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Conformational Isomerism in and Binding Properties to Alkali-Metals and an Ammonium Salt of *O*-Alkylated Homooxacalix[3]arenes.

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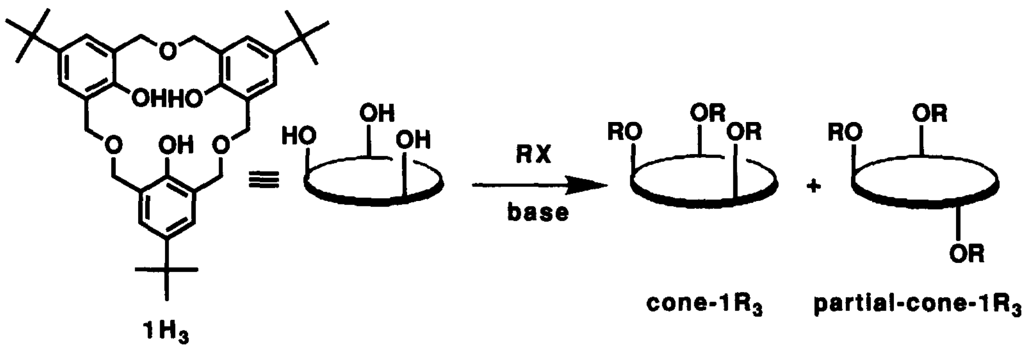
Abstract: 7,15,23-Tri-*tert*-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**1**H_3) was tri-*O*-alkylated with alkyl halides (RX: R=Me, Et, *n*-Pr, and *n*-Bu) in the presence of various bases and the products (**1**R_3) were analyzed by HPLC and ^{1}H NMR spectroscopy. It was found that (i) ring inversion which occurs through the oxygen-through-the-annulus rotation is allowed for **1**Me_3, **1**Et_3, and **1**Pr_3 whereas it is inhibited for **1**Bu_3, (ii) the cone/partial-cone equilibrium in **1**Et_3 and **1**Pr_3 is predominantly inclined to partial-cone, indicating the thermodynamic stability of partial-cone conformers, and (iii) in the product distribution of **1**Bu_3 partial-cone is yielded in preference for cone, indicating the kinetic preference for partial-cone. From the analysis of the reaction intermediates the possible reaction routes to cone- and partial-cone-**1**Bu_3 are discussed. **1**R_3 showed the selectivity toward K^+ among alkali metal cations and the cone conformers had the extractability (Ex%) higher than the partial-cone conformers. Cone-**1**R_3 showed the high affinity for $BuNH_3^+$ because of (averaged) C_3 symmetry common to both cone-**1**R_3 host and $BuNH_3^+$ guest.

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**H_3) in a low yield along with large amounts of linear ethers. In comparison to structural characteristics of a calixarene family, this compound attracted our interest because of the following five reasons: (i) compound **1**H_3 has a cavity composed of a 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**H_3 is much faster than that for calix[4]arenes because of the flexible ethereal linkages,[1-3] (iii) there are only two possible conformations, cone and partial-cone in *O*-alkylation products in contrast to four possible conformations in calix[4]arenes, so that the conformational isomerism can be much more simplified, (iv) the ethereal ring oxygens may act cooperatively with the phenolic oxygens upon the binding of metal ions, and (v) the basic structure has (averaged) C_3-symmetry which is particularly useful for the design of cyclic metal-ligands.

More recently, we examined the influence of *O*-substituents on the conformational isomerism of calix[4]arenes in detail.[4-8] Through these studies, we established that interconversion between conformers, which occurs through the oxygen-through-the-annulus rotation, can be sterically inhibited by *O*-substituents bulkier than ethyl group (*e.g.*, *n*-propyl group: Pr).[4-7] By using *n*-propyl bromide as an alkylation reagent, for example, one can thus synthesize a variety of conformational isomers[4-8] (including optically-active isomers[9-13]) from calix[4]arenes. To use compound **1** as a starting material for molecular design of such functionalized macrocycles, one must fully understand the conformational characteristics of *O*-alkylated $1H_3$. In this paper, we report systematic introduction of *O*-substituents (R) into $1H_3$, the possible reaction routes, the relative stability of the final products, interconversion between cone and partial-cone, *etc.* in detail.



Experimental

Materials

Compound $1H_3$ was prepared according to the method in the literature.[1,14]

7,15,23-Tri-*tert*-butyl-25,26,27-trimethoxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene ($1Me_3$). Compound $1H_3$ (500 mg, 0.868 mmol) was treated with oil-dispersed NaH (60%, 564 mg, 13.9 mmol) in DMF (30 ml) at 70 °C for 1 h. To this mixture was added methyl iodide (2.81 ml, 45.1 mmol) dropwise and the reaction mixture was stirred at 70 °C for 2 h. Water (30 ml) was added to decompose remaining NaH and the mixture was concentrated to dryness. The residue was extracted with ether. The ether solution was washed with water until the aqueous phase became pH 7 and dried over $MgSO_4$. The solution was evaporated to dryness and the residue was recrystallized from methanol: mp 145.5-147.5 °C, yield 32%; IR (nujol) no ν_{OH}, $\nu_{C\text{-}O}$ 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$, -50 °C) δ 1.28 (*t*-Bu, s, 27H), 3.13 (OCH_3, s, 9H), 4.49 (OCH_2, s, 12H), 7.28 (ArH, s, 6H). Anal. Calcd for $C_{39}H_{54}O_6$: C, 75.69; H, 8.80%. Found: C, 75.99; H, 9.01%. The singlet resonances for OCH_3, OCH_2, and ArH indicate that the ring is subject to the free rotation.

