Electronic Supplementary Information for:

Selective Binding and Release of Aspirin by an Encapsulating Receptor

Thanh V. Nguyen, Hiroshi Yoshida and Michael S. Sherburn*

Research School of Chemistry, Australian National University

Canberra, ACT 0200, Australia

E-mail: sherburn@rsc.anu.edu.au

Table of Contents

General Methods

Reactions were conducted under a positive pressure of dry nitrogen in oven-dried glassware. Tetrahydrofuran (THF), toluene and diethyl ether were dried over sodium wire and distilled from sodium benzophenone ketyl. Dichloromethane was dried by distillation from calcium hydride. $B(OMe)_3$ was dried by distillation from sodium metal. Magnesium sulfate was dried at 140 °C for 12 h prior to use. Commercially available reagents were used as purchased. Analytical thin layer chromatography was performed using plates precoated with silica gel 60 F_{254} (0.2 mm). Flash chromatography employed 230–400 mesh silica gel. Solvents used for chromatography are quoted as volume/volume ratios.

HPLC was performed using a Shimadzu CLASS-VP LC-10AD chromatography pump monitored by a Shimadzu SPD-10A VP UV detector and a Shimadzu RID-10A refractive index detector. Preparative HPLC employed an RTI Zorbax SIL column of pore size 7 μm, of internal diameter 21.2 mm and 25 cm length.

^{1}H NMR spectra were recorded at 800 MHz, 500 MHz and 300 MHz using a Bruker AVANCE 800, a Varian INOVA 500 or a Varian Unity Inova 300 spectrometer at 298 K. Data is expressed in parts per million (ppm) downfield shift from tetramethylsilane with residual solvent as an internal reference (δ 7.26 ppm for chloroform) and is reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J in Hz) and integration (number of protons).

^{13}C NMR spectra were recorded at 200 MHz, 125 MHz or 75 MHz using a Bruker AVANCE 800, a Varian INOVA 500 or a Varian Unity Inova 300 spectrometer at 298 K with complete proton decoupling. Data is expressed in parts per million (ppm) downfield shift relative to the internal reference (δ 77.2 ppm for the central peak of deuterated chloroform) and is reported as position (δ in ppm).

Compounds were prepared for IR spectroscopic analysis as mixtures in KBr pressed disks and the spectra were collected using a Perkin–Elmer Spectrum One spectrophotometer. All compounds were dried before analysis at *ca*. 50 °C and 0.1 mm Hg for 24 h.

Elemental analyses were obtained at the Microanalytical Unit at the Research School of Chemistry, Australian National University. All compounds were dried at *ca*. 50 °C and 0.1 mm Hg for 24–120 h before analysis.

Mass spectra were carried out on a Waters QTOF Ultima Instrument at the Biomolecular Mass Spectrometry Laboratory, School of Chemistry, University of Wollongong, Australia.

Melting points were recorded on a Reichert heating stage apparatus with a microscope and are uncorrected.

ITC binding studies were carried out using a MicroCal VP-ITC Isothermal Titration Calorimeter. See 'General Methods for Host-Guest Binding Studies' for more details.

Tetrabromo-superbowl **B** (Scheme 1, ● = Br, Compound **1**) and tetraprotio-cruciform pentamer **A** (Scheme 1, ● = H, Compound **6**) were prepared as described previously.[1]

Standard Drying Procedures for Organometallic Reactions

To a two-necked round-bottomed flask, fitted with a septum and a magnetic stirrer bar, containing the superbowl starting material, was added dry, freshly distilled THF (10 mL per 1 mmol of starting material). The resulting solution was evaporated to dryness and then heated at 80 °C at 0.1 mm Hg for 1 h. The vacuum was replaced with Ar, and the procedure was repeated two more times.

Experimental Procedures and Characterization Data for Superbowls Hosts

General Method for Free Radical Reductive Debromination of Tetrabromo-Superbowl (1)

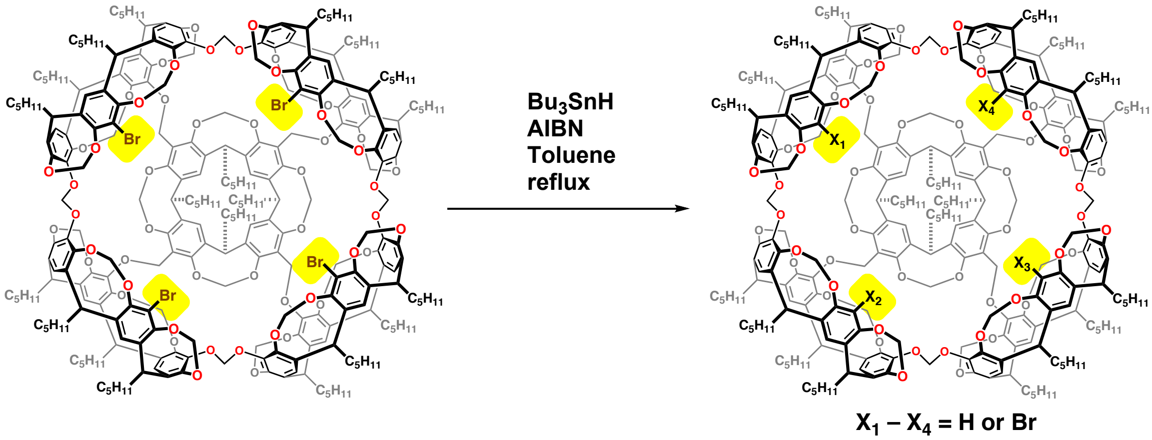


Table S1. Free radical reductive debromination of tetrabromo-superbowl (**1**).

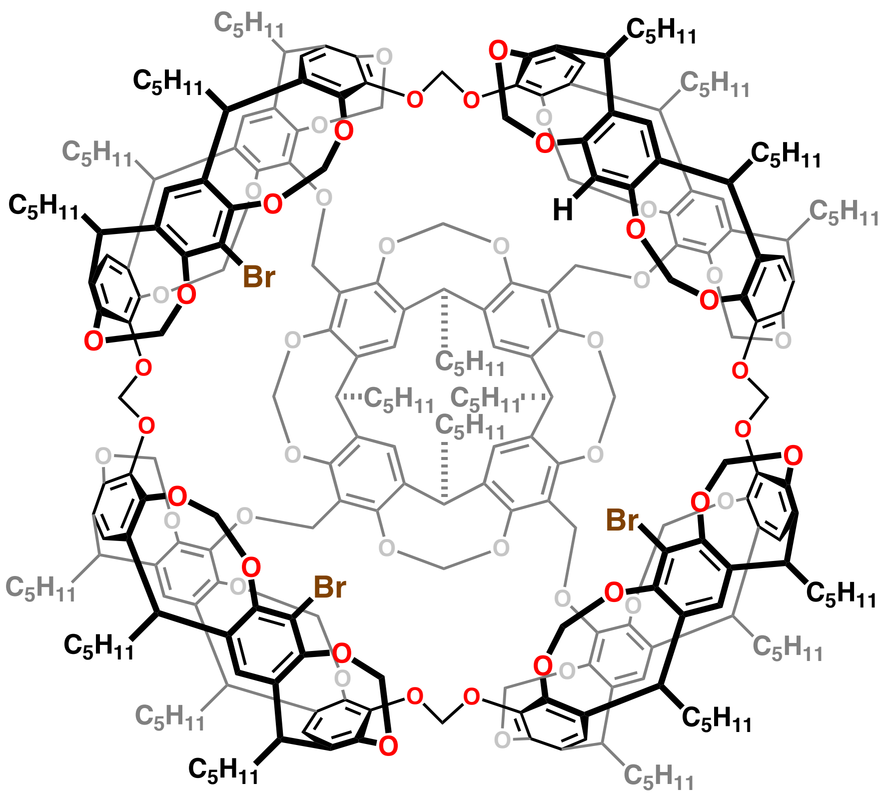
Superbowl derivatives	Molar equivalent of Bu_3SnH				
	1.1 equiv[a]	2.2 equiv[a]	3.3 equiv[a]	4.4 equiv[a]	16 equiv[b]
Br_4 (Table 1, Compound **1**)	35%	4%	1%	trace	
HBr_3 (Table 1, Compound **2**)	52%	26%	15%	5%	
distal-H_2Br_2 (Table 1, Compound **3**)	8%	30%	22%	11%	
proximal-H_2Br_2 (Table 1, Compound **4**)	4%	22%	18%	14%	
H_1Br_3 (Table 1, Compound **5**)	1%	15%	35%	15%	4%
H_4 (Table 1, Compound **6**)		3%	9%	54%	96%

[a] Percentage ratios obtained from HPLC peak area integration.

[b] Percentage ratios obtained from ^{1}H NMR integration.

To a stirred, degassed solution of tetrabromo-superbowl (**1**)[1] (94.0 mg, 20.0 μmol) in toluene (10 mL) under a nitrogen atmosphere was added tributyltin hydride (quantity as listed in Table S1). The reaction mixture was heated to 110 °C for 10 min, then AIBN (2.0 mg in 1 mL toluene, 10.0 μmol) was added. The reaction mixture was stirred at that temperature for another 4 h, then cooled to rt and diluted with more toluene. The resulting solution was washed successively with 30% aq. ammonium hydroxide solution, sat. aq. NaCl and dried over $MgSO_4$ before the solvent was removed *in vacuo*. The crude product was filtered through a short plug of silica to remove the majority of tin by-products. The products were separated by either repeated column chromatography (50 g silica, 4:6 to 6:4 dichloromethane/hexane, 2–3 times) or HPLC to give the family of H_nBr_{4-n}-superbowl products (entries 2–6, Table 1). For product ratios, analytical HPLC or ^{1}H NMR analyses were employed.

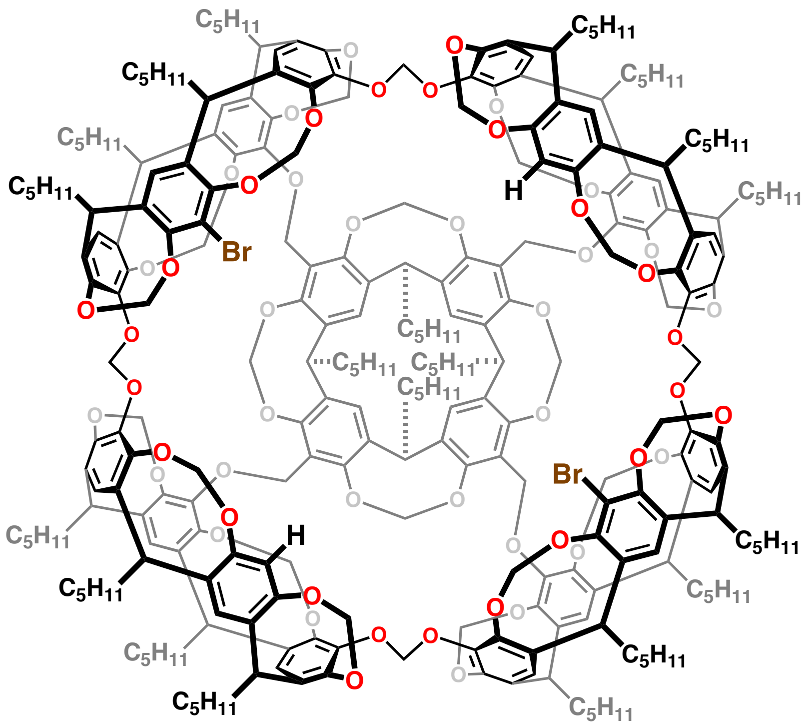
_C_-Pentyl tribromo-monoprotio-superbowl (Table 1, Compound 2)



2

Tribromo-monoprotio-superbowl **2** was obtained as a white solid: R_f = 0.43 (1:1 dichloromethane/hexane); mp > 310 °C (decomp.) (dichloromethane/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 4H), 7.12 (s, 1H), 7.09 (s, 3H), 6.87 (s, 1H), 6.85 (s, 3H), 6.84 (s, 4H), 6.83 (s, 4H), 6.53 (s, 1H), 6.11 (d, J = 6.5 Hz, 4H), 6.10 (d, J = 5.0 Hz, 2H), 6.06 (d, J = 7.0 Hz, 4H), 6.00 (d, J = 7.5 Hz, 2H), 5.98 (d, J = 7.5 Hz, 4H), 5.95 (d, J = 7.0 Hz, 2H), 5.91 (d, J = 7.0 Hz, 2H), 5.66 (d, J = 2.0 Hz, 2H), 5.59 (d, J = 2.0 Hz, 2H), 5.56 (d, J = 2.0 Hz, 2H), 5.54 (d, J = 2.0 Hz, 2H), 4.88 (dt, J = 3.0 Hz, J = 7.5 Hz, 4H), 4.80 (dt, J = 4.0 Hz, J = 8.0 Hz, 8H), 4.78 (dt, J = 1.5 Hz, J = 7.5 Hz, 6H), 4.74 (t, J = 8.0 Hz, 2H), 4.58 (dd, J = 6.5 Hz, J = 6.8 Hz, 4H), 4.55 (m, 4H), 4.54 (m, 8H), 4.38 (d, J = 7.0 Hz, 2H), 4.36 (dd, J = 2.0 Hz, J = 8.5 Hz, 6H), 4.23 (dd, J = 6.5 Hz, J = 6.8 Hz, 4H), 2.30–2.10 (m, 32H), 2.20–2.05 (m, 8H), 1.50–1.20 (m, 120H), 0.98–0.85 (m, 60H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 154.5, 154.4, 151.9, 148.9, 148.8, 147.1, 146.9 (two coincident resonances), 146.7, 146.5, 146.4, 143.7, 143.6, 141.1, 141.0, 140.9 (two coincident resonances), 139.8, 139.7, 139.5, 139.4, 139.1, 139.0, 138.6, 138.4, 129.0, 128.2, 121.9, 121.6, 119.8, 115.1, 114.2, 114.0, 112.5, 100.0, 99.7, 99.2, 97.2, 96.8, 66.3 (two coincident resonances), 37.3, 37.2, 36.8, 32.2, 32.0, 31.9, 31.8, 31.6, 30.4, 29.7, 27.7, 27.5, 27.4, 22.7, 14.1 ppm; IR (KBr) 2928, 2862, 1577 cm^{-1}; Nanospray ESI-MS *m/z*: 2305.63 ([*M+2H*]$^{++}$, 100%); Anal. Calcd. for $C_{268}H_{317}Br_3O_{52}$: C, 69.82; H, 6.93; found C, 69.71; H, 6.89.

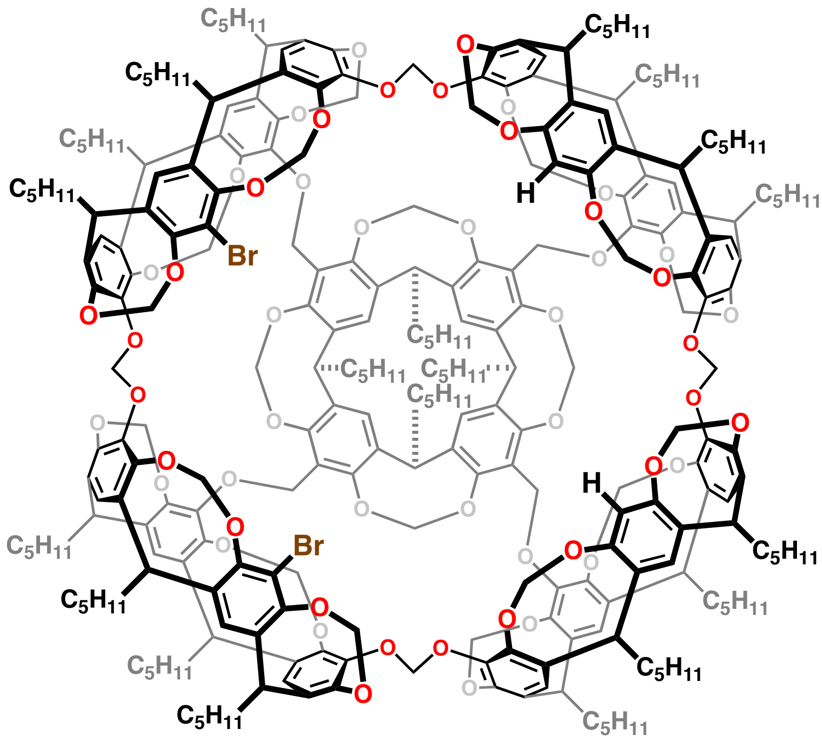
_C_-Pentyl _distal_-dibromo-diprotio-superbowl (Table 1, Compound 3)



3

Distal-dibromo-diprotio-superbowl **3** was obtained as a white solid: R_f = 0.32 (1:1 dichloromethane/hexane); mp > 310 °C (decomp.) (dichloromethane/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 4H), 7.12 (s, 2H), 7.07 (s, 2H), 6.87 (s, 8H), 6.85 (s, 4H), 6.48 (s, 2H), 6.12 (d, *J* = 6.5 Hz, 2H), 6.09 (dd, *J* = 6.0 Hz, *J* = 7.0 Hz, 6H), 5.97 (dd, *J* = 7.0 Hz, *J* = 7.5 Hz, 4H), 5.93 (d, *J* = 7.5 Hz, 2H), 5.88 (d, *J* = 6.0 Hz, 6H), 5.56 (m, 8H), 4.88 (t, *J* = 4.0 Hz, 4H), 4.78 (t, *J* = 7.0 Hz, 8H), 4.73 (t, *J* = 7.0 Hz, 8H), 4.55 (m, 16H), 4.38 (m, 6H), 4.29 (d, *J* = 6.5 Hz, 2H), 4.23 (m, 4H), 2.30–2.10 (m, 32H), 2.20–2.05 (m, 8H), 1.50–1.20 (m, 120H), 0.98–0.85 (m, 60H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 154.6, 152.1, 149.2, 147.3, 147.2, 147.1, 146.8, 146.7, 143.9, 142.3, 141.4, 141.2, 141.0, 140.9, 140.7, 140.1, 139.9, 139.7, 139.3, 138.9, 138.6, 122.0, 121.9, 120.1, 115.8, 114.8, 114.5, 112.8, 110.6, 100.2, 99.9, 97.3, 66.7, 66.1, 60.7, 37.6, 37.4, 37.1, 32.4, 32.1, 32.0, 30.8, 30.0, 27.9, 27.8, 27.6, 22.9, 21.3, 15.5, 14.4, 14.3 ppm; IR (KBr) 2928, 2861, 1577 cm^{-1}; Nanospray ESI-MS *m/z*: 2267.36 ([*M+2H*]$^{++}$, 35%), 2243.66 (100%); Anal. Calcd. for $C_{268}H_{318}Br_2O_{52}$: C, 71.04; H, 7.07; found C, 70.97; H, 7.32.

