Synthesis and Anion Binding Properties of the Bridged Urea Derivatives of Calix[4]arene

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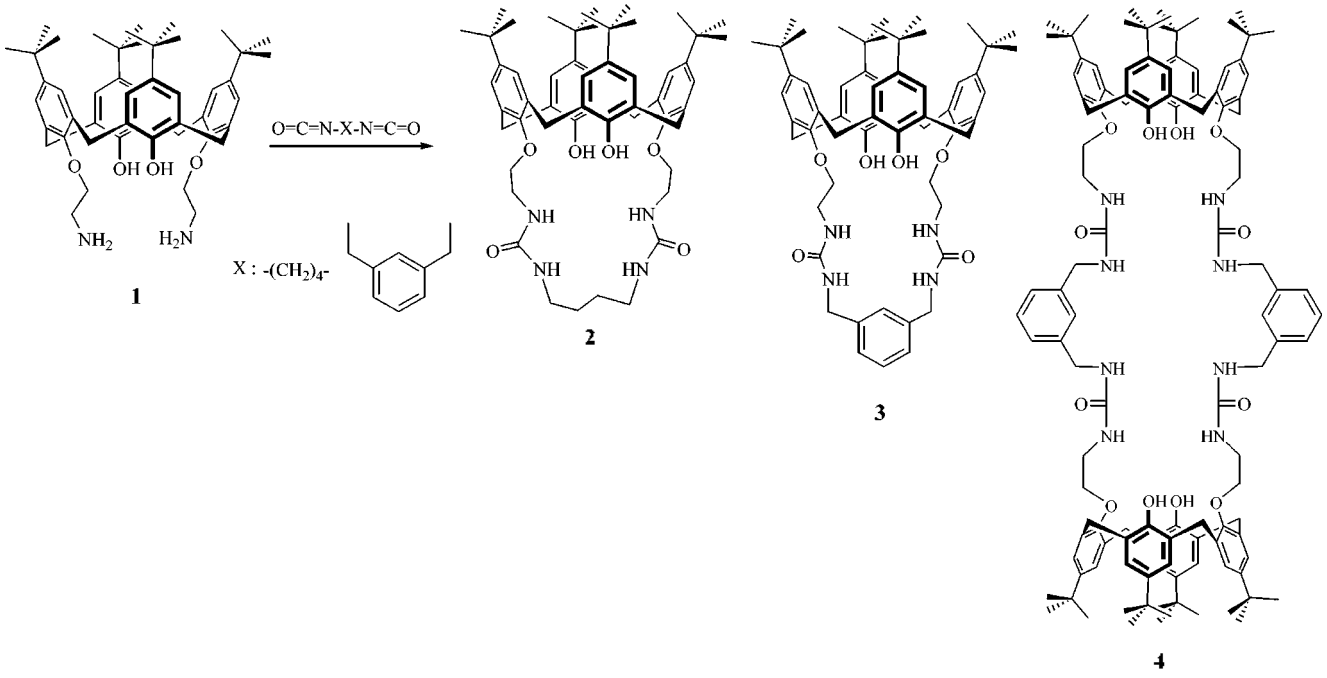
Selective complexation of anions is more demanding than that of cations due to the many reasons such as size, charge density, polarizability, solvation energy and pH-dependent acid-base equilibria.[1-3] Many successful positively charged receptors have been reported.[4-6] Though neutral receptor compounds for inorganic and organic anions have attracted attention due to many possible applications in aprotic media, but they are still very limited.

Urea derivatives have been utilized successfully as neutral host compounds for the various anion guests through hydrogen bonding.[7] Particularly, several successful anion receptors have been reported from the calixarene urea derivatives.[8-12] But, the bridged urea anion receptors have not reported yet. In order to develop the new anion receptor, several bridged urea derivatives of calix[4]arene were synthesized, which could increase the rigidity of the anion binding sites. To bridge lower rim of calix[4]arene, 1,3-bis(aminoethyl)oxycalix[4]arene **1** was treated with diisocyanate spanner. Lower rim bridged urea derivatives **2** and **3** were synthesized and their structural and anion binding properties were investigated. Also calix[4]quinone **5** and **6** were obtained by oxidation of **2** and **3**.

