Notes

Urea Derivatives of *p-tert*-Butylcalix[4]arenes: Anion Selective Neutral Receptors

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

Department of Chemistry and Institute of Basic Science, Chonnam National University, Kwangju 500-757, Korea
Received April 20, 1999

In comparison with the large variety of ligands which have been described for cation receptors,[1-3] the development of selective host molecules for anions is still in its infancy. The ligands for complexation of anions need to have comparatively large cavities, which have so far proved difficult to be synthesized. In addition, as the charge density of anions is low, the electrostatic forces with anions are weaker than those with cations. 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.[4,5] Anions have a wide variety of geometries[6] and comparatively large sizes, which have to be taken into account in the development of selective anion receptors.

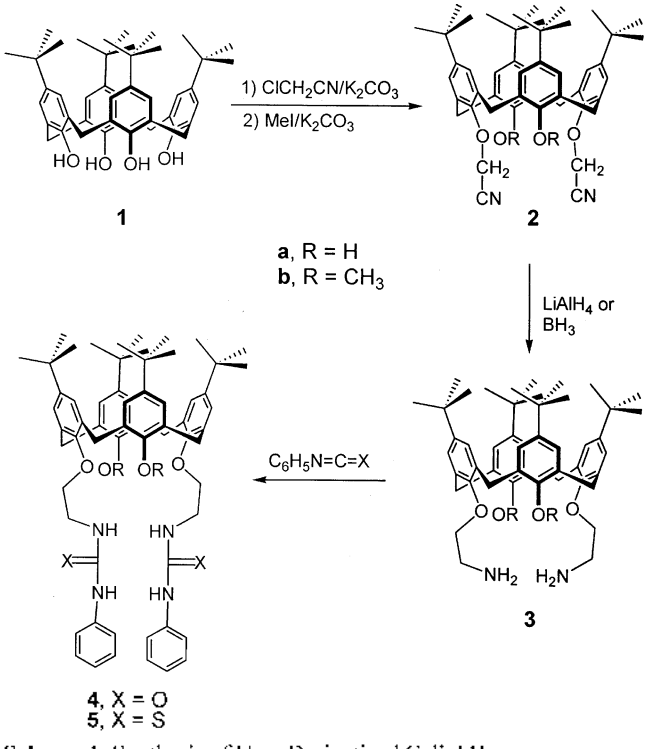
Reinhoudt and co-workers have reported that a selective complexation of Cl^- over Br^- and I^- can be achieved by the neutral urea receptors derived from the lower rim of calix[4]arene[7] and that three urea groups at the lower rim of calix[6]arene are well suited for complexation of tricarboxylate.[8] Both systems complex anions exclusively through hydrogen bonding. 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.*[9] in the complexation of dicarboxylate anion.

Recently we showed that the two urea units at the lower rim of calix[6]arene exhibits selectivity preference for Cl^- over $H_2PO_4^-$ > Br^- > $CH_3CO_2^-$ > HSO_4^-.[10] In order to develop the selective anion receptors, here we report the synthesis and complexation behavior of calix[4]arene based anion receptors **4a**, **4b**, **5a**, and **5b**. The binding study was conducted with proton NMR titration with the various anions such as F^-, Cl^-, Br^-, $CH_3CO_2^-$, and $H_2PO_4^-$.

Results and Discussion

For the synthesis of the bidentate phenylurea calix[4]arenes, the 1,3-bis(2-aminoethyloxy)calix[4]arene **3** was obtained by the reduction of the 1,3-bis(cyanomethyloxy)calix[4]arene **2**. The 1,3-bis(cyanomethyloxy)calix[4]arene **2** was prepared selectively by the reaction of *p-tert*-butylcalix[4]arene **1** with chloroacetonitrile in the presence of K_2CO_3.[11,12] Treatment of aminocalix[4]arene **3** with phenylisocyanate produced the urea derivative of calix[4]arene **4a** as shown in Scheme 1. Thiourea derivative **5a** was prepared similarly by treating aminocalix[4]arene **3** with phenylisothiocyanate. For the investigation of the effect of calixarene OH groups on anion binding, O-methylated host **4b** and **5b** were also synthesized. Since it is known that halide anions are good hydrogen bond acceptors and the urea moiety is a powerful hydrogen bond donor, halide anions would lead to complexation.

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) fluoride, chloride, bromide, dihydrogen phosphate, hydrogen sulfate, and acetate. In proton NMR experiments a large downfield shift of broad singlet NH proton resonance at δ 7.15 and the moderate downfield shift of doublets ortho protons of the phenyl group at δ 7.26 were observed upon addition of TBA chloride to host solution as shown in Figure 1.



Scheme 1. Synthesis of Urea Derivatized Calix[4]arenes.

