of the silyl carbamate **25**, givine 26% of benzyl *N*-benzyl-*N*-formylcarbamate (**26**).

3-Methyllumiflavin (3.1×10^{-3} M), silyl amine **29** (3.1×10^{-3} M), CD_3CN, 20 min. ^1H NMR analysis indicated that 3-methyllumiflavin disappeared to give a substance characterized by its ^1H NMR spectrum to be *N*-[(trimethylsilyl)methyl]benzaldimine (**30**) and 4a-benzyl-4a,5-dihydro-3-methyllumiflavin (**15**) as major and minor products, respectively, and that other products of unknown identity had formed. ^1H NMR for **30**: 0.03 (s, 9 H, TMS), 3.37 (d, J = 1.3 Hz, 2 H, N-CH_2), 7.42 and 7.68 (m, 5 H, aromatic), 8.17 (t, J = 1.3 Hz, 1 H, benzylidene). NMR-tube irradiation of a nondegassed solution of 3-methyllumiflavin and **29** gave *N*-benzylformamide **31** (42%) and *N*-[(trimethylsilyl)-methyl]benzaldimine (**30**) (35%) in a 1:1 ratio.

3-Methyllumiflavin (3.0×10^{-3} M), *N*-benzyl-*N*-methylamine (**32**) (3.8×101^{-3} M), CD_3CN, 10 min. ^1H NMR analysis indicated that 3-methyllumiflavin disappeared to give a substance characterized by its ^1H NMR spectrum to be *N*-methylbenzaldimine (**33**) and 4a-benzyl-4a,5-dihydro-3-methyllumiflavin (**15**) as major and minor products, respectively. ^1H NMR for **33**: 3.43 (d, J = 1.6 Hz, 3 H, N-CH_3), 7.42 and 7.70 (m, 5 H, aromatic) 8.29 (q, J = 1.6 Hz, 1 H, benzylidene). NMR-tube irradiation of a nondegassed solution of 3-methyllumiflavin and *N*-benzyl-*N*-methylamine (**32**) gave 100% conversion to *N*-methylbenzaldimine (**33**).

3-Methylumiflavin (3.3×10^{-3} M), benzylamine **34** (4.0×10^{-3} M), CD_3CN, 15 min. ^1H NMR analysis indicated that the amount of 3-methyllumiflavin and benzylamine decreased, and that *N*-benzylbenzaldimine (**35**) was formed as the sole product. A similar NMR tube reaction on a nondegassed solution gave of 3-methyllumiflavin and benzylamine gave complete conversion to *N*-benzylbenzaldimine (**35**).

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Supplementary Material Available: ^{13}C and ^1H NMR spectra for compounds **12**, **12-d$_2$**, **22**, **25**, **26**, **27**, and **28** (7 pages). Ordering information is given on any current masthead page.

Conformations and Structures of Tetra-*O*-alkyl-*p*-*tert*-butylcalix[4]arenes. How Is the Conformation of Calix[4]arenes Immobilized?

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p-*tert*-Butylcalix[4]arene ($1H_4$) was tetra-*O*-alkylated with alkyl halogens (RX: R = Me, Et, *n*-Pr, and *n*-Bu) in the presence of NaH as base, and the products ($1R_4$) were analyzed by HPLC and ^1H NMR spectroscopy. It was found that (i) ring inversion is suppressed by R greater than Et, (ii) the final conformer distribution in $1Pr_4$ and $1Bu_4$ is governed by the kinetic control, the main products being "cone" and "partial cone" (approximately in a 1:1 ratio), (iii) $1Me_4$ mostly exists as a thermodynamically stable partial-cone conformer, and (iv) $1Et_4$ shows an intermediary behavior between $1Me_4$ and $1Pr_4$: it mostly exists as a partial-cone conformer but slowly isomerizes to a "1,2-alternate" conformer at high temperature. The X-ray crystallographic analysis of partial-cone-$1Et_4$ was investigated. To clarify where and how the conformation of $1R_4$ is immobilized, we alkylated $1H_4$ in a stepwise manner. It was shown that when NaH is used as base, the conformation of $1Et_4$ is determined at the fourth ethylation step ($1HEt_3 \rightarrow 1Et_4$), whereas the conformation of $1Pr_4$ is determined at the third propylation step ($1H_2Pr_2 \rightarrow 1HPr_3$). The conformer distribution was significantly affected by alkali and alkaline earth metal cations used as base; in particular, it is worthy of mentioning that (i) when Cs_2CO_3 is used as base, 1,2-alternate-$1Pr_4$ is formed in addition to partial-cone-$1Pr_4$ and (ii) when $Ba(OH)_2$ is used as base, cone-$1Pr_4$ is yielded in 100% selectivity. On the basis of these studies, we discuss how the conformation of calix[4]arenes is immobilized.

Calix[4]arenes are cyclic oligomers made up from benzene units just as cyclodextrins are made up from glucose units. Although these two macrocyclic compounds have a similar cavity-shaped architecture, there exists a basic difference: the cyclodextrin cavity is conformationally fixed, whereas the conformational freedom still remains in the calixarene cavity.[1-7] It is known that unmodified *p*-*tert*-butylcalix[4]arene ($1H_4$) adopts a cone conformation because of strong hydrogen-bonding interactions among the OH groups, whereas introduction of alkyl or acyl substituents into the OH groups suppresses the conformational freedom because of steric hindrance (i.e., inhibition of the oxygen-through-the-annulus rotation) and results in conformational isomers.[1-13] However, a relation (if any) between the substituent effect and the conformer distribution has never been studied systemat-

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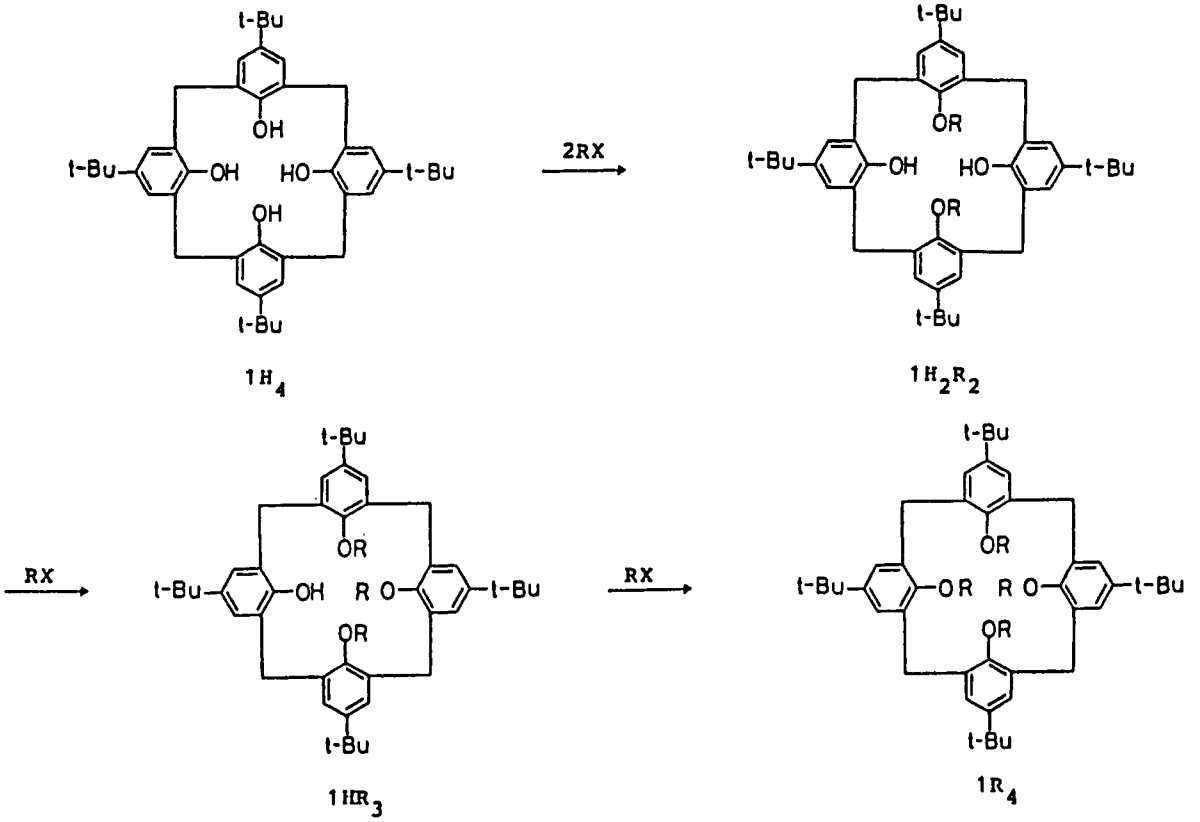
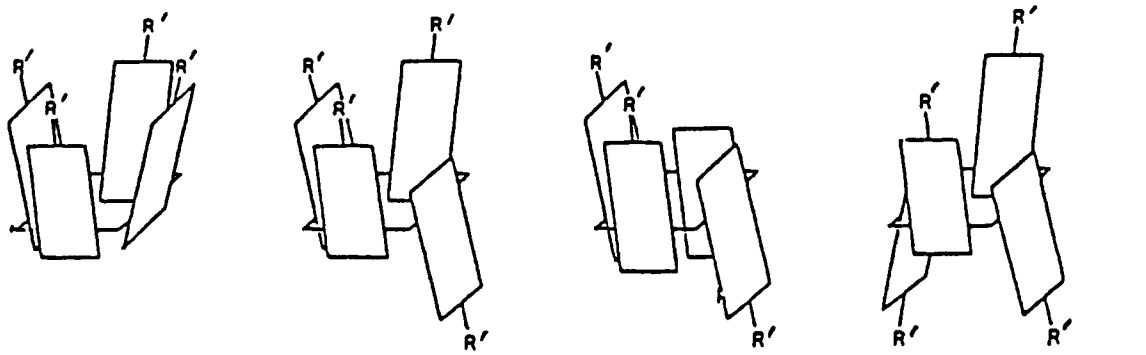


