Living Ring-Opening Polymerization of L-Lactide Catalyzed by Red-Al

Hong Li,*,† Chenhong Wang,† Feng Bai,† Jin Yue,† and Hee-Gweon Woo*,‡

The State Key Laboratory of Functional Polymer Materials for Adsorption and Separation, Institute of Polymer Chemistry, Nankai University, Tianjin, 300071, People's Republic of China, and Department of Chemistry and Nano Technology Research Center, Chonnam National University, Kwangju 500-757, Korea

Received October 30, 2003

Ring-opening polymerization (ROP) of L-lactide (LLA) was carried out in bulk and toluene solution, respectively, using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) as the catalyst (initiator). Experimental results show that Red-Al possesses typical characteristics of a living polymerization initiator. Bulk polymerization (110 °C, 48 h) of LLA gives a snow-white polymer of high isotacticity (≥95.2%), moderate molecular weight (MW) ($M_n = 2.3 \times 10^4$), and quite narrow MW distribution (MWD, PDI = 1.12). Investigation of the kinetics of the polymerization in toluene shows that plots of $\ln([M]_0/[M]_t)$ versus time and M_n (number-average MW) of synthesized PLLA versus monomer conversion are linear, which is a typical feature of living polymerization. The mechanism of the ROP was postulated on the basis of ^{1}H NMR monitoring of the polymerization. The synthesized PLLA shows high isotacticity. The degree of transesterification and stereoselectivity of the ROP by Red-Al were estimated according to ^{13}C NMR characterization of poly rac-LA.

Introduction

In recent years syntheses and tailoring of biocompatible and bioresorbable materials have attracted considerable attention due to the rapid development of biomedical engineering science. Polylactides (PLAs), homo- and/or copolymers derived from lactides (LLA, D,L-LA, glycolide, etc.), have been the preferential candidates for such functional materials' design[1−4] and are prepared mainly by ring-opening polymerization (ROP).[5,6] Due to the increasingly deep concerns about the cytotoxicity of stannous octoate, which is the most widely used catalyst for preparing PLAs via ROP, searching for tin-free initiators of high activity and biosafety is an impelling research subject in this field.[7−9] Recently we found out that ROP of LLA initiated by Red-Al, i.e., sodium bis(2-methoxyethoxy)aluminum hydride $Na^+[AlH_2(OCH_2CH_2OCH_3)_2]^-$, shows typical features of the living polymerization. Polymerization in bulk gives a PLLA with moderate MW, narrow MWD, and high isotacticity (Scheme 1). Polymerization kinetics and the mechanism of ROP of LLA using Red-Al are discussed in this paper. To our best knowledge, this is the first report on ROP of lactides initiated by Red-Al.

Scheme 1. Living Polymerization of LLA Initiated by Red-Al

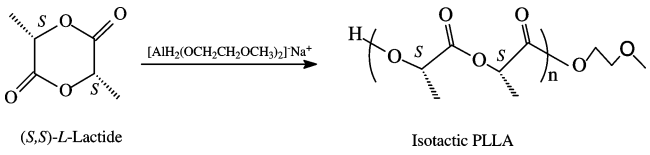

Table 1. Bulk Polymerization of LLA Catalyzed by Red-Al[a]

no.	temp, °C	time, h	yield, %	$M_n \times 10^{-4}$ [b]	PDI[c]
1	110	48	98.1	2.30	1.12
2	110	72	97.8	2.25	1.17
3	135	48	96.0	1.93	1.32

[a] $[M]_0/[I]_0 = 150$; $[M]_0$: initial molar number of LLA feed; $[I]_0$: initial molar number of Red-Al. [b] Measured by GPC. [c] Polydispersity index, i.e., M_w/M_n of the product polymer.

