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Stereoselective zwitterionic ring-opening polymerization of \textit{rac}-lactide

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Abstract: Stereoselective zwitterionic ring-opening polymerization (ZROP) poses a potentially great challenge in polymer chemistry because of its unique ion-pairing catalysis mechanism. Herein, a stereoselective ZROP of \textit{rac}-lactide (\textit{rac}-LA) was explored for synthesis of isotactic cyclic polylactides by using commercially available \textit{N}-heterocyclic carbene (NHC) catalysts at low temperature in tetrahydrofuran. The epimerization of lactide during ZROP can be inhibited at low temperature. The best isoselectivity can reach to a high value of \(P_m = 0.91\) associated with a high melting point \((T_m)\) of 193 °C. The resulting polylactides exhibit narrow molecular weight distributions \((M_w/M_n< 1.2)\) and inhibited transesterification as evidenced by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). The resulting polylactide is predominantly cyclic as evidenced by \(1H\) NMR and MALDI-TOF MS analyses.

Keywords: Stereoselective; Zwitterionic Ring-Opening Polymerization; \textit{N}-Heterocyclic Carbene.

1. Introduction

Polymavirus DNA was among the first identified cyclic polymers [1]. Since then, increasing attention has been directed to the synthesis and applications of cyclic polymers, because they exhibit unique properties that differ from their linear congeners [2-9]. However, cyclic polymers were initially synthesized using coupling reactions under extremely diluted conditions, which required a lot of solvents and usually resulted in low reaction rate and poor selectivity [2]. Recently, some efficient and selective polymerization reactions have been explored to synthesize cyclic polymers directly. Ring-opening metathesis polymerization (ROMP) has been developed by Grubbs and Veige to synthesize cyclic polyolefins [10-16] and polyalkynes [17]. Furthermore, since the pioneering work by Waymouth et al., zwitterionic ring-opening polymerization (ZROP) mediated by organic nucleophiles has proven to be a powerful and universal tool for synthesis of cyclic polyesters [18-24], cyclopeptides [25-27] and some other cyclic heterochain polymers [28-30].

Despite various monomers have been used to synthesize cyclic polymers, many challenges remain. For instance, the stereochemical control of cyclic polymers during polymerization poses new challenging goals for polymer chemists [15]. Perhaps especially for \textit{N}-heterocyclic carbene (NHC) mediatedZROP of simple cyclic monomers such as \textit{rac}-lactide (\textit{rac}-LA), the stereochemical control of resulting cyclic polylactides poses a great challenge because of the unique ion-pairing catalysis mechanism (Scheme 1a). In ZROP mediated by NHC, the reactive anion species forms an ion pair with the counter cation derived from NHC [18-20,22], in the absence of the directional coordination or hydrogen bonds (Scheme 1b and 1c) associated with limited conformational freedom for the catalytic
intermediate and good stereoselectivity during polymerization [31-35]. Nevertheless, highlighted by the excellent performance of specific chiral organic salts as phase-transfer catalysts for many asymmetric organic reactions [36-39], ZROP mediated by NHC might also exhibit stereoselectivity to synthesize stereospecific cyclic polymers.

![Scheme 1](image1)

**Scheme 1.** (a) NHC catalyzed ZROP of lactide; (b) Representative stereoselective coordination-insertion polymerization of lactide; (c) Representative hydrogen-bond catalyzed stereoselective ring-opening polymerization (ROP) of lactide.

![Scheme 2](image2)

**Scheme 2.** (a) Stereoselective ZROP of rac-LA to isotactic cyclic PLAs; (b) NHC organocatalysts.

## 2. Results and discussion

Herein, the stereoselective ZROP of rac-LA has been explored for the synthesis of isotactic polylactide (PLA) by using NHC catalysts. The polymerizations were terminated by the addition of carbon disulfide [18]. The $P_m$ of the PLAs were calculated by the analysis of the methine region of the homonuclear decoupled $^1$H NMR spectra [40,41].
At room temperature, the commercially available NHC IPr (Scheme 2) catalyzed ZROP of rac-LA and formed atactic PLA (Table 1, entry 1), indicating poor stereoselectivity. Moreover, for the optical pure monomer L-LA, an atactic PLA product was formed (Table 1, entry 2), because the NHC IPr can catalyze the epimerization of lactide at room temperature [42-44]. To address this issue, ZROP of rac-LA was explored at low temperatures (Table 1, entries 3-5). It was shown that the stereoselectivity of the ZROP was significantly increased as the reaction temperature decreased. At -30 °C, the $P_m$ value rose to 0.78 ($T_m = 180 ^\circ C$), and a higher value of $P_m = 0.91$ ($T_m = 193 ^\circ C$) was observed at -70 °C (Figure 1), indicating a good chain end control during ZROP at the low temperature. Moreover, the ZROP of L-LA at -70 °C generated highly optical pure poly(L-lactide) (PLLA) (Table 1, entry 6) ($P_m = 0.98$, $T_m = 165 ^\circ C$), indicating the epimerization of lactide has been inhibited at the low temperature. The isotactic cyclic polylactide obtained from rac-lactide exhibited higher melting point than that of optically pure cyclic PLLA, indicating the formation of stereocomplex [45].

