Bridging of Resorcin[4]arenes in the Chair Conformation to Cavitands Having Two Pairs of Axial and Equatorial Substituents

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Cavitands **18**−**22** were prepared in 29−90% yield by bridging of the *chair*-methylresorcin[4]arenes **3**−**7** with bromochloromethane. According to X-ray analysis of cavitand **19** and 1-D and 2-D NMR spectroscopy for **18**, the cavitands possess a stereochemistry with two adjacent aryl substituents in the axial position and the two others in the equatorial position. The starting methylresorcin-[4]arenes **3**−**7** were obtained exclusively in the chair conformation in 30−98% yield upon condensation of 2-methylresorcinol with aryl aldehydes.

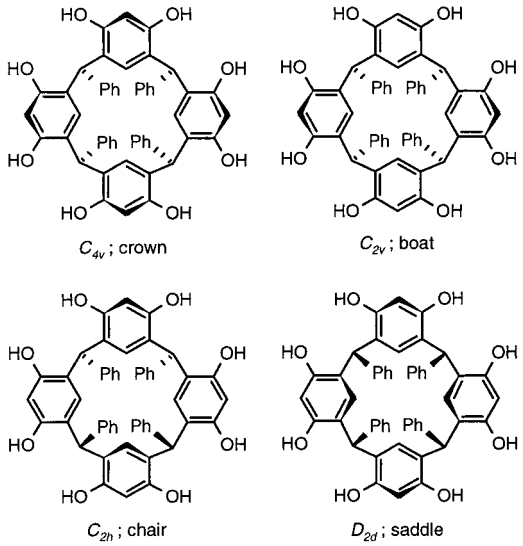
Introduction

Cavitands[1] are attractive building blocks for the construction of synthetic receptors because they have a rigid, bowl-shaped cavity that can be used as a platform for the attachment of ligating groups.[2] The cavity is formed by linking pairs of the eight adjacent phenolic groups of a resorcin[4]arene.

We are interested in methyl-substituted cavitands, because this methyl group provides a handle for upper rim functionalization. For instance, they can be easily (partly) converted via bromomethyl into aminomethyl-cavitands, which we have used for the preparation of (carbamoylmethyl)phosphoryl (CMPO)-functionalized cavitands[3] and (thio)urea-containing, cavitand-based anion receptors.[4]

Högberg[5] described the condensation of various benzaldehydes with resorcinol. Although the resorcin[4]-arenes formed can have four different conformations, crown (rccc, C_{4v}), boat (rcct, C_{2v}), chair (rctt, C_{2h}), and saddle (rtct, D_{2d}), he found that only two different stereoisomeric octols were formed, namely, the chair and the crown conformers (Chart 1). The ratio of both isomers depends on the reaction conditions, with the chair (**1**) and the crown conformers being the kinetically and thermodynamically determined products, respectively.[6] The

Chart 1



combination of a reversible aldol condensation and the difference in solubility of both isomers determines the outcome of the reaction. This was confirmed by Cram et al.[7] for the condensation of a series of substituted benzaldehydes with (substituted) resorcinol(s). They also found[7] that the condensation of 2-methylresorcinol with benzaldehyde gave methylresorcin[4]arene **2** exclusively in the chair conformation (>97%), indicating the possible influence of the methyl group on the conformation of the methylresorcin[4]arene (Chart 2).[8−10]

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(8) When the more polar boronic acid substituted benzaldehyde was condensed with 2-methylresorcinol in a 2:1 mixture of ethanol and HCl (37% in water), a mixture of chair and crown conformers was obtained, which was due to the higher solubility of both products. Lewis, P. T.; Davis, C. J.; Saraiva, M. C.; Treleaven, W. D.; McCarley, T. D.; Strongin, R. M. *J. Org. Chem.* **1997**, *62*, 6110.

(9) For a recent example, see: Curtis, A. D. M. *Tetrahedron Lett.* **1997**, *38*, 4295.

(10) We found that condensation of 2-methylresorcinol with aliphatic aldehydes exclusively affords resorcin[4]arenes in the crown conformation.[2b,3,4]

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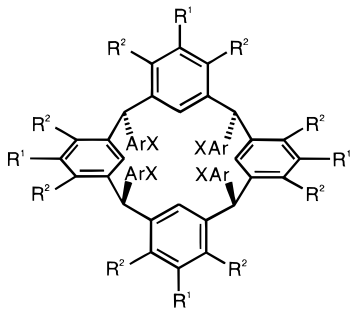
Chart 2



Octol	R^1	R^2	X
1	H	OH	H
2	Me	OH	H
3	Me	OH	*p*-OMe
4	Me	OH	*p*-Br
5	Me	OH	*p*-CN
6	Me	OH	*p*-NO_2
7	Me	OH	*m*-NO_2
8	Me	OAc	*p*-OMe
9	Me	OAc	*p*-Br
10	Me	OAc	*p*-CN
11	Me	OAc	*p*-NO_2
12	Me	OAc	*m*-NO_2

In the literature, so far only resorcin[4]arenes in the crown conformation were bridged to give the corresponding cavitands with all substituents in the axial position.[1] On the basis of an NMR study, Dalcanale et al.[11] have reported that the chair conformer of the resorcin[4]arene derived from resorcinol and 1-heptanal is in equilibrium with its crown conformer as a result of a ring-inversion conformational process. The crown conformer could be trapped by a bridging reaction with 2,3-dichloroquinoxaline to give the corresponding cavitand (which has two axial and two equatorial lower rim substituents) in 5% yield.[11,12]

In this paper, we describe a general route to cavitands, with yields up to 90% and starting from aryl-substituted methylresorcin[4]arenes in the chair conformation. The relative stereochemistry of the aryl-substituted cavitands, namely, two adjacent substituents paired in an axial and an equatorial orientation has been proven by X-ray analysis and various NMR techniques.

Results and Discussion

Synthesis. Condensation of 2-methylresorcinol with *p*-methoxy-, *p*-bromo-, *p*-cyano-, *p*-nitro-, and *m*-nitrobenzaldehyde in a refluxing 1:1 mixture of ethanol and HCl (37% in water) afforded 30−98% yields of the corresponding methylresorcin[4]arenes **3**−**7** exclusively in the chair conformation after the crude reaction mixture was washed with a small amount of cold methanol. Neither in the filtrate nor upon acetylation of the crude reaction mixture (to give **8**−**12**) could other conformers be detected.

