Supplementary Material for Chemical Communications

Metal Directed Assembly of Ditopic Containers and their Complexes with Alkylammonium Salts

Edoardo Menozzi, Julius Rebek, Jr.*

The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, MB-26, 10550 North Torrey Pines Road, La Jolla, California 92037.

Supporting Information.

Experimental Section.

General methods: All commercial reagents were ACS reagent grade and used as received. ^{1}H NMR spectra were recorded on Bruker DRX-600 (600 MHz) spectrometer at 300 K and all chemical shifts (δ) were reported in parts per million (ppm) relative to the proton resonances resulting from incomplete deuteration of the NMR solvents.

Electrospray ionization mass spectrometry (ESI-MS) experiments were performed on a Micromass LC-Time of Flight mass spectrometer.

Crystal structure of cavitand **1** and **hexaamide diol** cavitand were obtained from Bruker-SMART APEX Diffractometer equipped with a molybdenum tube, and highly oriented graphite monochromator.

Resorcinarene (R: C_2H_5),[1] hexanitro diol cavitand,[2] 4-4'-(α,α'-Dibromotolyl)pyridine,[3] $C_5H_{11}N(CH_3)_3Br$ and $(CH_3)_3N(CH_2)_{10}N(CH_3)_3Br_2$ salts[4] were prepared according to literature procedures. [Pt(dppp)(CF_3SO_3)$_2$] was prepared from the corresponding dichlorobis derivative following established procedure.[5]

Hexaamide diol cavitand. In a 250 mL flask is placed 0.500 g of hexanitro diol cavitand ($4.58\ 10^{-4}$ mol), 3. 68 g of $SnCl_2$ dihydrate ($1.63\ 10^{-2}$ mol), and a mixture of 40 mL of EtOH and 10 mL of concentrated HCl. The mixture is heated to reflux for 20 hours, under nitrogen. During the reaction the color changed from initially orange to pale yellow. The solvent is removed and the residue dissolved in 20 mL of degassed EtOAc. Propionyl chloride (1.6 mL, $1.83\ 10^{-2}$ mol) is added. This solution was vigorously stirred, and a solution of 7.0 g of K_2CO_3 in 25 mL of H_2O is added. Immediately after the

addition, gas evolution occurred while the reaction mixture turned milky opaque. After one hour of stirring the organic layer is separated and the aqueous layer extracted 3 times with 15 mL of EtOAc. The combined organic layers are washed with saturated $NaHCO_3$ solution. After removal of the solvent, the residue (0.520 g) is taken up in a 1:1 mixture of toluene/EtOH and hydrazine (0.4 mL) is added (cleaving of the esters). The mixture is heated to 75ºC for two hours. The solvents are removed to give a crude pale yellow solid (0.6 g) which is dissolved in 8 mL of CH_2Cl_2. To this solution Et_2O is added until a white precipitated is formed. The precipitated is filtered and dried under vacuum to give hexaamide diol cavitand in 54% yield (0.31 g).

MS (ESI, m/z): $[MH]^+$= 1250, calculated 1249.5; $[M+Na]^+$= 1272, calculated 1271.5. Where M= $C_{72}H_{76}N_6O_{14}$ (1248.54 amu).

^{1}H NMR (Acetone-d_6, 600 MHz): δ= 0.90-1.02 (m, 12H, C*H*$_3$); 1.11 (t, 6H, C*H*$_3$, J= 7.2 Hz); 1.21-1.26 (m, 12H, C*H*$_3$); 2.33-2.55 (m, 20H, C*H*$_2$-CH$_3$); 4.24 (t, 1H, C*H*Ar$_2$, J= 7.8 Hz); 5.61 (t, 2H, C*H*Ar$_2$, J= 8.4 Hz); 5.73 (t, 1H, C*H*Ar$_2$, J= 8.4 Hz); 6.76 (bs, 2H, ArO*H*); 7.51 (s, 2H, Ar*H*); 7.68 (s, 2H, Ar*H*); 7.70 (s, 2H, Ar*H*); 7.76 (s, 2H, Ar*H*); 7.89 (s, 2H, Ar*H*); 8.96 (bs, 2H, N*H*COR); 9.45 (bs, 2H, N*H*COR); 9.58 (bs, 2H, N*H*COR).

Phenylpyridyl hexaamide cavitand (1). 0.151 g (4.6 10^{-4} mol) of 4-4'-(α,α'-Dibromotolyl)pyridine and 0.127 g (9.2 10^{-3} mol) of K_2CO_3 are added under nitrogen to a solution of 0.23 g (1.84 10^{-4} mol) of hexaamide diol cavitand in 10 mL of dry DMF. The mixture is stirred at 80 °C for 16 h. The reaction is quenched by addition of 10 mL of water, and the resulting mixture is extracted with 15 mL of CH_2Cl_2. The organic layer is washed with water (3 x 15 mL), dried on Na_2CO_3 and evaporated. The black crude obtained is purified by column chromatography (SiO_2, CH_2Cl_2/EtOH 97.5:2.5) to give compound **1** as white solid in 37% yield (95 mg).

