Self-Assembly Behavior of Oligo(ethylene glycol) Substituted Polycaprolactone Homopolymers

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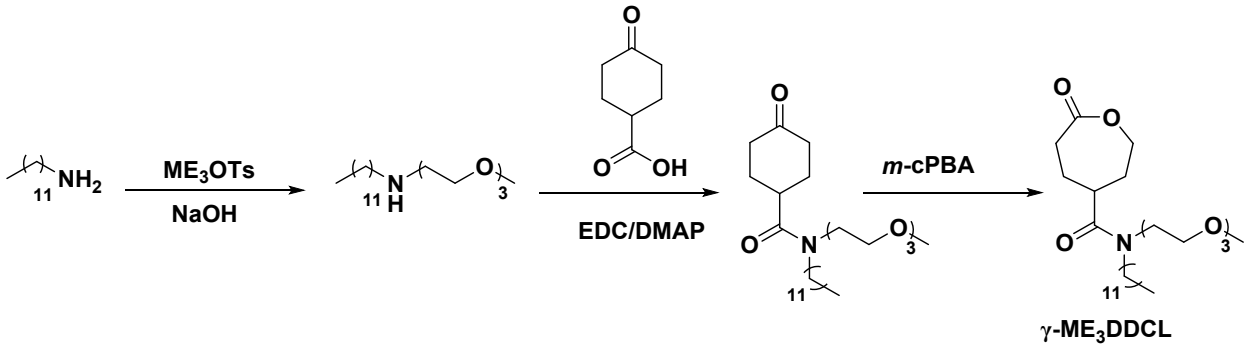
Supporting Information

Materials. All commercially available chemicals were obtained from Sigma-Aldrich or Fisher Scientific. Benzyl alcohol (BnOH) and tin (II) 2-ethyl hexanoate ($Sn(Oct)_2$) were purified by vacuum distillation before use. All glassware used for polymerizations was kept in an oven heated at 120 ˚C for 24 h and cooled down in a desiccator before use. Polymerization reactions were performed under a nitrogen atmosphere.

Instruments and Methods. A Bruker AVANCE III (500 MHz) nuclear magnetic resonance (NMR) instrument was used to collect ^1H spectra using $CdCl_3$ as the solvent. ESI-MS were acquired using an Agilent 1100 HPLC with a PLRP-S column for separation and an ABSciex 4000 QTRAP system for detection. Size exclusion chromatography (SEC) measurements were obtained using a Shimadzu HPLC instrument equipped with an Agilent column connected to the Shimadzu refractive index detector with *N,N*-dimethylformamide (DMF) as eluent, and poly(methyl methacrylate) (PMMA) standard calibration. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF) mass spectrum was obtained using a Shimadzu Biotech Axima Confidence

instrument in linear mode with dithranol matrix and sodium trifluoromethanesulfonate salt. Differential scanning calorimetry (DSC) was performed on a Mettler Toledo DSC-1 under nitrogen at 40 mL/min. A temperature-controlled Cary5000 UV-vis spectrometer was used for the turbidimetric assay of the synthesized polymers. Fluorescence spectroscopy of the samples was performed using Biotek Synergy H4 96-well plate reader. The size and distribution of the particles were measured through dynamic light scattering (DLS) using the Malvern Zetasizer Nano ZS instrument equipped with a He-Ne laser (633 nm) and 173˚ backscatter detector. Transmission electron microscopy (TEM) analysis was conducted using a JEM-1400+ TEM (JEOL USA Inc., MA) with 2% phosphotungstic acid stain.

Synthesis. γ-ME_2CL, γ-ME_3CL, and γ-ME_4CL monomers were synthesized according to the previously published procedure.[1]



Scheme S1. Synthesis of γ-ME_3DDCL monomer.

Procedure for the synthesis of N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)dodecan-1-amine

Methoxytriethylene glycol tosylate, ME_3OTs (4.0 g, 12.6 mmol), which was synthesized following a previously published literature[2], and dodecylamine (9.3 g, 50 mmol) were added into a flask, and the mixture was stirred at 120 °C overnight. The reaction mixture was allowed to cool at room

temperature, followed by the addition of NaOH (1.0 g, 25 mmol). The mixture was then stirred at 120 °C overnight, poured into water and extracted with chloroform. The product was isolated by chromatography using dichloromethane/methanol (2.8 g, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.85-0.87 (t, 3H), 1.22-1.33 (m, 18H), 1.45-1.52 (m, 2H), 2.35 (s, 1H), 2.58-2.61 (t, 3H), 2.77-2.82 (t, 2H), 3.39 (s, 3H), 3.54-3.69 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 14.19, 22.77, 27.46, 29.43, 29.66, 29.69, 29.71, 29.72, 29.75, 30.00, 32.00, 49.30, 50.02, 59.12, 70.40, 70.43, 70.60, 70.61, 72.03.

Procedure for the synthesis of N-dodecyl-N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-4-oxocylohexane-1-carboxamide

4-oxocyclohexane-1-carboxylic acid (0.5 g, 3.3 mmol), *N*-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)dodecan-1-amine) (1.0 g, 3.0 mmol), 4-(dimethylamino)pyridine (DMAP) (0.2 g, 1.5 mmol), and dichloromethane were cooled to 0 °C in a round-bottom flask. A solution of 1-ethyl-3-(3-dimethylamino)-propyl)carbodiimide hydrochloride (EDCl) (0.8 g, 4.0 mmol) in DCM was added dropwise to the cooled solution. The reaction was stirred overnight followed by evaporation of solvent *in vacuo*, then extraction with ethyl acetate. The product was isolated by chromatography using ethyl acetate (1.0 g, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86-0.89 (t, 3H), 1.18-1.30 (m, 18H), 1.47-1.53 (m, 1H), 1.56-1.63 (m, 1H), 1.99-2.10 (m, 4H), 2.30-2.39 (m, 2H), 2.58-2.49 (m, 2H), 2.84-2.91/3.07-3.13 (m, 1H), 3.31-3.41 (m, 5H), 3.51-3.65 (m, 12H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 14.20, 22.77, 26.95, 27.06, 27.81, 29.25, 29.28, 29.43, 29.50, 29.52, 29.68, 29.73, 32.00, 37.94, 38.19, 40.12, 40.16, 46.14, 46.27, 47.58, 49.35, 59.14, 69.43, 69.49, 70.51, 70.63, 70.67, 70.74, 70.82, 70.98, 72.01, 72.06, 174.37, 174.83, 210.24, 210.67.

