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Water-soluble *para*-Sulfonated 1,2;3,4-Calix[4]arene-*bis*crowns in the 1,2-Alternate Conformation

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Abstract

The preparation of a series of *p*-sulfonated 1,2;3,4-calix[4]arene-*bis*crowns in the *1,2-alternate* conformation is reported. These compounds are of two types: *symmetrical p*-sulfonated 1,2;3,4-calix[4]arene-*bis*crowns in which the two crown loops are the same and *unsymmetrical p*-sulfonated 1,2;3,4-calix[4]arene-*bis*crowns in which the two crown loops are different. The X-ray structures of two synthetic intermediates are given. Preliminary complexation studies showed the ligands to present pronounced Cs^+/Na^+ selectivities.

Introduction

Several families of macrocyclic molecules are at the origin of the present wide development of supramolecular chemistry. Crown ethers, cryptands and spherands were the first to be investigated thirty years ago [1]. Among others, calixarenes presently occupy a prominent place due to their ready access, easy chemical transformation and binding properties (or those of their various derivatives) towards cations, anions or neutral molecules, which make them important supramolecular hosts [2, 3]. Along with their development the idea to associate calixarenes to other members of macrocyclic families to attain more specific properties soon arose [4]: the *tetramer* is particularly well-suited for such a purpose since it forms a rather rigid platform with four extreme conformations: *cone*, *partial cone*, *1,2-alternate*, *1,3-alternate*, useful to build large molecular assemblies by functionalization at the upper or lower rim.

The introduction of polyether chains into the macrocyclic structure of calix[4]arenes at the level of the phenolic oxygen atoms has provided a family of ligands of considerable interest as selective ion transport agents and in particular as materials of possible practical importance in the treatment of nuclear waste [5]. These *calixcrowns* differ significantly from simple crown ethers in that metal ion binding is not solely determined by ether-oxygen donor interactions but appears also to involve the π-electrons of the phenyl groups of the calixarene moiety. The sub-family of 1,3-calix[4]arene-*bis*crowns in the *1,3-alternate conformation* has been proved to include highly selective extractants for *cesium* ions when the number of oxygen donor atoms in the polyether bridge is 6 [6]. In this family water-soluble 1,3-calix[4]arene-*bis*crown-6 derivatives, functionalized at the *para* position with sulfonic acid or sulfonamide groups, present very similar affinities for the *cesium* cation: it has been proposed to use such water-soluble ligands in nanofiltration techniques for removal of radioactive cesium ions from nuclear wastes [7].

In this paper we report the synthesis and complexing properties of a series of water-soluble 1,2;3,4-calix[4]arene-*bis*crowns (**15–19**) in the *1,2-alternate conformation* able to selectively complex cesium cations in water. These ligands may be useful materials because of the need of complexants with a high selectivity for Cs^+ over Na^+ at different stages in the treatment of nuclear wastes. The synthesis procedure here reported allowed us to prepare *symmetrical* 1,2-calix[4]arene-*bis*crowns in which the two crown ether units are the same and *unsymmetrical* 1,2-calix[4]arene-*bis*crowns in which the two crown ether units are different. Introduction of sulfonate groups on the phenyl rings leads to water-soluble ligands. Complexation studies were made by using ^{1}H-NMR spectroscopy.

Results and discussion

The synthesis of 1,2-calix[4]arene-*bis*crowns in a one-step reaction in *cone* and/or in *1,2-alternate* conformations is described in the literature: Pèpe *et al.* [8a] and Asfari *et al.* [8b] reported the synthesis in very low yield of 1,2;3,4-calix[4]-*bis*crown-5 in the *cone conformation* by reacting calix[4]arene with tetraethylene glycol ditosylate in acetonitrile in the presence of cesium carbonate. It was

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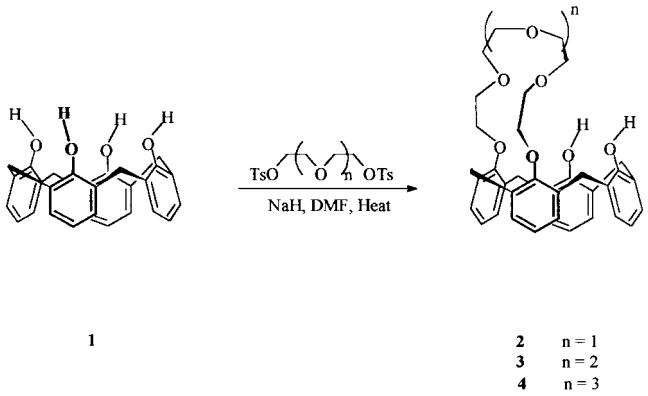
assumed that the *proximal* dialkylation was induced by a template effect due to the cesium cation [8]. Subsequently, Arduini *et al.* [9] reported that 1,2-bridged calix[4]arene-*bis*crowns can be obtained directly from calix[4]arenes (with or without *p-tert*-butyl groups on the calix unit) in the *cone* or in the *1,2-alternate* conformations depending on the base/solvent systems (NaH/DMF, tBuOK/toluene, tBuORb/toluene, tBuOCs/toluene) and on the length of the glycolic chain of the polyethylene glycol ditosylate. These authors concluded that by using a low polarity solvent and a soft cation it is possible, due to a template effect, to direct the synthesis of 1,2;3,4-calix[4]arene-*bis*crowns towards the 1,2-alternate conformation [9].

Our synthetic approach to 1,2;3,4-calix[4]arene-*bis*crowns in the *1,2-alternate conformation* takes advantage of the isolation of 1,2-calix[4]arene-*mono*crowns [10–12]. It involves the formation of 1,2-calix[4]arene-*mono*crowns, **2–4**, as precursors subsequently transformed into the desired 1,2;3,4-calix[4]arene-*bis*crowns **5–9**. Through this transformation we could prepare *symmetrical* 1,2;3,4-calix[4]arene-*bis*crowns **6** and **8** in which the two crown ether units are the same and *unsymmetrical* 1,2;3,4-calix[4]arene-*bis*crowns **5**, **7** and **9** in which the two crown ether units are different. The final step was to introduce the sulfonate groups through chlorosulfonylation-hydrolysis to obtain *para*-sulfonated 1,2;3,4-calix[4]arene-biscrowns **15–19**.

