Deep Cavitand Receptors with pH-Independent Water Solubility

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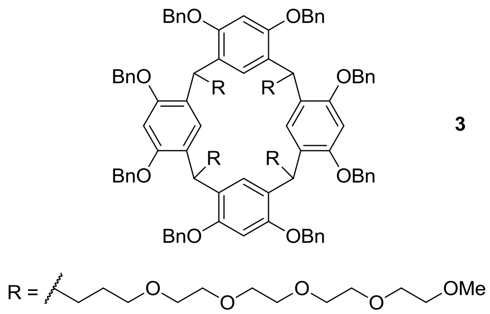
Supporting Information

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. DMSO-*d*$_6$, acetone-*d*$_6$, and D_2O ("100%" *d*) were purchased from Cambridge Isotope Laboratories, Inc. The pD of solutions used for NMR studies was adjusted with NaOD (30% in D_2O, 99.5% *d*) or DCl (35% in D2O, 99.5% *d*) solutions also purchased from CIL. Reaction progress during the preparation of all compounds was monitored using thin layer chromatography using Merck 60 F254 silica gel plates on aluminum foil. Column chromatography was performed using Silicycle R10030B 60 Å 230-400 mesh silica gel. Tetrahydrofuran and dimethylformamide were purchased from Mallinckrodt Baker and dried by passage through activated alumina columns on a Glass Contour solvent system (SG Water). Starting resorcinarene **2** was prepared according to previously reported procedures.[1,2] Guests **6a**-**c**, **9** and **10** were purchased from Aldrich and used as received. Cyclohexylamine hydrochloride (**7**) was prepared by gentle bubbling of HCl in an ethereal solution of cyclohexylamine (Aldrich). The precipitated solids were filtered and dried under high vacuum. Methyl quinuclidinium iodide (**8**) was prepared by addition of a slight excess of methyl iodide (Aldrich) to a solution of quinuclidine (Aldrich) in ethyl acetate under stirring. The solids were filtered, washed with diethyl ether and dried under high vacuum.

II. Synthetic Procedures and Characterization Data for **1** and **3**-**5**.

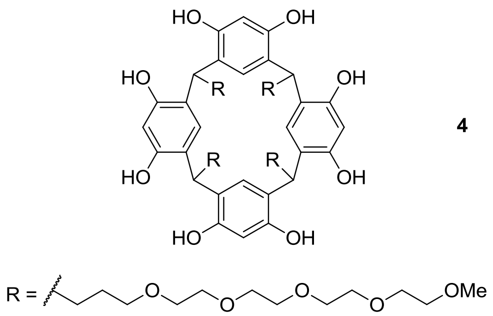
TEG-footed *O*-benzylresorcinarene 3.



3

Tetraethyleneglycol monomethyl ether (2.97 g, 14.28 mmol) was dissolved under argon in 34 mL of dry THF in a two necked 250 mL flask equipped with a reflux condenser. Sodium hydride (490 mg, 60%, 12.24 mmol) was added in small portions and the mixture stirred for 20 min. *O*-Benzylresorcinarene tetramesylate **2** (3.58 g, 2.04 mmol) was then added as a solid and the mixture was heated to reflux for 16 h. After this time the solvent was removed under reduced pressure and the crude product was dissolved in 250 mL of AcOEt and washed with water and brine. The organic layer was concentrated again to obtain a thick oil which was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 100:0, 98:2, 96:4) to furnish 3.76 g (74%) of the title compound in good purity. ^{1}H NMR (600 MHz, DMSO-*d*$_6$, 330 K): δ 1.46 (m, 8H, CH_2), 1.87 (m, 8H, CH_2), 3.22 (s, 12H), 3.30 (t, *J* = 6.7 Hz, 8H, CH_2), 3.33 (m, 8H, CH_2), 3.40 (m, 8H, CH_2), 3.43 (m, 8H, CH_2), 3.44-3.50 (m, 40H, CH_2), 4.63 (t, *J* = 6.8 Hz, 4H, CH, partial overlap with next resonance), 4.65 (d, *J* = 11.8 Hz, 8H, CH_2), 4.93 (d, *J* = 11.8 Hz, 8H, CH_2), 5.70 (s, 4H, CH), 6.73 (s, 4H, CH), 7.20 (bs, 40H, CH) ppm. ^{13}C NMR (150 MHz, DMSO-*d*$_6$, 330 K) δ 154.58 (Cq), 137.21 (Cq), 127.69 (CH), 126.96 (CH), 126.80 (CH), 125.30 (CH), 99.24 (CH), 71.05 (CH_2), 70.26 (CH_2), 69.83 (CH_2), 69.56 (CH_2), 69.55 (CH_2), 69.48 (CH_2), 69.34 (CH_2), 69.18 (CH_2), 57.72 (CH_3), 35.12 (CH), 30.53 (CH_2), 27.86 (CH_2). HRMS (ESI-TOF) calcd. for $C_{132}H_{169}O_{28}^{+}$ ($[M+H]^+$): 2202.1794; found: 2202.1800.

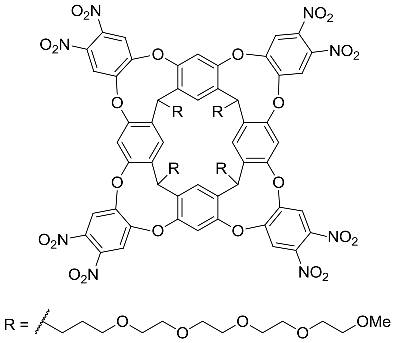
TEG-footed resorcinarene 4.



