

Calixcrowns and Related Molecules*

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Abstract. The synthesis of 1,2- and 1,3-calix[4]-*bis*-crowns, double calix[4]arenes and double calixcrowns have been shown to depend on the reaction conditions (nature of the base, structure of the ditosylates, and the stoichiometry of the reactants). The 1,3-alternate conformation of the 1,3-calix[4]-*bis*-crowns was shown to be favourable to the selective complexation of cesium cation. The observed Na^+/Cs^+ selectivity was exploited in separation processes using them as carriers in transport through supported liquid membranes (SLMs). The best Na^+/Cs^+ selectivity (1/45 000) was observed for the naphthyl derivative **7**. Calix(aza)crowns and 1,3-calix[4]-*bis*-(aza)-crowns were also produced through the preliminary formation of the Schiff base-calixarenes, which were further hydrogenated. The syntheses consisted of the 1,3-selective alkylation of calixarenes followed by cyclization into a 1,3-bridged calixarene or by the direct 1,3-capping of the calixarene with appropriate ditosylates. Soft metal complexation by these ligands is also presented.

Key words: 1,2- and 1,3-Calix[4]-*bis*-crowns, double calix[4]arenes, double calixcrowns, calix(aza)crowns, Na^+/Cs^+ selectivity, soft metal complexation.

1. Introduction

In the 25 years since Pedersen [1] reported on the synthesis and metal–cation complexing properties of crown ethers the number of crown ether compounds has been continuously increasing. Nowadays the synthesis of a crown ether molecule is directed toward a desired application (molecular and enantiomer recognition, asymmetric catalysis, redox properties, allosteric effect, replication, molecular assembly processes, etc.) [2]. To create these application-directed macrocycles chemists have developed the synthesis of macropolycycles or cage molecules [3] with a molecular framework which combines simple, already existing molecular elements, the functions of which are known. Hegelson *et al.* [4] prepared multistranded systems containing binaphthyl and related compounds with polyether chains for chiral recognition. Weber [5] described a series of multiloop ligands made from hexaphenol and crown ethers. These molecules, which had previously been synthesized as polytopic cation receptors, were observed to be surfactants having a novel construction principle. Sijbesma and Nolte [6] prepared a *bis*-aza-tetra-oxa-crown ether which acts as a molecular clip with allosteric binding properties. Nakano *et al.* [7] proposed a tri-crown ether oligomer as a mimic of the nature and coiling of gramicidin. Rumney and Kool [8] constructed hybrid circular molecules which

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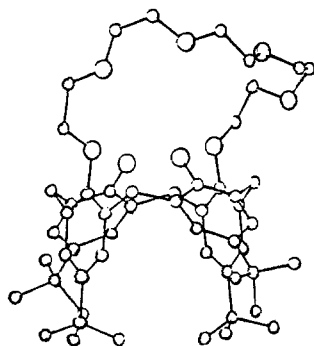


Fig. 1. The first calixcrown (Alfieri *et al.* [11]).

contain two oligonucleotide domains bridged by two oligoethylene glycol chains. These molecules bind with high affinity to complementary strands of RNA and DNA and display exceptional resistance to degradation by nucleases. Kobuke *et al.* [9] designed macrocycles containing both catechol functions and polyether groups with metal-assisted organization and cooperative metal binding.

