Electronic Supplementary Material (ESI) for Chemical Communications

Deep Cavitands featuring Functional Acetal-Based Walls

‡ Melissa Degardin, ‡ Eric Busseron, Dang-A Kim, Dariush Ajami, and Julius Rebek, Jr.*
‡ These authors contributed equally.

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

Supporting Information

I. General methods

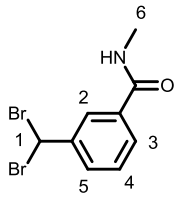
All reactions were carried out under an atmosphere of argon unless otherwise indicated. All reagents and anhydrous *N*,*N*'-Dimethylacetamide (DMA) were purchased from Aldrich and were used as received without further purification. All deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Analytical thin-layer chromatography (TLC) was performed on Silicycle 60 F254 glass-backed plates. Column chromatography was performed using Silicycle R10030B 60 Å 230-400 mesh silica gel. Hexaamide diol cavitand **1** was prepared according to the procedure[1] previously reported by our group. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz respectively, using a Bruker DRX-600 spectrometer equipped with a 5 mm QNP probe. Chemical shifts of ^{1}H NMR and ^{13}C NMR of characterized compounds are given in ppm by using $CHCl_3$ as reference (7.26 ppm for ^{1}H spectrum and 77.16 ppm for ^{13}C spectrum). Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), m (multiplet). MALDI-TOF spectra and high-resolution mass spectra (HRMS) were recorded respectively on an Applied Biosystems Voyager STR (2) apparatus and an Agilent ESI-TOF mass spectrometer. Molecular modeling (semi-empirical calculations) was carried out using the PM3 force field as implemented by Spartan.

II. Synthetic procedures of 6-8

- Synthetic procedures of **6** and **7**

p-halogenobenzalbromides **6** and **7** were prepared according to a previously reported procedure.[2]

- Synthetic procedure and characterization of *m*-methylamide benzal bromide **8**



First step

A solution of dimethylaminopyridine (300 mg, 2.46 mmol) and methylamine (2M in THF, 39 mL, 77.63 mmol) under nitrogen atmosphere was cooled in an ice bath. *m*-toluoyl chloride (2.55 mL, 19.41 mmol) was added dropwise to the mixture. After 2 hour of stirring at room temperature, an 1M aqueous solution of sodium hydroxide (80 mL) was introduced. The

medium was extracted with AcOEt (3*80 mL). The combined organic phases were combined, washed with 1M aqueous HCl (80 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to afford crude product (2.8 g, quantitative) which was used directly in the next step without further purification.

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 7.58 (s, 1H), 7.54-7.51 (m, 1H), 7.29- 7.26 (m, 2H), 6.46-6.33 (br s, 1H), 2.98 & 2.97 (2*s, 3H), 2.35 (s, 3H).

Second step

A mixture of the previous compound (1 g, 6.7 mmol), *N*-bromosuccinimide (2.625 g, 14.7 mmol, 2.2 equiv) and AIBN (110 mg, 0.67 mmol, 0.1 equiv) in CCl_4 (12 mL) was irradiated with an halogen lamp overnight. Then the precipitate was filtered and washed with CH_2Cl_2. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel (Eluent: CH_2Cl_2/AcOEt) to yield *m*-methylamide benzal bromide **8** as a white solid (83 mg, 4 %).

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 7.95 (s, 1H, H_2), 7.72-7.67 (m, 2H, H_3 H_5), 7.39 (t, $^3J_{ortho}$ = 7.8 Hz, 1H, H_4), 6.78-6.69 (br s, 1H, NH), 6.62 (s, 1H, H_1), 2.99 & 2.98 (2*d, 3H, H_6).

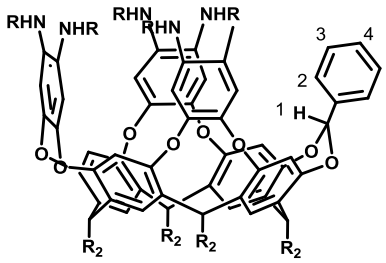
^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 167.37, 142.44, 135.21, 129.56, 129.13, 128.23, 125.16, 40.14, 27.05.

HRMS (ESI+): $[MH]^+$; calculated for $C_9H_{10}Br_2NO^+$: 305.9124; found 305.9129

III. General procedure A: synthesis of acetal cavitands 2-5

In a vial equipped with a screw cap were introduced hexaamide diol cavitand **1** (1 equiv), benzalbromide derivative **6-9** (4-4.6 equiv) and dry DMA. DBU (4 equiv) was added, the vial was flushed with nitrogen, sealed and heated in an oil bath at 70 °C for 3-4 days. The mixture was then evaporated to dryness *in vacuo*. The residue was diluted in AcOEt and washed with saturated aqueous $NaHCO_3$ solution (x1). After separation, the aqueous layer was extracted with AcOEt (x3). Organic layers were combined, dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography on silica gel column to afford the desired cavitand.

- Synthesis of hexaamide acetal cavitand **2**



R = $COCH_2CH_3$ R_2 = $C_{11}H_{23}$

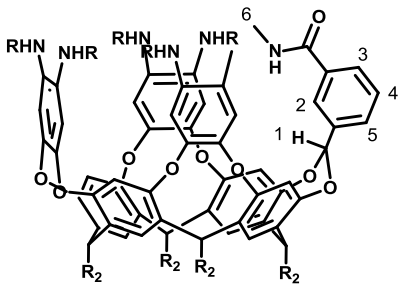
Hexaamide diol cavitand **1** (49 mg, 28 µmol), benzalbromide **9** (20 µL, 121 µmol) and DBU (20 µL, 134 µmol) were reacted according to general procedure **A** in dry DMA (3 mL) and purified with a gradient of elution (pure CH_2Cl_2, 10/90 AcOEt/CH_2Cl_2 then 40/60) to afford the desired hexaamide acetal cavitand **2** (48 mg, 86%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 9.62-9.4 (br s, 2H, NH), 9.41-9.27 (br s, 2H, NH), 8.07-7.94 (m, 4H, NH & H_2 or H_3), 7.59-7.50 (m, 6H, H_3 or H_2 & H_{arom}), 7.46 (t, 1H, ^{3}J = 7.3 Hz, H_4), 7.41-7.30 (br s, 2H, H_{arom}), 7.30-7.23 (m, 6H, H_{arom}), 6.99-6.91 (br s, 2H, H_{arom}), 5.81 (t, 1H, ^{3}J = 8.2 Hz, methine feet), 5.77 (t, 2H, ^{3}J = 8.2 Hz, methine feet), 5.36 (s, 1H, benzal hydrogen), 4.90 (t, 1H, ^{3}J = 8.0 Hz, methine feet), 2.53-2.18 (m, 20H, $COCH_2$ & CH_2 feet), 1.52-1.14 (m, 90H, CH_3 amide & CH_2 feet), 0.95-0.85 (m, 12H, CH_3 feet).

^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 173.52, 155.10, 154.74, 154.71, 154.59, 150.15, 149.76, 139.56, 138.31, 135.86, 135.70, 135.66, 129.00, 128.60, 128.30, 127.09, 124.48, 121.89, 121.79, 116.42, 107.36, 36.48, 33.64, 33.55, 32.61, 32.16, 32.10, 30.28, 30.08, 29.98, 29.96, 29.89, 29.88, 29.87, 29.58, 29.56, 28.27, 28.18, 28.14, 22.86, 22.85, 14.26, 10.52, 9.91.

MALDI-TOF: $[MNa]^+$; calculated for $C_{115}H_{152}N_6O_{14}Na^+$: 1864 found: 1864.

- Synthesis of heptaamide acetal cavitand **3**



R = $COCH_2CH_3$ R_2 = $C_{11}H_{23}$

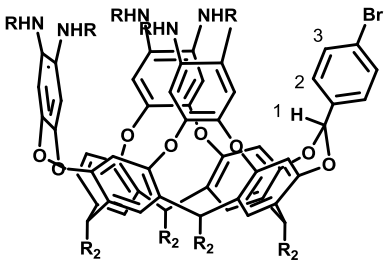
Hexaamide diol cavitand **1** (29 mg, 17 µmol), *m*-methylamide benzal bromide **8** (22.5 mg, 73 µmol) and DBU (11 µL, 74 µmol) were reacted according to general procedure **A** in dry DMA (800 µL) and purified with a gradient of elution (pure $CHCl_3$, 30/70 AcOEt/$CHCl_3$, 50/50, then 5/95 MeOH/$CHCl_3$) to give the desired heptaamide acetal cavitand **3** (26 mg, 83%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 9.80-9.32 (br s, 4H, NH), 9.18-8.78 (br s, 2H, NH), 8.07 (s, 1H, H_2), 8.04 (d, ^{3}J = 7.6 Hz, 1H, H_3 or H_5), 7.68-7.44 (m, 5H, NH & H_{arom}), 7.38 (t, ^{3}J = 7.6 Hz, 1H, H_4), 7.33-7.22 (m, 9H, H_{arom} & H_5 or H_3), 7.11-7.07 (br s, 2H, H_{arom}), 5.80 (t, ^{3}J = 8.2 Hz, 1H, methine feet), 5.79 (t, ^{3}J = 8.2 Hz, 2H, methine feet), 5.33 (s, 1H, benzal hydrogen), 4.81 (t, 1H, ^{3}J = 8.0 Hz, methine feet), 2.64- 1.89 (m, 23H, H_6 & $COCH_2$ & CH_2 feet), 1.55-1.01 (m, 90H, CH_3 amide & CH_2 feet), 0.92-0.83 (m, 12H, CH_3 feet).

^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 168.26, 154.92, 154.38, 154.28, 149.85, 139.27, 138.18, 136.04, 135.75, 135.49, 129.72, 128.67, 127.24, 125.81, 124.76, 122.10, 121.92, 121.33, 120.79, 116.89, 116.22, 106.52, 36.50, 33.59, 32.60, 32.29, 32.11, 30.53, 30.20, 29.99, 29.89, 29.58, 28.26, 28.18, 28.13, 22.87, 14.29, 10.55, 10.19.

HRMS (ESI+): $[MH]^+$; calculated for $C_{117}H_{156}N_7O_{15}^+$: 1899.1653 found: 1899.1634.

