Synthesis and Anion Binding Properties of the Trisurea Derivative of Calix[4]monoquinone

Youn Ju Ki, Sung Ok Kang, Eun Jin Cho, Seungwon Jeon, and Kye Chun Nam*

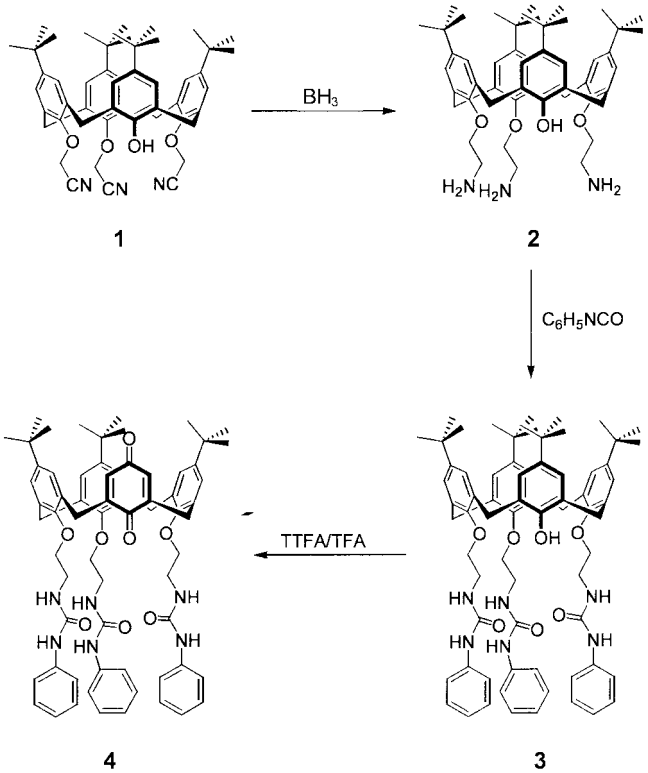
Department of Chemistry and Institute of Basic Science, Chonnam National University, Kwangju 500 -757, Korea
Received September 1, 2000

Selective complexation of anions is more demanding than that of cations due to the several aspects.[1] Even though Beer[2] and Reinhoudt[3] reported several examples of anion receptors recently, much less successful receptors than those of cations are reported. In recent years, however, increasing attention has focused upon anion complexation because of the important environmental consequences of the presence of excess nutrients such as nitrate and phosphate[4] as well as the extreme importance of anionic substrate in biochemistry.[5] In pursuit of developing anion receptor we synthesized several bisurea derivatives of calixarene and investigated their anion binding properties.[6] Also redox switchable receptors which have anion binding urea units as well as quinone moieties was also developed.[7] Particularly we reported[8] a bisurea derivative of calix[4]diquinone recently and it showed a selective binding property toward HSO_4^- ion. In a series of work of anion binding urea derivatives of calixarene, we synthesized a trisurea derivative of calix[4]monoquinone **4** and studied complexation behavior with anions. Even though this neutral anion receptor does not show a particular selectivity among anions, a high binding stability is observed through hydrogen bonding.

Results and Discussion

The urea derivative calix[4]arene **3** was obtained by the reaction of tris(aminoethyl)calix[4]arene **2** and phenylisocyanate in high yield as shown in Scheme 1. Tris(aminoethyl)calix[4]arene **2** was prepared by the BH_3 reduction of the corresponding cyano compound **1** which was obtained selectively by the reaction of *p-t*-butylcalix[4]arene and bromoacetonitrile in the presence of CaH_2.[9,10] Oxidation to quinone was conducted successfully with TTFA(thallium trifluoroacetate) in trifluoroacetic acid to afford a trisurea derivative calix[4]monoquinone **4** in 20% yield. The ^{1}H NMR spectrum of **3** shows two pairs of doublets at δ 3.3 and 4.2 for the bridge methylene protons, two triplets at δ 7.40 and 5.88 and a singlet at 7.85 for the NH protons, and a singlet at δ 6.72 and two doublets at δ 6.57 and 6.49 (J = 2.1 Hz) for the calixarene aromatic protons, and a singlet at δ 5.25 for the OH proton, indicating that **3** exist as a cone conformation. The ^{1}H NMR of **4** shows a similar spectrum as observed from **3**, but calixarene aromatic protons appear as three singlets at δ 6.68, 6.57 and 6.56.