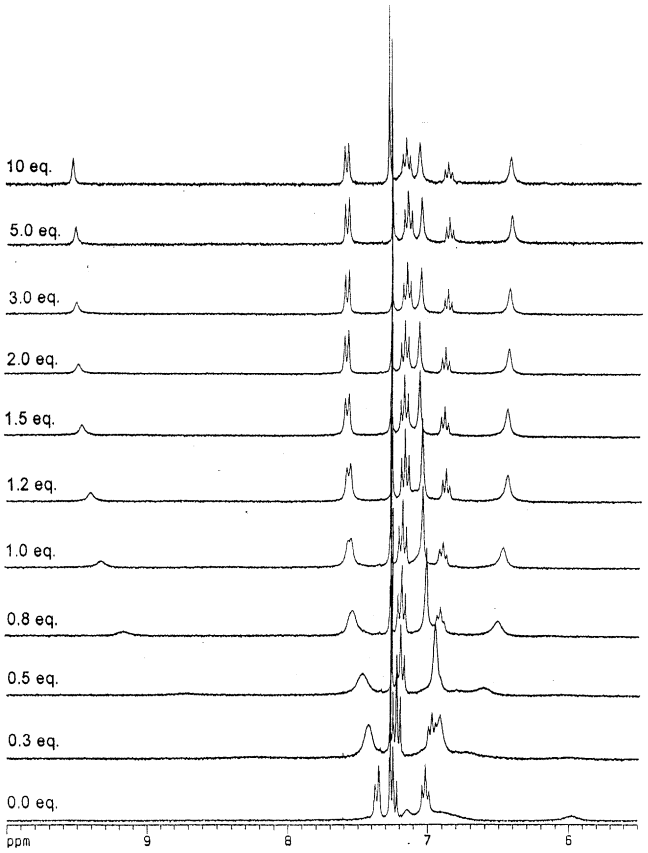


Figure 1. The partial ^{1}H NMR spectra of **4b** in the presence of TBA (tetrabutylammonium) Cl^- in $CDCl_3$. Numbers at the left side indicate the equivalent amounts of Cl^- added.

Also the slight upfield shift of a broad singlet of calixarene aromatic protons at δ6.90 was noticed. The ^{1}H NMR spectra of **4b** became broad in the beginning, but turned into a resolved spectral pattern when fully complexed with chloride ion. That is, the aromatic region consists of two singlets, two triplets and a doublet. This observation could be attributed to the conformational changes of **4b**, that is, chloride ion locking the calixarene into a cone conformation by complexing strongly with the amide protons. Any further significant change was not observed after one equivalent of TBA Cl , suggesting that **4b** 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. Calixarene aromatic signals became two singlets with the moderate change of the position, indicating that the anions bind at the opposite side of aromatic protons *i.e.* at the lower rim of calixarenes, but fix the motion of calixarene framework upon complexation. 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. Upon addition of anion to host solution, sometimes the NH signal was disappeared and reappeared, in this occasion, the signal from ortho proton of the phenyl ring near urea unit was used for the stability constant calculation.

The receptor **4b** exhibits remarkable thermodynamic stability for chloride over the receptor **4a** and **5a**. Obviously OH protons of calix[4]arene **4a** and **5a** inhibit the anion binding, presumably by the hydrogen bond with urea moieties. Continuous upfield shift of OH proton resonance at δ 8.7 was observed upon addition of chloride to the $CDCl_3$ solution of **4a**. Upfield shift suggests that calixarene OH protons form a hydrogen bond without anion, but in the presence of anion hydrogen bond is disturbed. This results contrast with those[10] of the urea derivatives of calix[6]arene, which shows the high stability constants with OH containing receptor over O-methyl analog of calix[6]arene. Calix[4]arene has a much smaller cavity than calix[6]arene and also shows a stronger hydrogen bond than calix[6]arene[14] hydroxy protons. Two OH protons in calix[4]arene **4a** and **5a** compete with anions for the binding of urea moieties, which obviously reduces the anion binding ability.

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

ligand	F^-[a]	Cl^-	Br^-	$H_2PO_4^-$	$CH_3CO_2^-$
4a	730	150	85[c]	270	495
4b	–[b]	3920	2430	1030	1150
5a	476[c]	61[c]	–[b]	100[c]	48[c]

[a]Tetrabutylammonium salts. Errors estimated to be <15%. [b]Very weak binding, a stability constant value could not be calculated in this solvent. [c]Ortho proton of the phenyl ring near urea unit was used for the stability constant calculation.

