Electronic Supplementary Information

Synthesis and characterization of valproic ester substituted amphiphilic polycaprolactone block copolymers

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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 at 110 °C.

Characterization

^{1}H NMR and ^{13}C NMR spectra of the synthesized monomers and polymers were recorded on a Bruker AVANCE III 500MHz NMR spectrometer at 25 °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. 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 polymer

samples were dissolved in THF, and the solutions were filtered through PTFE filters (0.45 μm) prior to injection.

Analysis of micelles using dynamic light scattering

The micelle size and the hydrodynamic diameter were measured using Malvern Zetasizer Nano ZS instrument equipped with a HE-Ne laser (6.33 nm) and 173^{o} back scatter detector. Polymeric micelles were prepared by dissolving copolymer (20 mg) in THF (0.5 mL) and introduced dropwise to 10 mL of DI water. The solution was stirred vigorously for a minimum of 5 hours in the fume hood to allow the formation of micelles as the THF evaporates. The micelle solution was passed through a 0.2 μm filter prior to the measurement.

Determination of critical micelle concentration (CMC)

Critical micellar concentration (CMC) was determined by fluorescence spectroscopy using pyrene as a fluorescent probe. A series of pyrene loaded micelles were prepared at various concentrations of polymers. Polymer was dissolved in THF and a constant amount of pyrene was added to keep the final pyrene concentration constant. Pyrene polymer mixture was alowly added into 10 mL of deionized water and the solutions were stirred vigorously for a minimum of 4 hours to self-assemble the polymers into micelles as the THF evaporated. Fluorescence excitation spectra (emission at 390 nm) were recorded on a Perkin-Elmer lS 50 BLluminescence spectrometer at 25^{o}. The intensity ratio of $I_{337.5}/I_{334.5}$ from pyrene excitation spectrum was plotted vs log concentration.

Transmission electron microscopy (TEM) images of micelles

TEM images were obtained using a JEOL JEM-1400 transmission electron microscope. The 200 mesh CF200-Cu grid was placed on a drop of the micelle suspension for a few seconds and the grid was stained using phosphotungstic acid.

Demonstration of biodegradability of polymers P1-P4

Polymers **P1**-**P4** (20 mg from each) were dissolved in 4 mL of pH 6.0 phosphate buffer in a sealed vial. The solution was sealed and stirred at 37 ^{o}C for 5 days. Periodically, 0.1 mL samples were removed from the reaction vessel and the molecular weights were analyzed by the SEC.

Synthesis of 4-hydroxycyclohexyl-2-propylpentanoate [1]

A solution of cyclohexane-1,4-diol (10.00 g, 0.086 mol) and N,N-dimethylaminopyridine (17.74 g, 0.086 mol) in tetrahydrofuran (70 mL) was added slowly to a solution of 2-propylpentanoic acid (13.65 mL, 0.086 mol) and N,N'-dicyclohexylcarbodiimide (10.50 g, 0.086 mol) in tetrahydrofuran (70 mL). The solution was refluxed at 60 ^{o}C overnight. The precipitated dicyclohexylurea was removed by filtration. The organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the product was isolated by flash chromatography (Rf = 0.4 in hexane: ethyl acetate = 70:30) to yield 5.4 g of colorless oil (0.022 mol, 60 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.92 (t, 6H), 1.32 (m, 4H), 1.48 (m, 6H), 1.58 (m, 2H), 1.98 (m, 4H) 2.34 (m, 1H), 3.76 (m, 1H), 4.80 (m, 1H), 4.92 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$): δC 176.07, 71.05, 68.99, 45.47, 34.76, 32.20, 28.57, 20.61, 14.02.

