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-calix-crowns 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 throught supported liquid membranes (SLMs). The best
Na^+/Cs^+ selectivity (1/49000) was observed for the naphtyl derivative <u>7</u>.
Calix(aza)crowns and 1,3-calix[4]-*bis*-(aza)-crowns were also produced throught
the preliminary formation of the Schiff-base-calixarenes which were further
hydrogenated. The syntheses consisted or via the 1,3-selective alkylation of
calixarenes followed by cyclization into a 1,3-bridge either the direct 1,3-capping
of the calixarene with appropriate ditosylates. Soft metal complexation by these
ligands is also presented.

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...) (2). To create these
application-directed-macrocycles chemists have developed the synthesis of macropolycycles or cage-molecules
(3) with molecular framework combining simple molecular elements already existing the functions of which are
known. Since 1991 we developped the synthesis of macropolycycles containing in their molecular structure the
monocyclic structure of calixarenes and crown ether elements. This combination drives in proximity 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 already showed evidence of such cation-
substrate contact during a triple inclusion by a calixarene (4). 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 (4).

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
polyetherchains. The first member of this family was produced by Alfieri et al. (5) who reacted pentaethylene
glycol ditosylate with *p-tert*-butylcalix[4]arene in basic conditions to produce 1,3-*p-tert*-butylcalix[4]crown-6.
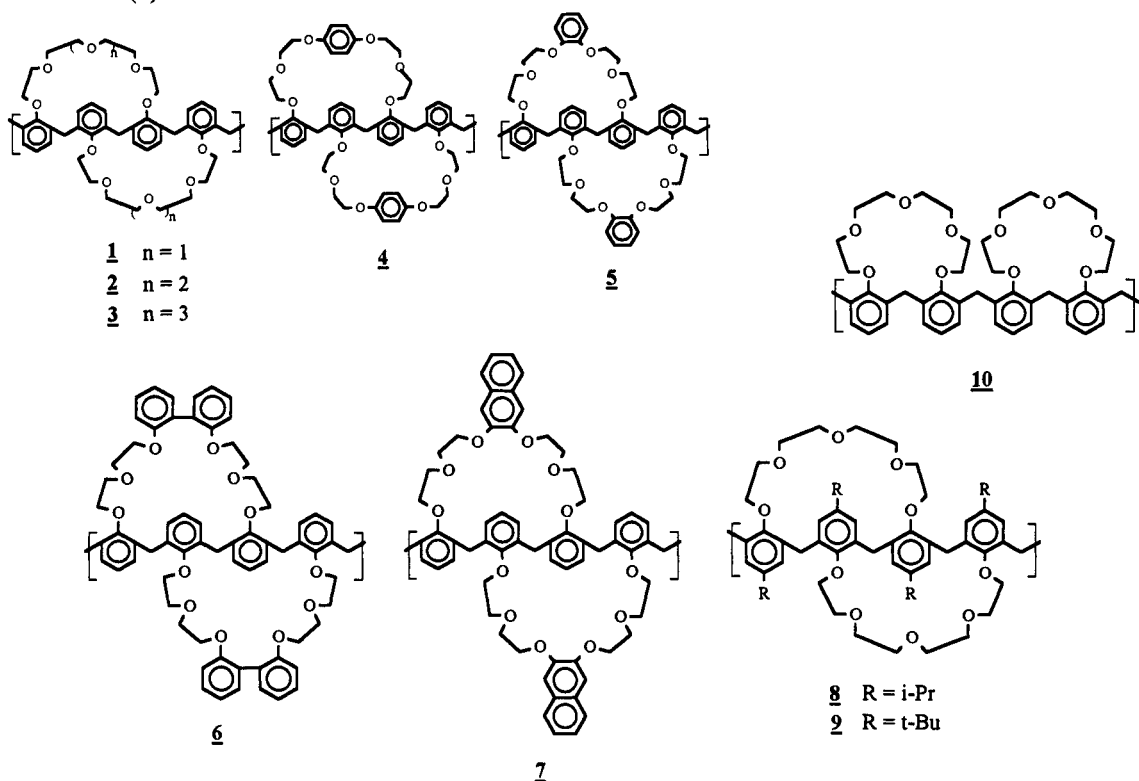
CALIXCROWNS

