Synthesis and Inclusion Properties of C_3-Symmetrically Capped Hexahomotrioxacalix[3]arenes with Ester Groups on the Lower Rim

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Keywords: Alkylation / Calixarenes / Ionophores / Molecular recognition

A triply bridged capped hexahomotrioxacalix[3]arene **4** with C_3-symmetry was synthesized by treatment of hexahomotrioxacalix[3]arene tricarboxylic acid **3** with 1,3,5-tris(bromomethyl)benzene in the presence of Na_2CO_3 in DMF. The complexation modes of **4** with cations differed according to the ionic size and properties of the guest cations, as was clearly elucidated by ^1H NMR titration spectra. Conformational studies on **4** in solution and in the solid state are also described.

Introduction

Thanks to their host-guest chemistry, calixarenes and related macrocycles have received considerable attention as ionophoric receptors[1−4] and potential enzyme mimics in biology.[5] Chemical modification of calixarene represents a simple, though effective and versatile, way to produce receptors with selective cation binding properties.[6−10] Calixarenes can be modified into different conformational isomers by introduction of large bulky substituents through alkylation on their phenolic oxygens, blocking interconversion by "oxygen-through-the-annulus" rotation.[11,12] Although less appropriate with the larger calix[6]arene,[13,14] a more effective approach is to build a bridge on the lower or upper rim[13,15] belonging to the capped calixarene. Using a durenyl bridge, a conformationally immobile cone conformer has been formed for calix[6]arene.[16] A triply bridged capped calix[6]arene with functional ester groups on the lower rim has also been synthesized, to bind with guanidinium ion,[17] as has one with capped thiabenzyl groups on the upper rim, to act as a preorganized host molecule for ammonium ions.[18] In complexation of this kind with guest molecules, the complexation-decomplexation exchange was slower than the NMR timescale. Among these kinds of capped calixarenes, there are two possible modes of complexation with guest molecules: in the cavity formed by the introduced functional groups, and in the cavity formed by the calix phenyl moieties. Is there any difference in complexation behavior with guest molecules? Because of the large structures of capped calixarenes so far reported, it is too complicated to elucidate them.

Hexahomotrioxacalix[3]arene has a more flexible conformation than calix[4]arene, because of the ether linkage, but the ring size is smaller than that of calix[6]arene. The basic C_3-symmetric structure would be expected to complex with primary ammonium ion RNH_3^+, which has potential functions not only in chemistry but also in biological systems. Unfortunately, because of the easier cleavage of its ethereal linkage, less attention has been paid it, especially its capped derivatives. Shinkai and co-workers have synthesized the capped hexahomotrioxacalix[3]arene, displaying high affinities for primary ammonium ions.[19] Meanwhile, hexahomotrioxacalix[3]arene derivatives with ester groups on the phenolic oxygens were also reported to show high selectivity for sodium cations, but lower affinities for larger potassium and cesium cations.[20] Although amide derivatives exhibited increased affinity for alkali metal cations, the selectivities for certain alkali metal cations decreased.[21]

We report here the synthesis of a triply bridged capped hexahomotrioxacalix[3]arene with ester functional groups on its lower rim. Because of its simple structure, with C_3 symmetry, it is easy to investigate its mode of complexation with guest molecules. The conformation and the complexation modes of host **4** as an ionophore, in comparison with uncapped host compound *cone*-**5**, are also discussed.

Results and Discussion

cone-Hexahomotrioxacalix[3]arene diethyl amide (**2**) was prepared by *O*-alkylation of hexahomotrioxacalix[3]arene (**1**) with *N,N*-diethyl chloroacetamide in the presence of NaH in refluxing THF, in 90% yield. Hydrolysis of cone amide **2** in a refluxing mixture of dioxane and water in the presence of NaOH afforded cone triacid **3**, in 51% yield. The ^1H NMR spectrum of **3** in $CDCl_3$ showed a single peak at $\delta = 1.14$ for the *tert*-butyl protons and a single peak at

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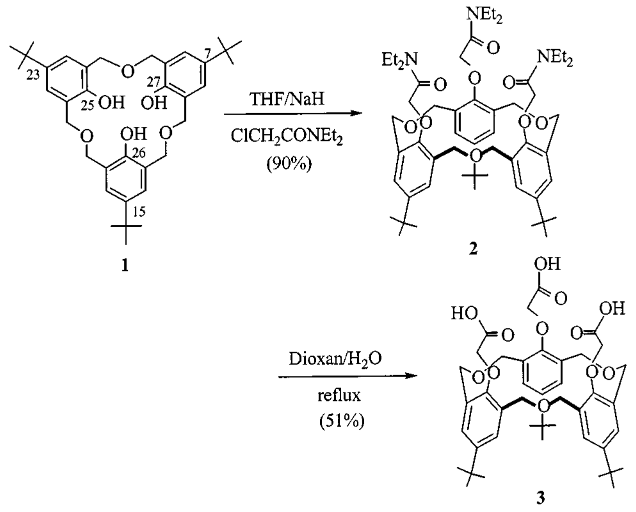
δ = 6.95 for the aromatic protons, in agreement with its C_3-symmetrical structure.