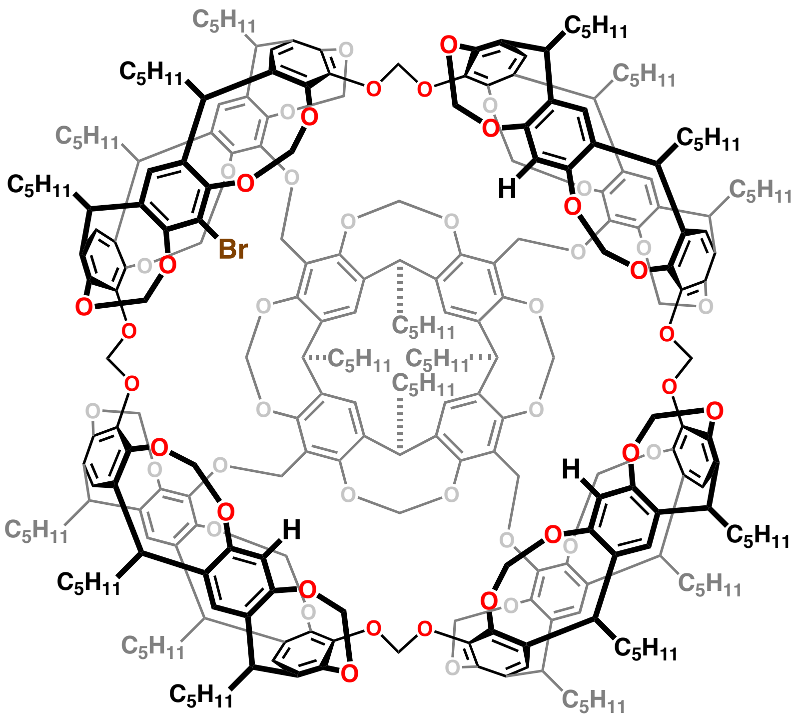
_C_-Pentyl _proximal_-dibromo-diprotio-superbowl (Table 1, Compound 4)



4

Proximal-dibromo-diprotio-superbowl **4** was obtained as a white solid: R_f = 0.37 (1:1 dichloromethane/hexane); mp > 310 °C (decomp.) (dichloromethane/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 4H), 7.12 (s, 2H), 7.09 (s, 2H), 6.87 (s, 2H), 6.86 (s, 2H), 6.85 (m, 6H), 6.85 (s, 2H), 6.51 (s, 2H), 6.12 (d, *J* = 6.5 Hz, 2H), 6.11 (d, *J* = 5.0 Hz, 2H), 6.08 (d, *J* = 5.5 Hz, 2H), 6.06 (d, *J* = 7.5 Hz, 4H), 5.98 (m, 4H), 5.90 (m, 6H), 5.69 (d, *J* = 2.0 Hz, 1H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.58 (d, *J* = 1.5 Hz, 2H), 5.54 (s, 2H), 5.52 (d, *J* = 1.5 Hz, 2H), 4.88 (t, *J* = 8.0 Hz, 4H), 4.79 (m, 12H), 4.73 (t, *J* = 8.0 Hz, 4H), 4.55 (m, 16H), 4.38 (d, *J* = 7.0 Hz, 4H), 4.36 (d, *J* = 3.5 Hz, 2H), 4.35 (d, J = 4.0 Hz, 2H), 4.23 (m, 4H), 2.30–2.20 (m, 32H), 2.20–2.05 (m, 8H), 1.50–1.20 (m, 120H), 0.98–0.85 (m, 60H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 154.6, 152.2, 149.0, 147.3, 147.1 (two coincident resonances), 147.0, 146.9, 146.8, 146.6, 143.9, 142.2, 141.4, 141.2, 141.1, 140.9, 140.1, 139.9, 139.6, 139.3, 138.9, 138.7, 122.1, 121.9, 120.0, 115.5, 114.8, 114.5, 112.8, 110.6, 100.2, 99.8, 97.3, 66.7, 66.1, 60.7, 37.6, 37.4, 37.1, 32.4, 32.2, 32.1, 30.7, 30.1, 27.9, 27.8, 27.6, 27.6, 22.8, 21.3, 15.4, 14.4, 14.3 ppm; IR (KBr) 2928, 2860, 1577 cm^{-1}; Nanospray ESI-MS *m/z*: 2267.50 ([*M+2H*]$^{++}$, 15%), 2215.88 (100%); Anal. Calcd. for $C_{268}H_{318}Br_2O_{52}$: C, 71.04; H, 7.07; found C, 71.24; H, 7.02.

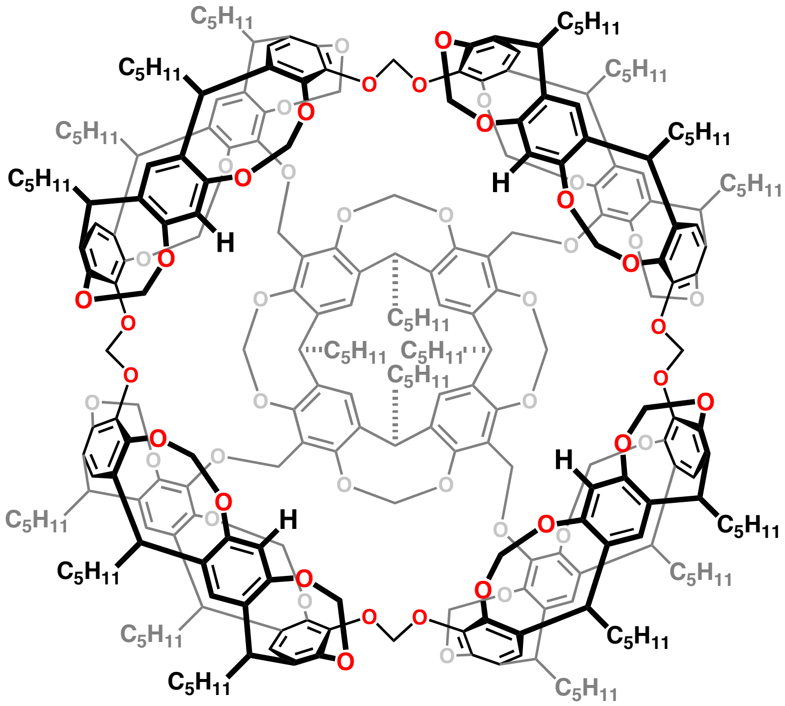
_C_-Pentyl monobromo-triprotio-superbowl (Table 1, Compound 5)



5

Monobromo-triprotio-superbowl **5** was obtained as a white solid: R_f = 0.20 (1:1 dichloromethane/hexane); mp > 310 °C (decomp.) (dichloromethane/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 4H), 7.13 (s, 3H), 7.10 (s, 1H), 6.90-6.80 (m, 12H), 6.50 (s, 3H), 6.14 (d, J = 5.1 Hz, 2H), 6.15-6.05 (m, 6H), 6.05-5.85 (m, 12H), 5.62 (s, 2H), 5.57 (s, 2H), 5.54 (s, 4H), 4.88 (m, 4H), 4.85-4.70 (m, 16H), 4.65-4.45 (m, 16H), 4.38 (m, 8H), 4.24 (m, 4H), 2.40–2.05 (m, 40H), 1.50–1.15 (m, 120H), 1.00–0.85 (m, 60H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 154.7, 154.6, 154.5, 152.0, 149.1 (two coincident resonances), 149.0, 147.2, 147.1 (two coincident resonances), 147.0, 146.8, 146.6, 143.8, 143.6, 141.1 (two coincident resonances), 141.0, 140.8, 140.0, 139.8, 139.7, 139.5, 139.2 (two coincident resonances), 138.7, 138.5 (two coincident resonances), 122.0, 121.7, 116.1, 115.4, 114.4, 114.2, 112.7, 100.2, 99.8, 97.3, 97.1, 66.4, 60.5, 37.3, 36.9, 36.8, 32.3, 32.1, 31.9, 31.7, 30.5, 29.9, 29.8, 27.8, 27.6, 27.5, 22.8, 20.9, 14.2 (two coincident resonances) ppm; IR (KBr) 2928, 2861, 1578 cm^{-1}; Nanospray ESI-MS *m*/*z*: 2226.33 ([$M+2H$]$^{++}$, 65%), 2208.42 (100%); Anal. Calcd. for $C_{268}H_{319}BrO_{52}$: C, 72.30; H, 7.22; found C, 72.04; H, 6.99.

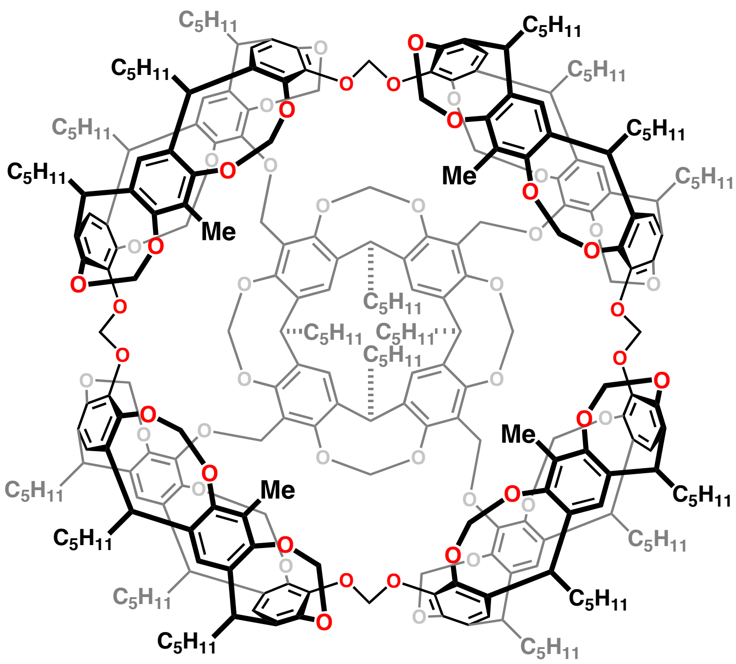
C-Pentyl tetraprotio-superbowl (Table 1, Compound 6)



6

Tetraprotio-superbowl **6** was obtained as a white solid: R_f = 0.11 (1:1 dichloromethane/hexane). Characterization data corresponded to that reported previously for a sample prepared by a different route.[1]

C-Pentyl tetramethyl-superbowl (Table 1, Compound 7)

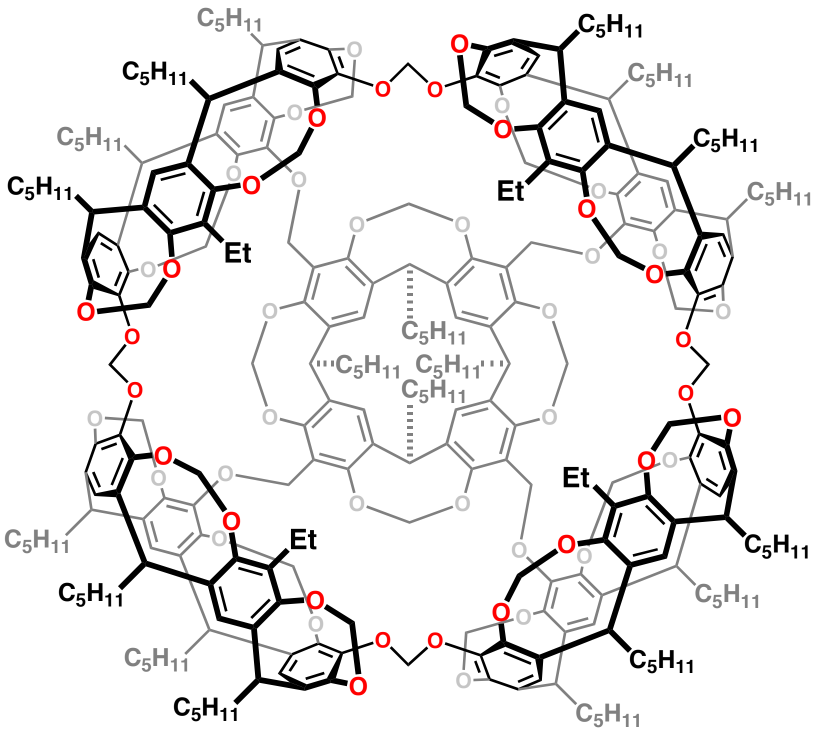


7

To a slurry of tetrabromo-superbowl **1** (94.0 mg, 20.0 μmol), dried according to the standard procedure, and sodium hydride[2] (20.0 mg, 60% in mineral oil, 0.50 mmol) in THF (10 mL) at −78 °C was added *t*-BuLi (300 μL of a 1.33 M solution in pentanes, 400 μmol, 20 equiv). After 30 seconds, methyl iodide (62.5 μL, 1.00 mmol) was added, the cooling bath was removed and the mixture was allowed to warm to rt and was stirred at this temperature for 4 h. After cautious addition of methanol, the organic solvents were removed *in vacuo*. The resulting residue was partitioned between water (20 mL) and dichloromethane (15 mL). The aqueous phase was extracted with more dichloromethane (2 × 10 mL). The combined organic phases were washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (20 g SiO_2, 40:60 dichloromethane/hexane) afforded the title compound **7** as a white solid (69.0 mg, 73%): R_f = 0.55 (7:3 dichloromethane/hexane); mp > 310 °C (decomp.) (dichloromethane/hexane); ^1H NMR (800 MHz, $CDCl_3$) δ 7.25 (s, 4H), 6.98 (s, 4H), 6.88 (s, 8H), 6.86 (s, 4H), 6.08 (d, J = 17.8 8H), 6.03 (d, J =17.8 Hz, 4H), 5.96 (d, J = 17.8 Hz, 8H), 5.62 (d, J = 5.2 Hz, 4H), 5. 53 (d, J = 5.2 Hz, 4H), 4.87 (t, J = 17.8 Hz, 4H), 4.79 (t, J = 17.8 Hz, 8H), 4.77 (t, J = 17.8 Hz, 8H), 4.57 (s, 8H), 4.50 (d, J =

16.3 Hz, 8H), 4.32 (d, J = 16.3 Hz, 8H), 4.26 (d, J = 16.3 Hz, 4H), 2.40–2.25 (m, 32H), 2.20–2.10 (m, 8H), 1.98 (s, 12H), 1.50–1.25 (m, 120H), 0.98–0.80 (m, 12H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 154.7, 153.7, 149.1, 147.0, 146.9, 143.8, 141.2, 139.8, 139.7, 138.7, 138.1, 131.2, 123.5, 122.2, 121.8, 118.2, 115.5, 114.9, 114.6, 100.4, 100.1, 99.5, 97.6, 66.6, 37.3, 37.2, 37.1, 32.4, 32.2, 30.6, 30.2, 29.9, 29.6, 27.9, 27.8, 27.7, 27.4, 22.9, 19.4, 14.4, 14.3 ppm; IR (KBr) 2927, 2859, 1577 cm^{-1}; Nanospray ESI-MS m/z: 2216.02 ([$M+2H$]$^{++}$, 100%); Anal. Calcd. for $C_{272}H_{328}O_{52}$: C, 73.75; H, 7.46; found C, 73.38; H, 7.60.