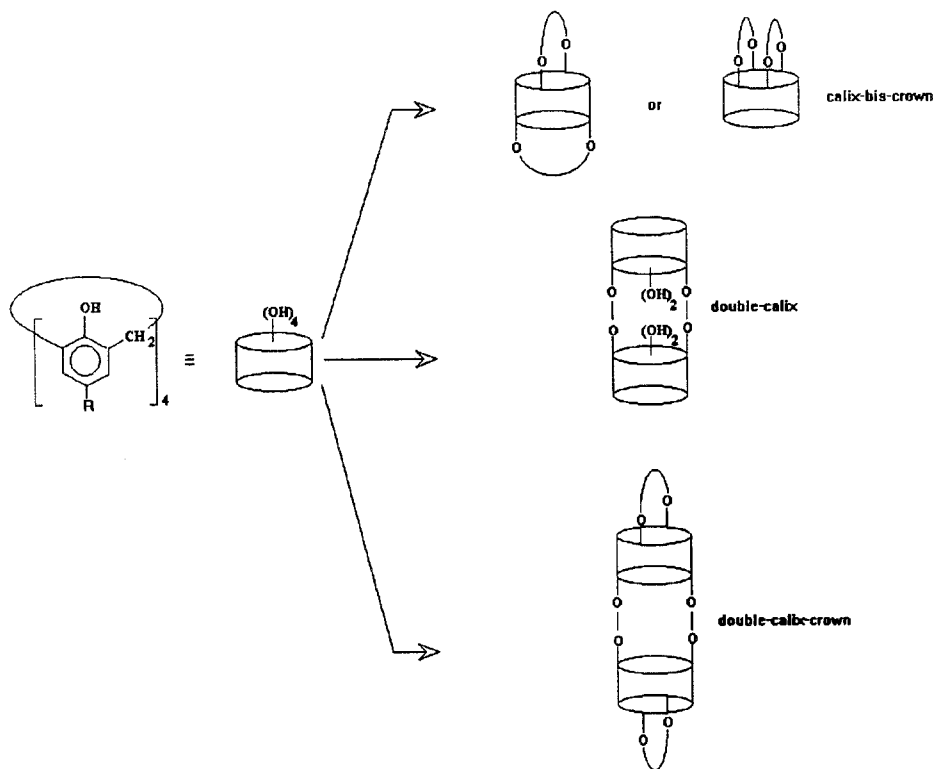
Since 1991 we have developed the synthesis of macropolycyclics containing in their molecular structure the monocyclic structure of calixarenes and crown ether elements. This combination gives a close coupling of the hydrophobic cavity of the calixarenes able to include organic substrates and the metal cation complexing sites of the crown ether, with potential interactions between them. We have already demonstrated evidence of such cation–substrate contact during a triple inclusion by a calixarene [10]. The crystal structure of the Eu(III) complex of *bis*-(homooxa)-*p*-*tert*-butylcalix[4]arene showed the Eu(III) to be coordinated to a DMSO molecule included in the hydrophobic cavity of the calixarene [10].

Calixcrowns refer to the family of macropolycyclic or cage molecules in which the monocyclic structures of calixarenes and crown ethers are combined through the bridging of phenolic oxygens of a calixarene by a polyether chain. The first member of this family was produced by Alfieri *et al.* [11], who reacted pentaethylene glycol ditosylate with *p*-*tert*-butylcalix[4]arene under basic conditions to produce 1,3-*p*-*tert*-butylcalix[4]crown-6, see Figure 1.

2. Calixcrowns

We have synthesized calixcrowns by systematic reactions of calix[4]arenes with various ditosylates. Depending on the reaction conditions (nature of the base, structure of the ditosylates, and the stoichiometry of the reactants) products with different topologies were isolated (Scheme 1).

The reaction of calix[4]arene with 4–6 equivalents of various ditosylates (containing 5, 6 or 7 oxygen atoms) in the presence of K_2CO_3 in refluxing acetonitrile produced 1,3-calix[4]-*bis*-crowns 1–7 in 60–80% yield [12] (Figure 2). The for-



Scheme 1. Different pathways to calixcrowns.

mation of **1–7** implies a preliminary *distal* 1,3-capping of the calix[4]arene by one glycolic chain. The second capping forces the calixarene to adopt the 1,3-alternate conformation which is effectively observed in the $^1\text{H-NMR}$ spectra. Similar reactions afforded 1,3-*p-iso*-propylcalix[4]crown-5 **8** (which shows the reaction to be general) and 1,3-*p-tert*-butylcalix[4]crown-5 **9** (for comparison with the published molecule [13]). When K_2CO_3 was replaced by Cs_2CO_3 we also isolated the 1,2-calix[4]-*bis*-crown-5 **10** isomeric to **1**, in 10% yield in which the capping by the glycolic chains is *vicinal* [14]. $^1\text{H-NMR}$ indicated that the calix[4]arene moiety is in the cone conformation [14]. 1,2-Dialkylations have been observed by other groups during the use of Cs_2CO_3 [15] and CsF [16].

The conformations of the 1,2- and 1,3-calix[4]-*bis*-crowns were ascertained by the determination of the X-ray structure of 1,3-*p-tert*-butylcalix[4]crown-5 **9** [17] and 1,2-calix[4]-*bis*-crown-5 **10** [14] (Figure 3).

