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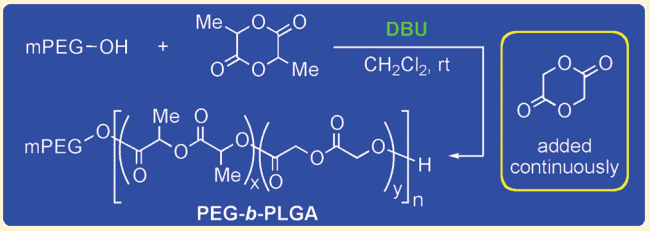
A Strategy for Control of "Random" Copolymerization of Lactide and Glycolide: Application to Synthesis of PEG-*b*-PLGA Block Polymers Having Narrow Dispersity

Haitao Qian, Adam R. Wohl, Jordan T. Crow, Christopher W. Macosko, and Thomas R. Hoye*

Departments of Chemistry and Chemical Engineering and Materials Science, University of Minnesota, Minneapolis, Minnesota 55455, United States

Supporting Information

ABSTRACT: Poly(lactic-*co*-glycolic acid) (PLGA) is a biodegradable copolymer that is also acceptable for use in a variety of biomedical applications. Typically, a random PLGA polymer is synthesized in a bulk batch polymerization using a tin-based catalyst at high temperatures. This methodology results in relatively broad polydispersity indexes (PDIs) due to transesterification, and the polymer product is often discolored. We report here the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a known, effective, and convenient organocatalyst for the ring-opening polymerization of cyclic esters, to synthesize random copolymers of lactide and glycolide. The polymerization kinetics of the homo- and copolymerizations of lactide and glycolide were explored via NMR spectroscopy. A novel strategy that employs a controlled addition of the more reactive glycolide monomer to a solution containing the lactide monomer, the poly(ethylene glycol) (PEG) macroinitiator, and DBU catalyst was developed. Using this tactic (semibatch polymerization), we synthesized a series of block copolymers that exhibited excellent correlation of the expected and observed molecular weights and possessed narrow PDIs. We also measured the thermal properties of these block copolymers and observed trends based on the composition of the block copolymer. We also explored the need for experimental rigor in several aspects of the preparations and have identified a set of convenient reaction conditions that provide polymer products that retain the aforementioned desirable characteristics. These polymerizations proceed rapidly at room temperature and without the need for tin-based catalysts to provide PEG-*b*-PLGAs suitable for use in biomedical investigations.



INTRODUCTION

Polyesters synthesized from ring-opening polymerization (ROP) of cyclic ester[1] monomers [lactones and dilactones (diolides)] have found wide application in the fields of drug delivery (microparticles, nanoparticles, or micelles),[2] tissue engineering (sutures and other biodegradable implants),[3,4] medical devices,[5] and single-use plastics[6] because of their biocompatibility and biodegradability. The most extensively studied of these polyesters are poly(lactic acid) (PLA) and poly(lactic-*co*-glycolic acid) (PLGA), the homopolymer of lactide (**1**) or random copolymer of **1** and glycolide (**2**), respectively.[7,8] Tin(II) octoate is widely used as a catalyst for the synthesis of PLA or PLGA.[9] However, tin-based catalysts are less than ideal from both chemical [e.g., broad polydispersities (PDIs)] and biological (e.g., toxicity) perspectives, especially in the synthesis of the more readily transesterified PLGAs.

The importance of PLGA microstructure has been demonstrated in a study of polyester hydrolytic degradation by Meyer and co-workers.[10] They demonstrated that microspheres made from PLGA copolymers having alternating lactic and glycolic acid units [from condensation polymerization of (*S*)-2-(2-hydroxyacetoxy)propanoic acid monomer] undergo chain scission ca. 2 times more slowly than those prepared from PLGA copolymers containing longer blocks of lactic and glycolic units. The observed difference in degradation rates was attributed to the difference in the rate of nucleophilic attack at the less sterically hindered glycolic carbonyls present in the blocks of glycolic repeat units.

Controlled homopolymerization of glycolide (**2**) is challenging because of the low solubility of both the monomer and resulting poly(glycolic acid) (PGA) homopolymer (or block copolymers) in common organic solvents. Copolymerization of glycolide (**2**) and lactide (**1**) provides an effective way to modify the chemical and physical properties of these polyesters for various applications, and PLGAs that comprise up to a 1:1 ratio of lactic to glycolic units are of practical interest.[11] Dong et al. developed a strategy for obtaining PLGA with exactly a 1:1 molar ratio of lactic to glycolic acid by polymerizing 3-methylglycolide (tin(II) octoate).[12] These polymerizations were shown to proceed with high monomer conversion and typical PDIs of 1.6−1.7. However, we are unaware of any protocols for random copolymerization of glycolide (**2**) and lactide (**1**) that produce

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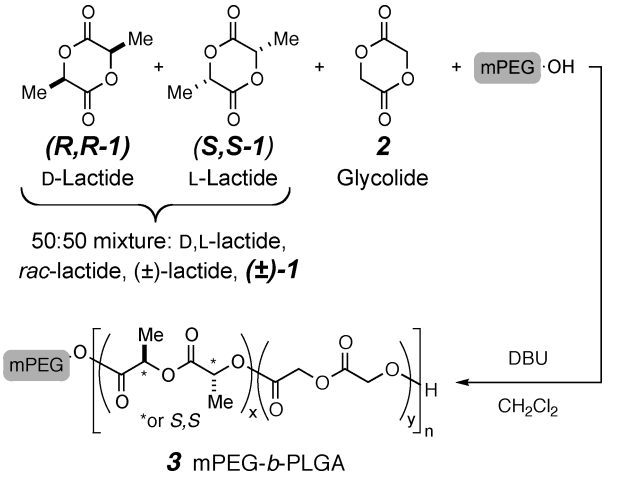
Scheme 1. Copolymerization of *rac*-Lactide [(±)-1] and Glycolide (2)



PLGAs having well-controlled molecular weights and narrow PDIs while minimizing the sequence length of the lactic and glycolic repeat units. This largely reflects differences in reactivity and solubility of these two monomers.[13] Thus, simple use of equimolar charges of glycolide (**2**) and lactide (**1**) results in polymers containing long glycolic blocks (at least in the absence of chain transfer). This adversely affects the solubility and PDI of the copolymer. Melt copolymerization of glycolide (**2**) and lactide (**1**) has often been used to prepare PLGA with high glycolic content. Under these conditions *in situ* transesterification of the polymer both randomizes the sequence and broadens the distribution of the PLGA.[11] During our attempts to synthesize PEG-*b*-PLGAs using Sn(II) catalysis, we observed PDI values greater than 1.7 and significant discoloration of the resulting PLGA copolymer. Thus, we felt there was room for improvement in the methods for preparation of well-defined PLGAs.

