Induced-Fit Molecular Recognition with Water-Soluble Cavitands

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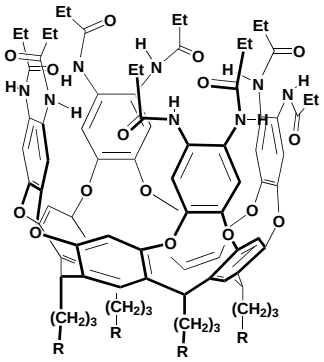
Abstract: Synthesis of novel water-soluble cavitands **1** and **2** and their complexes—the caviplexes—is described. The solubility in water derives from four primary ammonium groups on the lower rim and eight secondary amide groups on the upper rim. Cavitands **1** and **2** exist as D_{2d} velcraplex dimers in aqueous solution but the addition of lipophilic guests **15–24** induces conformational changes to the vase-like structures. The internal cavity dimensions are 8×10 Å, and the exchange rates of guests in the caviplexes are slow on the NMR timescale (room temperature and 600 MHz). The direct observation of bound species and the stoichiometry of the complexes is reported. The association constants (K_a) between 0.4×10^1 ($-\Delta G^{295} = 0.7$ kcal mol^{-1}) and 1.4×10^2 M^{-1} ($-\Delta G^{295} = 2.9$ kcal mol^{-1}) in D_2O and 1.4×10^1 ($-\Delta G^{295} = 1.7$ kcal mol^{-1}) and 2.8×10^4 M^{-1} ($-\Delta G^{295} = 6.0$ kcal mol^{-1}) in [D_4]methanol for aliphatic guests **16–24** were determined. Guest exchange rates of the new hosts **1** and **2** are considerably slower than rates observed for typical open-ended cavities in aqueous solution.

Keywords: cavitands · host–guest chemistry · molecular recognition · self-assembly

Introduction

Cavitands are open-ended container-molecules that act as hosts for complementary guests.[1] They were first prepared by Cram,[2] and subsequently used in the syntheses of carcerands,[3] the closed-surface container-molecules, and larger molecular cavities.[4] Self-assembled capsules are more recent incorporations and these have given a modern outlet for physical organic chemistry into the molecular recognition community.[5]

The binding properties of cavitands have been extensively studied in the solid state, the gas phase, and in organic solvents,[6–8] and the unusual kinetic stability of self-folding cavitands—hosts with intramolecular hydrogen bonds—has emerged.[9] Separate ^{1}H-NMR signals for free and bound guest at ambient temperatures allow the study of guest orientation inside the cavity of the host.[9, 10] The most recent versions involve self-complementary cavitands[11] with structural features common to self-replicating molecules and nanoscale unimolecular capsules that show promise as selective reaction chambers.[12] Much of the desirable behavior can be attributed to the intramolecular hydrogen bonds that maintain the shape of the cavitand and it is reasonable to raise questions regarding the effects of solvents that can compete for these hydrogen bonds. Accordingly, we present here the full account of the synthesis of water-soluble cavitands **1** and **2** (Figure 1) and relate their host–guest properties in that universal solvent.[13]



1 R = $CH_2OC(O)$-NH-$CH_2C(O)OCH_2C(CH_2OH)_2NH_3^+$ Cl^-
2 R = NH_3^+ $CF_3C(O)O^-$

Figure 1. Cavitands **1** and **2**.

At the outset, the seemingly incompatible chemical surfaces of these cavitands—the charged, hydrophilic ammonium groups at the lower rim and large lipophilic inner space of

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≈8 × 10 Å dimensions—rendered predictions of, say, their aggregation behavior or preferred shape at best, tenuous. We found that guest encapsulation controls the size and shape of cavitands; the induced fit of guests determines their folding and unfolding behavior. The complexes of such cavitands, the caviplexes, define **1** and **2** as unique among open-ended, water-soluble molecular hosts.

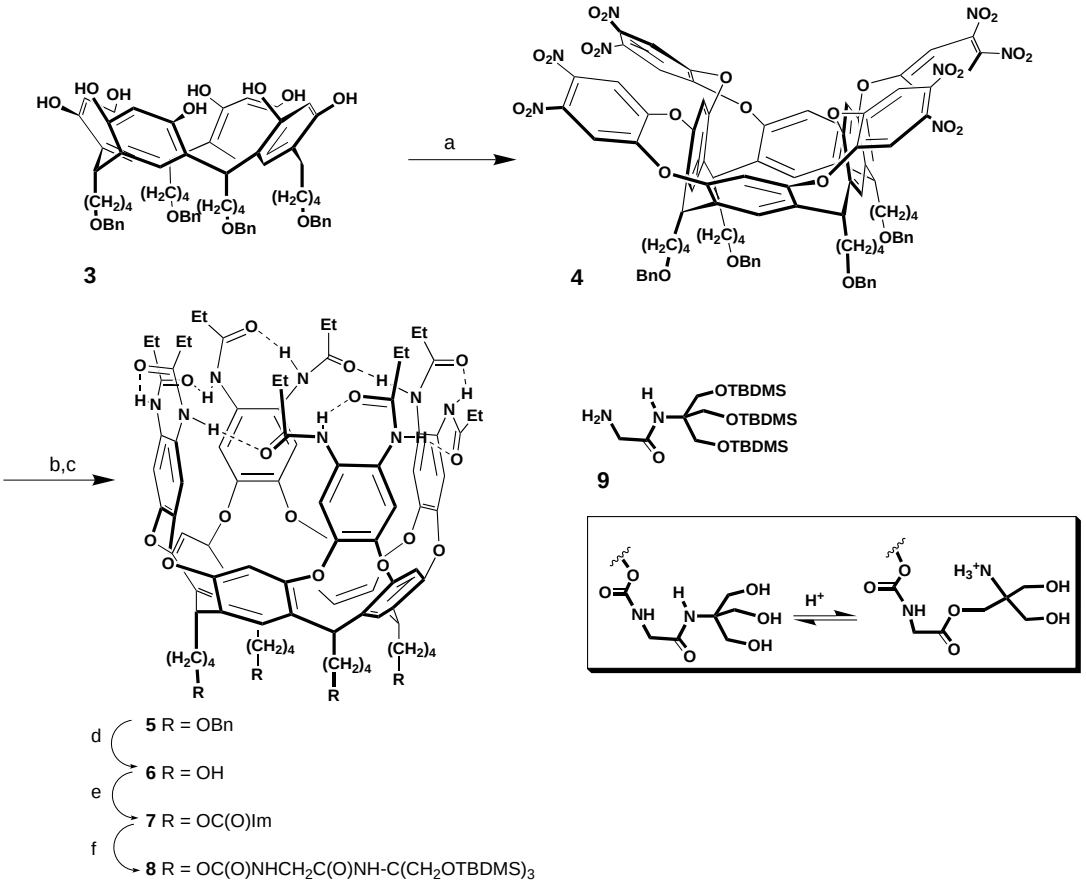
Results and Discussion

Synthesis (Scheme 1, Scheme 2): Resorcinarenes **3** and **10**[14] were prepared by the acid-catalyzed condensation of resorcinol with 4-*O*-benzylbutanal and 2,3-dihydrofuran, respectively, in EtOH. Resorcinarene **3** was then converted into octanitro cavitand **4** in 89% yield.