*Procedure for the synthesis of N-dodecyl-N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-7-oxoxepane-4-carboxamide (*γ-ME_3DDCL*)*

A solution of *N*-dodecyl-*N*-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-4-oxocylohexane-1-carboxamide (1.0 g, 2.2 mmol) in dichloromethane was added with a solution of 77% m-chloroperoxybenzoic acid (0.8 g, 3.7 mmol) in dichloromethane at 0°C. The reaction was stirred for 24 h then the solvent was evaporated *in vacuo*. The product was isolated by flash chromatography using hexane/ethyl acetate (0.8 g, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86-0.90 (t, 3H), 1.20-1.33 (m, 18H), 1.45-1.58 (m, 2H), 1.87-2.15 (m, 4H), 2.56-2.66 (m, 1H), 2.77-2.84/3.03-3.10 (m, 1H), 2.85-2.97 (m, 1H), 3.22-3.41 (m, 5H), 3.42-3.66 (m, 12H), 4.15-4.23 (m, 1H), 4.44-4.56 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 14.22, 22.79, 25.70, 25.76, 26.94, 27.06, 27.78, 29.45, 29.49, 29.52, 29.69, 29.71, 29.74, 28.80, 32.02, 32.20, 32.28, 32.43, 32.53, 40.87, 40.94, 46.12, 46.18, 47.66, 49.37, 59.16, 66.97, 67.21, 69.25, 69.41, 70.52, 70.63, 70.67, 70.73, 70.77, 72.02, 72.07, 173.99, 174.58, 175.30, 175.64. The m/z obtained from ESI-MS is 494.01 [$M+Na^+$], while the calculated m/z ([$M+H]^+$) is 471.36 ($C_{26}H_{49}NO_6$).

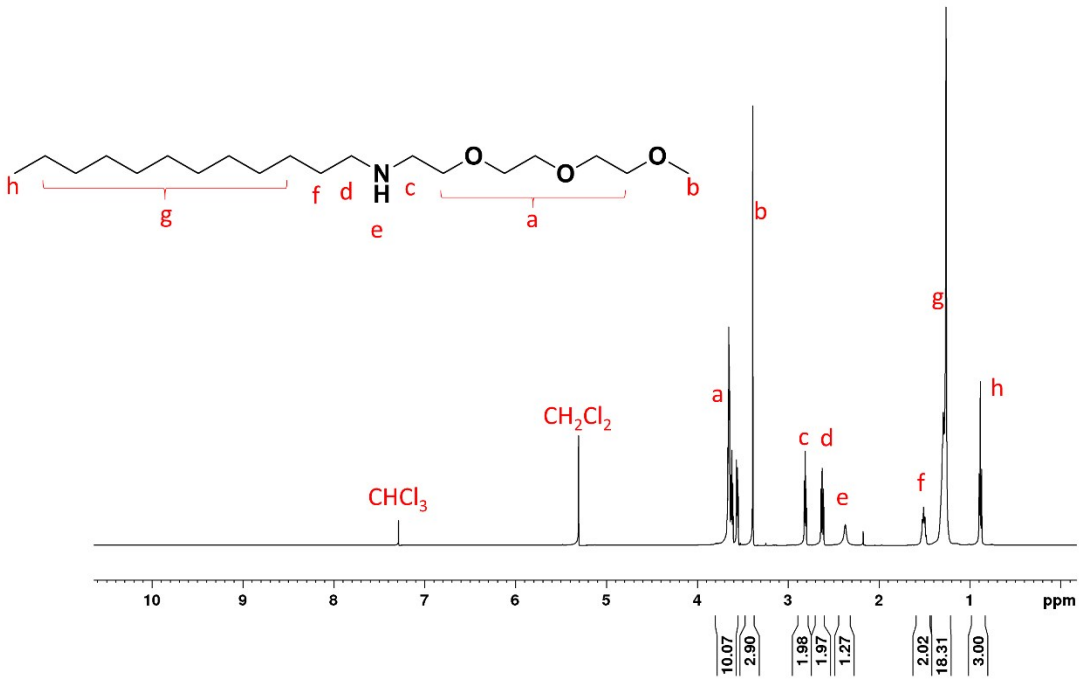


Figure S1. ^{1}H NMR spectrum of *N*-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)dodecan-1-amine.

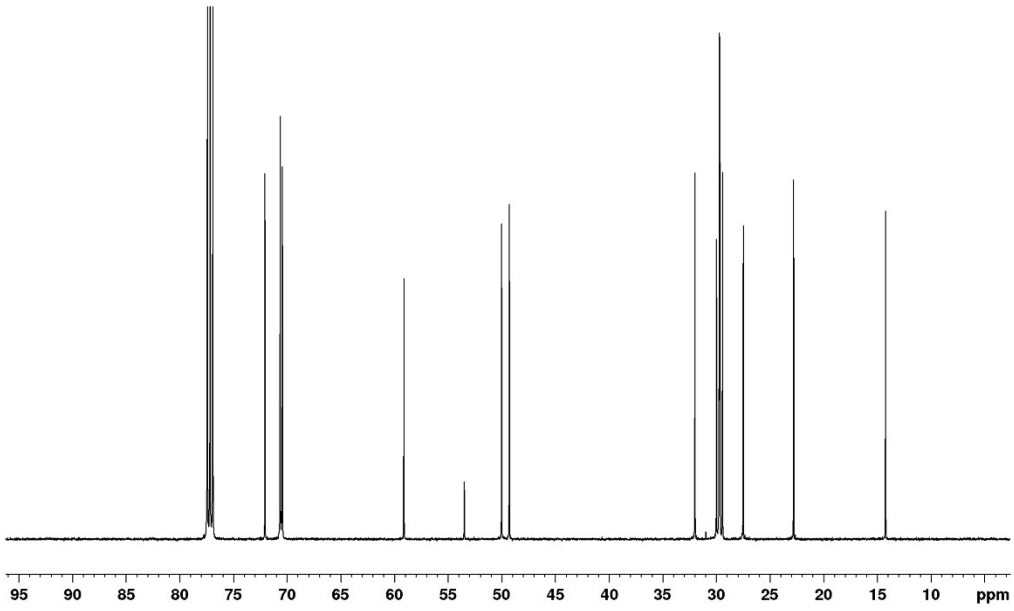


Figure S2. ^{13}C NMR spectrum of *N*-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)dodecan-1-amine.

