DOUBLY BRIDGED CALIX[8]CROWNS

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Received December 15, 2003
Accepted May 6, 2004

Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday.

Biscrowned calix[8]arenes were obtained by alkylation of *p-tert*-butylcalix[8]arene or calix[8]monocrowns with triethylene glycol ditosylate, in the presence of various bases. Of the 22 possible isomers, 1,4:2,5-, 1,3:2,5-, 1,4:2,3-, 1,4:5,8-, and 1,2:3,4-calix[8]biscrown-4 (**3**–**7**) were isolated in 7–30% yields. The presence of two crown bridges in 1,3:2,5- and 1,4:2,5-biscrown-4 (**4**, **5**) leads to a significant rigidness of the calix[8]arene macrocycle and implies inherent chirality. The increased preorganization of calix[8]biscrowns, with respect to monocrowns, leads to significant complexing abilities for alkali cations with a marked preference for Cs^+ over Na^+.

Keywords: Calixarenes; Calix[8]arenes; Conformation analysis; Complexation; Crown ethers; Host–guest chemistry; Inherent chirality; Intramolecular bridging.

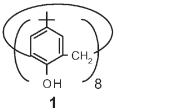
Calixcrowns[1], a class of hybrid compounds derived from combination of the calixarene[2] skeleton with crown-ether[3] chains, have attracted increasing research interests because of their remarkably selective complexing abilities[4]. Majority of work has been focused on the calix[4]arene framework, both singly and doubly bridged with crown chains of various length[4,5], while a more limited number of calix[5]crowns[6], calix[6]crowns[7], and calix[8]crowns[8–10] have been prepared. With respect to the last mentioned, we observed in our previous work[11] that introduction of a single polyether chain does not significantly affect the intrinsic mobility of the calix[8]arene macrocycle. The main effect is reduction of the available space for the passage through the calixarene hole. Since introduction of two or more bridges was expected to lead to more preorganized calix[8]crown derivatives, possibly able to host suitable guests, we were induced to examine the possibility

of double bridging of the parent macrocycle. In preliminary communications[10,12] we have reported several examples of doubly bridged calix[8]arene (calix[8]biscrowns) and now, following our previous paper on singly bridged derivatives[11], we give here full experimental data on synthesis and characterization of these compounds.

RESULTS AND DISCUSSION

Synthesis

The introduction of two crown-ether bridges in desired positions of the calix[8]arene skeleton is undoubtedly a hard task to perform, since in principle 22 calix[8]biscrown regioisomers (see below) can form with each specific bridging element. However, considering the quite surprising results in terms of yields and selectivity, obtained in the synthesis of calix[8]monocrowns by direct alkylation of the parent *p-tert*-butylcalix[8]arene (**1**)[11], we were induced to examine a similar route for the preparation of calix[8]biscrowns. Indeed, by forcing the conditions under which the monocrowns had been obtained, it was possible to prepare biscrowns in workable amounts.



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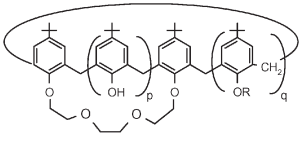

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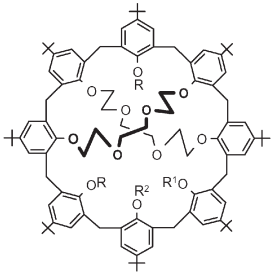
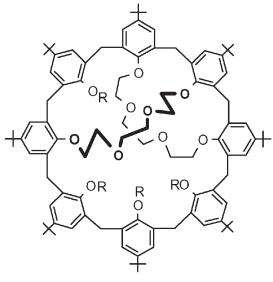
2b p = 1 q = 5
2c p = 2 q = 4
2d p = 3 q = 3



3 R = R¹ = R² = H
3a R = R¹ = R² = Me
3b R = R¹ = H R² = Me
3c R = R² = H R¹ = Me



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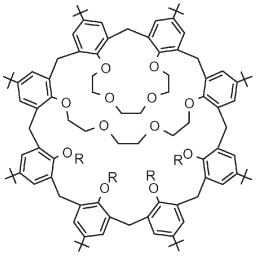

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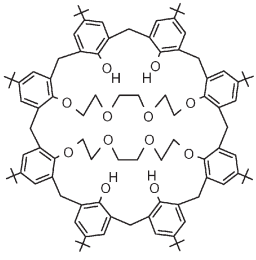

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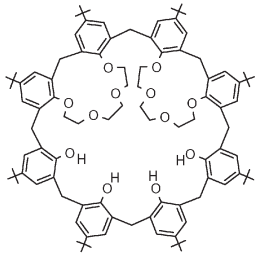

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Thus, alkylation of *p-tert*-butylcalix[8]arene (**1**) with 3 equivalents of triethylene glycol ditosylate in the presence of Cs_2CO_3 (8 equivalents) in refluxing acetone afforded, besides small amounts (14–15% total yield) of known calix[8]monocrown derivatives (1,2- (**2a**), 1,4- (**2c**), and 1,5-isomer (**2d**))[11], three new compounds (Table I, entry 1). These last were isolated by column chromatography and identified as 1,4:2,5-calix[8]biscrown-4 **3** (13%), 1,3:2,5-calix[8]biscrown-4 **4** (25%), and 1,4:2,3-calix[8]biscrown-4 **5** (2%)[12].

A similar alkylation of **1** in the presence of 8 equivalents of NaH in refluxing THF/DMF (10:1) followed by chromatographic separation led to 1,4:2,3-biscrown-4 **5** (12%) and 1,4:2,5-biscrown-4 **3** (1%), besides a significant amount (13%) of the known 1,4-monocrown **2c** (Table I, entry 2)[11,12]. From these results it is evident that direct double-crowning of **1** proceeds with fair regioselectivity mainly governed by the nature of the base.

Alkylation of preformed and well characterized monocrown derivatives is an obvious alternative for the synthesis of calix[8]biscrowns. This route may lead to compounds with different bridging patterns not easily attained by direct alkylation or it may serve as access to biscrowns with two different chains. In addition, as will be shown in the next section, it also represents an indispensable tool in structure assignment. Thus, the easily available 1,4-crown-4 **2c** [11] was reacted with 1 equivalent of triethylene glycol ditosylate in the presence of Cs_2CO_3 (8 equivalents) in refluxing acetone (Table I, entry 3). Column chromatography of the crude mixture gave 1,4:2,5-biscrown-4 **3**, 1,3:2,5-biscrown-4 **4**, and 1,4:2,3-biscrown-4 **5** with

TABLE I
Yield of calix[8]biscrown-4 in the alkylation of given substrates with $TsO(CH_2CH_2O)_3Ts$ in the presence of various bases (8 equivalents) under reflux

Entry	Substrate	Equiv. of alk. agent	Base	Solvent	Time h	Compound (%)
1	**1**	3	Cs_2CO_3	Me_2CO	25	**2a**,**2c**,**2d** (14–15), **3** (13), **4** (25), **5** (2)
2	**1**	3	NaH	THF/DMF (10:1)	67	**2c** (13), **3** (1), **5** (12)
3	**2c**	1	Cs_2CO_3	Me_2CO	5	**3** (30), **4** (18), **5** (12)
4	**2c**	1	KH	THF/DMF (10:1)	24	**6** (7)
5	**2b**	1	Cs_2CO_3	Me_2CO	6	**4** (7)
6	**2a**	1	K_2CO_3[a]	Me_2CO	53	**5** (3), **7** (7)

[a] 12 equivalents of base were used.

improved yields (30, 18, and 12%, respectively)[12]. KH-promoted alkylation of the same starting compound in THF/DMF under otherwise identical conditions led to the previously unreported, highly symmetrical 1,4:5,8-calix[8]biscrown-4 **6** (7%) (Table I, entry 4)[12].