Synthesis of 4-oxocyclohexyl-2-propylpentanoate [2]

Sulfuric acid (98%) (5 mL) was added slowly to a solution of potassium dichromate (8.00 g, 0.0272 mol) in 75 mL DI water. Compound [**1**] (5.50 g, 0.0227 mol) was added to the chromic acid solution dropwise and the solution turned to brownish green color immediately. The reaction mixture was reacted overnight at room temperature. The reaction mixture was extracted with diethyl ether (4 × 70 mL) and the ether layers were washed with water (50 mL). The ether

layer was dried over magnesium sulfate and concentrated in vacuo to obtain the product. (Rf = 0.5 in hexane: ethyl acetate = 7:3) to yield 4.35 g of colorless oil (0.0227 mol, 80 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.93 (t, 6H), 1.33 (m, 4H), 1.46 (m, 4H), 1.63 (m, 2H), 2.09 (m, 4H) 2.40 (m, 3H), 2.56 (m, 2H), 5.22 (m, 1H).^{13}C NMR (500 MHz, $CDCl_3$): δC 209.88, 175.84, 67.94, 45.46, 37.30, 34.74, 30.56, 20.67, 14.0.

Synthesis of γ-2-propylpentanoate-ε-caprolactone (M1)

A solution of 4-oxocyclohexyl -2-propylpentanoate [**2**] (1.37 g, 0.005 mol) in dichloromethane was added to a solution of 77% m-chloroperoxybenzoic acid (0.147 g, 0.0085 mol) in dichloromethane. The reaction was left overnight at room temperature. Potassium carbonate (4 g) and 10 mL of water were added to a solution and stirred overnight. The organic layer was separated and the water layer was extracted with dichloromethane (3 × 20 mL). The organic phase was dried over magnesium sulfate and concentrated in vacuo to yield 0.076 g (60%) of colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.93 (t, 6H), 1.3 (m, 4H), 1.47 (m, 2H), 1.63 (m, 2H), 2.00 (m, 2H) 2.07 (m, 1H), 2.13 (m, 1H), 2.41 (m, 1H), 2.57 (m, 1H), 2.93 (m, 1H), 4.18 (m, 1H), 4.46 (m, 1H), 5.17 (m, 1H). ^{13}C NMR (500 MHz, CDCl3): δC 175.42, 174.98, 69.45, 63.55, 45.37, 34.67, 34.20, 28.49, 27.70, 20.66, 13.99. Anal. Calculated for $C_{14}H_{24}O_4$: C, 65.60%; H, 9.44%. Found: C, 65.13%; H, 9.28%.

Synthesis of poly(ethylene glycol)-*b*-poly(γ-2-propylpentanoate-ε-caprolactone (P3)

γ-2-Propylpentanoate-ε-caprolactone (1.123 g, 4.4×10^{-3} mol) and polyethylene glycol (0.135 g, 6.73×10^{-5} mol) were transferred into a Schlenk flask and dried using vacuum. A stock solution of $Sn(Oct)_2$ in toluene (0.054 g, 1.34×10^{-4} mol) was added to the Schlenk flask under a nitrogen atmosphere. The reaction flask was introduced in a thermostated oil bath at 110 ^{o}C for four hours

under a nitrogen atmosphere. The polymer **P3** was recovered by precipitation in pentane. The monomer conversion was determined by ^{1}H NMR. Molecular weight of the polyethylene-*b*-poly(γ-2-propylpentanoate-ε-caprolactone) was determined by SEC. A similar procedure was carried out to synthesis **P1**, **P2**, and **P4**.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.89 (m, 6H), 1.28 (m, 4H), 1.41 (m, 2H), 1.58 (m, 2H), 1.88 (m, 4H), 2.33 (m, 2H), 2.57 (m, 1H), 3.38 (m, 3H), 3.64 (m, 4H), 4.10 (m, 2H), 4.25 (m, 2H), 4.60 (m, 1H), 5.0 (m, 1H).