1

2

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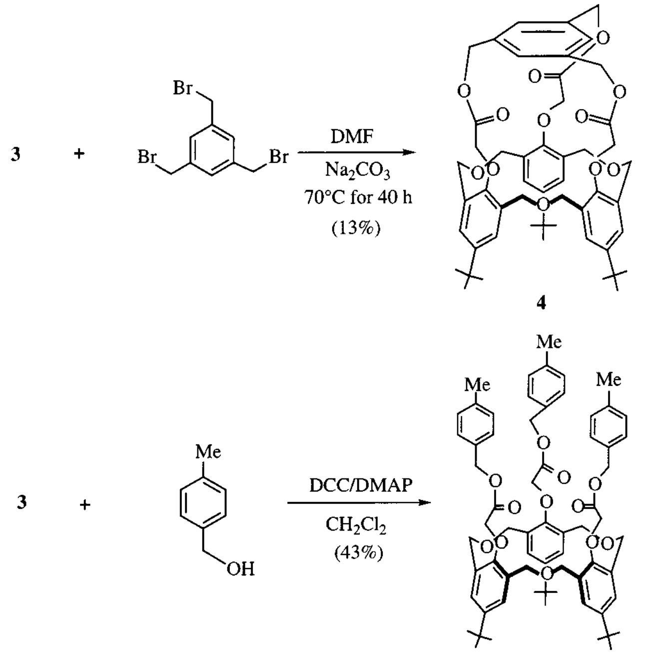


4

5

The attempted condensation of *cone*-**3** with 1,3,5-tris(bromomethyl)benzene in DMF in the presence of sodium carbonate as base afforded the novel capped hexahomotrioxacalix[3]arene **4** in 13% yield. In contrast, no product was obtained when potassium carbonate was used instead of sodium carbonate. This result seems to indicate that the template effect of the sodium cation might play an important role in the process of the condensation. After purification by silica gel column chromatography, followed by recrystallization, the structure of capped hexahomotrioxacalix[3]arene **4** was confirmed by ^1H and ^{13}C NMR spectroscopy, elemental analysis, and mass spectrometry. In particular, the positive ion FAB mass spectrum of **4** showed a peak at m/z = 887.2, which corresponds to the proposed structure of **4** in association with one sodium cation. Uncapped hexahomotrioxacalix[3]arene (**5**) was also synthesized by means of a condensation reaction between **3** and *p*-methylbenzyl alcohol in the presence of 4-(dimethylamino)pyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC), in 43% yield.

The ^1H NMR spectrum of **4** shows a singlet for the *tert*-butyl protons at δ = 1.04, and singlets for ArOCH_2Ph and the aromatic protons at δ = 4.11 and 6.93, respectively, indicating a C_3-symmetrical structure for **4**. The ^1H NMR spectrum of **4** showed solvent independence both in $CDCl_3$ and in [D_6]DMSO, and temperature independence in the range from −60 °C up to 100 °C, which means that compound **4** must have a rigid conformation. It has already been elucidated that the Δδ values between the bridge methylene protons in calixarene can be correlated to the adjacent aromatic rings.[22,23] Thus, in calix[4]arenes, the ArCH_2Ar methylene protons serve as a measure of the "flattening" of each phenyl unit: $\Delta\delta_H$ is generally 0.9 ppm for a system in the regular cone conformation, while in the "flattened" conformation $\Delta\delta_H$ is significantly less.[1] Provided that the concept established for calix[4]arenes is also applicable to these hexahomotrioxacalix[3]arenes, it should follow that the phenyl groups in capped hexahomotrioxacalix[3]arene **4** are more flattened than those in *cone*-hexahomotrioxacalix[3]arenes.[20,21]

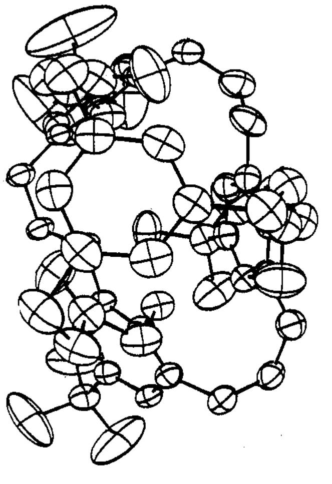
In the ^1H NMR spectrum of the capped hexahomotrioxacalix[3]arene **4**, the AB quadruplets of the bridge methylene protons were consistent with the cone conformation, while the Δδ separation between H_{ax} and H_{eq} (0.12 ppm) was smaller than those in the bridge methylene of uncapped **5** (0.35 ppm). These findings indicate that the capped hexahomotrioxacalix[3]arene **4** has a flattened-cone conformation. The aromatic protons of the cap phenyl ring appeared as a singlet peak at δ = 7.62, and in a lower magnetic range than the pendent phenyl protons in compound **5**; this indicated that the cap phenyl protons of **4** were shielded by carbonyl groups. Although the linked chain between calixarene and the cap phenyl ring had been extended to OCH_2COOCH_2Ar, the protons in the latter methylene $OCH_2COO\mathit{CH_2}$ were still at lower magnetic field (δ = 5.25) than the protons in compound **5** (δ = 5.09). While the first methylene protons $O\mathit{CH_2}COOCH_2$ are orientated on the inside of the concave cavity and subject to the ring-current shielding effect of the aromatic rings, they appeared at a higher magnetic field (Δδ = 0.33) than those in the uncapped hexahomotrioxacalix[3]arene **5**. The CPK molecular model showed that the carbonyl groups of compound **4** were orientated outside the cavity formed by three benzene rings, so as to reduce the electrostatic repulsion.

Although the capped compound **4** has a flattened-cone conformation with little difference in solution between chemical shift values of H_{ax} and H_{eq} protons, and the conformation was not altered either by solvent or by temperature, the X-ray showed in its geometric structure a cone conformation, with slight distortion from C_3 symmetry. The concave cavity of compound **4** is hydrophobic and can easily be solvated in organic phases. In the process of crystallization, solvent was expelled from the cavity and the calix benzene ring was fixed vertically in the solid state. Thus, no solvent inclusion phenomena were observed in the single-crystal X-ray analysis.

