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ORGANOCATALYTIC RING-OPENING POLYMERIZATION OF CYCLIC
LACTONES: DEVELOPMENT OF NEW CATALYSTS GUIDED BY MECHANISM.

BY:

JINAL U. POTHUPITIYA

A DISSERTATION IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

THE DEGREE OF DOCTOR OF PHILOSOPHY

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DOCTOR OF PHILOSOPHY DISSERTATION

OF

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ABSTRACT

The use of non-biodegradable polymeric materials has been a growing threat to the environment. Attention has been greatly focused on monomers derived from sustainable feedstocks for the development of biodegradable and environmentally friendly polyesters. Precisely tailoring such polymers with complex architecture and similar functionality to macromolecules used commercially has been a daunting challenge. Ring-opening polymerizations (ROP) of cyclic monomers is a good approach towards making well defined, structurally complex, and degradable macromolecules. In this regard developing effective and efficient catalyst systems to perform fast and controlled polymerizations to construct various polymer architectures is vital. Lately, great advances in ROP with respect to catalyst design in obtaining efficient transformations, and monomer designs for the development of degradable polymers are constantly being reported. Here in we discuss the development of H-bonding organic cocatalyst systems while catalyzing ROPs of cyclic lactones in a fast and controlled manner.

The complicated mechanistic interplay of (thio)urea/base H bonding organo-catalysts in ring-opening polymerization (ROP) of cyclic lactones has been broadly discussed in this work. Understanding these systems led to the design and development of a wide range of ureas and thioureas such as bis-(thio)ureas and tri-ureas that showed enhancement of rate for ROPs without compromising the control of the reaction. These new catalysts showed superior activity compared to the conventional mono-(thio)urea compounds such as cyclohexyl thiourea and base, which was the foundation of H-bonding thiourea/base catalyst systems. These systems showed comparable rates to metal catalysts commonly

used for the ROP of cyclic lactones. A comprehensive study to understand the catalyst activity has been performed. NMR studies and computational studies were used to show the modes of activity of these H-bonding catalyst systems and to understand the structure-activity relationship. These studies also revealed the activity of these catalysts not only in non-polar solvents but also in polar aprotic solvents such as acetone.

Commercially available urea known as trilocarban was used in the presence of a base to catalyze ROP of cyclic lactones. These systems showed enhanced rates and good control over the polymerization. Studies carried out using NMR titrations to understand the mode of monomer activation by urea suggested the presence of a hyperactive imidate species that exist in the transition state. Solvent-free ROPs of cyclic lactones conducted in the presence of urea/base cocatalyst systems showed fast rates and good control. These systems allowed one-pot copolymer synthesis which were inaccessible in solvent.

A Hammett-style relationship of thiourea and urea mediated ROP of valerolactone was performed to understand the activity of these systems which can undergo two types of mechanisms. This study also shows how substituent groups in the thio(urea) affects the rates of ROP. Studies carried out in polar and non-polar solvents suggested that the solvent used plays a dominant role in determining the mechanisms - neutral H-bonding and (thio)imidate mechanism - during ROP in the presence of (thio)urea and base systems. Evidence reveal that in polar solvents such as acetone the catalysts perform ROP via (thio)imidate type mechanism while in non-polar solvents the neutral H-bonding path is prevalent.

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I would like to thank my undergraduate advisors at the Institute of Chemistry Ceylon and every one of my teachers who has helped me throughout my academic career.

-Jinal U. Pothupitiya

PREFACE

This dissertation is written in Manuscript Format.

Chapter 1 is a review article which ties up the latest advancements in H-bonding (thio)urea catalyst systems, in achieving faster and controlled ROPs of cyclic lactones. Mechanistic understanding of the activity of (thio)urea catalysts in catalyzing ROP has been presented. (accepted 2019, *RSC, Organic & Biomolecular Chemistry*)

Chapter 2 shows how changing the amounts of thiourea catalyst in the reaction alters the monomer equilibrium concentration. This concept has been shown to be utilized to use this equilibrium shift to recover monomer. The monomer recovery study was conducted by me while Partha Datta conducted monomer equilibrium studies. (See Publication: Datta, P. P.; **Pothupitiya, J. U.**; Kiesewetter, E. T.; Kiesewetter, M. K. Coupled equilibria in H-bond donating ring-opening polymerization: The effective catalyst-determined shift of a polymerization equilibrium. *Eur. Polym. J.* **2017**, 95, 671-677)

Chapter 3 contains a study which shows the evolutionary development of bis-ureas and tris urea H-bond donating catalyst systems to perform ROP. Preliminary ROPs were mainly conducted by Kurt Fastnacht, Sam Spink, Nayanthara Dharmaratne. While most solvent screens were conducted by me. (See publication: Fastnacht, K. V.; Spink, S. S.; Dharmaratne, N. U.; **Pothupitiya, J. U.**; Datta, P. P.; Kiesewetter, E. T.; Kiesewetter, M. K. Bis- and Tris-Urea H-Bond Donors for Ring-Opening Polymerization: Unprecedented Activity and Control from an Organocatalyst. *ACS Macro Lett.* **2016**, 5 (8), 982-986.).

Chapter 4 is a study which shows the superior activity of a commercially available urea – triclocarban to perform ROP of cyclic lactones in non-polar and polar solvents. A comprehensive study of understanding this behavior was revealed (See publication. Dharmaratne, N. U.; **Pothupitiya, J. U.**; Bannin, T. J.; Kazakov, O. I.; Kiesewetter, M. K. Triclocarban: Commercial Antibacterial and Highly Effective H-Bond Donating Catalyst for Ring-Opening Polymerization. *ACS Macro Lett.* **2017**, 6 (4), 421-425)

Chapter 5 reveals the application of (thio)urea systems under solvent-free conditions. A clear understanding of the behavior of these catalysts have been shown using NMR studies. One-pot copolymer synthesis which was previously inaccessible in solvent was shown to be very effective. All solvent-free polymerizations of macrolactones and strained lactones valerolactone and caprolactone were conducted by me. Polymerizations of lactide were conducted by Nayanthara Dharmaratne, Terra Jouaneh, Kurt Fastnacht, and Danielle Coderre. (See publication. **Pothupitiya, J. U.**; Dharmaratne, N. U.; Jouaneh, T. M. M.; Fastnacht, K. V.; Coderre, D. N.; Kiesewetter, M. K. H-Bonding Organocatalysts for the Living, Solvent-Free Ring-Opening Polymerization of Lactones: Toward an All-Lactones, All-Conditions Approach. *Macromolecules* **2017**, 50 (22), 8948-8954)

Chapter 6 shows the structure-activity relationship of the (thio)ureas via Hammett style relationships. The operative mechanism has been shown to be very much dependent on the solvent system used. A mechanism has been proposed for the active species when using these (thio)urea systems. All experiments with thioureas were conducted by me while urea studies were conducted by Rukshika Hewawasam. (See publication. **Pothupitiya J. U.**; Hewawasam R. S.; Kiesewetter M. K. Urea and Thiourea H-bond

Donating Catalysts for Ring-opening Polymerization: Mechanistic Insights via Linear Free Energy Relationships. *Macromolecules* **2018**, *51* (8), 3203-321)

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**The Mechanistic Duality of (Thio)urea Organocatalysts for Ring-Opening
Polymerization**

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ABSTRACT

Among the various catalysts for ROP, H-bonding organocatalysts stand out in the precise level of reaction control they are able to render during ROP. The H-bonding class of organocatalysts are thought to effect ROP via dual activation of both monomer and chain end. (Thio)urea mediated ROP has experienced a renaissance as a new polymerization mechanism – mediated by imidate or thioimidate species – facilitates new modes of reactivity and new synthetic abilities. Indeed, the urea class of H-bond donors have shown to be more active than their corresponding thioureas. The imidate mechanism remains highly active in polar solvents and exhibits remarkable control – and ‘living’ behavior - under solvent-free conditions, and a broad range of temperatures is accessible. The advancements in synthetic abilities have all evolved through a greater understanding of reaction mechanism. Through the continued synergistic advances of catalysis and material, the (thio)urea class of catalyst can find use in a host of potential applications, research and industrial environments.

INTRODUCTION

Organocatalysis for polymer synthesis has come to be synonymous with the construction of precisely tailored materials through the ring-opening polymerization (ROP) of esters, carbonates and other cyclic monomers.^{1–10} While organocatalysts have gained a beachhead in the synthesis of other polymers,¹¹ a host of organic systems for transesterification polymerization have been developed.^{1,2,12–17} The purview of organocatalysts for polymerization are ‘living’ ROP. A living ROP is a type of chain growth polymerization characterized by the lack of chain transfer and termination events – a kinetic definition.¹⁸ A controlled, ‘living’, polymerization is one that features predictable molecular weights (M_n) and molecular weight distributions close to unity (polydispersity = $\bar{D} = M_w/M_n$) and is capable of yielding polymers with well-defined architectures.^{1,2,12} The selectivity of catalysts towards ROP versus non-enchainment reactions is vital to narrowing the molecular weight distribution.^{1,2,12,19,20} Additionally, functional group tolerance,^{1,2,21–24} activity of catalysts under a wide range of temperatures^{11,25–29} and pressure,^{30,31} and a variety of solvents and solvent-free conditions³² facilitate the implementation of diverse reaction conditions which facilitates advanced polymer design.

Among the various catalysts for ROP, H-bonding organocatalysts stand out in the precise level of reaction control they are able to render during ROP. The (thio)urea H-bonding class of organocatalysts are thought to effect ROP via dual activation of both monomer and chain end, Scheme 1.1.^{1,2,12,33} In this approach, a typical catalyst system consisting of a thiourea (TU) and base cocatalyst can render high functional group tolerance and yield polymers with predictable molecular weights and narrow M_w/M_n .^{1,2,4,34–36} Despite the high selectivity shown by this class of catalyst, the major disadvantage had

been the slow rates for ROP.^{34,35,37} The development of advanced catalyst systems continues apace, this shortcoming has largely been mitigated. Indeed, (thio)urea H-bond mediated ROP has experienced a renaissance as a new polymerization mechanism – mediated by imidate or thioimidate species – facilitates new synthetic abilities and new modes of reactivity, Scheme 1. It should be noted that there are many structural manifestations of H-bond mediated catalysts,^{11,38–41} but this review is narrowly focused on the evolution of the (thio)urea/base cocatalyst system as it pertains to the ROP of δ -valerolactone (VL), ϵ -caprolactone (CL) and lactide (LA), in particular.

(THIO)UREA H-BOND MEDIATED RING-OPENING POLYMERIZATION

The naissance of H-bond mediated ROP occurred in 2005 when the Takemoto thiourea (Figure 1.1) was applied for the polymerization of LA.⁴ This unimolecular, bifunctional catalyst consists of an H-bond donating moiety and an H-bond accepting moiety that can activate monomer and initiator/chain end, respectively (Scheme 1.2), yielding, in addition to typical ‘living’ behavior, highly selective ROP with minimum broadening of M_w/M_n even at monomer conversions $\geq 95\%$.⁴ However, the reaction time is protracted (2 days), and ROP is most effective in non-H-bonding solvents.⁴ This study cemented common themes among H-bond mediated catalysts for ROP: a 3,5-bistrifluoromethyl aryl group for its electron withdrawing abilities and a cyclohexyl group, which is not required versus other alkyl groups for catalysis.⁴ Amazingly, this study also revealed similar catalytic activity to the bifunctional Takemoto catalyst when bimolecular catalysts were employed; the thiourea **1-S** (Figure 1.2) plus *N,N*-dimethylcyclohexylamine (NCyMe₂) cocatalyzed ROP of LA demonstrated that covalently tethering the H-bond donor and acceptor is not essential.^{4,8} A base screen conducted using **1-S** and commercially available bases revealed (-)-sparteine to exhibit the highest activity, achieving 95% conversion of LA in 2 h (25-fold faster than the parent system), producing PLA with minimal epimerization and narrow M_w/M_n .⁸ Thiourea plus alkylamine base cocatalysts are limited to the ROP of LA.⁴²

For H-bond mediated ROP, strong organic base cocatalysts are required with thioureas (Tus) for the ROP of lactones other than lactide.³⁵ The guanidine base *N*-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) and amidine base 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) are only active for ROP of VL and CL from alcoholic initiators in the

presence of **1-S**. Under typical reaction conditions (2M monomer, 5 mol% cocatalysts), the MTBD or DBU plus **1-S** cocatalyzed ROP of VL ($[M]_0/[I]_0 = 100$) reached full conversion in ~4 h, and the polymerization of CL was much slower (full conversion in 2-5 days).⁴² Although slower than other catalyst systems, these cocatalysts are highly controlled, leading to polymers with narrow molecular weight distributions ($M_w/M_n \leq 1.08$), predictable molecular weights up to $[M]_0/[I]_0 = 200$ with good end group fidelity.⁴² The selectivity of these catalysts for monomer versus polymer could be ascribed to the high affinity of thiourea for *s-cis* esters (lactones) in contrast with negligible binding to *s-trans* esters (i.e. polymer backbone).^{1,2,42} In general, thioureas featuring aryl rings with strong electron withdrawing groups result in faster rates, but the trend is not robust.⁴³ Further, enhanced H-bonding to base cocatalyst will attenuate catalytic activity.^{16,35}

Mechanistic studies on the thiourea/alkylamine base mediated ROP of LA informed the development of advanced catalyst systems for ROP. Kinetic studies on the ROP of LA cocatalyzed by **1-S** and certain alkylamine bases (i.e. not all cocatalyst combinations) revealed second order dependence on $[1-S]_0$; a mechanistic account was proposed.⁴⁴ As a direct result, the bithiourea **2-S** was synthesized and applied with base cocatalysts for the ROP of lactide, which resulted in enhanced rates ($k_{2-S}/k_{1-S} \sim 12$).³⁷ Unexpectedly, the application of **2-S** (plus base cocatalyst) results in rate accelerated ROP versus **1-S** for *all* base cocatalysts and monomers examined, regardless of kinetics for the analogous **1-S** system. The **2-S** plus base cocatalyzed ROPs of LA and lactones exhibit similar rate equations ($\text{Rate} = k_{\text{obs}}[M]$; $k_{\text{obs}} = [2-S + \text{base}]_0[\text{initiator}]_0$) which suggests that **2-S** is acting as a discrete catalyst (one bithiourea per base per monomer in the transition state).^{34,37} Buttressed by computational studies³⁷ and indirect evidence,³⁴ an *activated-TU* mechanism

was proposed, whereby the ‘extra’ thiourea stabilizes the catalytic thiourea via H-bond activation, Figure 1.2. The ROP of cyclic lactones in the presence of **2-S** and base proceeded with lower catalyst loadings and enhanced rates compared to monothiourea **1-S**, yet selectivity and control are retained.³⁷ Since **2-S** proved to be superior to **1-S** in all comparisons, an obvious question becomes, *what about a trithiourea?* However, the trithiourea **3-S** is markedly inactive for ROP.³⁴ This observation was attributed to intramolecular H-bonding between all three thiourea moieties, generating a C₃ symmetric structure, rendering all thioureas inaccessible for catalysis.³⁴ Computational studies suggested that contracting the length of the H-bond donor moieties by changing C=S to C=O would break the C₃ symmetry and result in the generation of a ‘frustrated’ system that cannot form a completed, intramolecular H-bonded network, thereby liberating a urea moiety for monomer activation (Figure 1.3). The prediction proved prophetic, and the trisurea **3-O** proved to be the gateway, at least for our group, to the incredibly active imidate mediated polymerizations.

The ROP of VL with **3-O**/MTBD achieved full conversion 25 times faster than with **2-S**/MTBD, producing PVL in 3 min ($M_n = 7.5$ kDa, $M_w/M_n = 1.07$). The ROP of CL with **3-O**/MTBD was slower but was completed in 30 min compared to 10 h or 45 h with **2-S**/MTBD or **1-S**/MTBD, respectively. These transformations were not only more rapid but proceeded with high control, exhibiting the characteristics of a ‘living’ ROP. A comparative study conducted for the ROP of CL (2M from benzyl alcohol, M/I = 50) with the highly-active base 1,5,7-triazabicyclodec-5-ene (TBD), a go-to commercially available organocatalyst for ROP,⁴⁵ versus **3-O**/MTBD displayed the superior ROP abilities of the nascent urea H-bond donors: **3-O**/MTBD (33 mM) 26 min, 97% conversion, $M_w/M_n =$

1.05; TBD (33 mM) 140 min, 93% conversion, $M_w/M_n = 1.37$.³⁴ The marked success of **3-O** mediated ROP suggested that other urea H-bond donors would be active as well. Indeed, the monourea **1-O** and bisurea **2-O** were more active than the analogous thiourea H-bond donors when applied with a base cocatalyst for ROP.³⁴ A commercially available monourea H-bond donor, triclocarban (TCC), exhibits catalytic rates and selectivities for all lactone monomers that rival that of **3-O**. For reasons that are not entirely clear, the **2-S**/alkylamine system remains the more active and controlled system for the ROP of lactide.^{11,32}

The lower solubility of urea versus thiourea H-bond donors had restricted their application as catalysts, but almost all urea cocatalysts examined are fully soluble in the presence of base and/or monomer.^{34,46} The initial reports of urea plus base cocatalyst mediated ROP showed that stronger organic bases yielded more active ROP.^{34,47} This result stands in contrast to that of thiourea mediated ROP where catalytic activity is related to the binding between the cocatalysts (see above);^{44,48} this may have been the first indication that a different mechanism of enchainment was operative. The initial reports also disclosed that urea H-bond donors remain active in polar solvent, Figure 1.4. This result was particularly surprising giving the large suppression of rate in polar solvent (e.g. THF) displayed by thiourea H-bond donors.^{4,8,34,47} Again, it was becoming apparent that a new mechanism was engendering abilities that were historically out of reach.