Subsequent reduction and acylation with propanoyl chloride gave cavitand **5**. The benzyl groups were removed with Pd/C in EtOH/toluene and the resulting cavitand **6** was activated with CDI (1,1′-carbonyldiimidiazole) as the tetraimidazole derivative **7**. Reaction of **7** with glycine-derived TRIS derivative **9**[15] resulted in octaamide **8**. Desilylation with aqueous HCl gave the short-lived dodecahydroxy cavitand that, most likely, rapidly rearranged through an intramolecular acyl shift to the water-soluble, octahydroxy tetraammonium salt **1**. When desilylation was carried out under basic conditions (TBAF in a THF/MeOH mixture) the dodecahydroxy cavitand was formed exclusively and with a yield as high as 96%. Unaccountably, and much to our chagrin, this material was insoluble in water.

The lesson was not lost as it led to the synthesis of the streamlined, water-soluble cavitand **2**, by way of novel resorcinarene platform **13** (Scheme 2). The phenolic hydroxy groups of **10** were selectively protected through alkylation with benzyl bromide in acetone (K_2CO_3, NaI) and gave octakisbenzyloxy derivative **11** in 58% yield. The lower rim hydroxyls in **11** were then converted to NHBoc groups. Specifically, the azide derivative **12** was prepared by mesylation of **11** with MsCl (Et_3N, CH_2Cl_2, 91% yield) and further treatment with NaN_3 in DMF at 80 °C (76% yield). The one-pot reduction of **12** with Raney/Ni and H_2, then protection with Boc_2O in EtOAc/EtOH followed by debenzylation (Raney/Ni, H_2, EtOH) resulted in resorcinarene **13** in 86% overall yield. Alternatively, **11** was submitted to Mitsunobu reaction with EtOC(O)C(O)NHBoc, diethyl azodicarboxylate (DEAD), and PPh_3 in CH_2Cl_2 followed by the saponification (LiOH, THF/H_2O). The resulting octabenzyl resorcinarene was debenzylated with Raney/Ni and H_2 in EtOH resulting resorcinarene **13** in 32% overall yield from **11**.

In either case, resorcinarene **13** was then condensed with 1,2-difluoro-4,5-dinitrobenzene in DMF in the presence of Et_3N to afford octanitro cavitand **14** in 91% yield (Scheme 2). Reduction of **14** (Raney/Ni, H_2 in toluene/MeOH), subsequent acylation with propionyl chloride under Schotten–



Scheme 1. a) 1,2-Difluoro-4,5-dinitrobenzene, Et_3N, DMF, 70 °C, 12 h, 89%. b) $SnCl_2 \cdot 2H_2O$, EtOH, 78 °C. c) $C_2H_5C(O)Cl$ (≈10 equiv), Py (18 equiv), CH_2Cl_2, −78 °C, 21%. d) Pd/C, EtOH/toluene, 81%. e) CDI, THF, 72%. f) **9**, THF/toluene, 110 °C, 45%.

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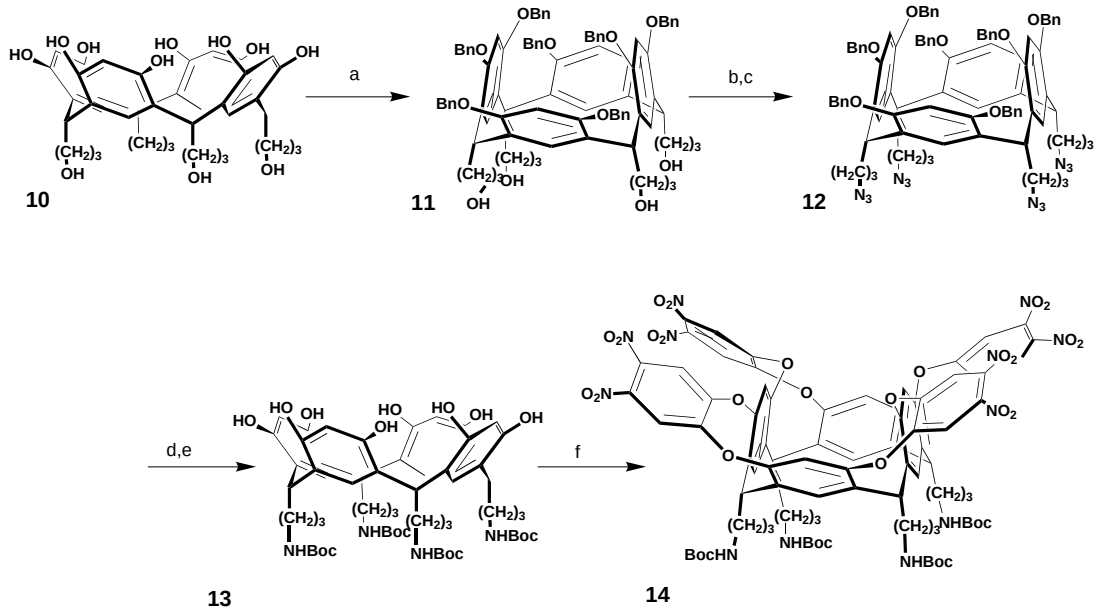

Scheme 2. a) BnBr, NaI, K_2CO_3, acetone, 58%. b) MsCl, Et_3N, CH_2Cl_2, 91%. c) NaN_3, DMF, 80°C, 76%. d) Boc_2O, Raney/Ni, H_2, EtOH/EtOAc, 90%. e) Raney/Ni, EtOH, 95%. f) 1,2-Difluoro-4,5-dinitrobenzene, Et_3N, DMF, 70°C, 91%.

Baumann conditions in EtOAc/H_2O, or better, in the presence of K_2CO_3 or in pyridene/CH_2Cl_2, followed by cleavage with TFA in CH_2Cl_2 gave octaamide **2** in 63% overall yield (Scheme 2).

Single crystal X-ray analysis: Diffraction quality crystals could be grown by slow recrystallization of **13** from hot MeOH. As might be expected, the molecule of **13** adopts a perfect "crown" conformation, stabilized through four O-H···OH intramolecular hydrogen bonds on neighboring resorcinol hydroxy groups (Figure 2). One of the pendant NHBoc groups is disordered over two positions with occupancy factors of 0.46 and 0.54. Two additional intramolecular C=O···H-N hydrogen bonds are formed between the neighboring NHBoc groups that are oriented in opposite directions. The bowl-shaped cavity of resorcarene **13** is filled with one MeOH molecule while several other MeOH molecules are hydrogen bonded to the resorcinol hydroxy groups. These solvent molecules, as well as the poor quality of the crystals, are responsible for the rather high *R* values.

The packing of **13** is shown on Figure 2. Two molecules of **13** form a centrosymmetric dimer through two hydrogen bonds between the symmetry-related carbonyl oxygens O13 and hydroxy groups O6.

Conformational behavior in solution: The ^{1}H-NMR spectra of compounds **1** and **2** in D_2O are sharp and exhibit a reduced symmetry at room temperature: six aromatic CH singlets in a 2:2:1:1:1:1 ratio are seen, and the CH methine proton is seen at $\delta \approx 4$ (Figure 3). The NMR spectra are concentration independent within the $\approx 0.5 \times 10^{-3}$ M – 5×10^{-3} M range and also temperature independent within the 295–340 K range. Broadening in the ^{1}H-NMR spectra of **1** was, however, observed at higher concentrations and is most probably due to some nonspecific lipophilic aggregation in aqueous media.

