A Bifunctional 1,3-Alternate Calix[4]arene Receptor Containing Urea and Crown Ether Moieties

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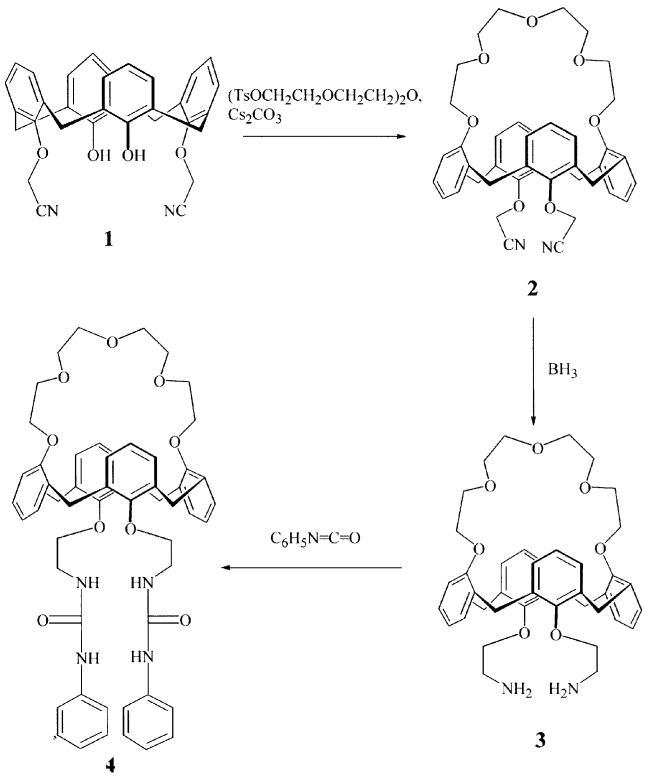
Introduction

Calix[4]arenes are important building blocks in supramolecular chemistry.[1,2] The calixarene framework provides a unique possibility to organize several binding sites in an array complementary to a potential guest. A variety of calixarene-based receptors for cations,[3] anions[4] and neutral molecules[5] have been synthesized in the past decade. Though anion recognition[6] appears to be a relatively new area of research, both positively charged and neutral receptors for anionic species have been prepared for the last few years.[7] The simultaneous binding of cationic and anionic guest species by ditopic receptors is a rapidly developing new field for ion pair recognition of environment and biological importance. By taking advantage of calixarene framework, a few neutral bifunctional receptors[8] were developed and showed the simultaneous complexation properties of hydrophilic anions and cations in organic media. Those receptors are, however, only focused on the cone conformers of calix[4]arene. It has been known[9] that 1,3-alternate conformation of calix[4]arene could provide the two excellent binding sites for guest molecules when the proper functionalization could be achieved. Here we report a new bifunctional receptor based on 1,3-alternate conformer of calix[4]arene, which contains urea and crown ether moieties at the opposite side of lower rim of calix[4]arene fixed in the 1,3-alternate conformation.

Our synthetic strategy is based on the attachment of both cation and anion binding sites to the rigid lipophilic calix[4]arene platform. It is known that urea moiety provides a binding site for anions and that crown ether fragment is capable of complexing cation.[10] By placing two urea groups at the one side of lower rim and crown ether moieties at the opposite side of lower rim (*vice versa*), we prepared a bifunctional receptor **4** and investigated the simultaneous binding properties of cation and anion guests.

Results and Discussion

1,3-Bis(cyanomethyl)oxycalix[4]arene **1** was prepared by alkylation of calix[4]arene with bromoacetonitrile in the presence of K_2CO_3 in acetonitrile.[11] Treatment of **1** with tetra(ethyleneglycol) ditosylate in the presence of Cs_2CO_3 produced calix[4]arene **2** in the 1,3-alternate conformation in 61% yield. It was observed accidentally that 1,3-alternate conformer **2** could change into partial cone conformation after 1 week in solution.[12] Subsequent reduction of **2** with borane-tetrahydrofuran complex gave quantitatively the corresponding diaminocalix[4]arene **3** which was fixed in 1,3-alternate conformation. Finally, reaction of **3** with phenylisocyanate in CH_2Cl_2 gave the bifunctional receptor **4** in 70% yield as shown in Scheme 1. The ^1H NMR spectrum of **4** shows the characteristics[13] of 1,3-alternate conformation such as a narrow range chemical shift of aromatic protons at δ 6.7-7.3 and a singlet like peak at δ 3.80 for bridge methylene protons. Due to the small $\Delta\nu$ on bridge methylene protons, a large singlet containing two very small outer peaks were observed instead of a pair of doublets. Four urea N-H protons appear as a singlet at δ 7.39 and a triplet at δ 5.44 as expected. The ^{13}C NMR spectra of **4** also confirmed the 1,3-alternate conformation, which showed one peak at δ



Scheme 1. Synthesis of bifunctional receptor.