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

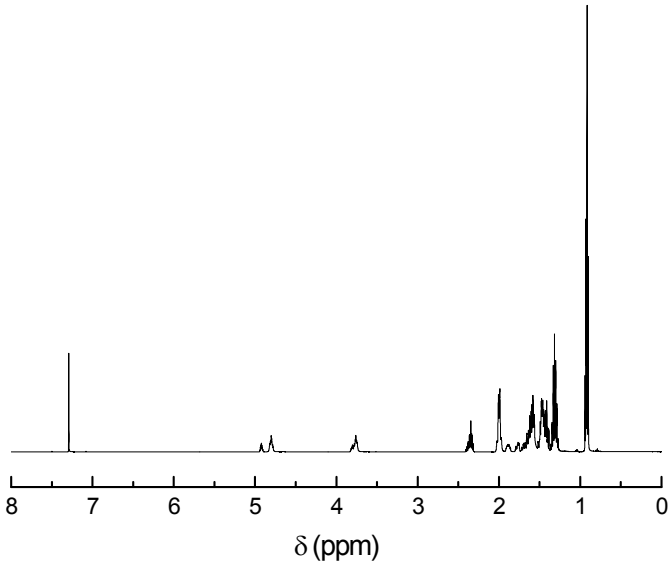

Figure S1. ^{1}H NMR spectrum of 4-hydroxycyclohexyl -2-propylpentanoate [**1**]

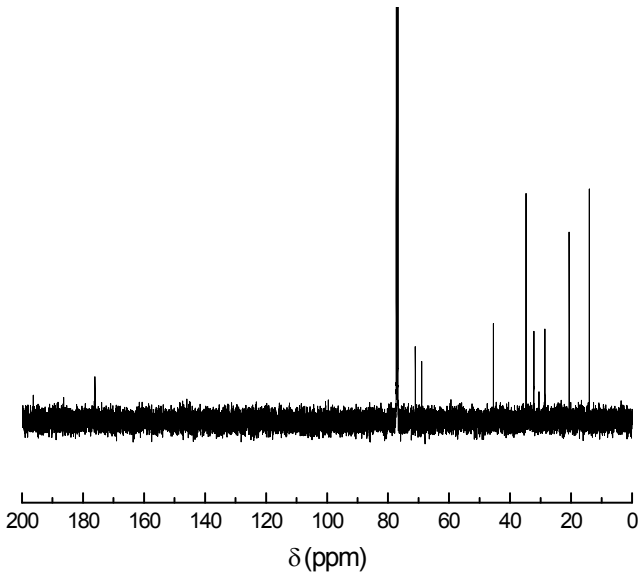

Figure S2. ^{13}C NMR spectrum of 4-hydroxycyclohexyl -2-propylpentanoate [**1**]

