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Sadatoshi Akabori[a]; Masatsugu Miura[a]; Masakazu Takeda[a]; Shun Yuzawa[a]; Yoichi Habata[a]; Toshio Ishii[b]
[a] Department of Chemistry, Faculty of Science, Toho University, Funabashi-shi, Chiba, Japan [b] School of Dental Medicine, Tsurumi University, Tsurumi-ku, Tsurumi, Japan

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Syntheses of diethyleneoxy bridged cryptophanes and their complexing abilities with alkali metal and alkylammonium cations

SADATOSHI AKABORI*[1], MASATSUGU MIURA[1], MASAKAZU TAKEDA[1], SHUN YUZAWA[1], YOICHI HABATA[1], and TOSHIO ISHII[2]

[1]*Department of Chemistry, Faculty of Science, Toho University, Funabashi-shi, Chiba 274 Japan;* [2] *School of Dental Medicine, Tsurumi University, Tsurumi-ku, Tsurumi 230, Japan*

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The anti- and syn-diethyleneoxy bridged cryptophanes (3a and 3b) were prepared by the direct trimerization of 1,5-bis[(4-hydroxymethyl)-2-methoxyphenoxy]-3-oxapentane, which was obtained by the reaction of diethyleneglycol ditosylate with vanillyl alcohol and/or by stepwise methods from vanillyl alcohol. The syn isomer (3b) showed highly selective complexing abilities for cesium, and the tetraethylammonium and triethylmethylammonium cations among the investigated alkali metal and alkylammonium cations as compared with those of the anti isomer (3a).

INTRODUCTION

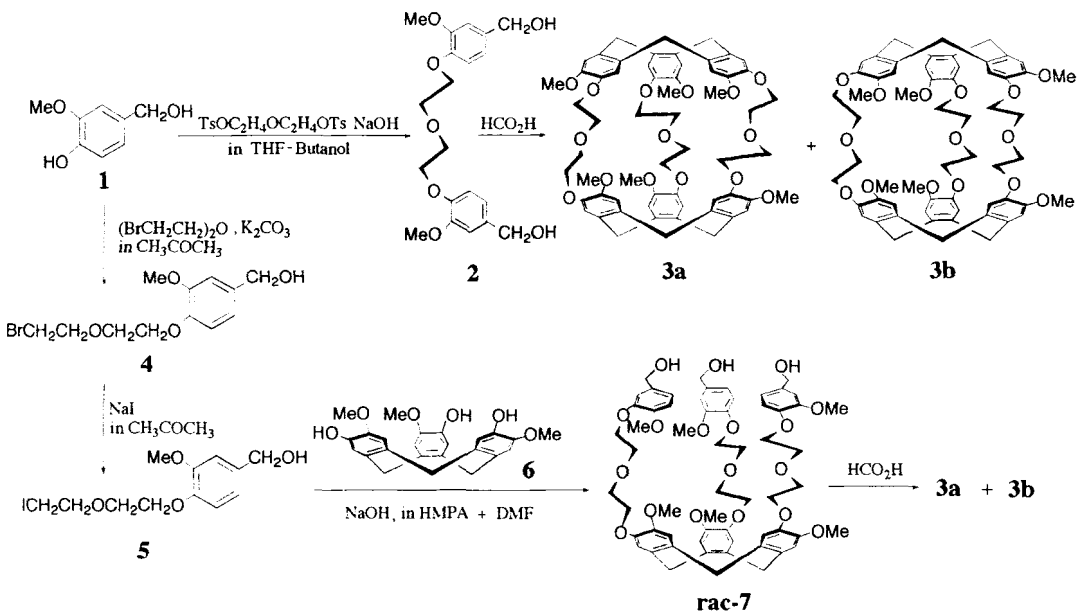
It is known that the spheroidal intramolecular cavity of macrobicyclic ligands is well adapted to the formation of stable and selective complexes with spherical cations.[1] Spherical macrotricycles such as cryptand should be the most favorable for the recognition of spherical guest moieties.[1,2] Collet et al. reported the syntheses of several kinds of cryptophanes and their complexing abilities with neutral guest molecules such as halomethane and with alkylammonium cations.[3–9] For example, cryptophane-E can selectively incorporate chloroform[9,10] and tetramethylammonium cations into the cavity. The cryptophanes, in which the bridges are relatively short, possess a roughly rigid spherical and lipophilic cavity and three windows that allow the suitable guests to enter. The size of the cryptophanes cavity and three windows can be changed by varying the length and the structure of the bridge unit. The syntheses and the extraction abilities of the relevant trimers of benzo-18-crown-5 and benzo-18-crown-8 (cycrotriveratlyrene crown ethers) were also investigated by two research groups.[11,12] In order to investigate the contributions of the hole and windows sizes, and the number of oxygen atoms of the cryptophane, we synthesized the diethyleneoxy bridged cryptophanes, in which the bridged chains and cavities of the three windows are longer and larger than those of cryptophane-E, and examined their complexing abilities with alkali metal and ammonium cations as charged guest ions.

