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Synthesis of Cone, Partial-Cone, and 1,3-Alternate 25,27-Bis[1-(2-ethyl)hexyl]- and 25,27-Bis[1-(2-*tert*-butoxy)ethyl]calix[4]arene-crown-6 Conformers as Potential Selective Cesium Extractants

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The preparation of 25,27-bis[1-(2-ethyl)hexyl]- and 25,27-bis[1-(2-*tert*-butoxy)ethyl]calix[4]arene-crown-6 combining one polyether crown-6 and one alkylchain O-attached on each side of a calix[4]arene in the cone, partial-cone, and 1,3-alternate conformations are reported. The control over 25,27-bisalkylcalix[4]arene-crown-6 conformation via varying specific reaction conditions was studied. The series of calix[4]arenes have been prepared by two routes, which differ in the order in which the alkyl or polyether groups were introduced. Moreover, methods have been developed to selectively prepare the cone and partial-cone conformers by using an appropriate base in the alkylation reactions. The conformations of these new derivatives have been probed by ^{1}H NMR analysis and X-ray crystallography. The ^{1}H and ^{13}C NMR spectra of 25,27-bis[1-(2-ethyl)hexyl]calix[4]arene-crown-6, 1,3-alternate **1**, cone **2**, and partial-cone **3** are also discussed.

Introduction

Calix[4]arenes, which are macrocyclic oligomers made up of phenol units linked by methylene bridges, are receiving increasing attention in the field of supramolecular chemistry. Calixarene-based ion receptors are far more size-selective than crown ethers, because the calixarene platform provides a highly preorganized architecture for the assembling of converging binding sites.[1−5] Owing to their cavity-shaped architecture, calixarenes are useful building blocks in the design of novel host molecules. In fact, calixarene derivatives can form inclusion complexes with cations or with neutral molecules. In particular, calix crown ethers have attracted intense interest as alkali-metals-selective extractants. The ion-sensing properties of such polymers can be modulated by varying the conformation of the calixarene platform, the size of the crown ether ring, and the length of the connecting spacer. It has been recently reported that 1,3-dialkoxycalix[4]arene-crown-6 derivatives probably represent the most potent synthetic complexing agents for such alkali-metal ions.[6−14] In particular, they are exceptionally selective ionophores for cesium ion, as a result of the complexation of cesium ion not only with crown ether but also with the two aromatic rings (cation/π-interaction) when fixed in the 1,3-alternate conformation.[15−17] Analogous behavior was noticed with bis-crown-6 ether derivatives in the 1,3-alternate conformation.[18−22]

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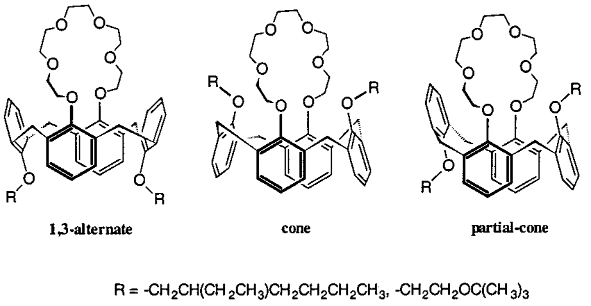


Figure 1. Three stable conformations of calix[4]arene-crown-6.

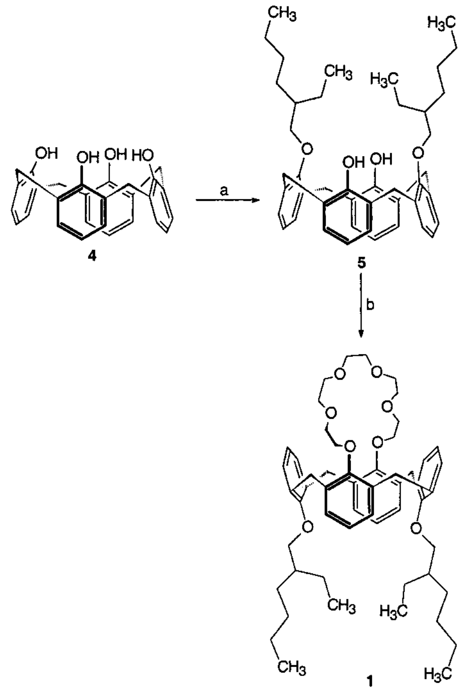
Recently involved in an industrial project focused on the selective removal of $^{137}Cs^+$ from medium level radioactive waste, we chose to synthesize new 1,3-dialkylcalix[4]arene-crown-6 conformers. Previous reports related that the most Cs^+-selective ligands were 1,3-dialkylcalix[4]arene-crown-6 compounds bearing long and/or ramified alkyl chains (i.e., propyl, octyl, and aryloxyoctyl)[4,9-11] fixed in the 1,3-alternate conformation.[23-25] The design of our synthetic approach was linked to these results, leading to the choice of a long and ramified alkyl chain (2-ethylhexyl) and a steric alkyloxyethyl group (*tert*-butoxyethyl). Moreover, the three possible conformers of each calix[4]arene-crown-6 were synthesized: the 1,3-alternate, the cone, and the partial-cone (Figure 1).

In this work we report results concerning the preparation of cone, partial-cone, and 1,3-alternate 25,27-bis[1-(2-ethyl)hexyl]- and 25,27-bis[1-(2-*tert*-butoxy)ethyl]calix[4]arene-crown-6 conformers and the discussion of ^1H NMR spectra of 25,27-bis[1-(2-ethyl)hexyl]calix[4]arene-crown-6, 1,3-alternate **1**, cone **2** and partial-cone **3**. Two pathways related to general synthetic methods were chosen for the preparation of the three series of calixarene-crown-6. They differed in the order in which the alkyl or polyether groups were introduced. The control of the stereochemistry has been achieved by using new experimental conditions, especially during alkylation reactions.

Methods and Discussion

Synthesis of 1,3-Alternate Calix[4]arene-crown-6. 25,27-Bis[1-(2-ethyl)hexyl]calix[4]arene-crown-6, 1,3-alternate **1** was synthesized from commercially available calix[4]arene **4**, according to the well-established method of Casnati and co-workers[11] (Scheme 1). Calix[4]arene **4** was reacted with 2.2 equiv of 2-ethylhexyl bromide in the presence of 2.4 equiv of K_2CO_3 as a base in refluxing CH_3CN for 5 days.[26] Crystallization of the crude reaction mixture from petroleum ether afforded the expected 1,3-dialkoxycalix[4]arene **5**. In fact, Casnati and co-workers[11] have shown previously that the reaction of 1,3-dialkoxycalix[4]arenes with pentaethylene glycol ditosylate in refluxing CH_3CN in the presence of Cs_2CO_3 was a method to obtain 1,3-dialkoxycalix[4]arene-crown-6 fixed in the 1,3-alternate conformation.[19,20] When applied to 1,3-dialkoxycalix[4]arene **5**, this reaction led to calix[4]arene-crown-6 ether **1** in a fixed 1,3-alternate conformation. No other isomers were isolated. The cyclization reaction to give the 1,3-alternate conformer **1** was probably due to the template effect of the Cs^+ ions[4] (Scheme 1).