4

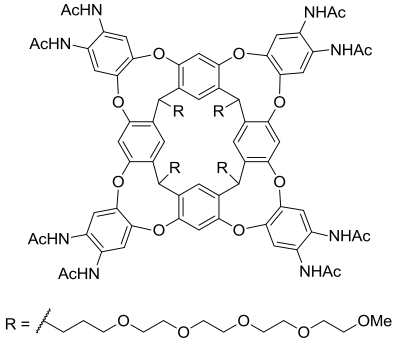
Benzyl protected resorcinarene **3** (2.70 g, 1.23 mmol) was stirred with Pd/C (1 g, 10% Pd w/w) in 50 mL of THF under hydrogen (45 bar) in a high pressure vessel for 24 h. The crude was filtered through Celite to remove the catalyst and the solvent was removed under reduced pressure. The crude was subjected to flash column chromatography (SiO_2, CH_2Cl_2/MeOH 97:3, 94:6, 93:7) to furnish 1.29 g (71%) of a waxy white solid. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 1.38 (m, 8H, CH_2), 2.05 (m, 8H, CH_2), 3.23 (s, 12H, CH_3), 3.38 (t, *J* = 6.7 Hz, 8H, CH_2), 3.41 (m, 8H, CH_2), 3.44 (m, 8H, CH_2), 3.48 (m, 48H, CH_2), 4.22 (t, *J* = 7.8 Hz, 4H, CH), 6.14 (s, 4H, CH), 7.17 (s, 4H, CH), 8.85 (s, 8H, OH) ppm. ^{13}C NMR (150 MHz, DMSO-*d*$_6$): δ 27.8 (CH_2), 30.3 (CH_2), 32.7 (CH), 58.0 (CH_3), 69.4 (CH_2), 69.6 (CH2), 69.8 (CH_2), 70.3 (CH_2), 71.3 (CH_2), 102.3 (CH), 122.8 (Cq), 125.0 (CH), 151.7 (Cq) ppm. HRMS (ESI-TOF) calcd. for $C_{76}H_{121}O_{28}^{+}$ ($[M+H]^+$): 1481.8038; found: 1481.8077.

TEG-footed octanitrocavitand 5.



TEG-footed resorcinarene **4** (268 mg, 0.181 mmol) and 1,2-difluoro-4,5-dinitrobenzene (148 mg, 0.723 mmol, 4.0 eq.) were dissolved in 4 mL of dry DMF under argon. Triethylamine (0.20 mL, 1.45 mmol, 8.0 eq.) was then added dropwise and the solution was stirred at 70 °C for 14 h. The volatiles were removed in vacuo and the product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 97:3). The resulting thick yellow oil was triturated in methanol to obtain, after drying under high vacuum, 240 mg (62%) of pale yellow powders. ^{1}H NMR (600 MHz, acetone-*d*$_6$, 330K): δ 1.59 (m, 8H, CH_2), 2.31 (m, 8H, CH_2), 3.29 (s, 12H, CH_3), 3.45-3.51 (m, 24H, CH_2), 3.53-3.60 (m, 48H, CH_2), 4.31 (t, *J* = 7.6 Hz, 4H, CH), 7.18 (bs, 4H, CH), 7.31 (s, 4H, CH), 8.07 (s, 8H, CH) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.93, 72.96, 71.54, 71.48, 71.36, 71.25, 71.21, 59.01, 37.16, 28.77, 28.23 ppm. HRMS (ESI-TOF) calcd. for $C_{100}H_{120}N_8NaO_{44}^{+}$ ($[M+Na]^+$): 2159.7290; found: 2159.7341.

TEG-footed octaacetamide cavitand 1.