- Synthesis of hexaamide *p*-bromo acetal cavitand **4**



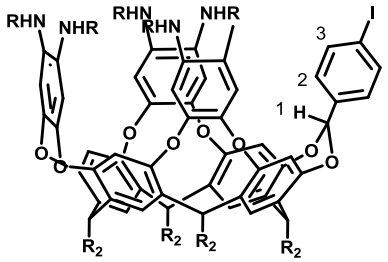
Hexaamide diol cavitand **1** (100 mg, 57 µmol), *p*-bromobenzalbromide **6** (86 mg, 262 µmol) and DBU (34 µL, 228 µmol) were reacted according to general procedure **A** in dry DMA (800 µL) and purified with a gradient of elution (pure CH_2Cl_2, 5/95 AcOEt/CH_2Cl_2, 10/90 then 30/70) to afford the desired hexaamide *p*-bromo acetal cavitand **4** (99 mg, 90%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 9.59-9.51 (br s, 2H, NH), 9.39-9.26 (br s, 2H, NH), 8.16-7.94 (br s, 2H, NH), 7.87 (d, 2H, ^{3}J = 8.2 Hz, H_2 or H_3), 7.65 (d, 2H, ^{3}J = 8.4 Hz, H_3 or H_2), 7.59-7.48 (m, 4H, H_{arom}), 7.37-7.21 (m, 8H, H_{arom}), 6.95-6.88 (br s, 2H, H_{arom}), 5.82 (t, ^{3}J = 8.2 Hz, 1H, methine feet), 5.77 (t, ^{3}J = 8.2 Hz, 2H, methine feet), 5.29 (s, 1H, benzal hydrogen), 4.87 (t, ^{3}J = 8.1 Hz, 1H, methine feet), 2.55-2.18 (m, 20H, CH_2 feet & $COCH_2$), 1.54-1.13 (m, 90H, CH_3 amide & CH_2 feet), 0.96-0.86 (m, 12H, CH_3 feet).

^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 173.85, 173.56, 155.10, 154.78, 154.60, 154.53, 150.12, 149.75, 138.49, 138.17, 136.03, 135.68, 131.73, 128.88, 128.32, 124.48, 123.17, 121.90, 121.68, 120.66, 116.43, 116.33, 106.92, 36.48, 33.63, 33.54, 32.60, 32.09, 30.86, 30.34, 30.26, 30.05, 29.96, 29.94, 29.86, 29.55, 28.25, 28.16, 28.12, 22.84, 14.25, 10.50, 9.92.

HRMS (ESI+): $[MH]^+$; calculated for $C_{115}H_{152}BrN_6O_{14}^+$: 1920.0544 found: 1920.0542.

- Synthesis of hexaamide *p*-iodo acetal cavitand **5**



R = $COCH_2CH_3$ R_2 = $C_{11}H_{23}$

Hexaamide diol cavitand **1** (97 mg, 55 µmol), *p*-iodobenzalbromide **7** (83 mg, 221 µmol) and DBU (33 µL, 221 µmol) were reacted according to general procedure **A** in dry DMA (800 µL) and purified with a gradient of elution (pure CH_2Cl_2, 5/95 AcOEt/CH_2Cl_2 then 20/80) to afford the desired hexaamide *p*-iodo acetal cavitand **5** (80 mg, 73%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 9.60-9.44 (br s, 2H, NH), 9.40-9.24 (br s, 2H, NH), 8.01-7.89 (br s, 1H, NH), 7.87 (d, 2H, ^3J = 8.3 Hz, H_2 or H_3), 7.75 (d, 2H, ^3J = 8.3 Hz, H_2 or H_3), 7.39-7.30 (br s, 1H, NH), 7.58-7.45 (br s, 4H, H_{arom}), 7.29 (s, 2H, H_{arom}), 7.28 (s, 2H, H_{arom}), 7.26 (s, 2H, H_{arom}), 7.25 (s, 2H, H_{arom}), 6.93-6.86 (br s, 2H, H_{arom}), 5.81 (t, 2H, ^3J = 8.2 Hz, methine feet), 5.77 (t, 2H, ^3J = 8.2 Hz, methine feet), 5.29 (s, 1H, H_1), 4.85 (t, 1H, ^3J = 8.1 Hz, CH feet below acetal), 2.55-2.17 (m, 20H, CH_2 feet & $COCH_2$), 1.53-1.14 (m, 90H, CH_3 amide & CH_2 feet), 0.93-0.88 (m, 12H, CH_3 feet).

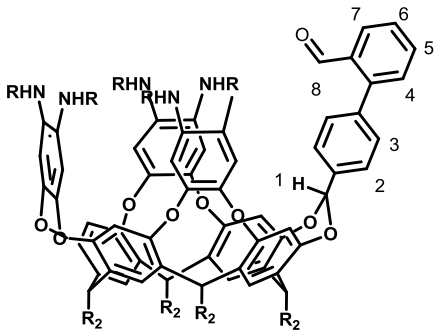
^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 174.57, 174.26, 155.77, 155.45, 155.31, 155.24, 150.83, 150.47, 139.84, 138.87, 138.49, 136.73, 136.38, 129.82, 129.00, 125.17, 122.60, 122.35, 121.45, 117.11, 117.03, 107.65, 95.80, 37.18, 34.34, 34.25, 33.28, 32.83, 31.59, 31.10, 30.98, 30.78, 30.69, 30.60, 30.29, 28.99, 28.89, 28.84, 23.58, 15.08, 15.01, 11.24, 10.67.

HRMS (ESI+): $[MH]^+$; calculated for $C_{115}H_{152}IN_6O_{14}^+$: 1968.0405 found: 1968.0325.

IV. General procedure B: synthesis of hexaamide formyl acetal cavitands 10-11

In a vial equipped with a screw cap were introduced iodo acetal cavitand **5** (1 equiv) and formylbenzene boronic acid derivative (2-2.9 equiv). Then a degassed aqueous solution (20 min bubbling N_2) of Na_2CO_3 (1M), degassed THF (20 min bubbling N_2) and $PdCl_2(PPh_3)_2$ (11-17% mol cavitand) were successively added. The mixture was degassed for 1 min with N_2 and the used needle was washed with degassed THF. The vial was flushed with N_2, sealed and stirred in an oil bath preheated at 70°C. After 24 hours at the same temperature, the crude was evaporated to dryness and was purified by flash chromatography on silica gel column to give the pure desired cavitand.

- Synthesis of hexaamide *o*-formyl acetal cavitand **10**



R = $COCH_2CH_3$ R_2 = $C_{11}H_{23}$

Iodo acetal cavitand **5** (35 mg, 18 µmol), 2-formylbenzene boronic acid (5.6 mg, 37 µmol), degassed solution of aqueous Na_2CO_3 (150 µL; 1M), and $PdCl_2(PPh_3)_2$ (1.3 mg, 2 µmol, 11% mol cavitand) were reacted according to general procedure **B** in degassed THF (375µL) and purified with a gradient of elution (CH_2Cl_2 pure, 5/95 AcOEt/CH_2Cl_2, 20/80, 30/70) to yield the desired hexaamide *o*-formyl acetal cavitand **10** (26 mg, 74%) as a white solid.

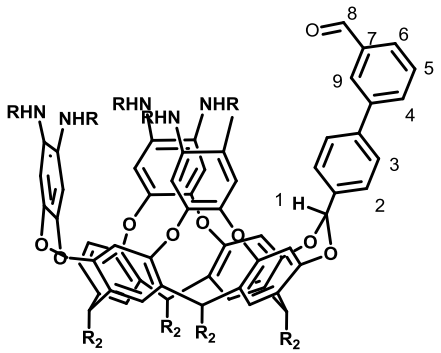
^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 10.08 (s, 1H, H_8), 9.59-9.46 (br s, 2H, NH), 9.40-9.28 (br s, 2H, NH), 8.14-8.01 (m, 4H, H_{arom} NH), 7.67 (t, ^{3}J = 7.5 Hz, 1H, H_{arom}), 7.59-7.47 (m, 8H, H_{arom}), 7.39-7.22 (m, 11H, H_{arom}), 7.00-6.93 (br s, 2H, H_{arom}), 5.80 (t, 1H, ^{3}J = 8.2 Hz, methine feet), 5.76 (t, 2H, ^{3}J = 8.2 Hz, methine feet), 5.43 (s, 1H, benzal hydrogen), 4.90 (t, ^{3}J = 8.1 Hz, methine feet), 2.54-2.16 (m, 20H, CH_2 feet & $COCH_2$), 1.53-1.09 (m, 90H, CH_3 amide & CH_2 feet), 0.95-0.85 (m, 12H, CH_3 feet).

^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 192.40, 173.85, 173.54, 155.08, 154.76, 154.55, 150.08, 149.74, 145.47, 139.40, 138.62, 138.27, 136.01, 135.66, 133.85, 131.01, 130.35, 128.32, 128.15, 127.15, 124.51, 121.92, 121.85, 120.67, 116.45, 107.04, 36.50, 33.63, 33.55,

32.61, 32.11, 30.87, 30.32, 30.24, 30.08, 30.00, 29.88, 29.58, 28.27, 28.18, 22.86, 14.36, 14.29, 10.52, 9.95.

HRMS (ESI+): $[MH]^+$; calculated for $C_{122}H_{157}N_6O_{15}^+$: 1946.1701 found: 1946.1729.

- Synthesis of hexaamide *m*-formyl acetal cavitand **11**



R = $COCH_2CH_3$ R_2 = $C_{11}H_{23}$

Iodo acetal cavitand **5** (33 mg, 17 µmol), 3-formylbenzene boronic acid (5.6 mg, 50 µmol), degassed solution of aqueous Na_2CO_3 (150 µL; 1M), and $PdCl_2(PPh_3)_2$ (1.8 mg, 3 µmol, 17% mol cavitand) were reacted according to general procedure **B** in degassed THF (300 µL) and purified with a gradient of elution (CH_2Cl_2 pure, 5/95 AcOEt/CH_2Cl_2, 20/80, 30/70) to afford the desired hexaamide *m*-formyl acetal cavitand **11** (24 mg, 73%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 10.10 (s, 1H, H_8), 9.58-9.46 (br s, 2H, NH), 9.38-9.26 (br s, 2H, NH), 8.13 (s, 1H, H_9), 8.10 (d, 2H, ^3J = 8.1 Hz, H_{arom}), 8.08-7.90 (br s, 2H, NH), 7.89 (dd, 2H, ^3J = 7.7 Hz, ^4J = 1.4 Hz, H_{arom}), 7.78 (d, 2H, ^3J = 8.2 Hz, H_{arom}), 7.65 (t, 1H, ^3J = 7.6 Hz, H_{arom}), 7.60-7.19 (m, 15H, H_{arom}), 7.01-6.93 (br s, 2H, H_{arom}), 5.81 (t, 1H, ^3J = 8.3 Hz, methine feet), 5.76 (t, 2H, ^3J = 8.2 Hz, methine feet), 5.42 (s, 1H, benzal hydrogen), 4.90 (t, 1H, ^3J = 8.0 Hz, methine feet), 2.56-2.14 (m, 20H, CH_2 feet & $COCH_2$), 1.71-0.66 (m, 102H, CH_3 amide & CH_2 feet & CH_3 feet).

