Supplementary Material (ESI) for Chemical Communications

Self-folding Cavitands: Structural Characterization of the Induced-Fit Model

Agustí Lledó and Julius Rebek, Jr.*

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

E-mail: jrebek@scripps.edu

Supporting Information

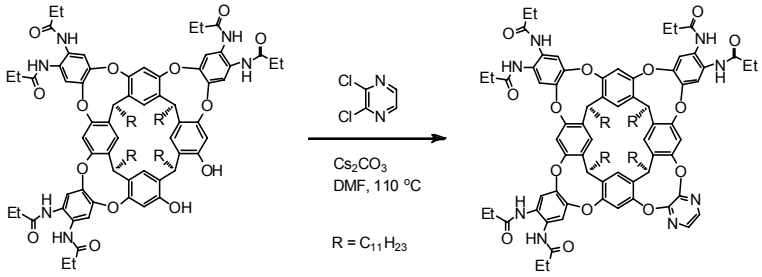
Contents:

I. General Experimental

^{1}H and ^{13}C NMR spectra were recorded at 300 K unless otherwise stated at 600 MHz and 150 MHz respectively, using a Bruker DRX-600 spectrometer equipped with a 5 mm QNP probe. The NMR data are reported as follows: chemical shift in ppm from internal tetramethylsilane (^{1}H and ^{13}C), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Chloroform-*d* and mesitylene-d_{12} were purchased from Cambridge Isotope Laboratories, Inc. Reaction progress during the preparation of all compounds was monitored using thin layer chromatography using Merck 60 F_{254} silica gel plates on aluminum foil. Column chromatography was performed using Silicycle R10030B 60 Å 230-400 mesh silica gel. Starting cavitand **2** was prepared according to the previously reported procedure.[1] Quinuclidine, 1-chloroadamantane and diamantane (*congressane*) were purchased from Aldrich and used as received.

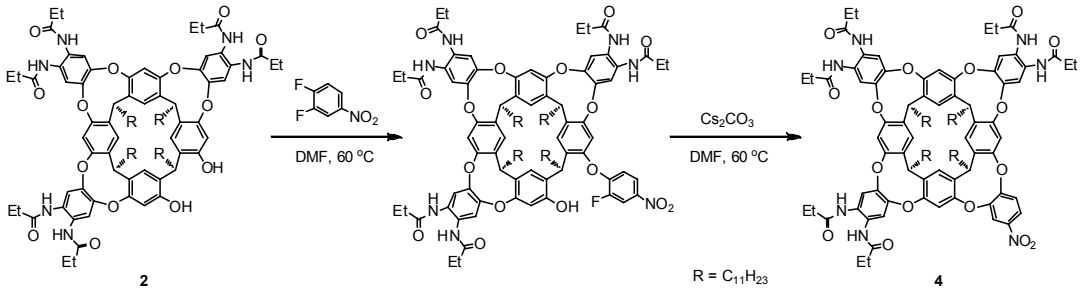
II. Synthetic Procedures and Characterization Data for 3-6.

Hexaamide-pyrazine Cavitand 3.



In a pressure tube were weighed hexaamidodiol cavitand **2** (136 mg, 0.0775 mmol), 2,3-dichloropyrazine (12.1 mg, 0.0814 mmol) and cesium carbonate (63 mg, 0.194 mmol). DMF was added (4.7 mL) and the tube was flushed with argon, sealed and heated to 100 ^{o}C with stirring for 18 h. The solvent was then removed under reduced pressure and the product was purified by flash chromatography (SiO_2, CH_2Cl_2/CH_3CN 8:2) to obtain a pale brown powder. The compound was further purified by recrystallization from EtOH to obtain 78 mg (55%) of a fine white powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (t, J = 6.9, 12H, 4 x CH_3 feet), 1.20-1.55 (m, 82H, 32 x CH_2 feet + 6 x CH_3 Et), 2.17-2.60 (m, 20H, 6 x CH_2 Et + 4 x CH_2 feet), 5.60 (t, J = 7.93 Hz, 1H, CH), 5.71 (t, J = 8.23 Hz, 2H, 2 x CH), 5.76 (t, J = 8.17 Hz, 1H, CH), 7.20 (s, 2H, 2 x CH_{Ar}), 7.25 (s, 4H, 4 x CH_{Ar}), 7.47 (s, 4H, 4 x CH_{Ar}), 7.54 (s, 2H, 2 x CH_{Ar}), 7.58 (s, 2H, 2 x CH_{Ar}), 8.04 (m, 4H, 2 x NH + 2 x CH_{Ar}), 9.33 (s, 2H, 2 x NH), 9.42 (s, 2H, 2 x NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.4, 155.1, 154.7, 154.3, 152.8, 150.1, 149.9, 136.5, 135.8, 135.6, 135.5, 124.0, 123.8, 121.7, 120.8, 120.1, 117.7, 116.6, 34.1, 33.6, 33.0, 32.2, 30.9, 30.4, 30.0, 30.01, 29.98, 29.94, 29.6, 28.3, 22.9, 15.5, 14.3, 10.7, 10.6, 9.9 ppm. MS (MALDI) calcd. for $C_{112}H_{149}N_8O_{14}^+$ ([M+H]$^+$): 1830; found: 1830. HRMS (ESI-TOF) calcd. for $C_{112}H_{147}N_8O_{14}^-$ ([M-H]$^-$): 1828.1042; found: 1828.1007.

