Bis- and Tris-Urea H-Bond Donors for Ring-Opening Polymerization: Unprecedented Activity and Control from an Organocatalyst

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Supporting Information

ABSTRACT: A new class of H-bond donating ureas was developed for the ring-opening polymerization (ROP) of lactone monomers, and they exhibit dramatic rate acceleration versus previous H-bond mediated polymerization catalysts. The most active of these new catalysts, a tris-urea H-bond donor, is among the most active organocatalysts known for ROP, yet it retains the high selectivity of H-bond mediated organocatalysts. The urea cocatalyst, along with an H-bond accepting base, exhibits the characteristics of a “living” ROP, is highly active, in one case, accelerating a reaction from days to minutes, and remains active at low catalyst loadings. The rate acceleration exhibited by this H-bond donor occurs for all base cocatalysts examined. A mechanism of action is proposed, and the new catalysts are shown to accelerate small molecule transesterifications versus currently known monothiourea catalysts. It is no longer necessary to choose between a highly active or highly selective organocatalyst for ROP.

The H-bonding catalysts for ring-opening polymerization (ROP) stand out among the highly controlled polymerization methods for their ability to tolerate functional groups while precisely controlling molecular weight and polydispersity.1–7 H-bond donating cocatalysts are believed to effect a “living” ROP via dual activation of monomer by a H-bond donor, usually a thiourea (TU), and activation of alcohol chain end by base cocatalyst.8,9 The exquisite and remarkable combination of rate and selectivity present in other fields (e.g., olefin polymerization catalysis)10,11 has yet to be paralleled in organocatalytic ROP, especially H-bond mediated transformations. The development of organocatalysts for polymerization has largely proceeded along divergent pathways toward highly selective1,10,12–13 or highly active1,14–16 catalysts. Indeed, the low activity of organocatalysts for ROP has been specifically identified as a shortcoming of the field, whereas highly active metal-containing catalysts for ROP are well-known.17 We recently disclosed a bisthiourea (bisTU) H-bond donating cocatalyst, 2-S in Figure 1, for the ROP of l-lactide (LA), which displayed enhanced catalytic activity (over mono-TU), but no reduction in reaction control.18 During the process of extending the utility of this system to other lactone monomers, we developed a trisurea (trisU, 3-O in Figure 1) H-bond donor featuring remarkable activity for the ROP of lactones. Not only does this cocatalyst demonstrate the utility of the under-explored urea motif (c.f. thiourea) of H-bond donors, but when applied with a H-bond accepting cocatalyst, it is the most active ROP organocatalyst known, and one whose enhanced rate does not come at the expense of reaction control, Scheme 1.

The effects of bisTU on the ROP of δ-valerolactone (VL) and ε-caprolactone (CL) were evaluated, and the rate acceleration in the presence of 2-S versus 1-S is general to both lactone monomers. For the ROP of either VL or CL (2 M, 100 mg) from benzyl alcohol in C6D6, the application of 2-S/MTBD (2.5 mol % each) produces a rate acceleration over the
Scheme 1. Highly Active and Highly Selective H-Bond Donor 3-O

Previous:

Herein:

Table 1. MTBD and Bis- or Tris thiourea Catalyzed ROP of VL and CL

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<th>entry</th>
<th>monomer</th>
<th>TU (mol %)</th>
<th>base (mol %)</th>
<th>time (min)</th>
<th>conv. (%)</th>
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<th>M_w/M_n</th>
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<td>MTBD (5%)</td>
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<td>8300</td>
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<tr>
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*a*Reaction conditions: VL or CL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (2 mol %), C_6D_6, r.t. *b*Monomer conversion was monitored via 1H NMR. *c*M_n and M_w/M_n were determined by GPC (CH_2Cl_2) vs polystyrene standards.
2 h, respectively. The rate acceleration for the ROP of CL with 3-O/MTBD is even more remarkable; this reaction achieves full conversion in 26 min. This constitutes a marked rate acceleration versus 2-S or 1-S with MTBD, which achieves full conversion in 10 or 45 h, respectively, and the polydispersities for the 3-O/MTBD catalyzed ROP of VL or CL remain less than M_w/M_n = 1.07, Table 2. The 3-O mediated ROPs of both monomers are highly controlled, exhibiting the characteristics of “living” polymerizations, see SI (Figures S7 and S9). Initiation of a CL ROP from 1-pyrenebutanol produces PCL from the ROP of LA shows only minor transesterification (m/z = ±72n; see Figure S14). A copolymerization of VL and CL was conducted with 3-O/MTBD. As determined by 1H NMR, the consumption of VL is almost complete prior to the incorporation of CL units, suggesting the formation of a gradient-copolymer (see SI, Figure S10 and Experimental Section; M_w = 21400; M_n/M_w = 1.29; 91% yield). The H-bond donor 3-O with MTBD is not active for the ROP of β-butyrolactone, which is consistent with other H-bonding ROP catalysts.a

It is proposed here that 3-O/MTBD catalyzed ROP occurs via an activated-urea mechanism, whereby a single 3-O activates a lactone and MTBD activates an alcohol chain end through H-bonding, Scheme 2. A plot of observed rate constant (k_obs) versus [3-O] for the ROP of VL from benzyl alcohol suggests that the ideal stoichiometry of the 3-O/MTBD catalyzed reaction is 1:1 (see SI, Figure S12). Further, the 3-O/MTBD catalyzed ROP of VL is first order in monomer (see SI, Figure S8), which suggests that a single 3-O molecule acting at one monomer is present in the transition state. This is consistent with previous reports that suggest that H-bonding

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**Table 2. Bis- and Tris-Urea Cocatalyzed ROP of Lactones**

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<th>entry</th>
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<th>TU or U (mol %)</th>
<th>[M]/[I]_o</th>
<th>time (min)</th>
<th>conv. (%)</th>
<th>M_w (g/mol)</th>
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**Scheme 2. Proposed Mechanism for 3-O/MTBD Catalyzed ROP**

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donors featuring multiple (thio)urea moieties activate one reagent prior to the TU-reactant complex undergoing further chemistry, and it is also consistent with a report of a urea-thiourea H-bond donating catalyst, which was proposed to be operative via an activated-(thio)urea mechanism. Indeed, ‘H NMR spectra (in acetone) of 1-O, 2-O, and 3-O show a progressive downfield shift of the N-H protons, which can be interpreted to arise from stronger intramolecular H-bonding in 3-O and 2-O versus 1-O. A multiurea activated mechanism (e.g., eq 1), which is reminiscent of a solvophobic pocket, cannot be ruled out. However, the marked inefficacy toward ROP of 3-S, which is geometrically able to adopt a conformation featuring strong intramolecular H-bonds (see Figure S13), suggests that the activated-urea mechanism is the more robust proposal.

Among catalysts for the ROP of lactones, the 3-O/base cocatalysts stand out due to the extremely rapid rate that they exhibit at room temperature. For comparison, we conducted the ROP of CL (2 M) from benzyl alcohol (1 mol %) with the bifunctional catalyst TBD, Table 2. The guanidine base, TBD (Figure 1), has been regarded as one of the most active organocatalysts available for the ROP of lactones. The TBD catalystized ROP of CL from benzyl alcohol (Table 2, entry 12) proceeds to 93% conversion in 140 min ($M_w/M_n = 1.37$), whereas the same ROP with 3-O/MTBD (Table 2, entry 8) achieves 97% conversion in 26 min ($M_w/M_n = 1.05$).

