Degradable Graft Copolymers by Ring-Opening Polymerization and RAFT

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Supporting Information

Materials

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and (-)-sparteine were dried over CaH_2, distilled and stored under inert atmosphere. Benzyl alcohol was dried and stored over 4 Å molecular sieves. 4-Methoxybenzyl alcohol was dried over 3 Å molecular sieves in dry CH_2Cl_2. 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea was synthesized as reported[1] and dried over CaH_2 in dry THF. Monomer **5** was dried over 3 Å molecular sieves in dry CH_2Cl_2. 5-methyl-5-ethoxycarbonyl-1,3-dioxan-2-one (**6**) was prepared according to the literature[2] and dried over 3 Å molecular sieves in dry CH_2Cl_2. Methyl acrylate (MA) and styrene were distilled over CaH_2 and stored below 4 ^oC. *N*-isopropylacrylamide (NiPAm) was recrystallized from a 9:1 mixture of hexanes/acetone and stored below 4 ^oC. Tetrahydropyran acrylate (THPA) was prepared as described previously[3] and stored below 4 ^oC. AIBN (2,2'-azo-bis(isobutyronitrile)) was recrystallized twice from methanol and stored in the dark below 4 ^oC. $CDCl_3$ was dried over 3 Å molecular sieves, distilled and degassed before use. CH_2Cl_2 and THF were purified over Innovative Technology SPS alumina solvent columns and degassed before use. All other solvents and chemicals were obtained from Sigma-Aldrich or Fischer Scientific and used as received.

General Considerations

Ring-opening polymerizations were performed under inert atmosphere in a glovebox. RAFT polymerizations were carried out under oxygen-free conditions using standard Schlenk-line

techniques. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400, AC-400, or DRX-500 spectrometer at 298 K. Chemical shifts are reported as δ in parts per million (ppm) and referenced to the chemical shift of the residual solvent resonances ($CHCl_3$: ^{1}H δ = 7.26 ppm; ^{13}C δ = 77.16 ppm). Mass spectra were recorded on a Bruker Esquire 2000 ESI spectrometer. Elemental analysis was performed in duplicate by Warwick Analytical Services. Gel-permeation chromatography (GPC) in $CHCl_3$ was conducted on a system composed of a Varian 390-LC-Multi detector suite fitted with differential refractive index, light scattering, and viscometer detectors equipped with a guard column (Varian Polymer Laboratories PLGel 5 μM, 50 × 7.5 mm) and two mixed D columns (Varian Polymer Laboratories PLGel 5 μM, 300 × 7.5 mm). The mobile phase was $CHCl_3$ at a flow rate of 1.0 mL min^{-1}. GPC in DMF was conducted on a Varian Polymer Laboratories PL-GPC 50 plus integrated GPC system with differential refractive index and ultraviolet detectors equipped with a guard column (Varian Polymer Laboratories PLGel 5 μM, 50 × 7.5 mm) and two mixed D columns (Varian Polymer Laboratories PLGel 5 μM, 300 × 7.5 mm). The mobile phase was DMF with 5 mM NH_4BF_4 at a flow rate of 1.0 mL min^{-1}. GPC samples were calibrated against Varian Polymer Laboratories Easi-Vials linear poly(styrene) standards (162-2.4 × 10^5 g mol^{-1}) or Varian Polymer Laboratories Easi-Vials linear poly(methyl methacrylate) standards (690-1.9 × 10^6 g mol^{-1}) using Cirrus v3.3 software. MALDI-ToF (matrix-assisted laser desorption ionization – time of flight) spectra were recorded using a Bruker Daltronics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with a positive ion ToF detection performed using an accelerating voltage of 25 kV. Samples were spotted onto a Bruker ground steel MALDI-ToF analytical plate through application of a small portion of a solution containing trans-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) as a matrix (20 μL of a 10 mg mL^{-1} solution in THF), sodium trifluoroacetate as a cationization agent (5 μL of a 10 mg mL^{-1} solution in THF), and

analyte (5 µL of a 10 mg mL^{-1} solution in THF) followed by solvent evaporation. The samples were measured in reflectron ion mode and calibrated by comparison to 2 x 10^3 poly(ethylene oxide) standards. Dynamic light scattering (DLS) measurements were taken on a Malvern Zetasizer NanoS instrument operating at 6 °C with a 4 mW He- Ne 633 nm laser module and the data analyzed using Malvern DTS 5.02 software and a cumulants fit analysis method. Transmission Electron Microscopy (TEM) samples were prepared by drop deposition and freeze drying of the solution onto copper/carbon grids that had been deposited with a thin film of graphene oxide prior to use.[4] Micrographs were collected at magnifications ranging from 8 to 100 K and calibrated digitally. Histograms of number-average particle diameters were generated from the analysis of a minimum of 100 particles from at least three different micrographs using Image J software. Lower critical solution temperature (LCST) measurements were analyzed using a Perkin-Elmer UV/vis Spectrometer (Lambda 35) equipped with a Peltier temperature controller at 500 nm with a heating/cooling rate of 1 $^oC\ min^{-1}$. An average of three heating/cooling cycles were recorded. Glass transition temperatures (T_g) were determined using a Mettler Toledo DSC1-STAR Differential Scanning Calorimeter (DSC) under a nitrogen stream (50 mL min^{-1}). Changes in heat flow were recorded between -40 and 240 ^oC over two cycles with a scan rate of 10 $^oC\ min^{-1}$ and a 5 minute isotherm at either end of the temperature range. The instrument was calibrated using indium metal standards supplied by Mettler Toledo and analysis of the data was performed using the STARe software package (version 9.30).

