Complexation of Alkali Metal Cations by Conformationally Rigid, Stereoisomeric Calix[4]arene Crown Ethers: A Quantitative Evaluation of Preorganization

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Abstract: Selective bridging of *p-tert*-butylcalix[4]arene (**1**) with tetra- and pentaethylene glycol ditosylate gives the 1,3-dihydroxy-*p-tert*-butylcalix[4]arene crown ethers **7** and **9** in good yields. The subsequent alkylation of the two phenolic groups of **7** and **9** with substituents (R) bulkier than CH_3 gives a series of conformationally rigid 1,3-dialkoxy-*p-tert*-butylcalix[4]arene crown ethers, which exist as a mixture of stereoisomers. Three isomeric compounds (**10a**, **10b**, and **10c**) have been obtained when R = C_2H_5. ^1H NMR and X-ray crystallography show a fixed-cone structure for **10a**, a partial cone for **10b**, and a 1,3-alternate for **10c**. Only the cone and the partial-cone stereoisomers have been isolated when R = *n*-C_3H_7, *i*-C_3H_7, and $CH_2C_6H_5$. The free energies of complexation of the calixcrowns and alkali metal picrate (MPi) salts, in $CDCl_3$, vary from −6 to −13.5 kcal mol^{-1}. All ligands are selective toward potassium cations, and in the case of calixcrown **10b** a K^+/Na^+ selectivity of 1.18×10^4 is found, which is the highest value observed so far for calixarene ligands and also for a synthetic ionophore. In all cases the partial cone isomer shows the highest free energy of complexation ($\Delta G°$), confirming our previous assumption that this is the preferred conformation for binding cations. The differences in binding free energies of complexation ($\Delta\Delta G°$) between the cone and the partial-cone isomers of the same calixcrown allow a quantitative evaluation of the preorganization concept. In the case of RbPic complexes of calixcrowns **10b** and **10a** this difference reaches the value of 4.9 kcal mol^{-1}. Variable-temperature ^1H NMR experiments indicate that the K^+ complex of the partial-cone stereoisomer **10b** is also kinetically more stable than the corresponding complex of the cone compound **10a**. The results obtained are explained on the basis of electronic and stereochemical arguments.

Introduction

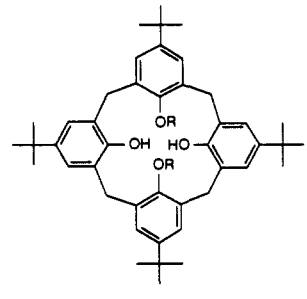
Calixarenes[1] have been used in the last few years as useful substructures for the synthesis of lipophilic[2] or water soluble[3] cation receptors and carriers. In particular *p-tert*-butylcalix[4]arene (**1**, Chart I), which is easily accessible in large quantities,[4] is a very convenient building block.[2] Compound **1** is conformationally mobile in solution,[5] although in the solid state it is present exclusively as a "cone" structure[6] due to strong intramolecular hydrogen bonding.

The introduction of substituents on the phenolic OH groups of compound **1** produces derivatives which have different shapes and conformational mobilities depending on the nature and the number of these substituents.[1] The introduction of four ester,[7,8] keto,[9] amide,[10] or mixed type[11] binding sites on the phenolic OH groups ("lower rim") of *p-tert*-butylcalix[4]arene (**1**) fixes this macrocycle in the "cone" structure, giving *sodium selective* cation receptors.

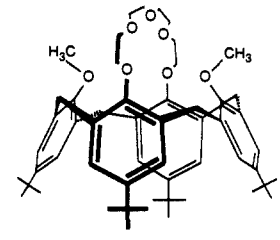
On the other hand, the selective 1,3-dialkylation of **1**,[12,13] followed by the introduction of suitable polyether bridges on the two remaining OH groups, has allowed us to synthesize a new family of *potassium selective* ionophores. In particular the 1,3-dimethoxycalix[4]arene crown ether (**2**) has shown a surprisingly high K^+/Na^+ selectivity both in extraction[12] and ISFET[14] measurements, whereas the more rigid calixspherand **3** gave complexes that are *kinetically stable* on a human time-scale, not only with Na^+ but also with K^+ and Rb^+ cations.[12]

During our previous studies on bridged 1,3-dimethoxycalix[4]arene crown ethers[12] several data were collected which indicated that the preferred conformation for binding in this new class of macrocyclic compounds must be the flattened partial cone, where one of the two alkyl groups is located inside the apolar cavity of the calix[4]arene and the other near the polyether ring. This arrangement of binding groups has been observed[12] in the X-ray

Chart I



1, R=H
6, R=C_2H_5



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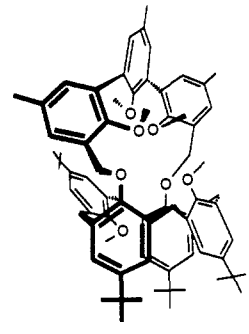

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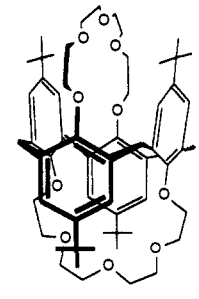

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(1) Gutsche, C. D. *Calixarenes*; Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989.
(2) Ungaro, R.; Pochini, A. In *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, The Netherlands, in press.

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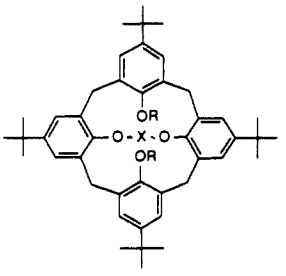
Chart II



2, R=CH_3, X=$CH_2CH_2(OCH_2CH_2)_3$
4a,b, R=$CH_2C_6H_5$, X=$CH_2CH_2(OCH_2CH_2)_3$
5, R=CH_3, X=$CH_2CH_2(OCH_2CH_2)_4$
7, R=H, X=$CH_2CH_2(OCH_2CH_2)_3$
9, R=H, X=$CH_2CH_2(OCH_2CH_2)_4$
10a-c, R=C_2H_5, X=$CH_2CH_2(OCH_2CH_2)_3$
11a,b, R=C_2H_5, X=$CH_2CH_2(OCH_2CH_2)_4$
12a,b, R=n-C_3H_7, X=$CH_2CH_2(OCH_2CH_2)_3$
13a,b, R=i-C_3H_7, X=$CH_2CH_2(OCH_2CH_2)_3$

structure of the RbPic complex of 1,3-dimethoxy-*p-tert*-butylcalix[4]arene crown-6 (**5**). The 1,3-bis(benzyloxy)-*p-tert*-butylcalix[4]arene crown-5 (**4a**), having a fixed cone conformation, gave much less stable complexes with potassium picrate in $CDCl_3$ at 25 °C. Moreover, the calixspherand **3** which formed the most stable complex ($\Delta G°$ = −18.1 kcal mol^{-1}) with KPic, shows a flattened partial-cone arrangement of the binding sites both in the free state and after complexation with alkali cations.[12] For this reason compound **3** can be considered a highly preorganized host molecule according to D. J. Cram's definition of preorganization.[15]

The objective of the present study was to investigate whether the complexing properties of calix[4]arene crown ethers (**2** and **5**) could be improved by reducing their conformational mobility. Our aim was to synthesize different and conformationally stable forms of the same calix[4]arene crown ethers and compare their complexing abilities. This would enable us to clarify the factors which control complexation by calixcrown receptors, to prove our postulate that the flattened partial cone is the optimal conformation for binding, and to evaluate quantitatively the preorganization concept.

Results and Discussion

Synthesis and Solution Structures of the Hosts. Examination of the CPK molecular models revealed that the replacement of methyl groups in compounds **2** and **5** with more bulky substituents could prevent the rapid interconversion of the different calix conformations and give stable isomers of the same compound.

Table I. Isolated Yield of Different Stereoisomers of 1,3-Dialkoxycalix[4]arene Crown Ethers

compd	conformation	yield, %
4a	cone	66
4b	partial cone	15
10a	cone	53
10b	partial cone	28
10c	1,3-alternate	13
11a	cone	59
11b	partial cone	31
12a	cone	42
12b	partial cone	28
13b	partial cone	73

Two different reaction routes were followed in order to obtain the desired products. First we treated 1,3-diethoxy-*p-tert*-butylcalix[4]arene (**6**) with NaH and tetraethylene glycol ditosylate, under the same conditions applied previously for the synthesis of dimethoxy- and bis(benzyloxy)calix[4]arene crown ethers (**2** and **4a**, respectively).[12] The reaction of **6** did not proceed smoothly and only after a much longer reaction time HPLC analysis showed evidence for the formation of calixcrown-type compounds. This indicates that bridging of the 1,3-dialkoxy-calix[4]arenes is very sensitive to the nature of the alkoxy substituents.

