Deeper Cavitands

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Cavitands are synthetic structures with curved, open-ended cavities.[1] The earliest cavitands were shallow, bowl-shaped structures **1a**,**b** prepared from resorcinarenes **2** through alkylation or silylation of the phenolic hydroxyls (Figure 1).[2,3] These cavitands are limited by their dimensions—ca. 9.0 Å wide and 3.0 Å deep—to interact only with small molecules: CH_2Cl_2, $CHCl_3$, CS_2, and $CH_3C{\equiv}CH$[3a−d] are weakly bound by them in solution. Subsequently, the rims were built up and the cavities deepened; **3**, for example, offers a depth of ∼8.0 Å. Its binding properties have been examined under a variety of conditions including on solid surfaces.[3−6] Cavitand **3a** complexed simple aromatic molecules.[4] We have now developed access to even deeper cavitands, capable of housing more sizable guests, and we communicate our methods here.

The deeper cavitands **3** are usually prepared by bridging the resorcinarene hydroxyl groups of **2a** with a preformed heterocycle, e.g., condensation with a 6,7-disubstituted-2,3-dichloroquinoxaline. The alternative involves the use of a simpler building block in the bridging reaction and then extension of the rim through heterocyclic synthesis. Specifically, the octanitro cavitand **4**[7] was obtained by reaction of **2a** with 1,2-difluoro-4,5-dinitrobenzene[8] in DMF at 70 °C in the presence of Et_3N. The NO_2 groups were hydrogenated with Ra/Ni in toluene, and the corresponding phenylenediamine units were condensed with 1,2-diketones. The resulting fused pyrazines provide the deepened cavities. Diethyl 2,3-dioxosuccinate[9] and acenaphthenequinone formed cavitands **6** and **7**, respectively, as yellow solids in 13 and 49% (Scheme 1). Lehn and others utilized a similar heterocyclization strategy to construct helicates and extended surfaces.[10]

The new cavitands **6** and **7** exist in solution as vase-like C_{4v} structures, as shown by the ^{1}H NMR spectra in various solvents (Figure 2). Only one set of signals was found for all groups of protons. However, unlike the rigid cavitand **3**, conformational dynamics were observed, in a process that is intermediate in rate on the NMR time scale (Figure 3). The ^{1}H NMR spectrum of cavitand **6** in $CDCl_3$ at 295 K displays sharp resonances except for the aromatic ring C−H_c (Figure 2). When the sample is warmed to 330 K, the H_c resonance emerges. Similarly, cavitand **7**, with its much deeper cavity, displayed broad resonances at 295 K in a variety of solvents (*p*-xylene-d_{10}, benzene-d_6, toluene-d_8, $CDCl_3$). Again, when the samples were heated (>330 K), sharp spectra characteristic of C_{4v} symmetry arose (Figure 2).

Functional group manipulations on the upper rim of **6** were uneventful. The eight ester groups are moderately activated and underwent conversion to the octacarboxamide **8** on treatment with an excess of *n*-butylamine in boiling ethanol. The presence of eight hydrogen bond donor and acceptor sites (the C(O)−NH functions) of **8** imparted a unique, strongly solvent- and temperature-dependent folding−unfolding behavior that will be described elsewhere. Saponification of **6** with aqueous LiOH resulted in quantitative conversion to the octaacid **9**.

The NMR chemical shifts of the bridging methines (H_a, Figure 2) in cavitands have been used to estimate the degree of their conformational mobility.[3e] Methine chemical shifts above 5.5 ppm indicate a stable "vase" conformation of C_{4v} symmetry, while shifts below 4.0 ppm are characteristic of the "kite" conformation. The latter has the four rim aromatics flipped outward and features C_{2v} symmetry. The conformational preferences are affected by solvation, dimerization, and complexation and can be diagnosed by the shift of the CH triplet resonance.