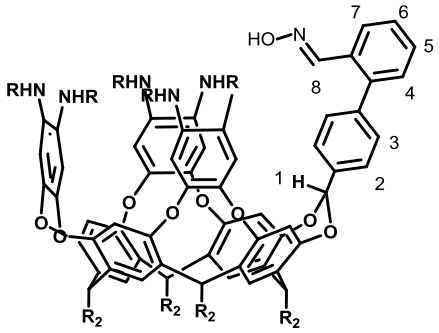
^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 192.37, 155.07, 154.74, 154.61, 154.57, 150.11, 149.75, 141.93, 140.43, 139.29, 138.27, 137.15, 135.97, 135.67, 133.19, 129.78, 129.17, 128.30, 128.12, 127.80, 127.40, 124.48, 121.91, 121.85, 120.69, 116.41, 107.11, 36.50, 33.64, 33.55, 32.60, 32.16, 32.11, 32.08, 30.87, 30.32, 30.08, 30.00, 29.98, 29.93, 29.88, 29.86, 29.63, 29.59, 29.58, 29.52, 29.12, 28.28, 28.18, 28.15, 26.84, 23.33, 22.87, 22.85, 14.31, 10.54, 10.52, 9.94.

HRMS (ESI+): $[MH]^+$; calculated for $C_{122}H_{157}N_6O_{15}^+$: 1946.1701 found: 1946.1718.

V. General procedure C: synthesis of hexaamide oxime acetal cavitands 12 and 13

To a solution of suitable hexaamide formyl acetal cavitand (1 equiv) in THF and NaOH aq 1M was added $NH_2OH \cdot HCl$ (8.5-11 equiv). After 24 hour of stirring at RT, CH_2Cl_2 and H_2O were introduced. HCl 1M was added until pH 6-7. Aqueous phase was extracted with CH_2Cl_2. Organic phases were combined, dried over Na_2SO_4, and concentrated to give the desired hexaamide oxime acetal cavitand.

- Synthesis of hexaamide *o*-oxime acetal cavitand **12**



R = $COCH_2CH_3$ R_2 = $C_{11}H_{23}$

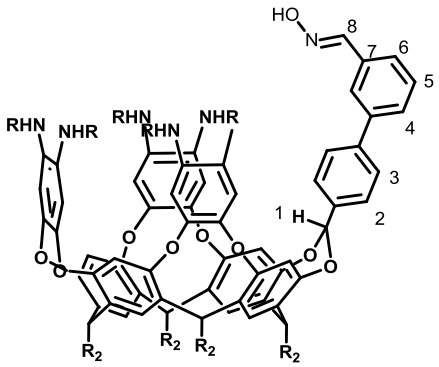
Hexaamide *o*-formyl acetal cavitand **10** (11.5 mg, 5.9 µmol) and $NH_2OH{\cdot}HCl$ (3.5 mg, 50.4 µmol) were reacted according to general procedure **C** in THF (250 µL) and NaOH aq 1M (250 µL) to give the desired hexaamide *o*-oxime acetal cavitand **12** (10 mg, 86%).

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 9.61-9.48 (br s, 2H, NH), 9.41-9.28 (br s, 2H, NH), 8.23 (s, 1H, H_8), 8.09 (d, ^3J = 7.5 Hz, 2H, H_{arom}), 7.96 (d, ^3J = 7.6 Hz, 2H, H_{arom}), 7.59-7.26 (m, H_{arom}), 5.84 (t, ^3J = 8.2 Hz, 1H, methine feet), 5.80 (t, ^3J = 8.2 Hz, 2H, methine feet), 5.45 (s, 1H, benzal hydrogen), 4.94 (t, ^3J = 8.0 Hz, 1H, methine feet), 2.60-2.16 (m, 20H, CH_2 feet & $COCH_2$), 1.56-1.13 (m, 90H, CH_3 amide & CH_2 feet), 0.98-0.85 (m, 12H, CH_3 feet).

^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 173.93 155.47, 155.12, 154.74, 154.60, 150.10, 149.75, 141.80, 140.36, 138.71, 138.37, 136.00, 135.72, 130.47, 130.26, 129.99, 128.53, 128.32, 127.97, 127.01, 126.61, 124.53, 121.95, 121.85, 120.64, 116.45, 107.27, 36.51, 33.84, 33.56 33.23, 32.62, 32.12, 30.91, 30.30, 29.89, 29.59, 28.19, 26.86, 22.87, 14.29, 10.55, 9.97, 8.57.

HRMS (ESI+): $[MH]^+$; calculated for $C_{122}H_{158}N_7O_{15}^+$: 1961.1810 found: 1961.1799.

- Synthesis of hexaamide *m*-oxime acetal cavitand **13**



R = $COCH_2CH_3$ R_2 = $C_{11}H_{23}$

Hexaamide *m*-formyl acetal cavitand **11** (24 mg, 12.3 µmol) and $NH_2OH{\cdot}HCl$ (9.4 mg, 135.3 µmol) were reacted according to general procedure **C** in THF (500 µL) and NaOH aq 1M (500 µL) to give the desired hexaamide *m*-oxime acetal cavitand **13** (23 mg, 95%).

^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ ppm 9.61-9.43 (br s, 2H, NH), 9.42-9.25 (br s, 2H, NH), 8.13 (s, 1H, H_8), 8.10-7.99 (m, 4H, H_{arom} & NH), 7.81-7.76 (m, 2H, H_{arom}), 7.72 (d, 2H, ^3J = 8.2 Hz, H_2 or H_3), 7.61 (d, 1H, ^3J = 7.7 Hz, H_4 or H_6), 7.56 (d, 1H, ^3J = 7.7 Hz, H_6 or H_4), 7.55-7.48 (br s, 3H, H_{arom}), 7.45 (t, 1H, ^3J = 7.7 Hz, H_5), 7.41-7.21 (m, H_{arom}), 7.01-6.92 (br s, 2H, H_{arom}), 5.80 (t, 1H, ^3J = 8.2 Hz, methine feet), 5.76 (t, 2H, ^3J = 8.0 Hz, methine feet), 4.90 (t, 1H, ^3J = 8.2 Hz, methine feet), 2.54-2.13 (m, 20H, CH_2 feet & $COCH_2$), 1.72-0.98 (m, 90H, CH_3 amide & CH_2 feet), 0.93-0.65 (m, 12H, CH_3 feet).

^{13}C NMR (150 MHz, $CDCl_3$, 300 K): δ ppm 173.56, 155.09, 154.74, 154.65, 154.56, 150.34, 149.75, 141.45, 141.10, 138.83, 138.30, 135.94, 135.66, 132.87, 129.42, 128.77, 128.28, 127.59, 127.35, 126.05, 125.90, 124.50, 121.92, 121.83, 120.68, 116.43, 107.38, 107.24, 37.51, 37.25, 36.50, 36.43, 33.84, 33.64, 33.55, 32.63, 32.16, 32.12, 32.09, 30.86, 30.09, 30.01, 29.98, 29.89, 29.86, 29.60, 29.58, 29.56, 29.52, 29.12, 28.87, 28.28, 28.19, 28.15, 27.66, 26.85, 23.33, 22.87, 14.35, 14.31, 14.29, 10.54.

HRMS (ESI+): $[MH]^+$; calculated for $C_{122}H_{158}N_7O_{15}^+$: 1961.1810 found: 1961.1757.

VI. Structures and computational studies of hexaamide acetal cavitand 2 and reference octaamide cavitand

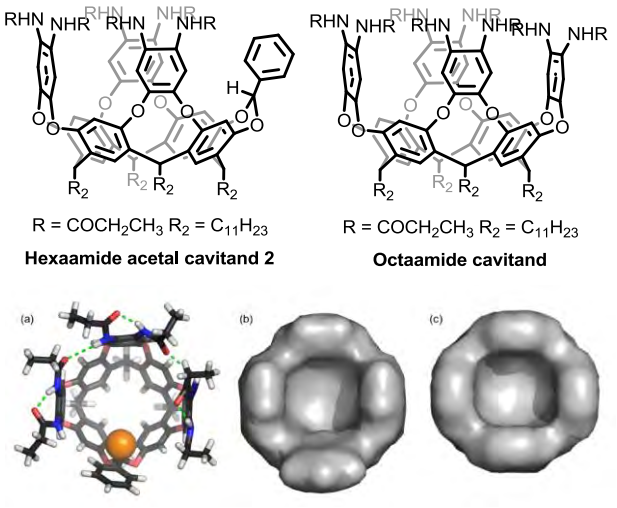


Figure S1. (a) 3D representation of the minimized-structure (Spartan, PM3) of hexaamide acetal cavitand **2** (benzal hydrogen highlighted in orange); Surfaces of the inner cavity determined with Pymol v1.3 of (b) cavitand **2** and (c) cavitand octaamide. Amide groups are not shown in (b) and (c) for clarity.

VII. Variable Temperature ^{1}H NMR experiments with hexa- and hepta-amide acetal cavitands 2 and 3 in chloroform-d_1

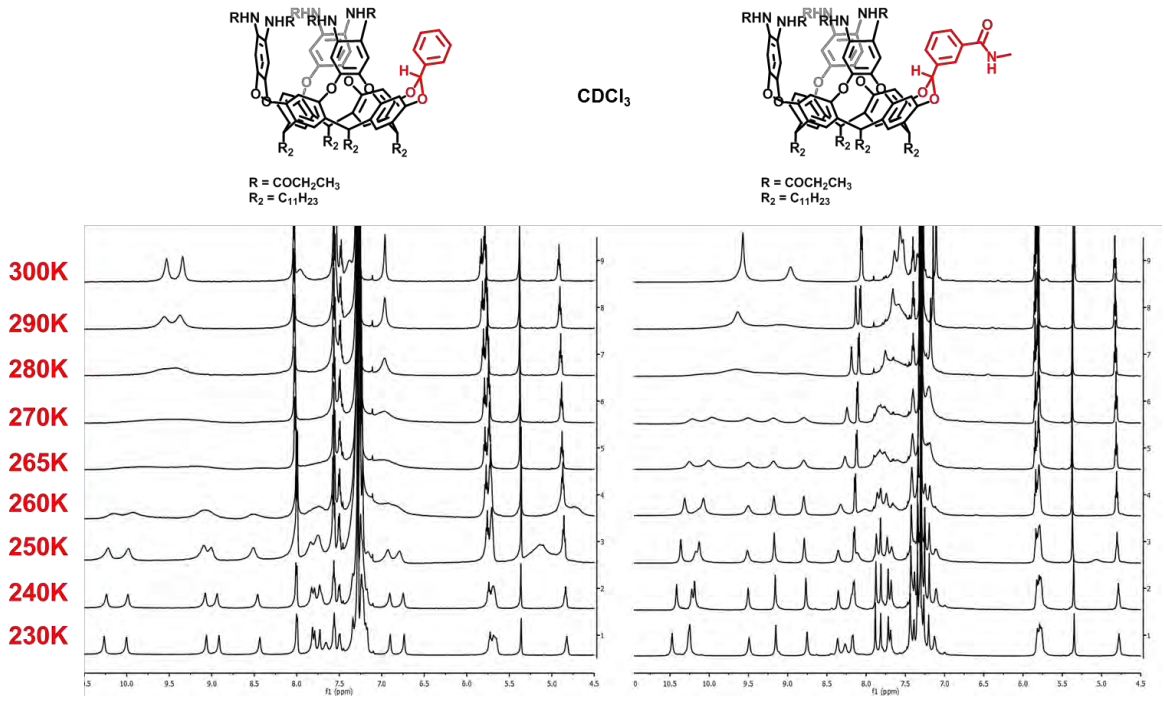


Figure S2. Variable Temperature NMR experiments with hexa- and hepta-amide acetal cavitands **2** and **3** in chloroform-d_1.

