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Synthesis of star-shaped poly(D,L-lactic acid-alt-glycolic acid) with multifunctional initiator and $SnOct_2$ catalyst

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Abstract

D,L-3-methylglycolide (MG) was successfully polymerized with multifunctional initiator (trimethylolpropane (TMP) or pentaerythritol (PTOL)) and stannous octoate ($SnOct_2$) catalyst in bulk at 110°C. The effects of molar ratios of monomer to initiator, monomer to catalyst and monomer conversion on the molecular weight of polymer were studied. For the homopolymerization of MG with TMP initiator and $SnOct_2$ catalyst, the molecular weight of polymer increases from 6840 to 35 010 with the molar ratio of monomer to initiator (45–450), and the molecular weight distribution is from 1.15 to 1.35. The results indicate that in the homopolymerization of MG, the molecular weight of polymer is proportional to the molar ratio of monomer to initiator and the monomer conversion. The molar ratio of monomer to catalyst has no influence on the molecular weight of polymer at least within the range of 500–4000. ^1H NMR spectra of the resulting polymers obtained from the homopolymerization of MG show that the homopolymerization of MG with TMP or PTOL initiator and $SnOct_2$ catalyst produced two types of three-arm or four-arm star-shaped polymers. The bulk ring-opening homopolymerization of MG proceeds through a "coordination–insertion" mechanism and follows the selective acyl–oxygen bond cleavage reaction. ^{13}C NMR spectroscopy indicates that the obtained poly(D,L-lactic acid-co-glycolic acid) (50:50, in molar ratio; D,L-PLGA50) has an alternating structures of lactyl and glycolyl units. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Multifunctional initiator; Ring-opening polymerization; Star-shaped poly(D,L-lactic acid-alt-glycolic acid)

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1. Introduction

Biodegradable aliphatic polyesters are increasingly investigated worldwide for pharmacological, biomedical, and environmental purposes [1–7]. Nowadays, the ring-opening polymerization of lactones and lactides is the method of choice for the production of biodegradable polymeric materials. Several metal complexes have been used as catalyst, especially metal carboxylates and alkoxides, such as stannous octoate ($SnOct_2$) and aluminum isopropoxide for the preparation of biodegradable aliphatic polyesters [8,9]. Among these metal complexes, $SnOct_2$ is the most widely used catalyst for research purposes and for the production of polylactones and polylactides because $SnOct_2$ is a highly efficient commercial catalyst and a permitted food additive in numerous countries [6,10]. However, $SnOct_2$ is not real initiator, but acts as Lewis acid catalyst to provide the ring-opening polymerization of lactones and lactides with a fast kinetics [11–14]. The Lewis acid catalyst would not be chemically bonded to the growing chains so that they can activate more than one chain. As a result, the molecular weight is not directly controlled by the molar ratio of monomer to catalyst, and the molecular weight distribution is broad. However, controlled polymerization has been achieved in using very dry systems with a controlled amount of a hydroxy-containing compound [15].

The well-defined macromolecular architecture provides a powerful tool to control or improve the polymer properties. Generally, star-shaped polymers can be prepared by two different routes: the "arm-first" [16] strategy and the "core-first" [17,18] approach on the basis of a multifunctional core used as initiator. Trollasas and Hedrick reported the synthesis of dendrimer-like star polylactone using a hexa hydroxy-functional compound initiator and $SnOct_2$ catalyst [19]. Arvanitoyannis et al. prepared the novel polylactides with aminohydroxymethylpropanediol or aminopropanediol initiator and $SnOct_2$ catalyst [20]. Kim et al. reported the

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Table 1
The results of the homopolymerization of MG with various amounts of TMP in bulk at 110°C and $[M]/[\mathrm{SnOct}_2] = 1000$, the polymerization time = 12 h

No.	$[M]/[I]$[a]	$M_{n,\mathrm{GPC}}$	$M_{n,\mathrm{th}}$[b]	$M_{n,\mathrm{NMR}}$	M_w/M_n[c]	Conversion (%)
1	45	6840	5580	5490	1.15	95.3
2	90	12 750	11 100	–	1.13	94.8
3	225	21 540	28 200	–	1.29	96.4
4	450	35 010	54 450	52 890	1.35	93.1

[a] M = MG, I = TMP.

