

Supporting Information

Organized polymeric submicron particles via self-assembly and crosslinking of double hydrophilic poly(ethylene oxide)-*b*-poly(*N*-vinylpyrrolidone) in aqueous solution

Jochen Willersinn,[†] Markus Drechsler,[‡] Markus Antonietti,^{†} Bernhard V.K.J. Schmidt^{†*}*

[†] Max-Planck Institute of Colloids and Interfaces; Department of Colloid Chemistry, Am Mühlenberg 1, 14476 Potsdam, Germany

[‡] Bayreuth Institute of Macromolecular Research (BIMF) - Laboratory for Soft Matter Electron Microscopy, University of Bayreuth, Universitätsstr. 30, 95440 Bayreuth, Germany

Synthesis of PEO₅₀₀-Macro CTA: 2-((Ethoxycarbonothioyl)thio)propionic acid [poly(ethylene oxide)methyl ether] ester

The PEO macro chain transfer agent was synthesized according to a procedure reported in literature.¹

2-Bromopropionic acid [poly(ethylene oxide)-methyl-ether]-ester (PEO-Br): Poly(ethylene oxide)monomethyl-ether (PEO-OH, 10.0 g, 0.5 mmol, 1.0 eq.) was placed in a dry, argon purged 100 mL two neck round bottom flask and dissolved in dry DCM (40.0 mL). Dry pyridine (0.11 mL, 1.35 mmol, 2.7 eq.) was added under stirring and the mixture was cooled with an ice water bath to 0 °C. 2-Bromopropionyl bromide (0.13 mL, 1.17 mmol, 2.33 eq.) was slowly added to the cooled reaction mixture. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. A white precipitate was filtered off and the reaction mixture was diluted with DCM (200 mL). The solution was washed with aqueous saturated ammonium chloride solution (4 x 40 mL), aqueous saturated sodium hydrogen carbonate solution (4 x 40 mL), deionized water (2 x 40 mL) and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was evaporated. The residue was re dissolved in a small amount DCM. The product was obtained by precipitation into ice cold diethyl ether, filtered and dried under reduced pressure. 2-Bromopropionic acid [poly(ethylene oxide)methyl ether] ester (PEO-Br) was obtained as a white solid (12.3 g, 0.62 mmol, 83% recovery). ¹H NMR (400 MHz, CDCl₃ δ) 4.38 (q, ³J = 6.9 Hz, 1H, CH), 4.30 (t, 2H, CH₂OC(O)), 3.62 (s), 3.85-3.4 (m, CH₂CH₂O PEO-backbone), 3.36 (s, 3H CH₃), 1.81 (d, ³J = 6.9 Hz, 3H, CH₃). *M*_{n,app,SEC} = 26000 g·mol⁻¹ (PEO equivalents in NMP), Đ = 1.1.

2-((Ethoxycarbonothioyl)thio)propionic acid [poly(ethylene oxide)methyl ether] ester (PEO-X): 2-Bromopropionic acid [poly(ethylene oxide)methyl ether] ester (PEO-Br, 8.0 g, 0.4 mmol, 1.0 eq.) was dissolved in dry DCM (45 mL) in a dry, argon purged 100 mL two neck round bottom flask. Dry pyridine (1.88 mL, 21.2 mmol, 53 eq.) was added and the reaction mixture was cooled to 0 °C. Potassium *O*-ethyl xanthate (1.96 g, 12.0 mmol, 30 eq.) was added slowly in portions. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. A white precipitate was filtered off and DCM (150 mL) was added. The solution was washed with aqueous saturated ammonium chloride solution (5 x 75 mL), aqueous saturated sodium hydrogen carbonate solution (5 x 75 mL), deionized water (1 x 75 mL) and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was purified by Soxhlet extraction with diethyl ether overnight. *2-((Ethoxycarbonothioyl)thio)propionic acid [poly(ethylene oxide)methyl ether] ester (PEO-X)* was obtained (7.5 g, 0.4 mmol, 93 % recovery). ¹H NMR (400 MHz, CDCl₃ δ) 4.61 (q, ³J = 7.1 Hz, 2H OCH₂CH₃), 4.39 (q, ³J = 7.4 Hz, 1H, CH), 4.28 (t, 2H, CH₂OC(O)), 3.62 (s), 3.85-3.4 (m, CH₂CH₂O PEO-backbone), 3.36 (s, 3H CH₃), 1.56 (d, ³J = 7.4 Hz, 3H, CH₃), 1.39 (t, ³J = 7.1 Hz, 3H, OCH₂CH₃). $M_{n,app,SEC} = 20000 \text{ g}\cdot\text{mol}^{-1}$ (PEO equivalents in NMP), $\bar{D} = 1.1$.

Synthesis of the crosslinker diethylene glycol bis(2-iodoethyl) ether

Diethylene glycol bis(2-iodoethyl) ether was synthesized according to the literature.²

Diethylene glycol bis(2-tosylethyl) ether: In a dry argon purged 250 ml round bottom Schlenk flask, tetraethylene glycol (5.0 g, 25.7 mmol, 1.0 eq.) was dissolved in dry triethylamine (200 ml). 4-toluenesulfonyl chloride (11.0 g, 57.9 mmol, 2.25 eq.) was added to the solution. The reaction mixture was stirred overnight at ambient temperature. Triethylamine was removed under reduced pressure. The resulting residue was extracted with ethyl acetate (4 x 30 ml) and a white

salt was filtered off. The organic phase was washed with saturated brine solution (1 x 80 ml), dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc/ Hexane = 1:1, R_f = 0.28) to afford diethylene glycol bis(2-tosylethyl) ether as a white solid (9.0 g, 70%, 17.92 mmol). ^1H NMR (400 MHz, CDCl_3 , δ) 7.79 (d, 3J = 8.3 Hz, 4H), 7.31 (d, 3J = 8.0 Hz, 4H), 4.15 (t, 3J = 4.8 Hz, 4H, $\text{CH}_2\text{-O-Tos}$), 3.67 (t, 3J = 4.9 Hz, 4H), 3.55 (m, 8H, $\text{CH}_2\text{-CH}_2\text{-}$), 2.44 (s, 6H, CH_3).

Diethylene glycol bis(2-iodoethyl) ether: In a dry argon purged 250 ml round bottom flask, diethylene glycol bis(2-tosylethyl) ether (8.0 g, 15.9 mmol, 1.0 eq.) was dissolved in acetone (100 ml). Sodium iodide (9.55 g, 63.7 mmol, 4 eq.) was added and the mixture was refluxed for 8 hours. The solvent was removed under reduced pressure. The residue was dissolved in DCM (100 ml) and washed with saturated brine solution (100 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to afford diethylene glycol bis(2-iodoethyl) ether as a yellow oil (5.95 g, 90%, 14.4 mmol). ^1H NMR (400 MHz, CDCl_3 , δ) 3.76 (t, 3J = 6.8 Hz, 4H, CH_2O), 3.67 (m, 8H), 3.26 (t, 3J = 7.1 Hz, 4H, CH_2I). ^{13}C -NMR (CDCl_3 , 400 MHz, 300 K, δ) 72 (I- CH_2CH_2), 71, 70, 3 (CH_2I).

