A New Calix[4]arene Binding Site. Strong Cooperativity in Cation Binding by a Two Site Receptor

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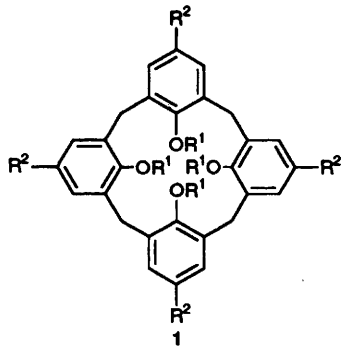
The new calix[4]arene derivatives **6** and **9**, which are both readily prepared from the cone conformations of calix[4]arene tetra-ethers, are both ionophores which show some Na^+/K^+ selectivity; the derivative **6** with two cation binding sites shows evidence for cooperativity between the two mechanically linked sites.

The development of calixarenes as a source of synthetic receptors for cations and, to some extent, neutral molecules has been an area of considerable activity in recent years.[1] In particular the 'lower rim' of calix[4]arenes has been used[2] as a site for a cation receptor by the attachment of suitable sidechains to the phenolic oxygens, for examples see **1**. The 'upper rim' has been used rather less as a receptor site although a number of synthetic approaches to upper rim functionality have been described,[1,3,4] and the formation of 'deep cavity' calixarenes by upper rim arylation has been the subject of recent communications.[5] Here we describe a calix[4]arene with a cation receptor site at the upper rim which may be combined with a second receptor site at the lower rim. The possibility of cooperativity between these two receptor sites is explored.

The calix[4]arene tetrabenzyl ether **2** is easily prepared[6] in good yield in a cone conformation free from other conformational species. Bromination[6] to give **3** and Suzuki arylation[7] with 3-benzyloxyboronic acid gives the octabenzyl ether **4**. Debenzylation of **4** gave the octahydroxycalix[4]arene **5** and alkylation with *N,N*-diethylchloroacetamide in the presence of sodium iodide converted **5** into the derivative **6** with a known cation binding site at the lower rim (*cf.* **1**) and a potentially new cation binding site at the upper rim. A rather similar reaction sequence of bromination and arylation using the cone conformation of calix[4]arene tetrabutyl ether **7** (prepared by alkylation of the cone conformation of the tributyl ether) gave the calix[4]arene derivative **8**. The octa-ether **8** was debenzylated and alkylated to give the derivative **9** which contains just the new upper rim binding site.

The cation binding properties of the new calix[4]arenes **6** and **9** have been compared with the known calix[4]arene **1b** using the picrate extraction procedure described by Cram and coworkers[8] which has been used by other groups for the examination of calixarene-based ionophores.[9] We note that the calix[4]arene derivatives **1b**, **6** and **9** in chloroform show pronounced extraction of picric acid and tetraethylammonium picrate from aqueous solutions in addition to extraction of sodium and potassium picrates. For this reason the extraction



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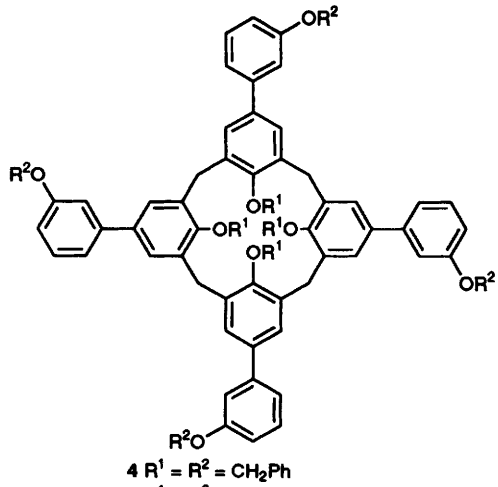
a $R^1 = CH_2CONEt_2$, $R^2 = Bu^t$
b $R^1 = CH_2CONEt_2$, $R^2 = H$

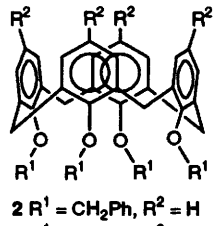


4 $R^1 = R^2 = CH_2Ph$
5 $R^1 = R^2 = H$
6 $R^1 = R^2 = CH_2CONEt_2$
8 $R^1 = Bu^n$, $R^2 = CH_2Ph$
9 $R^1 = Bu^n$, $R^2 = CH_2CONEt_2$

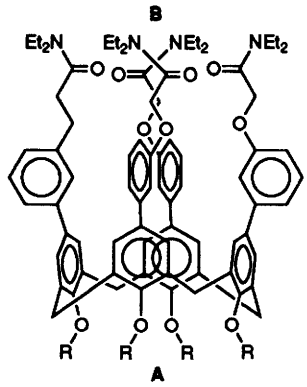
Table 1 Association constants (10^{-6} dm^3 mol^{-1})[a] for hosts **1a**, **6** and **9** and sodium and potassium salts

Salt	**1b**	**6**	$10^{-6} K_a$ **6–1b**[b]	**9**
NaSCN[c]	76.9 (71.4)	120 (74.9)	43	7.2 (45.7)
KSCN[c]	7.8 (50.3)	10.6 (54.0)	2.8	2.5 (35.2)
NaCl[c]	81.3 (68.9)	150 (74.1)	69	11.8 (47.9)
KCl[c]	18.7 (53.6)	19.8 (54.3)	1.1	4.9 (36.2)
Na picrate[d]	694 (70.7)	1568 (77.1)	874	169 (53.0)
K picrate[d]	134 (53.0)	267 (60.9)	133	66.5 (44.2)