Compared to the yields of the corresponding condensations with unsubstituted resorcinol,[5−7] the yields of **3**−**7** are higher. Reaction times of up to 4 weeks afforded the same yields whereas the conformation remained unchanged. This smooth formation of methylresorcin[4]arenes **3**−**7** and, in particular, the ability to synthesize methylresorcin[4]arene **6** in 30% yield (when starting from resorcinol, the corresponding resorcin[4]arene was not formed[7]) can be explained in terms of a higher electron density in 2-methylresorcinol than that in resorcinol. The electrophilic attack on the methylresorcinol by the benzaldehyde residues and, consequently, the ring closure of the tetramers to the methylresorcin[4]arenes **3**−**7** will be faster. The insolubility of **3**−**7** in the solvent mixture used results in the exclusive formation of the "kinetic" chair conformers.[5,6] Selectivity was lost when a 10:1 mixture of ethanol and HCl (37% in water) was used, in the case of methylresorcin[4]arene **4**, this 10:1 mixture gave a mixture of crown and chair conformers in a 3:5 ratio. Moreover, the yield of the condensation dropped from 98% to 25% because of the large amount of non-resorcin[4]arene side products formed.

Cavitand Formation. Despite the unfavorable chair conformation of methylresorcin[4]arenes **3**−**7**, treatment with 6−8 equiv of bromochloromethane in the presence of K_2CO_3 in DMF at 65 °C allowed faster formation of the bowl-shaped cavitands **18**−**22** than that in the corresponding reaction starting from *crown*-resorcin[4]-arenes,[13] in 29−90% yield. X-ray analysis and various NMR techniques (vide infra) confirmed that the lower rim aryl substituents have a different orientation, namely, adjacent substituents in pairs in an axial and an equatorial orientation.

The formation of the cavitands **18**−**22** is most probably the result of an equilibrium between resorcin[4]arenes **3**−**7** in the chair conformation and the corresponding crown conformers **13**−**17**, the latter being trapped by reaction with bromochloromethane (Scheme 1). The crown conformers **13**−**17** are energetically less favored because of the repulsion between the equatorial aryl substituents and the hydroxyl groups. However, this will partly be compensated for by hydrogen-bond formation between the hydroxyl groups.[14]

In contrast to the example of Dalcanale et al.[11] (vide supra), the crown conformers **13**−**17** could not be observed at various temperatures with ^{1}H NMR spectroscopy. In an ^{1}H NMR experiment with a solution of *chair*-methylresorcin[4]arene **4** and K_2CO_3 in DMF-d_7 at 65 °C, the corresponding crown conformer **14** could also not be observed. Instead, a very complex reaction mixture was obtained.[15]

It was not possible to isolate partly bridged intermediates from the reaction of resorcin[4]arene **4** with 2.5 equiv of bromochloromethane. In the ^{1}H NMR spectrum of the crude reaction mixture, only fully bridged cavitand **19** and starting material could be identified; cavitand **19** was isolated in 15% yield. Apparently, the formation of the

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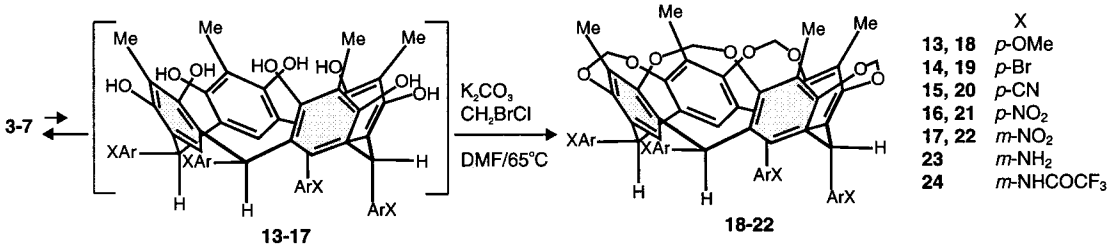
(12) Because the substituent−methine bonds have the ability to rotate through the ring during cavitand formation and because the chair conformer of a resorcin[4]arene has lower rim methyl substituents, this conformer can be fully bridged to a cavitand with all the substituents in the axial orientation. Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.

(13) Tucker, J. A.; Knobler, C. B.; Trueblood, K. N.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 3688.

(14) Lippmann, T.; Wilde, H.; Pink, M.; Schafer, A.; Hesse, M.; Mann, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1195.

(15) In part, the complex reaction mixture might be the result of deprotonation of the acidic triarylmethane hydrogen atom and subsequent quinone methide formation. This may also be the reason for the lower yields of some of the cavitands. Though a pseudorotation is not possible for *chair*-resorcin[4]arenes,[5] in a NOESY experiment with **4**, an exchange cross-signal was observed between the resonances of both different methyl groups when the reaction conditions used for cavitand synthesis were applied. This may be explained by a planar anion, formed by deprotonation at the acidic methine position, in which both methyl groups are magnetically equivalent.

Scheme 1. Proposed Mechanism for the Formation of Cavitands 18-22



first bridge is the rate-determining step for cavitand formation. This is in contrast to the "classical" *crown*-resorcin[4]arenes (i.e., those lacking a methyl group between the hydroxyl groups) for which the introduction of the final bridge proved to be the most difficult.[16]

The functional groups at the aryl substituents can easily be transformed; and this is illustrated by the reduction of cavitand **22** to the corresponding tetraamine **23** using Raney nickel and hydrazine monohydrate and the subsequent treatment of cavitand **23** with trifluoroacetic anhydride in pyridine to give the tetratrifluoroacetamide **24**.

X-ray Analysis. Crystallization of cavitand **19** from toluene gave single crystals suitable for X-ray analysis. The crystal structure (Figure 1a) clearly shows that two adjacent aryl substituents are in the axial orientation and the other two are in the equatorial orientation. The vertical plane of symmetry in the structure corresponds with the NMR data (vide infra). The crystal structure contains four toluene molecules for each cavitand. These slightly disordered solvent molecules are gathered into interconnected channels running parallel to all three unit cell axes. The total volume of these channels amounts to 40% of the unit cell volume. Because of this large solvent content, only a limited number of interactions between the cavitand molecules exists. The two most interesting of these, those involving the cavity created by the cavitand "bowl" and those involving the cavity created by the lower rim substituents, are depicted in Figure 1b.

