quad (9)$$

The K_{MY} value was determined as a mean of K_{MY} values computed by Eq. (7) using a series of experimental values of a and [H$^+$] during the course of titration.*5

The results are summarized in Table 2. These values are averages of multiple titrations for each metal ions.

b) By the Competitive Reaction Method for Transition Metal Ions. As the chelate stability constants of relatively high values can not be determined accurately by the direct pH titration method, the modified indirect method which employed the competitive reaction with the auxiliary ligand and the metal ion was applied to the transition metal chelates.

The mathematical treatment for this procedure is essentially the same as that developed by Schwarzenbach.[9] The equilibrium attained in this case can be written as follows:

$$MY^{2-} + H_3tren^{3+} + M'^{2+} \overset{K^*}{\rightleftharpoons} Mtren^{2+} + M'Y^{2-} + 3H^+$$

and

$$K^* = \frac{[Mtren][M'Y][H^+]^3}{[MY][H_3tren][M']} = \frac{K_{M'Y} \cdot K_{Mtren}}{\bar{K}_{H_3tren} \cdot K_{MY}} \quad (10)$$

where M' and *tren* represent the auxiliary metal ion, "calcium," and the auxiliary ligand, "triaminotriethylamine base," respectively. As the equilibrium constant of this reaction, K^*, is expressed in terms of the equilibrium constants of the component reactions, (6), (11), (12), and (13), K_{MY} can be calculated if one determines K^* experimentally:

$$M'^{2+} + Y^{4-} \rightleftharpoons M'Y^{2-}$$

$$K_{M'Y} = [M'Y]/[M'][Y] \quad (11)$$

$$M^{2+} + tren \rightleftharpoons Mtren^{2+}$$

$$K_{Mtren} = [Mtren]/[M][tren] \quad (12)$$

$$3H^+ + tren \rightleftharpoons H_3tren^{3+}$$

$$\bar{K}_{H_3tren} = [H_3tren]/[H]^3[tren] \quad (13)$$

According to the procedure described by Schwarzenbach, one can calculate the K^* value with the known amounts of ligands, metal ions, and alkali, and with the observed pH value. As has been described in the Experimental section, copper(II), nickel(II), zinc(II), and cobalt(II) were chosen as transition metal ions, but the stability constants of *dl*-DPEDTA with copper and cobalt could not be determined due to the slow equilibration. The results are summarized in Table 2.

Table 2. Chelate stability constants of PEDTA and *dl*-DPEDTA for selected metal ions
25±0.1°C; μ=0.1 (KCl)

Metal ions	log K_{MY}		
	PEDTA	*dl*-DPEDTA	EDTA[12]
Mg(II)	9.14±0.02	10.40±0.03	8.69
Ca(II)	10.90±0.03	12.11±0.01	10.59
Sr(II)	8.98±0.02	10.12±0.01	8.63
Ba(II)	8.06±0.01	9.11±0.01	7.76
Cu(II)	18.7 ±0.1	—[a]	18.8
Zn(II)	16.46±0.02	17.8 ±0.2	16.26
Co(II)	15.6 ±0.2	17.9 ±0.2	16.1
Ni(II)	18.5 ±0.2	—[a]	18.56

a) Stability constant could not be determined because of very slow equilibration.

11) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Hasse and Son, Copenhagen (1941).

*5 Such calculations were carried out at the Computation Center of Kyushu University.

12) G. Schwarzenbach, R. Gut and G. Anderegg, *Helv. Chim. Acta*, **37**, 936 (1954).

Results and Discussion

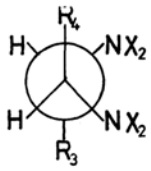
Acid Dissociation Constants. As is shown in Table 1, the acid dissociations of the first two steps are quite different from those of the last two steps. Thus, PEDTA and *dl*-DPEDTA are expected to exist as zwitter ions in an aqueous solution as in the case of EDTA, where the acid dissociation of the first two and the last two steps correspond to the dissociation of carboxylic protons and imino protons respectively. Therefore, it is convenient to discuss the dissociations of the first two steps and the last two steps separately when we consider the effect of phenyl substitution on the acidity of the ligands.

Since the titration of the ligand were carried out at concentrations less than 1×10^{-3} M, the values of pK_1 are not reliable enough for a detailed discussion. However, the values of pK_2, pK_3, pK_4 and ΔpK_{2-1} (pK_2-pK_1) are reliable enough for a meaningful interpretation of the results.

