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Aliphatic tertiary amine mediated synthesis of highly branched polylactide copolymers

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ABSTRACT

In the $Sn(Oct)_2$ catalyzed bulk copolymerization of L-lactide (LLA) and a large amount of branching comonomer 2,2-bis(hydroxymethyl)butyric acid (BHB) (LLA/BHB/$Sn(Oct)_2$ ratio is 5:1:0.05, 135 °C), low molecular weight of copolymers with inhomogeneous structure were generated. MALDI-TOF mass spectrum demonstrated that the lower molar mass fraction was dominated with the BHB homopolycondensation products; whereas the higher molar mass fraction was mainly composed of linear chains of poly(L-lactide) (PLLA) bearing one BHB unit. The addition of aliphatic tertiary amine to this polymerization system could effectively enhance the molecular weight of the obtained copolymers, whereas, aromatic tertiary amines and aliphatic primary and secondary ones were not so effective. The obtained PLLA copolymers were characterized by GPC, ^{1}H NMR, ^{13}C NMR and MALDI-TOF MS, which verified that they were composed of LLA and BHB units and had the highly branched structure. The degree of branching was about 0.23–0.30. Thermal analyses by TGA and DSC demonstrated that the resulting highly branched PLLA copolymers were amorphous. Compared with linear PLLA, the highly branched PLLA copolymers were thermally more stable and had lower T_g. The mechanism of aliphatic tertiary amine mediated synthesis of medium molecular weight of highly branched PLLA copolymers was proposed.

1. Introduction

Polylactide (PLA), a kind of biocompatible and biodegradable aliphatic polyester, has received a significant amount of interest in both academic and industrial research for a long time [1–4]. Its homo- and copolymers have been applied in a wide range of biological systems ranging from drug delivery to tissue engineering [2,5,6]. Linear PLA can be chemically synthesized either by the polycondensation of lactic acid or the ring-opening polymerization (ROP) of lactide (LA) that is a cyclic dimer of lactic acid. Compared with the polycondensation of lactic acids, ROP of cyclic monomers exhibits many advantages. For instance, mild reaction conditions are used; the formation of small molecule byproducts is avoided; well-defined polymers having lower polydispersities, higher molecular weight and high levels of end-group fidelity can be achieved with suitable catalyst [1,3].

Compared with their linear analogues having the same molecular weight, spherical branched polymers show the characters of lower solution and melt viscosity [7,8]. This has aroused the interest of researchers to synthesize variety of branched polymers to see whether they can exceed the performances of the traditional linear ones in certain application fields. Moreover, some new applications of these branched polymers are also explored. In the case of PLA, a variety of branched molecular architectures have been reported, such as star shaped [9–14], long-chain branched [15–18], hyperbranched ones [19]. The character of star-shaped PLA is that all linear PLA chains are tethered together by a core. The number of the functional terminal groups is decided by the functionality of the core molecule. Long-chain branched PLA polymers have been prepared through three ways. One is via a one-pot copolymerization of LA with a less reactive cyclic ABB′ inimer, such as mevalonolactone [16]. The resulting copolymers contained only 2.5 mol% of mevalonolactone branching units although the feed molar ratio of mevalonolactone/LA is 10:90. Akashi et al. reported another method to synthesize the long-chain branched PLA copolymers via the melt-polycondensation of AB_2 type macromonomer, 3,4-diacetoxycinnamic acid (DACA)-terminally conjugated PLA [17].

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Hedrick and co-workers prepared a new kind of long-chain branched PLA by a combination of dendrimer and star polymer synthetic methodology [18]. Firstly, a branched, multifunctional core initiated the ROP of LA to result in star polymers. Subsequently, branching molecules were coupled to the termini of the stars. The repetitive ROP of LA and coupling steps with branching molecules generated the so-called “dendrimer-like stars”. Frey and Wolf utilized a reactive hydroxyl-functional (ABB′) lactone inimer, 5-hydroxymethyl-1,4-dioxane-2-on, to copolymerize with LA, resulting in a series of long-chain branched or hyperbranched PLA copolymers [19]. Since the above-mentioned hydroxyl-functional cyclic lactone inimers are usually expensive or not commercially available, less expensive AB_2 type monomers are desired to be used as branching agent to copolymerize with the cyclic monomers. Commercially available AB_2 monomer 2,2-bis(hydroxymethyl) butyric acid (BHB) or bis(hydroxymethyl)propionic acid (BHP) has been ever copolymerized with cyclic lactones or LA [20–24]. However, only branched poly(ε-caprolactone) copolymers could be prepared through this approach because the primary hydroxyl groups of poly(ε-caprolactone) chains were active enough in the esterification reaction with the carboxylic acid groups of BHB or BHP units [20–22]. As for the copolymerization of BHB or BHP with LA, Gottschalk and Frey had claimed that the $Sn(Oct)_2$ catalyzed bulk copolymerization of L-lactide (LLA) with BHB would lead to hyperbranched PLA copolymers [23]. However, this conclusion had been proved to be wrong by Cooper and Storey [24] and Velthoen et al. [22]. They found that only the ROP of LA initiated by the hydroxyl groups of BHB or BHP happened, whereas the further esterification reaction resulting in branched structure could not be detected [22,24]. Thus, up to date the direct preparation of highly branched PLA through the copolymerization of LA with BHB or BHP in a one-pot procedure has not been achieved. In this paper we reported that highly branched PLA could be achieved by the $Sn(Oct)_2$ catalyzed bulk copolymerization of LA with BHB when aliphatic tertiary amine was introduced to this polymerization system. Furthermore, the mechanism of the formation of highly branched PLA was proposed.

2. Experimental

2.1. Materials

L-Lactide (LLA) was purchased from Beijing Yuan Sheng Rong (GLACO) Company and purified by recrystallization from toluene. 2,2-Bis(hydroxymethyl)butyric acid (BHB, 98%) was purchased from Aldrich and used directly. Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$, 97%), *N*,*N*-dimethylaniline (DMA, 99%) and tributylamine (TBA, 98%) were purchased from Alfa Aesar and used directly. *N*,*N*,*N*,*N*-tetramethyl-1,3-diaminopropane (TMDAP, 98%) was purchased from Su Zhou Sinocompound Technology Company and used as received. Pyridine (A.R.), *n*-hexylamine (A.R.), piperidine (A.R.), pentanoic acid (A.R.) and 1,6-henanediol (A.R.) were purchased from Tianjin Jiangtian Chemical Company and used directly. All solvents were of analytical grade and used as received. Polymethacrylate (PMMA) standards were purchased from American Polymer Standards Corporation.

