

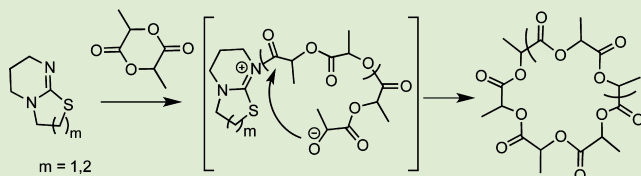
Zwitterionic Ring Opening Polymerization with Isothioureas

Xiangyi Zhang and Robert M. Waymouth*

Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

Supporting Information

ABSTRACT: Bicyclic isothioureas **1** and **2** mediate controlled ring opening polymerizations (ROP) of lactides in the absence of protic initiators to afford high molecular weight poly(lactides) (PLA) with narrow polydispersities. The cyclic structure of the resulting PLA was determined by dilute solution viscosity measurement and MALDI-TOF mass spectrometry. Compared to DBU initiator, isothioureas are more selective for producing cyclic PLA without appreciable linear contaminants. Mechanistic studies involving acyl amidinium support our hypothesis that DBU-initiated ZROP generates linear chains from a ketene aminal intermediate.



Zwitterionic ring opening polymerization (ZROP) mediated by organic nucleophiles has been developed as an effective strategy for the synthesis of cyclic polymers.^{1–7} In the absence of protic initiators, nucleophiles such as N-heterocyclic carbenes,^{1,6} pyridines,^{8,9} imidazoles,¹⁰ amidines,¹¹ tertiary amines,^{8,12,13} or phosphines⁹ can mediate the ring opening of strained cyclic monomers to form zwitterionic intermediates^{14,15} that propagate and cyclize to release macrocycles (Scheme 1). Lactones,^{1,2,16} thiolactones,⁸ N-carboxyanhydrides,^{6,17,18} or carbosiloxanes¹⁹ are among the types of monomers that can be polymerized with this approach, but the factors that control the rate of initiation, propagation, and cyclization and competitive side reactions remain incompletely understood and depend sensitively on the reactivities of nucleophilic initiator, the monomer, the nature of the reactive intermediates, and the polymerization conditions.^{1,4,20,21}

The ZROP of lactide with N-heterocyclic carbenes is rapid (minutes), but molecular weights >30 kDa are difficult to obtain.^{16,22,23} We recently reported that the amidine 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) was sufficiently nucleophilic to mediate the ZROP of lactide to generate cyclic poly(lactides) but was accompanied by the cogeneration of linear poly(lactides).¹¹ We had proposed that the linear poly(lactides) might arise from competitive deprotonation of the amidinium zwitterion to generate the neutral ketene aminal (KA, Scheme 2).¹¹

To test this hypothesis and to provide a strategy for eliminating this competitive pathway, we investigated the ZROP of lactide with the isothioureas^{24–26} **1** and **2**. While the isothioureas are less nucleophilic than the amidine DBU,^{27,28} we reasoned that the acylated isothiourea zwitterions would be unable to deprotonate to the ketene aminal and, thus, be less likely to generate linear chains. Herein, we employ ITU **1** and **2** as nucleophilic initiators for the ZROP of LA and compare the results with the DBU initiator.

The ROP of L-lactide in the absence of added alcohol initiators was carried out in dichloromethane at room temperature with ITU **1** or **2** as catalysts (Table 1). High

molecular weight PLAs with M_n ranging from 38000 to 66000 Da and polydispersities of $M_w/M_n = 1.3–1.7$ were produced at high conversion (~90%). The polymerization rates with isothioureas are significantly slower than those with DBU or NHCs. Kinetic studies (Figures S6 and S7, Supporting Information) indicate that this is likely due to the lower initiation efficiency for the ITU nucleophiles relative to DBU.^{27,28} The molecular weights of the PLAs generated from ITU **1** were lower than those from ITU **2** or DBU. The evolution of molecular weight (M_n) exhibits a linear correlation with monomer conversion (c), but extrapolation of M_n versus conversion plot to zero conversion does not go through the origin (Figure S2, Supporting Information).

