Supporting Information for:

Temperature-Sensitive Aliphatic Polyesters: Synthesis and Characterization of γ-Substituted Functional Caprolactone Monomers and Polymers

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Experimental

Materials

All commercial chemicals were purchased from Aldrich Chemical Co., Inc. and were used without further purification unless otherwise noted. Benzyl alcohol and stannous (II) 2-ethylhexanoate were purified by vacuum distillation prior to use. All polymerization reactions were conducted under purified nitrogen. The polymerization glassware and syringes were dried at 120 °C for at least 24 hours before use and cooled under a nitrogen atmosphere.

Synthesis of 4-octyloxycyclohexanol

A solution of 1,4-cyclohexanediol (5.8 g, 0.05 mol) in 70 mL DMF was slowly added to a solution of NaH (1.32 g, 0.55 mol) in 20 mL of DMF. The solution was stirred for 1 h at room temperature, after which the solution was heated to 50 °C. After 2 h, the solution was cooled to room temperature and 1-bromooctane (9.7 g, 0.05 mol) was slowly added. The reaction mixture was stirred overnight, followed by quenching with HCl (1M). The solution was extracted with diethyl ether (3x100 mL), the ether layers were combined and washed with water (7x150 mL). The ether layer was dried and concentrated in vacuo. The mono-protected alcohol was isolated as a mixture of cis and trans isomers by flash chromatography (R_f = 0.27, 0.31 in hexane: ethyl acetate = 7:3) to obtain 3.63 g of a yellow oil (0.016 mol, 32%).

^{1}H NMR (270 MHz, $CDCl_3$): δ_H 0.87 (t, 3H), 1.49 (m, 10H), 1.56 (m, 4H), 1.60 (m, 4H), 1.77 (m, 8H) 1.81 (m, 2H), 3.38 (m, 3H), 3.73 (m, 1H).

Synthesis of 4-octyloxycyclohexanone

Sulfuric acid 2M (10 mL) was added slowly to a solution of potassium dichromate (6.59 g, 0.22 mol) in water. A solution of 4-octyloxycyclohexanol (3.63 g, 0.016 mol) in tetrahydrofuran (THF) was slowly added to the potassium dichromate solution. After 3 h, the solution was extracted with diethyl ether (3x100 mL) and the ether layers were washed with water (3x150 mL). The ether layer was dried over magnesium sulfate and concentrated in vacuo to yield 2.92 g of a yellow oil product (0.013 mol, 81%).

^{1}H NMR (270 MHz, $CDCl_3$): δ_H 0.86 (t, 3H), 1.29 (m, 10H), 1.57 (m, 2H), 1.92 (m, 2H), 2.04 (m, 2H), 2.26 (m, 2H), 2.56 (m, 2H), 3.46 (t, 2H), 3.66 (m, 1H).

Synthesis of γ-octyloxy-ε-caprolactone

A solution of 4-octyloxycyclohexanone (2.91 g, 0.013 mol) in chloroform was added to a solution of 77% *m*-chloroperoxybenzoic acid (3.79 g, 0.022 mol) in chloroform under stirring. The reaction was left overnight followed by washing five times with saturated sodium bicarbonate and once with brine. The organic phase was dried over magnesium sulfate and concentrated in vacuo. The compound was isolated by flash chromatography (R_f = 0.45 in hexane: ethyl acetate=7:3) to yield 2.38 g of colorless oil (0.0098 mol, 75%).

^{1}H NMR (270 MHz, $CDCl_3$): δ_H 0.88 (t, 3H), 1.258 (br, 12H), 1.54 (m, 2H), 1.97 (m, 4H), 2.40 (ddd, 1H), 2.97 (ddd, 1H), 3.40 (m, 2H), 3.62 (m, 1H), 4.03 (ddd, 1H), 4.49 (ddd, 1H). ^{13}C NMR (270 MHz, CDCl3): δ_C 14.16, 22.71, 26.31, 27.46, 27.94, 29.32, 29.47, 30.09, 31.89, 34.14, 63.55, 68.47, 73.80, 176.24. Anal. Calculated for $C_{14}H_{26}O_3$: C, 69.38%; H, 10.81%. Found: C, 67.78%; H, 10.54%. EI MS m/z: [M+] 242.2.

Synthesis of 2-[2-(2-methoxyethoxy)ethoxy]ethyl-4-methylbenzenesulfonate

A solution of 4-toluenesulfonyl chloride (11.5 g, 0.06 mol) in dichloromethane (150 mL) was added drop-wise to a solution of 2-[2-(2-methoxyethoxy)ethoxy]ethanol (9.5 mL, 0.057 mol) and triethylamine (17 mL, 0.114 mol) in dichloromethane (20 mL) at 0°C under a nitrogen atmosphere. The formation of a white precipitate was observed. The reaction mixture was stirred at room temperature for 18 h and then poured into water (50 mL). The water layer was extracted with dichloromethane. The organic layers were combined and washed with 3M HCl (50 mL), sodium bicarbonate (50 mL), and water (50 mL). The organic phase was dried over magnesium sulfate. The solvent was removed in vacuo to yield 18.2 g of pale yellow oil (0.0564 mol, 99 %). ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 2.43 (s, 3H), 3.36 (s, 3H), 3.59 (m, 10H), 4.14 (t, 2H), 7.34 (d, 2H), 7.77 (d, 2H).

Synthesis of 4-2-[2-(2-methoxyethoxy)ethoxy]ethoxycyclohexanone

A solution of 1,4-cyclohexanediol (7.3 g, 0.063 mol) in 70 mL dimethylformamide (DMF) was slowly added to a NaH suspension in 30 mL DMF (1.77 g, 0.073 mol) under a nitrogen atmosphere. The solution was stirred for 1 h at room temperature, followed by heating at 50°C for 5 hrs. At this time, *2*-[2-(2-methoxyethoxy)ethoxy]ethyl-4-methylbenzenesulfonate (18.2 g, 0.057 mol) was added slowly to the solution under a nitrogen flow. The reaction was stirred at room temperature overnight and heated for 2 h before quenching with 1M HCl. DMF solvent was removed by vacuum distillation and the residual solid was extracted with diethyl ether. The product was concentrated in vacuo to yield 16 g of yellow oil which was was used directly in the next step. Sulfuric acid (98 %) (7.6 mL) was added slowly in an ice bath to a mixture of water (10 mL) and 19.7 g of potassium dichromate. The chromic acid was diluted with 50 mL water and was added to the product from the previous step. The reaction mixture was stirred overnight

followed by extraction with dichloromethane (3x150 mL). The organic layer was washed with a small amount of water. Extensive washing should be avoided as the product is partially soluble in water. The organic layer was dried and concentrated in vacuo and the product was isolated by flash chromatography (R_f = 0.33 in ethyl acetate) to yield 2.2 g (0.0085 mol, 13.4 %) of pale yellow liquid.

^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.94 (m, 2H), 2.07 (m, 2H), 2.24 (m, 2H), 2.58 (m, 2H), 3.36 (s, 3H), 3.67 (m, 13H).

Synthesis of γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone

A solution of 4-2-[2-(2-methoxyethoxy)ethoxy]ethoxycyclohexanone (2.1 g, 0.008 mol) in dichloromethane was added to a stirred solution of 77 % *m*-chloroperoxybenzoic acid (3.36 g, 0.0137 mol) in dichloromethane. The reaction was left overnight at room temperature. Potassium carbonate (4 g) and 10 mL of water were added to solution and stirred vigorously for 2 h. The organic layer was separated and the water layer was washed with dichloromethane, (2x20 mL). The organic phase was dried over magnesium sulfate and concentrated in vacuo. The product was isolated by flash chromatography (Rf = 0.3 in ethyl acetate) to yield 1.9 g (0.0072 mol, 90%) of pale yellow oil.

^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.85 (m, 4H), 2.31 (ddd, 1H), 2.89 (ddd, 1H), 3.27 (s, 3H), 3.55 (m, 13H), 3.96 (ddd, 1H), 4.41 (ddd, 1H). ^{13}C NMR (CDCl3): δ_C 27.38, 27.87, 33.99, 59.03, 63.46, 67.70, 70.55, 70.64, 70.67, 70.81, 71.93, 74.34, 176.16. Anal. Calculated for $C_{13}H_{24}O_6$: C, 56.51%; H, 8.75%. Found: C, 55.25%; H, 8.44%. EI MS m/z: [M+] 276.1.

