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New synthetic receptors based on calix[4]arenes for the selective recognition of ions and neutral molecules

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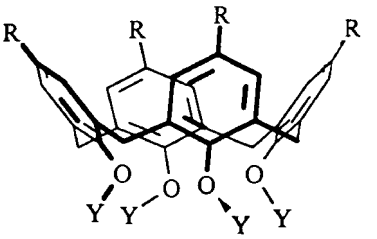
Abstract
The conformational properties of calix[4]arene derivatives have been exploited to synthesize new receptors for the selective encapsulation of metal ions and neutral molecules. 1,3-Dialkoxycalix[4]arene-crown-5 conformers fixed in the *1,3-alternate* structure are the most selective potassium ionophores known sofar which have a K^+/Na^+ selectivity higher than valinomycin. The corresponding crown-6 derivatives show a very high Cs^+/Na^+ selectivity which allows their use in the removal of ^{137}Cs from highly salted radioactive waste. Highly preorganized and rigid *cone* calix[4]arene derivatives, in which the $C_{2v} \Leftrightarrow C_{2v}$ interconversion is inhibited after the introduction of bridges at the lower and upper rim, are able to complex small organic molecules having acidic CH groups, both in the gas phase and in $CDCl_3$ solution.

INTRODUCTION

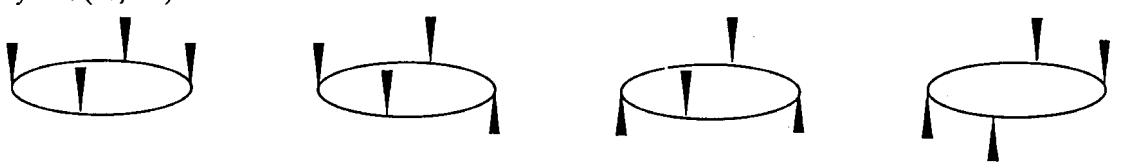
Calixarenes are ditopic receptor molecules which have received much attention in the last few years in Supramolecular Chemistry (1-8).

The lower rim of the calix (phenolic OH groups) can be easily functionalized and binding groups of different donor strength or coordinating characteristics can be attached to obtain metal ion ligands having the desired properties (3). In the case of calix[4]arenes (**1**), methods have been developed for the control of regio- and stereoselectivity in their lower rim functionalization. Beside tetrafunctionalization which is quite easy (1), mono-alkyl derivatives of calix[4]arenes can be obtained in good yields (9) and also proximal (10) or diametrical (11) difunctionalized, and trifunctionalized compounds (12) have been synthesized. The tetramethoxy and tetraethoxy derivatives of calix[4]arenes are conformationally mobile and their conformational preferences have been established in solution (13), in the solid state (4) and in the gas-phase by Molecular Mechanics (14).



1a: R = *t*-Bu, Y = H
1b: R = H, Y = H
2 : R = *t*-Bu, Y = CH_2COOt-Bu
3 : R = *t*-Bu, Y = CH_2CONEt_2

Bulkier substituents or bridges, block the macrocycles in one of the possible conformations i.e. *cone, partial cone, 1,3-alternate* or *1,2-alternate* and conditions have been found to obtain the desired stereoisomers in reasonably good yields (10, 15).



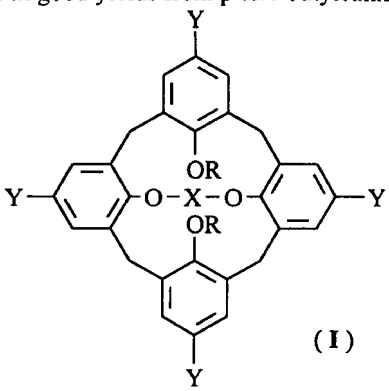
cone *partial cone* *1,3-alternate* *1,2-alternate*

We report in this paper the most recent results on alkali metal ions and neutral molecules recognition by functionalized calix[4]arenes.