1,2-Calix[4]arene-*mono*crowns. It has been reported elsewhere that the use of NaH in DMF for tetraalkylation of calix[4]arenes generates *syn*-1,2-dialkylated calix[4]arenes as general intermediates [13]. Therefore, calix[4]arene **1** was reacted with tetraethylene glycol ditosylate (2.5 equiv, 70 °C, 10 h), pentaethylene glycol ditosylate (2.5 equiv, 50 °C, 8 h) or hexaethylene glycol ditosylate (2.5 equiv, 50 °C, 28 h) in the presence of NaH (in excess) in dry *N*,*N*-dimethylformamide (DMF) to afford the corresponding 1,2-calix[4]arene-*mono*crowns **2–4** containing respectively 5, 6 and 7 oxygen atoms in the crown ether loop (see Scheme 1). The yields decreased from 71% to 48% and 20% with the increase of the length of the polyether chain probably due to unfavorable template effects. FAB-MS spectra and microanalysis of **2–4** showed that only one polyethylene glycol unit was added on calix[4]arene **1**. The room-temperature ^{1}H-NMR spectra of **2–4** in deuteriated choroform indicated the 1,2-bridging of the calix[4]arene: only one singlet is observed for the OH functions and two triplets (ratio 1:1) are detected for the *para* protons on the aromatic rings of the calix units showing the molecule to have a symmetry plane. The presence of 3 doublets (ratio 1:2:1) at 3.39 ppm, 3.35 ppm and 3.10 ppm with J = 12.8 Hz in the spectrum of **2** corresponding to the ArC***H***$_2$Ar *equatorial* methylene protons of 3 AB systems, 3 doublets (ratio 1:2:1) at 4.55 ppm, 4.47 ppm and 4.32 ppm with J = 12.7 Hz in the spectrum of **3** corresponding to the ArC***H***$_2$Ar *axial* methylene protons of 3 AB systems and 2 doublets (ratio 3:1) at 4.45 ppm and 4.31 ppm with J = 13.0 Hz in the spectrum of **4** corresponding to ArC***H***$_2$Ar *axial* methylene protons of 2 AB systems indicated that the calix unit adopted the cone conformation upon 1,2-bridging. The molecules present a pseudo symmetry plane passing by the glycol-O-Ar**C**H$_2$Ar-O-glycol ... HO-Ar**C**H$_2$Ar-OH opposite carbon atoms and perpendicular to the mean plane of the calixarene moiety.



1 **2** n = 1, **3** n = 2, **4** n = 3

Scheme 1. Synthesis of 1,2-calix[4]*mono*crowns **2–4**.

X-ray diffraction analysis of a sample of **2** recrystallized from nitromethane: methanol (1:1) was used to define its conformation in the solid state. The asymmetric unit in **2** $CH_3NO_2.0.5CH_3OH$ comprises two crystallographically independent molecules (noted A and B), represented in Figure 1. Both of them are in a distorted cone conformation, with some phenolic rings closer to the mean plane defined by the four methylenic carbon atoms than the other ones (dihedral angles: 73.1(1), 56.6(1), 65.3(1), 50.2(1)° in A, 87.6(1), 48.5(1), 65.0(1), 38.7(1)° in B). A nitromethane solvent molecule is located near the upper rim cavity of molecule A, with shortest C(nitromethane) ... C(aromatic) contacts of about 3.6 Å, which may account for the geometry difference evidenced by the dihedral angles. The ether bridge has a different conformation in the two molecules. However, in both cases, all the oxygen lone pairs are not directed towards the crown centre. The two unsubstituted phenolic oxygen atoms are involved in intramolecular hydrogen bonds. The location of hydrogen atoms shows that these bonds are different in molecules A and B: in A, the two bonds are between one of the phenolic oxygen atoms [O(6A), O(7A)] and one of the oxygen atoms bonded to the ether chain [O(1A), O(5A)], whereas in B, one of the bonds is analogous to that in A [between O(6B) and O(5B)] but the other is between the two phenolic oxygen atoms O(7B) and O(6B). This difference in the hydrogen bonding pattern is likely to be at the origin of the differences in geometry between the ether chains in the two molecules.

1,2;3,4-Calix[4]arene-*bis*crowns. We have previously reported the preparation of 1,3;2,4-calix[4]arene-*bis*crowns by a two-step synthesis via two consecutive 1,3- and 2,4-bridgings of calix[4]arene **1** [14]. The interest in such a two-step process resides in the possibility of obtaining *unsymmetrical* 1,3;2,4-calix[4]arene-*bis*crowns with two inequivalent crown ether loops and presenting two cavities with different binding properties [15–17]. The same strategy was used in this work. The isolation of *mono*crowns **2–4**

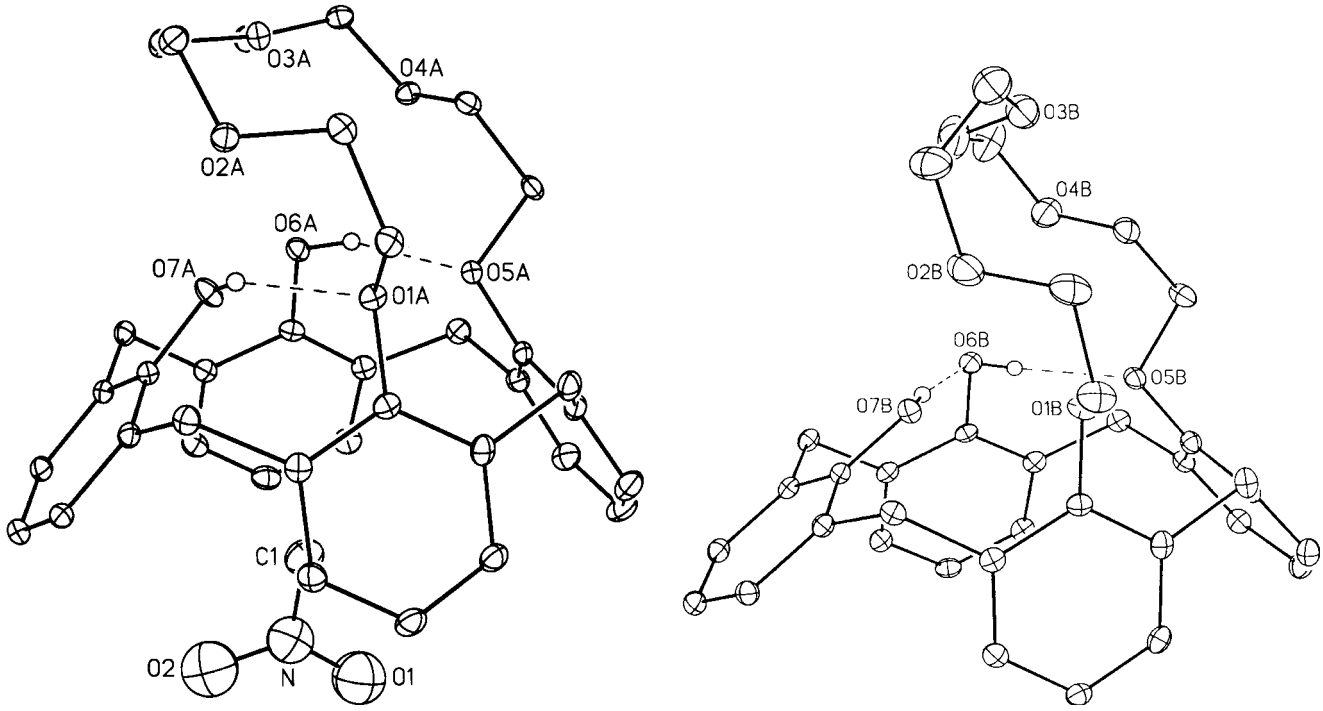
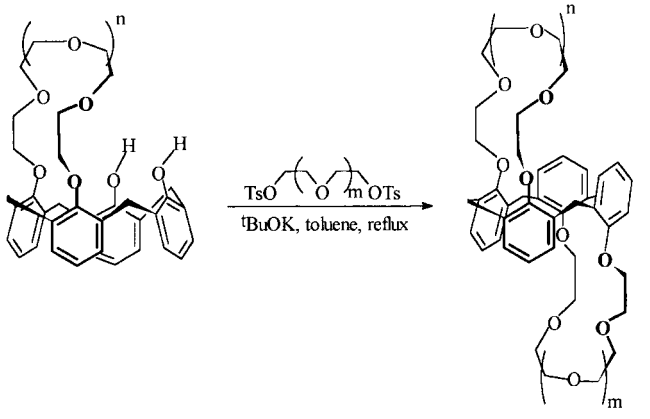


Figure 1. Molecules A and B in **2** $CH_3NO_2.0.5CH_3OH$. Phenolic protons are only represented for clarity. Hydrogen bonds represented as dashed lines.