Chart I. Conformational Isomers of $1R_4$



ically. To the best of our knowledge, considerable confusion still exists in the conformer distribution. For example, tetra-O-propylation results in "cone" and "partial cone" in a 1:1 ratio[12] and tetra-O-acetylation results in partial cone and "1,3-alternate",[8] whereas tetra-*O*-(ethoxycarbonyl)methylation results in cone.[14-17] To investigate the possible relation between the substituent effect and the conformer distribution, we alkylated $1H_4$ with alkyl halogens (from MeX to *n*-BuX) and carefully analyzed the tetra-O-alkylation products ($1R_4$) with HPLC and ^1H NMR spectroscopy. In addition, we carried out stepwise alkylation, analyzing the conformer distribution at each step. On the basis of these experimental results, we report the conformations and structures of these conformational isomers and discuss how the conformation of $1H_4$ is immobilized by O-alkylation.

Results and Discussion

Tetra-O-alkylation. Basically, there can exist four different conformers in calix[4]arenes: cone, partial cone, 1,2-alternate, and 1,3-alternate.[1-6] The structures of these conformers can be easily distinguished by the characteristic ^1H NMR patterns arising from the $ArCH_2Ar$ methylene protons: judging from symmetry of each conformer, cone, partial cone, 1,2-alternate, and 1,3-alternate will appear as a pair of doublets, two pairs of doublets, one singlet and a pair of doublets, and one singlet, respectively (Chart I).[3,4,9]

Compound $1H_4$ in THF–DMF (10:1 v/v) mixed solvent was treated with oil-dispersed NaH and then allowed to react with alkyl halogens (RX). The conformer distribution of tetra-O-alkylation products was determined by an HPLC method. In a separate study the conformers were

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Table I. Distribution of Conformational Isomers for Tetra-*O*-alkylation of $1H_4$ in the Presence of NaH[a]

RX	product $1R_4$	yield of $1R_4$[b] (%)	yield of isomer (%) cone	partial cone	1,3-alternate
MeI	$1Me_4$	100	trace[c]	92[c]	trace[c]
EtBr	$1Et_4$	100	0–14[e]	86–100[e]	0–1[e]
EtI	$1Et_4$	100	0–11[e]	89–100[e]	0–1[e]
n-PrBr	$1Pr_4$	100	42	55	3
n-PrBr	*d*	100	31	55	14
n-PrI	$1Pr_4$	100	15	81	4
n-BuBr	$1Bu_4$	100	50	47	3

[a] THF–DMF (10:1 v/v), 2 h at the reflux temperature. [b] Determined by an HPLC method. [c] The ^1H NMR spectrum ($CDCl_3$, −25 °C) indicated that $1Me_4$ consists of cone (2%), partial cone (92%), 1,2-alternate (5%), and 1,3-alternate (1%). [d] Calix[4]arene was used instead of $1H_4$. [e] The yields of isomers were affected by the reaction time (see text). A trace amount of 1,3-alternate-$1Et_4$ was included.

separated by a preparative TLC method and the structures were identified by the ^1H NMR spectra.[3,4,9] By using these $1R_4$'s as authentic samples we determined the yields of these conformers. When the yields of the conformers were lower than 10%, the isolation was very difficult. In such cases we estimated the yields directly from the ^1H NMR spectra. The results are summarized in Table I.

It is known that the methyl group is not bulky enough to suppress the oxygen-through-the-annulus rotation: the methoxy group can penetrate through the cavity of calix[4]arenes.[8,12] In HPLC analysis (mobile phase, chloroform–methanol (1:2 v/v)) $1Me_4$ appeared as a single peak. In 400-MHz ^1H NMR spectroscopy ($CDCl_3$, −25 °C) it showed two pairs of doublets for the $ArCH_2Ar$ protons (although there exist additional, weak peaks assignable to other conformers):[18a] one pair showed a large difference in the chemical shifts (δ 3.17 and 4.18, J = 12.82 Hz), which were assigned to H_{exo} and H_{endo} in the $ArCH_2Ar$ protons flanked by two syn phenol units. The other pair showed a relatively small difference in the chemical shifts (δ 3.79 and 3.84, J = 15.02 Hz), which were assigned to the $ArCH_2Ar$ protons flanked by two anti phenol units. As reported by Gutsche et al. previously,[3-5,9] this split pattern is commensurate with a partial-cone conformation.[18a] These peaks coalesced at about 60 °C. The findings indicate that, basically, $1Me_4$ is interconvertible among a few conformational isomers but predominantly exists as a partial-cone conformer (at least in $CDCl_3$).[19]

In contrast, $1Pr_4$ and $1Bu_4$ prepared by the reaction of $1H_4$ with RBr resulted in a cone and a partial-cone conformer approximately in a 1:1 ratio: for the $ArCH_2Ar$ methylene protons the cone conformer features a pair of doublets whereas the partial-cone conformer features two pairs of doublets (see Figure 1 in ref 12). Interestingly, we found that the reaction mixture contains a small amount of 1,3-alternate conformer. These conformers are

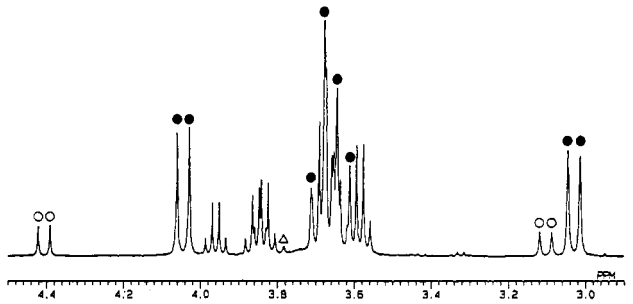


Figure 1. Partial ^1H NMR spectrum for the $ArCH_2Ar$ methylene protons in $1Et_4$ (the product was recovered after 2 h; $CDCl_3$, 25 °C): ○ cone, ● partial cone, △ 1,3-alternate. Other quartets are assigned to the OCH_2 methylene protons.

characterized by a single peak (integral intensity 8 H) for the $ArCH_2Ar$ protons (e.g., δ 3.80 for 1,3-alternate-$1Pr_4$). The ^1H NMR spectra were unaffected by the measurement temperature (−20 to +60 °C). The conformers were heated in 1,1,2,2-tetrachloroethane at the reflux temperature (147 °C) for 12 h, but isomerization of these conformers did not take place (confirmed by HPLC analysis). The same result was obtained when the solution was refluxed for 3 days. Thus, *n*-propyl and *n*-butyl groups are bulky enough to inhibit the oxygen-through-the-annulus rotation and therefore tetra-O-propylation and tetra-O-butylation result in conformationally immobile calix[4]arenes.