In addition to tin(II) octoate, other metal-containing catalysts have been studied for the ROP of lactide (**1**), glycolide (**2**), ring-strained lactones, and cyclic carbonates. These include zinc or aluminum alkoxides[11,14−17] and rare earth metal compounds.[14,17−20] Some of these catalysts also raise health safety concerns. Enzymatic ROP of lactones, lactide (**1**), and glycolide (**2**) has also been studied to address concerns about possible toxicity of heavy metal catalysts and initiators.[21]

A decade ago, the first organocatalytic ROP of lactide (**1**) was reported, using 4-(dimethylamino)pyridine (DMAP) and pyrrolidinopyridine as catalysts.[22] This was followed by the investigation of several other classes of organic small molecules as more potent catalysts for ROP of lactide (**1**) and other lactones. Among these, *N*-heterocyclic carbenes,[23] phosphines,[24] phosphazenes,[25] and amidines and guanidines[26] have been demonstrated to have unique properties that influence the synthesis of polyesters from different monomers. Many of these allow for better control of molecular weight and molecular weight distribution; some show enhanced functional group compatibility.

Here we report a strategy for the successful controlled "random" copolymerization (Scheme 1) of glycolide (**2**) and a racemic mixture of D- and L-lactide [50:50 **R,R-1** and **S,S-1**, which we will refer to as (±)-**1**] using poly(ethylene glycol) monomethyl ether (mPEG-OH) as a macroinitiator. The resulting amphiphilic mPEG-*b*-PLGA block copolymers (**3**) have well-controlled molecular weights (MWs) and MW distributions. The resulting poly(ethylene glycol) (PEG)-containing amphiphilic block copolymers (BCPs) of PLA and PLGA have practical applications in drug delivery systems.[27−29] Specifically, they can be used to formulate aqueous dispersions of hydrogels or nanoparticles. The use of well-defined PEG-*b*-PLAs and/or PEG-*b*-PLGAs to fabricate drug-containing nanoparticles may lead to more precise control of size, degradability, thermal properties (T_m and T_g), and release profiles in these applications.

EXPERIMENTAL SECTION

Materials and Methods. *rac*-Lactide [(±)-**1**] was purchased from Altasorb and was purified by recrystallization from toluene. L-Lactide (**S,S-1**) was purchased from Purac, recrystallized twice from toluene, and stored in a glovebox. Glycolide (**2**) was purchased from Altasorb and was purified by recrystallization from dry THF. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from Sigma-Aldrich, dried over calcium hydride, and distilled. mPEG-OH of molecular weight 2 and 5 kg mol^{-1} (K) was purchased from Aldrich and 10K from JenKem Technology. All polymerizations were conducted at ambient temperature.

Method A for Reagent and Catalyst Purification, Storage, and Handling (More Rigorous). Chloroform was washed with water and distilled from phosphorus pentoxide. Dichloromethane (CH_2Cl_2) was first dried by being passed through an activated alumina column and then distilled from calcium hydride (CaH_2). Tetrahydrofuran (THF) was first dried by being passed through an activated alumina column and then distilled from sodium and benzophenone. DBU was purified by distillation twice from CaH_2. Lactides and glycolide were stored and handled in a controlled atmosphere glovebox. mPEG-OHs were dried by azeotropic distillation with toluene at atmospheric pressure.

Method B for Reagent and Catalyst Purification, Storage, and Handling (Less Rigorous). CH_2Cl_2 and THF were dried by passing through an activated alumina column. DBU was purified by one distillation from CaH_2. Lactide and glycolide were stored in screw-capped containers under ambient lab atmosphere. mPEG-OHs were dried as a solution in dry dichloromethane overnight over activated molecular sieves (3 Å) in an airtight culture tube.

Polymer Characterization. ^{1}H NMR spectra were obtained on a Varian VI-300, Varian VXR-300, or Varian VXR-500 spectrometer in $CDCl_3$. Number-average molecular weight was calculated by comparison of the ratio of the integrations of the methine and methylene signals of PLA and PGA residues vs the methylene signal of PEG residues assuming the manufacturer-provided molecular weight of the mPEG-OH macroinitiator. For sequence analysis, ^{13}C NMR spectra were obtained on a Varian 400 instrument at 100 MHz in hexafluoroisopropanol; a 45° pulse and a relaxation delay of 5 s were used. Size-exclusion chromatography (SEC) was performed on an Agilent Technologies 1100 series liquid chromatograph equipped with a Hewlett-Packard 1047A refractive index detector. Chloroform was used as the mobile phase at an elution rate of 1 mL min^{-1}. The instrument was operated at 35 °C using a series of three PLgel 5 μm Mixed-C columns (Polymer Laboratories) with molecular weight range of 0.4K−400K. PDIs are reported with respect to polystyrene standards having molecular weights ranging from 5K to 1000K (Polymer Laboratories). Size-exclusion chromatography/multiangle light scattering (SEC/MALS) was performed using an Alltech 426 HPLC pump equipped with a Wyatt Technology Corporation Dawn DSP Laser photometer and an Optilab refractive index detector. Laser light scattering data were collected using a 633 nm wavelength at a 90° scattering angle. Tetrahydrofuran containing 1% tetramethylethylenediamine was used as the mobile phase at an elution rate of 1 mL min^{-1}. The instrument was operated at 25 °C using a series of three Phenomenex columns containing Phenogel 5 μm cross-linked styrene divinylbenzene with a molecular

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weight range of 5K−500K. The results were analyzed with ASTRA software. Differential scanning calorimetry (DSC) was performed using a TA Instruments model Q1000 differential scanning calorimeter that was calibrated using high-purity indium at a heating rate of 10 °C min^{-1}. Transitions were recorded during the second scan.