Table 1 records the effect of solvent on this signal for the new cavitands. In contrast to **3a** (R = $C_{11}H_{23}$), molecules **6** and **7** exhibit a very solvent-dependent methine (H_a) chemical shift. The CH triplet of **3a** is found at 5.5 ppm at room temperature in $CDCl_3$, while for **6** and **7** it is located upfield 4.6 ppm. In aromatic solvents, the methine signal for cavitand **3a** is found at ca. 6.0 ppm, while for cavitand **6** the CH triplet is detected at ca. 4.5 ppm and for **7** it is between 5.4 and 6.0 ppm. The same trend is observed at higher temperatures (>330 K). These suggest that the cavities of **6** and **7** are quite conformationally flexible (Figure 3) and prefer aromatic solvent molecules.

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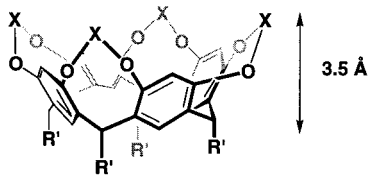
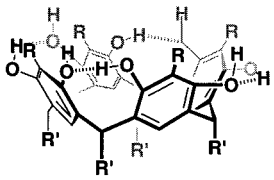
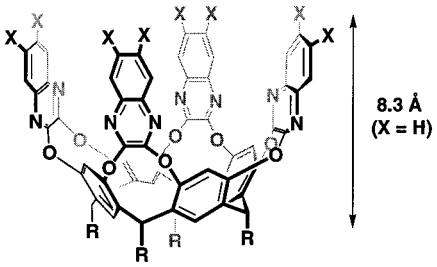


1a - X = $(CH_2)_n$; R' = alkyl
1b - X = $Si(Alk)_2$; R' = alkyl



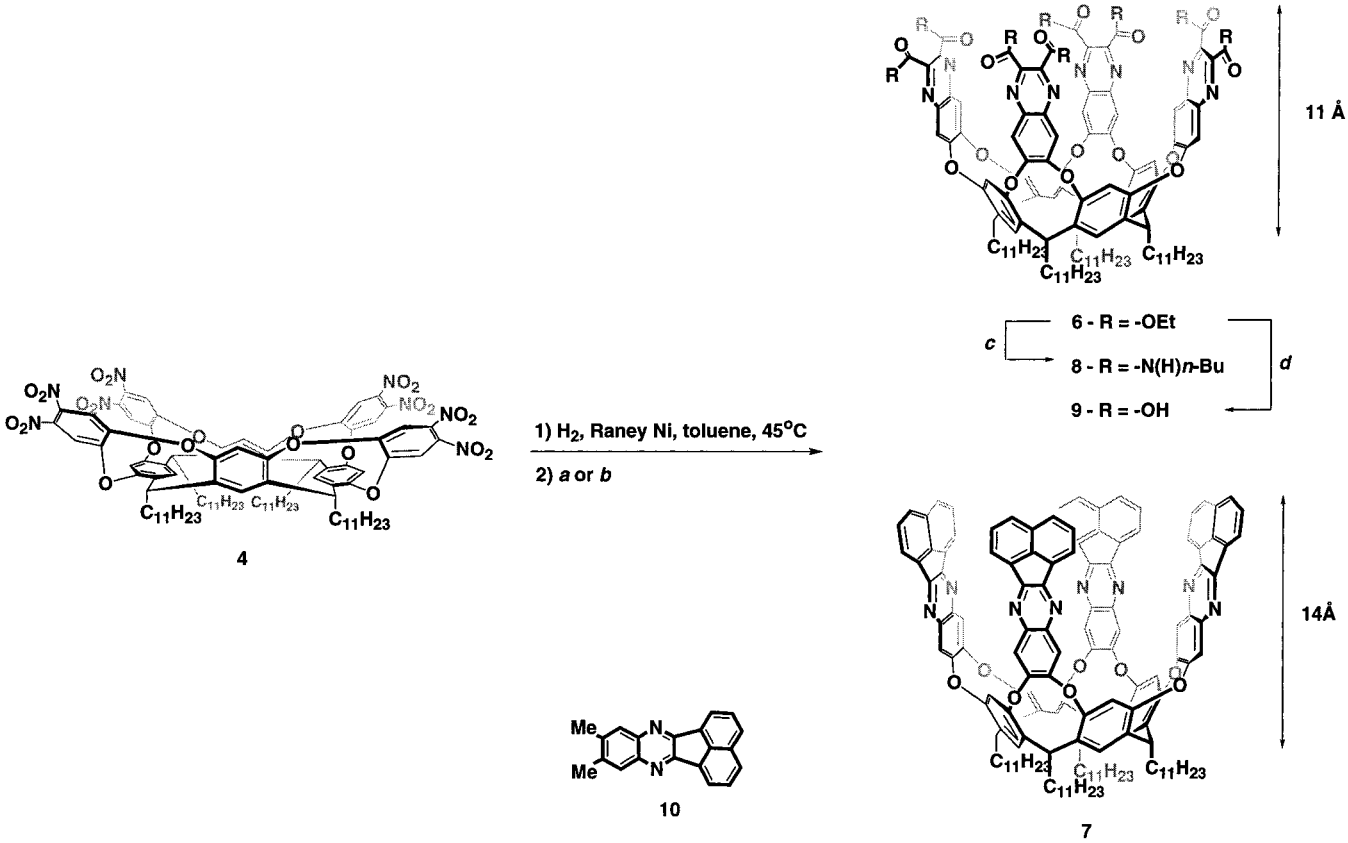
2a - R = H; R' = alkyl
2b - R = CH_3, CH_2CH_3; R' = alkyl