In small molecule transformations, urea H-bond donating catalysts have been observed to possess similar activity to their heavy chalcogen counterparts. The development of urea and thiourea H-bond donating catalysts continued apace until the turn of the millennium when several reports emerged that forced to choose between a highly active or highly selective catalyst in the ROP of VL (2 M, 100 mg, 1 equiv) from ethyl acetate (1.6 M) with benzyl alcohol (1.6 M) was conducted in C$_6$D$_6$. Observed rate constants ($k_{obs}$) at early reaction time were measured for each H-bond donor/MTBD cocatalyzed transesterification. These rate constants show the same trends in catalyst activity that were observed for the ROP reactions: 3-O is the most rapid catalyst and it is 1–2 orders of magnitude more rapid than 1-S, see SI (Table S1). This suggests a general role for the increased activation of esters by urea H-bond donors (vs thioureas), yet the slower rates for the transesterification of s-trans (vs s-cis) esters accounts for the low rate of transesterification.

Urea H-bond donors in combination with base catalysts have been shown to be highly effective for the ROP of lactones. Despite being among the most rapid organocatalysts for ROP, the 3-O/MTBD cocatalyzed ROPs of VL and CL are among the most controlled polymerizations, exhibiting the characteristics of "living" polymerizations and producing polymers with narrow $M_w/M_n$. The source of the rate acceleration versus mono- and bisurea H-bond donors is proposed to arise from successively increased intramolecular H-bond activation with each additional urea moiety. The reintroduction of the urea motif of H-bond donors to the lexicon of organocatalytic (ROP) chemistry provides a rich diversity of catalyst scaffolds to explore in mono-, bis-, tris-, and poly-H-bond donors. Previous to the discovery of trisurea cocatalyzed ROP, one was forced to choose between a highly active or highly selective organocatalyst; this age is over.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.6b00527.

**Experimental Section, NMR spectra, computational details, kinetics, $M_n$ vs conversion plots, small molecule transesterification data, low catalyst loadings, and GPC traces (PDF).**

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**Author Contributions**

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**Notes**

The authors declare no competing financial interest.

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REFERENCES


Rate Accelerated Organocatalytic Ring-Opening Polymerization of L-Lactide via the Application of a Bis(thiourea) H-bond Donating Cocatalyst

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ABSTRACT: A cocatalyst system consisting of an alkylamine base and a bis(thiourea) featuring a linear alkane tether is shown to dramatically increase the rate of ring-opening polymerization (ROP) of L-lactide versus previously disclosed monothiourea H-bond donors. Rate acceleration occurs regardless of the identity of the alkylamine cocatalyst, and the ROP remains controlled yielding poly(lactide) with narrow molecular weight distributions, predictable molecular weights and high selectivity for monomer. This H-bond mediated ROP of l-lactide constitutes a rare, clear example of rate acceleration with bis(thiourea) H-bond donors versus monothioureas, and the bis(thiourea) is shown to remain highly active for ROP at fractional percent catalyst loadings. Activation at a single monomer ester by both thiourea moieties is implicated as the source of rate acceleration.

INTRODUCTION

Thiourea (TU) H-bond donors \(^1\) have been a workhorse of organocatalytic transformations. \(^2\)−\(^5\) This class of compounds features a wide array of functional motifs and geometries and has been employed in a multitude of reactions including Henry reactions, hydroaminations, conjugate additions and ring-opening polymerization (ROP). \(^6\)−\(^12\) While the wealth of chemistry offered by H-bonding catalysts has attracted numerous research groups, these systems can require high catalyst loadings and/or long reaction times. A general means of producing rate-accelerated reactions with this widely used class of catalysts has been elusive. The thiourea 1 (Scheme 1), with a slate of base cocatalysts, has been widely applied to the synthesis of polyesters and polycarbonates via ROP. \(^13\),\(^14\) These systems are believed to effect “living” ROP via dual activation of monomer by 1 and of growing polymer chain by base, Scheme 1. \(^15\),\(^16\) Herein, we show a strategy for the rate enhancement of the ROP of l-lactide (l-LA) using bis(thiourea) H-bond donors with a variety of alkylamine cocatalysts, Figure 1. Such a rate acceleration is not usually observed upon switching from monothiourea to bis(thiourea) H-bond donating catalysts in small molecule systems. \(^17\)−\(^19\)