Scheme 1[a]



[a] Reagents and conditions: (a) $CH_3(CH_2)_3(CH_3CH_2)CHCH_2Br$, K_2CO_3, CH_3CN, reflux, 12%; (b) $TsO(CH_2CH_2O)_3Ts$, Cs_2CO_3, CH_3CN, reflux, 30%.

The structure of compound **1** was locked in the 1,3-alternate conformation as inferred from the ^1H NMR spectrum, which exhibits a singlet around 3.76 ppm attributed to the bridging methylene groups of the calix[4]arene moiety. The signal around 37 ppm for the methylene bridge carbons in the ^{13}C NMR spectrum confirmed the structure.

By using the same procedure, calix[4]arene **4** was reacted with 2.2 equiv of 2-*tert*-butoxyethyl bromide[27] in the presence of 2.4 equiv of K_2CO_3 in refluxing CH_3CN for 6 days.[28] Final purification of the crude product by chromatography on silica gel led to the monoalkylated calix[4]arene **6** in the cone conformation and surprisingly to the tetraalkylated calix[4]arene **7** in the 1,3-alternate conformation as a white solid. The ^1H NMR spectrum of **7** showed at 3.52 ppm the characteristic singlet for the methylene bridge protons. In the ^{13}C NMR spectrum the corresponding carbon absorption was present at 34.4 ppm.[29] The monoalkylated calix[4]arene **6** had a cone structure as indicated by the ^1H NMR spectrum. A typical pattern represented by two 2H doublets at 3.45 and 3.42 ppm for the equatorial protons, and two doublets at 4.51 and 4.28 ppm for the axial protons of the bridging

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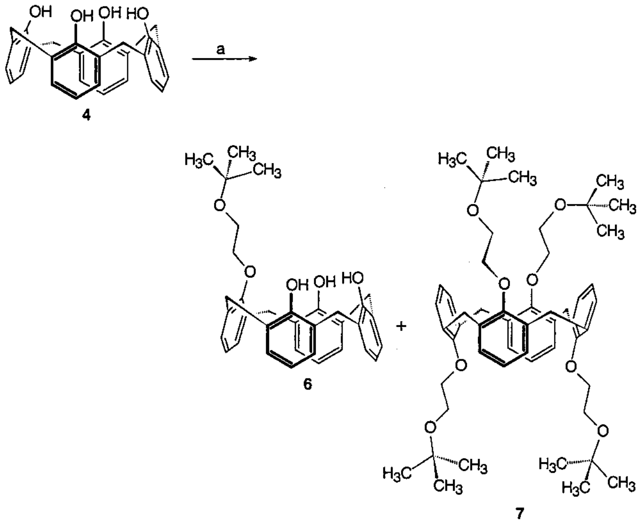
Scheme 2[a]



[a] Reagent and conditions: a: $(CH_3)_3COCH_2CH_2Br$, K_2CO_3, CH_3CN, reflux, 20% for **6** and 17% for **7**.

methylene ($ArCH_2Ar$) were observed. The spectrum also showed two sharp signals for the three OH groups, one at 9.25 ppm (2H) and one at 9.92 ppm (1H). This indicated that two H bonds were weaker than the other one and were those probably formed by the two opposite phenolic OH groups with the neighbor alkoxy oxygen atom, which bore less negative charge than a hydroxyl oxygen atom (Scheme 2).[30] These observations confirmed the cone conformation of derivative **6**.

The 1,3-dialkoxycalix[4]arene-crown-6 **8** analogue of **1** with 2-*tert*-butoxyethyloxy chains was synthesized from **4** according to the following sequence. Calix[4]arene diester **9** was prepared in a 55% yield by alkylation of the unsubstituted calix[4]arene **4** with ethyl bromoacetate in the presence of 1 equiv of K_2CO_3 as a base, in refluxing CH_3CN.[31-34] Treatment of **9** with pentaethylene glycol ditosylate and an excess of Cs_2CO_3 in refluxing CH_3CN gave the calix[4]arene-crown-6 diacid **10** in the 1,3-alternate conformation. Reduction of the diacid **10** with $LiAlH_4$ in THF at reflux gave the 25,27-bis(2-hydroxyethoxy)calix[4]arene-crown-6, 1,3-alternate **11** in 31% yield.[35] The synthesis of **8** was achieved by reaction of gaseous isobutene on calix[4]arene-crown-6 dialcohol **11** in CH_2Cl_2 in the presence of Amberlyst 15 resin under stirring at room temperature for 7 h (Scheme 3).[36,37] All compounds structures were assigned by ^1H NMR studies.

Synthesis of Cone Calix[4]arene-crown-6. The two 1,3-dialkoxycalix[4]arene-crown-6 cone isomers **2** and **12** were synthesized via **13**[11] by first bridging calix[4]arene **4** with pentaethylene glycol ditosylate in refluxing benzene with *t*-BuOK as the base.[38-41] The conformation of the intermediate **13** was assigned as a cone from the ^1H NMR spectrum. The signals from $ArCH_2Ar$ of the calixarene segment appeared as two doublets (4.41 and 3.36 ppm). The reaction of **13** with 2-ethylhexyl bromide or 2-*tert*-butoxyethyl bromide in THF/DMF (9/1, v/v) with NaH as the base, a standard procedure for the synthesis of cone conformers, produced **2** and **12** in 21% and 46% yield, respectively (Scheme 4).

The alkylation led selectively to the diametrically substituted 1,3-dialkoxycalix[4]arenes-crown-6 **2** and **12** in the cone conformation, as indicated by the ^1H NMR spectra. A typical AB pattern was observed for the methylene bridge $ArCH_2Ar$ protons ($J = 13.5-13.8$ Hz) at 4.40 and 3.18 ppm for **2** and 4.47 and 3.15 ppm for **12**. The high field doublets at 3.18 ppm for **2** and 3.15 ppm for **12** have been assigned to the equatorial protons of the methylene groups, whereas the low field signals at 4.40 ppm for **2** and 4.47 ppm for **12** were due to the axial protons.[7,38]

