Studies on the Synthesis and Thermal Properties of Copoly(L-lactic acid/glycolic acid) by Direct Melt Polycondensation

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ABSTRACT: A two-step direct copolymerization process of L-lactic acid (L-LA)/glycolic acid (GA) was developed. The first step was to produce an oligomer of L-LA/GA and then the oligomer was polymerized with binary catalyst tin chloride dihydrate/*p*-toluenesulfonic acid. In this way, the copoly(L-LA/GA) (PLGA), without any organic solvent, was synthesized directly. The thermal properties and solubility in chloroform of PLGA were studied by DSC and NMR. The results showed that the melting point of PLGA decreases with increasing mole fraction of GA units in copolymer. In addition, the melting point of polymer also decreased with increasing degree of racemization of polymer. The solubility of PLGA in chloroform decreased with the increase of the average lengths of the glycolic acid units. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 92: 2163–2168, 2004

Key words: lactic acid/glycolic acid; melt polymerization; copolymerization; thermal properties; solubility

INTRODUCTION

Poly(glycolic acid) (PGA) is the first kind of polymer used as an absorbable suture and is one of the earliest absorbable polymers for fracture-fixation devices. However, when used for absorbable fixation devices such as platelets, sticks, bolts, needles, and so on, the mechanical strength of PGA proved to be insufficient for those purposes. In addition, the integrity of PGA decreases rapidly over short periods because of degradation. This drawback prevents its application in areas where the polymer materials would be used over long periods of time.

Poly(L-lactic acid) (PLLA) is expected to have wide applications, not only as a biodegradable plastic but also as a biomedical material,[1–4] because of its excellent properties, such as mechanical strength, transparency, safety, and adjustable hydrolyzability. However, PLLA is not always a good polymer for film application because of its rigidity. Furthermore, it is difficult to produce foam with a high blow ratio because of the low melt tension of PLLA compared to that of polystyrene.

The main advantages of PLLA and PGA are good compatibility and safety. Because they are degradable in the human body, they are particularly suitable for application as implants that are used only temporarily during the healing process.

To extend the application area of PLLA (e.g., sustained release of drugs), some measures have been taken to adjust the properties of PLLA, such as degradability and crystallinity, for example. One way to modify the properties of PLLA is to make copolymers of L-lactic acid (L-LA) and glycolic acid (GA). By adjusting the percentage of comonomer, a copolymer, whose properties are between those of PLLA and PGA, can be obtained.

In this study, copoly(L-lactic acid/glycolic acid) (PLGA) was prepared by direct melt polycondensation instead of by the ring-opening process (ROP), which has already been extensively used.[3,4,7–10,19]

Ajioka's group[15,16] developed the solution polycondensation of L-LA/GA in 1995, breakthrough for direct synthesis, to obtain sufficiently high weight-average molecular weight (M_w) polymers. Solution polycondensation can successfully overcome difficulties in kinetic control, such as efficient removal of water and suppression of depolymerization of polymers. PLGA with high M_w can be prepared, after a relatively long reaction period at 160°C under high vacuum in diphenyl ether solution. However, the solvents introduce higher levels of complexity of both process control and purification of the end product, and thus the resultant polymers are very expensive to produce. In 2000, Kimura[14,17,18] developed a new melt and melt/solid polycondensation process to overcome these drawbacks, by which high M_w PLLA and PGA could be produced. In the present work various PLGAs were

produced by a process similar to that developed by Kimura. The effect of the amount of GA units, in the as-polymerized copolymer, on the thermal properties was studied. The influence of the GA content on the glass-transition temperature, solubility, and the melting temperature of the as-polymerized copolymer was also discussed.

EXPERIMENTAL

Materials

L-LA, as a 90 wt % aqueous solution (PH90, pharmaceutical grade), was purchased from Purac Corp. (The Netherlands). Glycolic acid dihydrate, tin (II) chloride dihydrate, *p*-tolulenesulfonic acid monohydrate (TSA), diethyl ether, tin powder, chloroform, and molecular sieve (3 Å) were purchased from Shanghai Chemical Corp. (China). The molecular sieve was activated at 300°C for 24 h. All other reagents were analytical grade and used as received.