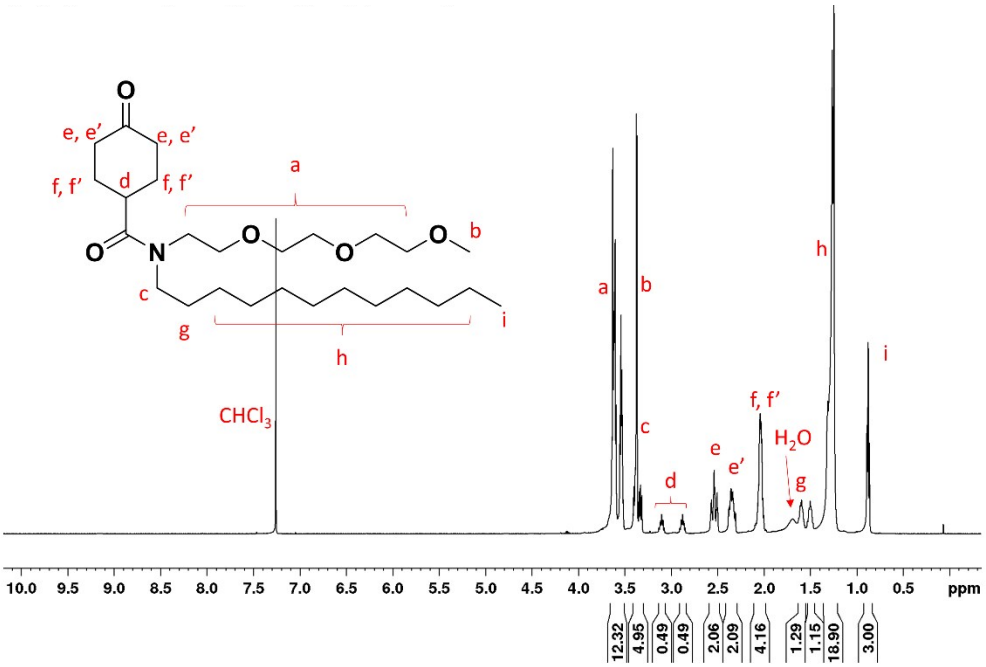


Figure S3. ^{1}H NMR spectrum of *N*-dodecyl-N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-4-oxocylohexane-1-carboxamide.

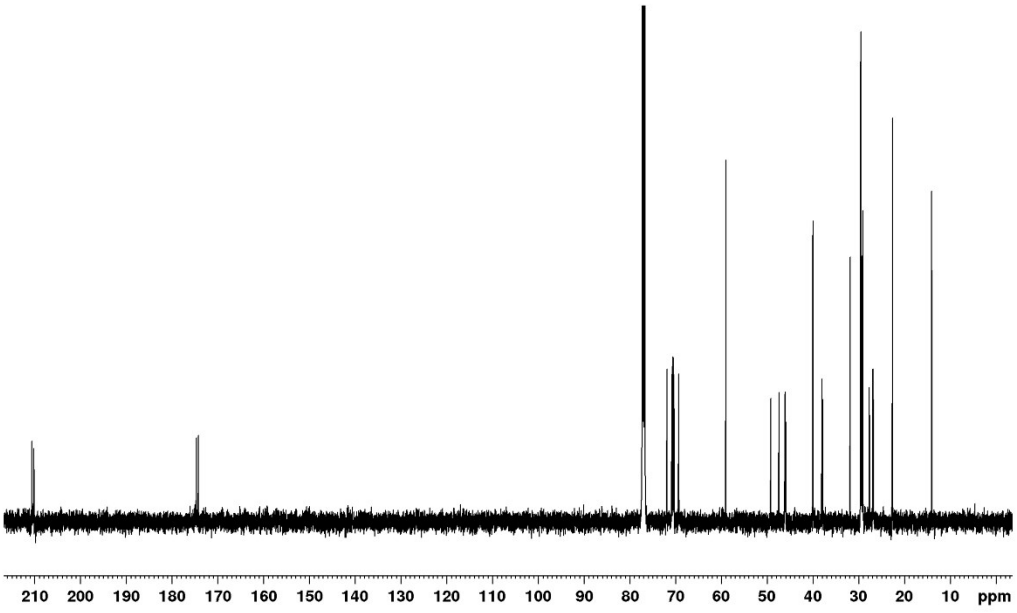


Figure S4. ^{13}C NMR spectrum of *N*-dodecyl-N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-4-oxocylohexane-1-carboxamide.

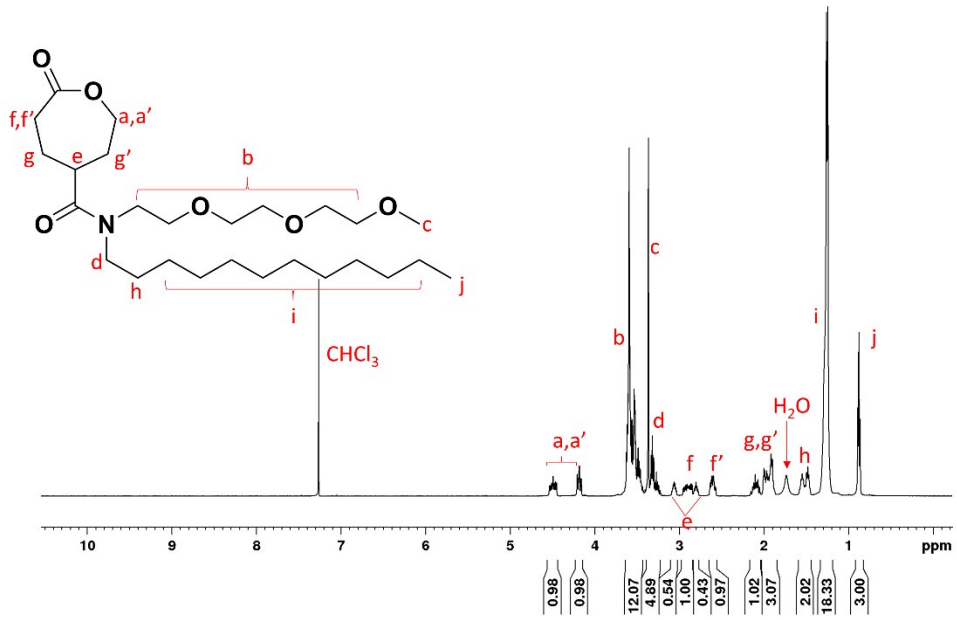


Figure S5. ^{1}H NMR spectrum of N-dodecyl-N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-7-oxoxepane-4-carboxamide (γ-ME_3DDCL).

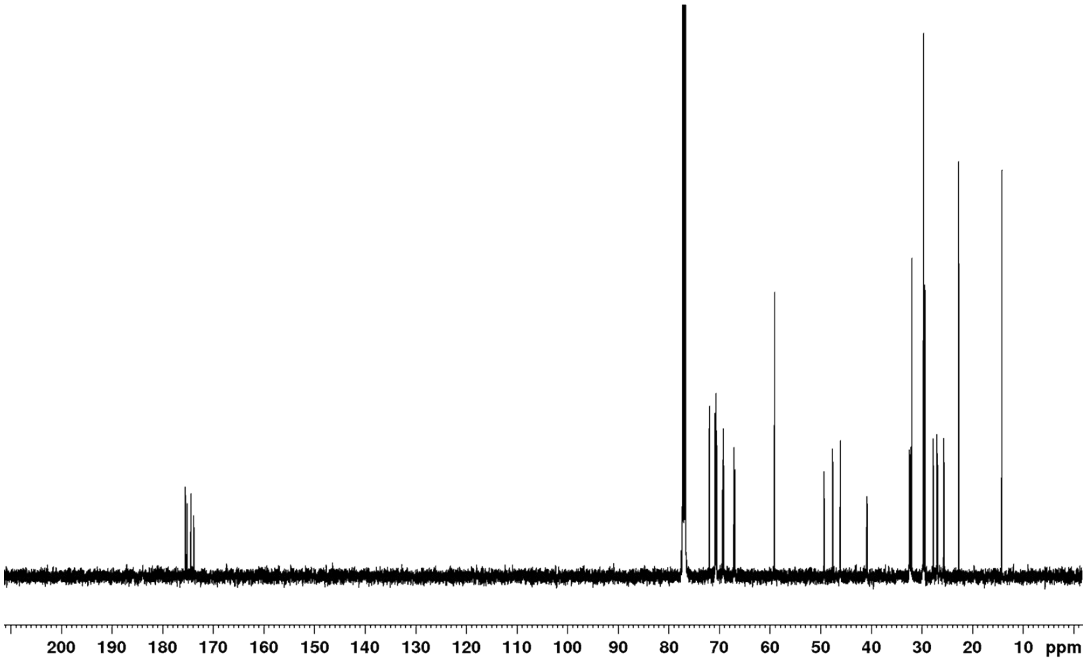


Figure S6. ^{13}C NMR spectrum of N-dodecyl-N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-7-oxoxepane-4-carboxamide (γ-ME_3DDCL).

