Articles

Synthesis of Star-Shaped Poly(ϵ-caprolactone)-*b*-poly(DL-lactic acid-*alt*-glycolic acid) with Multifunctional Initiator and Stannous Octoate Catalyst

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ABSTRACT: Two types of three-arm or four-arm star-shaped hydroxy-terminated poly(ϵ-caprolactone) (PCL) were successfully synthesized via the ring-opening polymerization of ϵ-caprolactone (CL) with multifunctional initiator, such as trimethylolpropane (TMP) or pentaerythritol (PTOL), and stannous octoate ($SnOct_2$) catalyst in bulk at 110 °C. The number-average molecular weight of PCL is proportional to the molar ratio of monomer to initiator. ^{1}H NMR spectroscopy of the resulting PCL indicates that it contains a primary hydroxy end group in each arm. The star-shaped PCL with hydroxy end groups can be used as a macroinitiator for block copolymerization with DL-3-methylglycolide (MG) using $SnOct_2$ catalyst in bulk at 115 °C. ^{1}H NMR spectra of the resulting block copolymers show that the molecular weights and the unit compositions of the block copolymers were controlled by the molar ratios of MG monomer to hydroxy groups of PCL and MG to CL in feed, respectively. Moreover, the molecular weights of the resulting block copolymers linearly increased with the increase of the molar ratios of MG to CL in feed. The molecular weight distributions of the block copolymers were rather narrow (M_w/M_n = 1.09−1.26). ^{13}C NMR spectra of the resulting block copolymers clearly show their diblock structures, that is, PCL as the first block and poly(DL-lactic acid-*alt*-glycolic acid) (DL-PLGA50) with alternating structures of lactyl and glycolyl units as the second block. Therefore, two types of three-arm or four-arm star-shaped diblock copolyesters comprising the first block PCL and the second block DL-PLGA50 were successfully synthesized via the sequential ring-opening polymerization of CL with multifunctional initiator and $SnOct_2$ catalyst and then followed by copolymerization with MG.

Introduction

Homopolymers and copolymers of glycolide (GA), lactides (LA), and ϵ-caprolactone (CL) are increasingly investigated worldwide for pharmacological, biomedical, agricultural, and environmental purposes.[1−4] In contrast to the traditional step-polycondensation method, the ring-opening polymerization of cyclic esters is an effective method for the preparation of the related aliphatic polyesters. The rapidly growing interest in biodegradable materials has also increased interest in catalysts and mechanisms concerning the ring-opening polymerization of lactones and lactides.[5] Several organometallic compounds such as alkoxides, carboxylates, and oxides,[6−10] some nontoxic compounds such as Fe acetate, Zn lactate, and Ca acetylacetonate,[11−13] and enzymes[14,15] have been successfully used as catalysts or initiators for the synthesis of aliphatic polyesters. However, $SnOct_2$ is the most widely used catalyst for the production of biodegradable polyesters because it is commercially available, easy to handle, soluble in common organic solvents and cyclic ester monomers, and a permitted food additive in numerous countries.[6,16−19] Generally, the molecular weights and the molecular weight distributions of aliphatic polyesters can be controlled by using very dry systems with a controlled amount of a hydroxy-containing compound initiator and $SnOct_2$ catalyst.[20,21] Recently, the generally accepted "coordination−insertion" mechanism for $SnOct_2$-catalyzed ring-opening polymerization of lactones and lactides has been demonstrated by Penczek et al.[22−24] and Kricheldorf et al.,[5] although there are still some debates.

The well-defined macromolecular architectures such as star polymers, hyperbranched polymers, and dendrimers are very attractive to many scientists because of their well-defined structure and ease of control of surface functionality.[25−29] Generally, star-shaped polymers can be prepared by two different routes: the "arm-first"[30] strategy and the "core-first"[31,32] approach on the basis of a multifunctional core used as initiator. Using the "core-first" approach, Hedrick et al. reported the synthesis of dendrimer-like star polylactone using a hexahydroxy-functional compound initiator and $SnOct_2$ catalyst.[33] Some other papers have reported the synthesis of the star-shaped polylactide with multifunctional initiator such as pentaerythritol (PTOL),[34,35] glycerol,[36] and aminopropanediol or aminohydroxymethylpropanediol[37] and $SnOct_2$ catalyst. In our previous paper, we reported the synthesis of star-shaped DL-

