Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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Online publication date: 29 October 2010

To cite this Article Guillon, Jean , Sonnet, Pascal , Malval, Jean-Pierre , Massip, Stéphane , Gosse, Isabelle , Léger, Jean-Michel , Lapouyade, René , Rochette, Jacques , Monti, Jean-Pierre and Jarry, Christian(2002) 'Synthesis and Cesium Binding Affinity of New 25,27-Bis(alkyloxy)calix[4]arene-crown-6 Conformers in Relation to the Alkyl Pendent Moiety', Supramolecular Chemistry, 14: 5, 437 — 451
To link to this Article: DOI: 10.1080/1061027021000002404
URL: http://dx.doi.org/10.1080/1061027021000002404

Supramolecular Chemistry, 2002 Vol. 14 (5), pp. 437–450

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(Received 8 January 2002; In final form 28 January 2002)

The preparation of new 25,27-bis(alkyloxy)calix[4]arenes-crown-6 in the cone, partial-cone and 1,3-alternate conformation is reported. We have also investigated the alkylation of the cone monoalkylated calix[4]arene-crown-6 achieved using Cs_2CO_3. This reaction afforded a mixture of cone and partial-cone calix[4]arenes-crown-6 having an alkyl chain *anti* or *syn* to the polyether ring. Conformations have been probed using ^1H, ^{13}C, 2D-NMR and NOESY analysis, and using X-ray crystallography. Extraction experiments using a two-phase solvent method involving cesium picrate were performed for these newly synthesized conformers. They reveal and confirm the strong preference for the 1,3-alternate conformers. The affinity of 1,3-alternate calixarenes for Cs^+ has been assessed by complexation measurements ($\log \beta$) using a spectrophotometric technique. No significant Cs^+ extraction difference was observed in relation to the nature of the alkyl chains on the aromatic rings. ^1H NMR studies of the 1,3-alternate calixarene Cs^+ complexes confirms the cation's spacial position between the two aromatic rings, due to cation–π interactions.

Keywords: Calix[4]arene-crown-6; Cesium extraction; Cesium complexation; Conformation; Atropisomer

INTRODUCTION

The chemistry of calix[4]arenes, cyclic tetramers composed of phenolic and methylene moieties, has received considerable attention in recent years. The available sites on these macrocyclic compounds can be easily modified to tailor them for many applications such as ionophores in catalysis, as heavy metal absorption agents, as alkali metal complexation agents and as chemical sensors [1–6]. In particular, calix-crown compounds show high affinity for the complexation of alkali and alkaline-earth metal cations [7–10]. Significant efforts have been directed towards the use of 1,3-dialkyloxycalix[4]arene-crown-6 in the sensing, monitoring and remediation of ^{137}Cs, a fission product present in the wastes generated during the reprocessing of irradiated nuclear fuels [11–15]. These species were claimed as selective ionophores for the cesium cation due to its complexation with crown ether and with the two aromatic rings bearing the alkyl chains, through particular interactions [7–20].

The selective removal of $^{137}Cs^+$ from medium level radioactive waste, an important environmental and technological problem, constitutes the continuation of our previous industrial project [21]. High affinity and selectivity towards Cs^+ was only reported for some calix[4]arenes-crown-6 bearing alkyl chains (i.e. *i*-propyl [7–10], *n*-propyl [7–10], and *n*-octyl [7–10]) in the 1,3-alternate conformation. Consequently, we have designed and synthesized new 1,3-dialkyloxycalix[4]arene-crown-6 for use as extractants. This approach was partially based on structure activity considerations. A five carbon atom minimum alkyl

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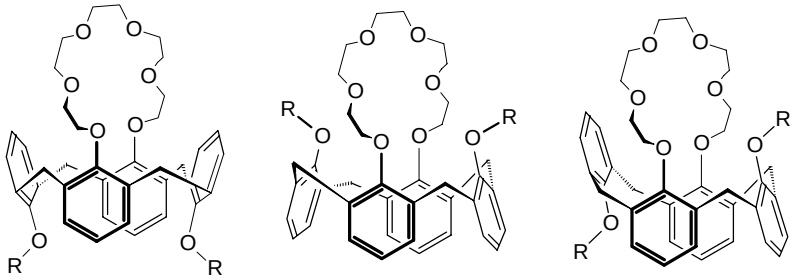
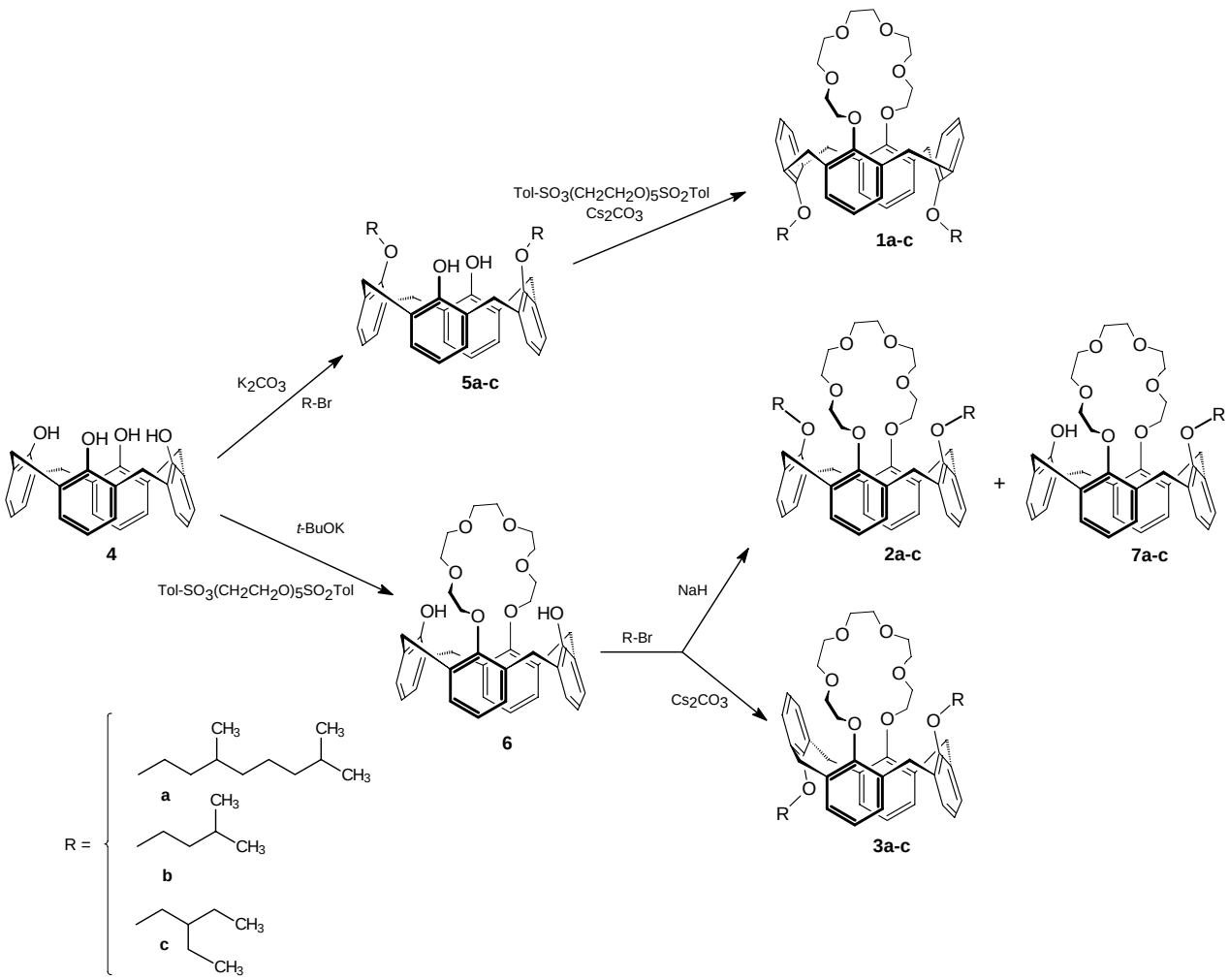
ISSN 1061-0278 print/ISSN 1029-0478 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/1061027021000002404



R = $-CH_2CH_2CHCH_3(CH_2)_3CH(CH_3)_2$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$

FIGURE 1 Stable conformations of 25,27-bis(alkyloxy)calix[4]arene-crown-6.

chains at the upper rim (aromatic nuclei) of the calix was introduced in order to obtain target compounds with a sufficient lipophilicity [22]. The flexibility parameter was investigated through modulations of the alkyl chain in order to restrict the flexibility of the calixarene-based ionophores. Indeed, these two structural parameters are related to the lipophilic behavior of the ligands towards extraction solvents [22]. On the other hand, the calix[4]arene-crown-6 conformation was claimed to influence the affinity towards alkali metal cations, as shown for the 1,3-diisopropoxycalix[4]arene-crown-6 elaborated in its three possible conformations, i.e. 1,3-alternate, cone, and partial-cone [7–10,19]. This led us to



SCHEME 1 Synthesis of calix[4]arene-crown-6 **1**–**3a**–**c** and **7a**–**c**.

synthesize new 1,3-bisalkyloxycalix[4]arene-crown-6 in their three possible conformations (Fig. 1). We also investigated the alkylation of the cone monoalkylated calix[4]arene-crown-6 achieved using Cs_2CO_3. This reaction afforded a mixture of cone and partial-cone calix[4]arenes-crown-6 having an alkyl chain *anti* or *syn* to the polyether ring. Conformations have been probed using ^1H, ^{13}C, 2D-NMR and NOESY analysis, and using X-ray crystallography.

Binding affinities of these new ligands for the Cs^+ have been determined by a two-phase solvent extraction experiment and by UV spectroscopy studies. These studies led to the determination of complexation parameters ($\log\beta$). A correlation between the extraction results and structural properties was found. Finally, cesium complexes have been prepared from the selected ligands **1a–c** and studied by ^1H NMR spectroscopy. The assignment of the spectral data shows and confirms the previously described existence of metal cation–π interactions. They were discussed with respect to the improved Cs^+ binding affinity of the ligands.

