Water-Soluble Thermoresponsive Polylactides

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ABSTRACT: Novel glycolides with pendent oligo(ethylene oxide) monomethyl ether substituents were synthesized. Subsequent ring-opening polymerization using 4-*tert*-butylbenzyl alcohol as the initiator and Sn(2-ethylhexanote)$_2$ as the catalyst yielded homogeneous oligo(ethylene oxide)-grafted polylactides with high molecular weights and low polydispersities. Polymers with short oligo(ethylene oxide) chains (1 or 2 ethylene oxide repeat units) are more hydrophilic than polylactide but insoluble in water, whereas polymers having 3 or 4 ethylene oxide repeat units are water-soluble. Aqueous solutions of polymers with 3 and 4 ethylene oxide repeat units in each pendent chain are thermoresponsive, with lower critical solution temperatures (LCSTs) at 19 and 37 °C, respectively. The LCST transitions were confirmed by cloud point measurements, variable temperature dynamic light scattering, and changes in line widths measured by variable temperature ^{1}H NMR spectroscopy.

Introduction

Lactide-based polymers are an important class of degradable aliphatic polyesters. Because of their biodegradability and biocompatibility, polylactides have long been used in medical applications as degradable sutures and implants and are currently being developed for controlled drug delivery and as degradable scaffolds for tissue engineering.[1−5] Compared to polyglycolide, polylactide is more hydrophobic which contributes to its slower degradation rate in vivo. A hydrophilic polylactide would be advantageous for some applications since it should have a faster degradation rate, and a polylactide with some degree of water solubility may resist protein fouling and prove particularly useful in drug delivery.

An obvious strategy for increasing the hydrophilicity of polylactide is to append a hydrophilic group such as a poly(ethylene glycol) chain or a carboxylic acid to the polymer structure. Structurally related polymers are thermoresponsive and exhibit a lower critical solution temperature (LCST) at near-ambient temperatures. One of the most studied LCST systems is aqueous solutions of poly(*N*-isopropylacrylamide) which undergoes a rapid and reversible sol−gel transition when heated through its LCST.[6−9] Besides *N*-isopropylacrylamide and its copolymers, polymers derived from poly(methacrylate)s,[10−12] poly(styrene)s,[13] poly(phosphazene)s,[14−17] poly(vinyl ether)s,[18,19] polyethers,[20] and chitosan[21] have been reported to exhibit LCST behavior. Although their unique phase transition suggests potential applications in fields such as drug delivery systems,[21−25] smart surfaces,[26,27] bioseparations,[28−30] controlled filtration,[31,32] and for controlling enzyme activity,[33] the vast majority of LCST polymers are nonbiodegradable, limiting their biomedical applications.

Not surprisingly, there also is substantial interest in developing thermoresponsive polylactides. For example, thermoresponsive injectable drug-delivery systems were developed from thermoresponsive poly(ethylene oxide) and polylactide diblock and triblock copolymers (PEO−PLA and PEO−PLA−PEO).[34] A disadvantage of such systems is that practical applications limit the allowable PEO block length, and manipulation of the transition temperature requires precise control over the length of lactide block. Furthermore, structural heterogeneity may lead to unpredictable degradation profiles, resulting in complicated drug release kinetics.

Recent reports suggest that introducing pendant oligo(ethylene oxide) groups onto a hydrophobic polymer backbone can be a general approach to new water-soluble thermoresponsive polymers.[11,13−16,18,19,21,35] For example, polymethacrylates that have two and three ethylene oxide units in the side chain exhibit LCSTs at 26 and 52 °C, respectively,[11] and PEO-grafted polystyrene with three and four ethylene oxide units in the side chain shows LCST behavior at 13 and 39 °C, respectively.[13] Additionally, the presence of PEO moieties can render the polymer resistant to protein adsorption, making them attractive biomaterials.[36] The few PEO-grafted polyesters[37−40] reported to date all suffer from either a low grafting density, backbone degradation, or a high polydispersity.

One strategy for tailoring the properties of polylactides is to replace the methyl group of the lactic acid repeat unit with substituents that alter the polymer's physical properties.[41] The effectiveness of this approach was illustrated by the successful synthesis of a various of substituted polylactides such as poly(phenyllactide),[42] polymandelide,[43] and alkyl-substituted polylactides.[44] Here we describe the synthesis and ring-opening polymerization of lactide monomers that have been functionalized with exact length oligo(ethylene oxide) chains. The resulting PEO-grafted polylactides should have predictable degradation behavior because of the inherent homogeneity of the monomer repeat unit. These polymers are water-soluble and show LCST behavior, suggesting applications in medicine such as localized drug delivery, where cool solutions of a drug and the protomatrix (below LCST) are injected at a desired site and localized as the mixture warms to body temperature and gels (above LCST).

Experimental Section

Materials. Ethylene glycol monomethyl ether (99%), di(ethylene glycol) monomethyl ether (99.6%), and tri(ethylene glycol) monomethyl ether (95%) were purchased from Aldrich and distilled before use. 1,6-Dibromohexane (96%), NaH (60% dispersion in mineral oil), diethyl oxalate (99%), and 5% platinum on activated carbon were obtained from Aldrich and used as received. Tetrahydrofuran (THF) was dried using an activated alumina column.