When *n*-PrI was used instead of *n*-PrBr, the yield of partial-cone-$1Pr_4$ was increased up to 81%. The result suggests that the reaction center in the partial-cone conformer is more reactive toward bulky *n*-PrI. Also interesting is the effect of the *p-tert*-butyl groups. When calix[4]arene was used instead of $1H_4$ (the alkylation reagent is *n*-PrBr), the yield of cone-$1Pr_4$ was decreased and that of 1,3-alternate was increased. Provided that the reactivity between the cone-$1H_4$ series and the cone-calix[4]arene series is the same, then the change in the yields is ascribed to the reactivity difference in other conformations. In 1,3-alternate-$1Pr_4$, the calix[4]arene edge is composed of two propyl groups and two *tert*-butyl groups. In the 1,3-alternate conformation of tetra-O-propylated calix[4]arene, on the other hand, it is composed of two propyl groups and two hydrogens. Thus, the steric crowding should be reduced. According to the computational study of conformational isomers of calix[4]arenes with AMBER,[18b] the E_{total} value for $1Me_4$ is in the order of 1,3-alternate < partial cone < cone < 1,2-alternate and the difference between 1,3-alternate and cone is 6.4 kcal mol^{-1}. When the *p-tert*-butyl groups are replaced with the methyl groups (the calculation for *p*-H is not reported[18b]), the differences are 5.4–9.3 kcal mol^{-1}.[18b] This implies that replacement of the *p-tert*-butyl groups with methyl groups does not affect the E_{total} difference between 1,3-alternate and cone. We calculated the final steric energies (E_{str}) by using MM2PP.[19] The E_{str} value for $1Me_4$ showed the same order as that of the E_{total} (1,3-alternate (=3.92 kcal mol^{-1}) < partial cone (=5.64 kcal mol^{-1}) < cone (=6.76 kcal mol^{-1}) < 1.2-alternative (=9.96 kcal mol^{-1}); the difference between 1,3-alternate and cone is 2.84 kcal mol^{-1}). In contrast, the order of the E_{str} values for tetra-O-methylated calix[4]arene is quite different (partial cone (=−1.60 kcal mol^{-1}) < 1.3-alternate (=−1.00 kcal mol^{-1}) < 1.2-alternate (=3.46 kcal mol^{-1}) < cone (=4.60 kcal mol^{-1})); the difference between 1,3-alternate and cone is 5.60 kcal mol^{-1}). These computational studies indicate that replacement of the *tert*-butyl groups with the methyl groups scarcely decreases the steric crowding in the 1,3-alternate conformer whereas replacement with hydrogens can greatly decrease the steric crowding and stabilize the

(18) (a) As reported by Gutsche et al.,[5] we also observed additional peaks other than partial-cone-$1Me_4$. This may be explained by an equilibrium between the "inside" form and the "outside" form,[5] although the theoretical calculation with MM2 gives the "inside" form an energy that is 5.0 kcal mol^{-1} higher than the energy of the "outside" form.[18b] More recently, Reinhoudt et al.[18c] assigned these peaks to the other three isomers of $1Me_4$. The conformer distribution we determined on the basis of ^1H NMR spectroscopy is recorded in footnote c to Table I. (b) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165. (c) Reinhoudt, D. N. Private communication.

(19) We recently found that partial-cone-$1Me_4$ is partly isomerized to cone-$1Me_4$ in polar solvents: Shinkai, S.; Iwamoto, K.; Araki, K.; Matsuda, T. *Chem. Lett.* **1990**, 1263. The shift in the equilibrium was accounted for by the difference in their dipole moments.

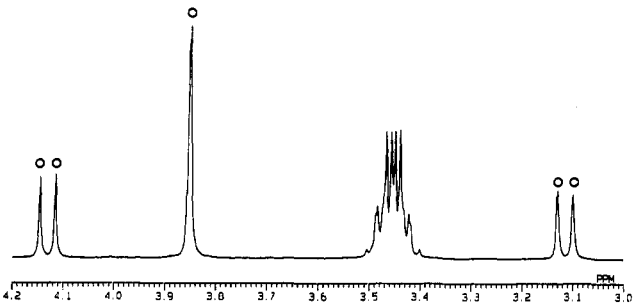


Figure 2. Partial ^1H NMR spectra for the $ArCH_2Ar$ methylene protons in 1,2-alternate-$1Et_4$ (the split pattern consists of a pair of doublets and a singlet; $CDCl_3$, 25 °C).

1,3-alternate conformer. More precisely, the E_{str} value for the cone is changed only to a smaller extent by replacement of the *tert*-butyl groups with hydrogens whereas those for other three conformers are greatly decreased. This suggests that the E_{str} values are basically associated with the steric crowding on the lower rim.

Tetra-O-ethylation of $1H_4$ with EtI in refluxing THF (67 °C) yielded three isomers detectable by HPLC. The product (analyzed after 2 h) contained partial-cone-$1Et_4$ (89%), cone-$1Et_4$ (11%), and 1,3-alternate-$1Et_4$ (less than 1%). The ^1H NMR spectrum of the mixture is shown in Figure 1.[20] When the reaction was continued for 4 h, the product contained partial-cone-$1Et_4$ (96%), cone-$1Et_4$ (4%), and 1,3-alternate-$1Et_4$ (less than 1%). After 1 day, only partial-cone-$1Et_4$ was detected. This indicates that the ethoxy group can rotate through the ring and isomerization from cone to partial cone takes place. This implies that $1Et_4$ possesses an intermediary character between conformationally mobile $1Me_4$ and conformationally immobile $1Pr_4$. In conclusion, tetra-O-methylation, which results in partial cone, is thermodynamically controlled whereas tetra-O-propylation and tetra-O-butylation, which result in cones and partial cones, are kinetically controlled. In tetra-O-ethylation, the initial products are kinetically controlled, but they are slowly isomerized under the thermodynamic control.

To accelerate the thermal isomerization we refluxed the conformer mixture of $1Et_4$ in 1,1,2,2-tetrachloroethane (bp 147 °C). The ^1H NMR spectrum measured after 2 h showed that, surprisingly, *the product contains 1,2-alternate-$1Et_4$* (45%) in addition to partial-cone-$1Et_4$ (49%), cone-$1Et_4$ (6%), and 1,3-alternate-$1Et_4$ (less than 1%). We isolated 1,2-alternate-$1Et_4$ by a preparative TLC method and identified it by ^1H NMR spectroscopy (Figure 2). A singlet (3.85 ppm, 4 H) and a pair of doublets (3.10 and 4.17 ppm, J = 12.2 Hz, 4 H) are seen from Figure 3. This split pattern for the $ArCH_2Ar$ protons is exactly commensurate with a 1,2-alternate conformation. We refluxed partial-cone-$1Et_4$ in THF, but isomerization to 1,2-alternate-$1Et_4$ did not easily take place. This suggests that 1,2-alternate-$1Et_4$ is the conformer that appears only in the high-temperature region. The reason in not understood well (the theoretical calculation for $1Et_4$ is not reported).

Stepwise O-Alkylation. Through the foregoing tetra-O-alkylation studies, a few questions arise: (i) why are the cone and the partial-cone conformer formed predominantly, and (ii) where and how is the conformation of these conformers immobilized? To answer these questions, we alkylated $1H_4$ in a stepwise manner and estimated the conformer distribution at each step. The results are summarized in Table II.

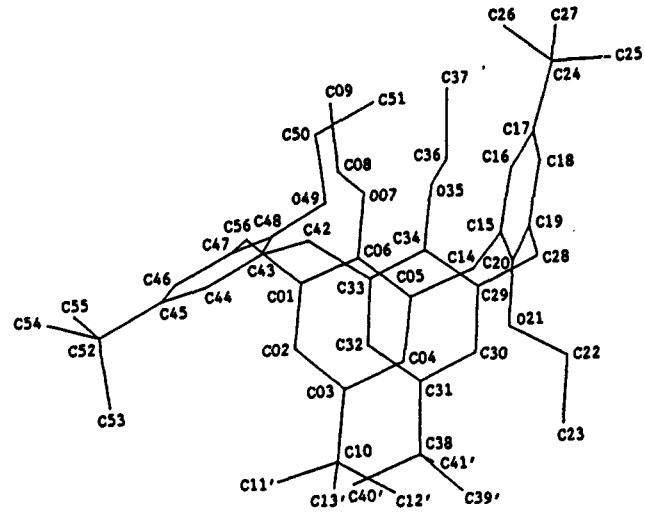


Figure 3. X-ray structure of partial-cone-$1Et_4$.

