Supporting information for: Monofunctionalised Cucurbit[6]uril Synthesis using Imidazolium Host-Guest Complexation

Nan Zhao,[†] Gareth O. Lloyd,[‡] and Oren A. Scherman[*,†]

Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom, and Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom

E-mail: oas23@cam.ac.uk

General Information:

All chemicals were used as reagent grade or higher and used without further purification unless otherwise stated. Ammonium hexafluorophosphate was purchased from Alfa Aesar. Hydrochloric acid (37%), toluene, dichloromethane, methanol and diethyl ether were obtained from Fisher Scientific. 1-Ethylimidazole (99%), 1-butylimidazole, 1,10-dibromodecane, 1,8-dibromooctane, allyl bromide, propargyl bromide 80% (w/w) toluene and spermine were purchased from Aldrich Chemicals. Ultra pure $(NH_4)_2S_2O_8$ was obtained from Bioproducts Ltd. NaOH was purchased from Breckland Scientific Supplies. MCI GEL CHP 20P resin was provided by Supelco.

^{1}H NMR, ^{13}C NMR, HMQC and HMBC spectra were recorded on a Bruker DRX-400 or DRX-500. Milli-Q water was produced by Synergy Ultrapure Water Systems. Mass Spectra were recorded on Thermos LTQ Velos.

[*]To whom correspondence should be addressed
[†]Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom
[‡]Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom

Synthesis:

3,3'-(Octane-1,8-diyl)bis(1-ethyl-imidazolium) bromide (1): 1-Ethylimidazole (5.5 mL, 50 mmol) and 1,8-dibromooctane (5.4 g, 20 mmol) were dissolved in toluene (50 mL) and refluxed for 12 hours. The solvent was decanted from the insoluble crude mixture, which was then triturated with diethyl ether (3×50 mL) and dried via vacuum to obtain the title compound **1** as a white solid (7.9 g, 85%). δ_H (400 MHz, D_2O) 8.72 (2H, s), 7.45 (2H, s), 7.43 (2H, s), 4.18 (4H, q, J = 7.4 Hz), 4.14 (4H, t, J = 6.9 Hz), 1.82 (4H, m, J = 6.8 Hz), 1.45 (6H, t, J = 7.0 Hz), 1.26 (8H, m); δ_C (100 MHz, D_2O) 134.64, 122.14, 121.85, 49.42, 44.69, 29.00, 27.71, 25.11, 14.35; HR-MS for $C_{18}H_{32}N_4Br^+$: calcd. *m/z* 383.1810, found *m/z* 383.1799; elemental analysis (%) calcd. for $C_{18}H_{32}N_4Br_2$: C, 46.56; H, 6.95; N, 12.07; Br, 34.42; found C, 46.13; H, 6.94; N, 11.81; Br,34.40.

3-(10-Bromodecyl)-1-butyl-1H-imidazol-3-ium bromide (3): 1-Butylimidazole (1.2 g, 10 mmol) and 1,10-dibromodecane (12 g, 40 mmol) were dissolved in 60 mL DCM and refluxed for 12 hours. The solvent was removed under vacuum and the residue was triturated with hexane (3× 30 mL), which was then purified by flash column chromatography (SiO_2) (CH_2Cl_2/MeOH = 19/1) to obtain the title compound as a yellowish liquid (1.65 g, 39%). δ_H (400 MHz, D_2O) 8.93 (1H, s), 7.55 (1H, s), 7.53 (1H, s), 4.22 (4H, t, J = 6.9 Hz), 3.39 (2H, t, J = 6.7 Hz), 1.74-1.85 (6H, m), 1.20-1.33 (14H, m), 0.87 (3H, t, J = 7.8 Hz); δ_C (100 MHz, D_2O) 135.30, 122.55, 122.34, 49.47, 49.27, 34.46, 32.60, 31.48, 29.61, 29.08, 28.67, 28.49, 27.88, 25.72, 18.83, 12.95; HR-MS for $C_{17}H_{32}N_2Br^+$: calcd. *m/z* 343.1749, found *m/z* 343.1771; elemental analysis (%) calcd. for $C_{17}H_{32}N_2Br_2$: C, 48.13; H, 7.60; N, 6.60; Br, 37.67; found C, 48.29; H, 7.76; N, 6.71; Br,37.62.

3-(10-Azidodecyl)-1-butyl-1H-imidazol-3-ium bromide (4): NaN_3 (0.2 g, 2.5 mmol) and compound **3** (0.4 g, 1 mmol) were dissolved in 10 mL deionised water and stirred for 12 hours at 60 °C. The solvent was then removed under vacuum and the residue was diluted with 30 mL of DCM. The mixture was then filtered and the remaining solid was washed with DCM (3×30 mL). The organic phase was combined and concentrated to give the title compound **4** as a yellow liquid (0.3 g, 84%). δ_H (400 MHz, D_2O) 8.72 (1H, s), 7.44 (2H, s), 4.14 (4H, t, J = 7.0 Hz), 3.26 (2H, t, J = 6.9 Hz),

1.82 (4H, m), 1.54 (2H, m), 1.22 (14H, m), 0.87 (3H, t, J = 7.4 Hz); δ_C (100 MHz, D_2O) 134.64, 122.35, 122.20, 51.09, 49.43, 49.20, 31.26, 29.20, 28.64, 28.45, 28.20, 26.12, 25.37; HR-MS for $C_{17}H_{32}N_5^+$: calcd. *m/z* 306.2658, found *m/z* 306.2649;

CB[6] functionalisation: Cucurbit[6]uril (500 mg, 0.5 mmol) and compound **1** (231 mg, 0.5 mmol) were dissolved in 50 mL Milli-Q water at 85 °C. $(NH_4)_2S_2O_8$ (114 mg, 0.5 mmol) was then added and the reaction was stirred at 85 °C for 12 hours. The reaction mixture was reduced to 3 mL under vacuum when $\mathbf{1}^{2+}\subset f$CB[6] complex just start to crystallise. The sample was ready for resin column separation.