IMIDATE MEDIATED RING-OPENING POLYMERIZATION

Consideration of the enchainment mechanism of the highly-active organocatalyst TBD provides a point of comparison for the enchainment mechanism of the nascent urea/base mediated ROP. TBD is highly active for a wide range of monomers; however, TBD-catalyzed ROP have been observed to lack selectivity and control especially at high monomer conversions.^{1,2,7,42} Mechanistically, the lowest energy enchainment pathway has been computationally and experimentally suggested to be H-bonding, where TBD acts as a bifunctional molecule activating both monomer and chain end (Scheme 1.3).^{1,2,49,50} The mode of activity displayed by TBD serves as an analogy to the advance made by Waymouth and coworkers whereby a thiourea is treated with a strong base to form a thioimide species, which is highly-active for ROP, Scheme 1.3.^{35,51} The treatment of a thiourea with strong bases like sodium and potassium methoxides form the thioimide salt and an alcohol which can be used as catalyst/initiator systems for the ROP of lactones. The thioimide (anionic thiourea) can function both as an H-bond donor and acceptor similar to TBD (Scheme 1.3).⁵¹ When the ROP of LA ($[LA]_0/[NaOCH_3]_0 = 200$) was conducted using 1-10 equivalents of thiourea to $NaOCH_3$, monomer conversion >90% was achieved in ≤ 6 min, where faster rates were seen with lower amounts of thiourea.⁵¹ However, a molar excess of thiourea to base was vital to minimize the molecular weight distribution of the PLA ($M_w/M_n = 1.55$ to 1.18). The identity of the alkoxide counterion was shown to influence the selectivity of ROP, and slower rates but enhanced selectivity were observed with K^+ versus Na^+ .⁵¹ The ROPs with thiourea/alkoxides showed characteristics of ‘living’ polymerizations. The transformations were controlled and highly selective compared to ROPs mediated by alkoxides alone, producing highly isotactic PLA with predictable

molecular weights and minimal epimerization. The adaptability of this system was shown by its efficacy in ROP of VL and CL. Computational and mechanistic studies indicate that the active catalyst species is characterized by the metal ion complexed to S, and a mode of enchainment was proposed, Scheme 1.3. The larger association constant for the binding of $\text{TU}^-\text{K}^+/\text{HO}^t\text{BU}$ to VL ($24 \pm 4 \text{ M}^{-1}$) versus ethyl acetate ($5 \pm 2 \text{ M}^{-1}$) indicates that the selectivity of the ROP is rendered by the different binding of the anionic adduct to the cyclic lactone versus the open chain ester.⁵¹

The treatment of a urea H-bond donor with a strong base forms a urea anion which is incredibly active and controlled in the ROP of lactones. One method of generating the urea anion (imidate) is to employ a strong inorganic base, alkoxide (e.g. KOCH_3) or hydride (e.g. KH). In the latter method, an *ex situ* alcohol initiator can be introduced. Just as neutral urea catalysts were previously shown to be much more active than their thiourea counterparts in performing ROP, Figure 1.4,^{34,47} the urea anions are much faster than the corresponding thiourea anions.³⁵ The slowest imidate was not only 25 times faster than the analogous thioimidate, but also exhibited enhanced selectivity.^{35,51} Kinetic studies indicated first order behavior in [monomer] and [initiator]₀ and inverse first order dependence on urea when $[\text{alkoxide}]_0 \leq [\text{urea}]_0$. This was suggested to be a result of reversible neutral urea:imidate dimer formation which could inhibit catalytic activity.^{35,52,53} This study also revealed a correlation between the pK_a of the urea or thiourea and its activity, where ureas with lower acidity form more active (basic) imidates/thioimidates.³⁵ Hence, ureas featuring more or stronger electron withdrawing groups produce urea anions that are less active for ROP, and an imidate is more active than its analogous thioimidate due to the increased acidity of thioureas versus ureas.^{34,35,43,47,54} The high selectivity and

versatility of imidates, unlike TBD, was attributed to the ability to fine tune the basicity and H-bond donating ability by changing the substituent groups on the phenyl ring.^{35,51} An *N*-methylated monofunctional urea exhibited slower rates and decreased selectivity compared to ureas featuring two N-H donors, suggesting a bifunctional mode of activation (c.f. TBD) is preferred.³⁵ These hyperactive imidate mediated H-bonding catalysts were reported to be faster and more selective than other organocatalysts, resembling some metal-containing catalysts in their activity.^{1,2,14,34,35,51}

When ureas or thioureas are subjected to strong organic bases, an equilibrium is established between neutral H-bond mediated ROP and the more active imidate mechanism. Our group studied the mechanism of triclocarban (TCC)/base mediated ROP, and a simple ¹H NMR experiment of TCC with and without base cocatalyst proved highly diagnostic, Scheme 1.4. Imidate formation is indicated by an upfield shift of TCC resonances in the presence of base, and cocatalyst H-bonding is indicated by the downfield shift of TCC resonances in the presence of base.⁴⁷ The equilibrium between neutral urea and imidate species (Scheme 4) shifts more towards imidate in the presence of stronger bases (BEMP-H⁺ pK_a^{MeCN} = 27.6 > MTBD-H⁺ pK_a^{MeCN} = 25.4 > DBU-H⁺ pK_a^{MeCN} = 24.3) and upon the application of polar solvent (which presumably stabilizes the charged catalyst species).^{47,54} More imidate character is associated with faster rates of ROP.^{35,47,54,55} However, once the H-bonding/imidate equilibrium is shifted mostly to imidate, catalytic activity will diminish if more acidic (thio)ureas or stronger bases are applied. This is also attributable to the reduced basicity of the resulting (thio)imidate; non-linear Hammett behavior has been observed.^{35,43,51} The very progress of the reaction was shown to influence the nature of the active catalyst because, during an ROP, the highly polar

monomer is converted to less polar polymer. Hence the H-bonding/imidate equilibrium (Scheme 1.4) was shown to shift towards neutral catalysts late in the ROP.¹¹ This may constitute an advantage of applying organic (versus alkoxides or hydrides) bases whose reactivity becomes attenuated late in the ROP, thereby increasing reaction control.¹¹

NEW REACTIONS AND ABILITIES

The development of new catalytic abilities – the imidate mechanism of enchainment – has provided new synthetic opportunities. For example, (thio)imidate mediated ROP are operative under solvent-free conditions.³² The polar lactone monomer is ironically a poor solvent for H-bond mediated ROP of lactones; the monomer interrupts cocatalyst H-bonding and severely attenuates reactivity. However, in solvent-free conditions, the urea plus base cocatalyst system is highly active for ROP. These conditions even allow for the synthesis of block copolymers that are inaccessible in solution conditions.³² New opportunities in additive manufacturing can be envisaged.

Imidate mediated enchainment allowed for the production of high molecular weight poly(γ -butyrolactone)s (P γ BLs) via selective ROP of “nonpolymerizable” γ -butyrolactone (γ BL) at -40°C.^{28,29} The utility of commercially available phosphazene super bases and (thio)ureas facilitated the formation of linear P γ BL initiated by the alcohol species. These species display among the highest activity for the organocatalytic ROP of γ BL.²⁸ The ROP of γ BL with alkoxide/urea catalysts show high activity even at -20°C. Although this system produces linear polymers, careful manipulation of monomer/catalyst/initiator was required to ensure initiation from the alcohol (versus monomer).²⁹ Those ROP using less acidic (thio)ureas displayed greater catalytic activity, presumably due to the generation of a more basic (thio)urea anion.

The utility of the imidate/neutral H-bonding duality of (thio)ureas were further demonstrated in a study where a sequential one pot copolymerization of epoxides and LA was reported.^{32,56} One pot synthesis of polyether-poly lactide copolymers has been successful only in a few cases.⁵⁶ The strong base required for the ROP of cyclic ethers can

lead to deleterious epimerization of LA and transesterification of PLA.⁵⁶ The **1-S** H-bond donor in the presence of tetrabutyl ammonium fluoride (TBAF) is effective for the copolymerization of glycidyl phenyl ether and LA, yielding polymers with predictable molecular weights and narrow dispersities ($M_w/M_n = 1.13 - 1.19$).⁵⁶ The proposed mechanism proceeds by an anionic initiation of the epoxide by TBAF; the addition of **1-S** allows the conversion of the incipient alkoxide to the **1-S** thioimide, which is competent for the controlled ROP of LA, Scheme 1.5. Hence, the mechanistic duality of the **1-S** system directly facilitates the one pot copolymerization of epoxide and LA.^{14,56-58}

CONCLUSION

Since the application of the Takemoto thiourea for ROP and the discovery that covalently tethering the H-bond donor and base cocatalyst is not essential, the field of (thio)urea mediated ROP has advanced in spurts to among the more active and controlled systems for the enchainment of cyclic monomers. (Thio)urea catalysts were conventionally known to follow a dual H-bonding mechanism with assistance of organic bases; however, the differing activity of these base cocatalysts and the ability to manipulate the H-bond donating ability by changing the acidity of (thio)ureas provided substantial evidence for a second mechanism. In the presence of weaker organic bases, (thio)ureas promote ROP via a neutral H-bonding mechanism, whereas with stronger bases they proceed via an imidate H-bonding mechanism which may exhibit dual H-bonding activity like TBD. In most cases, the recently developed urea class of H-bond donors were shown to be more active than their corresponding thioureas. The imidate mechanism remains highly active in polar solvents and exhibits remarkable control under solvent-free conditions, and high temperature applications are accessible.¹¹ It should be emphasized that the advancements in synthetic abilities have all evolved through a greater understanding of reaction mechanism. We expect that the enhanced utility – greater range of solvents, temperatures and substrates – will expose weakness and strengths of the nascent catalysts which will precipitate further advances, perhaps via mechanistic study. New substrates with new demands for selectivity remain to be studied. Through the continued synergistic advances of catalysis and material, the H-bonding class of catalyst can find use in a host of potential applications, research and industrial environments.

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Scheme 1.1. H-bonding versus Imidate Mediated ROP of Lactones

Scheme 1.2. Proposed activation pathway of covalently linked bifunctional thiourea in ROP of LA

Scheme 1.3. (upper) Bifunctional activation of monomer and initiator/chain end by TBD

(lower) Formation of imidate catalyst and suggested activation modality.

Scheme 1.4. Equilibrium between neutral versus imidate TCC with base

Scheme 1.5. ROP of epoxides and thiourea mediated conversion of alkoxide to alcohol and thioimdate for the ROP of lactones.

Figure 1.1. Strength of cocatalyst binding is predictive of catalytic activity.

Figure 1.2. Representative (thio)ureas in red and proposed *activated-TU* mode activation for multi-donors.

Figure 1.3. Monomer activation by *activated-3-O* and intramolecular deactivation of **3-S**.

Figure 1.4. The thiourea/base mediated ROP of lactones slows in polar solvent while urea/base mediated ROP remain active.

MANUSCRIPT – II

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Coupled Equilibria in H-Bond Donating Ring-Opening Polymerization: The Effective Catalyst-Determined Shift of a Polymerization Equilibrium

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ABSTRACT

In the classic view of catalysis, a catalyst cannot alter the thermodynamically-determined endpoint of a reversible reaction. This conclusion is predicated on the assumption that the catalyst does not perturb the energy of product or reactant or does so to an equal extent. In the H-bond mediated ring-opening polymerization (ROP) of lactone monomers, the strength of the interactions of thiourea with product and reactant are not equal, and the magnitudes of these interactions are of similar energy to the free energy of reaction. The total monomer concentration at equilibrium in the thiourea/base cocatalyzed ROP of lactones is shown to be a function of the initial concentration of thiourea. Because the binding of thiourea to monomer and the polymerization reaction itself are both reversible, the application of varying amounts of thiourea catalyst directly alters the total amount of monomer in the reaction solution at equilibrium, which can be recovered at the end of the reaction.

INTRODUCTION

The class of H-bond mediated catalysts for ROP, commonly a thiourea H-bond donor and one of a host of H-bond accepting base cocatalysts, rank among the most highly controlled polymerization techniques.¹⁻³ Catalysts of this class have been applied for the synthesis of well-defined and highly functionalized materials.⁴⁻⁶ The recent development of rapid catalysts for H-bond mediated ROP promises to extend the utility of these systems,^{3,7-10} yet our understanding of the modes of action of these catalysts remains incomplete. Catalyst systems consisting of thiourea/base are believed to be operative via the H-bond activation of lactone monomer by thiourea and of initiating/propagating chain end by base (e.g. DBU in Figure 2.1).¹¹⁻¹³ This mechanism is corroborated by ¹H NMR titration studies whereby lactones can be shown to H-bond to thiourea **1** (Figure 2.1), and base is observed to H-bond to benzyl alcohol, Eq. (2.1) and (2.2).¹³ Presumably, these ground state interactions persist in the transition state, giving rise to catalysis and allowing the ROP to reach equilibrium. The high selectivity exhibited by **1** for polymerization vs transesterification is thought to arise from the selective binding of thiourea to monomer (s-cis ester) vs polymer (s-trans esters); the binding of **1** to ethyl acetate (an s-trans ester) is too small to be measured by ¹H NMR titration.¹³ In the ROP of δ -valerolactone (VL), the free energy of binding of **1** to VL ($K_{eq} = 39$, or $\Delta G^{\circ} = -2.2$ kcal/mol, 300 K)¹³ is larger than the free energy of ROP, $\Delta G^{\circ} = -1.05$ to -1.44 kcal/mol.¹⁴ This relatively stronger binding of **1** to monomer vs ethyl acetate (polymer) effects a change in the relative energy of the reactant and product in the ROP reaction, producing an apparent change in the ROP equilibrium by the thiourea catalyst, **1**.

EXPERIMENTAL SECTION

General Considerations

All the polymerizations were conducted in an MBRAUN stainless steel glovebox with gas purification system under a nitrogen atmosphere. All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise. All glassware and stir bars were flame dried under nitrogen or baked at 140°C overnight prior to the introduction of reagents. Benzene-d₆ was purchased from Cambridge Isotope Laboratories and distilled from CaH₂ under nitrogen atmosphere. δ -Valerolactone (VL; 99%) and ϵ -caprolactone (CL) were distilled from CaH₂ under high vacuum. THF was purified on an Innovative Technologies solvent purification system. Benzyl alcohol was distilled from CaH₂ under high vacuum. 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (**1**) was synthesized and purified according to literature procedure.¹⁵ 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from TCI and used as received. NMR experiments were performed on a Bruker Avance 300 MHz or 400 MHz spectrometer. Mass spectrometry data was collected using a Thermo Electron (San Jose, CA, USA) LTQ Orbitrap XL Mass Spectrometer coupled with either an electrospray ionization (ESI) or an atmospheric-pressure chemical ionization (APCI) interface, yielding positive ions which were subsequently introduced into the instrument. For the infusion experiments, the tune conditions (10 μ L/min flow, sample concentration <20 μ g/mL in 50/50 v/v water/acetonitrile) were: ionspray voltage, 5000 V; capillary temperature, 275°C; sheath gas (N₂, arbitrary units), 8; auxiliary gas (N₂, arbitrary units), 0; capillary voltage, 35 V; and tube lens, 110 V. The instrument was calibrated for positive ions using Pierce LTQ ESI positive ion calibration solution (Lot # PC197784) before any analysis. For the

ion trap experiments, N₂ was used as a collision gas with normalized collision energies (NCE) between 10-25 eV for multistage fragmentation. Performance of high-energy collision (HCD) experiments were conducted with He as collision gas with NCE of 25 eV.

Synthesis of 2

A dried 100 mL Schlenk flask was charged with a stir bar under nitrogen. Dry tetrahydrofuran (25 mL), 2-methoxyethylamine (13 mmol, 1.2 mL) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (13 mmol, 2.5 mL) were added via syringe. The solution was stirred for 24 hours and subsequently removed of solvent under reduced pressure. The resulting solid product was purified via a silica gel column with 1% methanol in dichloromethane. Yield: 1.37 g, 60 %. HRMS *m/z* calcd (C₁₂H₁₂F₆N₂OS + H⁺) 347.0647, found 347.0648; NMR spectra below.

Example Ring-Opening Polymerization

In a typical polymerization, VL (0.100 g, 0.999 mmol) was added to a 7 mL scintillation vial containing a stir bar. In another 7 mL scintillation vial with stir bar, **1** (0.0185 g, 0.0499 mmol), DBU (7.47 μL, 0.0499 mmol), and benzyl alcohol (9.99 μmol) were added. C₆D₆ (0.4744 g, 0.499 mL) was divided equally between the vials. After stirring for 2 min, the VL solution was transferred via pipette to the vial containing catalysts and initiator. The entire solution was then moved to an NMR tube via pipette. Reaction progress was monitored by ¹H NMR.

Depolymerization Procedure

In air, **1** (0.0370 g, 0.199 mmol) was added to the NMR tube containing the reaction solution. The NMR tube was capped and shaken until the solution was homogeneous.

Reaction progress was monitored by ^1H NMR spectra. This process was repeated with a second addition of **1** (0.0462 g, 0.249 mmol).

Monomer Isolation

A typical polymerization reaction was carried out as described above, conditions: VL (202 mg, 2.0175 mmol), **1** (37.0 mg, 0.10 mmol), DBU (15.2 mg, 0.10 mmol), benzyl alcohol (2.2 mg, 0.020 mol) and C_6D_6 (949 mg, 999 μL). The reaction was stirred overnight, and conversion determined via ^1H NMR, 94%. Then, **2** (345.6 mg, 1.0 mmol) was added to the reaction solution. Ten hours after the addition of **2**, the reaction was quenched with benzoic acid (14.6 mg, 0.120 mmol), and analyzed via ^1H NMR to determine VL conversion to polymer, 81%. The reaction contents were transferred to a dry 25 mL round bottom flask. The flask was removed of volatiles via rotary evaporation, maintaining the water bath at room temperature. The monomer was isolated via Kugelrohr distillation: high vacuum (25-30 mTorr) for 2 hours at room temperature, 2 hours at 40°C with the receiving flask cooled to -78°C . Characterization matches commercially available material, Yield: 29.1 mg; 77%.

Binding study of Benzyl alcohol (BnOH) to 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) by titration method

Stock solutions of DBU and benzyl alcohol were prepared in C_6D_6 . In NMR tubes, varying amounts of each stock solution and neat C_6D_6 were added to each tube such that the total volume was 500 μL . The concentration of benzyl alcohol was kept constant at 1 mM and DBU was varied from 0 to 150 mM. A ^1H NMR spectrum of each tube was acquired at 300 K, and the chemical shift of the methylene proton of the BnOH ($-\text{CH}_2-$) was monitored, referencing each spectrum to residual benzene-H. The binding constant

between BnOH and DBU was then obtained using the curve fitting method,¹⁶⁻¹⁸ which matched the value determined from the Lineweaver-Burke method;^{19,20} 75 ± 3 , binding curve below.

Dependence of $[VL]_{eq}$ upon temperature

VL (0.100 g, 0.999 mmol) was added to a 7 mL scintillation vial containing a stir bar. A second 7 mL scintillation vial with stir bar was charged with: **1** (0.0185 g, 0.0499 mmol), DBU (7.47 μ L, 0.0499 mmol), and benzyl alcohol (9.99 μ mol). C₆D₆ (0.4744 g, 0.499 mL) was evenly divided between the vials. After stirring for 2 min, the VL solution was transferred via pipette to the vial containing catalysts and stirred to mix. The solution was transferred into an NMR tube via pipette. Reaction equilibrium was monitored vs temperature by variable temperature ¹H NMR. Data were acquired upon heating and cooling to confirm measurement. Heating/cooling data are within error, and the heating data is shown in Figure 2.12.

RESULTS AND DISCUSSION

The total concentration of monomer remaining at equilibrium in the **1**/DBU catalyzed ROP of VL from benzyl alcohol in C₆D₆ is a function of the initial concentration of **1**. The progress of these ROPs was monitored by ¹H NMR until reaction progress halted, and the total monomer concentration at equilibrium ([VL]_{T,eq}) was noted, Figure 2.2. Because **1**/VL binding is rapid and reversible, only [VL]_T is measurable by ¹H NMR ([VL]_T = [VL] + [VL·**1**]). The [VL]_{T,eq} is altered when [**1**]_o is varied in excess of the cocatalyst [DBU]_o. This latter observation is consistent with the previously observed prominent binding between cocatalysts, K_{eq} = 4200 for Eq. (2.3) (300 K).²¹ This strong binding suggests that **1** will primarily be associated with DBU until [**1**]_o = [DBU]_o, and any **1** in excess of [DBU]_o will be available to bind to monomer and is the effective concentration of **1** ([**1**]_{EFF} = [**1**]_o – [DBU]_o). The [VL]_{T,eq} increases linearly with increasing [**1**]_{EFF}, Figure 2.3. Reactions were controlled for temperature (300 K, unless stated otherwise), pressure, concentration of reagents, and [VL]_T was monitored vs an internal standard (C₆H₆). The solution volumes do not measurably change during the polymerization, see Figure 2.9. The observed variation in [VL]_{T,eq} cannot be due to minor temperature variations within the NMR probe; the temperature dependent change in [VL]_{eq} does not vary to the observed extremes over narrow temperature windows, (see Figure 2.12). The **1**/DBU catalyzed ROP has previously been shown to display first order evolution of [VL] vs time, a linear evolution of M_n vs conversion and predictable M_n (by [M]_o/[I]_o), characteristics of a ‘living’ polymerization.^{1,13} Increasing the concentration of the cocatalysts together alters [VL]_{T,eq} to a lesser extent than increasing [**1**]_{EFF}, see Figure 2.11.

In the envisaged scheme, the thiourea is explicitly added to the polymerization equilibrium by showing a reversible binding of lactone (M) to **1** (Eq. (2.4)) which competes with the enchainment of the monomer in the normal ROP equilibrium (Eq. (2.5)). Eq. (2.4) is microscopic reverse of the normal binding equilibrium between M and **1**. The polymer chain is shown in Eq. 2.4 and 2.1 in Eq. (2.5) for mass balance in the total process, and just like the normal ROP equilibrium expression, the concentration of polymer ($=[\text{initiator}]_0$) is thermodynamically irrelevant so long as $[M_n^*] = [M_{n+1}^*]$.¹⁴ This scheme describes the roles of thiourea in ROP as being analogous to both inhibitor and catalyst in enzyme kinetics.

