

Supporting Information

Dendronized Supramolecular Nano-Capsules: pH Independent, Water-Soluble, Deep-Cavity Cavitands Assemble via the Hydrophobic Effect

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Experimental

Materials: All reagents were purchased from Aldrich and were used without purification. 2,2-Bis(hydroxymethyl) propanoic acid, (bis-MPA,) was dried *in vacuo* prior to use. Dowex® 50x4 hydrogen form 50-100 mesh acid exchange resin was washed with methanol and filtered prior to use. All solvents were used directly from the bottle without additional purification. Deuterated solvents were purchased from Aldrich. NMR (¹H, ¹³C) spectra were recorded on Varian-400 and 500 MHz spectrometers at room temperature unless otherwise stated. Chemical shifts are reported in parts per million (ppm) relative to CDCl₃ (7.26 ppm for ¹H and 77.36 for ¹³C), (CD₃)₂SO (2.54 ppm for ¹H and 40.45 for ¹³C), and CD₃OD (3.34 for ¹H and 49.86 for ¹³C) as internal reference. MALDI spectra were collected using a Bruker-Daltonics MALDI-TOF Autoflex III mass spectrometer. The acetonide protected bis-MPA monomer, **1**, was prepared following the procedure previously reported by Gillies and Fréchet.¹ The octol cavitand, **1b**, was prepared following the synthetic methods previously reported by Gibb and Gibb.²

Nomenclature: The following nomenclature was used in order to simplify the identification of compounds and reagents. The prefix Ac- was designated for the acetonide protecting group. The dendron size and functionality on the acetonide protected cavitands were abbreviated Cav-([G-n]Ac_x)₈ where n = generation number and x = number of acetonide protecting groups per dendron. The dendron size and functionality on the hydroxyl-functionalized cavitands were abbreviated Cav-([G-n]OH_x)₈ where n = generation number and x = number of hydroxyls per dendron. *N,N*-dimethylaminopyridine was abbreviated as DMAP.

Synthesis and Characterization of **2**

General Dendronization Procedure for Preparation of ([G-n]Ac_x)₈. To a round bottom flask were added hydroxyl-terminated cavitand (62 μmol), 2 equivalents (per OH) of **1** and 0.5 molar equivalents (per OH) of DMAP. Pyridine (6 mL) and CH₂Cl₂ (4 mL) was added and the reaction was stirred vigorously for 4 hours. The reaction was monitored by MALD-TOF MS to determine the degree of coupling. After complete esterification was observed, the contents of the flask were transferred to a separatory funnel diluted with diethyl ether and extracted three times with NaHSO₄ followed by three times with NaHCO₃. The organic layer was then dried over anhydrous NaSO₄, filtered and evaporated to dryness. The white powdery product was then washed with methanol and placed in the refrigerator and then decant off the methanol to yield the Ac-protected dendronized cavitand.

General Deprotection Procedure for Preparation of ([G-n]OH_x)₈ Dendronized Cavitand. To a round bottom flask, ([G-n]Ac_x)₈ (35 μmol) was added with 8 cm³ Dowex® H⁺ in 4 mL toluene and 4 mL methanol. The temperature was adjusted to 70 °C and the reaction stirred vigorously for 2-3 hours. The deprotection of the dendronized cavitand was monitored by MALDI-TOF MS. When full deprotection was observed the Dowex® was filtered from the reaction using methanol. The filtrate was then reduced *in vacuo* to yield a clear oily solid.

Synthesis of Cav-([G-1]Ac)₈. The octol terminated cavitand, **1b** (0.101 g, 62.5 μmol), was esterified following the General Dendronization Procedure using 0.8177 g of Ac-protected Bis-MPA anhydride and 0.060 g DMAP to afford 0.1443 g of Cav-([G-1]Ac)₈ (80.6% yield). ¹H NMR (400 MHz CDCl₃): δ 1.07 (s, 12, -CH₃), 1.08 (s, 12, -CH₃), 1.24 (s, 12, -CH₃), 1.26 (s, 12, -CH₃), 1.33 (s, 24, -CH₃), 1.62 (p, 8, -CH₂-), 2.26 (q, 8, -CH₂-), 3.54 (d, 8, -OCH₂-), 3.57 (d, 8, -OCH₂-), 4.10 (d, 8, -OCH₂-), 4.12 (d, 8, -OCH₂-), 4.17 (t, 8, -COOCH₂-), 4.43 (s, 4, CH), 4.78 (t, 4, CH), 5.21 (s, 8, -ArCH₂OCO-), 5.94 (s, 4, ArH), 6.46 (d, 8, ArH), 6.50 (t, 4, ArH), 6.93 (t, 4, ArH), 7.11 (s, 4, ArH), 7.17 (s, 8, ArH). MALDI-TOF MS: Theo. Exact MW: [M + Na]⁺ m/z = 2888.123. Obs: [M + Na]⁺ m/z = 2888.18.

Synthesis of Cav-([G-1]OH₂)₈. The acetonide protected, dendronized cavitand Cav-([G-1]Ac)₈ (0.050 g, 17.45 μmol) was deprotected using Dowex® following the General Deprotection Procedure to afford 0.037 g of Cav-([G-1]OH₂)₈ (83.3% yield). ¹H NMR (400 MHz (CD₃)₂SO): δ 1.08 (s, 12, -CH₃), 1.15 (s, 12, -CH₃), 1.69 (p, 8, -CH₂-), 2.40 (q, 8, -CH₂-), 3.53-3.72 (m, 32, -OCH₂-), 4.22 (t, 8, -COOCH₂-), 4.60 (s, 4, CH), 4.73 (t, 4, CH), 5.22 (s, 8, -ArCH₂OCO-), 5.93 (s, 4, ArH), 6.50 (d, 8, ArH), 6.59 (t, 4, ArH), 6.93 (t, 4, ArH), 7.29 (d, 8, ArH), 7.33 (s, 4, ArH). MALDI-TOF MS: Theo. Exact MW: [M + Na]⁺ m/z = 2567.872. Obs: [M + Na]⁺ m/z = 2567.89.

Synthesis of Cav-([G-2]Ac₂)₈. The first generation deprotected, dendronized cavitand Cav-([G-1]OH₂)₈ (0.0994g, 39.06 μmol), was esterified following the General Dendronization Procedure using 0.3354g of the Ac-protected Bis-MPA anhydride, and 0.0382g of DMAP to afford 0.1810 g of Cav-([G-2]Ac₂)₈ (91.9 % yield). ¹H NMR (400 MHz CDCl₃): δ 1.09 (s, 24, -CH₃), 1.10 (s, 24, -CH₃), 1.25 (s, 12, -CH₃), 1.32 (s, 36, -CH₃), 1.36 (s, 24, -CH₃), 1.39 (s, 24, -CH₃), 1.40 (s, 24, -CH₃), 1.68 (q, 8, -CH₂-), 2.30 (q, 8, -CH₂-), 3.57 (d, 16, -OCH₂-), 3.60 (d, 16, -OCH₂-), 4.10 (d, 16, -OCH₂-), 4.13 (d, 16, -OCH₂-), 4.19 (t, 8, -COOCH₂-), 4.26-4.39 (m, 32, -OCH₂-), 4.52 (s, 4, CH), 4.78 (t, 4, CH), 5.23 (s, 8, -ArCH₂OCO-), 6.00 (s, 4, ArH), 6.48 (d, 8, ArH), 6.53 (t, 4, ArH), 6.96 (t, 4, ArH), 7.14 (s, 4, ArH), 7.17 (d, 8, ArH). MALDI-TOF MS: Theo. Exact MW: [M + Na]⁺ m/z = 5065.131. Obs: [M + Na]⁺ m/z = 5065.145.