2.2. Polymerization

Different ratio of LLA, BHB and amine additive were placed in a flask with a magnetic stirring bar. The mixture was degassed three cycles of vacuum-nitrogen purge. The flask was then immersed in an oil bath thermostated at 120 °C. Once the mixture was in the molten state, $Sn(Oct)_2$ (molar ratio of LLA/catalyst = 100) was introduced into the flask by a syringe under N_2 atmosphere. Immediately, the flask was placed in an oil bath thermostated at 135 °C and the mixture was stirred gently under the protect of N_2 atmosphere for 24 h. After cooling down to the room temperature, the mixture was dissolved in tetrahydrofuran and then precipitated in a solvent mixture of methanol and water (volume ratio is 1:3). The precipitation–purification procedure was repeated at least twice. The precipitants were collected and dried in vacuum for 48 h. Yellow brittle solid products were obtained.

2.3. Characterization

^1H and ^{13}C NMR spectra were recorded at 25 °C on a Varian INOVA 500 MHz spectrometer, operated at 500 MHz and 125 MHz, respectively. $CDCl_3$ was used as the solvent and the concentrations of samples for ^1H and ^{13}C NMR measurement are around 20 and 200 mg/mL, respectively. The chemical shifts (ppm) were referred to the internal calibration on the residual peak of $CDCl_3$ solvent (^1H and ^{13}C NMR signals of $CDCl_3$ are 7.26 and 77.36 ppm, respectively). Gel Permeation Chromatography (GPC) of the samples was carried out using a Viscotek GPC270 system. This system is equipped with an online GPC degasser (VE7510), one HPLC pump (VE1122), one TSKgel guard column H_{HR}-H (column size: 6.0 mm(ID) × 4.0 cm(L)), one GMH_{HR}-M mixed bed column (column size: 7.8 mm(ID) × 30.0 cm(L)), one GMH_{HR}-N mixed bed column (column size: 7.8 mm(ID) × 30.0 cm(L)) and three detectors. A refractive index (RI) detector (VE3580) is connected with a dual detectors system (Model 270) in parallel way. Freshly distilled DMF was filtered through membrane with an average pore size of 0.22 μm and used as an eluent at 55 °C. The flow rate was set to be 0.8 mL/min. Solutions of the samples in DMF (5–6 mg/mL) were kept at room temperature for 24 h, and then were filtered through membrane filters with an average pore size of 0.2 μm. A volume of 100 μL of the filtered solution was injected into the system for each run. Eleven PMMA standards were used for the conventional column calibration. OmniSEC software program was used for the acquisition and analysis of GPC data. Matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS) measurements were performed on a Bruker Daltonics Autoflex tof/tof III MALDI-TOF MS mass spectrometer equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. 2,5-Dihydroxybenzoic acid (DHB) was used as matrix and DMF was used as the solvent. FT-IR spectra were recorded on a Nicolet 5DXC FT-IR spectrometer. The measurement was done using KBr pellets, and the scanning range was 4000–400 cm^{-1}. Differential scanning calorimetry (DSC) measurement was carried out on a Netzsch DSC 204 F1 Thermal Analysis System in the temperature range of −40 to 180 °C at a heating rate of 10 °C/min. Glass transition temperature (T_g) was determined as the initial break point of the second heating process. Thermogravimetric analysis (TGA) was carried out on Netzsch STA 409 PC/PG in the temperature range of 30–700 °C at a heating rate of 10 °C/min and nitrogen flow rates of 30 mL/min. The onset decomposing temperature (T_o) and the maximum decomposition temperature (T_{max}) were interpreted as the initial and the final break points of the thermograms, respectively.

3. Results and discussion

The $Sn(Oct)_2$ catalyzed ring-opening polymerization (ROP) of lactide (LA) is verified as a living coordination–insertion mechanism under certain reaction condition [1,3]. In the presence of an initiator, generally primary or secondary hydroxyl or amino groups, linear polymers terminated with secondary hydroxyl groups are formed, whose molecular weight can be controlled through adjusting the ratio of monomer to initiator [3]. When LA was copolymerized with BHB at 130 °C using $Sn(Oct)_2$ as catalyst, it was proved through NMR that BHB merely acted as the initiator using its hydroxyl groups, whereas its carboxylic acid group was intact due to the inefficient esterification between the carboxylic acid and the secondary hydroxyl termini of the formed PLA chains [22,24]. The molecular weight of the resulting linear PLA could be controlled by varying the feed ratio of LA/BHB. Thus, larger amount of BHB monomers only led to the lower molar mass PLA polymers. In order to prepare highly branched polymers from the copolymerization of BHB and LA, how to activate the carboxylic acid group of BHB monomer was the key point. In this paper, aliphatic tertiary amine was attempted to activate the carboxylic acid of BHB for the synthesis of highly branched PLA (Scheme 1).

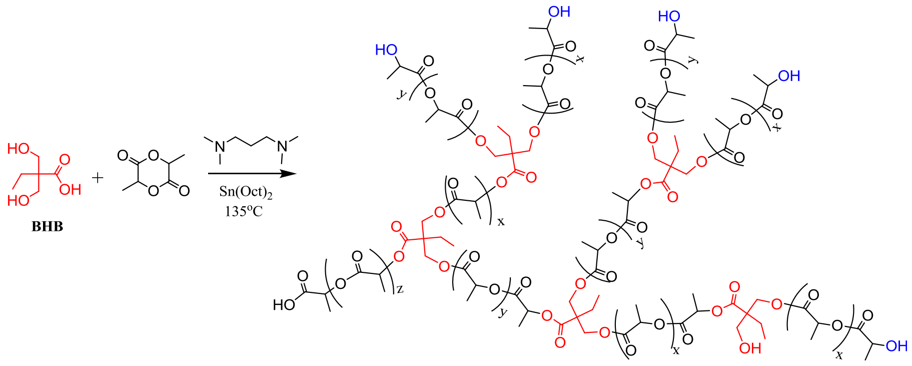
3.1. GPC measurement for the molecular weight evolution of the copolymers

In all the experiments the molar feed LLA/BHB ratio was set to be 5:1 (16.7 mol% BHB). Firstly aliphatic tertiary amine, *N*,*N*,*N*,*N*-tetramethyl-1,3-diaminopropane (TMDAP) was added to the mixture of BHB and LLA (molar feed TMDAP/BHB ratio is 1:1.45). The polymerization was performed in bulk at 125, 135 and 155 °C, respectively, for 24 h using $Sn(Oct)_2$ as catalyst (molar feed LLA/$Sn(Oct)_2$ ratio is 1:0.01). GPC was used to monitor the evolution of the molecular weight. The GPC profiles of unpurified copolymers obtained at different polymerization temperatures are shown in Fig. 1, where the one obtained at 125 °C has three signals at retention volume (RV) below 20 mL. The intense peak A (RV = 19.8 mL, $M_n \approx 50$ g/mol) can be assigned as the eluent solvent. The weak peak B (RV = 19.0 mL, $M_n \approx 197$ g/mol) can be assigned as the residual monomers that exist in all the ROP of LLA because it is an equilibrium reaction [25]. Peak C is very broad, covering the RV from 10.8 to 18.6 mL. Its M_n and weight-average molecular weight (M_w) are 2.76×10^3 and 3.02×10^4, respectively. Raising the polymerization temperature to 135 °C can effectively increase M_n. However, elevating the polymerization temperature to 155 °C is harmful for the formation of higher molecular weight of polymers. Therefore, all the following polymerizations were conducted at the medium temperature of 135 °C.

