Electronic Supplementary Material (ESI) for Polymer Chemistry

Supplementary Information

A triple thermoresponsive schizophrenic diblock copolymer

Qilu Zhang, [a] Jong-Dal Hong[b] and Richard Hoogenboom*[a]

[a] *Supramolecular Chemistry Group, Department of Organic Chemistry, Ghent University, Krijgslaan 281 S4, 9000 Ghent, Belgium; E-mail: richard.hoogenboom@ugent.be*

[b] *Department of Chemistry, University of Incheon, 119 Academy-ro Yeonsu-gu, Incheon 406-772, Republic of Korea*

Materials

All chemicals and solvents were commercially available and used as received unless otherwise stated. Dichloromethane (DCM), Toluene, dimethylacetamide (DMA), THF, methanol, $CDCl_3$, hexane are from Sigma Aldrich. DCM was distilled before use. Azobisisobutyronitrile (AIBN, 98%, Aldrich) was recrystallized from MeOH (twice) and stored in the freezer. 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid was purchased from Sigma Aldrich. Potassium hexacyanocobaltate(III) was purchased from Acros Organics. pH buffers are obtained from Sigma Aldrich (pH5) or prepared according to literature reports (pH8)[1]. All polymerization were performed under an argon atmosphere.

Instrumentation

^{1}H NMR spectra for the structure characterization were recorded on a Bruker 300 MHz FT-NMR spectrometer using $CDCl_3$ as solvent. NMR study of temperature triggered self-assembly of polymers was recorded by Bruker 500 MHz NMR spectrometer with deuterated pH buffers as solvent. Chemical shifts (d) are given in ppm relative to TMS.

Size-exclusion chromatography (SEC) was performed on an Agilent 1260-series HPLC system equipped with a 1260 online degasser, a 1260 ISO-pump, a 1260 automatic liquid sampler, a thermostatted column compartment, a 1260 diode array detector (DAD) and a 1260 refractive index detector (RID). Analyses were performed on a PSS Gram30 column in series with a PSS Gram1000 column at 50 C. DMA containing 50 mM of LiCl was used as an eluent at a flow rate of 1 ml min^{-}1. The SEC traces were analysed using the Agilent Chemstation software with the GPC add on. Molar mass and PDI values were calculated against PMMA standards.

Gas chromatography was performed on 7890A from Agilent Technologies with an Agilent J&W Advanced Capillary GC column (30 m, 0.320 mm, and 0.25 µm). Injections were performed with an Agilent Technologies 7693 auto sampler. Detection was done with a FID detector. Injector and detector temperatures were kept constant at 250 and 280 °C, respectively. The column was initially set at 50 °C, followed by two heating stages: from 50 °C to 100 °C with a rate of 20 °C /min and from 100 °C to 300 °C with a rate of 40 °C /min, and then held at this temperature for 0.5 minutes. Conversion was determined based on the integration of monomer peaks using DMA as internal standard.

Turbidity measurements were performed on a Cary 300 Bio UV-Visible spectrophotometer at a wavelength of 600 nm. The samples were first cooled to a suitable temperature to fully dissolve the copolymer (5 mg ml^{-1}), after which the sample was placed in the instrument and cooled to 5 °C. The transmittance was measured during at least two controlled cooling/heating cycles with a cooling/heating rate of 1 °C min^{-1} while stirring. Cloud point (CP) is given as the temperature when the transmittance goes through 50% during heating.

Dynamic light scattering (DLS) was performed on a Zetasizer Nano-ZS Malvern apparatus (Malvern Instruments Ltd) using disposable cuvettes. The excitation light source was a He−Ne laser at 633 nm, and the intensity of the scattered light was measured at 173°. This method measures the rate of the intensity fluctuation and the size of the particles is determined through the Stokes−Einstein equation

$$d(H)= kT/3\pi\eta D \qquad (1)$$

where d(H) is the mean hydrodynamic diameter, k is the Boltzmann constant, T is the absolute temperature, η is the viscosity of the dispersing medium, and D is the apparent diffusion coefficient. Polymer solutions at different pH were measured at various temperatures. Before starting the measurements, samples were incubated at specific temperature for at least 300s to reach equilibrium. All samples were filtered through Millipore membranes with pore sizes of 0.2 μm prior to measurement.

Synthetic method

Synthesis of methyl 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]*propionate*

A solution of 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (500 mg, 1.24mmol), methanol (1.5 ml, 37 mmol) in DCM (40 ml) was cooled to 0 °C in an ice water bath. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (285 mg, 1.49 mmol) and 4-dimethylaminopyridine (18.2 mg, 0.15 mmol) in DCM (20 ml) was added dropwise with vigorous stirring. Then the solution was allowed to react for 16 h in room temperature. After that, the solution was washed with water for two times followed by adding large amount of sodium sulfate. Then the mixture was filtrated after being stirred for 10 min. The filtrate was collected and dried on a rotary evaporator. The crude product was purified by flash column chromatography using ethyl acetate/hexane (1:1) as solvent system. The yellow product was collected after 24 h drying under vacuum(yield 75%). ^{1}H NMR was recorded as shown in Fig. S1.

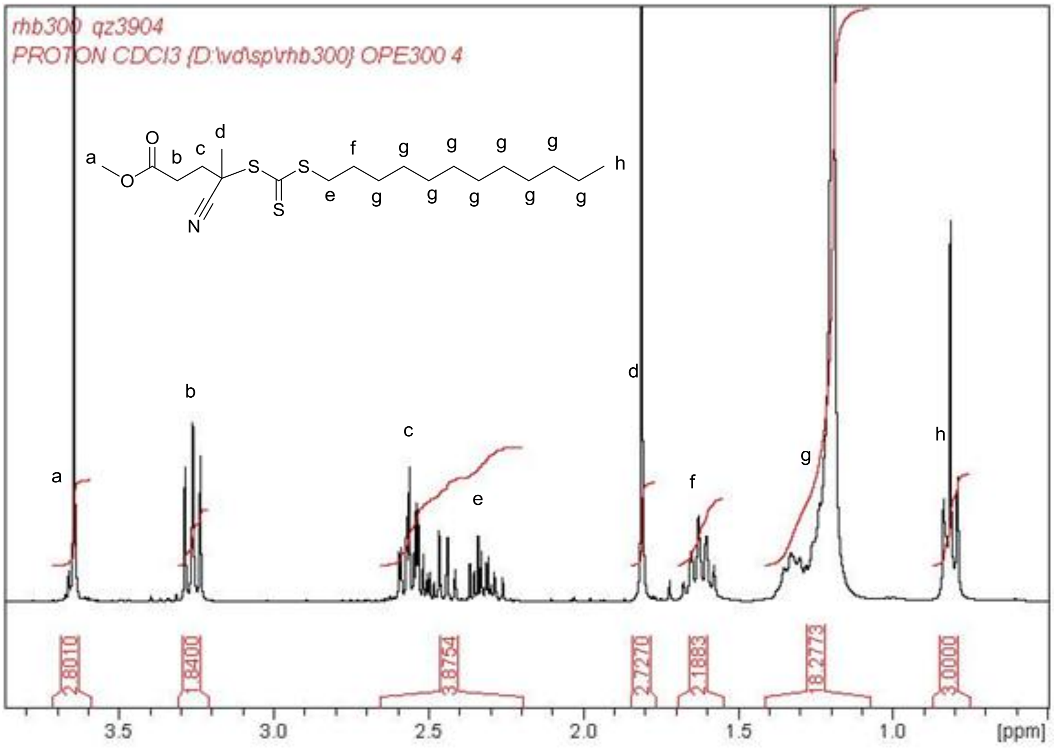


Fig. S1 ^{1}H NMR spectrum of methyl 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]propionate