7,15,23-Tri-*tert*-butyl-25,26,27-triethoxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene ($1Et_3$). This compound was synthesized from $1H_3$ and ethyl iodide in a similar manner to $1Me_3$: mp 155.3-157.7 °C, yield 70%; IR (nujol) no ν_{OH}, $\nu_{C\text{-}O}$ 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$, -50 °C) δ 0.15 and 1.15 (CH_3, t each (J = 6.8, 6.9 Hz), 3H and 6H), 1.31 and 1.36 (*t*-Bu, s, 18H and 9H), 1.84, 3.24, and 3.71 (OCH_2 in ethyls, q (J = 6.8 Hz), m, and m, 2H each), 4.1-4.9 (OCH_2 in ring, m, 12H), 7.34 (ArH, m, 6H). Anal. Calcd for $C_{42}H_{60}O_6$: C, 76.33; H, 9.15%. Found: C, 76.73; H, 9.51%. The two $CH_2C\underline{H}_3$ peaks in a 1:2 integral intensity ratio indicate that $1Et_3$ takes a partial-cone conformation.

7,15,23-Tri-*tert*-butyl-25,26,27-tripropoxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (1Pr3). This compound was synthesized from $1H_3$ and propyl iodide in a manner similar to $1Me_3$: mp 146.5-148.7 °C, yield 77%; IR (nujol) no ν_{OH}, ν_{C-O} 1200 cm^{-1}. The ^{1}H NMR spectrum ($C_2D_2Cl_4$, 30 °C) showed that the product is a mixture of two conformers. Cone-$1Pr_3$: δ 1.06 (*t*-Bu, s, 27H), 1.08 (CH_3, t (J = 8.0 Hz), 9H), 1.81 (CCH_2C, m, 6H), 3.45 (OCH_2 in propyls, t, 6H), 4.1-4.8 (OCH_2 in ring, not clear because of overlap with partial-cone-$1Pr_3$), 6.93 (ArH, s, 6H). Partial-cone-$1Pr_3$: δ 0.37 and 0.88 (CH_3, t each (J = 7.5, 7.5 Hz), 3H and 6H), 0.77 and 1.51 (CCH_2C, m each, 2H and 4H), 1.26 and 1.33 (*t*-Bu, s each, 18H and 9H), 2.50, 3.38, and 3.47 (OCH_2 in ethyl, t (J = 5.9 Hz), m, and m, 2H each), 4.1-4.8 (OCH_2 in ring, not clear because of overlap with cone-$1Pr_3$), 7.24 (ArH, m, 6H). The molar ratio estimated from the integral intensity was cone:partial-cone = 1.0:5.0. Anal. Calcd for $C_{45}H_{66}O_6$: C, 76.88; H, 9.46%. Found: C, 76.80; H, 9.40%.

25,26,27-Tributoxy-7,13,15-tri-*tert*-butyl-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (1Bu3). This compound was synthesized from $1H_3$ and *n*-butyl iodide in a manner similar to $1Me_3$: mp 119.2-120.5 °C, yield 63%; IR (KBr) no ν_{OH}, ν_{C-O} 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 0.64-0.70 (CH_3CH_2 in inverted phenyl, m, 5H), 0.90 (CH_3, t (J = 7.2 Hz), 6H), 1.27-1.36 (*t*-Bu and $C\underline{H_2}CH_3$, m, 31H), 1.58-1.54 ($OCCH_2$, m, 6H), 2.62 (OCH_2 in butyl in inverted phenyl, t (J = 6.8 Hz), 2H), 3.47 (OCH_2 in butyl, t (J = 6.8 Hz), 4H), 4.26-4.77 (OCH_2 in ring, m, 12H), 7.23, 7.29, and 7.34 (ArH, d, d (J = 2.5, 2.5 Hz), and s, 2H each). Anal. Calcd for $C_{48}H_{72}O_6$: C, 77.38; H, 9.74%. Found: C, 77.49; H, 9.99%. The splitting pattern in ^{1}H NMR shows that the isolated compound is partial-cone-$1Bu_3$. The reaction of $1H_3$ and *n*-butyl iodide was conducted in the presence of *t*-BuOK (instead of NaH). The HPLC analysis showed that the product was a mixture of partial-cone-$1Bu_3$ and an unknown compound. The unknown compound was isolated by a preparative TLC method (silica gel, chloroform): mp 163.0-164.2 °C, yield 15%; Mass (positive SIMS, *m*-nitrobenzyl alcohol matrix) $(M+Na)^+$ 767; IR (KBr) no ν_{OH}, ν_{C-O} 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 1.02 (CH_3, t (J = 7.3 Hz), 9H), 1.07 (*t*-Bu, s, 27H), 1.52-1.60 ($C\underline{H_2}CH_3$, m, 6H), 1.74-1.82 ($OCCH_2$, m, 6H), 3.58 (OCH_2 in butyls, t (J = 6.6 Hz), 6H), 4.60 (OCH_2 in ring, s, 12H), 6.96 (ArH, s, 6H). Anal. Calcd for $C_{48}H_{72}O_6$: C, 77.38; H, 9.74%. Found: C, 76.43; H, 9.76%. The high symmetry observed for the ^{1}H NMR spectrum shows that the unknown compound is cone-$1Bu_3$.