Analogous reaction performed on 1,3-crown-4 **2b**[11] using Cs_2CO_3 as the base afforded 1,3:2,5-biscrown-4 **4** (7%) (Table I, entry 5), while K_2CO_3-promoted alkylation of 1,2-crown-4 **2a** gave an additional new compound, 1,2:3,4-calix[8]biscrown-4 **7** (7%), besides the known 1,4:2,3-biscrown **5** (3%) (Table I, entry 6)[12].

Structure Assignment

The presence of two bridges in compounds **3**–**7** was proved by FAB(+) MS measurements, which often contained an intense $(M + Na)^+$ ion peak, while satisfactory elementary analyses were usually obtained. Concerning the assignment of the bridging pattern, as anticipated in previous section, it requires discrimination among a total of 22 possible biscrown regioisomers (Fig. 1). This was based on the following data: (i) the number of NMR sig-

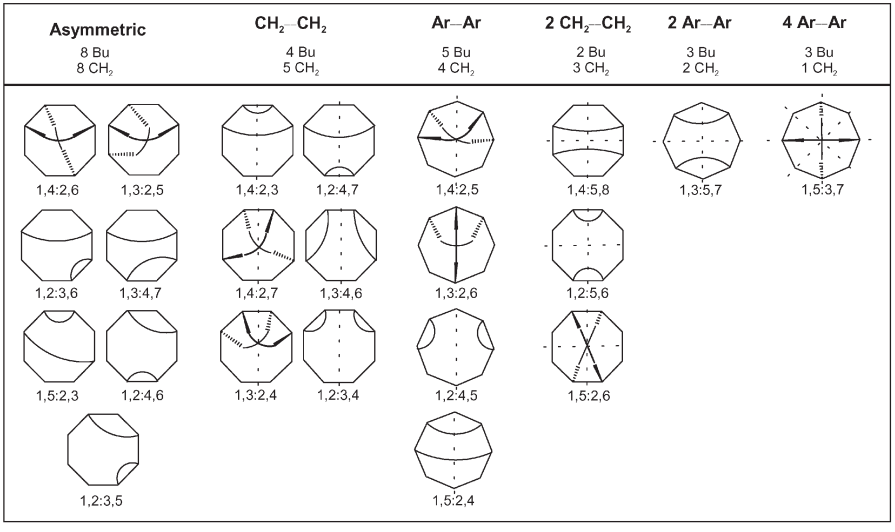

FIG. 1

Schematic representation of 22 possible calix[8]biscrown regioisomers grouped according to the number and type of symmetry elements. For each group, the number of expected NMR resonances for *t*-Bu and $ArCH_2Ar$ groups is reported. Symmetry elements bisecting two opposite aromatic rings (Ar–Ar symmetry) or two opposite $ArCH_2Ar$ groups (CH_2–CH_2 symmetry) are indicated

nals and their integrals; (ii) 2D NMR spectra; (iii) the number of free versus hydrogen-bonded OH groups[13,14]; (iv) independent synthesis of the doubly bridged compounds from a well characterized singly bridged calix[8]arene.

Conformational Features

In a previous work we observed that calix[8]monocrowns are conformationally mobile and that the main effect of the presence of a single transannular chain is the reduction of available space for the ring inversion process, which may occur by either the oxygen or the *tert*-butyl through the annulus pathway[11]. This effect is strongly dependent on the bridging positions of the crown chain. On these premises, it was expected that introduction of two polyether bridges should cause a stronger reduction in the conformational freedom of the calix[8]arene macrocycle. In addition, it could be argued that the bridging positions of the two chains should have an even more relevant effect on it.

In accordance with these arguments, the 1D ^{1}H and 2D COSY NMR spectra of 1,4:2,5-biscrown-4 **3** show one AB and three AX systems for the $ArCH_2Ar$ groups (Fig. 2), indicating a somewhat rigid structure. Obviously, this rigidness is a result of the steric requirement of the two crossing polyether chains which, in principle, could only interchange via their pas-

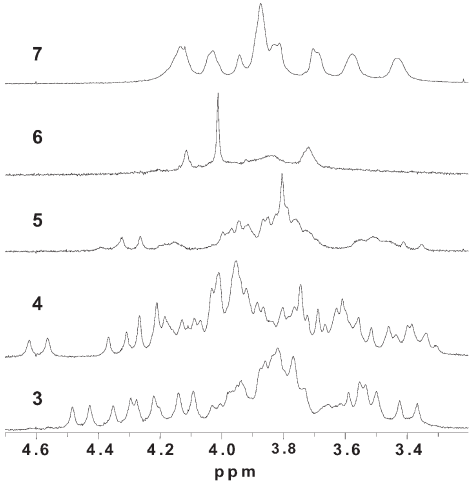

FIG. 2
Comparison of the methylene region of ^{1}H NMR spectra ($CDCl_3$, 295 K) of calix[8]biscrown-4 derivatives **3**–**7**

sage over the *t*-Bu groups. However, computer molecular modeling indicated the impracticability of this route, suggesting that the topology of the two crown bridges in **3** is permanently blocked[15]. Indeed, this conclusion found an experimental confirmation in the VT ^{1}H NMR spectra of **3** in DMSO-d_6, which showed no hint of coalescence up to 385 K for AB and AX systems of $ArCH_2Ar$ groups.

On the other hand, by analogy to smaller calixarene homologues[16], the residual OH groups of **3** are still freely swinging through the macrocycle as indicated by the presence of a single C_2-symmetry axis bisecting opposite aromatic rings. In fact, their blockage would lead to an asymmetric compound. These considerations can also be extended to the corresponding tetramethoxy derivative **3a**, obtained in 60% yield from **3** using a large excess of MeI in the presence of NaH in THF/DMF[17]. The presence of three methoxy and five *tert*-butyl signals in the ^{1}H NMR spectrum of **3a** proves that a C_2-symmetry axis is still present. Hence, the passage of the OMe groups through the annulus is fast on the NMR time scale.