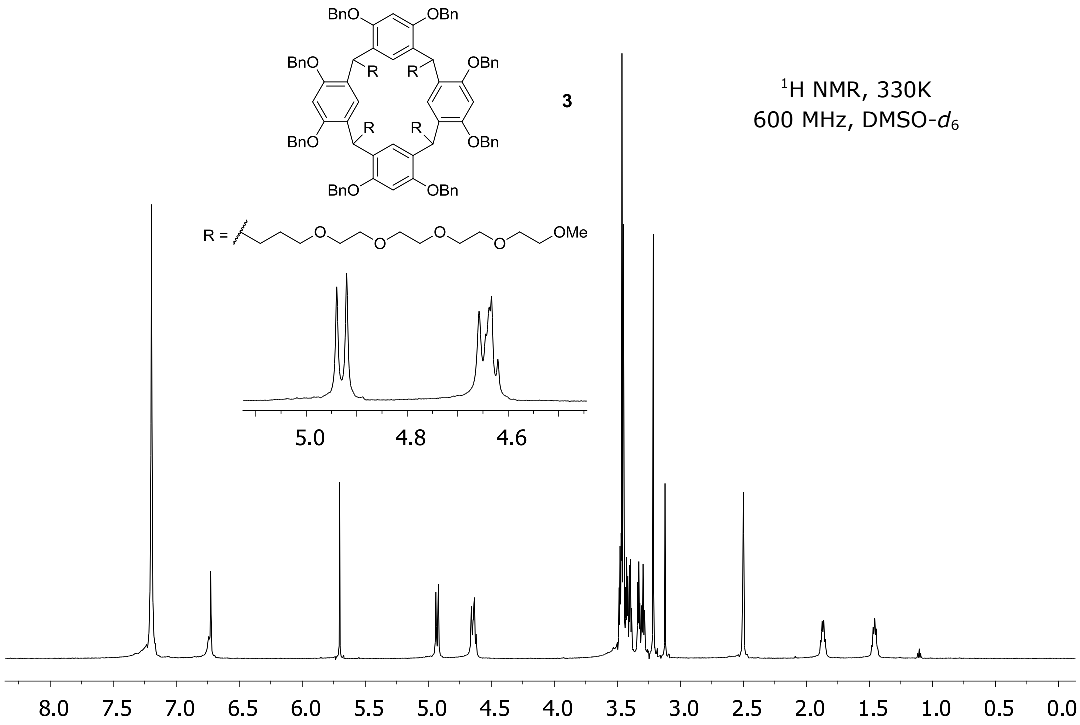


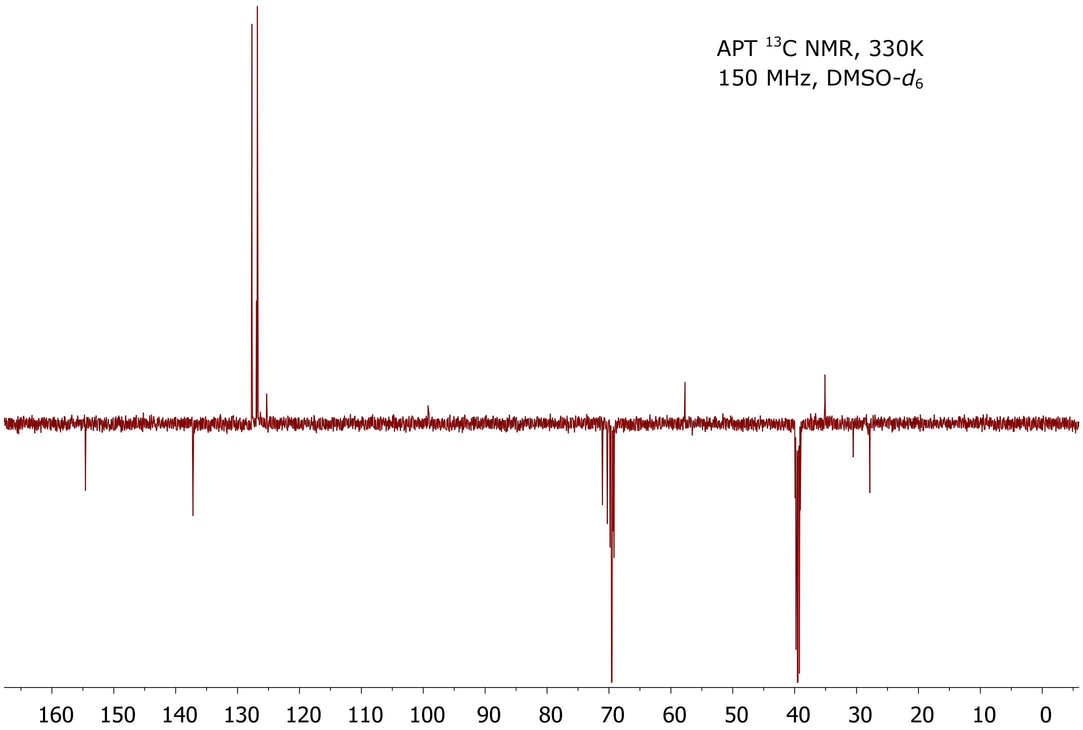
TEG-footed octanitro cavitand **5** (214 mg, 0.100 mmol) is dissolved in 4 mL of THF and a catalytic amount of Raney-Ni (previously washed with THF) is added as a suspension in 1 mL of THF. The flask is filled with hydrogen and the mixture stirred at 45 °C under hydrogen atmosphere for 16 h. At this point the hydrogen is evacuated and the flask purged with argon. The suspension is diluted with 5 mL of THF and triethylamine (0.56 mL, 4.0 mmol) is added followed by acetyl chloride (170 mL, 2.4 mmol). The mixture is stirred at room temperature for 2 hours and then filtered through a pad of Celite. The solvents are removed under reduced pressure and the crude product is purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 95:5, 94:6, 93:7) and recrystallized from isopropyl alcohol to obtain 135 mg (60%) of a white fine powder. ^{1}H NMR (600 MHz, acetone-d_6) δ 9.57 (s, 8H, NH), 7.96 (s, 4H, CH), 7.70 (s, 8H, CH), 7.50 (s, 4H, CH), 5.86 (t, J = 8.2 Hz, 4H, CH), 3.47 (m, 8H, CH_2), 3.54-3.64 (m, 64H, CH_2), 3.29 (s, 12H, CH_3), 2.49 (m, 8H, CH_2), 2.21 (s, 24H, CH_3), 1.63 (m, 8H, CH_2) ppm. ^{13}C NMR (150 MHz, acetone-d_6) δ 170.72 (C=O), 155.85 (Cq), 150.39 (Cq), 136.99 (Cq), 129.48 (Cq), 126.06 (CH), 121.76 (CH), 117.19 (CH), 72.80 (CH_2), 71.43 (CH_2), 71.38 (CH_2), 71.34 (CH_2), 71.20 (CH_2), 71.08 (CH_2), 58.92 (CH_3), 34.28 (CH), 29.15 (CH_2), 24.64 (CH_3) ppm. HRMS (ESI-TOF) calcd. for $C_{116}H_{154}N_8O_{36}^+$ ($[M+2H]^{2+}$): 1117.5227; found: 1117.5219.