Characterization. The molecular weights of polymers were determined by gel permeation chromatography (GPC) at 35 °C

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using two PLgel 10μ mixed-B columns in series (manufacturer-stated linear molecular weight range of 500−10 000 000 g/mol) with THF as the eluting solvent at a flow rate of 1 mL/min. A Waters 2410 differential refractometer was used as the detector, and monodisperse polystyrene standards were used to calibrate the molecular weights. The concentration of polymer solutions used for GPC was 1 mg/mL. Differential scanning calorimetry (DSC) analyses of the polymers were obtained using a TA DSC Q100. Samples were run under nitrogen at a heating rate of 10 °C/min, with the temperature calibrated using an indium standard. The reported glass transition temperatures correspond to the midpoint of the transition. Thermogravimetric analyses (TGA) were run in air at a heating rate of 10 °C/min using a Perkin-Elmer TGA-7. Elemental analyses were determined using a Perkin-Elmer 2400 CHNS/O analyzer. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz) spectra were acquired using either a Varian Gemini 300 spectrometer or a Varian UnityPlus-500 spectrometer with the residual proton signals from the $CDCl_3$ solvent used as the chemical shift standard. Spectra with NMR assignments are provided in the Supporting Information. Mass spectral analyses were carried out on a VG Trio-1 bench-top GC-MS. Variable temperature ^{1}H NMR (500 MHz) spectra were recorded on a thermoregulated Varian UnityPlus-500 spectrometer using 15 mg/mL polymer solutions in D_2O (D, 99.9%). For each temperature, the solution was equilibrated for 20 min before acquiring the data. Variable temperature dynamic light scattering (DLS) experiments were run on a temperature-controlled Protein Solutions Dyna Pro-MS/X system. All samples were filtered through a 0.2 μm Whatman PTFE syringe filter and then equilibrated in the instrument for 15 min at each temperature before taking the data used to calculate the hydrodynamic radius (R_h). The particle size uniformity was determined by a monomodal curve fit, which assumes a single particle size with a Gaussian distribution.

Synthesis of 1-Bromo-7,10-dioxaundecane (2a). A 2 L round-bottom flask containing 600 mL of dry THF was cooled to −25 to −35 °C under a blanket of nitrogen and charged with NaH (60% in mineral oil, 60 g, 1.5 mol) and 1,6-dibromohexane (96%, 508 g, 2.0 mol). Freshly distilled 2-methoxyethanol (76 g, 1.0 mol) was dissolved in 500 mL of dry THF and added dropwise into the stirred slurry over 5 h. After the addition was complete, the mixture was stirred at ∼−15 °C for 24 h and at 0 °C for 2 days. The solids were removed by filtration, and the solvent was removed by rotary evaporation to give a light yellow oil, which was purified by fractional distillation. The distillate at 58−60 °C (50 mTorr) gave 151 g of **2a** (63%) as a colorless oil. ^{1}H NMR: δ 3.53 (m, 2H), 3.49 (m, 2H), 3.42 (t, 2H, J = 6.59 Hz), 3.38 (t, 2H, J = 6.84 Hz), 3.34 (s, 3H), 1.84 (p, 2H), 1.59 (p, 2H), 1.38−1.46 (br m, 2H), 1.29−1.38 (br m, 2H). ^{13}C NMR: δ 71.93, 71.20, 69.95, 58.97, 33.71, 32.65, 29.33, 27.90, 25.22.

1-Bromo-7,10,13-trioxatetradecane (2b). Obtained using the procedure described for the synthesis of 1-bromo-7,10-dioxaundecane (**2a**) and purified by vacuum distillation (83−86 °C, 30 mTorr) to give 195 g of **2b** (69%) as a colorless oil. ^{1}H NMR: δ 3.60 (m, 4H), 3.56 (m, 2H), 3.52 (m, 2H), 3.42 (t, 2H, J = 6.59 Hz), 3.36 (t, 2H, J = 6.84 Hz), 3.34 (s, 3H), 1.82 (p, 2H), 1.56 (p, 2H), 1.38−1.46 (br m, 2H), 1.30−1.38 (br m, 2H). ^{13}C NMR: δ 71.94, 71.17, 70.63, 70.51, 70.08, 58.97, 33.75, 32.70, 29.40, 27.94, 25.27.

1-Bromo-7,10,13,16-tetraoxaheptadecane (2c). Obtained using the procedure described for the synthesis of 1-bromo-7,10-dioxaundecane (**2a**) and purified by vacuum distillation (108−112 °C, 30 mTorr) to give give 213 g of **2c** (65%) as a colorless oil. ^{1}H NMR: δ 3.61 (m, 8H), 3.51 (m, 4H), 3.41 (t, 2H, J = 6.59 Hz), 3.36 (t, 2H, J = 6.84 Hz), 3.33 (s, 3H), 1.82 (p, 2H), 1.54 (p, 2H), 1.37−1.45 (br m, 2H), 1.29−1.37 (br m, 2H). ^{13}C NMR: δ 71.88, 71.11, 70.56, 70.53, 70.45, 70.04, 58.93, 33.70, 32.65, 29.36, 27.90, 25.23.

1-Bromo-7,10,13,16,19-pentaoxaeicosane (2d). Obtained using the procedure described for the synthesis of 1-bromo-7,10-dioxaundecane (**2a**), except that **2d** was not purified by vacuum distillation since attempts to distill this compound caused significant decomposition. Instead, the excess 1,6-dibromohexane was removed from the light brown crude product under vacuum (10 mTorr) at 145 °C overnight and was used without further purification.. ^{1}H NMR: δ 3.57−3.64 (m, 16H), 3.48−3.55 (m, 5.5H), 3.39−3.43 (t, 2.7H, J = 6.59 Hz), 3.34−3.38 (t, 2.2H, J = 6.84 Hz), 3.32−3.34 (s, 3.8H), 1.77−1.85 (p, 2H), 1.50−1.59 (p, 2.6H), 1.37−1.45 (br m, 2.6H), 1.28−1.37 (br m, 2H). The integration of this compound was skewed due to contamination from elimination byproducts.