Synthesis of PmTEGMA macro-CTA, PmDEGMA macro-CTA and PDMAEMA macro-CTA

The procedure for mTEGMA is described her as representative example. mTEGMA, AIBN and CTA were first dissolved in toluene/DMA solvent mixture (80/20 *vol*) in a schlenk vial. The concentration of monomer was fixed at 2M. After degassing the solution three times by freeze-vacuum-thaw cycles, the schlenk vial was filled with Argon and immersed in a preheated oil bath at 70 ^{o}C while stirring. The polymerization was performed for the required time and stopped by immersing the schlenk vial into dry ice/isopropanol bath. The resulting polymer was isolated by precipitation in hexane (three times) followed by drying under reduced pressure at 50 ^{o}C. Conversion of the monomers was analysed by GC with DMA as internal standard. Size exclusion chromatography was used to evaluate number average molecular weight (Mn) and dispersity (Đ) of the obtained polymers. For kinetics study (Fig. S2), samples were withdrawn from the polymerization mixture under a flow of argon at different times. Macro-CTAs were synthesized as listed in table S1.

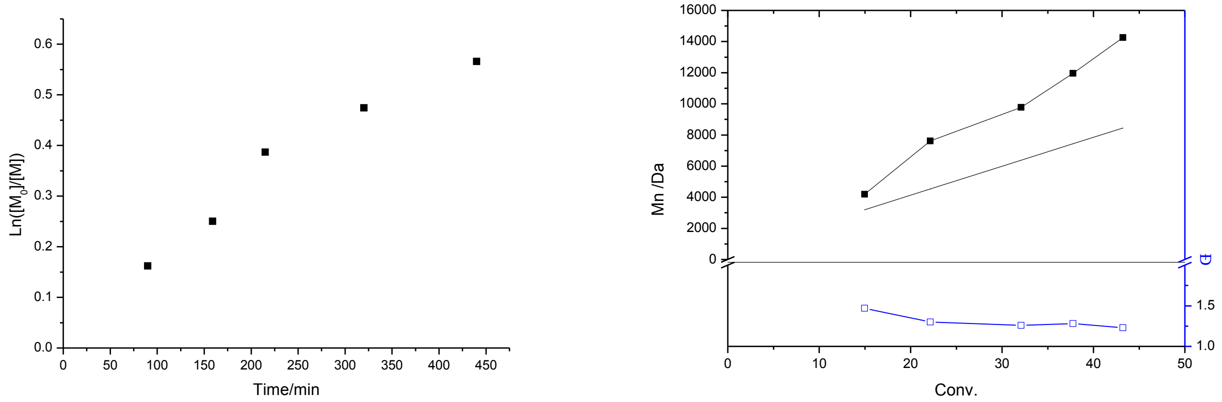


Fig. S2 Left: Pseudo-first-order kinetic plot for mTEGMA RAFT polymerization with monomer: CTA: AIBN=240: 3: 0.4. Right: Corresponding Mn and Đ versus conversion plot. The straight line represents theoretical Mn for different conversions.

Synthesis of block copolymers and subsequently functionalization

The synthesis of PmDEGMA-*b*-PDMAEMA is described here as representative example. DMAEMA, PmDEGMA macro-CTA and AIBN were first dissolved in a toluene/DMA mixture solvent (80/20 *vol*) in a schlenk vial. The concentration of monomer was fixed at 1.5 M. After degassing the solution three times by freeze-vacuum-thaw cycles, the schlenk vial was filled with Argon and immersed in a preheated oil bath at 70 ^{o}C while stirring. The polymerization was performed for the required time and stopped by immersing the reaction flask into dry ice isopropanol bath. The resulting polymer was isolated by precipitation in hexane (three times) followed by drying under reduced pressure. The polymer was dissolved in dichloromethane and excess amount of propylamine/mTEGA (methoxy tri(ethylene glycol) monoacrylate) were then added into the polymerization solution under argon. The solution was then allowed to react overnight for the aminolysis and thiol-ene reaction.

The resulting polymer was isolated by precipitation in hexane (three times) followed by drying under reduced pressure. Conversion of the monomers was analysed by GC with DMA as internal standard. Size exclusion chromatography was used to evaluate number average molecular weight (Mn) and dispersity (Đ) of the obtained polymers. For kinetics study (Fig. S3), samples were withdrawn from the polymerization mixture under a flow of argon at different times. Macro-CTA and block copolymers were synthesized as list in table S1.

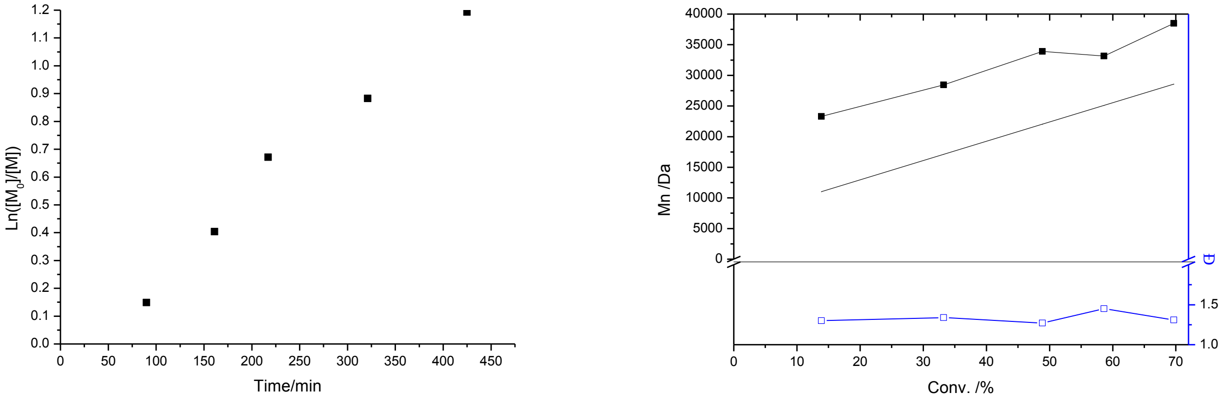


Fig. S3 Left: Pseudo-first-order kinetic plot for DMAEMA RAFT polymerization with monomer:PmDEGMA mCTA: AIBN=200: 1: 0.3. Right: Corresponding Mn and Đ versus theoretical Mn calculated based on conversion. The straight line represents theoretical Mn for different conversions.

