Upper Rim Urea Derivative of Calix[4]arene: Anion Selective Neutral Receptor

Kye Chun Nam,* Jong Chul Chun, Sung Ok Kang, and Seung Whan Ko

Department of Chemistry and Institute of Basic Science, Chonnam National University, Kwangju 500-757, Korea
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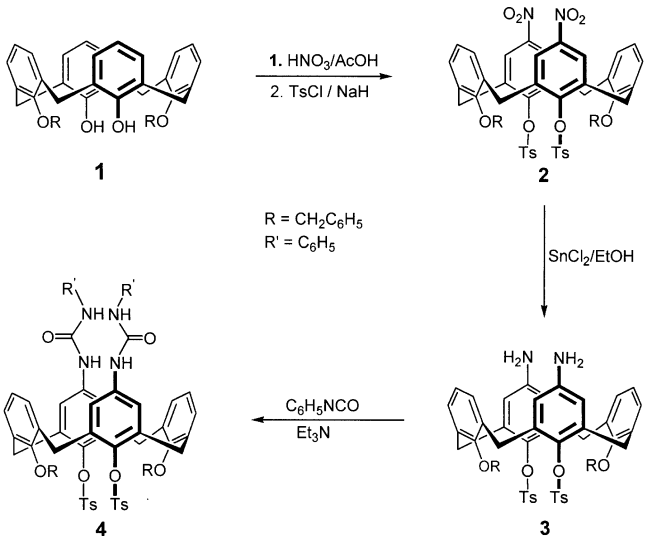
Selective complexation of anions is more demanding than that of cations in the view of the higher free energies of solvation, the low charge density of anions and the pH dependency of anion complexation.[1,2] In addition, as the charge density of anions is low, the electrostatic forces with anions are weaker than those with cations. Anions have a wide variety of geometries[3] and comparatively large sizes, which have to be taken into account in the development of selective anion receptors.

Reinhoudt and co-workers have reported that a selective anion complexation can be achieved through hydrogen bond by the neutral urea receptors derived from the lower rim of calixarenes.[4,5] The use of hydrogen bonding as sole interaction for the binding of anions implies that recognition is most pronounced in non-competitive solvents. The advantage of using hydrogen bond is that a hydrogen bond is highly directional in character. Correct orientation of the hydrogen bond donors and/or acceptors can provide selective anion recognition. The urea moiety is a powerful hydrogen bond donor as was recently shown by Hamilton *et al.*[6] in the complexation of dicarboxylate anion.

A basic rule for the precise recognition of guest molecules is that the host must have a rigid, well-defined cavity complementary in shape to that of the guest. The parent calix[4]arene, however, are conformationally mobile, and to make them immobile they must be altered in some fashion. One approach has been to introduce bulky groups[7-9] on the phenolic oxygens, which works very well with the calix[4]arenes. In a series of developing anion receptor we reported recently two urea derivatives of calixarene,[10,11] which have urea groups at the lower rim of calixarene. In order to develop the rigid anion receptor, we synthesized a upper rim urea derivative of calix[4]arene **4** with bulky groups on the phenolic oxygens and investigated the anion complexation properties. The binding study was conducted with proton NMR titration with the various anions such as F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, and $H_2PO_4^-$.

Results and Discussion

For the synthesis of the upper rim phenylurea calix[4] arene, the 1,3-di-aminocalix[4]arene **3** was obtained by the reduction of the 1,3-dinitrocalix[4]arene **2**. The 1,3-dinitrocalix[4]arene **2** was prepared selectively by the reaction of bisbenzylcalix[4]arene **1** with nitric acid and acetic acid in CH_2Cl_2. Treatment of aminocalix[4]arene **3** with phenylisocyanate produced the upper rim urea derivative of calix[4]arene **4** in high yield as shown in Scheme 1. The ^1H NMR spectrum of **4** showed a pair of doublets at δ 3.80 and



Scheme 1. Synthesis of urea derivative at the upper rim of calix[4]arene.