The molecular weights do not correlate to the initial monomer/initiator ratio $[M]_0/[I]_0$ and are significantly higher than the simple prediction based on $c \cdot [M]_0/[I]_0$. Similar behavior was observed for the zwitterionic ring-opening polymerization of lactones^{1,16,20–22} and is attributed to a slow rate of initiation relative to propagation.^{20,22} This is also evident in the kinetic behavior, where an induction period is observed followed by a first order disappearance of monomer (Figures S6 and S7, Supporting Information).

The cyclic structure of the PLA generated from isothioureas **1** and **2** was inferred by a combination of ¹H NMR spectroscopy, MALDI-TOF mass spectrometry, and dilute solution viscosity measurements. The ¹H NMR spectra of the PLA shows no observable end groups (Figure S1). A MALDI-TOF mass spectrum of a crude polymer sample obtained by quenching the reaction at low conversion (8%) with 4-nitrophenol shows molecular ions assigned as the sodium adducts of cyclic PLA (Figure 1). The inset of the figure presents a detailed picture of mass range from 4700 to 5300 and reveals two different populations of macromolecules separated by 72 mass units, which corresponds to the even-

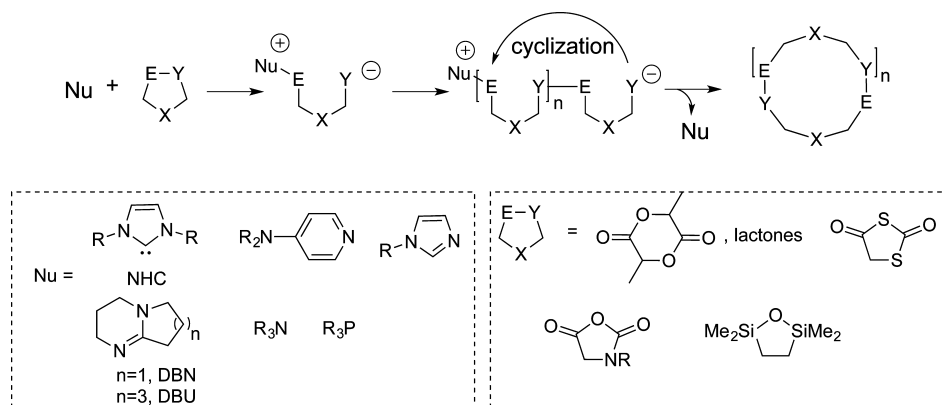
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Scheme 1. Nucleophilic Zwitterionic Ring-Opening Polymerization for the Synthesis of Cyclic Polymers



Scheme 2. Proposed Reaction Pathway for DBU-Initiated ROP of LA

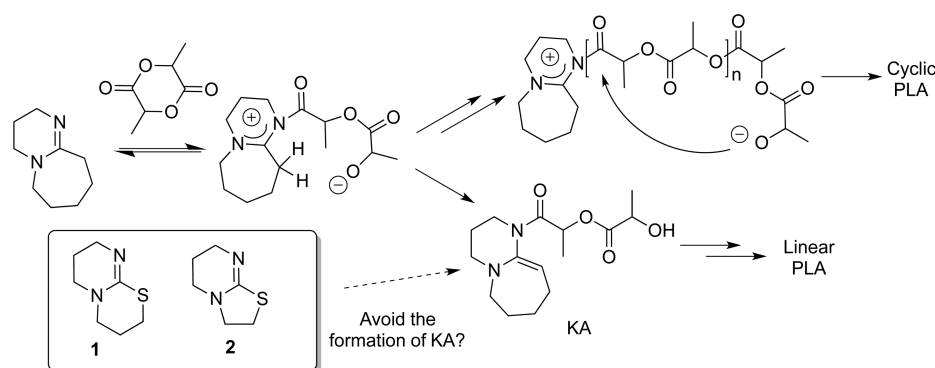


Table 1. ROP of LA by Isothioureas or DBU Catalysts in the Absence of Alcohol

entry	initiator	[LA] ₀ (mol/L)	[LA] ₀ /[I] ₀	time (h)	% conv. ^a	M _n ^b (Da)	PDI ^b	M _w ^c	η _x /η _{linear} ^d
1	ITU 1	2.0	20	42	94	48000	1.39	44000	0.68
2	ITU 1	2.0	10	23	95	38000	1.42	36000	0.68
3	ITU 2	2.0	20	135	86	66000	1.65	82000	0.67
4	ITU 2	2.0	10	93	89	53000	1.53	67000	0.68
5	DBU	1.0	100	1	89	58000	1.59	78000	0.84

^aConversion determined by ¹H NMR. ^bM_n and PDI determined by PS calibrated GPC in THF. ^cAbsolute molecular weight determined by GPC using multiangle light scattering (MALS). ^dRatio of intrinsic viscosity of PLA generated with nucleophiles relative to a linear PLA generated by TBD in the presence of alcohol initiators, determined by GPC with in-line viscometer and right angle light scattering.

and odd-numbered lactide repeat units in the cyclic polymers.

