

Core-cross-linked micelles made by RAFT polymerization with a polycationic outer shell based on poly(1-methyl-4-vinylpyridinium)

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SUPPORTING INFORMATION

Experimental details

Materials and methods. All manipulations were performed by Schlenk-line techniques under an inert atmosphere of dry argon. 4,4'-azobis(4-cyanopentanoic acid) (ACPA, >98%, Fluka), diethylene glycol dimethacrylate (DEGDMA, 95%, Aldrich), 1,3,5-trioxane (>99%, Aldrich), iodomethane (MeI, >98%, Sigma), hydrogen peroxide (H₂O₂, 50% wt in water, Sigma), phosphoric acid (H₃PO₄, 85% wt in water, Sigma), and hydrochloric acid (HCl, 37% wt in water, VWR) were used as received. 4-Vinyl pyridine (4VP, 95%, Sigma) and styrene (St, 99%, Acros) were distilled under reduced pressure prior to use. The RAFT agent 4-cyano-4-thiothiopropylsulfanyl pentanoic acid (CTPPA) or R₀-SC(S)SP_r (R₀ = -C(CH₃)(CN)CH₂CH₂COOH),^{1, 2} and 1-methyl-4-vinylpyridinium iodide (4VPM^{e+}I)³ were prepared according to previously described methods. The deionized water used for the syntheses and DLS analyses was obtained from a Purelab Classic UV system (Elga Lab-Water).

Characterization Techniques

NMR spectroscopy. All nuclear magnetic resonance spectra were recorded in 5 mm diameter tubes at 297 K on a Bruker Avance 400 spectrometer. The ¹H and ¹³C chemical shifts were determined using the residual peak of the deuterated solvent as internal standard and are reported in ppm (δ) relative to tetramethylsilane. Peaks are labelled as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m) and broad (br). For the CCM characterization, the chemical shift scale was calibrated on the basis of the solvent peak (δ 2.50 for DMSO, 3.58 and 1.73 for THF), and 1,3,5-trioxane (δ 5.20) was used as an integration reference. For the synthesis of the P4VP macroRAFT, monomer conversion was followed by ¹H NMR spectroscopy (300 MHz Bruker) in DMSO-*d*₆ at room temperature by the relative integration of the protons of the internal reference (1,3,5-trioxane) at 5.1 ppm and the vinylic protons of 4VP (at 5.4 and 5.9 ppm).

Size exclusion chromatography (SEC). SEC was performed in DMF (with LiBr) at 60 °C at a flow rate of 1.0 mL min⁻¹ by using a Viscotek TDA305 apparatus (SEC-DMF). All polymers were analyzed at a concentration of 3 mg mL⁻¹ after filtration through 0.45 μm pore size membrane. The separation was carried out on three columns from PSS GRAM (7 μ, 300 x 7.5 mm). The setup was equipped with a refractive-index (RI) detector (λ = 670 nm). The average molar masses (number-average molar mass *M*_n and weight-average molar mass *M*_w) and the dispersity (*D* = *M*_w/*M*_n) were derived from the RI signal by a calibration curve based on polystyrene standards (PS from Polymer Laboratories). The software used for data collection and calculation was OmniSec version 4.7 from Malvern Instruments.

Dynamic light scattering (DLS). The intensity-average diameters of the latex particles (*D*_z) and the polydispersity index (PDI) were obtained on a Malvern Zetasizer NanoZS equipped with a He-Ne laser (λ = 633 nm), operating at 25 °C. Samples were analyzed after dilution (with deionized water or ethanol) either unfiltered or after filtration through a 0.45 μm pore-size membrane. The procedure without filtration allowed verification of the presence of agglomerates. Each value was the average of five measurements. In each figure, the curves labelled N, V and I represent the instrumental responses in number, volume and intensity, respectively. The same unfiltered samples were used for zeta potential (ζ) measurement with the same instrument. The measured electrophoretic mobilities were then converted into zeta potentials using Smoluchowski's equation.

Transmission electron microscopy (TEM). The morphological analyses of the copolymer nano-objects were performed either at the Centre Technologique des Microstructures (CTμ), platform of the University Claude Bernard Lyon 1 (Villeurbanne, France) with a Philips CM120 transmission

electron microscope operating at 80 kV, or at the Centre de Microcaractérisation Raimond Castaing (Toulouse France) with a JEOL JEM 1011 transmission electron microscope working at 120 kV. Diluted latex samples were dropped on a formvar/carbon-coated copper grid and dried under vacuum for 48 hours.

Attempted polymerization of 1-methyl 4-vinylpyridinium iodide (4VPMe⁺I). A stock solution of water ACPA/NaHCO₃ was prepared with 5 mL of H₂O and dissolution of ACPA/NaHCO₃ (0.10 g / 0.10 g), [ACPA] = 71.4 mmol L⁻¹. 1-Methyl-4-vinylpyridinium iodide (0.35 g, 1.43 mmol), the CTPPA RAFT agent (7.8 mg, 28.2 μmol) and the degassed ACPA/NaHCO₃ stock solution (0.9 mL, 18 mg ACPA, 64.2 μmol) were dissolved in a mixture of dioxane (2 mL) and water (3 mL) in a Schlenk tube under Ar. The mixture was cooled to 0 °C and degassed with Ar for 40 min. Heating the mixture at 80 °C for 19 h did not lead to any polymerization (absence of monomer conversion evidenced by the NMR analysis).

RAFT polymerization of 4-vinylpyridine. A stock solution containing ACPA (10 mg g⁻¹) and NaHCO₃ (1.5 M) in deionized water was prepared. A portion of this stock solution (0.4 g, 4.2 mg ACPA, 0.0150 mmol), CTPPA (44.2 mg, 0.160 mmol), 4VP (998 mg, 9.49 mmol; 4VP/CTPPA = 59.3), ethanol (1 mL) and deionized water (1.67 mL) were added to a 50 mL flask with a magnetic stirrer bar. 1,3,5-Trioxane (19.0 mg, 0.211 mmol) was also added to the flask as an internal reference for the determination of the monomer conversion as a function of time by ¹H NMR. The solution in the septum-sealed flask was purged for 45 min with argon and then heated to 70 °C during 330 min in a thermostated oil bath under stirring, leading to a 93 % monomer conversion (56 4VP units per chain). Theoretical molar mass for the resulting R₀-4VP₅₆-SC(S)SPr = 6165 g mol⁻¹. SEC (THF): M_n = 5800 g mol⁻¹, D = 1.09.

Attempted chain extension starting from R₀-P4VPMe⁺I-SC(S)SPr.

1. *Preparation of the R₀-(4VPMe⁺I)₅₆-SC(S)SPr macroRAFT agent.* The macroRAFT agent prepared as described above (0.58 g, 0.1 mmol or 5.6 mmol of 4VP units) was dissolved in 10 mL of DMF. Then CH₃I (7.48 g, 52.68 mmol, CH₃I/4VP = ca. 10) was added at room temperature and the resulting solution was stirred overnight. A yellow precipitate was recovered and purified by dialysis against pure water, then dried by freeze-drying. Theoretical molar mass for R₀-(4VPMe⁺I)₅₆-SC(S)SPr = 14114 g mol⁻¹. ¹H NMR in DMSO-*d*₆: δ 8.77 (br) ca. 8 (br.) for the aromatic protons and 4.2 for the methyl protons.

2. *RAFT polymerization of styrene in the presence of R₀-(4VPMe⁺I)₅₆-SC(S)SPr.* The R₀-(4VPMe⁺I)₅₆-SC(S)SPr macroRAFT agent from the previous step (0.14 g, 0.01 mmol), styrene (0.31 g, 2.98 mmol), 0.06 g of the same ACPA solution as described above (10 mg g⁻¹, 0.6 mg ACPA, 0.002 mmol) and 1.41 g of a H₂O/EtOH (70:30, v/v) mixture (~1.5 mL) were added to a 10 mL flask. The mixture was purged with argon at 0 °C for 40 min then heated to 80 °C overnight. The polymerization was quenched by immersion of the flask in iced water. The overall styrene conversion (determined by gravimetric analysis) was < 5%.

Synthesis of R₀-4VP₅₆-*b*-S₂₄₇-SC(S)SPr diblock copolymer in a one-pot two-step process. A P4VP macroRAFT agent was first synthesized as described above (M_n = 5800 g mol⁻¹, D = 1.09). In a separate flask, styrene (4.959 g, 48 mmol) was dispersed in 14.3 g of deionized water and 4.91 g of EtOH, to which was also added the ACPA stock solution (0.4 g containing 4 mg of ACPA, 0.014 mmol). The resulting mixture was purged for 45 min with argon at 0 °C and then injected into the

flask containing the macroRAFT (16.62 mg, 0.16 mmol) under argon at 80 °C. After 3 h, 0.5 mL was withdrawn for analysis and the polymerization was quenched by immersion of the flask in iced water. The overall styrene conversion (82%) was determined by gravimetric analysis. The composition of the resulting R_0 -4VP₅₆-*b*-S₂₄₇-SC(S)SPr product was verified by NMR, SEC and TEM analyses (see Results and Discussion).

Synthesis of the R_0 -(4VPMe⁺I)₁₃₇-*b*-S₃₄₄-SC(S)SPr diblock copolymer. A stock solution of water ACPA/NaHCO₃ was prepared with 5 mL of H₂O and dissolution of ACPA/NaHCO₃ (0.10 g / 0.10 g), [ACPA] = 71.4 mmol L⁻¹.

1. Synthesis of the R_0 -4VP₁₃₇-SC(S)SPr macroRAFT agent. This macroRAFT agent was synthesized as described above, using an ACPA/NaHCO₃ stock solution (1.0 mL, 20 mg ACPA, 71.4 μmol), CTPPA (0.11 g, 0.39 mmol), 1,3,5-trioxane (internal standard, 0.49 g, 5.44 mmol) and degassed 4VP (5.89 mL, 5.74 g, 54.6 mmol; 4VP/CTPPA = 140), in 15 mL of a degassed H₂O/EtOH mixture (70:30 v/v) (total volume = 21.9 mL). The reaction took 7 h at 80 °C to reach 98% 4VP conversion. Aliquots were withdrawn periodically for monitoring by ¹H NMR in DMSO-*d*₆. This yields a polymer with average composition R_0 -4VP₁₃₇-SC(S)SPr (Theoretical molar mass = 14681 g mol⁻¹).

*2. MacroRAFT chain extension with styrene. Preparation of R_0 -4VP₁₃₇-*b*-S₃₄₄-SC(S)SPr.* To the solution of R_0 -4VP₁₃₇-SC(S)SPr obtained in the previous step were successively added degassed styrene (15.7 mL, 14.2 g, 136.5 mmol, S/macroRAFT = 350), the degassed ACPA/NaHCO₃ stock solution (7.0 mL, 140 mg ACPA, 499.5 μmol) and 47 mL of a degassed H₂O/EtOH mixture (70:30 v/v). The resulting reaction mixture (total volume = 92.1 mL) was stirred at 80 °C for 3 h. Aliquots were withdrawn periodically for monitoring by ¹H NMR in DMSO-*d*₆. Styrene consumption was almost complete (98.4%) and was accompanied by transformation of the initial suspension into a stable latex as a white opalescent stable dispersion. Theoretical molar mass for R_0 -4VP₁₃₇-*b*-S₃₄₄-SC(S)SPr = 50526 g mol⁻¹.

*3. Methylation of the poly(4-vinylpyridine) block. Preparation of R_0 -(4VPMe⁺I)₁₃₇-*b*-S₃₄₄-SC(S)SPr.* In a 250 mL round-bottom flask, the total volume of the R_0 -4VP₁₃₇-*b*-S₃₄₄-SC(S)SPr latex obtained above (0.39 mmol of polymer, corresponding to 53.4 mmol of 4VP units) was diluted with DMF (90 mL) and CH₃I (33.2 mL, 75.8 g, 534 mmol, ca. 10 equiv. vs. 4VP) was slowly added *via* syringe. The reaction mixture was then stirred at room temperature for 86.5 h, yielding a yellowish suspension. Vacuum filtration left the product as a yellow paste, which was further washed with distilled water (5 x 20 mL) and then extensively dried under vacuum, to afford 33.3 g of a yellow gummy solid, [R_0 -(4VPMe⁺I)₁₃₇-*b*-S₃₄₄-SC(S)SPr]·24(DMF) (molar mass = 71726 g mol⁻¹). The amount of residual DMF was determined by ¹H NMR in DMSO-*d*₆ (Figure S8). The sticky nature of the polymer rendered the washing, mother liquor decanting and drying processes rather problematic.

Preparation of a latex of a P4VPMe⁺I-*b*-PS amphiphilic block copolymer in four steps. A stock solution of water ACPA/NaHCO₃ was prepared with 5 mL of H₂O and dissolution of ACPA/NaHCO₃ (0.10 g / 0.10 g), [ACPA] = 71.4 mmol L⁻¹.

Step 1: Preparation of R_0 -4VP₁₃₇-SC(S)SPr. This polymer was prepared as described above, from 0.39 mmol of CTPPA in a total volume of 21.9 mL (70:30 v/v H₂O/EtOH mixture), yielding a polymer with theoretical molar mass = 14681 g mol⁻¹.

*Step 2. MacroRAFT chain extension with styrene. Preparation of R_0 -4VP₁₃₇-*b*-S₄₈-SC(S)SPr.* To the solution of R_0 -4VP₁₃₇-SC(S)SPr obtained in the previous step were successively added degassed styrene (2.24 mL, 2.03 g, 19.5 mmol, S/macroRAFT = 50) and the degassed ACPA/NaHCO₃ stock

solution (1.0 mL, 20 mg ACPA, 71.4 μmol). The resulting reaction mixture (total volume = 25.1 mL) was stirred at 80 °C for 4.5 h. Aliquots were withdrawn periodically for monitoring by ^1H NMR in $\text{DMSO-}d_6$. Styrene consumption was almost complete (98%) and was accompanied by transformation of the initial suspension into a stable latex of $\text{R}_0\text{-4VP}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$ macromolecules, self-assembled in the form of micelles to yield a white opalescent stable dispersion (DLS: $D_z = 24.4$ nm; PDI = 0.14). At this stage, the NMR spectrum in $\text{DMSO-}d_6$ allowed to determine the styrene conversion (97.5%), while the use of CDCl_3 ($\text{CDCl}_3/\text{H}_2\text{O}$ emulsion) allowed verifying the molar 4VP/S ratio per chain (ca. 3:1), which approximates the theoretical value (137/48). Molar mass calculated for $\text{R}_0\text{-4VP}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr} = 19683$ g mol^{-1} . The theoretical total polymer mass obtained was 7.68 g in a total volume of 25.1 mL.

Step 3. Methylation of the poly(4-vinylpyridine) block. Preparation of $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$. In a 250 mL round-bottom flask, the total volume of the $\text{R}_0\text{-4VP}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$ latex obtained in step 2 (0.39 mmol of polymer, corresponding to 53.4 mmol of 4VP units) were diluted with DMF (84 mL) and CH_3I (33.2 mL, 75.8 g, 534 mmol, ca. 10 equiv. vs. 4VP) was slowly added *via* syringe. The reaction mixture was then stirred at room temperature for 117 h, resulting in the formation of yellow precipitate that could be isolated from a yellowish solution by centrifugation. The yellow solid was further washed with DMF (5 x 6.0 mL), followed by diethyl ether (2 x 5.0 mL), and dried under vacuum to afford 8.15 g of a yellow powder, $[\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}] \cdot 38(\text{DMF})$ (formula determined by ^1H NMR in $\text{DMSO-}d_6$, molar mass = 41906 g mol^{-1} , 49.9% yield). All attempts to remove the residual 38 molecules of DMF per polymer chain were unsuccessful.

Step 4. Extension with a polystyrene block. Preparation of $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{345}\text{-SC(S)SPr}$. A portion of the $[\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}] \cdot 38(\text{DMF})$ polymer resulting from step 3 (0.3 g, 7.16 μmol) was dissolved in 6 mL of degassed water under Ar in a Schlenk tube to afford a pale yellow turbid suspension (DLS: $D_z = 276$ nm; PDI = 0.25). To this solution was added 1,3,5-trioxane (2.8 mg, 31.1 μmol) and degassed styrene (0.25 mL, 0.224 g, 2.15 mmol, 300 equiv. per chain). Then the degassed ACPA/ NaHCO_3 stock solution (0.25 mL, 4.9 mg ACPA, 17.5 μmol) was added and the resulting reaction mixture was stirred at 80 °C for 5 h, yielding a white opalescent stable dispersion. Styrene conversion = 99% (by ^1H NMR in $\text{DMSO-}d_6$). The resulting polymer, $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{345}\text{-SC(S)SPr}$, has a theoretical molar mass of 70076 g mol^{-1} . DLS: $D_z = 139.1$ nm, PDI = 0.11.

