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RESEARCH ARTICLE

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Direct melting polycondensation and characterization of poly(ε-caprolactone-*co*-lactic acid)

Abstract A kind of biodegradable material, poly(ε-caprolactone-co-lactic acid) [P(CL-*co*-LA)] was synthesized via the direct melting polycondensation of lactic acid (LA) and ε-caprolactone (CL). The influences of the polycondensation time, and the catalyst type on the intrinsic viscosity of P(CL-*co*-LA) were also investigated. The results indicate that P(CL-*co*-*dl*-LA), with an intrinsic viscosity of 0.4733 dL/g, can be prepared by direct melting polycondensation with the molar ratio LA/CL = 3:7 at 180°C and 70 Pa for 12 h, using 0.5% (mass fraction) of $SnCl_2$ as the catalyst. Compared with lactide ring-opening polycondensation (ROP), the direct melting polycondensation of LA and CL is more practicable and simple.

Keywords poly(ε-caprolactone-*co*-lactic acid), direct melting polycondensation, biodegradability

1 Introduction

Aliphatic polyesters such as poly(lactide) (PLA), poly(ε-caprolactone) (PCL) and their copolymer P(CL-*co*-LA) have received much attention because of their potential applications in controlled drug delivery, tissue engineering, and bone fixation due to their biodegradable and biocompatible properties [1].

Usually, copolymer P(CL-*co*-LA) can be synthesized by two-step polycondensation with LA and CL. The polycondensations of CL monomer (or PCL) with lactide (dimmer of lactic acid), or PCL with PLA, have been reported [2–4]. But, these processes are too long and the cost is high.

In this paper, we report the result of polycondensation of CL and LA by a direct melting method and the characterization of the obtained P(CL-*co*-LA).

2 Experimental

2.1 Materials

dl-LA and *l*-LA were supplied as a 99 wt% aqueous solution, ε-caprolactone was purchased from Aldrich, and $SnCl_2$ was purchased from Guangzhou Donghong Chemical Industry Factory. All these materials were used as received.

2.2 Polycondensation

All polycondensations were carried out in a round-bottomed flask equipped with a magnetic stirrer, which had been flame-dried. CL and LA in feed molar ratio $n(dl\text{-LA}):n(\text{CL}) = 3:7$ were introduced into the reactor for precondensation at 140°C under 70 Pa for 3 h. Then, catalyst $SnCl_2$ ($\omega\ (SnCl_2) = 0.5\%$) was added and the polycondensation was conducted at 180°C and 12 h for *dl*-LA, 180°C and 16 h for *l*-LA. The P(CL-*co*-LA) obtained was dissolved in $CHCl_3$, and the purified product was precipitated from methanol, and dried in vacuum at 50°C for 24 h with yield 45%–70%.

2.3 Measurements

The intrinsic viscosity $[\eta]$ of P(CL-*co*-LA) was measured in $CHCl_3$ at 25°C viscometrically. The structure was characterized by IR spectrometry and ^{1}H NMR spectrometry with a Vector-33 infrared spectrometer and a Germany Bruker NMR spectrometer.

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3 Results and discussion

3.1 The influence of polycondensation on the intrinsic viscosity [η] of P(CL-*co*-LA)

The melting polycondensation of CL and LA involves the ring-opening polycondensation of CL, the polycondensation of LA. Using stannous catalyst [5–7] the ring-opening polycondensation of CL reaches ~100% within 20 min. Therefore, the copolycondensation step was very important for the reaction rate of the system, where dehydration is the key to obtain high molecular weight polymer [8]. Therefore, the polycondensation of CL and LA was carried out without $SnCl_2$ to discuss the influence of polycondensation on the copolymer, the experiment results are listed in Table 1.