3a - X = H
3b - X = Br
3c - X = CH_3
R = alkyl

Figure 1. Resorcinarenes **2** and first generation cavitands **1** and **3**.

Scheme 1[a]



[a] (a) diethyl 2,3-dioxosuccinate, benzene, rt, 16 h (13%); (b) acenaphthenequinone, THF, HOAc, reflux, 6 h (49%); (c) *n*-butylamine, EtOH, reflux, 19 h (49%); (d) THF, $LiOH_{aq}$ (1 N), reflux, 1 h (100%).

The cavity dimensions of cavitands **6** and **7**, estimated by molecular mechanics,[11] are 11 and 14 Å deep, respectively. To our knowledge they are the deepest known open-ended cavities reported to date,[12] and since their interiors are undoubtedly solvated, an estimate was made concerning the number and types of solvent that can be accommodated within. Four molecules of $CHCl_3$ or three of benzene are easily modeled within cavitand **6**. Cavitand **7** can accommodate up to five molecules of $CHCl_3$ or four molecules of either benzene or toluene in its interior.

The complexation of a number of various guests—adamantane derivatives, cyclohexane derivatives, caprolactam and numerous aromatics—with **6** and **7** was attempted, but no binding was detected by ^1H NMR spectroscopy in either $CDCl_3$ or toluene-d_8. Apparently,

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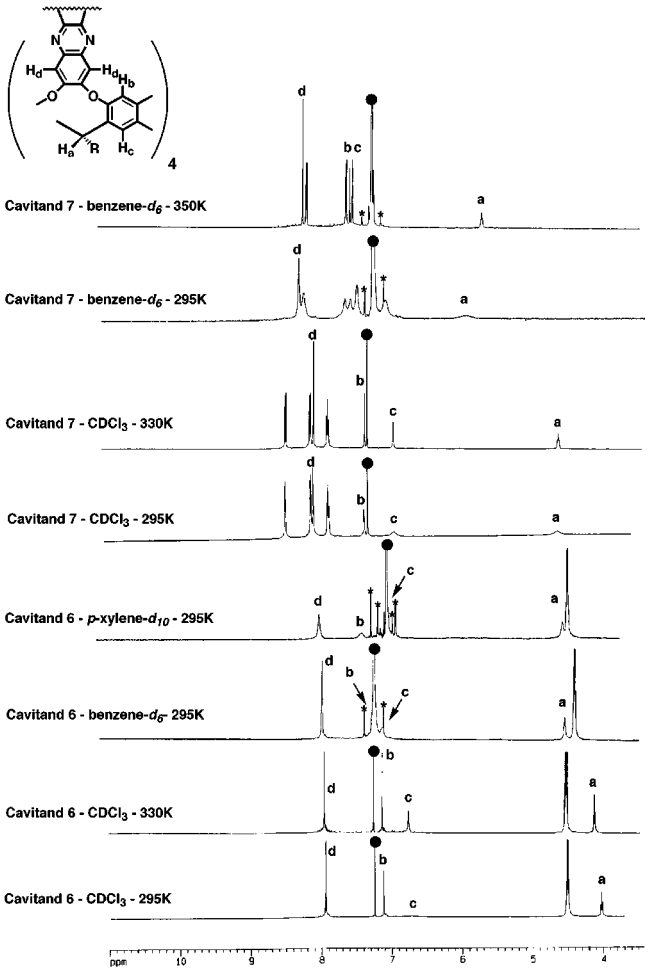

