ABA Type Copolymers of Lactide with Poly(ethylene glycol). Kinetic, Mechanistic, and Model Studies

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ABSTRACT: Block copolymers of lactide and poly(ethylene glycol) with various molar ratios were synthesized. Tin(II) bis(2-ethylhexanoate) has been used as a catalyst. Kinetic measurement and mechanistic studies suggest that the reactivity of the initiator, a hydroxyl group bearing reagent, is an important parameter on the polymerization course. In the case of primary and secondary alcohols, i.e., poly(ethylene glycol) and methyl lactate, it is found that when the initiator concentration exceeds the catalyst concentration, the number of chains formed exceeds the number of catalyst molecules. The chains are propagated through shifts of catalysts from one chain to another. In the case of tertiary alcohols, it appears that the number of chains formed is about the number of catalyst molecules. Therefore, by choosing an appropriate initiator, reaction course and molecular weight as well as molecular weight distribution can be designed. A model based on the assumptions of fast initiation reaction and random propagation reaction is established. Both initiator and catalyst are found to have an influence on the increase of molecular weight and molecular weight distribution.

Introduction

Numerous studies have been devoted to the syntheses, properties, and processing of biodegradable thermoplastics such as poly(ϵ-caprolactone), poly(L-lactide) (PLLA), and poly(3-hydroxybutyrate) (PHB).[1-3] The prime objective of these studies was to develop environmentally friendly polymers for agricultural, marine, and medical applications.[4-7] Biodegradable copolymers were also extensively investigated.[8,9] Copolymerization was usually performed to improve the processability and mechanical properties of these degradable polymers. More recently, the synthesis of low molecular weight block copolymers containing biodegradable sequences has attracted more attention.[10-12] For instance, ABA type copolymers of lactide and poly(ethylene glycol) were synthesized by several research groups.[4,9,13-15] These block copolymers have been used as compatibilizers and as precursor polymers for the synthesis of biodegradable elastomers and thermosets.[7,10,11,16,17] Researches on copolymerization using Al, Zn, and Sn compounds as catalysts have been published.[4,12,18,19] Concerning the reaction using a Sn compound as a catalyst, several reaction mechanisms were proposed.[19-21] However, due to insufficient key experimental data, it is virtually impossible to distinguish among the proposed reaction mechanisms.[20-23] Although it is well established that hydroxyl groups initiate the lactone polymerization,[1,21,24] carefully designed kinetic study was necessary to investigate the reaction mechanism. In this paper, kinetic measurements using high-resolution NMR spectroscopy have been carried out. A comparison between the experimental data and theoretical calculations based on the model gives good support to the proposed mechanism.

Experimental Section

Materials. L-Lactide and D,L-lactide were purchased from Purac Biochem BV (Gorinchem, The Netherlands). They were recrystallized from ethyl acetate and dried in vacuum (0.2 mmHg) over P_4O_{10}. Poly(ethylene glycol)s with molecular weights of 600 (PEG600), 1000 (PEG1000), and 2000 (PEG2000) were purchased from Aldrich Chemical Co. (Milwaukee, WI). Before use they were vacuum dried (0.2 mmHg) around 80 °C for 30 min. Tin(II) bis(2-ethylhexanoate) (Sigma Chemical Co., St. Louis, MO) was used as received. Pinacol (Aldrich), 2,3-butanediol, methyl (*S*)-(−)-lactate (Janssen, Geel, Belgium), and *tert*-butyl alcohol (E. Merck, Darmstadt, Germany) were dried before use.

Polymerizations. An example of a polymerization is given here. Under nitrogen, PEG1000 (15.00 g, 15 mmol) was introduced to a 50-mL three-necked flask equipped with a stirrer. The system was vacuum dried at 80 °C for 30 min. The flask was then purged with nitrogen and heated to 120 °C in an oil bath. Under nitrogen, lactide (10.80 g, 75 mmol) was charged into the flask. After the solid was molten, tin(II) bis(2-ethylhexanoate) (0.061 g, 0.15 mmol) was subsequently introduced into the flask and the time was recorded as the beginning point. At predetermined times samples were collected and analyzed immediately by ^{1}H NMR spectroscopy.

If the molar ratio of lactide over PEG was more than 15, the experimental procedure was slightly different. In this case the lactide was first molten and then added to the flask with predried PEG. After that the catalyst was added.

If initiators other than PEGs were used, the polymerization procedure was changed by adding the lactide to a flask. The lactide was dried at 80 °C in vacuum for 30 min and heated to the polymerization temperature. After that the initiator and the catalyst were added.

Characterizations. ^{1}H NMR spectra were recorded on a Bruker AM-400 NMR spectrometer. Conversion of the polymer was calculated from the relative intensities of the monomer and polymer methine quartet at 5.03 and 5.16 ppm or the methyl doublets at 1.59 and 1.69 ppm. A tetramethylsilane (TMS) signal was taken as the zero chemical shift.

IR spectra were measured using a Mattson Polaris FT-IR spectrometer with KBr pellets.

Molecular weights were determined using a Waters Associates GPC with tetrahydrofuran as the eluent. Calibration was carried out with polystyrene standards (Polymer Laboratories, Church Stretton, Shropshire, U.K.) in the range of 500−66 000.

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Scheme 1. Block Copolymerization of Lactide and Poly(ethylene glycol)

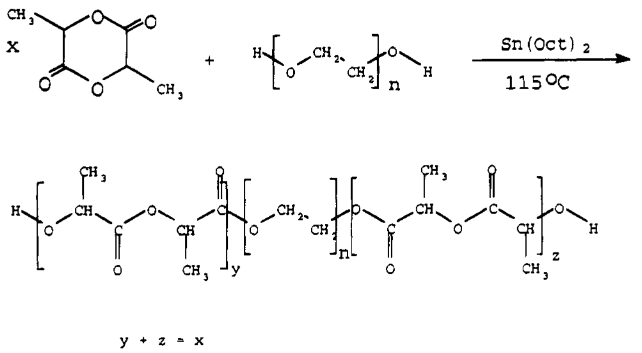


Table 1. Copolymers of Lactide and PEG in Various Molar Ratios (Polymerization Temperature, 115 °C; Catalyst, Sn(oct)$_2$ (1 mol% of the Hydroxyl Group in PEG))

mol wt of PEG	lactide	lactide/ copolymer[a] ratio	degree of polymn of lactide in copolymer[b]	properties of copolymer
1000	L	1/5	1/4.9	viscous
1000	D,L	1/5	1/4.8	viscous
1000	D,L	1/15	1/14.7	solid
1000	L	1/40	1/39.7	solid
2000	D,L	1/5	1/4.9	solid
150	D,L	1/5	1/4.8	liquid
500	D,L	1/4	1/4.7	liquid
600	D,L	1/10	1/9.8	waxy liquid
600	D,L	1/20	1/19.7	solid
600	L	1/3	1/2.9	liquid
600	L	1/20	1/19.6	solid

[a] Molar ratio of lactide over PEG. [b] Determined by ^{1}H NMR spectroscopy.