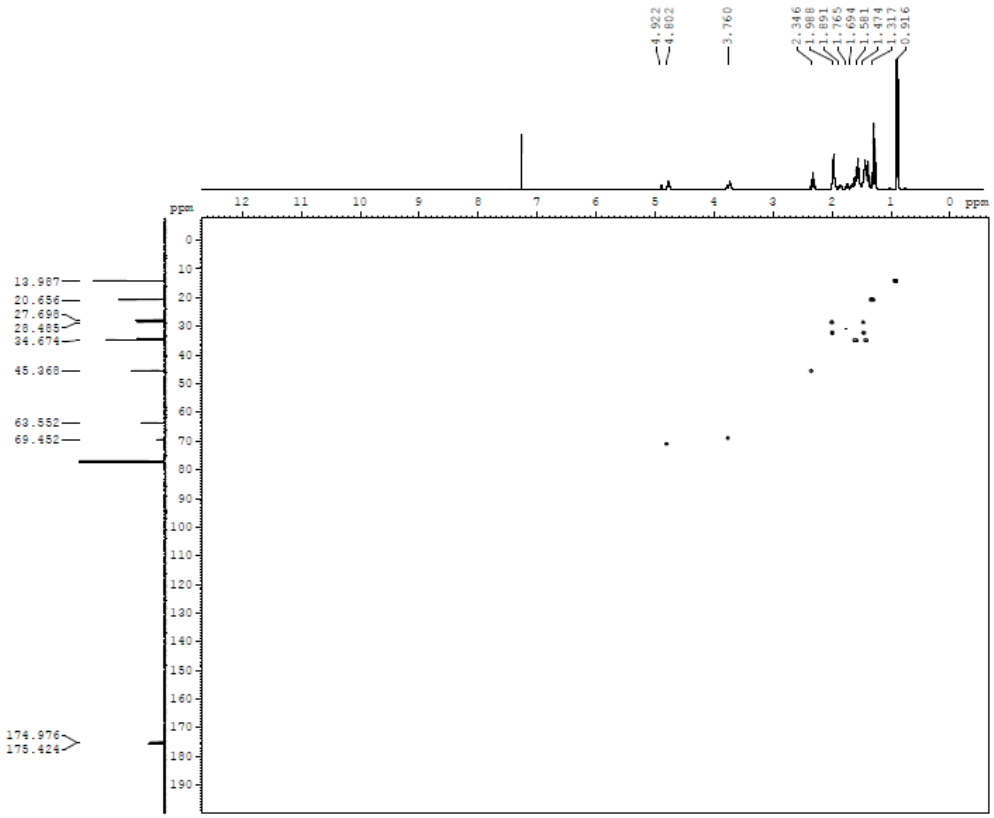

Figure S3. HSQC spectrum of 4-hydroxycyclohexyl -2-propylpentanoate [**1**]

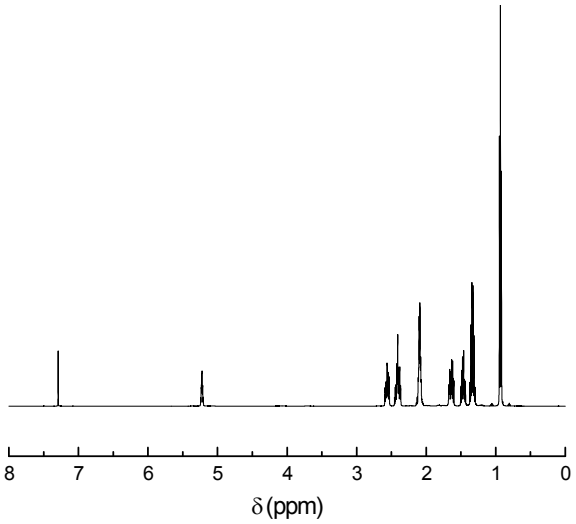

Figure S4. ^{1}H NMR spectrum of 4-oxocyclohexyl -2-propylpentanoate [**2**]