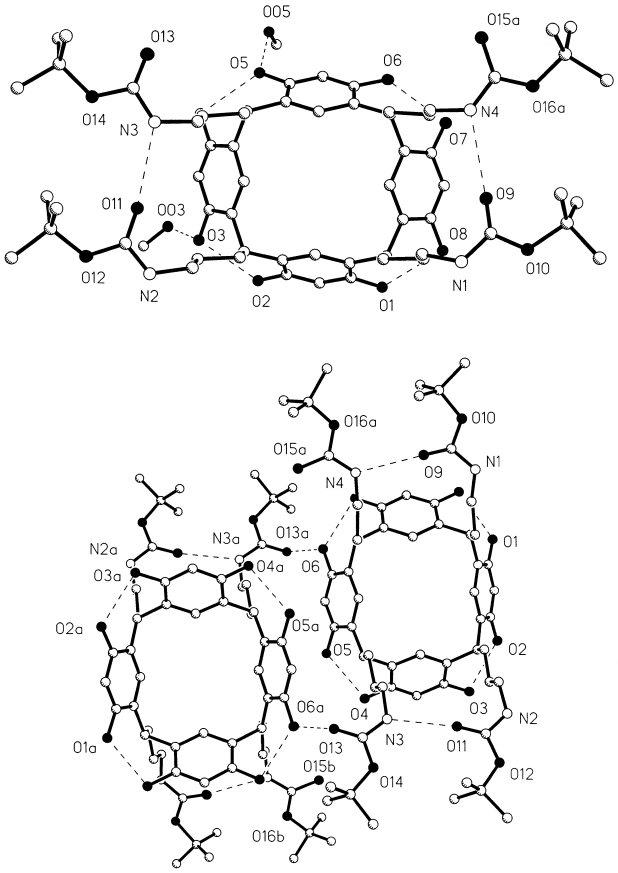

Figure 2. Top: Molecular conformation of resorcinarene **13** viewed from the narrow rim. Hydrogen atoms are omitted for clarity, and only one position of the disordered NHBoc groups is shown. Hydrogen bonds are indicated by dotted lines, but only two of the MeOH solvents hydrogen bonded to the resorcinol hydroxy groups are shown. The MeOH molecule included in the cavity is omitted for clarity. Heteroatoms are darkened and labelled. Bottom: crystal packing of **13**. Selected distances [Å] between the hydrogen bonding atoms: O1–O8 = 2.734(8), O2–O3 = 2.726(6), O3–O03 = 2.66(1), O4–O5 = 2.696(6), O6–O7 = 2.727(5), N3–O11 = 2.883(6), N4–O9 = 2.947(13), O007–O7 = 2.743(7), O6–O13A = 2.622(6).

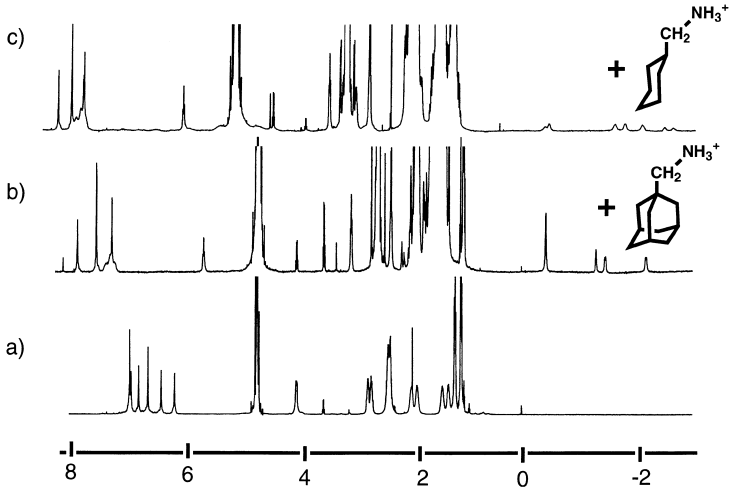

Figure 3. ^{1}H-NMR spectra (D_2O, 600 MHz, 295 K): a) cavitand **2;** b) complex **2·18;** c) complex **2·17**. Guests are present in ≈20-fold excess.

representing an average C_{4v} symmetry. One interpretation: MeOH is more lipophilic and is a better guest for the hydrophobic cavities of **1** or **2** than is water. This shifts the conformational equilibrium in MeOH from D_{2d} of the dimer to a C_{4v} vase-shaped structure by way of the (undetected) C_{2v} monomer (Figure 4).

The conformational features observed in aqueous solution for highly hydrophobic cavities **1** and **2** may be the result of hydrophobic collapse. In short, these guest-unfriendly structures did not bode well for molecular recognition of small targets in water.

Complexation in solution: Water-soluble calixarene and resorcinarene derived host-molecules are known to bind a variety of aryl- and alkylammonium cations.[17] Neutral guests such as adamantane, polycyclic aromatics, alcohols, and polyols (e.g., sugars, nucleosides, and nucleotides) and amino acids are also complexed.[18] Anionic guest-species, such as

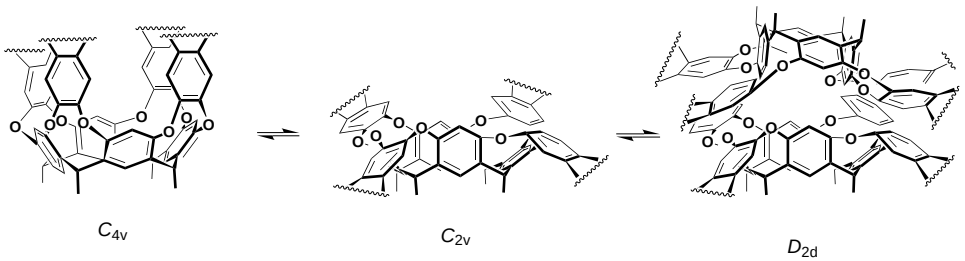

Figure 4. Proposed schematic representation of the $C_{4v} \rightleftharpoons C_{2v} \rightleftharpoons D_{2d}$ conformation equilibrium for water-soluble cavitands **1** and **2** in polar, protic media.

Hydrogen bonding sites on the periphery of the molecule may also be involved.

These spectral features are best reconciled with the existence of a dimeric D_{2d} velcraplex[16] for **1·1** and **2·2** in aqueous solution (Figure 4). Further evidence for the dimerization was obtained from electrospray ionization mass spectrometry (ESI-MS). Only peaks for the dimer **1·1** were observed from millimolar aqueous solution of **1**: at 4917 (negative ESI-MS, singly charged); at 2460 (positive ESI-MS, doubly charged); at 1640 (negative ESI-MS, triply charged); and at 1230 (negative ESI-MS, quadruply charged). Masses for the dimer **2·2** were also observed for cavitand **2** both in water and MeOH, at 3164 $[2M+H]^+$ and 1583 $[2M+2H]^+$. The dimerization in aqueous solution apparently maximizes the contacts of hydrophobic surfaces of the resorcinarene skeleton and the aromatic walls of **1** and **2** and buries them from the aqueous mileau.

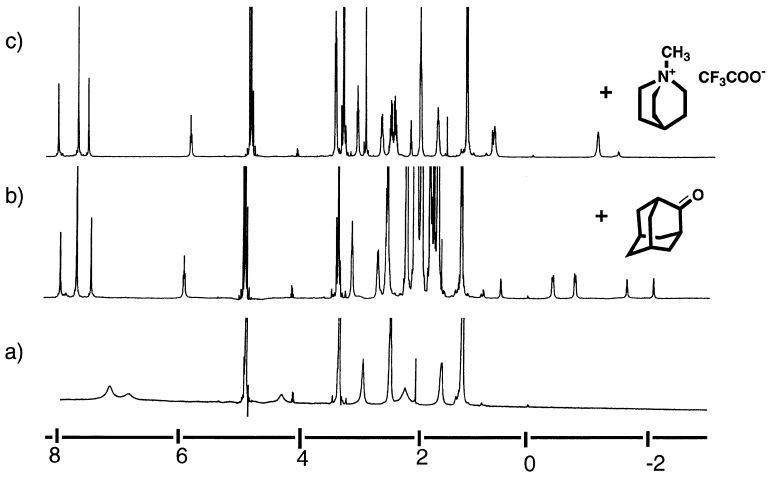

Figure 5. ^{1}H-NMR spectra ([D_4]methanol, 600 MHz, 295 K): a) cavitand **2;** b) complex **2·22**. The guest is present in ≈20-fold excess; c) complex **2·16**.

