Synthesis of Chelating Agents. XI. Synthesis and Chelating Behavior of Diaxial *trans*-Decahydronaphthylene-*trans*-2,3-dinitrilotetraacetic Acid*

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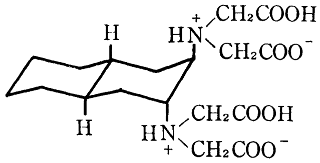
Diaxial *trans*-decahydronaphthylene-*trans*-2,3-dinitrilotetraacetic acid (D[A.A]TA) was synthesized by carboxymethylation of diaxial *trans*-decalin-*trans*-2,3-diamine. The acid dissociation constants as well as chelate stability constants for alkaline earth metal ions were determined by potentiometric titration. The probable structure and chelating behavior of D[A.A]TA in aqueous solutions were discussed in reference to some related complexane ligands.

With hoping to elucidate steric effect on chelate formation with complexane-type ligands, we have synthesized several 1,2-dinitrilotetraacetic acids and precursory diamines of specific configurations.

In continuation of the previous works,1) this paper deals with synthesis and chelating behaviors of diaxial *trans*-decahydronaphthylene-*trans*-2,3-dinitrilotetraacetic acid (D[A.A]TA), which was derived from diaxial *trans*-decalin-*trans*-2,3-diamine.2) Two six-membered rings in *trans*-decalin framework are well known to be incapable of inversion from one chair form to another on account of the rigid structure at the ring junctions.

Consequently, two nitrilodiacetic acid substituents in D[A.A]TA are in an antiperiplanar conformation, both pointing along the axial direction, providing configurations in respect to the amino groups are retained intact through the derivation and the cyclohexane ring under consideration takes a chair form.

Although this work had started with an aim of verifying the above anticipation, the presented results indicated that such a conformation was unlikely, in conclusion.



Structure 1

Experimental

Infrared and NMR spectra were measured on a JASCO DS-403G and Varian A-60 instruments, respectively, the latter with an internal reference of TMS or proton in heavy water, which was set at 5.0 ppm downfield from TMS.

Synthesis of Ligand. Diaxial trans-*Decahydronaphthylene*-trans-*2,3-dinitrilotetraacetic Acid* (D[A.A]TA, structure 1). The tetraacetic acid was synthesized by the alkaline condensation of bromoacetic acid with diaxial *trans*-decalin-*trans*-2,3-diamine (D[A.A]). Conditions of typical run was as follows.

A solution of 0.5 g (2.1 mmol) of D[A.A]·2HCl in 20 ml of water was placed in a 100 ml reaction vessel. The solution was made neutral to phenolphthalein with 5 M aqueous sodium hydroxide. Into this solution, a solution of 2 g (14.4 mmol) of bromoacetic acid in 10 ml of water, which had been neutralized in advance with sodium hydroxide solution below 10 °C, was added under stirring and the temperature of the solution was raised to 80 °C. The pH of the reaction mixture was maintained in the range of 9—10 (red to phenolphthalein) with an occasional addition of 5 M aqueous sodium hydroxide. After adding 12.5 mmol of sodium hydroxide, the resulting solution was acidified with conc. hydrochloric acid and was evaporated under reduced pressure. The residue was dissolved in water, followed by adjusting pH of the aqueous solution to 1.8 and stored in a refrigerator for a week to complete the precipitation of free D[A.A]TA. The crude product was then collected by filtration and recrystallized from water. Yield: 420 mg (51%). It decomposed at 186—188 °C. NMR (in D_2O): δ; 1—2.4 ppm (broad band with an appreciable quartet, 14H), 4.13, 3.86, 3.79, and 3.52 (double doublets, $J_{AB}=16.2$ Hz, 8H, two protons were concealed behind the double doublets). IR: ν_{COOH} 1753 cm^{-1}. Found: C, 51.99; H, 7.15; N, 6.59%. Calcd for $C_{18}H_{28}N_2O_8 \cdot H_2O$: C, 51.68; H, 7.18; N, 6.70%.