Preparation of PLGA

The first step was to produce the oligomer: given amounts of 90 wt % L-LA aqueous solution and glycolic acid dihydrate (typical quantities were 50.0 g L-LA and 4.2 g GA) were charged into a 100-mL three-neck flask. The flask was equipped with a mechanical stirrer and a reflux condenser packed with a molecular sieve (3 Å). The reaction system was connected with a vacuum system through a cold trap. The mixture of aqueous L-LA and GA dihydrate was then dehydrated at a constant temperature of 150°C by stepwise vacuumizing the reaction system: first, the reaction system was maintained at atmospheric pressure for 2 h, then at a reduced pressure of 13,300 Pa for 2 h, and finally under a pressure of 1300 Pa for more than 4 h. Thus viscous oligomers of L-LA and GA were formed and the amount of water removed from the system was measured. The removed water was subtracted from the initially charged hydroxy acids in aqueous solutions, and the resultant oligomer could be determined. After purification, the samples underwent ^{1}H-NMR testing, from which the degree of polymerization of the oligomer was calculated to be about 6. However, it was found that the signals of GA units could not be detected in the spectra, whereas those of L-LA units were clear. This implies that the resultant product was mainly the oligomer of L-LA. One possible reason is that GA units have a low rate of incorporation, under these conditions without catalyst, given that the relative reactivities of both monomers largely depend on the reaction conditions.[9] The other reason is that the amount of L-LA is much greater than that of GA in the monomer feed.

The second step was to produce the polymer: tin (II) chloride dehydrate (at a level of 0.4 wt % of the resultant oligomer) and TSA [with a 1/1 molar ratio of tin (II)/TSA] were used and a typical amount of catalyst substrates [0.1814 g tin (II) chloride dihydrate and 0.1548 g TSA] were mixed with oligomers in the flask. Along with pressure being reduced stepwise to reach 100 Pa, the mixture was gradually heated to an appropriate reaction temperature (typical reaction temperature was 180°C) under mechanical stirring. The reaction system was maintained under these conditions for a predetermined number of hours. As the reaction proceeded, the reaction system gradually became viscous, and the resultant L-lactide and glycolide were refluxed through the reflux condenser. At the end of the reaction, the flask was cooled under vacuum. The obtained product was then dissolved in chloroform and subsequently precipitated into diethyl ether. Finally, the resulting solids were filtered and dried under vacuum at 65°C. PLGA (90/10) was prepared from the mixture of L-LA/GA (90/10) (molar ratio of L-LA/GA being 90/10), whereas PLGA (70/30) was prepared from L-LA/GA (70/30). All samples of PLGA were kept in a desiccator with phosphorus pentoxide.

Polymer characterization

Both ^{13}C-NMR and ^{1}H-NMR spectra were carried out at a temperature of 300 K on a Bruker DMX-500 NMR spectrometer (Bruker Instruments, Billerica, MA). All polymer samples were dissolved in deuterated chloroform with tetramethylsilane as an internal standard. Chemical shifts (in ppm) were referenced relative to chloroform at 77.00 and 7.26 ppm in ^{13}C-NMR and ^{1}H-NMR spectra, respectively. ^{1}H-NMR spectra were acquired with a 1% solution at 500 MHz. The ^{13}C-NMR measurements were acquired on a 10% solution at 125 MHz, with a pulse angle of 25°, an acquisition time of 1.6 s, and a delay time of 10 s. The distribution and length of monomer sequence were investigated through ^{13}C-NMR spectra.

The melting point, the glass-transition temperature, and the enthalpy of fusion (ΔH_f) of polymers were determined by differential scanning calorimetry (DSC) on a modulated DSC 2910 thermal analyzer (TA Instruments, New Castle, DE) at a heating rate of 10°C/min.

RESULTS AND DISCUSSION

Thermal properties of as-polymerized PLGA

A series of copolymerizations of L-LA and GA were prepared. The effect of the amount of GA in the as-polymerized copolymer on the thermal properties was studied. The results are summarized in Table I.

TABLE I
Thermal Properties of As-Polymerized Copolymers of
L-Lactic Acid and Glycolic Acid in the Melt at 180°C

Glycolic acid (%) in copolymer	ΔH (J g^{-1})[a]	T_m (°C)[a]	T_g (°C)[a]	Crystallinity (%)[b]
0	53.65	156.4	ND	57.69
4.34	35.47	141.5	59.2	38.14
8.70	30.82	124.9	57.8	33.14
12.12	26.49	116.3	56.9	28.48
16.57	21.55	98.8	55.8	23.17
22.62	18.20	79.5	54.2	19.59
32.20	ND[c]	ND	52.8	ND

[a] Results from DSC determination.
[b] Calculated from DSC curve.[13]
[c] Not detected.