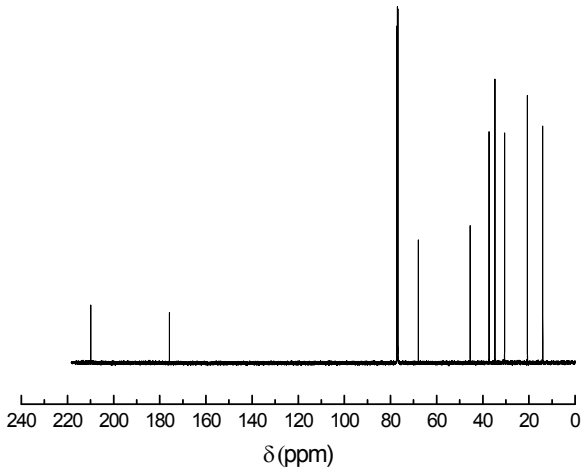

Figure S5. ^{13}C NMR spectrum of 4-oxocyclohexyl -2-propylpentanoate [**2]**

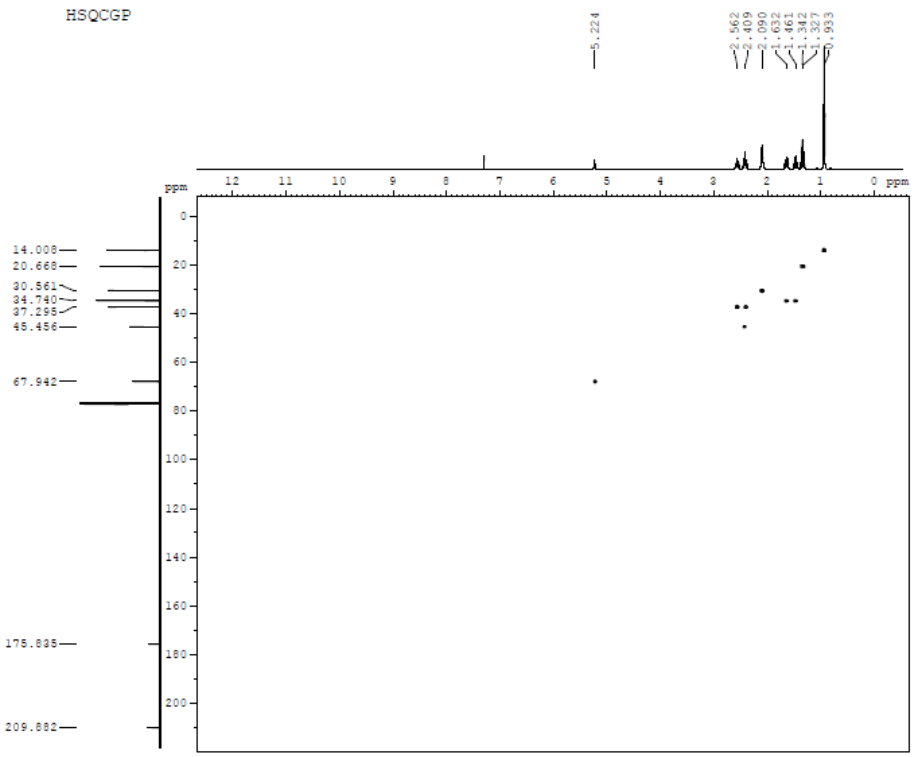

Figure S6. HSQC spectrum of 4-oxocyclohexyl -2-propylpentanoate [**2**]

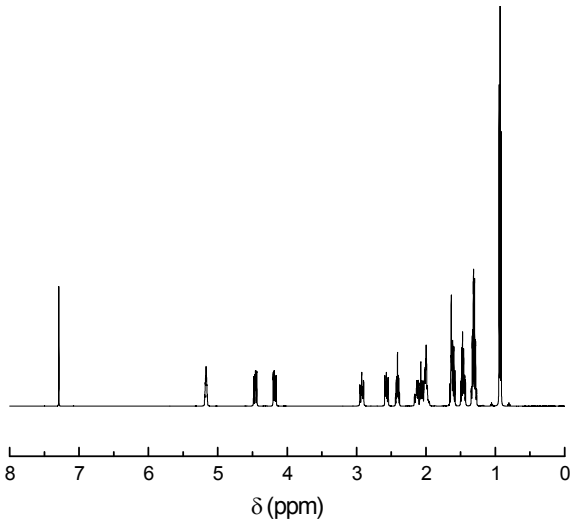

Figure S7. ^{1}H NMR spectrum of γ-2-propylpentanoate-ε-caprolactone (**M1**)