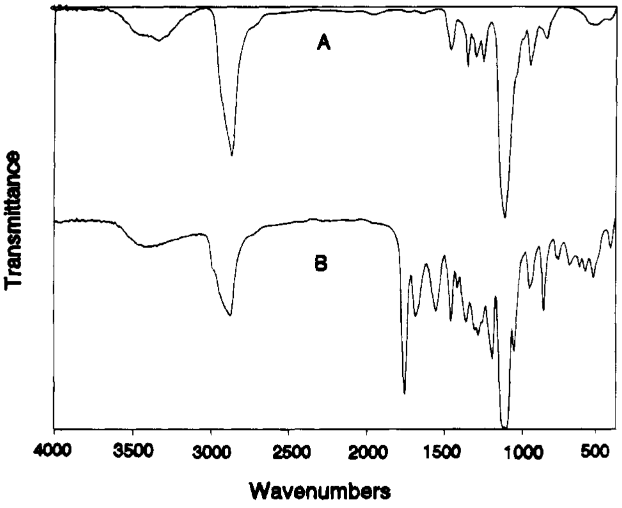


Figure 1. FTIR spectrum of PEG1000 (A) and the copolymer of PEG1000 with lactide (B). Absorbance at 1800 cm^{-1} in the copolymer confirms the presence of an ester structure.

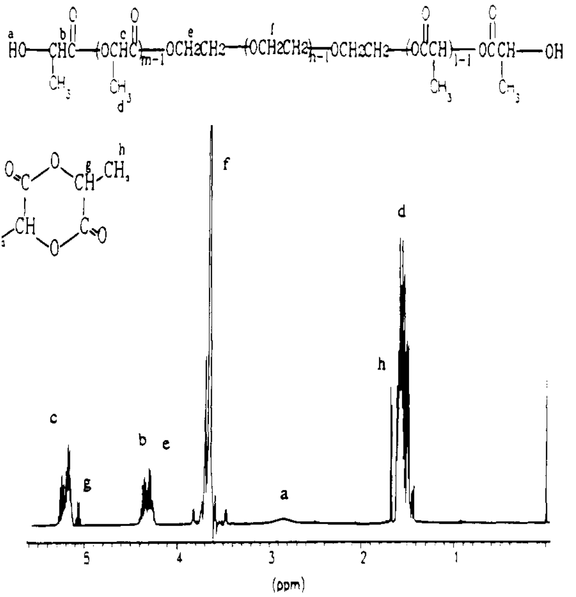


Figure 2. Proton NMR spectroscopy of the copolymer of poly[lactide-*b*-(ethylene glycol)] with a molar ratio of lactide to PEG1000 as 5:1. Polymerization temperature was 113 °C. The catalyst was Sn(oct)$_2$.

The column used was a PL gel (Polymer Laboratories) 1000 Å + 500 Å column combination. The flow rate was 1 mL/min.

Results and Discussion

Characterization of the Copolymer. The copolymerization is illustrated in Scheme 1. Various molar ratios of lactide to poly(ethylene glycol) have been used (Table 1). Molecular weights of the final copolymers, as determined by ^{1}H NMR, are in good agreement with that derived from the molar feed ratio. Figure 1 shows the IR spectrum of PEG1000 and a copolymer of molar ratio 1 to 5.0 of PEG1000 vs lactide. The absorption band at 1800 cm^{-1} indicates the ester group in the lactide unit. The linkage of PEG with lactide is confirmed by ^{1}H NMR (Figure 2). In Figure 2, the peak b + e at 4.3 ppm includes one methine proton and two methylene protons per chain end. One-sixth of the integration of this peak equals the number of chains. The peak f at 3.7 ppm belongs to those methylene protons of PEG which were not a direct neighbor to its end groups. Thus the apparent degree of polymerization (ADP) of the PEG is

$$\mathrm{ADP} = \frac{\left[f + \frac{2}{3}(b + e)\right]/4}{(b + e)/6} = 1 + \frac{3}{2}\frac{f}{b + e} \qquad (1)$$

where f, $(b + e)(2/3)$ and $(b + e)(1/6)$ denote the number of ethylene oxide protons, the number of methylene protons of PEG chain end monomers, and the number of chains, respectively. This apparent degree of polymerization was calculated to be 22.5. The degree of polymerization (DP) of PEG1000 has also been measured by end-group analysis through methacrylation modification of end groups.[25] Because this number is also 22.5, it indicates that the lactide was bonded to the PEG chain. Otherwise, ADP would be lower due to an increase of chain numbers.

The calculation above assumed that both chain ends of the PEG have been reacted. In order to confirm this, two reactions have been performed. First, the copolymer of L-lactide with PEG1000 of molar ratio 20:1 was extracted by alcohol at reflux for about 2 h. The ^{1}H NMR spectrum of the extracted polymer did not show a measurable change after the extraction. As alcohol dissolves PEG1000 in a few seconds, this confirms the copolymerization. Second, when the copolymer is methacrylated, the intensity at 4.3 ppm decreased to two-thirds of its original value.[25] Because methine proton shifts to lower field while the methylene protons remain unchanged, this suggests that the copolymer is of the ABA type. If an AM type copolymer was formed, the intensity would increase by one-third of its original value.

Kinetic Measurements. In this paper, in-situ observation of the polymerization by ^{1}H-NMR spectroscopy is used for kinetic and mechanistic studies. PEG of

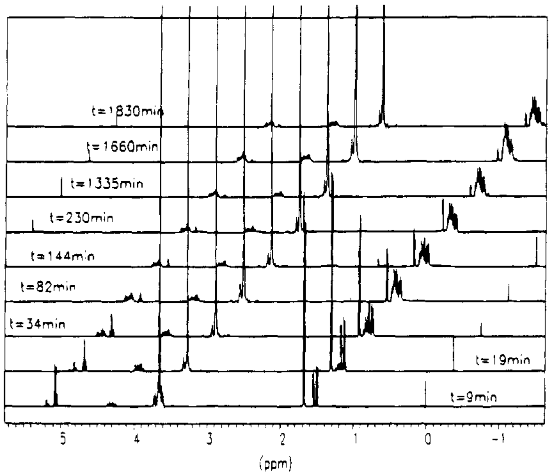


Figure 3. Kinetic measurement of the copolymerization of PEG1000 with lactide by ^{1}H NMR spectroscopy. Polymerization temperature was 113 °C. The catalyst was Sn(oct)$_2$, 0.01 mol equiv of the hydroxyl group of PEG.

