

## Synthesis, X-ray Structure and Anion Binding Properties of the Novel Urea Derivatives of Calix[4]arene Dimer

Eun Jin Cho, Byung Ju Ryu, Hyoung Min Yeo, Young Ju Lee, and Kye Chun Nam\*

Department of Chemistry and The Institute of Basic Sciences, Chonnam National University, Gwangju 500-757, Korea

\*E-mail: kcnam@chonnam.ac.kr

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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.<sup>1,2</sup> Anion plays a fundamental role in a wide range of chemical and biological processes, and numerous efforts have been devoted to the development of abiotic receptors for anion species,<sup>3</sup> but they are still very limited. Urea derivatives have been utilized successfully as neutral host compounds for the various anion guests through hydrogen bonding.<sup>4-7</sup> Recently for the development of cation calixtube, a number of dimeric structure of calix[4]arene biscrown were synthesized and their cation binding properties were investigated.<sup>8,9</sup> But, the calix[4]arene dimer structure of bridged urea anion receptors have not reported yet except our previous work which describe the bridged dimeric urea derivative of calix[4]arene as a minor side product.<sup>10</sup>

For the purpose of developing the calixtube of anion

receptors, we synthesized the urea bridged dimer of calix[4]arene **3** from the bridging reaction of diisocyanate calix[4]arene **2** and its aminocalix[4]arene precursor **1**. Also the oxidized quinone derivative **4** was obtained by the oxidation of **3** with TTFA (thallium trifluoroacetate). X-ray structure and anion binding properties were investigated.

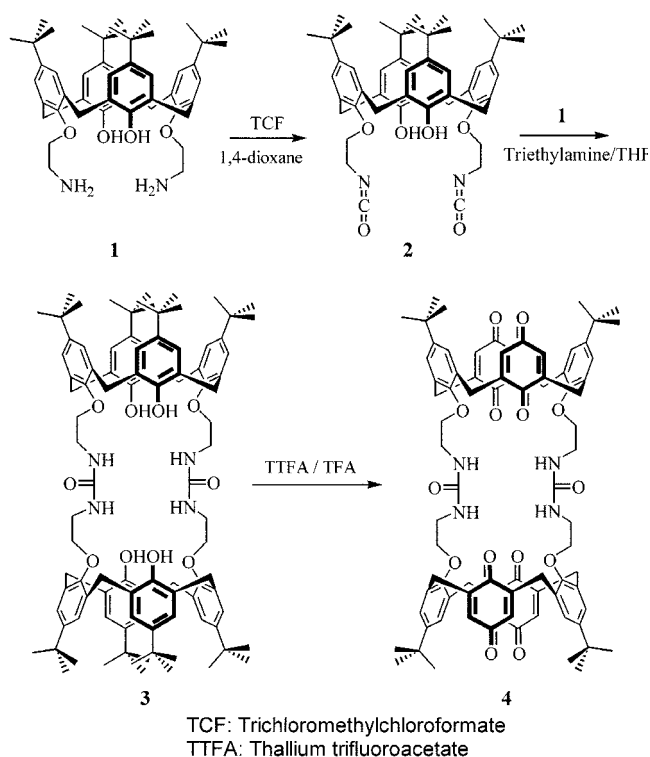
### Results and Discussion

Our first target compound is a macrocyclic urea dimer of calix[4]arene derivative of **3** as shown in Scheme 1. Bridging reaction was carried out with the treatment of aminocalix[4]arene **1**<sup>11</sup> with its isocyanate **2** which was prepared by treating **1** with TCF(trichloromethylformate) in 1,4-dioxane and used without separation. Bridge urea calix[4]arene dimer **3** was obtained in 40% yield from the column purification.

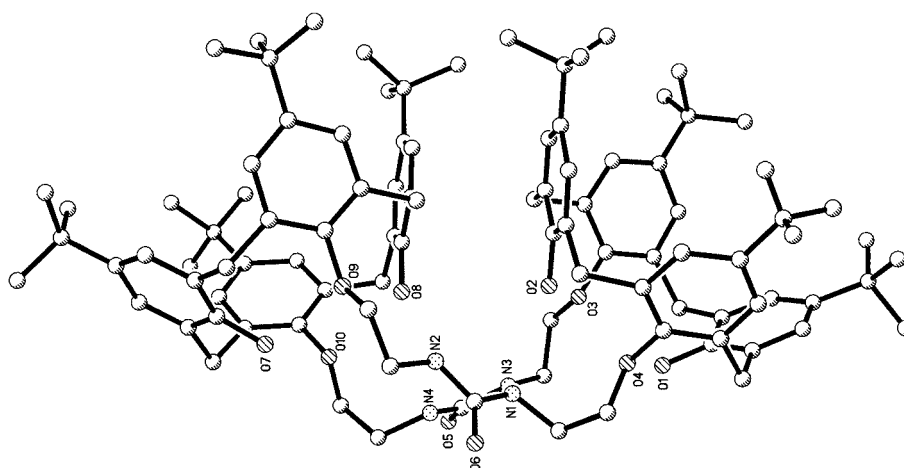
<sup>1</sup>H NMR spectrum of **3** showed a well defined characteristics of cone conformer such as two singlets at  $\delta$  6.99 and 6.89 for aromatic protons and a pair of doublets at  $\delta$  4.05 and 3.10 ( $J = 13.1$  Hz) for the bridge methylene protons. Urea N-H protons appeared as a broad triplet at  $\delta$  6.47 due to the quadruple moment of nitrogen atom. 1,3-Alternate conformer could provide a similar spectral feature, but <sup>13</sup>C NMR spectrum showed at about  $\delta$  33 ppm peak for the bridge carbon,<sup>12</sup> which clearly indicate that **3** exists as a cone conformation.