The ΔpK_{2-1} values of PEDTA and *dl*-DPEDTA are listed in Table 3, along with those of EDTA and its derivatives for the sake of comparison. In an aqueous solution, EDTA is considered to exist as the trans form with regard to the nitrilodiacetic acid groups, as this form is more stable than the skew form because of the electrostatic repulsion of the nitrilodiacetic acid groups. However, when the bulky phenyl groups are introduced to ethyleneic carbons, as in the cases of PEDTA and *dl*-DPEDTA, the skew form will become more stable than the trans form because of the steric hindrance of the substituted groups. A similar situation may also be expected for *dl*-DBTA. On the other hand, the trans form may be favored with EDTA, MEDTA, and *meso*-DBTA. These situations are illustrated in Fig. 4. It may be seen from Table 3 that the smaller ΔpK_{2-1} values are observed for the ligands of the trans form, while the larger ΔpK_{2-1} values are observed for the ligands of the skew form. These results may be explained as follows:

trans

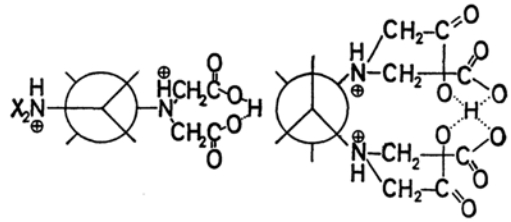
	R_1	R_2	X
EDTA	H	H	CH_2COOH
MEDTA	CH_3	H	CH_2COOH
meso-DBTA	CH_3	CH_3	CH_2COOH



skew

	R_3	R_4	X
PEDTA	C_6H_5	H	CH_2COOH
dl-DPEDTA	C_6H_5	C_6H_6	CH_2COOH
dl-DBTA	CH_3	CH_3	CH_2COOH

Fig. 4. Steric configuration of complexans.



trans skew

Fig. 5. Hydrogen bonding in carboxyl groups.

TABLE 3. ΔpK_{2-1} AND ΔpK_{4-3} VALUES OF VARIOUS LIGANDS

Ligand[a)]	Favorable form	ΔpK_{2-1}	ΔpK_{4-3}
PEDTA	skew	1.34	4.18
dl-DPEDTA	skew	1.55	4.50
EDTA[12)]	trans	0.67	4.10
MEDTA[13)]	trans	0.43	4.64
meso-DBTA[14,15)]	trans	0.7—0.9	4.9
dl-DBTA[14,15)]	skew	1.1	5.6

a) Abbreviations for the ligands.
MEDTA: 1-Methylethylenedinitrilotetraacetic acid
DBTA: 1,2-Dimethylethylenedinitrilotetraacetic acid

After the dissociation of the first carboxylic proton, the second carboxylic proton will be bonded by two carboxylic groups in the ligands of the trans form, whereas the proton will be bonded by four carboxylic groups in the ligands of the skew form, as is illustrated in Fig. 5. Therefore, the second proton is more difficult to dissociate in the skew-form ligands, resulting in the larger ΔpK_{2-1} values. This steric effect will be more pronounced in *dl*-DPEDTA than in PEDTA, so a higher ΔpK_{2-1} value is observed for *dl*-DPEDTA.

The dissociation of the last two steps are understood to be deprotonations from imino nitrogens. As the same pK_3 values are observed for PEDTA and *dl*-DPEDTA, pK_3 may not be influenced by the steric effect of the phenyl groups, but by the basicity of nitrogen. This effect may be explained clearly if one compare the acidities of benzyliminodiacetic acid (pK_1 2.24, pK_2 8.90) and methyliminodiacetic acid (pK_1 2.12, pK_2 9.65). In this

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case, the $-I$ effect of the phenyl group decreased the basicity of imino nitrogen, resulting in a decrease in the pK_2 value by 0.75 as compared with that of methyliminodiacetic acid. The difference in pK_3 values between PEDTA or *dl*-DPEDTA and EDTA is found to be 0.74, which is very close to that between benzyliminodiacetic acid and methyliminodiacetic acid. Thus, it may be concluded that the pK_3 values are influenced by the $-I$ effect of substituted phenyl groups, while they are not influenced by their steric effects.