POTASSIUM SELECTIVE CALIXCROWNS

Previously we have synthesized calix[4]arene podands (**2** and **3**) bearing four ester (16) or four amide (17) binding groups anchored at the lower rim, which have shown a very good sodium selectivity both in two phase extraction (2, 18) and in homogeneous solution (19). The tetramide ligand (**3**) was also able to form luminescent complexes with lanthanide ions both in solution (20) and in the solid state (21).

A second class of interesting metal ion ligands are the lower rim 1,3-bridged calix[4]arenes. The nature of the bridge X and of the alkyl groups R in **I** determine the conformation of the calix and the binding properties of the ligands. Among the many bridged calix[4]arenes which have been synthesized and studied (2, 3) we will describe a particular class, the calixcrowns, because they have shown a very subtle structural control on cation binding. The 1,3-dialkoxy-p-*tert*-butylcalix[4]arene-crown-5 derivatives (**4-6**) are potassium selective ionophores which can easily obtained in good yields from p-*tert*-butylcalix[4]arene (**1a**) (22 , 23).



(I)

X = -$(CH_2CH_2O)_3CH_2CH_2$-

4: R = Me, Y = *t*-Bu
5a: R = Et, Y = *t*-Bu *cone*
5b: R = Et, Y = *t*-Bu *partial cone*
5c: R = Et, Y = *t*-Bu *1,3-alternate*
6: R = *i*-Pr, Y = *t*-Bu *partial cone*
7: R = Me, Y = H
8a: R = *i*-Pr, Y = H *cone*
8b: R = *i*-Pr, Y = H *partial cone*
8c: R = *i*-Pr, Y = H *1,3-alternate*

Although all these ligands are selective for potassium cation, their efficiency strongly depends on the nature of the alkyl groups R and on the stereochemistry around the binding region (22, 23) (Fig. 1). The 1,3-dimethoxy derivative **4** is conformationally mobile, but adopts a flattened *cone* conformation both in the solid state and in solution (22). Upon complexation with a potassium cation the ligand **4** adopts a *partial cone* structure since one methoxy group is able to pass through the annulus on the bottom of the calix. Evidence for this conformational rearrangement was clearly shown by the ^1H NMR spectrum of the potassium picrate 1:1 complex in $CDCl_3$ (22). Compounds **5a-c** and **6** are conformationally rigid.

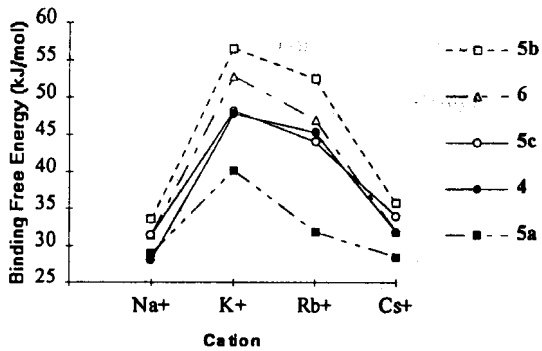
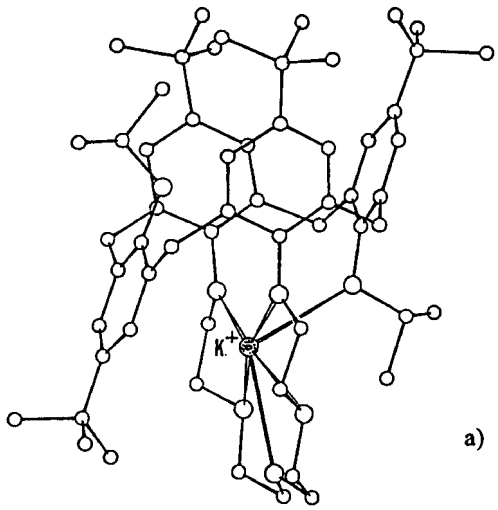