In an attempt to further increase the strength of the anion complexation the phenylthiourea derivatives **5** were synthesized. Due to the increased acidity of the NH protons of thiourea compared to urea (thiourea pK_a – 21.0; urea pK_a – 26.9),[15] the anion complexation was expected to be stronger. However, only much weaker binding and virtually no selectivity over the anion were observed for the **5a** as shown in Table 1 and no K values for the **5b** could be determined due to the peak broadness in the presence of anion. The reason for the weaker binding properties might be that the enhanced hydrogen donating ability of the thiourea groups more strongly promotes the competing intra and intermolecular hydrogen bonding than the anion binding affinity.[8]

Experimental Section

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(cyanomethyloxy)-26,28-dihydroxycalix[4]-arene (2a). was prepared by the known procedure.[11] mp >290 °C (decomp.)

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(cyanomethyloxy)-26,28-dimethoxycalix[4]-arene (2b). To a solution of 1.0 g (1.38 mmol) of **2a** and 0.66 g (27.5 mmol) of NaH in 60 mL of THF and 6 mL of DMF, 5.12 g (36.1 mmol) of CH_3I was added. After refluxed for 2 hrs. After cooling down to room temperature, 10 mL of MeOH was added and stirred for 30 min, then acidified with 2N HCl solution. The mixture was extracted with $CHCl_3$ (2 × 100 mL). The solvents were removed and the residue was triturated with MeOH to give 0.79 g (76%) of **2b**. mp 231-233 °C. ^{1}H NMR($CDCl_3$) δ 7.12 and 6.50 (s, 8H, ArH), 4.98 (s, 4H, OCH_2CN), 3.82 (s,

6H, OCH_3), 4.40 and 3.28 (pair of d, 8H, $ArCH_2Ar$ J = 13.2 Hz), 1.31 and 0.85 (s, 36H, *tert*-butyl).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-aminoethyloxy)-26,28-dihydroxycalix[4]-arene (3a). was prepared by the known procedure.[12] mp 143-145 °C.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-aminoethyloxy)-26,28-dimethoxycalix[4]-arene (3b). A 6 mL of 1 M BH_3/THF solution was added to 0.3 g of **2b** under nitrogen atmosphere and refluxed for 2 hrs. The solvents were removed and the residue treated with 10 mL of 2N HCl and refluxed for 1h. After cooling down to room temperature, 10% KOH solution was added until the solution became basic and extracted with $CHCl_3$ (2 × 40 mL). The solvents were removed and the residue triturated with MeOH to give 0.163 g (54.1%) of **3b**. mp > 238 °C, dec. ^{1}H NMR ($CDCl_3$) δ 7.15 and 6.53 (s, 8H, ArH), 4.38 (t, 4H, OCH_2), 3.88 (s, 6H, OCH_3), 4.21 and 3.25 (pair of d, 8H, $ArCH_2Ar$ J = 12.6 Hz), 3.52 (t, 4H, $-CH_2NH_2$), 1.33 and 0.82 (s, 36H, *tert*-butyl).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(N'-phenylureido) ethyl]oxy-26,28-dihydroxy-calix[4]arene (4a). To a 0.5 g (0.68 mmol) of **3a** in 20 mL of CH_2Cl_2, 0.15 mL of phenylisocyanate was added and the mixture was stirred for overnight under the nitrogen atmosphere. After removing the solvent, the residue was triturated with MeOH, filtered and dried to give 0.33 g (50%) of **4a**. ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 2H, -OH), 7.17-7.28 (m, 8H, ArH), 7.12 (br t, 2H, -NH), 7.01 and 7.07 (two s, 8H, ArH), 4.26, 4.22, 3.45, and 3.40 (two pair of d, 8H, $ArCH_2Ar$), 4.11 (t, 4H, $-OCH_2-$), 3.85 (q, 4H, $-CH_2N-$), 1.26 and 1.12 (two s, 36H, $-C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 155.9 (-NHCONH-), 149.0, 148.6, 148.3, 143.5, 138.8, 133.0, 128.9, 127.9, 126.2, 125.8, 123.1 and 120.3 (Ar), 76.2 ($-OCH_2-$), 40.2 ($-CH_2N-$), 34.2, 34.0, 32.1, 31.6 and 31.1 ($ArCH_2Ar$ and $-C(CH_3)_3$).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(*N*'-phenylureido) ethyl]oxy-26,28-dimethyloxycalix[4]arene (4b). To a 0.3 g (0.39 mmol) of **3b** in 10 mL of $CHCl_3$, 0.096 mL (0.88 mmol) of phenylisocyanate was added and the mixture was stirred for 30 min under the nitrogen atmosphere. At the end of reaction, 20 mL of 1N HCl solution was added, and stirred vigorously for 20 min, separated organic layer. The solvent were removed and the residue triturated with MeOH to give 0.27 g (79%) of **4b**. mp 244-247 °C. ^{1}H NMR ($CDCl_3$) δ 7.35-6.97 (m, 18H, ArH), 6.88 and 5.98 (broad s, -NH-CO-NH-), 4.15, 3.83, and 3.45 (broad m, 14H, $ArCH_2Ar$, $-OCH_2CH_2-$, OCH_3), 1.2 and 1.13 (s, 36H, *tert*-butyl). ^{13}C NMR ($CDCl_3$) δ 156.3 (-NHCONH-), 153.0, 144.8, 139.0, 133.9, 133.2, 129.0, 125.7, 123.1 and 120.1 (Ar), 72.8 ($-OCH_2-$), 40.5 ($-CH_2NH-$), 34.0, 33.9, 31.5 and 31.4 ($ArCH_2Ar$ and $-C(CH_3)_3$).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(*N*'-phenylthioureido) ethyl]oxy-26,28-dihydroxycalix[4]arene (5a). To a 0.5 g (0.68 mmol) of **3a** in 20 mL of CH_2Cl_2, 0.2 mL of phenylisothiocyanate and 0.2 mL of $(Et)_3N$ was added and the mixture was stirred for overnight under the nitrogen atmosphere. At the end of reaction 20 mL of 1N HCl solution was added, and stirred vigorously for 20 min, separated organic layer, and removed the solvent. The crude product was further purified by column chromatography (eluent $CHCl_3$: n-hexane : ethylacetate = 6 : 3 : 1) to give 0.35 g (51%) of **5a**. ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 2H, -OH), 7.86 (br t, 2H, -NH), 7.73 (s, 2H, -NH), 7.02-7.19 (m, 10H, ArH), 6.95 and 6.90 (two s, 8H, ArH), 4.11 (m, 8H, OCH_2CH_2N-), 3.85, 3.81, 3.29, and 3.24 (two pair of d, 8H, $ArCH_2Ar$), 1.24 and 1.08 (two s, 36H, $-C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 182.3 (-NHC-SNH-), 149.3, 148.4, 148.0, 142.9, 136.5, 132.9, 129.4, 127.4, 126.8, 126, 125.7 and 125.5 (Ar), 74.9 ($-OCH_2-$), 46.0 ($-CH_2NH-$), 34.1, 33.8, 32.2, 31.6 and 31.1 ($ArCH_2Ar$ and $-C(CH_3)_3$).