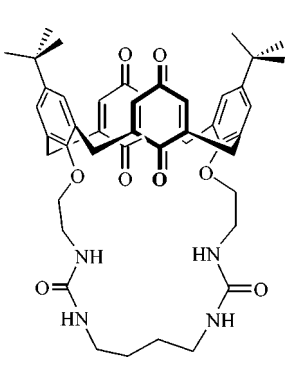
Results and Discussion

Our first target compounds are macrocyclic urea derivatives of **2** and **3** as shown in Scheme 1. Bridging reaction was carried out with the treatment of aminocalix[4]arene **1** with diisocyanates such as 1,4-diisocyanatobutane and 1,3-bis(cyanatomethyl)benzene in dilution condition. Four or five carbons between urea groups were considered to provide a suitable distance for the bridge from the reported results previously.[13] Bridge urea calix[4]arene **2** was obtained in high yield (about 60%) as a single product when 1,4-diisocyanatobutane treated with **1**. ^{1}H NMR spectrum of **2** showed a well defined characteristics of cone conformer such as two singlets at δ 7.07 and 6.81 for aromatic ring protons and two pairs of doublets at δ 4.23 and 3.38 (J = 13.4 Hz) for the bridge methylene protons. Urea N-H protons appeared as a broad triplet at δ 6.15 and 4.93 due to the quadruple moment of nitrogen atom. 1,3-Alternate conformer could provide a similar spectral feature, but ^{13}C NMR spectrum showed at δ 32 ppm peak for the bridge carbon.[14] which clearly indicate that **2** exist as a cone conformation.



Scheme 1

When starting calix[4]arene amine **1** was treated with 1,3-bis(isocyanatomethyl)benzene, two products with a similar ratio were obtained from the reaction. One product was assigned as **3** based on FAB mass ($C_{58}H_{74}N_4O_6$) which showed a molecular ion at 923.7 (M+1) peak. The ^1H and ^{13}C NMR spectra also showed the characteristics of the bridged cone conformer. The other product was a bridged dimeric 2+2 product **4** from the MALDI TOF mass ($C_{116}H_{148}N_8O_{12}$) which showed a molecular ion at 1846.6 (M-1) peak. Figure 1 shows ^1H NMR spectra of **3** and **4** in $CDCl_3$. Two singlets (δ 7.0) for the aromatic protons and two singlets (δ 1.3) for the *t*-butyl protons can be observed from both spectra. Also a pair of doublets at δ 3-4 ppm for the bridge methylene protons were observed. Due to the same symmetry, a similar pattern of spectrum should be demonstrated. Calix[4]quinone urea derivatives **5** and **6** were obtained when **2** and **3** treated with TTFA in trifluoroacetic acid solution.



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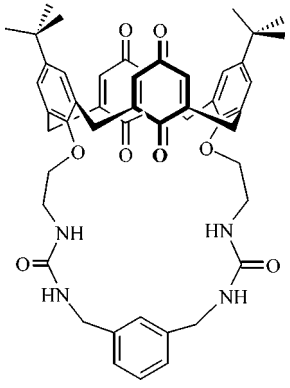

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The anion binding properties were investigated by the proton NMR titration in $CDCl_3$ solution in the presence of various anions such as tetrabutylammonium (TBA) chloride, dihydrogen phosphate, hydrogen sulfate and acetate. In proton NMR experiments a large downfield shift of two singlets NH proton resonances and the slight shift of aromatic protons were observed upon addition of TBA acetate to host **2** solution. Particularly two singlets for the urea NH signals shifted rapidly until addition of 1 equivalent TBA acetate. Further anion addition caused only a very slight downfield shift and any further significant change was not observed after one equivalent of TBA acetate, suggesting that **2** complexed with acetate ion 1 : 1 solution stoichiometry. Large chemical shift change of the NH protons in the

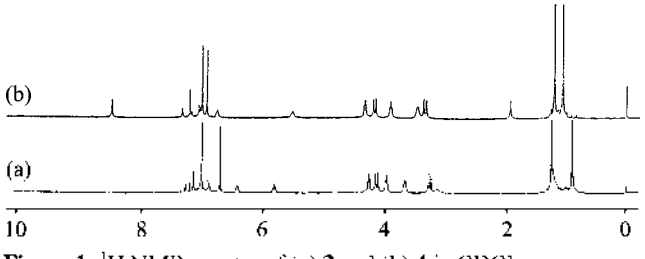

Figure 1. ^1H NMR spectra of (a) **3** and (b) **4** in $CDCl_3$.

