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Metal-Switching and Self-Inclusion of Functional Cavitands

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Abstract: Cavitands bearing both eight (**5**) and two (**13**) metal-ligating carboxymethylphosphonate groups on their rims were synthesized by Arbuzov reaction of the corresponding bromoacetamido cavitands with trialkyl phosphites. These exist in the vase conformation in $CDCl_3$ and are stabilized by a cyclic seam of hydrogen bonds. This structure was also found in the solid state for the octabromoacetamide **4a** and diphosphonate cavitand **13** by single-crystal X-ray analysis. Cavitands **5** and **13** form caviplexes in $CDCl_3$, CD_2Cl_2, and alcohol solutions with adamantane derivatives **15a**,**b**, quinuclidine **15d**, ammonium and phosphonium salts **14**, and drugs like ibuprofen **15c**, all of which are stable on the NMR time scale at 295 K. NMR spectroscopy reveals that at 223 K octaphosphonate **5b** exists in two forms: the major C_4-symmetrical compound is filled with solvent while the minor species shows intramolecular inclusion of a dialkoxyphosphoryl group. In methanol-d_4 **5** and **13** exist in a lower symmetry vase conformation with self-inclusion of one alkyl group. Interaction of these complexes with $La(OTf)_3$ results in a change in the conformation of the cavitand from vase to kite with concomitant and quantitative release of the encapsulated guests. Two to three equivalents of the lanthanide salt per equivalent of cavitand **5a**−**d** is necessary for the complete decomplexation of the included guest. The kite and the vase conformers equilibrate slowly on the NMR time scale at 295 K. The addition of good ligands for metal cations (nitrate or CMPO calixarene **16**) shifts the equilibrium to the vase-shaped caviplex and allows quantitative control of the binding and release of the guest. The lanthanide complexes of octaphosphonates **5** in methanol-d_4 are velcraplex-like dimers held together by four metal cations.

Introduction

Cavitands are open-ended host molecules with vase-shaped cavities in which complementary guest species can be detained.[1] Cavitands of varying depths and physical propertis are readily made through covalent bridging of neighboring hydroxy groups in resorcinarene octols **1**. In the solid state, cavitands form inclusion complexes (caviplexes) with various neutral molecules.[2] In solution, such complexes are usually kinetically unstable: their open-ended, shallow cavity provides little attraction for guests and the conformational freedom of the walls makes for other shapes.[3] The functionalization of the rim of *o*-phenylene-bridged cavitands with amide groups gave a cyclic array of intramolecular hydrogen bonds, which rigidified the vase conformation and hindered the release of the guests from the cavity.[4] It was found that such "self-folded" caviplexes are stable on the NMR time scale at room temperature, but guest-binding affinities are typically low. On the basis of this structural motif, larger host systems were developed which exhibited much stronger binding either by capping the cavitand pocket[5] or through secondary interactions such as acid−base contact with the cavitand walls.[6] The kinetic stability of self-folding caviplexes is a function of solvent: those solvents that compete for hydrogen bonds destroy the complexes. The equilibrium between kite and vase conformers of quinoxaline-bridged cavitands can be mediated by trifluoroacetic acid addition, which protonated the nitrogen atoms of the cavitand walls (for examples of kite and vase conformers of cavitands, see Figure 6).[7] An alternative means for controlling the release and uptake of the guest was desirable, and this work was undertaken to provide it.

The introduction of metal-ligating carboxylmethylphosphonate groups (compounds **5**)[8] at the cavitand rim was expected

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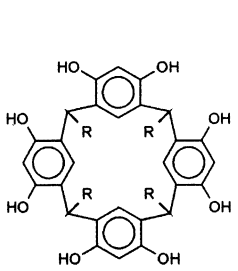
10.1021/ja0204269 CCC: $22.00

Chart 1



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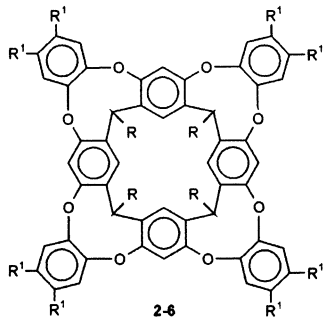
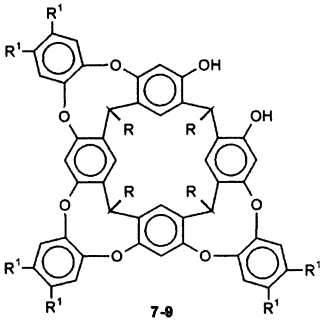


2-6

$R = C_2H_5$	**1a**
$R = CH_2CH_2CH_2OH$	**1b**
$R = C_{11}H_{23}$	**1c**

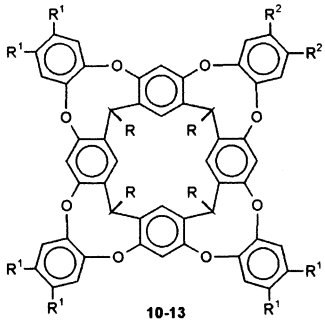
$R = C_2H_5$, $R^1 = NO_2$	**2a**
$R = CH_2CH_2CH_2OH$, $R^1 = NO_2$	**2b**
$R = C_{11}H_{23}$, $R^1 = NO_2$	**2c**
$R = C_2H_5$, $R^1 = NH_2$	**3a**
$R = CH_2CH_2CH_2OH$, $R^1 = NH_2$	**3b**
$R = C_{11}H_{23}$, $R = NH_2$	**3c**
$R = C_2H_5$, $R^1 = NHC(O)CH_2Br$	**4a**
$R = CH_2CH_2CH_2OC(O)CH_2Br$	**4b**
$R^1 = NHC(O)CH_2Br$	
$R = C_{11}H_{23}$, $R^1 = NHC(O)CH_2Br$	**4c**
$R = C_2H_5$, $R^1 = NHC(O)CH_2P(O)(OEt)_2$	**5a**
$R = CH_2CH_2CH_2OC(O)CH_2P(O)(OEt)_2$	**5b**
$R^1 = NHC(O)CH_2P(O)(OEt)_2$	
$R = C_{11}H_{23}$, $R^1 = NHC(O)CH_2P(O)(OEt)_2$	**5c**
$R = C_{11}H_{23}$, $R^1 = NHC(O)CH_2P(O)(OPr)_2$	**5d**
$R = C_{11}H_{23}$, $R^1 = NHC(O)CH_2P(O)(OH)_2$	**6**



7-9

R = Et

$R^1 = NO_2$	**7**
$R^1 = NH_2$	**8**
$R^1 = NHC(O)Et$	**9**



10-13

R = Et, $R^1 = NHC(O)Et$

$R^2 = NO_2$	**10**
$R^2 = NH_2$	**11**
$R^2 = NHC(O)CH_2Br$	**12**
$R^2 = NHC(O)CH_2P(O)(OEt)_2$	**13**

to offer cation-switched molecular containers. Both the C═O and P═O groups are involved in metal ligation. Accordingly, metal coordination is in direct competition with the cyclic array of hydrogen bonds. We report here the synthesis of self-folding cavitands **5** and **13** and show that the coordination of lanthanide cations to **5** results in the release of the guest from the cavity and the dimerization of cavitand molecules.[9] In addition, compounds **5** demonstrate an unprecedented intramolecular self-inclusion of phosphonate groups into the cavity of the octaphosphonate cavitand in solution and in the solid state.

Results and Discussion

Synthesis. Reaction of resorcinarene octols **1** with 4 equiv of 1,2-difluoro-4,5-dinitrobenzene in DMF in the presence of triethylamine readily gives octanitrocavitands **2** in 80−90% yields (Chart 1). Reduction of **2** with $SnCl_2$ in EtOH/HCl under reflux leads to the corresponding amines as their ammonium salts. Acylation with bromoacetyl chloride under Schotten−Baumann conditions ($EtOAc/H_2O$, K_2CO_3) leads to octabromooacetamides **4a**−**c**, which were purified by flash chromatography. Upon reduction of octanitrocavitand **2c**, the corresponding amine **3c** precipitates from the reaction mixture as the hydrochloride. Acylation of this material as above gives pure octabromoacetamide **4c** without need for chromatographic purification. The Arbuzov reaction of bromoacetamides **4a**−**c** with triethyl and tripropyl phosphite under reflux affords the desired phosphonates **5** in good yields. The reaction of octaphosphonate **5c** with an excess of Me_3SiBr followed by methanolysis leads to the corresponding cavitand octaphosphonic acid **6** in excellent yield.

The reaction of **1** with 3 equiv of 1,2-difluoro-4,5-dinitrobenzene (DMF, Et_3N) affords hexanitrocavitand **7** in 18% yield.[10] Reduction of cavitand **7** with $SnCl_2$ (EtOH/HCl) provides the corresponding hexamine **8**. The acylation of **8** with propionyl chloride, followed by selective cleavage of the esters with

(8) See for CMPO derivatives of calixarenes and cavitands. (a) Arnaud-Neu, F.; Böhmer, V.; Dozol, J.-F.; Grüttner, C.; Jakobi, R. A.; Kraft, D.; Mauprivez, O.; Rouquette, J.; Schwing-Weil, M.-J.; Simon, N.; Vogt, W. *J. Chem. Soc., Perkin. Trans. 2* **1996**, 1175−1182. (b) Arduini, A.; Böhmer, V.; Daelmau, L.; Desreux, J. F.; Dozol, J.-F.; Garcia Carrera, M. A.; Lambert, B.; Musigmann, C.; Pochini, A.; Shivanyuk, A.; Ugozoli, F. *Chem. Eur. J.* **2000**, *6*, 2135−2144. (c) Boerrigter, H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1997**, *62*, 7148−7155.

(9) For a preliminary communication, see: Amrhein, P.; Wash, P.; Shivanyuk, A.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 319−321.