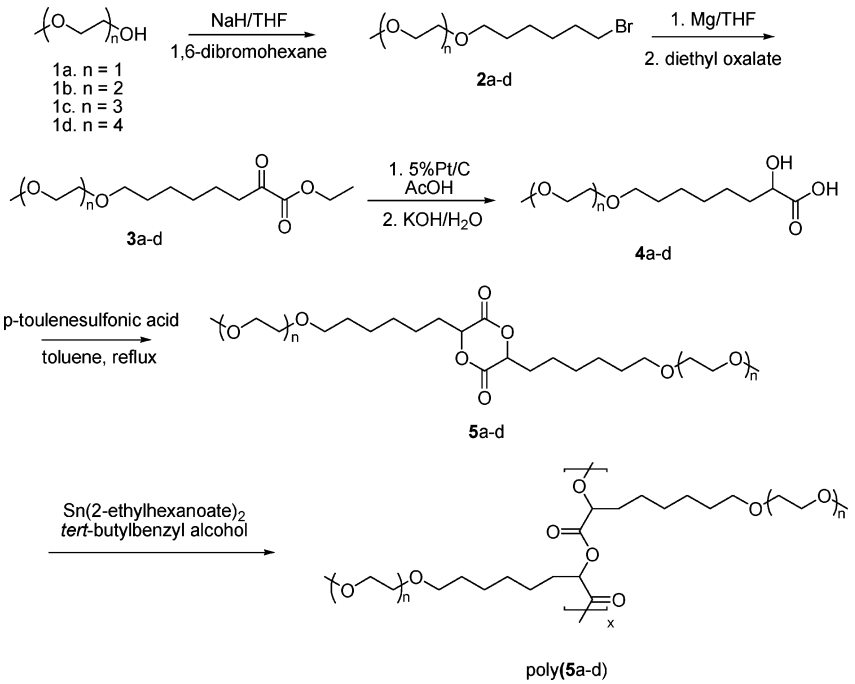
Synthesis of 2-Hydroxy-9,12-dioxatridecanoic Acid (4a). 1-Bromo-7,10-dioxaundecane (**2a**) was dissolved in 600 mL of dry THF and stirred with 24 g of magnesium turnings until the solution stopped boiling. The Grignard reagent was then added dropwise under nitrogen to a 2 L round-bottom flask containing a stirred solution of diethyl oxalate (56 g, 0.38 mol) in dry THF (500 mL) at −80 °C. The mixture was stirred for an additional hour at −80 °C and then was quenched by adding 300 mL of 2 M HCl into the reaction mixture. The water layer was extracted with ether (5 × 200 mL), and the combined organic layers were dried over $MgSO_4$. Filtration and removal of the solvents by rotary evaporation gave a light brown oil. After dissolving the oil in 500 mL ethanol and adding 1 g of 5% Pt/C and 15 g $NaHCO_3$, the α-keto ester was hydrogenated at 1500 psi. When ^{1}H NMR showed that the α-keto ester had fully reacted (disappearance of the triplet at 2.80 ppm), the solids were removed by filtration and the ethanol solution was concentrated by rotary evaporation to give a colorless oil. Saturated aqueous $NaHCO_3$ (1 L) was added and the mixture was heated to reflux for 3 days. When ^{1}H NMR showed the hydrolysis was complete (disappearance of the quartet at 4.30 ppm), the basic solution was continuously extracted with ether for 24 h. The ether layer was discarded and the aqueous layer was acidified with concentrated HCl to ∼pH = 1. After continuous extraction with ether for 48 h, the ether layer was dried over $MgSO_4$, filtered, and evaporated to dryness to give crude **4a** as a light brown oil which was purified by three crystallizations from ether at −40 °C followed by drying under vacuum (10 mTorr) at room temperature for 12 h to give 71 g of **4a** (80%) as white crystals. ^{1}H NMR: δ 4.21 (dd, 1H, J = 7.17 Hz, J = 4.39 Hz), 3.56 (m, 4H), 3.44 (t, 2H, J = 6.66 Hz), 3.37 (s, 3H), 1.80 (m, 1H), 1.67 (m, ^{1}H), 1.56 (p, 2H), 1.24−1.50 (br m, 6H). ^{13}C NMR: δ 178.35, 71.89, 71.38, 70.06, 69.73, 58.88, 33.83, 29.27, 28.82, 25.69, 24.45.

2-Hydroxy-9,12,15-trioxahexadecanoic Acid (4b). Obtained using the procedure described for the synthesis of 2-hydroxy-9,-12-dioxatridecanoic acid (**4a**), crystallizing the crude product once from ether at −80 °C and twice from ether at −40 °C. The resulting colorless oil was then dried under vacuum (10 mTorr) at room temperature for 12 h to give 72 g of **4b** (67%) as a colorless oil at room temperature. ^{1}H NMR: δ 4.20 (dd, 1H, J = 7.17 Hz, J = 4.39 Hz), 3.62 (m, 4H), 3.56 (m, 4H), 3.43 (t, 2H, J = 6.66 Hz), 3.35 (s, 3H), 1.78 (m, 1H), 1.66 (m, 1H), 1.55 (p, 2H), 1.24−1.48 (br m, 6H). ^{13}C NMR: δ 177.55, 71.68, 71.24, 70.34, 70.15, 69.96, 69.77, 58.75, 33.81, 29.12, 28.79, 25.61, 24.45.

2-Hydroxy-9,12,15,18-tetraoxanonadecanoic Acid (4c). Obtained using the procedure described for the synthesis of 2-hydroxy-9,12-dioxatridecanoic acid (**4a**), crystallizing the crude product twice from ether at −80 °C and twice from ether at −40 °C. The colorless oil was dried under vacuum (10 mTorr) at room temperature for 12 h to give 76 g of **4c** (61%). ^{1}H NMR: δ 4.20 (dd, 1H, J = 7.17 Hz, J = 4.39 Hz), 3.62 (m, 8H), 3.56 (m, 4H), 3.43 (t, 2H, J = 6.66 Hz), 3.35 (s, 3H), 1.78 (m, 1H), 1.66 (m, 1H), 1.55 (p, 2H), 1.24−1.48 (br m, 6H). ^{13}C NMR: δ 177.69, 71.77, 71.21, 70.44, 70.26, 69.97, 69.88, 33.83, 29.19, 28.78, 25.65, 24.47.

2-Hydroxy-9,12,15,18,21-pentaoxadocosanoic Acid (4d). Obtained using the procedure described for the synthesis of 2-hydroxy-9,12-dioxatridecanoic acid (**4a**), crystallizing the crude product five times from ether at −80 °C. The light brown oil was dried under vacuum (10 mTorr) at room temperature for 12 h to give 57 g of **4c** (41%). ^{1}H NMR: δ 4.20 (dd, 1H J = 7.08 Hz, J = 4.39 Hz), 3.62 (m, 12H), 3.56 (m, 4H), 3.43 (t, 2H, 2H, J = 6.59 Hz), 3.35 (s, 3H), 1.78 (m, 1H), 1.66 (m, 1H), 1.55 (p, 2H), 1.24−1.48 (br m, 6H). ^{13}C NMR: δ 177.37, 71.78, 71.21, 70.49, 70.43, 70.39, 70.26, 69.98, 69.91, 58.86, 33.84, 29.22, 28.79, 25.69, 24.46.