Table 1. Stability constants (K_a) data of the bridged urea calix[4]-arenes (**2**, **3**) and calix[4]quinones (**5**, **6**) in $CDCl_3$

Anion[a]	K/dm^3 mol^{-1}			
	2[b]	**3**[c]	**5**[b]	**6**[c]
Cl^-	59	107	136	98
HSO_4^-	–[d]	210	150	276
$H_2PO_4^-$	91	380	312	190
$CH_3CO_2^-$	185	722	1170	257

[a]Tetabutylammonium salts. Errors estimated to be ±10%. [b]Urea N-H proton chemical shift was used for caculation. [c]Xylenylmethylene proton chemical shift was used for calculation. [d]Unable to determine due to the weak binding.

presence of anion indicates that the anions bind the urea protons directly. Calixarene phenyl proton signals shifted slightly upon addition of anion, suggesting that the anions do not bind directly with aromatic protons.

The association constants of the various anions to the receptors are obtained from the resulting titration curves using EQ-NMR[15] and these values are presented in Table 1. A high selectivity for acetate was observed for the urea derivative of calix[4]diquinone **5**. The influence of quinone moieties for the anion binding might be the important factor for the selectivity of acetate. Urea proton signals disappeared when anions were added from host **3** and **6**. In this case, methylene proton signal next to xylenyl unit was used for the calculation.

In summary, we prepared two bridged urea derivatives of calix[4]arene from the reaction of **1** and diisocyanate. Calix-[4]diquinone derivatives were obtained by the oxidation of **2** and **3** with TTFA. A high selectivity for acetate was observed for the urea derivative of calix[4]diquinone **5**. Electrochemical properties for **5** and **6** are currently under investigation.

Experimental Section

5,11,17,23-Tetra-*tert*-butyl 25,27-[N-tetramethylene bridged bis(ureido)]ethyloxy-26,28-dihydroxycalix[4]-arene 2. To a solution of 0.50 g (0.68 mmol) of **1** in dried CH_2Cl_2 100 mL in the ice bath was dropped 0.10 mL (0.79 mmol) of 1,4-diisocyanatobutane in CH_2Cl_2 50 mL for 1.5 h. After 30 min, the solvent was removed and the crude product was purified by column chromatography (eluent: $CHCl_3$: Acetone = 1 : 1) to give 0.35 g (59%) of white powder **2**, mp 214-217 °C, ^1H NMR ($CDCl_3$) δ 7.45 (s, 2H, -OH), 7.07 (s, 4H, ArH), 6.81 (s, 4H, ArH), 6.15 (t, 2H, -NH), 4.93 (t, 2H, -NH), 4.23 and 3.38 (pair of d, 8H, $ArCH_2Ar$, J = 13.4 Hz), 4.06 (t, 4H, $-OCH_2-$), 3.81 (q, 4H, $-CH_2N-$), 3.20 (br s, 4H, $-CH_2N-$), 1.57 (br s, 4H, $-CH_2-$), 1.32 and 0.90 (s, 36H, $-C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 159.1 (-CO-), 150.2, 149.5, 147.9, 142.8, 132.9, 128.3, 126.2, and 125.8 (Ar), 76.7 ($-OCH_2-$), 41.0 and 40.5 ($-CH_2N-$), 34.4, 34.3, 32.0, 31.4, and 27.1 ($ArCH_2Ar$ and $-C(CH_3)_3$, $-CH_2-$).

5,11,17,23-Tetra-*tert*-butyl 25,27-[1,3-bis(N-methylbenzene)bridged bis(ureido)] ethyloxy-26,28-dihydroxycalix-[4]arene (1 : 1 monomer) 3 and 4. To a solution of 0.6 g