Table S1. Polymers synthesized by RAFT polymerization

Polymers	SEC		DP by conversion		DP by ^{1}H NMR[a]	
	Mn (kDa)	Đ	mOEGMA	DMAEMA	mOEGMA	DMAEMA
PmTEGMA$_{29}$-mCTA	14.57	1.24	35	0	29	0
PmDEGMA$_{49}$-mCTA	11.87	1.13	33	0	49	0
PmDMAEMA$_{50}$-mCTA	13.72	1.16	0	52	0	50
PmTEGMA$_{29}$-b-PDMAEMA$_{56}$	30.89	1.42	35	80	29	56
PmTEGMA$_{29}$-b-PDMAEMA$_{41}$	19.68	1.79[b]	35	50	29	41
PmDEGMA$_{49}$-b-PDMAEMA$_{81}$	31.21	1.29	33	64	49	81
PDMAEMA$_{50}$-b-PmDEGMA$_{86}$	35.96	1.18	39	52	86	50

[a] DP was calculated based on the ^{1}H NMR spectra of purified polymers (see Figs. S6-S12)

[b] It is not fully clear why this polymer has a larger PDI, but it might be related to the relatively low DP of both blocks causing incomplete stabilization of the RAFT equilibrium.

Evaluation of thermoresponsive behavior of PmTEGMA$_{29}$-*b*-PDMAEMA$_{41}$

A polymer solution of PmTEGMA$_{29}$-*b*-PDMAEMA$_{41}$ in pH5 buffer with 1 mM of $[Co(CN)_6]^{3-}$ was prepared and characterized by DLS at various temperatures, as shown in Fig.S4. The UCST transition from PDMAEMA-cored micelles to individual polymer chains occurred at 7 °C and the LCST transition to PmTEGMA-cored self-assembled structures occurred at 55 °C. Shortening the PDMAEMA block, thus, lowered both transition temperatures. In particular, the UCST transition is 5 °C lower, which can be ascribed to the decreased number of electrostatic interactions with the trivalent anion that need to be disrupted. The PDMAEMA-cored micelles of PmTEGMA$_{29}$-b-PDMAEMA$_{41}$ at low temperatures are also found to be smaller compared to the PmTEGMA$_{29}$-b-PDMAEMA$_{56}$, namely 31 nm instead of 44 nm to 31 nm at 7°C, which is due to shortening of the PDMAEMA block. The size of PmTEGMA-cored micelles at elevated temperatures is larger for the polymer with the shorter PDMAEMA block, as expected upon increasing the hydrophobic content.

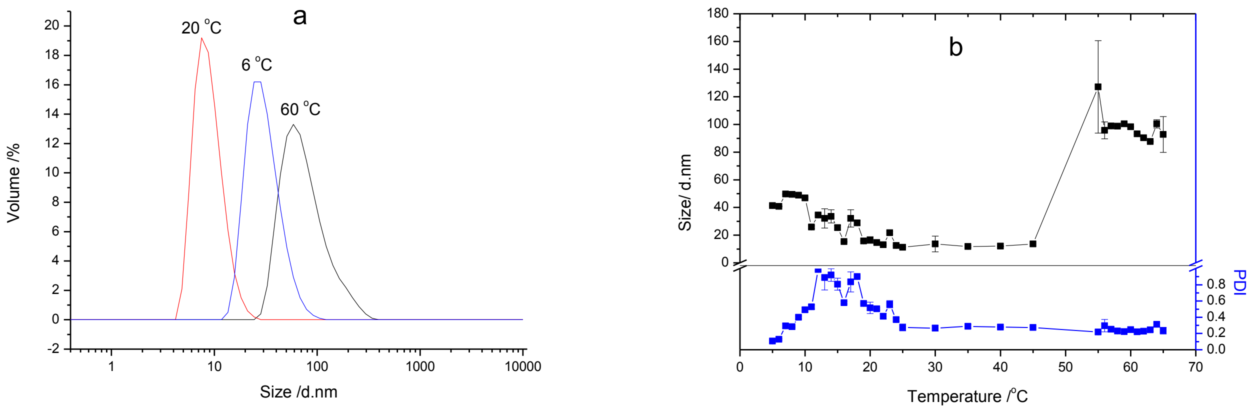


Fig. S4 a) Micelles and unimers size distribution and b) size versus temperature of PmTEGMA$_{29}$-*b*-PDMAEMA$_{41}$ aqueous solution at different temperatures (0.5 g/L in pH5 buffer with 0.1 M of NaCl and 1mM of $K_3[Co(CN)_6]$) determined by DLS. NaCl used to avoid ionic strength change upon adding of $K_3[Co(CN)_6]$ solution according to the literature[2].

Evaluation of thermoresponsive behavior of PmTEGMA$_{29}$-*b*-PDMAEMA$_{56}$ at pH8

A polymer solution of PmTEGMA$_{29}$-*b*-PDMAEMA$_{56}$ in pH8 buffer with 1 mM of $[Co(CN)_6]^{3-}$ was prepared and characterized by DLS at various temperatures, as shown in Fig.S5. The UCST transition from PDMAEMA-cored micelles to individual polymer chains occurred at 8 °C (Fig.S5 (a)). A fully precipitated state as indicated by the very large particles detected by DLS was observed at 54 °C, which is ascribed to the LCST of PDMAEMA at pH8(Fig.S5 (b)).

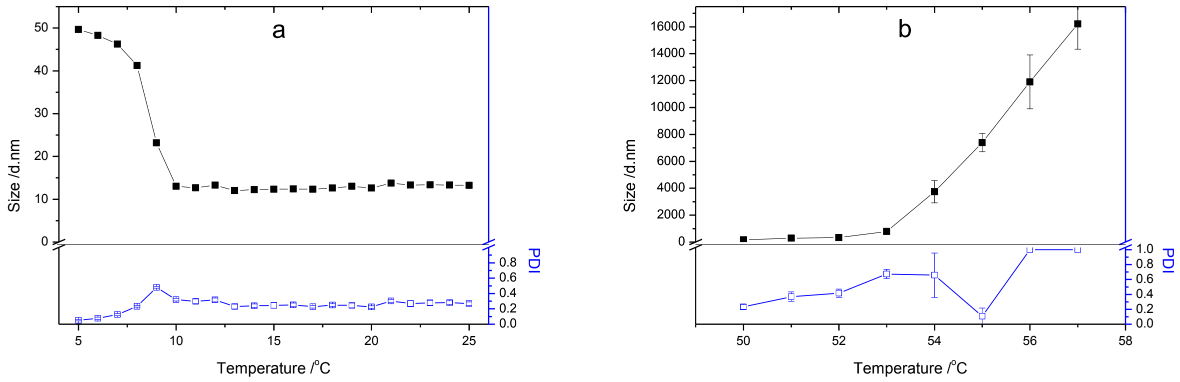


Fig. S5 Size versus temperature of PmTEGMA$_{29}$-*b*-PDMAEMA$_{56}$ aqueous solution at different temperatures (0.5 g/L in pH8 buffer with 0.1 M of NaCl and 1mM of $K_3[Co(CN)_6]$) determined by DLS. NaCl used to avoid ionic strength change upon adding of $K_3[Co(CN)_6]$ solution according to the literature[2]

