BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 3167—3170 (1970)

Synthesis of Chelating Agents. VII.*1 Synthesis and Chelating Behavior of 2,3-Dinitrilo-1,2,3,4-tetrahydronaphthalene-*N*,*N*,*N*′,*N*′-tetraacetic Acid*2

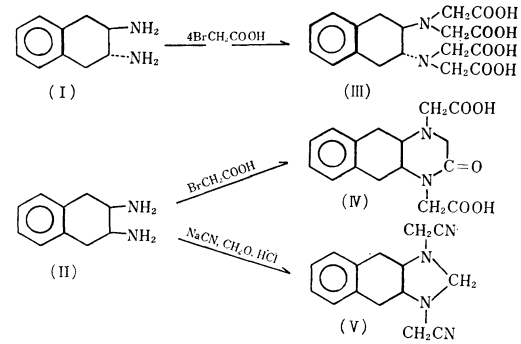
Tairoku YANO, Hiroshi KOBAYASHI and Keihei UENO

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka

(Received June 1, 1970)

trans-2,3-Dinitrilo-1,2,3,4-tetrahydronaphthalene-*N*,*N*,*N*′,*N*′-tetraacetic acid was synthesized by the carboxymethylation of *trans*-2,3-diaminotetrahydronaphthalene. The acid dissociation constants as well as the chelate stability constants for alkaline earth metal ions were determined by a potentiometric method. The results were compared with the values of other complexane ligands of the cycloalkane family.

Extensive investigations have been carried out on the relationship between the structures of complexane type ligands and their chelate stability constants.[1] In our previous paper, we reported on the effect of phenyl substitutions on the ethylenic carbons of ethylenedinitrilo-*N*,*N*,*N*′,*N*′-tetraacetic acid (EDTA) upon the chelate stability constants.[2] It was pointed out that the ease of taking a skew configuration with regards to the nitrilodiacetate groups plays an important role in governing the chelate stability constants of EDTA analogous ligands. In this connection, we have been interested in the synthesis of the derivatives of 1,2-cyclohexanedinitrilo-*N*,*N*,*N*′,*N*′-tetraacetic acid (C_yDTA) in which the ease of taking a skew configuration is controlled by fusing an additional cyclohexane or benzene ring to 4,5-position. This paper deals with the synthesis as well as the chelating behaviour of a new ligand, 2,3-dinitrilo-1,2,3,4-tetrahydronaphthalene-*N*,*N*,*N*′,*N*′-tetraacetic acid (THDTA). *trans*-THDTA was obtained by the carboxymethylation of *trans*-2,3-diamino-1,2,3,4-tetrahydronaphthalene, whereas *cis*-THDTA could not be obtained from the corresponding *cis*-diamine as in the case of *meso*-1,2-diphenyl ethylenedinitrilotetraacetic acid.[2] The acid dissociation constant and the chelate stability constants for alkaline earth metal ions of *trans*-THDTA, which were measured by the direct potentiometric titration method, were interpreted in relation to those of complexane ligands of the cycloalkane family.



Scheme

Experimental

IR spectra were measured with a Nippon Bunko Model DS 301 spectrophotometer, and NMR spectrum was obtained with a Varian A-60 spectrophotometer with tetramethylsilane as an internal standard.

Synthesis of Ligand. *trans-2,3-Dinitrilo-1,2,3,4-tetrahydronaphthalene-N, N, N′, N′-tetraacetic Acid (trans-THDTA) (III).* Tetraacetic acid was synthesized by the alkaline condensation of bromoacetic acid with *trans*-2,3-diamino tetrahydronaphthalene.*3 The condition of a typical run was as follows.

In a 100 m*l* reaction vessel, a solution of 1.8 g (0.008 mol) of *trans*-2,3-diamino tetrahydronaphthalene dihydrochloride in 30 m*l* of 50% ethanol was placed. The solution was neutralized to phenolphthalein with 7N aqueous sodium hydroxide. Into this solution, a solution of 6.86 g (0.046 mol) of bromoacetic acid in 10 m*l* of water which had been neutralized with sodium hydroxide solution below 10°C was added with stirring,

*1 Paper VI: Y. Moriguchi, M. Miyazaki and K. Ueno, This Bulletin, **41**, 1344 (1968).

*2 Contribution No. 208 from the Department of Organic Synthesis, Kyushu University.

1) For example, H. Kroll and M. Gordon, *Annals of New York Academy of Sciences*, **88**, 341 (1960).

