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Synthesis and Ion Selectivity of Conformers Derived from Hexahomotrioxacalix[3]arene

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The reaction of 7,15,23-tri-*tert*-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene ($1\mathrm{H}_3$) with ethyl bromoacetate yielded the cone conformer (cone-$1\mathrm{Es}_3$) as a minor product and the partial-cone conformer (partial-cone-$1\mathrm{Es}_3$) as a major product. Interconversion between these two conformers did not take place, indicating that the OCH_2CO_2Et group is bulky enough to inhibit the oxygen-through-the-annulus rotation. The conformer distribution was affected by the metal cation present in the base, suggesting the importance of the metal template effect. When NaH was used in THF, the partial-cone/cone ratio was 1.6–3.8; when Cs_2CO_3 was used in acetone, partial-cone-$1\mathrm{Es}_3$ was produced quantitatively. Two-phase solvent extraction established that cone-$1\mathrm{Es}_3$ shows Na^+ selectivity, whereas partial-cone-$1\mathrm{Es}_3$ shows K^+ selectivity. Cone-$1\mathrm{Es}_3$ showed high affinity toward RNH_3^+ cations, indicating that the structure of cone-$1\mathrm{Es}_3$ with C_3 symmetry is very suitable for the binding of RNH_3^+ cations with C_3 symmetry. ^{1}H NMR studies established that the phenyl units in cone-$1\mathrm{Es}_3$ are more or less flattened but stand up when a cationic guest is included. This paper thus demonstrates that $1\mathrm{H}_3$ is useful as a basic skeleton for the design of new ionophores, particularly those suitable for the recognition of guests with C_3 symmetry.

Introduction

In 1983, Dhawan and Gutsche[1] found that 2,6-bis(hydroxymethyl)-4-*tert*-butylphenol in refluxing xylene affords a cyclic ether, 7,15,23-tri-*tert*-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene ($1\mathrm{H}_3$) in low yield along with large amounts of linear ethers. In spite of the low yield, pure $1\mathrm{H}_3$ was successfully isolated by recrystallization from chloroform–methanol.[1] In comparison to the structural characteristics of the calixarene family,[2–8] this compound attracted our interest for the following reasons: (i) compound $1\mathrm{H}_3$ has a cavity composed of an 18-membered ring, which is comparable with that of calix[4]arene composed of a 16-membered ring, (ii) the rate of ring inversion for $1\mathrm{H}_3$ derivatives should be much faster than that for calix[4]arenes because of the flexibility of the ethereal linkages, (iii) there are only two possible conformations, cone and partial-cone, in contrast to four possible conformations in calix[4]arenes, so that the conformational isomerism is much more simplified, (iv) ethereal ring oxygens may act cooperatively with phenolic oxygens upon the binding of metal ions, and (v) the basic structure has C_3 symmetry which is expected to be particularly useful for the design of receptors for RNH_3^+.

Meanwhile, several groups have demonstrated that calix[*n*]aryl acetate derivatives serve as neutral ionophores, and in particular, calix[4]aryl acetate derivatives show excellent Na^+ selectivity.[9–15] The high Na^+ selectivity was accounted for by the hole-size selectivity and the rigidity of the ionophoric cavity. It was also shown that the metal selectivity of ionophoric calix[*n*]aryl acetates can be changed not only by the change in the ring size but also by the conformational change.[15] It thus occurred to us that introduction of ionophoric groups into $1\mathrm{H}_3$ would enable us to design a new class of ionophoric cavities with a different size and shape and provide novel calix[3]arene-based ionophores for metal and ammonium cations. We report here the selective synthesis of conformational isomers (cone and partial-cone) from the reaction of $1\mathrm{H}_3$ and ethyl bromoacetate, the metal selectivity of each conformer, and the binding-mode for metal and ammonium cations.

Results and Discussion

Metal Template Effects on the Selective Synthesis of Conformational Isomers. Previously, we found that in *O*-alkylation of calix[4]arenes the conformer distribution is profoundly affected by the metal template effects.[16–18] When the base used for *O*-alkylation contains the template metal (*e.g.*, Na^+), the cone results predominantly. On the other hand, when the base contains the

