Macromol. Symp. **2005**, *224,* 85-91

Ring-Opening Polymerization of L-Lactide in Supercritical Chlorodifluoromethane

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Summary: The ring-opening polymerization of L-lactide initiated by 1-dodecanol/stannous 2-ethylhexanoate (DoOH/Sn(Oct)$_2$) was carried out in supercritical chlorodifluoromethane at various reaction times, pressures, and temperatures. The monomer conversion increased to ca 70 % on increasing the reaction time to 25 h. The molecular weight of the product also increased to ca 75,000 g/mol over the same period. Increasing the pressure resulted in an accelerated polymerization rate. The pressure-induced increase in the rate of L-LA polymerization can be explained by the formation of chemical bonds in the transition state, which implies the production of a transition state with a lower partial molar volume than the reactants.

Keywords: biodegradable; kinetics; poly(L-lactide); ring-opening polymerization; supercritical fluid

Introduction

Polylactides have significant applications in the environmental and medical fields.[1] The purity of the polymer product is of concern, because residual monomers, catalysts, and solvents may pose risks when such materials are in contact with biological fluids or tissues.[2] The organic solvents used in the preparation of their microsphere are known to be difficult to remove completely and residual solvent may cause harmful side effects, for example, carcinogenesis, neurotoxicity, or teratogenicity.[3] The production of polylactides under solvent-free conditions, combined with the possible extraction of residual monomer, by using processes like the supercritical antisolvent recrystallization process,[4] shows great promise.

Supercritical carbon dioxide (scCO$_2$) has been shown to be a promising alternative solvent medium for polymerization by Desimone and others,[5] but its practical use has been

DOI: 10.1002/masy.200550608

limited because of the need for high CO_2 pressure to dissolve even small amounts of polar, amphiphilic, organometallic, or high-molecular-mass compounds, which reduces the number of possible homogeneous polymerizations to an extremely narrow range. For example, the emulsion polymerization of D,L-lactide and glycolide within $scCO_2$ with a fluorocarbon polymer surfactant as an emulsifying agent, demonstrated low molecular weights (MWs) ranging from 2,500 to 30,300 g/mol at various polymerization times.[6] Recently, we have reported that supercritical chlorodifluoromethane (scR22) can be successfully utilized as a solvent for the ring-opening polymerization (ROP) of L-lactide (L-LA),[4] wherein the polymerization proceeds in a homogeneous state in scR22 and results in high poly(L-lactide) (PLLA) molecular weights.[7,8]

This paper presents our investigations into the effects of reaction conditions (time, pressure, and temperature) on monomer conversion and PLLA molecular weight, in the stannous octoate initiated polymerization of L-LA in scR22.

Experimental

L-Lactide (L-LA) was purchased from Purac Biochem BV (Gorinchem, The Netherlands), and was recrystallized from ethyl acetate and dried in a vacuum (0.2 mmHg) over P_4O_{10}. Stannous (II) 2-ethylhexanoate ($Sn(Oct)_2$) (Sigma Chemical Co., St. Louis, MO, 99%) and 1-dodecanol (DoOH) (Aldrich, 99.5%) were purified by distillation under reduced pressure and dissolved in dry toluene. R22 of a certified purity of 99.99 wt % was purchased from the Solvey Gas Co., and was used as received. Toluene was dried by refluxing over a benzophenone-Na complex and distilled in a nitrogen atmosphere just prior to use.

Polymerization was conducted in a variable volume stainless steel high-pressure cell equipped with a magnetic stirring bar and an electrical heating mantle. L-LA (3.0 g), DoOH solution (0.9 mL of a 0.11 M solution in toluene; 1.0×10^{-4} mol of DoOH), and $Sn(Oct)_2$ solution (0.42 mL of a 0.24 M solution in toluene; 1.0×10^{-4} mol of $Sn(Oct)_2$) were added to the cell. After removing toluene under a vacuum, the reactor was heated to 50 °C and purged with nitrogen for 5 min. After cooling the reactor to room temperature, it was evacuated for 2 h using a liquid nitrogen cooled trap and then purged with nitrogen for an additional 10 min. The cell was then disconnected from the nitrogen line, evacuated, and connected to the R22 feed system. The cell was filled with liquid R22 to ca 30 bar at 50 °C by using an air-driven gas compressor (Maximator Schmidt Kranz & Co. GmbH), gradually heated to 110 °C to achieve the predetermined pressure, and then polymerization was allowed to proceed for the predetermined time. After cooling the reactor down to room temperature, R22 was vented through a needle valve into chloroform, to collect both the unreacted monomer and polymer. To quantify the conversions of L-LA, the cell was rinsed with chloroform to dissolve traces of the polymer and monomer. Both of these chloroform solutions were then poured into a large volume of cold methanol, and the precipitated PLLA was recovered by filtration and dried under vacuum at room temperature to a constant weight. Monomer conversion was determined gravimetrically.