26,27-Dibutoxy-7,15,23-tri-*tert*-butyl-25-hydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (1HBu2). Compound $1H_3$ (500 mg, 0.868 mmol) was treated with oil-dispersed NaH (60%, 70 mg, 1.74 mmol) in DMF (30 ml) at 70 °C for 1h. To this mixture was added butyl iodide (0.22 ml, 1.91 mmol) and the reaction mixture was stirred at 70 °C for 2h. Water (30 ml) was added and the precipitate formed was recovered by filteration. The raw product was purified by recrystallization from methanol: mp 148.6-150.5 °C, yield 52%; IR (KBr) ν_{OH} 3400 cm^{-1}, ν_{C-O} 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C) δ 0.68 (CH_3, t (J = 7.2 Hz), 6H), 0.95-1.31 (CCH_2CH_2C, m, 8H), 1.28 and 1.37 (*t*-Bu, s each, 9H and 18H), 3.06, 3.10, 3.32, and 3.36 ($ArOCH_2$, t each (J = 6.2, 6.2, 6.8, 6.8 Hz), 1H each), 4.25, 4.39, 4.44, 4.63, 4.69, and 4.69 ($ArCH_2O$, d each (J = 11.5, 10.5, 13.2, 11.5, 10.5, 13.2 Hz), 2H each), 6.96 (OH, s, 1H), 7.18, 7.28, and 7.52 (ArH, s, d, and d (J = 2.5, 2.5 Hz), 2H each). Anal. Calcd for $C_{44}H_{64}O_6$: C, 76.70; H, 9.36%. Found: C, 76.66; H, 9.30%. The rotation of unmodified OH group is still allowed, so that two *n*-butyl groups are regarded to be equivalent both in a cone and a partial-cone conformation. Therefore, one cannot specify the conformation from the ^{1}H NMR spectrum. To differentiate these two conformations we introduced a benzyl group into the OH group to inhibit the rotation. Compound $1HBu_2$ (50 mg, 0.073 mmol) was treated with oil-dispersed NaH (60%, 5.8 mg, 0.15 mmol) in DMF (15 ml) at 70 °C for 1 h. To this mixture was added benzyl bromide (0.03 ml, 0.22 mmol) and the reaction mixture was stirred at 70 °C for 1 h. Water (30 ml) was added and the product was extracted with ether. The ether solution was dried over $MgSO_4$ and concentrated to dryness. The residue was recrystallized from methanol: mp 132.9-134.2 °C, yield 53%; IR (KBr) no ν_{OH}, ν_{C-O} 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C) δ 0.67-0.76 (CH_3CH_2, m, 10H), 1.01-1.26 (CCH_2C, m, 4H), 1.26, 1.28, and 1.29 (*t*-Bu, s, 9H each), 2.59 and 3.28-3.37 ($ArOCH_2C$, m each, 2H each), 4.19-4.72 ($ArCH_2O$ and $ArOCH_2Ar$, m, 14H), 7.17-7.34 (ArH, m, 11H). The three unequivalent *t*-Bu peaks support the partial-cone conformation. Since the oxygen-through-the-annulus rotation is inhibited (see Results and Discussion), the precursor **1**HBu_2 adopts a partial-cone conformation in which the butyl groups are placed to the opposite side.

Solvent Extraction.

The method of two-phase solvent extraction was described previously.[7] We here 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 phase (5 ml; [calixarene] = 2.5 mM for $n\text{-}BuNH_3^+$).

Miscellaneous

In *O*-alkylation of **1**H_3, the progress of the reaction was monitored by an HPLC method: column, Zorbax ODS; mobile phase, chloroform: methanol = 1:8 v/v. For the TLC separation, silica gel and chloroform were used unless otherwise stated. ^1H NMR spectra were measured with a JEOL GX-400 NMR apparatus unless otherwise stated.

Results and Discussion

Inhibition of Ring Inversion by *O*-Substituents. It is known that four different conformers (cone, partial-cone, 1,2-alternate, and 1,3-alternate) can exist in conformationally-immobile calix[4]arenes.[4-8,15] In **1**R_3, on the other hand, only cone and partial-cone can exist. Thus, one can considerably simplify the conformational controversy in the **1**R_3 system. Figure 1 shows the temperature-dependent ^1H NMR spectra for the $ArCH_2OCH_2Ar$ methylene protons. **1**Me_3 gave a singlet resonance at -50 ~ 50 °C although the peak became somewhat broad at -50 °C. The result indicates that the methoxy groups in **1**Me_3 rotate rapidly through the annulus. The $ArCH_2OCH_2Ar$ methylene protons in **1**Et_3 appeared as sharp multiple peaks at -50 °C. With the temperature rise the peaks became broad and finally coalesced at around 50 °C. At low temperature region CH_3 and CH_2 protons in the ethyl groups appear in a 1:2 integral intensity ratio. This supports the view that **1**Et_3 predominantly exists as a partial-cone conformation.* The results indicate that ring inversion occurs in the speed of the NMR time-scale.

The ^1H NMR spectrum of **1**Pr_3 indicated that the product was a mixture of cone and partial-cone (*ca.* 1:6). As the shape of the ^1H NMR spectrum was scarcely changed by the temperature rise (up to 100 °C), we first considered that the propyl groups are bulky enough to inhibit the oxygen-through-the-annulus rotation of **1**R_3. We thus isolated the two conformers by a preparative TLC method. The HPLC analysis manifested, however,

* In the ^1H NMR spectrum at -50 °C very weak concomitant signals are observed. Provided that they arise from cone-**1**Et_3, the concentration is about 1 mol%.

