Electronic Supplementary Material (ESI) for ChemComm.
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Disulfides as Mercapto-Precursors in Nucleophilic Ring Opening Reaction of Polymeric Epoxides: Establishing Equimolar Stoichiometric Conditions in Thiol-Epoxy 'Click' Reaction

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General Methods and Materials

Glycidyl methacrylate, methyl methacrylate, ethyl α-bromoisobutyrate (EBiB) 4,4'-dinonyl-2,2'-dipyridyl (dNbpy), Cu(I)Br, phenyl disulfide, 2-hydroxyethyl disulfide, and sodium borohydride ($NaBH_4$) were purchased from commercial sources. PEG macroinitiator (5k) was prepared according to the procedure described in *Polymer chemistry*, 2012, *3*, 2342. NMR spectra were recorded on a Varian NMR system 500 MHz spectrometer, using DMSO-d_6 as the solvent. Gel permeation chromatography (GPC) (against polystyrene standards) was carried out in THF using a Waters system (Waters 1515 pump, Water 2414 refractive 5 index detector) with three styragel HR 0.5, HR 2, HR 4 columns. GPC (against polystyrene standards) in DMF (1% LiBr) was carried out using a Waters system (Waters 1515 pump, Water 2414 refractive 5 index detector) with four styragel HR 0.5, HR 5E, HR 4, HR 5 columns. Fourier Transform infrared (FT-IR) spectrometer with ATR (attenuated total reflection) was carried out on an Agilent Cary 630 FTIR.

Synthesis of Scaffolds

Synthesis of PGMA (**1**): glycidyl methacrylate (3 g, 21.11 mmol), 4,4'-dinonyl-2,2'-dipyridyl (dNbpy) (22.3 mg, 0.22 mmol), ethyl α-bromoisobutyrate (EBiB) (21.3 mg, 0.11 mmol), and anisole (3 mL) were added to a schlenk tube and purged by bubbling Ar for 30 min. Cu(I)Br (15.6 mg, 0.11 mmol) was added and Ar purging was continued for another 5 min. The reaction mixture was then stirred under inert atmosphere at room temperature for overnight. After this time, the reaction mixture was cooled to room temperature and precipitated into isopropanol, filtered, and passed through a small plug of silica gel using THF as an eluent. The organic solvent was reduced under low pressure and then precipitated into isopropanol. The obtained white powder was then dried under high vacuum conditions. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.30 (br s, COO**CH$_2$**), 3.74 (br s, COO**CH$_2$**), 3.21 (br s, CH$_2$**CH**CH$_2$O), 2.80 (br s, COOCH$_2$CH**CH$_2$**O), 2.66 (br s, COOCH$_2$CH**CH$_2$**O), 2.17 – 0.57 (br multiple signals, backbone). GPC(THF): M_n = 22100, M_w = 27900, PDI (M_w/M_n) = 1.26. GPC(DMF): M_n = 21200, M_w = 27000, PDI (M_w/M_n) = 1.27.

Synthesis of PMMA-*r*-PGMA (**6**): methyl methacrylate (2 g, 19.9 mmol), glycidyl

methacrylate (1.42 g, 9.99 mmol), 4,4'-dinonyl-2,2'-dipyridyl (dNbpy) (76 mg, 0.19 mmol), ethyl α-bromoisobutyrate (EBiB) (18 mg, 0.09 mmol), and anisole (4 mL) were added to a schlenk tube and purged by bubbling Ar for 30 min. Cu(I)Br (13mg, 0.09 mmol) was added and Ar purging was continued for another 5 min. The reaction mixture was then stirred under inert atmosphere at room temperature for 5 hrs. After this time, the reaction mixture was cooled to room temperature and precipitated into isopropanol, filtered, and passed through a small plug of silica gel using THF as an eluent. The organic solvent was reduced under low pressure and then precipitated into hexane. The obtained white powder was then dried under high vacuum conditions. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.32 (br s, COO**CH$_2$**), 3.74 (br s, COO**CH$_2$**), 3.56 (br s, O**CH3**), 3.17 (br s, CH$_2$**CH**CH$_2$O), 2.82 (br s, COOCH$_2$CH**CH$_2$**O), 2.65 (br s, COOCH$_2$CH**CH$_2$**O), 2.13 – 0.58 (br multiple signals, backbone). GPC(THF): M_n = 20300, M_w = 25200, PDI (M_w/M_n) = 1.20.