The second route gave better results. By slow addition procedures (influction)[16] the yield of the starting 1,3-dihydroxy-*p-tert*-butylcalix[4]arene crown ethers **7** and **9** was improved compared with our previously published preliminary results[17] to 53% (**7**) and 38% (**9**), respectively (Chart II). In the synthesis of 1,3-dihydroxy-*p-tert*-butylcalix[4]arene crown-5 (**7**) we also isolated the macrotricyclic *p-tert*-butylcalix[4]arene bis-crown-5 (**8**) in which the calix moiety adopts a 1,3-alternate structure because of the double 1,3-bridge.

Calixcrown **7** was dialkylated with ethyl iodide in THF/DMF in almost quantitative yield. HPLC analyses revealed the presence of three compounds in the reaction mixture with almost the same retention times. The relative yield of the three products reported in Table I are the mean values of several different runs of the same reaction and were determined by HPLC.

Pure compounds were obtained by preparative TLC chromatography on Al_2O_3 plates and the mass spectra indicated the same molecular weight (M^+, 862.58) for the three compounds. NMR (^1H and ^{13}C) and X-ray (vide infra) data allowed us to establish the structures of the isomeric compounds **10a–c** both in solution and in the solid state.

Compound **10a**, the most abundant (53% isolated yield) of the 1,3-diethoxy-*p-tert*-butylcalix[4]arene crown-5 stereoisomers, has a flattened-cone structure. The ^1H NMR spectrum shows two signals for the aromatic protons at δ 7.03 and 6.38, two doublets (J = 12.4 Hz) for the bridging methylene groups of the calix at δ 4.28 (H axial) and δ 3.06 (H equatorial), two singlets for the *tert*-butyl groups at δ 1.31 and 0.82, and only one type of signal for the two ethoxy groups. This is the typical pattern[7c] for *p-tert*-butylcalix[4]arene derivatives in the "flattened-cone" conformation and has also been observed in the 1,3-dimethoxy-calix[4]arene crown-5 (**2**)[12] of which the X-ray crystal structure, which we have recently determined (vide infra), shows this conformation.

The second compound isolated in 28% yield from the reaction of crown **7** with ethyl iodide has a partial-cone structure, which is clearly indicated by the typical 1:1:2 ratio of the *tert*-butyl singlets, by four signals for the aromatic protons, and by the two nonequivalent ethoxy groups.[1,18] In particular, the high-field shifts experienced by both the methylene quartet (δ 1.50) and the methyl triplet (δ −0.46) of one ethoxy group indicate that this group is located inside the cavity of the calix ("endo-positioned" OC_2H_5).

(3) Shinkai, S. In *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, The Netherlands, in press.
(4) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.
(5) Gutsche, C. D.; Bauer, L. J. *Tetrahedron Lett.* **1981**, *22*, 4763–4766. Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052–6059.
(6) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005–1007.
(7) (a) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981–982. (b) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreetti, G. D.; Ugozzoli, F. *Tetrahedron* **1986**, *42*, 2089–2100. (c) Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335–338.
(8) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. J. *J. Chem. Soc., Chem. Commun.* **1985**, 388–390. Chang, S. K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211–214.
(9) Ferguson, G.; Kaiter, B.; McKervey, M. A.; Seward, E. M. *J. Chem. Soc., Chem. Commun.* **1987**, 584–586.
(10) Calestani, G.; Ugozzoli, F.; Arduini, A.; Ghidini, E.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1987**, 344–346. Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, G.; Ugozzoli, F. *J. Inclusion Phenom.* **1988**, *6*, 114–134.
(11) Collins, E. M.; McKervey, M. A.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 372–375.
(12) Reinhoudt, D. N.; Dijkstra, P. J.; in 't Veld, P. J. A.; Bugge, K.-E.; Harkema, S.; Ungaro, R.; Ghidini, E. *J. Am. Chem. Soc.* **1987**, *109*, 4761–4762. Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567–7575.
(13) Van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1989**, *30*, 2681–2684.
(14) Van den Berg, A. PhD Thesis, University of Twente, 1988, p 81.
(15) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039–1134.
(16) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1–111.
(17) Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075–1076. Ungaro, R.; Pochini, A.; Andreetti, G. D. *J. Inclusion Phenom.* **1984**, *2*, 199–206.
(18) Bocchi, V.; Foina, D.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *Tetrahedron* **1982**, *38*, 373–378.

Table II. Association Constants (K_a) and Binding Free Energies ($-\Delta G°$) of Complexes of Hosts with Alkali Picrates in $CDCl_3$ Saturated with H_2O at 22 °C[a]

	Na^+		K^+		Rb^+		Cs^+	
compd	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}
2	1.1×10^5	6.7	3.0×10^8	11.4	1.1×10^8	10.8	4.7×10^5	7.6
4a	4.4×10^4	6.3	1.2×10^6	8.2	5.9×10^4	6.4	$<10^4$	<6
4b	8.7×10^4	6.7	1.3×10^7	9.5	2.0×10^6	8.6	1.6×10^5	7.1
10a	1.3×10^5	6.9	1.2×10^7	9.6	4.0×10^5	7.6	9.8×10^4	6.8
10b	7.5×10^5	8.0	8.9×10^9	13.5	1.5×10^9	12.5	1.6×10^6	8.5
10c	2.9×10^5	7.5	1.4×10^8	11.5	5.4×10^7	10.5	9.3×10^5	8.1
12a	1.2×10^5	6.9	5.5×10^6	9.2	5.6×10^5	7.8	1.8×10^5	7.2
12b	1.9×10^6	8.6	5.2×10^8	11.9	1.9×10^7	9.9	8.3×10^5	8.1
13b	2.7×10^5	7.5	1.7×10^9	12.6	2.0×10^8	11.2	3.0×10^5	7.6

[a] The association constants were determined as described by Cram et al.;[21a] the precision of the values is as described by Cram et al.[21b]

This reflects the frequently observed tendency of calixarenes[19a] and other macrocycles to fill their potential cavities with solvent molecules or with their own groups (self complexation).[19b]

The third compound, isolated in 13% yield, has a 1,3-alternate conformation as inferred from the 8 H singlet (δ 3.86) of the bridging methylenes of the calix, the two very close singlets for the aromatic (δ 7.03 and 6.97) and the *tert*-butyl protons (δ 1.37 and 1.28), and the equivalence of the two OC_2H_5 groups.

These solution structures of the three stereoisomers **10a–c** are in complete agreement with the X-ray results. No change was observed in the ^1H NMR spectra when each pure stereoisomer was heated in $CDCl_3$ at 90 °C (sealed tube for ~6 h), indicating that no interconversion of the three compounds occurs and that the observed distribution of products reflects kinetically controlled alkylation.[20] By following the same reaction scheme and changing the nature of the alkylating agent, a number of new stereoisomeric 1,3-dialkoxy-*p-tert*-butylcalix[4]arene crown ethers were synthesized and isolated in a pure form (Table I).

Crystal Structures. Five X-ray crystal structures relevant for this work have been determined. Details on the experimental procedures and crystallographic details are given in the experimental section.

The crystal structure of the conformationally mobile 1,3-dimethoxy-*p-tert*-butylcalix[4]arene crown-5 (**2**) is given in Figure 1a. The figure clearly shows the flattened cone conformation as anticipated on the basis of ^1H NMR data.[12] Both methoxy groups are located near the polyether ring, the oxygen lone pairs being directed into the cavity.

The structure of the KPic complex of 1,3-diethoxy-*p-tert*-butylcalix[4]arene crown-5 in the cone conformation (**10a**·KPic) is shown in Figure 1b. The K^+ ion is coordinated by seven oxygen atoms of the polyether ring and both ethoxy groups. When we compare the cone conformations of **2** and of **10a**·KPic, the more regular conformation is found in the case of the K^+ complex. This can be explained by the fact that for the complexation of the K^+ ion the oxygen atoms on the phenyl rings have to move outwards, giving rise to a less flattened cone conformation.

Figure 1c shows the results of the crystal structure determination of 1,3-diethoxy-*p-tert*-butylcalix[4]arene crown-5 in the partial-cone conformation (**10b**). The first ethyl group is in the hydrophobic cavity of the molecule, the other is in the vicinity of the macrocycle. As a consequence of the filling of the cavity by the first ethoxy group its oxygen lone pairs are located in a region outside the cavity.