Fig. 2 shows the GPC traces of unpurified copolymers prepared from the polymerizations in the presence of different amount of TMDAP. The feed ratio of amine to carboxylic group ([N]/[COOH]) is controlled between 1:3 and 2:1. Without the addition of TMDAP, the resulting copolymers are dominated with the low molar mass fraction (curve a in Fig. 2). However, the introduction of TMDAP effectively enhances the intensity of the high molar mass fraction.

To clearly see the effect of the amount of TMDAP on the molecular weight, the polymerization mixtures were precipitated in the excess solvent mixture of methanol and water (1:3 v/v) to remove the residual monomers, catalyst and amine additive. All the purified copolymers were also measured by GPC (Fig. S1 in Supporting Information), from which it can be seen that a lot of low molar mass entity in the polymerization mixture can be removed by this precipitation–purification method. The data interpreted from the GPC traces are listed in Table 1. It is clear that without TMDAP the M_n of the copolymer is only around 2200 g/mol. The presence of TMDAP can effectively increase the molecular weight. When the feed [N]/[COOH] ratio is in the range of 1:3–1:1.45, the M_n of the obtained copolymers is around ten thousands. Further raising the [N]/[COOH] ratio to be 1:1 or more generates copolymers with M_n lower than those from the lower feed [N]/[COOH] ratio. Moreover, the obtained copolymers also show broader molecular weight distribution. It has been verified by Cooper and Storey that in the $Sn(Oct)_2$ catalyzed bulk copolymerization of LLA and BHB the carboxylic acid group of BHB did not participate in the polymerization [24]. This led to the formation of only linear copolymers, not branched ones. When large amount of BHB was used, only low molar mass polymers were obtained. Herein, the significant enhancement of molecular weight implied that the carboxylic acid group of BHB participated in the polymerization due to the addition of TMDAP, resulting in copolymers with branched structure.

TMDAP is an aliphatic tertiary amine. In order to verify whether other amines were also so effective as TMDAP, we selected several representative amines, including another aliphatic tertiary amine tributylamine (TBA), aliphatic primary amine *n*-hexylamine, aliphatic secondary amine piperidine, aromatic tertiary amine *N*,*N*-dimethylaniline (DMA) and aromatic heterocyclic tertiary amine pyridine. The molar ratio of [N]/[COOH] was kept to be 1:1.45. The GPC profiles of the copolymers are shown in Fig. 3. It is clear that another aliphatic tertiary amine TBA shows the similar effect as TMDAP. Contrarily, the addition of aliphatic primary amine does not favor the formation of higher molecular weight of copolymers. The aliphatic secondary amine and the aromatic tertiary amines can increase the intensity of the higher molar mass fraction a little; however, their effectiveness is far worse than the aliphatic tertiary amine. Further raising the feed amount of pyridine and DMA can only enhance the content of higher molar mass fraction to a limited extent (Fig. S2 in Supporting Information), still being worse than TMDAP. Moreover, pyridine is better than DMA in elevating the molecular weight. Therefore it can be concluded that aliphatic tertiary amines are good promoters in the copolymerization of LLA with high amount of BHB comonomer to result in the high molecular weight of copolymers, whereas primary, secondary and aromatic tertiary amines are not.



Scheme 1. Synthesis of highly branched polylactide copolymers.

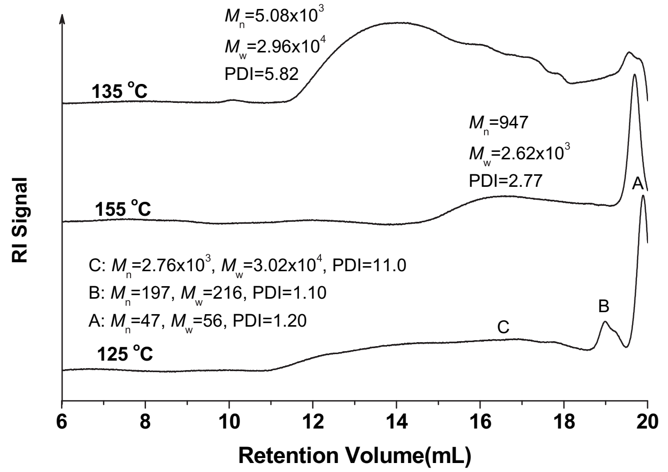


Fig. 1. The GPC profiles of unpurified copolymers derived from the copolymerization of LLA and BHB in the presence of *N*,*N*,*N*,*N*-tetramethyl-1,3-diaminopropane (TMDAP) (feed molar ratio of TMDAP/BHB/LLA is 0.69:1:5) at different polymerization temperature.

3.2. NMR analysis for the structural information of the copolymers

Polymerization conversion can be calculated according to the ^{1}H NMR spectra of the polymerization mixture. After 24 h at 135 °C, the methine signal of LLA monomer (5.05 ppm) became negligible (Fig. S3 in Supporting Information). Compared with the methine signal (5.19 ppm) of LA units in the copolymers, the conversion of LLA monomer was found to be more than 95% under the polymerization condition employed here. Furthermore, the signals from the BHB comonomer (the typical one is the methylene connected to hydroxyl groups at around 3.7 ppm) could not be detected by ^{1}H NMR, indicating that the conversion of BHB monomer was almost 100%. Fig. 4 shows the typical ^{1}H NMR spectra of purified copolymers prepared in the presence and absence of TMDAP, respectively. It is obvious that this precipitation–purification method can effectively removed the small amount of residual monomers, the amine additive and catalyst. From the ^{1}H NMR spectra of the purified copolymers, the structural information of the copolymers is interpreted (Table 1). The signals coming from BHB and LA units can be seen clearly. Without TMDAP, both hydroxyl groups of BHB molecules participate in the ROP or condensation reaction, which can be verified by the disappearance of the methylene signals at 3.77 ppm (signal f in Fig. 4) connected to hydroxyl groups of BHB. However, in the samples prepared with tertiary amine additives, it is found that some of the hydroxyl groups of BHB do not react since the signal f does not disappear completely. Theses BHB moieties bearing one hydroxyl group belong to linear units just like LLA units. According to the integrals of peak f and the methyl groups (peaks l and m) of BHB, the content of linear BHB unit was calculated to be about 9–17%. The other BHB molecules (83–91%) were supposed to be incorporated into the copolymers as the dendritic structures. The feed molar ratio of LLA to BHB was 5:1, whereas the molar ratio of LLA and BHB units in the copolymers was in the range of 2.9–5. The definition of the degree of branching (DB) for AB/AB$_2$ copolymer has been proposed by Hölter et al. as Eq. (1):

$$\mathrm{DB}^{\mathrm{stat}}_{\mathrm{AB/AB_2}} = 2\frac{1-x_{\mathrm{AB}}}{(2-x_{\mathrm{AB}})^2} \qquad (1)$$

Table 1
The structural parameters of purified copolymers derived from the copolymerization of LLA and BHB in the presence of different of amount of TMDAP[a].