[b] $M_{n,\mathrm{th}} = [M]/[I] \times M_{\mathrm{MG}} \times$ Conversion %, $M_{n,\mathrm{th}}$ denotes the number-average molecular weight of star-shaped D,L-PLGA50 copolymer.

[c] Weight-average molecular weight (M_w) and number-average molecular weight (M_n) are determined by GPC.

Table 2
The results of the homopolymerization of MG with various amounts of PTOL in bulk at 110°C and $[M]/[\mathrm{SnOct}_2] = 1000$, the polymerization time = 12 h

No.	$[M]/[I]$[a]	$M_{n,\mathrm{GPC}}$	$M_{n,\mathrm{th}}$	$M_{n,\mathrm{NMR}}$	M_w/M_n	Conversion %
1	50	7580	6480	6880	1.19	99.6
2	100	12 400	12 620	–	1.20	97.1
3	250	21 170	31 640	–	1.31	97.4
4	500	32 910	60 840	54 360	1.35	93.6

[a] M = MG; I = PTOL.

synthesis of star-shaped polylactide with pentaerythritol (PTOL) initiator and SnOct_2 catalyst [21,22]. Pennings et al. prepared the star-shaped polylactide-containing block copolymers by sequential melt ring-opening polymerization with PTOL initiator and SnOct_2 catalyst [23]. However, the process of polymerization has not been investigated in detail, and the essential characteristic of polymerization is not clear. In our previous paper, the homopolymerization of D,L-3-methylglycolide (MG) has been reported to give a linear poly(D,L-lactic acid-alt-glycolic acid) (50:50, in molar ratio; D,L-PLGA50) with SnOct_2 catalyst [24]. But, the molecular weight of polymer cannot be predicted by the molar ratio of monomer to catalyst, and the molecular weight distribution is broad (ratios of weight-average molecular weight (M_w) to number-average molecular weight (M_n): 1.5–2]. In this paper, we wish to report the homopolymerization of MG with multifunctional initiator such as trimethylolpropane (TMP) or PTOL and SnOct_2 catalyst and the star-shaped alternating D,L-PLGA50 copolymer thereof.

2. Experimental

2.1. Materials

SnOct_2 (Aldrich) was used as received. According to our previous paper [24], MG was synthesized via two step reactions with good yield. The first step is the synthesis of *O*-(2-bromopropionyl)glycolic acid via the acylation reaction of 2-bromopropionylbromide with glycolic acid, and the second step is the synthesis of MG via the cyclization reaction of the intermediate. Then, the crude product was recrystallized from dried ethyl acetate and toluene, respectively, and finally, sublimated under reduced pressure; the melting point of purified product was 62.5–63.5°C. The other reagents and solvents were local products. TMP (analytic reagent (AR)) was recrystallized from dried acetone, then dried for 12 h under reduced pressure. PTOL (AR) was sublimated under reduced pressure. Toluene was distilled from CaH_2 under N_2. Ethyl acetate and acetone were distilled from $\mathrm{P}_2\mathrm{O}_5$, respectively. Petroleum ether (distillation range: 60–90°C), methanol, and dichloromethane were used without further purification.

2.2. Methods

^{1}H NMR and ^{13}C NMR spectroscopy were performed on a Bruker ARX-400 spectrometer. Tetramethylsilane was used as an internal standard. Molecular weights and molecular weight distributions of the polymers were determined on a Waters 515 gel permeation chromatograph equipped with three Waters Styragel columns (HT2 + HT3 + HT4) at 35°C, THF as the eluent (1.0 ml/min), polystyrene as calibration standards, and Waters Millennium32 as data processing software.

