Revisiting the Water Binding of Small Cavitands: The Role of Benzene Hydrogen Bonding

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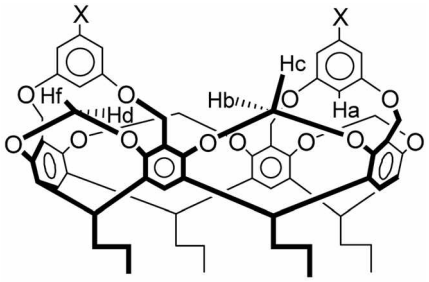
The solvent of biological systems, water, is hard to study in molecular recognition field due to its high polarity and small size. The strong hydrogen bonding interaction of water with themselves or other polar molecules makes it very hard to isolate and observe a single molecule in solution.

Small cavitands have been designed to accommodate small molecules such as alcohols.[1] Recently, we have reported the synthesis and water-specific binding property of C_{2v} cavitands **1-3** at low temperature.[2]

The CPK molecular model study as well as the experimental ^{1}H NMR study showed that these C_{2v} cavitands can not accommodate MeOH, EtOH, CH_3CN, CH_3CHO, CH_3NO_2, CH_4, or NH_4^+, but can accommodate H_2O due to its small cavity partially blocked by protons H_a of the bridging resorcinolic units (Figure 1(a)). When the temperature of the solutions of cavitands **1**, **2**, and **3** in water-saturated CD_2Cl_2 or $CDCl_3$ decreased to −70 °C, the intensity of 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 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.



1 : X = H
2 : X = CH_3
3 : X = $COOCH_3$

Scheme 1. C_{2v} cavitands.

The distinct peaks of free and complexed guests enable the direct calculation of K_a, which decreased in this order: cavitand **3** > cavitand **1** > cavitand **2**. This phenomena was explained as follows; A $COOCH_3$ group of host **3** increased the hydrophilicity to the gate of its cavity and H_2O molecules could be easily gathered and enter through the gate better than those of host **1** or **2**.[2]

Recently molecular recognitions based on sp^2 C-H···anion interactions have been reported.[3] As the molecular mechanics-optimized structure of H_2O@**1** (Fig. 1(b) and (c)) shows, the hydrogen bonding interactions between two C-H_a and OH_2 seems to be significant in the water-specific binding of these cavitands. To observe the effects of benzene hydrogen bonding various C_{2v} cavitands with *p*-X group to H_a hydrogen were synthesized and studied.

To increase the solubility of C_{2v} cavitands by incorporating long alkyl feet the synthetic route shown in Scheme 2 was followed (Scheme 2).[4] From tetrabromide **11**, tetrakisester **12**, tetrakis(hydroxymethyl)cavitand **13**, and then tetrakis(bromomethyl)cavitand **14** were obtained subsequently. The coupling of tetrakis(bromomethyl)cavitand **14** with 5-X-resorcinol (X = substituent) in K_2CO_3/DMF