(10) The corresponding octanitrocavitand **2a** is formed in 24% yield. Attempts to optimize the amount of formed hexanitro cavitand by varying the reaction conditions, e.g., temperature, mixing procedure, etc., did not lead to better results. For analogous synthesis, see: Lücking, U.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 8880−8889.

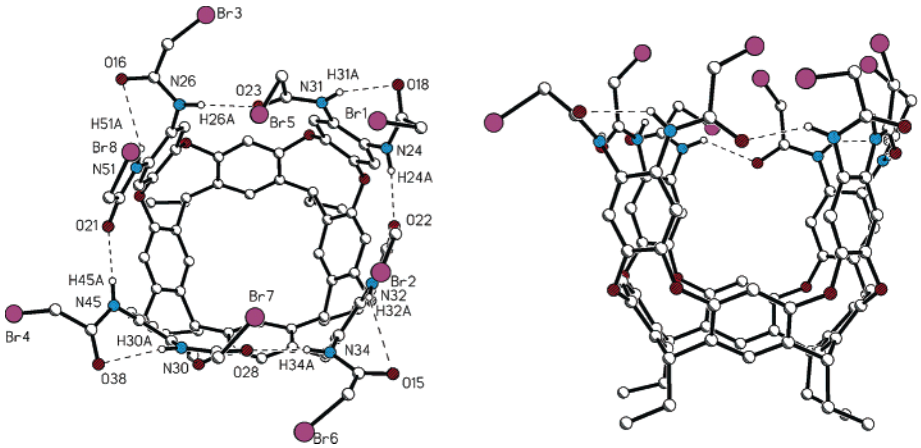


Figure 1. Single-crystal X-ray structure of **4a**. Hydrogen bonds are shown in dashed lines. Disordered solvent molecules are omitted for clarity. Selected interatomic distances between hydrogen-bonded atoms (Å): N24−O22 = 2.81(1); N26−O23 = 2.84(1); N30−O38 = 2.88(1); N31−O18 = 2.76(1); N32−O15 = 2.69(1); N34−O28 = 2.84(1); N45−O21 = 2.81(1); N51−O16 = 2.80(1).

hydrazine, affords hexaamide **9** in 60% overall yield. The two hydroxy groups in **9** were bridged with 1,2-difluoro-4,5-dinitrobenzene to give dinitrocavitand **10** in 79% yield. Reduction of **10** with $SnCl_2$ (EtOH, HCl) leads to the corresponding diamine **11**, which was acylated by bromoacetyl chloride ($EtOAc/H_2O$, K_2CO_3) to give dibromoacetamide **12**. Arbuzov reaction with triethyl phosphite transforms compound **12** into the bis-CMPO derivative **13** in 80% yield.

NMR and X-ray Crystallographic Studies. Crystal Structure of Octabromoacetamide 4a. Slow recrystallization of octabromoacetamide **4a** from a mixture of EtOAc and hexanes gives colorless transparent crystals suitable for single-crystal X-ray analysis. The molecule **4a** adopts the vase conformation in the solid state (Figure 1). Eight bromoacetamide fragments form a cyclic, chiral array of intramolecular hydrogen bonds with two bromine atoms pointing toward the cavity.[11] The crystal is a racemate containing both enantiomeric conformations related by a center of symmetry ($P\bar{1}$ space group). Electron density was found inside the cavity of **4a** corresponding to a severely disordered guest molecule, which was not identified.

Solution Characterization of Octabromoacetamides 4. The ^{1}H NMR spectrum of octabromoacetamides **4** in $CDCl_3$ contains one triplet for the methine protons of the bridges, one set of signals for the aromatic protons (three singlets in a 1:1:2 ratio), and one broad singlet corresponding to the NH protons. This pattern corresponds to the C_{4v}-symmetrical vase conformation of **4** and reflects the fast exchange between two cycloenantiomeric C_4-symmetrical arrangements of hydrogen-bonded amido groups. At 233 K this process becomes slow on the NMR time scale, and two signals are observed for the NH protons and the protons of the phenylene walls, as expected for the C_4-symmetrical arrangement. The $\Delta G^{\ddagger}$ of this process at coalescence temperature (T_c = 273 K) was calculated to be 12 kcal/mol, a value some 5 kcal/mol smaller than that for octaamide **4d**. This might be the result of an inductive effect of the bromine atoms, which decrease the carbonyl oxygens' acceptor abilities and weaken the strength of the intramolecular hydrogen bonds. Even so, octabromoacetamide **4c** forms kinetically stable complexes with adamantane and quinuclidine derivatives in $CDCl_3$ and CD_2Cl_2, similar to other self-folding cavitands.[4]

(11) For a similar structure, see: Shivanyuk, A.; Rissanen, K.; Körner, S.; Rudkevich, D. M.; Rebek, J., Jr. *Helv. Chim. Acta* **2000**, *83*, 1778−1790.

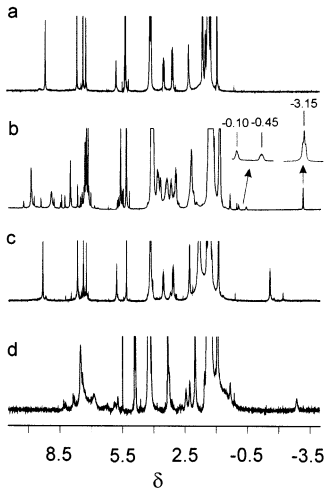
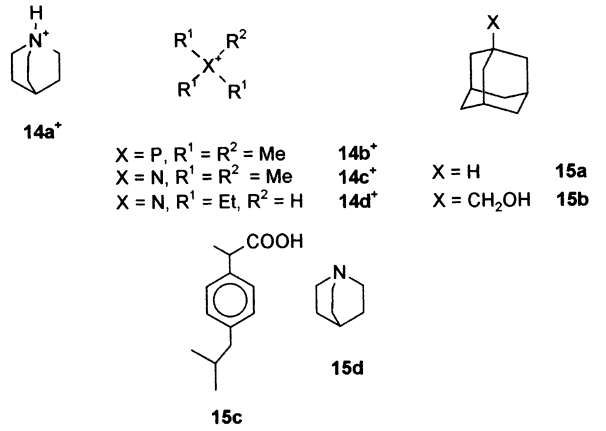


Figure 2. The ^{1}H NMR spectra of octaphosphonate **5c** (4 mM, 600 MHz): (a) at 295 K in CD_2Cl_2; (b) at 213 K in CD_2Cl_2 (the ratio of the major to minor species is 4:1); (c) in CD_2Cl_2 in the presence of 1 equiv of **14a**$^+Cl^-$; (d) in methanol-d_4 at 295 K.

Structure of Octaphosphonates 5 in Solutions. Octaphosphonates **5a**,**c**,**d** and dodecaphosphonate **5b** are readily soluble in both apolar, aprotic ($CHCl_3$, CH_2Cl_2, ArH) and protic polar solvents (alcohols). Cavitand **5b** is hydrophilic enough to be soluble in water at neutal pH. The ^{1}H NMR spectrum of **5c** measured at 295 K in CD_2Cl_2 shows one triplet for the protons of the methine bridges, two singlets for the protons of the resorcinol rings, one singlet for the protons of the *o*-phenylene bridges, and a broad resonance for the NH protons (Figure 2a). This is indicative of a time-averaged C_{4v}-symmetrical vase conformation. Four doublets correspond to the methylene protons close to the phosphoryl groups due to the diastereotopicity and vicinal coupling. The ^{31}P NMR spectrum shows one signal for the phosphorus atoms centered at 23.8 ppm. Upon cooling, the chiral C_4-symmetrical vase conformation appears and the corresponding lower symmetry NMR pattern is observed. At 213 K both the major C_4-symmetrical set and an additional minor set of sharp signals for the protons of the NH groups are observed corresponding to a C_1-symmetrical species (Figure 2b). Moreover, sharp signals are found in the upfield region of the spectrum, which were assigned by 2D ROESY to correspond to the protons of the methyl groups (triplet at −3.15

Chart 2



ppm, $\Delta\delta = -4.4$ ppm) and the methylenes (two multiplets at -0.1 and -0.45 ppm, $\Delta\delta$ of -2.4 and -2.7 ppm, respectively) of the diethoxyphosphoryl fragment. The integration suggests that an ethoxy group of one diethoxyphosphonate fragment is inside the π-basic cavity of **5c**. The fact that the NMR spectrum of **5c** does not depend on the concentration in the range 4−20 mM strongly suggests that this inclusion is *intramolecular*.[12] Analogous behavior was observed for the octapropoxyphosphonate **5d** and diphosphonate **13**. In the case of **5d** the triplet of the encapsulated propyl group emerges at -3.43 ppm ($\Delta\delta = -4.5$ ppm). The ^{1}H NMR spectrum of a 1:1 mixture of **5c** and **5d** is a superimposition of the resonances of the individual components and implies once again that the inclusion of the alkoxy group occurs in an intramolecular fashion. Similarly to simple cavitand octaamide **4d**, the octaphosphophosphonates **5** form 1:1 inclusion complexes with adamantane **15a**, 1-adamantylmethanol **15b**, and ibuprofen **15c**. These are all kinetically stable on the 600 MHz NMR time scale at room temperature in $CDCl_3$ and CD_2Cl_2. The signals of the complexes could be observed only in the presence of a large excess of the guest (20−50-fold) and reflect low binding affinities ($K_{ass.} < 10\ M^{-1}$).