2 n = 1
3 n = 2
4 n = 3

5 n = 1 m = 0
6 n = 1 m = 1
7 n = 1 m = 2
8 n = 2 m = 2
9 n = 3 m = 2

Scheme 2. Synthesis of 1,2;3,4-calix[4]*bis*crowns **5–9**.

allowed us to prepare either symmetrical or unsymmetrical 1,2;3,4-calix[4]arene-*bis*crowns by choosing the polyethylene glycol ditosylate for the second bridging. The general pathway is presented in Scheme 2.

Symmetrical 1,2;3,4-Calix[4]arene-*bis*crowns. Pappalardo *et al.* [11, 12] reported that the di-alkylation with alkylhalides of 1,2-calix[4]arene-*mono*crowns by using *t*-BuOK in toluene leads to the formation of O-tetrasubstituted calixarenes in the *cone* and *1,2-alternate conformations.* We decided therefore to use *t*-BuOK as base in toluene.

1,2-Calix[4]arene-*mono*crowns **2** and **3** were reacted respectively with triethylene and pentaethylene glycol ditosylates (1.1 equiv) in the presence of *t*-BuOK (in excess) in refluxing dry toluene for 28 h to afford 1,2;3,4-calix[4]arene-*bis*crowns **6** and **8**. They were purified by column chromatography and obtained in 41% and 17% yields, respectively. The difference in the yields may be explained by an increase in the length of the glycolic chain. FAB-MS spectra and microanalysis of **6** and **8** were in agreement with the presence of one calix[4]arene unit and two polyether elements. When comparing to the original calix[4]arene-*mono*crowns, the ^{1}H-NMR spectra of **6** and **8** indicated a higher symmetry for the molecule. The 1,2-alternate conformation could be assigned due to the presence of one AB system and one singlet (ratio 1:1) for the ArCH_2Ar methylene protons in the macroring. We also observed 4 of the 8 glycolic protons adjacent to the phenolic oxygens as multiplets shifted upfield at 2.87–2.75 ppm and 2.71–2.63 ppm for **6** and **8** respectively, probably due to the positioning of the 4 protons near the aromatic rings of the calix.

Compounds **6** and **8** present a center of symmetry which is the center of the calixarene unit. It can be assumed that the second bridging enforced the calix[4]arene-*mono*crowns in the cone conformation to adopt the *1,2-alternate* conformation by inversion of the oxygen phenolic atoms *through-the-annulus* of the macrocycle with a mechanism similar to the one observed during the enforcement of 1,3-calix[4]arene-*mono*crowns into 1,3-calix[4]arene-*bis*crowns in the 1,3-alternate conformation [14–16]. This inversion seems to be due to a preferential S_{N^2} substitution in a region of the calixarene in which the steric hindrance with the large tosyl groups is lowered. In 1990 Arduini *et al.* [18] reported the preparation of the 1,2;3,4-*p-tert*-butylcalix[4]arene-*bis*crown-5 in the cone conformation by reacting the *p-tert*-butyl-homologue of **2** with triethylene glycol ditosylate in the presence of *t*-BuOK in refluxing benzene. One can

assume that the induction towards the cone or the 1,2-alternate conformations is also dependent on the presence of *p-tert*-butyl groups on the calix unit.

Unsymmetrical 1,2;3,4-Calix[4]arene-*bis*crowns

In reaction conditions similar to the precedent ones, 1,2-calix[4]arene-*mono*crown-5 (**2**) was reacted with triethylene and pentaethylene glycol ditosylates to give 1,2;3,4-calix[4]arene-crown-4;crown-5 (**5**) (55% yield) and 1,2;3,4-calix[4]arene-crown-5;crown-6 (**7**) (39% yield), respectively. The reaction of 1,2-calix[4]arene-*mono*crown-7 (**4**) with pentaethylene glycol ditosylate gave 1,2;3,4-calix[4]arene-crown-6;crown-7 (**9**) (25% yield). FAB-MS spectra and microanalysis of **5**, **7** and **9** were in agreement with the presence of one calix[4]arene unit and the two desired polyether elements. The ^{1}H-NMR spectra of **5**, **7** and **9** indicated a lower symmetry for the molecules when compared to those of **6** and **8**. The spectrum of **5** is the most representative of this loss of symmetry. This spectrum presented 2 AB systems (ratio 1:1) for the glycol$_1$-O-ArC***H***$_2$Ar-O-glycol$_1$ and glycol$_2$-O-ArC***H***$_2$Ar-O-glycol$_2$ methylene protons. An additional AB system appears at 3.96 and 3.88 ppm with a J = 20.0 Hz for the 2 remaining Ar-***CH***$_2$-Ar methylene protons which become *diastereotopic* because of the presence of two different glycolic chains. A very similar AB system with a J = 17.5 Hz has been observed by Arnaud-Neu *et al.* [12b] for the corresponding methylene protons in the spectrum of related (1,2)-bridged *p-tert*-butylcalix[4]arene-crown-5 bearing two α-picolyl pendant groups. The spectrum of **7** presented 2 AB systems and one singlet (ratio 1:1:2) for the Ar-C***H***$_2$-Ar while this became one AB system and one singlet (ratio 1:1) in the spectrum of **9**. This is probably due to an increase in the length of the glycolic chains; the diastereotopic effects disappearing when the constraint of the molecular architecture decreases.

The crystal structure of **7** has been determined from a single crystal obtained by recrystallization from nitromethane : methanol (1:1). The molecule represented in Figure 2 does not present any crystallographically imposed symmetry. The conformation appears to be of the *1,2-alternate* type, but strongly distorted. The dihedral angles between the phenolic rings and the mean plane defined by the four methylenic carbon atoms, which are 82.40(6), 47.99(7), 46.58(8) and 78.15(7)°, indicate that two rings are closer to the mean plane than the other two; the rings most tilted are adjacent, and not alternate, ones. Each ether chain is connected to one of the two different canting type rings by each of its two ends. Some disorder is present in the six-membered ether chain, which evidences the flexibility of those molecules. The two protons attached to each of the two ether carbon atoms in the α position with respect to O(5) and O(6) are pointing towards the centre of the nearest aromatic rings, with distances as short as 3.10 Å. This may explain the upfield shift observed for these protons in the ^{1}H-NMR spectra due to the 1,2-alternate conformation.