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PLGA50 copolymer with PTOL or trimethylolpropane (TMP) initiator and $SnOct_2$ catalyst.[21] Heteroarm or miktoarm star block copolymers have been successfully prepared by living anionic and cationic polymerization.[38,39] It is also very interesting that Deng et al.[40] reported a chemoenzymatic route to synthesize a novel multiarm block copolymer of PLA and PCL with multifunctional 1-ethylglucopyranoside as an initiator. Feijen et al.[41] and Kimura et al.[42] reported the synthesis of linear block aliphatic copolyesters PCL-*b*-PL-LA and PL-LA-*b*-[*RS*]-poly(3-hydroxybutyrate)-*b*-PL-LA using $SnOct_2$ catalyst, respectively. However, it looks to us that the studies on the preparation of star-shaped block aliphatic polyesters using multifunctional initiator and $SnOct_2$ catalyst are rare.[43] In this article, we wish to report a convenient route for the synthesis of a star-shaped block aliphatic polyester, PCL-*b*-DL-PLGA50, in which the DL-PLGA50 block has alternating structures of glycolyl (G-) and lactyl (L-) units. Moreover, the star-shaped block copolyester can be considered as being synthesized from three different cyclic esters, i.e., CL, GA, and LA. So the star-shaped PCL-*b*-DL-PLGA50 copolymer could expectedly combine the excellent permeability of PCL block and the higher biodegradability of the DL-PLGA50 block.

Experimental Section

Materials. $SnOct_2$ (Aldrich) was used as received. CL (Acros) was distilled from CaH_2 in vacuo under N_2. According to our previous paper,[44] 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-bromopropionyl bromide 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. Trimethylolpropane (A.R., Analytic Reagent) was recrystallized from dried acetone and then dried for 12 h under reduced pressure. Pentaerythritol (A.R.) was sublimated under reduced pressure. Toluene was distilled from CaH_2 under N_2. Ethyl acetate and acetone were distilled from P_2O_5. Petroleum ether (distillation range: 60−90 °C), methanol, and dichloromethane were used without further purification.

Methods. ^{1}H NMR spectroscopy was performed on a Bruker ARX-400 spectrometer. ^{13}C NMR spectroscopy was performed on a Varian VXR-200 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 the calibration standard, and Waters Millennium32 as data processing software. The differential scanning calorimetry (DSC) analysis was carried out using a Shimadzu DSC-50 under nitrogen flow (10 mL/min) at 5 °C/min.

Homopolymerization of PCL. The polymerization tubes were kept at 110 °C for 24 h. About 0.5 mL of CL, 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 for about 5 min. A certain amount of $SnOct_2$ in dry toluene was added to the melt mixture, and the exhausting−refilling process was carried out again to remove the toluene. The tube was cooled after 24 h. The resulting product was dissolved in CH_2Cl_2 and poured dropwise into an excess of petroleum ether. The purified polymer was dried in a vacuum until constant weight. Then the monomer conversion was determined gravimetrically.

Table 1. Results of the Homopolymerization of ϵ-Caprolactone (CL) with Various Amounts of Pentaerythritol (PTOL) in Bulk at 110 °C and [CL]/[$SnOct_2$] = 1000; Polymerization Time = 24 h

no.	[M]/[I][a]	$M_{n,GPC}$	$M_{n,th}$[b]	$M_{n,NMR}$[c]	M_w/M_n[d]	conv (%)
1	40	6 500	4 500	5700	1.08	98.3
2	80	12 400	8 600	9200	1.17	94.2
3	120	21 500	13 300		1.25	97.4
4	160	27 000	17 300		1.20	95.0

[a] M = CL, I = PTOL. [b] $M_{n,th}$ = [M]/[I] × M_{CL} × conversion %; $M_{n,th}$ denotes the average-number molecular weight of star-shaped PCL. [c] $M_{n,NMR}$ is determined by ^{1}H NMR spectroscopy of star-shaped PCL. [d] Weight-average molecular weight (M_w) and number-average molecular weight (M_n) are determined by GPC.

