Polymerization of Lactides and Lactones. II. Ring-Opening Polymerization of ε-Caprolactone and DL-Lactide by Organoacid Rare Earth Compounds

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ABSTRACT: Ring-opening polymerization of lactone and lactide have been initiated with rare earth organoacid compounds, such as lanthanum acetate in bulk. The polymerization mechanism is in agreement with the "nonionic–coordination–insertion" mechanism, which involves the selective cleavage of the acyl–oxygen bond of the monomer. These organoacid rare earth initiators can give high yield of medium to high molecular weight products. An interesting aspect of this investigation is the good agreement between the performance of the initiator and the solubility of the initiator in the monomer. However, the relatively slow initiation step makes it difficult to control the molecular weight and results in a broad molecular weight distributions. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 71: 1941–1948, 1999

Key words: lactones; organoacid rare earth compound initiators; ring-opening polymerization

INTRODUCTION

Based on a series of unique properties, such as biocompatibility, biodegradability, and permeability to many drugs, polylactides and polylactones are receiving increasing attention for applications in the biomedical field, for example, as biodegradable sutures, artificial skins, and implantable carriers for drug delivery systems.[1]

Aliphatic polyesters can be synthesized by ring-opening polymerization of lactones and lactides in the presence of initiators. In general, tin(II) salts especially, tin(II) octoate[2–5] are widely being used as initiators for the ring-opening polymerization of lactones and lactides. However, for biomedical applications, the clinical problem is the toxicity of tin(II) salts. Therefore, many efforts have been made to eliminate the heavy metal ions in biomaterials.[6–8]

In recent years, rare earth compounds such as yttrium isopropoxide and lanthanide alkoxides, lanthanocene hydride, and alkyl compounds had been used as initiators for the ring-opening polymerization of lactones.[9–12] These catalysts were very effective in the polymerization of lactones. However, the initiators were sensitive to trace amounts of water and oxygen, and were difficult to prepare and to store. We have been investigating the rare earth metal initiators[13] in our laboratory, to find some new kind of initiators.

The purpose of the present article is to investigate the ring-opening polymerization of lactones and lactides with rare earth organoacid compounds, and to discuss the mechanism of the polymerization.

EXPERIMENTAL

Monomer

D,L-Lactide with m.p. 125–127°C was synthesized according to literature procedures.[14] Crude products were recrystallized three times from ethyl

Table I   Bulk Polymerization of LA with (CH₃COO)₃La

No.	Monomer/Initiator (w/w)	Time (h)	Temperature (°C)	Yield (%)	M_η ($\times 10^4$)
1	50	24	140	28.3	1.50
2	100	24	140	35.0	2.47
3	250	24	140	66.0	3.00
4	500	24	140	22.0	2.88
5	1000	24	140	37.0	5.48
6	2000	24	140	83.6	1.33
7	5000	24	140	63.0	1.02
8	10000	24	140	69.3	0.86
9	100	5	180	50.9	3.13
10	250	5	180	50.9	2.74
11	500	5	180	43.2	2.24
12	1000	5	180	85.7	5.01

acetate. ε-Caprolactone was purchased from Aldrich, and dried over calcium hydride for 48 h at room temperature, and then distilled under reduced pressure in a nitrogen atmosphere prior to use. The monomer was dried for 24 h at 25°C under reduced pressure (5 mmHg) before polymerization.

Initiators

The rare earth organoacid compounds were prepared by modified literature procedures.[15–22] Ten grams of lanthanum oxide was mixed with 11.1 g of glacial acetic acid in 100 mL of water. This mixture was stirred and reacted at 90°C for 1 h. The precipitate of the reaction mixture was removed by filtration, and the filtrate was evaporated at 100°C. The obtained white solid was washed with 30 mL methyl alcohol several times, filtered, and dried in vacuum at 150°C for 15 h. The pure lanthanum acetate was obtained in a yield of 94%. Other rare earth organoacid compounds, such as lanthanum formate, lanthanum propanoate, p-tulutic acid lanthanum salt, lanthanum chloroacetate, lanthanum trichloroacetate, lanthanum succinate, lanthanum phosphate, lanthanum chloride, yttrium trichloroacetate, samarium trichloroacetate, and neodymium trichloroacetate, were prepared through analogous procedures.