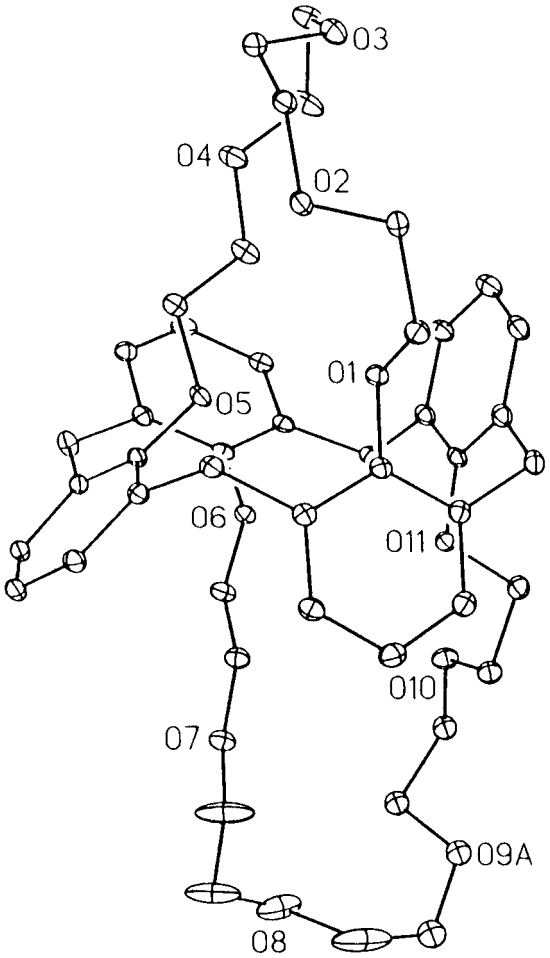


Figure 2. Molecular unit in compound **7**. Hydrogen atoms omitted for clarity. One of the two positions in the disordered chain is represented by dashed lines.

***p*-Sulfonated-1,2;3,4-calix[4]arene-*bis*crowns.** The preparation of the *p*-sulfonated 1,2;3,4-calix[4]arene-*bis*crowns was conducted, as already described for related calixarenic systems, by preliminary introduction of chlorosulfonyl functions on the *para* positions on the calixarene units [7, 19]. In a general manner, 1,2;3,4-calix[4]arene-*bis*crowns **5–9** were reacted with $ClSO_3H$ (in excess) in methylene chloride at −10 °C (see Scheme 3). Chlorosulfonylated 1,2;3,4-calix[4]arene-*bis*crowns **10–14** were isolated by column chromatography or by precipitation. The yields ranged from 13% to 72%. These compounds were used directly for subsequent hydrolysis. **10–14** were further treated with H_2O (in excess) in pyridine at room temperature for 2 h. *p*-sulfonated 1,2;3,4-calix[4]arene-*bis*crowns **15–19** were purified by crystallisation from acetone. The yields were almost quantitative. FAB-MS spectra and microanalysis of **15–19** showed that the sulfonate groups were introduced with Na^+ as counter ions probably because of the use of $NaHCO_3$ during their isolation. The ^{1}H-NMR spectra of **15–19** in deuteriated methanol or deuteriated water were very similar to those of **5–9** indicating that the 1,2-alternate conformation was maintained during the introduction of sulfonate groups on the calixarenes. Interestingly we could observe 2 doublets (ratio 1:1) at 7.55 ppm and 7.46 ppm with J = 2.2

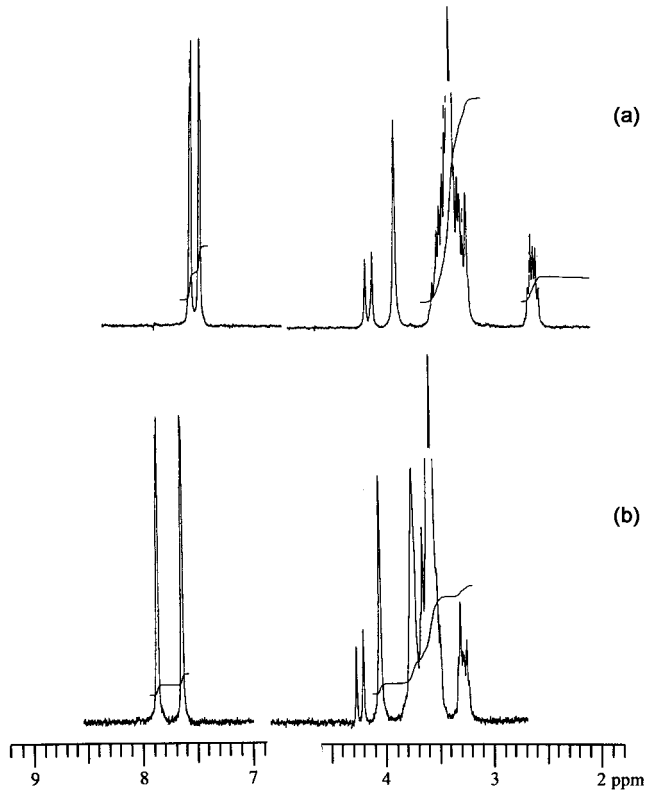


Figure 3. ^{1}H-NMR spectra of (a) free ligand **16** and (b) upon addition of $CsNO_3$ in D_2O.

Hz for the *meta* protons on the calix[4]arene in the spectrum of **16** while only two singlets were observed for the other calixarenes.

Preliminary complexation studies

Gaubert *et al.* [20] reported the selective Cs^+/Na^+ complexation-separation of a calix[4]resorcinoarene by using a nanofitration technique. This technique implies water-soluble complexing agents. Because of the presence of $-SO_3Na$ groups, *p*-sulfonated-1,2;3,4-calix[4]arene-*bis*crowns (**15–19**) are derivatives convenient for such a method. The suitability of (**15–19**) as ligands for Na^+ and Cs^+ was checked by the use of ^{1}H-NMR spectroscopy to study their complexation reaction. Preliminary experiments in which solid $NaNO_3$ or $CsNO_3$ salts were added in excess to $\sim 10^{-3}$ M solutions of (**15–19**) in D_2O showed that the ligands do complex Cs^+ and not Na^+ (no valuable changes from the free ligands spectra were observed). As an example Figure 3 shows the changes observed in the ^{1}H-NMR spectrum of **19** upon addition of $CsNO_3$ in D_2O. The more significant $\Delta\delta$ shift changes observed upon addition of Cs^+ salts are collected in Table 1. By assuming that the observed shifts are due to the proximity of the Cs^+ cation nearby the altered protons, the results are interpreted in the following manner:

1. The large magnitude of the shifts of the aromatic protons is explained in terms of some attachment of the Cs^+ ion to the aromatic π electrons. Such π-Cs^+ interactions have been observed several times [6].
2. The attachment of Cs^+ ion to the aromatic rings is also reflected by the observation that the complex multiplets associated with glycolic protons adjacent to the phenolic oxygens underwent the largest shifts. A linkage of the cesium with these oxygen donor atoms and the aromatic rings in a multiply bound manner can be assumed as in other related calixcrown systems [6]. These π-Cs^+ interactions may also be accompanied by a Cs^+–Na^+ exchange on the sulfonic group itself. The linkage of the cesium with the oxygen donor atoms can also be accounted for by introducing a conformational strain on the receptor leading to the changes observed on the aromatic protons shifts.
3. The lower field doublets component of the calixarene methylene bridge proton resonances, which are presumed to be due to 'axial' glycol-Ar-C*H*$_2$-Ar-glycol showed the smallest shifts as well as the singlets attributed to the remaining $ArCH_2Ar$, in agreement with a location of the Cs^+ ion nearer to the aromatic rings.
4. The largest changes in ^{1}H-NMR shifts are observed for ligand **18** because probably it is the most suited for Cs-complexation.