Cross-linking of the $\text{P4VPMe}^+\text{I-}b\text{-PS}$ amphiphilic block copolymer by DEGDMA.

(a) In the presence of styrene. Preparation of $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{345}\text{-}b\text{-(S}_{157}\text{-}co\text{-DEGDMA}_{13})\text{-SC(S)SPr}$. To the Schlenk tube containing the entire aqueous suspension of the $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{345}\text{-SC(S)SPr}$ polymer, prepared as described in the previous section starting from a $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$ (11.8 μmol) were successively added degassed styrene (0.193 g, 1.85 mmol, 157 equiv. per chain), DEGDMA (37 mg, 0.15 mmol, 13 equiv. per chain), and the degassed ACPA/ NaHCO_3 stock solution (0.5 mL, 10 mg ACPA, 35.7 μmol). The resulting reaction mixture was stirred at 80 °C for 2.5 h. After NMR monitoring ($\text{DMSO-}d_6$), a second (0.1 mL, + 3.5 h at 80 °C) and a third batch of the ACPA/ NaHCO_3 stock solution (0.1 mL, overnight at 80 °C) were added to reach complete conversion of the monomers. The final polymer, $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{345}\text{-}b\text{-(S}_{157}\text{-}co\text{-DEGDMA}_{13})\text{-SC(S)SPr}] \cdot 38(\text{DMF})$ (1.09 g, 12.2 μmol) has a theoretical molar mass of 89406 g mol^{-1} . The polymer content in the latex is 9.7 % w/w. DLS (unfiltered): $D_z = 143$ nm, PDI = 0.09. DLS after swelling with toluene by shaking for < 1 min at r.t. (unfiltered): $D_z = 156$ nm, PDI = 0.04. Volume increase: $(4/3)\pi[(156/2)^3 - (143/2)^3] = 4.57 \cdot 10^5$ nm³ (29.8% of the original volume).

(b) With neat DEGDMA. Preparation of R_0 -(4VPMe⁺I)₁₃₇-*b*-S₃₄₅-*b*-DEGDMA₁₅-SC(S)SPr. A new batch of $[R_0$ -(4VPMe⁺I)₁₃₇-*b*-S₃₄₅-SC(S)SPr]·38(DMF) polymer (7.16 μmol) was prepared as described above. To the Schlenk tube containing the entire aqueous suspension were successively added DEGDMA (25.9 mg, 0.107 mmol, 15 equiv. per chain), and the degassed ACPA/NaHCO₃ stock solution (0.08 mL, 1.7 mg ACPA, 6.07 μmol). The resulting reaction mixture was stirred at 80 °C for 5 h resulting in nearly complete monomer consumption (< 1% by ¹H NMR monitoring in DMSO-*d*₆) to yield $[R_0$ -(4VPMe⁺I)₁₃₇-*b*-S₃₄₅-*b*-DEGDMA₁₅-SC(S)SPr]·38(DMF). The polymer content in the latex is 7.9 % w/w. DLS (unfiltered): $D_z = 148$ nm, PDI = 0.09. DLS after swelling with toluene by shaking for < 1 min at r.t. (unfiltered): $D_z = 162$ nm, PDI = 0.10. Volume increase: $(4/3)\pi[(162/2)^3 - (148/2)^3] = 5.28 \cdot 10^5$ nm³ (23.7% of the original volume).

Preparation of a latex of a P4VPMe⁺I-*b*-PS amphiphilic nanogel copolymer.

(a) Without pre-heating. A R_0 -(4VPMe⁺I)₁₃₇-*b*-S₄₈-SC(S)SPr macroRAFT agent was first synthesized as described above. To the Schlenk tube containing a suspension of the precursor (7.16 μmol) in 6 mL of H₂O were successively added degassed styrene (0.25 mL, 0.224 g, 2.15 mmol, 300 equiv. per chain), DEGDMA (25.9 mg, 0.107 mmol, 15 equiv. per chain), and the degassed ACPA/NaHCO₃ stock solution (0.5 mL, 10 mg ACPA, 35.7 μmol). The resulting reaction mixture was stirred at 80 °C for 17 h to reach complete conversion of all monomers (¹H NMR monitoring in DMSO-*d*₆) and yield $[R_0$ -(4VPMe⁺I)₁₃₇-*b*-S₄₈-*b*-(St₃₀₀-*co*-DEGDMA₁₅)-SC(S)SPr]·38(DMF). The polymer content in the latex is 7.6 % w/w. DLS (filtered through a 0.45 μm pore filter): $D_z = 84.7$ nm (PDI = 0.05).

(b) With pre-heating. A second polymerization was carried out starting from the same macroRAFT agent and using the same amounts of all reagents. The only different is that the ACPA stock solution was not introduced initially. The reaction mixture was pre-heated with stirring at 80 °C for 30 min. A sample of this mixture was withdrawn and used for a DLS analysis ($D_z = 107.0$ nm, PDI = 0.10). The ACPA solution was then introduced and stirring was continued at 80 °C for 4 h (complete monomer consumption). The polymer content in the latex is 7.6 % w/w. DLS (unfiltered): $D_z = 101.4$ nm, PDI = 0.06. DLS after swelling with toluene by shaking for < 1 min at r.t. (unfiltered): $D_z = 110.5$ nm, PDI = 0.15. Volume increase: $(4/3)\pi[(110.5/2)^3 - (101.4/2)^3] = 1.61 \cdot 10^5$ nm³ (29.4% of the original volume).

Table S1. List of all polymers synthesized in this study and reference to their characterization.

Formula	SEC	NMR	DLS	TEM
R ₀ -4VP ₅₆ -SC(S)SPr	Figure S1	Figure 1a		
R ₀ -(4VPMe ⁺ I) ₅₆ -SC(S)SPr		Figure 1b		
R ₀ -4VP ₅₆ - <i>b</i> -S ₂₄₇ -SC(S)SPr	Figure S2		Figure 2a	Figure 2b
R ₀ -4VP ₁₃₇ -SC(S)SPr	Figure S3	Figure S4		
R ₀ -4VP ₁₃₇ - <i>b</i> -S ₃₄₄ -SC(S)SPr		Figure S5	Figure S6	Figure S6
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₃₄₄ -SC(S)SPr		Figure S8	Figure 3a	Figure 3b
R ₀ -4VP ₁₃₇ - <i>b</i> -S ₄₈ -SC(S)SPr	Figure S10	Figure S11, Figure S12	Figure S13	Figure S13
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₄₈ -SC(S)SPr		Figure S14, Figure S15	Figure S16	Figure S16
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₄₈ - <i>b</i> -S ₂₉₇ -SC(S)SPr		Figure S17	Figure 4, Figure S18-21	Figure S18
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₃₄₅ - <i>b</i> -(S ₁₅₇ - <i>co</i> -DEGDMA ₁₃)-SC(S)SPr		Figure S22, Figure 5	Figure 6a,b Figures S23-24	Figure 6c
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₃₄₅ -SC(S)SPr			Figure S25	
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₃₄₅ - <i>b</i> -DEGDMA ₁₅ -SC(S)SPr		Figure S26, Figure S27	Figure 7a,b, Figure S28-29	Figure 7c
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₄₈ - <i>b</i> -(S ₃₀₀ - <i>co</i> -DEGDMA ₁₅)-SC(S)SPr (direct heating with ACPA)		Figure S30	Figure S31	Figure S32
R ₀ -(4VPMe ⁺ I) ₁₃₇ - <i>b</i> -S ₄₈ - <i>b</i> -(S ₃₀₀ - <i>co</i> -DEGDMA ₁₅)-SC(S)SPr (ACPA addition after thermal equilibration)		Figure S33	Figure 8a-c, Figure S34-35	Figure 8d

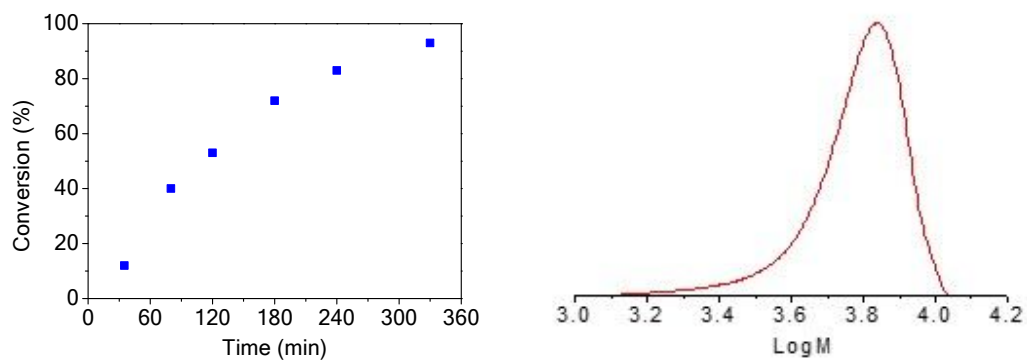


Figure S1. Conversion vs time curve for the RAFT polymerization of 4VP at 70 °C and SEC chromatogram of the resulting R_0 -4VP₅₆-SC(S)SPr.

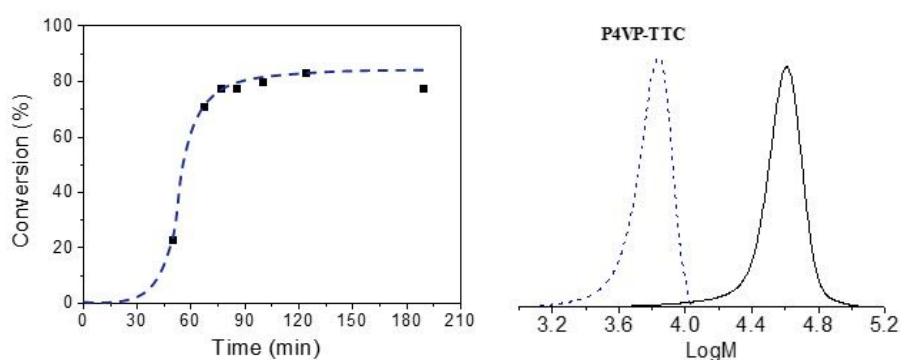


Figure S2. Conversion vs time curve for RAFT polymerization of styrene in H₂O/EtOH (70/30, v/v) mixture at 80 °C using the R_0 -4VP₅₆-SC(S)SPr macroRAFT agent (experimental points and arbitrary smoothed dashed line) and SEC chromatograms for the R_0 -4VP₅₆-SC(S)SPr macroRAFT and the R_0 -4VP₅₆-*b*-S₂₄₇-SC(S)SPr copolymer.

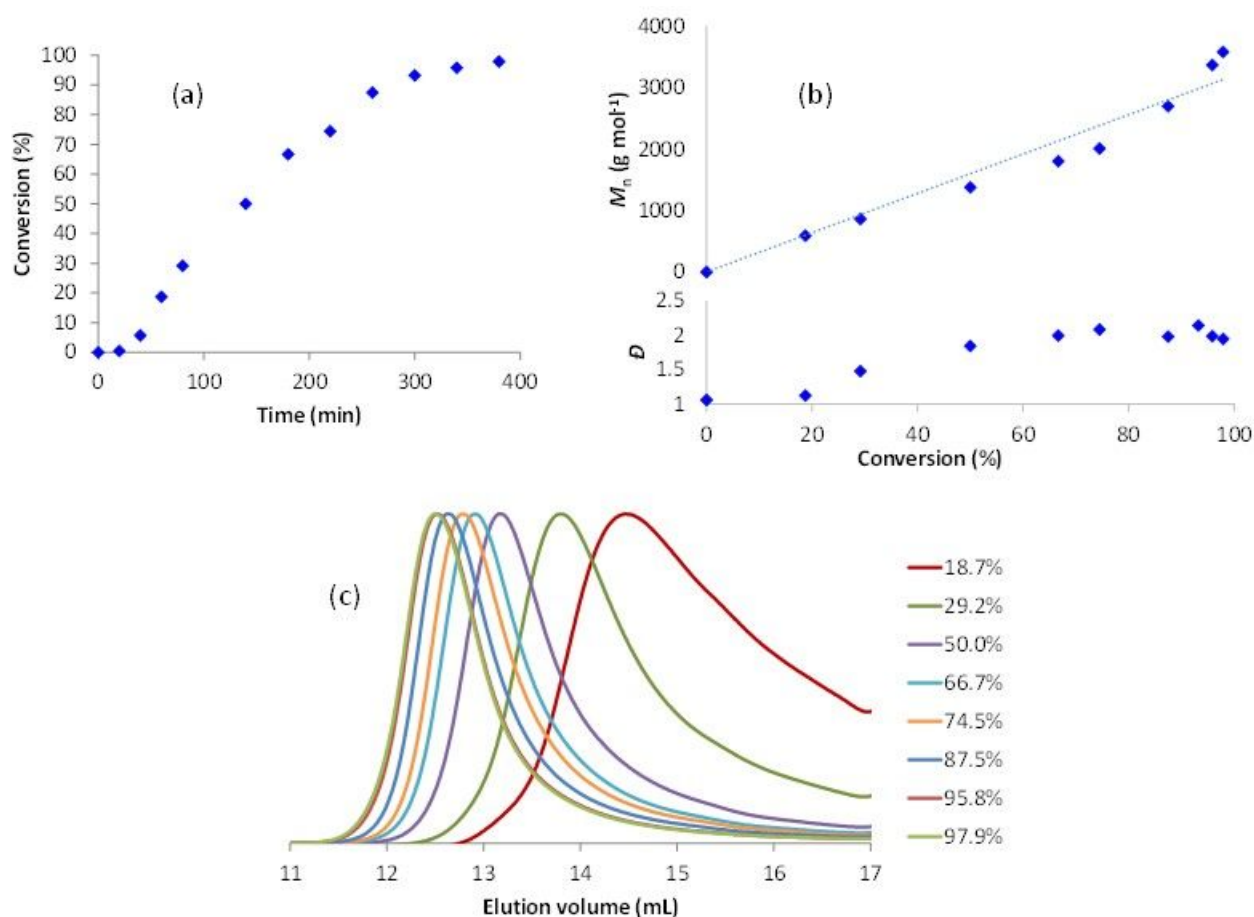


Figure S3. Synthesis of R_0 -4VP₁₃₇-SC(S)SPr: (a) monitoring (from the ¹H NMR data) of the monomer consumption; (b) evolution of the molar mass and D vs. conversion from the SEC analysis in DMF with added LiBr. (c) SEC traces evolution with conversion.

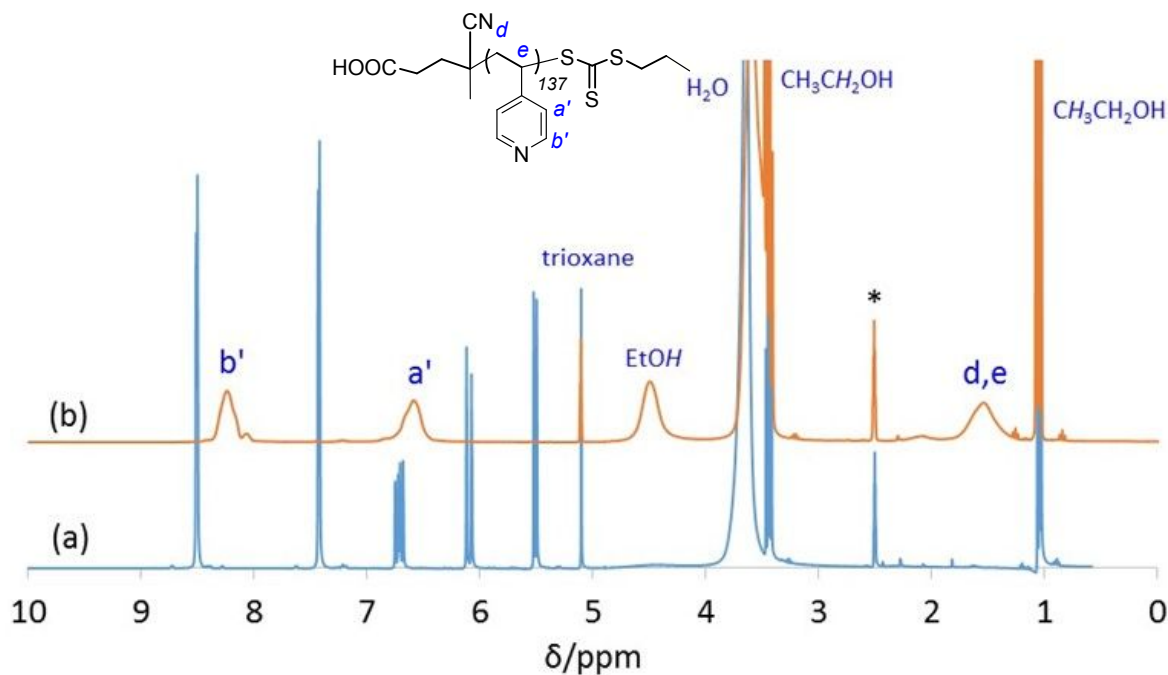


Figure S4. ¹H NMR spectra taken during the formation of R_0 -(4VP)₁₃₇-SC(S)SPr at $t = 0$ (a, blue) and 20 h (b, orange) by diluting an aliquot of the reaction mixture in DMSO- d_6 . The starred resonance

is due to the solvent. The CTPPA resonances are not observed at $t = 0$ because the compound is not soluble at room temperature.