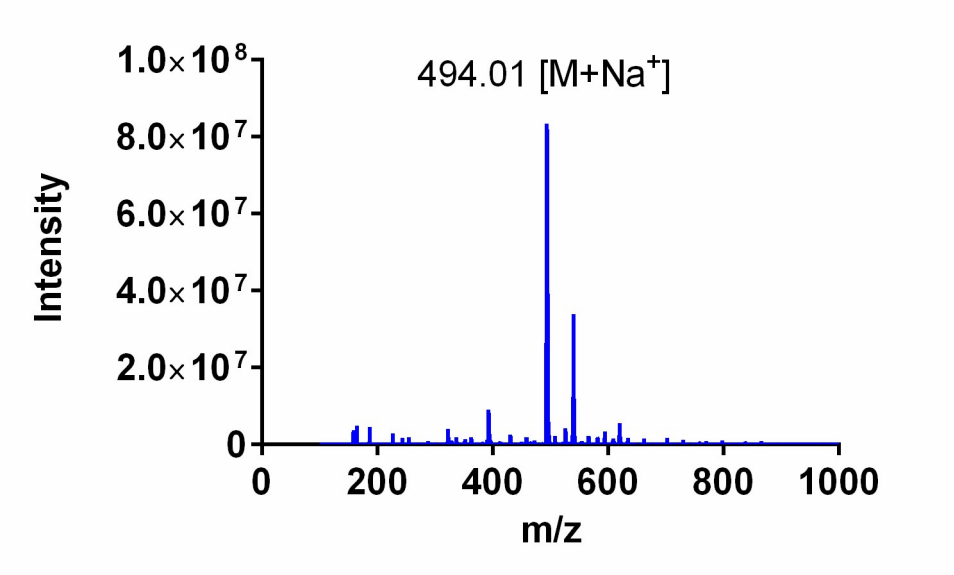


Figure S7. ESI-MS spectrum N-dodecyl-N-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-7-oxoxepane-4-carboxamide (γ-ME_3DDCL).

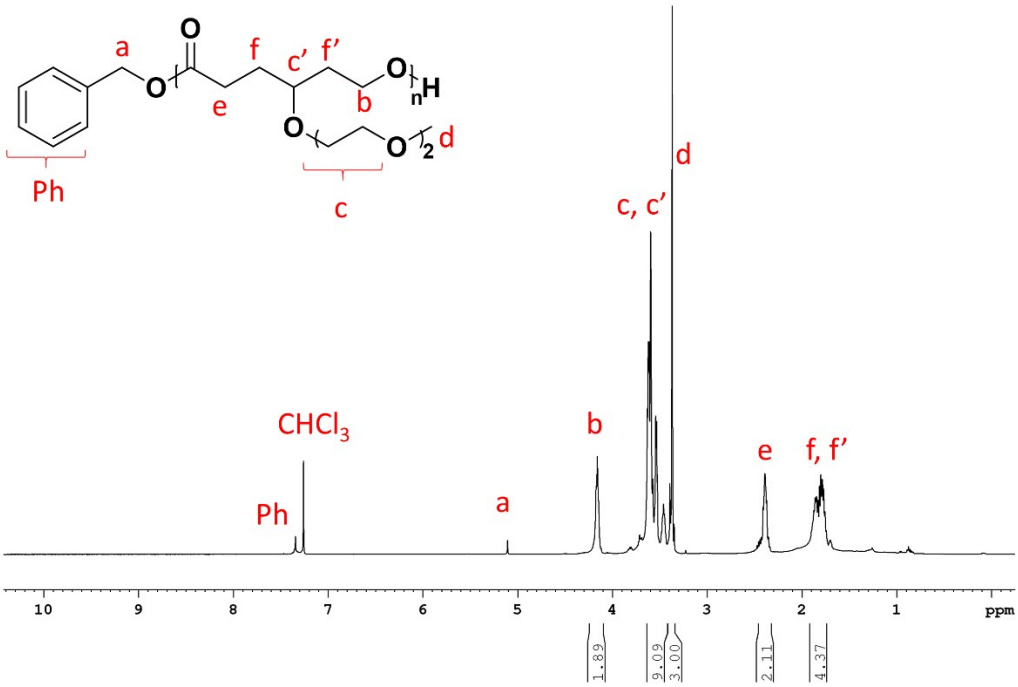


Figure S8. ^{1}H NMR spectrum of **P1b** (representative spectra of poly(γ-2-(2-methoxyethoxy)ethoxy-ε-caprolactone), PME_2CL).

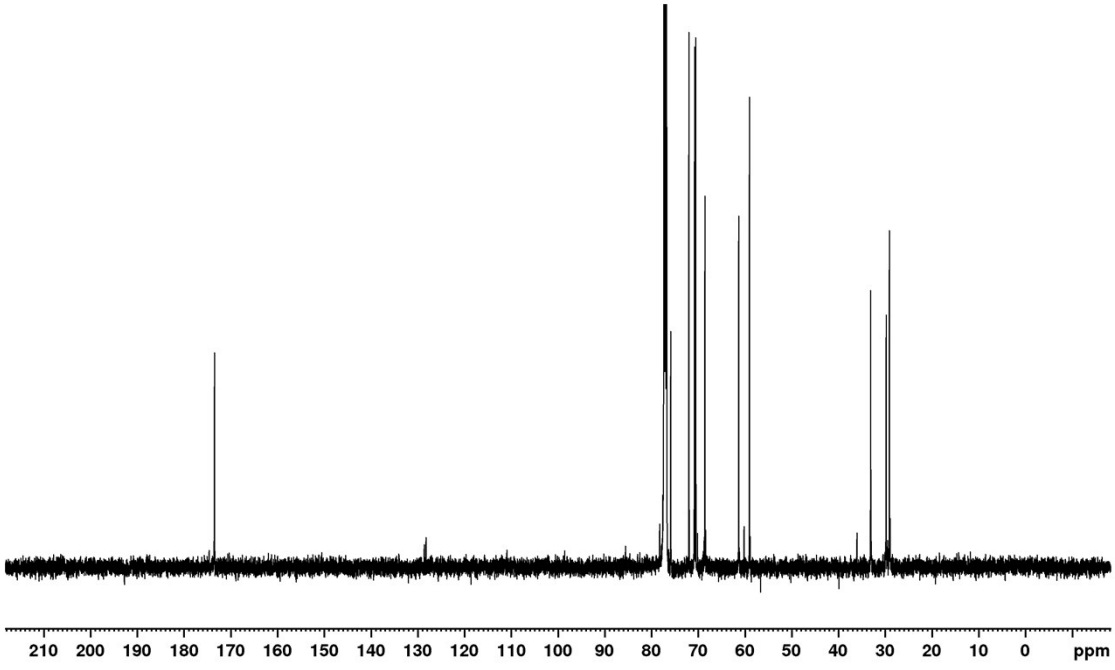


Figure S9. ^{13}C NMR spectrum of **P1b** (representative spectra of poly(γ-2-(2-methoxyethoxy)ethoxy-ε-caprolactone), PME_2CL).

