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Elucidating a Unified Mechanistic Scheme for the DBU-Catalyzed Ring-Opening Polymerization of Lactide to Poly(lactic acid)

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Abstract

The synthesis of poly(lactic acid), PLA, is facile in the presence of the cyclic, organic amidine catalyst 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU. Since DBU's catalytic capability was first reported by Lohmeijer and colleagues in 2006 for ring-opening polymerizations (ROP), there have been numerous studies conducted by a variety of groups on the catalytic functioning of DBU in the ROPs of cyclic esters resulting in a large body of un-unified material from a mechanistic standpoint. This lack of clarity will hamper engineering polymers with desired characteristics from cyclic ester and lactone monomers. The work outlined in this paper seeks to propose a unified picture of the mechanisms in the DBU catalyzed ROP of lactide. In providing this unified picture of the ROP our work encompassed: (i) proposing a detailed reaction network scheme, (ii) conducting syntheses of lactide and DBU over a range of initial concentrations, and (iii) kinetic modeling to further support the proposed reaction network. As a result, our work has produced: (i) kinetic data, (ii) a consistent, viable reaction scheme verified through kinetic modeling, (iii) deduced and quantified the interplay between polymerization routes facilitated by the presence of DBU, thus demonstrating the need for detailed kinetic studies to deconstruct complex reaction networks, (iv) the first experimental evidence in support of the combination of ketene aminal-ended chains with alcohol-ended chains, and (v) analyzed the robustness of the catalyst to acid contamination.

Graphical Abstract

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Supporting Information: Sections 1–4 Kinetic balance equations, Section 5 – Mechanisms, Section 6 – Zimm-Schulz distribution, Section 7 – Density Measurements, Section 8 – Parameter Fitting Algorithm, Section 9 GPC Time-Evolution Traces, Section 10 – Carbitol-DBU alcohol-catalysts *in-situ* ¹H NMR interactions, Section 11 – Estimate of acylation (combination) rate constant, Section 12 – Number-average M_n and PDI experimental to modeling comparisons, Section 13 – Excess catalysts and excess alcohol macro-initiator experimental to modeling comparisons, Section 14 – Experimental data used in modeling, Section 15 – Rate of Cyclization.

1. Introduction

The use of guanidines and amidines in the polymerization of cyclic esters has been reported on extensively in the literature. In 2006, Lohmeijer *et al.* first reported the use of the amidine 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU, along with the use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBD, and methylated TBD, MTBD, in the ROP of cyclic esters in the presence of an alcohol macro-initiator.² Since this seminal work, there have been a variety of papers that have investigated the polymerization of cyclic esters, primarily lactide, by DBU over a range of initial conditions and a host of alcohol macro-initiators and co-catalysts.^{1, 3–5} This work has left ambiguity about the mechanisms involved, and questions about what mechanistically is occurring when the polymerization is conducted under varying initial conditions, e.g. with or without an alcohol macro-initiator. This is especially the case when walking the fine line between hydrogen-bonding activation and acid-base equilibria reactions. To provide a clearer picture, we have proposed a mechanistic reaction scheme for the polymerization of lactide by DBU over a range of initial conditions to capture a variety of experimentally observed phenomenon. The reaction scheme was derived from several papers that used both experimental and computational approaches to describe the well-established nucleophilicity, basicity and hydrogen-bonding properties of DBU.^{2, 6–10} Shieh *et al.* further elucidated the functioning of DBU as a nucleophilic catalyst through 2001–2 in the esterification of carboxylic acid with dimethyl carbonate.^{7, 11} Shieh's work led Carafa and colleagues to shore up DBU's catalytic nature in 2011, in which they isolated the unprecedented ketene aminor.¹² Carafa's findings significantly influenced the proposed reaction scheme in this work; specifically, it was their isolation of the ketene aminor species and their emphasis on the ketene aminor as the key intermediate in acylation reactions. In 2012, Waymouth/Hedrick *et al.* showed the potential for DBU to catalyze the polymerization of lactide in the absence of an alcohol macro-initiator involving a hypothesized zwitterionic ROP (ZROP) mechanism. The ZROP mechanism for the DBU catalyzed ROP of lactide was theorized to be similar to that of N-heterocyclic carbene initiated polymerizations that undergo rapid propagation, $k_p = 48.7 \text{ s}^{-1}\text{M}^{-1}$.¹³ The papers by Lohmeijer and Waymouth/Hedrick were evidence for two competing pathways for the polymerization of lactide; each serving as one piece of the puzzle that when combined yield a more accurate picture of the reaction network. One pathway is mediated by alcohol-activation and the other through nucleophilic attack by DBU on the monomer. The first route is henceforth discussed as the activated-alcohol pathway (AAP), and the second route as the nucleophilic-attack pathway (NAP). There are several recent reviews that the reader should turn to for general background knowledge on the various mechanisms involved in ROP.^{14–16} Understanding quantitatively not only the mechanisms but their dynamic interplay is critical in order to engineer the polymerization of lactide for desired characteristics without the need for a costly, trial-and-error synthesis approach. In addition, to engineer precise sequences of copolymers comprised of varying combinations of cyclic esters or lactones will require a high level of resolution on the mechanisms involved, and accurate estimates of the kinetic parameters. In the following we outline a unified reaction scheme combined with a quantitative kinetic analysis parameterized with experimental data to provide the level of accuracy required to engineer DBU catalyzed ROP.

2. Methods and Procedures

2.1 Materials

Monomer *rac*-lactide (GC 99.5% purity, moisture content <200 ppm, free acid 1 meq/kg, equivalent is the amount to neutralize 1 mole of HCl, Altasorb) was purified frequently between use by recrystallizing twice from toluene and was kept in a sealed flask at -20 °C under inert atmosphere until use. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from Sigma-Aldrich and was used without further purification. DBU was stored in a nitrogen glovebox at ambient temperature. Monomethoxy/monohydroxy-terminated PEG, PEG-OH, (Sigma-Aldrich) of number-average molecular weight, $M_n = 5 \text{ kg mol}^{-1}$ and a polydispersity index, PDI = 1.056 was used as the alcohol macro-initiator. The PEG-OH was purified by heating under vacuum at elevated temperatures, 100 – 110° C, overnight.¹⁷ All solvents were kept under activated molecular sieves (3 Å) overnight before use. The reaction was terminated using reagent grade (99.5% purity) benzoic acid purchased from Sigma-Aldrich. Polymer precipitation was carried out using HPLC grade 2-propanol purchased from Sigma-Aldrich.

2.2 Characterization

¹H NMR spectra were measured at room temperature on a Bruker ARX 400 MHz or Bruker ARX 300 MHz spectrometer using a 5.0% (w/w) polymer solution in CDCl₃ purchased from Cambridge Isotope Laboratories, Inc. or CD₂Cl₂ purchased from Sigma-Aldrich to determine the number-averaged molecular weight (M_n). Size-exclusion chromatography (SEC) were performed on an Agilent Technologies 1200 series equipped with a Hewlett-Packard G1362A refractive index (RI) detector and three PLgel 5 µm MIXED-C columns. Tetrahydrofuran (THF) was used as the mobile phase at 35 °C and a flow rate of 1 mL min⁻¹. The SEC measured number-averaged molecular weight (M_n), weight-averaged molecular weight (M_w) and polydispersity index (PDI) determined using a polystyrene standard (Agilent Easi Cal) with molecular weights ranging from 1 kg mol⁻¹ to 200 kg mol⁻¹.