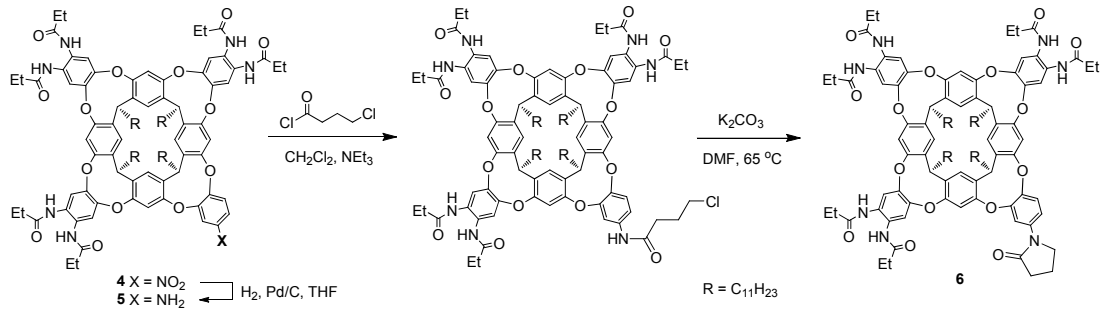
Hexaamide-mononitro Cavitand 4.



Hexaamidodiol cavitand **2** (520 mg, 0.296 mmol) and 3,4-difluoronitrobenzene (52 mg, 0.326 mmol, 1.10 eq.) were dissolved in 8.7 mL of dry DMF under argon. The flask was immersed in an oil bath at 60 ^{o}C, NEt_3 was added (62 μL, 0.445 mmol, 1.5 eq.) and the mixture stirred at this temperature for 16 h. The solvent was removed *in vacuo* and the product purified by flash chromatography (SiO_2, CH_2Cl_2/AcOEt 90:10 to 70:30) to obtain 397 mg (71%) of the open fluoro-nitro derivative as a white solid {^{1}H NMR (600 MHz, $CDCl_3$): δ0.89 (m, 12H), 1.09 (t, J = 7.6 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H), 1.18-1.51 (m, 84H), 2.10-2.54 (m, 20H), 4.39 (t, J = 8.2 Hz, 1H), 5.70 (t, J = 8.2 Hz, 1H), 5.77 (t, J = 8.2 Hz, 1H), 5.85 (t, J = 8.2 Hz, 1H), 6.66 (s, 1H), 6,75 (m, 2H), 6.82 (s, 1H), 7.17 (s, 1H), 7.20 (s, 1H), 7.28 (s, 2H), 7.30 (s, 1H), 7.36 (s, 1H), 7.40 (s, 1H), 7.42 (s, 1H), 7.53 (s, 2H), 7.59 (m, 2H), 7.87 (d, J = 8.8 Hz, 1H), 8.01 (s, 1H), 8.08 (d, J = 2.5 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 9.29 (s, 1H), 9.33 (s, 1H), 9.44 (s, 1H), 9.55 (s, 1H) ppm. ^{19}F NMR (565 MHz, $CDCl_3$): δ -128.5 (s) ppm. MS (MALDI-TOF) calcd. for $C_{114}H_{150}FN_7NaO_{16}$ ([M+Na]$^+$): 1951; found: 1915}. This open mononitro (395 mg, 0.209 mmol) and Cs_2CO_3 (102 mg, 0.313 mmol, 1.5 eq.) were dissolved in DMF under argon and the mixture was stirred at 60 ^{o}C for 16 h. The solvent was removed *in vacuo* and the residue treated with CH_2Cl_2 and 20 mL of 0.1M aq. HCl. The aqueous phase was