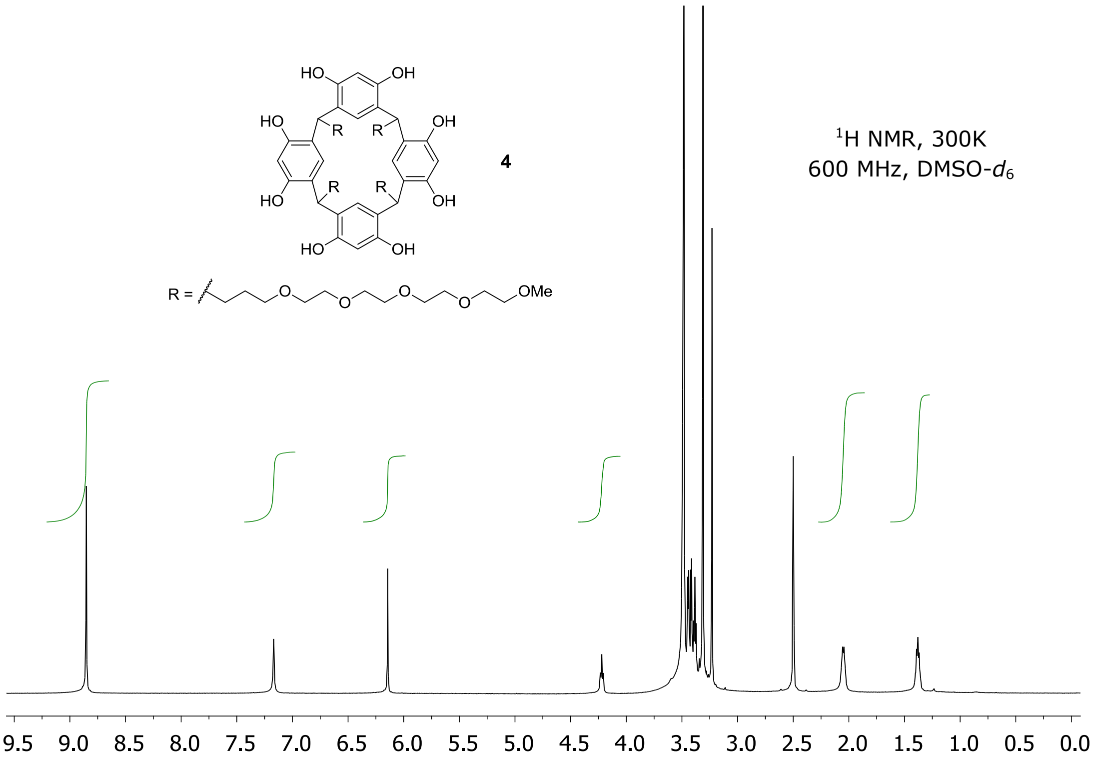
References

1. T. Haino, D. M. Rudkevich, A. Shivanyuk, K. Rissanen, J. Rebek and Jr., *Chem. Eur. J.*, 2000, **6**, 3797-3805.
2. B. C. Gibb, R. G. Chapman and J. C. Sherman, *J. Org. Chem.*, 1996, **61**, 1505-1509.