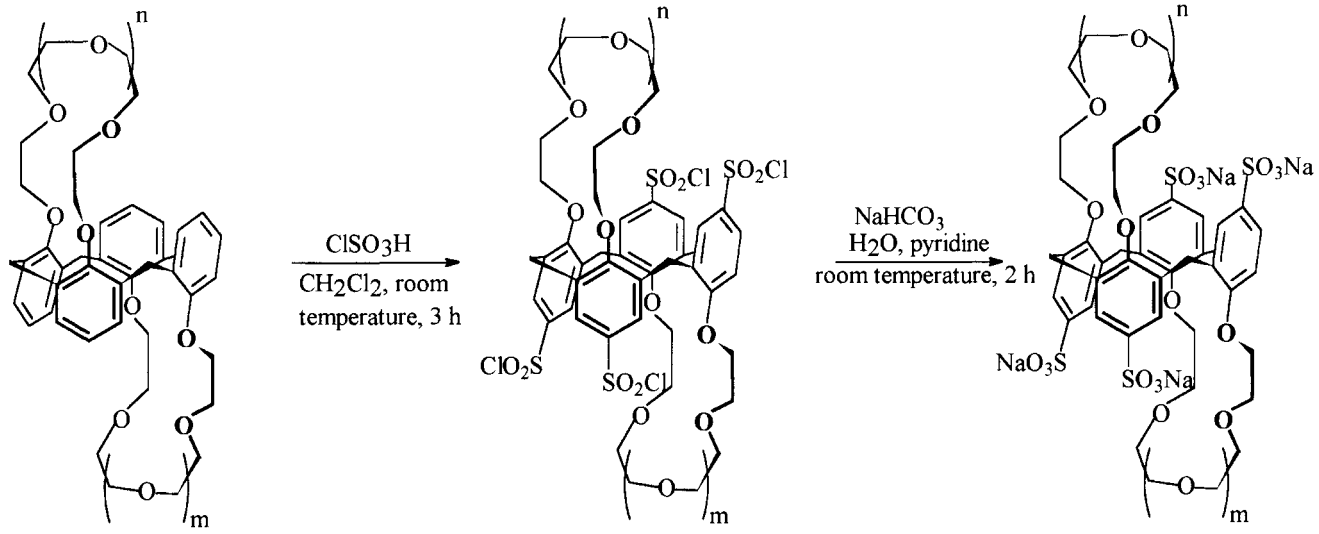
Experimental section

Materials

All reagents were commercial and used without further purification. Calix[4]arene **1** was prepared according to the literature [22]. The melting points (Mps) were taken on a Büchi apparatus in a capillary sealed under nitrogen. Silica columns were prepared with Keisegel Si 60 (40–63 μm) Merck (1.11567.1000). ^{1}H-NMR spectra were recorded at 200 MHz on a Bruker SY200 spectrometer. ^{13}C-NMR spectra were recorded at 400 MHz on a Brucker Avance spectrometer. The solvents are specified in the experimental section. Chemical shifts are given as δ values in ppm relative to TMS (δ = 0.00) as an internal standard. The FAB MS spectra were obtained on a VG-Analytical ZAB HF apparatus. Elemental analyses were determined at the Centre de Microanalyse of the Institut de Chimie de Strasbourg.

Synthesis of the compounds

1,2-calix[4]arene-crown-5 (2). A sample of 6.36 g (15.00 mmol) of calix[4]arene **1**, 3.00 g (75.00 mmol) of NaH, and 18.84 g (37.50 mmol) of tetraethylene glycol ditosylate in 1500 mL of dimethylformamide was heated at 50 °C for 10 h. Then methanol and water were added to the reaction mixture at room temperature. The solvents were removed to dryness. The residue was dissolved in CH_2Cl_2. Water was added and the mixture was acidified with concentrated HCl to pH $\sim$1. The organic layer was dried (Na_2SO_4), filtered and concentrated to give a residue which was precipitated with methanol to afford 6.22 g (71%) of **2** as a white solid:



5 n = 1 m = 0
6 n = 1 m = 1
7 n = 1 m = 2
8 n = 2 m = 2
9 n = 3 m = 2

10 n = 1 m = 0
11 n = 1 m = 1
12 n = 1 m = 2
13 n = 2 m = 2
14 n = 3 m = 2

15 n = 1 m = 0
16 n = 1 m = 1
17 n = 1 m = 2
18 n = 2 m = 2
19 n = 3 m = 2

Scheme 3. Synthesis of *p*-sulfonated 1,2;3,4-calix[4]*bis*crowns **15–19**.

Table 1. Changes in the ^{1}H-NMR shifts of **15–19** upon addition of $CsNO_3$ in D_2O

Compound	**H** in meta	Doublet AB system	Singlet AB system	Ar–O–C**H**$_2$–CH$_2$
15	7.55; 7.45	4.20; 4.09	4.05	2.82–2.77; 2.61–2.54
15⊂Cs^+	7.76; 7.57	4.26; 4.15	3.96	3.22; 3.00
16	7.55; 7.46	4.16	3.93	2.66–2.62
16⊂Cs^+	7.98; 7.65	4.21	4.03	3.29; 3.23
16⊂Na^+	7.55; 7.46	4.16	3.93	2.66–2.62
17	7.53; 7.44	4.13	3.92	2.58–2.43
17⊂Cs^+	7.70; 7.56	4.20	3.99	3.00–2.90; 2.80–2.70
18	7.55; 7.45	4.18	3.95	2.47–2.42
18⊂Cs^+	7.58; 7.46	4.13	3.92	2.62–2.57
19	7.52; 7.44	4.21–4.14	3.93	2.52–2.30
19⊂Cs^+	7.59; 7.55; 7.48	4.17	4.00	2.65; 2.30

m.p. 216–218 °C; ^{1}H-NMR ($CDCl_3$) δ 8.34 (s, 2H), 7.08–6.93 (m, 8H), 6.80 (t, 2H, J = 7.5 Hz), 6.60 (t, 2H, J = 7.4 Hz), 4.60–4.30 (m, 4H), 4.51 (d, AB system, 4H$_{ax}$, J = 12.8 Hz), 3.39 (d, AB system, 1H$_{eq}$, J = 12.8 Hz), 3.35 (d, AB system, 2H$_{eq}$, J = 12.8 Hz), 3.31 (d, AB system, 1H$_{eq}$, J = 12.8 Hz), 4.19–3.70 (m, 12H), FAB-MS *m/z* 583.7 ($M.H^+$). Anal. Calcd for $C_{36}H_{38}O_7.1/2CH_2Cl_2.1/2CH_3OH$: C, 69.31; H, 6.45. Found: C, 69.22; H, 6.48.