When *shorter* ditosylates were used *lower rim–lower rim* double calixarenes were obtained [18]. For instance, the reaction of calix[4]arene, *p-tert*-butyl- and 1,3-dimethoxy-*p-tert*-butylcalix[4]arene with 2 equivalents of triethylene glycol ditosylate lead to double calixarenes **11**, **12**, and **13** in very good yields (Figure 4). They were shown to consist of two calix[4]arene units linked by two distal glycolic

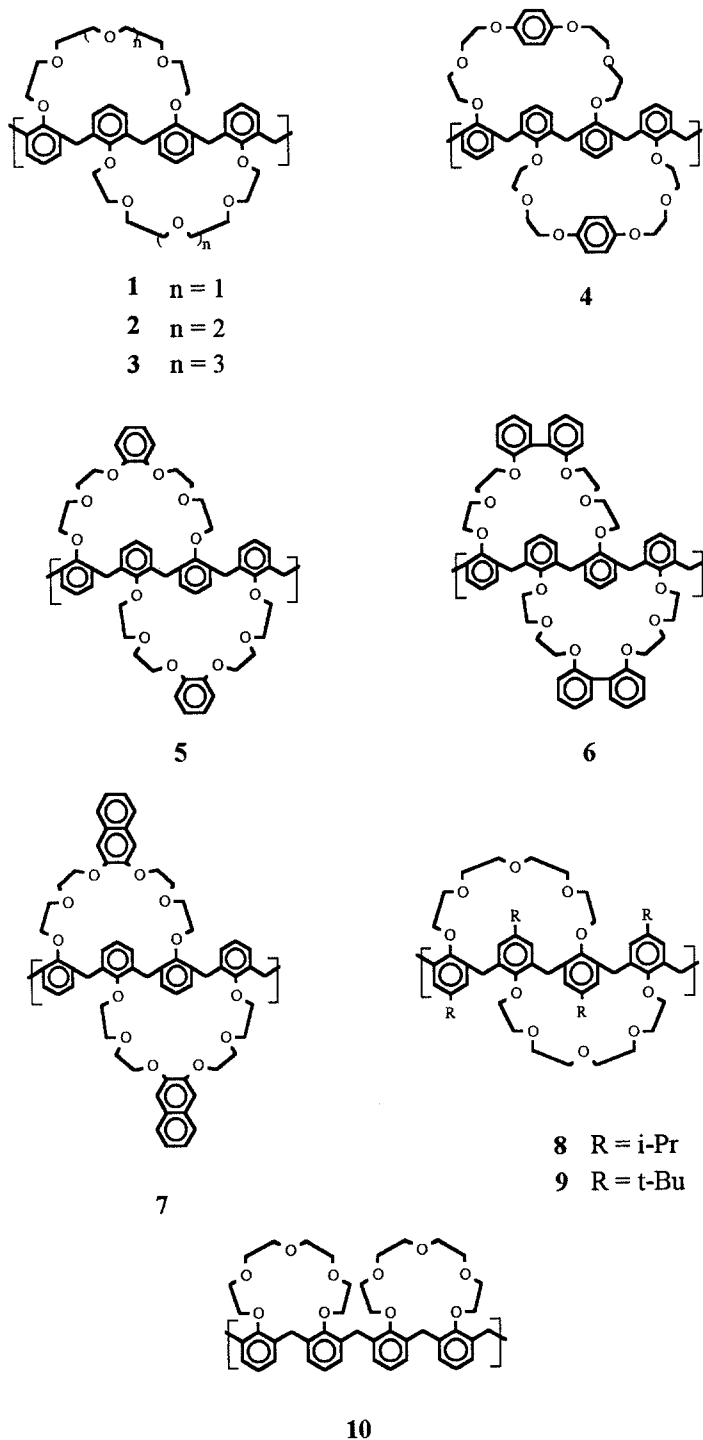


Fig. 2. 1,3-Calix[4]-bis-crowns.

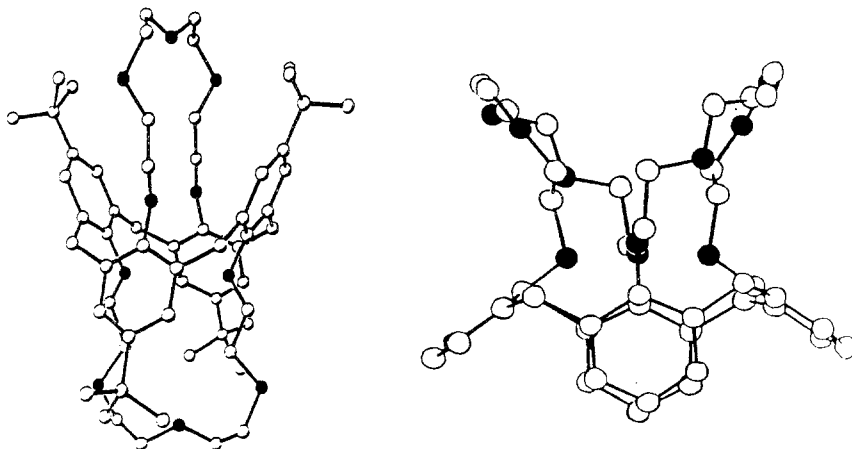


Fig. 3. 1,3-*p*-*tert*-Butylcalix[4]crown-5 **9**, and 1,2-calix[4]-*bis*-crown-5 **10**.