RESULTS AND DISCUSSION

Our approach was inspired by the use of bis(thiourea) catalysts in small molecule transformations as well as our own investigations into the nature of 1/base catalyzed ROP. \(^20\) During the course of mechanistic studies into the 1/base catalyzed ROP of lactide initiated from benzyl alcohol, we observed that some 1/alkylamine combinations, like 1/Me\(_6\)TREN in Scheme 1, exhibit second order kinetics in \([M]\). \(^21\) This observation suggests that two 1 molecules are kinetically relevant in the rate-determining step. The kinetic orders of the previously studied ROP reactions are base dependent, \(^21\) which hints at the possibility of exploiting these differences for the development of advanced catalyst systems. We reasoned that tethering two thiourea moieties could enhance the rate of the 1/base catalyzed ROPs which exhibit second order dependence upon \([1]\) and possibly enforce dual thiourea activation in the others, likewise enhancing rate.

Bis(thiourea) 2, \(^2\) combined with the alkyl amine base HMTETA (Figure 1), significantly accelerates the ROP of l-LA (1 M in CH\(_2\)Cl\(_2\)), initiated from benzyl alcohol ([M] \(_0\)/[I] \(_0\) = 100) versus the 1/HMTETA catalyzed ROP. Only the concentration of cocatalysts are varied between runs. The ROP of l-LA from benzyl alcohol achieves 90% conversion in 15 min when catalyzed by 2/HMTETA (2.5 mol % each), whereas the 1/HMTETA (5 mol % each) catalyzed reaction reaches 94% conversion in 90 min. This ROP is accelerated with 2 versus 1 when controlling for the concentrations of cocatalysts or the concentration of thiourea moiety present, Table 1. The reaction rate slows with a stoichiometric excess of HMTETA to 2 (Table 1, entries 3 and 4), which suggests that 1:1 stoichiometry of base:2 is optimal for ROP.

The rate acceleration exhibited by 2 vs 1 is a general trend and is independent of the identity of the alkylamine cocatalyst being employed. Several commercially available alkylamines in...
combination with 1 have been shown previously to be effective cocatalysts for the ROP of lactide. The effects of base cocatalyst identity upon ROP have been explained computationally and experimentally in terms of chelating H-bonding interactions with alcohol or varied cocatalyst interactions, respectively. A selection of these cocatalysts were evaluated in the 2/base cocatalyzed ROP of L-LA (Table 2). For all base cocatalysts examined, the 2/base cocatalyzed ROP was faster than the comparative 1/base catalyzed ROP. This rate acceleration occurs regardless of base identity or the reaction order in 1 exhibited in the 1/base catalyzed ROP of L-LA.

This H-bond mediated ROP of L-LA constitutes a rare, clear example of rate acceleration with bis(thiourea) H-bond donors versus monothioureas. Despite the increased rate, the ROPs cocatalyzed by 2 remain controlled and exhibit the characteristics of a “living” polymerization. In the 2/MeTREN catalyzed ROP of L-LA, the $M_n$ is predictable by $[M_0]/[I]$ and $M_w/M_n$ is narrow, < 1.05, Table 2, Entries 2–4. When initiated from pyrenebutanol, the RI and UV/vis signals overlap in the GPC trace of the resulting polymer which suggests end group fidelity, see Supporting Information. This conclusion is supported by MALDI–TOF analysis of a PLA sample which shows only the repeat pattern associated with PLA initiated from benzyl alcohol (see Supporting Information). Further, the sequential addition of LA monomer to a single polymerization solution results in quantitative chain-extension, see Supporting Information. These observations are consistent with those typically observed for the 1/base-catalyzed ROP of lactide.