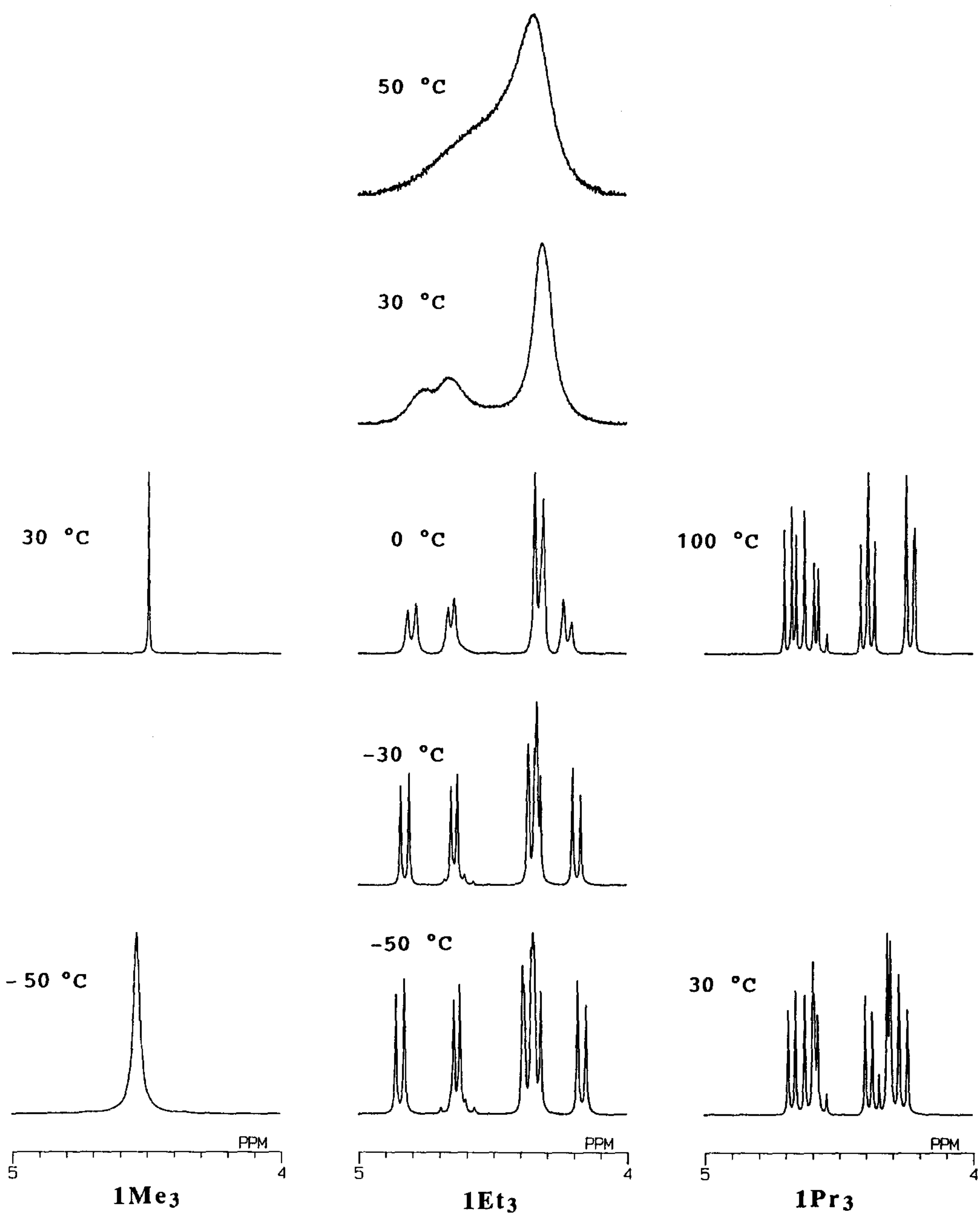


Figure 1. Partial ^1H NMR spectra for the $ArCH_2OCH_2Ar$ methylene protons in **1**R_3: solvent, $CDCl_3$ for **1**Me_3 and **1**Et_3 and $Cl_2CDCDCl_2$ for **1**Pr_3.

that the peak intensity ratio is time-dependent and the final ratio is cone:partial-cone = 1:6, both from cone-**1**Pr3 and from partial-cone-**1**Pr3. These findings reveal that (i) the rotation of **1**Pr3 is still allowed but the speed is much slower than the NMR time-scale and (ii) the conformer distribution of 1:6 is reached under the thermodynamic control.

Here, we synthesized **1**Bu3 in order to suppress the rotation by bulkier *O*-substituents. We separated cone-**1**Bu3 and partial-cone-**1**Bu3 by a preparative TLC method and heated each conformer at 100 °C for 5 h (solvent 1,1,2,2-tetrachloroethane). The HPLC analysis showed that no isomerization takes place under the condition. The results teach us that to isolate conformers stably from **1**R3 one has to employ an *O*-substituent bulkier than propyl groups.

The influence of *O*-substituents on the oxygen-through-the-annulus rotation of **1**R3 is compared with that in calix[4]arenes in Table 1. It is known that in the calix[4]arenes the ethyl group brings forth the steric hindrance for the rotation and the propyl group is bulky enough to inhibit the rotation.[7] In **1**R3, on the other hand, the propyl group only brings forth some steric hindrance and the rotation is inhibited by the further bulkier butyl group. The results consistently reveal that the rotation inhibition in **1**R3 is more difficult than that in calix[4]arene: in other words, the inner cavity of **1**R3 is apparently larger than that of calix[4]arene. The difference is attributed to two structural characteristics of **1**R3: *i.e.*, (i) the ring size of **1**R3 (18-membered ring) is greater than that of calix[4]arene (16-membered ring) and (ii) the ring of **1**R3 is more flexible than that of calix[4]arene because of three ethereal linkages.

