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Water-Soluble Resorcin[4]arene: Complexation of Anionic Aromatic Guests by Cooperativity of Electrostatic and Hydrophobic Interactions

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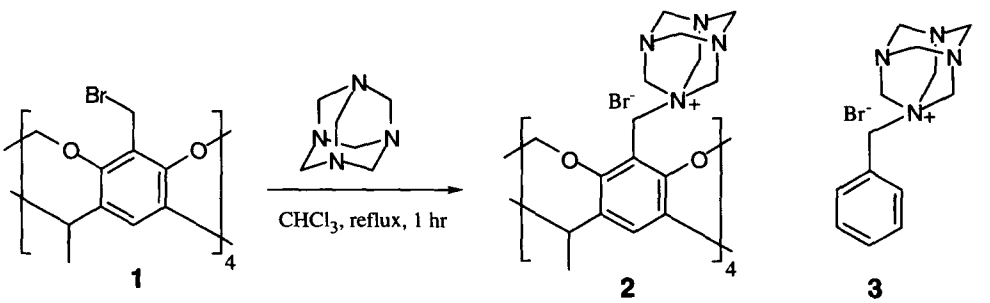
Abstract: Water-soluble resorcin[4]arene based cavitand **2** was synthesized by reaction of bromomethylcavitand **1** with hexamethylenetetramine. The bowl-shaped cavitand host **2** shows a good binding affinity to anionic aromatic guests with 1:1 binding in D_2O. The guest inclusion within the host cavity was confirmed by ^1H NMR spectroscopy. Electrostatic interaction as well as hydrophobic interaction turned out to cooperatively act as binding forces for a strong complex formation in water.

Keywords: Noncovalent interaction; Water-soluble resorcin[4]arene; Cooperativity; Complexation

Noncovalent intermolecular interactions play a major role in biological systems as well as in synthetic host-guest complexes. Most synthetic receptors for polar substrates bind effectively in relatively nonpolar solvents, relying mainly on hydrogen-bonding interactions as the driving force for binding,[1] but to mimic Nature the use of water-soluble synthetic receptors as simple models for enzymes and receptors has been the focus of interest of many chemists in recent years. Water-soluble cyclophanes[2] with large hydrophobic cavities represent, besides the cyclodextrins,[3] the major class of receptors capable of binding organic substrates in aqueous solution. Other approaches to water-soluble receptors use a bowl-shaped molecular scaffold such as the calix[4]arenes and resorcin[4]arenes as a hydrophobic binding cavity to which water soluble functional groups are attached.

In contrast to the water-soluble calix[4]arene derivatives,[4] there are only a few examples of water-soluble resorcin[4]arene based receptors.[5] Since anions are more strongly solvated than cations of comparable size,[6] studies on anion recognition has only recently received attention, in sharp contrast to the far more advanced studies on cation recognition.[7] In this communication we describe the complexation behavior of a water-soluble resorcin[4]arene based receptor **2** toward aromatic carboxylates in water. We also report the cooperative effects of electrostatic and hydrophobic interactions in host-guest complexation.



Scheme 1

The receptor **2** was prepared by reaction of the known bromomethylcavitand **1**[8] with hexamethylenetetramine in $CHCl_3$ (Scheme 1).[9] The benzylic proton resonance on the upper rim of the cavitand **2** appears at relatively

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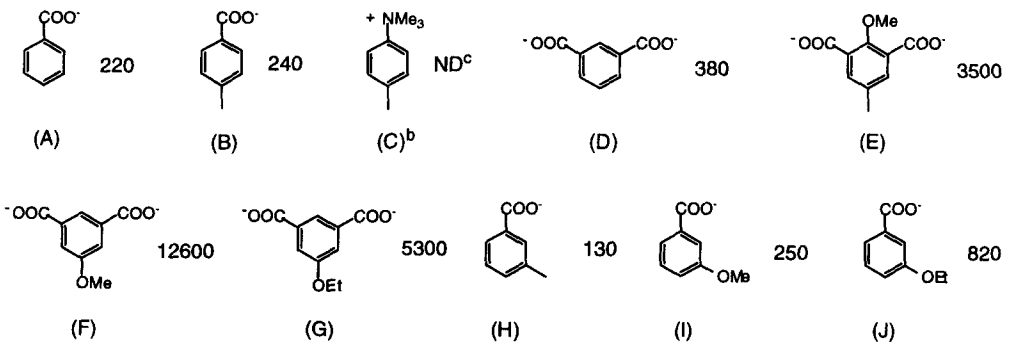
high field (3.80 ppm, $\Delta\delta$ 0.26 ppm) compared to that of the control compound **3**, which presumably indicates that the methylene protons are pointing toward the magnetically shielded region of the cavitand cavity and thus the ammonium moieties of hexamethylenetetramine may be located out of the cavity. This means that aromatic guests are accessible to the cavity free from steric hinderance. The presence of open cavity was confirmed by increased binding affinity for guests with the better fitting steric structure for the host cavity (*vide infra*). The solubility of the cavitand **2** turned out to be more than 40 mM in D_2O over a broad pH range due to the permanent charges of the quarternary ammonium salts. In fact, the host-guest complexation is demonstrated by the complexation-induced changes in chemical shift observed in the ^{1}H-NMR binding titrations. Analysis of titration data of the cavitand **2** with various anionic aromatic guests showed that the binding isotherms fit well to a 1:1 binding model. The calculated association constants are collected in Table 1. A Job ^{1}H NMR titration between **2** and guest F conducted in D_2O showed that maximum signal change was observed at 0.5 mol fraction of **2**, indicative of 1:1 binding, as shown in Scheme 2. Recently, Reinhoudt et al reported that 1:1 complexation with aromatic guests occurred for a similar host with pyridinium moieties instead of the ammonium moieties of **2**.[5d]