2) N. Okaku, Y. Toyoda, Y. Moriguchi and K. Ueno, This Bulletin, **40**, 2326 (1967).

*3 *trans*-Diamine (I) and *cis*-diamine (II) are new compounds, and the details of the synthetic procedures and the structural proof will be reported elsewhere along with the other new 1,2-diamines such as 2,3-diamino-decahydronaphthalenes.

and the temperature of the mixture was raised to 40°C. The pH of the reaction mixture was maintained at 9—10 (red to phenolphthalein) with an occasional addition of 7N aqueous sodium hydroxide. After adding 0.032 mole of sodium hydroxide, the resulting mixture was acidified with concentrated hydrochloric acid to pH 1.6—1.8. Monosodium salt of *trans*-THDTA was obtained as colorless precipitates. The free acid of THDTA was prepared by dissolving the sodium salt into hot water, followed by the readjustment of the pH of the solution to 1.8. The crude acid was recrystallized from hot water, to give the pure *trans*-THDTA, which was dried over phosphorous pentoxide in vacuum at 60°C for 10 hr. Yield 40%. It decomposed at 245°C. IR: ν_{CO}, 1740. 1620 cm^{-1}.

Found: C, 54.90; H, 5.69; N, 6.98%; mol. wt. (Neutrl. equiv.) 391. Calcd for $C_{18}H_{22}N_2O_8$: C, 54.82; H, 5.62; N, 7.10%; mol. wt. 394.

Attempted Synthesis of cis-THDTA. In order to obtain the *cis* isomer of tetraacetic acid, various reactions such as the alkaline condensation of bromoacetic acid with *cis*-diamine (II),*3 the alkaline condensation of ethyl bromoacetate with diamine in ethanol, or the cyanomethylation of diamine using hydrocyanic acid and formaldehyde, were tried. However, the isolated products were, instead of *cis*-THDTA, a ketopiperazine derivative and an imidazolidine derivative which were the cyclocondensation products of the reaction intermediates.

In the case of the alkaline condensation of bromoacetic acid, which is carried out under a similar condition to that described in the synthesis of the *trans* isomer, white precipitates (IV) were obtained from the acidified reaction mixture. The pure material which was recrystallized from hot water, melted at 205—217°C with decomposition. Yield 63%. The result of elementary analysis and infrared spectrum confirmed that the product (IV) is 1,4-diaza-2-keto-1,2,3,4,4a,9,9a,10-octahydroanthracene-1,4-diacetic acid (IV). IR (KBr): ν_{CO}, 1760, 1680, 1620 cm^{-1};

Found: C, 60.43; H, 5.63; N, 8.69%. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.63; H, 5.67; N, 8.80%.

In the case of the cyanomethylation, 1.3 g (0.016 mol) of 36% formaldehyde and 0.77 g (0.016 mol) of sodium cyanide were successively added into a cold solution of 1 g (0.004 mol) of the *cis*-diamine in 11 m*l* of 1.2N hydrochloric acid, and the resulting mixture was kept in a pressure bottle. It was allowed to stand for 45 hr at 40°C with occasional stirring. The white precipitates (V) from the reaction mixture was recrystallized from ethanol. Mp 180—183°C. From the result of elementary analysis, infrared spectrum and NMR spectrum, the product was proved to be 1,3-diaza-1,3-cyanomethyl-5,6-benzo-3a,4,7,7a-tetrahydroindane (V). IR (in Nujol): ν_{CN} 2220 cm^{-1}. NMR ($CDCl_3$): δ: 7.16 (strong singlet, 4H), 3.81 (doublet, J=3.5 Hz, 1H), 3.68 (strong singlet, 4H), 3.41 (doublet, J=3.5 Hz, 1H), 3.31 (broad band with fine structure, 2H), 2.73 (appreciable quartet, 4H).

Found: C, 71.49; H, 6.13; N, 22.69%. Calcd for $C_{15}H_{16}N_4$: C, 71.43; H, 6.35; N, 22.22%.

Determination of Acid Dissociation Constants and Chelate Stability Constants. The same apparatus as that described in a previous paper was employed.[4] Measurements were carried out at 25.0± 0.1°C in aqueous solutions under the ionic strength, μ, of 0.10 with potassium nitrate. For the determination of acid dissociation constants, 100 m*l* of a 0.8—0.9×10^{-3}M solution of the ligand was titrated with a solution of 0.1M potassium hydroxide freed from carbonate ion. For the determination of chelate stability constants with alkaline earth metal ions, the direct pH titration method was employed on 100 m*l* of a solution (8×10^{-4}M in ligand and in metal ions).