Much stronger host−guest interactions occur with positively charged quinuclidinium **14a**$^+$ and tetramethylphosphonium **14b**$^+$ cations (Chart 2).[13,14] The addition of 1 equiv of quinuclidine hydrochloride to the solution of **5c** in CD_2Cl_2 leads to practically complete formation of a 1:1 inclusion complex (Figure 2c). The methylene groups of the complexed cation emerge at 0.99 (NCH_2) and -1.42 (NCH_2CH_2) ppm, shifted upfield by 4.2 and 3.3 ppm, respectively, from uncomplexed **14a**$^+$ (Figure 2c). The most upfield signal at -1.96 ppm ($\Delta\delta = -4.1$ ppm) corresponds to the methine proton of the complexed quinuclidinium cation **14a**$^+$. Again, at 213 K the NH resonance splits as the cycloenantiomerics of the C_4-symmetrical conformation emerge. No intramolecular inclusion of the alkyl groups of the phosphoryl fragments is detected in this case, likely due to efficient filling of the cavity by bulky **14a**$^+$. Weak 1:1 complex formation is also observed with tetramethylammonium bromide **14c**$^+$ and triethylammonium chloride **14d**$^+$ ($K_{ass.} < 10\ M^{-1}$). Analogous complexation behavior is also found for cavitand phosphonates **5a**,**b**,**d** and **13**.

The NMR spectrum of **5c** in methanol-d_4 (Figure 2d) and ethanol-d_6 at 295 K contains a complicated set of signals for the protons of the cavitand, while broad signals are found in the upfield window, again due to inclusion of the ethoxyphosphoryl group into the cavity of the cavitand. A 2D COSY experiment revealed that the methine protons of the bridges emerge as three broadened resonances at 5.80, 5.74, and 5.62 ppm in a 1:1:2 ratio and indicates that the vase conformation, while intact, is desymmetrized. The integration of these resonances and the upfield signal show that *only one ethyl group* of one phosphonate fragment is included into the cavity. Analogous inclusion is observed also for octaphosphonates **5a**,**d** dodecaphosphonate **5b**, and diphosphonate **13** (see also the crystal structure in Figure 3). Interestingly, no such inclusion is detected in 2-propanol-d_8, presumably because the bulkier 2-propanol molecule is a better fit than an ethyl group for the cavity. In contrast, known hydrophilic self-folding cavitands substituted with ammonium groups at the feet exist in methanol as dimers (velcraplex) in a C_{2v}-symmetrical kite conformation.[13]

Crystal Structure of Diphosphonate 13. Single-crystal X-ray analysis reveals the exact geometry of the self-inclusion of one ethoxyphosphoryl group in the cavity of the cavitand. Slow diffusion of hexanes into a solution of diphosphonate **13** in CH_2Cl_2 results in diffraction quality single crystals. In the solid state **13** adopts a vase conformation (Figure 3). Peaks of electron density were found in the cavity, corresponding to a disordered guest molecule, which, unfortunately, could not be identified. Eight carbonyl groups form a cyclic array of hydrogen bonds at the rim of the cavitand in a chiral, C_4-symmetrical manner. The structure is again centrosymmetric (space group $C2/c$), showing that the crystal is a racemate. The low-symmetry molecule **13** (C_1 symmetry) resides on a special position with 2-fold symmetry, resulting in severe disorder of the pendant amide fragments. Namely, two phosphonates and six ethyl groups of the propionamides are disordered over eight positions with occupancy factors of 0.25 and 0.375, respectively.

Remarkably, the crystal structure shows that in one of the disordered conformations one ethyl group of the diethoxyphosphoryl fragment is *intramolecularly* included into the cavity of the cavitand (Figure 3, bottom). The consistency of this result with the NMR data described above suggests that the solid state self-inclusion is a valid snapshot for a moving picture describing the solution structures, and suggests that in the crystallization process the solvents (hexanes) can compete with this intramolecular inclusion. The distance between the methyl group of the included ethyl fragment and the center of the closest aromatic ring of the cavitand is 4.2 Å, a distance in accord with a strong diamagnetic shielding effect.

Solvophobic Effects in Phosphonate Cavitands. Cavitand octaphosphonic acid **6** is not soluble in pure methanol-d_4 or $CDCl_3$ but readily dissolves in a 9:1 mixture of these solvents, probably because this mixture can solvate both the lipophilic aliphatic chains and hydrophilic dihydroxyphosphoryl groups. Compound **6** becomes soluble in aqueous media in the presence of a base (K_2CO_3). The ^{1}H and ^{31}P NMR spectra of **6** are broadened but reveal that the cavitand exists in a vase conformation. The addition of quinuclidine **15d** results in the

(12) About self-inclusion of alkyl groups in cavitand dimers, see: (a) Ma, S.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 4977−4981. (b) Renslo, A. R.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4573−4582.

(13) (a) Haino, T.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 11253−11254. (b) Haino, T.; Rudkevich, D. M.; Shivanyuk, A.; Rissanen, K.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 3797−3805.

(14) Rafai Far, A.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 2854−2855.

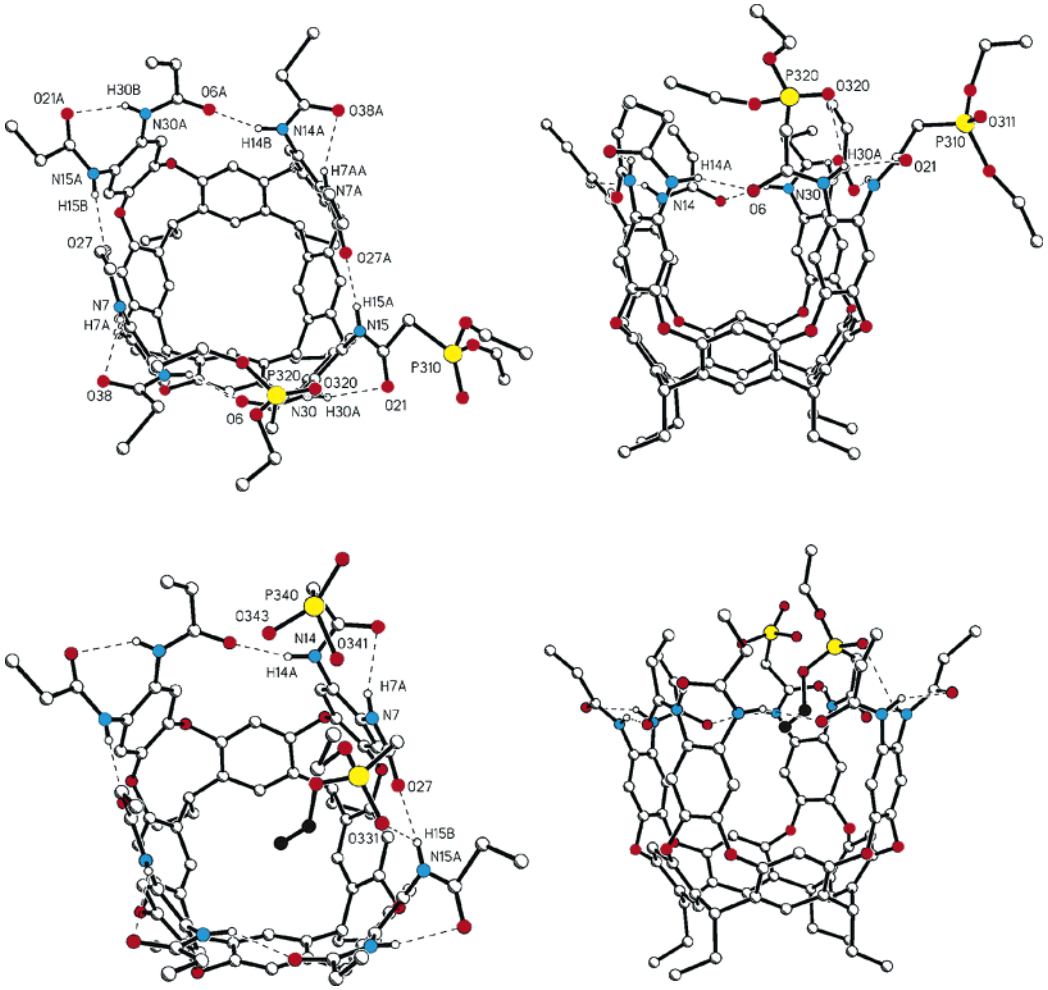


Figure 3. Single-crystal X-ray structure of the two partial occupancy conformations of hexapropionamide diphosphonate **13**. Top and side views of conformation without (top) and with (bottom) intramolecular inclusion of the ethyl group. C−H hydrogens and included guest are omitted for clarity. The strongly disordered ethyl groups of the P(340) phosphonate fragment (bottom) are not shown. Hydrogen bonds are shown in dashed lines. Carbon atoms of the included ethyl group are darkened. Selected interatomic distances (Å): O6A−N14A = 2.80(1); O38A−N7A = 2.84(1); O27A−N15 = 2.83(1); O21−N30 = 2.79(1); O320−N30 = 2.85(1); O331−N15A = 3.00(1).

formation of a kinetically stable 1:1 complex. Upon complexation the ^{31}P resonance of acid **6** shifts from 20.29 to 13.45 ppm, indicating some host−guest proton transfer.

Dodecaphosphonate **5b** exists in $CHCl_3$ and CH_2Cl_2 as a vase conformer showing typical ^{1}H NMR patterns and two ^{31}P resonances at 23.8 and 20.6 ppm in a 2:1 ratio. The ^{1}H NMR spectrum of dodecaphosphate **5b** in D_2O is broadened and contains four signals for the protons of the resorcinol rings and two singlets for the protons of the cavitand walls in accordance with a C_{2v}-symmetrical kite conformation. Accordingly, three signals are observed in the ^{31}P NMR spectrum: two for the phosphoryl groups attached to the upper rim and one for the phosphoryl groups at the feet. The kite conformation of **5b** in water is most probably stabilized through the formation of a dimer driven by solvophobic effects (for an example of this type of dimer see Figure 6). The addition of **14a**$^+$Cl$^-$ to the aqueous solution of **5b** results in immediate precipitation of a white solid. The ^{1}H NMR spectrum of this complex upon redissolving in methanol-d_4 revealed its 1:1 stoichiometry. The precipitation is likely caused by hydrophobic effects, that is, when **14a**$^+$ is added, **5b** makes a conformational change from the more polar kite to the more apolar vase conformation, resulting in a loss of solubility.