Figure 2. Downfield section of the ^{1}H NMR spectra of cavitands **6** and **7** (600 MHz). The solvent signals and the corresponding satellites are marked with "●" and "*", respectively. The letters on top of the peaks (a, b, c, and d) represent assignments made on the basis of COSY and ROESY spectra of analogues.

these solvents can fill the required space well enough and enjoy a high concentration advantage over the intended guest solutes. Modeling suggested that **7** can accommodate C_{60} (Figure 4) even though the round C_{60} is not well complemented by the square hole. The electron-rich walls of **7** and their considerable contact with incumbent C_{60} encouraged experiments, and strong complexation of C_{60} by **7** was indeed detected in the toluene solution. Specifically, addition of **7** to a toluene solution of C_{60} ($1.0-2.0 \times 10^{-5}$ M) led to an increase in the absorption of the band at 430 nm, characteristic of complexation (Figure 5).[13] Treatment of the titration data with the Benesi−Hildebrand equation[14,15] gave a value for the association constant, $K_a = 900 \pm 250$ M^{-1} at 293 ± 1 K, or a $\Delta G = -4.0 \pm 0.2$ kcal/mol. The binding isotherm provides a good fit to a 1:1 stoichiometry. Control experiments with model compound **10** and the "shallow" cavitand **3a** showed only very weak interactions ($K_a < 10$ M^{-1}). Unexpectedly, the UV/vis spectra showed no apparent binding of the slightly larger C_{70} in **7**. Accordingly, this example of selective complexation of fullerenes by resorcinarene-based compounds is one of the first reported.[13]

In summary, deeper cavitands of nanometric dimensions are now available for use as open-ended molecular containers. The cavities reported here feature wide openings with guest/solvent exchange fast on the NMR time scale. The uptake and release of guests involves the folding and unfolding of the host walls, motions that are influenced by solvent size and polarity. Cavitand **7** complexes C_{60} but not C_{70}, a behavior that augurs well for the use of these containers as selective reaction vessels, possibly even catalysts. These applications are the focus of current investigations.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 600 MHz spectrometer. The chemical shifts were measured relative to residual nondeuterated solvent resonances. Fast atom bombardment (FAB) mass spectra were obtained with a VG ZAB-VSE double-focusing high-resolution mass spectrometer equipped with a cesium ion gun; *m*-nitrobenzyl alcohol (NBA) was used as a matrix. For high-resolution mass spectral data (HRMS−FAB), for compounds with molecular weight ≤ 500, the measured masses always agreed to ≤ 5 ppm with the calculated values. For compounds with significantly higher molecular weight (≥2000), slightly lower resolution (≤10 ppm) was achieved.[16] Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry experiments were performed using 2,5-dihydroxybenzoic acid (DHB) as a matrix. Silica gel chromatography was performed with silica gel 60 (230−400 mesh). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under a nitrogen atmosphere. 1,2-Difluoro-4,5-dinitrobenzene,[8] diethyl 2,3-dioxosuccinate,[9] resorcinarene **2a**,[2c] and cavitand **3a**[4b] were synthesized in accordance with literature protocols. Molecular modeling was performed using the Amber* force field in the MacroModel 5.5 program.[11]

Optimized Procedure for Octanitro Cavitand 4. Resorcinarene **1a** (1.10 g, 1.0 mmol) and 1,2-difluoro-3,4-dinitrobenzene (0.90 g, 4.4 mmol) were suspended in anhydrous DMF (50 mL), and then Et_3N (2.23 mL, 16.0 mmol) was added dropwise via syringe. The resulting tan solution was slowly warmed to 70 °C and stirred at that temperature for 16 h. After cooling to room temperature, the mixture was poured onto acidic H_2O (pH ~ 1) and the bright yellow precipitate was filtered. The solids were dried under vacuum and then chromatographed on silica gel with CH_2Cl_2 as the eluent. The product obtained from the column was then triturated with MeOH (100 mL) and dried

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(14) Connors, K. A. *Binding Constants*; John Wiley and Sons: New York, 1987. No significant changes in the ^{1}H NMR spectra were detected in **7** upon C_{60} or C_{70} addition. Mass spectrometry measurements (MALDI and ESI) of 1:1 mixtures of **7** and C_{60} or C_{70} did not show the molecular ions for the complexes.

