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Preparation and Characterization of Substituted Polylactides

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ABSTRACT: We report the bulk polymerization of ethylglycolide (3,6-diethyl-1,4-dioxane-2,5-dione), isobutylglycolide (3,6-diisobutyl-1,4-dioxane-2,5-dione), and hexylglycolide (3,6-dihexyl-1,4-dioxane-2,5-dione) to high molecular weight polymers. The glycolides were prepared by two routes: the reaction of 2-bromoacyl bromides and α-hydroxy acids and the acid-catalyzed oligomerization of 2-hydroxy acids followed by thermal depolymerization of the oligomers in the presence of ZnO. Both methods gave the substituted glycolides as a mixture of diastereomers. The monomers were melt-polymerized using Sn(2-ethylhexanoate)$_2$, SnO, $SnBr_2$, $SnBr_4$, PbO, and Ph_4Sn with alcohol initiators. The polymerization rates depend on the steric bulk of the monomer, and the kinetic data for polymerizations using Sn(2-ethylhexanoate)$_2$ can be fit to an equilibrium model. High molecular weight poly(ethylglycolide), poly(isobutylglycolide), and poly(hexylglycolide) have T_g's of 12, 22, and −37 °C, respectively. These polymers are amorphous and decompose to monomer above 300 °C.

Introduction

Because of their biocompatibility and environmental degradability, polymers derived from lactic acid have long been important materials for medical applications.[1] Once used primarily as sutures and implants, poly(lactide) materials are now entering high volume areas such as packaging.[2,3] To be successful in these new applications, polylactides must be available that exhibit a broad spectrum of physical properties while retaining the degradability of the parent polymer. Typical approaches used to alter the physical properties of polylactides include copolymerization,[4−9] the preparation of block copolymers,[10−17] and the manipulation of the stereochemistry[18−21] of lactic acid precursors. In contrast, there have been few reports that describe the use of lactic acid derivatives as monomers or comonomers for the preparation of polylactides. In principle, many substituted lactic acid monomers could be prepared that, when polymerized, would yield polymers that exhibit a wider range of properties than is currently available from polylactides.

Derivatives of lactic acid offer many advantages as monomers. They are structural homologues of lactic acid, and thus much of the chemistry developed for the preparation of polylactides should be applicable to substituted lactides. Various substituted α-hydroxy acids are known byproducts of kraft pulping operations,[22] and it may be possible to isolate them from waste streams, or by analogy to the preparation of lactic acid, it may be possible to develop fermentation processes that yield a range of substituted lactic acid monomers. Because the structure of the polymer backbone is unchanged, the hydrolysis chemistry that is important for polylactide degradation should be retained in substituted polylactides. Although the toxicity of most substituted lactic acids is unknown, polymers derived from substituted lactic acids may, by analogy to polylactides, be biocompatible and degrade to benign products.

Our interest in polylactides lies in exploring their structure−property relationships. In particular, we have initiated a research effort to design poly(lactide)s with physical properties that mimic many of the high volume commercial polymers. Our approach is to manipulate the substitution pattern at the α-carbon of lactic acid and, through polymerization and copolymerization, access a family of degradable polymers whose physical characteristics are governed by the nature of group at the α-carbon. As an example of this approach, we describe in this paper the polymerization and characterization of alkyl-substituted polylactides, some of the simplest structural derivatives of polylactide. Because the IUPAC names of these monomers (Scheme 1) are somewhat cumbersome, we use the glycolide ring as the base structure and refer to them as ethylglycolide, isobutylglycolide, and hexylglycolide.

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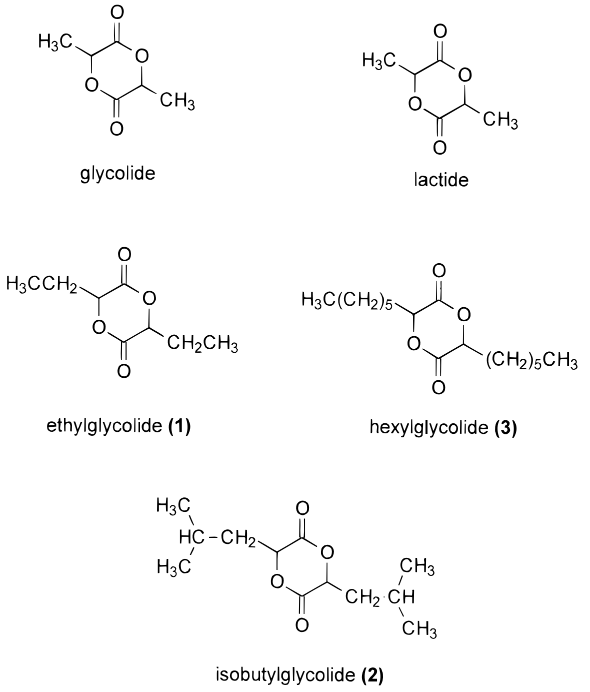
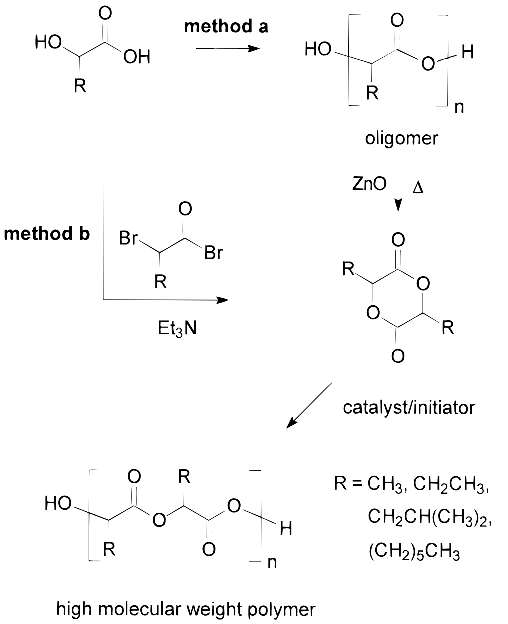
Scheme 1