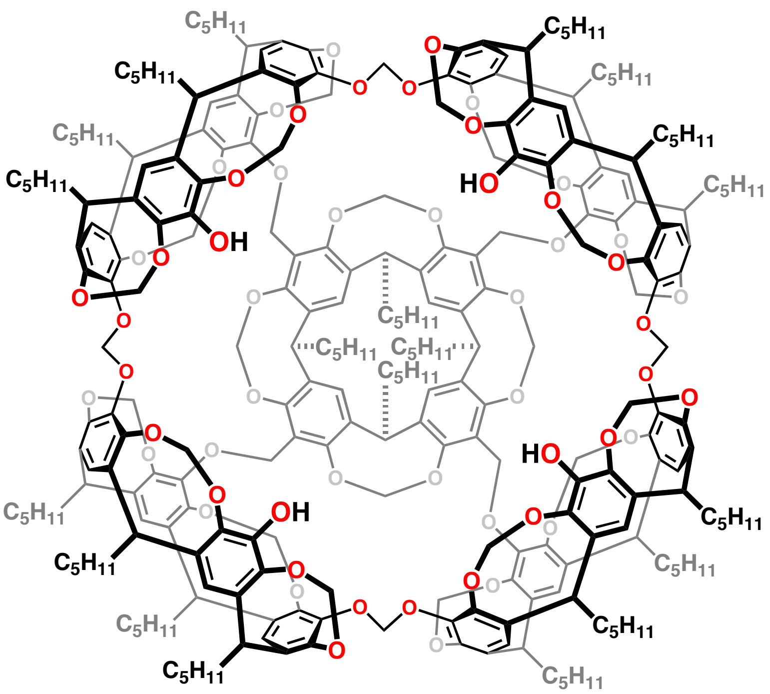
C-Pentyl tetraethyl-superbowl (Table 1, Compound 8)



8

To a slurry of tetrabromo-superbowl **1** (94.0 mg, 20.0 μmol), dried according to the standard procedure, and sodium hydride (40.0 mg, 60% in mineral oil, 1.00 mmol) in dry THF (10 mL) at −78 °C was rapidly added *t*-BuLi (500 μL of a 1.60 M solution in pentanes, 800 μmol, 40 equiv). After 10 min, ethyl iodide (100 μL, 1.25 mmol) was added, the cooling bath was removed and the mixture was allowed to warm to rt and stirred at this temperature for 4 h. After cautious addition of 5% aq. NH_4Cl, the organic solvents were removed *in vacuo*. The resulting aqueous mixture was extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (30 g SiO_2, 7:3 dichloromethane/hexane) afforded the title compound **8** as a white solid (66 mg, 74%): $R_f = 0.52$ (7:3 dichloromethane/hexane); mp > 300 °C (decomp.) (dichloromethane/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 4H), 6.98 (s, 4H), 6.87 (s, 12H), 6.07 (d, J = 6.5 Hz, 8H), 6.02 (d, J = 7.5 Hz, 4H), 5.99 (d, J = 6.5 Hz, 8H), 5.61 (d, J = 1.5 Hz, 4H), 5.54 (d, J = 2.0 Hz, 4H), 4.87 (t, J = 8.0 Hz, 4H), 4.78 (t, J = 7.5 Hz, 8H), 4.74 (t, J = 8.0 Hz, 8H), 4.56 (s, 8H), 4.51 (d, J = 7.0 Hz, 8H), 4.32 (d, J = 7.0 Hz, 8H), 4.25 (d, J = 7.5 Hz, 4H), 2.44 (q, J = 7.0 Hz, 8H), 2.30–2.06 (m, 40H), 1.50–1.25 (m, 120H), 1.03 (t, J = 7.5, 12H), 0.98–0.84 (m, 60H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.4, 149.0, 146.9, 146.8, 143.7, 141.0, 139.5, 139.4, 139.3, 138.5, 138.2, 129.3, 122.1, 121.6, 118.6, 115.5, 114.3, 100.3, 100.0, 97.4, 66.4, 37.2, 37.0, 32.3, 32.1, 32.0, 30.5, 30.2, 30.0, 27.8, 27.7, 27.6, 22.8, 18.8, 14.8, 14.3, 14.2 ppm; IR (KBr) 2928, 2861, 1577, 1490 cm^{-1}; Nanospray ESI-MS *m/z*: 2244.16 ([*M+2H*]$^{++}$, 100%); Anal. Calcd. for $C_{276}H_{336}O_{52}$: C, 73.90; H, 7.55; found C, 73.69; H, 7.62.

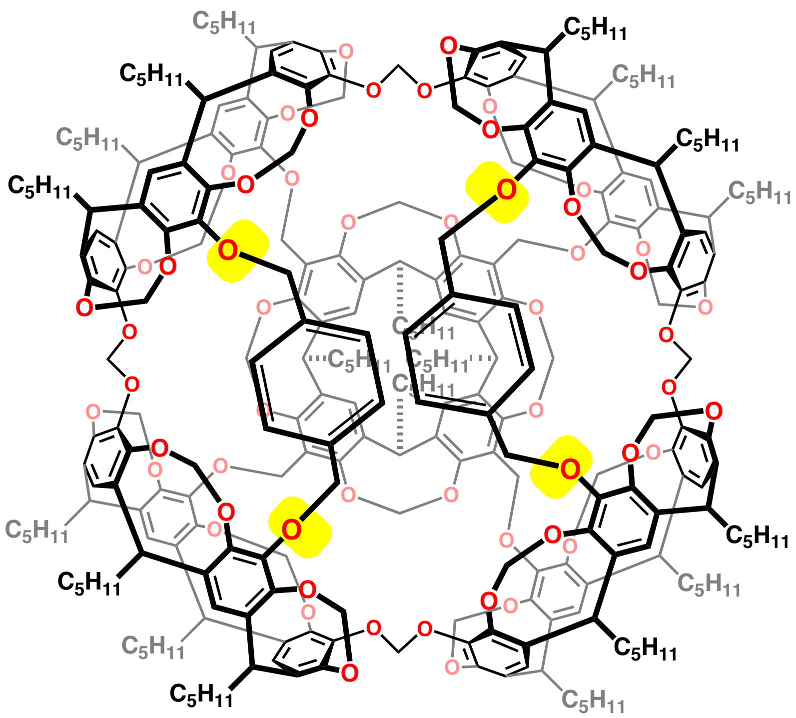
C-Pentyl tetrahydroxy-superbowl (S1)



S1

To a slurry of tetrabromo-superbowl **1** (94.0 mg, 20.0 μmol), dried according to the standard procedure, and sodium hydride (50.0 mg, 60% in mineral oil, 1.25 mmol) in THF (10 mL) at –78 °C was added *t*-BuLi (500 μL of a 1.6 M solution in pentanes, 800 μmol, 40 equiv). After 20 min, $B(OMe)_3$ (115 μL, 1.00 mmol, 50 equiv) was added, the cooling bath was removed and the mixture was allowed to warm to rt and was stirred at this temperature for 1 h. The resulting solution was cooled to –78 °C, cautiously quenched with a 1:1 mixture of 30% aq. H_2O_2 and 3.0 M aq. NaOH (10 mL) then stirred at rt for 18 h. After cautious addition of 30% aq. $Na_2S_2O_5$ to the reaction mixture at –78°C, the THF was removed *in vacuo*. The resulting aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (30 g SiO_2, 9:1 to 7:3 dichloromethane/diethyl ether) afforded the title compound **S1** as a white solid (36.0 mg, 40%): R_f = 0.23 (7:3 hexane/ethyl acetate); mp >300 °C (decomp.) (dichloromethane/ethanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 4H), 6.86 (s, 8H), 6.84 (s, 4H), 6.68 (s, 4H), 6.10 (d, J = 6.5 Hz, 8H), 5.95 (d, J = 6.6 Hz, 12H), 5.74 (br. s, 4H), 5.54 (s, 8H), 4.88 (t, J = 7.7 Hz, 4H), 4.78 (t, J = 7.7 Hz, 8H), 4.73 (t, J = 8.8 Hz, 8H), 4.58 (d, J = 4.58 Hz, 8H), 4.51 (s, 8H), 4.37 (d, J = 7.0 Hz, 8H), 4.21 (d, J = 7.2 Hz, 4H), 2.26–2.09 (m, 40H), 1.44–1.22 (m, 120H), 0.94–0.85 (m, 60H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 149.0, 147.0, 146.8, 143.6, 142.0, 140.8, 140.6, 139.7, 139.4, 139.1, 138.7, 138.4, 121.8, 121.7, 115.2, 114.5, 110.5, 100.0, 99.8, 97.1, 66.5, 37.2, 37.0, 36.8, 32.2, 31.9, 30.5, 29.8, 27.7, 27.6, 27.4, 22.7, 14.2, 14.1 ppm; IR (KBr) 3500–3200, 2930, 1468 cm^{-1}; FAB-MS m/z: 4437.2 ([M]$^+$, 100%). Anal. Calcd. for $C_{268}H_{320}O_{56}$: C, 72.54; H, 7.27; found C, 72.69; H, 7.32.

***para*-Xylyloxy-bridged superbowl (Table 1, Compound 9)**



9

To a solution of tetrahydroxy-superbowl **S1** (22.1 mg, 5.00 μmol), dried according to the standard procedure, in dry acetone (20 mL) under a nitrogen atmosphere was added Cs_2CO_3 (65.2 mg, 200 μmol) and α,α′-dibromo *para*-xylene (26.4 mg, 100 μmol). The reaction mixture was stirred for 18 h at 45 °C. The solvent was then removed *in vacuo* and the crude product was partitioned between dichloromethane (20 mL) and 2M aq. HCl solution (20 mL). The aqueous phase was extracted with more dichloromethane (2 × 5 mL). The combined organic phases were washed successively with sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over $MgSO_4$ then the solvent was removed *in vacuo*. The crude product was filtered through a short plug of silica with 100% dichloromethane. The filtrate was concentrated then filtered through another short plug of silica with dichloromethane/hexane mixture (3:7, 50 mL). The target *para*-xylyloxy-bridged superbowl, which stayed on top of the second silica plug, was washed down again with 100% dichloromethane. The final filtrate solution was concentrated to afford the practically pure **9** as a white solid (17.9 mg, 77%): R_f = 0.76 (8:2 dichloromethane/hexane); mp > 300 °C (decomp.) (dichloromethane/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 4H), 7.31 (d, J = 11.4 Hz, 8H), 6.87 (s, 8H), 6.82 (s, 4H), 6.79 (s, 4H), 6.17 (d, J

= 7.5 Hz, 4H), 6.15 (d, *J* = 7.5 Hz, 4H), 5.98 (d, *J* = 7.2 Hz, 4H), 5.94 (d, *J* = 7.2 Hz, 2H), 5.70 (d, *J* = 6.9 Hz, 2H), 5.61 (s, 2H), 5.50–5.36 (m, 6H), 5.34–5.24 (m, 4H), 5.10 (d, *J* = 7.2 Hz, 4H), 4.98–4.86 (m, 4H), 4.86–4.60 (m, 28H), 4.50–4.30 (m, 12H), 4.21 (d, *J* = 6.9 Hz, 2H), 4.15–4.04 (m, 6H), 2.35–2.00 (m, 40H), 1.55–1.20 (m, 120H), 1.00–0.80 (m, 60H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 154.2, 149.3, 148.2, 147.6, 147.2, 145.6, 143.6, 140.8, 140.0, 139.7, 139.4, 138.7, 138.4, 125.7, 121.8, 115.2, 114.7, 99.6, 99.4, 97.4, 95.7, 66.0, 37.1, 36.8, 32.5, 32.1, 32.9, 29.7, 29.5, 27.7, 27.4, 22.8, 14.3, 14.2 ppm; IR (KBr) 2928, 2863, 1570 cm^{-1}; Nanospray ESI-MS *m/z*: 2321.7620 ([*M+2H*]$^{++}$, 100%); Anal. Calcd. for $C_{284}H_{332}O_{56}$: C, 73.49; H, 7.21; found C, 73.34; H, 7.12.

Differential Line-broadening NMR Studies between Tetraprotio-Superbowl 6 and ASA

To derive more evidence for the two-point binding mode, a differential line-broadening NMR technique was employed.[3] The line-broadening NMR technique used in this work is an operationally simple method of adding a very small amount of the host (superbowl) to the guest (ASA) solution. Due to the fast interconversion between the bound and unbound guest at room temperature, the NMR signals for the guest will be broadened. By correlating the magnitude of the guest signal line-broadening with the amount of added host, useful information about the orientation of the guest relative to the host can be obtained. Generally, the more broadened the signal, the closer the proton associated with that signal to the shielding zone of the superbowl cavity.

Studies were carried out using INOVA 500 MHz NMR spectrometer at 25 °C. Linewidths of ASA signals were measured using internal functions of Varian software installed with the spectrometer.

Step 1: 10 mM ASA and 1 mM tetraprotio-superbowl **6** solutions in $CDCl_3$ were prepared and degassed. The ^{1}H NMR spectrum of a sample of 10 mM ASA solution (1 mL) in a standard NMR sample tube was recorded.

Step 2: 1 mM tetraprotio-superbowl **6** solution (10 μL) was added to the NMR tube. The solution was thoroughly mixed and allowed to equilibrate over 30 min. This brought the ratio of ASA/superbowl to 1000:1. The ^{1}H NMR spectrum of this sample was recorded.

Step 3: Repeating what was done in step 2 to the 1000:1 ASA/host sample from step 2 with another aliquot (10 μL) of 1 mM tetraprotio-superbowl **6** solution. This brought the ratio of ASA/superbowl to 500:1.

Step 4: Repeating what was done in step 2 to the 500:1 ASA/host sample from step 3 with another aliquot (20 μL) of 1 mM tetraprotio-superbowl **6** solution. This brought the ratio of ASA/superbowl to 250:1.

Step 5: Repeating what was done in step 2 to the 250:1 ASA/host sample from step 4 with another aliquot (60 μL) of 1 mM tetraprotio-superbowl **6** solution. This brought the ratio of ASA/superbowl to 100:1.

Linewidths of ASA signals were then measured and the linewidth change factor for each individual signal was calculated as:

$$\textbf{Linewidth change} = \frac{\textbf{(Broadened) linewidth}}{\textbf{Original linewidth (of free ASA)}}$$

The linewidths and linewidth change factors are summarized below:

ASA	Linewidths (Hz)				
Signal	Free ASA	1st addition	2nd addition	3rd addition	4th addition
CH_3	1.17143	1.25509	1.27825	1.33917	1.95619
H4	2.26952	2.23567	2.29385	2.32567	2.52343
H3	2.36157	2.41999	2.44081	2.52862	2.82509
H2	3.23121	3.16603	3.25627	3.36592	3.75931
H1	2.87987	2.97163	2.96416	3.05311	3.55749
COOH	461.424	468.995	505.644	535.936	620.251

Ratio	Linewidth change					
(ASA/host)	CH_3	H4	H3	H2	H1	COOH
1000:1	1.07	0.99	1.02	0.98	1.03	1.02
500:1	1.09	1.01	1.03	1.01	1.03	1.10
250:1	1.14	1.02	1.07	1.04	1.06	1.16
100:1	1.67	1.11	1.20	1.16	1.24	1.34

In Figure S1, linewidth changes (ratio of broadened linewidth relative to original free ASA linewidth) for individual protons were plotted against the ASA/host ratio. It is clear that the acetyl methyl of the ASA is the closest to the shielding zone of the superbowl cavity.

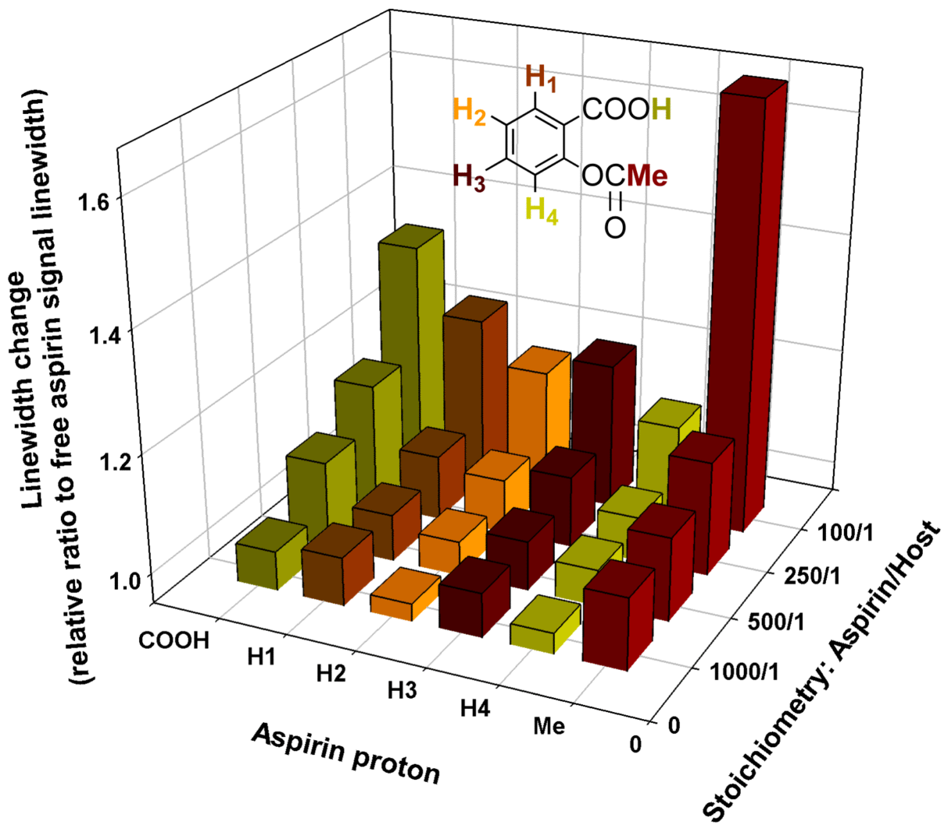


Figure S1. Line-broadening NMR studies of ASA/tetraprotio-superbowl **6** host mixture (500 MHz, $CDCl_3$, 25 °C)

Among the aromatic protons, the line-broadening levels decrease in the order: H1 ~ H3 > H2 ~ H4. This order is consistent with the two-point binding mode depicted in Figure S2.

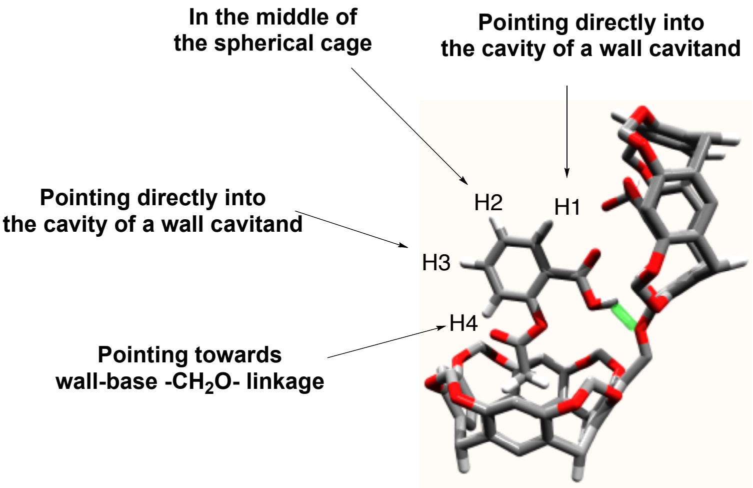


Figure S2. A two-point binding mode can rationalize the observed line-broadening effects of the superbowl upon ASA ^{1}H NMR signals.