Experimental Procedures

Synthesis of acetonide protected 2,2-bis(hydroxymethyl)propionic acid (1)

Acetonide-protected 2,2-bis(hydroxymethyl)propionic acid (**1**) was prepared according to the literature.[5] 2,2-bis(hydroxymethyl)propionic acid (10.0 g, 76.1 mmol), 2,2-dimethoxypropane (14.0 mL, 114 mmol) and *p*-toluenesulfonic acid (0.724 g, 3.80 mmol) were dissolved in acetone (70 mL). The solution was stirred at room temperature. After 2 h ammonium hydroxide was added until the reaction mixture was neutralised and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with water (2 x 50 mL) and the organic layer dried over $MgSO_4$. CH_2Cl_2 was removed under reduced pressure to yield a white solid. (8.24 g, 47.3 mmol, 62%). Characterisation data were in accordance with that previously reported.[5]

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.54 (br S, 1H, COO*H*), 4.17 (d, 2H, C(CH_3)CH_2O, *J* = 11.8 Hz), 3.64 (d, 2H, C(CH_3)CH_2O, *J* = 11.8 Hz), 1.43 (s, 3H, C(CH_3)$_2$), 1.39 (s, 3H, C(CH_3)), 1.16 (s, 3H, C(CH_3)CH_2O). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 179.9, 98.4, 66.3, 42.0, 25.4, 22.1, 18.6.

Synthesis of RAFT CTA (2)

Ethanethiol (2.36 mL, 31.9 mmol) and carbon disulfide (5.76 mL, 95.8 mmol) were added to a suspension of potassium triphosphate (7.45 g, 35.1 mmol) in acetone (300 mL) and stirred for 5 h at room temperature. 4-(Chloromethyl)benzyl alcohol (5.00 g, 31.9 mmol) was added and the mixture was stirred for a further 72 h. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (300 mL). The organic phase was washed with 1 M HCl (2 x 200 mL), water (2 x 200 mL) and brine (1 x 200 mL). The organic layer was dried over

$MgSO_4$. CH_2Cl_2 was removed under reduced pressure to yield a yellow solid (7.53 g, 29.1 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.36 – 7.30 (m, 4H, Ar), 4.68 (d, 2H, ArCH_2OH, J = 6.0 Hz), 4.61 (s, 2H, ArCH_2S), 3.38 (q, 2H, SCH_2CH$_3$, J = 7.4), 1.64 (t, 1H, OH, J = 6.0), 1.36 (t, 3H, CH$_2$CH_3, J = 7.4). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 223.5, 140.5, 134.6, 129.6, 127.4, 65.1, 41.1, 31.5, 13.2. Anal. Calcd for $C_{11}H_{14}OS_3$: C 51.1; H 5.5%. Found: 51.4; H, 5.5%. MS (ESI +ve): m/z 281 $[M+Na]^+$.

Synthesis of RAFT functionalized acetonide protected bis-MPA (3)

N-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.840 g, 4.38 mmol) was added to a solution of **1** (0.730 g, 4.19 mmol) and 4-(dimethylamino)pyridine (0.0256 g, 0.210 mmol) in dry CH_2Cl_2 (50 mL) at 0 ^{o}C. The solution was allowed to warm to room temperature and stirred for 30 min before the addition of **2** (1.13 g, 4.38 mmol). Following stirring of the solution for a further 44 h, the reaction mixture was washed with water (3 x 25 mL) and the organic layer was dried over $MgSO_4$. CH_2Cl_2 was removed under reduced pressure and the crude product was purified by column chromatography (silica, ethyl acetate: petroleum ether (1:1)) to yield a yellow solid (1.09 g, 2.63 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35 – 7.28 (m, 4H, Ar), 5.17 (s, 2H, ArCH_2O), 4.60 (s, 2H, ArCH_2S), 4.22 (d, 2H, C(CH$_3$)CH_2O, J = 11.8 Hz), 3.66 (d, 2H, C(CH$_3$)CH_2O, J = 11.8 Hz), 3.38 (q, 2H, SCH_2CH$_3$, J = 7.4 Hz), 1.43 (s, 3H, C(CH_3)$_2$,), 1.37 (s, 3H, C(CH_3)$_2$,), 1.35 (t, 3H, SCH$_2$CH_3, J = 7.4 Hz), 1.18 (s, 3H, C(CH_3)CH$_2$O). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 223.3, 174.0, 135.5, 135.2, 129.4, 128.1, 98.1, 66.2, 66.0, 41.9, 40.8, 31.4, 24.9, 22.4, 18.6, 13.1. Anal. Calcd for $C_{16}H_{26}O_4S_3$: C, 55.0; H, 6.3%. Found: C, 55.0; H, 6.3%. MS (ESI +ve): m/z 437 $[M+Na]^+$.