extracted twice with CH_2Cl_2 and the combined organic fractions were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. Flash column chromatography (SiO_2, CH_2Cl_2/AcOEt 100:0 to 80:20) afforded 271 mg (69%) of a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.89 (bt, 12H), 1.18-1.49 (m, 90H), 2.17-2.60 (m, 20H), 5.65 (t, J = 8.2 Hz, 1H), 5.73 (bt, 1H), 5.76 (bt, 1H), 5.79 (t, J = 8.4 Hz, 1H), 7.15 (s, 1H), 7.16 (s, 1H), 7.21 (2s, 2H), 7.23/7.25/7.28 (3s, 5H overall), 7.31 (s, 1H), 7.75 (s, 1H), 7.77 (s, 1H), 7.83 (s, 1H), 7.87 (dd, J = 9.0, 2.5 Hz, 1H), 8.01 (s, 1H), 8.08 (d, J = 9.0 Hz, 1H), 8.21 (d, J = 2.5 Hz, 1H), 8.61 (s, 1H), 8.97 (s, 1H), 9.07 (s, 1H), 9.76 (s, 1H), 9.81 (s, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.3, 174.8, 174.5, 172.8, 171.8, 158.8, 155.6, 155.3, 155.0, 154.8, 153.2, 151.1, 150.5, 150.4, 150.0, 149.2, 144.2, 136.4, 136.3, 136.0, 135.9, 135.5, 135.4, 135.2, 130.0, 129.6, 129.2, 127.7, 127.4, 126.8, 126.0, 124.4, 123.9, 121.5, 121.4, 121.2, 121.0, 120.4, 119.4, 117.0, 116.6, 116.5, 116.1, 33.5, 33.1, 32.6, 32.3, 32.1, 30.8, 29.9, 29.8, 29.6, 28.2, 22.9, 14.3, 11.0, 10.3, 10.2, 9.8 ppm. MS (MALDI-TOF) calcd. for $C_{114}H_{149}N_7O_{16}Na^+$ ([M+Na]$^+$): 1895.0952; found: 1895.

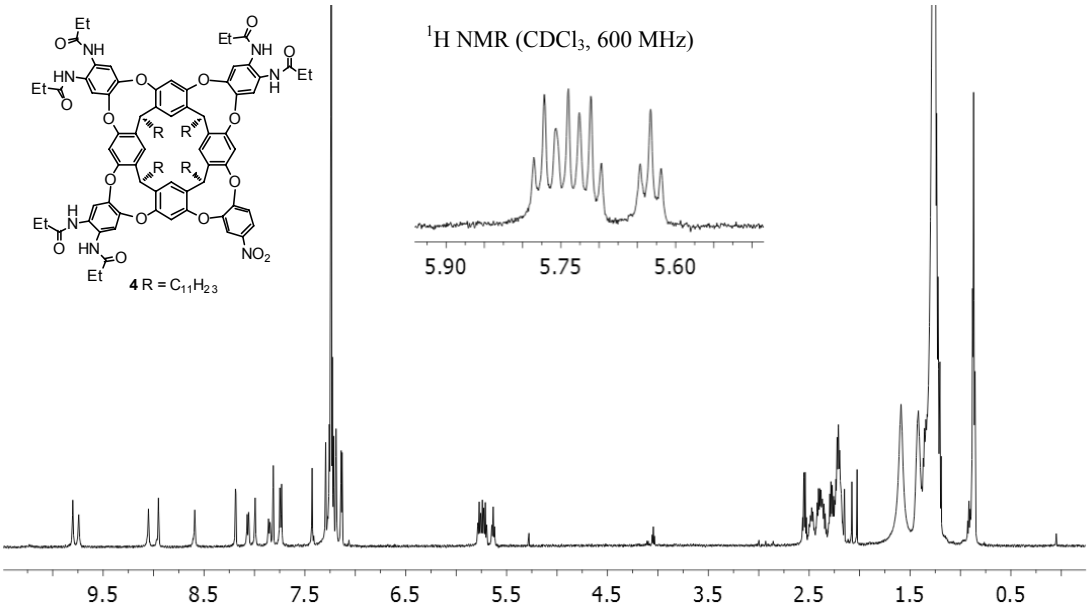
Heptaamide Cavitand 6.