Synthesis of PEG-*b*-PGMA (**7**): PEG macroinitiator (5k) (250 mg, 0.05 mmol), glycidyl methacrylate (500 mg, 3.52 mmol), 4,4'-dinonyl-2,2'-dipyridyl (dNbpy) (40.9 mg, 0.05 mmol), and anisole (1 mL) were added to a schlenk tube and purged by bubbling Ar for 30 min. Cu(I)Br (7.2 mg, 0.1 mmol) was added and Ar purging was continued for another 5 min. The reaction mixture was then stirred under inert atmosphere at room temperature for 3 hrs. After this time, the reaction mixture was cooled to room temperature and precipitated into isopropanol, filtered, and passed through a small plug of silica gel using THF as an eluent. The organic solvent was reduced under low pressure and then precipitated into isopropanol. The obtained white powder was then dried under high vacuum conditions. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.30 (br s, COO**CH$_2$**), 3.73 (br s, COO**CH$_2$**), 3.50 (br s, **CH$_2$CH$_2$**O), 3.22 (br s, CH$_2$**CH**CH$_2$O), 2.80 (br s, COOCH$_2$CH**CH$_2$**O), 2.66 (br s, COOCH$_2$CH**CH$_2$**O), 2.20 – 0.66 (br multiple signals, backbone). GPC(THF): M_n = 14600, M_w = 18400, PDI (M_w/M_n) = 1.26. GPC(DMF): M_n = 13600, M_w = 17000, PDI (M_w/M_n) = 1.24.

Post-Polymerization Modifications

Polymer **3**: To a solution of PGMA **1** (500 mg, 3.52 mmol of epoxy units) and phenyl disulfide (384 mg, 1.76 mmol (0.5 eq. per epoxy unit)) in THF (9 mL) at 0 °C, a solution of sodium borohydride (133 mg, 3.52 mmol (2 eq. per disulfide)) in water (1 mL) was added drop wise. The reaction was exothermic and evolution of hydrogen gas could be observed. The reaction mixture was then stirred at room temperature for 12 hours. After this time, the reaction mixture was precipitated into methanol thrice and then dried under high vacuum conditions. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 – 7.07 (br m, -S**Ph**), 5.33 (br s,

CH(**OH**)CH_2S), 4.05 – 3.71 (br m, COO**CH_2CH**(OH)), 2.98 (br d, CH(OH)**CH_2**S), 2.17 – 0.57 (br multiple signals, backbone). GPC(THF): M_n = 32000, M_w = 43500, PDI (M_w/M_n) = 1.36.

Polymer **5**: To a solution of PGMA **1** (30 mg, 0.21 mmol of epoxy units) and 2-hydroxyethyl disulfide (16 mg, 0.105 mmol (0.5 eq. per epoxy units)) in THF (0.9 mL) at 0 °C, a solution of sodium borohydride (8 mg, 0.21 mmol (2 eq. per disulfide)) in water (0.1 mL) was added drop wise. The reaction was exothermic and evolution of hydrogen gas could be observed. The reaction mixture was stirred at room temperature for 12 hours. After this time, the reaction mixture was precipitated into water thrice and then dried under high vacuum conditions. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.18 (br s, CH(**OH**)CH_2S), 4.80 (br m, -SCH_2CH_2**OH**), 4.10 – 3.70 (br m, COO**CH_2CH**(OH)), 3.56 (br s, -SCH_2**CH_2**OH), 2.64 (br s, **CH_2SCH_2**), 2.13 – 0.58 (br multiple signals, backbone). GPC(DMF): M_n = 30500, M_w = 38700, PDI (M_w/M_n) = 1.26.