Calculations

Calculation of the Acid Dissociation Constants. The titration curve of *trans*-THDTA is shown in Fig. 1. The acid dissociation scheme of the ligand can be expressed as follows:

$$H_4Y \rightleftarrows H_3Y^- + H^+$$
$$Ka_1 = [H_3Y^-][H^+]/[H_4Y]$$
$$H_3Y^- \rightleftarrows H_2Y^{2-} + H^+$$
$$Ka_2 = [H_2Y^{2-}][H^+]/[H_3Y^-]$$
$$H_2Y^{2-} \rightleftarrows HY^{3-} + H^+$$
$$Ka_3 = [HY^{3-}][H^+]/[H_2Y^{2-}]$$
$$HY^{3-} \rightleftarrows Y^{4-} + H^+$$
$$Ka_4 = [Y^{4-}][H^+]/[HY^{3-}]$$

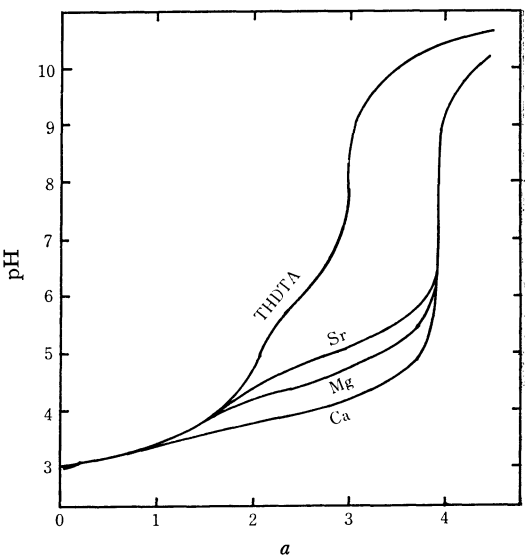


Fig. 1. Titration curves of THDTA.
Concn. of ligand and metal ions: 0.8×10^{-3}M
For the titration of ligand only: 0.9×10^{-3}M

It can be seen from Fig. 1 that the titration curve is essentially the same as that of EDTA and dissociation of the first two steps, third step and fourth step is clear. The acid dissociation constants of the ligand were calculated by two different methods; *i. e.*, the method of Schwarzenbach,[3] except that

3) G. Schwarzenbach, A. Willi and R. O. Bach, *Helv. Chim. Acta*, **30**, 1303 (1947).
4) T. Ando, This Bulletin, **36**, 1593 (1963).

an algebraic method of solution was used instead of a graphical one, and the method of Bjerrum as modified by McIntyre.[5]

a) Schwarzenbach's Method. The final equations for the first two dissociation steps are:

$$K_{a_2}[(2-a)C_A-[H^+]] - (aC_A+[H^+])[H^+]^2/K_{a_1} = [(a-1)C_A+[H^+]][H^+] \quad (1)$$

For the calculation of K_{a_3} and K_{a_4}, the following equations were used:

$$K_{a_3} = \{[H^+]\{(a-2)C_A+[H^+]-[OH^-]\}\}/\{C_A-\{(a-2)C_A+[H^+]-[OH^-]\}\} \quad (2)$$

$$K_{a_4} = \{[H^+](a-3)C_A-K_W\}/\{(4-a)C_A+[OH^-]\} \quad (3)$$

where a represents the moles of alkali added per mole of the ligand, C_A, the total ligand concentration and K_W, the ionic product of water.

b) Bjerrum's Method. The final equations for the first three dissociation steps are:

$$\bar{n} = J_1/K_{a_3} + J_2/K_{a_2}\cdot K_{a_3} + J_3/K_{a_1}\cdot K_{a_2}\cdot K_{a_3} \quad (4)$$

$$\bar{n}' = J_1'/K_{a_3} + J_2'/K_{a_2}\cdot K_{a_3} + J_3'/K_{a_1}\cdot K_{a_2}\cdot K_{a_3} \quad (5)$$

$$\bar{n}'' = J_1''/K_{a_3} + J_2''/K_{a_2}\cdot K_{a_3} + J_3''/K_{a_1}\cdot K_{a_2}\cdot K_{a_3} \quad (6)$$

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

$$J_n = (n-\bar{n})[H^+]^n \quad (7)$$

For the calculation of K_{a_4}, equation (3) was used.