(15) The results obtained through the Benesi−Hildebrand equation were confirmed by the use of a nonlinear regression analysis curve-fitting software developed in the laboratories of Prof. François N. Diederich at ETH, Zürich.

(16) For details on high-resolution mass spectrometry, see: (a) Rose, M. E.; Johnstone, R. A. W. *Mass Spectrometry for Chemists and Biochemists*; Cambridge University Press: Cambridge, 1982. (b) Jennings, K. R.; Dolnikowsi, G. G. *Methods in Enzymology*; McCloskey, J. A., Ed.; Academic Press: New York, 1990; p 37 and references therein.

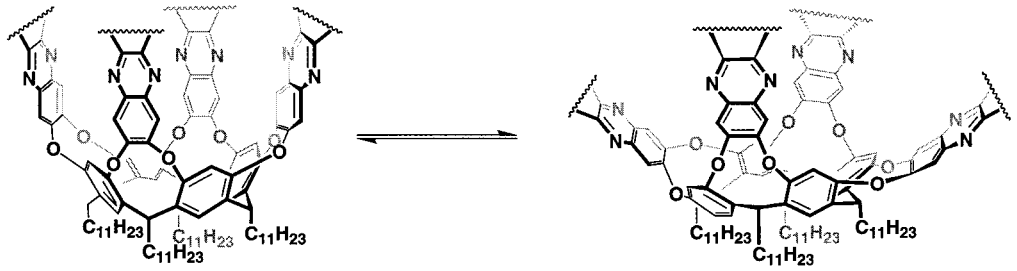

Figure 3. Proposed conformational dynamics for deep cavitands **6** and **7**.

Table 1. Chemical Shifts of Methine Triplets (H_a, Figure 2) in Cavitands 3a, 6, and 7 in Different Solvents

compd	solvent	temp (K)	chem shift (δ, ppm)[a,b,c]
3a[4]	$CDCl_3$	295	5.52
	benzene-d_6	295	6.06
	p-xylene-d_{10}	295	6.00
	toluene-d_8	295	6.05
6	$CDCl_3$	295	4.04
	$CDCl_3$	330	4.12
	benzene-d_6	295	4.47
	p-xylene-d_{10}	295	4.45
7	$CDCl_3$	295	4.57 (b)
	$CDCl_3$	330	4.55
	benzene-d_6	295	5.87 (b)
	benzene-d_6	350	5.60
	toluene-d_8	295	6.04 (b)
	toluene-d_8	380	5.56
	p-xylene-d_{10}	295	5.44 (b)
	p-xylene-d_{10}	380	5.18

[a] b, broad. [b] At 0.5 mM. [c] error, ± 0.05 ppm.

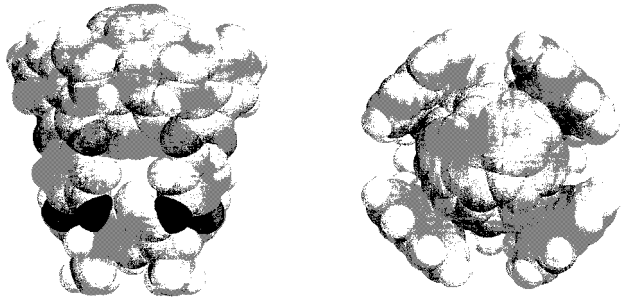

Figure 4. Side and top views of the energy-minimized[11] CPK models of C_{60}•cavitand **7** complex. The long alkyl "feet" are omitted for clarity.

under vacuum. The product was obtained as a pale yellow solid (1.40 g, 0.8 mmol; 80%). The spectral and analytical data agreed with the literature values.[7]