R_f= 0.45

MS (ESI, m/z): $[MH]^+$= 1415, calculated 1414.6. Where M= $C_{84}H_{83}O_{14}N_7$ (1413.6 amu).

^{1}H NMR (CD_2Cl_2, 600 MHz): δ= 0.97 (t, 6H, C*H*$_3$, J= 7.2 Hz); 1.04-1.10 (m, 12H, C*H*$_3$); 1.18 (m, 6H, C*H*$_3$); 1.26 (t, 6H, C*H*$_3$, J= 7.2 Hz); 2.20-2.50 (m, 20H, C*H*$_2$-CH$_3$); 4.76 (t, 1H, J= 8.4 Hz); 5.38 (s, 1H, C*H*PhPy); 5.62 (t, 2H, C*H*Ar$_2$, J= 8.4 Hz); 5.69 (t, 1H, C*H*Ar$_2$, J= 8.4 Hz); 6.95 (s, 2H, Ar*H*); 7.26 (s, 2H, Ar*H*); 7.29 (s, 2H, Ar*H*); 7.30 (bs, 2H,

Ar*H*); 7.34 (s, 2H, Ar*H*); 7.50 (s, 2H, Ar*H*); 7.55 (s, 2H, Ar*H*); 7.62 [bd, (AA' part of a AA'XX' system), 2H, PyH_m]; 7.78 [d, (AA' part of a AA'XX' system), 2H, PyPh*H*, J= 9.6 Hz]; 8.02 [d, (XX' part of a AA'XX' system), 2H, PyPh*H*, J= 9.6 Hz]; 8.20 (bs, 2H, N*H*COR); 8.66 [bd, (XX' part of a AA'XX' system), 2H, PyH_o]; 9.32 (bs, 2H, N*H*COR); 9.49 (bs, 2H, N*H*COR).

^{1}H NMR (Acetone-d_6, 600 MHz): δ= 0.99-1.04 (m, 12H, CH_3); 1.08-1.13 (m, 6H, CH_3); 1.17-1.28 (m, 12H, CH_3); 2.25-2.61 (m, 20H, CH_2-CH_3); 4.75 (t, 1H, C*H*Ar_2, J= 9.6 Hz); 5.51 (s, 1H, C*H*PhPy); 5.69-5.74 (m, 3H, C*H*Ar_2); 7.07 (s, 2H, Ar*H*); 7.59 (s, 2H, Ar*H*); 7.69 (s, 2H, Ar*H*); 7.71 [bd, (AA' part of a AA'XX' system), 2H, PyH_m]; 7.77 (s, 2H, Ar*H*); 7.80 (s, 2H, Ar*H*); 7.82 (s, 2H, Ar*H*); 7.84 (s, 2H, Ar*H*); 7.90 [d, (AA' part of a AA'XX' system), 2H, PyPh*H*, J= 7.8 Hz]; 8.07 [d, (XX' part of a AA'XX' system), 2H, PyPh*H*, J= 7.8 Hz]; 8.68 [bd, (XX' part of a AA'XX' system), 2H, PyH_o]; 8.85 (bs, 2H, N*H*COR); 9.40 (bs, 2H, N*H*COR); 9.59 (bs, 2H, N*H*COR).

General procedure for the self-assembly of *cis*-ditopic cavitand complex (2). Ditopic complex **2** was assembled by simply mixing cavitand **1** with [Pt(dppp)$(CF_3SO_3)_2$] metal precursor in a 2:1 molar ratio at room temperature in solvent like CH_2Cl_2, Acetone. In all cases, removal of the solvent under vacuum gave desired complex in quantitative yields.
MS (ESI, m/z): $[(MH)^+$-$CF_3SO_3^-]^{2+}$= 1793, calculated 1792.2; $[M\text{-}2CF_3SO_3^-]^{2+}$= 1718, calculated 1717.2. Where M= $C_{197}H_{192}O_{34}N_{14}F_6P_2PtS_2$ (3732.2 amu).