Table 2. Conversion of Lactide and PEG1000 as a Function of Time at Polymerization Temperature 113 °C with Catalyst Sn(oct)$_2$ (0.01 mol equiv of Hydroxyl Group of PEG1000) and without Catalyst (Molar Ratio of Lactide to PEG1000 is 5:1)

a. With Catalyst Sn(oct)$_2$

	reaction time (h)								
	0.15	0.31	0.57	1.20	2.40	3.81	5.57	22.15	26.81
convn of lactide (%)	27.7	50.0	67.7	86.1	89.3	90.8	93.6	95.3	96.4
convn of PEG1000 (%)	49.4	91.0	96.6	100	100	100.0	100	100.0	100.0

b. Without Catalyst

	reaction time (h)								
	0.082	0.25	0.55	1.30	2.00	3.33	5.01	6.58	21.58
convn of lactide (%)	2.8	8.8	17.1	34.7	44.2	56.1	66.3	70.1	91.7
convn of PEG1000 (%)	5.2	23.1	39.6	66.8	77.8	94.9	100.0	100	100.0

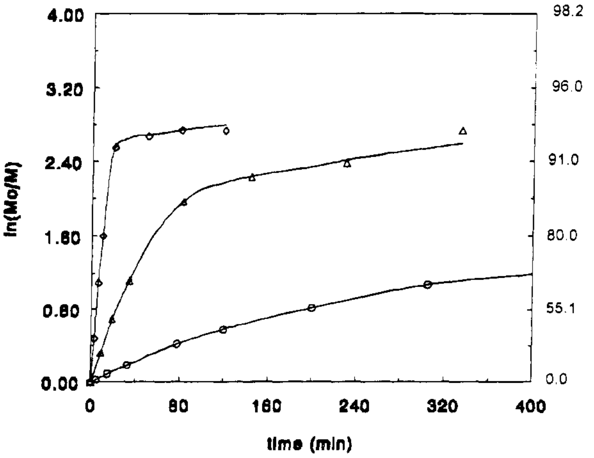


Figure 4. Logarithm of conversion and percentage conversion to polymer versus polymerization time. The polymerization temperature, molar ratio of lactide to PEG1000, and molar ratio of catalyst over the hydroxyl group of PEG1000 were as follows: (○) 113 °C, 5:1, no catalyst; (△) 113 °C, 5:1, 0.01 mol; (◇) 113 °C, 5:1, 0.05 mol.

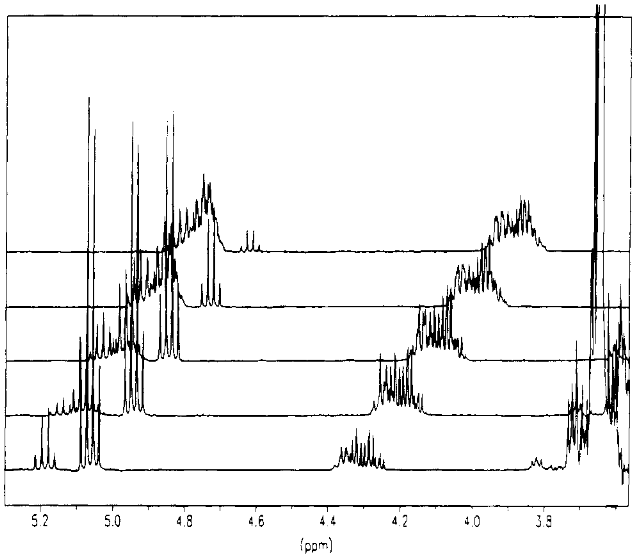


Figure 5. Change of the peak at 4.3 ppm of ^{1}H NMR spectroscopy during copolymerization of lactide and poly(ethylene glycol). Polymerization conditions as in Figure 3.

molecular weight 1000 is used for the kinetic studies. It is supposed that the mobility was not a controlling factor and the reaction at one end of the chain could not affect the reaction at the other chain end. Because PEG and polylactide are thought to be miscible in the amorphous phase[26] and because visually no phase separation is observed during the whole polymerization process, equal reactivity of both alcoholic chain ends is assumed.

Figure 3 shows the ^{1}H NMR spectra of the polymerization system during reaction at 113 °C. While the monomer concentration decreases as indicated by the peaks at 1.69 and 5.03 ppm, the polymer signals increase as seen from the peaks at 1.59 and 5.16 ppm. Table 2 lists some results of copolymerization of molar ratio 1 to 5.0 of poly(ethylene glycol) to lactide at 113 °C, both with and without a catalyst. Figure 4 shows the logarithm of monomer conversion versus polymerization time for the same system with an increasing concentration of Sn(oct)$_2$. It can be seen that, for the 66% conversion (to polymer), the uncatalyzed reaction takes ca. 300 min while the catalyzed reaction using 0.05 mol of Sn(oct)$_2$ equivalent to the hydroxyl group of PEG1000 takes 10 min. The linear relation between the logarithm of conversion of monomer, $\ln([M]_0/[M])$, and the reaction time at low conversion indicates that the reaction is first order in monomer. It assures that the supposition of independent reaction at two ends of the same chain is reasonable. The linear part of the uncatalyzed reaction reaches to ca. 40% of conversion, while the linear parts of catalyzed reactions reach to ca. 80% and 90% respectively for catalyst 0.01 and 0.05 mol equiv to the initiator. The rate constants obtained are 5.50×10^{-3} min^{-1} without catalyst and 3.45×10^{-2} 0.17 min^{-1} with catalyst.

The disappearance of the hydroxyl group in PEG can be monitored by measuring the intensity at 4.3 and 3.7 ppm in the ^{1}H NMR spectrum. The peaks at 4.3 ppm in the ^{1}H NMR spectra belong to the methine protons of lactide at chain end and methylene protons of PEG neighbor to the lactide unit. Figure 5 illustrates the change of the peak at 4.3 ppm during the reaction. The conversion of PEG can be calculated according to:

$$\text{conv of PEG (\%)} = \frac{\frac{1}{6}(b + e)}{\left[\frac{f}{4} + \frac{(b + e)}{6}\right]\frac{1}{\text{RU}}} \qquad (2)$$