That the ions corresponding to odd-numbered lactide units are of much lower intensity than the even-numbered ones indicated that cyclic PLAs are mainly formed via closing the two chain ends without notable backbiting or chain scrambling, at least at these low conversions. Further evidence for the cyclic structure of these PLAs was provided by the comparisons of the intrinsic viscosity of the PLAs generated from isothioureas 1 and 2 relative to a linear sample of similar molecular weight. The ratio of intrinsic viscosities $[\eta]_{\text{isothiourea}}/[\eta]_{\text{linear}} = 0.68$ (Figure S3, Supporting Information) is similar to that predicted (0.667) for a cyclic polymer in a theta solvent.²⁹ In contrast, a ratio of $[\eta]_{\text{DBU}}/[\eta]_{\text{linear}} = 0.84$ was observed for the PLA generated from DBU, consistent with a mixture of cyclic and linear chains in the latter case. These data indicate the isothioureas 1 and 2 exhibit a higher selectivity than DBU for forming cyclic chains.

The ring-opening polymerization of lactide with the isothioureas 1 and 2 in the absence of alcohol initiators is

consistent with a zwitterionic polymerization mechanism where the initiation step involves the nucleophilic addition²⁵ of the isothiourea to lactide to generate a zwitterionic intermediate. This intermediate can either cyclize to regenerate lactide or the neutral tricycle^{11,30} (likely a dormant species) or add additional monomer to propagate to larger zwitterions. The induction period observed in the kinetic behavior suggests that this initiation step is kinetically inefficient, either due to an unfavorable equilibrium constant (k_1/k_{-1}) for initiation or to a buildup of the dormant tricycle T₁ (Scheme 3). Cyclization of the growing zwitterions by either “backbiting” into internal esters of the growing zwitterions (path b) or at the isothiuronium terminus (path a) would liberate cyclic chains. The moderate increase in polydispersity with conversion indicates the possibility of chain transfer reactions such as the attack of active zwitterions on the internal esters of other zwitterions as well as cyclized chains, which has been previously proposed as the key step for the generation of high molecular weight cyclic polycaprolactone.²⁰