The first interaction shows one of the bromophenyl groups inside the cavitand "bowl". The shortest distances are found between the bromo atom and the methylene bridges. The second interaction occurs between the two molecules related by a crystallographic inversion center. The bromo atom of one molecule is located directly against the π systems of two axial bromophenyl groups of the neighboring symmetry-related molecule.[17] A $\pi-\pi$ interaction with another equatorial bromophenyl group of that molecule completes the interaction. These two interactions link the molecules into a two-dimensional network, perpendicular to the *b* axis.

NMR Analysis. The ^{1}H NMR spectra of cavitands **18**−**24** reveal the molecular structure in terms of symmetry operators. The ^{1}H NMR spectrum of cavitand **18**, for example, clearly shows that hydrogen atoms at positions 2−4, 6, and 7 give doubled signals integrating in a 1:1 manner (Figure 2). Hydrogen atoms at positions 1 and 5, however, resonate as three signals in a 1:2:1 fashion. Because this was only found for these two groups, it is clear that the cavitands have to possess an *inherently*

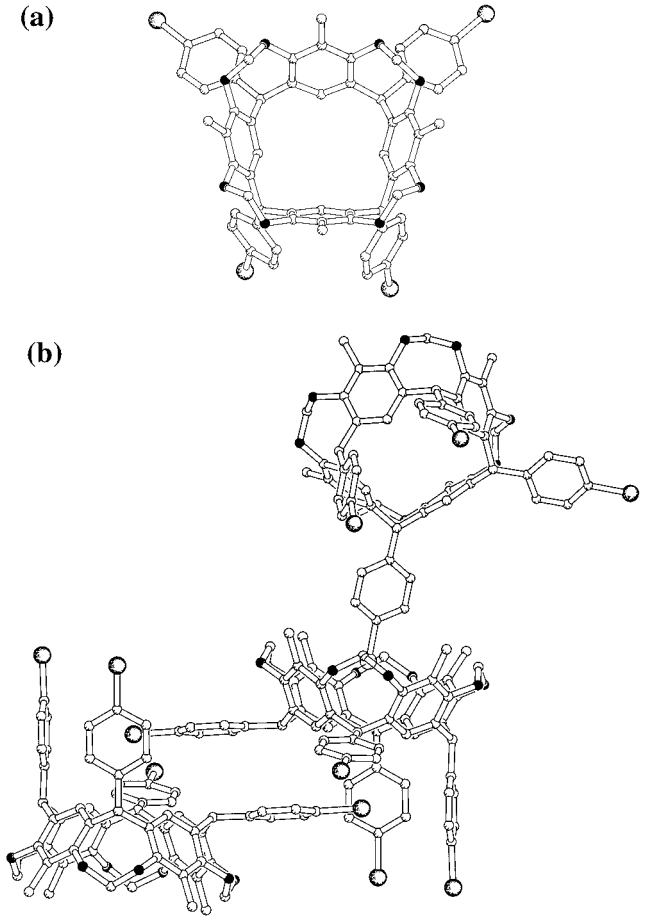


Figure 1. (a) X-ray crystal structure of cavitand **19** at 30% probability level. Hydrogen atoms and toluene solvent molecules have been omitted for clarity. (b) Interactions of the equatorial substituents and the cavitand bowl of cavitand **19** in the crystal structure. Hydrogen atoms have been omitted for clarity.

nonsymmetric structure, with groups aligned either at half of 1 and 5 or to both sides (2−4, 6, 7, and half of 1 and 5) of a plane of symmetry.

The broadening of one of the two methoxy signals indicates that there are different modes of freedom for the lower rim aryl substituents. From the NMR data, it follows that two different spatial orientations are present for the lower rim aryl substituents for which all observations made can be accounted for.

Subsequently, 2-D ^{1}H NMR spectroscopy was carried out to distinguish between these two possible spatial orientations and to assign the signals in the 1-D ^{1}H NMR spectrum.

^{1}H−^{1}H relayed COSY of cavitand **18** shows the *through-bond* connectivities between the two different sets of methylene bridge hydrogen atoms, with the first set at δ

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(17) Reddy, D. S.; Craig, D. C.; Desiraju, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 4090.

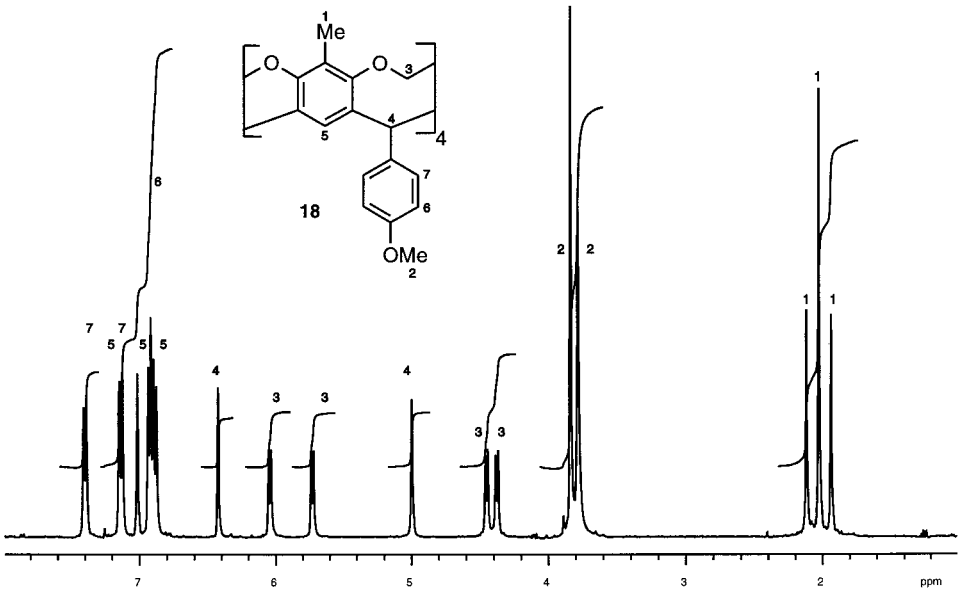

Figure 2. ^{1}H NMR spectrum of cavitand **18** showing the doubled and tripled signals.