The results of both calculations are summarized in Table 1. The values for K_{a_2}, K_{a_3} and K_{a_4} are in fairly good agreement for both methods.

Calculation of the Chelate Stability Constants. By analogy with C_yDTA, THDTA will form almost exclusively the 1 : 1 chelate with multivalent metal ions.

$$M + Y \rightleftarrows MY \quad K_{MY} = [MY]/[M][Y] \quad (8)$$

Therefore, the calculation of the chelate stability constant K_{MY} can be carried out according to Bjerrum's standard procedure.[6] The final equation can be written as follows:

$$K_{MY} = \{C_A-\alpha[Y^{4-}]\}/\{C_M-C_A+\alpha[Y^{4-}]\}\cdot[Y^{4-}] \quad (9)$$

where C_A and C_M represent the total concentration of the ligand and the metal ion, respectively, and

$$\alpha = [H^+]^4/K_{a_1}\cdot K_{a_2}\cdot K_{a_3}\cdot K_{a_4} + [H^+]^3/K_{a_2}\cdot K_{a_3}\cdot K_{a_4} + [H^+]^2/K_{a_3}\cdot K_{a_4} + [H^+]/K_{a_4} + 1 \quad (10)$$

$$[Y^{4-}] = \{(4-a)C_A-[H^+]+[OH^-]\}/\{4[H^+]^4/K_{a_1}\cdot K_{a_2}\cdot K_{a_3}\cdot K_{a_4} + 3[H^+]^3/K_{a_2}\cdot K_{a_3}\cdot K_{a_4} + 2[H^+]^2/K_{a_3}\cdot K_{a_4} + [H^+]/K_{a_4}\} \quad (11)$$

The K_{MY} value was determined as a mean of K_{MY} values which were computed by Eq. (9) using Bjerrum's pK_a values, and a series of experimental values of a and $[H^+]$ during the course of titration. The results are summarized in Table 2.

Table 2. Chelate stability constants of THDTA and related complexanes
25±0.1°C μ=0.10 (KNO_3)

Metal ion	log K_{MY}		
	trans-THDTA	*trans*-C_yDTA[8]	*trans*-CPDTA[9]
Mg(II)	10.28±0.01	10.97	9.05
Ca(II)	11.63±0.03	13.15	11.08
Sr(II)	9.56±0.03	10.45	9.45

Table 1. Acid dissociation constants of THDTA and related complexanes
25±0.1°C μ=0.10 (KNO_3)

	pK_{a_1}	pK_{a_2}	pK_{a_3}	pK_{a_4}	t, °C	Ref.
trans-THDTA	2.2[a]	3.48±0.02	5.96±0.03	10.26±0.01	25	
	1.9[b]	3.54±0.03	5.99±0.01	10.30±0.05		
trans-C_yDTA	2.43	3.52	6.12	12.35	20	7, 8
cis-C_yDTA	2.44	3.50	5.21	10.70	20	9
trans-CPDTA	1.75	2.63	7.44	10.26	20	10

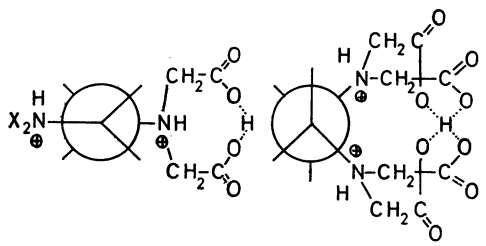
a) Schwareznbach method
b) Bjerrum method
trans-C_yDTA : *trans*-Cyclohexane-1,2-diaminetetraacetic acid
cis-C_yDTA : *cis*-Cyclohexane-1,2-diaminetetraacetic acid
trans-CPDTA : *trans*-Cyclopentane-1,2-diaminetetraacetic acid

5) B. P. Block and G. H. McIntyre, Jr., *J. Amer. Chem. Soc.*, **75**, 5667 (1953).
6) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Hasse & Son, Copenhagen (1941).
7) G. Schwarzenbach and H. Ackelman, *Helv. Chim. Acta*, **32**, 1682 (1949).
8) G. Anderegg, *ibid.*, **46**, 1834 (1963).
9) H. Kroll, *A E C Contract* (**30**—1) 2096, Annual Report (1960).
10) H. Kroll and M. Gordon, *Federation Proceedings*, **20**, 51 (1961).