Table I shows the effects of copolymerization on the thermal properties, as characterized by DSC. The heat of fusion, melting point, glass-transition temperature, and crystallinity are strongly affected by compositions of PLGA. The compositions of copolymers were determined by ^{1}H-NMR spectra. The molar fraction of GA moiety in PLGA can be calculated from the integrated area of peaks at 5.15 ppm attributed to methine protons in LA units and that of peaks at 4.60–4.90 ppm attributed to methylene protons in GA units of PLGA.[7,10,11] By assigning I_L to the integrated peak area at 5.15 ppm, I_G to the integrated peak area of at 4.6–4.9 ppm, and F_G to the mole fraction of GA, respectively, F_G can be calculated according to the following relationship:

$$F_G = I_G/(2I_L + I_G) \qquad (1)$$

Figure 1 shows typical DSC scans for the studied system. The PLLA homopolymer shows a sharp melting endotherm peaking at 155.7°C. Copolymerization
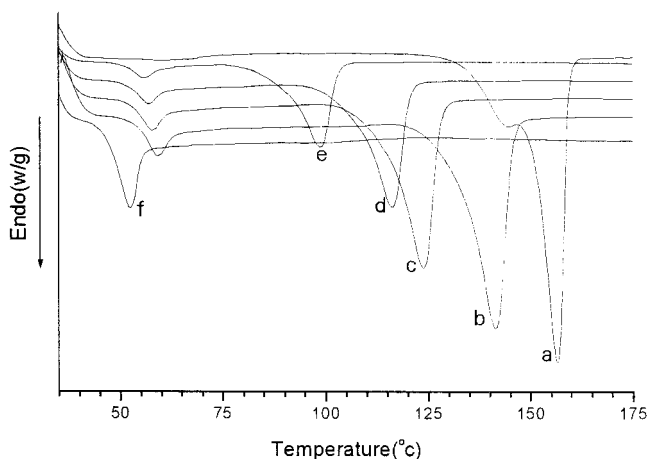

Figure 1 DSC thermograms of PLGA with different molar fractions of GA in samples: (a) 0%, (b) 4.34%, (c) 8.70%, (d) 12.12%, (e) 16.57%, (f) 32.20%.
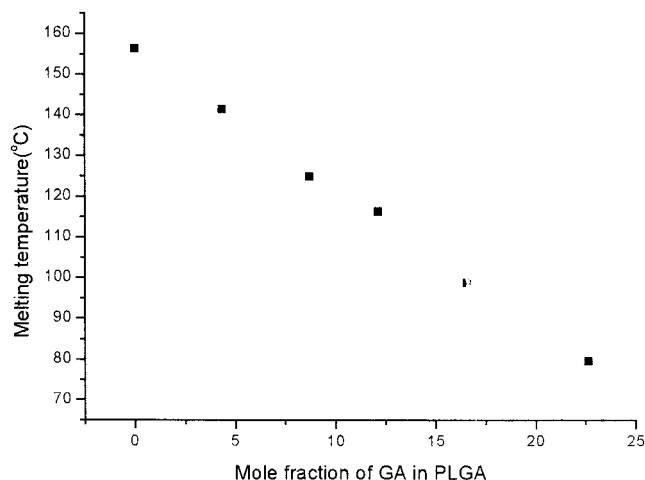

Figure 2 Melting point of PLGA as a function of GA fraction in PLGA.

of L-LA and GA results in decreasing melting temperature, glass-transition temperature, degree of crystallinity, and heat of fusion comparied with those of PLLA. In addition, the melting range becomes less sharp as the concentration of monomer L-LA decreases. The copolymer, containing 32.2% GA [PLGA (70/30)], shows the characteristics of an amorphous copolymer: the melting peak is absent and the glass-transition temperature has shifted to even lower temperatures.