Polymer **8**: To a solution of PMMA-*r*-PGMA **6** (30 mg, 0.07 mmol of epoxy units) and 2-hydroxyethyl disulfide (5.4 mg, 0.035 mmol (0.5 eq. per epoxy units)) in THF (0.9 mL) at 0 °C, a solution of sodium borohydride (2.6 mg, 0.07 mmol (2 eq. per disulfide)) in water (0.1 mL) was added dropwise into the solution. The reaction was exothermic and evolution of hydrogen gas could be seen. The reaction mixture was stirred at room temperature for 12 hours. After this time, the reaction mixture was precipitated into water thrice and then dried under high vacuum conditions. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.18 (br s, CH(**OH**)CH_2S), 4.80 (br s, -SCH_2CH_2**OH**), 3.98 – 3.74 (br m, COO**CH_2CH**(OH)), 3.54 (br s, SCH_2**CH_2**OH + O**CH_3** (PMMA)), 2.64 (br s, **CH_2SCH_2**), 2.13 – 0.58 (br multiple signals, backbone). GPC(THF): M_n = 27200, M_w = 33800, PDI (M_w/M_n) = 1.24.

Polymer **9**: To a solution of PEG-*b*-PGMA **7** (30 mg, 0.21 mmol of epoxy units) and 2-hydroxyethyl disulfide (16 mg, 0.105 mmol (0.5 eq. per epoxy units)) in THF (0.9 mL) at 0 °C, a solution of sodium borohydride (8 mg, 0.21 mmol (2 eq. per disulfide)) in water (0.1 mL) was added drop wise. The reaction was exothermic and hydrogen gas evolved. the reaction mixture was stirred at room temperature for 12 hours. After this time, the reaction mixture was diluted with water and then dialyzed (dialysis tube: cutoff 1 kDa) against DI water for 1day. Polymer solution was lyophilized to dryness to obtain the product. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.16 (br s, CH(**OH**)CH_2S), 4.80 (br m, -SCH_2CH_2**OH**), 4.05 – 3.70 (br m, COO**CH_2CH**(OH)), 3.56 (br s, -SCH_2**CH_2**OH), 3.50 (br s, **CH_2CH_2**O (PEG)), 2.63 (br s, **CH_2SCH_2**), 2.22 – 0.66 (br multiple signals, backbone). GPC(DMF): M_n = 18500, M_w =

23700, PDI (M_w/M_n) = 1.28.

Table 1. Solubility behavior of the synthesized polymers.

Polymer	Hexane	$CHCl_3$	DCM	THF	MeOH	DMSO	Water
3	-	-	++	+	-	++	-
5	-	+	++	-	-	++	-
8	-	++	++	+	++	++	-
9	-	-	-	-	++	++	++