Evaluation of thermoresponsive behavior of PDMAEMA$_{50}$-*b*-PmDEGMA$_{86}$

The self-assembly of PDMAEMA$_{50}$-*b*-PmDEGMA$_{86}$, having a larger PmDEGMA content than the PmDEGA$_{49}$-*b*-PDMAEMA$_{81}$ as discussed in the main manuscript, was first evaluated at 3 °C with different concentrations of $K_3[Co(CN)_6]$. It was found that the lowest concentration of trivalent counterion was 1.2 mM to form micelles (Fig. S5). However, DLS measurement at temperatures ranging from 20 to 40 °C showed that macroscopic precipitation occurred at 30 °C (data are not shown because the size is out of the range of DLS, but precipitation was also confirmed by visual inspection) demonstrating that the size of the two blocks should be accurately tuned to obtain triple-responsive behavior.

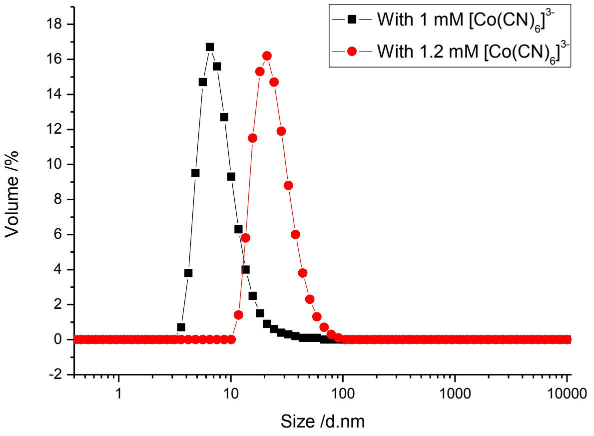
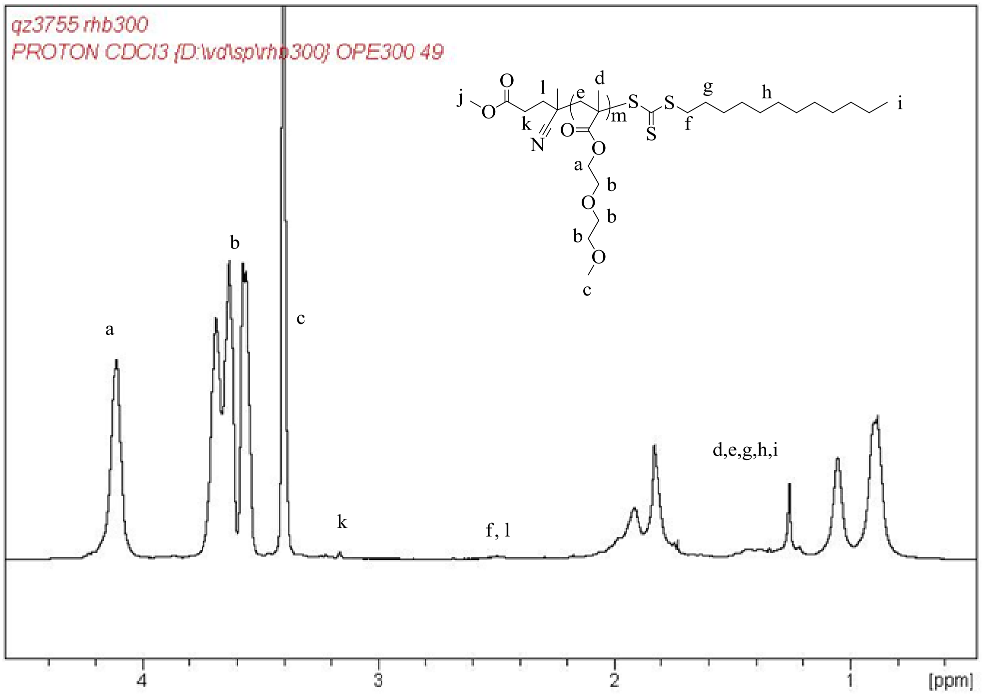


Fig. S6 Size distribution of PDMAEMA$_{50}$-*b*-PmDEGMA$_{86}$ in aqueous solution with different concentration of $K_3[Co(CN)_6$ (0.5 g/L in pH5 buffer, at 3 °C) determined by DLS. 0.1 M of NaCl was used to avoid ionic strength change upon adding of $K_3[Co(CN)_6]$ solution according to the literature[2].