Scheme 1. Synthesis of PEO-Grafted Polyglycolides



Synthesis of 3,6-Bis(7,10-dioxaundecyl)-1,4-dioxane-2,5-dione (5a). 2-Hydroxy-9,12-dioxatridecanoic acid (**4a**) (23.4 g, 0.1 mol) was placed in a 2 L round-bottom flask, along with 1 g of *p*-toluenesulfonic acid and ∼1.8 L of toluene. The solution was refluxed for 3 days, with the water removed azeotropically using a Barrett trap. After the toluene was removed by rotary evaporation, the residue was dissolved in 500 mL of diethyl ether, washed with saturated $NaHCO_3$, and dried over $MgSO_4$. Filtration and removal of the ether gave the crude product as a light brown oil, which was recrystallized from diethyl ether at −40 °C and then distilled (180 °C/3 mTorr) to give 9.6 g of **5a** (41%). ^{1}H NMR: δ 4.88 (dd, J = 8.30 Hz, J = 4.88 Hz), δ 4.83 (dd, J = 7.69 Hz, J = 4.27 Hz, 1H total for the signals at 4.88 and 4.83), 3.52 (m, 4H), 3.40 (t, 2H, J = 6.66 Hz), 3.34 (s, 3H), 1.8−2.1 (br m, 2H), 1.4−1.6 (br m, 4H), 1.24−1.4 (br m, 4H). ^{13}C NMR: δ 166.87, 165.66, 76.24, 75.41, 71.87, 71.20, 71.15, 69.89, 58.93, 31.75, 29.87, 29.27, 28.74, 28.60, 25.65, 24.38, 24.18. Anal. Calcd for $C_{22}H_{40}O_8$: C, 61.11; H, 9.26. Found: C, 60.80; H, 8.87. MS (*m*/*z*) 433.3 (M + 1).

3,6-Bis(7,10,13-trioxatetradecyl)-1,4-dioxane-2,5-dione (5b). Obtained as a colorless oil using the procedure described for the synthesis of 3,6-bis(7,10-dioxaundecyl)-1,4-dioxane-2,5-dione (**5a**). Distillation (190 °C/3 mTorr) gave 7.8 g of **5b** (28%). ^{1}H NMR: δ 4.88 (dd, J = 8.30 Hz, J = 4.88 Hz), δ 4.83 (dd, J = 7.69 Hz, J = 4.27 Hz, 1H total for the signals at 4.88 and 4.83), 3.62 (m, 4H), 3.57 (m, 4H), 3.40 (t, 2H, J = 6.66 Hz), 3.34 (s, 3H), 1.9−2.2 (br m, 2H), 1.47−1.7 (br m, 4H), 1.3−1.47 (br m, 4H). ^{13}C NMR: δ 166.87, 165.69, 76.28, 75.46, 71.88, 71.18, 71.12, 70.57, 70.45, 70.01, 58.94, 31.80, 29.93, 29.33, 28.79, 28.65, 25.70, 24.43, 24.22. Anal. Calcd for $C_{26}H_{48}O_{10}$: C, 60.00; H, 9.23. Found: C, 60.10; H, 9.60. MS (*m*/*z*) 521.1 (M + 1).

3,6-Bis(7,10,13,16-tetraoxaheptadecyl)-1,4-dioxane-2,5-dione (5c). Obtained as a colorless oil using the procedure described for the synthesis of 3,6-bis(7,10-dioxaundecyl)-1,4-dioxane-2,5-dione (**5a**). Distillation (210 °C/3 mTorr) gave 6.9 g of **5c** (21%). ^{1}H NMR: δ 4.88 (dd, J = 8.30 Hz, J = 4.88 Hz), δ 4.83 (dd, J = 7.69 Hz, J = 4.27 Hz, 1H total for the signals at 4.88 and 4.83), 3.62 (m, 8H), 3.57 (m, 4H), 3.40 (t, 2H, J = 6.66 Hz), 3.34 (s, 3H), 1.9−2.2 (br m, 2H), 1.47−1.7 (br m, 4H), 1.3−1.47 (br m, 4H). ^{13}C NMR: δ 166.84, 165.48, 76.05, 75.21, 71.64, 70.93, 70.88, 70.32, 70.29, 70.21, 69.80, 58.70, 31.54, 29.66, 29.15, 29.13, 28.61, 28.44, 25.51, 25.49, 24.21, 24.00. Anal. Calcd for $C_{30}H_{56}O_{12}$: C, 59.21; H, 9.21. Found: C, 59.34; H, 9.60. MS (*m*/*z*) 609.4 (M + 1).

3,6-Bis(7,10,13,16,19-pentaoxaeicosyl)-1,4-dioxane-2,5-dione (5d). Obtained as a light brown oil using the procedure described for the synthesis of 3,6-bis(7,10-dioxaundecyl)-1,4-dioxane-2,5-dione (**5a**). Distillation (238 °C/3 mTorr) gave 5.2 g of **5d** (15%) as a colorless oil. ^{1}H NMR: δ 4.88 (dd, J = 8.30 Hz, J = 4.88 Hz), δ 4.83 (dd, J = 7.69 Hz, J = 4.27 Hz, 1H total for the signals at 4.88 and 4.83), 3.62 (m, 12H), 3.57 (m, 4H), 3.40 (t, 2H, J = 6.66 Hz), 3.34 (s, 3H), 1.9−2.2 (br m, 2H), 1.47−1.7 (br m, 4H), 1.3−1.47 (br m, 4H). ^{13}C NMR: δ 166.90, 165.71, 76.31, 75.49, 71.88, 71.21, 71.16, 70.55, 70.52, 70.46, 70.03, 58.97, 31.84, 29.94, 29.38, 28.82, 28.69, 25.74, 24.46, 24.26. Anal. Calcd for $C_{34}H_{64}O_{14}$: C, 58.62; H, 9.19. Found: C, 58.30; H, 9.25. MS (*m*/*z*) 697.4 (M + 1).