Hexaamide acetal cavitand **2** shows coalescence of the signals of its amide hydrogens at 265 K whereas heptaamide acetal cavitand **3** shows the same phenomenon at 280 K. These results demonstrate that the cycloisomerization of the seam of hydrogen bonds is disturbed in **3** compared to **2**. Moreover, a higher coalescence temperature in **3** confirms that the new amide on the acetal wall interacts with the seam of hydrogen bond.

VIII. Energy-minimized structures of heptaamide acetal cavitand 3

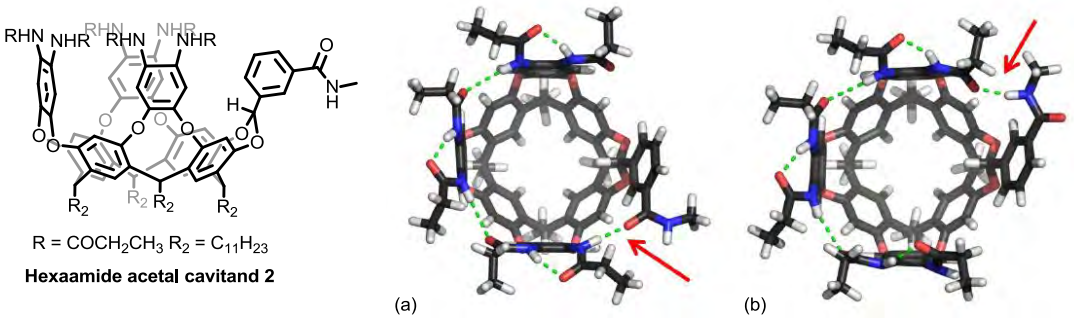


Figure S3. Structure and two energy-minimized structures (Spartan PM3) of heptaamide acetal cavitand **3** where the new amide acts as an hydrogen bond (a) acceptor and (b) donor; red arrows indicate the new hydrogen bonds; R_2 alkyl chain feets are omitted for clarity.

IX. Determination of association constants by ^{1}H NMR

NMR samples were prepared at 2 mM in cavitand in mesitylene-d_{12}. Binding experiments were carried out using guest molecules at variable concentrations. ^{1}H spectra were recorded at 300 K and 270 K. Association constants (1:1 complex) were deduced from the integration of protons corresponding to the free and bound species. The values reported in Table 1 are based from an average of at least three experiments.

X. Variable Temperature ^{1}H NMR experiment of host 2 with guest G10 (0.5 equiv) in mesitylene-d_{12}

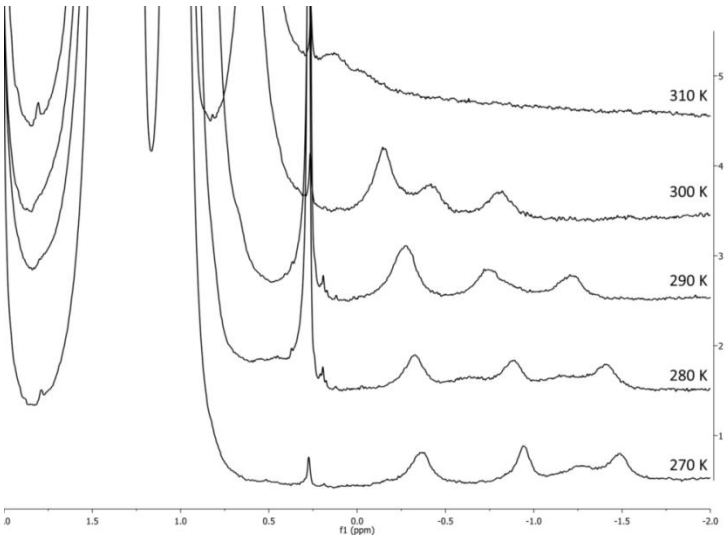


Figure S4. Upfield region of ^{1}H NMR spectra of Variable Temperature NMR experiments of hexaamide acetal cavitand **2** (2 mM) with guest **G10** (0.5 equivalent) in mesitylene-d_{12}.

XI. ^{1}H NMR spectrum of host 2 with G10 (1 equiv) in mesitylene-d_{12}

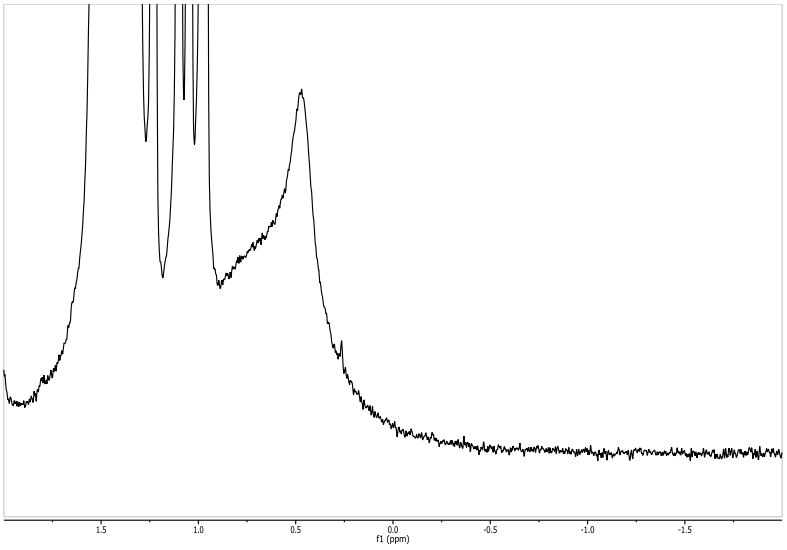


Figure S5. Upfield region of ^{1}H NMR spectrum of hexaamide acetal cavitand **2** (2 mM) with guest **G10** (1 equivalent) in mesitylene-d_{12} at 300 K.

XII. ^{1}H NMR spectra of both cavitands 2 and 3 with guests G4 – G6 in mesitylene-d_{12}

- Guest **G4**

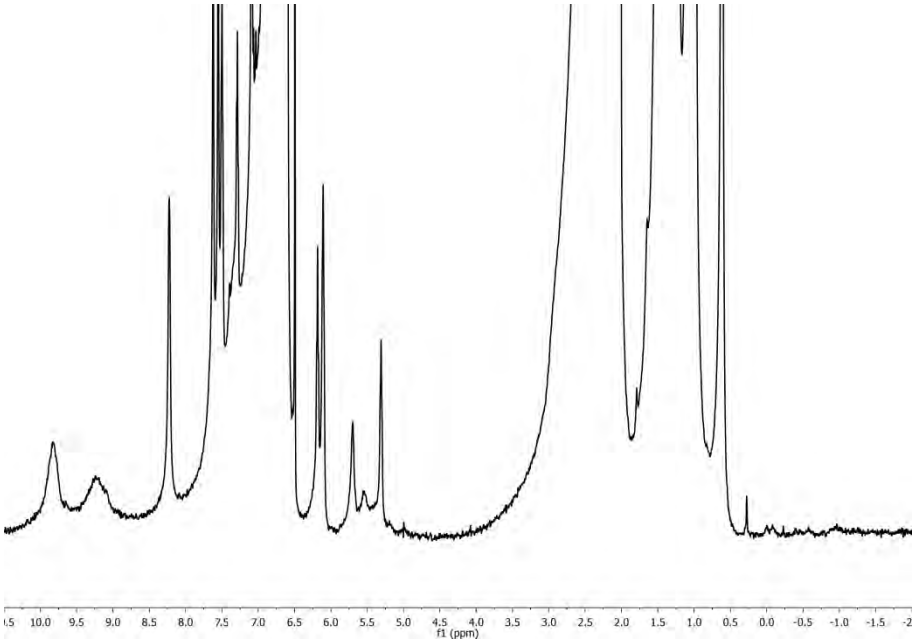


Figure S6. ^{1}H NMR spectrum (mesitylene-d_{12}, 300 K) of cavitand **2** (2 mM) with guest **G4** (1 equiv).

.

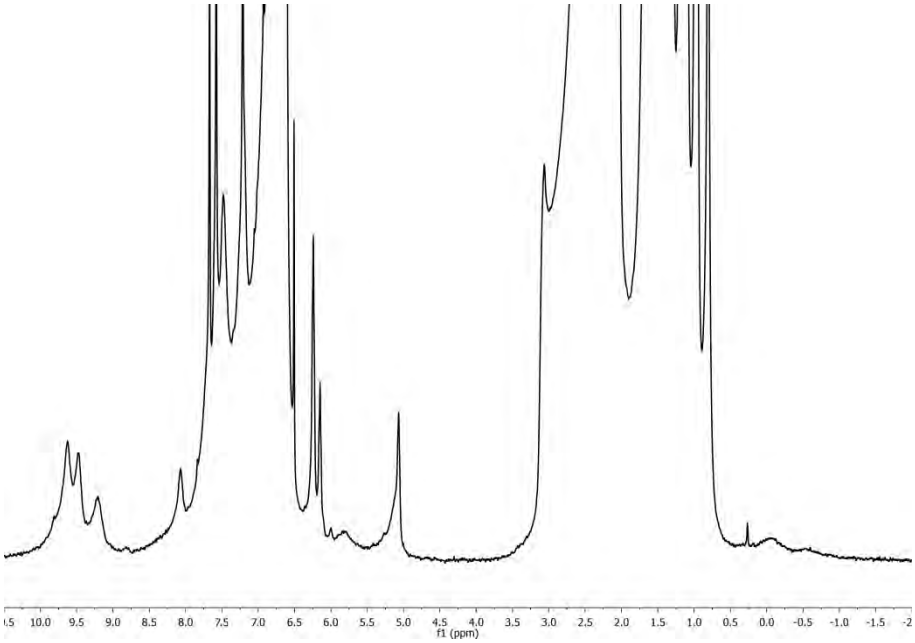


Figure S7. ^{1}H NMR spectrum (mesitylene-d_{12}, 300 K) of cavitand **3** (2 mM) with guest **G4** (1 equiv).