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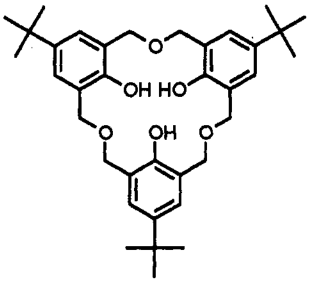
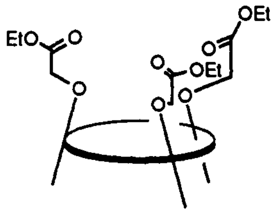
Table I. Conformer Distribution for the Reaction of $1H_3$ with Ethyl Bromoacetate

base (equiv for $1H_3$)	equiv of $BrCH_2CO_2Et$ for $1H_3$	solvent	temp (°C)	time (h)	yield (%) of $1Es_3$[a]	
					cone	partial-cone
NaH (2.2)	2.2	THF	67	3	9	14
NaH (3.3)	3.3	THF	67	3	20	52
NaH (9.0)	9.0	THF	67	3	20	75
NaH (3.6)	4.5	DMF	0	2	8	89
NaH (3.6)	4.5	DMF	70	3	6	90
Na_2CO_3 (9.0)	9.0	acetone	56	6	2	4
K_2CO_3 (9.0)	9.0	acetone	56	6	0	100
Cs_2CO_3 (9.0)	9.0	acetone	56	6	0	100
t-BuOK (3.3)	3.3	THF	67	2	22	78

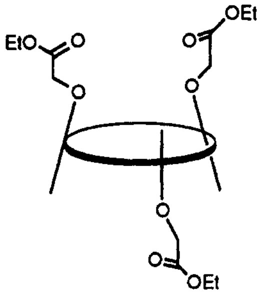
[a] The sole compound detected in the reaction mixture in addition to cone-$1Es_3$ and partial-cone-$1Es_3$ is $1H_3$, and the mass balance ($1H_3$ + cone-$1Es_3$ + partial-cone-$1Es_3$) is always kept to 100%.



$1H_3$

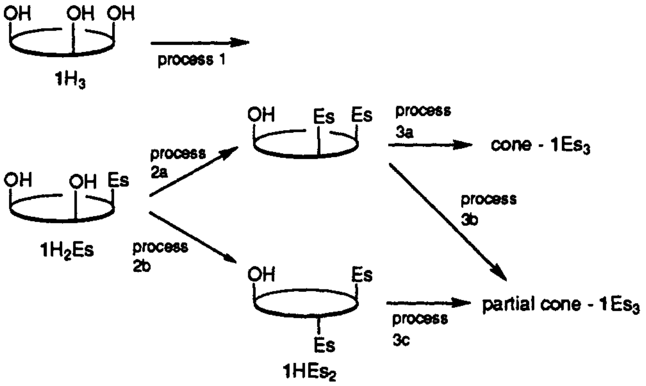


cone - $1Es_3$

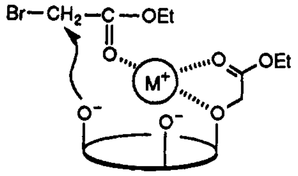


partial - cone - $1Es_3$

Scheme I



Scheme II



nontemplate metal (*e.g.*, Cs^+), the conformers with the inverted phenyl units (*e.g.*, partial-cone and 1,3-alternate) result predominantly. We first tested if this concept can also be applied to the reaction of ethyl bromoacetate with $1H_3$.

The reaction mixture obtained from the reaction in the presence of NaH was subjected to the HPLC analysis. We could detect only three peaks, one of which was assigned to unreacted $1H_3$. The remaining two compounds were separated by preparative TLC. ^1H NMR spectroscopy established that they are triester derivatives (*i.e.*, $1Es_3$); the major product gave a spectrum showing two kinds of inequivalent phenyl groups in a 1:2 ratio, whereas the minor product gave a spectrum with only one kind of phenyl group. Hence, these two compounds are identified as partial-cone-$1Es_3$ and cone-$1Es_3$, respectively. Interconversion between these two isomers did not take place even at 100 °C (24 h in 1,1,2,2-tetrachloroethane), indicating that the oxygen-through-the-annulus rotation of the OCH_2CO_2Et group is inhibited.