The X-ray crystal structure of calix[4]arene-crown-6 **12** has been determined (Figure 2). Details on the experimental procedure and crystallographic details are given in the Experimental Section. X-ray data confirmed the cone conformation in the solid state for **12** as anticipated on the basis of ^1H NMR data. Both *tert*-butoxyethoxy groups are located near the polyether ring, probably as a result of van der Waals interactions. In particular, the distance between one of the H-atom borne by C44 was found at 2.77 Å from the O19 of the polyether ring (3.33 Å between H-atom borne by C42 and O19). The two oxygen atoms bearing the alkyloxy chain are slightly directed out the cavity (distance 5.87 Å), leading to a shortening of the distance between the corresponding para C-atoms (4.15 Å). In an other way, the two other oxygen atoms bearing the polyether ring are pointed to the cavity in a very close proximity (3.32 Å) leading to a large lengthening of the corresponding para C-atoms (10.1 Å). In fact, the interplanar angle of the two aromatic rings linked by the polyether ring (C1−C6, C23−C28) is 68°, while the angle between the phenol groups bearing the *tert*-butoxyethoxy substituents (C30−C35, C45−C50) is 23°. The dihedral angles between the aromatic units of the calix[4]arene skeleton through the methylene carbons are 109.5(3)°, 110.7(3)°, 110.1(3)°, and 111.5(3)°, respectively. The polyether chain in this cone isomer does not adopt a regular conformation, described by the torsion angles O−C−C−O, which are 177.6(5)°, −168.4(4)°, −69.8(6)°, 77.1(5)°, and −174.5(3)°. Moreover, the C−O−C−C torsion angles (−101.7(6)°, 174.3(5)°, 88.0(6)°, −164.4(4)°, and −170.7(4)°) are also markedly different. In the crystal lattice, inter-calixarene contacts are achieved by van der Waals interactions and there are no solvent accessible voids.

Synthesis of Partial-Cone Calix[4]arene-crown-6. When 1,3-dihydroxycalix[4]arene-crown-6 **13** was reacted with 2-ethylhexyl bromide or 2-*tert*-butoxyethyl

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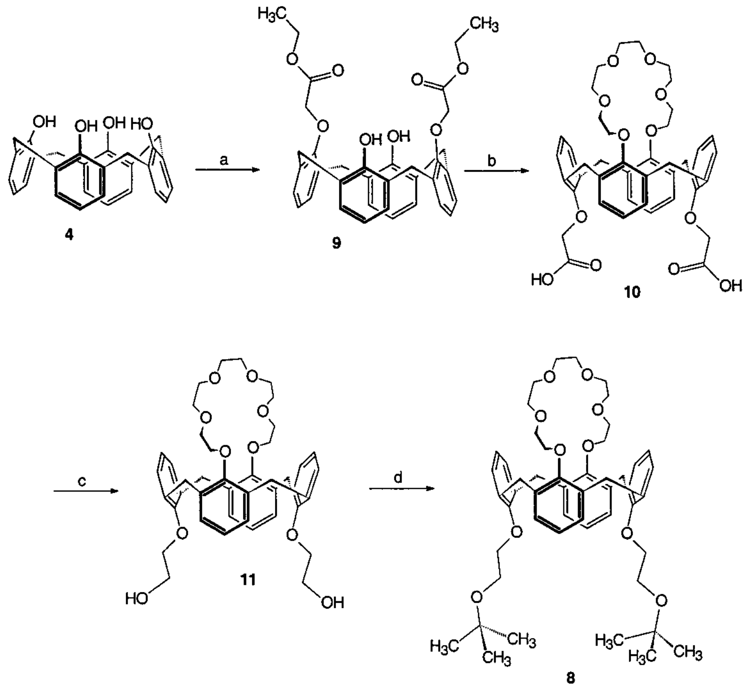
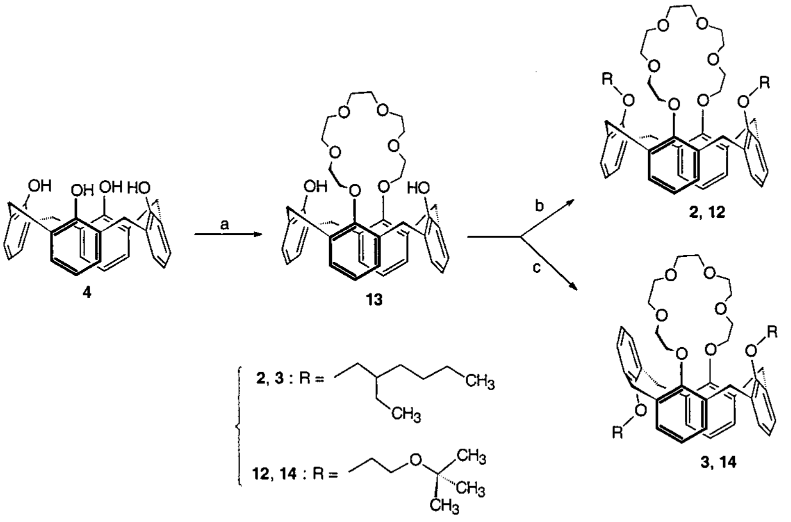
Scheme 3



Reagents and conditions: a: $BrCH_2COOCH_2CH_3$, K_2CO_3, CH_3CN, reflux, 55%; b: $TsO(CH_2CH_2O)_5Ts$, Cs_2CO_3, CH_3CN, reflux, 42%; c: $AlLiH_4$, THF, reflux, 36%; d: $CH_2{=}C(CH_3)_2$, Amberlyst 15 resin, CH_2Cl_2, rt, 96%.

Scheme 4



Reagents and conditions: a: $TsO(CH_2CH_2O)_5Ts$, *t*-BuOK, C_6H_6, reflux, 28%; b: $CH_3(CH_2)_3(CH_3CH_2)CHCH_2Br$ or $(CH_3)_3COCH_2CH_2Br$, NaH, THF/DMF, reflux, 21% for **2** and 12% for **12**; c: $CH_3(CH_2)_3(CH_3CH_2)CHCH_2Br$ or $(CH_3)_3COCH_2CH_2Br$, Cs_2CO_3, CH_3CN, reflux, 37% for **3** and 21% for **14**.

bromide in CH_3CN with Cs_2CO_3 in excess as the base, we only obtained the partial-cone conformers **3** and **14** in 37% and 21% yields, respectively (Scheme 4). The formation of the partial-cone conformation appears to be favored by the template effect of the Cs^+ ions.[4]

In the ^1H NMR spectrum of derivative **3**, the partial-cone structure was clearly indicated by the typical four signals for the aromatic meta protons at 6.99, 6.81, 6.78, and 6.58 ppm and by the two nonequivalent alkoxy groups of the 2-ethylhexyl chains at 3.64 and 2.61 ppm.[7,42]

Conclusion

In this work, we described the first synthesis of two new 25,27-bis(1-alkoxy)calix[4]arene-crown-6 in their three possible conformations: 1,3-alternate, cone, and partial cone. These different conformations have been assessed by ^1H NMR studies and confirmed by X-ray