^1H and ^{13}C NMR spectra of the synthesized compounds

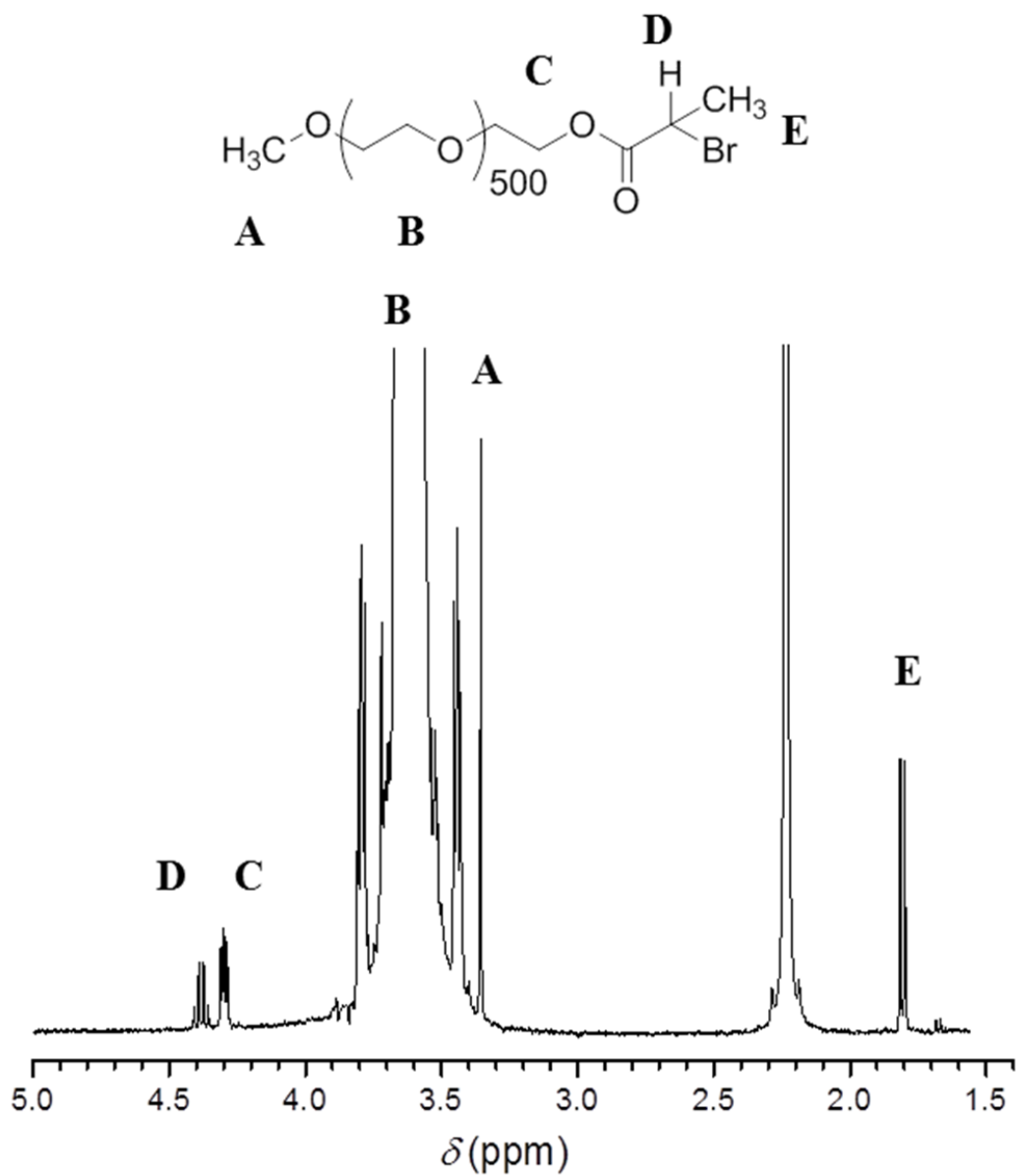


Figure S1. ^1H -NMR of PEO-Br recorded in CDCl_3 at 25 $^\circ\text{C}$.

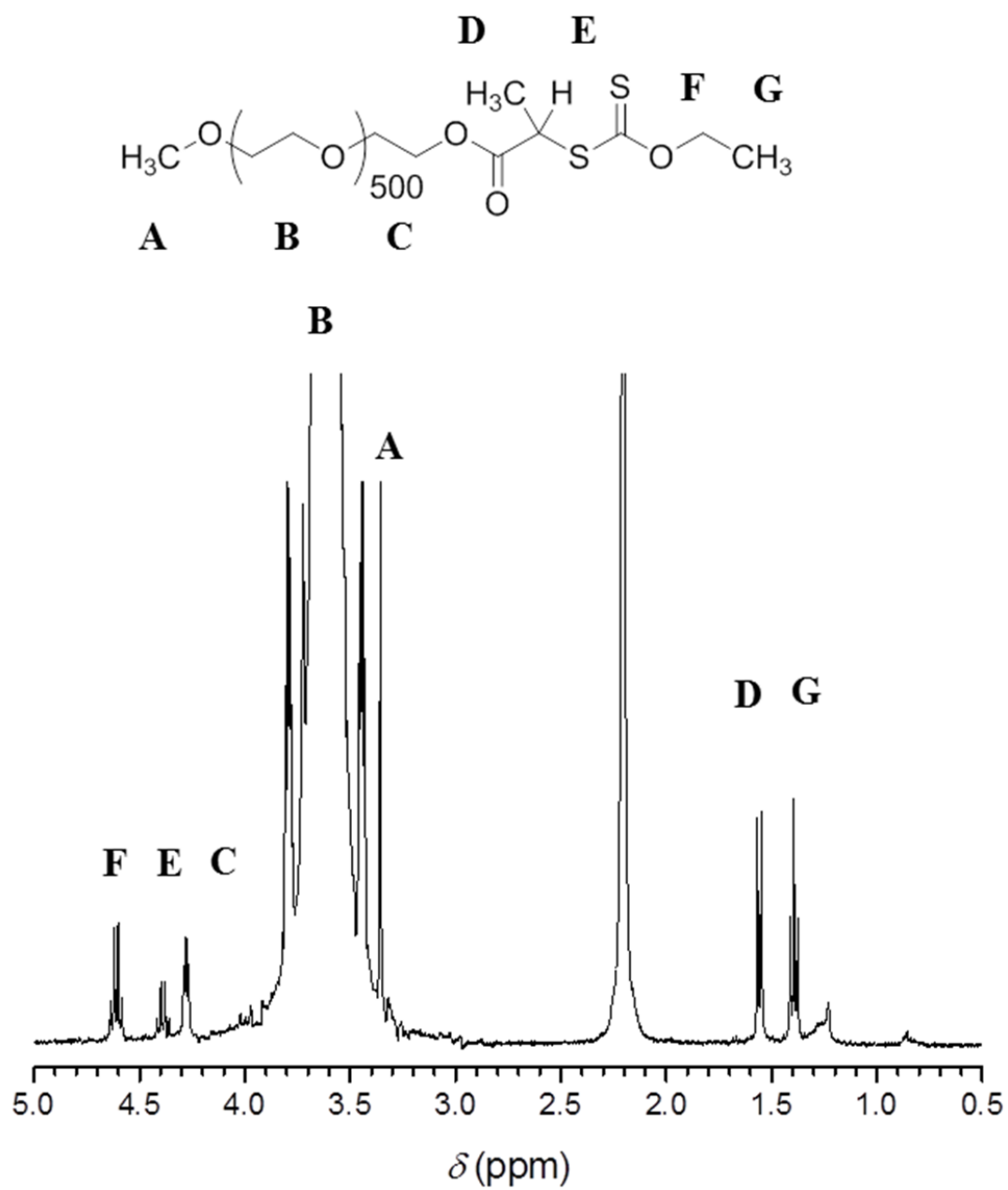


Figure S2. $^1\text{H-NMR}$ of PEO-X recorded in CDCl_3 at $25\text{ }^\circ\text{C}$.