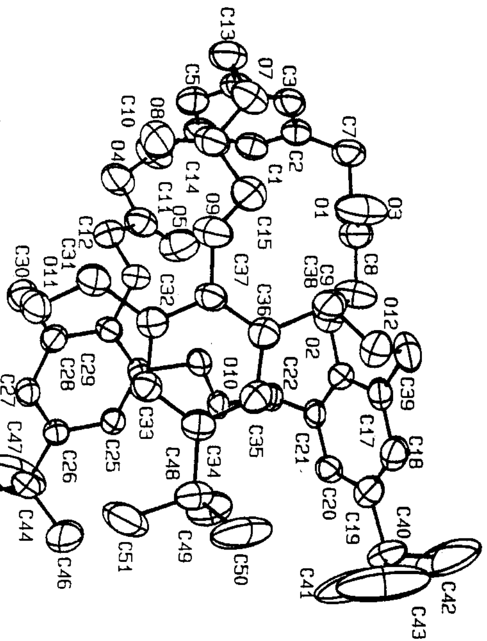
A single, colorless crystal of compound **4** suitable for X-ray crystallography was obtained by recrystallization from CH_2Cl_2. It crystallizes in the triclinic space group *P*1(bar) (No. 2). The perspective view of the crystal, with the atom numbering system, is shown in Figure 1. Three calix benzene rings tilt towards the cavity to some extent and maintain a normal cone conformation; the dihedral angles of the $C_{16}-C_{17}-C_{18}-C_{19}-C_{20}-C_{21}$, $C_{24}-C_{25}-C_{26}-C_{27}-C_{28}-C_{29}$, and $C_{32}-C_{33}-C_{34}-C_{35}-C_{36}-C_{37}$ planes with the plane defined by the oxo-methylene bridge have the values 66.3°, 54.8°, and 64.0°, respectively. However, the dihedral angle between the capped benzene ring and the plane defined by the bridge chain is 0.99°, showing that these planes are almost parallel with each other. The carbonyl oxygens (O_3, O_5, O_8) are orientated outside, against the concave cavity. Three aliphatic chains ($C_7-O_1-C_8-C_9-O_2$, $C_{10}-O_4-C_{11}-C_{12}-O_6$, $C_{13}-O_7-C_{14}-C_{15}-O_9$) are oriented randomly between the capped phenyl and calix benzene, they do not adhere to the C_{3v}-symmetrical conformation. For example, the distances between the carbonyl carbon atoms ($C_8-C_{11}-C_{14}-C_8$) are 5.323 Å, 4.682 Å, and 5.278 Å, respectively.

In order to investigate the ionophoric affinities of compound **4** for cations, the extractability of the capped compound **4** was determined by solvent extraction from aqueous phase to organic phase (methylene dichloride). In comparison, the extractability of the reference compound **5** was also estimated under similar conditions. The results are summarized in Figure 2.

It is known that calixarenes can be modified to be neutral ligands by introduction of ester or amide groups, and that affinity and selectivity depend on the calix[*n*]arene ring size and the substituents.[3,24,25] In solution, thanks to the C_3-symmetrical conformation with the ether linkage, compounds **4** and **5** exhibit high affinities for *n*-butylammonium ion and show excellent extractabilities. On the other hand, compound **4** has higher affinities for metal cations than compound **5** does, which might be attributable to the slower decomplexation rate of metal cations from capped compound **4**-metal complexes than from uncapped compound **5**-metal complexes. Although tris[(ethoxycarbonyl)methoxy]hexahomotrioxacalix[3]arene with the cone conformation has a higher selectivity for the sodium cation than for the potassium cation,[20] the alkali metal cation selectivity of compound **4** is high towards potassium cation, while almost zero towards lithium cation. The carbonyl groups in compound **4** are orientated outwards from the cavity, to reduce electrostatic repulsion. After binding with metal cations, however, they become turned inward to interact with the cations, together with phenolic oxygens. The three aliphatic chains are situated between the phenolic oxygens and capped phenyl ring, which inhibits them from approaching closely or separating too much. Therefore, the ionophoricity of the cavity composed of the three OCH_2COOCH_2 groups is suitable for the size of the potassium cation, because of the fixed terminal moieties, while a little large for sodium cation and too large for lithium cation. Because of the capped lower rim, cations are encapsulated into the cavity from the upper rim and the calix benzene rings act as a tunnel in these complexes.



top view



side view

Figure 1. X-ray structure of capped compound **4**: the thermal ellipsoids are drawn at 50% probability; hydrogen atoms are omitted for clarity

The association constants of receptors **4** and **5** for the picrates of these cations were determined in CH_2Cl_2/THF (99:1, v/v) according to the Benesi–Hildebrand equation,[26] which shows a very well-defined linear shape for a 1:1 interaction. The results are listed in Table 1. After addition of compound **4** or **5** to the solution of picrate, the absorption maximum peak was shifted from 358 nm to 378 nm, indicating the formation of a complex. In comparison with uncapped compound **5**, the capped compound **4**