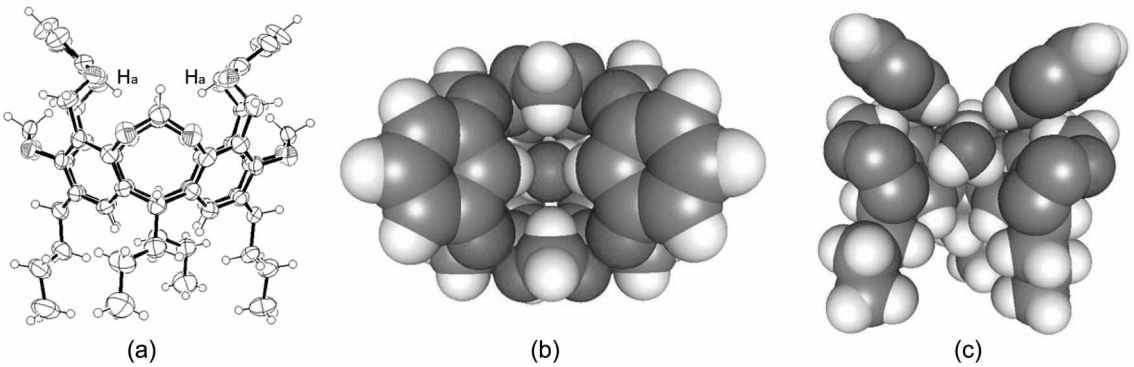
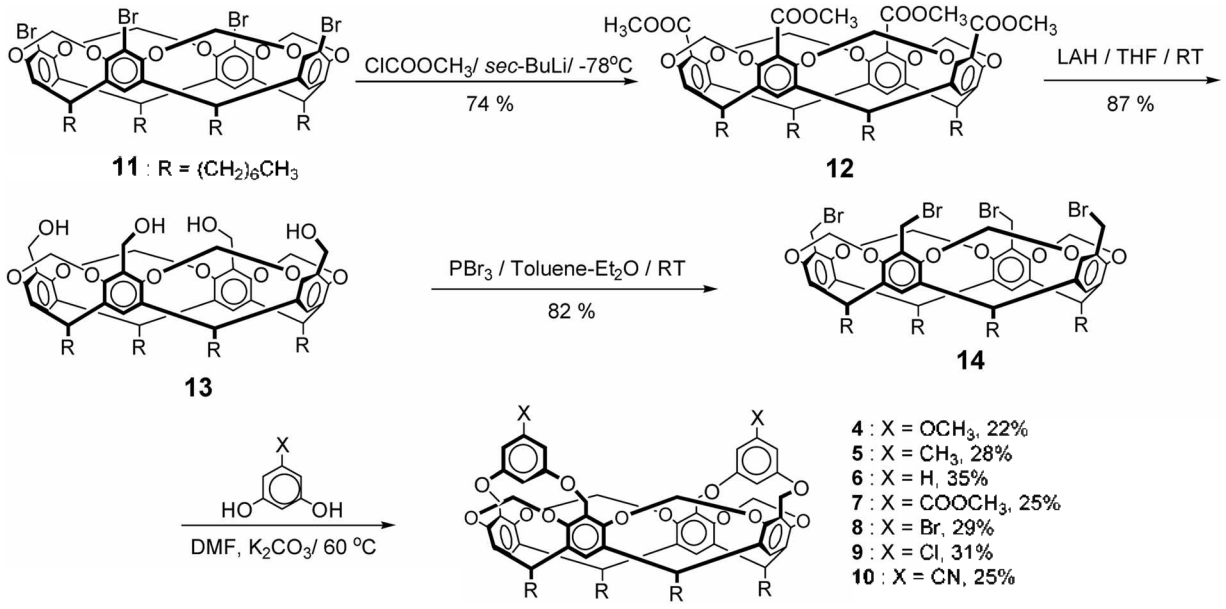


Figure 1. (a) X-ray crystal structure of cavitand **1**, (b), (c) Molecular mechanics-optimized structure of H_2O@**1** (CFF95 Force-field by Cerius2®) (b: top view, c: side view (the front wall was removed for clarity)).



Scheme 2. Synthesis of C_{2v} cavitands **4-10** (R = $(CH_2)_6CH_3$).

gave cavitands **4-10** in good yields (22%-35%). These C_{2v} cavitands have been fully characterized by NMR, FAB+ Mass spectra and elemental analyses.

Figure 2 shows the ^{1}H NMR spectra of cavitand **7** without or with 10 eq of NBu_4^+ X^- in $CDCl_3$ at 298 K. The chemical shifts changes upon anion complexation of H_a and H_b from 5.21 and 4.41 ppm for free **7**, respectively, imply the qualitative interactions between these protons and anions (H_a and H_b are illustrated in Scheme 1). The patterns of chemical shifts of these two protons according to the anions are similar; F^- (5.29, 4.43 ppm) ~ CN^- (5.32, 4.42 ppm) > Cl^- (5.27, 4.42 ppm) >> Br^- (5.21, 4.40 ppm) ≈ I^- (5.21, 4.40 ppm). These results show that F^- and CN^- best fit to the cavity and Cl^- fits rather improperly, but Br^- and I^- cannot fit the cavity due to their large size. But the quantitative evaluations of thermodynamic parameters for anion complexation were difficult due to the interference by water.