Sample	[N]/[COOH][b]	M_n[c]/10^4	M_w[c]/10^4	PDI[c]	LA/BHB in copolymer[d]	LBHB/BHB[e]	DB[f]
1	2:1	0.68	7.37	10.8	3.4	0.12	0.28
2	1:0.7	0.62	13.0	21.1	2.9	0.13	0.30
3	1:1	0.63	5.65	9.0	3.5	0.17	0.26
4	1:1.45	1.21	7.42	6.1	3.8	0.12	0.26
5	1:2	1.02	5.85	5.7	4.4	0.17	0.23
6	1:3	1.07	5.45	5.1	5	0.09	0.23
7	0	0.22	1.06	4.7	4.5	0	–

[a] Polymerization condition: feed ratio of LA/BHB is 5:1; polymerization temperature is 135 °C; Sn(Oct)$_2$ was used as catalyst.
[b] [N]/[COOH] represents the feed ratio of amino groups of added amine to the carboxylic acid group of BHB.
[c] M_n, M_w and PDI were obtained from GPC with PMMA as standard.
[d] LA/BHB in copolymer means the ratio of LA to BHB units in the formed polymers, which is calculated from ^{1}H NMR.
[e] LBHB/BHB means the ratio of linear BHB units to the total BHB units in the formed polymers, which is calculated from ^{1}H NMR.
[f] DB means degree of branching.

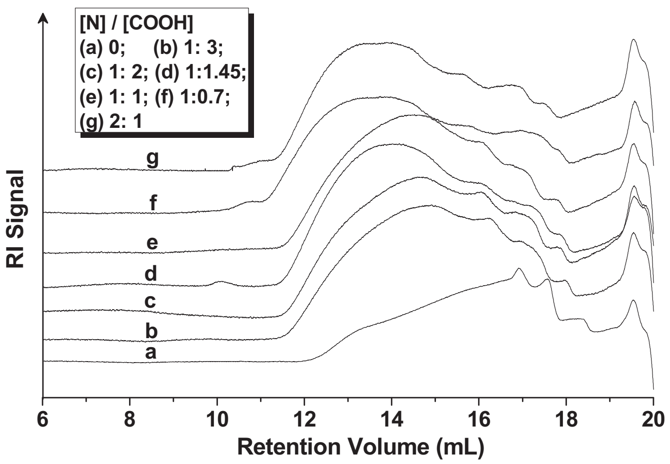


Fig. 2. The GPC profiles of unpurified copolymers derived from the copolymerization of LLA and BHB (feed molar ratio of BHB/LLA is 1:5) in the presence of different amount of *N*,*N*,*N*,*N*-tetramethyl-1,3-diaminopropane (TMDAP): the ratio of amino groups of TMDAP to the carboxylic acid groups of BHB is (a) 0; (b) 1:3; (c) 1:2; (d) 1:1.45; (e) 1:1; (f) 1:0.7; (g) 2:1.

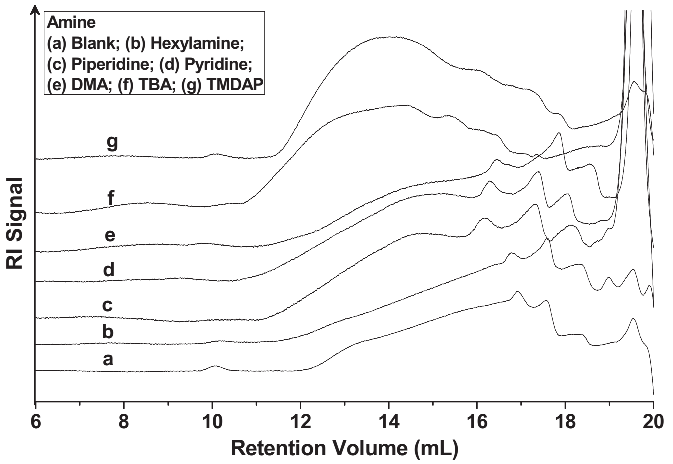


Fig. 3. The GPC profiles of copolymers derived from the polymerization of LLA with BHB (feed molar ratio of BHB/LLA is 1:5) in the presence of different kind of amines: (a) without amine; (b) hexylamine; (c) piperidine; (d) pyridine; (e) *N*,*N*-dimethylaniline (DMA); (f) tributylamine (TBA); (g) *N*,*N*,*N*,*N*-tetramethyl-1,3-diaminopropane (TMDAP) (the ratio of amino groups to the carboxylic acid groups is 1:1.45).

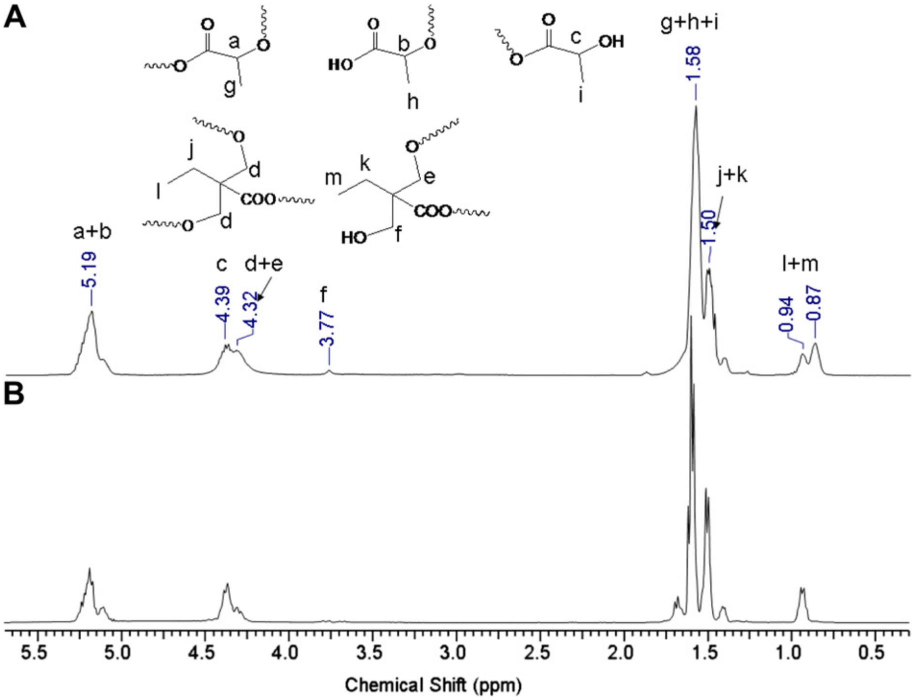


Fig. 4. The typical ^{1}H NMR of copolymers derived from the polymerization of LLA with BHB (feed molar ratio of BHB to LLA is 1:5) (A) in the presence of TMDAP ([N]/[COOH] = 1:1.45) and (B) in the absence of TMDAP.

where x_{AB} is the molar fraction of linear units including the AB monomers and the linear units formed by AB_2 monomers.