Table 1. Influence of *O*-substituents on the oxygen-through-the-annulus rotation in calix[4]arenes and homooxacalix[3]arenes[a]

O-Substituent	Calix[4]arene	Homooxacalix[3]arene
Me	Mobile, takes place on the NMR time-scale (T_C = 60 °C)	Mobile faster than the NMR time-scale (T_C < -50 °C)
Et	Immobile at room temperature but rotate at high temperature	Mobile, takes place on the NMR time-scale (T_C = 50 °C)
Pr	Immobile	Mobile but slower than the NMR time-scale
Bu	Immobile	Immobile

[a] The results for calix[4]arene are cited from Ref. 7.

Partial-cone - Cone Isomerism. Since the cone - partial-cone isomerism of **1**Pr3 can be conveniently followed by ^{1}H NMR spectroscopy, we determined the ratio as a function of temperature (Table 2). It is seen from Table 2 that the percentage of partial-cone-**1**Pr3 increases with increasing temperature. The corresponding van't Hoff plot is shown in Figure 2. From the least-squares computation (r = 0.96) we obtained ΔH = -0.94 kcal mol^{-1}, ΔS = -6.6 e.u., and ΔG_{298} = 1.02 kcal mol^{-1}. These thermodynamic parameters imply that partial-cone to cone isomerization accompanies the favorable ΔH decrease and the unfavorable ΔS increase: that is, the relative stability of partial-cone-**1**Pr3 (and probably, also of partial-cone-**1**Et3) arises from the ΔS term.

We previously determined the thermodynamic parameters for the partial-cone - cone equilibrium of 25,26,27,28-tetramethoxycalix[4]arene: ΔH = 1.15 kcal mol^{-1}, ΔS = 2.78 e.u., and ΔG_{298} = 0.32 kcal mol^{-1}.[16] These parameters imply that the partial-cone to cone isomerization accompanies the unfavorable ΔH

increase and the favorable ΔS increase: that is, the relative stability of the partial-cone conformer is rather based on the ΔH term. Namely, the factors supporting the stability of the partial-cone conformer are different mechanistically between the calix[4]arene and the homotrioxacalix[3]arene. The difference in the thermodynamics should be related to the difference in the ring structure, but the detail is not well understood. Anyhow, these two compounds show a contrastive temperature-dependence: in 25,26,27,28-tetramethoxycalix[4]arene cone increases with increasing temperature whereas in **1**Pr3 cone decreases with increasing temperature.

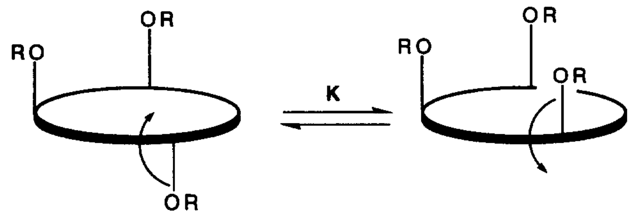


Table 2. Partial-cone - cone ratio of **1**Pr3 and equilibrium constants(K)[a]

Temperature / °C	Cone / Partial-cone	K
30	1.00/5.94	0.168
50	1.00/6.19	0.162
80	1.00/7.28	0.137
100	1.00/7.94	0.126

[a] Solvent $Cl_2CDCDCl_2$, K = [cone] / [partial-cone].

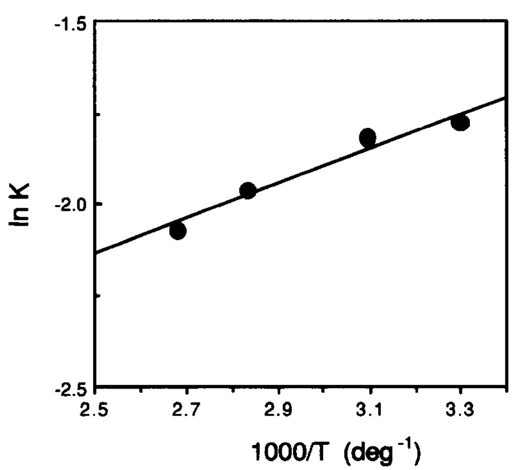


Figure 2. van't Hoff plot for the partial-cone - cone equilibrium of **1**Pr3.

Influence of Metal Cations in Base on the Conformer Distribution. We previously found for calix[4]arenes that the conformer distribution is sensitively affected by metal cations in base.[4-7] It was shown that template metal cations such as Na^+ which strongly interact with calix[4]arenes suppress the rotation of phenyl units, giving rise to less-rotated conformers (such as cone and partial-cone) whereas nontemplate metal cations such as Cs^+ which scarcely interact with calix[4]arenes cannot suppress the rotation of phenyl units, giving rise to rotated conformers (such as 1,2- and 1,3-alternate). Here, we examined the influence of metal cations present in the used base on the conformer distribution of **1**Bu_3. The results are summarized in Table 3.

It is seen from Table 3 that *O*-butylation of **1**H_3 predominantly yields partial-cone-**1**Bu_3. For example, partial-cone-**1**Bu_3 was obtained quantitatively or nearly quantitatively in DMF in the presence of NaH, K_2CO_3, or Cs_2CO_3. The results suggest that being different from the metal template effect operative in *O*-alkylation of calix[4]arene, this reaction is scarcely affected by the metal template effect. Probably, the **1**H_3 ring is so flexible that the $O^- \cdots M^+$ interaction is not strong enough to hold three O^- anions in the same side of the ring. After much trial and error, we eventually found that cone-**1**Bu_3 results in a significant yield when the strong base containing K^+ (*e.g.*, *t*-BuOK and K but not K_2CO_3) is used. It is still difficult to explain why only this kind of base yields cone-**1**Bu_3. We will discuss this problem later again.