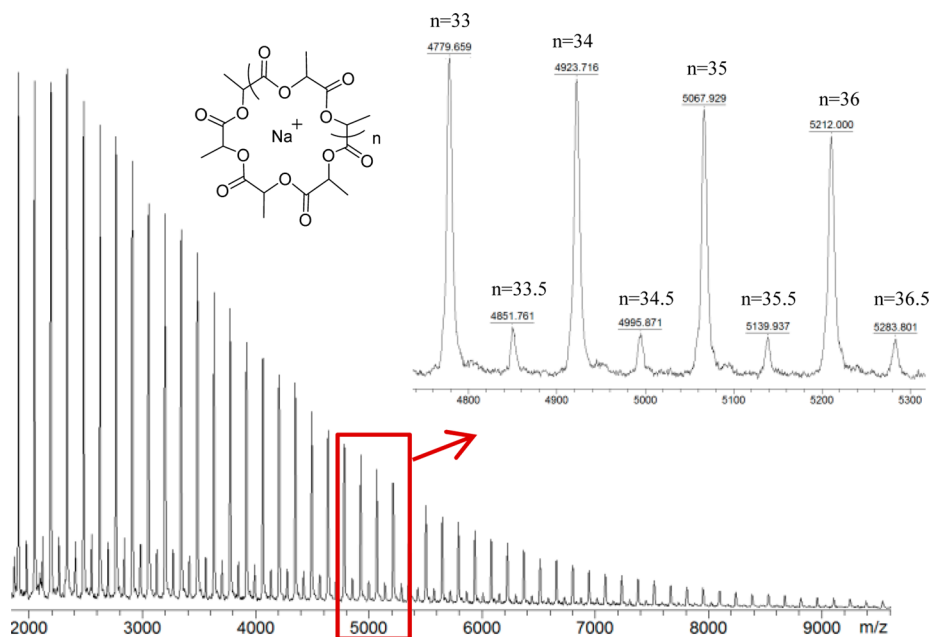
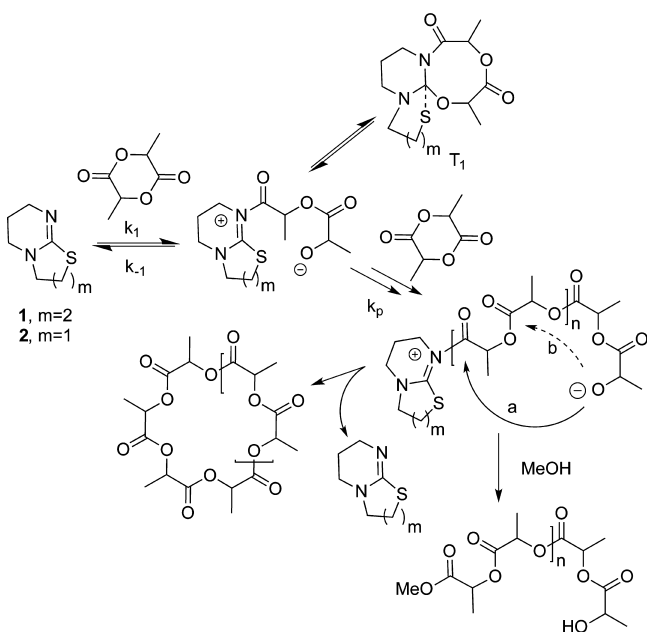


Figure 1. MALDI-TOF MS spectrum of a low molecular weight PLA generated by ITU 2.

Scheme 3. Proposed Mechanism for ZROP of Lactide with Isothioureas



The observation that even-numbered cyclic poly(lactides) predominate at low conversions suggest that cyclization at the isothiuronium terminus (path a) is preferred, at least for modest molecular weights ($M_n \leq 9000$ Da). That methanol and water terminated linear chains are observed in the MALDI mass spectra for polymer samples quenched at low conversions ($\sim 8\%$) and worked up in wet methanol (Figure S4, Supporting Information) is consistent with the methanolysis/hydrolysis of active zwitterions that have not cyclized.²⁰

Mechanistic studies were carried out to investigate the reactivity of the acylated isothioureas to provide independent evidence that the attack on acylisothiuroniums (the positive terminus of a zwitterion) by either the alkoxide chain end or methanol solvent (work up) would generate cyclic or linear

chains, respectively. Treatment of a toluene solution of isothioureas **1** or **2** with benzoyl chloride resulted in the precipitation of the acylated isothioureas **3** and **4** (Scheme 4a), which were isolated in 99% yield and characterized by ^1H and ^{13}C NMR and high-resolution mass spectrometry (Supporting Information).

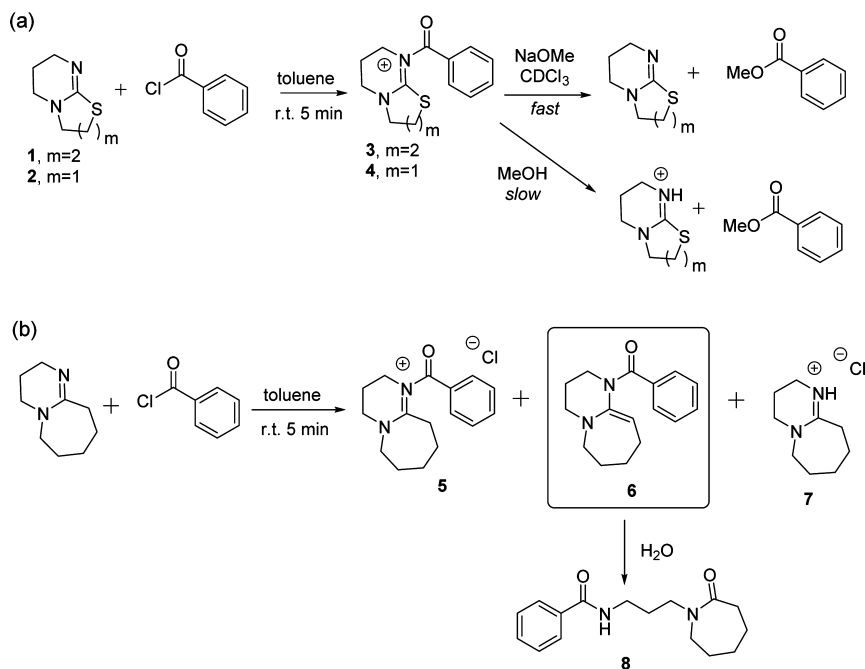
Treatment of **3** or **4** with 1.2 equiv of sodium methoxide in CDCl_3 at room temperature proceeded rapidly (80–90% in 30 min) to give methyl benzoate and free isothioureas. These results provide good chemical evidence for the cyclization step at the acyl isothiuronium terminus of the zwitterion (path a, Scheme 3).