Scheme 2



Experimental Section

Unless otherwise specified, ACS reagent grade starting materials and solvents were used as received from commercial suppliers without further purification. Proton nuclear resonance (^{1}H NMR) analyses were carried out at room temperature in deuterated chloroform ($CDCl_3$) on a Varian Gemini-300 spectrometer with the solvent proton signals being used as chemical shift standards. Mass spectral analyses were carried out on a VG Trio-1 Benchtop GC-MS.

Monomer Synthesis. General Procedure for Method a. A mixture of 10 g of the appropriate α-hydroxy acid and 0.2 g of *p*-toluenesulfonic acid in 700 mL of toluene was heated at reflux for 4 days, with the water removed azeotropically using a Barrett trap. The toluene solution was then cooled, washed with saturated $NaHCO_3$, and dried over $MgSO_4$. After removing the toluene, about 0.1 g of ZnO was added, and the residue was distilled under reduced pressure using a Kugelrohr distillation apparatus.

3,6-Diethyl-1,4-dioxane-2,5-dione (1). Ethylglycolide was collected at 180 °C (100 mTorr) and was dissolved in the minimum amount of ether needed to dissolve the product. The solution was cooled to −30 °C, and petroleum ether was added dropwise until the solution turned cloudy. The colorless crystals were collected by cold filtration and dried under vacuum to give 5.2 g (63%) of ethylglycolide as a colorless oil. ^{1}H NMR indicates that the product is a 1:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (dd), 4.83 (dd, 1H total for the signals at 4.88 and 4.83), 2.08 (m, 2H), 1.15 (tt, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.62, 166.58, 76.4, 75.6. mp 19.5−20.5 °C (lit.[23] 21−22 °C). MS (EI) m/z = 285.4 (M + 1).

Preparation via α-Bromoacyl Bromides, Method b. Under a nitrogen atmosphere, 0.90 g (8.7 mmol) of 2-hydroxybutyric acid and 2.1 g (8.7 mmol) of 2-bromobutyryl bromide were heated at 80 °C until HBr evolution ceased (0.5−2 h). The solution was cooled, and 100 mL of dry acetone was added followed by the dropwise addition of 2.2 mL (17 mmol) of triethylamine. The solution was heated to reflux for 3 h and then cooled to room temperature. After removing the acetone under reduced pressure, the residue was washed with saturated $NaHCO_3$ and extracted with ether, and the ether layer was dried over $MgSO_4$. After removing the ether, the dimer was purified by recrystallization as described above to give 0.62 g (41%) of ethylglycolide as a colorless oil. The product is approximately a 4:1 mixture of the R,R/S,S and R,S diastereomers.

3,6-Diisobutyl-1,4-dioxane-2,5-dione (2). Isobutylglycolide was collected at 120 °C (50 mTorr) and was recrystallized from ether. The white crystals were collected by filtration and dried under vacuum to give 6.1 g (71%) of isobutylglycolide as a white solid. ^{1}H NMR indicates that the product is approximately a 1:1 mixture of the R,R/S,S and R,S diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 (dd), 4.89 (dd), (1H total for the signals at 4.91 and 4.89), 1.8−2.0 (m, 3H), 0.95 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.28, 166.20, 74.88, 74.09, 40.37, 38.82, 24.07, 23.84, 23.02, 22.84, 21.29. 21.25. MS (m/q) 229.4 (M + 1); mp 167−167.5 °C (lit.[24] 169−170 °C).

3,6-Dihexyl-1,4-dioxane-2,5-dione (3). Hexylglycolide was collected at 145 °C (50 mTorr) and was recrystallized from ether. The white crystals were collected by filtration and dried under vacuum to give 5.8 g (65%) of hexylglycolide as a white solid. ^{1}H NMR indicates that the product is approximately a 1:1 mixture of the R,R/S,S and R,S diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (dd), 4.83 (dd), (1H total for the signals at 4.88 and 4.83), 2.01 (m, 2H), 1.4−1.6 (br m, 2H), 1.2−1.4 (br m, 6H), 0.85 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.95, 165.85, 76.42, 75.65, 31.99, 31.46, 31.41, 30.15, 28.74, 28.56. MS (m/z) 285.4 (M + 1), mp 78−80 °C.

