Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supporting Information for

A pH-responsive graftable supramolecular polymer with tailorable surface functionality by orthogonal halogen bonding and hydrogen bonding

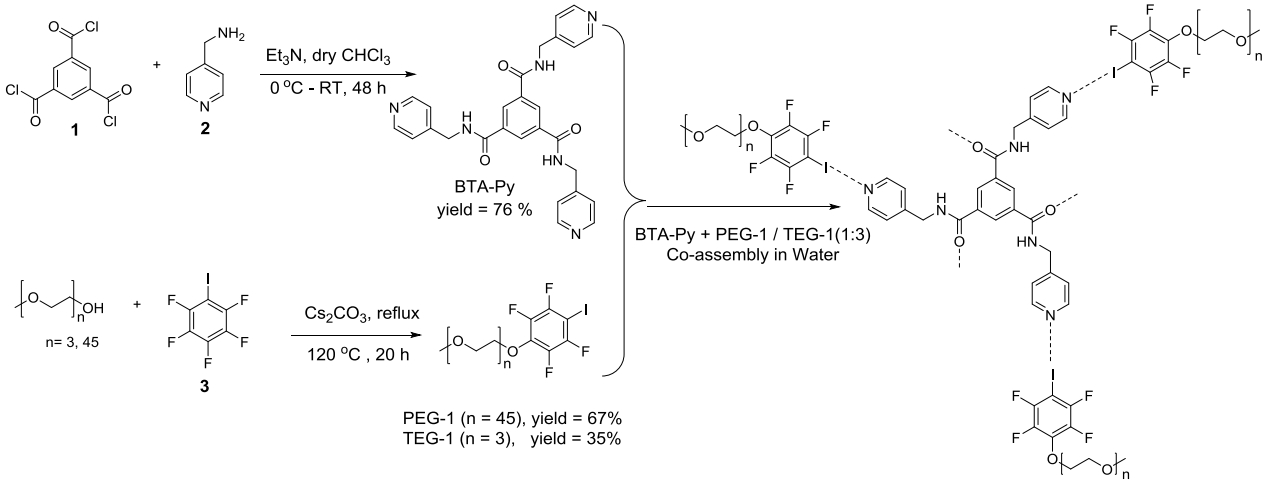
*Akshoy Jamadar and Anindita Das **

School of Applied and Interdisciplinary Sciences,
Indian Association for the Cultivation of Science, Jadavpur, Kolkata –700032, India.
*Corresponding author; Email: psuad2@iacs.res.in

Materials and Methods: All reagents were obtained from commercial suppliers and used without further purification unless otherwise mentioned. Iodopentafluorobenzene was purchased from Sigma Aldrich Chemical Co. Solvents were dried properly before setting up reaction. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 500 MHz, 400 MHz and 300 MHz NMR spectrometer using $CDCl_3$ and DMSO-D_6 as solvent. Chemical shifts (δ) are in ppm unit with TMS as the internal standard. The coupling constant (*J*) is reported in hertz (Hz). Column chromatography was carried out on silica gel (100-200 mesh). For UV-Vis studies, spectroscopic grade solvents were used and spectra were recorded in a JASCO V-750 spectrophotometer. Transmission Electron Microscopy (TEM) was performed in JEOL-2010EX machine and JEOL-JEM-2100F machine operating at an accelerating voltage of 200KV. FTIR spectra were obtained in a Perkin Elmer Spectrum 100 FT-IR Spectrometer. Fluorescence Microscopy images were captured in Olympus IX73 model. Dynamic Light Scattering (DLS) measurement was obtained from Malvern instrument.

Synthesis and Characterization

Synthesis of halogen bond acceptor (**BTA-Py)**[1] and halogen bond donor (**PEG-1)/(TEG-1)**[2] were achieved in one step using synthetic protocol as outlined in Scheme S1 following related literature procedures.



Scheme S1: Synthetic scheme for preparation of X-bond acceptor (**BTA-Py)** and donor **(PEG-1/ TEG-1)** and their proposed 1:3 X-bonded complex in water.

Synthesis of *N*^{1},*N*^{3},*N*^{5}-tris(pyridin-4-ylmethyl)benzene-1,3,5-tricarboxamide (BTA-Py)[1]: To a solution of 4-picolylamine (**2**) (691.2 mg, 6.39 mmol) and triethylamine (0.93 ml, 6.65 mmol)

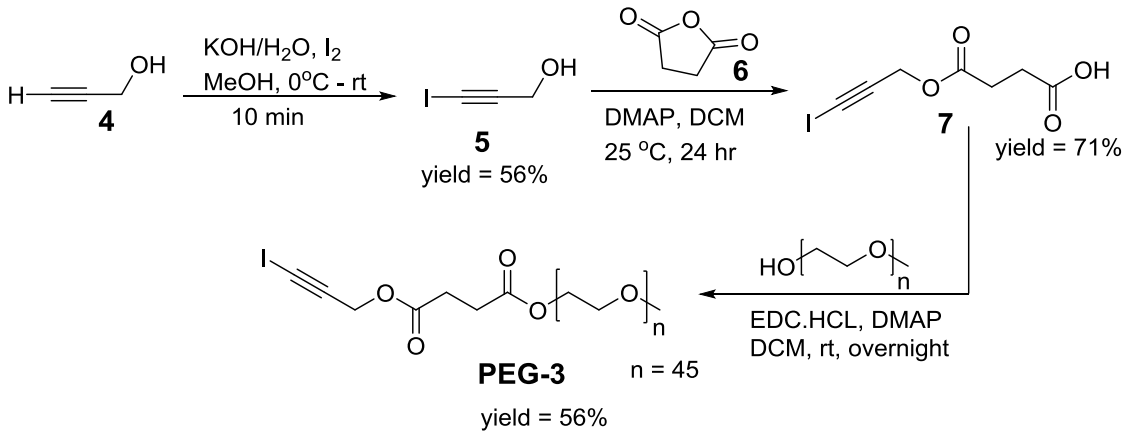
in dry $CHCl_3$ (20 ml), solution of benzene-1,3,5-tricarbonyl trichloride (**1**) (500 mg, 1.88 mmol) in dry $CHCl_3$ (10 ml) was added dropwise for 30 min through dropping funnel at 0^oC under inert atmosphere. After the addition was complete, the reaction mixture was allowed to stir for another 48 hr at r.t. under inert atmosphere. The white precipitate formed was filtered and washed with $CHCl_3$ and water before being dried under vacuum. Yield = 687 mg, 76%. ^{1}H-NMR (500 MHz, d_6-DMSO, ppm) δ 9.40 (t, *J* = 5.9 Hz, 3H), 8.58 (s, 3H), 8.51 (d, *J* = 5.9 Hz, 6H), 7.34 (d, *J* = 5.9 Hz, 6H), 4.55 (d, *J* = 5.9 Hz, 6H). ^{13}C NMR (101 MHz, d_6-DMSO, ppm). δ 165.6, 149.5, 148.3, 134.6, 128.9, 122.2, 41.9; HRMS m/z calculated for $C_{27}H_{24}N_6O_3H$ [BTA-Py + H]$^+$: 481.1988; experimentally found: 481.1982.

Synthesis of (2,3,5,6-tetrafluoro-4-iodophenoxy)-polyethylene glycol monomethyl ether (PEG-1)[2]: Iodopentafluorobenzene (**3**) (169.76 mg, 0.577 mmol) was added to a mixture of polyethylene glycol monomethyl ether-2000 (500 mg, 0.25 mmol) and Cs_2CO_3 (203.63 mg, 0.625 mmol). The whole mixture was refluxed without solvent under N_2 at 120 °C for 20 h. The crude reaction mixture was first extracted with hexane/water to remove the excess iodopentafluorobenzene. Then the aqueous layer was extracted with dichloromethane (DCM) thrice, dried with Na_2SO_4 and concentrated by vacuo. The polymer was further purified by precipitation in diethyl ether and dried in vacuum. Finally 380 mg yellowish white compound was obtained. Yield = 67 %. ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ 4.38 (m, 2H), 3.87-3.44 (br, PEG ≈ 180 H), 3.37 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 148.7, 145.7, 142.4, 138.9, 138.4, 79.5, 74.3, 72.0, 70.7, 70.0, 64.0, 61.5, 58.9. ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ – 121.4 to –121.5 (m, 2F), –153.9 to –154.1 (m, 2F).

Synthesis of (2,3,5,6-tetrafluoro-4-iodophenoxy)-triethylene glycol monomethyl ether (TEG-1)[2]: Pentafluoroiodobenzene (**3**) (2058.8 mg, 7.00 mmol) was added to a mixture of triethylene glycol monomethyl ether (500 mg, 3.048 mmol) and Cs_2CO_3 (1984 mg, 6.089 mmol). The whole mixture was heated without solvent under N_2 at 120 °C for 20 h. The crude reaction mixture was dissolved in DCM and the excess salt was extracted with water. The DCM layer was dried with Na_2SO4 and concentrated by vacuo. Finally the compound was purified by column chromatography (1:99 MeOH/DCM). The product was obtained as a transparent viscous liquid. Yield = 468 mg, 35 % . ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 4.40-4.38 (m, 2H), 3.84-3.82 (m, 2H), 3.73-3.68 (m, 2H), 3.66-3.61 (m, 4H), 3.55-3.52 (m, 2H), 3.37 (s, 3H). ^{13}C-NMR (101

MHz, $CDCl_3$, ppm): δ 148.4, 146.3, 142.5, 139.6, 138.5, 74.3, 71.9, 71.0, 70.7, 70.3, 64.1, 63.6, 59.1. ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -121.4 to -121.5 (m, 2F), –153.9 to –154.1 (m, 2F). HRMS m/z calculated for $C_{13}H_{15}F_4IO_4H$ $[TEG\text{-}1 + H]^+$: 439.0029, experimentally found: 439.0027.

