Supporting information for

Structurally Tunable pH-responsive Phosphine Oxide Based Gels by Facile Synthesis Strategy

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Synthesis and characterizations

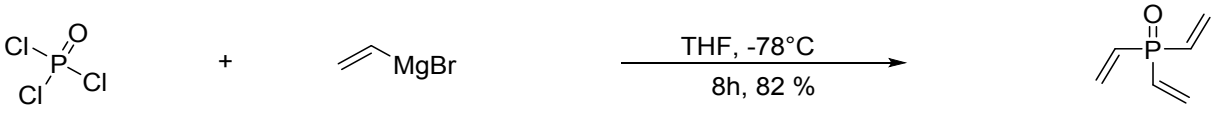
S1. Materials

Phosphoryl trichloride, vinyl magnesium bromide (1M in THF), dry THF, 1,6-dibromohexane, 1,10-dibromodecane, 1,3-di(piperidin-4-yl)propane, piperazine, piperidine, tert-butyl piperazine-1-carboxylate (**1**), cyanuric chloride (**6**), were obtained from Aldrich and used as received unless otherwise stated. The compounds trivinylphosphine oxide (TVPO),[1] 1,6-di(piperazin-1-yl)hexane (3),[2] 1,10-di(piperazin-1-yl)decane (5)[2] were synthesized via modified procedures (SI section S2) and 2,4,6-tri(piperazin-1-yl)-1,3,5-triazine (8)[3] was synthesized using procedure as described in the literature.

S2. Synthesis of TVPO and diamine derivatives

Synthesis of TVPO was done via Grignard reaction and purification carried out via sublimation. The long alkyl chain amines of bis-piperazine intermediates (**3**, **5**) were prepared via reaction of commercially available 1-Boc-piperazine with the dibromoalkanes (1,6-dibromohexane, 1,10-dibromodecane) and followed by deprotection of the tert-Boc group under acidic conditions (HCl 32%). Synthesis of compound **8** was achieved via a two-step methodology, in the first step 2,4,6-tri(piperazin-1-yl)-1,3,5-triazine (**7**) was first synthesized through a nucleophilic substitution reaction between cyanuric chloride **4** followed by deprotonation of the tert-Boc group under acidic conditions (HCl 32%).

S2.1 Trivinylphosphine oxide (TVPO)



TVPO

A solution of phosphoryl trichloride (9.1 mL, 100 mmol) was dissolved in anhydrous THF (300 mL), cooled to –78 °C and mechanically stirred under an atmosphere of dry nitrogen. Subsequently, vinyl magnesium bromide (1M in THF, 300 mL) was slowly added to the above mixture so that the temperature of the reaction mixture never exceeded –70 °C (the addition took 4 hours). After an additional 3 hours of stirring at –78 °C, 500 mL of cold (4 °C) ammonium chloride solution ([NH_4Cl] = 4 mol/L) was added to the still cold reaction solution and stirred for 5 min. The white precipitate containing insoluble inorganics compounds was

separated by filtration, affording a two-layer solution. The upper layer (THF) was separated and the aqueous layer was extracted twice with 400 mL chloroform. The organic layer was collected and dried over sodium sulfate (Na_2SO_4). After filtration, all volatiles were removed in vacuum and purification was done by sublimation to afford a white solid with 82% (31.5 g) yield.

^{1}H NMR (400.2 MHz, $CDCl_3$) δ (ppm): 6.1-6.3 (m, 9H, H-α, β).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 133.9 (t, C-β); 130.4 (dd, J_{CP} = 100 Hz, C-α).

^{31}P NMR (162.0 MHz, $CDCl_3$) δ (ppm): 17.4.

FTIR (KBr, powder, cm^{-1}): 3081(=CH), 3001 (–CH_2), 1596 (C=C), 1396 (–CH_2), 1172 (P=O), 975 (–C–P=O).

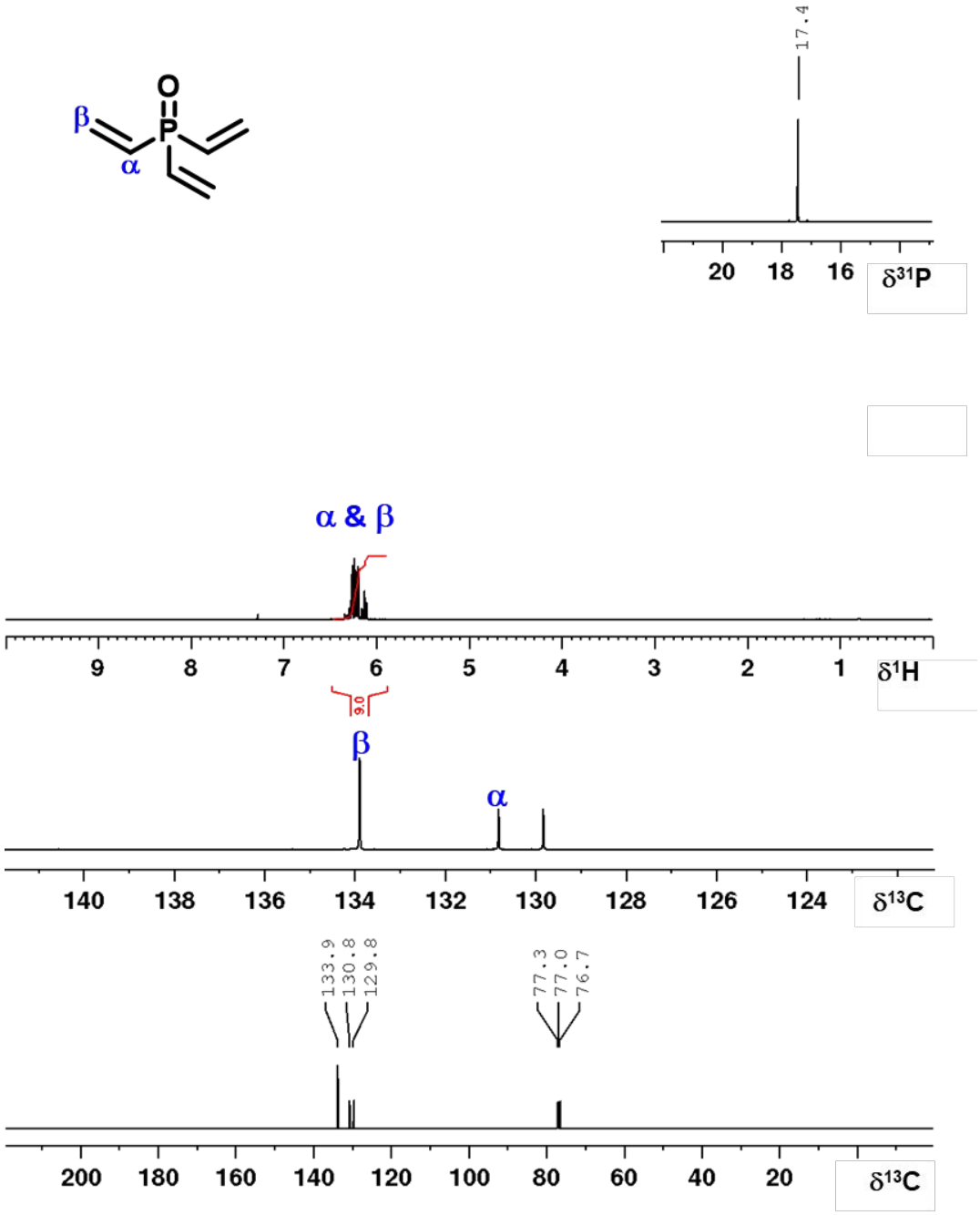


Figure S1: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **TVPO** ($CDCl_3$).

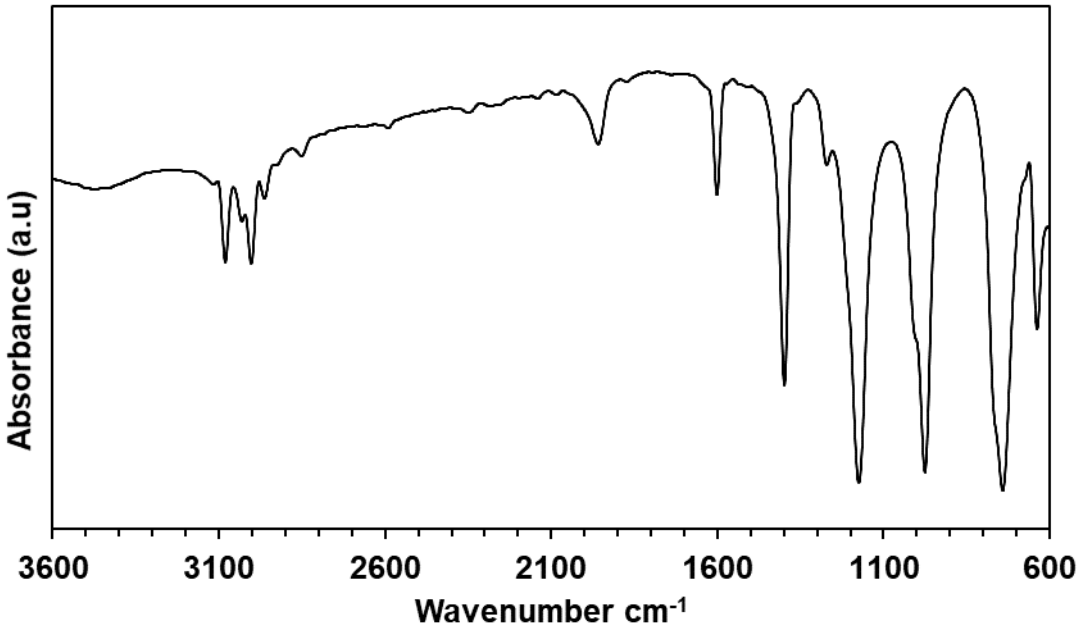
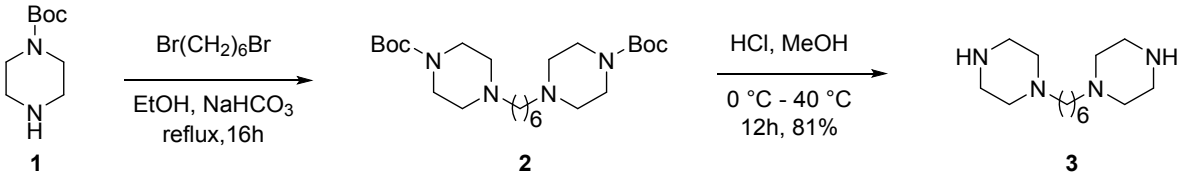


Figure S2: FTIR spectra of **TVPO**.

S2.2 Synthesis of 1,6-di(piperazin-1-yl)hexane (3)



In a round bottom flask tert-butyl piperazine-1-carboxylate (**1**) (9.3 g, 50 mmol), 1,6-dibromohexane (6.0 g, 25 mmol) and sodium bicarbonate ($NaHCO_3$) (8.4 g, 100 mmol) in ethanol (400 mL) were added at room temperature and heated to 100 ºC for 16 hours. After cooling to room temperature, the solvent was removed via rotary evaporation and the residue was dissolved in ethyl acetate (500 mL). The organic solution was washed with water (300 mL) and brine (200 mL), dried over sodium sulfate (Na_2SO_4) and evaporation of the solvent gave intermediate **2** as a white solid, which was used as such in the next step without any further purification.

In the second step, compound **2** (4.5 g, 10 mmol, 1.00 equiv) and methanol (64.6 mL) were added into a 500 mL flask. The solution was stirred at 0 ºC for 30 min and hydrochloric acid (37%, 7.65 mL, 210 mmol, 21 equiv.) was added dropwise over 70 min while the temperature was kept at around 0 ºC. The resulting slurry was stirred at 0 ºC for 1 hour; then the reaction mixture was allowed to reach room temperature over 2 hours. After stirring at 40 °C for an additional 12 hours, the organic components were removed via rotary evaporation, and the remaining aqueous solution was cooled to 0 ºC and adjusted to pH 14 using a10% (w/v) sodium hydroxide solution. The compound was extracted with chloroform (3 × 250 mL). The organic layer was collected, dried over Na_2SO_4 and concentrated in vacuo to obtain a white solid **3** with an overall 81% (5.1 g) yield.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.84 (t, 5.0 Hz, 8H, H-a); 2.45 (m (br), 8H, H-b); 2.34 (m, 4H, H-c); 1.53 (m, 4H, H-d); 1.35 (m, 4H, H-e).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 60.3 (t, C-c); 54.9 (t, C-b); 46.0 (t, C-a); 28.6 (t, C-e); 27.2 (t, C-d).

FTIR (KBr, powder, cm^{-1}): 3401 (H_2O), 3280 (–NH), 2927, 2782 (–CH_2), 1650 (–NH), 1461, 1415 (–CH_2), 1250, 1150 (–CN), 1131 (C–C).

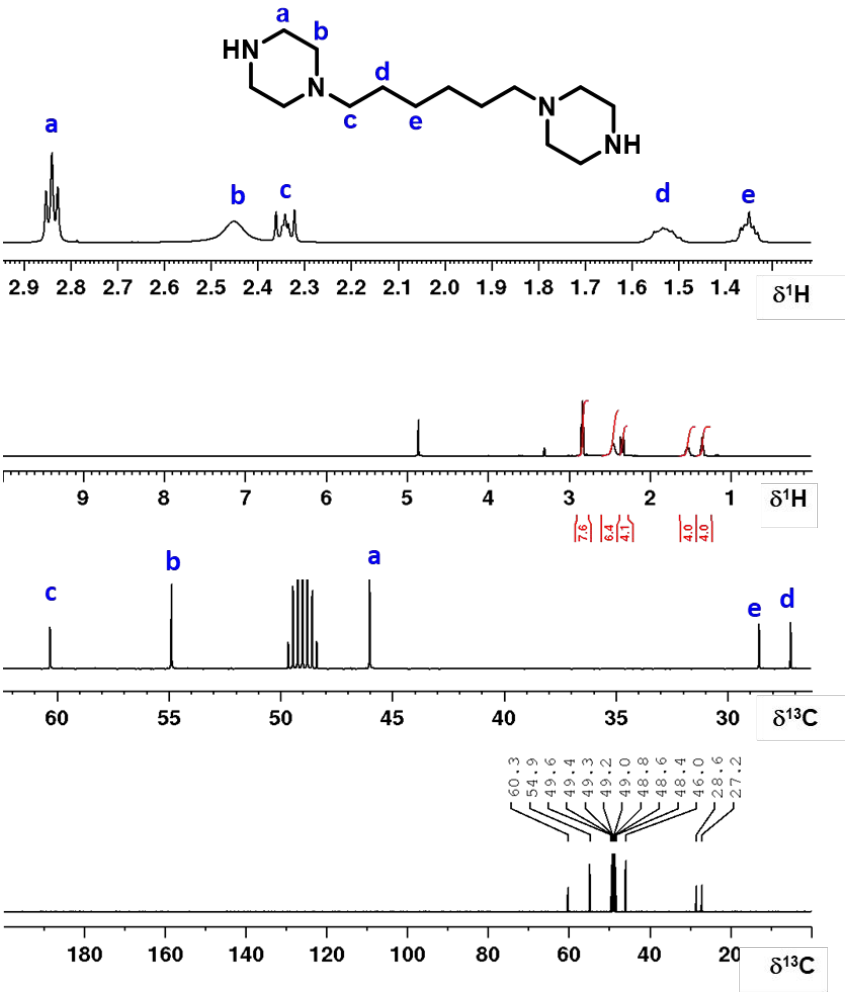


Figure S3: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **3** (CD_3OD).

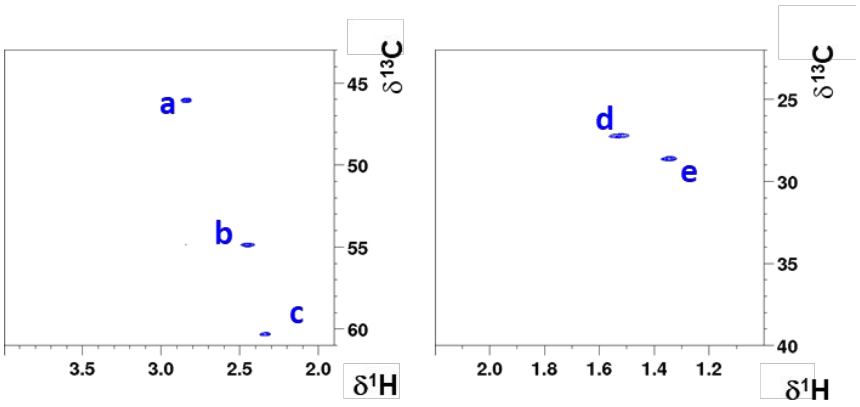


Figure S4: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of **3** (CD_3OD).

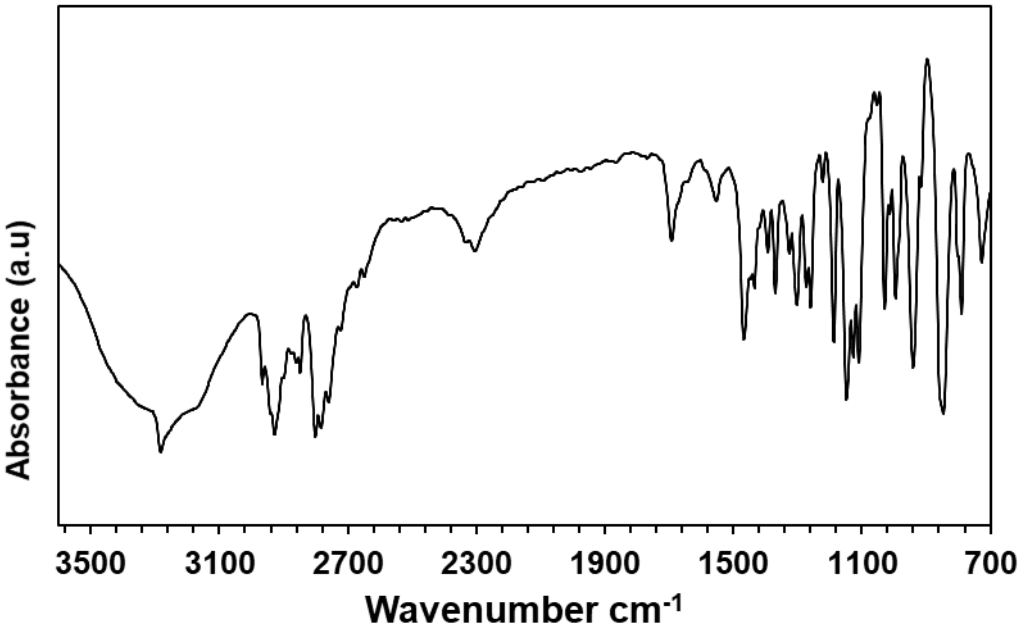
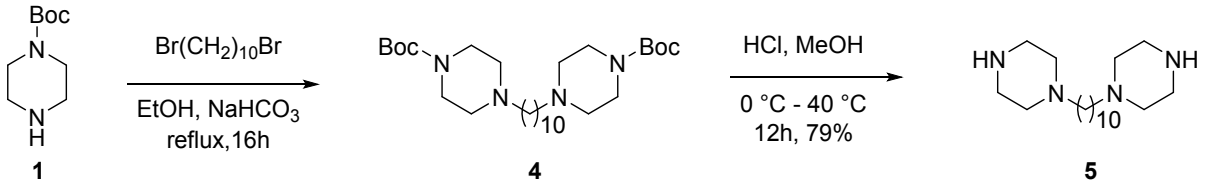


Figure S5: FTIR spectra of **3**.