III. NMR Spectra of **1** and **3**-**5.**



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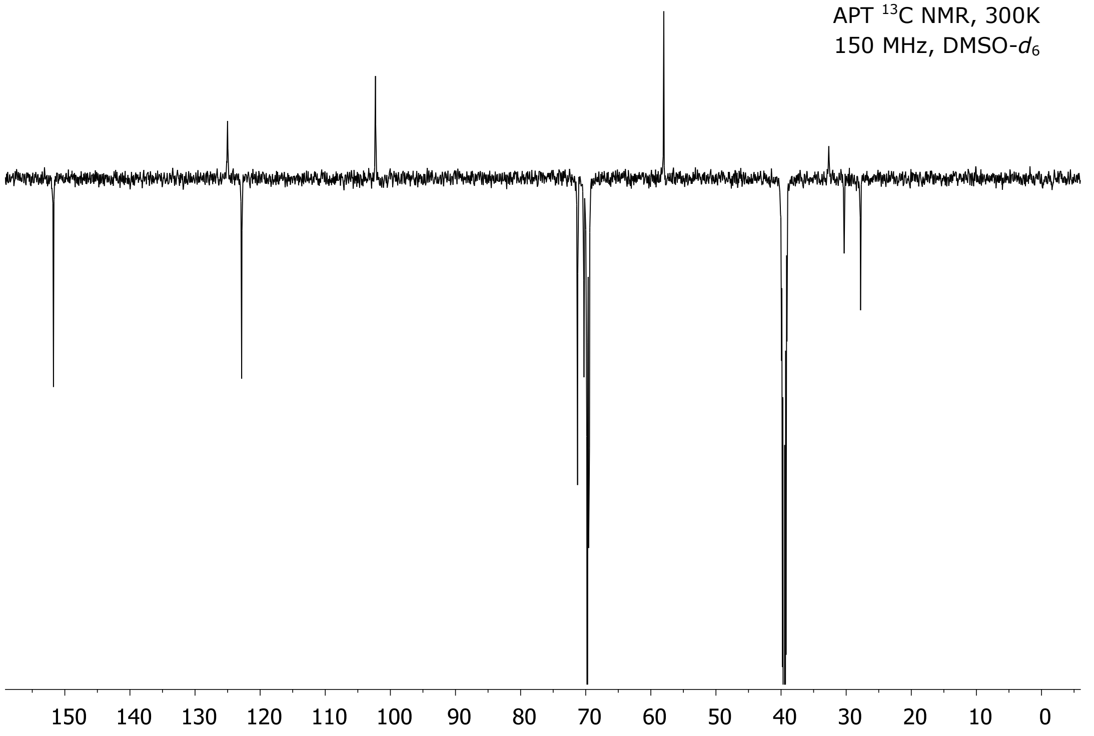
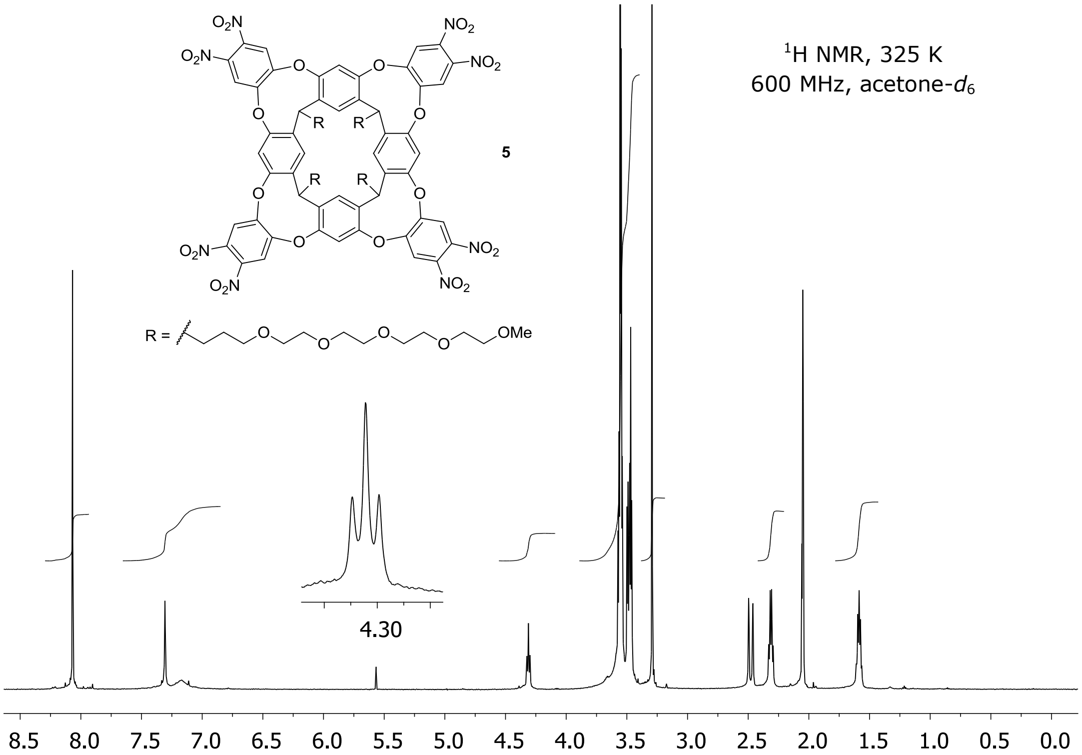
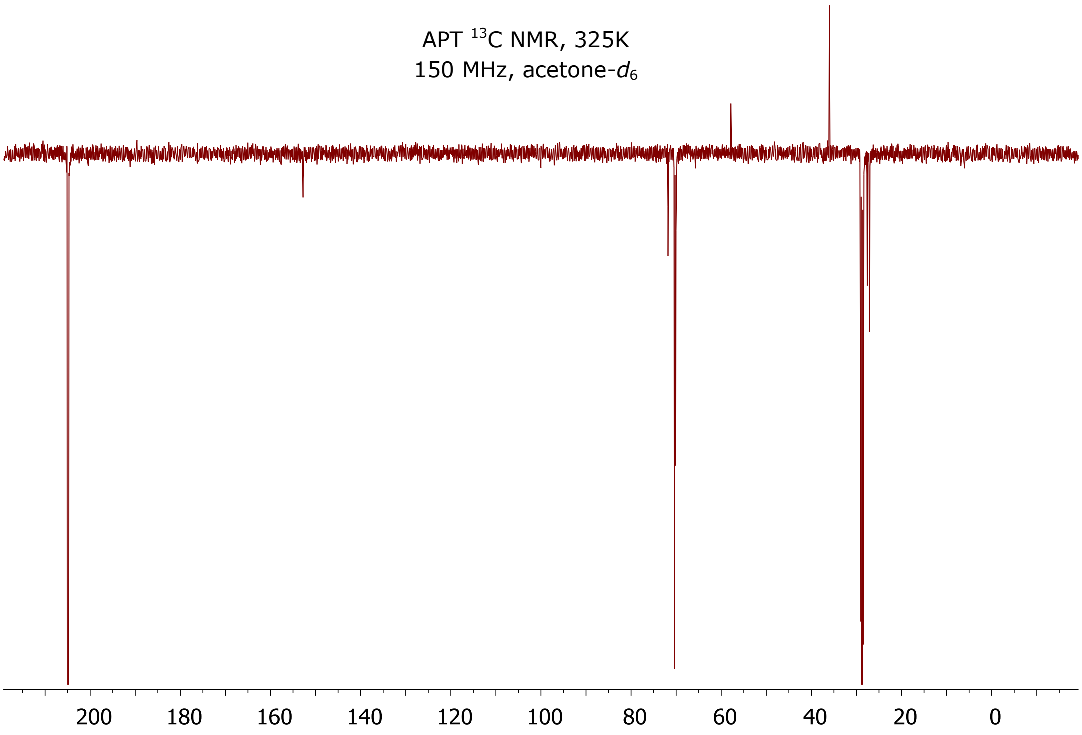
^{1}H NMR, 300K
600 MHz, DMSO-d_6