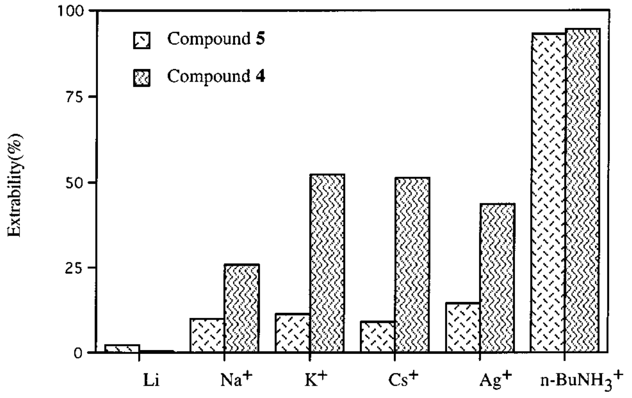


Figure 2. Liquid-liquid extractability spectra of capped compound **4** and uncapped compound **5** with the metal cations and *n*-butyl ammonium ion ([Host] = $1.25 \cdot 10^{-4}$ mol dm^{-3} in CH_2Cl_2, [Guest] = $1.25 \cdot 10^{-4}$ mol dm^{-3} in water at 25 °C)

was more highly preorganized for metal cations and primary ammonium ion, in which **4** binds the large nBuNH$_3{}^+$ and Cs$^+$ more strongly than uncapped **5** ($\Delta\Delta G° \approx -3$ kJ M^{-1}). This finding, together with the previously mentioned slower decomplexation rate of metal cations from capped compound **4**-metal complexes than from uncapped compound **5**-metal complexes, indicates that the larger sized nBuNH$_3{}^+$ and Cs$^+$ find it easier to enter the cavity of **4** than that of **5**. However, in comparison with the crown-type tricapped calix[6]arene,[17b] the selectivity of compound **4** was less high, which may be attributed to the effect of carbonyl groups. The binding site for Na$^+$ and K$^+$ in ester derivatives of homooxacalix[3]arene involved the phenol oxygens and carbonyl groups, which increase the affinity of **4** towards Na$^+$ and K$^+$. Relative to the crown-type tricapped calix[6]arene, which exhibited high Cs$^+$ affinity due to cation-π interactions, the selectivity towards cesium ion was reduced accordingly.[17b]

Table 1. Association constants ($K_{ass} \times 10^{-4}$, M^{-1}) and binding free energies ($\Delta G°$, kJ·M^{-1}) for host **4** and **5** with cations; measured in CH_2Cl_2/THF (99:1, v/v) at 27 °C; [MPic] = $1.0 \cdot 10^{-5}$ M^{-1}, [**4**] ([**5**]) = 0 to $5 \cdot 10^{-4}$ M^{-1}

	4		**5**		$\Delta\Delta G°$
	K_{ass}	$\Delta G°$	K_{ass}	$\Delta G°$	[$\Delta G°$(**4**) - $\Delta G°$(**5**)]
Na$^+$	5.27	-26.47	2.48	-24.64	-1.83
K$^+$	6.71	-27.06	2.28	-24.43	-2.63
Cs$^+$	5.76	-26.69	1.61	-23.59	-3.10
Ag$^+$	5.03	-26.36	2.77	-24.91	-1.45
nBuNH$_3{}^+$	7.64	-27.38	2.21	-24.36	-3.02

As a concave ionophore — that is, a cavity-shaped molecule with an inwardly-directed functionality embedded in the concave position — compound **4** was enabled to bind with metal cations and primary ammonium ions. The complexation mode was elucidated quantitatively by nuclear magnetic resonance titration. Interestingly, depending on the ionic size and properties, the complex behavior patterns were different in the complexation of compound **4** with these cations.

The C_3-symmetrical conformation of compound **4** make it well suited to bind with primary ammonium ions.[20,21] After titration with an equivalent of *n*-butylammonium ion in deuterated chloroform, peaks signals both of the complex of compound **4** and of the free host appeared separately. On increasing the amount of ammonium ion to excess, the signals due to compound **4** decreased and finally only the complex signals were observed. In the complex, in comparison to the free host, the aromatic protons of the capped phenyl ring were shifted to higher magnetic field while the protons of the calix benzene rings were shifted to lower field, which implies that the carbonyl groups were turned inward from the cavity and no longer affected the protons of the capped phenyl ring. Furthermore, the axial protons in the bridge methylene, affected by the calixarene conformation, were shifted to lower magnetic field while the equatorial protons shifted to higher field. The methylene protons ArOCH_2 were also shifted to lower field. The ammonium ion became encapsulated in the cavity formed by the benzene rings, and changed the conformation of compound **4**. The NH$_3$ protons interacted with three CO groups and phenolic oxygens, while the *n*-butyl chain remains positioned through the cavity of calix benzene rings. On the other hand, the protons of the ammonium ion encapsulated in the concave cavity were shifted to higher field (δ = 5.66) relative to their free counterparts (δ = 8.29) because of the shielding resonance of the calix benzene rings.

When uncapped compound **5** was treated with *n*-butylammonium ion, the changed chemical shifts were also observed, confirming the formation of the complex between **5** and ammonium ion. In contrast, no changes were observed for the introduced *p*-methylbenzyl protons, which implies that the *n*-butyl ammonium ion had entered into the cavity from the upper rim. The NH$_3$ protons were engaged in interaction with the CO groups and phenolic oxygens and the protons of the *n*-butyl chain was shifted to higher magnetic field, similarly to the case of compound **4**. Because compound **5** was uncapped, the $CH_3CH_2$$CH_2$ and NH$_3$ protons were not affected by shielding resonance from the top benzene ring, which was shifted no more to upper field (δ = 5.90) than that in the cavity of compound **4**.

Since the structural motif of nBuNH$_3{}^+$ is present in biologically important amines, homooxacalix[3]arenes and their derivatives should be able to bind with primary ammonium ions possessing potential functions not only in chemistry but also in biological systems. The ammonium ions complexed with compound **4** by entering the cavity formed by the calix benzene rings from the upper rim. Thus, if the alkylated substituent remained in the cavity and was shielded by the resonance of calix benzene rings, the protons on alkylated ammonium ion should correspondingly be shifted to higher field compared to their free counterparts. Therefore, the alkylammonium ion should be useful as a probe to estimate the cavity depth represented by the calix benzene cavity in homooxacalix[3]arene. Three kinds of alkylated substituents were checked by ^{1}H NMR titration; the results are listed in Table 2.