1,3-Bis(cyanomethyl)-trans-*cisoid*-trans-*perhydronaphtho[2,3-d]-imidazole.* To a cold solution of diequatorial *trans*-decalin-*trans*-2,3-diamine dihydrochloride (0.12 g, 0.5 mmol) in 0.4 M hydrochloric acid (3 ml), an aqueous 36% formaldehyde (0.16 g, 2 mmol) and sodium cyanide (98 mg, 2 mmol) was successively added and a resulting mixture was kept in a pressure bottle. The mixture was allowed to stand for 3 hr at room temperature with occasional shaking. The precipitate obtained was recrystallized from ethanol. IR: ν_{CN} 2240 cm^{-1}. Mp: 131—132 °C. Yield: 76 mg (59%). NMR (in $CDCl_3$): δ; 0.9—2 ppm (14H), 2.2—2.6 (2H), 3.62 (4H), 3.83 (2H). MS: *m/e***, 258 (M^+), 257 (M^+-1), 231 (M^+-27), 218 (M^+-40). Found: C, 69.91; H, 8.58; N, 21.54%. Calcd for $C_{15}H_{22}N_4$: C, 69.73; H, 8.58; N, 21.84%.

Diaxial trans-*decahydronaphthylene*-trans-*2,3-dinitrilotetraacetonitrile* was synthesized in a similar manner to that described above, except the reaction temperature being 40 °C. IR: ν_{CN} 2235 cm^{-1}. Mp: 167—171 °C. Yield: 49 mg (30%). NMR (in $CDCl_3$): δ; 0.8—1.9 ppm (14H), 2.8—3.1 (2H), 3.77 (8H). MS: *m/e***, 324 (M^+), 286 (M^+-38), 284 (M^+-40), 257 (M^+-67). Found: C, 66.23; H, 7.54; N, 25.34%. Calcd for $C_{18}H_{24}N_6$: C, 66.67; H, 7.41; N, 25.93%.

Determination of Chelate Stability Constants. The details of an apparatus were described previously.1) A pH measurement was carried out at 25.0 °C in an aqueous solution of ionic

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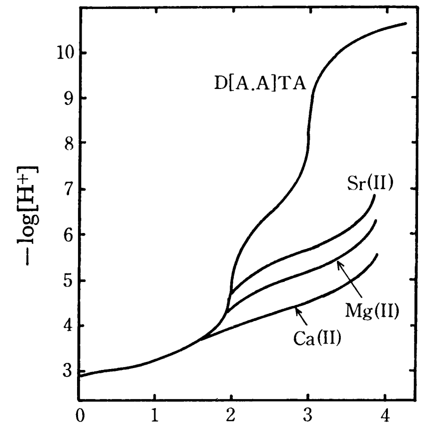
** Measured with a JEOL JMS-01SG by courtesy of Prof. Kawasaki and Miss Kawamura in Faculty of Pharmacy, Kyushu University, to whom the authors are grateful.

strength of 0.10 with potassium nitrate. Calibration of a pH-meter was also described previously.[1] Determination of a chelate stability constant with an alkaline earth metal ion involves direct pH titrations of 100 ml of a ligand solution in which concentration of the ligand was 1×10^{-3} M and a metal ion was present in 1: 1 and 10: 1 mole ratios of a metal nitrate to a ligand.

Calculation of Equilibrium Constants. Acid Dissociation Constants. The titration curve of D[A.A]TA is shown in Fig. 1. The definition of equilibrium constants discussed in this paper, are listed in Table 1. It can be seen from Fig. 1 that the acid dissociations of first two steps, third step and fourth step are clearly separated from each other. Therefore, the acid dissociation constants of the free ligand were calculated by the standard procedure.[3]

TABLE 1. DEFINITION OF EQUILIBRIUM CONSTANTS

1) Acid dissociation constnts of D[A.A] TA
$K_1=[H_3A^{1-}][H^+]/[H_4A]$
$K_2=[H_2A^{2-}][H^+]/[H_3A^{1-}]$
$K_3=[HA^{3-}][H^+]/[H_2A^{2-}]$
$K_4=[A^{4-}][H^+]/[HA^{3-}]$
2) Composite acid dissociation constants[4]
$K_3'=[H^+]([HA^{3-}]+[MHA^{1-}])/[H_2A^{2-}]$
$K_4'=[H^+]([A^{4-}]+[MA^{2-}]+[M_2A])/([HA^{3-}]+[MHA^{1-}])$
3) Chelate stability constants of D[A.A]TA
$K_{MHA}=[MHA^-]/[M^{2+}][HA^{3-}]$
$K_{MA}=[MA^{2-}]/[M^{2+}][A^{4-}]$
$K^{H}_{MHA}=[H^+][MA^{2-}]/[MHA^{1-}]$
$K_{M_2A}=[M_2A]/[M^{2+}][MA^{2-}]$



