Polymer 53 (2012) 5476–5479

Contents lists available at SciVerse ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Isotactic polycondensation of L-lactic acid with biogenic creatinine

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ARTICLE INFO

Article history:
Received 11 July 2012
Received in revised form
13 September 2012
Accepted 21 September 2012
Available online 26 September 2012

Keywords:
Polycondensation
Isotactic polymerization
Poly-L-lactic acid

ABSTRACT

Isotactic polycondensation of L-lactic acid (LLA) catalyzed by biogenic creatinine was carried out at 140–175 °C under sequentially reduced pressure (30–10 torr). The product poly-LLA (PLLA) possesses high optical purity (e.e. 96.1–98.7%) as well as narrow molecular weight distribution (PDI 1.74–1.85). ^{13}C NMR follow-up monitor of the polymerization demonstrated that the isotacticity of PLLA formed in the polymerization kept constant high values (isotacticity 97.8–99.5%) throughout the polymerization. The ^{1}H NMR structural characterization of the growing polymeric species in progress of the polycondensation revealed that the active catalytic species is a guanidinium formed in situ. A possible mechanism of the creatinine-catalyzed polycondensation was proposed.

1. Introduction

The increasing concerns with our eco-environment urge to develop and utilize biodegradable materials made from renewable resource [1–5]. Among the family of eco-friendly polymers PLA is the most important synthetic polyester which finds significant biomedical applications [6–9] and shows great potential to be an alternative to petrochemical plastics [10]. The physical and mechanical properties of PLA are critically dependent on its stereochemistry. Isotactic PLLA, a semi-crystallinic polymer, has a high melting transition temperature (Tm) and excellent mechanical properties. Whereas the atactic poly-(D,L)-LA (PDLLA) is an amorphous polymer with relatively low thermal transition temperature and mechanical properties [11,12]. PLLA with high isotacticity is predominately prepared by stereospecific ring-opening polymerization (ROP) of L-lactide [13–20]. Polycondensation is of practical significance for the PLA synthesis because, unlike the ROP method, it does not require high-purity monomer. However, up to date the metal catalysts developed for polycondensation of LLA cannot realize highly stereochemical-controlled polymerization in the absence of an activator. For example, polycondensation of LLA catalyzed by $SnCl_2 \cdot 2H_2O$, well-known as the best metal catalyst, undergoes severe racemization (up to 75%) [21] producing polymers with low optical purity [22]. Polymers used for medical applications should be free of any toxic metals. Controlled synthesis of biodegradable polymers by organic compound-catalyzed polymerization has thus attracted great attention in the last decade [17,23–26]. Our research has focused on the design and development of guanidine-based initiators/catalysts for the controlled synthesis of biodegradable polymers [24–30]. Creatinine is a biogenic organic base formed in arginine metabolism in human body. Previously we reported living ROP of lactide (LA) catalyzed by creatinine acetate [24]. Recently we successfully conducted isotactic polycondensation of LLA catalyzed by creatinine. Here we report the work. To the best of our knowledge this is the first highly isotactic polycondensation of LLA with a biogenic organic catalyst.

2. Experimental

2.1. Reagents and instrumentation

Creatinine (99%) was purchased from Aldrich Co. LLA (90wt%, optical purity 99.5%) was purchased from Musashino Chemical (China) Co., Ltd. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 500 Hz (^{1}H) and 100 Hz (^{13}C) with $CDCl_3$ as a solvent and tetramethylsilane as an internal reference. The molecular weight of the PLLA sample was measured with GPC on a PL-GPC 120 chromatograph equipped with a refractive index detector, and a set of two gel columns. The columns were

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http://dx.doi.org/10.1016/j.polymer.2012.09.044

calibrated with polystyrene standards. Analysis was performed with tetrahydrofuran as a solvent at a flow rate of 1.0 mL/min and a temperature of 40 °C.

2.2. Polycondensation

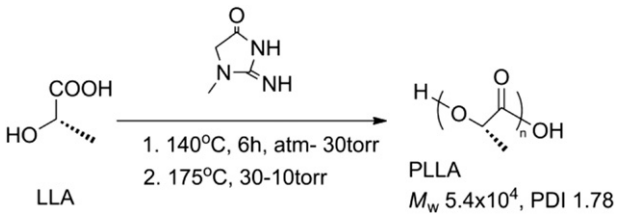
A typical procedure was as follows. To a three-necked flask the predetermined amount of LLA and creatinine (0.1 wt% relative to LLA) were added. The flask equipped with a mechanical stirrer and reflux condenser was connected to a vacuum-argon system. The mixture was heated to 140 ± 1 °C under successively reduced pressure of atm-30 torr in 4 h. The reaction was maintained at this condition for another 2 h, and a viscous liquid mixture of LLA oligomer (OLLA) was obtained. The mixture was then heated to 175 ± 1 °C while the pressure of the system was successively reduced to 10 torr in 24 h. The reaction was conducted for a predetermined time under 10 torr. At the end of polymerization the flask was cooled to room temperature. The contents were dissolved in acetone, the solution was then poured into cold water. The precipitate was collected, dried under vacuum for 48 h at 40 °C yielding a white solid. The solid product was then subjected to GPC, ^{1}H NMR and ^{13}C NMR analysis.

