Cucurbit[7]uril Enables Multistimuli Responsive Release from the Self-Assembled Hydrophobic Phase of a Metal Organic Polyhedron

Supporting Information

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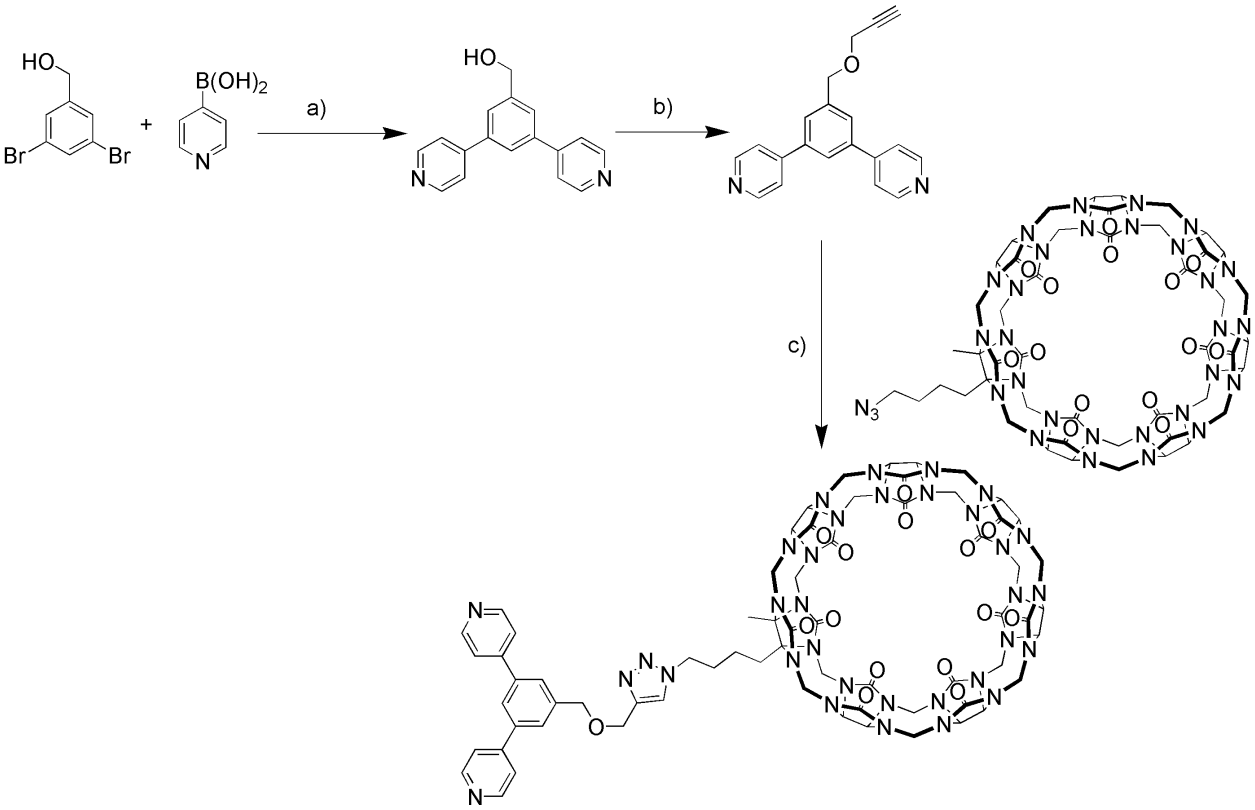
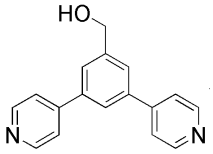
General Procedure

Starting materials were purchased from commercial suppliers and were used without further purification. Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. IR spectra were measured on a Thermo Nicolet NEXUS 670 FT/IR spectrometer by attenuated total reflectance (ATR) and are reported in cm^{-1}. NMR spectra were measured at 400, 500, or 600 MHz for ^{1}H and 100 and 125 MHz for ^{13}C using deuterated water (D_2O), deuterated chloroform ($CDCl_3$), or deuterated dimethyl sulfoxide (DMSO-d_6) as solvent. Chemical shifts (δ) are referenced relative to the residual resonances for HOD (4.79 ppm), $CHCl_3$ (7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C), and DMSO-d_6 (2.50 ppm for ^{1}H, 39.51 ppm for ^{13}C). Mass spectrometry was performed using a JEOL AccuTOF electrospray instrument for routine sample. TEM was performed on a JEOL JEM 2100. Energy dispersive spectroscopy (EDS) was done on scanning electron microscopy (SEM) using Hitachi SU-70. Molecular modeling (MMFF) was performed using Spartan '08 on a personal computer.

Synthetic Procedures and Characterization Data

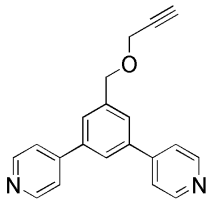


Scheme SI1. Synthesis of **1**. Conditions: (a) $Pd(PPh_3)_4$, K_3PO_4, H_2O:*p*-dioxane, 80 °C, 3 days, 72%; (b) Propargyl bromide, NaH, THF-DMF, 0 °C to room temperature, 3 h, 80 %; (c) Pericas Catalyst, H_2O-DMSO, 80 °C, 4 days, 55%.

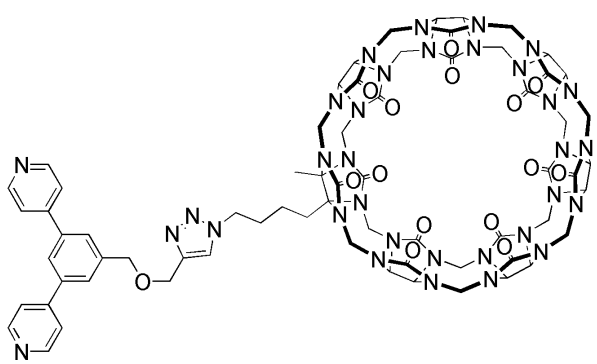


Compound 2. In a three-necked round-bottomed flask equipped with a condenser was charged with 3,5-dibrombenzyl alcohol (1.00 g, 3.76 mmol), pyridine-4-boronic acid (1.15 g, 9.35 mmol) and anhydrous potassium phosphate (6.38 g, 30.0 mmol) under N_2. Degassed (twice by freeze-pump-thaw) solvent mixture of H_2O:1,4-dioxane (1:1, 60 mL) was added into the flask and then $Pd(PPh_3)_4$ (434 mg, 0.376 mmol) was added to the solution. The reaction mixture was heated at 80 °C for 4 days. The solvent mixture was evaporated under reduced pressure. The solid was redissolved in chloroform (150 mL) and washed with water (3 x 150 mL). Chloroform solution was dried over anhydrous $MgSO_4$, and evaporated to concentrate the solution. The solution was loaded onto a silica gel column and eluted using $CHCl_3$:MeOH (95:5, R_f = 0.4) to afford the

desired compound as white solid (710 mg, 72%). Mp. 142–143 °C. IR (ATR cm^{-1}) 3226, 1592, 1549, 1400, 1031, 1004, 879, 817. ^1H NMR (400 MHz, $CDCl_3$, RT) δ = 8.71 (d, J = 6.1 Hz, 4H), 7.79 (t, J = 1.8 Hz, 1H), 7.72 (d, J = 1.4 Hz, 2H), 7.56 (d, J = 6.1 Hz, 4H), 4.89 (s, 2H), 2.08 (brs, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, RT) δ = 150.2, 147.8, 143.5, 139.3, 126.0, 124.6, 121.7, 64.4 ppm. MS (ESI, positive) *m/z* 263 (100% $[M+H]^+$).

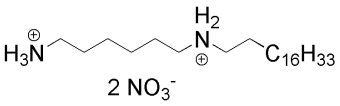


Compound 2a. In a three-necked round-bottomed-flask, compound **2** (200 mg, 0.762 mmol) and NaH (60% in mineral oil, 76.3 mg, 3.18 mmol) were taken under N_2 and the flask was kept inside an ice bath at -5 °C. Dry THF (5 mL) and dry DMF (5 mL) were added and the reaction mixture was stirred for 1 h. Then propargyl bromide (0.203 μL, 2.29 mmol) was added into the solution and stirred for 2 h while warming the flask to room temperature. Then H_2O (50 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The chloroform solution was dried over anhydrous $MgSO_4$ and evaporated to concentrate the solution. The concentrated solution was loaded onto a silica gel column and eluted using $CHCl_3$:EtOAc:NEt_3 (20:75:5, R_f = 0.25) to afford compound **2a** as pale yellow solid (183 mg, 80%). Mp. 134–135°C. IR (ATR cm^{-1}) 3231, 3013, 1590, 1549, 1401, 1257, 1222, 1091, 1077, 1037, 990, 884, 811, 741, 700. ^1H NMR (400 MHz, $CDCl_3$, RT): δ = 8.71 (d, J = 4.6 Hz, 4H), 7.80 (s, 1H), 7.71 (s, 2H), 7.56 (d, J = 4.6 Hz, 4H), 4.77 (s, 2H), 4.29 (d, J = 1.8 Hz, 2H), 2.52 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, RT): δ = 149.7, 148.2, 139.8, 139.9, 127.2, 125.2, 121.9, 79.2, 75.2, 71.0, 57.7 ppm. MS: (ESI, positive) *m/z* 301 (100% $[M+H]^+$).

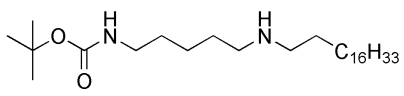


Compound 1. Compound **2a** (60.0 mg, 199 μmol), CB[7]-azide (50.0 mg, 39.2 μmol) and Pericas catalyst (2.30 mg, 3.80 μmol) were dissolved in DMSO-H_2O (1:1, 2.0 mL, degassed by N_2). The reaction mixture was heated at 80 °C for 4 days under N_2. The reaction mixture was poured into MeOH (2 mL) which resulted in a grey precipitate. The mixture was centrifuged for 10 min. The supernatant was decanted and the precipitate was washed with MeOH (3 × 5 mL) with sonication. The solid was collected

by centrifugation. The solid was dried under high vacuum to give compound **1** as white solid (38 mg, 62%). Mp. > 300 °C. IR (ATR cm^{-1}) 3426, 1720, 1469, 1420, 1380, 1312, 1231, 1179, 1084, 1034, 950, 823, 798, 756. ^{1}H NMR (600 MHz, D_2O, 1.0 equiv. PXDA, RT): δ = 8.64 (d, J = 4.2 Hz, 4H), 8.05 (s, 1H), 8.01 (s, 1H), 7.78 (m, 6H), 6.55 (s, 4H, PXDA), 5.78-5.39 (m, 26H), 5.27-5.18 (m, 2H), 4.85 (d, J = 14.0 Hz, 4H), 4.36 (t, 2H), 4.29 (d, J = 16.2 Hz, 2H), 4.20-4.24 (m, 4H), 4.13-4.05 (m, 6H), 3.95 (d, J = 15.6 Hz, 2H), 3.87 (s, 4H, PXDA), 2.09 (m, 2H), 1.51 (m, 2H), 1.41 (s, 3H), 0.84(m, 2H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6, RT) δ = 155.7, 155.5, 155.0, 154.9, 154.7, 154.6, 154.2, 146.8, 139.9, 137.5, 128.0, 126.0, 122.8, 80.1, 77.6, 77.2, 70.3, 70.0, 69.8, 69.6, 57.3, 52.2, 51.6, 48.4, 48.0, 44.7, 31.7, 19.7, 15.3 ppm. HR-MS: *m/z* 856.3296 ($[M•PXDA]^{2+}$, calcd. for $[C_{75}H_{81}N_{35}O_{15}]^{2+}$, 856.3338).

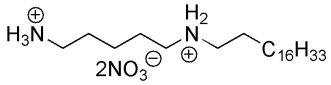


Compound [3•2NO_3^-]. Synthesis of compound [**3**•2Cl^-] was reported earlier.[1] Compound [**3**•2Cl^-] (166 mg, 0.377 mmol) was dissolved in water (2.0 mL) and treated with aqueous silver nitrate solution (134 mg in 2.0 mL water). The mixture was stirred at room temperature for 2 h and protected from light. The solid was separated from the solution by centrifugation and then obtained by filtration. Residual water was removed under reduced pressure to afford a white solid. The solid was redissolved in hot water and then placed in the refrigerator. A white precipitate was observed and collected by centrifugation. The solid was dried under high vaccum to afford [**3**•2NO_3^-] (173 mg, 93%). Mp. 115 °C. IR (ATR cm^{-1}) 2918, 2848, 1714, 1463, 1312, 1181, 1035, 1018, 827, 724. ^{1}H NMR (600 MHz, D_2O): δ = 3.01-2.95 (m, 6H), 1.65 (brs, 6H), 1.40-1.25 (m, 34H), 0.83 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ = 46.7, 46.4, 38.5, 31.2, 28.9, 28.8, 28.7, 28.6, 28.4, 26.4, 25.8, 25.4 ppm. MS: (ESI, positive) *m/z* 355.4 (100% $[M-H-2NO_3]^+$).

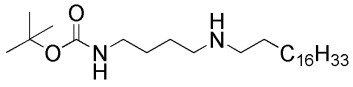


Compound 4a: *N*-Boc-1,4-diaminopentane (110 mg, 0.544 mmol) and 1-bromooctadecane (217 mg, 0.653 mmol) were dissolved in acetonitrile (5 mL). The solution was heated at 65 °C for 24 h. After the reaction a solid precipitate was observed. The reaction mixture was taken in a centrifuge tube and solid was collected by centrifugation. The solid was further washed with acetonitrile (3 × 5 mL) by sonication in a centrifuge tube and then collected by centrifugation. The solid material was dried

under high vaccum to afford compound **4a** as white solid (430 mg, 73%). Mp. 79 °C, IR (ATR cm^{-1}) 3377, 2916, 2850, 1686, 1518, 1471, 1364, 1275, 1238, 1168, 977, 867, 786, 716. ^1H NMR (600 MHz, $CDCl_3$) δ = 9.25 (s, 1H), 3.12 (t, J = 6.6 Hz, 2H), 2.94 (brs, 4H), 1.90 (m, 4H), 1.69 (brs, 1H), 1.53 (t, J = 7.2 Hz, 2H), 1.44 (s, 9H), 1.36-1.26 (m, 32H), 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, RT): δ = 156.2, 48.0, 47.6, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.1, 28.5, 26.9, 26.0, 25.5, 23.9, 22.7, 14.1. MS: (ESI, positive) *m/z* 455.4 (100%, $[M+H]^+$).

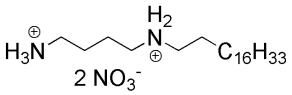


Compound [4•2NO_3^-] : Compound **4a** (200 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C using an ice bath. Then trifluoroacetic acid (3.0 mL) was added dropwise to the reaction mixture under N_2. The resultant mixture was stirred at RT for 2 h. The solvent was removed under reduced pressure to give a solid residue which was redissolved in CH_2Cl_2 (5 mL). The solvent was further evaporated and solid residue was slurried in ethanol (5 mL) and then evaporated to remove residual TFA. Then, the solid was dissolved in water (5mL) and treated with excess tetrabutyl ammonium nitrate (1.0 g). The resulting mixture was sonicated for 2 h. The solvent was evaporated to dryness and the solid residue was washed with acetonitrile (3 × 10 mL) to remove excess tetrabutyl ammonium salt. The solid residue was collected by centrifugation and dried under vacuum to afford [**4**•2NO_3^-] as white solid (150 mg, 71%). Mp. 90 °C. IR (ATR cm^{-1}) 2913, 2848, 1666, 1471, 1195, 1163, 1136, 1034, 832, 798, 718..^1H NMR (600 MHz, D_2O): δ = 3.05-3.00 (m, 6H), 1.76-1.66 (m, 6H), 1.47 (t, J = 7.8 Hz, 2H), 1.4-1.29 (m, 30H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, RT) δ = 46.6, 46.3, 38.4, 31.2, 28.9, 28.9, 28.8, 28.7, 28.6, 28.4, 26.3, 25.8, 25.4 ppm. MS: (ESI, positive) *m/z* 369.4 (100%, $[M-H-2NO_3]^+$).

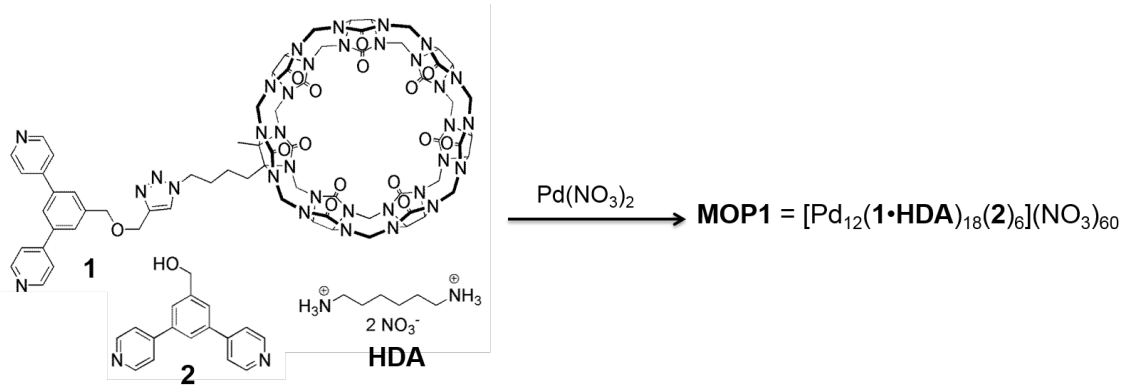


Compound 5a. *N*-Boc-1,4-diaminobutane (250 mg, 1.33 mmol) and 1-bromooctadecane (664 mg, 1.99) were dissolved in acetonitrile (5 mL). The solution was heated at 65 °C for 24 h. After the reaction, a solid precipitate was observed. The reaction mixture was transferred to a centrifuge tube and the solid was collected by centrifugation. The solid was further washed with acetonitrile (3 × 5 mL) by sonication in a centrifuge tube and collected by centrifugation. The

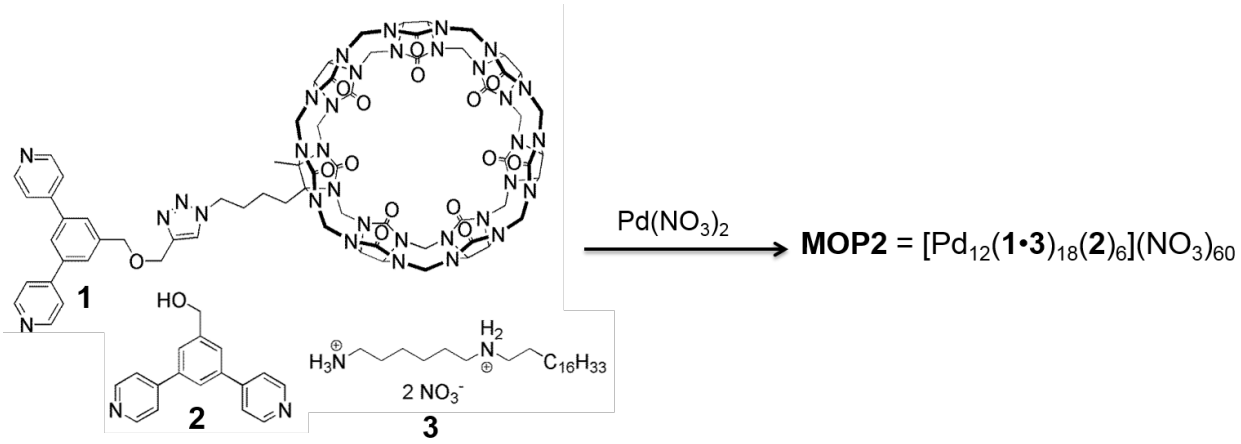
solid material was dried under high vacuum to afford compound **5a** as white solid (430 mg, 73%). Mp. 140-141°C. IR (ATR, cm^{-1}) 3375, 2916, 2849, 1684, 1518, 1471, 1245, 1169, 1043, 871, 717. ^{1}H NMR (600 MHz, $CDCl_3$, RT): δ = 9.05 (s, 1H), 3.15 (t, J = 6.7 Hz, 2H), 3.01 (brs, 2H), 2.95 (brs, 2H), 1.93 (t, J = 7.3 Hz, 2H), 1.89 (t, J = 7.7 Hz, 2H), 1.63 (t, J = 7.1 Hz, 2H), 1.44 (s, 9H), 1.36-1.25 (m, 32H), 0.87 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, RT) δ = 156.5, 47.9, 47.2, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.4, 27.3, 26.8, 25.9 ppm. MS: (ESI, positive) *m/z* 441.4 (100%, $[M+H]^+$).



Compound [5•2NO_3^-]. Compound **5a** (200 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C using an ice bath. Then trifluoroacetic acid (3.0 mL) was added dropwise to the reaction mixture under N_2. The resultant mixture was stirred at RT for 5 h. The solvent was removed under reduced pressure to give solid residue which was redissolved in CH_2Cl_2 (5 mL). The solvent was further evaporated and solid residue was slurried with ethanol (5 mL) and then evaporated to remove residual TFA. The solid was then dissolved in water (5mL) and treated with excess tetrabutyl ammonium nitrate (1.0 g). The mixture was sonicated for 2 h and then solvent was evaporated to dryness. Next, the solid residue was washed with acetonitrile (3 × 10 mL) to remove excess tetrabutyl ammonium salt. The solid residue was collected by centrifugation and dried under vacuum to afford [**3**•2NO_3^-] as white solid (142 mg, 67%). Mp. 105 °C. IR (ATR, cm^{-1}) 2917, 2848, 1467, 1447, 1397, 1162, 1046, 1033, 798, 720. ^{1}H NMR (600 MHz, D_2O, RT): δ = 2.98 (t, ^3J = 7.8 Hz, 4H), 1.69 (m, 6H), 1.42 (m, 30H), 0.85 (t, ^3J = 6.6 Hz, 3H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6, RT) δ = 46.6, 46.3, 38.4, 31.2, 28.9, 28.9, 28.8, 28.7, 28.6, 28.4, 26.3, 25.8, 25.4 ppm. MS: (ESI, positive) *m/z* 341.4 (100%, $[M-H-2NO_3]^+$).

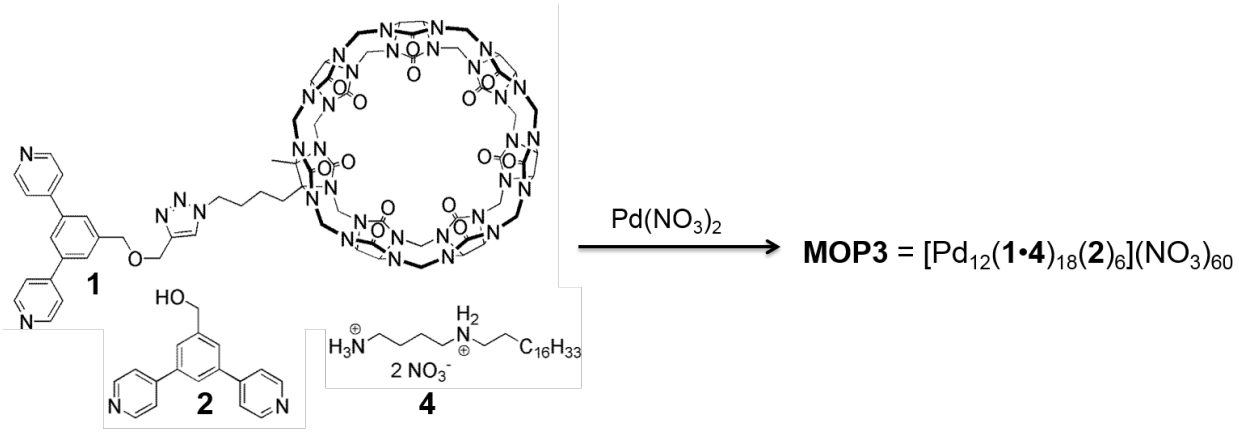


MOP1 = $[Pd_{12}(1•HDA)_{18}(2)_6](NO_3)_{60}$. Compound **1** (4.90 mg, 3.11 μmol) was dissolved in DMSO-d_6 (300 μL). Then, aqueous [**HDA**•$2NO_3$] (0.704 mg, 3.11 μmol, 30 μL) was added to the solution and stirred at 60 °C for 2 h. To the mixture compound **2** (0.272 mg, 1.04 μmol), and $Pd(NO_3)_2$ (1.11 mg, 4.15 μmol) were added and the resulting solution was stirred at 70 °C for 3d. The quantitative formation of **MOP1** was observed by ^{1}H NMR and DOSY NMR. Then solution of **MOP1** was transferred to a dialysis tube (MWCO 3500) and the solution was dialyzed for 2 d against D_2O (every 6 h D_2O was replaced fresh D_2O). Mp > 300 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.44 (brs), 8.26−7.91 (brm), 5.61 (m), 5.41−5.35 (m), 4.19−4.15 (m), 3.98 (s), 3.17 (s), 2.82 (s), 1.78 (brs), 1.62 (brs), 1.22−1.09 (m) ppm. DOSY NMR (600 MHz, DMSO-d_6) D = 2.90×10^{-11} m^2/s, ^{1}H NMR (600 MHz, D_2O) δ = 9.05 (brs), 8.05 (brs), 7.95 (brs), 5.78−5.72 (m), 5.56−5.51 (m), 4.35−4.23 (m), 3.65 (m), 3.17 (brs), 2.54 (m), 1.89 (s), 1.64 (brs), 1.36−1.26 (m), 0.86 (brs), 0.61 (brs) ppm. DOSY NMR (600 MHz, D_2O) D = 6.31×10^{-11} m^2/s.

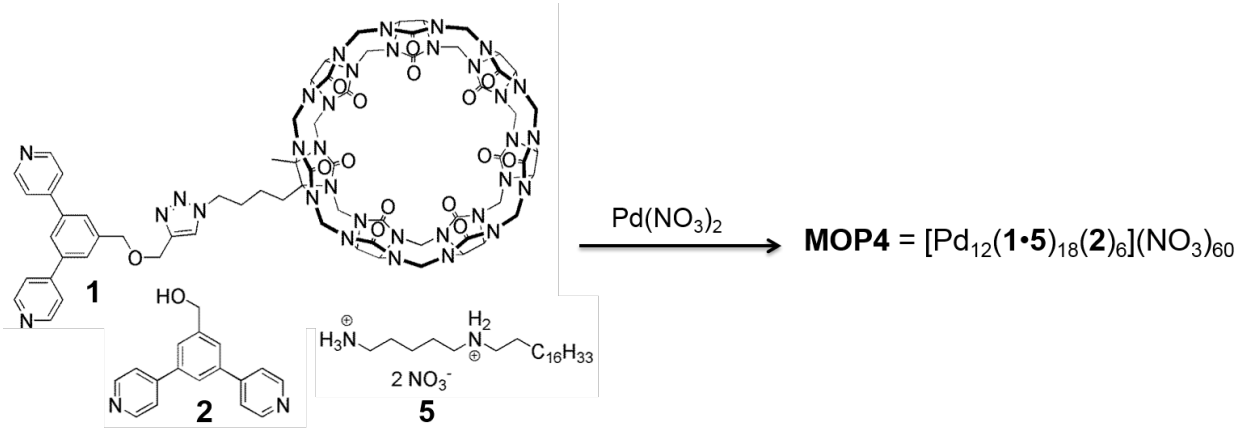


MOP2. Compound **1** (3.59 mg, 2.28 μmol) was dissolved in DMSO-d_6 (300 μL). Then an aqueous solution of [**3**•$2NO_3$] (1.13 mg, 2.28 μmol) was added to the solution and stirred for 2 h at 60 °C. To this mixture, compound **2** (0.199 mg, 0.76 μmol) and $Pd(NO_3)_2$ (0.810 mg, 3.04 μmol) were added and the resulting mixture was heated at 70 °C for 3 d. Quantitative formation of **MOP2** was observed by ^{1}H NMR and DOSY NMR. Then the solution of **MOP2** was transferred to a dialysis tube (MWCO 3500) and the solution was dialyzed for 2 d against D_2O

(every 6 h D_2O was replaced fresh D_2O). Mp > 300 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.41 (brs), 8.29−7.94 (brm), 5.66−5.59 (m), 5.41−5.34 (m), 4.19−4.15 (m), 3.98 (s), 3.35 (m), 3.17 (s), 1.82 (brs), 1.69 (brs), 1.43 (brs), 1.23−1.05 (m), 0.95−0.92 (m), 0.86−0.84 (m), 0.74 (brs), 0.52 (brs) ppm. DOSY NMR (600 MHz, DMSO-d_6) D = 3.41 × 10^{-11} m^2/s, ^{1}H NMR (600 MHz, D_2O) δ = 9.02 (brs), 8.04 (brs), 7.93 (brs), 5.73 (brs), 5.56 (brs), 4.27 (brs), 3.17 (m), 3.10 (brs), 2.97 (brs), 1.89 (brs), 1.63 (brs), 1.27−1.25 (m), 0.83 (brs), 0.59 (brs) ppm. DOSY NMR (600 MHz, D_2O) D = 7.94 × 10^{-11} m^2/s.



