Functionalization of Calix[4]arenes by Alkylation with 2-(Chloromethyl)pyridine Hydrochloride

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The syntheses, structures, and conformations of nine of the 13 possible [(2-pyridylmethyl)oxy]calix[4]arene conformers obtainable by direct substitution on calix[4]arenes **1a,b** are described. The conformer distribution in the exhaustive O-alkylation of **1a,b** with 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl) in *N,N*-dimethylformamide (DMF) is strongly affected by the base applied: NaH induces *only* cone conformers, while K_2CO_3 or Cs_2CO_3 lead preferentially to partial cone and/or 1,3-alternate conformers, depending on the para substituent of the starting calix[4]arene. Single-crystal X-ray analyses on tetra-O-alkylated cone **1k,l** and partial cone **2c** have been conducted. Molecule **1k** has a distorted cone conformation with pendant OCH_2Py groups; a methanol of solvation is hydrogen bonded to one pyridine N atom and is exo to the calix cavity. The crystal structure of **1l** contains two independent distorted cone shaped molecules per asymmetric unit which differ principally in the relative orientations of the OCH_2Py groups. In the partial cone conformer **2c** the conformation adopted is such that the pendant OCH_2Py group of the rotated aryl ring lies in, and effectively fills, the calix cavity produced by the remaining three aryl rings; as in **1k** a methanol of solvation is hydrogen bonded to a pyridine N atom exo to the calix cavity. Regioselective syn-proximal (1,2-) or syn-distal (1,3-) difunctionalization at the lower rim of calix[4]arenes has been also achieved. Syn-1,2-disubstituted derivatives have proved to be useful intermediates for the stereoselective synthesis of tri-O-alkylated cone conformers, calix[4]arenes with mixed ligating groups in the sequence AABB at the lower rim, for inherently chiral calix[4]arenes, and for the transfer of proximal regioselectivity from the lower to the upper rim. On the basis of stepwise O-alkylation of calix[4]arenes, and with the aid of MM2 calculations on the involved intermediates and their anions, a possible genesis of the various conformers is proposed.

Introduction

Calix[4]arenes, consisting of a cyclic array of phenol residues linked by methylene bridges, have attracted appreciable interest in recent years as useful building blocks for highly preorganized lipophilic cation receptors and carriers.[1] The free hydroxyl-containing calix[4]arenes are conformationally flexible molecules, and their conformational behavior is normally discussed in terms of four basic conformations, designated as cone, partial cone, 1,3-alternate, and 1,2-alternate, as depicted in Figure 1. Structural studies have shown that the parent compound *p-tert*-butylcalix[4]arene (**1a**) exists in the solid state in the cone conformation as a result of strong intramolecular hydrogen-bonding interactions among OH groups,[2] whereas dynamic ^1H NMR measurements have demonstrated a facile interconversion among the various conformers with an inversion barrier of 15.7 kcal mol^{-1} in $CDCl_3$.[3] However, the introduction of sufficiently large groups at the lower rim of calix[4]arenes suppresses the oxygen-through-the-annulus rotation, leading to conformationally immobile calix[4]arenes, which exist as discrete entities in one or another of the conformations.[4]

The properties of calix[4]arene-based host molecules are strongly influenced by the conformation of the calix[4]arene moiety,[5,6] so that the control of the conformation during the lower rim derivatization and the search for stereoselective syntheses of particular conformers are highly desirable. It has been shown that the conformational outcome in the functionalization of calix[4]arenes at the lower rim depends on the reaction conditions (temperature, solvent, base), the para substituent of the calix[4]arene, the steric requirement of the derivatizing agent, and its reactivity as an electrophile.[4c,7]

In a preliminary paper we have reported on the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metals.[8] Independently, Shinkai has extended this kind of functionalization to larger calixarenes.[9] Our original procedure was based on the reaction of calix[4]arenes with 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl) in *N,N*-dimethylformamide (DMF) in the presence of NaH, and by varying the molar ratios between the reactants and the

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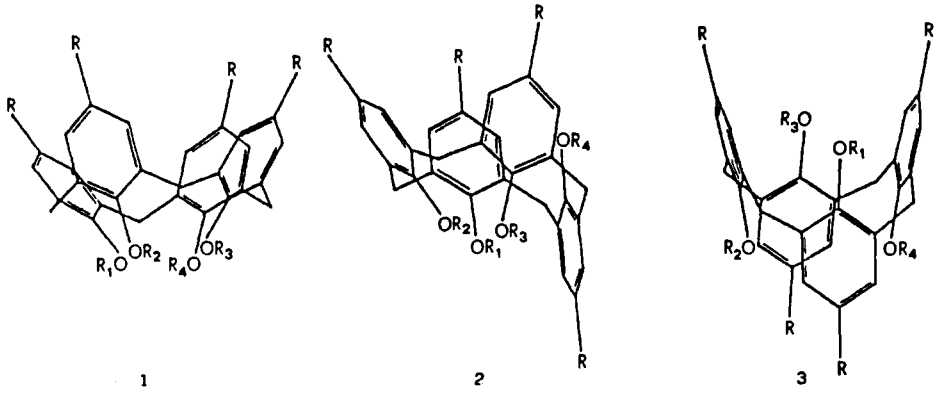
Chart I



1 2 3

	R	R_1	R_2	R_3	R_4
a	Me_3C	H	H	H	H
b	H	H	H	H	H
c	Me_3C	Pic	H	H	H
d	H	Pic	H	H	H
e	Me_3C	Pic	Pic	H	H
f	H	Pic	Pic	H	H
g	Me_3C	Pic	H	Pic	H
h	H	Pic	H	Pic	H
i	Me_3C	Pic	Pic	Pic	H
j	H	Pic	Pic	Pic	H
k	Me_3C	Pic	Pic	Pic	Pic
l	H	Pic	Pic	Pic	Pic

	R	R_1	R_2	R_3	R_4
a	Me_3C	Pic	H	Pic	Pic
b	H	Pic	H	Pic	Pic
c	Me_3C	Pic	Pic	Pic	Pic
d	H	Pic	Pic	Pic	Pic

	R	R_1	R_2	R_3	R_4
a	Me_3C	Pic	Pic	Pic	Pic
b	H	Pic	Pic	Pic	Pic

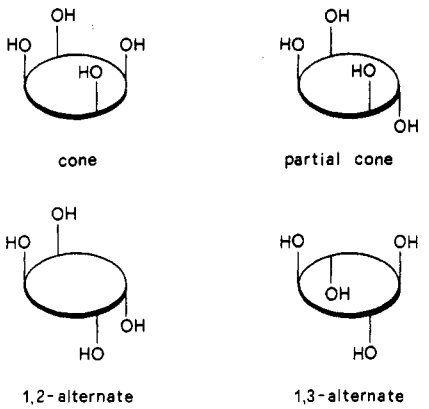


Figure 1. Schematic representation of the four basic conformations of calix[4]arenes.

reaction times, regioselective proximal di-O-alkylation or exhaustive tetra-O-alkylation could be realized. Remarkably, the reaction with NaH produced *only cone conformers*. We have now found that by using alkali metal carbonates (K_2CO_3, Cs_2CO_3) instead of NaH, tetra-O-alkylated partial cone and 1,3-alternate conformers become easily accessible.

In this paper we report full experimental data concerning the synthesis, structure, and conformation of nine of the 13 possible[7c] [(2-pyridylmethyl)oxy]calix[4]arene conformers obtainable by direct substitution on calix[4]arenes **1a,b**. The structures and conformation of the compounds synthesized are shown in Chart I. On the basis of stepwise alkylation of calix[4]arenes and analysis of the conformer distribution at each step, and with the aid of molecular mechanics calculations (MM2) on the

Table I. Product Composition in the Base-Catalyzed Exhaustive Alkylation of Calix[4]arenes with PicCl·HCl in DMF at 70 °C

				tetra-O-alkylated[a]		
starting material	PicCl·HCl (equiv)	base	reaction time (h)	cone	partial cone	1,3-alternate
1a	20	NaH	24	80		
1b	20	NaH	24	72		
1a	20	Cs_2CO_3	36	9	54	18
1b	20	K_2CO_3	36	9[b]	36[b]	55[b]

[a] Isolated yield. [b] Determined by ^1H NMR analysis of the product mixture.

involved partially-alkylated intermediates and their anions, a rationale for the conformational outcome of the exhaustive alkylation of calix[4]arenes with PicCl·HCl as a function of the identity and strength of the base used is also proposed.

Results and Discussion

Tetra-O-alkylation. Tetrakis[(2-pyridylmethyl)oxy]-calix[4]arene conformers were prepared by treating calix[4]arenes **1a,b** with PicCl·HCl (20 equiv) in anhydrous DMF at 70 °C in the presence of base (40 equiv). Table I summarizes the product composition as a function of the base applied. NaH affords only cone conformers, while alkali metal carbonates (K_2CO_3 or Cs_2CO_3) yield a mixture of cone, partial cone, and 1,3-alternate conformers in different ratios, depending on the para substituent of the starting calix[4]arene. Noteworthy, no 1,2-alternate conformers could be detected in the reaction mixtures. Separation of the reaction products into the pure components has been achieved by column chromatography (SiO_2 or basic Al_2O_3) using a gradient of ethyl acetate (AcOEt) in

Table II. Critical NMR Data and Conformations of [(2-Pyridylmethyl)oxy]calix[4]arenes 1-3[a]

compd	chemical shift, δ				
	$ArCH_2Ar$	$ArCH_2Ar$[b]	OCH_2Py	OCH_2Py[b]	conformation
1c	3.41, 4.24 (ABq, J = 13.6 Hz, 4 H)	32.28	5.27 (s, 2 H)	78.82	cone
	3.42, 4.49 (ABq, J = 13.0 Hz, 4 H)	32.98			
1d	3.44, 4.26 (ABq, J = 13.7 Hz, 4 H)	31.51	5.29 (s, 2 H)	78.61	cone
	3.46, 4.51 (ABq, J = 13.0 Hz, 4 H)				
1e	3.26, 4.37 (ABq, J = 13.1 Hz, 4 H)	31.46	4.88, 5.33 (ABq, J = 13.0 Hz, 4 H)	77.88	
	3.34, 4.27 (ABq, J = 13.7 Hz, 2 H)	31.47			cone
	3.43, 4.61 (ABq, J = 12.8 Hz, 2 H)	32.40			
1f	3.28, 4.41 (ABq, J = 13.0 Hz, 4 H)	30.92	4.88, 5.34 (ABq, J = 13.0 Hz, 4 H)	77.84	
	3.37, 4.36 (ABq, J = 13.7 Hz, 2 H)	31.78			cone
	3.48, 4.65 (ABq, J = 12.7 Hz, 2 H)	31.90			
1g	3.35, 4.31 (ABq, J = 13.1 Hz, 8 H)	31.50	5.19 (s, 8 H)	78.15	cone
1h	3.42, 4.36 (ABq, J = 13.2 Hz, 8 H)	31.26	5.19 (s, 8 H)	78.54	cone
1i	3.18, 4.34 (ABq, J = 12.5 Hz, 4 H)	30.66	4.72, 4.78 (ABq, J = 12.1 Hz, 4 H)	78.66	cone
	3.22, 4.33 (ABq, J = 13.4 Hz, 4 H)	31.44	4.98 (s, 2 H)	76.95	
1j	3.19, 4.36 (ABq, J = 13.0 Hz, 4 H)	30.52	4.77, 4.86 (ABq, J = 12.2 Hz, 4 H)	77.00	cone
	3.27, 4.37 (ABq, J = 13.7 Hz, 4 H)	30.88	5.10 (s, 2 H)	78.30	
1k	3.05, 4.39 (ABq, J = 12.6 Hz, 8 H)	30.68	4.99 (s, 8 H)	78.01	cone
1l	3.07, 4.37 (ABq, J = 13.7 Hz, 8 H)	31.24	5.13 (s, 8 H)	77.40	cone
2a	3.29, 4.27 (ABq, J = 12.8 Hz, 4 H)	32.39	4.46 (s, 2 H)	68.99	partial cone
	3.96, 4.12 (ABq, J = 17.5 Hz, 4 H)	39.21	4.89, 5.25 (ABq, J = 13.6 Hz, 4 H)	76.58	
2b	3.33, 4.18 (ABq, J = 13.2 Hz, 4 H)	31.15	4.70 (s, 2 H)	70.17	partial cone
	3.91, 4.05 (ABq, J = 16.1 Hz, 4 H)	37.88	4.91, 5.24 (ABq, J = 13.6 Hz, 4 H)	75.41	
2c	3.02, 4.18 (ABq, J = 12.2 Hz, 4 H)	31.20	4.43 (s, 2 H)	69.61	
	3.79, 3.90 (ABq, J = 16.7 Hz, 4 H)	38.98	4.72 (s, 2 H)	76.72	partial cone
			4.76, 4.85 (ABq, J = 12.9 Hz, 4 H)	75.64	
2d	3.09, 4.14 (ABq, J = 12.7 Hz, 4 H)	30.14	4.57, 4.69 (ABq, J = 11.7 Hz, 4 H)	77.09	
	3.68, 3.81 (ABq, J = 14.6 Hz, 4 H)	37.22	4.74 (s, 2 H)	76.02	partial cone
			4.83 (s, 2 H)	71.71	
3a	3.63 (s, 8 H)	39.02	4.73 (s, 8 H)	72.64	1,3-alternate
3b	3.71 (s, 8 H)	37.17	4.95 (s, 8 H)	72.36	1,3-alternate

[a] Multiplicities, coupling constants, and proton intensity ratios in parentheses. [b] Assigned by a DEPT experiment.

n-hexane or cyclohexane as an eluent. The molecular weights of the pure materials were deduced by low-voltage EI MS, and their structures were firmly established by NMR spectroscopy.

