ACS Macro Letters

Letter

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Amidine-Mediated Zwitterionic Polymerization of Lactide

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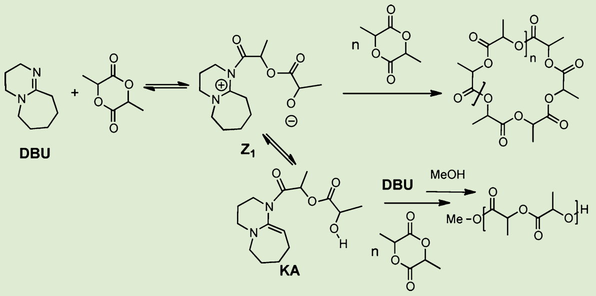
Supporting Information

ABSTRACT: The ring-opening polymerization (ROP) of lactide with DBU (1,8-diazabicyclo[5.4.0] undec-7-ene) is described. Room temperature polymerization using the neutral amine catalyst DBU in the absence of any other initiator produces polymers with narrow polydispersities and shows a linear relationship between molecular weight and conversion. The resulting polymers were characterized and determined to be cyclic. DFT calculations support a mechanistic hypothesis involving a zwitterionic acyl amidinium intermediate.



Organocatalysis is a versatile strategy for the ring-opening polymerization of lactones to generate poly(ester)s.[1−4] Due to their different mechanisms of enchainment relative to metal alkoxide initiators, organic catalysts can mediate ring-opening polymerization to generate novel architectures and topologies. In the presence of alcohol initiators, organic catalysts derived from *N*-heterocyclic carbenes, pyridines, phosphazenes, guanidines, and amidines generate linear polyesters. These neutral bases can activate alcohols by hydrogen-bonding to mediate the ring-opening of the lactone (path A, Figure 1). However, *N*-heterocyclic carbenes can also mediate ring-opening by a nucleophilic mechanism to generate zwitterionic intermediates (path B, Figure 1, illustrated for the carbenes).

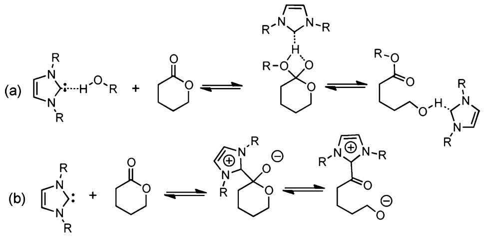


Figure 1. Proposed mechanisms of *N*-heterocyclic carbene mediated ring-opening polymerization of lactones.

Theoretical studies[5] suggest that, in solvents of modest polarity, the hydrogen-bonded mechanism is lower in energy than the nucleophilic pathway for carbenes,[6] guanidines,[7,8] and pyridines.[9] Nevertheless, the viability of a nucleophilic pathway was recently demonstrated by the ring-opening polymerization of lactones with *N*-heterocyclic carbenes in the absence of alcohol initiators.[10−14] In the absence of alcohol initiators, nucleophiles such as *N*-heterocyclic carbenes,[10−14] pyridines,[15] or imidazoles[16,17] mediate the zwitterionic ring-opening (ZROP) of lactones and *N*-carboxyanhydrides[18−21] to generate high molecular weight cyclic polymers.

The amidine DBU (1,8-diazabicyclo[5.4.0] undec-7-ene) is a catalyst for ring-opening polymerization of lactide but requires a thiourea cocatalyst for ring-opening of valerolactone and caprolactone.[22] Previous studies had indicated that DBU can hydrogen-bond to alcohol initiators, activating the alcohol for nucleophilic attack (Figure 1a). However, recent studies that indicate that DBU is a competent nucleophile[23−25] and can act as a nucleophilic catalyst[26−28] prompted us to investigate whether DBU can mediate the ring-opening of lactide in the absence of alcohol initiators. Herein, we provide evidence that the amidines DBU and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) can act as nucleophilic initiators to mediate the synthesis of cyclic polyesters.

The ring-opening polymerization of *racemic* lactide (LA) with DBU and benzyl alcohol (BnOH) as an initiator has been described previously in $CHCl_3$.[22] To explore the effect of solvent on the DBU-mediated alcohol initiated ROP of *rac*-lactide, a series of polymerizations were conducted in THF or CH_2Cl_2 (Table S1 and Figure S1, Supporting Information). Polymerization occurs readily at room temperature in both solvents, although the reactions conducted in THF are markedly slower than those conducted in CH_2Cl_2. The resulting polymers exhibit number average molecular weights (M_n) that increase with increasing conversion and correspond to the starting monomer to initiator ratio as well as narrow polydispersities for conversions <90%.