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<tr>
<th>entry</th>
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<th>mol % (bis)TU</th>
<th>mol % base</th>
<th>convn (%)</th>
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<th>$M_n$ (g/mol)</th>
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<td>90</td>
<td>20</td>
<td>17 100</td>
<td>1.04</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 M (0.7 mmol) L-LA, 0.007 mmol benzyl alcohol, CH$_2$Cl$_2$ (0.7 mL) and given amount of catalyst. Aliquots of the reaction were quenched with benzoic acid and characterized by GPC and $^1$H NMR. $^a$Conversion to polymer obtained by $^1$H NMR. $^b$Determined by GPC vs polystyrene standards.
Previously, the best means of effecting higher rates of ROP were to employ stronger bases which typically result in the rapid post polymerization broadening of $M_w/M_n$. However, the higher rates of these $2/\text{base}$-catalyzed ROPs are not associated with loss of selectivity for monomer; MALDI–TOF analysis confirms the remarkable selectivity of $2/\text{base}$ systems for monomer as multiples of $72 \text{ mol}/\text{z}$ which are associated with random chain scission are vanishingly small, see Supporting Information. The absence of these peaks in the MALDI–TOF suggests that near zero postpolymerization transesterification is occurring. Further, when the reaction solution was left to stir for 1 h after full conversion, the most active $2/\text{base}$ systems resulted in only modest erosion of $M_w/M_n$. After 1 h of stirring past full conversion, the initial $M_w/M_n$ for the $2/\text{HMTETA}$ (Table 1, entry 3) and $2/\text{MeTREN}$ (Table 2, Entry 2) experiments broadened only slightly to $M_w/M_n = 1.06$ for both samples. The $^{13}\text{C}$ NMR spectrum of poly($L$-lactide) shows only one resonance in the methine region, which suggests that the stereochemistry of the monomer is retained in the polymerization.

The bis(thiourea) (2) cocatalyst remains highly active at low concentrations which typically halt $1/\text{alkylamine}$ cocatalyzed ROP of lactide. For the ROP of $L$-lactide, the $2/\text{MeTREN}$ (0.5 mol %, Table 3, entry 2) catalyzed reaction proceeded to 98% conversion in 45 min ($M_w = 17 000$; $M_w/M_n = 1.05$) whereas the $1/\text{MeTREN}$ (1 mol %, Table 3, entry 1) catalyzed reaction only progressed to 3% conversion in 24 h. The same ROP with $2/\text{MeTREN}$ cocatalysts (0.1 mol %, Table 3, entry 4) progressed to full conversion in 180 min. The development of highly selective catalysts for ROP which remain highly active at low catalyst loadings is vitally important to the increased applicability of these systems. 

Tethered bis(thiourea)s, to our knowledge, have not been evaluated as ROP cocatalysts; however, such systems have been evaluated with mixed results as catalysts for small molecule transformations. Enhanced reaction rates have been observed when activation of two substrates is a possibility. However, rate acceleration with bis(thiourea)s is not general, although the introduction of chiral linkers facilitates increased enantioselectivity in some cases. The bis(thiourea) 2 does not feature a chiral linker and was not expected to alter the stereoselectivity of the ROP vis-à-vis monothiourea 1. The polymers resulting from the $1/\text{MeTREN}$ and $2/\text{MeTREN}$ catalyzed ROP of rac-$L$-lactide from benzyl alcohol (conditions from Table 2, entries 1 and 2) were analyzed by $^{13}\text{C}$ NMR (see Experimental Section). The $^1\text{H}$ decoupled $^{13}\text{C}$ NMR spectra suggested similar tacticities ($P_{m}(1) = 0.69$; $P_{m}(2) = 0.66$; where $P_m$ is the probability of propagating with the retention of stereochemistry). This is consistent with previous suggestions that organocatalytic H-bonding catalysts display chain-end controlled stereochemistry.