*To whom correspondence should be addressed.

RESULTS AND DISCUSSION

Syntheses of cryptophanes

The synthetic routes of cryptophane are shown in the scheme below. These methods are similar to those described by Collet et al..[4,5,8] 1,5-Bis[4-(hydroxymethyl)-2-methoxyphenoxy]-3-oxapentane (**2**) was prepared by the reaction of vanillyl alcohol (**1**) with diethylene glycol ditosylate in 73.4% yield. The direct intermolecular trimerization of **2** in formic acid gave the anti- and syn-diethyleneoxy bridged cryptophanes, **3a** and **3b**, in 1.9 and 2.9% yields, respectively. Compounds **3a** and **3b** were also obtained from vanillyl alcohol (**1**) using the stepwise method as shown in the reaction scheme. The reaction of **1** with bis(2-bromoethyl)ether produced (**4**) in 29.0% yield. The reaction of **5**, which was obtained by the reaction of **4** with sodium iodide in 86.4% yield, with C_3-cyclotriguaiacylene (**6**) gave rac-**7** in 53.4% yield. Finally, the intramolecular trimerization of rac-**7** in formic acid gave **3a** and **3b** in 20.5 and 28.8% yields, respectively. These yields of **3a** and **3b** from **1** using the



stepwise method were 3.9 and 2.7%, respectively, and these yields were superior to those (**3a**:1.9% and **3b**:2.9%) obtained using the direct method. The structures of **3a** and **3b** were determined using the ^{1}H-NMR and mass spectra, elemental analyses, and high-performance liquid chromatography. High-performance liquid chromatography[13] of **3a** using an optically active column (CHIRALPAK-OT(+)) showed two peaks (relative intensity is 1:1) due to the presence of optical isomers, however, compound **3b** showed only one peak. These results showed that **3a** is a racemic mixture and **3b** is a meso form. However, the optical resolution of **3a** was not completed, because our present study of the complexing ability of **3** with guest ions is concerned with the non-optically active ion as a guest molecule.

Complexing abilities of 3a and 3b with alkali metal and alkylammonium ions

The complexing abilities of the crown ether and its analogs with metal and ammonium cations depend on several factors: the cavity size of the ligands, cation diameter, spatial distribution of the ring binding sites, and the character of the heteroatoms, etc.[1] A study of the cryptophanes has also shown that a three dimensional agreement between the hole size of the host molecule and the size of the guest molecule leads to stable inclusion complexes. For example, cryptophane-E selectively incorporates the match-sized halomethane into the three-dimensional cavity. Therefore, in order to investigate the complexing abilities, the extraction abilities of **3a** and **3b** toward alkali and alkylammonium ions were estimated using the method described in a previous paper.[14] These results are summarized in Table 1. The extraction abilities of **3a** and **3b** toward alkali metal cations were low. However, **3a** and **3b** showed relatively higher extraction abilities toward the cesium cation. The most significant finding is the selective extraction ability of **3b** toward Cs^+ compared with **3a**. The significant extraction ability of **3b** toward Cs^+ may be attributed to the fitness of the symmetrical shapes of the host, and the presence of additional oxygens in the bridges compared with cryptophane-O[10] is certainly responsible for this behavior. It seems also obvious that, during the extraction of metal cations, **3a** demonstrates considerably less size selectivity. This phenomena is due to the ability of **3a** to undergo a conformational twist (**3b** can not twist as well) to better accommodate guests of different sizes. As shown in Table 1, it was also found that **3a** and **3b** showed relatively high extraction abilities toward the tetramethylammonium cations, while they showed little or negligible extraction abilities toward the ammonium, methylammonium, dimethylammonium, and trimethylammonium ions. Anti-**3a** showed a lower extraction ability than **3b** toward the tetramethylammonium cation.

Table 1 Extraction abilities of alkali metal and alkylammonim cations from the aqueous to the organic phase(%)[a,b]

Compd	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	CH_3NH^+	$(CH_3)_2NH_2^+$	$(CH_3)_3NH^+$	$(CH_3)_4N^+$
3a	5.6	7.6	20.1	16.2	21.4	1.4	0.7	0.7	2.2	17.8
3b	2.6	7.7	5.3	6.2	43.3	0.7	0.7	1.4	2.9	67.5

a) For alkali metals: Solvent = Water and dichloromethane (equal volume). Picric acid = 7.0×10^{-5} M. Metal nitrate = 0.1 M. **3a**(**3b**) = 2.3×10^{-5} M.

b) Solvent = Water and dichloromethane(equal volume). Picric acid 7.0×10^{-5} M. Alkylammonium ions = 0.1 M. **3a**(**3b**) = 7.0×10^{-5} M.