We 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 I).
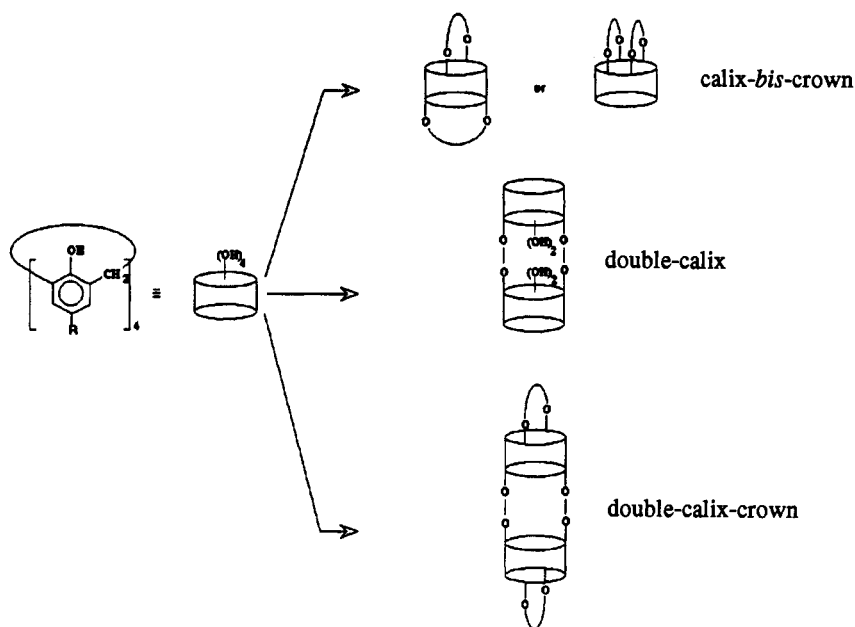
Scheme 1. Different pathways to calixcrowns

The reaction of calix[4]arene with 4-6 equiv. of various ditosylates (containing 5, 6, 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 (6). The formation of **1-7** implies a preliminary *distal* 1,3-capping of the calix[4]arene by one glycolic chain. The second capping enforces the calixarene to adopt the 1,3-alternate conformation which is effectively observed in the ^{1}H-NMR spectra. Similar reactions afforded 1,3-*p*-*iso*-propylcalix[4]crown-5 **8** (to evidence the reaction to be general) and 1,3-*p*-*tert*-butylcalix[4]crown-5 **9** (to compare to the published molecule (7)). 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* (8). ^{1}H-NMR indicated that the calix[4]arene moiety is in cone conformation (8).

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

4

5

10

6

7

8 R = i-Pr
9 R = t-Bu

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** (9) and 1,2-calix[4]-*bis*-crown-5 **10** (8).
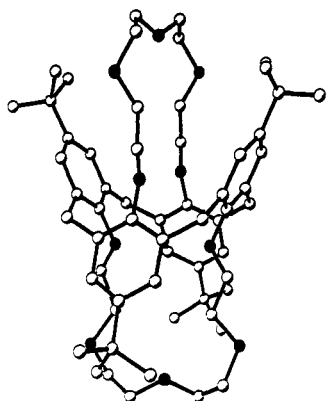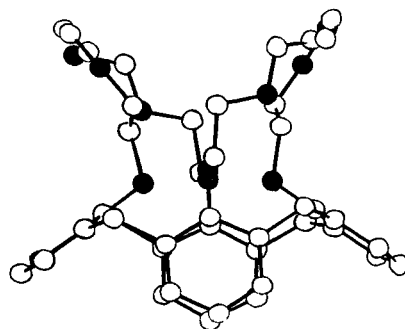

1,3-*p-tert*-butylcalix[4]crown-5 **9** (9)   1,2-calix[4]-*bis*-crown-5 **10** (8)

