Synthesis and Properties of Chiral Macrobicyclic and Macrotricyclic Cryptands Containing the *trans*-Tetrahydrofuran-2,5-diylbis(methylene) Subunit as the Chiral Center

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The macrobicyclic and macrotricyclic cryptands containing the *trans*-tetrahydrofuran-2,5-diylbis(methylene) molecular framework as the chiral subunit were prepared in optically active forms. The enantiomer recognition property of the macrotricyclic tetracarboxamide (+)-**6** in transport of enantiomeric molecules was examined, and the cation-binding abilities of the macrotricyclic and macrobicyclic amines **7**, **10**, and **13** were also investigated.

Azamacropolycyclic polyethers (cryptands), as well as crown ethers, are of interest in host-guest chemistry. Various kinds of optically active crown ethers have been prepared and their chiral recognition behaviors have been extensively studied.[1] On the other hand, little synthesis of optically active cryptand have been reported, and chiral recognition property of the compound has been scarcely investigated.

Chiral macrotricyclic cryptands yield complexes by using a macrocyclic subunit as anchor site for binding a substrate. With primary ammonium salts, the NH_3^+-group binds directly to the macrocycle, and with alkali salts of organic anions, a cascade process is involved with first binding of the alkali cation followed by electrostatic pairing with the molecular anion. When the substrates are chiral, enantiomer recognition is expected to occur in both cases.[2]

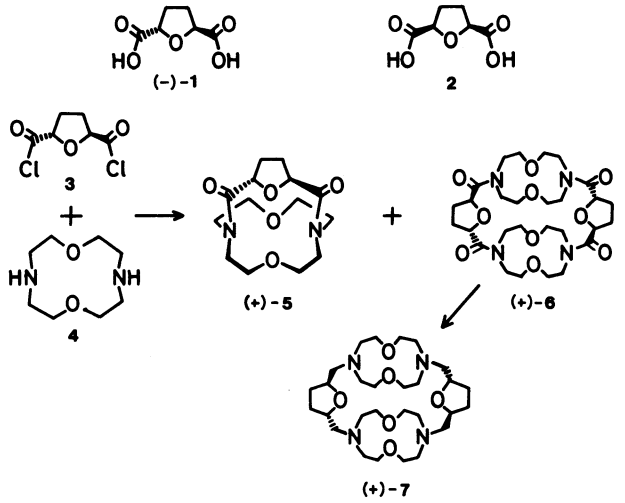
In our preceding papers,[3,4] we have reported the preparations and the enantiomer recognition properties of optically active crown ethers and open-chain polyethers which contained the *trans*-tetrahydrofuran-2,5-diylbis(methylene) subunit as the chiral center. Our continuing interest in chiral crown ethers and analogous compounds prompted us to prepare chiral macrotricyclic cryptand incorporating the *trans*-tetrahydrofuran-2,5-diylbis(methylene) subunit, and we present here our results on the syntheses and some properties of the chiral macrotricyclic and macrobicyclic cryptands.

Results and Discussion

One of our target compounds is the chiral cylindrical macrotricyclic cryptand containing two chiral centers, and Lehn and coworkers[2] have reported the synthesis of the cylindrical macrotricyclic tetracarboxamide by condensation of two molecules of the acid dichloride with two macrocyclic amine molecules.

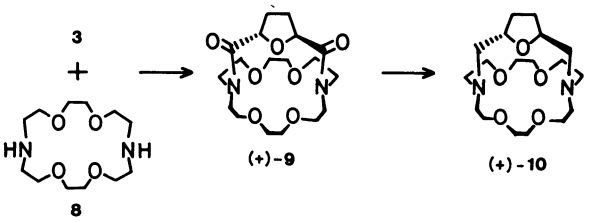
The synthetic strategy was to introduce the chiral centers by condensation of optically active acid dichloride with achiral macrocyclic amine. We previously reported the synthesis and the determination of absolute configuration of enantiomerically pure *trans*-tetrahydrofuran-2,5-dicarboxylic acid (**1**),[3] from which the chiral acid dichloride **3** was prepared. Treatment of (−)-(2*S*,5*S*)-**1**, $[\alpha]_D$ −5.4° (MeOH), with thionyl chloride gave the acid dichloride **3**, which was condensed with 1,7-diaza-12-crown-4 (**4**) in benzene in the presence of triethylamine under high dilution conditions.[5] Chromatography of the resulting mixture on alumina followed by recrystallization from benzene–hexane provided the desired macrotricyclic tetracarboxamide **6**, mp 240 °C (decomp), $[\alpha]_D$ +14.9° ($CHCl_3$), (26% yield) together with the macrobicyclic dicarboxamide **5**, mp 275 °C (decomp), $[\alpha]_D$ +41.0° ($CHCl_3$), (11% yield). The structures of these amides were proved by their mass spectra as well as elemental analyses and ^1H NMR spectra. The predominant formation of the macrotricyclic dimer **6** in condensation of **3** with **4** is rationalized by assuming that *trans*-tetrahydrofuran-2,5-dicarboxylic acid (**1**) contains diglycolic acid moiety.[2]

