

Calixcrowns: synthesis and properties

Kirsi Salorinne · Maija Nissinen

Received: 30 October 2007 / Accepted: 19 January 2008 / Published online: 6 February 2008
© Springer Science+Business Media B.V. 2008

Abstract The synthesis and properties of calix[*n*]crowns ($n = 4–8$), calix[*n*]biscrowns and their related compounds, resorcinarene crowns, have been discussed and reviewed. These macrocycles exhibit remarkable ionophoric properties toward alkali and alkaline earth metal cations, as well as, to tertiary amines. The selectivity and efficiency of calixcrowns in binding cations have been attributed to their structural features, which include substituent effects and size of the crown ether moiety and, conformation of the parent calixarene.

Keywords Calixcrown · Calixbiscrown · Complexation · Resorcinarene crown

Introduction

The first calixcrown, based on *p-tert*-butylcalix[4]arene with pentaethylene glycol bridge linking the 1,3-phenolic oxygens, was reported by Ungaro and co-workers in 1983 [1]. Since then the family of calixcrowns has grown immensely through incorporation of larger calix[*n*]arenes ($n = 5–8$) as the platform or controlling the bridging mode and conformation of the macrocycles. From early on calixcrowns were discovered to have ionophoric properties toward alkali and alkaline earth metal cations and, also to tertiary amines. Their binding selectivity is greatly determined by the number of oxygen atoms in the polyethylene glycol bridge, the nature of the substituents at the crown

bridge, and also by the stereochemistry of the calixarene skeleton at the binding site.

Calixcrowns, and especially, calix[4]crown-6 derivatives, have proven to be most advantageous in the field of nuclear waste treatment [2], which originates from their remarkable ability to bind cesium selectively in the presence of other alkali metal salts [3]. Other applications [4] include the use of calixcrowns in ion selective electrodes (ISE) [5], as transacylation catalysts [6] and in various separation techniques such as supported liquid membranes (SLM) [7] and nanofiltration techniques [8].

In this current paper, the synthesis and properties of calix[*n*]crown ethers and their related compounds, resorcinarene crowns, are reviewed. Due to the extensive work that has been done with calixcrowns, we have limited this survey to cover the basic calix[*n*]arene mono- and bis-crown ethers, without going into too much detail with their further functionalized derivatives or their related nitrogen containing macrocycles calixazacrown ethers.

Calix[4]crowns

Calix[4]crowns can easily be prepared by the reaction of calix[4]arene with the appropriate polyethylene glycol ditosylate in the presence of various bases. Shinkai and group discovered that alkali metal salt as the base served two purposes: dissociation of the hydroxyl groups and template effect by the alkali metal cation [9]. The mono-bridging of calix[4]arene can either result in 1,3- or 1,2-bridged calix[4]crowns, depending on the synthetic strategy. In general, weaker bases, such as M_2CO_3 , were found to produce the 1,3-bridged species whereas stronger bases, like MH, favored the production of 1,2-bridged species in relation to the template effect of the alkali metal [9]. The

K. Salorinne · M. Nissinen (✉)
Department of Chemistry, Nanoscience Center,
University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland
e-mail: maija.nissinen@jyu.fi

syntheses are usually carried out under high dilution conditions to prevent intermolecular bridging and they take from one to several days to complete. However, Tanaka and co-workers found out that the base promoted cyclization reaction of 1,3-dibenzylated-*p*-*tert*-butylcalix[4]arenes with polyethylene glycol ditosylates in the presence of large excess of NaH afforded calix[4]crown ethers in excellent to good yields under non-dilution conditions in less than one day [10]. Sodium cation was evidenced to play a crucial role by acting as a template in preorganizing the intermediate product in the favor of intramolecular bridging affording calix[4]crown ethers in a flattened cone conformation. Bitter et al. used a different approach by employing the Mitsunobu protocol, which entails the use of triphenylphosphine and diethyl azodicarboxylate (DEAD) in the presence of polyethylene glycol, to afford 1,3-bridged calix[4]crowns with the exception that 1,2-bridged calix[4]crown-3 is obtained exclusively when short chained diethylene glycol is used as the bridging agent [11]. The reactions were completed within 30 min with yields ranging from 30 to 50%.

The introduction of alkyl substituents on the phenolic hydroxyl groups of the calixarene controls the stereo- and regioselectivity of the calixcrowns. The alkylation can be achieved essentially by two different strategies: Alkylation of the bridged calix[4]crown ether or selective 1,2- or 1,3-dialkylation of the calix[4]arene followed by the introduction of the polyethylene glycol bridge [12]. When the alkyl group is bulkier than methyl the latter strategy is usually preferred since the bridging is very sensitive to the nature of the alkyl substituents [13]. Although the length of the crown ether bridge greatly determines the cation selectivity of these calixarene based ionophores, the conformation of the calixarene skeleton around the binding site

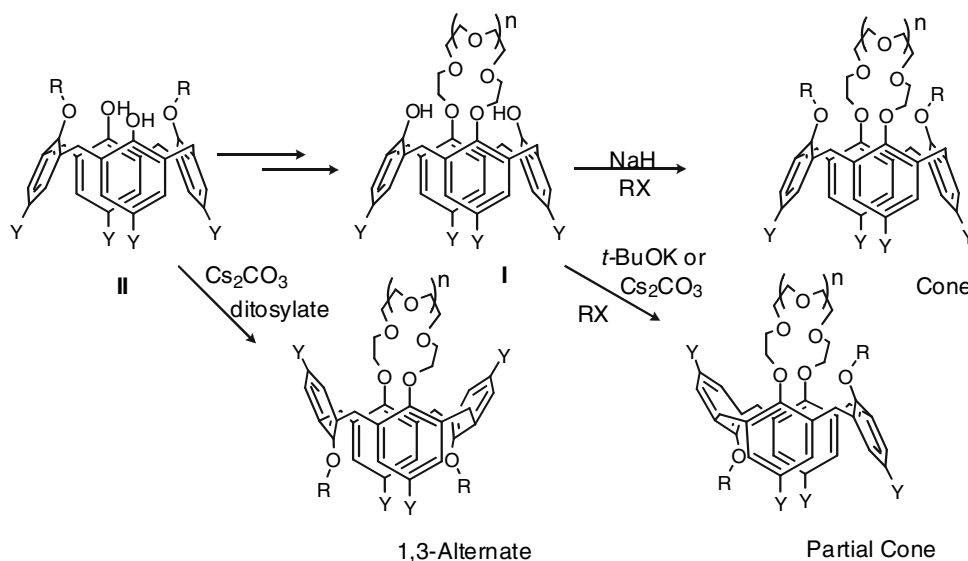
and the bulkiness of the alkoxy substituents also have a pronounced effect on the binding process [14].

Different methods have been developed to influence the conformation of the calix[4]crown ethers (Scheme 1). When 1,3-dihydroxycalix[4]crown ether (**I**) is dialkylated in the presence of sodium base cone isomer is obtained [15], while the use of potassium [16] or cesium [17] base gives the partial cone isomer. 1,3-Alternate conformation on the other hand can be achieved as a sole product by bridging the 1,3-dialkylated calix[4]arene (**II**) in the presence of Cs_2CO_3 , where the cesium cation serves as a template [12, 18]. Calix[4]crown ethers in the 1,2-alternate conformation were obtained by the reaction of 1,2-dialkylated-calix[4]arene with polyethylene glycol ditosylate in the presence of *t*-BuOK in toluene [19, 20]. This strategy, however, gave a mixture of isomers in cone and 1,2-alternate conformations and, it was observed that the nature of the crown ether moiety, as well as, the *p*-*tert*-butyl substituent at the upper rim of the calixarene skeleton were significant factors in determining the product distribution between these two conformers [20].

1,3-Bridged calix[4]crowns

The first calixcrowns, 1,3-*p*-*tert*-butylcalix[4]crown-5 [21] and crown-6 [1] ethers, were achieved by reacting *p*-*tert*-butylcalix[4]arene with one equivalent of tetra- or pentaethylene glycol ditosylate in the presence of two equivalents of *t*-BuOK in refluxing benzene, respectively. Both ligands were found to show ionophoric properties toward alkali metal cations. The reaction was later modified by Kim et al., who reported performing the mono bridging of calix[4]arene in the presence of one equivalent

Scheme 1 Schematic presentation of the different methods developed for the synthesis of 1,3-bridged calix[4]crown ethers in a specific conformation (Y = H, or *t*Bu)

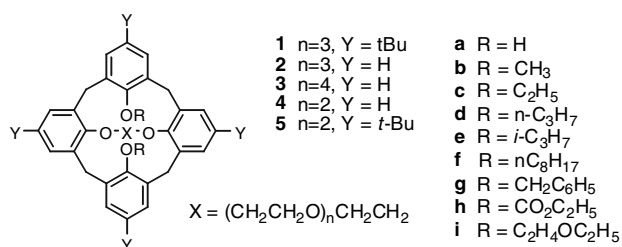


of K_2CO_3 as the base in refluxing acetonitrile with an improved yield of more than 70% [22].

Chang et al. were interested in the molecular recognition properties of these macrocycles toward alkyl and arylalkylamines [23, 24]. Based on their findings, *p*-*tert*-butylcalix[4]crown-6 showed significant extraction efficiency and increased selectivity in binding straight-chained alkylammonium picrates in the order of $H > Me > Et \approx Pr > Bu$, whereas with *p*-*tert*-butylcalix[4]crown-5, almost no selectivity and only poor extraction efficiency was detected, except for the ammonium guest [24]. In addition to the primary interaction between the crown ether bridge and the ammonium part of the guest, the molecular recognition ability of the calix[4]crown host was also attributed to the interaction of the alkyl moiety of the guest species with the calixarene backbone as was shown by NMR experiments [24].

Ungaro and co-workers prepared a series of 1,3-dialkoxy-*p*-*tert*-butylcalix[4]crown-5 ligands (Scheme 2), which showed selectivity toward potassium cation [13, 15]. The free 1,3-dimethoxy-*p*-*tert*-butylcalix[4]crown-5 (**1b**) was shown to exist in the cone conformation, but upon binding to potassium the conformation was changed to flattened partial cone as evidenced by both 1H NMR spectroscopy and X-ray crystallography [13]. The binding efficiency was greatly enhanced, however, by replacing the conformationally mobile methoxy groups by more bulkier ethyl, *n*-propyl and *i*-propyl substituents (**1c–e**) in a fixed partial cone conformation, which was explained by the preorganization of the host molecule [13]. The binding affinity was again decreased when benzyloxy substituent (**1g**) was used, as the calixarene skeleton was frozen in the cone conformation and could not adopt the more favorable partial cone conformation for binding potassium (Table 1). The X-ray crystal structure of the 1,3-diisopropoxy-*p*-*tert*-butylcalix[4]crown-5 (**1e**) complex with potassium picrate shows that potassium cation is coordinated to all five oxygen atoms in the crown ether ring and, to the rotated aromatic nucleus of calix[4]arene skeleton indicating the contribution of a cation– π interaction in the complex (Fig. 1) [25].

When 1,3-dimethoxy-calix[4]arene was used as a platform, it was observed that 1,3-alternate was the preferred



Scheme 2 Schematic presentation of 1,3-calix[4]crown ethers (**1–5**)

Table 1 Association constants ($\log K_a$) for the complexes of 1,3-calix[4]crown-5 derivatives **1** and **2** with potassium and sodium picrates in $CDCl_3$ [13, 15, 16]

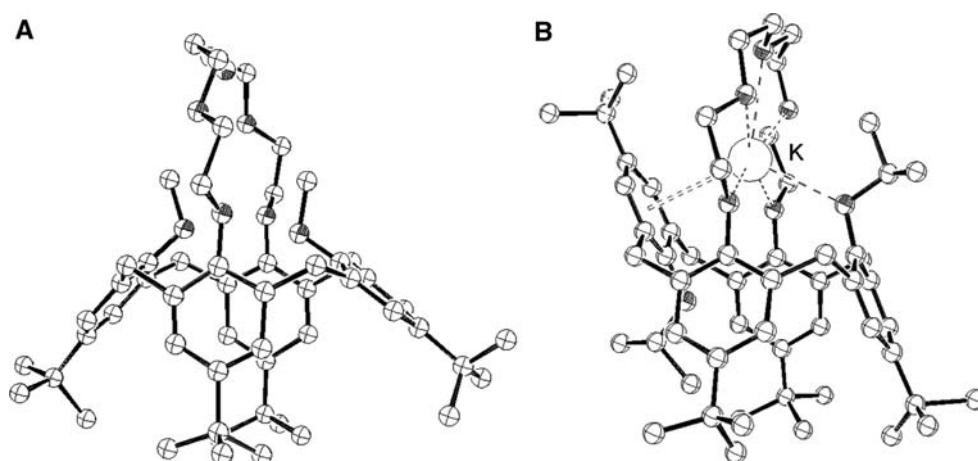
| Ligand | Conformation | K^+ | Na^+ |
|-----------|----------------|-------------------|-------------------|
| 1b | Mobile | 8.48 ^a | 5.04 ^a |
| 1c | <i>paco</i> | 9.95 ^a | 5.88 ^a |
| 1c | <i>1,3-alt</i> | 8.15 | 5.46 |
| 1d | <i>paco</i> | 8.72 ^a | 6.28 ^a |
| 1e | <i>paco</i> | 9.23 ^a | 5.43 ^a |
| 1g | <i>paco</i> | 7.11 ^a | 4.94 ^a |
| 2b | Mobile | 7.20 | 4.31 |
| 2c | <i>1,3-alt</i> | 9.77 | 4.38 |
| 2e | <i>1,3-alt</i> | 9.83 | 4.30 |
| 2e | <i>paco</i> | 8.90 | 4.74 |

^a The original K_a values have been converted to $\log K_a$ values to ease the comparison between the different ligands

conformation of 1,3-dimethoxy-calix[4]crown-5 (**2b**) upon binding potassium cation [16]. The same trend in the increase of the binding efficiency was observed as with the analogous *p*-*tert*-butylcalix[4]crown-5 ligands when the methoxy groups were replaced by ethyl and *i*-propyl substituents (**2c**, **e**) fixing the ligands in the 1,3-alternate conformation (Table 1). Although the selectivity and binding affinity between the corresponding unsubstituted and *p*-*tert*-butyl substituted calix[4]crown ligands toward potassium remained almost the same, the K^+/Na^+ selectivity was observed to be much higher with the unsubstituted calix[4]crown-5 derivatives [16]. This was explained by the less polar 1,3-alternate conformation, which hardly favors the complexation of Na^+ cation and, the cation– π interactions offered by two aromatic nuclei. The steric bulkiness of the *tert*-butyl groups at the *para* position when in 1,3-alternate conformation also cuts down the space around the binding site together with the alkoxy substituents, which make the partial cone conformation more acceptable in the case of *p*-*tert*-butylcalix[4]crown-5 derivatives [16, 25].