Polymerization Procedure

Polymerization of lactones and lactides took place in bulk. Monomer and initiator were added into a dried glass reactor, previously flamed and nitrogen purged several times, and then sealed under reduced pressure (5 mmHg). The reaction was carried out at constant temperature for a desir-

able period of time. The reaction mixture was terminated by cooling it in water. The reaction product was then dissolved in acetone, filtered, and precipitated with an excess of methanol. The purified product was dried under vacuum at 40°C for 48 h.

NMR Measurements

^{1}H-NMR and ^{13}C-NMR spectra of polymer were recorded in CDCl₃ with a Bruker AC-P 300 MHz apparatus at 25°C.

IR Measurements

IR spectra were recorded on a NICOLET MX-1 IR apparatus.

Molecular Weight Determination

Molecular weight and molecular distribution were determined by GPC with a Water Associates Model ALC/GPC 244 apparatus at room temperature, using THF as the solvent, and calibrated with polystyrene standards. Intrinsic viscosity of poly(D,L-Lactide) was measured with an Ubbelohde viscometer at 37°C in THF, and viscosity average molecular weight (M_η) was calculated from the equation:[23] $[\eta] = 1.04 \times 10^{-4} M_\eta^{0.75}$

RESULTS AND DISCUSSION

Bulk Polymerization of D,L-Lactide (LA) with Lanthanum Acetate

The results of polymerization of LA with lanthanum acetate in bulk are summarized in Ta-

Figure 1   Effect of reaction time on the bulk polymerization of LA. Conditions: M/I = 2000, 160°C.

ble I. These results indicate that lanthanum acetate is effective for the ring-opening polymerization of LA. Yields of 85% can be obtained within 5–24 h. Also, high reaction temperature accelerates the polymerization. Increasing the reaction time from 16–48 h in the case of monomer/initiator (M/I) (w/w) ratio = 2000 at 160°C has little influence on yield, but the molecular weight decreases from 80,000 down to 5300 (Fig. 1). There is indication of back-biting degradation at the longer reaction time. The molecular weight (M_n) increases with the increase in the monomer/initiator ratio, but they do not paralled the M/I ratio, especially at a low M/I ratio. To deal with this phenomenon in detail,

polymerization of LA with lanthanum acetate at very low M/I ratio was conducted. The results are summarized in Table II.

$M_{n\text{theoretical}}^*$ in Table II is calculated according to literature method [eq. (1)],[26] assuming living polymerization. Table II shows molecular weight; there was a difference between the theoretical and measured, and the molecular distribution is wide. These results suggest that the propagation step was much faster than that the initiation step. Furthermore, we isolated the unreacted initiator from the polymerization mixture with low M/I ratio by dissolving it in acetone and filtration. We found that during the polymerization of LA, a M/I ratio of < 500, the unreacted initiator began

Table II   Bulk Polymerization of LA with (CH$_3$COO)$_3$La

No.	M/I (w/w)	Yield (%)	M_n^* ($\times 10^4$)	M_n ($\times 10^4$)	M_w ($\times 10^4$)	M_w/M_n
1	0.5	56.0	0.026	0.39	0.51	1.31
2	1.0	48.0	0.022	0.28	0.38	1.36
3	10	62.6	0.069	1.49	2.10	1.41
4	20	51.0	0.110	1.21	1.84	1.52
5	50	31.2	0.163	1.34	2.36	1.76
6	100	29.3	0.3045	1.59	2.92	1.84

Reaction condition: 160°C, 0.5 h.

Calculated from equal $M_n^* = \dfrac{315.9 W_{M_0} X}{3 W_{\text{Initiator}}}$ (1).

to increase. This problem will be discussed in a later section of this article.

