Bifunctional Calix[4]arene Receptor : Cooperative Halides Binding with Cation

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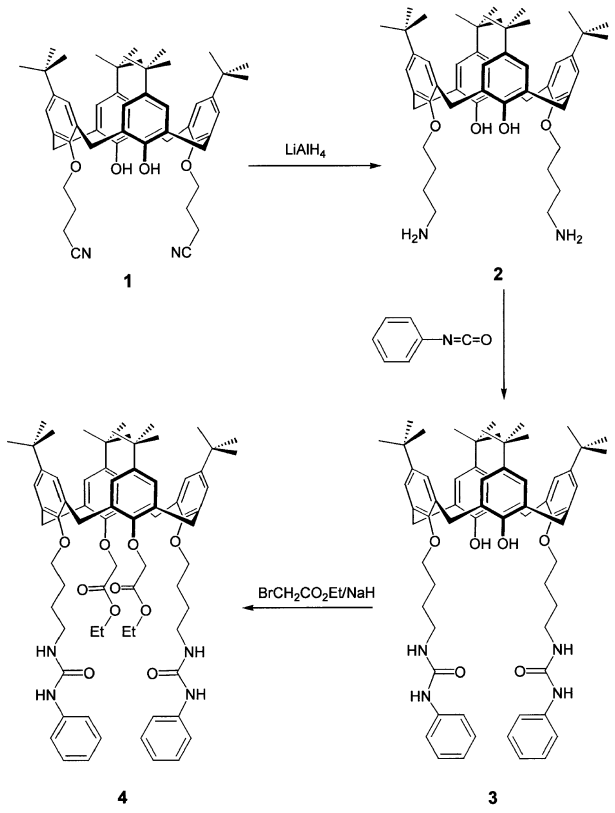
Development of bifunctional receptors of cation and anion guest is the exciting topic of coordination chemistry due to the fact that a large number of biological processes involve molecular recognition of cation and anion species. Most of the known synthetic receptors capture a particular anion without undergoing interaction with the cationic counterion. In a early study on simultaneous binding, Echmidtchen described the aza crown[1] containing ammonium salt moieties which bind such zwitterionic compounds as γ-aminoacid. A different strategy for simultaneous binding of cations and anions makes use of crown ethers containing σ-bonded metals having free coordination sites. The first clear-cut examples of this strategy are based on crown ethers with boric acid ester moieties.[2] In the interesting work on metalloclefts, Reinhoudt and co-workers have described the uranium-containing calixarene[3] and bifunctional receptor[4] containing urea groups at the upper rim of calix[4]arene and ester functionality at the lower rim of calix[4]arene in order to bind cation and anion simultaneously. Also Ungaro reported a ditopic receptor[5] which binds cation and carboxylate at the same time. Beer found a calixarene ditopic receptor[6] which was composed of Lewis acid metal center and calixarene ester and its capacity to bind alkali metal ion and iodide anion with positive cooperativity.

As a consequence of their upper and lower rim of topologies the calixarenes are attractive host molecules to modify and so create unique geometries for the recognition of target guest species. The combination of two binding sites, urea for anions and ethyl ester groups for cations, yields receptor that is capable of binding halide anions and alkali metal cations simultaneously. In order to increase the cooperative binding effect both binding sites are introduced at the lower rim of the calix[4]arene skeleton. We report here the synthesis of a new bifunctional receptor containing two urea moieties and two ester groups at the lower rim of calix[4]arene and the simultaneous binding properties of cation and anion guests were studied.

By taking advantage of a selective 1,3-alkylation, 1,3-bis(cyanopropyl)oxycalix[4]arene **1** was prepared by the reaction of *p-t*-butylcalix[4]arene and 4-bromobutyronitrile in the presence of K_2CO_3.[7] Reduction with $LiAlH_4$ yielded the corresponding aminocalix[4]arene **2**, which was transformed into urea derivative **3** when treated with phenylisocyanate. Finally metal binding ester groups were introduced by the reaction of **3** with ethyl bromoacetate in the presence of NaH (Scheme 1). In order to increase the cooperative binding properties, cone conformers of receptor **4**[8] are desired. Fortunately the high yield of cone product was obtained. The ^{1}H NMR spectrum of **4** shows a pair of doublets at δ 3.07 and 4.35 for the eight bridge methylene protons and two singlets at δ 0.78 and 1.23 for the four *t*-butyl protons. Also two singlets at δ 6.43 and 7.10 for the eight aromatic protons are observed. Four urea N-H protons appear as a singlet at δ 7.31 and a triplet at δ 5.67 as expected.



Scheme 1. Synthesis of Bifunctional Receptor **4**.