The effect of **1** upon an ROP equilibrium can be quantified by considering the known equilibria between a lactone (M in Eq. (2.4) and (2.5)), polymer chain and **1**. The equilibrium expression for the total reaction is given in Eq. (2.6). The substitution of the thiourea mass balance Eq. (2.7) into Eq. (2.6) followed by rearranging gives Eq. (2.8) (assuming $[M_n^*] = [M_{n+1}^*]$, see full derivation below (page 48)), which takes a linear form and describes the influence of $[1]_{\text{EFF}}$ upon $[M]_{\text{T,eq}}$. In the **1** mediated ROP of VL as described by Eq. (2.8) ($M = \text{VL}$), the total amount of monomer remaining at thermodynamic equilibrium ($[M]_{\text{T,eq}}$) is perturbed from the nominal ROP equilibrium ($[M]_{\text{eq}}$, the intercept of Eq. (2.8)) to an extent that is directly proportional to the effective concentration of **1** ($[1]_{\text{EFF}}$). As a check on the validity of this analysis, $[\text{VL}]_{\text{eq}}$ can be determined from the y-intercept in Figure 2.3: $[\text{VL}]_{\text{eq}} = 0.052 \text{ M}$. This value of $[\text{VL}]_{\text{eq}}$ is consistent with previous reports,¹⁴ and it is the inverse of the equilibrium constant for the ROP reaction, $K_{\text{eq5}} = 1/[\text{VL}]_{\text{eq}} = 19.1$ ($\Delta G^\circ_5 = -1.76 \pm 0.30 \text{ kcal/mol}$, 300 K), which is not affected by the changing $[1]_{\text{EFF}}$. The equilibrium constant for the total reaction, K_{eqT} , is the

enchainment equilibrium in the presence of **1**, and it is determined from the slope from Figure 2.3: $K_{eqT} = 0.57$ ($\Delta G^\circ_T = 0.34 \pm 0.01$ kcal/mol, 300 K). The difference between K_{eq5} and K_T , $\Delta\Delta G^\circ = 2.1 \pm 0.3$ kcal/mol, represents binding energy of the monomer to **1** ($1/K_{eq4}$), and this is in agreement with the independently measured value, $1/K_{eq4} = 39$ ($\Delta G^\circ_4 = 2.2$ kcal/mol, 300 K).¹³

A change in the location of the $M \cdot 1$ species on the reaction coordinate does not alter the conclusions, only the description, of the phenomenon being observed. In the energy surface described above, the non-ROP role of thiourea is akin to that of inhibitor in enzyme kinetics, where excess thiourea disfavors the formation of product (polymer). An equally valid and equivalent (see Thiourea as catalyst interpretation below) interpretation envisages the role of thiourea as purely catalyst, where the formation of $M \cdot 1$ occurs in a step intermediate to free monomer/thiourea and polymer formation, Eq. (2.9) and (2.10). The energy surfaces described by Eq. (2.4) and (2.5) or Eq. (2.9) and (2.10) are very shallow, with the largest gap ~ 2 kcal/mol, hence the system has free movement between the entire surface at room temperature. Indeed, re-deriving an equation to describe the influence of $[1]_{EFF}$ upon $[M]_{eq}$ (c.f. Eq. (2.8)) based on the thiourea as catalyst interpretation (Eq. (2.9) and (2.10)) produces the same Eq. (2.8) describing the influence of $[1]_{EFF}$ upon ROP equilibrium (see Thiourea as catalyst interpretation below (page 49)). This latter scheme qualitatively describes the role of (thio)urea in ROP as a thermodynamic trap for monomer prior to the endergonic enchainment of **1**-bound VL. This conceptual framework describes classic views of enzyme-substrate interactions and is consistent with the existence of a ‘Goldilocks’ H-bond donor featuring a monomer/thiourea binding constant that is ‘just right’.²² Regardless, H-bond donors have the ability to alter ROP

thermodynamics. We do not wish to suggest the application of large concentrations of H-bond donor in common practice, but rather seek to understand the observed effects so that improved catalysts for (de)polymerization might be generated.

An enzyme-induced ‘equilibrium shift’ has been observed for reactions taking place in enzymatic active sites versus those in free solution.²³ To our knowledge, such an effect has not been so clearly and controllably observed in homogeneous catalysis outside enzymatic systems. Because classic Michaelis-Menten kinetics consider an irreversible reaction, discussions regarding the energetic implications of the binding of substrate to enzyme have been largely considered with respect to the ramifications of enzyme/substrate adducts upon catalysis.^{24,25} In the biomimetic H-bond mediated ROP of lactones, the catalytic step is reversible, and the binding of **1** to monomer impacts the reaction thermodynamics too.

The addition of **1** to an ROP at equilibrium results in the generation of more monomer due to depolymerization, Figure 2.4. The **1**/DBU cocatalyzed ROP of VL from benzyl alcohol in C₆D₆ was monitored by ¹H NMR and was allowed to reach equilibrium at which point additional **1** was added to the NMR tube. The reaction progress was observed to reverse, establishing a new, increased, [VL]_{T,eq}, Figure 2.4. This process was repeated by the addition of another aliquot of **1**. The same effect is observed if the experiment is repeated on separately prepared and isolated polyvalerolactone. The addition of **1** to the reaction does alter the solution volume but not significantly so, see Figure 2.10. Elevated temperatures have previously been employed to favor depolymerization and monomer recovery,^{26,27} and organic catalysts have been applied for the depolymerization

of poly(ethylene terephthalate) with excess nucleophile,^{28–30} but we believe the current process is distinct from these observations.

The equilibrium perturbation by thiourea upon lactone monomers is not limited to **1** and VL. A new thiourea cocatalyst was synthesized, **2** in Figure 2.5, that exhibited much greater solubility in C₆D₆ (versus **1**). The application of progressively increased amounts of **2** to the ROP of VL at equilibrium allowed for the depolymerization of this reaction to [VL]_{T,eq} = 0.98 M. This is greater than the solubility-limited depolymerization of PVL with **1**, [VL]_{T,eq max} = 0.67 M. Analysis of the polymer over the course of the depolymerization experiment (see Figure 2.5) suggests a linear de-evolution of M_n, and M_w/M_n remains narrow throughout the reaction. The precise effects of the depolymerization upon the polymer are the subject of future investigation. Quenching a partially reverted ROP allows for the isolation of the depolymerized monomer. The **1**/DBU catalyzed ROP of VL (2 M, 202 mg) from benzyl alcohol was depolymerized to the extent possible by the application of **2**. The monomer was recovered from the reaction mixture after quenching and Kugelrohr distillation, (29.1 mg; 77% yield, see Experimental Section). The new thiourea, **2**, was also applied to control the endpoint in the ROP of ε-caprolactone (CL), Figure 2.6. The reduced efficacy of **2** in perturbing [M]_{T,eq} in the ROP of CL vs VL may be attributed to the increased ring strain of CL vs VL (i.e. reduced [CL]_{eq} vs [VL]_{eq} under normal conditions).

CONCLUSION

Nominally, the end point of an ROP is thermodynamically determined by a function of monomer ring strain and is described by the equilibrium monomer concentration ($[M]_{eq} = 1/K_{eq}$). The addition of thiourea to the ROP of VL or CL does not change $[M]_{eq}$ from that of an ROP in the absence of H-bond donor, hence the classic definition of ‘catalyst’ applies to thioureas. However, the H-bond donating ability of thiourea favors the depolymerization reaction to provide a lactone binding partner to thiourea. The rapid and reversible binding of thiourea to VL allows for monomer isolation and the effective thiourea-determined shift of a chemical equilibrium. At the very least, the effects of thiourea upon ROP represent a cautionary tale of superimposed equilibria, but perhaps H-bond donors can be applied to drive thermodynamic control with tandem catalysis or be applied to the chemical recycling of polymers.

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$$K_{eqT} = K_{eq4} \cdot K_{eq5} = \frac{[1]_{eq}}{[M \cdot 1]_{eq}} \quad (\text{Eq. 2.6})$$

$$[1]_O = [1]_{eq} + [M \cdot 1]_{eq} + [DBU]_O \quad (\text{Eq. 2.7})$$

$$[M]_{T,eq} = \frac{1}{1 + K_{eqT}} [1]_{EFF} + [M]_{eq} \quad (\text{Eq. 2.8})$$

Derivation of Eq. 2.8:

$$M \bullet \mathbf{1} + M_n^* \rightleftharpoons M_n^* + M + \mathbf{1} \quad (\text{Eq. 2.4})$$

$$M_n^* + M + \mathbf{1} \rightleftharpoons M_{n+1}^* + \mathbf{1} \quad (\text{Eq. 2.5})$$

$$[M]_{T,eq} = [M]_{eq} + [M \bullet \mathbf{1}]_{eq} \quad (\text{S1})$$

$$K_{eqT} = K_{eq4} \bullet K_{eq5} = \frac{[1]_{eq}}{[M \bullet 1]_{eq}} \quad (\text{Eq. 2.6})$$

$$[\mathbf{1}]_O = [\mathbf{1}]_{eq} + [M \bullet \mathbf{1}]_{eq} + [DBU]_O \quad (\text{Eq. 2.7})$$

$$K_{eq4} = \frac{[1]_{eq}[M]_{eq}}{[M \bullet 1]_{eq}} \quad (\text{S2})$$

Insert (7) into (6) and rearrange to get:

$$K_{eqT}[M \bullet \mathbf{1}]_{eq} = [\mathbf{1}]_O - [M \bullet \mathbf{1}]_{eq} - [DBU]_O \quad (\text{S3})$$

The effective concentration of $\mathbf{1}$, $[\mathbf{1}]_{EFF}$, is defined to be that in excess of DBU:

$$[\mathbf{1}]_{EFF} = [\mathbf{1}]_O - [DBU]_O \quad (\text{S4})$$

Insert eq. S4 into eq. S3:

$$K_{eqT}[M \bullet \mathbf{1}]_{eq} = [\mathbf{1}]_{EFF} - [M \bullet \mathbf{1}]_{eq} \quad (\text{S5})$$

$$[M \bullet \mathbf{1}]_{eq}(K_{eqT} + 1) = [\mathbf{1}]_{EFF} \quad (\text{S6})$$

$$([M]_{T,eq} - [M]_{eq})(K_{eqT} + 1) = [\mathbf{1}]_{EFF} \quad (\text{S7})$$

$$[M]_{T,eq}K_{eqT} + [M]_{T,eq} - [M]_{eq} - [M]_{eq}K_{eqT} = [\mathbf{1}]_{EFF} \quad (\text{S8})$$

$$[M]_{T,eq}(1 + K_{eqT}) = [\mathbf{1}]_{EFF} + [M]_{eq}(1 + K_{eqT}) \quad (\text{S9})$$

$$[M]_{T,eq} = \frac{1}{1 + K_{eqT}} [\mathbf{1}]_{EFF} + [M]_{eq} \quad (\text{Eq. 2.8})$$

Thiourea as catalyst interpretation:

$$M_n^* + M + \mathbf{1} \rightleftharpoons M \bullet \mathbf{1} + M_n^* \quad (\text{Eq. 2.9})$$

$$M \bullet \mathbf{1} + M_n^* \rightleftharpoons M_n^* + \mathbf{1} \quad (\text{Eq. 2.10})$$

$$K_{eq9} = \frac{[M \bullet \mathbf{1}]_{eq}}{[\mathbf{1}]_{eq}[M]_{eq}} \quad (\text{S10})$$

$$K_{eqT} = K_{eq9} \bullet K_{eq10} = \frac{1}{[M]_{eq}} \quad (\text{S11})$$

Insert definition of K_{eq10} into (S11) to get:

$$K_{eqT} = \frac{K_{eq9}[\mathbf{1}]_{eq}}{[M \bullet \mathbf{1}]_{eq}} \quad (\text{S12})$$

Rearrange and insert eq. 7 into eq. S12 and rearrange to get:

$$[M \bullet \mathbf{1}]_{eq} = \frac{K_{eq9}}{K_{eqT}} ([\mathbf{1}]_O - [M \bullet \mathbf{1}]_{eq} - [DBU]_O) \quad (\text{S13})$$

Insert eq. S4 into eq. S13:

$$[M \bullet \mathbf{1}]_{eq} + \frac{1}{K_{eq10}} [M \bullet \mathbf{1}]_{eq} = \frac{1}{K_{eq10}} [\mathbf{1}]_{EFF} \quad (\text{S14})$$

$$[M \bullet \mathbf{1}]_{eq} \left(1 + \frac{1}{K_{eq10}} \right) = \frac{1}{K_{eq10}} [\mathbf{1}]_{EFF} \quad (\text{S15})$$

$$([M]_{T,eq} - [M]_{eq}) \left(1 + \frac{1}{K_{eq10}} \right) = \frac{1}{K_{eq10}} [\mathbf{1}]_{EFF} \quad (\text{S16})$$

$$[M]_{T,eq} - [M]_{eq} + \frac{[M]_{T,eq}}{K_{eq10}} - \frac{[M]_{eq}}{K_{eq10}} = \frac{1}{K_{eq10}} [\mathbf{1}]_{EFF} \quad (\text{S17})$$

$$[M]_{T,eq} \left(1 + \frac{1}{K_{eq10}} \right) = \frac{1}{K_{eq10}} [\mathbf{1}]_{EFF} + [M]_{eq} \left(1 + \frac{1}{K_{eq10}} \right) \quad (\text{S18})$$

$$[M]_{T,eq} (K_{eq10} + 1) = [\mathbf{1}]_{EFF} + [M]_{eq} (K_{eq10} + 1) \quad (\text{S19})$$

$$[M]_{T,eq} = \frac{1}{1 + K_{eq10}} [\mathbf{1}]_{EFF} + [M]_{eq} \quad (\text{S20})$$

Figure 2.1. H-bond mediated ROP of VL.

Figure 2.2. Evolution of $[\text{VL}]_T$ vs time for ROPs with varied $[\mathbf{1}]_{\text{EFF}}$. Reaction conditions: VL (100 mg, 1.63 M), DBU (0.082 M), benzyl alcohol (0.016 M) in C_6D_6 with the given $[\mathbf{1}]_{\text{EFF}} = [\mathbf{1}]_0 - [\text{DBU}]_0$.

Figure 2.3. Total monomer concentration at equilibrium ($[VL]_{\text{T,eq}}$) vs $[1]_{\text{EFF}}$ for the reactions given above; slope = 0.636, intercept = 0.0524, $R^2 = 0.985$.

Figure 2.4. Concentration of VL vs time for the sequential addition of **1** to the ROP of VL in progress. Conditions: VL (100 mg, 0.9 M), DBU (0.045 M), benzyl alcohol (0.009 M) in C₆D₆ with the given $[\mathbf{1}]_{\text{EFF}} = [\mathbf{1}]_0 - [\text{DBU}]_0$.

Figure 2.5. Sequential addition of **2** to the ROP of VL. Conditions: VL (100 mg, 0.91 M), DBU (0.046 M), benzyl alcohol (0.009 M) in C_6D_6 with the given $[1]_{EFF} = [1]_O - [DBU]_O$.

Figure 2.6. $[\mathbf{2}]_0$ dependent evolution of $[\text{CL}]$ vs time. Conditions: $[\text{CL}]_0 = 1.6 \text{ M}$ (100 mg); $[\text{DBU}]_0 = 0.08 \text{ M}$; $[\text{benzyl alcohol}]_0 = 0.016 \text{ M}$; in C_6D_6 . (●) $[\mathbf{2}]_0 = 0.80 \text{ M}$; (●) $[\mathbf{2}]_0 = 0.41 \text{ M}$.

Figure 2.7. ^1H NMR spectra showing the polymerization of VL and subsequent depolymerization of poly(valerolactone) upon the addition of **1**. Reaction conditions: VL (0.499 mmol, 1 equiv, 1M in C_6D_6), benzyl alcohol (1 mol%, 4.99 μmol), DBU (5 mol%, 0.025 mmol) and **1** (5 mol%, 0.025 mmol). After reaching equilibrium, aliquots of **1** were added (20 mol%, 0.0999 mmol and 25 mol%, 0.125 mmol) at 781 min and 1441 min, respectively.

Figure 2.8. Selected expanded ^1H NMR spectra of from the polymerization of VL and subsequent depolymerization of poly(valerolactone) upon the addition of **1**. Reaction conditions: VL (0.499 mmol, 1 equiv, 1M in C_6D_6), benzyl alcohol (1 mol%, 4.99 μmol), DBU (5 mol%, 0.025 mmol) and **1** (5 mol%, 0.025 mmol). After reaching equilibrium, aliquots of **1** were added (20 mol%, 0.0999 mmol and 25 mol%, 0.125 mmol) at 781 min and 1441 min, respectively.

Figure 2.9. NMR tubes containing the top and bottom runs from Figure 2.2 (left and right tube, respectively). (left) Start of the reaction. (right) At equilibrium. See Figure 2.2 for conditions.

Figure 2.10. Reproduction of **1** addition experiment from Figure 2.3. Left tube is after all **1** additions, right tube is the starting conditions. See Figure 2.3 for conditions.

Figure 2.11. $[\text{VL}]_{T,\text{eq}}$ vs $[\text{catalysts}]_0$ for the ROPs when the initial concentrations of cocatalysts are varied together. Conditions: 2M VL, 0.02 M benzyl alcohol in C_6D_6 .

Figure 2.12. $[VL]_{eq}$ as a function of temperature. Conditions: VL (0.100 g, 0.999 mmol, 2M in C_6D_6), **1** (0.0740 g, 0.199 mmol), DBU (7.47 μ L, 0.0499 mmol), and benzyl alcohol (9.99 μ mol).

Figure 2.13. Titration curve for the BnOH/DBU binding in benzene- d_6 . Chemical shift of the benzylic protons vs [DBU]; solid line is the fit from the binding equation.

Figure 2.14. ^1H NMR (300 MHz, DMSO-d_6) of **2**.

Figure 2.15. ^{13}C NMR (75 MHz, DMSO-d_6) of **2**.

MANUSCRIPT – III

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

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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 mono-thiourea catalysts. It is no longer necessary to choose between a highly active or highly selective organocatalyst for ROP.

INTRODUCTION

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 selective^{1,9,12–15} or highly active^{16–19} 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.^{20,21} We recently disclosed a bithiourea (bisTU) H-bond donating cocatalyst, **2-S** in Figure 3.1, for the ROP of L-lactide (LA), which displayed enhanced catalytic activity (over mono-TU), but no reduction in reaction control.²² During the process of extending the utility of this system to other lactone monomers, we developed a trisurea (trisU, **3-O** in Figure 3.1) 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 3.1.

EXPERIMENTAL SECTION

General Considerations. All manipulations were performed in an MBRAUN stainless steel glovebox equipped with a gas purification system or using Schlenk technique under a nitrogen atmosphere. All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise. Tetrahydrofuran and dichloromethane were dried on an Innovative Technologies solvent purification system with alumina columns and nitrogen working gas. Benzene- d_6 and chloroform- d were purchased from Cambridge Isotope Laboratories and distilled from CaH_2 under a nitrogen atmosphere. δ -valerolactone (VL; 99%), ϵ -caprolactone (CL; 99%) and benzyl alcohol were distilled from CaH_2 under reduced pressure. 1,3-diaminopropane, 3,5-bis(trifluoromethyl)phenyl isocyanate and cyclohexylamine were purchased from Acros Organics. 3,5-bis(trifluoromethyl)phenyl isothiocyanate was purchased from Oakwood Products. 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) was purchased from TCI. Tris(2-aminoethyl)amine was purchased from Alpha Aesar. The H-bond donors **1-S**, **1-O** and **2-S** were prepared according to published procedures.^{23–25} NMR experiments were performed on Bruker Avance III 300 MHz or 400 MHz spectrometers. Size exclusion chromatography (SEC) was performed at 40 °C using dichloromethane eluent on an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm $\times$ 300 mm (5 μm , pore sizes: 103, 104, 105 Å). M_n and M_w/M_n were determined versus PS standards (500 g/mol–3150 kg/mol, Polymer Laboratories). Water and acetonitrile were all Optima HPLC grade solvents from Fisher Chemical (Fair Lawn, NJ, USA).

Mass spectrometry was performed using a Thermo Electron (San Jose, CA, USA) LTQ Orbitrap XL mass spectrometer affixed with either an atmospheric-pressure chemical

ionization (APCI) or electrospray ionization (ESI) interface, positive ions were produced and introduced into the instrument. Tune conditions for infusion experiments (10 μ L/min flow, sample concentration <20 μ g/mL in 50/50 v/v water/acetonitrile) were as follows: ionspray voltage, 5,000 V; capillary temperature, 275 $^{\circ}$ C; sheath gas (N_2 , arbitrary units), 8; auxiliary gas (N_2 , arbitrary units), 0; capillary voltage, 35 V; and tube lens, 110 V. Prior to analysis, the instrument was calibrated for positive ions using Pierce LTQ ESI positive ion calibration solution (lot #PC197784). Ion trap experiments used N_2 as a collision gas with normalized collision energies (NCE) between 10-25 eV for multistage fragmentation. High-energy collision (HCD) experiments were performed with He as the collision gas with a NCE of 25 eV.