MOP3. Compound **1** (4.50 mg, 2.86 μmol) was dissolved in DMSO-d_6 (300 μL). Then an aqueous solution of [**4**•2NO_3] (1.37 mg, 2.86 μmol) was added to the solution and the mixture stirred for 2 h at 60 °C. Compound **2** (0.250 mg, 0.953 μmol) and $Pd(NO_3)_2$ (1.02 mg, 3.81 μmol) were added and the resulting mixture was heated at 70 °C for 3 d. Quantitative formation of **MOP3** was observed by ^{1}H NMR and DOSY NMR. Then the solution of **MOP3** was transferred to a dialysis tube (MWCO 3500) and the solution was dialyzed for 3d against D_2O (every 6 h D_2O was replaced fresh D_2O). Mp > 300 °C, ^{1}H NMR (600 MHz, D_2O) δ = 9.07 (brs), 8.07 (brs), 7.95 (brs), 5.77−5.72 (m), 5.57−5.51 (m), 4.34−4.23 (m), 3.18 (brs), 3.07 (brs), 1.65 (brs), 1.38−1.28 (brs), 0.097 (s), 0.086 (brs) ppm. DOSY NMR (600 MHz, D_2O) D = 8.12 × 10^{-11} m^2/s.



MOP4. Compound **1** (3.2 mg, 2.03 μmol) was dissolved in DMSO-d_6 (300 μL). Then an aqueous solution of [**5**•2NO_3] (0.947 mg, 2.03 μmol) was added to the solution and stirred for 2 h at 60 °C. Compound **2** (0.177 mg, 0.677 μmol) and $Pd(NO_3)_2$ (0.722 mg, 2.71 μmol) were added and the resulting mixture was heated at 70 °C for 3 d. Quantitative formation of **MOP4** was observed by ^{1}H NMR and DOSY NMR. Then the solution of **MOP4** was transferred to a dialysis tube (MWCO 3500) and the solution was dialyzed for 2 d against D_2O (every 6 h D_2O was replaced fresh D_2O). Mp > 300 °C. ^{1}H NMR (600 MHz, D_2O) δ = 9.06 (brs), 8.08 (brs), 7.95 (brs), 5.78−5.75 (m), 5.54−5.51 (m), 4.29−4.24 (m), 3.65 (m), 3.17 (brs), 2.56 (brs), 2.35 (brs), 1.89 (s), 1.68 (brs), 1.37−1.22 (m), 0.95 (m), 0.86 (brs), 0.61 (brs) ppm. DOSY NMR (600 MHz, D_2O) D = 7.51×10^{-11} m^2/s.

General Procedure for Dye/Drug Encapsulation:

MOPs dissolved in water were added to solid Nile red or doxorubicin (pretreated with NEt_3). The mixture was stirred at room temperature for 2h. Then the mixture was centrifuged to remove insoluble dye/drug. Then the solution was filtered through a membrane syringe filter to obtain a clear solution of **NR@MOP** and **DOX@MOP**. As a control, the same amount of Nile red or doxorubicin was added to water and stirred for 2h at room temperature. After centrifugation followed by filtration gave an aqueous solution of **NR** and **DOX**.

General procedure for photoirradiation.

Trans-**6** or a mixture of *trans*-**6** with other compounds were transferred to an NMR tube and the NMR tube was caped rubber septum. The resulting solution was purged with N_2 for 10−15 min and then cap was sealed with teflon tape. The NMR tube was placed the inside a photoreactor and irradiated using λ = 350 nm light for 3h. The reaction was followed by ^{1}H NMR.

Mixture of **NR@MOP4** and 54 equiv. of *trans*−**6** was placed inside a fluorescence cuvette and the resulting solution was purged with N_2 for 10−15 min. The cuvette was sealed with a teflon cap and then placed inside a photoreactor. Photoirradiation at λ = 350 nm was continued for 4h and the fluorescence intensity of the resulting solution was measured to quantify the photochemical−triggered release of **NR** from **MOP4**.

Reference.

1) Zhang, M. Cao L. Isaacs, L. *Chem. Commun.* **2014**, *50*, 14756−14759.

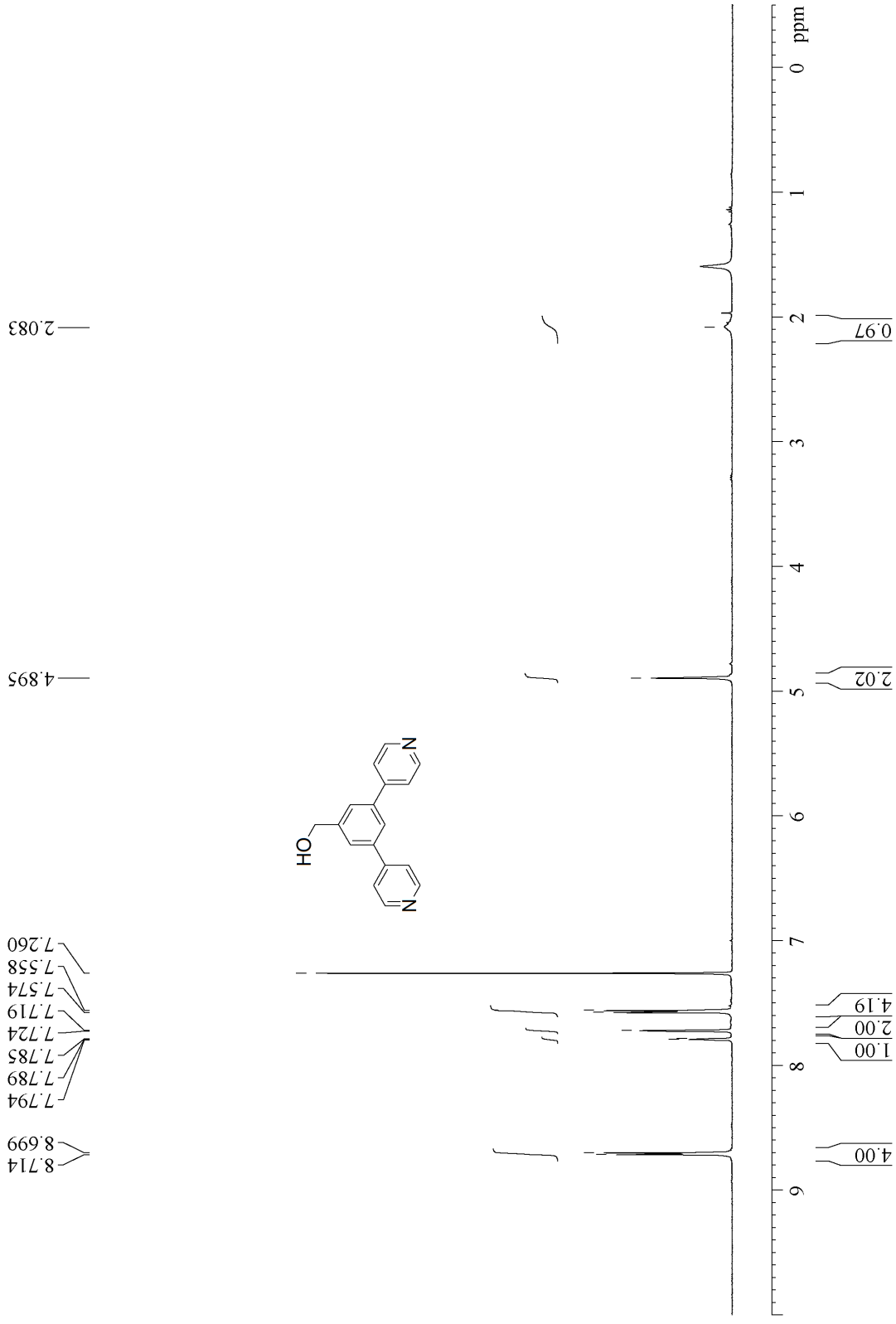


Figure S1. ^{1}H NMR recorded (400 MHz, $CDCl_3$, RT) for **2**.

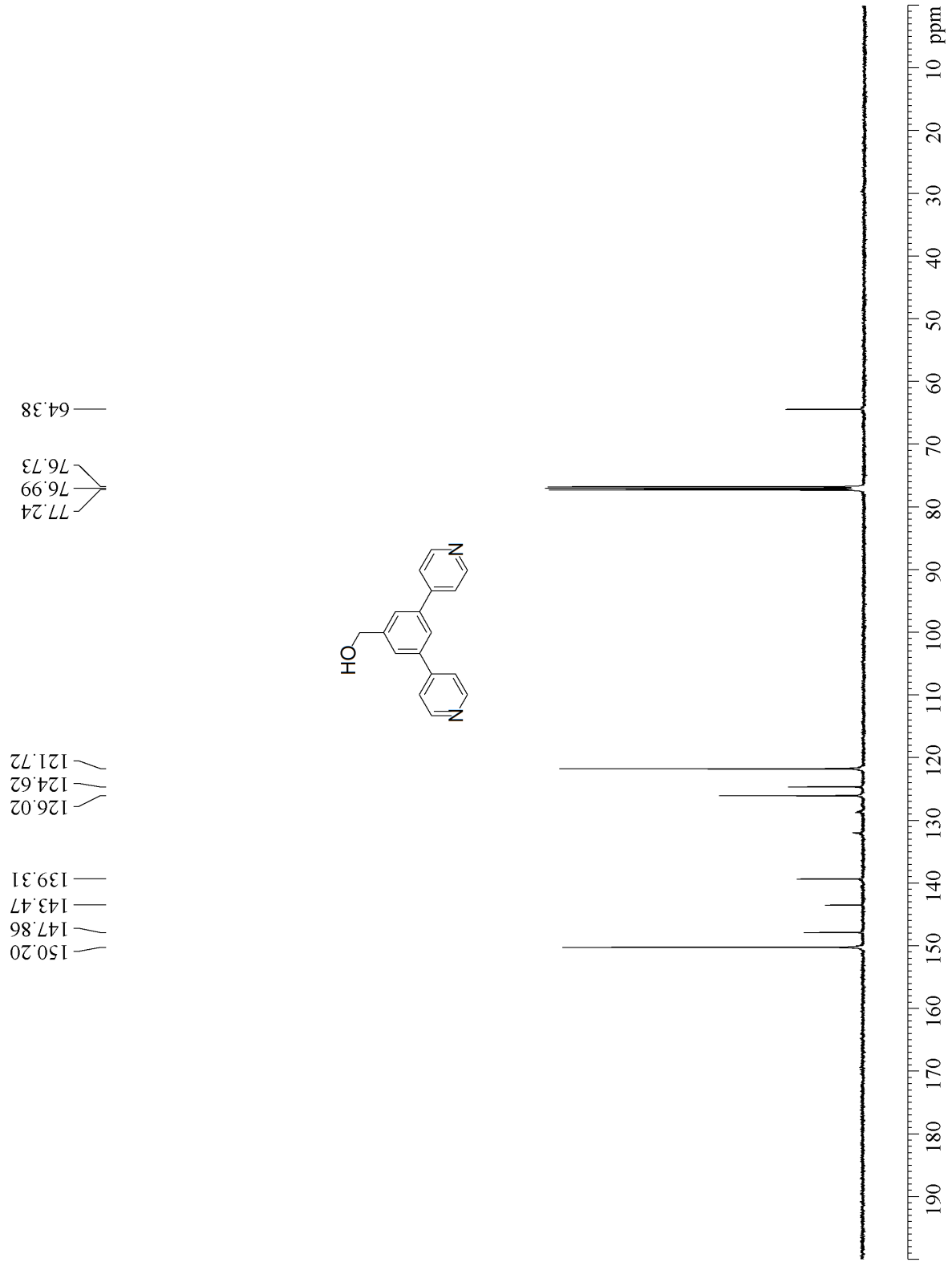


Figure S2. ^{13}C NMR recorded (125 MHz, $CDCl_3$, RT) for **2**.

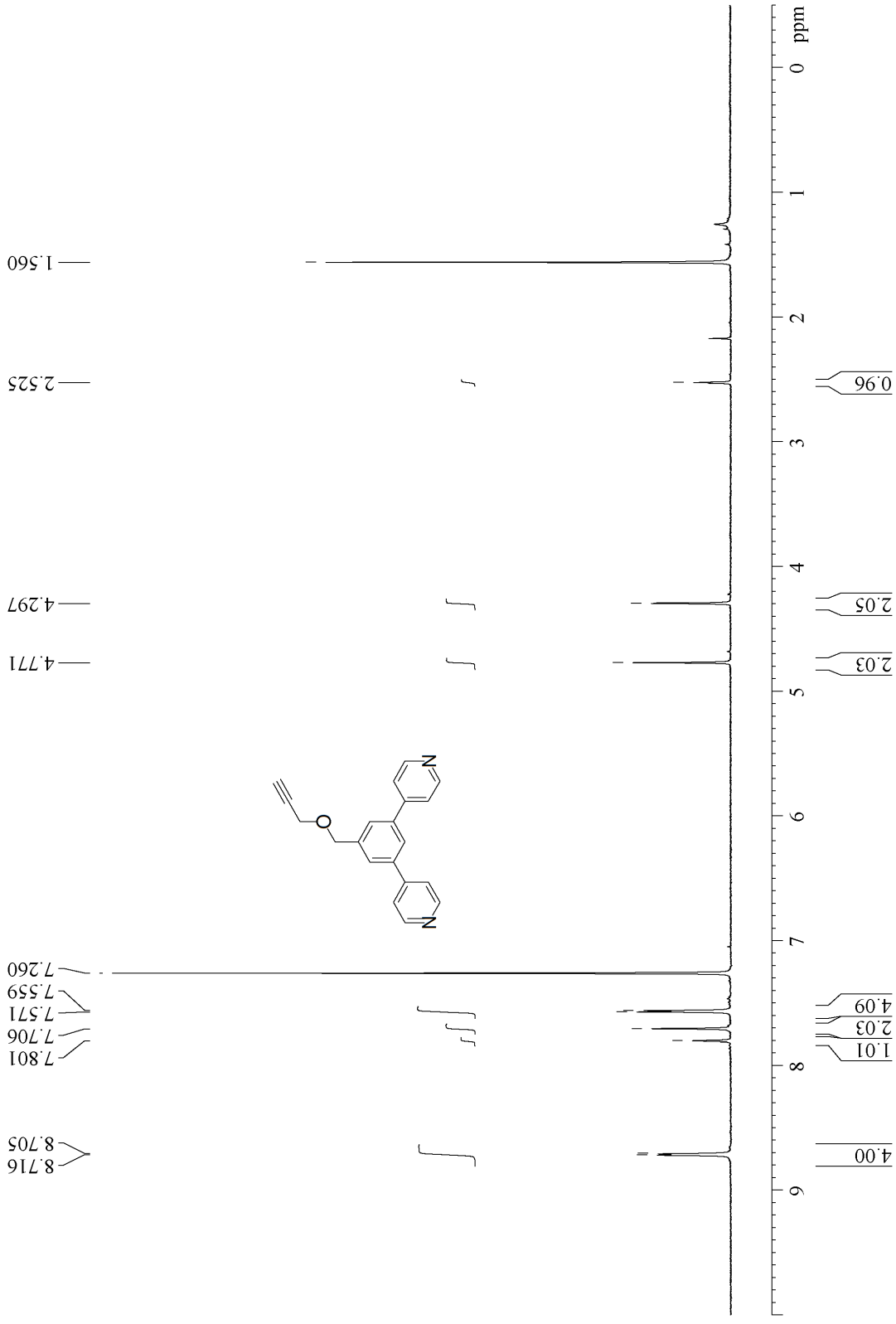


Figure S3. ^{1}H NMR recorded (400 MHz, $CDCl_3$, RT) for **2a**.

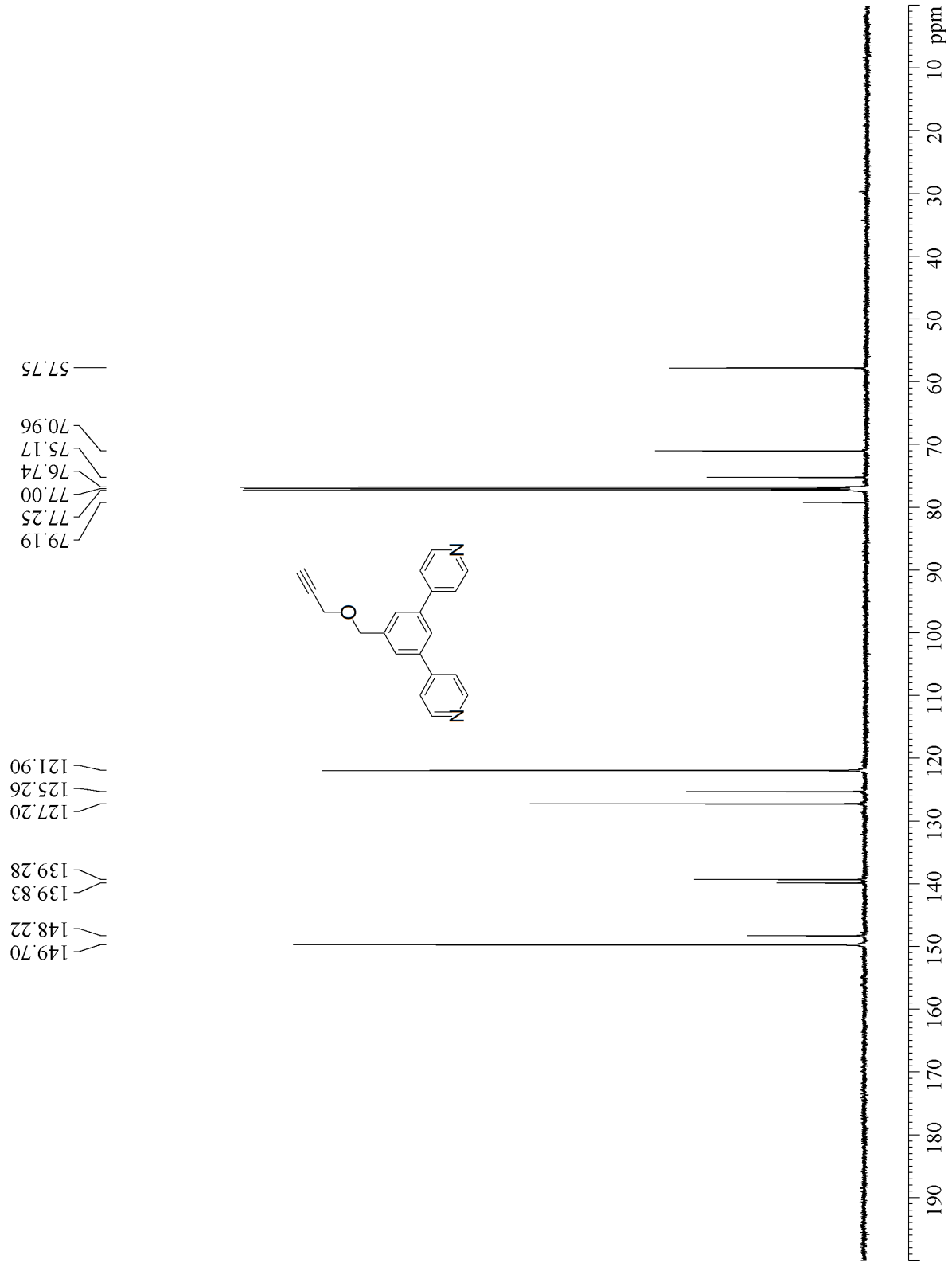


Figure S4. ^{13}C NMR recorded (125 MHz, $CDCl_3$, RT) for **2a**.

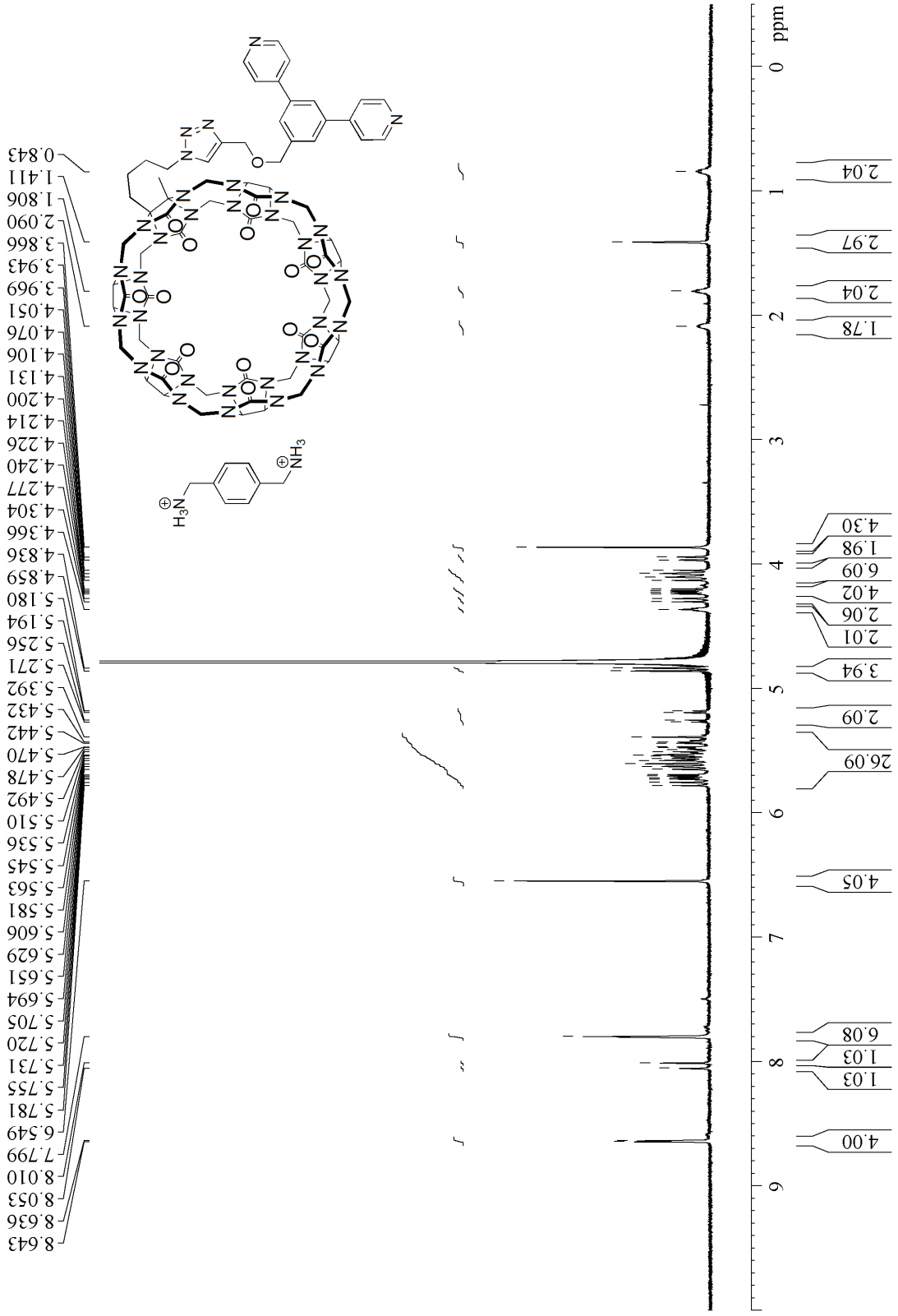


Figure S5. ^{1}H NMR recorded (600 MHz, D_2O, RT) for a mixture of **1** and PXDA.

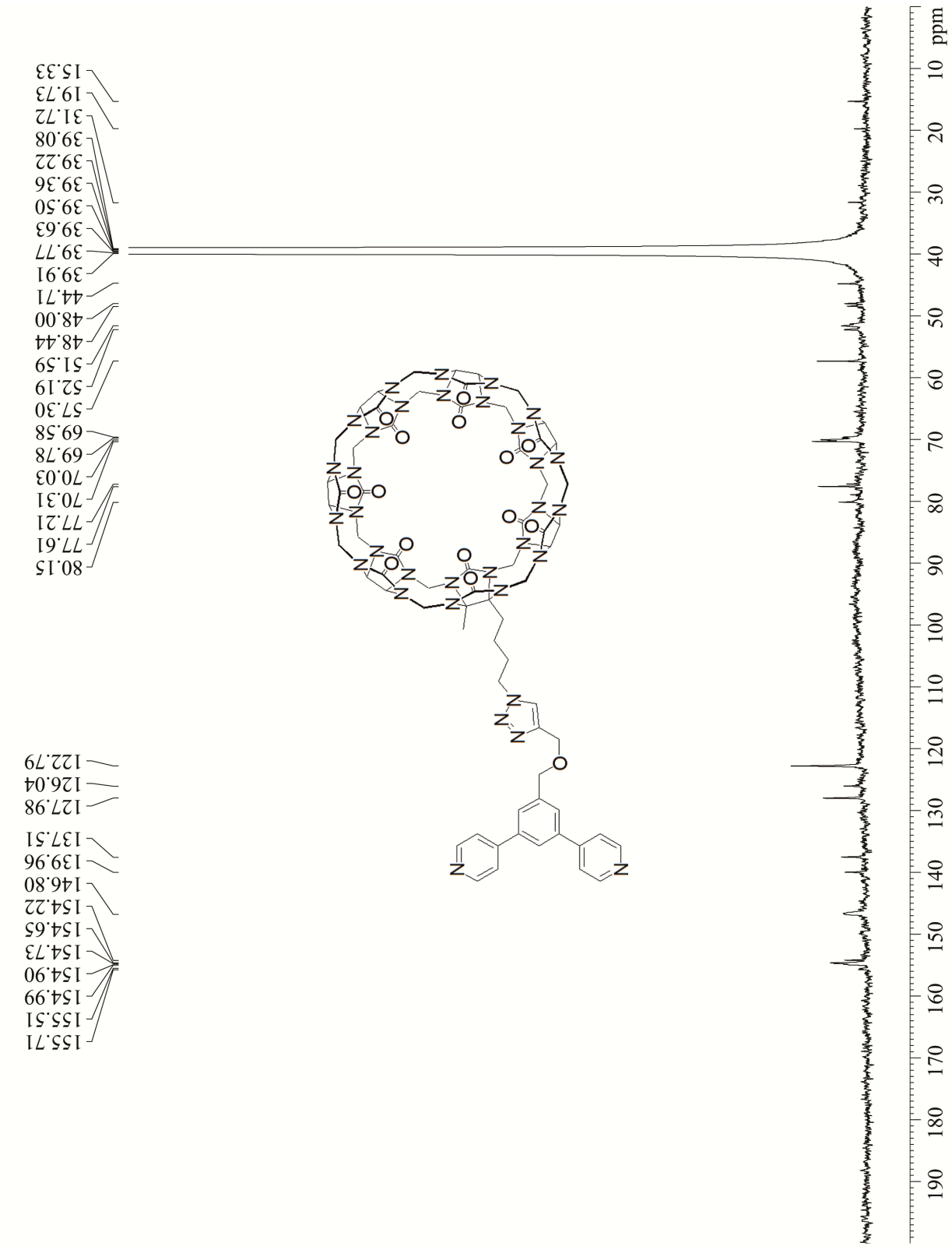


Figure S6. ^{13}C NMR recorded (150 MHz, DMSO, RT) for **1**.