RESULTS AND DISCUSSION

Synthesis of 1,3-alternate 25,27-bis(alkyloxy)calix[4]arene-crown-6

25,27-Bis(alkyloxy)calix[4]arenes-crown-6 **1a–c** were obtained in two steps from calix[4]arene **4** (Scheme 1) [7,8,21]. Treatment of calix[4]arene **4** with alkyl bromide and K_2CO_3 (molar ratio 1:2.2:2.4) in anhydrous CH_3CN at reflux afforded the di-*O*-alkylated derivatives **5a–c** in the cone conformation, as indicated by the ^1H NMR spectra [23]. A typical AB pattern was observed for the methylene bridge $ArCH_2Ar$ protons ($J = 12.95–12.90$ Hz) at 4.33–4.30 and 3.37 ppm for **5a–c**. Moreover, the ^{13}C NMR resonance for the relevant carbon was found at around 42.4–37.3 ppm. Alkylation of **5a–c** with penta(ethyleneglycol)ditosylate and Cs_2CO_3 as a base in refluxing CH_3CN gave calix[4]arene-crown-6 **1a–c** in the 1,3-alternate conformation. All compounds **1a–c** were locked in the 1,3-alternate conformation as inferred from the ^1H NMR spectra which exhibited a singlet around 3.85–3.74 ppm for the bridging methylene groups of the calix[4]arene moiety. The ^{13}C NMR spectra show one signal at 38.0–37.5 ppm, characteristic for *anti* oriented nuclei in the calix[4]arene [24,25]. The structure of conformer **1c** was confirmed by 2-D NMR. In its NOESY spectrum, strong through space correlations of all crown ether protons with the doublet at 7.11 ppm and the triplet at 6.79 ppm indicate that these signals belong to the aromatic rings bearing the alkyl groups. NOESY also clearly corroborate the 1,3-alternate conformation because the two types of aromatic protons in *meta* and *para* position of the crown ether nuclei (7.01 and 6.71 ppm) are correlated with the alkyloxy protons. In addition, the methylene protons $ArCH_2Ar$ correlate with the aromatic *meta* protons bearing the crown ether.

Synthesis of Cone 25,27-bis(alkyloxy)calix[4]arene-crown-6

The three 1,3-dialkoxycalix[4]arene-crown-6 cone isomers **2a–c** were synthesized via **6** [9,21] by first bridging calix[4]arene **4** with pentaethylene glycol ditosylate in refluxing benzene with *t*-BuOK as the base. Reaction of **6** with alkyl bromide in THF/DMF (9/1-v/v) with NaH gave a mixture of the dialkylated calix[4]arenes-crown-6 **2a–c** and monoalkylated calix[4]arenes-crown-6 **7a–c**, both in the cone conformation (Scheme 1). The monoalkylated calixarenes **7a–c** can be used as synthons useful for the preparation of bisalkylated mixed atropisomers [26]. As expected on the basis of symmetry considerations, (1,3)-cone conformers **2a–c** show one typical AB system formed by the axial protons (4.40–4.38 ppm) and by the equatorial protons (3.18–3.16 ppm) for the $ArCH_2Ar$ groups. Their ^{13}C resonances were found closed to 31 ppm [7,8,21]. In **2a–c**, the position of the doublets and the triplets due to the aromatic *meta* (7.14–7.13 and 6.07–6.00 ppm) protons and aromatic *para* (6.95–6.93 and 6.19–6.18 ppm) protons is suggestive of a distorted C_{2v} cone conformation in solution [27–29]. The 3D structure of **2b** was established by X-ray crystallography. The data are discussed further in comparison with those of its **3b** isomer. The NMR spectra of monoalkylated cone conformers **7a–c**, isolated during the alkylation of **6**, are consistent with a cone conformation. Their methylene protons $ArCH_2Ar$ show up two AB systems (relative intensity 4:4) with resonances for the respective carbons close to 31.5–30.7 and 31.0–30.6 ppm. The ^1H NMR spectra also showed a singlet for the mobile OH proton at 6.20–5.36 ppm (1H).

Synthesis of Partial-cone 25,27-bis(alkyloxy)calix[4]arene-crown-6

Alkylation of 1,3-dihydroxycalix[4]arene-crown-6 **6** with alkyl bromide and an excess of Cs_2CO_3 in dry CH_3CN at reflux afforded the dialkylated partial-cone **3a–c** (Scheme 1) [21]. The preparation of the partial-cone conformers appears to be favored by the template effect of the Cs^+ ions [4]. In the ^1H NMR spectrum of **3c**, the partial-cone conformation was substantiated by the presence of four doublets for the aromatic *meta* protons at 7.27, 7.10, 6.80 and 6.77 ppm, and two doublets (3.64 and 2.73 ppm) for the 2-ethylbutyloxyprotons. The conformation of **3b** was established by a single-crystal X-ray analysis.

TABLE I Crystal data and structure refinement for compounds **2b** and **3b**

Compound	**2b**	**3b**
Formula	$C_{48}H_{62}O_8$	$C_{48}H_{62}O_8$
Mol. wt.	766.98	766.98
Cryst. syst.	Triclinic	Triclinic
Space group	P_{-1}	P_{-1}
Cell parameters at 295 K		
a (Å)	12.586(1)	10.145(1)
b (Å)	12.698(1)	13.363(2)
c (Å)	15.481(4)	16.161(2)
α (deg)	82.71(1)	93.45(1)
β (deg)	77.85(1)	92.04(1)
γ (deg)	67.17(1)	97.09(1)
V (Å^3)	2226.4(6)	2168.2(5)
Z	2	2
D_{calc} (mg m^{-3})	1.144	1.175
F(000)	828	828
Crystal size (mm^3)	0.50 × 0.25 × 0.25	0.50 × 0.37 × 0.30
No. of unique refl. measd	6542	7159
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.054	1.047
R [$I > 2\sigma(I)$]	0.0945	0.0671
wR^2 [$I > 2\sigma(I)$]	0.2688	0.1966

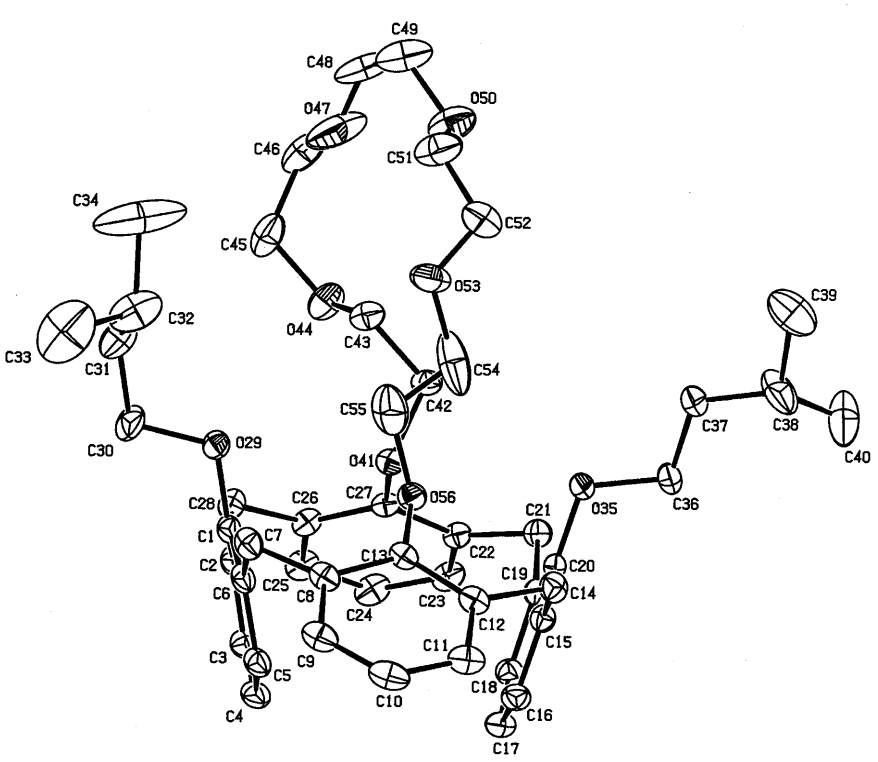
X-ray Analysis of Cone 2b And Partial-cone 3b Conformers

X-ray crystallography was conducted to confirm the three dimensional structures of the receptors. Unfortunately, suitable crystals were obtained only for the two conformers **2b** and **3b** (Table I). Views of the solid-state conformation of **2b** and **3b** are shown in Fig. 2. Molecule **2b** adopts a "pinched-cone" conformation commonly found in calix[4]arenes in the cone conformation with two opposite aromatic rings almost parallel and the remaining two almost normal to each other. Thus, the two rings C8–C13 and C22–C27, linked by the polyether chain, are almost parallel to one another. With respect to the reference methylene plane, C14, C21, C28, C7, the interplanar angles of C8–C13 and C22–C27 rings are 37.4(2)° and 38.3(1)°, respectively. The ring C1–C6, bearing the alkyl substituent, is inclined at 74.3(1)° from the reference plane, whereas the corresponding angle for ring C15–C20 is 78.6(1)°. In **3b**, the aromatic ring C15–C20, bearing one 3-methylbutyloxy pendant group, is on the opposite side of the plane of the bridging methylene groups (C21, C28, C7, C14) with respect to the remaining three aromatic rings. The dihedral angle between the C15–C20 ring and the reference methylene plane (C14, C21, C28, C7) was found normal at 85.0(1)°. The two aromatic rings linked by the polyether chain (C8–C13, C22–C27) are almost parallel to one another with interplanar angles of 88.9(1) and 86.6(1)° to the reference plane.