Synthesis of Cav-([G-2]OH₄)₈. The second generation acetonide protected, dendronized cavitand Cav-([G-2]Ac₂)₈ (0.1212 g, 24.04 μmol), and 8 cm³ Dowex® H⁺ was reacted following the General Deprotection Procedure to afford 0.0994 g of Cav-([G-2]OH₄)₈ (92.3% yield). ¹H NMR (300 MHz CD₃OD): δ 1.09 (s, 24, -CH₃), 1.10 (s, 24, -CH₃), 1.24 (s, 12, -CH₃), 1.27 (s, 12, -CH₃), 1.72 (b, 8, -CH₂), 2.43 (b, 8, -CH₂-), 3.52-3.67 (m, 64, -OCH₂-), 4.20-4.38 (m, 40), 4.59 (s, 4, CH), 4.75 (t, 4, CH), 5.25 (s, 8, -ArCH₂OCO-), 5.93 (s, 4, ArH), 6.48 (d, 8, ArH), 6.59 (t, 4, ArH), 6.94 (t, 4, ArH), 7.27 (d, 8, ArH), 7.36 (s, 4, ArH). MALDI-TOF MS: Theo. Exact MW: [M + Na]⁺ m/z = 4424.630. Obs: [M + Na]⁺ m/z = 4424.8.

Synthesis of Cav-([G-3]Ac₄)₈. The second generation deprotected dendronized cavitand Cav-([G-2]OH₄)₈ (0.0416 g, 8.250 μmol), was esterified following the General Dendronization Procedure using 0.3323 g of Ac-Bis-PA and 0.0370g of DMAP to afford 0.0778 g of Cav-([G-3]Ac₄)₈ (87.6% yield). ¹H NMR (400 MHz CDCl₃): δ 1.10 (s, 48, -CH₃), 1.13 (s, 48, -CH₃), 1.20 (s, 12, -CH₃), 1.22 (s, 24, -CH₃), 1.23 (s, 24, -CH₃), 1.28 (s, 12, -CH₃), 1.30 (s, 48, -CH₃), 1.33 (s, 48, -CH₃), 1.38 (s, 48, -CH₃), 1.39 (s, 48, -CH₃), 1.68 (b, 8, -CH₂-), 2.31 (b, 8, -CH₂-), 3.57 - 3.64 (m, 64, -OCH₂-), 4.09 - 4.14 (m, 64, -OCH₂-), 4.18-4.31 (m, 104), 4.53 (s, 4, CH), 4.79 (t, 4, CH), 5.22 (s, 8, -ArCH₂OCO-), 6.02 (s, 4, ArH), 6.48 (d, 8, ArH), 6.52 (t, 4, ArH), 6.97 (t, 4, ArH), 7.14 (s, 4, ArH), 7.20 (d, 8, ArH). MALDI-TOF MS: Theo. Avg. MW: [M + Na]⁺ m/z = 9425.24. Obs: [M + Na]⁺ m/z = 9425.2.

Synthesis of Cav-([G-3]OH₈)₈, 8. The third generation Ac-protected cavitand, Cav-([G-3]Ac₄)₈ (0.0850 g, 10.47 μmol), and Dowex® H⁺ (8 cm³) was added to a round bottom flask following the General Deprotection Procedure to afford 0.0644 g of Cav-([G-3]OH₈)₈ (87.7% yield). ¹H NMR (400 MHz CD₃OD): δ 1.13 (s, 96, -CH₃), 1.21 (s, 48, -CH₃), 1.27 (s, 24, -CH₃), 1.73 (t, 8, -CH₂-), 2.43 (s, 8, -CH₂-), 3.56-3.67 (m, 128, -OCH₂-), 4.16-4.33 (m, 104), 4.64 (s, 4, CH), 4.79 (t, 4, CH), 5.33 (s, 8, -ArCH₂OCO-), 5.96 (s, 4, ArH), 6.51 (d, 8, ArH), 6.58 (t, 4, ArH), 6.97 (t, 4, ArH), 7.32 (d, 8, ArH), 7.33 (s, 4, ArH). ¹³C NMR (125 MHz (CD₃)₂SO): δ 17.3 (CH₃), 17.4 (CH₃), 17.7 (CH₃), 17.8 (CH₃), 27.0 (CH₂), 29.7 (CH₂), 36.6 (CH₂), 46.6 (C), 46.8 (C), 46.9 (C), 50.8 (C), 50.9 (C), 64.3 (OCH₂), 65.1 (OCH₂), 66.0 (OCH₂), 106.6 (CH), 108.6 (CH), 109.8 (CH), 114.9 (CH), 115.6 (CH), 120.0 (CH), 125.2 (CH), 136.8 (CH), 140.0 (CH), 141.1 (CH), 156.3 (CH), 156.8 (CH), 160.8 (CH), 172.5 (C=O), 172.6 (C=O), 172.7 (C=O), 174.7 (C=O), 174.8 (C=O). MALDI-TOF MS: Theo. Avg. MW: [M + Na]⁺ m/z = 8143.15. Obs: [M + Na]⁺ m/z = 8143.1. Anal. calcd. for C₃₇₆H₅₂₈O₁₉₂•5H₂O: C, 55.01; H, 6.60. Found: C, 55.10; H, 6.66.