The reaction route from **1**H_3 to **1**Bu_3 can be illustrated as in Figure 3. In **1**HBu_2 the NMR signals for *t*-Bu groups appear as two singlet peaks at room temperature. If the inversion for the unmodified phenol unit is inhibited, *t*-Bu groups for **1**HBu_2, as well as the *O*-benzylated product of **1**HBu_2, should give three singlet peaks (see experimental section). This result indicates that ring inversion between partial-cone conformations rapidly takes place and the signal in the butoxy benzene unit should appear as an averaged peak. Therefore, the inversion for the unmodified phenol unit is allowed, as mentioned previously for calix[4]arenes.[6,7] Hence, the isolable conformational isomer does not exist in **1**H_2Bu. In **1**HBu_2, in contrast, cone-**1**HBu_2 and partial-cone-**1**HBu_2 can exist and cone-**1**Bu_3 results only from cone-**1**HBu_2 whereas partial-cone-**1**Bu_3 results from both cone-**1**HBu_2 and partial-cone-**1**HBu_2. In other words, cone-**1**Bu_3 cannot be found unless **1**HBu_2 contains the cone conformer. The HPLC analysis of **1**HBu_2 indicated that in the reaction mixture obtained in the presence of NaH, K_2CO_3, or Cs_2CO_3 a peak for partial-cone-**1**HBu_2 is detectable but a peak for cone-**1**HBu_2 is not. The result indicates that the conformation to yield partial-cone-**1**Bu_3 is already determined when the second butyl group enters and the path **1**H_2Bu $\longrightarrow$ cone-**1**HBu_2 $\longrightarrow$ partial-cone-**1**Bu_3 scarcely contributes to the formation of partial-cone-**1**Bu_3. In the reaction mixture obtained in the presence of *t*-BuOK or K, on the other hand, we could detect a small peak attributable to cone-**1**HBu_2. This suggests that the formation of cone-**1**Bu_3 should be rationalized in relation to the role of K^+ ion in the step from **1**H_2Bu to cone-**1**HBu_2. As described later in two-phase solvent extraction of alkali picrates, both cone-**1**Bu_3 and partial-cone-**1**Bu_3 show the extraction order of $K^+ > Cs^+ > Na^+ > Li^+$. Ex% for cone-**1**Bu_3 is higher for K^+ and Cs^+ whereas Ex% for partial-cone-**1**Bu_3 is higher for Na^+. This trend is in good agreement with the conformer distribution in Table 3: *i.e.*, partial-cone-**1**Bu_3 as a major product plus cone-**1**Bu_3 as a minor product result in the presence of Cs_2CO_3, K_2CO_3, *t*-BuOK, and K whereas only partial-cone-**1**Bu_3 results in the presence of NaH. The results imply that K^+ and Cs^+ favorably interact with three phenolic oxygens arranged in the same side whereas Na^+ favorably interacts with three phenolic oxygens across the ring. Provided that these interaction modes are extended to the reaction step from **1**H_2Bu to **1**HBu_2, the oxide anions will be held in the same side in the presence of K^+ or

Cs^+ whereas they will be placed to the opposite side in the presence of Na^+ (Figure 4). These conformational preferences well explain the final conformer distribution in **1**Bu_3.

Table 3. Influence of reaction conditions on the conformer distribution of **1**Bu_3[a]

Base (equiv.)	Solvent	Equiv. of *n*-BuI	Time /h	Distribution/% 1H_3	1H_2Bu	1HBu_2	1Bu_3 Cone	1Bu_3 Partial-cone
NaH(30)	DMF	30	5	0	0	0	0	100
NaH(3)	DMF	3	20	0	0	42[b]	0	58
NaH(3)	THF	3	24	100	0	0	0	0
Cs_2CO_3(20)	DMF	20	5	0	0	0	3	97
Cs_2CO_3(3)	DMF	3	20	0	0	55[b]	1	44
K_2CO_3(20)	DMF	20	20	0	0	0	1	99
t-BuOK(20)	DMF	20	20	0	0	0	24	76
t-BuOK(3)	DMF	3	20	4	17	18[c]	11	50
K(20)	DMF	20	5	47	14	19[c]	5	15

[a] Reaction temperature, 70 °C in DMF and reflux in THF.

[b] In HPLC analysis only partial-cone-**1**HBu_2 was detected.

[c] In HPLC analysis the small peak for cone-**1**HBu_2 was detected in addition to the large peak for partial cone-**1**HBu_2.

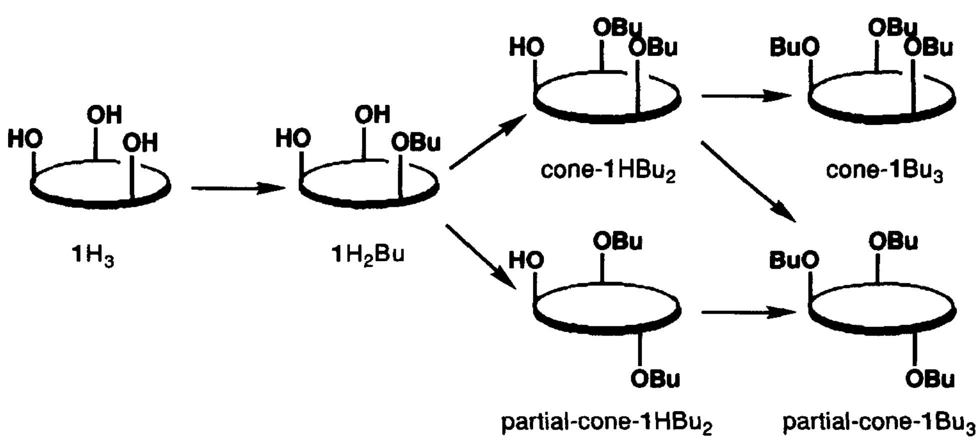


Figure 3. Reaction route from 1H_3 to 1Bu_3.