From Table 2, we can see that the NH proton on alkylammonium ions was shifted to higher magnetic field when it was encapsulated in the calix cavity. The maximum upper

Table 2. Values of Δδ for alkylammonium ions on complexation with host **4**

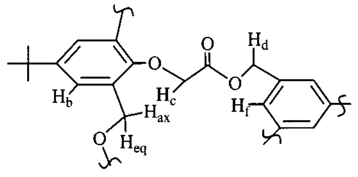
		CH$_3$[a]	CH$_3$*CH*$_2$[a]	CH$_3$CH$_2$*CH*$_2$[a]	*CH*$_2$N[a]	N*H*[a]
*n*BuNH$_3^+$	free	0.90	1.39	1.72	3.11	8.29
	complex	0.21	0.20	−0.55	0.20	5.66
	Δδ[b]	−0.69	−1.19	−2.27	−2.91	−2.63
EtNH$_3^+$	free	1.32			3.04	8.24
	complex	−0.68			0.11	–[c]
	Δδ[b]	−2.00			−2.93	–[c]
MeNH$_3^+$	free	2.61				–[c]
	complex	−0.12				–[c]
	Δδ[b]	−2.73				–[c]

[a] A minus signal (−) denotes a shift to higher field. – [b] Δδ values refer to the difference in chemical shift between the free alkylammonium picrates and the complex with host **4** in $CDCl_3/CD_3OD$ (5:1, v/v) determined at 270 MHz, 27 °C. – [c] Because of the fast exchange rate of NH protons in solution, their peaks did not appear in the NMR spectra.

field shift was observed with the protons in the $CH_2CH_2NH_3^+$ moiety and decreased with alkyl length. For example, in the case of the *n*-butylammonium ion, the protons in the $CH_2CH_2NH_3^+$ moiety were shifted to higher field by more than 2.0 ppm, while the protons in the CH_3CH_2 remainder were shifted to higher field only by 0.69 ppm and 1.19 ppm, respectively. The calix cavity of homooxacalix[3]arene is able to encapsulate *n*-butylammonium ion completely; the terminal $CH_2CH_2NH_3^+$ was located deep in the cavity, while CH_3CH_2 was located on the edge of the cavity. Among the different alkylammonium ions, very close proton chemical shift values were observed for encapsulated NH, as well as its two closest linked methylene units. This finding indicates that the $CH_2CH_2NH_3^+$ (or $CH_3CH_2NH_3^+$ and $CH_3NH_3^+$) elements were located in similar positions in the calix benzene ring cavity, and thus under similar resonance shielding conditions. It is reasonable to assume that the *n*-butylammonium chain is already long enough to protrude from the calixarene cavity: similar results have also been reported in the case of partial cone calix[5]arene and the complex of calix[5]arene with ammonium ions.[27]

Similar phenomena to those seen with *n*BuNH$_3^+$ were obtained in the titration of compound **4** with metal cations. In contrast, when compound **5** was titrated with metal cations, the peak signals become broad and too complicate to explain. In the case of compound **4** and metal cations, a kinetically stable (on the NMR timescale) complex was detected, as inferred from two separated sets of signals for both the free host **4** and the complex when equivalent quantities of compound **4** and metal cations were shaken for 24 h. The protons of the calix benzene rings were shifted to lower field, protons in the cap phenyl ring to upper field, which implies the metal cation was complexed with compound **4**. With increasing amounts of metal cations, the complex formed exclusively, except with cesium cation, in which the equilibrium between complex and free host was still present even after shaking for over a week. As already known, Δδ values between H_{ax} and H_{eq} in the bridge methylene moiety are related to the conformation of calixarene and this has been demonstrated to be applicable to hexahomotrioxaclix[3]arene. Compound **4** has a nearly planar form with Δδ of 0.12 ppm. After complexation with guest ions, the calix benzene rings was shifted perpendicularly so that the H_{eq} was positioned in the plane of the aromatic rings while H_{ax} was above the aromatic rings, making them shift to higher field and lower field, respectively. Thus, observed Δδ values between H_{ax} and H_{eq} were from 0.52 to 0.85 ppm (Table 3).

Table 3. Induced ^1H NMR chemical shifts (Δδ : in ppm) of capped compound **4** complexed with metal cations and *n*-butylammonium ion; [**4**] = $5 \cdot 10^{-3}$ mol dm^{-3} in $CDCl_3$ at 27°C; the solid guest (MI, *n*BuNH$_3$Cl 10 equiv.) was added using TMS as internal standard; minus (−) denotes the upfield chemical shift, others denotes downfield chemical shift; $\Delta\delta = \delta_{complex} - \delta_{free}$; $\Delta\delta(H_{ax} - H_{equiv.})$ was 0.12 ppm in free host **4**



	*t*Bu	H$_b$	H$_f$	H$_c$	H$_d$	ArC*H*$_2$O H$_{eq}$	 H$_{ax}$	 $\Delta\delta(H_{ax}-H_{eq})$[d]
Na$^+$	0.17	0.25	-0.04	0.49	0.12	-0.40	0.00	0.52
K$^+$	0.19	0.31	-0.09	0.59	0.00	-0.37	0.26	0.75
Cs$^+$	0.22	0.33	-0.09	0.64	-0.06	-0.28	0.40	0.80
Ag$^+$	0.19	0.31	-0.10	0.49	0.06	-0.37	0.11	0.60
*n*BuNH$_3^+$	0.19	0.34	-0.11	0.64	-0.04	-0.28	0.45	0.85

In addition to this observation, the signals for the aromatic protons and *tert*-butyl protons were slightly shifted downfield and the phenoxymethylene protons ArO*CH*$_2$-COOCH$_2$ also showed different chemical shifts. Thus, the methylene proton peak resonated at lower field at around δ = 4.60−4.75 (Δδ from 0.49 to 0.64 ppm) relative to that in the metal-free spectrum (δ = 4.11). These observations suggest that host cations should be bound to the ionophoric cavity — composed of three phenolic oxygens and three carbonyl group oxygens — due to electrostatic metal-oxygen interactions. The conformational changes of the carbonyl groups of the ArOCH$_2$*CO*OCH$_2$ moiety from their original outward orientation to the inside orientation, towards the calixarene cavity, might occur in the process of metal cation complexation. However, the peak pattern of protons in compound **4** was unchanged after complexation. This finding strongly suggests that the original C_3 symmetry might remain after complete metal cation complexation.