General Methods for Host-Guest Binding Studies

For ^{1}H NMR studies, a 1:1 mixture of the host (superbowl, 1 mM) and the guest (ASA, 1 mM) in $CDCl_3$ solution was prepared for each superbowl host. The spectrum of the mixture was then recorded and compared with the spectra of the free superbowl host and the free ASA/guest in the same solvent. Evidence of binding would be either the appearance of bound guest signals upfield from the free guest chemical shifts and/or splitting of the signals of unbound guest/host and the bound guest+host complex.

ITC binding studies were carried out using a MicroCal VP-ITC Isothermal Titration Calorimeter. All binding studies were carried out in chloroform (AR grade, degassed) solvent with the initial host concentrations varying from 0.5 to 2 mM and the initial guest concentration at 50 mM. The host solution was placed in the cell and the guest solution was injected by syringe. Baselines were corrected with titration of a solution of the guest into (blank) $CHCl_3$. Evidence for binding would be in the form of exothermic signals during injections of guest solution into host solution.

The rate of enthalpy change δH (μcal/sec) was monitored and plotted against time (sec or min). From that, the relationship between enthalpy change ΔH and molar ratio of the guest to the host can be deduced and plotted. Based on these two plots, the association constant K, binding stoichiometry N, enthalpy change ΔH and entropy change ΔS can be derived. Data were automatically processed by One Set of Sites model of Origin 7.0 software with manual integration adjustment if necessary, in the case of thermal overcompensating.

All experiments were performed in duplicate.

The ITC titration set-up was used throughout as:

Cell volume = 1.4365 mL;
Syringe volume = 297 μL;
Cell temperature = 25 °C;
Reference power = 30 μcal/sec;

Stirring speed = 300 rpm;

Initial delay = 300 sec;

Total number of injections = 42;

1^{st} injection = 1 μL during 2.5 sec with spacing from the next injection = 240 sec;

Each of 2^{nd} – 42^{nd} injections = 7 μL during 14 sec with spacing from the next injection = 180 sec.

ITC data output (rounding up to significant figures):

N = binding stoichiometry [Guest:Host] (binding ratio);

K = association constant (M^{-1});

ΔH = enthalpy change (cal mol^{-1});

ΔS = entropy change (cal $mol^{-1}K^{-1}$).

ITC experiments with compounds **1**, **2** and **8** were conducted according to the general procedure on page S21. No exotherm or endotherm greater than 0.3 μcal/sec was observed on mixing solutions of superbowl and aspirin, indicating no observable binding. Likewise, ^{1}H NMR experiments were conducted according to the general procedure. Upon mixing solutions of aspirin and superbowl, no chemical shift changes greater than 0.05 ppm were observed, indicating no observable binding.

ITC Profiles of Binding between Superbowl Hosts and ASA

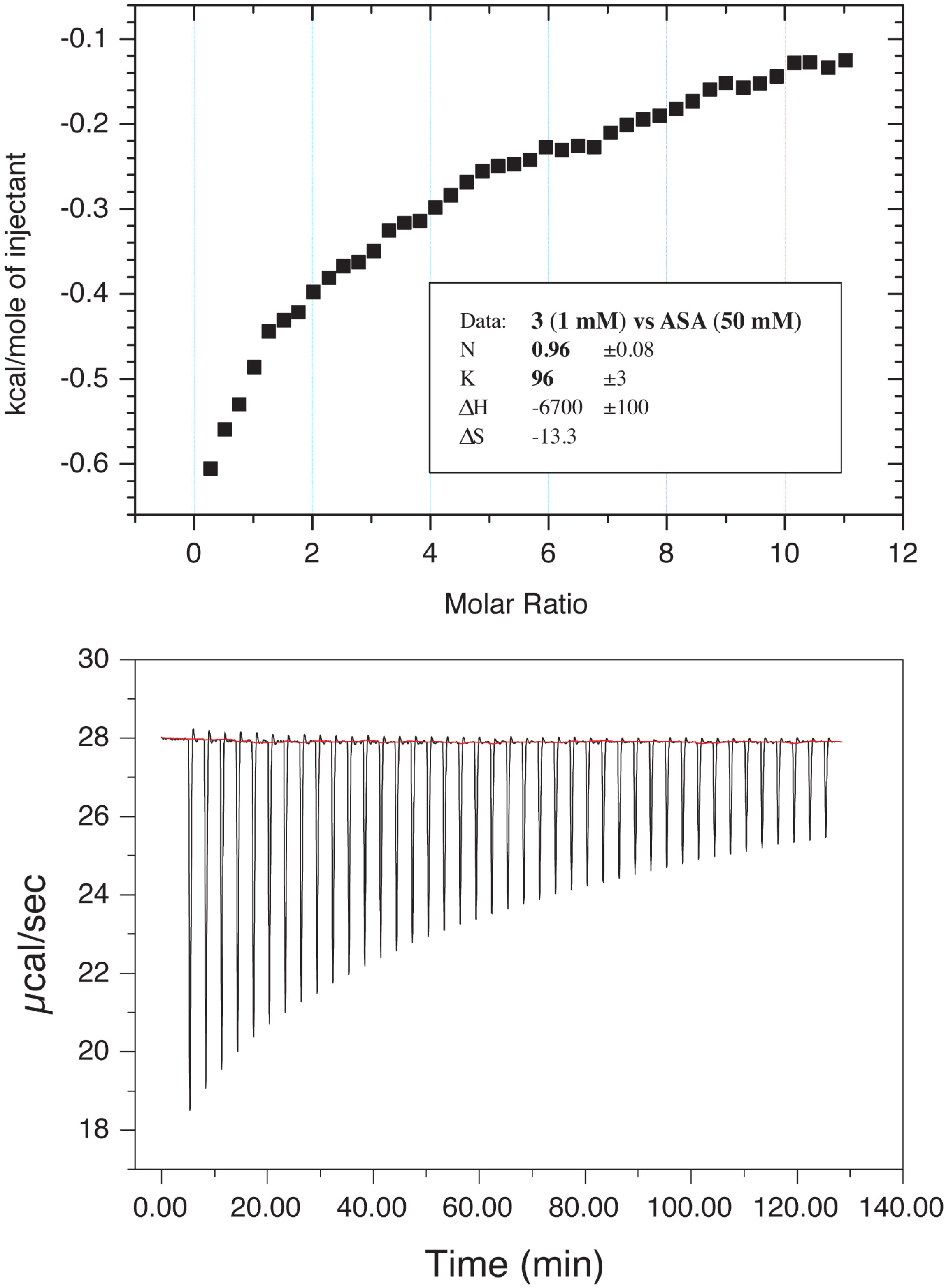


Figure S3. Binding study between *distal*-dibromo-diprotio-superbowl (**3**) and ASA (ITC, chloroform, 25 °C).

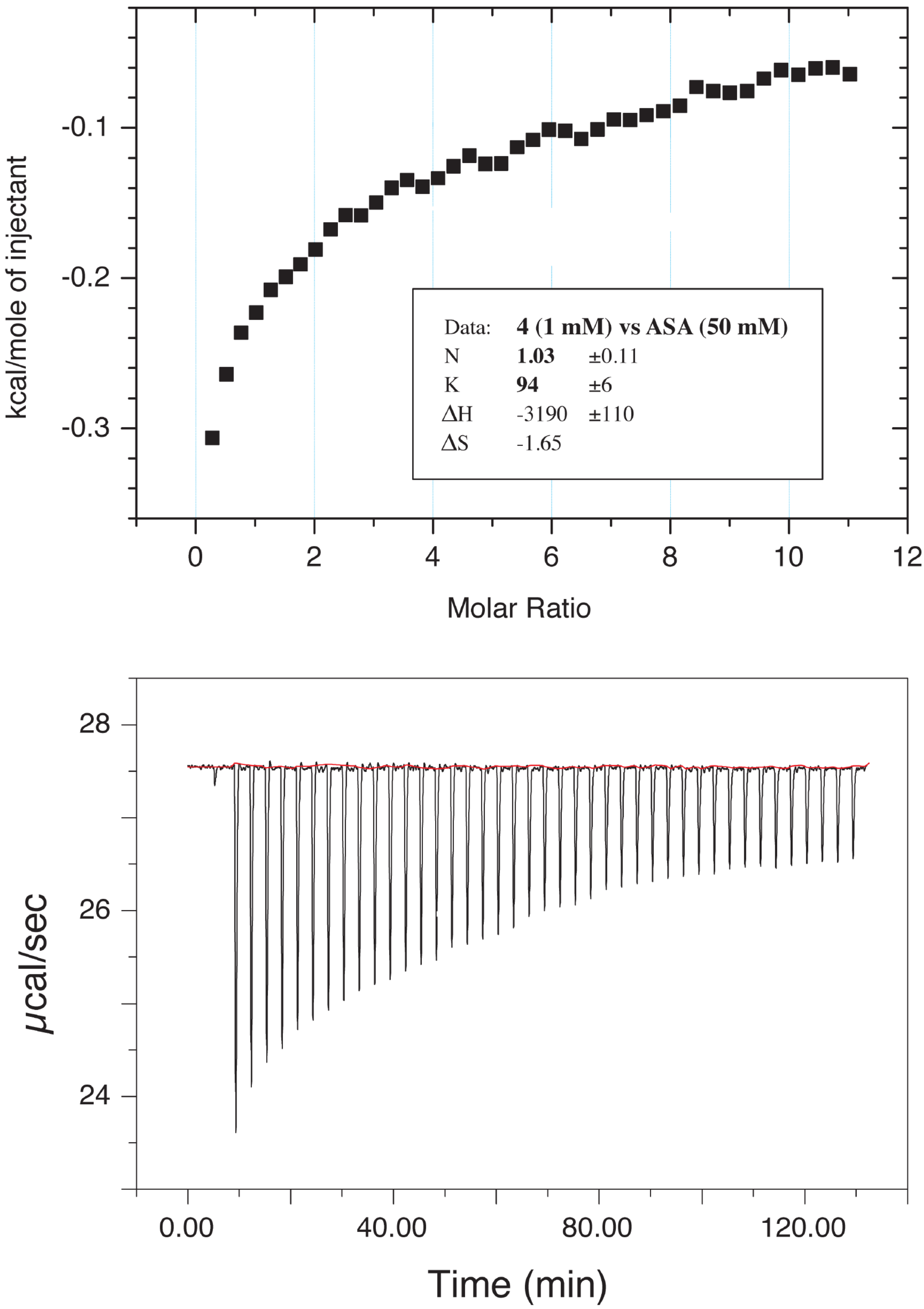
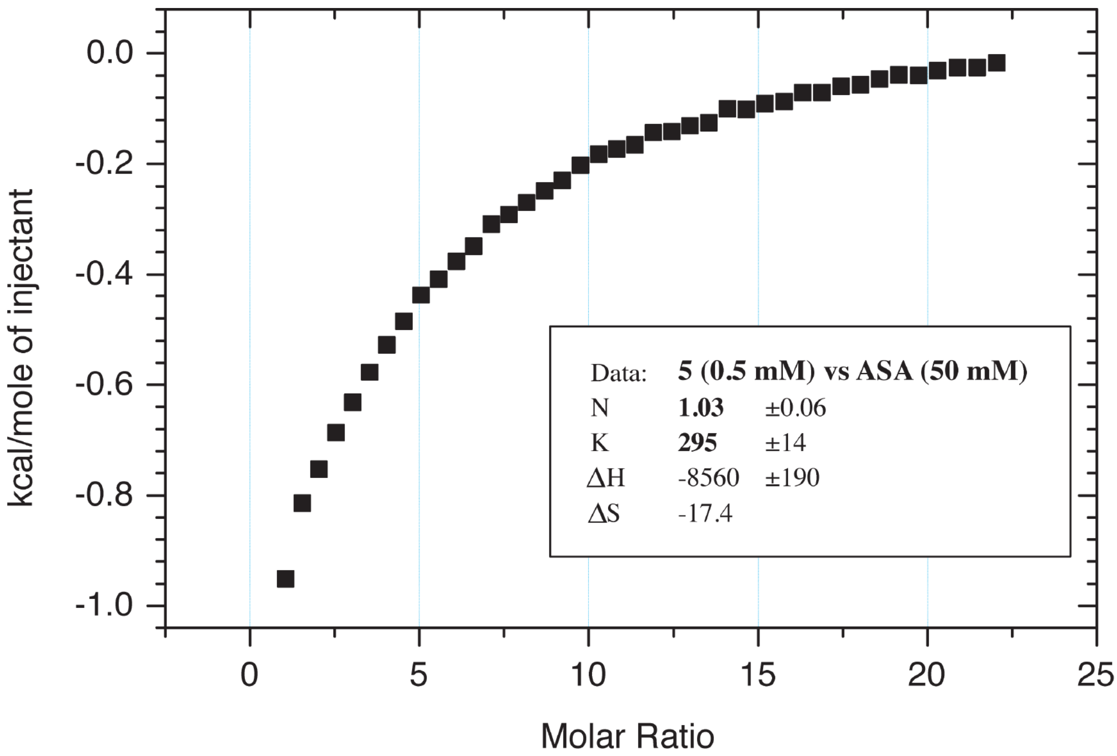


Figure S4. Binding study between *proximal*-dibromo-diprotio-superbowl (**4**) and ASA (ITC, chloroform, 25 °C).



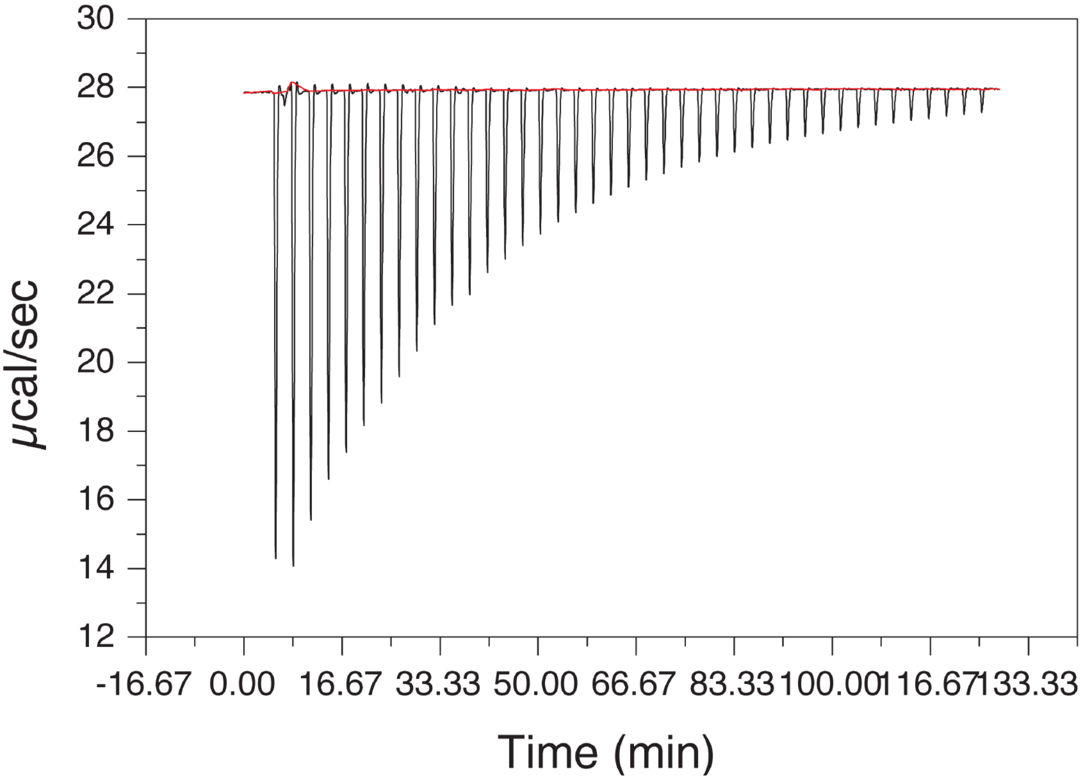


Figure S5. Binding study between monobromo-triprotio-superbowl (**5**) and ASA (ITC, chloroform, 25 °C).