The anion coordination properties were investigated by the proton NMR titration in $CDCl_3$ solution in the presence of various anions such as tetrabutylammonium (TBA) chloride, bromide, dihydrogen phosphate, hydrogen sulfate, and acetate. In proton NMR experiments a large downfield shift of broad singlet NH proton resonance at δ 7.51 and the moderate downfield shift of doublets ortho protons at δ 7.27 of the phenyl group were observed upon addition of TBA anions to host solution. Also the slight shift of three singlets of calixarene aromatic and quinone protons was noticed. Particularly a singlet at δ 7.51 for the amide NH signal shifted rapidly at around δ 8.3 upon addition of 1 equivalent TBA HSO_4^-. Further addition of HSO_4^- caused an only slight downfield shift. Any further significant change was not observed after one equivalent of TBA HSO_4^-, suggesting that **4** complexed with hydrogen sulfate ion 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. Calixarene aromatic and quinone signals changed a position slightly upon addition of anions, indicating that the anions bind at the opposite side of aromatic protons *i.e.* at the lower rim of calixarenes. The association constants of the various anions to the receptors are obtained from the resulting titration curves using EQ-NMR[11] and these values are presented in Table 1. Surprisingly the



Scheme 1. Synthesis of trisurea derivative Calix[4]monoquinone.

Table 1. Stability constants (K_a) in $CDCl_3$

	K/dm$_3$ mol^{-1}	
Anion	**3**	**4**
Cl^-	1425	17200
Br^-	290	6340
HSO_4^-	1600	15700
$H_2PO_4^-$	–[a]	13000
$CH_3CO_2^-$	–[a]	17200

[a]Due to the complexicity of spectra stability constant can not be calculated.

high stability constants of Cl^-, HSO_4^-, and $H_2PO_4^-$ were observed without much selectivity among them.

Previously we reported[6] that a bisurea derivative of calix[4]diquinone showed a high selectivity of HSO_4^- due to the additional hydrogen bonding between quinone and OH proton of HSO_4^-. Here high stability constants of HSO_4^- and $H_2PO_4^-$ could be attributed to the influence of the additional hydrogen bond with quinone moieties. On the other hand a strong binding of spherical chloride was not expected. It was reported[12] that chloride binding constant of the trisurea derivative of calix[6]arene was quite low and bromide binding was stronger than chloride, probably due to the preference of size of calix[6]arene toward bromide. But the trisurea derivative of calix[4]arene **4** showed a high binding with chloride and stronger than bromide. It could be explained that the size of calix[4]arene preferred smaller chloride. Even though the urea derivative calix[4]quinone **4** showed a high binding properties with anions, a simple trisurea calix[4]arene **3** showed a relatively low binding with anions due to the intramolecular hydrogen bond[13] between OH and urea groups.. Previously we also observed a similar binding properties for the bisurea derivative, that is, a calix[4]quinone derivative[6] showed a high binding, but a calix[4]arene derivative not. It is attributed to the intramolecular hydrogen bond[4c] between OH and urea groups, which make two urea units less available to the anion binding.

In pursuit of redox switchable receptors we prepared a trisurea derivative of calix[4]arene and its corresponding quinone and investigated their anion binding properties. The trisurea derivative calix[4]quinone **4** showed the high binding stability of HSO_4^-, Cl^-, $H_2PO_4^-$ without much selectivity and complexed 1 : 1 solution stoichiometry with anions. Redox properties of calix[4]quinone **4** in the presence of anion are currently in progress.

Experimental Section

5,11,17,23-Tetra-*t*-butyl-26,27,28-tris(cyanomethyloxy)-25-hydroxycalix[4]arene 1. To a solution 1 g (1.5 m mol) of *p-t*-butylcalix[4]arene in 23 mL of DMF, 0.6 g (14.2 m mol) of CaH_2 was added, and stirred for 7 days at 30 under N_2 atmosphere. The reaction mixture was added to a saturated NH_4Cl solution, stirred for 30 minute, and filtered. The precipitate was poured into ice water, and then extracted into $CHCl_3$. The organic layer was separated, then dried over anhydrous $MgSO_4$. After removing the solvents, the residue was triturated with methanol to yield 0.38 g (35%) of **1** as a white solid. ^{1}H NMR ($CDCl_3$) 7.19 and 7.13 (two s, 4H, ArH), 6.72 (s, 1H, OH), 6.66 and 6.54 (two d, 4H, ArH, J = 2.4 Hz), 4.86 (s, 2H, -OCH_2CN), 4.76 (s, 4H, -OCH_2CN), 4.36, 4.20, 3.42 and 3.40 (two pair of d, ArCH_2Ar, J = 13.5 Hz) 1.28, 1.27 and 0.86 (three s, 36H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 151.72, 150.00, 149.93, 148.54, 147.77, 142.63, 134.95, 131.67, 131.52, 128.68, 126.64, 125.95, 125.47 and 125.38 (Ar), δ 117.64 and 115.52 (-CN), δ 60.03 and 57.90 (-OCH_2-), δ 34.345, 33.950, 33.826, 32.216, 31.966, 31.685, 31.473, 30.835 (ArCH_2Ar, -C(CH_3)$_3$ and -CH_3).