^{1}H NMR (CD_2Cl_2, 600 MHz): δ= 0.95 (m, 12H, CH_3, J=7.2 Hz); 1.02-1.07 (m, 24H, CH_3); 1.16-1.20 (m, 12H, CH_3); 1.25 (t, 12H, CH_3, J= 7.2 Hz); 2.14-2.43 (m, 42H, $PCH_2CH_2CH_2$+CH_2-CH_3); 3.30 (bm, 4H, PCH_2CH_2); 4.77 (t, 2H, C*H*Ar_2, J= 8.4 Hz); 5.28 (s, 2H, C*H*PhPy); 5.60 (t, 4H, C*H*Ar_2, J= 8.4 Hz); 5.68 (t, 2H, C*H*Ar_2, J= 8.4 Hz); 6.83 (s, 4H, Ar*H*); 7.24 (s, 8H, Ar*H*); 7.26 (s, 8H, Ar*H*); 7.32 (s, 4H, Ar*H*); 7.34 (bd, 4H, PyH_m); 7.37 (bs, 8H, PPhH_m); 7.48-7.55 (m, 12H, PPh*Hp*+PyPh*H*+Ar*H*); 7.71 (bs, 8H, PPhH_o); 7.98 (d, 4H, PyPh*H*, J= 7.8 Hz); 8.17 (bs, 4H, N*H*COR); 9.07 (bd, 4H, PyH_o); 9.29 (bs, 4H, N*H*COR); 9.47 (bs, 4H, N*H*COR).

^{1}H NMR (Acetone-d_6, 600 MHz): δ= 0.98-1.02 (m, 24H, CH_3); 1.04-1.07 (m, 12H, CH_3); 1.19-1.26 (m, 24H, CH_3); 2.25 (m, 2H, $PCH_2CH_2CH_2$); 2.42-2.55 (m, 40H, CH_2-CH_3); 3.52 (bm, 4H, PCH_2CH_2); 4.69 (t, 2H, C*H*Ar_2, J= 7.8 Hz); 5.49 (s, 2H, C*H*PhPy);

5.67 (t, 4H, C*H*Ar$_2$, J= 7.8 Hz); 5.72 (t, 2H, C*H*Ar$_2$, J= 7.8 Hz); 7.00 (s, 4H, Ar*H*); 7.44 (t, 8H, PPhH_m, J= 7.2 Hz); 7.50 (m, 4H, PPhH_p); 7.57 (bs, 8H, Ar*H*); 7.67 (m, 8H, PyH_m+Ar*H*); 7.71-7.76 (m, 8H, PyPh*H*+Ar*H*); 7.81 (s, 4H, Ar*H*); 7.84 (s, 4H, Ar*H*); 7.90 (m, 8H, PPhH_o); 8.01 (bd, 4H, PyPh*H*); 8.77 (bs, 4H, N*H*COR); 9.10 (bd, 4H, PyH_o); 9.36 (bs, 4H, N*H*COR); 9.55 (bs, 4H, N*H*COR).

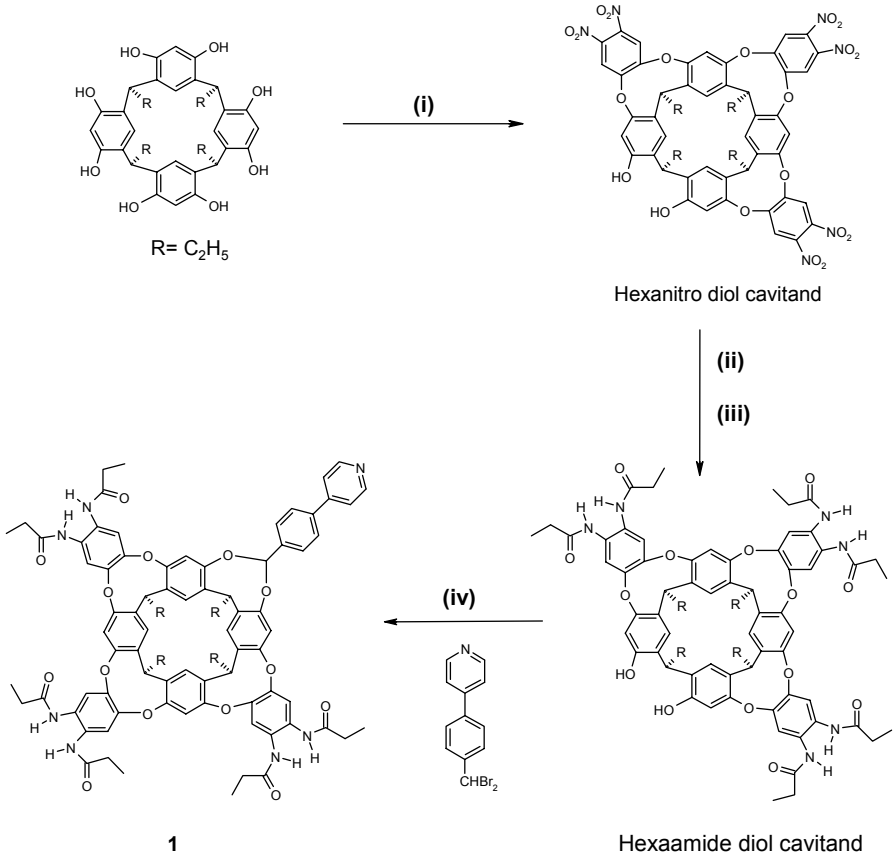
$C_5H_{11}N(CH_3)_3(CF_3SO_3)$ (3). To a solution of 140 mg (6.7 10^{-4} mol) of $C_5H_{11}N(CH_3)_3Br$ in 20 mL of dry CH_2Cl_2 and 3 mL of dry CH_3CN is added under nitrogen 200 mg (7.8 10^{-4} mol) of $AgCF_3SO_3$. The white solution is stirred at room temperature in the dark for 4 hours. The AgBr salt is removed by filtration and the solvent is evaporated under reduced pressure. The product is crystallized from ethyl ether to give **3** in 65% yield (122 mg).
MS (ESI, m/z): $[M\text{-}CF_3SO_3]^+$= 130, calculated 130.2. Where M= $C_9H_{20}N_1O_3F_3S_1$ (279.11 amu).
^{1}H NMR (Acetone-d_6, 600 MHz): δ= 0.92 (t, 3H, CH_3, J= 6.6 Hz); 1.40 (m, 4H, $CH_3(CH_2)_2$); 1.95 (m, 2H, $CH_2CH_2N(CH_3)_3$); 3.35 (s, 9H, $N(CH_3)_3$); 3.55(m, 4H, $CH_2N(CH_3)_3$).