The crystallization of copolyester yields smaller and less-perfect crystallites because the crystal lattice of L-LA units tends to exclude GA units. This incorporation causes lattice defects and results in decreases in overall crystallinity, heat of fusion, and melting temperature. When the molar fraction of GA in the feed is more than 30%, an amorphous copolyester is formed because crystallization is reduced by the decrease in the lengths of L-LA units. Dependency of the melting temperature, of as-polymerized PLGA on the copolymer composition, can be seen in Figure 2. Copolymerization lowers the melting point, except in rare instances where the different types of monomeric units are capable of replacing one another in their crystal lattices.

Apart from the effect of composition of PLGA on melting point, the effect of racemization on melting point was also investigated. The racemization was analyzed from ^{13}C-NMR spectra of PLLA, PDLLA, and PLGA. Figure 3 shows the carbonyl regions of these NMR spectra at 169–170 ppm. In Figure 3, PLLA and PDLLA were prepared by a process similar to that of PLGA preparation. In the spectra of PLGA, a new peak at 169.44 ppm appears and increases with GA fraction, which could result from LG (L-LA linked with GA) units. The assignments of signals, attributed to the isotactic (i) and syndiotactic (s) sequences of the
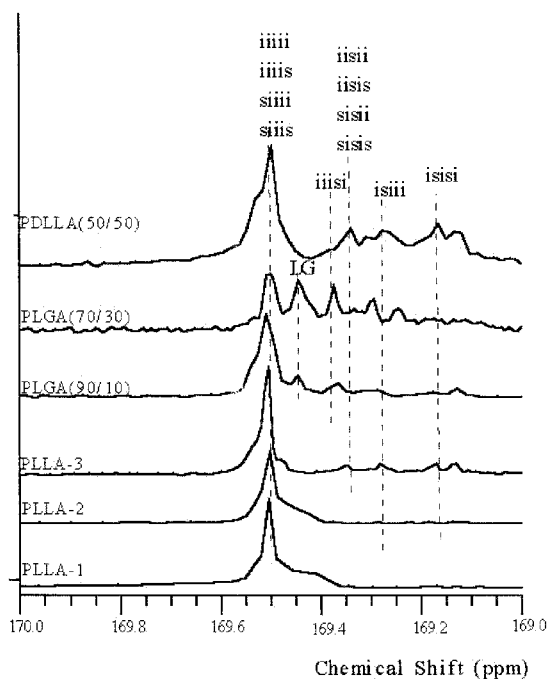
Figure 3 Carbonyl regions of ^{13}C-NMR spectra of PLLA, PDLLA, and PLGA: (i) isotactic, (s) syndiotactic.

Figure 4 Dependency of the glass-transition temperature and the degree of crystallinity of as-polymerized PLGA on the copolymer composition.

lactate units, are shown in Figure 3 according to the literature on PLLA, PDLLA, and poly(L-lactide-*co*-glycolide).[5,7,9,10,12,14] The degrees of racemization of polymer were calculated from the integral ratio of isotactic and syndiotactic sequence signals. It is known from the literature[5,7,9,10,12,14] that all signals for the spectra of PLLA, PDLLA, and poly(L-lactide-*co*-glycolide), from 169.0 to 169.4 ppm, are attributed to racemization. Compared with the spectra of PLGA (90/10) and PLGA (70/30) at 169.0–169.4 ppm, as shown in Figure 3, the intensities of carbon signals of PLGA (70/30), attributed to the racemic units, increase with GA fractions. The degree of racemization of PLGA (70/30) was higher than that of PLGA (90/10), which indicates that the addition of GA would increase the racemization of LA units. The relationships between degree of racemization and melting temperature of polymer are shown in Table II.
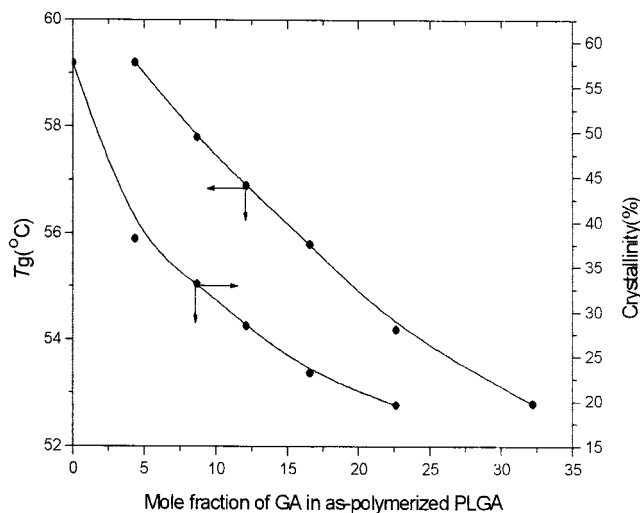
In Table II, the melting temperature of polymer clearly decreases with increasing degree of racemization. In comparison with the effect of different compositions of PLGA on the melting point of polymer, as shown in Table I, the effect of the degree of racemization of polymer is much more limited.