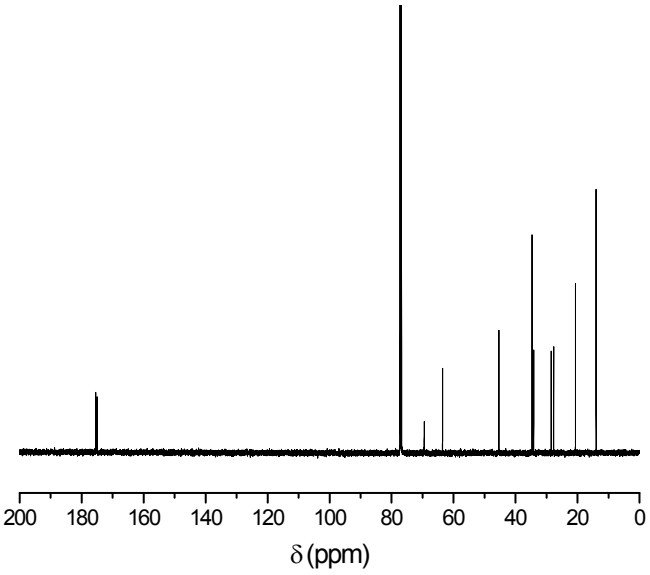

Figure S8 . ^{13}C NMR spectrum of γ-2-propylpentanoate-ε-caprolactone (**M1**)

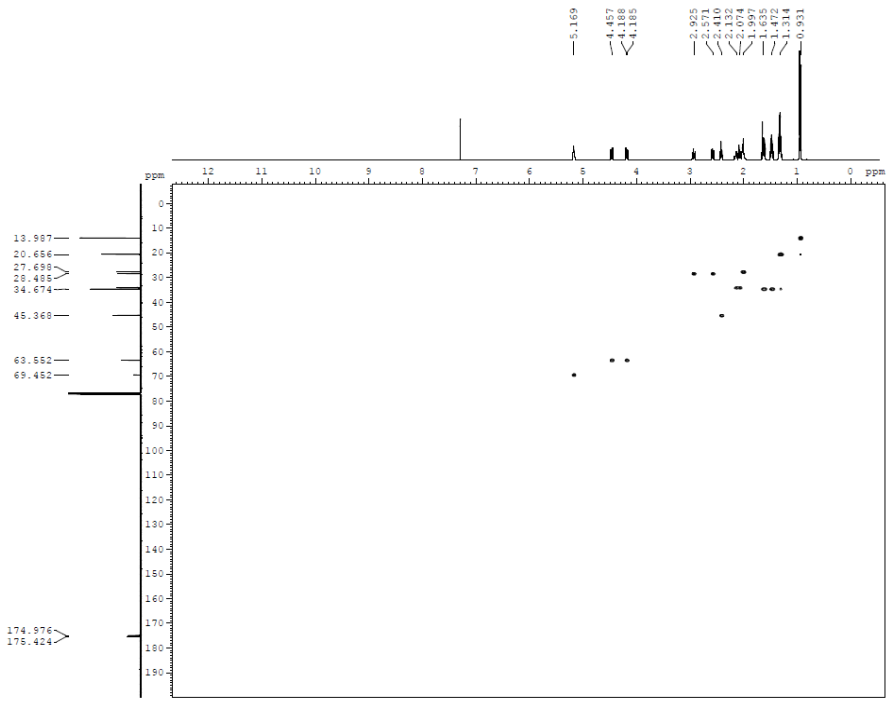

Figure S9. HSQC spectrum of γ-2-propylpentanoate-ε-caprolactone (**M1**)