In general, stereochemical assignments of calix[4]arenes with pyridine pendant groups followed unambiguously from distinctive ^1H NMR spectral patterns of the bridging methylene[7a,10] and OCH_2Py protons, arising from the substitution pattern at the lower rim and from conformation. For example, in tetra-O-alkylated calix[4]arenes the $ArCH_2Ar$ groups show up as one pair of doublets in the cone conformer, two pairs of doublets in the partial cone conformer, and one singlet in the 1,3-alternate conformer. The OCH_2Py protons display one singlet in cone and 1,3-alternate conformers, while in the partial cone conformer they give rise to two singlets and one pair of doublets (diastereotopic oxymethylenes) in the ratio 1:1:2. The ^{13}C NMR resonances of the pertinent carbons have also provided a diagnostic tool for distinguishing among various conformers; in agreement with the rule found by de Mendoza et al.,[11] the signals of the methylene groups connecting two adjacent phenyl moieties in a syn orientation (e.g., in the cone conformation) appear at 30.80 ± 0.65 ppm, and those of the OCH_2Py groups linked to them at 77.0 ± 1.65 ppm, while they show up at 38.1 ± 0.9 and 70.8 ± 1.8 ppm, respectively, when both phenyl moieties are anti oriented (e.g., in the 1,3-alternate conformation). Critical NMR patterns of [(2-pyridylmethyl)oxy]calix[4]arenes 1-3 are collected in Table II.

[(2-Pyridylmethyl)oxy]calix[4]arenes 1-3 give good-quality low-voltage EI MS, displaying relatively intense molecular ion peaks. The fragmentation pattern within each series of conformers is quite uniform; however, in no case do particular fragmentation pathways emerge that might allow a distinction among the various conformers to be made. The structures of cone **1k** and **1l** and partial cone **2c** were further confirmed by single-crystal X-ray analysis.

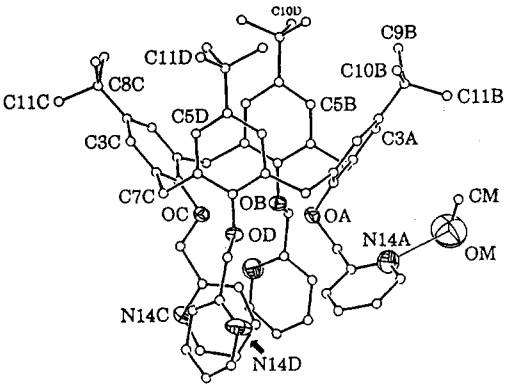


Figure 2. View of the molecule **1k** showing the hydrogen bonding pattern, general conformation, and our numbering scheme. For clarity, H atoms are omitted, C atoms are shown as small spheres of an arbitrary size, and the N and O atoms are shown as thermal ellipsoids drawn at the 35% probability level.

Structure Descriptions. The calixarene **1k** adopts a distorted cone conformation in the solid state (Figure 2); the conformation is defined by the angles which the aromatic rings make with the plane of the four CH_2 moieties which link them, viz. 127.4 (2)° (A), 98.7 (2)° (B), 128.2 (2)° (C), and 90.0 (2)° (D) (interplanar angles >90° indicate that the ring system is tilted so that its *tert*-butyl group is directed *away* from the ring cavity). Two opposite rings (A and C) are tilted at an interplanar angle of 75.6°, while rings B and D are almost parallel (interplanar angle 8.7 (3)°). This conformation leads to O···O separations of 4.02 Å between OA and OC and 5.36 Å between OB and OD.

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Table III. Selected Bond Lengths (Å) (Range and Mean) for Calixarenes 1k, 1l, and 2c[a]

bond	range	mean
	Molecule 1k	
C_{ar}–$O_{(ether)}$	1.390 (6)–1.398 (7)	1.394 (7)
C_{sp^3}–O	1.428 (7)–1.454 (7)	1.438 (7)
C_{sp^3}–C_{py}	1.491 (8)–1.497 (9)	1.494 (8)
C_{ar}–C_{sp^3}	1.514 (8)–1.540 (8)	1.523 (8)
C_{py}–N_{py}	1.273 (8)–1.356 (9)	1.331 (9)
C_{sp^3}–$C_{t\text{-Bumethyl}}$	1.317 (14)–1.518 (11)	1.456 (12)
	Molecule 1l	
C_{ar}–$O_{(ether)}$	1.351 (10)–1.382 (10)	1.369 (9)
C_{sp^3}–O	1.412 (12)–1.460 (10)	1.434 (10)
C_{sp^3}–C_{py}	1.472 (13)–1.506 (12)	1.496 (12)
C_{ar}–C_{sp^3}	1.506 (12)–1.538 (12)	1.525 (12)
C_{py}–N_{py}	1.322 (10)–1.374 (12)	1.341 (12)
	Molecule 2c	
C_{ar}–$O_{(ether)}$	1.377 (5)–1.388 (6)	1.383 (5)
C_{sp^3}–O	1.413 (8)–1.459 (8)	1.430 (8)
C_{sp^3}–C_{py}	1.451 (8)–1.477 (8)	1.466 (8)
C_{ar}–C_{sp^3}	1.512 (7)–1.549 (8)	1.536 (7)
C_{sp^3}–$C_{t\text{-Bumethyl}}$	1.427 (17)–1.575 (11)	1.515 (13)

[a] A full list of molecular dimensions is in the supplementary material. For 1l the phenyl rings were constrained to be rigid hexagons; for 2c, phenyl and pyridine rings were similarly constrained.

The O···O distances between adjacent ethereal O atoms are in the range 3.20 (1) to 3.50 (1) Å. The conformation thus adopted is very similar to that reported previously for related *tert*-butylcalix[4]arenes,[12] and it effectively precludes a solvent molecule being enclathrated in the cavity; a methanol of solvation is hydrogen bonded to a pyridine N atom but is exo to the cavity [N14A···O (methanol) 2.81 Å]. When a more open calixarene conformation is available and the guest solvent is suitable, enclathration within the calix cavity is known to occur, e.g., acetonitrile in tetraethyl *p-tert*-butylcalix[4]arene tetracarbonate.[13] Molecular dimensions are summarized in Table III and are as anticipated for such calixarenes.

Calixarene 1l (Figure 3) contains two independent distorted cone-shaped molecules in the asymmetric unit, and these differ principally in the relative orientation of the pendant pyridinyl-CH_2 groups. The conformations of both molecules in 1l are defined by the angles which the aromatic rings make with the plane of the four CH_2 moieties which link them, viz. 139.7° (A), 76.1° (B), 152.8° (C), and 77.5° (D) for molecule 1 and 139.6° (E), 84.7° (F), 154.2° (G), and 80.2° (H) for molecule 2. The two opposite rings (A and C; E and G) are tilted away from each other (interplanar angle 112.6° and 113.8°, respectively) so that their ethereal oxygens are forced toward one another with O···O separations of 3.282 (7) Å for OA and OC and 3.321 (7) Å for OE and OG. The other pairs of rings (B and D; F and H) are tilted toward each other (interplanar angle 26.5° and 15.2°, respectively) resulting in their ethereal oxygens pointing *away* from the calixarene cavity. The orientation of a pair of opposite phenyl rings in both molecules [B, D (molecule 1) and F, H (molecule 2)], the close approach of the ethereal oxygens (OA, OC and OE, OG), and the random orientation of the pyridine rings at the base of both molecules precludes the "trapping" of solvent in the calixarene cavity. Molecular dimensions are summarized in Table III.

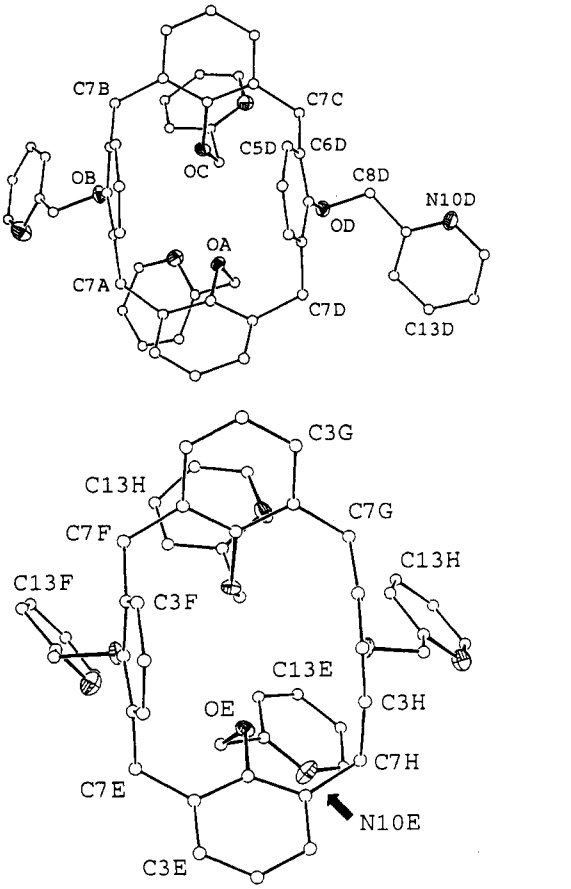

Figure 3. View of the both molecules of 1l showing the general conformation and our numbering scheme. For clarity, H atoms are omitted, C atoms are shown as small spheres of an arbitrary size, and the N and O atoms are shown as thermal ellipsoids drawn at the 25% probability level.

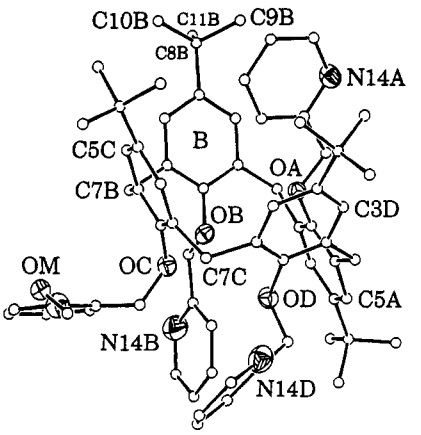

Figure 4. View of one of molecule 2c with its partial cone conformation showing the general conformation, and our numbering scheme. Atom sizes and ellipsoids are as in Figure 2.

Molecule 2c (Figure 4) has a partial cone conformation with one of the pyridine rings (A) positioned in the cone cavity with its nitrogen atom exo. The molecular conformation is defined by the angles that the four aromatic rings A–D make with the plane through the macrocyclic ring methylene groups (C7A, C7B, C7C, C7D): A (−120.7°), B (118.5°), C (118.2°), and D (108.1°). The A and C rings are almost parallel but oriented in opposite directions with a dihedral angle of 2.6°; the rings B, C, and D are tilted so that their *tert*-butyl groups are directed away from the calix cavity. The O···O separations of the cis-adjacent ethereal oxygens are in the range 3.03–3.72 Å. The con-

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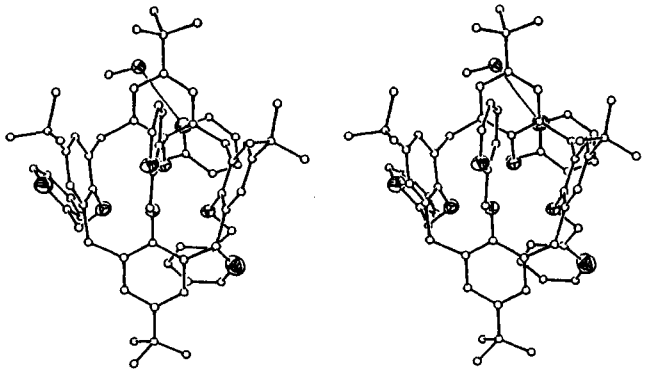

Figure 5. Stereoview of the molecule **2c** with its partial cone conformation showing the pyridinyl-CH_2 group in the calix[4]arene cavity. H atoms are omitted for clarity.

formation adopted by **2c** effectively precludes any solvent molecule being enclathrated in the cavity because the pyridine ring on ring A is positioned within the cavity; this may be clearly seen in the stereoplot of this structure in Figure 5. As in **1k** a methanol of solvation is hydrogen bonded to a pyridine N atom exo to the calix cavity (N14C···O (methanol) 3.02 Å). Molecular dimensions (summarized in Table III) are unexceptional.

Regioselective 1,2- or 1,3-Di-O-alkylation. Increased calix[4]arene/PicCl·HCl molar ratios and diminished reaction times gave mixtures of products representing various stages of alkylation. When **1a,b** were reacted with PicCl·HCl (4 equiv) for 1.5–3 h at 60 °C in the presence of NaH (excess) syn-proximal di[(2-pyridylmethyl)oxy]-calix[4]arenes **1e,f** were produced as the major components in 55–70% yield under optimum conditions, along with very small amounts of mono- and tri-O-alkylated derivatives **1c** and **1i,j**, respectively. The reaction with calix-[4]arene **1a** gave also a trace amount of syn-distal di[(2-pyridylmethyl)oxy]calix[4]arene **1g**, while in the alkylation of **1b** 1,3-di-O-alkylated **1h** was not detected in the reaction mixture.

This is the first example of 1,2-difunctionalization of calix[4]arenes by direct substitution at the phenolic oxygens.[8] Now other procedures,[14] including protection–deprotection methods,[7c,15] are being discovered. Very recently Reinhoudt et al.[16] have demonstrated that syn-1,2-di-O-alkylated calix[4]arenes are general intermediates in the NaH/DMF tetra-O-alkylation of calix[4]arenes and can be isolated in 15–55% yield when only 2.2 equiv of the electrophile is used.

