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Cyclopropenimine Superbases: Competitive Initiation Processes in Lactide Polymerization

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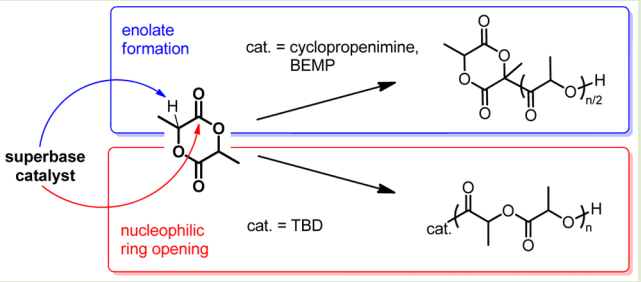
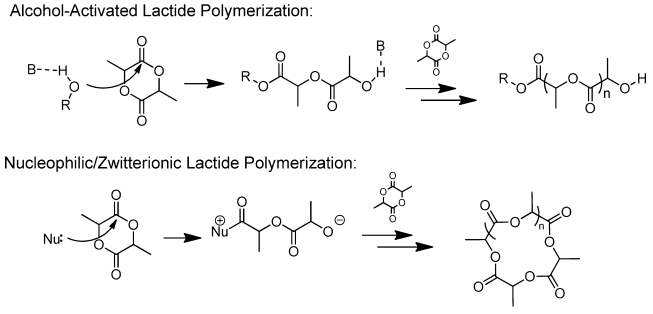
Supporting Information

ABSTRACT: Cyclopropenimine superbases were employed to catalyze the ring-opening polymerization of lactide. Polymerization occurred readily in the presence and absence of alcohol initiators. Polymerizations in the absence of alcohol initiators revealed a competitive initiation mechanism involving deprotonation of lactide by the cyclopropenimine to generate an enolate. NMR and MALDI-TOF analysis of the poly(lactides) generated from cyclopropenimines in the absence of alcohol initiators showed acylated lactide and hydroxyl end groups. Model studies and comparative experiments with guanidine and phosphazene catalysts revealed the subtle influence of the nature of the superbase on competitive initiation processes.



Organocatalysis has proven a versatile strategy for ring-opening polymerization reactions.[1−5] Organic molecules catalyze ring-opening polymerization (ROP) by a variety of mechanisms that are distinct from those of metal alkoxide initiators; the mild conditions and high functional group tolerance of many of these organic catalysts have provided new opportunities for macromolecular synthesis and design.[1,2] Superbases[6] such as N-heterocyclic carbenes (NHCs), guanidines, amidines, isothioureas, and phosphazenes have proven especially effective as organic catalysts for ROP; in the presence of alcohol initiators these catalysts can hydrogen bond to the alcohol or chain-ends to activate them for the ring-opening of strained monomers (Scheme 1, illustrated for lactide).[2] At low initiator (alcohol) concentrations, competitive initiation mechanisms can occur and can be probed by carrying out polymerizations in the absence of alcohols.[2,7] In the absence of alcohol initiators, N-heterocyclic carbenes,[8,9] amidines,[10] and isothioureas[11] mediate zwitterionic ring-opening polymerization reactions by a nucleophilic[12] mechanism; this latter strategy has proven useful for generating cyclic macromolecules.[9]

Scheme 1. Two Polymerization Mechanisms for Lactide with Organic Catalysts



Herein, we describe ring-opening polymerization reactions with another class of potent neutral bases derived from bis(dialkylamino)-cyclopropenimines.[13−15] Lambert recently showed that these compounds have comparable basicity to phosphazenes, are readily prepared in enantiomerically pure form, and are effective organocatalysts for enantioselective Michael and Mannich reactions of glycinate imines. We describe that these superbases are also potent organic catalysts for ring-opening polymerization but exhibit an additional competitive pathway involving the deprotonation of lactide to generate lactide enolates, which can initiate ring-opening polymerization. The behavior of the cyclopropenimine bases is compared to the guanidine TBD (1,5,7-triazabicyclo[4.4.0]-dec-5-ene) and the phosphazene BEMP (2-*tert*-butylimino-2-diethyl-amino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine).