Results and Discussion

Bulk Polymerization. Bulk polymerization of LLA initiated by Red-Al at 110 °C (a temperature slightly above the melting point of LLA) gives a polymer with moderate MW ($M_n = 2.30 \times 10^4$) and very narrow MWD (PDI = 1.12, Table 1, no. 1). Experimental results also indicate that prolonged reaction time (Table 1, no. 2) and high reaction temperature (Table 1, no. 3) lead to the broadening of the MWD of the formed polymer. This is possibly due to the intensification of intramolecular transesterification caused by back-biting chain transfer of the polymeric propagation species at prolonged reac-

* Corresponding authors. E-mail: hongli@nankai.edu.cn and hgwoo@chonnam.ac.kr.
† Nankai University.
‡ Chonnam National University.

(1) Cha, Y.; Pitt, C. *J. Controlled Release* **1989**, *8*, 259.
(2) Vert, M.; Li, S. M.; Splenlehauer, G.; Guerin, P. *J. Mater. Sci., Mater. Med.* **1992**, *3*, 432.
(3) Perego, G.; Cella, G. D.; Aldini, N. N.; Fini, M.; Giardino, R. *Biomaterials* **1994**, *15*, 189.
(4) Brunstedt, M. R.; Anderson, J. M. Materials for Drug Delivery. In *Material Science and Technology*; Cahn, R. W., Haasen, P., Kramer, E. J., Eds.; VCH: Weinheim, 1992.
(5) Middleton, J. C.; Tipton, A. J. *Biomaterials* **2000**, *21*, 2335.
(6) Albertsson, A.; Edlund, U.; Stridsberg, K. *Macromol. Symp.* **2000**, *157*, 39.
(7) Kricheldorf, H. R.; Saunders, I. K.; Damrau, D. O. *Macromol. Symp.* **2000**, *159*, 247.
(8) Kricheldorf, H. R.; Saunders, I. K.; Damrau, D. O. *Macromol. Symp.* **1999**, *144*, 269.
(9) Saunders, I. K.; Kricheldorf, H. R. *Macromol. Chem. Phys.* **1998**, *199*, 1081.

10.1021/om0342715 CCC: $27.50
Publication on Web 02/20/2004

Table 2. Kinetics of Solution ROP of LLA Initiated by Red-Al[a]

no.	time, h	conv, %[b]	$\ln[M]_0/[M]_t$	M_n
1	0	0	0	0
2	3.25	1.65	0.0166	313
3	6.00	3.75	0.0382	615
4	25.73	15.83	0.1723	2355
5	49.33	26.44	0.3071	3882
6	65.33	35.11	0.4325	5131

[a] Toluene solution, 70 ± 0.5 °C, initial molar ratio of $[LLA]_0/[I]_0 = 100$. [b] Obtained by integration of LLA vs PLLA resonances in the ^{1}H NMR spectrum.

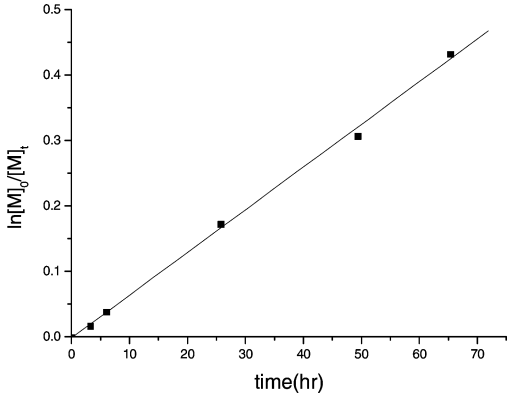

Figure 1. Plot of $\ln[M]_0/[M]_t$ vs time.

tion time and elevated temperature, and in both latter cases this chain transfer is usually unavoidable in the bulk polymerization of cyclic esters.

Kinetics of Solution Polymerization. To obtain the kinetic features of ROP of LLA initiated by Red-Al, polymerization was carried out in toluene at 70 °C (Table 2). The polymerization process was monitored with ^{1}H NMR spectroscopy. After calculating M_n of formed PLLA, conversion of LLA (calculated by ^{1}H NMR, Table 2), and $[M]_t$ (molar concentration of LLA at time t), plots of $\ln([M]_0/[M]_t)$ versus reaction time (t) and M_n versus conversion were made, respectively (Figures 1and 2).

The linear semilogarithmic plot of $\ln([M]_0/[M]_t)$ versus time (Figure 1) indicates that the polymerization is first-order with respect to monomer and that the concentration of active centers remains almost constant throughout the polymerization.