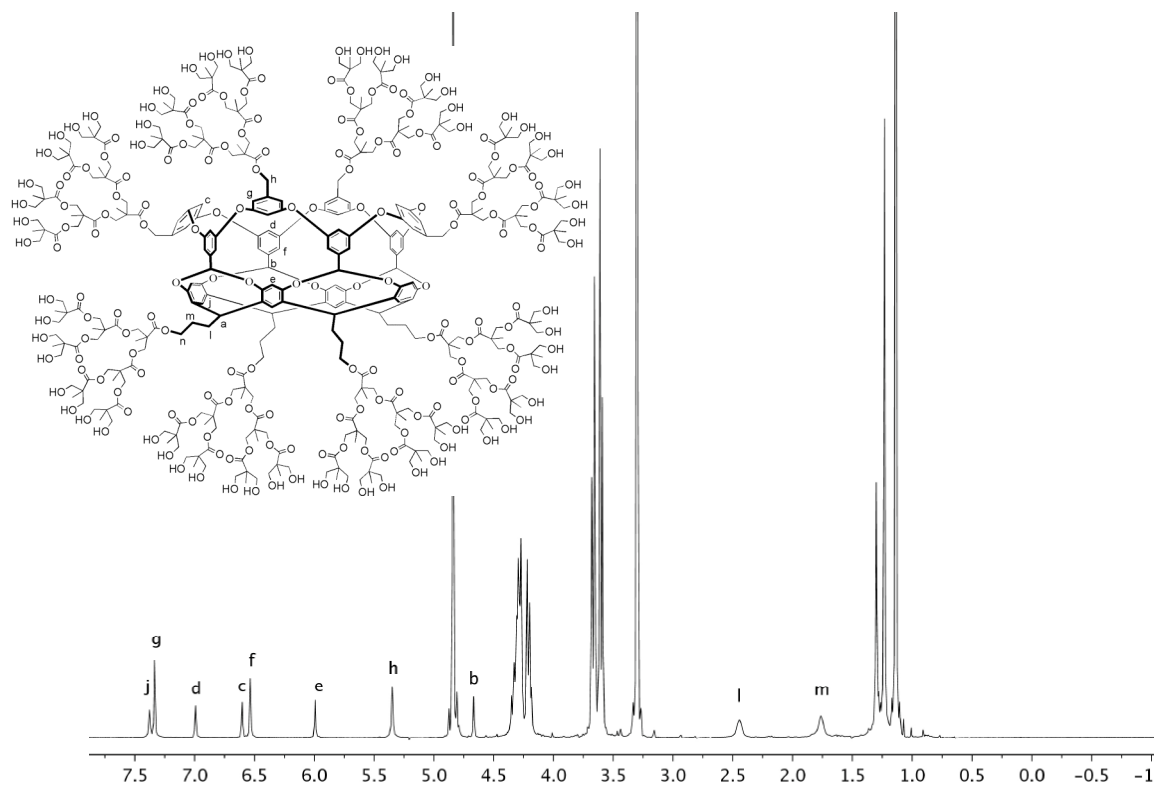


Figure S1. ^1H NMR spectrum of **2** (500 MHz, RT, CD_3OD)

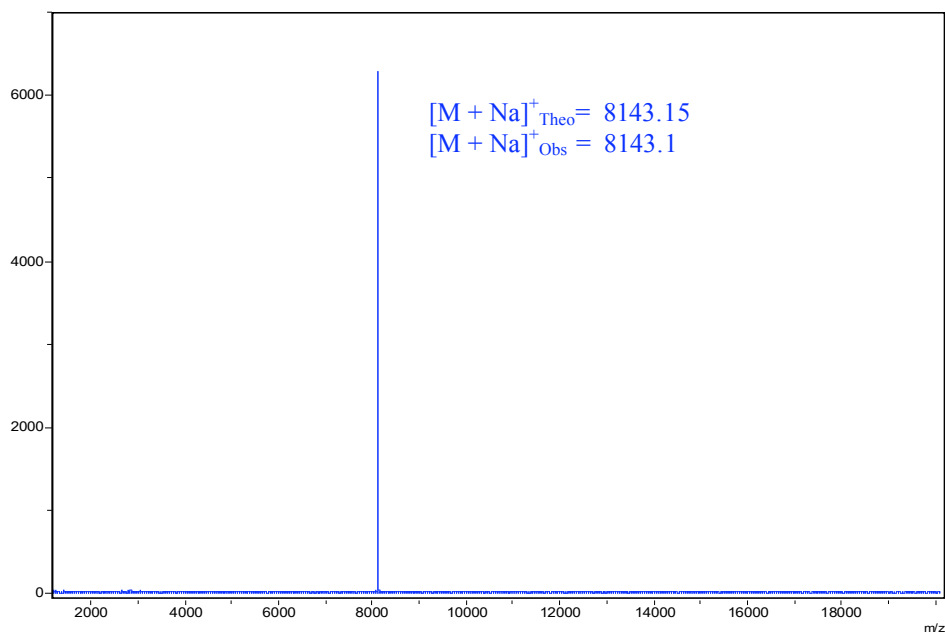


Figure S2. MALDI-TOF MS of **2** (matrix, α -cyano-4-hydroxycinnamic acid. Counter-ion source, sodium trifluoroacetate).

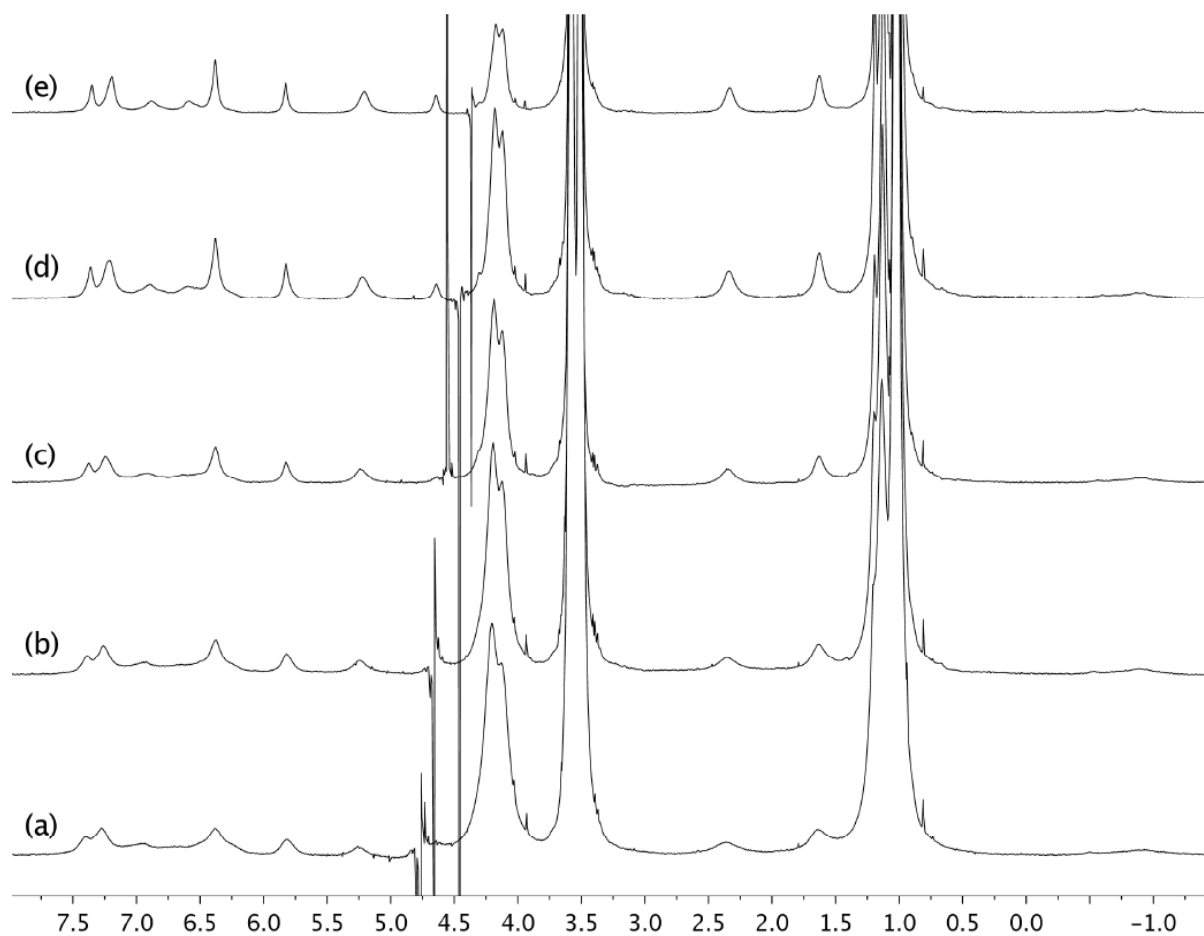


Figure S3. VT NMR spectra of **2** (0.8 mM) in pure D₂O (500 MHz). (a) 15 °C; (b) 25 °C; (c) 35 °C; (d) 45 °C; (e) 55 °C.