Three achiral cyclopropenimines bearing *N*-alkyl substituents (Table 1, right inset) were prepared.[13−15] Polymerizations of lactide initiated with 1-pyrenebutanol in the presence of catalytic amounts of cyclopropenimine **1** proceeded rapidly with greater than 85% conversion in 30 s (Table S1, Supporting Information). Molecular weights up to 13 kDa were obtained by controlling the monomer to alcohol ratio. The molecular

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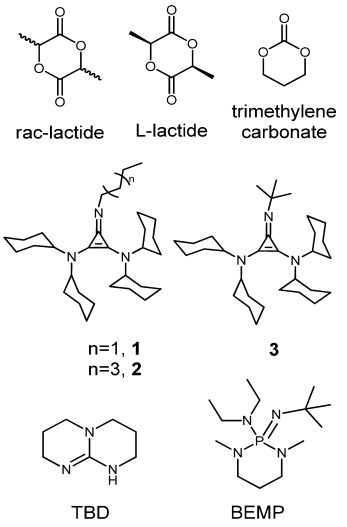
Table 1. Initiator-Free Ring-Opening Polymerization of Lactides with Cyclopropenimines[a]

entry	monomer	catalyst	cat. conc. (M)	solvent	time	conv. (%)	M_n[b]	M_w/M_n
1	rac-lactide	1	0.010	CH_2Cl_2	8 min	84	8390	1.42
2	rac-lactide	1	0.050	CH_2Cl_2	10 min	99	15300	1.57
3[c]	rac-lactide	1	0.007	C_6D_6	2 days	99	70700	1.46
4	L-lactide	1	0.010	CH_2Cl_2	8 min	93	11500	1.30
5	L-lactide	2	0.010	CH_2Cl_2	8 min	90	17300	1.46
6	rac-lactide	3	0.020	CD_2Cl_2	20 min	98	13100	1.38
7	rac-lactide	BEMP	0.010	CH_2Cl_2	8 min	65	8300	1.24
8	L-lactide[d]	TBD	0.0007	CH_2Cl_2	10 s	11	19000	1.39
9	carbonate[e]	1	0.010	CH_2Cl_2	22 hrs	3	-	-



[a]Conditions: 1.0 M monomer in solvent, room temperature. Quenched with either 4-nitrophenol or benzoic acid. [b]Determined by GPC vs polystyrene standards. [c]Saturated monomer solution. [d]0.35 M monomer solution. [e]Carbonate = trimethylene carbonate.

weight distributions ranged from 1.2 to 1.4 and generally increased over the course of the reaction. These data, coupled with the observations that polymeric ions corresponding to both odd and even lactic acid units were observed in the MALDI-TOF spectra (Figure S2, Supporting Information) suggest that competitive transesterification reactions occur, leading to chain-scrambling and chain-transfer reactions.[2,16]

To test for competitive nucleophilic polymerization mechanisms by the cyclopropenimines, we investigated the ring-opening polymerization of lactide with cyclopropenimines **1**−**3** in the absence of alcohols (Table 1).

Under these conditions, polymerization proceeded readily with rates only marginally slower than those observed in the presence of alcohol initiators. The molecular weights obtained ranged from M_n = 8000−70000 Da and were observed to increase with increasing conversion, but exhibited little correlation with the initial $[M]_0/[I]_0$ ratio (where I = cyclopropenimine, Table 1, entry 2).

Analysis of the resulting polymers by MALDI-TOF mass spectrometry (Figure S8, Supporting Information) revealed ions corresponding to exact multiples of lactide molecular weights. These data would be consistent with a cyclic polymer generated by a nucleophilic zwitterionic mechanism, but several lines of evidence indicate that a linear polymer is generated. Comparison of the dilute solution viscosities of a high molecular weight polylactide (PLA) prepared from the cyclopropenimine **1** and a known linear sample of polylactide were similar (Figure S10, Supporting Information), implicating a linear topology for both samples.[17] Furthermore, analysis of the purified polymer by ^{1}H NMR revealed two resonances indicative of polymer end groups: one at δ 4.37 ppm ($CDCl_3$), diagnostic of a methine proton adjacent to a terminal hydroxyl group and another end group signal at δ 5.01 ppm (Figure 1). These data are inconsistent with a nucleophilic zwitterionic mechanism, as observed for NHCs, amidines, and isothioureas,[9,11] but imply that, in the absence of alcohols, the cyclopropenimines initiate lactide polymerization by an alternate pathway.