PEG-*b*-PLA Synthesis. *Method A.* The following reaction mixture was prepared in a controlled atmosphere (N_2) glovebox. To a solution of *rac*-lactide [(±)-**1**, 100 mg, 0.694 mmol] and mPEG-OH (5K) (100 mg, 0.02 mmol) in 1 mL of chloroform was added DBU [1 mg, 1 mol % relative to (±)-**1**] in a screw-capped glass reaction vessel (e.g., culture tube). The solution was removed from the glovebox and stirred for 1 h. The vessel was opened, hydrochloric acid (1 N) was added immediately, and the mixture was washed with water and brine. The polymer was precipitated by dropwise addition of the chloroform solution with stirring into excess isopropanol. Solvent was removed from the resulting suspension of white polymer by either filtration or decantation, and the polymer was dried under vacuum at 50 °C overnight.

Method B. The following reaction mixture was prepared under ambient atmosphere in a fume hood. A solution of mPEG-OH in dry CH_2Cl_2 (0.5 g mL^{-1}) was dried over 3 Å molecular sieves overnight. A portion of this solution (2.0 mL) was added to a solution of *rac*-lactide [(±)-**1**] in 8 mL of dry CH_2Cl_2 in an oven-dried, screw-capped glass reaction vessel. DBU was added (10 μL), and the reaction vessel was tightly capped. The resulting solution was stirred for 1 h, and benzoic acid (150 mg) was added. This solution was concentrated to ∼30% of the original volume and then added dropwise with stirring into excess isopropanol. Solvent was removed from the resulting suspension of white polymer by either filtration or decantation, and the polymer was dried under vacuum at 50 °C overnight.

PEG-*b*-PLGA (3) Synthesis. *Method A.* The following operations were performed in a controlled atmosphere (N_2) glovebox. (i) mPEG-OH (5K, 150 mg) in CH_2Cl_2 (7 mL) together with a predetermined amount of *rac*-lactide [(±)-**1**] were combined in a round-bottomed flask containing a magnetic stir bar and closed with a septum. (ii) DBU was dissolved in CH_2Cl_2 at a concentration of 11 μL mL^{-1} in a round-bottomed flask closed with a septum. (iii) Glycolide (**2**) was dissolved in THF (2 mL) and taken up in a syringe. All three solutions (i−iii) were removed from the glovebox. Solution i was vigorously stirred. *Immediately* after the addition of solution ii (1 mL), solution iii was infused into the reaction vessel via a syringe pump at the rate of 0.2 mL min^{-1}. At the end of the infusion (10 min), solid benzoic acid (50 mg) was added to arrest the polymerization. The PEG-*b*-PLGA (**3**) was purified by precipitation twice into isopropanol from CH_2Cl_2 and dried at 50 °C under vacuum overnight.

Method B. The following three solutions were prepared in ambient atmosphere in a fume hood. (i) mPEG-OH (5K, 450 mg) was dissolved in CH_2Cl_2 (22 mL) together with a predetermined amount of *rac*-lactide [(±)-**1**] in an oven-dried round-bottomed flask containing a magnetic stir bar and closed with a septum. (ii) DBU was dissolved in CH_2Cl_2 at a concentration of 16.7 μL mL^{-1} in a screw-capped vial. (iii) Glycolide (**2**) was dissolved in THF (6 mL) and taken up in a syringe. Solution i was vigorously stirred. *Immediately* after the addition of solution ii (2 mL), solution iii was infused into the reaction vessel via a syringe pump at the rate of 0.6 mL min^{-1}. At the end of the infusion (10 min), solid benzoic acid (150 mg) was added to arrest the polymerization. As above, the PEG-*b*-PLGA (**3**) was purified by precipitation twice into isopropanol from CH_2Cl_2 and dried at 50 °C under vacuum overnight.

Shorthand Designation of the Polymers That Were Synthesized. PEG_x−PL_yA is used to designate our PEG-*b*-PLA diblock copolymers, and PEG_x−PL_yG_zA is used for PEG-*b*-PLGA. PEG_x−PL_yA has a PEG block with the number-average molecular weight (M_n) of *x* kDa and a lactic acid (LA) block with the average MW of *y* kDa. Similarly, PEG_x−PL_yG_zA has a PEG block with the average MW of *x* kDa and a lactic-*co*-glycolic acid (LGA) block comprising LA and GA of *y* and *z* kDa, respectively. PEG_x−PLL_yA refers to a PEG-*b*-PLA polymer in which pure L-lactide (i.e., **S,S-1**) was used rather than (±)-**1**. Essential data for each of the polymer samples prepared in this study are presented in Table 3.

RESULTS AND DISCUSSION

DBU is an organic base of low nucleophilicity that has found wide application as a catalyst for transesterification-like reactions. Waymouth, Hedrick et al.[26] have demonstrated that DBU and other superbases, such as 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD), catalyze ring-opening polymerization of lactide and other lactones. Moreover, these polymerizations occur in solution, at ambient temperature, and with impressive effectiveness to afford polyesters that have defined structure, controlled molecular weight, and controlled molecular weight distribution. Their findings that DBU is a less active catalyst than TBD [and thus more manageable for controlling undesired transesterification (chain transfer) during polymerization] prompted us to investigate its use for the preparation of PLGA moieties. Our interest in use of poly(ethylene glycol)-containing, amphiphilic block copolymers for various drug delivery applications led us to target PEG-*b*-PLGAs. Hence, we selected mPEG-OH as the (macro)initiator in the work reported here.