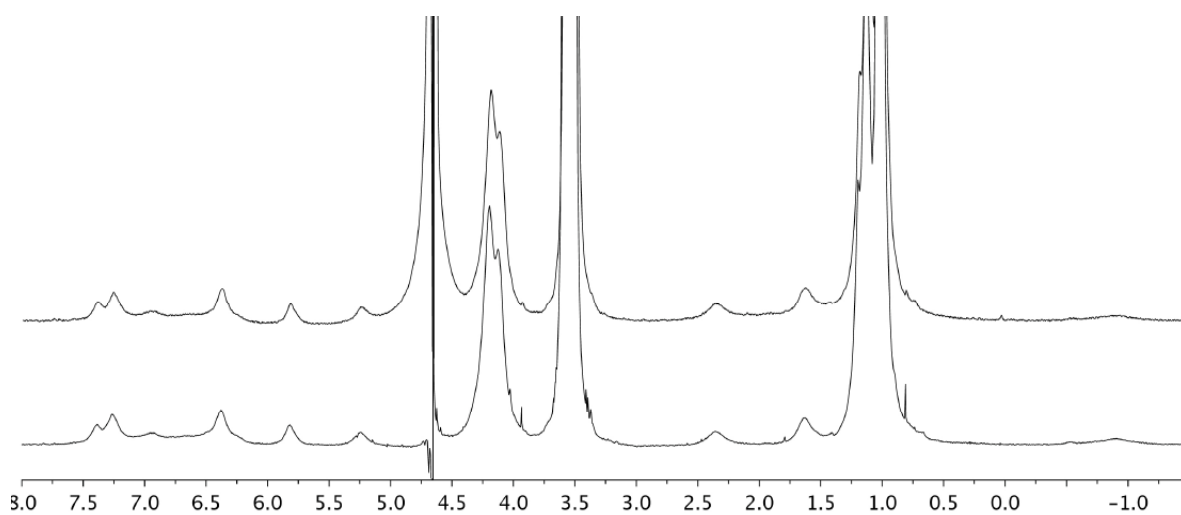


Figure S4. Dilution NMR spectra of **2** (500 MHz, Bottom: 0.8 mM; Top: 40 μM) in pure D₂O at 25 °C.

Complexes formed by 2

General Comments

All NMR titration were carried on Varian 500MHz spectrometer at 50 °C in D₂O. All binding results indicated that the exchange of free guests and bound guests is slow on the NMR time scale. The stoichiometry of each complex was judged by integration and the characteristic shift of signals from protons at the rim of the cavitand. The association constant between **2** and **3** was determined by simple integration of the signals in the ¹H NMR spectrum corresponding to free and bound **3**. This K_a ($7.5 \times 10^3 \text{ M}^{-1}$) is considerably weaker than that observed for **3** binding to **1a** ($1.0 \times 10^6 \text{ M}^{-1}$).

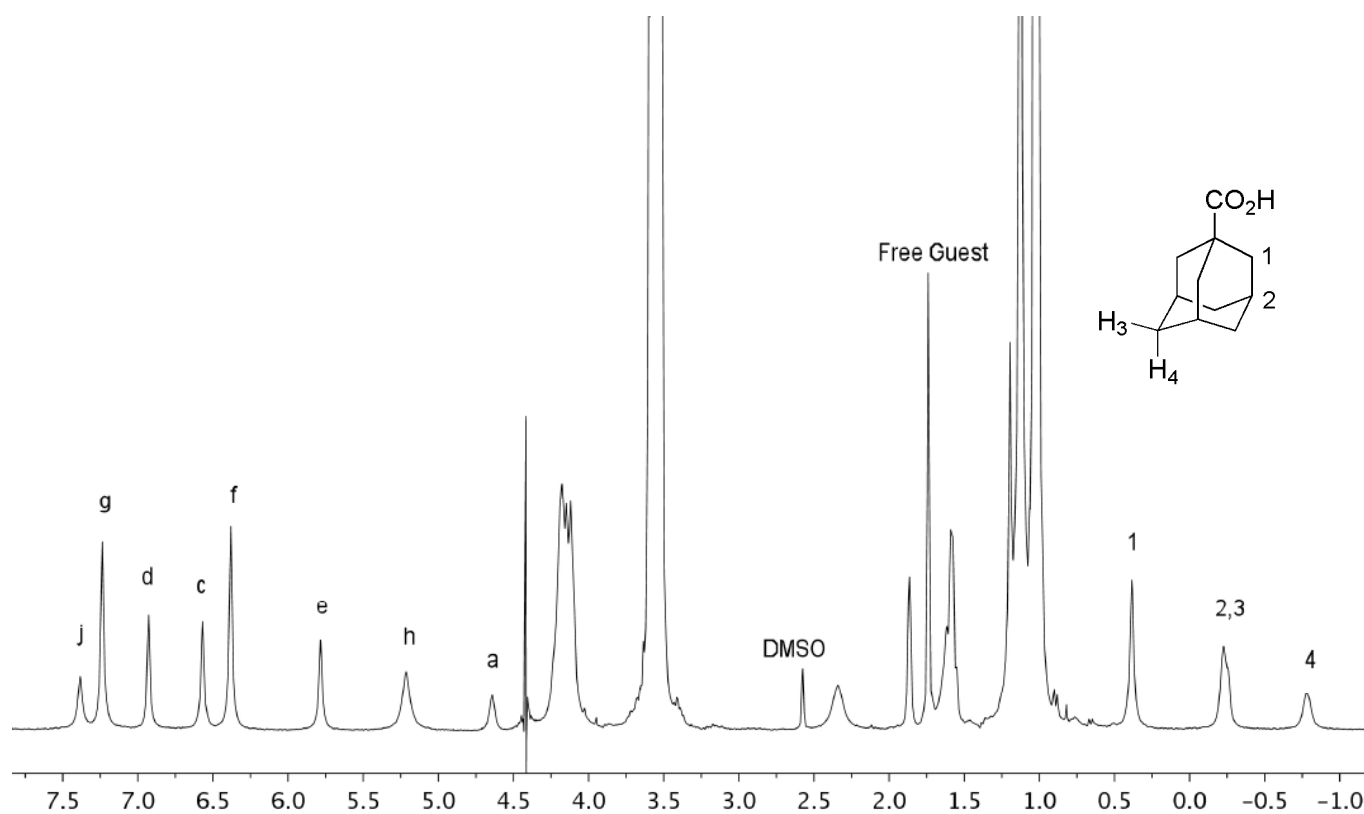


Figure S5. ¹H NMR spectrum of **3@2₂** (0.8 mM) in D₂O at 50 °C.