Synthesis of poly(γ-octyloxy-ε-caprolactone)

γ-Octyloxy-ε-caprolactone (0.93 g, 0.0038 mol) was dried by azeotropic distillation from toluene. The toluene-water azeotrope was collected first, followed by the removal of toluene under vacuum. The dried monomer was transferred into a flame-dried, 10 mL Schlenk flask under a nitrogen atmosphere. A stock solution of $Sn(Oct)_2$ in hexane (0.015 g, $3.8x10^{-5}$ mol) and a stock solution of benzyl alcohol in hexane ($4.1x10^{-3}$g, 3.8 $x10^{-5}$ mol) were added to the Schlenk flask under a nitrogen atmosphere. The reaction mixture was deoxygenated by three consecutive freeze-pump-thaw cycles and the vacuum of last cycle was cancelled with nitrogen. The reaction flask was introduced in a thermostated oil bath at 110°C. Samples were periodically withdrawn to follow the conversion and the evolution of the molecular weight. The samples collected at different reaction times were analyzed by ^{1}H NMR to estimate the monomer conversion. SEC chromatography was used to estimate the molecular weight of the synthesized polymers. A similar polymerization was performed under the same condition with a different molar ratio of monomer to catalyst to initiator of 200:1:1 and 500:1:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.88 (t, 3H), 1.27 (m, 10H), 1.52 (m, 2H), 1.80 (m, 4H), 2.37 (t, 2H), 3.39 (m, 3H), 4.16 (t, 2H).

Synthesis of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}

Polymerization of γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone was performed with the same procedure as γ-octyloxycaprolactone. Polymerization reactions were performed at molar ratios of monomer to catalyst to initiator of 100:1:1, 200:1:1 and 500:1:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.82 (m, 4H), 2.38 (t, 2H), 3.36 (s, 3H), 3.59 (m, 13H), 4.15 (t, 2H)

*Synthesis of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}-b-poly(γ-octyloxy-ε-caprolactone)***(P3)**

Both monomers were dried by azeotropic distillation from toluene before the reaction. Dried γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone (0.56 g, 2.0×10^{-3} mol) was transferred into a flame-dried, 10 mL Schlenk flask under a nitrogen atmosphere. A stock solution of $Sn(Oct)_2$ (0.008 g, 2.0×10^{-5} mol) in hexane and a stock solution of benzyl alcohol (0.0021 g, 2.0×10^{-5} mol) in hexane were added to the Schlenk flask under a nitrogen atmosphere. The reaction mixture was deoxygenated by three consecutive freeze-pump-thaw cycles and the vacuum of last cycle was cancelled with nitrogen. The reaction flask was introduced in a thermostated oil bath at 110°C for 6 hours. At this time a sample was collected to determine the monomer conversion by ^{1}H NMR. Molecular weight of the poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone} before addition of the second monomer was determined by SEC. Deoxygenated γ-octyloxy-ε-caprolactone (0.51 g, 2.0×10^{-3} mol) was added to the reaction flask under a nitrogen atmosphere and the reaction was left overnight.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.89 (t, 3H), 1.27 (m, 10H), 1.54 (m, 2H), 1.80 (m, 8H), 2.38 (m, 4H), 3.38 (m, 6H), 3.60 (m, 13H), 4.15 (m, 4H)

Synthesis of poly(γ-octyloxy-ε-caprolactone)-b-poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}(**P4**)

Both monomers were dried by azeotropic distillation from toluene before the reaction. Dried γ-octyloxy-ε-caprolactone (0.96 g, 3.9×10^{-3} mol) was transferred into a flame-dried 10 mL Schlenk flask under nitrogen. A stock solution of $Sn(Oct)_2$ (0.016 g, 3.9×10^{-5} mol) in hexane and a stock solution of benzyl alcohol (4.3×10^{-3} mol, 3.9×10^{-5} mol) in hexane were added to the Schlenk flask under a nitrogen atmosphere. The reaction mixture was deoxygenated by three consecutive freeze-pump-thaw cycles and the vacuum of last cycle was cancelled with nitrogen. The reaction flask was introduced in a thermostated oil bath at 110°C for 6 hours. At this time a sample was

collected to determine the monomer conversion by ^{1}H NMR. Molecular weight of poly(γ-octyloxy-ε-caprolactone) before addition of the second monomer was determined by SEC. Deoxygenated *γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone* (1.1 g, 3.9x10^{-3} mol) was added to the reaction flask under a nitrogen atmosphere and the reaction was left overnight. The polymer was recovered by precipitation in methanol.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.89 (t, 3H), 1.27 (m, 10H), 1.54 (m, 2H), 1.80 (m, 8H), 2.38 (m, 4H), 3.38 (m, 6H), 3.60 (m, 13H), 4.15 (m, 4H)

Analysis

^{1}H NMR spectra of the synthesized monomers were recorded on a JEOL 270 MHz NMR spectrometer at 25°C in $CDCl_3$. ^{1}H NMR spectra of the synthesized polymers were recorded on a Varian 500Hz spectrometer at 30°C in $CDCl_3$. ^{1}H NMR data are reported in parts per million as chemical shift relative to tetramethylsilane (TMS) as the internal standard. GC/MS was performed on an Agilent 6890- 5973 GC-MS workstation. The following conditions were used for all GC/MS analyses: injector and detector temperature, 250°C; initial temperature, 70°C; temperature ramp, 10°C /min; final temperature, 280°C. Molecular weights of the synthesized polymers were measured by size exclusion chromatography (SEC) analysis on a Viscotek VE 3580 system equipped with ViscoGEL columns (GMHHR-M), connected to a refractive index (RI) detectors. GPC solvent/sample module (GPCmax) was used with HPLC grade THF as the eluent, and calibration was based on polystyrene standards. Running conditions for SEC analysis were flow rate=1.0 mL/min, injector volume=100 μL, detector temperature=30°C, and column temperature=35°C. All the polymers samples were dissolved in THF, and the solutions were filtered through PTFE filters (0.45 μm) prior to injection.

Fluorescence measurements

Fluorescence spectra were recorded on a Perkin-Elmer LS 50 BL luminescence spectrometer at room temperature. Pyrene was used as fluorescence probe. Fluorescence excitation spectra of pyrene were obtained at various polymer concentrations ($1\text{-}10^{-5}$ g/L). Excitation wavelength was 390 nm and pyrene concentration was kept constant at $4.0\text{x}10^{-6}$ M. The intensity ratio of $I_{338}/I_{334.5}$ from pyrene excitation spectrum was plotted vs log C.

Dynamic light Scattering measurements

Particle size of the aqueous solution **P2** (0.3 wt.%) and **P3** (3 wt.%) were determined by using a Brookhaven 90Plus Dynamic Light Scattering Particle Size Analyzer (DLS). The polymer solutions were filtered with a 0.2 µM filter before measurements. Measurements were taken from 25 °C to 55 °C and 25 °C to 50 °C for **P2** and **P3,** respectively.

Optical Transmittance measurements

Optical transmittance of the aqueous solution of **P2** (0.3 wt.%) and **P3** (3 wt.%) were recorded using a Varian Cary 300 Bio UV-Vis spectrophotometer equipped with a digital temperature controller. The wavelength of 600 nm was used for the determination of could point. The range of the temperature was from 22 °C to 55°C for both polymer solutions. The temperature at which a 50% decrease of transmittance was observed is defined as the cloudy point.