Table 2. Results of the Homopolymerization of ϵ-Caprolactone (CL) with Various Amounts of Trimethylolpropane (TMP) in Bulk at 110 °C and [CL]/[$SnOct_2$] = 1000; Polymerization Time = 24 h

no.	[M]/[I][a]	$M_{n,GPC}$	$M_{n,th}$	$M_{n,NMR}$	M_w/M_n	conv (%)
1	30	6100	3400	3700	1.11	99.4
2	60	9200	6600	6200	1.16	96.3
3	90	14800	9900		1.24	96.0
4	120	21200	13000		1.29	94.8

[a] M = CL, I = TMP.

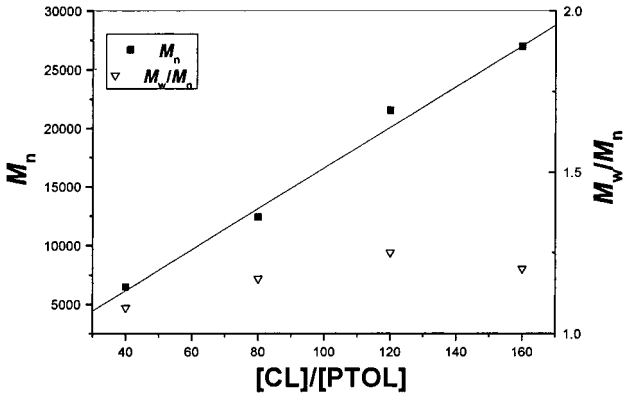


Figure 1. Dependence of M_n on the molar ratio of [CL]/[PTOL] with PTOL initiator and $SnOct_2$ catalyst in bulk at 110 °C.

Block Copolymerization. An amount of PCL with hydroxy end groups obtained above, MG, and a dry stirring bar were put into a tube. By a similar approach as described above and after adding $SnOct_2$ catalyst, the tube was immersed into an oil bath at 115 °C with vigorous stirring for 20 h. The resulting product was dissolved in CH_2Cl_2, poured dropwise into an excess of petroleum ether, and finally shaken with methanol. The purified polymer was dried in a vacuum until constant weight. Then the copolymer yield was determined gravimetrically.

Results and Discussion

Synthesis of Star-Shaped PCL with Hydroxy End Groups. The homopolymerization of CL 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 amount of initiator are compiled in Tables 1 and 2. It indicates that CL monomer can be completely consumed within 24 h. From Figure 1, it is shown that the average-number molecular weight (M_n) of the obtained PCL linearly increases with the molar ratio of monomer to initiator ([M]/[I]), and the molecular weight distribution is rather narrow (M_w/M_n = 1.08−1.29). The $M_{n,NMR}$ is consistent with the $M_{n,th}$: $M_{n,th}$ = [M]/[I] × M_{CL} × conversion % (shown in Tables 1 and 2). This indicates