4.37 and 4.46 (H_{in}) and the second at around δ 6.00 (H_{out}). Also, two AB-spin systems are recognized in the aromatic region: one set is located at δ 6.88 and 7.17 whereas the other set is located at δ 6.94 and 7.40. Several long-range COSY connections arising from ^4J coupled patterns can be identified; the most important is the connection between the signal at δ 4.99 (methine H) and the signals at δ 6.90 and 7.04 (CH−aromatic), respectively.

To properly assign the hydrogen atoms in view of the large induced shifts, ^{1}H−^{13}C heteronuclear multiple-quantum coherence (HMQC) spectroscopy was applied. All the ^{1}H-^{13}C connections were identified, of which the most elucidative are the connections between δ 41.6 and 56.1 (^{13}C) and δ 6.42 and 4.99 (^{1}H), respectively. This large difference in chemical shift between these two identically attached hydrogens is the result of a strong difference in magnetic shielding. It is important to note that the signal at δ 6.42 is proven by HMQC to belong to two of the methine hydrogen atoms and not to a CH of one of the aromatic systems.

The use of rotating-frame Overhauser enhancement spectroscopy (ROESY) and *NOESY* (Figure 3) leads to the elucidation of the spatial orientation of the different groups mentioned. Through-space contacts are limited because of the apparent structural aspects, and non-equivalent contacts are traced for the inner-placed aromatic hydrogen atoms (5 in Figure 2) at δ 6.90, 7.04, and 7.16 with the aromatic hydrogens meta to the methoxy at the aryl substituents, as expected. The signal at δ 7.04 interacts with that at δ 7.17, and the resonance at δ 7.16 interacts with that at δ 7.40 whereas the resonance at δ 6.90 shows cross contacts with both signals of the substituents mentioned before. Corresponding nonequivalent contacts are observed between the hydrogen atoms of the methyl groups (1 in Figure 2) and the hydrogen atoms at the methylene bridge resonating at δ 4.37 and 4.46 (H_{in}).

In contrast to the methine hydrogen atoms at δ 4.99 (4 in Figure 2) having a contact with two of the three inner-placed aromatic hydrogen atoms (5 in Figure 2), the methine hydrogen atoms at δ 6.42 do not exhibit any

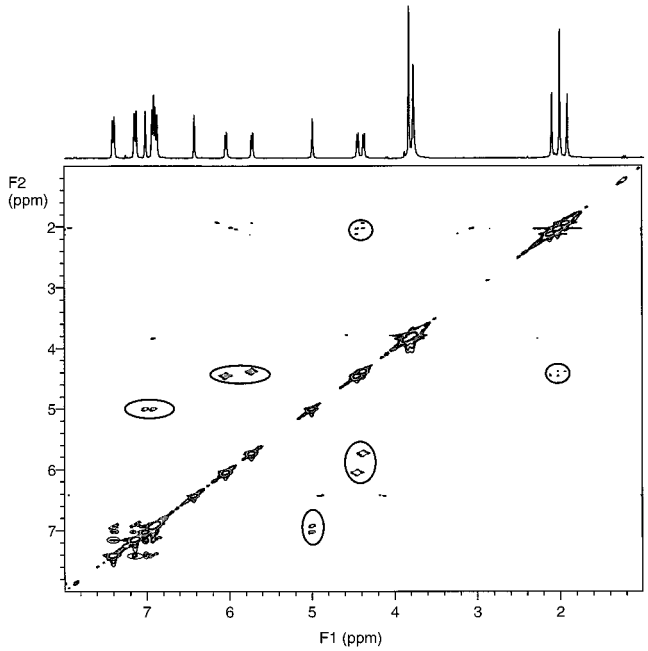

Figure 3. NOESY spectrum of cavitand **18**.

contacts. This observation, in addition to the large difference in chemical shifts for these methine hydrogen atoms, indicates a completely different orientation of the substituents at the lower rim.

Variation of both the temperature and the solvent from −65 ($CDCl_3$) to +100 °C ($C_6D_5NO_2$) does not alter any of our observations, except for the fairly large shift differences for the aromatic hydrogen atoms (5), which is probably due to the solvent effect of using $C_6D_5NO_2$ instead of CD_2Cl_2 or $CDCl_3$. The various NMR techniques also prove the relative stereochemistry of cavitands **18**−**24** with two adjacent axial and equatorial substituents at the lower rim.

In this paper, we demonstrated that aryl-substituted methylresorcin[4]arenes in the chair conformation, via the corresponding crown conformer, can easily be con-

verted into the corresponding cavitands which have two adjacent axial and two equatorial aryl substituents. Because of the relative stereochemistry at the lower rim, this type of cavitand represents an interesting class of compounds for various applications. For instance, suitable functional groups at the aryl substituents may allow the formation of large boxes via either metal coordination or hydrogen bonding. Work in this direction is currently being conducted.

Experimental Section

General. Melting points are uncorrected. Mass positive (FAB) spectra were obtained using *m*-nitrobenzyl alcohol as a matrix. Column chromatography was performed using silica gel 60 from Merck. All reactions were carried out under an argon atmosphere, and solvents were purified, if necessary, by standard procedures prior to use. Ethanol (95%) was used as received. DMF and pyridine were stored over 4 Å molecular sieves. The presence of solvents in the analytical samples was confirmed by ^{1}H NMR spectroscopy.