Optimized Procedure for Octaamino Cavitand 5. Octanitro cavitand **4** (704 mg; 0.40 mmol) was dissolved in toluene (150 mL), and to this solution was added a catalytic amount of Ra/Ni, prewashed with EtOH (2 × 5 mL) and toluene (2 × 5 mL). The resulting mixture was evacuated, and the reaction flask was filled with H_2. This operation was repeated three times, and the mixture was stirred for 12 h at 45 °C under an H_2 atmosphere. After cooling, the catalyst was filtered through a pad of CELITE and then rinsed with toluene (50 mL) and MeOH (2 × 50 mL). The filtrates were combined and evaporated under vacuum to give a brown solid (563 mg, 0.37 mmol; 93%) that was taken directly to the coupling step.

Octaester Cavitand 6. The crude octaamine **5** (563 mg; 0.37 mmol) was dissolved in anhydrous benzene (40 mL) and kept under N_2. Diethyl 2,3-dioxosuccinate (606 mg; 3.00 mmol) was added dropwise through a syringe, and the resulting solution was stirred at room temperature for 16 h. The solvent was removed under vacuum, and the remaining residue was chromatographed on silica gel eluting with a 7:3 mixture of hexanes and EtOAc. The product was obtained as a yellow solid (109 mg, 0.05 mmol; 13% from octanitro cavitand **4**): mp = 139−141 °C;

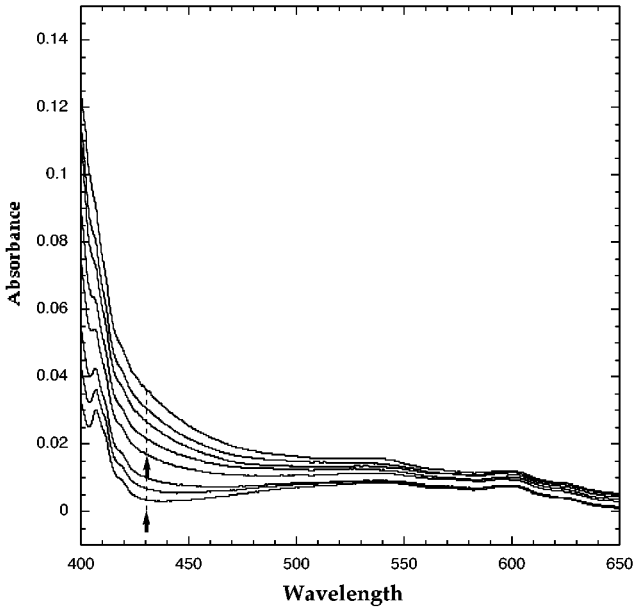

Figure 5. Absorption spectra of C_{60} (1.0×10^{-5} M) in the presence of **7** in toluene at 293 ± 1 K. The concentrations for **7** for the ascending curves are 0.0, 5.0×10^{-5}, 1.0, 1.5, 2.0, 2.5, 3.0 and 3.5×10^{-4} M, respectively.

^{1}H NMR ($CDCl_3$, 330 K) δ 7.95 (s, 8 H), 7.15 (s, 4 H), 6.76 (s, 4 H), 4.53 (q, J = 7.0 Hz, 16 H), 4.12 (t, J = 7.5 Hz, 4 H), 2.03−1.99 (m, 8 H), 1.46 (t, J = 7.0 Hz, 24 H), 1.32−1.20 (m, 72 H), 0.89 (t, J = 7.2 Hz, 12 H); ^{13}C NMR ($CDCl_3$, 330 K) δ 164.97, 154.17, 152.55, 144.13, 139.55, 132.33, 124.50, 119.24, 113.64, 62.89, 36.49, 32.18, 31.95, 29.84 (br), 29.76, 29.58, 27.34, 22.91, 14.36, 14.24; IR ($CDCl_3$, cm^{-1}) ν 2926, 2854, 1729, 1478, 1416, 898, 737; HRMS-FAB m/z 2317.9846 ([M + Cs]$^+$, calcd for $C_{128}H_{152}N_8O_{24}Cs$ = 2317.9974, error 5.5 ppm).