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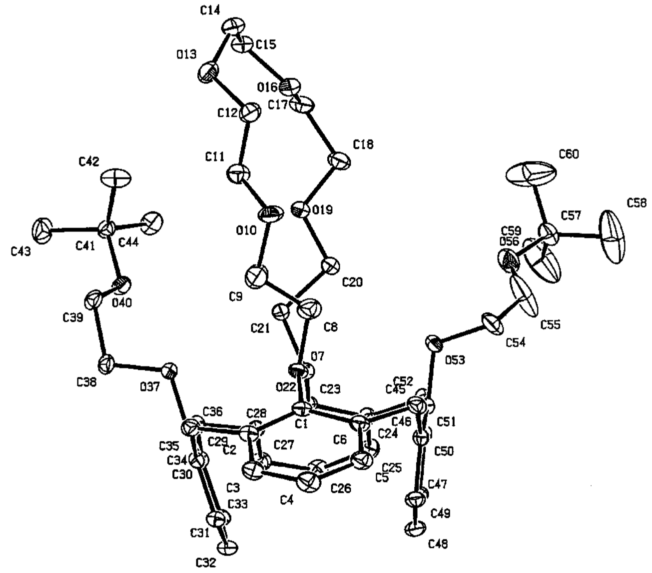

Figure 2. A view of **12** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level, H atoms are omitted for clarity.

structural analysis for compound **12**. These structural results emphasized the relation between the experimental conditions and the conformation of the obtained products. Moreover, the order in which the alkyl or polyether groups were introduced on the lower ring, was also important for the conformational aspect. The 1,3-alternate derivatives **1** and **8** have been obtained by first di-O-alkylation in the 1,3-position with a monofunctional reagent, followed by cyclization with the pentaethylene glycol ditosylate. In the case of the cone (**2** and **12**) and partial-cone calix[4]arenes (**3** and **14**), the order of introduction was reversed; the di-O-alkylation was achieved after the installation of the polyether chain. Moreover, useful methods have been developed to selectively prepare di-O-alkylated calix[4]arenes both in the cone and in the partial-cone conformations by choosing an appropriate base during the alkylation reactions. The conformation appears to be favored by a template effect of the metal ions present in solution. Thus, the reactions of alkylhalides with calix[4]arene-crown-6 **13** in the presence of NaH afforded the cone isomers, while in the presence of Cs_2CO_3 the partial-cone isomers were formed.

The potential applications of those calix[4]arene-crown-6 **1**−**3**, **8**, **12**, and **14** as carrier molecules to extract cesium radionuclide selectively from nuclear waste solutions are now under investigation. Nevertheless, for the cone isomer **12**, the conformational results obtained from the X-ray analysis are not in favor of such a chelating activity, whereas the conformation of 1,3-alternate isomers **1** and **8** could result in a better selectivity for Cs^+.

Experimental Section

General. Commercial reagents were used as received without additional purification. Melting points were determinated on a Kofler block and are uncorrected. IR spectra were recorded on a UNICAM MATTSON 1000 FTIR spectrophotometer. NMR spectra (^1H, ^{13}C, 2D-COSY) were recorded at 400 or 100 MHz with tetramethylsilane as an internal standard using a JEOL JNM-LA 400 spectrometer. Analytical TLC was carried out on 0.25 precoated silica gel plates (POLYGRAM SIL G/UV_{254}) with visualization by irradiation with a UV lamp. Silica gel 60 (70−230 mesh) was used for column chromatography.

25,27-Bis[1-(2-ethyl)hexyl]calix[4]arene, Cone (5).[43] A suspension of calix[4]arene **4** (6.0 g, 14.1 mmol), K_2CO_3 (4.69 g, 34 mmol), and 2-ethylhexyl bromide (6.0 g, 31 mmol) in CH_3CN (250 mL) was stirred under nitrogen for 5 days at reflux. The solvent was then evaporated at reduced pressure, and the residue was taken up with 10% HCl (150 mL) and extracted with CH_2Cl_2 (200 mL). The organic layer was separated, washed twice with water, dried over $MgSO_4$, charcoaled, and evaporated to dryness. Two successive crystallizations from hexane and then from petroleum ether gave **5** as white crystals (1.1 g, 12%): mp 176 °C; ^1H NMR ($CDCl_3$) δ 7.90 (s, 2H, O*H*), 7.06 (d, $J = 7.4$ Hz, 4H, Ar-*H* meta), 6.85 (d, $J = 7.6$ Hz, 4H, Ar-*H* meta), 6.69 (t, $J = 7.6$ Hz, 2H, Ar-*H* para), 6.65 (t, $J = 7.4$ Hz, 2H, Ar-*H* para), 4.36 (d, $J = 13.4$ Hz, 2H, ArCH_2Ar), 4.29 (d, $J = 13.4$ Hz, 2H, ArCH_2Ar), 3.86 (d, $J = 4.75$ Hz, 4H, OCH_2), 3.37 (d, $J = 12.8$ Hz, 1H, ArCH_2Ar), 3.36 (d, $J = 12.8$ Hz, 1H, ArCH_2Ar), 3.35 (d, $J = 12.8$ Hz, 1H, ArCH_2Ar), 3.34 (d, $J = 12.8$ Hz, 1H, ArCH_2Ar), 1.89 (m, 4H, C*H*CH_2), 1.71 (m, 6H, CH_2), 1.39 (m, 8H, CH_2), 1.05 (t, $J = 7.2$ Hz, 6H, CH_3), 0.92 (t, $J = 6.9$ Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 153.7 (Ar ipso),152.2 (Ar ipso), 133.2 (Ar ortho), 129.0 (Ar ortho), 128.5 (Ar meta), 128.1 (Ar meta), 125.2 (Ar para), 118.8 (Ar para), 79.3 (O*C*H_2), 40.8, 31.3, 29.9, 29.3, 23.7, 23.1 (*C*H_2), 14.2 (*C*H_3), 11.3 (*C*H_3); IR (KBr) λ_{max} 3410 (OH). Anal. Calcd for $C_{44}H_{56}O_4$: C, 81.45; H, 8.69. Found: C, 81.33; H, 8.78.