When *shorter* ditosylates where used *lower rim-lower rim* double-calixarenes were obtained (10). For instance, the reaction of calix[4]arene, *p-tert*-butyl- and 1,3-dimethoxy-*p-tert*-butylcalix[4]arene with 2 equiv. of triethylene glycol ditosylate lead to **double-calixarenes 11**, **12**, and **13** in very good yields. They were shown to consist of two calix[4]arene units linked by two distal glycolic chains. ^{1}H-NMR showed the calixarene moieties to be in cone conformation (10). Recently a double-calix[4]arene, very similar to **11-13**, linked with two tetraglycolic chains (R = monoglycol; R' = t-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 (11) . 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 (12). ^{1}H- and [13] 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).
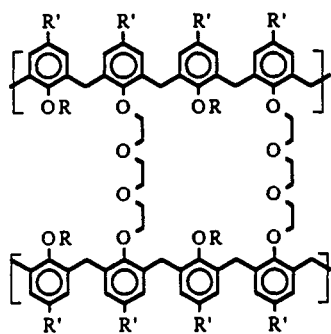
11 R = R' = H
**12** R = H   R' = t-Bu
13 R = Me   R' = t-Bu
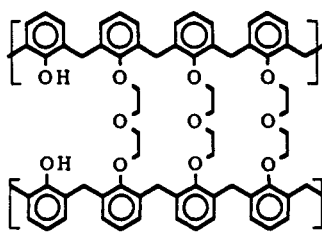
14
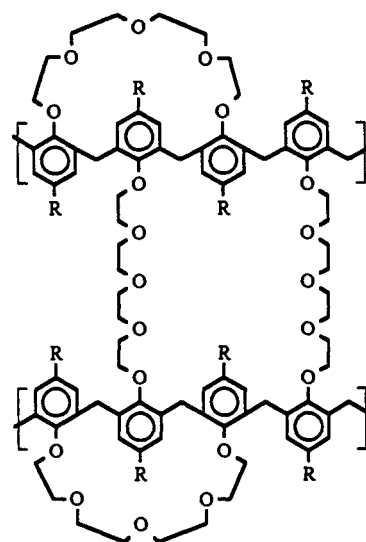
15 R = t-Bu

Subsequently to these results, we discovered a striking example of the formation of **a double-calix-crown** by changing the stoichiometry of the reactants. *p-tert*-Butylcalix[4]arene was treated with 15 equiv.-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 (13).

The preparation of 1,3-calix[4]-*bis*-crowns and double-calix-crowns was also performed with the mesitylene derived calix[4]arene or calix[4]mesitylene which exists in the only 1,3-alternate conformation (14) allowing to conclude that 1,3-calix[4]-*bis*-crowns are formed with longer glycolic chains while double-calix-crowns are formed with shorter and more rigid ones (15, 16).

n = 1
n = 2
n = 3
n = 4
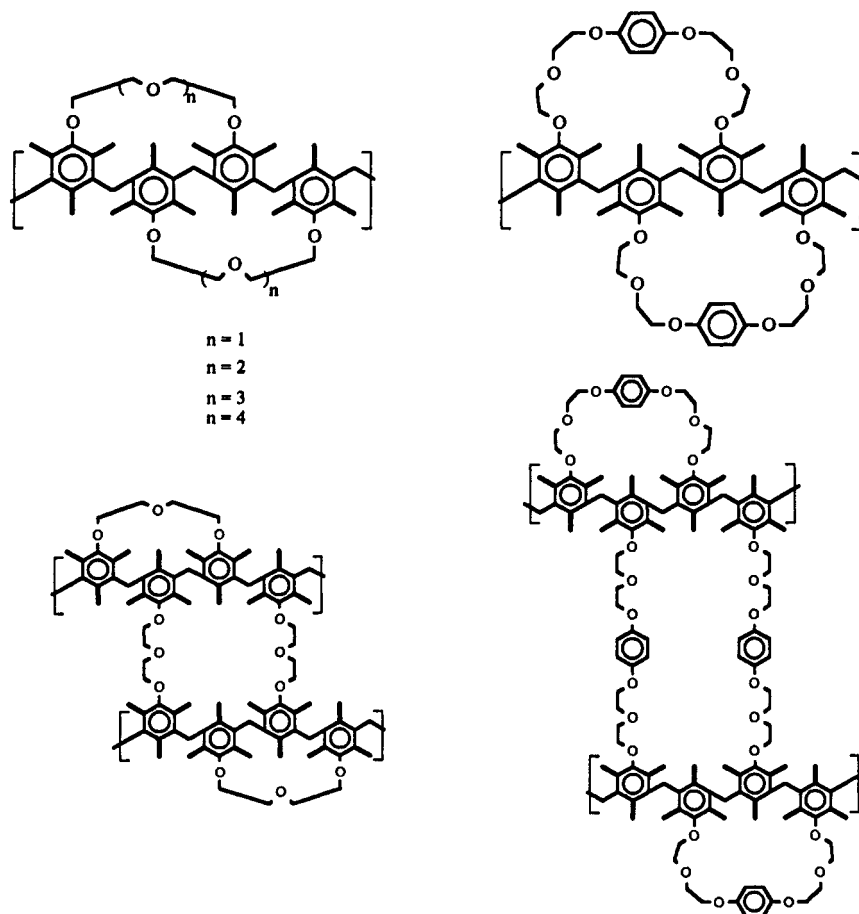
METAL COMPLEXATION PROPERTIES