Synthesis of polyethylene glycol monomethyl ether benzoate (PEG-2)[3]: To a round bottom flask polyethylene glycol monomethyl ether-2000 (500 mg, 0.25 mmol) and triethyl amine (12.64 mg, 0.125 mmol) were taken with 1.0 ml dry DCM. To this solution, benzoyl chloride (351.42 mg, 2.5 mmol) was added drop-wise under ice-cold condition. After 24 hr the crude reaction mixture was extracted with DCM/water. The organic phase was dried with Na_2SO_4 and concentrated by vacuo. The resultant polymer was purified by precipitation from diethyl ether and dried under vacuum. The product was collected as white amorphous solid (350 mg, yield = 65%). ^1H-NMR (400 MHz, $CDCl_3$, ppm): δ 8.05 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 4.48-4.45 (m, 2H), 3.89-3.42 (br, PEG ≈180 H), 3.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 166.6, 133.1, 130.2, 129.7, 128.5, 72.0, 70.7, 69.3, 64.3, 59.1.



Scheme S2: Synthetic scheme for preparation of **PEG-3**.

Synthesis of 3-Iodoprop-2-yn-1-ol (5): This compound was synthesized according to the literature procedure[4]. Propargyl alcohol (**4)** (1 g, 17.83 mmol) was dissolved in MeOH (18 mL) and cooled to 0 ^OC. KOH (2.5 g, 44.57 mmol) dissolved in H_2O (4 mL) was added in one portion to the solution. After 10 min, iodine (28.46 g, 112 mmol) was added to the solution. The mixture was stirred at 0 ^OC for 5 min before it was allowed to warm to room temperature. MeOH was

removed under reduced pressure and the crude product was partitioned between H_2O (20 mL) and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3X20 mL). The combined organic layers were dried by passing through Na_2SO_4 and concentrated in vacuo. The compound was collected as yellowish crystal (1.83 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.23 (s, 1H), 4.40 (s, 2H).

Synthesis of 4-((3-iodoprop-2-yn-1-yl)oxy)-4-oxobutanoic acid (7): This compound was synthesized according to the literature procedure[5]. DMAP (67.2 mg, 0.55 mmol) and succinic anhydride (**6**) (316.5 mg, 3.165 mmol) were dissolved in 2 mL dry CH_2Cl_2. Compound **5** (500 mg, 2.74 mmol) was slowly added to the suspension and the reaction mixture was left to react for 24 hr at rt. The reaction mixture was diluted with 15 mL of CH_2Cl_2, then 30 mL of water was added, followed by washing 3 times with 0.5 N HCl. The organic phase was dried over Na_2SO_4, filtered and concentrated. A white solid was obtained (550 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 4.84 (s, 2H), 2.67-2.71 (m, 4H). HRMS m/z calculated for $C_7H_7IO_4Na$ $[M+Na]^+$: 304.9287; experimentally found 304.9285.

Synthesis of PEG-3: This compound was synthesized according to the literature procedure[6]. To a 50 mL round-bottom flask, polyethylene glycol monomethyl ether-2000 (1 g, 0.5 mmol), was taken along with compound **7** (211.5 mg, 0.75 mmol), EDC·HCl (239.6 mg, 1.25 mmol), and DMAP (91.62 mg, 0.75 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature overnight before washing with water (2×15 mL) and DCM (2×20 mL). The extracted organic layer was dried with Na_2SO_4. The polymer was further purified by precipitation from diethyl ether and dried in vacuum. Finally 380 mg of white amorphous compound was obtained. Yield = 56 %. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 4.83 (s, 2H), 4.26-4.23 (m, 2H), 3.69-3.54 (br, PEG ≈ 180 H), 3.37 (s, 3H), 2.69-2.67 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 28.98, 29.72, 53.59, 59.06, 64.06, 69.08, 70.26, 70.48, 71.91, 87.93, 171.41, 172.12.

Experimental Procedures:

Solution preparation:

BTA-Py assembly in 1% acetic acid in water: 1.96 mg BTA-Py was placed in a glass vial. To this 2 ml 1% (v/v) acetic acid (0.17M, pH 2.5) in water was added to obtain a desired concentration of 2.0 mM. The solution was sonicated for few seconds and then heated to obtain a

molecularly dissolved state. On cooling, clear transparent solution was obtained. From this stock solution desired concentration was prepared by further dilution with 1% acetic acid solution, followed by heating and cooling. The final solution was allowed to stand for at least 1 hr prior to experimental measurements.

Preparation of 3:1 Donor-Accepter complex (PEG-1:BTA-Py): 4.0 mM stock solution of BTA-Py and PEG-1 were separately prepared in MeOH. 1.0 ml BTA-Py and 3.0 ml PEG-1 in MeOH were mixed together in a small glass vial. MeOH was slowly evaporated by keeping the vial in hot oven for several hours. The film obtained was dissolved in equal volume (4.0 ml) of water. The final BTA-Py and PEG-1 concentration becomes 1.0 mM and 3.0 mM, respectively in the mixture. The solution was sonicated for few seconds and then heated to obtain a molecularly dissolved state. Upon cooling, clear transparent solution was obtained which was allowed to stand at room temperature for at least 1.0 hr to attend equilibrium, prior to any physical measurements. Similar procedure was followed for sample preparation for different concentrations and with other donors.

Solubility test: A solution of BTA-Py and its mixture with various donors in water were prepared and their solution turbidity was monitored by cursory observation. In each case, the BTA-Py concentration was maintained at 1.0 mM.

UV-visible studies: 0.2 mM solution of **BTA-Py** in 1% acetic acid solution and MeOH were prepared as mentioned above. These solutions were transferred to a quartz cuvette of 0.1 cm path-length and UV-spectra were recorded and compared at 25 °C.

An aqueous solution of BTA-Py + PEG-1(1:3) and BTA-Py + TEG-1(1:3) were prepared as mentioned above. The concentration of BTA-Py was maintained at 0.1 mM. These solutions were transferred into 0.1 cm pathlength cuvette and the UV-Vis measurements were recorded at different temperature intervals.

For BTA-Py +PEG-3 (1:3), the VT UV-Vis spectra were recorded at BTA-Py conc. = 0.5 mM, as at BTA-Py conc. = 0.1 mM, no self-assembly was observed.

FTIR studies: Same protocol was followed as mentioned earlier for solution preparation. Concentration of BTA was maintained at 0.5 mM. Spectral measurements were carried out in the transmittance mode at a scan range = 4000-400 cm^{-1}.

2D Diffusion-Ordered Spectroscopy (DOSY) and Nuclear Overhauser Effect Spectroscopy (NOESY) NMR studies: A solution of BTA-Py + PEG-1 (1:3) was prepared in D_2O at a BTA

concentration of 5.0 mM following similar protocol as discussed earlier. For DOSY measurement of the individual components, BTA-Py and PEG-1 concentration were maintained at 5.0 mM and 15.0 mM, respectively. The data was recorded at 25 ^{o}C in Bruker 500 MHz instrument. A diffusion gradient duration (δ) of 1 ms and diffusion time (Δ) of 200 ms were used for the DOSY measurements. The diffusion coefficient values were obtained using TopSpin 2.1 software following a fitting procedure.

2D NOESY data was obtained from 300 MHz Bruker instrument at 25 ^{o}C. For recording the data, BTA-Py + PEG-1 (1:3) in D_2O was prepared with BTA concentration of 5.0 mM. The analysis was done in TopSpin 3.2 software. The mixing time (D_8) was kept at 0.2 sec.

Variable temperature ^{1}H NMR spectra were recorded in 300 MHz machine with the same sample. Spectral measurements were taken at different temperature intervals. After a desired temperature was reached, 2.0 min equilibrium time was maintained.

Dynamic Light Scattering (DLS) studies: DLS data were recorded from a mixture of BTA-Py +PEG-1(1:3) in water where BTA-Py and PEG-1 concentration were maintained at 0.5 mM and 1.5 mM, respectively. The particle size obtained was around 70 nm.

Transmission Electron Microscopy (TEM) studies: Solution of **BTA-Py** in 1% acetic acid solution and BTA-Py+PEG-1 (1:3) and BTA-Py+TEG-1 (1:3) in water were prepared at a BTA-Py concentration of 0.5 mM. Sample solutions were drop casted on copper grids and were left open to air for 48 h for slow drying prior to imaging.

Fluorescence microscopic studies: Nile red treated aqueous solution of BTA-Py+PEG-1 (1:3) (Concentration of BTA-Py = 0.5 mM) was placed between two clean glass slips and images were captured from a fluorescence microscope Olympus IX73 at 10X magnification. Nile red concentration was kept at 1x 10^{-2} mM.