Ungaro, Reinhoudt et al.,[17] No et al.,[18] Shinkai et al.,[7b] and McKervey et al.[19] have noticed that the reaction of

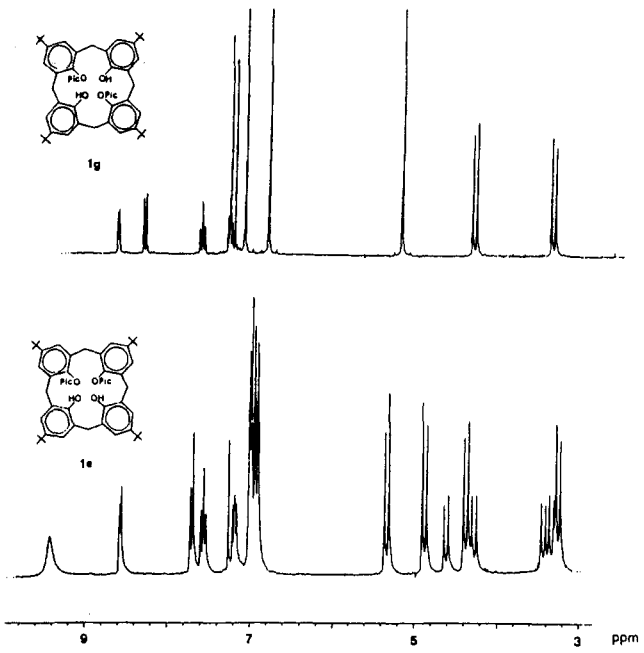

Figure 6. Methylene and aromatic regions in the ^1H NMR spectra of proximal and distal regioisomers **1e** and **1g**.

calix[4]arenes with electrophiles in acetone or acetonitrile in the presence of alkali metal carbonates (Na_2CO_3 or K_2CO_3) affords regioselectively 1,3-disubstituted calix-[4]arenes in good yield even in the presence of an excess of electrophile. In agreement with these findings, alkylation of calix[4]arene **1a** with an excess of PicCl·HCl (up to 8 equiv) in the presence of anhydrous Na_2CO_3 or K_2CO_3 in DMF at 70 °C afforded syn-distal di[(2-pyridylmethyl)oxy]calix[4]arene **1g** in 52–60% yield. On the other hand, reaction of **1b** with PicCl·HCl and K_2CO_3 under standard reaction conditions gave a complex mixture including products of partial and exhaustive alkylation, even under strictly stoichiometric amount of PicCl·HCl and reduced reaction time. This behavior closely resembles the autoaccelerative effect (all-or-nothing substitution) observed by Shinkai in the diazocoupling between calix-[4]arene **1b** and *p*-nitrobenzenediazonium ion.[20] However, mono-O-alkylated **1d** and 1,3-di-O-alkylated **1h** could be obtained, albeit in low yield, by refluxing **1b** with PicCl·HCl (2 equiv) and Bu^{t}OK (4 equiv) in anhydrous toluene for 20 h.

Syn-1,2- and syn-1,3-di-O-alkylated regioisomers can be easily distinguished by NMR spectroscopy, as illustrated in Figure 6 relative to the ^1H NMR spectra of **1e** and **1g**. The ^1H NMR spectrum of **1e** is characterized by a pattern of three pairs of doublets in the ratio 1:2:1 for the bridging methylenes, one pair of doublets for the oxymethylene protons, and a broad singlet for the OH groups at very low field. Conversely, the regioisomer **1g** displays the expected one pair of doublets for the bridging methylene groups, a singlet for the OCH_2Py groups, and a sharp singlet for the OH groups at a higher field as compared to **1e**. Syn-distal and syn-proximal regioisomers display also distinctively different ^{13}C NMR patterns. In particular, the syn-distal derivatives show two signals for the bridgehead carbon atoms (δ 127.61 and 132.32 ppm in **1g**, δ 127.69 and 132.82 ppm in **1h**) and one signal for the bridging methylenes (δ 31.50 ppm in **1g** and 31.27 ppm in **1h**), which are split in their syn-proximal regioisomers into four lines

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(20) Shinkai, S.; Araki, K.; Shibata, J.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 195.

Table IV. Product Composition in the Stepwise O-Alkylation of Calix[4]arenes with PicCl·HCl and Alkali Metal Carbonates[a]

starting material	PicCl·HCl (equiv)	base	reaction time (h)	tri-O-alkylated		tetra-O-alkylated		
				cone	partial cone	cone	partial cone	1,3-alternate
1e	1	Na_2CO_3	20	41[b]				
	1	K_2CO_3	8	85				
	1	CS_2CO_3	6	88				
	4	K_2CO_3	24	95[b]		5[b]		
	4	Cs_2CO_3	24	44[b]		9[b]	47[b]	
	10	Cs_2CO_3	24			7	74	
1f	1	Cs_2CO_3	6	98				
	4	Na_2CO_3	16	67[b]		33[b]		
	4	K_2CO_3	16			67[b]	33[b]	
	4	Cs_2CO_3	6				96	
1g	1	Cs_2CO_3	20	11	34		trace	trace
	10	Cs_2CO_3	20			trace	72	18
1h	1	Cs_2CO_3	6		44		4	18
	10	Cs_2CO_3	16				21[b]	79[b]

[a] Isolated yield. [b] Determined by ^1H NMR analysis of the product mixture.

of equal intensity (δ 127.41, 128.17, 133.18, and 133.54 ppm in **1e**, δ 128.18, 128.66, 134.46, and 134.51 ppm in **1f**) and three lines of roughly 1:2:1 intensity ratio (δ 30.92, 31.78, and 31.90 ppm in **1f**, δ 32.40 and 32.57 (accidental isochrony) ppm in **1c**].

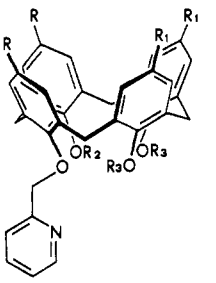
Although theoretically four different disubstituted intermediates, namely syn-1,2-, syn-1,3-, anti-1,2-, and anti-1,3-disubstituted calix[4]arenes can exist,[7c] direct substitution on the parent calix[4]arenes affords regioselectively syn-1,2- or syn-1,3-di-O-alkylated derivatives depending on the base used, with no trace of the other two possible conformers.

The availability of 1,2-difunctionalized calix[4]arenes opens up new perspectives for the construction of (i) calix[4]arenes with mixed ligating groups of the AABB type at the lower rim, whose complexing abilities may be eventually compared to those reported by Shinkai[6] and McKervey[19] having an ABAB substitution pattern, (ii) for the synthesis of chiral calix[4]arenes possessing an AABC sequence of functionalities at the lower rim,[21] and (iii) for the transfer of proximal regioselectivity from the lower to the upper rim, taking advantage in the latter case of the difference in reactivity of the phenol residues of the calix[4]arene framework. The synthesis of compounds **4–6**, shown in Chart II, provide good examples to these concepts.

Calix[4]arene **4**, endowed with pyridine and *tert*-butoxycarbonyl binding functionalities at the lower rim in the AABB sequence, was obtained in 68% yield by reacting **1f** with *tert*-butyl bromoacetate (4 equiv) in anhydrous THF in the presence of NaH. The cone structure of **4** is corroborated by a singlet for the *tert*-butyl groups, a set of three pairs of doublets for the bridging methylene protons in the ratio 1:2:1, and two AB systems (relative ratio 1:1) for the diastereotopic oxymethylene protons of the pendant functionalities in the ^1H NMR spectrum and by a set of three resonances for the bridging methylene carbons around 31 ppm in the ^{13}C NMR spectrum.

Dissolution of **1c** in MeI at room temperature produced the chiral *N*-methylpyridinium derivative **5** in a nearly quantitative yield! The reluctance of **5** to undergo further N-alkylation suggests the hypothesis that the lone pair of the residual ring nitrogen is directly involved in a sort of "self-complex" structure, with the *N*-methylpyridinium cation surrounded by oxygen and nitrogen donor atoms.

Chart II



	R	R1	R2	R3
4	H	H	Pic	$CH_2CO_2CMe_3$
5	Me_3C	Me_3C	$Pic(Me)^{\oplus}I^{\ominus}$	H
6	H	CH_2NMe_2	Pic	H

The ^1H NMR spectrum of **5** is characterized by a 24-line pattern (six AB systems) in the methylene region (δ 3.2–5.7 ppm) (Figure 7), a singlet for the *N*-methyl group at δ 4.45, and two broad signals for the OH groups at δ 8.97 and 8.48 ppm. The ^{13}C NMR spectrum further corroborates the cone structure by the presence of a set of four resonances for the bridged methylene carbons at δ 33.83, 33.50, 32.85, and 32.62 ppm. The enantiomers of **5** may provide useful reagents for the enantioselective methylation of suitable organic substrates.

In order to prove the transfer of regioselectivity from the lower to the upper rim, calix[4]arene **1f** was subjected to the classical Mannich reaction (CH_2O, Me_2NH) under conditions similar to those reported by Gutsche for the aminoalkylation of calixarenes.[22] The reaction afforded bis[(dimethylamino)methyl] derivative **6** (57%) with 100% regioselectivity. To the best of our knowledge, this is the first example of regioselective proximal difunctionalization at the upper rim of a preformed calix[4]arene.[23] ^1H and ^{13}C NMR spectra confirm that the cone structure of **1f** is completely retained after derivatization.

Stepwise O-Alkylation. In order to gain insight into the origin of conformational isomers in the base-catalyzed

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(23) Pochini et al. have reported that the upper rim formylation of a conformationally rigid calix[4]arene affords the 1,3-diformyl derivative as the major product, with less than 5% of the 1,2-regioisomer: Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 936.

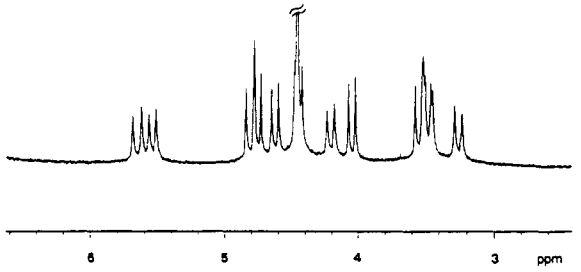


Figure 7. Methylene region in the ^1H NMR spectrum of racemic *N*-methylpyridinium derivative **5**.

exhaustive alkylation of calix[4]arenes with PicCl·HCl and to determine the stage at which the final conformation is fixed, a number of alkylation reactions with the two pairs of syn-di-O-alkylated regioisomers **1c,1g** and **1f,1h** have been carried out in anhydrous DMF by varying the electrophile molar ratio, reaction time, and base. The results are summarized in Table IV. Mostly, the product distribution is based on the actual isolated yields of the pure components. In those cases where separation was difficult, the product ratios were estimated by ^1H NMR analysis of the reaction mixture.

As mentioned before, cone conformers **1i,j** could be isolated in very low yield in the partial alkylation of **1a,b** with PicCl·HCl and NaH. We found that syn-proximally di-O-substituted calix[4]arenes are ideal precursors of tri-O-substituted derivatives in the cone conformation. Treatment of **1e,f** with PicCl·HCl (1 equiv) in DMF at 70 °C for a few hours in the presence of K_2CO_3 or Cs_2CO_3 (2 equiv) resulted in an almost quantitative yield of tri-O-substituted cone conformers **1i,j** with 100% stereoselectivity. An analogous stereoselectivity was observed in the reaction of **1e** with PicCl·HCl in the presence of Na_2CO_3, but the reaction was much slower with a conversion to **1i** of about 41% after 20 h at 70 °C.

Syn-distally disubstituted regioisomers **1g,h**, on the other hand, have proved to be useful intermediates to tri-O-alkylated partial cone conformers **2a,b**. **2a** was obtained in 34% yield (based on reacted **1g**) by reaction of **1g** with PicCl·HCl (1 equiv) under standard reaction conditions in the presence of Cs_2CO_3 (2 equiv). The reaction produced also tri-O-substituted cone conformer **1i** (11%) and trace amounts of tetra-O-alkylated partial cone **2c** and 1,3-alternate **3a**, along with recovered **1g** (ca. 40%). De-*tert*-butylated **1h** was shown to be more reactive than **1g** under analogous conditions, and by quenching the reaction after 6 h, the product consisted of tri-O-alkylated partial cone **2b** (44%, based on reacted **1h**), tetra-O-alkylated partial cone **2d** (4%), and 1,3-alternate **3b** (8%), along with recovered **1h** (27%).

Partial cone structures **2a,b** are supported by distinctive NMR patterns for the methylene and oxymethylene groups (Table II). The ^1H NMR spectra of tri- and tetra-O-alkylated partial cone conformers **2a–c** deserve a further comment. As a general trend, the heteroaromatic protons of the "inversed" pyridine ring are exposed to the ring current shielding effect operated by the two flanking phenyl residues of the calix[4]arene framework, and resonate at higher fields with respect to the protons of the other two pyridine substituents. Table V shows that the magnitude of this shielding, computed as the difference between pertinent protons of "up" and "down" pyridine rings, increases significantly on going from H_6 to H_3 protons. The remarkable shielding effect experienced by H_3 ($\Delta\delta$ = 2.21–2.85 ppm) and H_4 ($\Delta\delta$ = 0.73–1.14 ppm) protons of the inversed pyridine suggests that this pyridine ring is tightly accommodated inside the hydrophobic cavity in

Table V. Shielding Experienced by the Inversed Pyridine Protons in Partial Cone Conformers 2a–c

compd		chemical shift, δ			
		H_6	H_5	H_4	H_3
2a	Py up	8.50	7.06	7.19	7.46
	Py down	8.11	6.64	6.05	4.61
	$\Delta\delta$ (ppm)	0.39	0.42	1.14	2.85
2b	Py up	8.57	7.17	7.35	7.44
	Py down	8.33	6.93	6.62	5.23
	$\Delta\delta$ (ppm)	0.24	0.24	0.73	2.21
2c	Py up	8.48	7.11	7.54	7.23
	Py down	8.18	6.74	6.54	4.74
	$\Delta\delta$ (ppm)	0.30	0.37	1.00	2.49

a sort of self-inclusion complex, with the ring nitrogen oriented outwards the cavity. The whole conformation of partial cone conformers **2a–c** and in particular the configuration assumed by the inversed pyridine ring in solution are in full agreement with the results found in the solid state for **2c**.

Molecular mechanics calculations (MM2) have shown that in **2a** the trans configuration of the ring nitrogen relative to the ethereal oxygen is about 3.2 kcal mol^{-1} more stable than the cis configuration, as a result of electrostatic repulsion between the two heteroatoms. In **2b** this energy difference is slightly higher (ca. 4.2 kcal mol^{-1}). The minimum- and high-energy configurational isomers of **2a** and **2b** are shown in Figure 8. It is worth noting that in *tert*-butylated **2a** the high-energy conformer **2aa** still contains the inversed pyridine group inside the cavity due to a possible interaction with the surrounding *tert*-butyl groups, while in the corresponding de-*tert*-butylated conformer **2ba** the inversed pyridine moiety has moved quite outside the cavity, thus accounting for the less efficient shielding experienced by the pertinent heteroaromatic protons.