5,11,17,23-Tetra-*t*-butyl-26,27,28-tris(aminoethyloxy)-25-hydroxycalix[4]arene 2. A 5 mL of 1M BH_3 solution was added to 0.2 g of 1 under N_2 atmosphere and refluxed for 2 hr. The solvents were removed and 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 $CHCl_3$. Solvents were removed and residue triturated with methanol to yield 0.16 g (80%) of 2. ^{1}H NMR ($CDCl_3$) δ 7.16 and 7.07 (two s, 4H, ArH), 6.57 and 6.52 (two d, 4H, ArH), 4.36 and 4.24 (a pair of d, 4H, ArCH_2Ar, J = 12.6 Hz), 4.14 (t, 2H, -OCH_2, J = 5.1 Hz), 3.89 (m, 2H, CH_2NH), 3.69 (t, 4H, -OCH_2, J = 5.1 Hz), 3.28 and 3.24 (a pair of d, ArCH_2Ar, J = 12.0 Hz), 3.19 (m, 4H, CH_2NH), δ 1.34,1.32 and 0.82 (three s, 36H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 153.54, 151.65, 150.93, 150.29, 145.63, 140.74, 135.37, 131.77, 131.63, 129.93, 128.65, 125.43, 125.25 and 125.00 (Ar), 72.21 and 70.09 (-OCH_2-), 41.86 and 41.24 (-CH_2NH-), δ 34.88, 34.19, 34.13, 33.87, 33.75, 33.70, 32.18, 31.71 (ArCH_2Ar, -C(CH_3)$_3$ and -CH_3).

5,11,17,23-Tetra-*t*-butyl-26,27,28-tris[(N'-phenylureido)-ethyl]-25-hydroxy calix [4]arene 3. To a solution of 0.2 g (0.19 mmol) of 2 in 15 mL of CH_2Cl_2, 0.07 mL (3.4 mmol) of phenylisocyanate was added at room temperature. The reaction mixture was stirred for 1hrs under N_2 atmosphere. After removing the solvents, the residue was triturated with methanol to yield 0.12 g (62%) of 3. ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H, NH), 7.40 (t, 1H, NH), 7.14-6.92 (m, 15H, ArH), 6.72 (s, 2H, ArH), 6.57 and 6.49 (two d, 4H, ArH, J = 2.1 Hz), 5.88 (t, 2H, NH), 5.25 (s, 1H, OH), 4.25 and 4.20 (a pair of d, 4H, ArCH_2Ar, J = 12.6 Hz), 4.14 (t, 2H, -OCH_2, J = 6.9 Hz), 3.94-3.63 (m, 8H, CH_2NH), 3,34 and 3.25 (a pair of d, 4H, ArCH_2Ar, J = 13.8 Hz), 1.36 and 0.83 (three s, 36H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ 158.05 and 155.51 (-CO-), δ 153.70, 150.94, 148.92, 146.84, 146.42, 143.82, 139.01, 138.43, 135.14, 131.73, 130.81, 129.80, 129.25, 128.77, 126.07, 125.87, 125.63, 125.15, 123.44, 122.59, 119.44 and 119.12 (Ar), δ 71.53 and 68.14 (-OCH_2-), δ 41.49 and 40.68 (-CH_2NH-), δ 38.67, 34.25, 34.09, 33.75, 31.68, 31.65, 31.31 and 30.95 (ArCH_2Ar, -C(CH_3)$_3$, -CH_3).