Based on the structural information from the ^{1}H NMR, the DBs of the copolymers prepared in the presence of tertiary amine additives were calculated to be about 0.23–0.30, pointing out the highly branched structure of the obtained copolymers.

The copolymers prepared in the presence and absence of additives were also characterized by ^{13}C NMR (Fig. S4). The signals coming from the moieties of BHB and LA can be seen clearly. However, in the copolymers synthesized in the absence of amine additives, the signals assigned as the carbons of BHB are much weaker than those in the copolymers prepared in the presence of amine additives. This verifies again that aliphatic tertiary amine favors the formation of highly branched PLA copolymers. Since the structure of the linear copolymer is simple, most of its ^{13}C NMR signals are single peak. Whereas those of the highly branched copolymers are multiple peaks, such as the peaks from the methine carbons of LLA unit at 68.94 ppm (g), the carbonyl carbons of LLA unit at 169.30 ppm (h), the quaternary carbons of BHB units at 49.86–50.37 ppm (c and c′). This further proves the successful formation of complex highly branched structure due to the presence of amine promoter.

3.3. *MALDI-TOF MS analysis*

MALDI-TOF MS was used to interpret the structure and composition information of the obtained copolymers. Fig. 5 shows the spectrum of the copolymer prepared without amine additive. BHB unit can be observed over the entire mass range; however, its content is different in different mass regions. Below about 1000 Da the main distributions (a and b series in Fig. 5) are found to be the proton adduct of the copolymer chains. The proton source might come from the DHB matrix or the carboxylic acid group of the BHB comonomer. The molar mass (M) of the peaks in series a and b obeys to Eqs. (2) and (3), respectively:

$$M(\mathrm{a}) = (m/2) \times M(\mathrm{LA}) + 3M(\mathrm{BHB}) - 2M(\mathrm{H_2O}) + M\left(\mathrm{H^+}\right) \quad (2)$$

$$M(\mathrm{b}) = (m/2) \times M(\mathrm{LA}) + 2M(\mathrm{BHB}) - M(\mathrm{H_2O}) + M\left(\mathrm{H^+}\right) \quad (3)$$

where m is natural number; M(LA), M(BHB), $M(\mathrm{H_2O})$ and $M(\mathrm{H^+})$ represent the molar mass of LA, BHB, water and proton, respectively.

According to these two equations it can be known that each polymer chain in the low molar mass region contains more than one BHB units. More than one BHB units in the polymer chain mean that condensation reaction happens during the polymerization, and the theoretical condensation byproduct according to the copolymer structure shown in Scheme 1 is water. Thus, in Eqs. (2) and (3) different number of water molecules are subtracted. When

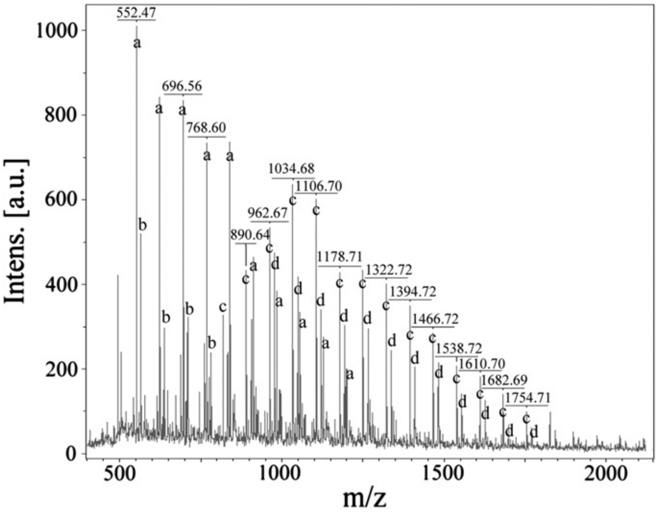


Fig. 5. MALDI-TOF MS of copolymer derived from the polymerization of LLA with BHB (feed molar ratio of BHB to LLA is 1:5) without any additive.

n BHB molecules are incorporated into the polymer chain, subtracting $n-1$ water molecules represents the formation of open-chained polymer. Whereas, subtracting n water molecules implies that cyclic polymers are formed. Thus, from Eqs. (2) and (3) it can be known that the polymers in the low molar mass region are mainly open-chained, not cyclic. The composition of this lower mass fraction is analyzed in detail. For example, the strong signal at 697 Da is composed of 3 BHB and 2 LA units, while the relatively weak signal at 841 Da means that 3 BHB and 3 LA are copolymerized together. It is obvious that the content of BHB units in this lower molar mass fraction is more than 50%, much higher than the feed amount of BHB. The higher content of BHB implies that condensation reaction happens. The primary hydroxyl groups of BHB are more reactive in condensation reaction than the secondary hydroxyl groups derived from the ring-opening of LLA, thus, it can be deduced that the condensation reaction mainly happens among BHB molecules, not between BHB and the secondary hydroxyl group of the formed lactate. Above 1000 Da the intense c and d series in Fig. 5 are found to be the sodium and potassium adduct of the copolymer chains, respectively, and they obey to Eq. (4).

$$M(\text{c or d}) = (m/2)\times M(\text{LA}) + M(\text{BHB}) + M\left(\text{Na}^{+}\text{ or K}^{+}\right) \quad (4)$$

where $M(\text{Na}^{+}$ or $\text{K}^{+})$ represents the molar mass of sodium or potassium cations.

It is found that only one BHB unit exists in each copolymer chain, indicating that this higher molar mass fraction is composed of only linear PLA polymer chains, not the highly branched ones. Thus, it can be concluded that the copolymers derived from the copolymerization of LA and BHB without additive are not homogeneous. Their higher molar mass fraction is dominated with the linear copolymer chains bearing one BHB moiety, whereas the lower molar mass fraction is dominated with the BHB homopolycondensation products.

The copolymers prepared with the addition of TMDAP were also measured by MALDI-TOF (Fig. 6). It is well known that polydisperse samples are rather difficult to analyze, because the detection of lower molar mass fractions is generally favored in terms of evaporation and ionization during the TOF measurements (mass discrimination effect) [26]. Since the obtained highly branched copolymers have not only high molecular weight, but also broad molecular weight distribution, the MALDI-TOF spectra cannot reflect the real molar mass distribution information. However, some structural information of the polymer chains can be interpreted, especially for the low molar mass fraction. Compared with Fig. 5, it is clear that the addition of TMDAP favors the formation of higher molecular weight of copolymers. This is the same as that observed from GPC. The distributions in Fig. 6 are the sodium and potassium adducts of the copolymer chains and they obey Eqs. (5)–(8).