APT ^{13}C NMR, 300K
150 MHz, DMSO-d_6

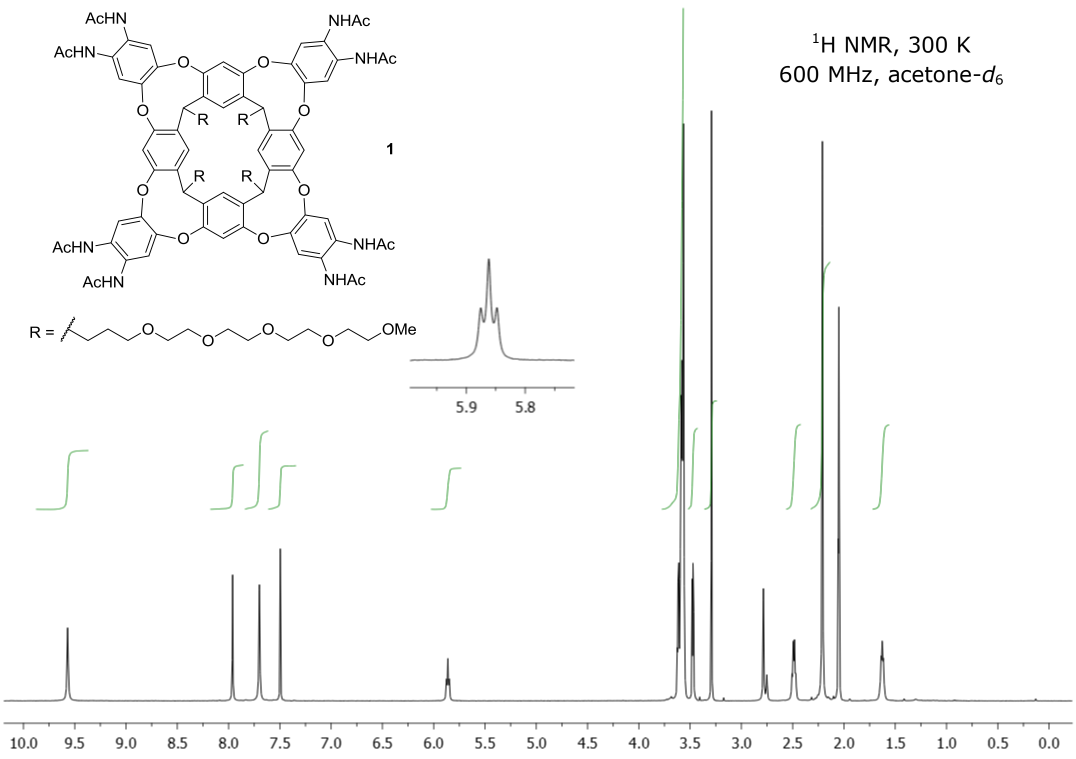


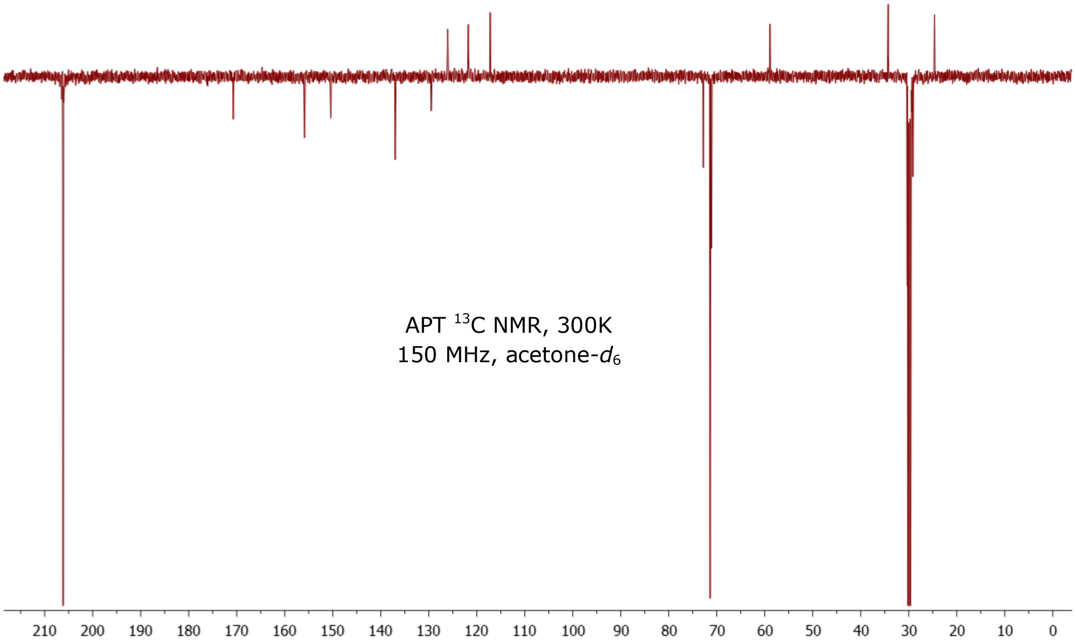
5

^{1}H NMR, 325 K
600 MHz, acetone-d_6



APT ^{13}C NMR, 325K
150 MHz, acetone-d_6


AcHN
NHAc
R
1
R = OMe
5.9
5.8
¹H NMR, 300 K
600 MHz, acetone-d6
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


APT ¹³C NMR, 300K
150 MHz, acetone-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