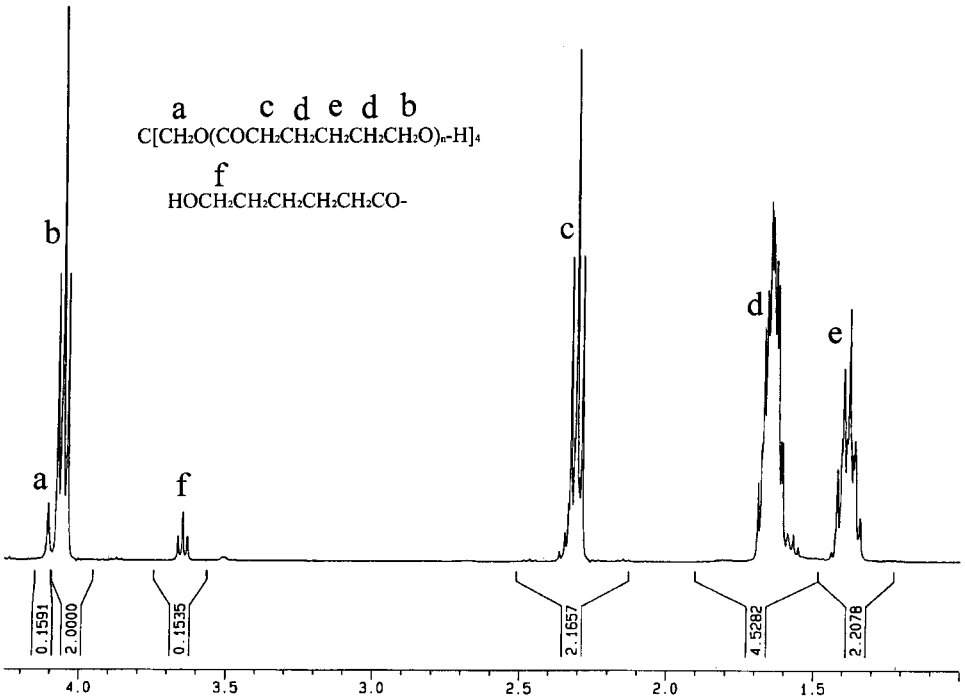


Figure 2. ^{1}H NMR spectroscopy of star-shaped poly(ϵ-caprolactone) obtained from the polymerization of ϵ-caprolactone with PTOL initiator and $SnOCt_2$ catalyst (no. 1, Table 1).

Table 3. Results of Block Copolymerization of MG Initiated with Hydroxy-Ended PCL in Bulk at 115 °C with $SnOct_2$ as Catalyst ([MG]/[$SnOct_2$] = 1000:1); Polymerization Time = 20 h

entry	MG/CL (mol/mol)	M_n	M_w/M_n	yield (%)
PCL (PTOL)-1[a]	0:1	6 500	1.08	98.3
PCL-*b*-DL-PLGA50-1	1:1	12 500	1.09	96.9
PCL-*b*-DL-PLGA50-2	2:1	19 000	1.14	97.6
PCL-*b*-DL-PLGA50-3	3:1	23 600	1.20	94.3
PCL (PTOL)-2[b]	0:1	12 400	1.17	94.2
PCL-*b*-DL-PLGA50-4	1:1	21 400	1.17	95.8
PCL-*b*-DL-PLGA50-5	2:1	33 800	1.14	96.2
PCL-*b*-DL-PLGA50-6	3:1	44 300	1.15	97.6

[a] PCL (PTOL)-1 obtained from the homopolymerization of CL with PTOL initiator and $SnOct_2$ catalyst as shown in no. 1, Table 1. [b] PCL (PTOL)-2 obtained from the homopolymerization of CL with PTOL initiator and $SnOct_2$ catalyst as shown in no. 2, Table 1

Table 4. Results of Block Copolymerization of MG Initiated with Hydroxy-Ended PCL in Bulk at 115 °C with $SnOct_2$ as Catalyst ([M]/[$SnOct_2$] = 1000:1); Polymerization Time = 20 h

entry	MG/CL (mol/mol)	M_n	M_w/M_n	yield (%)
PCL (TMP)-1[a]	0:1	6 100	1.11	99.4
PCL-*b*-DL-PLGA50-7	1:1	11 500	1.14	95.0
PCL-*b*-DL-PLGA50-8	2:1	16 200	1.16	95.9
PCL-*b*-DL-PLGA50-9	3:1	21 400	1.26	96.4
PCL (TMP)-2[b]	0:1	9 200	1.16	96.3
PCL-*b*-DL-PLGA50-10	1:1	18 000	1.13	95.7
PCL-*b*-DL-PLGA50-11	2:1	26 400	1.12	98.6
PCL-*b*-DL-PLGA50-12	3:1	36 200	1.15	97.4

[a] PCL (TMP)-1 obtained from the homopolymerization of CL with TMP initiator and $SnOct_2$ catalyst as shown in no. 1, Table 2. [b] PCL (TMP)-2 obtained from the homopolymerization of CL with TMP initiator and $SnOct_2$ catalyst as shown in no. 2, Table 2.

that the molecular weight of the PCL can be accurately predicted by the molar ratio of monomer to initiator and the monomer conversion and that the obtained PCL has three or four arms. Moreover, on the basis of Feijen et al.'s conclusion,[41] the $HOCH_2$ methylene proton signal (δ H^f = 3.65 ppm) in the spectrum of the obtained PCL shows that PCL was terminated by hydroxy end groups (Figure 2). Therefore, two types of three-arm and four-arm star-shaped PCL with hydroxy end groups were successfully synthesized from the homopolymerization of CL with TMP or PTOL initiator and $SnOct_2$ catalyst.