2.3. Homopolymerization

The polymerization tubes were kept at 110°C for 24 h. About 5.0 mmol of MG, various amounts of TMP or PTOL, and a dry stirring bar were put into the warm tube quickly. The tube was then connected to a Schlenkline, where an exhausting–refilling process was repeated three times. The tube was put into an oil bath at 110°C with vigorous stirring after the exhausting–refilling process was carried out again to remove the toluene. After vigorous stirring for about 5 min, a certain amount of SnOct_2 in dry toluene was added to the melt mixture. The tube was cooled after the desired reaction time. The resulting product was dissolved in $\mathrm{CH}_2\mathrm{Cl}_2$, poured dropwise into an excess of petroleum ether, and finally shaked with methanol. The purified polymer was dried in vacuum until constant weight. Then, the monomer conversion was determined gravimetrically.

3. Results and discussion

3.1. The homopolymerization of methylglycolide

3.1.1. The effect of multifunctional initiator on polymerization

The homopolymerization of MG was carried out with multifunctional initiator (TMP or PTOL) and SnOct_2 catalyst in bulk at 110°C. The results of the homopolymerization using various amounts of initiator are compiled in Tables 1

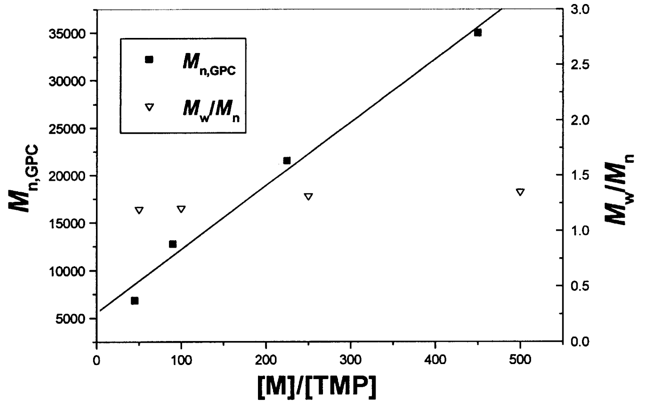


Fig. 1. Dependence of $M_{n,GPC}$ on the molar ratio of $[M]$/[TMP] with TMP initiator and $SnOct_2$ catalyst in bulk at 110°C.

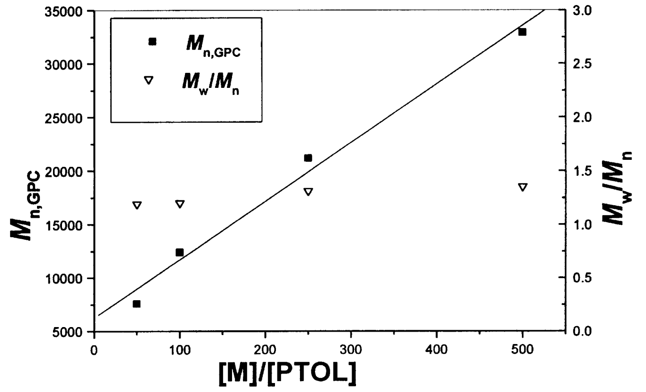


Fig. 2. Dependence of $M_{n,GPC}$ on the molar ratio of $[M]$/[PTOL] with PTOL initiator and $SnOct_2$ catalyst in bulk at 110°C.

and 2. It indicates that MG monomer can be completely consumed within 12 h. From Figs. 1 and 2, it is shown that the number-average molecular weight ($M_{n,GPC}$) of the obtained D,L-PLGA50 copolymer linearly increases with the molar ratio of monomer to initiator ($[M]/[I]$), and the molecular weight distribution is rather narrow (from 1.13 to 1.35). The $M_{n,NMR}$ is consistent with the $M_{n,th}$, $M_{n,th} = [M]/[I] \times M_{MG} \times$ Conversion%. This indicates that the molecular weight of the D,L-PLGA50 copolymer can be accurately predicted by the molar ratio of monomer to initiator and the monomer conversion and that the obtained D,L-PLGA50 copolymer has three or four arms. Therefore, two types of three-arm and four-arm star-shaped D,L-PLGA50 copolymers were successfully synthesized from the homopolymerization of MG with TMP or PTOL initiator and $SnOct_2$ catalyst, as shown in Scheme 1.