Contrary, the ^{1}H-NMR spectrum of **2** in [D_4]methanol is broad at room temperature and confirms some conformational dynamics (Figure 5). The spectrum sharpens at ≈330 K, (poly)carboxylates and nucleotides/phosphates, can be bound within the positively charged receptors featuring shallow cavities.[19] Recently, water-soluble, extended (≈20 Å in diameter) macrocyclic sugar clusters were prepared and adsorbed on silica (quartz) surfaces. They form strong complexes with 8-anilinonaphthalene-1-sulfonate (ANS) in aqueous solution.[18g]

Hydrophobic, van der Waals and also electrostatic interactions are the intermolecular forces for complex formation. Even strong affinity towards organic guests was detected in

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aqueous solution, but the complexes were not kinetically stable.[20] Instead, the binding events are fast on the NMR timescale, and only time-averaged signals can be seen.

We found that cavitands **1** and **2** behave differently. Their size and shape resemble those of known cavitands, but **1** and **2** are formed under thermodynamic control through the conformational folding and unfolding. Exchange between complexed and free guest species in water is slow on the NMR timescale. Admittedly, the criteria for kinetic stability are arbitrary-ambient temperatures at 600 MHz; but even so, the sharp and widely separated signals for free and bound guest species ($\Delta\delta \geq 3$) indicate substantial energetic barriers for guest exchange in and out of the cavities **1** and **2**. This behavior is unprecedented for open-cavity receptors in aqueous solution.[21]

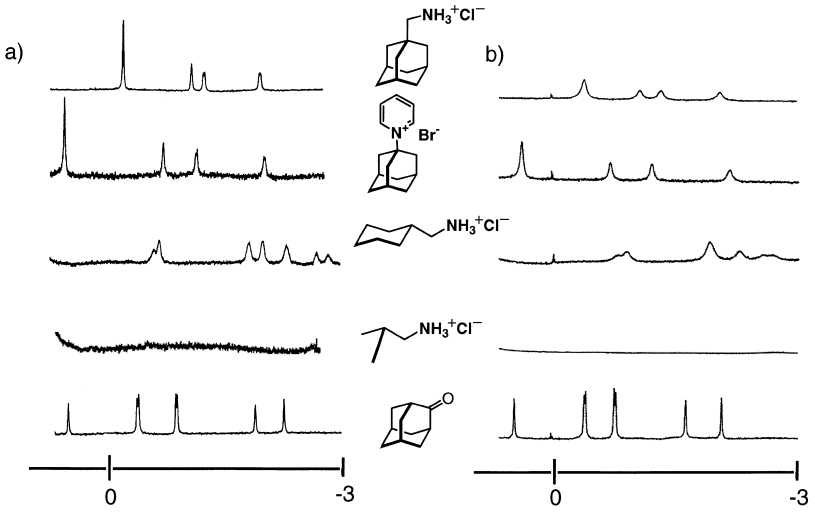

Figure 7. Upfield regions of the ^{1}H-NMR spectra (600 MHz, 295 K) of caviplexes with **2**: a) in D_2O; b) in [D_4]methanol. Guest structures are depicted in the middle. The upfield signals ($\delta = 0-3$) are due to the encapsulated species. The host and guest concentrations are 0.5 and 50 mM, respectively.

Addition of positively charged **15–19** and neutral **20–24** guests, that is *N*-methyl quinuclidinium trifluoroacetate, adamantane, cyclohexane, and camphor derivatives (Figure 6),

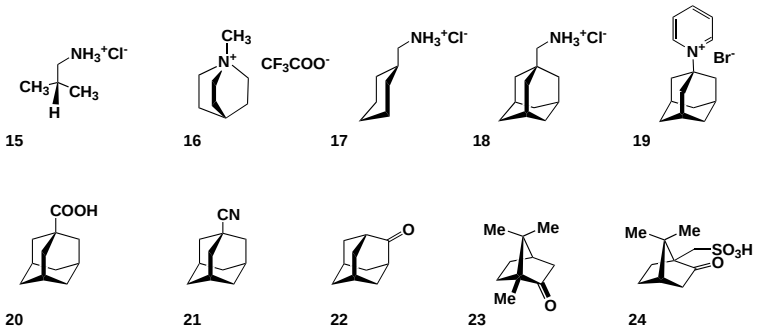

Figure 6. Guest molecules **15–24**.

resulted in the anticipated changes in the NMR spectra of **1** and **2**, both in D_2O and [D_4]methanol solutions (Figures 3, 5 and 7). Upon complexation with **15–22**, the symmetry of the host returns to a vase-shaped C_{4v} with one set of aromatic CH protons with 2:1:1 ratio and the methine CH triplet, shifted to $\delta \approx 6$. Moreover, new signals emerged between $\delta = 0$ and -3, characteristic for guests bound within the magnetically shielded environment (Figure 7).

The smaller *iso*-butyl ammonium hydrochloride (**15**) does not form a kinetically stable complex with **1** nor **2** at room temperature. Nonetheless, some recognition still takes place: the vase C_{4v} conformations of **1** and **2** are observed exclusively in D_2O. However, there are apparently not enough hydrophobic contacts within the host–guest complex to slow the exchange.

For cavitand **1**, the affinities are low: $-\Delta G = 3$ kcal mol^{-1} (295 K), and large excesses of the guests (= 11 equivalents for **16** and = 50 equivalents for **17** and **18**) were needed to observe the complexes by ^{1}H-NMR spectroscopy at millimolar concentrations.[13] Likewise, for D_2O solutions of host **2**, the moderate association constant values K_{ass} (see Table 1) from 0.4×10^1 M^{-1} ($-\Delta G^{295} = 0.7$ kcal mol^{-1}) of **2**·**18** to 1.4×10^2 M^{-1} ($-\Delta G^{295} = 2.9$ kcal mol^{-1}) of **2**·**22** were obtained directly from integration of the NMR spectra at 295 K. When **16** was added to the solution of **2**, a precipitate formed that was characterized as the 1:1 complex **2**·**16**. Unaccountably, notably higher values were obtained in [D_4]methanol solutions: K_{ass} from 1.7×10^1 M^{-1} ($-\Delta G^{295} = 1.7$ kcal mol^{-1}) of **2**·**18** to 2.8×10^4 M^{-1} ($-\Delta G^{295} = 6.0$ kcal mol^{-1}) of **2**·**16**.