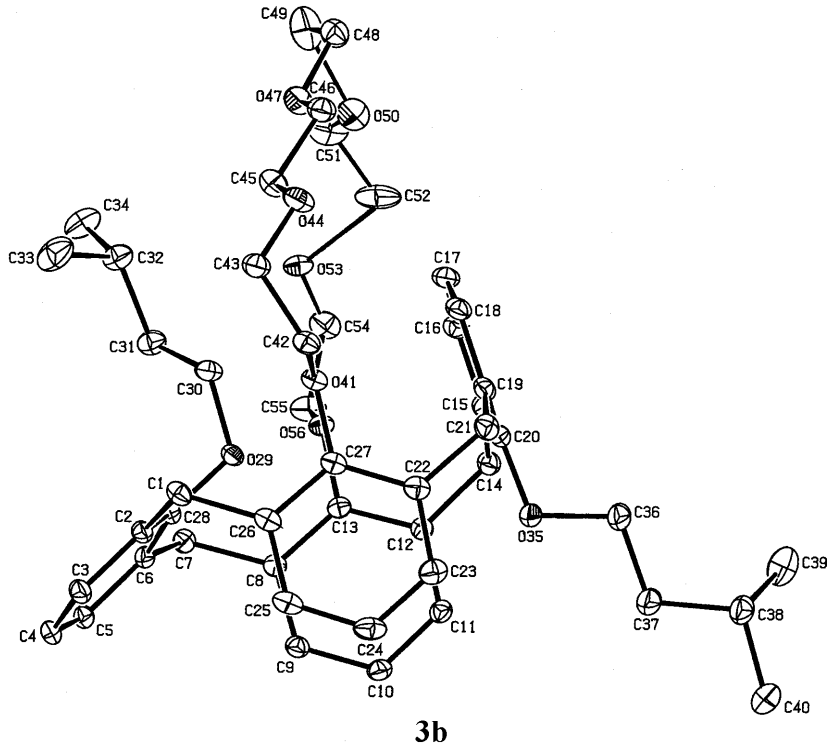
On the other hand, the ring C1–C6 containing the second 3-methylbutyloxy substituent is tilted back and makes a dihedral angle of 32.2(1)° with the methylene carbon plane. Not surprisingly, in both cone and partial-cone stereoisomers the polyether chains adopt various conformations. Moreover, they do not present a regular conformation. For **2b**, the torsion angles O–C–C–O are 173.7(7), −119.1(11), 37.3(19), −79.6(9), and −81.1(5)°, whereas the C–O–C–C torsion angles are 116.0(8), 150.9(10), −130.6(12), −172.5(13), and −177.8(6)°. For **3b**, the torsion angles O–C–C–O are 72.8(3), −175.7(3), 67.7(5), −91.0(10), and 44.2(5)°, whereas C–O–C–C angles are −154.5(6), −172.9(8), −178.4(3), 158.8(2) and 179.6(4)°. In both stereoisomers the inter-calixarene contacts are of the Van der Waals variety and there are no solvent accessible voids in the crystal lattice.

Synthesis of Cone, *Syn*- And *Anti*-partial-cone Atropisomers of Mixed 25,27-bis(alkyloxy)calix[4]arene-crown-6

Calix[4]arene-crown-6 with mixed alkyl chains can exist as four atropisomers, i.e. 1,3-alternate, cone, *syn*-partial-cone and *anti*-partial-cone, rarely described together in the literature [26]. The structure of each pair of isolated partial-cone isomers of calix[4]arenes-crown-6 with mixed alkyl chains are generally designated as *syn* and *anti*, according to whether the longer chain is on the same side or the opposite side with respect to the polyether chain. In this work, new mixed 25,27-bis(alkyloxy)calix[4]-arene-crown-6 were designed for complexation purposes. Our synthetic approach was based on the search of efficient protocols for the stereocontrolled introduction of mixed alkyl chains onto the calixcrown framework, leading to the four possible atropisomeric calix[4]arenes-crown-6. Consequently, we decided to use the different previously isolated mono-alkylated calixarenes **7** as synthons. In order to

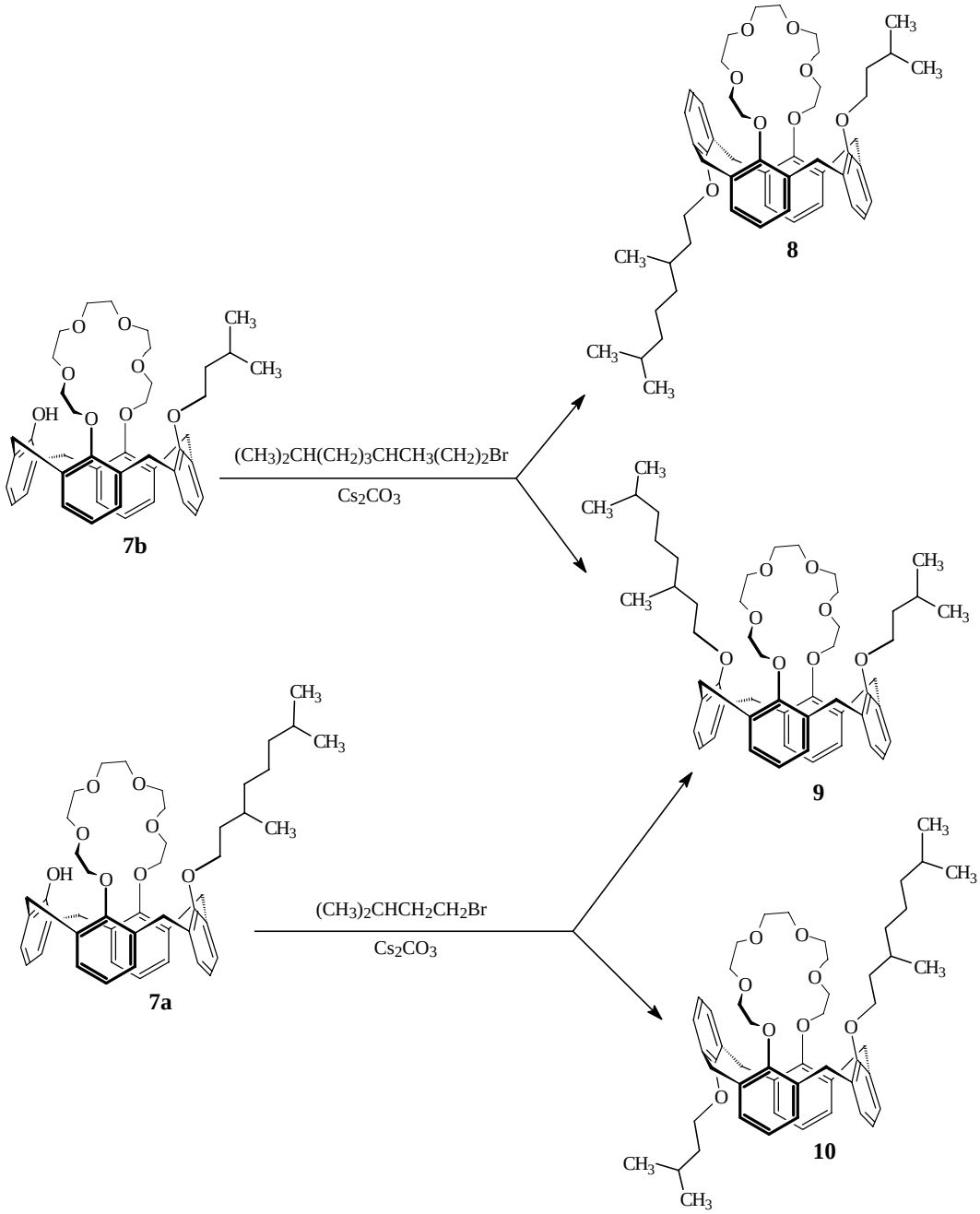


2b



3b

FIGURE 2 A view of **2b** and **3b** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level, H atoms are omitted for clarity.



SCHEME 2 Synthesis of atropisomers **8**, **9** and **10**.

obtain selectively the cone, *anti*- and *syn*-partial-cone conformers, we chose an appropriate base, i.e. NaH or Cs_2CO_3, for the final alkylation step.

The alkylation of 25-(alkyloxy)-27-hydroxycalix[4]arene-crown-6, cone **7b** with 3,7-dimethyloctyl bromide and Cs_2CO_3 in refluxing CH_3CN gave the conformationally locked and mixed dialkylated *anti*-partial-cone **8** (34%). Moreover, the cone **9** was isolated in 47% yield. A similar alkylation of calix[4]arene **7a** with 3-methylbutyl bromide afforded the cone calixarene **9** (34%) with the *syn*-partial-cone **10** (23%) (Scheme 2). The fourth 1,3-alternate isomer, not isolated during this work, will be synthesized by a classical synthetic pathway through mixed cone 25,27-bis(alkyloxy)calix[4]arene, followed by a typical cyclization with the pentaethylene glycol ditosylate and Cs_2CO_3.

Structural assignments of rigid calix[4]arene crown ethers **8**, **9** and **10** were firmly established by ^{1}H NMR and ^{13}C NMR spectroscopy, on the basis of distinctive spectral patterns of the bridging methylene protons and of the position of the resonances of pertinent carbons. For example, in the ^{1}H NMR spectrum of cone isomer **9**, a typical AB pattern was observed for

TABLE II Extraction percentage (Ex%) of cesium picrate by calix-crowns, from water to dichloromethane, at 20°C

Ligands	Cs^+
1a	51.5 ± 0.8
1b	53.9 ± 0.8
1c	50.5 ± 0.7
2a	2.4 ± 0.1
2b	0.7 ± 0.1
2c	1.6 ± 0.1
3a	12.3 ± 0.2
3b	14.0 ± 0.2
3c	13.2 ± 0.2
8	12.6 ± 0.2
9	2.0 ± 0.1
10	13.7 ± 0.2

Standard deviation σ_{n-1} on the mean of $n = 4$ experiments.

the methylene bridge $ArCH_2Ar$ protons (J = 13.45 Hz) at 4.32 and 3.10 ppm. The high field doublet at 3.10 ppm has been assigned to the equatorial protons of the methylene groups, whereas the low field signal at 4.32 ppm was due to the axial protons.

Finally, these synthetic pathways paved the way for the preparation of calix[4]arene crown ethers in a fixed cone, *anti*- or *syn*-partial-cone conformation. The cone 25-(alkyloxy)-27-hydroxycalix[4]arenes-crown-6 **7** are useful synthons for the preparation of calix[4]arene-crown-6 atropisomers, by using the described procedures.