Synthesis of PEG-*b*-PLA. We used the Waymouth/Hedrick methodology[26] first to prepare a series of PEG-*b*-PLA block copolymers using only lactide as the monomer. Thus, *rac*-lactide [(±)-**1**] was polymerized using mPEG-OH (MW = 2K or 5K) as the macroinitiator to afford PEG-*b*-PLA. When 1 mol % of DBU and monomer concentrations of ca. 0.5−2 M were used for polymerization at room temperature, >95% monomer conversions were observed in less than 1 h. We prepared a series of mPEG-*b*-PLA diblock copolymers of different molecular weight ratios. Each had a small PDI (cf. entries 1−6, Table 3) and was monomodal. This is in accordance with the fact that DBU does not cause extensive transesterification of PLA on the time scale of lactide ROP.[26] We observed (^{1}H NMR spectroscopy) a preference for production of isotactic arrays in these DBU-catalyzed ROPs of *rac*-lactide [(±)-**1**]. Interestingly, this contrasts with the known syndiotactic preference when tin(II) octoate is used as the polymerization catalyst[30] but is in agreement with the slight isotactic preference noted in TBD-catalyzed ROPs.[26] For a detailed discussion of the ^{1}H NMR analysis, see Figure S1 and related discussion in the Supporting Information.

Determining Glycolide to Lactide Reactivity Ratio during DBU-Catalyzed Polymerization. The organo-catalyzed copolymerization of glycolide (**2**) with lactide (**1**) is challenging. The low solubility in common organic solvents of both the monomeric glycolide and, especially, growing polymers that have a high glycolyl content can make the experiment problematic. Additionally, glycolide is, of course, much more reactive than lactide.[11,13] Thus, batch copolymerizations that have equimolar ratios of the glycolide and lactide monomers result in the synthesis of long blocks of polyglycolide, further reducing polymer solubility during copolymerization (as previously observed for cationic polymerizations[31]). Consequently, we are unaware of reports that describe either homopolymerization or copolymerization of glycolide by organocatalysis. We were interested in determining the relative reactivity of glycolide and lactide in order to design an essentially "random" copolymerization protocol.

Initial attempts to quantify the reactivity ratios of glycolide (**1**) and lactide (**2**) by subjecting a 1:1 mixture of the two monomers

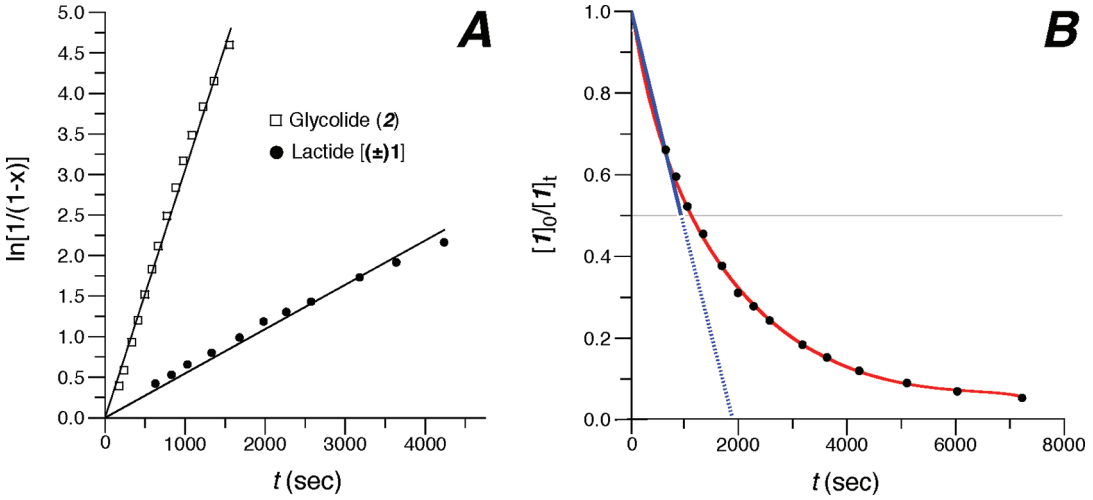

Figure 1. Lactide and glycolide homopolymerizations in $CDCl_3$ solvent at ambient temperature (reaction progress measured by ^1H NMR spectroscopic analysis) under the following conditions (cf. Table 1). For lactide [(±)-**1**]: {[$mPEG_{2K}$] = 5.0 mM; [(±)-**1**]$_0$:[$mPEG_{2K}$]:[DBU] = 264:1:1.32}; for glycolide (**2**): {[$mPEG_{2K}$] = 5.1 mM, [**2**]$_0$:[$mPEG_{2K}$]:[DBU] = 2.94:1:0.0066. (A) Plot of ln[1/(1 − *x*)] vs time (*x* = monomer conversion). (B) Experimentally observed (red) exponential decay of monomer concentration for lactide polymerization. The blue line denotes the approximate linear conversion during the first half-life of lactide consumption, which we then used to guide the choice of the (constant) rate of glycolide addition during subsequent syntheses of the PEG-*b*-PLGA copolymers.

to mPEG-initiated, DBU-catalyzed polymerization followed by NMR analysis were only marginally successful. Instead of observing copolymerization of both monomers, we noted the rapid consumption of the glycolide monomer via ROP, while nearly all of the lactide remained intact. Thus, we were unable to directly measure the copolymerization reactivity ratio, but it was clear that the glycolide had polymerized significantly faster than the lactide.

We then explored the relative reactivity of glycolide and lactide via parallel, independent homopolymerization experiments. Thus, analogous kinetic experiments utilizing lactide [(±)-**1**] vs glycolide (**2**) were conducted, leading eventually to the following sets of conditions from which comparative reactivities could be assessed. For lactide, [mPEG2K] = 5.0 mM and a ratio of [(±)-**1**]:[mPEG2K]:[DBU] = 264:1:1.32 were used. For the more reactive glycolide, much lower catalyst and initial monomer concentrations were used—namely, [mPEG2k] = 5.1 mM and the ratio of [**2**]:[mPEG2K]:[DBU] was 2.94:1:0.0066. In the case of glycolide (**2**), only polymers having short PGA blocks could be prepared because of solubility limitations of the oligomeric product. Waymouth and Hedrick have demonstrated that similar amidine-catalyzed ROPs (of valerolactone) show a first-order dependency on the monomer, alcohol initiator, and amine catalyst conentrations.[26] We assumed that this would also be the case for lactide or glycolide polymerizations, which is reflected in the rate expression shown in eq 1. The concentration of propagating hydroxyl groups equals the concentration of alcohol initiator used and remains constant throughout the polymerization as does, of course, the concentration of DBU catalyst. Thus, we hypothesized the reaction to be pseudo-first-order in monomer, since the apparent rate constant (k_{app}, eq 2) remains unchanged under a given set of conditions. This was then supported by observing linearity in the plots of ln[1/(1 − *x*)] vs time (*x* = monomer conversion) for both glycolide and lactide as shown in Figure 1A.

