Synthesis and Self-Assembly Processes of Monofunctionalized Cucurbit[7]uril

Supporting Information

*by Brittany Vinciguerra,[†] Liping Cao,[†] Joe R. Cannon, Peter Y. Zavalij, Catherine Fenselau, and Lyle Isaacs**

Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742

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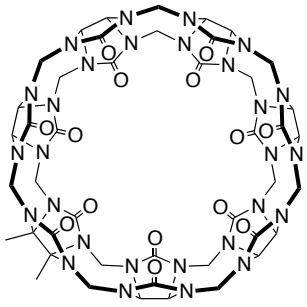
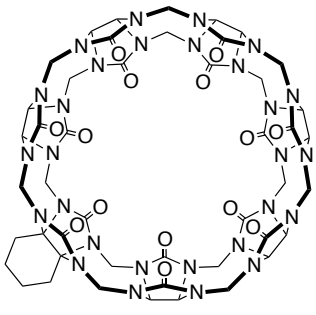
General Experimental Details. Starting materials were purchased from commercial suppliers were used without further purification. Compounds **SI1**, **15**, **16**, and Pericàs catalyst**18** were prepared according to the literature procedures.[1-4] Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. TLC analysis was performed using pre-coated plastic plates from Merck. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer and are reported in cm^{-1}. NMR spectra were measured on a spectrometers operating at 400, 500, or 600 MHz for ^{1}H and 100, 125, and 150 MHz for ^{13}C NMR spectra. Routine mass spectrometry was performed using a JEOL AccuTOF electrospray instrument (ESI). The mass spectrometric investigations of $\mathbf{20}_4$ were performed using an LTQ-Orbitrap XL (ThermoFisher, San Jose, CA).

Synthetic Procedures and Characterization Data



Compound $Me_2CB[7]$. A mixture of hexamer **1** (1.000 g, 1.03 mmol) and KI (0.230 g, 1.35 mmol) were dissolved in 9 M aqueous H_2SO_4 (5 mL) and then treated with $\mathbf{2}_{Me}$ (0.260 g, 1.03 mmol). The flask was then sealed with a rubber septum and heated at 110 °C for 30 min. The homogenous clear red mixture was poured into a 50 mL centrifuge tube and methanol (43 mL) was added, causing a white precipitate to appear. The mixture was sonicated for 5 min and then centrifuged at 7200 rpm for 8 min. The supernatant was discarded and acetone (45 mL) was added to the centrifuge tube. The mixture was sonicated until the solid was resuspended and then centrifuged at 7200 rpm for 8 min. The supernatant was discarded and the precipitate was dried under high vacuum overnight. The crude white powder (1.23 g) was analyzed by ^{1}H NMR in the presence of *p*-xylylene diamine and determined to be a mixture of approximately 50:50 CB[6]:$Me_2CB[7]$. The crude white

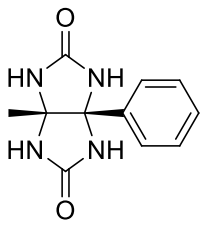
powder was dissolved in H_2O (30 mL) and sonicated for 5 min, yielding an orange solution. To this solution, 1 M aqueous KI solution (1.8 mL) was added. The mixture was shaken thoroughly and allowed to sit at RT for 10 min, causing a yellow-white precipitate to form. The mixture was centrifuged at 7200 rpm for 8 min. The supernatant was poured into methanol (100 mL) and centrifuged at 7200 rpm for 8 min. The supernatant was discarded and the solid was dried under high vacuum (0.69 g). The solid was redissolved in water (30 mL). The solution was treated with activated carbon (Fisher Chemical, Norit* Netural, C170-500, 4.00 g). The mixture was stirred for 24 h and then filtered. The solution was dried under high vacuum, yielding a white solid. After ^{1}H NMR analysis in the presence of **3**, the solid was determined to be pure dimethyl-CB[7] (0.380 g, 0.321 mmol, 31% yield). M.p. > 350 °C. IR (KBr, cm^{-1}): 1733s, 1473m, 1321m, 1235m, 1193m, 1117m, 806m. ^{1}H NMR (400 MHz, D_2O, as Me_2CB[7]•**3**, RT): 6.61 (s, 4H), 5.75-5.65 (m, 14H), 5.60-5.40 (m, 12H), 4.32 (d, J = 15.6, 4H), 4.26 (d, J = 15.6, 2H), 4.21 (d, J = 15.6, 4H), 4.16 (d, J = 15.6, 4H), 3.90 (s, 4H), 1.80 (s, 6H). ^{13}C NMR (125 MHz, D_2O, RT, 1,4-dioxane as internal standard): δ 157.3, 157.1, 157.0, 156.1, 78.9, 72.0, 71.9, 71.9, 71.8, 71.7, 71.6, 53.4, 53.0, 52.9, 49.2, 16.2. ESI-MS (**3** as guest): *m/z* 664 ([M•**3** + 2H]$^{2+}$). HR ESI-MS (**3** as guest): *m/z* 664.24531 ([Me_2CB[7]•**3** + 2H]$^{2+}$, $C_{52}H_{60}N_{30}O_{14}^{2+}$, calcd, for 664.24526). X-ray crystal structure.



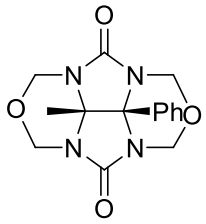
Compound CyCB[7]. A mixture of hexamer (1.000 g, 1.03 mmol) and KI (0.230 g, 1.35 mmol) were dissolved in 9 M aqueous H_2SO_4 (5 mL) and then treated with $\mathbf{2}_{Cy}$ (0.288 g, 1.03 mmol). The flask was then sealed with a rubber septum and heated at 110 °C for 30 min. The homogenous clear orange mixture was poured into a 50

mL centrifuge tube and methanol (43 mL) was added, causing a white precipitate to appear. The mixture was sonicated for 5 min and then centrifuged at 7200 rpm for 8 min. The supernatant was discarded and acetone (45 mL) was added to the centrifuge tube. The mixture was sonicated until the solid was resuspended and then centrifuged at 7200 rpm for 8 min. The supernatant was discarded and the precipitate was dried under high vacuum overnight. The crude white powder (1.17 g) was analyzed by ^{1}H NMR in the presence of *p*-xylylene diamine and determined to be a mixture of approximately 66:33 CB[6]: CyCB[7]. The crude white powder was dissolved in H_2O (40 mL) and sonicated for 5 min, yielding an orange solution. To this solution, 1M aqueous KI solution (3.0 mL) was added. The mixture was shaken thoroughly and allowed to sit at RT for 10 min, causing a yellow-white precipitate to form. The mixture was centrifuged at 7200 rpm for 8 min. The supernatant was poured into methanol (100 mL) and centrifuged at 7200 rpm for 8 min. The supernatant was discarded and the solid was dried under high vacuum (0.45 g). The solid was redissolved in water (30 mL). The solution was treated with activated carbon (Fisher Chemical, Norit* Netural, C170-500, 4.00 g). The mixture was stirred for 24 h and then filtered. The solution was dried under high vacuum, yielding a white solid. After ^{1}H NMR analysis in the presence of *p*-xylyene diamine, the solid was determined to be pure CyCB[7] (0.23 g, 0.188 mmol, 18% yield). M.p. > 350 °C. IR (KBr, cm^{-1}): 1728s, 1476s, 1323m, 1236m, 1193m, 1100w, 806m. ^{1}H NMR (400 MHz, D_2O, as CyCB[7]•**3**, RT): 6.65 (s, 4H), 5.79 (d, J = 15.6, 2H), 5.75 (d, J = 16.20, 8H) 5.72 (d, J = 16.2, 4H), 5.59 (d, J = 8.1, 2H), 5.56 (d, J = 8.1, 2H), 5.55-5.45 (m, 8H), 4.30 (d, J = 15.6, 2H), 4.28 (d, J = 16.2, 4H), 4.26 (d, J = 16.2, 4H), 4.21 (d, J = 16.2, 4H), 3.94 (m, 4H), 2.31 (m, 4H), 1.52 (s, 4H). ^{13}C NMR (125 MHz, D_2O, RT, 1,4-dioxane as internal standard): δ 156.4, 156.2, 156.2, 155.9, 76.5, 71.0, 70.9, 70.8, 70.8, 70.7, 70.6, 52.4, 52.0, 51.9, 48.0, 21.4, 12.8. ESI-

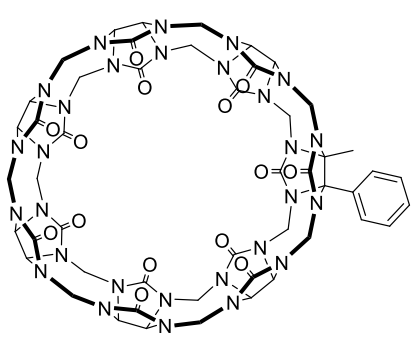
MS (**3** as guest): *m/z* 677 ([CyCB[7]•**3** + 2H]$^{2+}$). HR ESI-MS (**3** as guest): *m/z* 677.25205 ([CyCB[7]•**3** + 2H]$^{2+}$, $C_{54}H_{62}N_{30}O_{14}^{2+}$, calcd, for 677.2521).



Compound SI1. To 1-phenylpropane-1,2-dione (4.84 g, 32.7 mmol) was added a solution of urea (7.85 g, 130.8 mmol) in HCl (250 mL, 0.30 M), and the reaction mixture was capped. The reaction was then stirred at RT for 2 days. The precipitates were filtered, washed with H_2O (200 mL) and Et_2O (200 mL) sequentially, and then dried under high vacuum to yield **SI1** as a white solid (6.74 g, 29.1 mmol, 89 %). The ^{1}H NMR matches that reported in the literature.[4]

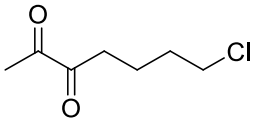


Compound 2$_{MePh}$. To a 50 mL flask was added a mixture of **SI1** (812 mg, 3.49 mmol), paraformaldehyde (504 mg, 16.8 mmol) in 9 M HCl (20 mL), and the flask was capped with a septum. The reaction was then stirred at RT for 24 h upon which time additional H_2O (20 mL) was added into the reaction mixture, and stirred for an additional 12 h. The precipitates were filtered, washed with H_2O (20 mL) and EtOH (10 mL) sequentially, dried under high vacuum to yield compound **2**$_{MePh}$ as a white solid (635 mg, 2.01 mmol, 58 %). M.p. 289-291 ˚C. IR (KBr, cm^{-1}): 3442w, 1740s, 1726s, 1469s, 1448m, 1413s, 1394m, 1385s, 1269m, 1206w, 1176s, 1127w, 1107w, 1079w, 1020s, 992w, 974w, 945m, 924w, 859m. ^{1}H NMR (400 MHz, DMSO-d_6): 7.60-7.50 (m, 3H), 7.50-7.40 (m, 2H) 5.36 (d, J = 11.2, 2H), 5.31 (d, J = 11.2, 2H), 5.01 (d, J = 11.2, 2H), 4.56 (d, J = 11.2, 2H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 157.7, 132.8, 129.8, 129.3, 127.7, 78.1, 73.9, 71.3, 70.5, 19.1 HR-MS: *m/z* 317.1235 ([M + H]$^+$, calcd. for $C_{15}H_{17}N_4O_4^+$, 317.1250).

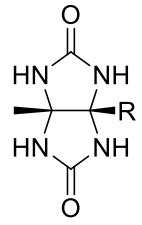


Compound MePhCB[7]. A mixture of **1** (973 mg, 1.0 mmol) and KI (224 mg, 1.35 mmol) were dissolved in 9M aqueous H_2SO_4 (5 mL) and then treated with $\mathbf{2_{MePh}}$ (380 mg, 1.2 mmol). The flask was then sealed with a rubber septum and heated at 110 ˚C for 30 min. The reaction solution was then poured into MeOH (40 mL) which resulted in a gray precipitate. The mixture was centrifuged at 7200 rpm for 5 min. The supernatant was decanted and the precipitate was washed with MeOH (40 mL × 3) and centrifuged at 7200 rpm for 5 min. The precipitate was dried under high vacuum to give crude, gray powder (1.32 g, includes 30% of MePh CB[7], 61% of CB[6] and 9% of unidentified products). The crude solid was dissolved in a solution of 88% formic acid/0.4 M HCl (1:1, v:v) (10 mL). The solution containing the crude solid was loaded onto a column (3 cm diameter) containing 20 cm Dowex 50WX2 ion-exchange resin pretreated with 88% formic acid/0.4 M HCl (1:1, v:v). The column was eluted with 88% formic acid/0.4 M HCl (1:1, v:v, 400 mL), and then 88% formic acid/0.6 M HCl (1:1, v:v, 400 mL), and then 88% formic acid/0.8 M HCl (1:1, v:v, 400 mL). The fraction purity was assessed by ^{1}H NMR using **3** as a probe. The appropriate factions were combined and solvent was removed by rotary evaporation and dried under high vacuum. The yellow solid was then washed with MeOH (40 mL) and centrifuged at 7200 rpm for 5 min. The supernatant was decanted and the precipitate was dried under high vacuum to give MePhCB[7] as a white powder (36 mg, 0.029 mmol, 2.9%). M.p. > 300 ˚C. IR (KBr, cm^{-1}): 3455s, 3001w, 2923w, 1730s, 1637m, 1472s, 1421m, 1337m, 1321s, 1235s, 1193s, 1101w, 1024w, 968m, 940w, 892w. ^{1}H NMR (500 MHz, D_2O, >1 equiv. **3**): 7.70-7.60 (m, 3H), 7.57 (s, unbound **3**), 7.30 (d, J = 6.9, 2H), 6.73 (s,

4H), 5.98 (d, J = 15.9, 2H), 5.90-5.70 (m, 12H), 5.70-5.45 (m, 10H), 5.41 (d, J = 9.1, 1H), 5.17 (d, J = 9.1, 1H), 4.45-4.10 (m, 14H), 4.27 (s, unbound **3**), 4.02 (s, 4H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, D_2O, dioxane as internal reference, >1 equiv. **3**): 156.9, 156.6, 156.6, 156.5, 156.5, 133.8, 133.7, 130.7, 130.1, 130.0, 129.6, 129.0, 128.0, 85.0, 80.2, 71.8, 71.7, 71.6, 71.5, 71.3, 71.2, 71.1, 71.1, 71.0, 53.5, 53.3, 52.8, 52.6, 52.3, 50.7, 49.5, 42.8, 42.3, 18.2 (only 34 of the 39 resonances expected were observed). HR-MS: *m/z* 695.2515 ($[M•\mathbf{3}+2H]^{2+}$, calcd. for $C_{49}H_{48}N_{28}O_{14}•C_8H_{14}N_2^{2+}$, 695.2531).

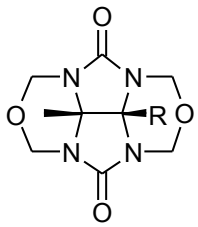


7-Chloroheptane-2,3-dione. To a solution of N,N'-diisopropyl 1,2-butanediimine[1] (10 g, 64.4 mmol) in 150 mL of THF maintained at 0 ˚C was added LDA (38.8 mL, 77.6 mmol) slowly for 1 h. The solution was stirred at 0 ˚C for another 6 h, followed by addition of a solution of 1-chloro-3-iodopropane (15.6 g, 76.4 mmol) in THF (20 mL). The reaction was stirred at 0 ˚C for 10 h upon which time 1 N HCl (320 mL) was added into the reaction mixture, and stirred for an additional 5 h at RT. The THF was removed by rotary evaporation, and the remaining aqueous layer was extracted with dichloromethane (300 mL × 3). The combined organic extracts were washed with 1 N HCl (200 mL), water (200 mL), and sat. aq. $NaHCO_3$ (200 mL) sequentially, and then dried over Na_2SO_4. The organic extracts were evaporated to afford almost pure compound **16**,[2] which was distilled (56-58 ˚C/0.05 mm Hg) to give the pure product (7.30 g, 44.9 mmol, 69 %) as yellow oil. IR (KBr, cm^{-1}): 2952w, 1715s, 1353w. ^{1}H NMR (400 MHz, $CDCl_3$): 3.54 (t, J = 6.2, 2H), 2.78 (t, J = 6.9, 2H), 2.33 (s, 3H), 1.85-1.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 198.6, 197.3, 44.4, 34.8, 31.7, 23.6, 20.3.



R = $CH_2CH_2CH_2CH_2Cl$

Compound 17. To compound **16** (9.4 g, 57.8 mmol) was added a solution of urea (10.4 g, 173.4 mmol) in HCl (50 mL, 0.3 M), and the flask was capped with a septum. The reaction was then stirred at RT for 1 day. The precipitates were filtered, washed with H_2O (30 mL × 2) and acetone (30 mL × 2) sequentially, and dried under high vacuum to yield **17** as a white solid (5.0 g, 20.3 mmol, 35 %). M.p. > 194 ˚C (dec.). IR (KBr, cm^{-1}): 2952w, 1723s, 1677s, 1502m, 1174m, 1139w, 1046w. ^{1}H NMR (500 MHz, DMSO-d_6): 7.19 (s, 2H), 7.09 (s, 2H), 3.62 (t, J = 6.5, 2H), 1.75-1.65 (m, 2H), 1.65-1.60 (m, 2H), 1.55-1.45 (m, 2H), 1.34 (s, 3H), ppm. ^{13}C NMR (125 MHz, DMSO-d_6): 159.6, 77.2, 75.5, 45.1, 34.5, 32.3, 21.5, 20.3 ppm. ESI-MS: *m/z* 247.1 ($[M+H]^+$).



R = $CH_2CH_2CH_2CH_2Cl$

Compound 12. To a flask was added a mixture of **17** (5.00 g, 20.3 mmol), 37% formalin solution (7.9 mL), H_2O (4.5 mL), and conc. HCl (15 mL), and the flask was capped with a septum. The reaction was then stirred at RT for 23 h upon which time additional H_2O (60 mL) was added, and the reaction stirred for an additional 5 h. The precipitates were filtered, washed with H_2O (200 mL) and EtOH (50 mL) sequentially, dried under high vacuum to yield compound **12** as a white solid (4.6 g, 13.9 mmol, 68 %). M.p. > 165 ˚C (dec.). IR (KBr, cm^{-1}): 3434m, 3013w, 2952w, 2882w, 1721s, 1475s, 1421s, 1388m, 1305m, 1245m, 1180m, 1146w, 1108w, 1063w, 1019m, 985w, 947w, 875w. ^{1}H NMR (500 MHz, $CDCl_3$): 5.53 (d, J = 11.1, 2H), 5.51 (d, J = 11.1, 2H), 4.82 (d, J = 11.1, 2H), 4.76 (d, J = 11.1, 2H), 3.61 (t, J = 6.2, 2H), 2.30-2.20 (m, 2H), 1.95-1.85 (m, 2H), 1.86 (s, 3H), 1.60-1.50 (m, 2H) ppm. ^{13}C NMR (125

MHz, $CDCl_3$): 157.6, 75.3, 73.5, 71.1, 70.8, 44.2, 31.9, 28.9, 21.4, 17.2 ppm. ESI-MS: *m/z* 331.1 ($[M+H]^+$).

Unsuccessful Reaction Between Hexamer 1 and 2_{Ph}. A mixture of **1** (9.7 mg, 0.01 mmol) and KI (0.22 mg, 1.35 mmol) were dissolved in 9 M aqueous H_2SO_4 (0.2 mL) and then treated with $\mathbf{2}_{Ph}$ (4.6 mg, 0.012 mmol). The flask was then sealed with a rubber septum and heated at 110 ˚C for 30 min. The reaction solution was then poured into MeOH (3 mL) which resulted in a gray precipitate. The mixture was centrifuged at 7200 rpm for 5 min. The supernatant was decanted and the precipitate was washed with MeOH (3 mL × 3) and centrifuged at 7200 rpm for 5 min. The precipitate was dried under high vacuum to give a crude, gray powder (10.9 mg). The crude material was assessed by ^{1}H NMR using **3** as a probe which showed the presence of CB[6] (94%) and unidentified products (6%).

Unsuccessful Reaction Between Hexamer 1 and 2_{CO2Et}. A mixture of **1** (9.7 mg, 0.01 mmol) and KI (0.22 mg, 1.35 mmol) were dissolved in 9 M aqueous H_2SO_4 (0.2 mL) and then treated with $\mathbf{2}_{CO2Et}$ (4.5 mg, 0.012 mmol). The flask was then sealed with a rubber septum and heated at 110 ˚C for 30 min. The reaction solution was then poured into MeOH (3 mL) which resulted in a gray precipitate. The mixture was centrifuged at 7200 rpm for 5 min. The supernatant was decanted and the precipitate was washed with MeOH (3 mL × 3) and centrifuged at 7200 rpm for 5 min. The precipitate was dried under high vacuum to give a crude, gray powder (11.1 mg). The crude material was assessed by ^{1}H NMR using **3** as a probe which showed the presence of CB[6] (96%) and unidentified products (4%).

Reaction Between 1 and 12 in 9M H_2SO_4. A mixture of **1** (9.7 mg, 0.01 mmol) was dissolved in 9 M aqueous H_2SO_4 (0.2 mL) and then treated with **12** (5 mg, 0.015 mmol). The flask was then sealed with a rubber septum and heated at 110 ˚C for 30 min. The reaction solution was

then poured into MeOH (3 mL) which resulted in a gray precipitate. The mixture was centrifuged at 7200 rpm for 5 min. The supernatant was decanted and the precipitate was washed with MeOH (3 mL × 3) and centrifuged at 7200 rpm for 5 min. The precipitate was dried under high vacuum to a give crude, gray powder (14.1 mg). The crude material was assessed by ^{1}H NMR using **3** as a probe which showed the presence of CB[6] (70%), **18** (25%), and unidentified products (5%).

Reaction Between 1 and 12 in Conc. HCl in the Presence of KI. A mixture of **1** (9.7 mg, 0.01 mmol) and KI (0.22 mg, 1.35 mmol) were dissolved in conc. HCl (0.2 mL) and then treated with **12** (5 mg, 0.015 mmol). The flask was then sealed with a rubber septum and heated at 110 ˚C for 30 min. The reaction solution was then poured into MeOH (3 mL) which resulted in a gray precipitate. The mixture was centrifuged at 7200 rpm for 5 min. The supernatant was decanted and the precipitate was washed with MeOH (3 mL × 3) and centrifuged at 7200 rpm for 5 min. The precipitate was dried under high vacuum to give a crude, gray powder (13.6 mg). The crude material was assessed by ^{1}H NMR using **3** as a probe which showed the presence of CB[6] (70%) and **18** (30%).

Reaction Between 1 and 12 in Conc. HCl Without Added KI. A mixture of **1** (9.7 mg, 0.01 mmol) was dissolved in conc. HCl (0.2 mL) and then treated with **12** (5 mg, 0.015 mmol). The flask was then sealed with a rubber septum and heated at 110 ˚C for 30 min. The reaction solution was then poured into MeOH (3 mL) which resulted in a gray precipitate. The mixture was centrifuged at 7200 rpm for 5 min. The supernatant was decanted and the precipitate was washed with MeOH (3 mL × 3) and centrifuged at 7200 rpm for 5 min. The precipitate was dried under high vacuum to give a crude, gray powder (13.9 mg). The crude material was

assessed by ^{1}H NMR using **3** as a probe which showed the presence of CB[6] (59%), **18** (39%), and unidentified products (2%).

Details of the Mass Spectrometric Investigations of 20$_4$. An aqueous solution of CB7 derivative **20** solution was diluted to 100μM and infused directly into an LTQ-Orbitrap XL (ThermoFisher, San Jose, CA). Precursor and product ion spectra following collisional induced dissociation at varying normalized collision energies (NCE) were acquired at maximum resolution. Theoretical spectra and neutral masses were produced using the incorporated Xcalibur 2.0 software suite.

Procedure to create the phase solubility diagrams for drugs with CB[7] or Me2CB[7]. To a solution of a known concentration of Me_2CB[7] in D_2O (pD = 2, adjusted with HCl) was added an excess amount of pharmaceutical agent. The heterogenous mixture was magnetically stirred at room temperature for 15 h. The mixture was then filtered through a sterile syringe filter with a 0.2 μm polyethersulfone membrane. To the homogenous solution was added $MeSO_3H$ or DMSO as internal standard of known concentration. The concentration of pharmaceutical agent was determined by ^{1}H NMR spectroscopy (400 MHz) by comparing the integral for the internal standard with the integrals for selected ^{1}H NMR resonances of the pharmaceutical agent.

References:

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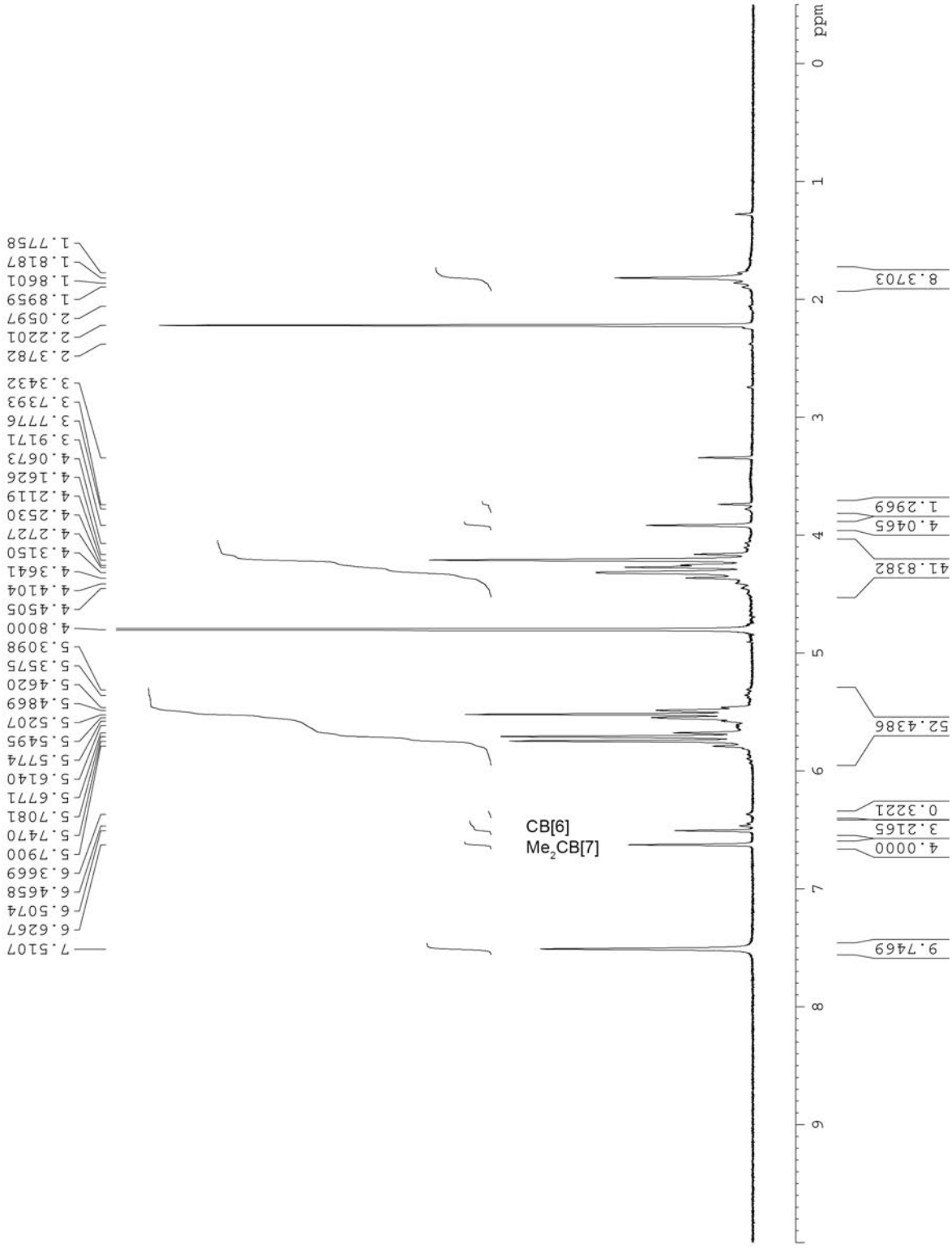


Figure S1. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the reaction between **1** and $\mathbf{2}_{Me}$ in the presence of **3** as a probe. ^{1}H NMR integration of the **3** binding region (6-7 ppm) allows us to determine the contents of the crude mixture (53% Me_2CB[7], 43% CB[6], and 4% unidentified).