1,2-calix[4]arene-crown-6 (3). Same procedure as for **2** with 2.12 g (5.0 mmol) of calix[4]arene, 1.00 g (25.00 mmol) of NaH and 7.24 g (12.50 mmol) of pentaethylene glycol ditosylate in 500 mL of dimethylformamide. Heating at 50 °C for 8 h. The last residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5) and precipitation with ethyl acetate to afford 1.52 g (48%) of **3** as a white solid: m.p. 180–182 °C; ^{1}H-NMR ($CDCl_3$) δ 8.68 (s, 2H), 6.98–6.92 (m, 8H), 6.76 (t, 2H, J = 7.5 Hz), 6.60 (t, 2H, J = 7.5 Hz), 4.55 (d, AB system, 1H$_{ax}$, J = 12.7 Hz), 4.53–3.62 (m, 20H), 4.47 (d, AB system, 2H$_{ax}$, J = 12.7 Hz), 4.32 (d, AB system, 1H$_{ax}$, J = 12.7 Hz), 3.38 (d, AB system, 1H$_{eq}$, J = 12.7 Hz), 3.35 (d, AB system, 3H$_{eq}$, J = 12.7 Hz). FAB-MS *m/z* 627.3 ($M.H^+$). Anal. Calcd for $C_{38}H_{42}O_8.1/2C_4H_8O_2$: C, 71.62; H, 6.91. Found: C, 71.69; H, 6.71.

1,2-calix[4]arene-crown-7 (4). Same procedure as **2** with 2.12 g (5.00 mmol) of calix[4]arene, 1.00 g (25.00 mmol) of NaH and 7.37 g (12.50 mmol) of hexaethylene glycol ditosylate in 500 mL of dimethylformamide. Heating at 50 °C for 28 h. The last residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5) to afford 0.67 g (20%) of **4** as a white solid : m.p. 206–208 °C. ^{1}H-NMR ($CDCl_3$) δ 8.85 (s, 2H), 7.06–6.86 (m, 8H), 6.74 (t, 2H, J = 7.3 Hz),

6.60 (t, 2H, J = 7.4 Hz), 4.61–3.54 (m, 24H), 4.45 (d, AB system, $3H_{ax}$, J = 13.0 Hz), 4.31 (d, AB system, $^1H_{ax}$, J = 13.0 Hz), 3.33 (d, AB system, $4H_{eq}$, J = 13.0 Hz). FAB-MS *m/z* 671.1 ($M.H^+$). Anal. Calcd for $C_{40}H_{46}O_9$: C, 71.62; H, 6.91. Found: C, 72.42; H, 6.17.

1,2;3,4-calix[4]arene-crown-4-crown-5 (5). A sample of 1.39 g (2.40 mmol) of **2**, 1.34 g (12.00 mmol) of *t*-BuOK, 1.23 g (2.70 mmol) of triethylene glycol ditosylate was refluxed in 1250 mL of toluene for 28 h. After cooling at room temperature 10–20 mL of water were added and the solvents were removed to dryness. The residue was solubilized in CH_2Cl_2 and the mixture was poured into water. The mixture was acidified with concentrated HCl to pH ∼2. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5) to afford 0.94 g (55%) of **5** as a white solid : m.p. 162–164 °C. ^{1}H-NMR ($CDCl_3$) δ 7.18–7.07 (m, 8H), 6.97–6.87 (m, 4H), 4.34 (d, AB system, $1H_{ax}$, J = 12.5 Hz), 4.22 (d, AB system, $1H_{ax}$, J = 12.5 Hz), 3.96 (d, AB system, 2H, J = 20.0 Hz), 3.88 (d, AB system, 2H, J = 20.0 Hz), 3.75-3.45 (m, 20H), 3.38–3.12 (m, 4H), 3.09 (d, AB system, $2H_{eq}$, J = 12.5 Hz), 2.84–2.75 (m, 4H). FAB-MS *m/z* 697.1 ($M.H^+$). Anal. Calcd for $C_{42}H_{48}O_9$. $1/2CH_2Cl_2$: C, 69.05; H, 6.68. Found: 69.20; H, 6.95.

1,2;3,4-calix[4]arene-*bis*crown-5 (6). Same procedure as for **5** with 0.145 g (0.24 mmol) of **2**, 0.140 g (1.20 mmol) of *t*-BuOK, 0.138 g (0.27 mmol) of tetraethylene glycol ditosylate in 125 mL of toluene, reflux for 28 h. The residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5) to afford 0.081 g (41%) of **6** as a white solid: m.p. 82–84 °C. ^{1}H-NMR ($CDCl_3$) δ 7.17 (d, 4H, J = 7.4 Hz), 7.13 (d, 4H, J = 7.4 Hz), 6.89 (t, 4H, J = 7.4 Hz), 4.23 (d, AB system, $2H_{ax}$, J = 12.6 Hz), 3.91 (s, 4H), 3.74–3.47 (m, 24H), 3.36–3.26 (m, 4H), 3.19 (d, AB system, $2H_{eq}$, J = 12.6 Hz), 2.87–2.75 (m, 4H). FAB-MS *m/z* 741.8 ($M.H^+$). Anal. Calcd for $C_{44}H_{52}O_{10}.1/3CH_2Cl_2$: C, 69.23; H, 6.90. Found: C, 69.20; H, 6.86.

1,2;3,4-calix[4]arene-crown-5,crown-6 (7). Same procedure as for **5** with 2.33 g (4.00 mmol) of **2**, 2.24 g (20.00 mmol) of *t*-BuOK, 2.50 g (4.40 mmol) of pentaethylene glycol ditosylate in 1800 mL of toluene, reflux for 45 h. The residue was purified by column chromatography (CH_2Cl_2/acetone = 90/10) to afford 1.23 g (39%) of **7** as a white solid: m.p. 94–96 °C. ^{1}H-NMR ($CDCl_3$) δ 7.19–7.10 (m, 8H), 6.89 (t, 4H, J = 7.5 Hz), 4.23 (d, AB system, $1H_{ax}$, J = 12.5 Hz), 4.20 (d, AB system, $1H_{ax}$, J = 12.5 Hz), 3.91 (s, 4H), 3.68–3.48 (m, 28H), 3.32–3.15 (m, 6H), 2.84–2.64 (m, 4H). FAB-MS *m/z* 785.3 ($M.H^+$). Anal. Calcd for $C_{46}H_{56}O_{11}$: C, 70.39; H, 7.19. Found: C, 70.31; H, 7.33.

1,2;3,4-calix[4]arene-*bis*crown-6 (8). Same procedure as for **5** with 1.37 g (2.19 mmol) of **3**, 1.22 g (11.00 mmol) of *t*-BuOK, 1.40 g (2.41 mmol) of pentaethylene glycol ditosylate in 1000 mL of benzene, reflux for 5 days. The residue was purified by column chromatography (CH_2Cl_2/acetone = 90/10) to afford 0.317 g (17%) of **8** as a yellow sticky oil. ^{1}H-NMR ($CDCl_3$) δ 7.12 (d, 8H, J = 7.5 Hz), 6.89 (t, 4H, J = 7.5 Hz), 4.26 (d, AB system, $2H_{ax}$, J = 12.5 Hz), 3.92 (s, 4H), 3.72–3.47 (m, 32H), 3.24–3.13 (m, 4H), 3.19 (d, AB system, $2H_{eq}$, J = 12.5 Hz), 2.71–2.63 (m, 4H). FAB-MS *m/z* 829.0 ($M.H^+$). Anal. Calcd for $C_{48}H_{60}O_{12}$: C, 66.85; H, 7.06. Found: C, 66.85; H, 7.02.