$C_{10}H_{20}[N(CH_3)_3]_2(CF_3SO_3)_2$ (4). To a solution of 190 mg (4.5 10^{-4} mol) of decamethoniumbromide in 25 mL of dry CH_2Cl_2 and 5 mL of dry CH_3CN is added under nitrogen 245 mg (9.5 10^{-4} mol) of $AgCF_3SO_3$. The white solution is stirred at room temperature in the dark for 4 hours. The AgBr salt is removed by filtration and the solvent is evaporated under reduced pressure. The product is crystallized from ethyl ether to give **4** in 82% yield (205 mg).
MS (ESI, m/z): $[M\text{-}CF_3SO_3]^+$= 407, calculated 407.3; $[M+Na]^+$= 579, calculated 579.2. Where M= $C_{18}H_{38}N_2O_6F_6S_2$ (556.21 amu).
^{1}H NMR (Acetone-d_6, 600 MHz): δ= 1.35-1.41 (m, 12H, CH_2); 1.92 (m, 4H, $CH_2CH_2N(CH_3)_3$); 3.33 (s, 18H, $N(CH_3)_3$); 3.55 (m, 4H, $CH_2N(CH_3)_3$).

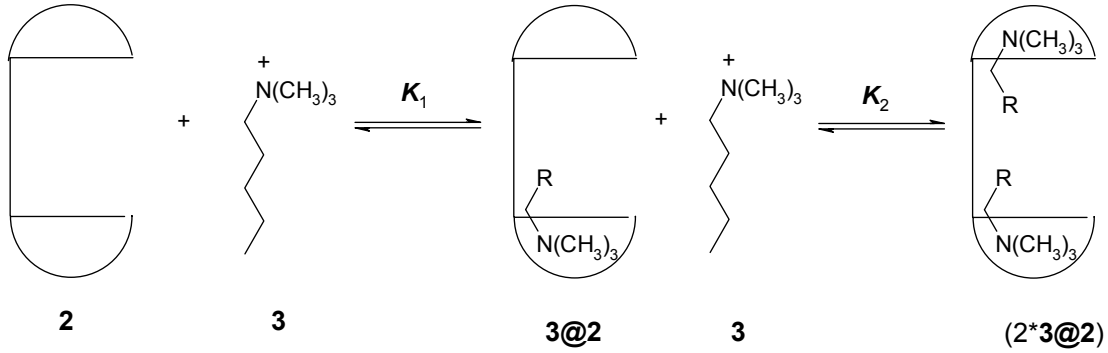
General procedure for Host-Guest complexation experiments. Solutions of the complexes were prepared by mixing acetone-d_6 solutions of cavitand **1** or molecular dimer **2** with acetone-d_6 solutions of guests **3** or **4**. Typically, 200 μL of guest solution at

~30 mM was added to 600 μL of a solution of host **1** or **2** at 2 mM concentration. The relative binding affinities of the guests to the cavitand were determined by direct integration of the corresponding $N(CH_3)_3$ peaks of the encapsulated and free guests at different guest/host ratio.