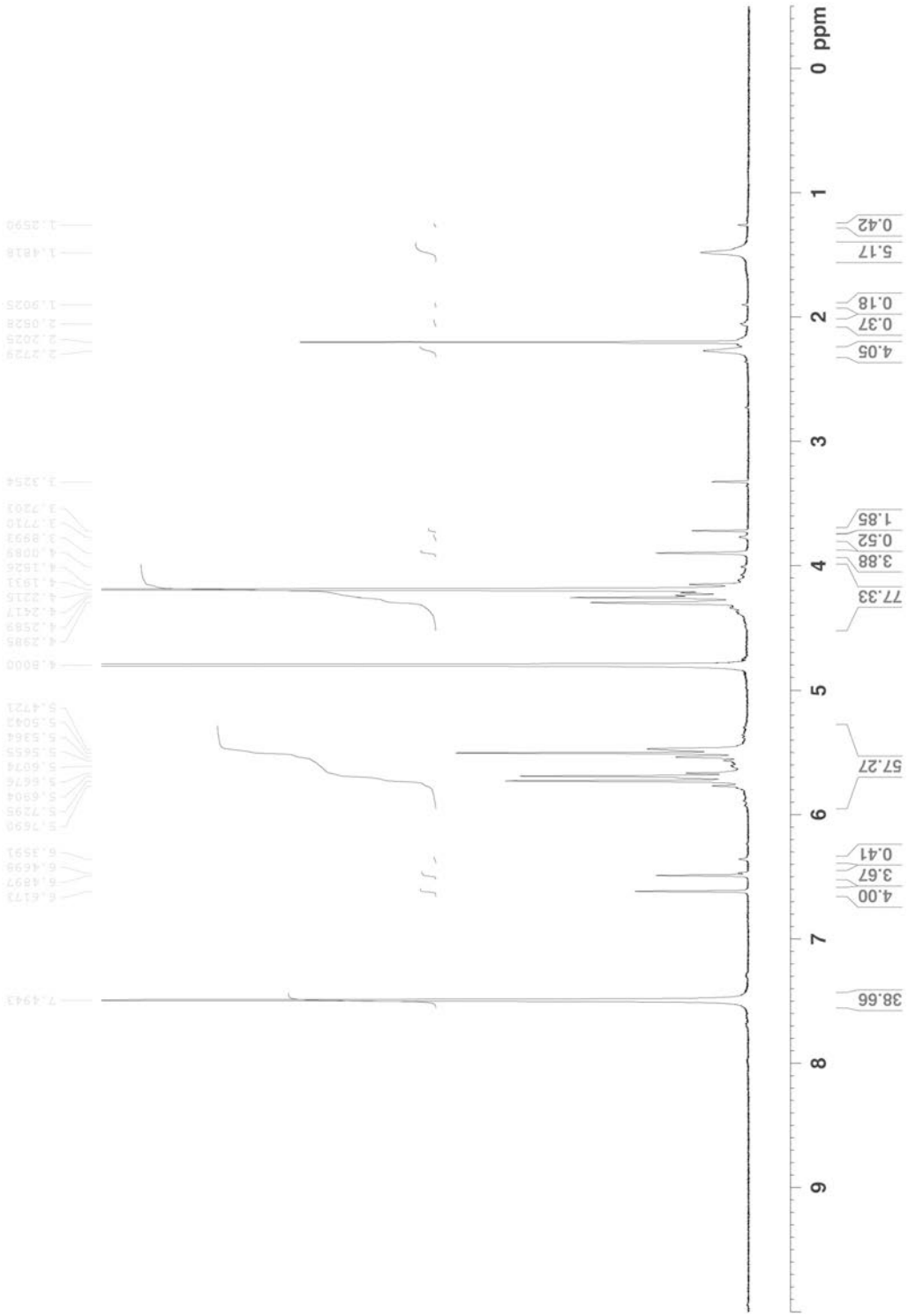


Figure S2. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the reaction between **1** and $\mathbf{2}_{Cy}$ in the presence of **3** as a probe. ^{1}H NMR integration of the **3** binding region (6-7 ppm) allows us to determine the contents of the crude mixture (50% CyCB[7], 45% CB[6], and 5% unidentified).

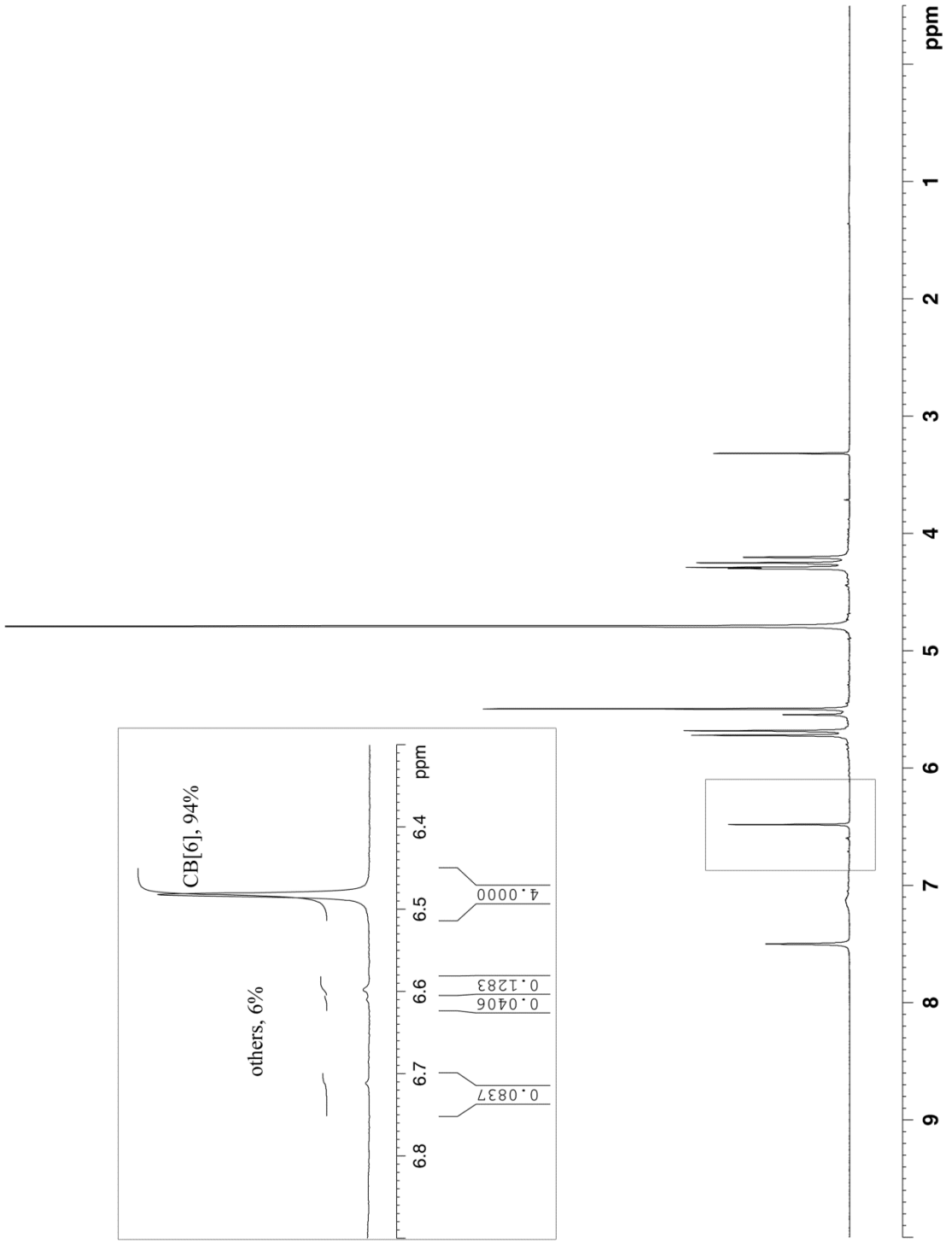


Figure S3. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the attempted cyclization of **1** and $\mathbf{2}_{Ph}$ in the presence of an excess of **3** as a probe.

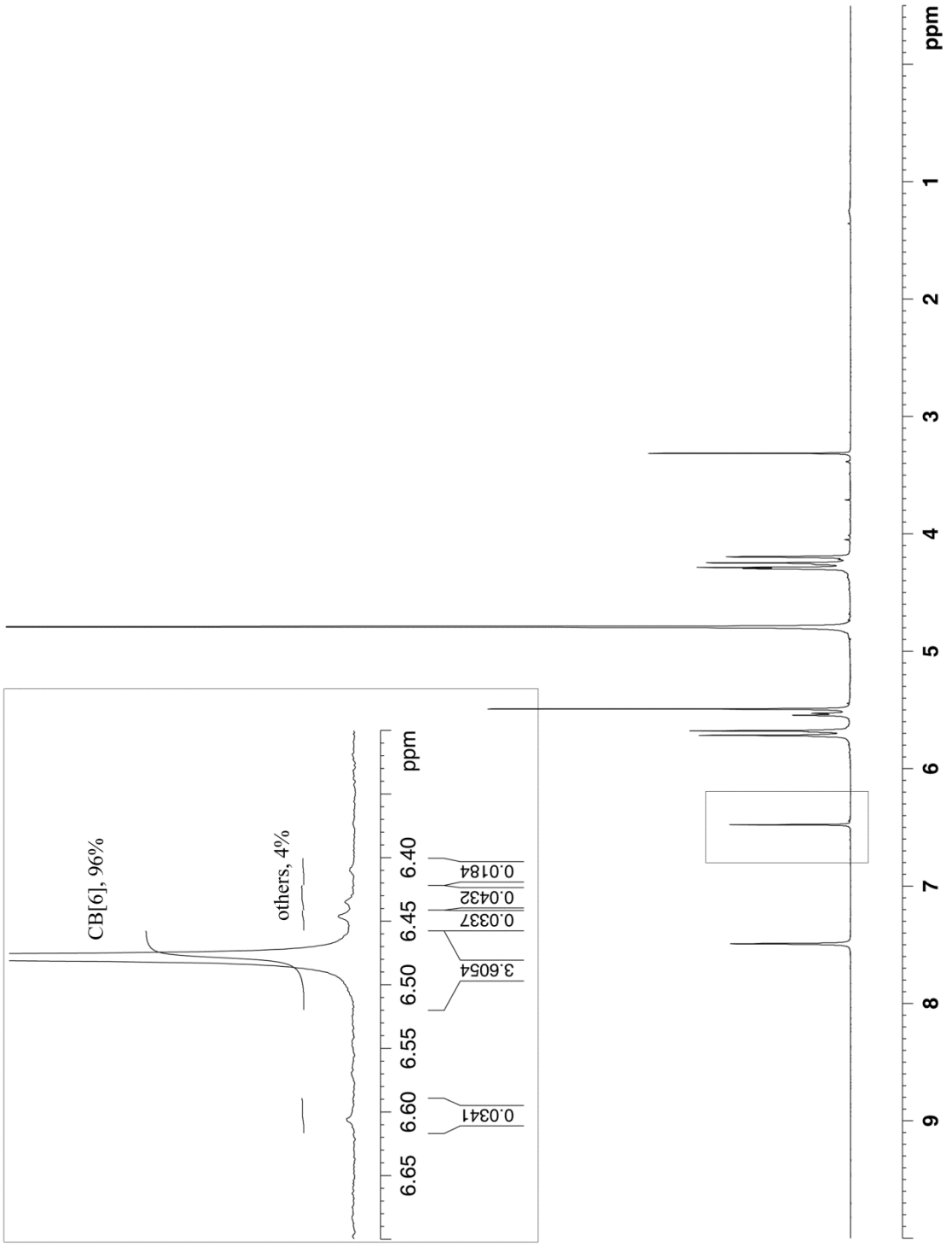


Figure S4. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the attempted cyclization of **1** and $\mathbf{2}_{CO2Et}$ in the presence of an excess of **3** as a probe.

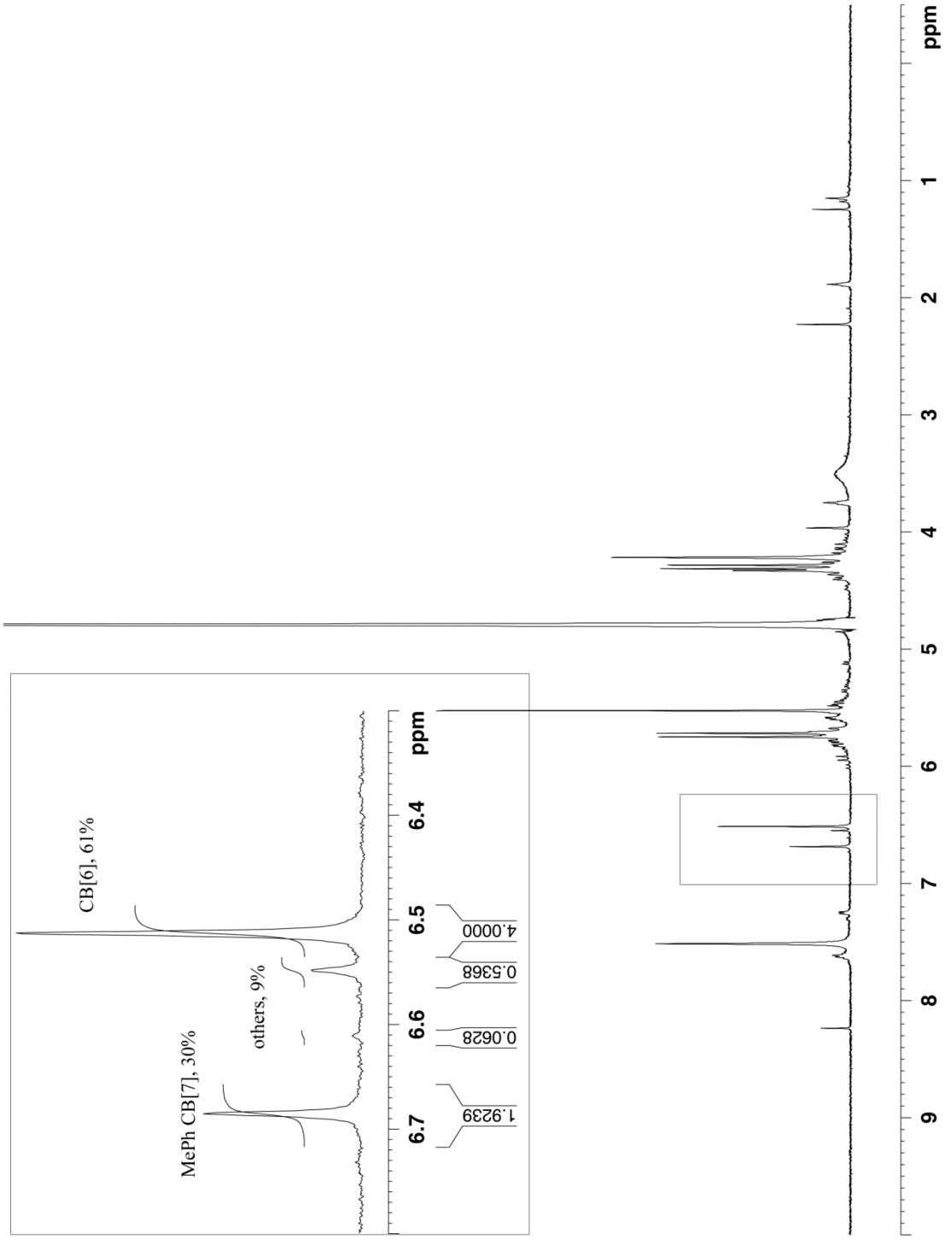


Figure S5. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the reaction between **1** and $\mathbf{2}_{MePh}$ in the presence of **3** as a probe. ^{1}H NMR integration of the **3** binding region (6-7 ppm) allows us to determine the contents of the crude mixture (30% MePhCB[7], 61% CB[6], and 9% unidentified).

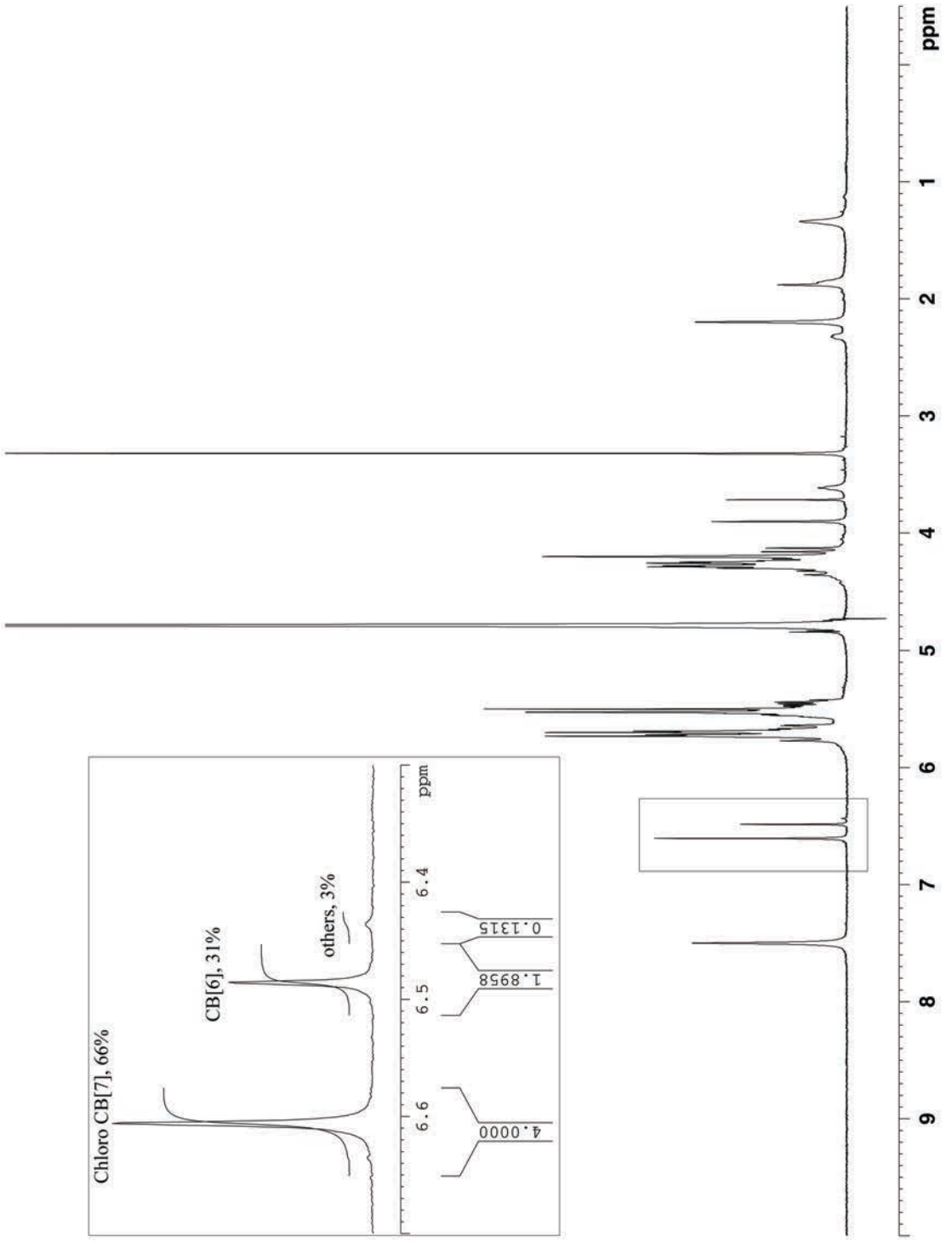


Figure S6. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the reaction between **1** and **12** in the presence of **3** as a probe. ^{1}H NMR integration of the **3** binding region (6-7 ppm) allows us to determine the contents of the crude mixture (66% **18**, 31% CB[6], and 3% unidentified).

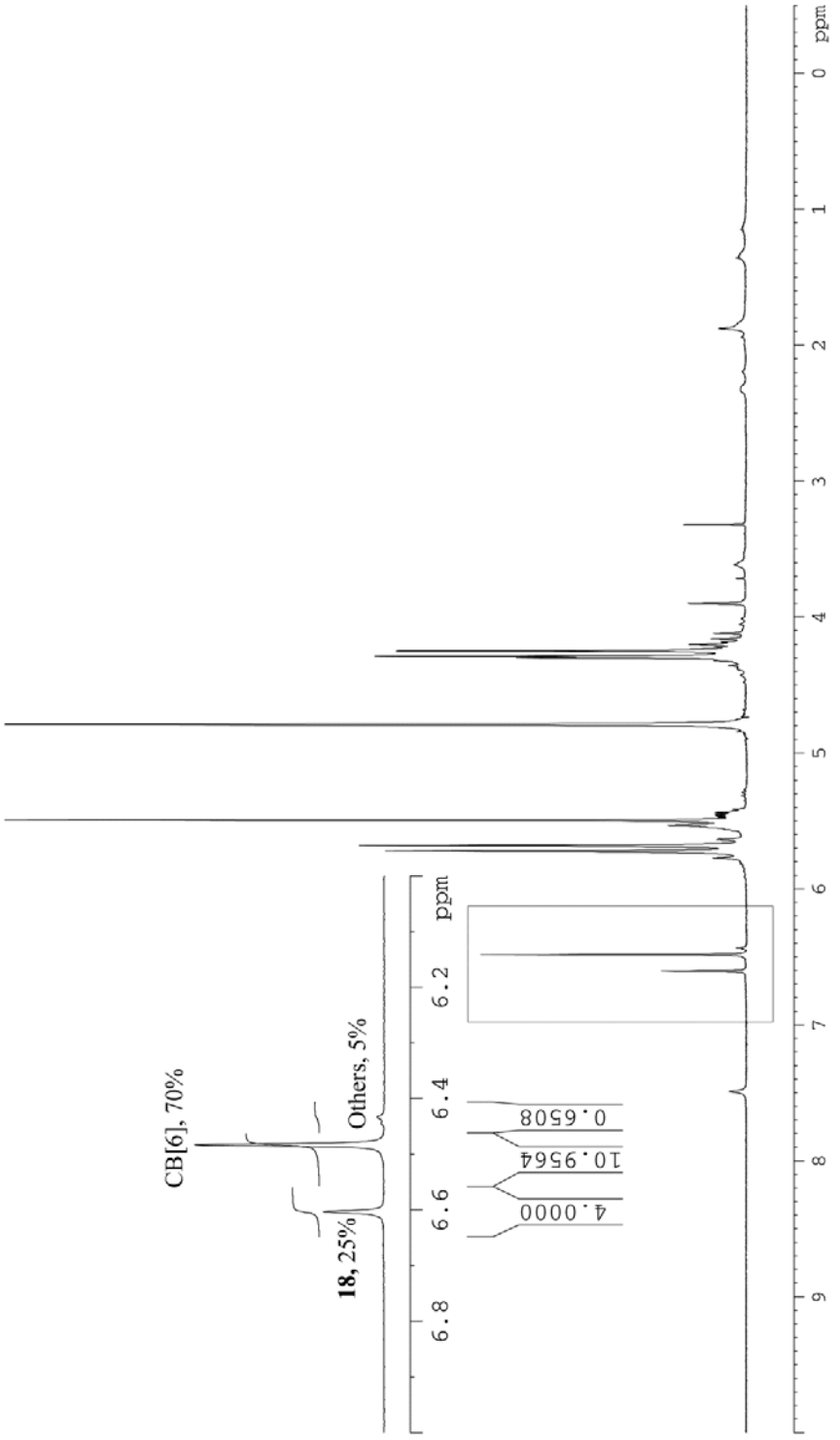


Figure S7. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the reaction between **1** and **12** in 9M H_2SO_4 without added KI in the presence of **3** as a probe. ^{1}H NMR integration of the **3** binding region (6-7 ppm) allows us to determine the contents of the crude mixture (25% **18**, 70% CB[6], 5% unidentified).

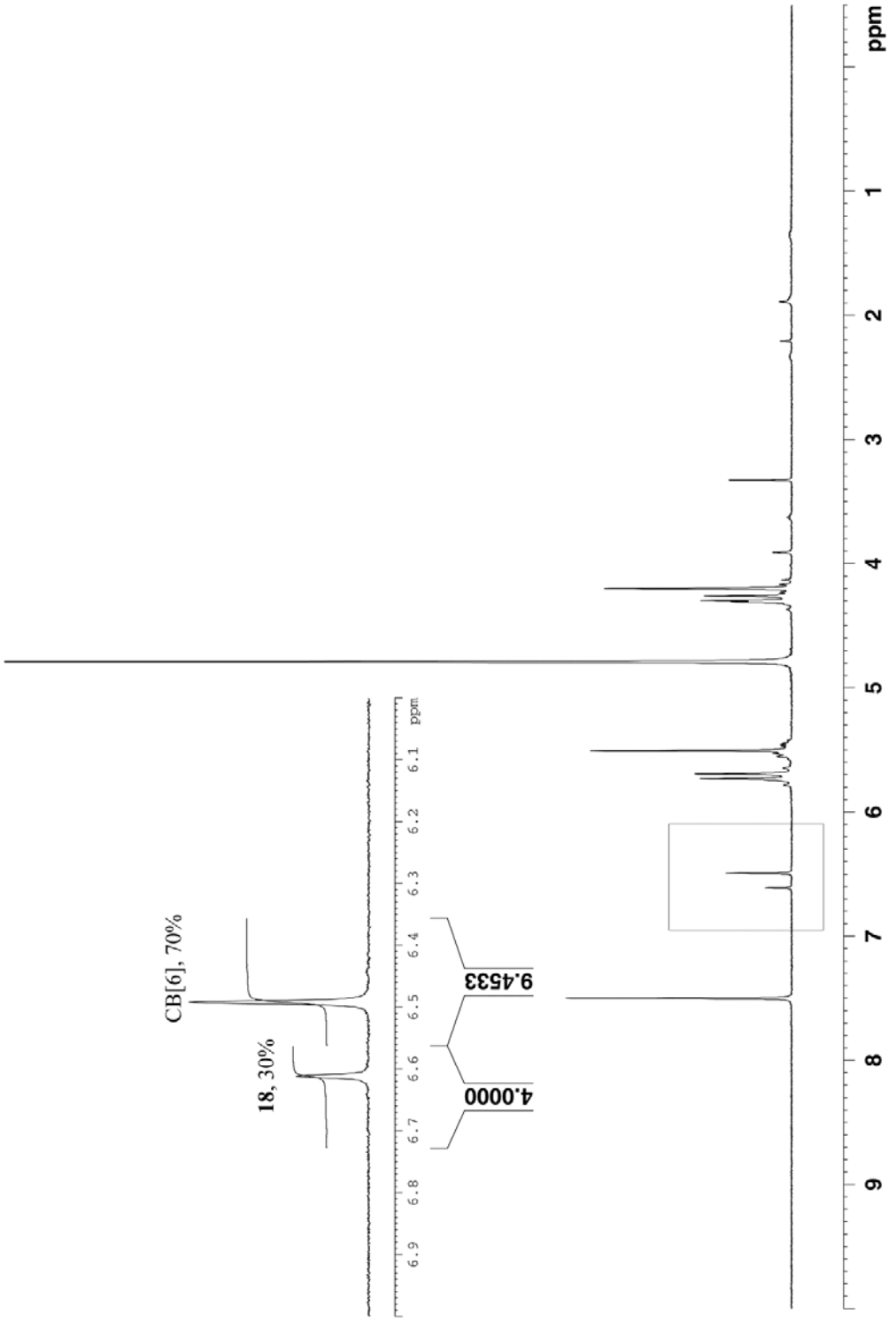


Figure S8. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the reaction between **1** and **12** in conc. HCl with KI as the template in the presence of **3** as a probe. ^{1}H NMR integration of the **3** binding region (6-7 ppm) allows us to determine the contents of the crude mixture (30% **18**, and 70% CB[6]).