High Cs^+ selectivity was observed with calix[4]crown-6 ligands fixed in the 1,3-alternate conformation [12, 18]. Since alkyl substituents smaller than ethyl are free to interconvert between different conformational isomers, a set of calix[4]crown-6 ligands with *i*-propyl, *n*-propyl and *n*-octyl substituents (**3c**, **d**, **f**) were prepared by the reaction of 1,3-dialkoxy-calix[4]arene with pentaethylene glycol ditosylate in the presence of Cs_2CO_3 in acetonitrile to produce the ligands in a fixed 1,3-alternate conformation in more than 80% yields (Scheme 2) [12, 18]. The cesium ion was believed to act as a template during the cyclization reaction to influence the desired conformation. The properties of the ligands were compared with the conformationally mobile 1,3-dimethoxy-calix[4]crown-6

Fig. 1 Crystal structure of (a) the free ligand **1b** [13] and (b) the complex **1e** · KPic [25] showing the contribution of both O···K and cation– π interactions. (Hydrogen atoms were not determined in the original structure for (b), picrate anion has been omitted for clarity)



(**3b**) and 1,3-diisopropoxy-calix[4]crown-6 (**3d**) in the cone conformation [12]. As was shown by the liquid-liquid extraction and binding studies, the ligands **3a–d** fixed in the 1,3-alternate conformation were superior in terms of selectivity toward cesium cation, and, had especially high Cs⁺/Na⁺ selectivity (Table 2) [12, 26]. Also, the ligand **3d**, when in cone conformation, is more exposed to extensive solvation compared to the 1,3-alternate isomer and, in addition, blocks the cesium from the binding site by the bulky isopropyl groups, which attributes to the selectivity as well [14]. The crystal structure of the cesium picrate complex of **3d** reveals that cesium cation is coordinated to all six oxygen atoms provided by the crown ether bridge and to two rotated aromatic nuclei (Fig. 2) [12]. These findings suggest that the ligand is highly preorganized when in 1,3-alternate conformation and offers favorable cation– π interactions afforded by the aromatic nuclei of the calixarene skeleton to stabilize the complex. The cation– π interaction between the metal and the two aromatic rings that make up the walls of the binding site was also observed in solution by fluorescence spectroscopy measurements [27].

Moyer et al. discovered that di-dehydroxylated calix[4]crown-6 ethers in the 1,3-alternate conformation exhibited increased Cs⁺/K⁺ and Cs⁺/Rb⁺ selectivity compared to the 1,3-dialkoxy-calix[4]crown-6 derivatives

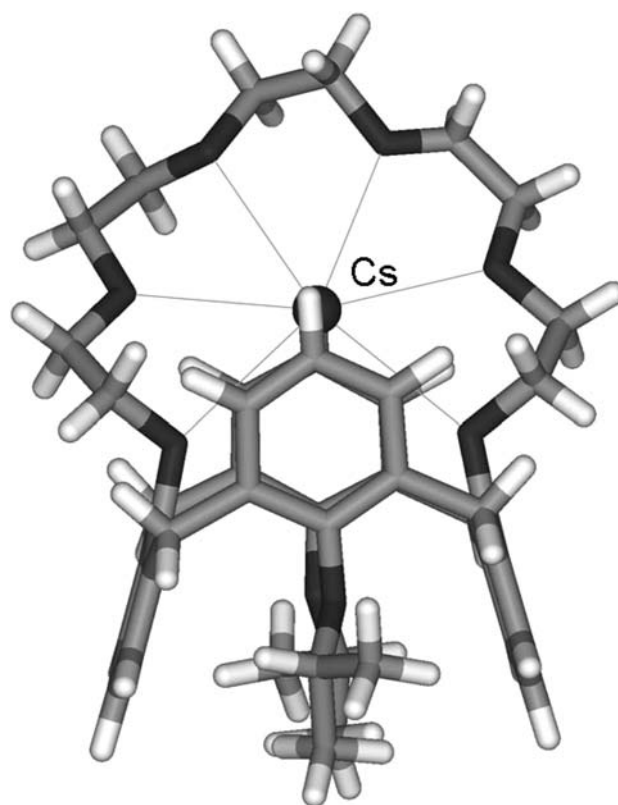


Fig. 2 Crystal structure of the complex **3e** · CsPic [12] in the 1,3-alternate conformation (picrate counter ion has been omitted for clarity)

Table 2 Association constants (log K_a) [12] for the complexes of 1,3-dialkoxy-calix[4]crown-6 derivatives **3** with cesium and sodium picrates in CHCl₃ and selectivity coefficients ($\alpha_{\text{Cs/Na}}$) [33]

| Ligand | Conformation | Cs ⁺ | Na ⁺ | $\alpha_{\text{Cs/Na}}$ |
|-----------|-----------------|-----------------|-----------------|-------------------------|
| 3a | Mobile | 6.0 | 4.3 | – |
| 3d | 1,3- <i>alt</i> | 8.6 | 5.1 | 10,500 |
| 3e | 1,3- <i>alt</i> | 8.8 | 5.2 | >28,500 |
| 3e | Cone | <4 | <4 | – |
| 3f | 1,3- <i>alt</i> | – | – | >33,000 |

[28, 29]. These findings showed that the selectivity in cation binding is not only affected by the number of the oxygen atoms in the crown ether bridge and by the conformation of the host but also by the appropriate modification of the substituents in the calixarene framework [29].

Shinkai and Yamamoto postulated that a shorter tetraethylene glycol bridge should provide a host with a smaller ionophoric cavity suitable for Li⁺ and Na⁺ cations [30].

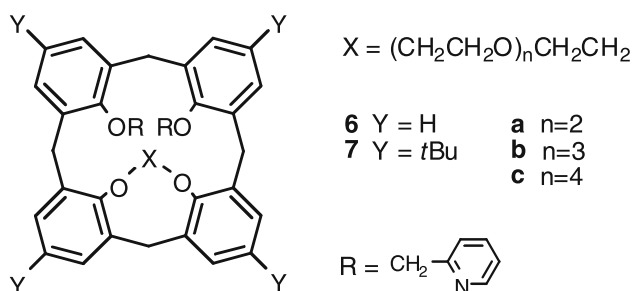
They prepared 1,3-bridged calix[4]crown-4 ethers (**4–5**; Scheme 2) by the reaction of tetraethylene glycol ditosylate with appropriate calix[4]arene in the presence of Na_2CO_3 followed by further modification by the addition of alkoxy substituents (ethyl, acetate and diethyl ether) affording ligands in cone, partial cone and 1,3-alternate conformations. Their selectivity measurements revealed that with ligand **4c** in the partial cone and ligand **5c** in the cone conformation the highest Na^+/K^+ selectivity was obtained, which was in the order of 10^5 as determined by ion selective electrodes (ISE) [30].

1,2-Bridged calix[4]crowns

Compared to 1,3-bridged calix[4]arenes, their 1,2-bridged regioisomers have been left to very little attention. This is probably due to the fact that their synthesis is not as straightforward and so far there hasn't been any feasible method to control their stereoselectivity.

Pappalardo and co-workers reported a synthetic strategy for the fabrication of 1,2-calix[4]crown ethers, which employed the selective 1,2-proximal dialkylation of the parent calix[4]arene followed by bridging with appropriate polyethylene glycol ditosylate in the presence of *t*-BuOK in refluxing toluene [19]. The resulting 1,2-dipicolylxy-calix[4]crowns (**6–7**) were afforded in a mixture of 1,2-alternate and cone conformations with an overall yield of 55–70% (Scheme 3) [19, 20]. It was observed that the presence of bulky *tert*-butyl substituents at the *para*-position of the calixarene framework played a role in the stereocontrol of the reaction, since the product distribution was shifted in the favor of the 1,2-alternate conformation in the absence of the *p*-*tert*-butyl groups with the longer polyether chains [19]. With the smaller triethylene glycol ditosylate, the reaction proceeded toward 1,2-alternate conformation regardless of the *para*-substituent of the calix[4]arene, which indicated the importance of the length of the polyether chain to the outcome of the stereochemistry in the reaction as well [20].

Complexation studies of 1,2-dipicolylxy-*p*-*tert*-butyl-calix[4]crown-5 (**7b**) with alkali metals showed that the



Scheme 3 1,2-Bridged calix[4]arenes (**6–7**)

selectivity of the ligand greatly depended on the conformation: cone isomer was selective toward K^+ , partial cone toward K^+ and Rb^+ and 1,2-alternate toward Cs^+ [31]. The picolylxy substituents were observed to contribute in the binding process as evidenced by NMR spectroscopy. The same trend in selectivity was also seen in the extraction experiments with alkali metal picrates. The efficiency and selectivity in binding alkali metal cations, however, was substantially smaller compared to the 1,3-bridged calix[4]arene derivatives [31].

Aromatic calix[4]crowns

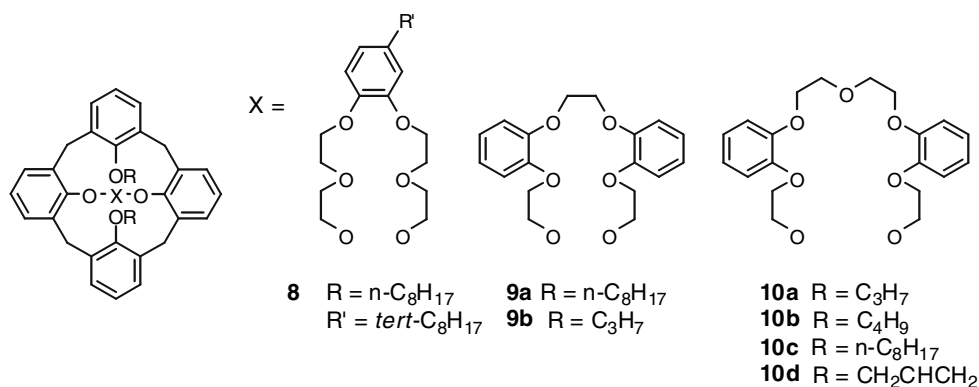
Introduction of aryl substituents into the polyether bridge has been observed to enhance the selectivity and efficiency of calix[4]crown-6 ethers with an increased lipophilicity by several authors. These improved features have been proven to be very important in using calixcrown based ionophores as selective cesium ion carriers [32, 33]. Incorporation of catechol spacers into the crown ether moiety replaces some of the sp^3 carbons by sp^2 ones, which rigidifies and flattens the glycolic bridge while making the ionophore more lipophilic and, therefore, more soluble in organic media [34]. Although the catechol unit does not influence the cesium binding directly, it disfavors the complexation of sodium cation as a result from the lower basicity of the catechol oxygens, and thereby, enhances the Cs^+/Na^+ selectivity [35, 36].

Kim et al. prepared a series of dibenzo derivatives of 1,3-dialkoxy-calix[4]crown-6 (**9b**) and crown-7 ethers (**10**) in the 1,3-alternate conformation (Scheme 4) [37, 38]. Their single ion transport studies through a bulk liquid membrane revealed that Cs^+/Na^+ selectivity was greatly enhanced with 1,3-dipropylxy-calix[4]crown-6 derivative (**9b**) by the addition of aromatic substituents in the crown ether moiety, while dibenzocrown-7 derivatives (**10**) showed only poor selectivity toward Cs^+ cation [38]. Ungaro and co-workers reported mono- and dibenzo derivatives of 1,3-dioctylxy-calix[4]crown-6 ethers (**8** and **9a**) [35]. Their observations were similar in the respect that the addition of aromatic spacers in the crown ether linkage improves the Cs^+/Na^+ selectivity of the parent calix[4]crown-6 ethers, although, the binding efficiency toward cesium was overall unaffected [35]. Enlarging the size of the crown ether moiety also decreased both the selectivity and efficiency to bind cesium cation, which in terms supports the importance of size complementarity in respect to selectivity [39].