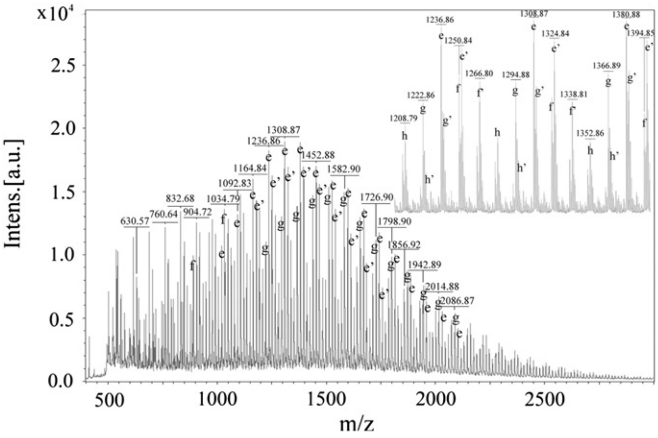


Fig. 6. MALDI-TOF MS of copolymer derived from the polymerization of LLA with BHB (feed molar ratio of BHB to LLA is 1:5) in the presence of TMDAP ([N]/[COOH] = 1:3).

$$M(\text{e or e}') = (m/2)\times M(\text{LA}) + 2M(\text{BHB}) - M(\text{H}_2\text{O}) + M\left(\text{Na}^{+}\text{ or K}^{+}\right) \quad (5)$$

$$M(\text{f or f}') = (m/2)\times M(\text{LA}) + M(\text{BHB}) + M\left(\text{Na}^{+}\text{ or K}^{+}\right) \quad (6)$$

$$M(\text{g or g}') = (m/2)\times M(\text{LA}) + 3M(\text{BHB}) - 2M(\text{H}_2\text{O}) + M\left(\text{Na}^{+}\text{ or K}^{+}\right) \quad (7)$$

$$M(\text{h or h}') = (m/2)\times M(\text{LA}) + 4M(\text{BHB}) - 3M(\text{H}_2\text{O}) + M\left(\text{Na}^{+}\text{ or K}^{+}\right) \quad (8)$$

From the enlarged mass region it can be seen clearly that the polymer chains have different number of BHB units incorporated. Moreover, in the main distributions (e and e′ series in Fig. 6) more than one BHB molecules exist in each copolymer chain. This indicates that the resulting copolymers have mainly the branched structure. According to the most intense signal at 1309 Da we calculate that this copolymer chain consists of 7 LA and 2 BHB units. The molar ratio of LA and BHB units in this copolymer chain is 3.5, which is in the range of 2.9–5 found from ^{1}H NMR.

In both Figs. 5 and 6, the associated signals of different series show an increment of 72 Da, which represents half of the mass of a lactide unit. This can be attributed to the normal transesterification reactions in the Sn(Oct)_2 catalyzed LA polymerization [27]. Moreover, in the MALDI-TOF spectra of the copolymers prepared with and without amine additive, no obvious signals from the cyclic polymer chains can be found.

3.4. Thermal properties determined by TGA and DSC

The thermal stability of the obtained highly branched copolymers was determined by TGA. All the TGA thermograms only showed one sharp transition. The onset decomposition temperatures (T_o) and the maximum decomposition temperature (T_{max}) of the polymers are read off from the initial and the final break points of the thermograms, respectively, and the results are listed in Table 2. For comparison, linear PLLA with M_n being around ten thousand was prepared and measured by TGA. The T_o and T_{max} values of linear PLLA were measured to be 253 and 273 °C, respectively. All the highly branched copolymers have a little lower T_o values, but higher T_{max} values than linear PLLA. The lower T_o values shown by the obtained highly branched copolymers can be

Table 2
Thermal properties obtained from DSC and TGA.

Sample[a]	[N]/[COOH][b]	T_g/°C	T_o/°C	T_{max}/°C
1	2:1	7.5	248	311
2	1:0.7	10.7	247	310
3	1:1	8.2	249	321
4	1:1.45	12.5	240	317
5	1:2	12.4	243	308
6	1:3	11.1	243	310

[a] Sample number is the same as that in Table 1.

[b] [N]/[COOH] represents the feed ratio of amino groups of added amine to the carboxylic acid group of BHB.

ascribed to their large amount of hydroxyl terminal groups connected to LLA units since hydroxyl-terminated PLA is liable to decompose to form cyclic monomer [33]. The higher T_{max} values exhibited by the highly branched copolymers might be due to the existence of BHB units in the copolymer that retard the further decomposition of LA units into cyclic monomers.

The obtained highly branched copolymers were also subjected to DSC measurement. Their thermal behavior was compared with those of linear PLLA. All the data interpreted from the second heating run curves of DSC are listed in Table 2. The linear PLLA had a melting temperature (T_m) of around 170 °C and a glass transition temperature (T_g) of about 55 °C. However, from the DSC curves (Fig. S5 in Supporting Information), it was found that the formed copolymers were amorphous since no obvious crystallization could be detected. This is a common character of highly branched polymer. The T_g values of all the highly branched copolymer are only around 10 °C, much less than that of linear PLLA. This can be attributed to the large amount of terminal groups of the highly branched copolymer since terminal groups have more freedom of mobility.

3.5. Branching mechanism

The molar feed ratio of LLA to BHB is 5:1. On the assumption that only the hydroxyl groups of BHB took part in the polymerization of LLA, the theoretical molecular weight of the resulting copolymer was only 868 g/mol. Whereas, the copolymers prepared without additive show higher molecular weight than this theoretical one according to the GPC and MALDI-TOF analyses. This can be attributed to the inhomogeneity of the formed copolymers. In the copolymer more BHB moieties exist in the lower molar mass fraction, and they are tethered together through the homo-condensation reaction among the carboxylic acid and primary hydroxyl groups of BHB (Scheme 2). In the higher molar mass fraction the content of BHB is low since it only acts as initiator for the ROP of LLA, resulting in the linear PLLA with molecular weight higher than the theoretical one (Scheme 2).