It may arise from the lack of symmetry of the cavity hole of **3a** compared with **3b**. The extraction efficiency of **3b** toward these ammonium cations is in the order $(CH_3)_4N^+ > (CH_3)_3NH^+ > (CH_3)_2NH_2^+ > CH_3NH_3^+ > NH_4^+$. These results suggest that the symmetrically substituted tetramethylammonium ion is well incorporated into the cavity of the host molecule and the complexing ability of the small-sized ammonium ions with the host molecule is relatively small due to the mismatched sizes of the host and guest molecules. Two complexing manners are possible. One is the incorporation of the guest ion into the center of the cavity of the host molecule and the other is the complexation of the guest cation into the psuedo crown ether ring formed by the two oxygen atoms of the two methoxy groups and the diethyleneoxy bridged chain from outside of the host molecule. The estimation of the extraction abilities of **3a** and **3b** toward the tetraethylammonium, triethylammonium, diethylammonium and ethylammonium cations were also carried out. However, we could not estimate the extraction abilities toward these ethyl substituted ammonium cations, because these ammonium ions showed higher distributions in organic solvents such as dichloromethane due to their lipophilic character[15] even in the absence of the host molecule.

^{1}H-NMR studies of the complexing abilities of 3a and 3b with alkylammonium cations

In order to investigate the above complexing abilities of **3a** and **3b** with various ammonium cations, ^{1}H-NMR spectral studies were carried out. The only ethyltripropylammonium cation used was the iodide as a counter anion while all the other ammonium cations used were picrates. As shown in Fig. 1, the ^{1}H-NMR spectra of $Et_3MeN^+Pic^-$ (Pic^- = picrate anion) in the solvent (CD_2Cl_2:CD_3OD = 9:1) at 210 K showed the methyl and methylene proton peaks of the ethyl group at δ 1.27 and 3.23, respectively, together with the peak of the methyl group at δ 2.90. The aromatic protons of the picrate anion appeared at δ 8.86. Adding 0.5 equivalent of **3b** in the above solutions, the new peaks due to the incorporated guest ammonium cation's protons appeared at δ −0.29 ($\underline{CH_3}CH_2N$), 0.54 and 0.38 ($CH_3\underline{CH_2}N$), and −0.40 (CH_3N). However, the peak of the picrate anion was slightly changed (+0.04 ppm) to δ 8.82. In general, the picrate anion peak of the guest molecules was not observed to have any chemical shift change in the complexes with each cryptophane (**3a** and **3b**). This seems to be affected by the alcohol (CD_3OD) solvation, and the picrate anion acts as a separated counter anion and can not enter the cavity of the host molecule. These results suggest that the inclusion of the guest cation into the cavity of **3b** is a slow exchange at this temperature on the time scale of this ^{1}H-NMR spectrometer. The huge upfield shift induced on the Et_3MeN^+ is consistent with the inclusion of the guest into the cavity of **3b**. Thus, **3b** reversibly complexes Et_3MeN^+ in solvent ($CDCl_2$:CD_3OD(9:1)), and the apparent stability constant of the **3b**-Et_3MeN^+ complex in this solvent was estimated from the approximate peaks areas to be K = 1.54 × 10^3M^{-1}, which is an apparent constant in competition with the solvent, and $-\Delta G$ is 3.06 Kcal/mol. Furthermore, ΔH and ΔS were estimated from the temperature dependence ^{1}H-NMR spectra measurements