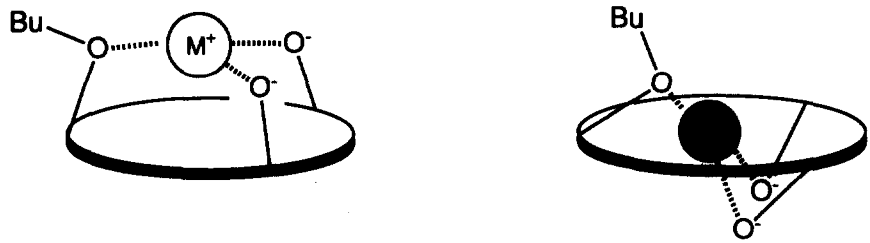


Figure 4. Interactions of $1H_2Bu$ with K^+ or Cs^+ to yield a cone (A) and of $1H_2Bu$ with Na^+ to y partial-cone (B).

Two-Phase Solvent Extraction and NMR Spectra of Metal Complexes. To estimate the selectivity of ionophoric cavities composed on homotrioxacalix[3]arene, we carried out two-phase sc extraction with conformationally-mobile $1Et_3$ and conformationally-immobile cone-$1Bu_3$ and partial-$1Bu_3$. As shown in Table 4, the cone isomers show K^+ selectivity, indicating that the size of the ionop cavity is comparable with that of K^+ ion. Although partial-cone-$1Bu_3$ also shows K^+ selectivity, the E lower than those for the cone isomers. To obtain further insights into the metal-binding mode we measur ^1H NMR spectra in the absence and the presence of potassium picrate (Figure 5). It is seen from Figure 5 t cone-$1Bu_3$ the δ values for the $ArOCH_2$ and ArH protons largely shift to lower magnetic field, supportii interaction between K^+ and the ethereal oxygens. In the absence of metal cations the $ArCH_2O$ meth protons appear as an AB pattern with a small δ difference (4.59 and 4.61 ppm). In the presence of K^+, (other hand, H_{ax} shifts to lower magnetic field (δ 4.81 ppm) and H_{eq} shifts to higher magnetic field (δ ppm).* In calix[4]arenes, it is established that Δδ between H_{ax} and H_{eq} is generally 0.9 ± 0.2 ppm for a s in the regular cone conformation and becomes smaller with the "flattening" of the phenyl unit.[15] Provide the concept can be also applied to homotrioxacalix[3]arenes, the phenyl units in cone-$1Bu_3$ are conside flattened in the absence of metal cations whereas they stand up to include K^+ in the cavity. We con however, that this assumption should be further confirmed by the X-ray studies and/or the computa studies. Since the δ values for the $ArCH_2O$ protons are strongly affected by the conformational chang difficult to judge if the $ArCH_2O$ oxygens contribute to the K^+ binding.

* H_{ax} and H_{eq} denote the $ArCH_2O$ methylene protons located near to and far from the benzene respectively.

Table 4. Percent extraction of alkali and ammonium picrates in CH_2Cl_2 at 25 °C[a]

Calixarene	Extractability (Ex%)				
	Li^+	Na^+	K^+	Cs^+	$n\text{-}BuNH_3^+$
1Et3	1.0	14.0	49.6	36.7	56.4
Cone-1Bu3	0.0	5.7	58.8	35.0	82.0
Partial-cone-1Bu3	0.0	11.9	34.9	23.6	31.5

[a] Organic phase (CH_2Cl_2, 5 ml) contains 1R3 (2.5 mM for alkali picrates and 3.5 mM for $n\text{-}BuNH_3^+$ picrate). Aqueous phase (5 ml) contains M^+Pic^- (0.25 mM), MOH (0.10 M), and MCl (0.50 M) for alkali picrates and $n\text{-}BuNH_3^+Pic^-$ (7.0×10^{-5} M) for $n\text{-}BuNH_3^+$.

In the partial-cone-1Bu3•K^+ complex, the $ArOCH_2$ protons in the two ordinary phenyl units shift to lower magnetic field (by 0.24 ppm) whereas those in the one inverted phenyl unit shift to higher magnetic field (by 0.54 ppm). This suggests that K^+ ion is mainly bound to the ArO oxygens in the two ordinary phenyl units and the *n*-butyl group in the inverted phenyl unit rotates into the cavity. Probably, this rotation is induced by steric repulsion between bound K^+ ion and the *tert*-butyl group in the inverted phenyl unit. In this complex the splitting pattern for the $ArCH_2O$ methylene protons is very complicated (basically, three pairs of doublets should appear) and the signals are partially overlapped with those for the $ArOCH_2$ methylenes. Hence, it is difficult to obtain useful information from the δ values for the $ArCH_2O$ protons.