In Figure 1d the crystal structure of the 1,3-alternate conformation of 1,3-diethoxy-*p-tert*-butylcalix[4]arene crown-5 (**10c**) is given. In this conformation both ethoxy groups are oriented in such a manner that the oxygen lone pairs are in the cavity.

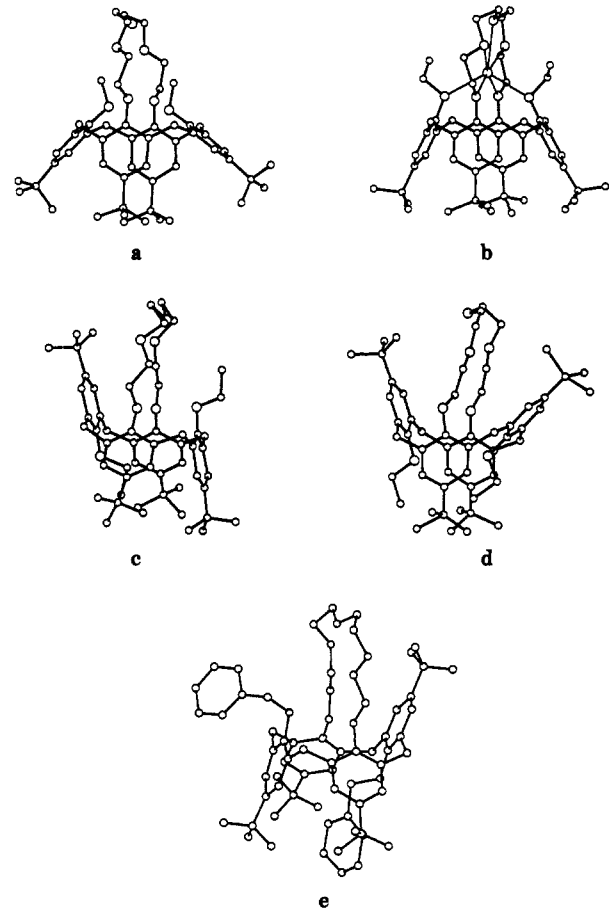


Figure 1. Crystal structure of **2**, **10a**·KPic, **10b**, **10c**, and **4b** (a–e, respectively).

Figure 1e gives the crystal structure of 1,3-bis(benzyloxy)-*p-tert*-butylcalix[4]arene crown-5 in the partial-cone conformation (**4b**). The position of the benzyloxy groups with respect to cavity and polyether ring is similar to that found in the corresponding diethoxy compound **10b** (Figure 1c).

Complexation Studies

Thermodynamic Stabilities of the Complexes. The association constants (K_a) and binding free energies ($-\Delta G°$) of the 1,3-dialkoxy-*p-tert*-butylcalix[4]arene crown ethers were determined by the two-phase (water, chloroform) picrate extraction method reported by Lein and Cram.[21a]

This is a convenient method especially for highly lipophilic host molecules and has been used previously in our groups to establish

(19) (a) Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1773–1779; Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiano, P. *J. Inclusion Phenom.* **1985**, *3*, 35–42. (b) Grootenhuis, P. D. J.; van Eerden, J.; Sudhölter, E. J. R.; Reinhoudt, D. N.; Roos, A.; Harkema, S.; Feil, D. *J. Am. Chem. Soc.* **1987**, *109*, 4792–4797.

(20) In the reaction of 1,3-diethoxycalix[4]arene **6** with tetraethylene glycol ditosylate, all three isomers are formed in low yield in the ratio **10a**:**10b**:**10c** = 2:1:1, indicating that in compound **6** the two ethoxy groups are able to invert their relative positions under reaction conditions (base).

(21) (a) Lein, G. M.; Cram, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 448–455. (b) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chau, L.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941.

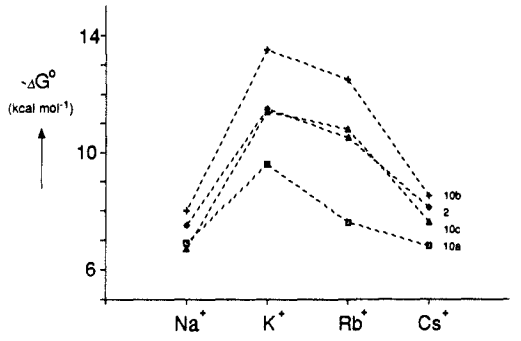


Figure 2. Gibbs free energy (-$\Delta G°$) of alkali cation complexation.

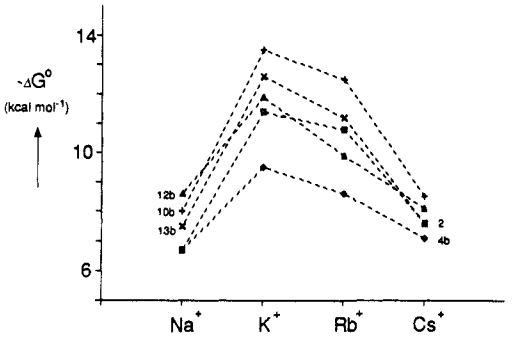


Figure 3. Gibbs free energy (-$\Delta G°$) of alkali cation complexation.

the complexing properties of other bridged calix[4]arenes.[12]

The K_a (M^{-1}) and -$\Delta G°$ (kcal mol^{-1}) values obtained are reported in Table II.

All ligands show peak selectivity toward K^+ cations, and, as anticipated, the partial-cone stereoisomers show a higher value of the association constant for all cations (Figure 2).

In the 1,3-diethoxy derivatives **10a–c** the sequence of binding efficiency for alkali metal cations between the three isomers is partial cone > 1,3-alternate > cone.

The difference in binding free energy of complexation ($\Delta\Delta G°$) between partial cone and cone depends on the cation that is complexed and can be as high as 4.9 kcal mol^{-1}, as in the case of Rb^+. This difference reflects, for each cation, the effect of having one single binding site in two different rigid geometries, one of them being the most suited (preorganized) for binding. In this sense it provides, for the first time, a quantitative evaluation of the preorganization concept.

The data show also that the cone stereoisomer of all compounds synthesized binds the most complementary cations (K^+ and Rb^+) less efficiently than the conformationally mobile 1,3-dimethoxy derivative **2**. The fixed cone conformation is not very sensitive to the nature of the R groups and the largest difference in $\Delta G°$ observed is 1.4 kcal mol^{-1} between R = C_2H_5 and R = $C_6H_5CH_2$, which could reflect electronic differences between the two groups being an electron-withdrawing benzyl ($\sigma^* = 0.22$) and a weak electron-donating ethyl ($\sigma^* = -0.10$) substituent.[22]

On the other hand all isomers in the partial-cone structures, except the dibenzyl derivative **4b**, are better ligands than the flexible compound **2** (Figure 3) and in the case of 1,3-diethoxy derivative **10b** the difference ($\Delta\Delta G°$) is 2.1 kcal mol^{-1} for the best complexed cation (K^+). Figure 3 shows that **10b** is *the most efficient* and also the *most selective* ligand of the series, supporting Cram's view[15] that preorganization often enhances both *efficiency* and *selectivity* in cation complexation.

In particular ligand **10b** exhibits a K^+/Na^+ selectivity of 1.18×10^4, a value higher than that shown by the mobile calixcrown **2** and the highest observed so far for a synthetic ionophore.

The cation complexing ability of compounds in the fixed partial-cone conformation is more strongly affected by the nature of the R group in 1,3-positions. The binding free energy difference ($\Delta\Delta G°$) between compound **10b** (R = C_2H_5) and compound **4b** (R = $C_6H_5CH_2$) in their potassium complexes is as high as 4.0 kcal mol^{-1}. To explain this difference one must consider not only electronic but also steric factors.

The X-ray crystal structures of the two ligands **10b** and **4b** in the partial-cone conformation are very similar (Figure 1c,e); one of the two alkoxy groups fills the hydrophobic cavity of the calix and the oxygen unshared electron pairs are oriented toward the exterior of the binding cavity. Upon complexation this "endo-positioned" alkoxy group has to rotate to bring the oxygen unshared electron pairs toward the interior of the cavity and, in this conformation, has to move upward in order to interact with the cation. The available X-ray data on the cation complexes of bridged calix[4]arenes[12] show, in fact, that in all cases the calix assumes a flattened partial-cone arrangement where one aromatic nucleus (the one bearing the "endo-positioned" alkoxy group) is almost parallel to the mean plane containing the bridging methylenes of the calix and perpendicular to the other three aromatic nuclei. In the case of 1,3-bis(benzyloxy)-*p-tert*-butylcalix[4]arene crown-5 in the partial-cone structure **4b**, this process could be hindered by steric or other more specific π/alkyl interactions[23] with the two adjacent *tert*-butyl groups of the calix thereby reducing the degree of interaction between the "endo-positioned" benzyloxy group and the cation and decreasing the binding free energy as well.