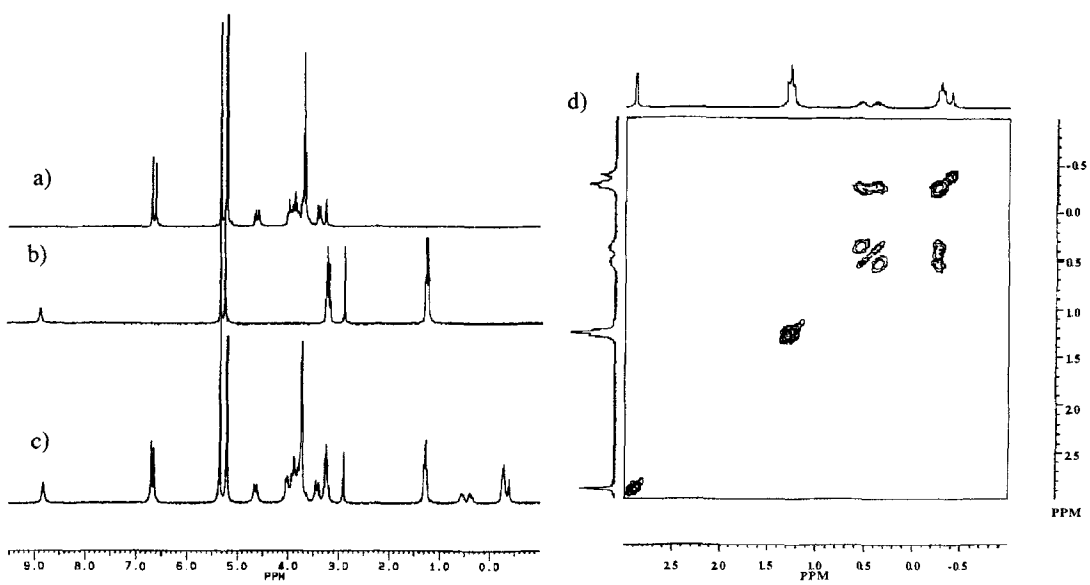


Figure 1 ^{1}H-NMR spectra (250 MHz) of $Et_3MeNPic$ in the presence of **3b** at 210K in CD_2Cl_2:CD_3OD = 9:1.(v/v). a) ^{1}H-NMR spectra of **3b** (5.0 × 10^{-3}M). b) ^{1}H-NMR spectra of $Et_3MeNPic$ (1.0 × 10^{-2}M). c) ^{1}H-NMR spectra of the mixture of $Et_3MeNPic$ (1.0 × 10^{-2}M) and **3b** (5.0 × 10^{-3}M). d) partial COSY spectra of c), new two multiplets (δ 0.54, 0.38) should be assigned to geminal protons of $N\underline{CH_2}CH_3$ of the complexed guest, due to correlation for the same peak.

Table 2 Equilibrium constants and thermodynamic parameters for the complexation of Anti- and Syn- diethyleneoxy bridged cryptophanes (**3a** and **3b**) with alkylammonium cations.[a])

		$n\text{-}Pr_3EtN^+$	Et_4N^+	Et_3MeN^+	Et_3NH^+	$EtMe_3N^+$	Me_4N^+
	K (10^3M^{-1})	0.07	0.98	0.69	0.67	0.68	0.89
Anti-form	ΔG (kcal/mol)	−1.80	−2.87	−2.73	−2.72	−2.72	−2.84
3a	ΔH (kcal/mol)	−3.50	−0.43	−0.53	−0.89	−0.39	−0.26
	ΔS (cal/mol/K)	−8.1	11.6	10.5	8.7	11.1	12.3
	K (10^3M^{-1})	0.14	1.51	1.54	1.46	1.03	1.18
Syn-form	ΔG (kcal/mol)	−2.07	−3.06	−3.06	−3.04	−2.89	−2.95
3b	ΔH (kcal/mol)	−2.62	−0.16	−0.88	−1.11	−0.85	0.73
	ΔS (cal/mol/K)	−2.6	13.8	10.4	9.2	9.7	17.5

a) The error range of ΔG were calculated to be ±0.03kcal/mol. The error ranges of ΔH and ΔS was estimated to be less than ±0.5 kcal/mol and ±2 cal/mol/K, respectively, from least-squares linear regression.