S2.3 Synthesis of 1,10-di(piperazin-1-yl)decane (5)



In a round bottom flask **1** (9.3 g, 50 mmol), 1,10-Dibromodecane (7.5 g, 25 mmol) and $NaHCO_3$ (8.4 g, 100 mmol) in ethanol (400 mL) were added at room temperature and heated to 100 ºC for 16 hours. After cooling to room temperature, the solvent was removed via rotary evaporation and the residue was dissolved in ethyl acetate (500 mL). The organic solution was washed with water (300 mL) and brine (200 mL), dried over sodium sulfate (Na_2SO_4) and evaporated to give intermediate **4** as a white solid, which was used for the next step without further purification.

Subsequently, in a 500 mL round bottom flask, compound **4** (5.1 g, 10 mmol, 1.00 equiv.) was dissolved in methanol (64.6 mL). The solution was stirred at 0 ºC for 30 min, then hydrochloric acid (37%) (7.6 mL, 210 mmol, 21 equiv.) was added over 70 min while the temperature was

kept at 0 °C. The resulting slurry was stirred at 0 ºC for 1 hour; the reaction mixture was then allowed to reach room temperature over 2 hours. After an additional stirring at 40 °C for 12 hours, the solvent was removed via using rotary evaporation and the remaining aqueous solution was cooled to 0 ºC and pH adjusted to 14 by using 10% (w/v) sodium hydroxide solution. The organic layer was collected, dried over Na_2SO_4 and concentrated in vacuo to obtain a final white solid **5** with an overall 79% (6.1 g) yield.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.87 (t, 5.0 Hz, 8H, H-a); 2.47 (m (br), 8H, H-b); 2.34 (m, 4H, H-c); 1.53 (m, 4H, H-d); 1.32 (m, 12H, H-e, f, g).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 60.3 (t, C-c); 54.6 (t, C-b); 45.9 (t, C-a); 30.6 (t, C-f, g); 28.7 (t, C-e); 27.2 (t, C-d).

FTIR (KBr, powder, cm^{-1}): 3226 (–NH), 2917, 2848, 2802 (–CH_2), 1552 (–NH), 1461, 1415 (–CH_2), 1250, 1150 (–CN), 1131 (C–C).

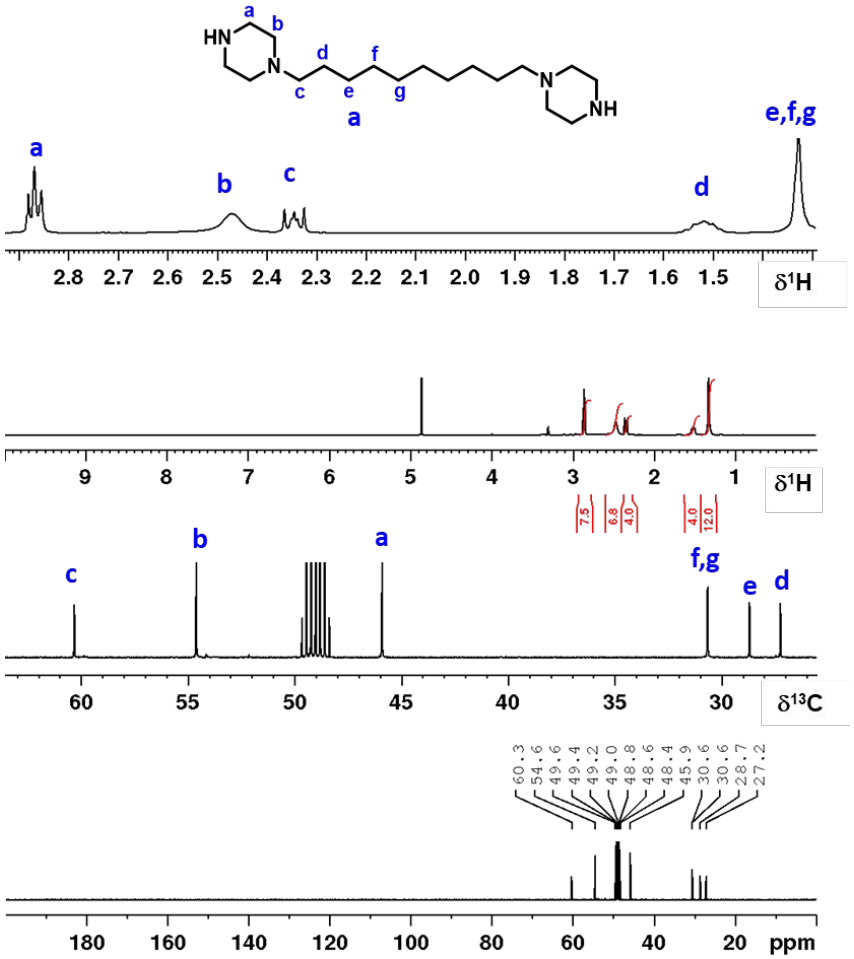


Figure S4: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **5** (CD_3OD).

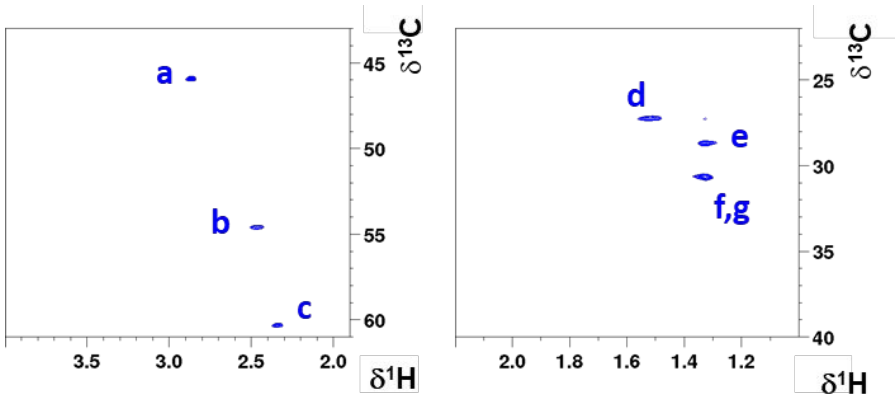


Figure S6: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of **5** (CD_3OD).

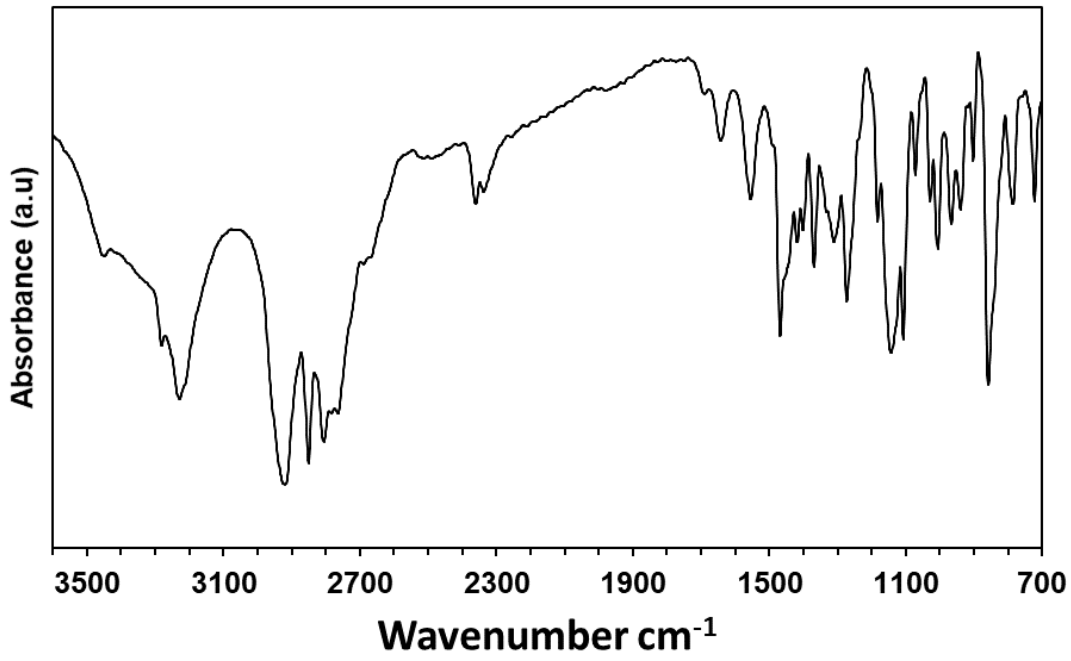
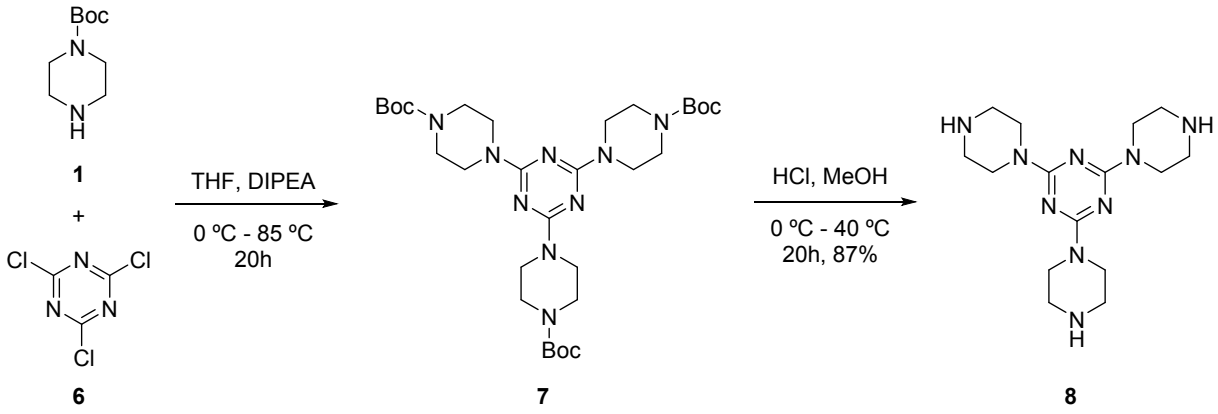


Figure S7: FTIR spectra of **5**.

S2.4 Synthesis of 2,4,6-tri(piperazin-1-yl)-1,3,5-triazine (8)



In a round-bottom flask, cyanuric chloride (**6**) (5.0 g, 26.66 mmol) in 160 mL of THF was added to tert-butyl piperazine-1-carboxylate (**1**) (16.6 g, 90 mmol) in 3 portions over 30 minutes at room temperature (reaction carried out under dry nitrogen gas). The reaction mixture was cooled to 0 ºC, and diisopropylethylamine (47.3 mL, 3-fold excess) was added dropwise. The reaction mixture was stirred at 0 ºC for one hour, then at room temperature for one hour and finally at 85 °C for 20 hours. Subsequently, THF was removed in vacuo and the residue was dissolved in 300 mL of CH_2Cl_2. This solution was washed with water (3 × 100 mL). The organic

layer was collected, dried over Na_2SO_4 and concentrated in vacuo to give **7** as white solid used as such in the next step without any further purification.

Compound **7** (6.3 g, 10 mmol, 1.00 equiv.) was dissolved in methanol (64.6 mL) in a 500 mL flask. The solution was stirred at 0 ºC for 30 min and hydrochloric acid (32%, 7.65 mL, 210 mmol, 21 equiv.) was added over 70 min while the temperature was kept at 0 °C. The resulting slurry was stirred at 0 ºC for 1 hour; then the reaction mixture was allowed to reach room temperature over 2 hours. After stirring at 40 °C for 12 hours, the volatiles were removed by using a rotary evaporator and the remaining aqueous solution was cooled to 0 ºC and the pH was adjusted to 14 by using 10% (w/v) sodium hydroxide solution. The alkaline solution was extracted with chloroform (3 × 250 mL). The organic layer was collected, dried over Na_2SO_4 and concentrated in vacuo to obtain a final white solid **8** with an overall 87% (2.9 g) yield.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 3.72 (m, 12H, H-b); 2.79 (m, 12H, H-a)

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 166.7 (s, C-c); 46.4 (t, C-a); 44.9 (t, C-b).

FTIR (KBr, powder, cm^{-1}): 3268 (–NH), 2912, 2821 (–CH_2), 1625 (–NH), 1554 (C=C), 1415 (–CH_2), 1250, 1150 (–CN), 1131 (C–C).

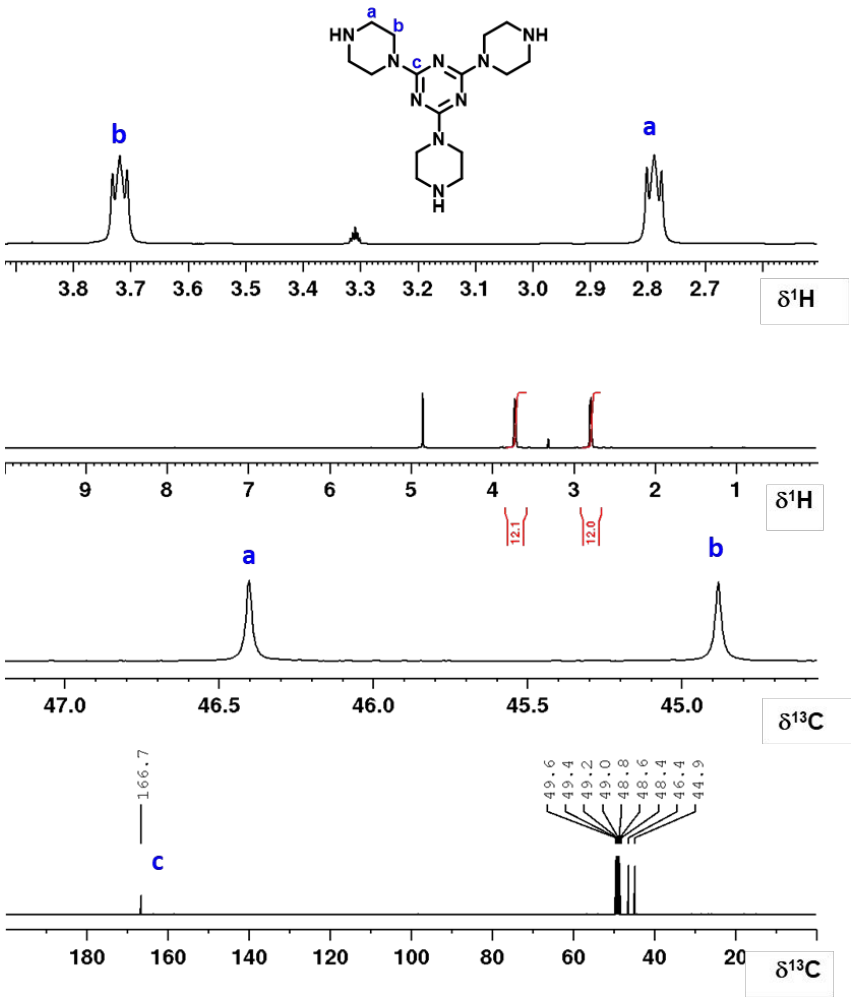


Figure S8: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **8** (CD_3OD).

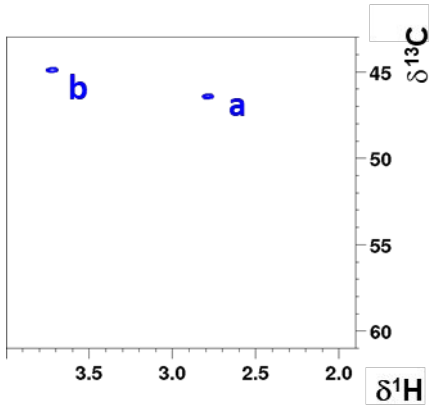


Figure S9: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of **8** (CD_3OD).

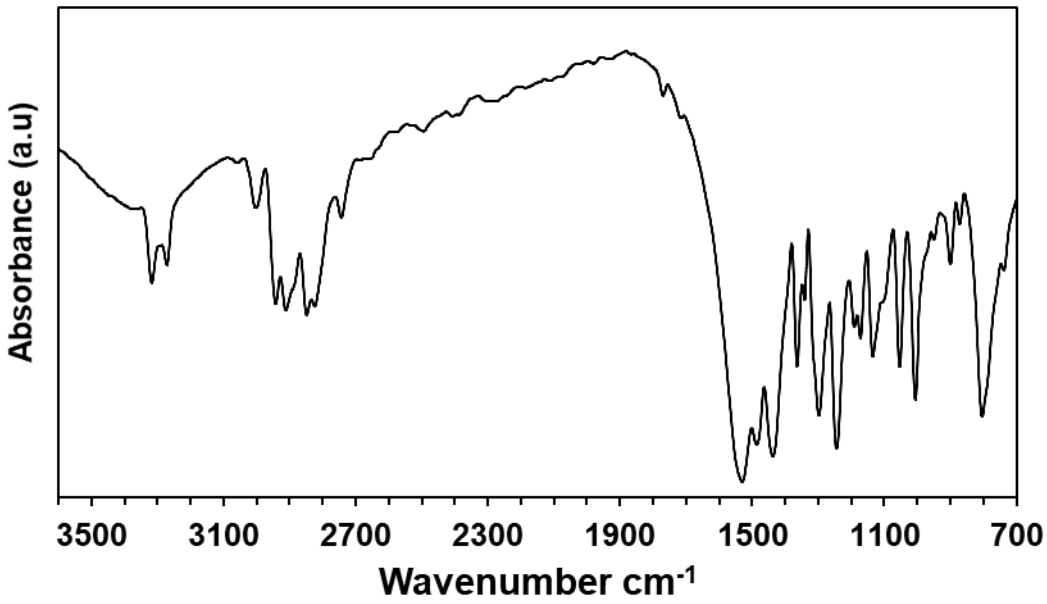


Figure S10: FTIR spectra of **8**.

S3. NMR characterizations of commercially used diamine derivatives

S3.1. NMR characterizations of piperazine

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.73 (s, 8H, H-a).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 44.8 (t, C-a).

FTIR (KBr, powder, cm^{-1}): 3212 (–NH), 2849 ($–CH_2$), 1625 (–NH), 1415 ($–CH_2$), 1250, 1150 (–CN), 1131 (C–C).