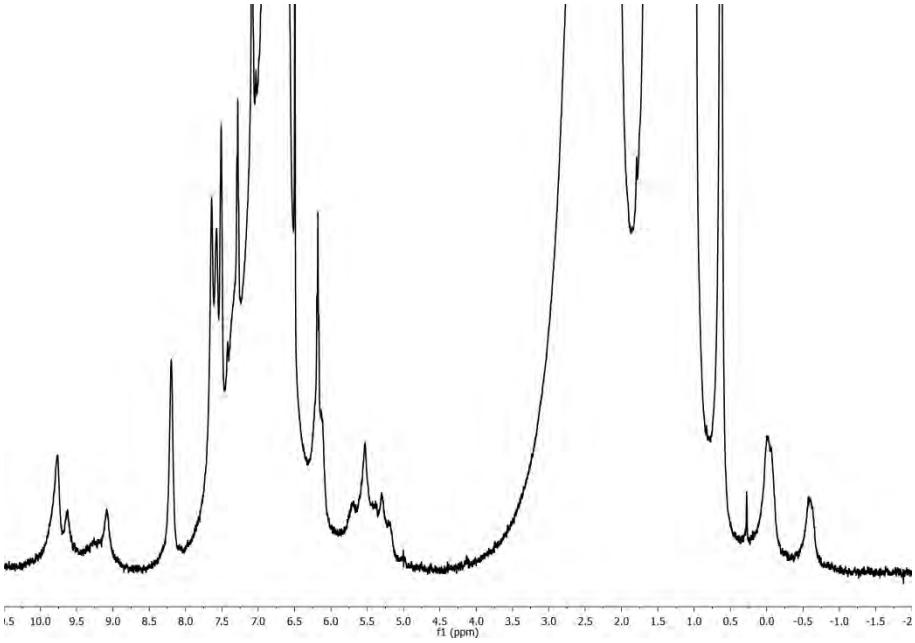


Figure S8. ^{1}H NMR spectrum (mesitylene-d_{12}, 270 K) of cavitand **2** (2 mM) with guest **G4** (1 equiv).

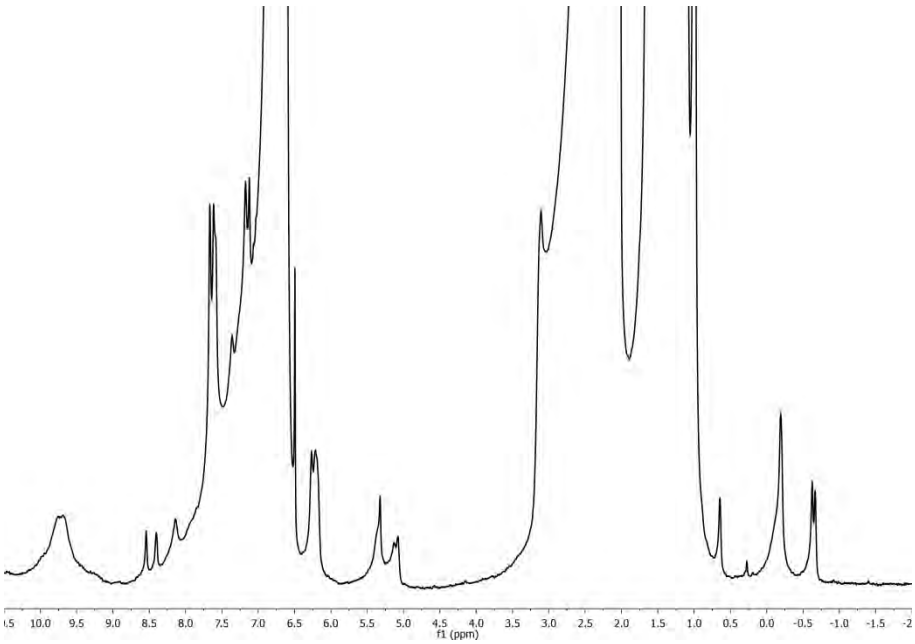


Figure S9. ^{1}H NMR spectrum (mesitylene-d_{12}, 270 K) of cavitand **3** (2 mM) with guest **G4** (1 equiv).

- Guest **G5**

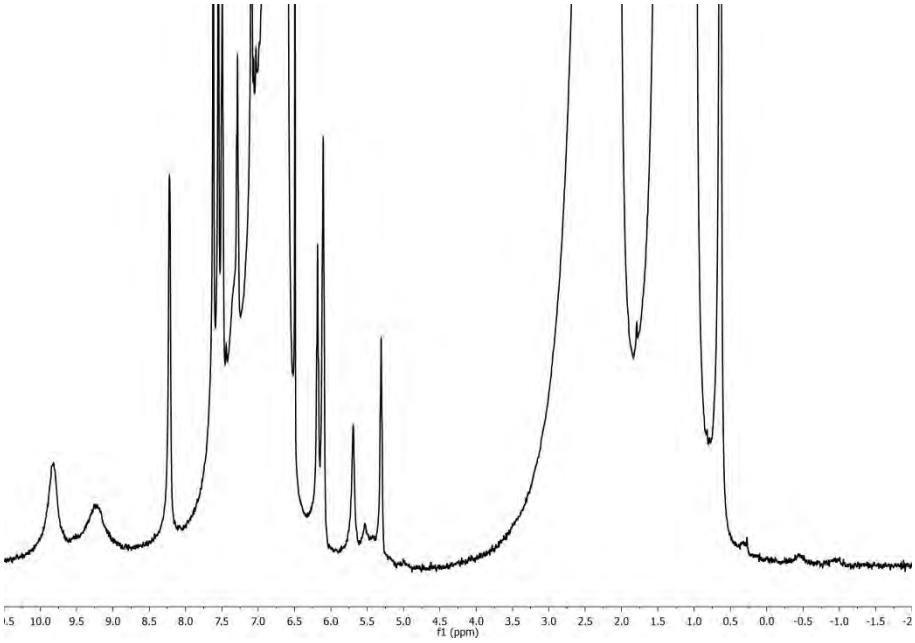


Figure S10. ^{1}H NMR spectrum (mesitylene-d_{12}, 300 K) of cavitand **2** (2 mM) with guest **G5** (1 equiv).

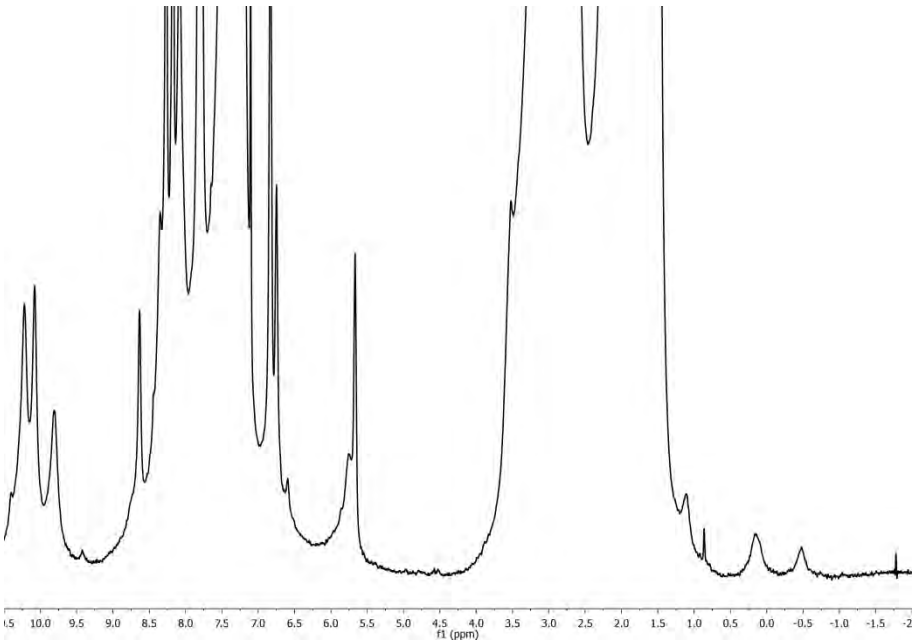


Figure S11. ^{1}H NMR spectrum (mesitylene-d_{12}, 300 K) of cavitand **3** (2 mM) with guest **G5** (1 equiv).

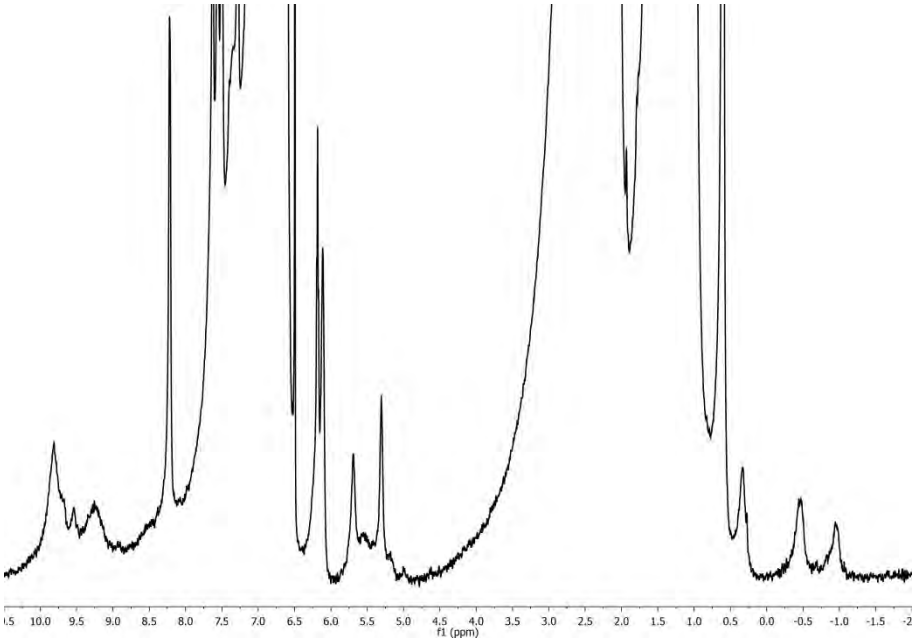


Figure S12. ^{1}H NMR spectrum (mesitylene-d_{12}, 270 K) of cavitand **2** (2 mM) with guest **G5** (1 equiv).

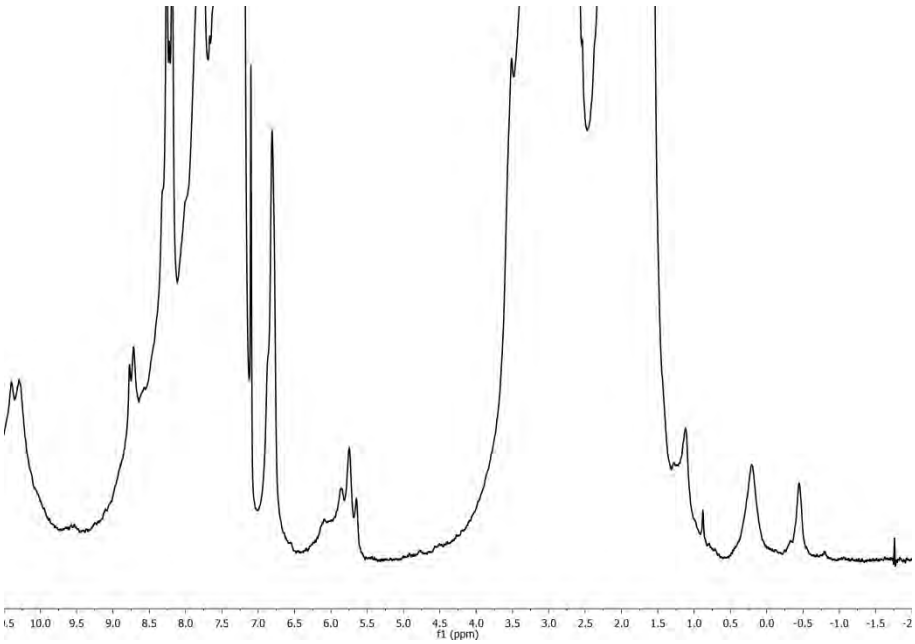


Figure S13. ^{1}H NMR spectrum (mesitylene-d_{12}, 270 K) of cavitand **3** (2 mM) with guest **G5** (1 equiv).