Experimental Section

All melting and boiling points are uncorrected. − IR (KBr or NaCl): Nippon Denshi JIR-AQ2OM. − ^1H NMR: Nippon Denshi JEOL GX-270 in $CDCl_3$, TMS as reference. − UV: Hitachi 220A spectrophotometer. − MS: Nippon Denshi JEOL-01 SG-2. − Elemental analysis: Yanaco MT-5.

Materials: *cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(*N,N*-diethylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**2**) was prepared according to a literature procedure.[21]

Preparation of *cone*-Hexahomotrioxacalix[3]arenetriacetic Acid (*cone*-3): Aqueous NaOH solution (1 N, 30 mL) was added to a mixture of *cone*-**2** (1.0 g, 1.14 mmol) in dioxane (30 mL). After the mixture had been refluxed for three days, it was condensed under reduced pressure, then acidified to pH 1−2. The dispersion was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with water (2 × 20 mL) and saturated brine (20 mL), dried (Na_2SO_4), and condensed under reduced pressure. The residue was washed with a small amount of diethyl ether to give the crude *cone*-**3** as a colorless solid. Recrystallization from methanol gave 440 mg (51.2%) of *cone*-**3**: Colorless powder, m.p. 227−229 °C. − IR (KBr): $\tilde{\nu}$ = 3400, 2975, 2915, 2867, 1758, 1483, 1456, 1363, 1234, 1199, 1094, 1058 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.14 (s, 27 H, *t*Bu), 4.44 (d, *J* = 12.7 Hz, 6 H, Ar*CH₂*O), 4.92 (d, *J* = 12.7 Hz, 6 H, Ar*CH₂*O), 4.46 (s, 6 H, ArO*CH₂*), 6.95 (s, 6 H, Ar-H). − ^{13}C NMR ($CDCl_3$/DMSO, 1:1): δ = 28.85, 31.43, 66.85, 67.90, 123.45, 128.43, 142.71, 150.35, 168.52. − MS (75 eV): *m*/*z* = 750 [M^+]. − $C_{42}H_{54}O_{12}$ (750.9): calcd. C 67.18, H 7.25; found C 67.36, H 7.40.

Preparation of Capped Hexahomotrioxacalix[3]arene (4): 1,3,5-Tris(bromomethyl)benzene (96 mg, 0.798 mmol) and sodium carbonate (852 mg, 8.04 mmol) were added to a solution of the cone conformation of 7,15,23-tri-*tert*-butyl-25,26,27-tris[(hydroxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene, *cone*-**3** (200 mg, 0.266 mmol) in DMF (140 mL). The mixture was heated at 70 °C for 40 h; then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with 10% aqueous sodium bicarbonate and water. The extract was dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (Wako C-300, 100 g) with hexane/ethyl acetate (1:1) as eluent to give crude **4** as a colorless solid. Recrystallization from CH_2Cl_2 gave 30 mg (13%) of compound **4**: Colorless prisms, m.p. 202−204 °C. − IR (KBr): $\tilde{\nu}$ = 2962, 2923, 2872, 1736 (C=O), 1484, 1453, 1385, 1363, 1232, 1184, 1126, 1096, 1064, 966, 894 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.04 (s, 27 H, *t*Bu), 4.11 (s, 6 H, ArO*CH₂*), 4.56 (d, *J* = 13.2 Hz, 6 H, Ar*CH₂*O), 4.68 (d, *J* = 13.2 Hz, 6 H, Ar*CH₂*O), 5.25 (s, 6 H, Ph*CH₂*), 6.93 (s, 6 H, Ar-H), 7.62 (s, 3 H, Ph-H). − ^{13}C NMR ($CDCl_3$): δ = 31.45, 34.27, 66.84, 68.57, 71.74, 125.64, 130.70, 132.71, 136.82, 146.62, 152.02, 168.12. − MS (75 eV) (FAB^+): *m*/*z* (%) = 887 (73.6) [M + Na]. − $C_{51}H_{60}O_{12}$ (865.0): calcd. C 70.81, H 6.99; found C 70.36, H 7.05.

