Water-Soluble Cavitands − Synthesis, Solubilities and Binding Properties

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Water-soluble cavitand receptors have been obtained by the introduction of ionizable groups (**5**, **21**–**28**, **39**) and neutral hydrophilic tetraethylene glycol based dendritic wedges (**19**, **20**). The synthesis of these cavitands and a study of their water solubilities and binding properties toward neutral organic guests (toluene, phenol, *p*-cresol) in water are described.

Introduction

Mimicry of biological recognition processes involves the selective binding of organic guests in aqueous environments. Water-soluble receptors based on calix[*n*]arenes[1] and resorcin[4]arene-based cavitands[2] are attractive host molecules for supramolecular chemistry in water. Water-soluble calix[4]arene-based receptors have been obtained by attachment of charged groups: some early examples contained quaternary ammonium groups,[3] sulfonates,[4] carboxylates or phosphates.[5] Calix[4]arenes have also been made soluble in water by attachment of neutral groups such as sugars[6,7] or long peptide chains,[8,9] or by functionalization with $SO_2N(C_2H_4OH)_2$[10] (silvanols) or tetraethylene glycol moieties.[11] We have used calix[4]arene−cyclodextrin combinations as fluorescent sensors[12−14] and receptors for porphyrin guests.[15] Aoyama et al. have functionalized resorcin[4]arenes with oligosugar moieties, the resulting highly hydrophilic clusters forming 1:1 complexes with a variety of hydrophobic dyes.[16]

Hong et al. studied water-soluble charged cavitands[17,18] as receptors for organic anionic or cationic guests (carboxylates or pyridinium salts). Sherman et al.[19] demonstrated how a hydroxy-footed cavitand (compare compound **17** in Scheme 3) could be made water-soluble by conversion of the hydroxy groups into phosphates and studied the binding affinities toward neutral organic guests.[20]

The binding of adenosine mono-, di-, and triphosphate (AMP, ADP, and ATP) to a tetrakis(phenylammidinium)-substituted cavitand has been described by Diederich et al.,[21] whilst the Cs^+-binding properties of an alkylaminomethyl-substituted cavitand at pH = 11 were studied by Lemaire et al.[22] We have investigated the 1:1 aqueous binding of (neutral) *p*-cresol and (anionic) *p*-toluenesulfonate by a tetrapyridinium-functionalized cavitand.[23] Two examples of water-soluble capsules based on the interconnection of two cavitands have been described. The first was a water-soluble carcerand reported by Cram et al.,[24] which was studied by other researchers shortly afterwards for its binding affinities toward neutral organic guests ($K_{ass} \approx 10^7$ M^{-1}).[25] The second was a metal-assembled cavitand dimer[26−30] able to bind neutral organic guests in water with relatively low binding constants ($K_{ass} \approx 10^2$ M^{-1}).

Because of the presence of a rigid hydrophobic cavity, the hydrophobic effect would be expected to have a large influence on the complexation behaviour of cavitands towards neutral organic guests. In this paper we describe the synthesis of novel types of water-soluble cavitands, together with studies of their water solubilities and binding properties. Water solubility was introduced by the attachment of (a) charged groups or (b) tetraethylene glycol groups or tetraethylene glycol based dendrimer wedges at the lower and upper rims.

Results and Discussion

Synthesis

The tetrakis(bromomethyl)-substituted cavitands **2**[23] and **3**[31] were synthesised by literature procedures. Treatment of the known cavitand **1**[19] with a small excess of potassium phthalimide in acetonitrile gave the cavitand tetraphthalimide **4**, which was converted into the corresponding tetraamine **5** by treatment with a large excess of hydrazine monohydrate (Scheme 1).

Tetracarboxylic acid **7**[32] was obtained by treatment of tetraphthalimide **4** with aqueous K_2CO_3 to give **6**, followed by acidification of the reaction mixture. Usually, strongly basic (pH > 12) reaction conditions are required for the hydrolysis of a phthalimide.[33] In this specific case, neighbouring group participation by the lower rim primary alco-

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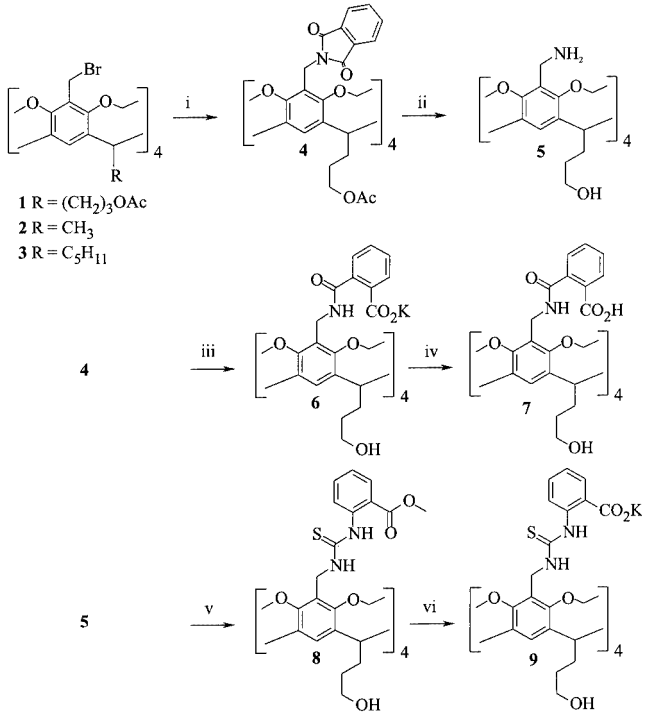


Scheme 1. Reagents and conditions: (i) KPhth, CH_3CN, reflux; (ii) hydrazine, EtOH, reflux, HCl; (iii) K_2CO_3, H_2O, room temp.; (iv) HCl, H_2O, room temp.; (v) 2-isothiocyanatobenzoate, MeOH, room temp.; (vi) KOH, H_2O, room temp.

hols[34] formed upon removal of the acetyl protective groups probably enabled the hydrolysis of the phthalimide moieties in **4** under such mild basic conditions.[35] Treatment of tetraamine **5** with methyl 2-isothiocyanatobenzoate gave cavitand **8**, which upon basic ester hydrolysis afforded the corresponding water-soluble tetracarboxylate potassium salt **9** (Scheme 1).

One route to neutral water-soluble cavitands is by attachment of tetraethylene glycol containing moieties both at the upper and the lower rims of (for example) cavitand **5**. For that purpose, the wedge **16** was synthesised (Scheme 2) by a divergent growth strategy.[36,37]

Reduction of the known tris(tetraethylene glycol)-functionalized methyl benzoate **10**[38] with $LiAlH_4$ in dry THF afforded the corresponding benzyl alcohol **12**, which was subsequently treated with $SOCl_2$ in CH_2Cl_2 to give benzyl chloride **13**. Conversion of **13** to benzylamine **14** was accomplished by treatment[39] with 1,1,3,3-tetramethyldisilazane and subsequent deprotection of the amino group with aqueous ammonia. Benzylation of the OH groups of methyl 3,4,5-trihydroxybenzoate with benzyl chloride **13** gave **15**, which upon saponification afforded carboxylic acid **16**.

Attachment of four tetraethylene glycol groups at the lower rim of cavitand **17** by treatment with tosyl tetraethylene glycol monomethyl ether in the presence of NaH in DMF gave the neutral water-soluble cavitand **18** in 72% yield (Scheme 3).[40] Coupling of the dendritic wedges **11**[38] and **16** to the upper rim of tetrakis(aminomethyl)tetrakis(3-hydroxypropyl) cavitand **5** by a standard EDC coupling procedure gave the neutral water-soluble cavitands **19** and **20**, respectively (Scheme 2).[41]

An excess (10 equiv.) of either **11** or **16** was present in each coupling reaction, and four amide bonds were obtained. In the coupling reaction with **16**, one additional ester was formed at the lower rim. Consequently, the structure of the neutral water-soluble cavitand **19** contained four G-1 substituents, while cavitand **20** had five G-2 substituents [M_w = 12276.4 (Maldi-TOF MS)].[42] Removal of excess wedge **11** from the corresponding reaction mixture was accomplished by dialysis. The dendrimer-substituted cavitands **19** and **20** dissolved in nearly all solvents, ranging in polarities from water to toluene. This property allowed for a very easy removal of excess wedge **16** from the reaction mixture, as the G-2 dendrimer **16** was insoluble in toluene. After dialysis, pure cavitand−dendrimer **20** was obtained.

Cavitand tetraamines **21**−**33** were prepared in nearly quantitative yields by solvolysis of bromomethyl cavitands **1**−**3** variously in *m*-xylidenediamine, 3-aminopropanol, ethylamine, *n*-propylamine, diethylamine, 1,4-phenylenediamine, or benzylamine and subsequent evaporation of the excess of amine (Scheme 4). After protonation of **21**−**33** by addition of HCl, the corresponding ammonium salts were water-soluble.

In a similar way, tetrapyridinium salts **34**−**36** were synthesised by solvolysis of cavitands **1**−**3** in pyridine. Tetrapyrazinium cavitands **37** and **38** were obtained in quantitative yields by solvolysis of **1** and **2** in pyrazine at 100 °C. The acetyl groups in **33** and **34** were removed by treatment with K_2CO_3 in MeOH, and purification by a standard dialysis procedure gave 3-hydroxypropyl-footed cavitands (**39** and **40**). Removal of the acetyl groups in **38** by this procedure gave a red and insoluble product.