IV. ESI-MS Spectra of **1·1** and **6a⊂1**.

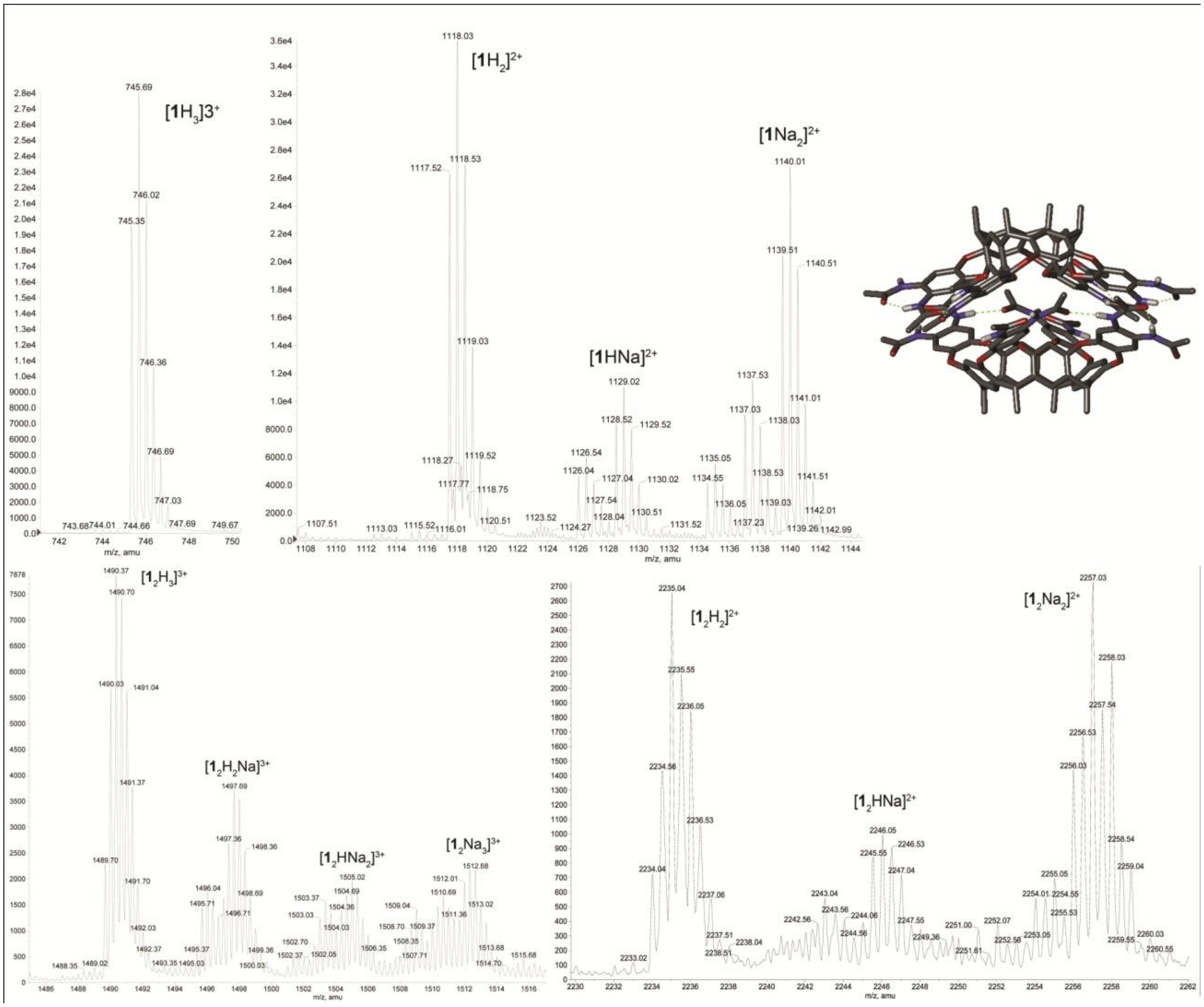


Figure S1. MS (ESI-TOF) of the velcrand dimer **1·1** in water solutions. Mono-, doubly- and triply charged states are observed. A stick molecular model showing the multiple π-π interactions is displayed on the right (molecular mechanics, MMFF force field).