$$\frac{d[\text{monomer}]}{dt} = -k[\text{DBU}][\text{propagating-OH}][\text{monomer}] \quad (1)$$

Table 1. Rate Constants for Glycolide and Lactide Polymerization

monomer	[$mPEG_{2K}$] (mM)	[DBU] (mM)	k_{app}[a] (s^{-1})	k[b] (10^5 (L/mol)^2 s^{-1})
lactide [(±)-**1**, 1.3 M]	5.0	6.6	550	1.7
glycolide (**2**, 15 mM)	5.1	0.033	3100	1800

[a] Apparent rate constant of pseudo-first-order ROP (cf. eq 2). [b] Third-order rate constant (cf. eq 1).

$$k_{app} = k[\text{DBU}][\text{propagating-OH}] \quad (2)$$

The apparent first-order rate constant (k_{app}, cf. eq 2) for each of these two pseudo-first-order polymerizations is given in Table 1 (column 4). The third order rate constant (k) for each, calculated according to eq 1, is given in column 5. The ratio of this latter pair of rate constants is ca. 10^3, favoring the more reactive glycolide monomer. This is larger than the reported relative reactivity of glycolide to lactide using tin(II) octoate at 200 °C, where the k_{rel} for these two monomers is 14:1.[32]

The large difference in ROP reactivity of the two monomers reflects collective differences in steric hindrance of both the electrophilic monomer and the nucleophilic hydroxyl group of the propagating polymer chain in this pair of homopolymerizations.[32] Knowledge of this reactivity difference guided our design of the following copolymerization experiments in which, of course, both monomers were simultaneously exposed to identical concentrations of catalyst and propagating hydroxyl groups. Thus, alteration of the relative amounts of each monomer was the obvious exploitable experimental variable.

PEG-*b*-PLGA Synthesis. One strategy for copolymerization of monomers with different propagation rate constants is to add the fast-reacting monomer continuously during the polymerization. In this manner, the inherent reactivity imbalance is compensated by the fact that at any instant the slow-reacting monomer is in excess. We adopted this "semi-batch polymerization"[33] strategy to target copolymers of lactide (**1**) and glycolide (**2**) having

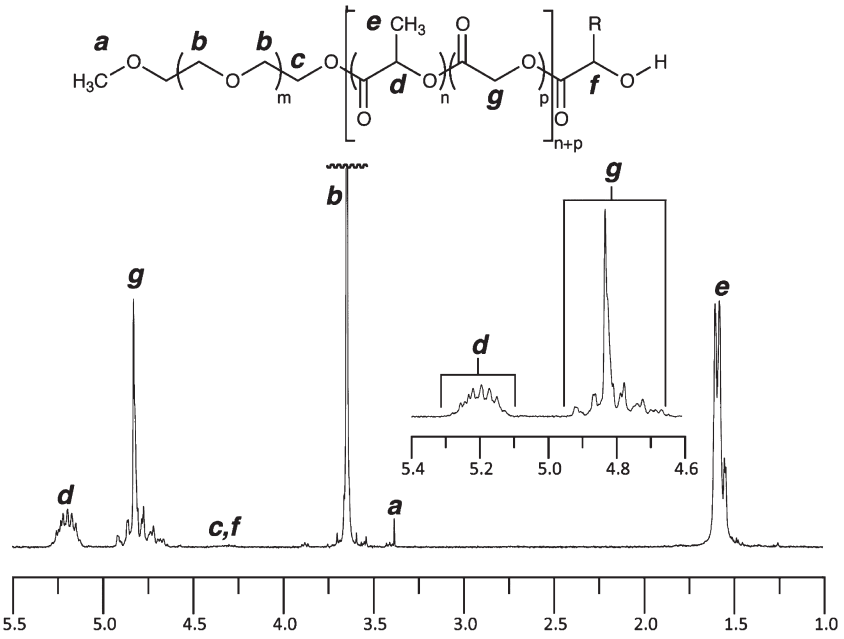

Figure 2. ^{1}H NMR spectrum of the block copolymer $PEG_5-PL_5G_5A$ obtained in $CDCl_3$.

Table 2. Comparison of Polymers Made by DBU-Catalyzed ROP Using Methods A vs B

polymer (targeted)	method	$M_{n(PEG)}$	$M_{n(PLGA)}$[a]	ratio[a,b] LA:GA	PDI[c]
PEG_2-PL_2A	A	2K	2.16K	100:0	1.08
PEG_2-PL_2A	B	2K	2.03K	100:0	1.15
PEG_5-PL_5A	A	5K	5.62K	100:0	1.06
PEG_5-PL_5A	B	5K	5.09K	100:0	1.06
PEG_5-$PL_{10}A$	A	5K	10.8K	100:0	1.05
PEG_5-$PL_{10}A$[d]	B	5K	10.1K−10.2K	100:0	1.08−1.09
PEG_5-$PL_{2.5}G_{2.5}A$	A	5K	4.90K	46:54	1.06
PEG_5-$PL_{2.5}G_{2.5}A$	B	5K	4.79K	50:50	1.05
PEG_5-PL_5G_5A	A	5K	10.4K	54:46	1.08
PEG_5-PL_5G_5A[d]	B	5K	10.2K−10.3K	52−54:46−48	1.09−1.17

[a] Results based on NMR spectroscopy.[34] [b] Mass ratio of the repeat units. [c] Results based on GPC measurements against a polystyrene standard. [d] Run in triplicate, giving the indicated ranges of values.