The source of the rate acceleration exhibited by bis(thiourea) 2 is proposed to be the activation at a single monomer ester by both thiourea moieties. While the possibility of 2 simultaneously binding base and monomer or simultaneous binding of monomer and polymer cannot be ruled out, the observed second order dependence upon $[1]$ for some $1/$alkylamine catalyzed ROPs of $L$-lactide strongly indicates that both thiourea moieties of 2 are involved in the activation of a single ester moiety in the transition state. Presumably, the role of 2 is to enforce this favorable catalytic mode even in those $1/$alkylamine systems which do not display second order dependence upon $[1]$, Scheme 2. This suggestion is consistent with computational studies of a bis(thiourea) catalyzed Morita–Buckingham reaction.
Baylis-Hillman reaction wherein a bisTU-nitrate complex is believed to react with an uncomplexed aldehyde rather than bind both reagents prior to reaction.\textsuperscript{23,24} With the exception of the short-strong variety, H-bonds are electrostatic in nature and do not require orbital overlap,\textsuperscript{10} hence the mode of the 2-lactide activation could be due to direct, dual-thiourea activation of a single ester moiety or an activated-TU mechanism.\textsuperscript{21} (Scheme 2). However, other unenvisioned processes are possible. Computational studies were conducted to differentiate between these mechanistic possibilities. Energies from geometry optimized structures (BSLYP/6-31G** in CH\textsubscript{2}Cl\textsubscript{2} solvent and the gas phase suggest that the C\textsubscript{2} symmetric 2 structure leading to the activated-TU transition state is more stable than the C\textsubscript{s} structure required for a dual-thiourea activation mechanism by 5.7 or 9.4 kcal/mol, respectively, eq 1 (see Supporting Information). Further, computations suggest that LA activation via the activated-TU structure (Scheme 2, left) is lower in energy than the dual-thiourea activation structure (Scheme 2, right), see Supporting Information. Future studies will be aimed at experimentally determining the source of this increased activity.

\section*{Conclusion}

Achiral, bis(thiourea) H-bond donating molecules have been shown to be highly effective cocatalysts for the ROP of lactide. The rate accelerated 2/alkylamine systems retain ROP control, exhibiting the characteristics of a "living" polymerization, a high selectivity for monomer and marked activity at low catalyst loadings. The reaction rate enhancement is postulated to occur via an activated-TU mechanism, but ongoing mechanistic studies are expected to provide further insight into the source of the potency of the bis(thiourea) systems. The addition of a second thiourea moiety to these H-bond donating systems introduces the possibility of a multitude of structural variations, each of which could have dramatic ramifications on the course of the ROP.

\section*{Experimental Section}

\textbf{General Considerations.} All manipulations were performed in an MBRAUN stainless steel glovebox equipped with a gas purification system under a nitrogen atmosphere. All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise. Dichloromethane, toluene and THF (HPLC grade) were dried on an Innovative Technology solvent purification system with activated alumina columns. Thiourea catalysts were prepared as previously described.\textsuperscript{7,25} \ensuremath{\text{\textsuperscript{L}}}-lactide and \text{\textsuperscript{R}}-lactide from Acros Organics were recrystallized from dry toluene prior to use. Benzyl alcohol was distilled from CaH\textsubscript{2} under high vacuum. Dialysis bags (MWCO = 3,000) were purchased from SpectraPor and stored in aqueous NaN\textsubscript{3} solution. NMR experiments were performed on a Bruker Avance 300 MHz spectrometer except decoupled experiments which were performed on a Varian 500 MHz NMR spectrometer. Size exclusion chromatography (SEC) was performed at 30 °C in dichloromethane (DCM) at 1.0 mL/min using an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm x 300 mm (5 μm; pore sizes = 10\textsuperscript{5}, 10\textsuperscript{4}, and 10\textsuperscript{3} Å) and multiwavelength detector (set to 254 nm) and refractive index detector connected in series. Molecular weight and M\textsubscript{w}/M\textsubscript{n} were determined versus PS standards (500 g/mol to 3150 kg/mol; Polymer Laboratories). MALDI–TOF data was acquired at the University of Akron Mass Spectrometry Center.