Table 3
The results of the homopolymerization of MG with different polymerization times in bulk at 110°C and $[M]/[TMP] = 90$, $[M]/[SnOct_2] = 1000$

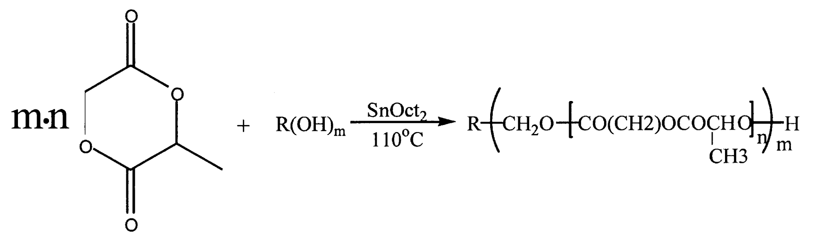
No.	$M_{n,GPC}$	$M_{n,th}$	M_w/M_n	Time (h)	Conversion %
1	3230	2820	1.04	0.33	24.0
2	4300	3840	1.06	0.50	32.8
3	8375	7560	1.06	2	64.7
4	10 570	9690	1.09	4	82.9
5	11 620	10 080	1.12	8	86.1
6	12 750	11 100	1.13	12	94.8

3.1.2. The effect of the monomer conversion on polymerization

The results of the homopolymerization of MG using TMP initiator and $SnOct_2$ catalyst with different polymerization times are compiled in Table 3. Fig. 3 shows that the $M_{n,GPC}$ of the obtained D,L-PLGA50 copolymers linearly increases with the monomer conversion. The molecular weight distribution is from 1.04 to 1.13 with the consumption of monomer. In all, Figs. 1–3 indicate that the polymerization of MG has some living characteristics when initiated with multifunctional initiator and $SnOct_2$ catalyst in bulk at 110°C.

3.1.3. The effect of $SnOct_2$ catalyst on polymerization

The results of the homopolymerization of MG with various amounts of $SnOct_2$ catalyst are compiled in Tables 4 and 5. Fig. 4 shows that the amount of $SnOct_2$ catalyst has no influence on the $M_{n,GPC}$ of the obtained D,L-PLGA50 copolymer. This also indicates that multifunctional compounds (TMP and PTOL) are real initiators, which can stoichiometrically control the molecular weight of the D,L-PLGA50 copolymer. Moreover, the molecular weight distribution is much lower when the amount of $SnOct_2$ catalyst used is much less (such as $[M]/[SnOct_2] = 4000$, $M_w/M_n = 1.10$). This may be attributed to the slow polymerization rate, and that the symmetry of the star-shaped D,L-PLGA50 copolymer can be effectively controlled.



(m = 3, 4)

Scheme 1.

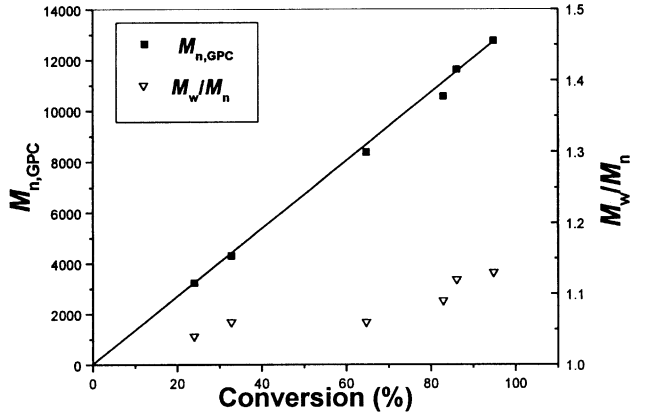


Fig. 3. Dependence of $M_{n,GPC}$ on the monomer conversion with TMP initiator and $SnOct_2$ catalyst in bulk at 110°C.