Mechanism of Polymerization

When the polymerization is carried out at relatively low temperature (140°C) and long reaction times as shown in Table I, the molecular weight of PLA does not paralleled the M/I ratio. Based on these experimental facts, it is necessary to discuss the mechanism of polymerization. In the case of the polymerization of LA, two ways are possible: the cleavage of an acyl–oxygen bond, and the cleavage of an alkylmetal–oxygen bond of monomer, as shown in eq. (2).

$$\text{(2)}$$

According to H. R. Kriecheldorf,[24,25] polymerization of lactone and lactide with metal alkoxide and cyclic Bu$_2$Sn-derived initiators and the polymerization of LA with lanthanum acetate might be run through the following two ways [eqs. (3) and (4)].

Initiation:

Propagation:

$$\text{(3)}$$

Initiation:

Propagation:

$$\text{(4)}$$

The differentiation propagation involved between acyl–oxygen cleavage [eq. (3)] and alkyl–oxygen cleavage [eq. (4)] is difficult to achieve via kinetic methods, whereas the clearcut end-group analyses could enable to a reliable distinction of both mechanisms.[26] The two methods best suited for a reliable qualitative and even quantitative end-group analysis of various kinds of end-groups are IR and ^{1}H-NMR spectroscopy.

To determine the mechanism of the ring-opening polymerization of lactide, LA and lanthanum acetate were reacted in bulk at 180°C for 30 min, and the final products were quantitatively recovered, purified (see Experimental), and then analyzed by IR and ^{1}H-NMR spectroscopy. The IR spectrum shows an absorption at 3500 cm^{-1}, which is characteristic of the hydroxyl functions. The IR spectrum of PLA showed that the strong band at 1758 cm^{-1} corresponded to a C=O stretch. As a reference, the ^{1}H-NMR of lanthanum acetate shows a peak at 1.93 ppm, which is assigned to methyl protons of (CH$_3$COO)$_3$La. The ^{1}H-NMR spectrum of polylactide (PLA) initiated by lanthanum acetate shows peaks at 1.54 and 5.17 ppm, which are assigned to methyl and methylene protons of the PLA chains, respectively, but no absorption of methyl protons of the initiator is observed. These results indicate that by using lanthanum acetate, there is no end group of the initiator in the PLA. Also, the ^{13}C-NMR of PLA with lanthanum trichloroacetate shows no absorption of the initiator. The analytical results indicate the polymerization of LA cannot occur according to eq. (4). If the polymeriza-

Table III   Bulk Polymerization of LA with $(CCl_3COO)_3La$

No.	LA/Initiator (w/w)	Time (h)	Yield (%)	M_η ($\times 10^4$)
1	1000	2	85.9	8.97
2	2000	2	84.2	11.25
3	5000	2	61.3	5.92
4	2000	8	87.4	10.31
5	2000	16	87.2	9.97
6	2000	24	86.5	9.17
7	2000	30	87.5	8.57

Polymerization temperature: 160°C.

tion proceeds through eq. (4), the final product should have the structure: HO—C(O)—CH(CH₃)—[O—C(O)—CH(CH₃)]$_n$—O—C(O)—CH₃, and the end group —CH₃ should lead to the absorption at 1.93 ppm. Does the polymerization of LA with lanthanum acetate occur according to eq. (3)? The end groups are as follows: HO—CH(CH₃)—C(O)—O—[CH(CH₃)—C(O)—O]$_n$—C(O)—CH₃. However, from IR and NMR of PLA the absorption of the end group —C(O)—O—C(O)—CH₃ was not observed. It is well known that compounds of —C(O)—O—C(O)—CH₃ are unstable and easy to decompose. Even if such end groups would form during the polymerization, it is possible that they undergo decomposition at a high reaction temperature and in the presence of active —OH groups. Based on the above discussion, it is suggested that the polymerization of LA with lanthanum acetate proceeds through the cleavage of the acyl–oxygen bond of lactone to generate the highly reactive La—O bond. The chain propagation is in agreement with the nonionic insertion of monomer at the La—O bond. Due to the high coordination of rare earth metal, the La—O bonds derived from lactide units are weaker and more reactive.

Polymerization of LA with Other Organoacid Rare Earth Compounds

To investigate the effect of acidity on the polymerization of LA, some other organoacid rare earth compounds were used as initiators. A series of polymerization was first conducted with LA and lanthanum trichloroacetate. The polymerizations were conducted in bulk at 160°C. The results, summarized in Table III, allow the following conclusions.