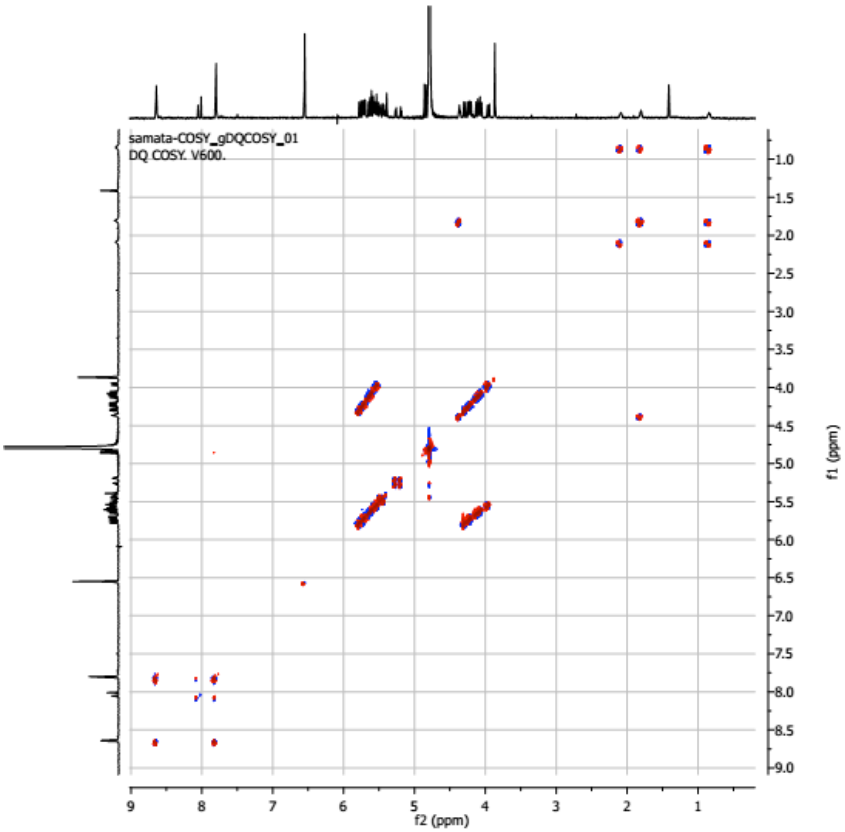


Figure S7. DQCOSY ^{1}H NMR spectrum recorded (600 MHz, D_2O, RT) for a mixture of **1** and PXDA.

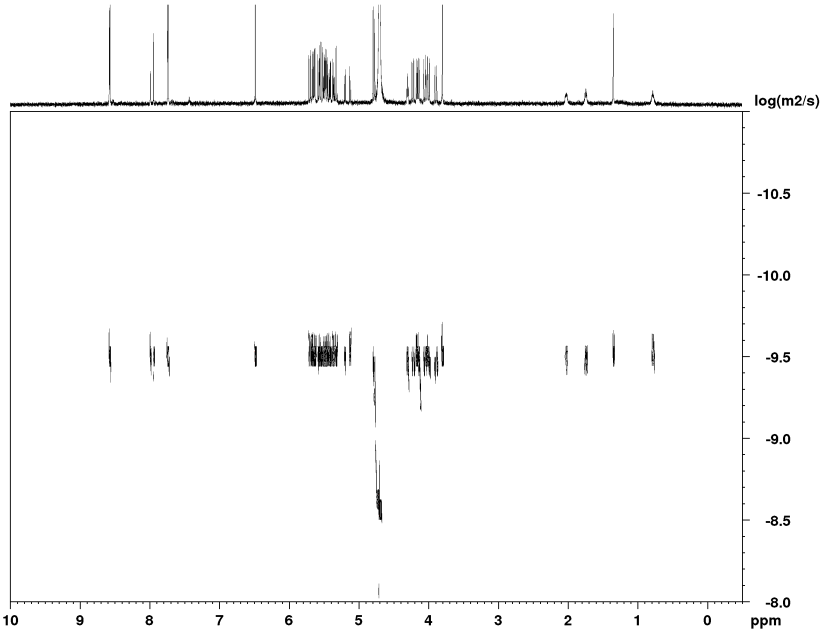


Figure S8. DOSY spectrum recorded (600 MHz, D_2O, RT) for a mixture of **1** and PXDA.

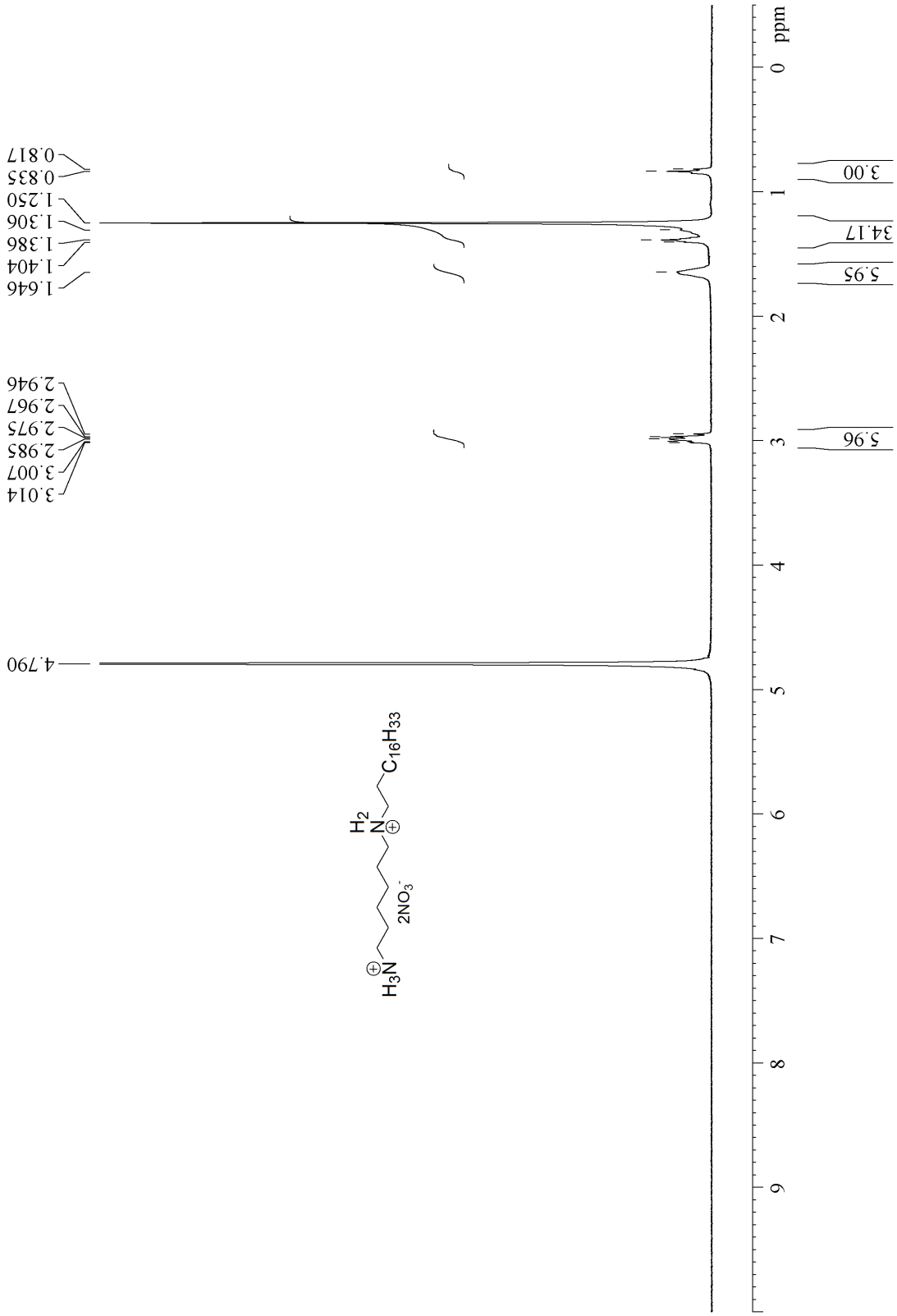


Figure S9. ^{1}H NMR recorded (400 MHz, D_2O, RT) for [**3**•$2NO_3^-$**]**.

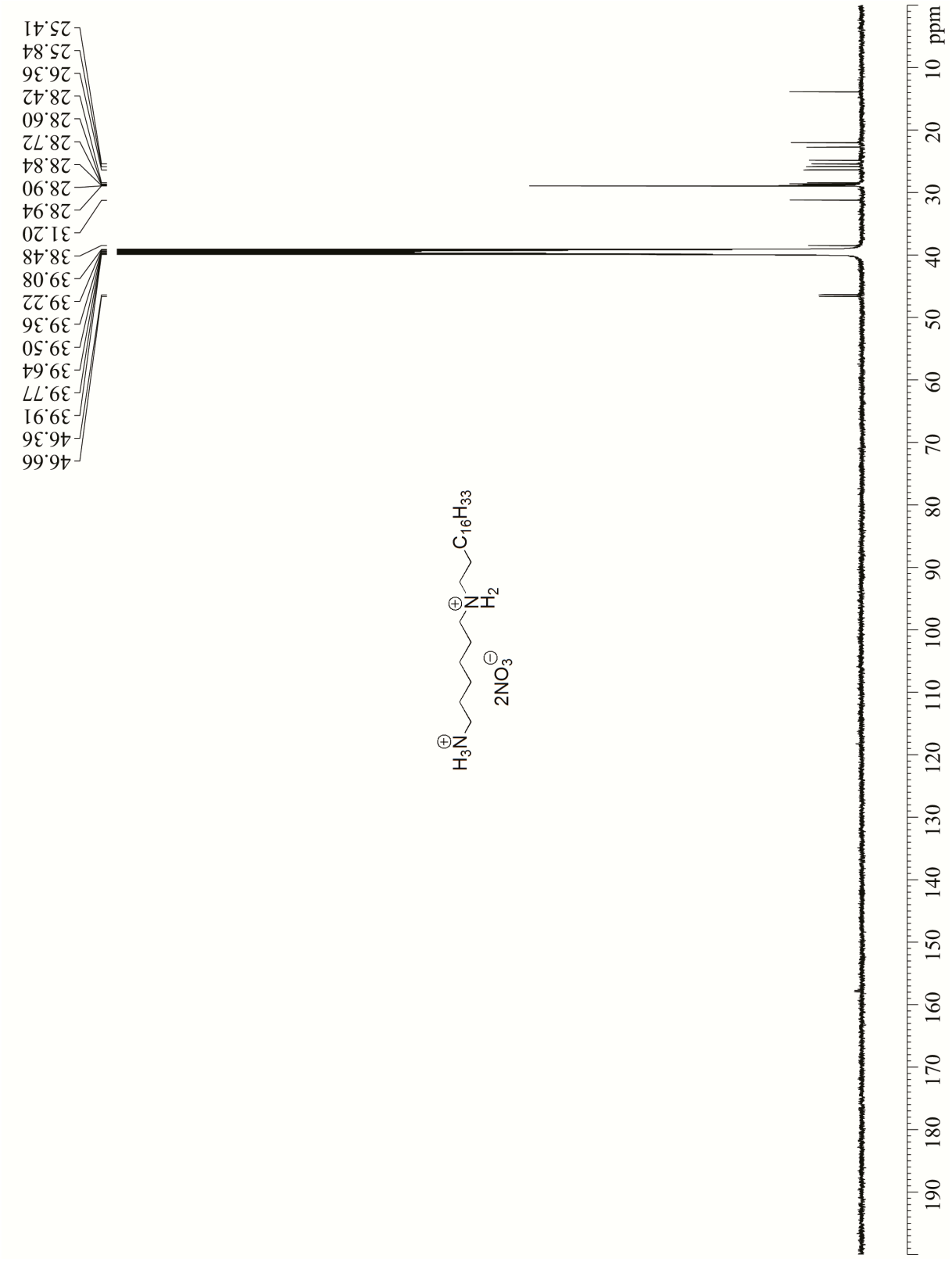


Figure S10. ^{13}C NMR recorded (150 MHz, DMSO, RT) for [**3**•$2NO_3^-$].

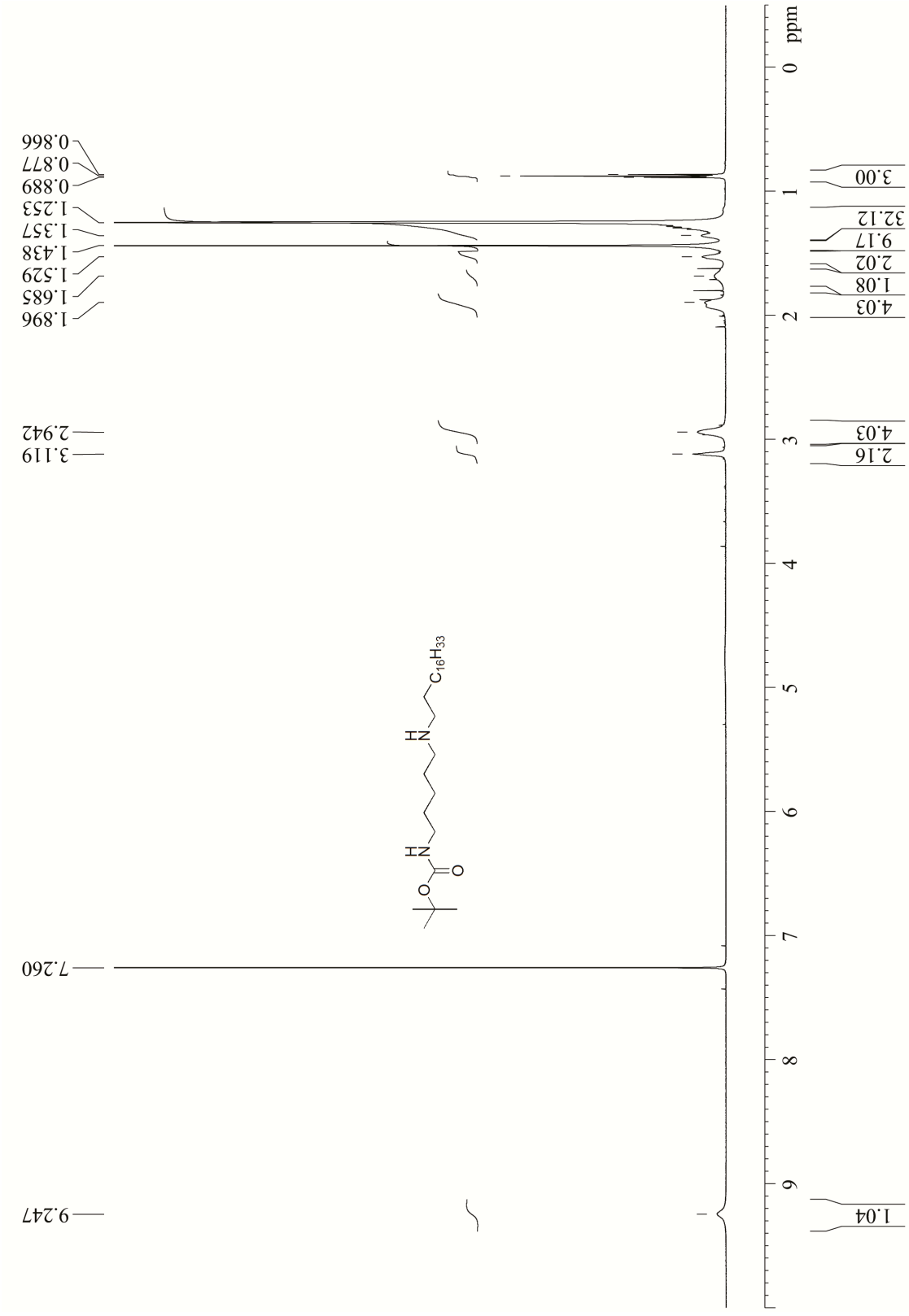


Figure S11. ^{1}H NMR recorded (600 MHz, $CDCl_3$, RT) for **4a**.

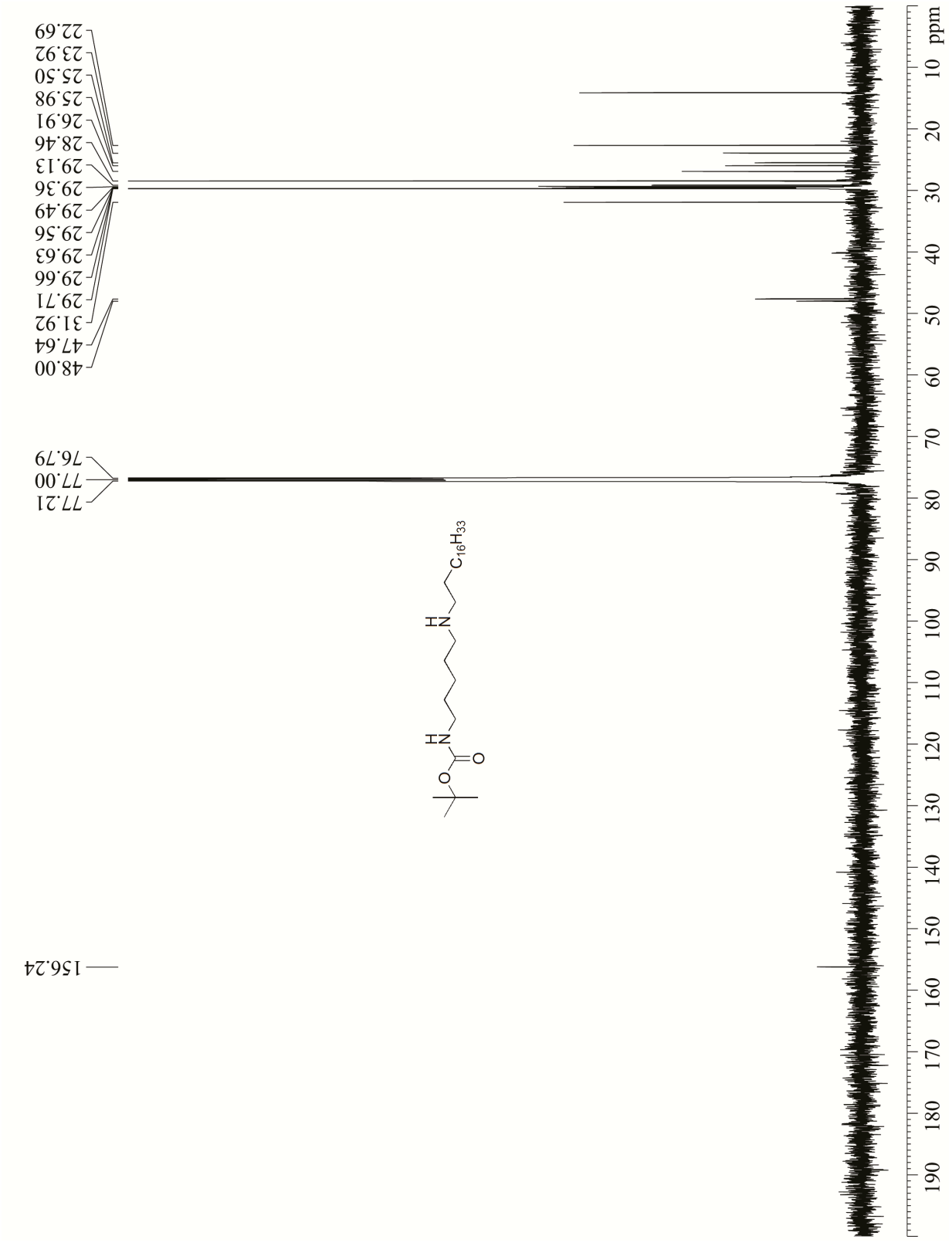


Figure S12. ^{13}C NMR recorded (150 MHz, $CDCl_3$, RT) for **4a**.

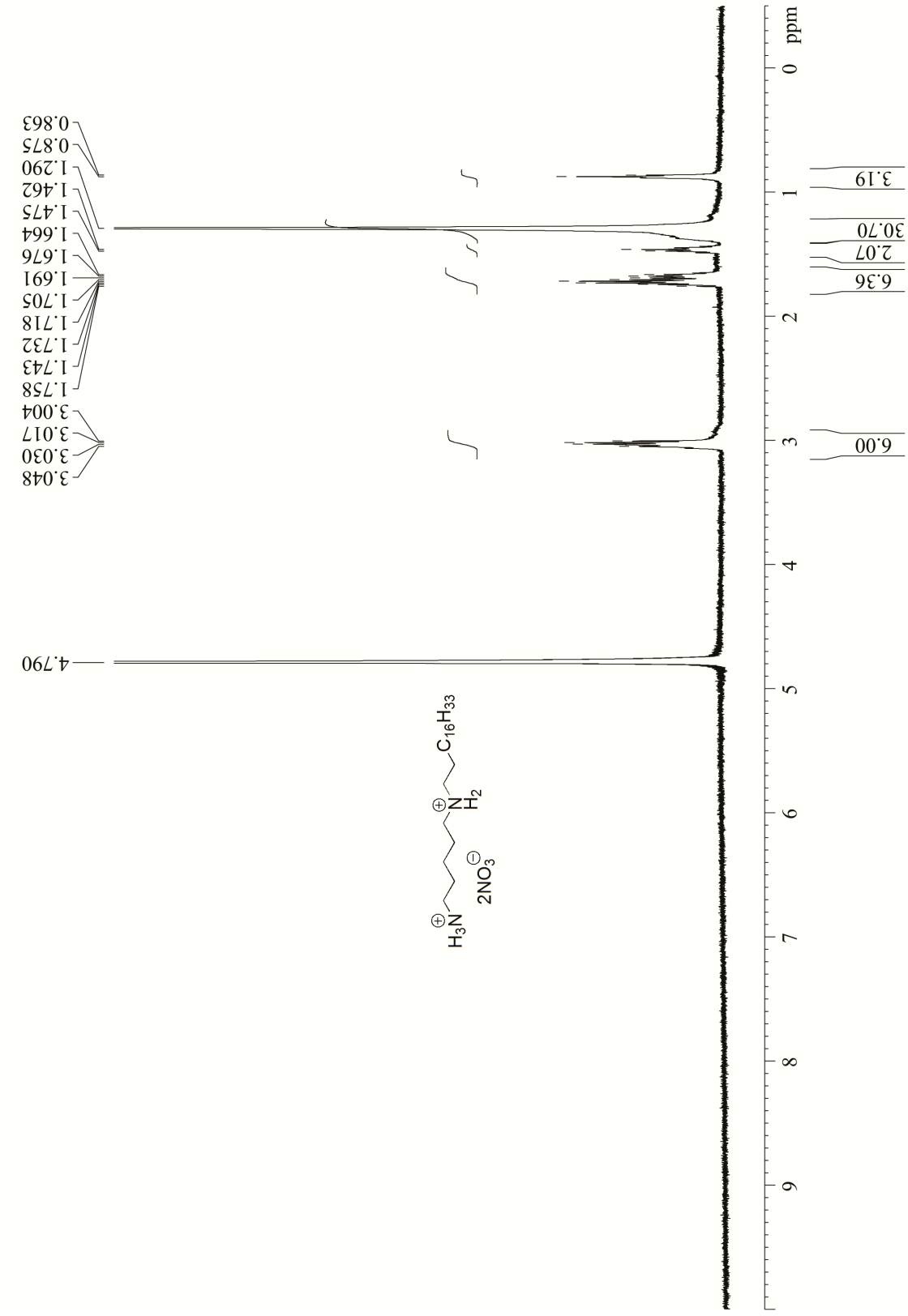


Figure S13. ^{1}H NMR recorded (600 MHz, D_2O, RT) for [**4**•2NO_3^-].

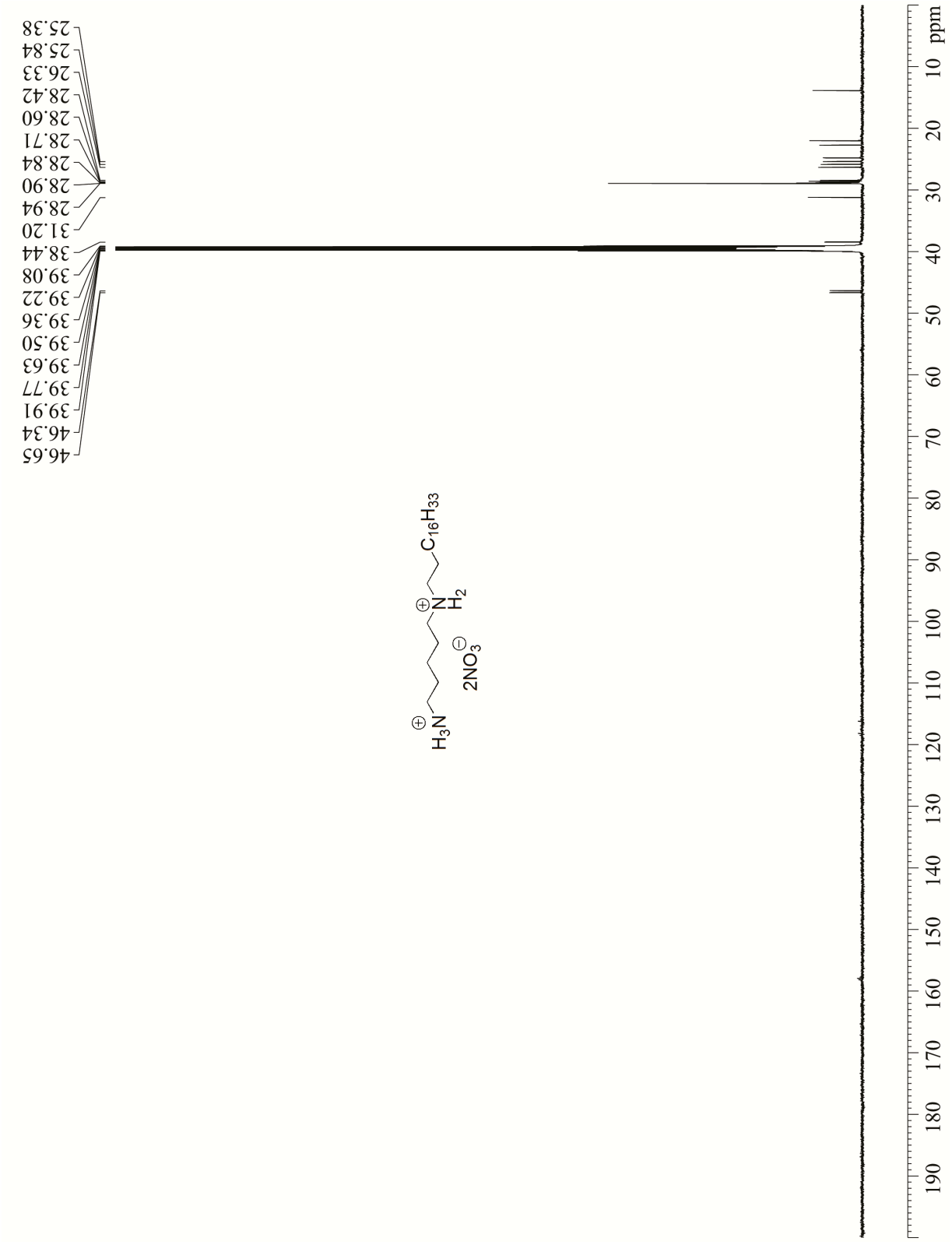


Figure S14. ^{13}C NMR recorded (150 MHz, DMSO, RT) for [**4**•$2NO_3^-$].