The variation of the formed polymer's M_n with monomer conversion (Figure 2) also shows a linear relationship. Thus, the features of the plots in Figures 1 and 2 are the typical characteristics of living polymerization.

End-Group Characterization of the PLLA. As mentioned above, the polymerization process was monitored by recording the ^{1}H NMR spectra of the formed PLLAs after the product mixture had been moisture-quenched (hydrolyzed) at different times (Figure 3). It can be seen clearly that with the proceeding of ROP the intensities of peak signals C ($\delta = 1.66-1.68$) and I ($\delta = 5.01-5.11$) corresponding to the monomer decrease, which implies the decrease of the monomer concentration. At the same time the intensities of signals B ($\delta = 1.53-1.58$) and J ($\delta = 5.11-5.27$) corresponding to PLLA increase, which implies the propagation of polymeric species. It can also be seen very clearly, from Figure 3, that as soon as the polymerization starts the

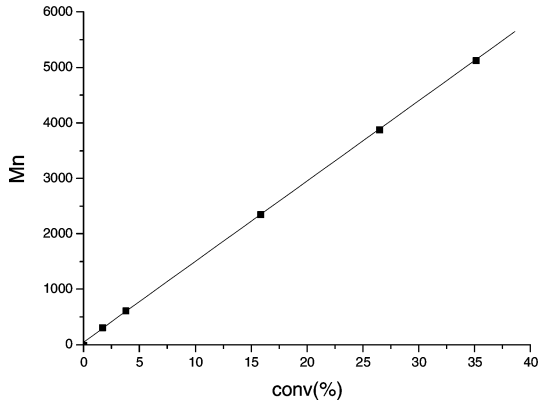

Figure 2. Plot of M_n of PLLA vs LLA conversion.

signals E, F, and G, corresponding to the ligand group $CH_3OCH_2CH_2O-$ in Red-Al, appear clearly in the ^{1}H NMR spectra of formed polymers, which implies $CH_3OCH_2CH_2O$ is one of two end-groups of PLLA synthesized. The characteristic peaks signals D ($\delta = 2.78-2.80$) of the −OH group and H ($\delta = 4.25-4.28$) of the methine group in the end-group $-CH(CH_3)OH$ are also clearly present in the ^{1}H NMR spectra, which indicates that $-CH(CH_3)OH$ is the another end-group of the synthesized PLLA.[10]

Mechanism Postulation. Red-Al was used to catalyze the ROP of LA for the first time; as far as we know, there are no other reports on the mechanism of Red-Al-initiated ROP. From the experimental results, discussed above, the mechanism is deduced to follow the coordination mechanism. To verify the conjecture, that is, to rule out the possibility of free radical and ionic polymerization, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a radical capture) and NaOH/MeOH/toluene (cation terminator) and BuOH/toluene (anion capture) of equimolar amount as Red-Al were added to the started polymerization systems (at reaction time 6 h), respectively. Polymerizations in all three systems were not terminated, but continued (Table 3). This verified our conjecture that the polymerization follows neither the radical nor the ionic mechanism.

According to a report of Z. Cerny et al., the structure of Red-Al in toluene is an open-chain oligomer **1** (Figure 4) in which two bidentate ligands, $-OCH_2CH_2OCH_3$, belonging to two neighboring Red-Al molecules are associated via a Na^+ ion.[11] To some extent this structure is quite similar to aluminum isopropoxide, which is well accepted as a coordination initiator.[12] On the basis of the investigation and considerations mentioned above, the mechanism of ROP using Red-Al is deduced to follow the coordination−insertion type, as shown in Figure 4.

