Synthesis and Binding Studies of Bowl-Shaped Hosts for Quaternary Ammoniums

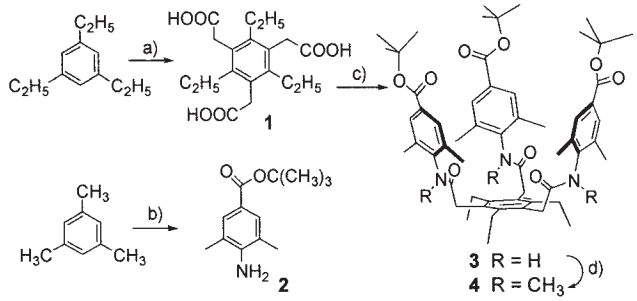
Kyu-Sung Jeong,* Kwang Hoon Shin, and Soong-Hyun Kim
Department of Chemistry, Yonsei University, Seoul 120-749, Korea

(Received August 12, 2002; CL-020678)

Two bowl-shaped hosts for quaternary ammonium salts were synthesized and their binding properties, along with the anion effect, were systematically examined and compared in $CDCl_3$.

A large number of artificial hosts for quaternary ammoniums (QA's) have been studied for the last decade, and provided much experimental evidence for the nature of noncovalent forces, especially the cation$-\pi$ interaction.[1,2] The hosts contain a rigid cavity for the QA binding surrounded by aromatic surfaces, like in calixarenes and cyclophanes.[2] Because QA salts exist as ion pairs in organic solvents, the coexisting counteranions have a significant influence on the binding of QA to the host. The electrostatic interaction of the ion pair may have either a negative or a positive effect on the QA binding as recently demonstrated by several groups including ours.[3] We herein prepared two new bowl-shaped hosts for QA and investigated systematically their binding properties with QA salts in $CDCl_3$.

The basic scaffold of the hosts is a hexasubstituted benzene that has been widely used as a molecular building block for the construction of artificial hosts.[4] The synthesis of hosts is outlined in Scheme 1. 2,4,6-Triethyl-1,3,5-tris(acetic acid) (**1**)[5] and *tert*-butyl 4-amino-3,5-dimethylbezoate (**2**)[6] were prepared from commercially available 1,3,5-triethylbezene and 1,3,5-trimethylbenzene, respectively. After reaction with oxalyl chloride, the acid **1** was coupled with the amine **2** to give the N–H host **3**, which was in turn converted into N–Me host **4**.[7]



Scheme 1. a) i) HBr/$(CH_2O)n$/$ZnBr_2$, 42% ii) NaCN/EtOH–H_2O, 95% iii) 50% aqueous H_2SO_4, 72%, b) i) fuming HNO_3/CH_3COOH, 97% ii) CrO_3–H_2SO_4/H_2O–CH_3COOH, 14% iii) $SOCl_2$, then *t*-BuOH–DMAP/$CHCl_3$, 83% iv) H_2, Pd–C/MeOH, 96%, c) $(COCl)_2$, then **2**/DMAP(cat), 45%, d) MeI–KOH/DMSO, 71%.

According to molecular modeling studies (Tripos, Sybyl 6.3), the hosts present the following features. First, three benzoate walls are all positioned to the same side as the result of alternative up and down conformation of adjacent substituents in the central benzene. Second, 3,5-dimethyl substituents of the benzoate walls enforce the aryl plane to be perpendicular to the amide plane and consequently the cavity becomes surrounded by the aryl surfaces. Finally three amide carbonyl groups are directed to the cavity of the host in a convergent way (Figure 1).

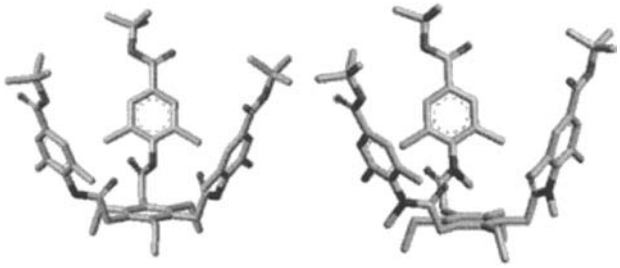


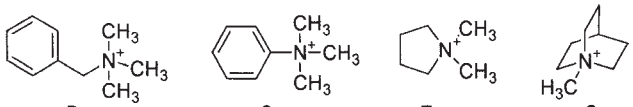
Figure 1. Energy-minimized (Tripos, Sybyl 6.3) structures of the N–H host **3** (left) and the N–Me host **4** (right).