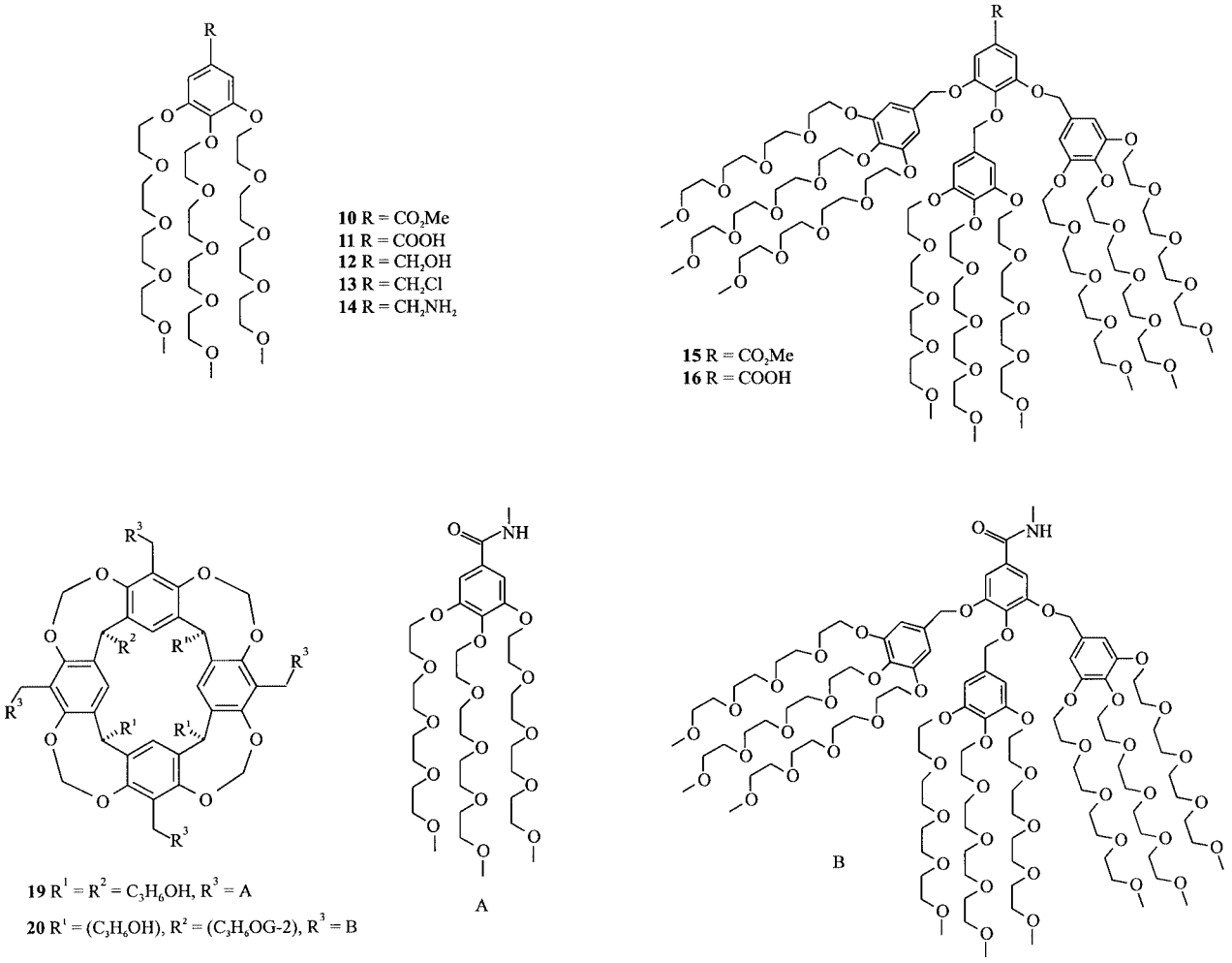
Potentiometry

For studies of the binding between neutral guests and cavitand tetra- or octaamines and tetracarboxylates in water, only one (*de*)protonated cavitand form should preferably be present. Potentiometry showed that the four deprotonations of the cavitand tetracarboxylic acid **7** took place in the region between pH = 6.4 and 8.3. Separate pK_a values could not be determined, but at pH ≥ 9 the cavitand carboxylates **7** and **9** were present as tetraanions. Binding studies were therefore conducted in D_2O at pD ≥ 9.

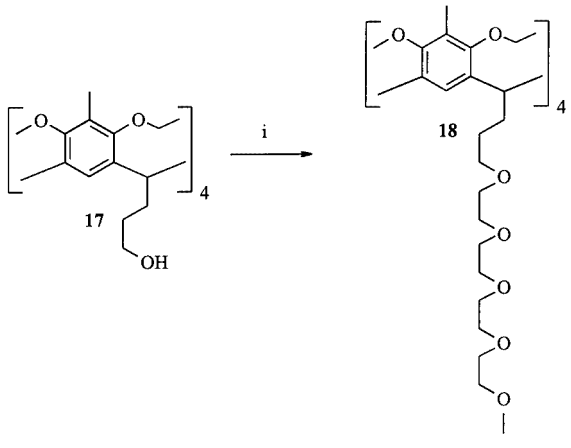
The last protonations of cavitand tetraamines **5**, **23**−**31**, **33**, and **39** took place between pH = 4.9 and 5.4 and for the octaamines **21**, **22**, and **32** between pH = 4.4 and 5.0. The first protonations of tetraamines **5**, **21**−**33**, and **39** took place in a pH range between 6.9 and 7.4, coinciding with the second protonation. Binding studies by ^{1}H NMR titration were therefore conducted at pD ≤ 3.0 in D_2O.

Solubilities of Cavitands in Water

The results of a study of the water solubilities of cavitands **5**, **7**, **9**, and **18**−**40** are summarized in Table 1. There are three separate groups of cavitands (I, II, III). The first group (I) (**18**−**20**) contains the neutral cavitands, soluble in



Scheme 2

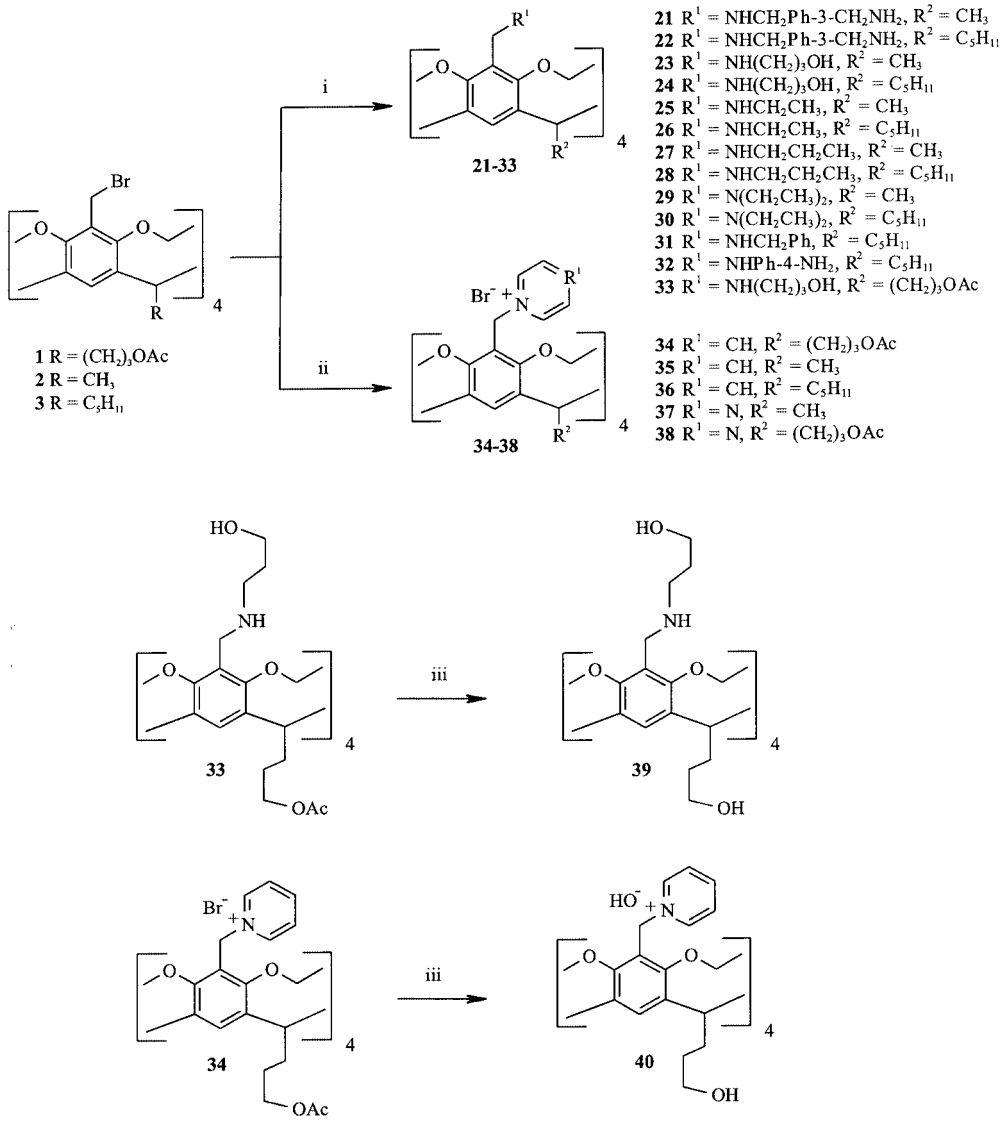


Scheme 3. Reagents and conditions: (i) tosyl tetraethylene glycol monomethyl ether, NaH, DMF, room temp.

water due to tetraethylene glycol residues. The second group (II) (**22**, **24**, **26**, **28**, **30**−**32**, **36**) comprises the charged cavitands with lower-rim pentyl groups, the third group (III) (**5**, **21**, **23**, **25**, **27**, **29**, **33**−**35**, **37**−**40**) charged cavitands with lower-rim methyl or 3-hydroxypropyl substituents.

Comparison of three neutral water-soluble cavitands (group I) shows that water solubility was strongly enhanced by increasing numbers of tetraethylene glycol chains present in the molecule: going from the four in **18** ($< 1{\cdot}10^{-3}$ mol·L^{-1}) to the twelve in **19** ($35{\cdot}10^{-3}$ mol·L^{-1}) and the 45 in **20** ($221{\cdot}10^{-3}$ mol·L^{-1}).[43] The water solubility of **20**, of 0.2 M, was extremely high in comparison to those of many other systems, both in this study and the literature. The effect of the temperature on the water solubilities of **18**−**20** was the reverse of that of the charged cavitands, as a result of the desolvation of tetraethylene glycol chains at elevated temperatures ($T\Delta S_{solv}$). Cavitands **18**−**20** were insoluble in water above ca. 75 °C.