Our interest was in application of recovery of **cesium** from wasted waters by solvent extraction processes using an extractant able to selectively bind the cesium in the presence of large amounts of sodium (17). Only those calixcrowns in the 1,3-alternate conformation were tested for complexation of alkali cations due the *spherical geometry* they offer comparable to spheric cryptands of Graf and Lehn (18). 1,3-Calix[4]-*bis*-crowns **1-3**, **5** and **7** were first shown to extract alkali ions except 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 ^1H-NMR. The presence of original and shifted signals of the protons of the polyetheral chain in a 1:1 integration ratio lended support to a location of the cation in one polyetheral loop. From the X-ray structure of **9** (9) the approximate radius of one polyether loop was determined to be ~ 1.5 A°, a size approximatively complementary to K^+ and Rb^+ leading to assume that calixcrown containing 6 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 chains. *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 crystalline structure of **9** (9).
Additional *solvent extraction* of alkali picrates from water phase to dichloromethane solutions and the UV-determination of the constants of complex formation of in methanol showed the selectivity of complexation to be in the order $Cs^+ > Rb^+ \sim K^+ > Na^+ > Li^+$ for those 1,3-calix[4]-*bis*-crowns **2**, **5**, and **7** containing 6 oxygens in the glycolic chain (19).
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. Ligand **15** extracted Li^+ (3%), Na^+(2%), K^+ (35%), Rb^+ (45%), Cs^+ (7%) with the hightest K values = 4.9 and 5.2 log units respectively for K^+ and Rb^+ (13).

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 throught supported liquid membranes (SLMs). They transported Cs^+ through microporous propylene support (NPOE) from acidic phase (HNO_3 1N, $NaNO_3$ 3N). The best Na^+/Cs^+ selectivity (1/45000) was observed for the naphtyl derivative **7** (20). The selectivity was attributed to π-metal interactions favorable to complexation of a large Cs^+ cation polarisable and poorly hydrated when compare to sodium cation.

CALIX(AZA)CROWNS

We precedently described the synthesis of calixcrowns by one-pot reactions. The **calix(aza)crowns** were constructed in a different approach. The synthesis began with the condensation of cone-1,3-dialdehyde derivative **16** with various primary diamines afforded **Schiff-base-*p-tert*-butylcalix[4]arenes 17-20** in cone conformation (21, 22). Hydrogenation of **18** and **19** with $NaBH_4$ produced chlorhydrates **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 (23).