SEC trace of $PmDEGMA_{49}$-mCTA

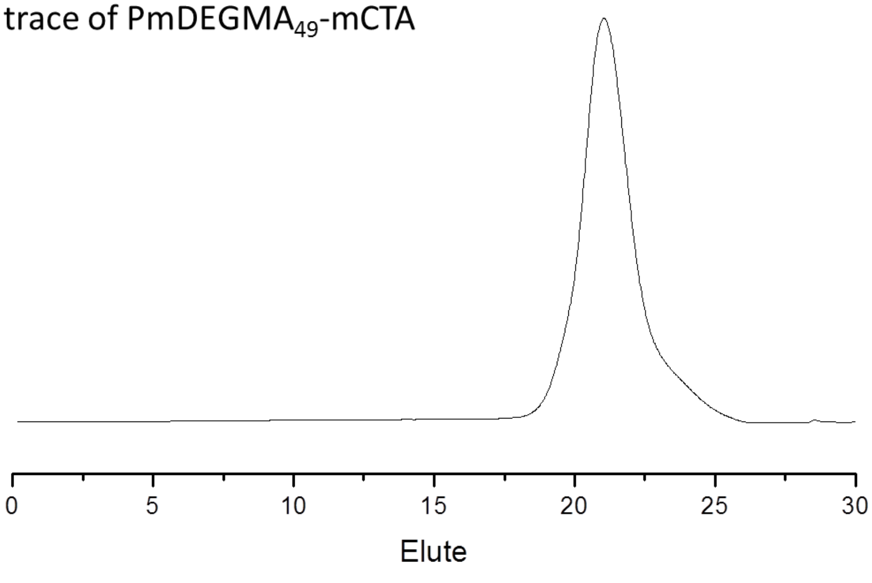
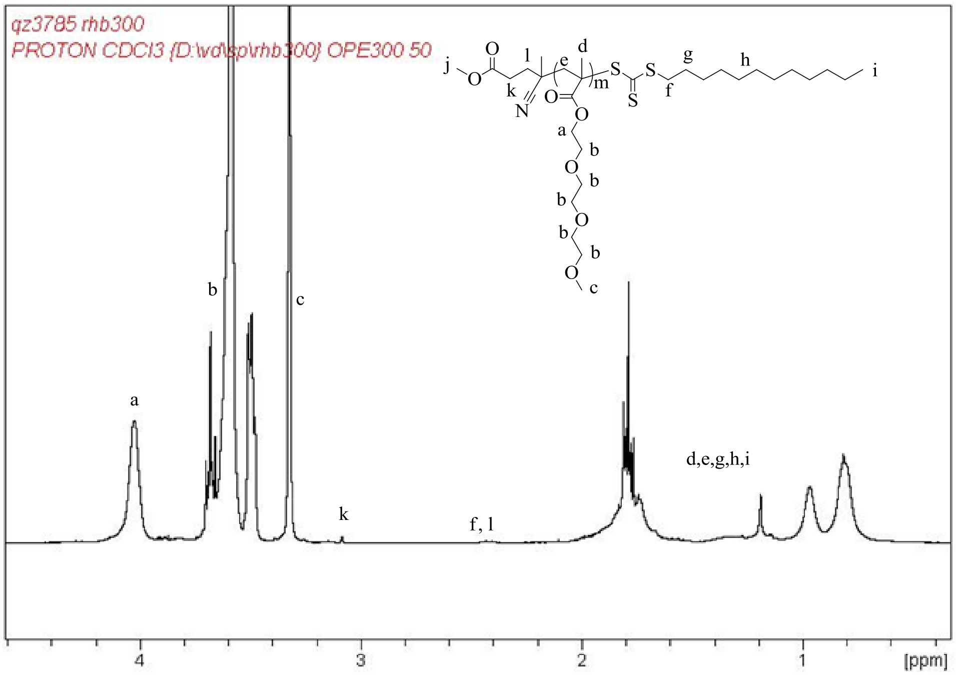


Fig. S7 ^{1}H NMR spectrum and SEC trace of $PmDEGMA_{49}$-mCTA



SEC trace of PmTEGMA$_{29}$-mCTA

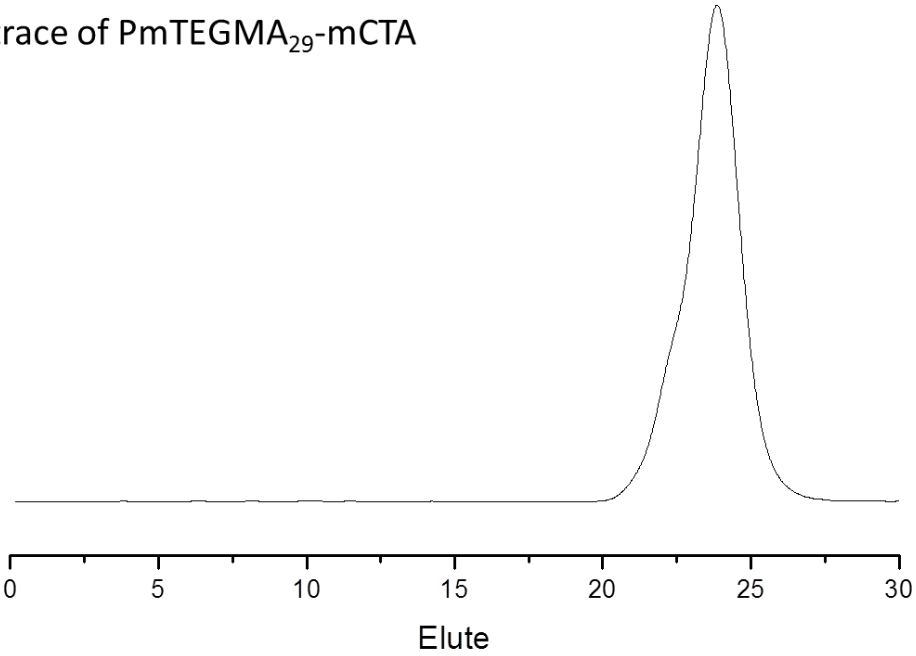
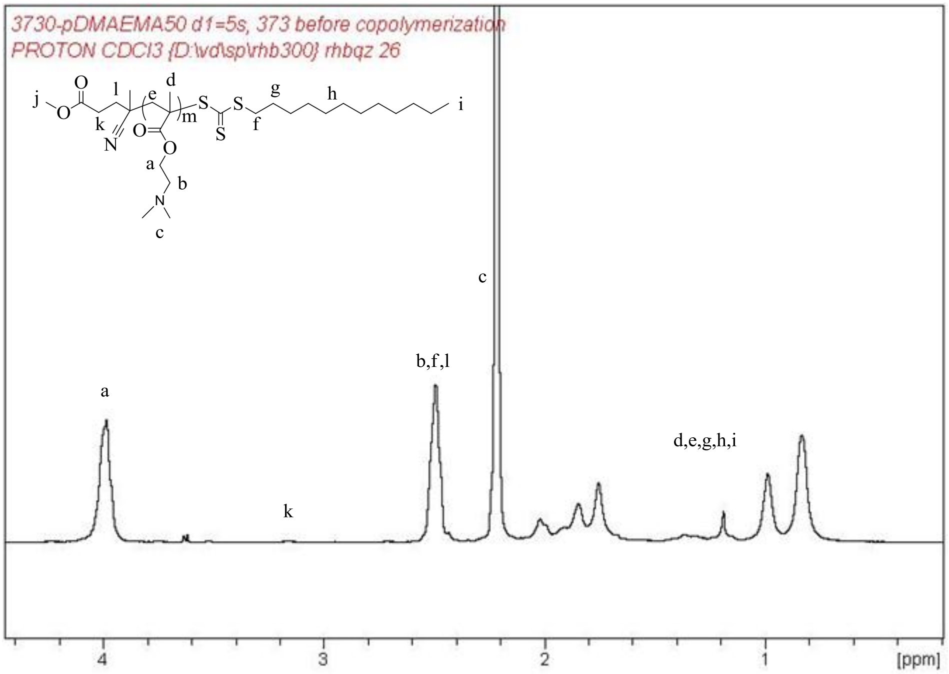