Bulk Polymerization of Substituted Glycolides. Solvent-free polymerizations were carried out in sealed tubes prepared from $^3/_8$ in. diameter glass tubing. A representative polymerization is described below. In an oxygen- and moisture-free drybox, a solution of catalyst in toluene ($\approx$0.01 M) and 0.1 g of monomer were added to the tube. The amount of catalyst solution added was determined by the desired monomer/catalyst ratio. For runs using catalysts that are insoluble in toluene (SnO, $SnBr_2$, $SnBr_4$, and PbO) the catalyst was added directly to the tube, and the walls of the tube were washed with solvent to ensure that all of the catalyst was added to the monomer. The solvent was removed in vacuo, and the tube was sealed and immersed in an oil bath at 130 °C. At the end of the polymerization, the tube was cooled and opened, and the polymer was dissolved in THF. A portion of the sample was evacuated to dryness and analyzed by NMR for conversion. After removal of the solvent, the polymer was dissolved in toluene and precipitated into methanol to remove residual catalyst. Typical polymer yields were >85%. For kinetic runs, multiple tubes were prepared, and individual tubes were removed from the heating bath at predetermined intervals and were cooled in ice and opened, and the contents were dissolved in THF. A portion of the sample was analyzed by GPC for molecular weight, and the remainder was evacuated to dryness

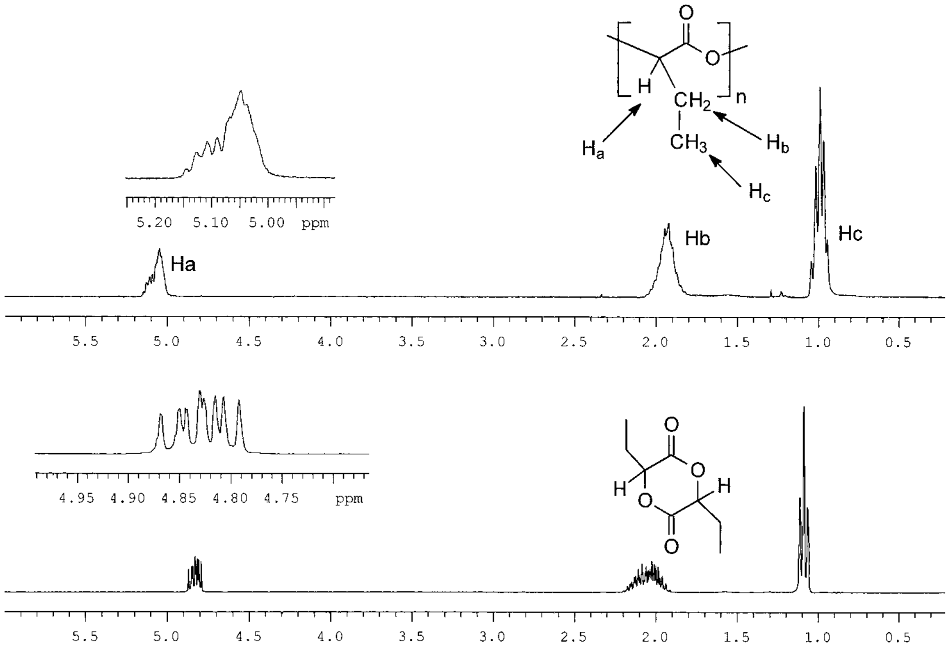


Figure 1. ^{1}H NMR spectra for ethylglycolide and poly(ethylglycolide).

and analyzed by NMR for conversion. Polymerizations that used alcohols as initiators were set up as described above, except that the appropriate amount of alcohol was added to the toluene solution of initiator just prior to adding the catalyst solution to the tube. For insoluble catalysts, tubes were first loaded with monomer and catalyst, and the alcohol initiator was directly added to the tube as a toluene solution.

Polymer Characterization. The molecular weights of polymers were determined by gel permeation chromatography (GPC) using a PLgel 20m Mixed A column and a Waters R401 differential refractometer detector at room temperature. THF was used as the eluting solvent at a flow rate of 1 mL/min, and monodisperse polystyrene standards were used to calibrate the molecular weights. The concentration of the polymer solutions used for GPC measurements was 1 mg/mL. Number-average molecular weights for ethylglycolide were obtained using a Wescan 230 membrane osmometer at 30 °C using toluene as the solvent. Osmotic pressures were determined at several polymer concentrations, and M_n was obtained from extrapolation of the π/c plot to $c = 0$. Differential scanning calorimetry (DSC) analyses of the polymers were obtained using a Perkin-Elmer DSC 7. Samples were run under a helium atmosphere at a heating rate of 10 °C/min, with the temperature was calibrated with an indium standard. Thermogravimetric analyses (TGA) were run both in air and under nitrogen at a heating rate of 10 °C/min using a Perkin-Elmer TGA 7. The mechanical properties of polymer samples were measured from −60 °C to room temperature using a Perkin-Elmer DMA 7 dynamic mechanical analyzer at a heating rate of 10 °C/min. The samples were analyzed in a parallel plate geometry at a frequency of 1 Hz with the dynamic stress set at 3×10^3 Pa. Samples were melt-pressed onto the lower plate (5 mm diameter) and were typically 2−3 mm thick.