Computational Details. The Spartan '14 package for Windows 7 was used for all computations. Computed structures were geometry optimized at the B3LYP/6-31G* level of theory. Reported energies were calculated in CH_2Cl_2 solvent and were calculated at the B3LYP/6-31G** level of theory from the DFT-optimized structures. Energies, structures and coordinates are given below.

Synthesis of 1-[3,5-bis(trifluoromethyl)phenyl thiourea]-3-aminopropane. A dried 50 mL Schlenk flask was charged with a stir bar, dichloromethane (15.0 mL) and 1,3-diaminopropane (0.45 mL, 5.40 mmol). 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.00 mL, 5.495 mmol) was added dropwise to the round bottom flask. The solution was stirred for 24 hours, and the solvent was removed under reduced pressure. The resulting solid was purified via silica gel column chromatography with 90 : 10, dichloromethane : methanol mobile phase. Yield: 21%. 1H NMR (300 MHz, DMSO) spectrum below.

Product was carried on without full characterization. ^1H NMR (300 MHz, $\text{C}_2\text{D}_6\text{OS}$) δ 1.6 (p, $J = 6$, 2H) 2.65 (t, $J = 6$, 2H) 3.54 (br, 2H) 7.69 (s, 1H) 8.23 (s, 2H).

Synthesis of 2-OS. 1-[3,5-bis(trifluoromethyl)phenyl thiourea]-3-aminopropane (100.8 mg, 0.292 mmol) was added to a dried 10 mL Schlenk flask containing dichloromethane (1 mL), 3,5-bis(trifluoromethyl)phenyl isocyanate (74.0 μL , 0.290 mmol). Product precipitated from solution and was isolated by decanting the solvent. Solid was recrystallized from dichloromethane and dried under high vacuum overnight. Yield: 70%. HRMS m/z calcd ($\text{C}_{21}\text{H}_{16}\text{F}_{12}\text{N}_4\text{OS} + \text{H}^+$) 601.0926, found 601.0893. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.74 (p, $J = 6$, 2H) 3.19 (q, $J = 6$, 2H) 3.55 (br, 2H) 6.75 (t, $J = 6$, 1H) 7.53 (s, 1H) 7.73 (s, 1H) 8.08 (s, 2H) 8.24 (s, 2H) 9.33 (s, 1H) 10.15 (s, 1H). ^{13}C NMR (75 MHz, $\text{acetone}-d_6$) δ 29.0, 36.8, 41.4, 113.0, 115.7, 116.8, 121.1, 121.5, 123.0 (q), 124.8, 130.2 (q), 141.5, 142.2, 154.5, 180.1.

Synthesis of 2-O. A dried 10 mL Schlenk flask was charged with a stir bar, dichloromethane (7 mL), 1,3-diaminopropane (35.9 μL , 0.43 mmol). 3,5-bis(trifluoromethyl)phenyl isocyanate (148.6 μL , 0.86 mmol) was added dropwise to the round bottom flask. The resulting slurry was stirred for 1 hr, filtered and washed with cold dichloromethane. Yield: 97%. HRMS m/z calcd ($\text{C}_{21}\text{H}_{16}\text{F}_{12}\text{N}_4\text{O}_2 + \text{H}^+$) 585.1154, found 585.1100. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.68 (p, $J = 6$ Hz, 2H) 3.22 (q, $J = 6$ Hz, 4H) 6.59 (t, $J = 6$, 2H) 7.58 (s, 2H) 8.14 (s, 4H) 9.39 (s, 2H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 30.3, 36.6, 113.3, 117.1, 123.3 (q), 130.5 (q), 142.6, 154.9.

Synthesis of 3-S. A dried 100 mL Schlenk flask was charged with a stir bar, tetrahydrofuran (50 mL), tris(2-aminoethyl) amine (1.05 mL, 6.84 mmol), 3,5-bis(trifluoromethyl)phenyl isocyanate (3.90 mL, 21.20 mmol). The solution was left to stir

for 24 hrs and the solvent was subsequently removed in vacuo. The resulting solid product was purified using a silica gel column with a 90 : 10, hexanes : ethyl acetate mobile phase. Product was removed of volatiles under high vacuum overnight. Yield: 87%. HRMS m/z calcd ($C_{33}H_{27}F_{18}N_7S_3 + H^+$) 960.1275, found 960.1262. 1H NMR (300 MHz, acetone- d_6) δ 2.82 (t, $J = 6$, 6H) 3.68 (m, 6H) 7.44 (s, 3H) 7.71 (br, 2H) 8.04 (s, 6H) 9.40 (br, 2H). ^{13}C NMR (75 MHz, acetone- d_6) δ 43.7, 53.7, 117.6, 123.3, 124.2 (q), 131.8 (q), 142.5, 182.1.

Synthesis of 3-O. A dried 100 mL Schlenk flask was charged with a stir bar, tetrahydrofuran (50 mL), tris(2-aminoethyl) amine (1.03 mL, 6.84 mmol), 3,5-bis(trifluoromethyl)phenylisocyanate (3.6 mL, 21.20 mmol). The solution was stirred for 24 hrs. The solvent was removed in vacuo. Resulting solid was purified using a silica gel column with a 96:4 dichloromethane:methanol mobile phase. Yield: 88%. HRMS m/z calcd ($C_{33}H_{27}F_{18}N_7O_3 + H^+$) 912.1961, found 912.1933. 1H NMR (300 MHz, acetone- d_6) δ 2.58 (t, $J = 3$, 6H) 3.21 (m, 6H) 6.32 (m, 2 H) 7.29 (s, 3H) 7.86 (s, 6H) 8.58 (s, 2H). ^{13}C NMR (75 MHz, acetone- d_6) δ 39.3, 55.8, 114.9, 118.3, 124.4 (q), 132.3 (q), 143.3, 156.3.

Example VL Polymerization Experiment. A 7 mL vial was charged with **3-O** (15.2 mg, 0.0167 mmol), MTBD (2.4 μ L, 0.0167 mmol), benzyl alcohol (2.08 μ L, 0.01999 mmol) and C_6D_6 (250 μ L). In a second 7 mL vial, VL (0.100 g, 0.999 mmol) was dissolved in C_6D_6 (249 μ L). The contents of the second vial were transferred to the first via pipette and stirred until homogenous, approximately 1 min. The contents were transferred to an NMR tube via pipette, and the reaction was monitored by 1H NMR. The reaction was quenched using benzoic acid (4.06 mg, 0.0333 mmol). Polymer was precipitated with the addition of hexanes. Supernatant was decanted and solid PVL was dried in vacuo. Yield: 89%, $M_n = 7,500$, $M_w/M_n = 1.07$.

Chain Extension Experiment. A 7 mL vial was loaded with **3-O** (13.3 mg, 0.015 mmol), MTBD (2.2 mg, 0.015 mmol), 1-pyrenebutanol (9.6 mg, 0.035 mmol), and C₆D₆ (219 μ L). In a second 7 mL vial, CL (100 mg, 0.876 mmol) and C₆D₆ (219 μ L) were loaded. The contents of the second vial were added to the first and stirred. After 15 min, a 150 μ L aliquot was taken from the reaction vial, quenched with benzoic acid (1.2 mg, 0.010 mmol), and additional CL (197.3 mg, 1.723 mmol) was added to the reaction vial. After another 50 min, a second aliquot was quenched with benzoic acid (1.2 mg, 0.010 mmol). Samples from both the first and second aliquots were then transferred to NMR tubes and conversion was determined via ¹H NMR analysis. The remainder of the aliquots was precipitated with the addition of hexane, and the supernatants were decanted. Each solid PCL sample was dried in vacuo, and GPC analysis was performed.

Example Copolymerization Experiment. A 7 mL vial was charged with **3-O** (15.2 mg, 0.0167 mmol), MTBD (2.4 μ L, 0.0167 mmol), benzyl alcohol (1.04 μ L, 0.00999 mmol) and C₆D₆ (250 μ L). In a second 7 mL vial, VL (0.100 g, 0.999 mmol) and CL (0.144 g, 0.999 mmol) were dissolved in C₆D₆ (249 μ L). The contents of vial 2 were transferred to the first via pipette and stirred until homogenous, approximately 5 sec. The contents were transferred to an NMR tube via pipette, and the reaction was monitored by ¹H NMR. The reaction was quenched using benzoic acid (4.06 mg, 0.0333 mmol). Polymer was precipitated with the addition of hexanes. Supernatant was decanted and solid polymer was dried in vacuo, 91% yield (196 mg), M_n = 21,400; M_w/M_n = 1.21.

Example ROP of Lactide. L-lactide (72 mg, 0.5 mmol) and *o*-dichlorobenzene (0.5 mL) were added into a 7 mL vial and stirred until a homogenous solution was obtained. To a second 7 mL vial, benzyl alcohol (2.163 mg, 0.02 mmol), Me₆TREN (0.008 mmol) and

3-O (0.008 mmol) were added. Contents from the first vial were transferred into vial 2 via Pasteur pipette. The contents were mixed and transferred to an NMR tube. Reaction progression was monitored by ^1H NMR. After 30 min, the reaction had reached 55% conversion and was quenched with benzoic acid. The reaction was removed of volatiles and treated with hexanes/isopropanol (1:1) to dissolve monomer. The residual polymer was subjected to dialysis in DCM against methanol. Yield: 38 mg, 52%; $M_n = 2,700$; $M_w/M_n = 1.11$.

Example Transesterification Experiment. Ethyl acetate (100 mg, 1.14 mmol), **1-S** (0.057 mmol) and C_6D_6 (0.22 mL) were added to a 7 ml glass vial. To a second 7 mL glass vial, benzyl alcohol (122.7 mg, 1.14 mmol), MTBD (0.057 mmol) and C_6D_6 (0.22 mL) were added. The contents of vial 2 were transferred via Pasteur pipette to vial 1, and the solution was stirred until homogeneous (1 min). The solution was transferred to an NMR tube, and reaction progression was monitored by ^1H NMR.

RESULTS AND DISCUSSION

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 C_6D_6 , the application of **2-S**/MTBD (2.5 mol % each) produces a rate acceleration over the traditional monothiourea (**1-S**/MTBD 5 mol % each) that is not associated with loss of reaction control, Table 3.1. The reactions retain the characteristics of “living” polymerizations, exhibiting a linear evolution of M_n versus conversion, first order consumption of monomer, M_n that is predictable by $[M]_0/[I]_0$ and a living chain end that is susceptible to chain extension, see Figures 3.2-7. The imine base, DBU, and phosphazene base, BEMP, are also effective cocatalysts for the ROP of lactones (with **2-S**), but the reaction is more active with MTBD cocatalyst, Table 3.1.

ROP involving **2-S** is suggested to proceed through an activated-TU mechanism, whereby one TU moiety activates the other, which in turn activates the monomer. The ROPs of VL and CL are first order in the consumption of monomer (Figure 3.3 and 3.10), which suggests one bisTU (**2-S**) molecule activating one monomer in the transition state. This is consistent with previous suggestions that H-bond-mediated ROP operates via dual activation of monomer by **1** and of alcohol chain end by base.¹ Because H-bonds require no orbital overlap and are electrostatic in nature,²⁶ we cannot rule out a dual-thiourea activated mechanism, Eq. 2.1. However, computational studies for the activation of lactones by **2-S** suggest an activated-TU mechanism is preferred over a dual-thiourea activation mechanism, Eq. 2.1; this assertion is also supported by the **2-S**/alkylamine cocatalyzed ROP of lactide.^{22,27}

The series of thiourea H-bond donating catalysts was extended to a trisTU H-bond donor, **3-S**, but this catalyst exhibits significantly reduced activity versus **1-S** or **2-S** in the TU/base cocatalyzed ROP of lactones, Table 3.1. This suggests that simply adding TU moieties does not result in faster ROP. Geometry optimized DFT computations suggest that a stable conformation of **3-S** is the C3 symmetric structure, see Figure 3.15 and 3.16. This calculated structure features a cyclic arrangement of the three TU moieties, each serving as a H-bond donor and a H-bond acceptor to each of the adjacent TU moieties with H-bond lengths of 2.61 ± 0.07 Å. We hypothesize that the added stability due to the three intramolecular H-bonds attenuates the activity of **3-S** (versus **2-S**). In contrast, the intramolecular H-bond activation in **2-S** leaves a TU moiety available for catalysis. Additive effects from multiple TU moieties are found in nature,²⁸ and such constructs have been observed to be beneficial to catalysis,^{22,29,30} although not universally so.^{24,31} Interested in extending the suite of H-bond-mediated catalysts, we noted that changing the C=S to the shorter C=O bond would be expected to disrupt the intramolecular H-bond network, freeing one urea moiety for catalysis. The trisurea H-bond donor (**3-O**) is predicted by DFT calculations to have much longer average H-bond lengths versus **3-S**, 2.92 ± 0.81 Å.

The application of the trisU (**3-O**) catalyst in combination with organic bases effects the fastest organocatalytic ROP of lactones that has been reported, yet the reaction remains highly controlled.^{3,17–21} The **3-O**/MTBD (1.67 mol % each) catalyzed ROP of VL (2 M, 100 mg) from benzyl alcohol (2 mol %) proceeds to full conversion in 3 min, Table 3.2. The comparable reactions with **2-S**/MTBD (2.5 mol % each) or **1-S**/MTBD (5 mol % each) achieve full conversion in 102 min or 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 3.2. The **3-O** mediated ROPs of both monomers are highly controlled, exhibiting the characteristics of “living” polymerizations, (see Figures 3.10 and 3.11). Initiation of a CL ROP from 1-pyrenebutanol produces PCL with overlapping refractive index and UV traces in the GPC, suggesting end-group fidelity; the “living” alcohol chain end is susceptible to chain extension by repeated additions of monomer, (see Figure 3.13). The **3-O**/MTBD cocatalysts remain active at low concentration; full conversion for the ROP of VL (2 M, C_6D_6) from benzyl alcohol ($[M]_0/[I]_0 = 50$) was achieved in 5 h at 0.25 mol % **3-O**/MTBD loading, (see Table 3.4).

The efficacy of **3-O**/base cocatalysts for the ROP of other ester and carbonate monomers was evaluated. The **3-O**/MTBD (1.67 mol %) cocatalysts are effective for the ROP of trimethylene carbonate (TMC). This reaction (100 mg TMC, 1 M in CH_2Cl_2) reaches 97% conversion in 1 min ($M_n = 9,000$; $M_w/M_n = 1.05$; $[M]_0/[I]_0 = 50$), which is more active than the **1-S**/DBU catalyzed ROP of TMC.⁵ For the ROP of LA, **3-O** (with tris[2-(dimethylamino)ethyl]amine) exhibits a solvent incompatibility with LA and PLA, resulting in the precipitation of polymer or catalyst prior to full conversion (see Figure 3.17). The best conversion was achieved in o-dichlorobenzene, 55% in 30 min ($M_n = 2,700$; $M_w/M_n = 1.11$; $[M]_0/[I]_0 = 25$; 52% yield). This is less active than our previously reported catalyst, **2-S**, which reaches full conversion in minutes.²² MALDI analysis of the PLA resulting from the ROP of LA shows only minor transesterification ($m/z = \pm 72n$; see Figure 3.17). 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 Figure 3.12 and Experimental Section; $M_n = 21,400$; $M_w/M_n = 1.29$; 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.⁸

It is proposed here that **3-O**/MTBD cocatalyzed 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 3.2. 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 Figure 3.14). Further, the **3-O**/MTBD cocatalyzed ROP of VL is first order in monomer (see Figure 3.9), 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-bond donors featuring multiple (thio)urea moieties activate one reagent prior to the TU-reagent complex undergoing further chemistry,^{22,32} 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.²⁸ Indeed, ^1H 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. 2.1), 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 3.15 and 3.16), 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 3.2. The guanidine base, TBD (Figure 3.1), has been regarded as one of the most active organocatalysts available for the ROP of lactones.¹⁶ The TBD catalyzed ROP of CL from benzyl alcohol (Table 3.2, entry 12) proceeds to 93% conversion in 140 min ($M_w/M_n = 1.37$), whereas the same ROP with **3-O**/MTBD (Table 3.2, 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.³³ The development of urea and thiourea H-bond donating catalysts continued apace until the turn of the millennium when several reports emerged that extolled the operational (e.g., increased solubility)^{34,35} and synthetic (e.g., higher yields and enantioselectivities)^{35–37} benefits of thioureas over ureas. In our estimation, the ubiquity of the thiourea motif in H-bond mediated transformations may be more due to the coincidental timing of these reports than any general superiority of thioureas over urea H-bonding catalysts. Indeed, ureas are more polar than thioureas and should be expected to be better H-bond activators,³³ and in some catalysis applications, urea catalysts are clearly superior.^{38,39} The late Margaret Etter may have presaged our observation of **3-O** as an effective H-bond donating catalyst in her characterization of aryl ureas featuring meta-electron withdrawing groups by noting that urea carbonyls are good H-bond acceptors.³⁸

The urea versions of **2** and **1** were synthesized and evaluated for their efficacy in the ROP of VL (2 M, 100 mg, 1 equiv.) from benzyl alcohol (2 mol %) in C₆D₆. In general,

all n-O (n = 1, 2, or 3) catalysts were more active than the corresponding n-S H-bond donors, Tables 3.1 and 3.2. For the 2-X (X = O, S, or OS) H-bond donors, the rate of ROP increases with the progressive substitution of O (versus S) and M_w/M_n remains low. These results suggest the increased utility of ureas versus thioureas for H-bond-mediated ROP. All reported urea catalysts are soluble under the desired reaction conditions with the exception of **2-O**, which requires an extra equivalent of MTBD to become homogeneous in C_6D_6 .⁴⁰ A plot of the observed rate constant (k_{obs}) versus [MTBD] for the ROP of CL from benzyl alcohol increases linearly under conditions $[MTBD] \leq [2-S]$, but becomes zero order in [MTBD] when $[MTBD] > [2-S]$, (see Figure 3.7). This suggests that the proper stoichiometry of the **2-S**/MTBD catalyzed reaction is 1:1. The catalysts (1–3 with MTBD) are all operative in CH_2Cl_2 , $CHCl_3$, and THF albeit with slightly reduced reaction rates or M_w/M_n (see Table 3.5).

Preliminary studies suggest that these catalysts exhibit the same reactivity trends in small molecule transesterification and, hence, may have general applicability beyond ROP. The transesterification of ethyl acetate (1.6 M) with benzyl alcohol (1.6 M) was conducted in C_6D_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 Table 3.3). This suggests a general role for the increased activation of esters by urea H-bond donors (versus thioureas), yet the slower rates for the transesterification of s-trans (versus s-cis) esters accounts for the low rate of transesterification post polymerization, (see Table 3.6).

CONCLUSION

Urea H-bond donors in combination with base cocatalysts 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.

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Entry	Monomer	TU (mol%)	Base (mol%)	Time (min)	Conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
1	VL	1-S (5%)	MTBD (5%)	110	94	8,300	1.06
2		2-S (2.5%)	MTBD (2.5%)	80	90	6,800	1.07
3		2-S (2.5%)	BEMP (2.5%)	84	91	8,900	1.06
4		2-S (2.5%)	DBU (2.5%)	90	86	8,400	1.05
5		3-S (1.67%)	MTBD (1.67%)	230	90	7 600	1.06
6	CL	1-S (5%)	MTBD (5%)	45 h	90	7,200	1.09
7		2-S (2.5%)	MTBD (2.5%)	10 h	89	7,200	1.11
8		3-S (1.67%)	MTBD (1.67%)	42 h	55	6,100	1.07

Table 3.1. MTBD and **1-S**, **2-S** or **3-S** catalyzed ROP of VL and CL. Reaction conditions: VL or CL (1.0 mmol, 1 equiv., 2M), benzyl alcohol (2 mol%), C_6D_6 . a) monomer conversion was determined via ^1H NMR. b) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) versus polystyrene standards.