2.3 Density Measurements

The poly(*rac*-lactic acid), PLA, syntheses were carried out over a variety of initial conditions involving at a minimum 25 mass percent of PEG and lactide relative to the solvent, dichloromethane (DCM). With this significant increase in mass of the solutes there is an accompanied increase in volume of the total solution that is greater than the volume of the solvent alone. As a result, the density of the resulting PEG, lactide and DCM solution was characterized to correct the initial concentrations due to the increase in volume from the additional mass. The density measurements were conducted using tared 1.5 mL vials, to which 1 mL of pre-made solutions of PEG, lactide and DCM were added with an automatic pipette. The measurements were carried out on a Denver Instruments M-220D Laboratory Scale. A total of 6 solutions were made with 3 vials containing either 0.65 M or 0.13 M lactide in DCM with 0.003, 0.01 or 0.05 M concentration of PEG. The measurements were taken in triplicate for a total of 18 data points. Additionally, the density of DCM was measured in the same way at $1.3010 \pm 0.053 \text{ g mL}^{-1}$, where the $\pm 95\%$ confidence intervals (CI) values are indicated. The overall density of the solution was statistically invariant over

the concentration ranges (SI Section 7, Figures 1 and 2), and therefore the literature density of 1.3266 g mL⁻¹ of DCM was used to correct the initial concentrations of the species in the reactor vials.

2.4 Polymer Synthesis

General outline of the PLA synthesis procedure—A stir bar was placed in a disposable amber glass vial (22 mL, Supelco) and capped with a rubber septum. The vials were then cycled thrice with vacuum and nitrogen at room temperature. The purified alcohol macro-initiator, PEG, was weighed and charged to a round bottom flask (250 mL). The appropriate weight of monomer, *rac*-lactide, was then added to the round bottom flask. Dichloromethane was added via syringe (typically 80 mL) to the round-bottom flask, followed by sonification to ensure dissolution of all solids. All solutions for an individual synthesis were made in bulk, and then allocated via syringe to reaction vials immediately after sonification. A concentrated solution containing the catalyst, DBU, was injected via a syringe to initiate the polymerization. The solution was stirred vigorously at room temperature for the entirety of the polymerization. The individual vials were terminated at varying times to collect time dependent polymerization data on a per batch basis.

Solid benzoic acid was added to the vial in 1–2× molar equivalence relative to the alcohol macro-initiator or DBU depending on which amount was greater, to terminate the polymerization. Following termination, the vial containing the poly(*rac*-lactic acid), DBU, PEG, lactide, benzoic acid and DCM were concentrated (> 50%, 10 minutes) under vacuum. The polymer was then immediately precipitated dropwise using excess 2-propanol. The white, crystalline precipitate was allowed to settle while the wash was poured off. The precipitate was then dried in a vacuum oven overnight (12 hours) to remove residual solvents before polymer characterization.

Three independent PLA synthesis replicates—In order to gauge the batch-to-batch variation and further understand the observed early cessation in monomer conversion in certain polymerizations, three independent PLA syntheses were conducted under the same conditions. Additionally, one of these PLA synthesis included the addition of catalysts at 30 minutes to investigate whether the polymerization could proceed to full monomer conversion. The batch solutions were made with molar ratios of PEG-OH:DBU = 4.9, and LA:DBU = 73.1. PEG-OH and lactide were charged to a round-bottom flask (38.896 g, 0.049 M, and 16.294 g, 0.707 M, respectively) with DCM solvent (160 mL). The batch solution was sonicated and 10 mL distributed to 12 pre-prepared amber glass vials. To initiate the polymerization, 870 µL of a concentrated DBU solution (16.7 µL DBU per 1 mL DCM) was injected into the reaction vial. At 30 minutes, 3 of the vials had an additional 500 µL of the concentrated DBU catalyst solution added. All reactions were terminated with benzoic acid (0.13 g, 0.130 M). The solutions were concentrated and the polymer was precipitated from excess 2-propanol. After removing the wash, the white precipitate was dried overnight in a vacuum oven to remove excess solvent.

2.5 Kinetic Modeling

In validating the proposed mechanisms for the DBU catalyzed ROP of lactide kinetic equations were derived, including the first three moments of the chain distributions, to describe the time-evolution of both the polymer chains (i.e., concentration, M_n , M_w and PDI) and reactive species. These equations were parameterized using the experimentally measured conversion data from our syntheses ($n = 50$ data points), as well as the inclusion of Waymouth/Hedrick *et al.* syntheses data ($n = 29$ data points) for increased consistency and for increased breadth of experimental conditions, all experimental data located in SI Section 14.¹ The coupled, non-linear ordinary differential equations describing the time evolution of the species are summarized in sections 1 – 4 of the Supporting Information (SI). The equations are stiff and require the use of numerical integration techniques based on numerical differentiation formulas (NDFs) that arise from backward differentiation methods (BDFs).^{18, 19} MATLAB was used to implement this numerical integration technique utilizing the built in ordinary differential equation 15 solver, ode15s. The time evolution of the lactide monomer concentration, [LA], the number- and weight-average molecular weights, M_n and M_w respectively, and the polydispersity, $PDI \equiv M_w/M_n$, were computed and compared to the experimental data. However, only the time-evolution of the monomer concentration was fitted to the experimental data. Thus, further confidence in the mechanisms of the model and the model's parameter calibration can be found in reasonable predictions for the time-evolution of the number-average molecular weight and PDI, Section 12 of SI. No correction was made for the non-monodispersed nature of the alcohol macro-initiator – PEG. The parameters in the kinetic model equations were calibrated through the application of the least-squares analysis method, in which the minimization of the sum of the square error (SSE) of the regression for all data points, N_i in all syntheses, $i = [1, E]$, is the goal-seek. The objective function is defined as:

$$SSE = \sum_{i=1}^E \sum_{j=1}^{N_i} \left([LA]_{exp.}(t_{i,j}) - [\widehat{LA}]_{pred.}(t_{i,j}, \hat{\mathbf{k}}) \right)^2 \quad (1)$$

Where, $\hat{\cdot}$ denotes an estimated quantity

The minimization of the SSE function is the goal-seek of two custom optimization routines implemented in the MATLAB environment. The optimization routines varied in the methods by which they sought out a global minimum in the SSE by varying the adjustable parameters in the vector $\hat{\mathbf{k}}$, $\hat{\mathbf{k}} = [1, P]$ where $\hat{\mathbf{k}} \in \mathbb{R}^P$ and P denotes the number of kinetic parameters.

The first optimization code made use of a coarse grain approach to search in a combinatorial fashion the pre-defined parameter space. The feasible parameter space, $\mathcal{F}$, was searched over several orders of magnitude, thus a log-space was implemented when searching. It should be noted that the feasible parameter space is rarely precisely known at the start, and must be constrained from the outset using physical intuition and experience. Knowing how to best constrain the space comes from understanding the limits of kinetic constants due to physical limitations, or from literature data from comparable reactions; the most reliable ab initio method for parameter guesses would come from quantum mechanical calculations, though these are time consuming and costly. A parameter space may become unfeasible with

certain combinations of kinetic parameters which cause significant solver errors, resulting in either premature termination of numerical integration routines or erroneous solutions. The optimization routines are only limited by the computation time associated with running all desired combinations. The total number of combinations is specified at the outset, and is determined by the number of intervals in the log-space, I , raised to the power of the number of parameters, P . total combinations = I^P .