Extraction of Cesium and Complexation Studies

A first estimation of the ionophoric properties of ligands **1a**–**c**, **2a**–**c**, **3a**–**c**, **8**, **9** and **10** was achieved with cesium picrate, according to the extraction method developed by Pedersen [30–32]. The results, expressed as extraction percentage (Ex%), are reported in Table II.

TABLE III Complexation data ($\log \beta$)* of some calix[4]arene-crown-6 and cesium chloride, in CH_3OH, at 25°C

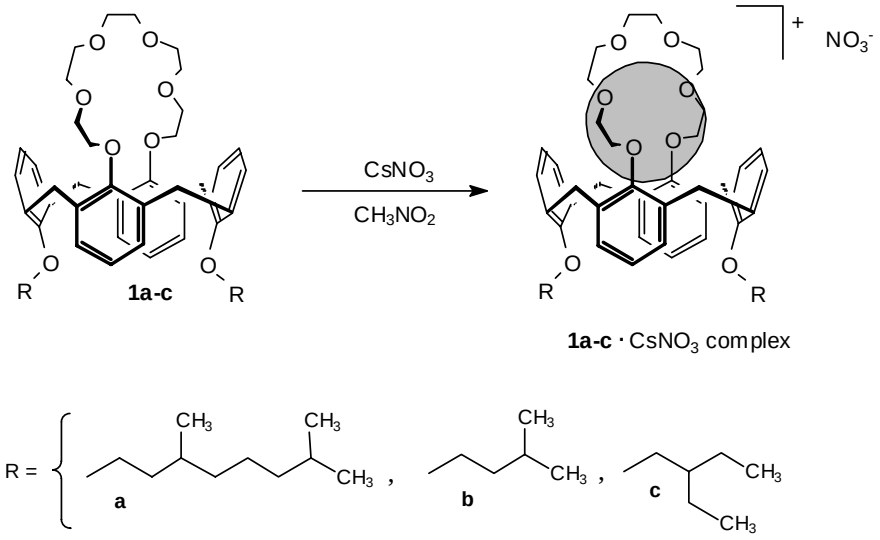
Ligands	Cs^+
1a	6.2 ± 0.9
1b	5.4 ± 0.8
1c	6.3 ± 0.9
3a	3.9 ± 0.7

*Standard deviation σ_{n-1} on the mean of a minimum of two experiments.

Complexation reactions were achieved with cesium chloride in CH_3OH and 1,3-alternate calix-crowns-6 **1a**–**c** and **3a** blocked in the partial-cone conformation. They were studied by UV absorption spectrophotometry [33–36]. The complexation data, expressed as $\log \beta$, are reported in Table III.

A full agreement between the extraction and the complexation data was noticed for all described calix-crowns. Crowns-6 **2a**–**c** and **9** in the cone conformation do not show selectivity for the cesium cation (Ex% = 0.7–2.4). This could be related to the destabilization of the cesium complexes due to the steric effect of the alkyl groups that face the polyether ring.

The partial-cone calixarenes **3a**–**c**, **8** and **10** are slightly more efficient than the cone analogs toward cesium extraction (Ex% = 12.3–14.0, $\log \beta = 3.9$ for **3a**), probably due to the interaction of one phenyl group with the complexed cesium cation [19]. A dramatic increase in the binding ($\log \beta = 5.4$–6.3) and in the extraction percentage of cesium cation (Ex% = 50.5–53.9) is observed for **1a**–**c** in the 1,3-alternate conformation. These favorable extraction results are explained by the preorganization of the ligand and by the fact that the less polar 1,3-alternate conformation allows the interaction of the cesium ion with the π-electron cloud of the arene rings [7].



SCHEME 3 Synthesis of **1a**–**c** $CsNO_3$ complexes.

TABLE IV ^{1}H NMR data for ligands **1a–c** and their cesium nitrate complexes in $CDCl_3$ at 25°C

Compound	H_{meta}*	H_{meta}†	H_{para}*	H_{para}†	OCH_2‡	$ArCH_2Ar$	OCH_2¶
1a	7.06	6.99	6.81	6.76	3.35	3.77	3.72–3.51 (m, 16), 3.45 (m, 4)
1b	7.07	7.01	6.82	6.79	3.34	3.85	3.69 (s, 4), 3.66–3.53 (m, 8), 3.45 (m, 8)
1c	7.11	7.01	6.79	6.71	3.47	3.74	3.70–3.62 (m, 16), 3.46–3.43 (m, 4)
1a·Cs^+	7.13	7.03	7.06	6.77	3.47	3.80	3.81–3.65 (m, 16), 3.58 (m, 4)
1b·Cs^+	7.15	7.06	7.09	6.82	3.57	3.74	3.97 (m, 4), 3.69 (m, 16)
1c·Cs^+	7.18	7.05	7.10	6.75	3.53	3.84	3.79 (m, 4), 3.71 (m, 12), 3.59 (m, 4)

* Aromatic protons of alkoxy-substituted rings. † Aromatic protons of the rings bearing the crown ether; H_{meta} = doublet, H_{para} = triplet. ‡ Alkyloxy protons. ¶ Crown-6 protons.

Concerning the alkyl pendent group influence, we noticed that Cs^+ extraction is not influenced by the variation of the length and the ramification of the aliphatic chains, confirming previously related studies achieved with 1,3-alternate dialkylcalix[4]-arenes-crown-6 bearing *n*-propyl, *i*-propyl, or *n*-octyl, as alkyl chains [7–9]. In order to confirm the metal-binding site interactions, a structural study was performed with metal complexes from selected ligands **1a–c**. The 1:1 metal complexes were prepared according to a previous procedure by reaction of **1a–c** dissolved in CH_3NO_3 with a large excess of $CsNO_3$ at 70°C during 15 h (Scheme 3) [37]. The non-reacted $CsNO_3$ was filtered and the solution slowly evaporated yielding orange crystals. As single crystals suitable for X-ray analysis have not been isolated, a ^{1}H NMR spectra study (500 MHz) was conducted.

Since **1a–c** were fixed in the 1,3-alternate structure, the complexes' spectra should be sensitive mainly to the interactions with the Cs^+ cation and not to the conformational rearrangement of the calixarene. On the other hand, high stability constants ($5.37 \leq \log\beta \leq 6.34$) have been found in CH_3OH between these ligand and Cs^+ cation (Table III). This ensures that the complexes are >98% formed at room temperature and at 1.5×10^{-2} M concentration of host and metal nitrate. Consequently, only the signals referring to these species are observed in the ^{1}H NMR spectra [8]. The protons signal assignment of the two different pairs of aromatic rings has been confirmed on the basis of ^{1}H NMR experiments with the free ligands **1a–c** and with their respective Cs^+ complexes. The ^{1}H NMR spectra of the cesium complex indicate that the crown ether is involved in complexation. Indeed, we noted a classical downfield chemical shift for the ether protons (Table IV).

Moreover, the aromatic protons in *para* and *meta* positions of the aromatic nuclei bearing the alkyloxy groups experience a large downfield shift upon complexation (Table IV). The largest shifts for Cs^+ were observed for the triplet of the *para* protons ($\Delta\delta = +0.31 - 0.25$ ppm), and also for the doublet of the *meta* protons with $\Delta\delta = +0.08 - 0.07$ ppm. This clearly indicates the existence of cation–π interactions in the studied 1,3-alternate complexes. Finally, the complexed Cs^+ cation interacts in solution not only with the crown ether moiety, but also with the two rotated aromatic rings bearing the alkyloxy groups of the 1,3-alternate conformation through these cation–π interactions [8,38–40].

Conclusion

In this work, we developed straightforward synthetic procedures for the preparation of 1,3-calix[4]-arene crown ethers in their three possible conformations (i.e. 1,3-alternate **1a–c**, cone **2a–c**, and partial-cone **3a–c**). For the synthesis of these new dialkyloxycalix[4]arene-crown ether conformers **1–3** we used two synthetic approaches: (i) the selective dialkylation of calix[4]arene **4** with alkyl bromide, followed by intrabridging of the dialkylated intermediates **5a–c** with oligo ethylene glycol ditosylate and base which gave 1,3-alternate calix-crown **1a–c**; (ii) the installation of the polyether chain to prepare intermadiate **6**, followed by dialkylation with alkyl bromide and NaH or Cs_2CO_3 as the base which afforded conformationally locked cone **2a–c** and **7a–c**, and partial-cone **3a–c** conformers, respectively. These two conformations appear to be favored by a template effect of the metal ions present in solution. The monoalkylated cone calix[4]arenes-crown-6 **7a–b**, isolated during the synthesis of **2a–b** were used as synthons for synthesizing new atropisomeric dialkyloxycalix[4]-arenes-crown-6. They were alkylated on the free hydroxy group leading to a mixture of cone and *syn* or *anti* partial-cone conformers. The conformations of all described new compounds have been assessed by NMR and X-ray studies. A quantification of the ionophoric properties of the new synthesized ligands was achieved by a two-phase solvent extraction involving cesium picrate and by UV spectroscopy studies. It led to the selection of the 1,3-alternate calix[4]arene-crown-6 **1a–c** as the most potent Cs^+ extractants. Results were also used to correlate the Cs^+ extraction of **1a–c** ligands with structural parameters, i.e. the variation of the length and the ramification of the aliphatic chains. Moreover, other parameter must be considered in terms of structure–activity relationship: a three carbon atom chain seems to be the minimal length required to restrict

the flexibility of the calixarene skeleton and to modulate the lipophilicity of the ligands. Finally, a cation–π interaction was noticed for the 1,3-alternate conformers **1a–c** by using ^{1}H NMR studies. It enlightens the metal binding site interaction implicated for the improved affinity of these ligands.