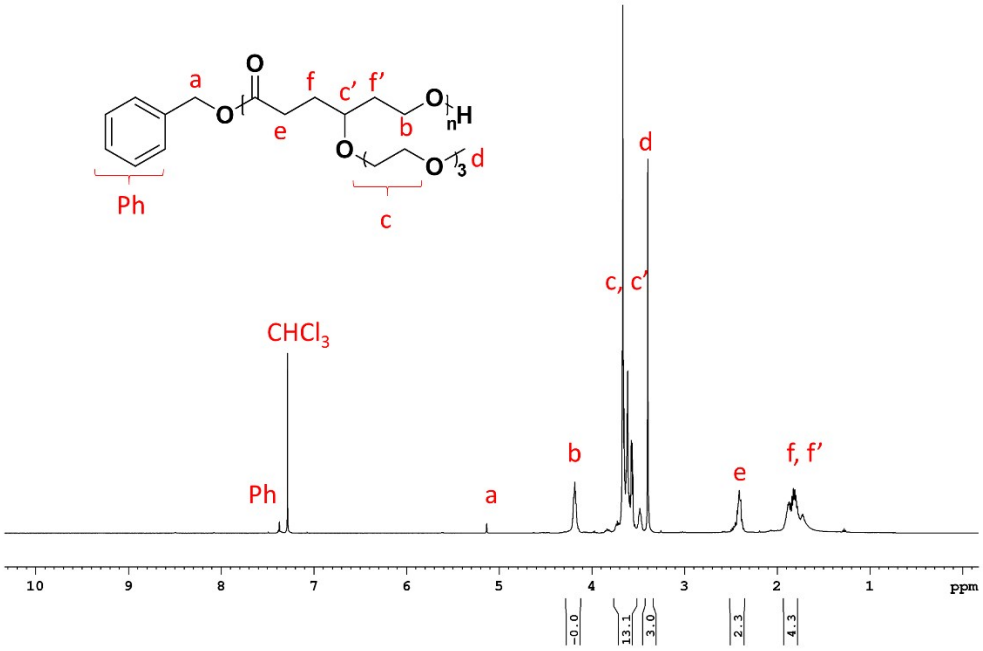


Figure S10. ^{1}H NMR spectrum of **P2b** (representative spectra of poly(γ-2-(2-(2-methoxyethoxy)ethoxy)ethoxy-ε-caprolactone), PME_3CL).

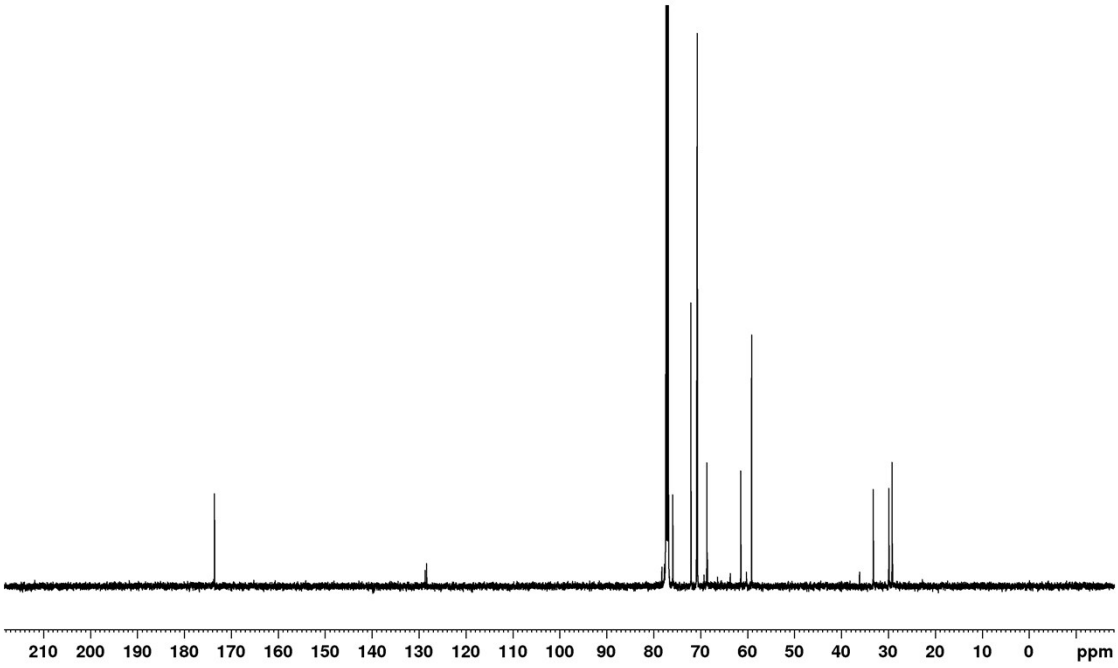


Figure S11. ^{13}C NMR spectrum of **P2b** (representative spectra of poly(γ-2-(2-(2-methoxyethoxy)ethoxy)ethoxy-ε-caprolactone), PME_3CL).