Bulk Polymerization of 3,6-Bis(7,10-dioxaundecyl)-1,4-dioxane-2,5-dione (5a). Solvent-free polymerizations were run in sealed tubes prepared from $^3/_8$ in. diameter glass tubing. Freshly distilled monomer **4a** (1.17 g) and a small magnetic stir bar were added to the tube and stirred under vacuum (3 mTorr) for 12 h at 105 °C. After cooling to room temperature and backfilling with argon, a syringe was used to add toluene solutions of the catalyst (Sn(2-ethylhexanoate)$_2$, 0.098 M, 56 μL, 0.2 mol %) and initiator (4-*tert*-butylbenzyl alcohol, 0.095 M, 57 μL, 0.2 mol %). After careful removal of the toluene under vacuum, the tube was sealed under vacuum and immersed into an oil bath at 130 °C and stirred magnetically for 4 h. At the end of the polymerization, the tube was cooled in ice water and opened. A portion of the polymer was analyzed by GPC to determine molecular weights (M_n = 148 500 g/mol, PDI = 1.31) and by NMR to evaluate conversion by comparing the methine resonances for the monomer (at ∼4.8 ppm) and polymer (∼5.1 ppm) (97%). The remaining polymer was dialyzed (molecular weight cutoff = 12−14 000) in acetone and dried under vacuum (4 mTorr) at 70 °C overnight to give 0.97 g of poly(**5a**) as a colorless viscous liquid (83%). ^{1}H NMR: δ 5.01−5.23 (br, 1H), 3.53−3.64 (br, 4H), 3.44−3.52 (br m, 2H), 3.39−3.43 (s, 3H), 1.82−2.03 (br, 2H), 1.55−1.70 (br, 2H), 1.28−1.53 (br, 6H). Anal. Calcd for $(C_{22}H_{40}O_8)_n$: C, 61.11; H, 9.26. Found: C, 61.18; H, 9.33.

Poly(3,6-bis(7,10,13-trioxatetradecyl)-1,4-dioxane-2,5-dione), Poly(5b). Obtained using the procedure described for the synthesis of poly(**5a**). Monomer **5b** (1.25 g) was dried at 115 °C and polymerized for 11 h at 130 °C. The monomer conversion was 82%, and M_n = 65 800 g/mol (PDI = 1.14). After dialysis and removal of solvent by rotary evaporation, the residue was dried

overnight under vacuum (4 mTorr) at 70 °C to give poly(**5b**) (0.96 g) as a colorless viscous liquid (77%). ^{1}H NMR: δ 5.01−5.23 (br, 1H), 3.64−3.72 (br, m, 4H), 3.54−3.64 (br, 4H), 3.43−3.52 (br, m, 2H), 3.37−3.43 (s, 3H), 1.83−2.05 (br, 2H), 1.54−1.69 (br, 2H), 1.25−1.52 (br, 6H). Anal. Calcd for $(C_{26}H_{48}O10)_n$: C, 60.00; H, 9.23. Found: C, 59.83; H, 9.11.

Poly(3,6-bis(7,10,13,16-tetraoxaheptadecyl)-1,4-dioxane-2,5-dione), Poly(5c). Obtained using the procedure described for the synthesis of poly(**5a**). Monomer **5c** (1.90 g) was dried at 120 °C and polymerized for 15 h at 130 °C. The monomer conversion was 73%, and M_n = 56 100 g/mol (PDI = 1.10). After dialysis and removal of solvent by rotary evaporation, the residue was dried under vacuum (4 mTorr) at 70 °C overnight to give 1.40 g of poly(**5c**) as a colorless viscous liquid (73%). ^{1}H NMR: δ 5.01−5.24 (br, 1H), 3.63−3.74 (br, m, 8H), 3.54−3.63 (br, 4H), 3.42−3.51 (br, m, 2H), 3.38−3.42 (s, 3H), 1.79−2.05 (br, 2H), 1.53−1.69 (br, 2H), 1.25−1.53 (br, 6H). Anal. Calcd for $(C_{30}H_{56}O_{12})_n$: C, 59.21; H, 9.21. Found: C, 59.13; H, 9.06.

Poly(3,6-bis(7,10,13,16,19-pentaoxaeicosyl)-1,4-dioxane-2,5-dione), Poly(5d). Obtained using the procedure described for the synthesis of poly(**5a**). Monomer **5d** (1.3 g) was dried at 130 °C and polymerized for 20 h at 130 °C. The monomer conversion was 74%, and M_n = 10 600 g/mol (PDI = 1.12). After dialysis and removal of solvent by rotary evaporation, the residue was stirred under vacuum (4 mTorr) overnight to give 0.68 g of poly(**5d**) as a light yellow liquid (52%). ^{1}H NMR: δ 5.01−5.23 (br, 1H), 3.64−3.71 (br, m, 12H), 3.55−3.63 (br, 4H), 3.43−3.50 (br, m, 2H), 3.38−3.42 (s, 3H), 1.80−2.05 (br, 2H), 1.54−1.69 (br, 2H), 1.25−1.52 (br, 6H). Anal. Calcd for $(C_{34}H_{64}O_{14})_n$: C, 58.62; H, 9.19. Found: C, 58.64; H, 9.08.