The reduction of (+)-**6** to the macrotricyclic tetramine **7** was carried out with lithium aluminium hydride in dry tetrahydrofuran (THF), and chromatography of the product on alumina afforded a 51% yield of **7**, $[\alpha]_D$ +32.5° ($CHCl_3$), as a colorless oil.

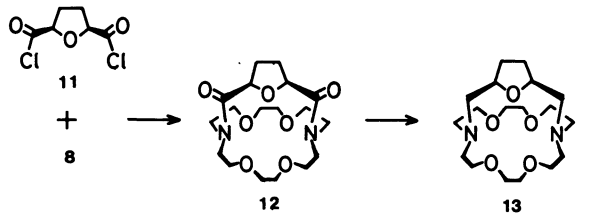


Next, we attempted to prepare the macrotricyclic cryptand, possessing the larger cavities than those of

(+)-**6**, by condensation of two molecules of **3** with two 1,10-diaza-18-crown-6 (**8**) molecules. Condensation of **3** with **8** in benzene was carried out by the same procedure described for the preparation of **6**. The product was chromatographed on alumina to give a 46% yield of the macrobicyclic dicarboxamide **9**, mp 203—205 °C, $[\alpha]_D$ +27.8° ($CHCl_3$), whose structure was also confirmed by the mass spectrum, and the cylindrical macrotricycle corresponding to **6** was not obtained. The dicarboxamide (+)-**9** was converted to the macrobicyclic diamine **10** by diborane reduction.[5] Refluxing of (+)-**9** with a freshly prepared diborane in dry THF gave the borane-amine adduct, which was hydrolyzed with 6M-hydrochloric acid (1 M=1 mol dm^{-3}) to afford the macrobicyclic diamine **10**, mp 190—192 °C, $[\alpha]_D$ +61.7° ($CHCl_3$), in 75% yield after recrystallization from hexane.



Finally, we prepared the macrobicyclic diamine incorporating achiral *cis*-tetrahydrofuran-2,5-diylbis-(methylene) residue. The acid dichloride **11** was obtained from *cis*-tetrahydrofuran-2,5-dicarboxylic acid (**2**) with thionyl chloride. Condensation of **11** with **8** under high dilution conditions followed by alumina column chromatography and recrystallization provided a 32% yield of **12**, mp 173—174 °C, and the cylindrical macrotricycle was not detected. Diborane reduction of **12** followed by hydrolysis with 6M-hydrochloric acid gave the achiral macrobicyclic diamine **13**, mp 208—209 °C, in 22% yield after recrystallization from hexane.



Chiral recognition property of the macrotricyclic tetracarboxamide (+)-**6** in transport of racemic primary ammonium cations; (±)-1,2-diphenylethylamine, (±)-2-aminotetralin and methyl (±)-phenylglycinate hydrochloride was examined and the results are given in Table 1.

The cryptand **6** has a higher enantiomer selectivity towards these guest molecules rather than 18-crown-6 and dibenzo-18-crown-6 derivatives incorporating the *trans*-tetrahydrofuran chiral center.[4] The cylindrical macrotricyclic cryptand (+)-**6** with D_2 symmetry contains two lateral and one central cavities.[6] Each lateral cavity possesses two chiral groups attached to nitrogen, and a large central cavity defined by the two macrocycles and the two bridges linking them incorporates two chiral subunits in the ring system. Both the lateral and the central cavities may bind NH_3^+-group, but in the complex formed by the binding of the substrate to the central cavity, the bound substrate may interact appreciably with the chiral center and therefore be subject to chiral discrimination.