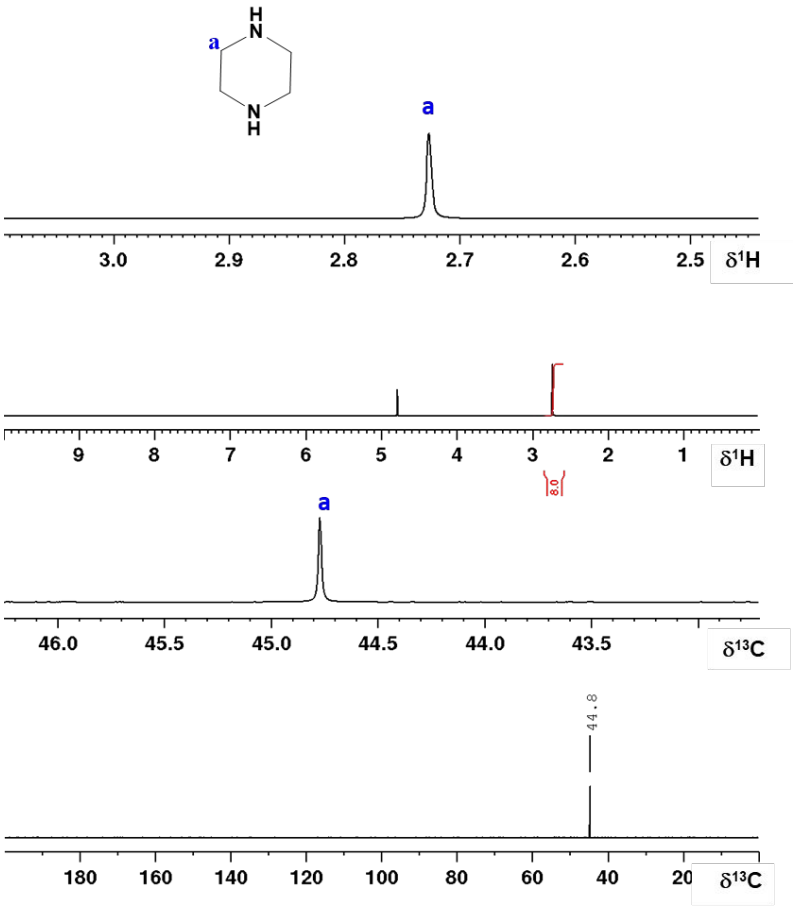


Figure S10: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **piperazine** (D_2O).

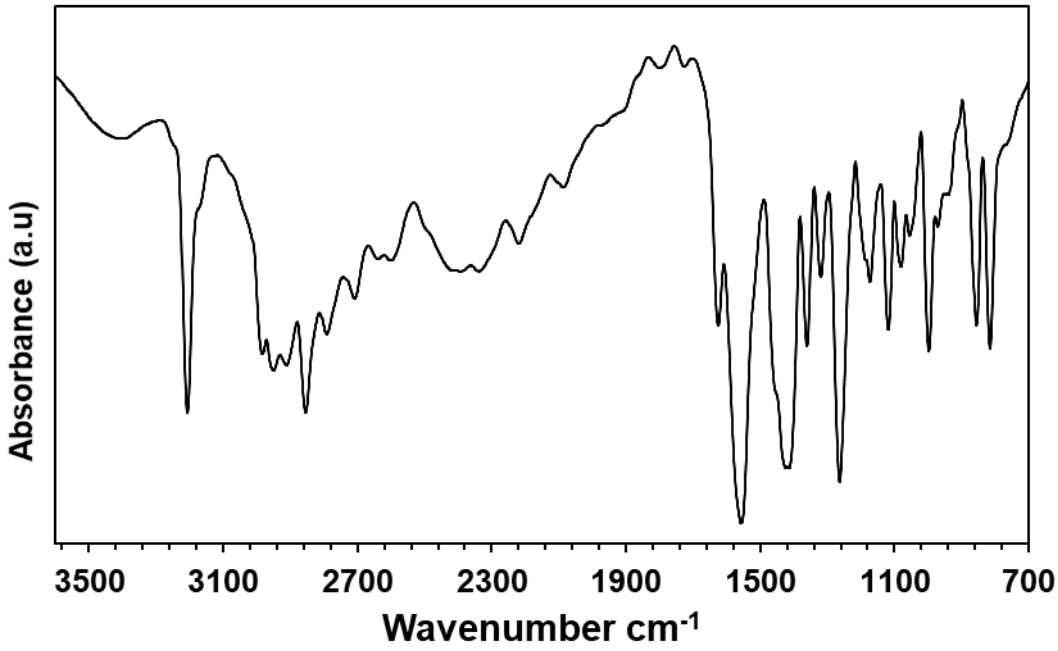


Figure S11: FTIR spectra of **piperazine**.

S3.2. NMR characterizations of piperidine

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.75 (m, 4H, H-a); 1.6-1.5 (m, 6H, H-b, c).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 47.7 (t, C-a); 27.5 (t, C-b); 25.9 (t, C-c).

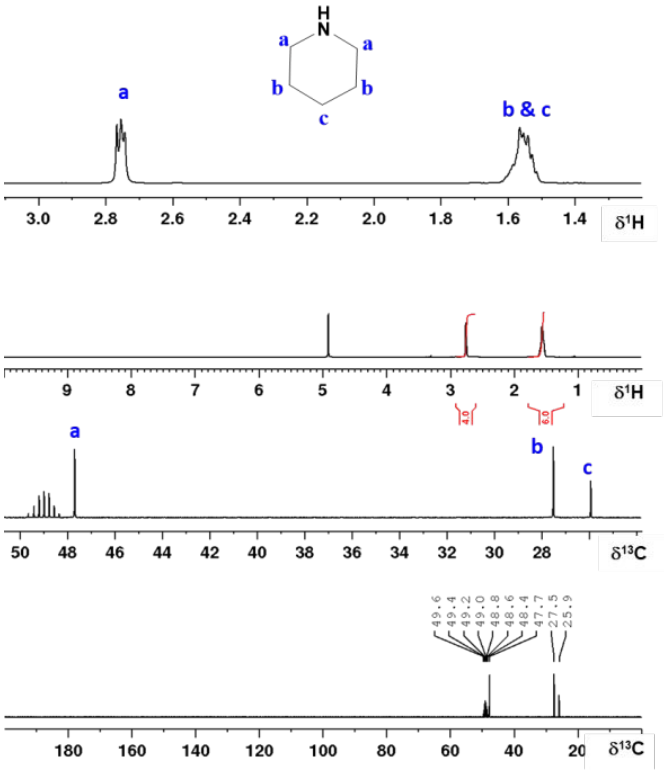


Figure S12: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of piperidine (CD_3OD).

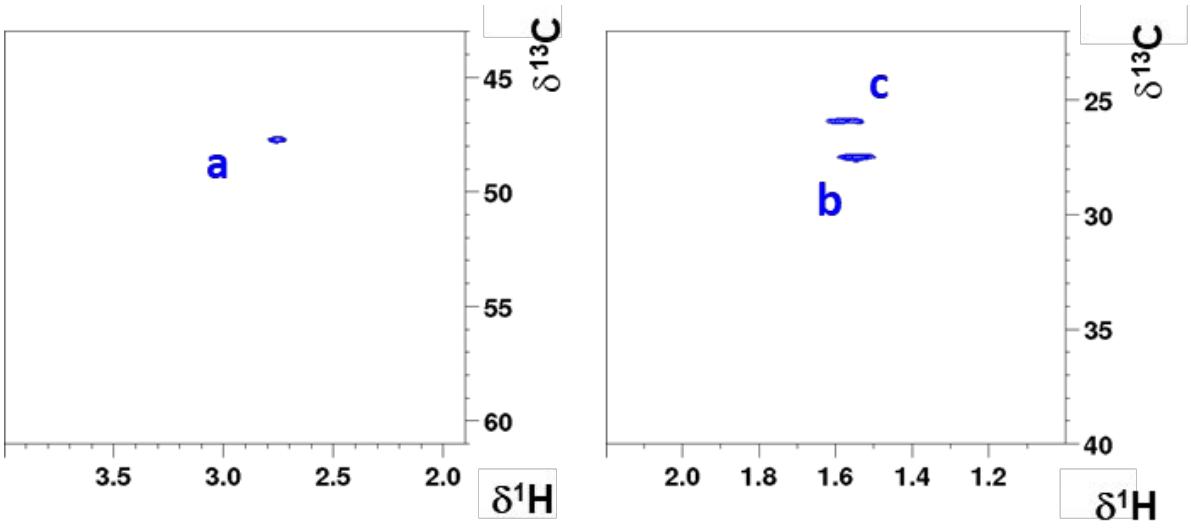


Figure S13: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of piperidine (CD_3OD).

S3.3. NMR characterizations of 1,3-di(piperidin-4-yl)propane

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 3.00 & 2.54 (dt, 12.3 + 3.5 Hz & td, 12.3 + 2.7 Hz, 4H & 4H, H-a); 1.68+1.10 (m (br), 4H & 4H, H-b); 1.35 (m, 4H, H-c, e); 1.23 (m, 4H, H-d).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 47.2 (t, C-a); 38.5 (t, C-d); 37.3 (d, C-c); 34.0 (t, C-b); 24.4 (t, C-e).

FTIR (KBr, powder, cm^{-1}): 3401 (H_2O), 3190 (–NH), 2915, 2838 (–CH_2, –CH), 1585 (–NH), 1444, 1415 (–CH_2), 1250, 1150 (–CN), 1131 (C–C).

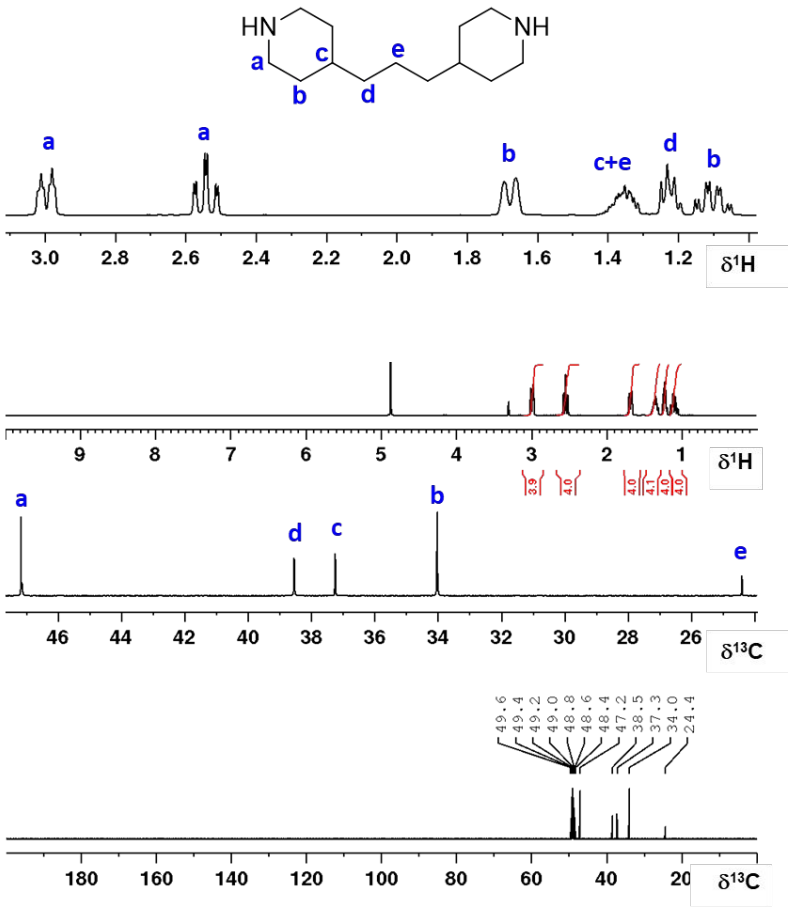


Figure S14: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of 1,3-di(piperidin-4-yl)propane (CD_3OD).

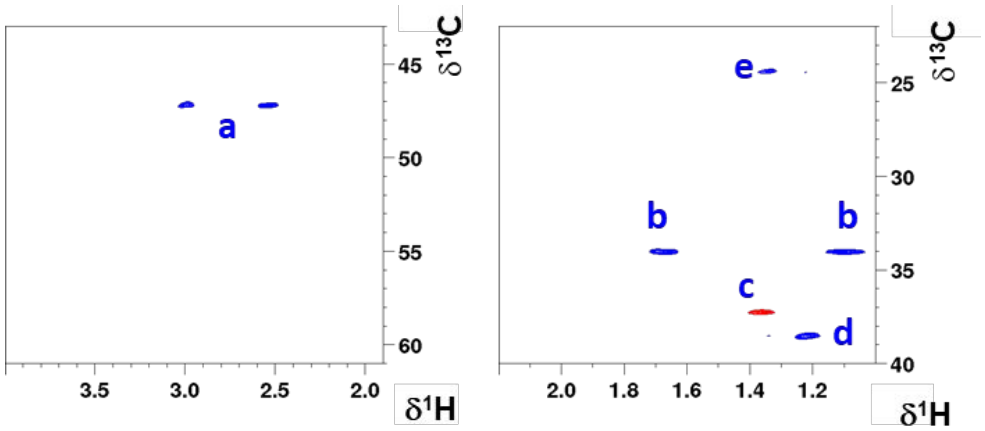


Figure S15: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of 1,3-di(piperidin-4-yl)propane (CD_3OD).

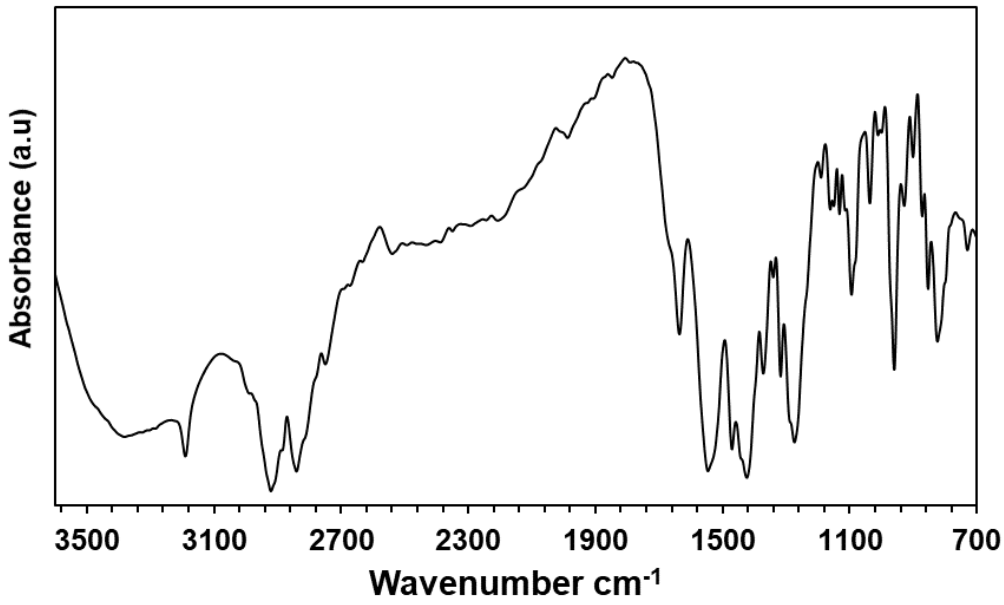


Figure S16: FTIR spectra of **1,3-di(piperidin-4-yl)propane**.

S4. Solvent affinity of gels (swelling behavior)

The solvent affinity of the gels was characterized by determining their swelling ratio (SR). The swelling ratio of gels was measured by soaking the gel in an individual solvent for 24 hours to reach equilibrium; the swelled gel was removed with a spatula and weighed. The swelling ratio (SR) of the gel was calculated with the following formula (Eq S1) where W_s is the weight of swollen gel and W_d represents the weight of the dry crosslinked gels respectively. In the case

of Gel-A, swelling behavior was studied from pH 2 to 9 under ambient laboratory temperature (22 ºC). The desired pH of the solutions was obtained by using HCl and NaOH solutions.

$$\text{Swelling Ratio (SR)} = \frac{Ws - Wd}{Wd} \qquad \text{.....} \qquad \text{Eq-S1}$$

It can be seen in figure S13 that changing the alkyl chain length in diamines, solvent affinity of gels changed from hydrophilic to hydrophobic.

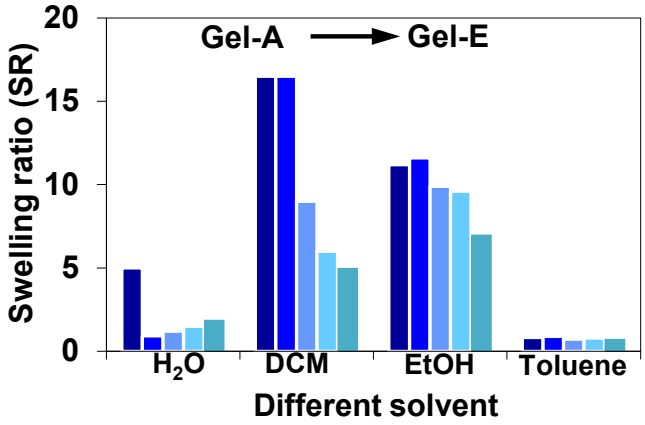


Figure S17: Swelling ratios of gels in different solvents demonstrating their solvent affinity.

S5. NMR characterization of gels

For a detailed discussion of the NMR data of Gel-A, see the main part of the manuscript.

S5.1 Synthesis of Gel-A

A solutions of TVPO (64.0 mg, 0.50 mmol) and piperazine (64.6 mg, 0.75mmol) in water (2.5 mL) was heated at 70 °C for 1 hour to obtain a transparent hydrogel.

^{1}H NMR (400.2 MHz, D_2O) δ (ppm): 2.79 (m, H-a); 2.63 (m, H-β1, β2); 2.49 (m (br), H-b, c); 2.09 (m, H-α).

^{13}C NMR (100.6 MHz, D_2O) δ (ppm): 52.1 (t, C-b); 51.1 (t, C-c); 49.7 & 49.1 (t, C-β1, β2); 43.9 (t, C-a); 23.7 (dd, J(C,P) = ca. 63 Hz, C-α [-CHD-]).

^{31}P NMR (162.0 MHz, D_2O) δ (ppm): 54.5-55.1.

FTIR (KBr, powder, cm^{-1}): 3386 (H_2O), 3263 (–NH), 2940, 2819 ($–CH_2$), 1654 (–NH), 1465 ($–CH_2$), 1128 (P=O), 998 (–C–P=O).