The second solver made use of a gradient search method, Trust-Region-Reflective Optimization, to search around the optimum solution from the coarse-grained combinatorial optimization conducted above. The Trust-Region-Reflective Optimization was again implemented in the MATLAB environment and made use of the built-in MATLAB lsqnonlin function.^{20–22} The function is designed to solve nonlinear least-squares problems with a user-defined initial guess for the parameters, $\mathbf{k}$, initial guesses provided from the coarse-grain optimization, and within user-defined parameter bounds, $k_p \in [l_p, u_p]$ confining $\mathcal{A}$ on $\{\mathbf{k} : \mathbf{l} \leq \mathbf{k} \leq \mathbf{u}\}$ where $\mathbf{l} \in \{\mathbb{R} \cup \{-\infty\}\}^P$ and $\mathbf{u} \in \{\mathbb{R} \cup \{\infty\}\}^P$. The bounds set around the initial guess in the gradient optimization routines, $\mathbf{l}$ and $\mathbf{u}$, were always plus/minus an order of magnitude around the initial guess, $k_p \pm 10 \times k_p$. The lsqnonlin function returns the Jacobian matrix from finite difference approximations, the partial derivatives of the function's output at each data point, indexed by i and j , with respect to each model parameter, indexed by p . The Jacobian matrix is used in the determination of standard errors associated with each parameter, $se(\hat{k}_p)$, the sensitivity of the function to a parameter, and the determination of the correlation coefficient between parameters in the kinetic model.²³

$$\begin{aligned} \text{Jacobian matrix } [N, P]: \mathbf{J} &= \left[\frac{\partial f([LA]_{i,j}, \hat{k}_d)}{\partial k_p} \right]_{\hat{k}_{d \neq p}} \\ \text{Standard error parameter } \hat{k}_p: se(\hat{k}_p) &= \hat{s} \sqrt{\{(J'J)^{-1}\}_{pp}} \\ \text{Standard deviation: } \hat{s} &= \sqrt{\frac{\text{Sum Square Error (Regression)}}{\text{degrees of freedom (Residual)}}} = \sqrt{\frac{SSE_{reg.}}{N-P}} \end{aligned}$$

The numerical integration of the coupled, ordinary non-linear differential equations for the proposed kinetic model based on the proposed mechanistic scheme is nested within the two optimization routines. Intuition from developing the mechanistic scheme along with physical insights, influenced both how the feasible parameter space, $\mathcal{A}$, was defined and the algorithm developed to search the parameter space.

3. Results and Discussion

The conversion of lactide and valerolactone catalyzed by DBU and the amidine-like catalyst MTBD in ROPs, have been reported to be described by a pseudo-first order kinetic model, eqn. (2), in which the apparent kinetic constant, k_{app} , for a given set of initial conditions remains fixed.^{2, 4}

$$\frac{d[LA]}{dt} = -k_{p(1,1)}[D]_o[I]_o[LA] = -k_{app}[LA] \quad (2)$$

The relation holds under the assumptions that the catalyst, $[D]_o$, and propagating alcohol concentrations remain constant, where the propagating alcohol concentration is equivalent to the initial concentration of the alcohol macro-initiator, $[I]_o$. It then follows that the apparent rate constant can be adjusted from experiment-to-experiment by correcting for the initial alcohol macro-initiator and catalyst concentrations. Under these assumptions a plot of the pseudo-first order conversion of lactide should yield a straight line, where the pseudo-first order conversion equation is defined as:

$$\ln \left(\frac{1}{1-X} \right) = k_{app}t, \text{ where } X \equiv \frac{[LA]_o - [LA]}{[LA]_o} \quad (3)$$

As is apparent in Figure 1 graph A, the plot of the normalized pseudo-first order monomer conversion does not always yield straight lines and the $k_{p(1,1)}$ extracted from k_{app} changes significantly over the range of initial monomer, catalyst and macro-initiator concentrations. This lack of linearity over changes in the molar ratios of $[ROH]:[DBU]$ and $[LA]:[DBU]$, notably at high conversions and when there is no alcohol macro-initiator present, along with the change in $k_{p(1,1)}$ are clear indications that there is much more occurring mechanistically than can be accounted for with the conventional pseudo-first order kinetic model. To account for this unquantified variance in the experimental data a unified reaction network scheme for the polymerization was formulated and is presented schematically in Figure 2 along with the mechanistic equations in Table 1. The unified reaction network captures the complexities associated with the DBU catalyzed ROP of lactide, solid and dashed lines Figure 1 graph B, where the simple pseudo-first order model falls short.

The proposed reaction network represents the unification of two competing initiation pathways originating from the innate nucleophilic and basic characteristics of DBU. These two properties are certainly not mutually exclusive and go hand-in-hand. In 2006, Lohmeijer *et al.* surmised that the propagation was a result of DBU activating an alcohol through hydrogen-bonding, defined in this work as the activated-alcohol pathway, AAP, see Figure 2 (purple arrows), and Table 1 – R5-8.² To further verify the alcohol-DBU interaction, three *in-situ* 1H NMR studies were conducted with carbitol and DBU, SI Section 10. These *in-situ* experiments exhibited a fast disappearance of the carbitol alcohol peak with broad peaks arising down field (~ 0.4 ppm) that were noted to be concentration dependent. Contrarily, from the seminal work of Bertrand *et al.* on DBU and DBN in 1993, cyclic amidines have since been known to be strong nucleophiles.⁶ That is DBU has the potential to directly react with highly polarized bonds, such as those of esters as found in the cyclic esters and lactones used as monomers in ROPs. The potential for DBU to function as a nucleophile attacking a carbonyl bond is captured in this work through the incorporation of the nucleophilic-attack pathway, NAP, in the proposed reaction scheme, see Figure 2 – blue and green arrows- and Table 1 – R1 through R4. The first reported experimental evidence supporting the NAP in a

polymerization is from the work by Waymouth/Hedrick *et al.* in 2011. They conducted three syntheses of PLA in the absence of a macro-initiator at 50, 100 and 200 molar ratios of [LA]:[DBU] in dichloromethane noting no relationship between molecular weight and the initial ratios of [LA]:[DBU]. Additionally, they carried out two syntheses of lactide (1 and 0.6 M) with 1% catalyst loading of DBU and 1% alcohol macro-initiator (benzyl alcohol) relative to the monomer concentration.¹ Their synthesis data have been incorporated with our synthesis data to enlarge our data set and cover a wider range of initial conditions, specifically those conditions under which no alcohol macro-initiator is used. The incorporation of their data strengthened the validity of our mutual experimental results, the reasonableness of the proposed reaction network, and the accuracy of the fitted kinetic parameters. Though Waymouth/Hedrick *et al.* indicated the importance of their experimental finding that DBU can facilitate the polymerization of lactide in the absence of a macro-initiator through a nucleophilic initiation of the monomer, the emphasis in the need to quantitatively understand this interplay remained implicit. Rather, in the same year, it was Bibal *et al.* who were the first to emphasize the importance in considering the complex interplay between AAP and NAP mechanisms in the ROPs of cyclic esters or lactones catalyzed by DBU.²⁴

Activated-Alcohol Pathway (AAP) and Modeling

Upon first glance of Figure 2 one will count a total of eight kinetic parameters used in the model, denoted by the red circles. To feasibly search such a parameter space over several orders of magnitude for each constant while maintaining the necessary resolution would require millions of iterations and weeks of computation time on a desktop computer. To greatly simplify this search, we have made use of the expansive data set, compiled from our syntheses and those of Waymouth/Hedrick *et al.*, in conjunction with mechanistic insights to fit the kinetic parameters using an algorithm outlined in the SI: Section 8. The first set of parameters to be fit are those solely in the AAP. This decision is a direct result from the analysis of Waymouth/Hedrick's DFT calculations that the equilibrium of the first step in the reaction pathway, R1 in Figure 2, lies greatly to the reactant side due to the highly unfavorable free enthalpies. The classical mechanism of the AAP was thus assumed to be dominant in 1:1 [ROH]:[DBU] or greater molar concentrations. Under this assumption, experimental data involving a 1:1 or greater molar ratio of [ROH]:[DBU] was first fit to the model, a total of 5 data sets, to obtain initial values for the kinetic parameters k_a^1 , k_d^1 , $k_{p(1,1)}^1$. In addition, to further reduce the parameter space, the equilibrium value for the first reaction, R5, was set to the literature value for the association constant between the DBU-like methylated-TBD, MTBD, with benzyl alcohol, $K_{eq}^1 = 14 \text{ M}^{-1}$ at 25 °C, as measured by Lohmeijer and colleagues. They noted that MTBD and DBU polymerized lactide at similar rates (pKa's of 25.49 and 24.34 in acetonitrile, respectively), while both fail to polymerize δ -valerolactone and ϵ -caprolactone.^{2, 25} Thus, the assumption that they share similar degrees of association, at least on the same order of magnitude, is likely accurate.²⁶ Using an equilibrium value of 14 M^{-1} is justified when one notes that fitting the experimental data without fixing the equilibrium constant yields a value of 14.5 M^{-1} . By using a value for the equilibrium constant, the parameter space is reduced even further to just k_d^1 and $k_{p(1,1)}^1$, which is highly desirable from a computational resources standpoint, and for the convergence of