Allyl-O-CB[6] (2a): To a solution of **1**⊂MonOH (20 mg) in anhydrous DMSO (1.5 mL), NaH (10 mg, 0.4 mmol) was added and stirred at room temperature for 15 minutes. Allyl bromide (0.5 mL, 5.8 mmol) was added subsequently at 0 °C and the reaction mixture was stirred at room temperature for 12 hours. The reaction was then diluted with 50 mL diethyl ether and filtered. The remaining solid was triturated with MeOH (3× 50mL) and dried under vacuum to give a yellow solid (15 mg, 72%). δ_H (400 MHz, D_2O) 5.98-5.85 (1H, m), 5.76-5.61 (10H, m), 5.55-5.39 (13H, m), 5.35-5.21 (2H, dd), 4.41 (2H, d, J = 15.8 Hz), 4.29-4.16 (10H, m), 3.95 (2H, d,J = 5.7 Hz); δ_C (125 MHz, D_2O) 155.02, 131.91, 118.68, 72.38, 70.19, 64.54, 51.26, 46.37; HRMS for $C_{39}H_{40}N_{24}O_{13}Na^+$: calcd. *m/z* 1075.3104, found *m/z* 1075.3099.

Propargyl-O-CB[6] (2b): To a solution of **1**⊂MonOH (20 mg) in anhydrous DMSO (1.5 mL), NaH (10 mg, 0.4 mmol) was added and stirred at room temperature for 15 minutes. Propargyl bromide (0.5 mL, 4.4 mmol) was added subsequently at 0 °C and the reaction mixture was stirred at room temperature for 12 hours. The reaction was then diluted with 50 mL diethyl ether and filtered. The remaining solid was triturated with MeOH (3×50mL) and dried under vacuum to give a yellow solid (8 mg, 38.5%). δ_H (400 MHz, D_2O) 5.70 - 5.60 (11H, m), 5.49-5.42 (12H, m), 4.43 (2H, d, J = 12.6 Hz), 4.22 (12H, m), 3.22 (1H, s); δ_C (100 MHz, D_2O) 156.38, 155.02, 97.01, 77.41, 77.00, 72.33, 70.17, 52.17, 51.29; HR-MS for $C_{39}H_{38}N_{24}O_{13}Na^+$: *m/z* calcd. 1073.2947,

m/z found 1073.2942.

General Procedure for "3+2" cycloaddition (3b): To a solution of **2b** (8 mg, 7.6 μmol) in milli-Q water (10 mL), compound **4** (5.9 mg, 15.8 μmol), trace amount of Cu_2SO_4 and sodium ascorbate were added respectively. The reaction was then stirred for 24 hours at room temperature and the solvent was removed under vacuum. The residue was triturated with MeOH (3$\times$ 50mL)and dried under vacuum to give **3b** as a light green solid (9 mg, 82.5%). HR-MS for $C_{56}H_{70}N_{29}O_{13}{}^{+}$: calcd. *m/z* 1356.5702, found *m/z* 1356.5701.

X-ray Crystal data for MonOH: MonOH was dissolved in a saturated Na_2SO_4 solution with acetone slowly defusing into the solution to afford a transparent crystal for X-ray Crystal analysis. $[(C_{36}H_{36}N_{24}O_{13})\cdot 2(Na_2SO_4)\cdot 23H_2O]$, M = 1711.34, 0.21 $\times$ 0.14 $\times$ 0.10 mm^3, monoclinic, space group $P2_1/c$ (No.14), a = 12.5406(2), b = 14.3352(3), c = 19.3242(5)Å, β = 102.9830(10)°, V = 3385.14(12) Å^3, Z = 2, D_c = 1.679 g/cm^3, F_{000} = 1888, MoKα radiation, λ = 0.71073 Å, T = 180(2) K, $2\theta_{max}$ = 50.0°, 21577 reflections collected, 5932 unique (R_{int} = 0.0379), Final *GooF* = 1.045, *R1* = 0.0908, *wR2* = 0.2671, *R* indices based on 4234 reflections with I > 2sigma(I (refinement on F^2), 562 parameters, 58 restraints. Lp and absorption corrections applied, μ = 0.266 mm^{-1}.

Separation:

Column packing: 80 mL CHP 20P resin was soaked in 100 mL methanol for 15 minutes. The solvent was decanted and the resin was then soaked in milli-Q water (100 mL) for 15 minutes. The H_2O-resin slurry was loaded and packed into a glass column (height = 35 cm, diameter = 2 cm). The resin column was then eluted with milli-Q water (1 L) and ready to use.

Column separation: The prepared sample was loaded onto the resin column. The column was then eluted with an amount of Milli-Q water equal to the bed volume of the resin (75 mL) and fractions were collected subsequently (10 mL per fraction). The separation process was monitored by mass spectroscopy. **1**⊂CB[6] was first eluted within fractions 10 to 20 followed by **1**⊂CB[6]-OH. There is a small overlap between the two CBs at fraction 20, however the majority of **1**⊂MonOH

could be separated within 30 fractions. After 30 fractions, 0.1% (w/w) NaOH was used as the eluent and **1**⊂BisOH was collected subsequently.

Column Regeneration: The column was washed with 1% (w/w) NaOH (400 mL) and Milli-Q water until neutral. The resin was then washed with 400 mL 50% MeOH, 400 mL MeOH, 400 mL 50% MeOH, 400 mL 20% MeOH and 1 L Milli-Q water respectively and ready for the next separation.