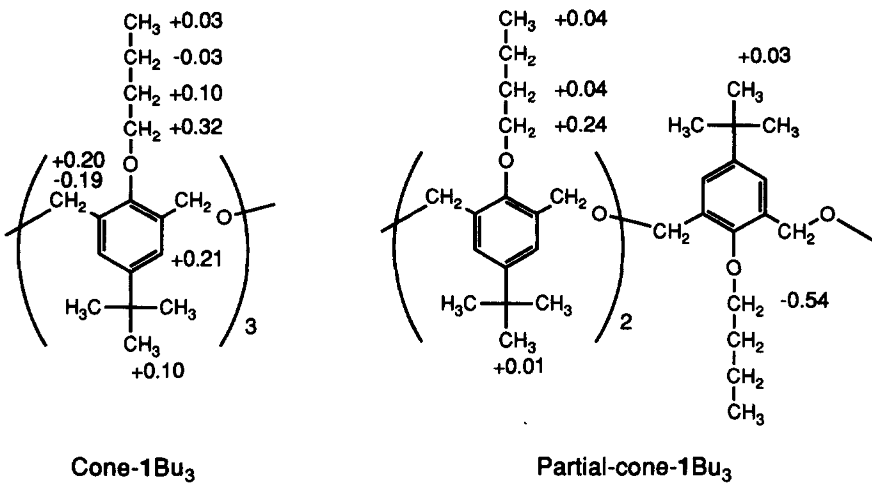


Figure 5. Chemical shift changes induced in the presence of K^+Pic^-: 250 MHz, $CDCl_3$:CD_3OD = 1:1 v/v, 25 °C, [1Bu3] = 3.5 mM, [K^+Pic^-] = 3.5 mM. + denotes the down-field shift and - denotes the up-field shift.

Two-Phase Solvent Extraction and NMR Spectra of Ammonium Complexes. It has been established that 18-crown-6 can strongly bind primary ammonium cations (RNH_3^+).[17] 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.[18] found that calix[6]aryl acetates with C_6 symmetry can bind RNH_3^+ whereas the binding to calix[4]aryl acetates occurs only weakly. The finding is rationalized on the same basis. It occurred to us that $1R_3$ (particularly, those with a cone conformation) with (averaged) C_3 symmetry might serve as an efficient receptor for RNH_3^+. As shown in Table 4, cone-$1Bu_3$ extracts n-$BuNH_3^+$ very efficiently whereas partial-cone-$1Bu_3$ does it slightly. Conformationally-mobile $1Et_3$ also binds n-$BuNH_3^+$ although the Ex% is somewhat lower than that of cone-$1Bu_3$. The ^1H NMR examination of the $1Et_3$ •n-$BuNH_3^+$ complex established that $1Et_3$ in the complex takes a cone conformation, indicating the importance of the three oxygens arranged in (averaged) C_3 symmetry. In such a sense, cone-$1Bu_3$ possesses an ideal ionophoric cavity pre-organized in (averaged) C_3 symmetry for the binding of n-$BuNH_3^+$.

Figure 6 shows chemical shift changes induced in the presence of n-$BuNH_3^+$. It is seen from Figure 6 that in cone-$1Bu_3$ the changes induced by n-$BuNH_3^+$ are very similar to those induced by K^+ (Figure 5). One can thus conclude that three hydrogen bonds are formed with three ArO oxygens arranged in (averaged) C_3 symmetry and three phenyl units stand up when the cavity includes n-$BuNH_3^+$. In partial-cone-$1Bu_3$ the down-field shift of $ArOCH_2$ protons in the ordinary phenyl units is also observed but the δ value of the $ArOCH_2$ protons in the inverted phenyl unit scarcely changes. Conceivably, two hydrogen bonds are formed with the two ArO oxygens and the steric crowding induced by the n-$BuNH_3^+$ is not so significant as to rotate the inverted phenyl unit.

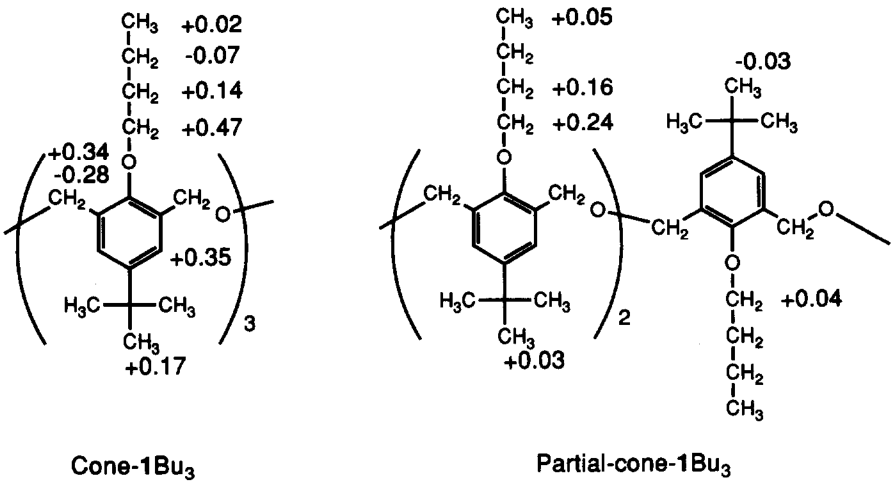


Figure 6. Chemical shift changes induced in the presence of n-$BuNH_3^+Pic^-$: 250 MHz, $CDCl_3$:CD_3CN = 1:1 v/v, 25 °C, [$1Bu_3$] = 3.5 mM, [n-$BuNH_3^+Pic^-$] = 3.5 mM. + denotes the down-field shift and - denotes the up-field shift.

Concluding Remarks

The molecular design of artificial receptors from calix[n]arenes has recently become a very active area of endeavor. In contrast, homotrioxacalix[3]arene has been left unutilized. This is probably because of the flexibility of the ring. In this paper we have demonstrated conformational equilibria, inhibition of interconversion between conformers, ion selectivity, *etc.* The results consistently suggest that homotrioxacalix[3]arene is a useful basic skeleton for the design of artificial receptors, particularly those with (averaged) C_3 symmetry. We believe that one can realize the various metal selectivities and even chiral recognition of ammonium cations by skillful modification of homotrioxacalix[3]arene. Our next research target is the design of super-uranophiles[19-22] from homotrioxacalix[3]arene.

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