chains. $^1\text{H-NMR}$ showed the calixarene moieties to be in the cone conformation [18]. Recently a double calix[4]arene, very similar to compounds **11–13**, linked with two tetraglycolic chains ($\text{R} = \text{monoglycol}$; $\text{R}' = t\text{-Bu}$) was shown to be a ditopic ionophore in which Na^+ or K^+ vibrates between the two metal-binding sites in the NMR time scale [19]. The treatment of *p*-*tert*-butylcalix[4]arene with diethylene glycol ditosylate afforded double-calix[4]arene **14** triply bonded via the oxygen atoms by glycolic chains [20]. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ displayed complex spectrometric data due to several conformations of the *p*-*tert*-butylcalix[4]arene subunits and/or *anti* or *syn* linkages [12].

Subsequent to these results, we discovered a striking example of the formation of a double calixcrown by changing the stoichiometry of the reactants. *p*-*tert*-Butylcalix[4]arene was treated with a 15 equivalent excess of tetraethylene glycol ditosylate to afford double *p*-*tert*-butylcalix[4]-*bis*-crown-5 **15** in which each calixarene unit is in the 1,3-alternate conformation and 1,3-capped by a tetraethylene glycolic chain [21].

The preparation of 1,3-calix[4]-*bis*-crowns and double calixcrowns was also performed with the mesitylene derived calix[4]arene or calix[4]mesitylene which exists only in the 1,3-alternate conformation [22], allowing us to conclude that 1,3-calix[4]-*bis*-crowns are formed with longer glycolic chains while double calixcrowns are formed with shorter and more rigid ones (Figure 5).

3. Metal Complexation Properties

Our interest was in the recovery of cesium from waste waters by solvent extraction using an extractant able to selectively bind the cesium in the presence of large amounts of sodium [25]. Only those calixcrowns in the 1,3-alternate conformation were tested for complexation of alkali cations due to the spherical geometry they

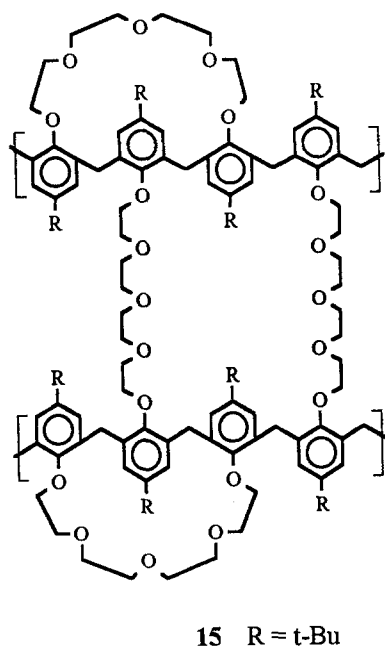
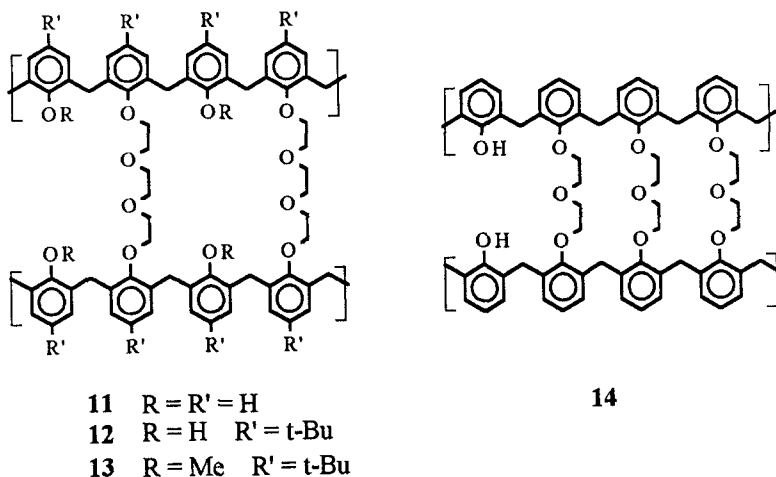


Fig. 4. Double calixarenes.