First, the polymerization of LA with lanthanum trichloroacetate is faster than that of lanthanum acetate. Second, the maximum PLA molecular weight with lanthanum trichloroacetate is higher than that with the lanthanum acetate. Third, the yield of product with lanthanum trichloroacetate is slightly higher. These conclusions clearly indicate that the initiation efficiency of lanthanum trichloroacetate is higher than that of lanthanum acetate at the same reaction conditions. Similar to the polymerization of LA with lanthanum acetate, increasing polymerization time from 2 to 30 h in the case of an M/I ratio of 2000 has little influence on the yield, but has a desirable influence on molecular weight. In addition, the molecular weight of PLA with lanthanum trichloroacetate increases with the increase of the M/I ratio, but does not parallel the M/I ratio, which suggests that the mechanism of LA polymerization with lanthanum trichloroacetate is similar to the mechanism of LA polymerization with lanthanum acetate.

The results of polymerization of LA with lanthanum trichloroacetate indicate that the initiation efficiency of strong acid rare earth compounds is higher than that of the weak acid rare earth compounds. For a better understanding of this effect, polymerization of LA with other organoacid rare earth compounds was investigated. The polymerization time was selected to provide maximum yield. The results are summarized in Table IV.

There are obvious differences in the performance of different organoacid rare earth initiators. The rate of polymerization with strong organoacid rare earth compounds is faster than that with weak organoacid rare earth compounds. As a reference, some stronger acid rare earth compounds, such as lanthanum oxide, *p*-tulutic acid lanthanum salt, lanthanum chloride, and lanthanum phosphate were used as initiators for LA polymerization. The polymerization of LA with these initiators did not occur even at 160°C for 60 h, which indicates that not all strong organoacids can initiate the polymerization of lactones, and that only those containing the structure of —COOH could initiate polymerization of LA more effectively than a weak organoacid.

Effects of Different Rare Earth Metal on the Polymerization of LA

The ring-opening polymerizations of LA with different rare earth metal compounds were carried

Table IV   Polymerization of LA with Organoacid Rare Earth Compounds

No.	Initiator	LA/Initiator	Time (h)	Temperature (°C)	Yield (%)	M_η ($\times\ 10^4$)
1	(HCOO)$_3$La	500	4	160	78	4.6
2	(CH$_3$COO)$_3$La	500	5	160	74	4.1
3	(CH$_3$CH$_2$COO)$_3$La	500	8	160	61	3.8
4	(C$_7$H$_7$COO)$_3$La	500	5	160	78	4.3
5	(ClCH$_2$COO)$_3$La	500	2	160	84	6.1
6	(CCl$_3$COO)$_3$La	500	1	160	86	7.2
7	$\left(\begin{smallmatrix}CH_2COO\\ \mid\\ CH_2COO\end{smallmatrix}\right)_3La_2$	500	8	160	60	3.2

out at 160°C, and the results are summarized in Table V.

In general, the rare earth elements are divided into two groups: one is light rare earth elements, such as La, Ce, Pr, Nd, Sm; the other is heavy rare earth elements, such as Ho, Er, Y, et al. The results in Table V reveal that the initiation efficiency of light rare earth compounds is higher than that of heavy rare earth compounds.

Comparison of Reaction Rate Between ε-Caprolactone (CL) and LA

Kricheldorf[27] reported that cationic initiators, such as ferric chloride, boron trifluoride, and fuorosulfonic acid favor the incorporation of CL, but the complexing catalysts, such as zinc chloride, aluminum isopropylate, and dibutyltin dimethylate favor the incorporation of LA. It was also demonstrated that anionic catalysts, such as tetramethylammonium benzoate and benzyltriphenylphosphonium chloride, favor the incorporation of LA. To investigate the polymerization rate of LA and CL initiated by organoacid rare earth compounds, the polymerizations of CL and LA were carried out at the same reaction temperature and monomer/initiator ratio. The results are recorded in Table VI.

We found that the polymerization time for LA to reach maximum yield is shorter than that for CL, and the maximum yield and molecular weight of PLA are both higher than that of the CL.