2.47 for the bridge methylene protons and two singlets at δ 6.10 and 7.10 for the urea N-H protons and a singlet at δ 5.83 for the aromatic protons with urea group. The ^{13}C NMR spectrum showed one signal at δ 32.14 for the bridge carbons, indicating that **4** has only *syn* oriented phenol rings[12] which implied **4** existed as a cone conformation, which could provide the suitable binding site for anions.

The anion binding properties were investigated by the proton NMR titration in $CDCl_3$ solution in the presence of various anions. In proton NMR experiments a large downfield shift of two singlet NH proton resonance at δ 7.09 and δ 6.12 were observed upon addition of TBA chloride to host solution as shown in Figure 1. Also the slight upfield shift of a triplet of aromatic protons at δ 7.25 and the slight downfield shift of a singlet of calixarene aromatic protons at δ 5.90 were noticed. The ^1H NMR spectra of **4** showed a resolved pattern throughout the titration with chloride ion. This observation could indicate that the conformation of **4** was not changed by complexing with chloride ion due to the conformational rigidity caused by the bulky groups at the lower rim. Any further significant change was not observed after one equivalent of TBA Cl^-, suggesting that **4** was complexed with chloride ion by 1 : 1 solution stoichiometry. Large chemical shift change of the NH protons in the presence of anion suggests that the anions bind the urea protons directly. The association constants of the various anions to the receptors are obtained from the resulting titration curves using EQ-NMR[13] and these values are presented in Table 1. The receptor **4** exhibits remarkable thermodynamic stability

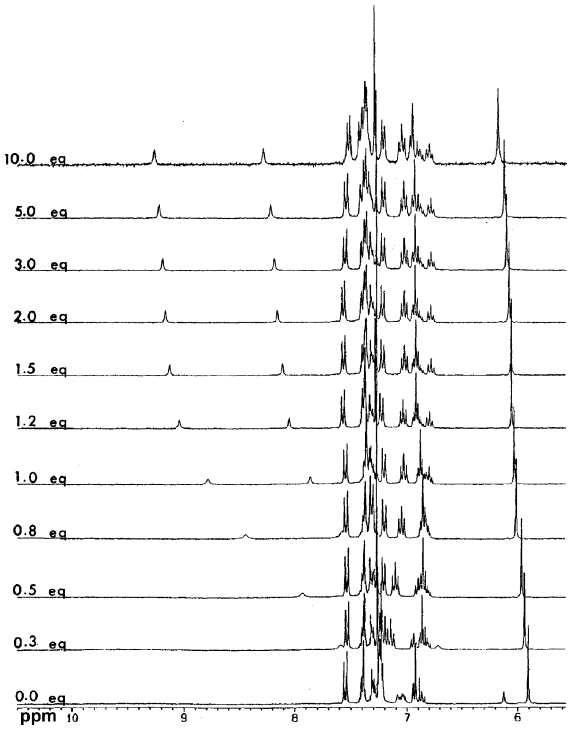


Figure 1. The partial ^{1}H NMR spectra of **4** in the presence of TBA (tetrabutylammonium) Cl^- in $CDCl_3$. Numbers at the left side indicate the equivalent amounts of Cl^- added.

Table 1. Stability constant data ($K_{ass.}$, M^{-1}) of urea derivative of calix[4]arene **4** in $CDCl_3$

ligand	F^{-a}	Cl^-	Br^-	I^-	$H_2PO_4^-$	$CH_3CO_2^-$
4	4315	1500	1390	790	600	1170

[a]Tetrabutylammonium salts. Errors estimated to be <15%.

for F^- over Cl^-, Br^-, I^-, $CH_3CO_2^-$ and $H_2PO_4^-$. This result suggests that two urea units at the upper rim of calix[4]arene **4** could provide the best suitable binding site for small fluoride ion. As expected from anion titration spectrum in Figure 1, **4** exist in a conformationally rigid structure which could fit to bind with F^-.

Experimental Section

25,27-Bis(benzyloxy)-26,28-dihydroxycalix[4]arene (1). was prepared by the known procedure.[14] mp 220-223 °C.