Results and Discussion

Monomer Synthesis. We synthesized four PEO-substituted glycolides using the synthethic steps shown in Scheme 1. First, the reaction of an oligo(ethylene glycol) monomethyl ether with 1,6-dibromohexane generated the corresponding hexyl bromide capped with an oligo(ethylene glycol) monomethyl ether. Grignard reagents generated from these functionalized oligo(ethylene glycol) monomethyl ethers were reacted with diethyl oxalate at −78 °C to provide the corresponding α-keto esters. Typically, the conversion of diethyl oxalate was >85%, with no detectable contamination from addition of a second Grignard equivalent to the α-keto esters. Catalytic hydrogenation of the crude ketoesters at 1500 psig using Pt/C yielded the α-hydroxy esters, but since purification of the esters proved difficult, the crude α-hydroxy esters were hydrolyzed and isolated as the α-hydroxy acids. To the best of our knowledge, none of the α-hydroxy acids were previously reported. Crystallization from ether at −80 and −40 °C gave the acids as colorless to light brown oils in overall yields of 41−80% based on diethyl oxalate. A representative ^{1}H NMR spectrum, that of the α-hydroxy acid **4b**, is shown in Figure 1. The methine proton of the acid appears as doublet of doublets at 4.20 ppm, while intense signals between 3.50 and 3.65 ppm are characteristic of the methylene protons of the ethylene oxide units. The methylene protons of the hexyl spacer adjacent to PEO segment appear as a triplet at 3.42 ppm and the *ω*-methoxy protons as a singlet at 3.35 ppm.

Dimerization of the α-hydroxy acids in refluxing toluene using *p*-toluenesulfonic acid as a catalyst yielded a mixture of the *R,S* and *R,R/S,S* diastereomers in ∼45% yield before distillation. The major byproducts consisted of linear oligomers, which could in principle be recycled or thermally cracked to yield additional monomer. A representative ^{1}H NMR spectrum, that of compound **5b**, is shown in Figure 1. The methine protons of the 3,6-disubstituted glycolide ring appear as two sets of doublets of doublets centered at 4.88 and 4.83 ppm; integration of these two peaks in the ^{1}H NMR spectrum of crude product

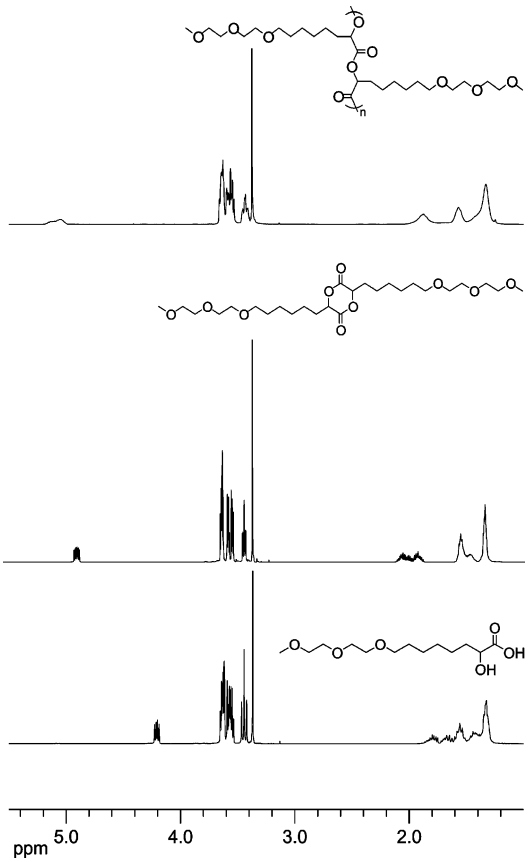


Figure 1. 300 MHz ^{1}H NMR spectra of **4b**, **5b**, and poly(**5b**).

confirms the 1:1 ratio of the *meso* to *rac* diastereomers expected for the statistical coupling of a racemic mixture of hydroxy acids. Crystallization from ether significantly alters the diastereomeric ratio, favoring isolation of the *meso* diastereomer. Similar results were obtained for the other glycolides. We note that ^{1}H NMR spectroscopy also provides a convenient method for monitoring the polymerization reaction. As shown in Figure 1 for glycolide **5b**, the methine peaks at 4.85 evolve into a broad peak at ∼5.10 ppm during polymerization, allowing straightforward calculation of the conversion of monomer to polymer.

Bulk Polymerization. Bulk polymerizations of the PEO-functionalized glycolides were run at 130 °C using 4-*tert*-butylbenzyl alcohol as the initiator and Sn(2-ethylhexanoate)$_2$ as the catalyst. The monomer:catalyst:initiator ratio for all polymerizations was 500:1:1. The hydrophilic segments in these PEO-functionalized monomers complicate monomer purification since residual alcohol or water in monomer can also act as initiator and lead to lower than expected molecular weights. Stringent monomer purification and drying processes were required to ensure pure and dry monomers and obtain high molecular weight polymers. All monomers were freshly distilled by Kügelrohr distillation after recrystallization and dried under vacuum at >100 °C before polymerization. (During distillation, the monomer epimerized to a statistical mixture of diastereomers.)

Polymerizations were run for 4−20 h, and then samples were analyzed by ^{1}H NMR spectroscopy for conversion by comparing the methine resonances for the monomer (at ∼4.8 ppm) and polymer (∼5.1 ppm). The crude polymers were purified by dialysis against acetone and dried under vacuum to give clear viscous liquids. Typical polymerization results are listed in Table 1, and the corresponding GPC traces of the crude polymers before dialysis are shown in Figure 2. The molecular weights,

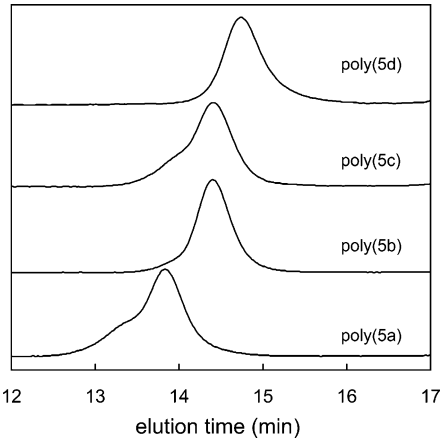


Figure 2. Gel permeation chromatography traces of crude poly(ethylene oxide)-grafted polylactides (~0.1 wt % polymer in tetrahydrofuran, elution rate = 1 mL/min).