Molecular Modeling. Structures of molecular dimer **2** and of inclusion complexes (2***3@2**) and **4@2** were built and minimized using molecular mechanics based on the MMFF force field with Spartan'04 software program. The length of the dimeric structure **2** was measured as a distance between the centroids of the cavities (defined as the barycenter of the four Ar-CH-Ar methynic carbon atom).



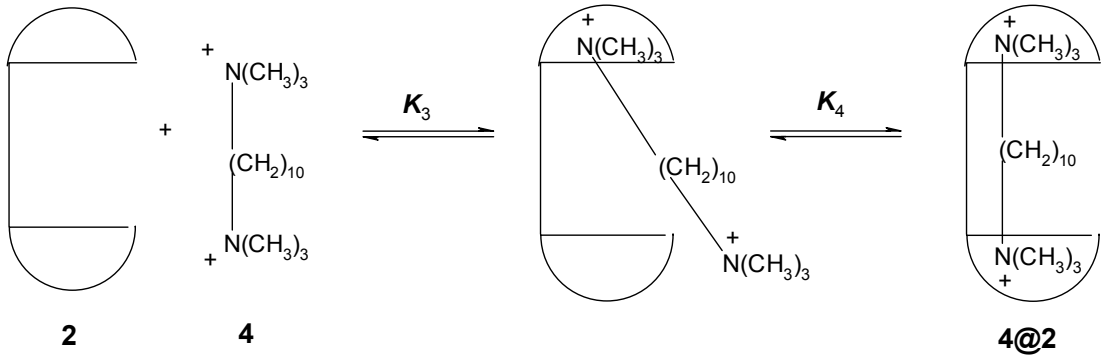
Scheme S1: i) 1,2-dinitro-4,5-difluorobenzene, DMF, 70ºC, 16h; ii) $SnCl_2$, EtOH/HCl, 70ºC, 16h followed by base work-up; iii) Propionyl chloride, AcOEt/H_2O, followed by deprotection with NH_2NH_2; IV) DMF, K_2CO_3, 80ºC, 16h, under N_2.



2 **3** **3@2** **3** (2***3@2**)

$$K_{a(2*\mathbf{3@2})} = K_1K_2 = \frac{[(2*\mathbf{3@2})]_{eq}}{[\mathbf{2}]_{eq} * [\mathbf{3}]^2_{eq}}$$

Scheme S2: The binding constant $K_{a(2*\mathbf{3@2})}$ can be divided in two intermolecular contributions: K_1 is a favored by a statistical factor of 2 and can be written as $K_1 = 2K_{inter}$; K_2 instead is unfavored by a statistical factor 2, therefore $K_2 = K_{inter}/2$. At the end $K_{inter} = \{K_{a(2*\mathbf{3@2})}\}^{1/2}$.



2 **4** **4@2**

$$K_{a(\mathbf{4@2})} = K_3K_4 = \frac{[(\mathbf{4@2})]_{eq}}{[\mathbf{2}]_{eq} * [\mathbf{4}]_{eq}}$$

Scheme S3: The binding constant $K_{a(\mathbf{4@2})}$ can be divided in two factors: K_3 is an intermolecular process and is favored by a statistical factor of 4. It can be written as $K_3 = 4K_{inter}$. K_4 instead is an intramolecular interaction and is unfavored by a statistical factor 2. Thus $K_4 = K_{intra}/2$. At the end $K_{a(\mathbf{4@2})} = 2K_{intra}K_{inter}$.

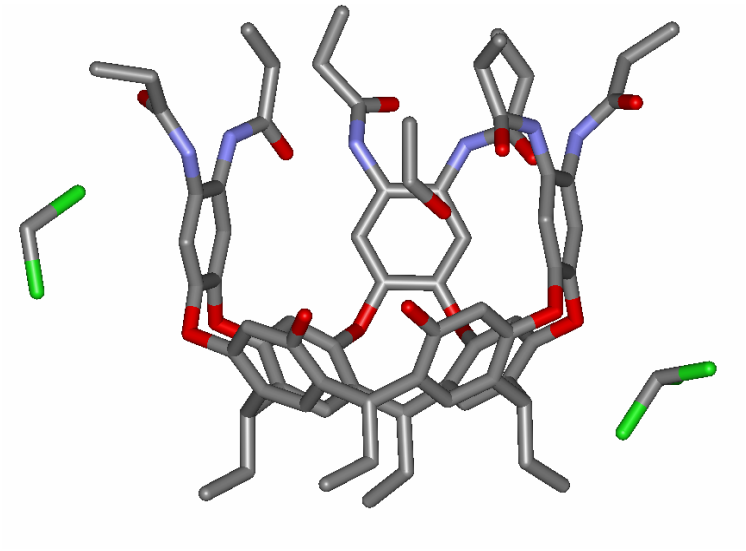


Figure S1: X-ray crystal of **hexaamide diol cavitand** crystallized from CH_2Cl_2/EtOH.