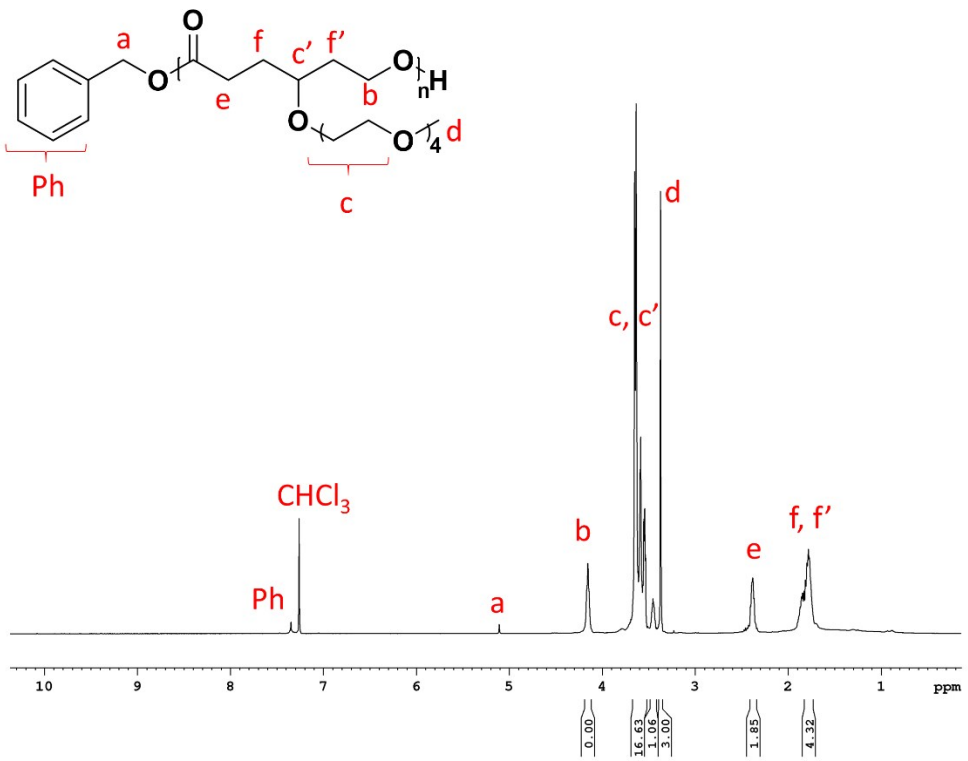


Figure S12. ^{1}H NMR spectrum of **P3b** (representative spectra of poly(γ-2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy-ε-caprolactone, PME_4CL).

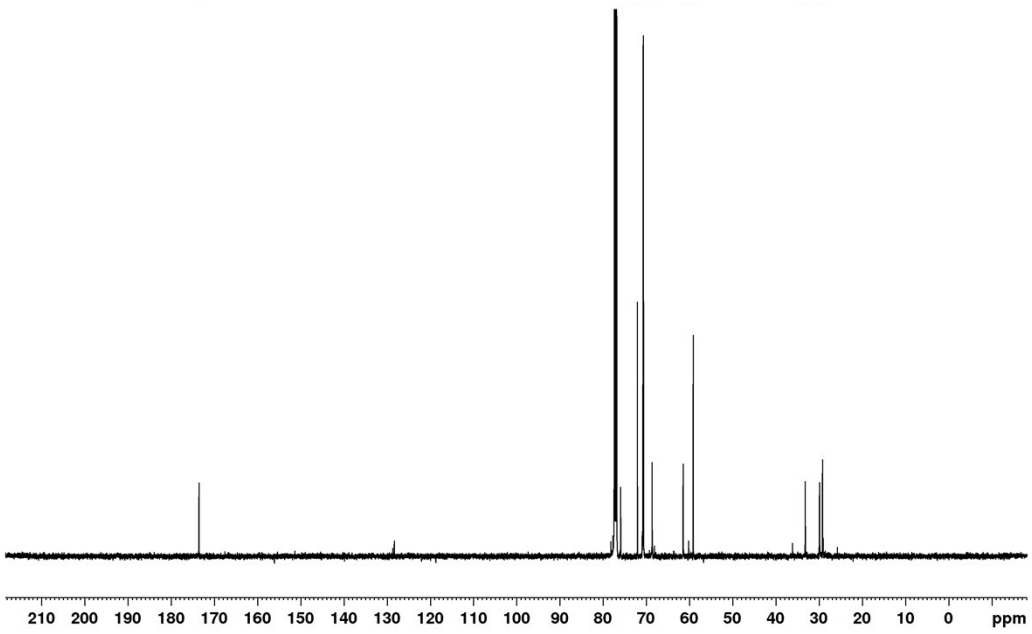


Figure S13. ^{13}C NMR spectrum of **P3b** (representative spectra of poly(γ-2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy-ε-caprolactone, PME_4CL).

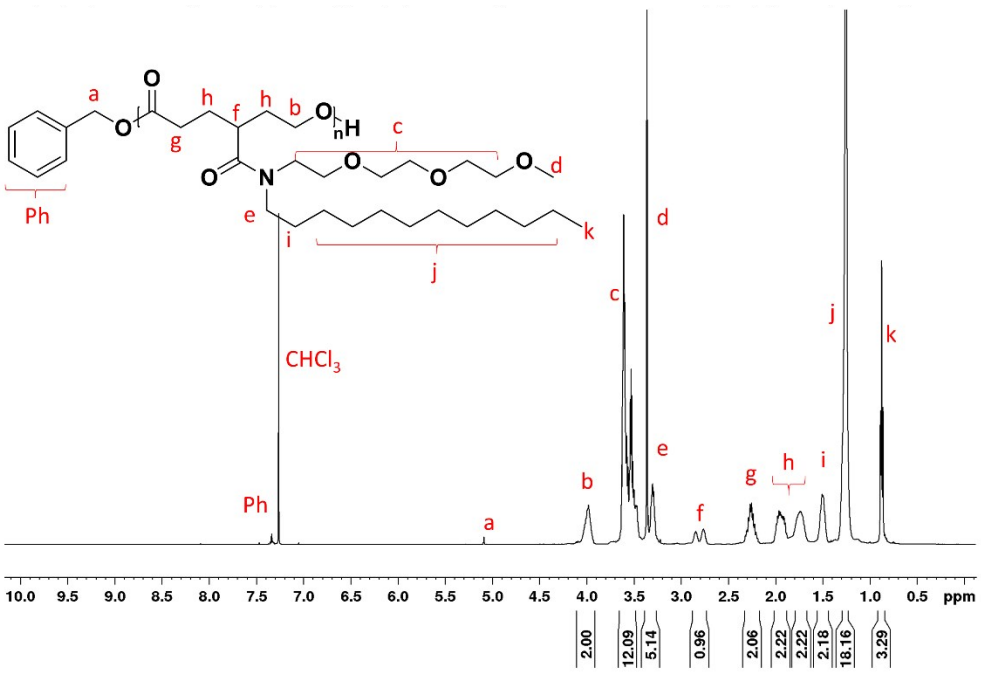


Figure S14. ^{1}H NMR spectrum of **P4** (poly(*N*-dodecyl-*N*-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-7-oxoxepane-4-carboxamide)), PME$_3$DDCL).