3. Results and discussion

3.1. Polymerization and product characterization

In the past decade polycondensation of LLA in the melt was thoroughly investigated with different metal catalysts. Among them tin(II) chloride dihydrate $SnCl_2{\cdot}2H_2O$ was recognized as the most active one in the absence of any activator [21,22]. Some obvious shortcomings, however, exist in the stannous salt catalyzed polycondensation: (1) Racemization occurs severely in the polymerization, and as a result an atactic polymer with low optical purity (e.e. 60%) was obtained [21]. (2) The yield of polymer was considerable low (37% for a PLLA with Mw 2.6×10^4) [22]. This was, to a large extent, due to that $SnCl_2{\cdot}2H_2O$ shows high depolymerization activity leading to rapid lactide formation, a back-biting side reaction [31]. (3) The potential cytotoxicity of the tin(II) salt arouses increasing concern about the biosafety of the biomedical matrices/devices, as well as the environmental hazard of the poison metal leak during degradation of the disposable articles made from the polymer [32,33]. With intent to overcome the above-mentioned shortages, polycondensation of LLA with a biogenic creatinine catalyst was successfully conducted (Scheme 1).

The polycondensation was followed and monitored by ^{1}H NMR and ^{13}C NMR. Isotacticities of the polymers formed in the polymerization were estimated based on the ^{13}C NMR spectra of the methine carbon in the PLLA molecules [34,35]. The ^{13}C NMR spectra of the formed PLLA were shown in Fig. 1. The characteristic peak signals corresponding to the isotactic sequence of PLLA were shown in Fig. 2. These experimental results showed that creatinine-catalyzed polycondensation of LLA proceeded in a stereochemical-controlled way featuring the constant high values



Scheme 1. Isotactic polycondensation of LLA catalyzed by creatinine.

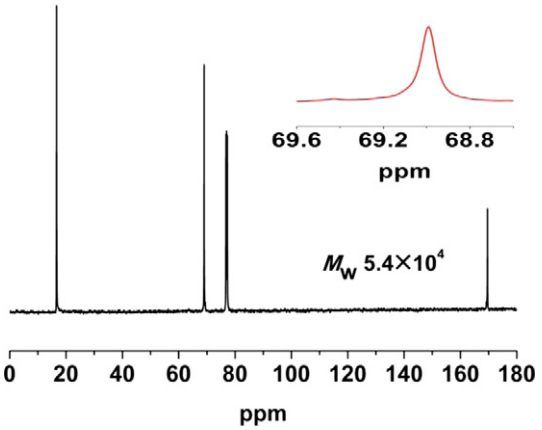


Fig. 1. The ^{13}C NMR spectrum of PLLA.

of isotacticity (97.8%–99.5%) and optical purity (e.e. 96.1–98.7%), as well as narrow molecular weight distribution (PDI 1.78–1.85) of product PLLA (Table 1).

Investigation into the polymerization kinetics was conducted by following the variation of $\overline{X}_n$ (number average polymerization degree) of formed PLLA with time. Linear relationship of $\overline{X}_n$ vs time was observed which indicated that the kinetics of the polycondensation was second order with respect to the reactive functional groups attached to monomeric/polymeric species including two first-order dependence to the concentration of carboxyl and hydroxyl groups respectively [36].

3.2. Polymerization mechanism

To have a knowledge of the polymerization mechanism, a growing polymeric species was carefully captured under argon and subjected to ^{1}H NMR characterization immediately. The ^{1}H NMR spectrum of the polymer (Fig. 3) revealed that the catalytic species was a creatinine guanidinium (G^+) which associated with a terminal carboxylate group (HO–PLLA–COO^-) of the growing PLLA molecule. The guanidinium was reasonably postulated to form in situ by the reaction of creatinine with a proton from the

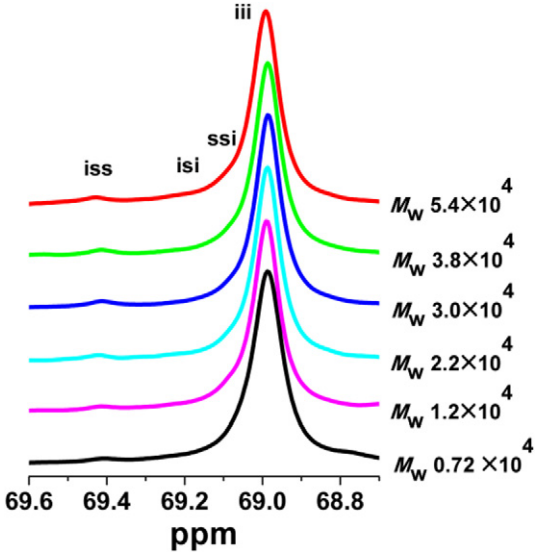


Fig. 2. ^{13}C NMR charaterization of the PLLA formed in the creatinine-catalyzed polycondensation of LLA.