Synthesis of RAFT functionalized diol (4)

Dowex 50W-X2 acidic resin (0.200 g) was added to a stirred solution of **3** (0.400 g, 0.964 mmol) in MeOH (50 mL). After stirring at room temperature for 16 h, the resin was removed by filtration before concentration of the solution *in vacuo* to yield **4** as a yellow soild (0.361 g, 0.964 mmol, 100%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35–7.28 (m, 4H, Ar), 5.17 (s, 2H, ArCH_2O), 4.60 (s, 2H, ArCH_2S), 3.92 (d, 2H, C(CH_3)CH_2O, J = 11.2 Hz), 3.72 (d, 2H, C(CH_3)CH_2O, J = 11.2 Hz), 3.38 (q, 2H, SC$H_2$$CH_3$, J = 7.4 Hz), 2.41 (br s, 2H, O*H*), 1.35 (t, 3H, SCH_2CH_3, J = 7.4 Hz), 1.07 (s, 3H, C(CH_3)CH_2O). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 223.4, 175.7, 135.6, 135.3, 129.6, 128.3, 68.5, 66.4, 49.4, 40.9, 31.5, 17.2, 13.2. Anal. Calcd for $C_{16}H_{22}O_4S_3$: C, 51.3; H, 5.9%. Found: C, 51.35; H, 5.8%. MS (ESI +ve): m/z 397 $[M+Na]^+$.

Synthesis of RAFT CTA functionalized carbonate monomer (5)

A solution of triphosgene (2.50 g, 8.42 mmol) in dry CH_2Cl_2 (30 mL) was added in stepwise portions over 30 minutes to a solution of **4** (4.67 g, 12.7 mmol) and pyridine (6.00 mL, 74.9 mmol) in dry CH_2Cl_2 (70 mL) at -78 ^{o}C. The reaction was stirred for 1 h at -78 ^{o}C and for a further 2 h at room temperature before being washed with saturated aqueous NH_4Cl solution (50 mL), 1M HCl (3 x 50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was dried over $MgSO_4$ and reduced under vacuum to yield a yellow solid that was recrystallized from THF/diethyl ether to yield **5** as a yellow solid (3.86 g, 9.64 mmol 76%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.37–7.26 (m, 4H, Ar), 5.19 (s, 2H, ArCH_2O), 4.70 (d, 2H, C(CH_3)CH_2O, J = 10.8 Hz), 4.61 (s, 2H, ArCH_2S), 4.20 (d, 2H, C(CH_3)CH_2O, J = 10.8 Hz), 3.38 (q, 2H, SC$H_2$$CH_3$, J = 7.4 Hz), 1.36 (t, 3H, SCH_2CH_3, J = 7.4 Hz), 1.33 (s, 3H, C(CH_3)CH_2O). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 223.3, 171.0, 147.5, 136.1, 134.4,

129.7, 128.6, 73.0, 67.5, 40.7, 40.3, 31.5, 17.6, 13.1. Anal. Calcd for $C_{17}H_{20}O_5S_3$: C, 51.0; H, 5.0%. Found: C, 50.7; H, 4.9%. MS (ESI +ve): m/z 423 $[M+Na]^+$.

General procedure for ring-opening polymerizations

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added to a solution of **5** and 4-methoxybenzyl alcohol (from a stock solution of 4-methoxybenzyl alcohol in dry CH_2Cl_2) in dry CH_2Cl_2. After the desired amount of time the polymerization was quenched by the addition of acidic amberlyst 15 resin. The resin was removed by filtration and the solvent removed under reduced pressure. The residual monomer and catalyst were removed by column chromatography (silica, ethyl acetate: petroleum ether (3:2)).

General procedure for RAFT polymerizations

The appropriate equivalents of polymer, AIBN and monomer were loaded into a dry ampoule and dissolved in chloroform. The reaction mixture was degassed *via* 4 freeze-pump-thaw cycles and refilled with nitrogen. The polymerization was initiated by immersion of the ampoule into an oil bath at 65 ^oC. After the desired length of time the polymerization was quenched by immersion of the ampoule in liquid N_2.