1,2;3,4-calix[4]arene-crown-6;crown-7 (9). Same procedure as for **5** with 0.670 g (1.00 mmol) of **4**, 0.561 g (5.00 mmol) of *t*-BuOK, 0.627 g (1.10 mmol) of pentaethylene glycol ditosylate in 520 mL of toluene, reflux for 5 days. The residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5) to afford 0.220 g (25%) of **9** as a white solid. M.p. 98–100 °C. ^{1}H-NMR ($CDCl_3$) δ 7.11 (d, 8H, J = 7.6 Hz), 6.88 (t, 4H, J = 7.6 Hz), 4.26 (d, AB system, $2H_{ax}$, J = 12.6 Hz), 3.90 (s, 4H), 3.67–3.45 (m, 36H), 3.21–3.09 (m, 4H), 3.17 (d, AB system, $2H_{eq}$, J = 12.6 Hz), 2.72–2.61 (m, 4H). FAB-MS *m/z* 873.2 ($M.H^+$). Anal. Calcd for $C_{50}H_{64}O_{13}$. $1/3CH_2Cl_2$: C, 67.07; H, 7.23. Found: C, 67.12; H, 7.56.

1,2;3,4-*p*-sulfonyl chloride calix[4]arene-crown-4;crown-5 (10). A sample of 0.940 g (1.34 mmol) of **5** in 20 mL of CH_2Cl_2 was maintained at −10 °C while adding drop wise 6.29 g (54.00 mmol) of chlorosulfonic acid ($ClSO_3H$). After stirring at room temperature for 3 h, ice-water and CH_2Cl_2 were added. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5) to afford 0.760 g (52%) of **10** as a yellow oil which was used without further purification. ^{1}H-NMR (CD_3OD/D_2O) a general broadening was observed for the spectrum: δ 7.40–7.22 (m, 8H), 4.15–2.30 (m, 36H).

1,2;3,4-*p*-sulfonyl chloride calix[4]arene-*bis*crown-5 (11). Same procedure as for **10** with 2.22 g (3.00 mmol) of **6** in 40 mL of CH_2Cl_2, 14.72 g (126.00 mmol) of $ClSO_3H$. The residue was precipitated with methanol to afford 2.42 g (71%) of **11** as a white solid which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ 7.87 (d, 4H, J = 2.5 Hz), 7.83 (d, 4H, J = 2.5 Hz), 4.61 (d, AB system, $2H_{ax}$, J = 13.5 Hz), 4.08 (s, 4H), 3.71–3.48 (m, 28H), 3.49 (d, AB system, $2H_{eq}$, J = 12.6 Hz), 3.8–2.98 (m, 4H).

1,2;3,4-*p*-sulfonyl chloride calix[4]arene-crown-5;crown-6 (12). Same procedure as for **10** with 1.00 g (1.27 mmol) of **7** in 20 mL of CH_2Cl_2, 5.82 g (50.00 mmol) of $ClSO_3H$. The residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5) to afford 0.900 g (72%) of **12** as a yellow oil which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ 7.85–7.78 (m, 8H), 4.60 (d, AB system, $1H_{ax}$, J = 13.7 Hz), 4.58 (d, AB system, $1H_{ax}$, J = 13.5 Hz), 4.12 (d, AB system, 2H, J = 16.5 Hz), 4.00 (d, AB system, 2H, J = 16.5 Hz), 3.90–3.32 (m, 34H), 3.09–2.95 (m, 4H).

1,2;3,4-*p*-sulfonyl chloride calix[4]arene-*bis*crown-6 (13). Same procedure as for **10** with 0.402 g (0.48 mmol) of **8** in 7 mL of CH_2Cl_2, 2.24 g (19.28 mmol) of $ClSO_3H$. The residue was purified by column chromatography (CH_2Cl_2) to afford 0.080 g (13%) of **13** as a yellow oil which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ 7.84 (d, 4H, J = 2.4 Hz), 7.79 (d, 4H, J = 2.4 Hz), 4.60 (d, AB system, $2H_{ax}$, J = 13.8 Hz), 4.08 (s, 4H), 3.82–3.45 (m, 40 H), 3.41 (d, AB system, $2H_{eq}$, J = 13.8 Hz), 3.05–2.95 (m, 4H).

1,2;3,4-*p*-sulfonyl chloride calix[4]arene-crown-6;crown-7 (14). Same procedure as for **10** with 0.221 g (0.25 mmol) of **9** in 5 mL of CH_2Cl_2, 1.17 g (10.00 mmol) of $ClSO_3H$. The residue was purified by column chromatography (CH_2Cl_2/acetone = 90/10) to afford 0.055 g (28%) of **14** as a yellow oil which was used without further purification. ^{1}H-NMR (CD_3OD) a general broadening was observed for the spectrum: δ 7.89–7.64 (m, 8H), 4.45–3.30 (m, 48H), 2.61–2.48 (m, 4H).

1,2;3,4-*p*-sulfonate calix[4]arene-crown-4;crown-5 (15). A sample of 0.600 g (0.55 mmol) of **10** in 5 mL of pyridine and 2 mL of H_2O was stirred at room temperature for 2 h. The solvents were evaporated, and the residue solubilized with a minimum amount of water and treated with a solution of 10% $NaHCO_3$ in water. Precipitation with acetone afforded 0.540 g (78%) of pure **15** as a grey solid. M.p: >260 °C. ^{1}H-NMR (D_2O) δ 7.55 (s, 4H), 7.45 (s, 4H), 4.20 (d, AB system, $1H_{ax}$, J = 12.6 Hz), 4.09 (d, AB system, $1H_{ax}$, J = 6.2 Hz), 4.05 (s, 4H), 3.58–3.16 (m, 26H), 2.82–2.77 (m, 2H), 2.61–2.54 (m, 2H). ^{13}C-NMR 28.07, 28.58, 37.31, 48.51, 55.93, 62.95, 68.48, 68.96, 69.14, 69.63, 69.81, 71.21, 71.61, 72.48, 126.50, 126.58, 127.00, 127.37, 128.17, 133.78, 133.94, 135.34, 135.52, 137.66, 137.98, 145.22, 145.34, 157.97, 158.10. FAB-MS *m/z* 1106.0 ($M.H^+$). Anal. Calcd for $C_{42}H_{44}O_{21}Na_4S_4.6H_2O.C_2H_6O$: C, 41.97; H, 4.96. Found: C, 41.96; H, 4.91.

1,2;3,4-*p*-sulfonate calix[4]arene-*bis*crown-5 (16). Same procedure as for **15** with 2.42 g (2.13 mmol) of **11** in 13 mL of pyridine and 2 mL of H_2O. Precipitation with acetone afforded 3.34 g (quantitative) of pure **15** as a white solid. M.p. 230–232 °C. ^{1}H-NMR (D_2O) δ 7.55 (d, 4H, J = 2.2 Hz), 7.46 (d, 4H, J = 2.2 Hz), 4.16 (d, $2H_{ax}$, J = 13.0 Hz), 3.93 (s, 4H), 3.58–3.27 (m, 28H), 3.28 (d, AB system, 2H, J = 13.0 Hz), 2.66–2.62 (m, 4H). ^{13}C-NMR 28.59, 37.21, 68.96, 69.01, 69.76, 71.74, 126.50, 127.25, 127.83, 133.63, 135.35, 138.06, 141.54, 147.62, 157.98. FAB-MS *m/z* 1149.7 (M.H+). Anal. Calcd for $C_{44}H_{48}O_{22}Na_4S_4.10H_2O$: C, 39.76; H, 5.16. Found: C, 39.69; H, 4.65.