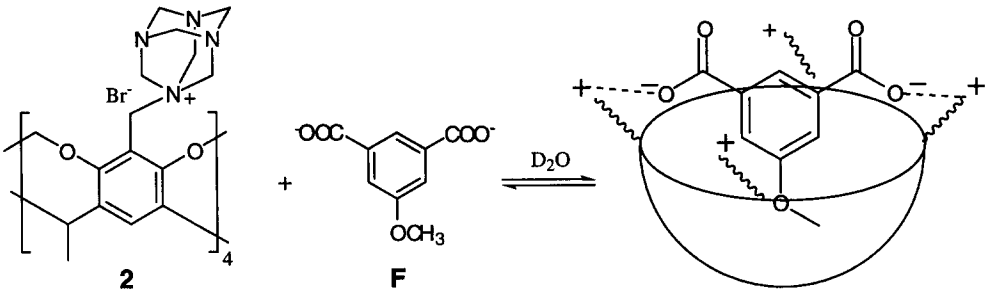
Table 1. Binding constants (M^{-1}) of the 1:1 host-guest complexes in D_2O[a]



[a] Binding constants were obtained by inverse titrations on the basis of the 1:1 binding model at 300 K. All counterions are Na^+. [b] Counterion is I^-. [c] No detectable complexation-induced ^{1}H NMR shift changes were observed.

Since the chemical shifts of **2** hardly change upon succesive addition of the guest solution to host **2** in D_2O, the inverse titrations were carried out by adding increasing amounts of the host solution to a standard solution of the target guest in D_2O. The cavitand **2** formed stronger complexes with the dianionic guests than with the monoanionic guests: Binding constants for monoanionic guests were ~10^2 M^{-1}, and those for dianionic guests were ~10^2 - ~10^4 M^{-1}. The fact that a positively charged guest (C) did not show any detectable CIS (complexation- induced shifts in ^{1}H NMR spectra) indicates that there is a considerable electrostatic contribution to the binding between **2** and anionic aromatic guests in water and these results agree with Koga's precedent report on the guest inclusion by water-soluble paracyclophanes.[10] Synthetic reference molecule **3** without hydrophobic binding cavity also did not show any detectable CIS with B, indicating that electrostatic interaction is not sufficient for a strong complex formation. It is noteworthy that the complex formation of **2** with E is an order of magnitude stronger than that with D which does not have the methyl moiety for deep inclusion inside the host cavity. This suggests the importance of hydrophobic interaction for the strong complex formation in aqueous media. On the contrary, the binding data for A, B, H and I show that monoanionic aromatic guests generally have similar binding strength, irrespective of the position and length of the alkyl side chain, though somewhat stronger binding was observed for guest J. This may be due to the loose complexation of monoanion guests with **2** by one-point electrostatic interaction. Therefore, hydrophobic interaction contributes less importantly to the complex formation with monoanion guests, though some hydrophobic effect was observed for guest J compared to guest I. Since two-point electrostatic interactions as with isophthalate series (D ~ G) may result in more rigid binding mode, it is thought that aromatic alkyl moiety on the position 5 of the isophthalate guests is able to more easily