Guest monitoring inside the cavity: As mentioned, previously reported water-soluble cavitands show fast complexation–decomplexation processes on the NMR timescale, and give averaged spectra. The geometries of the complexes must be inferred from the induced chemical shift changes. For the cases at hand, a direct view "from the

Table 1. Binding constants (K_{ass}, M^{-1}) and binding free energies ($-\Delta G^{295}$, kcal mol^{-1}) for the complexation of guests **16–18** and **22–24** with cavitand **2** in D_2O and [D_4]methanol.[a, b]

Guest	K_{ass}		$-\Delta G^{295}$	
	D_2O	CD_3OD	D_2O	CD_3OD
16	–	2.8×10^4	–	6.0
17	0.5×10^1	7.7×10^1	1.0	2.5
18	0.4×10^1	1.7×10^1	0.7	1.7
22	1.4×10^2	2.8×10^2	2.9	3.3
23	0.5×10^1		0.9	
24	2×10^1		0.5	

[a] Determined by ^{1}H-NMR spectroscopy, 295 K. [b] Error ≈ 10%.

inside" is available for molecules in **1** and **2** and the structural details concerning the orientation of the guest inside the host are more confidently made. First, integration clearly indicates that only one guest molecule **16–24** is accommodated inside the cavity. Second, the chemical shifts of the guest signals are directly related to their position inside the cavity (Figure 7). For the complexed 1-substituted adamantanes **18–21**, all four sets of the skeleton protons can be seen in the window in a 3:3:3:6 ratio (most upfield to least upfield). These represent the two doublets and two apparent singlets, respectively. The functional group at the 1-position is, accordingly, directed toward the open end at the top of the structure. Likewise, with 2-adamantanone (**22**), the carbonyl group is directed toward the top; four sets for the skeleton CH protons are clearly observed in a 2:2:4:4:2 ratio. The encapsulated cyclohexyl moiety of **17** exhibits seven broad signals between $\delta = 0$ and -3. The broadening may indicate the effects of the reduced symmetry of the guests inside the circle of amides and a reduced tumbling of these guests inside. The caviplex **1·16** with *N*-methyl quinuclidinium gives three upfield signals in a 1:6:6 ratio. With *N*-CD_3-quinuclidinium as guest, the spectrum does not change, which indicates that the *N*-methyl group is directed at the open ends of the cavitand in the complexes. The ROESY spectrum of the **2·16** complex in [D_4]methanol showed NOE connectivities of the methylene CH_2 signals of the complexed **16** with the signals for the aromatic wall CH protons of the host. Accordingly, the guest molecule floats in the cavity above the resorcinarene platform.

Complexation of chiral camphor (**23**) and camphor sulfonic acid (**24**) further reduces the symmetry of the host. In the caviplexes **2·23** and **2·24**, structure **2** is clearly C_4 symmetrical and lacking mirror planes. In the ^{1}H-NMR spectra (in D_2O) this results in a doubled set for the CH protons of the phenylene walls, while the CD-spectra (in methanol) show significantly enhanced complexation-induced responses (Figure 8).

Mechanistic considerations: In caviplexes **1** and **2**, the convex hydrocarbon surface of the guest finds its complement in the concave and π-bonded inner-surface of the host; hydrophobic and CH-π interactions contribute to the binding process. Maximal hydrophobic contacts can be established when the geometrical conditions are fulfilled. Indeed, for smaller *iso*-butyl ammonium hydrochloride (**15**) no kinetically stable complex is formed.

The energetic barriers for the conformational changes (Figure 4), for example from the kite (C_{2v}) and/or velcrand (D_{2d}) to the vase of C_{4v} symmetry usually amount to 10–12 kcal mol^{-1} in organic solvents,[16] but the value is unknown in aqueous solution. *Intermolecular* C=O···H-N hydrogen bonding between two cavitands in the dimeric velcraplexes **1·1** or **2·2** may add to this energetic barrier,[22] while the *intramolecular* C=O···H-N hydrogen bonds can stabilize the vase conformation and thus participate in guest complexation even in polar media.[23] Taken together, the large and energetically costly conformational changes that accompany by complexation—the induced fit—result in the high kinetic stability of the caviplexes in water.

Conclusion

Cavitands **1** and **2** represent new species of water-soluble molecular containers. The deep cavities here are open but exchange is slow since the uptake and release of guests involves significant conformational changes in the host. If even larger receptors can be made to show these properties in water, then more than one guest can be accommodated at the same time. The slow exchange could then guarantee that enough time is available for many types of interactions, even reactions, to take place between guests. This has already been accomplished with capsular species in organic solvents, but the use of cavitands as reaction vessels, especially for biologically relevant guests, remains a desirable goal.

Experimental Section

General: Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-300 and a Bruker DRX-600 spectrometers. The chemical shifts were measured relative to residual non-deuterated solvent resonances or TMS. High resolution matrix-assisted laser desorption/ionization (HR MALDI FTMS) mass spectrometry experiments were performed on an IonSpec HiResMALDI Fourier transform mass spectrometer. For high resolution mass spectral data, for compounds with molecular weight = 2000, lower than 10 ppm resolution was achieved.[24] Electrospray ionization (ESI) mass spectra were recorded on an API III Perkin–Elmer SCIEX triple quadrupole mass spectrometer. CD spectra were obtained on an AVIV 62DS spectrometer in MeOH. The HPLC analysis and preparative separation were performed with Waters 486 system. Silica gel chromatography was performed with silica gel 60 (EM Science or Bodman, 230–400 mesh). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under a nitrogen atmosphere. Compound **10** was synthesized in accord with the literature protocol.[14] Molecular mod-

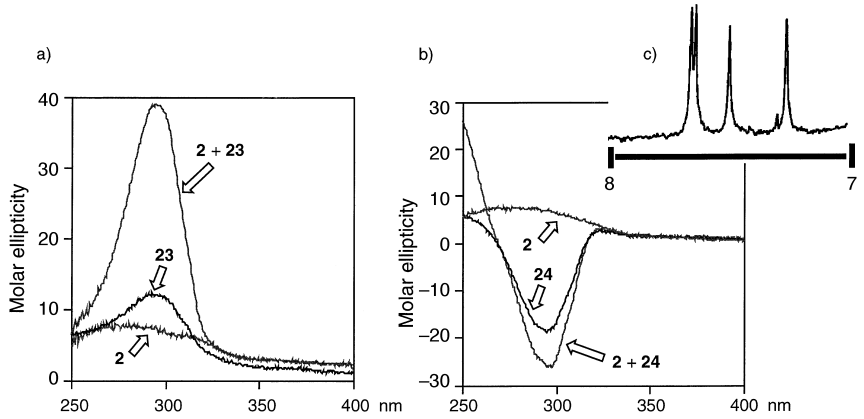

Figure 8. Portions of the spectra for the chiral caviplexes **2·23** and **2·24**. a) and b) the CD-spectra in [D_4]methanol; c) portion of the ^{1}H-NMR spectra, aromatic region (D_2O, 600 MHz, 295 K). The host and guest concentrations are 1 and 30 mM, respectively.

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eling was performed using the Amber* force field in the MacroModel 5.5 program.[25]

Resorcinarene (3): 5-Benzyloxypentanal (880 mg, 4.58 mmol) was added dropwise at 0 °C to a solution of resorcinol (500 mg, 4.55 mmol) in EtOH (4.2 mL) and conc. HCl (0.9 mL). The mixture was warmed up to 50 °C. After 7–12 h the mixture was poured into water, and the precipitate was filtered. The residual solid was purified by column chromatography on SiO_2 with hexane/EtOAc 1:1 to give compound **3** (674 mg, 52 %). M.p. 93–95 °C; ^{1}H NMR ([D$_6$]acetone): $\delta = 8.60$ (br s, 8H), 7.56 (s, 4H), 7.4–7.2 (m, 20H), 6.24 (s, 4H), 4.44 (s, 8H), 4.34 (t, ^3J(H,H) = 7.9 Hz, 4H), 3.44 (t, ^3J(H,H) = 5.7 Hz, 8H), 2.33 (q, ^3J(H,H) = 7.7 Hz, 8H), 1.65 (quint, ^3J(H,H) = 7.7 Hz, 8H), 1.38 (quint, ^3J(H,H) = 7.7 Hz, 8H); ^{13}C NMR ([D$_6$]acetone): $\delta = 152.8$, 140.2, 129.1, 128.2, 128.1, 125.6, 125.2, 103.8, 73.1, 71.1, 34.3, 34.1, 30.5, 25.6; HR MALDI-FTMS: m/z: 1159.5603 $[M + Na]^+$.