offer, comparable to the spheric cryptands of Graf and Lehn [26]. 1,3-Calix[4]-bis-crowns **1–3**, **5** and **7** were first shown to extract alkali ions, with the exception of Li^+ , from the corresponding solid picrates (Me^+Pic^-) in excess in a chloroform phase. The 1 : 1 (Me^+Pic^-)-**1–3**, **5** and **7** complexes were isolated as yellow solids. The stoichiometries were deduced from $^1\text{H-NMR}$. The presence of original and

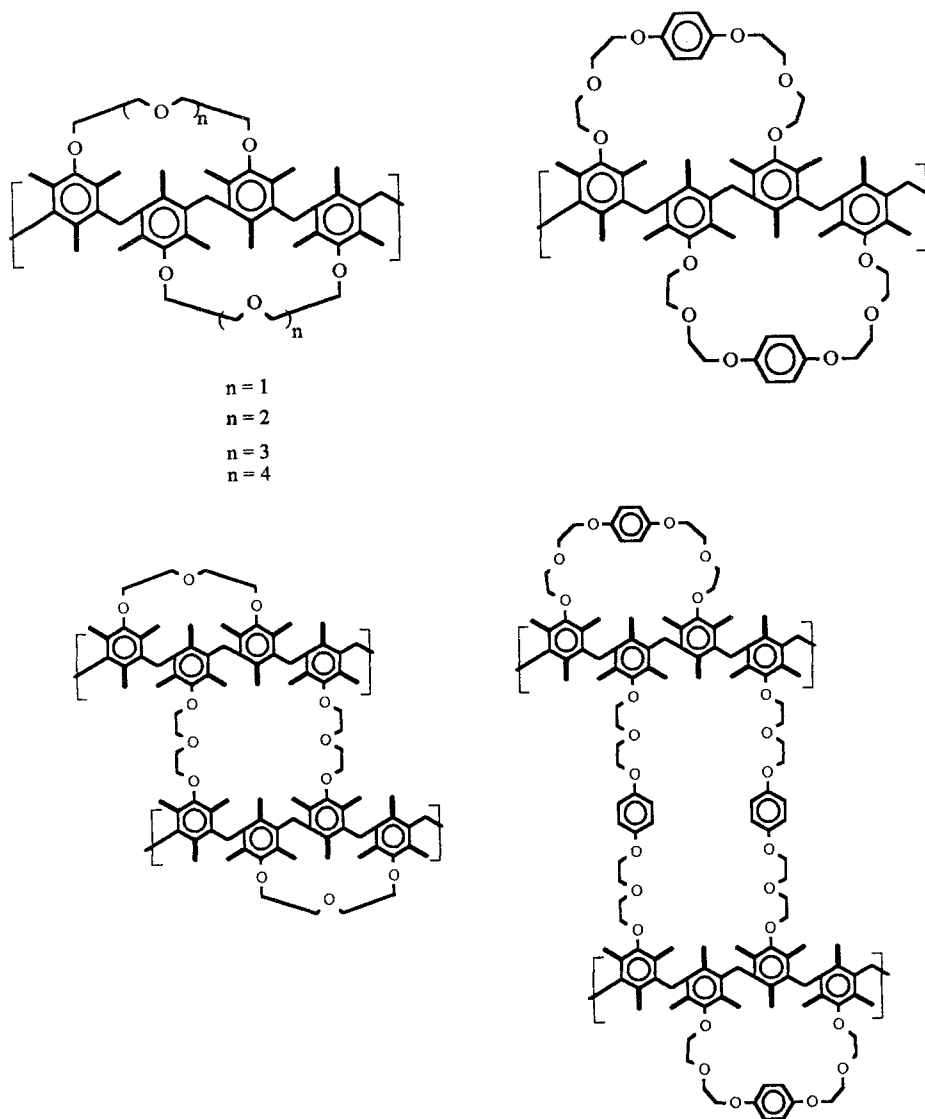


Fig. 5. 1,3-Calix[4]-bis-crowns and double calixcrowns derived from calix[4]arene or calix[4]mesitylene.

shifted signals of the protons of the polyether chain in a 1 : 1 integration ratio lends support to a location of the cation in one polyether loop. From the X-ray structure of **9** [17] the approximate radius of one polyether loop was determined to be $\sim 1.5 \text{ \AA}$, a size approximately complementary to K^+ and Rb^+ , leading us to assume that a calixcrown containing six oxygens may well fit with Cs^+ , as observed for **1–3**, **5** and **7**. 1,3-Calix[4]-bis-crowns **4** and **6** did not extract, probably due to a larger and more rigid glycolic chain. *p*-*iso*-Propyl and *p*-*tert*-butyl analogues **8** and **9** were

also unable to extract the cations. This was attributed to a shielding of the crown unit by the bulky *iso*-propyl and *p*-*tert*-butyl groups preventing the cation from complexation, as deduced from the crystal structure of **9** [17].

