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Small Cavitands Specifically Binding a Water Molecule

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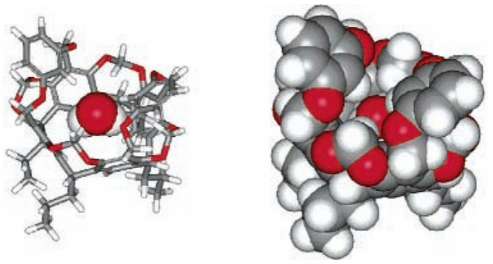
ABSTRACT

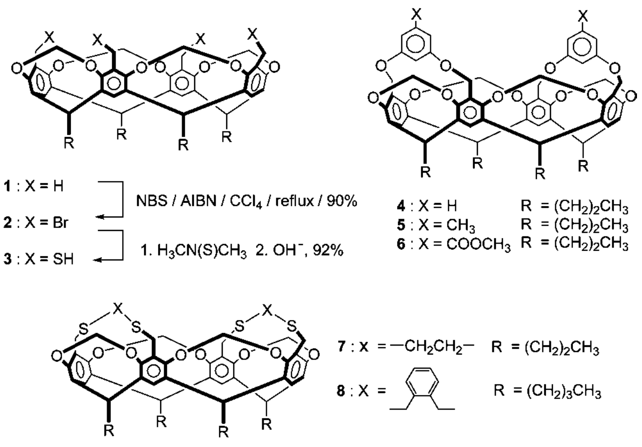


Three new C_{2v} cavitands based on resorcin[4]arene bind water specifically at low temperature in CD_2Cl_2 or $CDCl_3$ due to their complementarity to water as well as the solvophobic interaction. The averaged $\Delta H°$ and $\Delta S°$ values are -2.3 kcal mol^{-1} and -128 cal mol^{-1} K^{-1}, which gave the averaged $-\Delta G°$ of 1.9 kcal mol^{-1} at -50 °C in water saturated CD_2Cl_2 .

The specific guest complexation by synthetic hosts has been a goal of molecular recognition studies. Various container hosts for small guest molecules such as MeOH, EtOH, CH_3CN, CH_3NO_2, CH_3CN, and CH_3CHO have been reported.[1,2] Water is one of the most ubiquitous and most important molecules for biological systems. Recently, crystal structures of tetrameric[3] and octameric[4] water clusters have been observed in solid states. In solution, water adopts three-dimensional hydrogen-bonded networks according to temperature or pressure.[5] A host selectively binding a water in solution would enable the study of structure and properties of a single water molecule, but it is very difficult to separate a single water molecule from the bulk solution due to its small size and strong hydrogen bonds. Herein, we report on the synthesis and water-specific binding property of new C_{2v} cavitands at low temperature.

New C_{2v} cavitands **4**, **5**, or **6** were synthesized from tetrabromide **2**[6] by coupling in K_2CO_3/DMF with resorcinol, 2-methylresorcinol, or methyl 3,5-dihydroxybenzoate in 17, 15%, 19% yields, respectively (Scheme 1). Cavitands **7** or **8** were synthesized from tetrathiol **3**[7] by coupling in K_2CO_3/DMF with 1,2-dibromoethane or α,α′-dibromo-*o*-xylene in

Scheme 1. Synthesis of New C_{2v} Cavitands



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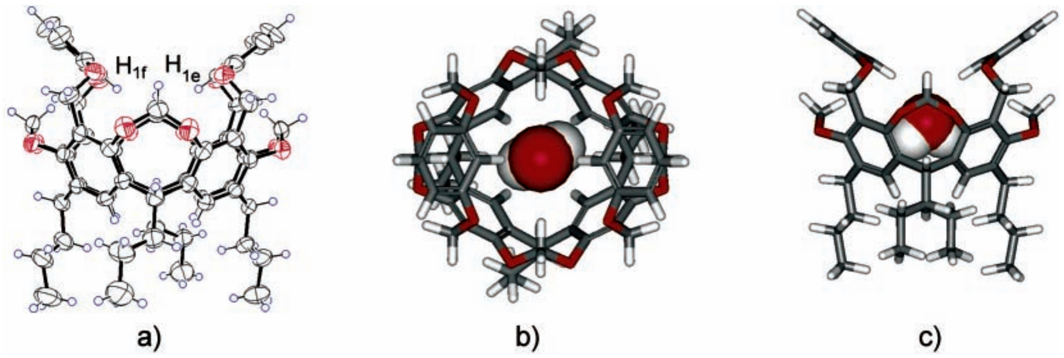