Fig. S8 ^{1}H NMR spectrum and SEC trace of PmTEGMA$_{29}$-mCTA



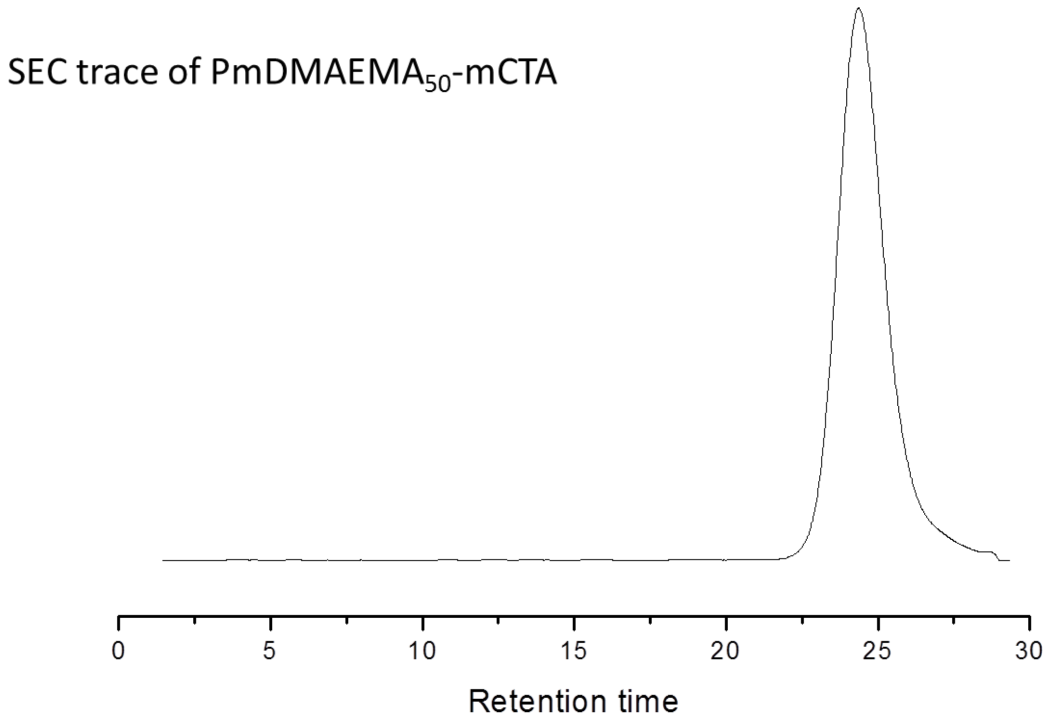
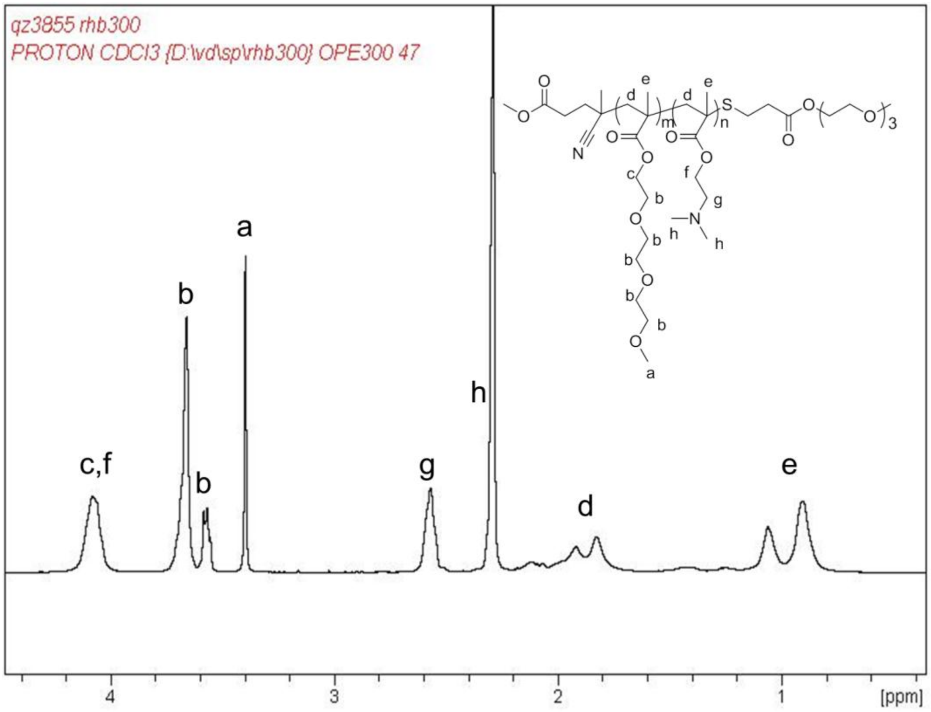