The ROP of *rac*-lactide in the absence of an alcohol was carried out with DBU or DBN as initiators (Table 1). No ring opening was observed in THF unless 0.1 M Bu_4NPF_6 was added to the THF solution.[29] Polymerization occurred readily

Received: June 4, 2012
Accepted: August 14, 2012
Published: August 23, 2012

dx.doi.org/10.1021/mz300276u | *ACS Macro Lett.* 2012, 1, 1113−1115

Table 1. Polymerization of Lactide with DBU or DBN

entry	CH_2Cl_2/THF	initiator	[LA]	[DBX]	$[M]_0/[I]_0$	% conv.[a]	M_n[b]	PDI[b]	M_w[c]	$\frac{\eta_{DBX}}{\eta_{linear}}$[d]
1	1:0	DBU,ROH	0.60	0.0060	100	92	17000	1.13		
2	0:1	DBU,ROH	0.60	0.0060	100	35	6800	1.13		
3	0:1	DBU	0.60	0.0060	100	0				
4	1:0	DBU	1.0	0.010	100	85	56000	1.63	73000	0.84
5	1:0	DBN	0.98	0.0097	100	31	37000	1.25	41000	0.78
6	1:1	DBU	1.0	0.0099	100	54	32000	1.47	48000	0.71
7	2:1	DBU	0.97	0.0098	100	62	38000	1.49	47000	0.74

[a] Conversion determined by ^1H NMR after quenching reaction at 60 min. [b] M_n and PDI determined by PS calibrated GPC. [c] M_w determined by GPC with MALS [d] Ratio of intrinsic viscosity of polylactide generated with DBX relative to a linear polylactide generated with alcohol initiators and IMes carbene (see SI); determined by GPC with in-line viscometer and RALS with comparison to linear PLA of similar M_w

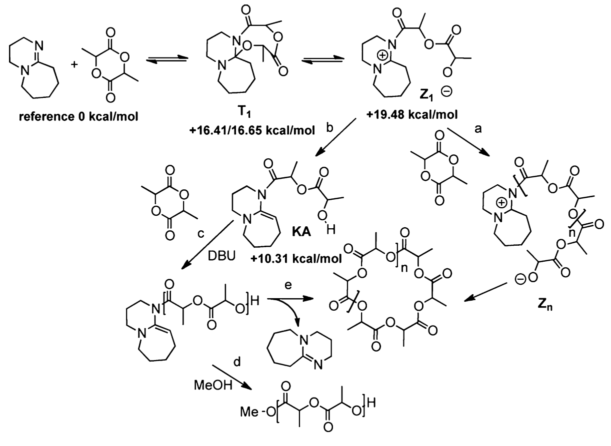
in CH_2Cl_2 or THF/CH_2Cl_2 mixtures to afford polylactides with molecular weights ranging from M_n = 32000−53000 Da and $M_w/M_n \leq 1.6$. For polymerizations carried out with DBU in CH_2Cl_2, the rate of polymerization was first order in [lactide]. The number average molecular weights (M_n) of the polylactide were observed to increase as a function of time and conversion.

The molecular weights did not differ markedly for DBU and DBN initiators when $[\text{lactide}]_0/[\text{DBX}]_0$ = 50, 100, or 200, indicating that there is no clear relationship between the molecular weights and the ratio $[M]_0/[DBX]_0$ (Figures S2−S4, Supporting Information, DBX = DBU or DBN). Similar behavior was observed for the zwitterionic ring-opening polymerization of lactide by *N*-heterocyclic carbene catalysts[12] and was attributed to slow and reversible initiation behavior.

A low molecular weight polylactide (M_n = 8300 Da) was generated from DBU by terminating the polymerizaton at low conversion (6%) and isolating the resultant polymer by dialysis in methanol. MALDI-TOF mass spectrometry revealed molecular ions attributed to cyclic polylactides, along with minor amounts of linear polylactides terminated with methyl esters (Figure S5). The intrinsic viscosities of the polylactides generated with DBX initiators in the absence of alcohols are lower than those of linear polylactides generated in the presence of an alcohol initiators (Table 1), providing additional evidence that the polylactides generated with DBX initiators are predominantly cyclic.[30]

The ratios of the intrinsic viscosities $[\eta_{DBX}]/[\eta_{linear}]$ ranged from 0.71 to 0.91, depending on the nature of the solvent and the initiator. For a pure cyclic polymer in a theta solvent, the ratio of the instrinsic viscosity of a cyclic polymer should be 0.667 of that of a linear polymer of the same molecular weight.[30] The increase in the ratio of intrinsic viscosities $[\eta_{DBX}]/[\eta_{linear}]$ as the amount of CH_2Cl_2 increases implies that samples prepared in this solvent have a higher fraction of linear chains. These results suggest that the zwitterionic polymerization of lactide with DBX initiators generates a mixture of cyclic and linear chains and is thus not as efficient a method for generating cyclic polymers as that with NHC catalysts.[10−14]

Scheme 1. Proposed Mechanism for the DBU-Mediated Polymerization of Lactide[a]



[a] DFT computed enthalpies are relative to the sum of the reactants (free DBU and free lactide) at infinite separation.