Treatment of de-*tert*-butylated **1f** with PicCl·HCl (4 equiv) and Na_2CO_3 (8 equiv) gave tri- and tetra-O-alkylated cone conformers **1j** and **1l** in the ratio 2:1, respectively, while substitution of K_2CO_3 for Na_2CO_3 resulted in fully alkylated **1l** and **2d** in the ratio 2:1. Strikingly, the reaction with Cs_2CO_3 was very fast and afforded partial cone **2d** in a nearly quantitative yield. Since these reactions have been shown to proceed through the intermediate tri-O-alkylated cone **1j**, we can conclude that in the final alkylating step the cone conformation is completely retained with Na^+ cation in the base, mainly retained with K^+, and completely inversed to partial cone with Cs^+. In agreement with these results, Shinkai has reported that the reaction of cone tri-*O*-propylcalix[4]arene and PrBr in DMF at 70 °C in the presence of Cs_2CO_3 yielded partial cone tetra-*O*-propylcalix[4]arene in 100% selectivity.[7e]

tert-Butylated **1e** proved to be less reactive than **1f**: alkylation with four equivalents of PicCl·HCl and K_2CO_3 gave only 5% conversion to fully alkylated cone **1k** along with **1i** (95%) after 24 h, while with Cs_2CO_3 after 24 h the product consisted of **1i** (44%), **1k** (9%), and **2c** (47%). Only with increasing amounts of Cs_2CO_3 (up to 10 equiv) was the conversion to tetra-O-alkylated product total, and partial cone **2c** could be isolated in 74% yield. Thus, with K^+ as the counter ion in the base the cone conformation is retained, and with Cs^+ partial cone is preferentially formed over cone.

On the basis of the foregoing results and with the aid of molecular mechanics calculations on the involved intermediates and their anions (see Experimental Section), a possible genesis of the various conformers in the base-catalyzed exhaustive alkylation of calix[4]arenes with

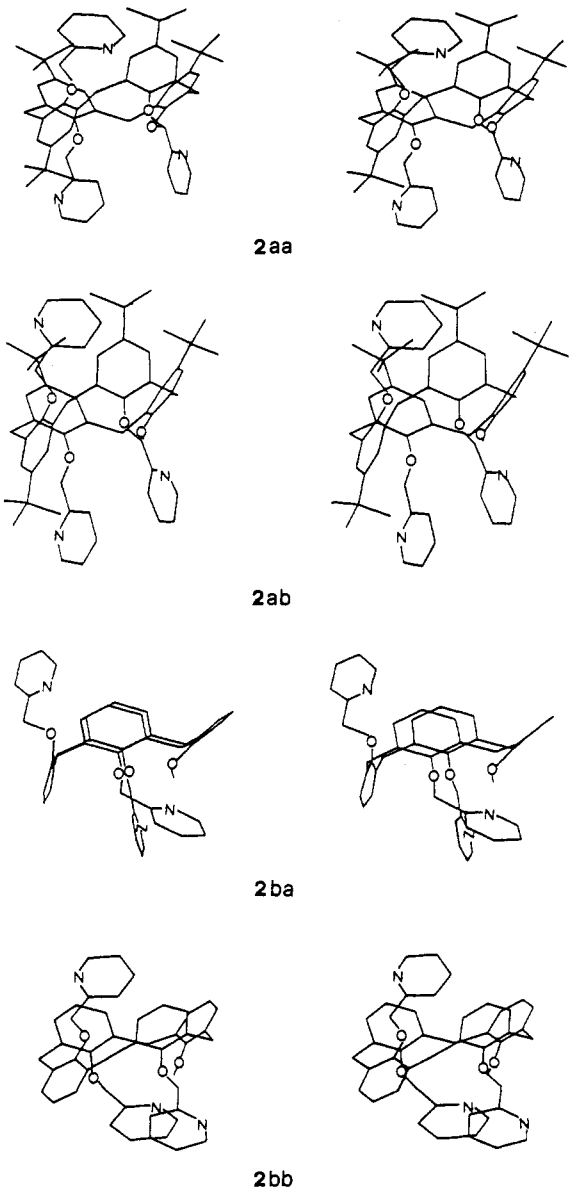


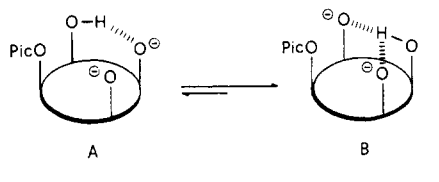
Figure 8. Computer-generated stereopairs of cis (**2aa** and **2ba**) and trans (**2ab** and **2bb**) configurational isomers of partial cone structures **2a** and **2b**.

PicCl·HCl in DMF at 70 °C can be proposed.

By assuming that the reaction proceeds through stepwise substitution of the OH groups, the first step is the monoalkylation of calix[4]arenes. The NMR spectra of monosubstituted calix[4]arenes **1c,d** account for a fixed cone conformation, which is unaffected by the temperature (T < 80 °C, $CDCl_3$). This means that the introduction of just one picolyl group suffices to curtail the conformational changes.

Control of regioselectivity for di-O-alkylation is achieved by a proper choice of the base. NaH (very strong base) promotes *regioselective proximal disubstitution*: under the reaction conditions (excess of base) a trianion will be generated, in which the phenoxide anion proximal to the OCH_2Py group will react preferentially (or exclusively) over the distal one because of a 2:1 statistic ratio, and above all because of a greater nucleophilic character (conjugated base of a weaker acid). The trianion intermediate is believed to adopt the cone conformation owing to a strong template effect of the Na^+ cation. Gutsche and co-workers have reported that the tetraanion generated from a calix[4]arene and 4 equiv of NaH exists in the cone conformation and that coalescence for conformational inversion occurs at 80 °C.[24]

Scheme I



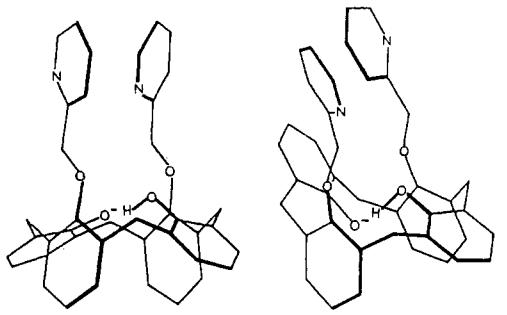


Figure 9. Computer-generated cone (left) and partial cone (right) conformations of $\mathbf{1h}^-$.

It has been argued[25] that a monoalkylated dianion intermediate and not a trianion might be the reactive species in the alkylation of calix[4]arenes with NaH/DMF, but adequate experimental evidence is still lacking. Anyway, if it is the case, an equilibrium between the two possible cone structures, shown in Scheme I, can be envisaged. MM2 calculations have shown that more favorable hydrogen bonding is established in structure B, which is about 4.9 – 6.2 kcal mol^{-1} (depending on the para substituent) more stable than the alternative structure A, thus accounting for the observed proximal regioselectivity in the NaH/DMF alkylation of calix[4]arenes.

The template effect of Na^+ is also operative in inducing and keeping the cone conformation for the products of further alkylation. As a matter of fact, *only* cone conformers have been isolated from the reaction mixtures when NaH or Na_2CO_3 are applied (Tables I and IV).

The use of relatively weak bases (alkali metal carbonates) instead of NaH results in *regioselective distal di-O-substitution*.[7b,17-19] In this case the more acidic OH group opposite to the OCH_2Py group will be deprotonated to afford a monophenoxide anion, whose negative charge will be stabilized by two hydrogen bonds, which keeps calix[4]arenes in the cone conformation. Therefore, depending on the identity and strength of the base applied, two different reaction pathways may operate, leading regioselectively to 1,2- or 1,3-di-O-alkylated intermediates.

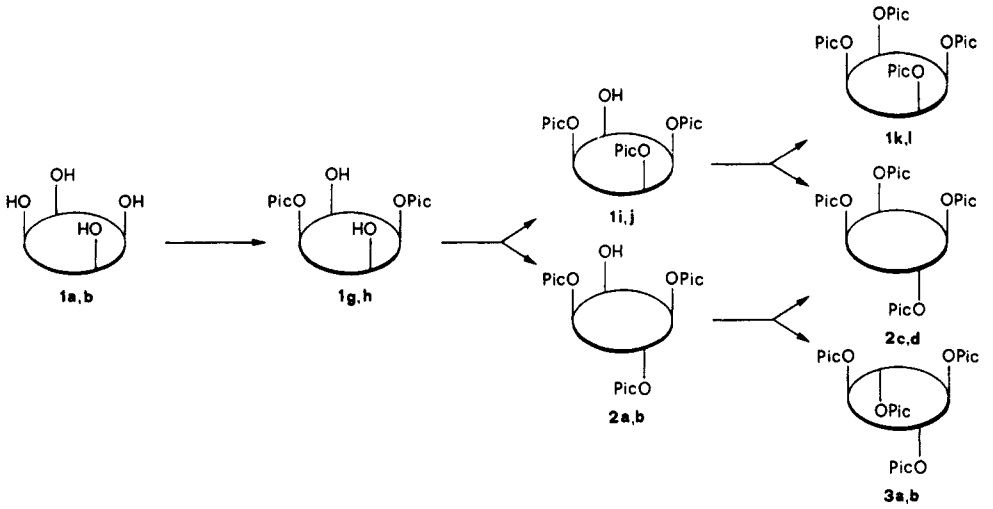
Hydrogen bond effects and the identity of the weak base seem to play a major role in determining the conformational outcome of the products of further alkylation of distally or proximally di-O-substituted calix[4]arenes.

In spite of the fact that syn-1,3-di-O-alkylated **1g,h** appear to be conformationally frozen in the cone conformation, the conformation and conformational mobility of their anions may be different. The monophenoxide anions generated by deprotonation of **1g,h** with weak bases can exist in either cone or partial cone conformation. MM2 calculations on $\mathbf{1h}^-$ indicate that the two conformers are almost isoenergetic and both approach a flattened cone conformation (Figure 9) by virtue of hydrogen bond for-

(24) Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I. *Pure Appl. Chem.* **1988**, *60*, 483. Gutsche, C. D.; Alam, I.; Iqbal, M.; Mangiafico, T.; Nam, K. C.; Rogers, J.; See, K. A. *J. Incl. Phenom.* **1989**, *7*, 73.

(25) Groenen, L. C. Private communication.

Scheme II

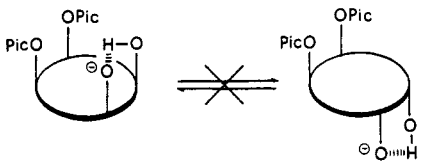


mation of the phenolate anion with the opposite OH group (OH···O distance ca. 2.5 Å). Provided that an equilibrium between the two conformers exists, the reactivity should be different if one considers that in the cone conformer the nucleophile in sterically crowded, while in the partial cone conformer the reaction center resides in the open and more accessible hydrophobic cavity. In agreement with these considerations, alkylation of de-*tert*-butylated **1h** with 1 equiv of PicCl·HCl afforded partial cone conformer **2b** in a surprising 100% selectivity. Compound **2b** was also isolated (in very low yield) and identified in the exhaustive alkylation of **1b** with PicCl·HCl in the presence of K_2CO_3. The steric energy of **1g** in the partial cone conformation is much lower (7.4 kcal mol^{-1}) than the cone conformer. In spite of this, alkylation of **1g** with PicCl·HCl (1 equiv) produced partial cone and cone tri-O-alkylated conformers **2a** and **1i** in only 3:1 ratio, the bulky *tert*-butyl substituents playing a deleterious role on the reactivity of the inversed phenoxide anion.

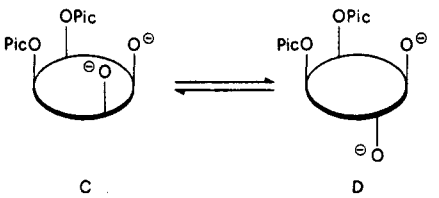
However, the conformer distribution in the alkylation of calix[4]arenes with PicCl·HCl does not appear to be completely determined in the third alkylation step, since interconversion of the residual phenoxide anion can still take place to some extent. Therefore, the conformational outcome will be established in the forth alkylation step by a delicate balance of the factors (steric effects, electrostatic repulsion among oxygens in contraposition to the template effect of the cation) affecting the cone ⇄ partial cone and/or partial cone ⇄ 1,3-alternate equilibria of the tri-O-alkylated phenoxide conformers. As a result, exhaustive alkylation of *tert*-butylated **1g** or de-*tert*-butylated **1h** with PicCl·HCl gives mainly partial cone **2b** or 1,3-alternate **3b**, respectively, bringing to light a possible influence of the para substituent on the conformer distribution. The major pathways in the exhaustive alkylation of calix[4]arenes with PicCl·HCl and alkali metal carbonates are summarized in Scheme II.

The monoanion of 1,2-alkylated calix[4]arenes **1e,f** can assume either cone or 1,2-alternate conformations, which are strongly stabilized over other conformations by very favorable hydrogen bond formation of the phenolate moiety with the adjacent OH group (OH···O distance ca. 2.3 Å) (Scheme III). Although MM2 calculations suggest that the relative energies of the two conformers are comparable (the difference is within 1–2 kcal mol^{-1}), the energy barrier for cone ⇄ 1,2-alternate conformational inversion is estimated to be very high, and the trisubstituted intermediate adopts the cone conformation.

Scheme III



Scheme IV



That the alkylation of calix[4]arenes with alkali metal carbonates proceeds through the formation of a monoanion intermediate and not a dianion was demonstrated by the following experiment. *syn-proximal*-**1e** was stirred at 70 °C for 1 h in the presence of excess of Cs_2CO_3 (5 equiv), followed by the addition of PicCl·HCl (1 equiv). If a dianion would be formed, an equilibrium between cone and partial cone dianion conformers C and D (Scheme IV) would be established, which should produce a mixture of tri-O-alkylated conformers. MM2 computation studies on the dianion of **1e** have shown a negligible energy difference between the two conformers (the strong electrostatic interaction of the two negatively charged oxygens is compensated by a lower value of the torsional term). However, the reaction yielded only conformer **1i**, ruling out the intermediacy of a dianion.