(range 210 to 300 K). In order to investigate the effect of the complexing abilities of **3** with the solvent, the complexing abilities of **3a** and **3b** with undeuterated solvent (CH_2Cl_2:CH_3OH(9:1)) were investigated by a similar method in the temperature range between 210 to 300 K. However, no complexing phenomena could be observed because the equilibrium of the complexation of **3a** and/or **3b** with the solvent is very fast on the time scale of this ^1H NMR due to the mismatch between the hole sizes of the host molecules and the solvent as guest molecules. Therefore, the complexing abilities of **3a** and **3b** with deuterated solvent (CD_2Cl_2:CD_3OD) are neglected in the calculation of the following thermal parameters. The measurements of the ^1H-NMR spectra were extended to other ammonium cations. These results are summarized in Table 2. Furthermore, the complexing abilities of **3a** and **3b** with primary and secondary ammonium cations such as $n\text{-}Pr_2NH_2^+$, $n\text{-}PrNH_3^+$, $Et_2NH_2^+$ and $EtNH_3^+$ were investigated, and no complexation was observed. These findings agree with the solvent extraction ability results of **3a** and **3b** as already described. It is, therefore, considered that the inclusion was also influenced by the shape and size of the guest molecule and the electron density of the cation's nitrogen atom. The relationship between the complexing abilities (−ΔG) of **3a** and **3b** and the volumes of the various guest ammonium cations are summarized in Fig. 2. As expected, the dependence of the complexing stabilities on the size of the guest cations was evidenced in both host cryptophanes. As described by Collet et al., cryptophane-E, in which the two cyclotriveratrylene units were bridged by the three propylene groups, was selectively complexed with tetramethylammonium cations. On the other hand, our synthesized cryptophanes, **3a** and **3b**, are bridged by the three diethyleneoxy chains, therefore, they obviously have larger cavities than cryptophane-E. Syn-**3b** exhibited the greatest stability for the Et_4N^+, Et_3MeN^+ and Et_3NH^+ complexes, while the anti-**3a** showed a higher inclusion ability toward Et_4N^+. The inclusion ability of **3a** is wholly inferior to that of **3b**. The cavity of **3b** appears to be slightly larger due to symmetry than that of **3a**. The windows between the two bridged chains in **3a**, in which the guest molecule should go through in order to be complexed, are slightly distorted compared to that of **3b**. The structural differences between **3a** and **3b** seem to reflect these results. The remarkable differences (ΔΔG = 0.33 and 0.32 Kcal/mol) of the complexing stability between **3a** and **3b** were observed in the complexes with the Et_3MeN^+ and Et_3NH^+ cations. In the complex of **3b** with Et_3MeN^+, the methylene protons of the incorporated guest cation appeared as two sets of multiplets at δ 0.54 and δ 0.38. In contrast, the complex of **3a** with Et_3MeN^+ showed the methylene protons due to the incorporated ammonium cation at δ 0.78 as a quartet. These results suggest that the incorporated Et_3MeN^+ in **3b** is more tightly bound than in **3a**. However, these phenomena could not be observed in the other complexes of **3a** and **3b**. Furthermore, this distinguishing feature of the complexation was observed in the case of Me_4N^+ with **3a** and **3b**. As already described, the −ΔG values of **3a** for the alkylammonium cations are shown to decline with a decrease in the cation volume. However, unexpectedly, the −ΔG value for the complexing stability (2.84 Kcal/mol) of **3a** with Me_4N^+ was higher than those of $EtMe_3N^+$, Et_3NH^+ and Et_3MeN^+. Also, the complexing ability of **3b** with

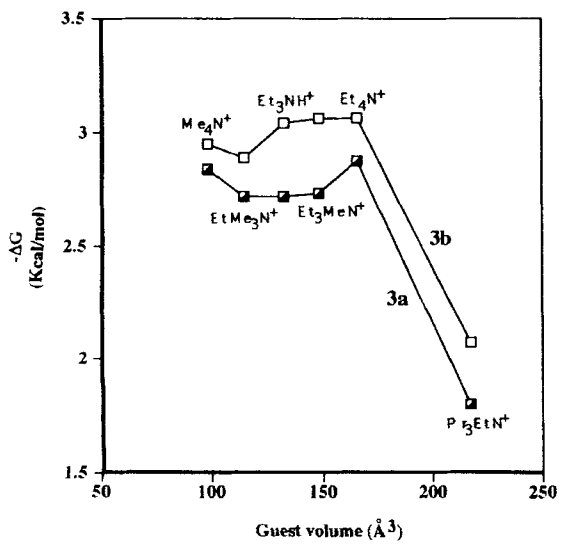


Figure 2 Correlation between -ΔG of the complexation of **3** with alkylammonium cations and the guest alkylammonium cation's volume (Å^3).

Me_4N^+ is higher than $EtMe_3N^+$. Therefore, both structural isomers, **3a** and **3b**, exhibited large complexing stabilities with Me_4N^+. The ΔS values for the complexation of **3a** with Et_4N^+ and Me_4N^+ are larger than those of the other guest cations. These results suggest that the possibility of recognition of the host molecule toward the guest cation was influenced by the shape and size of the guest cation. That is, Me_4N^+ and Et_4N^+ are the most symmetrically spherical guest cations among the investigated ammonium cations and can be fit into the ellipse cavities of **3a** and **3b**. Cryptophane **3a** in organic solvent showed less selectivity and smaller $-\Delta G$ values for the complexation with alkylammonium cations compared with that[10] of the water-soluble derivative of cryptophane-O in D_2O. This is attributed to the difference between the lipophilicities of the used solvents.

CONCLUSION

The anti and syn isomers of the diethyleneoxy bridged cryptophanes (**3a** and **3b**) were prepared. The syn isomer (**3b**) showed highly selective complexing abilities for cesium, tetraethylammonium, triethymethylammonium and triethylammonium cations among the investigated alkali metal and alkylammonium cations as compared with those of the anti isomer (**3a**), while **3a** and **3b** showed only a slight or no complexing abilities toward ammonium, primary ammonium and secondary ammonium cations.