Table II. Distribution of Conformational Isomers in Stepwise O-Alkylation in the Presence of NaH

starting material	RX	product yield of $1R_4$[a]		yield of isomer (%)		
		$1R_4$	%	cone	partial cone	1,3-alternate
$1H_4$	EtI	$1Et_4$	100	0–11[b]	89–100[b]	0–1[b]
$1H_2Et_2$	EtI	$1Et_4$	100	0–11[b]	89–100[b]	0–1[b]
cone-$1HEt_3$	EtI	$1Et_4$	100	0–10[b]	90–100[b]	0–1[b]
$1H_4$	*n*-PrBr	$1Pr_4$	100	42	55	3
$1H_2Pr_2$	*n*-PrBr	$1Pr_4$	100	45	52	3
cone-$1HPr_3$	*n*-PrBr	$1Pr_4$	100	100	0	0
partial-cone-$1HPr_3$	*n*-PrBr	$1Pr_4$	100	0	93	7

[a] Determined by an HPLC method. [b] The yields of isomers were affected by the reaction time.

The ^1H NMR spectrum of a 1,3-dipropylated compound ($1H_2Pr_2$) ($CDCl_3$, 25 °C) showed a pair of doublets for the $ArCH_2Ar$ protons at 3.29 and 4.25 ppm and was almost unaffected by the measurement temperature (−20 to +60 °C). This indicates that $1H_2Pr_2$ exists in a stable cone conformation. When this compound was treated with *n*-PrBr in the presence of NaH, the product ($1Pr_4$) was a mixture of a cone and a partial-cone conformer (45:52; a small amount of 1,3-alternate-$1Pr_4$ was also detected). This ratio is almost equal to that obtained in tetra-O-propylation of $1H_4$. Thus, one can conclude that the conformation is not yet determined in the stage of $1H_2Pr_2$ but it just remains in a thermodynamically stable single conformation.

To start the O-propylation reaction from the next step we synthesized a tri-O-propylated compound ($1HPr_3$). The product obtained by the reaction of $1H_2Pr_2$ and *n*-PrBr in the presence of NaH was found to be a mixture of two conformers by HPLC. They were isolated by a preparative TLC method and identified to be a cone and a partial-cone conformer of $1HPr_3$ by ^1H NMR spectroscopy (see Experimental Section). There exist two possible structures (HO-inversed and PrO-inversed) in partial-cone-$1HPr_3$. In the ^1H NMR spectrum ($CDCl_3$, 25 °C) a triplet for the CH_3 protons (integral intensity 3 H) appeared at −0.40 ppm. It is known that in ether derivatives of partial-cone calix[4]arenes the alkyl protons in the inversed phenol unit appear at an unusually high magnetic field.[21] Thus, the

(20) The single peak at 3.78 ppm can be assigned to the $ArCH_2Ar$ protons in 1,3-alternate-$1Et_4$ because (i) the peaks assignable to CH_3 and ArH in 1,3-alternate-$1Et_4$ are also observed in reasonable integral intensities and (ii) the single peak for the $ArCH_2Ar$ protons in 1,3-alternate-$1Pr_4$ appears at 3.80 ppm.

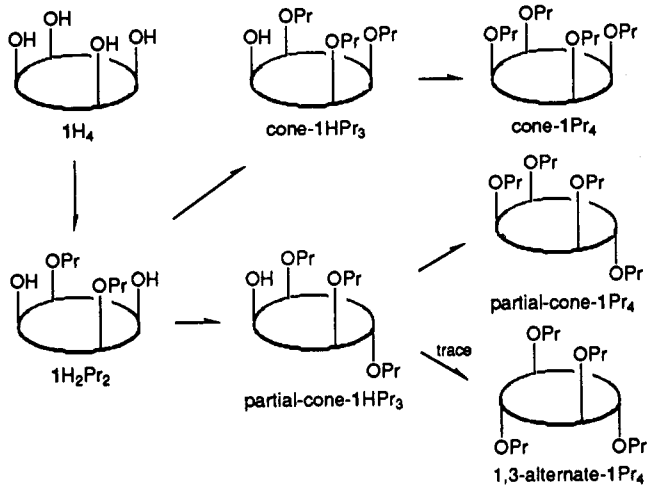
Chart II

HO-inversed partial-cone-1HPr$_3$ ($1H^{\alpha}Pr^{\beta}Pr^{\beta}Pr^{\beta}$)[a]

PrO-inversed partial-cone-1HPr$_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$)[a]

[a] This nomenclature for calixarene conformers, like that for porphyrin atropisomers, was suggested by the reviewer of this paper.

Scheme I



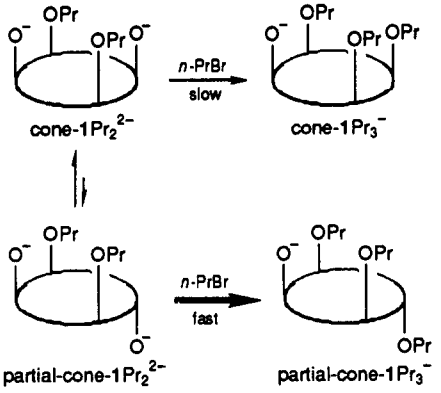
finding supports the view that partial-cone-1HPr$_3$ isolated from the reaction mixture is a PrO-inversed partial cone ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$; Chart II).

To confirm if these conformers isomerize under the conditions similar to those for tetra-O-propylation, we heated them in refluxing THF for 6 h. HPLC analysis established that neither cone-1HPr$_3$ nor partial-cone-1HPr$_3$ isomerizes. These results show that in 1HPr$_3$ the oxygen-through-the-annules rotation is inhibited.[21a] We alkylated cone- and partial-cone-1HPr$_3$ with *n*-PrBr in the presence of NaH. As expected, only cone-1Pr$_4$ was yielded from cone-1HPr$_3$. From partial-cone-1HPr$_3$, on the other hand, 93% of partial-cone-1Pr$_4$ and 7% of 1,3-alternate-1Pr$_4$ were obtained. The result indicates that 1,3-alternate-1Pr$_4$ is formed by the rotation of the OH group in partial-cone-1HPr$_3$ followed by O-propylation of the OH group. The foregoing results can be summarized as in Scheme I; that is, when NaH is used as base, the conformer distribution in 1Pr$_4$ is mostly determined in the third O-propylation step and interconversion between cone and partial cone scarcely occurs in the fourth O-propylation step.[21b]

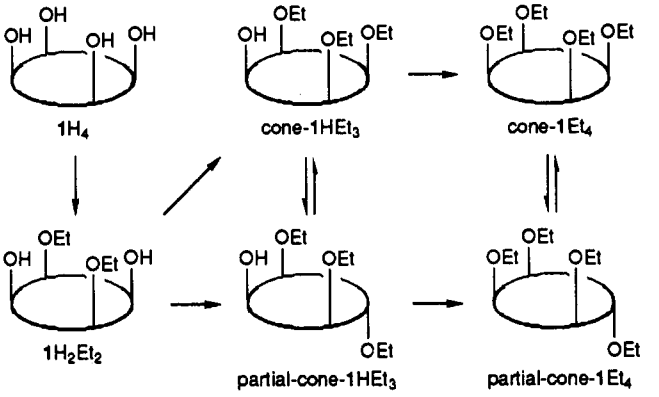
As mentioned above, 1H$_2$Pr$_2$ exists in a cone conformer in $CDCl_3$. This is also the case in THF-d_8. The ^{1}H NMR study of a disodium salt of 1H$_2$Pr$_2$ (i.e., 1Pr$_2^{2-}$) established that 1Pr$_2^{2-}$ also adopts a cone conformation because the ArCH$_2$Ar protons appear as a pair of doublets in THF-d_8 (δ 4.25 ppm for H$_{exo}$ and 3.29 ppm for H$_{endo}$, J = 12.82 Hz). Then, how is partial-cone-1HPr$_3$ formed from cone-1Pr$_2^{2-}$? This paradox is rationalized in terms of a compensation relationship between equilibrium and kinetics (Scheme II).