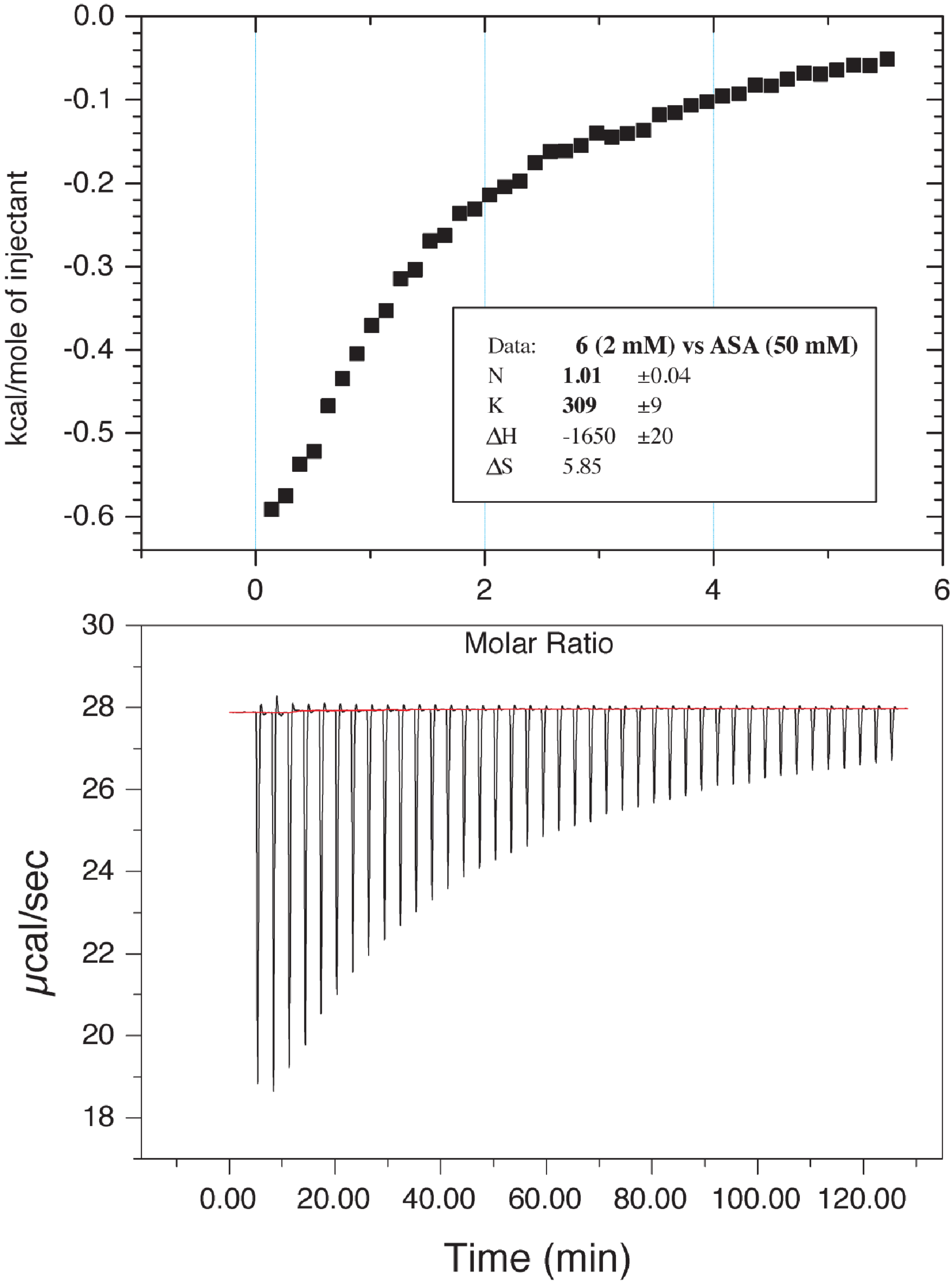


Figure S6. Binding study between tetraprotio-superbowl (**6**) and ASA (ITC, chloroform, 25 °C).

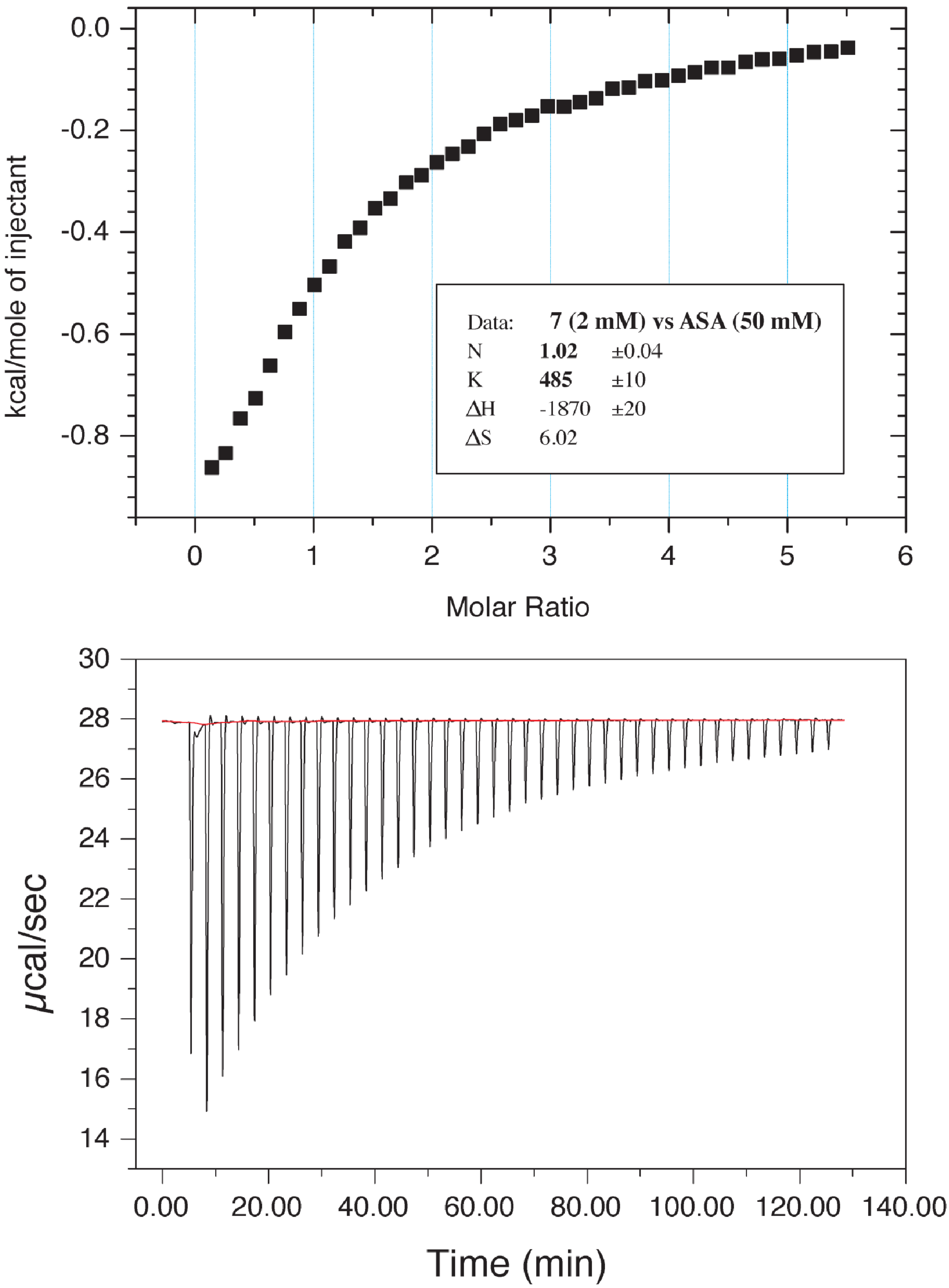


Figure S7. Binding study between tetramethyl-superbowl (**7**) and ASA (ITC, chloroform, 25 °C).

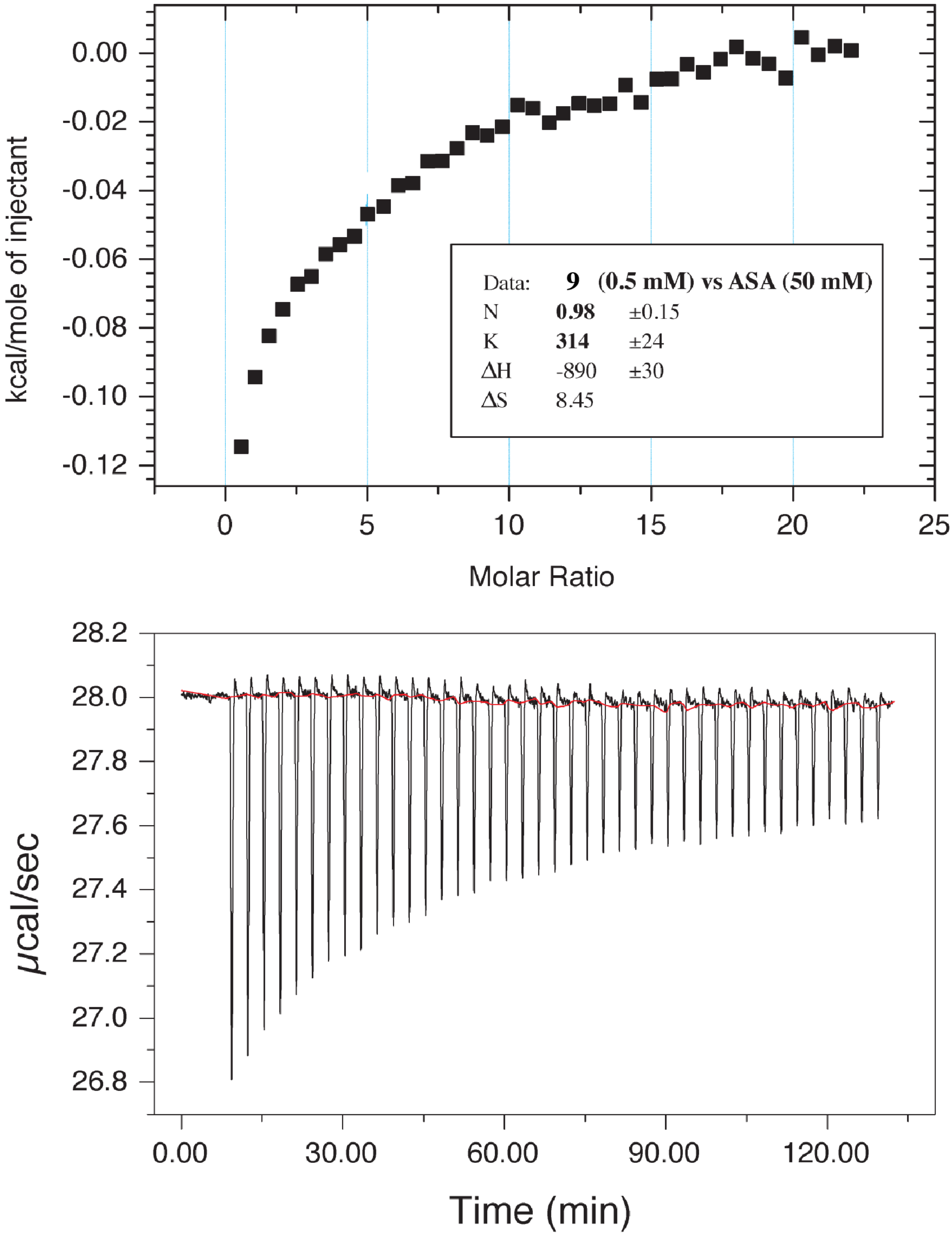


Figure S8. Binding study between *para*-xylyloxy-bridged superbowl (**9**) and ASA (ITC, chloroform, 25 °C).

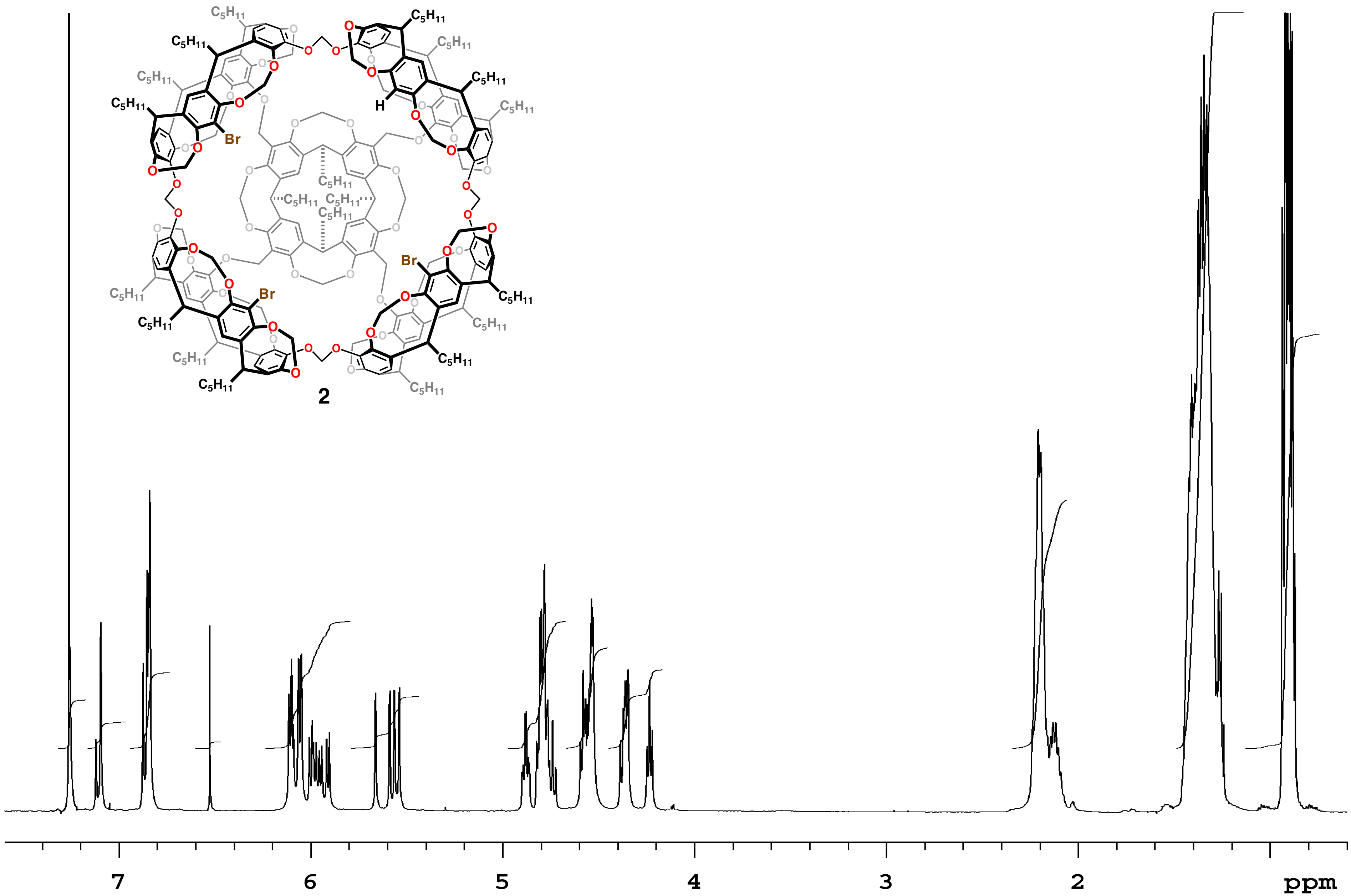
References

(1) E. S. Barrett, J. L. Irwin, A. J. Edwards and M. S. Sherburn, *J. Am. Chem. Soc.*, 2004, **126**, 16747–16749.

(2) Sodium hydride was used for drying purposes.

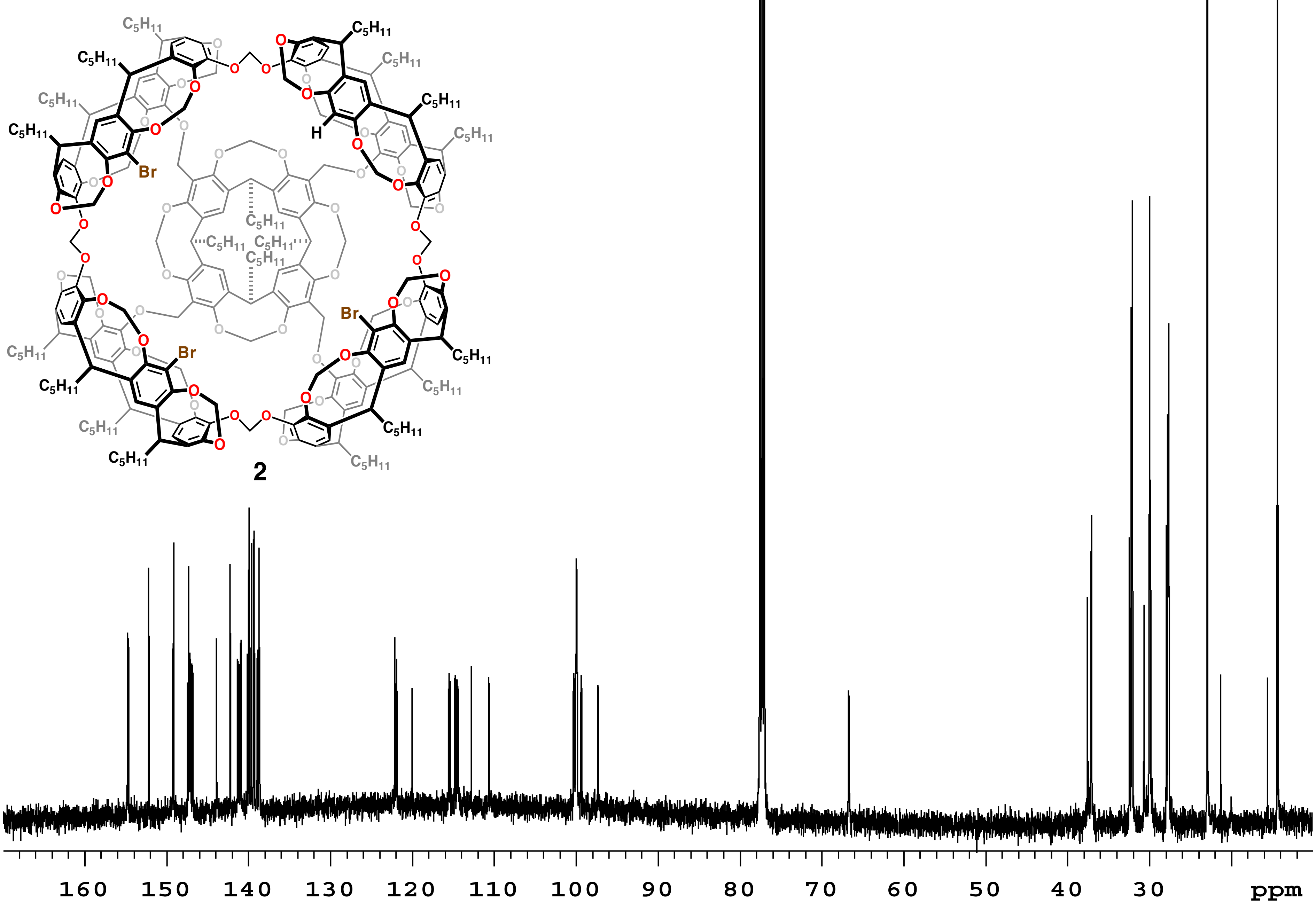
(3) (*a*) P. Balaram, A. A. Bothner-By and J. Dadok, *J. Am. Chem. Soc.*, 1972, **94**, 4015–4017. (*b*) P. Balaram, A. A. Bothner-By and E. Breslow, *J. Am. Chem. Soc.*, 1972, **94**, 4017–4018.