Our experimental results on the reaction of 1,2-disubstituted calix[4]arenes **1e,f** with PicCl·HCl and metal carbonates (Table IV) clearly show that in the final substitution step the template effect of the cation plays an important role in determining the ratio of cone and partial cone conformers. K^+ is more selectively bound to cone than to partial cone conformers, while Cs^+ induces a reversed and sharper selectivity for partial cone. These findings are in agreement with the extraction data of alkali metal picrates for cone **1k**, where selectivity follows the order $Na^+ > K^+ > Rb^+ > Cs^+$.[8]

Remarkably, syn-1,2- and syn-1,3-di-O-alkylated intermediates are generated in situ with excellent regioselectivity during the one-pot exhaustive alkylation of the parent calix[4]arenes with excess PicCl·HCl, so that the

reaction can be driven to the desired conformer(s) by a proper choice of the base.

The rationale proposed for 2-pyridylmethyl derivatization of calix[4]arenes is consistent with the conformational outcome of a large number of lower rim functionalizations reported in the literature, and the present results may therefore offer interesting perspectives for the synthesis of new, conformationally preorganized, calix[4]arene-based receptors.

Experimental Section

General Comments. Melting points were determined on a Kofler or Electrothermal melting point apparatus and are uncorrected. NMR spectra were taken on a Bruker AC-250 spectrometer for $CDCl_3$ solutions using Me_4Si as an internal standard. EI MS were recorded on a Kratos MS 50 double-focusing mass spectrometer, operating at 18 eV, equipped with a DS 90 data system. Elemental analyses were obtained from the Institute of Pharmaceutical Chemistry of the University of Catania. All chemicals were reagent grade and were used without further purification. Anhydrous DMF, THF, and toluene were purchased from Fluka. Compounds **1a**·toluene 1:1 complex[26] and **1b**[27] were prepared by literature procedures. All reactions were carried out under nitrogen.

Exhaustive Alkylation of 1a with PicCl·HCl and NaH: 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(2-pyridylmethyl)oxy]calix[4]arene, Cone Conformer (1k). A slurry of **1a** (0.74 g, 1 mmol) and 99% NaH (1.2 g, 50 mmol) in anhydrous DMF (20 mL) was gently warmed under stirring for 0.5 h. After the solution was cooled, PicCl·HCl (3.28 g, 20 mmol) was added and the reaction was warmed at 60 °C for 24 h. Addition of MeOH (2 mL) followed by dilution with water (100 mL) gave a solid which was recrystallized from MeOH to give **2a** (0.81 g, 80%) as white prisms: mp 231–233 °C; R_f = 0.45 (Al_2O_3, cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 1.10 (s, CMe_3, 36 H) 3.05 and 4.39 (ABq, J = 12.6 Hz, $ArCH_2Ar$, 8 H), 4.99 (s, OCH_2Py, 8 H), 6.84 (s, ArH, 8 H), 7.05 (ddd, J = 7.5, 4.9, 1.0 Hz, 5-PyH, 4 H), 7.27 (td, J = 7.6, 1.7 Hz, 4-PyH, 4 H), 7.67 (d, J = 7.8 Hz, 3-PyH 4 H), and 8.47 (ddd, J = 4.9, 1.7, 0.8 Hz, 6-PyH, 4 H); ^{13}C NMR δ 30.68, 31.40, 33.84, 78.01, 122.20, 123.24, 125.33, 133.57, 136.29, 144.93, 148.45, 152.58, and 158.14; MS m/z (relative intensity) 1012 (M^+, 4), 921 (100), 830 (50), 739 (23), 648 (17). Anal. Calcd for $C_{68}H_{76}N_4O_4$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.37; H, 7.65; N, 5.41.

Exhaustive Alkylation of 1b with PicCl·HCl and NaH: 25,26,27,28-Tetrakis[(2-pyridylmethyl)oxy]calix[4]arene, Cone Conformer (1l). The above procedure was followed except for the substitution of calix[4]arene **1b** (1 mmol). After the solution was quenched with MeOH (2 mL), the solvent was evaporated, and the residue was partitioned between water and $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The oily residue was chromatographed (column, basic Al_2O_3) by eluting with a gradient of AcOEt in cyclohexane to afford **1l** (0.57 g, 72%) as colorless crystals, mp 186–188 °C (AcOEt–*n*-hexane): R_f = 0.24 (Al_2O_3, cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 3.07 and 4.37 (ABq, J = 13.7 Hz, $ArCH_2Ar$, 8 H), 5.13 (s, OCH_2Py, 8 H), 6.58 (s, ArH, 12 H), 7.12 (ddd, J = 7.4, 4.9, 0.9 Hz, 5-PyH, 4 H), 7.46 (td, J = 7.6, 1.7 Hz, 4-PyH, 4 H), 7.71 (d, J = 7.8 Hz, 3-PyH, 4 H), and 8.48 (ddd, J = 4.9, 1.7, 0.8 Hz, 6-PyH, 4 H); ^{13}C NMR δ 31.24, 77.40, 122.45, 122.50, 123.50, 128.48, 134.86, 136.28, 148.79, 155.49, and 157.86; MS m/z 788 (M^+, 79), 697 (100), 680 (19), 605 (40), 587 (40), 512 (27), 496 (22), 387 (16). Anal. Calcd for $C_{52}H_{44}N_4O_4$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.95; H, 5.48; N, 7.01.

Exhaustive Alkylation of 1a with PicCl·HCl and Cs_2CO_3: 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(2-pyridylmethyl)oxy]calix[4]arene, 1,3-Alternate and Partial Cone Conformers (3a and 2c). A stirred mixture of **1a** (0.37 g, 0.5 mmol), PicCl·HCl (1.64 g, 10 mmol), and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (20 mL) was kept at 70 °C for 36 h. After being cooled, the reaction mixture was diluted with water (60 mL) and the solid which deposited was collected by filtration, dissolved in CH_2Cl_2, and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed (column, SiO_2) by eluting with a gradient of AcOEt in cyclohexane to give two main fractions.

Fraction A afforded 1,3-alternate conformer **3a** (90 mg, 18%) as white crystals: mp 278–280 °C dec (EtOH); R_f = 0.61 (cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 0.83 (s, CMe_3, 36 H), 3.63 (s, $ArCH_2Ar$, 8 H), 4.73 (s, OCH_2Py, 8 H), 6.57 (d, J = 7.8 Hz, 3-PyH, 4 H), 6.73 (s, ArH, 8 H), 7.14 (m, 5-PyH, 4 H), 7.55 (td, J = 7.7, 1.7 Hz, 4-PyH, 4 H), and 8.49 (dd, J = 4.7, 0.7 Hz, 6-PyH, 4 H); ^{13}C NMR δ 31.05, 33.53, 39.02, 72.64, 122.04, 122.45, 125.76, 132.86, 136.89, 144.74, 148.16, 153.67, and 158.09; MS m/z 1012 (M^+, 57), 921 (100), 920 (80), 904 (15), 865 (16), 830 (40), 812 (18). Anal. Calcd for $C_{68}H_{76}N_4O_4$·EtOH: C, 79.43; H, 7.71; N, 5.29. Found: C, 79.15, H, 7.92; N, 5.18.

Fraction B gave partial cone conformer **2c** (270 mg, 54%) as white prisms: mp 228–229 °C (MeCN); R_f = 0.44 (cyclohexane–AcOEt (1:1)); ^{1}H NMR δ 0.73 (s, CMe_3, 18 H), 1.13 (s, CMe_3, 9 H), 1.35 (s, CMe_3, 9 H), 3.02 and 4.18 (ABq, J = 12.2 Hz, $ArCH_2Ar$, 4 H), 3.79 and 3.90 (ABq, J = 16.7 Hz, $ArCH_2Ar$, 4 H), 4.43, 4.72 (s, OCH_2Py, 4 H), 4.74 (d, 3-Py′′H, 1 H), 4.76 and 4.85 (ABq, J = 13.0 Hz, OCH_2Py, 4 H), 6.54 (m, 4-Py′′H, 1 H), 6.57 (d, J = 2.2 Hz, ArH, 2 H), 6.74 (m, 5-Py′′H, 1 H), 6.86 (d, J = 2.2 Hz, ArH, 2 H), 6.92 (d, J = 7.6 Hz, 3-Py′H, 1 H), 6.98 (m, 5-Py′H, 1 H), 7.03 (s, ArH, 2 H), 7.11 (m, 5-PyH, 2 H), 7.14 (s, ArH, 2 H), 7.16–7.27 (m, 3-PyH and 4-Py′H, 3 H), 7.54 (td, J = 7.6, 1.6 Hz, 4-PyH, 2 H), 8.18 (dd, J = 4.1, 0.7 Hz, 6-Py′′H, 1 H), 8.29 (dd, J = 4.9, 0.7 Hz, 6-Py′H, 1 H), and 8.48 (dd, J = 4.1, 0.7 Hz, 6-PyH, 2 H); ^{13}C NMR δ 30.86, 31.20, 31.38, 31.58, 33.39, 33.85, 34.13, 38.98, 69.61, 75.64, 76.62, 120.12, 120.71, 121.74, 122.18, 123.10, 123.82, 124.92, 125.26, 126.02, 132.05, 133.20, 133.56, 134.99, 135.78, 136.45, 145.04, 145.14, 147.05, 147.85, 148.39, 152.34, 152.93, 153.08, 157.67, and 157.96; MS m/z 1012 (M^+, 19), 921 (100), 904 (20), 865 (22), 830 (82), 829 (86), 811 (52), 772 (35), 738 (36), 648 (27). Anal. Calcd for $C_{68}H_{76}N_4O_4$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.26; H, 7.72; N, 5.38.

Exhaustive Alkylation of 1b with PicCl·HCl and K_2CO_3: 25,26,27,28-Tetrakis[(2-pyridylmethyl)oxy]calix[4]arene, 1,3-Alternate and Partial Cone Conformers (3b and 2d). The above procedure was followed except for the substitution of **1b** (0.5 mmol) and K_2CO_3 (20 mmol). Usual workup gave a solid, which was chromatographed (column, Al_2O_3, cyclohexane–AcOEt (3:1)). The fastest moving components were discarded, and the more polar fraction was further purified by preparative TLC (SiO_2, *n*-hexane–AcOEt (1:1)) to afford two main fractions.

Fraction A gave 1,3-alternate conformer **3b** (130 mg, 33%) as white needles: mp 269–271 °C (CH_2Cl_2–*n*-hexane); R_f = 0.22; ^{1}H NMR δ 3.71 (s, $ArCH_2Ar$, 8 H), 4.95 (s, OCH_2Py, 8 H), 6.41 (t, J = 7.5 Hz, ArH, 4 H), 6.70 (d, J = 7.5 Hz, ArH, 8 H), 6.97 (d, J = 7.8 Hz, 3-PyH, 4 H), 7.31 (m, 5-PyH, 4 H), 7.70 (td, J = 7.7, 1.6 Hz, 4-PyH, 4 H), and 8.62 (d, J = 4.7 Hz, 6-PyH, 4 H); ^{13}C NMR δ 37.17, 72.36, 122.14, 122.37, 130.92, 134.04, 135.68, 148.55, 155.34, and 157.77; MS m/z 788 (M^+, 85), 697 (100), 696 (71), 680 (9), 606 (31), 605 (49), 587 (18), 513 (30), 512 (41), 496 (18). Anal. Calcd for $C_{52}H_{44}N_4O_4$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.82; H, 5.77; N, 6.98.

Fraction B provided partial cone conformer **2d** (87 mg, 22%): mp 221–223 °C (CH_2Cl_2–*n*-hexane); R_f = 0.05; ^{1}H NMR δ 3.09 and 4.14 (ABq, J = 12.7 Hz, $ArCH_2Ar$, 4 H), 3.68 and 3.81 (ABq, J = 14.6 Hz, $ArCH_2Ar$, 4 H), 4.57 and 4.69 (ABq, J = 11.7 Hz, OCH_2Py, 4 H), 4.74 (s, OCH_2Py, 2 H), 4.83 (s, OCH_2Py, 2 H), 6.2–7.4 (m, ArH + PyH, 24 H), 8.34 (d, J = 4.4 Hz, 6 Py′′H, 1 H), and 8.47 (m, 6 PyH and 6 Py′H, 3 H); ^{13}C NMR δ 30.14, 37.21, 71.72, 76.02, 77.09, 121.53, 121.79, 122.15, 122.54, 122.91, 123.60, 128.97, 129.06, 129.82, 130.51, 132.85, 133.48, 134.76, 135.88, 136.16, 136.34, 136.50, 147.09, 147.97, 148.91, 154.74, 155.53, 155.83, 156.80, 157.36, and 157.77; MS m/z 788 (M^+, 52), 697 (100), 696 (49), 680 (13), 606 (46), 605 (74), 513 (33), 512 (31), 496 (26). Anal. Calcd for $C_{52}H_{44}N_4O_4$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.73; H, 5.84; N, 6.87.

Partial Alkylation of 1a with PicCl·HCl and NaH. A mixture of **1a** (0.74 g, 1 mmol), NaH (0.24 g, 10 mmol), and PicCl·HCl (0.66 g, 4 mmol) in DMF was kept at 60 °C for 3 h and allowed to stir overnight at rt. Water was cautiously added to destroy the excess of NaH, and the solvent was evaporated in vacuo. After partitioning between water and $CHCl_3$, the organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed (column, SiO_2), by eluting with a gradient of

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AcOEt in cyclohexane, to give the following fractions.