the fitting to a global minimum by constraining the degrees of freedom in fitting the kinetic parameters. One final assumption was made in the first step of fitting the experimental data for the kinetic constant of initiation, Table 1 – R6. The assumption is that the constant of initiation, k_i^1 , is equal to the rate of propagation, $k_{p(1,1)}^1$, Table 1 – R7. Both activated-alcohol initiation and activated-alcohol propagation involve an activated alcohol undergoing nucleophilic attack at the carbonyl bond of the monomer, thus they are expected to occur at the same rate. This assumption inherently includes the assumption of equal reactivity's for chains of differing lengths. This assumption eliminates the added effect that $k_{p(1,1)}^1 = f(\text{chain length})$ that would serve to greatly convolute the model.²⁷ The fitting cycle, SI Section 8: Sub-Cycle 1, was conducted on syntheses data corresponding to entries 4 and 6 through 9 in Table 2 (n = 34), for the parameters $k_d^1, k_{p(1,1)}^1$, bounded on $0.01 \leq k_d^1 \leq 1 \times 10^4 \text{ s}^{-1}$ and $0.01 \leq k_{p(1,1)}^1 \leq 100 \text{ s}^{-1} \text{ M}^{-1}$, with 100 log-spaced iterations for both parameters within their respective parameter bounds. The initial estimates were $\hat{k}_d^1 = 4.33 \times 10^{-3} \text{ s}^{-1}$ and $\hat{k}_{p(1,1)}^1 = 3.20 \text{ M}^{-1} \text{ s}^{-1}$.

Nucleophilic-Attack Pathway (NAP) and Modeling

With the initial estimates for the propagation constant and the rate of association-dissociation between DBU and alcohol macro-initiators, the initial values for the parameters inherent to the NAP, k_a^2, k_d^2, k_{pt}^1 , Figure 2 – R1-2, can be estimated by again conducting a coarse-grain combinatorial search of the parameter space, SI Section 8: Sub-Cycle 3, with the goal-seek again being to minimize the SSE function. The parameters were bound on the intervals: $1 \times 10^{-6} \leq k_a^2 \leq 0.1 \text{ s}^{-1} \text{ M}^{-1}$; $0.01 \leq k_d^2 \leq 1 \times 10^6 \text{ s}^{-1}$; $1 \leq k_{pt}^1 \leq 1 \times 10^8 \text{ s}^{-1} \text{ M}^{-1}$.²⁸ The estimates for $k_d^1, k_{p(1,1)}^1$ were fixed at their initial estimates from fitting Sub-Cycle 1. The initial estimates for the inherent NAP kinetic parameters were found to be $\hat{k}_a^2 = 8.49 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$; $\hat{k}_d^2 = 6.43 \times 10^3 \text{ s}^{-1}$; $\hat{k}_{pt}^1 = 2.42 \times 10^6 \text{ s}^{-1} \text{ M}^{-1}$ from fitting the experimental data corresponding to entries 1–3 in Table 2 (n = 19).

Observing Acylation

Following a local optimization using the Trust-Region Reflective method utilizing data from syntheses 1–9 in Table 2 (n = 61) with the initial guesses for the parameters from the AAP and NAP coarse-grain fittings described above, it was clear that there were still missing pieces in the puzzle. The first clue was that the predicted number-average molecular weights for the syntheses conducted in the absence of alcohol macro-initiator, entries 1–3 in Table 2, were too low. Secondly, and more revealing than the low molecular weights, when qualitatively observing the GPC traces for the syntheses in either excess- or limited alcohol macro-initiator relative to DBU there were clear differences, syntheses 6 and 5 in Table 2. In excess alcohol the observed GPC traces over time were narrowly distributed, mono-modal and ceased to shift with cessation in monomer conversion, Figure 3 graph A. On the contrary, when in excess DBU the observed GPC time-evolution traces, Figure 3 graph B, is tri-modal and continues to shift long after monomer conversion has ceased. The shift and growth in polymer chains after monomer conversion has ceased is indicative of a

combination reaction, which will need to be accounted for to quantitatively model the polymerization. To our knowledge, this is the first direct experimental evidence for combination, also termed acylation, occurring in DBU catalyzed ROPs of lactide.

Ketene Aminals and Modeling Acylation

The question remained as to what species in the reaction network could account for this observed combination phenomenon. The proposed reaction scheme had already made use of reaction step R2 that involves the deprotonation of the acidic protons on the product of R1, denoted as species $D_{1,1}$, to a ketene aminal, $KA_{1,1}^*$, initiated chain.^{29, 30} This chain has on the one end the ketene aminal, and on the other end, a hydroxyl group that is prone to be activated by free DBU to further undergo quasi-anionic propagation. This explains the slow induction period observed in the experimental data for syntheses conducted in the absence of alcohol macro-initiators, Figure 4 graph A; this induction period can be explained with our proposed reaction scheme by considering that the equilibrium for reaction 1, R1 in Figure 2, lies far to the reactant side, modeling indicated $\hat{K}_{eq}^2 \cong 5.2 \times 10^{-6} \text{ M}^{-1}$. The conversion of the monomer only gains inertia as this equilibrium becomes upset by the deprotonation of the $D_{1,1}$ species by free DBU, $\hat{k}_{pt}^1 \cong 6.5 \times 10^5 \text{ s}^{-1} \text{ M}^{-1}$, to stabilized ketene aminal-ended chains. As the concentration of these stabilized ketene aminal-ended chains accumulates, there is an observed increase in the rate of monomer conversion. This is in stark contrast to polymerizations carried out in the presence of an alcohol macro-initiator that exhibit a complete lack of an induction period, Figure 4 graphs B through E. This lack of an induction period is due to the fact that the hydroxyl groups of the macro-initiator serve as immediately accessible stable terminals upon which to grow the polymer chains. This explanation for the induction period is not in agreement with the hypothesized reaction pathway proposed by Waymouth/Hedrick *et al.* (blue arrows in Figure 2) in conjunction with their DFT calculations (dashed, blue boxes in Figure 2). Their DFT results suggest an uphill climb when following the reaction potential energy surface, at least until the addition of a second monomer. Their modeling does not suggest a fast reaction, like that of reaction R2, which could serve to upset this unfavorable equilibrium associated with the R1 reaction in the NAP. Rather, in careful consideration of Carafa and colleague's 2008 and 2011 work on DBU functioning as an acyl transfer catalysts and their isolation of the ketene aminal species, that led to the proposition of the presence of a ketene aminal species in the DBU catalyzed ROP of lactide.^{10, 12} Carafa's work provided an explanation for the observed combination reaction and for the possibility of cyclization to occur, by demonstrating that acylated ketene aminals, similar to species $D_{1,1}$ and $KA_{1,1}^*$ in Figure 2, are reactive with methanol. From their work an estimate of the kinetic constant associated with the observed combination, R9 through R14 in Table 2, was found, SI Section 11. The estimated value was found to be $\hat{k}_{ac}^1 \cong 0.28 \pm 0.046 \text{ s}^{-1} \text{ M}^{-1}$ with the standard error reported.