(21) (a) Although the rotation of the Pr group is inhibited, the rotation of the OH group is still allowed. This is evidenced by the fact that the reaction of cone-1HPr$_3$ and *n*-PrBr in DMF at 70 °C yielded partial-cone-1Pr$_4$ in 100% selectivity. (b) However, this conclusion is limited to O-alkylation in the presence of NaH. Na^+ ion acts as a template metal ion to suppress the rotation of the OH group.

Scheme II



Scheme III



As partial-cone-1Pr$_2^{2-}$ is not detected by ^{1}H NMR spectroscopy, the equilibrium between cone and partial cone is inclined to cone. Instead, the reactivity of partial-cone-1Pr$_2^{2-}$ should be much higher than that of cone-1Pr$_2^{2-}$. As mentioned above, partial-cone-1HPr$_3$ isolated from the reaction mixture is a PrO-inversed one. This implies that among two oxide anions in partial-cone-1Pr$_2^{2-}$ the oxide anion in the inversed phenol unit is more reactive than that in the partial cone moiety. As a result, the lower concentration is compensated by the higher reactivity in the reaction with *n*-PrBr. The oxide anion in the partial-cone moiety is trapped on the narrow, sterically crowded lower rim whereas the oxide anion in the inversed phenol unit resides on the open upper rim. Probably, the higher reactivity of the oxide anion in the inversed phenol unit is accounted for by the reduced steric crowding around the reaction center. This also explains the low reactivity of two oxide anions in cone-1Pr$_2^{2-}$ that are both placed on the narrow lower rim.

The ^{1}H NMR spectrum of 1,3-diethylated compound 1H$_2$Et$_2$ ($CDCl_3$, 25 °C) showed a pair of doublets for the ArCH$_2$Ar protons (3.30 and 4.33 ppm) and was almost unaffected by the measurement temperature (−20 to +60 °C). This indicates that 1H$_2$Et$_2$ also adopts a cone conformation. However, the reaction of 1H$_2$Et$_2$ and EtI in the presence of NaH predominantly yielded partial-cone-1Et$_4$. This means that the conformation of 1Et$_4$ is not yet set in the stage of 1H$_2$Et$_2$. We synthesized 1HEt$_3$ with a cone conformation by the reaction of 1H$_4$ and EtI in the presence of Ba(OH)$_2$·8H$_2$O and BaO (vide post). Cone-1HEt$_3$ was conformationally stable at room temperature but slowly isomerized when heated in refluxing THF in the presence of NaH (1.2-fold of 1HEt$_3$; the main product was identified to be partial-cone-1HEt$_3$ from the ^{1}H NMR spectrum). Thus, these conformers are still interconvertible in the stage of 1HEt$_3$. In fact, when cone-1HEt$_3$ was alkylated with EtI in the presence of NaH, the main

Table III. Distribution of Conformational Isomers in Tetra-O-propylation of $1H_4$ with *n*-PrBr in the Presence of Alkali Carbonates and $Ba(OH)_2$[a]

base (equiv to $1H_4$)	time (h)	yield (%)	yield of isomer (%) cone	partial cone	alternate 1,2	alternate 1,3
NaH[b] (16)	1	100	42	55	0	3
Na_2CO_3 (40)	78	0	0	0	0	0
K_2CO_3 (40)	78	0	0	0	0	0
Cs_2CO_3 (10)	78	45	0	24	9	67
Cs_2CO_3 (40)	3	100	0	34	9	57
Cs_2CO_3 (80)	2	100	0	35	20	45
$Ba(OH)_2 \cdot 8H_2O$ (3) + BaO (5.8)	70	6	100	0	0	0
$Ba(OH)_2 \cdot 8H_2O$ (3)[c] + BaO (5.8)	3	100[c]	100[d]	0	0	0

[a] DMF, 70 °C. [b] THF, 67 °C. [c] 30 °C. [d] The yield of $1HPr_3$.

product was partial-cone-$1Et_4$ (Table II); that is, the conformer distribution is the same as that for tetra-O-ethylation of $1H_4$. The result is similar to the formation of partial-cone-$1HPr_3$ from cone-$1Pr_2^{2-}$. This implies that the conformer distribution in $1Et_4$ is determined in the fourth O-ethylation step or later than this step (that is, through cone–partial-cone interconversion of $1Et_4$; Scheme III).

Metal Template Effects on the Conformer Distribution. In tetra-O-alkylation of $1H_4$ described above, we used NaH as base for abstracting protons from the OH groups. Here, a question arises if the conformer distribution may be changed when other bases are used. The conformer distribution would be affected by alkali metal cations if they act as template metals in the step where the conformation is immobilized.

We used alkali carbonates as base because Na^+, K^+, and Cs^+ salts are commercially available. The results are summarized in Table III. The reaction of $1H_4$ and *n*-PrBr in DMF in the presence of Na_2CO_3 or K_2CO_3 did not yield $1Pr_4$ even in the presence of excess *n*-PrBr. The product recovered from these reaction systems was identified to be $1H_2Pr_2$ (yield 79%). Compounds $1H_2R_2$ (e.g., $1H_2Me_2$) have been synthesized by the reaction of $1H_4$ and diazomethane.[8,22] So, this is a new, convenient method for the selective synthesis of $1H_2R_2$.[23] In the presence of Cs_2CO_3, on the other hand, the reaction proceeded smoothly. HPLC analysis of the reaction products established that (i) the main products are partial-cone-$1Pr_4$ and 1,3-alternate-$1Pr_4$, (ii) the yield of 1,3-alternate-$1Pr_4$ is higher by 1.7–2.8-fold than that of partial-cone-$1Pr_4$, and (iii) the yield of partial-cone-$1Pr_4$ is increased with increasing Cs_2CO_3 concentration. As described above, the conformation is apparently immobilized in the step from $1H_2Pr_2$ to $1HPr_3$ when NaH is used as base (Scheme I). We treated cone-$1HPr_3$ with *n*-PrBr in DMF in the presence of Cs_2CO_3. We recovered partial-cone-$1Pr_4$ in 100% selectivity. The result implies that the OH group can still rotate across the calix[4]arene ring even in $1HPr_3$; that is, the retention of the conformation from $1HPr_3$ to $1Pr_4$ observed for the O-alkylation reaction in the presence of NaH is strongly subjected to the metal (Na^+) template effect. The facile rotation of the OH group in $1HPr_3$ in the presence of Cs_2CO_3 suggests that 1,3-alternate-$1Pr_4$ results from PrO-inversed partial-cone-$1HPr_3$ ($1H^{\alpha}Pr^{\alpha}Pr^{\beta}Pr^{\alpha}$). The yield of 1,3-alternate-$1Pr_4$ is decreased with increasing Cs_2CO_3 concentration. Although this reason is not clarified yet, we consider that the weak metal (Cs^+) template effect operates on the O-alkylation of partial-cone-$1HPr_3$ so as to retain the partial cone conformation.

Table IV. Crystal Data

chemical formula	$C_{52}H_{72}O_4$
fw	761.14
crystal system	monoclinic
space group	$P2_1/c$
cell dimensions	a = 19.805 (13) Å b = 12.220 (2) Å c = 20.233 (5) Å β = 100.55 (1)°
no. of formula units in the unit cell	4
D_c (g cm^{-3})	1.050
R (%)	14.3

Interestingly, we isolated 1,2-alternate-$1Pr_4$ in 9–20% yields. Although 1,2-alternate-$1Et_4$ is formed through thermal isomerization of partial-cone-$1Et_4$, 1,2-alternate-$1R_4$ has never been synthesized by direct O-alkylation of $1H_4$.[24] So, this is the first example for the synthesis of a 1,2-alternate conformer from $1H_4$. At present, it is not clear yet how 1,2-alternate-$1Pr_4$ is formed. As shown in Scheme I, if two PrO groups occupy a syn position, 1,2-alternate-$1Pr_4$ cannot be formed. It results only from $1H_2Pr_2$ with anti PrO groups. Conceivably, the reaction route is quite different from that in Scheme I.