Table 1 shows the association constants and binding energies for H_2O@cavitand by ^{1}H NMR experiment and *ab initio* calculations. As expected the affinity of water complexation mainly depends on the nature of substituent (X) of cavitand. Cavitand **6** (X=H) gave K_a (M^{-1}) = 103 and cavitands **7-10** with the better electron withdrawing group compared to H gave K_a (M^{-1}) = 211-379. But cavitands **4** and **5** with electron donating X group gave K_a (M^{-1}) = 76 and 74, respectively. These results strongly support that the hydrogen bonding interaction between sp^2 C-H···OH_2 plays an important role in the water complexation of these C_{2v} cavitands. The calculated binding energies in the gas phase were consistent with the experimental results in solution, *i.e.*, with electron-withdrawing substituents, the binding energy becomes stronger, while with electron-donating ones the energy becomes smaller.

In conclusion, these C_{2v} container hosts **4-10** showed the specific binding properties for H_2O in $CDCl_3$ at low temperature due to their complementarity to water, the solvophobic interaction of water, and the hydrogen bonding interaction

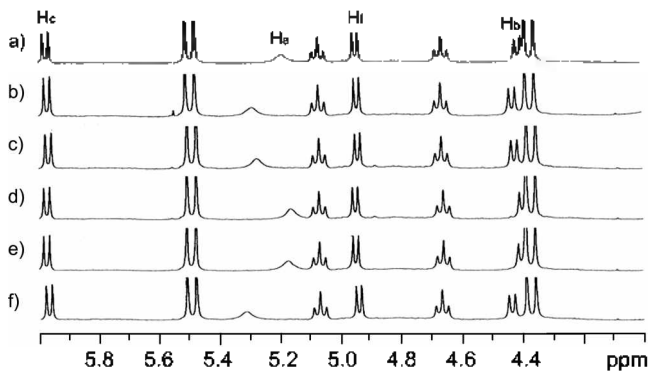


Figure 2. ^{1}H NMR spectra of cavitand **7** with or without 10 eq of NBu_4^+ X^- in $CDCl_3$ (298 K, 400 MHz). (a) free **7**, (b) $NBu_4^+F^-$@**7**, (c) $NBu_4^+Cl^-$@**7**, (d) NBu_4^+ Br^-@**7**, (e) NBu_4^+ I^-@**7**, (f) $NBu_4^+CN^-$@**7**.

Table 1. The association constants (K_a) and binding energies ($-\Delta G^o$) for H_2O@cavitand

Cavitand	K_a (M^{-1})[a]		$-\Delta G^o$ (kcal mol^{-1})	
	Exp.[b]		*Exp.*[b]	*Calcd*[c]
4	76		1.9	9.1
5 (2)	74(61)		1.9(1.8)	9.3
6 (1)	103(71)		2.0(1.9)	9.5
7 (3)	230(137)		2.4(2.2)	10.0
8	232		2.4	9.9
9	211		2.2	10.0
10	379		2.6	10.0
15 (X =NO_2)	–		–	10.5

[a]estimated Error ± 10%. [b]−50 °C in water-saturated CD_2Cl_2 (**1-3**) or $CDCl_3$ (**4-10**) using 400-MHz ^{1}H NMR Spectrometer. [c]*ab initio* calculations using B3LYP/6-31G** in the gas phase

between sp^2 C-H and O-H_2. The presence of hydrogen bonding interaction between sp^2 C-H and O-H_2 was confirmed by observing the relationships between their binding strength and the electronic effect of X groups.

Experimental

General coupling reaction between tetrakis(bromomethyl)cavitand 14 and 5-X-resorcinol; Tetrakis(bromomethyl)cavitand **14** (500 mg, 0.38 mmol) and bridging reagent (0.77 mmol) were dissolved in 20 mL of dry, degassed DMF. This solution was added dropwise over 1 hour to a stirred mixture of 30 mL of DMF and 1.07 g of K_2CO_3 heated to 60 °C. After 1 day, the reaction mixture was cooled to room temperature. K_2CO_3 was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was partitioned between CH_2Cl_2 (30 mL) and 3 N HCl (100 mL). The organic phase was washed with H_2O, brine, and then dried over $MgSO_4$. The organic phase was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the concentrate of the best portions was poured into a solvent to give a precipitate of pure cavitand.