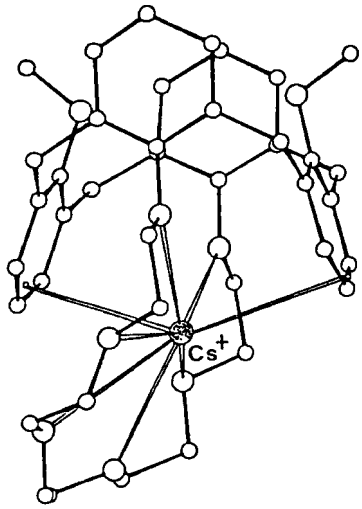
Fig. 1 Binding free energies (-ΔG°) of complexes of hosts **4, 5** and **6** with alkali picrates in $CDCl_3$ at 22°C.

Figure 1 reports the binding free energies (-ΔG°) for the complexation of alkali metal picrates in $CDCl_3$ saturated with H_2O established by Cram's method (18). Compound **5b**, in the fixed *partial cone* structure is more efficient than the *cone* and *1,3-alternate* isomers **5a** and **5c** and the conformationally mobile 1,3-dimethoxy derivative **4**. In the *partial cone* conformation one rotated nucleus can partecipate to complexation as shown by the X-ray crystal structure of the potassium complex of ligand **6** (Fig. 2a) (23).

On the basis of these results we have recently investigated (24) the behaviour of other calix[4]arene-crown-5 stereoisomers **8a-c** derived from unsubstituted calix[4]arene **1b**.



a)



b)

Fig. 2 X-ray crystal structures a) of the K^+ complex of ligand **6** and b) of the Cs^+ complex of ligand **10**.

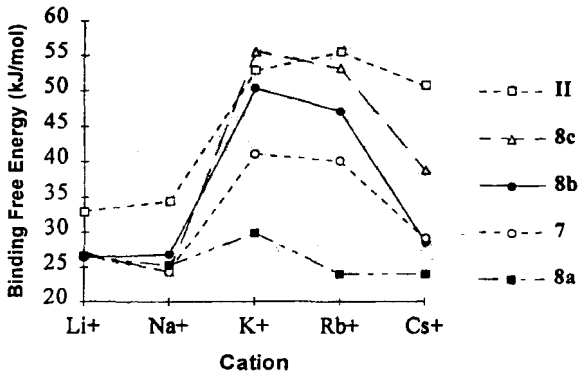


Fig. 3 Binding free energy (-ΔG°) of complexes of hosts **7**, **8** and valinomycin **II** with alkali picrates in $CDCl_3$ at 22°C.

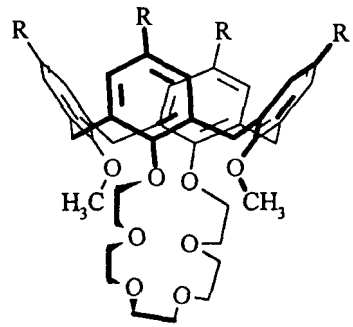
Also in this case, the conformationally mobile 1,3-dimethoxy derivative **7** is present in the *cone* conformation both in solid state and in solution. However, differently from **4**, compound **7** assumes a *1,3-alternate* conformation upon complexation with potassium picrate in CD_3CN or CD_3OD solution. The binding free energies (-ΔG°) in $CDCl_3$ saturated with H_2O strongly indicates that for the series of calixcrowns derived from unsubstituted calix[4]arene **1b**, the preferred conformation for binding potassium ion is the *1,3-alternate* followed by *partial cone* and *cone*. The K^+/Na^+ selectivity shown by **8c** (ΔΔG° = 31.2 kJ/mol) in $CDCl_3$ (Fig. 3) is the highest observed sofar for an ionophore, being also higher than that of valinomycin **II** in the same conditions (ΔΔG° = 18.4 kJ/mol).