X-ray Crystallographic Studies. To obtain further insights into the structures of conformational isomers, we carried out X-ray crystallographic studies of $1Et_4$. Although X-ray crystallographic studies of cone-shaped calix[4]arenes have frequently been reported,[25-27] the study of calix[4]arene conformers other than cone has been very limited. Bott et al.[28] found that the conformation of $1Me_4$ is modified either to 1,2-alternate or to 1,3-alternate through complexations with aluminum alkyl compounds. More recently, Grootenhuis et al.[18b] reported the crystal structure of partial-cone-$1Me_4$. We could not isolate good crystals from 1,2-alternate-$1Et_4$.[29] Instead, we could isolate single crystals of partial-cone-$1Et_4$. The crystal data are summarized in Table IV. The crystal system (monoclinic, space group $P2_1/c$) is similar to that of partial-cone-$1Me_4$ (monoclinic, space group $P2_1/a$).[18b] The stereoscopic view is illustrated in Figure 3. Two *tert*-butyl groups (C11–C13 and C39–C41) show a positional disorder in a 7:3 ratio (expressed with ′ and ″ in Tables V and VI of supple-

(22) Reinhoudt, D. N.; Dijikstra, R. J.; in't Veld, P. J. A.; Bugge, K. E.; Harkema, S.; Ungaro, R.; Ghidini, E. *J. Am. Chem. Soc.* **1987**, *109*, 4761.

(23) The similar method ($1H_4$ plus methyl *p*-toluenesulfonate in acetone in the presence of K_2CO_3) was recently reported: Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K. E.; Reinhoudt, D. N.; Herkema, S.; Ungaro, R.; Ugozzli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567. More recently, $1H_2Me_2$ was synthesized by the reaction of calix[4]arene and MeI in the presence of K_2CO_3: No, K.; Hong, M. *J. Chem. Soc., Chem. Commun.* **1990**, 572.

(24) Gutsche describes in his book (page 107 in ref 5) that their group isolated the tetra-*N,N*-dimethylthioureido derivative that assumed the 1,2-alternate conformation, but further characterization is not published.

(25) (a) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005. (b) Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1773. (c) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiani, P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 197.

(26) (a) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. J. *J. Chem. Soc., Chem. Commun.* **1985**, 388. (b) Ferguson, G.; Kaitner, B.; McKervery, M. A.; Seward, E. M. *Ibid.* **1987**, 584. (c) McKervery, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B. L. *J. Org. Chem.* **1986**, *51*, 3581.

(27) (a) Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 1709. (b) *Ibid.* **1988**, *110*, 610. (c) Coleman, A. W.; Bott, S. G.; Morley, S. D.; Means, C. M.; Robinson, K. D.; Zhang, H.; Atwood, J. L. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1361.

(28) Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Inclusion Phenom.* **1987**, *5*, 747.

(29) X-ray crystallographic studies on 1,2-alternate-$1Et_4$ will be soon reported by Reinhoudt et al. (private communication).

mentary material). Furthermore, thermal parameters are generally large, which may be characteristic of calixarene crystals.[30,31] Because of these reasons the final R value (0.143) was not particularly good. Similarly, the final R value (0.16) reported by Grootenhuis et al.[18b] for partial-cone-1Me_4 is not so good and the structure consists of two independent molecules in the asymmetric unit.

The X-ray structure in Figure 3 shows that the compound adopts a partial cone conformation, in which all α-carbons in ethoxy groups (OCH_2) point outward. In partial-cone-1Me_4 all methoxy groups point outward.[18b] Probably, this conformation is favorably adopted to reduce the steric crowding in the narrow calix[4]arene ring. More interesting is the fact that $-CH_2O-$ linkages are all in an anti conformation. We consider that this anti conformation not only provides the stable dihedral angle but also makes partial-cone-1Et_4 most compact so that they can efficiently pack in the crystal lattice. The dihedral angles between the four phenyl rings and the mean plane of the methylene groups are 87.4°, -84.5°, 86.5°, and 34.7°. These values are almost comparable with those observed for partial-cone-1Me_4: they are 88.3°, -88.0°, 84.8°, and 35.3°.[18b] The inversed phenyl unit in partial-cone-1Et_4 is more flattened (-88.0° in 1Me_4 to -84.5° in 1Et_4) and the so-called flattened phenyl unit (distal to the inversed phenyl unit) is slightly more flattened (35.3° in 1Me_4 to 34.7° in 1Et_4). The fact that the X-ray structure of partial-cone-1Et_4 is basically similar to that of partial-cone-1Me_4 suggests that the ethyl groups may not bring forth the additional steric crowding into the calix[4]arene ring. We carefully checked several spatial atomic distances where repulsion between two atoms may take place. We found that the distance between C26 and C51 (3.86 Å; CH_3 in t-Bu in the inversed phenyl unit and CH_3 in EtO in the flattened phenyl unit) is shorter than 2-fold of a van der Waals radius for the methyl group (4.0 Å = 2 × 2.0 Å). The result suggests the presence of steric repulsion between these two carbons; that is, when the flattened phenyl unit becomes more flattened, the ethyl group pushes against the t-Bu group in the inversed phenyl unit. As a result, the inversed phenyl unit is forced to be more flattened.

Conclusions

In this paper we have tried to clarify how the conformation of calix[4]arenes is immobilized by a stepwise O-alkylation method. We found that O-substituents larger than Et can inhibit the rotation of the phenol unit whereas the OH group can still rotate even in 1HPr_3. Thus, the final conformer distribution is strongly affected by the metal template effect; cone results when the metal (e.g., Na^+) can act as a template, but 1,3-alternate results when the metal (e.g., Cs^+) cannot act as a template. These findings are very useful for the selective syntheses of desired calix[4]arene conformers.

Experimental Section

Materials. Compound 1H_4 was prepared according to Gutsche's method.[32] The synthesis of 1Me_4 has been reported.[8,18b]

25,27-Diethoxy-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene (1H_2Et_2). Compound 1H_4 (1.0 g, 1.54 mmol) and EtI (0.50 mL, 6.16 mmol) were dissolved in DMF (20 mL), and the solution was heated in the presence of K_2CO_3 (426 mg, 3.08 mmol) at 70 °C for 6 h. The progress of the reaction was followed by an HPLC method (column, Zorbax-ODS 46 × 250 mm; mobile phase, MeOH:$CHCl_3$ = 4:1 v/v; these separation conditions were used throughout this study unless otherwise stated). When the yield of 1H_2Et_2 reached 80%, the reaction was ceased. When the reaction was continued further, we recovered a mixture of 1H_2Et_2, 1HEt_3, and 1Et_4.[33] The reaction mixture was diluted with water (200 mL) and extracted with chloroform. The chloroform layer was separated and dried over $MgSO_4$. After filtration, the filtrate was concentrated to dryness. The residue was recrystallized from chloroform–methanol: white powder, mp 273–275 °C, yield 65% (lit.[34] 278–281 °C, yield 90%); IR (Nujol ν_{OH} 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C) δ 1.00 and 1.27 (t-Bu, s each, 18 H each), 1.60 (CH_3, t, 6 H), 3.30 and 4.33 ($ArCH_2Ar$, d each, 4 H each), 4.08 (CH_2O, q, 4 H), 6.84 and 7.04 (ArH, s, 4 H each), 7.67 (OH, s, 2 H). Anal. Calcd for $C_{48}H_{64}O_4 \cdot CH_3OH$: C, 79.80; H, 9.30. Found: C, 79.73; H, 9.13.

25,26,27-Triethoxy-28-hydroxy-*p*-*tert*-butylcalix[4]arene (Cone-1HEt_3). Compound 1H_4 (1.0 g, 1.54 mmol) and EtI (0.75 mL, 9.24 mmol) were dissolved in DMF (20 mL), and the solution was heated in the presence of $Ba(OH)_2 \cdot 8H_2O$ (0.52 g, 1.76 mmol) and BaO (0.52 g, 3.38 mmol) at 70 °C for 1 h. The progress of the reaction was followed by an HPLC method. When the yield of 1HEt_3 reached 88%, the reaction was ceased. The product was isolated in a manner similar to that described for 1H_2Et_2: white powder, mp 212–213 °C, yield 70%; IR (Nujol) ν_{OH} 3530 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C) δ 0.83, 1.32, and 1.34 (t-Bu, s each, 18 H, 9 H, and 9 H, respectively), 1.49 and 1.70 (CH_3, t each, 6 H and 3 H, respectively), 3.16, 3.25, 4.31, and 4.35 ($ArCH_2Ar$, d each, 2 H each), 3.90 and 4.01 (CH_2O, q each, 4 H and 2 H, respectively), 5.67 (OH, s, 1 H), 6.54, 7.05, and 7.13 (ArH, s each, 4 H, 2 H, and 2 H, respectively). Anal. Calcd for $C_{50}H_{68}O_4$: C, 81.92; H, 9.35. Found: C, 81.72; H, 9.27. The splitting pattern for the $ArCH_2Ar$ protons (two pairs of doublets with a large chemical shift difference) indicates that this compound adopts a cone conformation.