We determined the partial-cone/cone ratio under the various reaction conditions (Table I). It is seen from Table I that (i) in the reaction in the presence of NaH, the partial-cone/cone ratio increases with increasing NaH concentration (*e.g.*, 1.6 at 2.2 equiv to 3.8 at 9.0 equiv in THF), (ii) DMF gives the partial-cone/cone ratio higher than THF, and (iii) in acetone, the reaction in the presence of Na_2CO_3 scarcely proceeds, whereas that in the presence of K_2CO_3 or Cs_2CO_3 it yields partial-cone-$1Es_3$ selectively and quantitatively. From these results, several critical questions arise with respect to the reaction mechanism. Firstly, why are mono- and di-*O*-alkylation products ($1H_2Es$ and $1HEs_2$, respectively) not detected? Secondly, why is partial-cone-$1Es_3$ formed in preference to cone-$1Es_3$? Thirdly, is there any significant relation between the partial-cone/cone ratio and the base? A route for this reaction is illustrated in Scheme I. The first question implies that in Scheme I the rate should be in the order of process 3 (fastest) > process 2 > process 1 (slowest). We previously investigated *O*-alkylation of $1H_3$ with simple alkyl halides (*e.g.*, *n*-BuI).[19] In the HPLC analysis of the reaction mixture we could detect the di-*O*-alkylation products.[19] This suggests that the first question will be solved in relation to the nature of the alkylation reagent. The crucial difference between $BrCH_2CO_2Et$ and *n*-BuI would be the metal-binding ability. Process 1 is a simple Williamson-type reaction. In process 2, on the other hand, the ester group in $1H_2Es$ can bind M^+ and $BrCH_2CO_2Et$ will coordinate to the bound M^+. As a result, the second *O*-alkylation reaction can occur pseudointramolecularly (as in Scheme II). This trend becomes further conspicuous in process 3. This situation induces the autoacceleration of the reaction; that is, the reaction will be accelerated in the order of process 3 > process 2 > process 1.

To answer the second and the third questions, one has to specify where the conformation is determined. In

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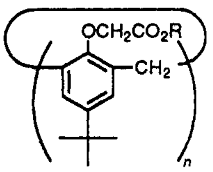
[19] Araki, K.; Inada, K.; Otsuka, H; Shinkai, S. *Tetrahedron*, in press.

O-alkylation with *n*-BuI we could isolate the di-*O*-alkylation product with a partial-cone conformation,[19] indicating that the conformation is determined in process 2. Unfortunately, $1HEs_2$ cannot be isolated in the present study. The experimental data in Table I suggest that the partial-cone/cone ratio is basically explained by the metal template effect. Through the studies on the conformer distribution of calix[4]arenes we already learned that the partial-cone is sterically less crowded than the cone and therefore formed predominantly. On the other hand, the cone results only when the template metal, which strongly interacts with phenolic oxygens, is present in the reaction system.[17-19] As described later, cone-$1Es_3$ shows Na^+ selectivity, whereas partial-cone-$1Es_3$ shows K^+ or Cs^+ selectivity. Examination of Table I reveals that a significant amount of cone-$1Es_3$ results only when the base contains Na^+ or K^+ and is strong (*e.g.*, NaH and *t*-BuOK but not K_2CO_3). These findings support the view that when substituents are introduced into hexahomotrioxacalix[3]arene it favorably yields a partial-cone conformer to reduce the steric crowding. Only when the template metal can hold the ester group(s) and the oxide group(s) on the same side of the calix[3]arene is the conformation immobilized to the cone. When a weak base is used, the undissociated OH group forms intramolecular hydrogen bonds with the dissociated O^- group, which will weaken the metal template effect arising from the $M^+\cdots O^-$ interaction. This change leads to the increase in the partial-cone.

Two-Phase Solvent Extraction of Alkali Metal. It was found by Ungaro *et al.*,[9-10] McKervey *et al.*,[12,13] and Chang *et al.*[11] that calix[*n*]arenes can be converted to neutral ligands by introduction of ester or amide groups into the OH groups. They demonstrated that the metal selectivity is dependent on the calix[*n*]arene ring size and, in particular, calix[4]aryl acetates and acetamides with a cone conformation show remarkably high Na^+ selectivity. The ring size and the ring flexibility are different between calix[4]arene and hexahomotrioxacalix[3]arene. It is thus interesting to assess what kind of ionophoric cavity cone-$1Es_3$ and partial-cone-$1Es_3$ provide. To the best of our knowledge, however, no precedent exists for molecular design of such hexahomotrioxacalix[3]arene-based ionophores. We estimated this through two-phase solvent extraction of alkali metal picrates and compared the data with those for calix[4]aryl acetates (2_4R). The results are summarized in Table II.