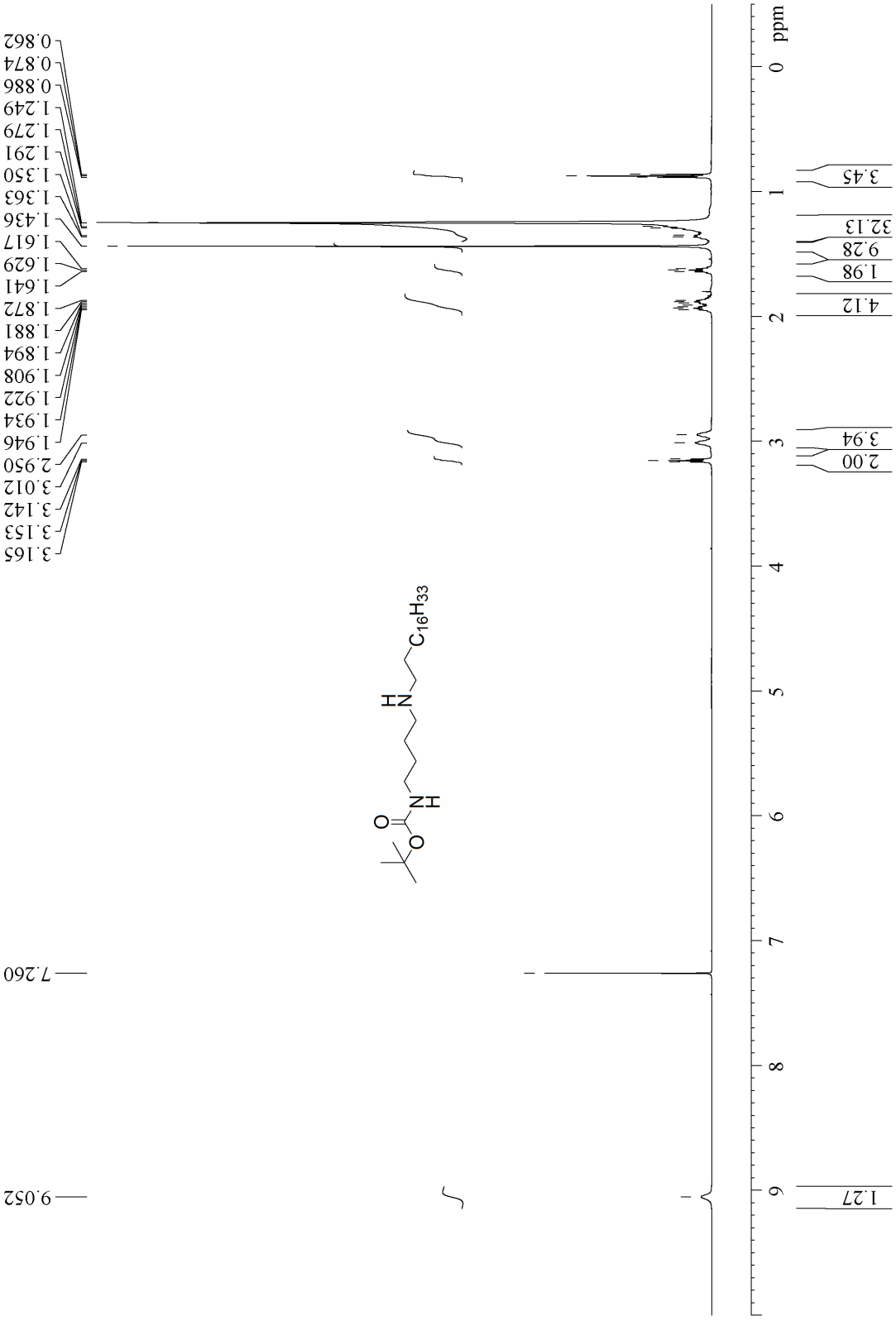


Figure S15. ^{1}H NMR recorded (600 MHz, $CDCl_3$, RT) for **5a**.

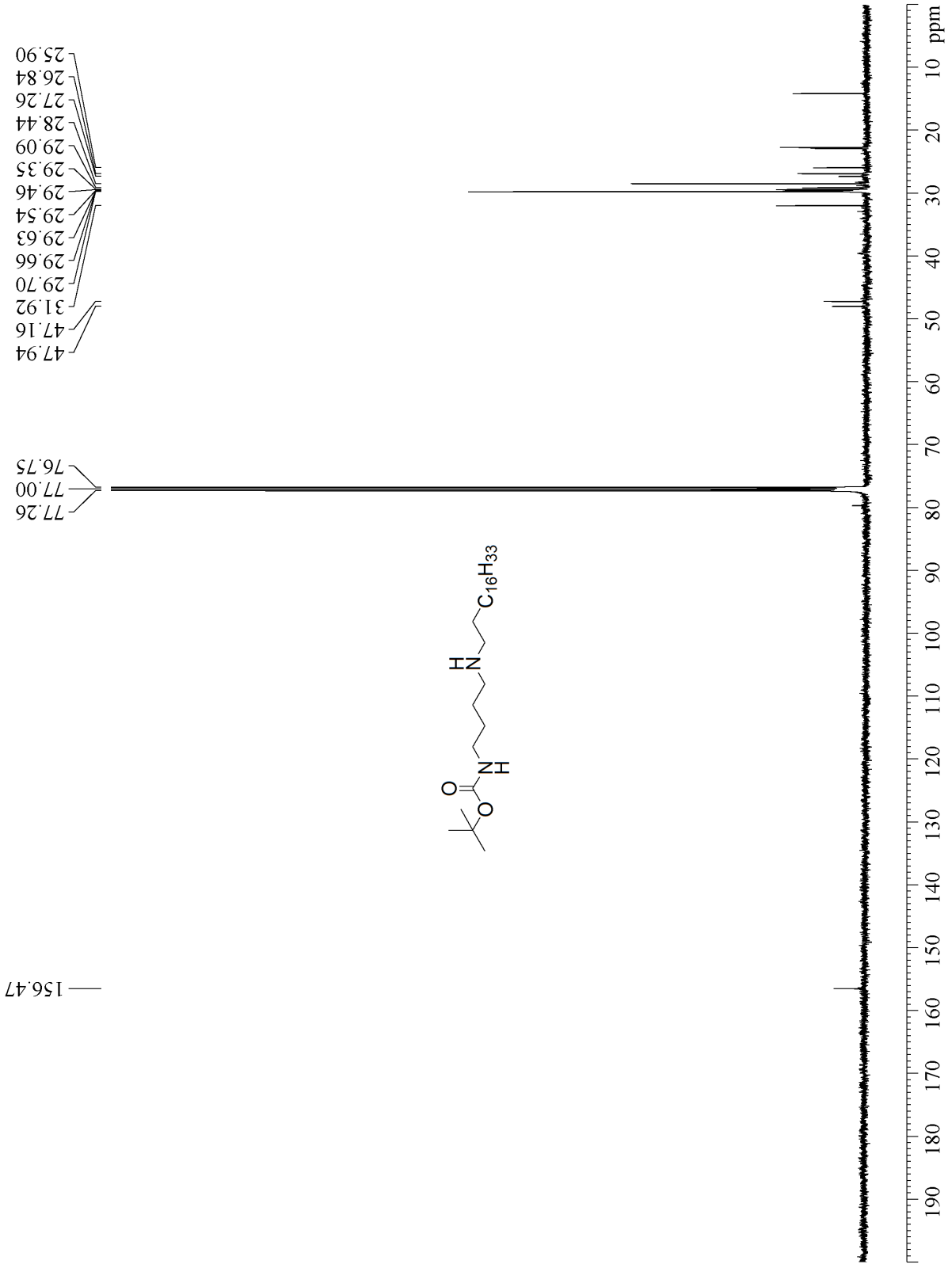


Figure S16. ^{13}C NMR recorded (125 MHz, $CDCl_3$, RT) for **5a**.

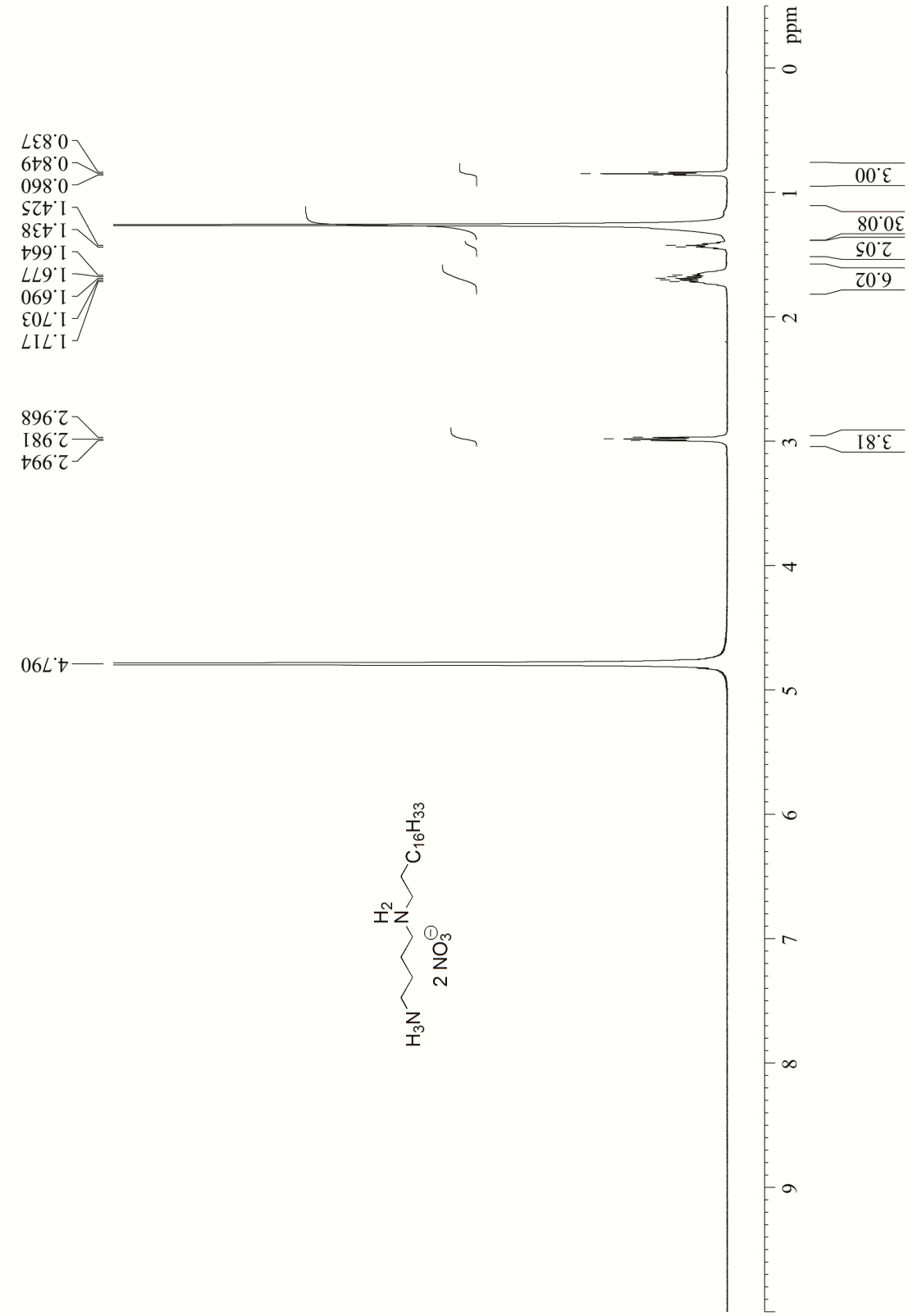


Figure S17. ^{1}H NMR recorded (600 MHz, D_2O, RT) for **5**.

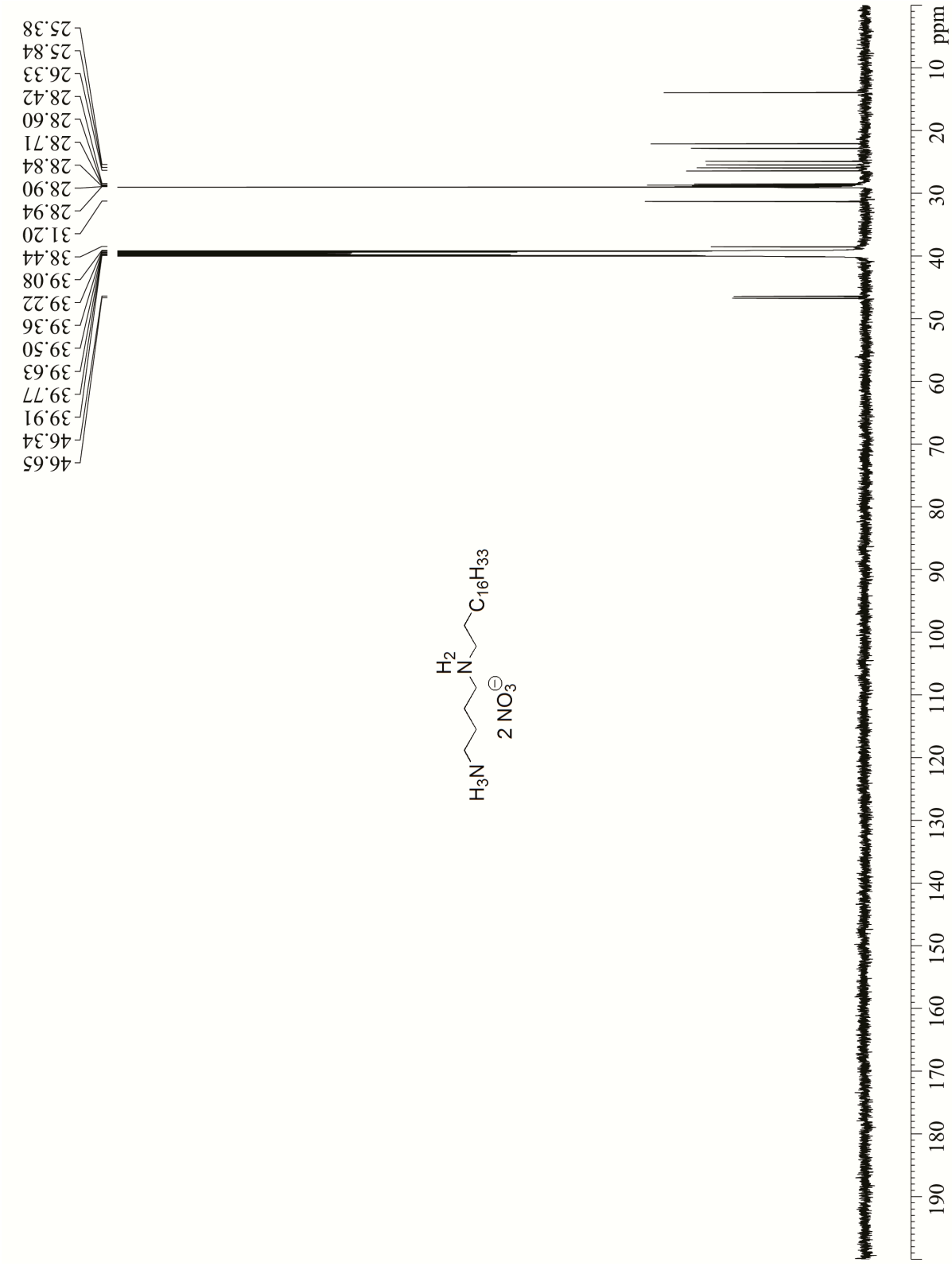


Figure S18. ^{13}C NMR recorded (125 MHz, D_2O, RT) for **5**.

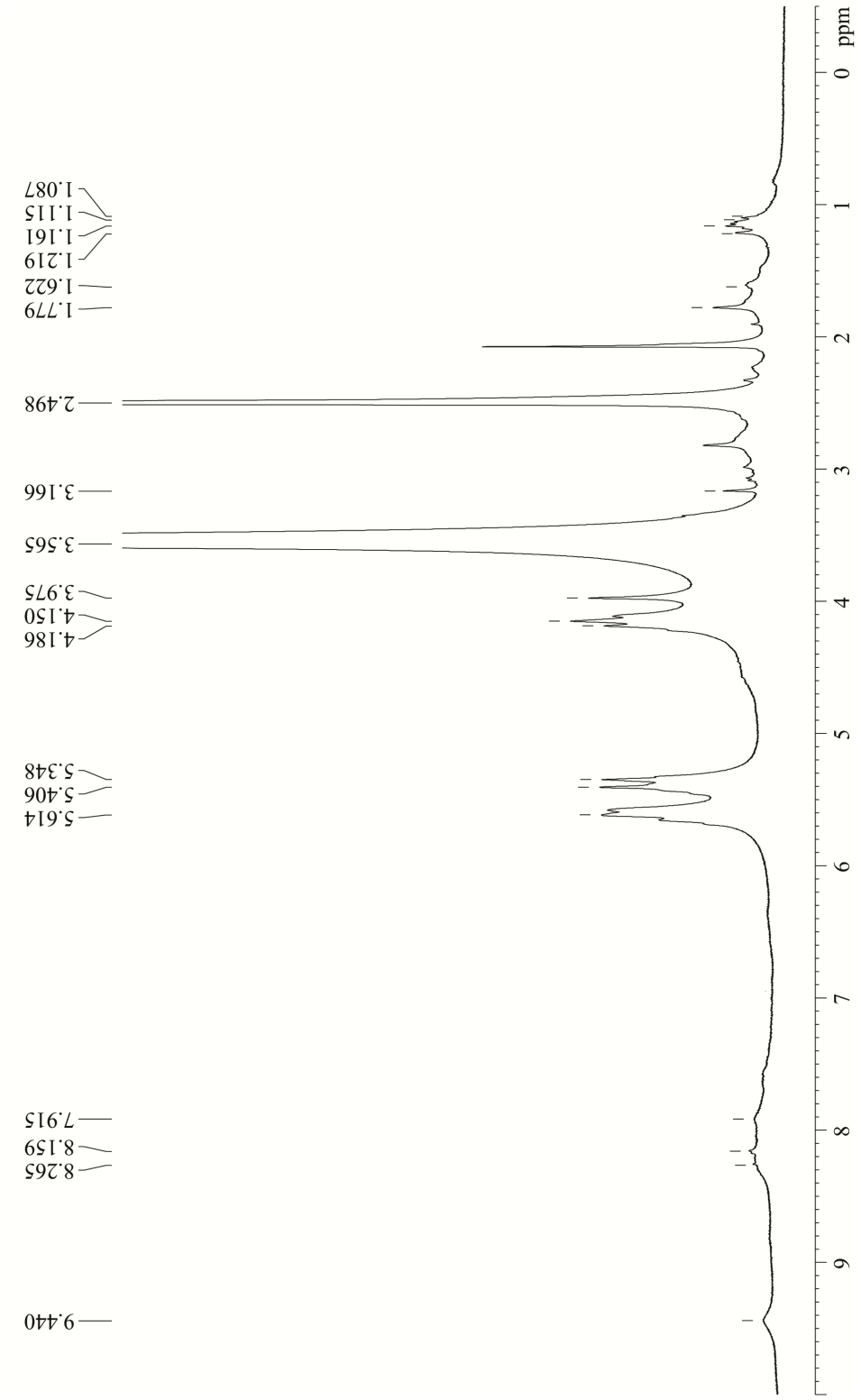


Figure S19. ^{1}H NMR recorded (600 MHz, DMSO-d_6, RT) for **MOP1** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{HDA})_{18}(\mathbf{2})_6](NO_3)_{60}$.

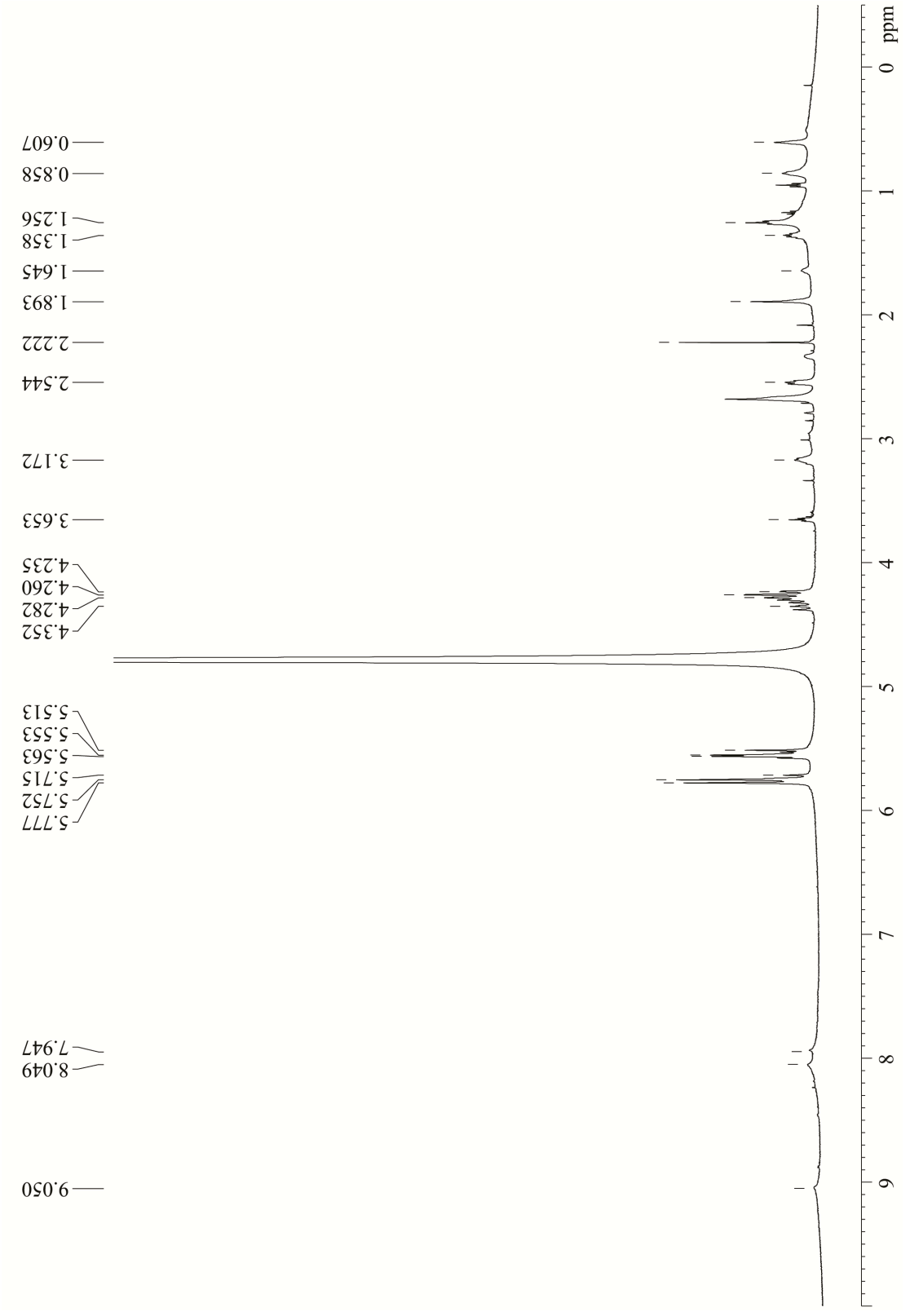


Figure S20. ^{1}H NMR recorded (600 MHz, D_2O, RT) for **MOP1** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{HDA})_{18}(\mathbf{2})_6](NO_3)_{60}$.

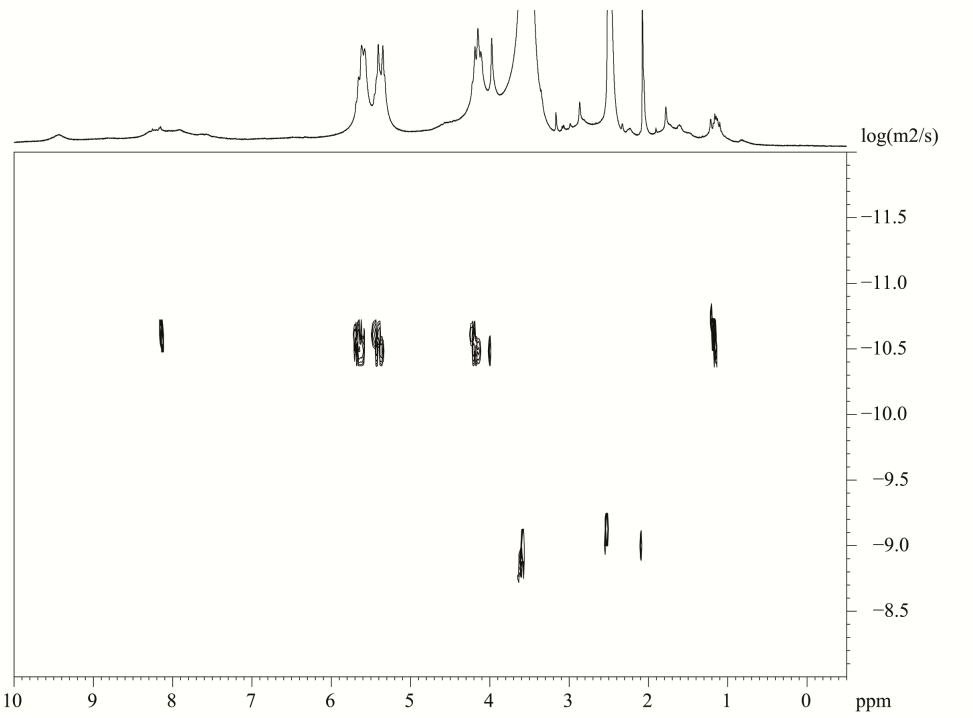


Figure S21. DOSY NMR recorded for (600 MHz, DMSO-d_6, 300 K) **MOP1** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{HDA})_{18}(\mathbf{2})_6](NO_3)_{60}$.