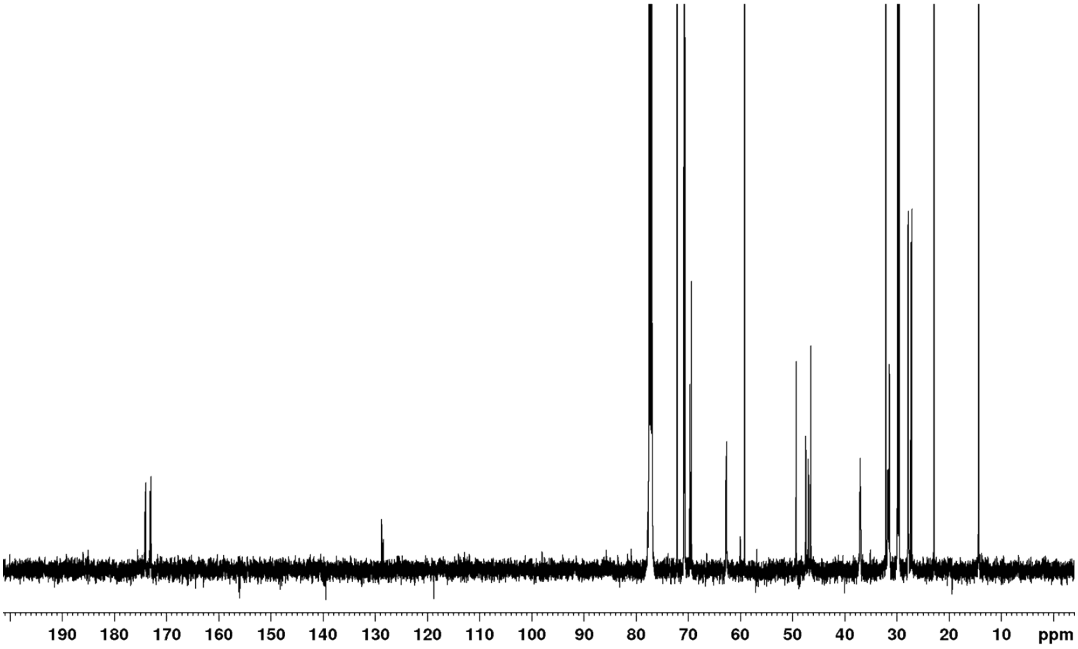


Figure S15. ^{13}C NMR spectrum of **P4** (poly(*N*-dodecyl-*N*-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-7-oxoxepane-4-carboxamide)), PME$_3$DDCL).

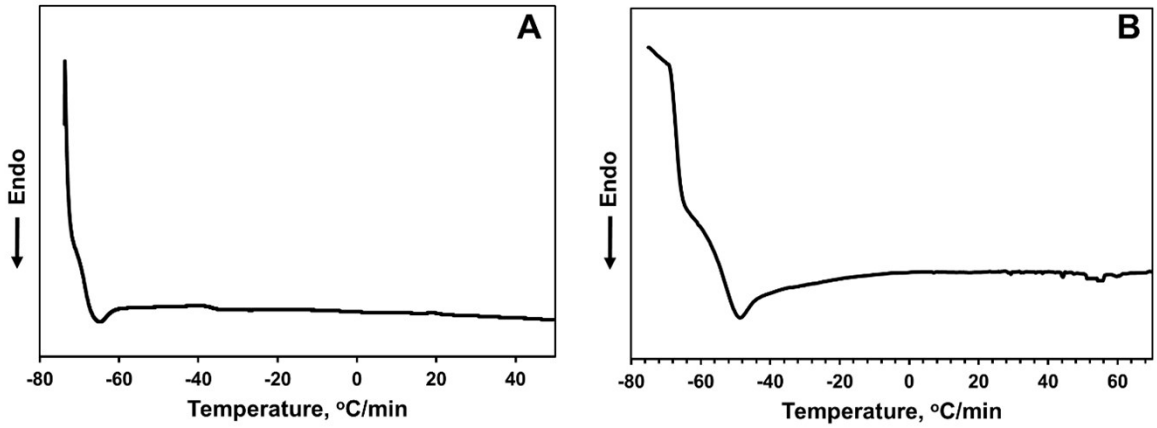


Figure S16. DSC thermograms of PME_3CL **(P2c)** (A) and PME_3DDCL **(P4)** (B).

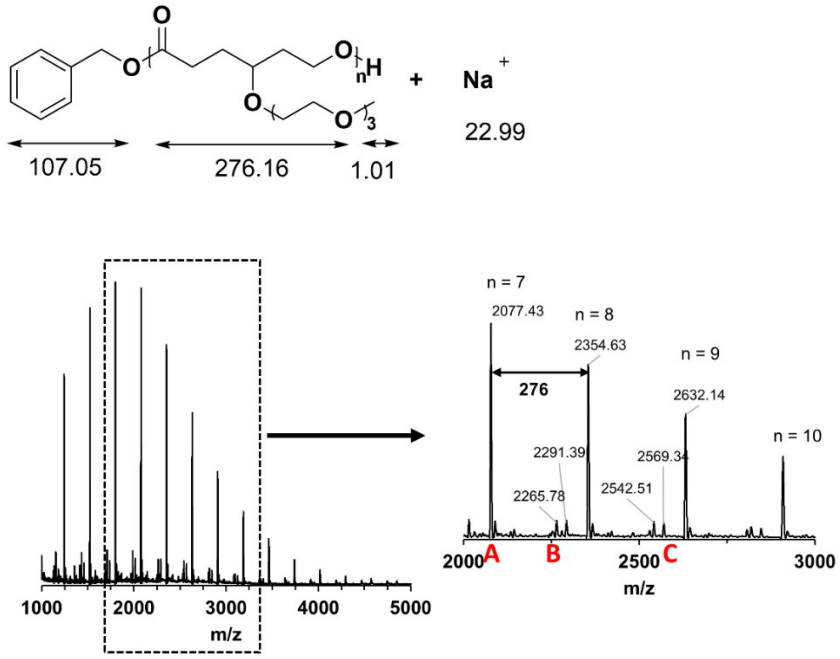


Figure S17. MALDI-ToF mass spectrum of the synthesized PME_3CL (**P2a**), mole ratio γ-ME_3CL:BnOH:$Sn(Oct)_2$ = 25:1:1

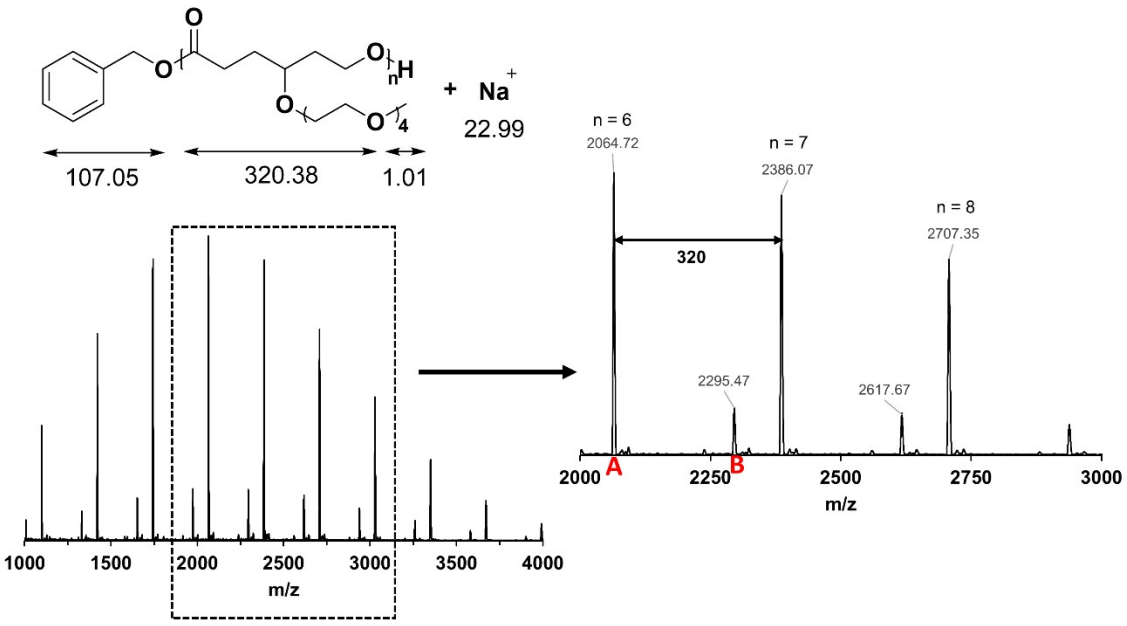


Figure S18. MALDI-ToF mass spectrum of the synthesized PME_4CL (**P3a**), mole ratio γ-ME_4CL:BnOH:$Sn(Oct)_2$ = 25:1:1