**Table 1** ZROP of rac-LA and L-LA mediated by NHCCatalysts.

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Cat.</th>
<th>M/C</th>
<th>Monomer</th>
<th>T (°C)</th>
<th>Time (min)</th>
<th>Conv. (%)</th>
<th>$M_n$ (kDa)</th>
<th>$M_w/M_n$</th>
<th>$P_m$</th>
<th>$T_m$ (°C)</th>
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<tr>
<td>1</td>
<td>IPr</td>
<td>20/1</td>
<td>rac-LA</td>
<td>25</td>
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<tr>
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<td>IPr</td>
<td>20/1</td>
<td>L-LA</td>
<td>25</td>
<td>5</td>
<td>37</td>
<td>3.5</td>
<td>1.22</td>
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<td>50</td>
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<td>0.78</td>
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<tr>
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<td>80</td>
<td>40</td>
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<tr>
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<td>6.2</td>
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<td>68</td>
<td>3.5</td>
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<tr>
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*a* Lactide 144 mg, THF 5 mL; *b* [Lactide]$_0$/[NHC]; *c* Conversion of monomer determined by $^1\text{H NMR}$; *d* $M_n$ and $M_w/M_n$ were obtained by GPC (using polystyrene as standard in THF) and $M_n$ was corrected by a correction factor of 0.58; *e* The $P_m$ of the PLAs were calculated by the analysis of the methine region of the homonuclear decoupled $^1\text{H NMR}$ spectra; *f* $T_m$ were obtained by using DSC analysis; *g* Benzyl alcohol was added (BnOH / NHC = 2 / 1).

**Figure 1.** Homonuclear decoupled $^1\text{H NMR}$ of PLAs: (a) Table 1, entry 1 ($P_m = 0.57$). (b) Table 1, entry 4 ($P_m = 0.91$) (in CDCl$_3$).
The resulting PLAs exhibited narrow molecular weight distributions \((M_w/M_n < 1.2)\) (Table 1, entries 3–6). Nevertheless, it was demonstrated that the ZROP of lactide is not a living polymerization, since it deviates from living behavior in several significant ways [20,22]. The resulting molecular weight of PLA is insensitive to changes in \([\text{Lactide}]_0/[	ext{NHC}]\) (Table 1, entries 4 and 5). Moreover, Waymouth’s kinetic simulations demonstrated that the initiator efficiency in the ZROP of lactide is low [20,22]. The matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) indicated inhibited transesterifications during ZROP, since the signals were separated by \(m/z\) 144 (corresponding to the mass of a lactide unit) (Figure 2a) [44,46,47]. The resulting PLA (Table 1, entry 4) was predominately cyclic, as evidenced by the plot of the \(m/z\) values (m) versus the number of rac-LA repeat units (Figure 2b) [18-20,22]. It was shown that these signals are odd-number multiples of 72 mass units (the mass of a half lactide unit), indicating one lactic acid moiety was lost during synthesis. In view of the fact that transesterification was inhibited during chain propagation, it is proposed that the lactic acid moiety was lost in the termination/cyclization step of ZROP (Scheme 3). In addition, no end groups were observed in the \(^1\)H NMR spectrum of the resulting PLA (Figure 3), supporting the formation of the endless topology of the cyclic PLA [18].

![Figure 2](image-url) (a) MALDI-TOF mass spectrum of cyclic PLA (Table 1, entry 4); (b) The plot of the \(m/z\) values (m) versus the number of rac-LA repeat units (n) for cyclic PLA (\(r = 1.000\)).
Linear PLAs were generated in the presence of an alcohol initiator using NHC catalysts (Table 1, entries 7 and 8) [45,48]. The stereoselectivities in the presence or absence of an alcohol initiator were closed. The sterically opened NHC IMes resulted in lower $P_m$ than that of IPr (Table 1, entry 9), indicating that the steric-hinderance effect of the imidazolium moiety can influence the reactive site [19], since a bulkier catalyst limits the conformational freedom for the catalytic intermediate [32]. The inactivity of the highly robust NHC IPP could be due to its blocked nucleophilic catalytic active site (Table 1, entry 10). These results indicated that the structure of NHC catalysts can influence the catalytic activity as well as stereoselectivity.