[a] Determined by equilibration of a 10^{-4} mol dm^{-3} solution of the host in $CHCl_3$ with a 10^{-4} mol dm^{-3} aqueous solution of the guest salt at *ca.* 20 °C, the units for K_a are consistent with the method and assumptions of ref. 8. The numbers in parentheses refer to the equilibrium percentage extraction of guest salt into the organic phase for equal volumes of organic and aqueous phases. [b] This column shows the difference in association constants for **1b** and **6** which is a crude estimate of the contribution of site **B** in **6**. [c] Concentration of salt in the aqueous layer determined by atomic absorption spectroscopy. [d] Concentrations of picrate in the aqueous and organic layers determined by UV absorption spectroscopy.



2 $R^1 = CH_2Ph$, $R^2 = H$
3 $R^1 = CH_2Ph$, $R^2 = Br$
7 $R^1 = Bu^n$, $R^2 = H$



A

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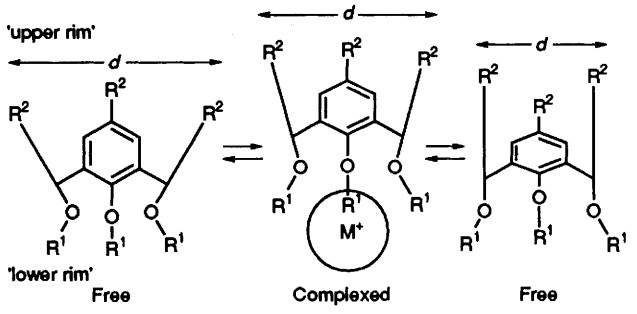

Fig. 1 Conformations of free and complexed calix[4]arene derivatives **1**. The descriptions 'upper rim' and 'lower rim' are used in accord with ref. 1.

of chloride and thiocyanate salts from aqueous solution has also been examined. The results of these various extraction experiments are reported in Table 1 which shows that all three salts give qualitatively similar results in spite of the differences in the anions.

The new calix[4]arene derivatives **9**, which contain just the upper rim binding site, show strong binding of sodium and potassium with modest selectivity for sodium. The interdependence of motion at upper and lower rims imposed by the rigid biaryl systems could lead to cooperativity between the two binding sites **A** and **B**, shown in **10**, of the bis-receptor **6** provided that complexation either at site **A** or at site **B** leads to more favourable geometry for complexation at the other binding site. Studies of the calix[4]arene **1a** by molecular dynamics[10] and crystallography[11,12] show that in the uncomplexed state an elongated cone conformation, having C_{2v} symmetry, is favoured, whereas the cation complexes require C_{4v} symmetry as summarised in Fig. 1. However, in the calixarene **6**, containing two binding sites, the conformational diagram **10** shows that perturbations at site **A** on complexation which involve changes in the tilt of the aromatic rings (Fig. 1) will be magnified by the rigid biaryl systems as larger perturbations at site **B**. This means that complexation at site **A**, which is expected to be the initial cation binding site on the basis of the data for calixarenes **1b** and **9** in Table 1, should set up a more favourable conformation for cation complexation at the second binding site **B**. In fact the effect appears to be significant and the results in Table 1 show some positive cooperativity in binding by the two site receptor **6** as compared with the sum of the binding by the two single site receptors **1b** and **9** when the guest cation is sodium but there is a rather smaller effect for binding potassium. However, since it is difficult to judge whether the calixarenes **1b** and **9** are accurate models for sites **A** and **B** in **6** and in view of the limited significance of K_a's estimated from extraction experiments this uncertainty was clarified by an examination of Na^+ binding by the two site receptor **6** using ^1H NMR spectroscopy. The ^1H NMR spectrum of the free host **6** is very different from that of the 2:1 Na^+ complex formed by the addition of a solution of NaSCN in CD_3OD to a solution of **6** in $CDCl_3$. A study of spectra recorded for Na^+:**6**, 0–2 shows that there are no signals in any of the spectra which are not assignable to either the free host **6** or the complex **6**·2Na^+, in particular there is no indication of detectable concentrations of the 1:1 complex **6**·Na^+. The addition of a large excess of salt solution does not result in any further change in the NMR spectrum. This result indicates that the enhancement of binding at site **B** by the pre-organisation associated with binding Na^+ at site **A** is substantial and is more than sufficient to offset the intrinsically weaker binding of site **B** which can be deduced from the results for compounds **1b** and **9** (Table 1).

In summary, binding Na^+ in the lower rim binding site **A** imposes the required 4-fold symmetry on the calix[4]arene system thus promoting binding at site **B**, probably by more than two orders of magnitude as compared with the binding at site **B** in the simpler receptor **9**.[13] This result may be compared with the allosteric medium effect which has been postulated[14] for simple calixarene derivatives related to **1**, in this case cation binding at the lower rim receptor site is enhanced by interaction of solvent with the upper hydrophobic cavity. The considerable distance between the two binding sites in **6** evidently avoids the unfavourable electrostatic situation that might lead to reduction in binding at the second site.[15]

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