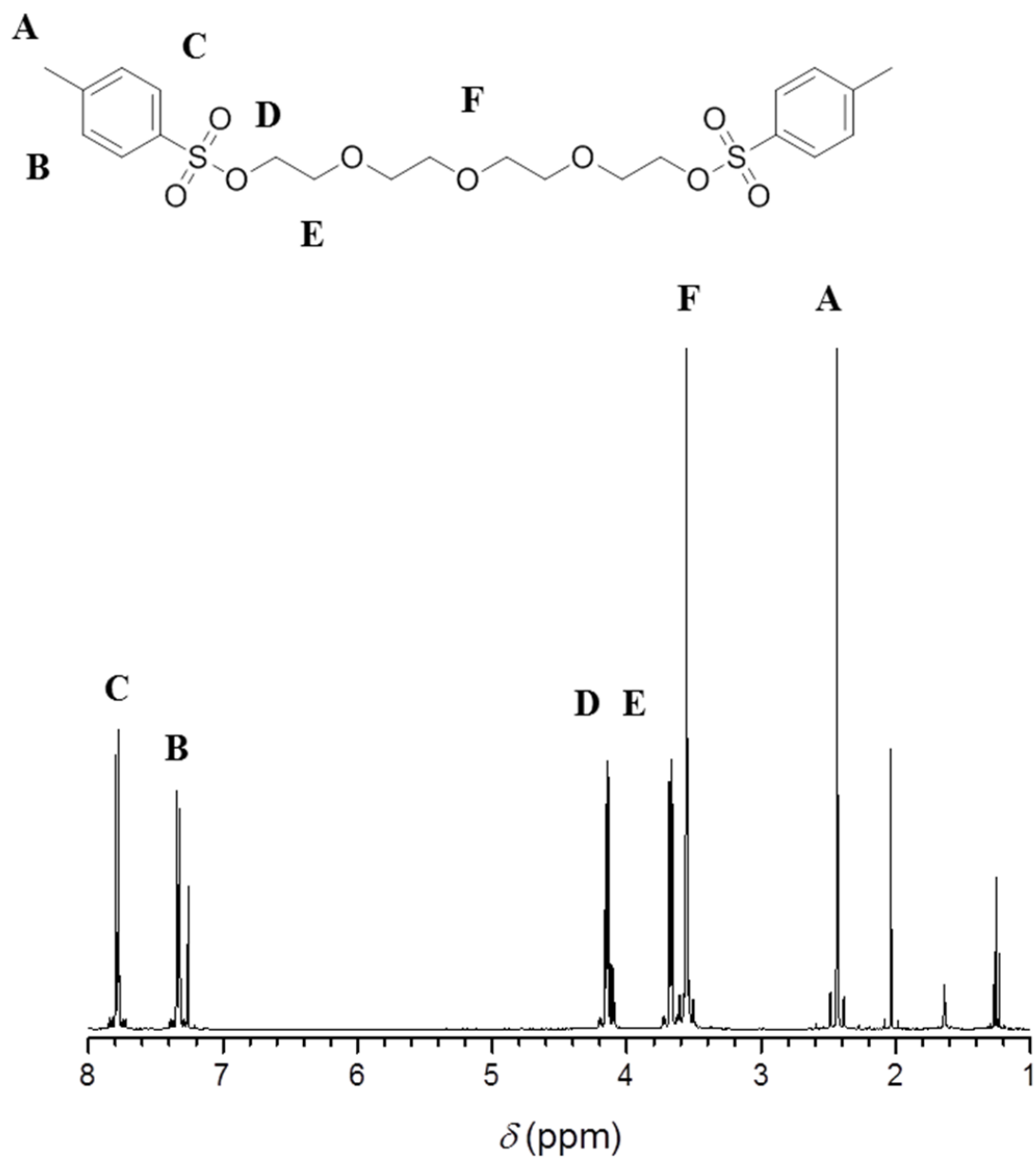


Figure S3. ¹H-NMR of diethylene glycol bis(2-tosylethyl) ether recorded in CDCl₃ at 25 °C.

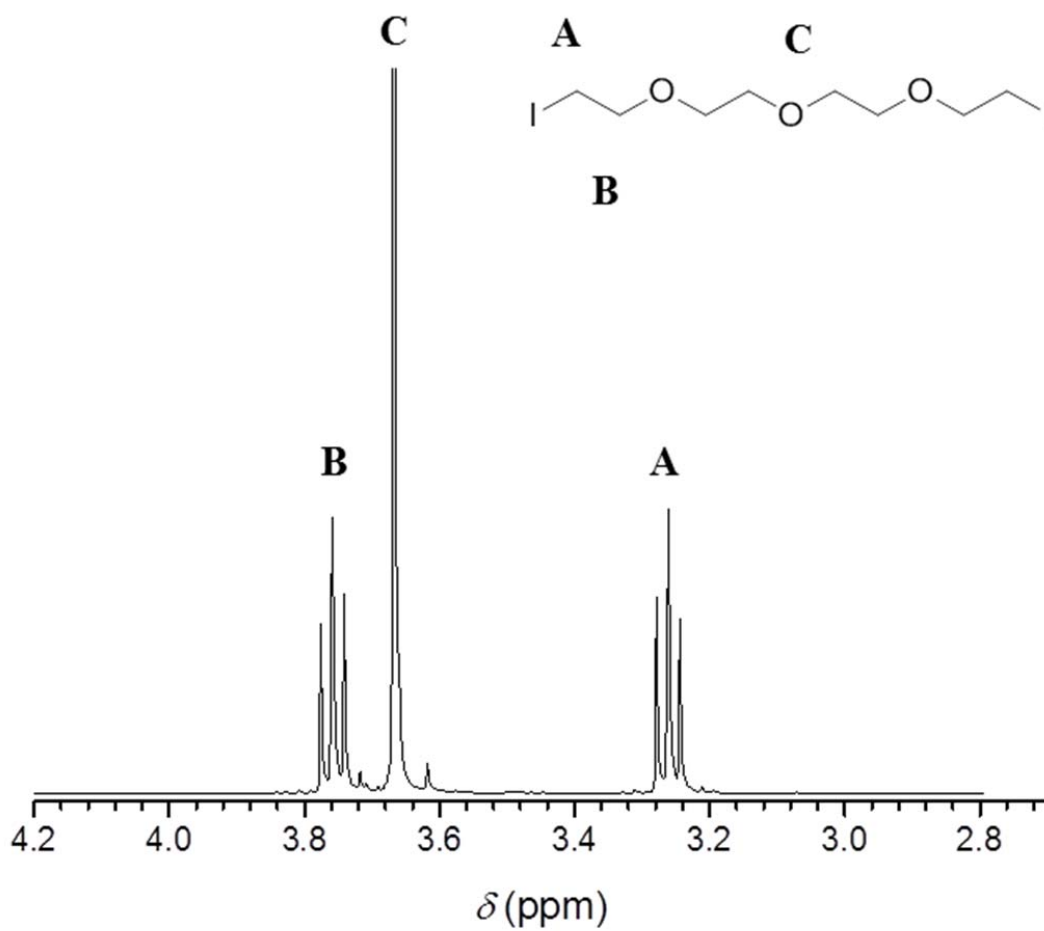


Figure S4. $^1\text{H-NMR}$ of diethylene glycol bis(2-iodoethyl) ether recorded in CDCl_3 at 25°C .

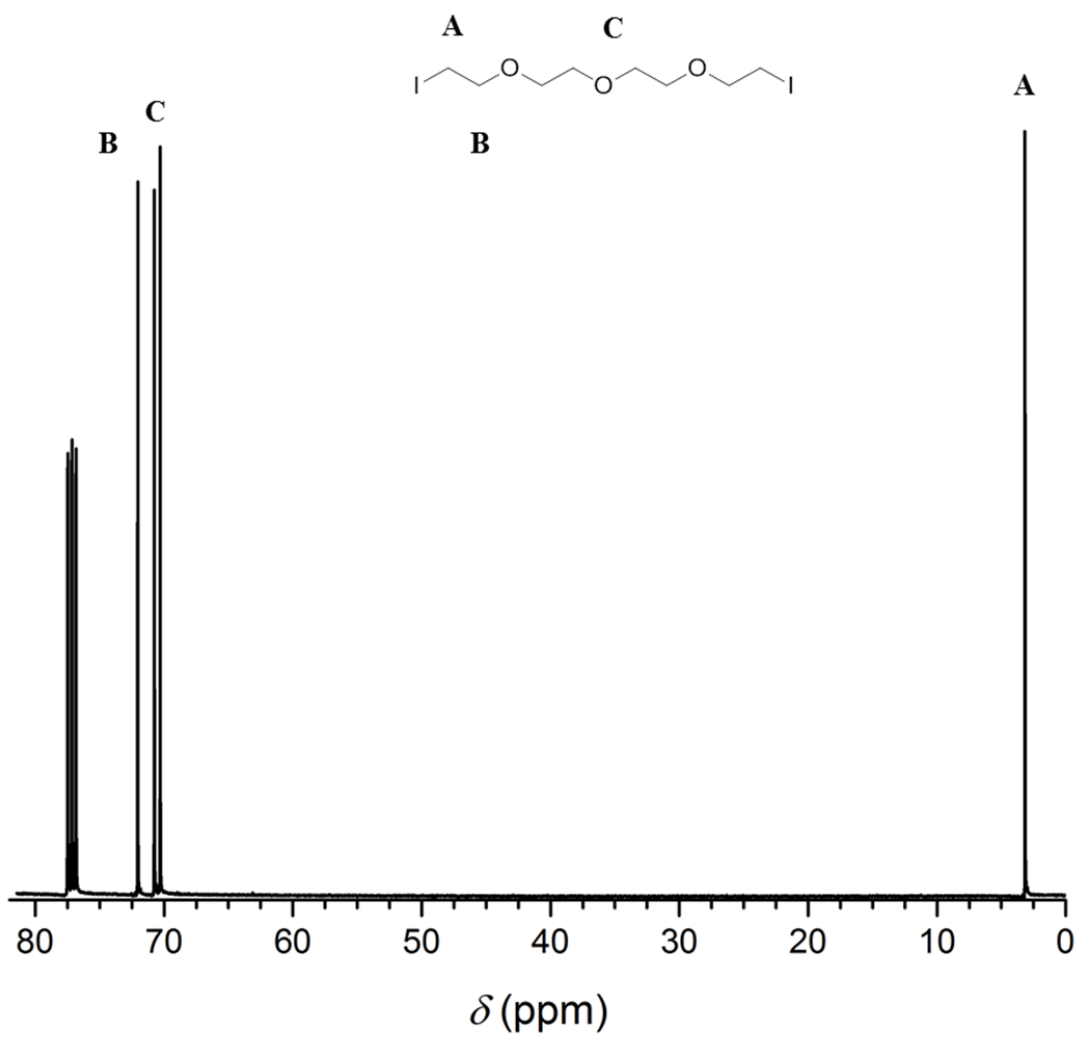


Figure S5. ¹³C-NMR of diethylene glycol bis(2-iodoethyl) ether recorded in CDCl₃ at 25 °C.