Table 1 shows that the highest water solubilities were observed for cavitands of group II. These cavitands, with hydrophobic pentyl groups at their lower rims, were of amphiphilic character. From ^{1}H NMR dilution experiments (D_2O; pD = 3−4) and ITC microcalorimetry (H_2O), it followed that they each had a critical aggregation concentration (CAC) typically between 6 and 10 mM. In all cases except for cavitand **31**, water solubilities of $> 300{\cdot}10^{-3}$ mol·L^{-1} were therefore observed. The benzyl ammonium substituted cavitand **31** very probably did not have the am-



Scheme 4. Reagents and conditions: (i) amine, room temp.; (ii) pyridine or pyrazine room temp.; (iii) K_2CO_3, H_2O

Table 1. Water solubilities at 25.0 °C

Compd.	pH	[10^{-3} mol·L^{-1}]	Compd.	pH	[10^{-3} mol·L^{-1}]	Compd.	pH	[10^{-3} mol·L^{-1}]
5	3.0	> 300	**24**	3.0	> 300	**33**	3.0	209
7	8.9	62	**25**	3.0	88	**34**	7.0	12
9	8.9	87	**26**	3.0	> 300	**35**	8.9	19[a]
18	7.1	< 1	**27**	3.0	81	**36**	7.0	53[b]
19	7.1	35	**28**	3.0	> 300	**37**	7.0	23
20	7.1	221	**29**	3.0	> 300	**38**	7.0	28
21	3.0	203	**30**	3.0	> 300	**39**	3.0	250
22	3.0	> 300	**31**	3.0	< 1	**40**	7.0	2
23	3.0	102	**32**	3.0	> 300			

[a] At pH = 7.0 the solubility was 16 mM (ref.[23]). [b] Used as a reference compound for water-solubility determinations; the solubility of the cavitand was determined by conductimetry at 20 °C (ref.[23]).

phiphilic character needed for aggregate formation in aqueous solution, the upper-rim polarity of this cavitand tetracation simply being too low for a significant solubility in water. We have previously reported the solubilities in water of three charged cavitands, aggregate formation by one of them having been proved by Transmission Electron Microscopy.[23,44] Aggregate formation has also been observed by the groups of Shinkai[45] and Tanaka[46] for calix[4]arenes

and resorcin[4]arenes, respectively, containing long hydrophobic substituents.

In methyl- and 3-hydroxypropyl-substituted cavitands (group III), the tendencies towards amphiphilic aggregation were absent[43] and substantially lower water solubilities, in the mM range, were measured. Comparison within group III between the water solubilities of methyl- and 3-hydroxypropyl-substituted cavitands shows that 3-hydroxypropyl-footed cavitand **39** had a higher water solubility ($250 \cdot 10^{-3}$ mol·L^{-1}) than the corresponding methyl-footed cavitand **23** ($102 \cdot 10^{-3}$ mol·L^{-1}). In the upper rim pyridinium group case, the methyl-footed cavitand **35** had a higher solubility than its 3-hydroxypropyl-footed analogue **40**.

Binding Studies

The binding of neutral hydrophobic guests (*p*-cresol, phenol, and benzene) by the water-soluble cavitands **5**, **19**−**28**, and **39** was studied by ^{1}H NMR titration[47,48] and ROESY NMR spectroscopy.[49] Stock solutions of *p*-cresol, phenol, or benzene[50] in D_2O were added to **5**, **19**−**28**, or **39** in D_2O. Subsequently, the complexation-induced chemical shifts in the ^{1}H NMR spectrum were plotted against the cavitand concentration and fitted to a simple 1:1 binding model by the least-squares method, giving the corresponding K_{ass} value for the host-guest system. This is illustrated in Figure 1 (a) for the complexation of cavitand **23** with *p*-cresol. The corresponding Job's plots [Figure 1 (b)] show maxima at 0.5 equiv. of guest, indicating 1:1 stoichiometry. The markers used in this study were the cavitand ArH atoms, the methylenedioxy bridges and the $ArCH_2N$ signals (and the $ArCH_3$ signal of the guest in the case of the binding of *p*-cresol). In most cases, more than one marker was used for the determination of the K_{ass}.

Figure 2 shows the effects of the addition of 4.0 equiv. of *p*-cresol to a solution of tetrakis(aminomethyl)tetrakis(3-hydroxypropyl) cavitand **5** (1.0 mM, pD = 2.9) in D_2O. The binding constant for *p*-cresol ($K_{ass} = 7.8 \cdot 10^2$ M^{-1}) was derived from the signal of the Ar-H atom.

The binding constants (Table 2) show that *p*-cresol typically bound more strongly than phenol and benzene to cavitands **5**, **19**−**28**, and **39**. This can reasonably be attributed to a good fit of the methyl moiety inside the hydrophobic cavitand cavity.[51]

The binding constants of the neutral water-soluble cavitands **19** and **20** (group I) and of the charged water-soluble cavitands **5**, **21**−**28**, and **39** (group II) are dealt with separately because their cavities differ strongly in chemical structure and physical properties.

Table 2 shows that the strongest complexation was observed for neutral water-soluble cavitands (group I), in particular *p*-cresol ($1.0 \cdot 10^4 - 1.7 \cdot 10^4$ M^{-1}), which might be due to the extra shielding caused by the dendritic wedges. A small but significant increase in binding strengths is found when the number of tetraethylene glycol based dendrimer wedges is increased (**19** vs. **20**). The cationic cavitands (group II) bound neutral guests more weakly in D_2O ($0.1 \cdot 10^3 - 2.9 \cdot 10^3$ M^{-1}). Within this group of cavitands, the

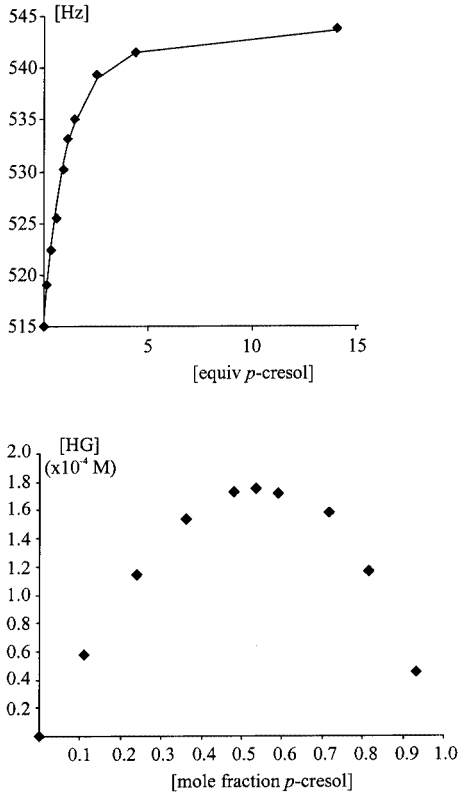


Figure 1. (a) ^{1}H NMR titration (D_2O) curve for the complexation-induced shifts of the Ar-Me group, and (b) Job's plot of cavitand **23** binding *p*-cresol ($K_{ass} = 1.8 \cdot 10^3$ M^{-1})

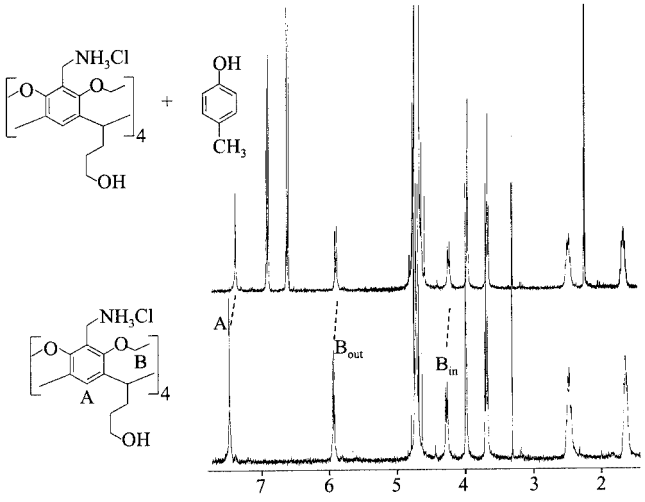


Figure 2. Upfield chemical shifts (ppm) for signals belonging to the ArH (A) and methylenedioxy bridge hydrogen atoms (B) in the *p*-cresol complex (D_2O, pD < 3.0, 2.0 mM) of cavitand **5**

binding of *p*-cresol increased with increasing size of the alkylammonium substituent.

In a ROESY NMR experiment with cavitand **27** in D_2O ($15.0 \cdot 10^{-3}$ mol·L^{-1}, pD = 2.9, 100% complex) and 4.4 equiv. of *p*-cresol, weak contacts between the Ar-H hydrogen atoms of *p*-cresol and the *n*-propylammoniummethyl substituents were observed.[52] A similar ROESY NMR ex-

Table 2. Binding constants determined by ^{1}H NMR titrations

Cavitand[a]	K_{ass} [*p*-cresol]	K_{ass} [phenol]	K_{ass}[b][benzene]
19	10.0	8.8	2.7*
20	17.0	10.2	6.9
5	0.8	0.6	0.1*
21	2.8	0.8	ND
22	2.9	0.7	ND
23	1.8	0.8	0.4
24	1.6	0.9	0.6
25	1.1	0.1	0.7
26	1.0	0.2	0.6
27	1.2	0.5	NB
28	1.3	0.7	NB
39	1.8	0.9	2.3*

[a] Binding constants (D_2O; $\times 10^3$ M^{-1}); ND = not determined because shifts were too small; NB = no binding observed. [b] An * is given when 80% complex formation could not be reached, at least 60% complex formation was observed.

periment corroborated the binding of *p*-cresol inside the cavitand cavity of **39**. Upon addition of 4.0 equiv. of *p*-cresol to a ^{1}H NMR sample of **39** in D_2O ($19.8\cdot10^{-3}$ mol·L^{-1}, pD = 3.0, 100% complex), clear contacts were observed between the inner hydrogen atoms of the cavitand methylenedioxy bridges and both Ar-H positions of *p*-cresol. The signal of the $ArCH_3$ moiety exhibited the largest shift upon binding (with respect to the other signals of *p*-cresol). *p*-Cresol was therefore most probably bound with the CH_3 pointing into the hydrophobic cavity and the OH group pointing toward the polar D_2O environment.

Conclusions

Different methods to make cavitands soluble in water have been described. They comprise the introduction of hydrophilic or charged moieties into the cavitand skeleton. The water solubility of the cavitands depended on the number and nature of the attached groups. The association constants for the binding of neutral aromatic guests by cationic and neutral water-soluble cavitands (**5**, **19**−**28**, and **39**) in D_2O ranged from $0.1\cdot10^3$ to $1.7\cdot10^4$ M^{-1}. To the best of our knowledge, this work represents the first study of the quantitative determination of the water solubilities of different types of appropriately functionalized cavitands.