Next, we studied extraction experiment for testing the chiral discrimination ability of the macrotricyclic amine **7** towards chiral molecular anion. Aqueous solution of potassium (±)-mandelate was extracted with a solution of (+)-**7** in $CDCl_3$. But, ^1H NMR spectrum of the organic layer obtained showed no signal due to the substrate. It appears that the molecular cavity of **7** is too small for inclusion of mandelate anion.

The macrobicyclic diamine **10** and **13** are analogues of cryptand 221[5] and possess the ethano bridge between C20 and C22 of the cryptand 221 molecular framework. We next turned our attention to the comparison of the cation-binding abilities of the macropolycyclic amines **7**, **10**, and **13** with that of

Table 2. Extraction of Alkali Metal Picrates

	Extractability/%				
	Li^+	Na^+	K^+	Rb^+	Cs^+
7	30	29	25	22	30
10	80	72	71	79	72
13	78	71	70	78	80
Cryptand 221	78	74	74	80	54

Table 1. Differential Transport of Enantiomeric Molecules through Bulk Liquid Membrane Containing (+)-**6**

Guest	Time / h	Transported / %	Configuration of dominantry transported enantiomer	Optical purity / %
(±)-1,2-Diphenylethylamine	3	10.1	S	46
(±)-2-Aminotetralin	5	10.3	R	25
Methyl (±)-phenylglycinate	12	11.0	R	16

Table 3. Transport Properties of Macrobicyclic Diamines

Host	Transport rate $\times 10^6$/mol h^{-1}				
	Li^+	Na^+	K^+	Rb^+	Cs^+
10	0.65	0.11	1.5	0.55	0.14
13	0.85	0.12	1.7	0.60	0.15

cryptand 221. The abilities were assessed by solvent extraction of aqueous solution of alkaline metal picrate with a chloroform solution containing cryptand. The results are summarized in Table 2.

As can be seen from Table 2, the alteration in the configuration of tetrahydrofuran moiety scarcely results in the variation in the cation-binding abilities of cryptands **10** and **13**. The striking difference between the cryptands **10** and **13** and the parent cryptand 221 is seen in their extractabilities for Cs^+ ion among alkali metal ions. The differences in extractabilities of three cryptands for the other alkali metal cations cannot be regarded as significant.

We also examined cation transport properties of **10** and **13** by using a chloroform liquid membrane system, and Table 3 lists the results.

Although potassium ion transport was most rapid in both cases, cryptands **10** and **13** hardly mediated transport of guest cations.

Experimental

Infrared spectral data were taken on a Hitachi 260-10 spectrophotometer, and ^{1}H NMR spectra were obtained from a JNM-MH-100 and a JNM-C-60. Chemical shifts are reported in parts per million (δ) down field from tetramethylsilane. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. Electronic spectral data were measured with a Hitachi 220A spectrophotometer and circular dichroism data were collected with a JASCO J-40 spectropolarimeter. Mass spectra were taken with a Hitachi RMS-4 spectrometer. Elemental analyses were determined on a Yanagimoto CHN-Corder, Type II. All melting and boiling points are uncorrected.

(2*S*,5*S*)-Tetrahydrofuran-2,5-dicarbonyl Dichloride (3). A mixture of (−)-(2*S*,5*S*)-tetrahydrofuran-2,5-dicarboxylic acid (**1**), $[\alpha]_D$ −5.4° (MeOH),[3] (1.50 g, 8.43 mmol) and thionyl chloride (10.5 g, 88.1 mmol) was stirred for 48 h at room temperature. The excess of thionyl chloride was evaporated under reduced pressure to give 1.60 g of **3**, which was used for the next reaction without further purification.

(+)-(3*S*,6*S*)-3,6-Epoxy-11,16-dioxa-1,8-diazabicyclo[6.5.5]-octadecane-2,7-dione (5) and (+)-(3*S*,6*S*,16*S*,19*S*)-3,6:16,19-Diepoxy-11,24,29,34-tetraoxa-1,8,10,21-tetraazatricyclo[20.5.5.5^{8,14}]-hexatriacontane-2,7,15,20-tetrone (6). The acid dichloride (**3**) (1.97 g, 10.0 mmol) and a mixture of 1,7-diaza-12-crown-4 (**4**)[5] (1.65 g, 9.48 mmol) and triethylamine (2.69 g, 26.6 mmol), each dissolved in 200 mL of dry benzene, were dripped over a period of 10.5 h from separate addition funnels into 400 mL of rapidly stirred dry benzene at room temperature. After the mixture was stirred for an additional 30 min, a precipitate was filtered off and the benzene was evaporated in vacuo. The residue was chromatographed on alumina. Fractions eluted with $CHCl_3$ gave 1.01 g of **5** (11% yield), which was recrystallized from benzene–hexane: mp 275 °C (decomp); $[\alpha]_D^{23}$ +41.0° (*c* 0.666, $CHCl_3$); IR (KBr) 1640, 1120, 1060 cm^{-1}; MS *m/z* 298 (M^+). Fractions eluted with $CHCl_3$–MeOH (95:5 v:v) afforded 2.35 g of **6** (26% yield), which was recrystallized from benzene–hexane: mp 240°C (decomp); $[\alpha]_D^{23}$ +14.9° (*c* 0.603, $CHCl_3$); IR (KBr) 1640, 1140, 1080, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.0—2.3 (8H, m, $-(CH_2)_2-$), 3.0—4.0 (32H, m, $-NCH_2CH_2O-$), 4.93 (4H, br s, CH); MS *m/z* 596 (M^+).