Table 1 Influence of polycondensation on the intrinsic viscosity of the copolymer

No.	Polycondensation time / h	Intrinsic viscosity / $(dL \cdot g^{-1})$
1	0	0.2346
2	0.5	0.2622
3	1	0.3080
4	3	0.3480
5	4	0.3345
6	5	0.3247
7	6	0.2360
8	7	0.2616

Reaction conditions: 170°C, 70 Pa and $n(dl\text{-LA}):n(\text{CL}) = 3:7$, $\omega(SnCl_2) = 0.5\%$, time 16 h.

The intrinsic viscosities of copolymers with prepolycondensation are higher than those without prepolycondensation, and the intrinsic viscosities of P(CL-*co*-LA) with prepolycondensation for 3 h reaches the maximum. Subsequently, the intrinsic viscosities of copolymer decline with the increase of prepolycondensation time.

Based on the prepolycondensation of CL and LA, the results and analysis of orthogonal test showed that, once the polymerization temperature of 180°C and feed molar ratio $n(\text{LA}):n(\text{CL}) = 3:7$ were fixed, the intrinsic viscosities of the copolymer was higher. Therefore, the influences of catalyst and melting copolycondensation time on the intrinsic viscosities of the copolymer were discussed under the reaction conditions of the polymerization temperature of 180°C and feed molar ratio $n(\text{LA}):n(\text{CL}) = 3:7$.

3.2 The influence of catalyst on intrinsic viscosity [η] of P(CL-*co*-LA)

3.2.1 The influence of different catalysts

Without catalysts, the direct polycondensation of P(CL-*co*-LA) was a slow reaction, and cyclic by-products were easily produced. Therefore, it was necessary and important to use catalysts to accelerate the reaction. The influences of different catalysts on the intrinsic viscosities of the copolymer are shown in Tables 2 and 3.

Table 2 Influence of different catalysts on P(CL-co-*dl*-LA) intrinsic viscosity

Catalysts	Intrinsic viscosity / $(dL \cdot g^{-1})$	State of catalyst in polycondensation
Sn	—	Good dispersibility, worse dissolubility
SnO	—	Good dispersibility, worse dissolubility
SnO_2	—	Normal dispersibility, easy sediment
SnC_2O_4	0.2821	Good dispersibility, bad dissolubility
$SnCl_2$	0.4733	Good dispersibility, better dissolubility
Zinc sterate	—	Good dispersibility, worse dissolubility
Zinc acetate	—	Good dispersibility, good dissolubility
ZnO	—	Good dispersibility, good dissolubility
Calcium lactate	0.2713	Good dispersibility, good dissolubility
TSA	0.3119	Good dispersibility, better dissolubility

Reaction conditions: 180°C, 70 Pa, 12 h, and catalyst quantity 0.5 wt%.

Table 3 Influence of catalysts on P (CL-co-*l*-LA) intrinsic viscosity

Catalyst kinds	Intrinsic viscosity / $(dL \cdot g^{-1})$	State of catalyst in polycondensation
Sn	0.2804	Good dispersibility, worse dissolubility
SnO	0.2836	Good dispersibility, worst dissolubility
SnO_2	—	Normal dispersibility, easy sediment
SnC_2O_4	—	Good dispersibility, bad dissolubility
$SnCl_2$	0.4121	Good dispersibility, better dissolubility
Zinc sterate	—	Good dispersibility, worse dissolubility
Zinc acetate	—	Good dispersibility, good dissolubility
ZnO	—	Good dispersibility, good dissolubility
Calcium lactate	—	Good dispersibility, good dissolubility
TSA	0.2964	Good dispersibility, better dissolubility

Reaction conditions: 180°C, 70 Pa, 16 h, and catalyst quantity 0.5 wt%.

It was obvious that the catalytic effect of $SnCl_2$ was the best, and the intrinsic viscosities of the copolymer were 0.4733 dL/g (Table 2) and 0.4121 dL/g (Table 3).

3.2.2 The influence of complex catalyst

In order to accelerate the reaction by acid, the influences of the complex catalysts of TSA and metal salt on the direct polycondensation of P(CL-*co*-LA) were investigated (Table 4).