![Scheme 3. Proposed mechanism for the chain termination/cyclization step.](image)

3. Experimental

3.1. Materials

L-Lactide (L-LA) and rac-Lactide (rac-LA) were purchased from J&K Chemical Ltd. and purified by recrystallization twice from dry hexane and dichloromethane. IPr and IMes was purchased from J&K Chemical Ltd. and used as received. IPP was synthesized by using the procedure in literature [49]. BnOH was purchased from Sinopharm Chemical Reagent Co. Ltd. and distilled from drying over Na.
Tetrahydrofuran (THF) was passed through purification columns. CDCl$_3$ (all 99.5 atom %D) was purchased from J&K Chemical Ltd. and dehydrated with 4 Å molecular sieves.

3.2. Methods

All experiments were carried out under a dry nitrogen atmosphere. $^1$H NMR spectra were recorded by a Bruker Ascend Tm 400 spectrometer at ambient temperature. $^1$H NMR chemical shifts were referenced to residual deuterated solvent peaks or the tetramethylsilane signal (0 ppm). Molecular weights and molecular weight distributions were determined by gel permeation chromatography (GPC) employing a series of two linear Styragel columns (HR2 and HR4) at an oven temperature of 45 °C. A Waters 1515 pump and Waters 2414 differential refractive index detector (30 °C) were used. The eluent was THF at a flow rate of 1.0 mL/min. A series of low polydispersity polystyrene standards was used for calibration. Matrix assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF MS) was recorded on a Bruker Atouflex Speed (The crude polymers were dissolved in dichloromethane and precipitated from methanol (2×) to remove impurities. Dithranol was used as matrix. Dichloromethane was used as solvent. NaI was added as the cation source.

3.3. Polymerization

Representative procedure for polymerization reactions (Table 1, entry 4): In a N$_2$-filled glove-box, rac-lactide (144 mg, 1.00 mmol) was dissolved in 4.5 mL THF. IPr (4 mg, 0.01 mmol) was dissolved in 0.5 mL THF. The solution of rac-lactide was cooled to -70 °C, then the solution of IPr was added. After 80 min, CS$_2$ (1 mL) was added. The solution was allowed to warm to room temperature. The solvent was removed in vacuo. Gained crude sample was used in $^1$H NMR, homonuclear decoupled $^1$H NMR, and GPC analyses. Conversion of monomer = 40%. $P_m$ = 0.91. $M_n$ = 5.0 kDa. $M_w/M_n$ = 1.11. The crude polymers were dissolved in dichloromethane and precipitated from methanol (2×) to remove impurities for MALDI-TOF MS analysis.

4. Conclusions

In summary, the stereochemical control during zwitterionic ring-opening polymerization (ZROP) poses a potentially great challenge for polymer chemists, since ZROP exhibits a unique ion-pairing catalysis mechanism. In this work, a stereoselective ZROP of rac-lactide (rac-LA) has been explored for the synthesis of isotactic cyclic polylactides by using commercially available $N$-heterocyclic carbene (NHC) catalysts at low temperatures in tetrahydrofuran. The epimerization of lactide during ZROP has been inhibited at low reaction temperature. The best isoselectivity can reach to a high value of $P_m$ (0.91) associated with a high melting point ($T_m$) (193 °C) of polylactide. The resulting polylactides exhibit narrow molecular weight distributions ($M_w/M_n < 1.2$) and inhibited transesterification as evidenced by MALDI-TOF MS analysis. The resulting polylactide is predominantly cyclic as evidenced by $^1$H NMR and MALDI-TOF MS analyses. The sterically opened NHC resulted in reduced stereoselectivity while highly robust NHC exhibited inactivity associated with the blocked nucleophilic catalytic active site. We believe that ZROP mediated by NHC has great potentials for synthesis of other stereospecific cyclic polymers.

Conflicts of Interest
There are no conflicts to declare.

Acknowledgements

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References

Graphical Abstract
Highlights
A stereoselective ZROP of rac-lactide generates isotactic cyclic polylactides. Commercially available N-heterocyclic carbene was used as catalysts at low temperatures. The resulting polylactides exhibit narrow molecular weight distributions ($M_w/M_n < 1.2$). The best isoselectivity can reach to a high value of $P_m = 0.91$. The resulting polylactide is predominantly cyclic as evidenced by $^1\text{H}$ NMR and MALDI-TOF MS analyses.