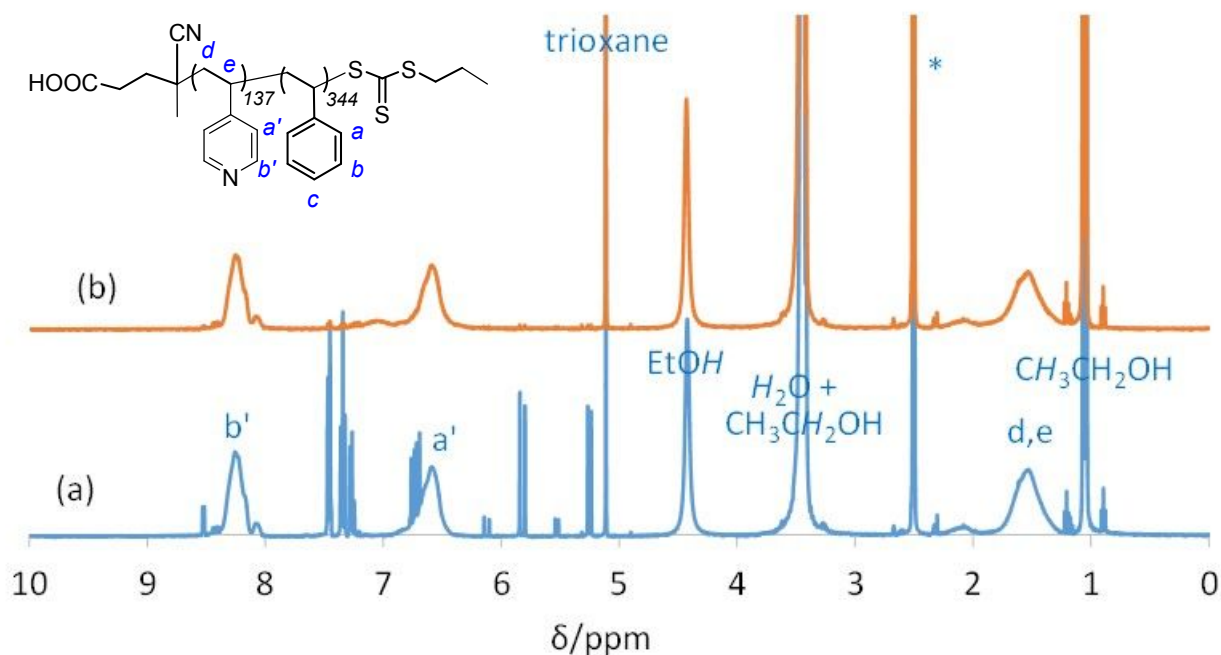


Figure S5. ^1H NMR spectra taken during the formation of $\text{R}_0\text{-4VP}_{137}\text{-}b\text{-S}_{344}\text{-SC(S)SPr}$ at $t = 0$ (a, blue) and 100 min (b, orange) by adding an aliquot of the reaction mixture to $\text{DMSO-}d_6$. The starred resonances are due to the NMR solvent. The PS block is not solvated by $\text{DMSO/EtOH/H}_2\text{O}$ and thus it is not visible in this solvent combination. Conversion = 98.4% (from the residual styrene resonances integrals). Unfortunately, neither CDCl_3 nor C_6D_6 was able to solvate the PS block.

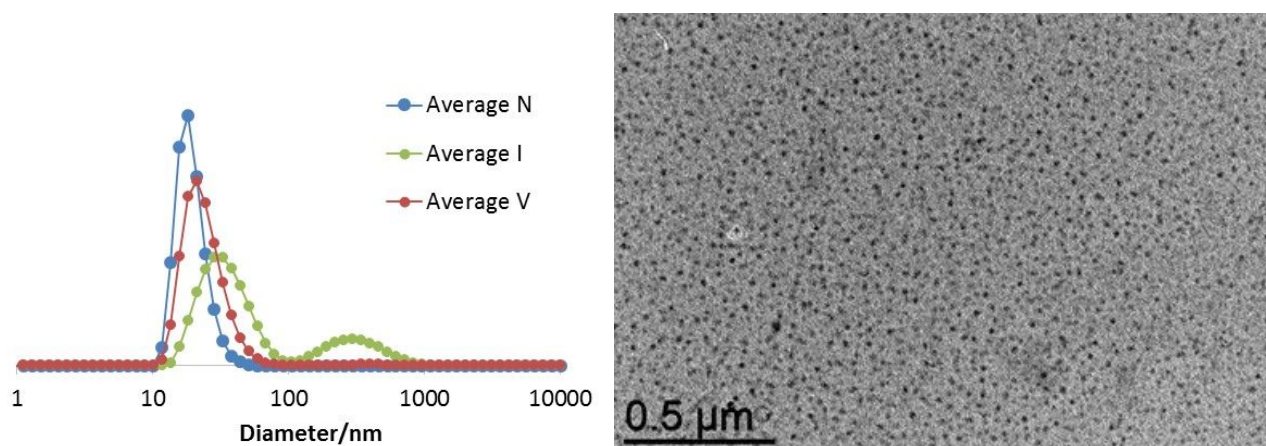


Figure S6. DLS in 75:25 water-EtOH (unfiltered sample, $D_z = 63$ nm, PDI = 0.39) (left) and TEM (right) characterization of the $\text{R}_0\text{-4VP}_{137}\text{-}b\text{-S}_{344}\text{-SC(S)SPr}$ latex.

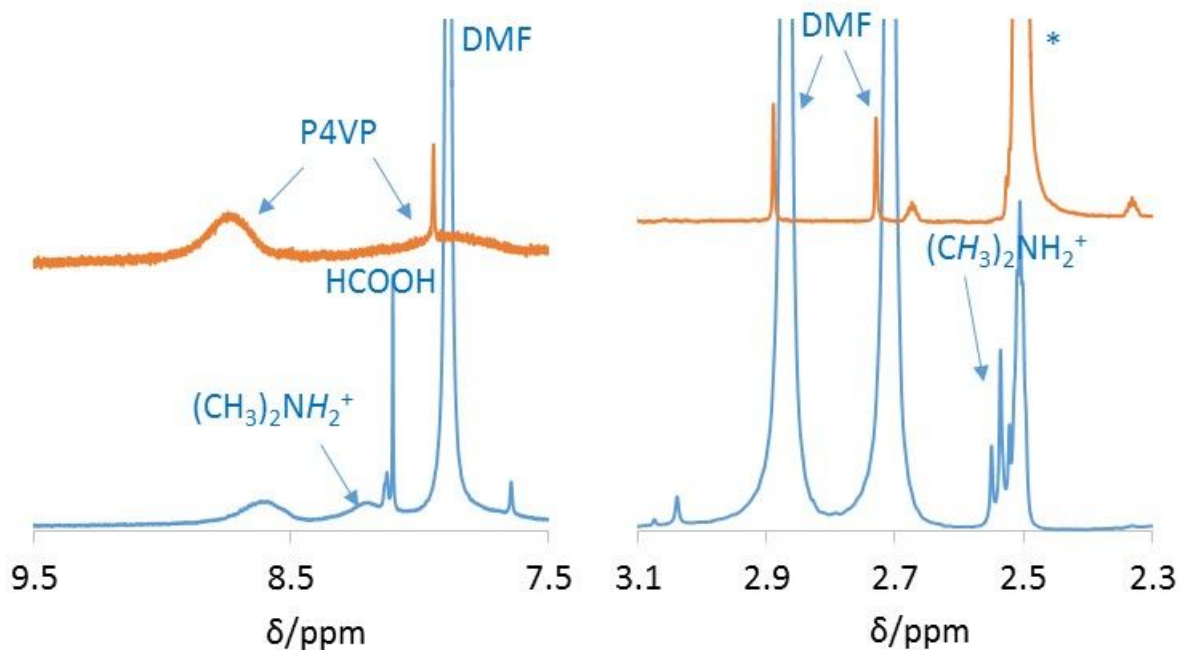


Figure S7. Excerpt in selected regions of the ^1H NMR spectra in $\text{DMSO-}d_6$ of $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{344}\text{-SC(S)SPr}$. Below (blue): crude reaction mixture; above (orange): isolated polymer after washing with DMF (full spectrum in Figure S8). The starred resonance with accompanying spinning side bands is due to the solvent.

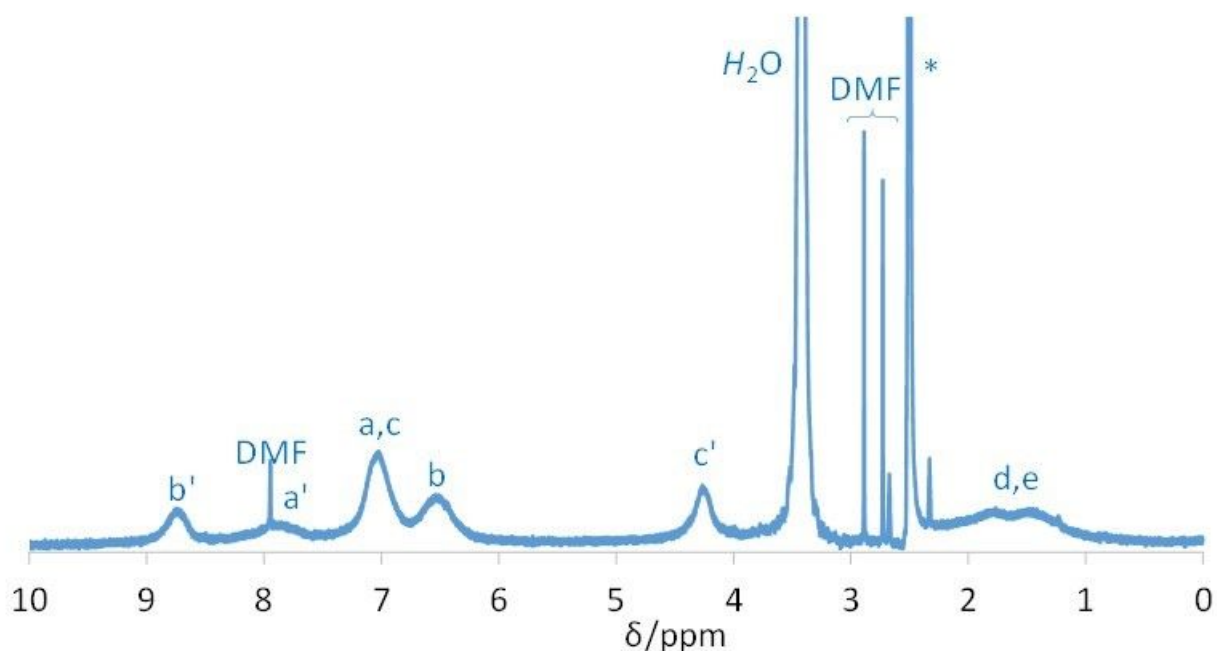


Figure S8. ^1H NMR spectrum in $\text{DMSO-}d_6$ of $[\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{344}\text{-SC(S)SPr}]\cdot 24(\text{DMF})$. The starred resonance with accompanying spinning side bands is due to the solvent. Note that the PS block is visible for this polymer in neat $\text{DMSO-}d_6$, presumably thanks to the presence of DMF, whereas it is not visible for the $\text{R}_0\text{-(4VP)}_{137}\text{-}b\text{-S}_{344}\text{-SC(S)SPr}$ precursor in a $\text{DMSO-}d_6/\text{EtOH}/\text{H}_2\text{O}$ mixture (Figure S5b).

Control experiments for the generation of Me_2NH_2^+ from the reaction of MeI with DMF in water.

No reaction takes place between DMF and water in the absence of acidity. The addition of MeI to water or to water-EtOH mixtures does not generate acidity (e.g. HI) because of immiscibility. However, the addition of a Brønsted acid (HCl or HI) to an aqueous solution of DMF induces hydrolysis of DMF with generation of Me_2NH_2^+ and formic acid (HCOOH), Figure S9. The alternative addition of MeI equally generates the Me_2NH_2^+ ion, formic acid and MeOH, plus a small amount of methyl formate, which led us to propose the mechanism shown in Scheme S1 for the action of MeI. The hydrolysis promoted by MeI generates HI, which then takes over to promote faster hydrolysis with formation of formic acid and methanol.

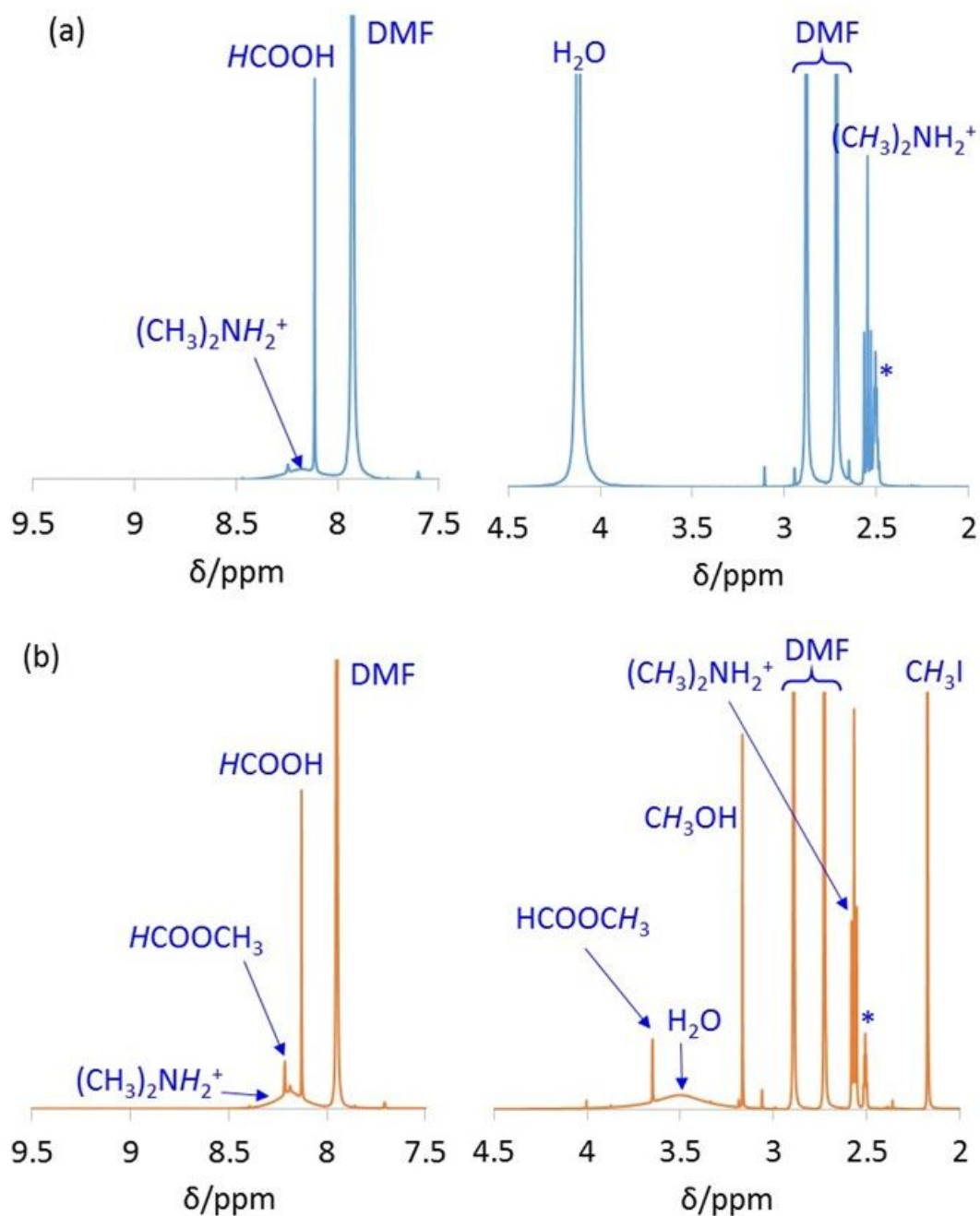


Figure S9. ^1H NMR spectra in $\text{DMSO-}d_6$ of the products obtained from the hydrolysis of DMF in water promoted by (a) HI and (b) MeI.