Molecular weights (MWs) and molecular weight distributions (MWDs) were determined by gel permeation chromatography (GPC) using a Waters 510 fluid unit, a Waters 717 plus autosampler, and a Waters 410 differential refractometer with a combination of three Shodex microstyragel® columns with molecular weight exclusion limits of 1500/70,000/400,000 g/mol. The column was eluted with $CHCl_3$ (flow rate of 1.0 mL/min at 30 °C) and calibrated with polystyrene standards over a MW range of 1,000 – 350,000.

Results and Discussion

Effect of time. A series of L-LA polymerizations initiated by $Sn(Oct)_2$ ($[LA]_0/[Sn]_0=200$ and $[DoOH]_0/[Sn]_0 = 0.63$) was carried out in scR22 at 110 °C and 200 bar, where $[LA]_0$ is the initial L-lactide concentration, $[Sn]_0$ is the initial $Sn(Oct)_2$ concentration, and $[DoOH]_0$ is the initial 1-dodecanol concentration. The reaction time dependences of monomer conversion and PLLA MW growth are shown in Figure 1. The monomer conversion increased to ca 70 % on increasing the reaction time to 25 h. The molecular weight of the product also increased to ca 75,000 g/mol over the same period. However, a further increase in the polymerization time to 40 h had little effect on either monomer conversion or on PLLA MW.

Effect of pressure. A series of L-lactide (L-LA) polymerizations initiated by $DoOH/Sn(Oct)_2$ was carried out at pressures ranging from 180 to 360 bar at a constant temperature of 110 °C (see entry 1-12 in Table 1). In all of these experiments, the ratio of monomer to R22 was held constant at 12.4 wt %. The polymerization rate constant, k_p, was determined according to a previously reported standard procedure,[7] and the results are listed in the last column of Table 1. It is noted that the higher pressure resulted in the higher polymerization rate, which indicates that the transition state corresponds to a

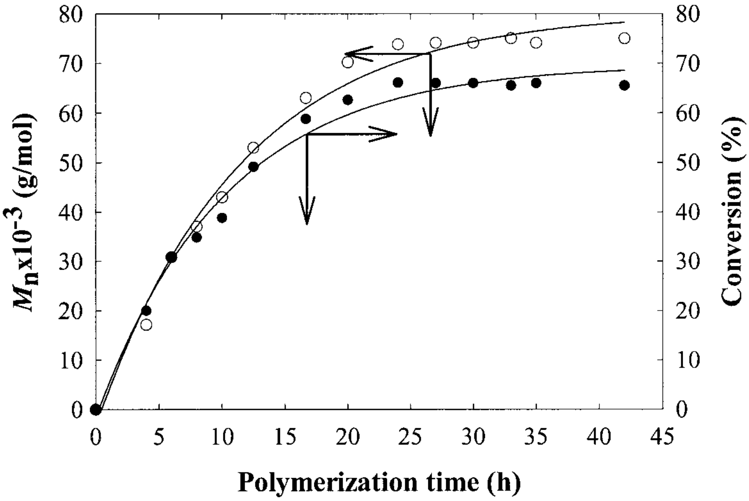

Figure 1. Relation between monomer conversion (○) and poly(L-lactide) molecular weight (●) by GPC at different times. Polymerization conditions: $[LA]_0 = 0.4$ mol/L, $[LA]_0/[Sn]_0 = 200$, $[DoOH]_0/[Sn]_0 = 0.63$ at 110 °C and 200 bar in supercritical chlorodifluoromethane.

volume contraction, i.e., the transition state occupies a smaller volume than the total volume of reactants, and as a consequence the rate of polymerization increased with increasing pressure.[9]

Our previous study[7] on the polymerization of L-LA initiated by $Sn(Oct)_2$ in scR22 has provided direct spectroscopic evidence for the covalent bonding between tin and the growing polyester chain end. Therefore, the proposed coordination-insertion mechanism in the ROP of L-LA involves covalent tin-alkoxide bond formation, coordination of the monomer to the tin-alkoxide bond, and monomer insertion into the tin-alkoxide bond by the cleavage of the acyl-oxygen bond of the monomer. Thus, the pressure-induced increase in the rate of L-LA polymerization can be explained by the formation of chemical bonds in the transition state, which implies the production of a transition state with a lower partial molar volume than the reactants (see Figure 2).[10] In the transition state, the alkoxy group nucleophilically attacks the monomer's carbonyl carbon, and a new C–O bond is formed between the monomer and the alkoxy group via a four-center transition state. The measured activation volume, −61 cm^3/mol, is quantitatively similar to that of cycloaddition, which lies in the range −30 to −50 cm^3/mol. Moreover, it is more negative than that of vinyl acetate[11] (−10.2 cm^3/mol) and styrene[12] (−11.3 cm^3/mol) in $scCO_2$, which may be due to the formation of the four-center cyclic transition state during the coordination-insertion mechanism. It should also be noted that the cyclic compounds have smaller partial molar volumes than their acyclic analogues.[9]