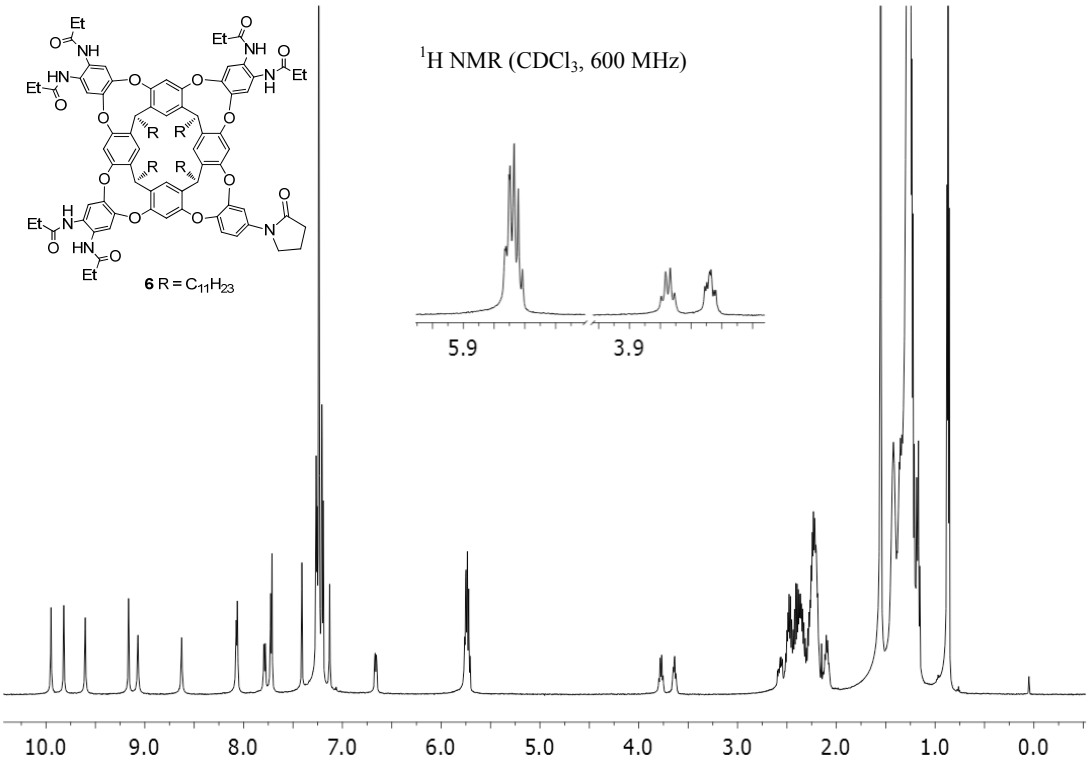


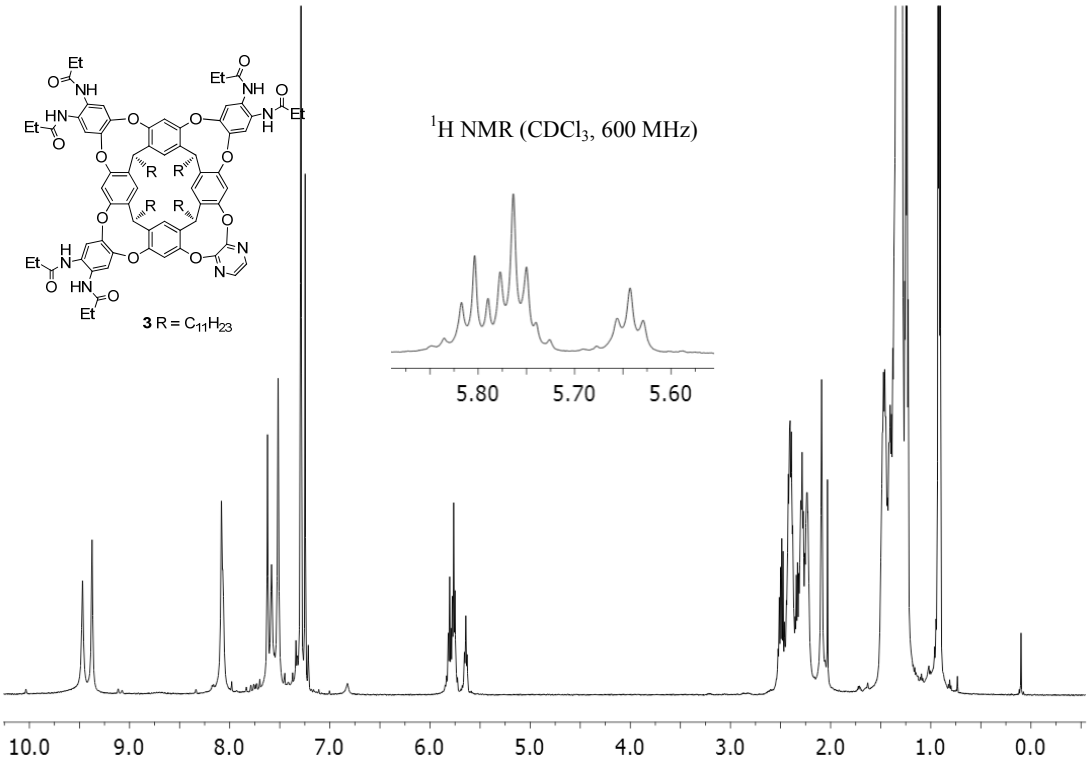
Hexaamido mononitro cavitand **4** (127 mg, 0.0671 mmol) was dissolved in 5 mL of THF. A catalytic amount of Pd/C (10% Pd) was added and the system purged with H_2. After stirring for 3 h at rt TLC showed disappearance of the starting material. The crude was filtered through celite under argon rinsing the pad with THF. The solvent was removed *in vacuo* to afford the amine as a colorless oil which was then redissolved in 8 mL of dry dichloromethane under argon. Triethylamine (28 μL, 0.201 mmol) and 4-chlorobutyryl chloride (15 μL, 0.134 mmol) were added sequentially and the mixture was stirred at rt for 45 min. The solvent was then removed *in vacuo* and the product was purified by flash column chromatography (SiO_2, CH_2Cl_2/AcOEt 9:1 to 7:3) to obtain 105 mg (80%, 2 steps) of the 4-chlorobutyrylamide derivative {^{1}H NMR (600 MHz, $CDCl_3$), characteristic resonances: δ 5.61 (t, J = 6 Hz, 1H, CH), 5.64 (t, J = 6 Hz, 1H, CH), 5.74 (t, J = 8.1 Hz, 1H, CH), 5.78 (t, J = 8.2 Hz, 1H, CH), 8.29 (bs, 1H, NH), 8.60 (bs, 1H, NH), 9.10 (bs, 1H, NH), 9.16 (s, 1H, NH), 9.19 (s, 1H, NH), 9.73 (s, 1H, NH), 9.75 (s, 1H, NH) ppm}. This compound (100 mg, 0.0513 mmol) was dissolved in 5 mL of dry DMF and 15 mg (0.108 mmol) of potassium carbonate were added. The mixture was heated at 65 °C for 2.5 h and the solvent was removed under reduced pressure. The product was purified by flash chromatography (SiO_2, CH_2Cl_2/AcOEt 1:1) and then recrystallized from ethanol to obtain 54 mg (55%) of a white powder. ^{1}H