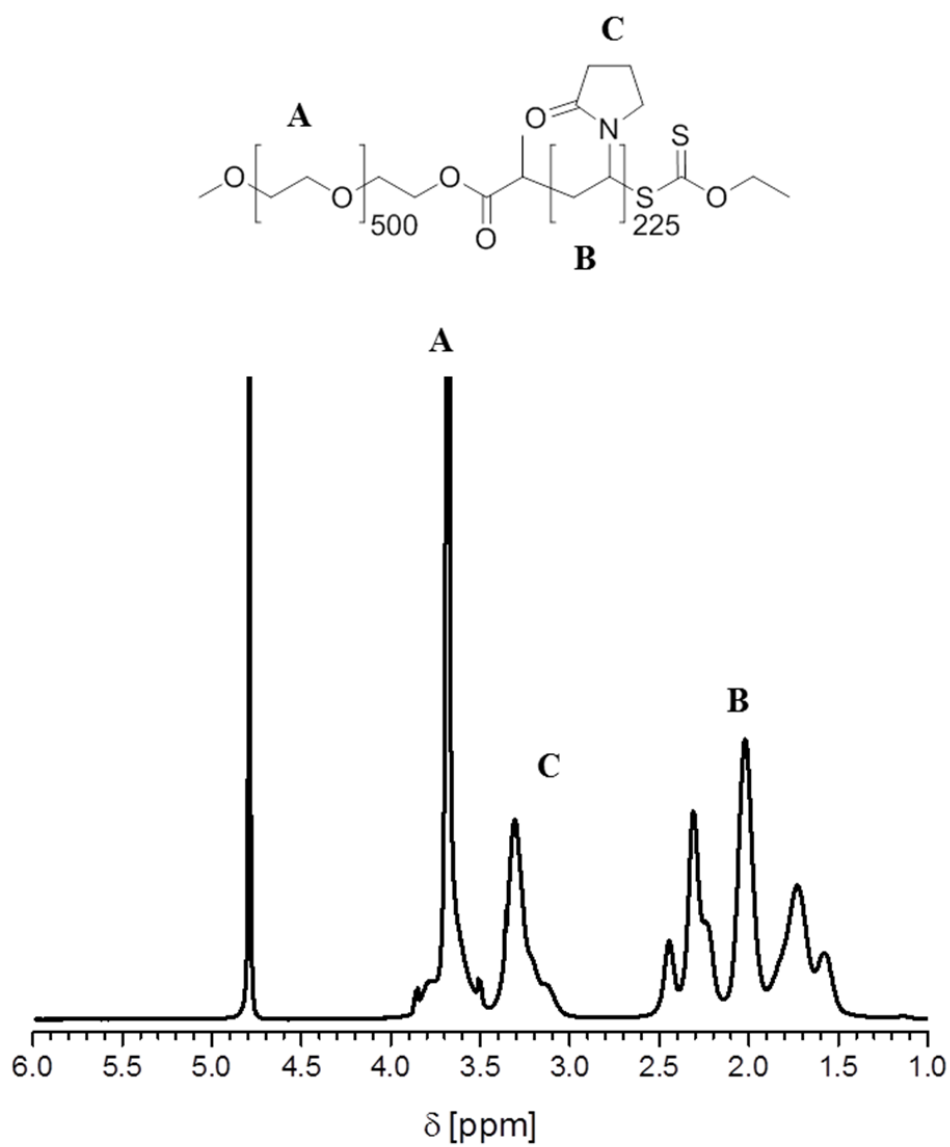


Figure S6. ¹H-NMR of PEO-*b*-PVP recorded in D₂O at 25 °C.

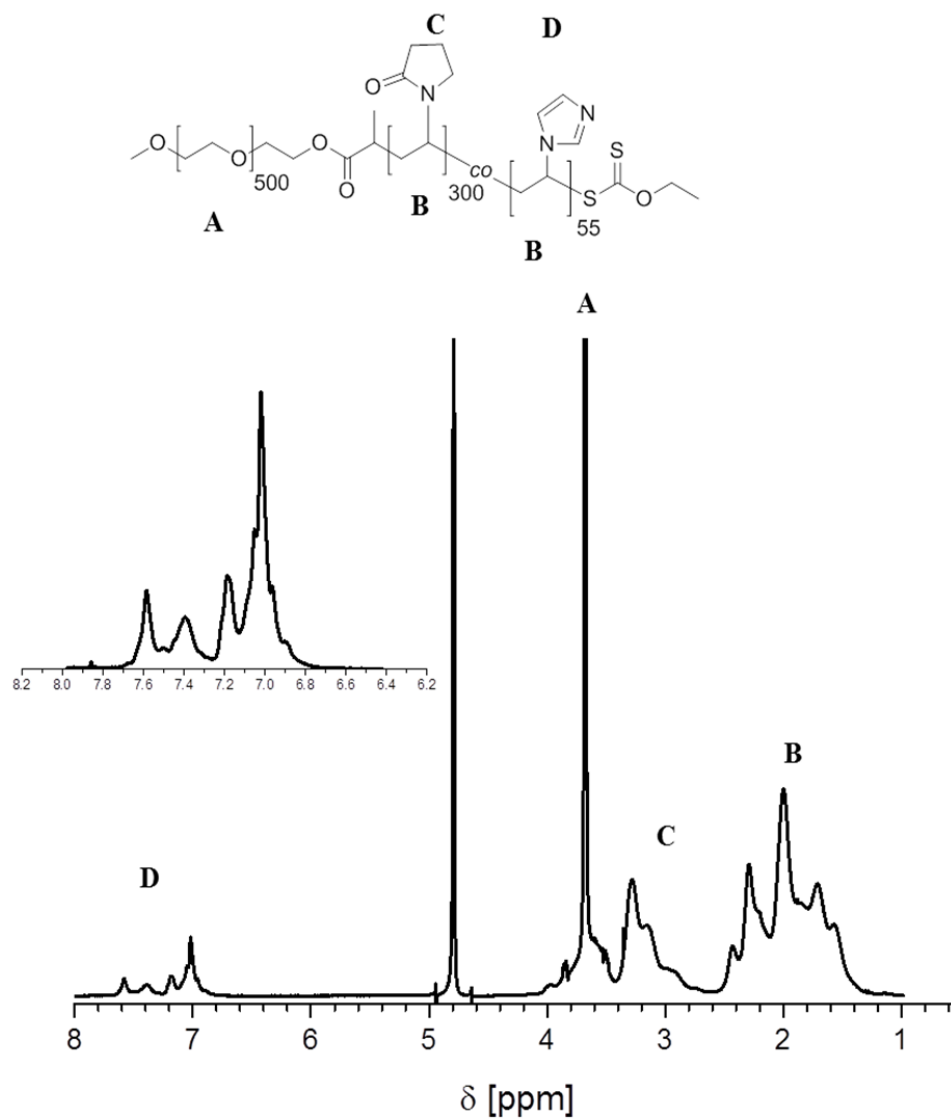


Figure S7. ¹H-NMR of PEO-*b*-P(VP-*co*-VIm) recorded in D₂O at 25 °C.

SEC chromatograms of synthesized block copolymers

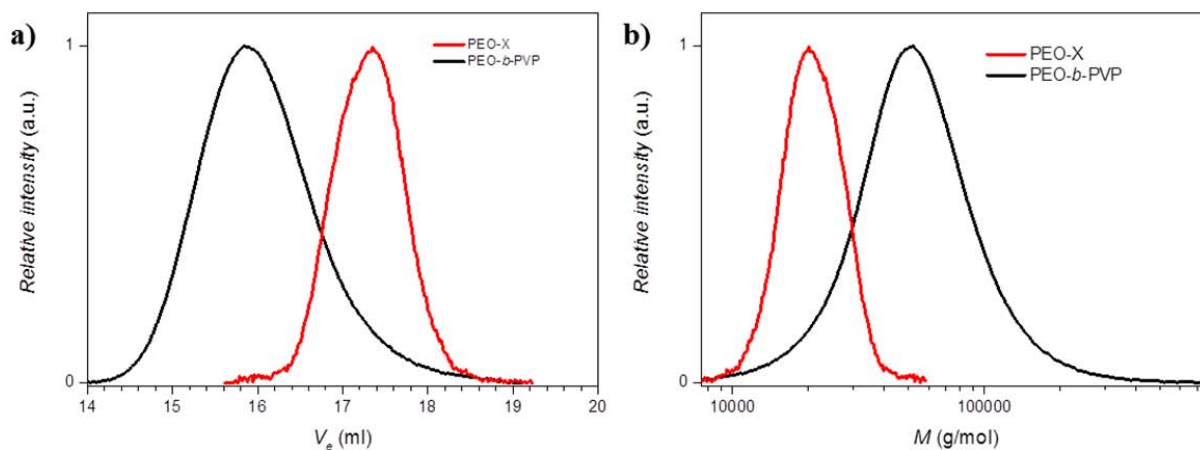


Figure S8. a) SEC elugram and b) corresponding molecular weight distribution of PEO-X and PEO-*b*-PVP in NMP at 70 °C.