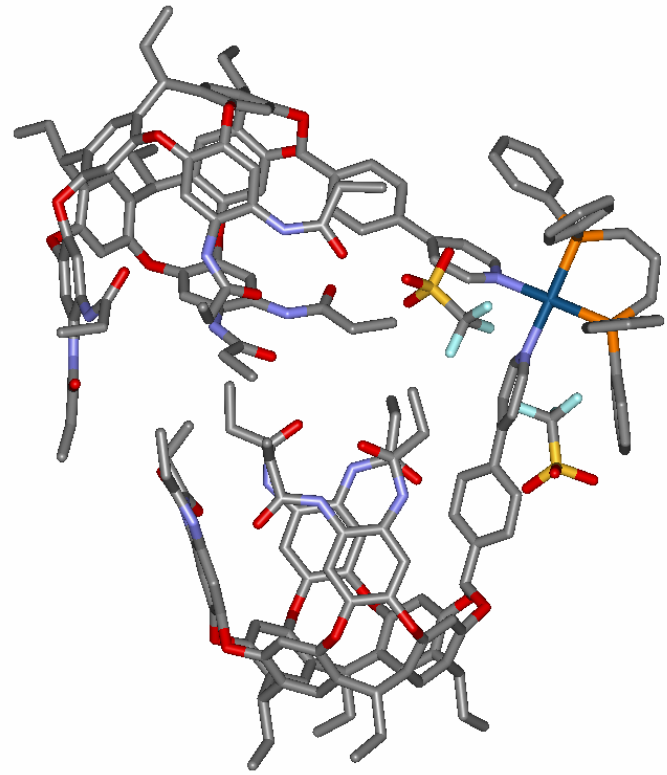


Figure S2: Energy minimized structure of ditopic complex **2.** The complex assumed a conformation with an approximate C_s symmetry. The distance between the centroids of the cavities is ~19 Å

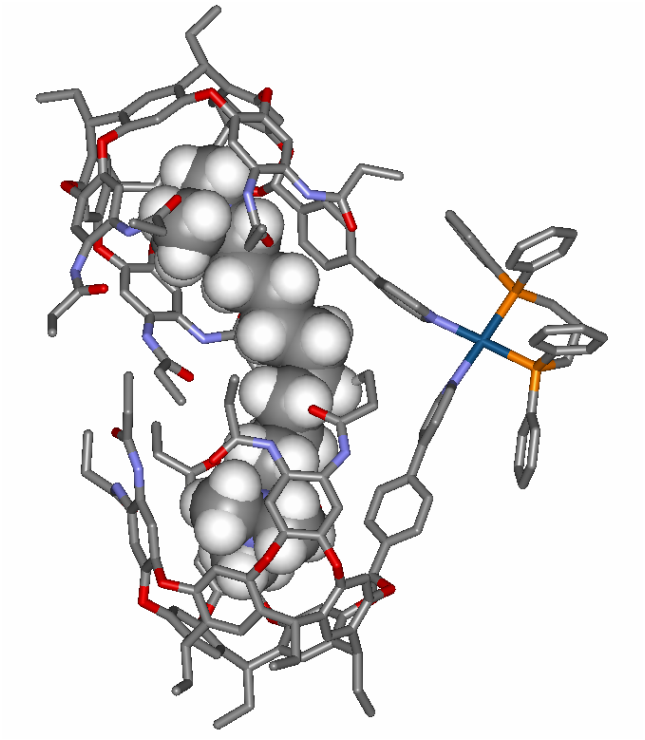


Figure S3: Energy minimized structure of **4@2**.