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

	K^b/dm^3 mol^{-1}					
	Cl^-	Br^-	I^-	$H_2PO_4^-$	HSO_4^-	CH_3COO^-
None	1054	288	208	790	840	2970
K^{+a}	5420	1550	808	–[c]	–[c]	–[c]

[a]Titration carried out in the presence of 1 equivalent of metal potassium perchlorate. [b]Errors estimated to be <10%. [c]Due to the instability of potassium complex in the presence of those anions, stability constants can not be calculated.

38.0 for the bridge methylene carbons as an indication of all *anti* oriented[14] phenolic rings.

The cation and anion binding properties of **4** were examined by ^{1}H NMR titration experiments in $CDCl_3$. The addition of 1 equivalent of $KClO_4$ caused a down field shift of aromatic and methylene protons, which was observed previously[15] in similar crown ether derivatives of calix[4]-arene. Further addition of $KClO_4$ does not make a change, suggesting that receptor-K^+ forms an 1 : 1 stoichiometry complexes and complexes are formed in solution with potassium ion at the crown ether group. Substantial down field shift of urea NH signal was observed when tetrabutyl-ammonium 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 were calculated from the titration results using EQNMR[16] for complexation with chloride, bromide and iodide in order to investigate binding

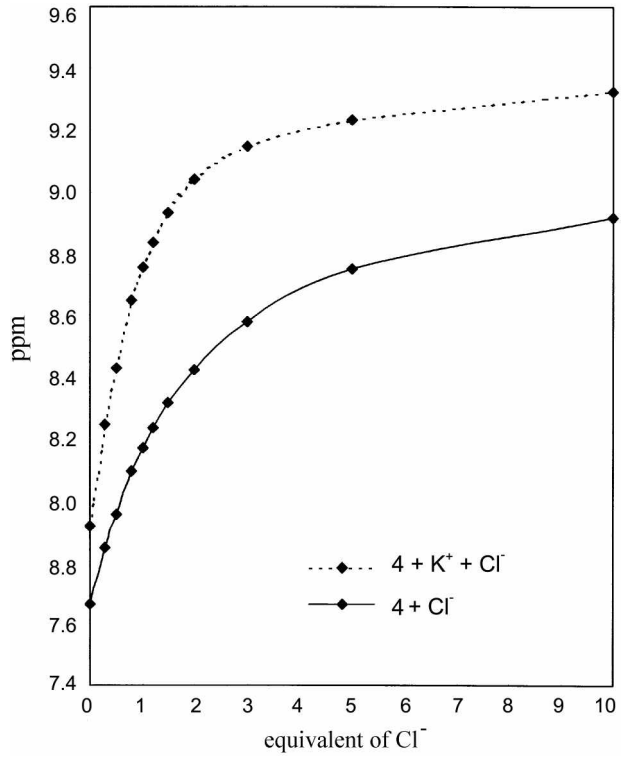

Figure 1. ^{1}H NMR chemical shift change of N-H proton of **4** in a mixture of CD_3CN and $CDCl_3$ (3:2 ratio) in the presence of chloride ion with and without K^+.

enhancement in the presence of potassium ion (Table 1). An enhancement in the strength of chloride ion binding is observed when potassium ion is bound simultaneously as shown in Figure 1. Chloride and bromide binding strength increase more than five fold and iodide binding four fold in the presence of potassium ion. This positive cooperative binding of the chloride, bromide and iodide in the presence of potassium could be attributed to electrostatic effect of the complexed metal cation. The structural change of ligand upon binding potassium ion was not clear based on ^{1}H NMR spectrum, indicating that electrostatic effect could be the major force for enhancing halide binding.

In conclusion, bifunctional receptor **4** can bind potassium cation and halide anions simultaneously with positive cooperativity.