MATERIALS AND METHOD

Commercially reagents were used as received without additional purification. Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and are uncorrected. IR spectra were recorded on a BRUKER IFS-25 spectrophotometer. Absorption spectra were measured on a PERKIN ELMER Lambda 2 UV–Vis. scanning spectrophotometer. NMR spectra were recorded with tetramethylsilane as an internal standard using a BRUKER AC 200 spectrometer (^{1}H, ^{13}C, 2D-COSY) or using a BRUKER AVANCE 500 spectrometer (^{1}H, NOESY). Splitting patterns have been designated as follows: s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; ddd = double double doublet; m = mutiplet. 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. Elemental analyses (C, H) for new compounds were performed by CNRS (Vernaison-France) and agreed with the proposed structures within ± 0.3% of the theoretical values. All solvents and reagents were purchased from Acros and Aldrich Chimie and used without further purification.

In NMR spectra, the "Ar" notation indicates the aromatic nuclei of the calixarene backbone, considering the phenol oxygen as the main substituent to which the *ipso*, *ortho*, *meta*, and *para* positions refer.

Synthesis of 25,27-bis(alkyloxy)calix[4]arene, Cone 5a–c (General Procedure)[†]

A suspension of calix[4]arene **4** (6.0 g, 14.1 mmol), K_2CO_3 (4.69 g, 34 mmol) and 31 mmol of various alkyl bromide 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 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, then from petroleum ether gave **5b–c** as white crystals. Pure compound **5a** was obtained by column chromatography (SiO_2, chloroform/hexane = 1/2).

[†]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.

25,27-bis(3,7-dimethyloctyloxy)calix[4]arene, Cone 5a

Colorless oil (27%). IR (KBr) ν 3335 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 2H, O*H*), 7.05 (d, J = 7.40 Hz, 4H, Ar-*H meta*), 6.89 (d, J = 7.45 Hz, 4H, Ar-*H meta*), 6.72 (t, J = 7.40 Hz, 2H, Ar-*H para*), 6.68 (t, J = 7.45 Hz, 2H, Ar-*H para*), 4.32 (d, J = 12.90 Hz, 4H, ArCH_2Ar), 4.03 (t, J = 6.95 Hz, 4H, OCH_2), 3.37 (d, J = 12.90 Hz, 4H, ArCH_2Ar), 1.99 (m, 6H, C*H* and CH_2), 1.46–1.17 (m, 14H, C*H* and CH_2), 1.04 (d, J = 6.30 Hz, 6H, CH_3), 0.89 (d, J = 6.60 Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 153.3 (Ar *ipso*), 152.2 (Ar *ipso*), 133.4 (Ar *ortho*), 128.8 (Ar *ortho*), 128.4 (Ar *meta*), 128.2 (Ar *meta*), 125.1 (Ar *para*), 118.9 (Ar *para*), 75.4 (OC H$_2$), 39.3 (*C* H$_2$), 37.3 (ArC H$_2$Ar), 37.0 (*C* H), 31.5 (*C* H$_2$), 29.8 (*C* H$_2$), 27.9 (*C* H), 24.6 (*C* H$_2$), 22.6 (*C* H$_3$), 19.9 (*C* H$_3$). Anal. Calcd for $C_{48}H_{64}O_4$: C, 81.77; H, 9.15. Found: C, 81.81; H, 9.22.

25,27-bis(3-methylbutyloxy)calix[4]arene, Cone 5b

White crystals (20%), mp 184°C. IR (KBr) ν 3340 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 2H, O*H*), 7.03 (d, J = 7.40 Hz, 4H, Ar-*H meta*), 6.90 (d, J = 7.50 Hz, 4H, Ar-*H meta*), 6.72 (t, J = 7.40 Hz, 2H, Ar-*H para*), 6.62 (t, J = 7.50 Hz, 2H, Ar-*H para*), 4.30 (d, J = 12.90 Hz, 4H, ArCH_2Ar), 4.01 (t, J = 6.80 Hz, 4H, OCH_2), 3.37 (d, J = 12.90 Hz, 4H, ArCH_2Ar), 1.98 (m, 6H, C*H*CH_2), 1.06 (d, J = 6.35 Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 153.4 (Ar *ipso*), 152.1 (Ar *ipso*), 133.4 (Ar *ortho*), 128.8 (Ar *ortho*), 128.3 (Ar *meta*), 128.1 (Ar *meta*), 125.2 (Ar *para*), 118.9 (Ar *para*), 75.3 (OC H$_2$), 38.8 (ArC H$_2$Ar), 31.4 (*C* H$_2$), 25.0 (*C* H), 22.8 (*C* H$_3$). Anal. Calcd for $C_{38}H_{44}O_4$: C, 80.81; H, 7.85. Found: C, 80.97; H, 7.93.

25,27-bis(2-ethylbutyloxy)calix[4]arene, Cone 5c

White crystals (20%), mp 205°C. IR (KBr) ν 3380 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 2H, O*H*), 7.06 (d, J = 7.30 Hz, 4H, Ar-*H meta*), 6.83 (d, J = 7.40 Hz, 4H, Ar-*H meta*), 6.70 (t, J = 7.30 Hz, 2H, Ar-*H para*), 6.65 (t, J = 7.40 Hz, 2H, Ar-*H para*), 4.33 (d, J = 12.95 Hz, 4H, ArCH_2Ar), 3.86 (d, J = 4.50 Hz, 4H, OCH_2), 3.37 (d, J = 12.95 Hz, 4H, ArCH_2Ar), 1.75 (m, 10H, C*H*CH_2), 1.04 (t, J = 6.60 Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 153.6 (Ar *ipso*), 152.0 (Ar *ipso*), 133.1 (Ar *ortho*), 128.9 (Ar *ortho*), 128.4 (Ar *meta*), 127.9 (Ar *meta*), 125.1 (Ar *para*), 118.7 (Ar *para*), 78.9 (OC H$_2$), 42.4 (ArC H$_2$Ar), 31.2 (*C* H), 23.0 (*C* H$_2$), 11.4 (*C* H$_3$). Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16. Found: C, 81.11; H, 8.25.

Synthesis of 25,27-bis(alkyloxy)calix[4]arene-crown-6, 1,3-alternate 1a–c (general Procedure)

25,27-Dialkoxycalix[4]arene, cone **5a–c** (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 atmosphere. The reaction mixture was refluxed for 24 h, then CH_3CN was removed under reduced pressure and the residue 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 by purified by column chromatography (SiO_2, ethyl acetate/hexane = 1/1) and crystallized from MeOH to afford **1a–c**.

25,27-bis(3,7-dimethyloctyloxy)calix[4]arene-crown-6, 1,3-alternate 1a

Pale yellow crystals (19%), mp 42°C. ^{1}H NMR ($CDCl_3$) δ 7.06 (d, $J = 7.45$ Hz, 4H, Ar-*H meta*), 6.99 (d, $J = 7.40$ Hz, 4H, Ar-*H meta*), 6.81 (t, $J = 7.45$ Hz, 2H, Ar-*H para*), 6.76 (t, $J = 7.40$ Hz, 2H, Ar-*H para*), 3.77 (s, 8H, ArCH_2Ar), 3.72–3.51 (m, 16H, OCH_2), 3.45 (m, 4H, OCH_2), 3.35 (t, $J = 6.00$ Hz, 4H, OCH_2), 1.58 (m, 6H, C*H* and CH_2), 1.33–1.06 (m, 14H, C*H* and CH_2), 0.89 (d, $J = 6.65$ Hz, 12H, CH_3), 0.84 (d, $J = 6.35$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.9 (Ar *ipso*), 156.4 (Ar *ipso*), 134.1 (Ar *ortho*), 133.6 (Ar *ortho*), 129.7 (Ar *meta*), 129.5 (Ar *meta*), 122.1 (Ar *para*), 71.1, 71.0, 70.9, 70.6, 69.7, 69.1 (OCH_2), 39.3 (CH_2), 37.9 (CH_2), 37.6 (ArCH_2Ar), 35.8 (CH_2), 30.3 (CH), 28.0 (CH_2), 24.8 (CH), 22.7 (CH_2), 22.6 (CH_3), 20.1 (CH_3). Anal. Calcd for $C_{58}H_{82}O_8$: C, 76.78; H, 9.11. Found: C, 76.87; H, 9.24.

25,27-bis(3-methylbutyloxy)calix[4]arene-crown-6, 1,3-alternate 1b

White crystals (11%), mp 78°C. ^{1}H NMR ($CDCl_3$) δ 7.07 (d, $J = 7.45$ Hz, 4H, Ar-*H meta*), 7.01 (d, $J = 7.45$ Hz, 4H, Ar-*H meta*), 6.82 (t, $J = 7.45$ Hz, 2H, Ar-*H para*), 6.79 (t, $J = 7.45$ Hz, 2H, Ar-*H para*), 3.85 (s, 8H, ArCH_2Ar), 3.69 (s, 4H, OCH_2), 3.66–3.53 (m, 8H, OCH_2), 3.45 (m, 8H, OCH_2), 3.34 (t, $J = 6.00$ Hz, 4H, OCH_2), 1.51 (m, 2H, C*H*), 1.08 (ddd, $J = 6.90$ and 6.00 Hz, 4H, CH_2), 0.86 (d, $J = 6.60$ Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.0 (Ar *ipso*), 156.5 (Ar *ipso*), 134.0 (Ar *ortho*), 133.6 (Ar *ortho*), 129.6 (Ar *meta*), 129.4 (Ar *meta*), 122.1 (Ar *para*), 71.1, 71.0, 70.9, 69.8, 69.7, 69.2 (OCH_2), 38.0 (ArCH_2Ar), 37.7 (CH_2), 25.4 (CH), 23.0 (CH_3). Anal. Calcd for $C_{48}H_{62}O_8$: C, 75.16; H, 8.15. Found: C, 75.21; H, 8.09.