The binding studies were first performed with N–H host **3** and benzyltrimethylammonium ($BTMA^+$) halides (**5**, X^-=Cl^-, Br^-, and I^-). Upon addition of the host **3** ($\sim$3 equiv) in $CDCl_3$, the signals for N^+CH_3 and N^+CH_2 of $BTMA^+\cdot Cl^-$ were significantly upfield shifted ($\Delta\delta$ = 1.5 and 1.8 ppm, respectively). This is a strong evidence for the QA guest locating inside the cavity surrounded by aryl surfaces of the host. However, the magnitude of the shifts is highly anion-dependent; $\Delta\delta$ = $\sim$1 ppm for $BTMA^+\cdot Br^-$ and $<$0.3 ppm for $BTMA^+\cdot I^-$ when equal amounts of the host **3** were added. Quantitative binding affinities were determined by nonlinear least squares fitting of ^{1}H NMR chemical shift changes observed by diluting a 1 : 1 mixture of host and guest in $CDCl_3$ at 23 $\pm$ 1 °C. The association constants (K_a's) were calculated to be $>3 \times 10^4$, 3.4 ($\pm$0.2) $\times 10^3$, and 1.7 ($\pm$0.2) $\times 10^3$ M^{-1} for $BTMA^+Cl^-$, $BTMA^+Br^-$, and $BTMA^+I^-$, respectively.

As suggested previously,[3] this anion dependence may be rationalized by hydrogen bonds between the amide NH hydrogen of the host **3** and the anion X^- of the guest.[8] The hydrogen-bonded anions may exert electrostatic interactions with the oppositely charged ammonium ions, especially in a less polar organic solvent, $CDCl_3$. Second, the hydrogen bond may increase the electron density on the amide carbonyl oxygens and consequently strengthen the cation–dipole and/or C–H$\cdots$O interactions.[9]

Next, we have prepared the N–Me host **4** that cannot directly interact with anions through hydrogen bonds. As seen in Figure 1, the energy-minimized structure[10] of the host **4** is very close to that of the N–H host **3**. When the host **4** was added to a $CDCl_3$ solution of various QA salts, the ^{1}H NMR signals of the N^+CH_n hydrogen were gradually upfield shifted ($\Delta\delta$ = 0.3–0.5 ppm), but the degree of the shifts is smaller compared with the N–H host **3**. The association constants are calculated by nonlinear least-square fitting of ^{1}H NMR titration curves[11] and the results are summarized in Table 1. Job's plots also confirm a 1 : 1 complex formation between the host **4** and each of the guests **5**–**8**.[12]

Trends in the binding affinity are as follows. The magnitude



5 6 7 8

Table 1. Association constants ($K_a \pm 10\%$) between the N–Me host **4** and ammonium guests in $CDCl_3$ at $23 \pm 0.5\,^{\circ}C$

Guest	K_a/M^{-1}	Guest	K_a/M^{-1}
5·Cl^-	570	**8**·I^-	490
5·Br^-	1160	$Et_4N^+ \cdot I^-$	140
5·I^-	1780	$Bu_4N^+ \cdot I^-$	no binding
6·I^-	3300	*t*-BuOH	no binding
7·I^-	2200		

of the association constants between host **4** and $BTMA^+ \cdot X^-$ is the order of $Cl^- < Br^- < I^-$, exactly opposite to that seen with the N–H host **3**. This is expected because tightening the ion pair weakens the cation binding to the cavity, like in the host **4** having no hydrogen-bonding site for anion. Second, two hosts **3** and **4** show nearly identical association constant ($\approx 1700\,M^{-1}$) toward $BTMA^+ \cdot I^-$, implying that iodide ion is poor hydrogen-bonding acceptor and exerts negligible anion effect. Third, the host **4** binds strongly to the small QA guests but negligibly either to a large guest $Bu_4N^+ \cdot I^-$ or to a neutral guest *tert*-butanol.

In conclusion, the coexisting counteranions have a large influence on the QA binding in organic solvents, but the magnitude depends on the nature of the host as well as the anion.

This work was supported by Korea Research Foundation (KRF-2000-041-D00190).

References and Notes

1 J. C. Ma and D. A. Dougherty, *Chem. Rev.*, **97**, 1303 (1997).

2 a) S. Shinkai, K. Araki, T. Matsuda, N. Nishiyama, H. Ikeda, I. Takasu, and M. Iwamoto, *J. Am. Chem. Soc.*, **112**, 9053 (1990). b) L. Garel, B. Lozach, J.-P. Dutasta, and A. Collet, *J. Am. Chem. Soc.*, **115**, 11652 (1993). c) A. Cattani, A. D. Cort, and L. Mandolini, *J. Org. Chem.*, **60**, 8313 (1995). d) A. Arduini, W. M. MaGregor, D. Paganuzzi, A. Pochini, A. Secchi, F. Ugozzoli, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, **1996**, 839. e) K. N. Koh, K. Araki, A. Ikeda, H. Otsuka, and S. Shinkai, *J. Am. Chem. Soc.*, **118**, 755 (1996).