CESIUM SELECTIVE CALIXCROWNS

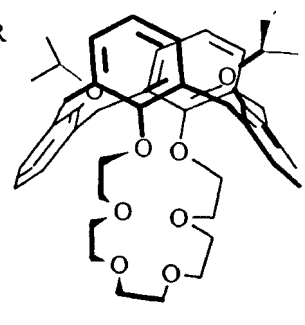
An even more convincing evidence of the importance of cation/π interaction in determining efficiency and selectivity in metal ion recognition is observed in calix[4]arene-crown-6 derivatives. The conformationally mobile 1,3-dimethoxy derivatives **9** and **10** are less efficient than the corresponding crown-5 (**4** and **7**) in complexing alkali metal cations with the exception of cesium for which they show a binding free energy (-ΔG°) of 37.3 kJ/mol for **9** and 33.8 kJ/mol for **10**, in $CDCl_3$ (25) (Fig. 4).

The cesium/sodium selectivity, which is important in radioactive waste treatment, shows a value of ΔΔG° = 10.9 kJ/mol for **9** and ΔΔG° = 9.5 kJ/mol for **10** in $CDCl_3$. Interesting observations on the binding mode of these ligands have been made by ^1H NMR (400 MHz) titration of ligand **10** with alkali metal picrates.

In CD_3CN solution at room temperature, the conformationally flexible free ligand **10** exists mainly in the *cone* conformation, so as its 1:1 sodium picrate complex. On the contrary the Cs^+Pic^- 1:1 complex clearly adopts a *1,3-alternate* conformation. The driving force for this conformational interconversion is the interaction of the cesium cation with two opposite aromatic nuclei (cation/π interaction). The definitive proof of the molecular structure of the cesium complex comes from X-ray diffraction studies (Fig. 2b) which show the *1,3-alternate* conformation for the calix and the absence of any coordination of the cation to the methoxy groups.



9: R = *t*-Bu **10**: R = H



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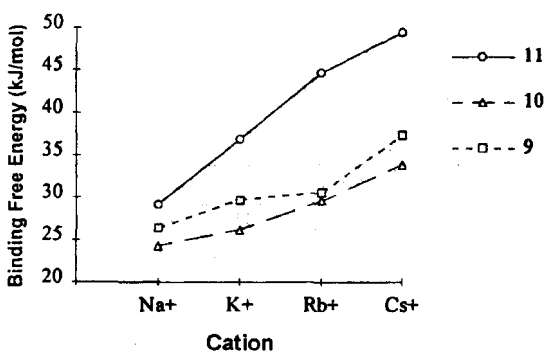


Fig. 4 Binding free energies (-ΔG°) of complexes of hosts **9-11** with alkali picrates in $CDCl_3$ at 22°C.

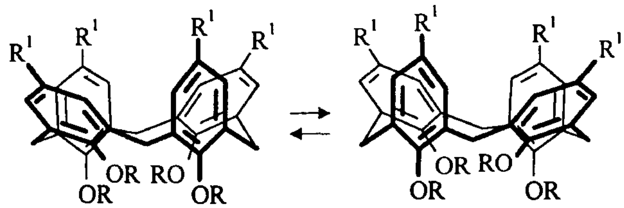
The crown ring is somewhat bent by the presence of the picrate anion in the coordination sphere of the cesium cation. These data suggest that the combination of the right size in the polyether ring and the calix[4]arene fixed in the *1,3-alternate* conformation could result in very efficient cesium selective ionophores. We therefore synthesized several calix[4]arene-crown-6 derivatives in the fixed *1,3-alternate* conformation and among them the most interesting compound is the di-*iso*-propoxy derivative **11**, which shows a very high efficiency in the complexation of alkali metal cations (except Na^+) and a Cs^+/Na^+ selectivity ΔΔG° = 20.2 kJ/mol in $CDCl_3$ (Fig. 4).