NMR. All spectra were recorded at ambient temperature (30 °C) unless stated otherwise. ^{1}H and ^{13}C NMR spectra were recorded at 250, 300, and 400 MHz in $CDCl_3$ unless stated otherwise. The chemical shifts are expressed relative to $CHCl_3$ for ^{1}H NMR (at δ 7.26) and ^{13}C NMR (at δ 76.91). NOESY,[18] ROESY,[19] total correlation spectroscopy (TOCSY) (MLEV 17),[20] and COSY[21] were performed using standard Varian pulse programs. The TOCSY (MLEV 17) experiments were performed with mixing times of 30 ms. The mixing times of the NOESY experiments ranged from 10 to 90 ms. The mixing time of the ROESY experiments consisted of a spin lock pulse of 2 kHz field strength with a duration of 30 ms, typically. All 2-D experiments were collected using 2-D hypercomplex data[22] and Fourier transformed in the phase-sensitive mode after weighting with shifted square sine-bells or shifted Gaussian functions. NMR data were processed by the standard VnmrS software packages on the Unity 400 WB host computers (SUN IPX and Sparc stations). Concentrations of the samples used were typically in the 5 mM range.

General Procedure for the Preparation of Methylresorcin[4]arenes 3−7. 2-Methylresorcinol (6.20 g, 50 mmol) was dissolved in a mixture of ethanol (20 mL) and HCl (37% in water, 20 mL), and the appropriately substituted benzaldehyde (50 mmol) was added portion wise at 0 °C over a period of 1 h. The reaction mixture was refluxed for at least 48 h, and after the mixture was cooled to room temperature, the precipitate formed was collected by filtration and made acid-free (pH 7) by washing it with water. The solid material was washed twice with cold methanol (20 mL) and dried in vacuo. The methanol washings mainly contained noncyclic impurities in addition to a small amount of the cyclic product that also consisted of the chair conformer.

2,8,14,20-Tetrakis(4-methoxyphenyl)-5,11,17,23-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,-10,12,16,18,22,24-octol (3): yield 8.37 g (69%) of off-white solid; mp > 320 °C; ^{1}H NMR [250 MHz; $(CD_3)_2SO$] δ 1.91 (s, 6 H), 2.09 (s, 6 H), 3.64 (s, 12 H), 5.35 (s, 2 H), 5.55 (s, 4 H), 6.12 (s, 2 H), 6.43 (d, $^2J_{AB}$ = 8.5 Hz, 8 H), 6.54 (d, $^2J_{AB}$ = 8.5 Hz, 8 H), 7.22 (s, 4 H), 7.55 (s, 4 H); FAB MS *m*/*z* 968.1 (M^+, calcd 968.4). Anal. Calcd for $C_{60}H_{56}O_{12}\cdot 3.5H_2O$: C, 69.82; H, 6.15. Found: C, 70.01; H, 6.32.

2,8,14,20-Tetrakis(4-bromophenyl)-5,11,17,23-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,-10,12,16,18,22,24-octol (4): yield 14.34 g (98%) of pink solid; mp > 320 °C; ^{1}H NMR [250 MHz; $(CD_3)_2SO$] δ 1.91 (s, 6 H), 2.08 (s, 6 H), 5.27 (s, 2 H), 5.63 (s, 4 H), 6.13 (s, 2 H), 6.57 (d, $^2J_{AB}$ = 8.5 Hz, 8 H), 7.08 (d, $^2J_{AB}$ = 8.5 Hz, 8 H), 7.60 (br s, 4 H), 7.70 (br s, 4 H); ^{13}C NMR [$(CD_3)_2SO$] δ 150.6, 143.4, 131.3, 129.9, 127.7, 122.5, 121.6, 118.1, 111.1, 110.7, 48.6, 9.9, 9.7; FAB MS *m*/*z* 1160.6 (M^+, calcd 1160.0). Anal. Calcd for $C_{56}H_{44}Br_4O_8\cdot 3.5H_2O$: C, 54.79; H, 4.19. Found: C, 54.50; H, 4.22.

2,8,14,20-Tetrakis(4-cyanophenyl)-5,11,17,23-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,-10,12,16,18,22,24-octol (5): yield 10.56 g (89%) of white solid; mp > 320 °C; ^{1}H NMR [300 MHz, $CDCl_3/CD_3OD$] δ 2.04 (s, 6 H), 2.15 (s, 6 H), 4.94 (s, 2 H), 5.79 (s, 4 H), 6.11 (s, 2 H), 6.83 (d, $^2J_{AB}$ = 8.4 Hz, 8 H), 7.28 (d, $^2J_{AB}$ = 8.4 Hz, 8 H); FAB MS *m*/*z* 946.9 ([M − H]$^-$, calcd 947.3). Anal. Calcd for $C_{60}H_{44}N_4O_8\cdot 2.0\ H_2O$: C, 73.16; H, 4.91; N, 5.69. Found: C, 73.02; H, 4.58; N, 5.42.

2,8,14,20-Tetrakis(4-nitrophenyl)-5,11,17,23-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3−5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,-16,18,22,24-octol (6): yield 3.83 g (30%) of white solid; mp > 320 °C; ^{1}H NMR [250 MHz, $(CD_3)_2SO$] δ 1.91 (s, 6 H), 2.09 (s, 6 H), 4.81 (s, 2 H), 5.88 (2 × s, 4 H), 6.10 (s, 2 H), 6.87 (d, $^2J_{AB}$ = 8.8 Hz, 8 H), 7.72 (d, $^2J_{AB}$ = 8.8 Hz, 8 H), 9.12 (s, 4 H), 9.43 (s, 4 H); FAB MS *m*/*z* 1027.6 ([M − H]$^-$, calcd 1027.3). Anal. Calcd for $C_{56}H_{44}N_4O_{16}\cdot 1H_2O$: C, 64.24; H, 4.43; N, 5.35. Found: C, 64.23; H, 4.20; N, 5.30.

2,8,14,20-Tetrakis(3-nitrophenyl)-5,11,17,23-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,-10,12,16,18,22,24-octol (7): yield 9.45 g (74%) of white solid; mp > 320 °C; ^{1}H NMR [250 MHz, $(CD_3)_2NCDO$] δ 1.95 (s, 6 H), 2.14 (s, 6 H), 4.75 (s, 2 H), 5.92 (s, 4 H), 6.20 (s, 2 H), 6.96−7.04 (m, 12 H), 7.38 (s, 4 H), 7.52−7.63 (m, 4 H), 7.82 (s, 4 H); FAB MS *m*/*z* 1028.9 (M^+, calcd 1028.3). Anal. Calcd for $C_{56}H_{44}N_4O_{16}$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.29; H, 4.26; N, 5.28.