NMR (600 MHz, $CDCl_3$): δ 0.87 (t, J = 6.9 Hz, 12H, 4 x CH_3), 1.13-1.48 (m, 82H, 32 x CH_2 feet + 6 x CH_3 Et), 2.04-2.64 (m, 24H, 6 x CH_2 Et + C_2H_4 lactam + 4 x CH_2 feet), 3.64 (td, 1H, J = 9.0, 3.6 Hz, CH_2-N lactam), 3.78 (dd, 1H, J = 17.5, 9.0 Hz, CH_2-N lactam), 5.73 (m, 4H, 4 x CH), 6.66 (d, J = 6.7 Hz, 1H, CH_{Ar}), 7.13 (s, 1H, CH_{Ar}), 7.19 (s, 1H, CH_{Ar}), 7.21 (m, 3H, 3 x CH_{Ar}), 7.23 (s, 1H, CH_{Ar}), 7.25-7.29 (m, 4H, 4 x CH_{Ar}), 7.41 (s, 1H, CH_{Ar}), 7.71 (s, 1H, CH_{Ar}), 7.73 (s, 1H, CH_{Ar}), 7.79 (d, J = 8.8, 1H, CH_{Ar}), 8.06 (d+s, 2H, 2 x CH_{Ar}), 8.63 (s, 1H, NH), 9.07 (s, 1H, NH), 9.17 (s, 1H, NH), 9.60 (s, 1H, NH), 9.82 (s, 1H, NH), 9.95, (s, 1H, NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.9, 174.7, 174.2, 172.8, 171.3, 155.50, 155.45, 155.41, 155.0, 154.8, 154.7, 150.8, 150.6, 149.5, 148.4, 136.1, 135.85, 135.79, 135.70, 135.6, 135.5, 135.4, 131.0, 129.7, 129.0, 128.8, 127.4, 127.2, 126.3, 124.0, 123.9, 123.8, 123.6, 121.5, 121.44, 121.38, 121.31, 120.7, 120.3, 117.4, 117.3, 116.9, 116.8, 116.6, 116.4, 49.8, 33.59, 33.55, 33.4, 33.1, 32.7, 32.6, 32.4, 32.3, 32.2, 31.00, 30.02, 29.95, 29.8, 29.7, 28.32, 28.30, 22.9, 14.4, 11.2, 11.0, 10.4, 10.0 ppm. MS (ESI-TOF) calcd. for $C_{118}H_{156}N_7O_{15}^+$ ([M+H]$^+$): 1911; found: 1911.

Selected NMR spectra.





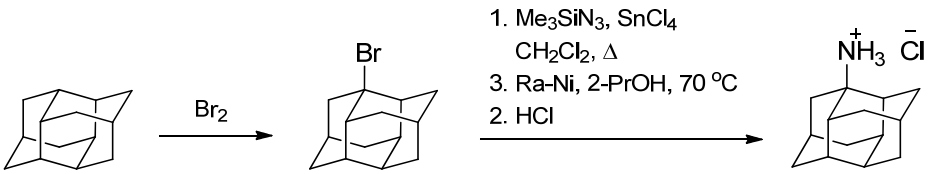


III. Preparation of guests 7 and $9^{+}Cl^{-}$.

_N_-Methylquinuclidine iodide, 7.[2]

N-Methylquinuclidinium iodide was prepared as previously reported by reaction of the amine with methyl iodide in AcOEt from which the compound crashes out. The solids were washed with ether and quickly transferred to a vial and dried under high vacuum with heating (40 °C). The product, a white powder, is quite hygroscopic.

1-Aminodiamantane hydrochloride, $9^{+}Cl^{-}$.



1-Aminodiamantane was prepared in a two step sequence from diamantane following established procedures.[3] The hydrochloride salt was obtained by bubbling HCl in a toluene solution of the amine for a few seconds. To the cloudy solution was added diethyl ether and the precipitate was collected and rinsed with fresh ether and dried under high vacuum.

IV. EXSY Experiments.

Two 2D NOESY spectra were taken sequentially at the reported temperature, one with 300 ms mixing time and then with 0 ms mixing time (Fig. S1). Spectra were recorded using the standard gradient pulsed NOESY sequence supplied with the Bruker software. Each of the 512 F1 increments was the accumulation of 32 scans. Before Fourier transformation, the FIDs were multiplied by a $\pi/2$ sine square function in both the F2 and the F1 domains. 1K_1K real data points were used, with a resolution of 1 Hz/point. The rate constants k_{-1} for the dissociation processes were calculated from integral values using the EXSYCALC program (Mestrelab Research, Santiago de Compostela). $\Delta G^{\neq}$ was obtained using the Eyring Equation:

$$k = (k_B T / h) e^{(-\Delta G^{\neq}/RT)}$$

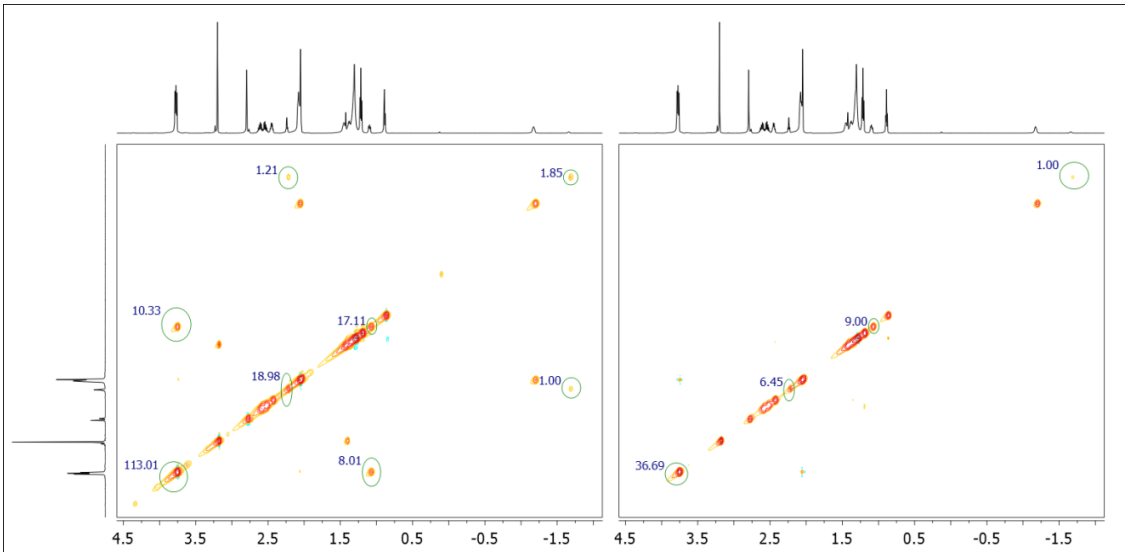


Figure S1. 2D NOESY spectra (600 MHz, acetone-d_6) at 300 ms (left) and 0 ms (right) mixing time for the system **1**·**7** ([**1**] = 3.35 mM, [**7**] = 21.3 mM). A 1D spectrum of free **7** in acetone-d_6 is shown on the vertical projection. The integrals shown correspond to the C**H**$_2$-N and C**H** resonances of the *N*-methylquinuclidinium cation which are upfield shifted 2.67 and 3.90 ppm respectively in the bound state.