Cavitand 4: 5-Methoxyresorcinol (107 mg) was used as a bridging reagent and a mixture of hexane:EtOAc = 8:1 was used as eluent for column chromatography. EtOH was used as a recrystallization solvent to give pure cavitand **4** as a white solid (108 mg, 22%). mp >300 °C (dec). MALDI-TOF: m/z 1319 [$(M + Na + NaOH)^+$ 30%], 1280 [$(M + Na)^+$ 100%]. Elemental analysis calcd for $C_{78}H_{96}O_{14}$: C, 74.49; H, 7.69. found: C, 74.12; H, 7.77. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.16 (s, 4H, ArH), 6.39 (d, 4H, J = 2.0 Hz, α to OCH_3), 5.94 (d, 2H, J = 8.0, noncyclic outer OCH_2O), 5.42 (d, 4H, J = 8.0, outer $ArCH_2O$), 5.05 (m, 4H, noncyclic methine + cyclic outer OCH_2O), 4.63 (t, 2H, J = 8.0, cyclic methine), 4.55 (br-s, 2H, γ to OCH_3), 4.38 (m, 6H, noncyclic inner OCH_2O + inner $ArCH_2O$), 3.76 (s, 6H, OCH_3), 3.53 (d, 2H, J = 6.8, cyclic inner OCH_2O), 2.34, 2.13 (m, 8H $CH_2(CH_2)_5CH_3$), 1.52-1.27 (m, 40H, $CH_2(CH_2)_5CH_3$), 0.91 (m, 12H, $CH_2(CH_2)_5CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 163.38, 162.14, 155.79, 150.58, 139.93, 138.10, 125.19, 120.57, 111.76, 105.88, 102.54, 96.42, 70.50, 55.95, 37.47, 37.32, 32.29, 32.25, 31.43, 30.29, 30.15, 30.11, 29.88, 29.71, 28.48, 28.40, 28.27, 23.11, 23.07, 14.53, 14.51.

Cavitand 5: Orcinol (96 mg) was used as a bridging reagent and a mixture of hexane:CH_2Cl_2 = 1:5 was used as eluent for column chromatography. CH_3CN was used as a recrystallization solvent to give pure cavitand **5** as a white solid (130 mg, 28%). mp > 300 °C (dec). MALDI-TOF: m/z 1288 [$(M + Na + NaOH)^+$, 30%], 1247 [$(M + Na)^+$, 100%]. Elemental analysis calcd for $C_{78}H_{96}O_{12}$: C, 76.44; H, 7.90. found: C, 75.85; H, 7.95. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.16 (s, 4H, ArH), 6.65 (s, 4H, α to CH_3), 5.96 (d, 2H, J = 8.0, noncyclic outer OCH_2O), 5.42 (d, 4H, J = 12.0, outer $ArCH_2O$), 5.07 (t, J = 8.0, 2H, noncyclic methine), 4.93 (d, 2H, J = 8.0, cyclic outer OCH_2O), 4.73 (br-s, 2H, γ to OCH_3), 4.63 (t, 2H, J = 8.0, cyclic methine), 4.42 (d, 2H, J = 8.0, noncyclic inner OCH_2O), 4.33 (d, 4H, J = 8.0, inner $ArCH_2O$), 3.42 (d, 2H, J = 4.0, cyclic inner OCH_2O), 2.29 (s, 6H, CH_3), 2.34, 2.13 (m, 8H $CH_2(CH_2)5CH_3$), 1.52-1.24 (m, 40H, $CH_2(CH_2)_5CH_3$), 0.89 (m, 12H, $CH_2(CH_2)_5CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 161.29, 155.83, 150.56, 143.43, 139.92, 138.10, 125.22, 120.50, 120.47, 116.13, 102.53, 96.45, 70.51, 37.46, 37.33, 32.28, 32.25, 31.42, 30.29, 30.15, 29.88, 29.78, 29.71, 28.48, 28.40, 28.27, 23.10, 23.06, 21.73, 14.53.