Additional solvent extraction of alkali picrates from the aqueous phase to dichloromethane solutions and the UV determination of the constants of complex formation in methanol showed the selectivity of complexation to be in the order $\text{Cs}^+ > \text{Rb}^+ \sim \text{K}^+ > \text{Na}^+ > \text{Li}^+$ for those 1,3-calix[4]-*bis*-crowns **2**, **5**, and **7** containing six oxygens in the glycolic chain [27].

By a similar method double *p*-*tert*-butylcalix[4]-*bis*-crown-**5** **15** was shown to be selective for K^+ and Rb^+ with a location of the cation in the central cavity [21]. Ligand **15** extracted Li^+ (3%), Na^+ (2%), K^+ (35%), Rb^+ (45%), Cs^+ (7%) with the highest *K* values of 4.9 and 5.2 log units, respectively, for K^+ and Rb^+ [21].

4. Industrial Application

The observed Na^+/Cs^+ selectivity was exploited in separation processes using 1,3-calix[4]-*bis*-crowns **2**, **5**, and **7** as carriers in transport through supported liquid membranes (SLMs). They transported Cs^+ through a microporous propylene support (NPOE) from an acidic phase (HNO_3 , 1N, NaNO_3 , 3N). The best Na^+/Cs^+ selectivity (1/45 000) was observed for the naphthyl derivative **7** [28]. The selectivity was attributed to π -metal interactions favorable to complexation of a larger Cs^+ cation, which is polarisable and poorly hydrated as compared to sodium cation.

5. Calix(aza)crowns

We have previously described the synthesis of calixcrowns by one-pot reactions. In a different approach the calix(aza)crowns were constructed by stepwise synthesis. The synthesis began with the condensation of cone-1,3-dialdehyde derivative **16** with various primary diamines to afford Schiff base-*p*-*tert*-butylcalix[4]arenes **17**–**20** in the cone conformation [29, 30]. Hydrogenation of **18** and **19** with NaBH_4 produced chlorohydrates **21**·HCl and **22**·HCl and subsequent deprotonation with NaOH lead to the di-aza-benzo-crown-ether-*p*-*tert*-butylcalix[4]arenes **21** and **22** in almost quantitative yield [31] (Figure 6).

In a similar manner we achieved the synthesis of *bis*-Schiff base-calix[4]mesitylenes **25** and **26** from the corresponding tetraaldehydes **23** and **24**. We could not hydrogenate **25** and **26** due to their low solubility in the usual solvents for the reaction (Figure 7).

We were unable to prepare the tetraaldehyde precursor corresponding to the calix[4]arene and the synthesis of the hydrogenated *bis*-Schiff base-calix[4]arene **27** was achieved by stepwise synthesis. Aldehyde **28** was prepared from salicylaldehyde and 2-(2-chloroethoxy)ethanol. Condensation of **28** with 1,4-diaminobutane lead to the Schiff base **29** which was hydrogenated with NaBH_4 to give the chlorhy-

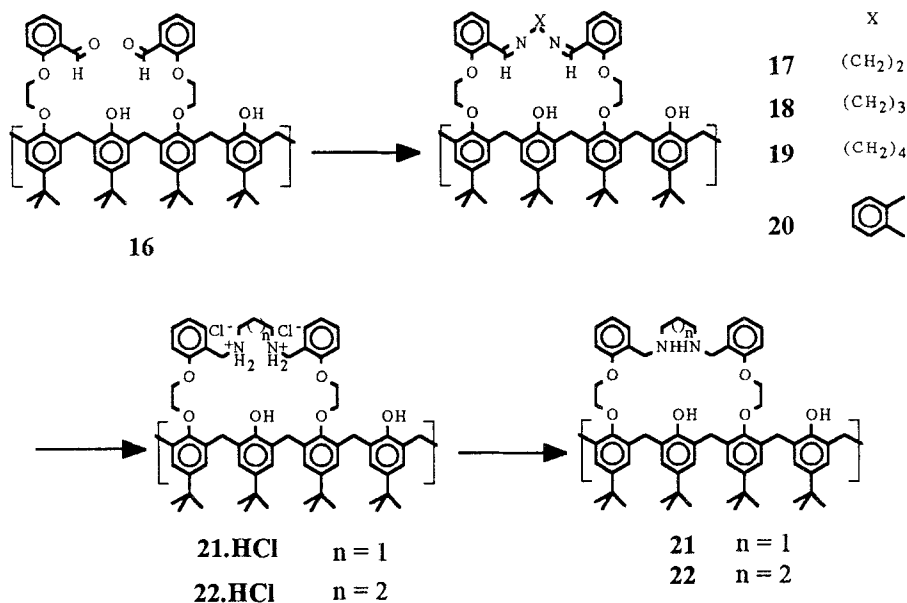


Fig. 6. Stepwise synthesis of calix(aza)crowns.