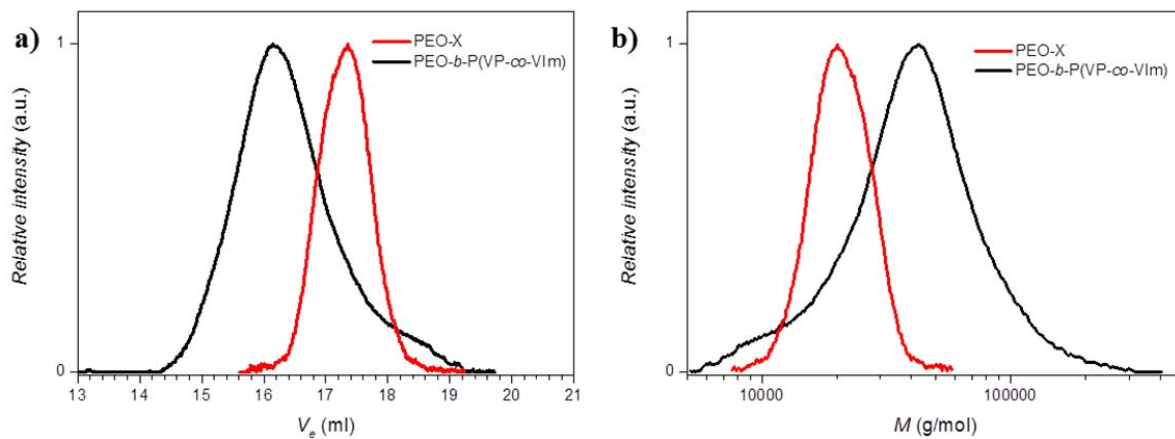


Figure S9. a) SEC elugram and b) corresponding molecular weight distribution of PEO-X and PEO-*b*-P(VP-*co*-VIm) in NMP at 70 °C.

Preparation of aqueous PEO-*b*-PVP and PEO-*b*-P(VP-*co*-VIm) block copolymer solutions.

The preparation of the aqueous block copolymer solutions with different concentrations are listed in Table S1.

Table S1. Preparation assessment for block copolymer solutions according to the attempted weight percentage.

Entry	Weight percentage	<i>m</i> (block copolymer) [g]	<i>m</i> (Millipore water) [g]	Added cross-linker solution [μL]
1	0.1	0.002	1.998	0.1
2	0.5	0.01	1.99	0.5
3	1.0	0.02	1.98	1.0
4	2.5	0.05	1.95	2.6
5	5.0	0.1	1.9	5.2
6	7.5	0.15	1.85	10.5

Table S2. pH values of 1.0 wt.% block copolymer solutions.

Entry	Block copolymer	pH
1	PEO- <i>b</i> -PVP	7.3
2	PEO- <i>b</i> -P(VP- <i>co</i> -VIm)	7.6
3	PEO- <i>b</i> -P(VP- <i>co</i> -VIm) (crosslinked)	7.5

Table S3. Zeta potential values of 0.1 wt.% block copolymer solutions.

Entry	Block copolymer	Zeta potential [mV]
1	PEO- <i>b</i> -PVP	-6.74
2	PEO- <i>b</i> -P(VP- <i>co</i> -VIm)	0.44
3	PEO- <i>b</i> -P(VP- <i>co</i> -VIm) (crosslinked in water)	1.09
4	PEO- <i>b</i> -P(VP- <i>co</i> -VIm) (crosslinked in DMF, dialyzed)	4.87

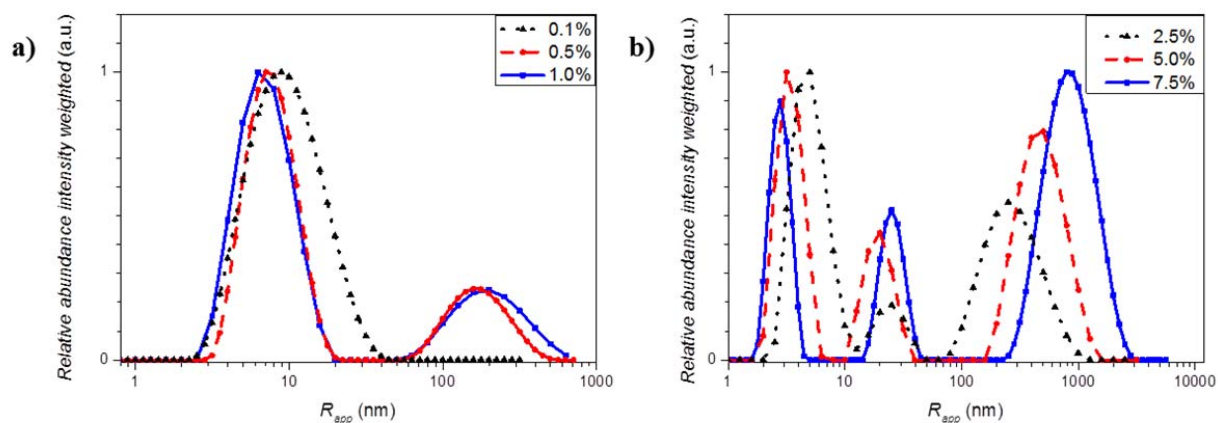


Figure S10. Particle size distributions of PEO-*b*-PVP block copolymer solutions at concentrations of a) 0.1, 0.5 1.0 wt.% and b) 2.5, 5.0, 7.5 wt.% determined via DLS at 25 °C.

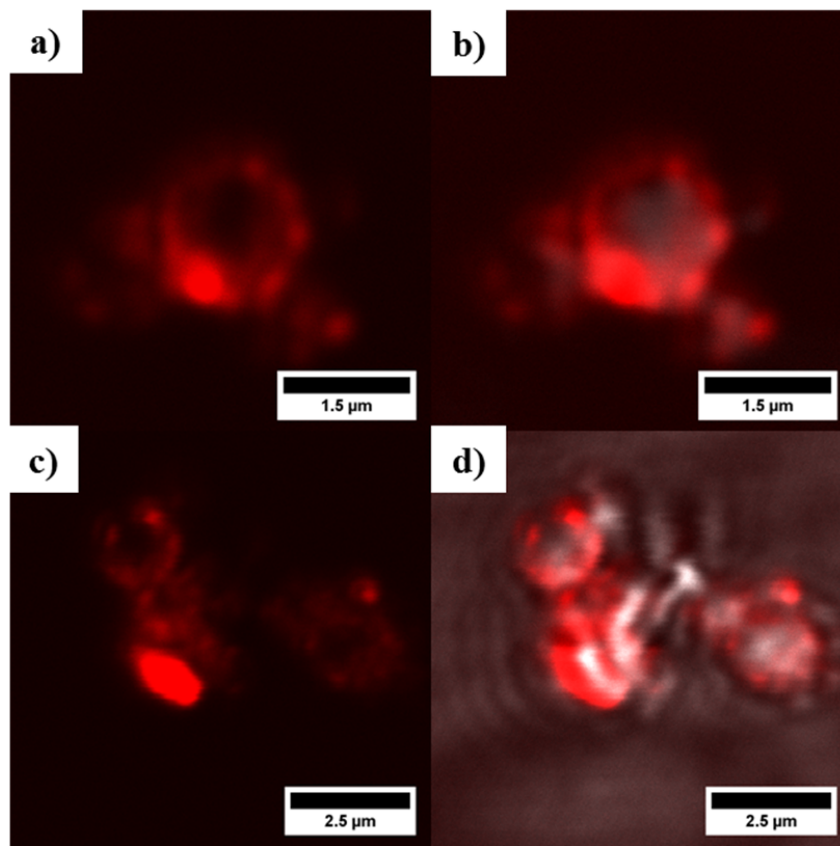


Figure S11. a) & c) Confocal micrographs of spherical particles of PEO₅₀₀-*b*-PVP₂₂₅ stained with Rhodamine B; b) & d) Corresponding DIC micrographs.

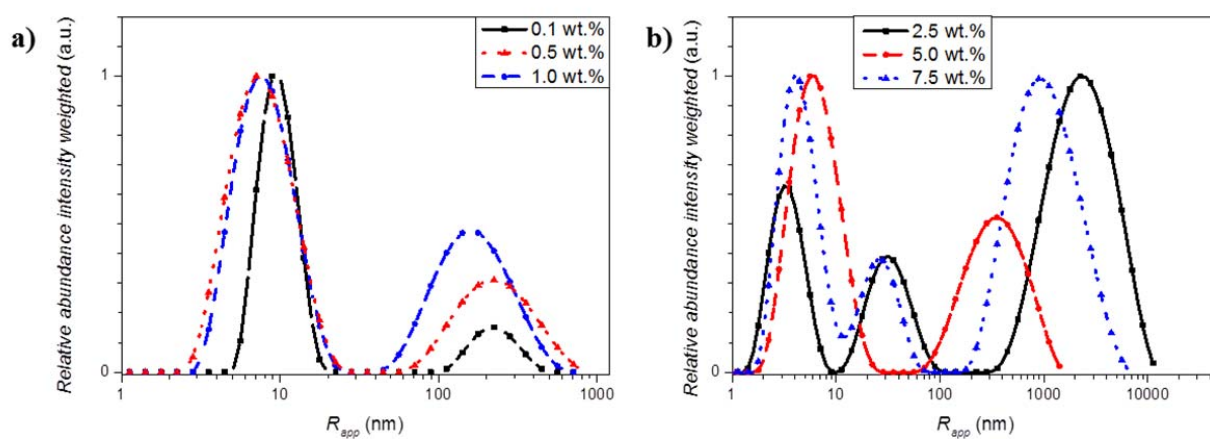


Figure S12. Particle size distributions of PEO-*b*-P(VP-*co*-VIm) block copolymer solutions at concentrations of a) 0.1, 0.5 1.0 wt.% and b) 2.5, 5.0, 7.5 wt.% determined via DLS at 25 °C.