Results

Monomer Synthesis. Substituted glycolides have been known for over a century, with the synthesis of ethylglycolide via the dimerization of the sodium salt of 2-bromobutyric acid reported as early as 1893.[23] We prepared substituted glycolides using the routes outlined in Scheme 2. Route a mirrors the standard method used to prepare the lactide dimer.[25] The appropriate α-hydroxy acid was first condensed in toluene to give low molecular weight oligomers, and cracking the oligomers under reduced pressure in the presence of a transesterification catalyst such as ZnO directly yielded the volatile dimer. In route b, an α-bromoacyl bromide was condensed with an α-hydroxy acid to form an ester, followed by ring closure to give the cyclic dimer.[26] In the preparation of ethylglycolide, method a gave the dimer in higher yields, but method b offers more flexibility in synthesis and can be used to synthesize unsymmetrical dimers.

Both synthetic methods yield a mixture of diastereomers. Thermal cracking of oligomer to the dimer consistently yields a near-statistical mixture of the R,S and R,R/S,S diastereomers. A representative example, that of ethylglycolide, is shown in Figure 1. The methine protons of the 3,6-disubstituted glycolide ring appear as doublet of doublets near δ 4.8. The signal for the R,S isomer appears at 4.88, while that from the R,R and S,S isomers is at 4.83. The near equal intensity of the peaks confirms the 1:1 mixture of R,R,/S,S and R,S diastereomers. Similar results were obtained for isobutylglycolide and hexylglycolide prepared by the thermal cracking route. ^{1}H NMR also provides a convenient method for following the polymerization reaction. As shown in Figure 1 for ethylglycolide, the methine peak at 4.85 evolves into a broad peak at 5.05 ppm, during polymerization, and thus the conversion to polymer can be calculated by integration of the two signals.

Catalyst Survey. We tested a variety of catalysts for their ability to polymerize substituted glycolides. Table 1 shows results from the polymerization of ethylglycolide; the data for isobutylglycolide and hexylglycolide polymerizations were similar. As shown in Table 1, runs without alcohol initiators often gave near-quantitative conversion to polymer, but SnO and $SnBr_2$ gave low conversions and low molecular weights. Both SnO and $SnBr_2$ are heterogeneous systems, and their poor activity is not surprising. However, the number-average molecular weights obtained from soluble catalysts varied greatly, ranging from 26 000 for Sn(2-ethylhexanoate)$_2$ to >100 000 for Ph_4Sn. Given a 100:1 monomer:catalyst ratio and assuming complete participation by all catalyst added to the polymerization, the M_n for these polymerizations should be near 17 000. Membrane osmometry results obtained in toluene indicate that the

Table 1. Bulk Polymerization of Ethylglycolide[a]

entry	catalyst	% conv[b]	$M_n \times 10^{-3}$	M_w/M_n
1	Sn(2-ethylhexanoate)$_2$	99	26.2	2.00
		95	16.0	1.73
2	Ph_4Sn	95	114	1.33
		96	15.5	1.88
3	SnO	7	5.4	1.15
		94	14.9	1.86
4	PbO	96	31.7	1.65
		97	13.9	1.90
5	$SnBr_4$	98	37.7	1.78
		98	15.2	1.89
6	$SnBr_2$	61	13.3	16.4
		97	13.9	1.82

[a] [Ethylglycolide]:[catalyst] = 100; polymerizations run at 180 °C for 2.5 h. [b] Determined by ^{1}H NMR; top entries for each catalyst are data for polymerizations with no added alcohol initiator. Bottom entries are polymerizations run using neopentyl alcohol as the initiator at a 1:1 ratio of catalyst to initiator.

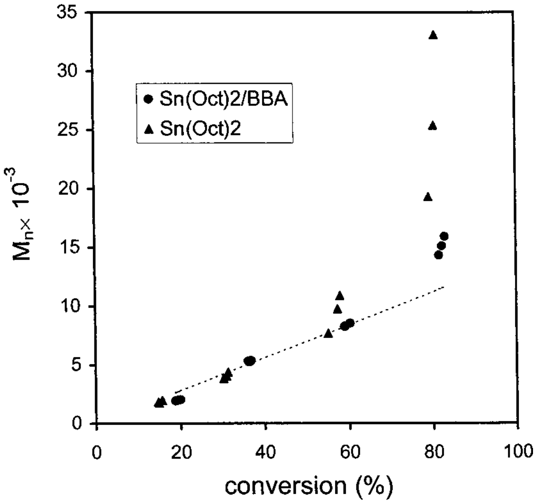


Figure 2. Bulk polymerization of ethyglycolide with (●) and without (▲) added *tert*-butylbenzyl alcohol as initiator. Polymerization conditions: 130 °C, [Sn(Oct)$_2$]/[*tert*-butylbenzyl alcohol] = 1, [monomer]/[catalyst] = 100.

number-average molecular weights of poly(ethylglycolide) and polystyrene determined from GPC data are comparable, and thus M_n values >17 000 are consistent with incomplete initiation. The effect of adding alcohol as an initiator (second row of each entry) is clear. All of the catalysts surveyed gave high conversions and molecular weights close to the theoretical values for M_n.