Interestingly enough, the selectivity measured in conditions of the real radioactive waste (4M $NaNO_3$, 1M HNO_3) as the ratio $\alpha = D(Cs^+)/D(Na^+)$ of the distribution coefficients (D) between water and ortho-nitrophenylhexyl ether (o-NPHE) reaches the value of $7x10^4$ in the case of compound **11**. Also the Cs^+/Sr^{2+} selectivity ($\alpha = 8x10^4$) is quite impressive (26).

What emerges from all these experimental results with calix[4]arene-crown ethers is that we have two control elements of efficiency and selectivity in metal ion complexation. The first one is the ring size (crown-5 favouring potassium and crown-6 cesium) and the second one is the calix conformation.

COMPLEXATION OF NEUTRAL MOLECULES IN *CONE* CALIX[4]ARENES

Most of the symmetrically substituted calix[4]arene *cone* isomers (12), adopt a *"flattened cone"* conformation in the solid state, showing a C_{2v} symmetry (1-8). This conformation has been also shown to be the most stable by Molecular Modeling (14). In solution, the ring inversion process is blocked when the substituents R at the lower rim are bulkier than ethyl (27), but some conformational flexibility still exists, and the C_{4v} symmetry, usually observed in the ^1H NMR spectra of these compounds, is considered to be the result of a rapid interconversion between two C_{2v} structures (28 ,29 ,30).



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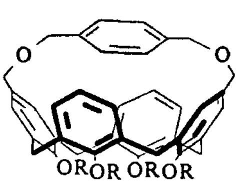
C_{2v} C_{2v}

For most of the uses of calix[4]arene *cone* isomers, this more subtle conformational interconversion is usually neglected. However we have recently observed that this flexibility influences the reactivity of functional groups introduced at the upper rim, expecially in the diametrical positions, favouring *intra*-molecular processes (31). Furthermore this residual flexibility is probably responsible for the negative results obtained in the complexation studies of calix[4]arene based cavitands in organic media.

In a preliminary study aimed at having direct experimental evidence of the flexibility of *cone* conformers of tetraalkoxycalix[4]arenes, we carried out a variable temperature ^1H NMR experiment on tetrakis(n-octyloxy)calix[4]arene (**12**: R = *n*-Oct, R^1 = H). Decreasing the temperature to 213 K the NMR spectrum changes, indicating freezing of the molecular motion in a *"flattened cone"* conformation (30).

In order to have less mobile hosts two general synthetic strategies for rigidifying the calix[4]arene skeleton were devised, taking advantage of our previous studies on the selective functionalization at both rims (11, 32). In the first approach, the apolar cavity of the calix[4]arene was enforced by introducing rigidifying groups at the diametrical position of the upper rim. Thus, new cavitands (13-15) having π-donor rigid bridges, were synthesized and their complexation properties towards neutral organic molecules tested.



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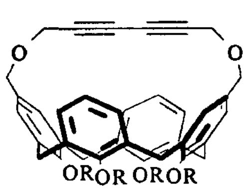

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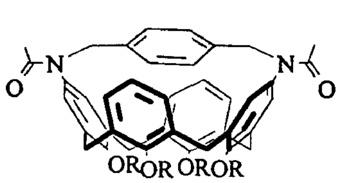

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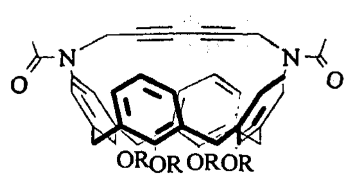

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TABLE 1. Gas-phase relative complexation constants of hosts **13**, **15**, **16** and neutral molecules.