The cation and anion binding properties were examined by ^{1}H NMR titration experiments in $CDCl_3$. The addition of 1 equivalent of $NaClO_4$ caused a down field shift of aromatic and methylene protons as observed previously in similar ester derivatives of calix[4]arene. Further addition of $NaClO_4$ does not make a change, suggesting that receptor-Na^+ forms a 1 : 1 stoichiometry complexes and complexes are formed in solution with sodium ion at the lower rim of ester groups. Substantial down field shift of urea NH signal was observed when tetrabutylammonium chloride, bromide and iodide salts were added, indicating that anion binding is taking place at the urea vicinity. The resulting titration curves indicated 1 : 1 complex stoichiometry. Stability constants (Table 1) were calculated from the titration results using EQNMR[9] for complexation with chloride, bromide and iodide in order

Table 1. Stability Constants (K_a) of **4** in $CDCl_3$

Metal[a]	Anion	K^b/dm^3 mol^{-1}
None	Cl^-	624
Na^+	Cl^-	2020
Li^+	Cl^-	1600
None	Br^-	225
Na^+	Br^-	1620
Li^+	Br^-	704
None	I^-	24.0
Na^+	I^-	616
Li^+	I^-	461

[a]Titration carried out in the presence of 1 equi. of metal cation salt, sodium or lithium perchlorates. [b]Errors estimated to be <10%.

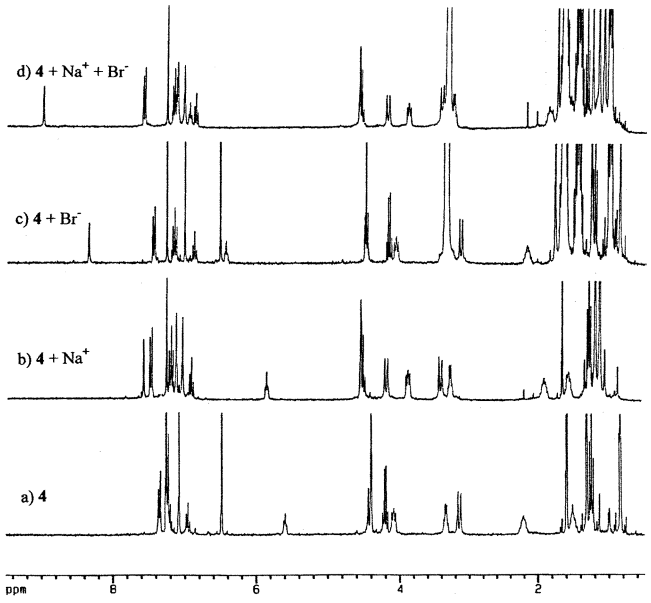


Figure 1. ^{1}H NMR spectra of **4** (a) without cation and anion, (b) with 1 equivalent of $NaClO_4$, (c) with 5 equivalents of TBABr, (d) with 1 equivalent of $NaClO_4$ and 5 equivalents TBABr in $CDCl_3$.

to investigate binding enhancement in the presence of alkali metal cations (Figure 1). A significant increase in the strength of anion binding is observed when the alkali metal cations are bound simultaneously. Chloride binding strength increase more than three fold, bromide binding seven fold and iodide binding 25 times in the presence of sodium ion. This positive cooperative binding of the chloride, bromide and iodide in the presence of sodium could be attributed to electrostatic effects of the complexed metal cation. Anion binding was enhanced more strongly in the presence of sodium rather than lithium cation, which can be explained by the fact that sodium is known to form highly selective complex with the lower-rim disubstituted calix[4]arene ethyl esters. Interestingly when excess tetrabutylammonium chloride was added in the sodium-receptor complex, it was observed that sodium ion became free from the complex slowly. It could be attributed to the fact that chloride binds most strongly among halide anions to the urea moieties, which disorient the cation binding ester sites. As a result, sodium binding mode become disturbed and finally lose the sodium. On the other hand chloride binding was maintained in the presence of lithium cation. Lithium is smaller than sodium and also binding strength is much weaker than that of sodium toward the ester sites, suggesting that size and binding strength play an important role for the bifunctionality of the ditopic receptor. This result suggests that selective binding does not come from binding strength only, but from the size and the appropriate binding strength.

In conclusion, bifunctional receptor **4** can bind alkali metal cations and halide anions simultaneously with positive cooperativity.

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8. 4, mp 238-239 °C; ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 2H, -NH), 7.25 (d, 4H, ArH, J = 8.4 Hz), 7.13 (t, 4H, ArH, J = 8.4 Hz), 7.00 (s, 4H, ArH), 6.86 (t, 2H, ArH, J = 7.4 Hz), 6.42 (s, 4H, ArH), 5.67 (t, 2H, -NH, J = 5.6 Hz), 4.36 and 3.07 (pair of d, 8H, $ArCH_2Ar$, J = 13.3 Hz), 4.11 (q, 4H, -OCH_2-, J = 7.1 Hz), 4.00 (t, 4H, -OCH_2-, J = 7.9 Hz), 3.26 (q, 4H, -CH_2N-, J = 6 Hz), 2.12 and 1.44 (m, 8H, -CH_2CH_2-), 1.16 (t, 6H, -CH_3, J = 7.1 Hz), 1.23 and 0.78 (s, 36H, -$C(CH_3)_3$), ^{13}C NMR ($CDCl_3$) 170.4 (-CO_2-), 156.3 (-CO-), 154.7, 151.8, 145.0, 144.9, 139.4, 135.1, 131.8, 128.9, 125.6, 124.9, 122.5 and 119.4 (Ar), 74.9, 72.1 and 61.1 (-OCH_2-), 40.1 (-CH_2N-), 34.0, 33.6, 31.7, 31.4, 31.1, 27.4 and 26.2 ($ArCH_2Ar$, -CH_2CH_2- and -$C(CH_3)_3$), 14.1 (-CH_3).
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