In contrast, the acylated isothioureas **3** and **4** are less reactive with methanol: **3** or **4** did not react readily with a stoichiometric amount of methanol in CDCl_3 at room temperature. However, stirring **3** or **4** in methanol for 6 h at room temperature liberated methyl benzoate and the protonated isothioureas. This observation is consistent with the generation of linear chains upon methanolic workup of the reaction; any macrozwitterions that have not yet cyclized should react with wet methanol to generate linear chains with methanol or water end groups (Scheme 3), as observed in the MALDI-TOF mass spectrum of the sample isolated after dialysis of the crude polymer sample in methanol overnight (Figure S4).

To contrast the behavior of the isothioureas to that of DBU, we also carried out analogous studies with the amidine. Treatment of a toluene solution of DBU with benzoyl chloride generated the acylated DBU **5** along with a significant amount of ketene aminal **6** and protonated DBU **7** as the side products (Scheme 4b). The ratio of **5** to **6** depends on the relative amount of DBU to benzoyl chloride and the order of addition, but we were unable to identify conditions that would lead to **5** as the sole product, which suggests that the rate of deprotonation of **5** by DBU is competitive to the rate of formation of **5** from DBU and benzoyl chloride.

The ketene aminal **6** was not stable under ambient conditions and quickly hydrolyzed to amide **8** during isolation.

Scheme 4. Synthesis and Reactivity of Acylisothiuronium (a) and Acylamidinium (b)



Similar observations were made by Quaranta in reactions of DBU with alkyl carbonates.³¹

These model studies provide evidence for the competitive formation of ketene aminals during the ZROP of lactones by DBU.²⁰ In addition, the different reactivity of the acylated isothioureas and acylated amidines reflect the higher selectivity of the isothioureas in generating cyclic macromolecules.

In summary, the bicyclic isothioureas **1** and **2** are competent nucleophilic initiators for the zwitterionic ring-opening polymerization of lactide to generate macrocyclic poly(lactides) with $M_n = 38000\text{--}66000$ Da. In the absence of protic initiators, the ZROP of lactide mediated by isothioureas **1** and **2** generate high molecular weight cyclic PLA under conditions where the amidine DBU generates mixtures of cyclic and linear chains. Mechanistic studies reveal that the acylated amidines are readily deprotonated to the ketene aminal, whereas the acylated isothioureas are not. These experimental results support our hypothesis that linear chains in the DBU-mediated ZROP of lactide comes from a ketene aminal intermediate. Isothioureas catalysts that effectively eliminate this unwanted pathway are more selective for the formation of cyclic PLA.

In addition, the observation that both amidines and isothioureas can mediate the nucleophilic zwitterionic ring-opening reactions implies that attempts to generate high molecular weight linear polymers (i.e., at high monomer/alcohol initiator ratio) utilizing thiourea/DBU or isothioureas cocatalyst systems^{32–34} are likely to be compromised by the competitive zwitterionic ring-opening polymerization mediated by the amidine as a nucleophile.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental details, synthetic procedures, and characterization data (NMR data and MALDI mass spectra). This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: waymouth@stanford.edu.

Notes

The authors declare no competing financial interest.

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