The results show that the complex catalyst of TSA and SnC_2O_4 was better than single SnC_2O_4 or TSA. Especially, when their complex weight ratio was 1:1, the intrinsic viscosities of the copolymer (0.3549 dL/g) were greatly increased. This is due to the increase in acidity of the reaction system, and the promotion for the dissolution of SnC_2O_4.

For the complex catalyst of TSA and $SnCl_2$, complex catalyst was better than single TSA, but worse than $SnCl_2$. The reason may be that the addition of TSA in the reaction system promoted the formation of a PCL oligmer (Fig. 1).

Based on the above, in order to simplify the experiment condition, only single $SnCl_2$ was chosen as the catalyst in the following experiment.

3.2.3 The influence of catalyst quantity

Using *dl*-LA and CL as starting materials and $SnCl_2$ as catalyst, under the experiment conditions of 180°C, 12 h and

Table 4 Influence of the complex catalysts of TSA and metal salt on P(CL-co-*dl*-LA) intrinsic viscosity

Complex catalysts and their weight ratio		Intrinsic viscosity / (dL·g^{-1})	State of catalyst in polycondensation
SnC_2O_4 + TSA	0:1	0.3119	Good dispersibility, good dissolubility
$w(SnC_2O_4):w(TSA)$	1:1	0.3549	Good dispersibility, better dissolubility
	2:1	0.3203	Good dispersibility, better dissolubility
	1:0	0.2821	Good dispersibility, better dissolubility
$SnCl_2$ + TSA	0:1	0.3119	Good dispersibility, better dissolubility
$w(SnCl_2):w(TSA)$	1:1	0.3912	Good dispersibility, better dissolubility
	2:1	0.4232	Good dispersibility, better dissolubility
	1:0	0.4733	Good dispersibility, better dissolubility

Reaction conditions: 180°C, 70 Pa, 12 h, and catalyst quantity 0.5 wt%.

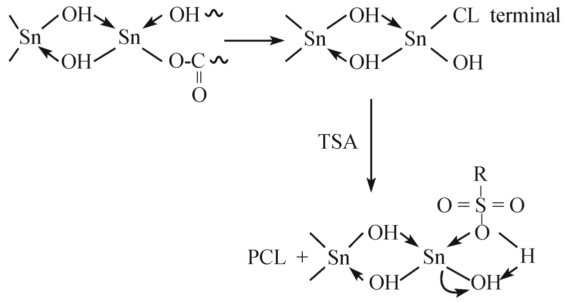


Fig. 1 Catalyatic mechanism of the complex catalyst of $SnCl_2$ and TSA

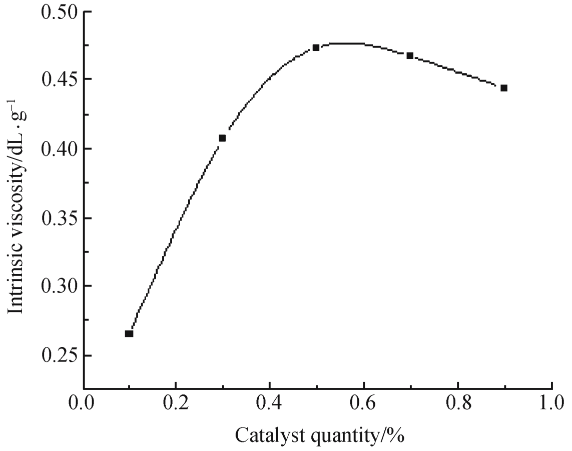


Fig. 2 Relationship between catalyst quantity and intrinsic viscosity

70 Pa, the influences of catalyst quantity on the intrinsic viscosity of P(CL-co-*dl*-LA) was shown in Fig. 2.

It was obvious that the best quantity was 0.5%. When the catalyst quantity was less than 0.5%, the intrinsic viscosity of P (CL-co-*dl*-LA) increased with the increase of catalyst quantity. Once the catalyst quantity was more than 0.5%, the thermal degradation was catalyzed by $SnCl_2$ also [9]. When *l*-LA and CL was catalyzed by 0.7% $SnCl_2$, crude copolymer became dark, which indicated the thermal degradation took place.