approximately equal composition by mass. We initiated polymerization of lactide with mPEG-OH, immediately (<1 s) began addition of glycolide at a constant rate, set the glycolide addition to finish at the time required to reach ca. 50% conversion of the lactide, and quenched the reaction (by addition of excess benzoic acid[26]) immediately upon completion of glycolide addition. A control experiment demonstrated that pretreatment of mPEG-OH/lactide with excess benzoic acid followed by addition of DBU did not result in polymerization. Because it was convenient to add glycolide at a constant rate, we approximated lactide consumption as if it were linear during its first half-life (see blue line in Figure 1B). In a typical run a solution containing [mPEG-OH] = 4 mM and $[(\pm)\text{-}\mathbf{1}]_0$ = 0.3 M in anhydrous CH_2Cl_2 was charged to the reaction vessel. The DBU catalyst (1 mol % based on the amount of mPEG-OH) was injected to this rapidly stirred solution. Addition via syringe pump of a solution of glycolide (**2**, 0.5 equiv vs the initial charge of lactide) was immediately (<1 s) begun. We judged the $t_{1/2}$ for lactide consumption to be ca. 10 min under these conditions, which we therefore set as the glycolide addition time. The polymerization progress was immediately then arrested, and the excess unreacted lactide was removed by precipitation.

The purified PEG-*b*-PLGA polymers were characterized by GPC and NMR analyses. The ^{1}H NMR spectrum of a typical product is shown in Figure 2. The small resonances for the carbinol protons *f* and for the methylene protons *c* at the linkage point between the PEG and PLGA blocks indicate that, again, the polymerization occurred with good functional fidelity. It can be inferred from this spectrum (i.e, from the integration ratio or resonances *g* to *d*) that we were able to achieve the targeted 50:50 mass ratio of glycolate to lactate reasonably well (cf. Tables 2 and 3). Finally, we judged from analysis of ^{13}C NMR data that the glycolide and lactide monomers were incorporated into the PLGA blocks with nearly random monomer distributions (see sequence length discussion, below).

Alternative PEG-*b*-PLGA Synthesis. We then explored whether less rigorous polymerization conditions, those described as method B in the Experimental Section, would allow us to

Table 3. Data for All Block Copolymers Synthesized in This Study[a]

entry	polymer (targeted)	method	$M_{n(PEG)}$	$M_{n(PLGA)}$[b]	ratio[c] LA:GA	PDI[d]	T_g[e] (°C)	T_m[e] (°C)
1	*PEG_2-PL_2A*	*A*	*2K*	*2.16K*	*100:0*	*1.08*	ND	39.3
2	PEG_2-PL_5A	A	2K	5.11K	100:0	1.07	1.6	ND
3	PEG_5-PL_2A	A	5K	2.10K	100:0	1.04	ND	54.1
4	*PEG_5-PL_5A*	*A*	*5K*	*5.62K*	*100:0*	*1.06*	ND	51.0
5	*$PEG_5-PL_{10}A$*	*A*	*5K*	*10.8K*	*100:0*	*1.05*	1.8	ND
6	$PEG_5-PL_{15}A$	A	5K	16.3K	100:0	1.07	16.1	ND
7	*$PEG_5-PL_{2.5}G_{2.5}A$*	*A*	*5K*	*4.90K*	*46:54*	*1.06*	−24.2	50.1
8	*$PEG_5-PL_5G_5A$*	*A*	*5K*	*10.4K*	*54:46*	*1.08*	−4.8	ND
9	$PEG_5-PL_{7.5}G_{7.5}A$	A	5K	16.1K	58:42	1.13	7.5	ND
10	$PEG_5-PL_{7.5}G_{7.5}A$	B[f]	5K	13.5K	47:53	1.15[g]	−2.8	ND
11	$PEG_5-PL_5G_5A$	A	5K	9.43K	56:44	1.10	−6.1	ND
12	$PEG_5-PL_{7.5}G_{2.5}A$	A	5K	8.44K	76:24	1.08	−12.9	ND
13	$PEG_5-PL_{15}G_5A$	B	5K	18.5K	77:23	1.65[h]	−0.8	ND
14	$PEG_{10}-PL_{2.5}G_{2.5}A$	B	10K	4.64K	53:47	1.04	ND	57.0
15	$PEG_{10}-PL_5G_5A$	B	10K	10.9K	54:46	1.04	−19.2	55.1
16	$PEG_{10}-PL_{7.5}G_{7.5}A$	B[i]	10K	15.7K	51:49	1.22[g]	−18.6	55.3
17	$PEG_{10}-PL_{10}G_{10}A$	B[f]	10K	16K	50:50	2.29[h]		
18	$PEG_{10}-PL_{3.75}G_{1.25}A$	B[f,j]	10K	4.30K	72:28	1.05	ND	56.5
19	$PEG_{10}-PL_{7.5}G_{2.5}A$	B[f,j]	10K	10.3K	78:22	1.05	ND	51.5
20	$PEG_{10}-PL_{11.75}G_{3.75}A$	B[f,j]	10K	12.0K	71:29	1.07	−23.3	50.1
21	$PEG_{10}-PL_{15}G_5A$[g]	B[f,j]	10K	20.3K	77:23	1.39	−3.5	ND

[a] Italicized information is reproduced from Table 2 and included here for comparison within sets having the same PEG block size and same polyester composition. [b] Results based on NMR spectroscopy. [c] Results based on NMR spectroscopy and presented as the mass ratio of the repeat units. [d] Results based on GPC measurements against a polystyrene standard. [e] Results obtained by DSC measurements (ND = none detected). [f] Reaction performed at 8-fold lower concentration than method B. [g] Minor asymmetric broadening noted in the GPC trace. [h] Asymmetric broadening noted in the GPC trace. [i] Reaction performed at 2-fold lower concentration than method B. [j] The amounts of glycolide and lactide used were 0.5 and 1.5 times those used in method B, in order to target a final 1:3 mass ratio within the PLGA block.

obtain polymers of comparable quality and with similar levels of control, thereby reducing the time and effort necessary to complete a polymerization experiment vis-à-vis the more careful protocols of method A. We compared the preparation of five polymers using both methods A and B. The results are given in Table 2 and demonstrate that in all cases both methods yielded polymers having molecular weights and monomer ratios similarly close to the targets. Note that in several instances we judged that the copolymers made by method B had slightly higher PDI values. Two of the polymerizations were carried out in triplicate, and the results were quite consistent among runs. Therefore, use of the less stringent method B conditions did not adversely affect the process or product.