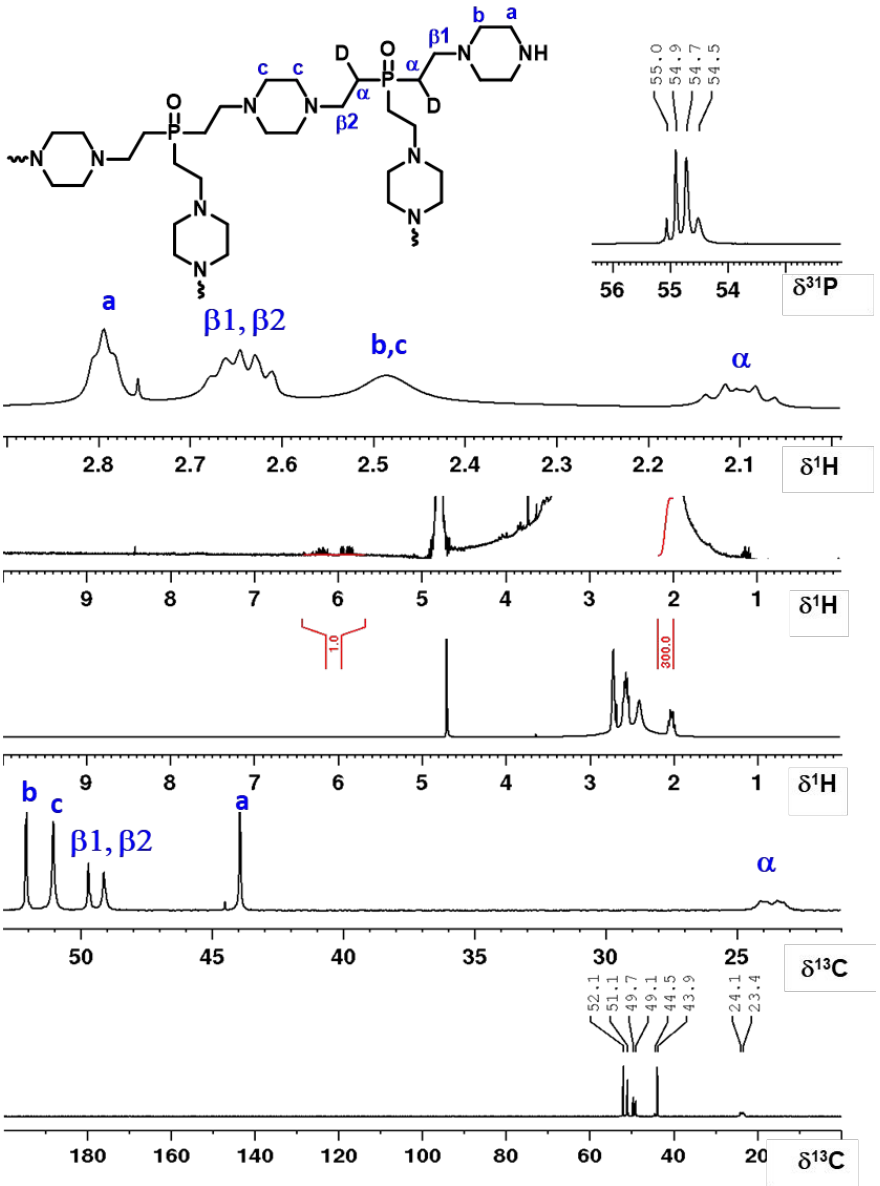


Figure S18: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **Gel-A** (D_2O).

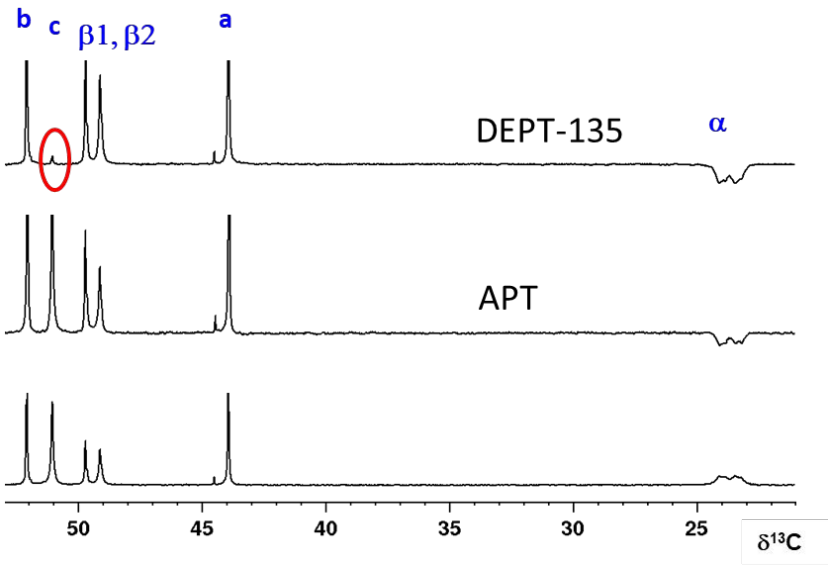


Figure S19: ^{13}C, ^{13}C APT and ^{13}C DEPT-135 NMR spectra with resonance assignments of **Gel-A** (D_2O).

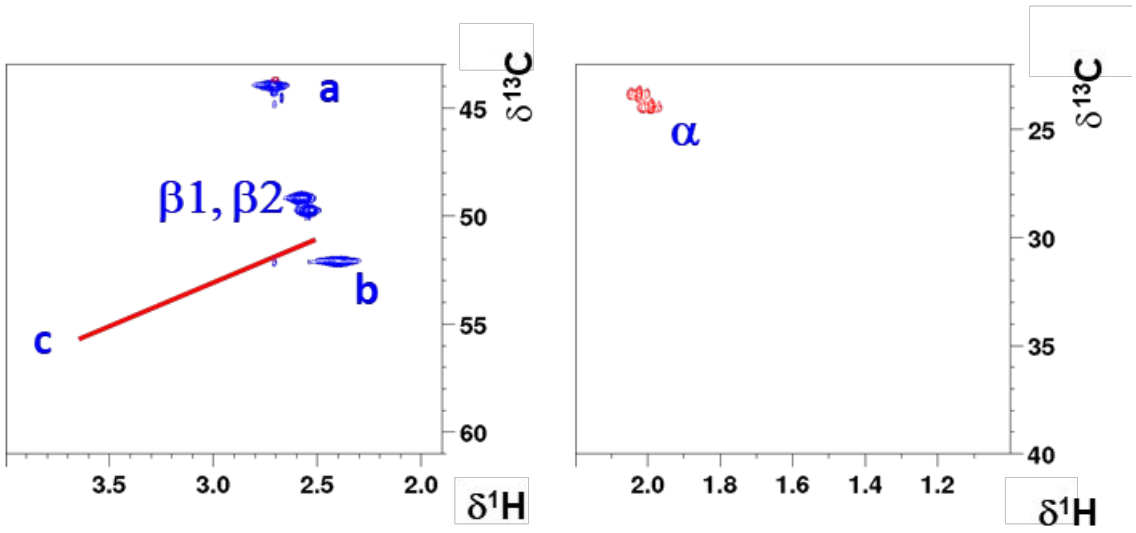


Figure S20: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of **Gel-A** (D_2O). The red line points to the missing correlation signal of positions c (chemical structure shown in Fig. S18).

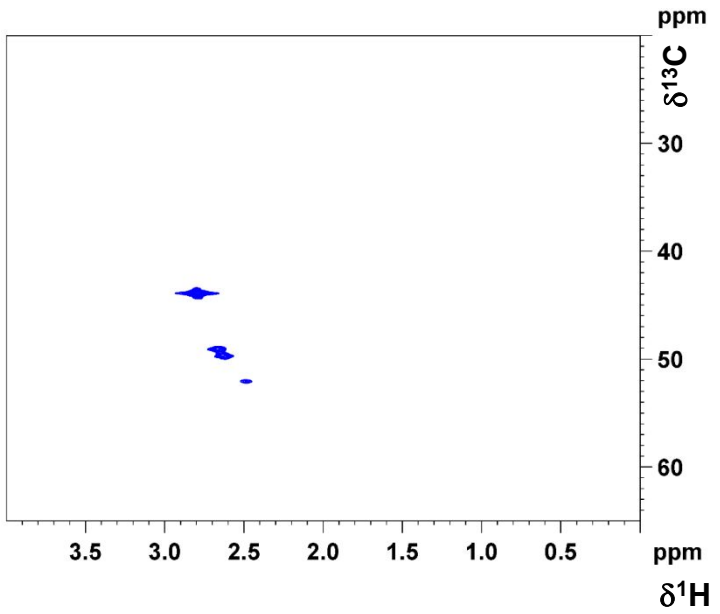


Figure S21: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of **Gel-A** (D_2O).

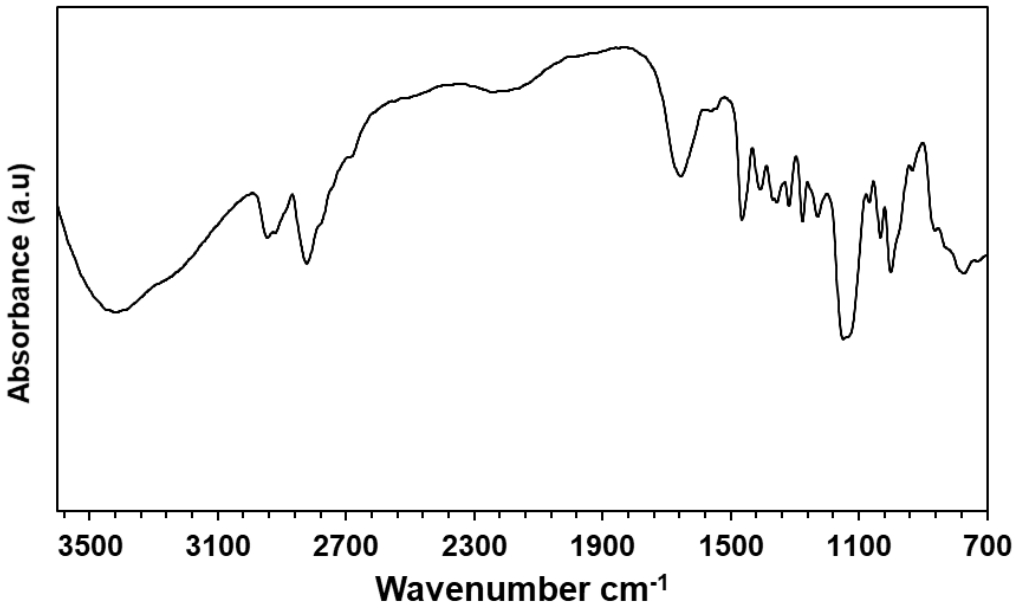
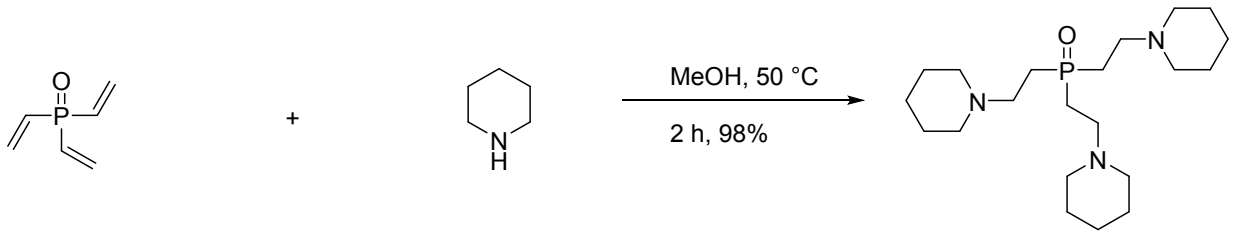


Figure S22: FTIR spectra of **Gel-A**.

S5.2 Synthesis of tris(2-(piperidin-1-yl)ethyl)phosphine oxide (9)



9

TVPO (64.0 mg, 0.50 mmol) and piperidine (127.7 mg, 1.5 mmol) were added to methanol (2.5 mL). The resulting mixture was stirred at 50 °C for 2 hours; the solvent was evaporated and the residue dried under vacuum to afford compound **9** with 98% (189 mg) yield.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.65 (m, 6H, H-β); 2.48 (m (br), 12H, H-a); 2.10 (m, 6H, H-α); 1.62 (m, 12H, H-b); 1.49 (m, 6H, H-c).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 55.1 (t, C-a); 52.2 (t, C-β); 26.7 (t, C-b); 26.5 (td, J_{CP} = 64.7 Hz, C-α); 25.2 (t, C-c).

^{31}P NMR (162.0 MHz, CD_3OD) δ (ppm): 52.1.

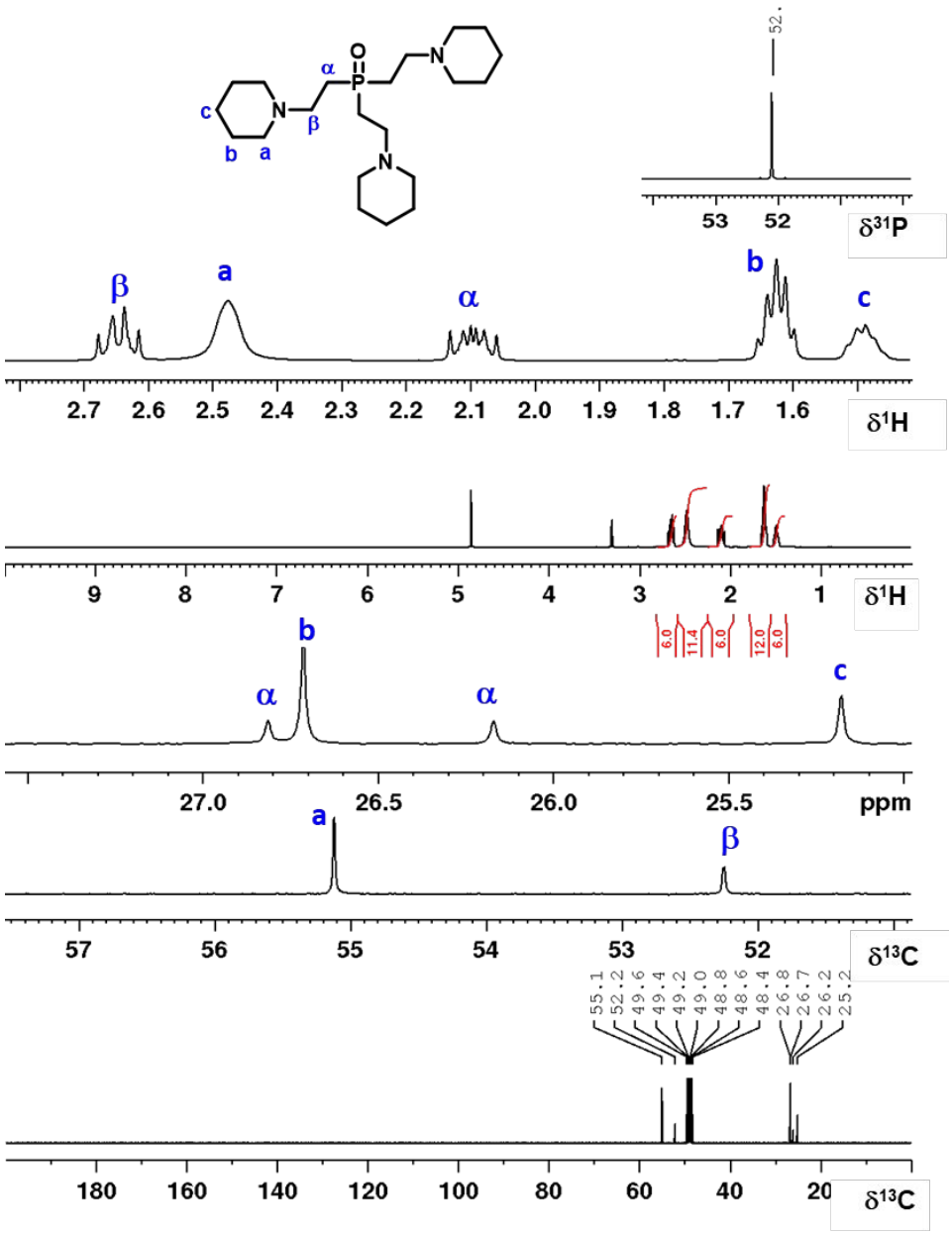
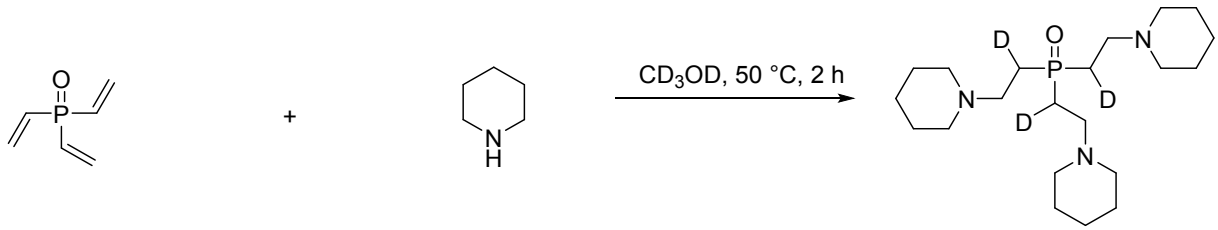


Figure S22: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **9** (CD_3OD).

S5.3 NMR characterization of tris(2-(piperidin-1-yl)ethyl)phosphine oxide (9-D) synthesized in CD_3OD.



9

TVPO (64.02 mg, 0.50 mmol) and piperidine (127.72 mg, 1.5 mmol) were added to CD_3OD (2.5 mL). The resulting mixture was stirred at 50 °C for 2 hours and NMR was measured.

Resonances of compound 9-D «in situ»: **(Contains piperidine)**

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.65 (m, 6H, H-β); 2.48 (m (br), 12H, H-a); 2.10 (m, 6H, H-α [-CH_2-]); 2.07 (m, 3H, H-α [-CHD-]); 1.62 (m, 12H, H-b); 1.49 (m, 6H, H-c).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 55.1 (t, C-a); 52.2 (t, C-β); 26.7 (t, C-b); 26.5 (td, J_{CP} = 64.6 Hz, C-α [-CH_2-]); 26.2 (dd, J_{CP} = 64.6 Hz, J_{CD} = 19.4 Hz, C-α [-CHD-]); 25.2 (t, C-c).

Resonances of piperidine:

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.75 (m, 4H, H-a); 1.7-1.6 (m, 6H, H-b,c).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 47.6 (t, C-a); 27.4 (t, C-b); 25.8 (t, C-c).