Synthesis of Star-Shaped PCL-*b*-DL-PLGA50 Copolyester. The star-shaped PCL with hydroxy end groups obtained above, such as PCL (PTOL)-1 or 2 and PCL (TMP)-1 or 2, can act as macroinitiator for the block copolymerization with MG in bulk at 115 °C using $SnOct_2$ as catalyst. The results are compiled in Tables 3 and 4. The yields of the block copolymers were very high (ca. 95%) at various molar ratios of MG to CL. Figure 3 indicates that the molecular weights of the block copolymers obtained from the copolymerization of

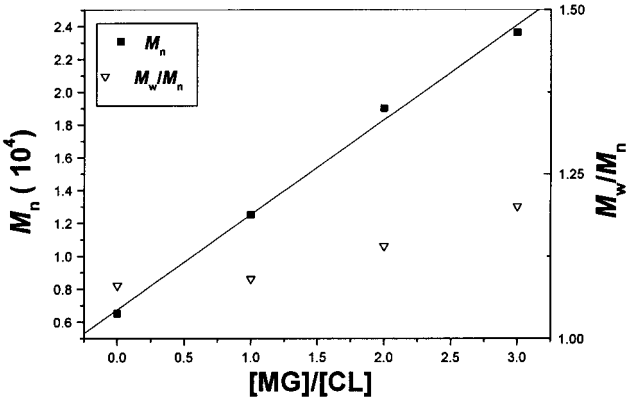


Figure 3. Dependence of M_n on the molar ratio of [MG]/[CL] with PCL (PTOL)-1 initiator and $SnOct_2$ catalyst in bulk at 115 °C.

PCL and MG linearly increased with the increase of the molar ratios of MG to CL in feed. The molecular weight distributions (M_w/M_n = 1.09−1.26) were rather narrow

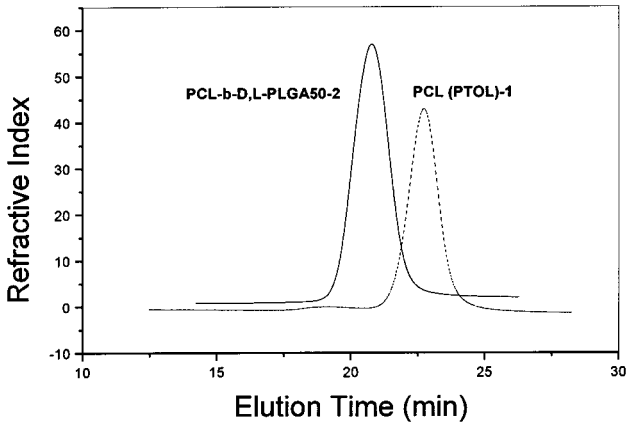
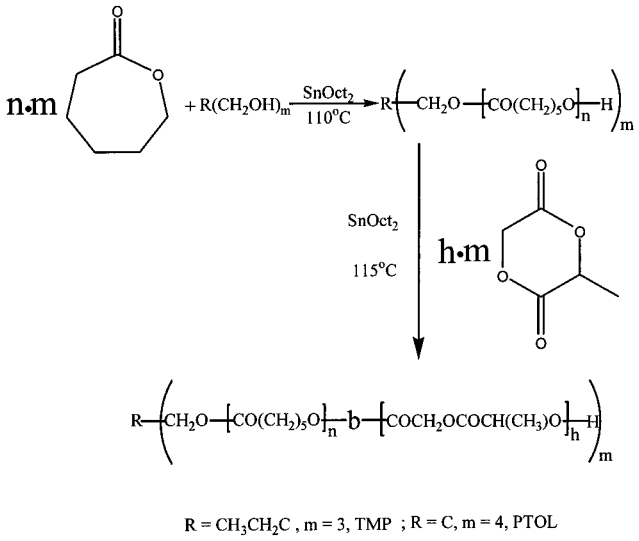


Figure 4. GPC curves of the star-shaped PCL (PTOL)-1 and the star-shaped PCL-*b*-DL-PLGA50-2 copolymer.