To capture the observed combination in our kinetic model, reactions R9 through R14 in Table 2 were included, and parameterized in additional fitting sub-cycles, see SI Section 8 – Sub-Cycles 5 and 6. Waymouth/Hedrick *et al.* have reported that cyclization is likely occurring to a modest degree in the DBU catalyzed ROP of lactide, but the polymerization

favored linear chains when in DCM.¹ Moreover, the rate of cyclization is expected to be highly dependent on the chain length, proportional to $n^{-3/2}$, indicating a rapidly diminishing probability with increasing chain length, see discussion in SI Section 15.²⁷ Thus, only combination reactions were considered in our modeling, while cyclization was neglected in the fitting. Furthermore the kinetic modeling results provide reasonable predictions without the incorporation of the details associated with cyclization; though to provide accurate predictions for the molecular weight profiles (M_n) combination had to be included. Cyclization is expected to occur in the DBU catalyzed ROP of lactide when approaching or in excess DBU relative to alcohol macro-initiator. The fitting proceeded first with a coarse-grain combinatorial search followed by a local Trust-Region Reflective optimization. The combinatorial search bounded the parameter space to $0.01 \leq k_{ac}^1 \leq 100 \text{ s}^{-1}\text{M}^{-1}$ on the assumption that the kinetic constant should reside somewhere on the order of magnitude of $10^{-1} \text{ s}^{-1}\text{M}^{-1}$. A log-space was implemented to search the region with 1,000 intervals, and the parameter was fit to syntheses data entries 1 through 9 ($n = 61$) in Table 2. The combinatorial search yielded an optimum value of $\hat{k}_{ac}^1 = 0.309 \text{ s}^{-1}\text{M}^{-1}$. This result is in excellent agreement with that value from the data of Carafa and colleagues reported above at $\sim 0.28 \text{ s}^{-1}\text{M}^{-1}$. A local Trust-Region search was then conducted on all fitted parameters up to this point ($k_{p(1,1)}^1, k_d^1, k_a^2, k_d^2, k_{pt}^1, k_{ac}^1$), the results of which are displayed in Table 3 under Fitting Cycle 1 in the values row.

DBU Deactivation Modeling

After completing the fitting up to Sub-Cycle 6 in Fitting Cycle 1, the amount of experimental variance captured, as is quantified by the coefficient of determination – R^2 , with regards to the concentration of the monomer over time is 0.933. While the proposed reaction scheme has captured a significant portion of the variance associated with the polymerization of lactide over a large range of initial conditions in both the presence and absence of alcohol macro-initiators, there remained an unexplained, random, sudden-onset in cessation of monomer conversion in certain polymerizations. As a result, three independent batch syntheses were conducted under the exact same conditions to analyze the observed batch-to-batch variation in the data, Figure 4 graph D. The syntheses were conducted at 5× molar excess alcohol macro-initiator relative to the catalysts, with a monomer concentration of 0.53 M lactide. In this extreme excess of initiator, the polymerization is expected to follow the mechanisms associated with the AAP. By following this pathway the polymer should exhibit narrow, mono-modal GPC traces that follow monomer conversion; these characteristics were indeed observed in the GPC traces, SI Section 9. What was unexpected was the degree of variation from batch-to-batch synthesis as is observed in the monomer concentration profiles in Figure 4 graph D. The initial rates of monomer consumption are all in very good agreement, but there is a sudden onset in complete cessation in polymerization.

The cessation in polymerization could be from prematurely terminating chains or catalyst poisoning. Both of these could be explained by an intrinsic mechanism in the reaction, or due to outside contamination, as it is known that dry-box conditions must be used in these syntheses.^{24, 31} As to the latter question, there is a lack of any pattern to the onset of

termination, other than it comes on quickly. The data from the 3 independent syntheses suggests a high degree of variation in the time of onset from batch-to-batch. These facts suggest there is an unaccounted outside variable affecting the polymerization that is changing from batch-to-batch; this variability rules out intrinsic deactivation mechanisms, such as R19 through R24 in Table 1. Given the organic catalyst's well known basicity, any presence of acidic species could lead to a poisoned catalyst either through competitive hydrogen-bonding or acid-base chemistry. The sources of the acidic species could be moisture infiltration from either the atmosphere or from the hygroscopic PEG. It is also known that the removal of residual lactic acid in the processing of lactide can be challenging, and often impurities remain.^{32, 33} The lactide used in our polymerizations was reported by Altasorb to have at a maximum 1 meq/kg of free acid content, which is equivalent to 10^{-6} moles acid per gram lactide. That translates to a concentration of free acid $>10^{-4}$ M in our reactions. With catalyst concentrations on the order of 10^{-2} M the free acid should only terminate a negligible amount of catalyst, if following a mechanism like that of R25 in Table 1. However, it can be expected that in the presence of an acidic species some of the free DBU would undergo a proton transfer that would generate a supramolecular complex, D^+ in Figure 2. Much akin to our proposed mechanism in R2, the protonated, complexed DBU species would have acidic protons susceptible to interaction with a basic species, i.e., free DBU. Thus, a small amount of acid deactivated DBU in the presence of free DBU would be susceptible to a cascade effect, reaction R26 in Figure 2 and Table 1. This effect gains momentum as the number of propagating acid-base complexed species, D^+ increases. Eventually as the effect propagates the hydrogen-bonded activation of the proton on the propagating hydroxyl, an equilibrium process, becomes un-recoverably upset to the disassociated state due to the consumption of free DBU. The consumption of the free DBU ultimately results in the observed cessation of polymerization. Mechanisms R17 and R18 in Table 1 cannot be ruled out, but are not necessary to capture the effect of DBU deactivation due to a contaminant species; thus, they have been left out of the modeling.

The question remained as to whether the catalyst is poisoned, or whether the propagating polymer chains are irreversibly terminated. To address this question, one of the 3 independent batch synthesis, entry 8 in Table 2, had an additional charge of DBU injected at 30 minutes, Figure 5 graphs A and B. The concentration profile of the monomer in the absence of an additional injection of catalyst remains stagnated around 90% conversion; while when there is an additional charge of DBU to the reactor, the monomer concentration decreases rapidly to $>96\%$ conversion within 10 minutes of the catalyst injection, Figure 5 graph A. As is observed in Figure 5 graphs A and B, both the PDI and the concentration of the monomer decrease with the addition of more catalyst. This result suggest that the polymer chains are undergoing continued polymerization, indicating that the catalyst has been poisoned rather than the irreversible termination of the polymer chains. The result also does not rule out the possibility of the cascade mechanism for catalyst deactivation.

To further support the catalyst deactivation mechanism proposed to occur through a cascade effect, and to access the accuracy of the kinetic parameters fitted in the absence of any deactivation, especially on the propagation constant, kinetic modeling was conducted. For this new round of kinetic modeling, two additional sets of syntheses data (total data points $n = 79$) were incorporated. The new data are from two syntheses that had underwent early

cessation in polymerization, only achieving 66 and 43 percent conversions at 60 minutes, entries 10 and 11 in Table 2, respectively. The proposed termination mechanisms introduce an additional two kinetic parameters into the kinetic model, k_t^4 and k_t^5 , bringing the total number of model parameters to 8. Additionally, there is an unknown initial condition for each synthesis. That unknown is the initial concentration of the acid contaminant. If the proposed mechanisms are reflective of the actual catalyst deactivation phenomenon, there should be an optimal set of kinetic parameters for k_t^4 and k_t^5 that are constant for all syntheses, while the initial concentration of acid contamination is allowed to float for each synthesis. Using the fact that k_t^4 and k_t^5 must be constant for all syntheses to constrain the search and as the condition for an optimal result, the minimization of the SSE objective function, a coarse-grain combinatorial fitting, Sub-Cycle 7 in SI Section 8, was conducted. At each combination of values for the kinetic constants k_t^4 and k_t^5 , the initial concentration of acid contamination was varied for each batch synthesis. The results of the contamination fitting are presented in Table 4, along with the theoretical maximum free acid concentration based on the free acid (1 meq per kg lactide) measurement from Altsorb. The bounds on the parameter search space for the kinetic constants are $1 \times 10^{-4} \leq k_t^4 \leq 100 \text{ s}^{-1} \text{ M}^{-1}$ and $1 \times 10^{-3} \leq k_t^5 \leq 1 \times 10^5 \text{ s}^{-1} \text{ M}^{-1}$ under the assumption that the first step in the cascade mechanism is slow, while the second mechanism would likely proceed at a faster rate. The acid contamination concentration was bounded from $1 \times 10^{-7} \text{ [K]} \text{ } 0.01 \text{ M}$. The modeling results for the contaminant indicated values on the same order of magnitude of the theoretical maximum free acid concentration. This indicates that in fact, termination by extremely low levels of a contaminant is feasible and that these solutions could contain contaminant concentrations sufficient to cause cessation in the polymerization.