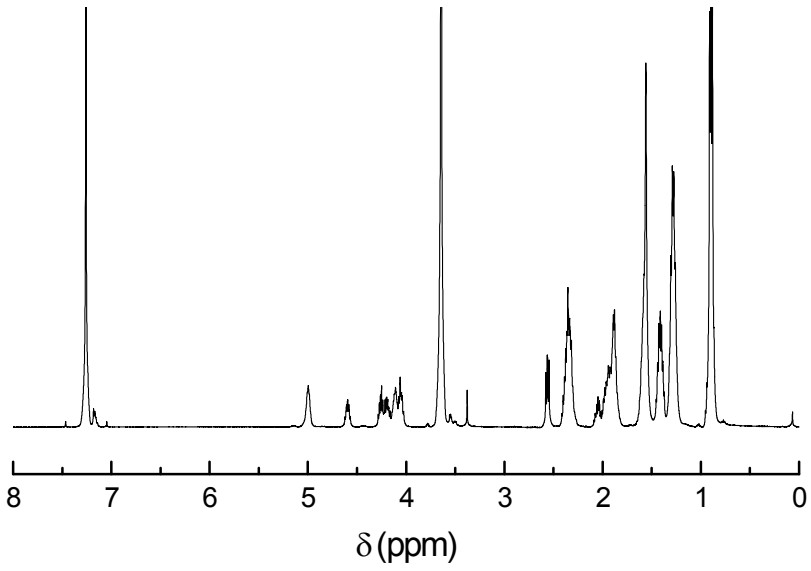

Figure S10. ^{1}H NMR spectrum of diblock copolymer **P1**

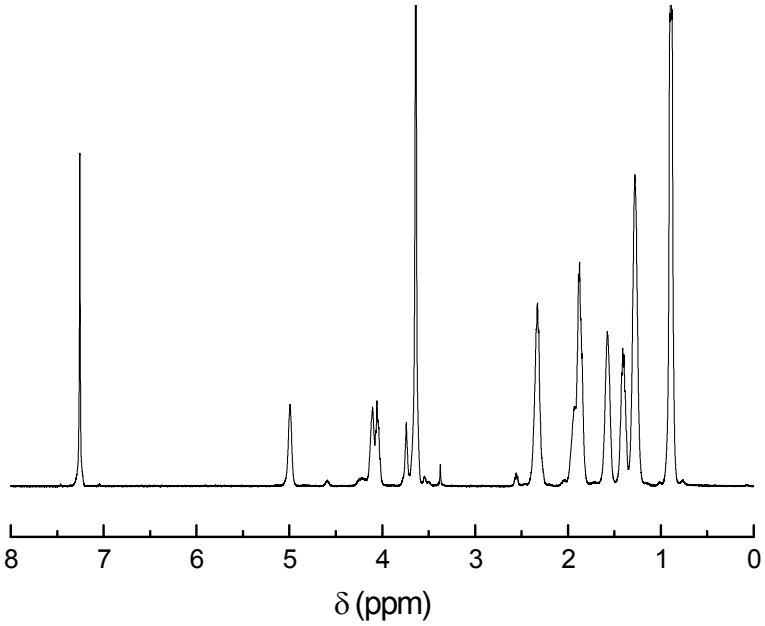

Figure S11. ^{1}H NMR spectrum of diblock copolymer **P2**

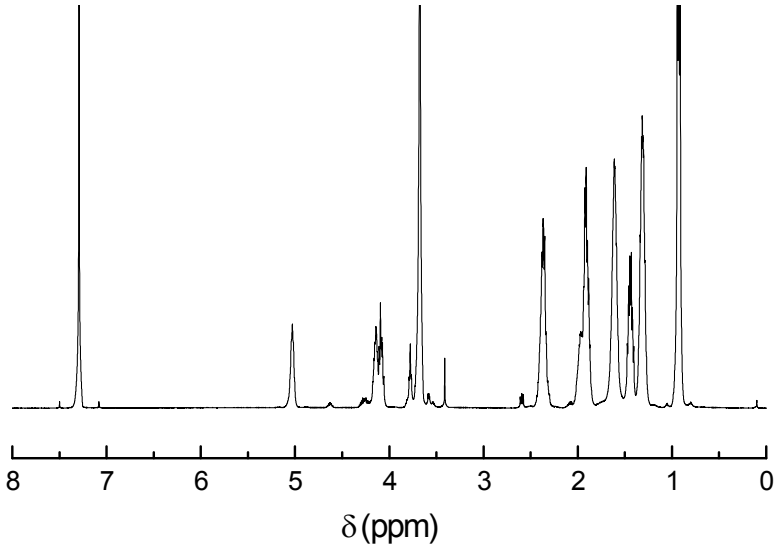

Figure S12. ^{1}H NMR spectrum of diblock copolymer **P3**

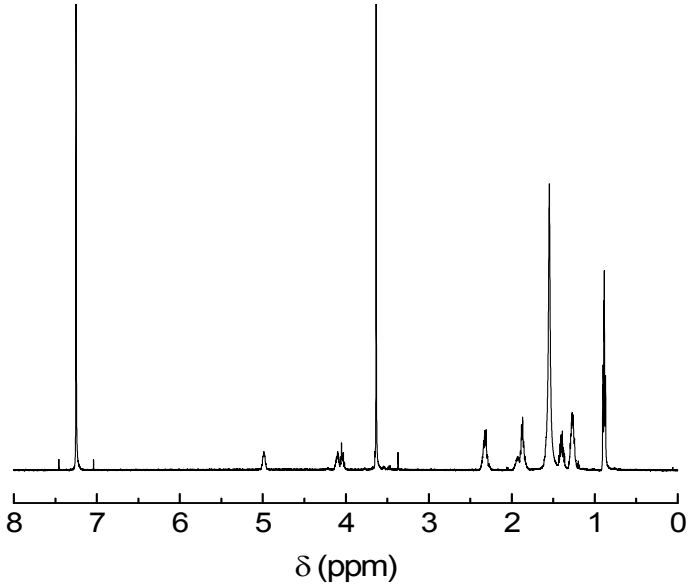