Experimental Section

General Remarks: Melting points are uncorrected. EI-MS and FAB-MS spectra, with 3-nitrobenzyl alcohol as a matrix, were recorded with a Finnigan MAT 90 spectrometer. Column chromatography was performed on 60 silica gel from Merck. Reactions in organic solvents were carried out under argon, and solvents were, if necessary, purified by standard procedures prior to use. The presence of solvents in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Tetrakis(3-acetoxy-*n*-propyl)-6,12,18,24-tetrakis(bromomethyl) cavitand **1**,[19] 6,12,18,24-tetrakis(bromomethyl)-tetramethyl cavitand **2**,[23] 6,12,18,24-tetrakis(bromomethyl)-tetrapentyl cavitand **3**,[31] methyl 3,4,5-tris(methyltetraethyleneoxy)benzoate (**10**),[38] 3,4,5-tris(methyltetraethyleneoxy)benzoic acid (**11**),[38] and the tetrapyridinium cavitands **35** and **36**[19] were synthesised by literature procedures.

NMR: All spectra were recorded at ambient temperature. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Inova NMR spectrometer at 300 MHz and 75.5 MHz, respectively. ROESY[53] spectra (400 MHz) were performed with standard Varian pulse programs, with a mixing time typically consisting of a spin lock pulse of 2 kHz field strength with a duration of 30 ms. These two-dimensional experiments were collected by using two-dimensional hypercomplex data[54] and Fourier-transformed in the phase-sensitive mode after weighting with shifted square sine-bells or shifted Gaussian functions. NMR spectroscopic data were processed by standard V NMRS software packages with Unity 400 WB host computers (SUN IPX and Sparc stations). The concentrations of the samples used were typically in the 5 mM range.

MALDI-TOF Mass Spectrometry:[55] Experiments were carried out with a Perkin−Elmer/PerSeptive Biosystems Voyager-DE-RP MALDI-TOF mass spectrometer (PerSeptive Biosystems, Inc., Framingham, MA, USA) equipped with delayed extraction. A 337-nm UV nitrogen laser, producing 2-ns pulses, was used, and the mass spectra were obtained in the linear and reflectron modes. Samples were prepared by mixing 10 μL of solution (1.0−5.0 mM) of the sample with 30 μL of a solution of 3 mg/L of 2,5-dihydroxybenzoic acid (DHB); 1 μL of the solution was loaded onto a gold sample plate and transferred into the vacuum of the mass spectrometer for analysis.

Potentiometry: The concentrations of the starting cavitand solutions [CO_2-free (!) Q2 water] of tetracarboxylates, tetracarboxylic acids, tetra- and octaamines, and their corresponding ammonium salts were typically 1.00 mM. They were titrated under N_2 with CO_2-free stock solutions of aqueous HCl or NaOH (purchased from Aldrich). The tetra- and octaamines dissolved in water upon addition of the first equivalent of HCl,[56] the tetracarboxylic acids upon addition of the first equivalent of NaOH. The measuring cell (20 mL) was charged with 15.00 mL of cavitand solution and, with stirring, HCl and NaOH stock solutions were injected. The injected volumes (60−80 μL) contained 0.1 equiv. of either aqueous NaOH or aqueous HCl. The pH was monitored after each injection, and the inflection points in the pH trajectory revealed the pK_b values for the secondary or primary amine groups and for the carboxylate groups.

Determination of Water Solubilities: Sample volumes of the (fully protonated or deprotonated) cavitands varying from 200 to 500 μL were taken from saturated aqueous solutions of the proper pH, which were thermostatted at 25.0 °C and subsequently freeze-dried. The residing cationic cavitand mass gave the cavitand water solubility per sample volume and was recalculated to mM. Residual masses of carboxylate solutions were corrected for NaOH content. After ultrasonication of emulsions of neutral water-soluble cavitands in water (Q2) for 1 h, and standing at 25.0 °C overnight, clear supernatants were obtained, 100 μL samples of which were freeze-dried. Measurements were carried out in duplicate, the error being estimated as between 5 and 7%.

Determination of Binding Constants: The concentrations of the cavitand tetra- and -octaammonium salts **5**, **21**−**30**, **32**, and **39**, the tetracarboxylates **7** and **9**, and of the neutral water-soluble cavitands **19** and **20** were between 0.2 and 5.0 μM. Stock solutions of guests in D_2O at concentrations 15−20 times those of the cavitand hosts were added until at least 60% (aiming at 80%) of complex

formation was observed. The binding constants were determined by plotting the guest-induced shifts for signals in the ^{1}H NMR spectra of the hosts against the equivalents of guests added, and also in some cases by that of the shifts observed for the signals of the guest against the equivalents of guests added. The binding constants were based on signals showing the largest guest-induced shifts. The experimental data were fitted by the least-squares method to a theoretical curve calculated with a 1:1 binding model. The experiments were carried out in triplicate with an error margin between 2 and 14%. In some cases, the experimental results showed guest-induced shifts too small for determination of a significant binding constant, and are denoted as not determined (ND). D_2O of pD $\leq$ 3.0 was prepared by addition of a concentrated DCl solution to D_2O (300 mL) until the pD was between 2.8 and 3.0. Stock solutions of cationic cavitand hosts **5**, **21**−**30**, **32**, and **39** (as their tetra-/octa-HCl salts), and also of the guests used, were made by dissolution. Stock solutions of neutral water-soluble cavitands and their guests were made by dissolution in D_2O. Tetracarboxylates were dissolved in D_2O and the pD was adjusted (if necessary) to $>$ 8.9 by addition of NaOH dissolved in D_2O.

Dialysis: Final purification of some water-soluble cavitands was accomplished by dialysis of an aqueous solution through a cellulose-based membrane with an M_w cutoff of 1000, to remove excess of low-molecular weight reagents not easily removable by standard purification. The cavitand-containing residues were dissolved in the smallest possible amount of H_2O and the solution was put into the dialysis tubing. This tubing was hung in a stirred beaker with Q_2 water (500−1000 mL). The water was refreshed twice a day for one week.

Tetrakis(3-acetoxypropyl)-tetrakis(phthalimidomethyl) Cavitand (4): A suspension of cavitand **1** (2.03 g, 1.61 mmol) and potassium phthalimide (1.81 g, 9.67 mmol) in acetonitrile (50 mL) was heated under reflux for 24 h. The reaction solvents were evaporated to dryness, and the residue was redissolved in CH_2Cl_2 (50 mL) and H_2O (200 mL). The organic layer was dried with Na_2SO_4 and concentrated to approximately 5 mL, after which the concentrate was transferred to a silica gel column (CH_2Cl_2). Separation by flash column chromatography (CH_2Cl_2/EtOAc = 1:3, R_f = 0.6) yielded **7** (1.93 g, 79%) as a white solid. M.p. $>$ 320 °C. ^{1}H NMR ($CDCl_3$): δ = 1.60−1.70 (m, 8 H, CH_2), 2.05 (s, 12 H, OAc), 2.22−2.35 (m, 8 H, CH_2), 4.13 (t, J = 6.0 Hz, 8 H, CH_2O), 4.44 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.67 (s, 8 H, $ArCH_2N$), 4.77 (t, J = 7.1 Hz, 4 H, ArCHAr), 5.80 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 7.07 (s, 4 H, ArH), 7.73−7.77 (m, 8 H, ArH), 7.82−7.86 (m, 8 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.4, 26.3, 26.5, 32.2, 35.9, 63.6, 99.1, 119.1, 121.1, 122.8, 131.5, 133.5, 137.0, 153.5, 167.4, 170.5 ppm. FAB MS: m/z = 1572.3 $[M - H]^-$, calcd. 1572.4. $C_{88}H_{76}N_4O_{24}\cdot 0.5CH_2Cl_2$ (1616.1): C 65.78, H 4.80, N 3.47; found C 65.88, H 4.95, N 3.27.

Tetrakis(aminomethyl)-tetrakis(3-hydroxypropyl) Cavitand (5): A suspension of tetraphthalimide **4** (1.00 g, 0.64 mmol) and hydrazine monohydrate (2 mL, large excess) in a mixture of EtOH (90 mL) and THF (10 mL) was heated under reflux overnight, after which HCl (32%, 3 mL) was added and refluxing was continued for 1 h. Concentrated NaOH (aq) was added dropwise to the cooled reaction mixture until pH $>$ 10, and **5** (0.54 g, 96%) was filtered off as a white solid. M.p. $>$ 320 °C. ^{1}H NMR ($CDCl_3$): δ = 1.47−1.60 (m, 8 H, CH_2), 2.26−2.40 (m, 8 H, CH_2), 3.59−3.66 (m, 16 H, $ArCH_2$, NH_2), 4.29 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.45−4.70 (m, 8 H, CH_2O), 5.91 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.67 (s, 8 H, $ArCH_2N$), 4.77 (t, J = 7.5 Hz, 4 H, ArCHAr), 5.80 (d, J_{AB} = 7.5 Hz, 4 H, OCHO), 7.29 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.4, 30.0, 33.3, 36.2, 60.7, 99.1, 120.8, 123.2, 128.0, 157.8 ppm. FAB MS: m/z = 884.4 $[M - H]^-$, calcd. 884.4. $C_{48}H_{60}N_4O_{12}\cdot 2.0HCl$ (956.4):[57] C 60.18, H 6.52, N 5.85; found C 60.55, H 6.25, N 5.85.