Cavitand 6: Resorcinol (85 mg) was used as a bridging reagent and a mixture of hexane:CH_2Cl_2 = 1:2 was used as eluent for column chromatography. EtOH was used as a recrystallization solvent to give pure cavitandas **6** as a white solid (162 mg, 35%). mp > 300 °C (dec). MALDI-TOF: m/z 1261 [$(M + Na + NaOH)^+$ 30%], 1221 [$(M + Na)^+$, 100%]. Elemental analysis calcd for $C_{76}H_{92}O_{12}$: C, 76.22; H, 7.74. found: C, 75.67; H, 7.78. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.38 (t, 2H, J = 8.0 resorcinol) 7.17 (s, 4H, ArH), 6.84 (d, 4H, J = 2.4, resorcinol), 5.98 (d, 2H, J = 8.0, noncyclic outer OCH_2O), 5.45 (d, 4H, J = 12.0, outer $ArCH_2O$), 5.05 (t, J = 8.0, 2H, noncyclic methine), 4.97 (br-s, 2H, resorcinol), 4.91 (d, 2H, J = 8.0, cyclic outer OCH_2O), 4.66 (t, 2H, J = 8.0, cyclic methine), 4.44 (d, 2H, J = 8.0, noncyclic inner OCH_2O), 4.34 (d, 4H, J = 12.0, inner $ArCH_2O$), 3.32 (d, 2H, J = 8.0, cyclic inner OCH_2O), 2.34, 2.13 (m, 8H $CH_2(CH_2)_5CH_3$), 1.52-1.24 (m, 40H, $CH_2(CH_2)_5CH_3$), 0.89 (m, 12H, $CH_2(CH_2)_5CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 161.63, 155.90, 155.17, 150.63, 140.03, 138.12, 132.88, 125.16, 120.53, 119.79, 119.41, 102.45, 96.39, 70.71, 37.49, 37.38, 32.30, 32.27, 31.44, 31.21, 30.30, 29.89, 29.72, 28.66, 28.49, 28.28, 23.11, 23.08, 14.55.

Cavitand 7: Methyl 3,5-dihydroxybenzoate (129 mg) was used as a bridging reagent and a mixture of Hexane:EtOAc = 8:1 was used as eluent for column chromatography. EtOH was used as a recrystallization solvent to give pure cavitand **7** as a white solid (128 mg, 25%). mp >300 °C (dec). MALDI-TOF: m/z 1377 [$(M + Na + NaOH)^+$, 30%], 1337 [$(M + Na)^+$, 100%]. Elemental analysis calcd for $C_{80}H_{96}O_{16}$: C, 73.15; H, 7.37. found: C, 72.55; H, 7.38. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.50 (s, 4H, α to $COOCH_3$) 7.18 (s, 4H, ArH), 5.98 (d, 2H, J = 8.0, noncyclic outer OCH_2O), 5.50 (d, 4H, J = 12.0, outer $ArCH_2O$), 5.21 (br-s, 2H, γ to $COOCH_3$), 5.07 (t, J = 8.0, 2H, noncyclic methine), 4.95 (d, 2H, J = 4.0, cyclic outer OCH_2O), 4.65 (t, 2H, J = 8.0, cyclic methine), 4.38 (m, 6H, noncyclic inner OCH_2O + inner $ArCH_2O$), 3.40 (d, 2H, J = 8.0, cyclic inner OCH_2O), 2.35, 2.13 (m, 8H $CH_2(CH_2)_5CH_3$), 1.52-1.26 (m, 40H, $CH_2(CH_2)_5CH_3$), 0.89 (m, 12H, $CH_2(CH_2)_5CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 165.98, 161.43, 155.88, 150.51, 140.02, 138.28, 134.94, 128.97, 124.73, 123.27, 120.91, 120.70, 102.42, 96.45, 70.79, 52.81, 37.51, 37.31, 32.27, 32.25, 30.27, 30.14, 30.11, 29.88, 29.78, 29.71, 28.45, 28.35, 28.24, 23.09, 23.06, 14.52, 14.51.

Cavitand 8: 2-Bromoresorcinol (145 mg) was used as a bridging reagent and a mixture of hexane:CH_2Cl_2 = 1:1 was

used as eluent for column chromatography. EtOH was used as a recrystallization solvent to give pure cavitand **8** as a white solid (152 mg, 29%). mp >300 °C (dec). MALDI-TOF: m/z 1417 [(M + Na + NaOH)$^+$, 30%], 1377 [(M + Na)$^+$, 100%]. Elemental analysis calcd for $C_{76}H_{90}Br_2O_{12}$: C, 67.35; H, 6.69. found: C, 66.79; H, 6.64. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.17 (s, 4H, ArH), 7.00 (s, 4H, α to Br), 5.92 (d, 2H, J = 8.0, noncyclic outer OCH_2O), 5.45 (d, 4H, J = 12.0, outer ArCH_2O), 5.08 (m, 4H, noncyclic methine + cyclic outer OCH_2O), 4.89 (br-s, 2H, γ to Br), 4.64 (t, 2H, J = 8.0, cyclic methine), 4.35 (m, 6H, noncyclic inner OCH_2O + inner ArCH_2O), 3.52 (d, 2H, J = 8.0, cyclic inner OCH_2O), 2.35, 2.13 (m, 8H $CH_2(CH_2)_5CH_3$), 1.52-1.26 (m, 40H, $CH_2(CH_2)_5CH_3$), 0.89 (m, 12H, $CH_2(CH_2)_5CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 161.85, 155.78, 150.51, 140.05, 138.26, 124.76, 124.68, 123.69, 120.76, 117.98, 102.39, 96.51, 70.88, 37.48, 37.28, 32.27, 32.23, 31.34, 30.26, 30.12, 29.87, 29.70, 28.44, 28.33, 28.23, 23.09, 23.05, 14.53, 14.50.