The mole fraction of GA units in PLGA also affects the glass-transition temperature and the degree of crystallinity. As shown in Figure 4, both the glass-transition temperature and the degree of crystallinity of as-polymerized PLGA decrease with increasing mole fraction of GA units in PLGA. This result is consistent with the ROP method for PLGA.[8]

Solubility of PLGA in chloroform

Effects of reaction time on PLGA solubility in chloroform were studied in detail. It was found that the solubility of PLGA decreases with reaction time at first. After the L-LA/GA oligomer was polymerized for 6 h, PLGA has the least solubility in chloroform. In the meantime, along with increasing reaction time,

TABLE II
Relation Between Racemization and Melting Point of Polymer[a]

	Sample[b]							
	PLLA-1	PLLA-2	PLLA-3	PLLA-4	PLGA-1 (90/10)	PLGA-2 (90/10)	PLGA-3 (90/10)	PLGA-4 (90/10)
Racemization (%)	0.0	6.76	19.4	40.0	12.5	17.5	29.3	34.5
T_m (°C)	156.4	155.7	149.6	ND	119.4	118.2	116.3	112.6
Mole % GA in PLGA	—	—	—	—	11.90	11.76	12.12	11.24

[a] Racemization (%) was calculated from carbonyl signals in ^{13}C-NMR; mole % GA in PLGA was calculated from ^{1}H-NMR.
[b] Samples were prepared under different reaction times and temperatures.

PLGA solubility increases again, and eventually it becomes soluble in chloroform.

The carbonyl carbon signal in ^{13}C-NMR is more suitable for analyzing unit lengths in copolymers because it is more sensitive to sequence effect than other signals such as methyl, methylene, and methine.[6,12] Figure 5 shows the carbonyl regions at 165–170 ppm of typical ^{13}C-NMR spectra of PLGA. In PLGA spectra, the carbonyl signals of GA units at 166.40 ppm show two peaks attributed to GG (GA linked with GA) and GL (GA linked with L-LA) units, respectively.[6,7,9,10,12] From the intensity ratios of the two carbonyl signals, the average lengths of GA units (L_G) and L-LA units (L_L) were calculated according to eqs. (2) and (3)[19]:

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

$$L_G = \frac{I_{GG} + I_{GL}}{I_{GL}} \quad (3)$$

where I_{LL} is the integral of carbonyl signals of LA units linked with LA and I_{LG} is the integral of carbonyl signals of LA units linked with GA. I_{GG} is the integral of carbonyl signals of GA units linked with GA and I_{GL} is the integral of carbonyl signals of GA units linked with L-LA.

Results of the average sequence lengths of PLGA are shown in Table III. The random copolymers of L-LA/GA, through direct melt polycondensation, may possess random sequences with an L_G value of about 1.[20] However, all the values of the lengths of GA units, after different reaction times are much greater than 1, which implies that the present reaction conditions ob-
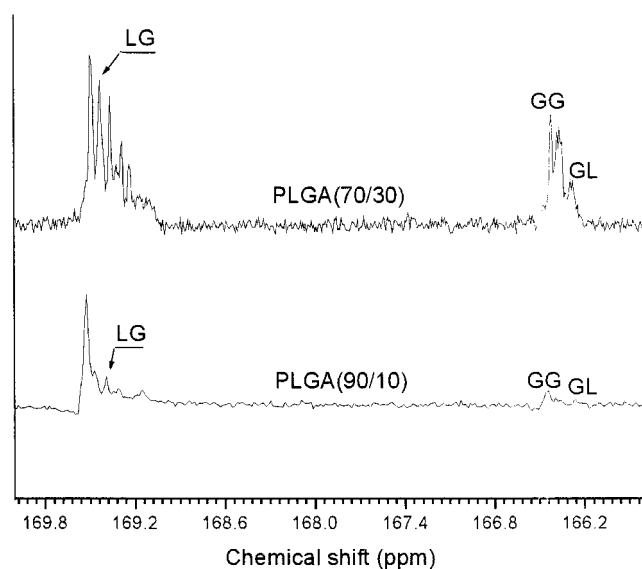
TABLE III
Average Sequence Lengths of PLGA (90/10) After Different Reaction Times