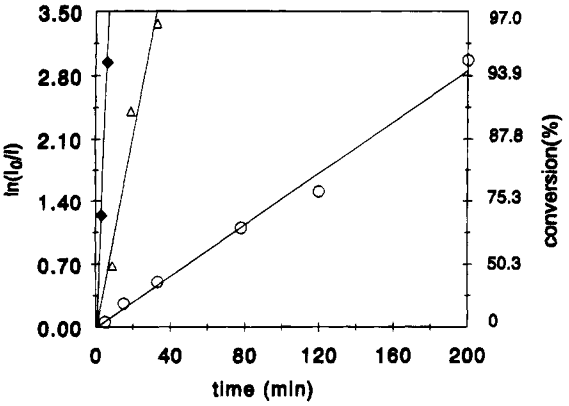


Figure 6. Logarithm and percentage consumption of PEG1000 versus time. Polymerization temperature of 113 °C: (○) no catalyst, (△) 0.01 mol of Sn(oct)$_2$, (◇) 0.05 mol equiv of Sn(oct)$_2$ to the hydroxyl group of PEG.

where *b*, *d*, and *e* are intensities of peaks defined in Figure 2, and RU is the number of repeating units of PEG. Figure 6 shows the logarithm of concentration of reacted PEG1000 (RU = 22.5) versus reaction time. From the linear correspondence it may be deduced that the reaction is first order in initiator. The rate constants are 1.42×10^{-2} min^{-1} without catalyst and 9.33×10^{-2} and 0.48 min^{-1} with catalyst 0.01 and 0.05 mol equiv to the hydroxyl group of the initiator.

If POL-OH stands for the PEG (a factor 2 has been considered), M stands for the lactides, the reaction may be written as:

$$\text{POL-OH} \xrightarrow[\text{M}]{k_0} \text{POL-MOH} \xrightarrow[\text{M}]{k_1} \text{POL-MMOH} \xrightarrow[\text{M}]{k_2} \xrightarrow[\text{M}]{k_3} \text{POL-MMMOH} \xrightarrow[\text{M}]{k_x} \quad (3)$$

Assuming that k_x is independent of the length of the growing chain, the kinetic equation without catalyst may be derived as:

$$-\text{d[M]/d}t = k_0[\text{POL-OH}][\text{M}] + k_x[\text{POL-MOH}][\text{M}] + k_x[\text{POL-MMOH}][\text{M}] + \ldots = \text{k}_0[\text{POL-OH}][\text{M}] + k_x\{[\text{POL-OH}]_0 - [\text{POL-OH}]\}[\text{M}] \quad (4)$$

where k_x denotes the propagating rate constant.

With a catalyst, the reaction may be a two-step reaction in which the catalyst first coordinates with lactide to activate the monomer. Then the activated monomer reacts with a hydroxyl group of PEG molecules.[21] The reaction may also be a termolecular reaction in which a lactide, catalyst, and hydroxyl group combine in the transition state. Although a termolecular reaction is very rare, there is no evidence to exclude such a reaction here. Both reactions give a similar apparent kinetic equation.

For a two-step reaction scheme, we have

$$\text{M} + \text{cat} \underset{k_{c-}}{\overset{k_{c+}}{\rightleftharpoons}} \text{M*cat} \quad (5)$$

$$\text{M*cat} + \text{POL-OH} \xrightarrow{k_0} \text{POL-MOH} \quad (6)$$

$$\text{M*cat} + \text{POL-M}_x\text{OH} \xrightarrow{k_x} \text{POL-M}_{x+1}\text{OH} \quad (7)$$

Suppose that reaction (5) is rapidly reversible such that reactions (6) and (7) become the rate-determining step and take into account that more propagation reactions may occur on one chain, then:

$$k_{c+}[\text{M}][\text{cat}] = k_{c-}[\text{M*cat}] \quad (8)$$

$$-\text{d[M]/d}t = \sum_{x=0} k_x[\text{M*cat}][\text{POL-M}_x\text{OH}] \quad (9)$$

Combination of (8) and (9) equals:

$$-\text{d[M]/d}t = \sum_{x=0}^{\infty} \frac{k_{c+}k_x}{k_{c-}}[\text{cat}][\text{POL-M}_x\text{OH}][\text{M}] \quad (10)$$

For a termolecular reaction, the following is directly available:

$$-\text{d[M]/d}t = \sum_{i=0}^{\infty} k_i[\text{cat}][\text{POL-M}_i\text{OH}][\text{M}] \quad (11)$$

where [POL-M$_i$OH] means the concentration of chains with degree of polymerization *i*.

Equation (11) is similar to (10). In the following derivation, (10) was used.

If initiation rate constant k_0 was the same as propagating rate constant k_x, the following is available:

$$-\text{d[M]/d}t = \sum_{x=0}^{\infty} \frac{k_{c+}k_x}{k_{c-}}[\text{cat}][\text{POL-M}_x\text{OH}][\text{M}] \approx k'[\text{cat}]\sum_{x=0}^{\infty}[\text{POL-M}_x\text{OH}][\text{M}] = k'[\text{cat}][\text{POL-OH}]_0[\text{M}] = k_{\text{M}}[\text{M}] \quad (12)$$

here k_0, k_1, k_2, ... are the rate constants of every step, and $k_0 = k_x$ (x = 1, 2, 3, ...). From the equation above, $\ln\{[\text{M}]/[\text{M}]_0\} = -k_{\text{M}}t$ could be obtained.

If $[\text{M}]_0 \gg [\text{POL-OH}]_0$, for example, 10 times larger, the change of the concentration of monomer was not important at the initial stage. Thus:

$$-\frac{\text{d[POL-OH]}}{\text{d}t} = \frac{k_{c+}k_0}{k_{c-}}[\text{cat}][\text{POL-OH}][\text{M}] = \frac{k_{c+}k_0}{k_{c-}}[\text{cat}] [\text{POL-OH}]\{[\text{M}]_0-[\text{POL-OH}]_0-\sum_{x=1}^{\infty}x[\text{POL-M}_x\text{OH}]) \approx k_0[\text{cat}][\text{POL-OH}][\text{M}]_0 = k_{\text{I}}[\text{POL-OH}] \quad (13)$$

that is, $\ln\{[\text{POL-OH}]/[\text{POL-OH}]_0\} = -k_{\text{I}}t$.