1H-NMR: 500 MHz, $CDCl_3$, 25 °C

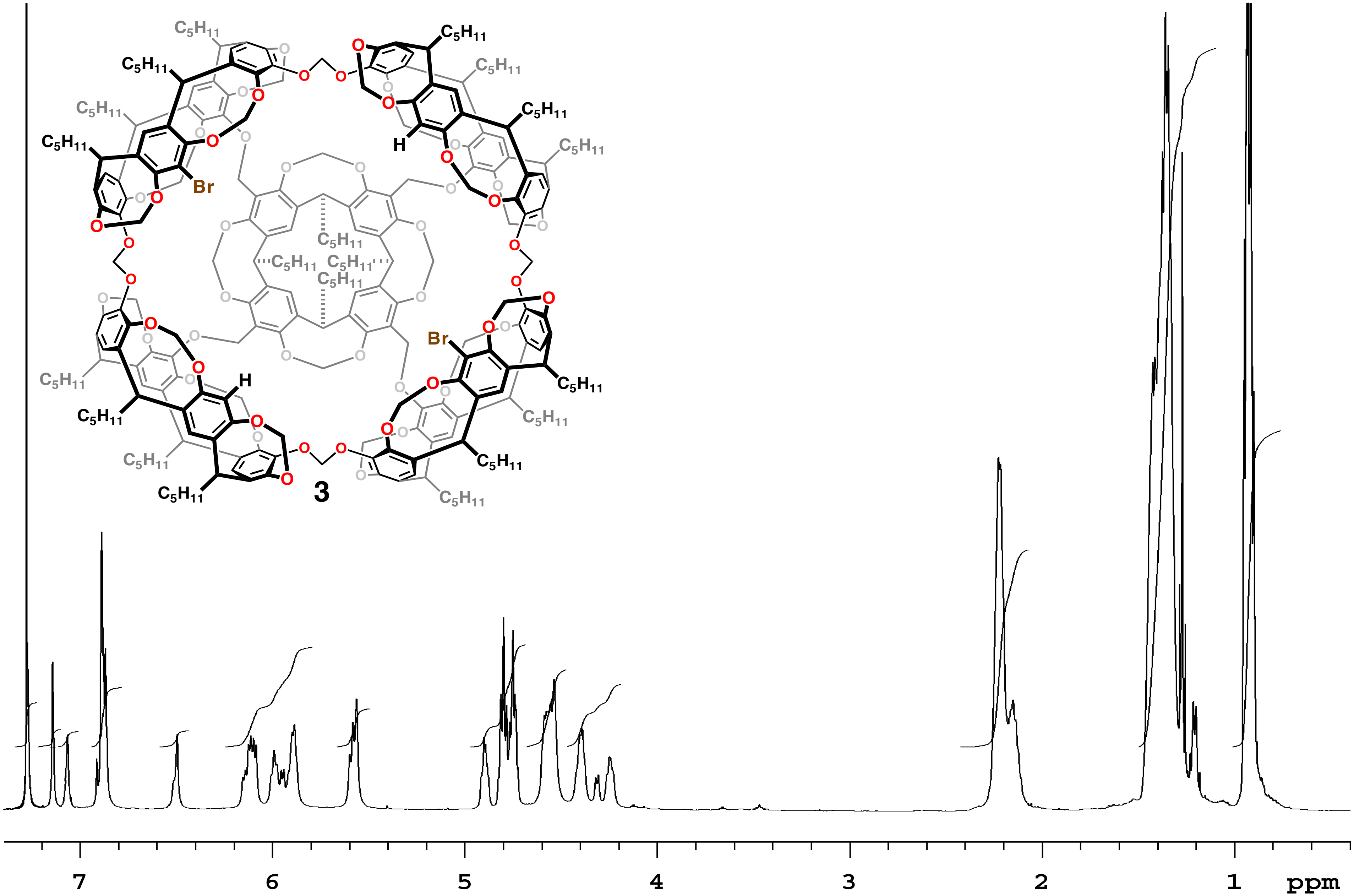


Supplementary Material (ESI) for Chemical Communications

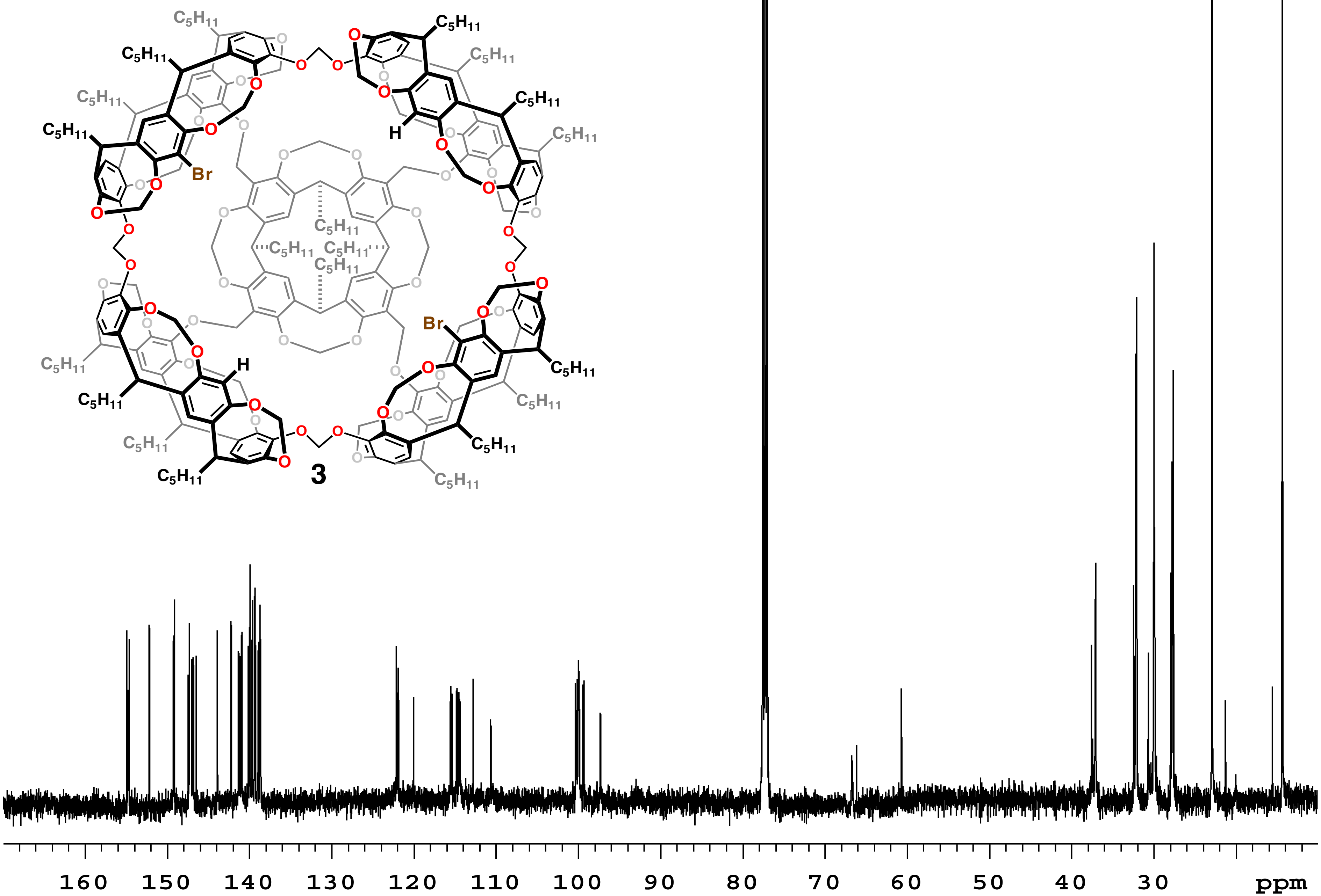
13C-NMR: 125 MHz, $CDCl_3$, 25 °C

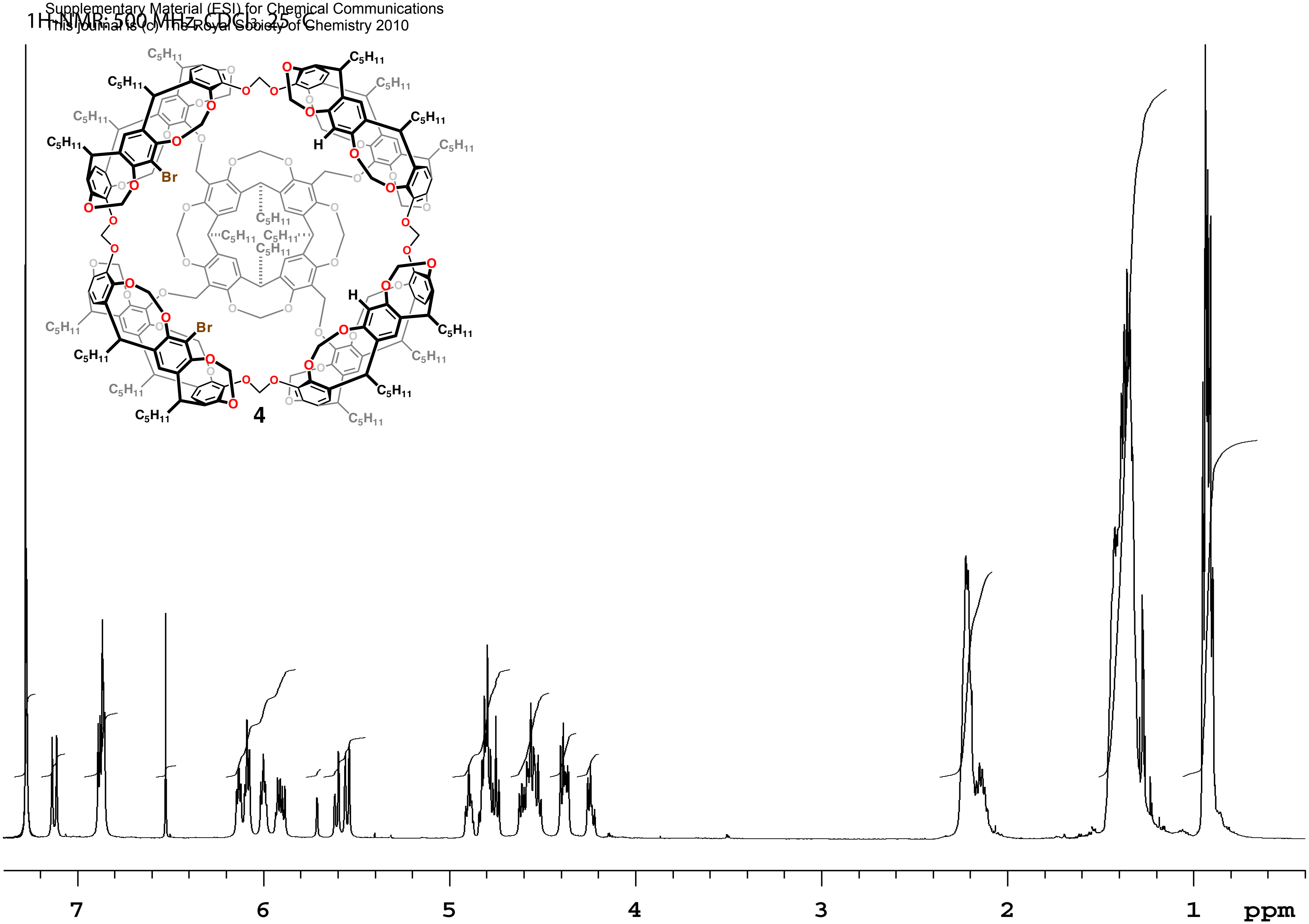


1H-NMR: 500 MHz, $CDCl_3$, 25 °C

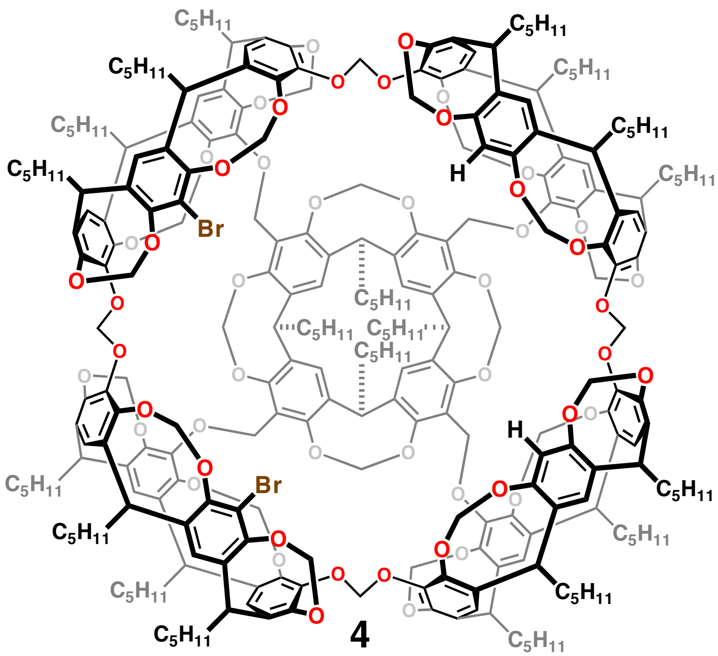


13C-NMR: 125 MHz $CDCl_3$, 25 °C

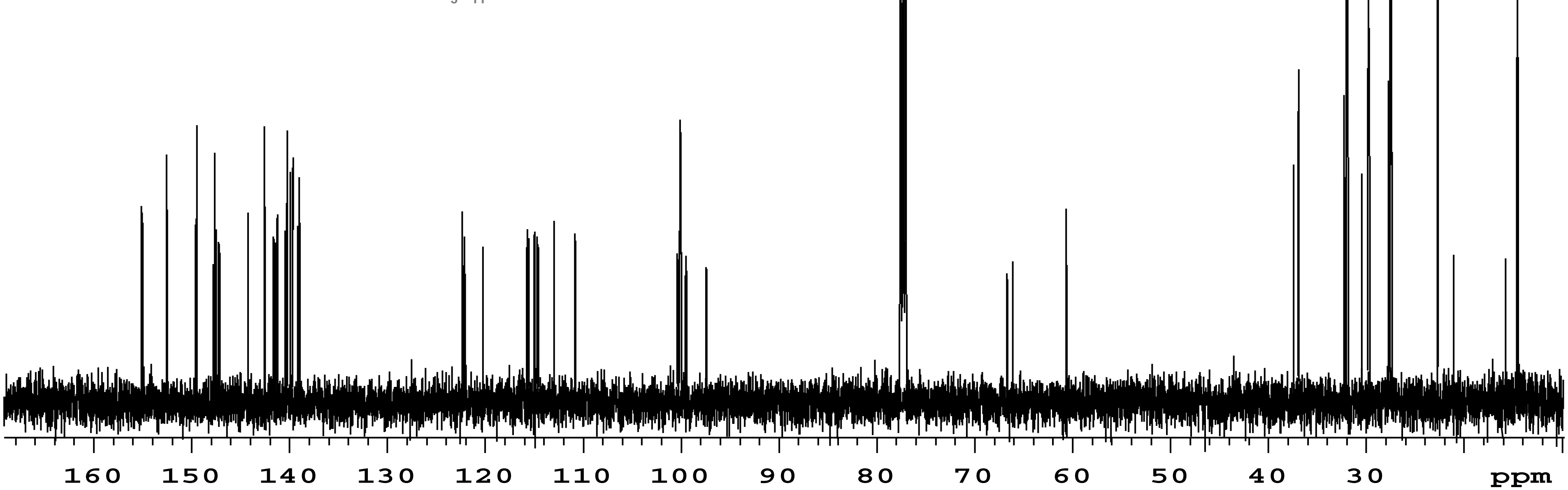



1H-NMR: 500 MHz, CDCl3, 25 °C
4
Br
Br
H
H
7
6
5
4
3
2
1
ppm

13C-NMR: 125 MHz, $CDCl_3$, 25 °C