Cram has clearly shown experimentally[15] and Kollman has confirmed by molecular mechanics calculations[24] that in a series of preorganized hosts, the binding free energies decrease rapidly with a decrease in the number of the ligating sites of the host.

^{1}H NMR Studies. ^{1}H NMR complexation studies on 1,3-diethoxy calixcrowns **10a–c** with alkali metal cations were performed to clarify the solution structures of the complexes and the conformational reorganization of the ligands upon complexation.

The 1:1 complexes of all three isomeric calixcrown ethers **10a–c** and potassium picrate were prepared and their ^{1}H NMR spectra recorded at ambient temperature in $CDCl_3$.

In the case of compound **10a** (cone structure) the two singlets of the aromatic and that of each of the *tert*-butyl protons become less different, indicating a more symmetrical and less flattened cone structure in the complex compared with the free ligand, in agreement with the X-ray crystal structure (Figure 1b).

In the K^+ complex of the 1,3-alternate stereoisomer **10c** only moderate (0.19 ppm max) and normal downfield shifts were observed for most of the signals which maintain the same pattern observed for the free ligand and indicate no large conformational reorganization upon complexation at ambient temperature.

The ^{1}H NMR spectrum of the K^+ complex of the partial-cone isomer **10b** shows significant differences compared with the free ligand.

The CH_3 signal of the "endo-positioned" ethoxy group, which is more clearly visible in the spectrum, moves 1.18 ppm downfield in the complex, indicating a rotation which brings the oxygen atom unshared electron pairs inside and the ethyl group outside the cavity of the calix. At the same time the *tert*-butyl singlets change from the 1:2:1 pattern of the free ligand to a 1:1:2 in the complex, mainly because one *tert*-butyl group (probably opposite to the "endo-positioned" OC_2H_5) moves 0.42 ppm downfield upon complexation.

In all compounds **10a–c** the ^{1}H NMR spectra of the 1:1 mixture of free ligand and KPic complex show the signals of both species at ambient temperature, indicating that the exchange of the cation is slow on the NMR (80 and 200 MHz) time scale for all isomers.

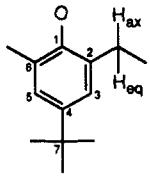
Variable-temperature experiments (at 80 MHz) gave a coalescence temperature T_c = 57 °C (ΔG^* = 21 kcal mol^{-1}) for the cone **10a**·K^+ and T_c = 122 °C (ΔG^* = 25 kcal mol^{-1}) for the partial cone isomer **10b**·K^+, both compounds retaining their structure upon heating.

(22) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; pp 7-2, 7-3.

(23) Andreetti, G. D.; Ori, O.; Ugozzoli, F.; Alfieri, C.; Pochini, A.; Ungaro, R. *J. Inclusion Phenom.* **1988**, *6*, 523–536.

(24) Kollman, P. A.; Wipff, G.; Sing, C. U. *J. Am. Chem. Soc.* **1985**, *107*, 2212–2219.

Chart III



These results indicate that the higher thermodynamic stabilities of the complexes of the partial cone (**10b**) parallel the lower rate of decomplexation.

Conclusions

The results obtained in this study show that in highly preorganized cation ligands, such as the bridged calix[4]arenes, the stability of the complexes can be strongly affected by subtle changes in the geometry around the binding region. In all cases the partial cone arrangement of the calix[4]arene subunit is the preferred conformation for binding in this new class of ionophores. Moreover, the comparison between the binding free energies of complexation ($\Delta\Delta G°$) of stereoisomeric crown ethers allows, for the first time, a quantitative evaluation of the preorganization concept.

Experimental Section

Melting points were determined with a Reichert or Electrothermal melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with Bruker WP-80 (80 MHz), AC-100 (100 MHz), CXP-200 (200 MHz), or 600 AM MHz (600 MHz) spectrometers in $CDCl_3$ unless otherwise indicated (Me_4Si as an internal standard). Mass spectra (EI) were obtained with a Varian MAT 311A and VG7070 EQ-HF spectrometer.

Absorbance readings in the UV-vis for association constants were taken on a Zeiss M4QIII and on a UVIKON 860 spectrophotometer. Microanalyses were carried out in the Laboratory of Chemical Analysis of the University of Twente and in the Istituto di Chimica Farmaceutica, Università di Parma.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl, while dimethylformamide (DMF) was distilled from KOH pellets and kept over molecular sieves (3 Å). Dropwise addition over a period of several hours was always carried out with a perfusor. All reactions were carried out in a nitrogen atmosphere. Chromatographic separations were performed on silica gel 60 (SiO_2) (E. Merck, particle size 0.040–0.063 mm, 230–240 mesh) or aluminum oxide (Al_2O_3) (E. Merck, neutral grade, particle size 0.063–0.300 mm, 70–230 mesh ASTM), whereas preparative TLC was performed on 60 F254 (Al_2O_3) preparative plates (E. Merck, thickness 1.5 mm).

HPLC analyses were performed with Waters instruments (model 6000 A pump, U6K injector, and model 440 UV detector at 254 and 280 nm).

See Chart III for numbering scheme.

26,28-Diethoxy-5,11,17,23-tetrakis(1,1-dimethylethyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecane-25,27-diol (6). A suspension of *p-tert*-butylcalix[4]arene/toluene (10.0 g, 13.5 mmol), K_2CO_3 (37.3 g, 270 mmol), and ethyl tosylate (5.50 g, 27 mmol) in 600 mL of dry CH_3CN was heated under reflux for 20 h. After evaporation of the solvent under reduced pressure, the crude product was boiled in 4 N KOH solution for 2 h. After cooling to room temperature and filtration, the crude product was purified by crystallization from EtOH/$CHCl_3$: yield 90%; mp 278–281 °C; mass spectrum, *m/e* 704.488 (M^+, calcd 704.480); ^1H NMR (200 MHz) δ 7.79 (s, 2 H, OH), 7.03 (s, 4 H, ArH), 6.85 (s, 4 H, ArH), 4.31 (d, $J_{ax,eq}$ = 12.8 Hz, 4 H, $ArCH_2Ar$, H_{ax}), 4.08 (q, J = 7.1 Hz, 4 H, OCH_2C), 3.31 (d, $J_{ax,eq}$ = 12.8 Hz, 4 H, H_{eq}), 1.62 (t, J = 7.1 Hz, 6 H, $OCCH_3$), 1.27 (s, 18 H, $C(CH_3)_3$), 1.01 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 150.5 and 150.0 (s, C-1), 146.7 and 141.4 (s, C-4), 132.9 and 128.1 (s, C-2 and C-6), 125.4 and 125.0 (d, C-3 and C-5), 71.9 (t, OCH_2), 33.9 and 33.8 (s, C-7), 32.0 (t, $ArCH_2Ar$), 31.7 and 31.1 (m, CH_3-7), 15.3 (q, $OCCH_3$). Anal. Calcd for $C_{48}H_{64}O_4 \cdot CH_3CH_2OH$: C, 79.96; H, 9.39. Found: C, 79.04; H, 9.36.

2,20,25,35-Tetrakis(1,1-dimethylethyl)-6,7,9,10,12,13,15,16-octahydro-28*H*-4,18-(methano[1,3]benzenomethano)-23,27-metheno-22*H*-dibenzo[*n*,*w*][1,4,7,10,13]pentaoxacyclotetracosin-29,32-diol (7). To a stirred and refluxing solution of *p-tert*-butylcalix[4]arene/toluene (0.732 g, 1.0 mmol) and *t*-ButOK (0.112 g, 1.0 mmol) in 40 mL of dry benzene was added dropwise tetraethylene glycol ditosylate (0.53 g, 1.0 mmol) in 30 mL of dry benzene over a period of 1.5 h. After 24 h refluxing a second portion of *t*-ButOK (0.112 g, 1 mmol) was added, and the reaction mixture refluxed for an additional 24 h, then cooled, treated with 1 N HCl, and extracted several times with diethyl ether. The combined organic layers were finally washed with water and the solvent was removed under reduced pressure. The crude product was dissolved in ethyl acetate, filtered, and chromatographed on silica gel (SiO_2, CH_2Cl_2/ethyl acetate = 4:1 v/v). The main product (R_f = 0.5) was obtained in 53% yield. A HPLC analysis on column LICHROSORB-MERCK (ethyl acetate/hexane = 70:30 v/v, 2 mL/min) shows a single peak with a retention time of 1.8 min: mp 246–248 °C; mass spectrum, *m/e* 806 (M^+); ^1H NMR (200 MHz) δ 7.20 (s, 2 H, OH), 7.12 (s, 4 H, ArH), 6.78 (s, 4 H, ArH), 4.41 (d, $J_{ax,eq}$ = 13.0 Hz, 4 H, $ArCH_2Ar$, H_{ax}), 4.10–3.70 (m, 16 H, OCH_2CH_2O), 3.32 (d, $J_{ax,eq}$ = 13.0 Hz, 4 H, H_{eq}), 1.33 (s, 18 H, $C(CH_3)_3$), 0.92 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 149.6 and 148.6 (s, C-1), 145.6 and 140.0 (s, C-4), 131.3 and 126.7 (s, C-2 and C-6), 124.2 and 123.7 (d, C-3 and C-5), 75.4 (t, $ArOCH_2$), 69.9, 69.8, and 69.2 (t, OCH_2CH_2O), 32.8 (s, C-7), 30.3 (t, $ArCH_2Ar$), 30.7 and 29.9 (m, CH_3-7). Anal. Calcd for $C_{52}H_{70}O_7 \cdot C_6H_{14}$: C, 79.69; H, 9.69. Found: C, 79.73; H, 9.14.