Quantitative Regulation of the Inclusion of Guests in the Cavitand through the Complexation of Lanthanide Cations by the Pendant Carbamoylmethylphosphonate Functional Groups. The addition of 1 equiv of **14a**$^+$Cl$^-$ to the solution of octaphosphonates **5** in methanol-d_4 results in a complete formation of the 1:1 inclusion complex, which is stable on the NMR time scale at 295 K. The ^{1}H NMR spectrum of the complex is sharp and contains one triplet for the methine protons of the bridges, two singlets for the protons of the resorcinol rings, and one singlet for the protons of the cavitand walls, corresponding to a C_{4v}-symmetrical vase conformation (Figure 4a). Accordingly, one sharp signal is observed in the ^{31}P NMR spectrum at 24.3 ppm. No signals are found in the ^{1}H NMR spectrum for the methylene protons closest to the phosphorus atoms. Their high acidity results in their fast exchange with solvent deuterium atoms. The methylene signals of the encapsulated cation are shifted upfield by 4.0 and 3.3 ppm, while the strongest shielding is again observed for the methine protons ($\Delta\delta = -4.0$ ppm). The stability constant of **5c**·**14a**$^+$ cannot be accurately determined from the NMR data, owing to the strong binding and broadened spectrum of free **5** in methanol-d_4. Analogous complexes are formed also with phosphonium and tetramethylammonium bromides **14b**,**c**$^+$Br$^-$ and triethylamine

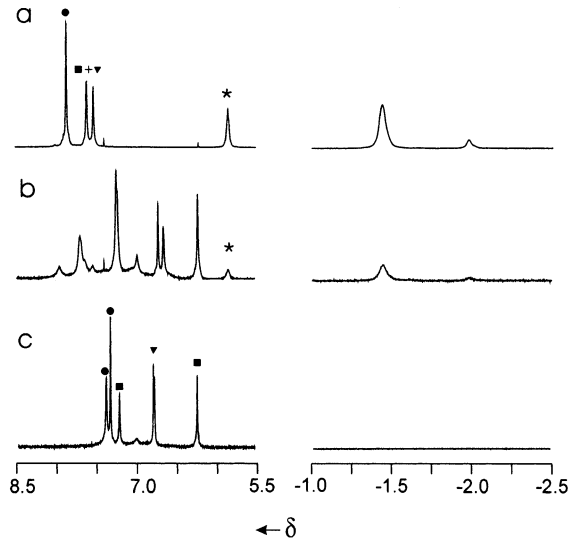


Figure 4. Upfield and downfield regions of the ^{1}H NMR spectra ([**5c**] = 2 mM, CD_3OD, 295 K, 600 MHz): (a) **5c·14**$^+$; (b) as in part a after the addition of 1 molar equiv of La(OTf)$_3$; (c) as in part a after the addition of 2 equiv of La(OTf)$_3$; (*) methine bridges; protons of the resorcinol rings (■) at 5-positions and (▼) at 2-positions; (●) the protons of the cavitand walls.

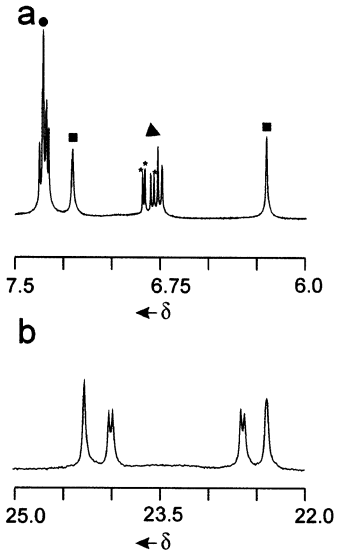


Figure 5. The ^{1}H (a) and ^{31}P (b) NMR spectra of **5c** + **5d** with 10 equiv of La(OTf)$_3$. Groups of signals are indicated. Protons of the resorcinol rings: (■) 5-positions; (▼) 2-positions; (●) protons of the cavitand walls. The signals of the heterodimer are indicated by asterisks; $CDCl_3$ (10%) was added to the solution in CD_3OD to prevent precipitation of the complex.

hydrochloride **14d**$^+$. No upfield shifts for the methyl protons of the phosphonate groups are observed in the ^{1}H NMR spectra of the inclusion complexes with the ammonium cations. The intermolecular inclusion of the bulky C−H basic guests efficiently competes with the entropically favored self-inclusion of the smaller ethoxy and propoxy groups, respectively, in the cavity of octaphosphonates **5c**,**d**. The same type of complexation is also observed for diphosphonate cavitand **13**.

The addition of 1 equiv of La(OTf)$_3$ to the solution of **5c·14a**$^+$ leads to the appearance of a new set of ^{1}H NMR signals for the cavitand (Figure 4b). This can be explained by the formation of a coordination complex between **5c** and La^{3+}, which equilibrates with the original inclusion compound slowly on the NMR time scale (verified by 2D ROESY). The addition of one more equivalent of the lanthanum salt results in complete disappearance of the original inclusion complex, as monitored by the disappearance of the resonance corresponding to encapsulated **14a**$^+$ (Figure 4d). The amount of the inclusion complexes can be easily varied simply by varying the amount of added La(OTf)$_3$. Thus metal ligation at the rim of cavitand **5c** results in quantitatively controlled release of the included cation **14a**$^+$ (Figure 4c, Figure 6 top). No changes were observed in the NMR spectrum upon further increase in the La(OTf)$_3$ concentration, suggesting that in the new complex one molecule of **5c** coordinates two lanthanum cations.

A 2D ROESY experiment revealed that **5c** exists as a C_{2v}-symmetrical kite conformer in this complex. Namely, four singlets correspond to the protons of the resorcinol rings while the protons of the cavitand walls emerge as two sharp singlets. The signal for the protons in the 5-positions of the coplanar resorcinol rings is found at 6.23 ppm, while the same protons for the parallel rings emerge at 7.60 ppm. This is indicative of cavitands in a kite conformation (Figure 6, bottom) and is caused by a shielding of the protons of the coplanar resorcinol rings by the parallel rings. The signals for the protons in the 2-positions of the resorcinol rings have a similar magnetic environment so that their chemical shifts are 6.73 and 6.76 ppm. The signal for the methine protons of the bridges is positioned at 4.3 ppm, which is characteristic of the kite conformers of deep cavitands. This probably results from a deshielding effect of the cavitand wall pointing outside of the macrocycle. Accordingly, the ^{31}P NMR spectrum of the lanthanide complexes exhibits two sharp singlets (1:1) for the phosphorus atoms. The same complexation was observed also for octaphosphonates **5a**,**d**, while in the case of dodecaphosphonate **5b** 3 equiv of La(OTf)$_3$ was necessary for complete release of the encapsulated **14a**$^+$. This requirement is likely due to the additional metal ligation by the carbamoylmethyl-diethoxyphosphoryl fragments attached to the feet of the cavitands. The ^{19}F NMR spectrum showed no induced chemical shifts for the fluorine atoms of the triflate counteranions and thus rules out the possibility of anion encapsulation. Cavitand **6** shows no complexation with La(OTf)$_3$, suggesting that the free acid prevents the formation of stable lanthanide complexes.

Surprisingly, the addition of 2−4 equiv of La(OTf)$_3$ to the solution of diphosphonate complex **13·14a**$^+$ does not cause a change in the conformation from vase to kite and does not release the included ammonium guest. Moreover, no large changes are detected in the ^{31}P and ^{1}H NMR spectra of **13·14a**$^+$ upon addition of La(OTf)$_3$, suggesting very weak, if any, metal ligation at all. These results are supported by mass spectrometry. In short, the high affinity of cavitand octaphosphonates **5a**,**c**,**d** and dodecaphosphonate **5b** for La^{3+} results from a cooperative effect between guest release, vase to kite conformational change, and metal coordination. Only in the kite conformation are all possible metal−ligand bonds formed, with a concomitant guest release. In the diphosphonate cavitand **13**, no enthalpy gain can be realized upon metal coordination to compensate for the loss of the enthalpy in breaking the seam of eight hydrogen bonds.

The following experiments proved that the La complexes of the cavitand octaphosphonates **5** have a dimeric velcrand-like structure. Mixing of complexes **5c** and **5d** in a 1:1 molar ratio leads to the ^{1}H NMR spectrum shown in Figure 5a. Two

broadened singlets correspond to the protons at the 5-positions of the resorcinol rings, and the protons in the 2-positions emerge as seven singlets in 1:1:1:1:2:1:1 ratio, while the protons of the cavitand walls show a complicated set of sharp overlapping singlets. This pattern results from the statistical formation of heterodimeric complex **5c·5d·**$4La^{3+}$ which coexists with homodimers **5c$_2$·**$4La^{3+}$ and **5d$_2$·**$4La^{3+}$. The ^{31}P NMR spectrum of the mixture (Figure 5b) reveals four signals in a 2:1:1:2 ratio, also indicating heterodimerization. Apparently, the gain in energy upon forming up to 32 new metal ligand bonds and releasing two guest molecules to form a dimer is enough to overcome the penalty in breaking 16 hydrogen bonds (8 from each monomer). However, in the case of the diphosphonate cavitand, the formation of 8 metal ligand bonds is not enough to overcome this penalty.

It was assumed that the addition of strong ligands for La^{3+} could disrupt the La complex of **5c** and reverse the formation of the vase-shaped inclusion complexes. This, indeed, takes place when bidentate nitrate anion or octadentate calix[4]arene CMPO ligand **16** (Chart 2) is added. The addition of chloride or bromide does not affect the complexation equilibrium (Figure 6).