Crosslinking of PEO-*b*-P(V-*co*-VIm) block copolymer solutions

Particle size distribution curves of PEO-*b*-P(V-*co*-VIm) block copolymer solutions with concentrations of 1.0, 2.5 and 5.0 wt.% were recorded before and after the addition of crosslinker solution. A strong difference in the DLS size distributions can be observed for 1.0 wt.% block copolymer solutions of PEO-*b*-P(VP-*co*-VIm). The relative abundance of the spherical particles increased by 50% and a broadening of the peak was observed. A new signal with an average apparent radius of 8500 nm was observed as well. This might indicate the formation of aggregated particles as a direct result of the crosslinking. Particles in close contact to each other have a certain probability to form interparticle linkages with the crosslinking agent and therefore form large aggregates of several particles. Aggregates of several particles can also be observed in the cross-linked solutions of a higher concentration.

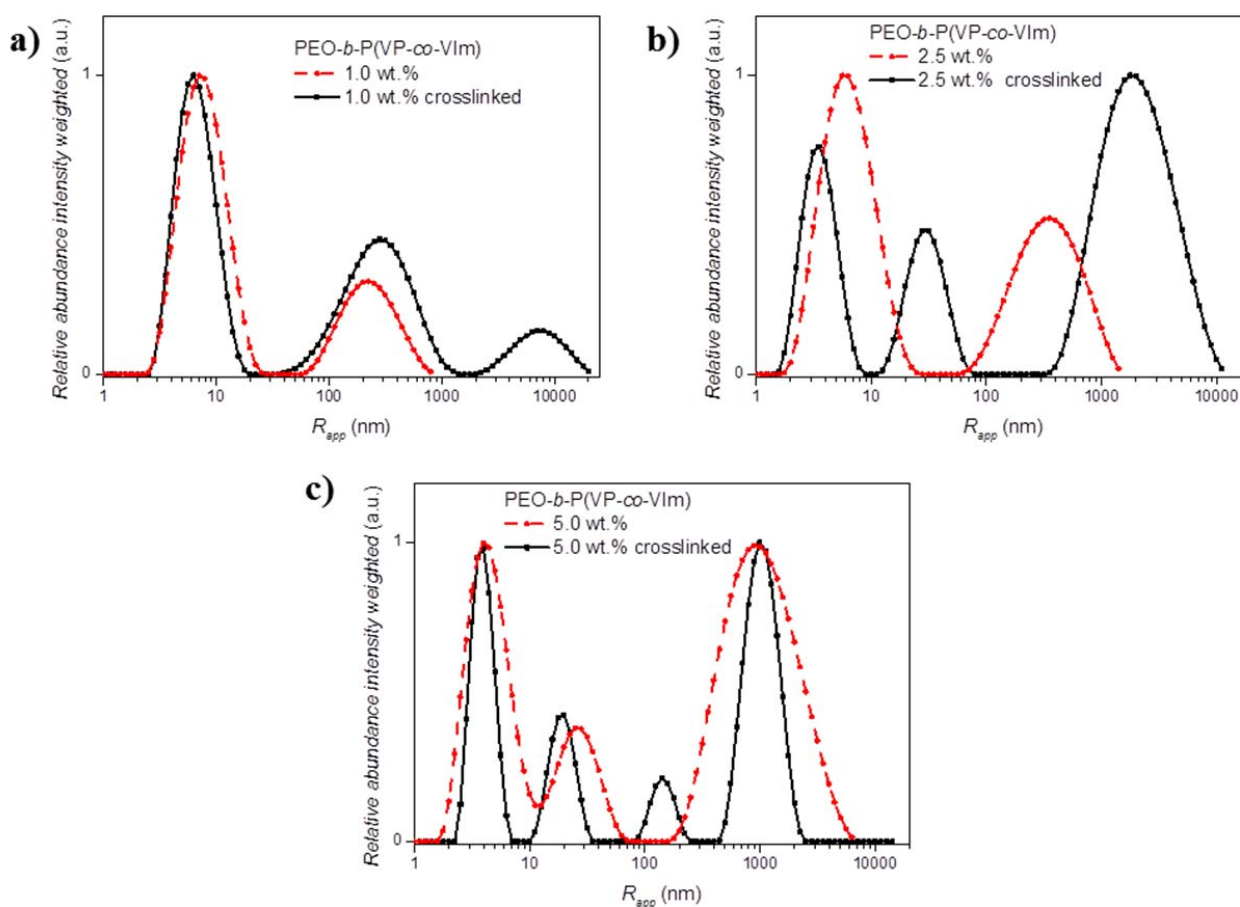


Figure S13. Particle size distributions of PEO-*b*-P(VP-*co*-VIm) block copolymer solutions at concentrations of a) 1.0 wt.%, b) 2.5 wt.% and c) 5.0 wt.% determined via DLS at 25 °C before and after the addition of crosslinker.

The circumstance of aggregation could be observed with confocal-DIC measurements of a Rhodamine B stained solution of crosslinked PEO-*b*-P(VP-*co*-VIm) with 5.0 wt.% block copolymer content. As visible from the LCSM micrographs in Figure S14, the submicron particles are highly aggregated. The particle aggregates were several micrometers large and consisted of many submicron sized particles.

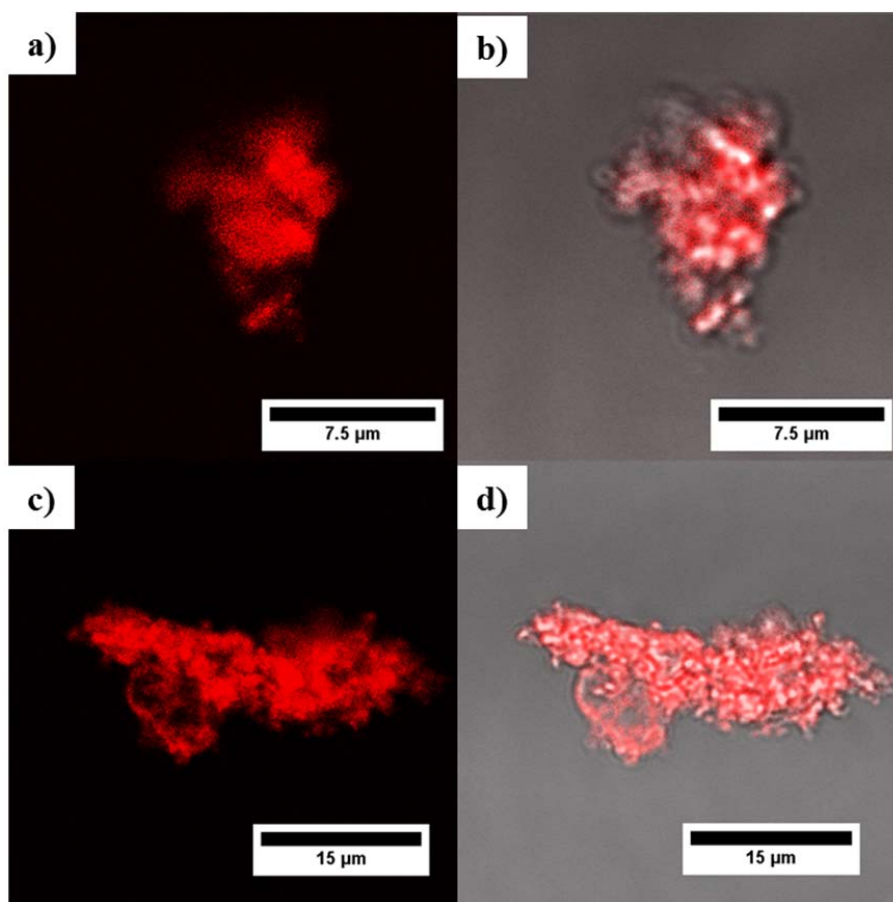


Figure S14. Confocal micrographs a) and c) and corresponding DIC micrographs b) and d) of aggregates of crosslinked PEO-*b*-P(VP-*co*-VIm) submicron particles stained with Rhodamine B in aqueous solution.