Interestingly, a different situation is observed for 1,4:5,8-biscrown-4 **6**, which is conformationally mobile as demonstrated by the presence of broad resonances for $ArCH_2Ar$ groups in its room temperature ^{1}H NMR spectrum (Fig. 2), which became three clear singlets (δ 4.14, 3.99 and 3.96, 1:2:1) at 330 K. This suggests that the two polyether chains must intercross to inhibit the flipping motion of aromatic rings and proves the relevant role of the bridging positions.

Accordingly, 1,3:2,5-biscrown-4 **4**, possessing two crossing chains, is conformationally blocked, as is proved by the presence of several AX systems in the crowded methylene region of its ^{1}H NMR spectrum (Fig. 2). On the other hand, 1,2:3,4-biscrown-4 **7**, lacking intercrossing chains, is conformationally mobile, as indicated by broad signals in the methylene region (Fig. 2).

A borderline situation is observed for 1,4:2,3-biscrown-4 **5**, which should be conformationally mobile since the two chains do not cross. However, its ^{1}H NMR spectrum clearly shows AX systems for $ArCH_2Ar$ groups, indicating conformational blockage (Fig. 2). This apparent contradiction can be explained considering that the 1,4-bridge, as demonstrated previously[11], inhibits the passage of *tert*-butyl groups through the annulus and, very likely, also the passage of the 2,3-chain is inhibited because of its bulkiness. Obviously, similar considerations can also apply to tetramethoxy derivative **5a**, whose ^{1}H NMR spectrum shows AX systems for $ArCH_2Ar$ groups.

Stereochemical Features

The presence of a sole C_2-symmetry axis in 1,4:2,5-biscrown-4 structure makes **3** inherently chiral[17]. As demonstrated in the previous section, the actual geometrical relationship of its crown bridges is permanent, thus making **3** not racemizable. In addition, it is worth noting that the residual mobility of OH-bearing rings has no influence in this respect since their motion cannot allow interconversion of enantiomers. First evidence of this inherent chirality was obtained by addition of excess Pirkle's reagent ((+)-(*S*)-1-(+)-(9-anthryl)-2,2,2-trifluoroethanol) to a $CDCl_3$ solution of **3** which, upon cooling to 4 °C for 72 h, caused doubling of *tert*-butyl and other resonances in the ^{1}H NMR spectrum[17]. A definitive proof was obtained by direct resolution of the racemate achieved by HPLC using Chiralpak AD or Chiralcel OD chiral stationary phases[17]. The latter gave inferior separation and resolution factors. Under optimized conditions, sufficient amounts of enantiomers of **3** were separated to allow the measurement of chiroptical properties. In particular, opposite specific optical rotations ($[\alpha]_D^{25}$ 30°) and specular quantitative CD spectra were obtained, indicating their enantiomeric nature.

Similarly, HPLC enantioresolution of tetramethoxy-1,4:2,5-biscrown-4 **3a** was achieved, however with inferior efficiency with respect to the parent

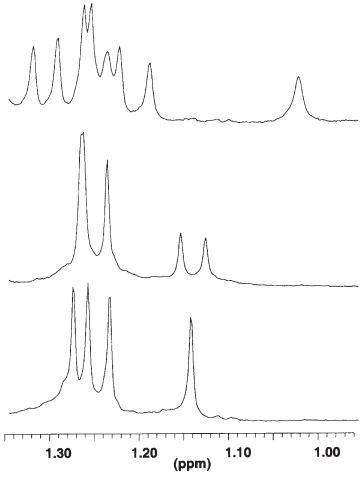

FIG. 3
tert-Butyl region of ^{1}H NMR spectra ($CDCl_3$, 295 K) of 1,4:2,3-calix[8]biscrown-4 **5** in the absence (bottom) and in the presence of 1 or 10 equivalents (middle and top, respectively) of (–)-(*S*)-α-methylbenzylamine

tetrahydroxy compound **3**. This suggested that hydrogen bonding among hydroxy groups of **3** and the stationary phase could play an important role in enantiodifferentiation[17]. In order to further clarify this aspect we prepared partially methylated derivatives of **3**, namely **3b** and **3c**. Their structure assignment and their HPLC enantiodifferentiation were previously reported[17].

An interesting stereochemical feature of 1,4:2,3-biscrown-4 **5** is a direct consequence of inhibited passage of the 2,3-chain through the annulus. In fact, this bridge must be situated above or below the mean plane containing the 1,4-crown, giving rise to two equivalents structures. Of course, this structure is achiral owing to the presence of a CH_2–CH_2 symmetry plane; however, splitting of ^{1}H NMR signals was observed upon addition of some chiral reagents ((*S*)-α-methylbenzylamine (Fig. 3), Pirkle's reagent, hydroquinidine, Eu(hfc)$_3$). This result is not surprising in the light of analogous splitting observed for symmetrical achiral calixarenes after addition of chiral reagents[18a,19], in the presence of which the enantiotropic groups in **5** became diastereotopic and anisochronous.

Complexation Tests

As demonstrated in a previous section, the presence of two polyether chains in calix[8]biscrowns causes a strong reduction in the conformational freedom of the calix[8]arene skeleton leading to somewhat rigid compounds when the bridges intercross each other. This suggests that calix[8]biscrowns could possess a more preorganized complexing site with respect to calix[8]monocrowns, which are inefficient ionophores because of their pronounced residual mobility[11]. This complexing potential was investigated for alkali cations by two-phase picrate extraction[20] and ^{1}H NMR experiments.

The result of alkali picrate extraction experiments (Table II) clearly indicates that the above considerations are correct. For example, 1,4:2,5-biscrown-4 **3** and 1,3:2,5-biscrown-4 **4** exhibited significant extraction ability toward alkali metal cations, thus confirming a good preorganization of the ionophoric cavity. This becomes more significant if compared to the undetectable complexing ability of the corresponding 1,4-calix[8]monocrown-4 (Table II). Improved efficiency was observed for methoxy derivatives **3a** and **4a** with respect to the parent hydroxy compounds, in accordance with a similar observation on calix[4]arene derivatives. In all instances a marked preference for Cs^+ was noted, whereas Na^+ was extracted with lower efficiency. This implies a good Cs^+/Na^+ selectivity factor in accordance with

TABLE II
Extraction percentage of alkali picrates by calix[8]biscrown-4 from water to dichloromethane at 20 °C

Ligands	Li^+	Na^+	K^+	Rb^+	Cs^+
3	≤1	≤1	1.7	3.8	6.8
3a	≤1	≤1	18.0	21.9	37.5
3b	≤1	≤1	2.0	5.8	7.0
3c	≤1	3.4	5.5	6.8	7.8
4	≤1	0.9	2.6	3.8	4.3
4a	1.2	1.4	4.8	5.6	7.8
5	≤1	≤1	≤1	≤1	5.8
5a	≤1	≤1	4.5	≤1	≤1
6	≤1	≤1	≤1	≤1	≤1
7	≤1	≤1	≤1	≤1	≤1
18-Crown-6[a]	<1	4.2	55.5	30.7	20.0
1,3-alternate-25,27-Dipropoxycalix[4]arene crown-6[b]	2.5	2.6	13.8	41.7	63.5

[a,b] Taken from ref. 21 and ref. 22, respectively.