Octanitro cavitand (4): Et_3N (5 mL, 36.1 mmol) was added dropwise at 0 °C to a mixture of resorcinarene **3** (2.60 g, 2.29 mmol) and difluorodinitrobenzene (1.9 g, 9.31 mmol) in DMF (100 mL). After stirring at 70 °C for 16 h, the reaction mixture was poured into ice water. The formed precipitate was filtered, dried, and purified by column chromatography (1.2 % MeOH in $CHCl_3$) to give **4** as a yellow powder (3.65 g, 89 %). M.p. > 250 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.64$ (s, 4H), 7.23 (s, 4H), 7.4–7.1 (m, 24H), 7.02 (s, 2H), 6.23 (s, 2H), 4.43 (s, 8H), 4.00 (t, ^3J(H,H) = 7.3 Hz, 4H), 3.43 (t, ^3J(H,H) = 6.2 Hz, 8H), 2.2–1.2 (m, 24H).

Octaamide (5): A mixture of the octanitro derivative **4** (3.00 g, 1.67 mmol) and $SnCl_2 \cdot 2H_2O$ (11.0 g, 48.8 mmol) in EtOH (150 mL) and conc. HCl (25 mL) was refluxed for 6 h and then poured onto ice. The pH was adjusted to 10 with 2 M aq. NaOH. The aqueous phase was extracted with CH_2Cl_2 (2 ×) and the organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo to give the crude octaamine cavitand which was immediately used without further purification. To the solution of the octaamine in CH_2Cl_2 (100 mL) was added pyridine (2.60 mL) and propionyl chloride (1.4 mL, 16.1 mmol) at −78 °C. The mixture was gradually warmed up to rt, poured into water, and extracted with EtOAc. The organic layer was washed with 10 % aq. HCl, aq. $NaHCO_3$, brine, and concentrated. The residue was purified by column chromatography (70 % EtOAc/hexane) to give desired compound **5** (706 mg, 21 %) as a pale yellow solid. M.p. 153–155 °C; ^{1}H NMR ([D$_6$]benzene): $\delta = 9.87$ (s, 4H), 9.71 (s, 4H), 7.87 (s, 4H), 7.67 (s, 4H), 7.32 (d, $J = 7.5$ Hz, 8H), 7.24 (t, ^3J(H,H) = 7.5 Hz, 8H), 7.39 (s, 4H), 7.18 (s, 4H), 7.13 (t, ^3J(H,H) = 7.5 Hz, 4H), 6.31 (t, ^3J(H,H) = 8.2 Hz, 4H), 4.33 (s, 8H), 3.33 (t, ^3J(H,H) = 6.4 Hz, 8H), 2.5–2.3 (m, 8H), 2.4–2.1 (m, 8H), 2.0–1.8 (m, 8H), 1.8–1.6 (m, 8H), 1.8–1.5 (m, 8H), 1.16 (t, ^3J(H,H) = 6.8 Hz, 12H), 0.98 (t, ^3J(H,H) = 6.8 Hz, 12H); ^{13}C NMR ([D$_6$]benzene): $\delta = 174.3$, 172.4, 155.6, 155.4, 151.0, 149.7, 139.6, 136.2, 129.4, 124.1, 121.7, 116.9, 72.8, 70.5, 33.8, 32.7, 32.2, 30.1, 29.7, 25.2, 10.8, 10.1; HR MALDI-FTMS: m/z: 2023.9392 $[M + Na]^+$.

Tetrahydroxy cavitand (6): Cavitand **5** (270 mg) was dissolved in a mixture of EtOH/toluene 3:1 (28 mL) and a catalytic amount of 10 % Pd/C. The resulting mixture was evacuated and the reaction flask was filled with H_2. After stirring for 24 h, the mixture was filtered through a Celite pad and concentrated. The crude product was purified by column chromatography (4 % MeOH/$CHCl_3$) to give desired tetraol **6** (199 mg, 81 %). ^{1}H NMR ([D$_6$]acetone): $\delta = 9.49$ (s, 8H), 7.95 (s, 4H), 7.72 (s, 8H), 7.50 (s, 4H), 5.82 (t, ^3J(H,H) = 8.1 Hz, 4H), 3.7–3.5 (m, 8H), 2.6–2.3 (m, 24H), 1.7–1.6 (m, 8H), 1.5–1.4 (m, 8H), 1.21 (t, ^3J(H,H) = 7.6 Hz, 24H); ^{13}C NMR ([D$_6$]acetone): $\delta = 175.6$, 155.7, 149.5, 137.0, 129.5, 126.0, 121.8, 117.1, 62.6, 34.7, 33.9, 32.8, 31.4, 25.5, 10.7; HR MALDI-FTMS: m/z: 1663.7152 $[M + Na]^+$.

Tetracarbonylimidazolyloxy cavitand (7): CDI (100 mg, 616.7 μmol) was added to a solution of **6** (100 mg, 61.0 μmol) in THF (3 mL), and the mixture was heated under reflux for 24 h, then poured into ether. The resulting solid was collected by filtration and dried to give **7** (76 mg, 72 %) which was directly used in the next step. ^{1}H NMR ([D$_6$]acetone): $\delta = 9.50$ (s, 8H), 8.12 (s, 4H), 7.49 (s, 4H), 7.73 (s, 8H), 7.53 (s, 4H), 7.45 (s, 4H), 5.87 (t, ^3J(H,H) = 8.1 Hz, 4H), 4.44 (t, ^3J(H,H) = 6.5 Hz, 8H), 2.6–2.4 (m, 24H), 2.0–1.8 (m, 8H), 1.6–1.5 (m, 8H), 1.21 (t, ^3J(H,H) = 7.5 Hz, 24H); ^{13}C NMR ([D$_6$]acetone): $\delta = 174.4$, 155.9, 150.3, 149.6, 137.9, 136.7, 131.3, 129.6, 125.7, 121.8, 118.1, 117.3, 69.1, 34.2, 32.2, 31.3, 29.0, 25.0, 10.6.

Octaamide (8): A solution of **7** (226 mg, 0.132 mmol) and amine **9** (1.50 g, 3.23 mmol) in toluene (8 mL) and THF (1 mL) was heated at 110 °C for 3 d. The reaction mixture was purified by column chromatography (50 % EtOAct/hexane) to give desired product **8** (228 mg, 45 %). M.p. 115–117 °C; ^{1}H NMR ([D$_6$]acetone): $\delta = 9.49$ (s, 8H), 7.92 (s, 4H), 7.72 (s, 8H), 7.52 (s, 4H), 6.60 (br s, 4H), 6.56 (s, 4H), 5.86 (t, ^3J(H,H) = 8.1 Hz, 4H), 4.06 (t, ^3J(H,H) = 6.4 Hz, 8H), 3.90 (s, 24H), 3.71 (d, ^3J(H,H) = 5.9 Hz, 8H), 2.6–2.4 (m, 24H), 1.8–1.7 (m, 8H), 1.5–1.4 (m, 8H), 1.21 (t, ^3J(H,H) = 7.6 Hz, 24H), 0.91 (s, 108H), 0.05 (s, 72H); ^{13}C NMR ([D$_6$]acetone): $\delta = 174.4$, 169.7, 157.7, 155.8, 150.3, 136.9, 129.5, 125.8, 121.8, 117.2, 65.6, 62.7, 61.3, 45.9, 34.4, 32.5, 31.4, 26.4, 25.3, 18.9, 10.7, −5.2; ESI-MS: m/z: 3830, 3852 $[M]^+$, $[M + Na]^+$.