3.2. Mechanism of polymerization

Preliminary experiments have shown that the polymerization of MG could be carried out until high monomer conversion when initiated with multifunctional initiator and $SnOct_2$ catalyst in bulk at 110°C. ^1H NMR spectrum of the D,L-PLGA50 copolymer obtained with TMP initiator (Fig. 5) clearly shows that besides the typical signals of the main chain of the D,L-PLGA50 copolymer at 1.55 (δH^c), 4.78 (δH^b), and 5.25 ppm (δH^a), there are additional signals of the end groups of copolymer, i.e. the signals assigned to the proton (g) on lactyl end group ($\delta H^g = 4.42$ ppm), the proton (h) on glycolyl end group ($\delta H^h = 4.28$ ppm), and the proton (f) on the methyleneoxy end group ($\delta CH_2O = 4.10$ ppm). No carboxylic acid proton could be detected. On the assumption that each polyester chain is selectively capped by a hydroxy group at one end and a methyleneoxy group at the other end, $M_{n,NMR}$ calculated from the ^1H NMR spectrum is in good agreement with $M_{n,th}$ as shown in Tables 1 and 2.

Table 4
The results of the homopolymerization of MG with various amounts of $SnOct_2$ catalyst in bulk at 110°C and $[M]/[PTOL] = 100$

No.	$[M]/[SnOct_2]$	$M_{n,GPC}$	M_w/M_n	Time (h)	Conversion %
1	250	10 220	1.40	12	99.4
2	500	12 250	1.16	12	96.0
3	1000	12 400	1.20	12	97.1
4	2000	12 670	1.11	24	98.0
5	4000	12 540	1.10	36	97.6

Table 5
The results of the homopolymerization of MG with various amounts of $SnOct_2$ catalyst in bulk at 110°C and $[M]/[TMP] = 90$

No.	$[M]/[SnOct_2]$	$M_{n,GPC}$	M_w/M_n	Time (h)	Conversion %
1	250	13 070	1.33	12	100
2	500	12 820	1.28	12	96.8
3	1000	12 750	1.13	12	94.8

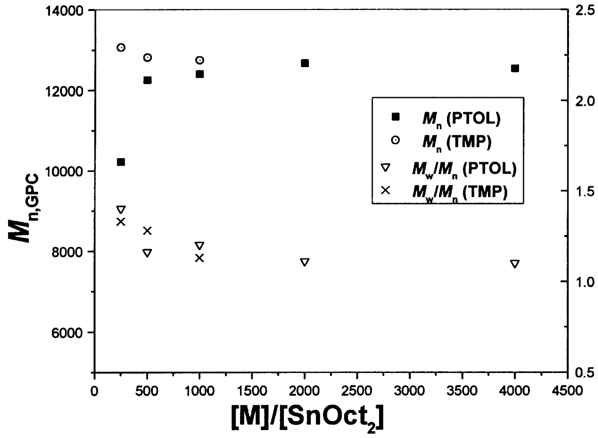


Fig. 4. Dependence of $M_{n,GPC}$ on the various amount of $SnOct_2$ for PTOL or TMP initiated polymerization of MG in bulk at 110°C.

This observation convincingly confirms that MG molecule has been inserted into the "CH_2–O" bonds of the initiator through the selective acyl–oxygen cleavage of the monomer. The above result indicates that the ring-opening polymerization of MG conforms to the "coordination–insertion" mechanism (shown in Scheme 2). From the ^1H NMR spectrum (Fig. 5), the integral intensities of δH^g and 1/2 δH^h are evaluated about 60.2 and 39.8%, respectively. We postulate the two probabilities of the resulting end groups $CH(CH_3)OH$ (L–OH) and CH_2OH (G–OH) are consistent with those of the ring opening through acyl–oxygen cleavage via sites 1 and 2, respectively. These values would correspond well to the preferential ring opening at one side of MG ring (i.e. the least hindered carbonyl groups).