++ = high solubility, + = good solubility, - = insoluble

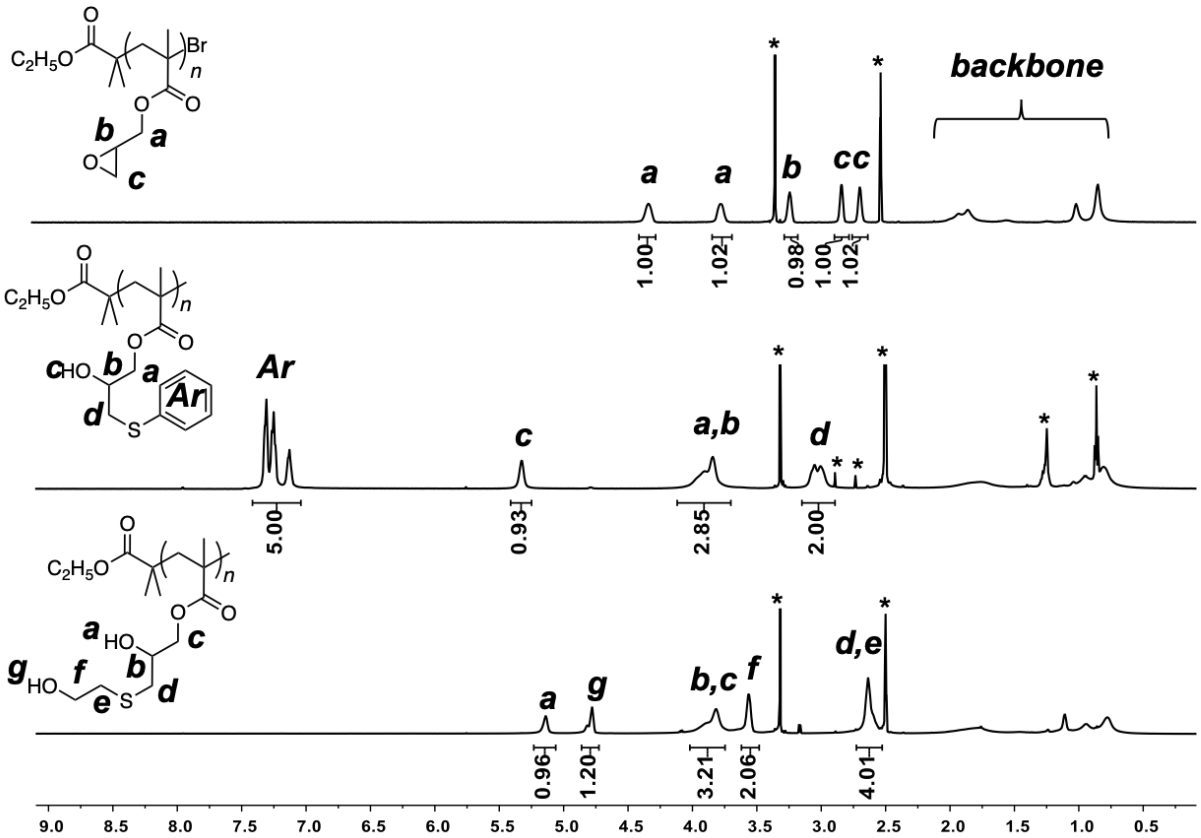

Figure S1. ^{1}H-NMR of polymer **1**, **3**, and **5** in deuterated dimethylsulfoxide (DMSO). The residual solvent signals from water, DMSO, dimethylformamide, and hexanes are shown with an asterisk.