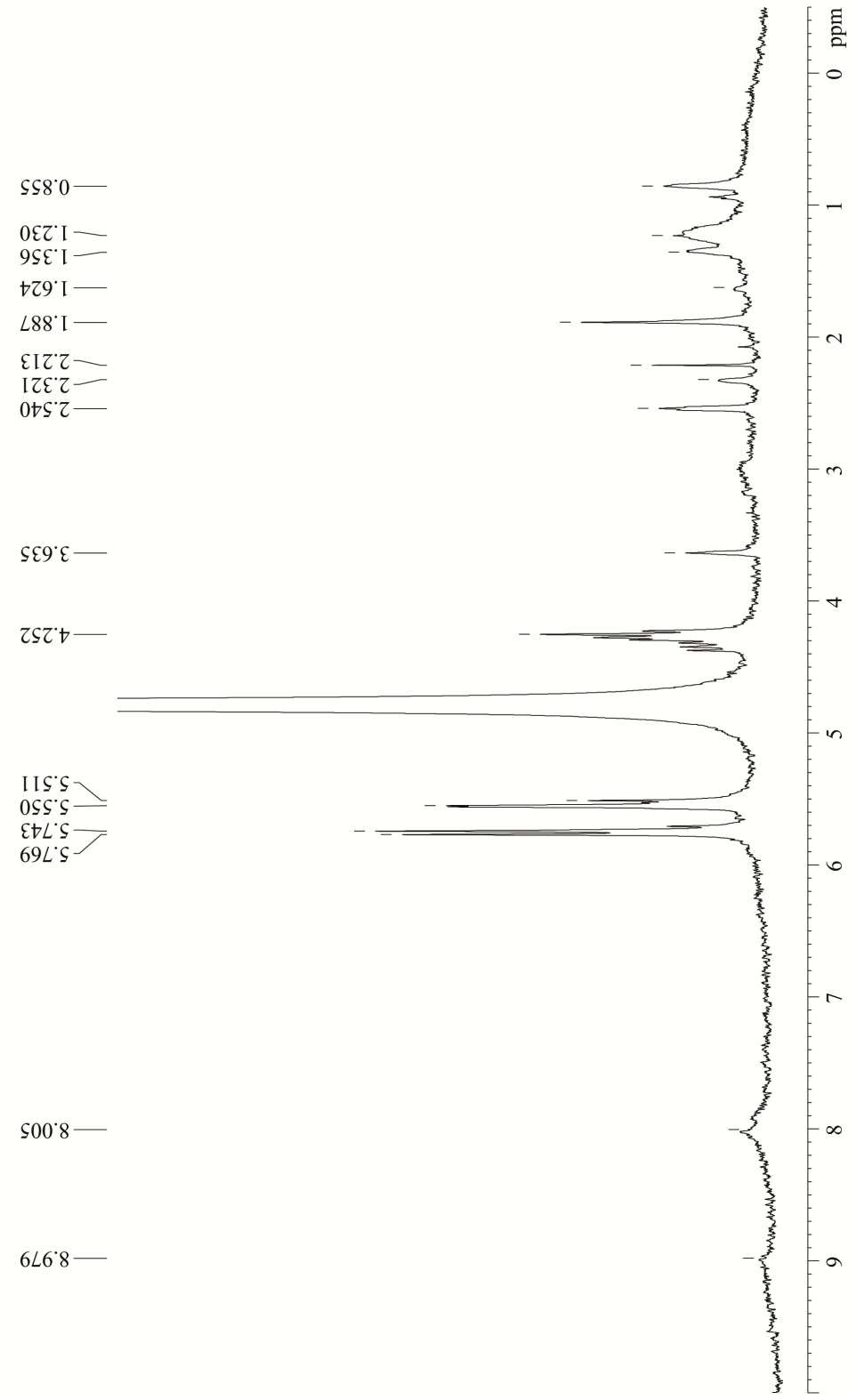


Figure S22. ^{1}H NMR recorded for (600 MHz, D_2O, RT) mixture of **MOP1** and 24 equiv. of **ADA** to afford $Pd_{12}(\mathbf{1}\bullet\mathbf{ADA})_{18}(\mathbf{2})_6](NO_3)_{42}$.

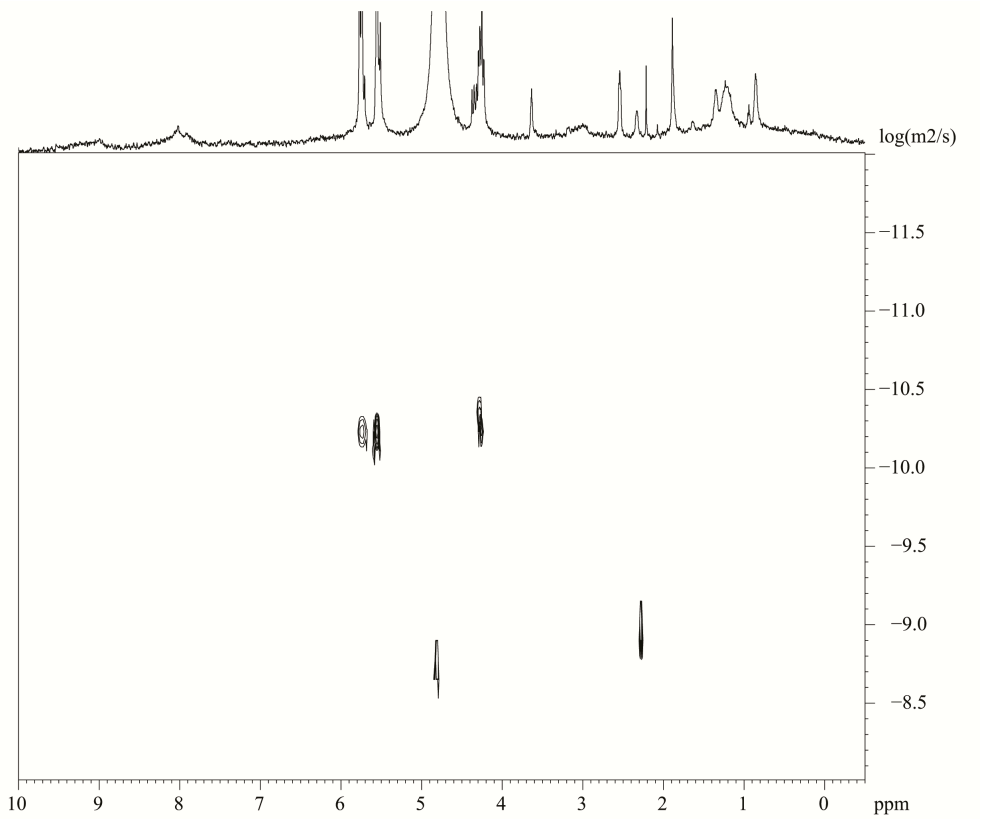


Figure S23. DOSY NMR recorded for (600 MHz, D_2O, RT) **MOP1** and 24 equiv. of **ADA**.

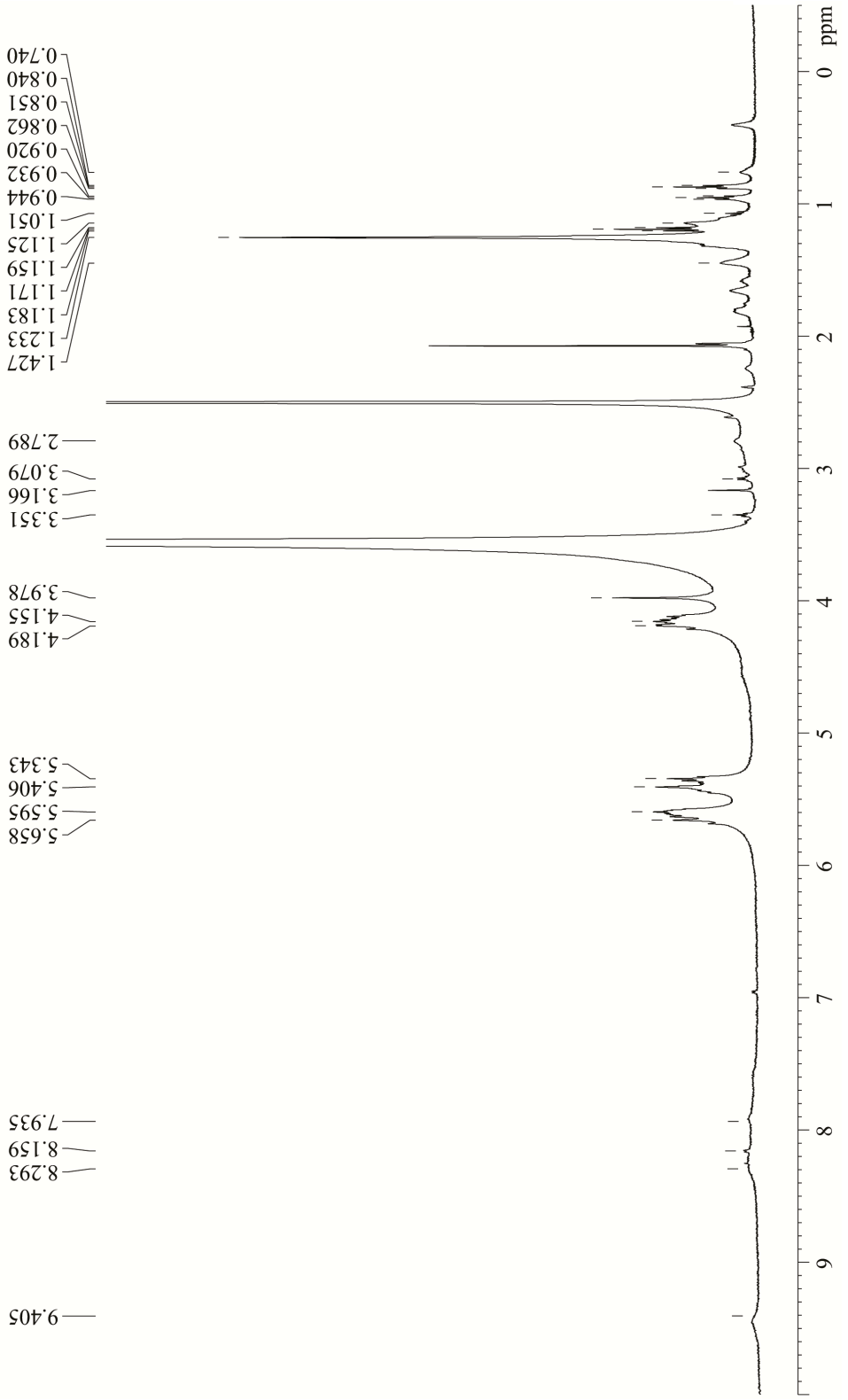


Figure S24. ^{1}H NMR recorded (600 MHz, DMSO-d_6, RT) for **MOP2** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{3})_{18}(\mathbf{2})_6](NO_3)_{60}$.

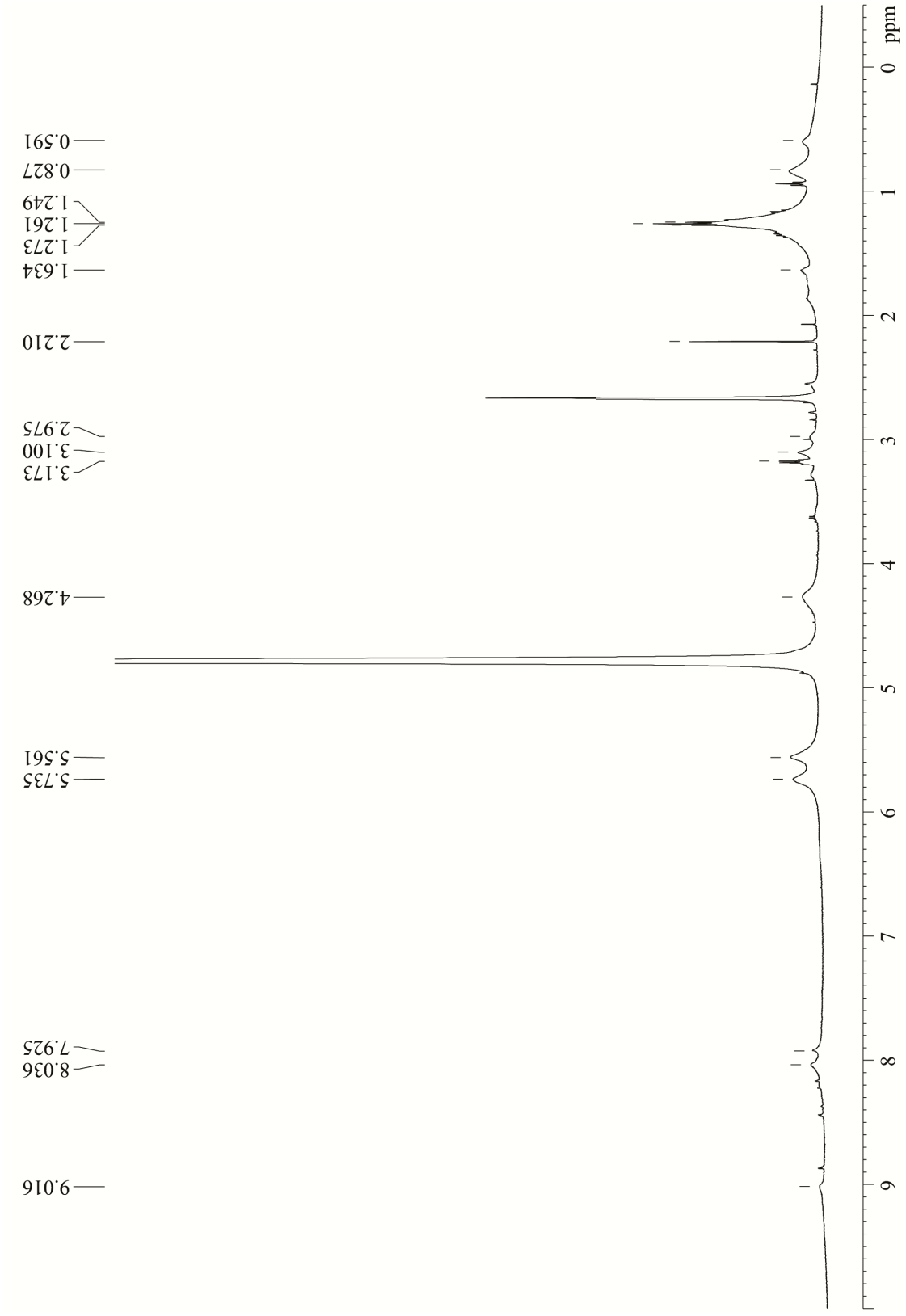


Figure S25. ^{1}H NMR recorded (600 MHz, D_2O, RT) for **MOP2** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{3})_{18}(\mathbf{2})_6](NO_3)_{60}$.

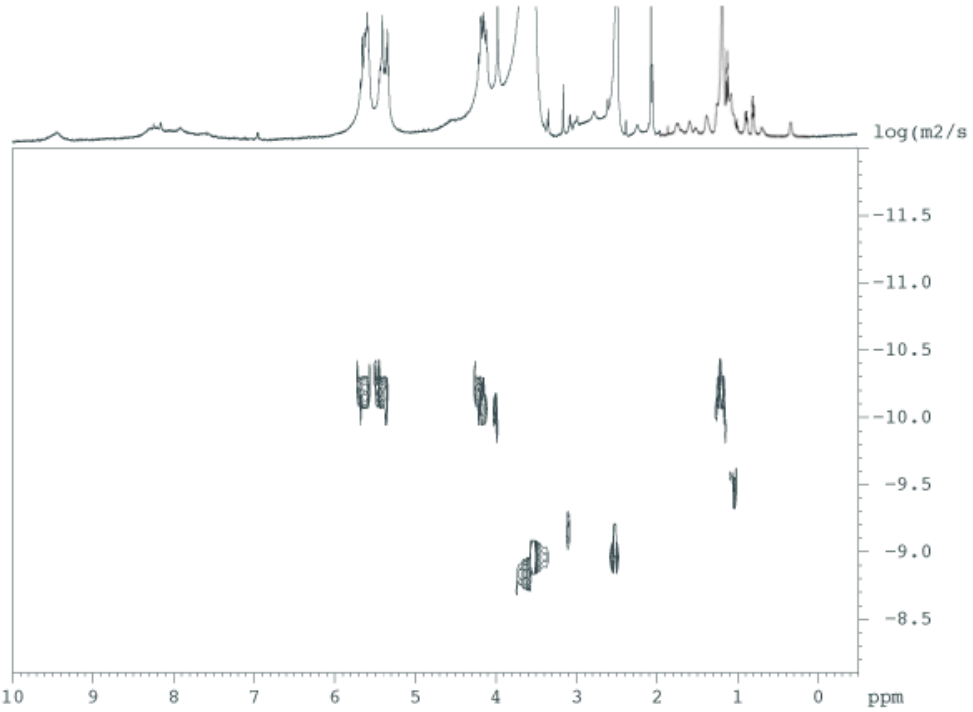


Figure S26. DOSY NMR recorded (600 MHZ, DMSO-d_6, 300 K) for **MOP2** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{3})_{18}(\mathbf{2})_6](NO_3)_{60}$.

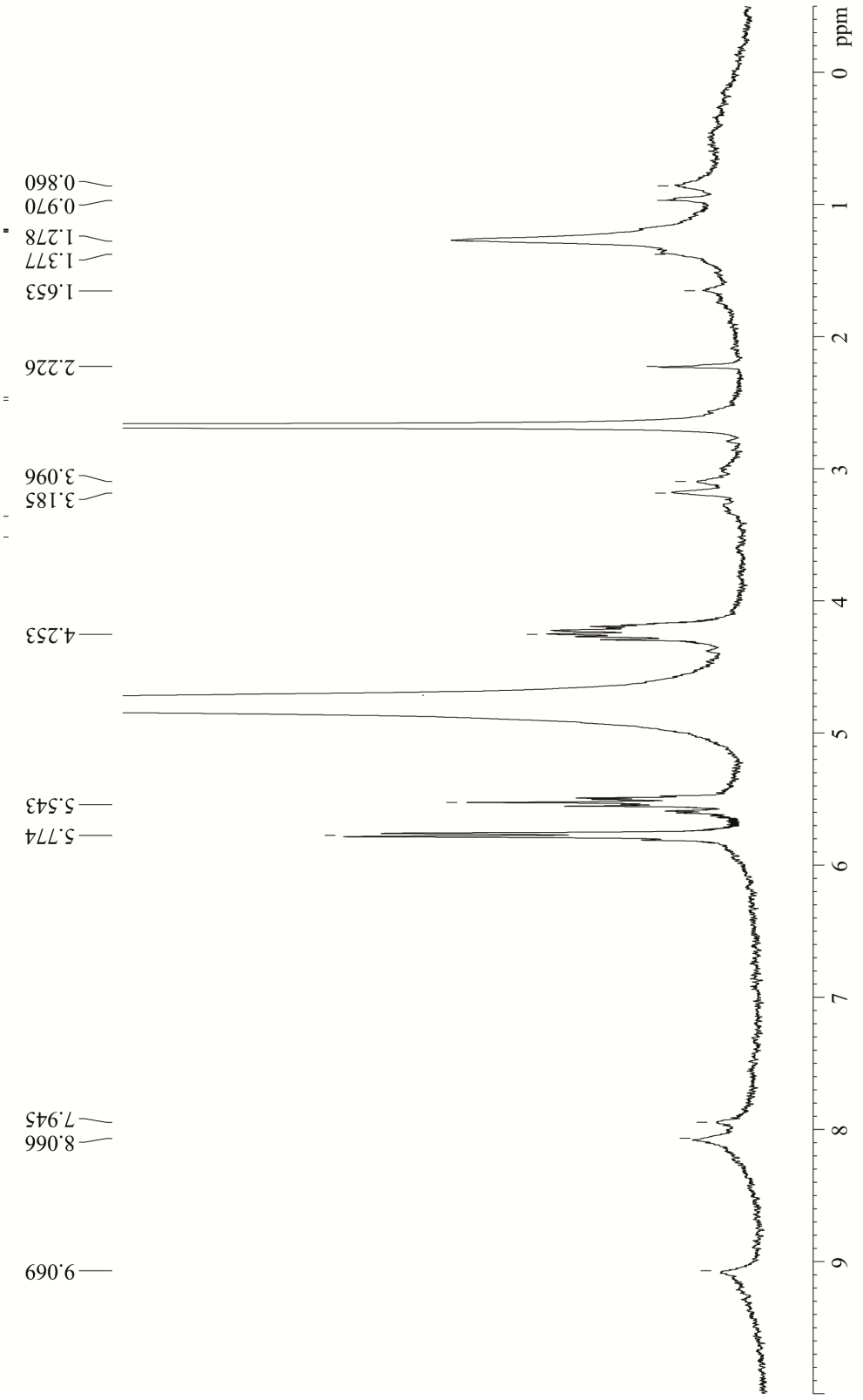


Figure S28. ^{1}H NMR recorded (600 MHz, D_2O, RT) for **MOP3** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{5})_{18}(\mathbf{2})_6](NO_3)_{60}$.

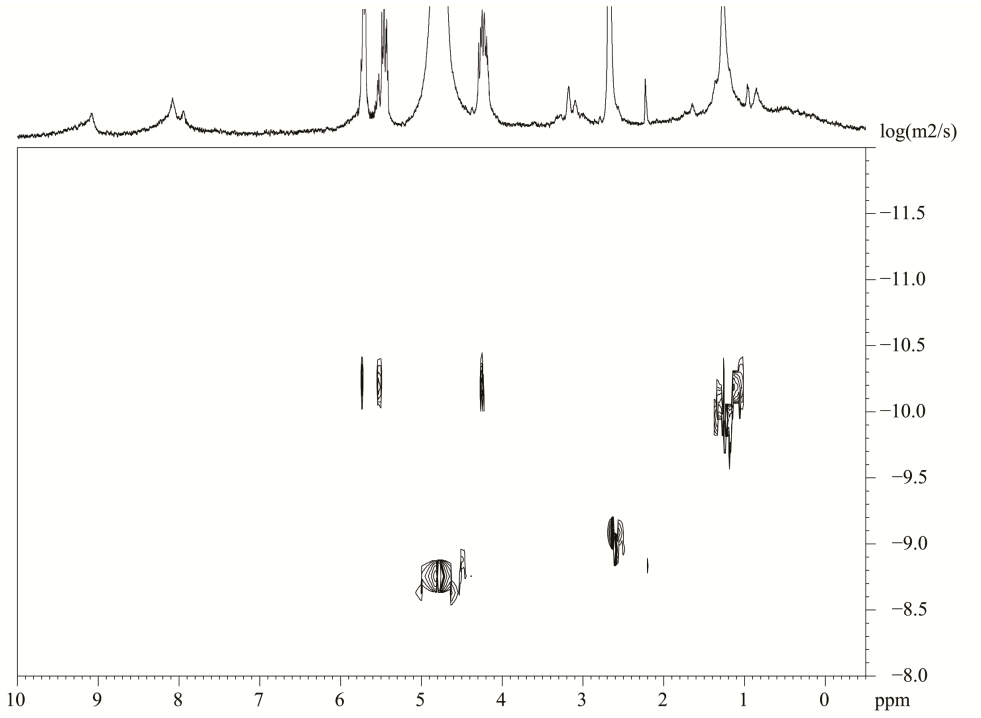


Figure S29. DOSY NMR recorded for (600 MHz, D_2O, RT) **MOP3**. = $[Pd_{12}(\mathbf{1}\bullet\mathbf{5})_{18}(\mathbf{2})_6](NO_3)_{60}$.

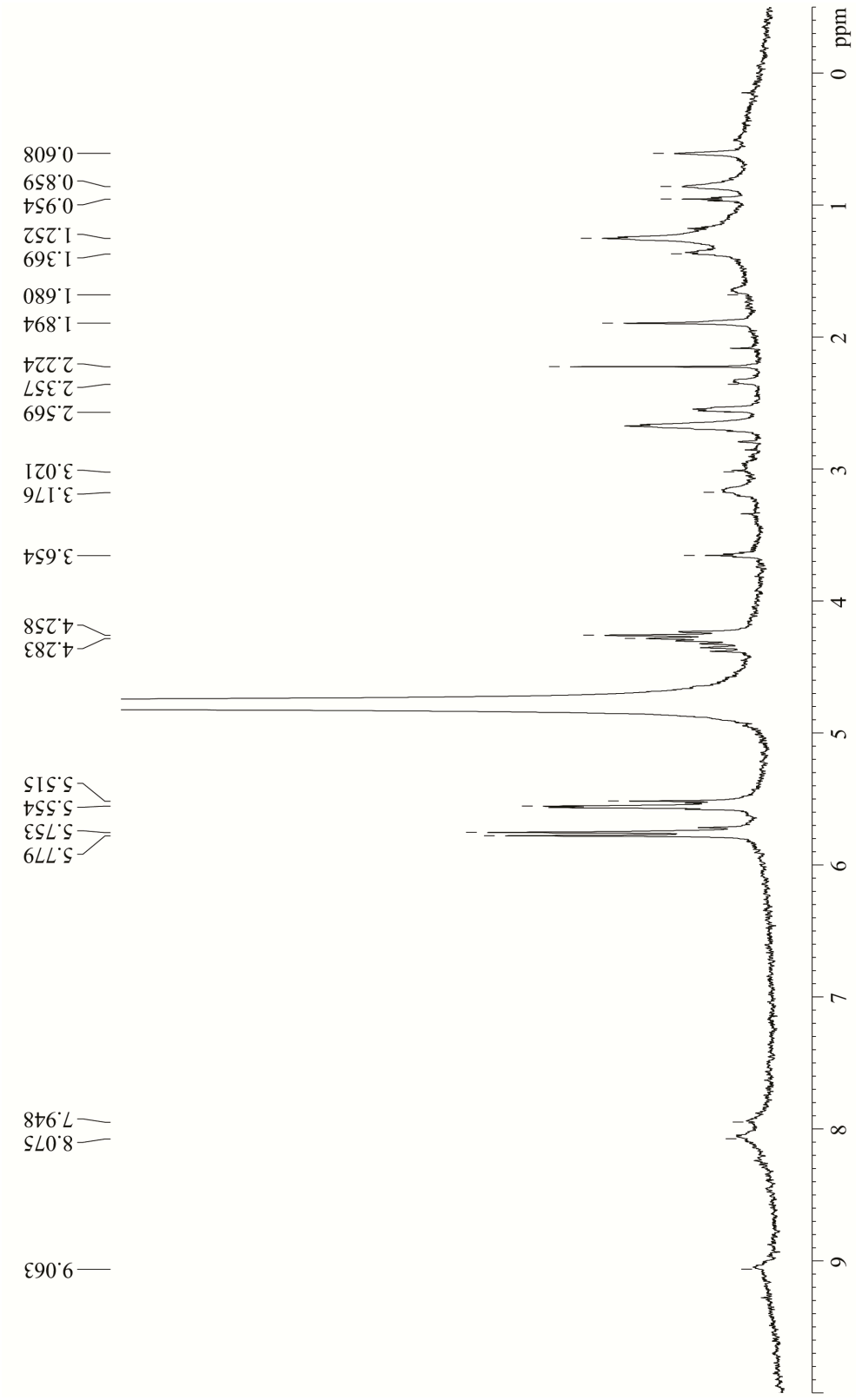


Figure S30. ^{1}H NMR recorded (600 MHz, D_2O, 300 K) for **MOP4** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{4})_{18}(\mathbf{2})_6](NO_3)_{60}$.

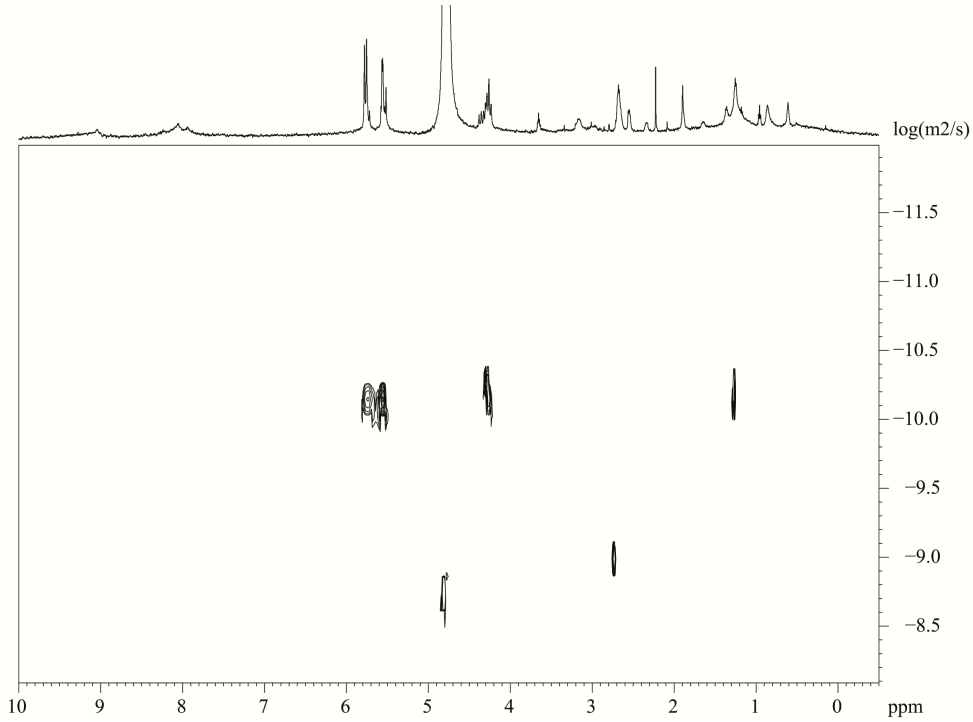


Figure S31. DOSY NMR recorded for (600 MHz, D_2O, RT) **MOP4** = $[Pd_{12}(\mathbf{1}\bullet\mathbf{5})_{18}(\mathbf{2})_6](NO_3)_{60}$.