As cyclopropenimines are potent bases (pK_a of conjugate acid approximately 27 in CH_3CN),[13] we reasoned that these

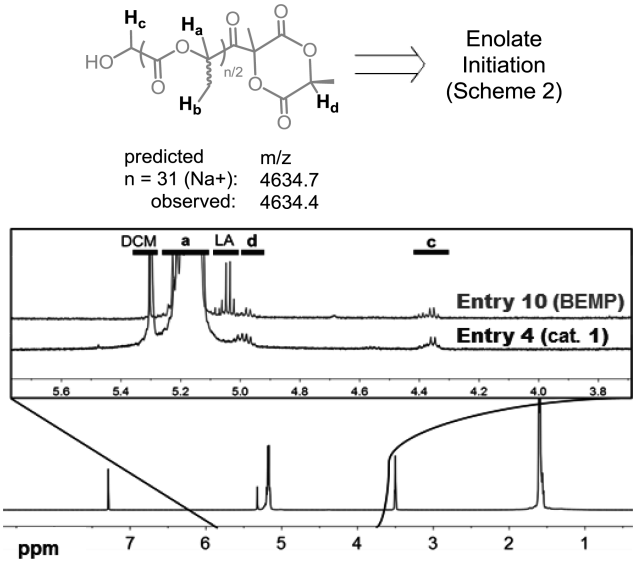


Figure 1. ^{1}H NMR ($CDCl_3$) spectra of entry 1 enlarged to show methine region with comparison to entry 7. LA = lactide monomer.

superbases might deprotonate lactide to a lactide enolate, which subsequently initiates the polymerization of lactide (Scheme 2). Several recent reports have indicated that Zr, Zn, or Li enolates can initiate lactide polymerization.[18−22]

The end group resonance observed spectrum at δ = 5.01 ppm in the ^{1}H NMR spectra (H_d of Figure 1) is consistent with that expected for a methine proton of an alkylated lactide[23] and is inconsistent with an O-acylated lactide, as the methine proton of the silyl enolate of lactide (prepared independently) exhibits a resonance at δ 4.41 ppm (Figures S14−S16, SI). These data, as well as model studies described below, indicate that initiation involves acylation of lactide enolate at carbon rather than at oxygen.

To assess if the cyclopropenimine is capable of deprotonating lactide, lactide was treated with cyclopropenimine **1** (1:2 ratio) in C_6D_6 at room temperature. The addition of **1** to lactide results in the rapid disappearance of the lactide methine

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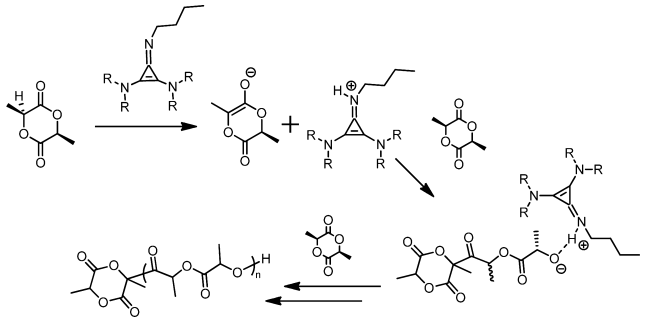
Scheme 2. Proposed Enolate Initiation Mechanism



resonance at δ = 3.67 ppm (Figure S13, Supporting Information), consistent with the deprotonation of lactide to the lactide enolate.

Furthermore, epimerization of lactide monomers to form *meso*-lactide is observed during early stages of the polymerization reaction and polymerizations of L-lactide produce a small amount of atactic sequences, suggesting that reversible deprotonation occurs (Figures S5 and S12, Supporting Information).

To provide further evidence that enolates[18−21] initiate the polymerization of lactide under these reaction conditions, the enolate of methyl isobutyrate was generated with lithium diisopropylamide (LDA) and utilized as an initiator for lactide polymerization.[24] Generation of the enolate of methyl isobutyrate with LDA in the presence of excess ester at −78 °C, followed by the addition of 25 equiv of L-lactide resulted in the conversion of 69% of the lactide within 10 min to generate polylactide. Analysis of the MALDI-TOF mass spectra of the resulting polymer yielded ions corresponding to linear polylactide with methyl isobutyrate end groups. Analysis of the ^{13}C NMR of the resulting low molecular weight polylactide (M_n ∼ 2700 Da) was consistent with a 2,2-dimethyl methyl acetate end group resulting from acylation at the carbon center of the methyl isobutyrate enolate initiator (Figures S17−S19, Supporting Information). These results are consistent with literature examples of carbon alkylation of methyl isobutyrate[25−28] and indicate that ester enolates initiate lactide polymerization by a Claisen-type condensation at the carbon of the initiating enolate.