MonOH: $\mathbf{1}^{2+}$⊂MonOH fractions from the column separation were collected and dried under vacuum to give a white solid which was then triturated with MeOH (3×45 mL). The residue was refluxed in DCM in the presence of NH_4PF_6 for 48 hours. The solvent was then decanted and the sediment was washed with MeOH (3×45 mL), and dried under vacuum to give MonOH as a white solid (60 mg, 12%). HR-MS for $C_{36}H_{35}N_{24}O_{13}^{+}$: calcd. *m/z* 1011.2810, found *m/z* 1011.2795.

BisOH: $\mathbf{1}^{2+}$⊂BisOH fractions from the column separation were collected and dried under vacuum to give a white solid which was then triturated with MeOH (3×45 mL). The residue was refluxed in DCM in the presence of NH_4PF_6 for 48 hours. The solvent was then decanted and the sediment was washed with MeOH (3×45 mL), and dried under vacuum to give BisOH as a white solid. HR-MS for $C_{36}H_{36}N_{24}O_{14}Na^{+}$: calcd. *m/z* 1051.2735, found *m/z* 1051.2730.

Oxidation product ratios:

After functionalisation with APS, a range of *f*CB[6] molecules were generated with one to twelve hydroxyl groups, the ratios of which were found to be highly dependent on the amount of APS used When 1 equivalent of APS oxidant was added, only MonOH and BisOH as well as a small amount of TriOH were found in the solution (Figure 1 a). Increasing the APS concentration to 2.5 equivalents allowed for the formation of higher order *f*CB[6] molecules from MonOH to TetOH (Figure 1 b). Unfortunately, when only 0.5 equivalents of APS was used, the reaction did not proceed to any significant extent and any produced MonOH could not be separated. Thus one equivalent of oxidant was used with a reaction time of 12 h for all further functionalisation reactions.

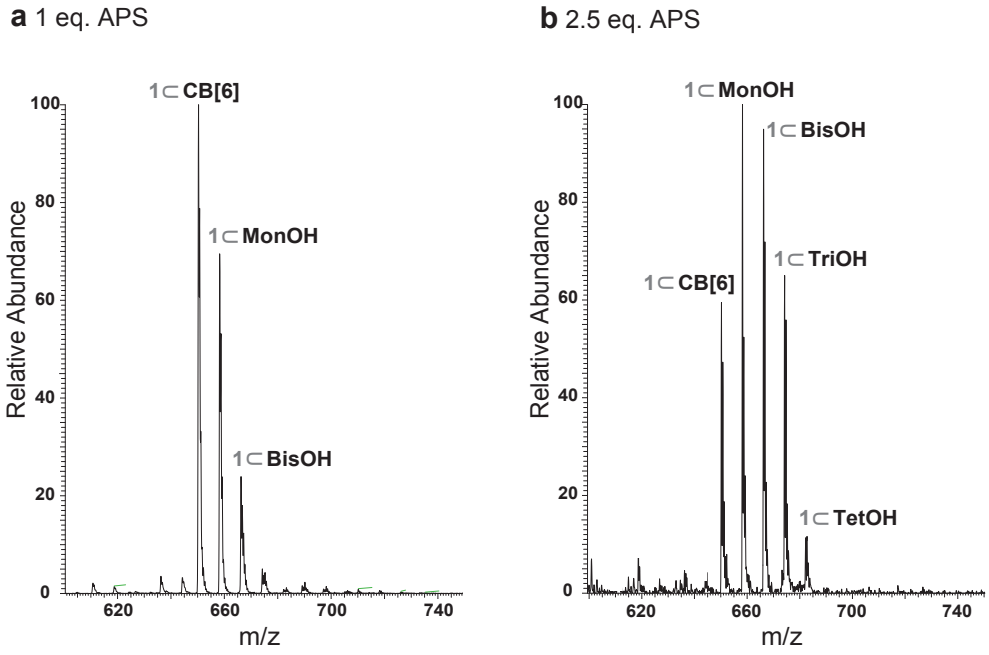


Figure 1: ESI-MS spectra depicting a) reaction mixture of CB[6] and 1 equivalent of APS in the presence of **1** at time = 12 h; b) reaction mixture of CB[6] and 2.5 equivalents of APS in the presence of **1** at time = 12 h.

Control Experiments:

CB[6] oxidation using 1 equivalent $K_2S_2O_8$ without guest 1: The oxidation procedure for CB[6] developed by Kim's group was repeated with the addition of only one equivalent of KPS. A slurry of cucurbit[6]uril (50 mg, 0.05 mmol) and $K_2S_2O_8$ (13 mg, 0.05 mmol) in Milli-Q water (2.5 mL) was degassed and heated at 85 °C for 6 hours. CB[6] was not fully dissolved even after the reaction. In order to determine the ratios of *f*CB[6] in reaction mixture, mass spectroscopy was employed. An bisimidazolium guest with hexyl linker (C_6Bisim) was added into mass spec sample as the solubility enhancement reagent. This guest processes a higher binding affinity with *f*CB[6] than compound **1**, eliminating the possibilities of *f* CB[6] binding with other ions, such as NH_4^+ and K^+. The mass spectrum of reaction mixture in the presence of C_6Bisim was shown in Figure 2 a. A mixture of MonOH to PenOH were observed with MonOH in very low ratio (10%). Therefore, high yield of MonOH can not be achieved by simply changing the ratio of oxidant.