Fraction A afforded **5,11,17,23-tetra-*tert*-butyl-25-[(2-pyridylmethyl)oxy]-26,27,28-trihydroxycalix[4]arene (1c)** (22 mg, 3%): mp 275–277 °C (lit.[21] mp 276–277 °C); R_f = 0.32 (cyclohexane–AcOEt (4:1)); ^{1}H NMR δ 1.19 (s, CMe_3, 9 H), 1.20 (s, CMe_3, 18 H), 1.22 (s, CMe_3, 9 H), 3.41 and 4.24 (ABq, J = 13.6 Hz, $ArCH_2Ar$, 4 H), 3.42 and 4.49 (ABq, J = 13.0 Hz, $ArCH_2Ar$, 4 H), 5.27 (s, OCH_2Py, 2 H), 6.97 (d, J = 2.3 Hz, ArH, 2 H), 7.04 (s, ArH, 2 H), 7.07 (d, J = 2.3 Hz, ArH, 2 H), 7.10 (s, ArH, 2 H), 7.31 (ddd, J = 7.1, 4.9, 1.7 Hz, 5-PyH, 1 H), 7.86 (td, J = 7.5, 1.7 Hz, 4-PyH, 1 H), 7.92 (bd, J = 7.7 Hz, 3-PyH), 8.66 (d, J = 4.9 Hz, 6-PyH, 1 H), and 9.70 (bs, OH, 3 H); ^{13}C NMR δ 31.22, 31.46, 32.28, 32.98, 33.88, 33.96, 34.21, 78.82, 122.53, 123.34, 125.63, 125.71, 126.47, 127.38, 128.11, 128.24, 133.53, 137.33, 142.96, 143.44, 147.83, 148.10, 148.46, 149.25, 149.88, and 156.04; MS m/z 739 (M^+, 39), 648 (100), 647 (85), 629 (33), 612 (26), 611 (19). Anal. Calcd for $C_{50}H_{61}NO_4$: C, 81.15; H, 8.31; N, 1.89. Found: C, 80.92; H, 8.36; N, 1.78.

Fraction B gave a trace amount of a component, whose analytical and spectral data were identical with those of **1g** (see below).

Fraction C yielded ***syn*-*proximal*-5,11,17,23-tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-dihydroxycalix[4]arene (1e)** (0.58 g, 70%): mp 204–206 °C; R_f = 0.14 (cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 1.11, 1.19 (s, CMe_3, 36 H), 3.26 and 4.37 (ABq, J = 13.1 Hz, $ArCH_2Ar$, 4 H), 3.34 and 4.27 (ABq, J = 13.7 Hz, $ArCH_2Ar$, 2 H), 3.43 and 4.61 (ABq, J = 12.8 Hz, $ArCH_2Ar$, 2 H), 4.88 and 5.33 (ABq, J = 13.0 Hz, OCH_2Py, 4 H), 6.91, 6.94, 6.99 and 7.01 (d, J = 2.3 Hz, ArH, 8 H), 7.18 (m, 5-PyH, 2 H), 7.56 (td, J = 7.7, 1.6 Hz, 4-PyH 2 H), 7.70 (d, J = 7.7 Hz, 3-PyH, 2 H), 8.56 (d, J = 4.8 Hz, 6-PyH 2 H), and 9.42 (bs, OH, 2 H); ^{13}C NMR δ 31.21, 31.47, 32.40, 32.57, 33.74, 33.96, 77.88, 122.24, 122.59, 125.21, 125.93, 127.41, 128.17, 133.18, 133.54, 136.80, 141.87, 146.39, 148.67, 149.16, 152.00, and 157.37; MS m/z 830 (M^+, 100), 739 (82), 738 (77), 720 (18), 648 (39), 647 (36). Anal. Calcd for $C_{56}H_{66}N_2O_4$: C, 80.92; H, 8.00; N, 3.37. Found: C, 80.77; H, 7.95; N, 3.25.

Fraction D provided **5,11,17,23-tetra-*tert*-butyl-25,26,27-tris[(2-pyridylmethyl)oxy]-28-hydroxycalix[4]arene, cone conformer (1i)** (46 mg, 5%): mp 219–222 °C; R_f = 0.47 (Al_2O_3, cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 0.85 (s, CMe_3, 18 H), 1.33, 1.36 (s, CMe_3, 18 H), 3.18 and 4.34 (ABq, J = 12.5 Hz, $ArCH_2Ar$, 4 H), 3.22 and 4.33 (ABq, J = 13.4 Hz, $ArCH_2Ar$, 4 H), 4.72 and 4.78 (ABq, J = 12.1 Hz, OCH_2Py, 4 H), 4.98 (s, OCH_2Py, 2 H), 6.51 (s, OH, 1 H), 6.54, 6.66 (d, J = 2.4 Hz, ArH, 4 H), 6.95 (m, 5-Py′H, 1 H), 7.07, 7.19 (s, ArH, 4 H), 7.08 (m, 5-PyH, 2 H), 7.27 (d, J = 7.7 Hz, 3-PyH, 2 H), 7.32 (m, 4-Py′H, 1 H), 7.44 (td, J = 7.6, 1.8 Hz, 4-PyH, 2 H), 8.34 (m, 3-Py′H and 6-Py′H, 2 H), and 8.42 (ddd, J = 4.9, 1.7, 0.9 Hz, 6-PyH, 2 H); ^{13}C NMR δ 30.62, 31.03, 31.45, 31.70, 31.75, 33.73, 33.85, 34.17, 76.95, 78.66, 121.83, 122.53, 122.76, 124.10, 125.14, 125.19, 125.85, 128.33, 131.79, 132.27, 135.49, 136.11, 136.37, 141.36, 145.75, 146.14, 147.30, 148.89, 150.76, 150.92, 153.07, 156.86, and 158.15; MS m/z 921 (M^+, 100), 830 (72), 829 (34), 739 (36), 738 (35), 720 (14), 683 (17), 648 (23), 647 (15). Anal. Calcd for $C_{62}H_{71}N_3O_4$: C, 80.74; H, 7.76; N, 4.56. Found: C, 80.44; H, 7.61; N, 4.48.

Partial Alkylation of 1b with PicCl·HCl and NaH. The above procedure was followed except for the substitution of **1b** (1 mmol) and reduced reaction time (1.5 h). The reaction mixture was purified by column chromatography (SiO_2) to afford two main fractions.

Fraction A gave ***syn*-*proximal*-25,26-bis[(2-pyridylmethyl)oxy]-27,28-dihydroxycalix[4]arene (1f)** (0.35 g, 58%): mp 193–195 °C; R_f = 0.08 (cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 3.28 and 4.41 (ABq, J = 13.0 Hz, $ArCH_2Ar$, 4 H), 3.37 and 4.36 (ABq, J = 13.7 Hz, $ArCH_2Ar$, 2 H), 3.48 and 4.65 (ABq, J = 12.7 Hz, $ArCH_2Ar$, 2 H), 4.88 and 5.34 (ABq, J = 13.0 Hz, OCH_2Py, 4 H), 6.58 (t, J = 7.5 Hz, ArH, 2 H), 6.78 (t, J = 7.5 Hz, ArH, 2 H), 6.9–7.0 (m, ArH, 6 H), 7.05 (dd, J = 7.5, 1.6 Hz, ArH, 2 H), 7.14 (ddd, J = 7.3, 4.9, 1.1 Hz, 5-PyH, 2 H), 7.46 (td, J = 7.6, 1.7 Hz, 4-PyH, 2 H), 7.56 (d, J = 7.7 Hz, 3-PyH, 2 H), 8.58 (d, J = 4.9 Hz, 6-PyH, 2 H), and 9.72 (bs, OH, 2 H); ^{13}C NMR δ 30.92, 31.78, 31.90, 77.84, 120.00, 122.17, 122.80, 124.69, 128.18, 128.32, 128.66, 128.76, 128.87, 129.16, 134.46, 134.51, 136.95, 148.78, 151.47, 154.31, and 157.20; MS m/z 606 (M^+, 84), 515 (58), 514 (100), 496 (52), 423 (21), 405 (11), 387 (22). Anal. Calcd for $C_{40}H_{34}N_2O_4$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.02; H, 5.58; N, 4.66.

Fraction B yielded **25,26,27-tris[(2-pyridylmethyl)oxy]-28-hydroxycalix[4]arene, cone conformer (1j)** (70 mg, 10%) as a thick oil which solidified on standing: mp 147–150 °C; R_f = 0.27 (Al_2O_3, cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 3.19 and 4.36 (ABq, J = 13.0 Hz, $ArCH_2Ar$, 4 H), 3.27 and 4.37 (ABq, J = 13.7 Hz, $ArCH_2Ar$, 4 H), 4.77 and 4.86 (ABq, J = 12.2 Hz, OCH_2Py, 4 H), 5.10 (s, OCH_2Py, 2 H), 5.78 (bs, OH, 1 H), 6.50 (m, ArH, 6 H), 6.75 (t, J = 7.4 Hz, ArH, 1 H), 6.98 (m, 5-Py′H and ArH, 2 H), 7.08 (d, J = 7.4 Hz, ArH, 2 H), 7.12 (m, 5-PyH, 2 H), 7.16 (d, J = 7.4 Hz, ArH, 2 H), 7.34 (td, J = 7.7, 1.7 Hz, 4-Py′H, 1 H), 7.42 (d, J = 7.6 Hz, 3-PyH, 2 H), 7.52 (td, J = 7.6, 1.7 Hz, 4-PyH, 2 H), 8.04 (d, J = 7.8 Hz, 3-Py′H, 1 H), 8.37 (d, J = 4.8 Hz, 6′-PyH, 1 H), and 8.48 (d, J = 4.8 Hz, 6-PyH, 2 H); ^{13}C NMR δ 30.52, 30.88, 77.00, 78.30, 119.04, 122.04, 122.46, 122.55, 123.56, 123.75, 124.19, 128.12, 128.28, 128.44, 129.08, 129.81, 132.55, 133.30, 135.95, 136.39, 136.43, 147.75, 148.94, 153.21, 153.42, 155.54, 156.73, and 157.44; MS m/z 697 (M^+, 42), 606 (43), 605 (21), 515 (47), 514 (43), 496 (26), 424 (22), 423 (34), 93 (100). Anal. Calcd for $C_{46}H_{39}N_3O_4$: C, 79.17; H, 5.63; N, 6.02. Found: C, 79.38; H, 5.56; N, 5.88.

***syn*-*distal*-5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(2-pyridylmethyl)oxy]-26,28-dihydroxycalix[4]arene (1g).** A mixture of **1a** (2.96 g, 4 mmol), PicCl·HCl (5.24 g, 32 mmol), and anhydrous K_2CO_3 (18 g) in DMF (100 mL) was heated at 70–80 °C for 20 h. After being cooled to room temperature, the reaction mixture was diluted with water (250 mL) and the precipitate obtained was filtered, washed with water, and dried. Extraction of the solid with boiling *n*-hexane (4 × 40 mL) gave pale yellow crude crystals of **1g** (2.4 g), which were dissolved in CH_2Cl_2 and passed through a short alumina column (eluent *n*-hexane–AcOEt (1:1)). Evaporation of the solvent and recrystallization from *n*-hexane gave pure **1g** (2 g, 60%) as white prisms: mp 250–252 °C; R_f = 0.25 (cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 0.93, 1.30 (s, CMe_3, 36 H), 3.35 and 4.31 (ABq, J = 13.1 Hz, $ArCH_2Ar$, 8 H), 5.19 (s, OCH_2Py, 4 H), 6.80, 7.08 (s, ArH, 8 H), 7.21 (s, OH, 2 H), 7.26 (m, 5-PyH, 2 H), 7.60 (td, J = 7.7, 1.6 Hz, 4-PyH, 2 H), 8.29 (d, J = 7.8 Hz, 3-PyH, 2 H), and 8.61 (d, J = 4.9 Hz, 6-PyH, 2 H); ^{13}C NMR δ 30.95, 31.50, 31.69. 33.84, 33.93, 78.15, 121.26, 122.48, 125.07, 125.64, 127.61, 132.32, 137.22, 141.68, 147.30, 148.95, 149.45, 150.60, and 157.67; MS m/z 830 (M^+, 100), 739 (50), 738 (61), 720 (20), 648 (14), 647 (15), 611 (11). Anal. Calcd for $C_{56}H_{66}N_2O_4$: C, 80.92; H, 8.00; N, 3.37. Found: C, 80.59; H, 7.98; N, 3.19. The use of Na_2CO_3 instead of K_2CO_3 resulted in a lower yield of **1g** (52%).

Partial Alkylation of 1b with PicCl·HCl and Bu^{t}OK. A mixture of **1b** (0.424 g, 1 mmol), PicCl·HCl (0.328 g, 2 mmol), and Bu^{t}OK (0.448 g, 4 mmol) in anhydrous toluene (25 mL), was refluxed for 20 h. The mixture was partitioned between water and $CHCl_3$. The organic layer was separated from the water layer, dried (Na_2SO_4), and concentrated. The residue was chromatographed (column, SiO_2) eluting with a gradient of AcOEt in cyclohexane to give two main fractions.

Fraction A afforded **25-[(2-pyridylmethyl)oxy]-26,27,28-trihydroxycalix[4]arene (1d)** (150 mg, 29%): mp 291 °C (dec over 250 °C) (CH_2Cl_2–MeOH), R_f = 0.49 (cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 3.44 and 4.26 (ABq, J = 13.7 Hz, $ArCH_2Ar$, 4 H), 3.46 and 4.51 (ABq, J = 13.0 Hz, $ArCH_2Ar$, 4 H), 5.29 (s, OCH_2Py, 2 H), 6.66 (t, J = 7.5 Hz, ArH, 3 H), 6.88 (t, J = 7.5 Hz, ArH, 1 H), 6.99 (d, J = 7.5 Hz, ArH, 2 H), 7.00 (dd, J = 7.5, 1.6 Hz, ArH, 2 H), 7.06 (dd, J = 7.5, 1.6 Hz, ArH, 2 H), 7.10 (d, J = 7.5 Hz, ArH, 2 H), 7.30 (m, 5-PyH, 1 H), 7.83 (m, 3- and 4-PyH, 2 H), 8.68 (d, J = 4.8 Hz, 6-PyH, 1 H), and 9.55 (bs, OH, 3 H); ^{13}C NMR δ 31.51, 31.88, 78.61, 120.84, 121.78, 122.31, 123.45, 126.13, 128.42, 128.75, 129.37, 134.33, 137.43, 149.28, 149.36, 150.76, 152.06, and 155.85; MS m/z 515 (M^+, 84), 423 (91), 405 (26), 387 (7), 93 (100). Anal. Calcd for $C_{34}H_{29}NO_4$: C, 79.20; H, 5.67; N, 2.72. Found: C, 78.95; H, 5.77; N, 2.66.