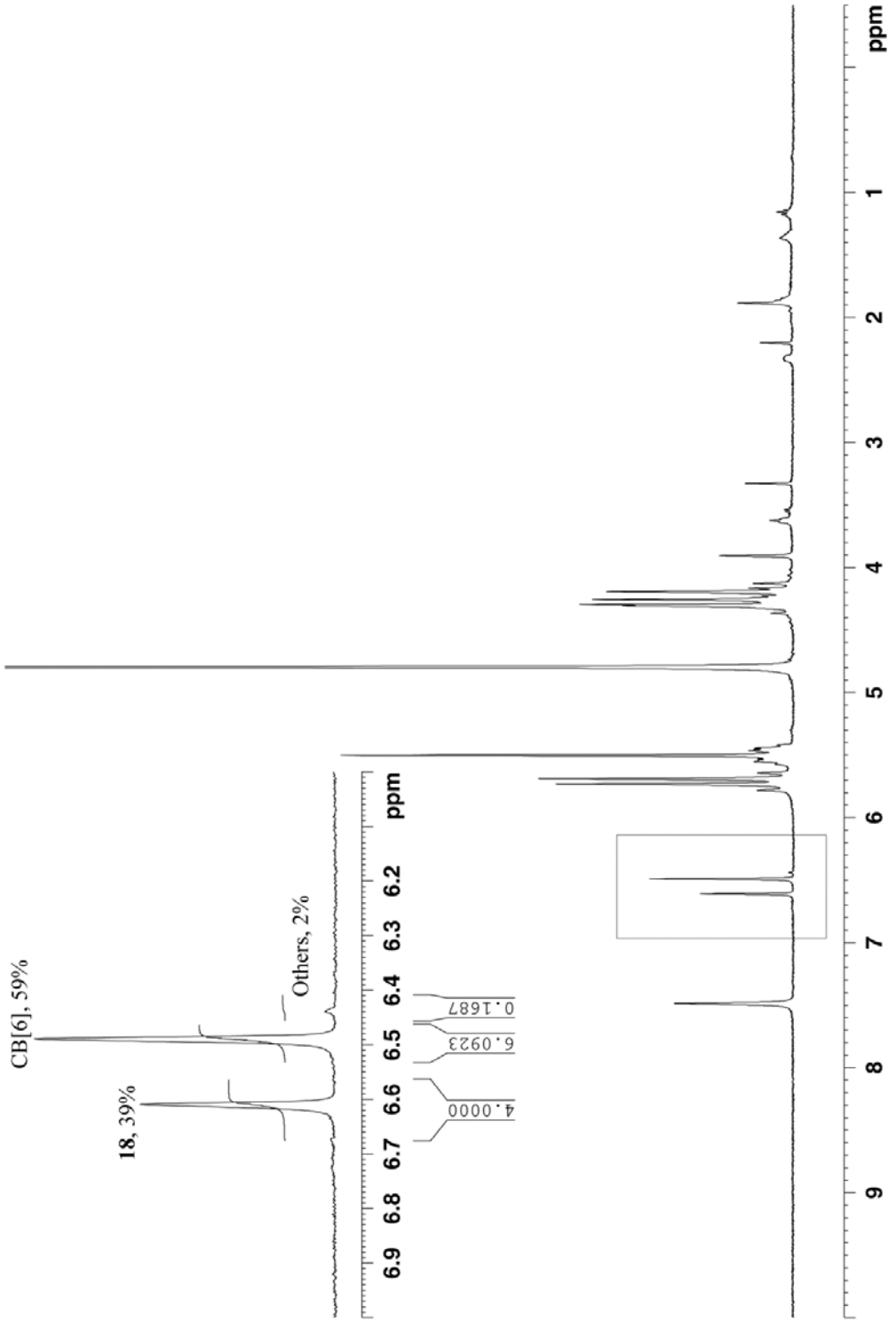


Figure S9. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for the crude reaction mixture from the reaction between **1** and **12** in conc. HCl without added KI in the presence of **3** as a probe. ^{1}H NMR integration of the **3** binding region (6-7 ppm) allows us to determine the contents of the crude mixture (39% of **18**, 59% of CB[6] and 2% unidentified).

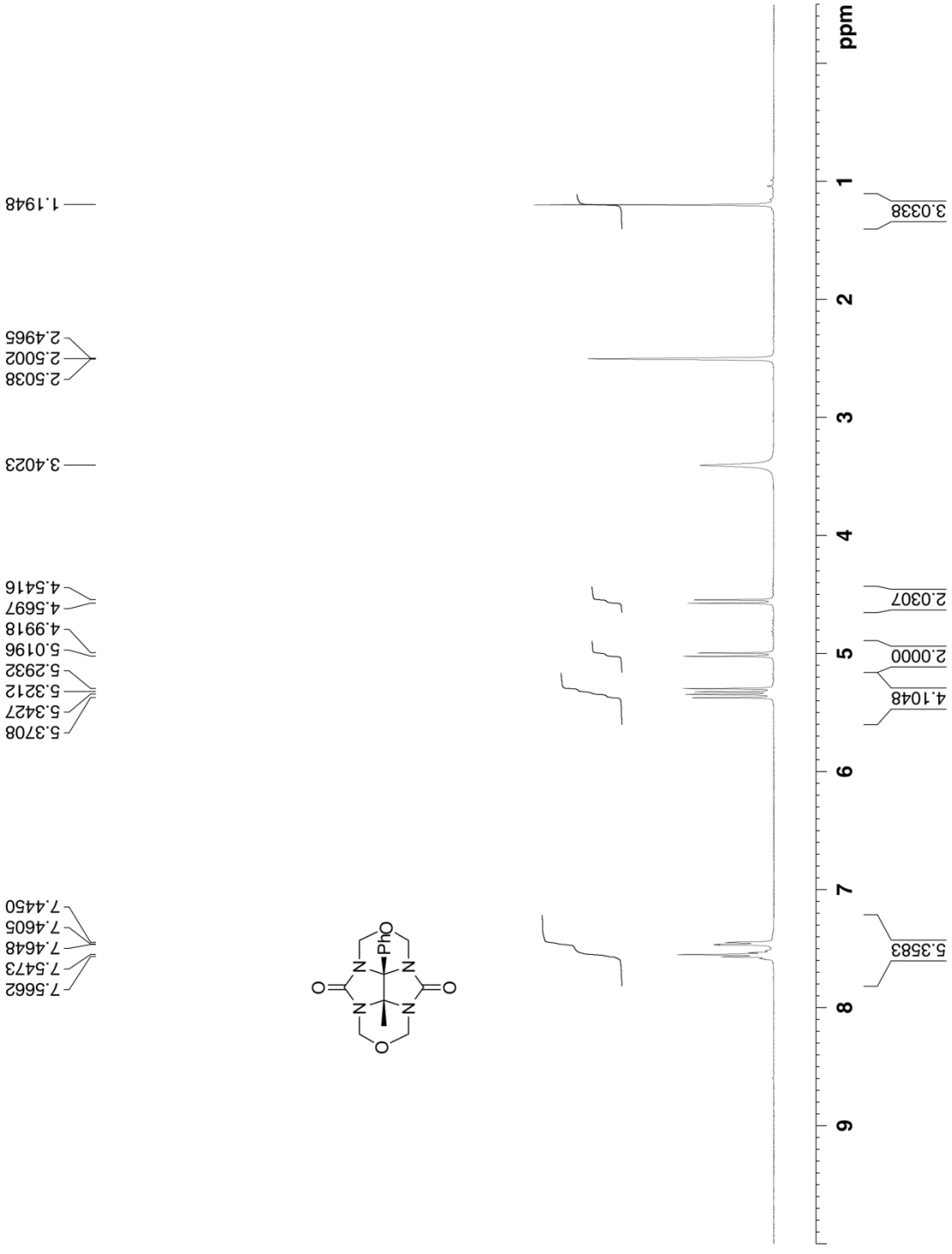


Figure S10. ^{1}H NMR spectra recorded (400 MHz, DMSO-d_6, RT) for compound $\mathbf{2}_{\mathrm{MePh}}$.

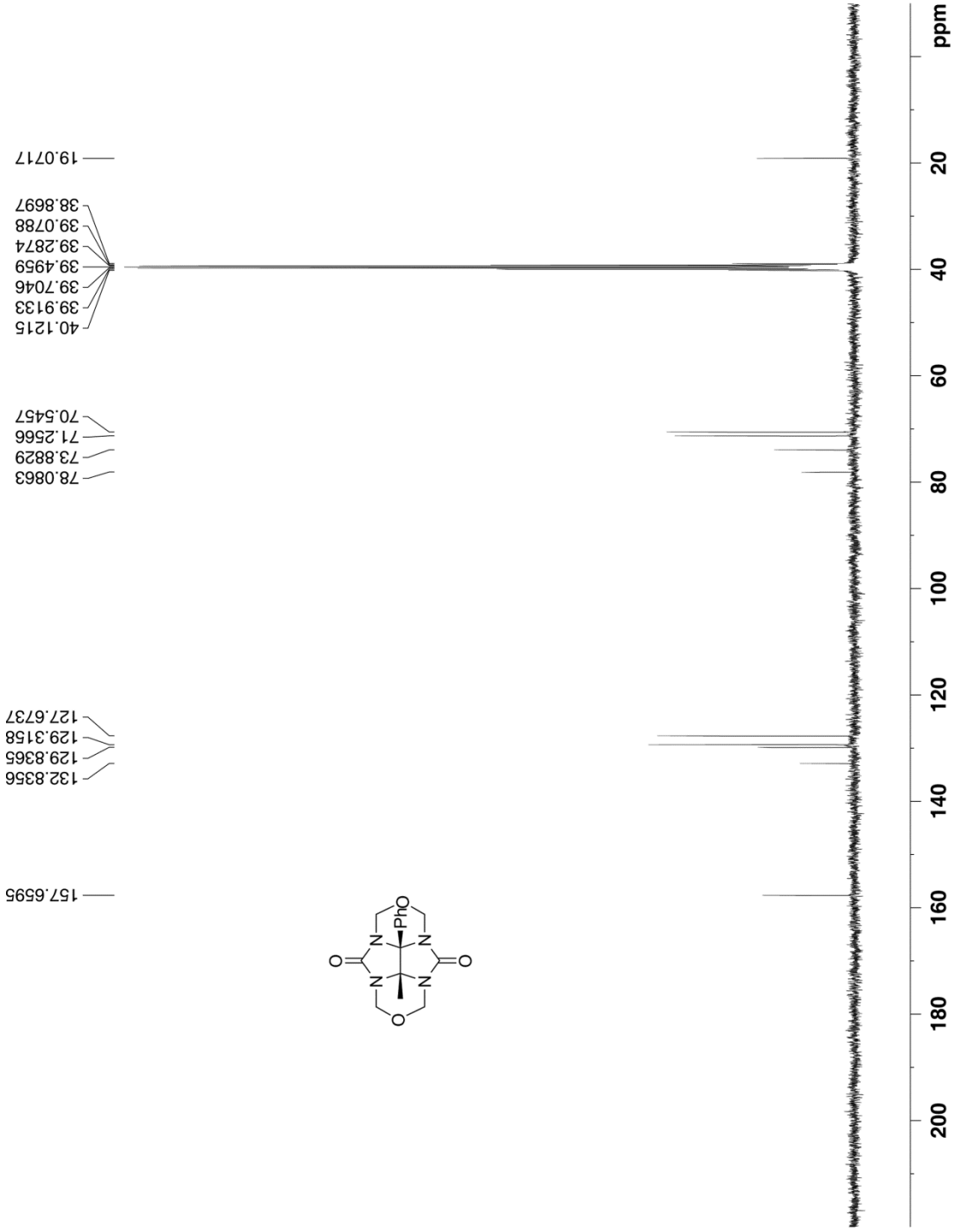


Figure S11. ^{13}C NMR spectra recorded (100 MHz, DMSO-d_6, RT) for compound $\mathbf{2}_{\mathrm{MePh}}$.

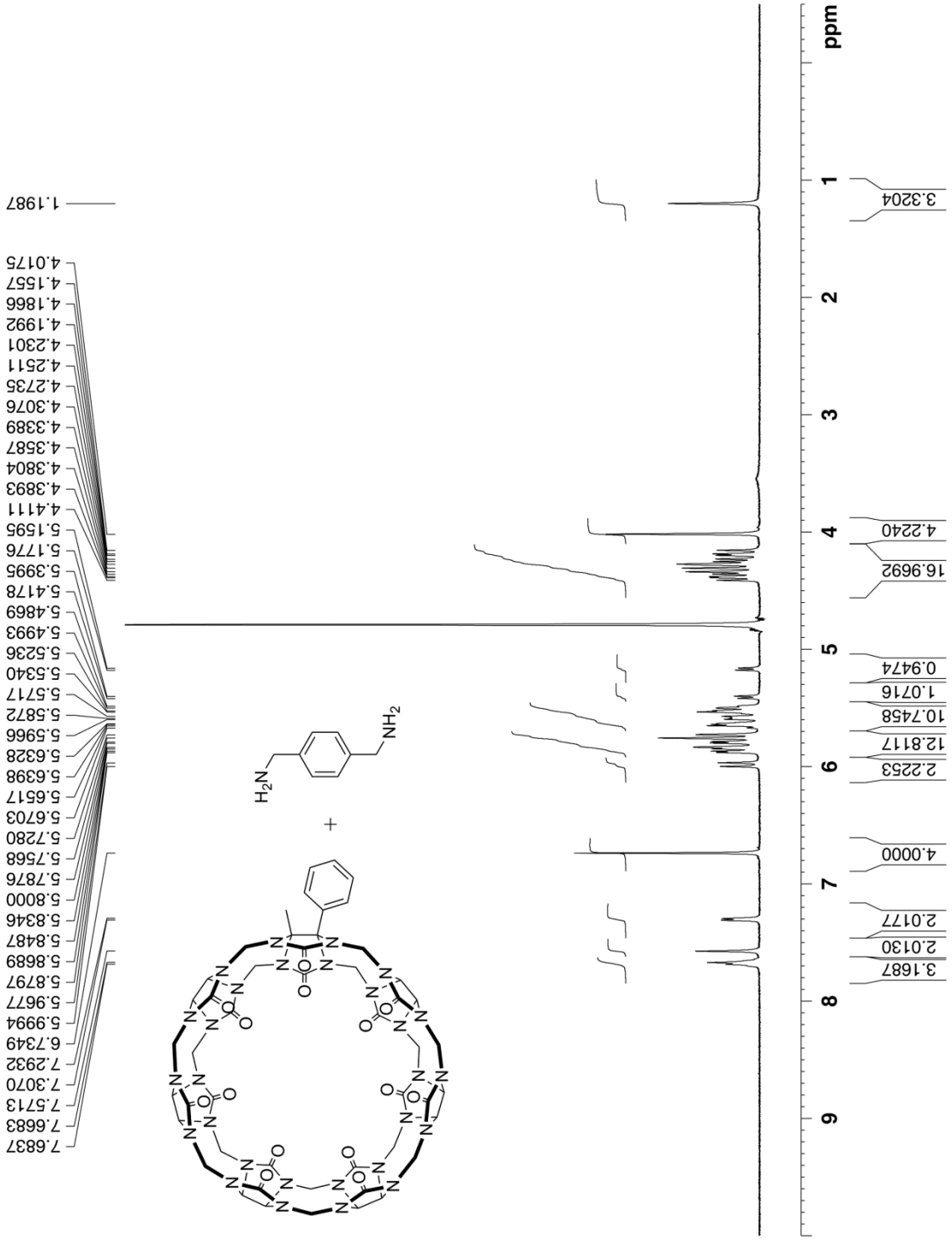


Figure S12. ^{1}H NMR spectra recorded (500 MHz, D_2O, RT) for MePhCB[7] and excess **3.**

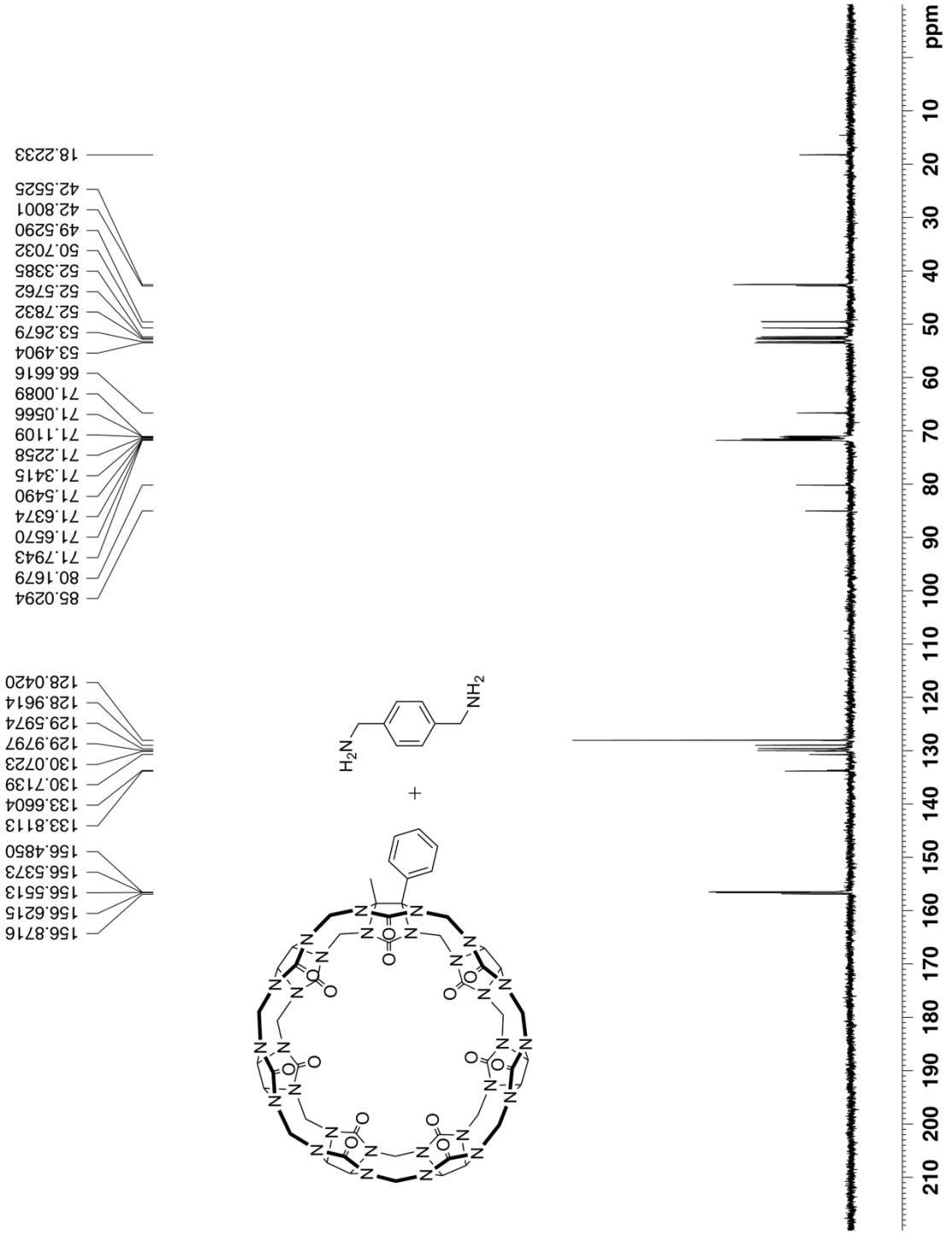


Figure S13. ^{13}C NMR spectrum recorded (125 MHz, D_2O, dioxane as internal reference, RT) for a mixture of MePhCB[7] and **3**.

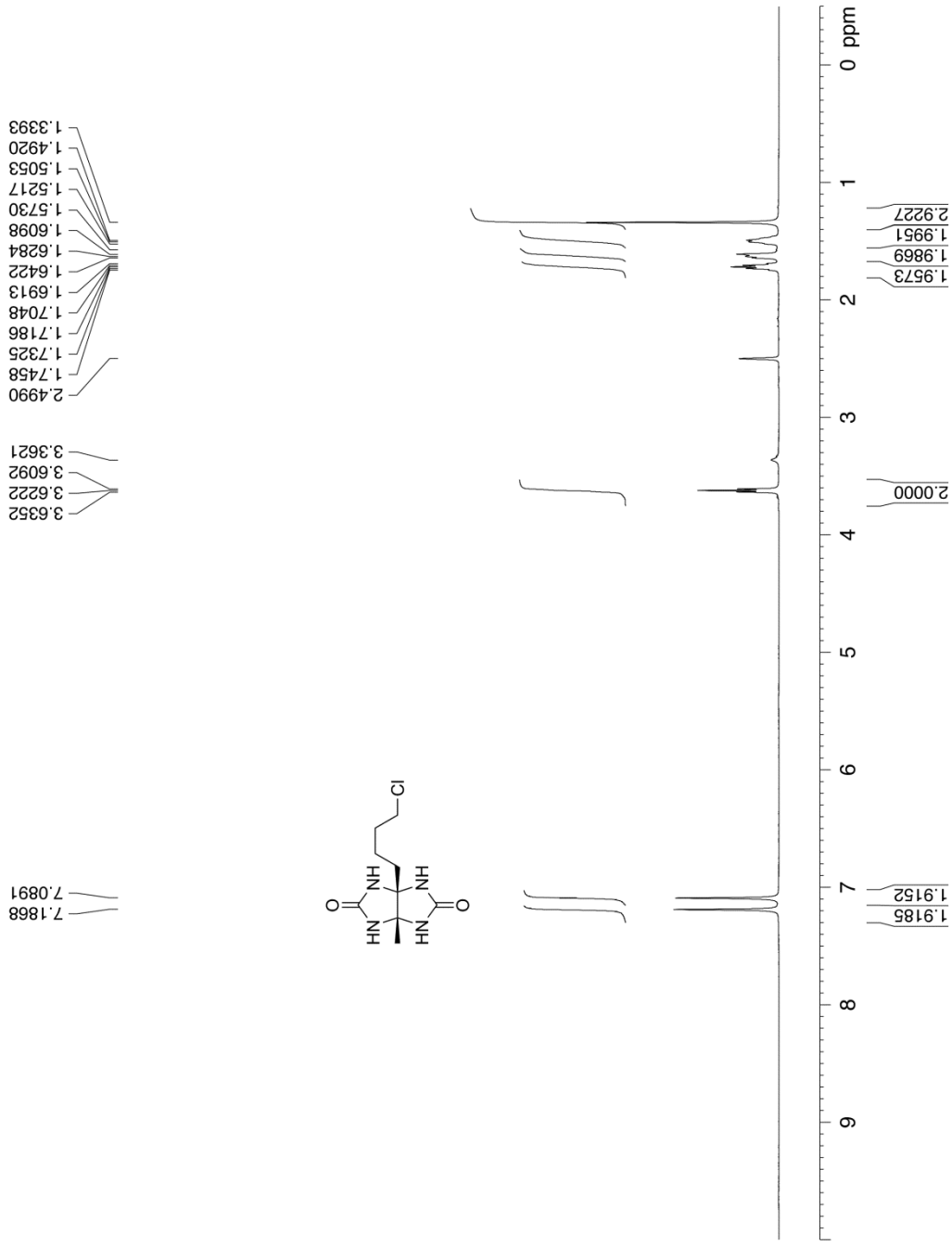


Figure S14. ^{1}H NMR spectra recorded (500 MHz, DMSO-d_6, RT) for compound **17**.