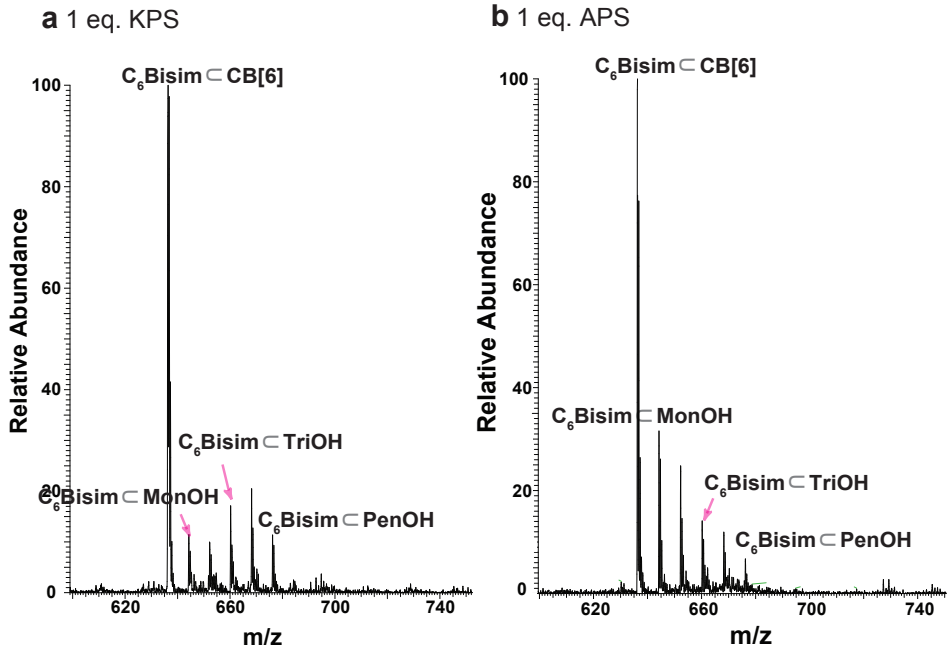


Figure 2: ESI-MS spectra depicting a) reaction mixture of CB[6] and 1 equivalent of KPS at time = 6 h; b) reaction mixture of CB[6] and 1 equivalent of APS at time = 12 h.

CB[6] functionalisation using 1 equivalent $(NH_4)_2S_2O_8$ without guest 1: A slurry of cucurbit[6]uril (50 mg, 0.05 mmol) and $(NH_4)_2S_2O_8$ (11 mg, 0.05 mmol) in Milli-Q water (5mL) was

heated at 85 °C for 12 hours. CB[6] was not fully dissolved after the reaction. The mass spectrum of reaction mixture in the presence of C_6Bisim was shown in Figure 2 b. A mixture of MonOH to PenOH were observed with MonOH in the ratio of 30%. Compared to Figure 2 a, the slightly increased ratio of MonOH formation is probably due to the weaker binding between NH_4^+ ions with CB[6] portals than potassium ions. However, the ratio of MonOH is still not as high as in Figure 1 a. Therefore, the addition of imidazolium guest during reaction greatly enhanced the percentage of MonOH and reduced the formation of other *f*CB[6].

NMR Characterisation of MonOH and BisOH isomers:

MonOH:

Partial ^{1}H NMR of MonOH:

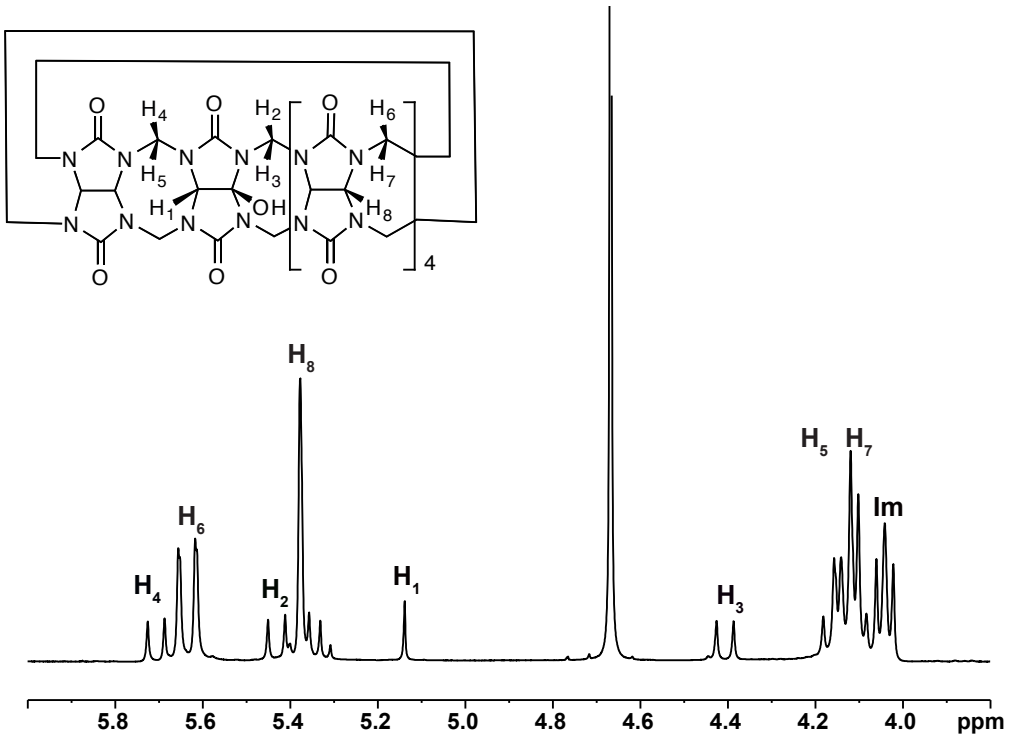
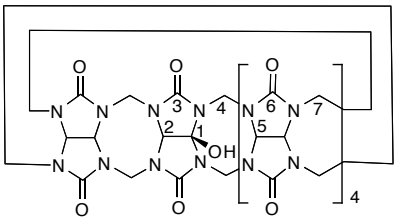


Figure 3: Partial ^{1}H NMR spectrum of **1**⊂MonOH

Fractions of **1**⊂ MonOH after the resin chromatography were collected and dried under vacuum. The complex was then redissolved in D_2O. The presence of **1** greatly increased the solubility of MonOH thus enhanced the resolution of the spectra.