Because most proposed mechanisms for solution and bulk polymerization of lactide invoke participation of water[27] or alcohol[28−31] as the initiator, we added *tert*-butylbenzyl alcohol (BBA) to polymerizations to gain better control of the molecular weight and molecular weight distribution. Without the added alcohol, the polymerization is initiated by residual moisture or alcohols that are present as impurities in the polymerization, and because the amounts of such impurities vary from run to run, the catalyst efficiency should also vary. A polymerization of ethylglycolide shows the importance of the added alcohol (Figure 2). The results from six Sn(Oct)$_2$-catalyzed polymerizations are shown, three without an alcohol initiator and three where 1 equiv of *tert*-butylbenzyl alcohol was added. Those runs with alcohol show a linear relationship between molecular weight and conversion up to >60% conversion and, compared to runs without added alcohol, less scatter in the experimental data.

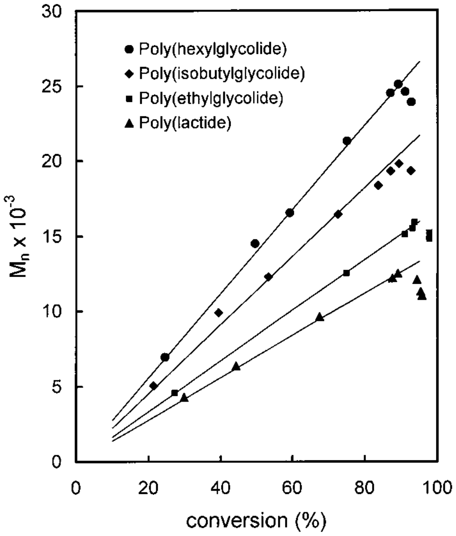


Figure 3. Molecular weight versus conversion for the bulk polymerization of substituted glycolides: (▲) lactide, (■) ethylglycolide, (●) hexylglycolide, (◆) isobutylglycolide. Polymerization conditions: 130 °C, [Sn(Oct)$_2$]/[*tert*-butylbenzyl alcohol] = 1, [monomer]/[catalyst] = 100.

Figure 3 shows the evolution of molecular weight with conversion for the polymerization of lactide, ethylglycolide, isobutylglycolide, and hexylglycolide. The molecular weight increases linearly with conversion and nearly reaches the theoretical values, 14 000 for polylactide, 17 000 for poly(ethylglycolide), 23 000 for poly(isobutylglycolide), and 28 000 for poly(hexylglycolide). These data show one characteristic expected of a living polymerization, a linear relationship between M_n and conversion. We can also use these data to check the validity of the M_n values obtained by GPC. For the molecular weights to be correct, the slopes of the M_n vs conversion curves must correspond to the molecular weight of the monomer. The measured slopes for the lactide, ethylglycolide, isobutylglycolide, and hexylglycolide data are 140, 168, 228, and 280 g/mol, which match well the monomer molecular weights of 144, 172, 228, and 284 g/mol. The drop in molecular weight at the end of the run has been observed previously in lactide polymerizations and is usually attributed to intramolecular transesterification reactions that form cyclic products and decrease the number-average molecular weight.[32]

Polymerization Kinetics. Ring-opening polymerizations of lactides and lactones typically follow first-order kinetics[33] that can be expressed by eq 1,

$$R = -\frac{d[M]}{dt} = k_p[M][cat] \tag{1}$$

where [M] and [cat] are the concentrations of monomer and catalyst and k_p is the rate constant for propagation. For the case of a living polymerization, [cat] is constant and integration of eq 1 yields

$$-\ln([M]_t/[M]_0) = k_p[cat]_0 t \tag{2}$$

where $[M]_t$ is the concentration of the monomer at time t, $[M]_0$ is the initial monomer concentration (at $t = 0$), and $[cat]_0$ is the initial concentration of catalyst. The data taken below 80% conversion are linear, and k_p[cat] values were extracted from the slopes of the plots (Table 2). Equation 2 indicates that a plot of $-\ln([M]_t/[M]_0)$

Table 2. Polymerization Rates

monomer	k_p[I] (s^{-1}) × 10^3 from conversion vs time data	 from fit to equilibrium model
lactide	6.2	6.7
ethylglycolide	4.8	4.7
hexylglycolide	3.7	3.7
isobutylglycolide	3.0	3.0

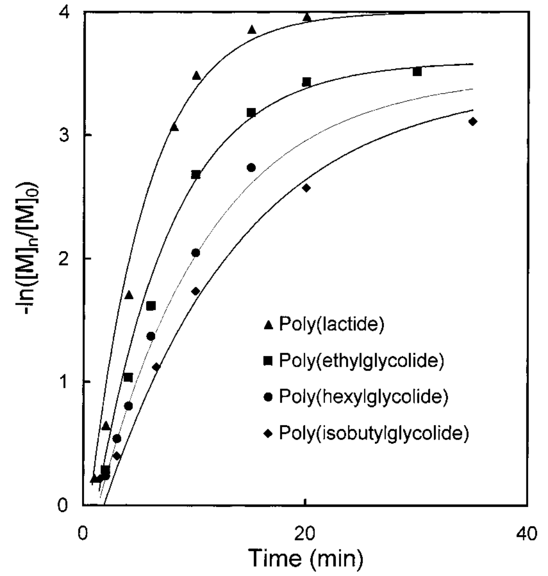


Figure 4. Bulk polymerization of substituted glycolides: (▲) lactide, (■) ethylglycolide, (●) hexylglycolide, (◆) isobutylglycolide. Polymerization conditions: 130 °C, [Sn(Oct)$_2$]/[*tert*-butylbenzyl alcohol] = 1, [monomer]/[catalyst] = 100.