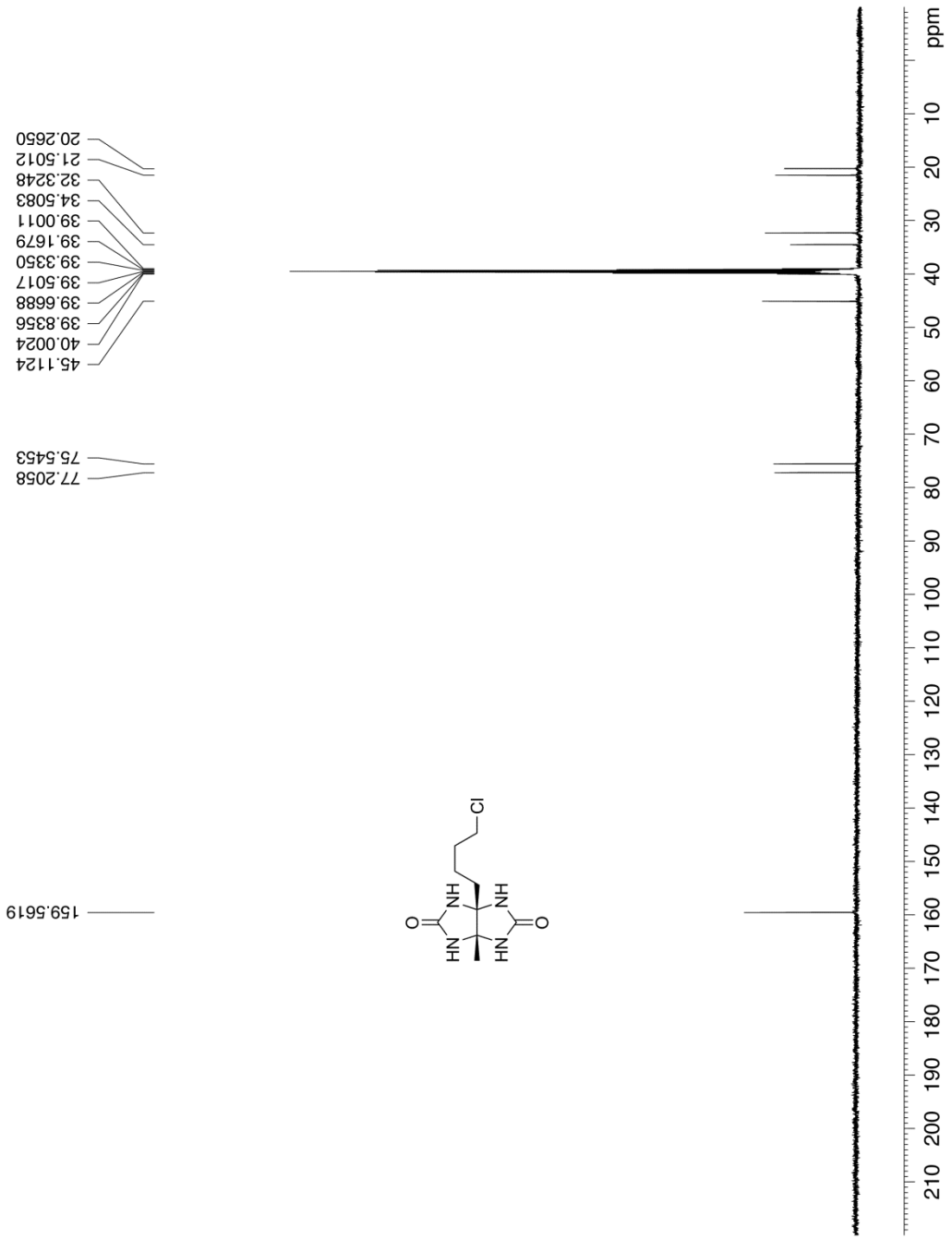


Figure S15. ^{13}C NMR spectra recorded (125 MHz, DMSO-d_6, RT) for compound **17.**

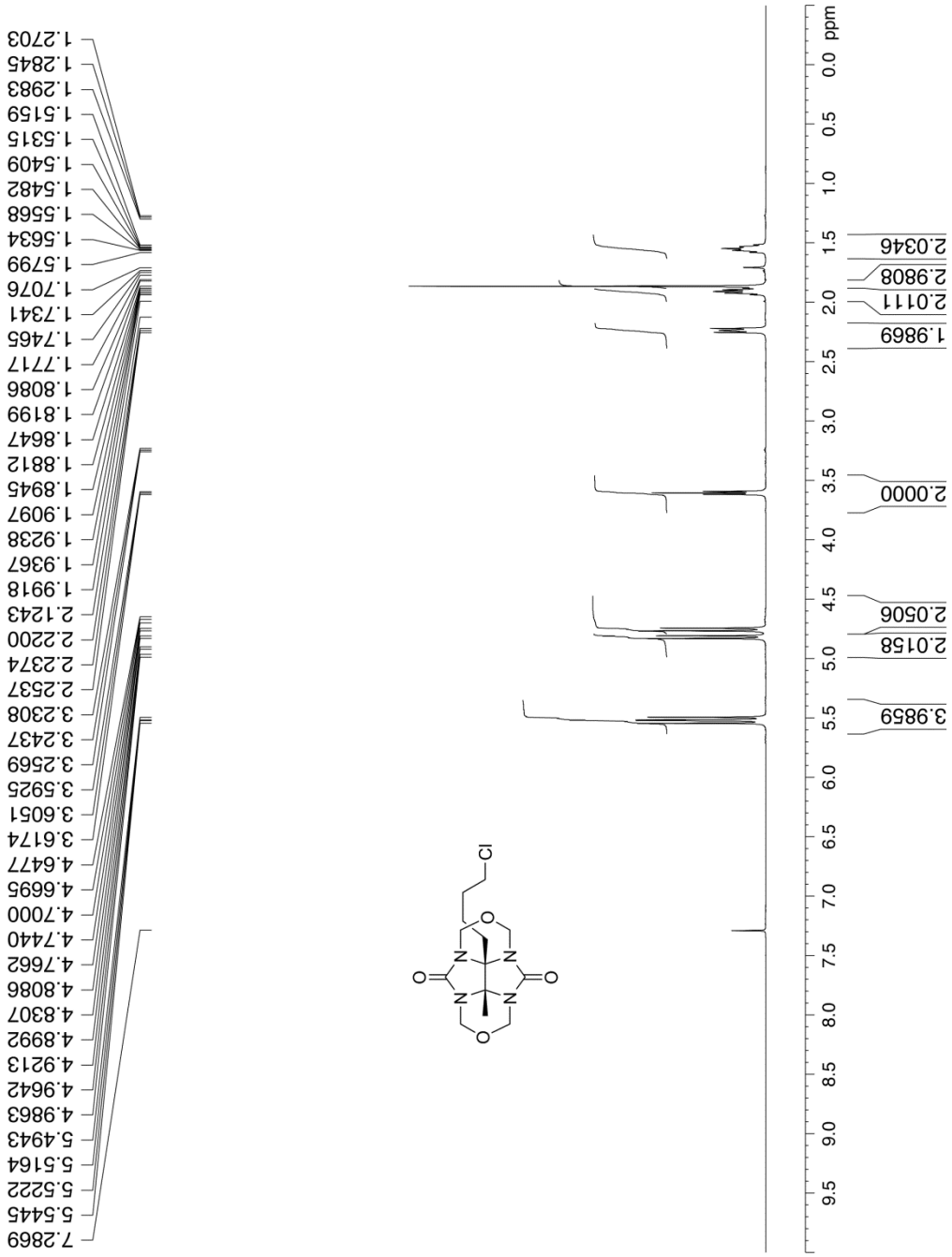


Figure S16. ^{1}H NMR spectra recorded (500 MHz, $CDCl_3$, RT) for compound **12.**

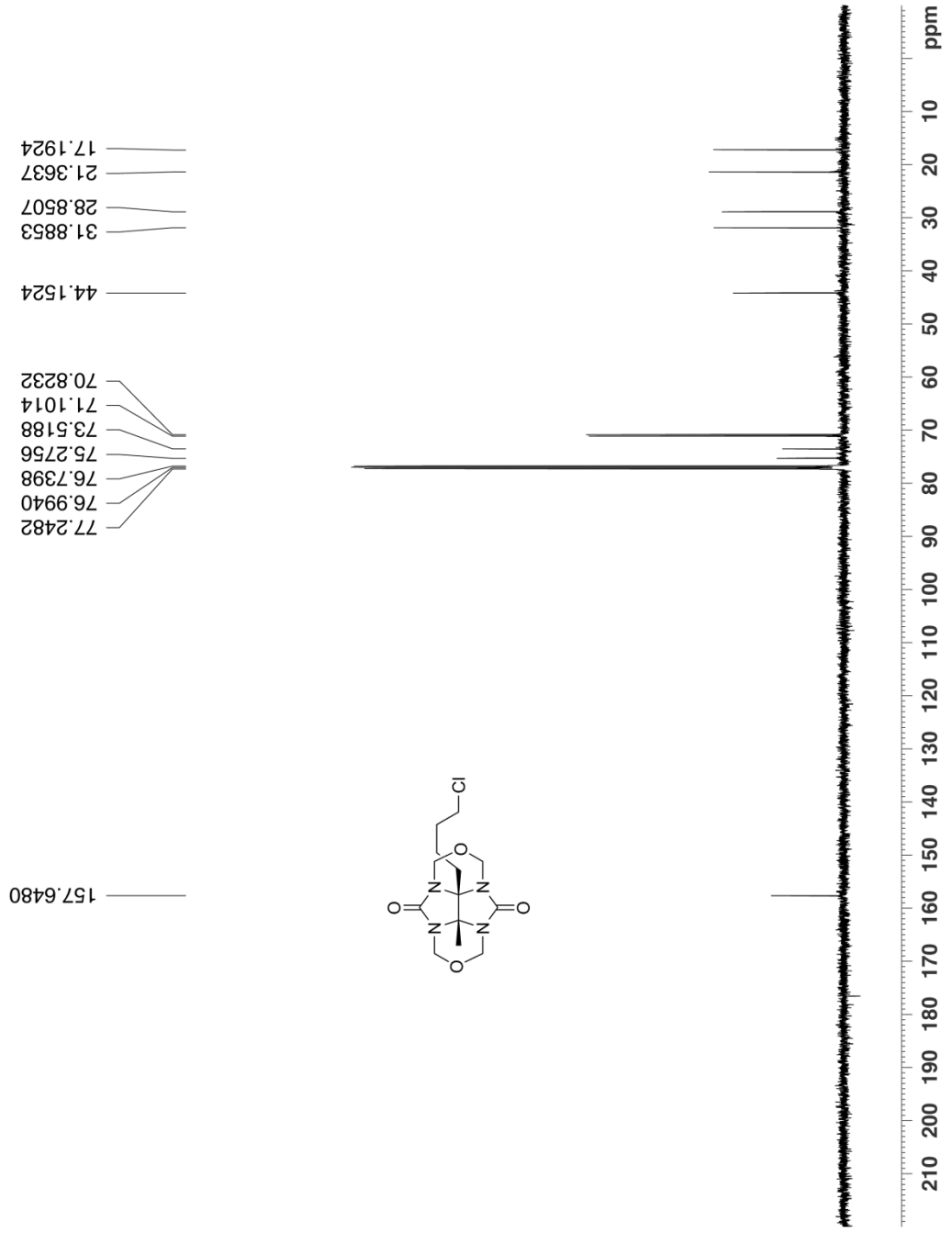


Figure S17. ^{13}C NMR spectra recorded (125 MHz, $CDCl_3$, RT) for compound **12.**

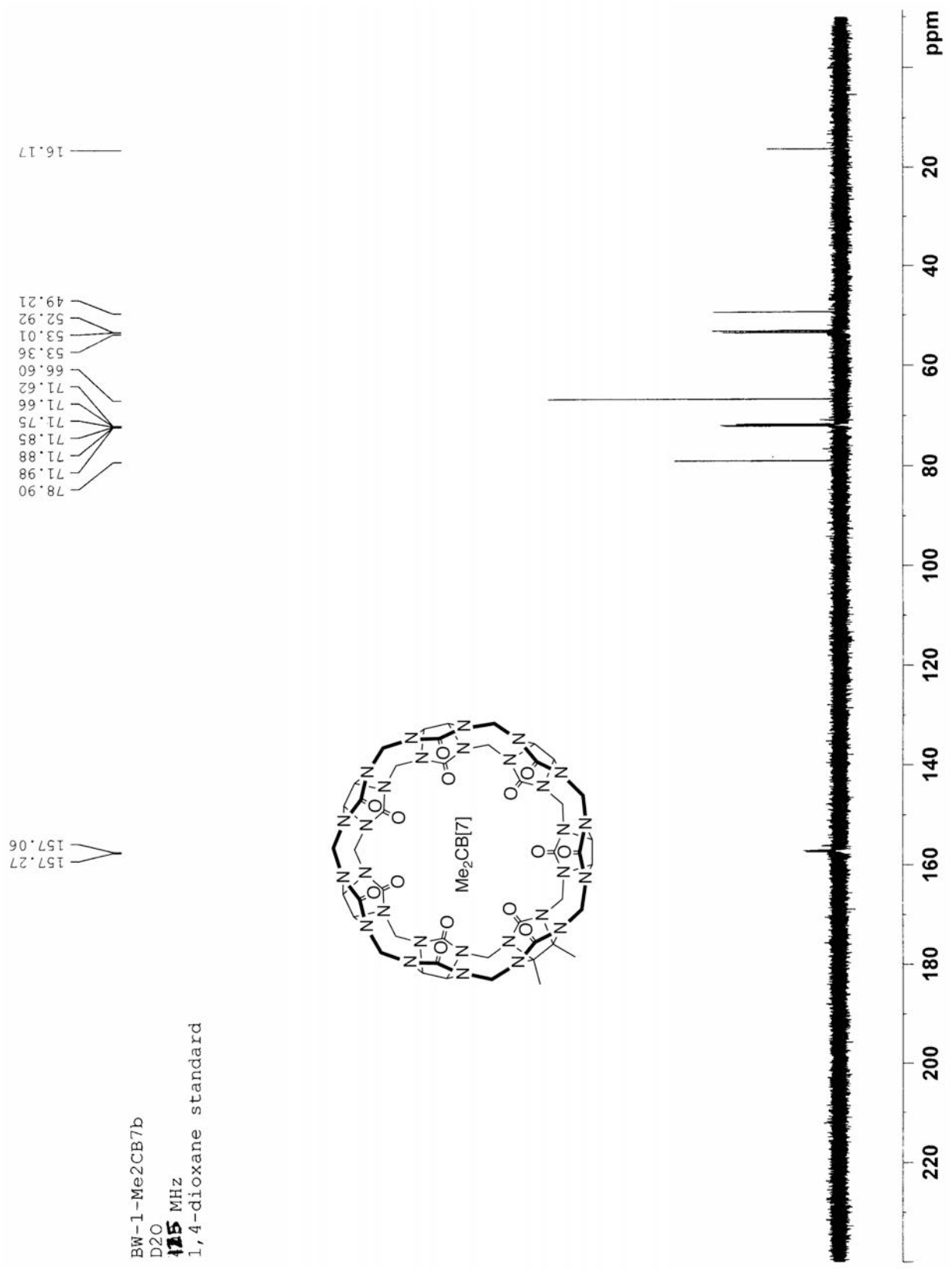


Figure S18. ^{13}C NMR spectra recorded (100 MHz, D_2O, RT) for $Me_2CB[7]$.

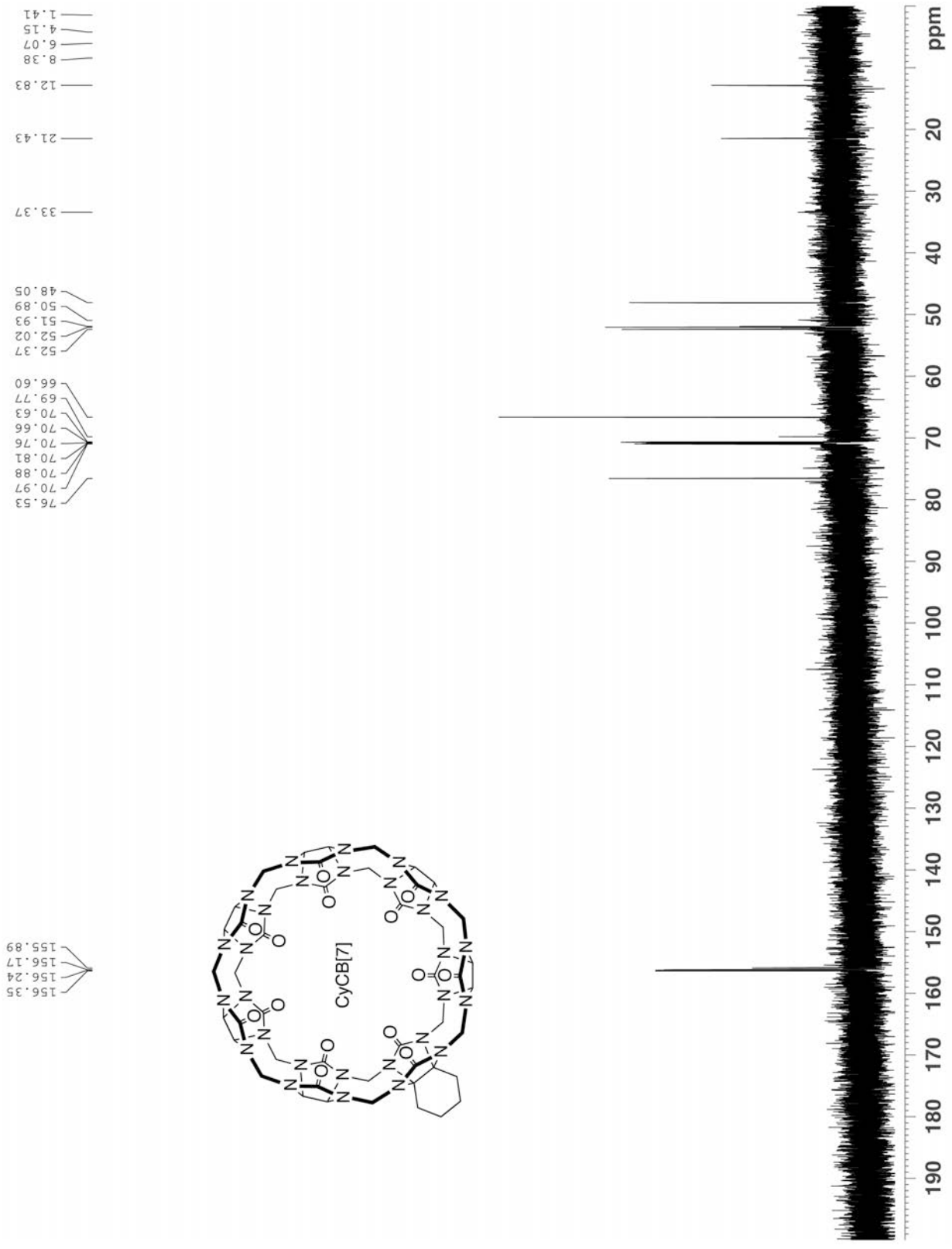


Figure S19. ^{13}C NMR spectra recorded (100 MHz, D_2O, RT) for CyCB[7].

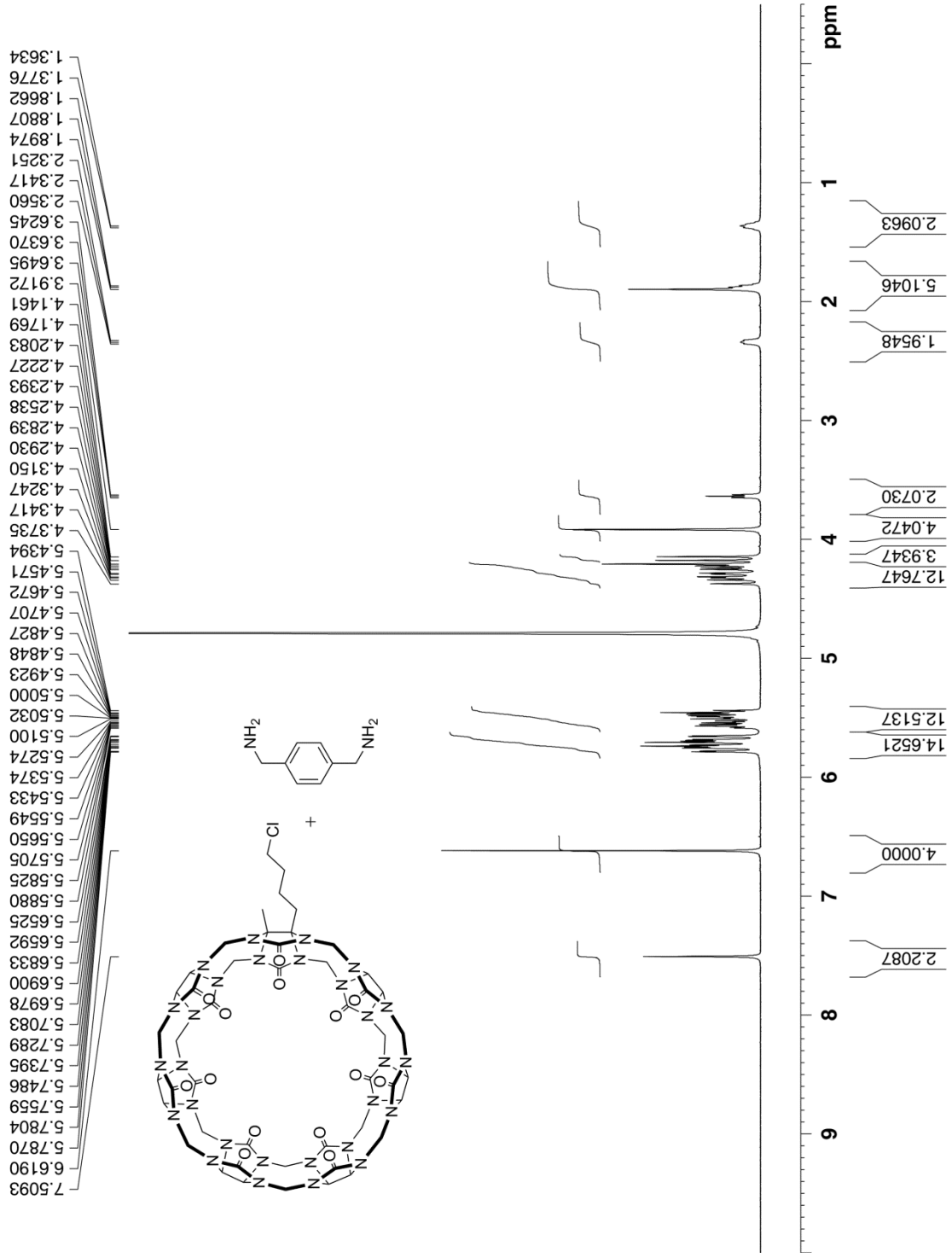


Figure S20. ^{1}H NMR spectra recorded (500 MHz, D_2O, RT) for **18** and excess **3.**

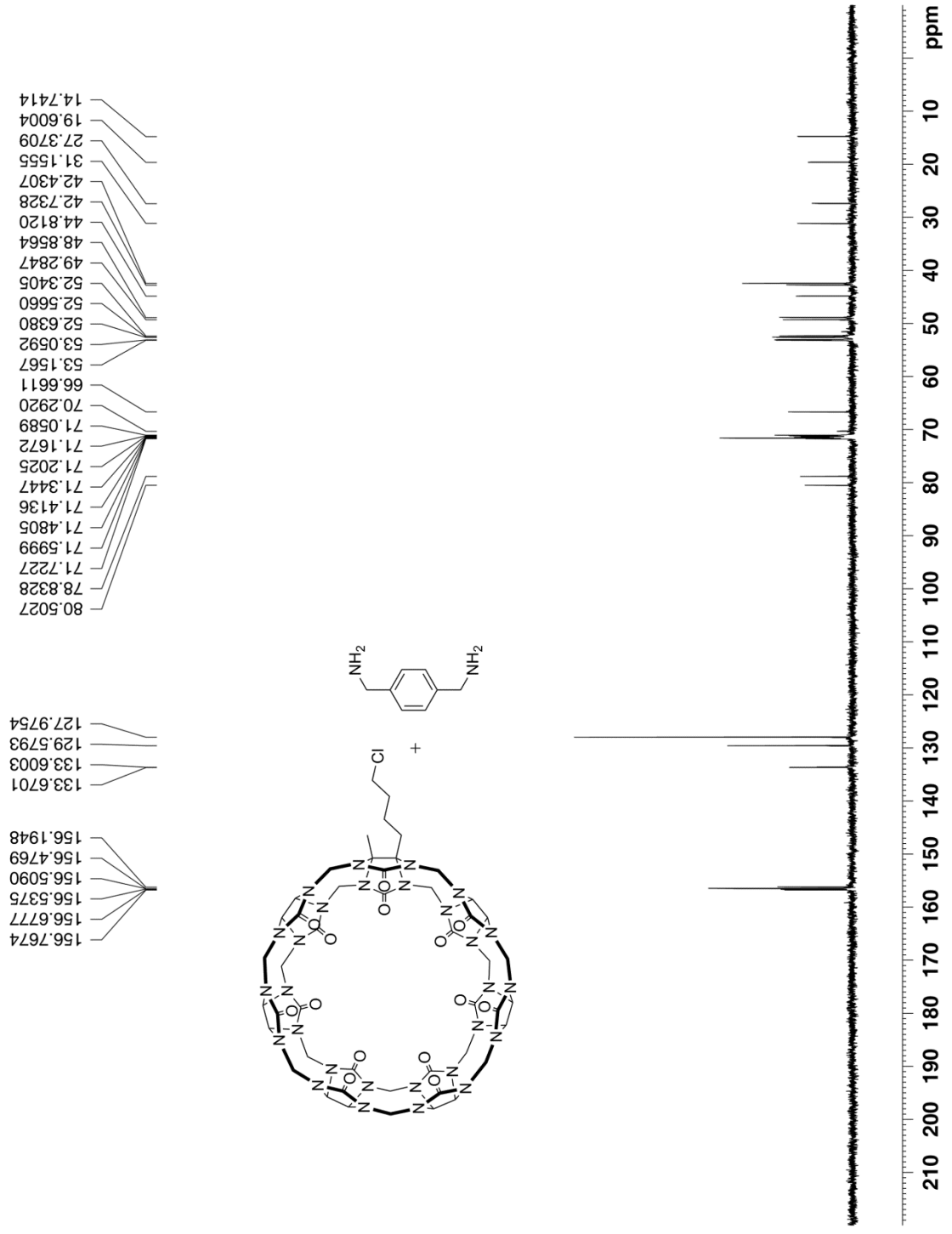


Figure S21. ^{13}C NMR spectra recorded (125 MHz, D_2O, RT) for **18•3.**

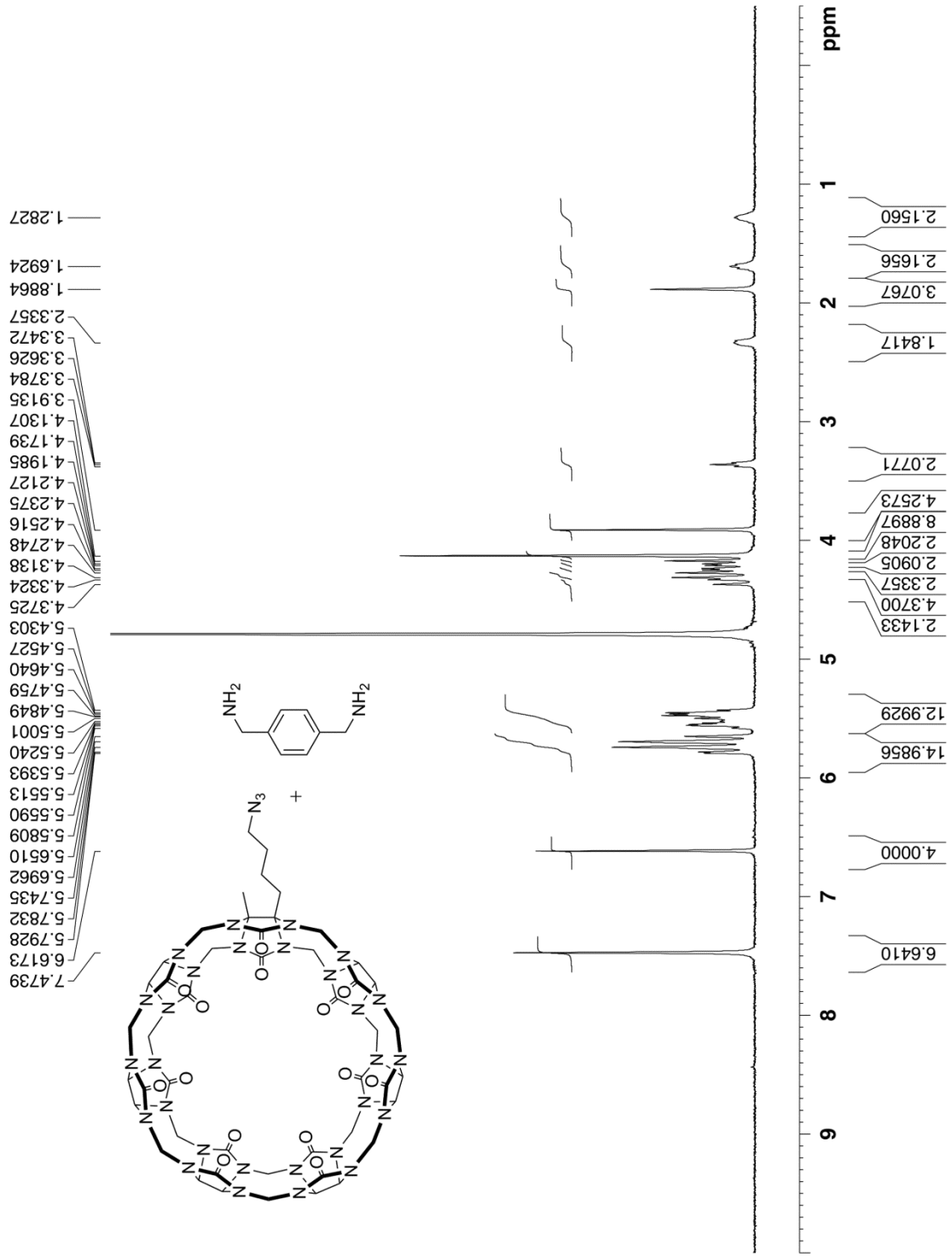


Figure S22. ^{1}H NMR spectrum recorded (400 MHz, D_2O, RT) for a mixture of **19** and excess **3**.