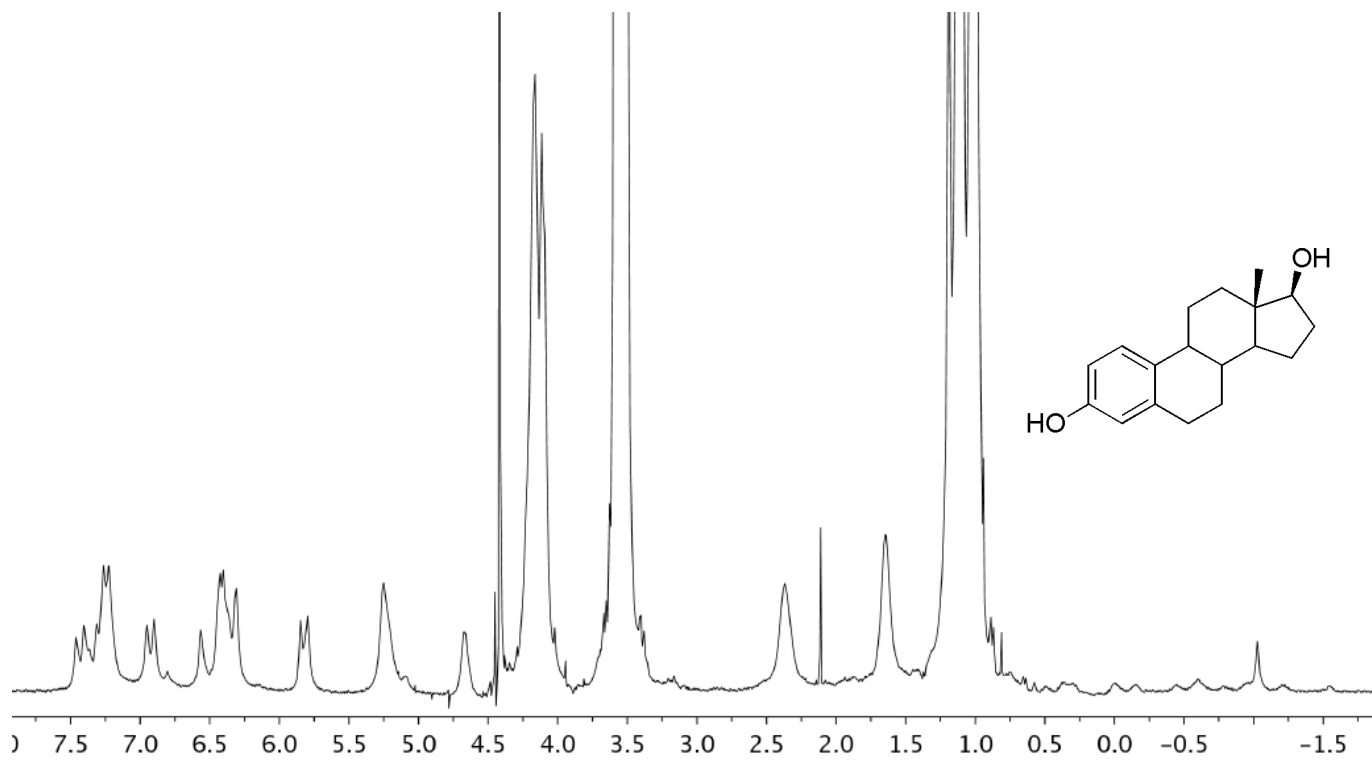


Figure S6. ¹H NMR spectrum of 4@2₂ complex (0.8 mM) in D₂O at 50 °C.

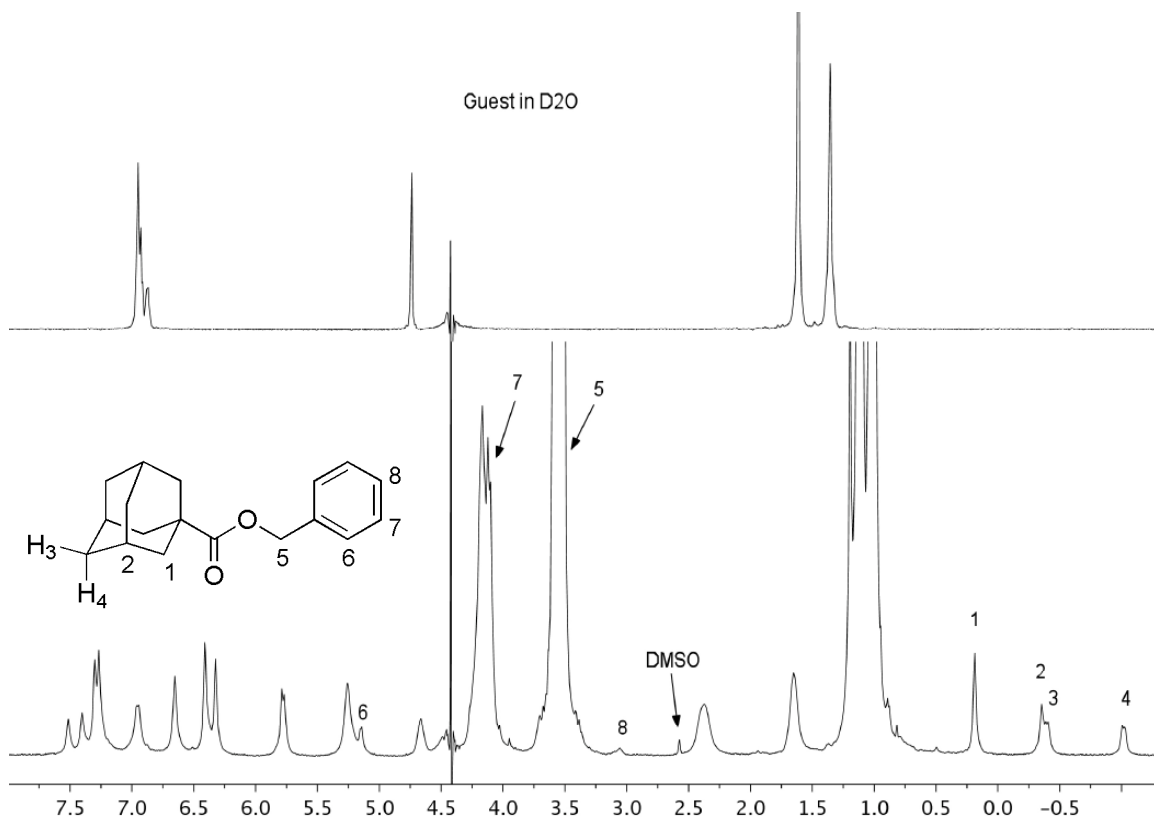


Figure S7. ^1H NMR spectra of $5@2_2$ (0.8 mM) in D_2O at 50°C . (Proton 5 was assigned by comparing above NMR with the binding NMR of this guest with **1a**).²