Scheme 1. Synthesis of Star-Shaped PCL-*b*-DL-PLGA50 Copolyester



R = CH_3CH_2C , m = 3, TMP ; R = C, m = 4, PTOL

in every case. Figure 4 shows the typical GPC curves of the block copolymers as compared with those of original star-shaped PCL. This indicates that in each block copolymer the peak is shifted toward a higher molecular weight region compared with that of its original PCL with little change in molecular weight distribution. These preliminary results show that the block copolymerization of the star-shaped PCL with hydroxy end groups and MG monomer using $SnOct_2$ catalyst was successful under the experimental conditions used (shown in Scheme 1).

A typical ^{1}H NMR spectrum of the block copolymer obtained from the copolymerization of PCL and MG with $SnOct_2$ catalyst (Figure 5) clearly shows that besides the typical signals of the main chain of the DL-PLGA50 copolymer at 1.65 (δ H^e), 4.80 (δ H^b), and 5.25 ppm (δ H^a) and the typical signals of the main chain of the PCL at 4.07 (δ H^c), 2.32 (δ H^d), 1.65 (δ H^e), and 1.39 ppm (δ H^f), there are additional signals of the end groups of the obtained block copolymer, that is, the signals assigned to the proton (g) on the lactyl group (δ H^g = 4.42 ppm) and the proton (h) on the glycolyl group (δ H^h = 4.28 ppm), which is the end groups of the DL-PLGA50 copolymer, and the proton (i) on the methyleneoxy group of PTOL initiator (δ H^i = 4.15 ppm). No carboxylic acid proton could be detected. It is seen that the $HOCH_2$ methylene proton signal at 3.65 ppm for the original PCL disappeared, and the new signals at 4.28 and 4.42 ppm for the produced end groups of DL-PLGA50 block were observed. This demonstrates that the PCL had completely copolymerized with MG to form a block copolymer within the detection limits of NMR. The $M_{n,NMR}$ of the first block PCL is equal to 5200 (calculated from Figure 5), which is in agreement with the $M_{n,NMR}$ (5700) (calculated from Figure 2) of the original PCL, and these values are near the $M_{n,th}$ (4500) (shown in Table 1). The $M_{n,NMR}$ of the second block DL-PLGA50 copolymer is equal to 11 600 (calculated from Figure 5), which is also in agreement with the $M_{n,th}$ (10 200). The molar fraction of CL monomer in the resulting block