Figure 1 showed an X-ray structure of calix[4]arene urea derivative **3**. Two calix[4]arene units existed as a cone structure connected with two urea moieties at the middle of bridging units. Table 1 showed the detail data for X-ray structure **3**. From the X-ray structure it was observed that inside two phenyl rings of each calix[4]arene faced each other which could provide binding pocket for aromatic unit with anion such as benzoate.

The anion binding properties were investigated by the proton NMR titration in CDCl<sub>3</sub> solution in the presence of various anions such as tetrabutylammonium (TBA) chloride, bromide, iodide, acetate and benzoate. In proton NMR experiments any meaningful changes of chemical shift for urea NH protons and aromatic proton resonances were not observed upon addition of TBA anions to host **3** solution. Only a slight upfield shift for OH protons was observed when ligand **3** was treated with anions such as benzoate,



**Scheme 1**

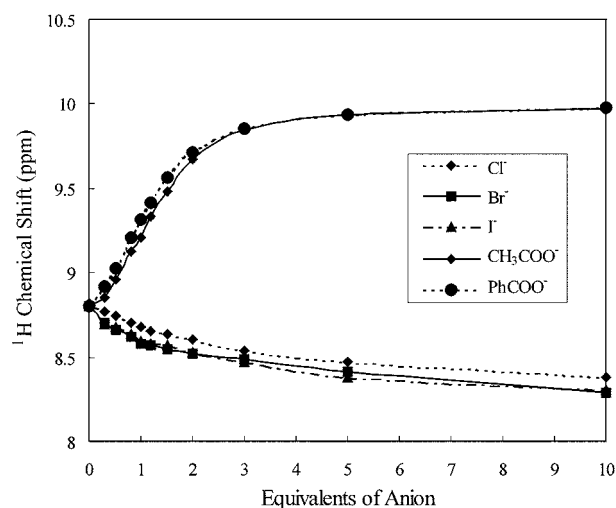


**Figure 1.** Crystal structure of **3**.

**Table 1.** Crystal data and structure refinement for **3**

Empirical formula	C <sub>101</sub> H <sub>129</sub> Cl <sub>3</sub> N <sub>4</sub> O <sub>12</sub>
Formula weight	1697.43
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 12.3639(4) α = 105.7410(10)° b = 19.0542(6) β = 96.5110(10)° c = 21.8000(7) γ = 94.6230(10)°
Volume	4877.8(3) Å <sup>3</sup>
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Goodness-of-fit on F <sup>2</sup>	0.959
Final R indices [I > 2σ(I)]	R1 = 0.0825, wR2 = 0.2129
R indices (all data)	R1 = 0.2059, wR2 = 0.2879
Extinction coefficient	0.0148(11)
Largest diff. peak and hole	0.827 and -0.924 e.Å <sup>-3</sup>

acetate and chloride. A singlet at  $\delta$  8.23 ppm was shifted upfield slightly when benzoate, acetate or chloride was added, suggesting that those anions bind with outside OH protons, which could disrupt the intramolecular hydrogen bond of OH protons resulting a slight upfield shift. Due to the acidic protons on two hydroxyl groups, anion binding was inhibited considerably. But, a high selectivity for acetate was observed when ligand **3** was oxidized to calix[4]quinone **4** with thallium trifluoroacetate. A triplet at  $\delta$  8.82 ppm for N-H proton was shifted downfield dramatically until two equivalents of acetate was added as shown in Figure 1, indicating that ligand **4** and acetate bind 1 : 2 ratio. Due to the bridge of urea unit between two calix[4]arene, a rotation of urea N-H protons can be inhibited considerably which can be an important factor for 1 : 1 binding. A similar change was observed with benzoate. On the other hand, a slight upfield shift of a triplet at  $\delta$  8.82 ppm was observed when chloride or bromide was added, suggesting that spherical shape of halide ions bind weakly with urea protons which could interfere an intramolecular H-bond of urea protons each other. The association constant was obtained



**Figure 2.** <sup>1</sup>H NMR chemical shift of N-H proton for ligand **4** in the presence of anions.

from the resulting titration curves using EQ-NMR.<sup>13</sup>  $K_1$  for acetate was 700 and  $K_2$  was 300. Removal of acidic protons from ligand **3** obviously enhances the acetate binding considerably by allowing hydrogen bond only with urea N-H protons. From the X-ray structure aromatic anions such as benzoate could be placed inside two phenyl rings of the ligand, but the direction of the urea protons may not be proper for the benzoate binding.