5,11,17,23-Tetra-*tert*-butyl-25,27-di[(*N*'-phenylthioureido)ethyl]oxy-26,28-dimethoxycalix[4]arene (5b). To a 0.3 g (0.39 mmol) of **3b** in 10 mL of $CHCl_3$, 0.186 mL (1.56 mmol) of phenylisothiocyanate was added and the mixture was stirred for 30 min under the nitrogen atmosphere. At the end of reaction 20 mL of 1N HCl solution was added, and stirred vigorously for 20 min, separated organic layer. The solvent were removed and the residue triturated with MeOH to give 0.29 g (82%) of **5b**. mp 213-216 . ^{1}H NMR ($CDCl_3$) δ 7.78 and 6.47 (broad m, 4H, -NH-CO-NH-), 7.35-7.05 (m, 18H, ArH), 4.07, 3.91, 3.42 and 3.09 (broad m, 14H, $ArCH_2Ar$, $-OCH_2CH_2-$, OCH_3), 1.34 and 0.94 (s, 36H, *tert*-butyl). ^{13}C NMR ($CDCl_3$) δ 181.2 (-NHCSNH-), 144.6, 135.9, 131.8, 130.3, 127.6 and 125.4 (Ar), 72.0 ($-OCH_2-$), 46.2 ($-CH_2NH-$), 34.1, 33.6, 31.7 and 31.2 ($ArCH_2Ar$ and $-C(CH_3)_3$).

^{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.

Acknowledgment. We are indebted to the 1998 Chonnam National University Research Fund for generous support of this work.

References

1. Atwood, J. A.; Davies, J. E.; MacNicol, D. D.; Vögtle F. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Elsevier Science Ltd. : Oxford, UK, 1996; Vol. 1.
2. Lehn, J. M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89.
3. Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. F.; Kaitner, B.; Lough, A. J.; Mckervey, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 8681.
4. Dietrich, B. *Pure Appl. Chem.* **1993**, *65*, 1457.
5. Atwood, J. L.; Holman, K. T.; Steed, J. W. *Chem. Comm.* **1996**, 1401.
6. Rason, L. *Aust. J. Chem.* **1976**, *29*, 1635.
7. Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815.
8. Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448.

9. Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369.
10. Nam, K. C.; Kim, D. S.; Yang, Y. S. *Bull. Korean Chem. Soc.* **1998**, *19*, 1133.
11. Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3137.
12. Szemes, F.; Hlesek, D.; Chen, 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. *Inorganic Chemistry*, **1996**, *35*, 5868.
13. Hynes, M. J. *J. Chem. Soc. Dalton Trans.* **1993**, 311.
14. Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.
15. Bordwell, E.; Algrim, D. J.; Harrelson, Jr. J. A. *J. Am. Chem. Soc.* **1988**, *110*, 5903.