Fraction B gave ***syn*-*distal*-25,27-bis[(2-pyridylmethyl)oxy]-26,28-dihydroxycalix[4]arene (1h)** (70 mg, 11%): mp 271 °C (dec over 255 °C) (CH_2Cl_2–MeOH), R_f = 0.21 (cyclohexane–AcOEt (2:1)); ^{1}H NMR δ 3.42 and 4.36 (ABq, J = 13.2 Hz, $ArCH_2Ar$, 8 H), 5.19 (s, OCH_2Py, 8 H), 6.67–6.74 (m, ArH, 4 H), 6.88, 7.09 (d, J = 7.5 Hz, ArH, 8 H), 7.24 (m, 5-PyH, 2 H), 7.51 (td, J = 7.7, 1.7 Hz, 4-PyH, 2 H), 7.80 (s, OH, 2 H), 8.24 (d, J = 7.8 Hz, 3-PyH, 2 H), and 8.62 (bd, J = 4.7 Hz, 6-PyH, 2 H); ^{13}C NMR δ 31.27, 78.54, 119.16, 121.31, 122.57, 125.65, 127.79, 128.63, 129.16, 132.82, 137.33, 149.04, 151.65, 153.21, and 157.10; MS m/z 606

Table VI. Summary of Cell Data, Data Collection, and Refinement Details

compd	[*t*-BuC$_6$H$_2$CH$_2$(OCH$_2$py)]$_4$,0.6(MeOH) **1k**	[C$_6$H$_3$CH$_2$(OCH$_2$py)]$_4$ **1l**	[*t*-BuC$_6$H$_2$CH$_2$(OCH$_2$py)]$_4$,0.5(MeOH) **2c**
formula	C$_{68}$H$_{76}$N$_4$O$_4$,0.6(CH$_4$O)	C$_{52}$H$_{44}$N$_4$O$_4$	C$_{68}$H$_{76}$N$_4$O$_4$,0.5(CH$_4$O)
fw	1033.6	788.9	1029.4
color, habit	colorless block	colorless block	colorless block
crystal size, mm	0.15, 0.32, 0.55	0.25, 0.30, 0.40	0.29, 0.29, 0.35
cryst syst	monoclinic	monoclinic	monoclinic
a, Å	12.103 (5)	20.705 (5)	15.349 (4)
b, Å	12.535 (3)	18.831 (4)	16.705 (4)
c, Å	40.494 (6)	20.995 (3)	24.504 (8)
β, °	96.42 (2)	92.37 (1)	93.86 (3)
V, Å^3	6105 (5)	8179 (5)	6269 (3)
space group	$P2_1/c$	$P2_1/a$	$P2_1/c$
Z	4	8	4
F(000)	2221	3328	2212
d_{calc}, g cm^{-3}	1.13	1.28	1.09
μ, cm^{-1}	0.6	0.8	0.6
2θ range, deg	4–45	4–44	4–50
2θ range for setting angles, deg	10–15	10–34	11–22
temp, °C	21	21	18
reflcns measured	8796	10700	11220
unique reflcns	8600	10496	10958
reflcns with $I > 3\sigma(I)$	3950	3408 ($2.5\sigma(I)$)	4668
no. variables in LS	703	551	611
least-squares type	full-matrix	blocked matrix	blocked matrix
p in weights	0.001	0.001	0.001
R, R_w,	0.066, 0.083	0.064, 0.066	0.083, 0.090
density in final Δ-map, e Å^{-3}	0.37	0.32	0.59
final shift/error ratio	0.02	0.04	0.11

(M$^+$, 100), 515 (45), 514 (48), 496 (40), 423 (29), 405 (14), 387 (23). Anal. Calcd for $C_{40}H_{34}N_2O_4$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.01; H, 5.73; N, 4.42.

5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris[(2-pyridylmethyl)oxy]-28-hydroxycalix[4]arene, Partial Cone Conformer (2a). A mixture of **1g** (0.415 g, 0.5 mmol), PicCl·HCl (0.082 g, 0.5 mmol), and Cs_2CO_3 (0.325 g, 1 mmol) in anhydrous DMF (10 mL) was heated at 70 °C for 20 h. After being cooled, the reaction mixture was diluted with water (40 mL), and the resulting precipitate was collected by suction filtration, dissolved in DCM, and dried over Na_2SO_4. Evaporation of the solvent left a residue, which was chromatographed (column, SiO_2) eluting with a gradient of AcOEt in cyclohexane to afford the following fractions.

Fraction A gave a trace amount of **3a** (<1%).

Fraction B provided **2a** (90 mg, 34% based on reacted **1g**) as white crystals: mp 190–194 °C (EtOH), R_f = 0.27 (cyclohexane–AcOEt (3:1)); ^{1}H NMR (300 MHz) δ 0.71 (s, CMe$_3$, 18 H), 1.00, 1.38 (s, CMe$_3$, 18 H), 3.29 and 4.27 (ABq, J = 12.8 Hz, ArCH$_2$Ar, 4 H), 3.96 and 4.12 (ABq, J = 17.5 Hz, ArCH$_2$Ar, 4 H), 4.46 (s, OCH$_2$Py′, 2 H), 4.61 (d, J = 8.1 Hz, 3-Py′H, 1 H), 4.89 and 5.25 (ABq, J = 13.6 Hz, OCH$_2$Py, 4 H), 6.05 (td, J = 8.0, 1.7 Hz, 4-Py′H, 1 H), 6.64 (m, 5-Py′H, 1 H), 6.66 (d, J = 2.3 Hz, ArH, 2 H), 6.85 (d, J = 2.3 Hz, ArH, 2 H), 7.03 (s, ArH, 2 H), 7.06 (m, 5-PyH, 2 H), 7.17 (s, ArH, 2 H), 7.19 (td, J = 7.5, 1.7 Hz, 4-PyH, 2 H), 7.46 (d, J = 7.9 Hz, 3-PyH, 2 H), 8.11 (d, J = 4.7 Hz, 6-Py′H, 1 H), 8.18 (s, OH, 1 H), and 8.50 (d, J = 4.9 Hz, 6-PyH, 2 H); ^{13}C NMR δ 30.82, 31.26, 31.83, 32.39, 33.52, 33.85, 34.04, 39.21, 68.99, 76.58, 120.07, 120.85, 121.69, 122.06, 124.73, 125.13, 125.87, 128.55, 132.09, 132.79, 136.40, 137.18, 141.66, 146.17, 146.48, 146.60, 148.38, 150.51, 152.07, 152.51, 153.24, 157.08, and 157.66; MS m/z 921 (M$^+$, 100), 830 (30), 829 (77), 828 (42), 739 (20), 738 (22), 720 (10), 648 (16), 611 (17). Anal. Calcd for $C_{26}H_{71}N_3O_4$: C, 80.74; H, 7.76; N, 4.56. Found: C, 80.97; H, 7.51; N, 4.40.

Further elution afforded unreacted **1g** (ca. 40%) and **1i** (40 mg, 11%).

25,26,27-Tris[(2-pyridylmethyl)oxy]-28-hydroxycalix[4]arene, Partial Cone Conformer (2b). The above procedure was followed except for the substitution of **1h** (0.2 mmol). The reaction was quenched after 6 h by diluting with water. The resulting precipitate was collected by filtration and dried. The crude reaction mixture was column chromatographed (SiO_2) eluting with a gradient of AcOEt in cyclohexane to afford the following fractions.

Fraction A gave unreacted **1h** (ca. 27%).

Fraction B provided **2b** (44 mg, 44% based on reacted **1h**) as colorless crystals: mp 204–207 °C, R_f = 0.25 (cyclohexane–AcOEt (1:1)); ^{1}H NMR (300 MHz) δ 3.33 and 4.18 (ABq, J = 13.2 Hz, ArCH$_2$Ar, 4 H), 3.91 and 4.05 (ABq, J = 16.1 Hz, ArCH$_2$Ar, 4 H), 4.70 (s, OCH$_2$Py′, 2 H), 4.91 and 5.24 (ABq, J = 13.6 Hz, OCH$_2$Py, 4 H), 5.23 (d, J = 9.8 Hz, 3-Py′H, 1 H), 6.28 (t, J = 7.5 Hz, ArH, 2 H), 6.62 (m, 4-Py′H and ArH, 4 H), 6.78 (t, J = 7.4 Hz, ArH, 1 H), 6.81 (bd, J = 6.3 Hz, ArH, 2 H), 6.93 (m, 5-Py′H, 1 H), 6.99 (d, J = 7.4 Hz, ArH, 2 H), 7.14 (d, J = 7.4 Hz, ArH, 2 H), 7.17 (m, 5-PyH, 2 H), 7.35 (td, J = 7.6, 1.8 Hz, 4-PyH, 2 H), 7.44 (d, J = 7.8 Hz, 3-PyH, 2 H), 7.55 (s, OH, 1 H), 8.33 (d, J = 4.9 Hz, 6-Py′H, 1 H), and 8.57 (d, J = 4.5 Hz, 6-PyH, 2 H); ^{13}C NMR δ 31.15, 37.88, 70.17, 75.41, 119.04, 121.39, 122.24, 123.57, 124.08, 128.26, 129.05, 129.43, 129.88, 132.94, 133.07, 133.85, 136.15, 136.87, 146.93, 148.66, 153.20, 153.25, 153.88, 154.90, 156.69, and 157.35; MS m/z 697 (M$^+$, 100), 606 (51), 515 (42), 514 (78), 513 (62), 512 (33), 496 (33), 387 (58). Anal. Calcd for $C_{46}H_{39}N_3O_4$: C, 79.19; H, 5.63; N, 6.02. Found: C, 78.71; H, 5.84; N, 5.80.

From further elution 1,3-alternate **3b** (18%) and partial cone **2d** (4%) were also isolated.

25,26-Bis[(2-pyridylmethyl)oxy]-27,28-bis[[(*tert*-butoxycarbonyl)methyl]oxy]calix[4]arene (4). A mixture of **1f** (0.303 g, 0.5 mmol) and NaH (0.048 g, 2 mmol) in anhydrous THF (10 mL) was heated at 50 °C under stirring for 0.5 h. After the solution was cooled at rt, *tert*-butyl bromoacetate (0.39 g, 2 mmol) in THF (5 mL) was added dropwise, and the mixture was refluxed for 1.5 h. MeOH (1 mL) was then added, and the solvent was evaporated. The residue was partitioned between water and $CHCl_3$ and the organic layer separated from the water layer, dried, and concentrated. The crude product was chromatographed (column, SiO_2) eluting with cyclohexane–AcOEt (3:1 v/v) to give **4** (284 mg, 68%): mp 139–142 °C; ^{1}H NMR δ 1.41 (s, CMe$_3$, 18 H), 3.01 and 4.21 (ABq, J = 13.6 Hz, ArCH$_2$Ar, 2 H), 3.16 and 4.62 (ABq, J = 13.7 Hz, ArCH$_2$Ar, 4 H), 3.27 and 4.81 (ABq, J = 13.8 Hz, ArCH$_2$Ar, 2 H), 4.62 and 4.71 (ABq, J = 15.8 Hz, OCH$_2$CO$_2$CMe$_3$, 4 H), 5.07 and 5.12 (ABq, J = 12.7 Hz, OCH$_2$Py, 4 H), 6.61 (m, ArH, 12 H), 7.16 (m, 5-PyH, 2 H), 7.55 (td, J = 7.6, 1.7 Hz, 4-PyH, 2 H), 7.83 (d, J = 7.7 Hz, 3-PyH, 2 H), and 8.48 (d, J = 4.9 Hz, 6-PyH, 2 H); ^{13}C NMR δ 28.05, 30.94, 31.34, 31.76, 71.63, 77.63, 80.99, 122.38, 122.50, 123.37, 128.42, 134.55, 134.68, 134.76, 134.90, 136.24, 148.70, 155.68, 155.77, 158.04, and 169.10. Anal. Calcd for $C_{52}H_{54}N_2O_8$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.51; H, 6.70; N, 3.12.

5,11,17,23-Tetra-*tert*-butyl-25-[(2-pyridylmethyl)oxy]-26-[[[2-(*N*-methylpyridinium)]methyl]oxy]-27,28-di-

hydroxycalix[4]arene Iodide (5). A solution of **1f** (0.249 g, 0.3 mmol) in MeI (5 mL) was stirred at rt in a stoppered flask for 24 h. Analytically pure **5** (0.26 g, 90%) precipitated from the reaction mixture as a pale yellow powder: mp 163–164 °C; ^{1}H NMR δ 1.13 (s, CMe_3, 9 H), 1.15 (s, CMe_3, 9 H), 1.23 (s, CMe_3, 18 H), 3.2–4.6 (m, $ArCH_2Ar$, 8 H), 4.45 (s, *N*-Me, 3 H), 4.75 and 5.53 (ABq, J = 13.0 Hz, OCH_2Py, 2 H), 4.80 and 5.64 (ABq, J = 16.1 Hz, OCH_2-*N*-MePy, 2 H), 6.92, 6.93, 6.98, 7.23 (d, J = 2.3 Hz, ArH, 4 H), 7.05–7.08 (m, ArH, 4 H), 7.34 (m, 5-PyH, 1 H), 7.40 (d, J = 7.7 Hz, 3-PyH, 1 H), 7.66 (m, 4-PyH and 3,4,5-*N*-MePy, 4 H), 8.47 and 8.97 (bs, OH, 2 H), 8.67 (d, J = 4.9 Hz, 6-PyH, 1 H), and 9.23 (d, J = 5.0 Hz, 6-*N*-MePyH, 1 H); ^{13}C NMR δ 31.10, 31.27, 31.40, 31.50 [$C(CH_3)_3$], 32.62, 32.85, 33.50, 33.83 ($ArCH_2Ar$), 33.73, 33.88, 34.05, 34.16 [$C(CH_3)_3$], 46.12 (*N*-CH_3), 71.13 (OCH_2-*N*-MePy), 77.66 (OCH_2Py), 123.19, 123.39, 125.10, 125.25, 125.74, 126.25, 126.43, 126.83, 127.02, 127.14, 127.83, 128.89, 132.45, 132.54, 133.41, 134.90, 137.34, 141.78, 142.72, 144.48, 146.17, 147.30, 147.66, 148.01, 148.87, 150.37, 150.44, 152.02, 154.64, and 156.26. Anal. Calcd for $C_{57}H_{69}IN_2O_4$: C, 70.28; H, 7.14; N, 2.88. Found: C, 69.87; H, 7.35; N, 2.61.