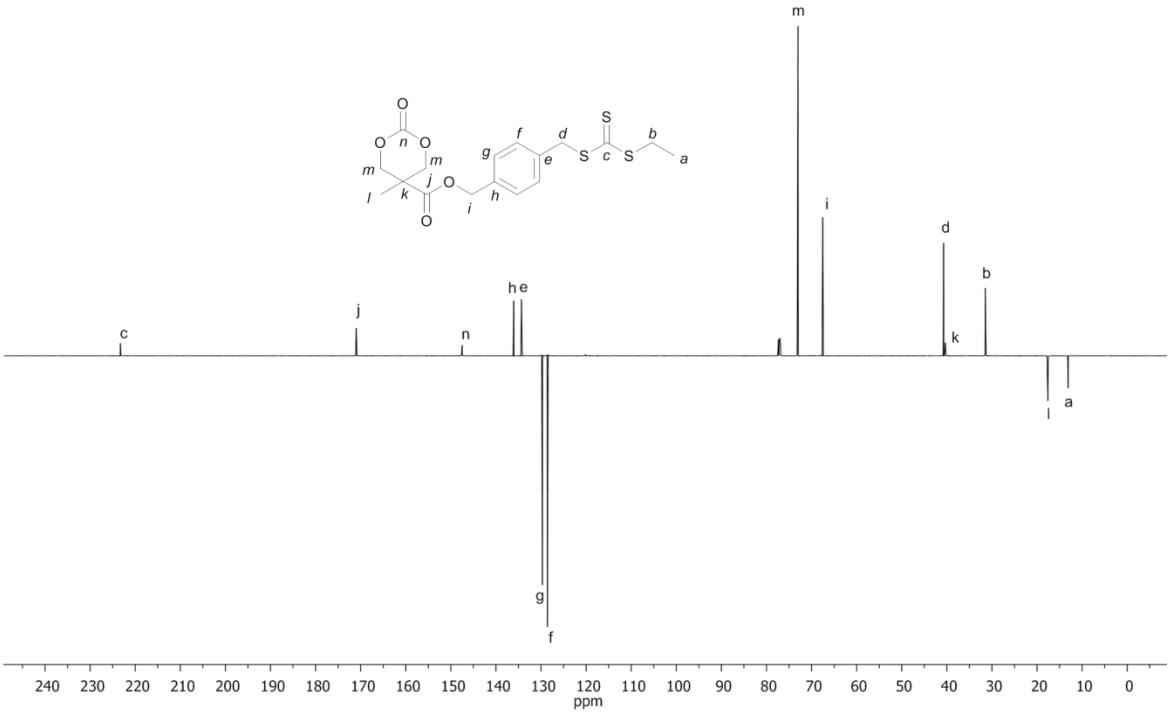
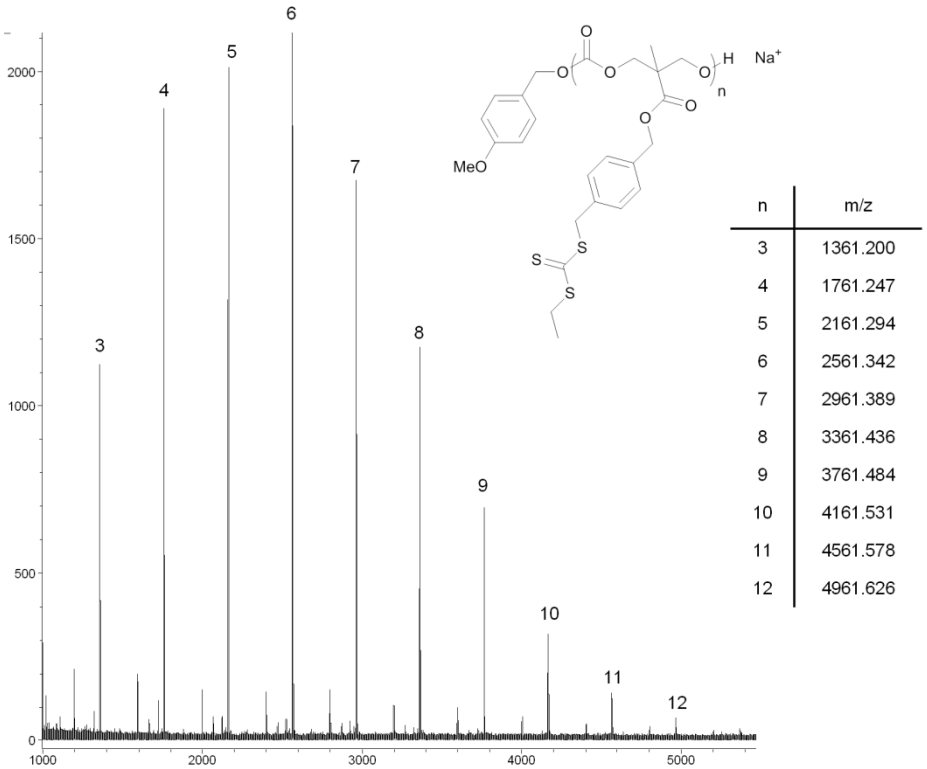


Figure S1. ^{13}C NMR spectrum of RAFT CTA functional carbonate monomer **5** in $CDCl_3$ (100 MHz, 298 K).



n	m/z
3	1361.200
4	1761.247
5	2161.294
6	2561.342
7	2961.389
8	3361.436
9	3761.484
10	4161.531
11	4561.578
12	4961.626

Figure S2. MALDI-ToF MS of RAFT CTA functionalized polycarbonate (reflectron mode).