Quenching the copolymerization at ca. 50% lactide conversion effectively establishes the proof of principle of the described semibatch methodology. From a practical perspective, it likely would be advantageous to convert the lactide to a higher degree of polymerization. We demonstrated proof of principle by polymerizing the lactide through three half-lives. To maintain the near "random" lactyl to glycolyl distribution in the product, a total of 87.5 mol % of glycolide relative to lactide was added, and the rate of its infusion was halved after each of the first and second half-times (i.e., after 10 and 20 min with a total addition time of 30 min). In the experiment we targeted a $PEG_5-PL_{4.38}G_{4.38}A$ polymer. A small aliquot was removed from the polymerization mixture after 10 and 20 min. They contained polymers with compositions that were measured to be $PEG_5-PL_{3.1}G_{2.5}A$ and $PEG_5-PL_{3.8}G_{3.4}A$ vs the theoretical $PEG_5-PL_{2.5}G_{2.5}A$ and $PEG_5-PL_{3.75}G_{3.75}A$, respectively (^{1}H NMR). The final sample of bulk polymer had a composition of $PEG_5-PL_{4.4}G_{4.3}A$ and a PDI of 1.19. While unoptimized, this experiment establishes the ability to achieve higher levels of lactide conversion while maintaining narrow polydispersities.

High MW PEG-*b*-PLGA Synthesis. Because polyesters with high glycolate content are notorious for their limited solubility,[35] we viewed it important to establish some of the limits of both the PEG and PLGA block sizes as well as the PLGA compositions that could be prepared using this new methodology. The results of these experiments are reported in entries 14−21 of Table 3. It can be seen from entries 7−10 that we were able to consistently and reproducibly generate PEG-*b*-PLGAs having PLGA blocks of MW up to 10K. However, attempts to synthesize a 5K−15K PEG-*b*-PLGA ($PEG_5-PL_{7.5}G_{7.5}A$, entry 9) revealed a limitation. In this case, the reaction mixture became heterogeneous prior to conclusion of the polymerization and resulted in abnormally high lactic acid content. Presumably the inhomogeneity is the result of the growing glycolic acid content (total mass % of the block copolymer), which ultimately caused the polymer to become insoluble. Characterization of this sample showed that it possessed a PLGA block having a molecular weight lower than that targeted and an atypically broad PDI.

We then turned to a different strategy—the use of lower reaction concentration to improve product solubility as the PLGA blocks grew larger. Thus, performing the reaction 8-fold more dilute than in method B allowed the synthesis of the 5K−15K PEG-*b*-PLGA ($PEG_5-PL_{7.5}G_{7.5}A$, entry 10). However, that modification alone still fell short when we attempted to prepare the yet larger 5K−20K analogue (i.e., $PEG_5-PL_{10}G_{10}A$);

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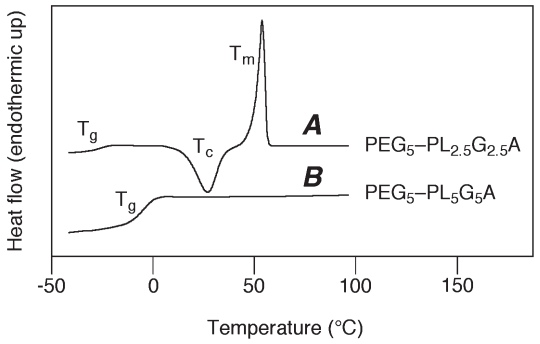

Figure 3. Representative DSC plots showing typical melting (A) and glass transition (B) behavior.

again heterogeneity prior to the end of the polymerization time was observed. Increasing solubility by use of a longer 10K PEG macroinitiator led to no substantial improvement (entry 17). However, we were finally able to prepare the 5K−20K PEG-*b*-PLGA PEG_{10}-$PL_{15}G_5A$ (entry 21, albeit with an atypically large PDI) by increasing the lactic acid content of the PLGA block to 75 wt %. From these experiments, we conclude that if one desires polymers having PLGA blocks with narrow PDIs, the scope of the reported methodology is limited to the synthesis of PEG-*b*-PLGAs having PLGA block sizes of less than ca. 20K.

Thermal Properties. The melting and glass transition properties (T_m and T_g) of the PEG-*b*-PLA and PEG-*b*-PLGA block copolymers were measured by DSC, and the results for each block copolymer are presented in Table 3. High molecular weight PEG homopolymer is highly crystalline ($T_m \sim 63$ °C). Consistent with this fact and as the data in Table 3 clearly show, every block copolymer sample containing a PEG block of greater than 40 wt % showed a melting exotherm at ca. 50 °C. This observation indicates that the polyether and polyester blocks in these samples are phase-separated (likely into lamellar phases) so that the PEG is able to crystallize.[36] One example (entry 7 in Table 3) is shown in Figure 3A.

The diblock copolymers with PEG blocks of less than 40 wt % show a single T_g but no evidence of a melting exotherm (e.g., Figure 3B, entry 8 in Table 3), suggesting that the polyether and polyester blocks are phase mixed. The T_g of PEG, PGA, and PLA homopolymers are approximately −40, 35, and 55 °C, respectively.[32,37] The T_g values of the diblock copolymers with PEG fraction <0.4 follow a general trend that can be rationalized by the Fox equation; that is, the T_gs of these copolymers are correlated with the weighted average of the T_gs for each of the PEG, lactyl, and glycolyl components. This is also consistent with the interpretation that a PEG-*b*-PLGA copolymer with <40 wt % PEG is a single phase at room temperature.

A few additional general trends can be seen in the T_m and T_g data in Table 3: (i) increased MW of the polyether block tends to result in lower T_g values; (ii) increased MW of the polyester block tends to result in higher T_g values; and (iii) increased lactic (relative to glycolic) acid content in the polyester block tends to result in higher T_g values. These observations offer guidance for the design of PEG-*b*-PLGAs having compositions leading to specific thermal properties.