2_nR

Table II. Percent Extraction of Alkali Metal Picrates in CH_2Cl_2 at 25 °C[a]

calixarene	extractability (Ex%)				
	Li^+	Na^+	K^+	Cs^+	n-$BuNH_3^+$
cone-$1Es_3$	7.1	78.9	64.5	49.1	77.1
partial-cone-$1Es_3$	0.0	25.6	88.4	81.9	42.3
cone-2_4Et	17.6	100	86.1	24.6	24.4
partial-cone-2_4Et	5.2	62.1	94.3	49.9	6.2
2_6Et					41.1
2_6Bu^t					58.4

[a] The organic phase (CH_2Cl_2, 5 mL) contains a calixarene ionophore (2.5 mM for alkali metal picrates and 3.5 mM for n-$BuNH_3^+$). The aqueous phase (5 mL) contains M^+Pic^- (0.25 mM), MOH (0.10 M), and MCl (0.50 M) for alkali metal picrates and n-$BuNH_3^+Pic^-$ (7.0 × 10^{-5} M) for n-$BuNH_3^+$.

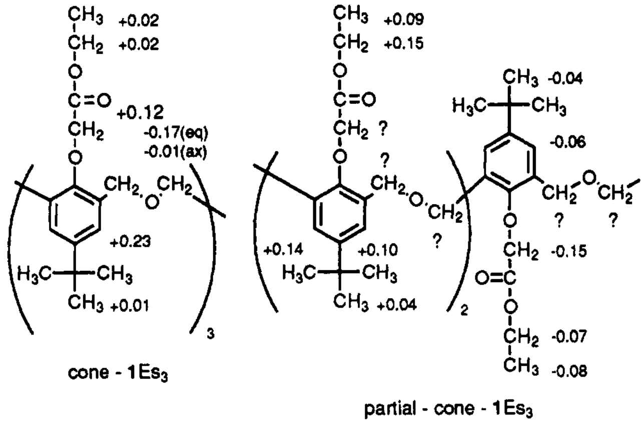


Figure 1. Changes in δ_H induced in the presence of alkali metal cations (250 MHz, $CDCl_3$:CD_3OD = 1:1, v/v, 25 °C). + denotes the downfield shift, and − denotes the upfield shift. ? denotes that the assignment is difficult because of the peak overlapping. For cone-$1Es_3$, [cone-$1Es_3$] = [Na^+Pic^-] = 10 mM; for partial-cone-$1Es_3$, [partial-cone-$1Es_3$] = [K^+Pic^-] = 2.5 mM.

As shown in Table II, it is already known that cone-2_4 shows Na^+ selectivity whereas partial-cone-2_4 shows K^+ selectivity. Cone-$1Es_3$ also shows high Na^+ selectivity although the Ex% is somewhat lower than that for cone-2_4. This indicates that the ionophoricity of the cavity composed of three OCH_2COEt groups is comparable with that in cone-2_4 composed of four OCH_2COEt groups and the cavity fits the size of Na^+; that is, the hexahomotrioxacalix[3]arene ring (18-membered) is larger than the calix[4]arene ring (16-membered), but the difference of only two atoms is not large enough to change the ion selectivity. The inferior Ex% value is probably attributed to the ring flexibility arising from the ethereal linkages in the ring. In contrast, partial-cone-$1Es_3$ shows K^+ selectivity, the Ex% being almost comparable with that for partial-cone-2_4. Partial-cone-$1Es_3$ also shows the high affinity for Cs^+, the Ex% being much higher than that for partial-cone-2_4. These Ex% values are basically in line with the metal template effect on the conformer distribution.

Figure 1 shows the changes in δ_H induced by added alkali metal cations. In cone-$1Es_3$, when an equimolar amount of sodium picrate was added a large down-field shift was observed for the ArH protons and a small down-field shift for the OCH_2CH_3 ethyl protons. Our previous study showed that in 2_4Et Na^+ strongly interacts with the CH_2-CO carbonyl oxygens and the OCH_2CH_3 ethyl protons largely shift to lower magnetic field (0.10 ppm and 0.19 ppm, respectively).[14,20] The difference suggests that in cone-$1Es_3$ the ArO phenolic oxygens play a primary role in the binding of Na^+ and the contribution of the CH_2CO carbonyl oxygens is relatively small. Another interesting feature is the upfield shift observed for the $ArCH_2O$ methylene protons. In calix[4]arenes, it is established that $\Delta\delta_H$ between H_{ax} and H_{eq} is generally 0.9 ± 0.2 ppm for a system in the regular cone conformation and zero for