Sample[a]	$f_G{}^{b}$ (%)	$F_G{}^{c}$ (%)	Reaction time (h)	Average sequence length[d]	
				L_L	L_G
PLGA-h3 (90/10)	10.0	12.58	3	6.53	2.52
PLGA-h6 (90/10)	10.0	16.72	6	6.70	4.60
PLGA-h9 (90/10)	10.0	14.17	9	11.25	3.71
PLGA-h12 (90/10)	10.0	13.80	12	17.52	2.84
PLGA-h15 (90/10)	10.0	12.12	15	17.47	2.40

[a] Samples were prepared as follows: the first step (to make oligomer) was the same for all PLGA samples, while reaction time of the second step was changed. Reaction temperature of all samples of PLGA was 180°C. The value of L_L of oligomer was 6.40 and the value of L_G of oligomer was not detected.
[b] Molar fraction of GA in feed.
[c] Molar fraction of GA in copolymers calculated from ^{1}H-NMR.
[d] Calculated from ^{13}C-NMR.

viously give a sequential block copolymer of L-LA/GA instead of a random copolymer. In the ROP route for copolymerization of glycolide with L,L-dilactide, truly random sequences in the resultant PLGA also were never obtained by Kricheldorf.[9]

As shown in Table III, when the reaction time was 3–6 h, L_G increased quickly from 2.52 to 4.60 but with little change of L_L. With increasing reaction time after 6 h, however, L_G decreased gradually from 4.60 to 2.40, whereas L_L increased sharply from 6.70 to 17.52 initially and then had a small decrease in the case of the reaction times of 15 h. This suggests that GA has a higher reactivity compared with that of L-LA. Thus in copolymerization of L-LA with GA, the GA moiety can be polymerized preferentially, which leads to the formation of long GA blocks at first and results in the largest value of L_G. Therefore, the copolymer of PLGA prepared at a short reaction time has poor solubility in chloroform. With increasing reaction time, L-LA can be built in as GA is depleted. It can also be found, from the decrease of F_G, that the fractions of L-LA in copolymers increased. Over time, the lengths of the GA units in copolymers slowly decreased continuously and eventually would be equilibrated by a transesterification reaction. It is well known that poly(glycolide) and copolymers of glycolide, with long glycolide monomeric units, are usually insoluble in most common solvents including chloroform. The racemization and shortening length of GA units result in increasing solubility of PLGA in chloroform.

Figure 5 ^{13}C-NMR spectra (125 MHz) of PLGA (carbonyl region) obtained in CDCl$_3$ solutions.

CONCLUSIONS

A series of copolymerizations of L-LA and GA was prepared by direct melt polycondensation. In this case, the heat of fusion, melting temperature, glass-transition temperature, and crystallinity were strongly affected by compositions of PLGA. The melting temperature of PLGA decreased with increasing mole fraction of GA units in the copolymer. When the molar fraction of GA in the feed was greater than 30%, amorphous copolyester was formed because crystallization was reduced by the decrease of the lengths of L-LA units. On the other hand racemization, promoted by the addition of GA monomer, could also play an important role in the decrease of T_m and crystallinity of PLGA.[9] Thus the DSC measurements showed good agreement with the NMR sequence analysis. The mole fraction of GA units in PLGA had a similar effect on glass-transition temperature and heat of fusion of PLGA.

The solubility of PLGA in chloroform did not depend on the average lengths of the L-LA units (L_L) but mostly on the average lengths of the GA units (L_G) and decreased with the increase of L_G. With increasing reaction time, the solubility of PLGA decreased to a minimum at first and then increased. From the results of ^{1}H- and ^{13}C-NMR, GA showed higher reactivity in copolymerization than L-LA. From the results of sequence lengths of GA and L-LA, transesterification could occur during polymerization, and would decrease sequence lengths of GA and L-LA units. The reaction conditions described in this article would give sequential block copolymers instead of random copolymers of L-LA/GA.

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