Entry	Monomer	TU or U (mol%)	[M] ₀ /[I] ₀	Time (min)	Conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
1	VL	1-O (5%)	50	70	90	6,100	1.08
2		2-OS (2.5%)	50	88	90	8,100	1.07
3		2-O (2.5%) ^d	50	34	90	8,000	1.07
4		3-O (1.67%)	50	3	89	7,500	1.07
5			100	6	90	15,000	1.04
6			200	10	92	28,600	1.02
7			500	16	92	41,500	1.02
8	CL	3-O (1.67%)	50	26	97	7,900	1.05
9			100	57	94	18,500	1.02
10			200	116	94	30,700	1.03
11			500	166	93	58,600	1.03
12 ^d		TBD (1.67%)	50	140	93	10,400	1.37

Table 3.2. **1-O**, **2-O** or **3-O** and MTBD cocatalyzed ROP of lactones. Reaction conditions: VL or CL (1.0 mmol, 1 equiv., 2M), urea or thiourea (given mol%), MTBD (mol% matched to H-bond donor). a) Monomer conversion monitored via ¹H NMR. b) M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards. c) **2-O** (2.5 mol%) and MTBD (5 mol%) cocatalysts. d) no (thio)urea or MTBD cocatalysts were used in this run.

Entry	TU or U (mol%)	k_{obs} (1/min) ^a	[EA] _{eq} (M) ^b
1	1-S (5%)	0.000 80	1.08
2	1-O (5%)	0.003 57	0.88
3	2-S (2.5%)	0.000 55	0.99
4	2-O (2.5%)	0.004 10	0.99
5	3-S (1.67%)	0.000 61	1.19
6	3-O (1.67%)	0.002 11	0.89

Table 3.3. Transesterification of ethyl acetate. a) Observed rate constant for the first order disappearance of [EA] versus time. Rate constant was extracted from the linear portion of the data, up to ~20% conversion. b) Concentration of ethyl acetate remaining at equilibrium.

Entry	mol% cats. (each)	Time (min)	Conv ^a	M_n^b	M_w/M_n^b
1	1.67	3	89	7,500	1.07
2	1	10	91	7,100	1.07
3	0.5	40	93	7,700	1.07
4	0.25	300	93	7,200	1.07
5	0.1	24hr	0	NA	NA

Table 3.4. Low **3-O/MTBD** Cocatalyst Loadings in the ROP of VL. Reaction conditions: VL(0.998 mmol, 1 equiv., 2M), C_6D_6 and benzyl alcohol (2 mol%). a) Monomer conversion was monitored via 1H NMR. b) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) versus polystyrene standards.

Entry	Solvent	Time (min)	Conv ^a	M_n^b	M_w/M_n^b
1	C ₆ D ₆	4	91	12,200	1.04
2	CH ₂ Cl ₂	5	90	14,800	1.05
3	CHCl ₃	5	90	7,000	1.07
4	Cl-C ₆ H ₅	4	93	10,000	1.08
5	THF	5	89	13,600	1.05

Table 3.5. Solvent Screen in the **3-O**/MTBD Cocatalyzed ROP of VL. Reaction conditions:

VL (0.998 mmol, 1 equiv., 2M), 1 mol% benzyl alcohol, a) monomer conversion was monitored via ¹H NMR. b) M_n and M_w/M_n were determined by GPC.

Entry	Monomer	Time (min)	Conv ^a	M_n^b	M_w/M_n^b
1	VL	3	93	6,200	1.10
2	VL	6	93	6,300	1.12
3	VL	60	94	6,600	1.21
4	CL	25	91	9,000	1.04
5	CL	60	98	10,000	1.05
6	CL	120	99	10,000	1.09

Table 3.6. Post-polymerization Transesterification in **3-O**/MTBD Cocatalyzed ROP.

Reaction conditions: VL (0.998 mmol, 1 equiv., 2M), 2 mol% benzyl alcohol, a) monomer conversion was monitored via ^1H NMR. b) M_n and M_w/M_n were determined by GPC.

Eq. 3.1. Intramolecular conformational arrangement of **2-S** done computationally.

Scheme 3.1. Highly active and highly selective H-bond donor **3-O**.

Scheme 3.2. Proposed mechanism for **3-O**/MTBD catalyzed ROP.

Figure 3.1. Base and (thio)urea cocatalysts evaluated for ROP.

Figure 3.2. M_n versus conversion for the **2-S**/MTBD catalyzed ROP of VL. Conditions: VL (2.994 mmol, 1 equiv., 1M in C_6D_6), benzyl alcohol (2 mol%, 0.0598 mmol), MTBD (5 mol%, 0.1497 mmol) and **2-S** (5 mol%, 0.1496 mmol). (blue is M_n , red is M_w/M_n).

Figure 3.3. First order evolution of [VL] versus time for the **2-S**/MTBD catalyzed ROP of VL. Conditions: VL (0.999 mmol, 1 equiv., 2M in C₆D₆), benzyl alcohol (2.0 mol%, 0.0199 mmol), MTBD (5.0 mol%, 0.0499 mmol) and **2-S** (5.0 mol%, 0.0499 mmol).

Figure 3.4. M_n versus $[VL]_0/[I]_0$ for the **2-S**/MTBD catalyzed ROP of VL. Conditions: VL (0.999 mmol, 1 equiv., 1M in C₆D₆), benzyl alcohol (2 mol%, 0.0199 mmol), MTBD (5.0 mol%, 0.0499 mmol) and **2-S** (5.0 mol%, 0.0499 mmol).

Figure 3.5. GPC traces of the polymer resulting from the **2-S**/MTBD (5 mol% each, 0.0499 mmol) cocatalyzed ROP and subsequent chain extension of VL (0.999 mmol, then 0.999 mmol more) from 1-pyrenebutanol (0.0199 mmol) in C₆D₆ (999 μ L).

Figure 3.6. Observed rate constant (k_{obs} , min^{-1}) versus [MTBD] in the **2-S**/MTBD catalyzed ROP of VL. Conditions: VL (0.999 mmol, 1 equiv, 1M in C_6D_6), benzyl alcohol (2 mol%, 0.0199 mmol), MTBD (2.5 mol%, 0.025M).

Figure 3.7. Observed rate constant (k_{obs} , h^{-1}) versus [**2-S**] in the **2-S**/MTBD catalyzed ROP of CL. Conditions: CL (0.999 mmol, 1 equiv., 2M in C_6D_6), benzyl alcohol (2 mol%, 0.0199 mmol), **2-S** (0.05M).

Figure 3.8. M_n vs conversion of VL for the **3-O**/MTBD catalyzed ROP of VL. Conditions: VL (0.999 mmol, 1 equiv., 2M in C_6D_6), benzyl alcohol (1mol%, 0.0199 mmol), MTBD (1.67 mol%, 0.0166 mmol) and **3-O** (1.67 mol%, 0.0166 mmol). (blue is M_n , red is M_w/M_n).

Figure 3.9. First order evolution of $[VL]$ vs time for the **3-O**/MTBD catalyzed ROP of VL. Conditions: VL (0.999 mmol, 1 equiv., 2M in C_6D_6), benzyl alcohol (2 mol%, 0.0199 mmol), MTBD (1.67 mol%, 0.0166 mmol) and **3-O** (1.67 mol%, 0.0166 mmol).

Figure 3.10. M_n vs conversion for the **3-O**/MTBD catalyzed ROP of CL. Conditions: CL (1.752 mmol, 1 equiv, 2M in C_6D_6), benzyl alcohol (2 mol%, 0.035 mmol), MTBD (1.67 mol%, 0.029 mmol) and **3-O** (1.67 mol%, 0.029 mmol). (blue is M_n , red is M_w/M_n).

Figure 3.11. First order evolution of $[CL]$ vs time for the **3-O**/MTBD catalyzed ROP of CL. Conditions: CL (1.752 mmol, 1 equiv., 2M in C_6D_6), benzyl alcohol (2 mol%, 0.035 mmol), MTBD (1.67 mol%, 0.029 mmol) and **3-O** (1.67 mol%, 0.029 mmol).

Figure 3.12. First order evolution of [CL] and [VL] vs time for the **3-O**/MTBD catalyzed copolymerization of CL. Conditions: CL (1.752 mmol, 1 equiv., 2M in C₆D₆), benzyl alcohol (2 mol%, 0.035 mmol), MTBD (1.67 mol%, 0.029 mmol) and **3-O** (1.67 mol%, 0.029 mmol).

Figure 3.13. GPC traces of the polymer resulting from the **3-O**/MTBD (1.67 mol% each, 0.015 mmol) cocatalyzed ROP and subsequent chain extension of CL (0.876 mmol, then 1.1723 mmol more) from 1-pyrenebutanol (0.035 mmol) in C₆D₆ (219 μ L).

Figure 3.14. Observed rate constant (k_{obs} , min^{-1}) vs [3-O] in the 3-O/MTBD catalyzed ROP of VL. Conditions: VL (0.999 mmol, 1 equiv., 0.5M in C_6D_6), benzyl alcohol (2 mol%, 0.0199 mmol), MTBD (1.67 mol%, 0.0166 mmol, 0.008 M).

Figure 3.15. DFT B3LYP//6-31G** geometry optimized structures of **3-S**.

Figure 3.16. DFT B3LYP//6-31G** geometry optimized structures of **3-O**.

Figure 3.17. MALDI-TOF of the PLA resulting from the **3-O**/(tris[2-(dimethylamino)ethyl]amine) catalyzed ROP of L-LA.

Figure 3.18. Downfield half of the ^1H NMR spectra (acetone + trace benzene- d_6 (lock), 400 MHz) of (upper) **1-O**, (middle) **2-O**, and (lower) **3-O**. The progressive downfield shift of the NH protons is indicative of increased (**2-O** versus **3-O**) intramolecular H-bonding.

Figure 3.19. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) of **2-O**.

Figure 3.20. ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) of **2-O**.

Figure 3.21. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) of 1-[3,5-bis(trifluoromethyl)phenyl thiourea]-3-aminopropane.

Figure 3.22. ¹H NMR (300 MHz, DMSO-*d*₆) of **2-OS**.

Figure 3.23. ^{13}C NMR (75 MHz, acetone- d_6) of **2-OS**.

Figure 3.24. ^1H NMR (300 MHz, $\text{acetone-}d_6$) of **3-O**.

Figure 3.25. ^{13}C NMR (75 MHz, acetone- d_6) of **3-O**.

Figure 3.26. ^1H NMR (300 MHz, $\text{acetone-}d_6$) of **3-S**.

Figure 3.27. ^{13}C NMR (75 MHz, acetone- d_6) of **3-S**.

Computational Data
Dual-thiourea activation in DCM

Job type: Single point.
Method: RB3LYP
Basis set: 6-31G**
Number of shells: 258
Number of basis functions: 818
Multiplicity: 1

Solvation: dichloromethane [SM8]
Free Energy of Solvation : -111.5381226 kJ/mol
SCF total energy: -3369.3171898 hartrees

SPARTAN '14 Properties Program: (Win/64b)
Use of molecular symmetry disabled

Release 1.1.8

Atom	Cartesian Coordinates (Angstroms)		
	X	Y	Z
1 C C1	3.0236320	1.8782697	-1.5793812
2 S S1	2.4865855	3.2691914	-2.3431680
3 N N1	4.1615953	1.8195168	-0.8199347
4 H H4	4.3807088	0.9334757	-0.3754557
5 N N2	2.4147858	0.6395117	-1.6440053
6 H H3	2.8892309	-0.0770555	-1.1048418
7 C C2	1.1325107	0.2212543	-2.0380878
8 C C4	-1.4114202	-0.8709745	-2.5894579
9 C C3	0.9092347	-1.1643141	-1.9771559
10 C C6	0.0704432	1.0587976	-2.4057200
11 C C5	-1.1820850	0.5015117	-2.6687443

12 C C7	-0.3459752	-1.7004420	-2.2407846
13 H H6	1.7244618	-1.8277314	-1.7058464
14 H H7	0.2227144	2.1268062	-2.4722793
15 H H10	-2.3930742	-1.2817497	-2.7895526
16 C C10	4.9143846	2.9692703	-0.3332953
17 H H11	4.5344106	3.8436800	-0.8652759
18 H H14	5.9699149	2.8446241	-0.6074915
19 C C12	3.4027906	3.4954232	1.7271696
20 H H15	2.9363627	4.2861218	1.1280701
21 H H18	3.4772296	3.8782160	2.7517105
22 N N3	2.5369424	2.3192087	1.7215030
23 H H20	2.9203006	1.4691364	1.3284096
24 C C13	1.2067155	2.3544009	1.9901580
25 N N4	0.6109505	1.1232290	1.7699492
26 H H22	1.2548396	0.3613405	1.5797141
27 C C14	-0.7331750	0.7225280	1.7506543
28 C C15	-3.3546714	-0.3089651	1.5817556
29 C C16	-1.8288593	1.5927093	1.6175975
30 C C17	-0.9686276	-0.6575333	1.7958613
31 C C18	-2.2638136	-1.1643464	1.7001179
32 C C19	-3.1155194	1.0670046	1.5420799
33 H H21	-1.6699138	2.6600289	1.5790835
34 H H23	-0.1285243	-1.3372930	1.8897131
35 H H26	-4.3634555	-0.6988767	1.5185011
36 S S2	0.4404338	3.7350223	2.5568843
37 C C9	4.8032256	3.1640599	1.1907223
38 H H5	5.2007974	2.2820671	1.7151565
39 H H66	5.4672919	3.9953370	1.4584577
40 C C8	-2.3348816	1.4323499	-2.9566642
41 C C11	-0.5287562	-3.1927444	-2.1923754
42 C C20	-2.4486148	-2.6540574	1.7596442
43 C C21	-4.2949114	1.9896479	1.3633098
44 F F1	-1.5855148	-3.2933792	0.9172092
45 F F2	-3.6909519	-3.0390037	1.4192127
46 F F3	-2.1937480	-3.1488662	2.9941791
47 F F4	-5.2867990	1.6844871	2.2341956
48 F F5	-4.8239995	1.8788063	0.1239271
49 F F6	-3.9711423	3.2821442	1.5505404
50 F F7	-1.9478724	2.4963754	-3.6880106
51 F F8	-2.8730393	1.9085369	-1.8120448
52 F F9	-3.3238961	0.8070089	-3.6323087
53 F F10	-1.7988703	-3.5416596	-1.9232477
54 F F11	-0.1879272	-3.7820470	-3.3600940
55 F F12	0.2611471	-3.7628518	-1.2373203
56 O O1	3.4367224	-0.7462457	0.7948371
57 C C22	3.2789749	-1.9494030	0.9874045
58 O O2	2.0981603	-2.3565783	1.4442692
59 C C23	4.3678470	-2.9558988	0.6627870
60 H H1	5.3107962	-2.5327712	1.0237134
61 C C25	1.7615096	-3.7600728	1.7091266
62 H H2	1.8528809	-3.8888231	2.7924874
63 C C24	4.1149410	-4.3742363	1.1861986
64 C C26	2.6466391	-4.7344629	0.9547784
65 H H9	4.4431817	-2.9637701	-0.4338844
66 H H12	0.7120346	-3.8367938	1.4267382

67 H H16	4.7842542	-5.0791288	0.6833204
68 H H17	4.3433540	-4.4264428	2.2584168
69 H H19	2.4193356	-5.7464532	1.3082089
70 H H24	2.4038772	-4.7036553	-0.1143083

Activated-TU plus VL in DCM

Job type: Single point.
 Method: RB3LYP
 Basis set: 6-31G**
 Number of shells: 258
 Number of basis functions: 818
 Multiplicity: 1

Solvation: dichloromethane [SM8]
 Free Energy of Solvation : -77.8518861 kJ/mol
 SCF total energy: -3369.3245007 hartrees

SPARTAN '14 Properties Program: (Win/64b)
 Use of molecular symmetry disabled

Release 1.1.8

		Cartesian Coordinates (Angstroms)		
Atom		X	Y	Z
1 C C1		0.6186602	3.4506147	-0.4942311
2 S S1		-0.1839783	4.1767400	0.8241190
3 N N1		1.9063132	3.7081440	-0.8145935
4 H H4		2.3364448	3.0985513	-1.5079477
5 N N2		0.0531547	2.5251892	-1.3346437
6 H H3		0.7188179	2.0849533	-1.9741357
7 C C2		-1.1547538	1.8052874	-1.2340656
8 C C4		-3.4580090	0.1851075	-1.1642309
9 C C3		-1.1316466	0.5028274	-1.7487208
10 C C6		-2.3542935	2.3143430	-0.7172609

11 C C5	-3.4821723	1.4924413	-0.6759791
12 C C7	-2.2707223	-0.2955969	-1.7112994
13 H H6	-0.2138590	0.1114105	-2.1743285
14 H H7	-2.4085778	3.3304717	-0.3544325
15 H H10	-4.3392201	-0.4410508	-1.1138825
16 C C10	2.8027843	4.6914441	-0.2147555
17 H H11	2.2071707	5.3416025	0.4302030
18 H H14	3.1967392	5.3095899	-1.0312663
19 C C12	3.6869285	3.6006471	1.9812784
20 H H15	3.4926792	4.4774002	2.6093305
21 H H18	4.5555740	3.0769033	2.3864867
22 N N3	2.5249512	2.7335360	2.1290191
23 H H20	1.6271786	3.2234830	2.1204578
24 C C13	2.5094968	1.3974966	1.9057752
25 N N4	1.2256902	0.8893739	1.9753434
26 H H22	0.5039979	1.5998622	2.0720812
27 C C14	0.6984366	-0.4058478	1.8631176
28 C C15	-0.5781053	-2.9147839	1.6314277
29 C C16	1.4548726	-1.5782301	1.7537946
30 C C17	-0.7080836	-0.5063312	1.8791934
31 C C18	-1.3281747	-1.7434602	1.7746406
32 C C19	0.8068657	-2.8102748	1.6216030
33 H H21	2.5337814	-1.5241645	1.7735517
34 H H23	-1.3157391	0.3883894	1.9709278
35 H H26	-1.0674423	-3.8761542	1.5331906
36 S S2	3.9137885	0.5130018	1.5863986
37 C C9	3.9823780	4.0499365	0.5409167
38 H H5	4.3622406	3.1976526	-0.0342216
39 H H66	4.7977458	4.7836087	0.5904183
40 C C8	-4.7350832	2.0133800	-0.0202682
41 C C11	-2.1500066	-1.7036538	-2.2285185
42 C C20	-2.8297569	-1.8589628	1.8102446
43 C C21	1.6636565	-4.0277290	1.4065496
44 F F1	-3.4379221	-0.6675959	1.9789275
45 F F2	-3.2341444	-2.6701329	2.8116355
46 F F3	-3.3103570	-2.3975544	0.6612719
47 F F4	2.2021271	-4.0279014	0.1506788
48 F F5	0.9720086	-5.1765982	1.5310462
49 F F6	2.7028943	-4.0758489	2.2624221
50 F F7	-4.7381778	1.7499162	1.3069433
51 F F8	-5.8465881	1.4468122	-0.5385132
52 F F9	-4.8560965	3.3509353	-0.1561754
53 F F10	-3.3293734	-2.3455705	-2.2770265
54 F F11	-1.6167016	-1.7291299	-3.4757367
55 F F12	-1.3143128	-2.4466695	-1.4544742
56 C C27	3.2831624	-2.6893528	-2.7877261
57 C C26	4.2042838	-1.8989580	-1.8562757
58 C C23	1.8607816	-2.1796104	-2.6467576
59 H H1	1.4433504	-2.4372747	-1.6707839
60 O O3	1.7549042	-0.7255085	-2.7677807
61 C C24	4.1439872	-0.4106729	-2.2166165
62 H H2	4.5853662	0.2219220	-1.4415431
63 C C25	2.7476791	0.1196308	-2.4682591
64 O O4	2.4921707	1.3173809	-2.4670203
65 H H19	4.7032344	-0.2167170	-3.1438153

66 H H24	1.1890437	-2.5577159	-3.4195913
67 H H25	3.8858802	-2.0439632	-0.8171413
68 H H27	5.2374791	-2.2545185	-1.9257839
69 H H29	3.6188117	-2.5973989	-3.8292343
70 H H30	3.2857759	-3.7555044	-2.5347410

3-S vacuum

Job type: Single point.