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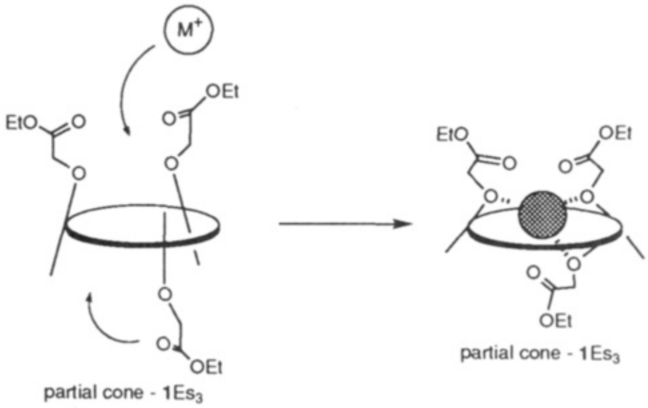
Scheme III



a system in the regular 1,3-alternate conformation.[21] In the absence of Na^+ $\Delta\delta_H$ is 0.40 ppm, whereas in the presence of Na^+ $\Delta\delta_H$ becomes 0.56 ppm. Provided that the concept established in calix[4]arenes is also applicable to the hexahomotrioxacalix[3]arenes, it follows that the phenyl groups in cone-$1Es_3$ are more flattened than those in cone-calix[4]arenes and stand up when Na^+ enters into the ionophoric cavity. Since the δ_H values for the $ArCH_2O$ methylene protons are strongly affected by the conformational change, it is difficult to know whether the $ArCH_2O$ oxygens contribute to the metal-binding. At present, we presume from the examination of the CPK molecular model that they are not used for the binding of Na^+ because three ArO phenolic oxygens and three CH_2CO carbonyl oxygens suffice for inclusion of Na^+ and the coordination of the $ArCH_2O$ oxygens induces distortion of the ring.

The binding of K^+ to partial-cone-$1Es_3$ is more complicated. The major question is whether the OCH_2CO group in the inverted phenyl unit contributes to the metal-binding. From Figure 1 we can notice two significant chemical shift changes in partial-cone-$1Es_3$. Firstly, compared with cone-$1Es_3$ the upfield shift for the ArH protons in the ordinary two phenyl units becomes smaller, whereas that for the OCH_2CH_3 protons becomes larger. This change teaches us that the CH_2CO carbonyl oxygens are more included in the metal-binding. Secondly, the δ_H values of the $OCH_2CO_2CH_2CH_3$ protons in the inverted phenyl unit move to higher magnetic field. This suggests that the ester group moves into the cavity and undergoes the shielding effect of two benzene rings (as in Scheme III). In calix[4]arenes a conformational change in one phenyl unit causes conformational changes in other phenyl units to minimize the ring distortion.[22,23] We consider that this is probably not the case in $1Es_3$ because the 18-membered ring including three ethereal linkages is very flexible. If so, the conformational change in the inverted phenyl unit is induced to allow the ester group to coordinate to K^+. We now consider that K^+ is sandwiched by two ordinary ester groups and one inverted ester group.

Two-Phase Solvent Extraction of Ammonium Cations. It has been established that 18-crown-6 can strongly bind primary ammonium cations (RNH_3^+).[24] This is rationalized in terms of stereochemical matching between D_{3d} symmetry in 18-crown-6 and C_3 symmetry in RNH_3^+. More recently, Chang *et al.*[25] found that hexameric $\mathbf{2_6R}$ with C_6 symmetry can bind RNH_3^+, whereas the binding to tetrameric $\mathbf{2_4R}$ occurs only weakly. This finding is also rationalized on the same basis. It occurred to us that cone-$1Es_3$ with C_3 symmetry might serve as an efficient receptor for RNH_3^+. We here estimated the binding ability of $\mathbf{1R_3}$ through two-phase solvent extraction and compared the results with those of $\mathbf{2_nR}$.

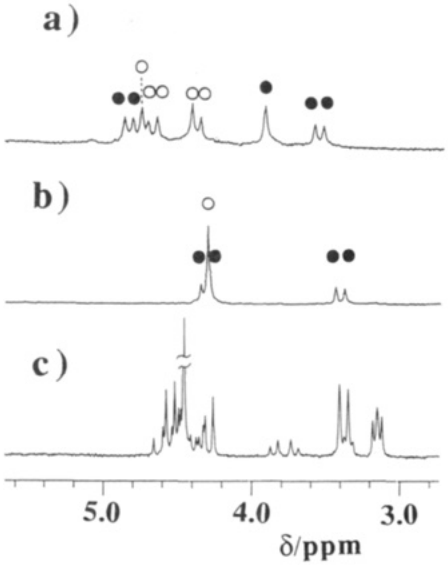


Figure 2. Partial ^{1}H NMR spectra of $\mathbf{2_6Bu^t}$ (400 MHz, 30 °C): (a) no additive in $CDCl_3$, (b) with an equimolar amount of K^+Pic^- in $(CDCl_2)_2$, (c) with an equimolar amount of n-$BuNH_3^+Pic^-$ in $(CDCl_2)_2$. ● and ○ denote the signals for $ArCH_2Ar$ and OCH_2CO, respectively. The spectrum of $\mathbf{2_6Bu^t}$ in the absence of the additive in $(CDCl_2)_2$ shows the similar splitting pattern, but chemical shifts for the $ArCH_2Ar$ protons overlap with those for the OCH_2CO protons. Hence, we here illustrated the spectrum in $CDCl_3$.