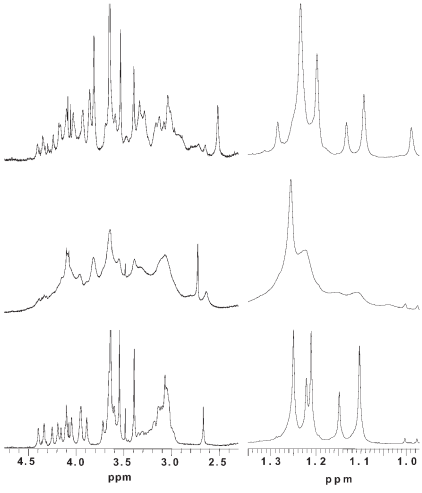

FIG. 4
Methylene and *tert*-butyl regions of ^1H NMR spectra ($CDCl_3$, 295 K) of free ligand **3a** (bottom) and 24 h after the addition of solid cesium picrate (middle). The corresponding regions of the ^1H NMR spectrum of $Cs^+ \subset$ **3a** complex at 275 K is also reported (top)

other calix[8]biscrown-3 derivatives[10b]. The Cs^+/Na^+ selectivity peak of the best-performing biscrown derivative **3a** appears to be higher than that of the classic 18-crown-6 (Table II), which is notorious for its high K^+/Na^+ preference[21]. However, the **3a** results are significantly less selective in comparison to 1,3-alternate calix[4]crown-6 (Table II)[22], which belongs to the most Cs^+/Na^+ selective ionophores currently known[23].

Complexation of cesium cation by **3a** and **4a** was also followed by ^1H NMR experiments. Addition of solid cesium picrate to a $CDCl_3$ solution of **3a** led to profound spectral changes in the *tert*-butyl region of its ^1H NMR spectrum (Fig. 4), while less pronounced shifts were observed for **4a**. In addition to chemical shift changes, the Cs^+–**3a** complex formation causes a broadening of NMR resonances due to the slowing down of a dynamic process. The process is blocked, on the NMR time scale, at temperatures below 280 K where a sharp spectrum containing six *tert*-butyl resonances is obtained indicating an asymmetric conformation. This phenomenon is probably attributable to hindrance of the swinging motion of methoxylated rings (see above), which could be also involved, in addition to the crown chains, in the complexation of the Cs^+ cation.

CONCLUSIONS

The intrinsic mobility of the calix[8]arene macrocycle requires the introduction of bridging scaffolding elements for the preparation of preorganized calix[8]arene hosts. Because previous work demonstrated that a single polyether chain is ineffective in this regard, introduction of two crown bridges was investigated as a more efficient shaping of the calix[8]arene skeleton. The results reported in this paper demonstrate that doubly crowned calix[8]arenes can be obtained by direct alkylation of *p-tert*-butylcalix[8]arene with triethylene glycol ditosylate in the presence of various bases. Alternatively, they can be synthesized by analogous alkylation of known calix[8]monocrown derivatives.

This last approach is also an indispensable tool in bridging-pattern assignment for the 22 possible isomers, since the preexistence of a bridge with known pattern strongly reduces the number of structures compatible with spectroscopic data.

From the conformational viewpoint, the introduction of two polyether chains can lead to inhibition of the flipping motion of aromatic rings through the calix[8]arene macrocycle, in particular when the two crowns cross each other or when they are close enough to mutually exert steric hindrance. As an additional consequence, the crossing of crown bridges

leads to inherent chirality in the case of 1,3:2,5- or 1,4:2,5-biscrown derivatives, in some cases confirmed by enantioselective HPLC resolution and chiroptical properties.

The increased rigidity of calix[8]biscrown derivatives leads to a better preorganization with respect to calix[8]monocrowns. Consequently, significant complexing abilities toward alkali cations are observed with a marked preference for Cs^+ over Na^+.

EXPERIMENTAL

General

Melting points were measured on a Mel Temp II Laboratory Devices and are uncorrected. ^1H and ^{13}C NMR spectra were acquired on a Bruker ARX 250 spectrometer (^1H at 250.13 MHz and ^{13}C at 62.9 MHz). Chemical shifts (δ) are expressed in ppm downfield from internal TMS, coupling constants (*J*) are given in Hz. FAB MS measurements were performed on a VG-ZAB 2-SE instrument, using 3-nitrobenzyl alcohol as matrix. Elemental analyses were obtained from the Department of Pharmaceutical Sciences, University of Catania. Column chromatography was carried out on SiO_2 (Kieselgel 60, 63–200 μm, Merck). All chemicals were reagent grade and were used without further purification. Anhydrous THF and DMF were purchased from Aldrich. *p-tert*-Butylcalix[8]arene (**1**)[24] and calix[8]monocrown-4 **2a**–**2c** [11] were prepared as reported.

Synthesis of Calix[8]biscrowns by Cs_2CO_3-Promoted Alkylation of *p-tert*-Butylcalix[8]arene

A suspension of **1** (0.50 g, 0.38 mmol) in Me_2CO (36 ml) was stirred in the presence of Cs_2CO_3 (1.00 g, 3.08 mmol) at reflux for 30 min. Triethylene glycol ditosylate (0.530 g, 1.15 mmol) dissolved in Me_2CO (4 ml) was then slowly added and the mixture refluxed under stirring for 25 h. After evaporation under vacuum the residue was triturated with 0.1 M HCl (50 ml), collected by filtration, washed with MeOH and dried. The crude product was subjected to column chromatography (SiO_2, gradient AcOEt/cyclohexane) to afford 1,4:2,5-calix[8]biscrown-4 **3** and 1,3:2,5-calix[8]biscrown-4 **4**, in addition to small amounts of 1,4:2,3-calix[8]biscrown-4 **5** (2%) and known monocrown derivatives (14–15% of a mixture of 1,2-monocrown-4 **2a**, 1,4-monocrown-4 **2c**, and 1,5-monocrown-4 **2d**).