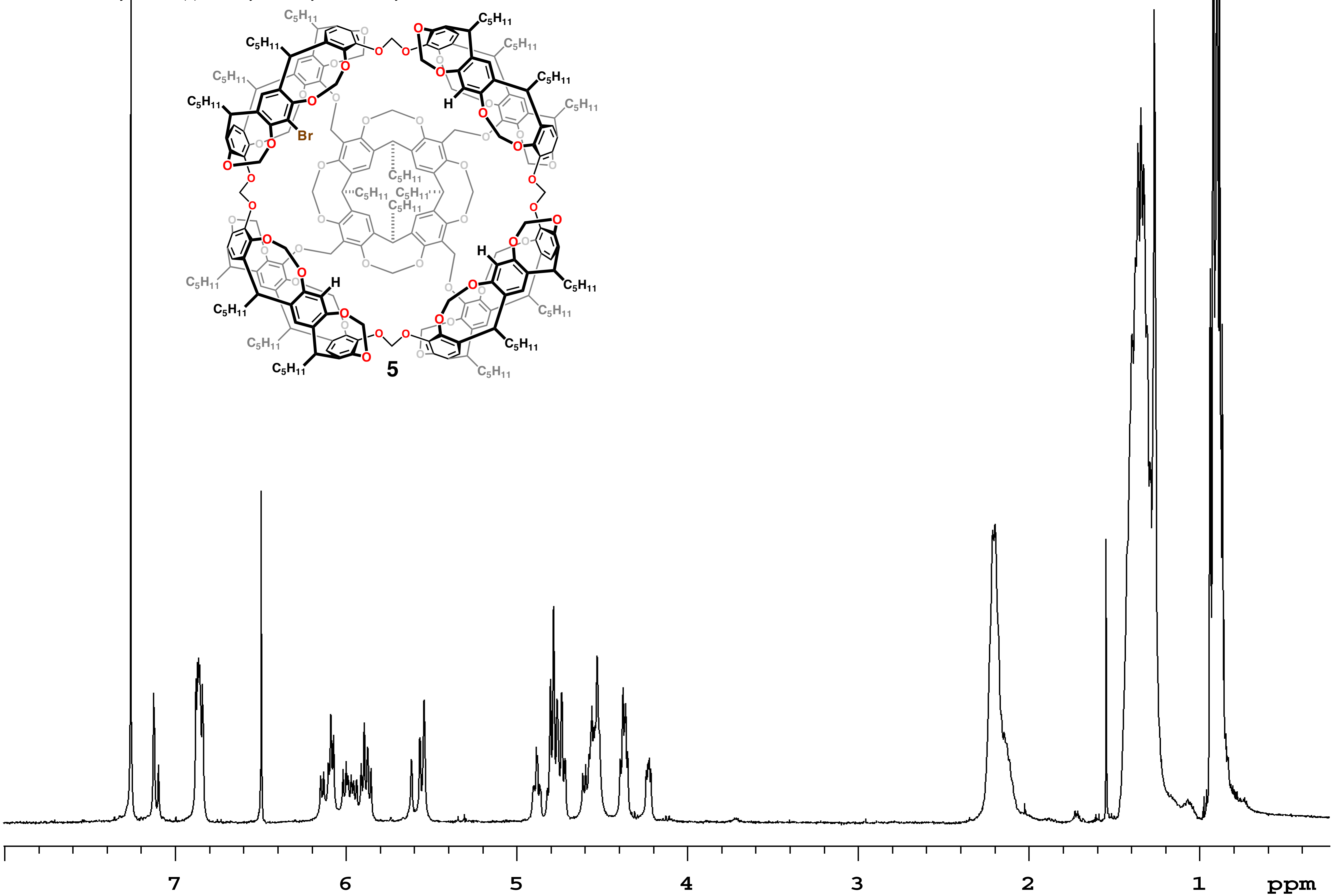


4

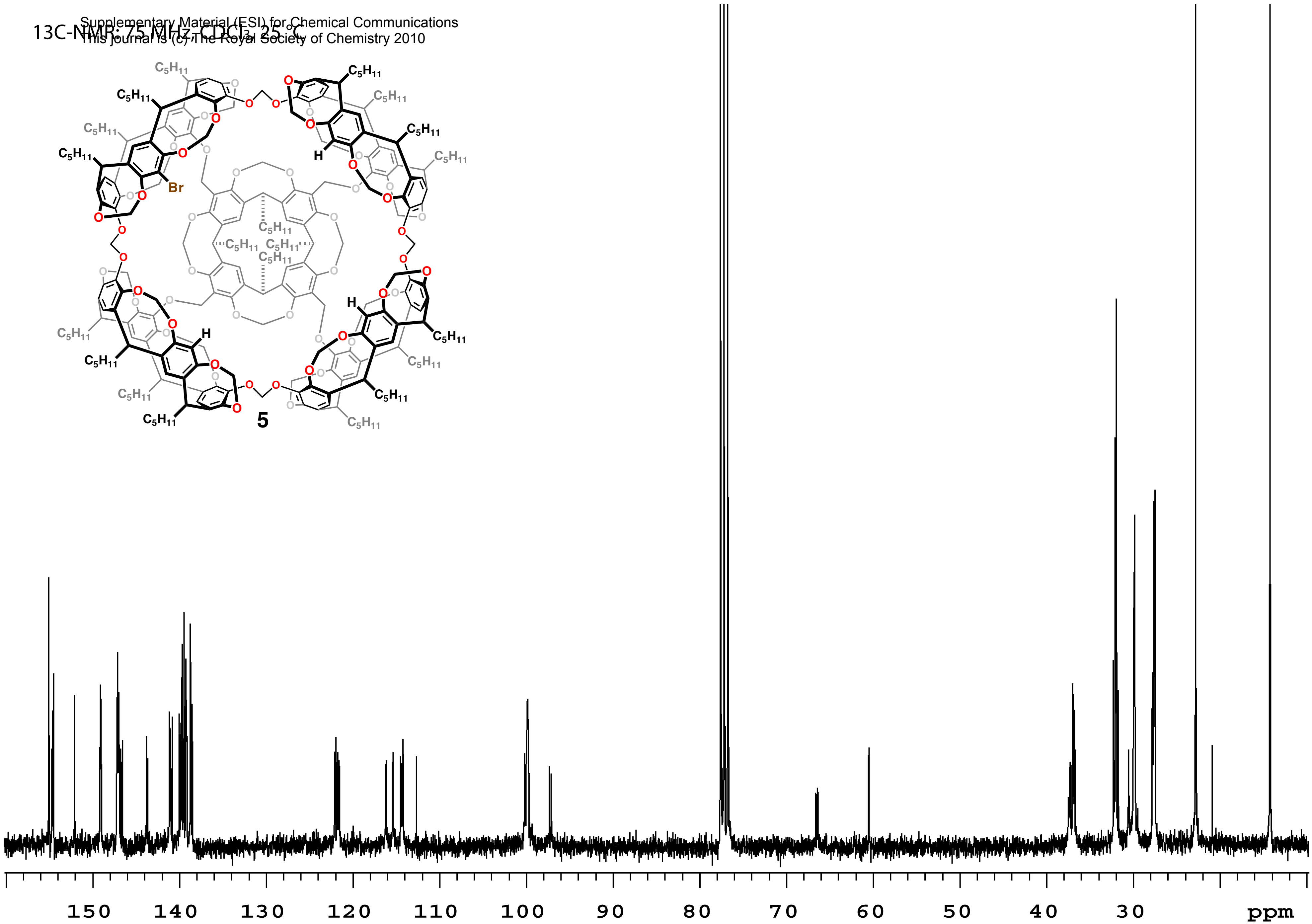


Supplementary Material (ESI) for Chemical Communications

^{1}H-NMR: 300 MHz, $CDCl_3$, 25 °C

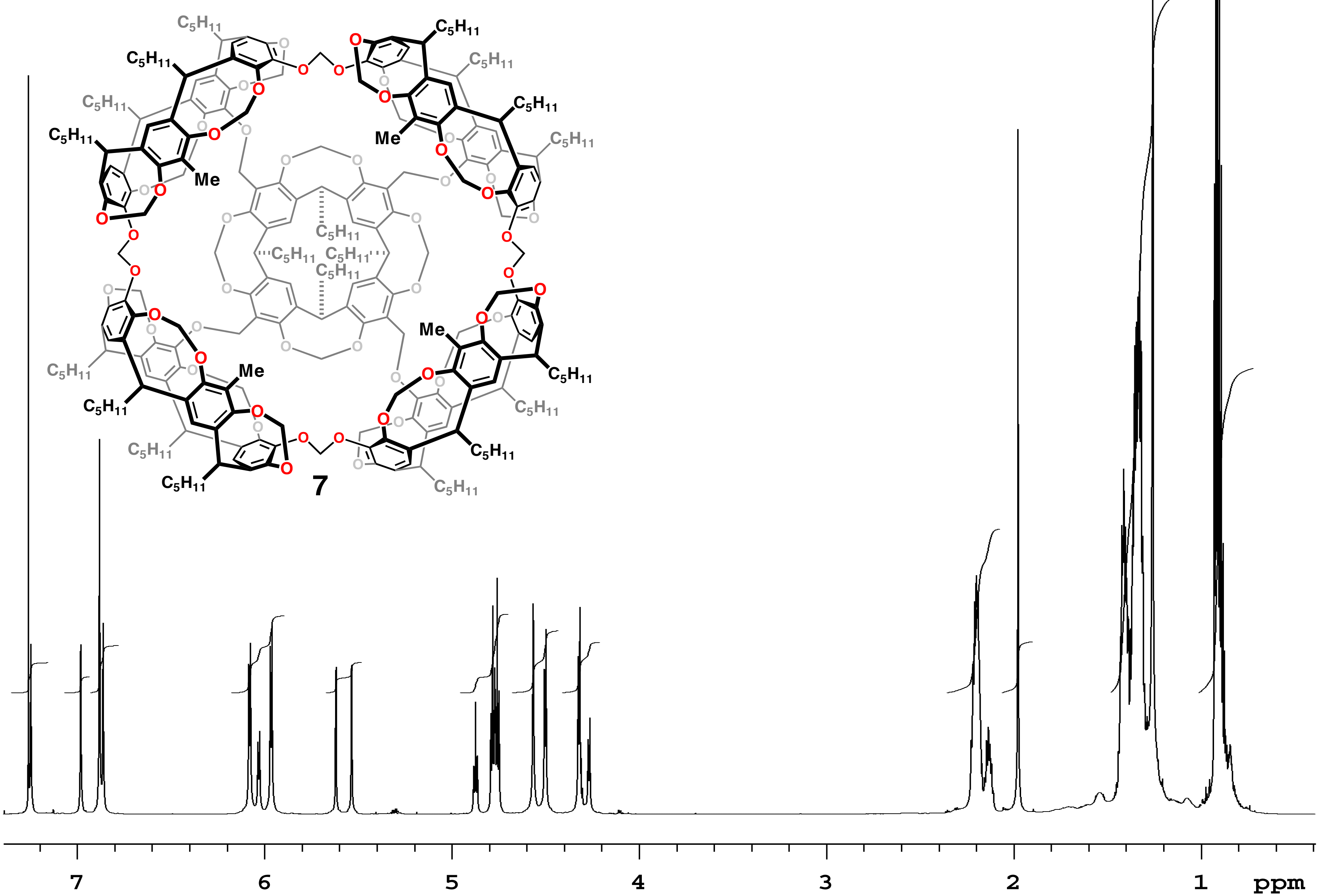


13C-NMR: 75 MHz, $CDCl_3$, 25 °C

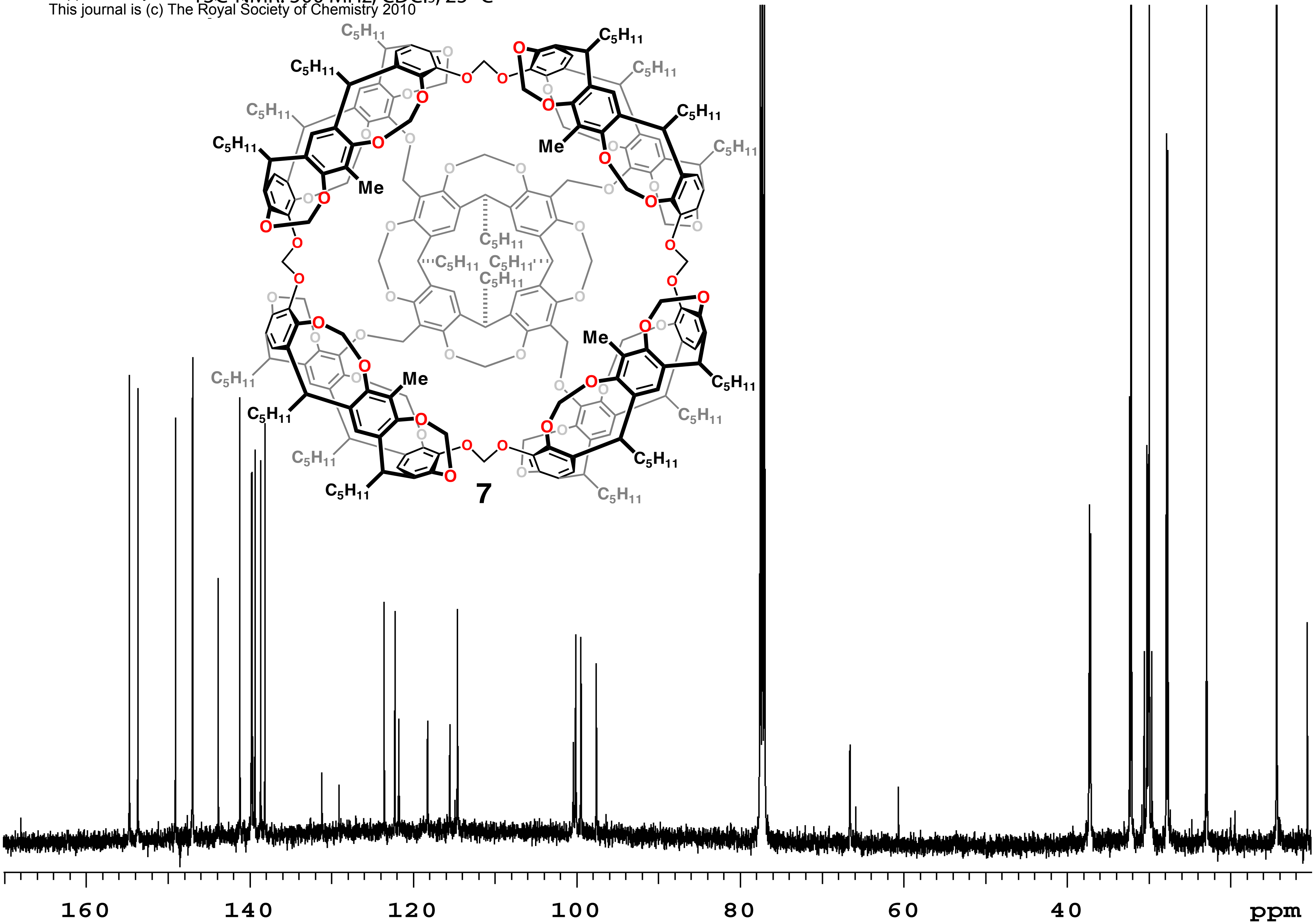


Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2010

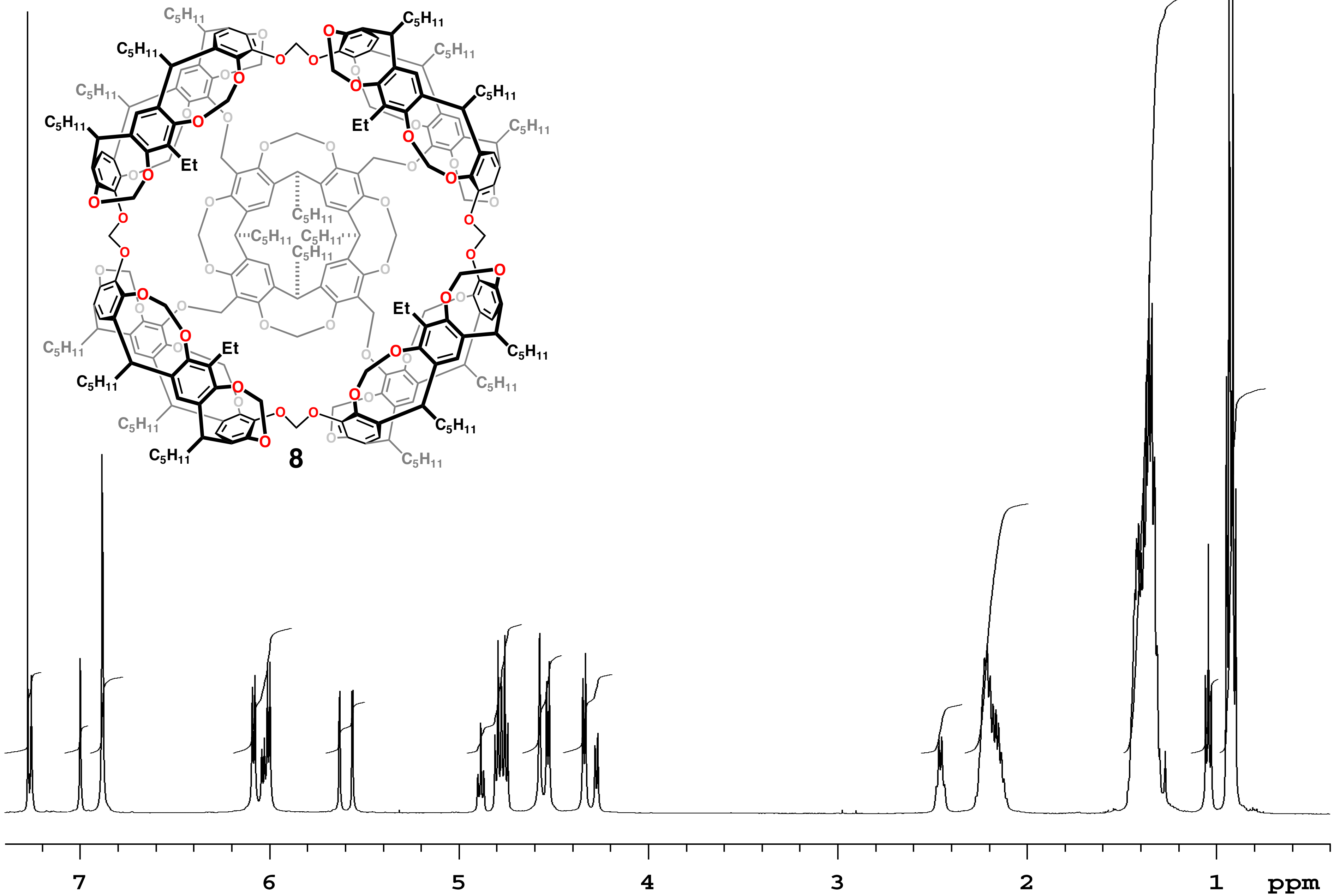
1H-NMR: 800 MHz, CDCl3, 25 °C



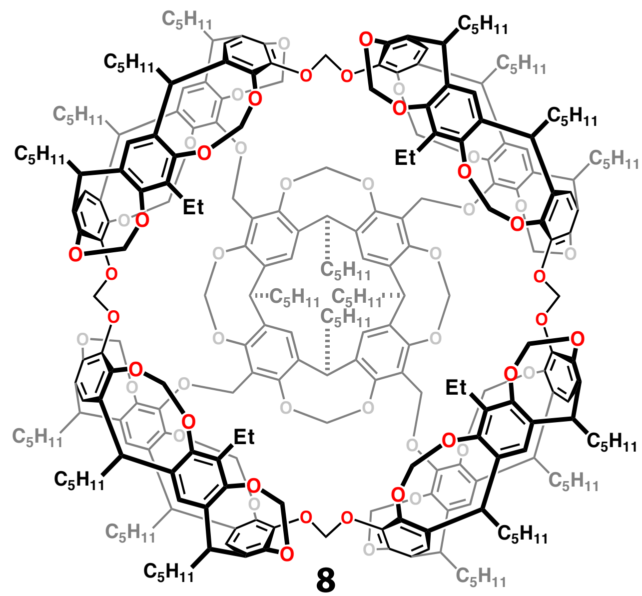
^{13}C NMR: 500 MHz, $CDCl_3$, 25 °C