3 a) K.-S. Jeong, K.-M. Hahn, and Y. L. Cho, *Tetrahedron Lett.*, **39**, 3779 (1998). b) S. Kubik, *J. Am. Chem. Soc.*, **121**, 5846 (1999). c) S Bartoli and S. Roelens, *J. Am. Chem. Soc.*, **121**, 11908 (1999). d) V. Böhmer, A. D. Cort, and L. Mandolini, *J. Org. Chem.*, **66**, 1900 (2001). e) S. Bartoli and S. Roelens, *J. Am. Chem. Soc.*, **124**, 8307 (2002).

4 G. Hennrich and E. V. Anslyn, *Chem.—Eur. J.*, **8**, 2219 (2002).

5 C. Walsdorff, W. Saak, and S. Pohl, *J. Chem. Res., Synop.*, **1996**, 282.

6 J. P. Schaefer and T. Miraglia, *J. Am. Chem. Soc.*, **86**, 64 (1964).

7 Physical and spectroscopic properties of the N–H host **3**: mp $> 300\,^{\circ}C$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.67 (br s, 3NH), 7.59 (s, 6H), 3.93 (s, 6H), 2.80 (q, $J = 7.3$ Hz, 6H), 2.13 (s, 18H), 1.53 (s, 27H), 1.29 (t, $J = 7.3$ Hz, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.2, 165.3, 143.1, 137.6, 135.1, 130.8, 130.4, 129.5, 81.2, 28.3, 18.6, 15.0; FABMS $m/z =$ 968.5 (7%) for $[M{\cdot}Na]^+$, 944.5 (12%) for $[M\text{-}H]^+$; Anal. Calcd for $C_{57}H_{75}N_3O_9$: C, 72.35; H, 7.99; N, 4.44. Found: C 72.38; H, 7.95; N, 4.45. Physical and spectroscopic properties of the N–Me host **4**: mp $>$ 192–193 $^{\circ}C$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.79 (s, 6H), 3.17 (s, 6H), 3.14 (s, 9H), 2.36–2.29 (m, 24H), 1.61 (s, 27H), 0.92 (t, $J = 7.2$ Hz, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.1, 165.3, 144.9, 141.1, 136.1, 131.7, 130.4, 129.4, 81.6, 34.7, 28.3, 17.5, 14.3; FABMS $m/z =$ 988.7 (100%) for $[MH]^+$, 987.5 (45%) for $[M]^+$; Anal. Calcd for $C_{60}H_{81}N_3O_9$: C, 72.92; H, 8.26; N, 4.25. Found: C 72.96; H, 8.26; N, 4.25.

8 The formation of the hydrogen bond is evident in the ^1H NMR spectra. When $\approx$3 equivalents of $BMTA^+X^-$ were added to a $CDCl_3$ solution of the host (1 mM), large downfield shifts of the NH signal were observed, $\Delta\delta = 2.4$, 1.9, and 0.7 ppm for X=Cl, Br, and I, respectively. For hydrogen bonding interaction between anions and amide NH's, see: a) F. P. Schmidtchen and M. Berger, *Chem. Rev.*, **97**, 1609 (1997). b) K. Choi and A. D. Hamilton, *J. Am. Chem. Soc.*, **123**, 2456 (2001).

9 a) S. Tomàs, M. C. Rotger, J. F. González, P. M. Deyà, P. Ballester, and A. Costa, *Tetrahedron Lett.*, **36**, 2523 (1995). b) S. Tomàs, R. Prohens, M. Vega, M. C. Rotger, P. M. Deyà, P. Ballester, and A. Costa, *J. Org. Chem.*, **61**, 9394 (1996).

10 This structure is the energy-minimized one of the host **4** when complexed with tetramethylammonium guest inside the cavity. In the ^1H NMR spectroscopy, the free host **4** contains a small amount ($\approx$5%) of conformational isomer in $CDCl_3$, but only one set of ^1H NMR signals was observed upon the complex formation. Therefore, the guest binding seems to induce the host structure in a way of maximizing intermolecular noncovalent interactions.

11 a) R. S. Macomber, *J. Chem. Educ.*, **69**, 375 (1992). b) K.-S. Jeong, Y. L. Cho, S.-Y. Chang, T.-Y. Park, and J. U. Song, *J. Org. Chem.*, **64**, 9459 (1999). c) Y. L. Cho, H. Uh, S.-Y. Chang, H.-Y. Chang, M.-G. Choi, I. Shin, and K.-S. Jeong, *J. Am. Chem. Soc.*, **123**, 1258 (2001).

12 K. A. Corners, "*Binding Constants*," John Wiely & Sons, New York (1984), p 24.