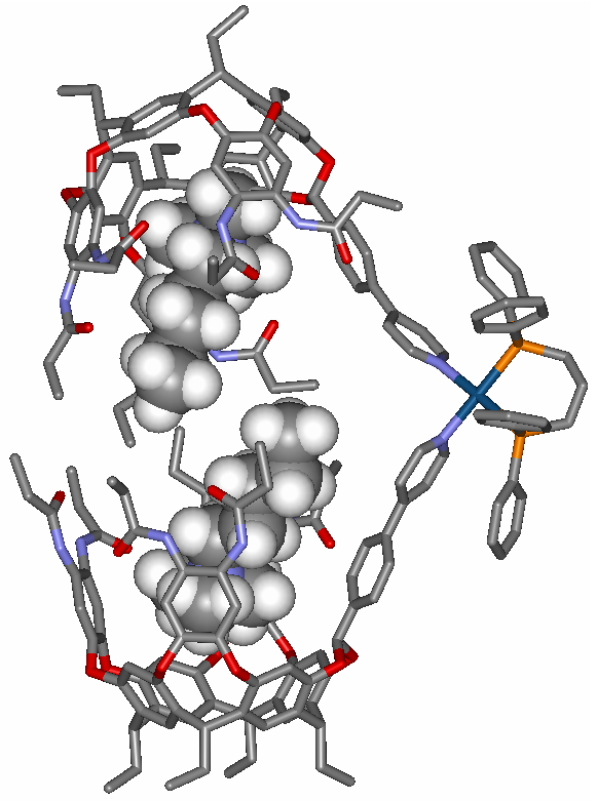


Figure S4: Energy minimized structure of (2***3@2**).

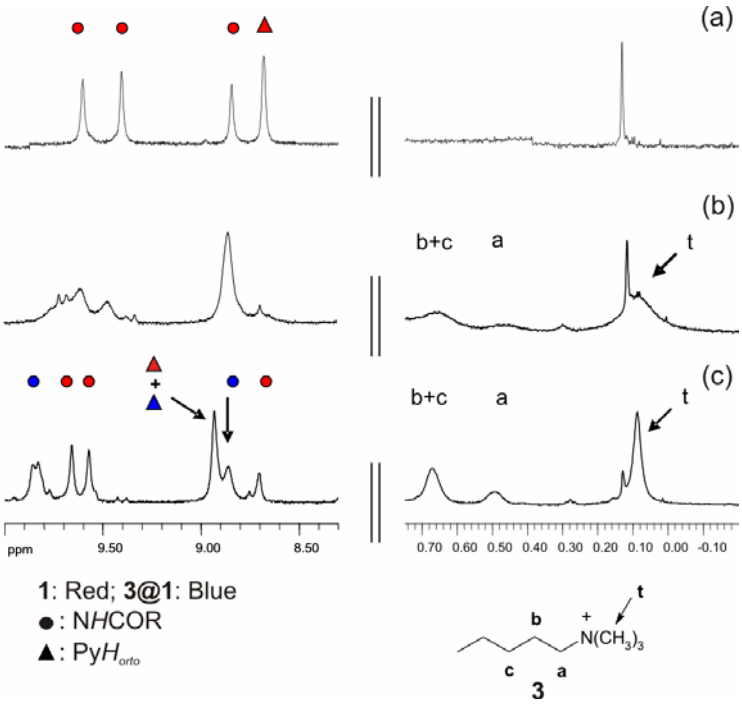


Figure S5: Down-field and up-field regions of the ^{1}H NMR (600 MHz, acetone-d_6): (a) Cavitand **1** at 300K; (b) **3@1** at 273K; (c) **3@1** at 253K. At [**1**]= 2 mM; [**3**]= 30 mM.

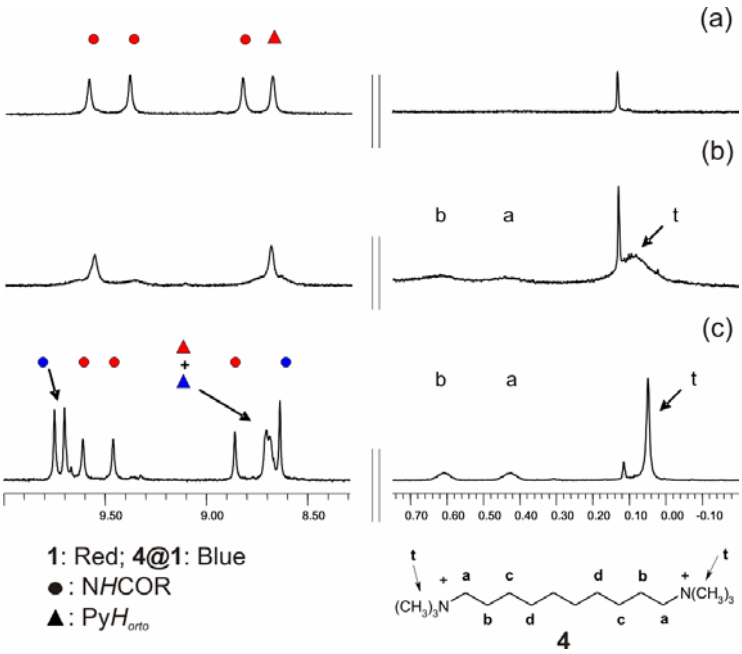


Figure S6: Down-field and up-field regions of the ^{1}H NMR (600 MHz, acetone-d_6): (a) Cavitand **1** at 300K; (b) **4@1** at 273K; (c) **4@1** at 253K. At [**1**]= 2 mM; [**4**]= 35 mM.