1,4:2,5-Calix[8]biscrown-4 **3**: White powder (75.4 mg, 13%). M.p. 207–210 °C. R_F 0.38 (AcOEt/cyclohexane, 1:4 v/v). For $C_{100}H_{132}O_{12}$ calculated: 78.70% C, 8.72% H; found: 78.40% C, 8.70% H. ^1H NMR ($CDCl_3$, 295 K): 1.19, 1.21, 1.25, 1.28, 1.35 s- 18 H, 18 H, 9 H, 18 H, 9 H, respectively ($C(CH_3)_3$); 3.39 and 4.55 AX system, 4 H, J = 14.1 ($ArCH_2Ar$); 3.53 and 4.32 AX system, 4 H, J = 13.9 ($ArCH_2Ar$); 3.56 and 4.25 AX system, 4 H, J = 13.8 ($ArCH_2Ar$); 3.60–4.05 overlapped, 24 H (OCH_2CH_2); 4.06 and 4.17 AB system, 4 H, J = 15.5 ($ArCH_2Ar$); 6.95–7.25 overlapped, 16 H (ArH); 7.59, 8.51, 8.92 s- 1 H, 2 H, 1 H, respectively (ArOH). ^{13}C NMR ($CDCl_3$, 295 K): 31.07, 32.0 (t, $ArCH_2Ar$); 31.3, 31.5 (q, CH_3); 33.9, 34.2 (s, $(C(CH_3)_3$); 70.0, 70.8, 71.5, 74.3 (t, OCH_2CH_2); 125.0, 125.2, 125.6, 125.7, 126.0, 126.4 (d, ArCH); 126.6, 126.8, 127.6, 133.0, 133.3, 133.4, 133.5 (s, $ArCCH_2$); 141.4, 142.8, 143.1,

146.5, 147.0 (s, ArC*t*-Bu); 148.3, 148.7, 150.6, 151.1, 151.6 (s, ArCO). FAB(+) MS, *m/z*: 1547 $(M + Na)^+$.

1,3:2,5-Calix[8]biscrown-4 **4**: White powder (145 mg, 25%). M.p. 170 °C (dec). R_F 0.47 (Me_2CO/cyclohexane, 1:4 v/v). For $C_{100}H_{132}O_{12}$ calculated: 78.70% C, 8.72% H; found: 78.97% C, 8.75% H. ^{1}H NMR ($CDCl_3$, 340 K): 1.22, 1.24, 1.25, 1.26, 1.29, 1.30 s- 9 H, 18 H, 9 H, 9 H, 9 H, 18 H, respectively ($C(CH_3)_3$); 2.70, 2.87, 3.11 m- 1 H each; 3.30–4.27 overlapped, 34 H ($ArCH_2Ar$ and OCH_2CH_2); 4.28, 4.34, 4.48 d- 1 H each, J = 12.2, 15.0, 14.9, respectively ($ArCH_2Ar$); 7.03–7.22 overlapped, 16 H (ArH); 7.39, 8.47, 8.64, 8.95 s- 1 H each (ArOH). ^{13}C NMR ($CDCl_3$, 295 K): 31.4, 31.6 (q, CH_3); 30.0, 30.2, 31.9, 32.5 (t, $ArCH_2Ar$); 33.9, 34.2 (s, $C(CH_3)_3$); 69.4, 70.6, 71.1, 71.4, 71.9, 73.1, 74.3, 74.7 (t, OCH_2CH_2); 124.9, 125.1, 125.2, 125.3, 125.4, 125.6, 125.7, 125.8, 126.0, 126.4, 126.8, 126.9, 127.1 (d, ArCH); 126.8, 126.9, 127.5, 127.1, 127.6, 127.9, 132.9, 133.3, 133.8, 133.9, 134.2, 134.4 (s, $ArCCH_2$)); 141.8, 143.0, 143.2, 143.5, 146.1, 146.7, 147.1, 147.2 (s, ArC*t*-Bu); 148.1, 148.5, 149.7, 150.5, 151.4, 151.5, 153.5 (s, ArCO). FAB(+) MS, *m/z*: 1547 $(M + Na)^+$.

Synthesis of Calix[8]biscrowns by NaH-Promoted Alkylation of *p-tert*-Butylcalix[8]arene

To a suspension of **1** (1.00 g, 0.77 mmol) in THF/DMF (63/7 ml) was added NaH (148 mg, 6.17 mmol) under stirring. The mixture was refluxed for 30 min and triethylene glycol ditosylate (1.06 g, 2.31 mmol) in THF (10 ml) was then added dropwise. The reaction mixture was refluxed under stirring for 67 h. After cooling the solvent was removed under vacuum to leave a residue which was suspended in 0.1 M HCl (100 ml). Workup of the mixture followed the previous procedure to give 1,4:2,3-calix[8]biscrown-4 **5**, besides monocrown derivative **2c** (13%) and a small amount 1,3:2,5-biscrown **4** (1%).

1,4:2,3-Calix[8]biscrown-4 **5**: White powder (141 mg, 12%). M.p. 148–150 °C. R_F 0.16 (AcOEt/cyclohexane, 1:4 v/v). For $C_{100}H_{132}O_{12}$ calculated: 78.70% C, 8.72% H; found: 78.92% C, 8.74% H. ^{1}H NMR ($CDCl_3$, 295 K): 1.14, 1.24, 1.26, 1.28 s- 18 H each ($C(CH_3)_3$); 3.38 d, 1 H, J = 14.0 ($ArCH_2Ar$); 3.39–4.24 overlapped, 36 H ($ArCH_2Ar$ and OCH_2CH_2); 4.29 d, 2 H, J = 15.0 ($ArCH_2Ar$); 5.09 d, 1 H, J = 15.5 ($ArCH_2Ar$); 6.95 br s, 4 H (ArH); 7.03–7.20 overlapped, 12 H (ArH); 8.60, 8.80 br s- 2 H each (ArOH). ^{13}C NMR ($CDCl_3$, 295 K): 29.3, 30.7, 31.2, 31.8, 32.2 (t, $ArCH_2Ar$); 31.4, 31.5, 31.6 (q, CH_3); 33.9, 34.2, 34.3 (s, $C(CH_3)_3$); 70.3, 70.8, 71.4, 73.0, 73.7 (t, OCH_2CH_2); 124.9, 125.6, 126.0, 127.2 (d, ArCH); 126.8, 127.6, 127.7, 127.9, 132.6, 132.7, 133.3, 133.5 (s, $ArCCH_2$); 143.1, 143.5, 145.5, 147.2 (s, ArC*t*-Bu); 147.8, 148.3, 151.3, 152.6 (s, ArCO). FAB(+) MS, *m/z*: 1547 $(M + Na)^+$.

Synthesis of Calix[8]biscrowns by Cs_2CO_3-Promoted Alkylation of 1,4-Calix[8]monocrown-4 **2c**

Cs_2CO_3 (193 mg, 0.590 mmol) was added under stirring to solution of 1,4-calix[8]crown-4 **2c** (104 mg, 0.0740 mmol) in Me_2CO (15 ml). The mixture was kept under reflux for 30 min, then a solution of triethylene glycol ditosylate (34 mg, 0.074 mmol) in Me_2CO (5 ml) was added dropwise. The reaction was refluxed for 5 h. Usual workup of the crude product followed by column chromatography (SiO_2, gradient Et_2O/CH_2Cl_2) afforded 1,4:2,5-calix[8]-biscrown-4 **3**, 1,4:3,5-calix[8]biscrown-4 **4**, and 1,4:2,3-calix[8]biscrown-4 **5** in 30, 18, and 12% yield, respectively.