Relation Between Solubility and Initiation Efficiency

Further studies showed that different initiators had different solubility in the monomer, which may also be related to the different performance during polymerization. To explain this phenomenon in detail, the solubility of organoacid rare earth initiators was compared as follows: (1) solubility of initiators in LA monomer:

$$(CCl_3COO)_3La > (ClCH_2COO)_3La > (HCOO)_3La$$
$$> (C_7H_7COO)_3La, (CH_3COO)_3La > (CH_3COO)_3La$$
$$(CCl_3COO)_3La > (ClCH_2COO)_3La > (HCOO)_3La$$
$$> (C_7H_7COO)_3La, (CH_3COO)_3La > (CH_3COO)_3La$$
$$> \left(\begin{smallmatrix}CH_2COO\\ \mid\\ CH_2COO\end{smallmatrix}\right)_3 La_2; (CCl_3COO)_3La$$
$$> (CCl_3COO)_3Nd > (CCl_3COO)_3Sm;$$

Table V   Bulk Polymerization of LA with Different Rare Earth Compounds

No.	Initiator	LA/Initiator	Time (h)	Temperature (°C)	Yield (%)	M_η ($\times\ 10^4$)
1	(CCl$_3$COO)$_3$Y	500	30	160	78	5.9
2	(CCl$_3$COO)$_3$La	500	1	160	86	7.2
3	(CCl$_3$COO)$_3$Sm	500	10	160	81	6.9
4	(CCl$_3$COO)$_3$Nd	500	11	160	81	7.1

Table VI   Bulk Polymerization of LA and CL

No.	Initiator	Monomer	Time (h)	Temperature (°C)	Yield (%)	M_η ($\times 10^4$)
1	$(CCl_3COO)_3La$	LA	1	160	86	7.2
2	$(CCl_3COO)_3La$	CL	2	160	88	3.4
3	$(CCl_3COO)_3Y$	LA	30	160	78	5.9
4	$(CCl_3COO)_3Y$	CL	36	160	80	2.9
5	$(CH_3COO)_3La$	LA	5	160	74	4.1
6	$(CH_3COO)_3La$	CL	12	160	68	2.1

and (2) the solubility difference of lanthanum trichloroacetate in CL and LA LA > CL The comparison above and the results shown in Table IV and V suggest that the initiation efficiency increases with increasing solubility of initiators in monomer. During the polymerization of LA with organoacid rare earth compounds, unreacted initiator was found, especially at a lower M/I ratio, and even when M/I reached 0.5, high molecular weight polymer ($M_\eta = 2 \times 10^3$) was produced. These results indicate that only the dissolved part of initiator can take part in the polymerization. Because different organoacid rare earth compounds have different solubility in monomer, the performance of initiator is different. In other words, the higher the solubilities of initiators in monomer, the higher the initiation efficiency. For strong acid rare earth compounds, such as $(C_7H_7SO_3)_3La$, La_2O_3, $LaCl_3$, $La(SO_4)_3$, $LaPO_4$, the polymerization can not occur even after 60 h because of their poor solubility in LA. The solubility of initiators in monomer is determined by the structure. The organoacid rare earth compounds usually contain the structure of —COO^-, which is similar to the structure of LA and other lactones; thus, these initiators have a limited solubility in monomer. With increasing acidity of the organoacid, initiator polarity leading to increased solubility hence increased initiation efficiency.

CONCLUSIONS

This study has shown that the polymerization of lactide and lactones can be efficiently initiated by organoacid rare earth compounds according to a "nonionic coordination-insertion" mechanism, which involves the selective cleavage of the acyl–oxygen bond of the monomer. The polymerization mechanism is in agreement with the reported results on the polymerization of lactide in the presence of cyclic Bu_2Sn-derived initiators, and is supported by ^{1}H-NMR and IR data. These organoacid rare earth initiators can give a high yield of medium to high molecular weight products when the polymerizations are conducted in bulk.

An interesting aspect of this investigation is the good agreement between the performance of the initiator and the solubility of the initiator in monomer. However, the relatively slow initiation step makes it difficult to control the molecular weight, and results in a broad molecular weight distributions.

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