The observation that trimethylene carbonate (TMC) polymerizes with cyclopropenimine **1** only in the presence of alcohol initiators (entry 9 vs entry S5) is readily explained by the lack of enolizable protons of this carbonate monomer.

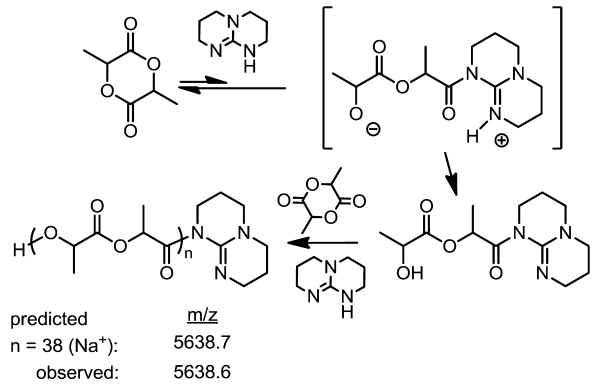
As several superbases have been used as organocatalysts for ring-opening polymerization,[2] we sought to compare the behavior of the cyclopropenimines (pK_a conjugate acid ∼ 27) to two other basic organocatalysts, 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (TBD, pK_a conjugate acid ∼ 26.0) and 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, pK_a conjugate acid ∼ 27.6[29]).

The ring-opening polymerization of lactide in the absence of alcohols with the phosphazene BEMP (Table 1, entry 7) was slightly slower but displayed similar polymer end group resonances (δ 5.01 and 4.37 ppm, see Figure 1) and MALDI spectra to those of cyclopropenimines, indicative of an enolate-initiated polymerization mechanism.

In contrast, lactide polymerization with the guanidine TBD was much faster and reached higher molecular weight than with either the cyclopropenimines or the phosphazene BEMP (Table 1, entry 8). The polymerization is first order in monomer and displays a linear relationship between conversion and molecular weight (Figure S21, Supporting Information). Furthermore, when the product polylactide was analyzed by MALDI, the masses corresponded to polylactide chains with attached TBD end groups.

The presence of polymer-bound TBD strongly implies a nucleophilic initiation by TBD, in contrast to the deprotonation mechanism for cyclopropenimine and phosphazene bases. The nucleophilicity of TBD has previously been demonstrated in both lactone polymerizations and acyl transfer model studies.[30,31] In the latter case, a stable, neutral adduct of butyrolactone with TBD was observed and characterized.[32] Whereas this formed an H-bonded, 8-membered ring that was disfavored for polymerization, our results indicate that the analogous lactide intermediate propagates rapidly (Scheme 3).

Scheme 3. Proposed Mechanism for Initiation and Polymerization of Lactide by TBD, Including TBD-Bound Polylactide Detected by MALDI



In summary, superbases are a versatile class of catalysts for organocatalytic ring-opening polymerization reactions, whose polymerization behavior depends sensitively on their basicity, nucleophilicity, and the presence or absence of alcohol initiators. In the presence of alcohol initiators, these superbases catalyze ring-opening polymerization by hydrogen-bond activation of initiating or propagating alcohols. However, at low initiator (i.e., alcohol) concentrations, competitive reactions of the superbases with lactone monomers can lead to alternate mechanisms of initiation and polymerization. These competitive mechanisms can lead to a broadening of the molecular weight distributions, particularly at high [monomer]/[initiator] ratios. Polymerization of lactones in the absence of alcohols can illuminate these alternative pathways and reveal a range of behaviors. N-Heterocyclic carbenes,[8,9] amidines,[10] and isothioureas[11] act as nucleophilic initiators, mediating zwitterionic ring-opening polymerizations to generate cyclic polyesters. Herein we demonstrated that cyclopropenimine and phosphazene superbases deprotonate lactide to generate enolates that initiate lactide polymerization. The guanidine TBD exhibits mixed behavior, involving nucleophilic initiation to generate a covalent acylated guanidine which likely propagates by an H-bond mechanism.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, GPC traces, MALDI, and ESI-MS of polymers and model studies. The Supporting Information is available free

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Notes

The authors declare no competing financial interest.

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