(+)-**5**: Found: C, 56.43; H, 7.34; N, 9.52%. Calcd for $C_{14}H_{22}O_5N_2$: C, 56.36; H, 7.34; N, 9.39%.

(+)-**6**: Found: C, 56.16; H, 7.30; N, 9.35%. Calcd for $C_{28}H_{44}O_{10}N_4$: C, 56.36; H, 7.34; N, 9.39%.

(+)-(3*S*,6*S*,16*S*,19*S*)-3,6:16,19-Diepoxy-11,24,29,34-tetraoxa-1,8,10,21-tetraazatricyclo[20.5.5.5^{8,14}]hexatriacontane (7). A solid $LiAlH_4$ (200 mg, 4.20 mmol) was added by portions to a solution of (+)-**6** (500 mg, 0.900 mmol) in 75 mL of dry THF at room temperature and then the mixture was refluxed for 16 h. To the chilled reaction mixture was slowly added 10% aqueous NaOH solution and a deposited solid was filtered off. The solvent was evaporated in vacuo and the residue was dissolved in 20 mL of $CHCl_3$. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on alumina, and fractions eluted with $CHCl_3$–MeOH (95:5 v:v) gave 230 mg of **7** (51% yield) as a colorless oil: $[\alpha]_D^{23}$ +32.5° (*c* 0.560, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.4—2.2 (8H, m, $-(CH_2)_2-$), 2.6—2.9 (24H, m, $-NCH_2-$), 3.5 (16H, t, *J*=5 Hz, $-OCH_2-$), 3.9—4.2 (4H, m, CH). Found: C, 61.95; H, 9.50; N, 10.33%. Calcd for $C_{28}H_{52}O_6N_4$: C, 62.19; H, 9.69; N, 10.36%.

(+)-(20*S*,23*S*)-20,23-Epoxy-4,7,13,16-tetraoxa-1,10-diazabicyclo[8.8.6]tetracosane-19,24-dione (9). Condensation of **3** (2.39 g, 1.21 mmol) with 1,10-diaza-18-crown-6 (**8**);[5] (3.10 g, 11.2 mmol) was carried out by the same procedure described for the preparation of **5** and **6**. The product was chromatographed on alumina and fractions eluted with $CHCl_3$ gave 2.48 g of **9** (46% yield), which was recrystallized from benzene–hexane: Mp 203—205 °C; $[\alpha]_D^{22}$ +27.8° (*c* 0.410, $CHCl_3$); IR (KBr) 1660, 1110, 1060 cm^{-1}; MS *m/z* 386 (M^+). Found: C, 55.63; H, 7.89; N, 7.19%. Calcd for $C_{18}H_{30}O_7N_2$: C, 55.94; H, 7.83; N, 7.25%.

(+)-(20*S*,23*S*)-20,23-Epoxy-4,7,13,16-tetraoxa-1,10-diazabicyclo[8.8.6]tetracosane (10). To a solution of (+)-**9** (1.46 g, 3.00 mmol) in dry THF (20 mL) was added a freshly prepared solution of diborane (18 mmol) in 27 mL of dry THF at room temperature, and then the mixture was refluxed for 18 h. After cooling to room temperature, 3 mL of water was added to the mixture and the mixture was stirred for 1 h at room temperature. After the mixture was concentrated in vacuo, 70 mL of $CHCl_3$ was added to the residue and a deposited inorganic solid was filtered off. The solvent was evaporated in vacuo, and 50 mL of ether and 5 mL of 6M-HCl were added to the residue. After the mixture was stirred for 1 h at room temperature, the acidic aqueous layer was separated and the organic layer was extracted with water. The combined aqueous solutions were made alkaline with 25% aqueous NaOH solution and extracted with $CHCl_3$. The extract was dried over Na_2SO_4