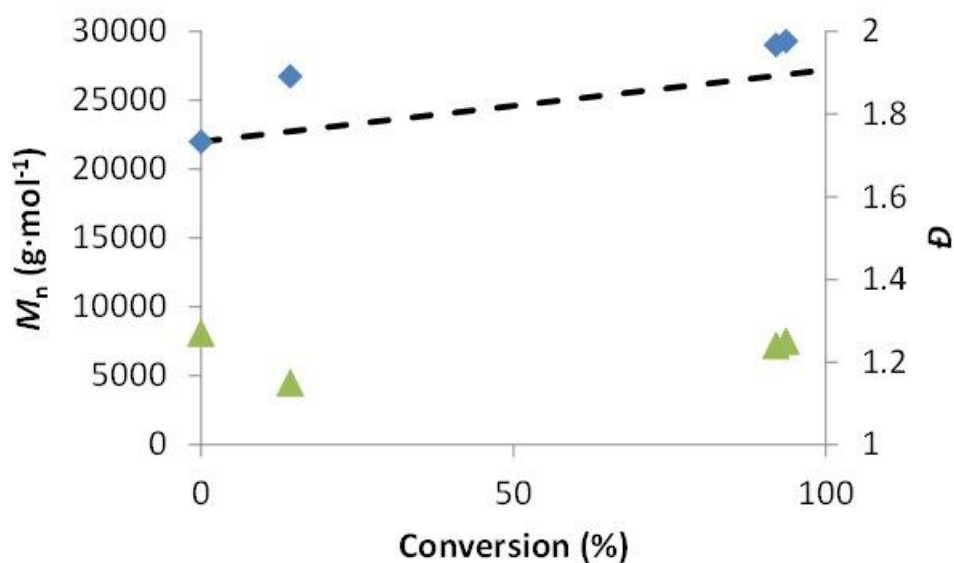


Figure S10. Molar mass and dispersity as a function of conversion, from the SEC monitoring, for the chain extension of the R_0 -4VP₁₃₇-SC(S)SPr macroRAFT agent leading to R_0 -4VP₁₃₇-*b*-S₄₈-SC(S)SPr.

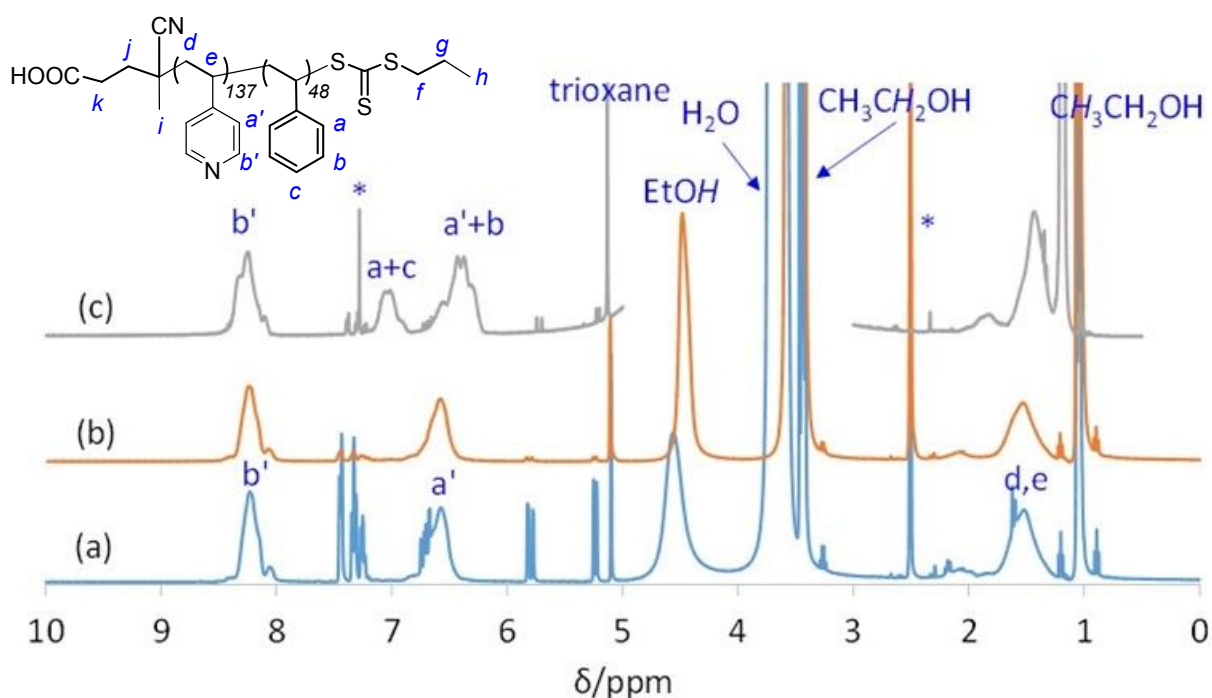


Figure S11. ¹H NMR spectra taken during the formation of R_0 -4VP₁₃₇-*b*-S₄₈-SC(S)SPr at $t = 0$ (a, blue) and 4.5 h by adding an aliquot of the reaction mixture to DMSO-*d*₆ (b, orange) or to CDCl₃ (c, grey). The starred resonances are due to the NMR solvent, DMSO-*d*₆ in (a) and (b), CDCl₃ in (c). The PS block is solvated by CDCl₃ (c) but not by DMSO/EtOH (b) and thus it is not visible in this solvent combination. Conversion = 97.5% (from the residual styrene resonances integrals). By relative integration of the broad resonances attributed to P4VP (8.25 ppm and 7.02 ppm) and PSt + P4VP (6.56-6.30 ppm) in CDCl₃, the 4VP/S ratio is approx. 3:1, which is in agreement with the expected value.

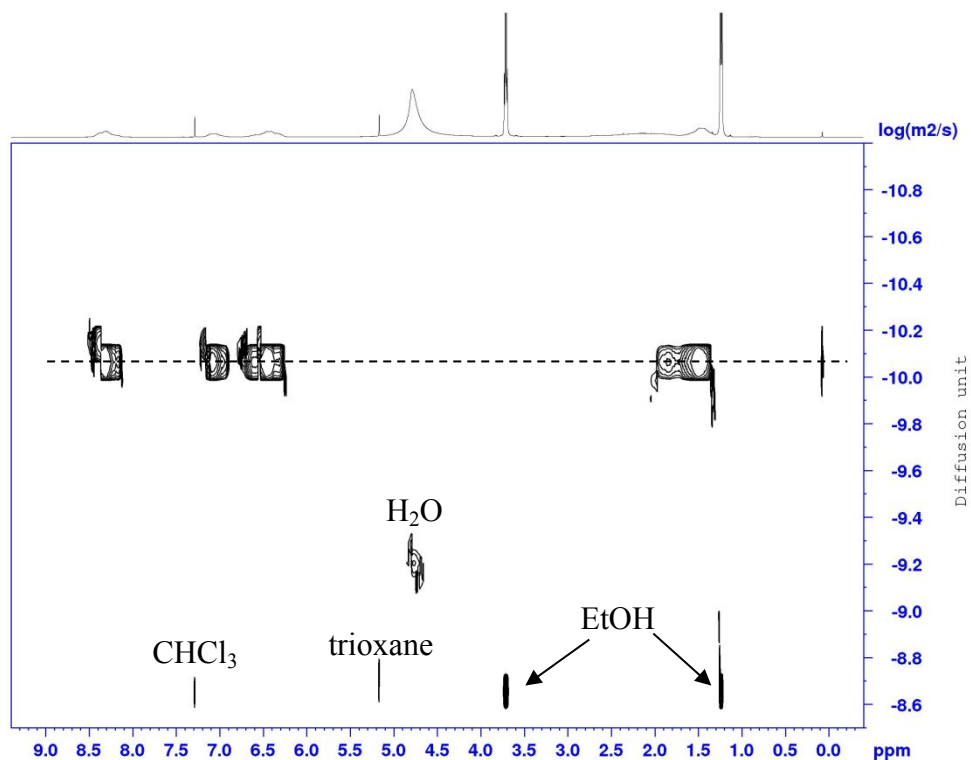


Figure S12. ^1H DOSY NMR spectrum of $\text{R}_0\text{-4VP}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$ in CDCl_3 .

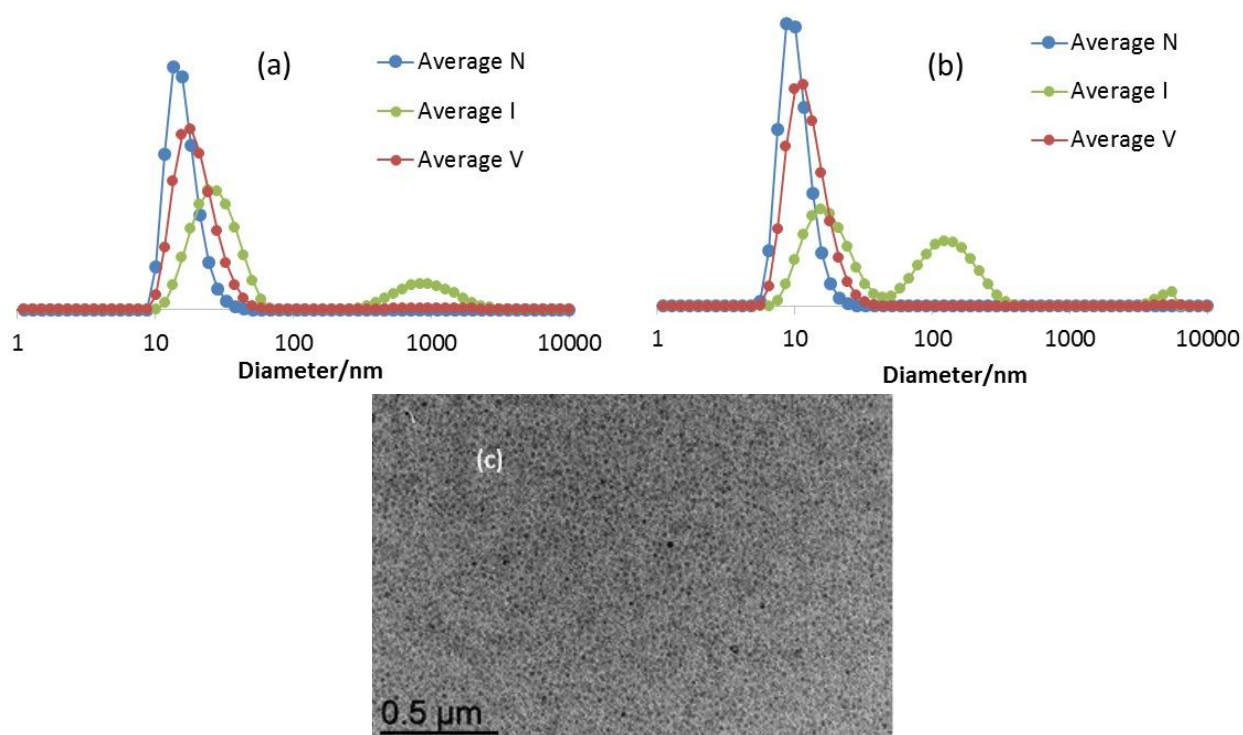


Figure S13. DLS and TEM characterization of the $\text{R}_0\text{-4VP}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$ latex. (a) DLS in ethanol (unfiltered sample, $D_z = 24.4$ nm and $\text{PDI} = 0.14$); (b) DLS in 75:25 water-ethanol (unfiltered sample, $D_z = 30.0$ nm and $\text{PDI} = 0.48$); (c) TEM.

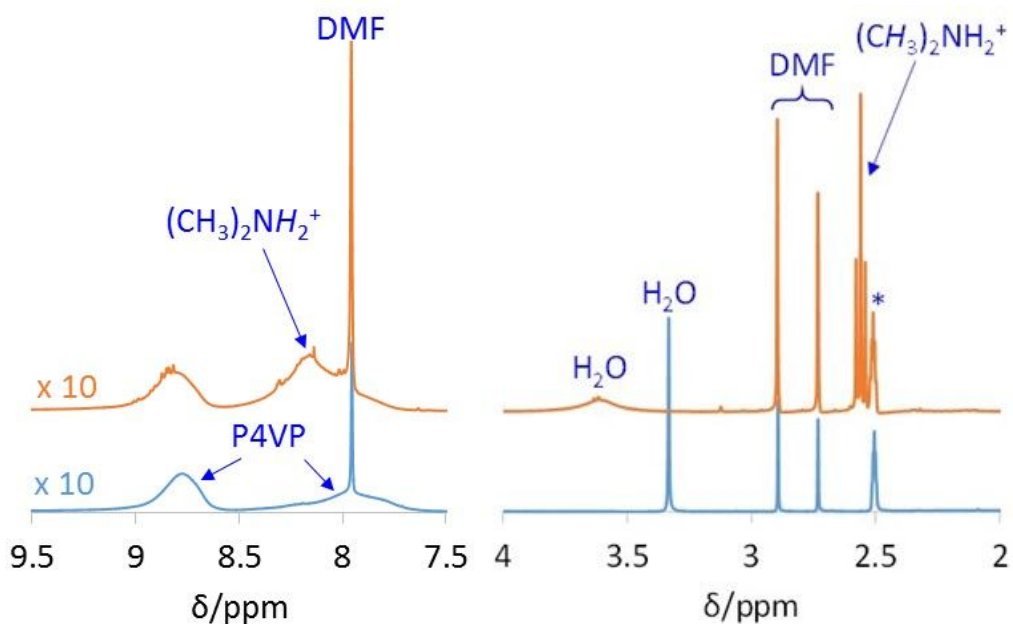


Figure S14. Excerpt in selected regions of the ^1H NMR spectra in $\text{DMSO-}d_6$ of $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$. Above (orange): crude reaction mixture; below (blue): isolated polymer after washings with DMF and ether (full spectrum in Figure S15). Note how the water resonance is displaced and broadened by the presence of Me_2NH_2^+ .

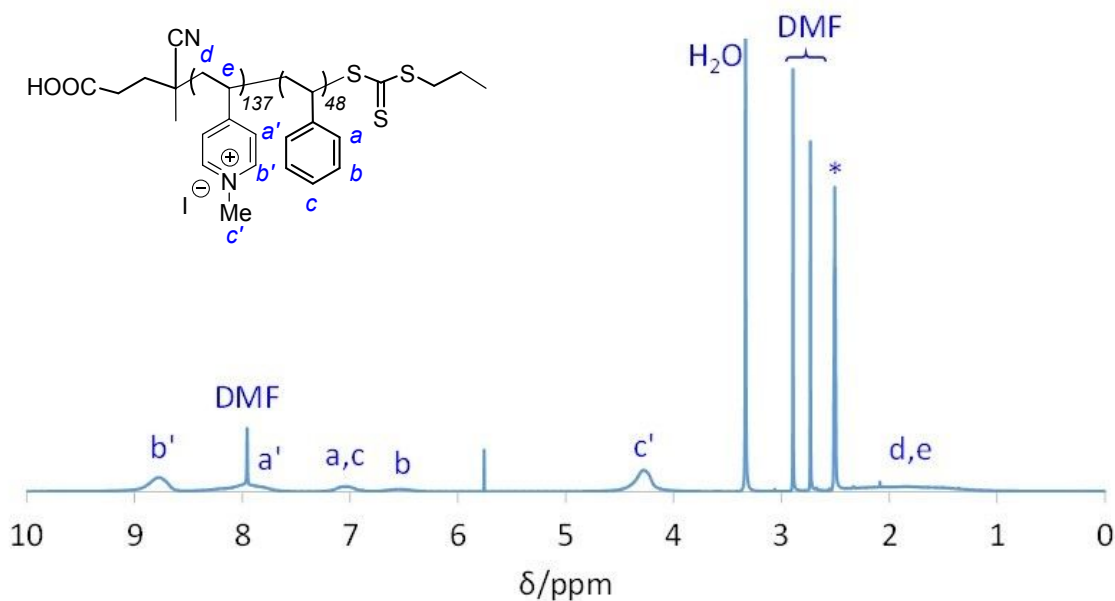


Figure S15. ^1H NMR spectrum in $\text{DMSO-}d_6$ of $[\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}] \cdot 38(\text{DMF})$. The starred resonance is due to the solvent. Once again, the PS block is visible for this polymer in neat $\text{DMSO-}d_6$, like for the analogous polymer with a longer PSt block in Figure S8, whereas it is not visible for the $\text{R}_0\text{-(4VP)}_{137}\text{-}b\text{-S}_{48}\text{-SC(S)SPr}$ precursor in a $\text{DMSO-}d_6/\text{EtOH}$ mixture (Figure S5b).