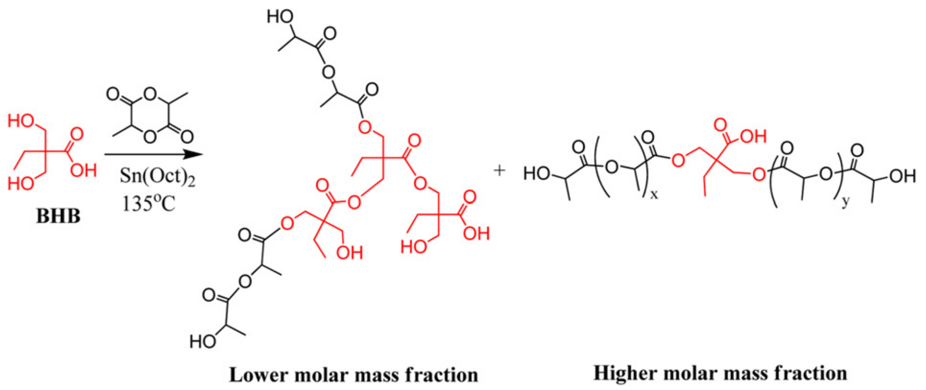
Aliphatic tertiary amines are good promoters for the synthesis of higher molecular weight of highly branched PLA copolymers. The mechanism is proposed as Scheme 3. Aliphatic tertiary amines can effectively transform the carboxylic group of BHB into carboxylate anion due to the neutralization reaction of acid–base. This can be seen clearly from the FT-IR spectra (Fig. 7A) of the mixture of TBA with BHB in the different ratio of [N]/[COOH]. The carboxylic acid group of BHB molecules has the intense peak at 1708 cm^{-1} characteristic for the C=O stretching bond frequency, whose intensity can be lowered by the addition of TBA. Moreover, a new peak appears at 1575 cm^{-1} characteristic for the C=O stretching bond frequency of carboxylate anion. When the ratio of [N]/[COOH] reaches 1:1, the characteristic peak of carboxylic acid completely disappears. This indicates that the aliphatic tertiary amine can neutralize with the carboxylic acid group of BHB nearly quantitatively. From the FT-IR spectra of the mixture of BHB with the aromatic tertiary amines DMA and pyridine (Fig. 7B), it can be known that unlike the aliphatic tertiary amines, the aromatic ones cannot effectively neutralize with BHB even much excess amount is used. This is because the basicity of DMA ($pK_b = 8.9$) and pyridine ($pK_b = 8.8$) is much weaker than the aliphatic tertiary amine ($pK_b = 3.2$). Primary and secondary aliphatic amines can effectively neutralize with the carboxylic acid just like the aliphatic tertiary one due to their similar basicity. However, it has been known that they are also good initiators for ROP of cyclic lactone and lactide [28–32]. At high temperature primary and secondary amines can react with LLA easily to form neutral amide that cannot react with carboxylic acid. Therefore, only the aliphatic tertiary amine can effectively transform the carboxylic acid into carboxylate anion in the copolymerization of LLA and BHB due to its relatively strong basicity and inertness in the polymerization.

Model experiments were conducted to prove whether carboxylate anion can initiate the ROP of LLA. In the polymerization reaction BHB was replaced by pentanoic acid (PA). From ^{1}H NMR spectra (Fig. S6 in Supporting Information) it can be seen that the methine signal of lactate (5.16 ppm) appears and becomes more intense upon prolonging the reaction time, whereas the intensity of methine signals of LLA monomer at 5.05 ppm decreases gradually. From this evidence it can be deduced that carboxylate anion can initiate the ROP of LLA. The more direct evidence comes from the mass spectrum (Fig. 8). It is found that the main distribution is the sodium adducts of the copolymer chains, and it obeys Eq. (9):

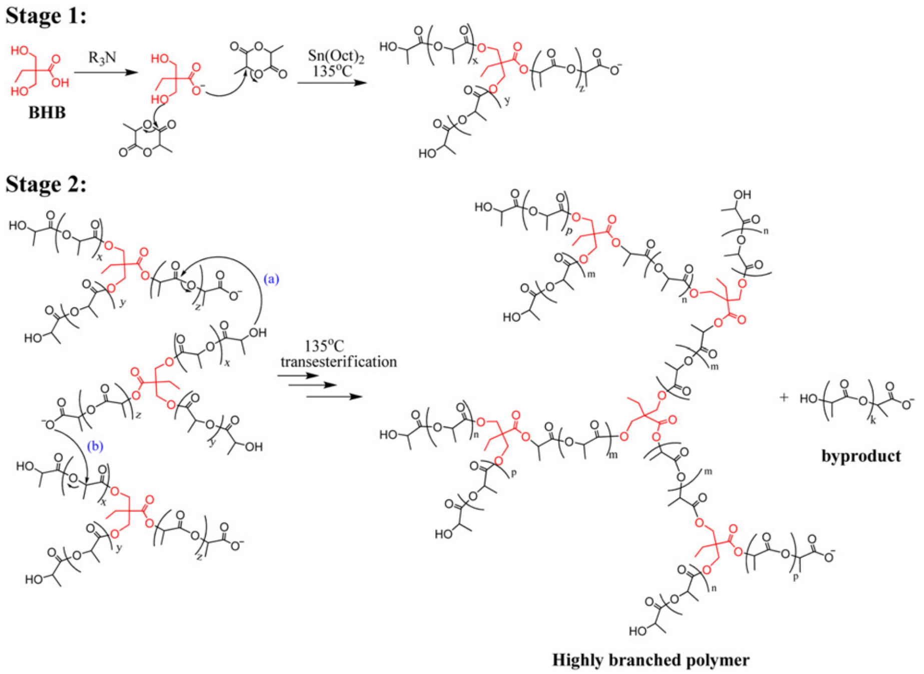
$$M = M(\mathrm{PA}) + (m/2) \times M(\mathrm{LA}) + M\left(\mathrm{Na}^+\right) \tag{9}$$

where $M(\mathrm{PA})$ and $M(\mathrm{Na}^+)$ represent the molar mass of pentanoic acid and sodium cation, respectively.

From Eq. (9) it is clear that each polymer chain contains only one PA unit and different amount of LA moieties. For example, the most intense signal at 2213 Da is composed of 1 PA and 14.5 LA units. Kinetic studies monitored by ^{1}H NMR demonstrate that the initiating activity of carboxylate anion is lower than that of hydroxyl group (Fig. S7 in Supporting Information), however, the difference is not of orders of magnitude. Therefore, it can be deduced that the formed carboxylate anion of BHB has the chance to attack the methine carbon of LLA to form lactate anion. The formed lactate anion repeatedly attack the methine carbon of LLA, resulting in



Scheme 2. $Sn(Oct)_2$ catalyzed copolymerization of LLA with BHB.



Scheme 3. Proposed mechanism of $Sn(Oct)_2$ catalyzed copolymerization of LLA with BHB in the presence of aliphatic tertiary amine.