25,27-bis(2-ethylbutyloxy)calix[4]arene-crown-6, 1,3-alternate 1c

White crystals (12%), mp 71°C. ^{1}H NMR ($CDCl_3$) δ 7.11 (d, $J = 7.40$ Hz, 4H, Ar-*H meta*), 7.01 (d, $J = 7.50$ Hz, 4H, Ar-*H meta*), 6.79 (t, $J = 7.40$ Hz, 2H, Ar-*H para*), 6.71 (t, $J = 7.50$ Hz, 2H, Ar-*H para*), 3.74 (s, 8H, ArCH_2Ar), 3.70–3.62 (m, 16H, OCH_2), 3.47 (d, $J = 5.00$ Hz, 4H, OCH_2CH), 3.46–3.43 (m, 4H, OCH_2), 1.63 (m, 2H, C*H*), 1.24 (m, 8H, CH_2), 0.84 (t, $J = 7.35$ Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.7 (Ar *ipso*), 156.3 (Ar *ipso*), 133.6 (Ar *ortho*), 133.5 (Ar *ortho*), 130.3 (Ar *meta*), 130.2 (Ar *meta*), 121.7 (Ar *para*), 121.6 (Ar *para*), 75.1, 71.2, 70.9, 70.5, 70.0, 69.9 (OCH_2), 42.0 (CH), 37.5 (ArCH_2Ar), 22.9 (CH_2), 11.2 (CH_3). Anal. Calcd for $C_{50}H_{66}O_8$: C, 75.53; H, 8.37. Found: C, 75.76; H, 8.45.

Synthesis of 25,27-bis(alkyloxy)calix[4]arene-crown-6, Cone 2a–c, and 25-(alkyloxy)-27-hydroxycalix[4]arene-crown-6, Cone 7a–c (general Procedure)

A solution of calix[4]arene-crown-6 6 (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. Alkyl 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. The oily residue was purified by column chromatography (SiO_2, ethyl acetate/hexane = 1/4) to afford **2a** and **7a**, (SiO_2, ethyl acetate/hexane = 2/3) to afford **2b** and **7b** and (SiO_2, ethyl acetate/hexane = 1/1) to afford **2c** and **7c**.

25,27-bis(3,7-dimethyloctyloxy)calix[4]arene-crown-6, Cone 2a

Pale yellow oil (20%). ^{1}H NMR ($CDCl_3$) δ 7.13 (d, $J = 7.35$ Hz, 4H, Ar-*H meta*), 6.93 (t, $J = 7.35$ Hz, 2H, Ar-*H para*), 6.19 (t, $J = 7.40$ Hz, 2H, Ar-*H para*), 6.07 (d, $J = 7.40$ Hz, 4H, Ar-*H meta*), 4.38 (d, $J = 13.40$ Hz, 4H, ArCH_2Ar), 4.26 (t, $J = 7.20$ Hz, 4H, OCH_2), 4.01 (t, $J = 7.20$ Hz, 4H, OCH_2), 3.75 (m, 16H, OCH_2), 3.16 (d, $J = 13.40$ Hz, 4H, ArCH_2Ar), 1.94–1.53 (m, 6H, C*H* and CH_2), 1.37–1.14 (m, 14H, C*H* and CH_2), 0.94 (d, $J = 6.30$ Hz, 6H, CH_3), 0.85 (d, $J = 6.55$ Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.2 (Ar *ipso*), 155.0 (Ar *ipso*), 136.8 (Ar *ortho*), 132.0 (Ar *ortho*), 129.0 (Ar *meta*), 127.3 (Ar *meta*), 122.1 (Ar *para*), 73.9, 72.5, 71.0, 70.6, 70.8, 70.7, 69.7 (OCH_2), 39.3 (CH_2), 37.3 (CH_2), 30.9 (ArCH_2Ar), 30.0 (CH), 27.9 (CH_2), 24.6 (CH), 22.7 (CH_2), 22.6 (CH_3), 19.8 (CH_3). Anal.

Calcd for $C_{58}H_{82}O_8$: C, 76.78; H, 9.11. Found: C, 76.76; H, 9.19.

25,27-bis(3-methylbutyloxy)calix[4]arene-crown-6, Cone 2b

White crystals (33%), mp 120°C. ^{1}H NMR ($CDCl_3$) δ 7.13 (d, $J = 7.30$ Hz, 4H, Ar-*H meta*), 6.94 (t, $J = 7.30$ Hz, 2H, Ar-*H para*), 6.19 (t, $J = 7.35$ Hz, 2H, Ar-*H para*), 6.05 (d, $J = 7.35$ Hz, 4H, Ar-*H meta*), 4.38 (d, $J = 13.45$ Hz, 4H, ArCH_2Ar), 4.26 (t, $J = 7.30$ Hz, 4H, OCH_2), 4.03 (t, $J = 7.30$ Hz, 4H, OCH_2), 3.73 (m, 16H, OCH_2), 3.18 (d, $J = 13.45$ Hz, 4H, ArCH_2Ar), 1.84 (m, 6H, C*H* and CH_2), 0.99 (d, $J = 6.20$ Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.9 (Ar *ipso*), 155.6 (Ar *ipso*), 137.4 (Ar *ortho*), 133.6 (Ar *ortho*), 129.7 (Ar *meta*), 128.0 (Ar *meta*), 122.8 (Ar *para*), 78.3, 74.6, 73.1, 71.7, 71.4, 70.3 (OCH_2), 39.8 (CH_2), 31.5 (ArCH_2Ar), 25.9 (C H), 23.4 (CH_3). Anal. Calcd for $C_{48}H_{62}O_8$: C, 75.16; H, 8.15. Found: C, 75.22; H, 8.29.

25,27-bis(2-ethylbutyloxy)calix[4]arene-crown-6, Cone 2c

Pale yellow oil (10%). ^{1}H NMR ($CDCl_3$) δ 7.14 (d, $J = 7.30$ Hz, 4H, Ar-*H meta*), 6.95 (t, $J = 7.30$ Hz, 2H, Ar-*H para*), 6.18 (t, $J = 7.50$ Hz, 2H, Ar-*H para*), 6.00 (d, $J = 7.50$ Hz, 4H, Ar-*H meta*), 4.40 (d, $J = 13.60$ Hz, 4H, ArCH_2Ar), 4.25 (t, $J = 7.40$ Hz, 4H, OCH_2), 3.96 (t, $J = 7.40$ Hz, 4H, OCH_2), 3.70 (m, 12H, OCH_2), 3.59 (d, $J = 5.30$ Hz, 4H, OCH_2), 3.18 (d, $J = 13.60$ Hz, 4H, ArCH_2Ar), 1.78–1.26 (m, 10H, C*H* and CH_2), 0.99 (t, $J = 7.30$ Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.1 (Ar *ipso*), 155.2 (Ar *ipso*), 136.8 (Ar *ortho*), 132.8 (Ar *ortho*), 129.2 (Ar *meta*), 127.3 (Ar *meta*), 122.2 (Ar *para*), 122.0 (Ar *para*), 77.6, 72.2, 71.1, 71.0, 70.7, 69.5 (OC H_2), 42.1 (C H), 30.8 (ArC H_2Ar), 23.4 (C H_2), 11.1 (C H_3). Anal. Calcd for $C_{50}H_{66}O_8$: C, 75.53; H, 8.37. Found: C, 75.64; H, 8.27.

25-(3,7-dimethyloctyloxy)-27-hydroxycalix[4]arene-crown-6, Cone 7a

Pale yellow oil (30%). IR (KBr) ν 3445 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$) δ 7.13 (d, $J = 7.40$ Hz, 2H, Ar-*H meta*), 7.04 (d, $J = 7.40$ Hz, 2H, Ar-*H meta*), 6.93 (t, $J = 7.40$ Hz, 1H, Ar-*H para*), 6.69 (t, $J = 7.40$ Hz, 1H, Ar-*H para*), 6.46 (m, 6H, Ar-*H meta* and Ar-*H para*), 5.40 (s, 1H, O*H*), 4.66 (d, $J = 13.70$ Hz, 2H, ArCH_2Ar), 4.43 (d, $J = 12.85$ Hz, 2H, ArCH_2Ar), 4.11 (m, 6H, OCH_2), 3.85 (m, 10H, OCH_2), 3.68 (m, 4H, OCH_2), 3.51 (m, 2H, OCH_2), 3.24 (d, $J = 13.70$ Hz, 2H, ArCH_2Ar), 3.22 (d, $J = 12.85$ Hz, 2H, ArCH_2Ar), 2.08 (m, 1H, C*H*), 1.62–1.16 (m, 9H, C*H* and CH_2), 1.07 (d, $J = 6.55$ Hz, 3H, CH_3), 0.81 (d, $J = 6.50$ Hz, 3H, CH_3), 0.80 (d, $J = 6.50$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.4 (Ar *ipso*), 153.8 (Ar *ipso*), 153.2 (Ar *ipso*), 136.6 (Ar *ortho*), 133.0 (Ar *ortho*), 129.7 (Ar *ortho*), 128.8 (Ar *meta*), 128.1 (Ar *meta*), 127.9 (Ar *meta*), 123.1 (Ar *para*), 122.6 (Ar *para*), 118.3 (Ar *para*), 75.0, 73.0, 72.6, 71.5, 70.2 (OC H_2), 39.1 (C H_2), 37.3 (C H_2), 36.1 (C H), 30.7, 30.6 (ArC H_2Ar), 30.2 (C H_2), 27.8 (C H_2), 24.8 (C H), 22.6 (C H_3), 22.4 (C H_3), 20.0 (C H_3). Anal. Calcd for $C_{48}H_{62}O_8$: C, 75.16; H, 8.15. Found: C, 75.33; H, 8.19.