Cavitand (1): *Procedure A*: TBAF (100 mg) at 0 °C was added to the solution of **8** in THF (4 mL) and MeOH (0.1 mL). The reaction mixture was stirred overnight, concentrated in vacuo, and the residue was purified by column chromatography on ODS (70 % MeOH/H_2O) to give the dodecahydroxy cavitand (13.6 mg, 96 %). Preparative HPLC purification was also used with a BETASIL C18 column (150 × 4.6 mm) with flow of 1.25 mL min^{-1}. ^{1}H NMR ([D$_4$]methanol): $\delta = 7.3–6.8$ (m, 8H), 6.7–6.5 (m, 4H), 6.4–6.1 (m, 4H), 4.16 (br s, 4H), 3.97 (br s, 8H), 3.73 (br s, 8H), 3.69 (s, 24H), 2.6–2.4 (m, 24H), 2.1–1.9 (m, 8H), 1.7–1.5 (m, 8H), 1.4–1.2 (m, 24H).

Procedure B: A solution of **8** in MeOH and few drops of 5 % aq. HCl was stirred for 1 h at 0 °C and carefully concentrated. The residue was purified by HPLC (reversed-phase, ODS) to afford **1** (27.5 mg, 62 %). ^{1}H NMR (D_2O, 295 K): $\delta = 7.00$ (s, 4H), 6.92 (s, 4H), 6.74 (s, 2H), 6.62 (s, 2H), 6.37 (s, 2H), 6.16 (s, 2H), 4.23 (s, 8H), 3.99 (br s, 4H), 3.9–3.7 (m, 8H), 3.82 (s, 8H), 3.62 (s, 16H), 2.5–2.2 (m, 16H), 2.0–1.7 (m, 8H), 1.5–1.3 (m, 8H), 1.11 (t, ^3J(H,H) = 7.5 Hz, 24H); ESI-MS: m/z: 4917 $[M]^-$, 1640 $[M]^{3-}$, 1230 $[M]^{4-}$, 2460 $[M]^{2+}$; HR MALDI-FTMS: m/z: 2480.0522 $[M + Na]^+$.

Octabenzylresorcinearene (11): NaI (50 g) and K_2CO_3 (90 g) were added to the solution of resorcinarene **10** (30 g) in acetone (1 L). After stirring for 1 h, benzylbromide (52 mL) was added to the suspension and the reaction mixture was heated under reflux for 4–7 d and then concentrated in vacuo. The residue was diluted with EtOAc and the insoluble solids were filtered off. The filtrate was concentrated and the formed crystals were separated to give **11** (35 g, 58 %). M.p. 193–195 °C; ^{1}H NMR ([D$_6$]acetone, 59 °C): $\delta =$ 7.4–7.2 (m, 40H), 6.96 (s, 4H), 6.75 (s, 4H), 4.95 (d, ^2J(H,H) = 11.7 Hz, 8H), 4.82 (t, ^3J(H,H) = 7.4 Hz, 4H), 4.74 (d, ^2J(H,H) = 11.7 Hz, 8H), 3.55 (dt, ^3J(H,H) = 6.0 Hz, ^3J(H,H) = 5.3 Hz, 8H), 3.1 (m, 4H), 2.1–2.0 (m, 8H), 1.62 (quint, ^3J(H,H) = 6.8 Hz, 8H); HR MALDI-FTMS: m/z: 1463.6881 $[M + Na]^+$.

Resorcinearene (12): Methanesulfonylchloride (7 mL) was added dropwise to the stirred solution of **11** (27 g, 18.7 mmol) in CH_2Cl_2 (500 mL) and Et_3N (35 mL) at 0 °C. After 3 h the solution was poured into 10 % aq. HCl. The aqueous layer was extracted with CH_2Cl_2. The organic phaze was washed with saturated $NaHCO_3$ solution and concentrated to result the corresponding tetrasulfonate (30 g, 91 %). ^{1}H NMR ([D$_6$]acetone, 50 °C): $\delta =$ 7.4–7.1 (m, 40H), 6.93 (br s, 4H), 6.80 (s, 4H), 4.98 (d, ^2J(H,H) = 11.6 Hz, 8H), 4.82 (t, ^3J(H,H) = 7.5 Hz, 4H), 4.71 (d, ^2J(H,H) = 11.6 Hz, 8H), 4.22 (t, ^3J(H,H) = 6.6 Hz, 8H), 2.94 (s, 12H), 2.2–2.0 (m, 8H), 1.9–1.7 (m, 8H); ^{13}C NMR ([D$_6$]acetone, 50 °C): $\delta = 156.7$, 139.0, 129.3, 128.5, 128.4, 127.0, 126.8, 100.6, 71.8, 71.7, 37.5, 36.8, 31.5, 29.2. To the solution of the above compound (30 g) in DMF (300 mL) was added NaN_3 (6.5 g) and the mixture was stirred for 12 h at 70 °C and then concentrated and diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was concentrated in vacuo, and the residue was recrystalized from ethylacetate to give compound **12** (20 g, 76 %). ^{1}H NMR ([D$_6$]acetone, 50 °C): $\delta = 7.4–$ 7.1 (m, 40H), 6.93 (br s, 4H),s 6.79 (s, 4H), 4.98 (d, ^2J(H,H) = 11.6 Hz, 8H), 4.80 (t, ^3J(H,H) = 7.5 Hz, 4H), 4.74 (d, ^2J(H,H) = 11.6 Hz, 8H), 3.26 (t, ^3J(H,H) = 7.0 Hz, 8H), 2.2–2.0 (m, 8H), 1.7–1.6 (m, 8H); ^{13}C NMR ([D$_6$]acetone, 50 °C): $\delta = 156.7$, 139.0, 129.2, 128.5, 128.4, 127.1, 100.6, 71.7, 52.6, 36.8, 32.7, 28.8; ESI-MS: m/z: 1564 $[M + Na]^+$.

Resorcinearene (13): *Procedure A*: Raney/Ni (cat.) was added to the mixture of **12** (405 mg, 0.263 mmol) and Boc_2O (250 mg, 1.146 mmol) in EtOH (20 mL) and EtOAc (20 mL). The solution was stirred at 40 °C for 12 h, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding *N*-Boc-protected resorcinarene (433 mg, 90 %). ^{1}H NMR ([D$_6$]acetone, 50 °C): $\delta = 7.4–7.1$ (m, 44H), 6.78 (s, 4H), 5.96 (s, 4H), 5.1–4.9 (m, 8H), 4.78 (t, ^3J(H,H) = 7.0 Hz, 4H), 4.9–4.6 (m, 8H), 3.15–3.05 (m, 8H), 2.1–1.9 (m, 8H), 1.7–1.5 (m, 8H), 1.36 (s, 32H). To the solution of the above compound in EtOH was added catalytic amount of Raney/Ni and the suspension was stirred for

5 h at 45 °C. The resulting solution was filtered through a pad of Celite and concentrated in vacuo to give resorcinarene **13** (210 mg, 95 %). M.p. 220–225 °C (decomp); ^{1}H NMR ([D$_6$]acetone): $\delta = 8.46$ (s, 8H), 7.49 (s, 4H), 6.24 (s, 4H), 5.15 (br s, 4H), 4.30 (t, ^3J(H,H) = 7.9 Hz, 4H), 3.15 (dt, ^3J(H,H) = 6.9 Hz, ^3J(H,H) = 6.6 Hz, 8H), 2.35–2.25 (m, 8H), 1.5–1.4 (m, 8H), 1.42 (s, 36H); ^{13}C NMR ([D$_6$]acetone): $\delta = 157.0$, 152.8, 125.1, 124.9, 103.8, 78.6, 58.6, 41.3, 34.5, 31.8, 28.9; ESI-MS: *m*/*z*: 1140 $[M + Na]^+$, 1116 $[M - H]^+$.