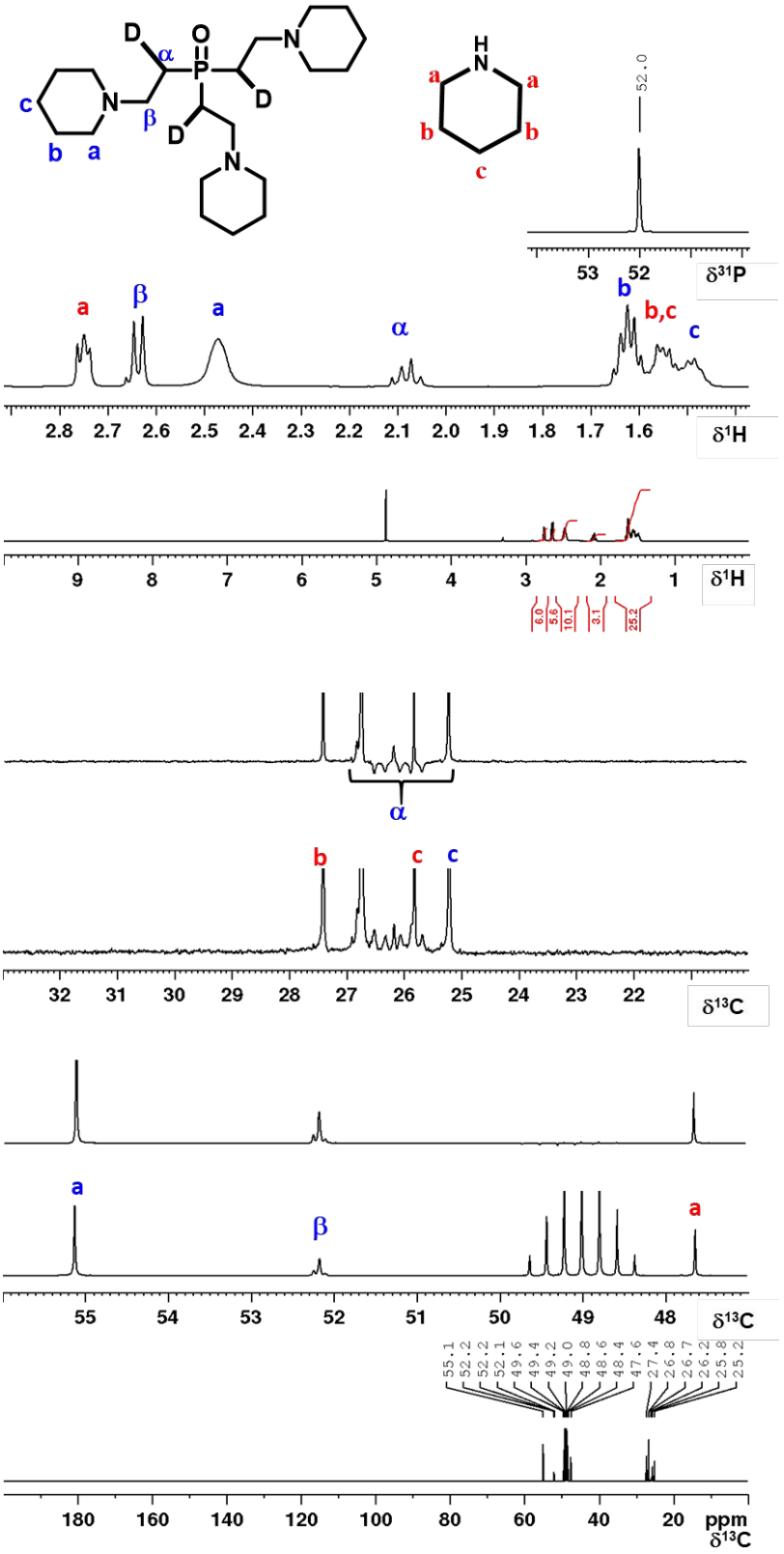


Figure S23: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **9** (CD_3OD).

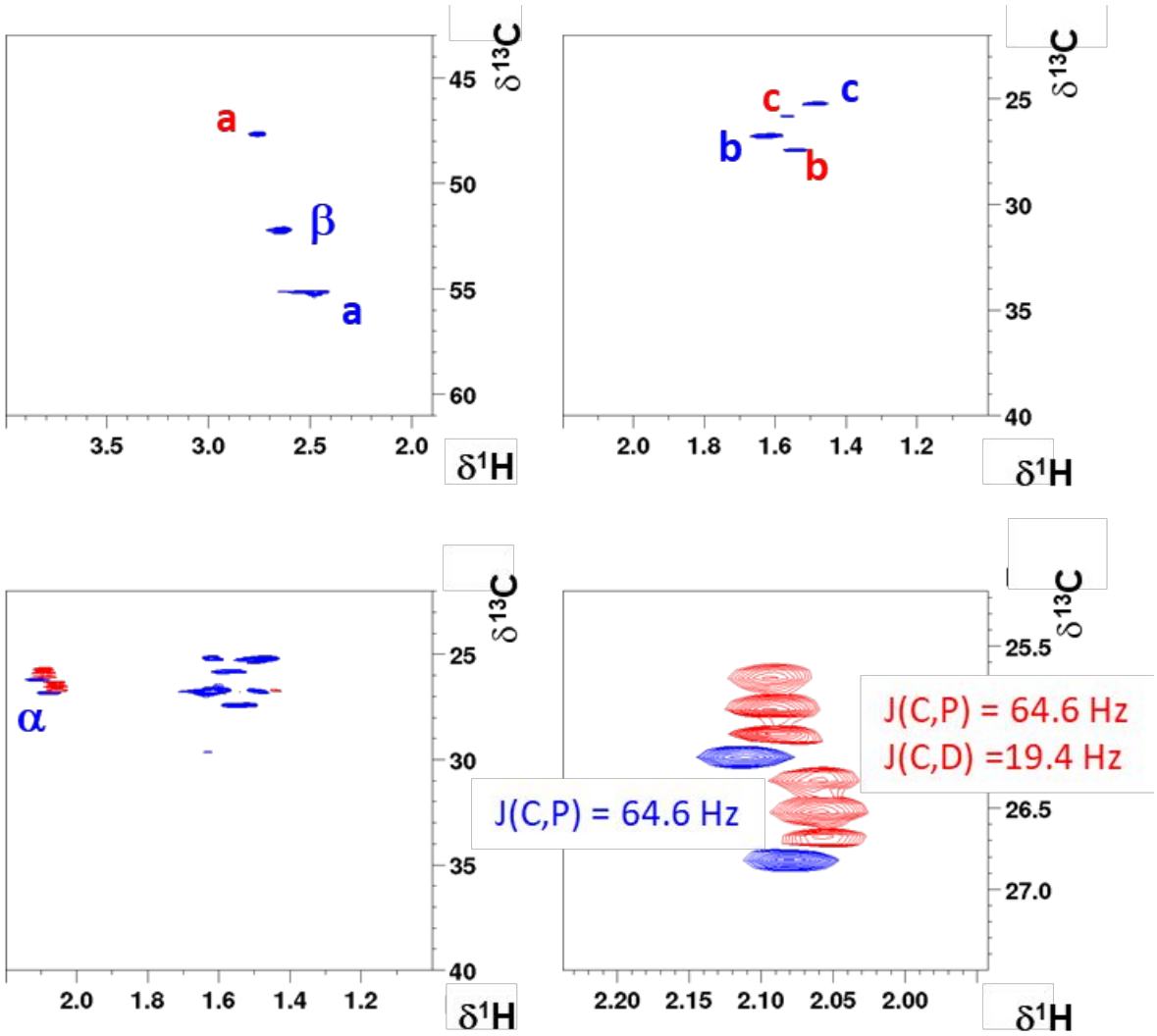


Figure S24: Expanded regions of ^{1}H-^{13}C HSQC NMR spectrum with assigned cross peaks of **9** (CD_3OD).

S5.4 NMR characterization of Gel-B

TVPO (64.0 mg, 0.50 mmol) and 1,3-di(piperidin-4-yl)propane (157.7 mg, 0.75 mmol) were added into ethanol (2.5 mL) and heated at 70 °C for 2 hours to obtain a transparent hydrogel.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 3.15-2.97 & 2.67-2.50 (m, H-a); 3.10-2.93 & 2.14-1.99 (m, H-a1); 2.78-2.62 (m, H-β); 2.06 (m, H-α); 1.87-1.70 & 1.38-1.19 (m, H-b1); 1.83-1.64 & 1.25-1.06 (m, H-b); 1.49-1.22 (m, H-c, c1, d, d1, e, e1).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 54.7 (t, C-a1); 51.8 (t, C-β); 47.2 (t, C-a); 38.6 (t, C-d); 37.9 (t, C-d1); 37.3 (d, C-c); 36.8 (d, C-c1); 34.1 (t, C-b); 33.3 (t, C-b1); 26.3 (dd, J(C,P) = ca. 68 Hz, C-α [-CHD-]); 24.7 (t, C-e1); 24.4 (t, C-e).

^{31}P NMR (162.0 MHz, CD_3OD) δ (ppm): 54.7; 42.1.

FTIR (KBr, powder, cm^{-1}): 3361 (–NH), 2917, 2844 ($–CH_2$), 1646 (–NH), 1448 ($–CH_2$), 1151 (P=O), 970 (–C–P=O).

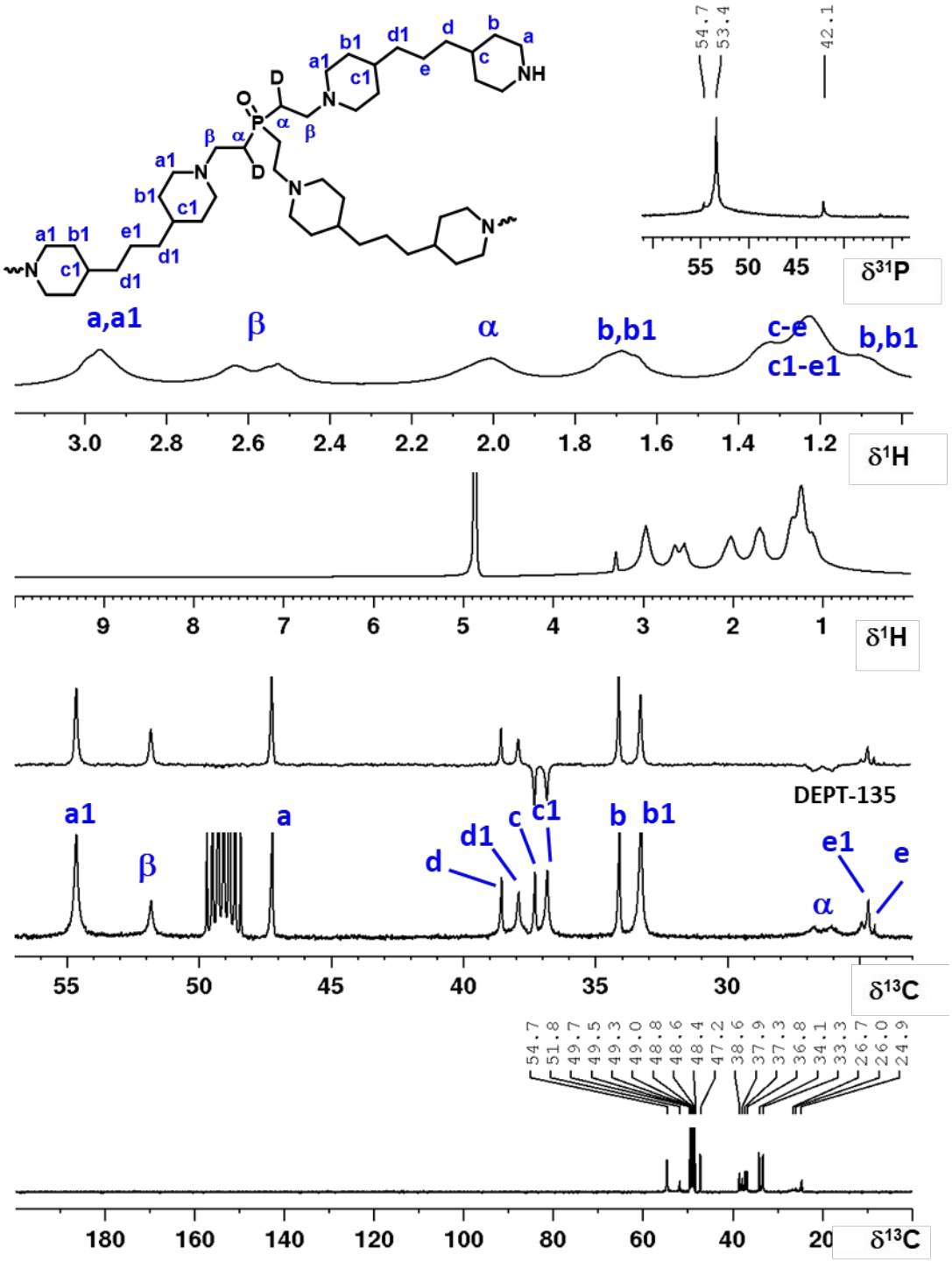


Figure S25: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **Gel-B** (CD_3OD).

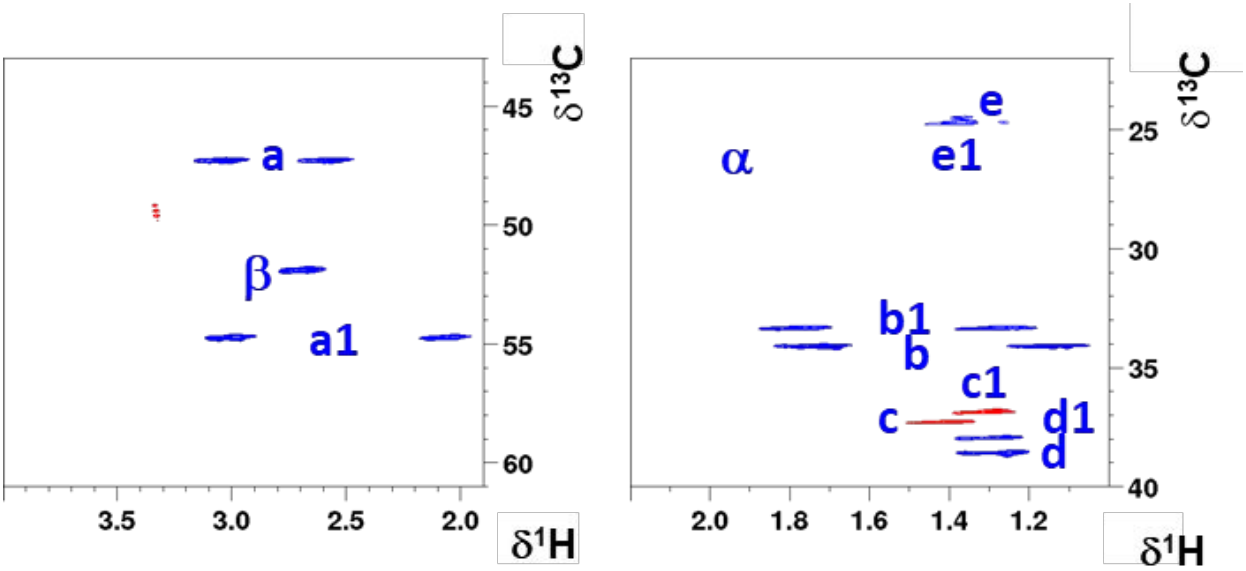


Figure S26: HSQC spectra region with cross peaks of **Gel-B** (CD_3OD).

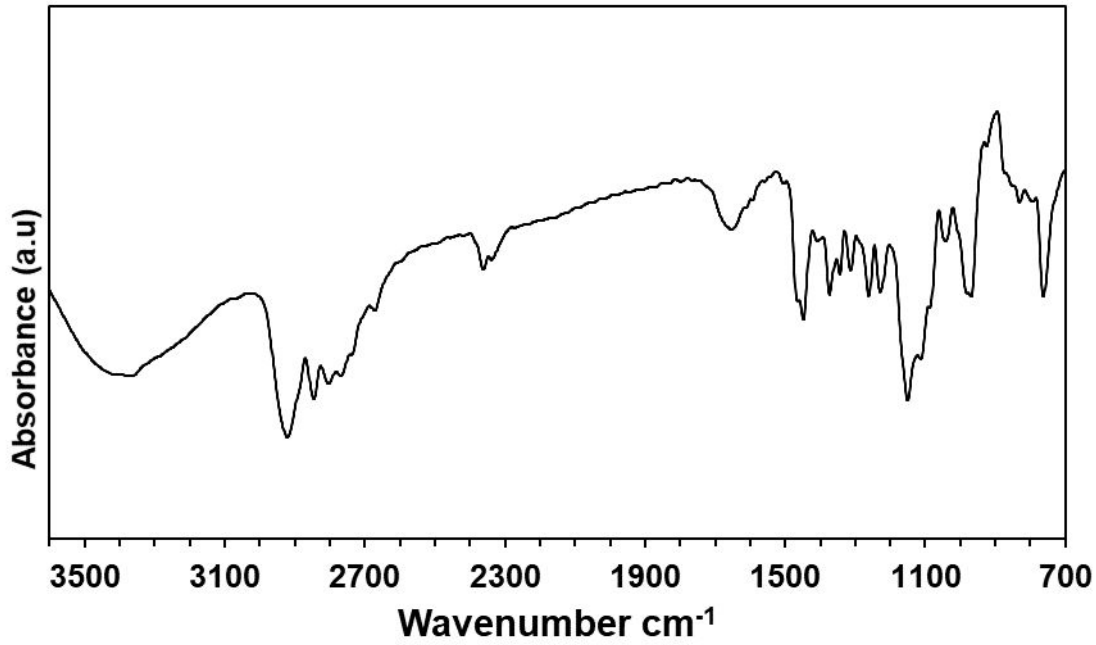


Figure S27: FTIR spectra of **Gel-B**.

S5.5 NMR characterization of Gel-C

TVPO (64.02 mg, 0.50 mmol) and **7** (190.5 mg, 0.75mmol) were dissolved in ethanol (2.5 mL). The resulting mixture was heated at 70 °C for 16 h, and a colorless transparent gel was obtained.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.84 (m, H-a); 2.68 (m, H-β); 2.56-2.42 (m, H-a1, b, b-1); 2.36 (m, H-c1); 2.34 (m, H-c); 2.09 (m, H-α); 1.53 (m, H-d, d1); 1.35 (m, H-e1).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 60.3 (t, C-c); 59.6 (t, C-c1); 54.8 (t, C-b); 54.0 (t, C-b1); 53.5 (t, C-a1); 51.5 (t, C-β); 46.0 (t, C-a); 28.5 (t, C-e1); 27.4 (t, C-d1); 27.2 (t, C-d); 26.5 (dd, J(C,P) = ca. 64 Hz, C-α [-CHD-]).

^{31}P NMR (162.0 MHz, CD_3OD) δ (ppm): 52.6; 40.5.

FTIR (KBr, powder, cm^{-1}): 3361 (–NH), 2927, 2807 ($–CH_2$), 1635 (–NH), 1456 ($–CH_2$), 1153 (P=O), 970 (–C–P=O).