Table 1. Bulk Polymerization Results for Poly(ethylene oxide)-Functionalized Glycolides

monomer	time (h)	conv (%)[a]	M_n(theor)[b]	M_n[c]	PDI[c]
5a	4	97	209 500	148 500	1.31
5b	11	82	169 000	65 800	1.14
5c	20	73	221 900	56 100	1.10
5d	20	74	257 500	10 600	1.12

[a] Monomer conversion was measured by ^{1}H NMR spectroscopy. [b] $M_{n(theo)}$ = [monomer]/[initiator] × monomer molecular weight × conversion. [c] M_n and PDI data are from crude polymers before dialysis and measured by gel permeation chromatography in tetrahydrofuran using polystyrene standards for calibration. All polymerizations were run at 130 °C with a monomer/initiator ratio of 500.

measured by GPC and reported relative to polystyrene standards, were lower than the theoretical values in all cases. In contrast, polylactides characterized under similar GPC conditions usually provide molecular weights comparable to the values expected from the monomer to initiator ratio. Lower than expected molecular weights could be due to residual alcohol or water in the monomer or simply indicate that the PEO segments in the side chains alter the hydrodynamic radius of the polymer in THF, leading to lower relative molecular weights. The latter seems to be important for polymers with long PEO segments. We analyzed poly(**5a**) and poly(**5d**) on a GPC system equipped with a multiangle light scattering detector. The M_n calculated for poly(**5a**) was within 5% of the value obtained using polystyrene standards, while M_n determined for poly(**5d**) by light scattering was ~2 times the molecular weight obtained using polystyrene standards (20 800 vs 10 600). We also observed that multiple distillations of monomer or higher distillation temperatures generally led to slower polymerization rates but lower molecular weights, suggesting that thermal decomposition may introduce impurities into the monomer. The contributions of these effects may be responsible for the occasional shoulders seen on the high molecular weight side of GPC traces (see the data for poly**(5a)** peak and poly**(5c)** in Figure 2).

The TGA profiles for all four polymers were similar, with the onset for decomposition at around 300 °C (see Figure S1, Supporting Information). We often observed a small weight loss at low temperatures. Since its magnitude depended on the length of time the sample was held at 135 °C prior to starting the run, we assigned it to the loss of hydrogen-bonded water. The DSC scans (see Figure S2, Supporting Information) show a weak glass transition at ~−25 °C, consistent with extensive research on poly(methacrylate) comb polymers showing that T_gs decrease as the length of the side chains in comb polymers increase.[45]

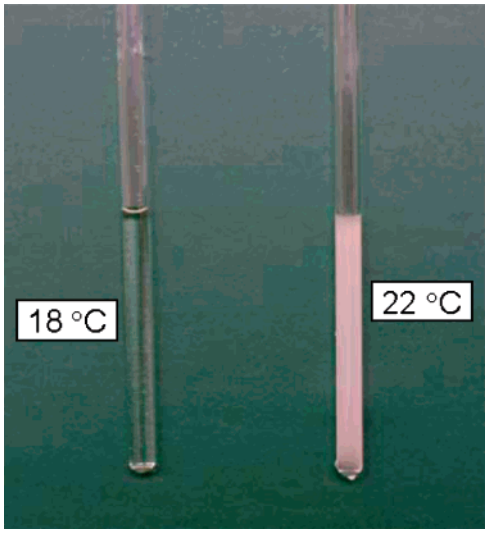


Figure 3. Photograph showing the lower critical solution temperature behavior of poly(**5c**) in D_2O. The polymer concentration was ~15 mg/mL.

Aqueous Solubility and Solution Properties of PEO-Grafted Polylactides. Poly(**5a**) and poly(**5b**) are insoluble in water. Although hydration of the hydrophilic side chains precludes a precise measurement of the contact angle, the polymers are clearly more hydrophilic than poly(hexyl glycolide) (contact angles of 50−75° compared to 100° for poly(hexyl glycolide). Poly(**5c**) and poly(**5d**) are water-soluble and form clear solutions at temperatures below their LCST. To determine the cloud points, we prepared aqueous solutions of poly**(5c)** (M_n, GPC = 59 800, PDI = 1.16) and poly(**5d**) (M_n, GPC = 10 600, PDI = 1.12) with a concentration of 15 mg/mL in 5 mm NMR tubes. Solutions of poly**(5c)** were transparent below 19 °C and suddenly turned cloudy at 20 °C during the course of heating (Figure 3). After 24 h at 25 °C, an obvious precipitate settled at the bottom of the tube, but the precipitate redissolved when the solution was cooled. Similarly, solutions of poly(**5d**) exhibited a cloud point at 38 °C. Apparently, the cloud point increases with the length of PEO chain, as has been reported for other PEO-grafted polymers.[10,13]

We also used variable temperature ^{1}H NMR measurements to study the phase transitions of poly(**5c**) and poly(**5d**) solutions (15 mg/mL) in D_2O. Their ^{1}H NMR spectra at various temperatures are shown in Figure 4 and Figure 5; the height and position of the water peak were used as internal references. When a solution of poly(**5c**) was heated from 4 to 18 °C, there were no visible changes in the height and shape of the proton signal from the terminal methoxy group. When heated to 25 °C, the peak broadened and the peak height noticeably decreased, indicating a phase transition from a soluble to an insoluble state somewhere between 18 and 25 °C, consistent with the cloud point measurements. For poly(**5d**), the height of the methoxy peak decreased and broadened between 35 and 45 °C, again consistent with cloud point measurements that place the transition at 38 °C.

We analyzed the NMR data by plotting the line width at half-height as a function of temperature for the methoxy resonance. The data shown in Figure 6 confirm transitions at ~17 °C for poly(**5c**) and ~37 °C for poly(**5d**).