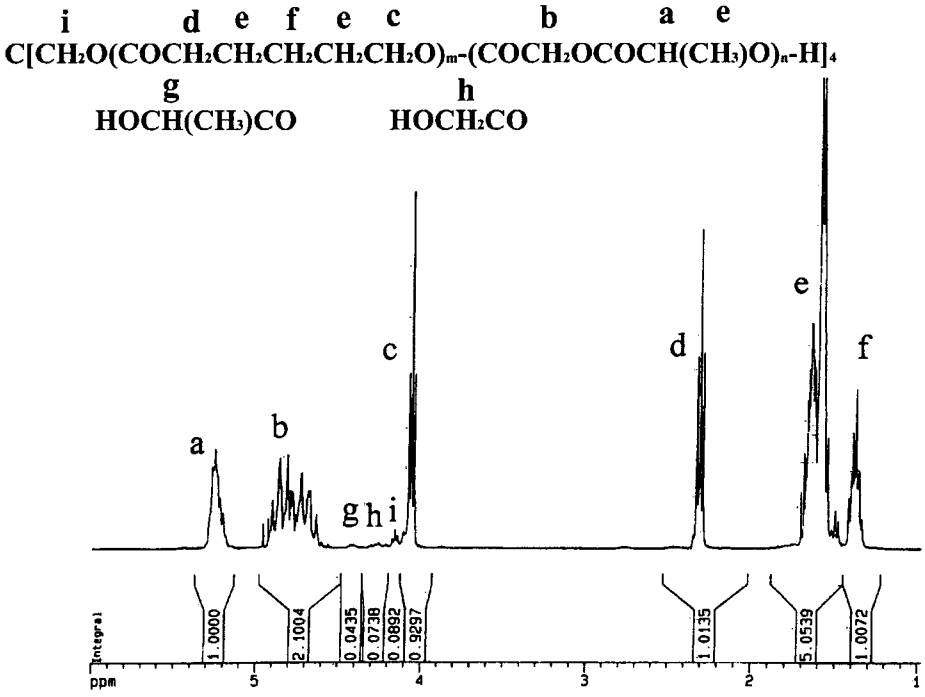


Figure 5. ^{1}H NMR spectrum of four-arm star-shaped block copolymer: PCL-*b*-DL-PLGA50-2.

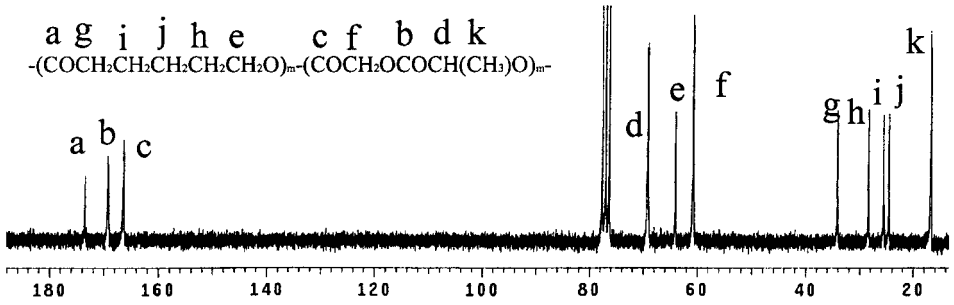
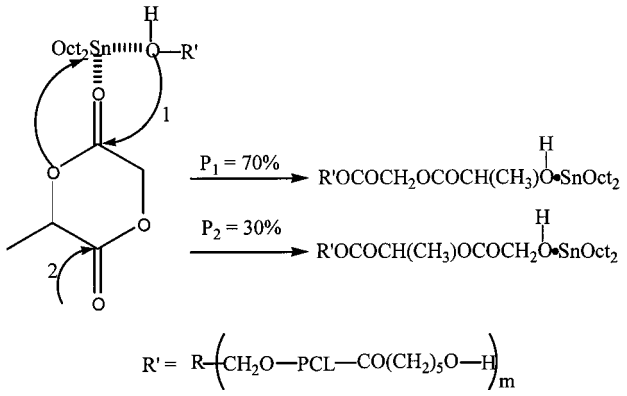


Figure 6. ^{13}C NMR spectrum of four-arm star-shaped block copolymer: PCL-*b*-DL-PLGA50-2.

Scheme 2. Ring-Opening Block Copolymerization Mechanism of MG with Multifunctional Initiator and $SnOct_2$



copolymer is about 33.0% (calculated from Figure 5), which is in good agreement with the molar fraction of CL in feed (33.3%). These results show that the molecular weights and the unit compositions of the produced block copolymers were controlled by the molar ratios of MG monomer to hydroxy groups of PCL and MG to CL in feed, respectively. Moreover, these conclusions convincingly confirm that MG molecules have been inserted into the "CH_2−OH" bonds of the hydroxy end groups on PCL chain through the selective acyl−oxygen cleavage of the monomer. The above result indicates that the ring-opening block copolymerization of MG conforms to the "coordination−insertion" mechanism (shown in Scheme 2). From the ^1H NMR spectrum (Figure 5), the integral intensities of δ H^g and $^1/_2\delta$ H^h are evaluated at about 58% and 42%, 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 site 1 and site 2, respectively. These values would correspond well to the preferential ring-opening at one side of MG ring (i.e., site 1, the least hindered carbonyl groups). According to the reported literature,[17,21,44,45] the probability of the occurrence of an G−L−G triad is $^1/_2$-$(P_1^2 + (1 - P_1)^2)$; $P_1 = 0.70$ and $P_2 = 0.30$ can be calculated, where 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.