\textbf{Example ROP of 1-Lactide.} In a typical polymerization, \text{\textsuperscript{L}}-LA (100 mg, 0.7 mmol) was added to a 20 mL glass vial containing a stir bar, both of which were baked at 140 °C overnight. In another dried 20 mL glass vial with stir bar, 2 (17.5 μmol), Me\textsubscript{2}TREN (17.5 μmol) and benzyl alcohol (0.007 mmol) were added. Solvent (CH\textsubscript{2}Cl\textsubscript{2}, 1 M in \text{\textsuperscript{L}}-LA) was added to both vials to bring the total volume of solvent to the desired level, approximately equal portions of solvent per vial. After stirring for 5 min, the \text{\textsuperscript{L}}-LA solution was transferred via pipet to the vial containing catalysts and initiator. Aliquots were removed from the reaction with a micropipet at predetermined time points and quenched by the addition of benzoic acid (2 mol equivalents to base). The vial was removed from the glovebox, solvent removed under vacuum, conversion determined via \textsuperscript{1}H NMR, and the polymer was precipitated from CH\textsubscript{2}Cl\textsubscript{2} by treatment with hexanes. The hexanes supernatant was decanted, and the polymer removed of volatiles under reduced pressure. Yield: 80%. M\textsubscript{w}/M\textsubscript{n} = 1.03; M\textsubscript{w}(GPC) = 17 500. Comparative reactions were run side-by-side at room temperature.

\textbf{For Determination of Selectivity for Monomer.} An aliquot of the reaction mixture was allowed to stir for 1 h at full conversion and the polymer was reanalyzed by GPC: M\textsubscript{w}/M\textsubscript{n} = 1.06; M\textsubscript{w}(GPC) = 17 100.

\textbf{For the Chain-Extension Experiment.} The 2/Me\textsubscript{2}TREN (2.5 mol %) catalyzed ROP of LA (0.69 mmol, 1 equiv, 0.5 M in CH\textsubscript{2}Cl\textsubscript{2}) from benzyl alcohol (2 mol %) was stirred to full conversion (30 min) and an aliquot withdrawn. An additional 0.60 mmol of LA (to account for aliquot volume) was added to the reaction, and the process repeated at 60 min with a third addition of LA (0.49 mmol). Aliquot 1: M\textsubscript{w} = 13
Determination of $P_m$. The standard polymerization procedure was repeated but with rac-LA (100 mg, 0.7 mmol). The polymerization solution was stirred for enough time to achieve 90% conversion (to minimize postpolymerization reactivity). The reaction was quenched by the addition of benzoic acid and conversion determined by $^1$H NMR. The polymer was then dialyzed in methanol for 24 h to remove any trace of monomer impurity. The pure monomer was dissolved in chloroform-$d$ and analyzed by $^1$H-decoupled $^1$C NMR at 70 °C. The procedure for determining $P_m$ is thoroughly described elsewhere. Briefly, the experimental intensities of the five tetrads resulting from theROP of rac-lactide were simulated using MNova software. The theoretical intensities of these resonances are determined from Markovian statistics from the $P_m$ value. A calculated value of $P_m$ was determined using Excel by systematically varying $P_m$ subject to the minimization in the difference between the experimental and calculated tetrad intensities.

Computational Details. Computational experiments were performed in Spartan '14 (Windows 7). Structures were geometry optimized at the DFT B3LYP/6-31G* level of theory in the gas phase. Energies in CH$_2$Cl$_2$ solvent were calculated as Single Point energies from the DFT-optimized structures. Energies, computed structures, and coordinates of optimized structures are given in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.5b01320.

Experimental details, kinetic plot, $M_n$ vs conversion, GPC traces, computed structures, energies and coordinates (PDF)

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Notes

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REFERENCES

(27) The simultaneous activation of both ester moieties of lactide by 2 is a geometric possibility, but such dual-ester activation would not be expected to display the observed rate dependence in [1].