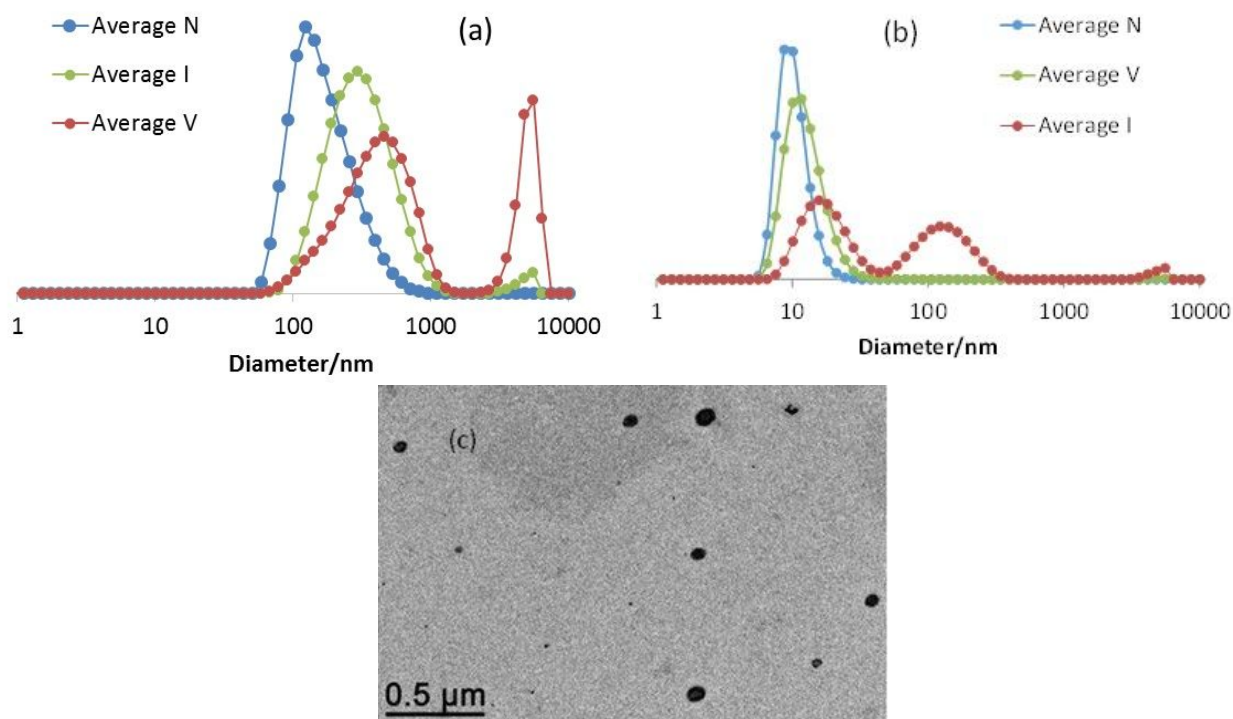


Figure S16. DLS and TEM characterization of the $[R_0-(4VPMe^+I)_{137}-b-S_{48}-SC(S)SPr]$ latex. (a) DLS in water (unfiltered, $D_z = 276$ nm, PDI = 0.25); (b) DLS in 75:25 water-EtOH (unfiltered; $D_z = 30.0$ nm, PDI = 0.48). (c) TEM of a sample deposited from a suspension in 100% water.

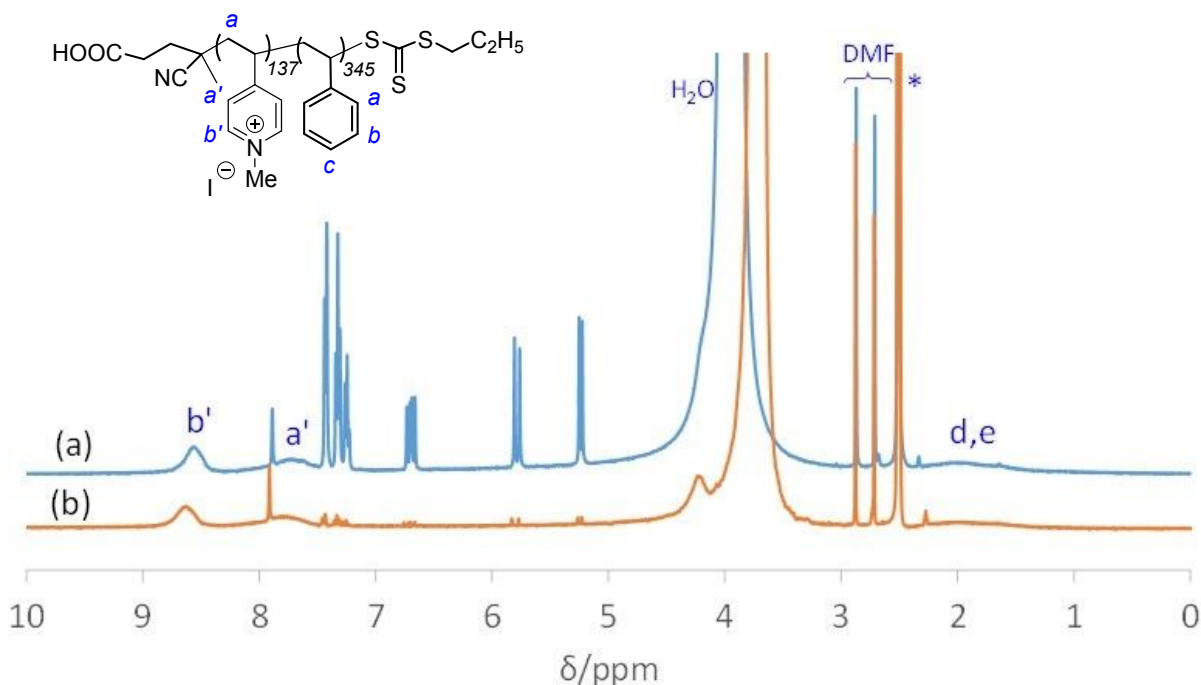


Figure S17. 1H NMR monitoring (in $DMSO-d_6$) of the styrene consumption in the chain extension of $R_0-(4VPMe^+I)_{137}-b-S_{48}-SC(S)SPr$, leading to $[R_0-(4VPMe^+I)_{137}-b-S_{345}-SC(S)SPr] \cdot 38(DMF)$: initial spectrum (a, blue spectrum); final spectrum (99% monomer conversion, b, orange spectrum). The starred resonance is due to the solvent. The resonances of the polystyrene core are not visible because it is not swollen by $DMSO/H_2O$.

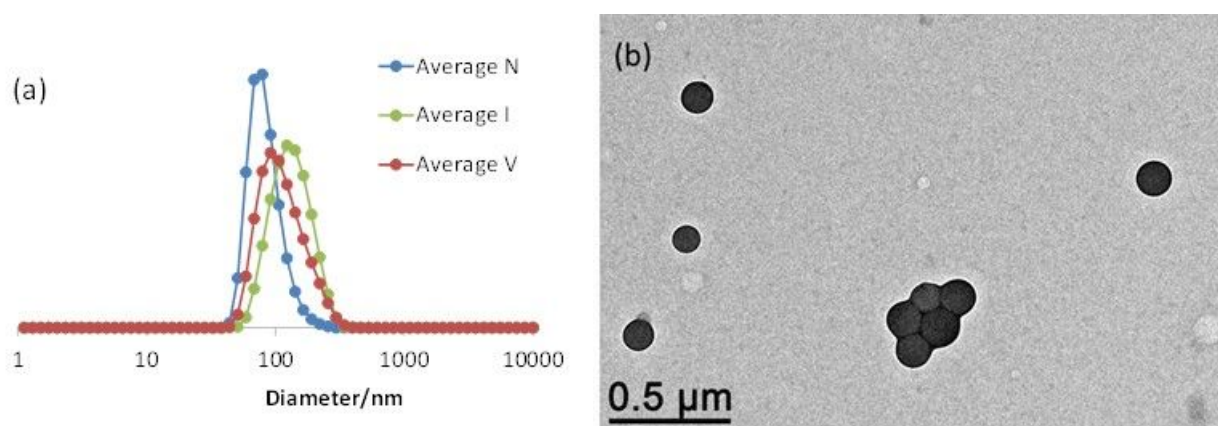


Figure S18. DLS (a, unfiltered sample) and TEM (b) characterization of the R_0 -(4VPM e^+I) $_{137}$ - b -S $_{48}$ - b -S $_{297}$ -SC(S)SP r latex ($D_z = 115.9$ nm, PDI = 0.06).

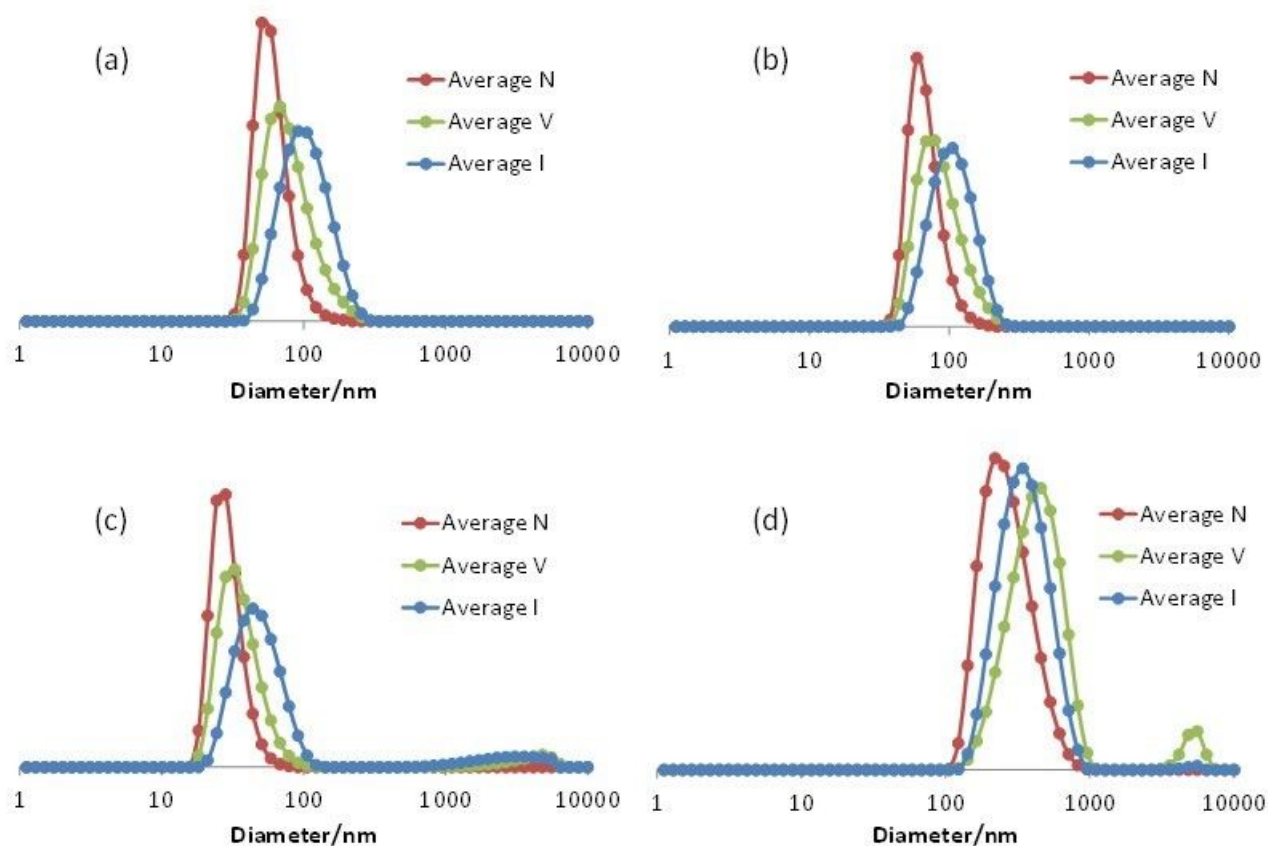


Figure S19. DLS study of a R_0 -(4VPM e^+I) $_{140}$ - b -S $_{50}$ - b -S $_{297}$ -SC(S)SP r polymer latex: (a) as synthesized ($D_z = 94.6$ nm; PDI = 0.14); (b) after swelling with toluene at room temperature ($D_z = 98.2$ nm; PDI = 0.10); (c) as (a), after heating for 24 h at 90 °C ($D_z = 48.5$ nm; PDI = 0.03); (d) as (b), after heating for 18 h at 80 °C ($D_z = 312.6$ nm; PDI = 0.17). All measurements were carried out on unfiltered samples.

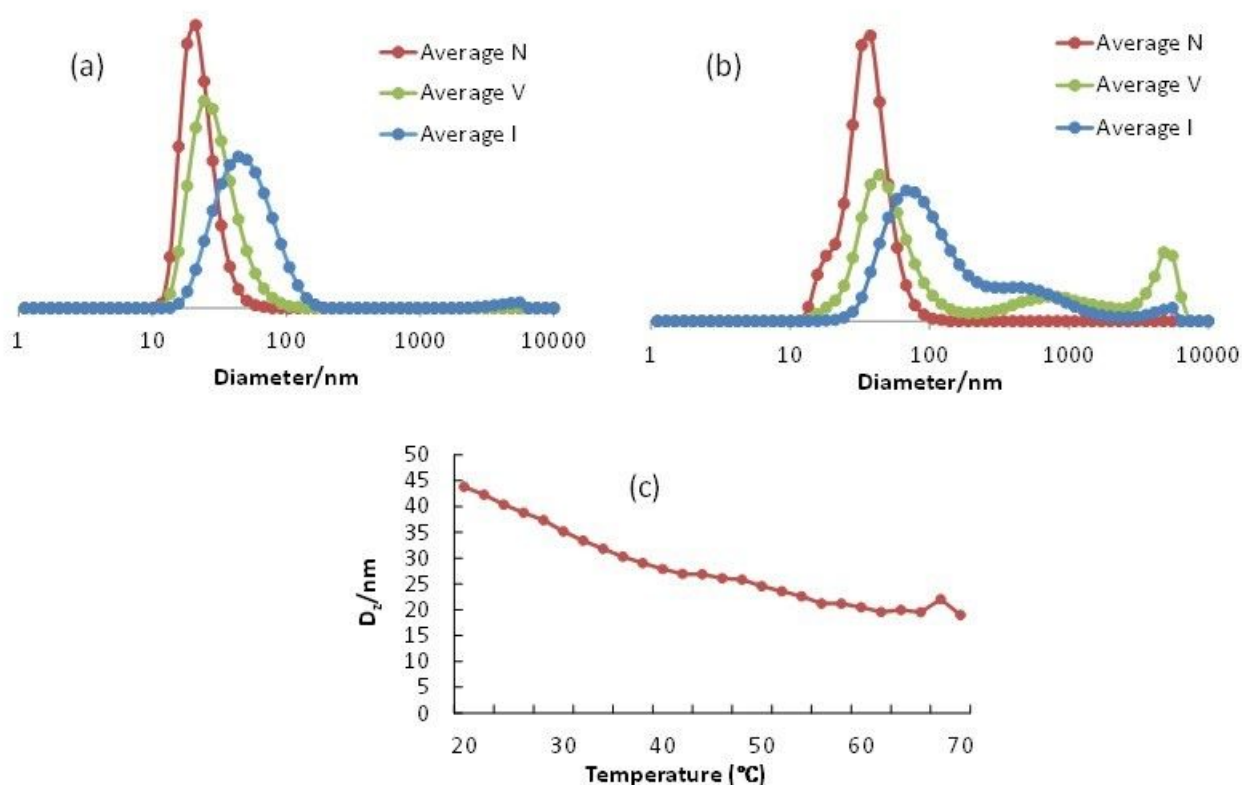


Figure S20. DLS of R_0 -(4VPMe⁺I)₁₃₇-*b*-S₄₈-*b*-S₂₉₇-SC(S)SPr: (a) after freeze-drying and dispersion in DMSO at room temperature ($D_z = 43.8$ nm, PDI = 0.22); (b) after heating for 24 h at 90 °C ($D_z = 96.2$ nm, PDI = 0.42); (c) dependence of D_z on temperature (measurements were carried out on the same solution kept in a thermostatic DLS cell, using a 2 minute equilibration time and 5 measurements at each temperature).