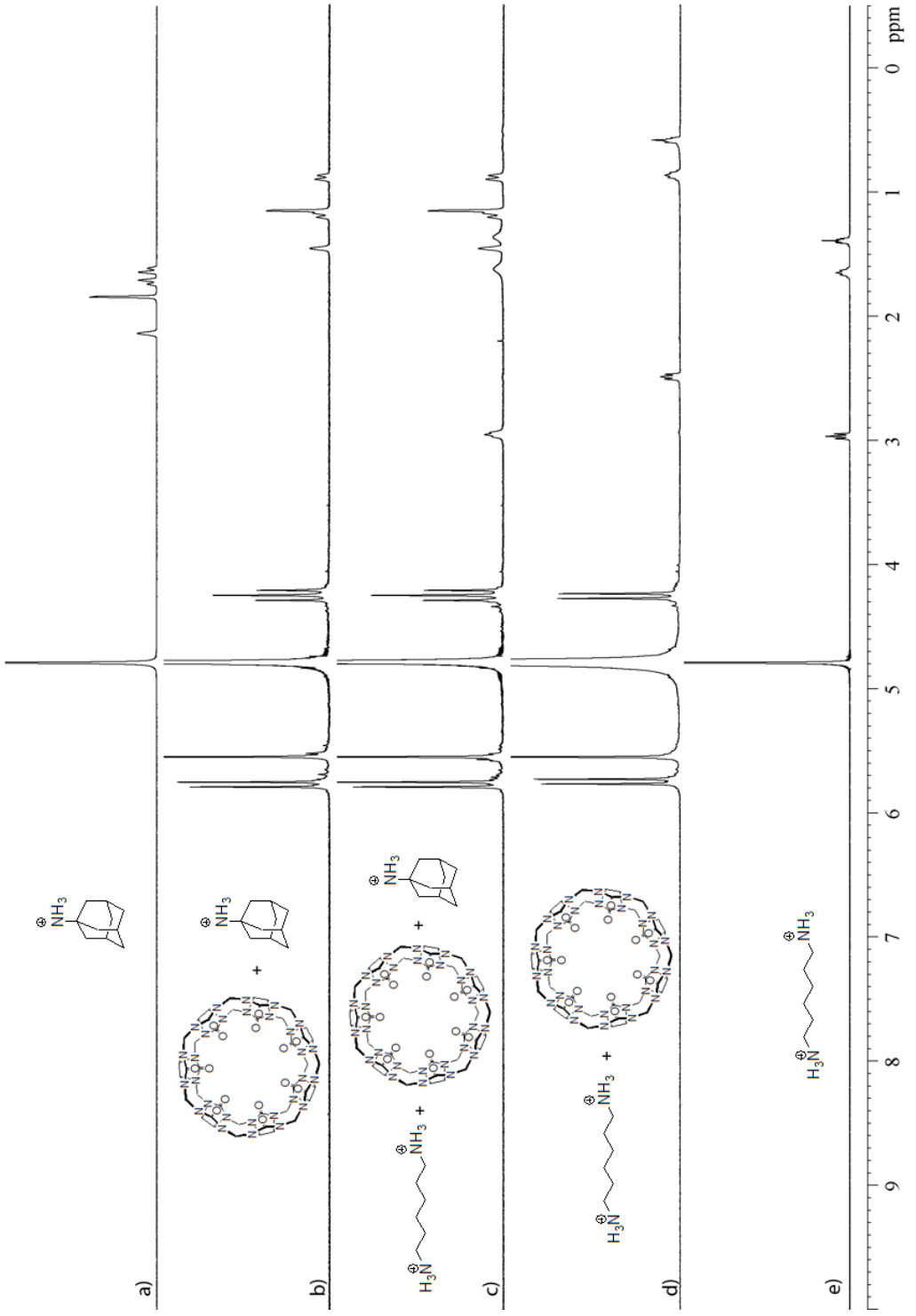


Figure S32. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT, pH 7.4, 10 mM sodium phosphate buffer) for a) **ADA**, b) a mixture of CB[7] (200 µM) and **ADA** (200 µM), c) a mixture of CB[7] (200 µM), **HDA** (200 µM) and **ADA** (200 µM), d) a mixture of CB[7] (200 µM) and **HDA** (200 µM), e) **HDA**.

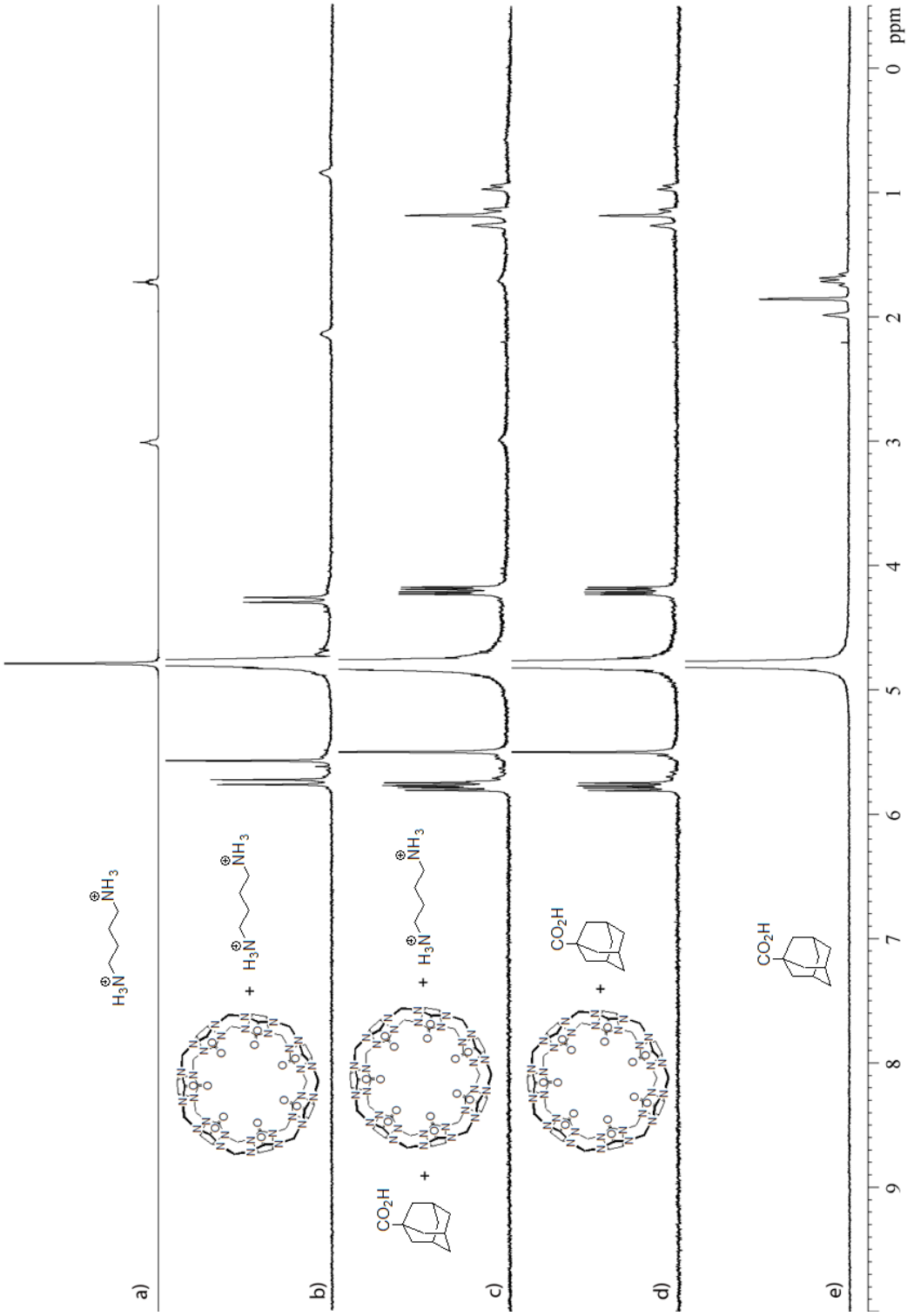


Figure S33. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) for a) **BDA**, b) CB[7] (200 μM) and **BDA** (200 μM), c) a mixture of CB[7] (200 μM), **BDA** (200 μM) and **ADAc** (200 μM), d) a mixture of CB[7] (200 μM) and **ADAc** (200 μM), e) **ADAc**.

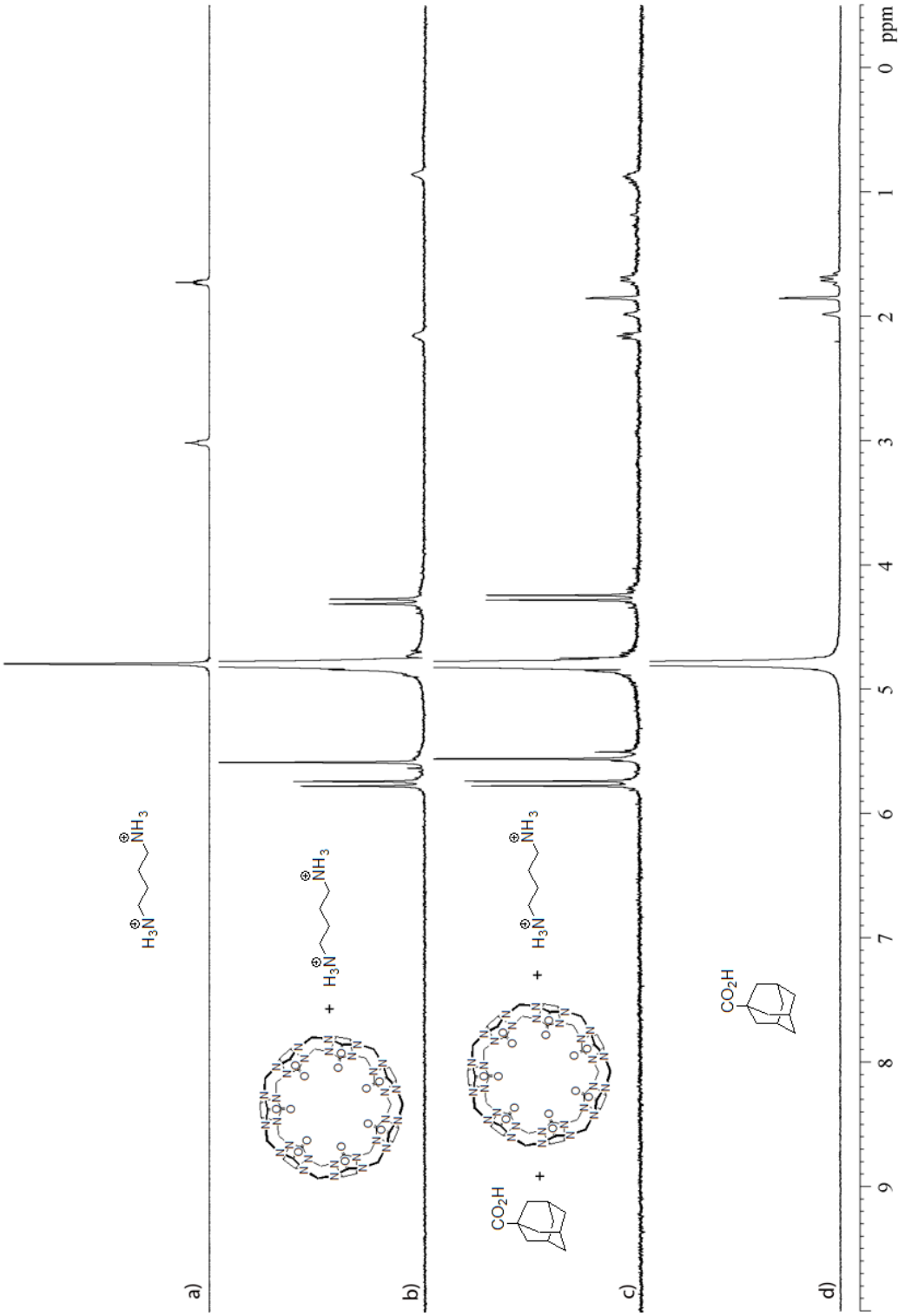


Figure S34. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 7.4, 10 mM sodium phosphate buffer) for a) **BDA**, b) a mixture of CB[7] (200 μM) and **BDA** (200 μM), c) a mixture of CB[7] (200 μM), **BDA** (200 μM) and **ADAc** (200 μM), d) **ADAc**.

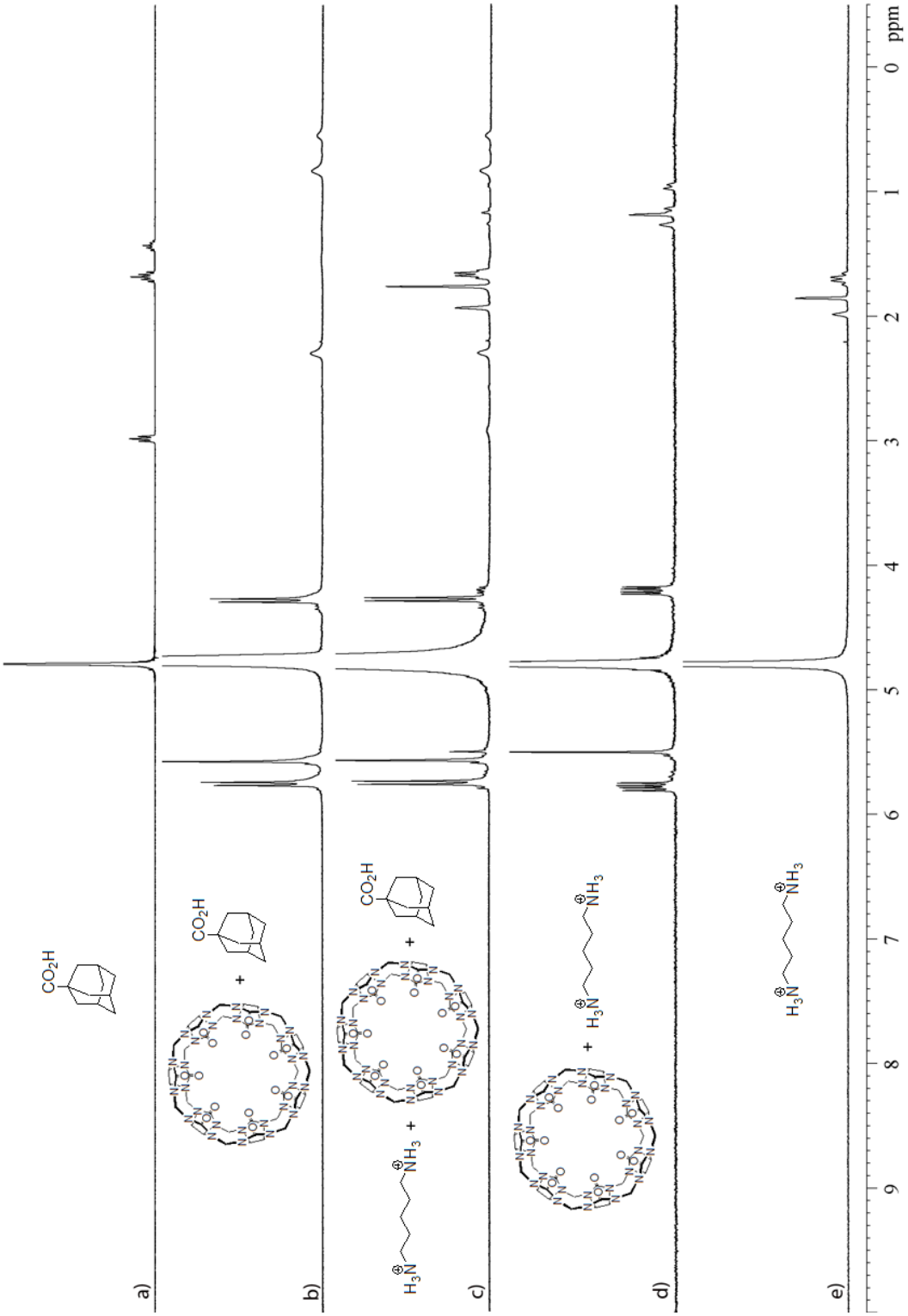


Figure S35. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) a) **ADAc**, b) CB[7] (200 μM) and **ADAc** (200 μM), c) a mixture of CB[7] (200 μM), **PDA** (200 μM) and **ADAc** (200 μM), d) a mixture of CB[7] (200 μM) and **PDA** (200 μM), e) **PDA**.

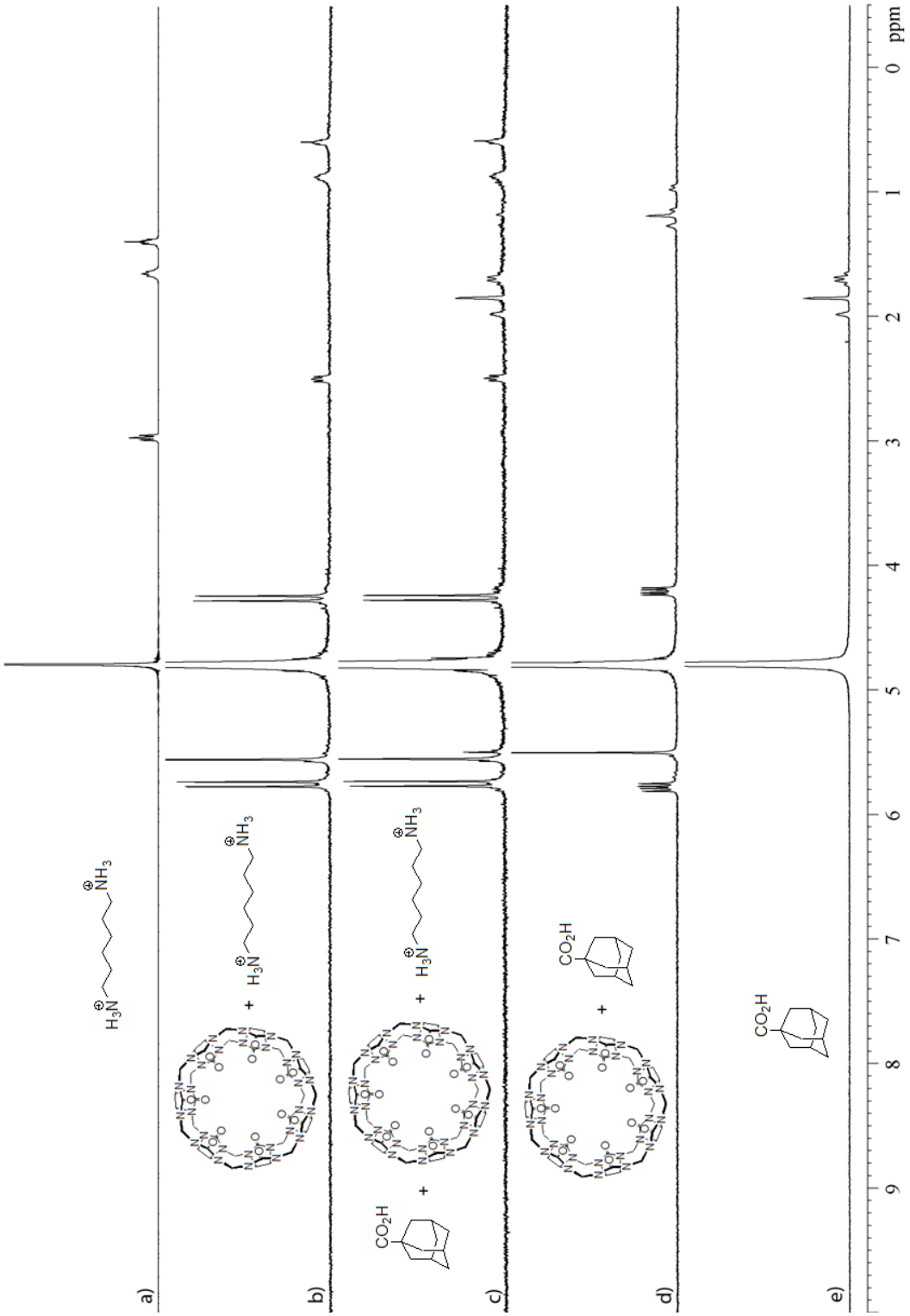


Figure S36. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) a) **HAD**, b) CB[7] (200 μM) and **HDA** (200 μM), c) a mixture of CB[7] (200 μM), **HDA** (200 μM) and **ADAc** (200 μM), d) a mixture of CB[7] (200 μM) and **ADAc** (200 μM), e) **ADAc**.

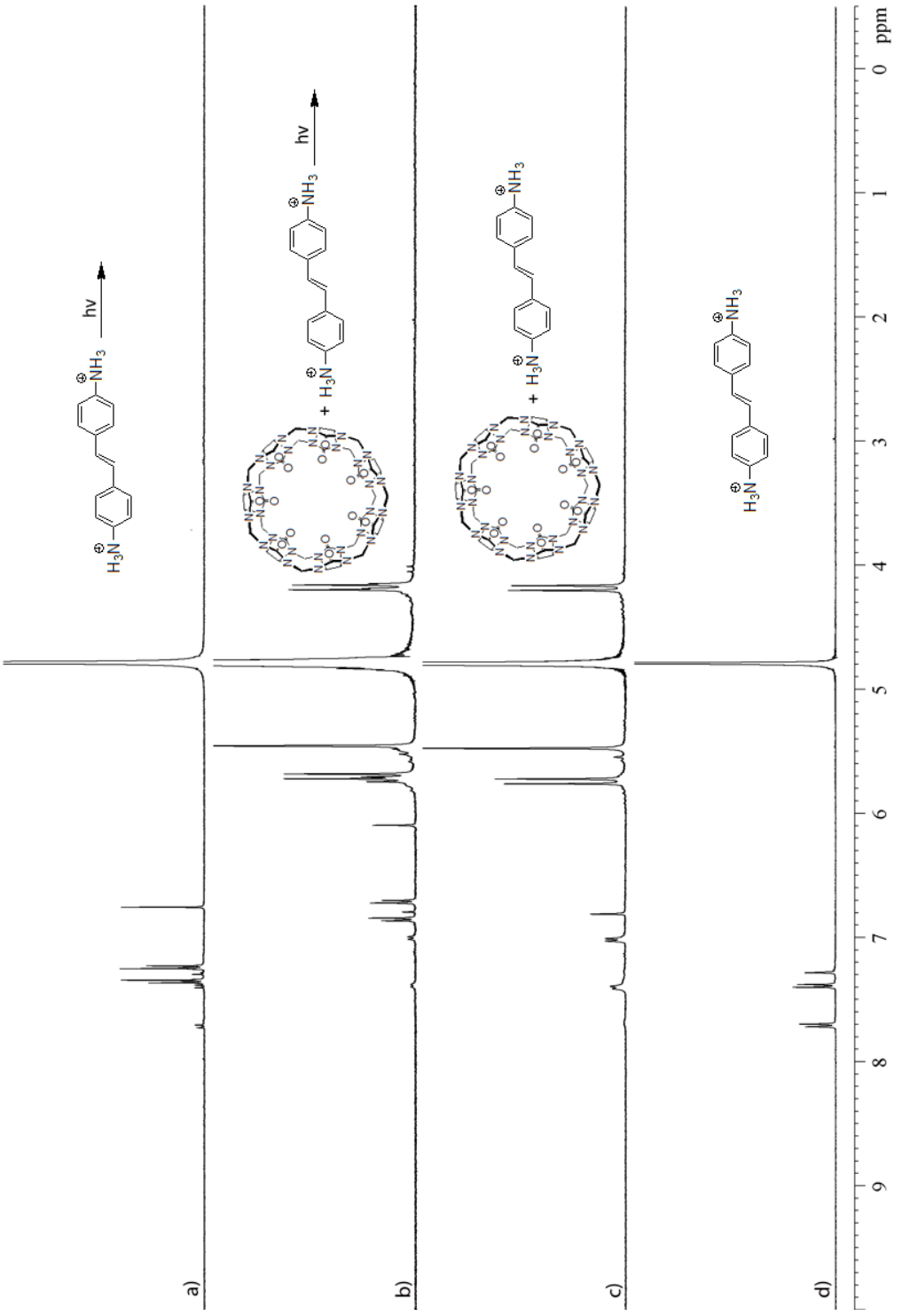


Figure S37. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) for a) *trans*-**6** (50 µM) after irradiation for 3h at λ = 350 nm, b) a mixture of CB[7] (50 µM) and *trans*-**6** (50 µM) after irradiation for 3h at λ = 350 nm, c) a mixture of CB[7] (50 µM) and *trans*-**6** (50 µM), d) *trans*-**6**.

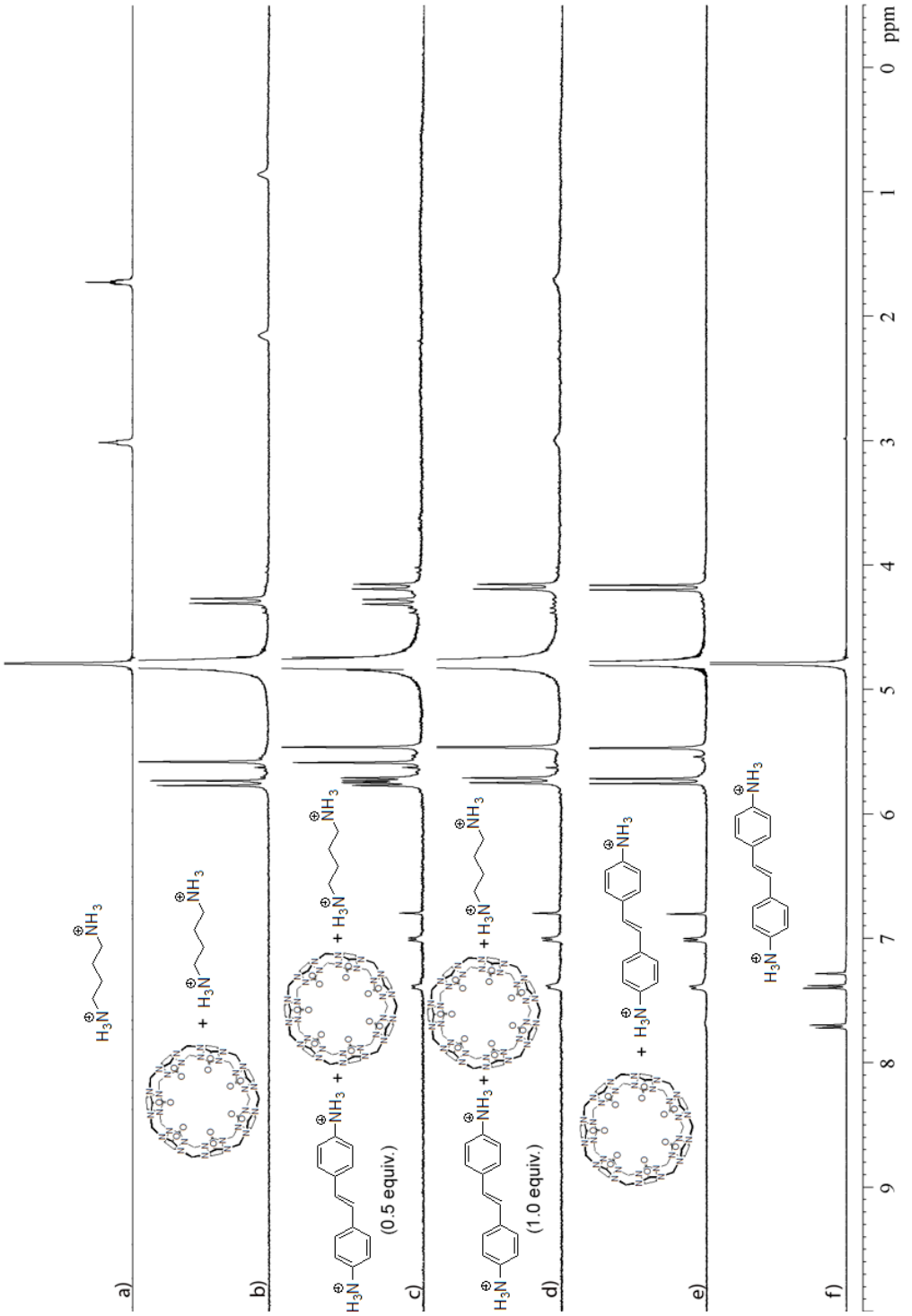


Figure S38. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) for a) **BDA**, b) CB[7] (100 μM) and **BDA** (100 μM), c) a mixture of CB[7] (100 μM), **BDA** (100 μM) and *trans*-**6** (50 μM), d) a mixture of CB[7] (100 μM), **BDA** (100 μM) and *trans*-**6** (100 μM), e) CB[7] (100 μM) and *trans*-**6** (100 μM), f) *trans*-**6**.