Cavitand Tetracarboxylic Acid 7: Cavitand tetraphthalimide **4** (1.00 g, 0.64 mmol) was suspended in MeOH (60 mL), after which $CHCl_3$ (about 30 mL) was added until the cavitand had dissolved. K_2CO_3 (1.00 g, large excess) was added. Stirring of the reaction mixture overnight at room temperature gave a suspension that was concentrated to dryness. The residue was redissolved in MeOH (50 mL), and H_2O (20 mL) was added twice, with stirring of the reaction mixture at room temperature for 24 h, to redissolve the cavitand. Evaporation of the solvent gave a mixture of tetracarboxylate **6** and K_2CO_3. Dissolution of the reaction mixture in H_2O (20 mL) and adjustment of the pH to 3.1 gave tetracarboxylic acid **7** (961 mg, 95%) as a white solid. M.p. 293−295 °C. ^{1}H NMR (**6**, D_2O, pD = 9.0): δ = 1.62 (br. s, 8 H, CH_2), 2.44 (br. s, 8 H, $ArCCH_2$), 3.72 (br. s, 8 H, CH_2O), 4.43 (s, 8 H, $ArCH_2N$), 4.46 (d, J_{AB} = 7.9 Hz, 4 H, OCHO), 6.12 (d, J_{AB} = 7.9 Hz, 4 H, OCHO), 7.29−7.40 (m, 4 H, ArH), 7.30−7.48 (m, 12 H, ArH), 7.34 (s, 4 H, ArH) ppm. ^{13}C NMR [D_2O, pD = 9.0, reference $CH_3C(O)CH_3$]: δ = 22.7, 25.4, 29.6, 33.6, 36.5, 99.8, 120.2, 123.5, 126.6, 127.5, 128.6, 129.8, 133.5, 137.5, 137.5, 153.0, 171.2, 180.7 ppm. FAB MS (**7**): m/z = 1477.9 $[M]^+$, calcd. 1477.5. $C_{80}H_{76}N_4O_{24}$ (1476.5): C 65.21, H 4.93, N 3.80; found C 65.17, H 4.85, N 3.82.

Cavitand Tetrabenzoate 8: Tetraamine **5** (202 mg, 0.23 mmol) was added to a solution of methyl 2-isothiocyanatobenzoate (620 mg, 3.21 mmol) in MeOH (5.0 mL). After the reaction mixture had been stirred for 1 h at room temperature, CH_2Cl_2 (40 mL) was added, and the product was filtered off as white solid (380 mg, 94%). M.p. 236−238 °C (dec.). ^{1}H NMR (CD_3OD): δ = 1.38−1.57 (m, 8 H, CH_2), 2.10−2.36 (m, 8 H, CH_2), 3.22 (s, 12 H, OCH_3), 3.42−3.61 (m, 8 H, CH_2), 3.39 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 4.54 (t, J = 6.8 Hz, 4 H, ArCHAr), 5.45 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 5.60 (br. s, 8 H, $ArCH_2$), 7.10−7.22 (m, 8 H, ArH), 7.17 (s, 4 H, ArH), 7.53−7.58 (m, 4 H, ArH), 7.77−7.82 (m, 4 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 26.0, 30.6, 31.1, 42.5, 60.5, 99.7, 117.0, 119.8, 123.4, 126.5, 133.3, 137.0, 152.5, 161.4, 175.3 ppm. FAB MS: m/z = 1527.7 $[M - 4\,MeOH + H]^+$, calcd. 1527.3. $C_{84}H_{88}N_8O_{20}S_4\cdot 2.0CH_2Cl_2$ (1827.8): C 60.34, H 5.15, N 6.22, S 7.34; found C 60.17, H 4.85, N 5.82, S 6.99.

Cavitand Tetracarboxylate 9: Benzoate **8** (165.8 mg, 0.10 mmol) was dissolved in water (10.00 mL, pH = 9.0, KOH) by heating to 60 °C until no solid material was observed. Freeze-drying and dissolution of the residue in D_2O (10.00 mL) gave a stock solution (10.0 mM, pD = 8.9) of cavitand tetracarboxylate **9**. ^{1}H NMR (D_2O, pD = 8.9): δ = 1.53−1.64 (m, 8 H, CH_2), 2.25−2.43 (m, 8 H, CH_2), 3.60−3.72 (m, 8 H, OCH_2), 4.37 (d, J_{AB} = 7.4 Hz, 4 H, OCHO), 4.55 (t, J = 8.4 Hz, 4 H, ArCHAr), 5.62 (d, J_{AB} = 7.5 Hz, 4 H, OCHO), 5.69 (s, 8 H, $ArCH_2N$), 7.29−7.44 (m, 12 H, ArH), 7.72−7.79 (m, 4 H, ArH), 7.86−7.92 (m, 4 H, ArH) ppm.

3,4,5-Tris(methyltetraethyleneoxy)benzyl Alcohol (12): A solution of methyl 3,4,5-tris(methyltetraethyleneoxy)benzoate (**10**) (10.00 g, 480 mmol) in THF (50 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (1.82 g, 4.80 mmol) in dry THF (100 mL). The reaction mixture was stirred at room temperature for 2 h, after which it was quenched by dropwise addition of H_2O (5 mL). The reaction solvents were evaporated to dryness and the residue was redissolved in H_2O (50 mL), after which the solution was acidified to pH = 2. Extraction with Et_2O (2 × 200 mL) and drying of the extracts with $MgSO_4$ gave **12** (9.05 g, 94%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ = 3.23 (br. s, 9 H, OCH_3), 3.52−3.90 (m, 42 H,

OCH_2), 4.15−4.22 (m, 6 H, $ArOCH_2$), 4.42 (s, 2 H, $ArCH_2O$), 6.53 (s, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 38.7, 57.1, 68.8, 69.1, 69.3, 70.0, 70.2, 70.2, 71.3, 71.5, 109.1, 132.9, 138.4, 152.0 ppm. FAB MS: *m*/*z* = 726.3 $[M + H]^+$, calcd. for $C_{33}H_{60}O_{16}$: 726.4.

3,4,5-Tris(methyltetraethyleneoxy)benzyl Chloride (13): A solution of thionyl chloride (1.34 g, 11.22 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **12** (1.00 g, 1.38 mmol) in CH_2Cl_2 (50 mL). After the reaction mixture had been stirred for 1 h, it was concentrated to dryness to give **13** (1.01 g, 100%) as a yellowish oil. ^1H NMR ($CDCl_3$): δ = 3.23 (br. s, 9 H, OCH_3), 3.53−3.88 (m, 42 H, OCH_2), 4.12−4.21 (m, 6 H, OCH_2), 4.38 (s, 2 H, $ArCH_2Cl$), 6.46 (s, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 46.0, 58.4, 68.4, 69.1, 69.9, 70.0, 70.1, 70.2, 71.4, 71.5, 107.8, 132.2, 138.0, 152.1 ppm. EI MS *m*/*z* = 744.3651 $[M]^-$, calcd. for $C_{34}H_{61}ClO_{15}$: 744.3700.

3,4,5-Tris(methyltetraethyleneoxy)benzylamine (14): A mixture of KH (35% in mineral oil, 100 mg, 0.74 mmol) and 1,1,3,3-tetramethyldisilazane in THF (10 mL) was stirred at 0 °C for 1 h, after which a solution of benzyl chloride **13** (500 mg, 0.67 mmol) in THF (5 mL) was added. After stirring for an additional 2 h at 0 °C, the reaction mixture was quenched with NH_4Cl (aq) and acidified with 0.5 N HCl (9.5 mL). The pH of the reaction mixture was adjusted to 8.0−9.0 with dilute NH_4OH, after which the reaction mixture was extracted with Et_2O (2 × 100 mL). Drying of the combined organic layers with Na_2SO_4, followed by precipitation by addition of *n*-hexane (400 mL), gave **14** (208 mg, 68%) as a white solid. M.p. 30−35 °C. ^1H NMR (D_2O): δ = 3.23 (br. s, 9 H, OCH_3), 3.40−4.10 (m, 48 H, OCH_2), 4.48 (s, 2 H, $ArCH_2$), 6.56 (s, 2 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 50.2, 58.1, 68.4, 69.3, 69.7, 70.0, 70.0, 70.2, 71.3, 71.5, 106.9, 132.5, 137.9, 152.1 ppm. FAB MS: *m*/*z* = 726.3 $[M]^+$, calcd. for $C_{34}H_{63}NO_{15}$: 726.4. $C_{34}H_{63}NO_{15}\cdot 2.0H_2O$ (761.9): C 53.60, H 8.86, N 1.84; found C 53.77, H 8.82, N 2.10.

G-2−Methyl Benzoate 15: A mixture of methyl 3,4,5-trihydroxybenzoate (89.0 mg, 0.48 mmol), 3,4,5-tris(methyltetraethyleneoxy)benzyl chloride (**13**) (1.15 g, 17.38 mmol), and K_2CO_3 (900 mg, 68.13 mmol) in DMF (75 mL) was stirred at 65 °C overnight. The reaction solvents were evaporated to dryness, and the residue was taken up in a mixture of CH_2Cl_2 (100 mL) and H_2O (50 mL), after which the organic layer was washed with H_2O (2 × 400 mL) and the solvents were evaporated to dryness. Purification of the residue by the standard dialysis procedure gave **15** (0.83 g, 78%) as a yellow-brown oil. ^1H NMR (D_2O): δ = 3.36−3.42 (m, 30 H, OCH_3), 3.52−3.60 (m, 18 H, OCH_2), 3.60−3.78 (m, 72 H, OCH_2), 3.78−3.90 (m, 18 H, OCH_2), 3.92 (t, *J* = 6.0 Hz, 2 H, OCH_2), 4.07−4.22 (m, 34 H, OCH_2), 5.05 (br. s, 6 H, $ArCH_2O$), 6.59 (s, 2 H, ArH), 6.66 (s, 2 H, ArH), 6.67 (s, 2 H, ArH), 7.34 (s, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.6, 57.5, 58.4, 64.2, 68.1, 68.2, 68.7, 69.1, 69.1, 69.2, 69.9, 70.0, 70.2, 70.8, 71.3, 71.7, 74.0, 76.7, 105.8, 106.1, 106.5, 107.5, 109.0, 112.3, 121.5, 124.7, 131.5, 132.3, 133.1, 136.4, 137.0, 137.2, 137.4, 137.5, 139.8, 141.7, 151.8, 151.9, 152.0, 152.2, 152.3, 165.7 ppm. FAB MS: *m*/*z* = 2333.7 $[M + Na]^+$, calcd. for $C_{110}H_{188}NaO_{50}$: 2333.2.