The thermoresponsive behavior of the polymer solutions also can be monitored by variable temperature dynamic light scattering measurements (DLS). Shown in Figure 7 are the DLS results for aqueous solutions of poly(**5c**) (3 mg/mL) at different temperatures. When the solution was heated from 10 to 21 °C,

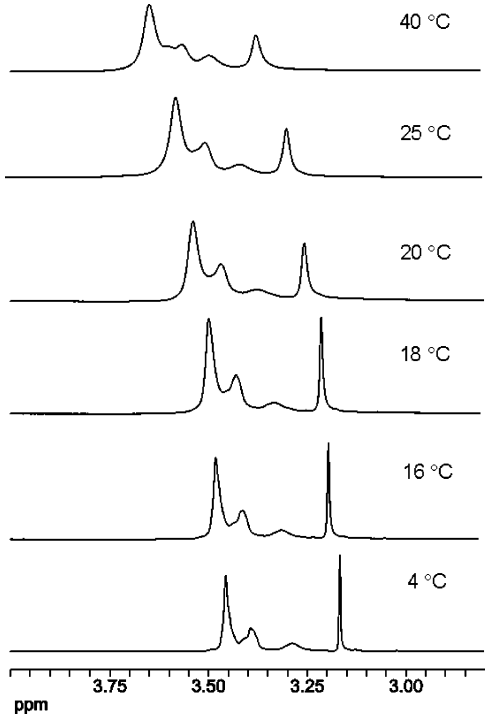


Figure 4. 500 MHz ^{1}H NMR spectra of poly(**5c**) (M_n = 56 100 g/mol, PDI = 1.10) in D_2O (15 mg/mL) at different temperatures.

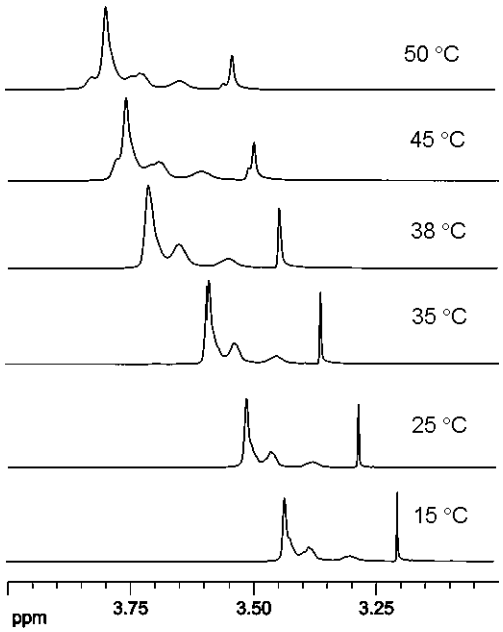


Figure 5. 500 MHz ^{1}H NMR spectra of poly(**5d**) (M_n = 10 600 g/mol, PDI = 1.12) in D_2O (15 mg/mL) at different temperatures.

the average hydrodynamic radius of the polymer particles in solution remained constant at ~5 nm. Further heating to 22 °C caused a drastic increase in the average hydrodynamic radius to hundreds of nanometers, and the variability of this value is consistent with polymer agglomeration. The DLS results for an aqueous solution of poly(**5d**) (3 mg/mL) are shown in Figure 8. Between 25 and 38 °C, the average hydrodynamic radius of the particles is essentially constant within experimental error, but heating the solution to 39 °C induces an increase in hydrodynamic radius to hundreds of nanometers, suggesting the polymer chains changed from a hydrated state to an agglomerated insoluble state.

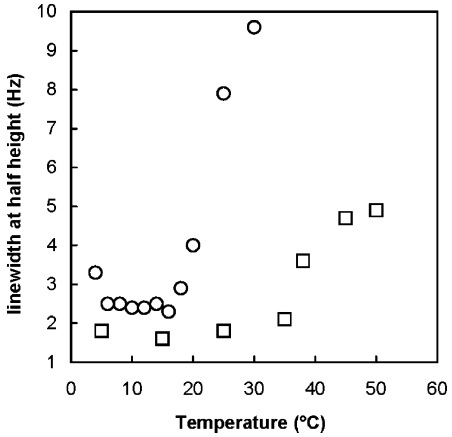


Figure 6. Evolution of the ^{1}H NMR line width of the methoxy resonance with temperature for poly(**5c**) (circles) and poly**(5d)** (squares). The experiments were run in D_2O (15 mg/mL).

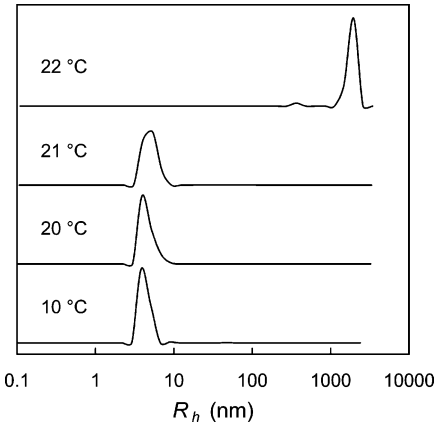


Figure 7. Dynamic light scattering results for poly(**5c**) (M_n = 56 100 g/mol, PDI = 1.10) in water (3 mg/mL) at different temperatures.

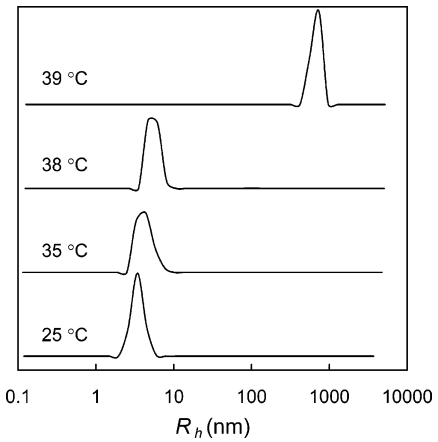


Figure 8. Dynamic light scattering results for poly(**5d**) (M_n = 10 600 g/mol, PDI = 1.12) in water (3 mg/mL) at different temperatures.

Conclusions

We successfully synthesized a series of lactides that have one oligo(ethylene glycol) monomethyl ether chain per lactic acid residue. Their subsequent ring-opening polymerization yielded high molecular weight PEO-grafted polylactides with narrow molecular weight distributions. Poly**(5a)** and poly**(5b)**, having 1 and 2 PEO repeat units in the pendant chain, are hydrophilic but are not water-soluble. Poly**(5c)** and poly**(5d)**, having longer PEO chains, are water-soluble, and we detected lower critical solution temperatures for both polymers. The cloud points of poly**(5c)** and poly**(5d)** in aqueous solutions were ~19

and 37 °C, respectively, which we confirmed by variable temperature ^{1}H NMR and DLS measurements.

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Supporting Information Available: TGA and DSC scans of polymers **5a**−**d** (Figures S1 and S2) and assigned ^{13}C and ^{1}H NMR spectra of compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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