25,27-Bis[1-(2-ethyl)hexyl]calix[4]arene-crown-6, 1,3-Alternate (1). 25,27-Dialkoxycalix[4]arene, cone **5** (1.1 g, 1.7 mmol) was dissolved in CH_3CN (250 mL) and added to an excess of Cs_2CO_3 (2.22 g, 6.82 mmol) and pentaethylene glycol di-*p*-toluenesulfonate (1.04 g, 1.9 mmol) under nitrogen atm. The reaction mixture was refluxed for 24 h, then CH_3CN was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (150 mL) and 10% HCl (100 mL). The organic layer was separated, washed twice with water, dried over $MgSO_4$, charcoaled, and evaporated to dryness. The oily residue was crystallized from MeOH to afford **1** (0.44 g, 30%) as white crystals: mp 102 °C; ^1H NMR ($CDCl_3$) δ 7.12 (d, $J = 7.4$ Hz, 4H, Ar-*H* meta), 7.01 (d, $J = 7.4$ Hz, 4H, Ar-*H* meta), 6.78 (t, $J = 7.4$ Hz, 2H, Ar-*H* para), 6.68 (t, $J = 7.4$ Hz, 2H, Ar-*H* para), 3.76 (s, 8H, ArCH_2Ar), 3.72 (m, 8H, OCH_2), 3.63 (m, 8H, OCH_2), 3.60 (m, 4H, OCH_2), 3.55 (m, 2H, OCH_2), 3.49 (m, 2H, OCH_2), 1.78 (m, 2H, OCH$_2$C*H*), 1.38−1.20 (m, 16H, CH_2), 0.94 (t, $J = 6.8$ Hz, 6H, CH_3), 0.86 (t, $J = 7.4$ Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 157.7 (Ar ipso), 156.5 (Ar ipso), 133.7 (Ar ortho), 133.5 (Ar ortho), 130.7 (Ar meta), 130.5 (Ar meta), 121.7 (Ar para), 75.9, 71.5, 71.1, 70.6, 70.5 (O*C*H_2), 40.9 (OCH$_2$*C*H), 37.3 (Ar*C*H$_2$Ar), 30.5, 29.5, 23.6, 23.4 (*C*H_2), 14.2 (*C*H_3), 11.32 (*C*H_3). Anal. Calcd for $C_{54}H_{74}O_8$: C, 76.20; H, 8.76. Found: C, 76.31; H, 8.91.

25-(*tert*-Butoxyethoxy)-26,27,28-trihydroxycalix[4]arene, Cone (6) and **25,26,27,28-Tetra(*tert*-butoxyethoxy)calix[4]arene, 1,3-Alternate (7).** A suspension of calix[4]arene **4** (5.0 g, 11.8 mmol), K_2CO_3 (3.9 g, 28.2 mmol) and 2-*tert*-butoxyethyl bromide (4.69 g, 25.9 mmol) in CH_3CN (250 mL) was stirred under nitrogen for 5 days at reflux. The solvent was then evaporated at reduced pressure, and the residue was taken up with 10% HCl (150 mL) and extracted with CH_2Cl_2 (200 mL). The organic layer was separated, washed twice with water, dried over $MgSO_4$, charcoaled, and evaporated to dryness. The residue was chromatographed on silica gel with CH_2Cl_2 as first eluant to afford **6** as white crystals (1.24 g, 20%): mp 227 °C; ^1H NMR ($CDCl_3$) δ 9.92 (s, 1H, O*H*), 9.25 (s, 2H, O*H*), 7.08 (d, $J = 7.6$ Hz, 2H, Ar-*H* meta), 7.04 (d, $J = 7.6$ Hz, 2H, Ar-*H* meta), 7.00 (m, 4H, Ar-*H* meta), 6.86 (t, $J = 7.6$ Hz, 1H, Ar-*H* para), 6.68 (t, $J = 7.6$ Hz, 1H, Ar-*H* para), 6.65 (t, $J = 7.6$ Hz, 2H, Ar-*H* para), 4.51 (d, $J = 13.0$ Hz, 2H, ArCH_2Ar), 4.28 (d, $J = 13.8$ Hz, 2H, ArCH_2Ar), 4.25 (m, 4H, OCH_2), 3.99 (m, 2H, OCH_2), 3.45 (d, $J = 13.8$ Hz, 2H, ArCH_2Ar), 3.42 (d, $J = 13.0$ Hz, 2H, ArCH_2Ar), 1.38 (s, 9H, CH_3);

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[43] The name calix[4]arene is used instead of the official Chemical Abstracts name: 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-dodecaene-25,26,27,28-tetrol.

^{13}C NMR ($CDCl_3$) δ 151.9 (Ar ipso), 150.8 (Ar ipso), 149.9 (Ar ipso), 134.9, 129.5, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 126.2, 122.0, 121.2 (Ar), 76.3 (O*C*H$_2$), 73.9 (O*C*H$_2$), 60.7 (O*C*(CH$_3$)), 32.2 (Ar*C*H$_2$Ar), 31.5 (Ar*C*H$_2$Ar), 27.8 (*C*H$_3$); IR (KBr) λ_{max} 3355 and 3185 (OH). Anal. Calcd for $C_{34}H_{36}O_5$: C, 77.86; H, 6.87. Found: C, 78.01; H, 6.72. Next, CH_2Cl_2/MeOH (90/10, v/v) as second eluent gave **7** as white crystals (1.65 g, 17%): mp 210 °C; ^{1}H NMR ($CDCl_3$) δ 7.15 (d, *J* = 7.46 Hz, 8H, Ar-*H* meta), 6.57 (t, *J* = 7.46 Hz, 4H, Ar-*H* para), 3.84 (t, *J* = 4.67 Hz, 8H, OC*H*$_2$), 3.69 (t, *J* = 4.67 Hz, 8H, OC*H*$_2$), 3.52 (s, 8H, ArC*H*$_2$Ar), 1.33 (s, 36H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 155.5 (Ar ipso), 133.4 (Ar ortho), 130.1 (Ar meta), 121.3 (Ar para), 73.0 (O*C*H$_2$), 72.6 (O*C*H$_2$), 61.2 (O*C*(CH$_3$)), 34.4 (Ar*C*H$_2$Ar), 27.6 (*C*H$_3$). Anal. Calcd for $C_{52}H_{72}O_8$: C, 75.73; H, 8.73. Found: C, 75.52; H, 8.70.

25,27-Bis[(ethoxycarbonyl)methoxy]-26,28-dihydroxycalix[4]arene, Cone (9). A mixture of calix[4]arene **4** (12.06 g, 28.4 mmol), K_2CO_3 (4.32 g, 31.2 mmol) and ethyl bromoacetate (6.31 mL, 56.8 mmol) in CH_3CN (300 mL) was refluxed under nitrogen for 24 h. After filtration the solvent was removed and the residue was dissolved in CH_2Cl_2 (200 mL) and 10% HCl (200 mL). The organic layer was washed twice with water and dried over $MgSO_4$. After evaporation of CH_2Cl_2 the crude product was chromatographed on silica gel using CH_2Cl_2 as eluant to give **9** as white crystals (9.32 g, 55%): mp 168 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 2H, O*H*), 7.04 (d, *J* = 7.5 Hz, 4H, Ar-*H* meta), 6.90 (d, *J* = 7.5 Hz, 4H, Ar-*H* meta), 6.74 (t, *J* = 7.5 Hz, 2H, Ar-*H* para), 6.65 (t, *J* = 7.5 Hz, 2H, Ar-*H* para), 4.72 (s, 4H, OC*H*$_2$CO), 4.47 (d, *J* = 13.2 Hz, 4H, ArC*H*$_2$-Ar), 4.32 (q, *J* = 7.15 Hz, 4H, OC*H*$_2$), 3.39 (d, *J* = 13.2 Hz, 4H, ArC*H*$_2$Ar), 1.34 (t, *J* = 7.15 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.8 (*C*O), 152.9 (Ar ipso), 152.3 (Ar ipso), 133.1 (Ar ortho), 129.1 (Ar ortho), 128.4 (Ar meta), 128.1 (Ar meta), 125.5 (Ar para), 119.1 (Ar para), 72.4 (O*C*H$_2$CO), 61.3 (O*C*H$_2$), 31.4 (Ar*C*H$_2$Ar), 14.1 (*C*H$_3$); IR (KBr) λ_{max} 3390 (OH), 1755 (C=O).