Synthesis of 1,4:5,8-Calix[8]biscrown-4 6 by KH-Promoted Alkylation of 1,4-Calix[8]monocrown-4 **2c**

KH (18 mg, 0.45 mmol) was added under stirring to a solution of 1,4-calix[8]crown-4 **2c** (80 mg, 0.056 mmol) in THF/DMF (7/0.7 ml). The mixture was refluxed for 30 min and then a solution of triethylene glycol ditosylate (26 mg, 0.057 mmol) in THF (1 ml) was added dropwise. The reaction mixture was refluxed under stirring for 24 h. Usual workup of the reaction mixture followed by column chromatography (SiO_2, gradient AcOEt/cyclohexane) afforded 1,4:5,8-calix[8]biscrown-4 **6** in 7% (6 mg) yield, white powder. M.p. 240 °C dec. R_F 0.30 (AcOEt/cyclohexane, 1:4 v/v). For $C_{100}H_{132}O_{12}$ calculated: 78.70% C, 8.72% H; found: 78.45% C, 8.75% H. ^{1}H NMR ($CDCl_3$, 330 K): 1.23, 1.30 s- 36 H each ($C(CH_3)_3$); 3.78, 3.83, 3.87 m- 8 H each (OCH_2CH_2); 3.96, 3.99, 4.14 br s- 4 H, 8 H, 4 H ($ArCH_2Ar$); 7.09 and 7.17 AB system, 8 H, J = 3.2 (ArH); 7.13 br s, 8 H (ArH); 7.93 s, 4 H (ArOH). ^{13}C NMR ($CDCl_3$, 295 K): 29.7, 30.1 (t, $ArCH_2Ar$); 31.3, 31.6 (q, CH_3); 33.9, 34.2 (s, $C(CH_3)_3$); 69.9, 70.4, 74.6 (t, OCH_2CH_2); 125.5, 125.7, 126.2 (d, ArCH); 126.9, 127.4, 133.0, 133.2 (s, $ArCCH_2$); 142.0, 146.9 (s ArC*t*-Bu); 149.5, 151.0 (s, ArCO). FAB(+) MS, *m/z*: 1547 $(M + Na)^+$.

Synthesis of 1,3:2,5-Calix[8]biscrown-4 4 by Cs_2CO_3-Promoted Alkylation of 1,3-Calix[8]monocrown-4 **2b**

To a solution of 1,3-calix[8]crown-4 **2b** (76 mg, 0.054 mmol) in Me_2CO (15 ml) was added Cs_2CO_3 (141 mg, 0.43 mmol) under stirring. The mixture was kept under reflux for 30 min, then a solution of triethylene glycol ditosylate (25 mg, 0.054 mmol) in Me_2CO (1 ml) was added dropwise. The reaction was refluxed under stirring for 6 h. Following usual workup, the crude product was subjected to preparative TLC (SiO_2, AcOEt/cyclohexane, 1:4 v/v), to afford 1,3:2,5-calix[8]biscrown-4 **4** in 7% (6 mg) yield.

Synthesis of Calix[8]biscrowns by K_2CO_3-Promoted Alkylation of 1,2-Calix[8]monocrown-4 **2a**

K_2CO_3 (55 mg, 0.40 mmol) was added under stirring to a solution of 1,2-calix[8]crown-4 **2a** (70 mg, 0.049 mmol) in Me_2CO (5 ml). The suspension was refluxed for 30 min and then triethylene glycol ditosylate (23 mg, 0.05 mmol) in Me_2CO (1 ml) was added dropwise. The reaction mixture was refluxed under stirring for 30 h and an additional amount of K_2CO_3 (27 mg, 0.195 mmol) was added. The reaction was stirred under reflux for additional 24 h. Usual workup of the reaction mixture followed by preparative TLC (SiO_2, AcOEt/cyclohexane, 1:4 v/v) afforded 1,4:2,3-calix[8]biscrown-4 **5** (3%) and 1,2:3,4-calix[8]biscrown-4 **7**.

1,2:3,4-Calix[8]biscrown-4 **7**: White powder (5 mg, 7%). M.p. 184–187 °C. R_F 0.21 (Me_2CO/cyclohexane, 1:4 v/v). For $C_{100}H_{132}O_{12}$ calculated: 78.70% C, 8.72% H; found: 78.60% C, 8.73% H. ^{1}H NMR ($CDCl_3$, 295 K): 1.10, 1.23, 1.24, 1.26 s- 18 H each ($C(CH_3)_3$); 3.43, 3.58, 3.70, 3.87, 4.03, 4.12 br m- 4 H, 4 H, 4 H, 16 H, 4 H, 8 H, respectively (OCH_2CH_2 and $ArCH_2Ar$); 6.93 s, 4 H (ArH); 7.02 d, 2 H, J = 2.3 (ArH); 7.11–7.14 overlapped, 10 H (ArH); 8.57, 9.15 br s- 2 H each (ArOH). ^{13}C NMR ($CDCl_3$, 295 K): 28.8, 29.7, 32.2 (t, $ArCH_2Ar$); 31.3, 31.5 (q, CH_3); 33.9, 34.2 (s, $C(CH_3)_3$); 70.1, 70.2, 71.0, 73.3, 73.4 (t, OCH_2CH_2); 124.8, 125.4, 125.6, 125.8, 126.1, 126.6 (d, ArCH); 127.5, 132.3, 133.9, 133.2 133.3 (s, $ArCCH_2$); 143.1, 143.7, 145.4, 146.6 (s, ArC*t*-Bu); 147.5, 149.0, 151.1, 152.8 (s, ArCO). FAB(+) MS, *m/z*: 1547 $(M + Na)^+$.