From (12) and (13) it can be said that reaction is first degree in [M] as well as [POL-OH] at lower conversion in accordance with the results observed. Further:

$$\frac{k_{\text{I}}}{k_{\text{M}}} = \frac{[\text{M}]_0}{[\text{POL-OH}]_0} \quad (14)$$

suggested that the rate constant ratio is dependent on the feed ratio. For the reaction with the molar ratio of monomer to initiator as 5:1, the experimental data of catalyzed reaction gives:

$$k_{\text{I}}/k_{\text{M}} = 9.33 \times 10^{-2}/3.45 \times 10^{-2} = 2.70$$

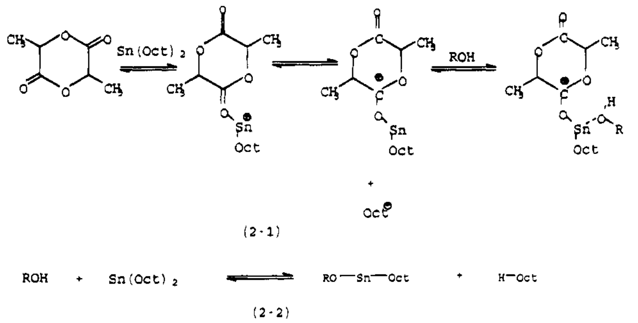
while $[\text{M}]_0/[\text{POL-OH}]_0 = 5.0/2 = 2.5$ (one poly(ethylene glycol) contains two hydroxyl groups). Here, $k_{\text{I}}/k_{\text{M}}$ is larger than $[\text{M}]_0/[\text{POL-OH}]_0$. This may be that, at the first stage, obvious deviations were introduced through the substitution of initiation rate constant k_0 for the propagation rate constant k_x in (12) and the substitution

Table 3. Rate Constants of Various Molar Ratios (PEG1000 as Initiator, $Sn(oct)_2$ as Catalyst, Lactide as Monomer; 1 mol of PEG Taken as 2 mol of POL-OH)

no.	lactide/ POL-OH	cat/ POL-OH	temp (°C)	k_M (min^{-1})	k_I (min^{-1})	k_I/k_M
1	2.5	0	113	5.5×10^{-3}	1.42×10^{-2}	2.50
2	2.5	0.010	113	3.45×10^{-2}	9.33×10^{-2}	2.70
3	2.5	0.050	113	0.17	0.48	2.80
4	20	0.011	117	3.50×10^{-2}	*c*	*c*
5	20	0.051	115	0.18	*c*	*c*

[a] Molar ratio of lactide over the hydroxyl end group of an initiator. [b] Molar ratio of catalyst over the hydroxyl end group of an initiator. [c] Could not be measured.

Scheme 2. Possible Intermediate Formed in the Polymerization System (Catalyst, Tin(II) Octoate; Monomer, Lactide; Initiator, Alcohol)



of $\{[M]_0 - [POL\text{-}OH]_0 - x[POL\text{-}M_xOH]\}$ by $[M]_0$ in (13) due to the propagation reactions.

When the molar ratio of monomer to initiator is high, the initiators would be consumed soon after the reaction starts. The effect would have a small contribution to the apparent rate constant. Table 3 lists the feed ratios and rate constant ratios.

Mechanism of Polymerization. The polymerization mechanisms of lactide with most stannous compound catalysts are still not clear.[1,21] Although the insertion to a Sn–alkoxy bond mechanism has been proposed for tin oxides, it is not fit for $Sn^{II}(oct)_2$ due to the fact that energetically unfavorable anhydride end groups would be formed.[21,27] In fact, it has been proven[22] that no end group other than a hydroxyl group was formed. Further, when tin halogen, tributyltin acetate, or thioacetate compounds were used as catalysts, hydroxyl-containing impurities were necessary to make the reaction proceed.[1,19,21,26–28] While the addition of acid did not affect the molecular weight, the addition of alcohols reduced the molecular weight greatly.[29]

From the discussion above, it is possible that the polymerization starts with the formation of a Sn–O linkage. In tin(II) bis(2-ethylhexanoate) catalyzed polymerization of lactide, this may occur through a combination of lactide to $Sn^{II}(oct)_2$ (Scheme 2, 2-1) or through a combination of alcohol with $Sn^{II}(oct)_2$ (Scheme 2, 2-2). Because p- or d-orbitals of Sn(II) molecules may coordinate to the carbonyl group in lactide,[21,30–33] Scheme 2 (2-1) is possible. Scheme 2 (2-2) also seems possible. The choice between these two needs more experimental details.

The chemical shift of the methyl protons, as shown in Figure 7, changes from δ 1.69 to δ 1.4–1.6 during polymerization. At the beginning of the reaction, two clearly separated doublets are present in the spectra. The doublets are the signals of the methyl protons of lactide bonded to the end groups of PEG. As the reaction proceeds the peaks become broadened and overlapped due to the increase of lactide unit in the chain. Up to 80–90% conversion of the initiator, little polymerization has taken place, as can be seen in Figure 3 at a reaction time of $t = 19$ min in the range of 1.51–1.63 ppm. As the ratio of initiator to catalyst is 100:1, this will lead to the conclusion that the catalyst shifted from one initiator to another. Table 1 shows that the degree of polymerization is in agreement with the feed ratio. Because no high molecular weight polymer was found by NMR and GPC at an earlier stage of the reaction, sudden chain growth is excluded. From Figures 4 and 6, it can be seen that at conversions of PEG1000, e.g., 95%, the conversions of lactide of both catalyzed and uncatalyzed polymerization are comparable, indicating that $Sn(oct)_2$ catalyzes both initiation and propagation processes. All these results confirm that the catalyst shifted between initiators as well as growing chains.