Fig. S9 ^{1}H NMR spectrum and SEC trace of PDMAEMA$_{50}$-mCTA



SEC trace of PmTEGMA$_{29}$-b-PDMAEMA$_{56}$

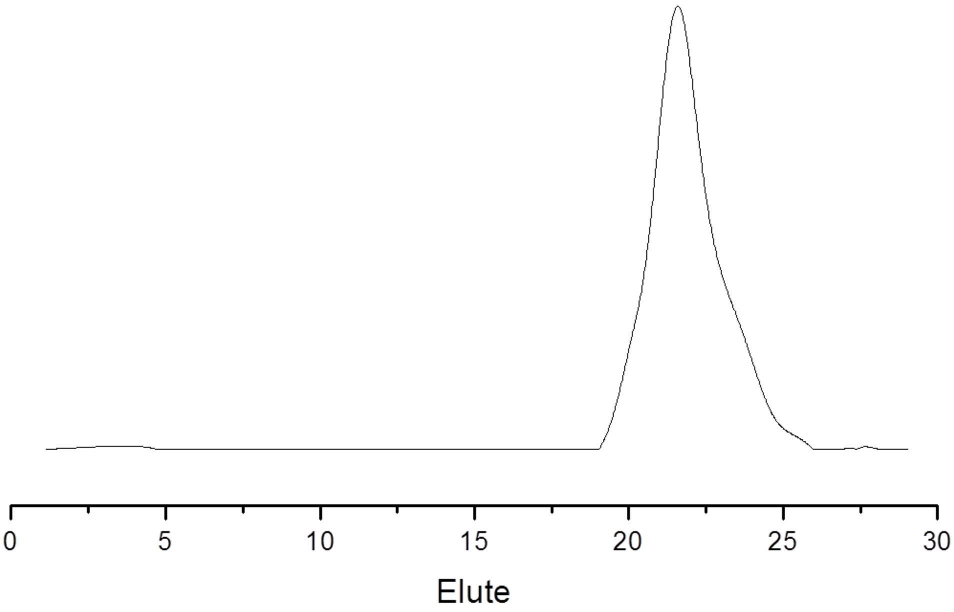
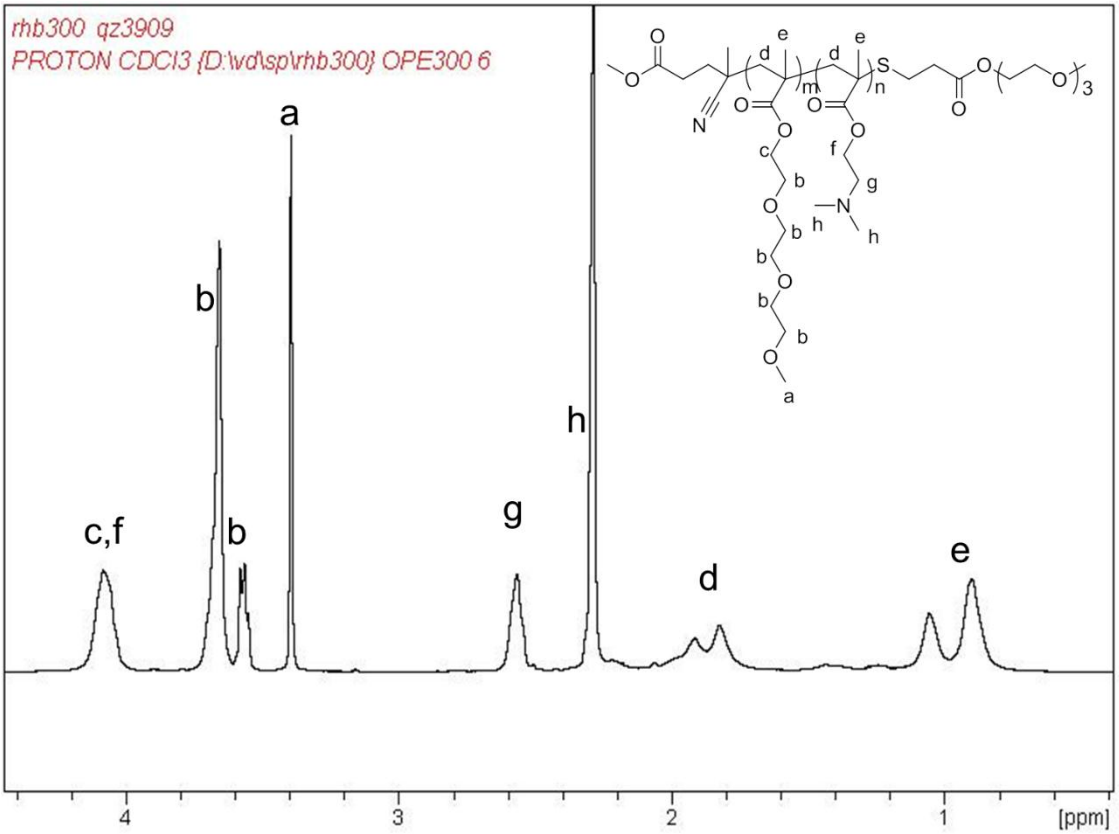