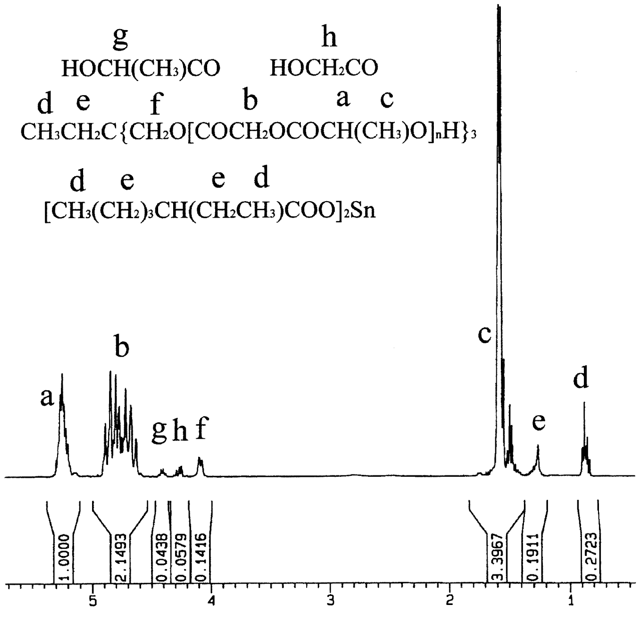
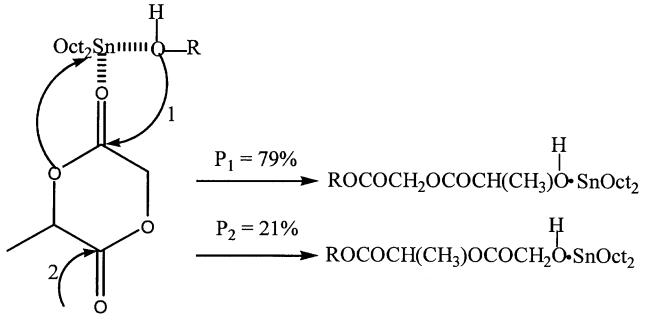


Fig. 5. ^1H NMR spectrum of star-shaped poly(D,L-lactic-alt-glycolic acid) obtained from the polymerization of MG with TMP initiator and $SnOct_2$ catalyst in bulk at 110°C.



Scheme 2.

According to the conclusion reported by Benabdillah et al. [25], the probability of the occurance of a G–L–G triad is $1/2(P_1^2 + (1 - P_1)^2)$, $P_1 = 0.73$, $P_2 = 0.27$ can be calculated, respectively, P_1 and P_2 denote the probabilities of the existence of the two types of ring opening. This conclusion will be evaluated by the ^{13}C NMR analysis. The similar result can also be obtained for PTOL initiated polymerization of MG.

In ^{13}C NMR spectrum of the D,L-PLGA50 copolymer obtained with TMP initiator, several signals were observed as shown in Fig. 6. These peaks were probably due to the presence of different distributions of counit sequences due to the asymmetry of the MG molecule and the two probabilities of ring opening through acyl–oxygen cleavage. From the noncarbonyl carbon region of ^{13}C NMR spectrum in Fig. 6(a), it is shown that these fine structures can be observed for the carbon of CH(CH$_3$) (69.0–69.5 ppm). According to the papers reported by Benabdillah et al. [25] and Kricheldorf et al.[26], respectively, the presence of carbon triplet signals led us to assume that the peaks corresponded to the G–L–G, L–L–G, and G–L–L triads. The integral intensities of carbon signals are evaluated about 18, 69, and 13%, respectively; these values correspond well to the intermediate case of preferential ring opening at one side of the MG molecule ($P_1 = 0.81$, $P_2 = 0.19$). This result is approximately in agreement with that obtained from ^{1}H NMR analysis. In the same way, from the carbonyl region of ^{13}C NMR spectrum in Fig. 6(b), it is shown that fine structures can also be observed for the carbon of CO (lactic acid, 169.2–169.5 ppm), and $P_1 = 0.83$, $P_2 = 0.17$ can be obtained, respectively. Therefore, the average probabilities for the two types of ring opening: $P_1 = 0.79$, $P_2 = 0.21$ are obtained. The above result indicates that the main chain of the star-shaped D,L-PLGA50 copolymer obtained from the polymerization of MG with multifunctional initiator and SnOct$_2$ catalyst mainly has alternating structures of lactyl and glycolyl units.