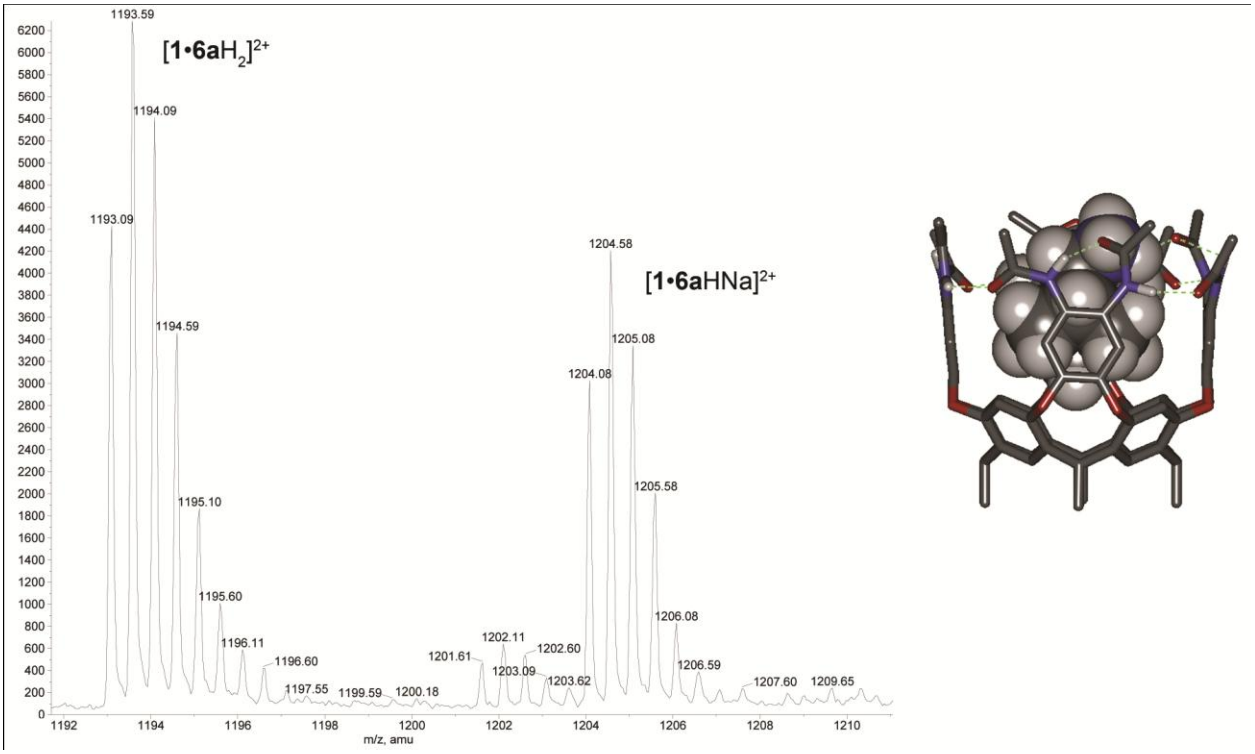


Figure S2. MS (ESI-TOF) of complex **6a**⊂**1** ionized from a water solution and a molecular model (molecular mechanics, MMFF force field). The buried guest is shown in CPK mode.

V. Diffusion Data.

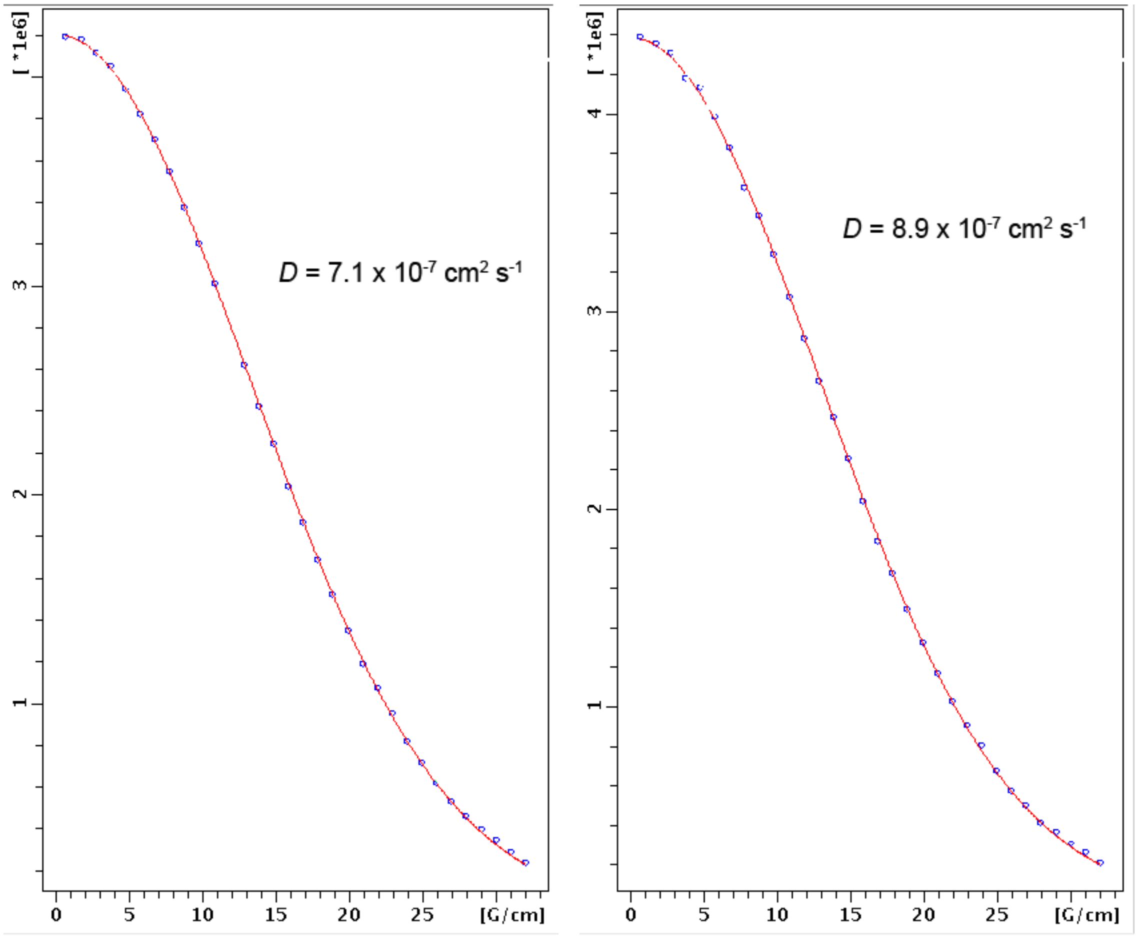


Figure S3. Intensity decay curves and exponential fit for selected resonances of **1·1** (left) and **6a⊂1** (right) in D_2O.