Method: RB3LYP

Basis set: 6-31G**

Number of shells: 328

Number of basis functions: 1062

Multiplicity: 1

SCF total energy: -4648.8994977 hartrees

Atom	Cartesian Coordinates (Angstroms)		
	X	Y	Z
1 C C2	2.7640909	1.5991396	-1.8183489
2 S S1	2.7485580	3.1262167	-1.0447103
3 N N1	3.9056042	0.9614619	-2.1515710
4 H H5	3.8171067	0.0156768	-2.5219318
5 N N2	1.6401143	0.8812915	-2.1324001
6 H H6	1.7976801	-0.1118807	-2.3241979
7 C C3	0.3013170	1.2854719	-2.3201684
8 C C4	-2.3985949	1.8898648	-2.8274305
9 C C5	-0.6568049	0.2633989	-2.3905650
10 C C6	-0.0979427	2.6145578	-2.5214042

11 C C7	-1.4411826	2.8999161	-2.7585829
12 C C8	-1.9912618	0.5700573	-2.6483517
13 H H7	-0.3550712	-0.7708386	-2.2578626
14 H H8	0.6245689	3.4167849	-2.4885809
15 H H10	-3.4400894	2.1260593	-3.0079652
16 C C10	5.2607492	1.4663694	-1.9949113
17 H H11	5.2004357	2.3893175	-1.4161725
18 H H14	5.6613762	1.7333310	-2.9831061
19 C C12	5.2614840	1.0846459	2.2224675
20 H H15	5.6552614	1.8030174	2.9553352
21 H H18	5.2238331	0.1128850	2.7169096
22 N N3	3.8972486	1.4512082	1.8763081
23 H H20	3.7898009	2.2354648	1.2335711
24 C C13	2.7688079	0.8382435	2.2910562
25 N N4	1.6323822	1.4610792	1.8454412
26 H H22	1.7761138	2.1258750	1.0805754
27 C C14	0.2952149	1.3955875	2.2898815
28 C C15	-2.4076716	1.4772893	3.0662460
29 C C16	-0.1001634	0.8644173	3.5247431
30 C C17	-0.6697046	1.9795466	1.4542447
31 C C18	-2.0048731	2.0203529	1.8476473
32 C C19	-1.4452920	0.9000425	3.8901120
33 H H21	0.6266397	0.4189908	4.1874706
34 H H23	-0.3707644	2.4090036	0.5031227
35 H H26	-3.4498786	1.4932500	3.3590253
36 S S2	2.7872540	-0.5873993	3.2373224
37 C C9	6.1953142	0.4363981	-1.3527427
38 H H66	6.1888855	-0.4701462	-1.9683179
39 C C11	-1.8674470	4.3253073	-3.0057754
40 C C20	-3.0179504	-0.5330077	-2.6738316
41 C C21	-3.0397027	2.5973303	0.9165316
42 C C22	-1.8526707	0.3468162	5.2322748
43 F F1	-3.5124705	1.6644908	0.0579004
44 F F2	-2.5334476	3.6035368	0.1693208
45 F F3	-4.1002269	3.0852263	1.5924522
46 F F4	-1.7965399	1.2987129	6.1932143
47 F F5	-1.0460150	-0.6600559	5.6273026
48 F F6	-3.1163949	-0.1241728	5.2138338
49 F F7	-3.0493461	4.5979143	-2.4148542
50 F F8	-2.0241180	4.5658245	-4.3285172
51 F F9	-0.9633317	5.2130042	-2.5444791
52 F F10	-4.0540158	-0.2298086	-3.4835079
53 F F11	-2.4869431	-1.6987577	-3.1065017
54 F F12	-3.5312931	-0.7659805	-1.4445504
55 H H2	7.2278878	0.8305944	-1.4034350
56 N N5	5.8050047	0.0710587	0.0077225
57 C C1	5.3031898	-2.3644845	-0.2073505
58 H H12	5.7187878	-3.3500893	0.0462233
59 N N6	3.9444816	-2.2719799	0.3039059
60 H H13	3.8481195	-2.1103761	1.3062523
61 C C23	2.8079859	-2.3397588	-0.4200681
62 N N7	1.6771503	-2.2902165	0.3516485
63 H H16	1.8200060	-1.9728928	1.3139804

64 C	C24	0.3476586	-2.6736662	0.0707355
65 C	C25	-2.3355466	-3.4584339	-0.2512243
66 C	C26	-0.0128164	-3.5441791	-0.9645950
67 C	C27	-0.6411242	-2.2147546	0.9557636
68 C	C28	-1.9660771	-2.6107041	0.7933034
69 C	C29	-1.3494205	-3.9144412	-1.1196988
70 H	H17	0.7365180	-3.9304652	-1.6412965
71 H	H19	-0.3679088	-1.5593844	1.7769814
72 H	H24	-3.3673969	-3.7561716	-0.3826470
73 S	S3	2.8039171	-2.4388198	-2.1286046
74 C	C30	-3.0225496	-2.0715427	1.7241143
75 C	C31	-1.6964523	-4.8350935	-2.2620423
76 F	F13	-3.4712995	-0.8605647	1.3225534
77 F	F14	-2.5472708	-1.9197359	2.9816806
78 F	F15	-4.0938615	-2.8882522	1.7904528
79 F	F16	-3.0010486	-5.1748762	-2.2628214
80 F	F17	-0.9777024	-5.9799826	-2.2020364
81 F	F18	-1.4211603	-4.2665814	-3.4560206
82 H	H25	5.2463778	-2.3130804	-1.2958413
83 C	C32	6.2160596	-1.2822943	0.3756853
84 H	H9	7.2550846	-1.5046887	0.0680968
85 H	H27	6.2005151	-1.3631277	1.4678909
86 C	C33	6.1849094	1.0733869	1.0009875
87 H	H1	6.1513581	2.0605765	0.5272716
88 H	H33	7.2243617	0.9408821	1.3561298

3-O in vacuum

Job type: Single point.
Method: RB3LYP

Basis set: 6-31G**
 Number of shells: 325
 Number of basis functions: 1050
 Multiplicity: 1

SCF total energy: -3680.0562311 hartrees

Atom	Cartesian Coordinates (Angstroms)		
	X	Y	Z

1 C C2	-2.8191769	-1.4459723	1.9139004
2 N N1	-3.6837952	-2.1887576	1.1546312
3 H H5	-3.3678728	-2.4709288	0.2289292
4 N N2	-1.4891232	-1.8088459	1.7201386
5 H H6	-1.3189721	-2.6347168	1.1595125
6 C C3	-0.3503171	-1.2225691	2.2807562
7 C C4	2.0493416	-0.0862620	3.2500984
8 C C5	0.8981553	-1.7653417	1.9324703
9 C C6	-0.3880865	-0.1375919	3.1660749
10 C C7	0.8077738	0.4196093	3.6248772
11 C C8	2.0751581	-1.2017548	2.4093743
12 H H7	0.9430649	-2.6421333	1.2986243
13 H H8	-1.3417631	0.2382549	3.5069152
14 H H10	2.9675834	0.3607257	3.6085817
15 C C10	-5.1238809	-2.0446915	1.3102056
16 H H11	-5.2929735	-1.5776720	2.2812241
17 H H14	-5.5727231	-3.0456003	1.3512156
18 C C12	-5.0034839	2.3026999	1.1529605
19 H H15	-5.4141876	2.8510338	2.0107121
20 H H18	-5.1638710	2.9229996	0.2706689
21 N N3	-3.5626078	2.1839246	1.3289192
22 H H20	-3.2552643	1.5176639	2.0341170
23 C C13	-2.7075480	2.4561068	0.2947921
24 N N4	-1.3695918	2.4426817	0.6796475
25 H H22	-1.1808298	2.3856234	1.6730415
26 C C14	-0.2468647	2.6493585	-0.1300865
27 C C15	2.1192833	2.9594669	-1.6481134
28 C C16	-0.3128602	2.8382121	-1.5177245
29 C C17	1.0130801	2.6622575	0.4901460
30 C C18	2.1732307	2.8145091	-0.2614320
31 C C19	0.8652741	2.9766362	-2.2530596
32 H H21	-1.2765799	2.9083830	-1.9996946
33 H H23	1.0841378	2.5679058	1.5672095
34 H H26	3.0246836	3.0602805	-2.2319525
35 C C9	-5.8077784	-1.2796189	0.1690927
36 H H66	-5.6264522	-1.8391170	-0.7522703
37 C C11	0.7017128	1.6374689	4.4992039
38 C C20	3.3929018	-1.7795935	1.9584829
39 C C21	3.4964690	2.7661755	0.4591288
40 C C22	0.7286742	3.0647507	-3.7472031
41 F F1	3.7883104	1.5106720	0.8698746
42 F F2	3.4783570	3.5405298	1.5685110

43 F F3	4.5149046	3.1852040	-0.3163414
44 F F4	-0.1933562	3.9728184	-4.1229471
45 F F5	0.3041618	1.8626279	-4.2545865
46 F F6	1.8827161	3.3625955	-4.3652558
47 F F7	1.8768286	2.0056603	5.0334528
48 F F8	-0.1816778	1.4698727	5.5017425
49 F F9	0.2438951	2.7088936	3.7708375
50 F F10	4.3632951	-1.5832125	2.8730045
51 F F11	3.3009087	-3.1113309	1.7348205
52 F F12	3.8139235	-1.2205603	0.8016466
53 H H2	-6.9020118	-1.3084428	0.3481495
54 N N5	-5.3242305	0.0878459	-0.0254913
55 C C1	-4.9805141	-0.0027500	-2.5265910
56 H H12	-5.3647749	0.4806546	-3.4344254
57 N N6	-3.5335039	0.1592466	-2.4979075
58 H H13	-3.2003848	1.0939897	-2.2725799
59 C C23	-2.7136441	-0.8963614	-2.2004932
60 N N7	-1.3641707	-0.5966324	-2.3694008
61 H H16	-1.1452379	0.2902806	-2.8060456
62 C C24	-0.2640861	-1.4257205	-2.1210107
63 C C25	2.0520690	-2.9541406	-1.5814598
64 C C26	-0.3764353	-2.7544235	-1.6878494
65 C C27	1.0182818	-0.8888841	-2.3224627
66 C C28	2.1546345	-1.6471006	-2.0585374
67 C C29	0.7775112	-3.4885720	-1.4103902
68 H H17	-1.3550647	-3.2014190	-1.5908365
69 H H19	1.1224511	0.1238865	-2.6959210
70 H H24	2.9366803	-3.5290567	-1.3426359
71 C C30	3.5015073	-1.0197297	-2.3155295
72 C C31	0.5869700	-4.8638394	-0.8351782
73 F F13	3.6211695	0.1677586	-1.6766378
74 F F14	3.6770187	-0.7671852	-3.6332394
75 F F15	4.5179740	-1.8043213	-1.9139979
76 F F16	1.7373992	-5.5432264	-0.7016732
77 F F17	-0.2571635	-5.6138996	-1.5707294
78 F F18	0.0265986	-4.7772247	0.4138683
79 H H25	-5.1789666	-1.0708885	-2.6262966
80 C C32	-5.7176408	0.6174481	-1.3316820
81 H H9	-6.8064816	0.5068331	-1.5117772
82 H H27	-5.5059394	1.6890298	-1.3407401
83 C C33	-5.7494111	0.9645796	1.0671436
84 H H1	-5.5772680	0.4377785	2.0084475
85 H H33	-6.8350147	1.1876081	1.0191279
86 O O1	-3.1162551	-2.0179532	-1.8707390
87 O O2	-3.1675940	-0.5810756	2.7256196
88 O O3	-3.0718983	2.7369773	-0.8530852

MANUSCRIPT – IV

Published in ACS Macro Letters

**Triclocarban: commercial antibacterial and highly effective H-bond donating
catalyst for ring-opening polymerization**

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ABSTRACT

The antibacterial compound, triclocarban (TCC), is shown to be a highly effective H-bond donating catalyst for ring-opening polymerization (ROP) when applied with an H-bond accepting base cocatalyst. These ROPs exhibit the characteristics of ‘living’ polymerizations. TCC is shown to possess the high activity characteristic of urea (vs thiourea) H-bond donors. The urea class of H-bond donors is shown to remain highly active in H-bonding solvents, a trait that is not displayed by the corresponding thiourea H-bond donors. Two H-bond donating ureas that are electronically similar to TCC are evaluated for their efficacy in ROP, and a mechanism of action is proposed. This ‘off-the-shelf’ H-bond donor is among the most active and most controlled organocatalysts for the ROP of lactones.

EXPERIMENTAL SECTION

General Considerations. All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise. Triclocarban (TCC), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from TCI. Tris[2-(dimethylamino)ethyl]amine (Me₆TREN) and 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) were purchased from Alfa Aesar. Benzyl alcohol and 1,2-dichlorobenzene were distilled under high vacuum from calcium hydride. THF was dried on an Innovative Technology solvent purification system. DMF was dried over 4 Å molecular sieves for 48 h prior to use. 1-pyrenebutanol was purchased from Sigma Aldrich. δ -valerolactone (VL), ϵ -caprolactone (CL) and β -butyrolactone (BL) were distilled from calcium hydride under high vacuum. L-Lactide (L-LA) was purchased from Acros Organics and recrystallized from dry toluene. Benzene-*d*₆ and chloroform-*d* were purchased from Cambridge Isotope Laboratories and distilled from calcium hydride. Acetone-*d*₆ was purchased from Cambridge Isotope Laboratories and stored over 4 Å molecular sieves for 48 h prior to use. Experiments were conducted using pre-dried glassware in an MBRAUN or INERT stainless steel glovebox or using a Schlenk line under nitrogen atmosphere. NMR experiments were conducted on a Bruker Avance III 300 MHz or 400 MHz spectrometer or a Varian 500 MHz spectrometer. Gel Permeation Chromatography (GPC) was performed at 40 °C using HPLC grade dichloromethane eluent on an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm $\times$ 300 mm (5 μ m, pore sizes: 10³, 10⁴, 50 Å). M_n and M_w/M_n were determined versus polystyrene standards (500 g/mol-3150 kg/mol, Polymer Laboratories). Mass spectrometry was performed using a Thermo Scientific (San

Jose, CA, USA) LTQ Orbitrap XL mass spectrometer affixed with either an atmospheric-pressure chemical ionization (APCI) or electrospray ionization (ESI) interface, positive ions were produced and introduced into the S2 instrument. Tune conditions for infusion experiments (5 $\mu\text{L}/\text{min}$ flow, sample concentration 5 $\mu\text{g}/\text{mL}$ in 50/50 v/v water/methanol) were as follows: ionspray voltage, 5 kV; capillary temperature, 275 $^{\circ}\text{C}$; sheath gas (N_2 , arbitrary units), 8; auxiliary gas (N_2 , arbitrary units), 2; capillary voltage, 35 V; and tube lens, 90 V. Prior to analysis, the instrument was calibrated for positive ions using Pierce LTQ ESI positive ion calibration solution (lot #PC197784). Ion trap experiments used N_2 as a collision gas with normalized collision energies (NCE) between 10-25 eV for multistage fragmentation. High-energy collision (HCD) experiments were performed with He as the collision gas with a NCE of 25 eV.

Example ring-opening polymerization of VL. To a 7 mL vial, TCC (15.7 mg, 0.05 mmol), VL (100 mg, 1.0 mmol) and benzene- d_6 (250 μL) were added. The contents were stirred until the solution became homogenous. To a second 7 mL vial, benzyl alcohol (4.3 mg, 0.04 mmol), MTBD (7.6 mg, 0.05 mmol) and benzene- d_6 (250 μL) were added. The contents in the second vial were transferred to the first vial via Pasteur pipette, and the contents were agitated to mix. The reaction solution was then transferred to an NMR tube, and the progress of the reaction monitored by ^1H NMR. The reaction was quenched by the addition of benzoic acid (6.1 mg, 0.05 mmol). Polymer isolated by precipitation with hexanes contains residual TCC that can be removed by repeated precipitation or washing with methanol. PVL was removed of volatiles under high vacuum prior to characterization. Yield 89%, M_n (GPC)= 5,400, M_w/M_n = 1.09, M_n (NMR) = 2,700.

Example post-polymerization transesterification. To a 7 mL vial, TCC (15.7 mg, 0.05 mmol), VL (100 mg, 1.0 mmol) and benzene- d_6 (250 μ L) were added. The contents were stirred until the solution became homogenous. To a second 7 mL vial, benzyl alcohol (1.1 mg, 0.01 mmol), MTBD (7.6 mg, 0.05 mmol) and benzene- d_6 (250 μ L) were added. The contents in the second vial were transferred to the first vial via Pasteur pipette, and the contents were agitated to mix. Three 50 μ L aliquots from the reaction were quenched at 20 min, 45 min and 60 min using benzoic acid (6.2 mg, 0.05 mmol). Polymer in each aliquot was then isolated by precipitation with hexanes. PVL was removed of volatiles under high vacuum prior to characterization by GPC: M_n = 22,300, 23,900, 23,900, M_w/M_n = 1.02, 1.03, 1.03 respectively.

Example chain extension experiment. To a 7 mL vial, TCC (15.7 mg, 0.05 mmol), VL (100 mg, 1.0 mmol) and benzene- d_6 (250 μ L) were added. The contents were agitated until the solution became homogenous. To a second 7 mL vial, 1-pyrenebutanol (5.5 mg, 0.02 mmol), MTBD (7.6 mg, 0.05 mmol) and benzene- d_6 (250 μ L) were added. The contents of the second vial were transferred to the first vial via Pasteur pipette, and the contents were agitated to mixed. After 13 min, a 100 μ L aliquot from the reaction was quenched using benzoic acid (6.2 mg, 0.05 mmol), and VL (100 mg, 1.0 mmol) was added to the reaction vial. A second 100 μ L aliquot from the reaction vial was quenched in 27 min using benzoic acid (6.2 mg, 0.05 mmol). Conversion of VL in the two aliquots were then determined by ^1H NMR, followed by the isolation of PVL and characterization by GPC.

Example ring-opening polymerization of L-Lactide. A first 7 mL vial was charged with TCC (15.8 mg, 0.05 mmol), Me₆TREN (13.4 μ L, 0.05 mmol) and benzyl alcohol (1.0 μ L, 0.01 mmol). A second 7 mL vial was charged with L-LA (144.1 mg, 1 mmol) and acetone-

d_6 (1000 μ L). The contents of the second vial were added to the first vial, and the resulting mixture was vigorously shaken until homogenous. The reaction mixture was transferred to an NMR tube via pipette, and the reaction progress was monitored by ^1H NMR. The reaction was quenched with benzoic acid (0.1 mmol). The reaction mixture was removed of volatiles under reduced pressure, dissolved in minimal dichloromethane, and the polylactide (PLA) was precipitated with the addition of hexanes. The supernatant was decanted, and the precipitate was subjected to high vacuum to remove volatiles.

Example binding experiment. For the titration of **1-O** with CL, stock solutions of **1-O** and CL were prepared in benzene- d_6 . Into several NMR tubes, varying amounts of each solution were added to each tube along with neat benzene- d_6 such that the final volume of each sample was 0.4 mL. The final concentrations were $[\textbf{1-O}] = 0.005\text{M}$ and $0.25\text{M} < [\textbf{CL}] < 2.25\text{ M}$. ^1H -NMR spectra (referenced to residual benzene-H) were acquired for each tube at 300 K and the chemical shift of the *ortho*-protons of **1-O** was noted. Binding constants were determined by the curve fitting method,³³⁻³⁵ and these values match those determined from the Lineweaver-Burke method.^{36,37} Binding curves are shown below (Figures 4.15).

Example synthesis of 1-(4-chlorophenyl)-3-phenylurea (mono-CC). A dried Schlenk flask was charged with 4-chlorophenylisocyanate (598.2 mg, 3.90 mmol) and ~10 mL dried DCM. Next, aniline (0.36 mL, 3.95 mmol) was added via syringe. Immediately upon addition of aniline, a white precipitate formed. The reaction mixture was filtered and rinsed 3 times with cold DCM to provide a pure white powder (846.1 mg, 3.43 mmol, 88.1 % yield). Characterization matches literature;³⁸ NMR spectra below; ^{13}C NMR (CD_3OD , 100 MHz): $\delta = 155.2, 140.3, 139.5, 129.5, 129.4, 128.5, 124.0, 121.6, 120.5$.

Example synthesis of 1-(3,4-dichlorophenyl)-3-phenylurea (di-CC). A dried Schlenk flask was charged with 3,4-dichlorophenylisocyanate (731.8 mg, 3.89 mmol) and ~10 mL dried DCM. Next, aniline (0.36 mL, 3.95 mmol) was added via syringe. Immediately upon addition of aniline a white precipitate formed. The reaction mixture was filtered and rinsed 3 times with cold DCM to provide a pure white powder (1.01 g, 3.59 mmol, 92.7 % yield). Characterization matches literature;³⁹ NMR spectra below; ¹³C NMR (CD₃OD, 100 MHz): δ = 154.87, 140.81, 140.16, 133.32, 131.48, 129.89, 126.14, 124.12, 121.39, 120.53, 119.60.