In Scheme 1, we present one mechanistic hypothesis for the ring-opening polymerization of lactide with DBX initiators. The ring-opening polymerization observed in the absence of alcohol initiators strongly implies that the amidines DBU and DBN can function as nucleophilic initiators. Attack of DBU on lactide would generate the zwitterion $\mathbf{Z_1}$ in analogy to mechanisms proposed for the activation of acyl halides and dialkyl carbonates with DBU.[28] The acylated amidinium zwitterion could react by several pathways. Ring-closure would generate the neutral tricycle $\mathbf{T_1}$,[31] which would likely be a dormant species. Addition of lactide to the alkoxide of the zwitterion would result in chain growth to larger zwitterions $\mathbf{Z_n}$ (path a), in analogy to that proposed for the zwitterionic ring-opening polymerization with NHC's.[10−14] Cyclization by attack of the alkoxide on the acyl amidinium would release a cyclic polylactide and DBU.

Alternatively, as acyl amidinium ions are readily deprotonated to generate ketene aminals,[28] deprotonation of the zwitterion could generate the neutral ketene aminal **KA** (path b). In the presence of excess DBU, this ketene aminal could undergo chain growth[22] to generate linear polylactides terminated with the ketene aminal end group. As acylated ketene aminals are known to acylate alcohols,[28] it is possible that these ketene aminals could also cyclize to generate cyclic polylactides. Linear polylactides could result from esterification of the ketene aminal terminated chains upon methanol workup. This latter pathway provides one possible rationale for the formation of mixtures of cyclic and linear chains.

DFT calculations were carried out to investigate the relative enthalpies (and electronic energies) of the proposed intermediates $\mathbf{Z_1}$, $\mathbf{T_1}$, and **KA**. Optimized structures, relative electronic energies (see SI), and enthalpies at 298 K were calculated using Gaussian 09[32] at the M06[33]/6-31+G(d,p) level of theory (see SI for computational details) in dichloromethane with the CPCM[34] solvent model and are referenced to DBU and lactide at infinite separation. DFT analysis suggests that the first intermediate formed from DBU and lactide is a neutral tricycle $\mathbf{T_1}$ that forms with an enthalpic barrier of 23.3 kcal/mol at 298.15 K and exists as two conformers (ΔH_{298} = 16.41 and 16.65 kcal/mol). The intermediate, $\mathbf{Z_1}$, is calculated to be less stable than $\mathbf{T_1}$ (ΔH_{298} = 19.48 kcal/mol); the transition state located for the ring-opening of $\mathbf{T_1}$ to generate $\mathbf{Z_1}$ has a calculated enthalpy of 23.38 kcal/mol, 7.23 kcal higher in energy than $\mathbf{T_1}$. The ketene aminal **KA** is calculated to be more stable than either $\mathbf{T_1}$ or $\mathbf{Z_1}$ (ΔH_{298} = 10.31 kcal/mol), but the transition state for deprotonation of the zwitterion to generate **KA** has a calculated enthalpy of 30.15 kcal/mol. Methanolysis of **KA** to liberate linear methyl esters is calculated to have an enthalpic barrier of 26.85 kcal/mol (Figure S8) from **KA**. These calculations indicate that the intermediates $\mathbf{Z_1}$, $\mathbf{T_{1,}}$ and **KA** are energetically accessible; the higher barriers associated with the formation and methanolysis of **KA** is consistent with the formation of minor amounts of linear chains observed experimentally (Scheme 1).

In summary, the ring-opening polymerization of lactide with the amidines DBU and DBN occurs readily in the absence of alcohol initiators, implicating that amidines can function as nucleophiles for the ring-opening of lactide. Theoretical studies implicate the formation of amidine zwitterions that react by several pathways to generate a mixture of linear and cyclic polylactides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic and computational methods including DFT optimized atomic coordinates, molecular orbitals, and energy plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge support from the NSF (NSF-DMR1001903 and GOALI NSF-CHE-0645891), a Gabilan Stanford Graduate Fellowship for H.A.B, and the Stanford University Center for Molecular Analysis Design Postdoctoral Fellowship for A.G.D.C. Work at the Molecular Foundry (MALDI-TOF MS) was supported by the Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231. We thank Dr. Eun Ji Shin for useful discussion. We acknowledge Professor Dan Stack for access to the Redox Computer Cluster (Stanford University) to run the DFT computations.

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