25,27-Bis[(hydroxycarbonyl)methoxy]calix[4]arene-crown-6, 1,3-Alternate (10). 25,27-Bis[(ethoxycarbonyl)-methoxy]-26,28-dihydroxycalix[4]arene, cone **9** (18.7 g, 31.3 mmol) was dissolved in CH_3CN (1.3 L) and added to an excess of Cs_2CO_3 (40.86 g, 125 mmol) and pentaethylene glycol di-*p*-toluenesulfonate (18.85 g, 34.5 mmol) under nitrogen atmosphere. The reaction mixture was refluxed for 24 h, then CH_3CN was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (400 mL) and 10% HCl (400 mL). The organic layer was separated, washed twice with water, dried over $MgSO_4$, charcoaled, and evaporated to dryness. Column chromatography (SiO_2, CH_2Cl_2/MeOH, 95/5, v/v) gave **10** as white crystals (9.75 g, 42%): mp 198 °C; ^{1}H NMR ($CDCl_3$) δ 7.15 (d, *J* = 7.4 Hz, 4H, Ar-*H* meta), 7.06 (d, *J* = 7.4 Hz, 4H, Ar-*H* meta), 6.99 (t, *J* = 7.4 Hz, 2H, Ar-*H* para), 6.88 (t, *J* = 7.4 Hz, 2H, Ar-*H* para), 6.73 (br, 2H, O*H*), 4.11 (s, 4H, OC*H*$_2$CO), 3.93 (d, *J* = 16.3 Hz, 4H, ArC*H*$_2$Ar), 3.86 (d, *J* = 16.3 Hz, 4H, ArC*H*$_2$Ar), 3.69 (s, 4H, OC*H*$_2$), 3.66 (m, 4H, OC*H*$_2$), 3.61 (m, 4H, OC*H*$_2$), 3.37 (m, 8H, OC*H*$_2$); ^{13}C NMR ($CDCl_3$) δ 169.4 (*C*O), 156.2 (Ar ipso), 153.6 (Ar ipso), 133.5 (Ar ortho), 133.4 (Ar ortho), 129.9 (Ar meta), 129.4 (Ar meta), 124.2 (Ar para), 124.1 (Ar para), 71.1, 70.9, 70.7, 70.1, 69.6, 66.9 (O*C*H$_2$), 37.6 (Ar*C*H$_2$Ar); IR (KBr) λ_{max} 3480−2590 (OH), 1740 (C=O). Anal. Calcd for $C_{42}H_{46}O_{12}$: C, 67.92; H, 6.20. Found: C, 68.11; H, 6.35.

25,27-Bis(2-hydroxyethoxy)calix[4]arene-crown-6, 1,3-Alternate (11). To a solution of calix[4]arene diacid **10** (2.8 g, 3.8 mmol) in anhydrous THF (70 mL) was added $LiAlH_4$ (0.71 g, 18.9 mmol) in small portions at 0 °C, and the mixture was stirred for 2 h at room temperature. After 2 h, the reaction mixture was refluxed for 3 h. After cooling, ice was added carefully in small portions until a precipitate had formed, and the THF was filtered. The precipitate was treated with another portion of THF, and the combined organic layers were evaporated to dryness. The residue was extracted with AcOEt (150 mL) and 10% HCl (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, and evaporated. The crude product was crystallized from MeOH to give pure **11** as white crystals (0.97 g, 36%): mp 151 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 (d, *J* = 7.45 Hz, 4H, Ar-*H* meta), 7.09 (d, *J* = 7.45 Hz, 4H, Ar-*H* meta), 6.93 (t, *J* = 7.45 Hz, 2H, Ar-*H* para), 6.92 (t, *J* = 7.45 Hz, 2H, Ar-*H* para), 3.92 (d, *J* = 17 Hz, 4H, ArC*H*$_2$-Ar), 3.87 (d, *J* = 17 Hz, 4H, ArC*H*$_2$Ar), 3.70 (s, 4H, OC*H*$_2$), 3.64 (t, *J* = 4.6 Hz, 8H, OC*H*$_2$), 3.58 (t, *J* = 6.6 Hz, 4H, OC*H*$_2$-CH$_2$OH), 3.51 (t, *J* = 4.6 Hz, 4H, OC*H*$_2$), 3.33 (t, *J* = 4.6 Hz, 4H, OC*H*$_2$), 3.08 (m, 4H, OCH$_2$C*H*$_2$OH), 2.52 (t, *J* = 6.6 Hz, 2H, O*H*); ^{13}C NMR ($CDCl_3$) δ 156.5 (Ar ipso), 156.1 (Ar ipso), 133.7 (Ar ortho), 133.6 (Ar ortho), 129.6 (Ar meta), 129.5 (Ar meta), 123.2 (Ar para), 71.4, 71.0, 70.8, 70.7, 69.1, 68.7, 61.1 (O*C*H$_2$), 38.1 (Ar*C*H$_2$Ar); IR (KBr) λ_{max} 3470 (OH). Anal. Calcd for $C_{42}H_{50}O_{10}$: C, 70.59; H, 7.00. Found: C, 70.72; H, 6.93.

25,27-Bis(2-*tert*-butoxyethoxy)calix[4]arene-crown-6, 1,3-Alternate (8). To a solution of calix[4]arene dialcohol **11** (0.16 g, 0.23 mmol) in CH_2Cl_2 (20 mL) was added Amberlyst 15 resin (0.2 g). With magnetic stirring, isobutene was slowly added at −5 °C during 20 min, and the reaction mixture was maintained at room temperature. After 7 h, the reaction was stopped by removal of the Amberlyst 15 resin by filtration. The solvent was removed by rotary evaporation, leaving **8** as white crystals (0.18 g, 96%): mp 162 °C; ^{1}H NMR ($CDCl_3$) δ 7.05 (d, *J* = 7.5 Hz, 4H, Ar-*H* meta), 7.02 (d, *J* = 7.5 Hz, 4H, Ar-*H* meta), 6.75 (t, *J* = 7.5 Hz, 2H, Ar-*H* para), 6.69 (t, *J* = 7.5 Hz, 2H, Ar-*H* para), 3.72−3.59 (m, 24H, OC*H*$_2$ and ArC*H*$_2$-Ar), 3.48 (t, *J* = 5.1 Hz, 4H, OC*H*$_2$), 3.46 (t, *J* = 6 Hz, 4H, OC*H*$_2$CH$_2$C(CH$_3$)$_3$), 3.19 (t, *J* = 6 Hz, 4H, OCH$_2$C*H*$_2$C(CH$_3$)$_3$), 1.17 (s, 18H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 156.3 (Ar ipso), 133.9 (Ar ortho), 133.7 (Ar ortho), 130.1 (Ar meta), 129.9 (Ar meta), 122.1 (Ar para), 121.7 (Ar para), 72.8, 71.3, 71.2, 70.9, 70.4, 70.2, 70.0 (O*C*H$_2$), 59.9 (*C*(CH$_3$)$_3$), 37.2 (Ar*C*H$_2$Ar), 27.6 (*C*H$_3$). Anal. Calcd for $C_{50}H_{66}O_{10}$: C, 72.64; H, 7.99. Found: C, 72.82; H, 7.87.