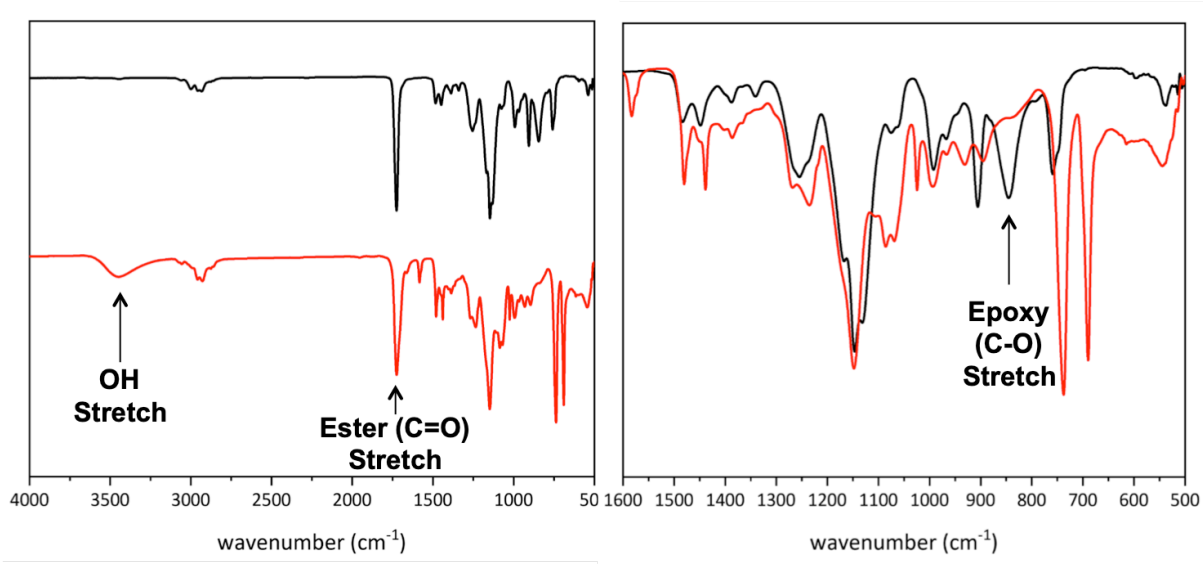

Figure S2. IR spectra of polymer **1** (black) and **3** (red). The shoulder at the ester stretch in polymer **3** is due to contamination with dimethylformamide (1660 cm^{-1}).