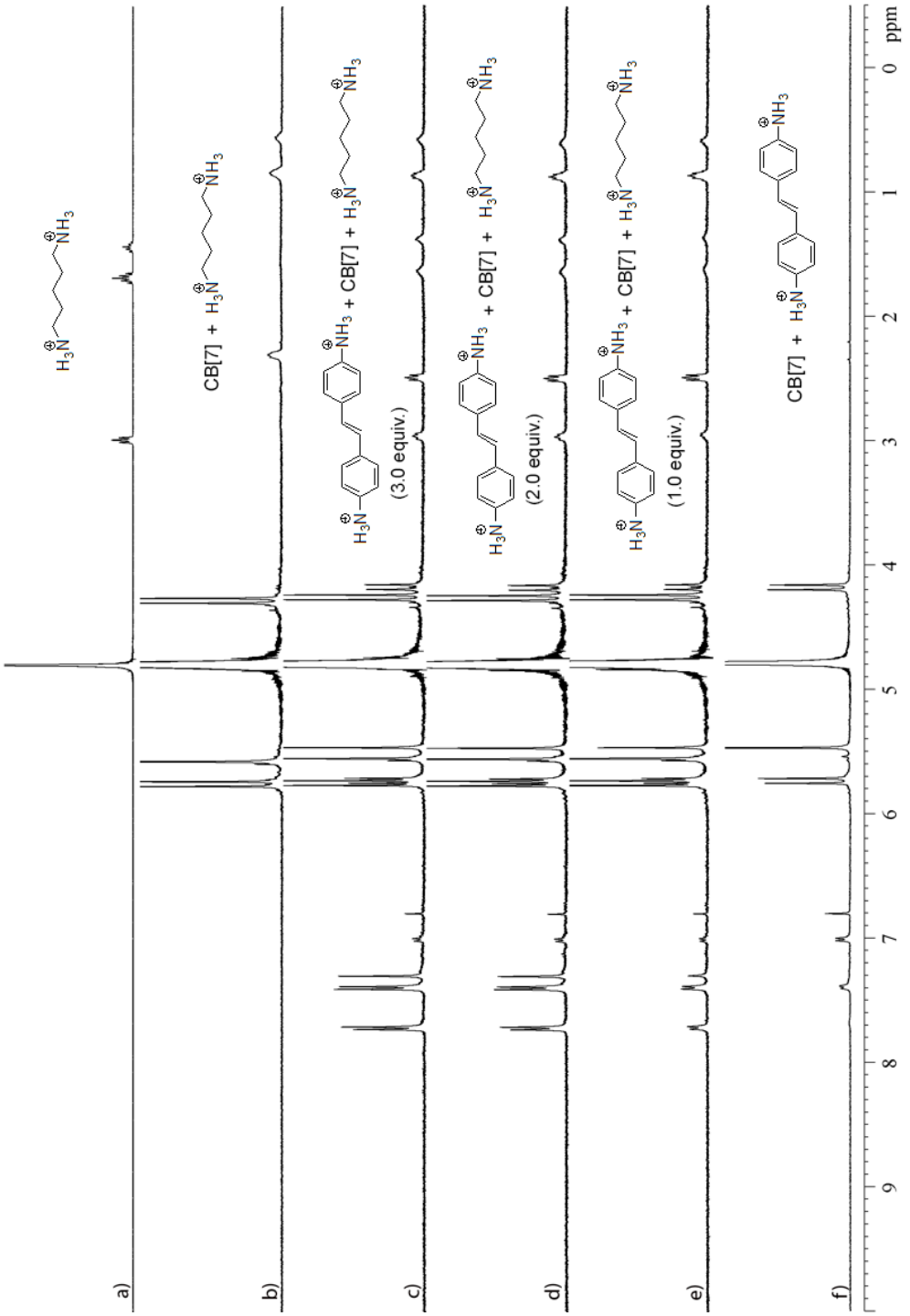


Figure S39. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) a) **PDA**, b) CB[7] (100 µM) and **PDA** (100 µM), c) a mixture of CB[7] (100 µM), **PDA** (100 µM) and *trans*-**6** (300 µM), d) a mixture of CB[7] (100 µM), **PDA** (100 µM) and *trans*-**6** (200 µM), e) a mixture of CB[7] (100 µM), **PDA** (100 µM) and *trans*-**6** (100 µM), f) CB[7] (100 µM) and *trans*-**6** (100 µM).

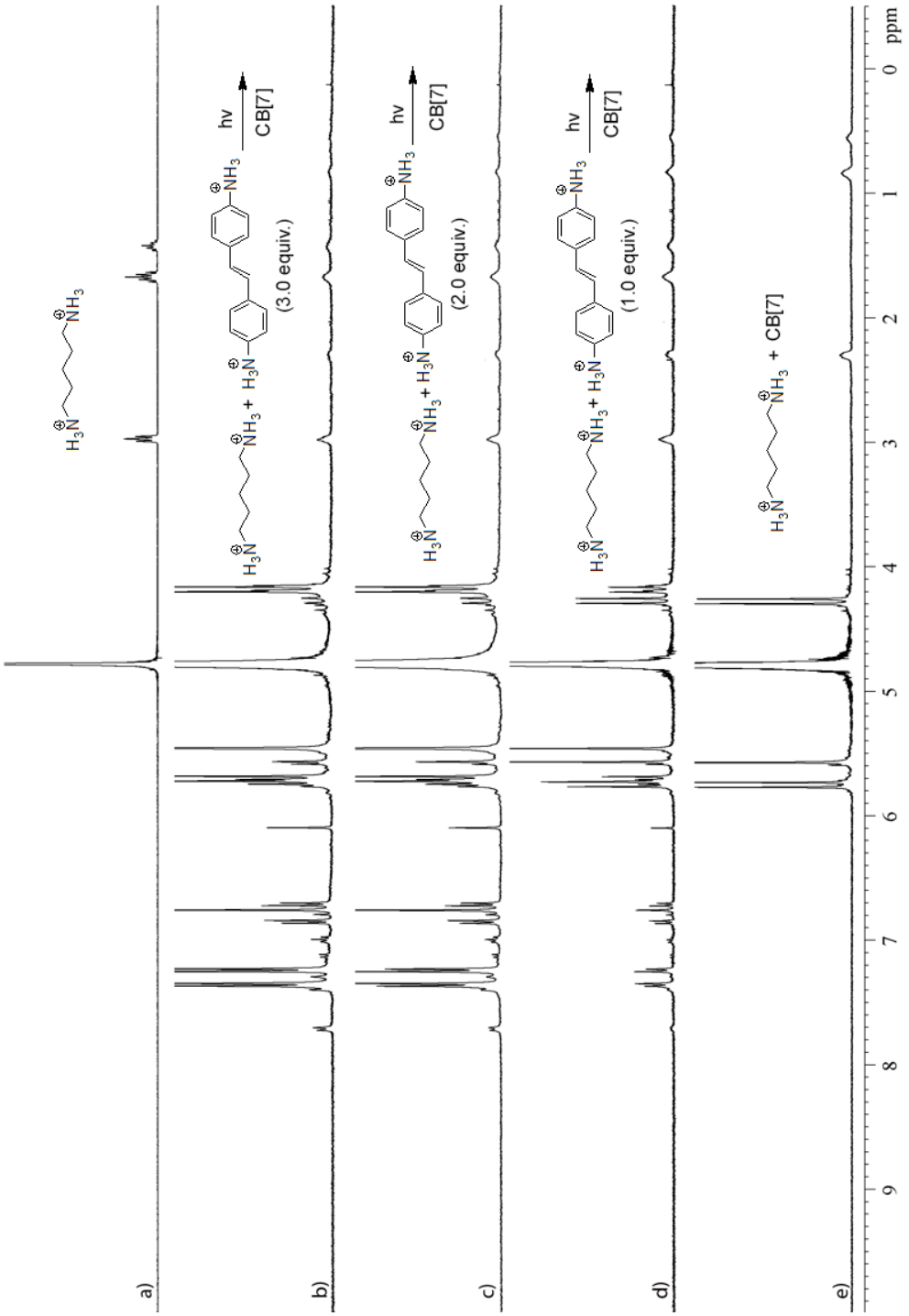


Figure S40. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) a) **PDA**, b) a mixture of CB[7] (50 µM), **PDA** (50 µM) and *trans*-**6** (150 µM) after irradiation of 3 h at 350 nm, c) a mixture of CB[7] (50 µM), **PDA** (50 µM) and *trans*-**6** (100 µM) after irradiation of 3 h at 350 nm, d) a mixture of CB[7] (50 µM), **PDA** (50 µM) and *trans*-**6** (50 µM) after irradiation of 3 h at 350 nm, e) CB[7] (50 µM) and **PDA** (50 µM).

Figure S41. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) a) CB[7] (100 μM) and **HDA** (100 μM), b) a mixture of CB[7] (100 μM), **HDA** (100 μM) and *trans*-**6** (100 μM), c) a mixture of CB[7] (100 μM), **HDA** (100 μM) and *trans*-**6** (200 μM), d) a mixture of CB[7] (100 μM), **HDA** (100 μM) and *trans*-**6** (300 μM), e) **HDA**.

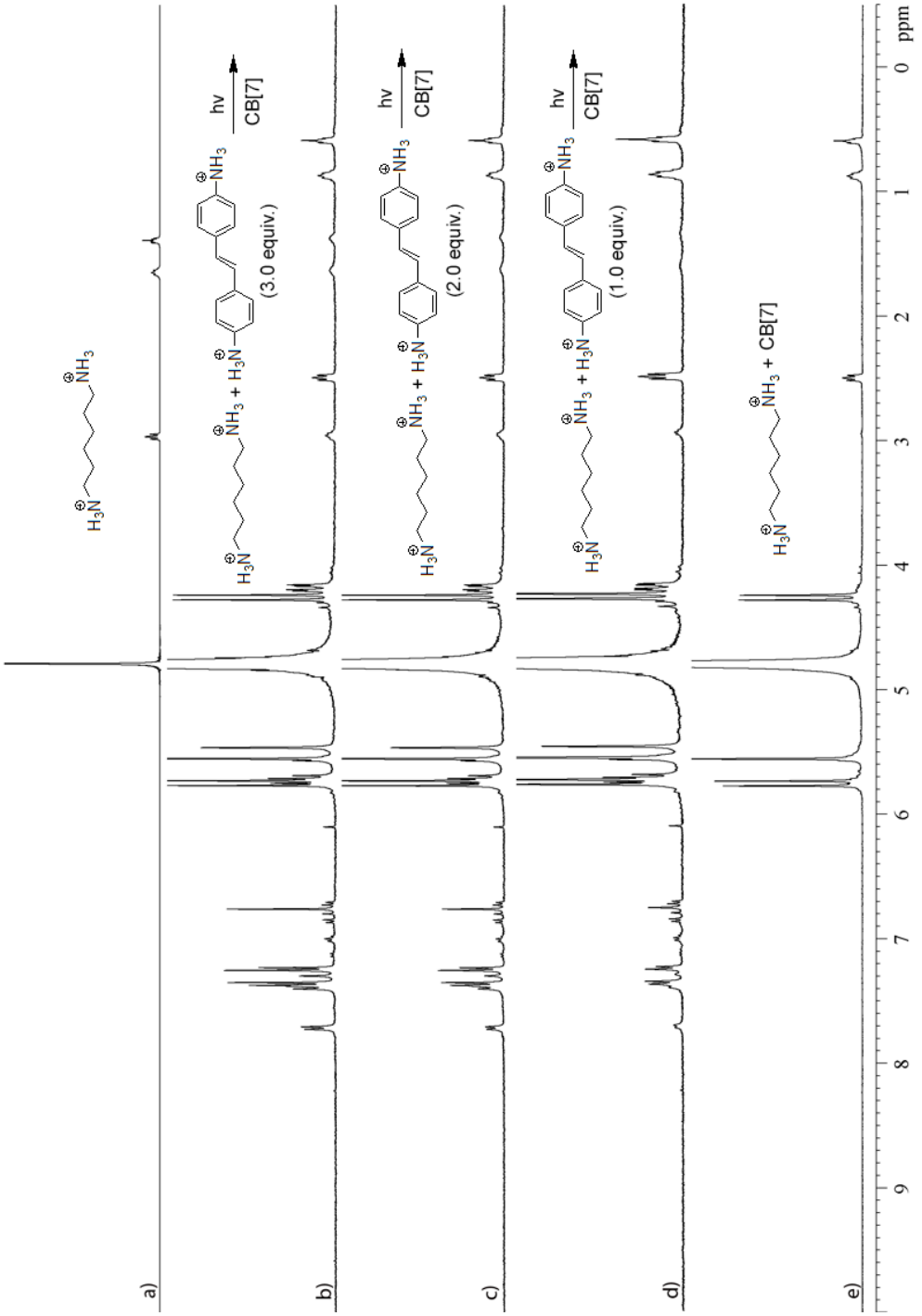


Figure S42. ^{1}H NMR of recorded (D_2O, 400 MHz, RT, pH 5.8, 10 mM sodium acetate buffer) (a) **HDA**, (b) a mixture of CB[7] (50 µM), **HDA** (50 µM) and *trans*-**6** (150 µM) after irradiation of 3 h at 350 nm, (c) a mixture of CB[7] (50 µM), **HDA** (50 µM) and *trans*-**6** (100 µM) after irradiation of 3 h at 350 nm, d) a mixture of CB[7] (50 µM), **HDA** (50 µM) and *trans*-**6** (50 µM) after irradiation of 3 h at 350 nm, (e) CB[7] (50 µM) and **HDA** (50 µM).

Size Measurement using *Stokes-Einstein* Equation:

$$D = K_B T/6\pi\eta r$$

D = Diffusion Coefficient

K_B = Boltzmann's constant

π = viscosity coefficient

r = hydrodynamic radius

Viscosity coefficient (η) for DMSO-d_6 at 27 °C = 1.99 cps

Viscosity coefficient (η) for D_2O at 27 °C = 0.89 cps

Table S1. Diffusion coefficient (D), experimentally measured diameter and estimated diameter based on MMFF computation.

	Diffusion coefficient (m^2/s)	Measured diameter (nm) from *Stokes-Einstein* Euqation	Estimated diameter (nm)
MOP 1 (in DMSO-d_6)	2.90×10^{-11}	7.6	8.2
MOP 1 (in D_2O)	6.31×10^{-11}	7.8	8.2
MOP 2 (in DMSO-d_6)	3.4×10^{-11}	6.6	NA
MOP 2 (in D_2O)	7.94×10^{-11}	6.2	NA
MOP 3 (in D_2O)	8.12×10^{-11}	6.1	NA
MOP 4 (in D_2O)	7.51×10^{-11}	6.6	NA
MOP1 with **ADA**	6.5×10^{-11}	7.7	8.2

UV/Vis and Fluorescence Spectroscopy

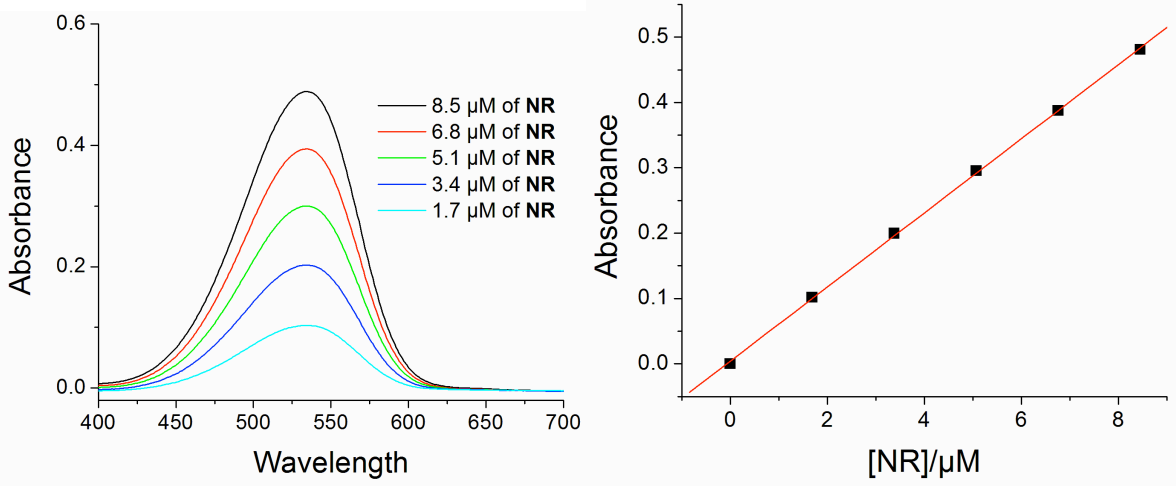


Figure S43. Calibration Curve of nile red (**NR**) by UV/Vis absorption measured at 538 nm (CH_3CN/H_2O = 19:1).

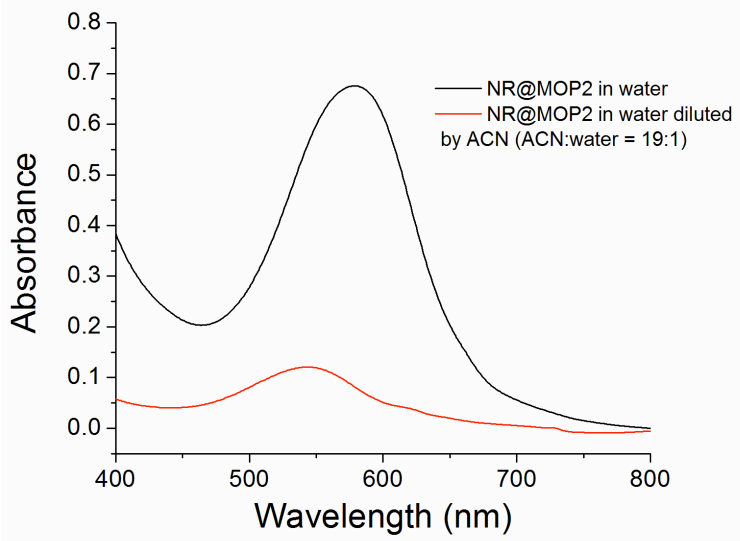


Figure S44. (Left) UV/Vis Spectra of **NR@MOP2** ([**MOP2**] = 6 μM) in water and **NR@MOP2** upon dilution with acetonitrile ([**MOP2**] = 0.3 μM in CH_3CN/H_2O= 19:1).

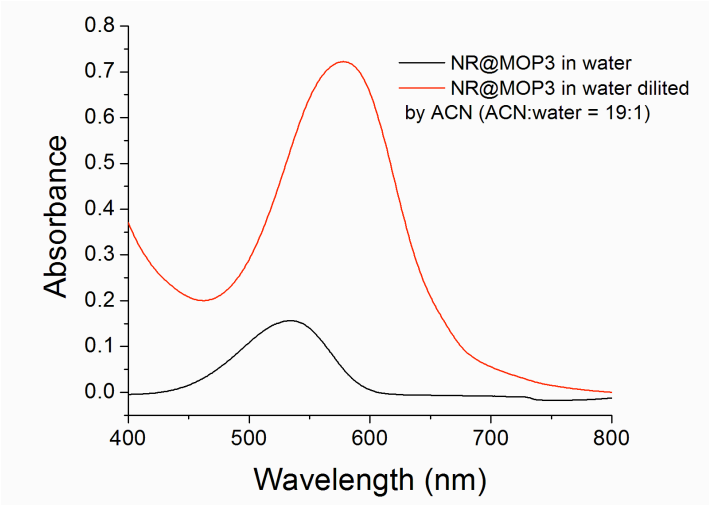


Figure S45. UV/Vis Spectra of **NR@MOP3** ([**MOP3**] = 6 μM) in water and **NR@MOP3** upon dilution with acetonitrile ([**MOP3**] = 0.3 μM in CH_3CN/H_2O= 19:1).

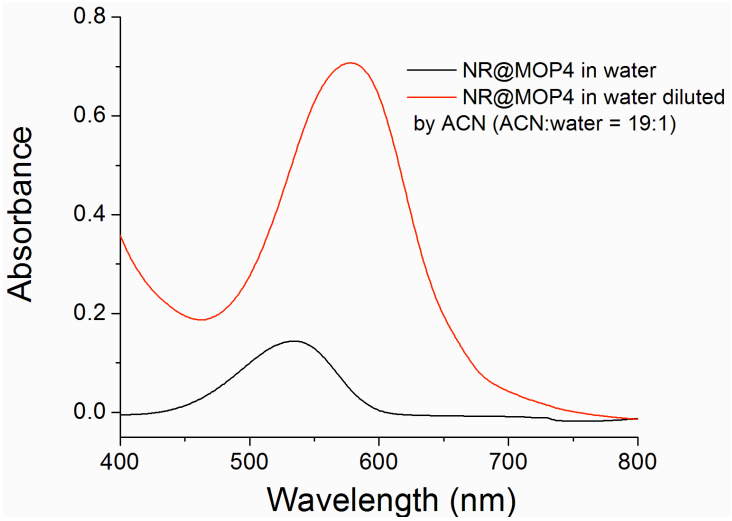


Figure S46. UV/Vis Spectra of **NR@MOP4** ([**MOP4**] = 6 μM) in water and **NR@MOP4** upon dilution with acetonitrile ([**MOP4**] = 0.3 μM in CH_3CN/H_2O= 19:1).

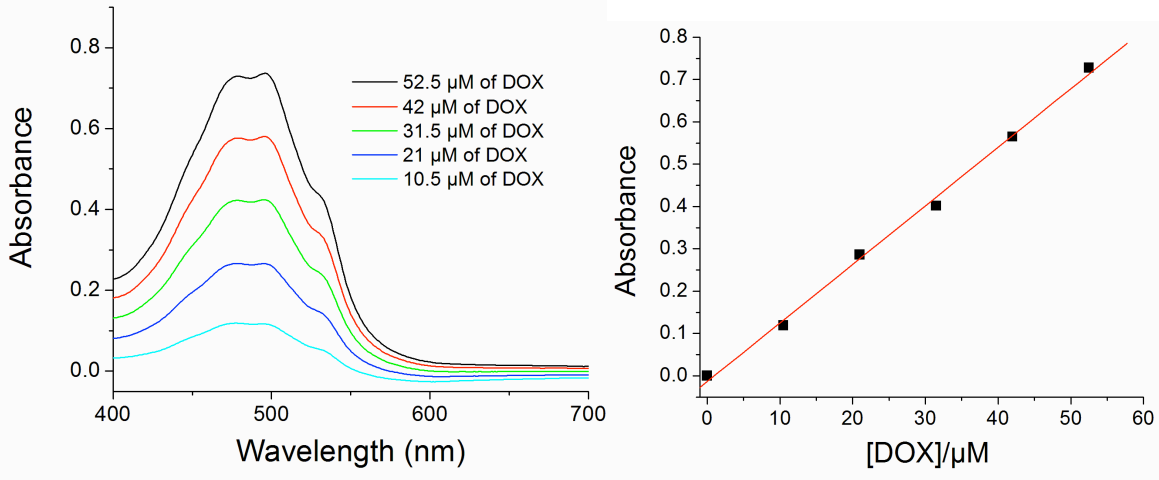


Figure S47. Calibration Curve of doxorubicin (**DOX**) by UV/Vis absorption measured at 476 nm (CH_3CN/H_2O = 19:1).

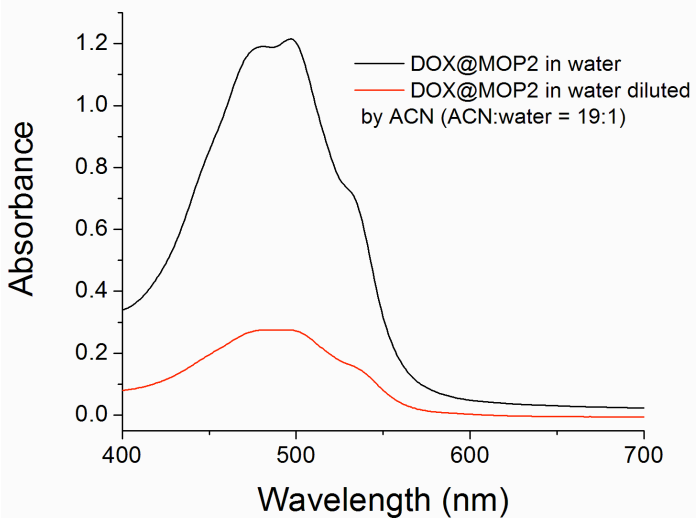


Figure S48. (Left) UV/Vis Spectrum of **DOX@MOP2** ([MOP2] = 40 μM) and **DOX@MOP2** upon dilution with acetonitrile. ([**MOP2**] = 2.0 μM in CH_3CN/H_2O= 19:1).

Table S2. Absorbance of **NR**/**DOX** with **MOP2–4** at 541 nm (for **NR**) and 476 nm (for **DOX**) in CH_3CN/H_2O (19:1), the concentration of **NR** and **DOX** calculated by the calibration curve of **NR** and **DOX** respectively, and the calculated number of **NR** and **DOX** dissolved in **MOP2–4**.