RESULTS AND DISCUSSION

H-bond mediated ring-opening polymerization (ROP) has attracted interest due to the highly controlled nature of these transformations.¹⁻⁴ These mild, highly functional group tolerant catalysts, especially the bimolecular systems consisting of a (thio)urea H-bond donor plus H-bond accepting base, have facilitated the construction of precise polymer architectures, multiblocks, and well-defined systems.^{3,5-8} Targeted efforts by several groups toward rate-accelerated, H-bond mediated ROP seek to address a critical shortcoming of the field: low activity.⁹⁻¹² For example, our group has recently disclosed the utility of urea H-bond donors for rate accelerated ROP;¹³ thiourea H-bond donors have been used in organocatalytic ROP for more than a decade, but are less active.³ Another barrier to the wide implementation of this chemistry is the paucity of commercially available H-bond donors. Most (thio)urea catalysts are synthesized via a “click” reaction of an appropriate amine and iso(thio)cyanate.^{3,14,15} While simple, this stands in contrast to the wide array of readily available H-bond accepting base cocatalysts and adds a synthetic step prior to conducting polymerization chemistry. Certainly, the ready availability of chemical reagents and catalysts facilitates the wide implementation of chemical transformations. In this context, the antibacterial compound, triclocarban (TCC, Figure 4.1), recently banned as a hand soap additive by the FDA, captured our attention.¹⁶ It is an electron-deficient biaryl urea, similar to the slate of urea and multiurea H-bond donating catalysts that we recently showed to be highly active for ROP.¹³ While TCC has attracted considerable scientific interest as an antibacterial compound, possible bioaccumulate, and possible environmental toxin, we believe that this readily available compound has not previously been employed as a catalyst.¹⁷⁻¹⁹ The efficacy of TCC/amidine base

combinations for the ROP of lactone monomers was evaluated, Table 4.1. All reactions were conducted in C₆D₆ and conversion monitored by ¹H NMR. The guanidine base, MTBD, exhibited faster rates than the imine base, DBU, and it was used for further experimentation. The ROP of δ -valerolactone (VL) from benzyl alcohol is highly controlled, exhibiting the characteristics of a living polymerization: linear evolution of M_n vs conversion, first order consumption of monomer and M_n predictable from $[M]_0/[I]_0$, (Figures 4.2 and 4.3). This behavior is typical among organocatalysts for ROP. Initiation of a VL (1.0 mmol) ROP catalyzed by TCC/MTBD (0.05 mmol each) from 1-pyrenebutanol (0.02 mmol) and subsequent addition of a second monomer portion (1.0 mmol) exhibits overlapping UV and refractive index traces in the gel permeation chromatogram (GPC) of the resulting polymer (Figure 4.4), suggesting end group fidelity and a chain end that is susceptible to chain-extension. The TCC/MTBD (5 mol %) cocatalysts are also effective for the ROP of ϵ -caprolactone (CL), producing a similarly well-behaved ROP. The ROP rates exhibited by TCC/MTBD represent a significant advance over those exhibited by **1-S**/MTBD, yet the reactions remain highly controlled. By comparison, for $[M]_0/[I]_0 = 50$ from benzyl alcohol in C₆D₆, the **1-S**/MTBD-catalyzed ROPs of VL and CL achieve full conversion in 110 min and 45 h, respectively (c.f. Table 4.1).¹³ Entry 2 (Table 4.1) was attempted on a 200 mg scale, producing nearly identical polyvalerolactone (24 min, 90% conv, $M_n = 18100$, $M_w/M_n = 1.04$), which suggests that scale-up is feasible.

We have embarked on a research program aimed at mitigating the low activity of H-bond mediated transformations without sacrificing the precise control typical of these catalysts. In this vein, electron deficient aryl ureas have proved to be particularly efficacious; our lab

previously disclosed the rapid rates exhibited by mono-, bis-, and tris-urea H-bond donors for the ROP of lactones.¹³ In general, urea H-bond donors are more active for ROP than their corresponding thioureas. This trend extends to the urea anions which, besides being remarkably active and controlled catalysts for ROP, are much more active than the corresponding thiourea anions.^{10,12} The uncharged H-bond donor **3-O**, in combination with MTBD (0.017 mmol each), effects the ROP of VL (1.0 mmol) from benzyl alcohol (0.02 mmol) in C₆D₆ in 3 min.¹³ While the analogous reaction with TCC/MTBD (0.05 mmol each) achieves full conversion in a slower 14 min, the commercial availability of the TCC catalyst is expected to be a boon to the wider application of this and similar systems. Additionally, the TCC/MTBD cocatalysts exhibit high selectivity for monomer (vs polymer). When a fully converted PVL reaction solution remains unquenched, the M_n and M_w/M_n are minimally altered over an hour: 20 min, $M_n = 22300$, $M_w/M_n = 1.02$; 60 min, $M_n = 23900$, $M_w/M_n = 1.03$ (c.f. Table 4.1, entry 2), which may constitute an advantage versus other highly active systems for ROP.^{10,12-13}

Urea H-bond donors remain active in polar, H-bond accepting solvent. A long-standing limitation of H-bond mediated catalysis is the often narrow window of nonpolar solvents in which these catalysts are operable.^{20,21} We had previously observed that the urea H-bond donor **3-O** remains active in THF and hypothesized that TCC would exhibit similar behavior, and a solvent screen was conducted for the TCC/MTBD catalyzed ROP of VL (Table 4.5). In DMF, the reaction time is extremely attenuated, and the reaction does not achieve >83% conversion. In THF, the ROP remains highly active (90% conv in 30 min), but M_w/M_n (=1.23) broadens. The result in acetone is surprising in that the reaction rate does not slow versus C₆D₆, and the M_w/M_n remains narrow, Table 4.2. The ROP rates for

all thiourea H-bond donors drop considerably versus their rates in C₆D₆,¹³ Table 4.3. The TCC/MTBD catalyzed ROP of VL in acetone-*d*₆ remains controlled and exhibits the characteristics of a “living” polymerization (Figures 4.7 and 4.8). The polymer samples resulting from the initiation of a VL (1.0 mmol, 2 M) ROP from 1-pyrenebutanol (0.02 mmol) catalyzed by TCC/MTBD (0.05 mmol each) and subsequent chain extension show overlapping UV and RI traces in the GPC (Figure 4.9), which suggests end-group fidelity and that there is no initiation from the enol form of acetone-*d*₆.

When TCC and Me₆TREN cocatalysts (5 mol % each) are applied for the ROP of L-lactide (1.0 mmol) from benzyl alcohol (0.01 mmol) in acetone-*d*₆, the ROP reaction exhibits “living” behavior (Figures 4.12 and 4.13). In contrast to the ROP of VL, CL, or carbonate monomers, mild base cocatalysts are required for the ROP of lactide.^{21–24} The poly(lactide) was isolated and analyzed by selectively decoupled ¹H NMR, revealing the polylactide (PLA) to be ~ 90% isotactic (Figure 4.17), which suggests minor epimerization. The MALDITOF analysis of the same PLA sample shows the presence of ± 72 *m/z* repeat units, indicating that postpolymerization transesterification is occurring to a minor extent. This latter observation is in contrast to **2-S** H-bond donating catalyst, which effects the ROP of LA in the virtual absence of postpolymerization transesterification.²³

H-bond donating biaryl ureas were synthesized and applied in catalytic ROP to determine the origin of the enhanced rates of TCC (vs **1-O**). These catalysts, here dubbed monoclocarban (mono-CC)^{25,26} and diclocarban (di-CC)²⁶ in Figure 4.1, were applied to the ROP of VL in C₆D₆; we believe these molecules have not previously been used as catalysts. The TCC/MTBD (5 mol % each) cocatalyzed ROP of VL (1.0 mmol, 2 M) from benzyl alcohol (0.01 mmol) in C₆D₆ reaches 91% conversion in 22 min (Table 4.1). The

H-bond donors di-CC or mono-CC plus MTBD (5 mol % each) exhibit similar activity to TCC, but di-CC is the most active of the three H-bond donors (88% conversion in 15 min for di-CC and 37 min for mono-CC). The ROP of VL catalyzed by di-CC/MTBD exhibits the characteristics of a “living” polymerization (Figure 4.18). The similar rates exhibited by TCC and di-CC toward ROP may suggest that the additional chlorine atom in TCC (vs di-CC) is not essential for catalysis or that the additional electron withdrawing effects from the “extra” chlorine atom in TCC versus di-CC are inhibitory to catalysis. The latter possibility recalls similar effects that have been observed for extremely electron deficient thioureas,^{27,28} and these observations suggest that the augmented activity of the biaryl TCC (vs **1-O**) can be approximated by functionalization at a single aryl ring. Certainly, the increased efficacy of TCC (vs **1-O**) for ROP calls into question the primacy of the bis(trifluoromethyl)aryl group, at least for urea H-bond donors.²⁷ While the commercial availability of TCC may be a boon to the application of H-bond mediated transformations in polymer synthesis laboratories, we expect that the development of advanced catalyst architectures will benefit from the more synthetically modular catalyst scaffold of di-CC. The enhanced efficacy of TCC and all urea H-bond donors in C₆D₆ could be attributed to the stronger binding of ureas vs thioureas to monomer.²⁰ The limited solubility of TCC and **n-O** in nonpolar solvent in the absence of base cocatalyst limits the extent to which we can quantitatively probe this hypothesis by measuring binding constants to monomer. For example, TCC is insoluble in benzene in the absence of H-bond acceptor, and binding constants for this compound could not be measured. However, the binding constants of **1-O** and **1-S** to CL were independently measured in C₆D₆ and are consistent with the long-held hypothesis: for **1-O**, $K_{eq} = 41 \pm 1$ (300 K) and for **1-S**, $K_{eq} = 28 \pm 1$ (300 K).²⁴

However, a binding constant rationale cannot be used to explain the ROP activity observed in acetone. As expected, when the **1-O**/monomer binding study is repeated in acetone-*d*₆, there is no observed change in chemical shift of **1-O** up to ~ 1000 equiv of monomer, which suggests very weak ($K_{eq} \sim 1$) or no binding in acetone-*d*₆. While we have previously observed **1-S** to exhibit a marked effect on a ROP reaction in the near absence of binding to monomer,^{29,30} these questions collectively reinforce a recently proposed mechanism.¹² While this study was ongoing, “hyperactive” urea anions for ROP, generated by the action of alkoxides upon aryl and alkyl ureas, were disclosed; these systems are incredibly active yet controlled, exhibiting rates that rival traditional metal-based systems.¹² The proposed mechanism of action whereby an active urea anion catalyst is generated by the deprotonation of a urea by alkoxide is distinct from traditional H-bond mediated ROP by neutral catalysts, and we sought to investigate the feasibility of this mechanism for TCC/imine bases. As opposed to the quantitative deprotonation of TCC by potassium methoxide, one could envisage an equilibrium established between urea plus base and the corresponding salt, eq 1. ¹H NMR spectra in acetone-*d*₆ of TCC and TCC plus MTBD or DBU (5 mM each species) show an upfield shift of the TCC resonances upon treatment with base that would be associated with the formation of an anionic character at the urea (Figure 4.21). Repeating this experiment with highly basic BEMP (Figure 4.1, BEMP-H⁺ $pK_a^{MeCN} = 27.6$)³¹ establishes a pattern of increased upfield shift with increasing pK_a (MTBD-H⁺ $pK_a^{MeCN} = 25.4$; DBU-H⁺ $pK_a^{MeCN} = 24.3$).³² Repeating the TCC/BEMP ¹H NMR experiment with a deficient amount of BEMP (2.5 mM) shows only one set of resonances for TCC, suggesting that the equilibrium in eq 1 is dynamic on the ¹H NMR time scale.

The ^1H NMR experiments suggest that TCC/BEMP would be the most imidate-like species (i.e., eq 1 further to the right) and presumably the most active TCC/organic base catalyst pair yet examined herein. Indeed, the BEMP/TCC (0.05 mmol) catalyzed ROP of VL (1 M, 1 mmol) from benzyl alcohol (0.01 mmol) in benzene achieves full conversion in 3 min (Table 4.3). Higher reaction concentrations can be employed, but the reaction becomes difficult to monitor, fully converting within seconds at 2 M VL. The same ROP of VL fails to reach full conversion in THF or acetone- d_6 within 30 min. In C_6D_6 , the ROP is highly controlled and exhibits the characteristics of a “living” polymerization (Figure 4.10), and the $[\text{M}]_0/[\text{I}]_0$ series (Table 4.3) is notable for the high predictability of M_n even when considered against other organocatalytic systems. Further, M_w/M_n broadens slowly postpolymerization (Table 4.3, entry 2: 3 min, $M_n = 22400$, $M_w/M_n = 1.04$; 6 min, $M_n = 24100$, $M_w/M_n = 1.07$; 15 min, $M_n = 24700$, $M_w/M_n = 1.15$; 90% conv. for all aliquots). TCC/BEMP is ineffective for the ROP of β -butyrolactone, consistent with other urea and thiourea H-bond donors.^{13,20}

We propose that the TCC/base cocatalyzed ROP of ester monomers proceeds through a mixed mechanism where the identity of the dominate catalyst largely depends on the pK_a of the cocatalysts. The ^1H NMR spectrum of TCC plus Me_6TREN shows very slight downfield shift of the TCC resonances and broadening of the N–H resonances which could be attributed to H-bonding; there is no evidence to suggest the formation of imidate character at the urea for this cocatalyst pair (c.f. TCC/BEMP, Figure 4.21). Accordingly, we propose that TCC/base cocatalyzed ROP is capable of effecting ROP through a classic dual H-bond mechanism mediated by neutral catalysts or an imidate mediated mechanism, the primary determination of which mode is dominate rests with the pK_a of the base. In

the case of TCC plus Me₆TREN, we proposed a primarily neutral catalyst mechanism versus BEMP, which may proceed primarily through an imidate mechanism, Scheme 4.1. Certainly, the rate of the TCC/BEMP ROP recalls that of the alkoxide-generated urea anions.¹² This mechanistic proposal is an extension of the recent work with “hyperactive” urea anion catalysts for ROP, taking into account weakly basic cocatalysts.¹² For the present system, it is unclear if the conjugate acid of the base serves as a H-bond donor or primarily serves to deprotonate the urea. The complicated and sensitive interplay of cocatalyst/reagent interactions requires more study to be thoroughly understood.

CONCLUSION

The antibacterial TCC has been shown to be a highly-effective cocatalyst for ring-opening polymerization. The commercially available H-bond donor, when applied with an H-bond accepting base cocatalyst, is among the most active organic catalysts for the ROP of esters, yet it exhibits the characteristics of a ‘living’ polymerization, producing well-defined polymers. The activity of this catalyst can be approximated by other mono- and di-chloro biaryl urea H-bond donor(s), which adds synthetic flexibility for the generation of future H-bond donating ureas. We suspect that the ROP of lactone monomers is just one application that can offer new roles to old reagents, in this case the antibacterial compound now banned in hand soap, TCC.

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entry	mon.	$[\text{M}]_0/[\text{I}]_0$	time (min)	conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
1 ^d	VL	100	81	90	18 900	1.06
2		100	22	91	19 900	1.05
3		50	14	90	8 500	1.08
4		200	46	90	35 900	1.09
5		500	125	90	72 900	1.02
6	CL	100	132	90	21 200	1.06

Table 4.1. MTBD and TCC Catalyzed ROP of VL and CL. Reaction conditions: VL or CL (1.0 mmol, 1 equiv, 2M), benzyl alcohol, C_6D_6 . a) monomer conversion was monitored via ^1H NMR. b) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) vs polystyrene standards. d) DBU (5 mol%, 0.05 mmol) cocatalyst was employed (no MTBD).

entry	TU or U (mol%)	time (min)	conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
1	TCC (5%)	13	89	10 000	1.09
2	1-S (5%)	1200	89	9 500	1.21
3	1-O (5%)	60	91	11 900	1.08
4	2-S (2.5%)	1020	90	11 400	1.28
5	2-O (2.5%)	20	90	10 800	1.15
6	3-S (1.7%)	7440	89	12 100	1.16
7	3-O (1.7%)	20	89	10 300	1.13

Table 4.2. Urea or Thiourea Plus MTBD Cocatalyzed ROP of VL in Acetone. Reaction conditions: VL (1.0 mmol, 1 equiv, 2M), benzyl alcohol (2 mol%), and MTBD (same mol% as U/TU), acetone-d₆. a) monomer conversion was monitored via ¹H NMR. b) M_n and M_w/M_n were determined by GPC (CH₂Cl₂) vs polystyrene standards.

entry	mon.	[M] ₀ /[I] ₀	time (min)	conv. ^a (%)	<i>M</i> _n ^b (g/mol)	<i>M</i> _w / <i>M</i> _n ^b
1	VL	50	1	87	11 900	1.04
2		100	3	90	22 400	1.04
3		200	6	90	47 900	1.06
4		500	10	90	108 800	1.05
5 ^d	CL	100	6	90	16 500	1.04

Table 4.3. Triclocarban Plus BEMP Cocatalyzed ROP of VL and CL. Reaction

conditions: VL or CL (1.0 mmol, 1 equiv, 1M), benzyl alcohol, C₆D₆. a) monomer

conversion was monitored via ^1H NMR. b) M_n and M_w/M_n were determined by GPC

(CH₂Cl₂) vs polystyrene standards. d) CL (1.0 mmol, 1 equiv, 2M).

O=C1OCCCC1 + Oc1ccccc1CO
 $\xrightarrow[\text{C}_6\text{D}_6, \text{ r.t.}]{\text{urea and MTBD}}$
O=C1OCCCC1OCc2ccccc2

VL (1 equiv. (2M))

Entry	urea	[M] _o /[I] _o	time (min)	conv. (%) ^a	<i>M</i> _n ^b	<i>M</i> _w / <i>M</i> _n ^b
1	TCC	50	14	90	8500	1.08
2		100	22	91	19900	1.05
3		200	46	90	35900	1.0
4		500	125	90	72900	1.02
5	di-CC	50	15	88	6000	1.04
6		100	20	89	12000	1.04
7		200	78	94	25000	1.03
8		500	180	89	64000	1.06

Table 4.4. Chain Length Variation for the TCC or di-CC plus MTBD cocatalyzed ROP of

VL. a) Conversion determined by ¹H NMR. b) *M*_n and *M*_w were obtained by GPC.

Entry	Solvent	time (min)	conv. (%) ^a	M_n^b	M_w/M_n^b
1	benzene- <i>d</i> ₆	22	91	19,900	1.06
2	acetone- <i>d</i> ₆	22	89	19,400	1.11
3	chloroform- <i>d</i>	273	89	19,100	1.08
4	THF	30	89	14,700	1.23
5	DMF	600	83	9,000	1.41

Table 4.5. Solvent Screen of TCC/MTBD cocatalyzed ROP of VL. a) Conversion determined by ¹H NMR. b) M_n and M_w were obtained by GPC.

Entry	$[M]_0/[I]_0$	time (min)	conv. (%) ^a	M_n^b	M_w/M_n^b
1	50	13	88	7400	1.11
2	100	20	88	14100	1.10
3	200	32	89	22600	1.09
4	500	45	89	44700	1.08

Table 4.6. Chain Length Variation for the TCC/MTBD cocatalyzed ROP of VL in acetone-*d*₆. a) Conversion determined by ¹H NMR. b) M_n and M_w were obtained by GPC.

Scheme 4.1. Proposed mechanism for TCC/base cocatalyzed ROP.

Figure 4.1. Base and (thio)urea cocatalysts evaluated for ROP.

Figure 4.2. First order evolution of VL vs time for the TCC/MTBD catalyzed ring-opening polymerization of VL. Conditions: VL (2 M, 1 mmol), benzyl alcohol (1mol%, 0.01 mmol), TCC (5mol%, 0.05 mmol), MTBD (5 mol%, 0.05 mmol) in benzene- d_6 .

Figure 4.3. M_n (blue) and M_w/M_n (orange) vs conversion for the TCC/MTBD catalyzed ring-opening polymerization of VL. Conditions: VL (2 M, 1 mmol), benzyl alcohol (1mol%, 0.01 mmol), TCC (5mol%, 0.05 mmol), MTBD (5 mol%, 0.05 mmol) in benzene- d_6 .

Figure 4.4. GPC traces of the polymers resulting from the chain extension experiment of VL. Conditions: VL (2 M, 1mmol), 1-pyrenebutanol (2mol%, 0.02mmol), TCC (5mol%, 0.05 mmol), MTBD (5 mol%, 0.05 mmol) in benzene- d_6 , and subsequent chain extension by the addition of VL (1mmol).