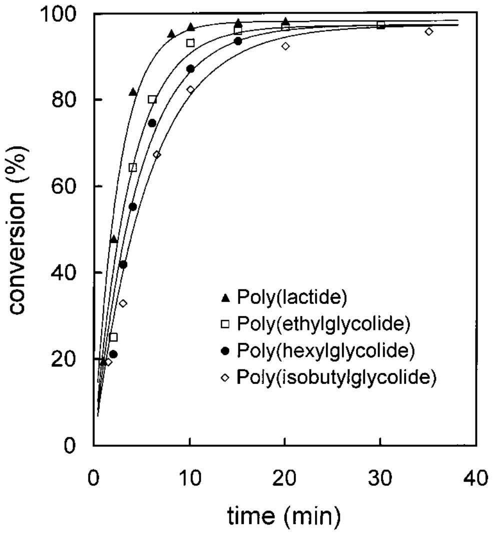


Figure 5. Conversion versus polymerization time for the bulk polymerization of substituted glycolides: (▲) lactide, (■) ethylglycolide, (●) hexylglycolide, (◆) isobutylglycolide. The data were fitted using an equilibrium model. Conditions: 130 °C, [Sn(Oct)$_2$]/[*tert*-butylbenzyl alcohol] = 1, [monomer]/[catalyst] = 100.

versus *t* should be linear, but the data in Figure 4 show strong deviations from first-order kinetics at conversions above 80% ($-\ln([M]_t/[M]_0 = 1.6$) and that the conversion saturates near 97% conversion. The saturation behavior can be seen more clearly in Figure 5, where the data are replotted on a linear conversion scale. We considered two possible causes for the behavior shown: (1) that the kinetic results indicate an equilibrium polymerization,[34,35] and (2) the possibility that catalyst is lost during polymerization (i.e., [cat] is not constant). The catalyst loss hypothesis comes from our work on the solution polymerization of ethylglycolide, where during solution polymerizations in toluene we recovered an insoluble white precipitate that analyzes for a Sn/hydroxybutyric acid polymer. If this polymer is inactive as a catalyst, then formation of the precipitate would correspond to a net decrease in [cat].

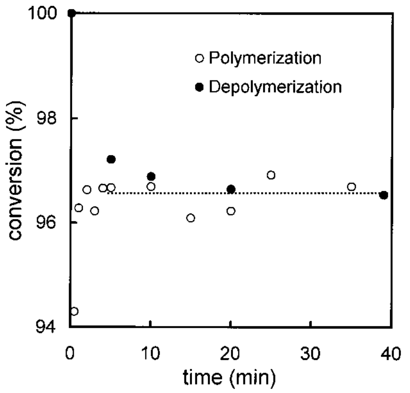


Figure 6. Polymerization/depolymerization data for the bulk polymerization of ethylglycolide. Conditions: 200 °C, [Sn(Oct)$_2$]/[*tert*-butylbenzyl alcohol] = 1, [monomer]/[catalyst] = 100.

To decide which case is more reasonable, we studied the depolymerization reaction for ethylglycolide. If the polymerization is indeed an equilibrium reaction, then depolymerization should give the same $[M]_{eq}$ as polymerization. We scrupulously purified samples of high molecular weight polymer to eliminate all monomer in the polymer and then carried out simultaneous polymerization and depolymerization reactions under the same conditions. As shown in Figure 6 for the case of ethylglycolide, both the polymerization and depolymerization reaction reached the same $[M]_{eq}$, about 3%. To test the catalyst loss hypothesis, we tried to initiate the bulk polymerization of ethylglycolide using the Sn/hydroxybutyric acid polymer. The polymerization reached 97% conversion, consistent with equilibrium control.

The kinetics of bulk polymerizations of lactide have been analyzed as equilibrium reactions.[35] The kinetic equations for such reactions are the following:

$$[\mathrm{M}]_t = [\mathrm{M}]_{eq} + ([\mathrm{M}]_0 - [\mathrm{M}]_{eq})e^{-k_p[\mathrm{I}]t} \qquad (3)$$

$$X = \left(1 - \frac{[\mathrm{M}]_{eq}}{[\mathrm{M}]_0}\right)(1 - e^{-k_p[\mathrm{I}]t}) \qquad (4)$$

In these equations, $[M]_{eq}$ is the monomer concentration at equilibrium, and X is the conversion $(([M]_0 - [M]_t)/[M]_0)$. We used eq 4 to fit the data shown in Figure 5, and the results match the equilibrium model well. The values of k_p[cat] needed for the fit differed by less than 10% from those determined from the kinetic data of Figure 4. Both data sets appear in Table 2.