	X
17	$(CH_2)_2$
18	$(CH_2)_3$
19	$(CH_2)_4$
20	

21.HCl   n = 1
22.HCl   n = 2

21   n = 1
22   n = 2
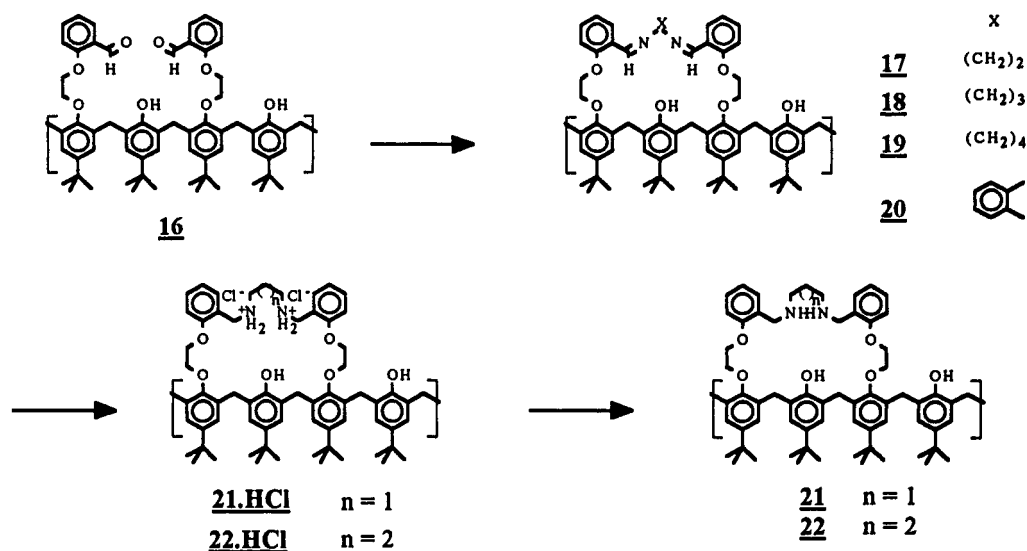
In a similar manner we achieved the synthesis of *bis*-**Schiff-base-calix[4]mesitylenes 25** and **26** from the corresponding tetraaldehydes **23** and **24**. We could not hydrogenate **25** and **26** due to their low solubility in the usual solvents for carrying out the reaction.

23 n = 0
24 n = 1

25 n = 0
26 n = 1
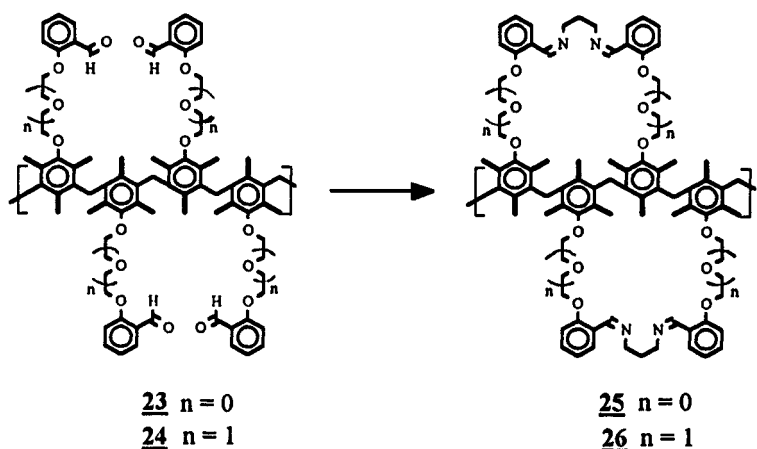
We were unable to prepare the tetraaldehyde precursor corresponding to the calix[4]arene and the synthesis of the hydrogenated *bis*-Schiff-base-calix[4]arene **27** was achieved by stepwise synthesis. Aldehyde **28** was prepared from salicylaldehyde and 2-(2-chloroethoxy)-ethanol. Condensation of **28** with 1,4-diaminobutane lead to the Schiff-base **29** which was hydrogenated with $NaBH_4$ into the chlorhydrate **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 equiv. of **31** in conditions previously described lead to the tetratosylate derivative **32**. Detosylation of compound **32** with H_2SO_4 produced the expected **1,3-calix[4]-*bis*-(di-aza-di-benzo-crown-6) 27**.