and concentrated to give a solid, which was recrystallized from benzene–hexane to afford 785 mg of **10** (57% yield): Mp 190—192 °C; $[\alpha]_D^{23}$ +61.7° (*c* 0.505, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.1—2.0 (4H, m, $-(CH_2)_2-$), 2.4—3.0 (12H, m, $-NCH_2-$), 3.1—3.8 (16H, m, $-OCH_2-$), 4.0—4.3 (2H, m, CH). Found: C, 60.15; H, 9.57; N, 7.80%. Calcd for $C_{18}H_{34}O_5N_2$: C, 60.30; H, 9.56; N, 7.82%.

***cis*-Tetrahydrofuran-2,5-dicarbonyl Dichloride (11).** By the same procedure described for the preparation of **3**, *cis*-tetrahydrofuran-2,5-dicarbonyl dichloride (**11**) (3.60 g) was prepared from *cis*-tetrahydrofuran-2,5-dicarboxylic acid (**2**)[7] (3.30 g, 0.0205 mol) and thionyl chloride (21.0 g, 0.176 mol). Without further purification, the product was used in the next reaction.

(20*S*,23*R*)-20,23-Epoxy-4,7,13,16-tetraoxa-1,10-diazabicyco-[8.8.6]tetracosane-19,24-dione (12). In the same manner described for the preparation of **5** and **6**, the acid dichloride **11** (1.20 g, 6.09 mmol) was condensed with 1,10-diaza-18-crown-6 (**8**) (1.55 g, 5.92 mmol), and the product was chromatographed on alumina. Fractions eluted with $CHCl_3$ provided 810 mg, of **12** (32% yield), which was recrystallized from benzene–hexane: Mp 173—174 °C; IR (KBr) 1650, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.7—2.2 (2H, m, $-(CH_2)_2-$), 2.3—3.2 (6H, m, $-(CH_2)_2-$ and $-NCH_2-$), 3.5—4.4 (20H, m, $-NCH_2-$ and $-OCH_2-$); MS *m/z* 386 (M^+). Found: C, 55.80; H, 7.86; N, 7.11%. Calcd for $C_{18}H_{30}O_7N_2$: C, 55.94; H, 7.83; N, 7.25%.

(20*S*,23*R*)-20,23-Epoxy-4,7,13,16-tetraoxa-1,10-diazabicyclo-[8.8.6]tetracosane (13). Treatment of **12** (650 mg, 1.68 mmol) with a solution of diborane (8.04 mmol) in dry THF followed by hydrolysis with 6M-HCl was carried out by the same procedure described for the preparation of **10**. The same workup described for **10** gave a solid which was recrystallized from hexane to provide 130 mg of **13** (22% yield): Mp 208—209 °C. Found: C, 60.18; H, 9.53; N, 7.80%. Calcd for $C_{18}H_{34}O_5N_2$: C, 60.30; H, 9.56; N, 7.82%.

Enantiomer Differential Transport. Enantiomer differential transport was carried out in a conventional apparatus which consisted of an outer cylindrical glass vessel (24.5 mm inner diameter) and a central glass tube (15.5 mm inner diameter). The 0.005 M $CHCl_3$ solution of the host separated the inner aqueous phase (0.1 M HCl) and the outer aqueous phase (0.08 M HCl) which contained $LiPF_6$ (0.4 M) and the racemic guest (0.04 M). The $CHCl_3$ layer was stirred at a constant speed (60 rpm) at 25±1 °C.

Cation Transport. The same apparatus described above was used. The $CHCl_3$ (5 mL) layer contained the cryptand (2.4×10^{-4} M) and the outer aqueous layer (5 mL) contained the metal picrate (2.4×10^{-4} M). The $CHCl_3$ layer was stirred at 25±1 °C.

Extraction Procedure. The aqueous solution (5 mL) of the metal picrate (2.4×10^{-4} M) and the $CHCl_3$ solution (5 mL) containing the host (2.4×10^{-4} M) were placed in a screw cap glass tube (30 mL) and the tube was shaken for 30 min at room temperature. Extraction of the picrate was followed by monitoring the absorbance at 357 nm of the aqueous phase.

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