^{1}H and ^{13}C NMR Spectra

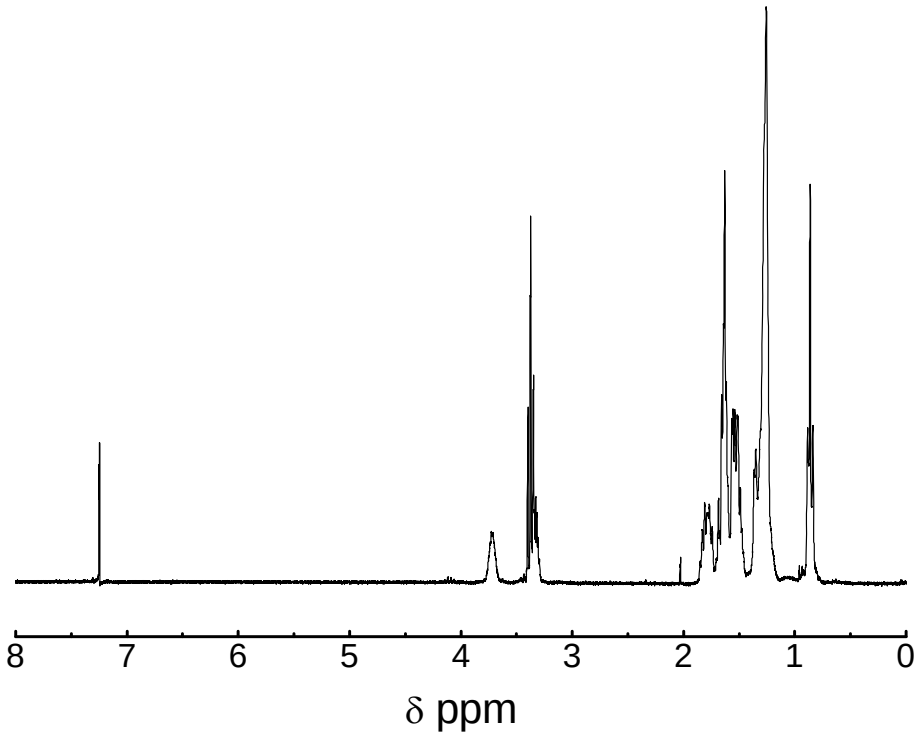

Figure S1. ^{1}H NMR spectrum of 4-octyloxycyclohexanol

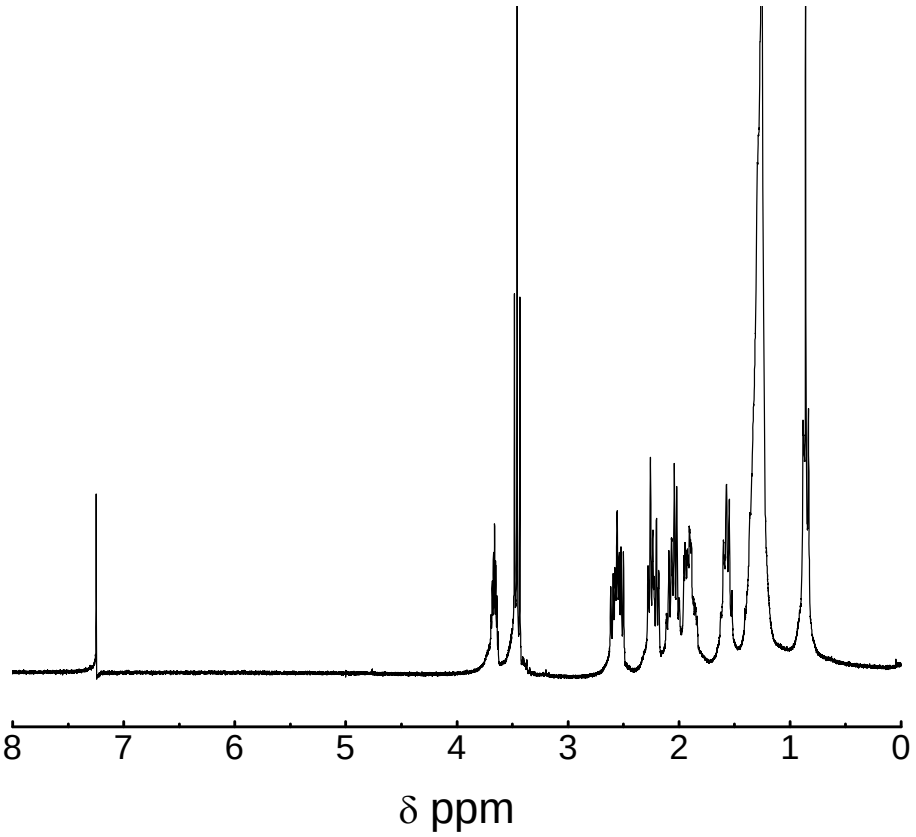

Figure S2. ^{1}H NMR spectrum of 4-octyloxycyclohexanone

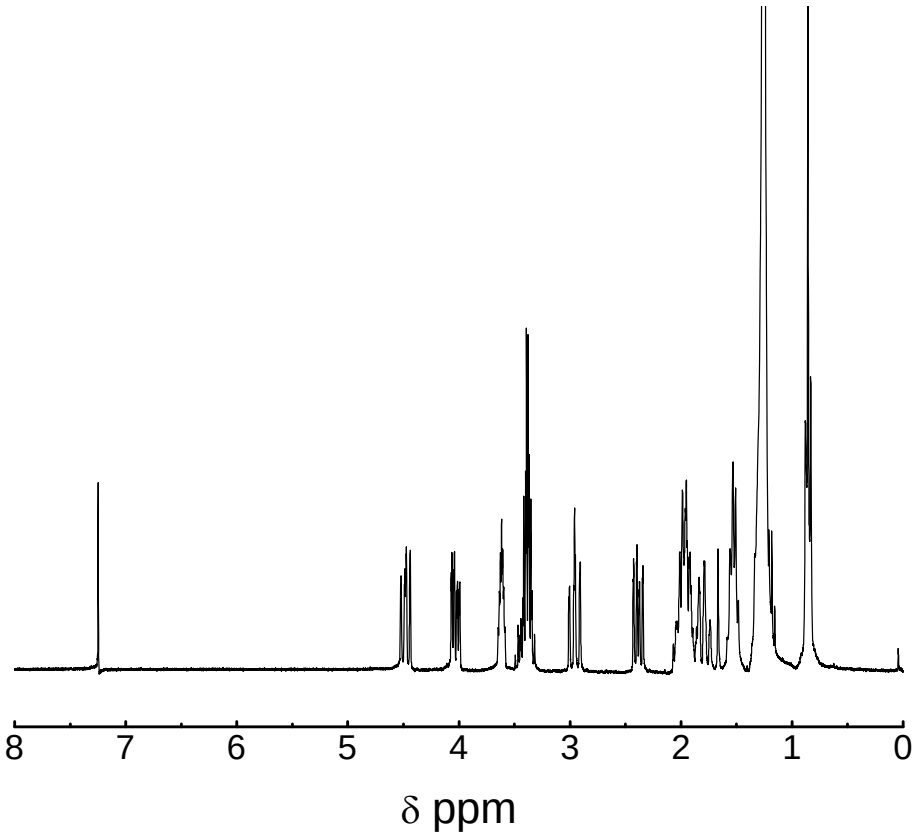

Figure S3. ^{1}H NMR spectrum of γ-octyloxy-ε-caprolactone

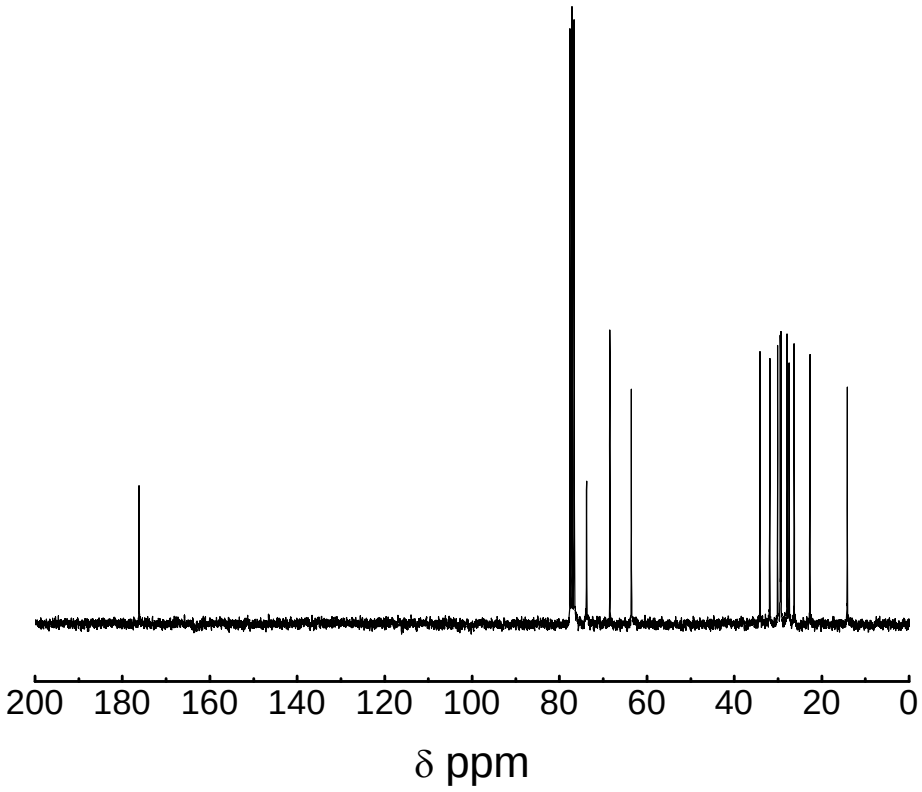

Figure S4. ^{13}C NMR spectrum of γ-octyloxy-ε-caprolactone