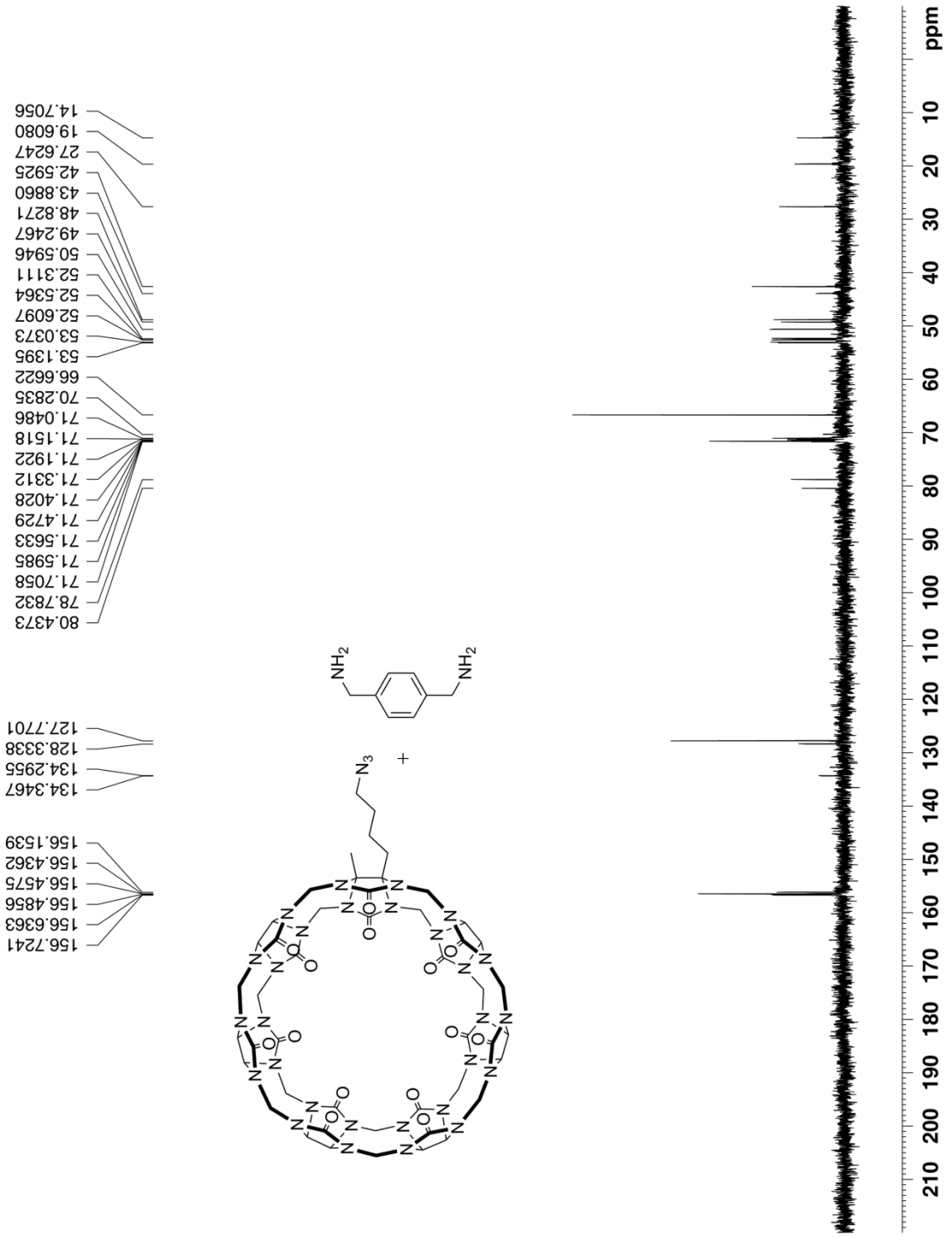


Figure S23. ^{13}C NMR spectrum recorded (125 MHz, D_2O, dioxane as internal reference, RT) for a mixture of **19** and **3**.

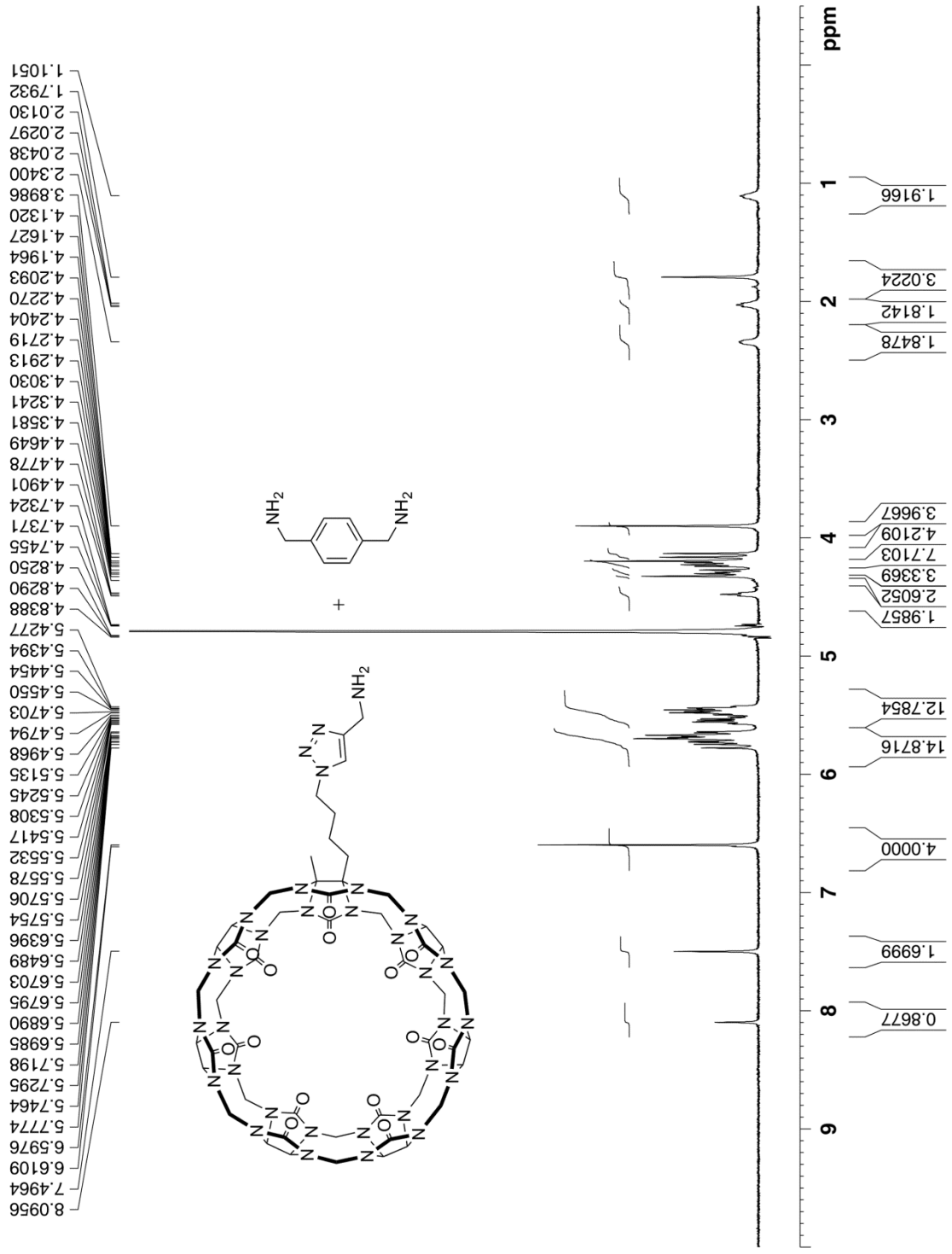


Figure S24. ^{1}H NMR spectrum recorded (500 MHz, D_2O, RT) for a mixture of **20** and excess **3**.

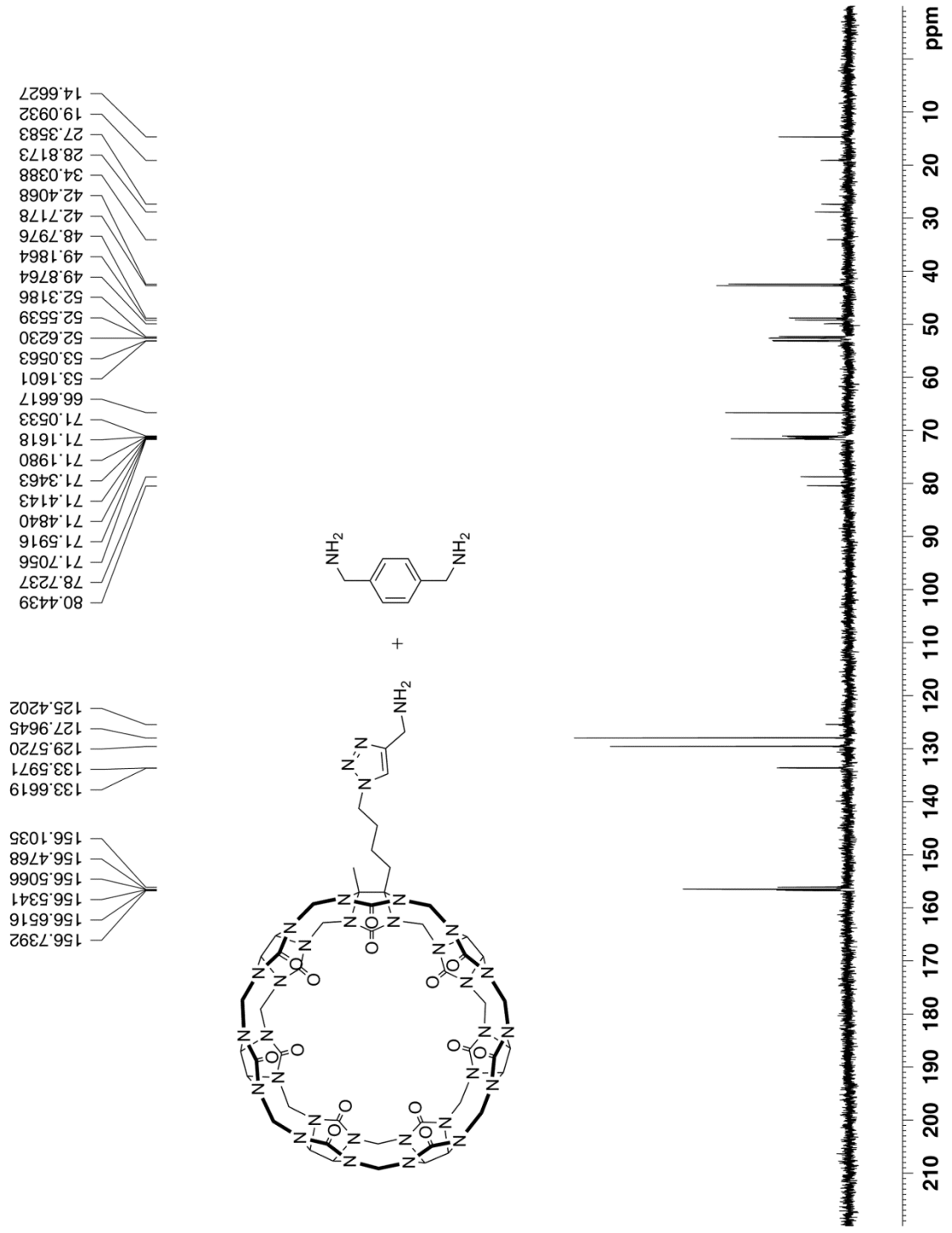
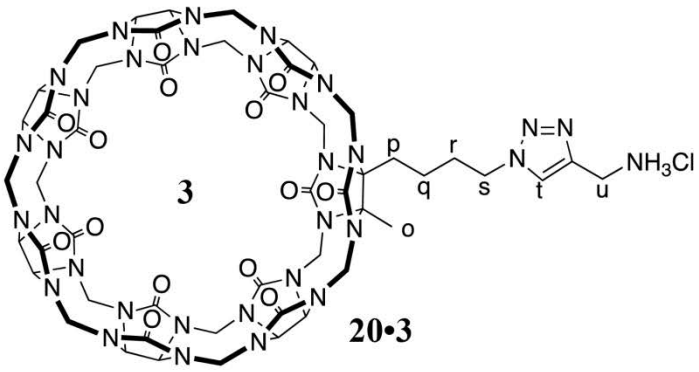


Figure S25. ^{13}C NMR spectrum recorded (125 MHz, D_2O, dioxane as internal reference, RT) for a mixture of **20** and **3**.



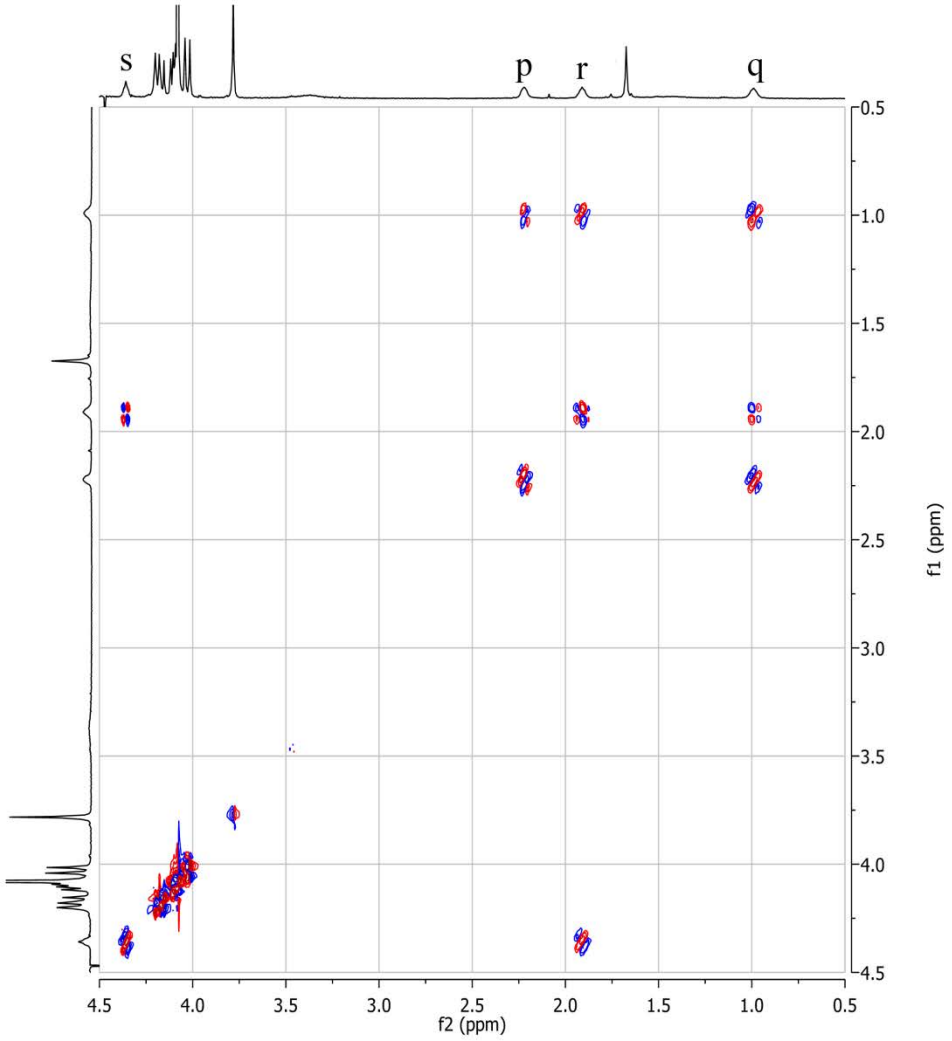


Figure S26. Partial DQCOSY ^{1}H NMR spectrum recorded (600 MHz, D_2O, RT) for the monomeric complex **20•3**.

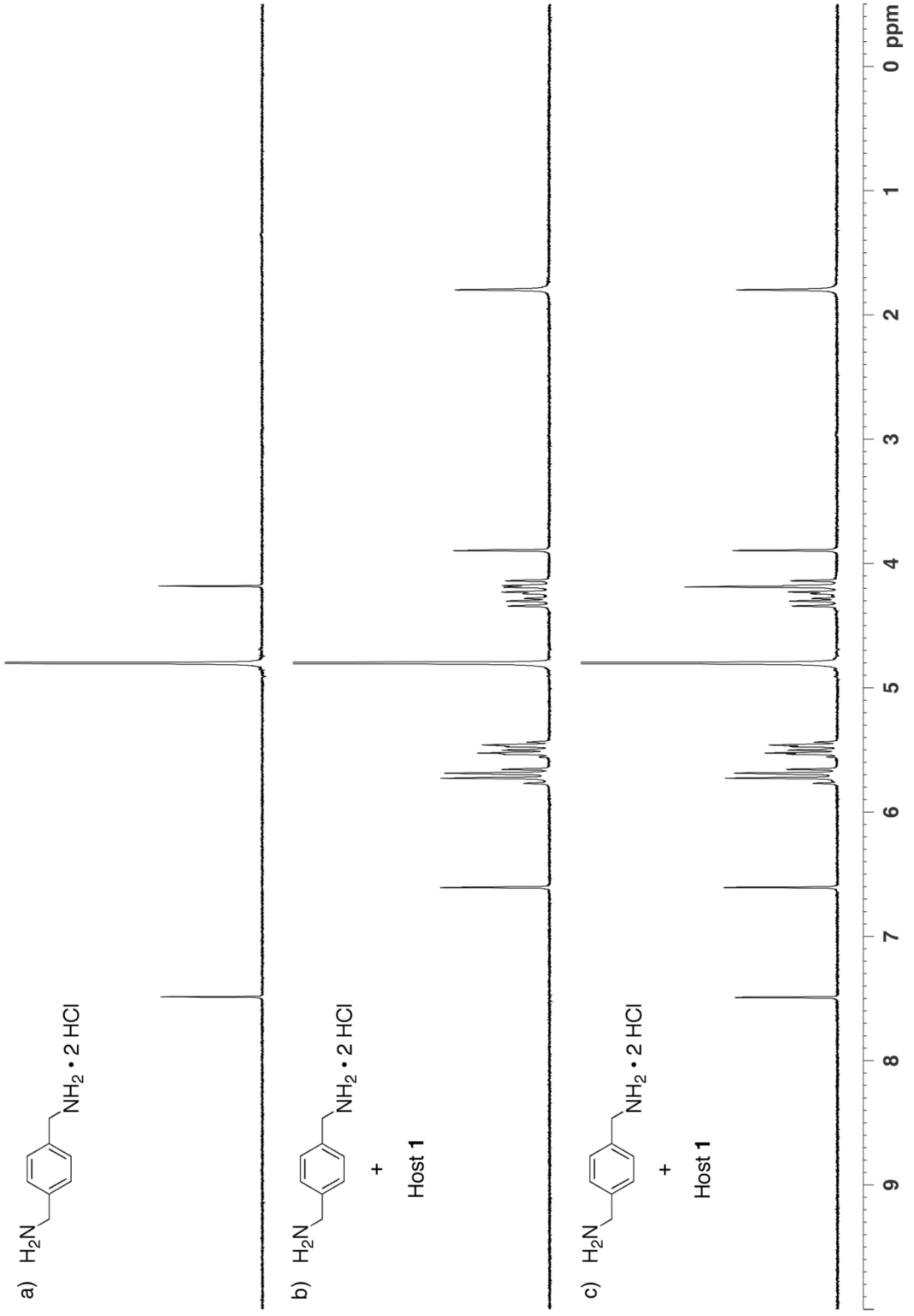


Figure S27. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **3** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **3** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **3** (1 mM). (Host1 = $Me_2CB[7]$)

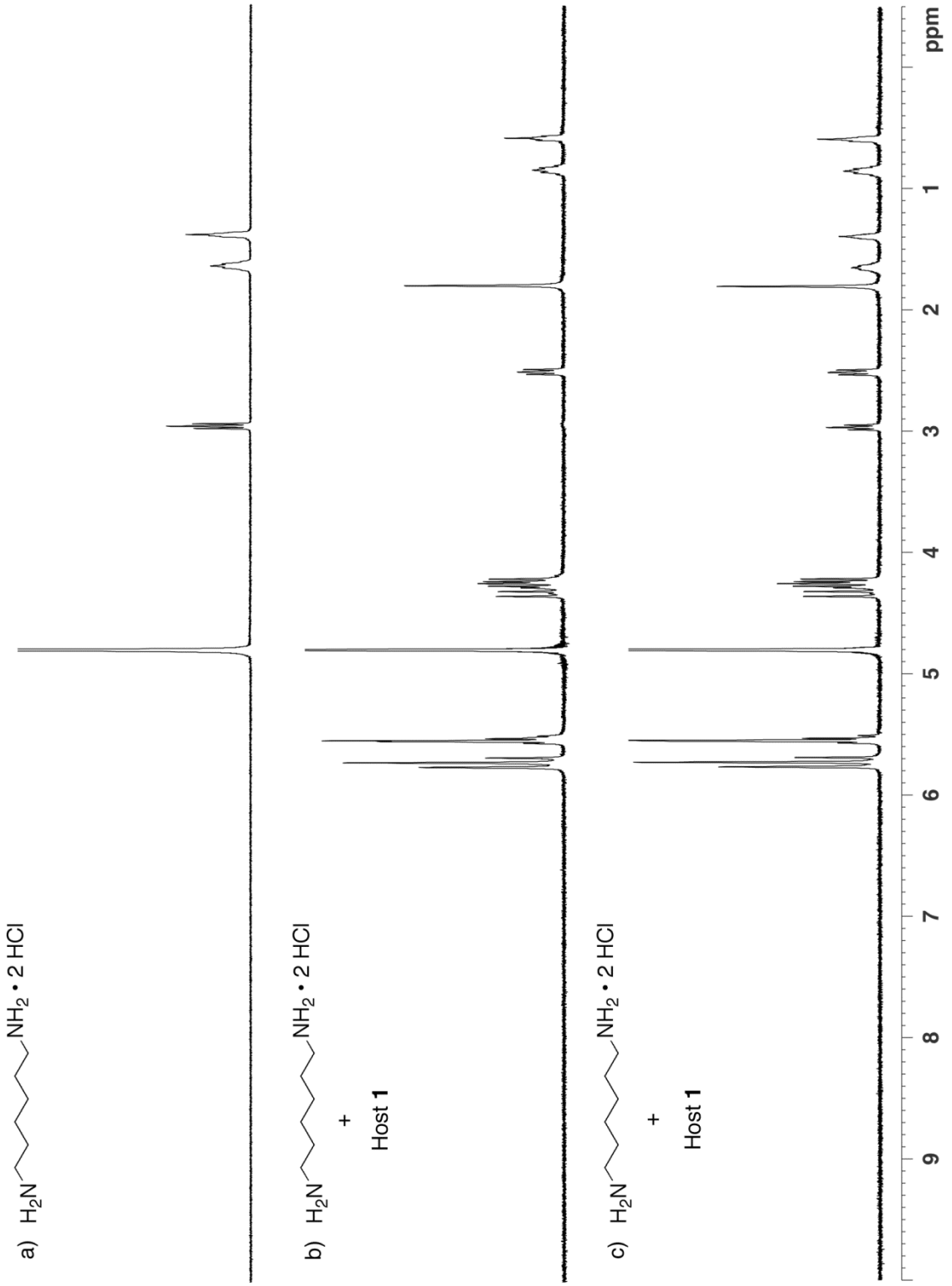


Figure S28. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **4** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **4** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **4** (1 mM). (Host1 = $Me_2CB[7]$)

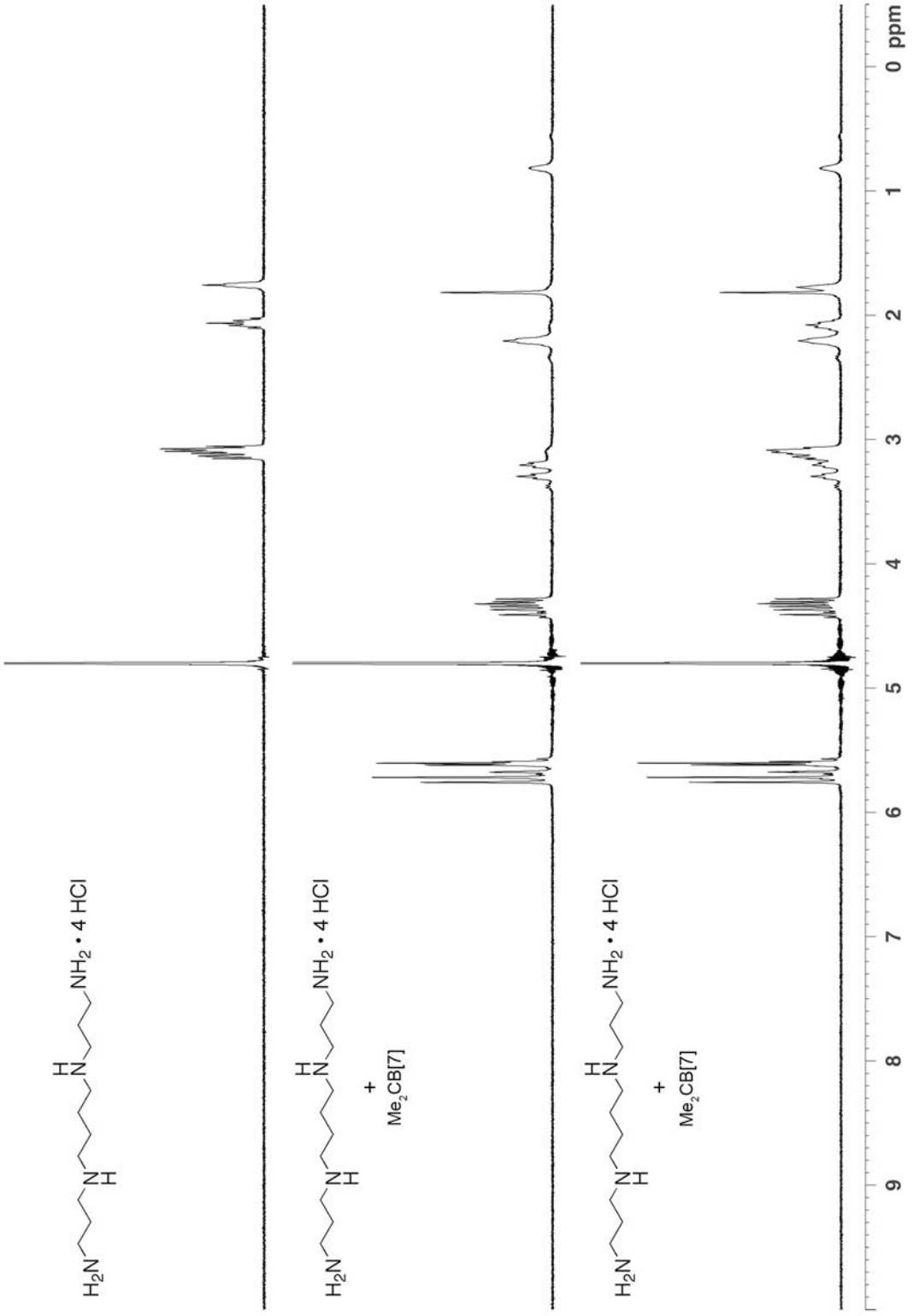


Figure S29. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for: a) **5** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **5** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **5** (1 mM).