An additional proof for the existence of the dimeric structure stemmed from the mass spectrometric study of the heterodimer experiment. The ESI-mass spectrum of this solution shows peaks at *m*/*z* 1279 and 1309 Da corresponding to [**5c·5d** + 2La − H]$^{5+}$ and [**5c·5d** + 2La + OTf]$^{5+}$. The spectrum also showed cations [**5c$_2$** + 2La + OTf − H]$^{4+}$, [**5c·5d** + 2La + 2OTf]$^{4+}$, and [**5c·5d** + 4La + 8OTf]$^{4+}$ with *m*/*z* of 1693, 1674, and 1967 Da, respectively. Similarly, the spectra of complexes between **5c** and Eu^{3+}, Dy^{3+}, Ho^{3+}, Tm^{3+}, Yb^{3+} triflates contain peaks corresponding to dimeric dications [**5c$_2$** + 2Ln + OTf − H]$^{4+}$ while no complexation occurs between **5c**,**d** and $Ce(OTf)_4$. Unfortunately, the paramagnetic nature of these cations hampered the NMR studies of the complexes in solution. The ESI-mass spectrum of a methanol solution of **13·14a**$^{+}$ + $4La(OTf)_3$ contains a main peak at 1822 Da corresponding to the 1:1 inclusion complex, and no peaks could be detected for La complex(es) of diphosphonate **13**. This is in accordance with the low affinity of **13** for $La(OTf)_3$ found in solution by NMR spectroscopy (see above).

Numerous attempts to obtain diffraction quality single crystals of the lanthanide complexes of octaphosphonates **5** were unsuccessful. Molecular modeling[15] studies suggest that four quartets of ligating arms at the edges of a velcraplex-like dimer (Figure 6) would provide four efficient binding sites for octacoordinated lanthanide cations. The arrangement of ligating arms in a binding site of the dimer is similar to that in tetra-CMPO calix[4]arene **16**, which is a strong receptor for lanthanides.[8] Cooperation of these binding sites (maximum 32 coordination bonds) would result in a high stability of the dimeric complex, while the long distances between the binding sites should considerably decrease the electrostatic repulsion between the complexed cations.

Conclusion and Outlook

Octaphosphonates **5** are a novel class of easily available, self-folding container compounds forming kinetically stable inclusion complexes both in apolar media like CD_2Cl_2 and $CDCl_3$ and in highly polar alcohols. The ability of **5** to form 1:1 inclusion complexes with ammonium cations can be externally regulated via competing complexation of two La^{3+} ions at the periphery of the molecular cavity. This complexation results in a conformational change from a vase to a kite and dimerization of the kite to accommodate better coordination of the lanthanides in a velcraplex-like dimer. Four bidentate carboxymethyl-phosphonate groups on each edge of the dimer provide an ideal binding site for the La^{3+} ion, so that one dimer can complex four cations. The selective release and uptake of guest molecules can be controlled by the interplay of metal and complexing agent (e.g., NO_3^-, **16**).

Octaphosphonates **5** and diphosphonate **13** exhibit an unprecedented intramolecular inclusion of one alkoxy group of one of the dialkoxyphosphoryl fragments in the intramolecular

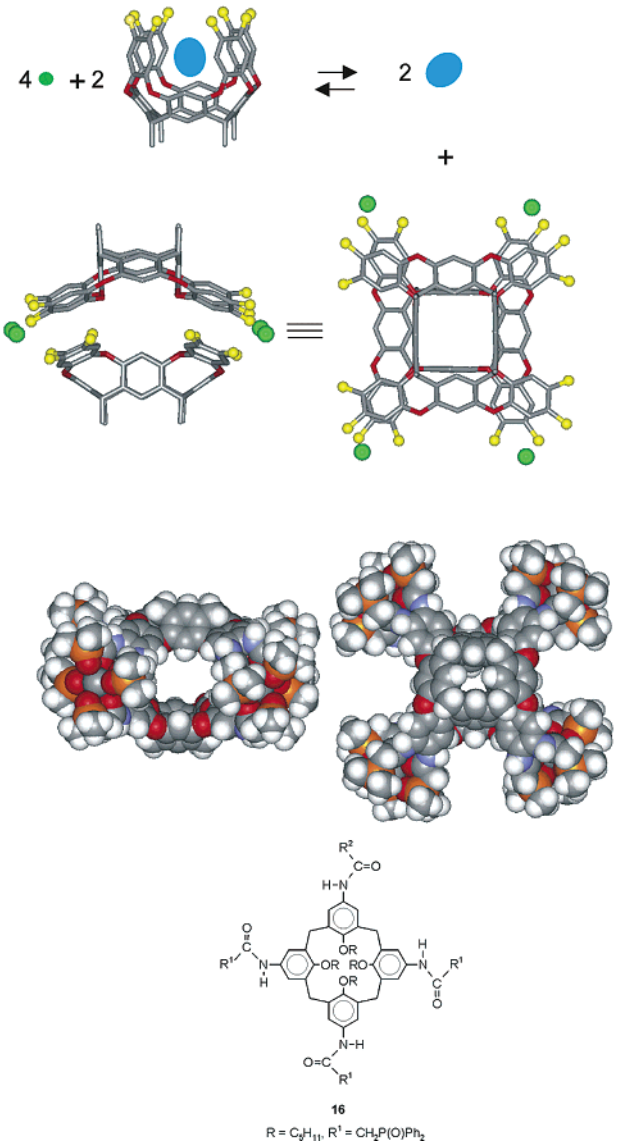


Figure 6. The equilibrium between vase-shaped inclusion complex and dimeric lanthanide complexes of **5**: yellow ball, ligating arm; green ball, lanthanide cation; blue ellipse, included guest (top). Possible structutre of the 2:4 complex of **5** is shown in space-filling presentations (middle). Pendant alkyl chains are omitted for clarity, and alkoxy groups of phosphonate fragments are substituted by methyls. The line structure of CMPO calix[4]arene **16** (bottom).

(15) PCMODEL is distributed by Serena Software, Dr. Kevin E. Gilbert, P.O. 3076, Bloomington, IN 47402; Discover, version 2.9.5; May 1994; Biosym Technologies, 9685 Scranton Road, San Diego, CA 92121-4778.

cavity of the cavitand. This is observed in solution as well as in the solid state. The degree of this self-inclusion depends on the temperature and the nature of the solvent and varies from 20% in CD_2Cl_2 at 213 K to 100% in methanol-d_4 at 295 K. This dependence results mainly from the size of the solvent molecule and its ability to act as a guest for the cavity.

The facile synthesis of octaphosphonates **5** and their exceptional ability to complex two lanthanide cations coupled with the high lipophilicity of the resulting 2:4 dimeric metal complex make them attractive candidates for further studies as cooperative chelators and extraction agents for lanthanide and actinide cations.

Experimental Section

The 1D ^{1}H, ^{13}C, ^{19}F, ^{31}P, 2D ROESY, DQF-COSY, and variable-temperature NMR spectra were recorded on a Bruker DRX 600 (600 MHz) spectrometer using the solvent signals as internal reference. Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry experiments were performed on a PerSeptive Biosystems Voyager-Elite mass spectrometer with delayed extraction, using 2,5-dihydroxybenzoic acid (DHB) as a matrix. Electrospray ionization (ESI) mass spectra were recorded on an API III Perkin-Elmer SCIEX triple-quadrupole mass spectrometer. Melting points were measured on a MEL-TEMP II apparatus and are uncorrected. Resorcinarenes **1a**−**c**[16] and octanitro cavitands **2b**,**c**[4,13a,b] were prepared by known procedures. All guests were purchased from Aldrich and Fluka and were used without further purification.

Octanitro Cavitand 2a. To a solution of resorcinarene **1a** (3 g, 5 mmol) and 1,2-difluoro-4,5-dinitrobenzene (4.04 g, 20 mmol) in 120 mL of DMF was added NEt_3 (10.55 mL, 80.7 mmol, 2.01 equiv with respect to the aromatic OH) dropwise. An immediate color change to orange occurred. The mixture was heated to 65 °C for 19.5 h. The solvent was removed in vacuo and the residue treated with CH_2Cl_2 (20 mL). The precipitate was filtered off and washed with CH_2Cl_2 (2 × 5 mL). The precipitate was suspended in methanol and sonicated for 5 min. After suction filtration the precipitate was washed with methanol (10 mL) to afford 2.86 g of the octanitro cavitand as a yellow solid. After evaporation of the mother liquor and suspension of the residue in methanol followed by treatment of the collected precipitate with methanol, another 2.76 g was obtained, resulting in an overall yield of 90%: mp > 300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.84 (s, 8H), 8.26 (s, 4H), 7.85 (s, 4H), 5.41 (br m, 4H), 2.43−2.33 (m, 8H), 0.94−0.92 (t, J = 7.0 Hz, 3H); MALDI-MS (DHB) m/z 1210 ($M^+ - NO_2$). Anal. Calcd for $C_{60}H_{40}N_8O_{24}$·2MeOH: C, 56.37; H, 3.66; N, 8.48. Found: C, 56.40; H, 4.00; N, 8.21.