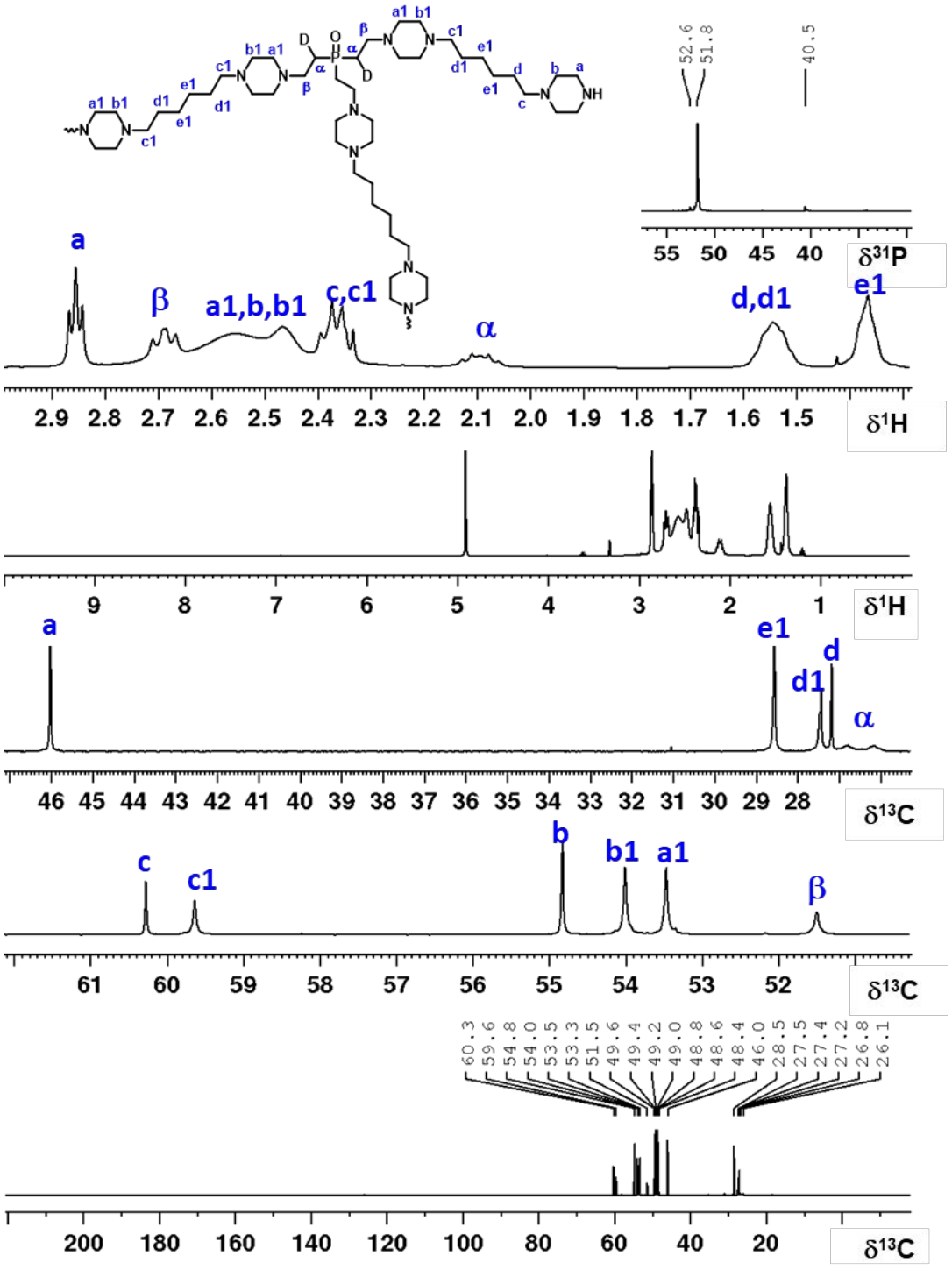


Figure S28: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **Gel-C** (CD_3OD).

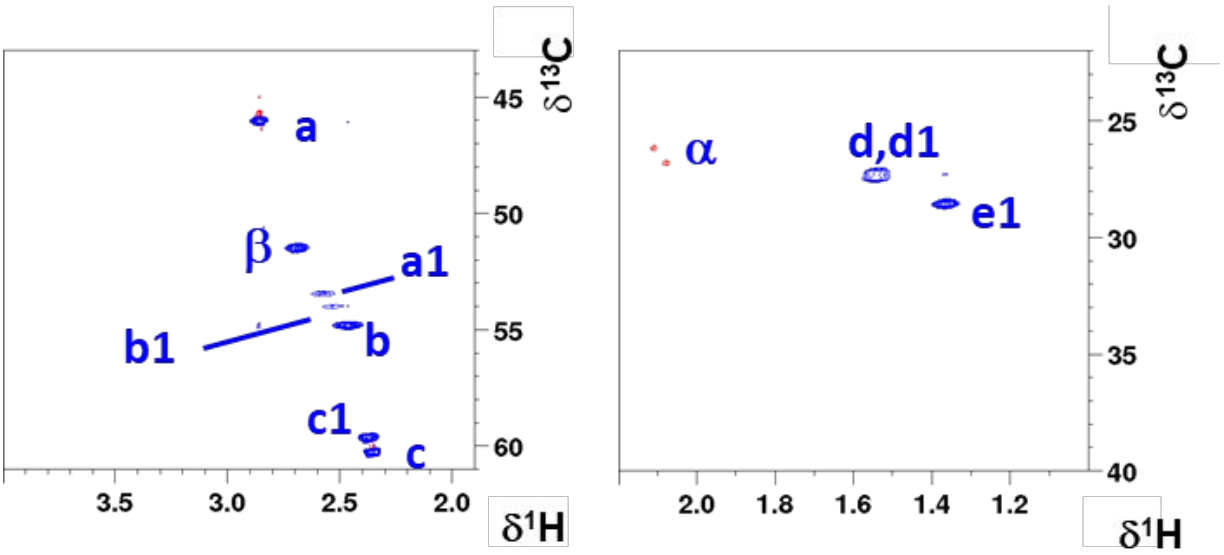


Figure S29: HSQC spectra region with cross peaks of **Gel-C** (CD_3OD).

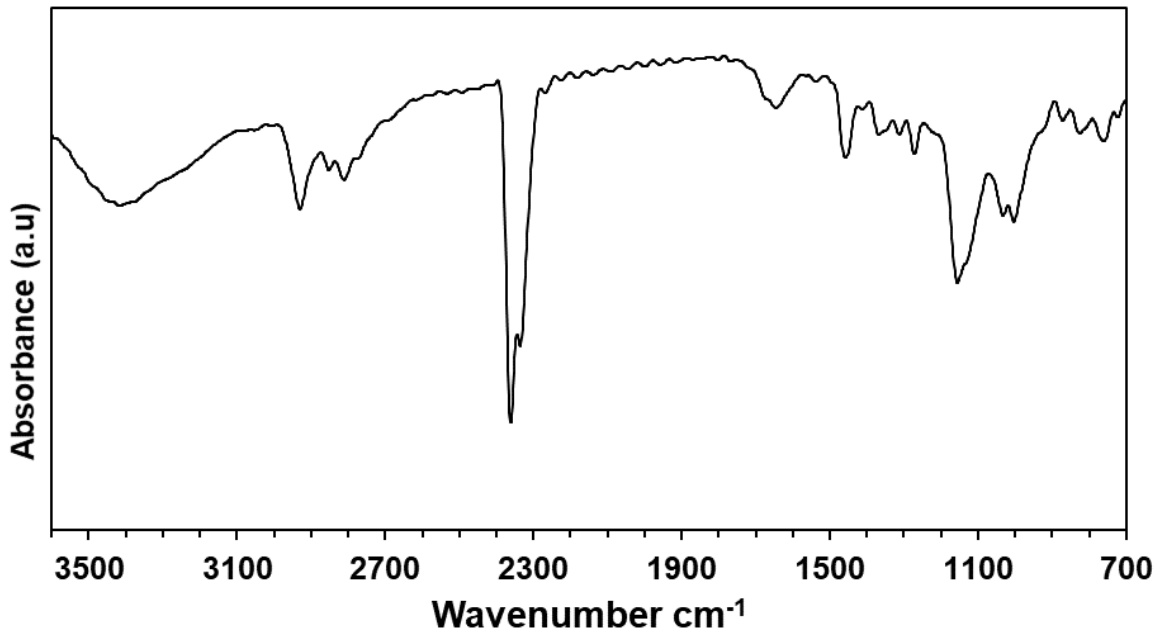


Figure S30: FTIR spectra of **Gel-C**.

S5.6 NMR characterization of Gel-D

TVPO (64.02 mg, 0.50 mmol) and **8** (232.89 mg, 0.75mmol) were added to ethanol (2.5 mL). The resulting mixture was heated at 70 °C for 24 h, and a colorless transparent gel was obtained.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 2.88 (m, H-a); 2.68 (m, H-β); 2.56-2.42 (m, H-a1, b, b-1); 2.35 (m, H-c, c1); 2.09 (m, H-α); 1.53 (m, H-d, d1); 1.44-1.26 (m, H-e, e1, f1, g1).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 60.2 (t, C-c); 59.7 (t, C-c1); 54.4 (t, C-b); 54.0 (t, C-b1); 53.4 (t, C-a1); 51.5 (t, C-β); 45.9 (t, C-a); 30.6 (t, C-f1, g1); 28.7 (t, C-e); 28.6 (t, C-e1); 27.4 (t, C-d1); 27.2 (t, C-d); 26.5 (dd, J(C,P) = ca. 64 Hz, C-α [-CHD-]).

^{31}P NMR (162.0 MHz, CD_3OD) δ (ppm): 52.8; 40.6; 34.7.

FTIR (KBr, powder, cm^{-1}): 3362 (–NH), 2925, 2807 ($–CH_2$), 1635 (–NH), 1456 ($–CH_2$), 1153 (P=O), 980 (–C–P=O).

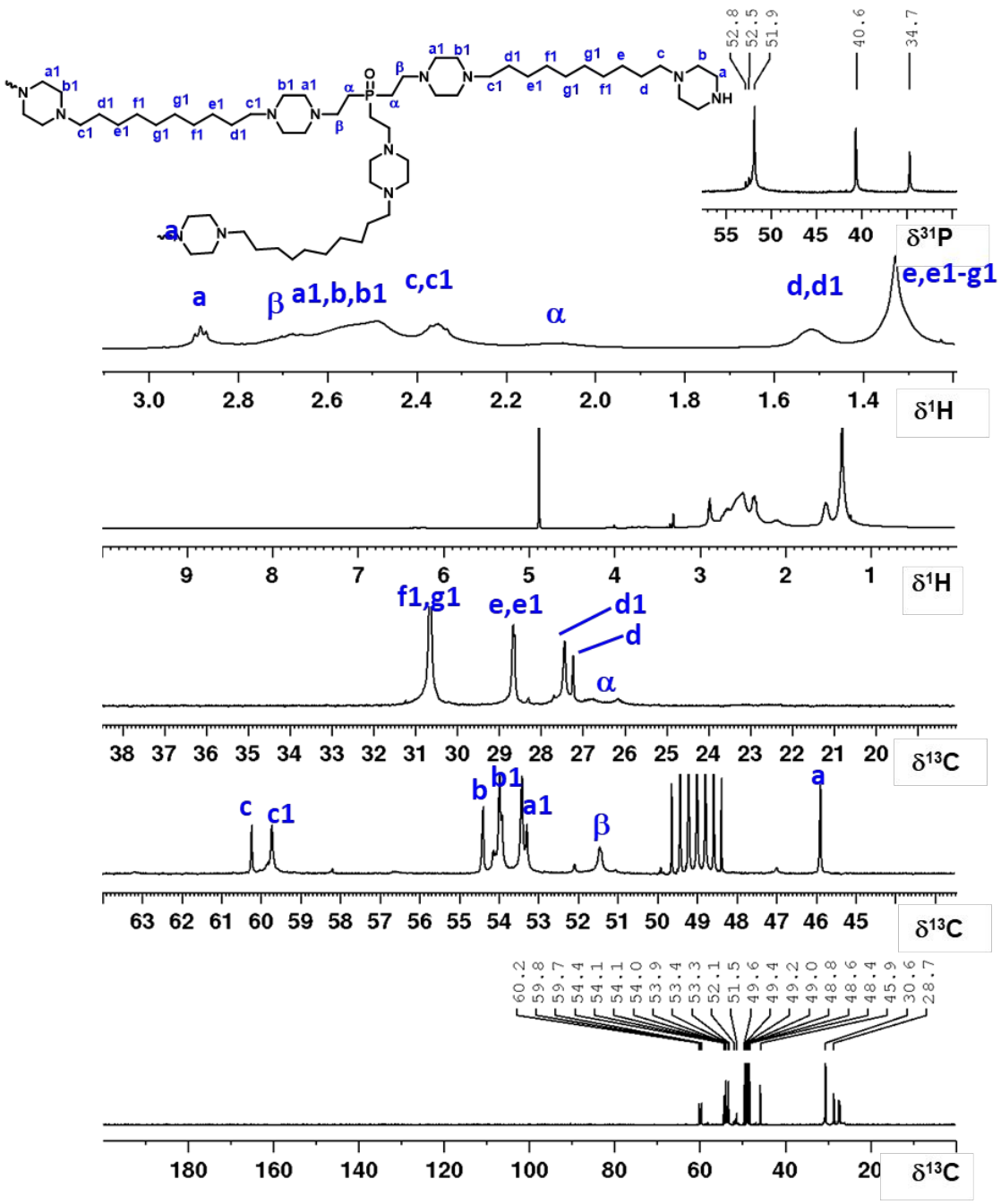


Figure S31: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **Gel-D** (CD_3OD).

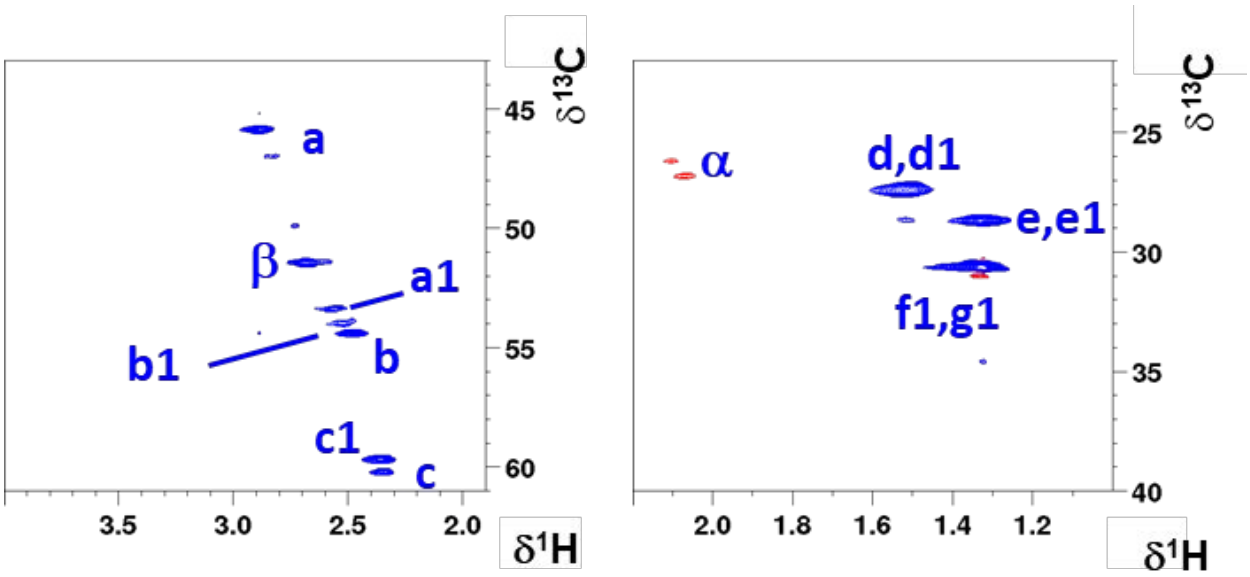


Figure S32: HSQC spectra region with cross peaks of **Gel-D** (CD_3OD).

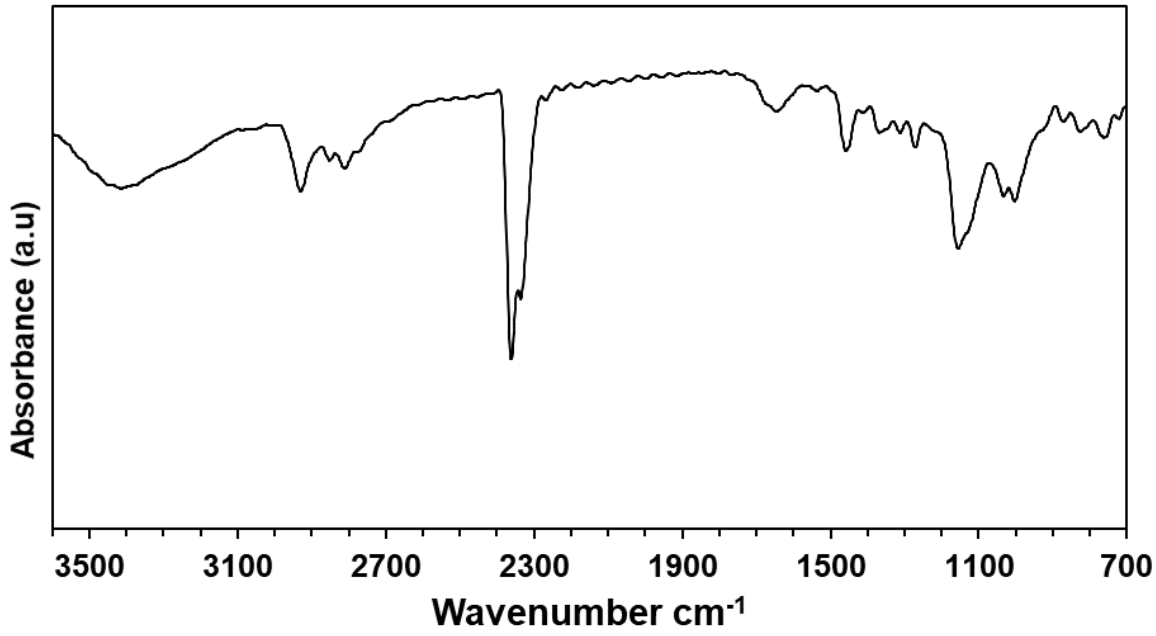


Figure S33: FTIR spectra of **Gel-D**.

S5.7 Synthesis of Gel-E

TVPO (64.0 mg, 0.50 mmol) and 2,4,6-tri(piperazin-1-yl)-1,3,5-triazine (166.7 mg, 0.50 mmol) were added in ethano (2.5 mL) . Resulting solution was heated at 70 °C for 24 hours to obtain a colorless transparent gel.