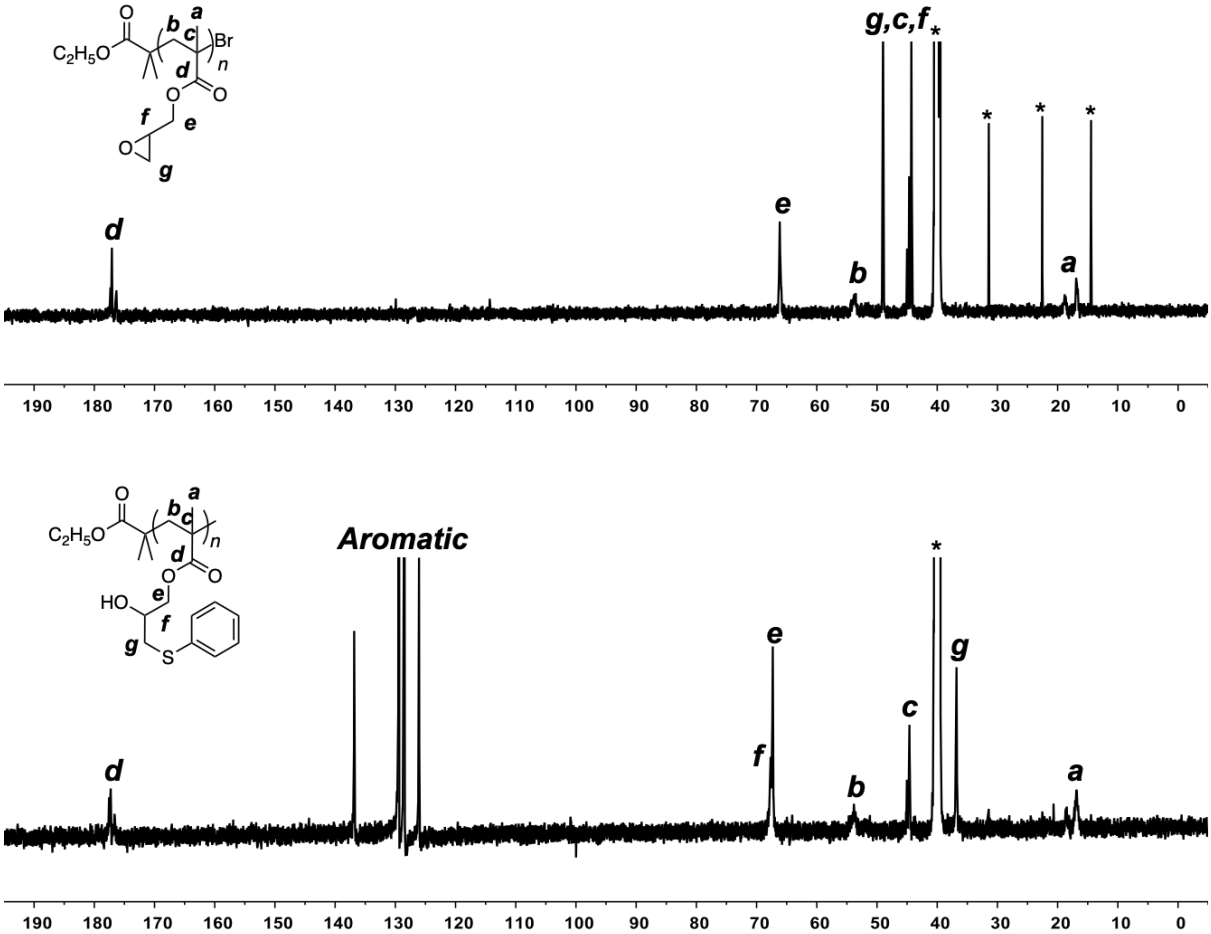

Figure S3. ^{13}C-NMR of polymer **1** (top) and **3** (bottom) in deuterated dimethylsulfoxide. The residual solvent (DMSO and hexanes) signals are shown with an asterisk.

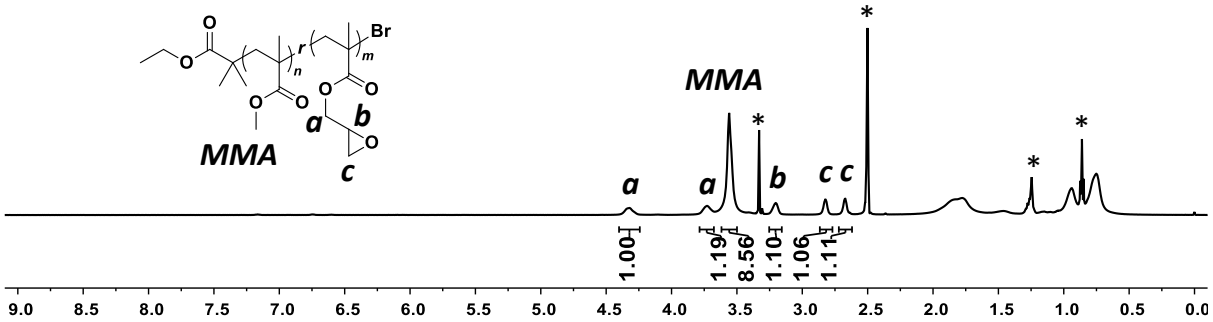

Figure S4. ^{1}H-NMR of polymer **6** in deuterated dimethylsulfoxide. (DMSO). The residual solvent signals from water, DMSO, and hexanes are shown with an asterisk.