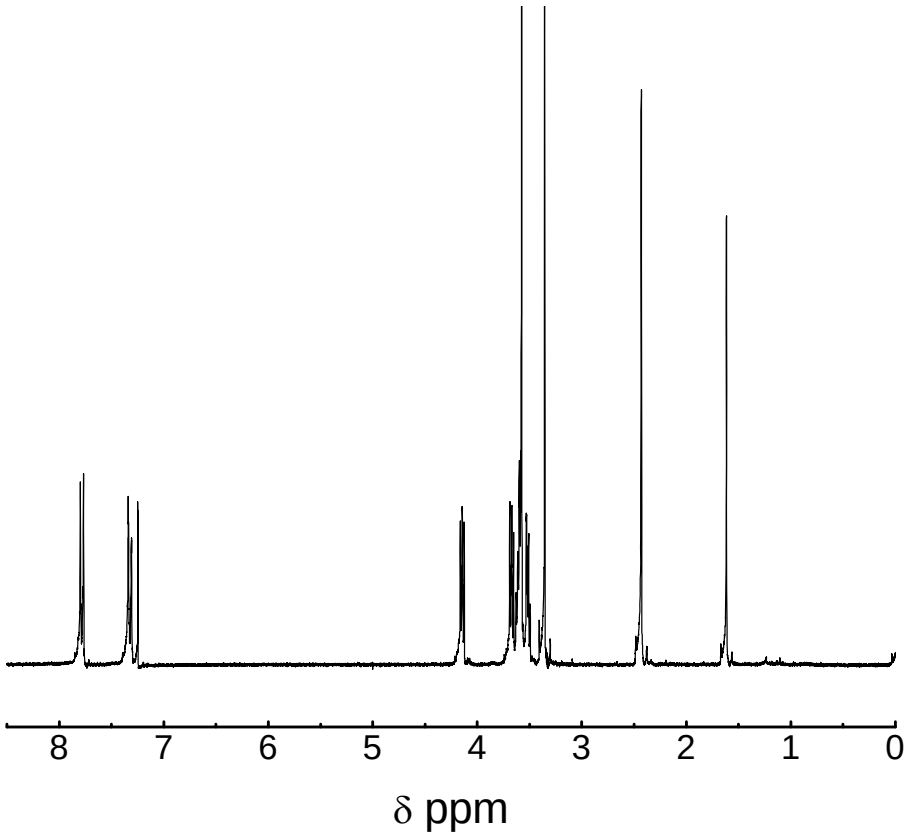

Figure S5. ^{1}H NMR spectrum of 2-[2-(2-methoxyethoxy)ethoxy]ethyl-4-methylbenzenesulfonate

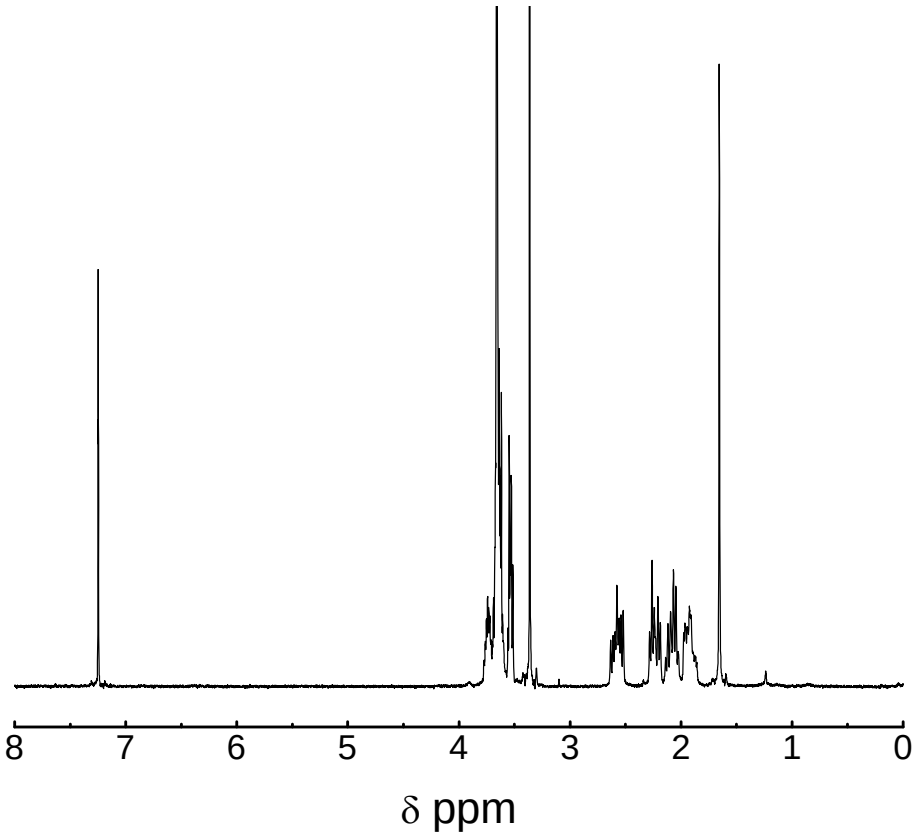

Figure S6. ^{1}H NMR spectrum of 4-2-[2-(2-methoxyethoxy)ethoxy]ethoxycyclohexanone

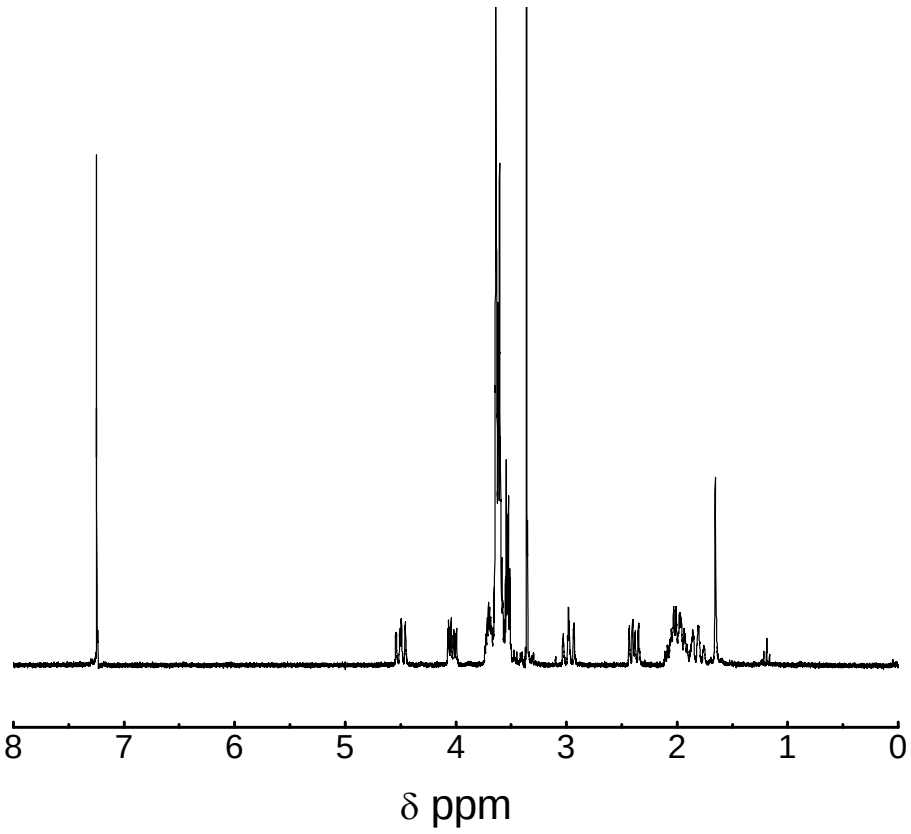

Figure S7. ^{1}H NMR spectrum of **γ**-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone

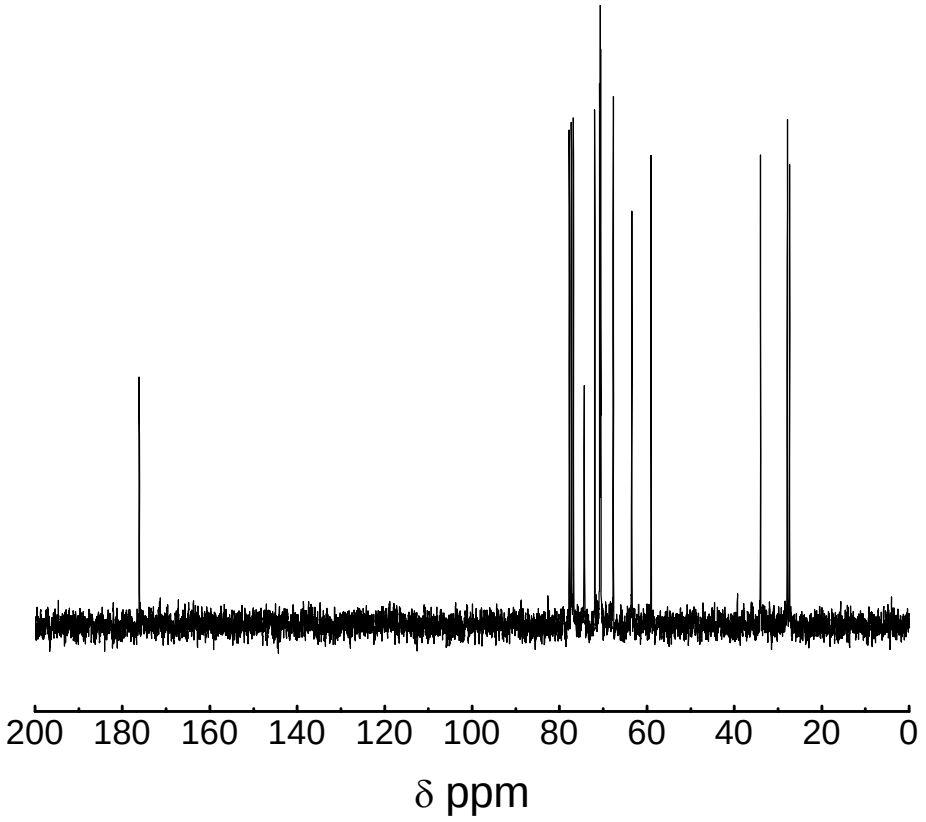

Figure S8. ^{13}C NMR spectrum of γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone

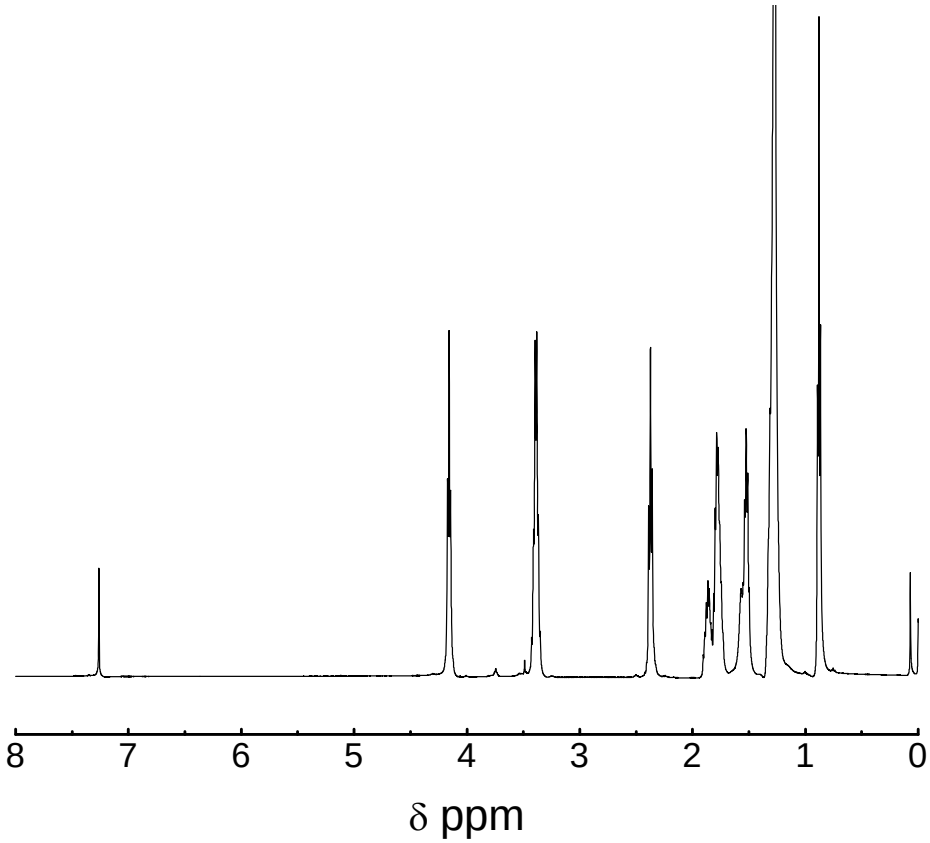

Figure S9. ^{1}H NMR spectrum of poly(γ-octyloxy-ε-caprolactone) (**P1**)

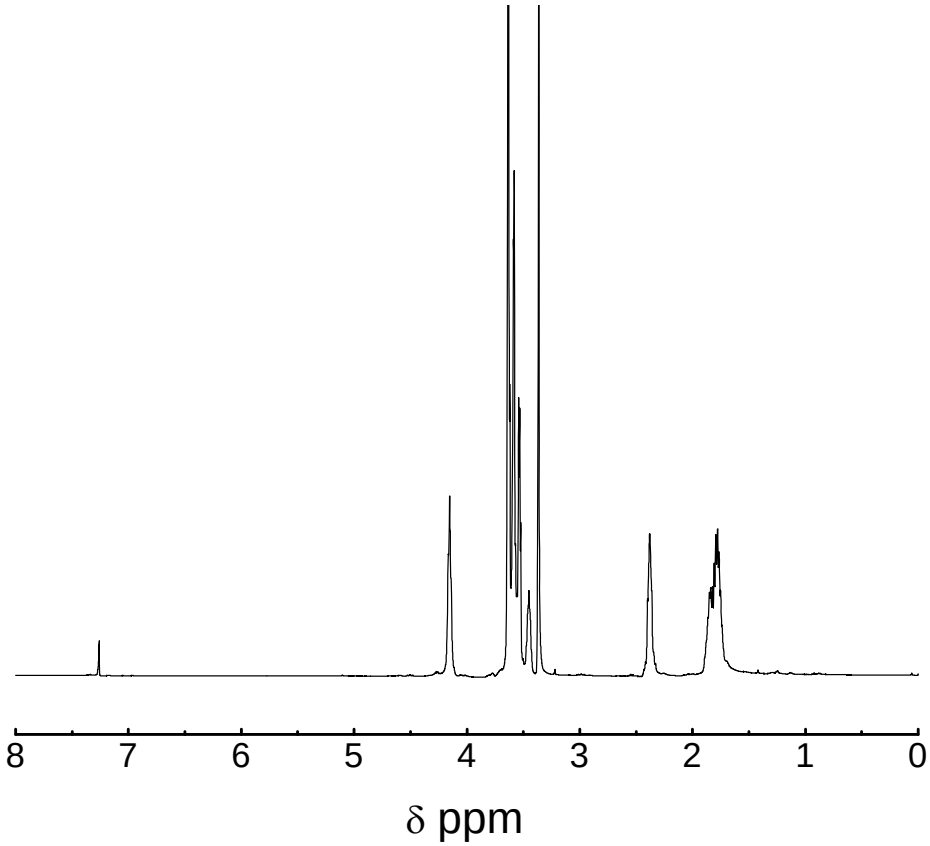

Figure S10. ^{1}H NMR spectrum of poly{**γ**-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone} (**P2**)