Cavitand 9: 2-Chlororesorcinol (112 mg) was used as a bridging reagent and a mixture of hexane:CH_2Cl_2 = 1:1 was used as eluent for column chromatography. CH_3CN was used as a recrystallization solvent to give pure cavitand **9** as a white solid (104 mg, 31%). mp > 300 °C (dec). MALDI-TOF: m/z 1327 [(M + Na + NaOH)$^+$, 80%], 1289 [M + Na)$^+$, 100%]. Elemental analysis calcd for $C_{76}H_{90}Cl_2O_{12}$: C, 72.08; H, 7.16. found: C, 71.50; H, 7.19. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.17 (s, 4H, ArH), 6.85 (s, 4H, α to Br), 5.93 (d, 2H, J = 8.0, noncyclic outer OCH_2O), 5.45 (d, 4H, J = 12.0, outer ArCH_2O), 5.08 (m, 4H, noncyclic methine + cyclic outer OCH_2O), 4.86 (br-s, 2H, γ to Br), 4.64 (t, 2H, J = 8.0, cyclic methine), 4.35 (m, 6H, noncyclic inner OCH_2O + inner ArCH_2O), 3.52 (d, 2H, J = 8.0, cyclic inner OCH_2O), 2.35, 2.13 (m, 8H $CH_2(CH_2)_5CH_3$), 1.52-1.26 (m, 40H, $CH_2(CH_2)_5CH_3$), 0.89 (m, 12H, $CH_2(CH_2)_5CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 161.78, 155.78, 150.50, 140.03, 138.26, 137.37, 124.68, 120.76, 120.59, 117.47, 102.41, 96.50, 70.83, 37.48, 37.28, 32.27, 32.23, 31.34, 30.26, 30.12, 29.87, 29.70, 28.44, 28.33, 28.23, 23.09, 23.05, 14.52, 14.50.

Cavitand 10: 1,2-Dihydroxybenzonitrile (104 mg) was used as a bridging reagent and a mixture of hexane:EtOAc = 8:1 was used as eluent for column chromatography. CH_3CN was used as a recrystallization solvent to give pure cavitand **10** as a white solid (118 mg, 25%). mp > 300 °C (dec). MALDI-TOF : m/z 1309 [(M + Na + NaOH)$^+$, 80%], 1269 [(M + Na)$^+$, 100%]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28 (s, 4H, α to CN), 7.12 (s, 4H, ArH), 5.94 (d, 2H, J = 8.0, noncyclic outer OCH_2O), 5.53 (d, 4H, J = 12.0, outer ArCH_2O), 5.35 (br-s, 2H, γ to Br), 5.15 (m, 4H, noncyclic methine + cyclic outer OCH_2O), 4.66 (t, 2H, J = 8.0, cyclic methine), 4.0 (d, 4H, J = 12.0, inner ArCH_2O), 4.33 (d, 2H, J = 8.0, noncyclic inner OCH_2O), 3.59 (d, 2H, J = 8.0, cyclic inner OCH_2O), 2.37, 2.15 (m, 8H $CH_2(CH_2)_5CH_3$), 1.55-1.26 (m, 40H, $CH_2(CH_2)_5CH_3$), 0.89 (m, 12H, $CH_2(CH_2)_5CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 161.31, 155.38, 149.99, 139.50, 137.94, 123.83, 122.83, 120.48, 117.21, 115.88, 101.79, 95.88, 70.34, 37.17, 36.83, 31.85, 31.82, 30.86, 29.81, 29.68, 29.46, 29.28, 27.98, 27.79, 22.68, 22.64, 14.11, 14.09.

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