Additional Figures:

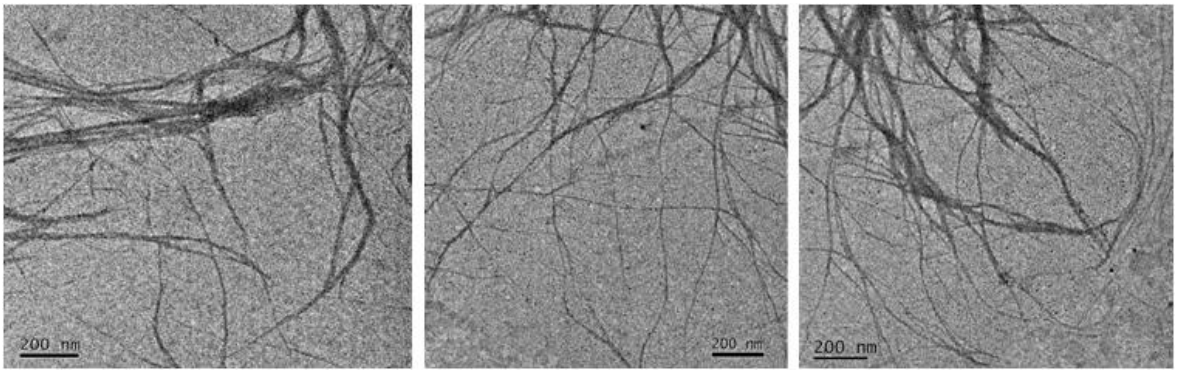
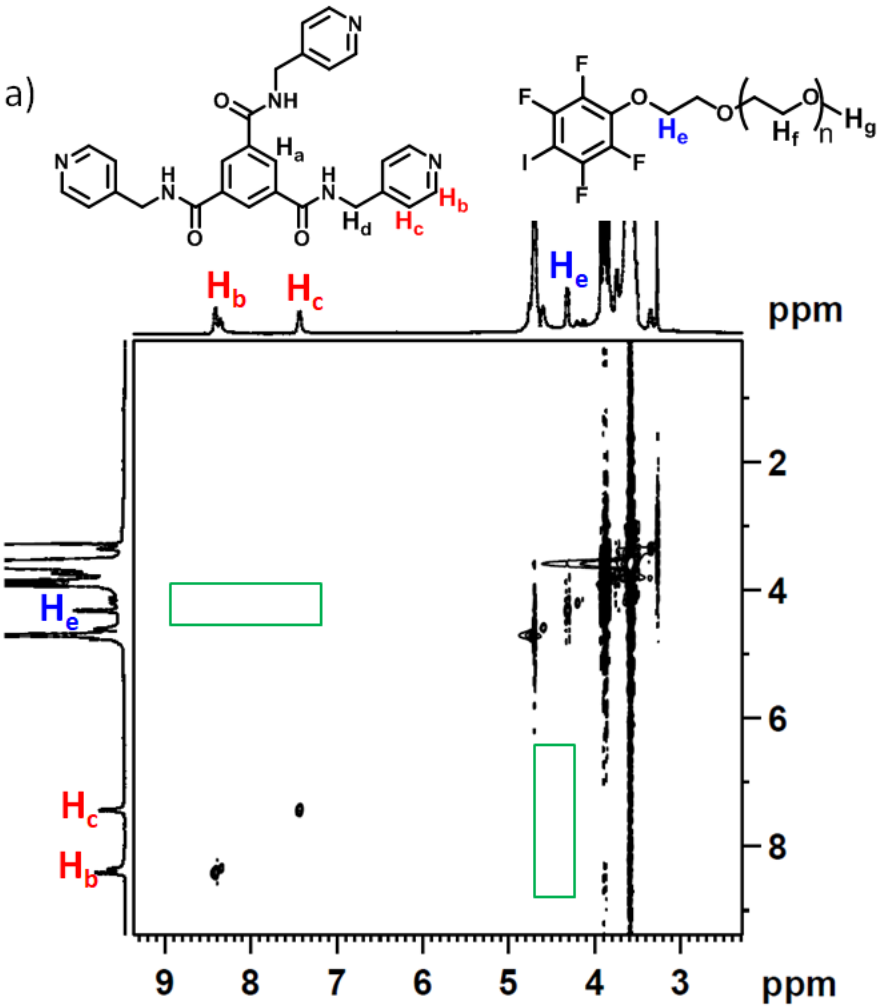


Figure S1: TEM images of self-assembled BTA-Py in 1% acetic acid in water. Concentration = 0.5 mM.



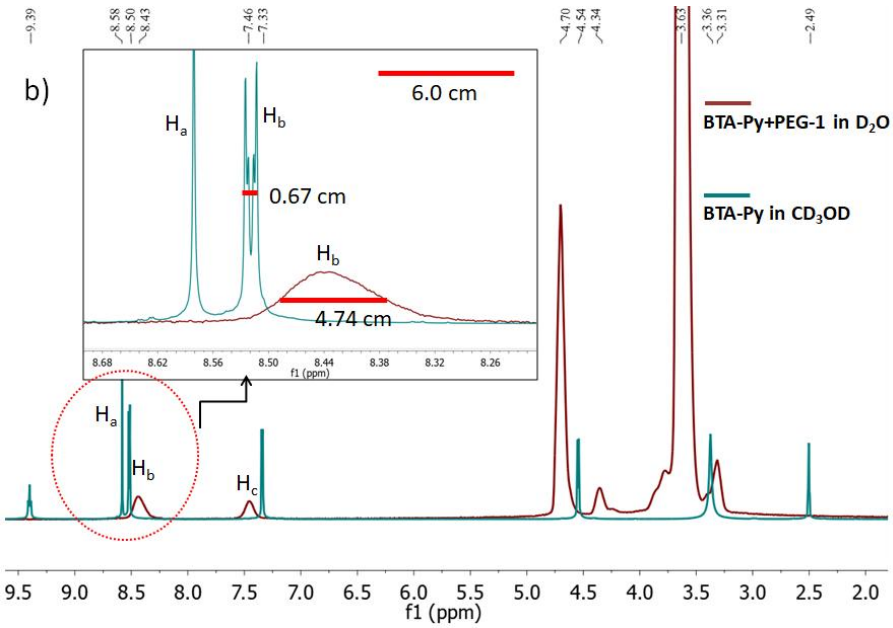


Figure S2: a) 2D NOESY spectrum of BTA-Py+PEG-1(1:3) (D_2O, 25 ^oC). BTA-Py concentration = 5.0 mM. The mixing time (D_8) for NOE was 0.2 sec. No cross signal between pyridyl protons of BTA-Py and methylene protons of PEG-1 was observed in the highlighted region. b) ^1H NMR stack plot of BTA-Py+PEG-1 in D_2O and BTA-Py in CD_3OD at 25 ^oC, showing selected aromatic region. Inset: extent of peak broadness measured for H_b signal going from molecularly dissolved state in CD_3OD to formation of supramolecular polymer in D_2O. Full width at half maximum shows 86% peak broadness for H_b signal in D_2O.

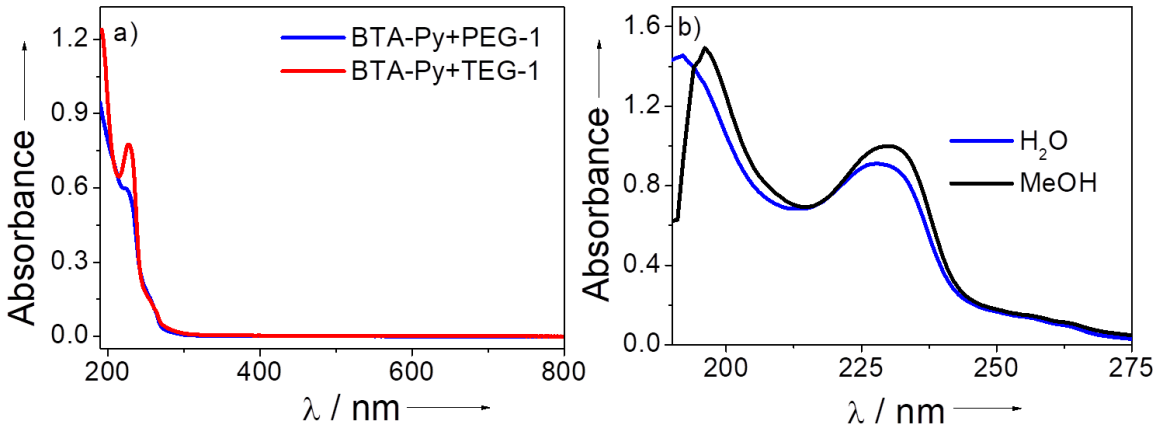


Figure S3: a) UV-Vis absorption spectra of BTA-Py+PEG-1(1:3) and BTA-Py+TEG-1(1:3) in water showing no charge-transfer band between pyridyl and iodotetrafluorophenyl moiety; b) UV-Vis spectra of BTA-Py+TEG-1(1:3) in water and MeOH. Blue shifted spectrum in water indicates H-type stacking of BTA-Py core in the co-assembled state. Concentration of BTA-Py = 0.1 mM, Path length = 0.1 cm.

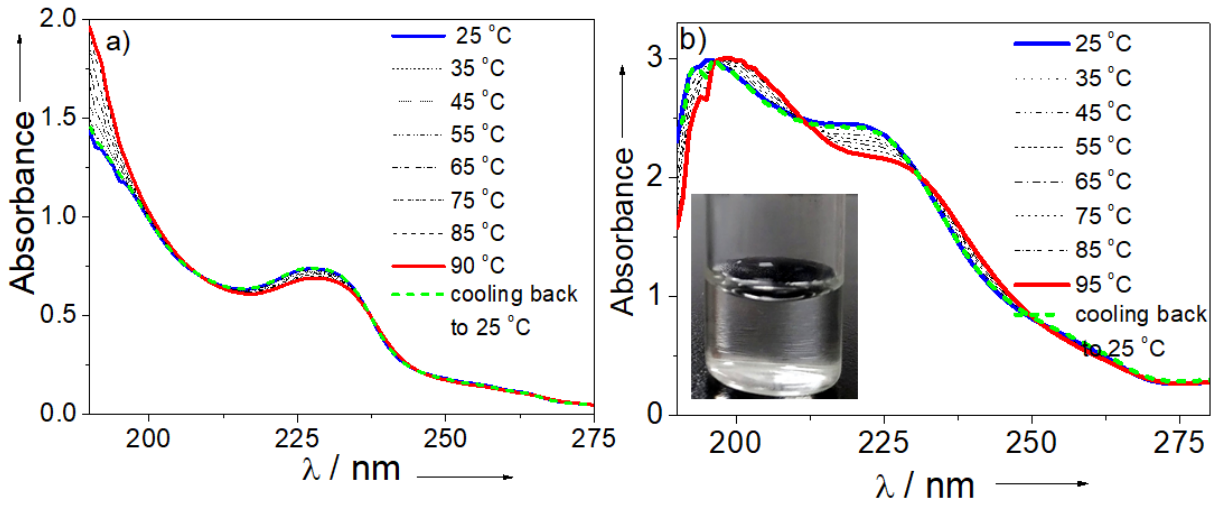


Figure S4: Variable-temperature UV-Vis absorption spectra of an aqueous solution of a) BTA-Py+PEG-1(1:3) (BTA-Py C = 0.1 mM) showing hyperchromic shift with increasing temperature, b) BTA-Py+PEG-3(1:3) (BTA-Py C = 0.5 mM; Inset: solution picture) showing bathochromic shift with increasing temperature. Path length = 0.1 cm. Note: At BTA-Py C = 0.1 mM, BTA-Py+PEG-3 mixture does not self-assemble unlike in case of PEG-1. This suggests weaker assembly of BTA-Py with PEG-3 donor.