Doubly bridged calix[4]arenes

Double bridging of calix[4]arenes gives rise to host molecules, which have two potential binding sites within the

Scheme 4 Mono- (**8**) and dibenzo (**9–10**) derivatives of calix[4]crown ethers



same molecule. These macrotricyclic compounds can be achieved by two different strategies: direct double bridging of the parent calix[4]arene [32] or stepwise bridging through a mono-bridged species [40]. The latter strategy enables the use of unsymmetrical crown units, thus, producing ditopic ligands with two distinctly different binding sites, whereas the direct method is often used with symmetrical calix[4]biscrown ethers, although the synthesis itself might be arranged in a stepwise fashion. The same regiocontrol as countered with mono-bridged calix[4]arenes applies to doubly crowned calix[4]arenes, i.e. the use of milder bases results in 1,3-bridged species while stronger bases give 1,2-bridged species [9]. 1,2-Bridged calix[4]biscrowns can exist in two different conformations: 1,2-alternate or cone [20]. For 1,3-bridged calix[4]crowns there is only one possible conformation, which is 1,3-alternate.

Symmetrical calix[4]bis-crowns

1,3-Alternate conformation

Asfari et al. described a synthetic strategy for 1,3-calix[4]biscrown ethers in the 1,3-alternate conformation, which entailed the reaction of calix[4]arene with 2–4 equivalents of the appropriate ethylene glycol ditosylate in the presence of excess K₂CO₃ in refluxing acetonitrile with yields ranging from 50 to 80% [32, 41, 42]. A number of 1,3-calix[4]biscrown-6 derivatives with different

substituents at the crown ether moiety were prepared by the same authors (Scheme 5) [32, 34, 43, 44].

Complexation studies showed that all calix[4]biscrown-6 derivatives (**11b**, **12–14**) had greater affinity toward cesium cation over the other alkali metal cations, but exhibited differences in Cs⁺/Na⁺ selectivity depending on the crown ether substituents [43, 45]. In general, the introduction of aromatic spacers in the crown ether loop decreased both the extraction ability and complex stability toward Na⁺ cation, thus, increasing the Cs⁺/Na⁺ selectivity, which was also the case with the mono-crown analogs (Table 3) [45]. In addition to increased lipophilicity, the aromatic subunits seem to add to better size complementarity in respect to cesium cation by rigidifying the crown ether unit, as well as, affecting the basicity of the donor oxygen atoms, which in part decreases the complex stability with sodium [43]. Biscrown-5 derivative (**11a**) showed higher extraction affinity toward K⁺ and Rb⁺ cations [46], as expected, but interestingly enough, formed stronger complex with cesium than did any of the bis-crown-6 derivatives except for the bis-dibenzocrown-6 (**13**) [45].

Although 1:2 complex formation was expected with calix[4]biscrown ethers with alkali metal cations compared to their mono-crown analogs, it was found that in solution a mixture of 1:1 and 1:2 complex species was evidenced by conductivity [47] and NMR [45, 48] measurements of calix[4]biscrown-6 derivatives with the larger alkali metal cations. The smaller lithium and sodium cations were observed to form only 1:1 complex species [47]. Mono-nuclear complexation was also observed in the liquid-

Scheme 5 Derivatives of calix[4]biscrown ethers (**11–15**) in the 1,3-alternate conformation

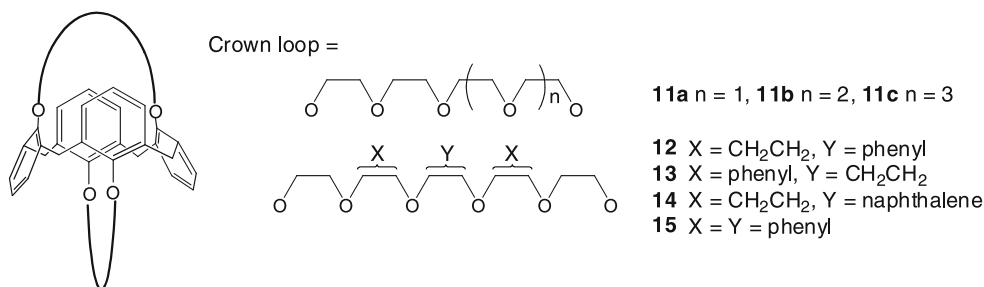


Table 3 Stability constants ($\log \beta_{11}$) [45] of the complexes of ligands **11**–**14** with cesium and sodium picrates in acetonitrile and selectivity coefficients ($\alpha_{\text{Cs}/\text{Na}}$) [32]

| Ligand | Cs ⁺ | Na ⁺ | $\alpha_{\text{Cs}/\text{Na}}$ |
|-----------------------|-----------------|-----------------|--------------------------------|
| 11a | 5.4 | 3.5 | – |
| 11b | 4.9 | 1.97 | 1,500 |
| 12 | 4.9 | 1.5 | 19,000 |
| 13^a | 6.3 | <1 | – |
| 14 | 4.9 | 1.4 | 29,000 |

^a From Ref. [43]

liquid extraction experiments of the ligands with alkali metal cations [32, 45]. Cesium complexation studies performed by ¹³³Cs and ¹H NMR spectroscopy to gain more information on complexation mechanism revealed that, in a 1:1 complex, the cesium cation is able to shuttle from one binding site to the other through the π -basic calixarene cavity [48a]. Upon excess amount of the cation, both binding sites become occupied resulting in a symmetrical binuclear complex [48].

X-ray crystal structure analyses of calix[4]biscrown-6 derivatives (**11b**, **12**–**14**) confirmed the existence of both mono- and binuclear species upon complexation with cesium [48]. The most striking evidence obtained from the crystal structures of the solvent adducts of the free ligands [43, 48, 49] compared with their complexed species [43, 48, 50] was that the changes encountered in the conformation of the ligand upon binding to cesium were relatively small (Fig. 3). The complexing mode and the environment of the cesium ion was similar in fashion to the structure obtained with the mono-crown analog (Fig. 2) and, comparable within the complexes of the different biscrown-6 derivatives. These results clearly showed that the calix[4]biscrown-6 ligands are highly preorganized and offer a perfect fit for cesium cation. However, it should be

mentioned that the crown ether moieties of the ligands are highly flexible and adopt different conformations when there are no interacting ions or solvent molecules present, which has been found to be the case with less polar solvents [48b, 51]. In these cases, some conformational reorganization of the ligand is required for binding to take place [51].

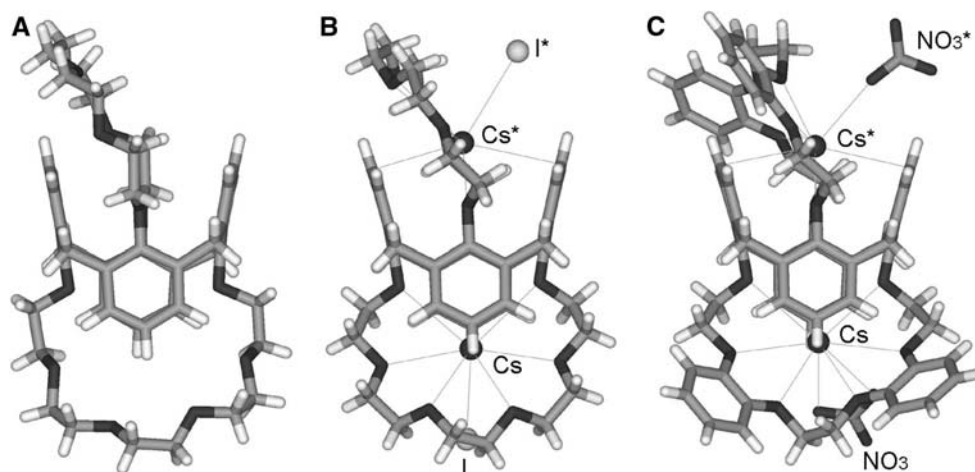
The mono-nuclear potassium complex of calix[4]biscrown-6 (**11b**) was very similar in structure to the cesium complexes of biscrown-6 derivatives, although, the binding mode was somewhat less optimal for potassium and lacked the cation– π interaction with the calixarene cavity as was shown by X-ray crystal studies [52]. The binuclear sodium complex on the other hand differed greatly from the respective cesium complex, and particularly was shown to coordinate to only three oxygen atoms at the end of the crown ether ring and, additionally to a water molecule inside the cavity [52].

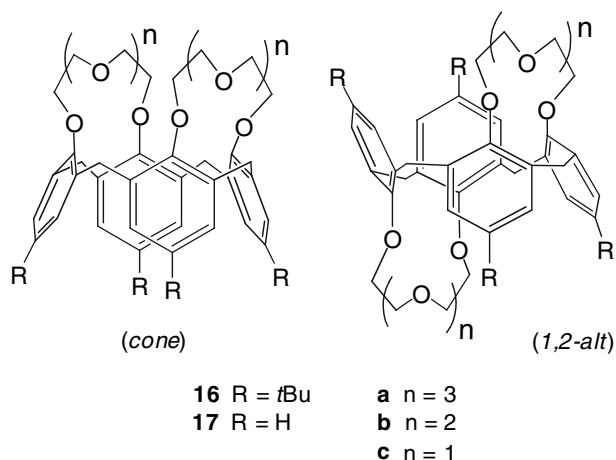
Enlarging the crown ether moiety to contain 7 oxygen atoms was observed to decrease the cesium extraction ability for both calix[4]biscrown-7 [53] and dibenzo calix[4]biscrown-7 [34] ligands in the 1,3-alternate conformation, which emphasizes the importance of the ring size in respect to the cation complementary.

Cone and 1,2-alternate conformations

Arduini et al. reported that selective dealkylation protocol afforded 1,2-*p*-*tert*-butylcalix[4]crown-5 ether in a cone conformation [54]. The method included introducing tetraethylene glycol bridge to a parent 1,2-dimethoxy-*p*-*tert*-butylcalix[4]arene in the presence of *t*-BuOK in refluxing benzene according to the standard procedure. Demethylation of the methoxy groups followed by the second bridging finally gave 1,2-*p*-*tert*-butylcalix[4]biscrown-5 (**16a**) [54] (Scheme 6).

Fig. 3 Crystal structures of (a) the free **11b** [48b] and (b) of the binuclear cesium complexes **11b**·2CsI [50a] and (c) **13**·2CsNO₃ [43] in the 1,3-alternate conformation. Solvent molecules are omitted for clarity





Scheme 6 1,2-Calix[4]biscrown ethers (**16–17**)

Direct synthetic strategy using *p*-*tert*-butylcalix[4]arene as the scaffold was observed to give different stereoisomers depending on the reaction conditions. The reaction of *p*-*tert*-butylcalix[4]arene with two equivalents of triethylene glycol ditosylate using NaH as the base in DMF gave 1,2-*p*-*tert*-butylcalix[4]biscrown-4 (**16b**) ether in the cone conformation with 45% yield, whereas, performing the same reaction in the presence of *t*-BuOK in toluene afforded the ligand in 1,2-alternate conformation in 40% yield [55, 56]. The stereochemical control was explained by the cation template effect, in which sodium coordination favors the cone conformation, while the 1,2-alternate conformation affords better environment for potassium through the added cation- π interaction. With longer tetraethylene glycol ditosylate the same reaction using *t*-BuORb as the base in toluene gave 1,2-*p*-*tert*-butylcalix[4]biscrown-5 (**16a**) in a cone conformation, whereas, a stepwise protocol using NaH in DMF in the first bridging followed by *t*-BuOCs as the base in toluene in the second step, resulted in 1,2-alternate conformation as the major isomer [55]. Interestingly, using unsubstituted calix[4]arene as the platform, both direct and stepwise methods afforded only the cone isomer regardless of the base used [55]. This was in contradiction to the results obtained by Pappalardo et al., which showed that a stepwise method using 1,2-

calix[4]crown-4 as the platform gave a mixture of products in cone and 1,2-alternate conformations using *t*-BuOK as the base in toluene in the bridging reaction [20]. The ratio between the two stereoisomers was shown to be dependent on the length of the bridging agent as the amount of 1,2-alternate conformation increased with longer polyethylene glycol ditosylates [20]. Asfari et al. isolated the unsubstituted 1,2-calix[4]biscrown-5 (**17a**) in a cone conformation as a result of the reaction of calix[4]arene with two equivalents of tetraethylene glycol ditosylate in acetonitrile in the presence of large excess of Cs₂CO₃, although from a mixture of products and with only 9% yield [57].

Unsymmetrical calix[4]bis-crowns

The synthesis of an unsymmetrical calix[4]biscrown proceeds in a stepwise fashion through a mono-crown derivative, to which the second crown loop is then added according to the standard procedures [58]. The first bridging step is usually carried out in the presence of K₂CO₃ in refluxing acetonitrile, whereas the second step has been reported done in the presence of K₂CO₃ [58] or Cs₂CO₃ [22] as the base. The attachment of two different crown bridges in calix[4]arene enables the investigation of the factors controlling the cation selectivity in respect to the different substituents in each of the crown loop [40].