Octabromoacetamide Cavitand 4a. In a 1000 mL flask was placed octanitro cavitand **2a** (1 g, 0.796 mmol) together with $SnCl_2$ dihydrate (8.61 g, 27.25 mmol, 6 equiv with respect to the NO_2 groups) under an N_2-gas atmosphere. An ethanolic HCl solution (15 mL of concentrated HCl in 100 mL of EtOH) was added and the mixture heated to reflux for 21.5 h. The solvents were removed in vacuo. To the residue was added K_2CO_3 (15.4 g) as a solid followed by a degassed 1:1 mixture (500 mL) of ethyl acetate and an aqueous solution of K_2CO_3 (7.7 g). The mixture was stirred vigorously, and bromoacetyl chloride (2.65 mL, 31.8 mmol, 5 equiv with respect to NH_2) was added in one portion. After 5 min of stirring another portion of bromoacetyl chloride (2.65 mL) was added. After 2 h concentrated HCl (15 mL) was added to stop the reaction. The organic layer was separated and the aqueous layer extracted three times with ethyl acetate (30 mL). The combined organic layers were washed with water (2 × 30 mL), 10% $NaHCO_3$ solution (2 × 30 mL), and brine. After drying ($MgSO_4$), the solvent was evaporated to afford cavitand **4a** (1.065 g, 67%) as a colorless solid: mp 280−285 °C dec; R_f = 0.76 (hexane/EtOAc, 1:1); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.55 (s, 8H, NH), 7.58 (s, 8H), 7.41 (s, 4H), 7.28 (s, 4H), 5.71−5.68 (t, J = 8.3 Hz, 4H), 4.10−4.08 (d, J = 11.7 Hz, 8 H), 4.03−4.01 (d, J = 11.7 Hz, 8H), 2.39−2.34 (quintet, J = 7.3 Hz, 8H), 1.07−1.04 (t, J = 7.2 Hz, 12H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 166.7 (C═O), 166.5 (C═O), 155.0, 150.8, 136.2, 127.9, 124.5, 121.6, 116.3, 35.8, 29.2, 25.7, 12.6.

Dodecabromoacetamido Cavitand 4b. Tetrahydroxy octanitro cavitand **1b** (1.0 g, 0.73 mmol) was reduced with $SnCl_2$ (10 g, 60 equiv) under the conditions described for **4a**. The hydrochloride salt **2b** precipitated out of solution and was collected, washed with MeOH (50 mL), and dried to give 940 mg (90%) of **2b** as a colorless solid.

To a solution of salt **2b** (500 mg, 0.35 mmol) dissolved in degassed ethyl acetate (30 mL) was added bromoacetyl chloride (0.7 mL, 8.4 mmol, 24 equiv). A solution of K_2CO_3 (2 g) in degassed water (30 mL) was then added. The mixture was vigorously stirred for 4 h at room temperature under nitrogen. After 2 h another portion of bromoacetyl chloride (0.7 mL, 8.4 mmol, 24 equiv) was added to complete the acetylation. The ethyl acetate layer was separated, and the aqueous layer was extracted once with ethyl acetate (50 mL). The combined organic layers were washed two times with saturated $NaHCO_3$ solution (100 mL). The aqueous layer was in turn extracted with dichloromethane (50 mL). The organic layers were dried ($MgSO_4$) and the solvents removed in vacuo. The resulting material was dissolved in CH_2Cl_2. Methanol was added dropwise, and the resulting precipitate was filtered off and washed with small amounts of methanol. Flash chromatography on silica gel was performed (CH_2Cl_2/MeOH (100:1) to give after drying in vacuo the desired dodecabromoacetamido cavitand (278 mg, 31%): mp > 300 °C; R_f = 0.81 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.63−9.42 (m, 8H), 7.71−7.27 (m, 16H), 5.84 (t, J = 8.0 Hz, 4H), 4.34 (m, 8H), 4.17 (s, 8H), 4.05−3.95 (m, 16H), 2.40 (br m, 8H), 1.77 (m, 8H), 1.26 (m, 8H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 167.8, 166.8, 155.1, 150.7, 136.0, 127.9, 124.2, 121.5, 116.5, 66.5, 62.7, 33.7, 31.8, 29.2, 27.1.

Octabromoacetamido Cavitand 4c. Octanitro cavitand **2c** (2 g, 1.14 mmol) and $SnCl_2$ dihydrate (12.3 g, 54.50 mmol) were suspended in a mixture of EtOH (200 mL) and concentrated HCl (15 mL). The mixture was degassed and set under a N_2-gas atmosphere. After heating to reflux for 18.5 h the solvent was removed and K_2CO_3 (22 g) was added as a solid followed by an aqueous solution (200 mL) of K_2CO_3 (11 g). Ethyl acetate (200 mL) was added followed by bromoacetyl chloride (7.6 mL, 90.8 mmol). The addition of the acid chloride was performed in two equal portions within 5 min while the mixture was vigorously stirred. The reaction mixture was stirred for another 135 min and then treated with concentrated HCl (15 mL). The organic layer was separated and the aqueous layer extracted three times with ethyl acetate. The combined organic layers were washed with 5% sodium bicarbonate solution and then water and dried (Na_2SO_4). Evaporation of the solvent gave compound **4c** as a light brown solid (1.8 g, 64%): mp 210 °C dec; R_f = 0.83 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 9.61 (br s, 4H, NH), 7.52 (br s, 8H), 7.33 (s, 4H), 7.22 (s, 4H), 5.79−5.76 (t, J = 8.2 Hz, 4H), 4.03 (d, J = 11.4 Hz, 8H), 3.98 (d, J = 11.2 Hz, 8H), 2.29−2.25 (m, 8H), 1.47−1.45 (m, 8H), 1.41−1.37 (m, 8H), 1.33−1.29 (m, 60H), 0.92−0.89 (t, J = 6.9 Hz, 12H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 166.8, 154.9, 161.1, 136.1, 127.7, 124.3, 121.8, 116.4, 33.7, 32.7, 30.2, 30.1, 29.8, 28.8, 28.4, 23.1, 14.5; MS (ESI) 2490 (M + H), 2527 (M + K). Anal. Calcd for $C_{112}H_{136}Br_8N_8O_{16}$·$C_6H_{12}$: C, 55.07; H, 5.80; N, 4.35. Found: C, 55.29; H, 5.87; N, 4.28.

Octaphosphonate Cavitand 5a. In a 50 mL flask fitted with a condenser was placed octabromoacetamide cavitand **4a** (577 mg, 0.291 mmol). After addition of $P(OEt)_3$ (4 mL) the mixture was refluxed for 2.5 h. After removal of the solvent and drying under high vacuum the residue was dissolved in CH_2Cl_2 (5 mL) and precipitated with hexanes to give octaphosphonate cavitand (697 mg, 99%): mp 220−222 °C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.25 (s, 8H, NH), 7.69 (s, 8H), 7.36

(16) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305−1312.

(s, 4H), 7.25 (s, 4H), 5.70−5.67 (t, J = 8.3 Hz, 4H), 4.19−4.11 (m, 16H), 4.10−4.08 (m, 16H), 3.57−3.51 (dd, J = 14.0 Hz, $J_{P,H}$ = 7.0 Hz, 8H), 3.11−3.05 (dd, J = 13.9 Hz, $J_{P,H}$ = 8.0 Hz, 8H), 2.37−2.30 (quintet, J = 7.6 Hz, 8H), 1.33−1.31 (t, J = 7.2 Hz, 24H), 1.23−1.20 (t, J = 7.0 Hz, 24H), 1.06−1.03 (t, J = 7.2 Hz, 12H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.19 (s, 8H, NH), 7.61 (s, 8H), 7.28 (s, 4H), 7.22 (s, 4H), 5.68−5.65 (t, J = 7.8 Hz, 4H), 4.19−4.13 (m, 32H), 3.56−3.50 (dd, J = 14.2 Hz, $J_{P,H}$ = 6.4 Hz, 8H), 3.09−3.03 (dd, J = 14.0 Hz, $J_{P,H}$ = 8.2 Hz, 8H), 2.31−2.28 (quintet, J = 7.6 Hz, 8H), 1.32−1.29 (m, 48H), 1.03−1.01 (t, J = 7.2 Hz, 12H); ^{31}P NMR (243 MHz, CD_2Cl_2) δ 23.83; ^{31}P NMR (243 MHz, $CDCl_3$) δ 23.41; MALDI-MS (DHB) m/z 2444 (M^+), 2466 (M + Na^+); ESI-MS (DHB) m/z 2464 (M + Na^+); exact mass (M + Na^+) 2463.7062, $C_{108}H_{144}N_8O_{40}P_8$ requires 2463.7602.

Dodecaphosphonate Cavitand 5b. Dodecabromoacetamide **4b** (100 mg, 0.04 mmol) was dissolved in triethyl phosphite (1 mL) and heated to reflux for 1 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2. Slow addition of hexanes and filtration of the resulting colorless precipitate gave after drying in vacuo the desired dodecaphosphonate cavitand **5b** (119 mg, 94%) as a colorless solid: mp 81−83 °C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.21 (br s, 8H), 7.65 (s, 8H) 7.62 (s, 4H), 7.21 (s, 4H), 5.82−5.79 (t, J = 8.3 Hz, 4H), 4.27−4.04 (m, 56H), 3.52−3.48 (m, 8H), 3.08−2.98 (m, 16H), 2.50−2.48 (m, 8H), 1.72−1.70 (m, 8H), 1.31−1.27 (m, 48H), 1.19−1.17 (t, J = 6.7 Hz, 24H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 166.4, 165.1, 155.4, 150.1, 133.1, 128.7, 125.1, 121.2, 116.6, 65.7, 63.6, 63.3, 63.1, 37.0−34.6 (J_{PC} = 127 Hz), 33.6−30.7 (J_{PC} = 132 Hz), 28.0, 27.5, 16.7, 16.7; ^{31}P NMR (243 MHz, CD_2Cl_2) 23.84 (8P), 20.56 (4P); ESI-MS m/z 3296 (M + Na^+); exact mass M^+ 3295.9275, $C_{136}H_{196}N_8O_{60}P_{12}Na$ (M + Na^+), requires 3295.9166.