		13		16		15	
G_1/G_2		Ka	% compl.	Ka	% compl.	Ka	% compl.
MeCOO*n*-Pr/ *n*-PrOH	1:1	>50	30	3.7	50	18	70
MeCOO*t*-Bu/MeCOO*n*-Pr	1:1	4.2	30	3.8	80	2.7	80
MeCOO*t*-Bu/ *t*-BuOH	3:1	>50	10	1.4	50	4.5	75
t-BuOH / *i*-PrOH	1:1	/	< 5	1.9	75	4.6	70
MeCOO *i*-Pr / *i*-PrOH	3:1	>50	20	5.7	70	33	90
MeCOO *i*-Pr /MeCOOEt	2:1	2.5	15	2.3	90	2.1	90
MeCOEt/ MeCOOEt	1:1	0.81	40	1.7	85	1.8	90
MeCN/ MeCOOEt	2:1	0.13	30	0.82	75	0.58	90
MeCN / C_6H_6	2:1	/	< 5	>50	45	>50	70

In order to enhance the host-guest interactions and prevent solvation of the host and guest the complexing abilities of these new cavitands were investigated in the gas-phase (33), using a mass spectrometric technique (34). In Table 1 the relative complexation constants of hosts **13**, **15** and **16** towards guests G_1 and G_2, in competition, are listed. The first macroscopic feature is that cavitands **15** and **16** strongly interact with most candidate guests to give extensive complexation (60-90%) whereas the percentage of cavitand **13** undergoing host-guest complexation is low (10-40%) and that of cavitand **14** is negligible, as for nonbridged calixarenes. The existence of a rigid cavity seems to be a fundamental requisite for observing strong gas-phase supramolecular interactions. The cavitands exhibiting the highest complexation efficiency are also quite selective; **15** and **16** strongly interact with esters, ketones and acetonitrile, but weakly with benzene and alcohols. Thus, the complex stability seems to be determined by multiple interactions between the acidic methyl hydrogens of the guest (α to the electron-withdrawing groups) and the π electrons of the host cavity and of the bridge.

In the second and complementary synthetic approach, rigidifying units were introduced at the lower rim, keeping the upper rim available for further functionalization. The choice of the rigidifying units was made in order to reach the best compromise between their chemical stability and rigidity of the host. By reacting calix[4]arene **1a** or **1b** in DMF with diethylene glycol di-*p*-toluenesulfonate in the presence of an excess of NaH (10) the proximal bis-crowns **17a** and **17b** have been obtained in 30% and 55% yield respectively. The temperature independent ^{1}H NMR spectra indicate that these compounds have an almost immobile *cone* structure, imposed by bridges.

TABLE 2. Association constant Ka (M^{-1}) of **17a** and **17b** and neutral organic molecules in $CDCl_3$ at 300 K

	$MeNO_2$	$CH_2(CN)_2$
17a: R = t-Bu	26	6
17b: R = H	5	17

The tendency of hosts **17a** and **17b** to undergo host-guest interaction has been evaluated towards neutral molecules having acidic C-H bonds (e.g. $MeNO_2$ and $CH_2(CN)_2$) in $CDCl_3$ using ^{1}H NMR (35). Both receptors cause a significant upfield shift (0.3-0.9 ppm) of the methyl and methylene protons of the guest, which indicates the coordination of the guest inside the π-electron rich cavity of the calixarene. ^{1}H NMR titrations show a 1:1 stoichiometry between hosts and guests and provide quantitative data on their complexation (see Table 2).

The association constants reported in Tab. 2 show that malonitrile is better bound than the less acidic nitromethane by host **17b**, while host **17a** gives the opposite results. This different behaviour can be ascribed to a shape-selectivity due to the presence of *tert*-butyl groups at the upper rim of host **17a**, which favours complexation of the less acidic, but less bulky nitromethane.

As expected, mobile hosts, e.g. tetrakis(2-ethoxyethoxy)calix[4]arenes (**12**: R = $C_2H_4OC_2H_5$, R^1 = H, *t*-Bu) do not show complexation. These results point out the importance of preorganization of the host and represent the first example of neutral organic molecule complexation by calixarenes in organic media.

ACKNOWLEDGEMENTS

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