Kim et al. were interested in the influence of the crown size on metal ion recognition. They prepared a series of unsymmetrical calix[4]biscrown ethers (**18**) in the 1,3-alternate conformation, in which the crown size i.e., the number of oxygen atoms was different in the two crown loops (Scheme 7) [22]. Two phase extraction and bulk liquid membrane transport experiments showed that the ligand **18b** with crown-5 (and crown-7) moiety exhibited selectivity toward potassium and the ligand **18c** with crown-6 (and crown-7) moiety had selectivity over cesium cation, as expected (Table 4). Ligand **18a** with both crown-5 and crown-6 bridges incorporated in the same framework, on the other hand, had controversial results: whereas extraction experiments showed preference over potassium

Scheme 7 Unsymmetrical calix[4]biscrown derivatives in the 1,3-alternate conformation (**18–22**)

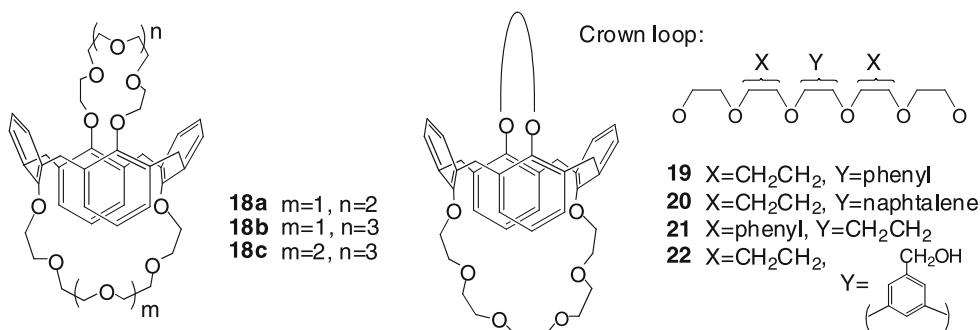


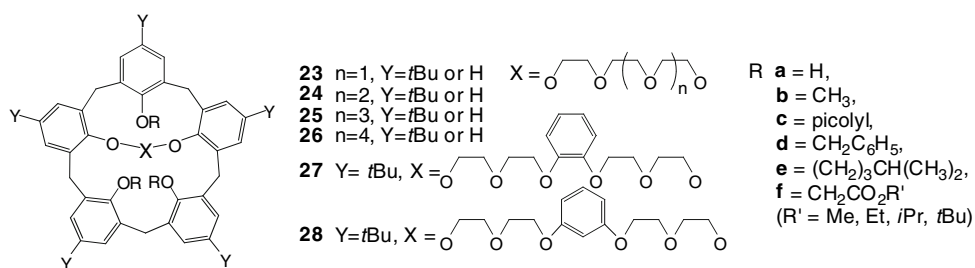
Table 4 Association constants (Log K_a) for the unsymmetrical calix[4]biscrown ligands with alkali metal picrates [22]

| Ligand | Cs ⁺ | K ⁺ | Na ⁺ |
|-----------------------|-----------------|----------------|-----------------|
| 11a | – | 9.48 | 7.94 |
| 11b | 9.08 | – | 6.42 |
| 18a | 8.74 | 9.57 | 7.94 |
| 18b | 7.72 | 9.65 | 8.03 |
| 18c | 8.51 | 7.51 | 7.66 |
| 21^a | 9.28 | – | 6.45 |

^a From Ref. [60]

cation, cesium, in turn, was favored in the liquid membrane transport studies [22]. The ditopic nature of the ligand **18a** was finally revealed by X-ray crystallographic and NMR spectroscopic analyses, which showed that the complexation of potassium occurred in the crown-5 cavity and that of cesium in the crown-6 cavity of the macrocycle, respectively [59]. The same ligand also formed a 1:2 complex with two potassium cations, in which the potassium cation in the crown-6 loop interacted more with the crown ether part of the binding site. Based on these studies the authors concluded that the driving force for the complex formation comes from the electrostatic interaction between the cation and the crown ether oxygen atoms, whereas the cation- π interaction offered by the π -orbitals of the two rotated aromatic rings is a minor factor [59].

The effect of the aromatic substituent in the crown ether bridge on selectivity toward cesium was explored by the aid of the unsymmetrical calix[4]biscrown-6 ligands **19–22** [40, 58, 60]. NMR spectroscopy and X-ray crystallography were used to study the complexation behavior of cesium in detail. Changes in the proton chemical shifts of the ligands **19–21** upon complex formation confirmed that cesium was located in the modified crown cavity [40, 60]. The same preferential was observed in the crystal structure of ligand **19** with cesium picrate, showing the complexed cesium only in the modified crown loop (Fig. 3c) [40]. In the crystal structure of ligand **21** with cesium picrate it was evident that cesium was complexed in both of the crown ether pockets, but based on structural analysis it was concluded that cesium was more tightly encapsulated by the crown loop with the aromatic substituents [60].

Scheme 8 1,3-calix[5]crowns (**23–28**)

Higher calix[n]crowns

The ionophoric properties of calixcrowns in terms of selectivity and efficiency toward alkali metal cations have been attributed to the size of the crown ether moiety and to the conformation of the calixarene framework. In addition, the size of the macrocyclic cavity formed by the calixarene can also be influenced by employing higher calix[n]crowns with larger cavities. This, however, adds to the possible regioisomers formed as the number of the oxygen atoms available for the bridging increases by the size of the calix[n]arene used. The bridging also constrains the mobility of the larger calix[n]arene skeleton, which is an important factor in preorganization of the host molecule and, therefore, in selectivity and efficiency in the complexation process.

Calix[5]crowns

The reaction of the parent calix[5]arene ($Y = H$ or tBu) with one equivalent of the appropriate glycol ditosylate in the presence of CsF in refluxing acetonitrile afforded the 1,3-bridged calix[5]crowns (**23a–28a**) in moderate to excellent yields (Scheme 8) [61, 62]. In the case of the longer hexaethylene glycol ditosylate, the 1,2-bridged isomer was also obtained [61]. Subsequent alkylation of the ligands gave the 2,4,5-trialkoxy-1,3-calix[5]crown derivatives. 1H NMR spectroscopic characterization of the ligands provided the evidence of the existing cone conformation [62].

The binding properties of the calix[5]crowns toward alkali metal cations were investigated by means of liquid-liquid extraction and complexation experiments [62]. The studies revealed few interesting aspects compared to the calix[4]crown analogs. All trimethoxy-calix[5]crown ethers studied (**23b–27b**) showed a preference toward cesium regardless of the size of the crown bridge, although, it seemed to have an effect on the efficiency of the ligands in the order of crown-5 > -4 > -6. The best selectivity and efficiency toward cesium was observed with the trimethoxy-1,3-*p-tert*-butylcalix[5]crown-5 (**24b**), which was quite different from the results obtained for the calix[4]-crown analogs [62].

Pappalardo and Parisi studied the binding properties of the 2,4,5-trialkoxy-1,3-*p*-*tert*-butylcalix[5]crown-6 (**25**) derivatives in the cone conformation toward alkyl ammonium picrates [63]. The calix[5]crown macrocycle possesses two distinct binding sites: the hydrophilic crown ether pocket and the preorganized hydrophobic calix[5]-arene cavity. This arrangement was observed to give two binding modes, *endo*- and *exo*-cavity binding, which also served as the primary factor controlling the selectivity between the linear and branched alkyl ammonium cations together with steric effects brought by the bulkiness of the alkoxy substituents, as well as, the *p*-*tert*-butyl group in the upper rim of the calix[5]crown ligand [63]. NMR spectroscopic investigations showed trialkoxy-1,3-*p*-*tert*-butylcalix[5]crown-6 ligands to be selective toward linear alkyl ammonium cations, which were complexed preferentially in the *endo*-cavity formation with the ammonium part pointing toward the crown ether end of the ligand, whereas, branched alkyl ammonium cations were shown to form 1:1 *exo*-complexes exclusively [63]. The triether derivatives of the parent *p*-*tert*-butylcalix[5]crown-6 (**25b–e**) were more selective compared to the triester derivatives (**25f**), which displayed both *endo*- and *exo*-cavity binding upon complexation with the alkyl ammonium cations [63c].

Calix[6]crowns

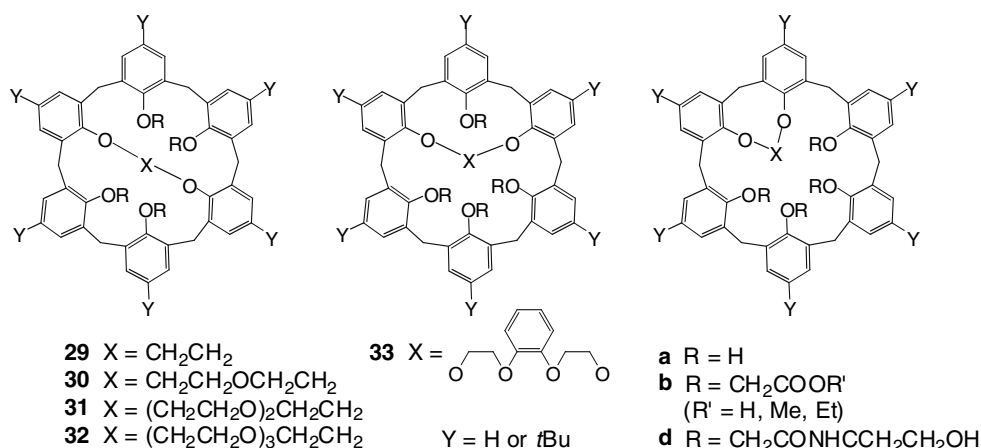
The mono-bridging of calix[6]arene can result in three different regioisomers: 1,2-, 1,3- or 1,4-bridged calix[6]-crown ethers. As a result of the large calix[6]arene cavity, the mono-bridged species can adopt different conformations, depending on the alkoxy substituent used, which needs to be larger than acetate group in order to prevent through the annulus rotation of the aromatic rings and freeze the conformation [66a]. Casnati et al. were able to

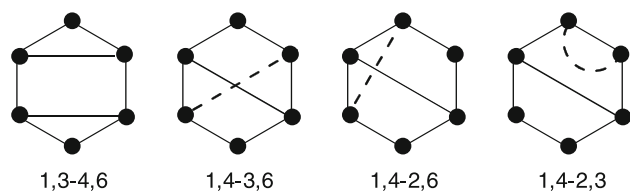
achieve 1,4-calix[6]crown-5 ethers (Y = H or *t*Bu) by reacting the parent calix[6]arene with one equivalent of tetraethylene glycol ditosylate in the presence of *t*-BuOK in benzene with moderate yields (Scheme 9) [64]. Chen et al. investigated the influence of the reaction conditions on the regioselectivity of the products [65]. The reaction of *p*-*tert*-butyl-calix[6]arene with one equivalent of polyethylene glycol ditosylate in the presence of 8–10 equivalents of K₂CO₃ as the base in refluxing acetonitrile gave only 1,2-calix[6]crown-2 and 1,4-calix[6]benzocrown-4 ethers as the sole products in low yields, whereas with all the other polyethylene glycol ditosylates investigated, mixtures of different regioisomers were obtained [65]. However, when the reaction of the parent calix[6]arene with triethylene glycol ditosylates was carried out in refluxing toluene in the presence of K₂CO₃, the 1,4-bridged species were obtained exclusively with moderate yields [66]. Subsequent alkylation or acetylation of the phenolic oxygens provided the tetra substituted 1,4-calix[6]crown ligands in the cone conformation [64, 66].

The complexation properties of 1,4-*p*-*tert*-butylcalix[6]crown-4 (**31**) and -benzocrown-4 (**33**) ligands were investigated toward alkali metal cations [66]. Although, the ligands showed very poor affinity toward any of the alkali metal cations, their tetraester derivatives were far better extractants and showed higher affinity toward the smaller lithium and sodium cations. In addition, the tetraester derivative of 1,4-*p*-*tert*-butylcalix[6]crown-4 (**31b**) showed high selectivity toward sodium, whereas, remarkable lithium selectivity was observed with the tetraester derivative of 1,4-*p*-*tert*-butylcalix[6]benzocrown-4 (**33b**) [66].

Calix[6]biscrown ethers can be obtained via the same direct or stepwise synthetic strategies as their calix[4]biscrown analogs, although, the number of possible regioisomers is much higher (Scheme 10). Blanda et al. used the direct double bridging strategy in the reaction of 1,4-diallyloxy-calix[6]arene with triethylene glycol ditosylate in

Scheme 9 Calix[6]crown ethers (**29–33**)





Scheme 10 Schematic presentation of the double bridging patterns of calix[6]biscrowns (only the four isolated patterns of the possible eight are shown)

THF/DMF (90:10) using NaH as the base [67]. The reaction gave 1,4-diallyloxy-calix[6]-2,6-3,5-biscrown-4 ether in a mixture of cone and 1,2,3-alternate conformations with 20–30% yield. Both stereoisomers were observed to have high selectivity and affinity to bind cesium as 1:1 complex, which was evidenced by NMR and mass spectroscopy, X-ray crystallography and liquid–liquid extraction experiments. However, the selectivity of the cone conformer was distinctively higher compared to that of the 1,2,3-alternate conformation [67]. Recently, a one-step synthesis for the preparation of *p*-*tert*-butylcalix[6]-1,4-2,5-biscrown-4 in more than 60% total yield was reported by using two equivalents of triethylene glycol ditosylate and three equivalents of K_2CO_3 in refluxing xylene [68].