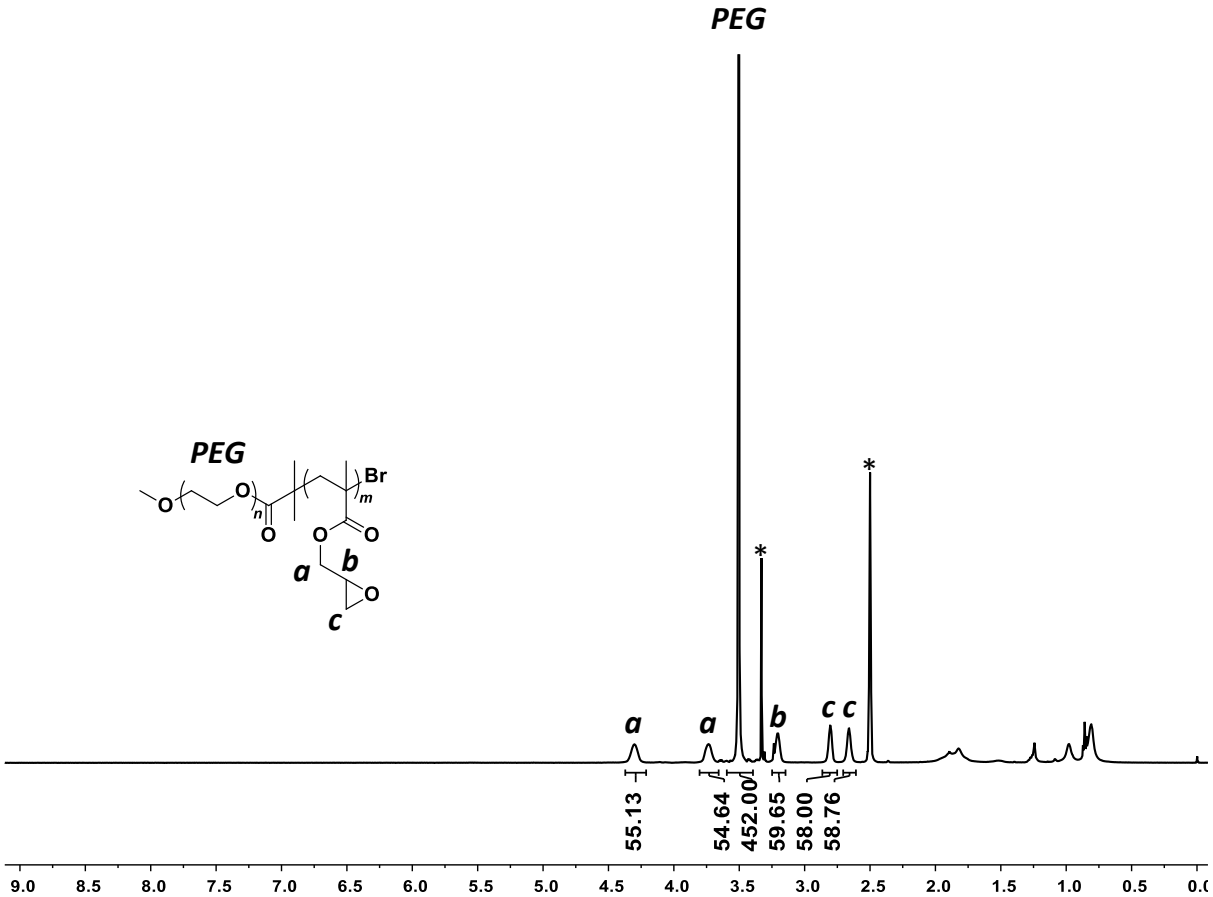

Figure S5. ^{1}H-NMR of polymer **7** in deuterated dimethylsulfoxide (DMSO). The residual solvent signals from water and DMSO are shown with an asterisk.

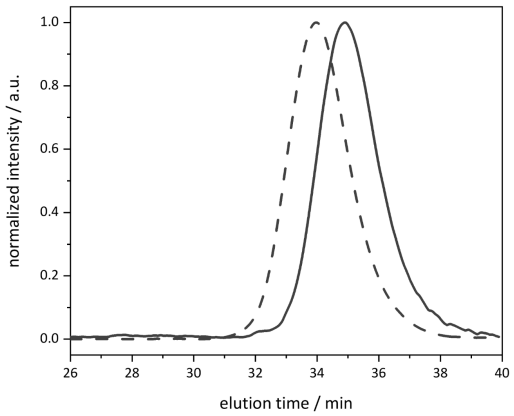

Figure S6. GPC traces for polymers **1** (solid line) and **5** (dash line) in DMF with 1% LiBr.

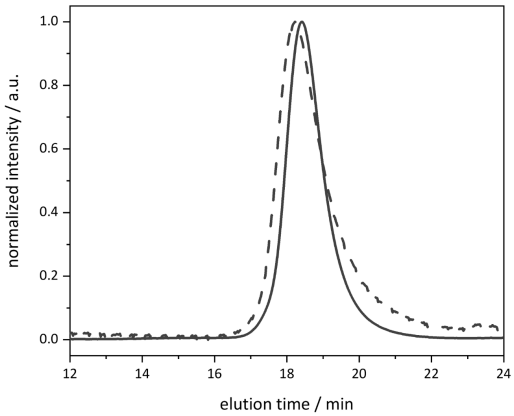

Figure S7. GPC traces for polymers **6** (solid line) and **8** (dash line) in THF.