4. Conclusion

Two types of star-shaped poly(D,L-lactic acid-alt-glycolic acid) were successfully synthesized from the homopolymerization of MG with multifunctional initiators (TMP and PTOL) and SnOct$_2$ catalyst in bulk at 110°C. In the homopolymerization of MG, the molecular weight of the alternating D,L-PLGA50 copolymer is rather proportional to the molar ratio of monomer to initiator and the monomer conversion within the monomer conversion range. The ring-opening polymerization mechanism of MG corresponds to a "coordination–insertion" mechanism, which involves the selective cleavage of the acyl–oxygen bond of the monomer. Based on the ^{1}H NMR and ^{13}C NMR

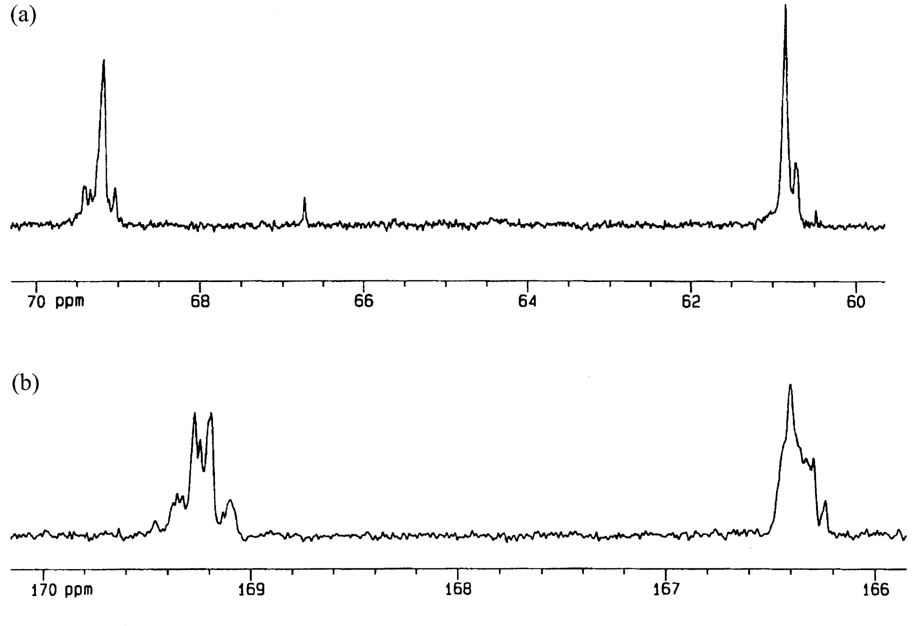


Fig. 6. (a) The noncarbonyl region of ^{13}C NMR spectrum of D,L-PLGA50 copolymer obtained with TMP initiator and SnOct$_2$ catalyst in bulk at 110°C, and (b) the carbonyl region of ^{13}C NMR spectrum of D,L-PLGA50 copolymer obtained with TMP initiator and SnOct$_2$ catalyst in bulk at 110°C.

analyses, the selective cleavage of the acyl–oxygen bond of the monomer mainly occurs at the least hindered carbonyl groups ($P_1 = 0.79$, $P_2 = 0.21$). Moreover, the amount of multifunctional initiator used has no influence on the probability of ring opening through the acyl–oxygen of the monomer.

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