Exhaustive Methylation of 1,4:2,5-Calix[8]biscrown-4 **3**

A solution of **3** (52 mg, 0.034 mmol) in anhydrous THF/DMF (5/0.5 ml) and NaH (26 mg, 1.1 mmol) was stirred at reflux for 30 min. Two aliquots of CH_3I (68 μl each, 1.1 mmol) were then added over a 30 min interval and the reaction stirred under reflux for additional 30 min. Evaporation under vacuum left a residue which was suspended in 1 M HCl, collected by filtration, dried and purified by column chromatography (SiO_2, gradient AcOEt/cyclohexane) to give tetramethoxy-1,4:2,5-calix[8]biscrown-4 **3a** (32 mg, 60%). White powder. M.p. 130–133 °C. R_F 0.58 (AcOEt/cyclohexane, 1:4 v/v). For $C_{104}H_{140}O_{12}$ calculated: 78.95% C, 8.92% H; found: 79.10% C, 8.90% H. ^{1}H NMR ($CDCl_3$, 295 K): 1.10, 1.15, 1.21, 1.22, 1.25 s- 18 H, 9 H, 18 H, 9 H, 18 H, respectively ($C(CH_3)_3$); 2.90–3.36 overlapped 24 H (OCH_2CH_2); 3.38, 3,54, 3.63 s- 3 H, 3 H, 6 H (OCH_3); 3.64 d, 2 H, J = 15.3 ($ArCH_2Ar$); 3.70 d, 2 H, J = 14.9 ($ArCH_2Ar$); 3.93 d, 4 H, J = 15.2 ($ArCH_2Ar$); 4.08 d, 2 H, J = 12.4 ($ArCH_2Ar$); 4.14 d, 2 H, J = 11.2 ($ArCH_2Ar$); 4.23 d, 2 H, J = 14.8 ($ArCH_2Ar$); 4.37 d, 2 H, J = 15.3 ($ArCH_2Ar$); 6.87 d, 2 H, J = 2.3 (ArH); 6.88 br s, 4 H (ArH); 6.91 s, 2 H (ArH); 6.99 d, 2 H, J = 2.2 (ArH); 7.12 s, 2 H (ArH); 7.14 d, 2 H, J = 2.3 (ArH); 7.18 d, 2 H, J = 2.3 (ArH). ^{13}C NMR ($CDCl_3$, 295 K): 29.2, 30.6, 31.6, 34.18 (t, $ArCH_2Ar$); 31.4, 31.5 (q, CH_3); 33.7, 34.2 (s, $C(CH_3)_3$); 59.8, 60.3, 60.8 (q, OCH_3); 69.9, 70.1, 71.1, 72.2 (t, OCH_2CH_2); 124.8, 125.5, 125.9, 126.3, 126.4, 126.5 (d, ArCH); 132.3, 133.1, 133.2, 133.4, 133.6, 133.7, 134.2 (s, $ArCCH_2$); 145.4, 145.7, 145.9 (s, ArC*t*-Bu); 153.3, 153.6, 153.9, 154.4 (s, ArCO). FAB(+) MS, *m/z*: 1581 $(M + H)^+$.

Monomethylation of 1,4:2,5-Calix[8]biscrown-4 **3**

A solution of **3** (78 mg, 0.051 mmol) in anhydrous THF/DMF (5/0.5 ml) was refluxed under stirring for 30 min in the presence of CsF (10 mg, 0.066 mmol). CH_3I (26 μl, 0.41 mmol) was then added and the reaction mixture refluxed for 24 h. After a second addition of CsF (10 mg, 0.066 mmol) and CH_3I (26 μl, 0.41 mmol) the reaction was kept under reflux for 20 h. Following usual workup, the crude product was subjected to preparative TLC (SiO_2, Et_2O/CH_2Cl_2, 1:33 v/v) to afford 7-methoxy-1,4:2,5-calix[8]biscrown-4 **3b** and 6-methoxy-1,4:2,5-calix[8]biscrown-4 **3c**.

7-Methoxy-1,4:2,5-calix[8]biscrown-4 **3b**: White powder (57 mg, 80%). M.p. 174–178 °C. R_F 0.20 (Et_2O/CH_2Cl_2, 5:95 v/v). For $C_{101}H_{134}O_{12}$ calculated: 78.76% C, 8.77% H; found: 78.53% C; 8.75% H. ^{1}H NMR ($CDCl_3$, 295 K): 1.16, 1.17, 1.21, 1.27, 1.35 s- 9 H, 18 H, 18 H, 18 H, 9 H, respectively ($C(CH_3)_3$); 3.37 and 4.38 AX system, 4 H, J = 14.2 ($ArCH_2Ar$); 3.42–3.89 overlapped, 24 H (OCH_2CH_2); 3.64 and 4.27 AX system, 4 H, J = 14.4 ($ArCH_2Ar$); 3.94 s, 3 H (OCH_3); 3.96 and 4.05 AB system, 4 H, J = 15.6 ($ArCH_2Ar$); 4.00 and 4.16 AB system, 4 H, J = 15.4 ($ArCH_2Ar$); 6.96 d, 2 H, J = 2.0 (ArH); 7.00–7.05 overlapped, 6 H (ArH); 7.12 and 7.24 AX system, 4 H, J = 2.3; 7.15 s, 2 H (ArH); 7.26 s, 2 H (ArH); 7.68, 7.82 s- 1 H, 2 H, respectively (ArOH). ^{13}C NMR ($CDCl_3$, 295 K): 30.4 30.9 (t, $ArCH_2Ar$); 31.3, 31.4, 31.7 (q, CH_3); 33.9, 34.18, 34.2 (s, $C(CH_3)_3$); 62.1 (q, OCH_3); 69.4, 69.8, 70.7, 71.1, 73.7, 74.2 (t, OCH_2CH_2); 124.8, 125.0, 125.2, 125.6, 125.7, 126.4 (d, ArCH); 126.9, 127.1, 133.0, 133.1, 133.2, 133.4 (s, $ArCCH_2$); 141.3, 142.2 (s, ArC*t*-Bu); 146.4, 146.9, 147.3, 149.8, 151.6 (s, ArCO). FAB(+) MS, *m/z*: 1539 $(M + H)^+$.

6-Methoxy-1,4:2,5-calix[8]biscrown-4 **3c**: White powder (9 mg, 12%). M.p. 189–192 °C. R_F 0.24 (Et_2O/CH_2Cl_2, 5:95 v/v). For $C_{101}H_{134}O_{12}$ calculated: 78.76% C, 8.77% H; found: 79.00% C, 8.79% H. ^{1}H NMR ($CDCl_3$, 295 K): 1.11, 1.14, 1.19, 1.21, 1.22, 1.27, 1.31, 1.33 s- 9 H each ($C(CH_3)_3$); 3.32 and 4.44 AX system, 2 H, J = 14.7 ($ArCH_2Ar$); 3.38 and 4.30 AX system, 2 H, J = 14.5 ($ArCH_2Ar$); 3.45–3.90 overlapped, 24 H (OCH_2CH_2); 3.53 and 4.22 AX