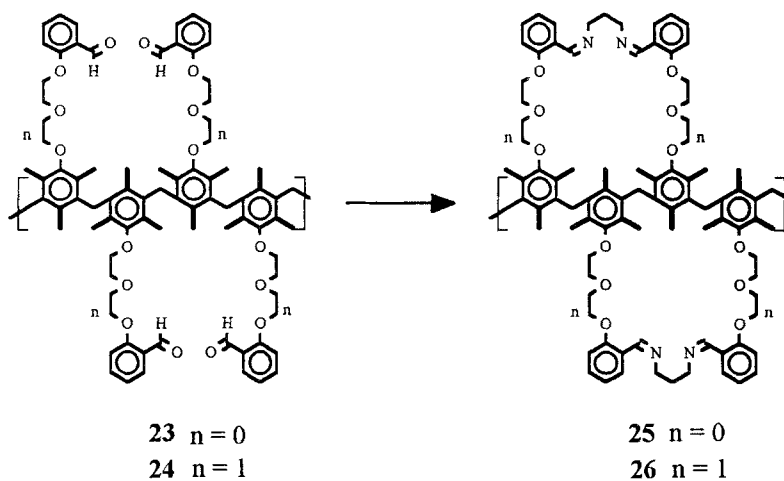


Fig. 7. bis-Schiff base-calix[4]mesitylenes.

drate **30**·HCl. Deprotonation with NaOH lead to the di-aza-di-benzo-tetraethylene glycol **30** which was transformed into tetratosylate derivative **31**. The reaction of calix[4]arene with 2 equivalents of **31** using conditions previously described leads to the tetratosylate derivative **32**. Ditosylation of compound **32** with H_2SO_4 produced the expected 1,3-calix[4]-bis-(di-aza-di-benzo-crown-6) **27**.