Cavitand 7. To a solution of crude octaamine **5** (248 mg, 0.16 mmol) in anhydrous THF (27 mL) and glacial HOAc (1 mL) was added acenaphthenequinone (372 mg, 2.04 mmol). The initial suspension was refluxed under an N_2 atmosphere for 6 h. The solvents were removed under vacuum, and the remaining solid was suspended in acetone (70 mL) with stirring for 30 min. The remaining solids were filtered, rinsed with acetone, and then dried under vacuum to give the title compound as a tan solid (214 mg, 0.10 mmol; 49% from octanitro cavitand **4**): mp > 270 °C; ^{1}H NMR ($CDCl_3$, 330 K) δ 8.41 (d, J = 6.8 Hz, 8 H), 8.06 (d, J = 8.1 Hz, 8 H), 8.02 (s, 8 H), 7.82 (t, J = 7.5 Hz, 8 H), 7.29 (s, 4 H), 6.89 (s, 4 H), 4.55 (t, J = 7.2 Hz, 4 H), 2.06 (q, J = 7.2 Hz, 8 H), 1.31−1.17 (m, 72 H), 0.83 (t, J = 7.1 Hz, 12 H); ^{1}H NMR (benzene-d_6, 350 K) δ 8.13 (s, 8 H), 8.07 (d, J = 6.7 Hz), 7.51 (d, J = 8.4 Hz), 7.46 (s, 4 H), 7.43 (s, 4 H), 7.13 (t, J = 7.5 Hz, 8 H), 5.60 (t, J = 7.2 Hz, 4 H), 2.36 (q, J = 7.2 Hz, 8 H), 1.56−1.51 (m, 8 H), 1.45−1.42 (m, 8 H), 1.36−1.29 (m, 56 H), 0.90 (t, J = 6.8 Hz, 12 H); ^{1}H NMR (*p*-xylene-d_{10}, 380 K) δ 8.07 (d, J = 6.7 Hz, 8 H), 8.03 (s, 8 H), 7.61 (d, J = 8.2 Hz, 8 H), 7.37 (s, 4 H), 7.35 (t, J = 7.5 Hz, 8 H), 7.26 (s, 4 H), 5.18 (t, J = 7.7 Hz, 4 H), 2.30 (q, J = 7.4 Hz, 8 H), 1.54−1.49 (m, 8 H), 1.41−1.37 (m, 8 H), 1.31−1.25 (m, 56 H), 0.86 (t, J = 7.0 Hz, 12 H); ^{13}C NMR ($CDCl_3$, 330 K) δ 154.43, 153.57, 149.99, 138.65, 136.30, 132.16,

130.05, 129.14, 128.55, 124.19, 121.69, 119.70, 113.80, 35.61, 31.85, 29.62 (br), 29.33, 29.27, 27.20, 22.56, 13.91; IR ($CDCl_3$, cm^{-1}) ν 2927, 2854, 1601, 1485, 1429; HRMS-FAB *m/z* 2237.9717 ($[M + Cs]^+$, calcd for $C_{144}H_{136}N_8O_8Cs$ = 2237.9535, error 8.1 ppm).

***n*-Butyl Octacarboxamide Cavitand 8**. A 25 mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was charged with octaester **6** (50 mg, 23.0 μmol), absolute EtOH (10 mL), and *n*-butylamine (1 mL, 10.0 mmol). The resulting mixture was heated under reflux, and the consumption of the starting material was followed by TLC (3:2 hexanes/EtOAc). After 19 h the volatiles were removed under vacuum and the residue was chromatographed on silica gel, eluting with a 3:2 mixture of hexanes and EtOAc (R_f = 0.31). The product was obtained as a yellowish solid (27 mg, 11.3 μmol; 49%): mp = > 270 °C; ^{1}H NMR (*p*-xylene-d_{10} + 20% v/v DMSO-d_6) δ 8.74 (s, 8 H), 8.51 (t, J = 5.2 Hz, 8 H), 8.06 (s, 4 H), 7.79 (s, 4 H), 5.59 (m, 4 H), 3.49−3.46 (m, 16 H), 2.53−2.48 (m, 8 H), 1.70−1.66 (m, 16 H), 1.48−1.44 (m, 32 H), 1.29−1.25 (m, 56 H), 0.99 (t, J = 7.3 Hz, 24 H), 0.90 (t, J = 6.8 Hz, 12 H); IR ($CDCl_3$, cm^{-1}) ν 3427, 3304, 2959, 2929, 2856, 1671; HRMS-FAB *m/z* 2534.3612 ($[M + Cs]^+$, calcd for $C_{144}H_{192}N_{16}O_{16}Cs$ = 2534.3757, error 5.7 ppm); MALDI-MS *m/z* 2405 ($[M + H]^+$, calcd for $C_{144}H_{192}N_{16}O_{16}H$ = 2404.2), 4811 ($[M_2 + H]^+$, calcd for $C_{288}H_{384}N_{32}O_{32}H$ = 4807.5).