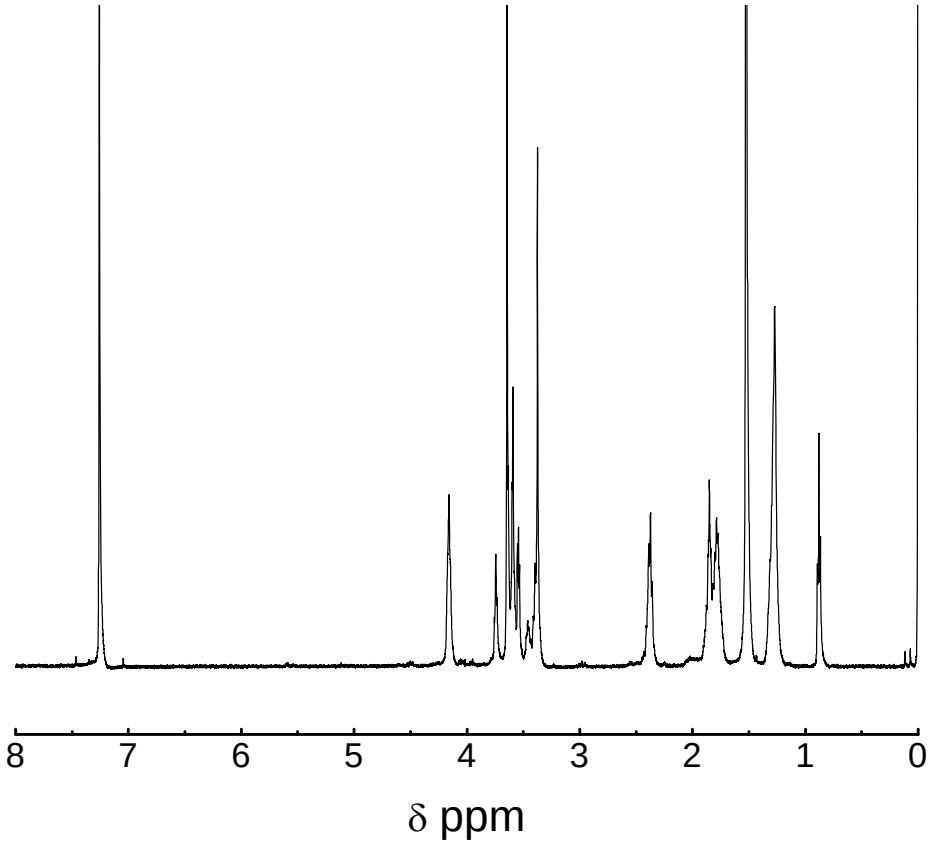

Figure S11. ^{1}H NMR spectrum of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}-*b*-poly(γ-octyloxy-ε-caprolactone) (**P3**); the copolymer contains 48.7 mol % of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}

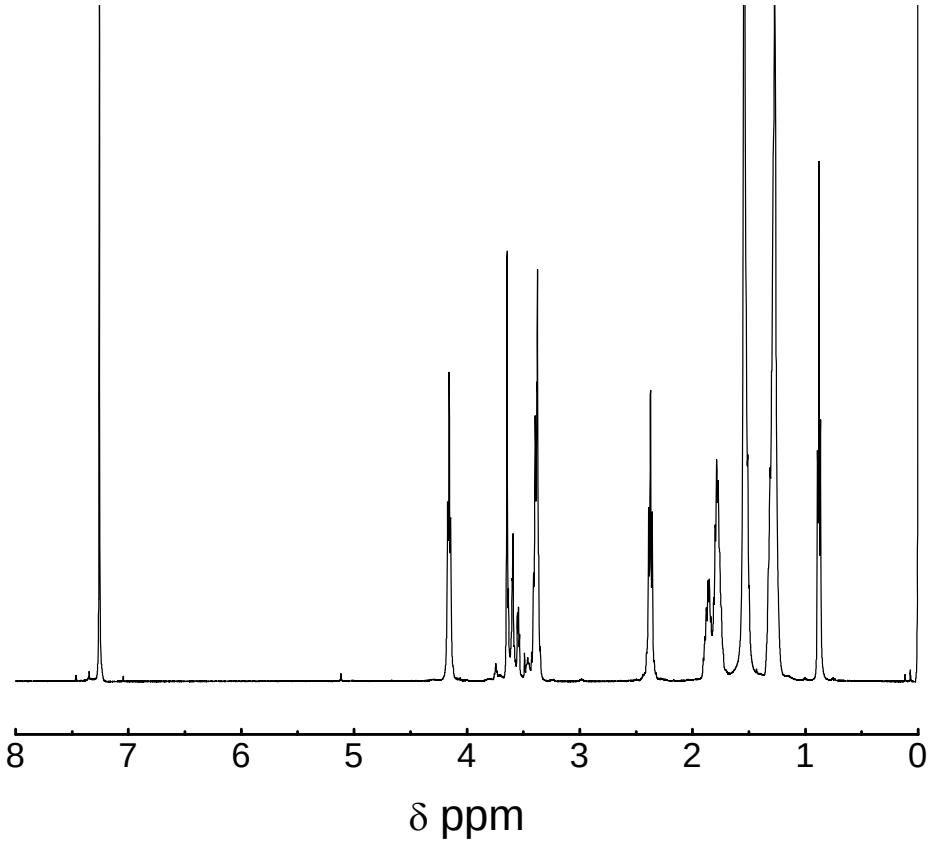

Figure S12. ^{1}H NMR of poly(γ-octyloxy-ε-caprolactone)-*b*-poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}(**P4**); the copolymer contains 21.2 mol % of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone

Table S1. Apparent constant rates for ring-opening polymerization of monomers **M1** and **M2**

Monomer	**[M] : [Sn] : [BnOH]**	**$K_{p,app}$ (s^{-1})**
M_1	100 : 1 : 1	3.59×10^{-4}
M_1	200 : 1 : 1	1.72×10^{-4}
M_1	500 : 1 : 1	9.33×10^{-5}
M_2	100 : 1 : 1	3.13×10^{-4}
M_2	200 : 1 : 1	1.49×10^{-4}
M_2	500 : 1 : 1	5.14×10^{-5}

Determination of critical micellar concentration

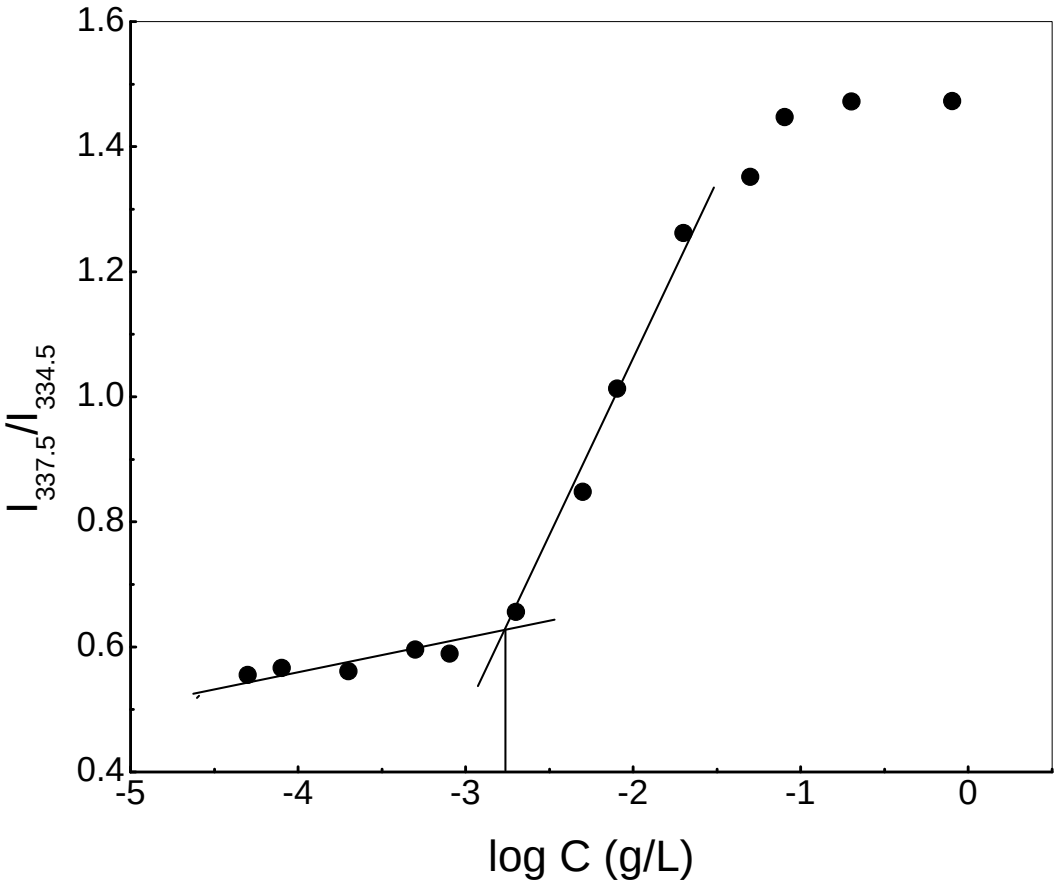

Figure S13. Dependence of intensity ratio $I_{337.5}/I_{334.5}$ (from pyrene excitation spectra) as a function of **P3** concentration. [Py]=4.0x10^{-7} M, λ_{em}=390 nm, T=25°C.