Preparation of *cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(4-methylbenzylcarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (5): *p*-Methylbenzyl alcohol (98 mg, 0.8 mmol) and DMAP (50 mg, 0.399 mmol) were added to a solution of *cone*-**3** (100 mg, 0.133 mmol) in CH_2Cl_2 (12 mL). The mixture was then stirred at 0 °C while a solution of DCC (165 mg) in CH_2Cl_2 (5 mL) was added dropwise. The solution was stirred for one hour at 0 °C and for an additional 15 h at room temperature. After completion, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and filtered. The filtrate was washed sequentially with 10% citric acid, water, 5% sodium bicarbonate, water, and brine. The extract was dried (Na_2SO_4), and concentrated. Excess of *p*-methylbenzyl alcohol was removed by glass tube oven (GTO) and the residue was then chromatographed through silica gel (Wako C-300, 100 g), with $CHCl_3$/ethyl acetate (19:1) as eluent, to give crude **5** as a colorless solid. Recrystallization from methanol gave 60 mg (43%) of compound **5**: Colorless prisms, m.p. 164.5−166 °C. − IR (KBr): $\tilde{\nu}$ = 2960, 2928, 2864, 1757 (C=O), 1482, 1458, 1363, 1261, 1191, 1095, 1069, 806 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.06 (s, 27 H, *t*Bu), 2.31 (s, 9 H, Ph−CH_3), 4.47 (d, 6 H, *J* = 12.7 Hz, Ar*CH₂*O), 4.82 (d, 6 H, *J* = 12.7 Hz, Ar*CH₂*O), 4.44 (s, 6 H, ArO*CH₂*), 5.09 (s, 6 H, Ph*CH₂*), 6.92 (s, 6 H, Ar-H), 7.12 (d, 6 H, *J* =7.81 Hz, Ph-Hb), 7.23 (d, 6 H, *J* =7.81 Hz, Ph-Ha). − ^{13}C NMR ($CDCl_3$): δ = 20.70, 30.47, 33.69, 66.01, 69.71, 70.33, 125.98, 128.20, 128.75, 130.43, 132.06, 138.0, 145.78, 152.45, 169.08. − MS (75 eV): *m*/*z* = 1062 [M^+]. − $C_{66}H_{78}O_{12}$ (1063.3): calcd. C 74.55, H 7.39; found C 74.53, H 7.36.

Picrate Extraction Measurements: The alkali metal picrates ($1.25 \cdot 10^{-4}$ M) were prepared in situ by dissolving the alkali metal hydroxide in $1.25 \cdot 10^{-4}$ M picric acid; triply distilled water was used for all aqueous solutions. Similarly, silver picrate was prepared in situ by dissolving silver nitrate in $1.25 \cdot 10^{-4}$ M picric acid. Two-phase solvent extraction was carried out between water (5 mL, [alkali picrate] = $1.25 \cdot 10^{-4}$ M) and CH_2Cl_2 (5 mL, [ionophore] = $1.25 \cdot 10^{-4}$ M). The two-phase mixture was shaken in a stoppered flask for 24 h at 25 °C. We confirmed that this period is sufficient to attain the distribution equilibrium. This was repeated three times, and the solutions were left standing until phase separation was complete. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen.[28]

^1H NMR Complexation Experiments: To a $CDCl_3$ solution ($3 \cdot 10^{-3}$ M) of **4** in an NMR tube was added 10 equivalents of guest molecule. The spectrum was recorded after addition and the temperature of the NMR probe kept constant at 27 °C.

Capped Hexahomotrioxacalix[3]arene 4-*n*BuNH₃Cl Complex: ^1H NMR ($CDCl_3$): δ = 1.23 (s, 27 H, *t*Bu), 4.28 (d, *J* = 8.8 Hz, 6 H, Ar*CH₂*O), 4.75 (s, 6 H, ArO*CH₂*), 5.13 (d, *J* = 8.8 Hz, 6 H, Ar*CH₂*O), 5.21 (s, 6 H, Ph*CH₂*), 7.27 (s, 6 H, Ar-H), 7.51 (s, 3 H, Ph-H).

Capped Hexahomotrioxacalix[3]arene 4-CsI Complex: ^1H NMR ($CDCl_3$): δ = 1.26 (s, 27 H, *t*Bu), 4.28 (d, *J* = 8.8 Hz, 6 H, Ar*CH₂*O), 4.75 (s, 6 H, ArO*CH₂*), 5.08 (d, *J* = 8.8 Hz, 6 H, Ar*CH₂*O), 5.19 (s, 6 H, Ph*CH₂*), 7.26 (s, 6 H, Ar-H), 7.53 (s, 3 H, Ph-H).

Capped Hexahomotrioxacalix[3]arene 4-$AgSO_3CF_3$ Complex: ^1H NMR ($CDCl_3$): δ = 1.23 (s, 27 H, *t*Bu), 4.19 (d, *J* = 8.8 Hz, 6 H, Ar*CH₂*O), 4.60 (s, 6 H, ArO*CH₂*), 4.79 (d, *J* = 8.8 Hz, 6 H, Ar*CH₂*O), 5.31 (s, 6 H, Ph*CH₂*), 7.24 (s, 6 H, Ar-H), 7.52 (s, 3 H, Ph-H).

Crystal Data and Refinement Details for 4: The unit cell constants were derived from least-squares analysis of the settings, on an

Enraf−Nonius CAD4 FR 586 diffractometer, for 25 reflections in the range 29.9° $< \theta <$ 31.8°. The intensities of all independent reflections with 4° $< 2\theta <$ 144° were measured with $\omega-2\theta$ scan (ω scan width = $0.8 + 0.14 \tan \theta$); Ni-filtered Cu-K_α radiation (λ = 1.54184 Å) was used. − The structure was solved by direct methods (SIR88[29]) and difference-Fourier syntheses, and refined using the full-matrix, least-squares method. All calculations were performed on a Micro VAX 3100 computer using a MolEN program package.[30]

Crystallographic Data for 4: Recrystallized from CH_2Cl_2. Crystal data: $C_{51}H_{60}O_{12}$; M = 864.99, crystal size: 0.18 × 0.21 × 0.28 mm, triclinic $P\bar{1}$, a = 1420.15 (14), b = 1523.28 (12), c = 1152.39 (9) pm; α = 102.1354 (63)°, β = 109.8100 (74)°, γ = 84.2657 (71)°; $V = 2291.89\ (36) \times 10^{-30}$ m^3; Z = 2; D_c = 1.253 Mgm^{-3}, R = 0.0794, R_w = 0.114 for 8523 unique reflections.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-142599. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[1] [1a] C. D. Gutsche, *Prog. Macrocyclic Chem.* **1987**, *3*, 93−165. − [1b] B. Xu, T. M. Svager, *J. Am. Chem. Soc.* **1993**, *115*, 1159−1160. − [1c] S. G. Bott, A. W. Coleman, J. L. Atwood, *J. Chem. Soc., Chem. Commun.* **1986**, 610−611.