Fig. S10 ^{1}H NMR spectrum and SEC trace of PmTEGMA$_{29}$-b-PDMAEMA$_{56}$



SEC trace of PmTEGMA$_{29}$-b-PDMAEMA$_{41}$

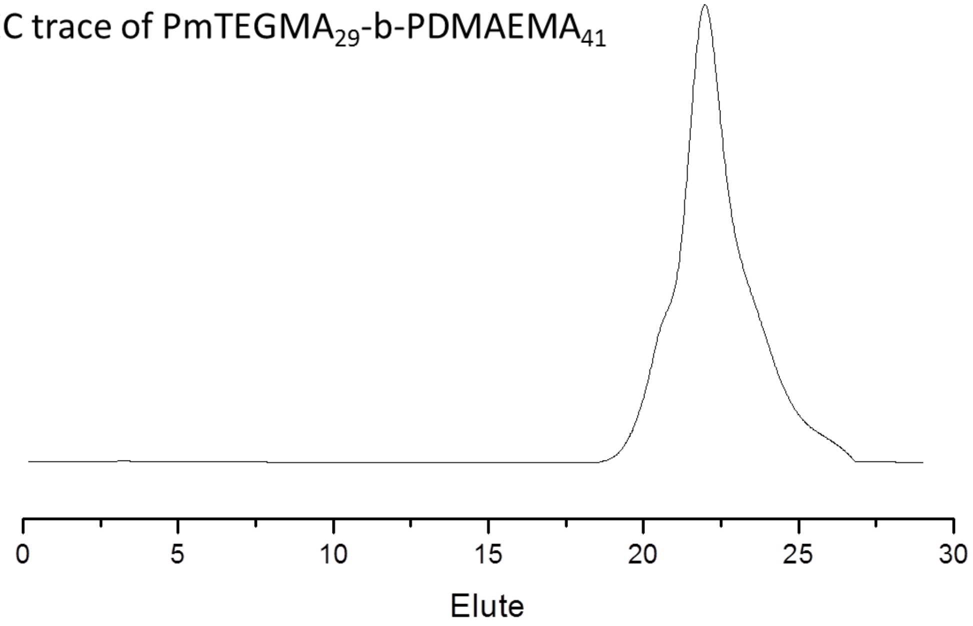


Fig. S11 ^{1}H NMR spectrum and SEC trace of PmTEGMA$_{29}$-b-PDMAEMA$_{41}$

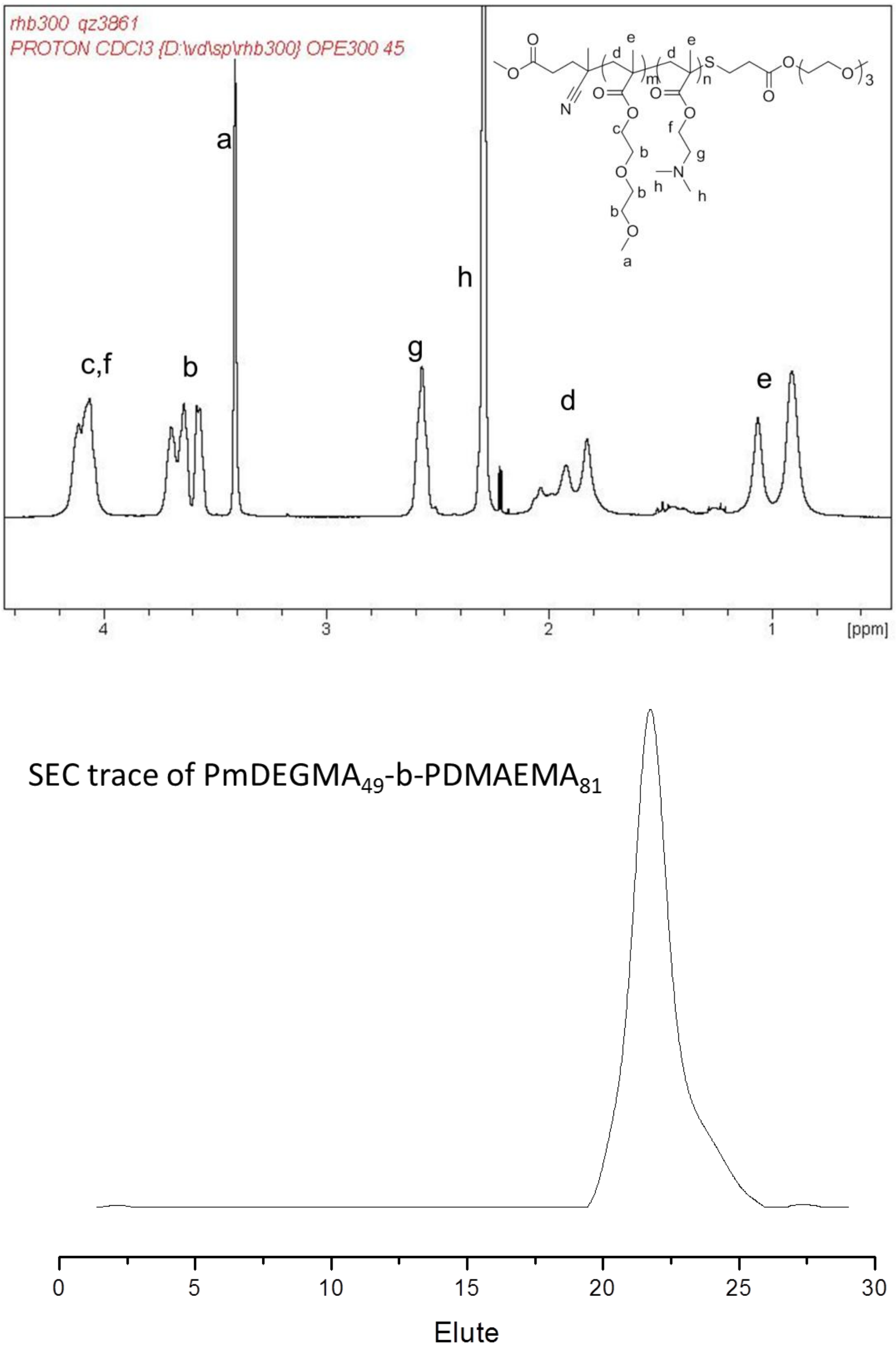
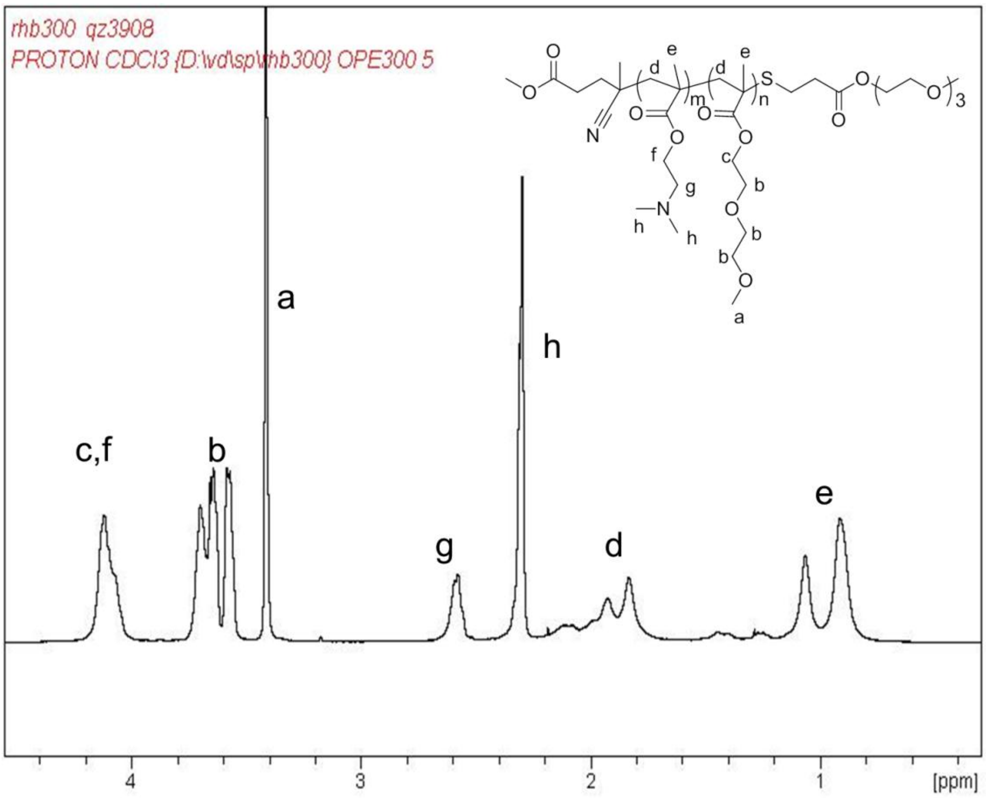


Fig. S12 ^{1}H NMR spectrum and SEC trace of PmDEGMA$_{49}$-b-PDMAEMA$_{81}$



SEC trace of $PDMAEMA_{50}$-b-$PmDEGMA_{86}$

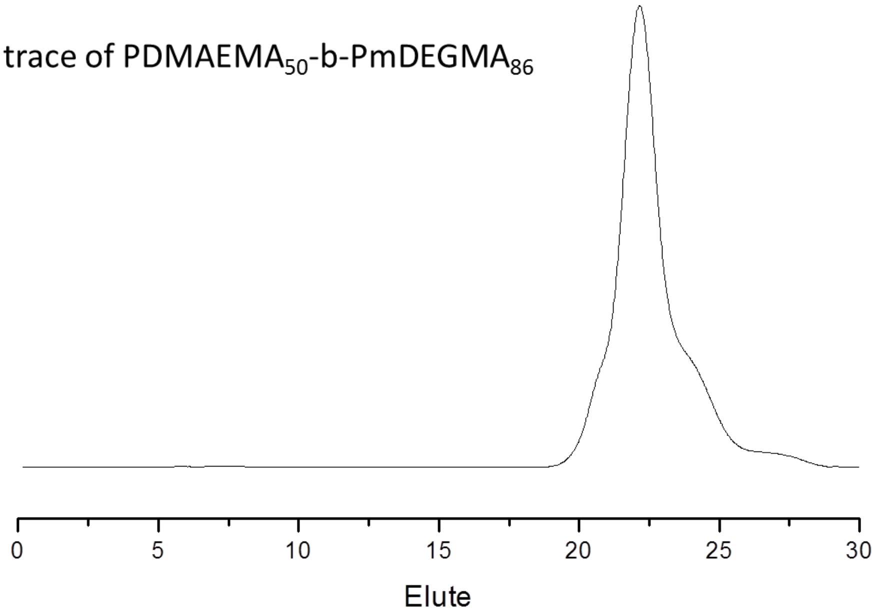


Fig. S13 ^1H NMR spectrum and SEC trace of $PDMAEMA_{50}$-b-$PmDEGMA_{86}$

References

1. R.A. Robinson, R.H. Stokes, *Electrolyte solutions*, 2nd ed., rev. London, Butterworths, 1968
2. F. A. Plamper, A. Schmalz and A. H. E. Müller, *J. Am. Chem. Soc.*, 2007, **129**, 14538.