Figure S13. ^{1}H NMR spectrum of diblock copolymer P3 after 3 days in pH 6 phosphate buffer at 37 ^{o}C.

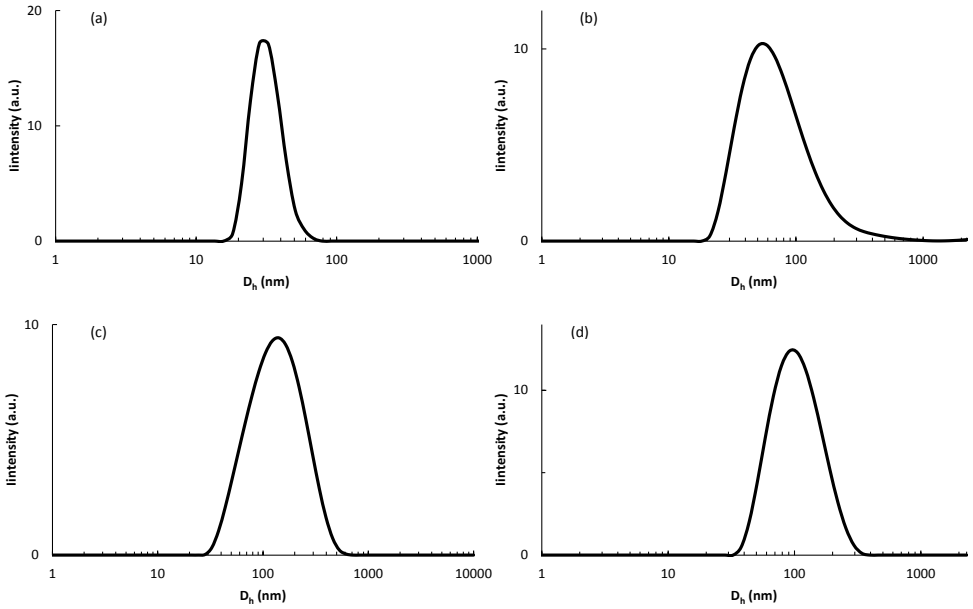

Figure S14. Hydrodynamic diameter (D_h) analysis of micelles at room temperature using dynamic light scattering: (a) **P1**, (b) **P2**, (c) **P3**, (d) **P4**