25,27-Dipropoxy-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene (1H_2Pr_2). Compound 1H_4 (1.0 g, 1.54 mmol) and n-PrBr (0.56 mL, 6.16 mmol) were dissolved in DMF (20 mL), and the solution was heated in the presence of K_2CO_3 (426 mg, 3.08 mmol) at 70 °C described for 24 h. The product was isolated in a manner similar to that described for 1H_2Et_2: white powder, mp 247–249 °C, yield 79%; IR (Nujol) ν_{OH} 3375 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C) δ 0.94 and 1.29 (t-Bu, s each, 18 H each), 1.26 (CH_3, t, 6 H), 1.96–2.05 ($CH_2(CH_3)$, m, 4 H), 3.29 and 4.25 ($ArCH_2Ar$, d each, 4 H each), 3.93 (OCH_2, t, 4 H), 6.75 and 7.04 (ArH, s each, 4 H each), 7.75 (OH, s, 1 H). Anal. Calcd for $C_{50}H_{68}O_4$: C, 81.92; H, 9.35. Found: C, 81.63; H, 9.35.

25,26,27-Tripropoxy-28-hydroxy-*p*-*tert*-butylcalix[4]arene (Cone-1HPr_3). Compound 1H_4 (1.0 g, 1.54 mmol) and n-PrI (4.2 mL, 46.2 mmol) were dissolved in DMF (20 mL), and the solution was stirred at room temperature for 1 h in the presence of $Ba(OH)_2 \cdot 8H_2O$ (1.7 g, 5.4 mmol) and BaO (1.59 g, 2.36 mmol). The product was isolated in a manner similar to that described for 1H_2Et_2: white powder, mp 194–196 °C, yield 63%; IR (Nujol) ν_{OH} 3530 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C) δ 0.81, 1.30, and 1.32 (t-Bu, s each, 18 H, 9 H, and 9 H, respectively), 0.96 and 1.10 (CH_3, t each, 3 H and 6 H, respectively), 1.82–2.00 and 2.28–2.38 ($CH_2(CH_3)$, m each, 2 H and 4 H, respectively), 3.15, 3.22, 4.29, and 4.33 ($ArCH_2Ar$, d each, 2 H each), 3.73 and 3.81 (OCH_2, t each, 4 H and 2 H, respectively), 5.54 (OH, s, 1 H), 6.47, 6.48, 7.03, and 7.10 (ArH, d, d, s, and s, respectively, 2 H each). Anal. Calcd for $C_{53}H_{74}O_4$: C, 82.12; H, 9.62. Found: C, 82.35; H, 9.51. The split pattern for the $ArCH_2Ar$ protons (two pairs of doublets with a large chemical shift difference) indicates that this compound adopts a cone conformation.

25,26,27-Tripropoxy-28-hydroxy-*p*-*tert*-butylcalix[4]arene (Partial-Cone-1HPr_3). Compound 1H_4 (1.0 g, 1.54 mmol) and n-PrBr (5.6 mL, 61.6 mmol) were dissolved in acetone (20 mL), and the solution was refluxed for 14 h in the presence of Cs_2CO_3 (2.0 g, 6.16 mmol). HPLC analysis showed that the reaction mixture contains 59% of partial-cone-1HPr_3. The reaction

(30) For example, 15 carbons possess $U11$ ($U \times 1000$, Å^2) greater than 100. Among them, carbons with $U11 > 120$ are C9, C13, C25, C27, C37, C39, C40, C53, C54, and C55. These are all assigned to carbons in EtO or t-Bu groups.

(31) Shinkai, S.; Araki, K.; Matsuda, T.; Nishiyama, N.; Ikeda, H.; Takasu, I.; Iwamoto, M. *J. Am. Chem. Soc.* **1990**, *112*, 9053.

(32) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.

(33) Apparently, the rate for 1HEt_3 → 1Et_4 is faster than that for 1H_2Et_2 → 1HEt_3.

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mixture was diluted with water and then extracted with chloroform. The chloroform layer was separated and dried over $MgSO_4$. After filtration, the filtrate was concentrated to dryness, the residue being subjected to a preparative TLC separation (silica gel, chloroform–hexane (1:3 v/v)), R_f = 0.48: white powder, mp 169–171 °C, yield 48%; IR (Nujol) ν_{OH} 3350 cm^{-1}; ^1H NMR ($Cl_2CDCDCl_2$, 25 °C) δ –0.65 and 0.97 (CH_3, t each, 3 H and 6 H, respectively), 0.45–0.56, 1.53–1.65, and 1.72–1.84 ($CH_2(CH_3)$, m each, 2 H each), 1.16, 1.22, and 1.39 (*t*-Bu, s each, 18 H, 9 H, and 9 H, respectively), 1.45, 3.51–3.57, and 3.87–3.94 (OCH_2, t, m, and m, respectively, 2 H each), 3.22, 3.86, and 4.18 ($ArCH_2Ar$, d, s, d, respectively, 2 H, 4 H, 2 H, respectively), 6.94, 7.00, 7.03, and 7.18 (ArH, d, s, d, and s, respectively, 2 H each), 7.27 (OH, s, 1 H). Anal. Calcd for $C_{53}H_{74}O_4$: C, 82.12; H, 9.62. Found: C, 81.31; 9.49. Aromatic protons in cone-1HEt_3 appeared as singlets whereas those in cone-1HPr_3 and partial-cone-1HPr_3 appeared as two singlets and two dublets (J = 2.4 Hz). Probably, meta protons in two propylated phenyl units are inequivalent because of steric crowding on the lower rim.