Octaphosphonate Cavitand 5c. Octabromoacetamide cavitand **4c** (235 mg, 94 μmol) was suspended in $P(OEt)_3$ (2 mL, 12.42 mmol). The mixture was heated at reflux for 1 h, and then the solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 (1.5 mL) and then reprecipitated with hexane. The light yellow precipitate was filtered off and washed with small amounts of hexane to afford pure **5c** (223 mg, 77%): mp 118−120 °C; ^{1}H NMR (CD_2Cl_2, 600 MHz) δ = 9.13 (s, 8H, NH), 7.57 (s, 8H), 7.25 (s, 4H), 7.13 (s, 4H), 5.67−5.64 (t, J = 8.1 Hz, 4H), 4.07−4.02 (m, 16H), 4.01−3.97 (m, 16H), 3.45−3.39 (m, 8H), 3.00−2.94 (m, 8H), 2.21−2.17 (m, 8H), 1.37−1.36 (m, 8H), 1.24−1.19 (m, 96H), 1.12−1.09 (t, J = 6.6 Hz, 16H), 0.82−0.79 (t, J = 7.3 Hz, 12H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 164.6, 154.8, 149.7, 135.8, 128.1, 123.7, 120.7, 116.2, 63.1−62.6 (dd, J_{PC} = 73.6 Hz, J_{PC} = 5.8 Hz), 36.9−36.0 (d, J_{PC} = 128.7 Hz), 33.5−32.4 (d, J_{PC} = 160.9 Hz), 32.0, 29.9, 29.5, 28.1, 22.8, 16.2, 14.0; ^{31}P NMR (243 MHz, CD_2Cl_2) δ 23.8; MS (MALDI) 2947 (M^+).

Octaphosphonate cavitand 5d was prepared similarly to **5c** from **4c** (308 mg, 0.124 mmol) and $P(OPr)_3$ (4 mL, 17.3 mmol). Light yellow solid 393 mg (100%): mp 128−130 °C; ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 9.17 (s, 8H, NH), 7.65 (s, 8H), 7.37 (s, 4H), 7.24 (s, 4H), 5.78−5.75 (t, J = 7.7 Hz, 4H), 4.06−3.97 (m, 32H), 3.58−3.52 (m, 8H), 3.10−3.04 (m, 8H), 2.30−2.29 (m, 8H), 1.68−1.58 (m, 24H), 1.45 (br m, 8H), 1.31−1.27 (m, 108 H), 0.93−0.84 (m, 24H); ^{31}P NMR (243 MHz, CD_2Cl_2) δ 23.6; MS (MALDI) 3169 (M^+), 3191 (M + Na^+).

Octaacid Cavitand 6. Octaphosphonato cavitand **5c** (123 mg, 0.042 mmol) was dissolved in CH_2Cl_2 (10 mL) under an argon atmosphere. To this solution was added bromotrimethylsilane (0.17 mL, 2 equiv with respect to the ester groups), and the mixture was stirred for 20 h at room temperature. After removal of the solvents in vacuo, the remaining pale yellow solid was treated with a solvent mixture (60 mL) of methanol and CH_2Cl_2 (5:1) and stirred for 12 h. Removal of the solvents gave **6** as a light yellow amorphous solid: ^{1}H NMR (600 MHz, $CDCl_3$/MeOH-d_4 (9:1)) δ 7.59 (br s, 4H), 7.23 (s, 4H), 7.18 (s, 4H), 5.69 (br s, 4H), 4.14 (s, 4H), 2.18 (br s, 12H), 1.40 (br s, 2H), 1.24 (m, 56 H), 0.86−0.84 (t, J = 6.6 Hz, 12 H); ^{31}P NMR (243 MHz, $CDCl_3$/MeOH-d_4 (9:1)) δ 20.29; MS (MALDI) 2499 (M^+).

Hexanitro Cavitand 7. To a solution of resorcinarene **1a** (1.5 g, 2.5 mmol) and 1,2-difluoro-3,4-dinitrobenzene (1.50 g, 7.44 mmol, 2.97 equiv) in anhydrous DMF (100 mL) was added NEt_3 (2.3 mL, 16.25 mmol). After the flask was purged with N_2-gas, the mixture was heated to 70 °C for 18.5 h. The solvent was evaporated and the residue treated with methanol. After sonification of the mixture for 5 min the precipitate was filtered off and washed with small amounts of methanol. Flash chromatography on silica gel was performed with CH_2Cl_2/EtOAc (100:1 → 100:3 → 100:5) to give hexanitro cavitand **7** (492 mg, 18%) as a yellow solid and octanitro cavitand **2a** (550 mg, 24%): mp > 300 °C; R_f = 0.08 (CH_2Cl_2/EtOAc 95:5); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.74 (s, 2H), 7.73 (s, 2H), 7.69 (s, 2H), 6.99 (br s, 2H), 6.8 (br s, 2H), 6.66 (br s, 2H), 6.10 (s, 2H), 4.26−4.23 (t, J = 7.6 Hz, 4H), 3.92−3.89 (dt, J = 7.6 Hz, 3H), 2.20−2.10 (m, 8H), 0.98−0.90 (m, 12H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 153.0, 152.6, 152.4, 129.1, 127.9, 125.2 (br), 119.5 (br), 117.5, 38.5, 38.3, 36.3, 27.0, 25.5, 25.1, 12.1, 11.8, 11.6; exact mass 1115.2173 (M + Na^+), $C_{54}H_{40}N_6O_{20}$ requires 1115.2189.

Hexaamido Diol Cavitand 9. In a 50 mL flask was placed hexanitro cavitand **7** (388 mg, 0.357 mmol), $SnCl_2$ dihydrate (2.87 g, 12.7 mmol), and a mixture of EtOH (30 mL) and concentrated HCl (8 mL). The mixture was heated to reflux for 20.5 h. During the reaction the color changed from initially orange to pale yellow. The solvent was removed and the residue dissolved in degassed EtOAc (20 mL). Propionyl chloride (620 μL, 7.14 mmol, 5 equiv) was added. This solution was vigorously stirred, and a degassed solution of K_2CO_3 (6.1 g) in H_2O (20 mL) was added. Immediately after the addition, gas evolution occurred while the reaction mixture turned milky opaque. After 3 min of stirring a second portion of propionyl chloride (620 μL) was added. After 1 h of stirring was added concentrated HCl until no further gas evolution was noticed. The organic layer was separated and the aqueous layer extracted 3 times with EtOAc (15 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed. The residue again was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution. After drying ($MgSO_4$) and removal of the solvent, the residue (440 mg) was taken up in a 1:1 mixture of toluene/EtOH and hydrazine (0.4 mL) was added (cleaving of the esters). The mixture was heated to 80 °C for 3.5 h. The solvents were removed to give a crude pale yellow solid (433 mg). Flash chromatography was performed on silica gel with the solvent mixture CH_2Cl_2/MeOH (100:2 → 100:3.5 → 100:5) to give hexaamide diol cavitand **9** (267 mg, 60%) as a colorless solid: mp 283−285 °C (dec); R_f = 0.56 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.57 (br s, 4H), 8.61 (br s, 2H), 7.54 (br s, 2H), 7.38 (br s, 2H), 7.33 (s, 2H), 7.29 (s, 2H), 7.21 (s, 2H), 6.84 (br s, 2H), 5.74−5.71 (t, J = 8.2 Hz, 1H), 5.65−5.62 (t, J = 8.3 Hz, 2H), 4.19 (br t, 1H), 2.55−2.35 (m, 9H), 2.34−2.30 (m, 3H), 2.29−2.22 (m, 8H), 1.82 (br s, 6H), 1.32−1.30 (t, J = 7.7 Hz, 6H), 1.29−1.26 (t, J = 8.4 Hz, 6H), 1.07−1.04 (t, J = 7.2 Hz, 3H), 1.00−0.98 (t, J = 7.2 Hz, 6H), 0.93−0.91 (t, J = 7.2 Hz, 3H); ^{1}H NMR (600 MHz, acetone-d_6) δ 9.56 (s, 2H), 9.45 (s, 2H), 9.22 (s, 2H), 9.00 (s, 2H), 8.04 (s, 2H), 7.77 (s, 2H), 7.72 (s, 2H), 7.69 (s, 4H), 7.53 (s, 2H), 6.77 (s, 2H), 5.74 (br t, 1H), 5.63−5.62 (m, 2H), 4.25−4.23 (br t, 1H), 2.58−2.43 (m, 12H), 2.39−2.30 (br m, 8H), 1.28−1.22 (m, 12H), 1.11 (br m, 6H), 1.01 (br t, 3H), 0.98 (br t, 6H), 0.93 (br t, 3H); ^{13}C NMR (150.9 MHz, acetone-d_6) δ 173.8 (C═O), 172.8 (C═O), 155.4, 155.0, 152.6, 150.0, 149.8, 149.3, 137.1, 136.3, 130.6, 129.5, 129.0, 128.2, 128.1, 127.1, 127.1, 125.4, 124.9, 116.6, 109.6, 36.6, 36.2, 35.8, 30.8, 30.7, 30.0, 26.3, 25.5, 25.2, 12.5, 10.1, 10.1, 9.4; exact mass 1271.5324 (M + Na^+), $C_{72}H_{76}N_6O_{14}$ requires 1271.5311.