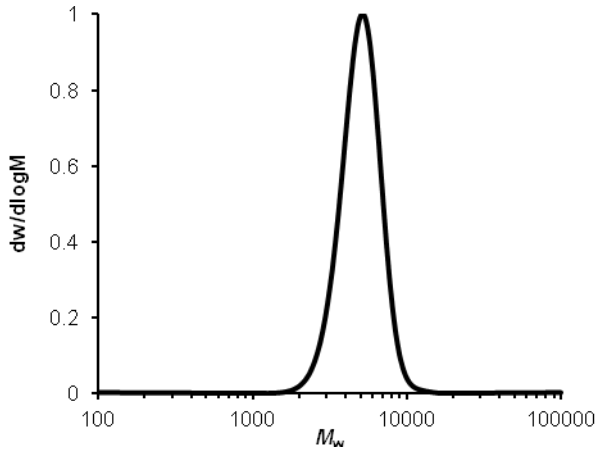


Figure S3. SEC trace of poly(**5**) (M_n = 4.8 kDa, $Đ$ = 1.09) ($[M]_0/[I]_0$ = 20, [**5**] = 0.25 M, using 5 mol% DBU and 4-methoxybenzyl alcohol as an initiator).

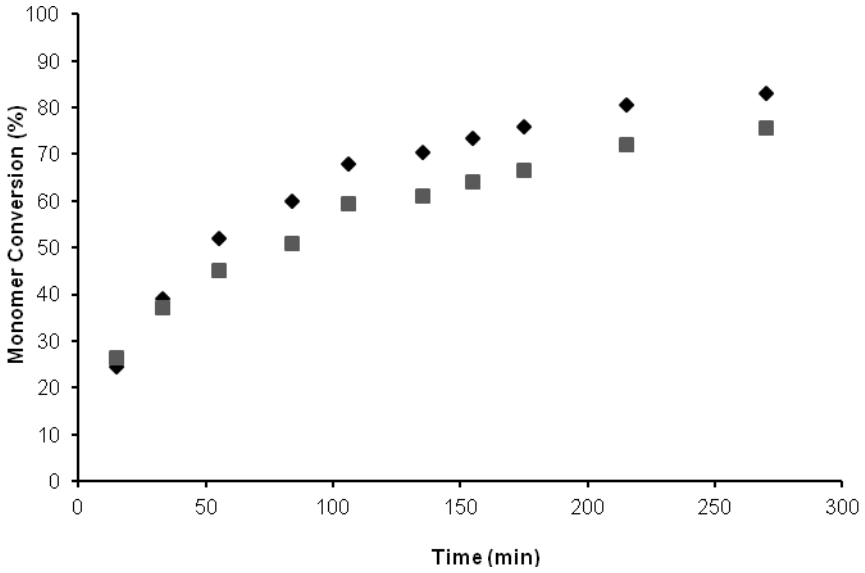


Figure S4. Monomer conversion *versus* time for monomer **5** (diamonds) and **6** (squares) during a 1:1 copolymerization (**5**:**6**) (monomer conversion determined by ^{1}H NMR spectroscopy).

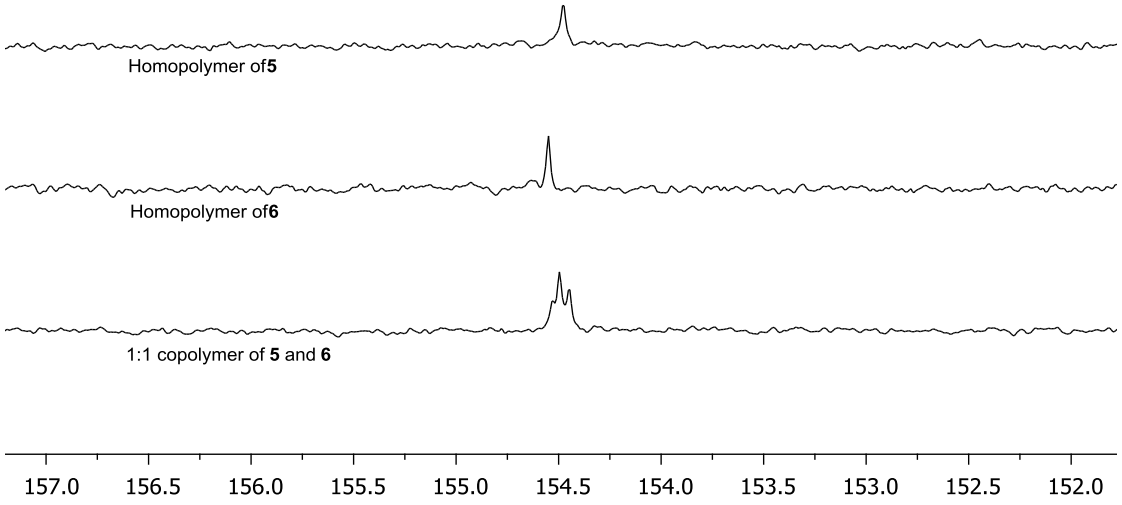


Figure S5. ^{13}C NMR spectra of poly(**5**), poly(**6**) and 1:1 copolymer (**5**:**6**) in $CDCl_3$ (100 MHz, 298 K).