25,27-Dihydroxycalix[4]arene-crown-6, Cone (13). To a stirred and refluxing solution of calix[4]arene **4** (10 g, 23.5 mmol) and *t*-BuOK (5.29 g, 47.1 mmol) in dry benzene (400 mL) was added dropwise pentaethylene glycol ditosylate (12.88 g, 23.5 mmol) in dry benzene (150 mL) over a period of 6 h. After 3 days of refluxing, the reaction mixture was cooled and treated with 10% HCl. The organic layer was washed with water (2 × 350 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was chromatographed on silica gel with CH_2Cl_2 as first eluent and AcOEt as the second one. The obtained residue was triturated in cooled AcOEt, filtered, and dried to give **13** as white crystals (4.12 g, 28%): mp 223 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (s, 2H, O*H*), 7.06 (d, *J* = 7.4 Hz, 4H, Ar-*H* meta), 6.83 (d, *J* = 7.4 Hz, 4H, Ar-*H* meta), 6.70 (t, *J* = 7.4 Hz, 2H, Ar-*H* para), 6.67 (t, *J* = 7.4 Hz, 2H, Ar-*H* para), 4.41 (d, *J* = 13.1 Hz, 4H, ArC*H*$_2$Ar), 4.14 (m, 4H, OC*H*$_2$), 4.01 (m, 4H, OC*H*$_2$), 3.92 (m, 4H, OC*H*$_2$), 3.83 (m, 4H, OC*H*$_2$), 3.70 (s, 4H, OC*H*$_2$), 3.36 (d, *J* = 13.1 Hz, 4H, ArC*H*$_2$Ar); ^{13}C NMR ($CDCl_3$) δ 153.2(Ar ipso), 151.9 (Ar ipso), 133.0 (Ar ortho), 128.8 (Ar ortho), 128.4 (Ar meta), 128.0 (Ar meta), 125.2 (Ar para), 118.8 (Ar para), 76.3, 71.5, 70.9, 69.7 (O*C*H$_2$), 31.0 (Ar*C*H$_2$Ar); IR (KBr) λ_{max} 3360 (OH).

General Procedure for the Synthesis of 25,27-Dialkoxycalix[4]arene-crown-6, Cone (2) and (12). A solution of calix[4]arene-crown-6 **13** (6.22 g, 9.93 mmol) in THF/DMF (9/1, 180 mL) and NaH (75% oil, 0.8 g, 25 mmol) was stirred under nitrogen for 1 h. 2-Ethylhexyl bromide or 2-*tert*-butoxyethyl bromide (25 mmol) was then added, and the reaction mixture was refluxed for 48 h. After the removal of most of the solvent under reduced pressure the mixture was taken up in water and extracted with CH_2Cl_2 (130 mL). The organic layer was washed twice with water, dried over $MgSO_4$, and evaporated to dryness. After purification, 25,27-dialkoxycalix[4]arene-crown-6, cone **2** and **12** were obtained in 21% and 46% yield, respectively.

25,27-Bis[1-(2-ethyl)hexyl]calix[4]arene-crown-6, Cone (2). The oily residue was submitted to column chromatography on silica gel (SiO_2, AcOEt/hexane, 50:50, v/v) to give **2** as a pale yellow oil (21%): ^{1}H NMR ($CDCl_3$) δ 7.14 (d, *J* = 7.5 Hz, 4H, Ar-*H* meta), 6.95 (t, *J* = 7.5 Hz, 2H, Ar-*H* para), 6.17 (t, *J* = 7.5 Hz, 2H, Ar-*H* para), 5.98 (d, *J* = 7.5 Hz, 4H, Ar-*H* meta), 4.40 (d, *J* = 13.8 Hz, 4H, ArC*H*$_2$Ar), 4.24 (t, *J* = 7.7 Hz, 4H, OC*H*$_2$), 3.95 (t, *J* = 7.7 Hz, 4H, OC*H*$_2$), 3.68 (m, 12H, OC*H*$_2$), 3.58 (d, *J* = 6 Hz, 4H, OC*H*$_2$), 3.18 (d, *J* = 13.8 Hz, 4H, ArC*H*$_2$Ar), 1.80 (m, 2H, C*H*), 1.73 (m, 2H, C*H*$_2$), 1.55 (m, 6H, C*H*$_2$), 1.35 (m, 6H, C*H*$_2$), 1.26 (m, 2H, C*H*$_2$), 0.98 (t, J = 7.4 Hz, 6H, C*H*$_3$), 0.91 (t, J = 6.6 Hz, 6H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 158.2 (Ar ipso), 155.3 (Ar ipso), 137.1 (Ar ortho), 132.8 (Ar ortho), 129.2 (Ar meta), 127.3 (Ar meta), 122.2 (Ar para), 121.9 (Ar para), 77.9, 72.3, 71.1, 70.9, 70.7, 69.5 (O*C*H$_2$), 40.5 (*C*H), 30.7 (Ar*C*H$_2$Ar), 30.4 (*C*H$_2$), 29.1 (*C*H$_2$), 23.8 (*C*H$_2$), 23.1 (*C*H$_2$), 14.2 (*C*H$_3$), 11.0 (*C*H$_3$). Anal. Calcd for $C_{54}H_{74}O_8$: C, 76.20; H, 8.76. Found: C, 76.43; H, 8.72.