Chen and others were successful in preparing calix[6]biscrowns in a stepwise fashion starting from the mono-bridged calix[6]crown ether [69, 70]. The second bridging was then achieved by using NaH as the base in DMF at 70 °C with moderate to excellent yields. This route can result in symmetrical or unsymmetrical calix[6]biscrowns depending on the nature of the second bridging agent used. The reaction of the parent 1,4-calix[6]crown-4 ($Y = H$ or *t*Bu) with triethylene glycol ditosylate produced the symmetrical calix[6]-1,4-2,5-biscrown-4 ethers ($Y = H$ or *t*Bu) exclusively [69–71].

The use of different polyethylene glycol ditosylate in the second bridging afforded unsymmetrical calix[6]biscrown ethers with varying regiochemistry in respect to the 1,4-link of the first bridge: Ko et al. reported 1,4-2,5-bridging pattern [71] with 1,4-calix[6]crown as the parent, whereas Chen and Lo were able to get 1,4-2,6- 1,4-2,5- or 1,4-2,3-bridged species [70, 72] using the parent 1,4-*p*-*tert*-butylcalix[6]crown as the starting calix[6]arene mono-crown.

Liquid–liquid extraction studies of the calix[6]biscrown ethers, in general, showed a greater affinity toward the larger alkali metal cations potassium and cesium. However, alkylation or acetylation of the *p*-*tert*-butylcalix[4]-1,4-2,5-biscrown-4 in the alternate conformation afforded the *syn*/*anti*-3,6-dialkoxy-*p*-*tert*-butylcalix[4]-1,4-2,5-biscrown-4 [73]. It was observed that the Cs^+/Na^+ selectivity and affinity was greatly improved with the diester derivative in *syn* orientation compared to the respective unsubstituted

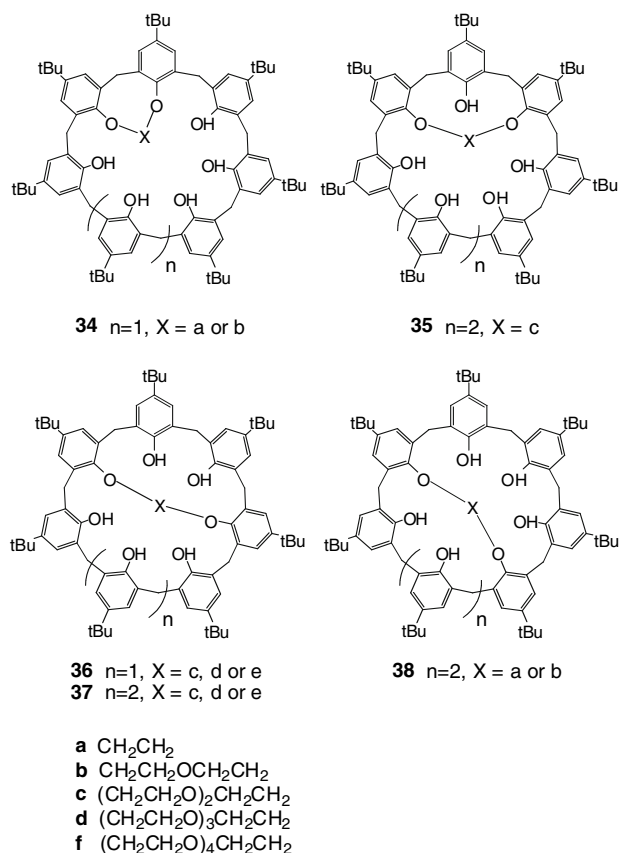
calix[6]biscrown-4 [73]. The complex stoichiometry was shown to be 1:1 by mass spectroscopy analysis.

Calix[7]- and calix[8]crowns

The chemistry of the higher calix[7]- and calix[8]crowns may be attributed to the extensive research done by Neri and collaborators in this field [74–82]. The synthesis of the first calix[8]crown was based on the strategy to use 1,3,7,5-tetrasubstituted *p*-*tert*-butylcalix[8]arene as the platform, since the preliminary investigations to use the unsubstituted *p*-*tert*-butylcalix[8]arene were unsatisfactory. Thus, the slow addition of three equivalents of tetraethylene glycol ditosylate in the mixture of 1,3,7,5-tetraalkoxy derivative of *p*-*tert*-butylcalix[8]arene and Cs_2CO_3 in THF afforded the tetrasubstituted *p*-*tert*-butylcalix[8]-1,3-5,7-biscrown-5 as the major isomer in more than 50% yield [74]. Since then, Neri and group were able to find the right reaction conditions in order to employ the unsubstituted *p*-*tert*-butylcalix[8]arene in the intramolecular bridging reaction to produce mono- and doubly bridged calix[8]arenes in a regiocontrolled way [75].

The major factor determining the outcome of the bridging mode was ascribed to the base used and its strength to deprotonate the parent calix[8]arene in order to form the intramolecular polyethylene glycol bridge [76]. The mono-bridging of calix[8]arene can lead to four different regioisomers: 1,2-, 1,3-, 1,4- or 1,5-calix[8]crown (Scheme 11). The reaction of *p*-*tert*-butylcalix[8]arene with polyethylene glycol ditosylate in the presence of a strong base, NaH or KH, in THF/DMF (10:1) resulted in 1,4-bridged (**37**) ligand, which was explained by the intermediate 2,4,6,8-tetraanion formed. When moderate Cs_2CO_3 was used as the base in DMF, the reaction gave 1,5-bridged species (**38**) with high yield through the intermediate 3,5,7-trianion. Finally, the use of a weaker K_2CO_3 as the base in refluxing acetonitrile afforded the 1,3-bridged ligand (**35**) as a major product, which was assigned to the 3-monoanion intermediate [75a, 76].

As for the other calix[*n*]biscrowns discussed above, the double bridging can be achieved via direct or stepwise methods. The reaction of the parent 1,4-*p*-*tert*-butylcalix[8]crown-4 (**37c**) with one equivalent of triethylene glycol ditosylate in acetone gave *p*-*tert*-butylcalix[8]-1,4-2,5-biscrown-4 as the major isomer and *p*-*tert*-butylcalix[8]-1,4-2,7-biscrown-4 as minor component with 38 and 14% yields, respectively [75b]. When the reaction was run in THF/DMF using KH as the base, small amount of *p*-*tert*-butylcalix[8]-1,4-5,8-biscrown-4 isomer was obtained. Stepwise method was also applied in the preparation of *p*-*tert*-butylcalix[8]-1,5-3,7-biscrown-3 (**39a**), which involved the use of Cs_2CO_3 as the base in DMF in the first

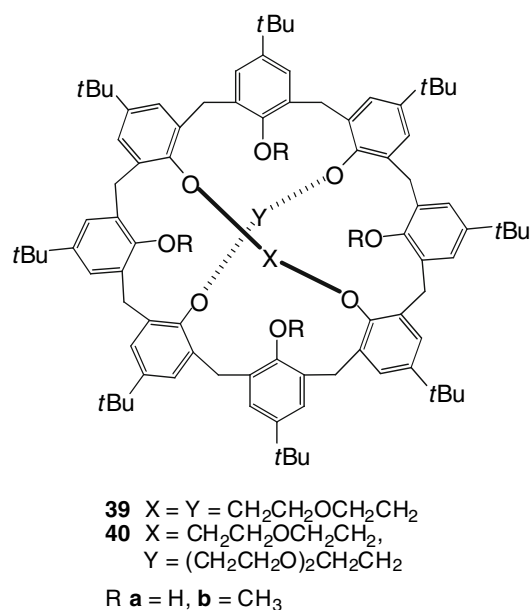


Scheme 11 Calix[7]- and calix[8]crown ethers (**34–38**)

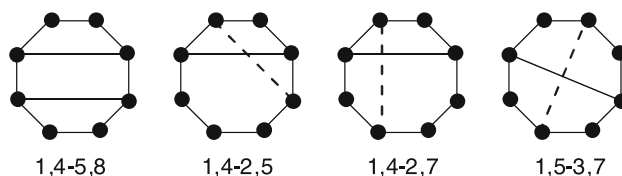
step and NaH as the base in DMF/THF in the second step (Scheme 12) [77]. Although the stepwise method produced the desired ligand in excellent yield, the direct method using NaH as the base gave the ligand in poor yield.

Two-phase extraction studies of the ligand **38a** showed affinity toward all alkali metal picrates, although, the ligand had superior preference toward cesium cation in addition to high Cs^+/Na^+ selectivity [77a]. For the tetramethoxy derivative of *p*-tert-butylcalix[8]-1,5-3,7-biscrown-3 (**39b**) the binding affinity decreased substantially along with the Cs^+/Na^+ selectivity [77a]. Based on the same synthetic strategy and conditions, unsymmetrical *p*-tert-butylcalix[8]-1,5-crown-3-3,7-crown-4 (**40**) was obtained, although the yield was only 10% [78] (Scheme 13).

With calix[7]crowns there are three possible stereoisomers formed: 1,2-, 1,3- and 1,4-bridged species. The reaction of *p*-tert-butylcalix[7]arene with shorter ethylene and diethylene glycol ditosylates in the presence of K_2CO_3 in refluxing acetonitrile afforded 1,2-*p*-tert-butylcalix[7]crown-2 and -3 ethers (**34**) as major isomers in 20 and 25% yields, respectively [79]. With two equivalents of the longer tri-, tetra- and pentaethylene glycol ditosylates using Cs_2CO_3 as the base in refluxing acetone, the same reaction gave 1,4-*p*-tert-butylcalix[7]crown-4, -5 and -6 ethers (**36**)



Scheme 12 *p*-tert-Butylcalix[8]-1,5-3,7-biscrowns (**39–40**)



Scheme 13 Schematic presentation of the double bridging patterns of calix[8]biscrowns (only the four isolated patterns are shown from the total of nine possible)

in **75**, **30** and **20%** yields, respectively [79]. Both direct and stepwise double bridging of *p*-tert-butylcalix[7]arene with diethylene glycol ditosylate in the presence of Cs_2CO_3 in refluxing acetone afforded *p*-tert-butylcalix[7]-1,4-2,3-biscrown-3 in excellent yield [80].

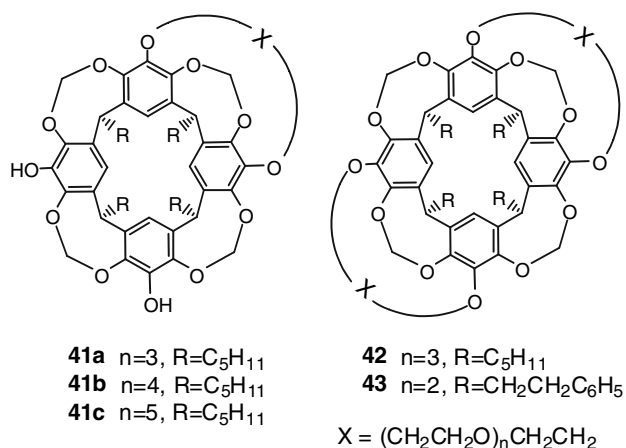
The singly bridged 1,4-calix[7]crown-4 (**36c**) and 1,5-calix[8]crown-3 (**37b**) ligands were shown to have a conformational template effect upon reacting with alkali metal carbonates in DMF at 70 °C forming LM^+ salts as evidenced by NMR spectroscopy and X-ray crystallography [81, 82]. The alkali metal cations act as templates, around which the calixarene skeleton is folded in a tub-shaped conformation. With 1,5-calix[8]crown-3 (**37b**) the effectiveness of templation was observed to be higher with cesium, whereas with 1,4-calix[7]crown-4 (**36c**) it was higher with potassium and rubidium cations [81, 82].

Resorcinarene crowns

Resorcinarenes or calix[4]resorcinarenes belong to the family of calixarenes and share a lot of common features in their

chemistry. The difference between these two macrocycles is the repeating aromatic unit in their framework: calixarenes are built from phenols, whereas, resorcinarenes are composed of resorcinol units. When considering intramolecular bridging of the phenolic oxygens with polyethylene glycol chains, the very essential difference between resorcinarenes and calixarenes come into play—the number of oxygen atoms available for bridging. In addition, the hydroxyl groups are situated on the upper rim of the resorcinarene framework, which enables the crown ether bridging on the open end of the cavity.