Polymer Properties. To determine the properties of the polymers, bulk polymerizations using a monomer:catalyst ratio of 300:1 were run at 130 °C to give polymers with molecular weights between 40 and 50 000 g/mol (Table 3). The crude polymers were purified by precipitation into methanol and dried to constant weight. All polymers obtained from the polymerization of substituted glycolides are colorless and are soluble in

Table 3. Polymer Properties

polymer	$M_n \times 10^{-3}$	M_w/M_n	T_g (°C)
polylactide	35.2	1.89	66
poly(ethylglycolide)	45.6	1.78	15
poly(hexylglycolide)	43.2	1.91	−37
poly(isobutylglycolide)	47.3	1.83	22

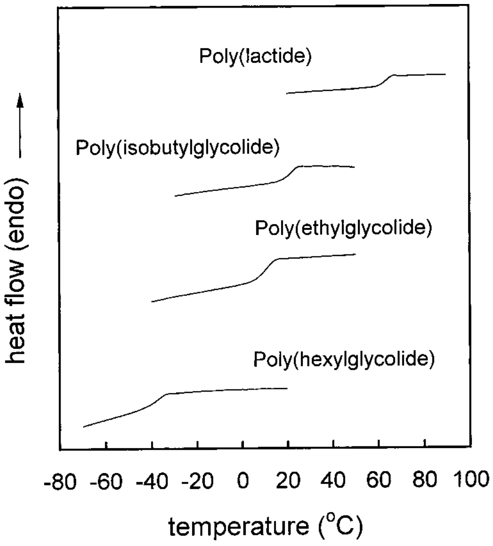


Figure 7. DSC runs (second heating scan after flash quenching from 100 °C) for substituted poly(glycolide)s. Heating rate: 10 °C/min under helium.

solvents ranging from benzene to $CHCl_3$. Flexible films can be either melt-pressed at 150 °C or cast from solvent. Because of the low T_g's for the polymers, the films tend to be somewhat tacky regardless of the molecular weight, and characterization of the polymers by polarized optical microscopy showed that none of the polymers are crystalline. Given that the monomer used in the polymerizations is a mixture of R,R, S,S, and RS diastereomers, the lack of crystallinity is not surprising.

DSC scans were used to measure the glass transition temperatures for all the polymers, and the results appear in Figure 7 and Table 3. Overall, thermal analysis data show that the T_g's of the substituted glycolides range from −37 °C for poly(hexylglycolide) to 66 °C for polylactide. For polymers substituted with linear alkyl groups, the T_g's decreased as the length of the alkyl group increased. For these polymers, the flexible pendent group reduces T_g by acting as an internal plasticizer, lowering the frictional interaction between chains. Conversely, the branched pendent group of poly(isobutylglycolide) hinders rotation of the polymer backbone, resulting in a higher T_g.

We further investigated the properties of poly(ethylglycolide) using thermal and dynamic mechanical analyses. DSC runs show a T_g near 12 °C, with no sign of crystallinity. A T_g of 12 °C is lower than that of polylactide itself (66 °C) and in line with our expectation that increasing the length of the side chain should lead to a decrease in T_g. DMA runs support the T_g assignment made from DSC data. As shown in Figure 8, the tan δ trace for the polymer shows a peak near 12 °C which is nearly coincident with the baseline inflection seen in the DSC data. In addition, the DMA probe position trace shows the expected behavior for a polymer heated to above T_g, expansion followed by penetration of the probe through the sample.

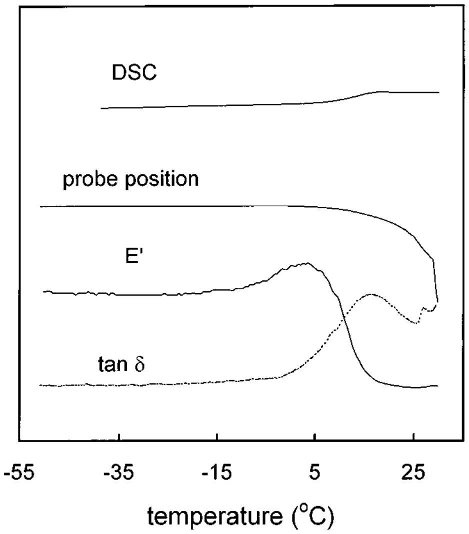


Figure 8. Thermal analysis results for poly(ethylglycolide). The bottom three traces are DMA results for a sample in a parallel plate geometry. Heating rate: 10 °C/min under helium (DSC) or N_2 (DMA).

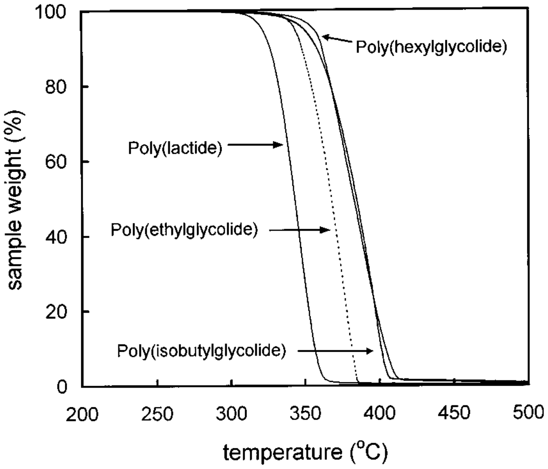


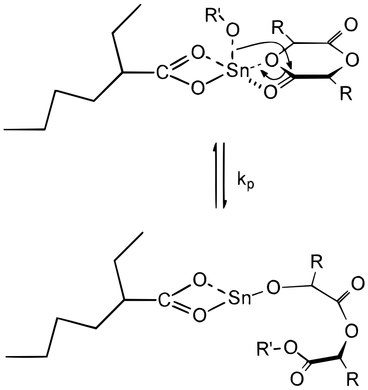
Figure 9. Thermogravimetric analysis results for substituted poly(glycolide)s run in air. Heating rate: 10 °C/min.