As recorded in Table II, $\mathbf{2_6Et}$ and $\mathbf{2_6Bu^t}$ gave the Ex% higher than cone-$\mathbf{2_4Et}$, indicating the importance of the C_6-symmetrical framework for the binding of RNH_3^+. The slightly higher Ex% for $\mathbf{2_6Bu^t}$ than that for $\mathbf{2_6Et}$ is explained by the increase in the lipophilicity of $\mathbf{2_6Bu^t}$ bearing the *tert*-butyl groups. Importantly, cone-$1Es_3$ gave the Ex% (77.1%) much higher than $\mathbf{2_6Et}$ and $\mathbf{2_6Bu^t}$ (41.1% and 58.4%, respectively). Partial-cone-$1Es_3$ with one inverted ester group gave the Ex% much lower than cone-$1Es_3$. This indicates that to attain the high Ex% for RNH_3^+ three ester groups arranged in C_3 symmetry is indispensable.

By using ^{1}H and ^{13}C NMR spectroscopy we investigated how and where cone-$1Es_3$ and $\mathbf{2_6R}$ bind ammonium cations. As shown in Figure 2, both the $ArCH_2Ar$ methylene protons and OCH_2CO methylene protons in $\mathbf{2_6Bu^t}$ gave a pair of doublets (δ_H 3.55 and 4.81 ppm for $ArCH_2Ar$ and 4.34 and 4.71 ppm for OCH_2CO) and a singlet resonance (δ_H 3.91 ppm for $ArCH_2Ar$ and 4.78 ppm for OCH_2CO) with an integral intensity of 2:1 (Figure 2a). As shown in Figure 3, we can count eight different conformations for calix[6]arene.[26] Among them, only a 1,2,3-alternate confor-

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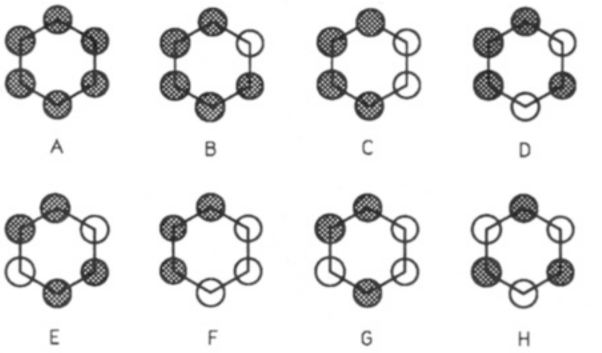

Figure 3. All conformations possible for calix[6]arene: ○ denotes that the phenyl unit is inverted.

mation (F) is consistent with the above splitting pattern. The 1,2,3-alternate conformation is also observed for other conformationally-mobile hexa-*O*-substituted calix[6]arenes.[27,28] When an equimolar amount of potassium picrate was added, the $ArCH_2Ar$ methylene signals and the OCH_2CO methylene signals changed to a pair of doublets and a singlet resonance, respectively (Figure 2b). This implies that the conformation changes from a 1,2,3-alternate to a cone (A) so that six ester carbonyls can interact with a bound K^+ ion. When an equimolar amount of *n*-butylammonium picrate was added, the $ArCH_2Ar$ methylene signals changed into AB patterns with a large chemical shift difference (4H each) and an AB pattern with a small chemical shift difference (2H each). This splitting pattern is similar to that of a partial-cone in calix[4]arenes, suggesting that the likely conformation is B in Figure 3 or a cone with one flattened phenyl unit.[29] This finding suggests that the binding of an ammonium cation is effected by immobilizing three 1,3,5-esters to the same side of the calix[6]arene ring and does not require a regular cone conformation.