3,7,25,29-Tetrakis(1,1-dimethylethyl)-11,12,14,15,17,18,20,21,33,34,36,37,39,40,42,43-hexadecahydro-1,23:9,31-dimethano-5*H*,27*H*-tetrabenzo[*n*,*q*,*f*,*i*][1,4,7,10,13,19,22,25,28,31]decaoxacyclohexatriacontin (8). During the preparation of **7** a second product was isolated from the fraction of the crude product insoluble in ethyl acetate. Compound **8** could be obtained in a pure form by crystallization from tetrachloroethylene: yield 10%; mp > 300 °C; mass spectrum, *m/e* 964 (M^+); ^1H NMR (200 MHz) δ 6.90 (s, 8 H, ArH), 3.75 (s, 8 H, $ArCH_2Ar$), 3.70–3.20 (m, 22 H, OCH_2CH_2O), 3.10–2.80 (m, 10 H, OCH_2CH_2O), 1.15 (s, 36 H, $C(CH_3)_3$); ^{13}C NMR δ 153.8 (s, C-1), 144.4 (s, C-4), 132.7 (s, C-2 and C-6), 124.8 (d, C-3 and C-5), 73.5, 70.9, 70.1, and 66.9 (t, OCH_2CH_2O), 39.2 (t, $ArCH_2Ar$), 34.0 and 31.9 (m, CH_3-7). Anal. Calcd for $C_{60}H_{84}O_{10}$: C, 74.66; H, 8.77. Found: C, 73.21; H, 8.19.

2,23,28,38-Tetrakis(1,1-dimethylethyl)-6,7,9,10,12,13,15,16,18,19-decahydro-31*H*-4,21-(methano[1,3]benzenomethano)-26,30-metheno-25*H*-dibenzo[*q*,*z*][1,4,7,10,13,16]hexaoxacycloheptacosin-32,35-diol (9). This compound was obtained by the same procedure used for **7** and using pentaethylene glycol ditosylate. Preparative TLC on silica gel (SiO_2, ethyl acetate/THF = 95:5 v/v) gave the product in 38% yield. The purity of the isolated compound was checked by means of HPLC analysis with use of a μ-Porasil column (THF/ethyl acetate = 50:50 v/v, 2.0 mL/min); mp 236–237 °C; mass spectrum, *m/e* 850 (M^+); ^1H NMR (200 MHz) δ 6.98 (s, 4 H, ArH), 6.65 (s, 4 H, ArH), 6.78 (s, 2 H, OH), 4.28 (d, $J_{ax,eq}$ = 13.0 Hz, 4 H, $ArCH_2Ar$, H_{ax}), 4.20–3.70 (m, 20 H, OCH_2CH_2O), 3.20 (d, $J_{ax,eq}$ = 13.0 Hz, 4 H, H_{eq}), 1.26 (s, 18 H, $C(CH_3)_3$), 0.86 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 150.4 and 149.7 (s, C-1), 146.5 and 141.0 (s, C-4), 132.2 and 127.6 (s, C-2 and C-6), 125.2 and 124.8 (d, C-3 and C-5), 76.1 (t, $ArOCH_2$), 71.6, 70.9, and 69.9 (t, OCH_2CH_2O), 33.8 (s, C-7), 31.3 (t, $ArCH_2Ar$), 31.7 and 30.9 (m, CH_3-7). Anal. Calcd for $C_{54}H_{74}O_8$: C, 76.20; H, 8.76. Found: C, 76.73; H, 9.12.

General Procedure for the Preparation of the 1,3-Dialkoxy-*p-tert*-butylcalix[4]arene Crown Ethers. To a stirred solution of unsubstituted *p-tert*-butylcalix[4]arene crown ethers **7** or **9** (1.24 mmol) in 40 mL of dry THF and 8 mL of dry DMF was added sodium hydride (0.14 g, ~3 mmol) followed by the proper alkyl halide (2.5 mmol). The reaction mixture was refluxed for 3 h, after which no starting material was detected on TLC plates (SiO_2, CH_2Cl_2/ethyl acetate = 4:1 v/v).

Most of the solvent was then removed under reduced pressure, and the residue was poured into 0.5 N HCl solution and extracted several times with chloroform. The combined organic solutions were washed with water, and the solvent was removed under reduced pressure to give a crude reaction product which was analyzed by HPLC (ROSIL C-18 column, acetonitrile/water = 70:30 v/v, 1 mL/min). The reported percentage of the alkylated crown ether isomers represents an average of the HPLC analyses of five or more crude reaction products. The pure isomers were obtained by preparative TLC (Al_2O_3, ligroin (40/60)/acetonitrile = 4:50 v/v). The same eluent was used for TLC analyses. All compounds, after isolation using TLC plates, were boiled with methanol/water and filtered after cooling.

29,32-Bis(phenylmethoxy)-2,20,25,35-tetrakis(1,1-dimethylethyl)-6,7,9,10,12,13,15,16-octahydro-28*H*-4,18-(methano[1,3]benzenomethano)-23,27-metheno-22*H*-dibenzo-[*n*,*w*][1,4,7,10,13]pentaoxacyclotetracosin (4a,b). The reaction of benzyl chloride and crown **7** showed after workup, the presence of two spots on TLC corresponding to two isomers **4a,b**, which were isolated by preparative TLC (Al_2O_3, ligroin (40/60)/acetonitrile = 95:5 v/v).

"Cone" Isomer 4a. It has a lower R_f on TLC and represents 73% of the crude reaction mixture. Isolated yield 66%. It shows the same physical and spectroscopic properties of compound **4a**, reported previously.[12]

"Partial-Cone" Isomer 4b. This compound has a higher R_f on TLC and represents 17% of the crude reaction product: mp 218–220 °C; isolated yield 15%; mass spectrum, *m/e* 986 (M^+); ^1H NMR (80 MHz) δ 7.3–7.1 (m, 10 H, ArH), 6.9–6.7 (m, 7 H, ArH), 6.05 (br s, 1 H, ArH), 4.88 (s, 2 H, *exo*-CH_2Ar), 4.19 (d, $J_{ax,eq}$ = 12.0 Hz, 2 H, $ArCH_2Ar$, H_{ax}), 3.9–3.6 (m, 20 H, OCH_2CH_2O and $ArCH_2Ar$), 2.91 (d, $J_{ax,eq}$ = 12.0 Hz, 2 H, H_{eq}), 2.40 (s, 2 H, *endo*-CH_2Ar), 1.43 (s, 9 H, $C(CH_3)_3$), 1.17 (s, 18 H, $C(CH_3)_3$), 0.78 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 154.4, 154.1, and 151.4 (s, C-1), 145.6, 145.0, and 144.3 (s, C-4), 139.2, 137.5, 136.9, 133.8, 133.6, and 133.2 (s, Ar), 130.4, 129.4, 128.8, 128.1, 127.4, 127.2, 126.3, 125.9, 125.6, and 124.8 (d, Ar), 77.7 (t, CH_2Ar), 73.7 (t, $ArOCH_2$), 71.7, 71.3, 70.6, and 70.4 (t, OCH_2CH_2O), 38.4 (t, CH_2Ar), 33.8 and 33.5 (s, C-7), 31.7, 31.5, and 30.9 (m, CH_3-7), 30.7 (t, $ArCH_2Ar$). Anal. Calcd for $C_{66}H_{82}O_7$: C, 80.27; H, 8.38. Found: C, 80.18; H, 8.45.