Sample	Abs at 541 (**NR**) & 476 (**DOX**)	[**MOP**]/μM	[**NR**]or [DOX]/μM	No. of **NR**
NR@MOP2	0.125	0.3	2.13	7
NR@MOP3	0.153	0.3	2.6	9
NR@MOP4	0.142	0.3	2.39	8
DOX@MOP2	0.237	2.0	18.5	8

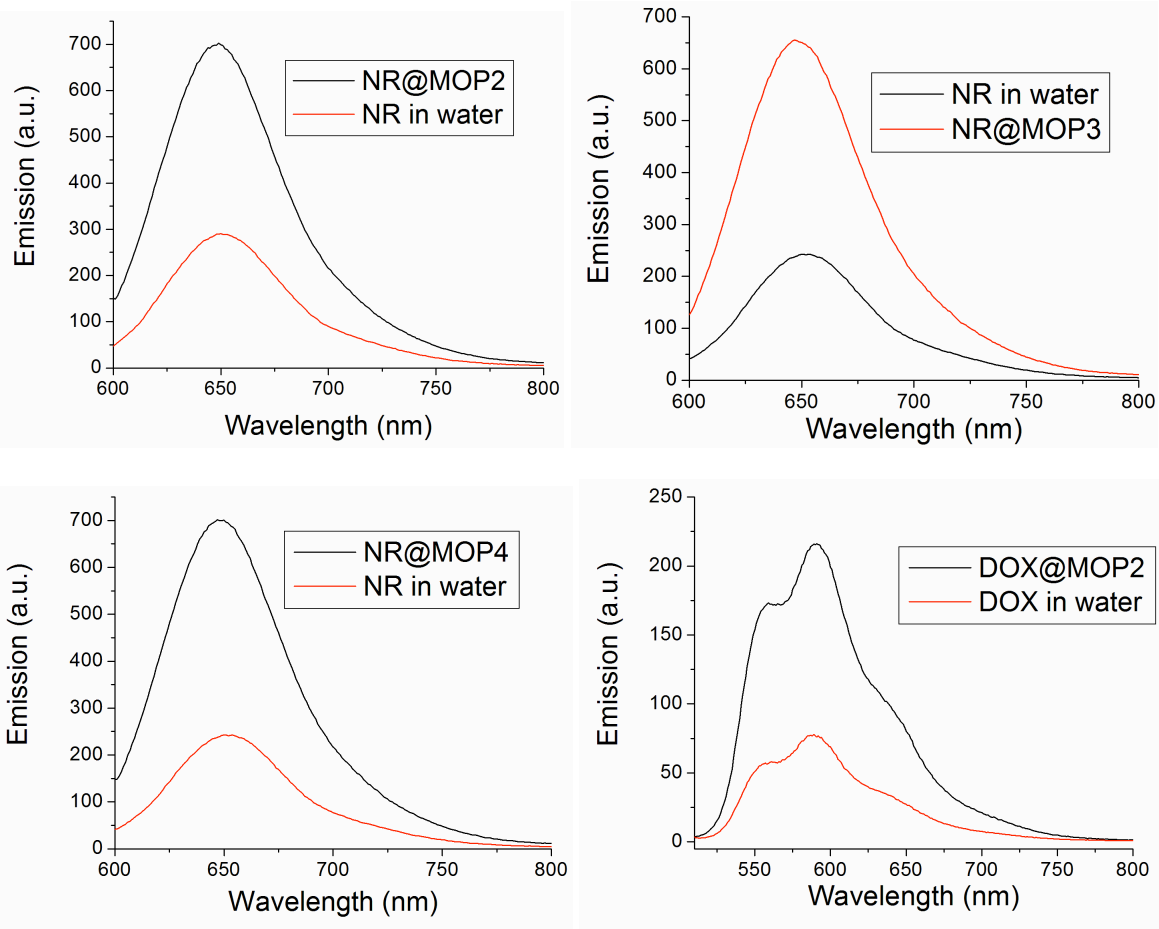


Figure S49. Comparison of fluorescence intensity of **NR@MOP** with same concentration of free **NR** in water. For (Top, left) **MOP2** with [**NR**] = 5 μM, (top, right) **MOP3** with [**NR**] = 5 μM and (bottom, left) **MOP4** with [**NR**] = 5 μM. (Bottom, right) Comparison of fluorescence intensity of **DOX@MOP2** with same concentration of free **DOX** ([**DOX**] = 20 μM) in water. For free **NR**, slight ACN (water:ACN = 99:1) was added to make stock solution of 5 μM **NR** in water.

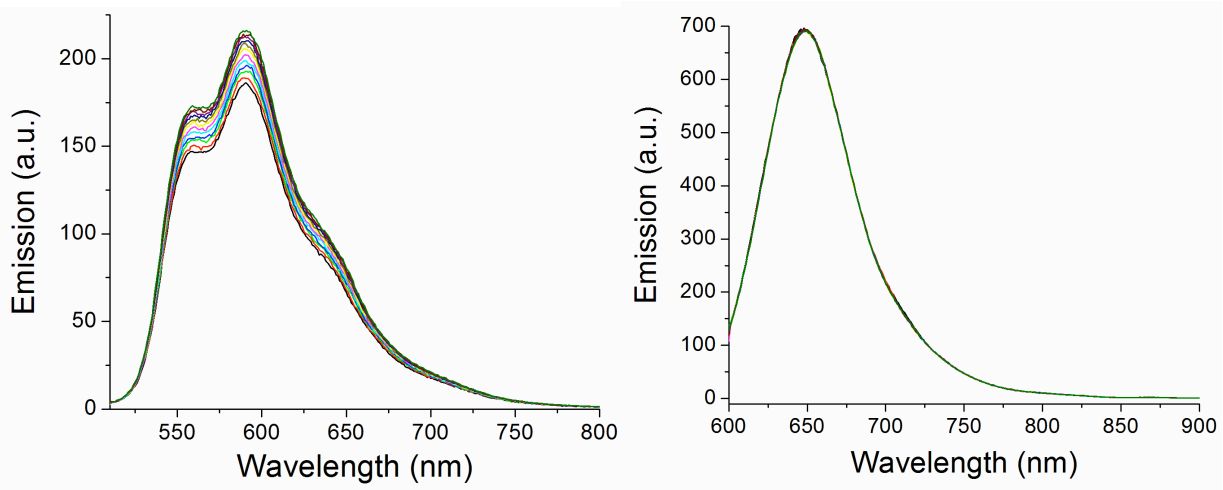


Figure S50. Fluorescence emission spectra of (left) **DOX@MOP2** ([**DOX**] = 20 μM) and (right) **NR@MOP2** ([**NR**] = 5 μM) over period of 12h at pH 7.4.

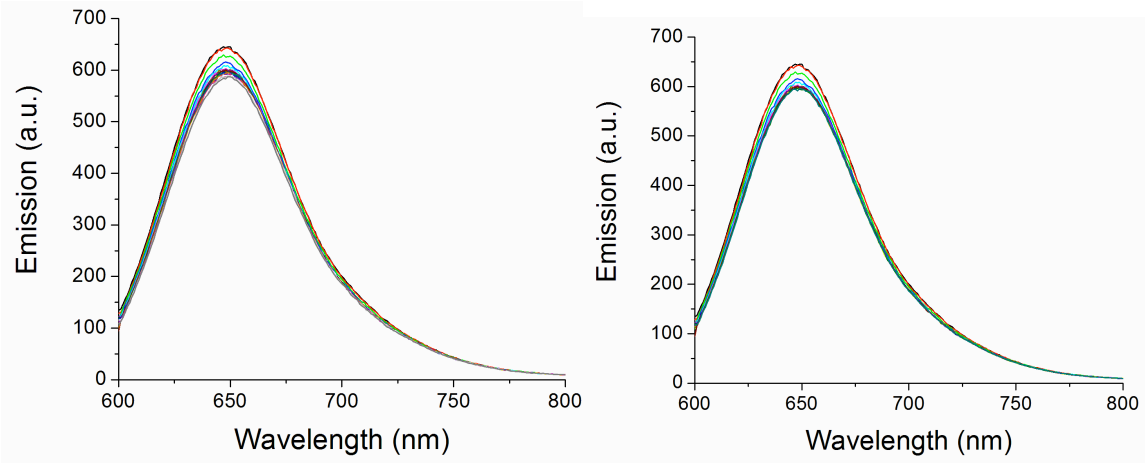


Figure S51. (Left) Fluorescence spectra of **NR@MOP3** ([**NR**] = 5 μM) with increasing concentration **ADAc** at pH 7.4. (Right) Fluorescence spectra of **NR@MOP3** ([**NR**] = 5 μM) at pH 5.8 over period of 12 h.

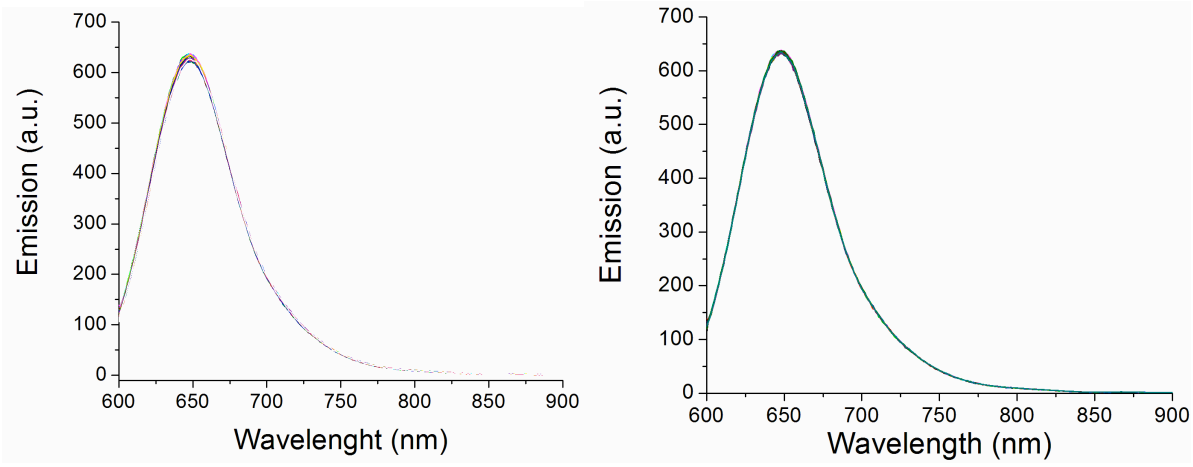


Figure S52. Fluorescence emission spectra of **NR@MOP4** ([**NR**] = 5 μM) with (left) increasing concentration of *trans*−**6** and (right) over a period of 12h at pH 7.4 in sodium phosphate buffer.

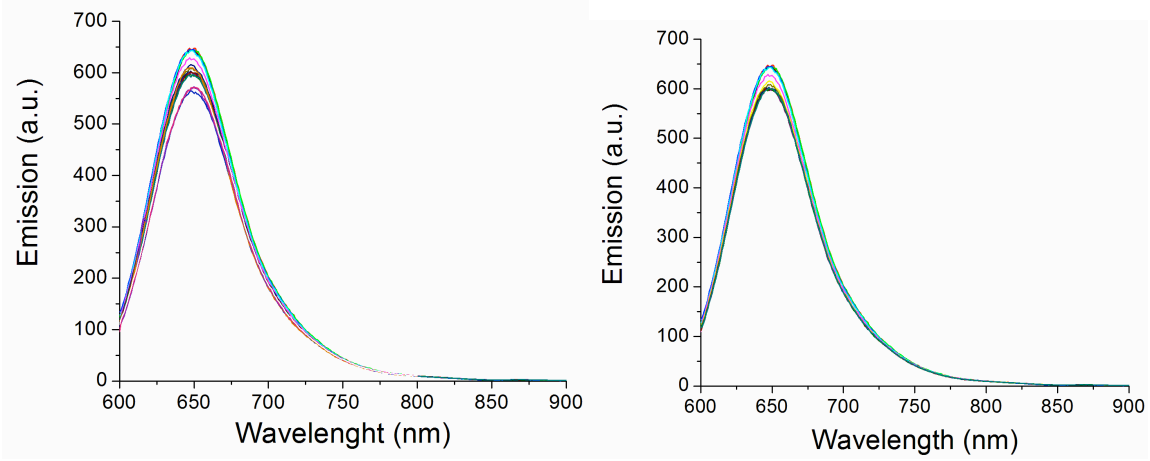


Figure S53. (Left) Fluorescence emission spectra of **NR@MOP4** ([**NR**] = 5 μM) with increasing concentration of *trans*−**6** and (right) over a period of 12h at pH 5.8 in sodium acetate (10 mM) buffer.

Measurement of critical micelle concentration (CMC).

We first prepared the required solution of [**3**•2NO_3] (2.0 mM) by dissolving the calculated quantity of [**3**•2NO_3] in required volume of water. In order to determine critical micelle concentration (CMC) of [**3**•2NO_3], we needed to prepare several working solutions. Appropriate aliquots were taken from the stock solution of [**3**•2NO_3] and diluted by water to achieve the following concentrations: 2.0, 1.83, 1.66, 1.5, 1.33, 1.17, 1.0, 0.83, 0.67, 0.5, 0.33 mM.

Nile red (**NR**) was used as dye for the experiment. By dissolving calculated quantity of **NR** in required volume of acetonitrile gave 0.78 mM stock solution of **NR**. 10 µL of **NR** solution was added to each working solution and vortexed for a minute. Then UV/Vis spectra were recorded and the absorbance at 580 nm was plotted versus the concentration of [3•2NO_3].

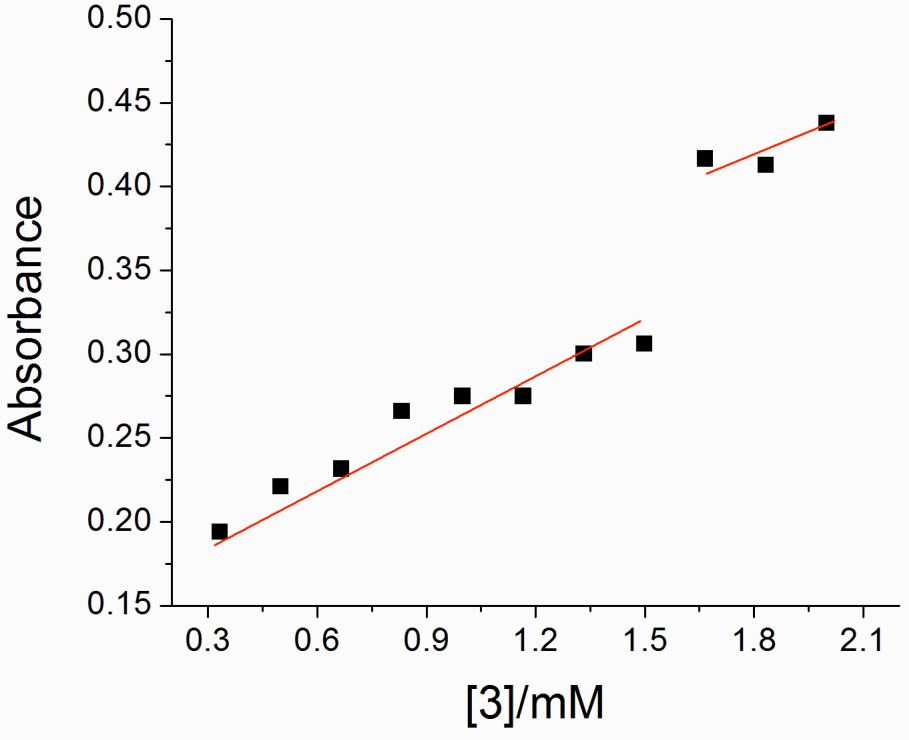


Figure S54. Critical micelle concentration (CMC) determination of [**3**•2NO_3] in water. Absorbance at 580 nm was plotted versus concentration.

Transmission Electron Microscopy

The samples were prepared on a carbon-coated Cu grid (400 mesh) by adding the solution of **MOP1** and **MOP2**. After evaporation of solvent TEM images were recorded. Uniformly sized spheres with a size of around ~7 nm can be clearly observed.

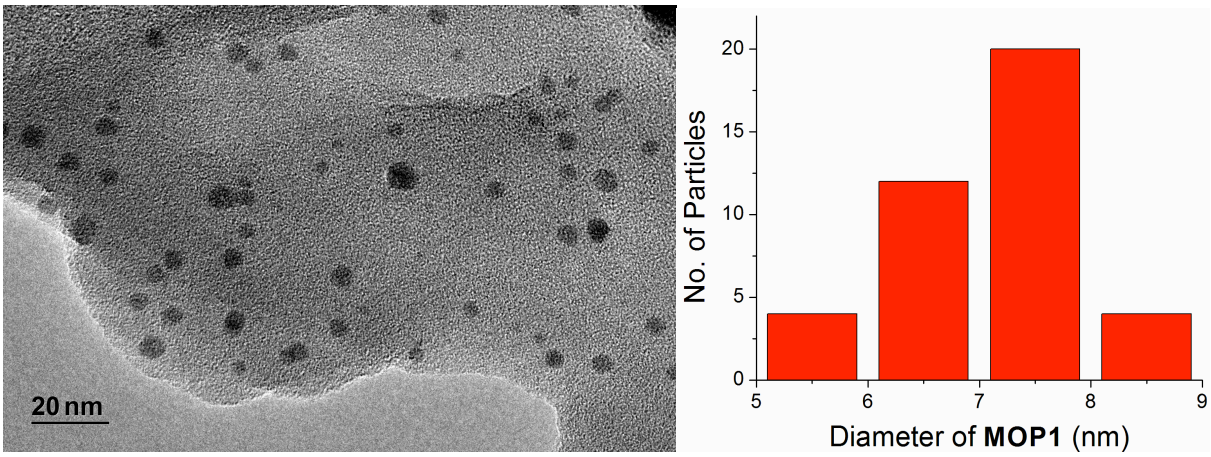


Figure S55. TEM image of **MOP1** and its distribution profile of 40 particles.

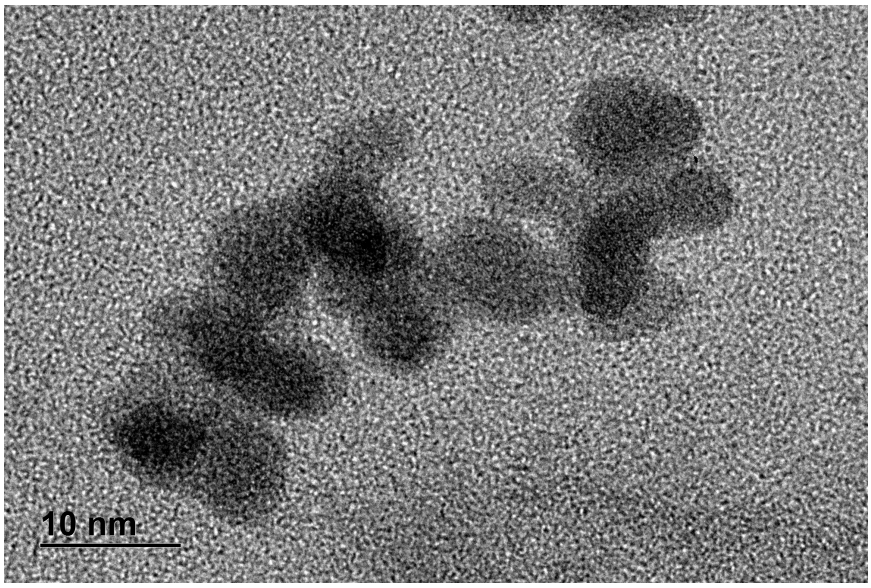


Figure S56. TEM image of **MOP2** and average diameter of 10 particles is 6.5 nm.

Energy Dispersive Spectroscopy on SEM

The samples were prepared by depositing a DMSO solution (700 μM) of **MOP 1** and **MOP 2** on carbon film. After evaporation of DMSO solvent the EDS spectra were recorded.

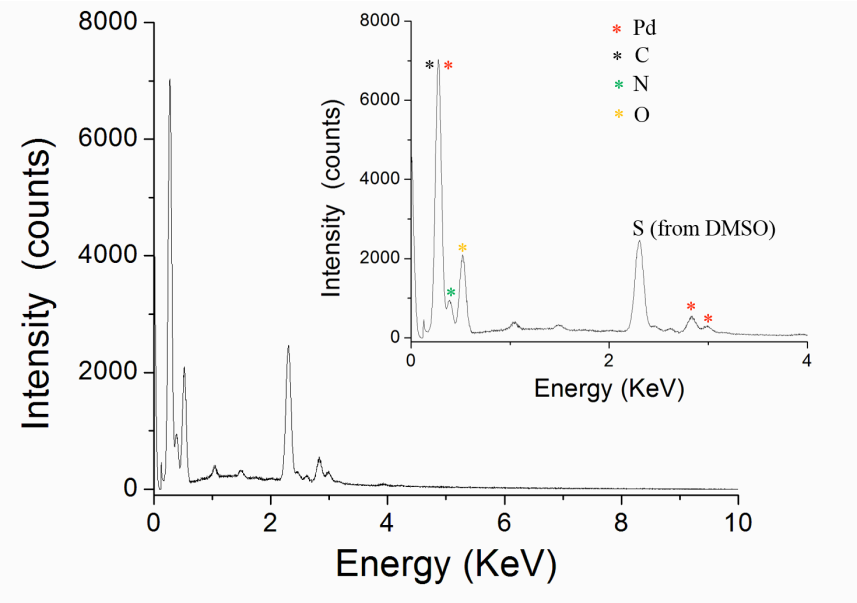


Figure S57. EDS spectrum of **MOP 1**. (Inset) Zoomed view of EDS spectrum of **MOP 1**.

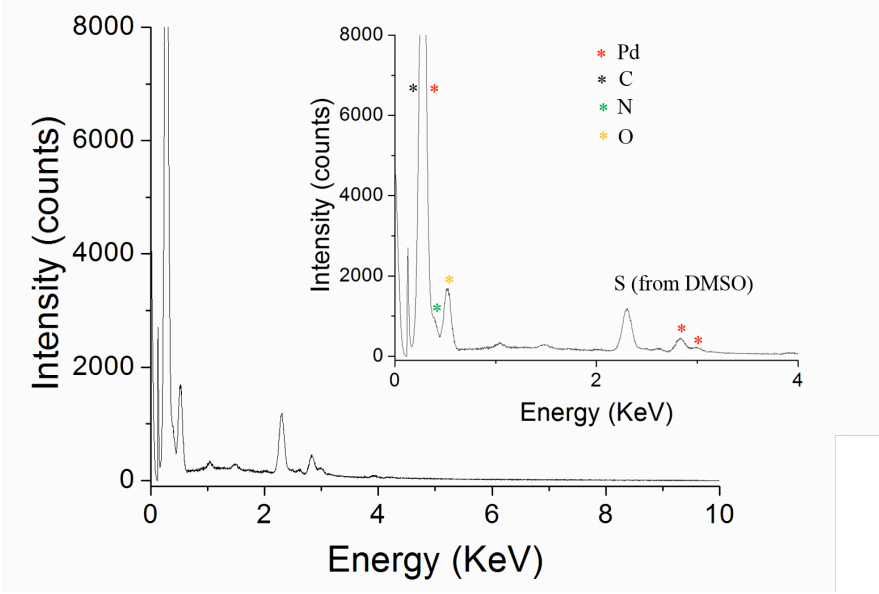


Figure S58. EDS spectrum of **MOP 2**. (Inset) Zoomed view of EDS spectrum of **MOP 2**.

Molecular Modelling

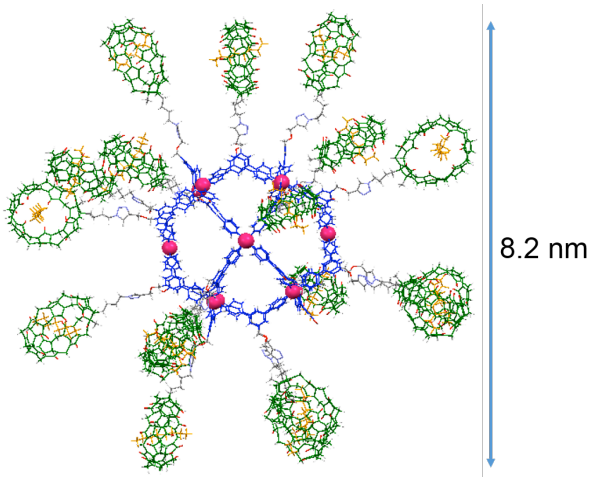
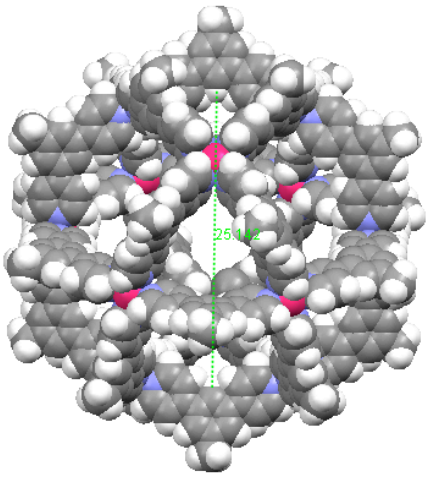


Figure S59. Spartan optimized structure of **MOP1**.

Calculation of hydrocarbon occupancy within MOP2



Diameter of empty sphere within **MOP** is 2.5 nm as measured from Spartan optimized structure.

Empty volume = $4/3\pi r^3$ = 8184.5 Å^3.

Taking 55% solution for packing coefficient to be upper limit, available volume for hydrocarbon (V_a) = 4501 Å^3.

Van der Waals radius for carbon (r_w) = 1.7 Å,

Van der Waals Volume (V_w) for carbon = 20.6 Å^3.

Van der Waals radius for hydrogen (r_w) = 1.2 Å,

Van der Waals Volume (V_w) for hydrogen = 7.2 Å^3.

V_w for CH_3 = 42.2 Å^3, V_w for CH_2 = 35 Å^3.

Assuming equal contribution from 18 alkyl chains, volume available for each hydrocarbon chain = $V_a/18$ = 250 Å^3.

Volume for $CH_3(CH_2)_6$ = 252 Å^3.

Approximately 1/3 tail of each C_{18} hydrocarbon tail is able to penetrate and produces highly densed hydrophobic environment within **MOP**.

In Vitro Study

Cell Culture

HeLa cells were grown in DMEM (Gibco Corp) with 10% feral calf serum (FCS, ATLANTA biologicals) and 1% penicillin/streptomycin (Pen/Strep, Gibco Corp) at 37 °C and 5% CO_2. THP-1 cells were grown in RPMI (ATCC) with 10% heat inactivated fetal calf serum (FCS, Atlanta Biologicals) at 37°C and 5% CO_2.

Cytotoxicity of MOP2

The cytotoxicity of **MOP2** was evaluated using CellTiter 96 aqueous nonradioactive cell proliferation assay (Promega Corporation). First, 5×10^4 HeLa cells/well were plated overnight in a 96 well plate (Corning). Then cells were incubated for 24 h with a concentration range of **MOP2** from 0.0007-50μM. MTS solution was added for 1 h. Absorbance at 490 nm was measured. Percentage of viable cells was calculated using an untreated group as control using as follows: Cell viability (%) = $(ABS_{sample}/ABS_{untreated}) \times 100$.

Uptake of NR@MOP2

1 x 10^6 THP-1 cells left untreated or incubated with **NR@MOP2** (6 μM NR equivalent) or **NR** at 6 μM for 20 min. Cells were washed three times with phosphate buffered saline and analyzed for increased red fluorescence by flow cytometry using a 585/42 nm emission filter on a Canto II Flow Cytomerter (BD Bioscience). For each condition, a minimum of 20,000 cells were collected. Data are depicted in histogram format with relative fluorescence intensity depicted on the x-axis and cell count on the y-axis. Figure is representative of two independent experiments.

Fluorescence Microscopy

1×10^5 HeLa cells/well were seeded overnight on a 24-well plate containing a glass coverslip. Then cells were incubated for 1 h with **NR@MOP2** (6 μM **NR** equivalent) or **NR** at 6 μM. Cells were washed 3 times. Cells nuclei were stained with DAPI stain for 5 min. Coverslips were mounted on glass slides, and the cells were observed using a Zeiss AxioObserver

fluorescence microscope. Images were acquired using the same parameters for all samples. Figure is representative of two independent experiments.