- Guest **G6**

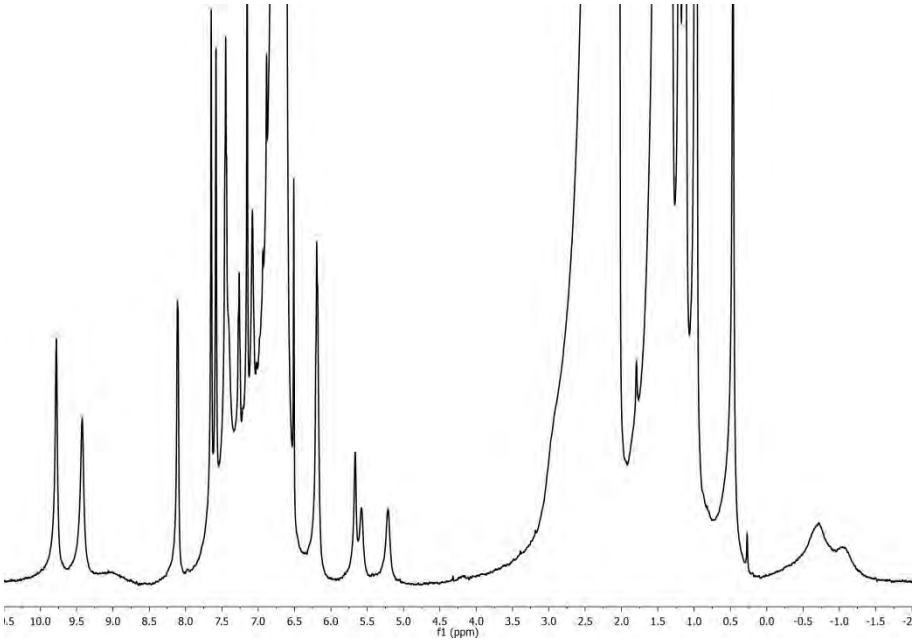


Figure S14. ^{1}H NMR spectrum (mesitylene-d_{12}, 300 K) of cavitand **2** (2 mM) with guest **G6** (1 equiv).

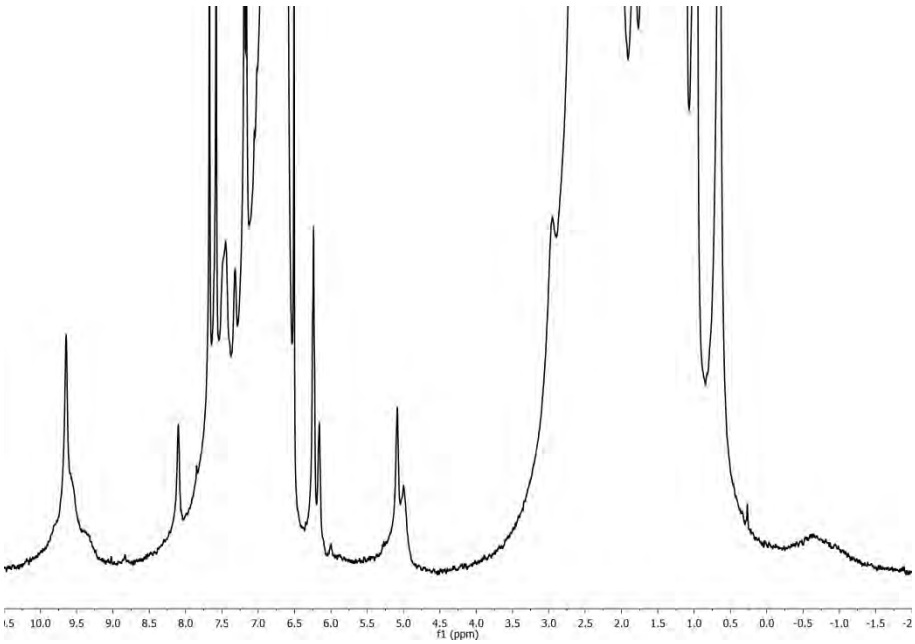


Figure S15. ^{1}H NMR spectrum (mesitylene-d_{12}, 300 K) of cavitand **3** (2 mM) with guest **G6** (1 equiv).

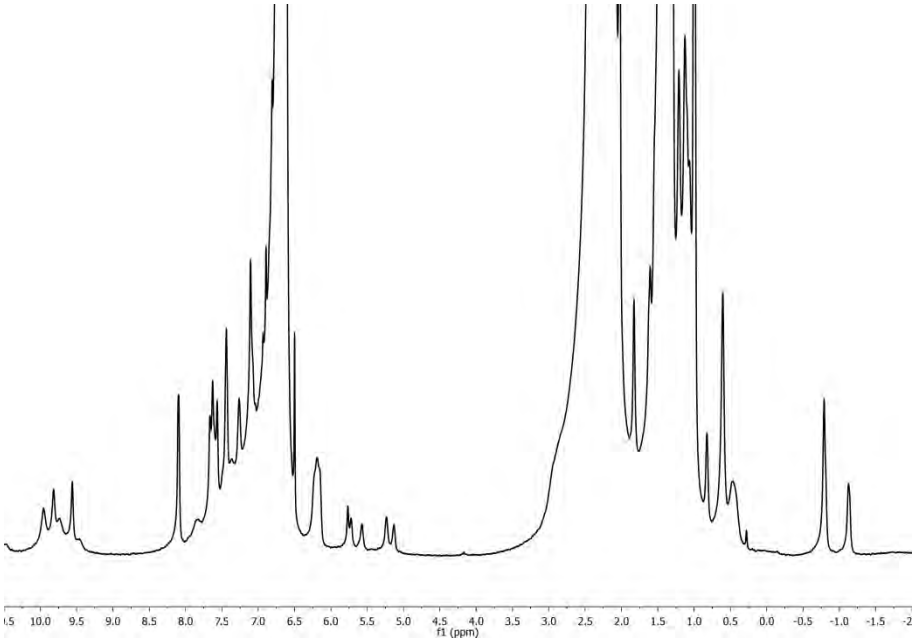


Figure S16. ^{1}H NMR spectrum (mesitylene-d_{12}, 270 K) of cavitand **2** (2 mM) with guest **G6** (1 equiv).

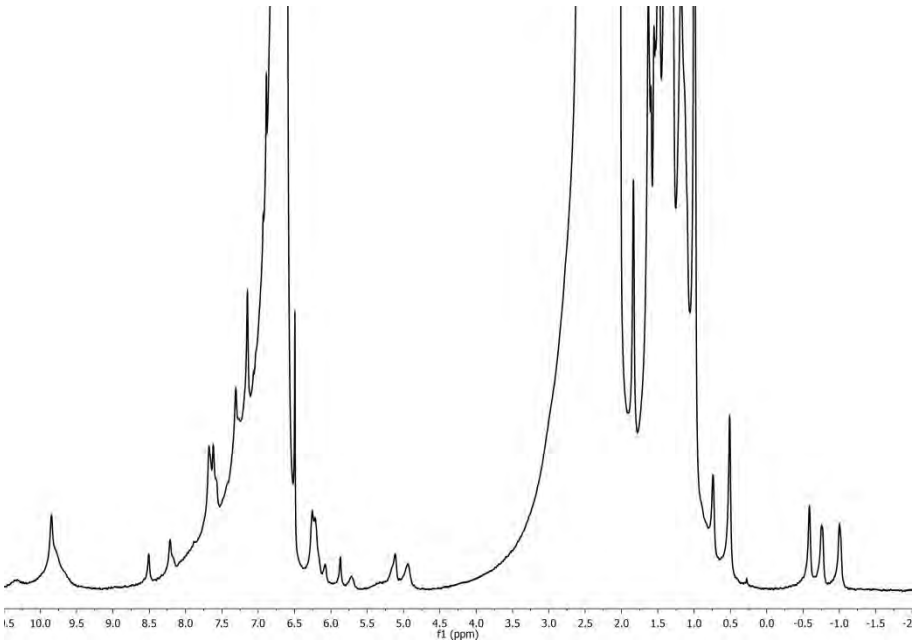


Figure S17. ^{1}H NMR spectrum (mesitylene-d_{12}, 270 K) of cavitand **3** (2 mM) with guest **G6** (1 equiv).

XIII. 2D NOESY spectra of both cavitand 2 and 3 with guest G6

- Cavitand **2** / guest **G6**

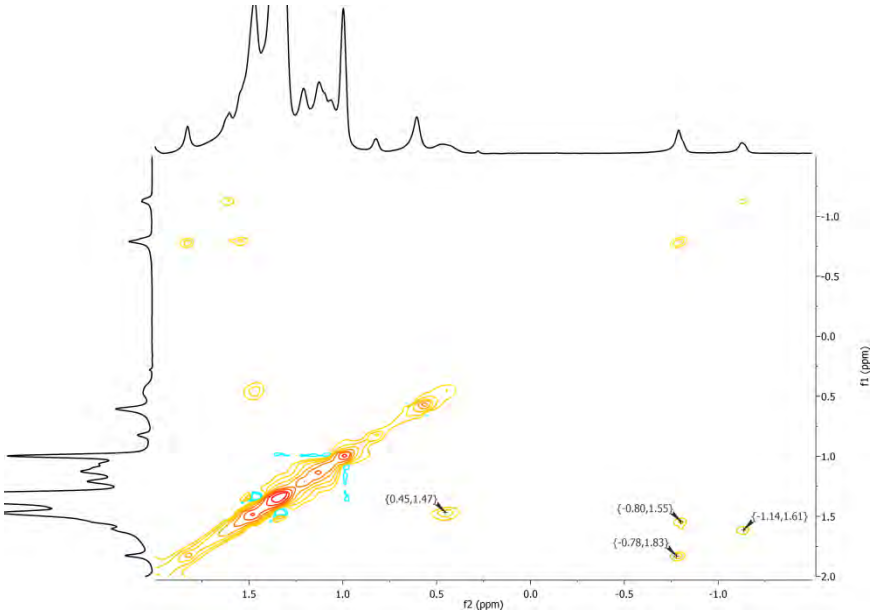


Figure S18. NOESY spectrum (mesitylene-d_{12}, 270 K) of cavitand **2** with guest **G6** (mixing time 300 ms).