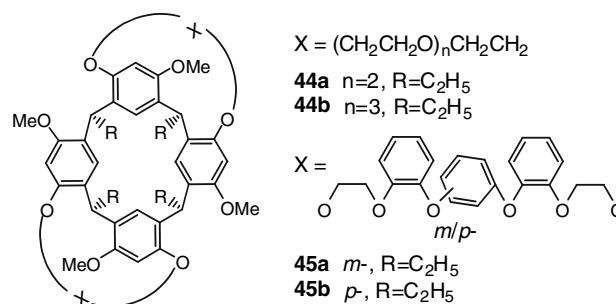
Reinhoudt et al. used a tetrahydroxy resorcinarene cavitand (R_5H_{11}) as the platform (Scheme 14), which offered four hydroxyl groups for intramolecular bridging [83]. The mono-bridging, thus, can result in two different regioisomers, 1,2-bridged or 1,3-bridged resorcinarene cavitands. The same base promoted intramolecular cyclization strategy as depicted for calix[4]crowns was employed, and the reaction of tetrahydroxy resorcinarene cavitand with one equivalent of pentaethylene glycol ditosylate in the presence of sodium base, NaH or Na_2CO_3 , in DMF afforded the 1,2-crown[5]cavitand (**41b**) [84] in 20–30% yield, although, with equal amount of the unreacted starting cavitand. With the longer hexaethylene glycol ditosylate as the bridging agent in the presence of NaH in DMF 1,2-crown[6]cavitand (**41c**) was obtained with a reasonable yield, whereas, with shorter tetraethylene glycol ditosylate the reaction did not proceed at all. The use of K_2CO_3 or Cs_2CO_3 as the base in DMF gave the bis-crown[5]cavitand (**42**) as the major isomer, although in relatively low yield [83]. Kang et al. succeeded in preparing bis-crown[4]cavitand (**43**) in 25% yield by treating the parent tetrahydroxy resorcinarene cavitand ($R = CH_2CH_2C_6H_5$) and three equivalents of triethylene glycol ditosylate with K_2CO_3/Cs_2CO_3 in DMA [85]. Liquid-liquid extraction and bulk liquid membrane studies with alkali metal picrates showed that the ligand had a preference toward sodium with high Na^+/K^+ selectivity [85].



Scheme 14 1,2-crown[n]cavitands and bis-crown[n]cavitands (**41–43**)

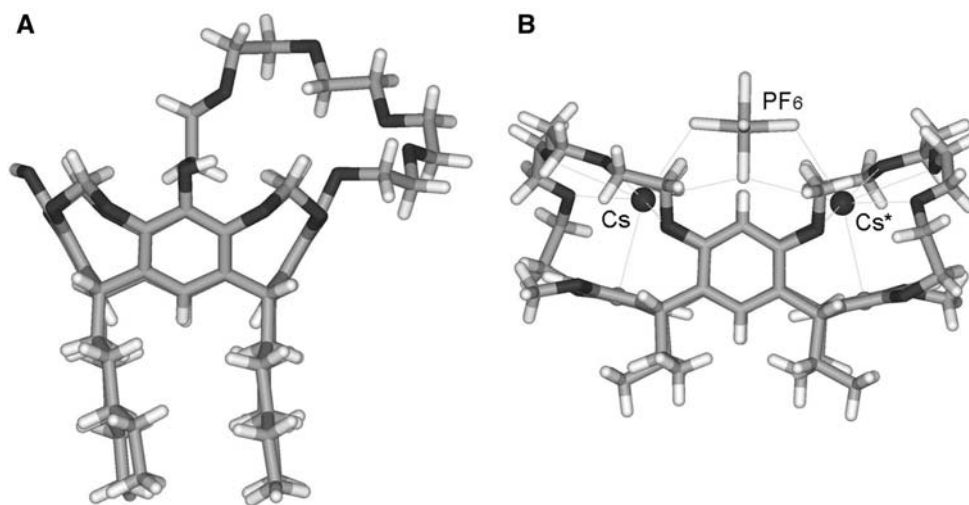
Salorinne and Nissinen had a different approach in obtaining resorcinarene bis-crown ethers. They decided to employ tetrasubstituted resorcinarene as the platform, which had only four hydroxyl groups available for intramolecular bridging, thus, narrowing down the number of possible isomers [86]. The reaction of tetramethoxy resorcinarene ($R = C_2H_5$) with two equivalents of tri- or tetraethylene glycol ditosylate in the presence of Cs_2CO_3 in DMF afforded tetramethoxy resorcinarene bis-crown-4 (**44a**) and bis-crown-5 (**44b**) in 20% yields (Scheme 15). In comparison to crown[n]cavitands, in which the resorcinarene skeleton is locked in the crown conformation, tetramethoxy resorcinarene bis-crown ethers adopt a boat conformation having two binding sites on the same side of the cavity bottomed with an aromatic unit belonging to the resorcinarene core (Fig. 4).

Complexation studies revealed that tetramethoxy resorcinarene bis-crown-5 formed 1:2 (ligand:cation) complexed species with the larger alkali metal cations with preference to cesium, as was evidenced by NMR spectroscopy and X-ray crystallography (Fig. 4) [86, 87]. The crystal structure of the tetramethoxy resorcinarene bis-crown-5 complex with cesium hexafluorophosphate revealed that the cation was coordinated to the crown ether oxygens in a similar manner as was observed with calix[4]crown complexes. In addition, the complex was stabilized by the cation– π interactions offered by the resorcinarene cavity (Fig. 4) [87]. The addition of aromatic substituents in the crown ether moiety was believed to enhance the selectivity of the ligand (**45**) toward cesium by offering more favorable cation– π interactions. In fact, the addition of three aromatic spacers in the crown ether bridge did increase the selectivity of the ligand **45a** toward cesium, although, the efficiency was decreased [87]. This was explained by the better shape and size selectivity offered by the crown-5 pocket compared to the tribenzo-crown-6 derivative.



Scheme 15 Tetramethoxy resorcinarene bis-crown ethers (**44–45**)

Fig. 4 Crystal structures of (a) the free ligand **41b** [83] and (b) of the complex **44b**·2CsPF₆ [87] (solvent molecules and non-coordinating PF₆⁻ counter ion are omitted for clarity)



Conclusions

In conclusion, the chemistry of calix[4]crown and -bis-crown ethers is well documented and show that the properties of these macrocycles are governed by the size and nature of the crown ether bridge in addition to the conformation adopted by the calix[4]arene framework. Numerous examples show that these calixarene based ionophores have proven their abilities as extractants or complexation agents, and show high selectivity and affinity toward alkali metal cations. One of the important applications that make use of the unique properties of calix[4]crowns are found in the field of nuclear waste treatment.

However, less is known about the chemistry of the higher calix[*n*]crowns and resorcinarene crowns, although, their chemistry and different structural properties compared to calix[4]crowns present interesting possibilities in the field of host–guest chemistry and, hopefully, are to be discovered in more detail in the future.

Beyond the scope of this review, the chemistry of calixcrowns continues as their properties are influenced by further derivatization of the calixcrown framework. Some of the recent examples include the addition of water soluble [88] or proton di-ionizable [89] pendant groups, which add more dimension to the parent calixcrowns by tuning their already existing properties more suitable to be employed in various applications. The chemistry of calixcrowns has not found its limits so far.

Acknowledgements Financial support from the Academy of Finland is greatly acknowledged (project 211240).

References

- Alfieri, C., Dradi, E., Pochini, A., Ungaro, R., Andreotti, G.D.: Synthesis, and X-ray crystal and molecular structure of a novel macrobicyclic ligand: crowned *p*-*t*-butyl-calix[4]arene. *J. Chem. Soc. Chem. Commun.* 1075–1077 (1983)
- Vicens, J.: Applied and fundamental research: their mutual stimulation in the real world of chemistry—developing calixbis-crowns for nuclear waste treatment. *J. Inclusion Phenom. Macrocycl. Chem.* **55**, 193–196 (2006)
- Thuery, P., Nierlich, M., Asfari, Z., Vicens, J., Dozol, J.F.: Complexes of sodium and cesium perrhenates with calix[4]arene bis(crown-6): a model for pertechnetate ion extraction. *Polyhedron* **19**, 1749–1756 (2000) and references therein
- For a review, see: Sharma, K.R., Agrawal, Y.K.: Analytical potentialities of calix-crown ethers. *Rev. Anal. Chem.* **23**, 133–158 (2004)
- (a) Kim, S., Kim, H., Noh, K.H., Lee, S.H., Kim, S.K., Kim, J.S.: Potassium ion-selective membrane electrodes based on 1,3-alternate calix[4]crown-5-azacrown-5. *Talanta* **61**, 709–716 (2003); (b) Mahajan, R.K., Kumar, M., Sharma, V., Kaur, I.: Cesium ion selective electrode based on calix[4]crown ether ester. *Talanta* **58**, 445–450 (2002)
- (a) Cacciapaglia, R., Casnati, A., Mandolini, L., Ungaro, R.: The barium(II) complex of *p*-*tert*-butylcalix[4]arene-crown-5: a novel nucleophilic catalyst with transacylase activity. *J. Am. Chem. Soc.* **114**, 10956–10958 (1992); (b) Cacciapaglia, R., Casnati, A., Mandolini, L., Schiavone, S., Ungaro, R.: Barium(II)-ion assisted monoacetylation of partial-cone calix[4]arene-crown-5 diacetate. A convenient preparation of partial-cone calix[4]arene-crown-5 monoacetate. *J. Chem. Soc. Perkin Trans.* **2**, 369–371 (1993); (c) Cacciapaglia, R., Mandolini, L., Arnecke, R., Böhmer, V., Vogt, W.: Barium(II) complexes of calixcrowns derived from *p*-*tert*-butylcalix[5]arene as potential transacylation catalysts. Regio- and stereo-selective monoacylation of the calixcrown. *J. Chem. Soc. Perkin Trans.* **2**, 419–423 (1998)
- (a) Kim, J.K., Kim, J.S., Shul, Y.G., Lee, K.W., Oh, W.Z.: Selective extraction of cesium ion with calix[4]arene crown ether through thin sheet supported liquid membranes. *J. Memb. Sci.* **187**, 3–11 (2001); (b) Reichwein-Buitenhuis, E.G., Visser, H.C., de Jong, F., Reinhoudt, D.N.: Kinetic versus diffusion control in carrier-mediated cotransport of alkali cations through supported liquid membranes. *J. Am. Chem. Soc.* **117**, 3913–3921 (1995); (c) Nijenhuis, W., Buitenhuis, E., de Jong, F., Sudholter, E.J.R., Reinhoudt, D.N.: Calixcrowns as selective potassium cation carriers in supported liquid membranes. *J. Am. Chem. Soc.* **113**, 7963–7968 (1991)
- Nicod, L., Pellet-Rostaing, S., Chitry, F., Lemaire, M.: Synthesis of water soluble molecular receptor from calix[4]arene-bis-