25-(3-methylbutyloxy)-27-hydroxycalix[4]arene-crown-6, Cone 7b

White crystals (24%), mp 176°C. IR (KBr) ν 3540 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$) δ 7.14 (d, $J = 7.30$ Hz, 2H, Ar-*H meta*), 7.04 (d, $J = 7.30$ Hz, 2H, Ar-*H meta*), 6.94 (t, $J = 7.30$ Hz, 1H, Ar-*H para*), 6.69 (t, $J = 7.30$ Hz, 1H, Ar-*H para*), 6.44 (m, 6H, Ar-*H meta* and Ar-*H para*), 5.36 (s, 1H, O*H*), 4.67 (d, $J = 13.70$ Hz, 2H, ArCH_2Ar), 4.42 (d, $J = 12.90$ Hz, 2H, ArCH_2Ar), 4.05 (m, 6H, OCH_2), 3.84 (m, 10H, OCH_2), 3.68 (m, 4H, OCH_2), 3.43 (m, 2H, OCH_2), 3.23 (d, $J = 13.70$ Hz, 2H, ArCH_2Ar), 3.21 (d, $J = 12.90$ Hz, 2H, ArCH_2Ar), 2.15 (m, 2H, CH_2), 1.75 (m, 1H, C*H*), 1.07 (d, $J = 6.65$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.5 (Ar *ipso*), 154.7 (Ar *ipso*), 154.2 (Ar *ipso*), 137.6 (Ar *ortho*), 133.9 (Ar *ortho*), 130.6 (Ar *ortho*), 129.7 (Ar *meta*), 129.0 (Ar *meta*), 128.6 (Ar *meta*), 124.0 (Ar *para*), 123.5 (Ar *para*), 119.1 (Ar *para*), 76.0, 74.4, 73.5, 72.5, 71.2, 71.0 (OC H_2), 38.2 (C H_2), 31.5, 31.0 (ArC H_2Ar), 26.7 (C H), 24.0 (C H_3). Anal. Calcd for $C_{43}H_{52}O_8$: C, 74.11; H, 7.52. Found: C, 74.28; H, 7.71.

25-(2-ethylbutyloxy)-27-hydroxycalix[4]arene-crown-6, Cone 7c

White crystals (33%), mp 137°C. IR (KBr) ν 3450 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$) δ 6.79 (d, $J = 7.30$ Hz, 2H, Ar-*H meta*), 6.72 (d, $J = 7.30$ Hz, 2H, Ar-*H meta*), 6.62 (m, 7H, Ar-*H meta* and Ar-*H para*), 6.55 (t, $J = 7.30$ Hz, 1H, Ar-*H para*), 6.20 (s, 1H, O*H*), 4.58 (d, $J = 13.45$ Hz, 2H, ArCH_2Ar), 4.48 (d, $J = 13.10$ Hz, 2H, ArCH_2Ar), 4.23 (m, 2H, OCH_2), 3.98 (m, 6H, OCH_2), 3.78 (m, 12H, OCH_2), 3.57 (m, 2H, OCH_2), 3.25 (d, $J = 13.45$ Hz, 2H, ArCH_2Ar), 3.20 (d, $J = 13.10$ Hz, 2H, ArCH_2Ar), 1.95 (m, 1H, C*H*), 1.57 (m, 4H, CH_2), 0.97 (t, $J = 7.35$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.4 (Ar *ipso*), 154.8 (Ar *ipso*), 152.4 (Ar *ipso*), 135.0 (Ar *ortho*), 134.4 (Ar *ortho*), 134.2 (Ar *ortho*), 129.4 (Ar *meta*), 128.5 (Ar *meta*), 128.0 (Ar *meta*), 123.3 (Ar *para*), 122.1 (Ar *para*), 118.8 (Ar *para*), 77.9, 74.5, 71.9, 71.3, 70.4, 69.9 (OC H_2), 41.5 (C H), 30.8, 30.6 (ArC H_2Ar), 23.2 (C H_2), 11.0 (C H_3). Anal. Calcd for $C_{44}H_{54}O_8$: C, 74.34; H, 7.65. Found: C, 74.54; H, 7.76.

Synthesis of 25,27-bis(alkyloxy)calix[4]arene-crown-6, Partial-cone 3a–c (general Procedure)

A solution of calix[4]arene-crown-6 **6** (2 g, 3.2 mmol), Cs_2CO_3 (4.11 g, 12.6 mmol) and alkyl 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, ethyl acetate/petroleum ether = 1/3) to afford **3a–c**.

25,27-bis(3,7-dimethyloctyloxy)calix[4]arene-crown-6, Partial-cone 3a

Colorless oil (29%). ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 7.45 Hz, 2H, Ar-*H meta*), 7.07 (t, J = 7.45 Hz, 1H, Ar-*H meta*), 6.95 (m, 3H, Ar-*H meta* and *para*), 6.69 (m, 6H, Ar-*H meta* and *para*), 4.26 (d, J = 12.85 Hz, 2H, ArCH_2Ar), 3.98 (m, 2H, OCH_2), 3.78 (m, 24H, OCH_2 and ArCH_2Ar), 3.15 (d, J = 12.85 Hz, 2H, ArCH_2Ar), 2.93 (t, J = 6.60 Hz, 2H, OCH_2), 1.65–0.96 (m, 20H, CH and CH_2), 0.87 (m, 15H, CH_3), 0.69 (d, J = 6.40 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.4 (Ar *ipso*), 156.6 (Ar *ipso*), 155.5 (Ar *ipso*), 136.2 (Ar *ortho*), 135.3 (Ar *ortho*), 134.0 (Ar *ortho*), 133.7 (Ar *meta*), 131.3 (Ar *meta*), 129.9 (Ar *meta*), 129.0 (Ar *para*), 123.0 (Ar *para*), 122.7 (Ar *para*), 73.1, 72.2, 71.8, 71.0, 70.8, 70.7 (OCH$_2$), 39.9 (CH$_2$), 38.1 (CH), 37.9 (CH$_2$), 37.0 (CH), 31.4 (CH$_2$), 30.4, 30.1 (ArCH$_2$Ar), 28.5 (CH$_2$), 25.2 (CH$_2$), 25.1 (CH), 23.3 (CH$_3$), 23.2 (CH$_3$), 20.4 (CH$_3$). Anal. Calcd for $C_{58}H_{82}O_8$: C, 76.78; H, 9.11. Found: C, 76.85; H, 9.19.

25,27-bis(3-methylbutyloxy)calix[4]arene-crown-6, Partial-cone 3b

White crystals (31%), mp 165°C. ^{1}H NMR ($CDCl_3$) δ 7.44 (d, J = 7.45 Hz, 2H, Ar-*H meta*), 7.07 (t, J = 7.45 Hz, 1H, Ar-*H*para), 6.93 (m, 4H, Ar-*H meta* and *para*), 6.72 (t, J = 7.45 Hz, 1H, Ar-*H para*), 6.63 (m, 4H, Ar-*H meta* and *para*), 4.24 (d, J = 12.95 Hz, 2H, ArCH_2Ar), 3.95 (m, 2H, OCH_2), 3.76 (m, 24H, OCH_2 and ArCH_2Ar), 3.13 (d, J = 12.95 Hz, 2H, ArCH_2Ar), 3.05 (t, J = 6.80 Hz, 2H, OCH_2), 1.50 (m, 4H, CH and CH_2), 1.16 (q, J = 6.80 Hz, 2H, CH_2), 0.85 (d, J = 6.10 Hz, 6H, CH_3), 0.74 (d, J = 6.50 Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.6 (Ar *ipso*), 156.8 (Ar *ipso*), 155.8 (Ar *ipso*), 135.3 (Ar *ortho*), 133.7 (Ar *ortho*), 131.6 (Ar *ortho*), 130.0 (Ar *meta*), 129.2 (Ar *meta*), 129.1 (Ar *meta*), 123.0 (Ar *para*), 122.8 (Ar *para*), 122.7 (Ar *para*), 73.3, 72.5, 72.0, 71.2, 71.1 (OCH$_2$), 40.0 (CH$_2$), 38.5 (CH$_2$), 37.4 (CH), 31.6 (ArCH$_2$Ar), 25.7 (CH), 23.8 (CH$_3$), 23.5 (CH$_3$). Anal. Calcd for $C_{48}H_{62}O_8$: C, 75.16; H, 8.15. Found: C, 75.29; H, 8.33.

25,27-bis(2-ethylbutyloxy)calix[4]arene-crown-6, Partial-cone 3c

Colorless oil (28%). ^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 7.45 Hz, 2H, Ar-*H meta*), 7.01 (d, J = 7.45 Hz, 2H, Ar-*H meta*), 6.95 (m, 3H, Ar-*H para*), 6.80 (d, J = 7.45 Hz, 2H, Ar-*H meta*), 6.77 (d, J = 7.45 Hz, 2H, Ar-*H meta*), 6.58 (t, J = 7.45 Hz, 1H, Ar-*H para*), 4.37 (d, J = 12.50 Hz, 2H, ArCH_2Ar), 3.86–3.69 (m, 22H, OCH_2 and ArCH_2Ar), 3.64 (d, J = 6.00 Hz, 2H, OCH_2), 3.25 (d, J = 12.50 Hz, 2H, ArCH_2Ar), 3.24 (m, 2H, OCH_2), 2.73 (d, J = 6.00 Hz, 2H, OCH_2), 1.68–1.22 (m, 6H, CH and CH_2), 0.83 (t, J = 7.40 Hz, 6H, CH_3), 0.67 (m, 4H, CH_2), 0.43 (t, J = 7.40 Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.2 (Ar *ipso*), 156.9 (Ar *ipso*), 155.8 (Ar *ipso*), 136.7 (Ar *ortho*), 134.1 (Ar *ortho*), 133.9 (Ar *ortho*), 130.7 (Ar *meta*), 129.9 (Ar *meta*), 129.1 (Ar *meta*), 128.7 (Ar *para*), 123.3 (Ar *para*), 122.8 (Ar *para*), 79.0, 73.9, 72.5, 71.8, 71.5, 70.9, 70.0 (OCH$_2$), 41.9 (CH), 41.8 (CH), 38.3 (CH$_2$), 30.9 (ArCH$_2$Ar), 23.7 (CH$_2$), 22.7 (CH$_2$), 11.6 (CH$_3$), 11.5 (CH$_3$). Anal. Calcd for $C_{50}H_{66}O_8$: C, 75.53; H, 8.37. Found: C, 75.78; H, 8.39.