Procedure B: DEAD (0.47 mL, 2.89 mmol) was added at 0 °C to the solution of the resorcinearene **11** (1.00 g, 0.694 mmol), PPh_3 (787 mg, 3.00 mmol), and $EtO_2CC(O)NHBoc$ (651 mg, 3.00 mmol) in THF (20 mL) and the reaction mixture was then stirred for 12 h at rt. The solvent was evaporated in vacuo and the residue was purified by column chromatography to give the corresponding *N*,*N*-(Boc)C(O)CO$_2$Et derivatized benzyloxy compound (1.52 g, 98 %). The above compound (1.4 g, 0.625 mmol) was dissolved in THF (10 mL) and water (7.5 mL), and then LiOH (180 mg) was added to the stirred solution. After 3 h at 0 °C, the reaction mixture was poured into acidic water. The aqueous layer was extracted with EtOAc. The product was purified by column chromatography to give the *N*-Boc benzyloxy compound (394 mg, 34 %). ^{1}H NMR ([D$_6$]acetone): $\delta = 7.4–7.1$ (m, 44H), 6.78 (s, 4H), 5.96 (s, 4H), 5.1–4.9 (m, 8H), 4.78 (t, ^3J(H,H) = 7.0 Hz, 4H), 4.9–4.6 (m, 8H), 3.15–3.05 (m, 8H), 2.1–1.9 (m, 8H), 1.65–1.50 (m, 8H), 1.36 (s, 32H). To the solution of this compound in EtOH was added catalytic amount of Raney/Ni, and the suspension was stirred for 5 h at 45 °C. The resulting solution was filtered through Celite and concentrated in vacuo to give the desired **13** (210 mg, 95 %).

Octanitro cavitand (14): Et_3N (0.76 mL, 5.48 mmol) was added to the solution of resorcinarene **13** (700 mg, 0.626 mmol) and dinitrodifluorobenzene (540 mg, 2.65 mmol) in DMF (30 mL) and the reaction mixture was stirred for 12 h at 70 °C. The mixture was poured into acidic water and the resulting precipitate was collected by filtration, dried, and purified by column chromatography to give **14** (1.00 g, 91 %). M.p. > 260 °C; ^{1}H NMR ([D$_6$]acetone, 50 °C): $\delta = 7.65$ (s, 8H), 7.00 (s, 4H), 6.3 (br s, 4H), 4.03 (t, ^3J(H,H) = 7.5 Hz, 8H), 3.15 (m, 8H), 2.3–1.9 (m, 8H), 1.5–1.4 (m, 8H), 1.42 (s, 36H).

Octaamide cavitand (2): Raney/Ni (cat.) was added to the solution of **14** (210 mg, 0.13 mmol) in toluene (10 mL) and MeOH (3 mL). The mixture was stirred at 40 °C for 16 h under H_2 atmosphere, and then the catalyst was filtered off. The solvent was removed in vacuo. The residue was redissolved in CH_2Cl_2 (50 mL), and then Et_3N (0.2 mL) and propionylchloride (0.2 mL) were added at −40 °C. The reaction mixture was warmed slowly to rt and stirred for 1 h. The mixture was poured into acidic water, and the aqueous layer was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and concentrated in vacuo. The residue was purified by column chromatography to give the corresponding octaamide (170 mg, 66 %). M.p. 240–245 °C (decomp); ^{1}H NMR ([D$_6$]acetone): $\delta = 9.51$ (s, 8H), 7.91 (s, 4H), 7.72 (s, 8H), 7.52 (s, 4H), 6.16 (br s, 4H), 5.28 (br s, 4H), 3.21 (m, 8H), 2.55–2.4 (m, 24H), 1.65–1.5 (m, 8H), 1.44 (s, 36H), 1.22 (t, ^3J(H,H) = 7.5 Hz, 24H); ^{13}C NMR ([D$_6$]acetone): $\delta = 174.3$, 171.0, 156.9, 155.7, 1503, 150.0, 136.9, 129.5, 125.6, 121.8, 117.2, 78.6, 60.6, 41.4, 34.8, 31.3, 28.9, 10.7; ESI-MS: *m*/*z*: 1981 $[M - H + {}^{13}C]^+$, 2018 $[M + K]^+$. This compound (13.2 mg, 6.66 mmol) was dissolved in CH_2Cl_2 (3 mL), and TFA (2 mL) was added dropwise to the solution. After stirring for 30 min at rt, the solution was concentrated in vacuo to give cavitand **2** (13.0 mg, 96 %). ^{1}H NMR (D_2O): $\delta = 6.94$ (s, 4H), 6.91 (s, 2H), 6.78 (s, 2H), 6.61 (s, 2H), 6.38 (s, 2H), 6.14 (s, 4H), 4.00 (m, 4H), 2.8–2.6 (m, 8H), 2.5–2.2 (m, 16H), 2.0–1.8 (m, 8H), 1.6–1.2 (m, 8H), 1.22 (t, ^3J(H,H) = 7.5 Hz, 12H), 1.09 (t, ^3J(H,H) = 7.5 Hz, 12H); ESI-MS (in H_2O): 3164 $[2M + H]^+$, 1583 $[2M + 2H]^{2+}$; (in MeOH): 3735 $[2M + 5TFA + H]^+$, 3619 $[2M + 4TFA + H]^+$, 3506 $[2M + 3TFA + H]^+$, 3392 $[2M + 2TFA + H]^+$, 3278 $[2M + TFA + H]^+$, 3164 $[2M + H]^+$, 1697 $[2M + TFA + 2H]^{2+}$.

X-ray crystallography: Crystallographic data measurements at 170.0(2) K by a Kappa CCD, Mo$_{K\alpha}$ radiation (graphite monochromator, $\lambda = 0.7107$ Å). The data was processed with Denzo-SMN v0.93.0.[26] No absorbtion corrections were applied. Solution by direct methods[27] and refinement with full matrix versus F^2.[28] The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors and refined as riding atoms.

Compound **13**: $C_{60}H_{84}O_{16}N_4$, crystal size $0.4 \times 0.2 \times 0.15$ mm^3, triclinic, $P\bar{1}$, $a = 14.9991(8)$ Å, $b = 16.9911(8)$ Å, $c = 17.842(1)$ Å, $\alpha = 100.071(3)°$, $\beta = 108.163(3)°$, $\gamma = 103.377(3)°$, $Z = 2$, $V = 4050.6(4)$ Å^3, $\rho_{calcd} = 1.039$ g cm^{-3}, $2\Theta_{max} = 49.92°$, $\mu = 0.08$ mm^{-1}, $F(000) = 1355$, $-17 \le h \le 17$, $-20 \le k \le 20$, $-20 \le l \le 21$, 939 parameters, $R1 = 0.1285$, w$R2 = 0.3335$ (for 8418 refl. $I > 2\sigma(I)$), $R1 = 0.1898$, w$R2 = 0.3786$ for all 14017 reflections ($R_{int} = 0.056$), $S = 1.075$, $\Delta\rho$ (min, max) = −0.45–0.78 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143909. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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