29,32-Diethoxy-2,20,25,35-tetrakis(1,1-dimethylethyl)-6,7,9,10,12,13,15,16-octahydro-28*H*-4,18-(methano[1,3]benzenomethano)-23,27-metheno-22*H*-dibenzo[*n*,*w*][1,4,7,10,13]pentaoxacyclotetracosin (10a–c). By the general procedure the reaction of crown **7** and ethyl iodide gave a mixture of three isomers in 94% yield.

"Cone" Isomer 10a. This compound is the slowest on TLC plates and represents the major component (56%) of the crown ether mixture: isolated yield 53%; mp 193–195 °C; mass spectrum, *m/e* 862.577 (M^+; calcd 862.575); ^1H NMR (200 MHz), δ 7.03 (s, 4 H, ArH), 6.38 (s, 4 H, ArH), 4.28 (d, $J_{ax,eq}$ = 12.4 Hz, 4 H, $ArCH_2Ar$, H_{ax}), 4.20–3.70 (m, 20 H, OCH_2), 3.06 (d, $J_{ax,eq}$ = 12.4 Hz, 4 H, H_{eq}), 1.44 (t, *J* = 7.1 Hz, 6 H, $OCCH_3$), 1.31 (s, 18 H, $C(CH_3)_3$), 0.82 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 155.1 and 152.2 (s, C-1), 145.0 and 144.0 (s, C-4), 135.4 and 133.1 (s, C-2 and C-6), 125.5 and 125.0 (d, C-3 and C-5), 72.5, 72.0, 71.3, 70.9, and 70.2 (t, OCH_2), 34.1 (s, C-7), 31.9 and 31.2 (m, CH_3-7), 31.1 (t, $ArCH_2Ar$), 16.0 (q, $OCCH_3$). Anal. Calcd for $C_{56}H_{78}O_7$: C, 77.92; H, 9.11. Found: C, 77.04; H, 9.09.

"Partial-Cone" Isomer 10b. This compound has an intermediate R_f on TLC and represents 30% of the crude reaction product: isolated yield 28%; mp 208–211 °C; mass spectrum, *m/e* 862.578 (M^+; calcd 862.575); ^1H NMR (200 MHz) δ 7.20 (d, *J* = 2.4 Hz, 2 H, ArH), 7.16 (s, 2 H, ArH), 6.97 (d, *J* = 2.4 Hz, 2 H, ArH), 6.89 (s, 2 H, ArH), 4.35 (d, $J_{ax,eq}$ = 11.9 Hz, 2 H, $ArCH_2Ar$, H_{ax}), 4.00–3.40 (m, 22 H, OCH_2CH_2O, $ArCH_2Ar$, and *exo*-OCH_2C), 3.21 (d, $J_{ax,eq}$ = 11.9 Hz, 2 H, H_{eq}), 1.44 (s, 9 H, $C(CH_3)_3$), 1.50 (q, *J* = 7.0 Hz, 2 H, *endo*-OCH_2C), 1.41 (t, *J* = 7.0 Hz, 3 H, *exo*-$OCCH_3$), 1.27 (s, 18 H, $C(CH_3)_3$), 1.07 (s, 9 H, $C(CH_3)_3$), –0.46 (t, *J* = 7.0 Hz, 3 H, *endo*-$OCCH_3$); ^{13}C NMR δ 154.2 and 152.0 (s, C-1), 145.6 and 144.1 (s, C-4), 136.2, 133.6, 133.5, and 132.9 (s, C-2 and C-6), 126.0, 125.9, 125.2, and 124.9 (d, C-3 and C-5), 73.8 (t, $ArOCH_2$), 71.3, 71.0, and 70.6 (t, OCH_2), 65.4 (t, *exo*-OCH_2C), 38.9 (t, *endo*-OCH_2C), 34.1 (s, C-7), 31.8, 31.6, and 31.4 (m, CH_3-7), 30.4 (t, $ArCH_2Ar$), 15.9 (q, *exo*-$OCCH_3$), 14.8 (q, *endo*-$OCCH_3$). Anal. Calcd for $C_{56}H_{78}O_7 \cdot 2CH_3OH$: C, 75.12; H, 9.35. Found: C, 75.68; H, 9.27.

"1,3-Alternate" Isomer 10c. This compound is the fastest on TLC and also the less abundant (14%) of the three isomers: isolated yield 13%; mp 205–207 °C; mass spectrum, *m/e* 862.578 (M^+; calcd 862.575); ^1H NMR (200 MHz) δ 7.03 (s, 4 H, ArH), 6.97 (s, 4 H, ArH), 3.86 (br s, 8 H, $ArCH_2Ar$), 3.70–2.80 (m, 20 H, OCH_2), 1.37 (s, 18 H, $C(CH_3)_3$), 1.28 (s, 18 H, $C(CH_3)_3$), 0.43 (t, *J* = 6.9 Hz, 6 H, $OCCH_3$); ^{13}C NMR δ 154.9 and 154.3 (s, C-1), 144.4 and 144.0 (s, C-4), 133.2 and 133.0 (s, C-2 and C-6), 125.5 and 125.2 (d, C-3 and C-5), 73.3, 70.7, 67.4, and 65.0 (t, OCH_2), 39.2 (t, $ArCH_2Ar$), 34.0 (s, C-7), 31.9 and 31.7 (m, CH_3-7), 15.0 (q, $OCCH_3$). Anal. Calcd for $C_{56}H_{78}O_7 \cdot 2CH_3OH$: C, 75.12; H, 9.35. Found: C, 75.51; H, 9.16.

By using a previously reported procedure[12] and starting from 26,28-diethoxy-*p*-*tert*-butylcalix[4]arene (**6**) the three isomers **10a–c** were obtained in 43% overall yield and relative percentage of 21% of **10a**, 11% of **10b**, and 9% of **10c**.

(10a–c)·KPic Complexes. Each ligand dissolved in $CHCl_3$ was stirred for several hours in the presence of solid potassium picrate (excess). After filtration and slow evaporation of the solvent a yellow precipitate formed, which was dried in vacuo (room temperature, 0.1 mmHg). **10a**·KPic: ^1H NMR (200 MHz) δ 8.83 (s, 2 H, picrate), 7.16 (s, 4 H, ArH), 6.95 (s, 4 H, ArH), 4.35 (d, $J_{ax,eq}$ = 12.5 Hz, 4 H, $ArCH_2Ar$, H_{ax}), 4.30–3.70 (m, 20 H, OCH_2), 3.34 (d, $J_{ax,eq}$ = 12.5 Hz, 4 H, H_{eq}), 1.53 (t, *J* = 7.0 Hz, 6 H, $OCCH_3$), 1.24 (s, 18 H, $C(CH_3)_3$), 1.01 (s, 18 H, $C(CH_3)_3$). **10b**·KPic: ^1H NMR (200 MHz) δ 8.83 (s, 2 H, picrate), 7.32 (s, 2 H, ArH), 7.28 (s, 2 H, ArH), 7.06 (d, *J* = 3.0 Hz, 2 H, ArH), 6.93 (d, *J* = 3.0 Hz, 2 H, ArH), 4.20 (d, $J_{ax,eq}$ = 12.0 Hz, 2 H, $ArCH_2Ar$, H_{ax}), 4.10–3.30 (m, 26 H, OCH_2 and $ArCH_2Ar$), 1.49 (s, 9 H, $C(CH_3)_3$), 1.32 (s, 9 H, $C(CH_3)_3$), 1.26 (t, *J* = 7.0 Hz, 3 H, *exo*-$OCCH_3$), 1.13 (s, 18 H, $C(CH_3)_3$), 0.72 (t, *J* = 7.0 Hz, 3 H, *endo*-$OCCH_3$). **10c**·KPic: ^1H NMR (200 MHz) δ 8.83 (s, 2 H, picrate), 7.14 (s, 4 H, ArH), 7.06 (s, 4 H, ArH), 4.10–3.30 (m, 28 H, OCH_2 and $ArCH_2Ar$), 1.32 (s, 18 H, $C(CH_3)_3$), 1.28 (s, 18 H, $C(CH_3)_3$), 0.62 (t, *J* = 7.0 Hz, 6 H, $OCCH_3$).

32,35-Diethoxy-2,23,28,38-tetrakis(1,1-dimethylethyl)-6,7,9,10,12,13,15,16,18,19-decahydro-31*H*-4,21-(methano[1,3]benzenomethano)-26,30-metheno-25*H*-dibenzo[*q*,*z*][1,4,7,10,13,16]hexaoxacycloheptacosin (11a,b). By the general procedure the reaction of crown **9** and ethyl iodide gave a mixture of two compounds in 95% yield.