Octaacid Cavitand 9. Cavitand **6** (109 mg; 0.05 mmol) was dissolved in THF (2 mL), and to the resulting solution was added aqueous LiOH (8 mL of a 1 N solution) slowly. The mixture was heated under reflux for 1 h; after that time the reaction was complete by TLC (2:1 hexane/ethyl acetate). The mixture was cooled to 0 °C and acidified with 1 N HCl. The solids were filtered and washed with cold water (20 mL). The product was obtained as a tan solid after drying in high vacuum overnight (98 mg, 0.05 mmol; ~100%): mp > 270 °C; ^{1}H NMR (DMSO-d_6) δ 14.05 (br, 8H), 8.55 (s, 8H), 7.69 (s, 4H), 7.30 (s, 4H), 4.76 (br, 4H), 2.26 (br, 8H), 1.21−1.14 (m, 72H), 0.82 (t, J = 6.8 Hz, 12H); ^{1}H NMR (acetone-d_6) δ 12.32 (br, 8H), 8.08 (s, 8H), 7.46 (s, 4H), 7.21 (s, 4H), 4.31 (t, J = 7.4 Hz, 4H), 2.18−2.15 (m, 8H), 1.28−1.16 (m, 72H), 0.86 (t, J = 6.9 Hz, 12H); IR (THF, cm^{-1}) ν 3463, 2920, 2851, 1728, 1478, 1209, 1068, 905.

9,10-Dimethylacenaphtho[1,2-*b*]quinoxaline (10). 3,4-Dimethyl-1,2-phenylenediamine (136 mg; 1.0 mmol) was dissolved in benzene (5 mL), and acenaphthenequinone (273 mg; 1.5 mmol) was added. The heterogeneous mixture was heated under reflux for 8 h. After cooling, the solvent was removed under vacuum and the residue was chromatographed on silica gel (95:5 hexanes/EtOAc). The product was obtained as a white solid (169 mg, 0.6 mmol; 60%): mp > 270 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, J = 6.9 Hz, 2 H), 8.07 (d, J = 8.4 Hz, 2 H), 7.96 (s, 2 H), 7.82 (t, J = 7.6 Hz, 2 H), 2.52 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 153.34, 140.02, 139.59, 136.07, 132.18, 129.97, 129.15, 128.92, 128.61, 121.52, 20.32; IR (CH_2Cl_2, cm^{-1}) ν 3054, 2986, 1421, 896; HRMS-FAB *m/z* 283.1235 ($[M + H]^+$, calcd for $C_{20}H_{14}N_2H$ = 283.1235, error 0.0 ppm).

Determination of the Association Constant. Binding studies were performed in toluene solution at 293 ± 1 K. A 1 mL volume of toluene was placed in both the sample cell and the reference cell, and 14 μL of a 1.0×10^{-3} M C_{60} (or C_{70}) stock solution was added to the sample cell, giving a final concentration of 2.0×10^{-5} M. An aliquot from the 1.0×10^{-2} M stock solution of compounds **3a**, **7**, or **10** was added to the sample cell and to the reference cell, and after homogenization, the absorption spectrum was recorded. Additional aliquots of **3a**, **7**, or **10** were added to both cells, and the spectrum was recorded after each addition. The association constant was calculated from the absorption intensities changes at 430 nm for C_{60} and 420 nm for C_{70} using the Benesi−Hildebrand equation.[14,15] All experiments were performed at least in triplicate.

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Supporting Information Available: Representative ^{1}H and ^{13}C NMR, UV/vis spectra, and binding isotherm. This material is available free of charge via the Internet at http://pubs.acs.org.

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