system, 2 H, *J* = 15.0 ($ArCH_2Ar$); 3.63 and 4.51 AX system, 2 H, *J* = 15.0 ($ArCH_2Ar$); 3.81 and 4.11 AB system, 4 H, *J* = 15.5 ($ArCH_2Ar$); 3.94 and 4.12 AB system, 2 H, *J* = 16.0 ($ArCH_2Ar$); 3.95 s, 3 H (OCH_3); 3.96 and 4.16 AB system, 2 H, *J* = 11.3 ($ArCH_2Ar$); 6.79 and 7.11 AX system, 2 H, *J* = 2.0 (ArH); 6.88 d, 1 H, *J* = 2.0; 6.90 and 7.09 AB system, 2 H, *J* = 2.0 (ArH); 6.91–7.26 overlapped, 9 H (ArH); 7.10 and 7.21 AX system, 2 H, *J* = 2.1 (ArH); 7.57, 8.01 s, 1 H, 2 H, respectively (ArOH). ^{13}C NMR ($CDCl_3$, 295 K): 29.7, 30.4, 30.7, 32.0, 31.1 (t, $ArCH_2Ar$); 31.3, 31.5, 31.7 (q, CH_3); 34.0, 34.2, (s, $C(CH_3)_3$); 61.7 (q, OCH_3); 69.4, 69.8, 70.0, 70.7, 70.8, 71.3, 73.1, 73.4, 74.7, 75.1 (t, OCH_2CH_2); 124.4, 124.9, 125.1, 125.3, 125.5, 125.6, 125.8, 126.3, 126.6, 126.9 (d, ArCH); 127.0, 127.8, 132.5, 132.9, 133.3, 133.4 (s, $ArCCH_2$); 141.2, 141.9, 142.5, 145.9, 146.0, 146.8, 146.9, 147.6 (s, ArC*t*-Bu); 149.7, 150.1, 150.6, 151.0, 151.6, 152.1, 152.4, 153.2 (s, ArCO). FAB(+) MS, *m/z*: 1539 $(M + H)^+$.

Exhaustive Methylation of 1,3:2,5-Calix[8]biscrown-4 **4**

NaH (54.0 mg, 2.25 mmol) was added to a solution of **4** (107 mg, 0.070 mmol) in anhydrous THF (5 ml) and the suspension was stirred at reflux for 30 min. CH_3I (140 µl, 2.25 mmol) was added and the resulting mixture was refluxed overnight. Evaporation under vacuum left a residue which was suspended in 1 M HCl, collected by filtration, washed with MeOH, and dried to give tetramethoxy-1,3:2,5-calix[8]biscrown-4 **4a** (104 mg, 95%). White powder. M.p. 150–153°C. R_F 0.28 (AcOEt/cyclohexane, 1:4 v/v). For $C_{104}H_{140}O_{12}$ calculated: 78.95% C, 8.92% H; found: 78.72% C, 8.80% H. ^1H NMR ($CDCl_3$, 295 K): 1.02, 1.04, 1.14, 1.19, 1.23, 1.33, 1.34 s- 9 H, 9 H, 9 H, 18 H, 9 H, 9 H, 9 H, respectively ($C(CH_3)_3$); 2.10–4.40 overlapped, 40 H ($ArCH_2Ar$ and OCH_2CH_2); 3.36, 3.54, 3.59, 3.78 s- 3 H each (OCH_3); 6.78 br s, 3 H (ArH); 6.95 d, 1 H, *J* = 2.2; 6.98 br, 1 H (ArH); 7.02 br s, 5 H; 7.05 d, 1 H, *J* = 2.5 (ArH); 7.16 d, 1 H, *J* = 2.2 (ArH); 7.18 d, 1 H, *J* = 2.5 (ArH); 7.20 br s, 1 H (ArH); 7.26 br s, 2 H (ArH). ^{13}C NMR ($CDCl_3$, 295 K): 29.7, 30.2, 30.4, 30.9 (t, $ArCH_2Ar$); 31.3, 31.4, 31.6 (q, CH_3); 34.2 (s, $C(CH_3)_3$); 60.0, 60.4, 61.0 (q, OCH_3); 69.2, 69.6, 69.7, 69.9, 70.6, 70.7, 70.9, 71.0, 71.8, 72.6, 72.8 (t, OCH_2CH_2); 124.3, 124.7, 125.0, 125.1, 125.6, 125.9, 126.3, 126.5, 127.1, 127.4, 127.6 (d, ArH); 132.0, 132.4, 132.6, 132.9, 133.1, 133.3, 133.4, 133.6, 133.7, 134.2, 134.5 (s, $ArCCH_2$); 145.2, 145.6, 145.8 (ArC*t*-Bu); 152.7, 152.8, 153.4, 153.9, 154.1, 154.3, 154.6 (s, ArCO). FAB(+) MS, *m/z*: 1581 $(M + H)^+$.

Exhaustive Methylation of 1,4:2,3-Calix[8]biscrown-4 **5**

To a solution of **5** (53 mg, 0.035 mmol) in anhydrous THF (5 ml) was added NaH (27.0 mg, 1.12 mmol) under stirring. The mixture was refluxed for 30 min and then CH_3I (70 µl, 1.12 mmol) was added. The reaction was refluxed for 20 h under stirring. Evaporation under vacuum left a residue which was suspended in 1 M HCl, collected by filtration, dried, and purified by preparative TLC (SiO_2, AcOEt/cyclohexane, 1:4 v/v) to give tetramethoxy-1,4:2,3-calix[8]biscrown-4 **5a**. White powder (30 mg, 58%). M.p. 160–163 °C. R_F 0.19 (AcOEt/cyclohexane, 1:4 v/v). For $C_{104}H_{140}O_{12}$ calculated: 78.95% C, 8.92% H; found: 78.66% C, 8.94% H. ^1H NMR ($CDCl_3$, 295 K): 0.97, 1.06, 1.13, 1.31 s, 18 H each ($C(CH_3)_3$); 2.73–4.30 overlapped, 34 H ($ArCH_2Ar$ and OCH_2CH_2); 3.33, 3.58 s, 6 H each (OCH_3); 3.40 and 4.99 AX system, 2 H, *J* = 14.8 ($ArCH_2Ar$); 3.66 and 4.38 AX system, 4 H, *J* = 15.8 ($ArCH_2Ar$); 6.69 d, 2 H, *J* = 2.2 (ArH); 6.81 d, 2 H, *J* = 2.2 (ArH); 6.93 d, 2 H, *J* = 2.4 (ArH); 6.96 d, 2 H, *J* = 2.4 (ArH); 7.02 d, 2 H, *J* = 2.3 (ArH); 7.17 br s, 6 H (ArH). FAB(+) MS, *m/z*: 1581 $(M + H)^+$.

Picrate Extraction Experiments

These measurements (Table II) were performed following Pedersen's procedure[20a]: equal volumes (5 ml) of solution at equal concentration (2.5×10^{-4} mol/l) of calix[8]biscrown-4 derivative (in CH_2Cl_2) and alkali metal picrate (in H_2O) were magnetically stirred for 8 days at 20 °C in a thermostatted stoppered vial. The two phases were separated and the extraction percentage ($A_0 - A/A_0 \times 100$) was determined by measuring the absorbance (A) of aqueous phase at 356 nm and the corresponding absorbance (A_0) of a blank experiment.

Financial support from the Italian MIUR (COFIN-2003, Supramolecular Devices Project) is gratefully acknowledged. Thanks are due to Mr R. Rapisardi (I.C.T.P.-Sez. di Catania, C.N.R.) for FAB MS measurements, to Mrs C. Rocco (I.C.B.-Sez. di Catania, C.N.R.) for NMR spectra acquisition.

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