General Procedure for the Acetylation of Methylresorcin[4]arenes 3−7. To a suspension of the crude methylresorcin-[4]arenes **3**−**7** [prepared from 0.1 mmol of 2-methylresorcinol and 0.1 mmol of the appropriately substituted benzaldehyde, in pyridine (10 mL)] was added a 50-fold excess of acetic anhydride at 0 °C. After the reaction mixture was stirred for 1 h, the clear solution was evaporated to dryness. Subsequent TLC analysis showed only one product in addition to the baseline spot. Purification by column chromatography (SiO_2, chloroform/diethyl ether = 1:9) yielded the pure acetylated methylresorcin[4]arenes **8**−**12**.

4,6,10,12,16,18,22,24-Octaacetoxy-2,8,14,20-tetrakis(4-methoxyphenyl)-5,11,17,23-tetramethylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecaene (8): yield 99 mg (76%) of white solid; mp > 320 °C; ^{1}H NMR (250 MHz) δ 1.79 (s, 6 H), 1.91 (s, 6 H), 2.12 (s, 12 H), 2.16 (s, 12 H), 3.40 (s, 12 H), 5.13 (br s, 4 H), 5.78 (br s, 2 H), 6.20 (s, 2 H), 6.50−6.80 (m, 16 H); FAB MS *m*/*z* 1306.2 ([M + 2H]$^+$, calcd 1306.5). Anal. Calcd for $C_{76}H_{72}O_{20}$: C, 69.93; H, 5.56. Found: C, 69.60; H, 5.26.

4,6,10,12,16,18,22,24-Octaacetoxy-2,8,14,20-tetrakis(4-bromophenyl)-5,11,17,23-tetramethylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecaene (9): yield 136 mg (90%) of white solid; mp > 320 °C; ^{1}H NMR (300 MHz) δ 1.76 (s, 6 H), 1.87 (s, 6 H), 2.07 (br s, 12 H), 2.16 (br s, 12 H), 5.19 (br s, 4 H), 5.72 (br s, 2 H), 6.08 (br s, 2 H), 6.55−6.8 (br m, 8 H), 7.1−7.3 (m, 8 H); FAB MS *m*/*z* 1501.1 {[M + H]$^+$, calcd 1500.1 (based on highest isotope signal)}. Anal. Calcd for $C_{72}H_{60}Br_4O_{16}\cdot 2$pyridine: C, 59.36; H, 4.25; N, 1.69. Found: C, 59.72; H, 4.28; N, 1.59.

4,6,10,12,16,18,22,24-Octaacetoxy-2,8,14,20-tetrakis(4-cyanophenyl)-5,11,17,23-tetramethylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-

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15,17,19(26),21,23-dodecaene (10): yield 117 mg (90%) of white solid; mp > 320 °C; ^{1}H NMR (300 MHz) δ 1.52 (s, 6 H), 1.61 (s, 6 H), 1.80 (br s, 24 H), 4.8−5.3 (br s, 2 H), 5.12 (br s, 4 H), 5.83 (br s, 2 H), 6.4−6.7 (m, 8 H), 6.95−7.1 (m, 8 H); FAB MS *m/z* 1286.5 (M^+, calcd 1286.3). Anal. Calcd for $C_{76}H_{60}N_4O_{16}$·0.5 H_2O: C, 70.53; H, 4.75; N, 4.33. Found: C, 70.27; H, 4.68; N, 4.34.

4,6,10,12,16,18,22,24-Octaacetoxy-2,8,14,20-tetrakis(4-nitrophenyl)-5,11,17,23-tetramethylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecaene (11): yield 34 mg (25%) of white solid; mp > 320 °C; ^{1}H NMR [300 MHz, $CDCl_3$/$(CD_3)_2$-SO] δ 1.75 (s, 6 H), 1.87 (s, 6 H), 2.00 (br s, 24 H), 5.37 (br s, 4 H), 5.48 (br s, 2 H), 6.15 (br s, 2 H), 6.85 (m, 8 H), 7.71 (m, 8 H); FAB MS *m/z* 1365.5 ([M + H]$^-$, calcd 1365.4). Anal. Calcd for $C_{72}H_{60}N_4O_{24}$·0.1 $CHCl_3$: C, 62.88; H, 4.40; N, 4.07. Found: C, 62.66; H, 4.35; N, 4.17.

4,6,10,12,16,18,22,24-Octaacetoxy-2,8,14,20-tetrakis(3-nitrophenyl)-5,11,17,23-tetramethylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecaene (12): yield 56 mg (41%) of white solid; mp > 320 °C; ^{1}H NMR (250 MHz) δ 1.85 (s, 6 H), 1.94 (s, 6 H), 2.09 (br s, 24 H), 5.44 (br s, 4 H), 7.13 (br s, 4 H), 7.26−7.32 (m, 8 H), 7.85−7.88 (m, 4 H), 8.60−8.65 (m, 8 H); FAB MS *m/z* 1365.5 ([M + H]$^-$, calcd 1365.4). Anal. Calcd for $C_{72}H_{60}N_4O_{24}$·0.3$CHCl_3$: C, 61.98; H, 4.34; N, 4.00. Found: C, 62.04; H, 4.31; N, 4.17.

General Procedure for the Preparation of Cavitands 18−22. A suspension of the methylresorcin[4]arenes **3**−**7** (1 mmol), bromochloromethane (0.79 g, 6.0 mmol, 6 equiv), and K_2CO_3 (3.0 g, large excess) in DMF (50 mL) was stirred at 65 °C for 10 h. After the reaction mixture cooled to room temperature, the excess of base was filtered off, and the solvent was removed in vacuo. The residue was taken up in chloroform (200 mL) and washed twice with water (100 mL). After the organic layer was dried over $MgSO_4$, the solution was concentrated to approximately 5 mL and directly put on a silica gel column.