5,17-Dinitro-25,27-bis(benzyloxy)-26,28-(tolylsulfonyloxy)calix[4]arene (2). To a solution of 1.0 g (0.16 mmol) of OH analog of **2** which was prepared by the reaction of 1 with nitric acid (90%), and 0.3 g of NaH (45%) in 50 mL of THF, 1.0 g (0.5 mmol) of toluene-4-sulfonyl chloride was added. After overnight the solvents were removed and the residue was extracted with chloroform. The organic layer was removed and triturated with methanol. The crude product was purified by recrystallization from $CHCl_3$-MeOH to give 1.14 g (71%) of **2**. Mp 260-264 °C. ^{1}H NMR ($CDCl_3$) δ 7.03-7.48 (m, 24H, ArH), 6.82 (s, 4H, $ArHNO_2$), 5.10 (s, 4H, $ArCH_2O$-), 3.82 and 2.53 (a pair of d, 8H, J = 14.7 Hz, $ArCH_2Ar$), 2.45 (s, 6H, $TsCH_3$). ^{13}C NMR ($CDCl_3$) δ 154.55, 149.03, 146.04, 144.71, 137.10, 135.96, 135.85, 131.70, 130.85, 129.96, 129.89, 128.87, 128.57, 128.45, 124.12, and 122.70 (Ar and -CO-), 76.02 ($ArCH_2O$-), 32.13 ($ArCH_2Ar$), 21.76 ($ArCH_3$).

5,17-Diamino-25,27-bis(benzyloxy)-26,28-(tolylsulfonyloxy)calix[4]arene (3). A mixture of 0.93 g (0.9 mmol) **2** and 1.9 g of (9 mmol) $SnCl_2$ $2H_2O$ in 50 mL of EtOH was refluxed for 12 h. After cooling down, the mixture was neutralized with NaOH and extracted with $CHCl_3$. The solvents were removed and the residue was triturated with methanol to give 0.68 g (78%) of **3**. Mp 230-232 °C. ^{1}H NMR ($CDCl_3$) δ 7.2-7.5 (a pair of d, 8H, J = 8.1 Hz, TsH), 6.80-7.42 (m, 16H, ArH), 5.37 (s, 4H, ArH with amino group), 5.08 (s, 4H, $ArCH_2O$-), 2.35-3.75 (a pair of d, 8H, J = 14.1 Hz, $ArCH_2Ar$), 2.41 (s, 6H, $TsCH_3$).

5,17-Di(N-phenylureido)-25,27-bis(benzyloxy)-26,28-(tolylsulfonyloxy) calix[4]arene (4). A mixture of 0.5 g (0.51 mmol) **3** and 0.12 g (1.3 mmol) of phenylis ocyanate in 20 mL of $CHCl_3$ was stirred overnight and added 50 mL of $CHCl_3$. Washing with water separated the organic layer and removed the solvents. The residue was triturated with methanol to give 0.49 g (81%) of **4**. Mp 234-238 °C. ^{1}H NMR ($CDCl_3$) δ 6.88-7.56 (m, 34H, ArH), 6.10 (s, 2H, -NH-), 5.83 (s, 4H, ArH with urea group), 5.08 (s, 4H, $ArCH_2O$-), 2.47-3.80 (a pair of d, 8H, J = 14.1 Hz, $ArCH_2Ar$), 2.42 (s, 6H, $TsCH_3$). ^{13}C NMR ($CDCl_3$) δ 155.12, 153.35, 145.24, 141.76, 138.08, 136.61, 136.48, 135.94, 134.67, 132.45, 130.79, 129.64, 129.41, 128.94, 128.85, 128.24, 128.20, 123.37, 122.95, 120.75, 119.56 (Ar and -CO-), 75.62 ($ArCH_2O$-), 32.14 ($ArCH_2Ar$), 21.67 ($ArCH_3$).

^{1}H NMR Titration. A 0.5 mL of 4×10^{-3} M solution of the host in $CDCl_3$ was prepared. To this solution 0, 0.3, 0.5, 0.8, 1.0, 1.2, 1.5, 2.0, 3.0, 5.0, and 10 equivalents of the tetrabutylammonium salts were added in the NMR tube and the spectra were recorded. The chemical shifts of the NH protons and ortho protons of phenyl group near urea unit were followed and plotted against the equivalents of guest added. ^{1}H NMR spectra and titration were recorded on a 300 MHz spectrometer.

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