A typical ^{13}C NMR spectrum of PCL-*b*-DL-PLGA50-2 is shown in Figure 6. It indicates that the star-shaped PCL-*b*-DL-PLGA50 copolymer does not present any intermediate signals between the one carbonyl of PCL (δ 173.5 ppm) and the other two carbonyls of DL-PLGA50 copolymer (δ 169.3 ppm, lactyl; δ 166.4 ppm, glycolyl) and so clearly demonstrates the pure diblock structure of the PCL-*b*-DL-PLGA50. It can also be seen that there is only one peak for each of the carbonyls, and no splitting phenomenon is detected. It indicates that the DL-PLGA50 block has alternating structures of lactyl and glycolyl units. This is consistent with our previous studies.[21,44,45] The above results convincingly show that the star-shaped PCL-*b*-DL-PLGA50 copolymers have been successfully synthesized via the block copolymerization of star-shaped PCL with hydroxy end groups and MG monomer using $SnOct_2$ catalyst in bulk at 115 °C.

Table 5. Thermal Properties of Three-Arm and Four-Arm Star-Shaped Block Copolymer: PCL-*b*-DL-PLGA50

entry	T_{g1} (°C)[a]	T_{g2} (°C)[b]	T_m (°C)[c]	ΔH (J/g)[d]	f (%)[e]
PCL (PTOL)-1			49.4	77.2	55.3
PCL-*b*-DL-PLGA50-1		26.5	41.8	25.1	18.0
PCL-*b*-DL-PLGA50-2			43.2	5.4	3.9
PCL-*b*-DL-PLGA50-3			44.4	3.9	2.8
PCL (TMP)-1			51.9	75.0	53.8
PCL-*b*-DL-PLGA50-7			46.2	37.6	27.0
PCL-*b*-DL-PLGA50-8			44.2	21.4	15.3
PCL-*b*-DL-PLGA50-9			46.1	6.9	4.9
DL-PLGA50 ($SnOct_2$)[f]		42.3			

[a] T_{g1} denotes the glass transition temperature of PCL block segments. [b] T_{g2} denotes the glass transition temperature of DL-PLGA50 block segments. [c] T_m denotes the maximum melting point of PCL block segments. [d] Heat of melting of crystalline PCL block segments. [e] The degree of crystallinity of PCL block segments. [f] DL-PLGA50 ($SnOct_2$) was synthesized from the polymerization of MG with $SnOct_2$ catalyst in bulk at 110 °C.

The DSC characterization of the star-shaped PCL-*b*-DL-PLGA50 copolymers is given in Table 5. The star-shaped PCL-*b*-DL-PLGA50 copolymers with different compositions apparently have different thermal properties. The PCL block segments would be separated from the block copolymers when its content is higher than 25%. For the four-arm star-shaped PCL-*b*-DL-PLGA50-1 copolymer (shown in Table 5), the degree of crystallinity (f) is 18.0%. When the DL-PLGA50 block length in copolymer increases to double that in PCL-*b*-DL-PLGA50−2 copolymer (shown in Table 5), its f decreases to 3.9%. Then, with the continuous increase of the DL-PLGA50 block length in copolymer such as PCL-*b*-DL-PLGA50−3, it has no apparent effect on the f of copolymer (f = 2.8%, shown in Table 5). However, the maximum melting points of PCL block segments in block copolymers are around 43 °C and have no apparent difference. For the three-arm star-shaped block copolymer, similar results can be obtained (shown in Table 5).

Conclusion

Two types of three-arm or four-arm star-shaped PCL-*b*-DL-PLGA50 block copolymers were successfully synthesized via the block copolymerization of star-shaped PCL with hydroxy end groups and MG monomer using $SnOct_2$ catalyst in bulk at 115 °C. The molecular

weights and the unit compositions of the star-shaped block copolymers were controlled by the molar ratios of MG monomer to hydroxy groups of PCL and MG to CL in feed, respectively. The ring-opening block copolymerization mechanism of MG corresponds to a "coordination−insertion" mechanism, which involves the selective cleavage of the acyl−oxygen bond of the monomer.

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Supporting Information Available: Figures showing dependence of M_n on the molar ratios of [CL]/[TMP] and [MG]/[CL] with different initiators and $SnOct_2$ catalysts in bulk at 110 and 115 °C as well as GPC curves of PCL (TMP)-2 and PCL-*b*-DL-PLGA50-10 copolymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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