1,21,23,25-Tetrakis(4-methoxyphenyl)-7,11,15,28-tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxin (18) was isolated after flash chromatography (SiO_2, $CHCl_3$/EtOAc = 1:1, R_f = 0.6) as an off-white solid: yield 382 mg (38%); mp > 320 °C; ^{1}H NMR (400 MHz) δ 1.95 (s, 3 H), 2.04 (s, 6 H), 2.12 (s, 3 H), 3.78 (s, 6 H), 3.83 (s, 6 H), 4.37 (d, $^2J_{AB}$ = 6.0 Hz, 2 H), 4.46 (d, $^2J_{AB}$ = 6.6 Hz, 2 H), 4.99 (s, 2 H), 5.73 (d, $^2J_{AB}$ = 6.0 Hz, 2 H), 6.04 (d, $^2J_{AB}$ = 6.6 Hz, 2 H), 6.42 (s, 2 H), 6.88 (d, $^2J_{AB}$ = 8.0 Hz, 4 H), 6.90 (s, 1 H), 6.94 (d, $^2J_{AB}$ = 8.4 Hz, 4 H), 7.04 (s, 2 H), 7.16 (s, 1 H), 7.17 (d, $^2J_{AB}$ = 8.0 Hz, 4 H), 7.40 (d, $^2J_{AB}$ = 8.4 Hz, 4 H); ^{13}C NMR δ 157.9, 157.6, 155.2, 154.4, 137.9, 137.5, 136.2, 136.0, 132.4, 132.0, 130.1, 129.9, 128.2, 128.0, 127.1, 127.0, 125.6, 125.3, 124.1, 113.4, 113.2, 98.5, 97.8, 56.1, 55.3, 55.2, 41.6, 10.6, 10.5, 10.5; FAB MS *m/z* 1016.9 (M^+, calcd 1016.4). Anal. Calcd for $C_{64}H_{56}O_{12}$·2.5$CHCl_3$: C, 60.85; H, 4.49. Found: C, 60.85; H, 4.49.

1,21,23,25-Tetrakis(4-bromophenyl)-7,11,15,28-tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxin (19) was isolated after flash chromatography (SiO_2, $CHCl_3$, R_f = 0.4) as a white solid crystallizing from the eluent: yield 1.09 g (90%); mp > 320 °C; ^{1}H NMR (400 MHz) δ 1.91 (s, 3 H), 2.00 (s, 6 H), 2.10 (s, 3 H), 4.33 (d, $^2J_{AB}$ = 6.0 Hz, 2 H), 4.42 (d, $^2J_{AB}$ = 6.6 Hz, 2 H), 4.92 (s, 2 H), 5.68 (d, $^2J_{AB}$ = 6.0 Hz, 2 H), 6.03 (d, $^2J_{AB}$ = 6.6 Hz, 2 H), 6.40 (s, 2 H), 6.89 (s, 1 H), 6.93 (s, 2 H), 6.96 (s, 1 H), 7.06 (d, $^2J_{AB}$ = 8.0 Hz, 4 H), 7.33 (d, $^2J_{AB}$ = 8.4 Hz, 4 H), 7.43 (d, $^2J_{AB}$ = 8.0 Hz, 4 H), 7.50 (d, $^2J_{AB}$ = 8.4 Hz, 4 H); ^{13}C NMR δ 155.4, 154.5, 153.8, 153.1, 139.5, 139.3, 137.2, 136.6, 135.7, 135.4, 131.1, 130.9, 129.0, 127.4, 126.8, 126.1, 124.7, 124.7, 123.7, 120.1, 119.5, 98.5, 97.7, 55.9, 42.0, 10.3, 10.2, 10.1; FAB MS *m/z* 1210.1 ([M+2H]$^-$, calcd 1210.0). Anal. Calcd for $C_{60}H_{44}Br_4O_8$·0.5$CHCl_3$: C, 57.11; H, 3.53. Found: C, 57.12; H, 3.54.

1,21,23,25-Tetrakis(4-cyanophenyl)-7,11,15,28-tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxin (20) was isolated after flash chromatography (SiO_2, $CHCl_3$, R_f = 0.4) as a white solid crystallizing from the eluent: yield 1.09 g (90%); mp > 320 °C; ^{1}H NMR (250 MHz) δ 1.57 (s, 3 H), 1.67 (s, 6 H), 1.76 (s, 3 H), 4.0−4.3 (m, 4 H), 4.63 (s, 2 H), 5.26 (d, $^2J_{AB}$ = 6.2 Hz, 2 H), 5.62 (d, $^2J_{AB}$ = 6.3 Hz, 2 H), 5.62 (s, 2 H), 6.02 (s, 1 H), 6.18 (s, 2 H), 6.78 (s, 2 H), 6.98 (d, $^2J_{AB}$ = 7.9 Hz, 4 H), 7.11 (d, $^2J_{AB}$ = 8.0 Hz, 4 H), 7.28 (d, $^2J_{AB}$ = 7.9 Hz, 4 H), 7.36 (d, $^2J_{AB}$ = 8.0 Hz, 4 H); ^{13}C NMR δ 155.6, 154.9, 154.0, 153.3, 146.2, 145.8, 137.8, 136.4, 135.4, 135.1, 131.7, 129.9, 128.0, 126.5, 119.2, 118.5, 110.2, 109.8, 98.5, 97.8, 60.4, 21.0, 14.2; FAB MS *m/z* 997.4 ([M + H]$^+$, calcd 997.3). Anal. Calcd for $C_{64}H_{44}N_4O_8$·1.0$CHCl_3$: C, 73.31; H, 4.24; N, 5.30. Found: C, 73.12; H, 4.35; N, 5.06.

7,11,15,28-Tetramethyl-1,21,23,25-tetrakis(4-nitrophenyl)-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxin (21) was isolated after flash chromatography (SiO_2, EtOAc, R_f = 0.7) as an orange solid: yield 0.46 g (42%); mp > 320 °C; ^{1}H NMR [300 MHz, $CDCl_3$/$(CD_3)_2$SO] δ 2.01 (s, 3 H), 2.04 (s, 6 H), 2.06 (s, 3 H), 4.41 (d, $^2J_{AB}$ = 5.8 Hz, 2 H), 4.43 (d, $^2J_{AB}$ = 5.6 Hz, 2 H), 5.18 (s, 1 H), 5.59 (s, 2 H), 6.03 (d, $^2J_{AB}$ = 5.8 Hz, 2 H), 6.05 (d, $^2J_{AB}$ = 5.6 Hz, 2 H), 6.38 (br s, 2 H), 6.42 (s, 1 H), 7.01 (br s, 2 H), 7.34 (m, 4 H), 7.58 (m, 4 H), 8.08 (m, 4 H), 8.27 (m, 4 H); FAB MS *m/z* 1076.1 (M^+, calcd 1076.3). Anal. Calcd for $C_{60}H_{44}N_4O_{16}$·2.5H_2O: C, 64.34; H, 4.12; N, 4.98. Found: C, 64.37; H, 4.48; N, 4.75.