Figure S5: An aqueous solution of BTA-Py+PEG-1(1:3) (left) and BTA-Py (right) in two vials placed in a water bath set at 60 ^{o}C with a thermometer dipped inside. BTA-Py concentration = 1.0 mM. At 60 ^{o}C BTA-Py dispersion in water was turbid, while BTA-Py+PEG-1(1:3) was transparent due to stable X-bonded complex formation.

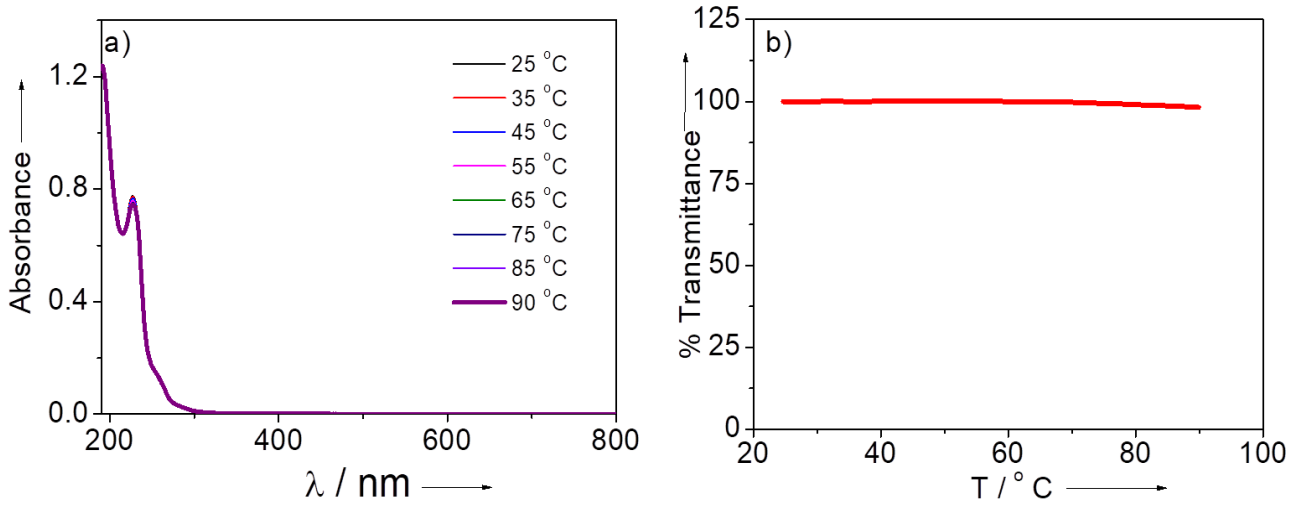


Figure S6: a) UV-Vis absorption spectra of BTA-Py+TEG-1(1:3) in water at different temperature showing no base line scattering and its b) Transmittance (at 400 nm) vs. temperature plot suggesting lack of solution turbidity due to absence of LCST. Concentration of BTA-Py = 0.1 mM.

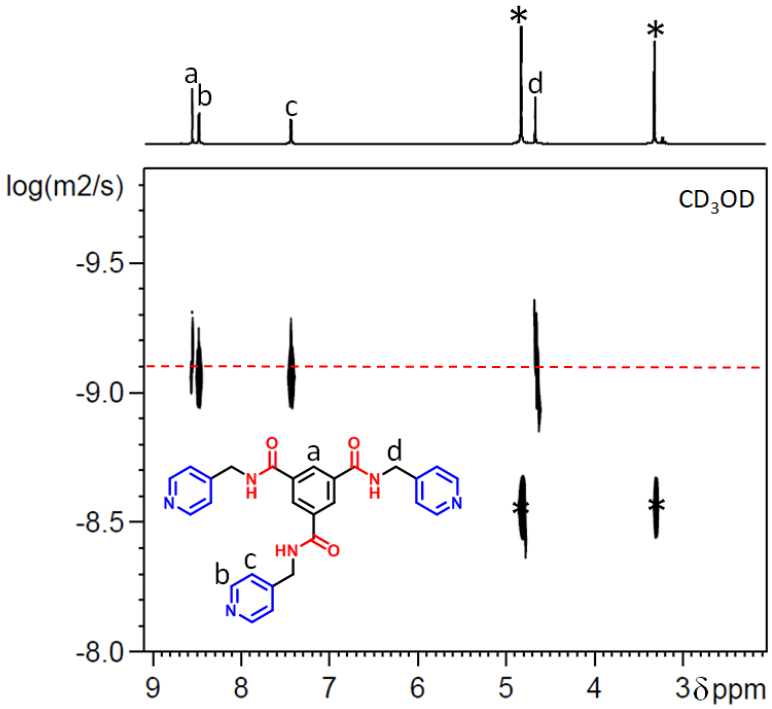


Figure S7: 2D DOSY spectrum of BTA-Py (C = 5 mM) in CD_3OD at 25 ^oC. '*' denotes solvent signal. Diffusion coefficient (D) is plotted in logarithmic scale against the chemical shift (δ).
D = 2.55 x 10^{-9} m^2/s.

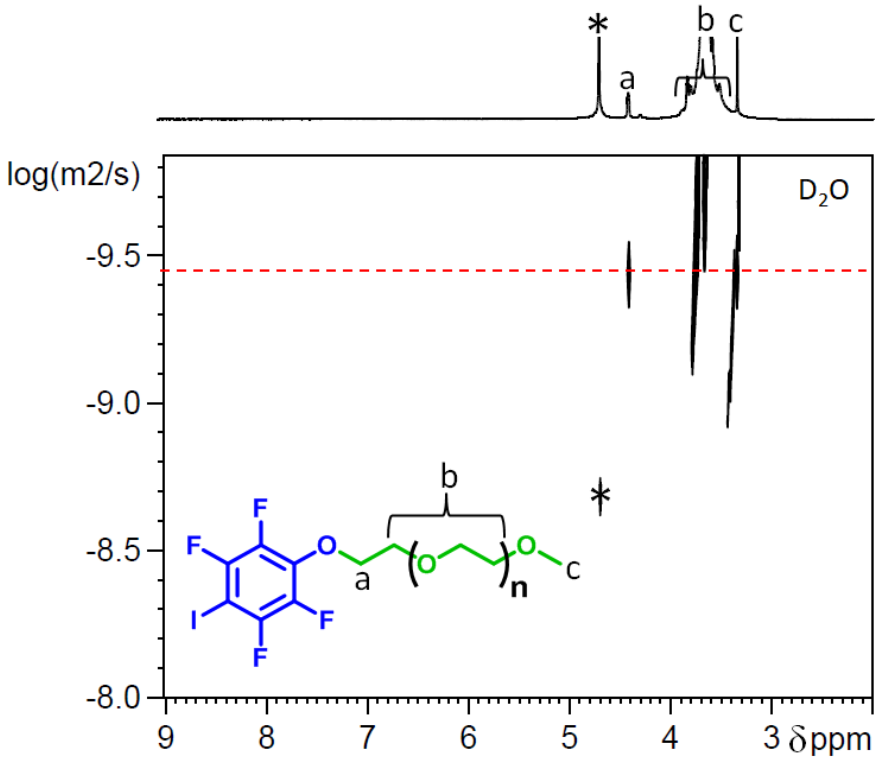


Figure S8: 2D DOSY spectrum of PEG-1 (C = 15 mM) in D_2O at 25 ^oC. '*' denotes solvent signal. Diffusion coefficient (D) is plotted in logarithmic scale against the chemical shift (δ). D = 1.01 x 10^{-9} m^2/s.

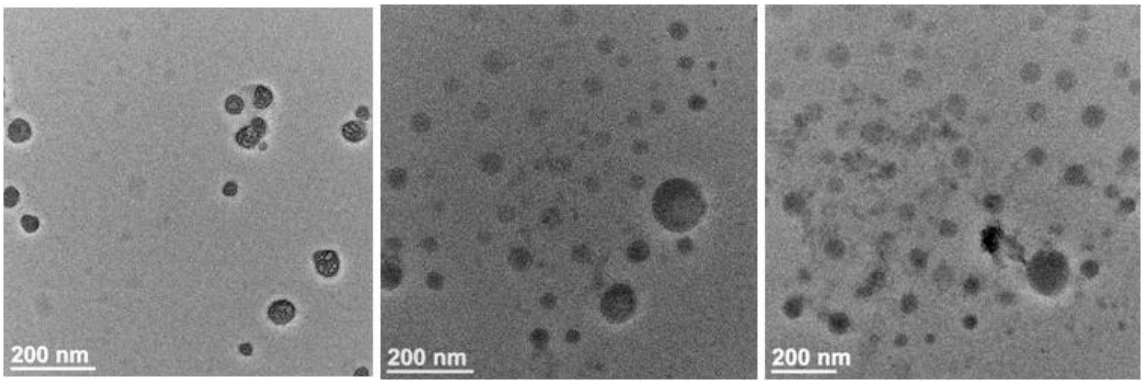


Figure S9: TEM images of self-assembled BTA-Py+PEG-1 (1:3) in water showing micelle like particles. Concentration of BTA-Py = 0.5 mM.