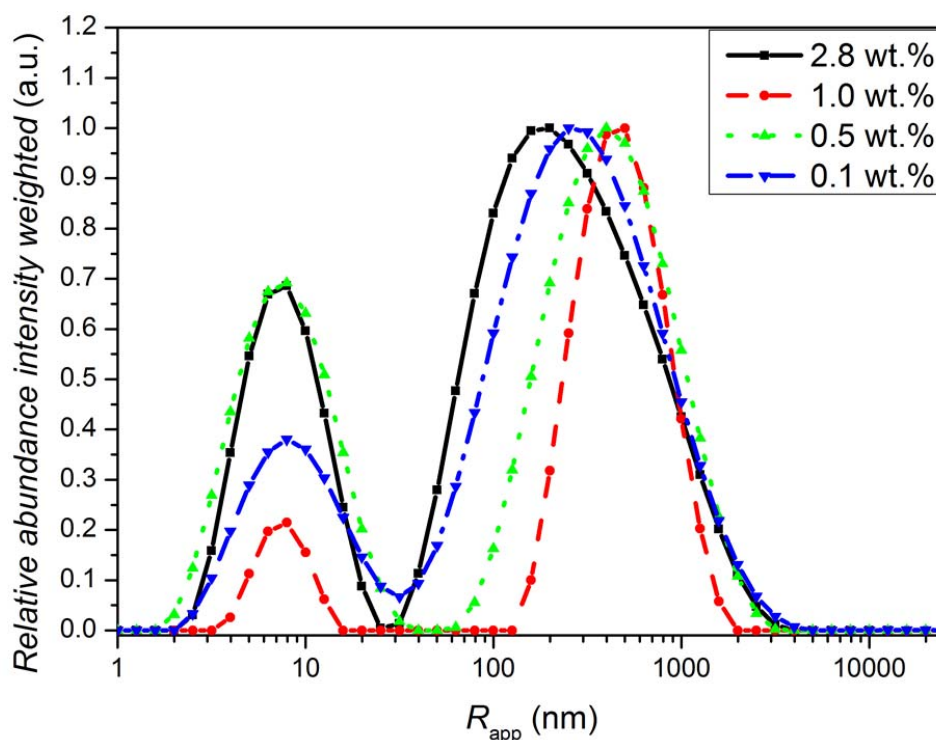


Figure S15. DLS dilution experiment of crosslinked PEO-*b*-P(VP-*co*-VIm) particles in water.

Solution investigations of PEO and PVP homopolymers in DMF

Block copolymers of PEO and PVP turned out to be well soluble in DMF. Therefore, the solubility of the homopolymers in DMF was investigated as well and 2.5 wt.% solutions of the corresponding homopolymers in DMF were analyzed via DLS. As visible from the size distribution curves in Figure S16, the homopolymers dissolve well in DMF and possess an average apparent radius corresponding to the free dissolved polymer chains.

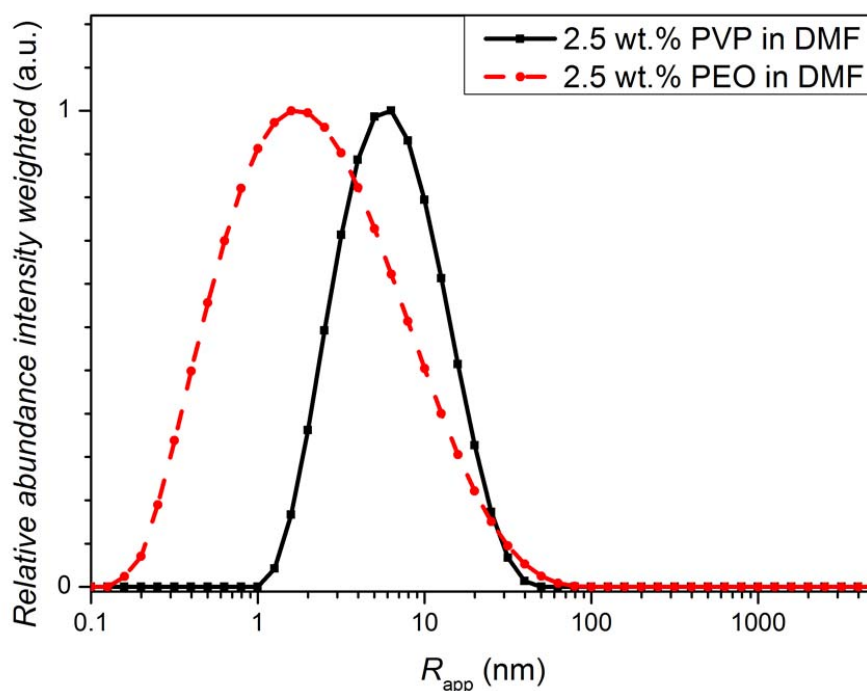


Figure S16. Particle size distributions of PEO and PVP homopolymers in DMF.

Dilution of crosslinked PEO-*b*-P(VP-*co*-VIm) block copolymers in DMF

In order to assess the stability of PEO-*b*-P(VP-*co*-VIm) submicron particles upon dilution in DMF, a 5.0 wt.% solution self-assembled particles was crosslinked according to the previous mentioned procedure and subsequently diluted to 2.5 and 1.0 wt.% solutions. The solutions were then examined via DLS at 25 °C. As visible from the particle size distributions in Figure S17 the average hydrodynamic radii of the self-assembled and crosslinked particles do not change upon increasing dilution. The average hydrodynamic radius maintains in a region between 600 nm and 200 nm.

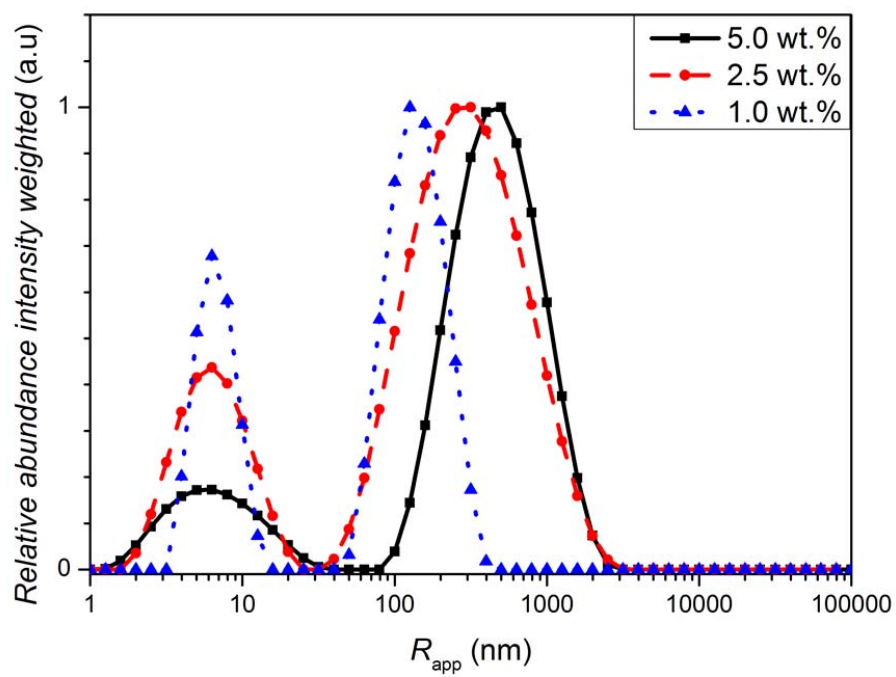


Figure S17. Particle size distributions of diluted PEO-*b*-P(VP-*co*-VIm) block copolymer solutions in DMF after crosslinking.

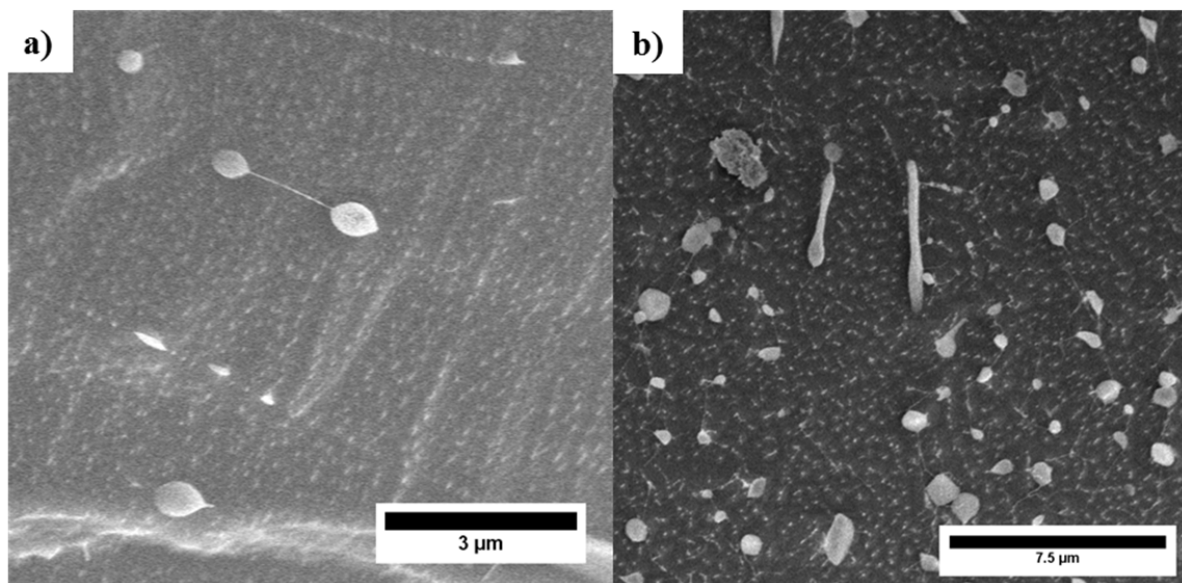


Figure S18 Cryo SEM micrographs displaying a lower magnification of crosslinked PEO-*b*-P(VP-*co*-VIm) submicron particles in a) water and b) DMF.