During the polymerization, in the presence of LLA, the coordination of LLA molecules with the Al atom in Red-Al makes the latter dissociate into a monomolecular species that is bound with the LLA molecule, forming a four-membered-ring transition state, **2**. Propagation proceeds via the fission of the acyl−oxygen bond in LLA and the insertion of the cleaved LLA residue $-O-CH-(CH_3)-CO-O-CH(CH_3)-CO-$ into the Al−O bond between

(10) Bao-Tsan, K.; Chu-Chieh, L. *J. Am. Chem. Soc.* **2001**, *123*, 7973
(11) Cerny, Z.; Fusek, J.; Machacek, J.; Kriz, O.; Casensky, B. *J. Organomet. Chem.* **1996**, *516*, 115.
(12) Albertsson, A. C., Varma, I. K. *Adv. Polym. Sci.* **2002**, 157, 2.

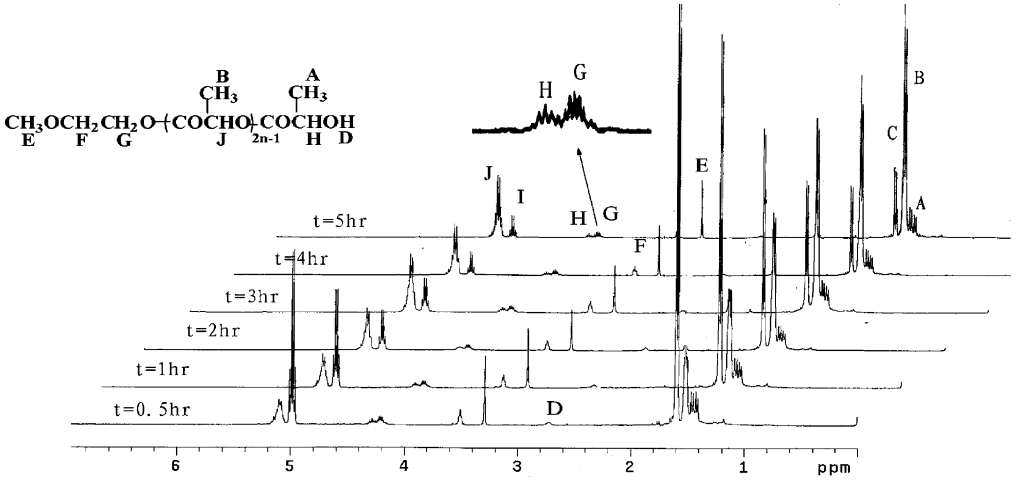

Figure 3. Overlaid ^{1}H NMR spectra of synthesized PLLA (polymerization at 70 °C, in toluene, $[LLA]_0 = 1$ M, $[LLA]_0/[I]_0 = 30$).

Table 3. Effect of Additives in ROP of LLA Initiated by Red-Al[a]

no.	time, h	conv, %	M_n[b]	additive	total time, h	conv, %	M_n
1	6	31.8	2365		12	63.1	4613
2	6	31.8	2365	BuOH	12	62.3	4536
3	6	31.8	2365	TEMPO	12	63.7	4656
4	6	31.8	2365	NaOH	12	61.8	4520

[a] Polymerization in toluene at 70 °C, $[LLA]_0/[I]_0 = 50$. Additives were added after the polymerization proceeded for 6 h. [b] Measured by ^{1}H NMR spectrum.

Al and the alkoxy ligand in Red-Al molecules. Hydrolyzing the active macromolecular propagation species **3** gives the final PLLA molecule **4**, bearing CH_3OCH_2-CH_2O and OH as its two end-groups. ^{1}H NMR characterization of the product polymer demonstrated the above postulation.

Degree of Transesterification in ROP of DLLA by Red-Al. For the ROP following the coordination−insertion mechanism, the fission of the acyl−oxygen bond in the LLA molecule does not change the chirality of the carbon in the methine. In this case the transesterification shows no influence on the stereoregularity of formed PLLA. To obtain the stereoselectivity of the initiator Red-Al in ROP, rac-LA(D, L-LA) was chosen as the monomer.

The stereoregularity estimation based on the ^{13}C NMR spectrum (Figure 5) showed that the synthesized PLLA is of high isotacticity (≥95.2%) and low racemation degree (≤2%). The cause of the latter is due to the monomer not being 100% optically pure (commercial LLA from Aldrich with ee of 98%).