EXPERIMENTAL SECTION

Melting points were determined using a Yazawa micro m.p. apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Brucker AC250 spectrometer (250 MHz) and Hitachi R-1100 spectrometer (60 MHz) with $(CH_3)_4Si$ as the internal standard. Elemental analyses were carried out using a Perkin-Elmer 2400 instrument. Electron impact (EI) and field desorption (FD) were recorded on a Hitachi M-80 and M-2000 spectrometers, respectively. The high-performance liquid chromatography (HPLC) was carried out with a JASCO HPLC system with a chiralpak-OT(+) column monitored with UV absorption measurements.

MATERIALS

Vanillyl alcohol **1**,[16] diethyleneglycol ditosylate,[17] bis(2-bromoethyl) ether[18] and c_3-cyclotriguaiacylene **6**[19] were prepared according to the procedures described in the literatures.

Syntheses of 3a and 3b: using the direct method: 1,5-Bis[4-hydroxymethyl-2-methoxyphenoxy]-3-oxapentane 2

The vanillyl alcohol **1** (54.1 g, 0.35 mol) was dissolved in 240 mL of 1-butanol and 35 mL of aqueous NaOH (10 mol/dm^3) was then added, and the mixture was stirred at room temperature under a nitrogen atmosphere. Diethyleneglycol ditosylate (70.0 g, 0.17 mol) in THF (140 mL) was added dropwise to the mixture over 1h. The solution was refluxed for 2 h, and the reaction mixture was then concentrated in vacuo. The residue was poured into water, and the precipitate was filtered off. The solid was recrystallized from ethanol to give **2** as a white powder. Yield 73.4%; mp 100–101°C; MS (EI) m/z 378 (M^+); Anal. Calc. for $C_{20}H_{26}O_7$: C, 63.38; H, 6.93%. Found: C, 63.34; H, 7.09%; ^{1}H-NMR (60 MHz; $CDCl_3$): 6.8–6.9 (m, 6H), 4.6 (s, 4H), 3.85–4.2 (m, 8H), and 3.8 (s, 6H).

Diethyleneoxy bridged Cryptophane—Anti (rac-3a) and Syn (meso-3b)

Compound **2** (2.0 g, 5.3 mmol) was dissolved in formic acid (1 L). This solution was stirred at 55–60°C for 2 h, and the reaction mixture was evaporated under vacuum. The resulting solid was dissolved in $CHCl_3$, and the solution was washed with water, dried, and evaporated. The isolation of **3a** was carried out by fractional crystallization from acetonitrile. The crude crystal of **3a** was collected by filtration and washed with acetonitrile, and dissolved in $CHCl_3$. This solution was then chromatographed on alumina using ethanol/chloroform (3:1, v/v) as the eluant. The main fraction was concentrated and the residue was recrystallized from chloroform/methanol to give **3a** as colorless plates. Yield 1.9%; mp 298–300°C; MS (FD) m/z 1026 ($M^+ - 1$); Anal. Calc. for $C_{60}H_{66}O_{15}$: C, 70.16; H, 6.48%. Found: C, 66.46; H, 6.77%; ^{1}H-NMR (60 MHz; $CDCl_3$): 6.65–6.87 (m, 12H), 4.68 (d, J = 13.2 Hz, 6H), 3.85–4.25 (m, 24H), 3.75 (s, 18H), and 3.43 (d, J = 13.2 Hz, 6H). The above filtrate was evaporated under vacuum. The isolation of **3b** was carried out by fractional crystallization from benzene. The crude crystal of **3b** was collected by filtration, washed with benzene, and dissolved in CH_2Cl_2. This solution was then chromatographed on silica gel using ethyl acetate/acetone (3:1, v/v) as the eluant. The main fraction was concentrated and the residue was recrystallized from dichloromethane/methanol to give **3b** as colorless plates. Yield 2.9%; mp 266–267°C; MS (FD) m/z 1026 ($M^+ - 1$); Anal. Calc. for $C_{60}H_{66}O_{15}$: C, 70.16; H, 6.48%. Found: C, 69.1; H, 6.06%; ^{1}H-NMR (60 MHz; $CDCl_3$): 6.67–6.90 (m, 12H), 4.71 (d, J = 13.2 Hz, 6H), 3.82–4.22 (m, 24H), 3.79 (s, 18H), and 3.44 (d, J = 13.2 Hz, 6H).