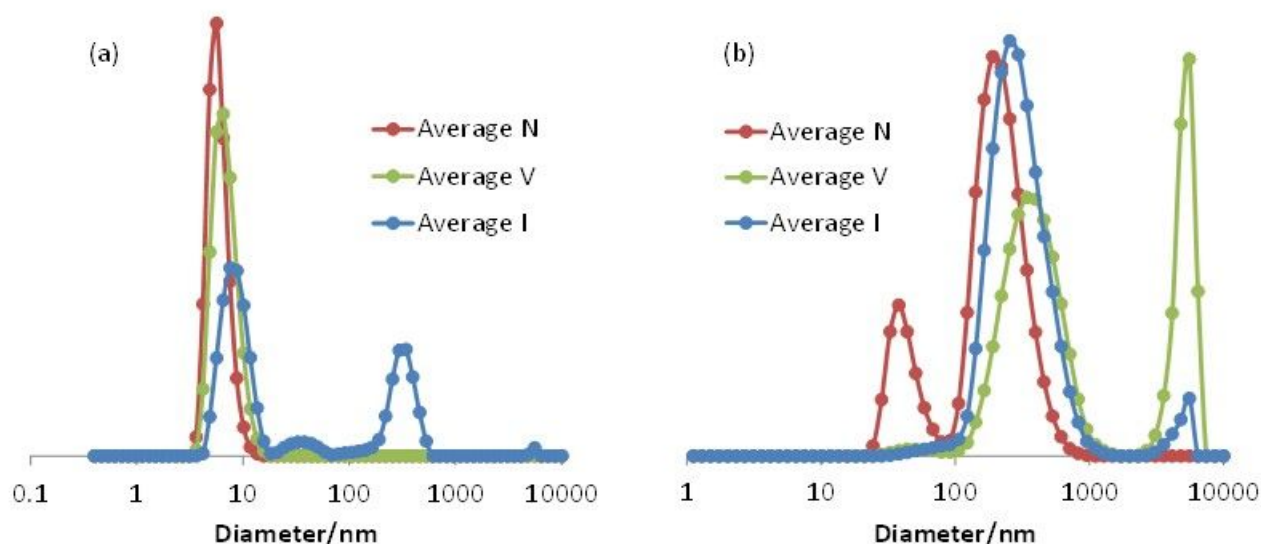


Figure S21. (a) DLS of R_0 -S₂₆₃-SC(S)SPr in toluene; (b) DLS of R_0 -(4VPMe⁺I)₁₃₇-*b*-S₄₈-*b*-S₂₉₇-SC(S)SPr after freeze-drying, dispersion in a DMSO/toluene 80:20 (v/v) mixture, and heating for 24 h at 90 °C ($D_z = 253.7$ nm, PDI = 0.36). Both samples were unfiltered.

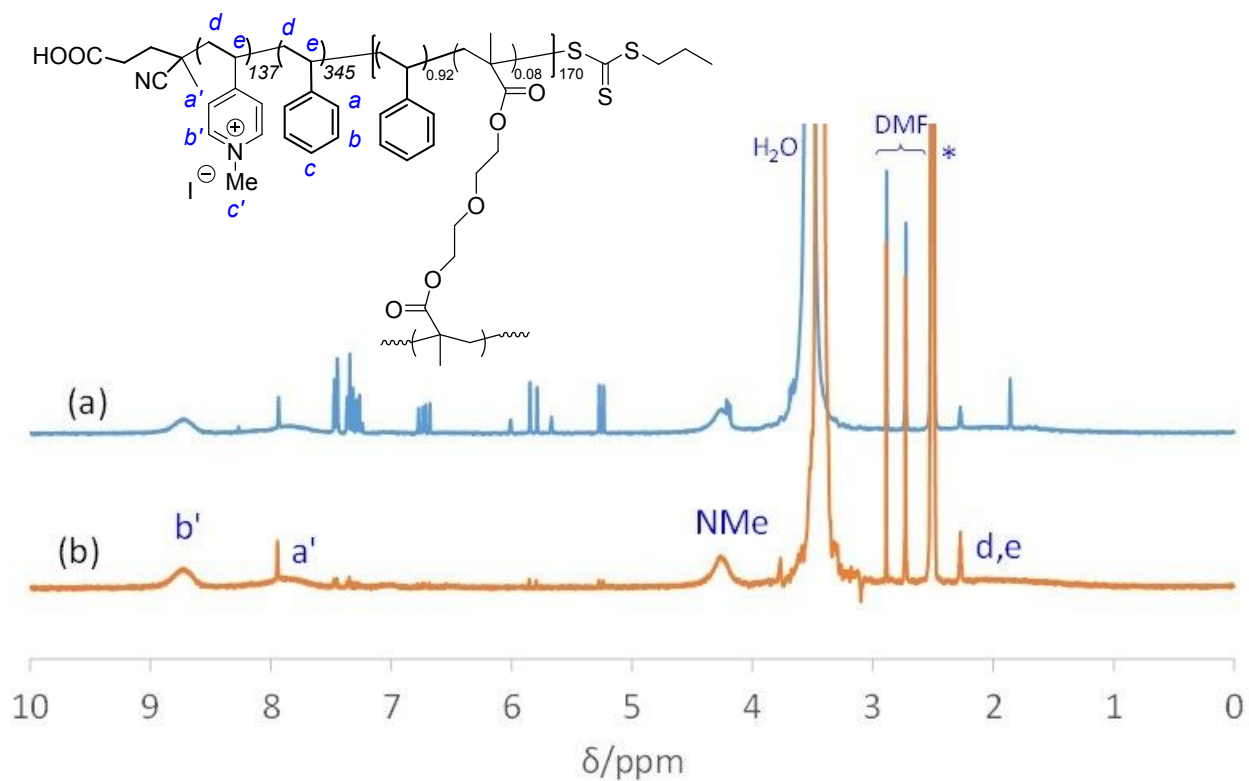


Figure S22. ^1H NMR monitoring (in $\text{DMSO-}d_6$) of the styrene/DEGDMA consumption in the cross-linking of $\text{R}_0\text{-(4VPMe}^+\text{I}^-)_{137}\text{-}b\text{-S}_{345}\text{-SC(S)SPr}$, leading to $\text{R}_0\text{-(4VPMe}^+\text{I}^-)_{137}\text{-}b\text{-S}_{345}\text{-}b\text{-(S}_{157}\text{-CO-DEGDMA}_{13})\text{-SC(S)SPr}$. (a) initial spectrum; (b) final spectrum (89% conversion). The starred resonance is due to the residual solvent protons. The resonances of the polystyrene core are not visible because the core is not swollen by DMSO.

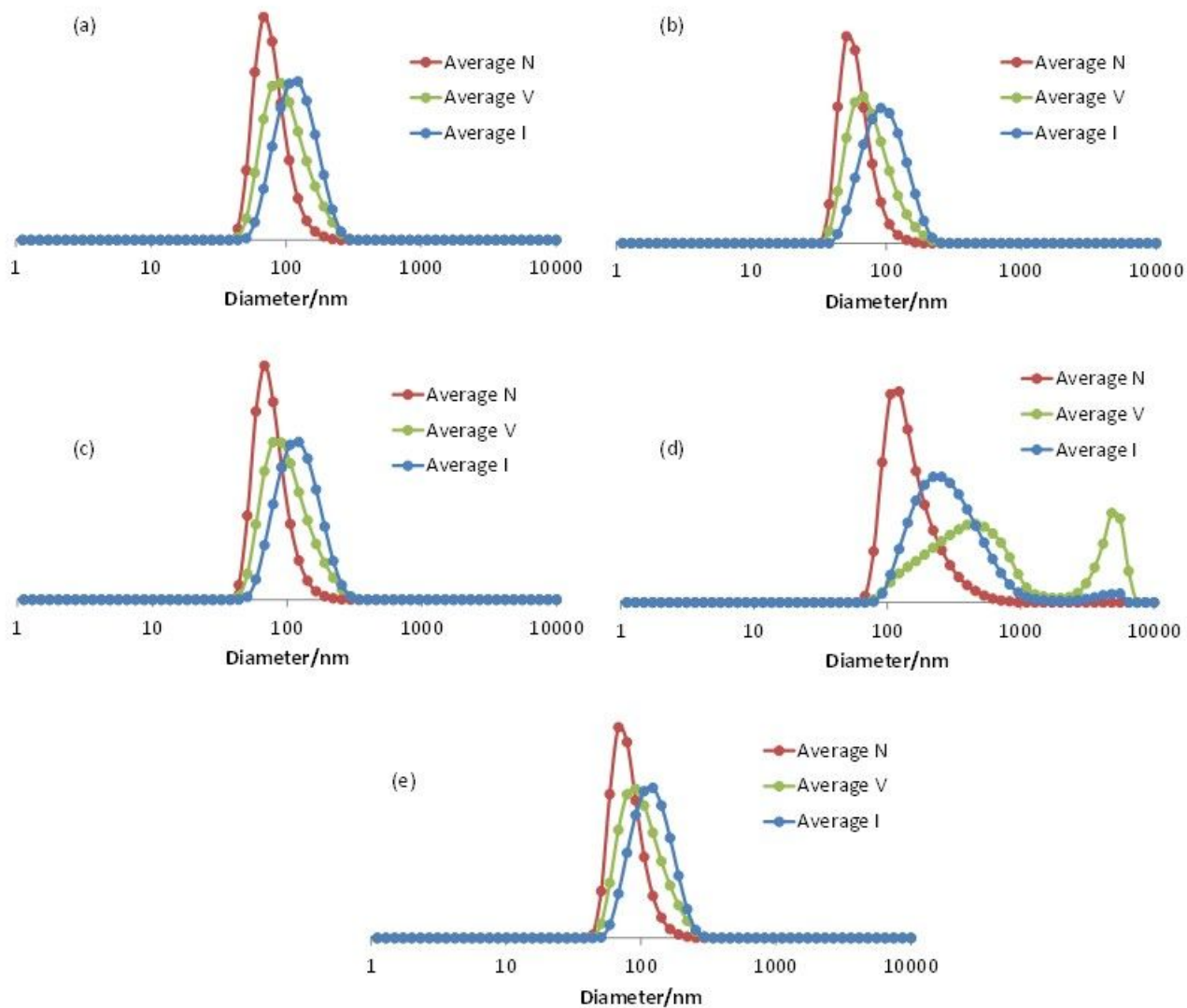


Figure S23. DLS analysis of the R_0 -(4VPMe⁺I⁻)₁₄₀-*b*-S₃₅₀-*b*-(S₁₃₅-*co*-DEGDMA₁₅)-SC(S)SPr latex (a) as synthesized ($D_z = 110.6$, PDI = 0.10); (b) after heating at 90 °C for 24 h ($D_z = 89.7$, PDI = 0.10); (c) swollen with toluene ($D_z = 112.3$, PDI = 0.10); as (c), after heating for 24 h at 90 °C ($D_z = 254.1$, PDI = 0.24); (e) after free-drying and redispersion in water ($D_z = 112.3$ nm, PDI = 0.09).

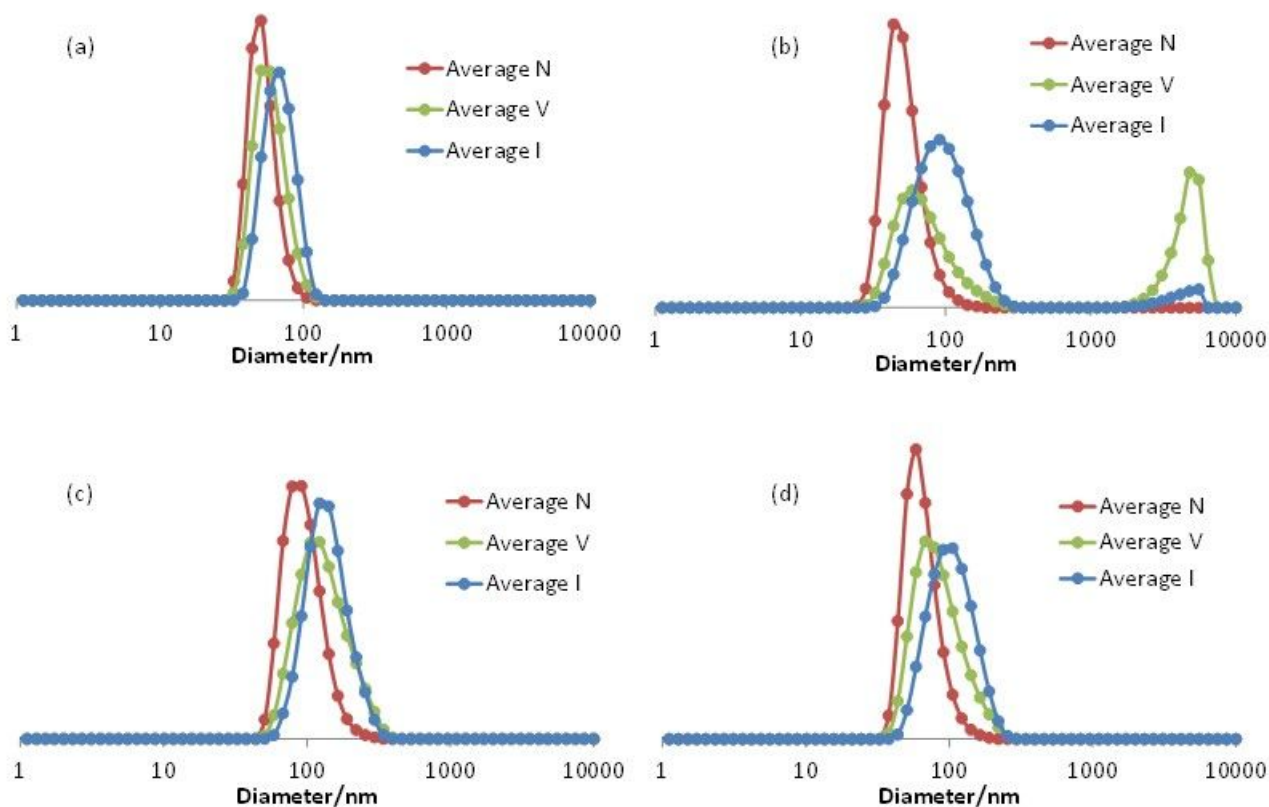


Figure S24. DLS analysis of $R_0-(4VPMe^+I)_{140}-b-S_{350}-b-(S_{135}-co-DEGDMA_{15})-SC(S)SPr$ after freeze-drying and redispersion: (a) in neat DMSO at room temperature ($D_z = 63.6$ nm, PDI = 0.09); (b) as (a) after heating at 90 °C for 24 h ($D_z = 94.3$ nm, PDI = 0.25); (c) in DMSO/toluene 80:20 (v/v) at room temperature ($D_z = 130.2$ nm, PDI = 0.15); (d) as (c) after heating at 90 °C for 24 h ($D_z = 95.8$ nm, PDI = 0.13). All measurements were carried out on unfiltered samples.

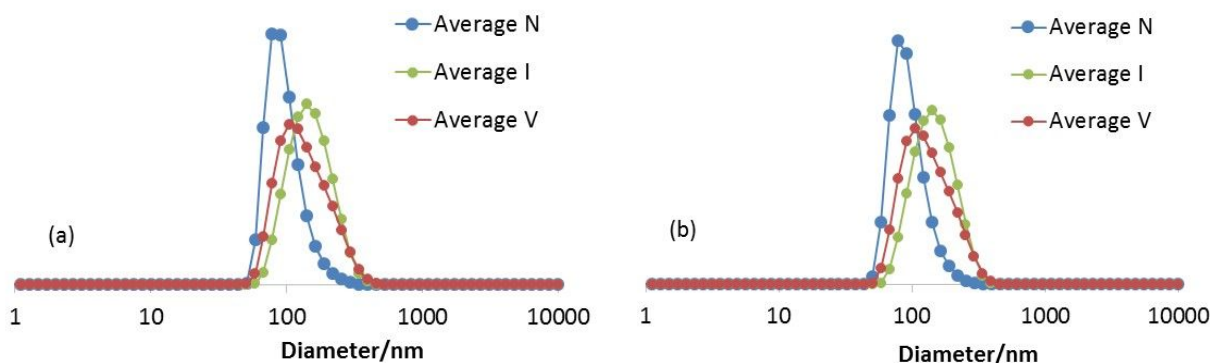


Figure S25. DLS analysis of the $R_0-(4VPMe^+I)_{137}-b-S_{345}-SC(S)SPr$ latex used for the crosslinking with pure DEGDMA. (a) Before addition of DEGDMA ($D_z = 139.1$ nm, PDI = 0.11). (b) After addition of DEGDMA ($D_z = 137.3$ nm, PDI = 0.11). All measurements were carried out on unfiltered samples.