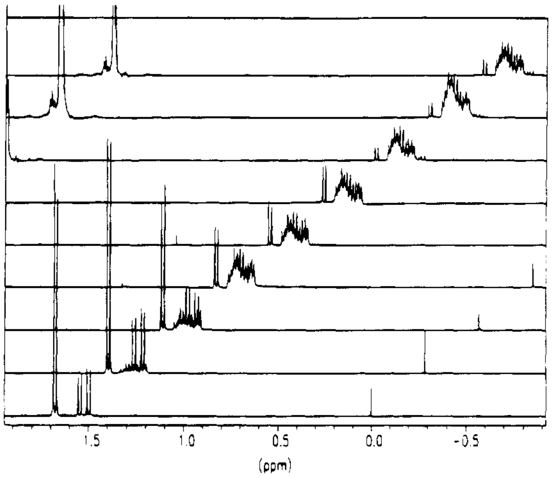
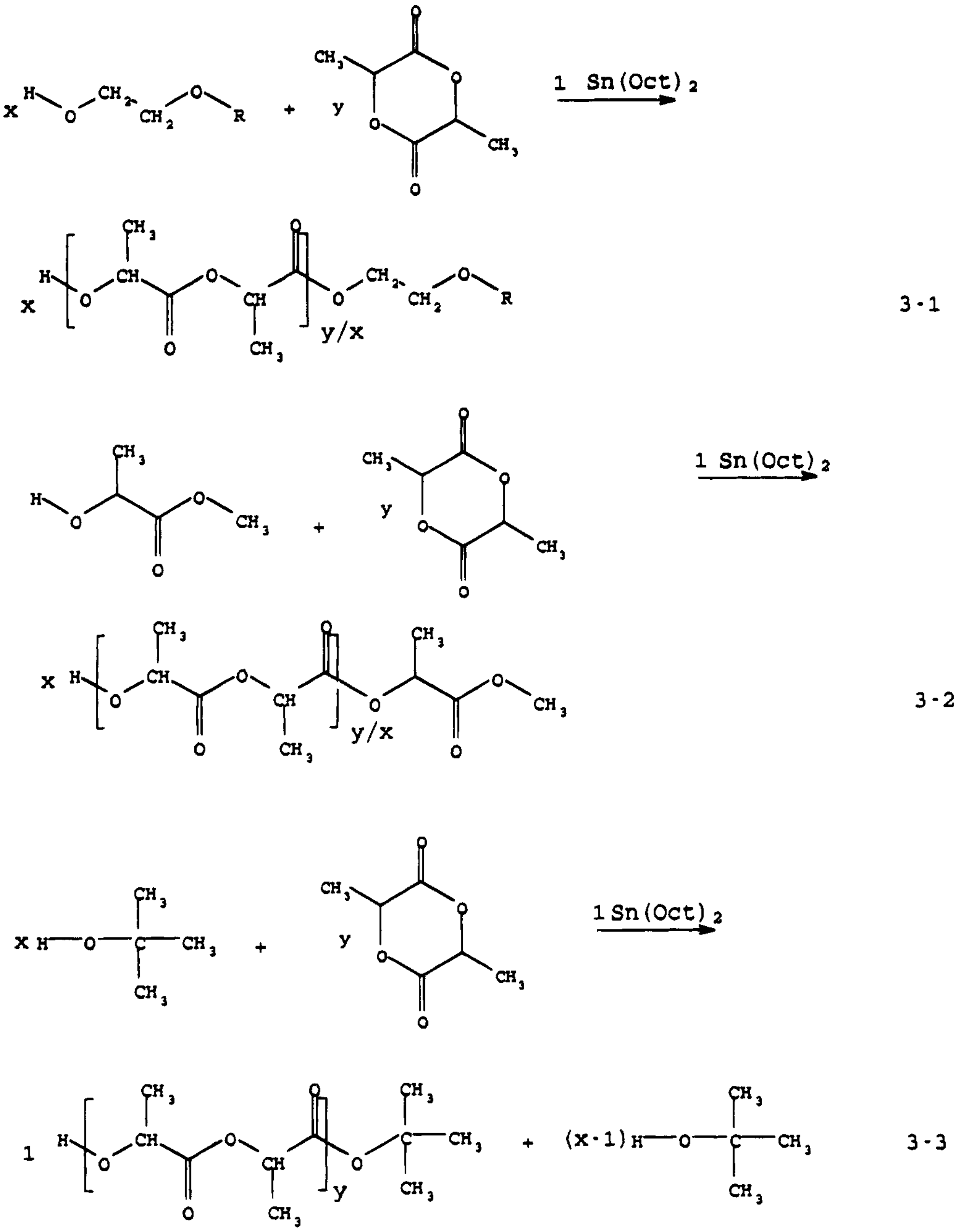


Figure 7. Change of intensity at the chemical shift of the methyl proton during polymerization. Polymerization temperature was 113 °C. The catalyst was $Sn(oct)_2$, 0.01 mol equiv to the hydroxyl group of PEG.

The consumption of initiator depends on the reactivity of the initiator. In this study primary alcohols (triethylene glycol and PEGs), secondary alcohols (methyl lactate and 2,3-butanediol), and tertiary alcohols (pinacol and *tert*-butyl alcohol) have been used as initiators. Scheme 3 illustrates the initiation reaction scheme. The primary alcohols were consumed fast. Only a little propagation was found before the primary alcohol was completely reacted, as already seen in Figures 4 and 6. The secondary alcohols were consumed slower than the primary ones. Figure 8 shows ^{1}H NMR spectra of the methyl lactate initiated polymerization course. The consumption of methyl lactate can be realized by investigating the change of peaks at 3.74 and 3.78 ppm. The singlet at 3.78 ppm denotes the methyl proton of methyl lactate before reaction, and the peak at 3.74 ppm denotes the one after reaction. Further, because the two doublets between 1.4 and 1.6 ppm, as seen in the first curve of Figure 7 which indicates the initiation reaction is prior to the propagation reaction, do not appear here, the propagation occurs at the primary stage. In fact, even the earliest sample showed a peak at 1.61 ppm which implied propagation. Because methyl lactate should have a reactivity similar to that of a propagating lactate end group, it leads to the conclusion that a intramolecular propagating process, i.e., the sudden chain growth, is not significant in these polymerizations. The tertiary alcohols reacted even more slowly. Pinacol did not go to initiation but instead rearranged to yield pinacolone. The water produced in the rearrangement initiated the reaction. *tert*-Butyl alcohol initiated the reaction slowly. Figure 9 displays ^{1}H NMR spectra of a *tert*-butyl alcohol initiated reaction. The singlets at

Scheme 3. Reaction of Lactide with Alcoholic Initiators of Different Types



1.45 and 1.27 ppm denote the reacted and unreacted initiator. It was seen that large amounts of initiator, indicated at 1.27 ppm, remained unreacted even after all of the monomers were consumed. This indicated that intermolecular propagating processes did not take place.

This reaction seems different from a normal step reaction, i.e., the condensation reaction, although a comparable mechanism has been suggested.[20] In the condensation polymerization, a polymer chain reacts with either a chain or a monomer. There is no active site in a real sense. But in the lactide polymerization, in one step only one monomer may be added to a chain. The maximum number of active sites does not change during reaction as the concentration of the initiator does not change.

In summary, the reaction is supposed to proceed along the mechanism illustrated in Scheme 4. When the lactide/catalyst complex meets a hydroxyl group ((1) of Scheme 4), reaction would takes place ((2), (3), and (4) of Scheme 4). Then, another lactide monomer will coordinate to the Sn atom to form a new complex ((5) of Scheme 4). This intermediate may react with the hydroxyl group via both intramolecular attack ((a) of Scheme 4) or intermolecular attack ((b) of Scheme 4) to have a chain growth or chain transfer growth. This process may last until all the monomer is consumed.