- crown-6. *Tetrahedron Lett.* **39**, 9443–9446 (1998) and references therein
9. Yamamoto, H., Sakaki, T., Shinkai, S.: Regioselective synthesis of 1,2- and 1,3-bridged calix[4]crowns. What are the factors controlling the regioselectivity? *Chem. Lett.* 469–472 (1994)
 10. Tsue, H., Takimoto, T., Tamura, R., Kikuchi, C., Tanaka, S.: A facile synthesis of dibenzylated *p-tert*-butylcalix[4]crowns under non-diluted conditions. *Lett. Org. Chem.* **1**, 276–279 (2004)
 11. Csokai, V., Grun, A., Bitter, I.: Unprecedented cyclisations of calix[4]arenes with glycols under the Mitsunobu protocol: Part 1: a new perspective for the synthesis of calixcrowns. *Tetrahedron Lett.* **44**, 4681–4684 (2003)
 12. Casnati, A., Pochini, A., Ungaro, R., Ugozzoli, F., Arnaud, F., Fanni, S., Schwing, M.J., Egbering, R.J.M., de Jong, F., Reinhoudt, D.N.: Synthesis, complexation, and membrane transport studies of 1,3-alternate calix[4]arene-crown-6 conformers: a new class of cesium selective ionophores. *J. Am. Chem. Soc.* **117**, 2767–2777 (1995)
 13. Ghidini, E., Ugozzoli, F., Ungaro, R., Harkema, S., El-Fadi, A.A., Reinhoudt, D.N.: Complexation of alkali metal cations by conformationally rigid, stereoisomeric calix[4]arene crown ethers: a quantitative evaluation of preorganization. *J. Am. Chem. Soc.* **112**, 6979–6985 (1990)
 14. Bocchi, C., Careri, M., Casnati, A., Mori, G.: Selectivity of calix[4]arene-crown-6 for cesium ion in ISE: effect of the conformation. *Anal. Chem.* **67**, 4234–4238 (1995)
 15. Dijkstra, P.J., Brunink, J.A.J., Bugge, K.E., Reinhoudt, D.N., Harkema, S., Ungaro, R., Ugozzoli, F., Ghidini, E.: Kinetically stable complexes of alkali cations with rigidified calix[4]arenes: synthesis, X-ray structures, and complexation of calixcrowns and calixspherands. *J. Am. Chem. Soc.* **111**, 7567–7575 (1989)
 16. Casnati, A., Pochini, R., Ungaro, R., Bocchi, C., Ugozzoli, F., Egberink, R.J.M., Struijk, H., Lugtengerg, R., de Jong, F., Reinhoudt, D.N.: 1,3-Alternate calix[4]arenecrown-5 conformers: new synthetic ionophores with better K^+/Na^+ selectivity than valinomycin. *Chem. Eur. J.* **2**, 436–445 (1996)
 17. Guillon, J., Sonnet, P., Malval, J.P., Massip, S., Gosse, I., Leger, J.M., Lapouyade, R., Rochette, J., Monti, J.P., Jarry C.: Synthesis and cesium binding affinity of new 25,27-bis(alkyloxy)calix[4]arene-crown-6 conformers in relation to the alkyl pendent moiety. *Supramol. Chem.* **14**, 437–450 (2002)
 18. Ungaro, R., Casnati, A., Ugozzoli, F., Pochini, A., Dozol, J.F., Hill, C., Rouquette, H.: 1,3-Dialkoxycalix[4]arenecrowns-6 in 1,3-alternate conformation: cesium-selective ligands that exploit cation–arene interactions. *Angew. Chem. Int. Ed.* **33**, 1506–1509 (1994)
 19. Pappalardo, S., Petringa, A., Parisi, M., Ferguson, G.: Novel 1,2-bridged calix[4]crowns in the 1,2-alternate conformation. *Tetrahedron Lett.* **37**, 3907–3910 (1996)
 20. Ferguson, G., Lough, A.J., Notti, A., Pappalardo, S., Parisi, M.F., Petringa, A.: 1,2-Bridged calix[4]arene monocrowns and biscrowns in the 1,2-alternate conformation. *J. Org. Chem.* **63**, 9703–9710 (1998)
 21. Ungaro, R., Pochini, A.: New ionizable ligands from *p-t*-butylcalix[4]arene. *J. Inclusion Phenom.* **2**, 199–206 (1984)
 22. Kim, J.S., Lee, W.K., Sim, W., Ko, J.W., Cho, M.H., Ra, D.Y., Kim, J.W.: Calix[4]arenes bridged with two different crown ether loops: influence of crown size on metal ion recognition. *J. Inclusion Phenom. Macrocycl. Chem.* **37**, 359–370 (2000)
 23. Song, B.M., Chang, S.K.: Molecular recognition of butylamines by calix[4]-crown ethers. *Bull. Korean Chem. Soc.* **14**, 540–542 (1993)
 24. Jung, Y.E., Song, B.M., Chang, S.K.: Molecular recognition of alkyl and arylalkylamines in dichloromethane and chloroform by calix[4]-crown ethers. *J. Chem. Soc. Perkin Trans.* **2**, 2031–2034 (1995)
 25. Ugozzoli, F., Ori, O., Casnati, A., Pochini, A., Ungaro, R., Reinhoudt, D.N.: Evidence for cation– π interactions in calix-crown · KPic complexes from X-ray crystal structure analysis and energy calculations. *Supramol. Chem.* **5**, 179–184 (1995)
 26. Sachleben, R.A., Bryan, J.C., Das, G., Descazeaud, T., Sun, Y., Moyer, B.A.: Synthesis, structure, and extraction properties of paco-calix[4]arene crown-6 ethers. *J. Inclusion Phenom. Macrocycl. Chem.* **43**, 55–64 (2002)
 27. Prodi, L., Bolletta, F., Montalti, M., Zaccheroni, N., Casnati, A., Sansone, F., Ungaro, R.: Photophysics of 1,3-alternate calix[4]arene-crowns and of their metal ion complexes: evidence for cation– π interactions in solution. *New J. Chem.* **24**, 155–158 (2000)
 28. Sachleben, R.A., Urvoas, A., Bryan, J.C., Haverlock, T.J., Hay, B.P., Moyer, B.A.: Dideoxygenated calix[4]arene crown-6 ethers enhanced selectivity for caesium over potassium and rubidium. *Chem. Commun.* 1751–1752 (1999)
 29. Sachleben, R.A., Bryan, J.C., Engle, N.L., Haverlock, T.J., Hay, B.P., Urvoas, A., Moyer, B.A.: Rational design of cesium-selective ionophores: dihydrocalix[4]arene crown-6 ethers. *J. Org. Chem.* 4862–4869 (2003)
 30. Yamamoto, H., Shinkai, S.: Molecular design of calix[4]arene-based sodium-selective electrodes which show remarkably high $10^{5.0}$ – $10^{5.3}$ sodium/potassium selectivity. *Chem. Lett.* 1115–1118 (1994)
 31. Arnaud-Neu, F., Ferguson, G., Fuangswasdi, S., Notti, A., Pappalardo, S., Parisi, M.F., Petringa, A.: Synthesis, structural characterization, and alkali-metal complexation of the six possible (1,3)- and (1,2)-bridged *p-tert*-butylcalix[4]crown-5 conformers bearing (-picolyl pendant groups). *J. Org. Chem.* **63**, 7770–7779 (1998)
 32. Asfari, Z., Bressot, C., Vicens, J., Hill, C., Dozol, J.F., Rouquette, H., Eymard, S., Lamare, V., Tournois, B.: Doubly crowned calix[4]arenes in the 1,3-alternate conformation as cesium-selective carriers in supported liquid membranes. *Anal. Chem.* **67**, 3133–3139 (1995)
 33. Hill, C., Dozol, J.F., Lamare, V., Rouquette, H., Eymard, S., Tournois, S., Vicens, J., Asfari, Z., Bressot, C., Ungaro, R., Casnati, A.: Nuclear waste treatment by means of supported liquid membranes containing calixcrown compounds. *J. Inclusion Phenom. Mol. Recognit. Chem.* **19**, 399–408 (1994)
 34. Kim, J.S., Suh, I.H., Kim, J.K., Cho, M.H.: Selective sensing of caesium ions by novel calix[4]arene bis(dibenzocrown) ethers in an aqueous environment. *J. Chem. Soc. Perkin Trans.* **1**, 2307–2311 (1998)
 35. Lamare, V., Dozol, J.F., Ugozzoli, F., Casnati, A., Ungaro, R.: X-ray crystal structures and molecular modeling studies of calix[4]dibenzocrowns-6 and their alkali metal cation complexes. *Eur. J. Org. Chem.* 1559–1568 (1998)
 36. Casnati, A., Sansone, F., Dozol, J.F., Rouquette, H., Arnaud-Neu, F., Byrne, D., Fuangswasdi, S., Schwing-Weill, M.J., Ungaro, R.: New calix[4]arene-monobenzo- and dibenzo-crown-6 as cesium selective ionophores in the radioactive waste treatment: synthesis, complexation and extraction properties. *J. Inclusion Phenom. Macrocycl. Chem.* **41**, 193–200 (2001)
 37. (a) Kim, J.S., Cho, M.H., Yu, I.Y., Pang, J.H., Kim, E.T., Suh, I.H., Oh, M.R., Ra, D.Y., Cho, N.S.: Calix[4]arene dibenzocrown ethers as cesium ionophore. *Bull. Korean Chem. Soc.* **18**, 677–680 (1997); (b) Kim, J.S., Ohki, A., Cho, M.H., Kim, J.K., Ra, D.Y., Cho, N.S., Bartsch, R.A., Lee, K.W., Oh, W.Z.: Complexation and conformational flexibility of calix[4]arene dibenzocrown ethers. *Bull. Korean Chem. Soc.* **18**, 1014–1017 (1997); (c) Kim, J.S., Yu, I.Y., Pang, J.H., Kim, J.K., Lee, Y.I., Lee, K.W., Oh, W.Z.: New calix[4]arene dibenzocrown ethers for selective sensing of cesium ion in an aqueous environment. *Microchem. J.* **58**, 225–235 (1998)

38. (a) Kim, J.S., Pang, J.H., Yu, I.Y., Lee, W.K., Suh, I.H., Kim, J.K., Cho, M.H., Kim, E.T., Ra, D.Y.: Calix[4]arene dibenzocrown ethers as caesium selective extractants. *J. Chem. Soc. Perkin Trans. 2*, 837–846 (1999); (b) Kim, J.S., Ohki, A., Ueki, R., Ishizuka, T., Shimotashiro, T., Maeda, S.: Cesium-ion selective electrodes based on calix[4]arene dibenzocrown ethers. *Talanta* **48**, 705–710 (1999)
39. Casnati, A., Della Ca', N., Sansone, F., Ugozzoli, F., Ungaro, R.: Enlarging the size of calix[4]arene-crowns-6 to improve Cs⁺/K⁺ selectivity: a theoretical and experimental study. *Tetrahedron* **60**, 7869–7876 (2004)
40. Asfari, Z., Thuery, P., Nierlich, M., Vicens, J.: Unsymmetrical calix[4]-bis-crowns-6 with unequivalent crown loops. *Tetrahedron Lett.* **40**, 499–502 (1999)
41. Asfari, Z., Pappalardo, S., Vicens, J.: New preorganized calix[4]arenes. Part I. A doubly-crowned calix and a double-calixcrown derived from 4,6,10,12,16,18,22,24,25,26,27,28-dodecamethyl-5,11,17,23-tetrahydroxycalix[4]arene. *J. Inclusion Phenom. Mol. Recognit. Chem.* **14**, 189–192 (1992)
42. Wenger, S., Asfari, Z., Vicens, J.: Synthesis of two calix[4]arenes constrained to a 1,3-alternate conformation by diazabenzocrown ether bridging. *Tetrahedron Lett.* **35**, 8369–8372 (1994)
43. Lamare, V., Dozol, J.F., Fuangswasdi, S., Arnaud-Neu, F., Thuery, P., Nierlich, M., Asfari, Z., Vicens, J.: A new calix[4]arene-bis(crown ether) derivative displaying an improved cesium over sodium selectivity: molecular dynamics and experimental investigation of alkali-metal ion complexation. *J. Chem. Soc. Perkin Trans. 2*, 271–284 (1999)
44. Asfari, Z., Lamare, V., Dozol, J.F., Vicens, J.: A tribenzo modified 1,3-calix[4]-bis-crown-6: a highly selective receptor for cesium. *Tetrahedron Lett.* **40**, 691–694 (1999)
45. Arnaud-Neu, F., Asfari, Z., Souley, B., Vicens, J.: Binding properties of calix[4]-bis-crowns towards alkali cations. *New J. Chem.* **20**, 453–463 (1996)
46. Kim, J.S., Lee, W.K., Ra, D.Y., Lee, Y.I., Choi, W.K., Lee, K.W., Oh, W.Z.: Potassium sensing calix[4]arene crown ethers. *Microchem. J.* **59**, 464–471 (1998)
47. D'Aprano, A., Vicens, J., Asfari, Z., Salomon, M., Immarino, M.: Complexation of alkali metal cations by calix[4]arene-bis-crown-6 in methanol, acetonitrile and propylene carbonate. *J. Solut. Chem.* **25**, 955–970 (1996)
48. (a) Asfari, Z., Naumann, C., Vicens, J., Nierlich, M., Thuery, P., Bressot, C., Lamare, V., Dozol, J.F.: 1,3-Calix[4]-bis-crown-6. Cesium complexation studies by ¹³³Cs- and ¹H-NMR spectroscopy. Evidence for mononuclear and binuclear complexes from X-ray diffraction. Modeling of the metal complexation. *New J. Chem.* **20**, 1183–1194 (1996); (b) Thuery, P., Nierlich, M., Bryan, J.C., Lamare, V., Dozol, J.F., Asfari, Z., Vicens, J.: Crown ether conformations in 1,3-calix[4]arene bis(crown ethers): crystal structures of a caesium complex and solvent adducts and molecular dynamics simulations. *J. Chem. Soc. Dalton Trans.* 4191–4202 (1997)
49. Thuery, P., Nierlich, M., Asfari, Z., Vicens, J.: Crystal structures of 1,3-calix[4]-bis-crown-6 · 3CH₃CN and 1,3-calix[4]-bis-(benzo-crown-6 · 3CH₃CN). *J. Inclusion Phenom. Mol. Recognit. Chem.* **27**, 169–178 (1997)
50. (a) Tuery, P., Nierlich, M., Lamare, V., Dozol, J.F., Asfari, Z., Vicens, J.: Caesium iodide complex of 1,3-calix[4]-bis-crown-6. *Acta Crystallogr. C* **52**, 2729–2731 (1996); (b) Thuery, P., Nierlich, M., Bressot, C., Lamare, V., Dozol, J.F., Asfari, Z., Vicens, J.: Crystal and molecular structures of binuclear caesium complexes with 1,3-calix[4]-bis-crown-6 and 1,3-calix[4]-bis-benzo-crown-6. *J. Inclusion Phenom. Mol. Recognit. Chem.* **23**, 305–312 (1996)
51. Bryan, J.C., Chen, T., Levitskaia, T.G., Haverlock, T.J., Barnes, C.E., Moyer, B.A.: Solvation of calix[4]arene-bis-crown-6 molecules. *J. Inclusion Phenom. Macrocycl. Chem.* **42**, 241–245 (2002)
52. Thuery, P., Nierlich, M., Lamare, V., Dozol, J.F., Asfari, Z., Vicens, J.: Potassium and sodium complexes of 1,3-calix[4]-bis-crown-6: crystal and molecular structures, ¹H-NMR investigation and molecular dynamics simulation. *Supramol. Chem.* **8**, 319–332 (1997)
53. Khriifi, S., Guelzim, A., Baert, F., Asfari, Z., Vicens, J.: Calix-crown binding to caesium (X-ray structural determination of a 1,3-alternate calix[4]arene-biscrown-7 ligand). *J. Inclusion Phenom. Mol. Recognit. Chem.* **29**, 187–195 (1997)
54. Arduini, A., Casnati, A., Dodi, L., Pochini, A., Ungaro, R.: Selective 1,2-functionalization of calix[4]arenes at the lower rim. Synthesis of a new type of bis-calixcrown ether. *J. Chem. Soc. Chem. Commun.* 1597–1598 (1990)
55. Arduini, A., Domiano, L., Pochini, A., Secchi, A., Ungaro, R., Ugozzoli, F., Struck, O., Verboom, W., Reinhoudt, D.N.: Synthesis of 1,2-bridged calix[4]arene-biscrowns in the 1,2-alternate conformation. *Tetrahedron* **53**, 3767–3776 (1997)
56. Arduini, A., Domiano, L., Pochini, A., Secchi, A., Ungaro, R., Ugozzoli, F., Struck, O., Verboom, W., Reinhoudt, D.N.: Synthesis of 1,2-bridged calix[4]arene-biscrowns in the 1,2-alternate conformation. *Tetrahedron* **53**, 3767–3776 (1997)
57. (a) Asfari, Z., Astier, J.P., Bressot, C., Estienne, J., Pepe, G., Vicens, J.: Synthesis, characterization, and X-ray structure of 1,2-bis-crown-5-calix[4]arene. Modeling of metal complexation. *J. Inclusion Phenom. Mol. Recognit. Chem.* **19**, 291–300 (1994); (b) Pepe, G., Astier, J.P., Estienne, J., Bressot, C., Asfari, Z., Vicens, J.: 1,2-Bis-crown-5-calix[4]arene. *Acta Crystallogr. C* **51**, 726–729 (1995)
58. Asfari, Z., Nicolle, X., Vicens, J., Dozol, J.F., Duhart, A., Harrowfield, J.M., Skelton, B.W., White, A.H.: Ditopic calixcrowns with inequivalent crown loops: synthesis and structural characterization of an unsymmetrical calix[4]arene-biscrown-6. *J. Inclusion Phenom. Macrocycl. Chem.* **33**, 251–262 (1999)
59. Kim, J.S., Lee, W.K., Suh, I.H., Kim, J.G., Yoon, J., Lee, J.H.: Heterogeneous binuclear complexation of 1,3-alternate calix[4]-bis-crown bearing two different crown rings. *J. Org. Chem.* **65**, 7215–7217 (2000)
60. Kim, J.S., Lee, W.K., Lee, S.H., Kim, J.G., Suh, I.H., Kim, J.Y., Kim, J.W.: Cesium complex of an unsymmetrical calix[4]crown-dibenzocrown-6. *J. Inclusion Phenom. Macrocycl. Chem.* **40**, 183–187 (2001)
61. Kraft, D., Arnecke, R., Böhmer, V., Vogt, W.: Regioselective synthesis of calixcrowns derived from *p*-*tert*-butylcalix[5]arene. *Tetrahedron* **49**, 6019–6024 (1993)
62. Arnaud-Neu, F., Arnecke, R., Böhmer, V., Fanni, S., Gordon, J.L.M., Schwing-Weill, J.M., Vogt, W.: Crown ether derivatives of calix[5]arenes: synthesis and complexation properties. *J. Chem. Soc. Perkin Trans. 2* 1855–1860 (1996)
63. (a) Pappalardo, S., Parisi, M.F.: Selective endo-calix complexation of linear alkylammonium cations by functionalized (1,3)-*p*-*tert*-butylcalix[5]crown ethers. *J. Org. Chem.* **61**, 8724–8725 (1996); (b) Gattuso, M., Notti, A., Pappalardo, S., Parisi, M.F.: Dual binding mode of alkylammonium cations to (1,3)-calix[5]-crown-6 triesters. *Tetrahedron Lett.* **39**, 1969–1972 (1998); (c) De Salvo, G., Gattuso, G., Notti, A., Parisi, M.F., Pappalardo, S.: Shape recognition of alkylammonium ions by 1,3-bridged calix[5]arene crown-6 ethers: endo- vs exo-cavity complexation. *J. Org. Chem.* **67**, 684–692 (2002)
64. Casnati, A., Jacopozzi, P., Pochini, A., Ugozzoli, F., Cacciapaglia, R., Mandolini, L., Ungaro, R.: Bridged calix[6]arenes in the cone conformation: new receptors for quaternary ammonium cations. *Tetrahedron* **51**, 591–598 (1995)
65. (a) Chen, Y., Li, J., Xin, J., Zhong, Z., Gong, S., Lu, X.: Syntheses of lower-rim-1,3-crowned calix[6]arenes and their