Results and Discussion

Acid Dissociation Constants. It may be convenient to discuss the acid dissociation constants and chelate stability constants of *trans*-THDTA in comparison with those of *trans*-C_yDTA which has a similar skeletal structure to *trans*-THDTA. As shown in Table 1, the pK_{a_1} and pK_{a_2} values are quite different from pK_{a_3} and pK_{a_4} values. Thus, *trans*-THDTA is expected to exist as zwitter ions in an aqueous solution as in the case of *trans*-C_yDTA, where the acid dissociations of the first two and the last two steps are known to correspond to the dissociation of carboxylic protons and ammonium protons, respectively.

In an aqueous solution, *trans*-C_yDTA is considered to exist as the skew form with regard to the nitrilodiacetate groups, as this form is more stable thermodynamically than the trans form because of the steric repulsions of axial protons at 3 and 5 positions and the axial nitrilodiacetate group at 1 position. On the other hand, the trans form is more stable than the skew form for EDTA because of the electrostatic repulsion of the two nitrilodiacetate groups. It is easily recognized from Table 3 that the smaller ΔpK_{2-1} ($pK_{a_2}-pK_{a_1}$) values are obtained for the ligands having the trans configuration, while the larger ΔpK_{2-1} values are obtained for the ligands having the skew configuration. This result may be explained as follows. After the dissociation of the first carboxylic proton, the second carboxylic proton will be bound by two carboxylic groups in the ligand of the trans form. On the other hand, the proton will be bound by four carboxylic groups in the ligand of a skew form. Therefore, the second proton is more difficult to dissociate in the skew form ligands, resulting in the larger ΔpK_{2-1} values. This situation is schematically shown in Fig. 2. Thus, *trans*-THDTA is also considered to take the skew configuration with regard to the nitrilodiacetate groups.



trans skew

Fig. 2. Hydrogen bonding in carboxylic groups.

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

Ligand	ΔpK_{2-1}	Favorable configuration of two nitrilodiacetate groups.
trans-THDTA	1.29	skew
trans-C_yDTA	1.15	skew
cis-C_yDTA	1.06	skew
EDTA[11]	0.67	trans
MEDTA[12]	0.43	trans
trans-CPDTA	0.51	trans

MEDTA: 1-Methylethylenedinitrilo-*N*,*N*,*N'*,*N'*-tetraacetic acid.

The ease of dissociation of the third proton is usually correlated with the electrostatic repulsion of protonated nitrogens, and that of the fourth proton with the basicity of nitrogen as well as the ease of hydrogen bond formation between the two nitrogen atoms. It is seen from Table 1 that the smallest pK_{a_3} is observed for *cis*-C_yDTA and the largest for *trans*-CPDTA in cycloalkane derivatives. Kroll explained the differences of pK_{a_3} values by estimating the N–N distances of these ligands as 2.0 Å for *cis*-C_yDTA and 3.5 Å for *trans*-CPDTA.[1] However, his estimation for *cis*-C_yDTA does not seem to be reasonable. According to our estimation, the N–N distance of *cis*-C_yDTA, *trans*-(e,e)-C_yDTA as well as *trans*-THDTA have about the same value 2.8 Å. Therefore, the electrostatic repulsion of protonated nitrogens may be the same order for these ligands. It is likely that pK_{a_3} of these ligands are influenced by some other factors.

The values of pK_{a_4} are approximately the same except for *trans*-C_yDTA, and the result can not clearly be correlated with the effect caused by the fusion of aromatic ring to cyclohexane ring.

Chelate Stability Constants. The stability constants of the alkaline earth chelates of *trans*-THDTA are listed in Table 2, along with those of *trans*-C_yDTA and *trans*-CPDTA. Although the values for *trans*-THDTA lie in between those for *trans*-C_yDTA and *trans*-CPDTA, not much difference is found among those values. We should wait for more detailed discussion on the chelate stability constants, until we get other ligands of the cycloalkane family.

Thus, the fusing of benzene ring to the cyclohexane ring does not influence greatly the acid dissociation constants and the chelate stability constants. It is necessary to compare these results with that of the complexanes derived from trans decahydronaphthalene, where the puckering of cyclohexane ring is not allowed.

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

12) J. H. Grines, A. J. Huggard and S. P. Wilford, *J. Inorg. Nucl. Chem.*, **25**, 1225 (1963).