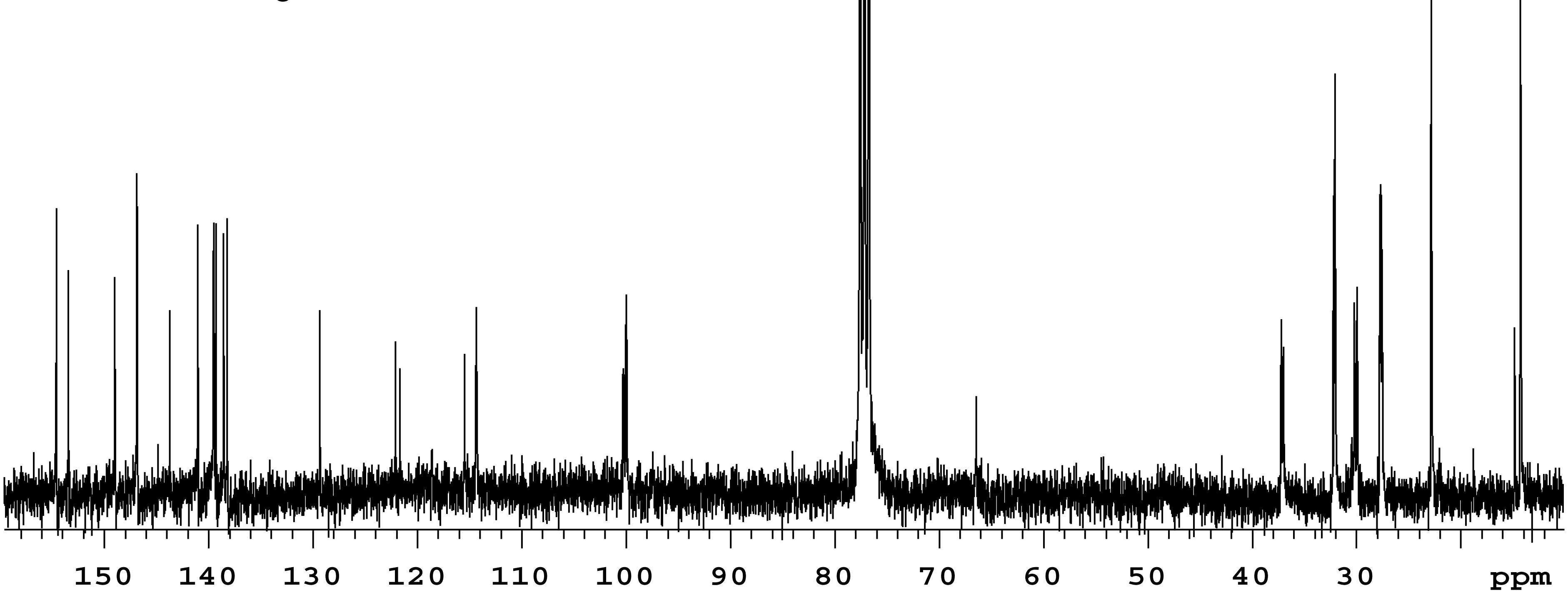
1H-NMR: 500 MHz, $CDCl_3$, 25 °C



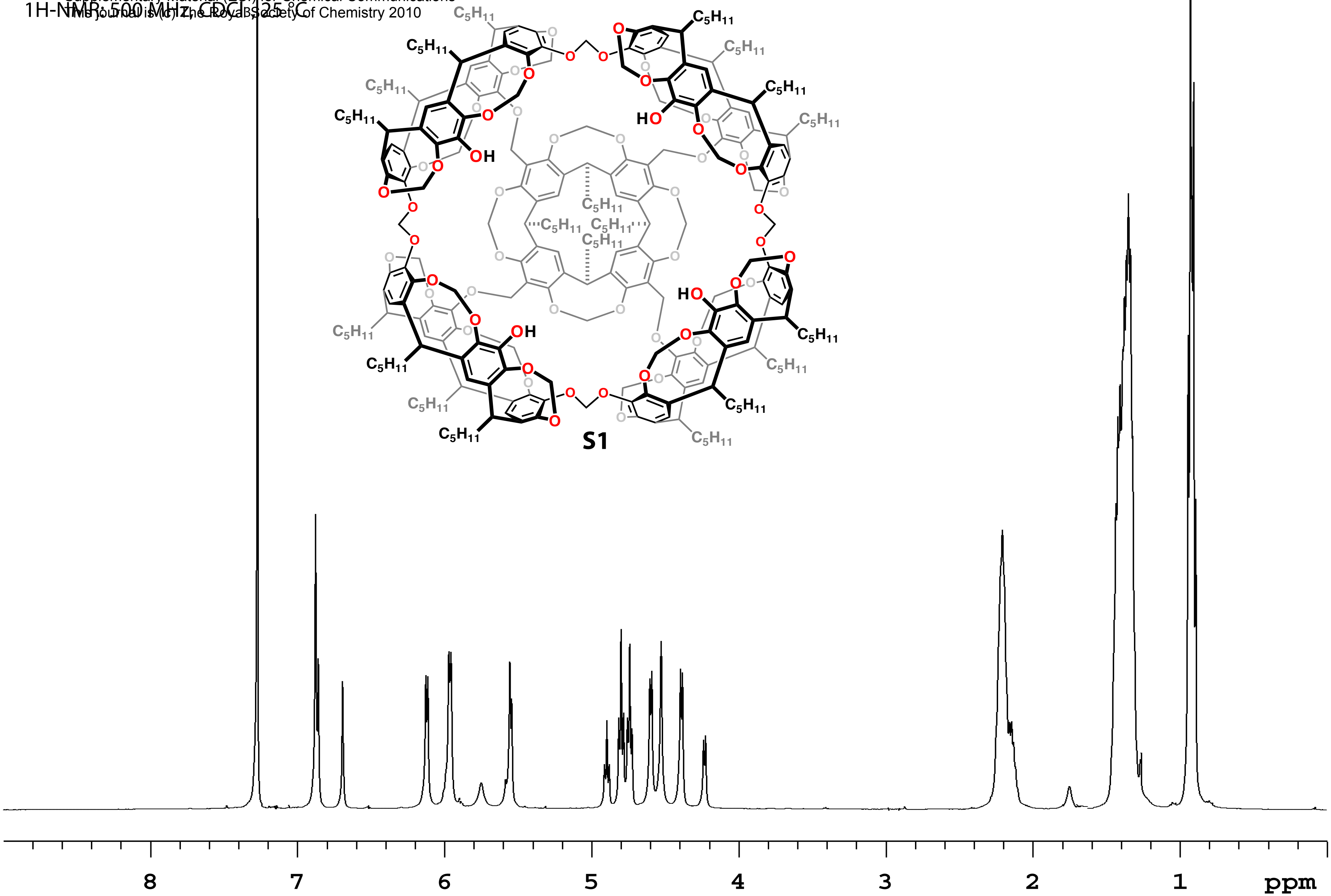
13C-NMR: 125 MHz, CDCl$_3$, 25 °C



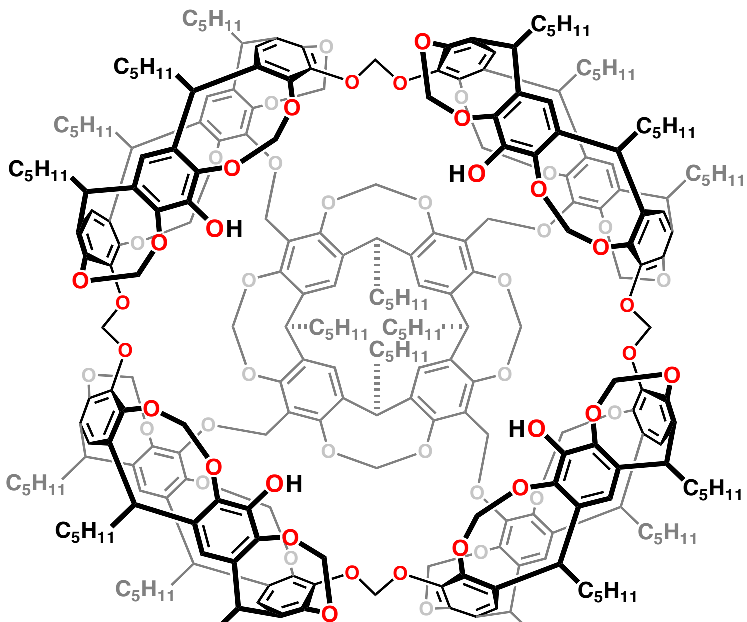
8



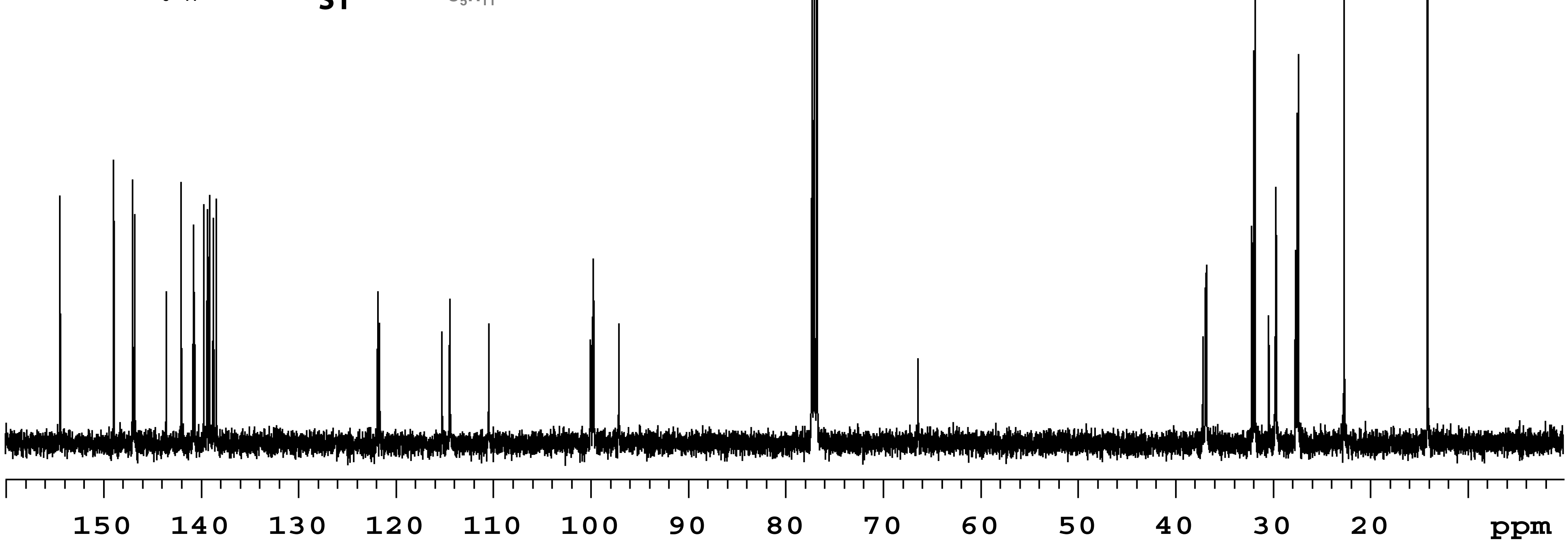
1H-NMR: 500 MHz, $CDCl_3$, 25 °C



13C-NMR: 125 MHz, CDCl3, 25 °C

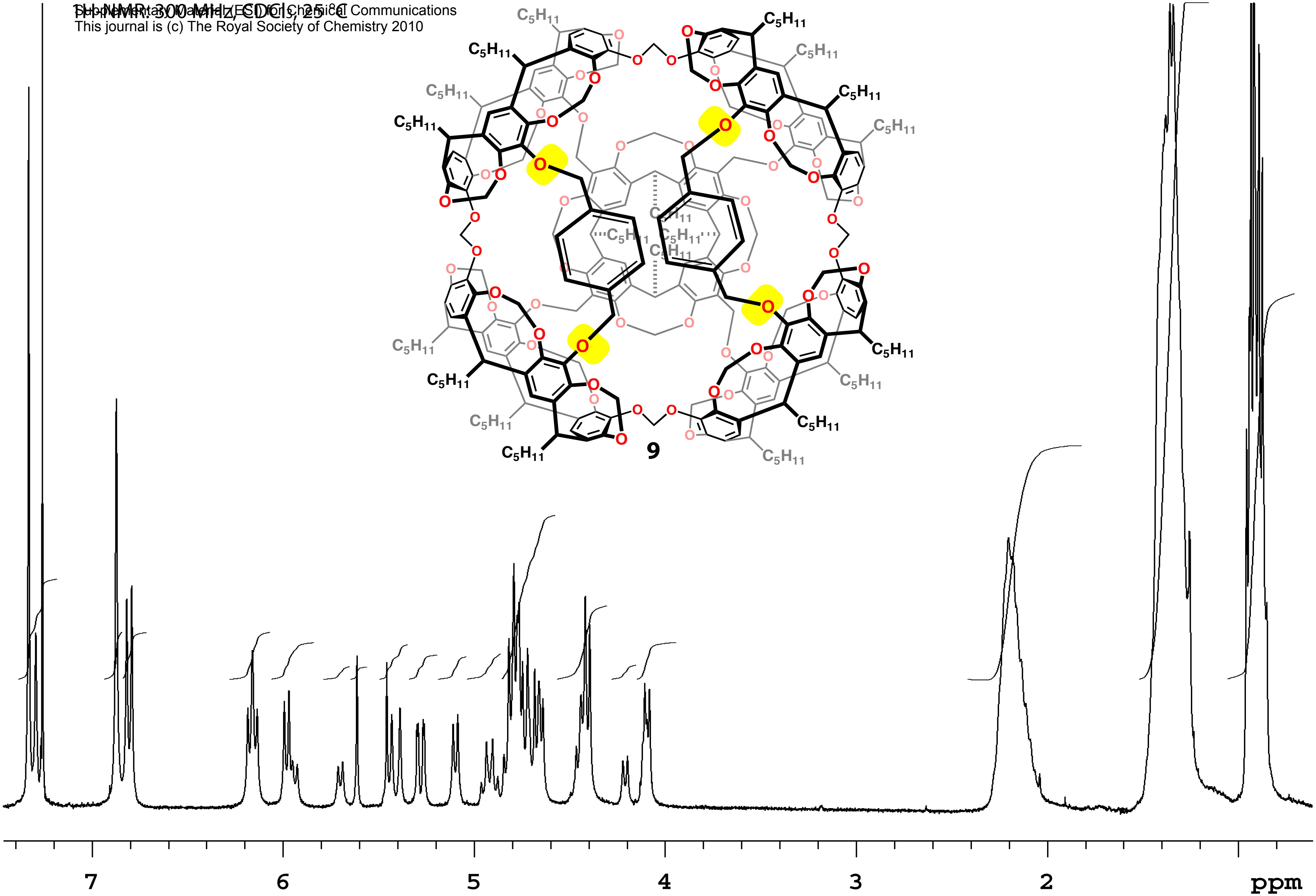


S1



Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2010

^{1}H-NMR: 300 MHz, $CDCl_3$, 25 °C



13C-NMR: 75 MHz, $CDCl_3$, 25 °C