G-2−Carboxylic Acid 16: An aqueous solution (50 mL) of G-2−methyl benzoate **15** (1.00 g, 4.44 mmol) at pH = 10.24 was heated under reflux for 72 h, after which the pH was adjusted to 7.0 by addition of dilute HCl (aq). The reaction mixture was concentrated to approximately 10 mL, and purification by the standard dialysis procedure gave **16** (941 mg, 94%) as a yellow-brown oil. ^1H NMR (D_2O): δ = 3.30−3.44 (m, 27 H, OCH_3), 3.44−3.60 (m, 18 H, OCH_2), 3.60−3.68 (m, 72 H, OCH_2), 3.68−3.76 (m, 18 H, OCH_2), 3.87 (t, *J* = 5.9 Hz, 2 H, OCH_2), 4.00 (t, *J* = 6.1 Hz, 16 H, OCH_2), 4.06 (t, *J* = 6.0 Hz, 18 H, OCH_2), 4.95 (br. s, 6 H, $ArCH_2O$), 6.54 (s, 2 H, ArH), 6.56 (s, 2 H, ArH), 6.59 (s, 2 H, ArH), 7.29 (s, 2 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 58.3, 67.8, 68.0, 68.0, 68.2, 68.9, 69.1, 69.8, 69.9, 70.1, 71.3, 71.6, 71.7, 71.7, 105.6, 105.7, 106.1, 106.8, 109.4, 123.4, 131.1, 132.2, 132.9, 136.4, 136.8, 137.2, 137.4, 142.5, 151.6, 151.8, 151.9, 152.1, 170.2 ppm. Maldi-TOF MS: *m*/*z* = 2296.4 [M], 2319.4 $[M + Na]^+$, 2335.5 $[M + K]^+$, calcd. for $C_{109}H_{186}O_{50}$: 2296.6.

Tetraethylene Glycol Substituted Cavitand 18: A mixture of cavitand **17** (120 mg, 0.15 mmol), NaH (60% in mineral oil, 300 mg, large excess), and tosyl tetraethylene glycol monomethyl ether (620 mg, large excess) in DMF (10 mL) was stirred overnight. Addition of H_2O (5 mL) and concentration to dryness was followed by column chromatography of the residue (Et_2O, R_f = 0.2), giving **18** (166 mg, 72%) as a colourless oil. ^1H NMR (CD_3OD): δ = 1.61−1.68 (m, 8 H, CH_2), 1.97 (s, 12 H, $ArCH_3$), 2.27−2.41 (br. s, 8 H, OCH_2), 3.38 (s, 12 H, OCH_3), 3.53−3.65 (m, 56 H, OCH_2), 3.65−3.76 (br. s, 8 H, OCH_2), 4.26 (d, J_{AB} = 6.9 Hz, 4 H, OCHO), 4.70−4.82 (m, 4 H, ArCHAr), 5.89 (d, J_{AB} = 6.9 Hz, 4 H, OCHO), 6.75 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 19.2, 26.5, 29.2, 36.6, 52.2, 58.5, 63.1, 69.4, 70.0, 71.4, 101.2, 115.3, 127.8, 136.9, 138.3, 153.1 ppm. FAB MS: *m*/*z* = 1608.7 $[M + Na]^+$, calcd. for $C_{84}H_{128}NaO_{28}$: 1608.8.

G-1-Substituted Cavitand 19: A mixture of tetraamine **5** (27 mg, 30.5 μmol), G-1−carboxylic acid **11** (100 mg, 134 μmol), EDC (26 mg, 152 μmol), and *t*BuOH (18.0 mg, 152 μmol) in CH_2Cl_2 (30 mL) was stirred for 7 d, after which the solvents were evaporated to dryness. The residue was redissolved in H_2O (10 mL) and purified by the standard dialysis procedure to afford **19** (103 mg, 89%) as a bright yellow oil. ^1H NMR ($CDCl_3$): δ = 1.42−1.56 (m, 8 H, CH_2), 2.24−2.42 (m, 8 H, CH_2), 3.35−3.80 (m, 200 H, $ArCH_2$, OCH_2CH_2O, CH_2O, OCH_3), 3.98−4.23 (m, 24 H, $ArOCH_2$), 4.30 (br. s, 8 H, $ArCH_2N$), 4.33 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.48 [s, 8 H, $ArCH_2(O)$], 4.67 (s, 8 H, $ArCH_2N$), 4.71 (t, *J* = 7.5 Hz, 4 H, ArCHAr), 5.89 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 6.94 (br. s, 2 H, NH), 6.88 (s, 8 H, ArH), 7.24 (br. s, 2 H, NH), 7.30 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.6, 30.2, 33.7, 36.4, 57.2, 60.8, 67.7, 68.1, 68.9, 69.4, 69.6, 69.7, 69.8, 71.0, 71.7, 99.5, 105.8, 107.5, 120.0, 123.6, 128.8, 137.4, 140.1, 151.2, 151.8, 153.5, 166.8 ppm. Maldi-TOF MS: *m*/*z* = 3799.4 $[M + Na]^+$, calcd. for $C_{184}H_{292}N_4NaO_{76}$: 3799.3.

G-2-Substituted Cavitand 20: A mixture of tetraamine **5** (27 mg, 30.5 μmol), G-2−carboxylic acid **16** (620 mg, 268 μmol), EDC (26 mg, 152 μmol) and *t*BuOH (18.0 mg, 152 μmol) in CH_2Cl_2 (50 mL) was stirred for 7 d, after which the reaction solvents were evaporated to dryness. The residue was redissolved in H_2O (10 mL). Extraction with toluene (5 × 50 mL), concentration of the combined layers to dryness, and dialysis of the residue by the standard procedure gave **20** (165 mg, 44%) as a greenish oil. ^1H NMR (CD_3OD): δ = 1.36−1.58 (m, 8 H, CH_2), 2.12−2.60 (m, 16 H, CH_2O, $ArCCH_2$), 3.16−3.24 (br. s, 135 H, OCH_3), 3.20−4.20 (m, 722 H, OCHO, $ArCH_2N$, OCH_2), 4.36−4.38 (br. s, 1 H, ArCHAr), 4.44−4.54 (br. s, 3 H, ArCHAr), 4.92 (s, 4 H, $ArCH_2O$), 4.93 (s, 2 H, $ArCH_2O$), 5.00 (s, 24 H, $ArCH_2O$), 5.09−5.10 (br. s, 4 H, $ArCH_2O$), 5.19−5.22 (br. s, 6 H, $ArCH_2O$), 5.44 (m, 2 H, OCHO), 5.99 (d, J_{AB} = 6.9 Hz, 2 H, OCHO), 6.08−6.17 [m, 4 H, NHC(O)], 6.62 (s, 8 H, ArH), 6.68 (s, 2 H, ArH), 6.69 (s, 16 H, ArH), 6.80 (s, 1 H, ArH-cav), 6.85 (s, 2 H, ArH-cav), 6.96 (s, 1 H, ArH-cav), 7.16 (s, 1 H, ArH), 7.17 (s, 1 H, ArH), 7.19 (s, 1 H, ArH), 7.21 (s, 1 H, ArH), 7.39 (s, 8 H, ArH), 7.54−7.63 (br. s, 2 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 29.7, 30.0, 30.0, 34.5, 34.6, 40.4, 40.6, 40.8, 62.2, 64.7, 65.2, 65.3, 71.9, 72.1, 73.0, 73.7, 73.8, 74.0, 74.0,

74.8, 75.1, 75.2, 75.5, 75.7, 76.0, 76.4, 78.3, 80.5, 81.0, 81.1, 81.4, 83.5, 100.7, 101.1, 101.6, 110.1, 110.2, 113.3, 114.7, 121.3, 127.4, 127.8, 128.0, 133.0, 135.5, 135.9, 136.4, 138.8, 141.0, 141.2, 141.4, 145.8, 146.4, 154.9, 155.8, 155.9, 155.1, 157.0, 168.3 ppm. Maldi-TOF MS: m/z = 12361 [M + 4 Na − 3 H]$^+$ and 12378 [M + 3 Na + K − 3 H]$^+$, calcd. for [$C_{593}H_{977}N_4Na_4O_{76}$ − 3 H]$^+$: 12356 + 5 (^{13}C atoms) = 12361.

General Procedure for the Synthesis of Tetraamines 21−33 and Their HCl Salts: Samples of the appropriate tetrakis(bromomethyl)-substituted cavitands **1** (220 mg, 0.21 mmol), **2** (300 mg, 0.25 mmol) or **3** (100 mg, 0.076 mmol) were solvolysed in 4.0−5.0 mL of the appropriate amine, pyridine, or pyrazine (at 100 °C) and stirred overnight, after which the excess of amine was removed in vacuo. For analytical reasons,[58] samples of tetraamines were recrystallised from CH_2Cl_2/MeOH to give pure samples of the tetra- and octaamines. The ammonium salts used for binding studies were obtained by dissolving the tetraamines in 1 N HCl, followed by freeze-drying.

Tetrakis[({[3-(aminomethyl)phenyl]methyl}amino)methyl]-tetramethyl Cavitand 21: The general procedure yielded **21** (199 mg, 100%) as a glass-like, colourless oil. M.p. 148−150 °C. ^{1}H NMR (**24**·4.0DCl, D_2O, pD = 3.0): δ = 1.61 (d, J = 8.2 Hz, 12 H, CH_3), 3.92 (s, 8 H $ArCH_2N$), 4.04 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 4.08 (s, 8 H, cav$CNCH_2Ar$), 4.14 (s, 8 H, cavCH_2N), 4.79 (q, J = 5.9 Hz, 4 H, ArCHAr), 5.67 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 7.22−7.40 (m, 12 H, ArH), 7.24 (s, 4 H, ArH), 7.52 (s, 4 H, cavArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 30.7, 39.8, 42.2, 49.7, 98.9, 116.6, 122.4, 129.4, 129.6, 129.8, 130.8, 132.8, 138.9, 152.2 ppm. FAB MS: m/z = 1185.6 [M + H]$^+$, calcd. for $C_{72}H_{80}N_8O_8$: 1185.6.