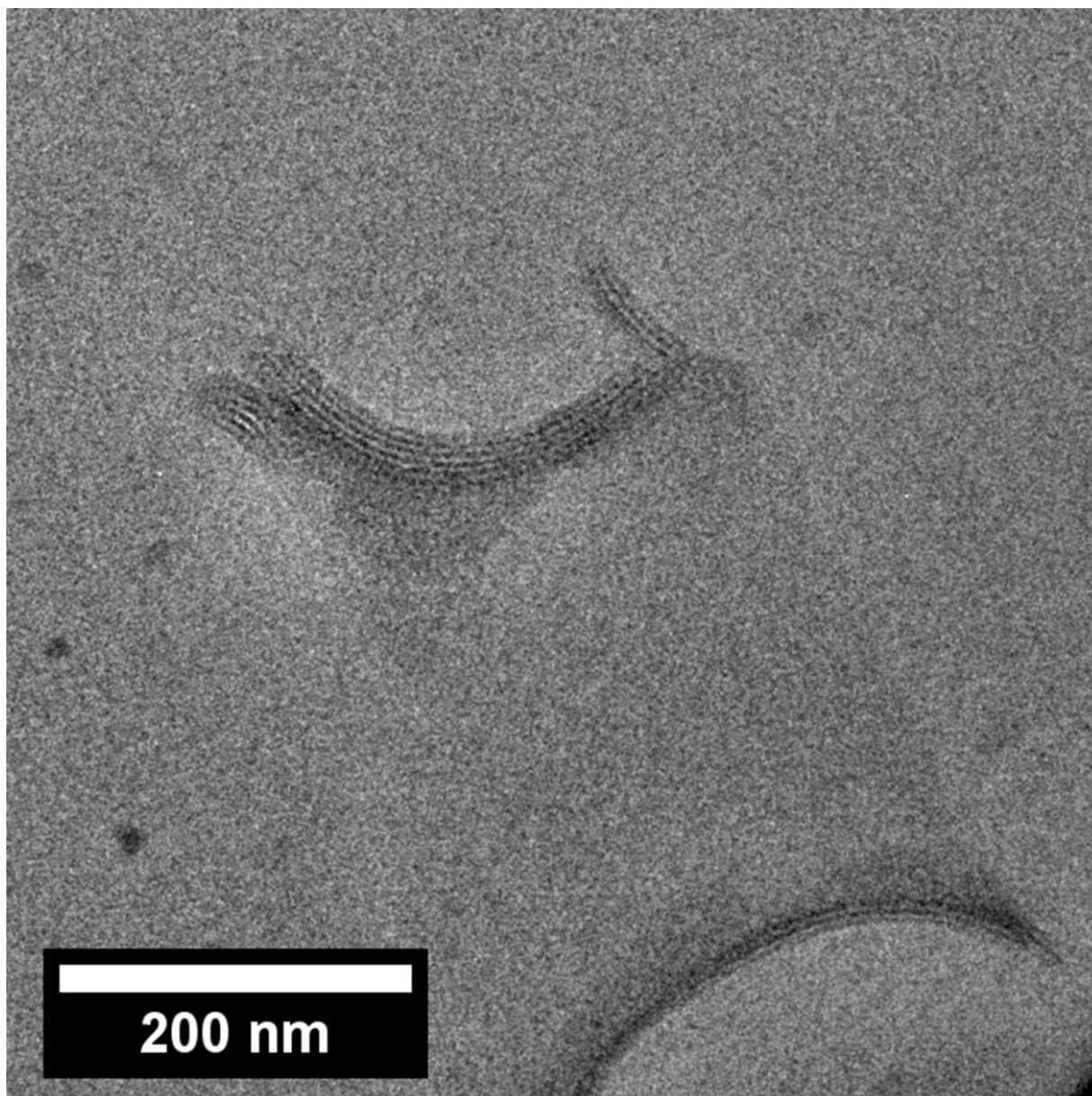


Figure S19. Magnified cryo TEM micrograph displaying complex membrane structures formed from PEO-*b*-P(VP-*co*-VIm). The layers with a stronger contrast correspond to the crosslinked P(VP-*co*-VIm) block. The iodine is responsible for the stronger contrast.

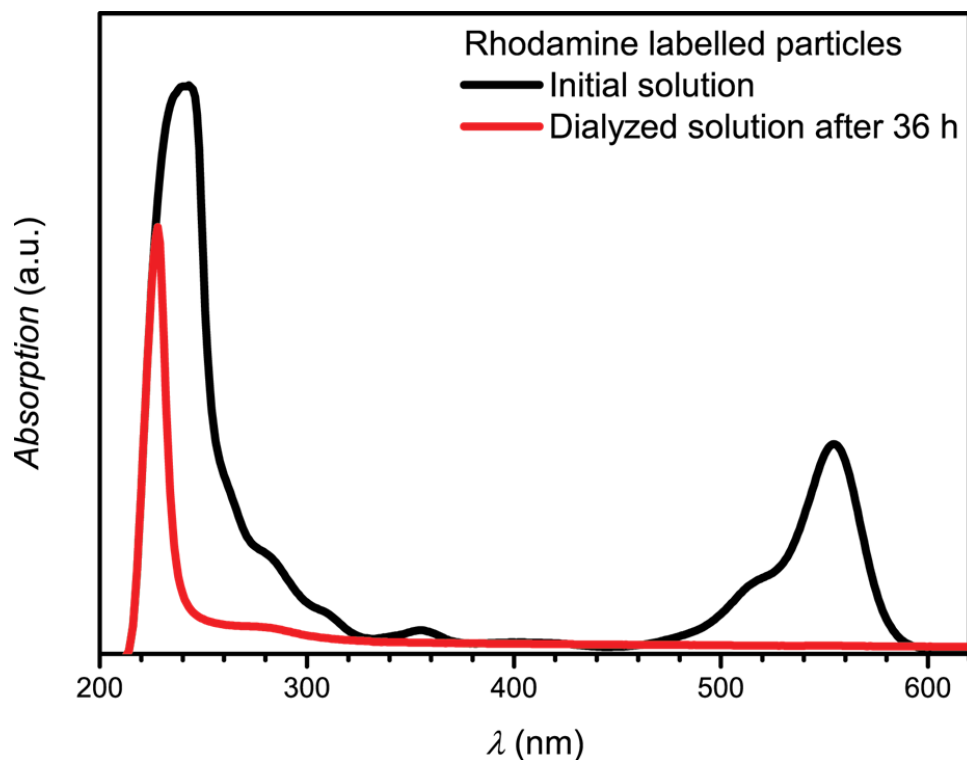


Figure S20. UV-Vis spectra of the Rhodamine B labelled crosslinked PEO-*b*-P(VP-*co*-VIIm) particles before and after dialysis against Millipore water.

LSCM/DIC z-axis scan of Rhodamine B stained PEO-*b*-PVP submicron particles (Video file)

The video displays a z-axis scan through a selected PEO-*b*-PVP submicron particle stained with Rhodamine B. As seen in the video, the particle's spherical structure can be assessed by the concentration of dye at the outside of the membrane. In coincidence to the LSCM micrographs in Figure 1 and Figure S11, the particle interior has a low concentration of dye which is similar to the external solution.

REFERENCES

- (1) Pound, G.; Aguesse, F.; McLeary, J. B.; Lange, R. F. M.; Klumperman, B. Xanthate-mediated copolymerization of vinyl monomers for Amphiphilic and double-hydrophilic block copolymers with poly(ethylene glycol) *Macromolecules* **2007**, *40*, 8861.
- (2) Shao, M.; Dongare, P.; Dawe, L. N.; Thompson, D. W.; Zhao, Y. M. Biscrown-Annulated TTFAQ-Dianthracene Hybrid: Synthesis, Structure, and Metal Ion Sensing *Org. Lett.* **2010**, *12*, 3050.