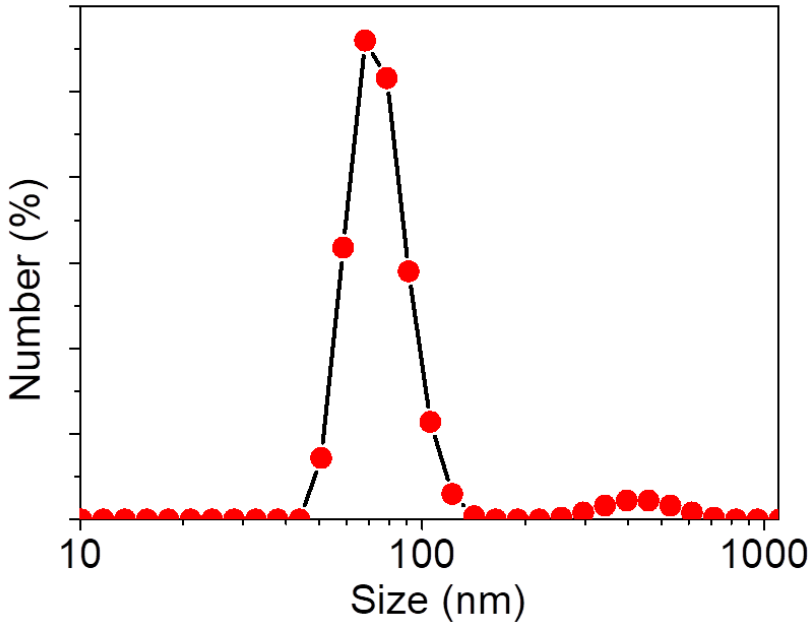


Figure S10: DLS data from a solution of BTA-Py+PEG-1(1:3) in water showing particle size of 70 nm. Concentration of BTA-Py = 0.5 mM.

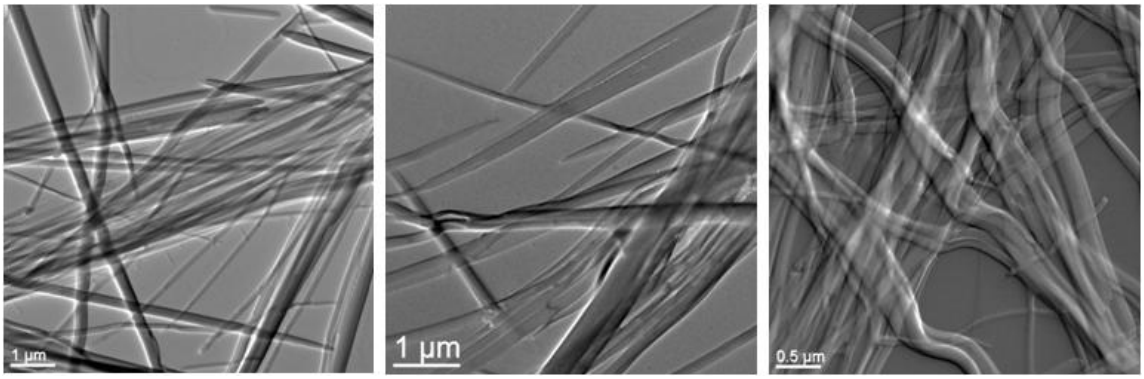


Figure S11: TEM images of self-assembled BTA-Py+TEG-1 (1:3) in water showing thick fibrillar morphology. Concentration of BTA-Py = 0.5 mM.

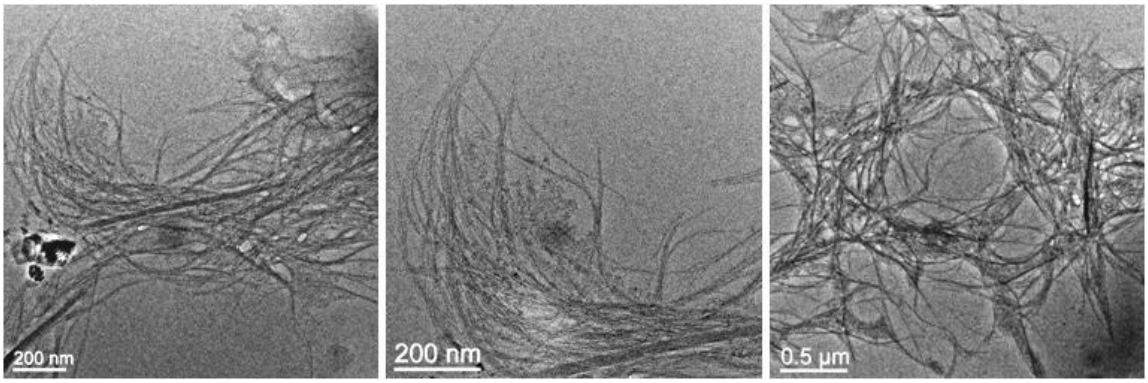
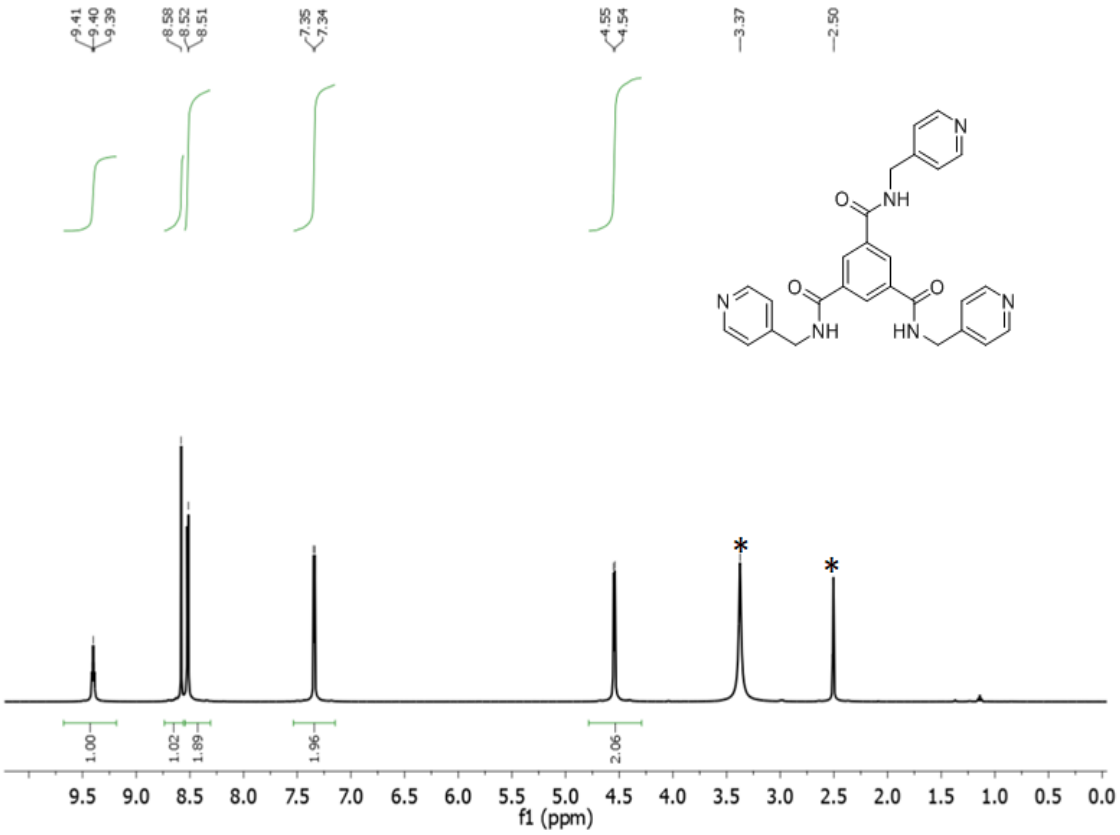


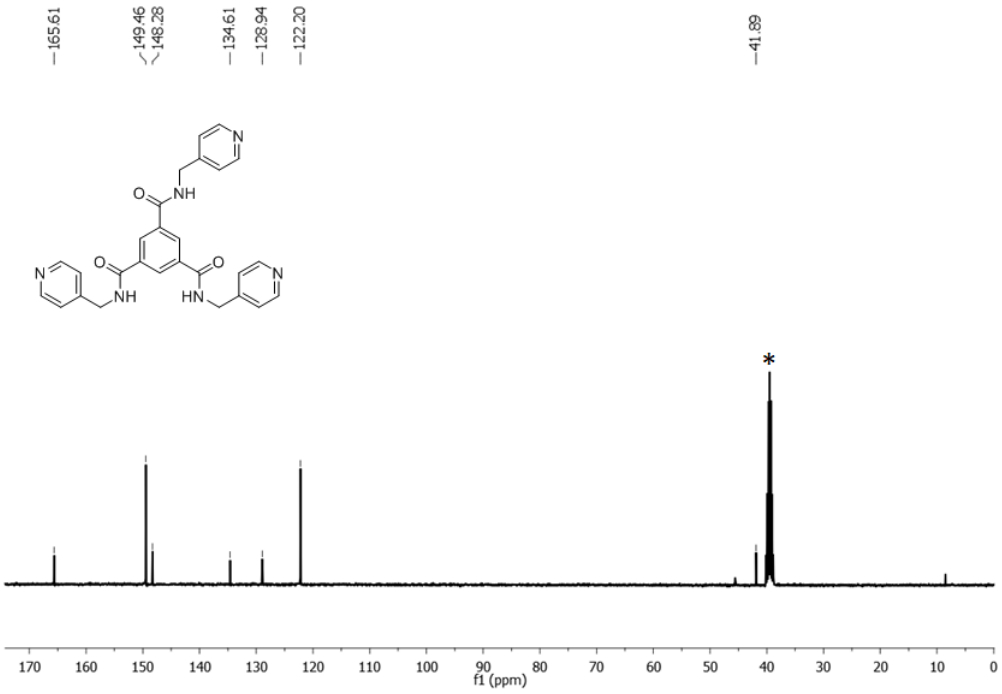
Figure S12: TEM images of self-assembled BTA-Py+PEG-1 (1:3) in 1% acetic acid in water showing switching from micelle to fibrillar morphology due to cleavage of the grafted PEG-1 chains. Concentration of BTA-Py = 0.5 mM.