Syntheses of 3a and 3b by the stepwise method: 4-(5-Bromo-3-oxapentoxy)-3-methoxybenzenemethanol 4

A mixture of vanillyl alcohol **1** (11.5 g, 0.075 mol), bis (2-bromoethyl)ether (34.7 g, 0.15 mol), and potassium carbonate (10.3 g, 0.075 mol) in 40 mL of acetone was refluxed under a nitrogen atmosphere for 10 h. The reaction mixture was concentrated under vacuum. Water (50 mL) was added to the residue, and the mixture was then extracted with ether. The ethereal layer was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column with diethylether as the eluant. The main fraction was concentrated and the residue was recrystallized from diethylether to give **4** as needles. Yield 29.0%; mp 52.0–53.0°C; MS (EI) m/z 304 ($M^+ - 1$); Anal. Calc. for $C_{12}H_{17}O_4Br$: C, 47.23; H, 5.62%. Found: C, 47.03; H, 5.64%; ^{1}H-NMR (60 MHz; $CDCl_3$): 6.87–7.03 (m, 3H), 4.62 (s, 2H) 4.09–4.34 (m, 2H), 3.78–4.09 (m, 4H), 3.86 (s, 3H), 3.34–3.65 (m, 2H), and 1.80 (s, 1H).

4-(5-Iodo-3-oxapentoxy)-3-methoxybenzenemethanol 5

Compound **4** (1.53 g, 5 mmol) and sodium iodide (1.5 g, 10 mmol) in 20 mL of acetone were refluxed for 16 h. After the reaction mixture was concentrated, water was added to the residue, and the mixture was extracted with ether. The extract was evaporated, and the residual solid was recrystallized from diethylether to give **5** as colorless needles. Yield 86.4%; mp 60.0–61.0°C; MS (EI) m/z 352 ($M^+ - 1$); Anal. Calc. for $C_{12}H_{17}O_4I$: C, 40.92; H, 4.87%. Found: C, 41.19; H, 4.76%; ^{1}H-NMR (60 MHz; $CDCl_3$): 6.85–7.08 (m, 3H), 4.53–4.78 (s, 2H) 4.09–4.36 (m, 2H), 3.65–4.09 (m, 4H), 3.87 (s, 3H), 3.14–3.50 (m, 2H), and 1.53–1.78 (s, 1H)

2,7,12-Tris[2-[2-(4-hydroxymethyl-2-methoxyphenoxy)ethoxy]ethoxy]-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a.d.g]cyclononene (rac-7)

The c_3-cyclotriguaiacylene **6** (408 mg, 1 mmol) was dissolved in 20 mL of DMF-HMPA (1:1, v/v). To the solution was added 25% aqueous NaOH solution (0.5 mL), and the mixture was stirred at room temperature under a nitrogen atmosphere for 10 min, followed by the addition of **5** (1.35 g, 3 mmol). After the mixture had stirred at room temperature for 1 h, further amounts of 25% aq. NaOH solution (0.125 mL) and **5** (0.33 g, 0.75 mmol) were added. After the reaction was continued for 1 h, the reaction mixture was poured into water, the precipitate was isolated using suction filtration, and dried in air. The crude material was chromatographed on a silica gel column with ethyl acetate as the eluant. The main fraction was concentrated to give **7** as an amorphous powder. Yield 53.4%; mp 45.0–48.0°C; MS (FD) m/z 1080 ($M^+ - 1$); ^{1}H-NMR (60 MHz; $CDCl_3$): 6.72–7.04 (m, 15H), 4.70 (d, J = 15Hz, 3H), 4.53 (s, 6H), 4.01–4.35 (m, 12H), 3.63–4.01 (m, 12H), 3.75 (s, 18H), and 3.49 (d, J = 15Hz, 3H).

Diethyleneoxy bridged Cryptophane—Anti (rac-3a) and Syn (meso-3b)

A mixture of **7** (108 mg, 0.075 mol) and tetrachloromethane (1 mL) in 200 mL of formic acid was stirred at 55–60°C for 3 h. Water was added, and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column using ethyl acetate as the eluant. The faster moving **3b** was obtained and was recrystallized from dichloromethane/methanol to give **3b** as colorless plates. Yield 28.8%; mp 266–267°C; MS (FD) m/z 1026 ($M^+ - 1$); Anal. Calc. for $C_{60}H_{66}O_{15}$: C, 70.16; H, 6.48%. Found: C, 69.1; H, 6.06%. ^{1}H-NMR (60 MHz; $CDCl_3$) :6.67–6.90 (m, 12H), 4.71 (d, J = 13.2 Hz, 6H), 3.82–4.22 (m, 24H), 3.79 (s, 18H), and 3.44 (d, J = 13.2 Hz, 6H).