Sequence Length of Monomer Units in the PLGAs. Because the chemical shifts of the ester carbonyl carbons are sensitive to subtle electronic differences, ^{13}C NMR spectroscopy can be used

Table 4. Average Sequence Length of Lactide ($\overline{L_L}$) and Glycolide ($\overline{L_G}$) As Measured by ^{13}C vs ^{1}H NMR Spectroscopies

entry	polymer (targeted)	$\overline{L_L}^a$	$\overline{L_G}^a$	$\overline{L_L}/\overline{L_G}^a$	LA/GA[b]
1	$PEG_5-PL_{2.5}G_{2.5}A$	3.68	5.31	40.9/59.1	40.3/59.7
2	$PEG_5-PL_5G_5A$	4.57	4.31	51.5/48.5	48.8/51.2
3	$PEG_5-PL_{7.5}G_{2.5}A$	7.73	3.00	72.0/28.0	71.7/28.3
4	$PEG_5-PL_5G_5A$	4.90	4.57	51.7/48.3	50.7/49.3
5	$PEG_5-PL_{7.5}G_{7.5}A$	4.90	4.54	51.9/48.1	52.2/47.8

[a] Sequence lengths and their ratio calculated from ^{13}C NMR results according to eqs 3 and 4. [b] Molar ratio of lactic to glycolic units calculated from integration of ^{1}H NMR data.

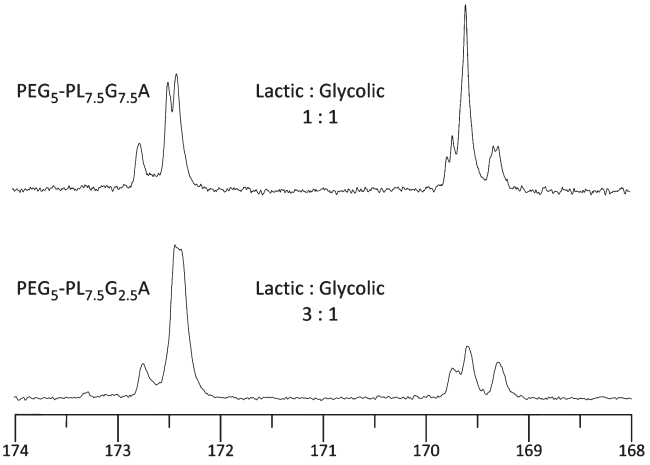

Figure 4. ^{13}C NMR spectra (in hexafluoroisopropanol[31,38]) of two PEG-*b*-PLGA block copolymers of different compositions.

to ascertain the average number of adjacent lactic (or glycolic) dyads in a PLGA backbone.[31,38] The NMR spectral data for several PLGA samples (Table 4) were used to calculate sequence lengths of both LA and GA repeating units using eqs 3 and 4.[13,39]

$$\overline{L_L} = 2\frac{I_{LL}}{I_{LG}} + 2 \quad (3)$$

$$\overline{L_G} = 2\frac{I_{GG}}{I_{GL}} + 2 \quad (4)$$

Representative data for two of these, having a 50:50 vs a 75:25 LA:GA composition, are shown in Figure 4. $\overline{L_L}$ and $\overline{L_G}$ are the average sequence lengths of both the lactyl and glycolyl repeat units, respectively; I_{LL}, I_{LG}, I_{GG}, and I_{GL} are the signal intensities of the lactyl−lactyl, lactyl−glycolyl, glycolyl−glycolyl, and glycolyl−lactyl structures (I_{LG}should be equivalent to I_{GL} if the carbonyl resonances are equally sensitive). Good agreement was observed by comparing the ratio of lactide to glycolide sequence lengths deduced from this ^{13}C NMR analysis ($\overline{L_L}/\overline{L_G}$) to that observed by integration of the methine vs methylene resonances of the backbone protons for lactic to glycolic units, which lends confidence to the reliability of the ^{13}C NMR method.

The expectation value for each of the sequence lengths of both lactic and glycolic dyads for a truly random copolymerization of lactide and glycolide is 4.00 (recall that each propagation event delivers two of the same acid backbone units since each monomer is dimeric).[40] In the case of $PEG_5-PL_5G_5A$ (Table 4, entry 2)

the average sequence of the lactyl unit, $\overline{L_L}$, is 4.57 and of $\overline{L_G}$ is 4.31. These differences from the theoretical value likely arise from some combination of the use of constant rather than a diminishing rate of addition of glycolide, error in the measured rate constant ratio, imperfect mixing, and inherent difference in cross-reactivity ratios that attend each of four possible propagation partners. When the glycolide feed rate was decreased to obtain the $PEG_5-PL_{7.5}G_{2.5}A$ polymer, $\overline{L_G}$ was observed to decrease to 3.00 while $\overline{L_L}$ increased to 7.73 (Table 4, entry 3).

CONCLUSIONS

The high activity of DBU makes it a convenient catalyst for the synthesis of PEG-*b*-PLA block copolymers having well-controlled sizes and narrow distribution. To expand this chemistry to the synthesis of PEG-*b*-PLGAs, with a "random" PLGA copolymer block, we determined the reactivity ratio to be approximately 1000:1 for glycolide (**2**) to lactide (**1**) in homopolymerizations. We developed a new, semibatch PEG-*b*-PLGA synthesis strategy in which the continuous addition of glycolide approximated the conversion curve of lactide throughout its first half-life. This resulted in a convenient method for the preparation of PEG-*b*-PLGAs of various block sizes and monomer ratios. As a consequence of the controlled copolymerization of lactide and glycolide, MW, composition, sequence length, and distribution (and therefore physical properties) of PEG-*b*-PLGA block copolymers could be easily manipulated for different applications. We determined that the limitation of this method was the synthesis of PLGA blocks with MW greater than 20K, likely due to crystallization and subsequent precipitation before completion of the polymerization. This strategy was found to give reproducible results, allowing the convenient preparation of PEG-*b*-PLGA block copolymers that could be useful in a variety of applications. The general principles explored here should be applicable to the copolymerization of glycolide and lactide with other less reactive lactones for the preparation of various copolymers.

ASSOCIATED CONTENT

Supporting Information. Discussion of the ^1H NMR analysis of stereoregularity of the PEG-*b*-PLA polymers and the results of SEC/MALS experiments to assess absolute molecular weight. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: hoye@umn.edu.

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