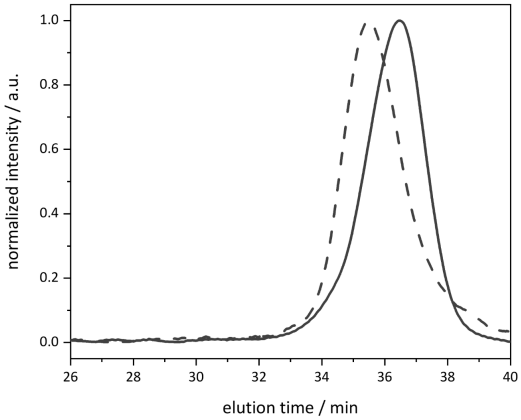

Figure S8. GPC trace for polymers **7** (solid line) and **9** (dash line) in DMF with 1% LiBr.

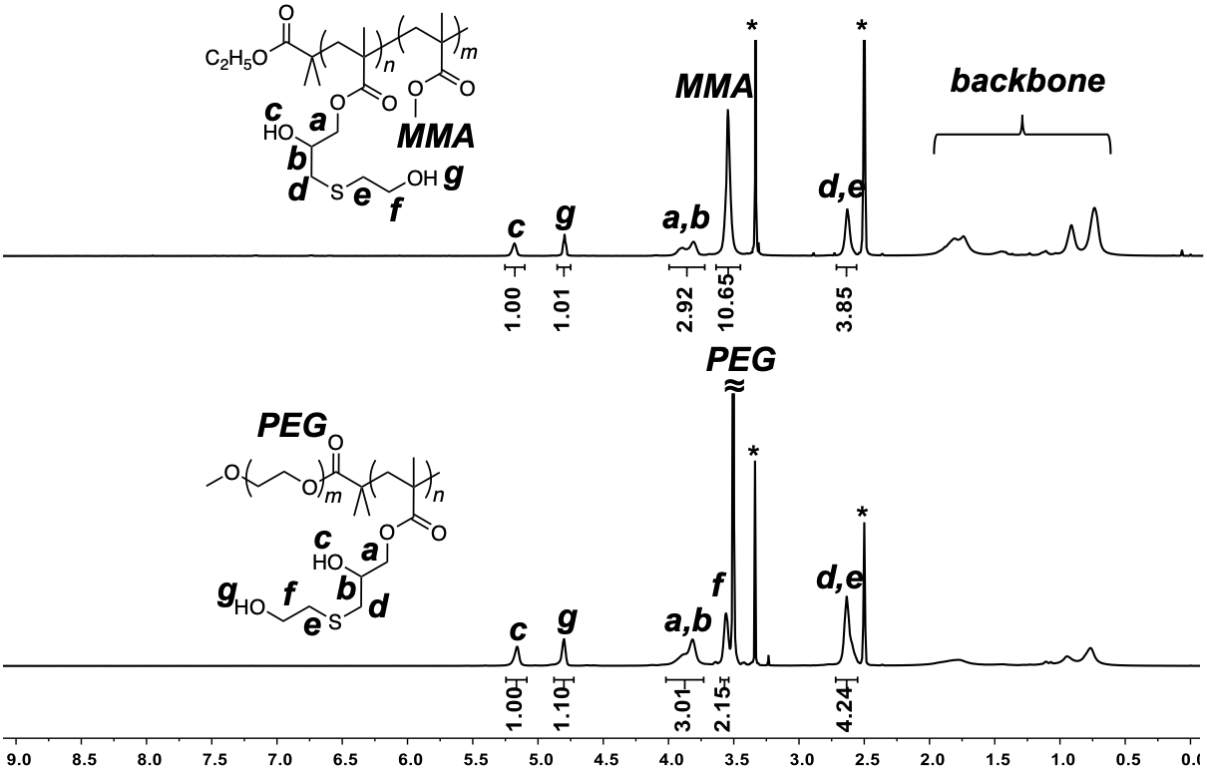

Figure S9. ^{1}H-NMR of polymer **8** and **9** in deuterated dimethylsulfoxide (DMSO). The residual solvent signals from water and DMSO are shown with an asterisk.