Tetrakis[({[3-(aminomethyl)phenyl]methyl}amino)methyl]-tetrapentyl Cavitand 22: The general procedure gave **22** (343 mg, 96%) as a white solid. M.p. 140−142 °C. ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, J = 7.5 Hz, 12 H, CH_3), 1.32−1.45 (m, 24 H, CH_2), 2.14−2.21 (m, 8 H, CH_2), 3.52 (s, 8 H, $ArCH_2N$), 3.74 (s, 8 H, cav$CNCH_2Ar$), 3.87 (s, 8 H, cavCH_2N), 4.20 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 4.75 (t, J = 8.1 Hz, 4 H, ArCHAr), 5.62 (d, J_{AB} = 7.1 Hz, OCHO), 7.06 (s, 4 H, ArH), 7.16−7.25 (m, 8 H, ArH), 7.25−7.37 (m, 8 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 22.2, 27.1, 29.6, 31.5, 36.4, 42.1, 45.8, 53.0, 98.7, 118.8, 125.3, 126.3, 126.6, 128.0, 137.5, 139.9, 142.6, 153.0 ppm. FAB MS: m/z = 1409.6 [M + H]$^+$, calcd. 1409.9. $C_{88}H_{112}N_8O_8$ (1408.9): C 74.97, H 8.01, N 7.95; found C 75.05, H 7.88, N 7.81.

Tetrakis{[(3-hydroxypropyl)amino]methyl}-tetramethyl Cavitand 23: The general procedure afforded **23** (186 mg, 95%) as a yellowish oil. ^{1}H NMR (**23**·4.0DCl, D_2O, pD = 3.0): δ = 1.77−1.83 (m, 8 H, CH_2), 1.78 (d, J = 8.0 Hz, 12 H, CH_3), 2.95−3.00 (m, 8 H, OCH_2), 3.55−3.60 (m, 8 H, CH_2N), 3.96 (s, 8 H, $ArCH_2N$), 4.18 (d, J_{AB} = 6.9 Hz, 4 H, OCHO), 4.86 (q, J = 6.0 Hz, ArCHAr), 5.94 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 7.64 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 26.9, 30.8, 40.2, 44.5, 58.5, 99.2, 116.7, 122.4, 139.1, 152.5 ppm. FAB MS: m/z = 941.4 [M + H]$^+$, calcd. for $C_{52}H_{69}N_4O_{12}$: 941.4.

Tetrakis{[(3-hydroxypropyl)amino]methyl}-tetrapentyl Cavitand 24: The general procedure yielded **24** (298 mg, 100%) as a white solid. M.p. 199−201 °C. ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.4 Hz, 12 H, CH_3), 1.40−1.48 (m, 24 H, CH_2), 1.52−1.81 (m, 8 H, CH_2), 2.14−2.21 (m, 8 H, CH_2), 2.65−2.72 (m, 8 H, CH_2O), 3.59 (s, 8 H, $ArCH_2N$), 3.66−3.79 (m, 8 H, NCH_2), 4.20 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 4.67 (t, J = 6.4 Hz, 4 H, ArCHAr), 5.80 (d, J_{AB} = 7.1 Hz, OCHO), 7.09 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 27.6, 30.5, 32.0, 37.0, 43.0, 49.3, 64.0, 99.8, 119.5, 125.4, 138.0, 153.6 ppm. FAB MS: m/z = 1165.7 [M + H]$^+$, calcd. 1165.8. $C_{68}H_{100}N_4O_{12}$·0.8CH_2Cl_2 (1233.5): C 66.99, H 8.30, N 4.54; found C 67.06, H 8.31, N 4.26.

Tetrakis[(ethylamino)methyl]-tetrapentyl Cavitand 25: The general procedure gave **25** (170 mg, 99%) as a white solid. M.p. 209−211 °C. ^{1}H NMR (**25**·4.0DCl, D_2O, pD = 3.0): δ = 1.11 (t, J = 7.3 Hz, 12 H, CH_3), 1.81 (d, J = 7.2 Hz, 12 H, CH_3), 2.63 (q, J = 7.0 Hz, 8 H, NCH_2), 3.85 (s, 8 H, $ArCH_2N$), 4.30 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 4.99 (q, J = 6.1 Hz, 4 H, ArCHAr), 5.95 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 7.48 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 16.7, 33.1, 43.1, 43.8, 101.0, 121.8, 125.3, 140.3, 154.8 ppm. FAB MS: m/z = 821.4 [M + H]$^+$, calcd. 821.4. $C_{48}H_{60}N_4O_8$·1.0HBr·0.6H_2O (912.8):[57] C 63.16, H 6.87, N 6.14; found C 63.14, H 6.85, N 5.77.

Tetrakis[(ethylamino)methyl]-tetrapentyl Cavitand 26: The general procedure afforded **26** (260 mg, 98%) as a white solid. M.p. 198−200 °C. ^{1}H NMR ($CDCl_3$): δ = 0.81 (t, J = 6.7 Hz, 12 H, CH_3), 1.00 (t, J = 7.1 Hz, 12 H, $NCCH_3$), 1.13−1.36 (m, 24 H, CH_2), 2.05−2.15 (m, 8 H, CH_2), 2.55 (q, J = 7.0 Hz, 8 H, NCH_2), 3.49 (s, 8 H, $ArCH_2N$), 4.26 (d, J_{AB} = 6.9 Hz, 4 H, OCHO), 4.67 (t, J = 8.0 Hz, 4 H, ArCHAr), 5.80 (d, J_{AB} = 6.8 Hz, OCHO), 6.98 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 15.0, 22.7, 27.6, 30.1, 32.0, 36.9, 42.7, 43.5, 99.3, 119.4, 125.9, 138.0, 153.5 ppm. FAB MS: m/z = 1045.7 [M + H]$^+$, calcd. 1045.7. $C_{64}H_{92}N_4O_8$·0.3CH_2Cl_2 (1070.9): C 72.12, H 8.72, N 5.23; found C 72.14, H 8.49, N 4.94.

Tetrakis[(propylamino)methyl]-tetramethyl Cavitand 27: The standard procedure yielded **27** (180 mg, 99%) as a white solid. M.p. 122−125 °C. ^{1}H NMR (**27**·4.0DCl, D_2O, pD = 3.0): δ = 0.91 (t, J = 7.3 Hz, 12 H, CH_3), 1.48−1.60 (m, 8 H, CH_2), 1.72 (d, J = 7.3 Hz, 12 H, $ArCCH_3$), 2.80 (t, J = 7.6 Hz, 8 H, CH_2N), 4.14 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 4.85 (q, J = 7.3 Hz, 4 H, ArCHAr), 5.95 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 7.62 (s, 4 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 12.0, 16.7, 32.8, 43.3, 51.4, 71.6, 101.1, 121.8, 125.4, 140.4, 154.8 ppm. FAB MS: m/z = 877.5 [M + H]$^+$, calcd. 877.5. $C_{52}H_{68}N_4O_8$·1.3CH_2Cl_2 (987.6): C 64.83, H 7.21, N 5.67; found C 64.75, H 7.22, N 5.39.

Tetrakis[(diethylamino)methyl]-tetramethyl Cavitand 29: The general procedure yielded **29** (194 mg, 100%) as a white solid. M.p. 95−97 °C. ^{1}H NMR (**29**·4.0DCl, D_2O, pD = 3.0): δ = 0.98 (t, J = 7.3 Hz, 24 H, CH_3), 1.70 (d, J = 7.4 Hz, 12 H, CH_3), 2.45 (q, J = 7.0 Hz, 16 H, NCH_2), 3.17 (s, 8 H, $ArCH_2N$), 4.24 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 4.98 (q, J = 8.1 Hz, 4 H, ArCHAr), 5.86 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 7.17 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.0, 16.3, 31.3, 46.3, 99.5, 119.1, 124.8, 138.9, 154.4 ppm. FAB MS: m/z = 933.7 [M + H]$^+$, calcd. 933.6. $C_{56}H_{76}N_4O_8$·1.0CH_2Cl_2 (1018.2): C 67.24, H 7.72, N 5.50; found C 67.03, H 7.57, N 5.13.

Tetrakis[(diethylamino)methyl]-tetrapentyl Cavitand 30: The general procedure afforded **30** (290 mg, 99%) as a colourless, glass-like oil. ^{1}H NMR ($CDCl_3$): δ = 0.83 (t, J = 6.7 Hz, 12 H, CH_3), 1.07 (t, J = 7.0 Hz, 24 H, $NCCH_3$), 1.12−1.39 (m, 24 H, CH_2), 2.02−2.15 (m, 8 H, CH_2), 2.50 (q, J = 7.0 Hz, 16 H, NCH_2), 3.29 (s, 8 H, $ArCH_2N$), 4.21 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 4.71 (t, J = 7.9 Hz, 4 H, ArCHAr), 5.83 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 7.04 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.9, 14.1, 22.7, 27.6, 32.0, 37.0, 42.7, 46.6, 99.7, 119.8, 124.2, 138.0, 153.8 ppm. FAB MS: m/z = 1157.7 [M + H]$^+$, calcd. for $C_{72}H_{108}N_4O_8$: 1157.8.

Tetrakis[(benzylamino)methyl]-tetrapentyl Cavitand 31: The general procedure yielded **31** (329 mg, 100%) as a white, sticky oil. ^{1}H

NMR (CD_3OD): δ = 0.82 (t, J = 6.6 Hz, 12 H, CH_3), 1.20−1.36 (m, 24 H, CH_2), 2.00−2.21 (m, 8 H, CH_2), 3.69 (br. s, 16 H, $ArCH_2NCH_2Ar$), 4.14 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.66 (t, J = 7.4 Hz, 4 H, ArCHAr), 5.76 (d, J_{AB} = 7.3 Hz, 4 H, OCHO), 7.09 (s, 4 H, ArH), 7.30 (br. s, 20 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 13.3, 22.0, 26.8, 29.1, 31.2, 36.0, 49.7, 99.8, 114.2, 121.5, 128.4, 129.0, 129.3, 129.7, 137.5, 153.3 ppm. FAB MS: m/z = 1293.6 $[M + H]^+$, calcd. for $C_{84}H_{100}N_4O_8$: 1293.8.