^{1}H NMR (400.2 MHz, CD_3OD) δ (ppm): 3.80 (m, H-b1); 3.72 (m, H-b); 2.79 (m, H-a); 2.72 (m, H-β); 2.50 (m, H-a1); 2.14 (m, H-α).

^{13}C NMR (100.6 MHz, CD_3OD) δ (ppm): 166.6 (s, C-c); 53.8 (t, C-a1); 51.7 (t, C-β); 46.4 (t, C-a); 44.8 (t, C-b); 44.1 (t, C-b1); 26.6 (dd, J(C,P) = ca. 63 Hz, C-α [-CHD-]).

^{31}P NMR (162.0 MHz, CD_3OD) δ (ppm): 52.9; 40.8.

FTIR (KBr, powder, cm^{-1}): 3310 (–NH), 2946, 2807 ($–CH_2$), 1618 (–NH), 1542 ($–CH_2$), 1145 (P=O), 995 (–C–P=O).

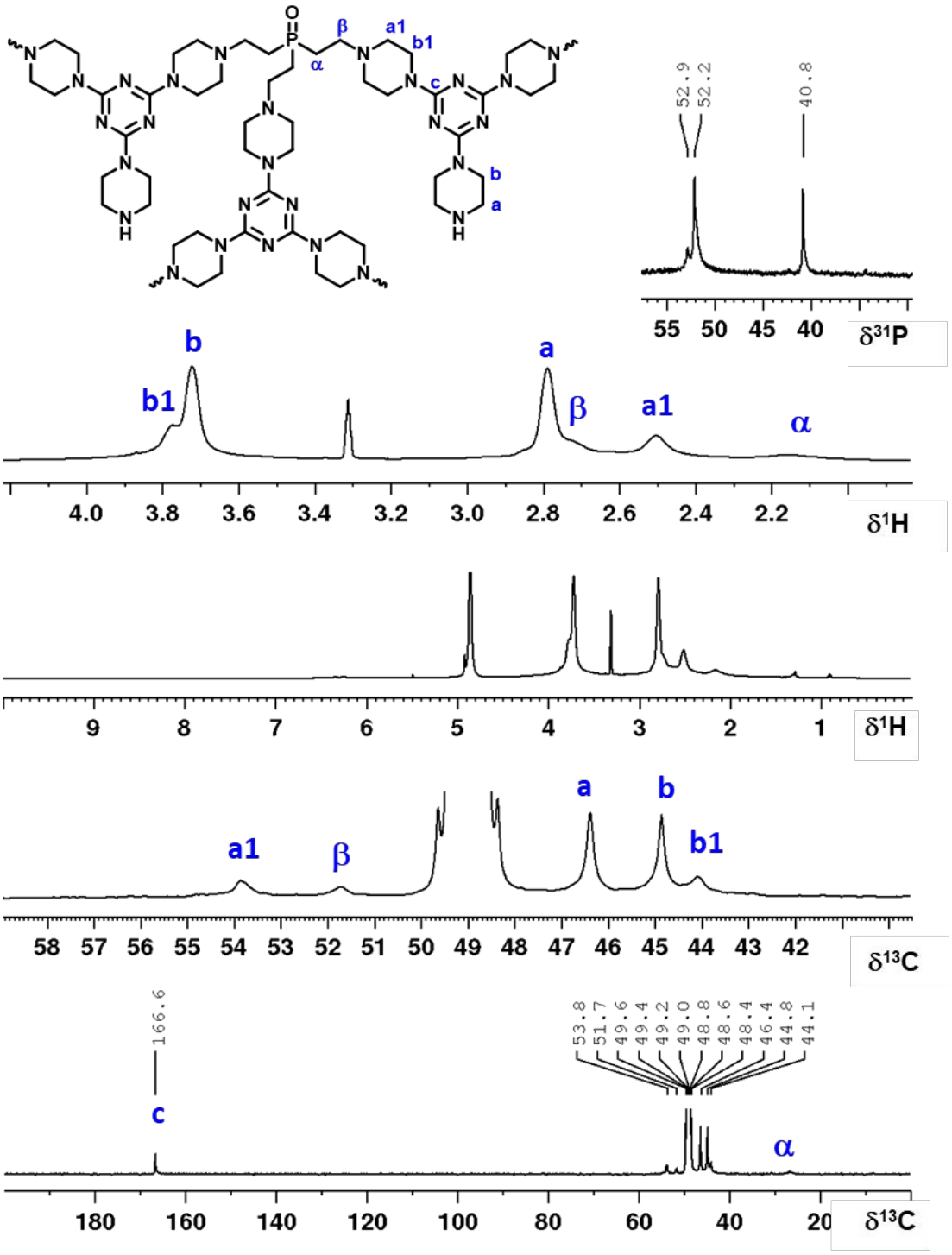


Figure S34: ^{1}H and ^{13}C NMR spectra with expanded regions of interest and with resonance assignments of **Gel-E** (CD_3OD).

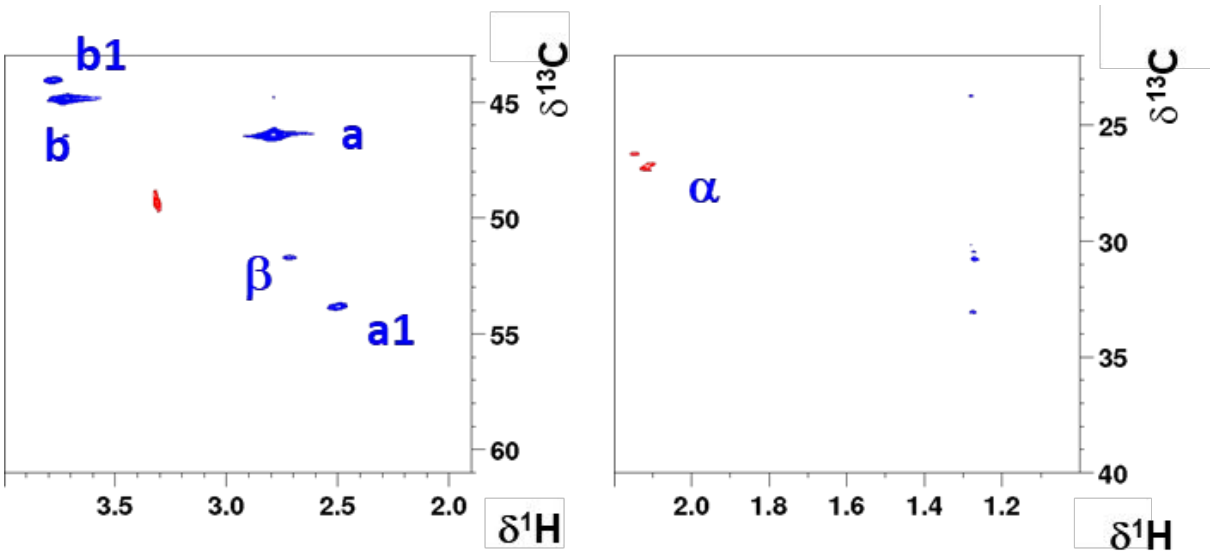


Figure S35: HSQC spectra region with cross peaks of **Gel-E** (CD_3OD).

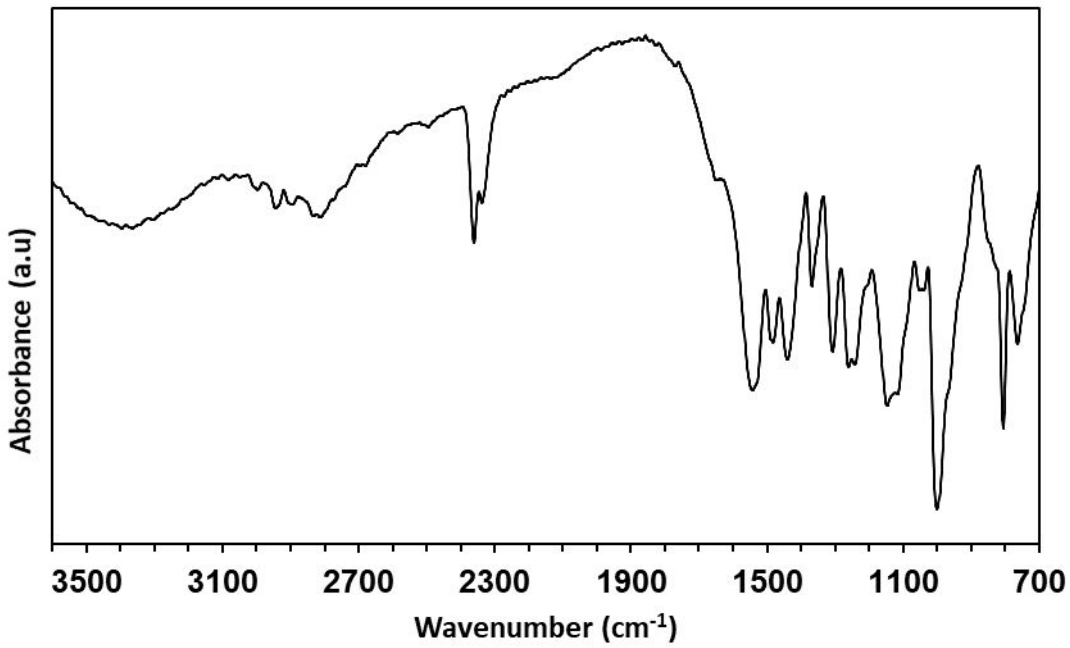


Figure S36: FTIR spectra of **Gel-C**.

S6. SAXS analysis of gels

The SAXS measurements were conducted on a Bruker Nanostar instrument (Bruker AXS GmbH, Karlsruhe, Germany). The setup is equipped with micro-focus copper radiation (wavelength CuKα 1.5406 Å) and a gas detector with 2048×2048 pixels. More details about SAXS setup is provided elsewhere[12]. The scattering profiles have been recorded at the sample-detector distance of 107 cm providing the reliable q-range between 0.06 t0 2.2 nm-1 ($q = (4\pi/\lambda) \sin(\theta)$, where 2θ is the scattering angle). The samples were measured inside quartz capillaries of 1.5 mm outer diameter and wall thickness of 0.1 mm (Hilgenberg GmbH, Malsfeld, Germany). The profiles were corrected for background subtraction taking into account the transmission signal from all samples as well as empty capillary and the one filled with the solvent(a new home-designed and built semi-transparent beamstop was mounted which allowed a dedicated and precise background subtraction). The capillaries had been wax-sealed and the measurement chamber were evacuated (to 0.1 mbar) prior to measurement to reduce the air scattering. All experiments were performed at room temperature (22 °C).

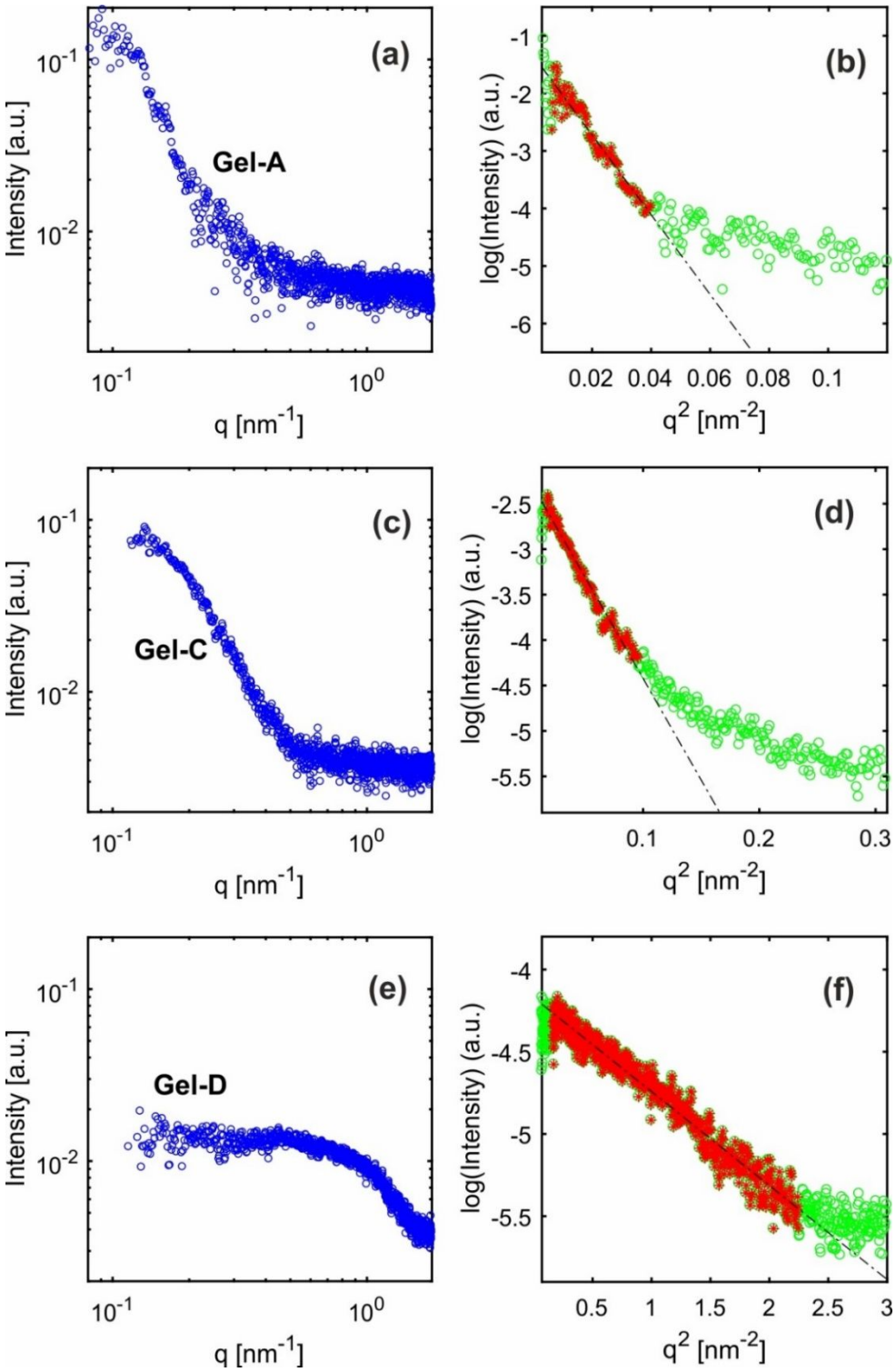


Figure S37: The scattering profiles (A, C and E) and their corresponding Guinier fits (B, D and F) for different Gel samples. From the Guinier fits, the radius of gyration has been obtained as 14.4±2.5, 8.2±0.9 and 1.3±0.01 nm for **Gel-A**, **Gel-C** and **Gel-D**, respectively. All samples were prepared in methanol.

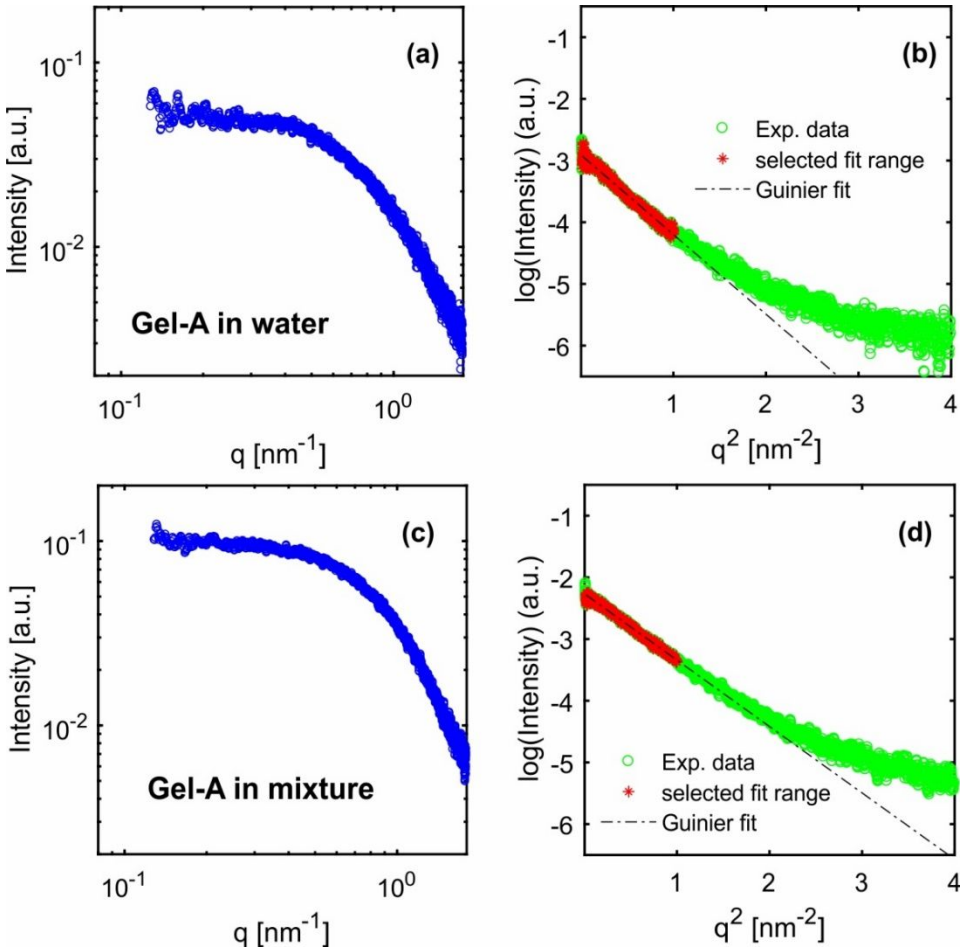


Figure S38: The scattering profile (A) and the corresponding Guinier fits (B) of **Gel-A** prepared in water and water-methanol mixture (1:1) (C and D). From the Guinier fits, the radius of gyration is calculated as 1.8 nm.

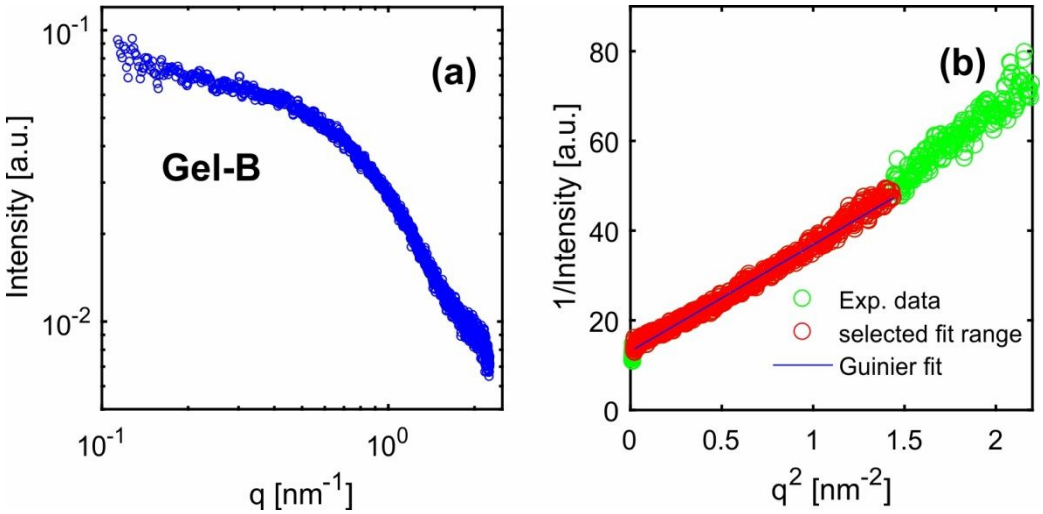


Figure S39: The scattering profile (A) and the linearize form of Ornstein-Zernike fit (inverse scattering intensity versus squared of scattering vector) (B) of the **Gel-B** in methanol. The behaviour confirms the Gaussian chain configuration with 1.3 nm correlation length in the system.