Figure 1. (a) X-ray crystal structure of cavitand **4** (solvent molecules are omitted for clarity. Structure shows 50% ellipsois probability). (b, c) Molecular mechanics-optimized structure of **4**@H_2O (CFF95 Force-field by Cerius2) (b, top view; c, side view). Cavitand is represented as a bond framework while the H_2O molecule is rendered as a space-filling model.

45 and 36% yields, respectively. These new C_{2v} cavitands have been fully characterized by NMR, FAB+ mass spectra, and elemental analyses.[8]

The CPK molecular model study showed that these new C_{2v} cavitands could not accommodate MeOH, EtOH, CH_3CN, CH_3CHO, CH_3NO_2, CH_4, or NH_4^+ but could accommodate H_2O due to the small cavity partially blocked by protons H_{1f} and H_{1e} of the bridging resorcinolic units (Figure 1a).

The water-binding properties were not verified by X-ray crystallographic study of a single crystal of **4**, which was grown at room temperature by slow evaporation of mixed solution (CH_2Cl_2/toluene) (Figure 1a).

The complex formations were studied by ^1H NMR spectrometer from 25 °C to −70 °C in water-saturated CD_2Cl_2 or $CDCl_3$. Cavitands **4**−**6** did not show any detectable complexing behavior for H_2O until −20 °C in CD_2Cl_2 or $CDCl_3$. For example, cavitand **6** showed only a free H_2O peak at 1.53 ppm in water-saturated CD_2Cl_2 at 25 °C (Figure 2a). When the temperature was deceased to −50 °C, a new signal appeared at −2.56 ppm (Figure 2b). The far upfield shifts of the complexed guest's peaks ($\Delta\delta = -4.09$) are typical to container hosts having aromatic shells. When an excess of D_2O was added at room temperature and the ^1H NMR spectrum was measured at below −50 °C, the complexed and free peaks of water disappeared due to the fast exchange between D_2O and complexed H_2O as well as free H_2O (Figure 2c). Cavitands **4** and **5** showed the similar water binding properties in water-saturated CD_2Cl_2 or $CDCl_3$, and the ratios of complexed water molecule to cavitands **4**, **5**, and **6** at −50 °C are 0.24, 0.21, and 0.40, respectively. However, none of them complexed water in acetone-d_6 at low temperature.