Experimental Section

25,27-Bis(cyanomethyl)oxy-26,28-dihydroxycalix[4]arene (1) was prepared by the known procedure.[11]

25,27-Bis(cyanomethyl)oxycalix[4]arene-crown-5 (2). To a stirred solution of 0.2 g (0.4 mmol) of **1** and 0.5 g (1.5 mmol) of Cs_2CO_3 in 30 mL of CH_3CN, 0.2 g (0.4 mmol) of tetraethylene glycol ditosylate was added and the reaction mixture was left to stir at room temperature for 20 h. The solvent was removed and the residue was treated with $CHCl_3$ (100 mL) and water (100 mL). The organic layer was separated and the solvent was removed. The crude products were purified by column chromatography (eluent, $CHCl_3$: *n*-hexane : ethyl acetate = 6 : 3 : 1) to give the 1,3-alternate product **2** (0.16 g, 61%). mp > 329 °C dec.; ^{1}H NMR ($CDCl_3$) δ 7.21 and 7.16 (two d, 8H, ArH, J = 7.5 Hz), 7.00 (m, 4H, ArH), 3.97 and 3.90 (pair of d, 8H, $ArCH_2Ar$, J = 16.2 Hz), 3.53 (m, 16H, $-OCH_2-$), 3.20 (t, 4H, $-OCH_2-$, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 156.1, 154.1, 134.3, 134.2, 130.2, 129.9, 124.5 and 124.4 (Ar), 116.3 (-CN), 72.3, 70.6, 69.7, 69.1 and 55.6 ($-OCH_2-$), 37.8 ($ArCH_2Ar$).

25,27-Bis(4-aminoethyl)oxycalix[4]arene-crown-5 (3). A 10 mL of 1M BH_3 solution was added to 0.2 g (0.3 mmol) of **2** under nitrogen atmosphere and refluxed for 2 h. The solvents were removed and the residue treated with 10 mL of 2 N HCl and refluxed for 1 h. After cooling down to room temperature, 10% KOH solution was added until the solution became to basic and extracted with $CHCl_3$ (2 × 40 mL). The solvent was removed to afford compound **3** as a white solid 0.17 g (85 %). ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 4H, ArH, J = 7.5 Hz), 7.07 (d, 4H, ArH, J = 7.5 Hz), 6.92 (m, 4H, ArH), 3.89 (s, 8H, $ArCH_2Ar$), 3.65 (m, 4H, $-OCH_2-$), 3.56 (m, 8H, $-OCH_2-$), 3.48 (t, 4H, $-OCH_2-$, J = 7.5 Hz), 3.01 (t, 4H, $-OCH_2-$, J = 6.9 Hz), 2.50 (t, 4H, $-NCH_2-$, J = 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 156.4, 156.3, 134.1, 133.6, 129.1, 129.0, 122.9 and 122.7 (Ar), 73.0, 71.2, 70.8, 69.4, and 67.5 ($-OCH_2-$), 41.4 ($-CH_2N-$), 38.1 ($ArCH_2Ar$).

25,27-Bis[(N-phenylureido)butyloxy]calix[4]arene-crown-5 (4). To a 0.2 g (0.3 mmol) of **3** in 20 mL of CH_2Cl_2, 0.1 mL of phenylisocyanate was added and the mixture was stirred for 3 h under the nitrogen atmosphere. After removing the

solvent. the residue was triturated with MeOH, filtered and dried to give 0.19 g (70%) of **4**. ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 2H, -NH), 7.29 (d, 4H, ArH, J = 7.5 Hz), 7.21 (t, 4H, ArH, J = 7.5 Hz), 7.12 (d, 4H, ArH, J = 7.5 Hz), 7.00 (m, 6H, ArH), 6.89 (t, 2H, ArH, J = 7.5 Hz), 6.78 (t, 2H, ArH, J = 7.5 Hz), 5.44 (s, 2H, -NH), 3.80 (s, 8H, $ArCH_2Ar$), 3.65 (m, 4H, $-OCH_2-$), 3.58 (m, 4H, $-OCH_2-$), 3.52 (t, 4H, $-OCH_2-$, J = 6.9 Hz), 3.13 (t, 4H, $-NCH_2-$, J = 6.9 Hz), 2.99 (br s, 4H, $-OCH_2-$), 2.93 (br s, 4H, $-OCH_2-$); ^{13}C NMR ($CDCl_3$) δ 156.4, 156.1, 155.8, 139.1, 134.9, 134.1, 129.8, 129.5, 129.1, 123.1, 122.9, and 120.1 (Ar), 73.1, 70.9, 70.0, 69.5, and 68.3 ($-OCH_2-$), 40.7 ($-CH_2N-$), 38.0 ($ArCH_2Ar$).

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