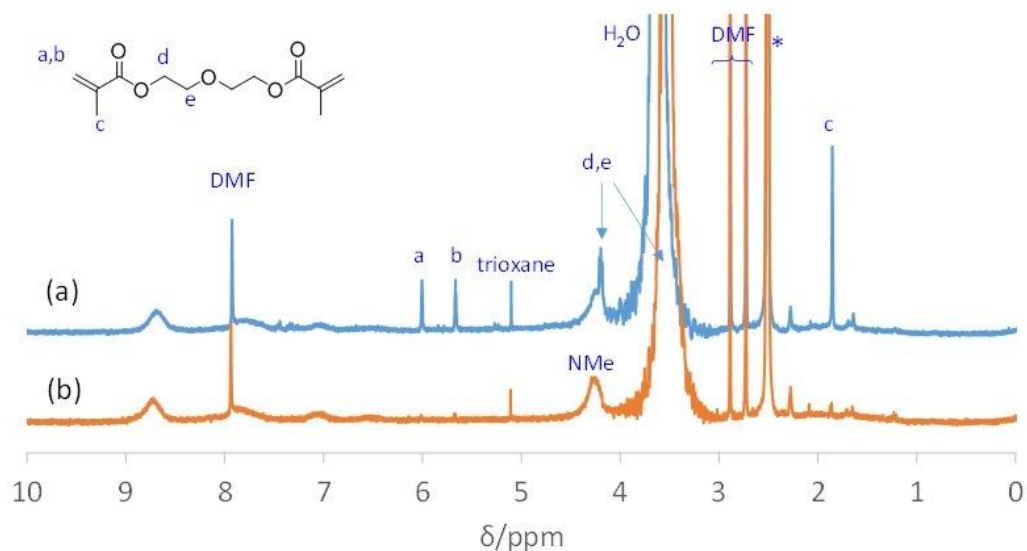


Figure S26. ^1H NMR monitoring (in $\text{DMSO-}d_6$) of the cross-linking reaction with pure DEGDMMA to yield the $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{345}\text{-}b\text{-DEGDMA}_{15}\text{-SC(S)SPr}$ latex: initial spectrum (a, blue); final spectrum (b, orange).

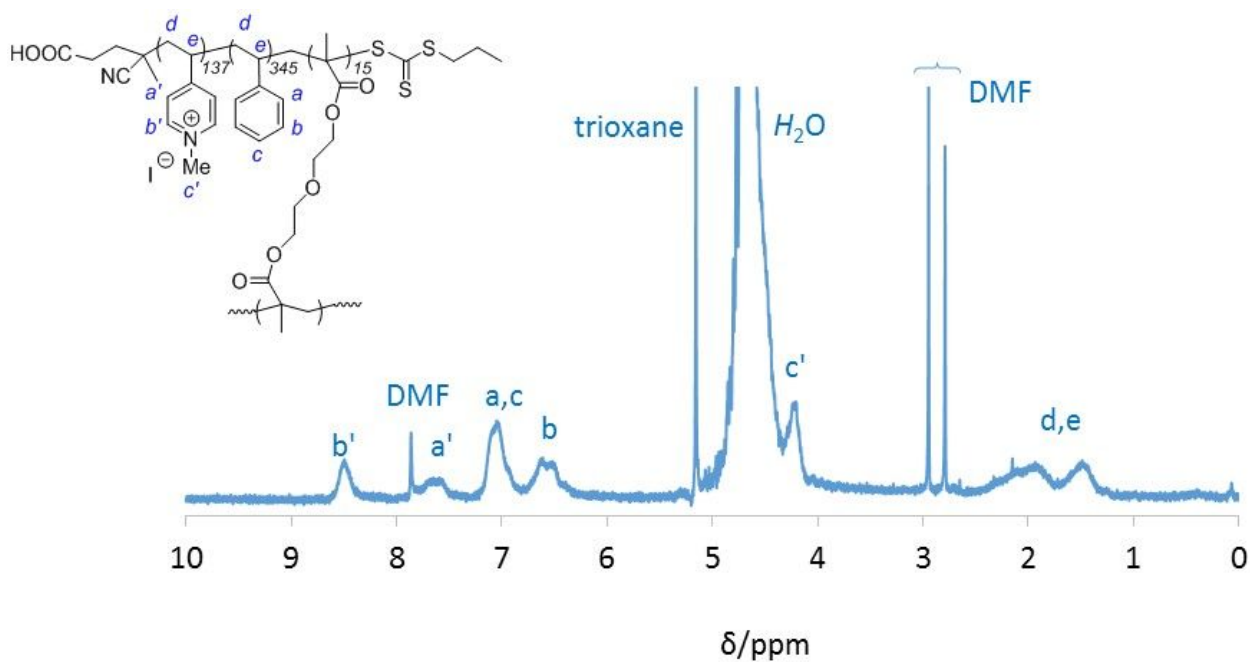


Figure S27. ^1H NMR spectrum of the $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{345}\text{-}b\text{-DEGDMA}_{15}\text{-SC(S)SPr}$ latex with added D_2O and with the PS core swollen by CDCl_3 .

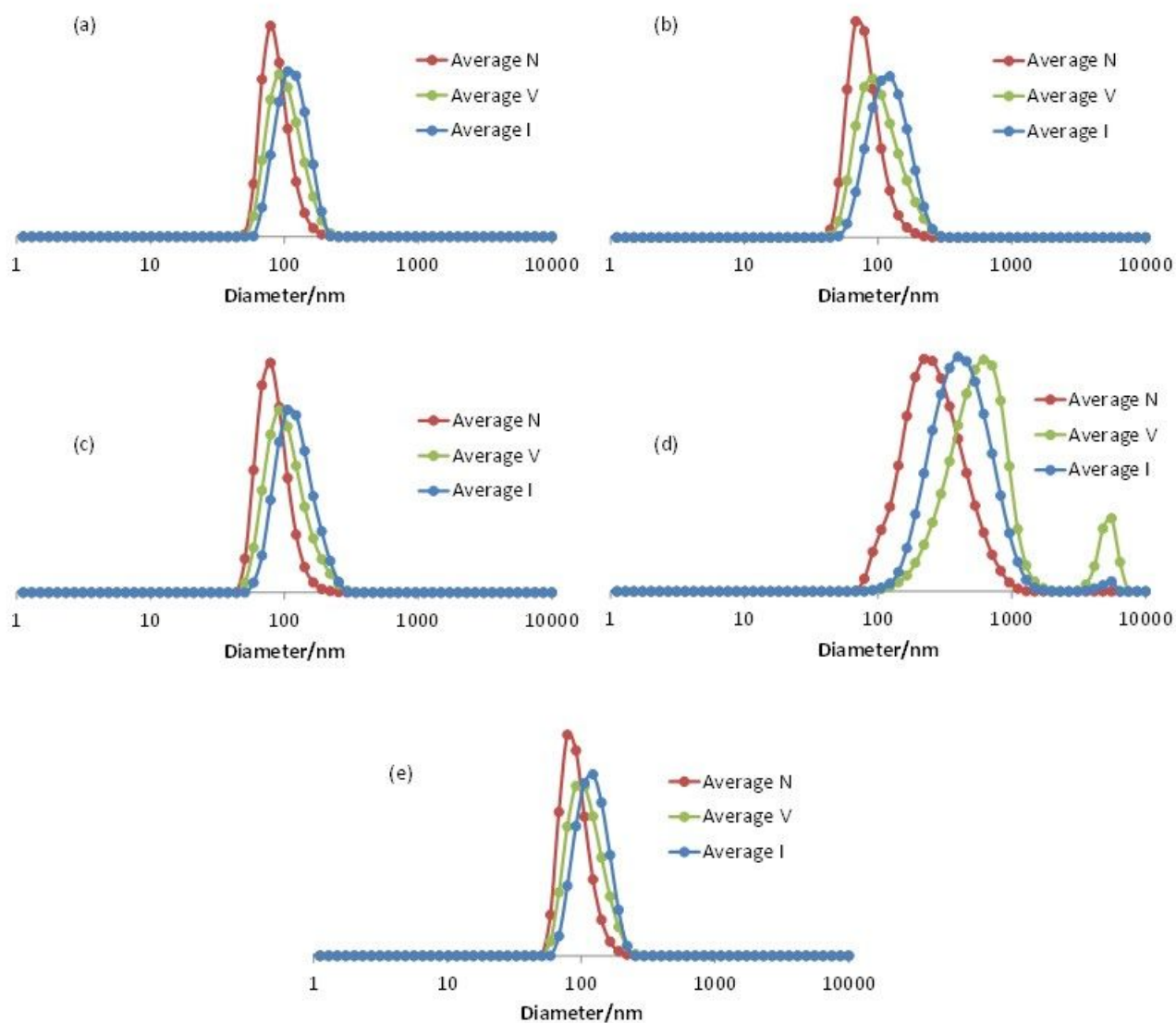


Figure S28. DLS analysis of the R_0 -(4VPMe⁺I)₁₄₀-*b*-S₃₅₀-*b*-DEGDMA₁₅-SC(S)SPr latex (a) as synthesized ($D_z = 109.6$, PDI = 0.04); (b) after heating at 90 °C for 24 h ($D_z = 112.9$ nm, PDI = 0.09); (c) swollen with toluene ($D_z = 116.7$, PDI = 0.15); (d) as (c) after heating for 24 h at 90 °C ($D_z = 381.0$, PDI = 0.24); (e) after free-drying and redispersion in water ($D_z = 129.6$ nm, PDI = 0.13). All measurements were carried out on unfiltered samples.

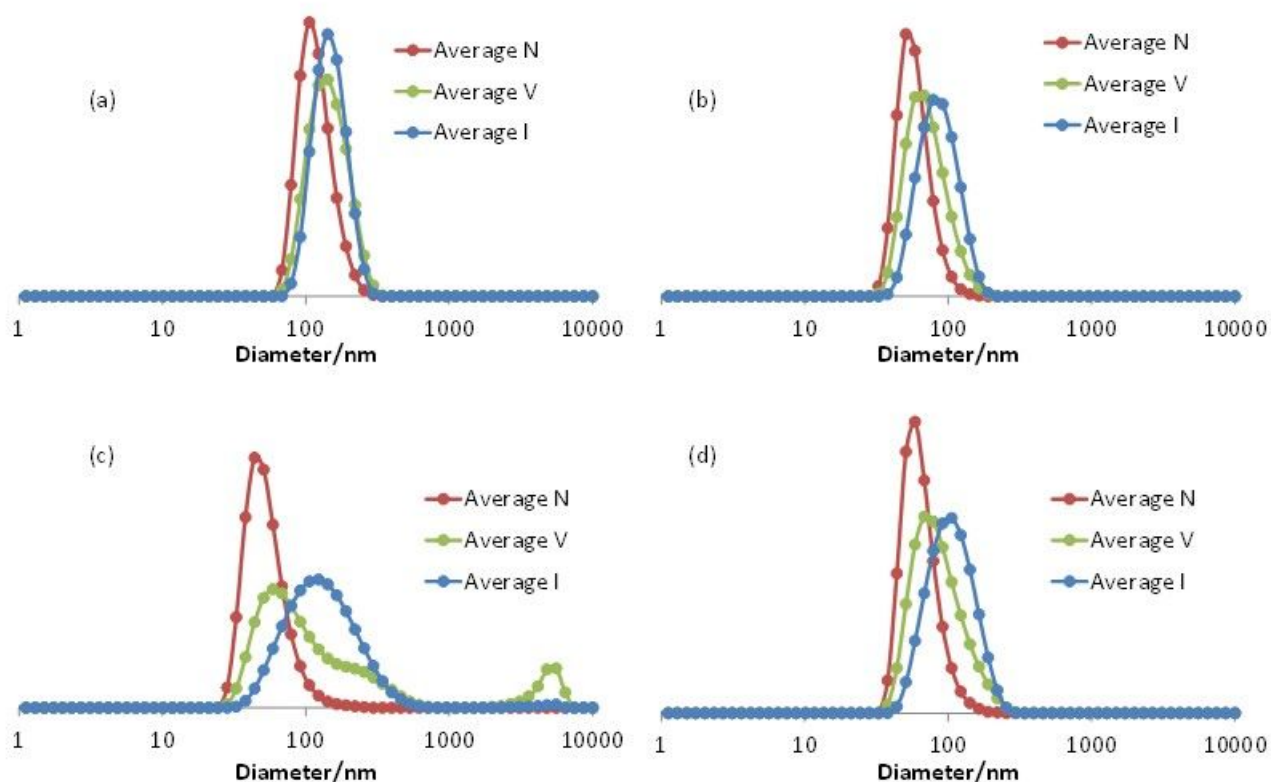


Figure S29. DLS analysis of $R_0-(4VPMe^+I)_{140}-b-S_{350}-b-DEGDMA_{15}-SC(S)SPr$ after freeze-drying and redispersion: (a) in neat DMSO at room temperature ($D_z = 104.4$ nm, PDI = 0.06); (b) as (a) after heating at 90 °C for 24 h ($D_z = 80.6$ nm, PDI = 0.08); (c) in DMSO/toluene 80:20 (v/v) at room temperature ($D_z = 110.2$ nm, PDI = 0.25); (d) as (c) after heating at 90 °C for 24 h ($D_z = 95.9$ nm, PDI = 0.12). All measurements were carried out on unfiltered samples.

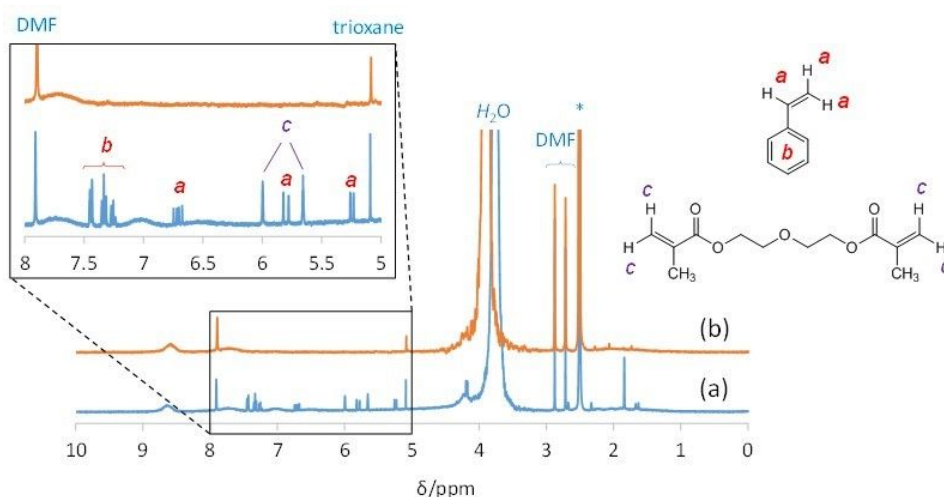


Figure S30. 1H NMR monitoring (in $DMSO-d_6$) of the $R_0-(4VPMe^+I)_{137}-b-S_{48}-b-(S_{300}-co-DEGDMA_{15})-SC(S)SPr$ nanogel synthesis. (a) Initial spectrum ($t = 0$). (b) After 17 h.