NMR and HRMS Spectra

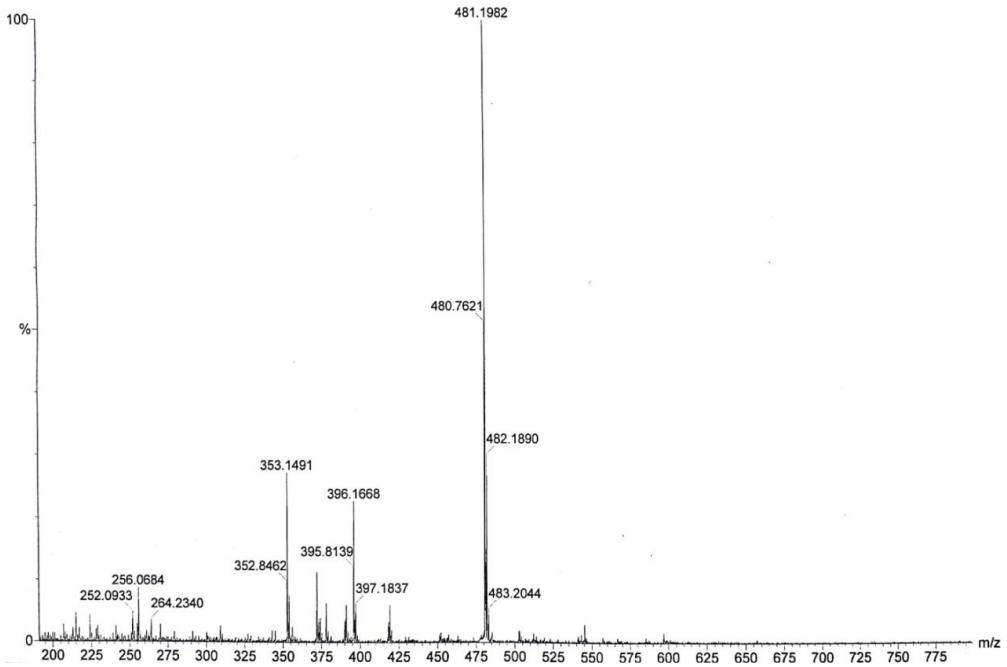
^{1}H NMR spectrum of BTA-Py. (*) denotes solvent peaks.



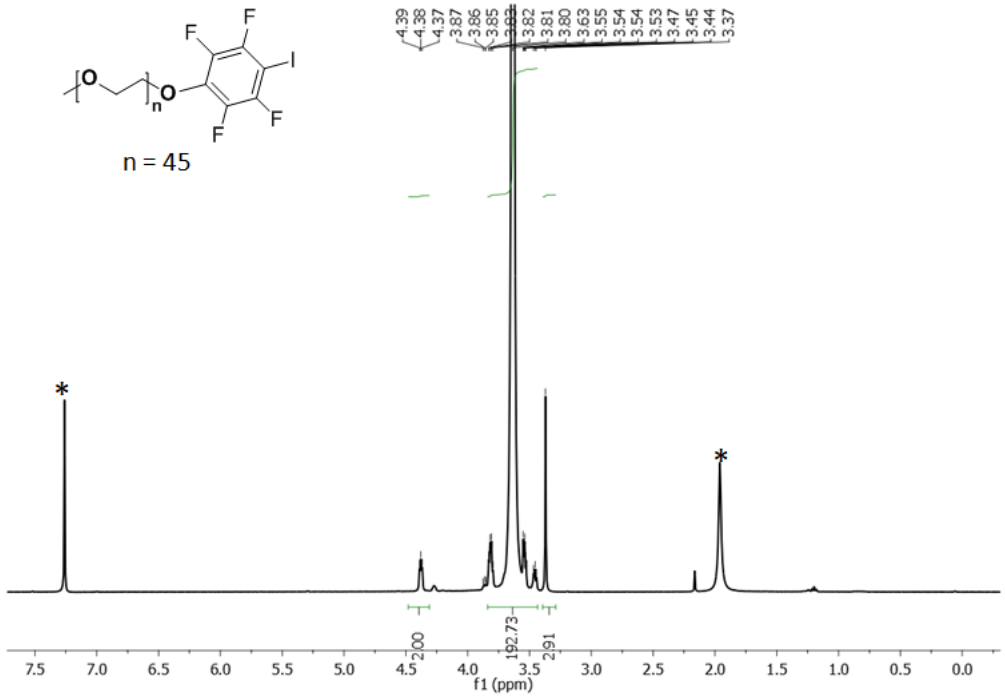
^{13}C NMR spectrum of BTA-Py. (*) denotes solvent peaks.



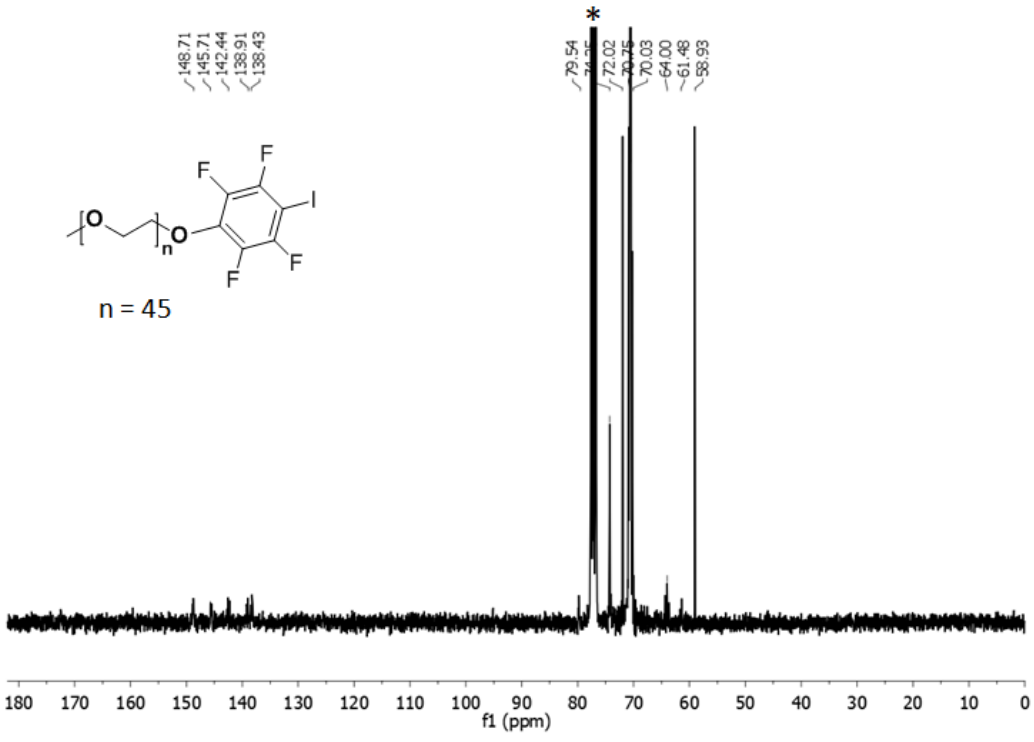
HRMS Spectrum of BTA-Py.



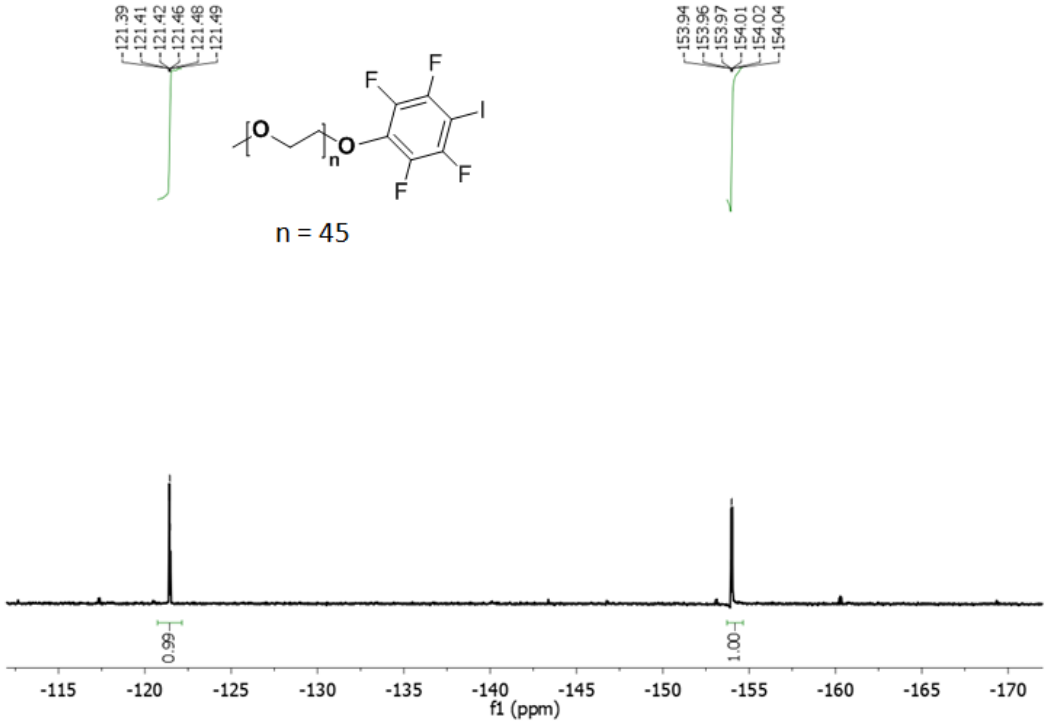
^{1}H NMR spectrum of PEG-1. (*) denotes solvent peaks.