When compared to normal CB[6], monohydroxylated CB[6]'s symmetry and electron density distribution are perturbed by the additional group, especially the electronic environment near the hydroxyl oxygen. Proton H_3, located close to the oxygen through space, experiences a 0.2 ppm downfield shift compared to less affected H_7, indicating the decrease of electron density around H_3. At the same time, the electron density around H_2 and C_4 is increased as H_2 shows an upfield shift of 0.2 ppm and C_4 also shifts upfield in comparison with the unchanged H_6 and C_7. Therefore, the electron density distribution for H_3– C_2– H_2 bonds are partially polarized in the presence of the hydroxyl oxygen. This additional group also has an inductive effect towards the C_1– C_2 bond, resulting in their downfield shifts as shown in Figure 4. The small singlets around H_8 arise from the other equatorial protons affected by the hydroxyl group. However, there are some unexpected chemical shift patterns for H_1, H_4, H_5 and C_3 imparted by the oxygen. The large upfield shift of H_1 (0.3 ppm compared to H_8) is interesting because it moves back to the location of H_8 once the hydroxyl group undergoes further allylation and propargylation (see reactions in the application subsection). The theory behind this long range effect across CB[6]'s ring structures is still under investigation. By utlising different guests, the relative positions between H_2 and H_8 changed as seen from comparison of Figure 3 here and Figure 2 in the paper.



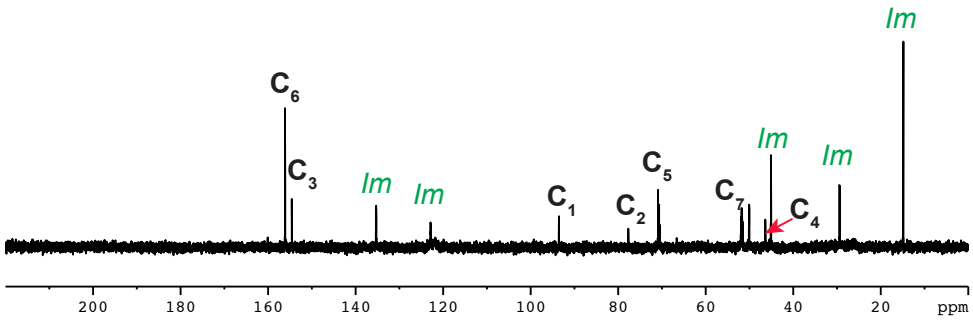


Figure 4: Partial ^{13}C NMR of MonOH

Partial COSY of MonOH:

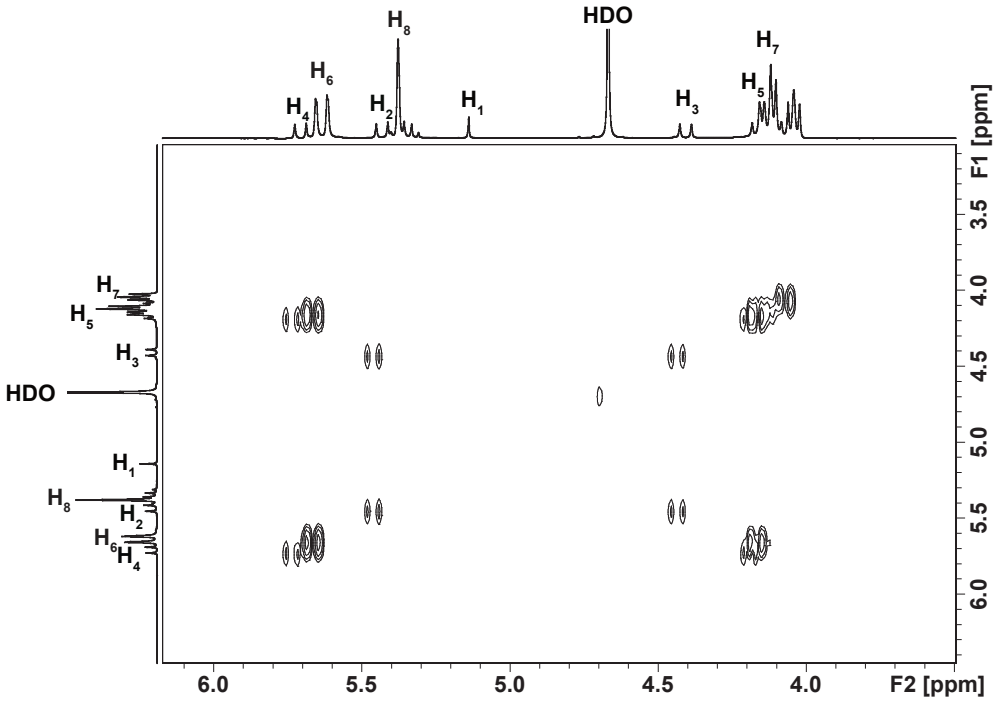


Figure 5

Partial HMQC of MonOH:

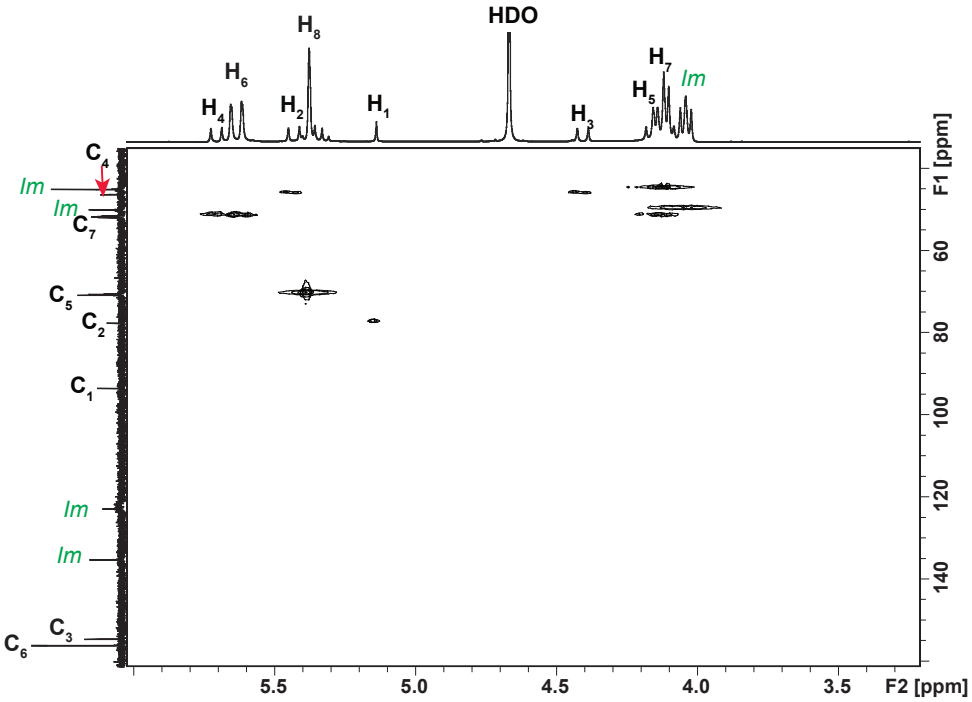


Figure 6

Partial HMBC of MonOH:

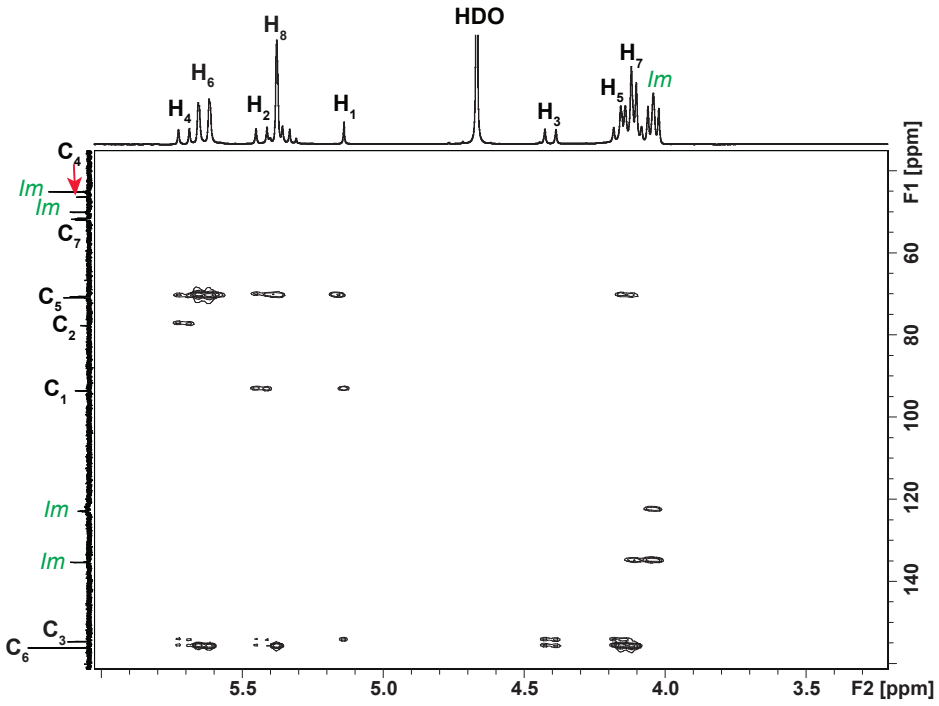


Figure 7

BisOH

The ^{1}H NMR spectrum for BisOH shares similar patterns with MonOH, however, with different integral values as expected. The relative position of the two hydroxyl groups on CB[6] cannot be assigned from current NMR data or mass spectra.

Partial ^{1}H NMR of BisOH:

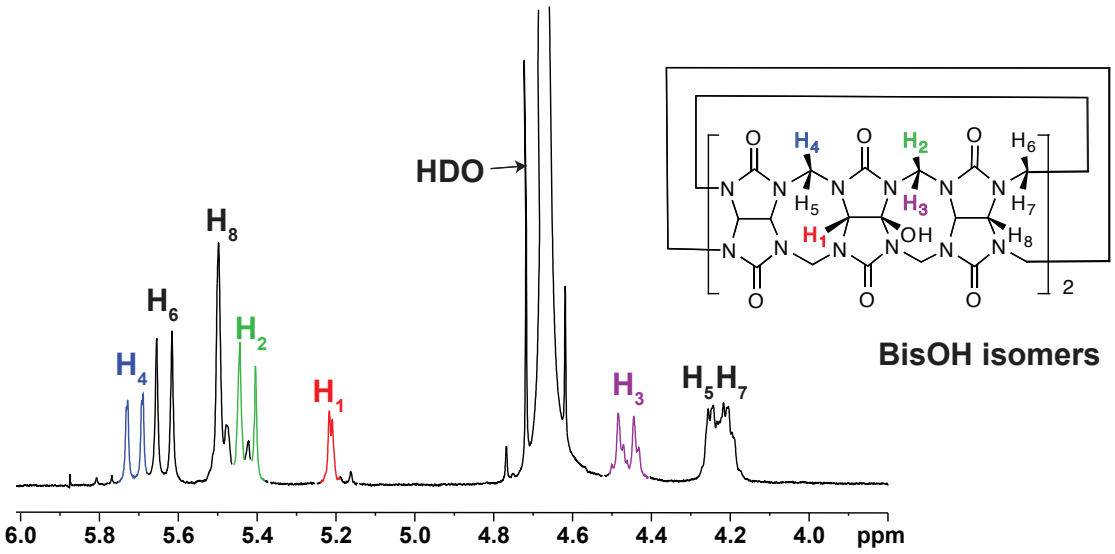
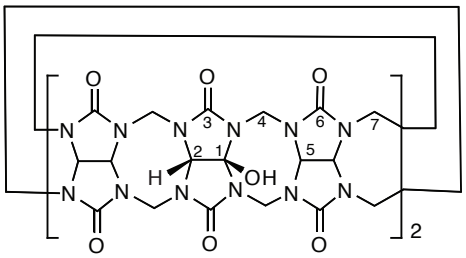