V. ^{1}H NMR spectrum and molecular model of 2·2 in mesitylene-d_{12}.

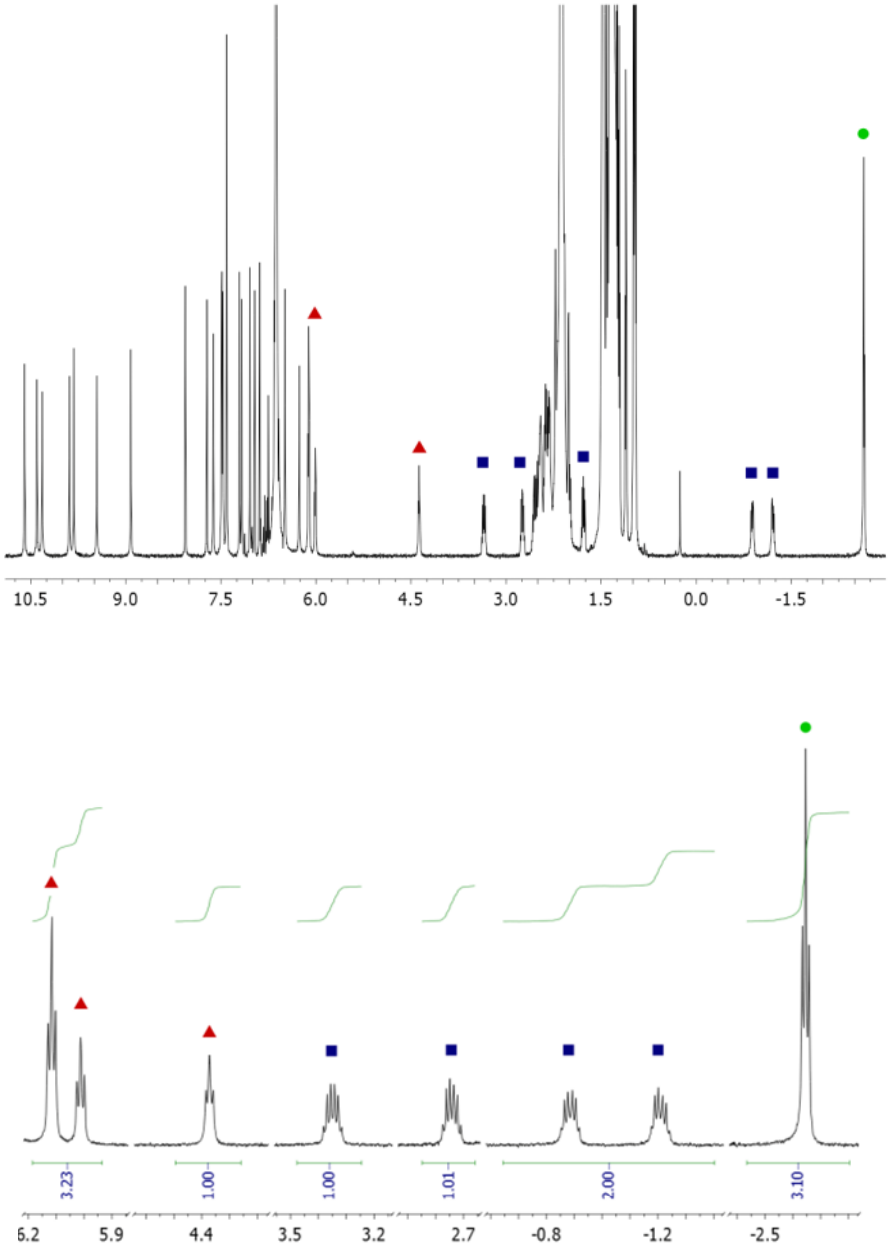


Figure S2. ^{1}H NMR (600 MHz) spectrum of **2·2** in mesitylene-d_{12} ([**2**] = 3 mM). Red triangles indicate the methine resonances of the resorcinarene core; blue squares and green dots are respectively CH_2 and CH_3 resonances from the propionamide groups. One of the Et substituents of each cavitand moiety lies in the hydrophobic pocket of the other one and is shifted upfield (δ -0.90, -1.20 and -1.65 ppm) whereas another one lies in an anisotropically deshielded area outside the cavitand's walls and is shifted downfield (δ 2.75 and 3.35 ppm). The splitting of the CH_2 into diastereotopic nuclei evidences the cavitand's chirality. This arises from a clockwise/counterclockwise arrangement of the amide groups which interconvert slowly in the NMR time scale.

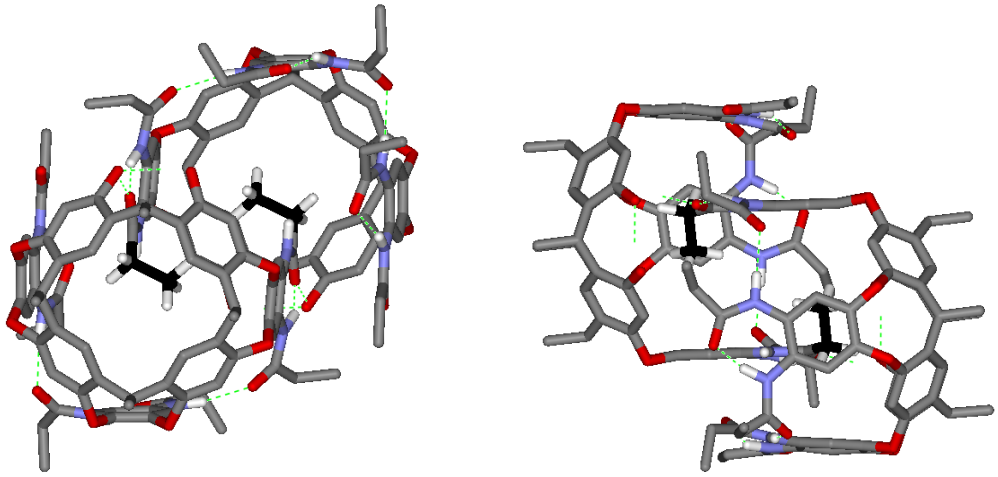


Figure S3. Two views of an optimized model (Spartan 04, MMFF) of **2·2**. The introverted Et groups are shown in black. Some hydrogens are omitted for clarity.

[1] T. Iwasawa, P. Wash, C. Gibson, J. Rebek, *Tetrahedron,* 2007, **63**, 6506.
[2] J.-Y. Kazock, M. Taggougui, B. Carre, P. Willmann, D. Lemordant, *Synthesis*, 2007, **24**, 3776.
[3] T. M. Gund, M. Nomura, P. V. R. Schleyer, *J. Org. Chem.,* 1974, **39**, 2987; T. M. Gund, P. V. R. Schleyer, G. D. Unruh, G. J. Gleicher, *J. Org. Chem.,* 1974, **39**, 2995; M. C. Davis, D. A. Nissan, *Synth. Commun.*, 2006, **36**, 2113.