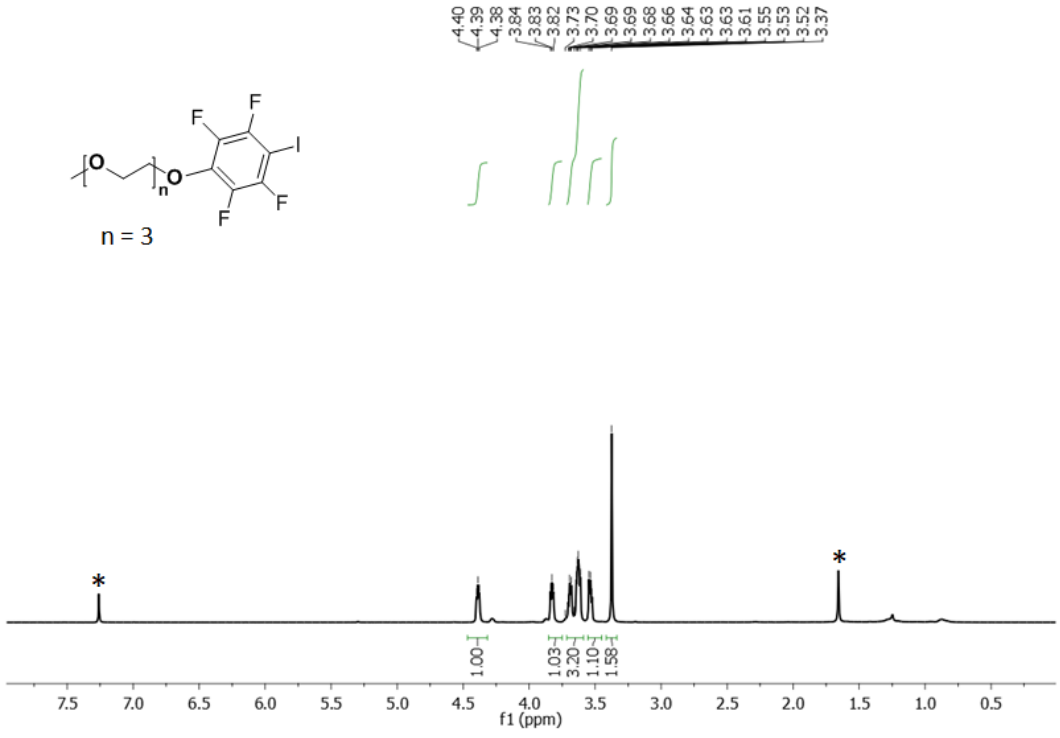
^{13}C NMR spectrum of PEG-1. (*) denotes solvent peaks.



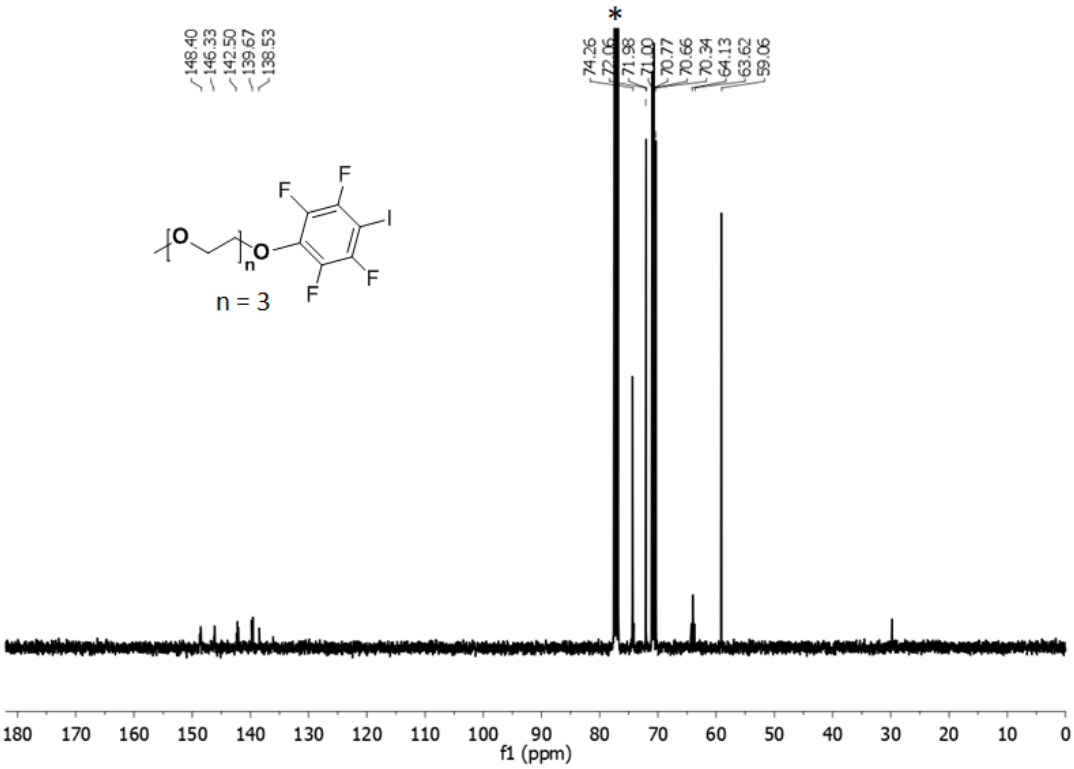
^{19}F NMR spectrum of PEG-1 in $CDCl_3$.



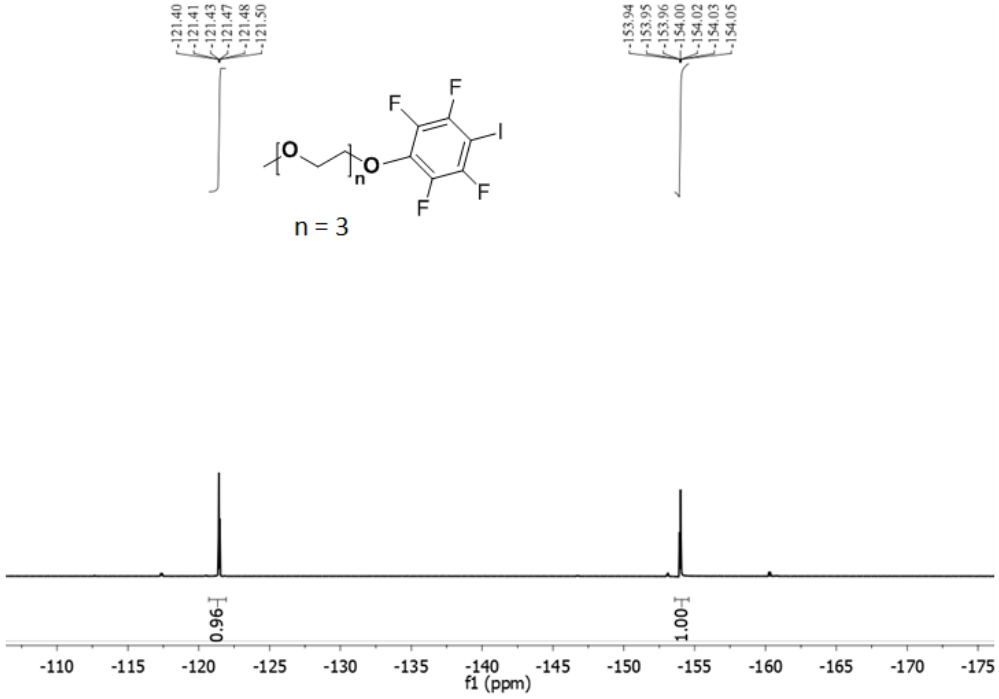
^{1}H NMR spectrum of TEG-1. (*) denotes solvent peaks.



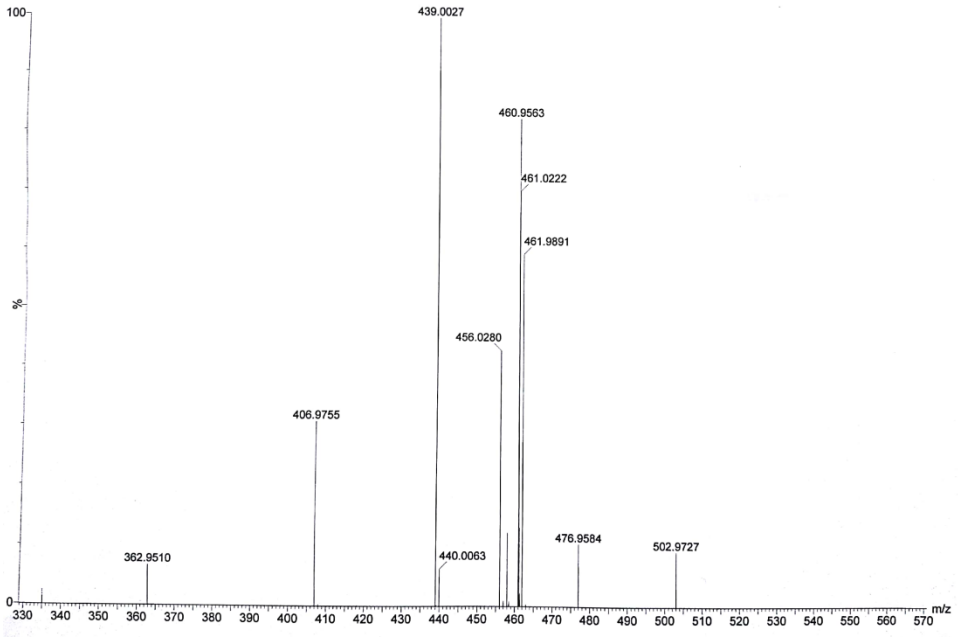
^{13}C NMR spectrum of TEG-1. (*) denotes solvent peaks.