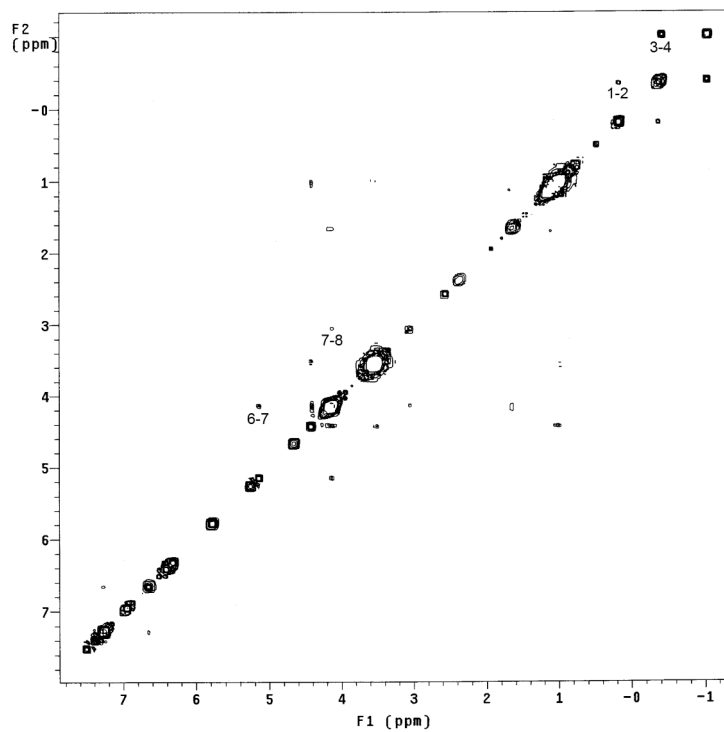


Figure S8. COSY spectrum of $5@2_2$ (0.8 mM) in D_2O at 50°C .

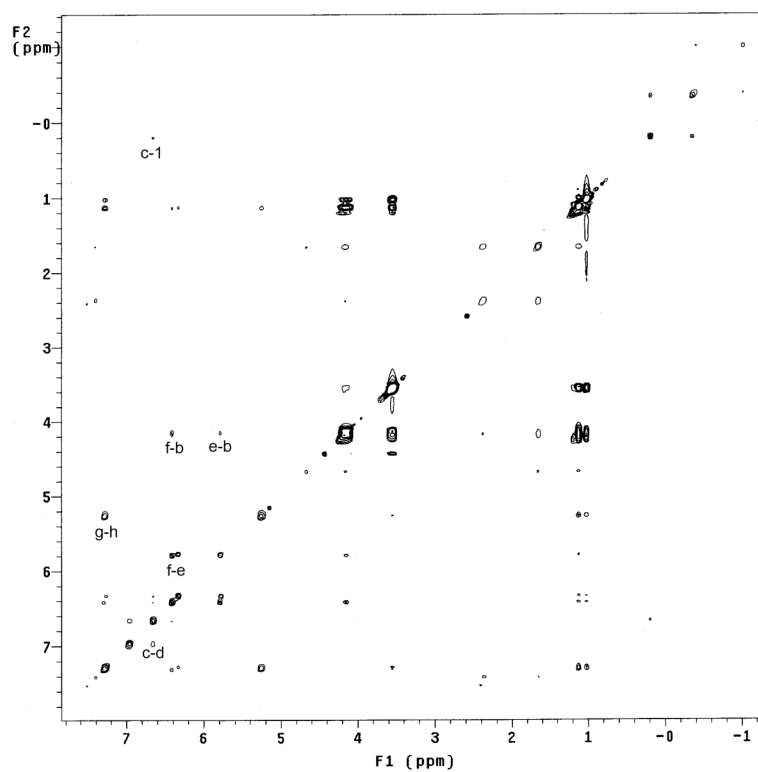


Figure S9. NOESY spectrum of **5@2₂** (0.8 mM) with in D₂O at 50 °C.

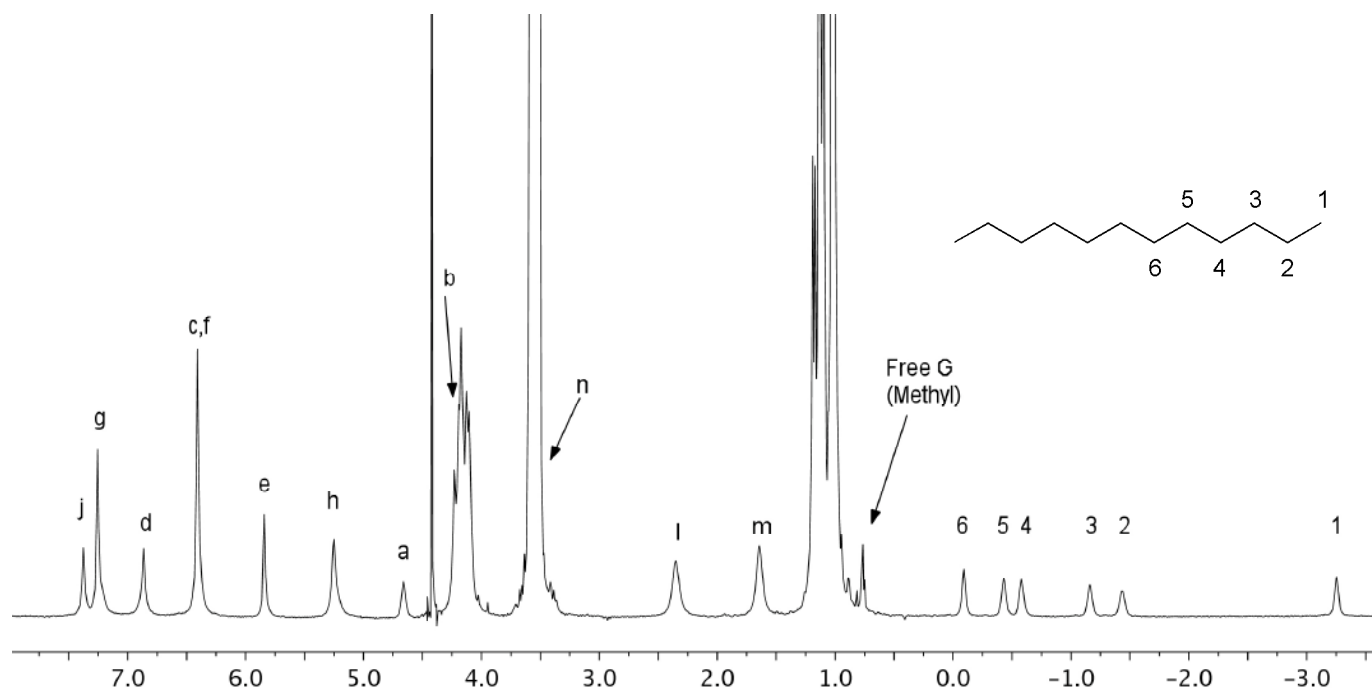


Figure S10. ^1H NMR spectrum of $6@2_2$ (0.8 mM) in D_2O at $50\text{ }^\circ\text{C}$.