28   **29**   **30.HCl**   **30**   **31**


32 R = Ts
27 R = H
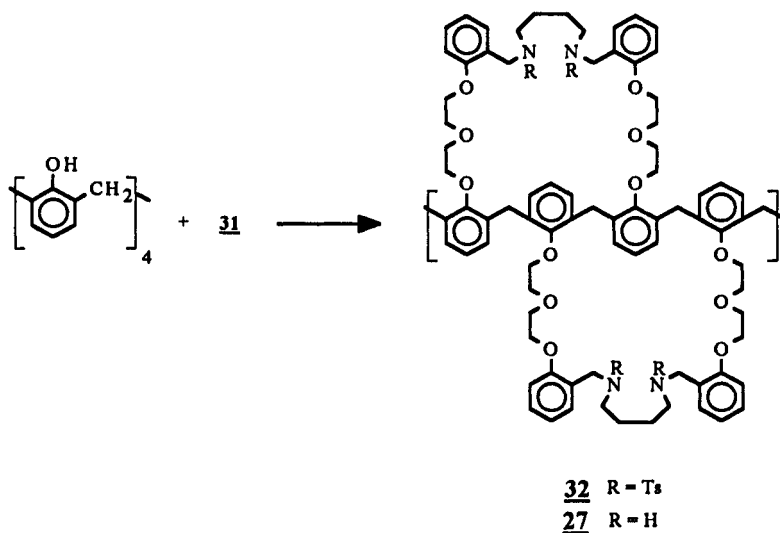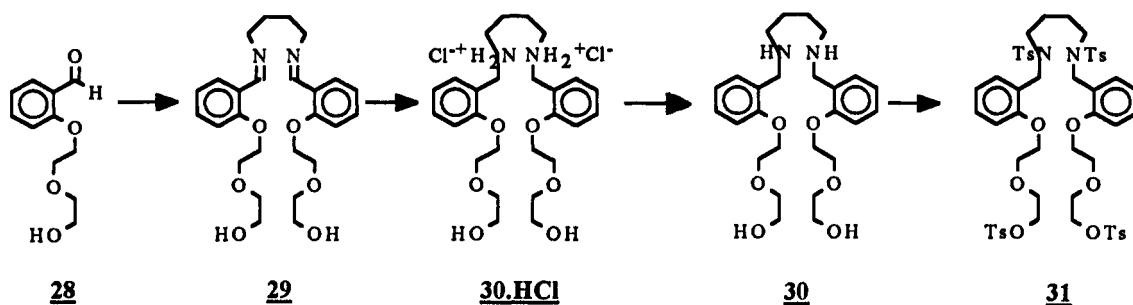
III. 2. METAL COMPLEXATION

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 in neutral conditions (21). In a general manner **17** was observed to extract less than its 3 carbons and 4 carbons containing homologues (21). Alkali and alkaline earth cations were poorly extracted (21). Heavy metal cations are better extracted with higher preference for Pb^{2+} (15% and 18% with **18** and **19** respectively) (21). 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%) (21). 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 (Table 1) (21). As was foreseen from extraction results, the binding ability depends on the lenght of the Schiff-base bridge. The optimal cavity size for Eu^{3+} and for larger Pb^{2+} is for the bridge containing three carbons (21).

Zinc cation complexation by di-aza-benzo-crown-ether-*p-tert*-butylcalix[4]arene **21** in $CDCl_3/CH_3OH$ was studied by monitoring the ^{1}H-NMR upon addition of Zn^{2+}. The plot of data obtained after mixing indicated a well-define titration curve with mole ratio 1:1 and 2:1 untill complete addition of 6 equiv. of Zn^{2+}. The reaction

solution reach equilibrium after 26 days fitting with a total formation of a 2:1 complex. Analysis of data by employing two equations :

$$M + L \Leftrightarrow ML$$
$$ML + L \Leftrightarrow ML_2$$
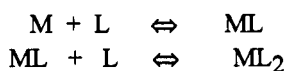
with $\log K_1 = 3.6$ and $\log K_2 = 3.0$. All the results were rationalized by a rapid chelation of a first Zn^{2+} by the two nitrogens followed by a slower entering of a second Zn^{2+} in the remaining six oxygens array (23).

CONCLUSION

To summarize, in this work we presented the synthesis of calixcrowns and calix(aza)crowns. Calixcrowns were prepared by 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-calix-crowns. 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 $Na^+/Cs^+ \sim 1/45000$.

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 complex preferentially 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 the receptor to occlude two metals by two distinguishible steps.

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