(*a*)

Fig. 1. Potentiometric titration curves of alkaline earth metal-chelates at 25.0 °C in 0.10 M KNO_3 with molar ratio of metal ion to ligand; 1: 1. Concentration of D[A.A]TA: 1×10^{-3} M.

Chelate Stability Constants. As the two nitrilodiacetic acid groups of the ligand are situated on the opposite sides of the rigid cyclohexane ring, the ligand may form MA type as well as M_2A type chelates. Accordingly, the chelate stability constants for alkaline earth metal ions were calculated by the Schwarzenbach's procedure,[4] assuming the formation of MA, MHA and M_2A type chelates. The procedure of calculation was a standard one, using the composite acid dissociation constants K_3' and K_4' on the titration data of 10: 1 solution.

Computations were carried out by use of a FACOM 230-60 of the Computor Center in Kyushu University.

Results and Discussion

Synthesis. D[A.A]TA was obtained by carboxymethylation of diaxial *trans*-decalin-*trans*-2,3-diamine. Although no direct evidence was provided, it is reasonable on the basis of the employed reaction conditions that configurations in respect to the substituents are regarded to be retained intact.

Cyanomethylation and carboxymethylation were also applied to 2,3-*cis*- and diequatorial 2,3-*trans*-diamine derivatives of *trans*-decalin under various conditions. Both isomeric diamines afforded no definite product except an imidazolidine derivative by cyanomethylation of the diequatorial *trans*-diamine. It is likely that, upon the cyanomethylation of the 1,2-diamino groups in the close vicinity to each other such as the above diamines, an imidazolidine ring closure proceeds prior to the fourth cyanomethylation reaction, giving no tetracyanomethyl derivative.[5,6]

The fact that the expected tetracyanomethyl- and tetracarboxymethyl derivatives were afforded only from the diaxial 2,3-*trans*-diamine in which two amino groups were separated apart from each other, is regarded as an indication of little steric interaction between the two amino groups on the reaction processes, as well as another support for the configuration of D[A.A]TA.

TABLE 2. ACID DISSOCIATION CONSTANTS AND ΔpK (2−1) AND ΔpK (4−3) VALUES OF D[A.A]TA AND RELATED COMPOUNDS

Compound	pK_1	pK_2	pK_3	pK_4	ΔpK (2−1)	ΔpK (4−3)	Favorable configuration of two NDA groups
D[A.A]TA	2.26	3.04	6.47	10.61	0.78	4.14	skew
t-THDTA[5]	1.9	3.54	5.99	10.30	1.64	4.31	skew
t-1,2-CYDTA[7]	2.40	3.55	6.14	11.70	1.15	5.56	skew
t-1,2-CPDTA[8]	2.41	2.92	7.42	10.31	0.51	2.89	*trans*
EDTA[9]	1.99	2.67	6.16	10.23	0.68	4.07	*trans*
1,3-CYDTA[10]	1.77	2.57	8.55	10.91	0.80	2.36	—
1,4-CYDTA[10]	2.07	2.52	9.04	10.86	0.45	1.82	—

t-THDTA: 1,2,3,4-Tetrahydronaphthylene-*trans*-2,3-dinitrilotetraacetic acid. CYDA: Cyclohexylenedinitrilotetraacetic acid. *t*-1,2-CPDTA: *trans*-1,2-Cyclopentylenedinitrilotetraacetic acid.

Acid Dissociation. Table 2 summarizes the acid dissociation constants of D[A.A]TA, along with those of some related complexane ligands. In the deprotonation process of a tetrabasic complexane, the first two steps and the last two correspond to the dissociation of carboxylic protons and ammonium protons, respectively.