Hexaamide Dinitro Cavitand 10. A solution of cavitand **9** (132 mg, 0.106 mmol) was dissolved in DMF (20 mL). To this solution was added NEt_3 (0.58 mL, 0.42 mmol, 4 equiv), and the mixture was heated to 85 °C for 22.5 h. Another portion of NEt_3 (0.27 mL, 0.21 mmol) was added by then and the mixture stirred for another 20 h at the elevated temperature. The reaction mixture was poured into a 1:1 mixture (100 mL) of EtOAc and 5% HCl. The organic layer was separated and the aqueous phase extracted 3 times with ethyl acetate

(20 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). After evaporation of the solvent an orange oily residue remained. Flash column chromatography on silica gel was performed with the solvent mixture CH_2Cl_2:MeOH (100:2 → 100:5 → 100:10 → 0:100) to give **10** (118 mg, 79%) as an orange amorphous solid: $R_f = 0.28$ (CH_2Cl_2/MeOH 95:5); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.46 (s, 2H), 9.34 (s, 2H), 8.20 (s, 2H), 8.18 (s, 2H), 7.66 (s, 2H), 7.58 (s, 4H), 7.41 (s, 2H), 7.38 (s, 2H), 7.37 (s, 2H), 7.30 (s, 2H), 5.74−5.71 (t, $J = 8.3$ Hz, 2H), 5.71−5.68 (t, $J = 8.3$ Hz, 1H), 5.56−5.53 (t, $J = 8.2$ Hz, 1H), 2.54−2.30 (m, 20H), 1.31−1.22 (m, 18H), 1.09−1.06 (t, $J = 7.2$ Hz, 6H), 1.06−1.01 (m, 6H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 174.2 (C═O), 174.1 (C═O), 173.8 (C═O), 156.4, 155.9, 155.3, 154.6, 149.8, 149.7, 149.6, 139.7, 137.2, 136.1, 135.9, 135.5, 128.7, 128.2, 124.6, 124.0, 122.1, 121.4, 120.8, 120.6, 116.8, 116.3, 35.9, 35.8, 35.7, 31.2, 31.2, 30.4, 26.3, 25.8, 25.5, 12.6, 12.6, 10.5, 10.5, 9.9; exact mass 1435.5209 ($M + Na^+$), $C_{78}H_{76}N_8O_{18}$ requires 1435.5170.

Hexaamide Dibromoacetamide Cavitand 12. To a mixture of cavitand **10** (118 mg, 0.095 mmol) and $SnCl_2$ dihydrate (1.317 g, 5.838 mmol) in EtOH (30 mL) was added concentrated HCl (2 mL). The reaction mixture was heated to 45 °C for 17 h. The solvents were removed and the greenish semisolid dissolved in ethyl acetate. Bromoacetyl chloride (299 mg, 1.9 mmol, 20 equiv, 280 μL) was added followed by an aqueous solution of K_2CO_3 (1.62 g in 30 mL of H_2O). After 15 min of vigorous stirring another portion of bromoacetyl chloride (140 μL, 10 equiv) was added. The mixture was stirred for 5 h before HCl (10%, 10 mL) was added. The organic layer was separated and the aqueous layer extracted 3 times with ethyl acetate. The combined organic layers were washed with brine (30 mL), saturated $NaHCO_3$ solution (40 mL), and again brine (30 mL). After drying ($MgSO_4$), the solvents were removed. Flash chromatography on silica gel was performed with the solvent mixture ethyl acetate/hexanes (1:4 → 1:2 → 1:1 → ethyl acetate) to afford cavitand **12** (40 mg, 26%) as a colorless solid: mp > 250 °C; $R_f = 0.50$ (EtOAc/hexanes, 1:1); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.55 (br s, 4H), 9.28 (s, 4H), 7.59 (br s, 8H), 7.41 (s, 2H), 7.40 (s, 2H), 7.30 (s, 2H), 7.29 (s, 2H), 5.73−5.69 (t, $J = 8.4$ Hz, 4H), 4.05−4.03 (d, $J = 11.7$ Hz, 2H), 3.96−3.94 (d, $J = 11.5$ Hz, 2H), 2.53−2.34 (m, 20H), 1.28−1.26 (m, 18H), 1.07−1.05 (m, 12H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 174.1 (C═O), 155.2, 155.0, 150.7, 149.9, 136.2, 136.0, 135.9, 128.5 (br), 124.1, 124.0, 121.4, 121.3, 120.3, 116.5, 116.4, 35.7, 31.2 (br), 29.0, 25.7, 18.8, 12.6, 10.5; exact mass 1615.3971 ($M + Na^+$), $C_{82}H_{82}N_8O_{16}Br_2$ requires 1615.4107.

Diphosphonate Cavitand 13. In a 50 mL round bottom flask were placed cavitand **12** (35 mg, 21.98 μmol) and $P(OEt)_3$ (1 mL). The solution was heated to 105 °C for 4.5 h. After removal of the remaining $P(OEt)_3$ in vacuo and drying of the residue under high vacuum, the residue was dissolved in CH_2Cl_2 (3 mL). Hexanes were added, and the precipitate was filtered off and washed with small amounts of hexanes to give diphosphonate cavitand **13** (30 mg, 80%) as a colorless solid: mp > 300 °C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.48 (s, 4H), 9.32 (s, 4H), 7.64 (s, 2H), 7.57 (s, 2H), 7.55 (s, 2H), 7.39 (s, 4H), 7.34 (br s, 2H), 7.29 (s, 4H), 5.69−5.64 (m, 4H), 4.18−4.15 (m, 4H), 4.09 (br m, 4H), 3.26−3.20 (dd, $J_{P,H} = 7.1$ Hz, $J = 14.0$ Hz, 2H), 3.03−2.98 (dd, $J_{P,H} = 7.6$ Hz, $J = 13.9$ Hz, 2H), 2.58−2.34 (m, 20H), 1.32−1.22 (m, 30H), 1.07−1.05 (m, 12H); ^{13}C NMR (150.9 MHz, CD_2Cl_2) δ 174.1 (C═O), 164.9, 155.2, 155.1, 155.1, 150.1, 149.9, 149.8, 136.0, 136.0, 135.9, 135.8, 128.6, 128.4, 128.2, 124.0, 124,0, 121.6, 121.5, 121.1, 121.0, 116.6, 116.4, 63.3−63.1 (dd, $J_{P,C} = 19.5$ Hz, $J_{P,C} = 6.5$ Hz), 37.8−37.0 (d, $J_{P,C} = 131.1$ Hz), 35.7−35.0 (d, $J_{P,C} = 114.4$ Hz), 35.7, 32.0, 31.2, 25.8, 25.6, 23.0, 16.6, 16.5, 12.6, 10.6, 10.1; ^{31}P NMR (243 MHz, CD_2Cl_2) δ 22.46; exact mass 1731.6413 ($M + Na^+$), $C_{90}H_{102}N_8O_{22}P_2$ requires 1731.6476.

NMR Titration Experiments. Stock solutions of **5** (4 mM), **13** (4 mM), **14a**$^+$Cl$^-$ (4 mM), and La(OTf)$_3$ (8 mM) in MeOH-d_4 were used for titrations. The solution of 1:1 complexes **5**−**14a**$^+$ and **13**−**14a**$^+$ was prepared by mixing corresponding stock solutions in a 1:1 ratio. The complexes **5**−**14a**$^+$ and **13**−**14a**$^+$ were titrated with a La(OTf)$_3$ stock solution by the addition of 0.25 equiv portions.

Crystallographic Data. Crystallographic data were collected at 117(2) K using a Siemens SMART[17] diffractometer equipped with a CCD area detector using Cu Kα ($\lambda = 1.54180$ Å) radiation. Data in the frames corresponding to an arbitrary hemisphere of data were integrated using SAINT.[18] Data were corrected for Lorentz and polarization effects and were further analyzed using XPREP.[19] An empirical absorption correction based on the measurement of redundant and equivalent reflections and an ellipsoidal model for the absorption surface was applied using SADABS. The structure solution and refinement were performed using SHELXTL[18] (refining on F^2). For **4a** all bromine atoms of the cavitand were refined anisotropically, while all other atoms were refined isotropically. For **13** all non-disordered C, O, and N atoms of the cavitand were refined anisotropically; all other atoms were refined isotropically. Hydrogens were treated as riding atoms.

4a: $C_{94}H_{62}N_8O_{16}Br_8 \cdot x$(disordered solvent), triclinic $P\bar{1}$ (No. 2), $a = 14.7937(6)$ Å, $b = 17.8890(7)$ Å, $c = 18.2308(8)$ Å, $\alpha = 87.653(2)^o$, $\beta = 71.100(2)^o$, $\gamma = 83.745(2)^o$, $Z = 2$, $V = 4537.3(3)$ Å^3, $\rho = 1.61$ g cm^{-3}, $\mu = 4.811$ cm^{-1}, $2\Theta_{max} = 49.35°$, R1 = 0.101, wR2 = 0.272 (for 6649 reflections $I > 2\sigma(I)$), R1 = 0.115, wR2 = 0.282 (for 8122 independent reflections, 8122 unique, $R_{int} = 0.053$), 556 parameters, 15 restraints, $S = 1.04$, $\Delta\rho$ (max/min) = 2.62/−1.33 e Å^{-3}.

13: $C_{88}H_{48}N_8O_{22}P_2 \cdot x$(disordered solvent), monoclinic $C2/c$, $a = 19.817(4)$ Å, $b = 29.334(6)$ Å, $c = 17.757(4)$ Å, $\beta = 102.94(3)^o$, $Z = 4$, $V = 10060(4)$ Å^3, $\rho = 1.17$ g cm^{-3}, $\mu = 1.01$ cm^{-1}, $2\Theta_{max} = 88.98°$, R1 = 0.142, wR2 = 0.409 (for 2976 reflections $I > 2\sigma(I)$), R1 = 0.152, wR2 = 0.426 (for all 11540 independent reflections, 3523 unique, $R_{int} = 0.039$), 589 parameters, 9 restraints, $S = 2.035$, $\Delta\rho$ (max/min) = 0.46/−0.32 e Å^{-3}.

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Supporting Information Available: Details of crystal structure determination, solution, and refinement in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) *SMART, Area Detector Software Package*; Siemens Industrial Automation, Inc.: Madison, 1995.
(18) *SAINT, SAX Area Detector Integration Program*, version 4.024; Siemens Industrial Automation, Inc.: Madison, 1995.
(19) Sheldrick, G. *SHELXTL*; Siemens Industrial Automation, Inc.: Madison, 1993.