- Cavitand **3** / guest **G6**

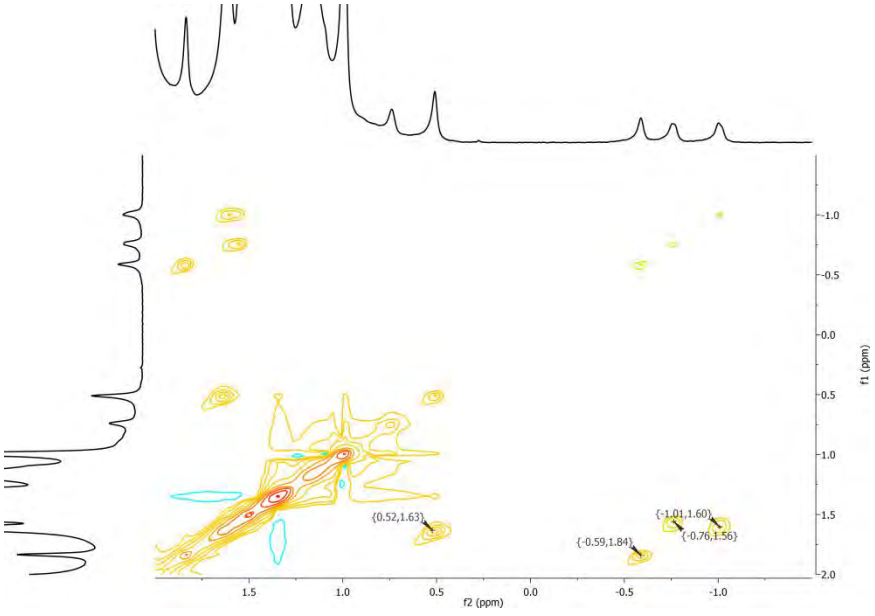
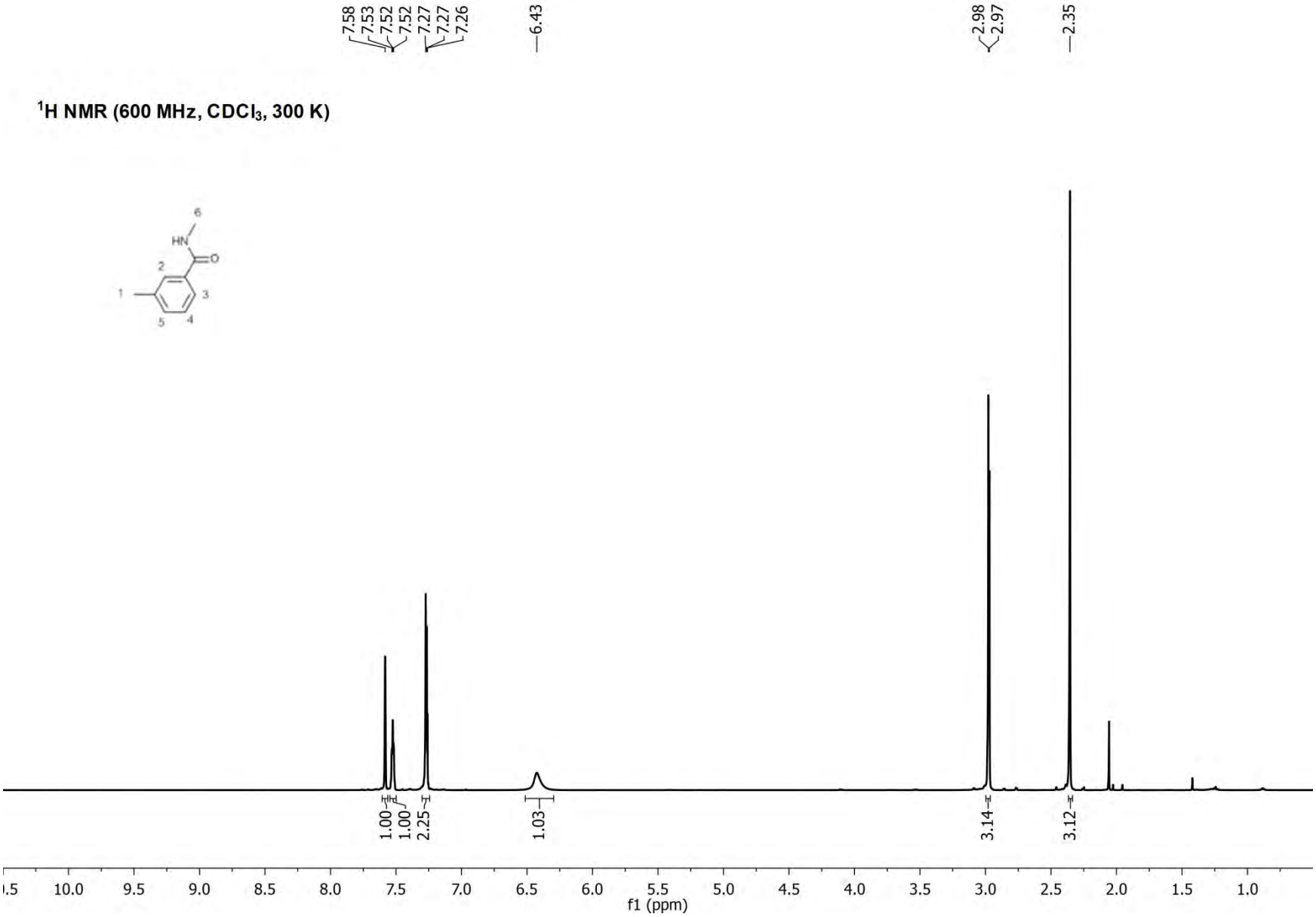


Figure S19. NOESY spectrum (mesitylene-d_{12}, 270 K) of cavitand **3** with guest **G6** (mixing time 300 ms).

XIV. References

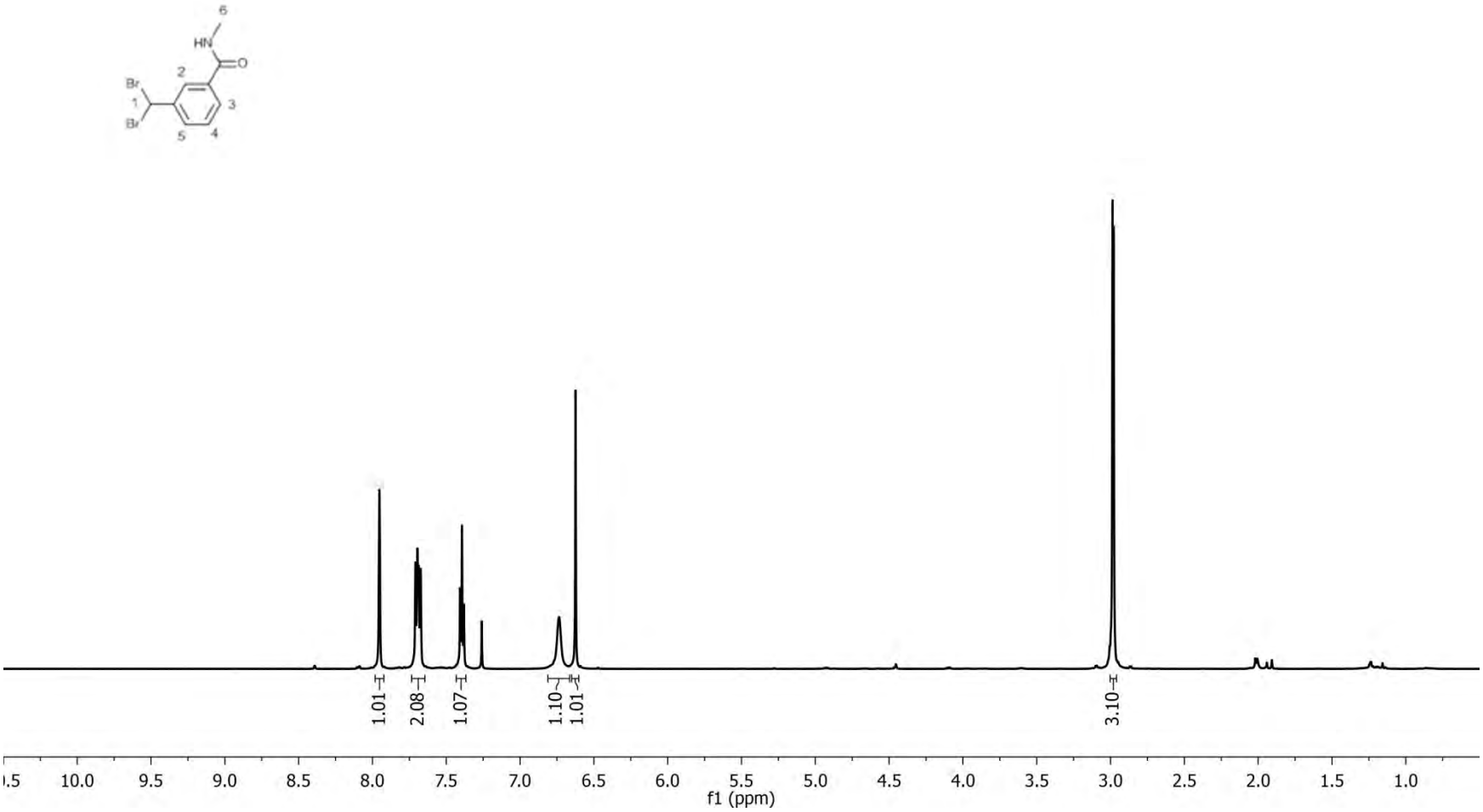
[1] T. Iwasawa, P. Wash, C. Gibson, J. Rebek Jr, *Tetrahedron* **2007**, *63*, 6506-6511.
[2] H. P. Xi, C. L. D. Gibb, B. C. Gibb, *J Org Chem* **1999**, *64*, 9286-9288.