General Procedure for the Synthesis of 25-(3,7-Dimethyloctyloxy)-27-(3-methylbutyloxy)calix[4]-arene-crown-6, *Anti*-partial-cone 8, 25-(3,7-dimethyloctyloxy)-27-(3-methylbutyloxy)calix[4]-arene-crown-6, Cone 9 And 25-(3,7-dimethyloctyloxy)-27-(3-methylbutyloxy)calix[4]arene-crown-6, *Syn*-partial-cone 10

A solution of 25-(3-methylbutyloxy)-27-hydroxycalix[4]arene-crown-6, cone **7b** or 25-(3,7-dimethyloctyloxy)-27-hydroxycalix[4]arene-crown-6, cone **7a** (0.8 mmol), Cs_2CO_3 (2.4 mmol) and 3,7-dimethyloctyl bromide or 3-methylbutyl bromide (0.9 mmol) was refluxed in CH_3CN (80 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, ethyl acetate/petroleum ether = 1/3) to afford **8** and **9** starting from **7b**, and **9** and **10** starting from **7a**.

25-(3,7-Dimethyloctyloxy)-27-(3-methylbutyloxy)calix[4]arene-crown-6,* Anti-*partial-cone 8

Colorless oil (34%). ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 7.45 Hz, 2H, Ar-*H meta*), 7.07 (t, J = 7.45 Hz, 1H, Ar-*H para*), 6.91 (m, 4H, Ar-*H meta* and *para*), 6.72 (t, J = 7.45 Hz, 1H, Ar-*H para*), 6.64 (m, 4H, Ar-*H meta* and *para*), 4.24 (d, J = 12.80 Hz, 2H, ArCH_2Ar), 3.98 (m, 2H, OCH_2), 3.78 (m, 24H, OCH_2 and ArCH_2Ar), 3.12 (d, J = 12.80 Hz, 2H, ArCH_2Ar), 3.01 (t, J =

6.65 Hz, 2H, OCH_2), 1.51 (m, 5H, CH and CH_2), 1.13 (m, 8H, CH and CH_2), 0.86 (m, 12H, CH_3), 0.70 (d, $J = 6.40$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.8 (Ar *ipso*), 156.1 (Ar *ipso*), 155.1 (Ar *ipso*), 135.8 (Ar *ortho*), 134.6 (Ar *ortho*), 133.4 (Ar *ortho*), 133.1 (Ar *meta*), 130.9 (Ar *meta*), 129.4 (Ar *meta*), 128.5 (Ar *para*), 122.4 (Ar *para*), 122.1 (Ar *para*), 72.6, 71.8, 71.3, 70.5, 70.4 (OCH$_2$), 39.3 (CH$_2$), 37.8 (CH$_2$), 37.4 (CH$_2$), 36.7 (CH$_2$), 30.9 (ArCH$_2$Ar), 29.7 (CH), 29.5 (CH), 28.0 (CH), 23.1 (CH$_2$), 22.8 (CH$_3$), 22.7 (CH$_3$), 22.6 (CH$_3$), 19.8 (CH$_3$). Anal. Calcd for $C_{53}H_{72}O_8$: C, 76.04; H 8.67. Found: C, 76.24; H 8.79.

25-(3,7-Dimethyloctyloxy)-27-(3-methylbutyloxy)calix[4]arene-crown-6, Cone 9

Colorless oil (47% from **7b** and 34% from **7a**). ^{1}H NMR ($CDCl_3$) δ 7.06 (d, $J = 7.35$ Hz, 4H, Ar-*H meta*), 6.87 (t, $J = 7.35$ Hz, 2H, Ar-*H para*), 6.12 (t, $J = 7.40$ Hz, 2H, Ar-*H para*), 5.98 (d, $J = 7.40$ Hz, 4H, Ar-*H meta*), 4.32 (d, $J = 13.45$ Hz, 4H, ArCH$_2$Ar), 4.18 (t, $J = 7.20$ Hz, 4H, OCH_2), 3.95 (t, $J = 7.20$ Hz, 4H, OCH_2), 3.66 (m, 16H, OCH_2), 3.10 (d, $J = 13.45$ Hz, 4H, ArCH_2Ar), 1.78-1.50 (m, 7H, CH and CH_2), 1.27–1.07 (m, 6H, CH and CH_2), 0.91 (d, $J = 6.35$ Hz, 6H, CH_3), 0.87 (d, $J = 6.80$ Hz, 3H, CH_3), 0.84 (d, $J = 6.50$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.2 (Ar *ipso*), 155.0 (Ar *ipso*), 136.8 (Ar *ortho*), 132.9 (Ar *ortho*), 129.0 (Ar *meta*), 127.3 (Ar *meta*), 122.1 (Ar *para*), 73.9, 72.4, 71.0, 70.8, 70.7, 69.7 (OCH$_2$), 39.1 (CH$_2$), 39.0 (CH$_2$), 37.3 (CH$_2$), 30.9 (ArCH$_2$Ar), 30.0 (CH), 27.9 (CH$_2$), 25.2 (CH$_2$),25.0 (CH), 24.3 (CH), 22.8 (CH$_3$), 22.7 (CH$_3$), 19.3 (CH$_3$). Anal. Calcd for $C_{53}H_{72}O_8$: C, 76.04; H 8.67. Found: C, 76.16; H 8.81.

25-(3,7-Dimethyloctyloxy)-27-(3-methylbutyloxy)calix[4]arene-crown-6, **Syn-***partial-cone 10*

Pale yellow oil (23%). ^{1}H NMR ($CDCl_3$) δ 7.36 (d, $J = 7.45$ Hz, 2H, Ar-*H meta*), 6.99 (t, $J = 7.45$ Hz, 1H, Ar-*H para*), 6.90 (m, 4H, Ar-*H meta* and *para*), 6.58 (m, 5H, Ar-*H meta* and *para*), 4.19 (d, $J = 12.85$ Hz, 2H, ArCH$_2$Ar), 3.89 (m, 2H, OCH_2), 3.79–3.51 (m, 24H, OCH_2 and ArCH$_2$Ar), 3.07 (d, $J = 12.85$ Hz, 2H, ArCH_2Ar), 2.89 (t, $J = 6.75$ Hz, 2H, OCH_2), 1.61–0.91 (m, 13H, CH and CH_2), 0.83 (d, $J = 6.70$ Hz, 8H, CH_3), 0.79 (d, $J = 6.40$ Hz, 6H, CH_3), 0.66 (d, $J = 6.55$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.9 (Ar *ipso*), 156.1 (Ar *ipso*), 154.9 (Ar *ipso*), 135.6 (Ar *ortho*), 134.7 (Ar *ortho*), 133.3 (Ar *ortho*), 133.1 (Ar *meta*), 130.8 (Ar *meta*), 129.3 (Ar *meta*), 128.4 (Ar *para*), 122.4 (Ar *para*), 122.1 (Ar *para*), 72.6, 71.6, 71.2, 70.8, 70.3 (OCH$_2$), 39.3 (CH$_2$), 39.2 (CH$_2$), 37.6 (CH$_2$), 36.7 (CH$_2$), 36.4 (CH), 30.9 (ArCH$_2$Ar), 29.8 (CH), 27.8 (CH), 24.8 (CH$_2$), 24.6 (CH$_3$), 22.8 (CH$_3$), 19.8 (CH$_3$). Anal. Calcd for $C_{53}H_{72}O_8$: C, 76.04; H, 8.67. Found: C, 76.21; H, 8.82.

X-ray Data

The structure of compounds **2b** and **3b** has been established by X-ray crystallography (Fig. 2). Colorless single crystals of **2b** and **3b** were obtained by slow evaporation from methanol/chloroform (80/20) solution. 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$K\alpha$ radiation and a graphite monochromator up to $\theta = 55°$. No intensity variation of 2 standard reflections monitored every 90 min was observed. The data were corrected for Lorentz and polarization effects and absorption effects were treated empirically [41]. The crystals data are listed in Table I. The structure was solved by direct methods Shelx 86 [42] and refined using Shelx 93 [43] suite of programs. Crystallographic data for the structures **2b** and **3b** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-169349 and CCDC-169350[‡].

Picrate Extraction Measurements

Picrate extraction experiments (Table II) were performed following Pedersen's procedure [8,30–34]: 5 ml of a 2.5×10^{-4} M aqueous picrate solution and 5 ml of a 2.5×10^{-4} M solution of calixarene in CH_2Cl_2 were vigorously agitated in a stoppered glass tube with a mechanical shaker for 2 min, then magnetically stirred in a thermostated water-bath at 20 ± 0.1°C for 30 min, and finally left standing for an additional 30 min. The concentration of picrate ion remaining in the aqueous phase was then determined spectrophotometrically as previously described (maximum absorption A of the picrate ion at 355 nm, $\varepsilon = 14285\ \text{mol}^{-1}\,\text{l}\,\text{cm}^{-1}$). The percentage extraction (Ex%) was calculated from the absorbance A of the aqueous phase measured at 355 nm using the following expression: $\text{Ex}\% = 100(A_0 - A)/A_0$, A_0 being the absorbance of the aqueous phase of a blank experiment carried out without calixarene.

The cesium picrate was prepared as described elsewhere [8,31] by stepwise addition of a 2.0×10^{-2} M aqueous picric acid solution to a 0.14 M aqueous solution of cesium hydroxide, until neutralization which was checked by pH control with a glass electrode. They were then rapidly washed with ethanol and diethyl ether before being dried *in vacuo* for 24 h.

[‡]Supplementary X-ray crystallographic data: Cambridge Crystallographic Data Centre, University Chemical Lab, 12 Union Road, Cambridge, CB2 1EZ, UK; E-mail: . E-mail: deposit@ccdc.cam.ac.uk

Complexation Constant Measurements

The complexation constants β of the metal–ligand complexes were determined in CH_3OH by a UV absorption method in the wavelength range 250–350 nm, in which β is the constant ratio $([ML^+]/[M^+][L])$ corresponding to the equilibrium $M^+ + L \leftrightarrow ML^+$ (M^+ is Cs^+ and L is the ligand). The absorption changes in the UV spectra of the ligands were recorded as cesium ions (CsCl) were progressively added ($0 \leq$ ratio ≤ 4) to the medium (CH_3OH) containing a fixed amount of receptor (2.1×10^{-4} M). We have assumed a 1/1 stoichiometry and obtained the calculation of β complexation constants (Table III), according to the Valeur method [36].

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