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(8) For **4**: mp >300 °C dec. FAB+ MS m/z 973.1 (M^+, 100); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97, 1.13 (t, 12H, $CH_2CH_2CH_3$), 1.27, 1.55 (m, 8H, $CH_2CH_2CH_3$), 2.14, 2.35 (m, 8H $CH_2CH_2CH_3$), 3.31 (d, 2H, $J = 7.2$, cyclic inner OCH_2O), 4.34 (d, 4H, $J = 12.0$, inner $ArCH_2O$), 4.45 (d, 2H, $J = 8.0$, noncyclic inner OCH_2O), 4.68 (t, 2H, cyclic $ArCH$), 4.91 (d, 2H, $J = 7.2$ cyclic outer OCH_2O), 4.97 (s, 2H, resorcinol's H), 5.09 (t, 2H, noncyclic $ArCH$), 5.45 (d, 4H, $J = 12.0$, outer $ArCH_2O$), 5.98 (d, 2H, $J = 8.0$, noncyclic outer OCH_2O), 6.84 (d of d, 4H, resorcinol's H), 7.19 (s, 4H, ArH), 7.36 (t, 2H, resorcinol's H); ^{13}C NMR (CDCl3, 100 MHz) δ 14.51, 14.74 ($CH_2CH_2CH_3$), 21.26, 21.49 ($CH_2CH_2CH_3$), 30.35, 33.42 ($CH_2CH_2CH_3$), 36.93, 37.09 ($ArCH$), 70.74 ($ArCH_2O$), 96.36 (cyclic OCH_2O), 102.57 (noncyclic OCH_2O), 120.66, 125.04, 138.02, 139.96, 150.53, 155.84 (resorcin[4]aren's ArC), 11.20, 119.84, 132.96, 161.60 (resorcinol's ArC). Anal. Calcd for $C_{62}H_{64}O_{12}$: C, 74.06; H, 6.21. Found: C, 74.30; H, 6.19. For **5**: mp >310 °C dec; FAB+ MS m/z 1001.1 (M^+, 100); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96, 1.13 (t, 12H, $CH_2CH_2CH_3$), 1.26, 1.55 (m, 14H, $CH_2CH_2CH_3$ + orcinol's $CH3$), 2.12, 2.34 (m, 8H $CH_2CH_2CH_3$), 3.40 (d, 2H, $J = 7.2$, cyclic inner OCH_2O), 4.32 (d, 4H, $J = 12.1$, inner $ArCH_2O$), 4.43 (d, 2H, $J = 7.6$, noncyclic inner OCH_2O), 4.68 (t, 2H, cyclic $ArCH$), 4.79 (s, 2H, γ to orcinol CH_3), 4.93 (d, 2H, $J = 6.4$ cyclic outer OCH_2O), 5.08 (t, 2H, noncyclic $ArCH$), 5.39 (d, 4H, $J = 8.0$, outer $ArCH_2O$), 5.96 (d, 2H, $J = 8.0$, noncyclic outer OCH_2O), 6.65 (s, 4H, ArH), 7.18 (s, 2H, α to orcinol CH_3); ^{13}C NMR (CDCl3, 100 MHz) δ 14.50, 14.71 ($CH_2CH_2CH_3$), 21.26, 21.46 ($CH_2CH_2CH_3$), 21.76 ($ArCH_3$), 30.37, 33.42 ($CH_2CH_2CH_3$), 36.91, 37.08 ($ArCH$), 70.53 ($ArCH_2O$), 96.45 (cyclic OCH_2O), 102.61 (noncyclic OCH_2O), 120.59, 125.18, 138.08, 143.49, 150.52, 155.80 (resorcin[4]arene's ArC), 116.03, 120.76, 139.88, 161.25 (ArCOOH's ArC). Anal. Calcd for $C_{62}H_{64}O_{12}$: C, 74.38; H, 6.44. Found: C, 74.06; H, 6.35. For **6**: mp >290 °C dec; FAB+ MS m/z 1089.1 (M^+, 100); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96, 1.13 (t, 12H, $CH_2CH_2CH_3$), 1.28, 1.56 (m, 8H, $CH_2CH_2CH_3$), 2.14, 2.35 (m, 8H $CH_2CH_2CH_3$), 3.40 (d, 2H, $J = 7.2$, cyclic inner OCH_2O), 3.90 (s, 6H, $COOCH_3$), 4.39 (m, 6H, inner $ArCH_2O$ + noncyclic inner OCH_2O), 4.69 (t, 2H, cyclic $ArCH$), 4.95 (d, 2H, $J = 6.8$ cyclic outer OCH_2O), 5.10 (t, 2H, noncyclic $ArCH$), 5.14 (s, 2H, γ to $COOCH_3$), 5.49 (d, 4H, $J = 12.0$, outer $ArCH_2O$), 5.98 (d, 2H, $J = 8.0$, noncyclic outer OCH_2O), 7.12 (s, 4H, ArH), 7.50 (s, 4H, α to $COOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.46, 14.68 ($CH_2CH_2CH_3$), 21.21, 21.46 ($CH_2CH_2CH_3$), 30.27, 30.33 ($CH_2CH_2CH_3$), 36.87, 37.11 ($ArCH$), 52.88 ($COOCH_3$), 70.82 ($ArCH_2O$), 96.43 (cyclic OCH_2O), 102.47 (noncyclic OCH_2O), 120.78, 124.64, 134.95, 138.23, 150.44, 155.82 (resorcin[4]arene's ArC), 120.94, 123.17, 139.99, 161.37 (ArCOOH's ArC), 165.99 ($C{=}O$). Anal. Calcd for $C_{64}H_{64}O_{14}$: C, 70.57; H, 5.92. Found: C, 70.33; H, 5.87. For **7**: mp >280 °C dec; FAB+ MS m/z 942 (M^+, 100); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91, 1.16 (t, 12H, $CH_2CH_2CH_3$), 1.27, 1.67 (m, 8H, $CH_2CH_2CH_3$), 1.58 (s, 8H, SCH_2CH_2S), 2.04, 2.36 (m, 8H, $CH_2CH_2CH_3$), 3.58 (d, 4H, $J = 14.0$, inner $ArCH_2S$), 3.84 (d, 4H, $J = 14.0$, outer $ArCH_2S$), 4.19 (d, 2H, $J = 8.0$, cyclic inner OCH_2O), 4.55 (t, 2H, cyclic $ArCH$), 4.76 (d, 2H, $J = 6.4$, noncyclic inner OCH_2O), 5.23 (t, 2H, noncyclic $ArCH$), 5.76 (d, 2H, $J = 8.0$ cyclic outer OCH_2O), 5.86 (d, 2H, $J = 6.8$, noncyclic outer OCH_2O), 7.05 (s, 4H, ArH). For **8**: mp >300 °C dec; FAB+ MS m/z 1149.6 (M^+, 100); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.02−1.10 (m, 12H, $CH_2CH_2CH_3$), 1.29−1.50 (m, 16H, $CH_2CH_2CH_2CH_3$), 2.20, 2.90 (q, 8H $CH_2CH_2CH_2{-}CH_3$), 2.78, 2.94 (d, 8H, SCH_2ArCH_2S), 3.73, 3.82 (d, 8H, $ArCH_2S$), 4.28 (2H, $J = 6.8$, cyclic inner OCH_2O), 4.84 (m, 4H, cyclic outer OCH_2O+ noncyclic inner OCH_2O), 4.84 (t, 2H, cyclic $ArCH$), 4.93 (t, 2H, noncyclic $ArCH$), 6.08 (d, 2H, $J = 7.6$, noncyclic outer OCH_2O), 7.16 (s, 4H, ArH), 7.21, 7.52 (m, 8H, SCH_2ArCH_2S).