Tetra-O-alkylation of 1H$_4$ in the Presence of NaH. Compound 1H$_4$ (1.0 g, 1.54 mmol) was treated with oil-dispersed NaH (1.0 g, 25 mmol) in THF (25 mL)–DMF (2.5 mL), and then alkyl halogen (80.8 mmol) was added. The reaction mixture was refluxed for 2 h. Excess NaH was decomposed with methanol. The mixture was diluted with water (300 mL) and extracted with chloroform (100 mL × 2). In this stage the conformer distribution was determined by an HPLC method. The chloroform layer was separated and dried over $MgSO_4$. After filtration, the filtrate was concentrated to dryness. The residue was subjected to a preparative TLC separation (silica gel, chloroform–hexane (1.3 v/v)). Partial-cone-1Et$_4$: R_f = 0.41, mp 263–265 °C, isolated yield 40%; ^1H NMR ($CDCl_3$, 25 °C) δ 1.00, 1.32, and 1.42 (CH_3, t each, 3 H, 3 H, and 6 H, respectively), 1.04, 1.35, and 1.38 (*t*-Bu, s each, 18 H, 9 H, 9 H, respectively), 3.03, 3.63, 3.70, and 4.05 ($ArCH_2Ar$, d each, 2 H each), 3.56–3.69 and 3.78–3.89 (OCH_2, m each, 6 H and 2 H), 6.58, 6.86, 7.09, and 7.20 (ArH, d, d, s, and s, respectively, 2 H each). Anal. Calcd for $(C_{13}H_{18}O)_4$: C, 82.06; H, 9.53. Found: C, 81.91; H, 9.64. Cone-1Pr$_4$: R_f = 0.67, mp 246–247 °C, isolated yield 38%; ^1H NMR ($CDCl_3$, 25 °C) δ 0.99 (CH_3, t, 12 H), 1.08 (*t*-Bu, s, 36 H), 2.02 ($CH_2(CH_3)$, m, 8 H), 3.11 and 4.42 ($ArCH_2Ar$, d and d, 4 H each), 3.81 (OCH_2, t, 8 H), 6.77 (ArH, s, 8 H). Anal. Calcd for $(C_{14}H_{20}O)_4$: C, 82.30; H, 9.87. Found: C, 81.96; H, 9.96. Partial-cone-1Pr$_4$: R_f = 0.58, mp 283–284 °C, isolated yield 41%; ^1H NMR ($CDCl_3$, 25 °C) δ 0.70, 0.80, and 1.00 (CH_3, t each, 3 H, 3 H, and 6 H, respectively), 1.04, 1.33, and 1.40 (*t*-Bu, s each, 18 H, 9 H, 9 H, respectively), 1.52, 1.69, and 1.84 ($CH_2(CH_3)$, m each, 2 H, 2 H, and 4 H, respectively), 3.04, 3.64, 3.70, and 4.10 ($ArCH_2Ar$, d each, 2 H each), 3.52–3.38 and 3.80–3.71 (OCH_2, m each, 6 H and 2 H), 6.60, 6.85, 7.08, and 7.19 (ArH, d, d, s, and s, respectively, 2 H each). Anal. Calcd for $(C_{14}H_{20}O)_4 \cdot 0.5CH_3OH$: C, 81.44; H, 9.92. Found: C, 81.61; H, 9.68. Cone-1Bu$_4$: R_f = 0.68, mp 175–176 °C, isolated yield 37%; ^1H NMR ($CDCl_3$, 25 °C) δ 1.01 (CH_3, t, 12 H), 1.08 (*t*-Bu, s, 36 H), 1.45 ($CH_2(CH_3)$, m, 8 H), 2.01 ($CH_2(CH_2O)$, m, 8 H), 3.11 and 4.42 ($ArCH_2Ar$, d and d, 4 H each), 3.86 (OCH_2, t, 8 H), 6.77 (ArH, s, 8 H). Anal. Calcd for $(C_{15}H_{22}O)_4$: C, 82.52; H, 10.16. Found: C, 82.48; H, 10.11. Partial-cone-1Bu$_4$: R_f = 0.47, mp 262–263 °C, isolated yield 39%; ^1H NMR ($CDCl_3$, 25 °C) δ 0.86, 0.94, and 0.98 (CH_3, t each, 3 H, 3 H, and 6 H, respectively), 1.04, 1.34, and 1.40 (*t*-Bu, s, 18 H, 9 H, and 9 H, respectively), 1.15–1.22 and 1.42–1.50 ($CH_2(CH_3)$, m each, 2 H and 6 H, respectively), 1.52–1.60, 1.68–1.72, and 1.80–1.86 ($CH_2(CH_2O)$, m each, 2 H, 2 H, and 4 H, respectively), 3.04, 3.62, 3.69, and 4.12 ($ArCH_2Ar$, d each, 2 H each), 3.52–3.61 and 3.73–3.79 (OCH_2, m each, 6 H and 2 H, respectively), 6.58, 6.85, 7.08, and 7.21 (ArH, d, d, s, and s, respectively). Anal. Calcd for $(C_{15}H_{22}O)_4$: C, 82.52; H, 10.16. Found: C, 81.97; H, 9.91.

1,2- and 1,3-Alternate-1Pr$_4$. Compound 1H$_4$ (500 mg, 0.77 mmol) and *n*-PrBr (3.79 g, 30.8 mmol) were dissolved in DMF (20 mL), and the solution was heated in the presence of Cs_2CO_3 (10 g, 30.8 mmol) at 70 °C for 5 h. The reaction mixture was diluted with water (200 mL) and extracted with chloroform (100 mL × 2). The chloroform layer was separated and dried over $MgSO_4$. At this stage the conformer distribution was determined by an HPLC method. 1,2- and 1,3-alternate-1Pr$_4$ were isolated in a manner similar to that described for cone-1Pr$_4$. 1,2-Alternate-1Pr$_4$: R_f = 0.70, mp 279–280 °C, isolated yield 6%; ^1H NMR ($CDCl_3$, 25 °C) δ 0.58 (CH_3, t each, 12 H), 0.69–0.82 and 1.11–1.24 ($CH_2(CH_3)$, m each, 4 H each), 1.29 (*t*-Bu, s, 36 H), 3.10, 3.85, and 4.17 ($ArCH_2Ar$, d, s, and d, respectively, 2 H, 4 H, and 2 H, respectively), 3.27 and 3.35 (OCH_2, m each, 4 H each), 6.99 and 7.15 (ArH, d each, 4 H each). A singlet for *t*-Bu and the split pattern for the $ArCH_2Ar$ protons are consistent with a 1,2-alternate conformation. 1,3-Alternate-1Pr$_4$: R_f = 0.38, mp 339–341 °C, isolated yield 49%; ^1H NMR ($CDCl_3$, 25 °C) δ 0.61 (CH_3, t, 12 H), 0.94–1.03 ($CH_2(CH_3)$, m, 8 H), 1.26 (*t*-Bu, s, 36 H), 3.30 (OCH_2, t, 8 H), 3.80 ($ArCH_2Ar$, s, 8 H), 6.95 (ArH, s, 8 H). Anal. Calcd for $(C_{14}H_{20}O)_4$: C, 82.30; H, 9.87. Found: C, 82.12; H, 9.97. A singet for the $ArCH_2Ar$ protons is a sign characteristic of an 1,3-alternate conformation.

Thermal Isomerization of 1Et$_4$. Isomerization of 1Et$_4$ was carried out in 1,1,2,2-tetrachloroethane. The progress of the reaction was followed by an HPLC method. After the equilibrium was attained, partial-cone-1Et$_4$ and 1,2-alternate-1Et$_4$ were isolated by a preparative TLC method (silica gel, chlorofrom–hexane (1:3 v/v)). The yields of cone-1Et$_4$ and 1,3-alternate-1Et$_4$ were too low to isolate. We thus estimated the yields from the ^1H NMR spectra ($CDCl_3$, 25 °C). Cone-1Et$_4$: δ 1.08 (*t*-Bu, s, 36 H), 1.53 (CH_3, t, 12 H), 3.11 and 4.41 ($ArCH_2Ar$, d each, 4 H each), 3.96 (OCH_2, q, 8 H), 6.79 (ArH, s, 8 H). 1,3-Alternate-1Et$_4$: δ 0.70 (CH_3, t, 12 H), 1.28 (*t*-Bu, s, 36 H), 3.32 (OCH_2, q, 8 H), 3.78 ($ArCH_2Ar$, s, 8 H), 6.99 (ArH, s, 8 H). 1,2-Alternate-1Et$_4$: R_f = 0.62 (chloroform:hexane = 1:4 (v/v)), mp 225–226 °C, isolated yield 36%; ^1H NMR ($CDCl_3$, 25 °C) δ 0.60 (CH_3, t, 12 H), 1.29 (*t*-Bu, s, 36 H), 3.12, 3.85, and 4.13 ($ArCH_2Ar$, d, s, and d, respectively, 2 H, 4 H, and 2 H, respectively), 3.40–3.50 (OCH_2, m, 8 H), 7.01, and 7.16 (ArH, d each, 4 H each). Anal. Calcd for $(C_{13}H_{18}O)_4$: C, 82.06; H, 9.53%. Found: C, 81.82; H, 9.72.

Theoretical Calculations. The calculations on conformers of 1Me$_4$ and 25,26,27,28-tetramethoxycalix[4]arene were performed with Toray Computer Aided Molecular Engineering System (MM2PP). A constant dielectric with ε = 1.5 was used. Starting geometries were manually input by use of the MOLDA-4 mode of the program. From cone-1Me$_4$ with C_{4v} symmetry the other three conformations were easily derived by the adjustment of the dihedral angles.

X-ray Diffraction. Partial-cone-1Et$_4$ was recrystallized from *n*-hexane. The crystals (monoclinic) were subjected to X-ray analysis. Integral intensities were collected by using Mo Kα radiation by the $\theta - 2\theta$ scan technique up $2\theta = 120°$. Reflections used to determine all dimensions were 25 ($30° < 2\theta \leq 38°$). The data collection range was $3° \leq 2\theta \leq 50°$, and the scan speed was 4° min^{-1}. Of the 8506 reflections measured, the number of reflections observed was 3814 ($I > 3\sigma(I)$, where σ is the standard deviation observed from the counting statics). The structure was solved by the direct method (MULTAN 78). Then, the structure was refined by the full-matrix least-squares procedure with anisotropic thermal parameters. The final R value was 0.143.

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Supplementary Material Available: Three crystallographic tables containing bond lengths, bond angles, and spacial atomic distances where repulsion may take place (3 pages). Ordering information is given on any current masthead page.