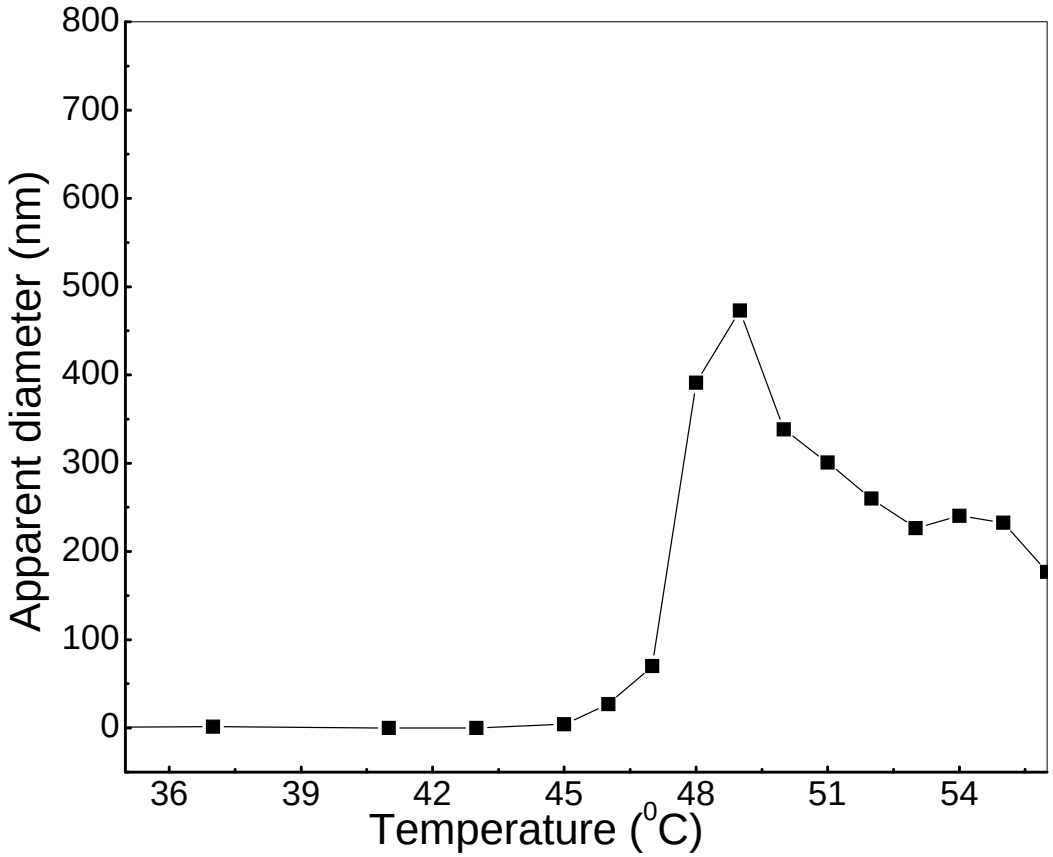

Figure S14. Temperature dependence of hydrodynamic diameter change of a aqueous solution of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone} (**P2**)

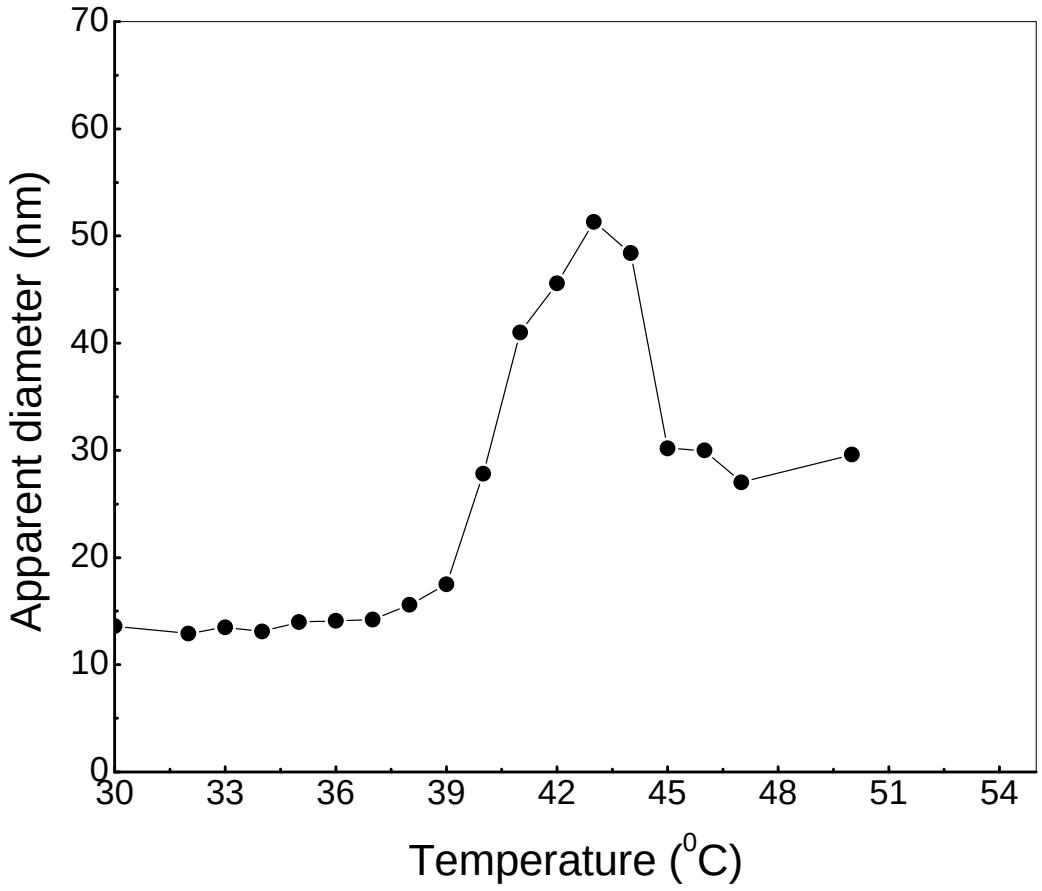

Figure S15. Temperature dependence of hydrodynamic diameter change of a aqueous solution of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}-*b*-poly(γ-octyloxy-ε-caprolactone) (**P3**)

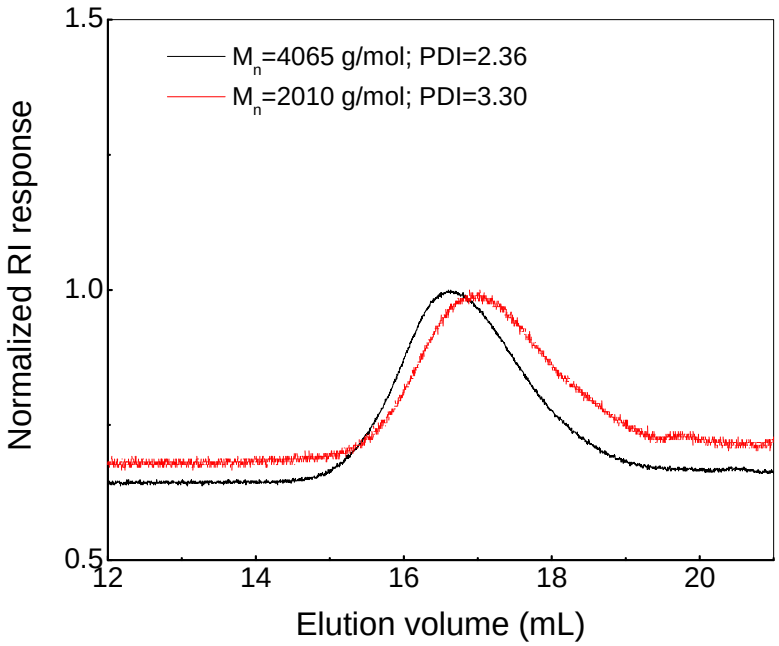

Figure S16. SEC traces of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone} (**P2**) before (black) and after 6 days in buffer at pH=6 (red) (top)