Figure 8

Partial ^{13}C NMR of BisOH:



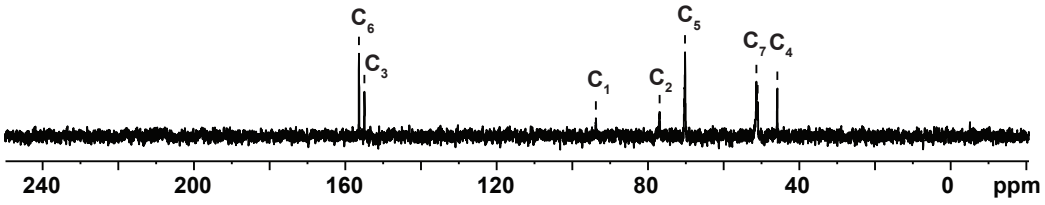


Figure 9

Partial COSY NMR of BisOH:

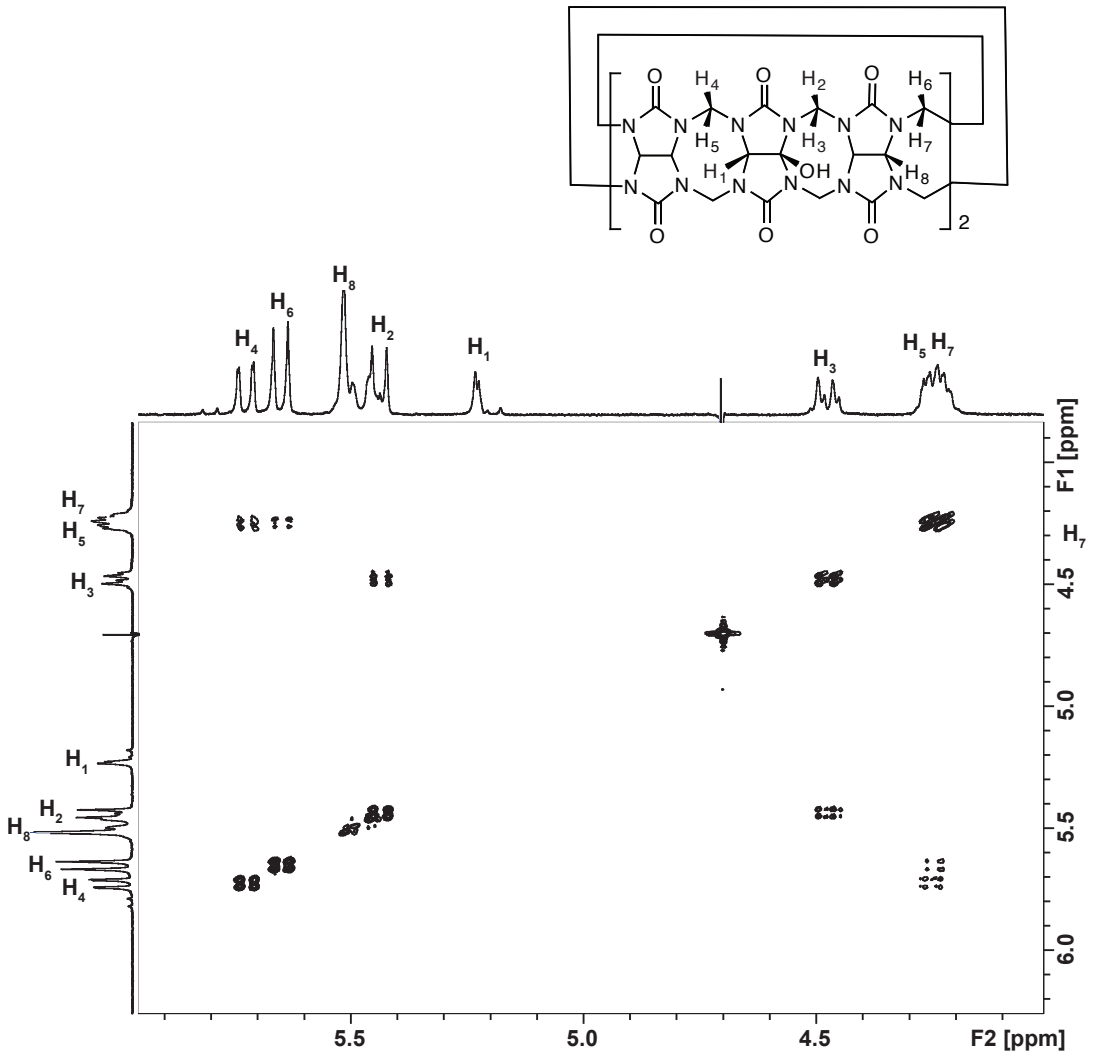


Figure 10

Partial HMQC NMR of BisOH:

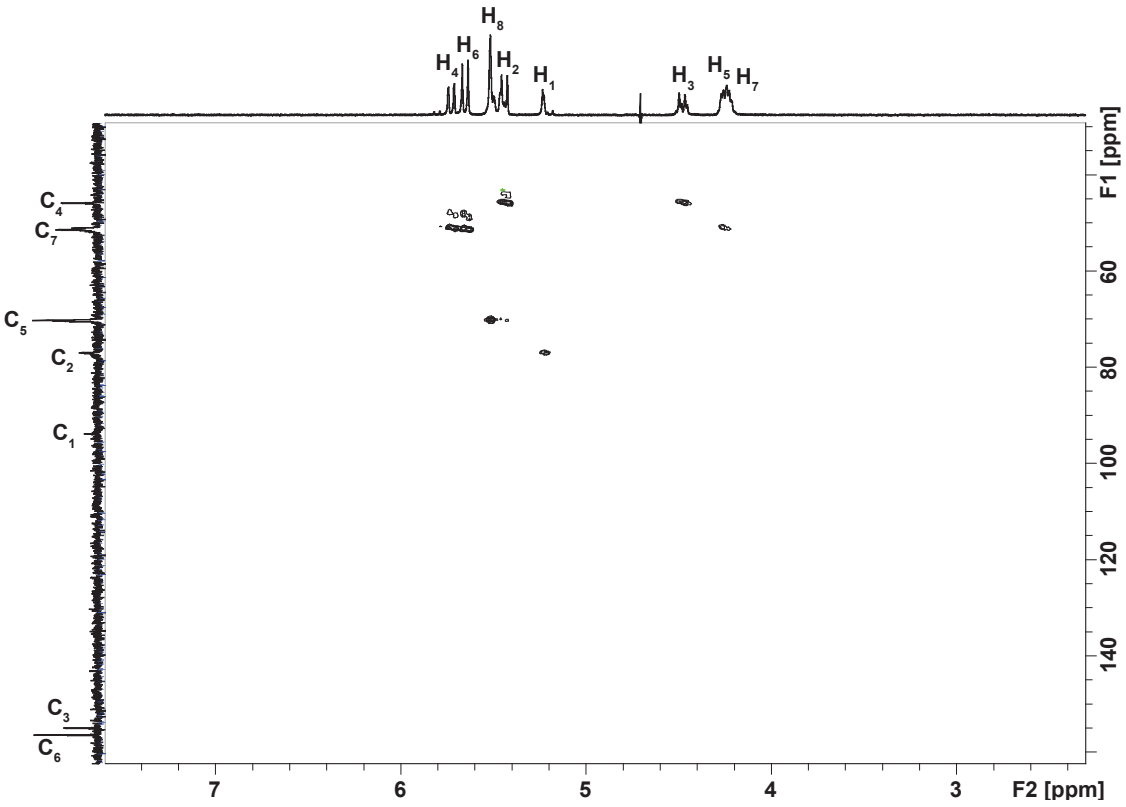


Figure 11

Partial HMBC NMR of BisOH:

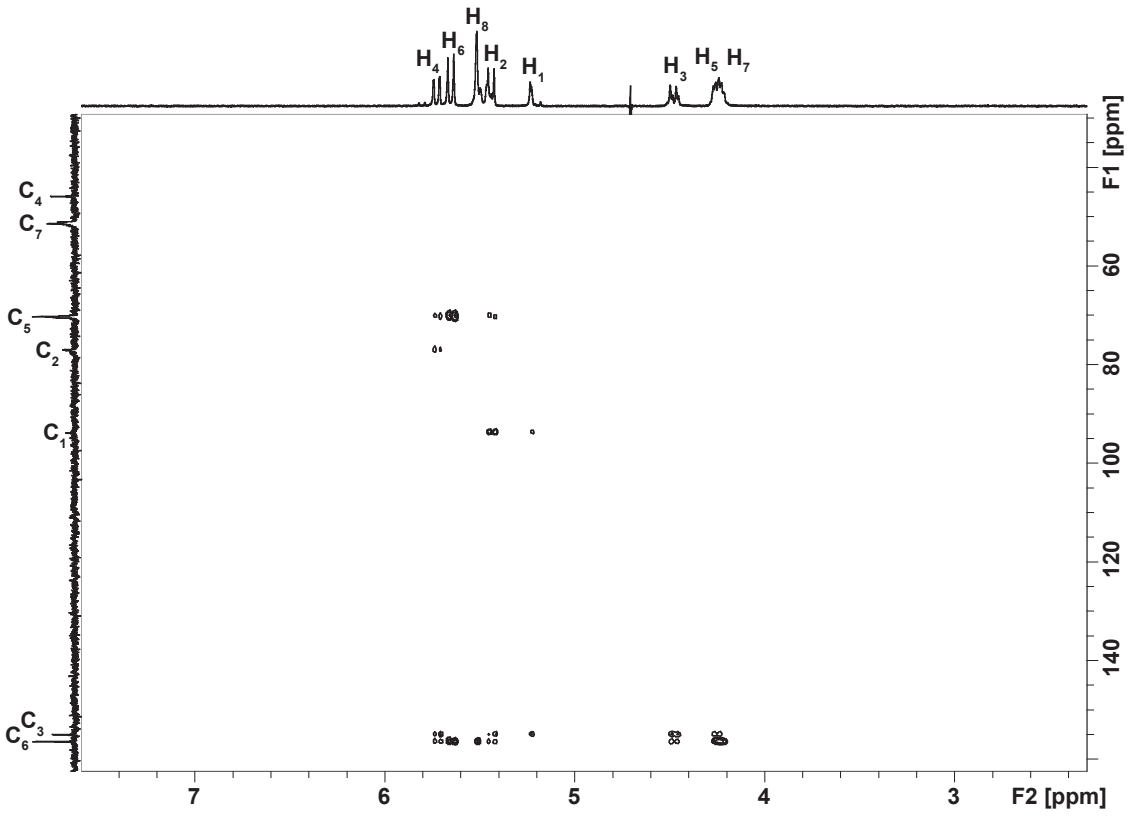


Figure 12