3.3 The influence of copolycondensation time on intrinsic viscosity [η] of P(CL-*co*-LA)

Under the best catalyst quantity $SnCl_2$ 0.5% and 180°C, 70 Pa, the influences of the melting copolycondensation time on the copolycondensation of *dl*-LA, *l*-LA and CL were respectively investigated, and the results are shown in Tables 5 and 6.

Table 5 Influences of copolycondensation time on P(CL-*co*-*dl*-LA) intrinsic viscosity

Run	Copolycondensation time / h	Intrinsic viscosity / (dL·g^{-1})
1	0	0.0911
2	6	—
3	7	—
4	10	0.3144
5	12	0.4733
6	14	0.3616
7	16	Dark crude copolymer couldn't give purified product

Table 6 Influences of copolycondensation time on P(CL-*co*-*l*-LA) intrinsic viscosity

Run	Copolycondensation time / h	Intrinsic viscosity / (dL·g^{-1})
1	0	0.0723
2	8	The purified product was too little to test the viscosity
3	10	0.3134
4	13	0.3467
5	16	0.4121
6	17	Dark crude copolymer couldn't give purified product

It was obvious that the appropriate melting copolycondensation time for *dl*-LA and CL was 12 h, but for *l*-LA and CL it was 16 h. A longer time caused the thermal degradation of the copolymer and oxidation of the reactant. In the end, no purified product could be obtained from the black reaction system.

3.4 The structure characterization of P(CL-*co*-LA)

3.4.1 FTIR

The spectra of FTIR of P (CL-*co*-*dl*-LA) and P (CL-*co*-*l*-LA) were almost the same. IR data of P(CL-*co*-*dl*-LA) (KBr, cm^{-1}): 1736, carbonyl group (C=O) in copolyester, strong; 1196, 1164, 1100, ether bond (C–O–C) of ester group in copolyester, strong; 2944, 2866, 1458 and 1359, saturated C–H bond (CH_3, CH_2, CH) in copolyester; 3544, hydroxyl group (OH) in copolyester, weak (Fig. 3).

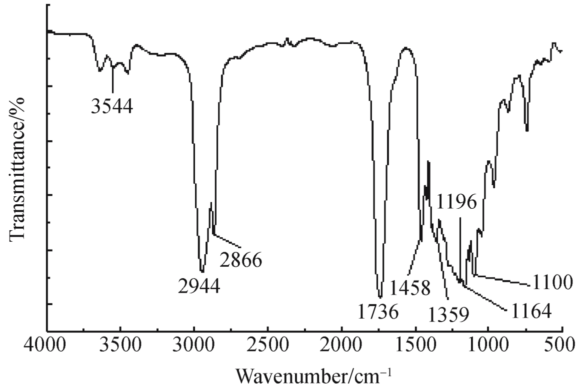


Fig. 3 IR spectra of P(CL-*co*-*dl*-LA)

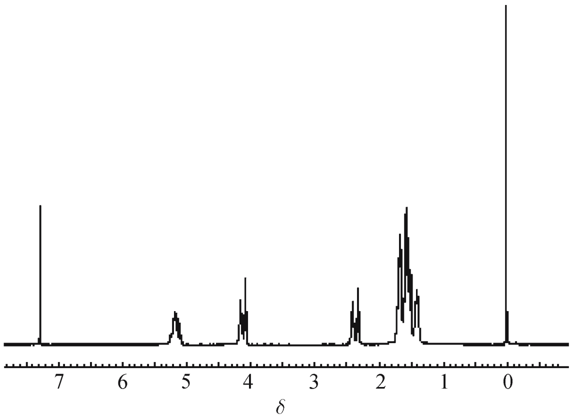


Fig. 4 ^{1}H NMR spectra of P (CL-*co*-*dl*-LA)

The recorded data were consistent with the data in literatures [4,10,11], which indicated the product indeed was the copolymer of CL and LA. Especially, the absorption of 1458 cm^{-1} was ascribed to the introduced CH_2, which did not exist in the homopolymer of LA.