5,11,17,23-Tetra-*t*-butyl-26,27,28-tris[(N'-phenylureido)-ethyl]-calix[4]-25-quinone 4. To a solution of 1 g (1 mmol) of **3** in 7.5 mL of TFA, 0.6 g (1 mmol) of TTFA was added. The reaction mixture was stirred for 2 hrs, under N2 atmosphere. After removing the solvent, the residue was treated with 50 mL of ice/water, and then was extracted with $CHCl_3$. The organic layer was separated and then dried over anhy-

drous. After removing the solvent, the residue was triturated with methanol. Column chromatography from $CHCl_3$: *n*-hexane : ethyl acetate (6 : 3 : 1) gave 0.2 g of yellow product. ^{1}H NMR ($CDCl_3$) δ 7.51 (s, 2H NH), 7.27-6.92 (m, 15H, ArH) 6.68 and 6.56 (two d, 4H, ArH, J = 2.4 Hz), 6.70 (s, 2H, ArH), 6.29 (bs, 2H NH), 4.18-3.14 (20H, a pair of d, $ArCH_2Ar$, t, $-OCH_2$, m, CH_2NH), 1.34 and 0.96 (two s, 36H, $-C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 188.62 and 186.33 (-CO-), 157.65, 156.74, 153.12, 147.93, 146.49, 145.68, 138.88, 135.29, 132.93, 132.48, 129.61, 129.05, 128.89, 126.97, 126.66, 125.86, 125.16, 122.85, 120.05, 119.84 and 119.40 (Ar), δ 74.21 and 71.27 ($-OCH_2-$), δ 40.723 and 40.0 ($-CH_2NH-$), δ 34.205, 33.815, 31.921, 31.642, 31.189 and 30.946 ($ArCH_2Ar$, $-C(CH_3)_3$, $-CH_3$).

Acknowledgment. This work was supported by Korea Research Foundation Grant (KRF-2000-015-DP0304). NMR spectra were taken at the Korea Basic Science Institute, Kwangju, Korea.

References

1. Dietrich, B. *Pure Appl. Chem.* **1993**, *65*, 1457.
2. (a) Beer, P. D.; Drew, M. G. B.; Hazlewood, C.; Hesek, D.; Hodacova, J.; Stokes, S. E. *J. Chem. Soc. Chem. Comm.* **1993**, 229. (b) Beer, P. D.; Drew, M. G. B.; Hesek, D.; Nam, K. C. *Chem. Comm.* **1997**, 107. (c) Beer, P. D.; Drew, M. G. B.; Hodacova, J.; Stokes, S. E. *J. Chem. Soc., Dalton Trans.* **1995**, 3447. (d) Beer, P. D.; Dent, S. W. *Chem. Comm.* **1998**, 825. (e) Szemes, F.; Hesek, D.; Chem. Z.; Dent, S. W.; Drew, M. G. B.; Goulden, A. J.; Graydon, A. R.; Grieve, A.; Mortimer, R. J.; Wear, T.; Weightman, J. S.; Beer, P. D. *Inorg. Chem.* **1996**, *35*, 5868.
3. (a) Scheerder, J.; Fochi, M.; Engbersen, J. F. L.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815. (b) Scheerder, J.; Engbersen, J. F. L.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448. (c) Morzherin, Y.; Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1993**, *58*, 7602.
4. Sfriso, A.; Pavoni, B. *Environmental Technol* **1994**, *15*, 1.
5. Lange, L. G.; Riodan, J. F.; Valle, B. L. *Biochemistry* **1974**, *13*, 4361.
6. (a) Nam, K. C.; Kim, D. S.; Yang, Y. S. *Bull. Korean Chem. Soc.* **1998**, *19*, 1133. (b) Nam, K. C.; Chun, J. C.; Kang, S. O.; Ko, S. W. *Bull. Korean Chem. Soc.* **1999**, *20*, 1108. (c) Nam, K. C.; Kang, S. O.; Ko, S. W. *Bull. Korean Chem. Soc.* **1999**, *20*, 953.
7. (a) Jeong, H.; Choi, E. M.; Kang, S. O.; Nam, K. C.; Jeon, S. *Bull. Korean Chem. Soc.* **1999**, *20*, 1232. (b) Jeong, H.; Choi, E. M.; Kang, S. O.; Nam, K. C.; Jeon, S. *J. Electroana. Chem.* **2000**, *485*, 154.
8. Nam, K. C.; Kang, S. O.; Jeong, H. S.; Jeon, S. *Tetrahedron Lett.* **1999**, 7343.
9. Shimizu, H.; Iwamoto, K.; Fijimoto, K.; Shinkai, S. *Chem. Lett.* **1991**, 2147.
10. Nam, K. C.; Kang, S. O.; Chun, J. C. *Bull. Korean Chem. Soc.* **1997**, *18*, 1050.
11. Hynes, M. J. *J. Chem. Soc. Dalton Trans.* **1993**, 311.
12. Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448.
13. Intramolecular hydrogen bond was confirmed by the upfield shift of OH proton signal in the ^{1}H NMR spectrum when anions were added.