7,11,15,28-Tetramethyl-1,21,23,25-tetrakis(3-nitrophenyl)-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxin (22) was isolated after flash chromatography (SiO_2, EtOAc, R_f = 0.7) as an orange solid: yield 0.31 g (29%); mp > 320 °C; ^{1}H NMR (400 MHz) δ 1.92 (s, 3 H), 2.01 (s, 6 H), 2.10 (s, 3 H), 4.37 (d, $^2J_{AB}$ = 5.8 Hz, 2 H), 4.42 (d, $^2J_{AB}$ = 6.2 Hz, 2 H), 4.99 (s, 2 H) 5.59 (d, $^2J_{AB}$ = 5.8 Hz, 2 H), 6.01 (d, $^2J_{AB}$ = 6.2 Hz, 2 H), 6.58 (s, 2 H), 6.87 (s, 1 H), 6.92 (s, 1 H), 6.95 (s, 2 H), 7.20−7.42 (m, 10 H), 7.80 (d, $^2J_{AB}$ = 8.9 Hz, 1 H), 8.03 (d, $^2J_{AB}$ = 8.8 Hz, 1 H), 8.05 (s, 2 H), 8.33 (s, 2 H); FAB MS *m/z* 1075.9 (M^-, calcd 1076.3). Anal. Calcd for $C_{60}H_{44}N_4O_{16}$·2.5H_2O: C, 64.34; H, 4.12; N, 4.98. Found: C, 64.37; H, 4.48; N, 4.75.

7,11,15,28-Tetramethyl-1,21,23,25-tetrakis(3-trifluoroacetamidophenyl)- 2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxin (24). Cavitand **22** (1.0 g, 0.93 mmol) and Raney nickel (cat. amount in H_2O) were suspended in a mixture of EtOH (20 mL) and acetic acid (1 mL). Hydrazine monohydrate (5 mL, large excess) was added, and the mixture was refluxed for 24 h. Filtration and evaporation of the solvent yielded the crude tetraamine **23** which, for purification reasons, was directly converted to the tetratrifluoroacetamide by dissolving it in CH_2Cl_2 (20 mL) and pyridine (5 mL) and adding trifluoroacetic anhydride (2 mL, large excess). The reaction mixture was stirred at room temperature for 24 h, and the solvent was removed. Chromatography (SiO_2, EtOAc/CH_2Cl_2/Et_3N = 10:5:1, R_f = 0.8) gave cavitand **24** as a white solid: yield 0.74 g (52%); mp > 320 °C; ^{1}H NMR (400 MHz; mixture of rotamers) δ 1.92 (s, 3 H), 1.95 (s, 6 H), 1.98 (s, 3 H), 4.36 (d, $^2J_{AB}$ = 7.1 Hz, 2 H), 4.40 (d, $^2J_{AB}$ = 6.8 Hz, 2 H), 4.96 (s, 1 H), 5.61 (d, $^2J_{AB}$ = 7.1 Hz, 2 H), 5.96 (d, $^2J_{AB}$ = 6.8 Hz, 2 H), 6.42 (s, 2 H), 6.99 (s, 1 H), 7.07 (m, 2 H), 7.14−7.18 (m, 4 H), 7.25 (m, 2 H), 7.28 (m, 2 H), 7.29 (br s, 2 H), 7.32 (m, 2 H), 7.33 (br s, 2 H), 7.63 (m, 2 H), 7.96 (m, 2 H), 8.07 (br m, 2 H), 8.12 (br m, 2 H); ^{13}C NMR δ 155.4, 154.8, 142.6, 142.1, 137.6, 137.0, 135.9, 135.7, 132.2, 129.1, 129.0, 127.7, 127.5, 126.6, 125.6, 125.2, 123.7, 119.3, 118.5, 118.3, 98.9, 98.2, 60.8, 42.9, 10.9, 10.7; FAB MS *m/z* 1341.2 ([M + H]$^+$, calcd 1341.3). Anal. Calcd for $C_{68}H_{48}F_{12}N_4O_{12}$·0.7 H_2O: C, 60.33; H, 4.15; N, 3.68. Found: C, 60.33; H, 4.50; N, 3.78.

Crystal Data for Cavitand 19. $C_{60}H_{44}Br_4O_8$·4C_7H_8: M_r = 1949.74, colorless, plate-shaped crystal (0.1 × 0.4 × 0.5 mm), orthorombic, space group *Pccn* (No. 56) with a = 20.8586(19) Å, b = 24.551(2) Å, c = 28.182(3) Å, V = 14432(2) Å^3, Z = 8, D_x = 1.455 g cm^{-3}, F(000) = 6460, μ(Mo Kα) = 22.9 cm^{-1}, 19 422 reflections measured, 13 135 independent, (0.7° < θ <

25.4°, ω scan, $T = 150$ K, Mo Kα radiation, graphite monochromator, $\lambda = 0.710\ 73$ Å) on an Enraf-Nonius CAD4 turbo diffractometer on a rotating anode. Data were corrected for Lp effects and for a linear decay of 6% of the reference reflections but not for absorption. The structure was solved by automated direct methods (SHELXS-97).[23] Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL-97)[24] for 743 parameters; no observance criterion was applied during refinement. Refinement converged at a final $wR2$ value of 0.2518, $R1 = 0.0964$ (for 5538 reflections with $F_0 > 4\sigma(F_0)$, $S = 1.003$. Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms.

Disorder models were introduced to describe the toluene solvent molecules. A final difference Fourier showed no residual density outside −0.65 and +1.18 e Å^{-3}. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre; see Notice to Authors, issue no. 1.

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Supporting Information Available: Supporting Information Available: X-ray data for cavitand **19**, including tables of atomic coordinates, bond lengths, and bond angles (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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