In summary, we prepared a bridged urea derivatives of calix[4]arene dimer and calix[4]quinone. A high selectivity for acetate was observed for the calix[4]quinone **4**. Electrochemical properties for **4** are currently under investigation.

## Experimental Section

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(N-bridged ureido)-ethyl]oxy-26,28-dihydroxy biscalix[4]arene 3.** To a solution of 0.31 g (0.41 mmol) of **1** in 30 mL of 1,4-dioxane was added 0.5 mL (4.1 mmol) of trichloromethyl chloroformate (TCF) and the reaction solution refluxed for 3 hours. After the solvent was removed under reduced

pressure and the residue was dried for 1 hr under the vacuum condition. At the same flask, the 30 mL of dried THF was poured and 0.58 mL (4.1 mmol) of triethylamine was added in ice-acetone bath and 0.4 g (0.54 mmol) of **1** in THF 20 mL was dropped and stirred for 6 hours. After removing the solvent, the residue was taken up in  $\text{CHCl}_3$  and washed with water. The organic solvent was evaporated and the residue was purified by column chromatography (eluent;  $\text{CHCl}_3$  : MeOH = 200 : 1) to yield 0.26 g (40%) of white powder **3**. mp 251-253 °C  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.23 (s, 4H, -OH), 6.99 (s, 8H, ArH), 6.89 (s, 8H, ArH), 6.47 (br t, 4H, -NH), 4.05 and 3.10 (a pair of d, 16H,  $\text{ArCH}_2\text{Ar}$ ,  $J = 13.1$  Hz), 4.05 (br t, 8H,  $-\text{OCH}_2-$ ), 3.91 (br q, 8H,  $-\text{CH}_2\text{N}-$ ), 1.29 and 1.073 (two s, 72H,  $-\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ), 158.5 ( $-\text{NHCONH}-$ ), 149.7, 149.0, 147.7, 142.4, 133.2, 128.1, 125.8 and 125.6 (Ar), 76.3 ( $-\text{OCH}_2-$ ), 41.0 ( $-\text{CH}_2\text{N}-$ ), 34.1, 33.9, 31.6 and 31.1 ( $\text{ArCH}_2\text{Ar}$  and  $-\text{C}(\text{CH}_3)_3$ ). FAB MS  $m/z$  1522.1 ( $\text{M}^+$ , Calcd 1522.1).

**5,17-Di-tert-butyl-26,28-bis[(N-ureido)ethyl]oxy-25,27-biscalix[4]diquinone 4.** To a 0.3 g (0.2 mmol) of **3** in trifluoroacetic acid 20 mL, 1.07 g (1.97 mmol) of thallium trifluoroacetate was added and the mixture stirred in the dark under the nitrogen atmosphere for 3 hours. The solvent was then removed and the residue poured into ice water (50 mL). The product was then extracted with  $\text{CHCl}_3$  (100 mL), and the solvent removed. The crude product was purified by column chromatography (eluent;  $\text{CHCl}_3$  : MeOH = 100 : 1) to give a yellow powder **4** 0.07 g (37%); mp 218-220 °C  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.82 (b t, 4H, -NH), 6.81 (d, 8H, ArH,  $J = 6.3$  Hz), 6.68 (d, 8H, ArH,  $J = 5.7$  Hz), 4.26 and 4.17 (two d, 12 H,  $\text{ArCH}_2\text{Ar}$  and  $-\text{OCH}_2\text{CH}_2-$ ,  $J = 13.2$  Hz and  $J = 12.9$  Hz) 3.91 (d, 4H,  $-\text{OCH}_2\text{CH}_2-$ ,  $J = 9.3$  Hz), 3.65 (q, 4H,  $-\text{CH}_2\text{N}-$ ), 3.11 (m, 12H,  $\text{ArCH}_2\text{Ar}$  and  $-\text{CH}_2\text{N}-$ ), 0.99 (s, 36H,  $-\text{C}(\text{CH}_3)_3$ ). FAB MS  $m/z$  1354.6 ( $\text{M}^+$ , Calcd 1354.6).

**Supplementary Material.** Crystallographic data for the

structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-260336). That data can be obtained free of charge from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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