In respect to the magnitude of difference between the pK-values of the first two, ΔpK(2—1), and that between the last two, ΔpK(4—3), the tetrabasic complexanes can be classified into two groups. As discussed previously,[2] a complexane ligand, in which two nitrilodiacetic acid (NDA) groups are far remote from each other, gives a relatively smaller ΔpK values, in comparison with those with two NDA groups in close proximity to each other. And as far as concerned with acid dissociation process, D[A.A]TA behaves in a quite similar manner to those of the latter group.

If the above presumption is true regarding the spatial relationship between the two NDA groups in this compound, a cyclohexane ring bearing the substituents must take a skew-boat form, in which the vicinal NDA groups can be in a synclinal conformation.

TABLE 3. CHELATE STABILITY CONSTANTS OF D[A.A]TA AND RELATED COMPLEXANES 25.0 °C, μ=0.10 (KNO_3)

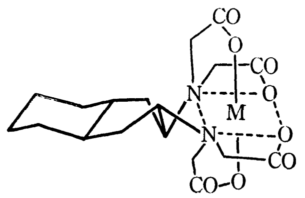
Compound	$\log K_{MA}$		
	Mg(II)	Ca(II)	Sr(II)
D[A.A]TA	10.36	11.54	9.34
t-THDTA[5]	10.28	11.63	9.56
t-1,2-CYDTA[11]	10.3	12.2	9.97
t-1,2-CPDTA[8]	9.05	11.08	9.45
EDTA[12]	8.69	10.70	8.63
1,3-CYDTA[10]	4.64	4.77	—
1,4-CYDTA[10]	4.30	4.19	—
N-Me-IDA[13]	3.44	3.75	2.85

N-Me-IDA:*N*-Methyliminodiacetic acid

Chelate Stability. Stability constants of the alkaline earth metal chelates of D[A.A]TA are listed in Table 3 along with those of some related complexane-type ligands. The value of $\log K_{M_2A}$ of D[A.A]TA, being negative, indicated that this ligand formed predominantly a 1:1 chelate with alkaline earth metal ions. The values of K_{MA} also agreed well with those obtained by the Bjerrum's method, where the formation of an M_2A type chelate was neglected.

Tetrabasic complexanes in Table 3 may be classified in respect to the capability of two NDA groups coordinating to a same metal ion. Those with NDA groups which are spatially separated apart from each other, show much lower chelate stabilities than those with the ligand substituents in the vicinity to each other. Each NDA group in the former class, at the extremity, would coordinate independently to a separate metal ion. The $\log K_{MA}$ value of such a tetrabasic complexane could be estimated to fall in the range of 3—4, if a statistical correction of 0.3 was applied to those of *N*-methyliminodiacetic acid.

As one can seen in Table 3, D[A.A]TA belongs to the class of the high chelate stability, the value being comparable to that of *t*-1,2-CYDTA, in which two NDA groups are in a synclinal form. Combined with the value of K_{M_2A} of D[A.A]TA, these results provide strong evidences for the conclusion that six donor atom on the D[A.A]TA are in a conformation favorable for coordinating simultaneously to a single metal ion. A molecular model study indicates that D[A.A]TA can work as a hexadentate ligand only in the case where the dihedral angle between the two NDA groups falls in the *syn*-region, and that, in turn, the cyclohexane ring bearing the NDA groups must be in a skew-boat form, as shown in structure 2.



Structure 2

The enthalpy difference between the chair and skew-boat form in *trans*-decalin is calculated to be 5.5 kcal/mol.[14] The steric instability of the skew-boat form in D[A.A]TA, however, can be compensated enough by the relatively large free energy gain with the formation of coordination bonds.

One might notice that *t*-1,2-CPDTA behaves in similar manner to 1,3- and 1,4-CYDTA rather than to *t*-1,2-CYDTA upon a reaction with proton, while in the reverse manner with divalent metal ions. This would be most probable on account of sizes of cations. When *t*-1,2-CPDTA takes a half-chair form, two NDA groups are in synclinal conformation, possibly coordinating to a metal ion which has much larger radius than proton.

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