To access the effect of the contamination on the rate constants, a second iteration of modeling was conducted, using the predicted contamination concentrations presented in Table 4, to access the accuracy of the kinetic data from Fitting Cycle 1. The second round of fitting results for Cycle 2, Sub-Cycle 6 are presented in Table 3, along with the percent change in values from Fitting Cycle 1, Sub-Cycle 6 to Fitting Cycle 2, Sub-Cycle 6. From the percent change values it can be noted that the propagation constant was affected slightly with only a 9.5 percent change, increasing from 3.28 to $3.59 \text{ s}^{-1} \text{ M}^{-1}$. The slight change in the propagation constant with the addition of the catalyst poisoning mechanism indicates that even in the absence of accounting for this effect, the estimated propagation constant remains relatively insensitive. The rate of dissociation between the alcohol and catalyst, k_d^1 , underwent a 67.5 percent increase maintaining the same order of magnitude. This increase is also not highly unexpected, because there is a minimum threshold at which the association-dissociation rate of the hydrogen-bonding between the alcohol and catalyst becomes insufficiently sensitive to holistic kinetic analysis. Thus, it may very well be that the rate predicted for k_d^1 is underestimated, therefore, it should be taken as a threshold value. The kinetic parameters in the NAP mechanisms underwent decreases in their respective values with k_d^2 undergoing the largest, -97.7 , percent change. These changes corresponded to a -31.5 percent change in the equilibrium constant, K_{eq}^2 , between the catalyst, DBU, and the monomer, lactide. Correspondingly, the rate of intramolecular proton transfer, k_{pt}^1 , decreased

as well by -72.9 percent. The ratio between of $k_{pt}^1:k_d^2$ remained unchanged in both fittings at 4276. This indicates that these values are in fact correlated, not surprisingly, exhibiting a characteristic ratio in order to yield an accurate solution; understanding this ratio would help to constrain further kinetic studies. A further comparison between the estimated standard errors between the two fittings show that the standard error associated with the propagation constant did not decrease as significantly as those associated with the other kinetic constants, Table 3. The estimate of the standard error of each parameter is achieved through the weighting of the estimated standard deviation, $\hat{s}$, by a function of the partial derivatives, the Jacobian, of the predicted lactide concentration with respect to each parameter. Analyzing the standard errors provides an indication of the relative sensitivities of the model prediction, lactide concentration profile, with respect to each parameter. This implies that the propagation constant maintains a significant amount of sway on the model prediction, indicating that the propagation constant resides at the base of a very steep minimum, or that it may not reside in a minimum. Whereas the other parameters have likely reached minimums or valleys, as indicated by their insensitivity as reflected in the standard error.

Reasonableness of Kinetic Parameters

The parameterized kinetic constants used in the modeling are presented in the values row of Fitting Cycle 2 in Table 3, along with the contaminant concentrations in Table 4. The estimate for the equilibrium constant between the alcohol and DBU species used the literature value for MTBD of $14 \text{ M}^{-1.2}$. The parameterization of k_d^1 and k_a^1 , where $k_a^1 = K_{eq}^1 \cdot k_d^1$, gave a value of $\hat{k}_d^1 = 7.06 \times 10^{-3} \text{ s}^{-1}$. The reason for incorporating the forward and reverse rates was to capture the fact that all alcohol chains underwent polymerization, even when the alcohol chains were in excess of DBU. As the kinetic rates of association-dissociation increases, they eventually reach rates that are too fast to make a difference in the estimation of the parameters through kinetic modeling. Thus the estimate for $\hat{k}_d^1$ is likely a threshold value. It is not an issue if $\hat{k}_d^1$ is a threshold value, because the model is primarily concerned with accurately capturing the rate of propagation. Since a measured literature value was used for the equilibrium constant, 14 M^{-1} , the order of magnitude of the number of activated alcohols, through hydrogen-bonding activation, is believed to be accurate as discussed earlier. As for the rate of propagation estimated at $3.59 \text{ s}^{-1} \text{ M}^{-1}$, it is believed that it is as well a reasonable value for the propagation rate. A propagation constant of $3.59 \text{ s}^{-1} \text{ M}^{-1}$ ($\text{pK}_a = 24.34$ for DBU in MeCN) puts the value below that characteristic of zwitterionic polymerizations, $k_p = 48.7 \text{ s}^{-1} \text{ M}^{-1}$, of N-heterocyclic carbenes (pK_a 's 27–28 in MeCN), but greater than that for the coordination-insertion mechanisms of metal alkoxide catalysts, $k_p \cong 0.5$ to $2.2 \text{ s}^{-1} \text{ M}^{-1.13, 25, 34-36}$. The value for the kinetic parameters in the NAP mechanisms are understood to be accurate given that they reflect the insights from the DFT modeling conducted by Waymouth/Hedrick *et al.*¹ The insight being that the interaction between DBU and the monomer is not favored, thus the estimated equilibrium value for this interaction of $5.20 \times 10^{-6} \text{ M}^{-1}$ reflects the DFT modeling results. The kinetic constant for the rate of combination, amidine-mediated alcohol acylation, k_{ac}^1 , was found to be $0.309 \text{ s}^{-1} \text{ M}^{-1}$. This value is in agreement with the data from Carafa *et al.* that was used to provide an estimate for the acylation reaction on the order of $10^{-1} \text{ s}^{-1} \text{ M}^{-1.12}$.

Additionally, these kinetic parameters, calibrated through fitting only the experimental monomer time-dependent concentration profiles, provided reasonable predictions for the number-average molecular weights and PDIs for the syntheses, SI Section 12. When modeling the GPC time-evolution traces using the Schultz-Zimm distribution, which was used to expand the moments into full distributions for the ketene aminal-ended and the alcohol-ended chains, can qualitatively and even quantitatively reproduce trends for the emergence and time-evolution of peaks associated with the combination reactions, SI Section 13. The model's quantitative prediction capacity over a wide-range of conditions, supports the calibration of the kinetic parameters, and that the proposed mechanisms in the model are reflective of reality.

Furthermore, an additional comparison to recently published experimental results was conducted, Figure 6. The data of Dubois and coworkers' for the DBU-catalyzed ROP of LA was used.³⁷ The rate of propagation was corrected for the difference in solvents with the kinetic data from Hoye/Macosko *et al.*¹ This was done by extracting a rate of propagation constant from the Hoye/Macosko data of $1.33 \text{ s}^{-1} \text{ M}^{-1}$ for the polymerization conducted in chloroform.⁴ Waymouth/Hedrick have also made note of the difference in the rate of polymerization due to different solvents. In Figure 6, it is observed that the proposed holistic model yields excellent correlation to this new set of experimental data using the corrected rate of propagation for chloroform. All other kinetic constants were left the same on the assumption that the rate of propagation would be the most effected due to a solvent change. Note that the experimental data in Figure 6 covers a wide range of DBU:ROH:LA ratios far beyond what the model was originally calibrated to. The observed agreement lends further weight that the hypothesized mechanisms are fundamental, and that the kinetic calibration is accurate.

One additional experiment was conducted in our lab in triplicate for comparison to the calibrated model at a new set of monomer, alcohol macro-initiator and catalyst concentrations, [LA]:[DBU] and [ROH]:[DBU] ratios of 116 and 1.16 respectively, Figure 7. The calibrated model was used to provide a prediction of the polymerization and is represented by the solid blue line in Figure 7, see SI Section 12 Figure 6 for M_n and PDI data. The rate of propagation is that of $3.59 \text{ s}^{-1} \text{ M}^{-1}$ as is appropriate for DCM. The contamination concentration is set to a molar concentration of 0. Excellent agreement is observed between the model's prediction to that of the experiment, lending further validity to the reasonableness of the calibrated model.