11,17-Bis[(dimethylamino)methyl]-25,26-bis[(2-pyridylmethyl)oxy]-27,28-dihydroxycalix[4]arene (6). A mixture of **1f** (0.182 g, 0.3 mmol), $(CH_3)_2NH$ 40% (0.176 g, 1.56 mmol), and CH_2O 37% (0.127 g, 1.56 mmol) in THF–AcOH (5:1 v/v, 3 mL) was refluxed under stirring for 24 h. Progress of the reaction was followed by monitoring the disappearance of **1f** on TLC (Al_2O_3, cyclohexane–AcOEt (2:1)). The solvent and volatile reactants were evaporated in vacuo, and the residue was treated with saturated aqueous K_2CO_3 solution, extracted with Et_2O, and dried (Na_2SO_4). Evaporation of the solvent gave a solid which on recrystallization furnished colorless crystals of **6** (123 mg, 57%): mp 167–170 °C (cyclohexane–CH_2Cl_2); ^{1}H NMR δ 2.14 (s, NMe_2, 12 H), 3.15 and 3.22 (ABq, J = 12.6 Hz, CH_2NMe_2, 4 H), 3.28 and 4.38 (ABq, J = 13.0 Hz, $ArCH_2Ar$, 4 H), 3.36 and 4.31 (ABq, J = 13.7 Hz, $ArCH_2Ar$, 2 H), 3.48 and 4.65 (ABq, J = 12.7 Hz, $ArCH_2Ar$, 2 H), 4.88 and 5.33 (ABq, J = 13.0 Hz, OCH_2Py, 4 H), 6.78 (t, J = 7.5 Hz, ArH, 2 H), 6.87 (d, J = 2.0 Hz, ArH, 2 H), 6.89 (d, J = 2.0 Hz, ArH, 2 H), 6.96 (dd, J = 7.6, 1.6 Hz, ArH, 2 H), 7.04 (dd, J = 7.5, 1.6 Hz, ArH, 2 H), 7.18 (ddd, J = 7.2, 4.9, 1.3 Hz, 5-PyH, 2 H), 7.56 (td, J = 7.6, 1.7 Hz, 4-PyH, 2 H), 7.61 (d, J = 7.7 Hz, 3-PyH, 2 H), 8.59 (ddd, J = 4.9, 1.6, 0.8 Hz, 6-PyH, 2 H), and 9.63 (bs, OH, 2 H); ^{13}C NMR δ 30.79, 31.60, 31.70, 45.10, 63.82, 77.77, 122.11, 122.68, 124.51, 127.81, 128.29, 128.69, 128.95, 129.05, 129.52, 129.74, 134.41, 136.83, 148.70, 150.40, 154.17, and 157.07. Anal. Calcd for $C_{46}H_{48}N_4O_4$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.90; H, 6.58; N, 7.64.

Tri-O-alkylated Cone Conformers 1i and 1j. A mixture of syn-proximal di-O-alkylated calix[4]arene (0.5 mmol), Cs_2CO_3 (0.32 g, 1 mmol), and PicCl·HCl (0.5 mmol) was heated at 70 °C for a few hours. Progress of the reaction was checked by TLC (cyclohexane–AcOEt (1:1)) following the disappearance of the starting materials. When the reaction was complete, the solvent was evaporated and the residue dissolved in DCM, filtered, and passed through a short column (Al_2O_3) by eluting with cyclohexane–AcOEt (1:1) mixture. Evaporation of the solvent gave the desired trisubstituted cone conformer, in high yield (Table IV).

Structural Analyses. Details of the X-ray experimental conditions, cell data, data collection and refinement for compounds **1k**, **1l**, and **2c** are concisely summarized in Table VI. The cell and intensity data were collected with an Enraf Nonius CAD4 diffractometer using graphite monochromatised Mo-Kα radiation. Calculations were carried out using the SDP-Plus system of programs and data therein,[28] with SHELX76[29] and with SHELXS86.[30] The structures were solved by direct methods. Hydrogen atoms (visible in difference maps) were allowed for (as riding atoms, C–H 0.95 Å) and refinement was by least-squares calculations on F with all non-H atoms allowed anisotropic motion for **1k** and **2c**; because of the paucity of data for **1l**, the ring carbon atoms were refined with isotropic thermal parameters. In **1k** the phenyl rings were constrained to be rigid hexagons with standard bond lengths; in **2c** the phenyl and pyridine rings were similarly constrained. The decision as to which was a nitrogen atom and which was a carbon in the pyridine rings was unequivocally made in each case from difference maps (by unambiguous location of all pyridine H atoms). In both **1k** and **2c** a methanol of solvation was found hydrogen bonded to a pyridine N atom (in **1k** the methanol has 0.6 occupancy and its O atom is 2.81 Å from pyridine nitrogen N14A; in **2c** the methanol has 0.5 occupancy with the O atom 3.02 Å from N14C).

Selected dimensions are in Table III. Figures 3–6 are views of the molecules prepared with the aid of ORTEPII[31] and PLUTON.[32]

Table VII. Results of Molecular Mechanics Calculations[a]

	E_t	E_{vdw}	E_{str}	E_{bnd}	E_{tor}	E_{ele}	E_{hbd}	E_b
dianions **1d**								
proximal	15.3	18.3	1.7	4.0	9.0	−18.8	1.1	0.0
distal	9.1	15.9	1.6	3.5	9.9	−23.1	1.1	0.2
1f	22.1	14.8	1.7	4.5	14.6	−13.7	0.0	0.2
anions **1f**								
cone	4.9	14.8	1.8	4.2	15.0	−32.7	1.6	0.2
1,2-alternate	4.0	10.6	1.7	5.5	14.8	−30.3	1.4	0.3
1h	30.1	18.0	2.0	6.4	16.8	−13.1	−0.4	0.3
anions **1h**								
cone	15.7	18.0	1.8	5.6	15.7	−30.1	0.8	0.4
partial cone	16.0	15.4	1.8	6.3	20.7	−29.3	0.9	0.2
1j	41.0	15.4	2.0	6.0	20.0	−2.2	−0.3	0.0
anions **1j**								
cone	44.5	14.8	2.0	5.4	18.9	3.3	0.0	0.1
partial cone	42.0	13.5	1.8	5.4	19.5	1.6	0.0	0.2
2ba[b]	43.2	12.5	2.2	8.5	23.9	−4.5	0.0	0.6
2bb[b]	39.0	15.0	1.8	5.5	19.0	−2.0	−0.3	0.0
anions **2b**								
partial cone	35.2	11.8	1.7	5.7	20.0	−4.0	0.0	0.0
1,3-alternate	43.3	14.4	2.0	6.7	18.3	1.5	0.0	0.4
dianions **1c**								
proximal	27.0	20.7	5.0	8.9	17.0	−26.8	1.4	0.6
distal	22.1	21.0	5.1	8.5	15.7	−30.5	1.6	0.7
1e	35.0	20.1	4.7	8.8	15.6	−14.6	0.0	0.4
monoanions **1e**								
cone	20.1	20.2	4.7	8.8	16.0	−31.7	1.2	0.9
1,2-alternate	22.2	18.5	4.8	10.1	16.0	−29.5	1.4	0.9
dianions **1e**								
cone	53.3	17.3	5.0	8.8	20.7	0.5	0.0	1.0
partial cone	53.6	17.7	4.8	8.4	16.3	5.5	0.0	0.9
1g	42.7	21.5	5.0	10.6	18.7	−13.7	−0.3	0.9
anions **1g**								
cone	38.8	25.4	5.0	10.9	24.9	−29.1	0.5	1.2
partial cone	31.4	20.5	4.8	10.4	22.0	−28.2	0.9	1.0
2aa[b]	52.3	16.2	5.0	11.8	20.0	−1.0	−0.4	0.9
2ab[b]	49.1	16.2	5.0	11.9	18.5	−2.9	−0.5	0.9
anions **2a**								
partial cone	54.0	20.5	5.2	11.1	22.8	−6.7	0.0	1.1
1,3-alternate	56.6	16.6	5.3	12.8	19.5	1.1	0.0	1.3
1i	55.5	20.1	5.0	10.4	21.9	−2.6	−0.2	0.9
anions **1i**								
cone	58.6	19.9	5.0	9.7	20.4	2.7	0.0	0.9
partial cone	55.8	18.1	4.9	9.0	22.1	0.8	0.0	0.9

[a] All the energies are in kcal/mol. E_t is the sum of various terms. E_{vdw} denotes the van der Waals energy; E_{str} is the bond stretching energy; E_{bnd} is the bending energy; E_{tor} is the torsional energy; E_{ele} denotes the electrostatic energy and hydrogen bonding energy; E_{hbd} is used to fine tuning the geometry of hydrogen bond; E_b is the sum of stretch-bend cross term and improper torsional energy. [b] See Figure 8 for relative structures.

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Additional material available from the Cambridge Crystallographic Data Centre comprises atom coordinates, thermal parameters, and a full listing of bond lengths and angles for the compounds. Copies of the structure factor listing are available from the authors.

MM2 Calculations. The program used to calculate the structures in MACROMODEL by Steel using modified MM2 force field.[33] Several days of calculations have been necessary on a Vax Station 3100. The algorithm used to minimize structure potential energy was the block diagonal matrix Newton–Raphson procedure (BDNR).[34] One proceeded by iterative calculation using as convergence criterion the energy gradient until it reached a low value of the order 10^{-2} kJA^{-1} mol^{-1}. Unfortunately, one cannot be sure by molecular mechanics procedure whether or not global minimum is reached, and sometimes the molecule is located in a saddlepoint or hilltop.[35] Such circumstances are checked by looking at the sign of the eigenvalues of the second derivative matrix: if only one is negative (imaginary one), then the structure is at a saddlepoint and if more than one is negative it is at a hill top. In no case did we have imaginary eigenvalues for the structure obtained; that is, the energies are relative to minimum structures. We moved the atoms of the most important dihedral angles that determined the structure and reminimized the new structures to be sure that the global minimum was found.

In order to understand the relative stability of different conformations of a calixarene, it is necessary to split the steric energy in its additive components:

$$E_t = E_{str} + E_{bnd} + E_{tor} + E_{vdw} + E_{ele} + E_{hbd} + E_b$$

The meaning of the various terms in the equation are defined in Table VII. The difference in the stretching term for the various conformers is so small that it can be neglected; therefore, our attention has been mainly focused on electrostatic, torsional and bonding terms, as well as nonbonded interactions. Table VII shows the relative importance of each of these terms in defining the steric energy.

Although the programs used do not allow us to evaluate solvent and metal template effects on the stability of a given structure, the results obtained provide a qualitative picture of the factors affecting the conformational equilibria of the anions; more importantly the conclusions that can be drawn appear to be in pretty good agreement with the experimental findings.

From a scrutiny of Table VII, the distal dianion of **1d** is about 6.2 kcal mol^{-1} more stable than the alternative proximal dianion (Scheme I). The longer distance between the two negatively charged oxygens in the distal form accounts for its smaller electrostatic and van der Waals energies. This may indicate that the formation of this dianion is faster. The results on **1c** suggest a similar trend, so that one can conclude that the bulky para substituent does not influence significantly the above equilibrium.

It is worthy of note that cone and partial cone anions of **1h** have a comparable steric energy because of a fine balance between van der Waals and torsional terms; however, the corresponding para substituted anions (anions of **1g**) show a strong difference (7.4 kcal mol^{-1}) in their steric energies. With the exception of the electrostatic term, all other terms in the partial cone conformer are smaller than those in the cone conformer, due to a strong stacking interaction between the rotated *tert*-butyl group and a pyridine ring.

Monoanions of **1f** in the cone and 1,2-alternate conformations (Scheme III) have almost the same energy, while the cone conformation of *tert*-butylated compound **1e** is about 2.1 kcal mol^{-1} more stable than the 1,2-alternate conformer. Although rotated *tert*-butyl groups interact favorably with the juxtaposed pyridine rings (E_{vdw} is smaller than that in the cone conformation), bend and electrostatic terms are slightly larger. The electrostatic term likely increased because of a larger distance between partially charged negative and positive centers.

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Registry No. **1a**, 60705-62-6; **1b**, 74568-07-3; **1c**, 123207-96-5; **1d**, 139584-71-7; **1e**, 123207-95-4; **1f**, 123207-98-7; **1g**, 123207-97-6; **1h**, 139584-72-8; **1i**, 123239-32-7; **1j**, 123207-99-8; **1k**, 139683-30-0; **1k**·$^3/_5$MeOH, 139756-44-8; **1l**, 139584-73-9; **2a**, 123239-32-7; **2b**, 123207-99-8; **2c**, 139683-31-1; **2c**·$^1/_2$MeOH, 139756-45-9; **2d**, 139683-32-2; **3a**, 139584-74-0; **3b**, 139683-33-3; **4**, 139584-75-1; **5**, 139606-53-4; **6**, 139584-76-2; PicCl·HCl, 6959-47-3; $(CH_3)_2NH$, 124-40-3; *t*-butyl bromoacetate, 5292-43-3.

Supplementary Material Available: For molecules **1k**, **1l**, and **2c**, tables listing final fractional coordinates and esd's for all non-H atoms, calculated hydrogen coordinates, molecular dimensions, anisotropic thermal parameters, mean plane data, and selected torsion angles; and for molecules **1k** and **1l**, difference map sections through the pyridine rings to show the H-location clearly (61 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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