Thus, the dependence of the reaction mechanism on the initiator can be explained as follows. As the active chain ((6) of Scheme 4) may go to either an intramolecular or intermolecular reaction via (a) or (b) of Scheme 4, the reactivity of R-OH which may be an initiator or other chain without catalyst will influence the tendency. When the initiator is highly reactive, i.e., when R-OH is a primary alcohol, the reaction through an intermolecular process (b), i.e., chain transfer, will have high priority. In other words, the catalyst prefers to react with the initiator. When the initiation rate is comparable with the propagation rate, as in the case of methyl lactate, the choice between (a) and (b) is even. Both these two cases result in chain transfer growth on the chain. When the initiator is far less reactive, as in the case of *tert*-butyl alcohol, however, intermolecular processes (b) will not occur so that one catalyst can only react with one initiator, resulting in the chain growth

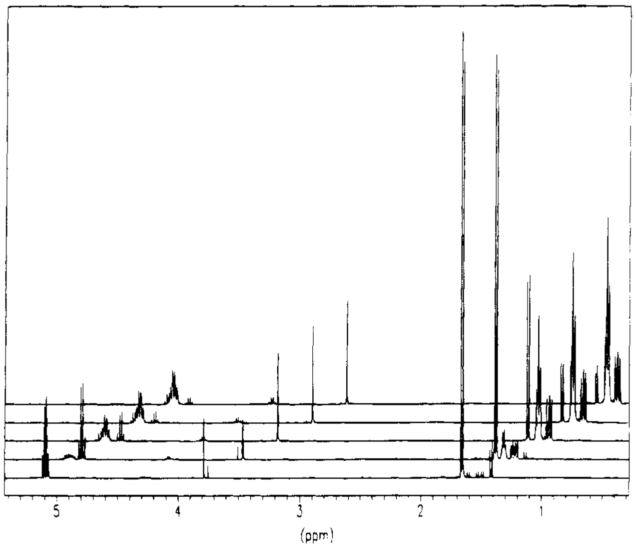


Figure 8. ^{1}H NMR spectra during polymerization of lactide initiated by methyl lactate. Polymerization temperature was 115 °C. The catalyst was Sn(oct)$_2$, 0.01 mol equiv to the initiator.

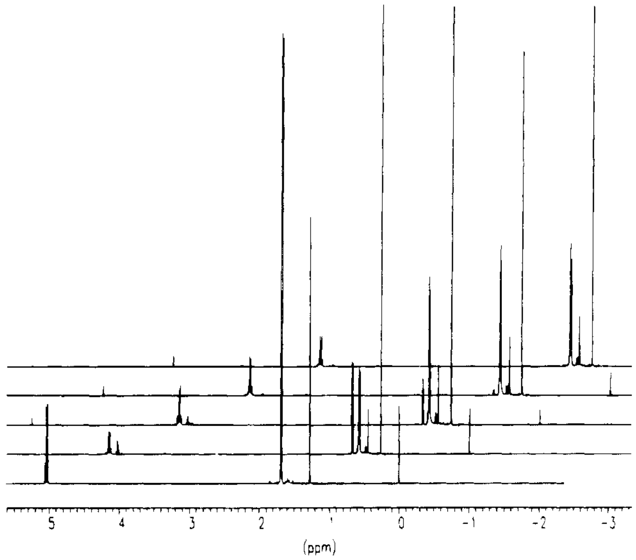


Figure 9. ^{1}H NMR spectra during polymerization of lactide initiated by *tert*-butyl alcohol. Polymerization temperature was 115 °C. The catalyst was Sn(oct)$_2$, 0.01 mol equiv to the initiator.

polymerization. Therefore, by choosing an appropriate initiator, reaction course and molecular weight as well as molecular weight distribution can be designed.

Modeling. Molecular weight[11,16,20,21] and molecular weight distribution[21] were reported to increase with conversion. Based on the supposed mechanism derived above, a simple model can be constructed to calculate molecular weight or molecular weight distribution versus conversion or reaction time. Thus, consider a system containing initiator molecules I, catalyst molecules C, and monomer molecules M. Suppose $[\mathrm{M}] \gg [\mathrm{I}] > [\mathrm{C}]$ and in each step there are [C] numbers of monomer M reacted with [C] numbers of I to produce polymer IM$_i$, where i is the number of time this I is chosen. The reaction occurs in such a way that at each step the [C] numbers of I are chosen randomly from [I] molecules of I. Suppose that the initiation rate is the same as the propagating rate; in this way, when all M are consumed, the average step of the reaction is

$$m_{\max} = [\mathrm{M}]/[\mathrm{C}] \tag{15}$$

The probability at each step an I was chosen is

$$P = [\mathrm{C}]/[\mathrm{I}] \tag{16}$$

The probability that i number of monomer M has reacted with an I at the mth step can then be written as:

$$P^i(1 - P)^{m-i} \tag{17}$$

Accounting for the number of ways I may be selected, the probability of finding i monomers in an I after the mth step equals

$$P_i = \frac{m!}{i!(m - i)!}P^i(1 - p)^{m-i} \tag{18}$$

(18) is nothing but the binomial distribution familiar to us. The statistical mean should be

$$M_i = \sum_{i=0}^{m}\{iP_i\} = mP \tag{19}$$

The number-average molecular weight should be

$$\bar{M}_\mathrm{n} = \frac{\sum_{i=0}^{m}\{n_i(M^0 + M_i)\}}{\sum_{i=0}^{m} n_i} = \sum_{i=0}^{m}\left\{\frac{n_i}{\sum_{i=0}^{m} n_i}(M^0 + M_i)\right\} = M^0 + \sum_{i=0}^{m}\{P_iM_i\} = M^0 + mPM \tag{20}$$

where n_i is the number of chains with i lactide units, $M_i = iM$ is its molecular weight, M is the molecular weight of lactide, and M^0 is the molecular weight of the initiator.

The weight-average molecular weight should be

$$\bar{M}_\mathrm{w} = \frac{\sum_{i=0}^{m}\{n_i(M^0 + M_i)^2\}}{\sum_{i=0}^{m}\{n_i(M^0 + M_i)\}} = M^0 + \frac{MM^0\sum_{i=0}^{m}(P_ii) + \sum_{i=0}^{m}\{P_ii^2M^2\}}{\sum_{i=0}^{m}\{M^0 + P_iM_i\}} M^0 + MmP + \frac{M^2mP(1-P)}{M^0 + MmP} \tag{21}$$

Thus:

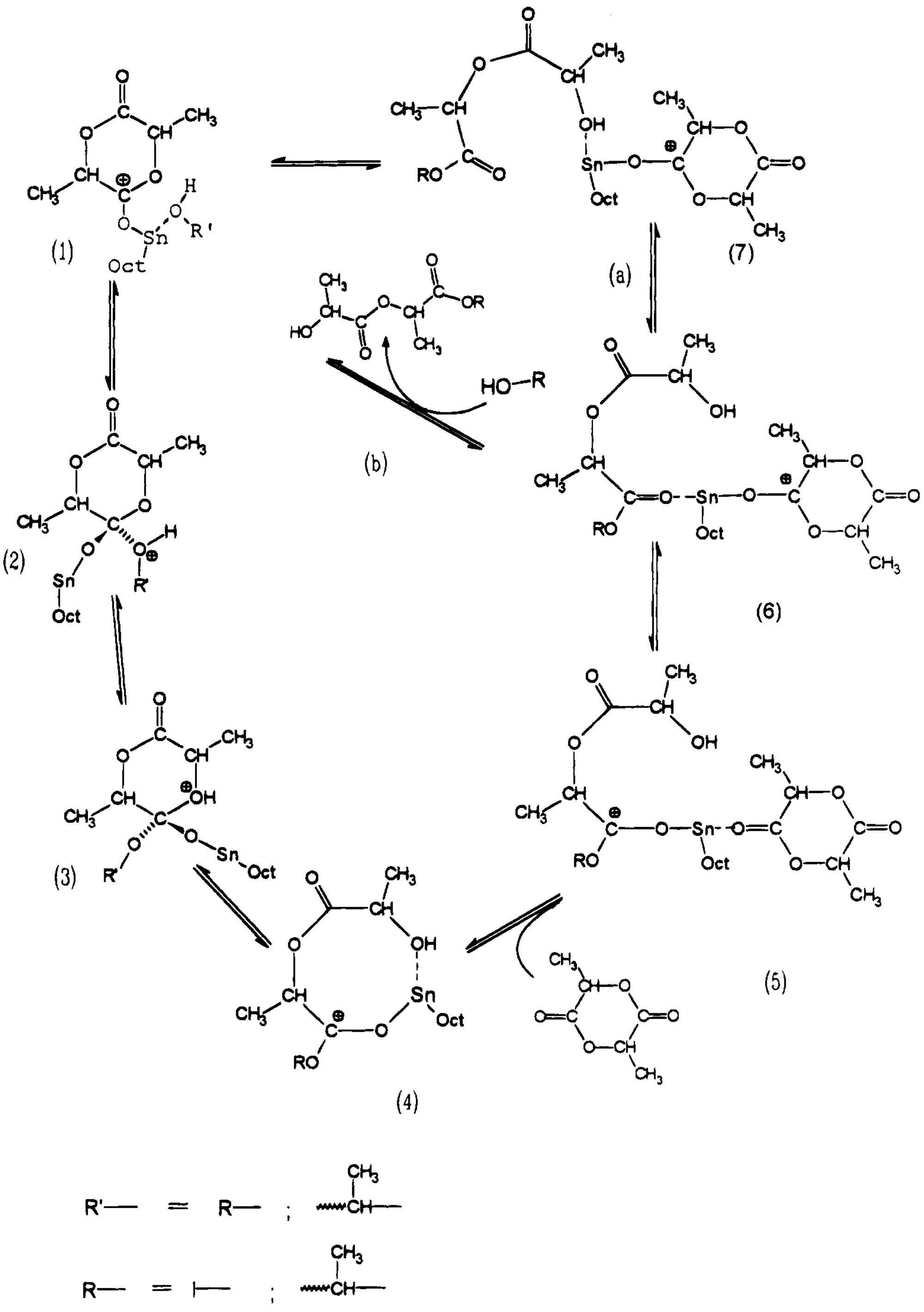
$$\frac{\bar{M}_\mathrm{w}}{\bar{M}_\mathrm{n}} = 1 + \frac{M^2mP(1-P)}{(M^0 + MmP)^2} \tag{22}$$

Knowing that

$$m = \frac{[\mathrm{M}]_0 - [\mathrm{M}]}{[\mathrm{C}]} \tag{23}$$

is the number of steps the reaction has gone, from (20) it can be seen that molecular weight changes with steps

Scheme 4. Reaction Mechanism of the Sn(oct)$_2$-Catalyzed Lactide Polymerization



of reaction, i.e., conversion of polymerization. In fact, substituting (16) and (23) into (20) and as it is known from (12) that $[M] = [M]_0 \exp\{-k_M t\}$, the following equation can be derived:

$$M_n = M^0 + \frac{[M]_0 - [M]}{[C]}\frac{[C]}{[I]}M = M^0 + \frac{[M]_0}{[I]}M(1 - e^{-k_M t}) \quad (24)$$

Figure 10 shows the molecular weight growth during polymerization as calculated from (24) and derived on the NMR experimental data. They are in fair agreement.

It is worth mentioning that, according to this model, growth of the molecular weight and molecular weight distribution not only changes with conversion but also changes with initiator and catalyst through their ratio P (eq 16). If the amount of catalyst is equal to that of initiator, monodisperse polymer is expected to occur.

This model is oversimplified. First, the possibility that a intramolecular growth process takes place is considered to be the same as that of the intermolecular growth process. If this is true, the growth of a monomer on one chain will not depend on whether the catalyst is previously bound on this chain. Second, the difference between initiation and propagation is ignored. Also, the ester–ester interchange, which has been claimed to be important in this polymerization,[34] is not considered. These factors will increase the molecular weight distribution and exert more influence when m becomes larger or P reaches its limit 1. Analysis including these effects will be found in a successive paper.

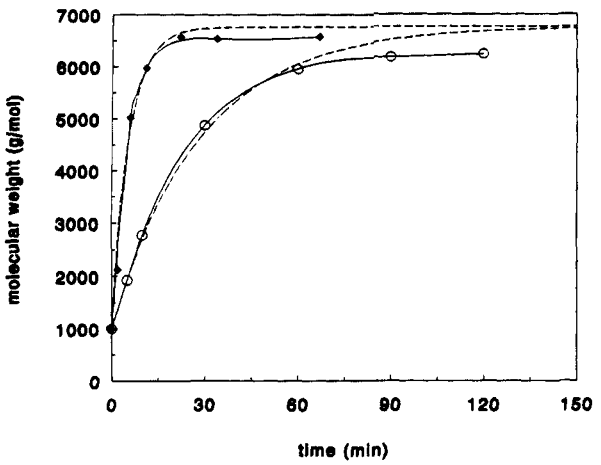


Figure 10. Molecular weight growth during polymerization. The dashed lines are drawn according to the model. The solid lines are drawn based on ^{1}H NMR spectroscopic data. Polymerization temperature and molar ratio of L-lactide:hydroxyl group of PEG1000:Sn(oct)$_2$ was (○) 117 °C, 20:1:0.011 and (◆) 115 °C, 20:1:0.051.

Conclusions

Kinetic measurements indicate that the polymerization is first order in the monomer at lower conversion and first order in the initiator. The active center is not bound to a single chain end when the reactivity of the initiator is high. Inter- and intramolecular propagating processes are determined by the reactivity of the initiator. Modeling of the reaction shows that growth of the molecular weight and molecular weight distribution not only depends on conversion but also depends on the initiator and catalyst.

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