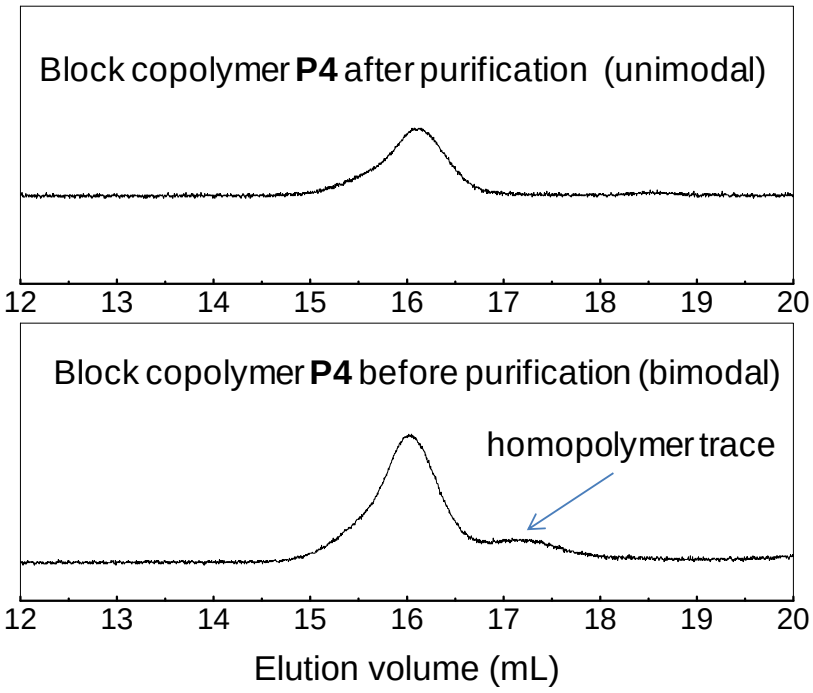

Figure S17. SEC traces of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}-*b*-poly(γ-octyloxy-ε-caprolactone) (**P4**) before purification (M_n=9765 g/mol; PDI=1.55) (bottom) and after purification (M_n=13900 g/mol; PDI=1.15) (top)

Electronic Supplementary Material (ESI) for Journal of Materials Chemistry

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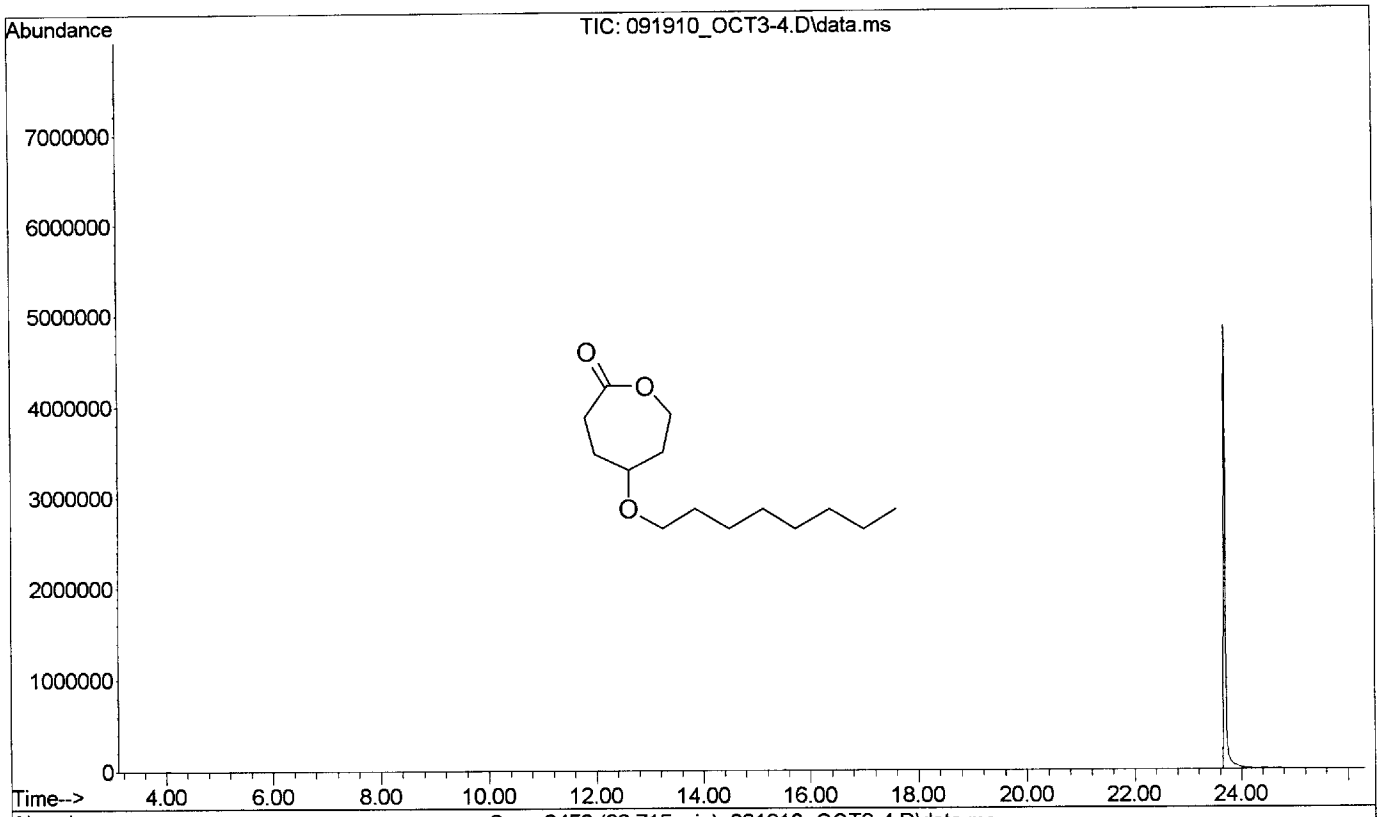

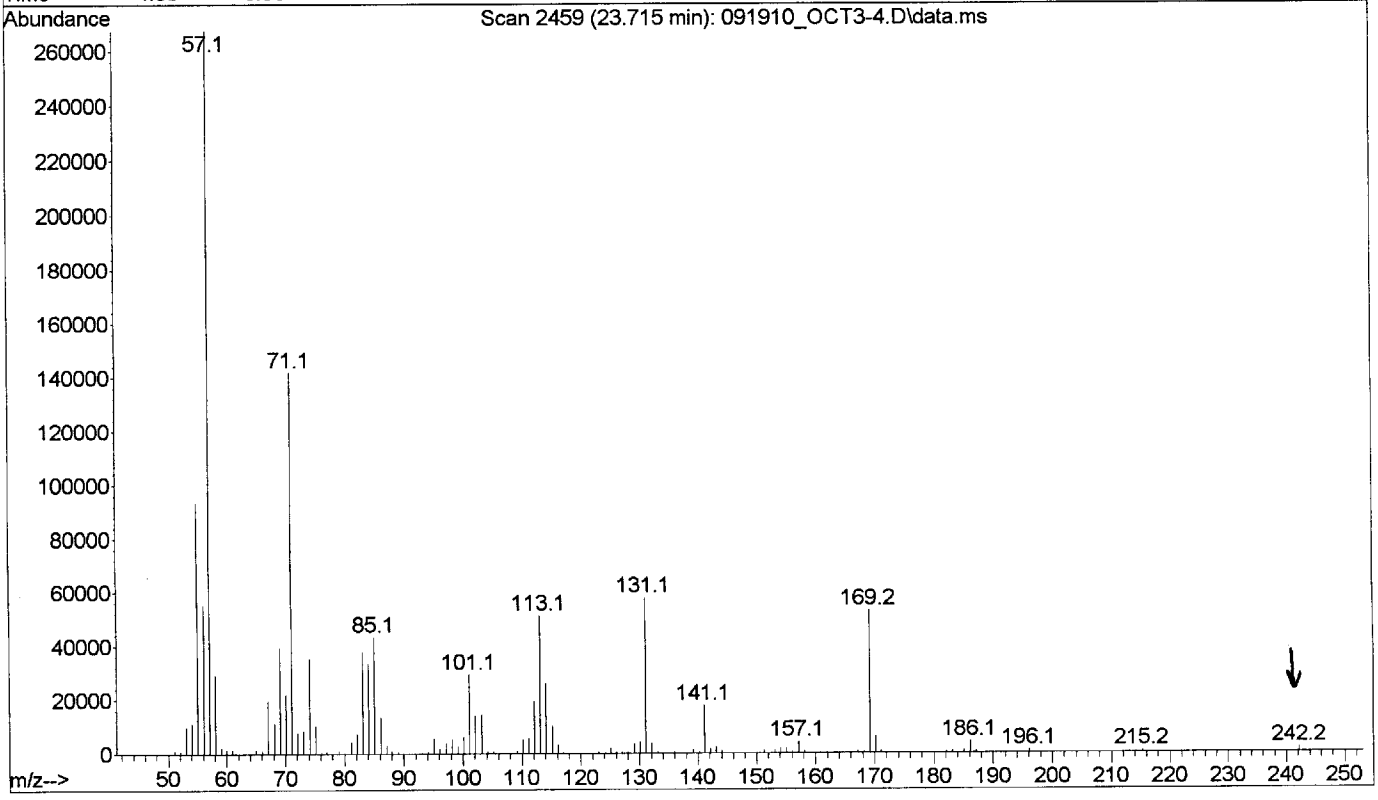

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Instrument : GCMS
Sample Name: pure meee
Misc Info : monomer M_2
Vial Number: 1