25,27-Bis(2-*tert*-butoxyethoxy)calix[4]arene-crown-6, Cone (12). The oily residue was chromatographed on silica gel (SiO_2, AcOEt/petroleum ether, 75:25, v/v) to give **12** as white crystals (46%): mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, J = 7.4 Hz, 4H, Ar-*H* meta), 6.92 (t, J = 7.4 Hz, 2H, Ar-*H* para), 6.21 (t, J = 7.4 Hz, 2H, Ar-*H* para), 6.09 (d, J = 7.4 Hz, 4H, Ar-*H* meta), 4.47 (d, J = 13.5 Hz, 4H, ArC*H*$_2$Ar), 4.29 (t, J = 7.3 Hz, 4H, OC*H*$_2$), 4.02 (t, J = 7.3 Hz, 4H, OC*H*$_2$), 3.91 (t, J = 4.5 Hz, 4H, OC*H*$_2$), 3.72 (m, 12H, OC*H*$_2$), 3.68 (s, 4H, OC*H*$_2$), 3.15 (d, J = 13.5 Hz, 4H, ArC*H*$_2$Ar), 1.23 (s, 18H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 158.2 (Ar ipso), 154.7 (Ar ipso), 136.8 (Ar ortho), 133.1 (Ar ortho), 128.9 (Ar meta), 127.3 (Ar meta), 122.2 (Ar para), 122.0 (Ar para), 74.9, 72.9, 72.6, 71.0, 70.9, 70.7, 69.8 (O*C*H$_2$), 60.5 (*C*(CH$_3$)$_3$), 30.9 (Ar*C*H$_2$Ar), 27.6 (*C*H$_3$). Anal. Calcd for $C_{50}H_{66}O_{10}$: C, 72.64; H, 7.99. Found: C, 72.77; H, 7.94.

General Procedure for the Synthesis of 25,27-Dialkoxycalix[4]arene-crown-6, Partial-Cone (3) and **(14).** A solution of calix[4]arene-crown-6 **13** (2 g, 3.2 mmol), Cs_2CO_3 (4.11 g, 12.6 mmol), and 2-ethylhexyl bromide or 2-*tert*-butoxyethyl bromide (7 mmol) was refluxed in CH_3CN (300 mL) for 60 h. After evaporation of the solvent, the mixture was taken up in CH_2Cl_2 (180 mL) and 10% HCl (150 mL). The organic layer was washed with water (2 × 130 mL), dried over $MgSO_4$, and evaporated to dryness. The oily residue was chromatographed on silica gel (SiO_2, AcOEt/petroleum ether, 25:75, v/v) to afford **3** and **14** as an oil in 24% and 37% yield, respectively.

25,27-Bis[1-(2-ethyl)hexyl]calix[4]arene-crown-6, Partial-Cone (3). Colorless oil (37%); ^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 7.4 Hz, 2H, Ar-*H* meta), 7.01 (d, J = 7.4 Hz, 2H, Ar-*H* meta), 6.99 (t, J = 7.4 Hz, 1H, Ar-*H* para), 6.95 (d, J = 7.4 Hz, 2H, Ar-*H* meta), 6.81 (t, J = 7.4 Hz, 1H, Ar-*H* para), 6.79 (d, J = 7.4 Hz, 2H, Ar-*H* meta), 6.78 (t, J = 7.4 Hz, 1H, Ar-*H* para), 6.58 (t, J = 7.4 Hz, 1H, Ar-*H* para), 4.37 (d, J = 12.8 Hz, 2H, ArC*H*$_2$Ar), 3.86 (s, 4H, OC*H*$_2$), 3.82−3.71 (m, 18H, OC*H*$_2$ and ArC*H*$_2$Ar), 3.64 (d, J = 5.9 Hz, 2H, OC*H*$_2$), 3.24 (d, J = 12.8 Hz, 4H, ArC*H*$_2$Ar), 2.61 (m, 2H, OC*H*$_2$), 1.70 (m, 1H, C*H*), 1.58 (m, 1H, C*H*$_2$), 1.41 (m, 1H, C*H*$_2$), 1.25 (m, 6H, C*H*$_2$), 1.14 (m, 2H, C*H*$_2$), 0.88−0.77 (m, 12H, C*H*, C*H*$_2$ and C*H*$_3$), 0.71−0.54 (m, 3H, C*H*$_2$), 0.38 (t, J = 7.3 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 157.4 (Ar ipso), 156.2 (Ar ipso), 155.0 (Ar ipso), 136.1 (Ar ortho), 133.4 (Ar ortho), 133.2 (Ar ortho), 129.9 (Ar meta), 129.2 (Ar meta), 128.4 (Ar meta), 128.1 (Ar para), 122.7 (Ar para), 122.1 (Ar para), 78.5, 73.5, 71.9, 71.0, 70.8, 70.2, 69.3 (O*C*H$_2$), 39.7 (*C*H), 37.4 (*C*H), 30.3 (Ar*C*H$_2$Ar), 30.2, 29.3, 28.9, 28.8, 23.6, 23.1, 23.0, 22.3 (*C*H$_2$), 14.2, 14.1, 10.7, 10.6 (*C*H$_3$). Anal. Calcd for $C_{54}H_{74}O_8$: C, 76.20; H, 8.76. Found: C, 76.11; H, 8.59.

25,27-Bis(2-*tert*-butoxyethoxy)calix[4]arene-crown-6, Partial-Cone (14). Yellow oil (24%); ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 7.5 Hz, 2H, Ar-*H* meta), 7.06 (d, J = 7.5 Hz, 2H, Ar-*H* meta), 6.92 (t, J = 7.5 Hz, 1H, Ar-*H* para), 6.90 (d, J = 7.5 Hz, 2H, Ar-*H* meta), 6.76 (t, J = 7.5 Hz, 1H, Ar-*H* para), 6.40 (m, 2H, Ar-*H* para), 6.33 (d, J = 7.5 Hz, 2H, Ar-*H* meta), 4.15 (d, J = 13 Hz, 2H, ArC*H*$_2$Ar), 3.98 (m, 2H, OC*H*$_2$), 3.83−3.48 (m, 26H, OC*H*$_2$ and ArC*H*$_2$Ar), 3.19 (m, 2H, OC*H*$_2$), 3.01 (d, J = 13 Hz, 4H, ArC*H*$_2$Ar), 1.25 (s, 9H, C*H*$_3$), 0.82 (s, 9H, C*H*$_3$). Anal. Calcd for $C_{50}H_{66}O_{10}$: C, 72.64; H, 7.99. Found: C, 72.52; H, 8.11.

X-ray Data. The structure of compound **12** has been established by X-ray crystallography (Figure 2). Colorless single crystal (0.35 × 0.30 × 0.20 mm^3) of **12** was obtained by slow evaporation from methanol/chloroform (80/20) solution: monoclinic, space group $P2_1/n$, $a = 14.423(2)$, $b = 14.771(2)$, $c = 22.145(6)$ Å, $\beta = 93.69°$, $V = 4708(2)$ Å^3, $Z = 4$, $d_{calcd} = 1.167$ Mg.m^{-3}, FW = 827.03 for $C_{50}H_{66}O_{10}$, $F(000) = 1784$. The unit cell dimensions were determined using the least-squares fit from 25 reflections ($25° < \theta < 35°$). Intensities were collected with an Enraf-Nonius CAD-4 diffactometer using the Cu Kα radiation and a graphite monochromator up to $\theta = 55°$. No intensity variation of two standard reflections monitored every 90 min was observed. The data were corrected for Lorentz and polarization effects and for empirical absorption correction.[44] The structure was solved by direct methods Shelx 86[45] and refined using Shelx 93[46] suite of programs.

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Supporting Information Available: Figures S1−3 and table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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