The decomposition temperatures of polymers measured using TGA define the limiting use temperatures of the polymers. As shown in Figure 9, the TGA plots for all polymers are similar, with the onset for decomposition shifting to higher temperatures as the size of the alkyl group increases. We found that all polymers decomposed to their monomers, and thus the shift does not necessarily imply increased stability for these poly(glycolide)s but more likely reflects the lower volatility of monomers that have large substituents. In trial depolymerization reactions run on 0.1 g scales, we recovered over 93% of polymer mass as monomers. TGA runs in air and under N_2 show only slight differences in their decomposition curves, comparable to the variations seen for polymers from different batches.

Discussion

Poly(ethylglycolide), poly(isobutylglycolide), and poly(hexylglycolide) represent the first members of a potentially large family of polymers derived from substituted lactic acids. A number of substituted glycolides are known including those substituted with long-chain alkyl and unsaturated groups. To a first approximation, much of the chemistry known about lactides and lactide

Scheme 3



polymerizations should be applicable to simple derivatives of lactic acids. For example, in the absence of degradation pathways that complicate the ring−chain equilibrium, substituted lactides should be available through the well-established acid-catalyzed depolymerization of low molecular weight prepolymers. Our small scale (10 g) depolymerizations gave satisfactory yields of the substituted glycolides; however, we expect that the yields are sensitive to scale, and running the depolymerizations on larger scales should improve the yield substantially.

In contrast to the thermal cracking results, the preparation of ethylglycolide by method b gave a mixture enriched in the R,R and S,S diastereomers. It seems plausible that the different ratios of diastereomers observed directly result from the different temperatures used in the syntheses. High-temperature depolymerization yields a near statistical mixture of diastereomers (no selectivity), while solution-based reactions at lower temperatures favor the formation of the more stable R,R and S,S diastereomers. These isomers can adopt the boat conformation favored in the lactide system and place the alkyl substituents in equatorial positions that minimize steric interactions.

Ring-opening polymerization of the substituted lactides is facile, though a bit slower than lactide itself. The propagation step of glycolide polymerization is depicted in Scheme 3. The glycolide ring is arbitrarily drawn in a planar conformation with the R groups in equatorial positions, although a more realistic representation would need to account for the boatlike conformation of the ring seen from X-ray studies[36−38] and the mixture of glycolide diastereomers used in the polymerizations. The polymerization rate of glycolide is faster than lactide ($R{=}CH_3$), because the steric bulk of the methyl group hinders nucleophilic attack at the ring carbonyls. Increasing the size of the ring substituent should decrease the polymerization rate further. Returning to Figure 4, we see that the rates of polymerization follow the expected trend: lactide > ethylglycolide > hexylglycolide > isobutylglycolide. A survey of lactide monomers by Hall[39] showed that ring substitution plays a major role in defining the polymerizability of lactides. For example, 3,3,6,6-tetramethyl-1,4-dioxane-2,5-dione, obtained by adding two methyl groups to the lactide ring, does not undergo ring-opening polymerization. Presumably, nucleophilic attack by either the initiator or the growing polylactide chain is too hindered to lead to polymer.

No crystallinity was found for the substituted glycolides, probably because the monomers used were mixtures of diastereomers. Thus, the practical use of these polymers as structural materials is limited to their T_g's, which are at or below room temperature. It is well-known that atactic polylactides derived from mixtures of R,R, S,S, and R, S lactides are amorphous polymers with T_g's near 60 °C. Polylactides derived from enantiometrically pure lactides are semicrystalline polymers with melting points that range from 160 to 210 °C depending on their degree of crystallinity.[18] We expect that substituted glycolides prepared from a single diastereomer will also be crystalline.

Finally, we note that substituting the glycolide ring with alkyl groups should increase the hydrophobic character of the resulting polymer. Thus, poly(glycolide)s or copolymers that contain a substituted glycolide comonomer should degrade slower than polylactide. Studies of the degradation rates are in progress, and the preliminary data appear to support a decreased degradation rate. The results of that study will be reported elsewhere.

Conclusions

Substituted poly(glycolide)s can be readily prepared by adopting synthetic procedures similar to those used to prepare polylactides. Bulk polymerizations using a variety of catalysts with alcohol initiators give high conversions and predictable molecular weights. The rates of the polymerizations are controlled by the steric bulk of the substituents on the glycolide ring, and the kinetic data can be fit by an equilibrium model. The T_g's of the polymers decreased as the length of the pendent side chain on the glycolide ring increased, but branching in the side chain led to an increase in T_g. The polymers decompose in high yield to monomer when heated to 300 °C, allowing simple recycling of the monomer. These new polymers broaden the scope of physical properties than can be obtained from the polylactides.

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