- complexation abilities toward cations. *Synth. Commun.* **29**, 705–711 (1999); (b) Li, J., Chen, Y., Lu, X.: Selective bridging of *p*-*tert*-butylcalix[6]arene with polyethylene glycol ditosylates. *Tetrahedron* **55**, 10365–10374 (1999)
66. (a) Chen, Y., Yang, F., Gong, S.: Molecular design and synthesis of a calix[6]crown-based lithium-selective ionophore. *Tetrahedron Lett.* **41**, 4815–4818 (2000); (b) Yang, F., Chen, Y.: Ion complexation properties of calix[6]arene derivatives: I. 1,4-calix[6]crown-4 derivatives. *Supramol. Chem.* **12**, 445–450 (2001)
67. Blanda, M.T., Farmer, D.B., Brodbelt, J.S., Goolsby, B.J.: Synthesis and alkali metal ion binding properties of two rigid stereochemical isomers of calix[6]arene bis-crown-4. *J. Am. Chem. Soc.* **122**, 1486–1491 (2000)
68. Guan, B., Gong, S., Wu, X., Li, Z., Chen, Y.: One-step synthesis of *p*-*tert*-butylcalix[6]-1,4-2,5-biscrown-4 and its tosyloxyethoxyethylate derivative. *J. Inclusion Phenom. Macrocycl. Chem.* **54**, 81–84 (2006)
69. (a) Chen, Y., Yang, F., Lu, X.: Synthesis of *p*-*tert*-butylcalix[6]-1,4-2,5-bis-crowns. *Tetrahedron Lett.* **41**, 1571–1574 (2000); (b) Chen, Y., Yang, F., Thuery, P., Nierlich, M., Vicens, J.: Crystal structure and complexing properties of *p*-*tert*-butylcalix[6]-1,4-2,5-bis(crown-4). *J. Inclusion Phenom. Macrocycl. Chem.* **42**, 261–263 (2002)
70. Chen, Y., Li, H.: Syntheses of novel types of calix[6]bis-crowns and related compounds. *New J. Chem.* **25**, 340–343 (2001)
71. Ko, S.W., Ryu, B.J., Park, K.M., No, K.H., Kim, J.S., Nam, K.C.: Synthesis, X-ray structure and binding properties of calix[6]arene-1,4-2,5-biscrowns. *Bull. Korean Chem. Soc.* **25**, 957–958 (2004)
72. Chen Y.Y., Li, H.B.: Synthesis and characterization of *p*-*tert*-butylcalix[6]-1,4-crown-4-2,6-crown-5, *p*-*tert*-butylcalix[6]-1,4-crown-4-2,3-crown-5. *Chem. Lett.* 1208–1209 (2000)
73. Guan, B., Gong, S., Wu, X., Chen, Y.: Stereoisomerism and complexation behaviour of functionalized *p*-*tert*-calix[6]-1,4-2,5-biscrown-4. *Tetrahedron Lett.* **46**, 6041–6044 (2005)
74. Geraci, C., Piattelli, M., Neri, P.: Preorganization of calix[8]arenes. Synthesis of basket-shaped doubly-crowned calix[8]arenes. *Tetrahedron Lett.* **36**, 5429–5432 (1995)
75. (a) Geraci, C., Piattelli, M., Neri, P.: Regioselective synthesis of calix[8]crowns by direct alkylation of *p*-*tert*-butylcalix[8]arene. *Tetrahedron Lett.* **37**, 3899–3902 (1996); (b) Geraci, C., Piattelli, M., Neri, P.: Inherent chirality in calix[8]arenes exploiting the steric constraint of two intercrossing polyether chains. *Tetrahedron Lett.* **37**, 7627–7630 (1996)
76. Geraci, C., Piattelli, M., Chessari, G., Neri, P.: Singly bridged calix[8]crowns. *J. Org. Chem.* **65**, 5143–5151 (2000)
77. (a) Geraci, C., Chessari, G., Piattelli, M., Neri, P.: Cation encapsulation within a ten-oxygen spheroidal cavity of conformationally preorganized 1,5-3,7-calix[8]bis-crown-3 derivatives. *Chem. Commun.* 921–922 (1997); (b) Geraci, C., Bottino, A., Piattelli, M., Gavuzzo, E., Neri, P.: Interplay between cone and partial-cone geometry in doubly-bridged calix[8]arenes investigated by X-ray and 2D NMR. *J. Chem. Soc. Perkin Trans. 2*, 185–187 (2000)
78. Gregoli, L., Russo, L., Steffo, I., Gaeta, C., Arnaud-Neu, F., Hubscher-Bruder, V., Khazaali-Parsa, P., Geraci, C., Neri, P.: Synthesis and complexing properties of 1,5:3,7-doubly bridged calix[8]arenes with mixed spanning elements. *Tetrahedron Lett.* **45**, 6277–6281 (2004)
79. Martino, M., Gaeta, C., Gregoli, L., Neri, P.: Regioselective intramolecular bridging of *p*-*tert*-butylcalix[7]arene. *Tetrahedron Lett.* **43**, 9521–9525 (2002)
80. Martino, M., Gaeta, C., Neri, P.: Regioselective double intramolecular bridging of *p*-*tert*-butylcalix[7]arene. *Tetrahedron Lett.* **45**, 3387–3391 (2004)
81. (a) Consoli, G.M.L., Cunsolo, F., Geraci, C., Neri, P.: Remarkable alkali cation template effect in 1,5-bridged calix[8]arenes. *Org. Lett.* **3**, 1605–1608 (2001); (b) Consoli, G.M.L., Cunsolo, F., Geraci, C., Gavuzzo, E., Neri, P.: Alkali cation ‘conformational templation’ in 1,5-bridged calix[8]arenes: a single crystal X-ray proof. *Tetrahedron Lett.* **43**, 1209–1211 (2002)
82. Gaeta, C., Martino, M., Neri, P.: Conformational templation in a singly bridged calix[7]arene derivative induced by alkali metal cations. *Org. Lett.* **8**, 4409–4412 (2006)
83. Higler, I., Boerrigter, H., Verboom, W., Kooijman, H., Spek, A.L., Reinhoudt, D.N.: A modular approach to potential synthetic receptors with large surfaces based on crown[n]cavitands. *Eur. J. Org. Chem.* 1597–1607 (1998)
84. Same abbreviation, which was introduced by the author, has been used to distinguish between different regioisomers: x,y-crown[n]cavitand, where x and y denote the bridging mode of the crown ether moiety and n the length of the crown ether bridge
85. Kang, A., Kim, S.K., Nakamura, K., Park, J.H., Yoon, Y.J., Lee, K.D., Yoon, J.: A new cavitand ionophore bearing two rigid crown ether groups. *Tetrahedron Lett.* **46**, 245–248 (2005)
86. Salorinne, K., Nissinen, M.: Novel tetramethoxy resorcinarene bis-crown ethers. *Org. Lett.* **8**, 5473–5476 (2006)
87. Salorinne, K., Nissinen, M.: Alkali metal complexation properties of resorcinarene bis-crown ethers: effect of the crown ether functionality and preorganization on complexation. *Tetrahedron* **64**, 1798–1807 (2008)
88. Some recent examples: (a) Pellet-Rostaing, S., Chitry, F., Spitz, J.A., Sorin, A., Favre-Reguillon, A., Lemaire, M.: New water-soluble calix[4]arene-bis(benzocrown-6) for caesium-sodium separation by nanofiltration-complexation. *Tetrahedron* **59**, 10313–10324 (2003); (b) Mathieu, A., Asfari, Z., Thuery, P., Nierlich, M., Faure, S., Vicens, J.: Water-soluble para-sulfonated 1,2;3,4-calix[4]arene-biscrowns in the 1,2-alternate conformation. *J. Inclusion Phenom. Macrocycl. Chem.* **40**, 173–181 (2001); (c) Pellet-Rostaing, S., Chitry, F., Nicod, L., Lemaire, M.: Synthesis and complexation properties of 1,3-alternate calix[4]arene-bis(crown-6) derivatives. *J. Chem. Soc. Perkin Trans. 2*, 1426–1432 (2001)
89. Some examples: (a) Tu, C., Surowiec, K., Bartsch, R.A.: Efficient divalent metal cation extractions with di-ionizable calix[4]arene-1,2-crown-4 compounds. *Tetrahedron* **63**, 4184–4189 (2007); (b) Tu, C., Liu, D., Surowiec, K., Purkiss, D.W., Bartsch, R.A.: Di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-5 and -crown-6 compounds in the cone conformation: synthesis and alkaline earth metal cation extraction. *Org. Biomol. Chem.* **4**, 2983–2944 (2006); (c) Talanov, V.S., Talanova, G.G., Gorbunova, M.G., Bartsch, R.A.: Calix[4]arene-bis(dibenzocrown-6-ethers) with one proton-ionizable group. *Tetrahedron Lett.* **43**, 1629–1631 (2002); (d) Talanov, V.S., Talanova, G.G., Bartsch, R.A.: New proton-ionizable, cesium-selective calix[4]arene-bis(crown-6-ethers) with markedly enhanced extraction efficiency. *Tetrahedron Lett.* **41**, 8221–8224 (2000)