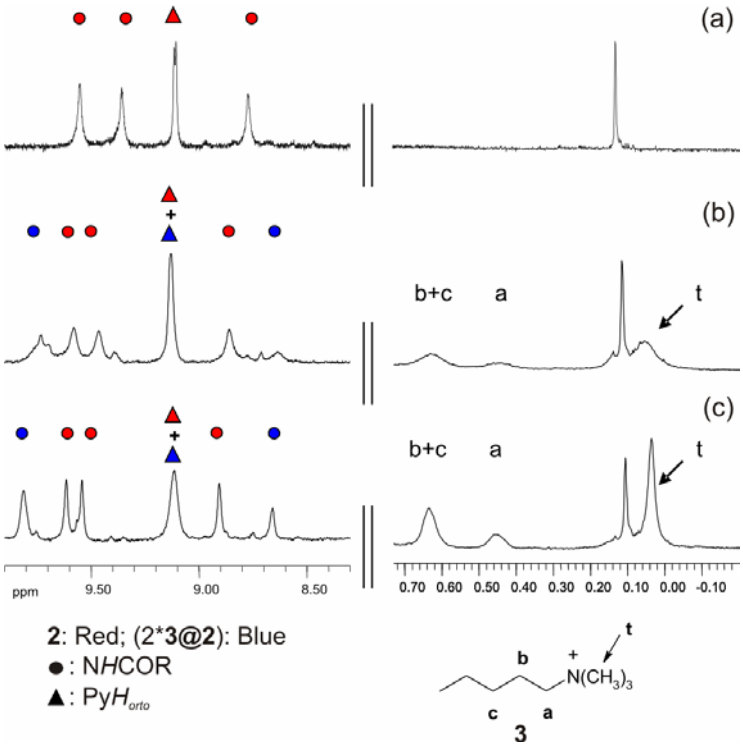


Figure S7: Down-field and up-field regions of the ^{1}H NMR (600 MHz, acetone-d_6): (a) Molecular dimer **2** at 300K; (b) (2***3@2**) at 273K; (c) (2***3@2**) at 253K. At [**2**]= 2 mM; [**3**]= 30 mM.

Compound	**Hexaamide diol cavitand**
Empirical formula	$C_{75}H_{94.50}Cl_{2.50}N_6O_{20.50}$
Formula weight	1496.69
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P1 (No. 2, C_i^1)
Unit cell dimensions	*a* = 15.133(3) Å alpha = 112.60(3)°
	b = 15.339(3) Å beta = 103.94(3)°
	c = 18.436(4) Å gamma = 92.58(3)°
Volume, *Z*	3789.0(13) $Å^3$, 2
Density (calculated)	1.312 Mg/m^3
Absorption coefficient	0.179 mm^{-1}
F(000)	1586
Crystal size	0.36 x 0.26 x 0.24 mm
θ range for data collection	1.25 to 25.00°
Limiting indices	$-17 \le h \le 17$; $-17 \le k \le 18$, $-21 \le l \le 21$
Reflections collected	28181
Independent reflections	13290 (R_{int} = 0.0586)
Completeness to θ = 25.00º	99.6 %
Absorption correction	Empirical
Max. and min. transmission	0.9582 and 0.9382
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13290 / 0 / 970
Goodness-of-fit on F^2	1.027
Final *R* indices (I>2σ (I)]	*R*1 = 0.0938, *wR*2 = 0.2523
R indices (all data)	*R*1 = 0.1435, *wR*2 = 0.2907
Extinction coefficient	0.0026(7)
Largest diff. peak and hole	1.111 and -0.662 *e*$Å^{-3}$

Table S1: Crystal data and structure refinement for **hexaamide diol cavitand**.

[1] Tunstad, L.; 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.
[2] Amrhein, P.; Shivanyuk, A.; Johnson, D. W.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 10349-10358.
[3] E. Menozzi; R. Pinalli; E. Speets; B. J. Ravoo; E. Dalcanale; D. N. Reinhoudt. *Chem. Eur. J.* **2004**, *10*, 2099-2106.
[4] Cipriani, A.; Fracassini M. C.; Germani, R.; Savelli, G.; Bunton, C. A. *J. Chem. Soc. Perkin Trans II*, **1987**, 547-551.
[5] a) S. Fallis, G. K. Anderson, N. P. Rath, *Organometallics* **1991**, *10*, 3180-3184. b) P. J. Stang, D. H. Cao, S. Saito, A. M. Arif, *J. Am. Chem. Soc.* **1995**, *117*, 6273-6283.