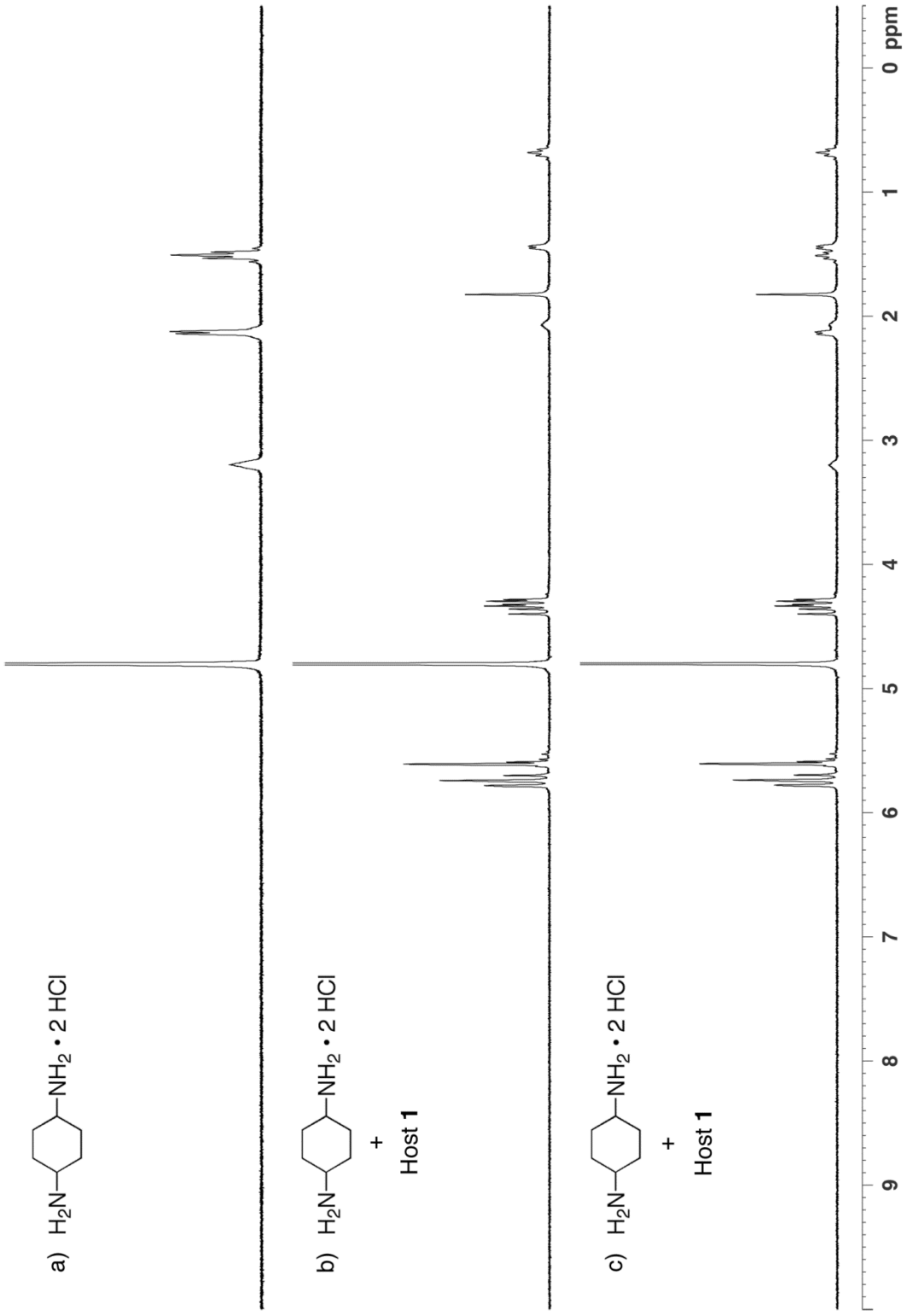


Figure S30. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **7** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **7** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **7** (1 mM). (Host1 = $Me_2CB[7]$)

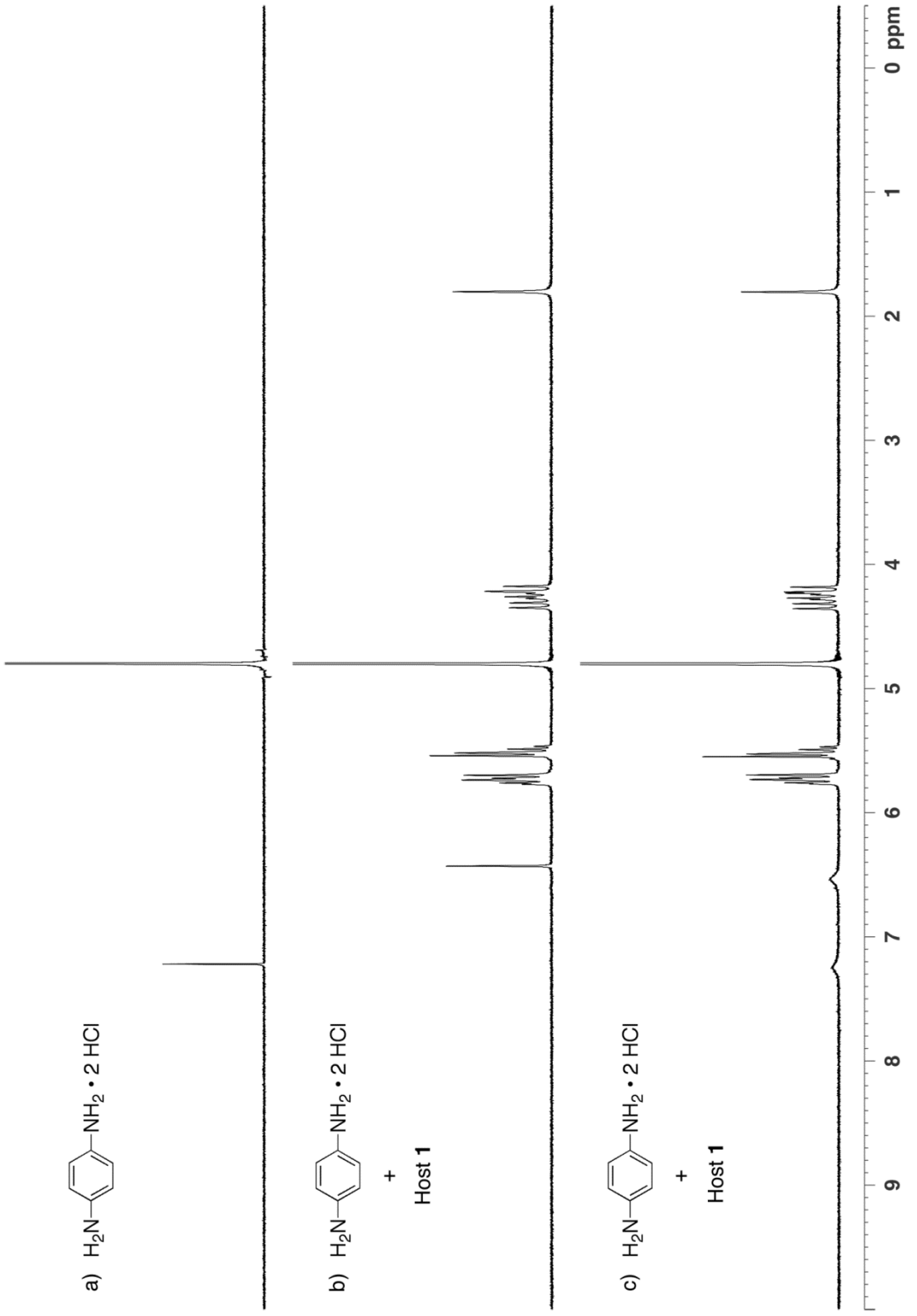


Figure S31. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **6** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **6** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **6** (1 mM). (Host1 = $Me_2CB[7]$)

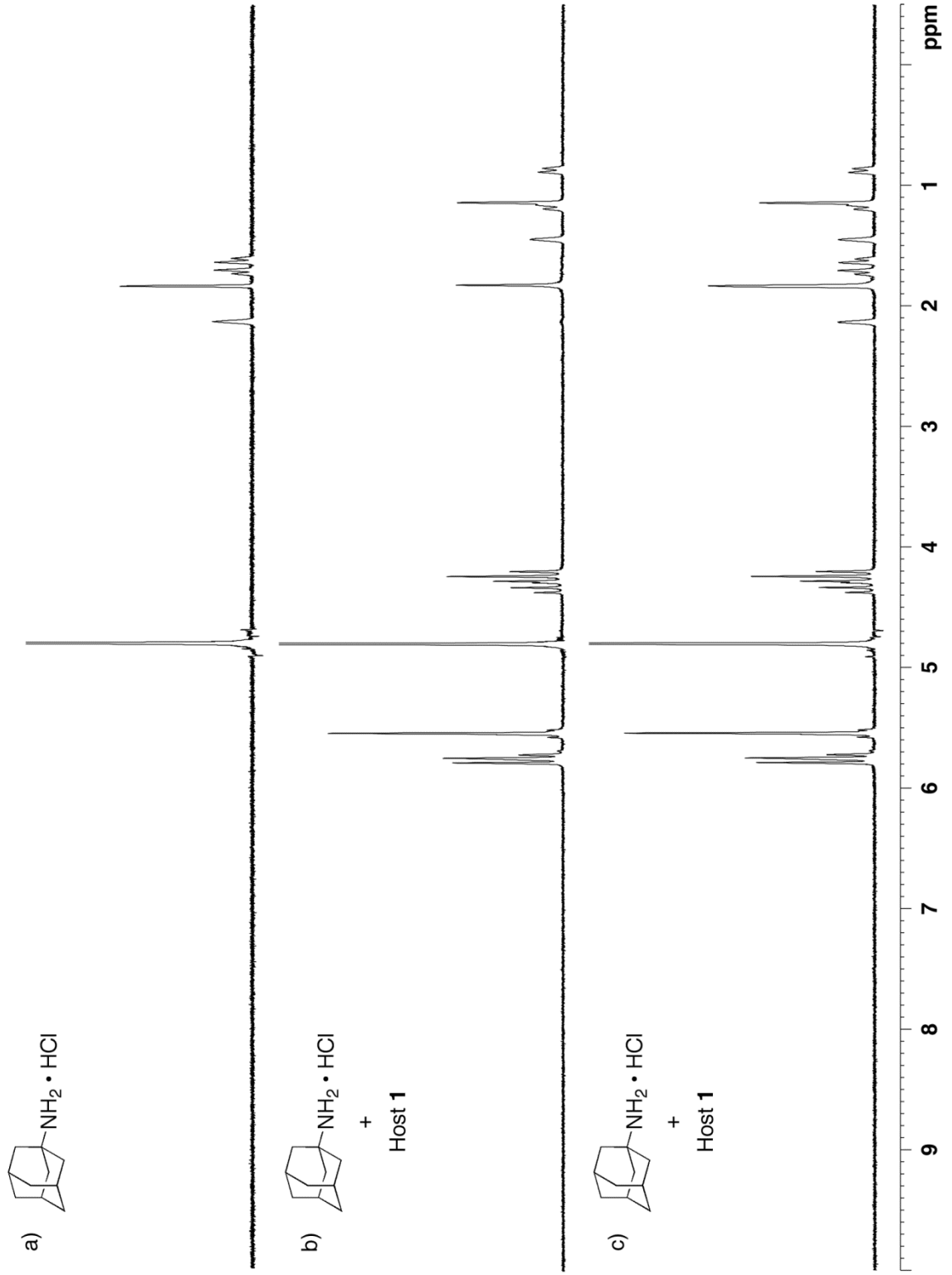


Figure S32. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **9** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **9** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **9** (1 mM). (Host1 = $Me_2CB[7]$)

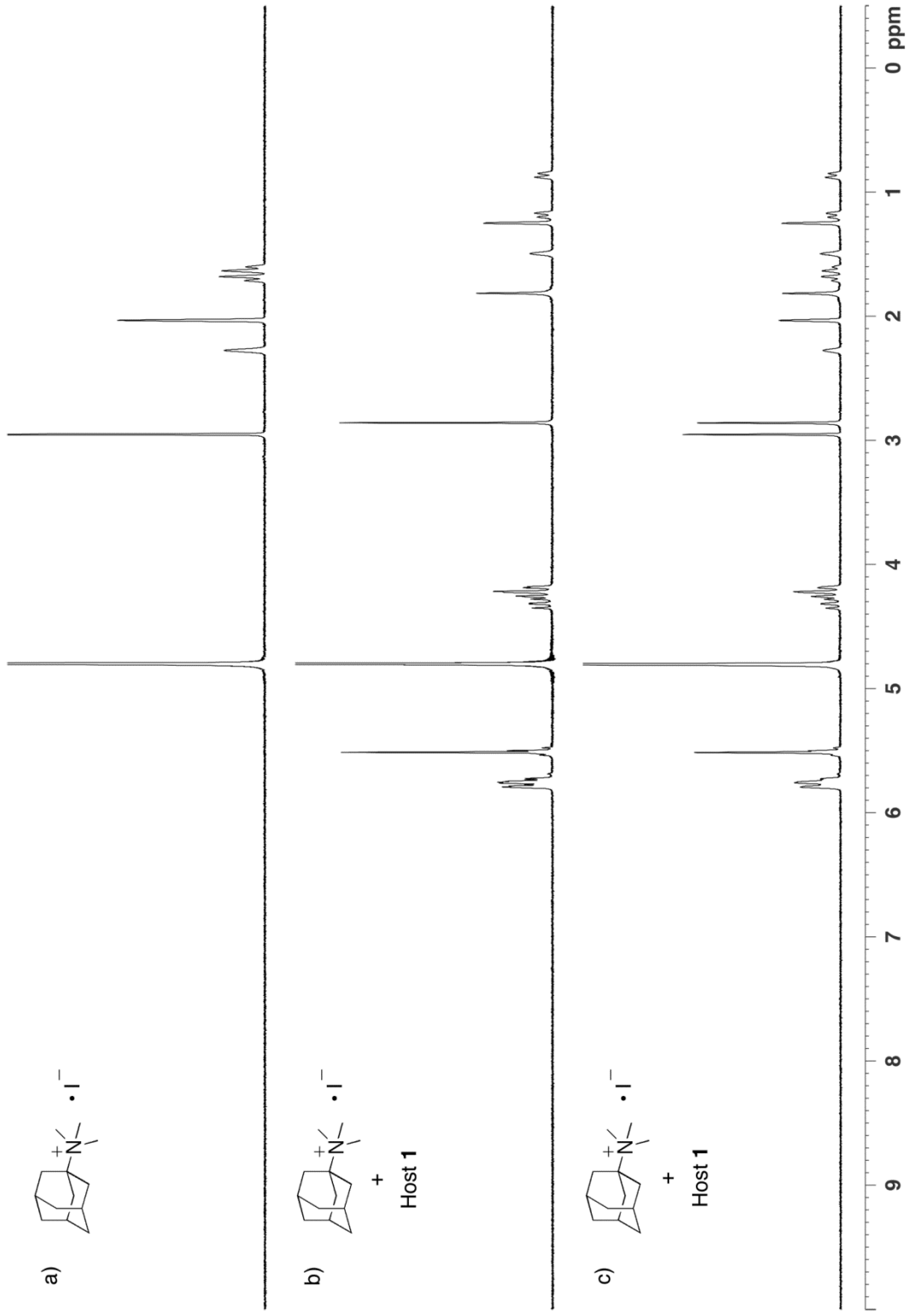


Figure S33. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **10** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **10** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **10** (1 mM). (Host1 = $Me_2CB[7]$)

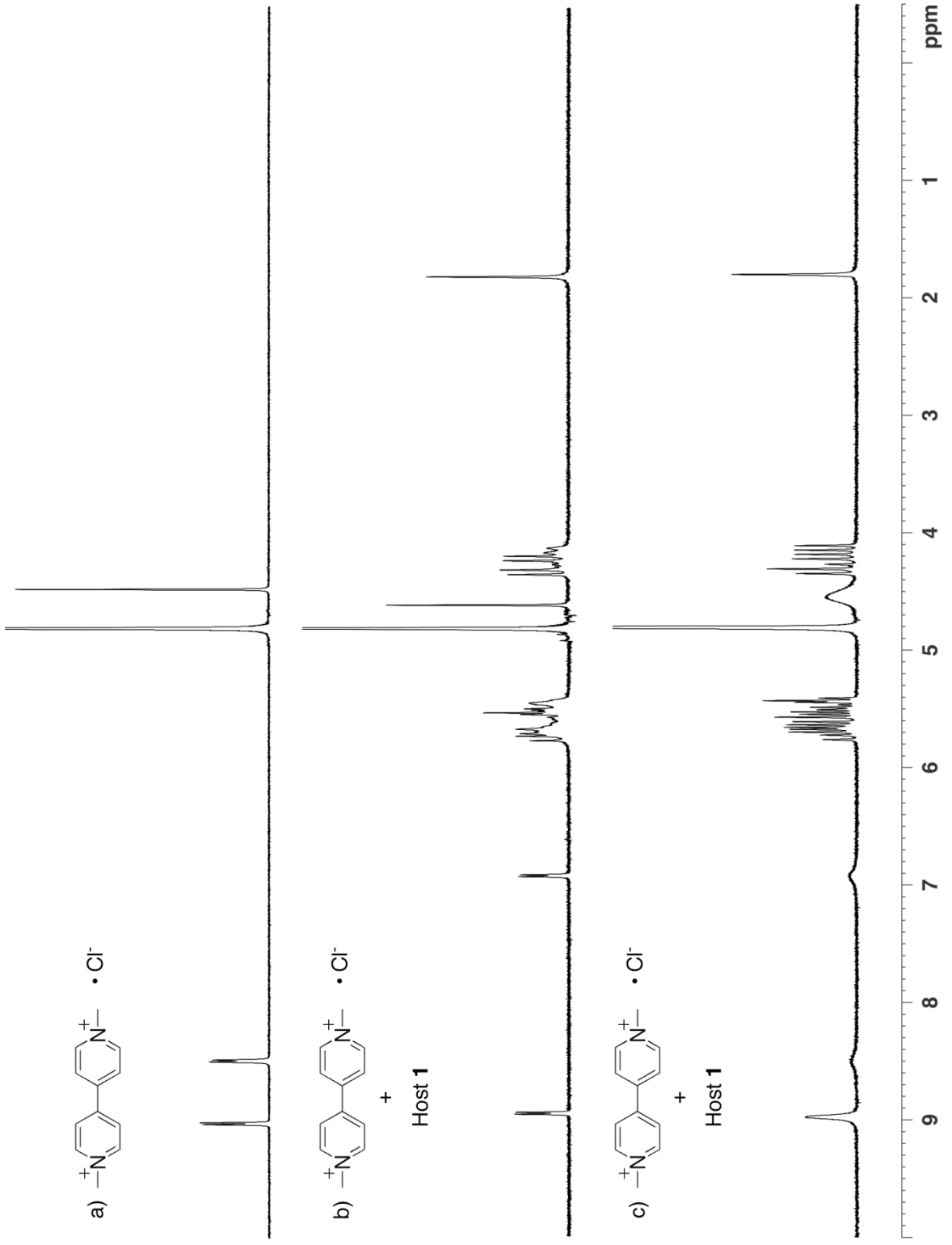


Figure S34. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **8** (0.5 mM), b) a 1:1 mixture of $Me_2CB[7]$ (0.5 mM) and **8** (0.5 mM), and c) a 1:2 mixture of $Me_2CB[7]$ (0.5 mM) and **8** (1 mM). (Host1 = $Me_2CB[7]$)

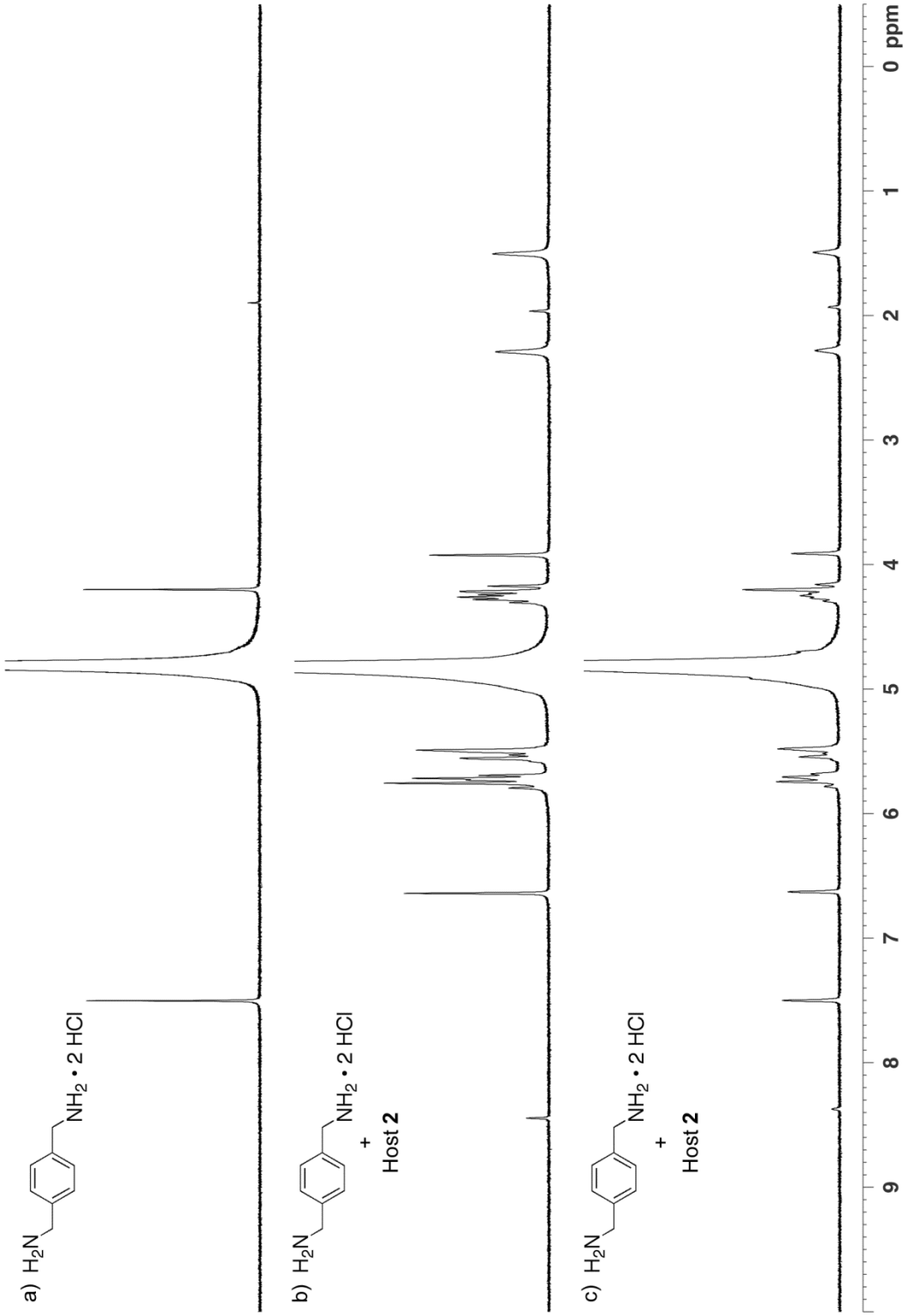


Figure S35. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **3** (0.5 mM), b) a 1:1 mixture of CyCB[7] (0.5 mM) and **3** (0.5 mM), and c) a 1:2 mixture of CyCB[7] (0.5 mM) and **3** (1 mM). (Host2 = CyCB[7])

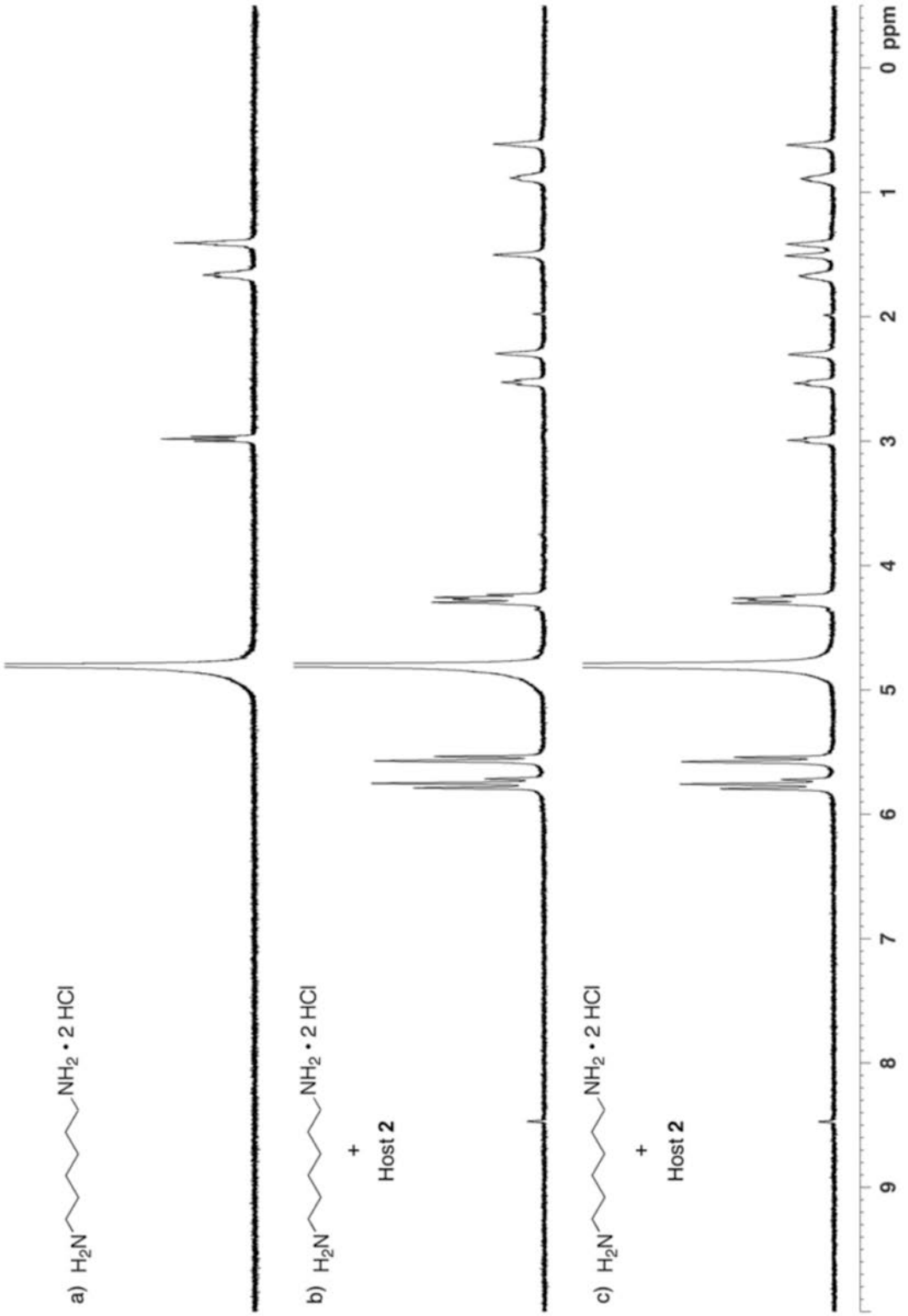


Figure S36. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **4** (0.5 mM), b) a 1:1 mixture of CyCB[7] (0.5 mM) and **4** (0.5 mM), and c) a 1:2 mixture of CyCB[7] (0.5 mM) and **4** (1 mM). (Host2 = CyCB[7])