After the dissociation of the third proton, the last proton is considered to be held between two nitrogen atoms through hydrogen bonding. Therefore, the pK_4 value may be influenced by the basicity of nitrogen as well as by the ease of hydrogen-bond formation between the two nitrogen atoms: these effect may be measured by means of the ΔpK_{4-3} (pK_4-pK_3) value. It may be seen from Table 3 that the methyl-substituted ligands, such as MEDTA, *meso*-DBTA, and *dl*-DBTA, have larger ΔpK_{4-3} values than does EDTA. This may be due to the $+I$ effect of methyl groups; in the case of *dl*-DBTA, which perfers the skew form, the higher nitrogen basicity and the easier hydrogen-bond formation result in the largest ΔpK_{4-3} value. It is interesting to note that the ΔpK_{4-3} values of PEDTA and *dl*-DPEDTA are also larger than that of EDTA. This indicates that the steric effect of phenyl groups overcomes the $-I$ effect of phenyl groups on the dissociation of the fourth proton of PEDTA and *dl*-DPEDTA.

Chelate Stability Constants. The chelate stability constants of PEDTA and *dl*-DPEDTA for alkaline earth metals and selected transition metal ions are shown in Table 2. The order of the stability constants of these ligands for metal ions is found to follow the Irving-Williams stability order, as in the cases of other complexane-type ligands.

It is well known that the basicity of the donor atom is in a linear relationship with the chelate stability for the homologous series of the ligands; many examples, such as salicylaldehyde derivatives and iminodiacetic acid derivatives, have been reported. Figure 6 shows such plots for the ligands of the EDTA derivatives that are listed in Table 3. In this figure, the stability constants for calcium are plotted against pK_3+pK_4, which is related to the basicity of the nitrogen atoms. It may be noticed that the plots of the ligands, except for *meso*-DBTA, PEDTA, and *dl*-DPEDTA, are on a straight line; however, the plots of PEDTA and *dl*-DPEDTA show exceptionally high stability constants at their pK_a values. This result may be explained in terms of the steric effect of the substituted groups.

The factors influencing the chelate stability constants of complexanes may be classified into

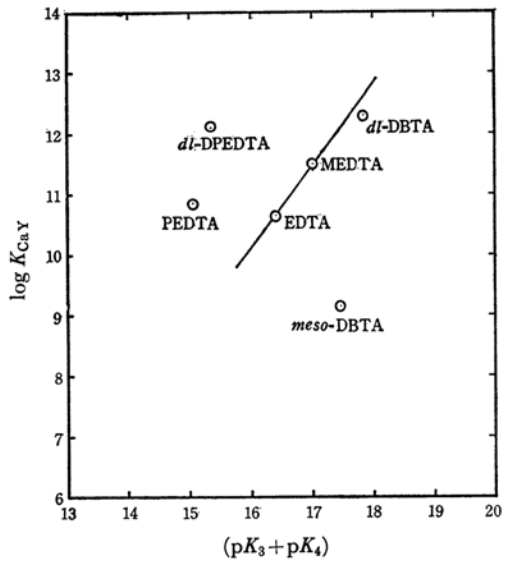

Fig. 6. Relationship between the chelate stability constant and the basicity of donor nitrogen. The abbreviations for the ligands are reffered to Table 3.

the acceptor property and the ionic radius of the metal ion, the donor property of the coordinating sites, and the ease with which the ligand forms a steric configuration which is favorable for chelate formation. Now, if the metal ion is fixed to one kind, and if the kind of ligand is limited to the derivatives of EDTA, the chelate stabilities may be influenced only by the basicity of the nitrogen atoms of the ligand and by the ease with which ligands form the skew configuration with regard to the nitrilodiacetic acid groups, because the rest of the factors are equal for such ligands. Furthermore, the ease of skew formation is greatly influenced by the steric effect of substituents introduced on the ethylenic carbons of the ligands.

Now, the introduction of a phenyl group is much more favorable for the ligand taking the skew configuration than is the introduction of methyl groups. Thus, PEDTA and *dl*-DPEDTA will take the skew configuration more easily than will EDTA and methyl-substituted EDTA. This effect results in the higher chelate stability constants for PEDTA and *dl*-DPEDTA, even though these ligands have lower pK_a values than that of EDTA.

From these results, one may expect a ligand of an exceptionally high chelate stability if one can introduce bulky substituents with an $+I$ effect to the ethylenic carbons of EDTA.

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