point inside the apolar cavity for a strong complex formation. In fact, Me protons on the position 5 of the isophthalate guests (E, F, and G) experienced large upfield shifts upon saturation, which reflects the fact that Me protons reside in the shielding region of the internal cavity of **2**; $\Delta\delta$ (CH_3) of E = -3.37 ppm, $\Delta\delta$ (CH_3) of F = -3.70 ppm, $\Delta\delta$ (CH_3) of G = -3.54 ppm.[11] This is an example of the CH-π interaction, which should be more advantageous by hydrophobic effects in water.[12] Furthermore, aromatic protons on the positions 4 and 6 of the guests also showed upfield shifts upon binding to **2**; $\Delta\delta$ (ArH) of E = -1.38 ppm, $\Delta\delta$ (ArH) of F = -1.08 ppm, $\Delta\delta$ (ArH) of G = -0.58 ppm. Comparing binding strength for F with that for E and G, it turned out that F has an appropriate length of the alkyl chain for the most effective hydrophobic interaction in the host cavity, together with carboxylates being located at the optimum position for electrostatic interactions with quartenary ammonium salts. So, in case of complexation with F both electrostatic and hydrophobic interactions are acting cooperatively to exert strong binding. All the binding data taken together, the binding mode can be proposed as follows (Scheme 2).



Scheme 2

The minimum energy structure of the complex between **2** and E was obtained from the MC/SD conformational searching[13] with MacroModel V5.5 utilizing the MM2* force field[14] and the GB/SA solvation model for water.[15] Inspection of the computer-generated structure of the complex (Figure 1) indicates that the methyl group on the position 5 of 2-methoxy-5-methylisophthalate (E) can be imbedded within the hydrophobic cavity formed by the aromatic walls.[16]

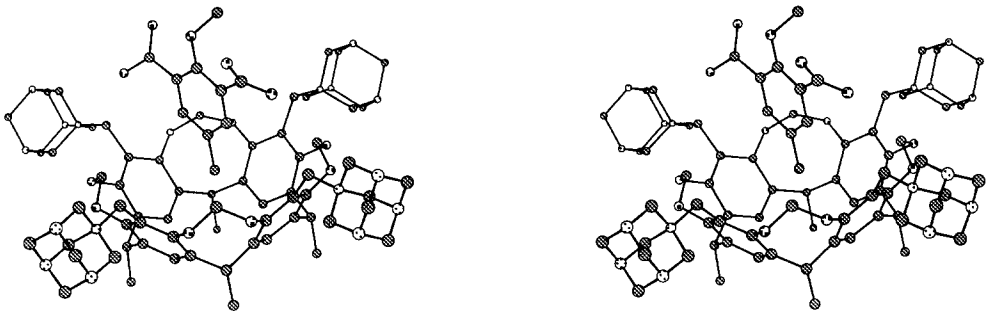


Figure 1. Energy-minimized structure of the complex between **2** and E shown in stereoview. Hydrogens have been omitted for clarity.

In summary, we have synthesized a bowl-shaped cavitand with water-soluble quarternary ammonium salts on the upper rim. The water-soluble host **2** shows a good binding affinity to anionic aromatic guests with 1:1 binding in D_2O. Electrostatic interaction as well as hydrophobic interaction cooperatively act as binding forces for a strong complex formation in water.

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9. Preparation of **2**: To a solution of hexamethylenetetramine (58mg) in chloroform (15ml) was added compound **1** (100mg) and the mixture was heated at reflux with stirring for 1hr. The resulting white solid was filtered and washed with chloroform, then it was dried to afford 150 mg (95%) of **2**. Spectral data of **2**: ^{1}H NMR (300 MHz, D_2O) δ 7.86 (s, 4H, Ar*H*), 6.12 (d, J=7.16 Hz, 4H, -OCH_{out}H$_{in}$O-), 5.05 (s, 24H, -CH_2N$^+$(CH_2N)$_3$-), 4.97 (q, J=7.56 Hz, 4H, ArC*H*(CH_3)-), 4.54 (dd, J_a=13.0 Hz, J_b= 55.2 Hz, 24H, NCH_2N), 4.21 (d, J=7.00 Hz, 4H, -OCH$_{out}H_{in}$O-), 3.85 (s, 8H, ArCH_2N$^+$-), 1.86 (d, J=7.10 Hz, 12H, ArCH(CH_3)Ar); ^{13}C NMR (75 MHz, D_2O) δ 154.4, 140.0, 125.3, 112.3, 78.7, 72.2, 70.3, 51.0, 32.2, 16.1; FAB-MS m/z 1445 (M - Br$^-$); HRMS (FAB$^+$) *m/z* calcd for $C_{64}H_{84}N_{16}O_8Br_3$ 1445.4187, found 1445.4189.
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16. The computer-generated structure of the complex between **2** and F also indicates that the methoxy group on the position 5 of F is pointing inside the hydrophobic cavity.