The chemical shift changes for cone-$\mathbf{1}Es_3$ are illustrated in Figure 4. In ^1H NMR spectroscopy, complexation of n-$BuNH_3^+$ induces the large downfield shift of the OCH_2CO and ArH protons. The downfield shift of the OCH_2CO protons can be rationalized by both the $C{=}O \cdots HN^+$ interaction and the $ArO \cdots HN^+$ interaction, but the downfield shift of the ArH protons can be rationalized only by the $ArO \cdots HN^+$ interaction. We thus consider that not only the ester carbonyl oxygens but also the ethereal oxygens play a crucial role in the binding of RNH_3^+. This view is also supported by ^{13}C NMR spectroscopy. The large downfield shift was observed not only for the n-$BuNH_3^+$-binding OCH_2CO carbons ($\Delta\delta_C = 0.39$–0.74 ppm) but also for the aromatic 1-C and 4-C carbons ($\Delta\delta_C = 0.76$–1.87 ppm).

As mentioned above, $\Delta\delta_H$ between H_{ax} and H_{eq} of the $ArCH_2Ar$ methylene protons in calix[4]arenes serves as a measure of the "flattening". In cone-$\mathbf{2}_4Et$, $\Delta\delta_H$ decreases upon the binding of alkali metal cations. In cone-$\mathbf{2}_4Et$, $\Delta\delta_H$ decreases upon the binding of Na^+, indicating that the phenyl units are flattened so that the ester groups can coordinate to Na^+.[20] In cone-$\mathbf{1}Es_3$, on the other hand, $\Delta\delta_H$ increases from 0.40 ppm to 0.56 ppm in the binding of Na^+ and 0.41 ppm to 0.92 ppm in the binding of n-$BuNH_3^+$. Provided that the $\Delta\delta$ rule established in calix[*n*]arenes is applicable to homotrioxacalix[3]arenes, the finding implies that the phenyl groups are flattened in the absence of guests but stand up when the guest is included. Using CPK molecular models, we tried to image the cation-induced conformational change which is compatible with the above NMR spectral data. Compounds $\mathbf{2}_6R$ tend to adopt a 1,2,3-alternate conformation, probably to reduce the steric crowding. Although it changes to a cone or nearly-cone conformation upon the cation-binding, the ionophoric cavity comprising the 24-membered ring is relatively rigid and seems to be a little too large to interact with RNH_3^+ through the hydrogen-bonds. Particularly, it seems so when the calix[6]arene ring adopts a regular cone conformation. In contrast, the 18-membered ring of hexahomotrioxacalix[3]arene including three ethereal linkages is relatively flexible and the ionophoric cavity exactly fits the size of RNH_3^+. Hence, the ester groups can be flattened in the absence of RNH_3^+. When RNH_3^+ is included, the ester groups stand up to constitute an ionophoric cavity with neat C_3 symmetry.

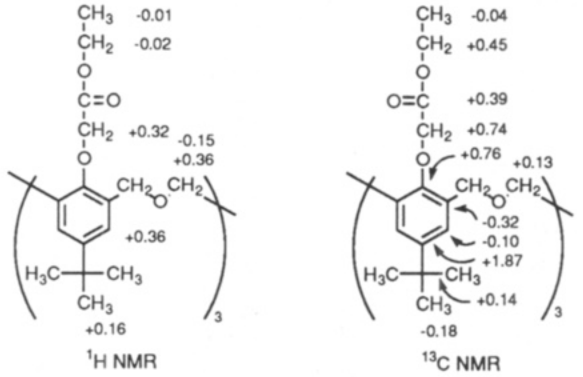

Figure 4. Changes in δ_H and δ_C induced in the presence of n-$BuNH_3^+Pic^-$ (250 MHz for ^1H NMR and 63 MHz for ^{13}C NMR, $CDCl_3$: CD_3CN = 3:1, v/v, 25 °C). + denotes the downfield shift, and − denotes the upfield shift: [cone-$\mathbf{1}Es_3$] = [n-$BuNH_3^+Pic^-$] = 10 mM.

Concluding Remarks

The molecular design of artificial receptors from calix[*n*]arenes has recently become a very active area of endeavor. In contrast, hexahomotrioxacalix[3]arene has been left unutilized. This is probably because of the flexibility of the ring. The present paper demonstrates, however, that hexahomotrioxacalix[3]arene is also useful for the design of a Na^+-selective ionophore because the conformational isomerism, inherent to calix[*n*]arenes, is more simplified. Particularly important is the specific recognition of ammonium cations which becomes possible because of C_3 symmetry common to both host and guest. We believe that one can realize the various metal selectivities and even chiral recognition of ammonium cations by the skillful modification of hexahomotrioxacalix[3]arene.

Experimental Section

Materials. $\mathbf{1}H_3$ and $\mathbf{2}_nR$ were synthesized according to the literature.[1,9–15] For recrystallization of $\mathbf{1}H_3$ we used *n*-hexane-cyclohexane.[30]

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[27] Kanamathrareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160.