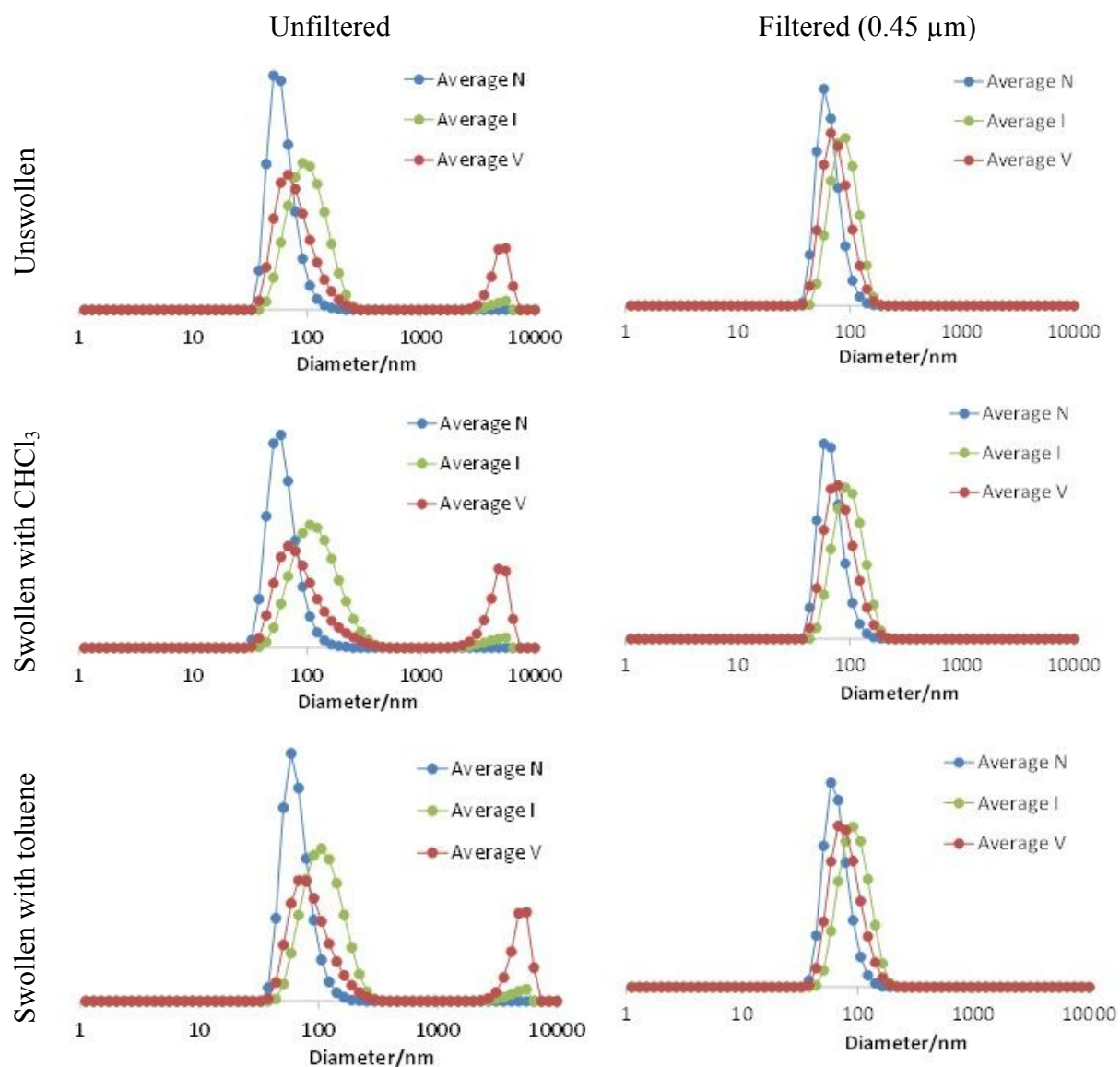


Figure S31. DLS analysis of the nanogel $R_0-(4VPMe^+I)_{137}-b-S_{48}-b-(S_{300}-co-DEGDMA_{15})-SC(S)SPr$ latex, as synthesized or swollen with either $CHCl_3$ or toluene.

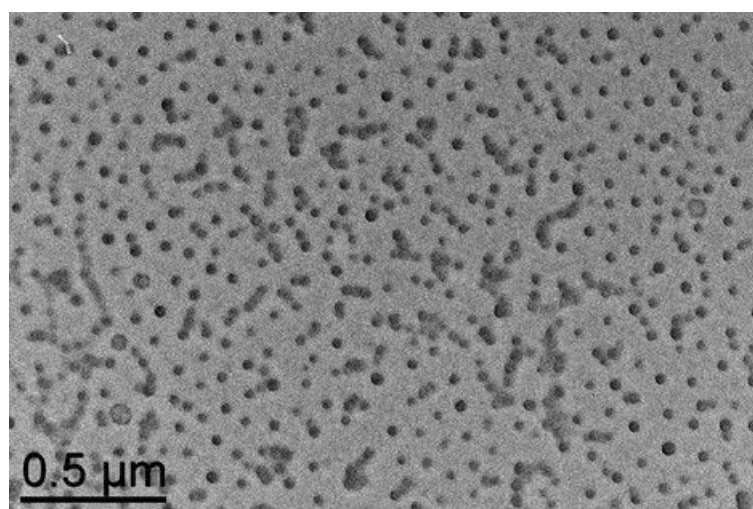


Figure S32. TEM image of the $R_0-(4VPMe^+I)_{137}-b-S_{48}-b-(S_{300}-co-DEGDMA_{15})-SC(S)SPr$ nanogel particles.

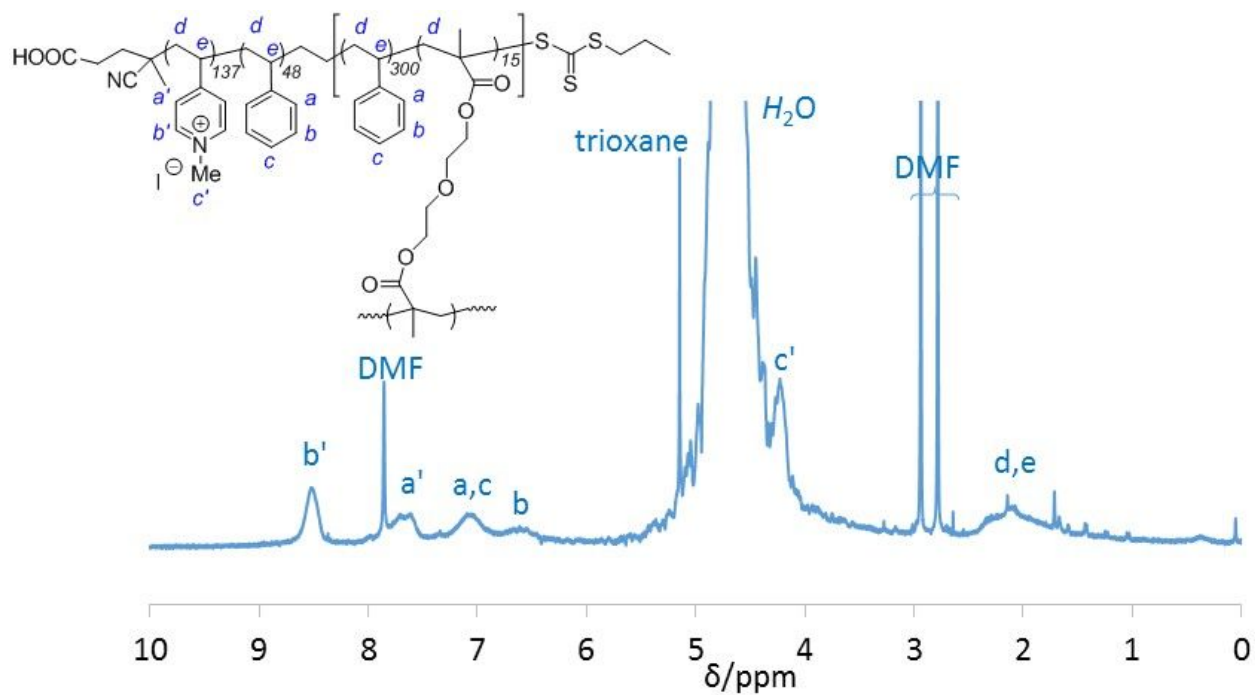


Figure S33. ^1H NMR spectrum of the $\text{R}_0\text{-(4VPMe}^+\text{I)}_{137}\text{-}b\text{-S}_{48}\text{-}b\text{-(S}_{300}\text{-}co\text{-DEGDMA}_{15}\text{)-SC(S)SPr}$ latex with added D_2O and with the PS core swollen by CDCl_3 .

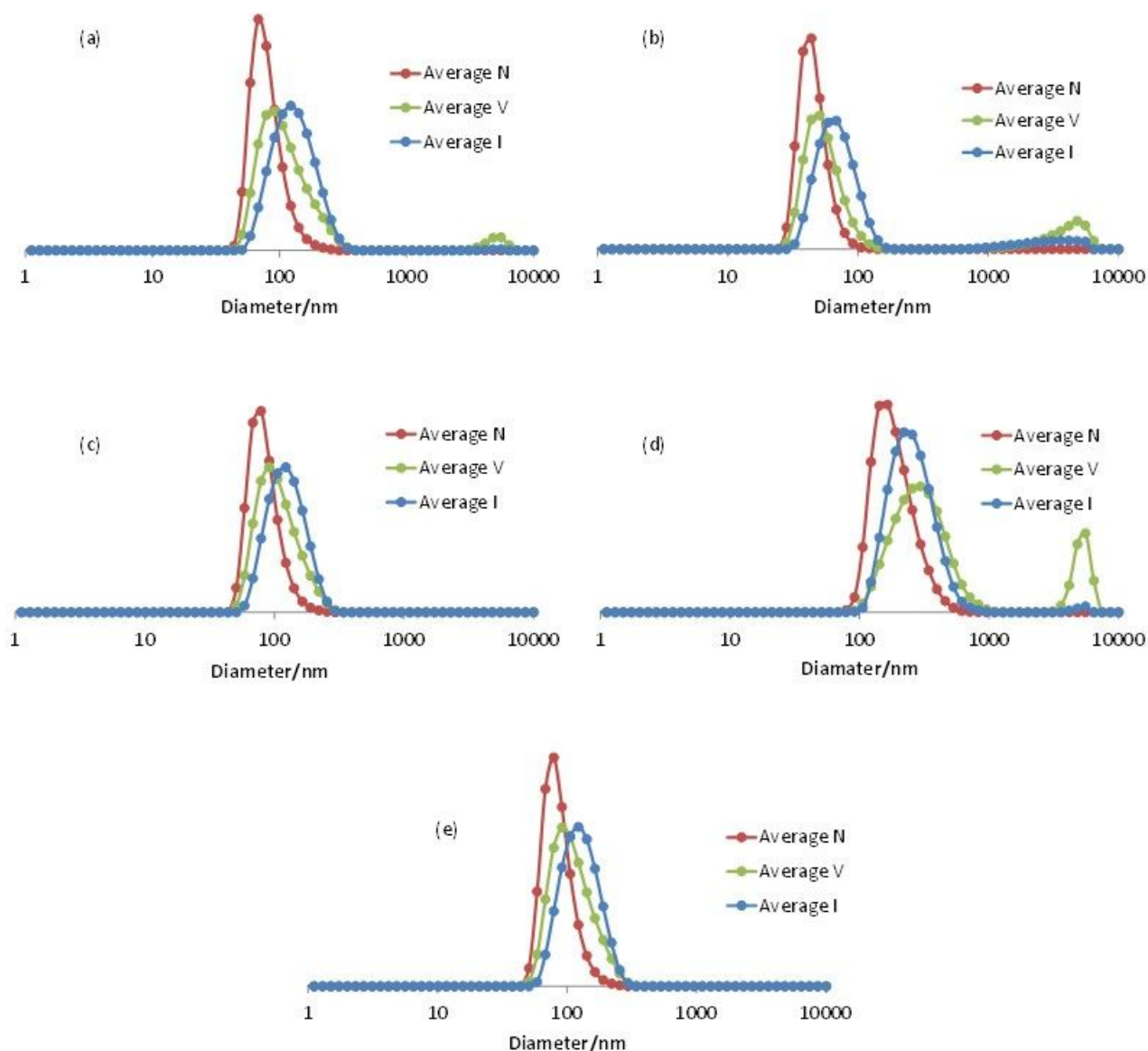


Figure S34. DLS analysis of the $R_0-(4VPMe^+I)_{140}-b-S_{50}-b-(S_{300}-co-DEGDMA_{15})-SC(S)SPr$ nanogel latex (a) as synthesized ($D_z = 121.0$, $PDI = 0.14$); (b) after heating at $90\text{ }^\circ\text{C}$ for 24 h ($D_z = 70.0$ nm, $PDI = 0.25$); (c) swollen with toluene ($D_z = 113.6$, $PDI = 0.13$); (d) as (c), after heating for 24 h at $90\text{ }^\circ\text{C}$ ($D_z = 237.8$, $PDI = 0.19$); (e) after freeze-drying and redispersion in water ($D_z = 116.4$ nm, $PDI = 0.14$). All measurements were carried out on unfiltered samples.

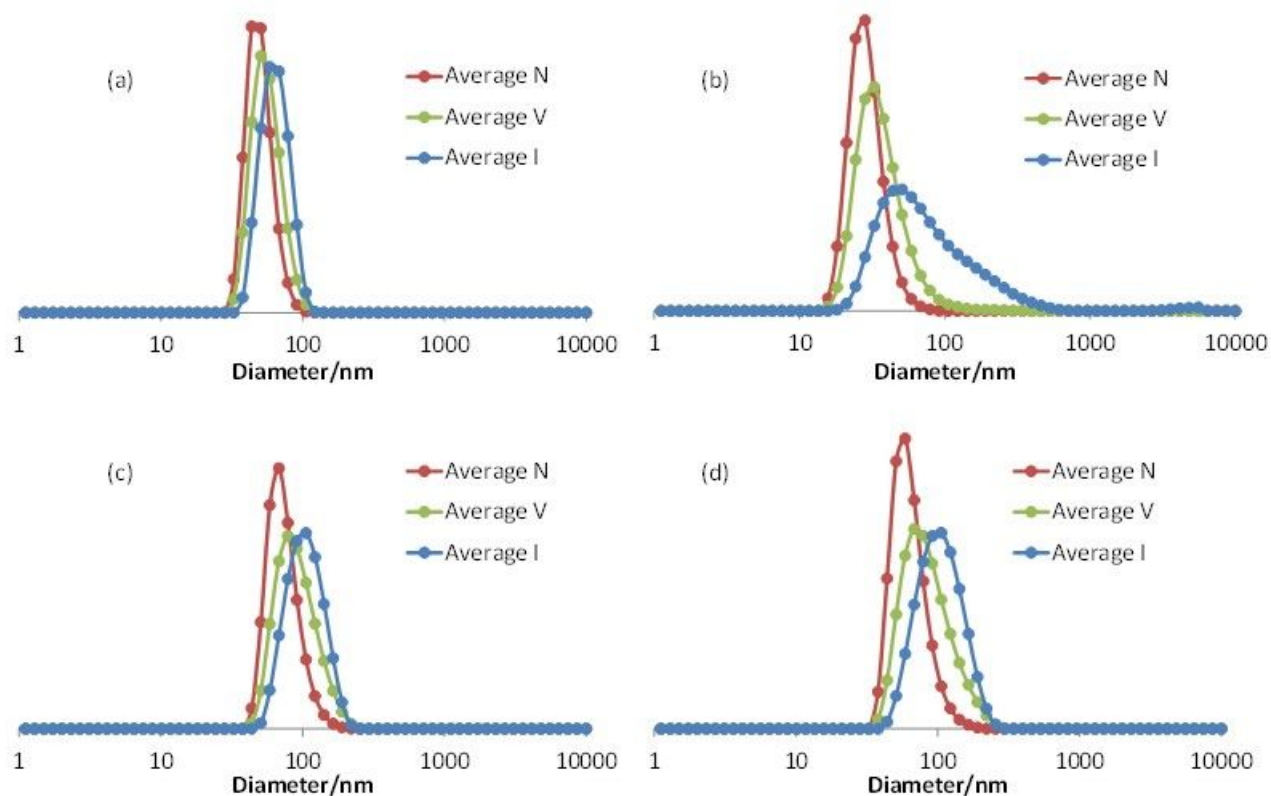


Figure S35. DLS analysis of $R_0-(4VPMe^+I)_{140}-b-S_{50}-b-(S_{300}-co-DEGDMA_{15})-SC(S)SPr$ after freeze-drying and redispersion: (a) in neat DMSO at room temperature ($D_z = 60.8$ nm, PDI = 0.06); (b) as (a) after heating at 90 °C for 24 h ($D_z = 59.2$ nm, PDI = 0.28); (c) in DMSO/toluene 80:20 (v/v) at room temperature ($D_z = 110.1$ nm, PDI = 0.03); (d) as (c) after heating at 90 °C for 24 h ($D_z = 94.9$ nm, PDI = 0.12). All measurements were carried out on unfiltered samples.

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3. Alunni, S.; Laureti, V.; Ottavi, L.; Ruzziconi, R. Catalysis of the beta-elimination of HF from isomeric 2-fluoroethylpyridines and 1-methyl-2-fluoroethylpyridinium salts. Proton-activating factors and methyl-activating factors as a mechanistic test to distinguish between concerted E2 and E1cb irreversible mechanisms. *J. Org. Chem.* **2003**, 68 (3), 718-725 DOI: 10.1021/jo020603o.