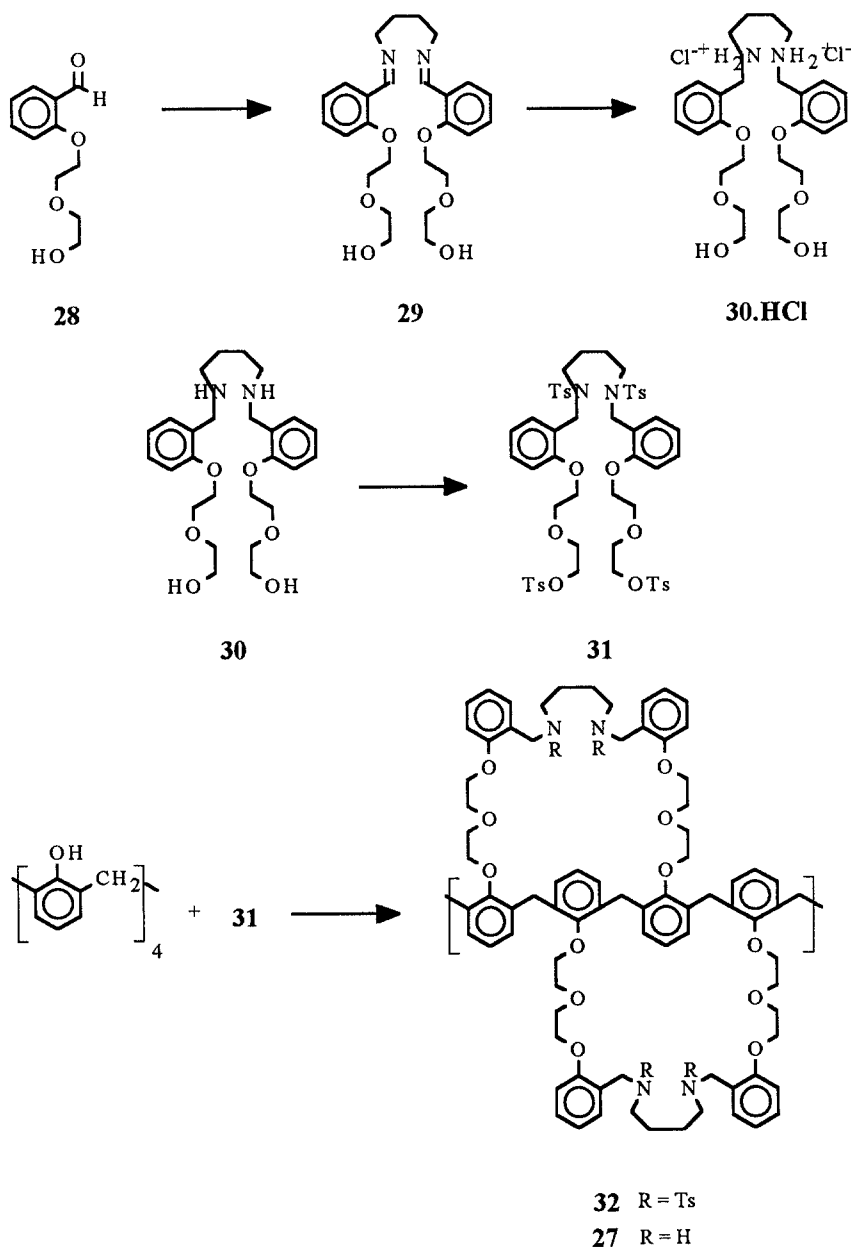


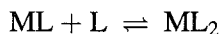
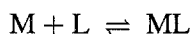
Fig. 8. Stepwise synthesis of hydrogenated *bis*-Schiff base-calix[4]arene **27**.

6. Metal Complexation

Preliminary binding properties of Schiff base-*p-tert*-butylcalix[4]arenes **17–20** were tested by solvent extraction of alkaline, alkaline earth metal, Mn, Fe, Co, Ni, Cu, Cd, Pb, Y, Pr, Nd, Eu, Gd, Yb picrates into dichloromethane under neutral

conditions [29]. In a general manner **17** was observed to extract less than its 3- and 4-carbon-containing homologues [29]. Alkali and alkaline earth cations were poorly extracted [29]. Heavy metal cations are better extracted, with higher preference for Pb^{2+} (15% and 18%) with **18** and **19**, respectively [29]. In the lanthanide series, there is an extraction selectivity for Nd^{3+} (12%) and Eu^{3+} (13%) ions with **18** and for Eu^{3+} (14%) with **19**. The best extracted metal ions were tested with the aromatic ligand **20** which showed a good extracting ability for Cu^{2+} (24%) [29]. The more efficient systems in extraction were studied in complexation by UV-visible spectrometry. All the data were interpreted by the presence of 1 : 1 complexes [29]. As was foreseen from the extraction results, the binding ability depends on the length of the Schiff base bridge. The optical cavity size for Eu^{3+} and for the larger Pb^{2+} is the bridge containing three carbons [29].

Zinc cation complexation by di-aza-benzo-crown-ether-*p-tert*-butylcalix[4]-arene **21** in $\text{CDCl}_3/\text{CH}_3\text{OH}$ was studied by monitoring the $^1\text{H-NMR}$ upon addition of Zn^{2+} . The plot of data obtained after mixing indicated a well-defined titration curve with mole ratio 1 : 1 and 2 : 1 until complete addition of 6 equivalents of Zn^{2+} . The reaction solution reached equilibrium after 26 days, fitting with a total formation of a 2 : 1 complex. The data were analyzed by employing two equations:



with $\log K_1 = 3.6$ and $\log K_2 = 3.0$. All the results were rationalized by a rapid chelation of a first Zn^{2+} by the two nitrogens followed by a slower entry of a second Zn^{2+} into the remaining six-oxygen array [31].

7. Conclusions

To summarize, in this paper we have presented the synthesis of calixcrowns and calix(aza)crowns. Calixcrowns were prepared by a one-pot procedure. Depending on the nature of the reactants and on the experimental conditions one can induce the reaction towards the formation of calix-*bis*-crowns, double calixarenes or double calixcrowns. Alkali metal complexation ability of the calixcrowns was studied and the selectivity of complexation was observed to depend on the number of oxygens in the polyether chain. This fundamental study found an application in the transport of Cs^+ through SLMs with selectivity $\text{Na}^+/\text{Cs}^+ \sim 1/45\,000$.

Calix(aza)crowns and 1,3-calix[4]-*bis*-(aza)crowns were constructed via the Schiff base intermediates. The Schiff base-calixarenes were observed to preferentially complex soft cations, probably due to the presence of nitrogen atoms. The best systems were for Pb^{2+} and Eu^{3+} with stability constants ~ 5 log units. Zn^{2+} complexation by a calix(aza)crown was studied, showing that the receptor occludes two metals by two distinguishable steps.

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