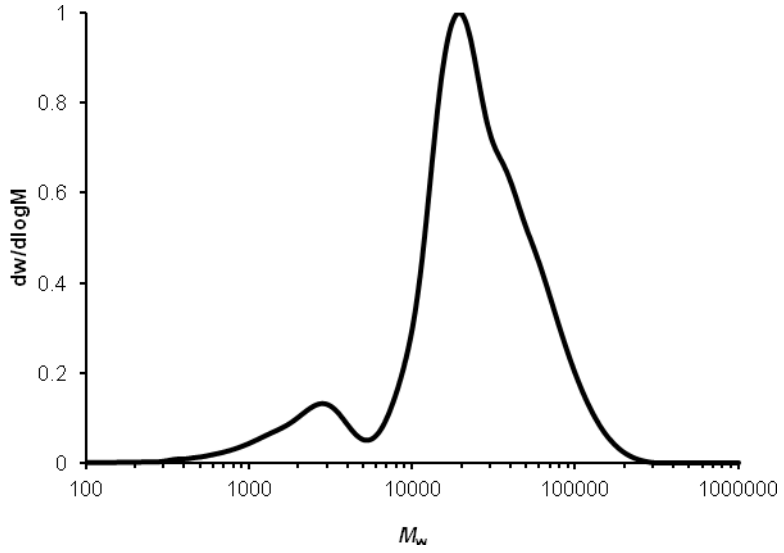


Figure S6. SEC trace of poly(**6**-*co*-**5**-*graft*-styrene) (M_n = 9.6 kDa, $Đ$ = 3.28) (polymerization performed in $CHCl_3$ at 65 ^oC, [CTA]:[AIBN]:[styrene] = 1:0.1:50, [starting polymer] = 0.01 M).

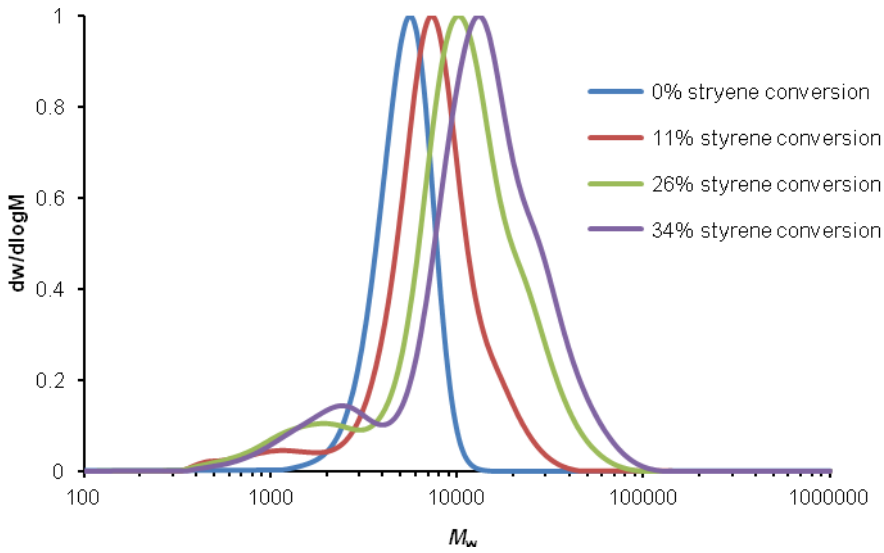


Figure S7. Evolution of SEC traces during preparation of poly(**6**-*co*-**5**-*graft*-styrene) (polymerization performed in $CHCl_3$ at 65 ^oC, [CTA]:[AIBN]:[styrene] = 1:0.1:50, [starting polymer] = 0.003 M).

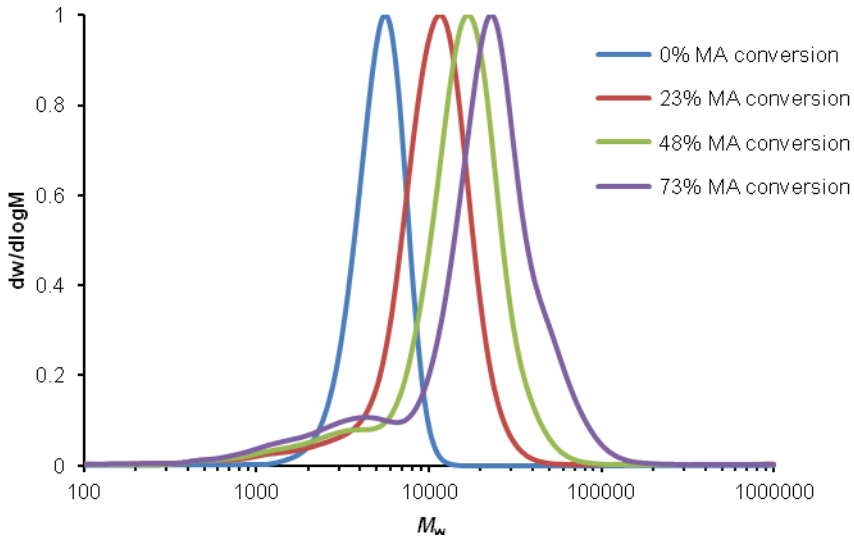


Figure S8. Evolution of SEC traces during preparation of poly(**6**-*co*-**5**-*graft*-MA) (polymerization performed in $CHCl_3$ at 65 ^oC, [CTA]:[AIBN]:[MA] = 1:0.1:50, [starting polymer] = 0.003 M).