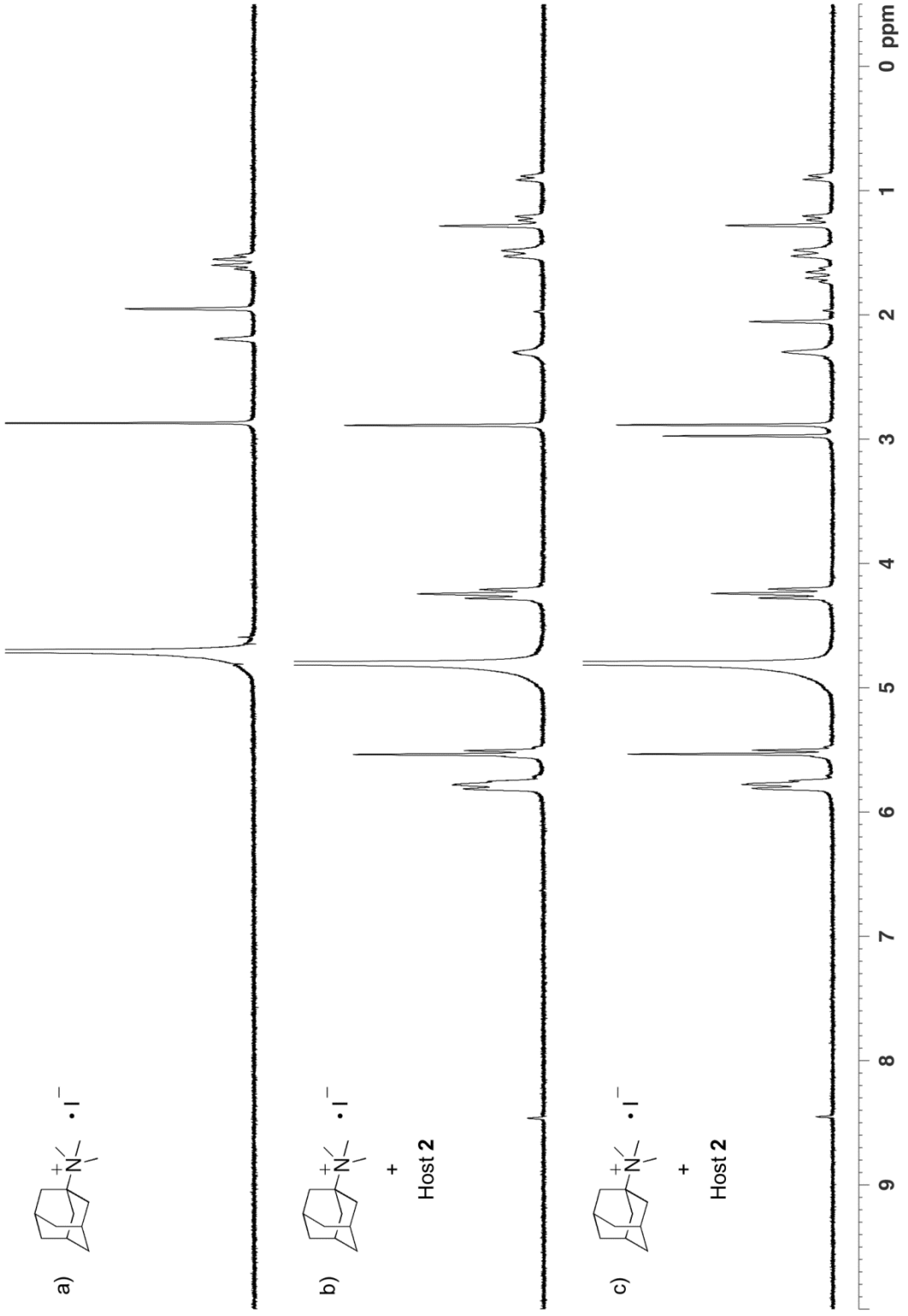


Figure S37. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **10** (0.5 mM), b) a 1:1 mixture of CyCB[7] (0.5 mM) and **10** (0.5 mM), and c) a 1:2 mixture of CyCB[7] (0.5 mM) and **10** (1 mM). (Host2 = CyCB[7])

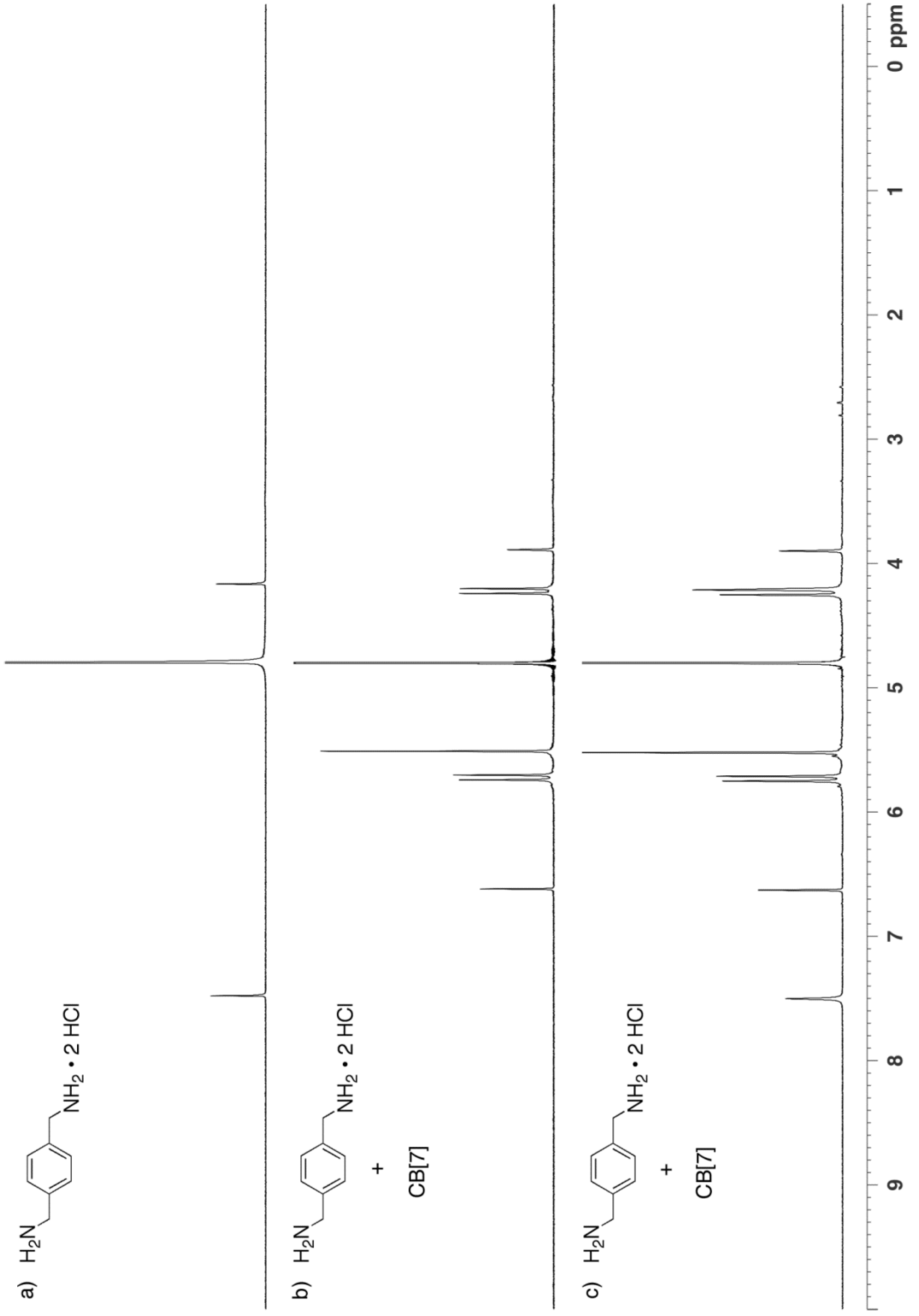


Figure S38. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **3** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **3** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **3** (1 mM).

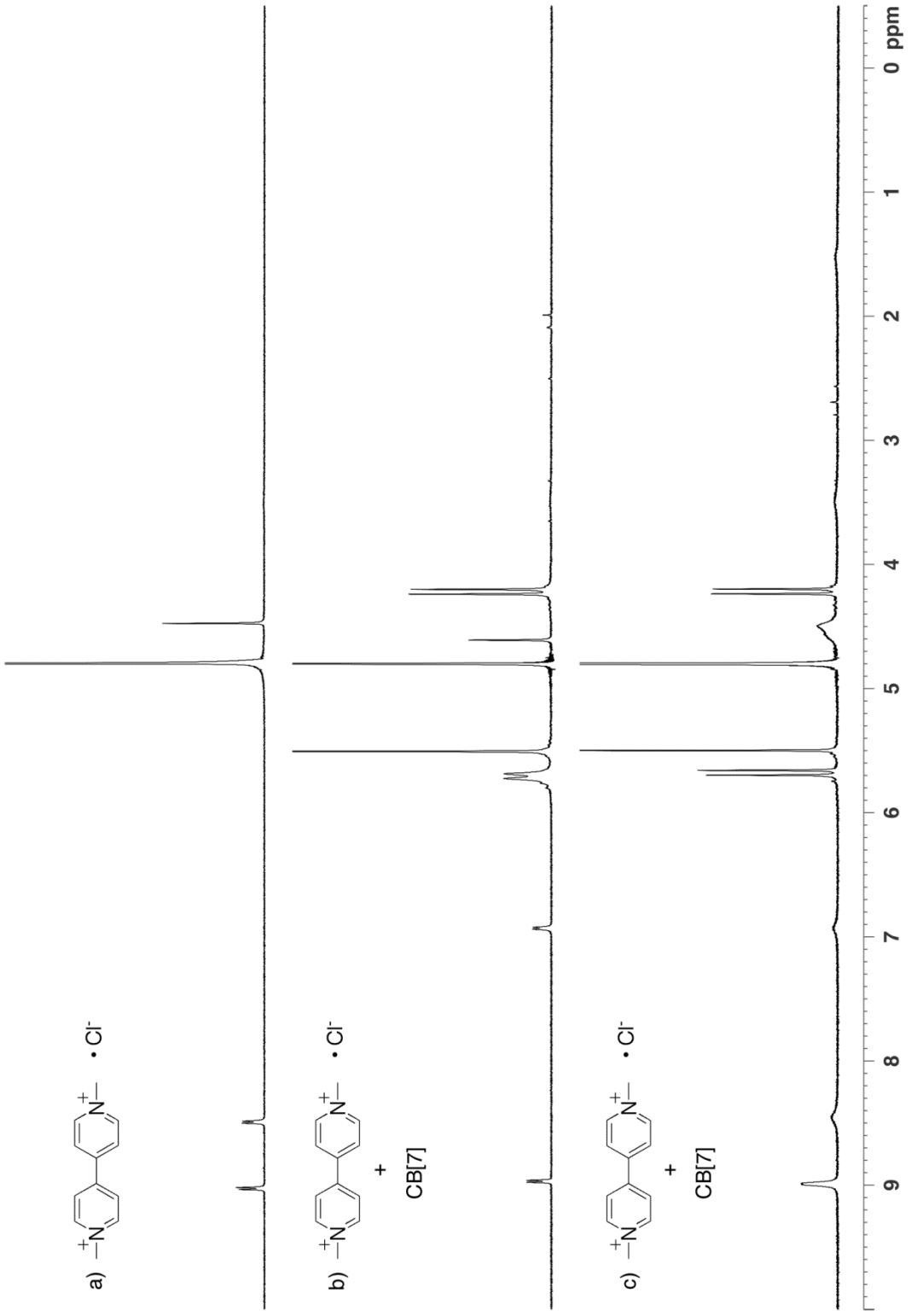


Figure S39. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **8** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **8** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **8** (1 mM).

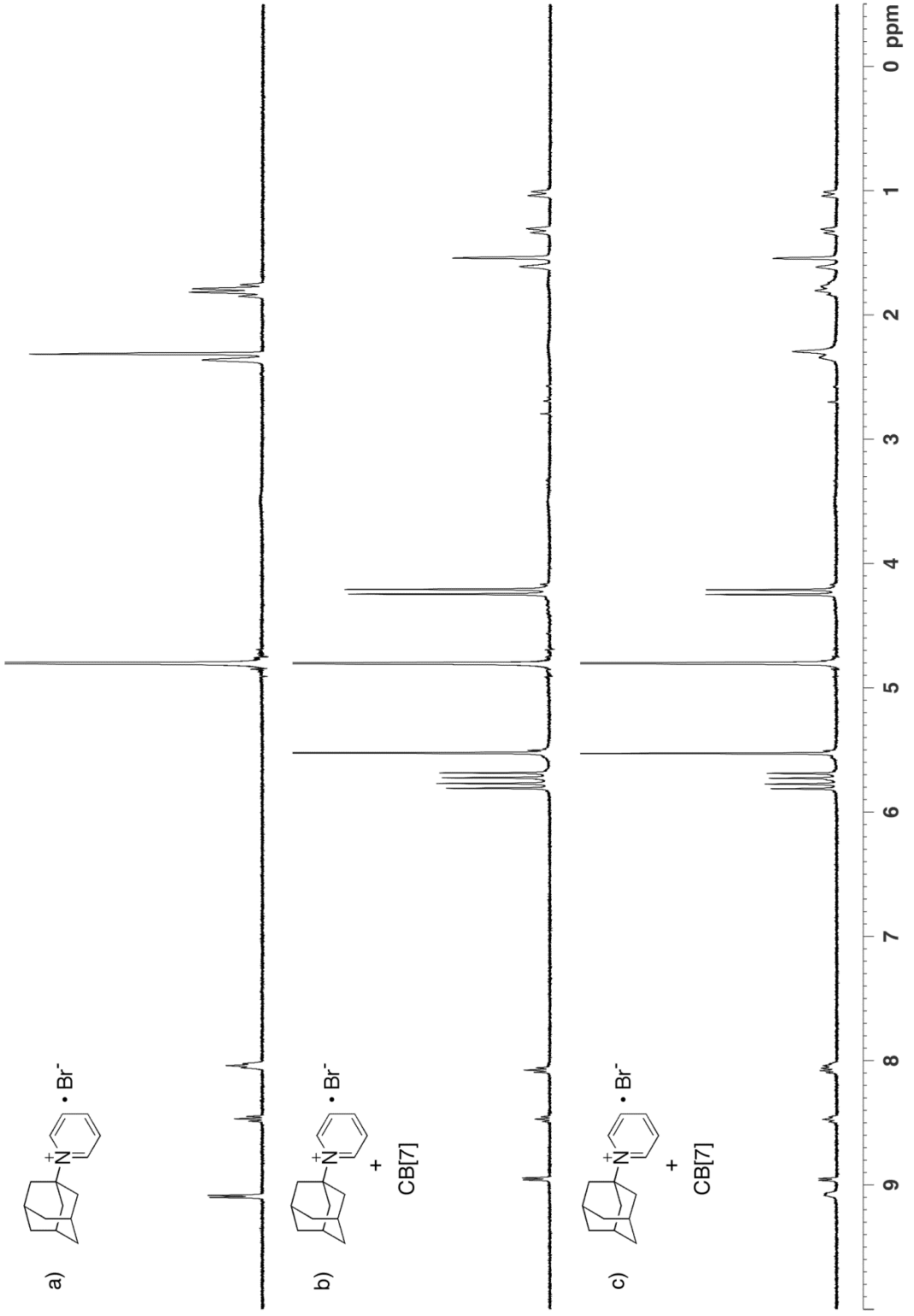


Figure S40. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **11** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **11** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **11** (1 mM).

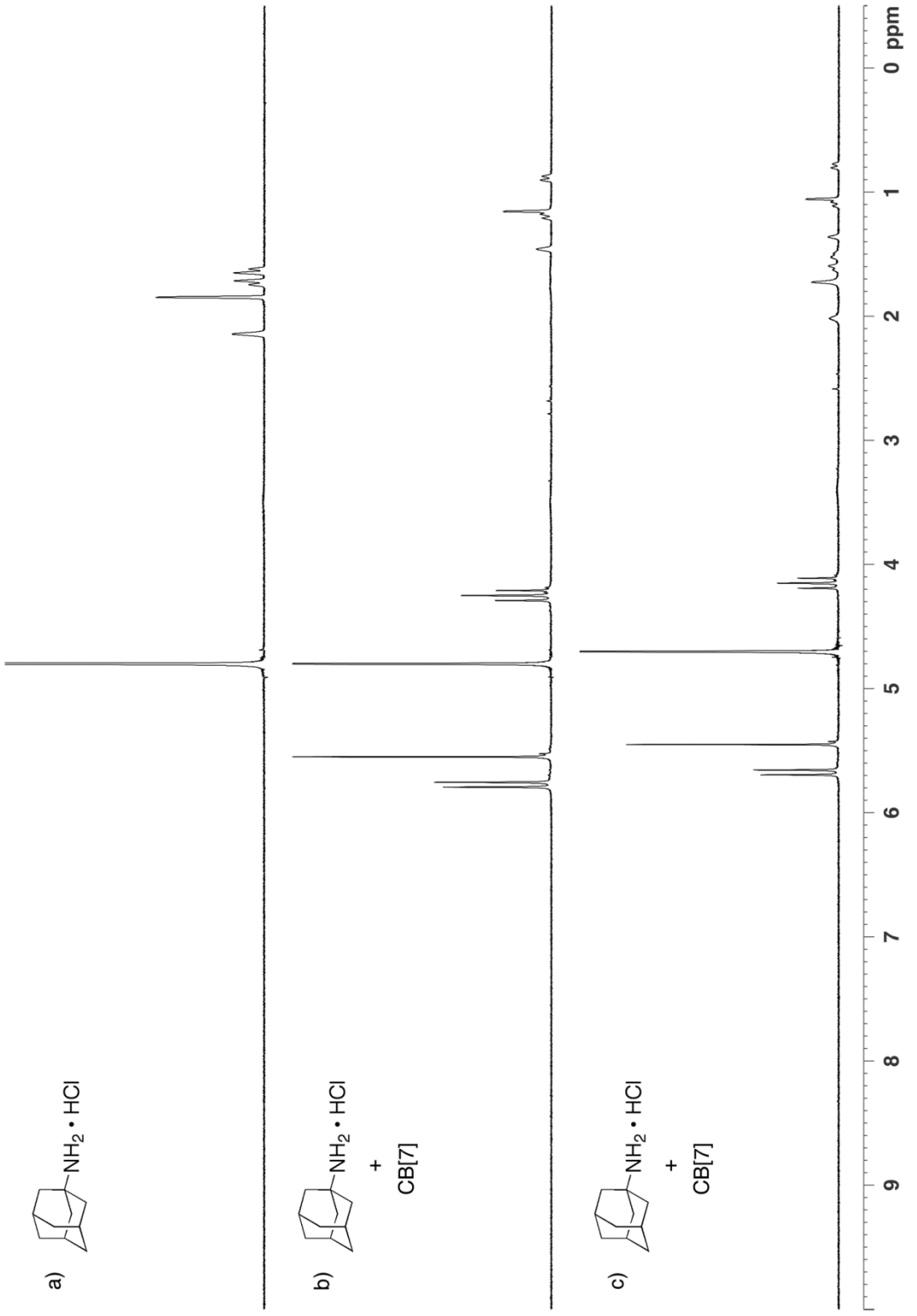


Figure S41. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **9** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **9** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **9** (1 mM).

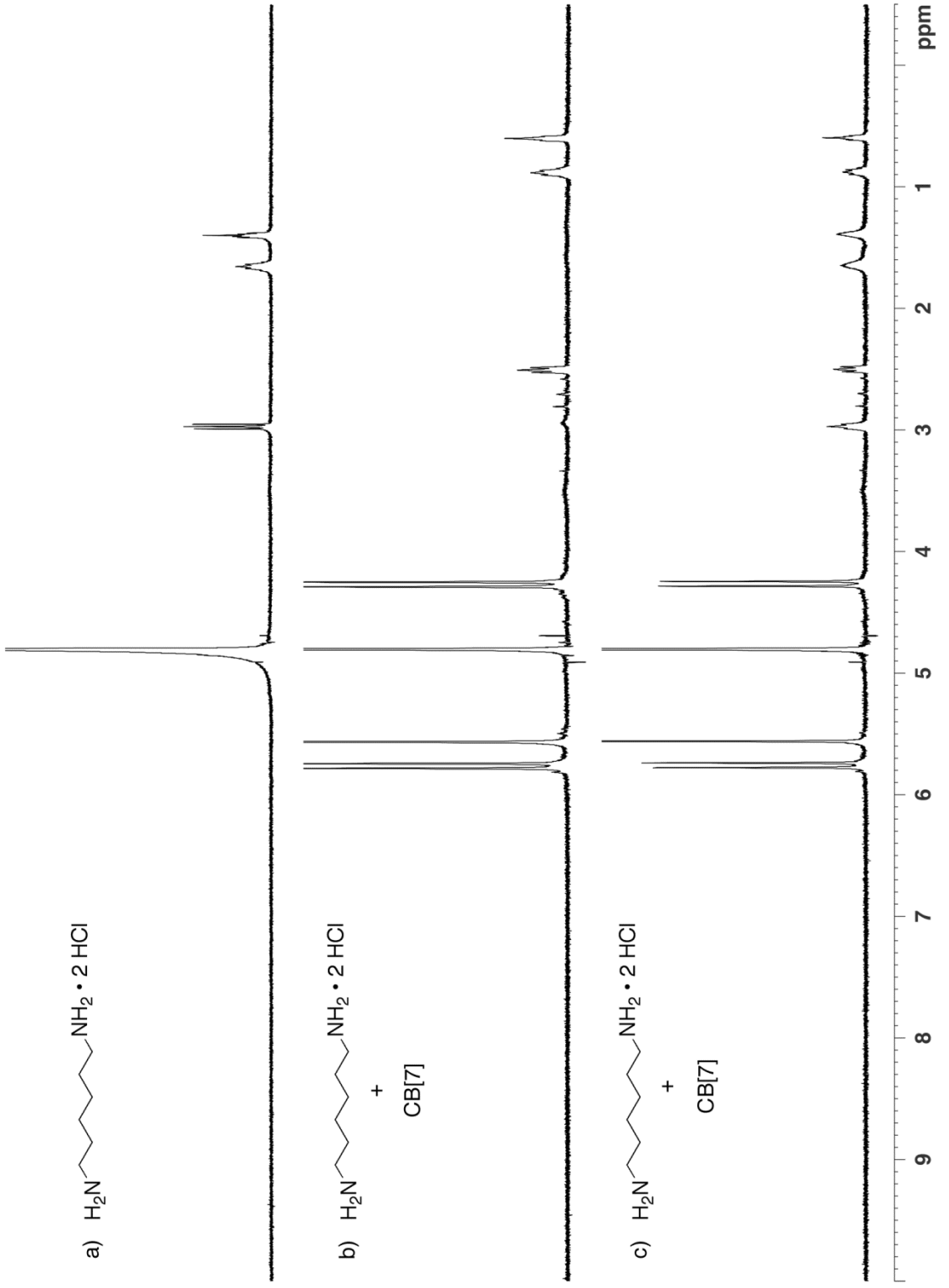


Figure S42. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **4** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **4** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **4** (1 mM).

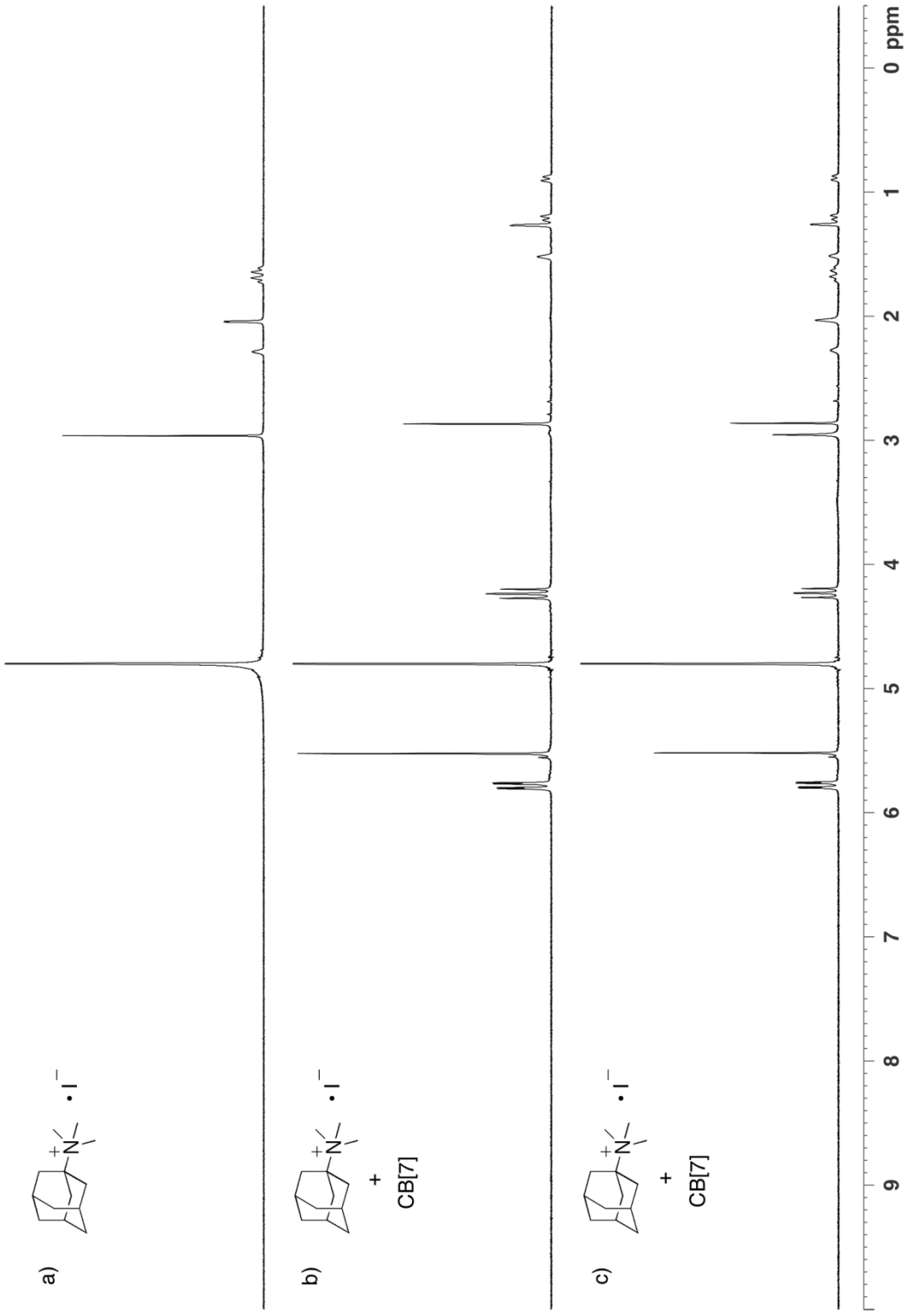


Figure S43. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **10** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **10** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **10** (1 mM).