[2] A. Anduni, A. Pochini, S. Reverber, R. Ungaro, G. D. Andretti, F. Ugozzoli, *Tetrahedron* **1986**, *42*, 2089−2100.

[3] S. K. Chang, I. Cho, *J. Chem. Soc., Perkin Trans. 1* **1986**, 211−214.

[4] [4a] P. Zerr, M. Mussrabi, J. Vicens, *Tetrahedron Lett.* **1991**, *32*, 1879−1880. − [4b] C. D. Gutsche, L. J. Bauer, *J. Am. Chem. Soc.* **1985**, *107*, 6052−6059.

[5] [5a] S. Shinkai, *Tetrahedron* **1993**, *49*, 8933−8963. − [5b] J. M. Lehn, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89−112. − [5c] D. J. Cram, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009−1020.

[6] V. Bocchi, D. Foina, A. Pochini, R. Ungaro, *Tetrahedron* **1982**, *38*, 373−378.

[7] G. Ferguson, B. Kaitner, M. A. Mckervey, E. M.Seward, *J. Chem. Soc., Chem. Commun.* **1987**, 584−585.

[8] F. Arnaud-Neu, M.-J. Schwing-Weill, K. Ziat, S. Cremin., S. J. Harris, M. A. Mckervey, *New J. Chem.* **1991**, *15*, 33−37.

[9] [9a] G. D. Andreetti, G. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, *J. Inclusion Phenom.* **1987**, *5*, 123−126. − [9b] S. K. Chang, I. Cho, *Chem. Lett.* **1987**, 947−948.

[10] [10a] E. Ghidini, F. Ugozzoli, R. Ungaro, El-Fadl S. Harkema, A. Abu, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1990**, *112*, 6979−6985. − [10b] A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, G. D. Andreetti, G. Calestani, F. Ugozzoli, *J. Inclusion Phenom.* **1988**, *6*, 119−134.

[11] [11a] V. Böhmer, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713−715. − [11b] C. D. Gutsche, *Calixarene*, Royal Society of Chemistry, Cambridge, **1989**.

[12] T. Yamato, Y. Saruwatari, S. Nagayama, K. Maeda, M. Tashiro, *J. Chem. Soc., Chem. Commun.* **1992**, 861−862.

[13] C. D. Gutsche, I. Alam, *Tetrahedron* **1988**, *44*, 4689−4694.

[14] S. Shinkai, K. Araki, O. Manabe, *J. Chem. Soc., Chem. Commun.* **1988**, 187−189.

[15] T. Saiki, K. Goto, N. Tokitoh, R. Okazaki, *J. Org. Chem.* **1996**, *61*, 2924−2925.

[16] K. C. Nam, Y. J. Choi, D. S. Kim, J. M. Kim, J. C. Chun, *J. Org. Chem.* **1997**, *62*, 6441−6443.

[17] [17a]K. Araki, K. Akao, H. Otsuka, K. Nakashima, F. Inokuchi, S. Shinkai, *Chem. Lett.* **1994**, 1251−1254. − [17b] H. Otsuka, Y. Suzuki, A. Ikeda, K. Araki, S. Shinkai, *Tetrahedron* **1998**, *54*, 423−446.

[18] M. Takeshita, S. Nishio, S. Shinkai, *J. Org. Chem.* **1994**, *59*, 4032−4034.

[19] M. Takeshita, F. Inokuchi, S. Shinkai, *Tetrahedron Lett.* **1995**, *36*, 3341−3344.

[20] K. Araki, N. Hashimoto, H. Otsuka, S. Shinkai, *J. Org. Chem.* **1993**, *58*, 5958−5963.

[21] H. Matsumoto, S. Nishio, M. Takeshita, S. Shinkai, *Tetrahedron* **1995**, *51*, 4647−4654.

[22] S. Kanamathareddy, C. D. Gutsche, *J. Org. Chem.* **1992**, *57*, 3160−3166.

[23] F. Cunsolo, M. Piattelli, P. Neri, *J. Chem. Soc., Chem. Commun.* **1994**, 1917−1918.

[24] C. D. Andreetti, G. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, *J. Inclusion Phenom.* **1987**, *5*, 123.

[25] M. A. Mckervey, E. M. Seward, G. Ferguson, B. Ruhl, S. Harris, *J. Chem. Soc., Chem. Commun.* **1985**, 388−390.

[26] H. A. Benesi, J. H. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2073−2707.

[27] [27a] R. Cacciapaglia, L. Mandolini, R. Arnecke, V. Böhmer, W. Vogt, *J. Chem. Soc., Perkin Trans. 2* **1998**, 419−423. − [27b] F. Arnaud-Neu, S. Fuangswasdi, A. Notti, S. Pappalardo, M. F. Parisi, *Angew. Chem. Int. Ed.* **1998**, *37*, 112−114.

[28] C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 2495−2496.

[29] M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, D. Viterbo, *J. Appl. Crystallogr.* **1989**, *22*, 389.

[30] *MolEN, An Interactive Structure Solution Procedure*, Enraf−Nonius, Delft, The Netherlands, **1990**.

Receiced April 10, 2000
[O00185]