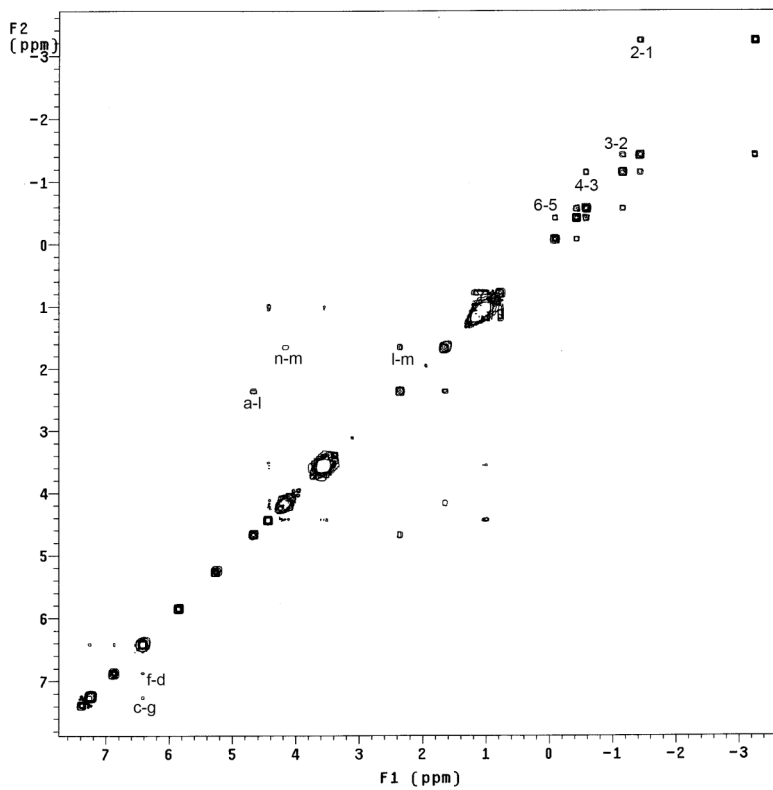


Figure S11. COSY spectrum of $6@2_2$ (0.8 mM) in D_2O at $50\text{ }^\circ\text{C}$.

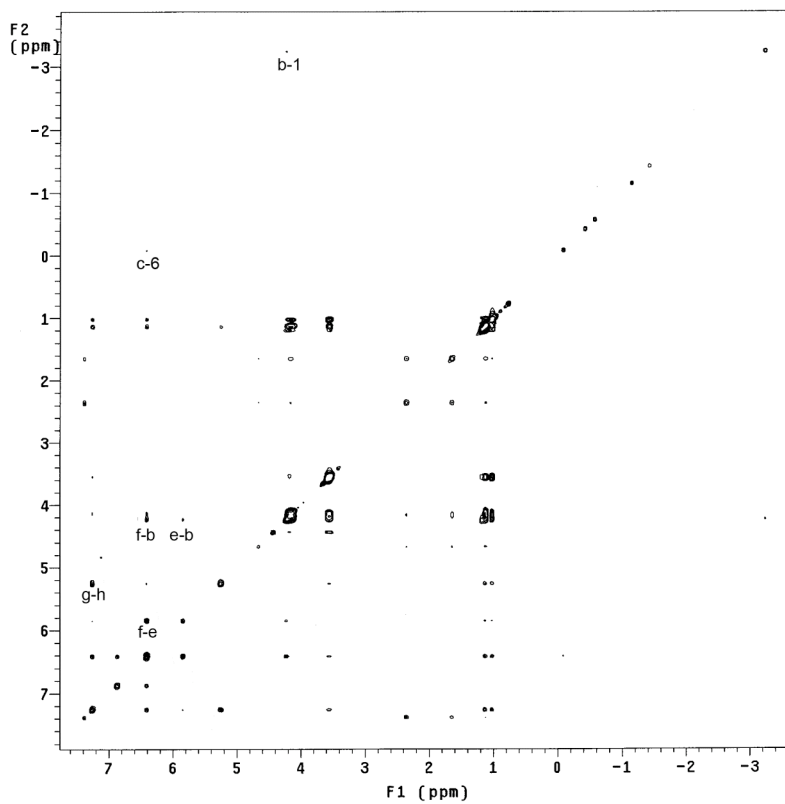


Figure S12. NOESY spectrum of **6@2₂** (0.8 mM) in D₂O at 50 °C.

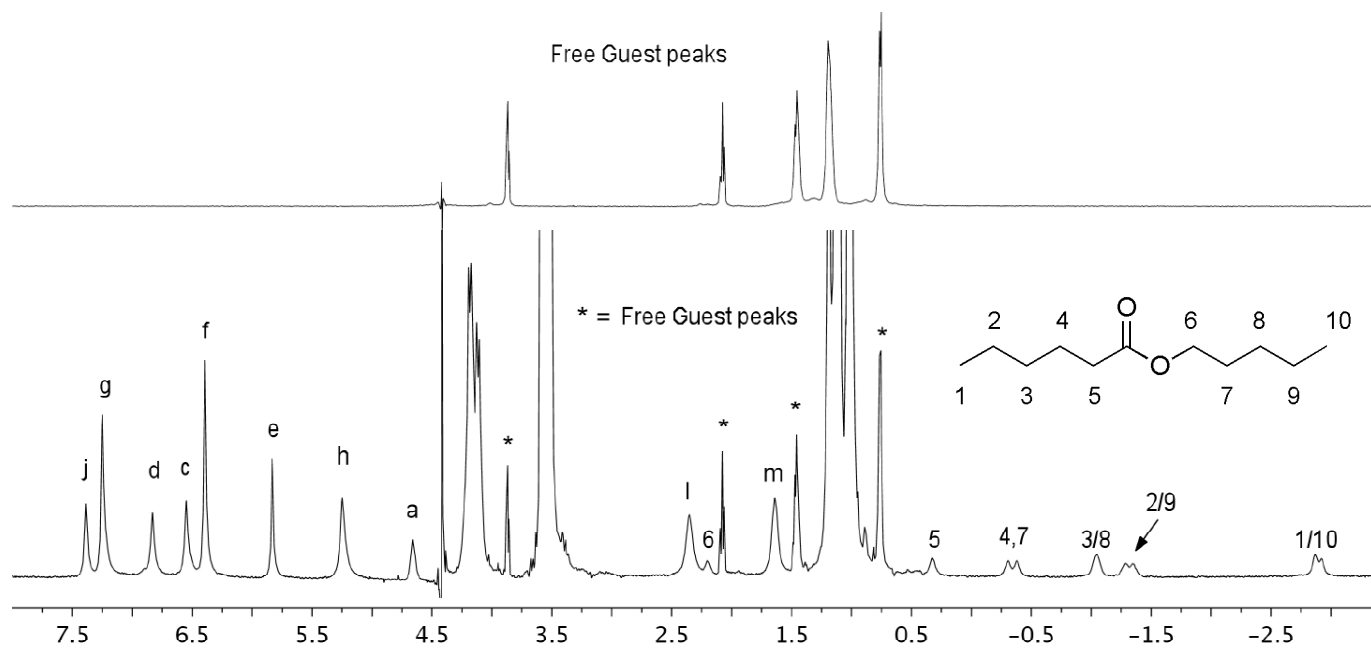


Figure S13. ^1H NMR spectrum of $7@2_2$ (0.8 mM) in D_2O at $50\text{ }^\circ\text{C}$.