Table 1. ROP of L-LA in scR22 initiated by DoOH/$Sn(Oct)_2$ at 110°C[a]

entry	P (bar)	react time (h)	conv (%)	$M_{n,GPC}/10^3$ (g/mol)	MWD	$k_p \times 10^4$ (s^{-1})
1	180	1.5	33.0	15.0	1.45	
2	180	3.0	58.5	21.5	1.50	0.80
3	180	4.0	69.9	30.0	1.52	
4	250	1.5	39.3	16.5	1.51	
5	250	3.0	64.3	23.0	1.55	0.96
6	250	4.0	75.1	30.0	1.60	
7	300	1.0	31.6	10.5	1.41	
8	300	2.0	54.2	17.0	1.49	1.06
9	300	3.0	68.3	29.5	1.55	
10	360	1.0	33.0	12.5	1.50	
11	360	2.0	57.3	18.5	1.58	1.14
12	360	3.0	70.1	26.0	1.60	

[a] $[LA]_0$ = 0.4 mol/L, c_{R22} = 40.8% w/v, and $[LA]_0/[Sn]_0$ = 210 and $[DoOH]_0/[Sn]_0$ = 1.0. $[LA]_0$ is the initial L-lactide concentration, $[DoOH]_0$ the initial DoOH concentration, and $[Sn]_0$ the initial $Sn(Oct)_2$ concentration.

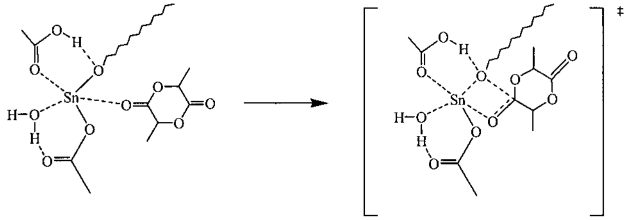

Figure 2. Coordination-insertion mechanism of L-LA polymerization; coordination of the monomer to the tin-alkoxide bond (**1**) and the four-center transition state (**TS**).

Table 2. ROP of L-LA in scR22 initiated by DoOH/$Sn(Oct)_2$ at 250 bar.[a]

entry	T (°C)	react time (h)	conv (%)	$M_{n,GPC}/10^3$ (g/mol)	MWD	$k_p \times 10^4$ (s^{-1})
13	100	1.5	18.1	7.5	1.42	0.41
14	100	3.0	39.3	16.5	1.45	
15	100	4.0	45.1	20.5	1.55	
16	110	1.5	39.3	16.5	1.51	0.96
17	110	3.0	64.3	23.0	1.55	
18	110	4.0	75.1	30.0	1.60	
19	120	0.5	25.9	10.0	1.55	1.51
20	120	1.0	45.1	21.0	1.62	
21	120	1.3	51.3	19.5	1.69	
22	130	0.3	39.5	16.5	1.62	4.10
23	130	0.7	58.2	22.5	1.68	
24	130	1.0	75.7	29.5	1.75	

[a] $[LA]_0/[Sn]_0 = 210$ and $[DoOH]_0/[Sn]_0 = 1.0$. $[LA]_0$ is the initial L-lactide concentration, $[DoOH]_0$ the initial DoOH concentration, and $[Sn]_0$ the initial $Sn(Oct)_2$ concentration.

Effect of temperature. The effect of temperature on the polymerization rate was investigated in a series of polymerizations conducted at temperatures ranging from 100 to 130 °C and at a constant pressure of 250 bar (see Table 2). In all of these experiments, the ratio % of monomer to R22 was held constant at 12.4 wt %. The polymerization rate increased with increasing temperature. According to the relationship $\partial(\ln k)/\partial(1/T) = -E_a/R$, the activation energy was calculated to be 88.7 kJ/mol, which is higher than the value obtained for the ROP of L-LA initiated by $Sn(Oct)_2$ in bulk (70.9±1.5 kJ/mol).[13] The slower kinetics in scR22 is attributed to the competition between R22 and the monomer for coordination to the active coordinate site. In this sense, the higher activation energy also reflects a partial blocking of the active coordinate site by R22.

Conclusion

Supercritical chlorodifluoromethane can be successfully utilized as a solvent for the ring-opening polymerization of L-LA. The pressure-induced increase in the rate of L-LA polymerization implies the production of a transition state with a lower partial molar volume than the reactants. The observed activation energy (88.7 kJ/mol), which is higher than the value recorded in bulk, reflects a partial blocking of the active coordinate site by chlorodifluoromethane.

Acknowledgement

The authors are grateful to the Korean Ministry of Commerce, Industry, and Energy, Korea, for its support (Project No. 10011159).

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