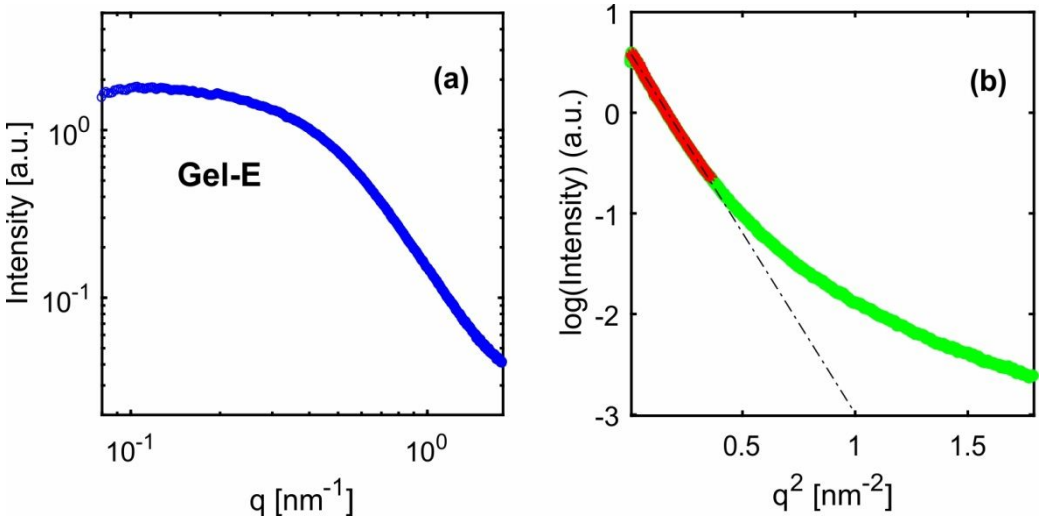


Figure S40: The scattering profile (A) and the corresponding Guinier fit of **Gel-E** prepared in methanol. The fit signifies a radius of gyration as 3.3 nm.

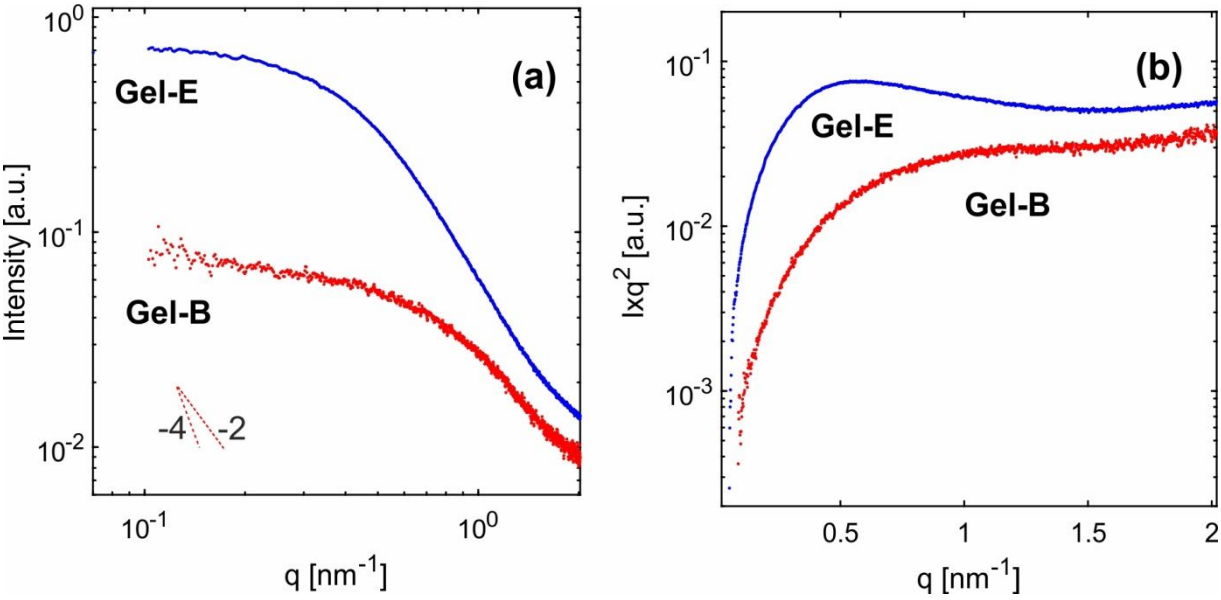


Figure S41: The scattering curves (a) and the Kratky plots (b) of the polymerised **Gels-B** and G**el-E**, prepared in methanol. The **Gel-B** demonstrates Gaussian chain behaviour while **Gel-E** shows the signature of some collapsed chain domains.

S7. Drug release of hydrogel (Gel-A).

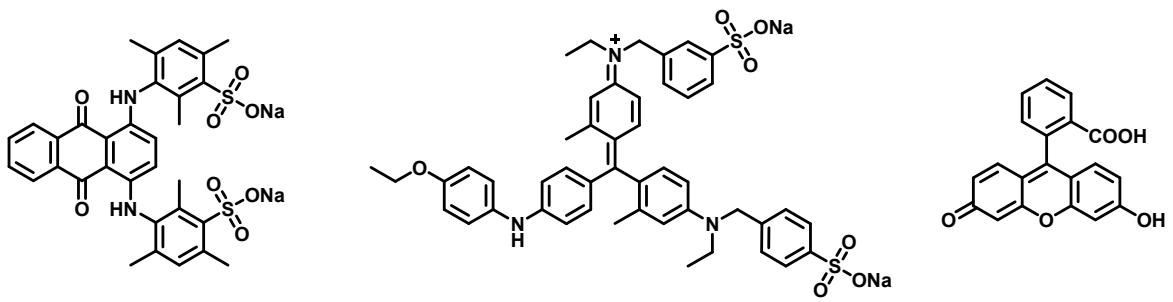


Figure S42: Structure of dyes used in this work: **(A) Acid Blue 80**; **(B)** Fluorescein and **(C) Acid Blue 90**.

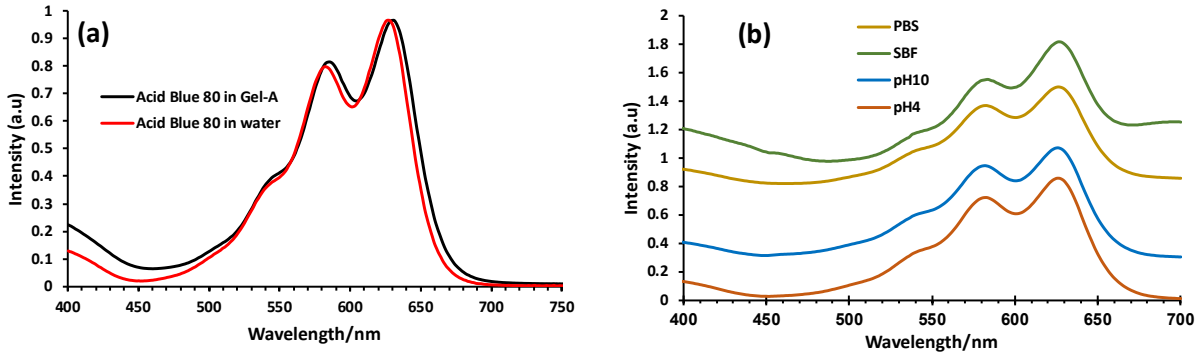


Figure S43: (a) The absorption spectra of **Acid Blue 80** in water and in **Gel-A (b)** in simulated body fluid (SBF), PBS buffer (pH 7.4),at pH 4 and pH 10.

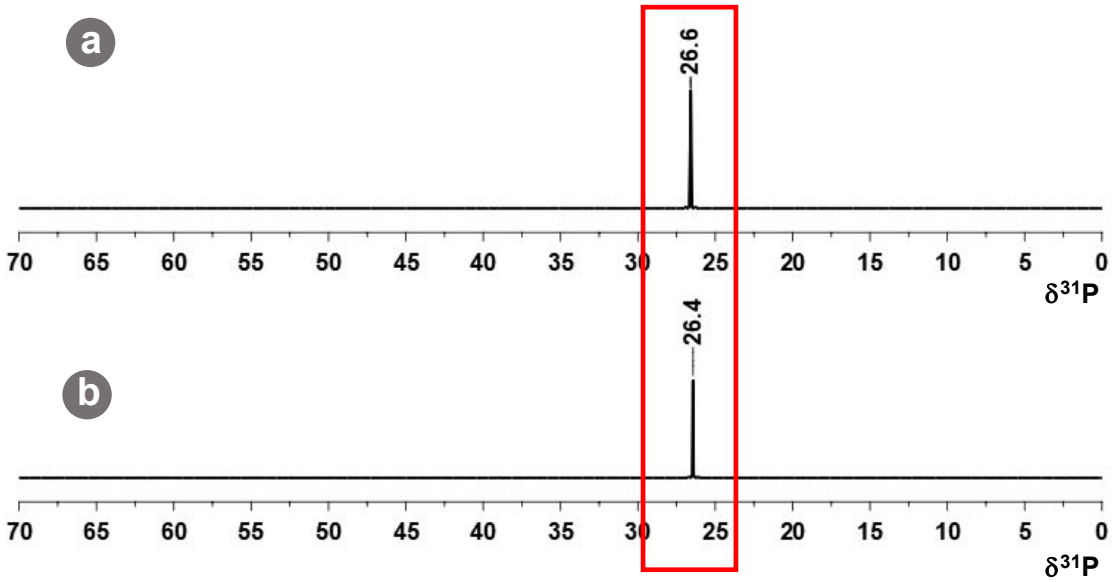


Figure S44: (a) ^{31}P NMR spectra of **TVPO** (**D_2O**) with expanded regions of interest **(b)** ^{31}P NMR spectra measured after heating **TVPO** with **Acid blue 80** in **D_2O** at 60 ℃ for 1 hour**.**

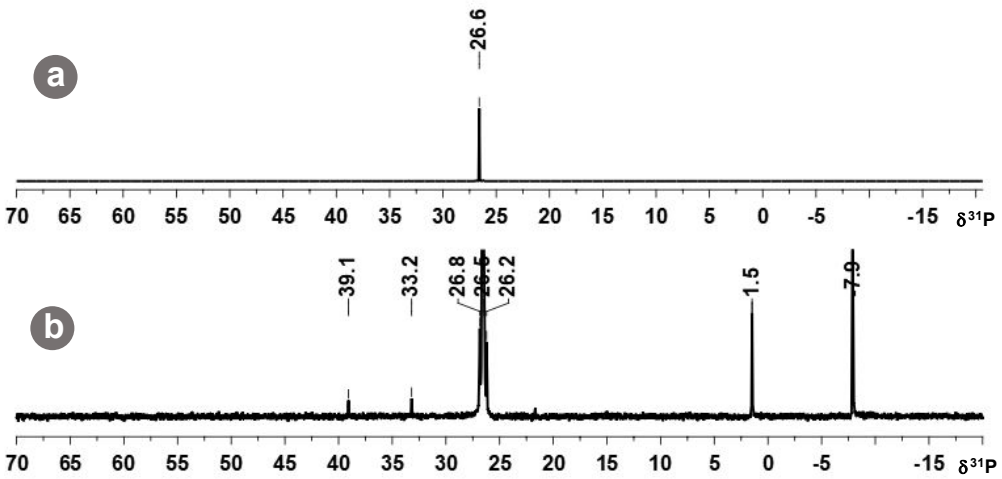


Figure S45: (a) ^{31}P NMR spectra of **TVPO** (**D_2O**) with expanded regions of interest **(b)** ^{31}P NMR spectra measured after heating **TVPO** with **Acid blue 90** in **D_2O** at 70 ℃ for 1 hour**.**

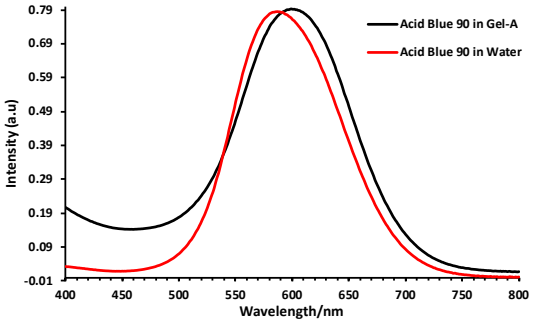


Figure S46: The absorption spectra of the **Acid Blue 90** in water and in **Gel-A**.

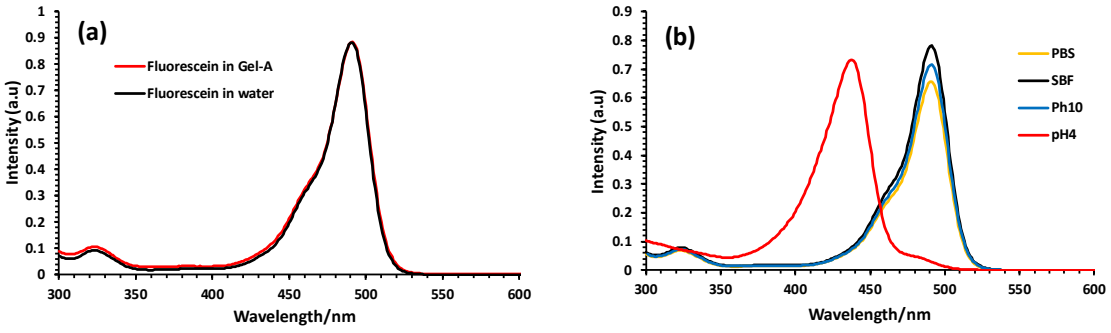


Figure S47: (a) The absorption spectra of the of **Fluorescein** in water and in **Gel-A (b)** the absorption spectra of the of **Fluorescein** in **Gel-A** in simulated body fluid (SBF), PBS buffer (pH 7.4), at pH 4 and pH 10.

S8. Cytotoxicity of hydrogel (Gel-A)

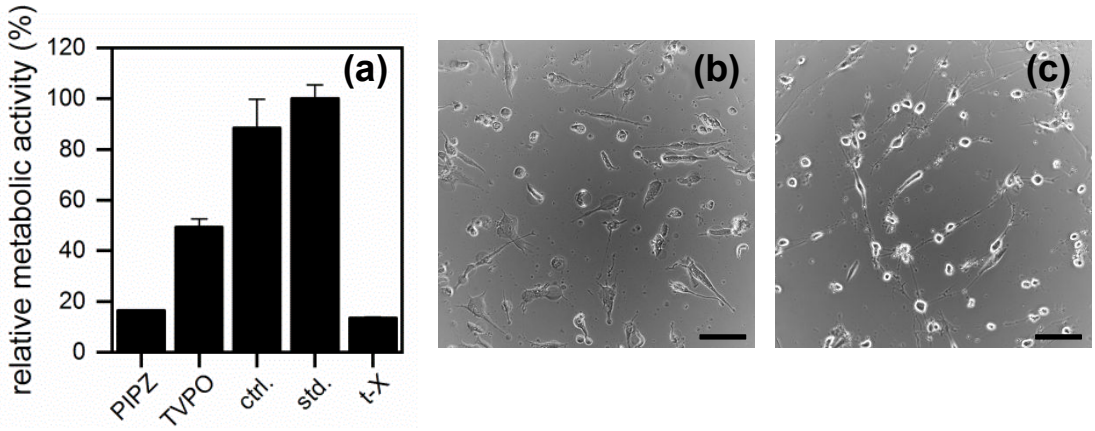


Figure S48: **(a)** Cell metabolic activity of NHDF treated with 10% v/v solutions of piperazine (PIPZ) or TVPO in cell culture media was assessed in comparison to aged media (ctrl.) and fresh media (std.). Triton-X (t-X) served as the positive control for a cytotoxic substance and cell lysis. After 24 hours in culture, the metabolic activity of PIPZ or TVPO treated cells was strongly reduced, compared to the control groups, providing evidence for a cytotoxic effect of these two substances. **(b)** and **(c)** light microscopy images of PIPZ or TVPO treated NHDF, respectively. A round morphology and detaching NHDF is indicative for a cytotoxic effect of the monomers. Scale bar: 10 µm.

S9. Thermal stability of the hydrogel (Gel-A)

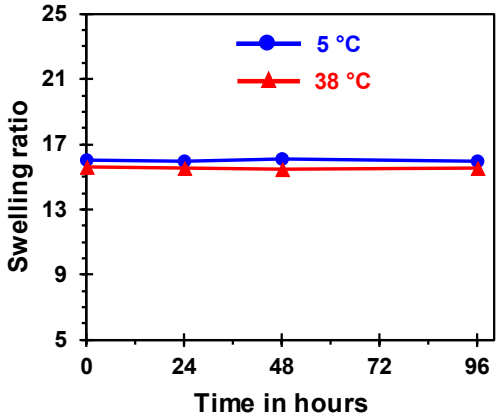


Figure S49: Change is the swelling ratio of the hydrogel at 5 ℃ and 38 ℃ over 4 days. No change in swelling ratio (SR) during storage at 38 ℃ indicates that hydrogel is stable at physiological temperature.

S10. Differential scanning calorimetry (DSC)

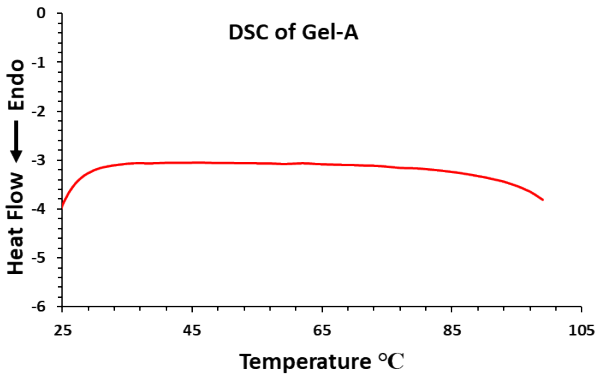


Figure S50: Differential scanning calorimetry (DSC) date of **Gel-A**.

References

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