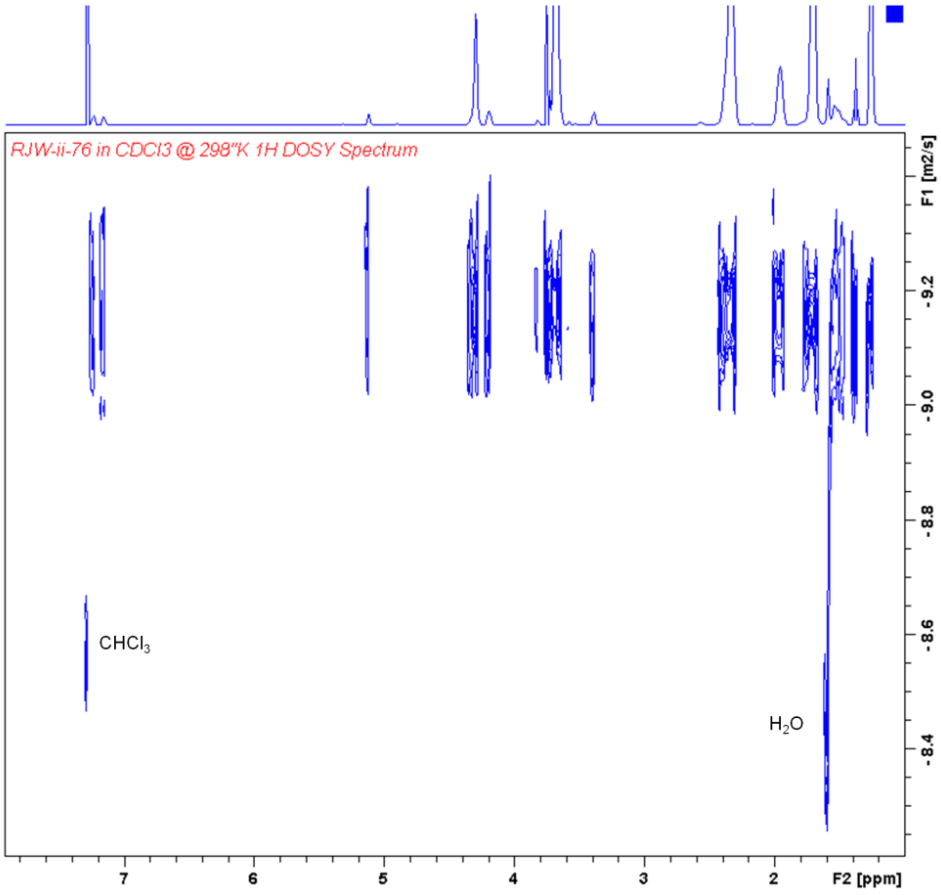


Figure S9. ^{1}H DOSY spectrum of poly(**6**$_{13}$-*co*-**5**$_{7}$-*graft*-MA$_{39}$) in $CDCl_3$ (500 MHz, 298 K).

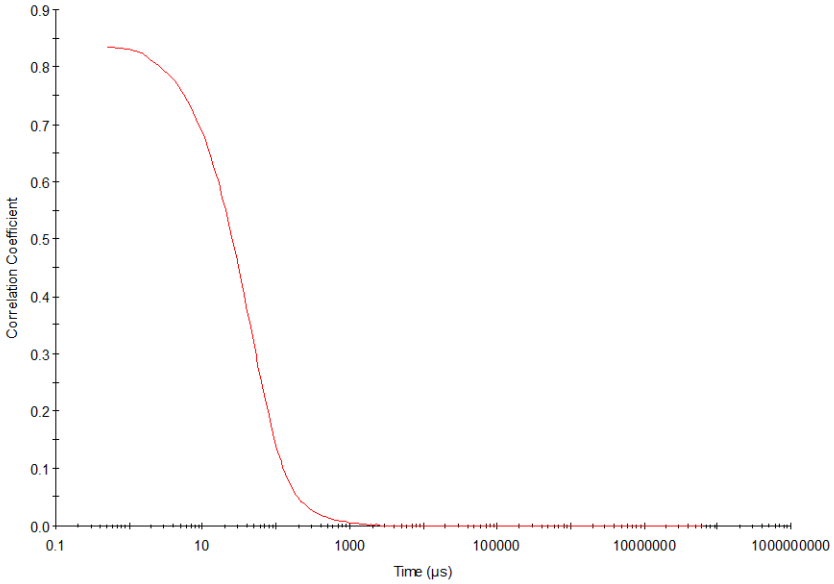


Figure S10. Correlation function for poly(**6**$_{13}$-*co*-**5**$_{4}$-*graft*-NiPAm$_{40}$) micelles at 1 mg mL^{-1} in nanopure water.