Quantitative estimation of the degree of transesterification and stereoselectivity in ROP of LA can be made by means of ^{13}C NMR characterization, because the methine carbon signal in the repeat unit of PLA molecules is sensitive to the tetrad. The ^{13}C NMR spectrum of the methine carbon in the synthesized poly rac-LA (PDLLA) is shown in Figure 6.

The degree of transesterification can be determined by[13]

$$T = I_{ssi}/I_{max}$$

where T denotes the transesterification coefficient, I_{ssi} is the intensity of the *ssi* tetrad, and I_{max} is the maximum intensity of the *ssi* or *iss* tetrad. In the single-addition Bernoullian statistics the intensity *iss* and *ssi* are equal, that is,

$$T = I_{ssi}/I_{max} = I_{iss}/I_{max} = 8I_{ssi} = 8I_{iss}\,(I_{max} = 0.125)$$

From Figure 6, T is calculated as 11.91%, which means the degree of transesterification in the ROP by Red-Al is very low. This is also the characteristic of living polymerization. In this case, the stereoregularity of formed PDLLA can be determined by[14]

$$P_i = 1 - 2I_{isi}$$

where P_i stands for the possibility of forming a new *i*-dyad and I_{isi} is the intensity of the *isi* tetrad. From Figure 6, P_i is calculated as 45.8%, so the stereoregularity of PDLLA is predominantly isotactic.

Conclusion

Red-Al proves to be quite an active initiator for ROP of LLA. Kinetic investigation on the polymerization in toluene shows that ROP of LLA initiated by Red-Al possesses typical characteristic features of the living polymerization. The mechanism of the ROP by Red-Al was postulated to follow the coordination type on the basis of the investigation of ^{1}H NMR spectral data of the polymers formed at different reaction times and on the additive effect of the ROP. The ^{13}C NMR spectral characterization of the methine carbon in the repeat unit of PDLLA indicates that the degree of transesterification in the ROP is very low (≤11.91%) and that the synthesized PLLA is of very high isotacticity (95.2%).

Experimental Section

Materials and Instrumentation. All manipulations were carried out under UHP grade argon using standard Schlenk techniques. Red-Al (70 wt % in toluene) was purchased from

(13) Bero, M.; Kasperczyk, J.; Jedlinski, Z. *Makromol. Chem.* **1990**, *191*, 2287.
(14) Coudane, J. O.; Schwach, G.; Vert, M. *J. Polym. Sci.: Polym. Chem.* **1997**, *35*, 1651.

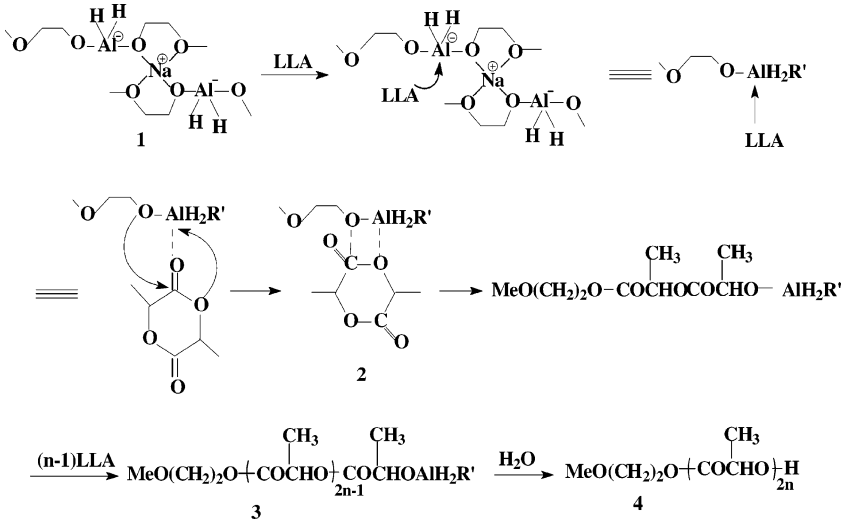

Figure 4. Proposed mechanism for ROP of LLA by Red-Al.