"Cone" Isomer 11a. This compound has the lowest R_f and was obtained in 59% yield: mp 203 °C; mass spectrum, *m/e* 906.608 (M^+; calcd 906.601); ^1H NMR (600 MHz) δ 7.04 (s, 4 H, ArH), 6.52 (s, 4 H, ArH), 4.36 (d, $J_{ax,eq}$ = 12.5 Hz, 4 H, $ArCH_2Ar$, H_{ax}), 4.22–4.17 (m, 8 H, $ArOCH_2CH_2$), 3.87 (q, *J* = 6.8 Hz, 4 H, OCH_2C), 3.85–3.70 (m, 12 H, OCH_2CH_2O), 3.12 (d, $J_{ax,eq}$ = 12.5 Hz, 4 H, H_{eq}), 1.52 (t, *J* = 6.8 Hz, 6 H, $OCCH_3$), 1.27 (s, 18 H, $C(CH_3)_3$), 0.87 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 154.3 and 152.3 (s, C-1), 145.1 and 144.2 (s, C-4), 135.2 and 132.5 (s, C-2 and C-6), 125.4 and 124.6 (d, C-3 and C-5), 72.5 (t, $ArOCH_2$), 71.2, 71.1, 70.8, 70.5, and 69.9 (t, OCH_2CH_2O), 34.1 and 33.7 (s, C-7), 31.7, 31.5, and 31.3 (m, CH_3-7), 31.0 (t, $ArCH_2Ar$), 29.7 (t, OCH_2C), 16.0 (q, $OCCH_3$). Anal. Calcd for $C_{58}H_{82}O_8 \cdot CH_3OH$: C, 75.44; H, 9.23. Found: C, 75.72; H, 9.28.

"Partial-Cone" Isomer 11b. This compound was obtained in 31% yield: mp 207 °C; mass spectrum, *m/e* 906.597 (M^+; calcd 906.601); ^1H NMR (200 MHz) δ 7.18 (s, 2 H, ArH), 7.15 (s, 2 H, ArH), 6.89 (br s, 2 H, ArH), 6.64 (br s, 2 H, ArH), 4.25 (d, $J_{ax,eq}$ = 12.4 Hz, 2 H, $ArCH_2Ar$, H_{ax}), 4.10–3.40 (m, 28 H, OCH_2 and $ArCH_2Ar$), 3.07 (d, $J_{ax,eq}$ = 12.4 Hz, 2 H, H_{eq}), 1.40 (s, 9 H, $C(CH_3)_3$), 1.34 (s, 9 H, $C(CH_3)_3$), 1.30 (t, *J* = 7.0 Hz, 3 H, *exo*-$OCCH_3$), 1.05 (s, 18 H, $C(CH_3)_3$), 0.87 (t, *J* = 7.0 Hz, 3 H *endo*-$OCCH_3$); ^{13}C NMR δ 153.0 (s, C-1), 143.6 (s, C-4), 136.2, 133.5, 133.3, and 131.6 (s, C-2 and C-6), 126.1, 125.8, 125.7, and 124.9 (d, C-3 and C-5), 73.2 (t, $ArOCH_2$), 71.3, 71.1, 70.8, 70.5, 70.3, and 70.1 (t, OCH_2CH_2O), 66.7 (t, *exo*-OCH_2C), 38.3 (t, *endo*-OCH_2C), 34.1 (s, C-7), 31.9, 31.7, and 31.4 (m, CH_3-7), 30.7 (t, $ArCH_2Ar$), 16.2 (q, *exo*-$OCCH_3$), 15.9 (q, *endo*-$OCCH_3$). Anal. Calcd for $C_{58}H_{82}O_8$: C, 76.78; H, 9.11. Found: C, 76.14; H, 9.27.

29,32-Dipropoxy-2,20,25,35-tetrakis(1,1-dimethylethyl)-6,7,9,10,12,13,15,16-octahydro-28*H*-4,18-(methano[1,3]benzomethano)-23,27-metheno-22*H*-dibenzo[*n*,*w*][1,4,7,10,13]pentaoxacyclotetracosin (12a,b). The general procedure in the reaction of crown **7** and *n*-propyl iodide afforded a mixture of two isomers **12a,b** in 89% yield.

"Cone" Isomer 12a. It represents 53% of the crude reaction mixture: isolated yield 42%; mp 224–226 °C; mass spectrum, *m/e* 890.619 (M^+; calcd 890.606); ^1H NMR (600 MHz) δ 7.11 (s, 4 H, ArH), 6.43 (s, 4 H, ArH), 4.36 (d, $J_{ax,eq}$ = 12.5 Hz, 4 H, $ArCH_2Ar$, H_{ax}), 4.32–4.20 (m, 6 H, $ArOCH_2$), 3.90–3.60 (m, 14 H, OCH_2), 3.13 (d, $J_{ax,eq}$ = 12.5 Hz, 4 H, H_{eq}), 1.96 (m, 4 H, CCH_2C), 1.34 (s, 18 H, $C(CH_3)_3$), 1.05 (t, *J* = 7.4 Hz, 6 H, $CCCH_3$), 0.80 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 155.0 and 152.5 (s, C-1), 145.0 and 144.0 (s, C-4), 135.4 and 131.7 (s, C-2 and C-6), 125.6 and 124.5 (d, C-3 and C-5), 77.7 (t, $ArOCH_2$), 72.6, 72.0, 71.3, and 70.1 (t, OCH_2), 34.1 (s, C-7), 31.7 and 31.2 (m, CH_3-7), 31.1 (t, $ArCH_2Ar$), 23.5 (t, CCH_2C), 10.8 (q, $CCCH_3$). Anal. Calcd for $C_{58}H_{82}O_7 \cdot 3CH_3OH$; C, 74.20; H, 9.59. Found: C, 74.76; H, 9.13.

"Partial-Cone" Isomer 12b. It represents 36% of the crude reaction mixture: isolated yield 28%; mp 230–233 °C; mass spectrum, *m/e* 890.609 (M^+; calcd 890.606); ^1H NMR (600 MHz) δ 7.12 (d, *J* = 2.2 Hz, 2 H, ArH), 7.08 (s, 2 H, ArH), 6.85 (d, *J* = 2.2 Hz, 2 H, ArH), 6.82 (s, 2 H, ArH), 4.29 (d, $J_{ax,eq}$ = 12.0 Hz, 2 H, $ArCH_2Ar$, H_{ax}), 3.82–3.42 (m, 22 H, OCH_2 and $ArCH_2Ar$), 3.14 (d, $J_{ax,eq}$ = 12.0 Hz, 2 H, H_{eq}), 1.79 (m, 2 H, *exo*-CCH_2C), 1.71 (t, *J* = 7.1 Hz, 3 H, *exo*-$CCCH_3$), 1.37 (s, 9 H, $C(CH_3)_3$), 1.20 (s, 18 H, $C(CH_3)_3$), 1.00 (s, 9 H, $C(CH_3)_3$), 0.86 (t, *J* = 7.4 Hz, 2 H, *endo*-OCH_2CC), –0.10 (m, 2 H, *endo*-CCH_2C), –0.18 (t, *J* = 7.1 Hz, 3 H, *endo*-$CCCH_3$); ^{13}C NMR δ 154.1 (s, C-1), 145.3 and 144.1 (s, C-4), 136.0, 133.5, and 132.7 (s, C-2 and C-6), 126.0, 125.7, 125.3, and 124.6 (d, C-3 and C-5), 73.8 (t, $ArOCH_2$), 71.3, 71.1, and 70.5 (t, OCH_2CH_2O), 39.0 (t, *exo*-CCH_2C), 34.1 (s, C-7), 31.8, 31.6, and 31.3 (m, CH_3-7), 30.4 (t, $ArCH_2Ar$), 23.2 (t, *endo*-CH_2CC), 22.3 (t, *endo*-CCH_2C), 10.3 (q, *exo*-$CCCH_3$), 10.2 (q, *endo*-$CCCH_3$). Anal. Calcd for $C_{58}H_{82}O_7 \cdot 4CH_3OH$: C, 73.05; H, 9.69. Found: C, 73.80; H, 9.75.

29,32-Bis(1-methylethoxy)-2,20,25,35-tetrakis(1,1-dimethylethyl)-6,7,9,10,12,13,15,16-octahydro-28*H*-4,18-(methano[1,3]benzomethano)-23,27-metheno-22*H*-dibenzo[*n*,*w*][1,4,7,10,13]pentaoxacyclotetracosin (13b). By the general procedure, the reaction of crown **7** and isopropyl iodide mainly gave one product although HPLC analyses, under the same conditions as previously reported, showed the presence of a second unidentified isomer in less than 10% relative yield.