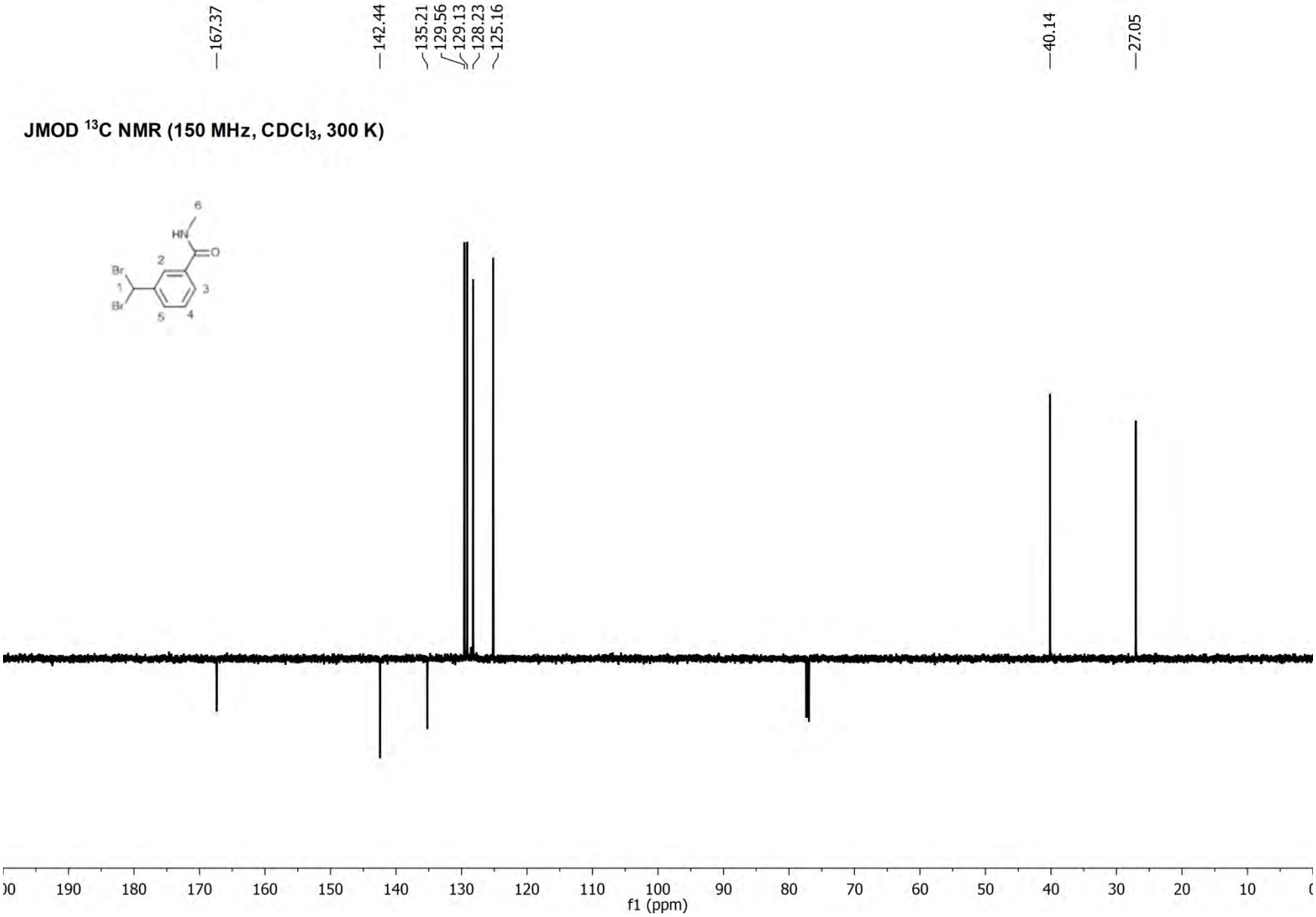
XV. NMR Spectra

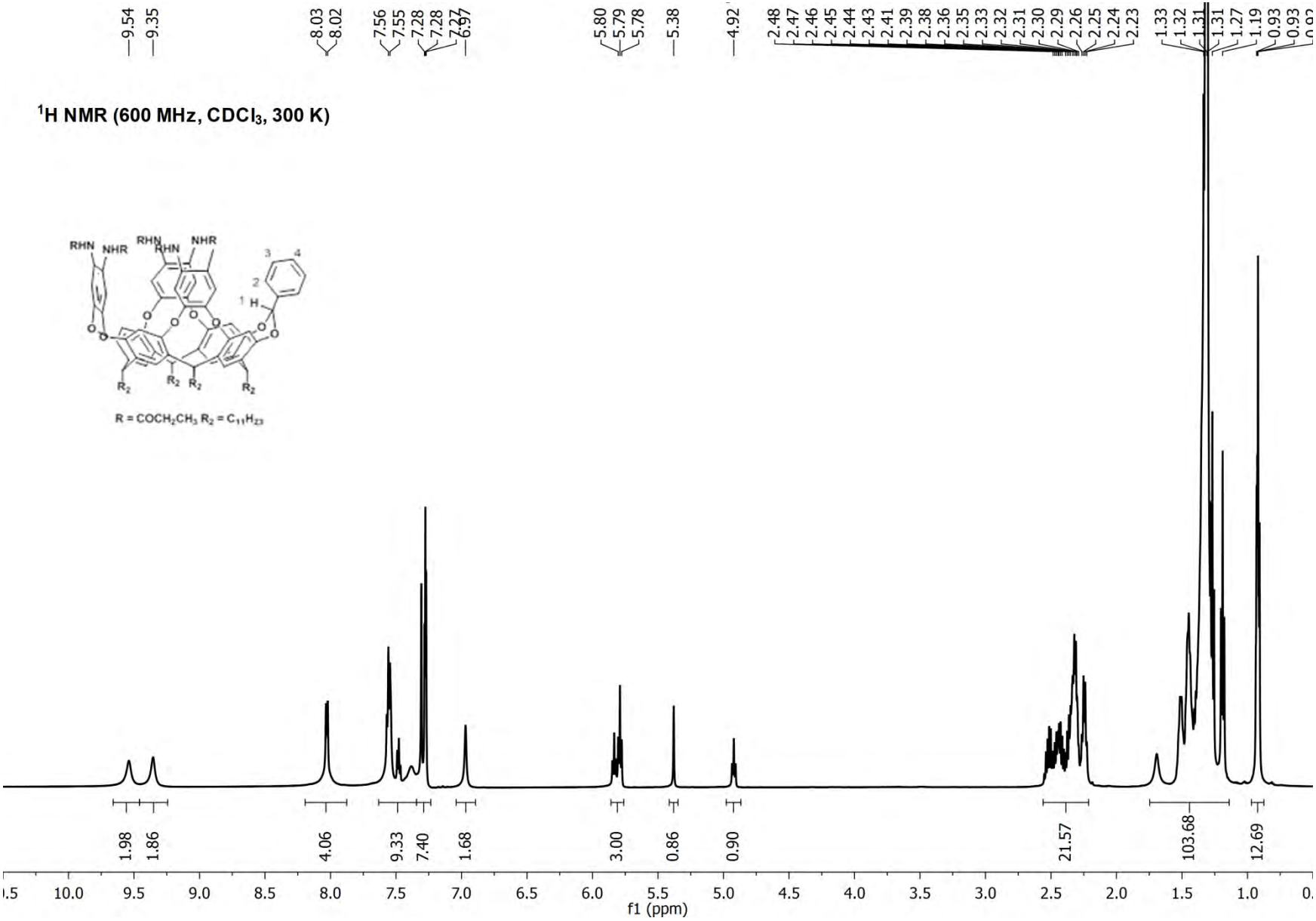


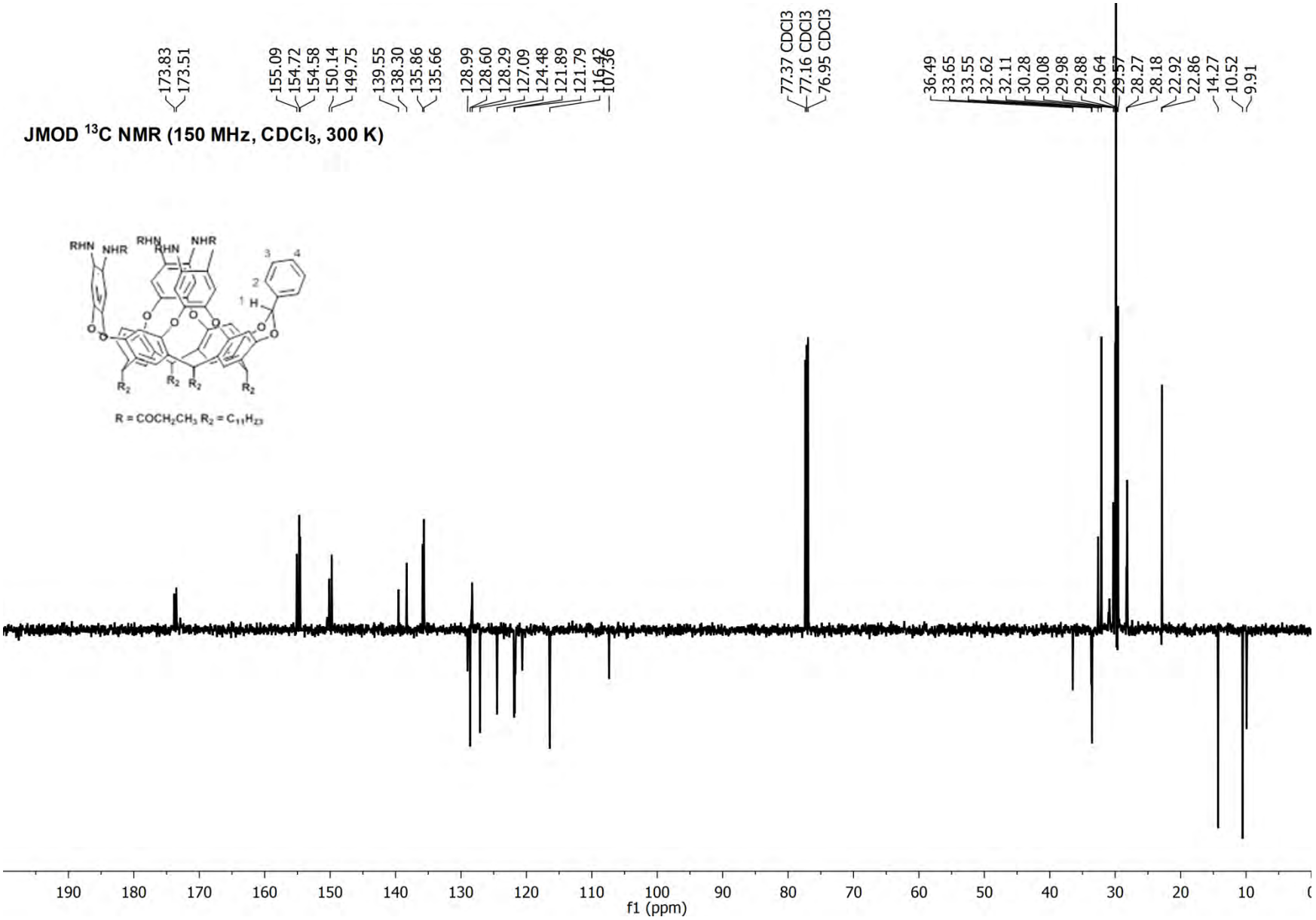
^{1}H NMR (600 MHz, $CDCl_3$, 300 K)

^{1}H NMR (600 MHz, $CDCl_3$, 300 K)








173.83
173.51
155.09
154.72
154.58
150.14
149.75
139.55
138.30
135.86
135.66
128.99
128.60
128.29
127.09
124.48
121.89
121.79
116.42
107.36
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
36.49
33.65
33.55
32.62
32.11
30.28
30.08
29.98
29.88
29.64
29.57
28.27
28.18
22.92
22.86
14.27
10.52
9.91
JMOD 13C NMR (150 MHz, CDCl3, 300 K)
RHN
NHR
R = COCH2CH3 R2 = C11H23
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)