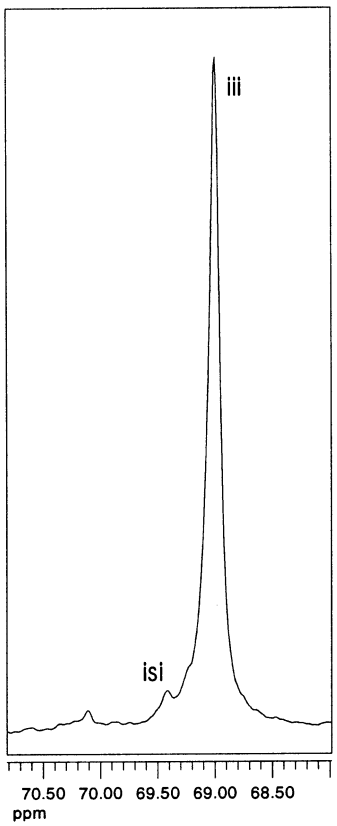

Figure 5. ^{13}C NMR spectrum of the methine carbon in PLLA (110 °C, 10 h, $[LLA]_0/[I]_0 = 100$, bulk polymerization).

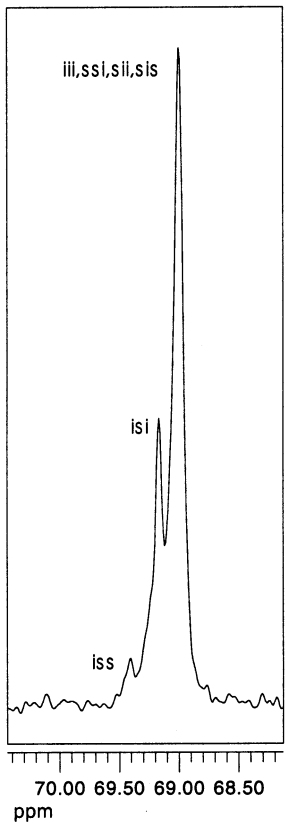

Figure 6. ^{13}C NMR spectrum of the methine carbon in PDLLA (130 °C, 10 h, $[DLLA]_0/[I]_0 = 100$, bulk polymerization).

Aldrich and used by dilution with freshly distilled toluene. LLA (98%, Aldrich) was recrystallized three times from ethyl acetate, dried under vacuum. Dry, oxygen-free solvents were used throughout. Glassware was flame-dried before use.

^1H and ^{13}C NMR spectra were recorded on a Varian Unity plus 400 (400 MHz) spectrometer operating at 400 MHz (^1H) and 100 MHz (^{13}C) using $CDCl_3$ as a reference. MWs of the polymer samples were measured by size exclusion chromatography (SEC) on a Waters 1525 chromatograph equipped with a refractive index detector and a set of three columns, Styragel HT2, HT3, and HT4. Columns were calibrated using monodisperse polystyrene standard. Analysis was performed at 30 °C using THF as solvent at a flow rate of 1.0 mL/min. The number-average MW (M_n) and polydispersity index (PDI) of the synthesized polymers were calculated on the basis of PLA calibration.

Catalytic Polymerization. For bulk polymerization the monomer (LLA or DL-LA) was placed in a Schlenk flask with a rubber septum and a magnetic stirrer. The flask was purged thoroughly with argon. Red-Al in toluene was then added to the stirred mixture using a syringe. After toluene was thoroughly evaporated off, the flask was sealed under vacuum and then placed in a silicon oil bath. Polymerization was carried out at a temperature of 110 ± 2 °C for 48 h. The flask was opened at room temperature, and the contents were dissolved

in acetone. Polymer was precipitated from water, and filtration followed by drying at 40 °C in vacuo yielded a snow-white solid.

Solution polymerization was carried out at 70 ± 0.5 °C in toluene following a procedure similar to the bulk polymerization except that no solvent-expelling operation is needed. For kinetic experiments the samples were taken from the reaction mixture at the desired time during the polymerization.

Acknowledgment. This research was financially supported by the National Natural Science Foundation of China (Project No. 20074016). H.L. acknowledges Dr. P. Le-Perchec of CNRS-LMOPS, France, for the very helpful discussion during the visit to the laboratory.

OM0342715