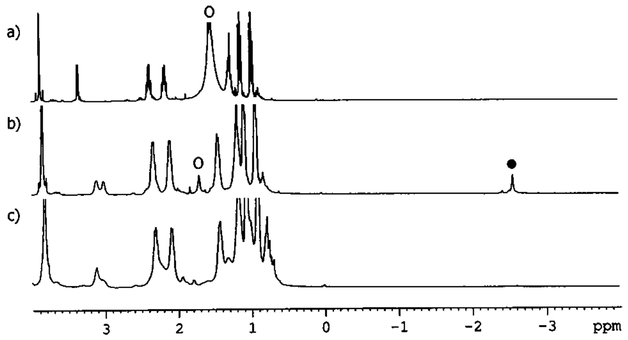

Figure 2. ^1H NMR (400 MHz, H_2O saturated CD_2Cl_2) spectra: (a) **6** at 25 °C; (b) **6** at −50 °C; (c) **6** + D_2O at −50 °C. [**6**] = 9 mM. Symbols designate the protons of (○) free H_2O, (●) complex H_2O.

Cavitands **1**, **7**, and **8** did not show the binding ability for H_2O or any other small molecules from +25 to −70 °C. The fully opened gate (cavitand **1**) or the partially closed flexible gate (ethylenedioxy for cavitand **7** or 1,3-bis(thiomethylene)benzene for **8**) cannot impose a substantial energy barrier against the fast release of water. Instead, the small cavities of cavitands **4**−**6** were blocked by the inner protons such as H_{1f} and H_{1e} of cavitand **4**, which makes their cavities complementary to water.

When the temperature decreased to −70 °C, the intensity of the free H_2O peak was decreased due to water freezing. On the contrary, the peak intensity of complexed water was unchanged or even slightly increased. This interesting phenomenon implies that the energy barrier for decomplexation of H_2O is substantially high compared to that for complexation at −70 °C due to the solvophobic driving force. Therefore, the binding constants (K_a) were gradually increased as the temperature decreased.