(0.81 mmol) of **1** in dried CH_2Cl_2 180 mL in the ice bath was added 0.45 mL (0.87 mmol) of 1,3-bis(isocyanatomethyl)-benzene in CH_2Cl_2 50 mL for 1.5 h. After 30 min. the solvent evaporated under reduced pressure and the crude product was subjected to column chromatography (eluent; $CHCl_3$: Acetone = 2 : 1) to give white powder **3** (R_f = 0.39) 0.15 g and a 2+2 dimeric **4** (R_f = 0.10) 0.12 g. **3**; mp 202-205 °C. ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 2H, -OH), 7.25 (s, 1H, ArH), 7.06 (t, 1H, ArH), 7.05 (s, 4H, ArH), 6.94 (d, 2H, ArH, J = 7.6 Hz), 6.75 (s, 4H, ArH), 6.45 (t, 2H, -NH), 5.82 (t, 2H, -NH), 4.31 (d, 4H, -CH_2N-, J = 5.5 Hz), 4.19 and 3.32 (pair of d, 8H, ArCH_2Ar, J = 13.2 Hz), 4.03 (t, 4H, -OCH_2-, J = 4.6 Hz), 3.72 (q, 4H, -CH_2N-, J = 4.7Hz), 1.29 and 0.94 (s, 36H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 159.2 (-CO-), 149.5, 147.4, 142.7, 140.0, 132.2, 128.3, 128.2, 125.8, 125.5, 125.4 and 123.2 (Ar), 76.0 (-OCH_2-), 43.7 and 40.4 (-CH_2N-), 34.0, 33.9, 31.6, 31.4 and 31.0 (ArCH_2Ar and -C(CH_3)$_3$). MS (FAB) *m z* 923.7 (M+1$^+$). Dimer **4**: mp 246-249 °C. ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 2H, -OH), 7.35 (s, 1H, ArH), 7.25 (t, 1H, ArH), 7.11 (d, 2H, ArH, J = 7.9 Hz), 7.05 (s, 4H, ArH), 6.98 (s, 4H, ArH), 6.79 (t, 2H, -NH), 5.55 (t, 2H, -NH), 4.37 (d, 4H, -CH_2N-, J = 5.6 Hz), 4.24 and 3.41 (pair of d, 8H, ArCH_2Ar, J = 13.0 Hz), 3.95 (t, 4H, -OCH_2-, J = 4.8 Hz), 3.52 (q, 4H, -CH_2N-), 1.25 and 1.10 (s, 36H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 158.4 (-CO-), 149.3, 148.8, 147.9, 143.0, 140.5, 133.0, 128.7, 128.1, 126.6, 126.2, 126.1 and 125.7 (Ar), 75.9 (-OCH_2), 44.0 and 39.6 (-CH_2N-), 34.2, 33.9, 32.2, 31.6 and 31.1 (-ArCH_2Ar- and -C(CH_3)$_3$). MS (MALDI TOF) m/z 1846.6 (M-1$^+$).

5,17-Di-*tert*-butyl-26,28-[N-tetramethylene bridged bis-(ureido)]ethyloxy-calix[4]-25,27-diquinone 5. To a 1.0 g (1.14 mmol) of **2** in trifluoroacetic acid 50 mL, 1.2 g (2.0 mmol) of thallium trifluoroacetate was added and the mixture stirred in the dark under the nitrogen atmosphere for 2 h. The solvent was then removed and the residue poured into ice water (100 mL). The product was then extracted with $CHCl_3$ (200 mL), and the solvent removed. The crude product was purified by column chromatography (eluent; $CHCl_3$: MeOH = 20 : 1) to give a yellow powder 0.3 g (32%). mp 190 °C softening, ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 4H, ArH), 6.68 (s, 4H, ArH), 5.88 (t, 4H, -NH), 5.10 (t, 4H, -NH), 3.97 and 3.24 (pair of d, 8H, ArCH_2Ar, J = 13.1 Hz), 3.80 (t, 4H, -OCH_2-), 3.64 (q, 4H, -CH_2N-), 3.20 (q, 4H, -CH_2N-), 1.62 (m, 4H, -CH_2-), 1.09 (s, 18H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 190.2, 187.4, 160.5 (-CO-), 154.7, 150.0, 148.5, 134.3, 130.7 and 128.3 (Ar), 75.0 (-OCH_2-), 42.3 and 41.6 (-CH_2N-), 35.7, 33.6, 32.9 and 28.8 (ArCH_2Ar, -C(CH_3)$_3$, and -CH_2-).

5,17-Di-*tert*-butyl 26,28-[1,3-bis(N-methylbenzene)-bridged bis(ureido)]ethyloxy calix[4]-25,27-diquinone 6. Following the procedure described for **5**, **6** was obtained in 35% yield. mp >250 °C dec, ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H, ArH), 7.10 (t, 1H, ArH), 7.02 (d, 2H, ArH), 6.80 (s, 4H, ArH), 6.69 (s, 4H, ArH), 6.30 (t, 2H, -NH), 6.15 (t, 2H, -NH), 4.40 (d, 4H, -CH_2N-), 3.78 and 3.20 (pair of d, 8H, ArCH_2Ar), 3.66 (t, 4H, -OCH_2-), 3.50 (m, 4H, -CH_2N-), 1.09 (s, 18H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 189.0, 185.5, 158.8 (-CO-), 153.3, 148.0, 146.7, 139.6, 132.7, 128.8, 128.4, 126.8, 125.9 and 123.7 (Ar), 73.6 (-OCH_2-), 43.9 and 40.5 (-CH_2N-), 34.1, 32.5 and 31.2 (ArCH_2Ar and -C(CH_3)$_3$).

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