"Partial-Core" Isomer 13b. It was obtained in 73% yield after recrystallization from CH_3OH: mp 216–218 °C; mass spectrum, *m/e* 891 (M^+); ^1H NMR (100 MHz) δ 7.20 (d, *J* = 2.4 Hz, 2 H, ArH), 7.04 (s, 2 H, ArH), 6.94 (s, 2 H, ArH), 6.82 (d, *J* = 2.4 Hz, 2 H, ArH), 4.39 (d, $J_{ax,eq}$ = 11.8 Hz, 2 H, $ArCH_2Ar$, H_{ax}), 4.10–3.35 (m, 22 H, OC-

Table III. Crystal Data and Data Collection Parameters

compd	2	4b	10a·KPic	10b	10c
formula	$C_{54}H_{74}O_7$	$C_{66}H_{82}O_7$	$C_{62}H_{80}KN_3O_{14}$	$C_{56}H_{78}O_7$	$C_{56}H_{78}O_7$
fw	835.2	987.4	1130.4	863.2	863.2
diffractometer	Siemens AED	Enraf-Nonius CAD4	Enraf-Nonius CAD4	Siemens AED	Siemens AED
lattice type	orthorhombic	monoclinic	monoclinic	monoclinic	monoclinic
space group	*Pnn2*	$P2_1/c$	$P2_1/c$	$P2_1$	$P2_1/n$
cell dimensions					
a (Å)	14.357 (9)	15.162 (6)	18.835 (4)	13.174 (6)	14.279 (3)
b (Å)	23.067 (9)	19.928 (8)	16.226 (3)	20.539 (7)	23.909 (4)
c (Å)	15.592 (9)	19.958 (8)	20.636 (3)	19.568 (7)	15.519 (2)
α (deg)	90	90	90	90	90
β (deg)	90	108.21 (4)	96.09 (1)	101.71 (4)	105.20 (2)
γ (deg)	90	90	90	90	90
V (Å^3)	5163 (4)	5728 (7)	6262 (3)	5184 (3)	5113 (2)
Z	4	4	4	4	4
radiation	Cu Kα (1.5410 Å)	Mo Kα (0.7107 Å)	Mo Kα	Cu Kα	Cu Kα
D_{calc} (g/cm^3)	1.074	1.145	1.200	1.106	1.121
μ (cm^{-1})	5.14	0.68	1.43	5.26	5.33
2θ range (deg)	6–140	6–50	6–45	6–140	6–140
no. of unique refl					
measd	5289	7117	8404	10142	8714
obsd [$I > 3\sigma(I)$]	3358	2292 [$I > 2\sigma(I)$]	2319	4091	5038
no. of variables	525	658	406	675	403
R (%)	14	9.3	10.7	10.6	12
R_w (%)	14	7.7	11.1	10.6	12

H_2CH_2O, $ArCH_2Ar$, and OCH), 3.19 (d, $J_{ax,eq}$ = 11.8 Hz, 2 H, H_{eq}), 1.42 (s, 9 H, $C(CH_3)_3$), 1.33 (d, J = 6.1 Hz, 6 H, *exo*-$C(CH_3)_2$), 1.27 (s, 18 H, $C(CH_3)_3$), 1.04 (s, 9 H, $C(CH_3)_3$), −0.04 (d, J = 6.1 Hz, 6 H, *endo*-$C(CH_3)_2$); ^{13}C NMR (100 MHz) δ 154.3 152.7, and 150.7 (s, C-1), 144.6, 143.7, and 143.4 (s, C-4), 135.3, 133.4, 132.2, and 131.8 (s, C-2 and C-6), 125.8, 125.7, 124.9, and 124.3 (d, C-3 and C-5), 77.4 (d, *exo*-OCH), 73.9 (t, $ArOCH_2$), 71.0 and 70.3 (t, OCH_2CH_2O), 69.7 (d, *endo*-OCH), 41.0 (t, $ArCH_2Ar$), 34.0 and 33.8 (s, C-7), 31.9, 31.7, and 31.5 (m, CH_3-7), 30.5 (t, $ArCH_2Ar$), 22.8 (q, *exo*-$C(CH_3)_2$), 21.4 (q, *endo*-$C(CH_3)_2$). Anal. Calcd for $C_{58}H_{82}O_7 \cdot CH_3OH$: C, 76.75; H, 9.39. Found: C, 76.38; H, 9.16.

X-ray Diffraction. X-ray diffraction measurements were performed on different diffractometers using the $\omega/2\theta$ scanning mode. The most relevant data collection parameters are displayed in Table III.

Measured intensities were corrected for Lorentz and polarization effects. The structures were solved by direct methods using MULTAN.[25] The data measured on the Siemens diffractometer were refined by using the SHELX[26] package. Geometrical calculations were done by using PARST.[27] The data measured with the Enraf-Nonius diffractometer were processed with the SDP package.[28] Scattering factors for all structures were taken from the International Tables for X-ray Crystallography.[29]

In most of the structures disorder was found, particularly in the *tert*-butyl groups, the picrate anion, and the crown ether part of the molecule, resulting in rather low accuracy of the resulting parameters.

The space group of **2** (Figure 1a) can be *Pnmn* or *Pnn2*. The latter space group was chosen on the basis of the refinement. The *tert*-butyl groups were found to be disordered in all four phenolic units. The disordering was consistent with two different orientations of the *tert*-butyl groups, which were treated as rigid bodies with isotropic thermal parameters. The occupancies of the different orientations were refined. The other parameters refined were overall scale factor, atomic positional parameters, and anisotropic thermal parameters for the non-hydrogen atoms. Hydrogen atoms were put in calculated positions with a C–H distance of 1.08 Å. Refinements were done with full-matrix least squares, using unit weights.

The structure of **4b** (Figure 1e) has been refined with anisotropic parameters for all non-hydrogen atoms. The hydrogen atoms were put at calculated positions (C–H distance 0.95 Å) and treated as riding on their parent atoms in the full-matrix least-squares refinements.

In the crystal structure of **10a**·KPic (Figure 1b) severe disorder was found in the picrate ion, making it impossible to obtain the geometry of the anion with precision. Attempts to describe the disorder with a two position model were not successful. The description of the disorder by means of anisotropic thermal parameters resulted in a number of non-positive definite descriptions of the (apparent) thermal motion. Eventually the picrate anion was refined with isotropic thermal parameters, giving rise to high values for the thermal motion and very inaccurate atomic positions. The rest of the non-hydrogen atoms were refined with isotropic thermal parameters, except for the K^+ ion and the atoms in the *tert*-butyl and ethoxy groups, for which anisotropic thermal parameters were used. Hydrogens for the calixarene molecule were put in calculated positions (C–H distance 0.95 Å) and treated as riding atoms in the full matrix refinements.

The structure of **10b** (Figure 1c) contains two independent molecules with small differences in geometry. Refinements, using unit weights, were made by blocked least squares. In order to keep the number of parameters tractable the structure was refined with isotropic thermal parameters for the non-hydrogen atoms, with the exception of the atoms in the ethoxy group and the crown ether part, which were refined anisotropically. Geometrical constraints were imposed on two *tert*-butyl groups. No hydrogen atoms have been used in the calculations.

In the crystal structure of **10c** (Figure 1d) disorder was found in three *tert*-butyl groups and the crown ether part of the molecule. The structure was refined by using the full-matrix least-squares method with isotropic thermal parameters for all atoms. The disorder was described with two positions, the occupancy factor of which was varied, for all the atoms in the disordered part of the molecule. Positions for the hydrogen atoms were obtained from difference Fourier syntheses and from calculations. No hydrogen atoms were taken into account for the *tert*-butyl groups and the crown ether chain.

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Supplementary Material Available: Tables of coordinates and anisotropic thermal parameters for non-hydrogen atoms, coordinates and isotropic thermal parameters of hydrogen atoms, bond distances, and angles for the crystal structures (57 pages). Ordering information is given on any current masthead page.

(25) Main, P.; Woolfson, M. M.; Lessinger, G.; Germain, G.; Declerq, G. P. *MULTAN 80: a system of computer programs for automatic solution of crystal structures*; Universities of York, England, and Louvain, Belgium, 1980.
(26) Sheldrick, G. M. *SHELX: a program for crystal structure determination*; University of Cambridge, England, 1980.
(27) Nardelli, M. *Computers Chemistry* **1983**, *7*, 95–97.
(28) B. A. Frenz and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, The Netherlands, 1983.
(29) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. 4.