To demonstrate the practical application of the insights garnered with a unified reaction network for the DBU catalyzed ROP of lactide, 48×1 hour-long *in-silico* polymerizations were conducted to access what fraction of the total number of initiated chains are ketene aminal-ended, Figure 8 graph

A: fraction ketene aminal-ended chains $\equiv \frac{[KA-ended]_{max, value}}{[KA-ended]_{max, value} + [ROH]_{max, value}}$. The DBU catalyst concentration was maintained at 0.01 M, while both the alcohol macro-initiator and lactide concentrations were varied from 0 – 0.05 M and 0.2 – 1.6 M, respectively. The contaminant concentration was set to 0.0 M. The results of the *in-silico* polymerizations immediately indicate that at the typical [ROH]:[DBU] molar ratio of 1 and [LA]:[DBU]

molar ratios of 100, there will be a high number of ketene aminal-ended chains present during the synthesis representing a population of 0.05 to 0.10 of the total number of initialized chains. From the syntheses conducted in our work, it was observed that molar ratios of [ROH]:[DBU] = 0.4 and [LA]:[DBU] = 72 (Table 2 entry 5), resulted in a dramatic increase in the PDI from 1.13 to 1.30, relative to the synthesis conducted at [ROH]:[DBU] molar ratio of 2.1 (Table 2 entry 6). It is worth noting that the PDI in excess DBU (Table 2 entry 5) no longer represents the breadth of a single distribution, because as is observed in Figure 3 graph B, the distribution is tri-modal due to the undesired acylation reaction. Thus, Figure 6 is immediately useful in reaction engineering to ensure that conducted polymerizations favor “living” characteristics, by ensuring that the alcohol macro-initiator molar ratio relative to the catalyst is sufficiently large, i.e., > 1.5 – 2.0. These estimates of PDI in the approach to excess catalyst relative to alcohol macro-initiator neglect the possibility for DBU-nucleophilic transesterification. Our modeling suggest that only in this regime of high molar ratios of the alcohol macro-initiator to the catalyst, can the desired living polymerization proceed.

4. Conclusion

In summary, our work has produced a unified mechanistic scheme for the DBU catalyzed ROP of lactide along with a quantitative kinetic analysis, that can reliably reproduce experimentally observed monomer, number-average molecular weight, and PDI time-dependent profiles. The constant of propagation, $k_{p(1,1)}^1$, was found to be $3.59 \text{ s}^{-1} \text{ M}^{-1}$, which is in good agreement with literature values for ROPs, residing between the literature values for the kinetic constants of the slow, coordination-insertion propagation mechanism of metal alkoxide catalysts and that of the fast, zwitterionic propagation mechanism for N-heterocyclic carbenes. Through a combination of polymerization syntheses, the influence of the molar ratios, [ROH]:[DBU] and [LA]:[DBU], on the degree of “living-ness” the polymerization exhibits was investigated. The mechanistic studies further highlighted the undesired nucleophilic-activation of the monomer by DBU, leading to the hypothesized ketene aminal-ended chain. This ketene aminal species undergoes both further propagation and eventually undergoes a combination reaction with alcohol-ended chains. It is the very presence of the ketene aminal species that serves to upset the desired living-polymerization. Quantitatively understanding the dynamic interplay between these two routes of initiation, AAP and NAP, is shown to be invaluable in ensuring that the reaction is properly engineered from the outset to exhibit the traits of a living polymerization by the control of molar ratios. Finally, the sensitivity of the polymerization to contamination, what is speculated to be acid contamination, was investigated. From this investigation it was reasoned that it was in fact the catalyst, DBU, experiencing a sudden onset in deactivation, rather than the living-polymer chains becoming irreversibly terminated. Furthermore, a cascade mechanism by which the catalyst deactivation could proceed was proposed and supported through kinetic analysis. The kinetic modeling results suggest that the catalyst is highly sensitive to low levels of contaminants in the system, which would pose significant difficulties to scaling-up the reaction.

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Figure 1.

The normalized conversion based on pseudo-first order monomer conversion kinetics, eqn. (2), is displayed. The data covers PLA syntheses ranging from no alcohol macro-initiator to $5\times$ molar excess alcohol macro-initiator relative to DBU. **(A)** Only the experimental data. **(B)** The experimental data as compared to optimized modeling results for each synthesis, formulated from the proposed kinetic scheme. NOTE: In the legends (*) denotes PLA syntheses data from Waymouth/Hedrick *et al.*¹ Due to the transformed y-axis the deviations at high monomer conversions become greatly exaggerated relative to values at low conversions.

Figure 2.

Above is the proposed reaction network for the DBU catalyzed ROP of lactide. The pathway outlined in purple, R5–R8, reside in the activated-alcohol pathway, AAP. The blue/green arrows denote the convergence of the nucleophilic-attack pathway, NAP, with that of the AAP. Dotted lines indicate information that was taken from literature. The blue pathway, the blue dotted lines, denotes the hypothesized pathway as proposed by Waymouth/Hedrick *et al.* that indicates an anionic propagation mechanism initiated by the nucleophilic nature of DBU on the monomer.² In stark contrast, the green pathway, R1–R4, denotes the convergence of the AAP and NAP to both undergo a quasi-anionic propagation mechanism. Dashed lines/circles denote prior literature values. ** Free enthalpies relative to free DBU and free lactide calculated in DFT calculations performed by Waymouth/Hedrick *et al.*²

Figure 3.

GPC measured molecular weight distributions at various time points. (A) The synthesis was carried out with lactide, alcohol macro-initiator, PEG-OH, and DBU. The alcohol macro-initiator was in $2.1\times$ molar excess relative to DBU, Table 2 entry 6. No excessive broadening was noted in the distributions with time, and excellent agreement between the observed distributions and the modeling results was obtained. (B) The synthesis was carried out with lactide, alcohol macro-initiator, PEG-OH, and DBU, with DBU in $2.4\times$ molar excess relative to the alcohol macro-initiator, Table 2 entry 5. The polymerization ceased at a monomer conversion of $> 99\%$ after 20 minutes. Note the immediate multi-modality of the GPC traces. The polymerization is characterized with an increasing peak on the left shoulder which reaches a maximum at ~ 20 minutes (blue arrow). After 20 minutes, the peak disappears and the appearance of a peak on the right shoulder occurs (yellow arrow).

Figure 4.

Experimental data (points) and modeling results (lines) for the monomer concentration profiles over a range of initial conditions. (A) No alcohol macro-initiator, entries 1–3 Table 2. (B) Excess alcohol relative to catalyst and excess catalyst relative to alcohol, entries 6–5 Table 2, respectively. (C) 1:1 ROH:DBU, entries 4 and 9 Table 2. (D) 5x molar excess alcohol relative to catalyst, entries 7–8 and 11 Table 2. (E) Early cessation in polymerization, entries 10 and 11 Table 2. (*) denotes data from Brown *et al.*²

Figure 5.

Data from the addition of catalyst, DBU, to the reactor at 30 minutes into the polymerization to access whether or not the polymer chains were terminated or the catalyst was poisoned.

(A) The monomer concentration profile as compared to the profile injected with additional catalyst. Monomer Conversion at 40 minutes without catalysts addition is ~90 % and with addition ~96 %. (B) The ^1H NMR number average molecular weight and PDI profiles compared to the addition of catalyst. Note the continued decrease in PDI in the presence of additional catalyst.

Figure 6.

Comparison of the experimental data from Dubois and colleagues for the DBU catalyzed ROP of LA, black squares. The experimental results are compared to the models predictions for the propagation rate in DCM, red circles, and in chloroform, blue triangles. The rate of propagation in DCM, $3.59 \text{ s}^{-1} \text{ M}^{-1}$, was corrected using the kinetic data from Hoyer/Macosko *et al.* to a value of $1.33 \text{ s}^{-1} \text{ M}^{-1}$.

Figure 7.