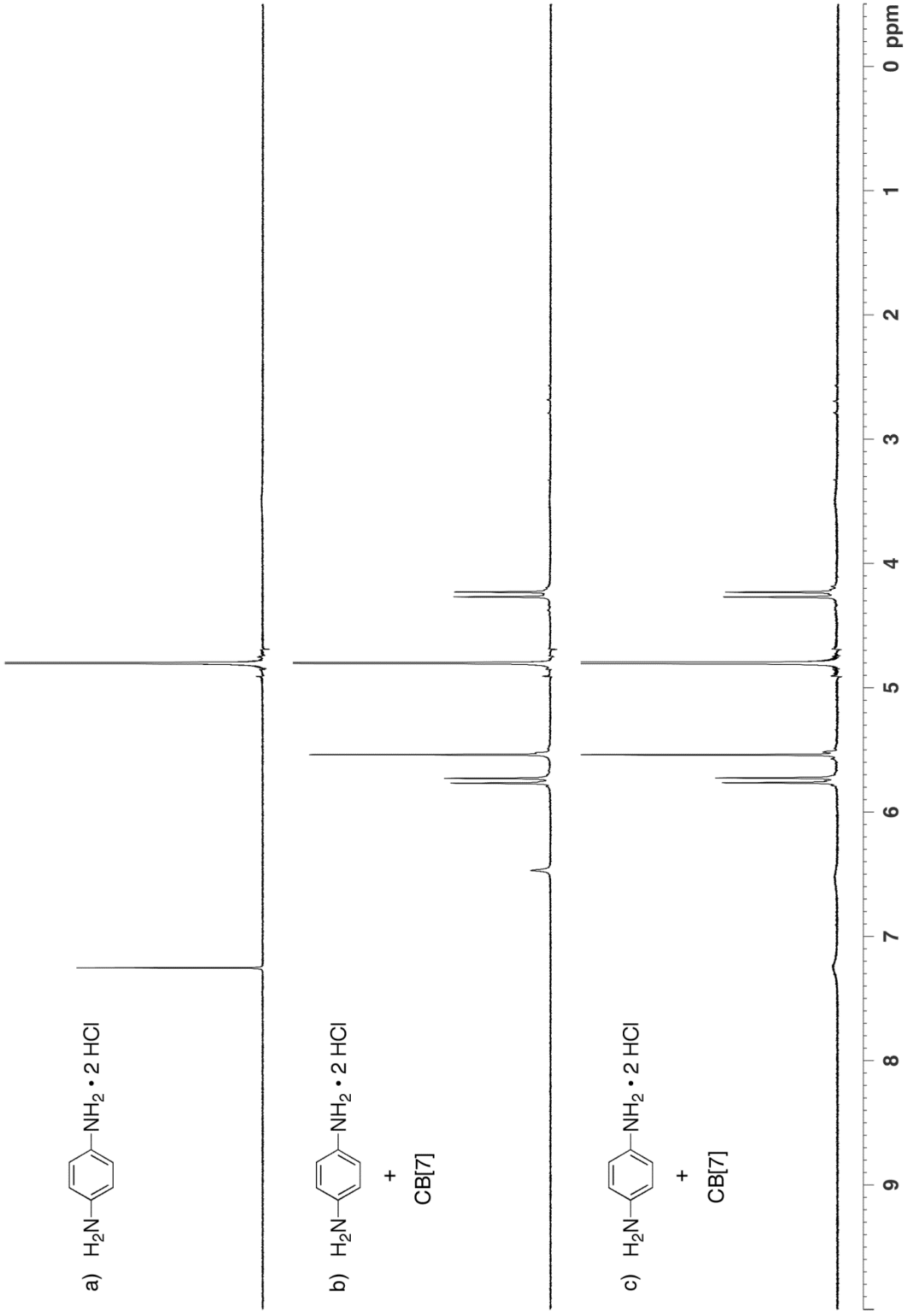


Figure S44. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **6** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **6** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **6** (1 mM).

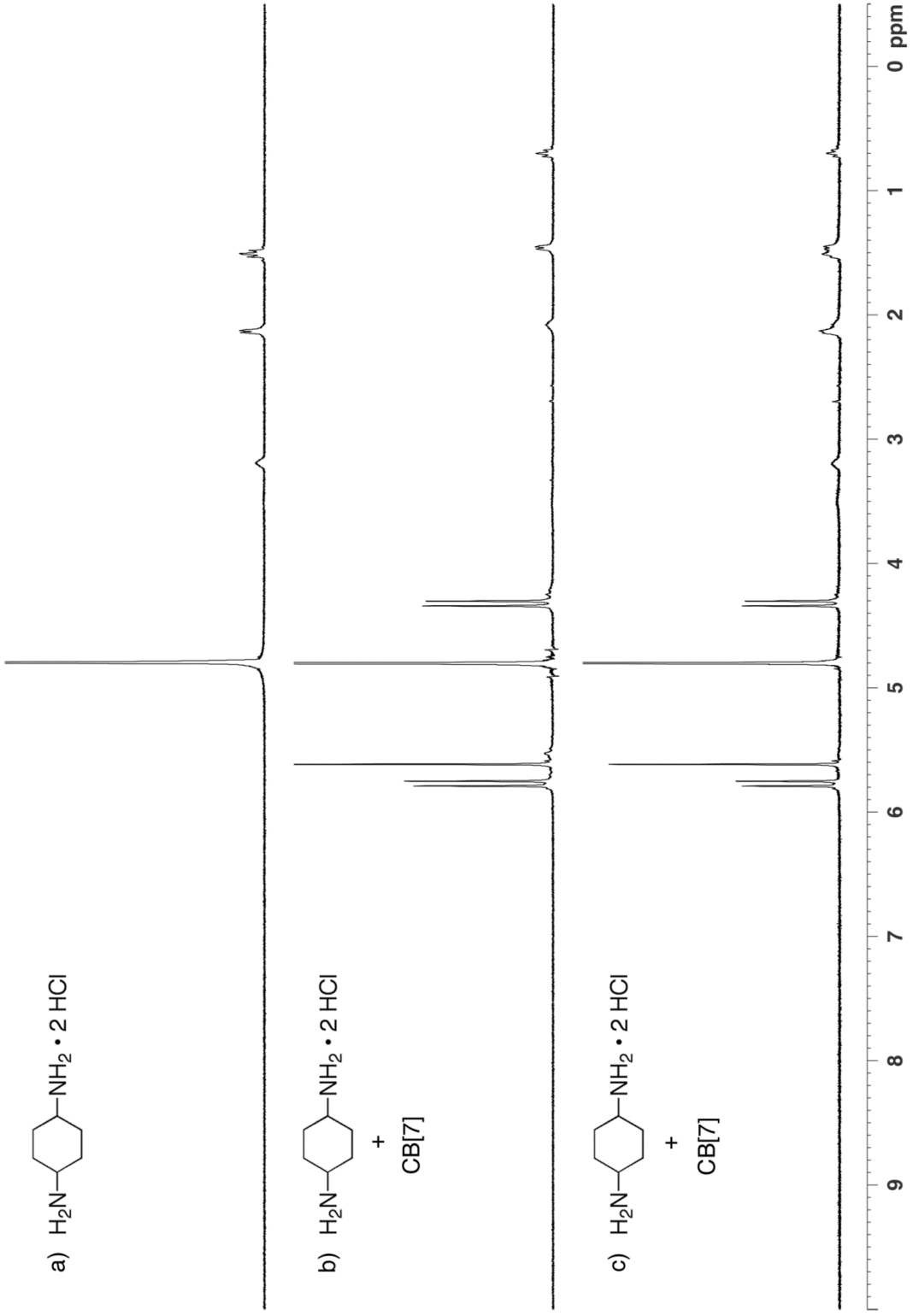


Figure S45. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for : a) **7** (0.5 mM), b) a 1:1 mixture of CB[7] (0.5 mM) and **7** (0.5 mM), and c) a 1:2 mixture of CB[7] (0.5 mM) and **7** (1 mM).

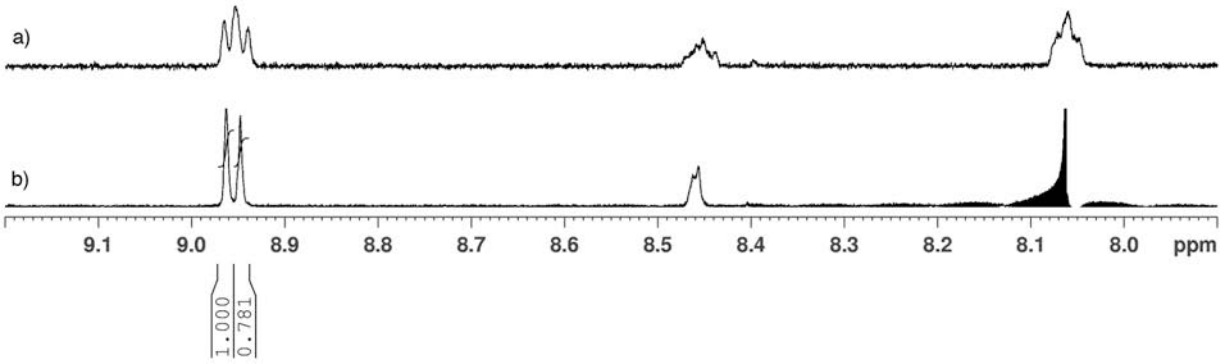


Figure S46. ^{1}H NMR spectra recorded (600 MHz, 50 mM CD_3CO_2D buffer, pD 4.74, RT) for: a) a mixture of CB[7] (0.77 mM), Me_2CB[7] (0.77 mM), and **11** (0.77 mM) b) the same sample as part a, but with homodecoupling by irradiation of the signal at 8.06 ppm.

Details of the Crystal Structure of $Me_2CB[7]$. A colorless prism-like specimen of $C_{52}H_{80}I_2N_{30}O_{25}$, approximate dimensions 0.34 mm × 0.43 mm × 0.44 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker APEX-II CCD system equipped with a graphite monochromator and a MoKα sealed tube (λ = 0.71073 Å). Data collection temperature was 200 K.

The total exposure time was 22.73 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 104851 reflections to a maximum θ angle of 25.00° (0.84 Å resolution), of which 13325 were independent (average redundancy 7.869, completeness = 99.8%, R_{int} = 3.85%, R_{sig} = 2.87%) and 10588 (79.46%) were greater than $2\sigma(F^2)$. The final cell constants of a = 23.750(4) Å, b = 49.017(8) Å, c = 13.018(2) Å, V = 15155.(4) $Å^3$, are based upon the refinement of the XYZ-centroids of 9437 reflections above 20 σ(I) with 4.580° < 2θ < 54.07°. Data were corrected for absorption effects using the multi-scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6300 and 0.7300.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P c c n, with Z = 8 for the formula unit, $C_{52}H_{80}I_2N_{30}O_{25}$. The final anisotropic full-matrix least-squares refinement on F^2 with 1028 variables converged at R_1 = 7.62%, for the observed data and wR_2 = 17.67% for all data. The goodness-of-fit was 1.000. The largest peak in the final difference electron density synthesis was 1.436 $e^-/Å^3$ and the largest hole was -1.601 $e^-/Å^3$ with an RMS deviation of 0.078 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.560 g/cm^3 and F(000), 7264 e^-.

Crystallographic References: APEX2 Version 2010.11-3 (Bruker AXS Inc.) SAINT Version 7.68A (Bruker AXS Inc., 2009) SADABS Version 2008/1 (G. M. Sheldrick, Bruker AXS Inc.) XPREP Version 2008/2 (G. M. Sheldrick, Bruker AXS Inc.) XS Version 2008/1 (G. M. Sheldrick, *Acta Cryst.* (2008). A**64**, 112-122) XL Version 2008/4 (G. M. Sheldrick, *Acta Cryst.* (2008). A**64**, 112-122) Platon (A. L. Spek, *Acta Cryst.* (1990). A**46**, C-34)

Table S1. Sample and crystal data for UM2261.

Identification code	2261	
Chemical formula	$C_{52}H_{80}I_2N_{30}O_{25}$	
Formula weight	1779.26	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal size	0.34 × 0.43 × 0.44 mm	
Crystal habit	colorless prism	
Crystal system	orthorhombic	
Space group	P c c n	
Unit cell dimensions	a = 23.750(4) Å	α = 90°
	b = 49.017(8) Å	β = 90°
	c = 13.018(2) Å	γ = 90°
Volume	15155.(4) $Å^3$	
Z	8	

Density (calculated)	1.560 Mg/cm^3
Absorption coefficient	0.924 mm^{-1}
F(000)	7264

Table S2. Data collection and structure refinement for UM2261.

Diffractometer	Bruker APEX-II CCD	
Radiation source	sealed tube, MoKα	
Theta range for data collection	2.18 to 25.00°	
Index ranges	$-28 \le h \le 28$, $-57 \le k \le 58$, $-15 \le l \le 15$	
Reflections collected	104851	
Independent reflections	13325 [R(int) = 0.0385]	
Coverage of independent reflections	99.8%	
Absorption correction	multi-scan	
Max. and min. transmission	0.7300 and 0.6300	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	13325 / 374 / 1028	
Goodness-of-fit on F^2	1.000	
Final R indices	10588 data; $I>2\sigma(I)$	$R_1 = 0.0762$, $wR_2 = 0.1708$
	all data	$R_1 = 0.0890$, $wR_2 = 0.1767$
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.05P)^2+49.67P]$, $P=(\max(F_o^2,0)+2F_c^2)/3$	
Largest diff. peak and hole	1.436 and -1.601 $eÅ^{-3}$	
R.M.S. deviation from mean	0.078 $eÅ^{-3}$	

$R_{int} = \Sigma|F_o^2 - F_o^2(\text{mean})| / \Sigma[F_o^2]$
$R_1 = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$
$\text{GOOF} = S = \{\Sigma[w(F_o^2 - F_c^2)^2] / (n - p)\}^{1/2}$
$wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$

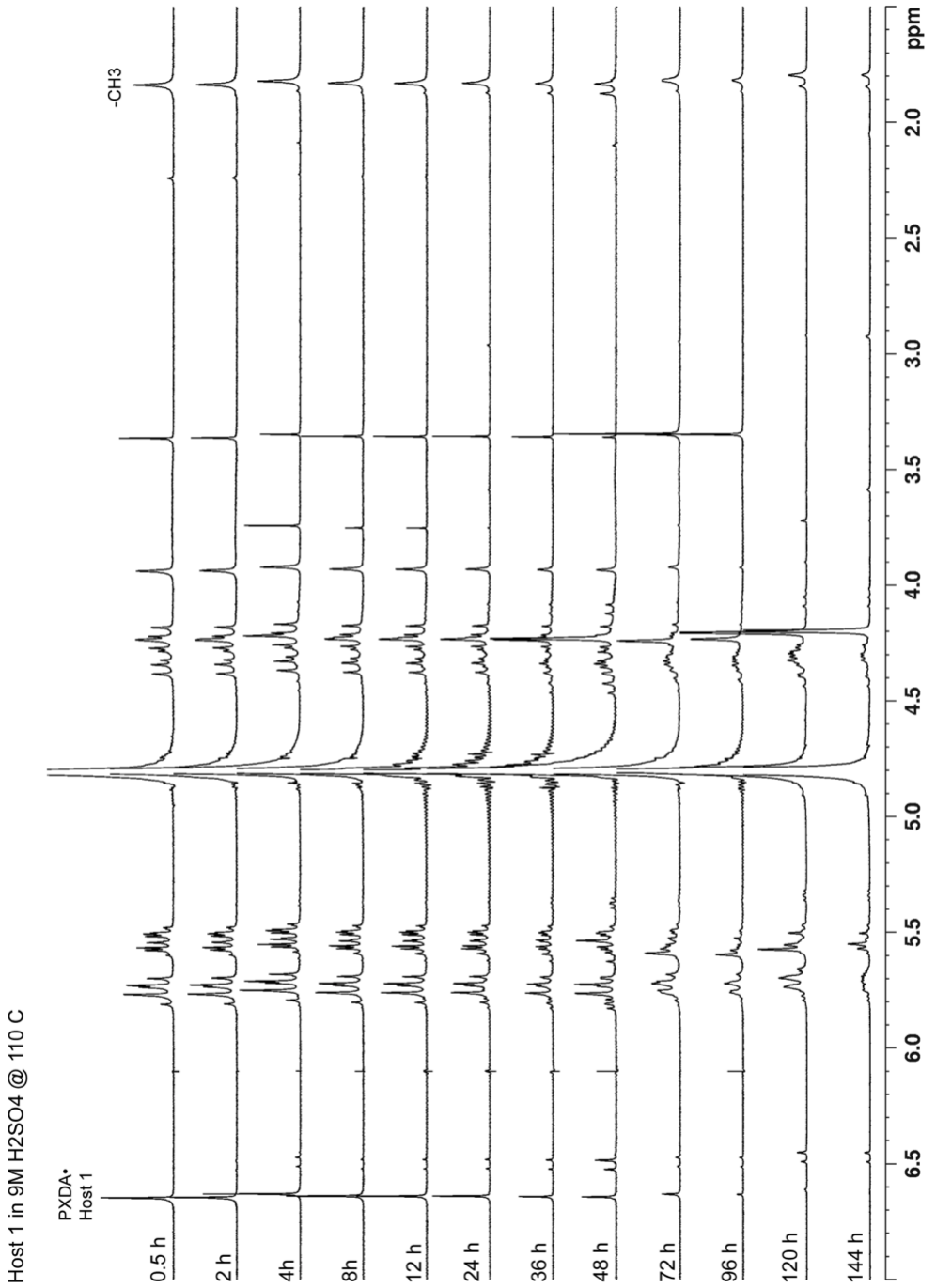


Figure S47. Decomposition of $Me_2CB[7]$ in 9M H_2SO_4 at 110 ˚C. ^1H NMR spectra recorded (400 MHz, D_2O, RT) for aliquots of the reaction mixture in the presence of excess guest **3** as a function of time.

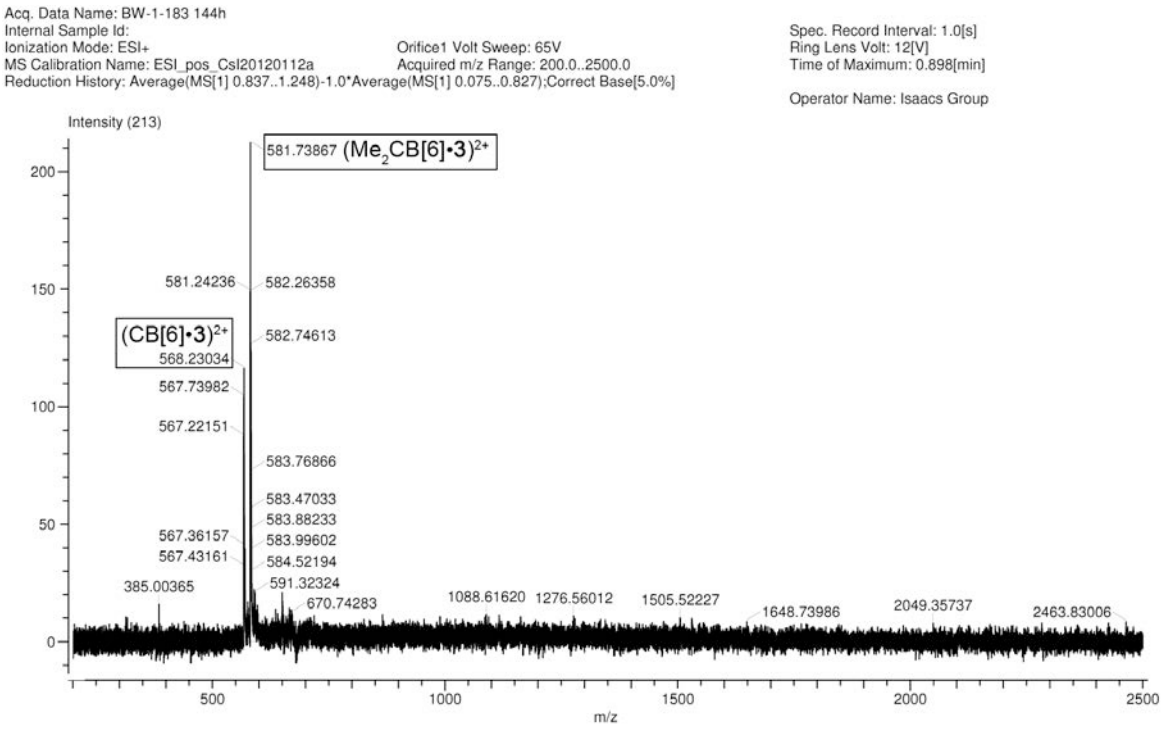


Figure S48. Electrospray mass spectrum recorded for the sample from Figure S44 at time = 144h.

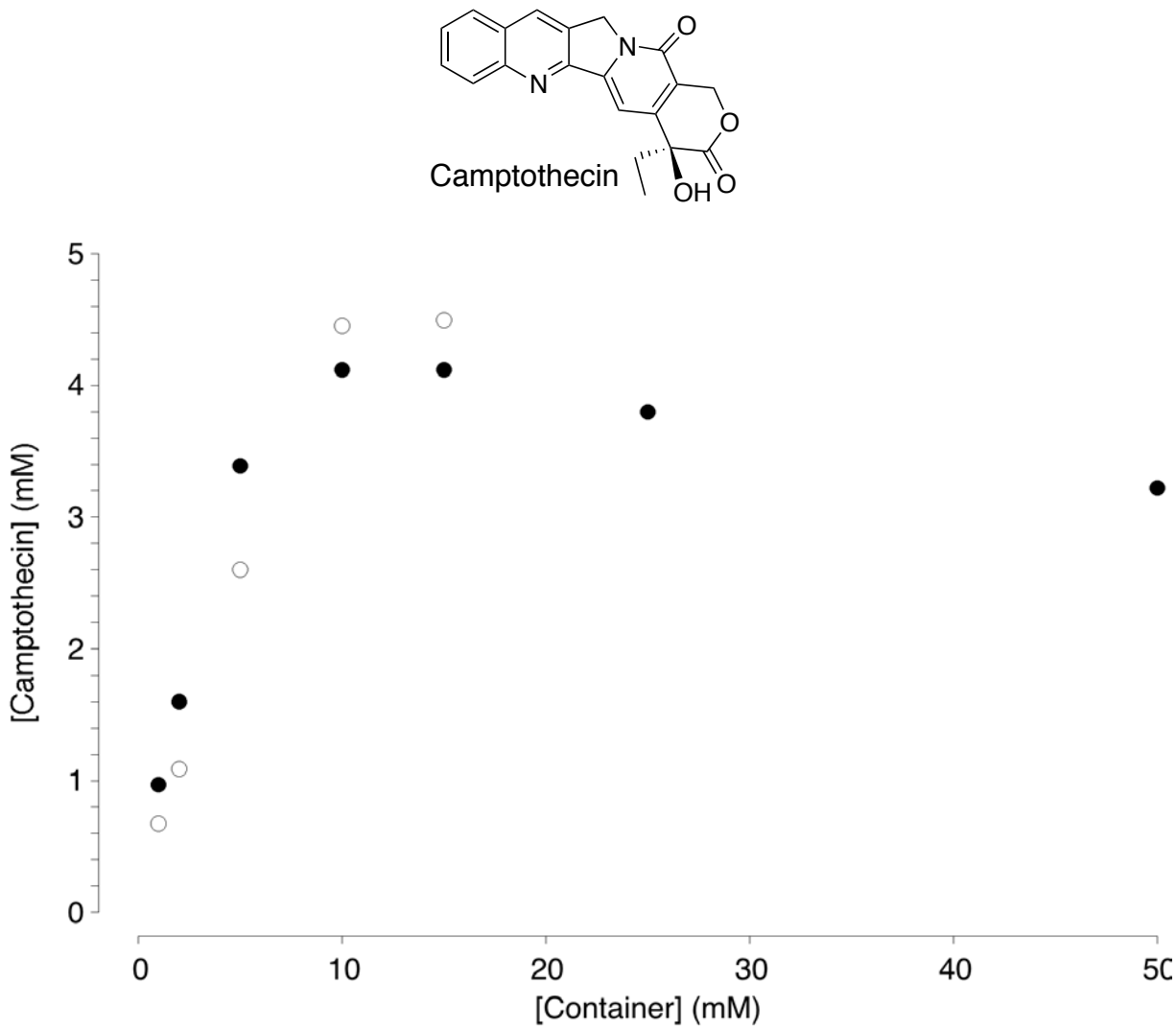


Figure S49. Phase solubility diagram constructed (D_2O, DCl, pH 2.0, room temperature) for the solubilization of camptothecin in the presence of CB[7] (o) or Me_2CB[7] (•).

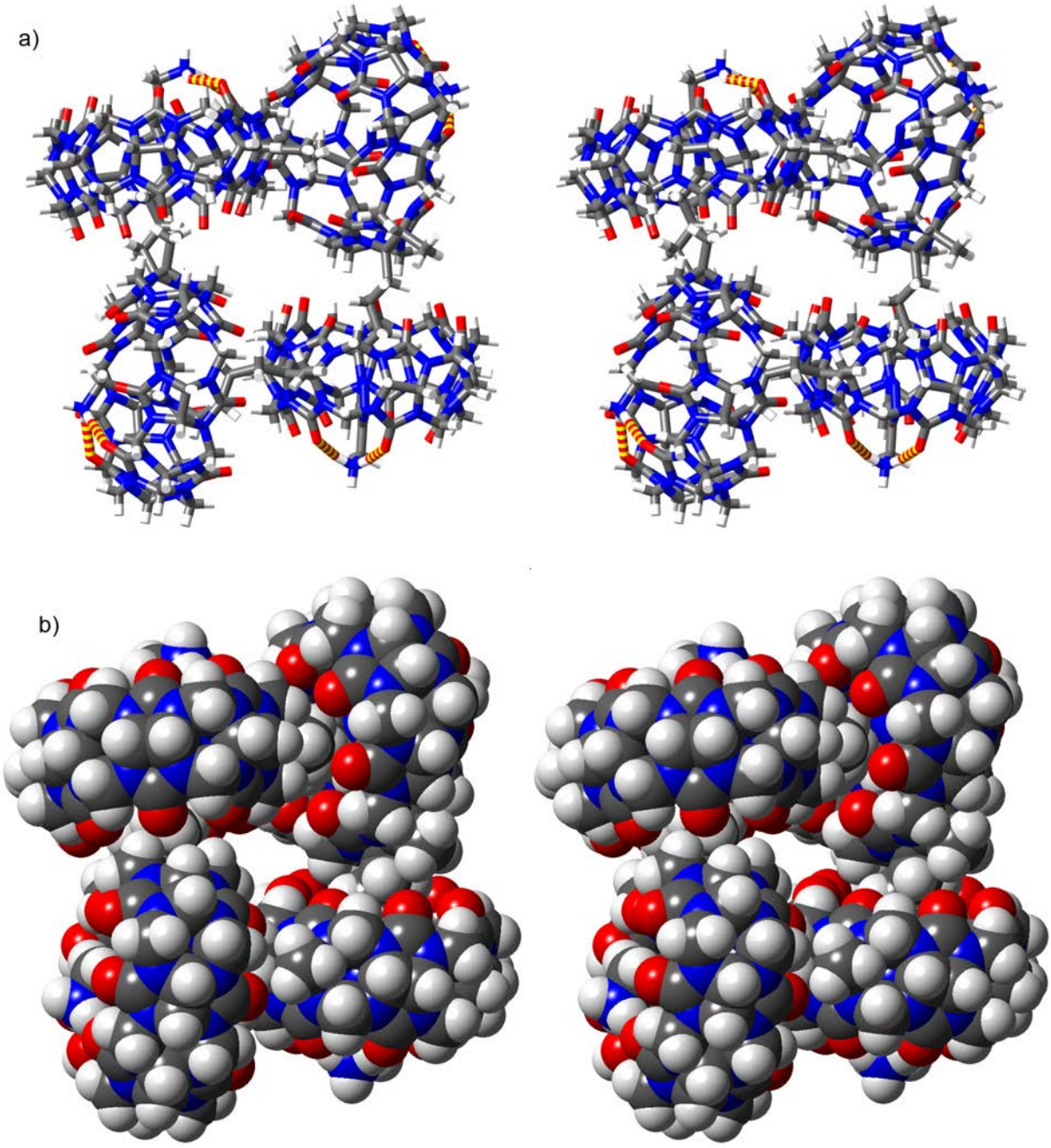


Figure S50. Cross-eyed stereoviews of MMFF minimized models of u,u,u,u-**20**$_4$: a) line bond structure, and b) space filling. Color-code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow striped.