Tetrakis{[(*p*-aminophenyl)amino]methyl}-tetrapentyl Cavitand 32: Bromomethyl cavitand **3** (70 mg, 0.058 mmol) was solvolysed in 1,4-phenylenediamine (2.0 g) at 160 °C. The cooled mixture was dissolved in MeOH (5 mL) and stirred overnight, after which the solid material was removed by filtration. Concentration of the filtrate to dryness and dissolution of the residue in 1.0 M HCl (4 mL) was followed by dialysis. Octaamine **32** precipitated upon adjustment of the pH to > 12 with NaOH (conc.) and was filtered off. Recrystallization from $MeOH/CH_2Cl_2$ gave **32** (41 mg, 54%) as an off-white solid. M.p. > 320 °C. ^1H NMR ($CDCl_3$): δ = 0.73 (t, J = 6.8 Hz, 12 H, CH_3), 1.10−1.20 (m, 24 H, CH_2), 1.98−2.20 (m, 8 H, CH_2), 2.60−2.05 (br. s, 12 H, NH, NH_2), 3.84 (s, 8 H, $ArCH_2$), 4.21 (d, J_{AB} = 7.3 Hz, 4 H, OCHO), 4.59 (t, J = 7.6 Hz, 4 H, ArCHAr), 5.72 (d, J_{AB} = 7.3 Hz, 4 H, OCHO), 6.41 (s, 16 H, ArH), 6.92 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 27.6, 30.1, 32.0, 37.0, 39.7, 77.2, 99.8, 115.4, 115.5, 119.8, 125.5, 138.3, 153.7 ppm. FAB MS: m/z = 1296.6 $[M + H]^+$, calcd. 1296.7. $C_{80}H_{96}N_8O_8 \cdot 1.5H_2O$ (1324.7): C 72.55, H 7.52, N 8.46; found C 72.58, H 7.46, N 8.60.

Tetrakis(3-acetoxypropyl)-tetrakis{[(3-hydroxypropyl)amino]methyl} Cavitand 33: The general procedure yielded **33** (98 mg, 100%) as a yellowish, viscous oil. ^1H NMR (**33**·4.0DCl, D_2O, pD < 2): δ = 1.52−1.70 (br. s, 8 H, CH_2), 1.65−1.78 (m, 8 H, CH_2), 1.95 (s, 12 H, OAc), 2.38−2.54 (br. s, 8 H, $ArCCH_2$), 3.11 (t, J = 6.8 Hz, 8 H, OCH_2), 4.22−4.31 (m, 8 H, CH_2N), 4.03 (s, 8 H, $ArCH_2$), 4.24 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 4.60−4.80 (m, 4 H, ArCHAr), 6.00 (d, J_{AB} = 7.0 Hz, 4 H, OCHO), 7.66 (s, 4 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.0, 25.9, 27.7, 29.3, 29.8, 37.0, 37.6, 41.0, 45.4, 59.2, 61.7, 100.1, 117.8, 123.8, 138.8, 153.8, 174.4; 1284.6 ppm. FAB MS: m/z = 1285.8 $[M + H]^+$, calcd. for $C_{68}H_{92}N_4O_{20}$: 1285.6.

Tetrakis(3-acetoxypropyl)-tetrakis(pyridiniummethyl) Cavitand 34: The general procedure gave **34** (123 mg, 100%) as a white, sticky oil. ^1H NMR (D_2O): δ = 1.52−1.58 (m, 8 H, CH_2), 1.84 (s, 12 H, OAc), 2.26−2.50 (m, 8 H, CH_2), 4.01 (t, J = 5.7 Hz, 8 H, CH_2O), 4.55 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.69 (t, J = 5.1 Hz, 4 H, ArCHAr), 6.20 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 7.66 (s, 4 H, ArH), 7.94 (t, J = 7.5 Hz, 8 H, ArH), 8.44 (t, J = 7.1 Hz, 4 H, ArH), 8.76 (d, J = 5.7 Hz, 8 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 25.2, 29.8, 36.6, 54.2, 57.9, 64.3, 99.9, 119.7, 124.7, 144.0, 152.9, 172.9 ppm. FAB MS: m/z = 1625.4 $[M + Na]^+$, calcd. for $C_{76}H_{80}Br_4N_4NaO_{16}$: 1625.1.

Tetramethyl-tetrakis(pyraziniummethyl) Cavitand 37: The general procedure afforded **37** (217 mg, 100%) as a white solid. M.p. < 320 °C. ^1H NMR (D_2O): δ = 1.86 (d, J = 7.8 Hz, 12 H, CH_3), 4.75 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.94 (q, J = 7.8 Hz, 4 H, ArCHAr), 5.86 (s, 8 H, $ArCH_2N$), 6.27 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 7.91 (s, 4 H, ArH), 9.02 (br. s, 8 H, ArH), 9.36−9.47 (m, 8 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 15.1, 31.4, 55.4, 99.8, 118.4, 124.7, 136.5, 136.6, 136.7, 139.4, 150.7, 152.9 ppm. FAB MS: m/z = 1384.1 $[M]^-$ (based on the highest isotope peak), calcd. 1384.1. $C_{56}H_{80}Br_4N_8O_8 \cdot 4.0H_2O$ (1449.0): C 49.58, H 4.46, Br 23.26, N 8.26; found C 49.70, H 4.22, Br 22.84, N 7.92.

Tetrakis(3-acetoxypropyl)-tetrakis(pyraziniummethyl) Cavitand 38: The general procedure yielded **38** (125 mg, 100%) as a red, glass-like oil. ^1H NMR (D_2O): δ = 1.49−1.57 (m, 8 H, CH_2), 1.93 (s, 12 H, OAc), 2.35−2.43 (m, 8 H, CH_2), 4.03 (t, J = 6.6 Hz, 8 H, OCH_2), 4.56 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.67 (t, J = 6.6 Hz, 4 H, ArCHAr), 5.73 (s, 8 H, $ArCH_2N$), 6.20 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 7.68 (s, 4 H, ArH), 8.90 (br. s, 8 H, ArH), 9.30−9.34 (m, 8 H, ArH) ppm. ^{13}C NMR (D_2O, reference $(CH_3)_2CO$): δ = 18.3, 24.1, 34.7, 54.1, 59.3, 62.8, 98.1, 116.7, 122.6, 134.8, 136.6, 149.2, 151.5, 172.1 ppm. FAB MS: m/z = 1627.9 $[M]^-$ (based on the highest isotope peak), calcd. for $C_{72}H_{76}Br_4N_8O_{16}$: 1627.9.

Tetrakis(3-hydroxypropyl)-tetrakis{[(3-hydroxypropyl)amino]methyl} Cavitand 39: A mixture of cavitand **33** (198 mg, 0.18 mmol) and K_2CO_3 (0.53 g, large excess) in MeOH (15 mL) was heated under reflux overnight. Evaporation to dryness and dialysis by the standard procedure gave **39** (113 mg, 65%) as a sticky, orange oil. ^1H NMR (**39**·4.0DCl, D_2O, pD = 3.0): δ = 1.46−1.60 (br. s, 8 H, CH_2), 1.79−1.96 (m, 16 H, CH_2), 2.39−2.61 (br. s, 4 H, $ArCCH_2$), 3.08 (t, J = 6.2 Hz, 8 H, CH_2N), 3.54−3.70 (m, 16 H, CH_2O), 4.01 (s, 8 H, $ArCH_2N$), 4.23 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 4.86 (t, J = 6.8 Hz, 4 H, ArCHAr), 6.04 (d, J_{AB} = 7.1 Hz, 4 H, OCHO), 7.77 (s, 4 H, ArH) ppm. ^{13}C NMR (CD_3OD): δ = 27.8, 29.3, 30.0, 37.7, 59.3, 59.5, 61.9, 100.0, 117.8, 129.4, 138.8, 153.8 ppm. FAB MS: m/z = 1150.9 $[M + Na]^+$, calcd. for $C_{60}H_{84}N_4NaO_{16}$: 1150.4.

Tetrakis(3-hydroxypropyl)-tetrakis(pyridiniummethyl) Cavitand 40: A mixture of cavitand **34** (123 mg, 0.076 mmol) and K_2CO_3 (0.50 g, large excess) in MeOH (20 mL) was heated under reflux overnight. Concentration to dryness and dialysis by the standard procedure gave **40** (83 mg, 61%) as a sticky, dark red oil. ^1H NMR (D_2O): δ = 1.35−1.43 (m, 8 H, CH_2), 2.23−2.34 (m, 8 H, CH_2), 3.53 (t, J = 6.3 Hz, 8 H, CH_2O), 4.52 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 4.65 (t, J = 6.6 Hz, 4 H, ArCHAr), 5.59 (s, 8 H, $ArCH_2N$), 6.20 (d, J_{AB} = 7.2 Hz, 4 H, OCHO), 7.55 (s, 4 H, ArH), 7.93 (t, J = 6.9 Hz, 8 H, ArH), 8.43 (t, J = 7.2 Hz, 4 H, ArH), 8.75 (d, J = 5.4 Hz, 8 H, ArH) ppm. ^{13}C NMR (D_2O, reference $(CH_3)_2CO$): δ = 25.0, 28.9, 36.2, 53.9, 60.7, 99.4, 119.6, 123.2, 127.7, 138.2, 143.8, 145.5, 152.7 ppm. FAB MS: m/z = 1487.5 $[M + K]^+$ (based on the highest isotope peak), calcd. for $C_{68}H_{72}Br_4KN_4O_{12}$: 1487.7.

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[42] The reason why five G-2 substituents were introduced in the case of cavitand **20** is not clear. A possible reason might be that the excess of wedge added in this case was larger than that in the case of cavitand **19**.
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[48] Excess HCl was used to ensure the use of fully protonated cavitand hosts. The addition of buffers (salts) would be expected to interfere with the binding of organic guests by cavitand tetraammonium salts.
[49] Guest binding was predominantly entropy-driven, since the heat effects were too small for determination of association constants by ITC microcalorimetry.
[50] Unfortunately, toluene had to be excluded as a guest, since it has a moderate solubility of 5.7 mM in water; the desired saturation point of at least 80% in complex formation could not be reached.
[51] CPK-molecular models showed that the methyl group filled the cavity to a larger extent than a hydrogen atom at the same position.
[52] Both types of CH_2N moieties in cavitand **27** seem to have a contact with both types of Ar-H hydrogen atoms. Unfortunately, the signal-to-noise ratio in some parts of this spectrum is rather low and these "contacts" are in such a part.
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[56] The first pK_a could not be determined, because the tetraamine was insoluble in water.
[57] HCl or HBr content was observed in FAB MS spectra showing the molecular masses with additional masses corresponding to 1 or more equiv. of HCl or HBr. This content originated from starting materials (**1**−**3**) and/or workup procedures involving HCl.
[58] The HCl salts were very hygroscopic, and elemental analyses were therefore unsuccessful. In addition, FAB MS data of the corresponding ammonium salts were of poor quality. Samples of tetraamines were therefore analysed by elemental analysis (in cases of solids) and by FAB MS to prove the purity of these compounds.

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