[28] Ikeda, A.; Nagasaki, T.; Shinkai, S. *J. Phys. Org. Chem.* **1992**, *5*, 699.

[29] In ref 25, Chang *et al.* state that the conformation of calix[6]aryl acetates changes to a cone on the addition of *n*-butylammonium picrate, but the splitting pattern in Figure 2 is not commensurate with the "regular" cone.

7,15,23-Tri-*tert*-butyl-25,26,27-tris[(ethoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene ($1Es_3$). The cone isomer was synthesized by the reaction of $1H_3$ with ethyl bromoacetate. Compound $1H_3$ (808 mg, 1.40 mmol) was treated with oil-dispersed NaH (370 mg, 9.24 mmol) in anhydrous THF (140 mL), and then ethyl bromoacetate (1.54 g, 9.24 mmol) was added. The reaction mixture was refluxed for 3 h under a N_2 stream. Excess NaH was decomposed with EtOH. The product mixture was filtered, the filtrate being concentrated to dryness. The residue was dissolved in $CHCl_3$. The solution was washed with aqueous 1 M HCl and saturated aqueous NaCl and dried over $MgSO_4$. After filtration, the filtrate was concentrated to dryness. The residue (slightly yellow solid) was subjected to a preparative TLC separation (silica gel, chloroform: ethyl acetate = 19:1, v/v): mp 73–74 °C, yield 9%; IR (KBr disk) $\nu_{C=O}$ 1750 cm^{-1}, ν_{CO} 1190 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ 1.08 (*t*-Bu, s, 27H), 1.33 ($OCCH_3$, t, 9H), 4.26 (OCH_2C, q, 6H), 4.49 (OCH_2CO, s, 6H), 4.52 and 4.91 (OCH_2Ar, d each, 6H each), 6.95 (ArH, s, 6H). Anal. Calcd for $C_{48}H_{60}O_{12}\cdot CHCl_3$: C, 61.66; H, 7.08. Found: C, 61.32; H, 7.02.

The partial-cone isomer was synthesized in the presence of K_2CO_3. Compound $1H_3$ (0.60 g, 1.04 mmol), K_2CO_3 (1.29 g, 9.36 mmol), and ethyl bromoacetate (1.56 g, 9.36 mmol) were reacted in refluxing acetone (30 mL). The reaction was continued for 16 h under a N_2 stream. After filtration, the filtrate was concentrated to dryness. The residue was dissolved in chloroform. The solution was washed with aqueous 1 M HCl and saturated aqueous NaCl and dried over $MgSO_4$. After filtration, the solution was concentrated to dryness, and the residue was recrystallized from $CHCl_3$–EtOH: mp 146–148 °C; yield 85%; IR (KBr disk) $\nu_{C=O}$ 1750 cm^{-1}, ν_{CO} 1190 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C) δ 1.06 and 1,21 (CCH_3, t each, 3H and 6H), 1.25 and 1.33 (*t*-Bu, s each, 18H and 9H), 3.22, 4.22, and 4.51 (OCH_2CO, s, d, and d, 2H each), 3.79 and 4.10 (OCH_2C, q each, 2H and 4H), 4.17, 4.23, 4.34, 4.63, 4.95, and 5.05 (OCH_2Ar, d each, 2H each), 7.19, 7.23, and 7.28 (ArH, d, d, and s, 2H each). Anal. Calcd for $C_{48}H_{66}O_{12}$: C, 69.04; H, 7.97. Found: 68.84; H, 7.91. From the splitting patterns with a 1:2 integral intensity ratio the conformation of this compound is assigned to partial-cone.

HPLC Analysis. The conformer distribution was determined by a HPLC method (column, Zorbax ODS; mobile phase, methanol). The peaks appeared in the order of $1H_3$ (shortest retention time), partial-cone-$1Es_3$, and cone-$1Es_3$.

Solvent Extraction. The method of two-phase solvent extraction was described previously.[15,18] We used an aqueous phase (5 mL; $[M^+Pic^-] = 0.25$ mM, $[MOH] = 0.10$ M, and $[MCl] = 0.50$ M for alkali metal cations and $[n\text{-}BuNH_3^+Pic^-] = 7.0 \times 10^{-5}$ M for $n\text{-}BuNH_3^+$) and a dichloromethane solution (5 mL; $[1Es_3] = 2.5$ mM for alkali metal cations and 3.5 mM for $n\text{-}BuNH_3^+Pic^-$).

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(30) Zerr, P.; Mussurabi, M.; Vicens, J. *Tetrahedron Lett.* 1991, *32*, 1879.