The distinct peaks of free and complex guests enable the direct calculation of K_a as shown in Figure 3. Generally, K_a values decreased in this order: cavitand **6** > cavitand **4** > cavitand **5**. Probably the polar ester group could induce the complexation of polar guest better. A $COOCH_3$ group of host **6** increased the hydrophilicity to the gate of the cavity, and H_2O molecules could be easily gathered and enter through the gate better than those of host **4** or **5**.

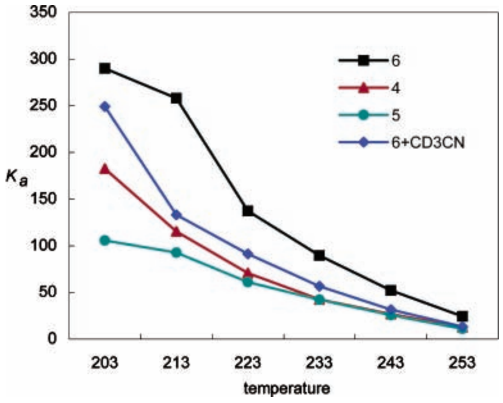

Figure 3. Binding constants (K_a) of cavitands **4**−**6** at various temperatures in water saturated CD_2Cl_2.

Table 1. Thermodynamic Parameters for Cavitand@H_2O at −50 °C in Water-Saturated CD_2Cl_2[a]

cavitand	K_a (M^{-1})[b]	−ΔG° (kcal mol^{-1})	ΔH° (kcal mol^{-1})	ΔS° (cal mol^{-1} K^{-1})
4	71	1.9	−2.3	−128
5	61	1.8	−2.1	−128
6	137	2.2	−2.5	−110
6 + CD_3CN	91	2.0	−2.6	−170

[a] 400-MHz ^1H NMR spectrometer was used. [b] Estimated error ±10%.

As the temperature decreased, the complexed H_2O molecule stays in the cavity. When CD_3CN was added to the solution of cavitand **6** in H_2O saturated CD_2Cl_2, the K_a value was slightly decreased due to the increased polarity of solution, which lessons the solvophobic interaction.

A molecular mechanics calculation using the Cerius2 program with the CFF95 force field was carried out for cavitand **4** by geometry optimization of the water-emitting process through the upper and lower gates.[9,10] As the complexed water molecule approached the upper or lower gate, the total stabilized energy gradually increased. The maximum stabilized energy on upper or lower gate was calculated to be 123 and 129 kcal/mol, respectively,[11] which implies that water-emitting through the upper gate is favored. Entering through the upper gate is similarly favored, which is consistent with the large effect on K_a of the functional groups on the resorcinolic unit (x of cavitands **4**, **5**, and **6**).

Table 1 shows the thermodynamic parameters for complexation obtained from the Van't Hoff equation by variable-temperature ^1H NMR experiments. All of these complexing processes was enthalpically favored and entropically disfavored. Generally, host−guest complexations of container hosts in non-hydroxylic media are enthalpically favored and entropically disfavored, with ΔH ° values ranging from −3 to −8 kcal mol^{-1} and ΔS ° from −12 to −18 cal mol^{-1} K^{-1}.[12] In these water-complexing processes, averaged ΔH° and ΔS° values are −2.3 kcal mol^{-1} and −128 cal mol^{-1} K^{-1}, respectively. This entropically disfavored process may be due to the filling of empty cavity by free H_2O.

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(11) Computational results obtained using software programs from Molecular Simulations Inc. Dynamics calculations performed with the Discover program using the CFF91 force-field, ab initio calculations performed with the Dmol program and graphical displays generated with the Cerius2 molecular modeling system.

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The attempted complexations of NH_4^+, MeOH, EtOH, CH_3CN, acetic acid, or DMA in dry CD_2Cl_2 or $CDCl_3$ at low temperature failed even under an excess of these potential guests.

In conclusion, new C_{2v} container hosts **4**−**6** showed the specific binding properties for H_2O in CD_2Cl_2 or $CDCl_3$ at low temperature due to their complementarity to water as well as the solvophobic interaction of water. More refined manipulations on these cavitands for specific water binding at room temperature are ongoing.

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Supporting Information Available: Details of crystal structure determination solution and refinement (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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