The slower moving **3a** was also obtained and was recrystallized from chloroform/methanol to give pure **3a** as colorless plates. Yield 20.5%; mp 298–300°C; MS (FD) m/z 1026 ($M^+ - 1$); Anal. Calc. for $C_{60}H_{66}O_{15}$: C, 70.16; H, 6.48%. Found: C, 66.46; H, 6.77%; ^{1}H-NMR (60 MHz; $CDCl_3$): 6.65–6.87 (m, 12H), 4.68 (d, J = 13.2 Hz, 6H), 3.85–4.25 (m, 24H), 3.75 (s, 18H), and 3.43 (d, J = 13.2 Hz, 6H).

Determination of Anti (rac-3a) and Syn(meso-3b) structures

The configurations of **3a** and **3b** were determined using HPLC with chiralpak-OT(+) as the column,[13] and they were resolved on this column with good selectivity. The chromatographic condition were as follows: column temperature, 5°C; wavelength, 230 nm; and flow-rate, 1 mL/min. The HPLC was carried out using methanol as an eluent and **3a** and **3b** in chloroform solution was injected into the HPLC.

The retention times of **rac-3a** were 13.5 and 83.8 min. The ratio of the two peaks was found to be 1:1, and the retention time of **meso-3b** was 25.5 min as a single peak. Therefore, **3a** and **3b** were determined as a chiral and an achiral molecules, respectively.

Solvent Extraction of 3a and 3b for alkali metal cation

Equal volumes (5 mL) of chloroform that contained 7×10^{-5} M of **3a** or **3b**, an aqueous solution that contained 0.1 M of metal nitrate, and 7.0×10^{-5} M of picric acid were mixed and agitated for 10 min. The solution was then separated using centrifugation. The upper solution was withdrawn and its absorbance was measured at 380 nm. Similar extraction and measurement methods were performed with a mixture of pure chloroform, an aqueous solution containing 0.1 M metal nitrate, and $7.0 \times$

10^{-5} M picric acid. The extraction abilities were calculated using the following equation:

$$\text{Extraction ability} = (\text{Ao} - \text{A})/\text{Ao} \times 100.$$

Ao is the absorbance in the absence of the host, and A is the absorbance in its presence.

Solvent Extraction of 3a and 3b for Ammonium picrate

Equal volumes (5 ml) of chloroform that contained 7.0×10^{-5} M of **3a** or **3b**, and an aqueous solution containing 0.1 M of amine or hydroxy tetramethylammonium and 7.0×10^{-5} M of picric acid were mixed and agitated for 10 min. The solution was then separated using centrifugation. The upper solution was withdrawn and its absorbance was measured at 380 nm. Similar extraction and measurement methods were performed with a mixture of pure chloroform, an aqueous solution containing 0.1 M of amine or hydroxy tetramethyl ammonium, and 7.0×10^{-5} M picric acid. Extraction abilities were calculated using the above equation.

Complexation studies

All measurements of ^{1}H-NMR spectra were carried out by Brucker AC250 (250 MHz) spectrometer in CD_2Cl_2:CD_3OD = 9:1 (v/v). The guest alkylammonium cations were used as the picrate salts expected n-Pr_3EtN^+, and the picrates were prepared according to the methods described in the literature,[20] while n-Pr_3EtN^+ was used as n-Pr_3EtNI after purified with the recrystallazation of commercial one. The peaks of the complexed guest cation frequently appeared in the vicinity of TMS, so that the peak of the undeuterated dichloromethane of the solvent at δ 5.33 ppm was employed as the internal standard. All concentrations of guest ammonium cations were ca. 1.0×10^{-2} M and all concentrations of **3a** and/or **3b** as host were ca. 5.0×10^{-3} M. Each equilibrium constant (K) and free energy change (ΔG) for the complexations of **3a** and/or **3b** with various ammonium cations were estimated by the integral ratio between the approximate peaks' area of the free and included guest cation. Influence of the solvent for the complexation of **3a** and/or **3b** were measured by using the undeuterated solvent (CH_2Cl_2:CH_3OH = 9:1) contained ca. 20% deuterated (CD_2Cl_2:CD_3OD = 9:1), however, the incorporated peaks of CH_2Cl_2 and CH_3OH into the cavity of the host molecule (**3**) could not observed at any temperature (210–300K). Thus, the complexation of **3** with deuterated solvent were neglected on the consideration of the complexation of **3a** and/or **3b** with various alkylammonium cations. The changes of entalpy and entropy for the complexation (ΔH and ΔS) were calculated by the plot ΔG vs T, which were given by variable temperature ^{1}H-NMR (mainly at 210, 230, 250, 270 and 300K), according to the equation $\Delta G = \Delta H - T\Delta S$.

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