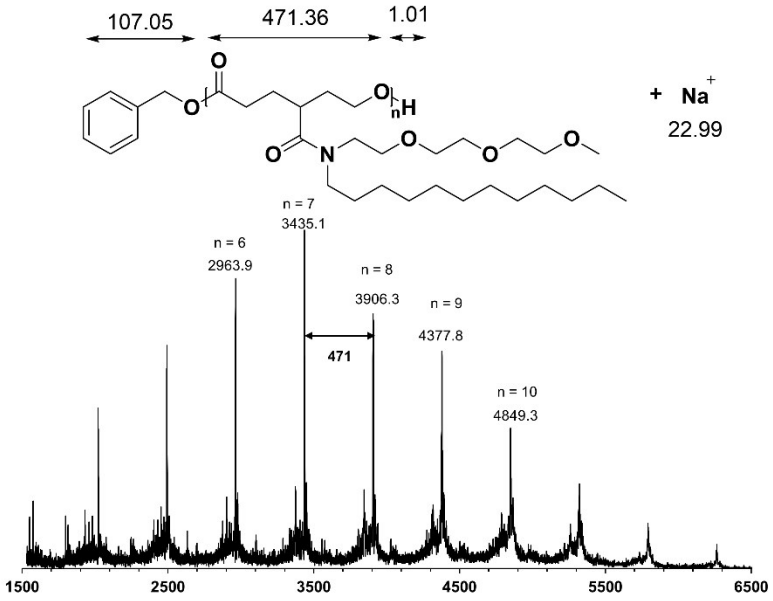


Figure S19. MALDI-ToF mass spectrum of the synthesized PME_3DDCL, mole ratio γ-ME_3DDCL:BnOH:$Sn(Oct)_2$ = 15:1:1

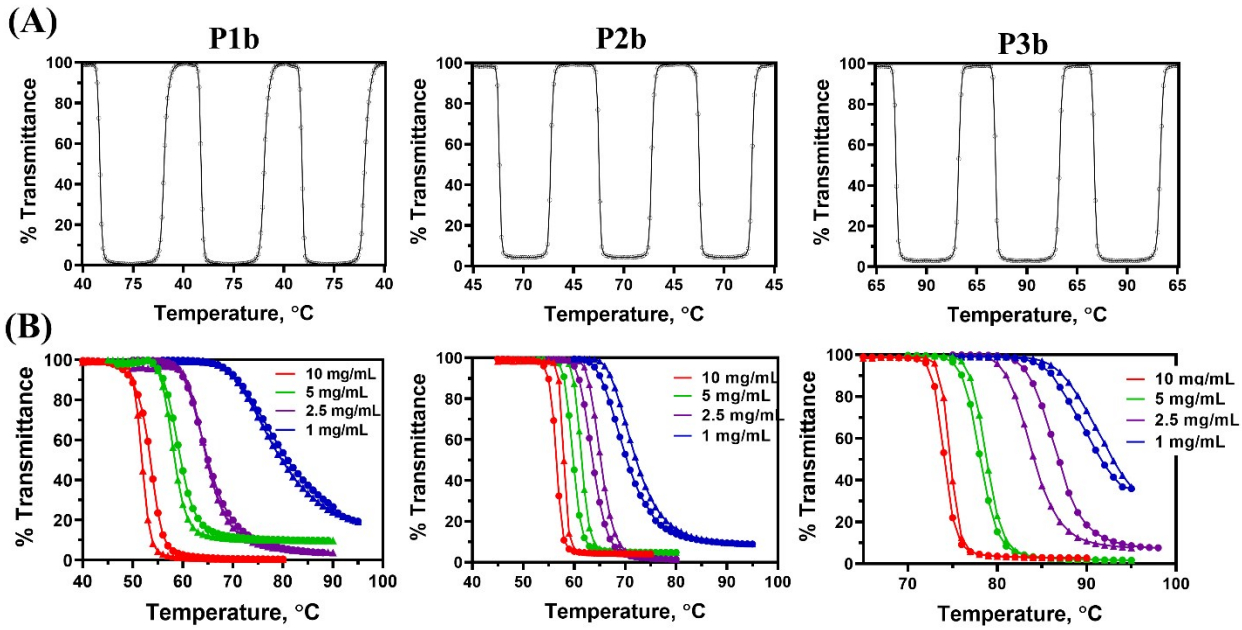


Figure S20. (A) Turbidity curves obtained from an aqueous solution of the polymers (10 mg/mL) after multiple heating and cooling cycles; (B) Dependence of T_{cp} on the polymer concentration (Δ is heating and ○ is cooling).

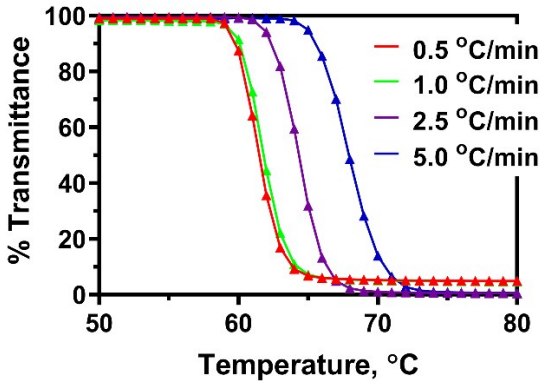


Figure S21. Effect of various heating rates on the T_{cp} of an aqueous solution of PME_3CL **(P2b)** (5 mg/mL).

1. Soltantabar, P.; Calubaquib, E. L.; Mostafavi, E.; Biewer, M. C.; Stefan, M. C. Enhancement of Loading Efficiency by Coloading of Doxorubicin and Quercetin in Thermoresponsive Polymeric Micelles. *Biomacromolecules* **2020,** 21 (4), 1427-1436 DOI: 10.1021/acs.biomac.9b01742.

2. Hao, J.; Servello, J.; Sista, P.; Biewer, M. C.; Stefan, M. C. Temperature-sensitive aliphatic polyesters: synthesis and characterization of γ-substituted caprolactone monomers and polymers. *J. Mater. Chem.* **2011,** 21 (29), 10623-10628 DOI: 10.1039/C1JM11288K.