Table 1
Polycondensation of LLA in the melt catalyzed by creatinine.[a]

Run	Time h	M_w[b] 10^4	PDI[b]	Iso[c] %	$[\alpha]_D^{25}$ deg.	OP[d] %e.e.	Yield[e] %	T_g[f] °C	T_{mL}[f] °C	T_{mH} °C	Color
1	10	0.72	1.80	99.5	−154	98.7	90.0	47.7	135.7	148.1	w[g]
2	20	1.2	1.85	98.3	−152	97.4	88.7	52.6	144.2	152.7	w
3	45	2.2	1.74	98.2	−151	96.8	88.0	60.0	154.4		w
4	60	3.0	1.80	98.3	−152	97.4	87.6	60.7	156.4	162.1	w
5	76	3.8	1.81	98.8	−153	98.1	87.1	61.1	156.7		w
6	96	5.4	1.78	97.8	−150	96.1	85.0	62.3	156.4	161.8	Pby[h]

[a] 175 ± 1 °C, 10 torr, 0.1 wt% creatinine.
[b] Measured by GPC.
[c] Isotacticity.
[d] Optical purity.
[e] Isolated yield.
[f] Measured by DSC.
[g] White.
[h] Pale bright yellow.

carboxyl (−COOH) in LLA/PLLA molecules as we previously demonstrated [24]. The creatinine-catalyzed polycondensation was hence postulated to follow the addition–elimination mechanism [37]. The guanidinium forms a tight association with the carbonyl-oxygen in the carboxyl of LLA/OLLA molecules so as to enhance the electrophilicity of the carbonyl-carbon [38–40]. The attack of a hydroxyl terminal of another LLA/OLLA molecule upon the carbonyl-carbon followed by the elimination of H_2O leads to the ester bond formation. The proposed polymerization mechanism was shown in Scheme 2. In the melt polycondensation of LLA, the reaction medium is actually the melted PLLA with low polarity. The terminal carboxylate (−COO^-) in the PLA chain is a weak nucleophile in the less-polar medium, at the same time, the steric hindrance of the terminal carboxylate group in the PLLA chain is very high. Thus, the possible racemization via α-proton abstraction in $SnCl_2$-catalyzed polycondensation [31] was greatly reduced in the creatinine-catalyzed polycondensation of LLA.

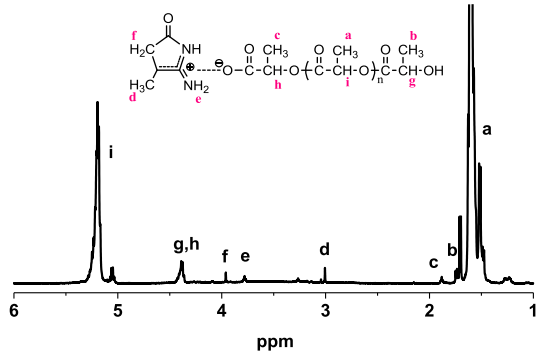
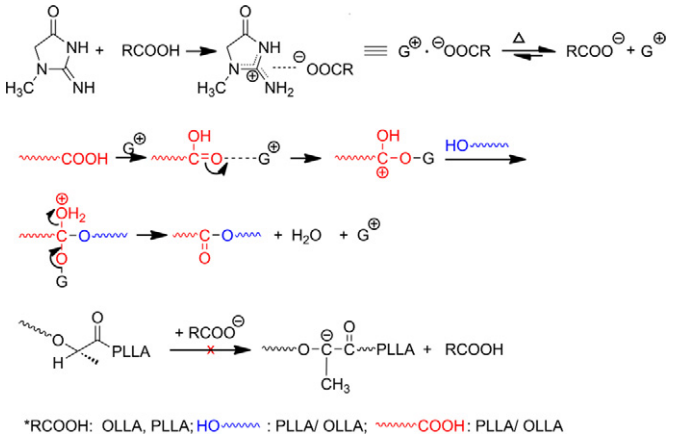


Fig. 3. ^{1}H NMR spectrum of the growing polymeric molecule in creatinine-catalyzed polycondensation of LLA (measured at 25 °C, 500 MHz, $CDCl_3$ solvent).



Scheme 2. Proposed mechanism of creatinine-catalyzed polycondensation of LLA.

4. Conclusion

In conclusion, isotactic polycondensation of LLA catalyzed by biogenic creatinine was successfully conducted. Experimental investigation demonstrated that the isotacticity of product PLLA kept constant high value (97.8–99.5%) throughout the polymerization. To the best of our knowledge, this is the first report on highly isotactic polycondensation of LLA with a biogenic organic catalyst.

Acknowledgments

Hong Li appreciates the financial support from NSFC for the project of "Living and stereospecific ROP of functional morpholine-2,5-diones derived from LA and α-amino acids with bicyclic guanidinium carboxylates" (NSFC grant No. 21074057).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.polymer.2012.09.044.

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