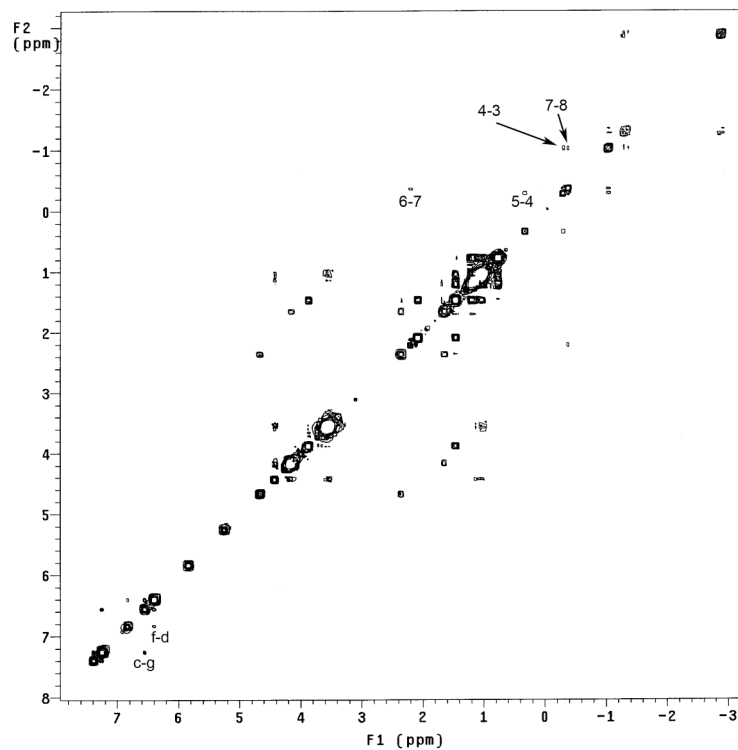


Figure S14. COSY spectrum of $7@2_2$ (0.8 mM) in D_2O at $50\text{ }^\circ\text{C}$.

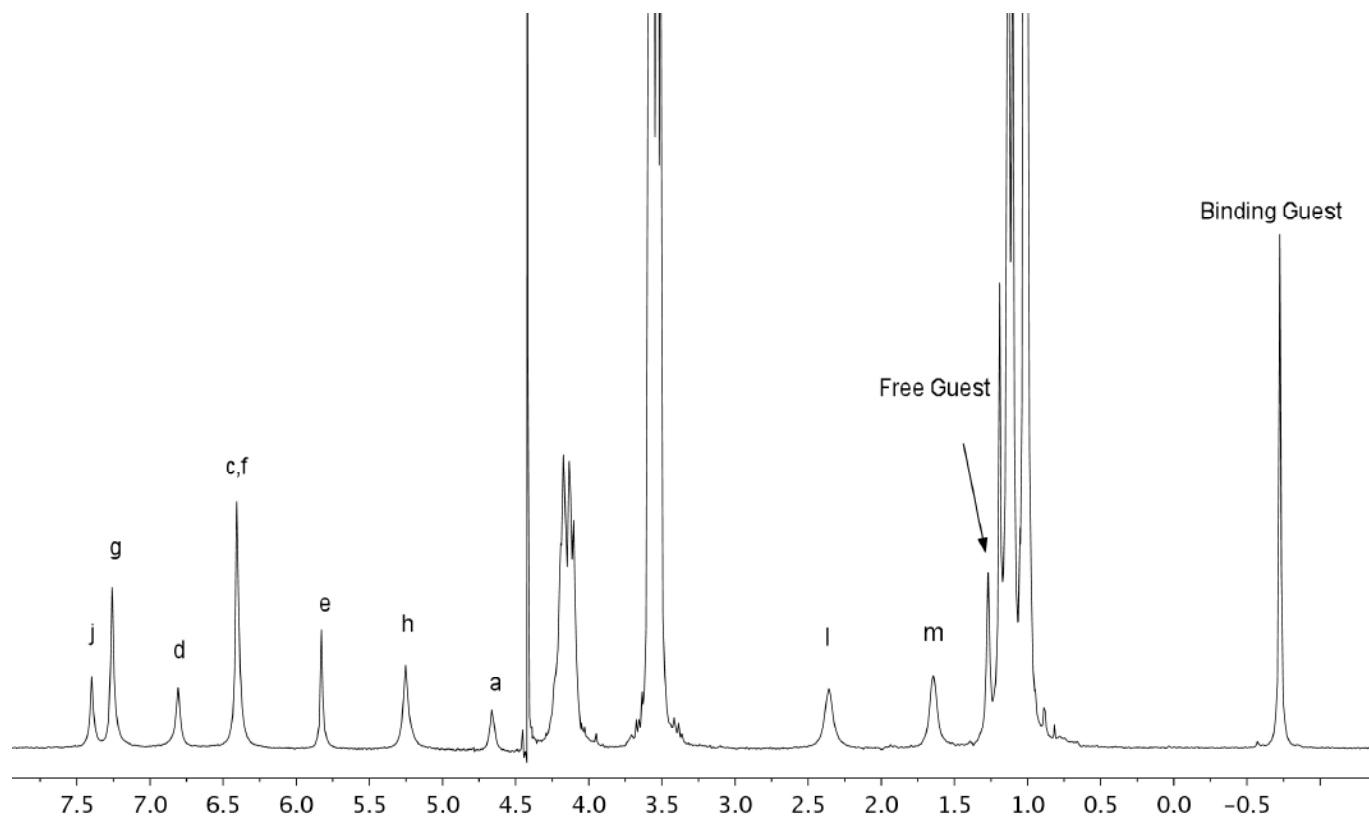


Figure S15. ^1H NMR spectrum of $8@2_2$ (0.8 mM) in D_2O at $50\text{ }^\circ\text{C}$.

References

- ¹ Gillies, E. R.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137-14146.
- ² Gibb, C.L.D.; Gibb, B.C. *J. Am. Chem. Soc.* **2004**, *126*, 11408-11409.