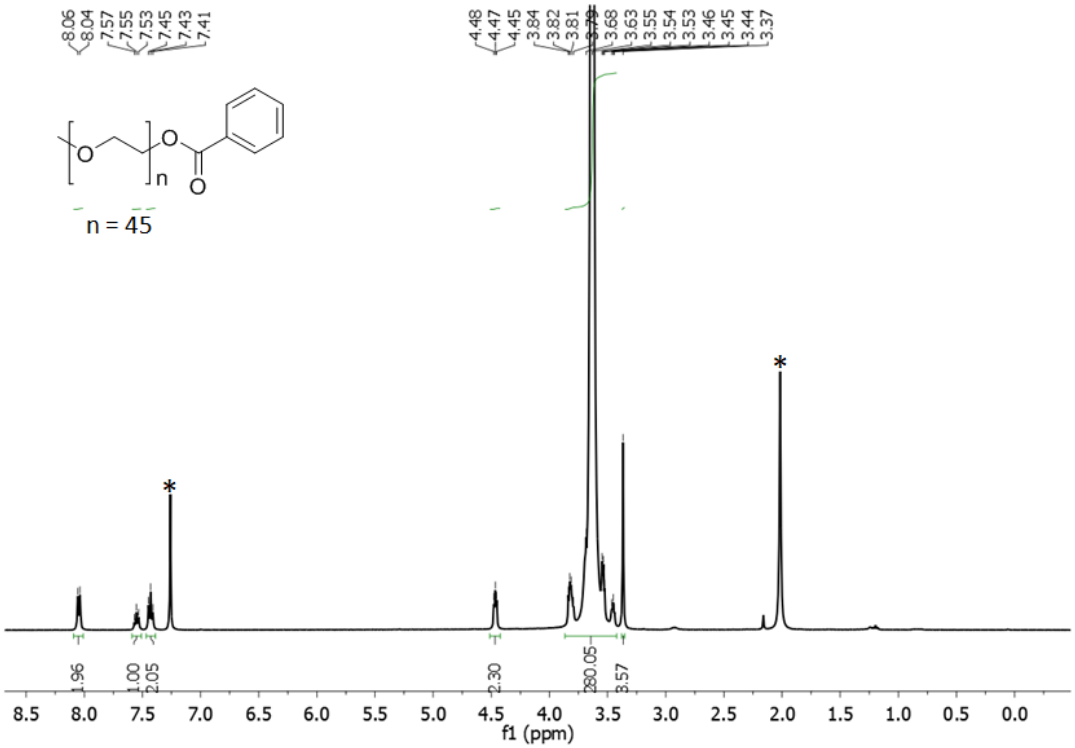
^{19}F NMR spectrum of TEG-1 in $CDCl_3$.



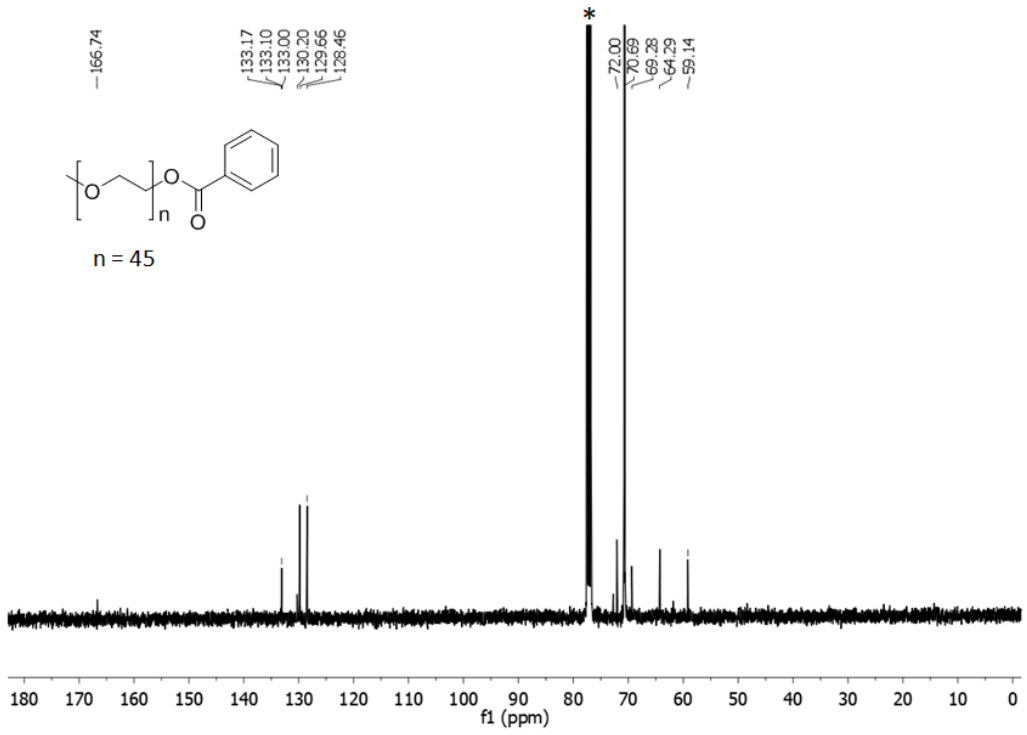
HRMS Spectrum of TEG-1



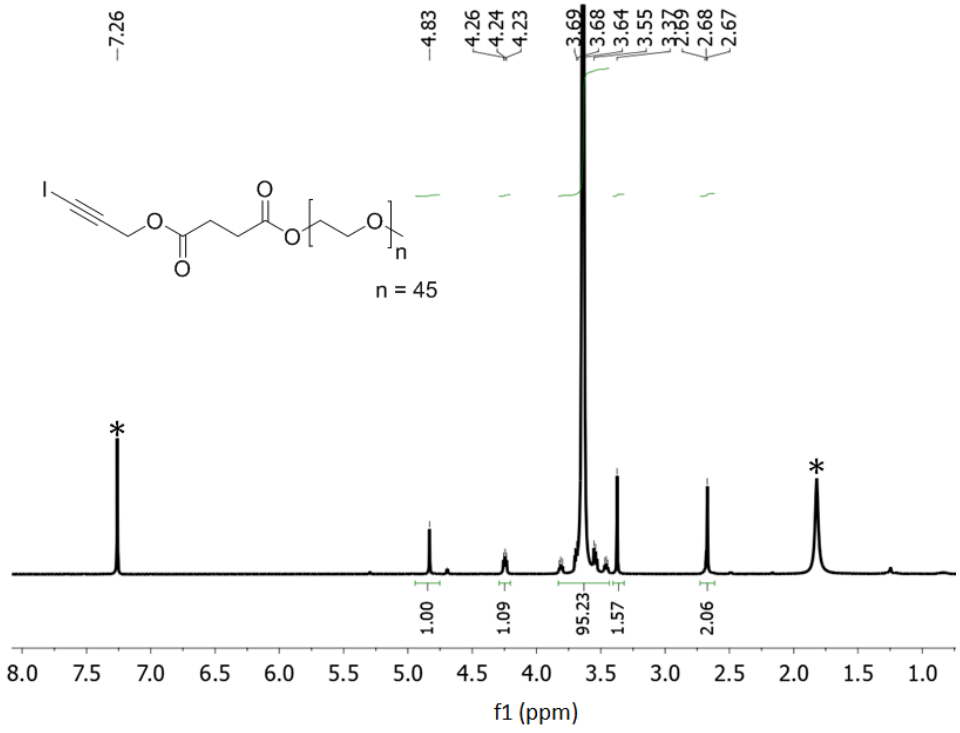
^{1}H NMR spectrum of PEG-2. (*) denotes solvent peaks.



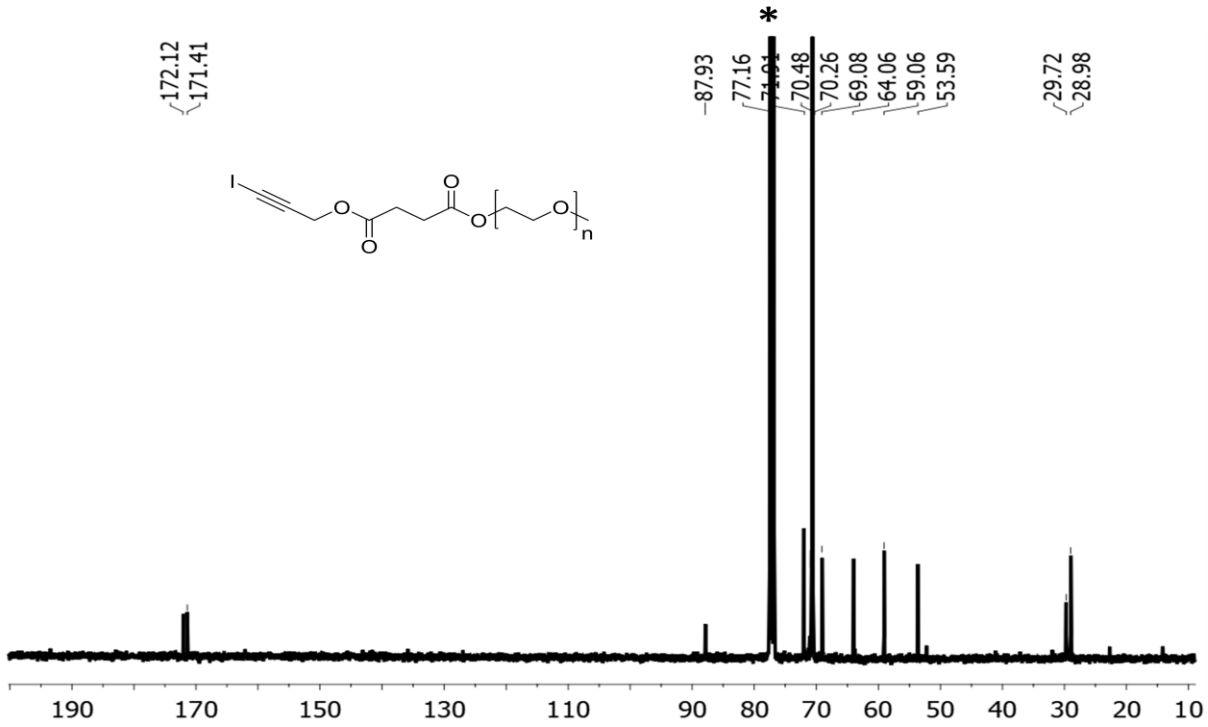
^{13}C NMR spectrum of PEG-2. (*) denotes solvent peaks.



^{1}H NMR spectrum of PEG-3. (*) denotes solvent peaks.



^{13}C NMR spectrum of PEG-3. (*) denotes solvent peaks.



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