Comparison of experimental data for the DBU catalyzed ROP of LA carried out thrice in our lab at a new set of initial monomer, alcohol macro-initiator and catalyst concentrations. [LA]:[DBU] = 116 and [ROH]:[DBU] = 1.16, [LA] = 0.87 M. All three synthesis are from the same bulk batch and split into three trials. Time samples were terminated in 2× excess benzoic acid. Black squares represent the conversion of lactide from the ^1H NMR calculated ratio of LA and PLA. The red circles represent the ^1H NMR calculated conversion from the PLA to PEG methylene to methine peaks. The error bars correspond to two times the standard deviation where $n = 3$ for each point, except for 30 and 60 seconds for which $n = 2$. The experimental results are compared to the models predictions for the propagation rate in DCM, solid blue line. As is noted, there is excellent agreement between the models prediction with that of the experimental data. For the PDI and M_n data, see SI Section 12 – Figure 6.

Figure 8.

Contour map from 48 *in-silico* DBU catalyzed ROPs of lactide. The polymerizations were conducted over a range of $[ROH]:[DBU]$ and $[LA]:[DBU]$ molar ratios. The concentration of DBU was fixed at 0.01 M and the concentrations for the alcohol macro-initiator and monomer were changed accordingly. Syntheses were modeled over a time span of 1 hour, and with the acid contaminant concentration set to 0 M. **(A)** The color-contour map depicts the max fraction of the total number of polymer chains that are ketene aminal-ended, increasing in fraction from right to left. **(B)** The color-contour map displays the PDI as a function of the characteristics ratios. The PDI experiences a rapid increase as the excess DBU limit is approached and passed.

Table 1

Mechanisms associated with the proposed reaction network scheme presented in Figure 2.

Initiation/Propagation:	
<i>Nucleophilic-attack pathway (NAP)</i>	
(R1)	$D + M \xrightleftharpoons{k_a^2, k_d^2} D_{1,1}$
(R2)	$D_{1,1} + D \xrightarrow{k_{pt}^{inter}} K A_{1,1}^*$
(R3)	$K A_{1,m-1}^* + M \xrightarrow{k_{p(1,1)}^1} K A_{1,m}^*$
(R4)	$K A_{1,m}^* \xrightleftharpoons{k_a^1, k_d^1} K A_{1,m} + D$
<i>Activated-alcohol pathway (AAP)</i>	
(R5)	$D + I \xrightleftharpoons{k_a^1, k_d^1} [D-I]$
(R6)	$[D-I] + M \xrightarrow{k_i^1} D_{1,1}^*$
(R7)	$D_{1,n-1}^* + M \xrightarrow{k_{p(1,1)}^1} D_{1,n}^*$
(R8)	$D_{1,n}^* \xrightleftharpoons{k_a^1, k_d^1} R_{1,n} + D$
(R7)	$D_{1,n-1}^* + M \xrightarrow{k_{p(1,1)}^1} D_{1,n}^*$
(R8)	$D_{1,n}^* \xrightleftharpoons{k_a^1, k_d^1} R_{1,n} + D$
Acylation:	
<i>Combination</i>	
(R9)	$K A_{1,n}^* + I \xrightarrow{k_{ac}^1} D_{1,n}^* + D$
(R10)	$K A_{1,n}^* + R_{1,m} \xrightarrow{k_{ac}^1} D_{1,m+n}^* + D$
(R11)	$K A_{1,n}^* + K A_{1,m} \xrightarrow{k_{ac}^1} K A_{1,m+n}^* + D$
(R12)	$K A_{1,n} + K A_{1,m} \xrightarrow{k_{ac}^1} K A_{1,m+n} + D$
(R13)	$K A_{1,n} + I \xrightarrow{k_{ac}^1} R_{1,n} + D$

Cyclization^a

DBU Deactivation Mechanisms:^b

Cascade

^aCyclization was not fit in the modeling.

^bThese represent all considered deactivation mechanisms, but only R25 and R26 were fit in the modeling. The reasons for this are discussed further in the DBU Deactivation Modeling section.

Table 2

Synthesis data for the ROP of lactide catalyzed by DBU

Entry	Initiator ^b	[LA] ^c	[LA]:[DBU]	[ROH]:[DBU]	% conv. ^d	$M_n^{Theor,f}$	$M_n^{NMR,g}$	$M_n^{GPC,k}$	PDI ^k
1	DBU ^{d,e}	0.90	50.0	0.0	0.94	7200	n.d.	45181	1.97
2	DBU ^a	0.90	98.1	0.0	0.83	14126	n.d.	56265	1.62
3	DBU ^a	0.90	200.0	0.0	0.64	28800	n.d.	43675	1.47
4	DBU,BnOH ^a	0.90	100.0	1.0	0.94	14400	n.d.	13536	1.35
5	DBU,PEG-OH ^g	0.60	72.3	0.4	> 0.99	31028	31498	14680	1.30
6	DBU,PEG-OH ^g	0.57	72.3	2.1	0.93	9958	9824	8766	1.12
7	DBU,PEG-OH ^h	0.53	73.1	4.9	0.82	7148	6768	7204	1.10
8	DBU,PEG-OH ^h	0.53	73.1	4.9	0.91	7148	6956	7465	1.11
9	DBU,BnOH ^a	0.56	100.0	1.0	0.92	14400	n.d.	13248	1.12
10	DBU,PEG-OH ⁱ	0.12	14.0	0.4	0.43	10040	7088	7729	1.06
11	DBU,PEG-OH ^{h,i}	0.53	73.1	4.9	0.66	7148	6421	5941	1.13

^aPLA syntheses data from Waymouth/Hedrick *et al.*

^bThe alcohol macro-initiator is either benzyl alcohol (BnOH, monodispersed) or PEG-OH (poly-dispersed, PDI = 1.056, M_n = 5.0 kDa).

^cConcentrations have been corrected for the increase in reactor volume due to an increase in mass.

^dConversions reported at 60 minutes.

^eData reported from sampling at 30 minutes.

^fTheoretical number-average molecular weight calculated at 100% conversion. For systems without alcohol macro-initiators, the theoretical molecular weight was calculated from $MW_{monomer} \times [LA]_0 / [DBU]_0$. For systems with alcohol macro-initiators, the theoretical molecular weight was calculated from $MW_{monomer} \times [LA]_0 / [DBU]_0$.

^gBoth experiments conducted at same [LA]₀ and [DBU]₀ in either excess or limited alcohol macro-initiator relative to DBU.

^hRepresent three independent batch syntheses conducted at exactly the same concentrations of monomer, catalyst and macro-initiator to access batch-to-batch variation.

ⁱReactions that ceased too early to yield reliable kinetic data without further inclusion of possible termination and/or catalyst poisoning reactions.

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^1H NMR at room temperature. Number-average molecular weight calculated from ratios of integration of methine signals of PLA compared to the methylene signals of the known PEG-OH measured in CDCl_3 at 5 wt. % sample with

M_n and PDI determined by polystyrene calibrated GPC.

Summary of the kinetic parameter calibration. Kinetic constants used in modeling are those values from Fitting Cycle 2

d_{TT} The percent change in the values from Fitting Cycle 1 to 2.

Table 4

Summary of the model predicted contamination concentration for each synthesis. Comparison made with the theoretical maximum free acid concentration based on the maximum free acid in lactide data from Altsorb.

entry	Synthesis	Predicted [K] M $\times 10^{-4}$	Theor. Max [K] M $\times 10^{-4}$
1	*LA:DBU = 50, ROH:DBU = 0.0	0.03	n.d.
2	*LA:DBU = 98, ROH:DBU = 0.0	0.05	n.d.
3	*LA:DBU = 200, ROH:DBU = 0.0	0.00	n.d.
4	*LA = 1 M, LA:DBU = 100, ROH:DBU = 1.0	0.36	n.d.
5	LA:DBU = 72, ROH:DBU = 0.4	< 0.00	0.848
6	LA:DBU = 72, ROH:DBU = 2.1	1.15	0.807
7	(2) LA:DBU = 73, ROH:DBU = 4.9	15.26	0.744
8	(3) LA:DBU = 73, ROH:DBU = 4.9	7.54	0.744
9	*LA = .6 M, LA:DBU = 100, ROH:DBU = 1.0	0.14	n.d.
10	LA:DBU = 14, ROH:DBU = 0.4	1.84	0.178
11	(1) LA:DBU = 73, ROH:DBU = 4.9	100.00	0.743