3.4.2 ^{1}H NMR

The spectra of ^{1}H NMR of P(CL-*co*-*dl*-LA) and P(CL-*co*-*l*-LA) were also similar (Fig. 4). ^{1}H NMR data of P (CL-*co*-*dl*-LA) ($CDCl_3$ as solvent and TMS as internal standard, δ): 5.08 (H_b), 4.12 (H_f), 2.32 (H_c), 1.65 (H_d), 1.50 (H_a), 1.39 (H_e) (Fig. 5). These data were consistent with the data in literatures [4,10,11].

The multiple peak split showed that the copolymer of CL and LA was a random copolymer. It was reported in the literature [11] that the $HOCH_2$ group in terminal PCL pigment in the copolymer of CL and LA had an adsorption at δ 3.65. However, this absorption was not found in the spectra of ^{1}H NMR. Therefore, the copolymer P(CL-*co*-LA) synthesized in this experiment was terminated by PLA pigment (Fig. 5).

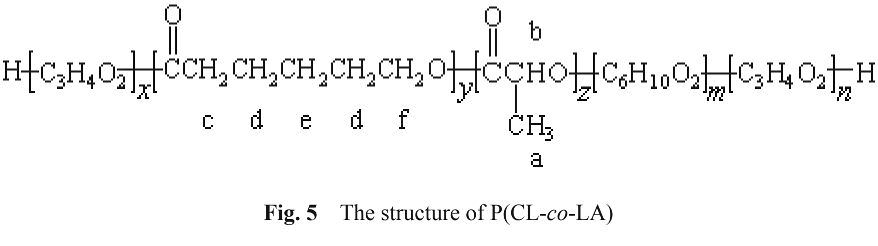
4 Conclusion

(1) Prepolycondensation can improve the intrinsic viscosity of the copolymer in the direct melting copolycondensation of LA and CL.

(2) Respectively using *dl*-LA, *l*-LA and CL as starting materials, under 180°C and 70 Pa, P(CL-*co*-*dl*-LA) with an intrinsic viscosity of 0.4733 dL/g can be prepared by direct melting copolycondensation of *dl*-LA and CL in a molar ratio of 3:7 at 180°C and 70 Pa for 12 h, with 0.5% (mass fraction) $SnCl_2$ as the catalyst, and that P(CL-*co*-*l*-LA) with an intrinsic viscosity of 0.4121 dL/g can be produced by direct melting copolycondensation of *l*-LA and CL in the same conditions for 16 h.

(3) The intrinsic viscosities of copolymers using the complex catalysts of TSA and SnC_2O_4 are higher than those of the copolymers only using the single catalyzer TSA or SnC_2O_4, but not greater than those of the copolymers only using $SnCl_2$ as the catalyst.

(4) Compared with the lactide two-step method, the direct melt copolycondensation for P(CL-*co*-LA) has a shorter process with less consumption of reagents and materials. The novel synthetic way is beneficial to its application in biomedical fields such as drug delivery and tissue engineering scaffolds.



$$H{-}\!\left[C_3H_4O_2\right]_x\!\left[\overset{O}{\overset{\|}{C}}\underset{c}{CH_2}\underset{d}{CH_2}\underset{e}{CH_2}\underset{d}{CH_2}\underset{f}{CH_2}O\right]_y\!\left[\overset{O}{\overset{\|}{C}}\overset{b}{\underset{\underset{a}{CH_3}}{\underset{|}{C}}}HO\right]_z\!\left[C_6H_{10}O_2\right]_m\!\left[C_3H_4O_2\right]_n\!H$$

Fig. 5 The structure of P(CL-*co*-LA)

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