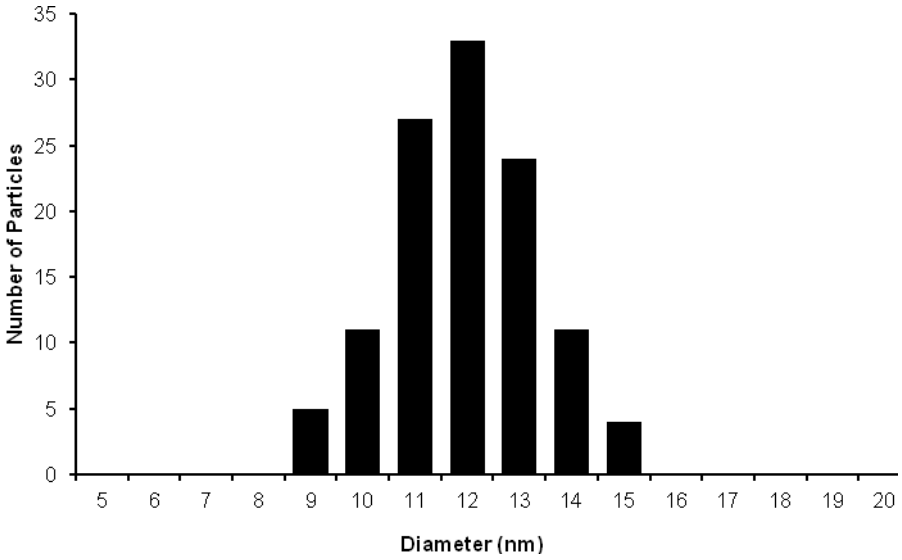


Figure S11. TEM size distribution histogram for poly(**6**$_{13}$-*co*-**5**$_4$-*graft*-NiPAm$_{40}$) micelles.

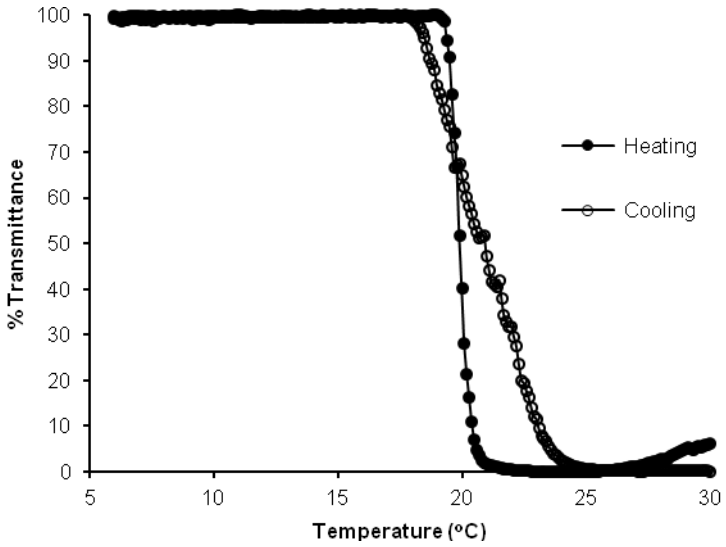


Figure S12. Percentage transmittance *versus* temperature plot for poly(**6**$_{13}$-*co*-**5**$_4$-*graft*-NiPAm$_{40}$) at 1mg mL^{-1} in nanopure water (heating/cooling rate 1 ^{o}C min^{-1}).

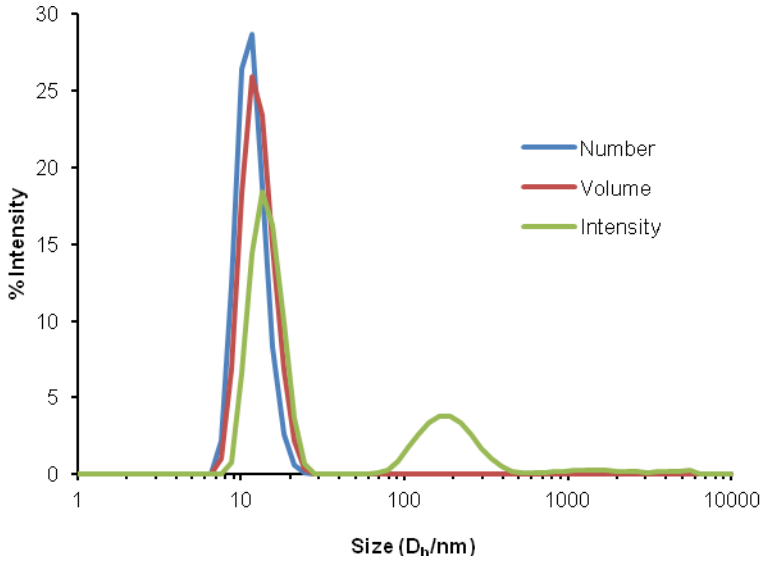


Figure S13. DLS data for micelles prepared from poly(**6**$_{13}$-*co*-**5**$_4$-*graft*-NiPAm$_{40}$) formed after a heating/cooling cycle.

References

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