1,2;3,4-*p*-sulfonate calix[4]arene-crown-5;crown-6 (17). Same procedure as for **15** with 0.260 g (0.22 mmol) of **12** in 2 mL of pyridine and 0.2 mL of H_2O. Precipitation with acetone afforded 0.270 g (quantitative) of pure **17** as a white solid. M.p. >260 °C. ^{1}H-NMR (D_2O) δ 7.53 (s, 4H), 7.44 (s, 4H), 4.13 (d, AB system, $2H_{ax}$, J = 12.7 Hz), 3.92 (s, 4H), 3.53–3.06 (m, 32H), 3.33 (d, AB system, $2H_{eq}$, J = 12.7 Hz), 2.58–2.43 (m, 4H). FAB-MS *m/z* 1193.0 ($M.H^+$). Anal. Calcd for $C_{46}H_{52}O_{23}Na_4S_4.15H_2O$: C, 37.46; H, 5.65. Found: C, 37.71; H, 4.45.

1,2;3,4-*p*-sulfonate calix[4]arene-*bis*crown-6 (18). Same procedure as for **15** with 0.080 g (0.065 mmol) of **13** in 0.5 mL of pyridine and 0.1 mL of H_2O. Precipitation with acetone afforded 0.074 g ($\sim$ quantitative) of pure **18** as a white solid. m. p. >260 °C. ^{1}H-NMR (D_2O) δ 7.55 (s, 4H), 7.45 (s, 4H), 4.18 (d, AB system, $2H_{ax}$, J = 13.0 Hz), 3.95 (s, 4H), 3.52–3.25 (m, 36H), 3.11–3.06 (m, 2H), 2.47–2.42 (m, 4H). ^{13}C-NMR 28.72, 37.39, 68.89, 69.74, 69.96, 70.40, 70.60, 126.38, 127.09, 133.87, 135.45, 137.92, 15.97. FAB-MS *m/z* 1237.1 ($M.H^+$). Anal. Calcd for $C_{48}H_{56}O_{24}Na_4S_4.8H_2O$: C, 41.73; H, 5.26. Found: C, 41.73; H, 4.97.

1,2;3,4-*p*-sulfonate calix[4]arene-crown-6;crown-7 (19). Same procedure as for **15** with 0.055 g (0.043 mmol) of **14** in 0.5 mL of pyridine and 0.2 mL of H_2O. Precipitation with acetone afforded 0.044 g (80%) of pure **19** as a white solid. m.p. >260 °C. ^{1}H-NMR (D_2O) δ 7.52 (s, 4H), 7.44 (s, 4H), 4.21–4.14 (m, 2H), 3.93 (s, 4H), 3.51–3.07 (m, 42H), 2.52–2.30 (m, 4H). FAB-MS *m/z* 1280.9 ($M.H^+$). Anal. Calcd for $C_{50}H_{60}O_{25}Na_4S_4.22H_2O$: C, 35.80; H, 6.25. Found: C, 35.85; H, 6.17.

Crystal structures

Crystal data for **2**.CH_3NO_2.0.5CH_3OH, $O_{16.5}N_1C_{73.5}H_{81}$, M = 1242.39; monoclinic, space group $P2_1/c$, a = 19.0712(5), b = 19.1279(9), c = 17.9576(5) Å, β = 98.231(2)°; V = 6483(3) Å^3; Z = 4; d_{calc} = 1.273 g cm^{-3}; μ = 0.090 mm^{-1}; $F(000)$ = 2644; T = 123(2) K.

Crystal data for **7**, $O_{11}C_{46}H_{56}$, M = 784.91; monoclinic, space group $P2_1/n$, a = 15.2314(6), b = 12.9616(4), c = 20.7273(8) Å; β = 99.664(2)°; V = 4034(2) Å^3; Z = 4; d_{calc} = 1.292 g cm^{-3}; μ = 0.091 mm^{-1}; $F(000)$ = 1680; T = 100(2) K.

The data were collected on a Nonius Kappa-CCD area detector diffractometer using graphite monochromated MoKα radiation (0.71073 Å). The lattice parameters were determined from ten images recorded with 1° φ-scans and later refined on all data. A 180° φ-range was scanned with 2° steps during data recording. The crystal-to-detector distance was fixed to 30 and 28 mm for **2**.CH_3NO_2.0.5CH_3OH and **7**, respectively. The data were processed with the HKL package [22]. The structures were solved by direct methods with SHELXS-86 [23] and subsequent Fourier-difference synthesis and refined by full-matrix least-squares on F^2 with SHELXL-93 [24]. No absorption correction was made. **2**.CH_3NO_2.0.5CH_3OH contains two solvent molecules, a nitromethane one and a badly resolved methanol one which is located near a symmetry centre and has been given a 0.5 occupancy. In **7**, a part of the six-membered ether chain was disordered and four atoms have been modelled with two positions with occupancy factors constrained to sum to unity. All non-hydrogen atoms were refined anisotropically, with the exception of those of the methanol solvent molecule in

2.CH_3NO_2.0.5CH_3OH and the disordered ones in **7**. The phenolic protons in **2**.CH_3NO_2.0.5CH_3OH were found on the Fourier-difference map and introduced as riding atoms with a displacement parameter equal to 1.2 times that of the attached oxygen atom. All the other hydrogen atoms in both compounds were introduced at calculated positions (unless in the disordered parts) as riding atoms, with a displacement parameter equal to 1.2 times that of the attached carbon atom. Final *R* factors: *R1* = 0.089, *wR2* = 0.227 for **2**.CH_3NO_2.0.5CH_3OH, *R1* = 0.068, *wR2* = 0.171 for **7**. The molecular drawings were done with SHELXTL [25]. All calculations were performed with a Silicon Graphics R5000 workstation.

Conclusion

In this paper, we report the synthesis of *p*-sulfonated-1,2;3,4-calix[4]arene-*bis*crowns (**15–19**) in the 1,2-alternate conformation. They are constituted of a calix[4]arene unit in the 1,2-alternate conformation bearing two crown loops attached in a syn-1,2-O-dialkylation manner. We have been able to prepare symmetrical *p*-sulfonated-1,2;3,4-calix[4]arene-*bis*crowns in which the two crown loops are identical and unsymmetrical *p*-sulfonated-1,2;3,4-calix[4]arene-*bis*crowns in which the two crown loops are different. Preliminary complexation experiments in deuteriated water indicated that these ligands can be selective for cesium ion towards sodium ion. This observation makes them good candidates as extractants for radioactive waste management and disposal within the industrial prospects of membrane processes.

We are currently studying the binding properties of these compounds towards alkali metal cations in water by thermodynamic techniques. Our objectives for the future are to prepare *p*-sulfonated-1,2;3,4-calix[4]arene-*bis*crowns in the *cone* conformation and some of their complexes with alkali metal cations and to determine their molecular structure.

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