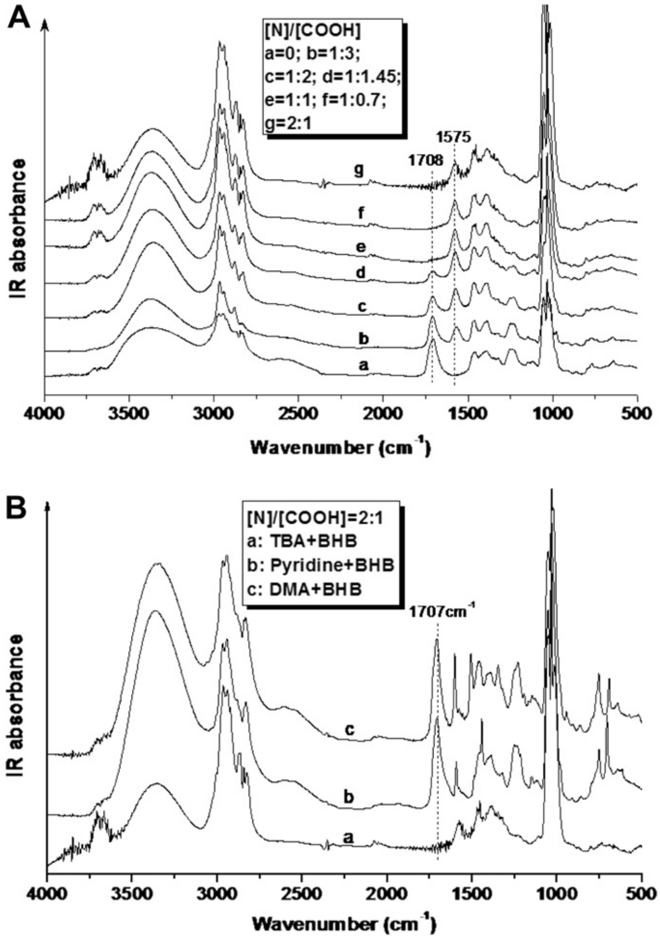


Fig. 7. FT-IR spectra of mixtures of (A) TBA and BHB with different [N]/[COOH] ratio: (a) 0; (b) 1:3; (c) 1:2; (d) 1:1.45; (e) 1:1; (f) 1:0.7; (g) 2:1; (B) BHB with different amine at [N]/[COOH] = 2:1 (a) TBA; (b) pyridine; (c) DMA.

a PLA chain terminated with one lactate anion. The hydroxyl groups of BHB can initiate the ROP of LLA through attacking the carbonyl carbon of LLA, resulting in PLA chains terminated with secondary hydroxyl groups. The formed polymer molecules can be regarded as two kinds of AB_2 macromonomers. With respect to the first kind of AB_2 macromonomer, the two B functional groups are the hydroxyl groups, while the A functional group is not the lactate anion, but the ester groups of short PLA chain derived from the carboxylate anion of BHB. Intermolecular transesterification reaction due to the nucleophilic attacking of hydroxyl groups to the carbonyl carbons of A groups leads to the formation of higher molecular weight of branched polymers. Meanwhile, lactate salt or linear PLA oligomers

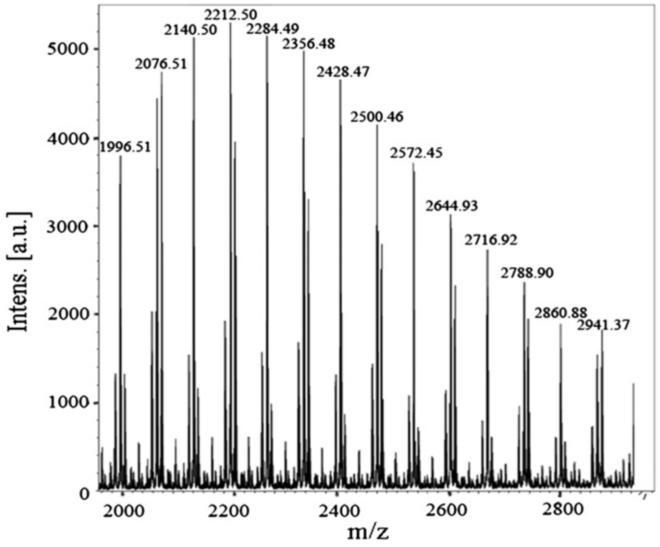


Fig. 8. Mass spectrum of copolymer derived from the $Sn(Oct)_2$ catalyzed polymerization of LLA in the presence of TBA and pentanoic acid at 135 °C for 1 h (feed molar ratio of pentanoic acid to LLA is 1:5, [N]/[COOH] = 1:1.45).

as byproduct is produced. In the case of the second kind of AB_2 macromonomer, A functional group is the lactate anion, while the two B functional groups are not the hydroxyl groups, but the ester groups of short PLA chain derived from the hydroxyl groups of BHB. Intermolecular transesterification reaction due to the nucleophilic attacking of carboxylate anion to the methine carbons of B groups also results in the higher molecular weight of branched polymers.

4. Conclusions

Medium molecular weight of highly branched PLA copolymers was successfully prepared by the $Sn(Oct)_2$ catalyzed bulk copolymerization of LLA with BHB (feed ratio of LLA to BHB to $Sn(Oct)_2$ is 5:1:0.05) using aliphatic tertiary amine as promoter. Aromatic amines and aliphatic primary and secondary ones were not so effective as aliphatic tertiary one due to their weak basicity or high reactivity for the ring-opening of LLA monomer. The optimized polymerization temperature was about 135 °C. When the feed ratio of amino groups to carboxylic acid groups ([N]/[COOH]) was in the range of 1:3 to 1:1.45, the M_n of the resulting copolymers relative to the linear PMMA was around ten thousands. Further raising the ratio of [N]/[COOH] to be 1:1 or more reduced the M_n and broadened their molecular weight distribution. NMR spectra proved the existence of both LA and BHB units in the copolymers, and their ratios were in the range of 2.9–5. Moreover, about 9–17% of BHB moieties existed in the state of linear structure. The DB value of the obtained highly branched copolymers was about 0.23–0.30. MALDI-TOF MS also verified that more than one BHB comonomers were incorporated into the copolymer molecules. The resulting highly branched PLA copolymers were amorphous. Compared with linear PLLA, the highly branched PLA copolymers were thermally more stable and had lower T_g.

The mechanism of formation of medium molecular weight of hyperbranched PLA copolymers was proposed as follows: aliphatic tertiary amine can stoichiometrically neutralize with carboxylic acid group of BHB. The formed carboxylate anion of BHB and its two hydroxyl groups could initiate the ROP of LA, resulting in AB_2 type macromonomer terminated with two hydroxyl groups and one carboxylate anion. Intermolecular transesterification reaction among these macromonomers led to the formation of higher molecular weight of hyperbranched polymers.

Without the aliphatic tertiary amine as promoter, the resulting copolymer had relatively low molecular weight and its structure was inhomogeneous verified by MALDI-TOF MS. Its lower molar mass fraction was dominated with the BHB homopolycondensation products, whereas its higher molar mass fraction was dominated with the linear copolymer chains with BHB merely as initiator.

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Appendix. Supporting information

Supplementary data related to this article can be found online at doi:10.1016/j.polymer.2011.12.045.

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