Figure 4.5. First order evolution of CL vs time for the TCC/MTBD catalyzed ring-opening polymerization of CL. Conditions: CL (2 M, 1 mmol), benzyl alcohol (1mol%, 0.01mmol), TCC (5mol%, 0.04 mmol), MTBD (5 mol%, 0.04 mmol) in benzene- d_6 .

Figure 4.6. M_n (blue) and M_w/M_n (orange) catalyzed ring-opening polymerization of CL. Conditions: CL (2 M, 1mmol), benzyl alcohol (1mol%, 0.01 mmol), TCC (5mol%, 0.04 mmol), MTBD (5 mol%, 0.04 mmol) in benzene- d_6 .

Figure 4.7. Approach to equilibrium evolution of [VL] vs time for the TCC/MTBD catalyzed ring-opening polymerization of VL. Conditions: VL (2.1 M, 2mmol, 1 equiv.), benzyl alcohol (1mol%, 0.02 mmol), TCC (5mol%, 0.1 mmol), MTBD (5 mol%, 0.1 mmol) in acetone- d_6 . $[VL]_{eq} = 0.22$ M

Figure 4.8. M_n (blue) and M_w/M_n (orange) vs conversion for the TCC/MTBD catalyzed ring-opening polymerization of VL. Conditions: VL (2.1 M, 2 mmol, 1 equiv.), benzyl alcohol (1 mol. %, 0.02 mmol), TCC (5 mol. %, 0.1 mmol), MTBD (5 mol. %, 0.1 mmol) in acetone- d_6 .

Figure 4.9. GPC traces of the polymers resulting from the chain extension of PVL in acetone. Conditions: VL (2 M, 1 mmol), 1-pyrenebutanol (2 mol%, 0.02mmol), TCC (5 mol%, 0.05 mmol), MTBD (5 mol%, 0.05 mmol) in acetone- d_6 , and subsequent chain extension by the addition of VL (1 mmol).

Figure 4.10. M_n (blue) and M_w/M_n (orange) vs conversion for the TCC/BEMP catalyzed ring-opening polymerization of VL. Conditions: VL (1 M, 1 mmol), benzyl alcohol (1 mol%, 0.01 mmol), TCC (5 mol%, 0.05 mmol), BEMP (5 mol%, 0.05 mmol) in benzene- d_6 .

Figure 4.11. GPC traces of the polymers resulting from the chain extension experiment of VL. Conditions: VL (1 M, 1 mmol), 1-pyrenebutanol (2 mol%, 0.02mmol), TCC (5 mol%, 0.05 mmol), BEMP (5 mol%, 0.05 mmol) in benzene- d_6 , and subsequent chain extension by the addition of VL (1 mmol).

Figure 4.12. First order evolution of [L-LA] vs time for the TCC/Me₆TREN catalyzed ring-opening polymerization. Conditions: L-LA (1 M, 1 mmol), benzyl alcohol (1 mol %, 0.01 mmol), TCC (5 mol %, 0.05 mmol), Me₆TREN (5 mol %, 0.05 mmol) in acetone-*d*₆.

Figure 4.13. M_n (blue) and M_w/M_n (orange) vs conversion for the TCC/Me₆TREN catalyzed ring-opening polymerization of L-LA. Conditions: L-LA (1 M, 1 mmol), benzyl alcohol (1 mol. %, 0.01 mmol), TCC (5 mol. %, 0.05 mmol), Me₆TREN (5 mol. %, 0.05 mmol) in acetone-*d*₆.

Figure 4.14. MALDI-TOF of the PLLA resulting from TCC/Me₆TREN cocatalyzed ROP of L-lactide. The major pattern (blue line) is due to whole repeat units $m/z = (\text{Na}^+ + \text{benzyl alcohol} + n \cdot \text{LA})$ while the minor pattern (red line) is due to half repeat units generated by post-polymerization transesterification $m/z = (\text{Na}^+ + \text{benzyl alcohol} + (n+1/2) \cdot \text{LA})$. All m/z bear a benzyl alcohol initiator.

Figure 4.15. Titration binding curve for the CL/**1-O** binding in benzene- d_6 . Chemical shift of the *o*-phenyl protons vs [CL]; solid line is the fit from the binding equation.

Figure 4.16. Titration binding curve for the CL/**1-S** binding in benzene- d_6 . Chemical shift of the *o*-phenyl protons vs [CL]; solid line is the fit from the binding equation.

Figure 4.17. Methine region of the methyl-decoupled ^1H NMR spectrum of PLLA obtained via TCC/ Me_6TREN cocatalyzed ROP of L-LA (500 MHz, 25 $^\circ\text{C}$).

Figure 4.18. (upper) First order evolution of $[VL]$ vs time for the di-CC/MTBD catalyzed ROP of VL. (lower) The ROP displays a linear evolution of M_n (blue) vs conversion and narrow M_w/M_n (orange). Conditions: VL (2 M, 1.0 mmol), benzyl alcohol (2.0 mol%, 0.02mmol), di-CC (5.0 mol%, 0.05 mmol), MTBD (5 mol%, 0.05 mmol) in benzene- d_6 .

Figure 4.19. (upper) ^1H NMR (CD_3OD , 400 MHz) spectrum of mono-CC. (lower) ^{13}C NMR (CD_3OD , 100 MHz) spectrum of mono-CC.

Figure 4.20. (upper) ^1H NMR (CD₃OD, 400 MHz) spectrum of di-CC. (lower) ^{13}C NMR (CD₃OD, 100 MHz) spectrum of di-CC.

Figure 4.21. Downfield portion of the ^1H NMR spectra of TCC plus base ($[\text{TCC}] = [\text{base}] = 5 \text{ mM}$) in acetone- d_6 .

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**H-bonding Organocatalysts for the Living, Solvent-free Ring-Opening
Polymerization of Lactones: Towards an All-Lactones, All-Conditions Approach**

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ABSTRACT

The developing urea class of H-bond donors facilitates the solvent-free ROP of lactones at ambient and elevated temperatures, displaying enhanced rates and control versus other known organocatalysts for ROP under solvent-free conditions. The ROPs retain the characteristics of living polymerizations despite solidifying prior to full conversion, and copolymers can be accessed in a variety of architectures. One-pot block copolymerizations of lactide and valerolactone, which had previously been inaccessible in solution phase organocatalytic ROP, can be achieved under these reaction conditions, and one-pot triblock copolymers are also synthesized. For the ROP of lactide, however, thioureas remain the more effective H-bond donating class. For all (thio)urea catalysts under solvent-free conditions and in solution, the more active catalysts are generally more controlled. A rationale for these observations is proposed. The trichlorocarbene (TCC) plus base systems are particularly attractive in the context of solvent-free ROP due to their commercial availability which could facilitate the adoption of these catalysts.

INTRODUCTION

Conducting ring-opening polymerization under solvent-free conditions is an appealing strategy from several perspectives. Such situations include industrial polymerizations,¹ ‘green’ processes² and other applications where use and disposal of solvent is of concern as well as the ROP of macrolactones and other monomers with high equilibrium monomer concentration $[M]_{eq}$ where neat conditions are suggested by reaction thermodynamics.^{3–5} The H-bonding class of organocatalysts – consisting of urea or thiourea plus base – stand out among the controlled methods for ROP in their precise control for polymerization over transesterification,^{6,7} but they have not been widely applied to solvent-free ROP. These catalysts have facilitated the construction of highly tailored polymers including highly functionalized monomer feeds.^{8–13} Thiourea/base systems are widely viewed as operating through an H-bond mediated pathway whereby thiourea H-bond activates monomer and base cocatalyst activates the initiating/propagating chain end, Scheme 5.1.^{12–14} Nascent urea/base systems are believed to effect their highly active ROP via an imidate mediated mechanism that is more analogous to that of the guanidine organocatalyst 1,5,7-triazabicyclodec-5-ene (TBD) than their heavy chalcogen counterparts, Scheme 5.1.^{15–17} Among the larger pantheon of organic catalysts, TBD, which can operate via an H-bond mediated mechanism,^{18–20} has become popular for solvent-free ROP of strained and macrolactones,^{20–22} and certainly, metal-containing²³ and enzymatic catalysts^{24–26} are often used under solvent free conditions. The amidine organocatalyst, 1,8-diazabicycloundec-7-ene (DBU), has also been applied for the ROP of lactide in eutectic monomer blends.²⁷ Regardless, (thio)urea systems have not been applied in solvent free conditions because, ironically, highly polar lactone monomers are poor

solvents for the H-bond ROP mediated by thioureas.^{13,28} However, several urea/base cocatalysts have been recently shown to be effective in polar solvent,^{16,17} which led us to speculate that these systems may remain active under solvent-free conditions. The trichlorocarbene (TCC)^{17,29} plus base systems seemed particularly attractive in this context due to their commercial availability which could facilitate wider adoption by the polymer community.

EXPERIMENTAL SECTION

General Considerations. All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise. Ethylene Brassylate was purchased from Sigma Aldrich. Benzyl alcohol was distilled from calcium hydride under high vacuum. 1-pyrenebutanol was purchased from Sigma Aldrich. δ -valerolactone (VL) and ϵ -caprolactone (CL) were distilled from calcium hydride under high vacuum. L-Lactide (L-LA) was purchased from Acros Organics and recrystallized from dry toluene. 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) were purchased from Tokyo Chemical Industry Co. LTD. and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) from Acros Organics. Benzene- d_6 and chloroform- d were purchased from Cambridge Isotope Laboratories and distilled from calcium hydride. Experiments were conducted using pre-dried glassware in an MBRAUN or INERT stainless steel glovebox under N_2 atmosphere. NMR experiments were conducted on a Bruker Avance III 300 MHz or 400 MHz spectrometer, and 1H decoupled spectra were acquired on a Varian 500 MHz spectrometer. Gel Permeation Chromatography (GPC) was performed at 40 °C using HPLC grade dichloromethane eluent on an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm $\times$ 300 mm (5 μ m, pore sizes: 10^3 , 10^4 , 50 Å). M_n and M_w/M_n were determined versus polystyrene standards (500 g/mol-3150 kg/mol, Polymer Laboratories). DSC experiments were conducted using a Shimadzu DSC-60A instrument, calibrated with an indium standard using aluminum pans under inert conditions.

Example solvent-free ROP. A 1 mL vial was charged with TCC (6.3 mg, 0.019 mmol), benzyl alcohol (0.86 mg, 0.008 mmol), VL (200 mg, 1.995 mmol), magnetic stir

bar and stirred until homogeneous. A second vial was charged with MTBD (3.06 mg, 0.019 mmol) and VL (200 mg, 1.99 mmol) and agitated to mix. The contents of the second vial were transferred to the first vial using a Pasteur pipette, and the solution was stirred. Reaction progress was monitored by taking aliquots of the reaction mixture – either ~1.5 μ L solution or a small amount of solid extracted via spatula – at different time intervals and quenched in a solution of benzoic acid in chloroform-d. Conversion was determined via ^1H NMR. The polymer was isolated by precipitating with hexanes, and the volatiles were removed under high vacuum before characterization via GPC.

Example solvent-free ROP with TBD. A 1 mL vial was charged with TBD (2.8 mg, 0.019 mmol), benzyl alcohol (0.86 mg, 0.008 mmol), VL (400 mg, 3.99 mmol), magnetic stir bar and stirred vigorously to mix. The TBD does not completely dissolve under these reaction conditions. Reaction progress was monitored by taking aliquots of the reaction mixture – either ~1.5 μ L solution or a small amount of solid extracted via spatula – at different time intervals and quenched in a solution of benzoic acid in chloroform-d. Conversion was determined via ^1H NMR. The polymer was isolated by precipitating with hexanes, and the volatiles were removed under high vacuum before characterization via GPC.

Example solution ROP of LA. A 7 mL vial was charged with **2-S** (10.7 mg, 0.0174 mmol), L-LA (100 mg, 0.694 mmol), benzyl alcohol (0.72 μ L, 0.00694 mmol) and toluene (0.25M, toluene 2.77mL). PMDTA (3.63 μ L, 0.0174 mmol) was loaded into a 2 mL vial equipped with septa cap. The vials were transferred from the glovebox to an oil bath adjusted to the specific temp. The contents of vial 1 were transferred into vial 2. Aliquots

were taken via syringe and quenched using a CH₂Cl₂ solution of benzoic acid and conversion was monitored by ¹H NMR.

Example one-pot copolymerization. A 7 mL vial was charged with TCC (6.3 mg, 0.019 mmol), benzyl alcohol (1.72 mg, 0.016 mmol), VL (400 mg, 3.99 mmol), magnetic stir bar and stirred until homogeneous. A second vial was charged with BEMP (5.48 mg, 0.019 mmol) and CL (455.8 mg, 3.99 mmol) and mixed well. The contents of the second vial was transferred to the first vial using a Pasteur pipette, and the mixture was left to stir. Reaction progress was monitored by taking aliquots of the reaction mixture – either ~1.5 μL solution or a small amount of solid extracted via spatula – at different time intervals and quenched in a solution of benzoic acid in chloroform-d. Conversion was determined via ¹H NMR. The polymer was isolated by precipitating with hexanes, and the volatiles were removed under high vacuum before characterization via GPC.

Example ROP of L-LA. A 7 mL vial was charged with **2-S** (17.1 mg, 0.028 mmol), benzyl alcohol (3 mg, 0.028 mmol), L-LA (400 mg, 2.77 mmol), stir bar, and the contents were heated to 100°C to melt the sample. A second vial was charged with PMDTA (4.80 mg, 0.028 mmol), and PMDTA was transferred via a 10 μL syringe to the first vial and the mixture was left to stir. The reaction was monitored by taking aliquots of the reaction mixture via spatula and quenching in a solution of benzoic acid in chloroform-d. Reaction progress was monitored via ¹H NMR. The polymer was then isolated by precipitating with methanol, and the volatiles were removed under high vacuum before characterization via GPC.

Determination of percent isotacticity. The ¹³C and ¹H decoupled NMR spectra of the isolated polymer were acquired on a Varian 500 MHz at 50°C. The samples for ¹³C and

^1H NMR were prepared as 10 % w/v and 1% w/v solutions, respectively, in CDCl_3 . The ^1H NMR spectrum of the polymer was obtained by selective decoupling by irradiating the methyl region, and tacticity was determined from the methine region according to published procedures, see manuscript for references.

Direct-from-monomer negative mold. A 7 ml polypropylene vial was charged with TCC (13.7 mg, 0.049 mmol), benzyl alcohol (15.6 mg, 0.049 mmol), VL (1000 mg, 10 mmol) and agitated to mixed. The top inside wall of a clean vial cap was charged with BEMP (13.7 mg, 0.049 mmol), which clings to the surface of the cap. The vial was capped with the BEMP containing cap and shaken vigorously to coat the inner wall of the vial during the course of the ROP (~30 sec). The reaction vessel was removed from the glove box. The PVL vial negative is easily freed from the reaction vial.

RESULTS AND DISCUSSION

ROP of Strained Lactones. The solvent-free TCC/base cocatalyzed ROP of δ -valerolactone (VL) from benzyl alcohol at room temperature exhibits the characteristics of a living polymerization. Initial studies were performed on VL (solvent-free, 3.99 mmol) using benzyl alcohol initiator (0.2 mol %), TCC H-bond donor and one of three base cocatalysts (DBU, MTBD or BEMP in Table 5.1). The TCC/base (0.02 mmol each) catalyst systems displayed the same rate trends in neat VL as in solution¹⁷: BEMP > MTBD > DBU, Table 5.1. Polymerizations were conducted in a glovebox, and aliquots were withdrawn, quenched in a CDCl₃ solution of benzoic acid and conversion monitored by ¹H NMR (see Experimental Section). Despite solidification of the reaction mixture during the ROP (~60% conversion), the TCC/MTBD cocatalyzed ROP of VL from benzyl alcohol displays the characteristics of a living polymerization: linear evolution of M_n vs conversion, narrow M_w/M_n , first order evolution of [monomer] (Figure 5.1) and M_n predictable from $[M]_0/[I]_0$ (Table 5.1). ¹H NMR analysis of the polyvalerolactone (PVL) reaction mixture of each system (at $[M]_0/[I]_0 = 100$) confirms the consumption of benzyl alcohol initiator suggesting good initiator efficiency. When the same polymerization is initiated from pyrenebutanol, the resulting PVL displays overlapping UV/vis and RI traces in the GPC chromatogram (Figure 5.2). The TCC/BEMP system displays the same living behavior, but it was too active to effectively monitor at 0.02 mmol catalysts (4 mmol VL), although reduced catalyst loadings remain active (>0.004 mmol, the lowest evaluated) and controlled, see Table 5.5 and Figures 5.3 and 5.2. The TCC/BEMP and TCC/MTBD systems were also applied for the ROP of ϵ -caprolactone (CL). The reaction rates and molecular weight dispersities are attenuated versus the ROP of VL, but both reactions

remain controlled and display living behavior (Figure 5.4 and Table 5.6). PVL and PCL samples can be freed of catalysts impurities by washing with methanol, but PVL samples containing residual catalysts showed no alteration of their materials properties up to 0.5 mol% catalysts loading (the highest loading tested).

Both cocatalysts are required for efficient ROP. Solutions of TCC plus benzyl alcohol (0.1 mol % each) in VL (1 equiv) were stored at room temperature and periodically monitored for 60 days and showed no conversion. Solutions of BEMP or MTBD (0.5 mol%) in VL (1 equiv) were less stable towards conversion at room temperature, reaching 7% and 17% conversion, respectively, after 21 days. Both VL solutions of base were more stable when stored at -10°C, the BEMP solution showing zero conversion to polymer after 20 days, see Figure 5.5. We presume that the observed conversions are due to initiation from base.³⁰ Despite being inert separately, the combined solutions can yield an ROP so rapid, that the combined solvent-free solutions (10 mmol VL, 0.049 mmol TCC/BEMP each, 0.020 mmol benzyl alcohol) can be used to make a negative mold of the reaction vessel in 30 sec (Figure 5.6) directly from monomer. Potential application can be envisaged.

Among H-bond mediated catalysts for ROP, urea/base cocatalysts stand out for the activity and control they exhibit in solvent-free ROP conditions. Among other organic catalysts that have been applied for neat ROP,^{31–33} TBD is of particular interest in the context of the present studies.^{21,22} Some reports of TBD-mediated solvent-free ROP are conducted in the melt or describe ROP to amorphous polymers,^{21,22} which would be expected to produce the narrow molecular weight distributions typical of solution processes. In our hands, TBD (Table 5.1, entry 7) exhibits similar rates as TCC/MTBD

for solvent-free ROP of VL but with broadened M_w/M_n versus the ROP with the urea/base cocatalysts. However, TCC/BEMP produces the narrowest M_w/M_n and is the most active examined under these conditions. When used alone, strong bases have also been shown to effect the ROP of lactones. For example, BEMP has been applied to the room temperature, solvent-free ROP of VL without an H-bond donating cocatalyst.³¹ The ROP appeared to be living in nature but sluggish, reaching full conversion to poly(valerolactone) (PVL) in days and displaying a broadened M_w/M_n .³¹ We believe the ability to conduct rapid and highly controlled ROP of lactones like VL and CL under solvent-free and non-melt conditions constitutes an advantage of the TCC/base cocatalysts over other (organo)catalyst systems.

The observation of highly active TCC/base cocatalyzed ROP under solvent-free conditions corroborates an imidate mechanism of action, Scheme 5.1. Several H-bond donors were evaluated for the solvent-free ROP of VL (Table 5.2), and these results suggest that urea H-bond donors are more effective than thiourea H-bond donors for the ROP of strained lactones. This observation is consistent with a cocatalyst binding argument for thiourea/base cocatalyzed ROP,^{28,34} as the cocatalyst interactions would be greatly attenuated in polar VL solvent whereas thiourea-VL binding should remain active in neat monomer. For the urea/base cocatalyzed ROP under an imidate mechanism, the efficacy of the catalysts would not be disturbed by the polar reaction environment. This is confirmed by NOESY NMR experiments of acetone- d_6 solutions of TCC/MTBD or TCC/BEMP which show intermolecular contact, indicating the formation of the imidate (Figure 5.7). NOESY experiments on **1-S**/MTBD and **1-S**/BEMP show no intermolecular communication in acetone- d_6 or C_6D_6 , which suggests that thioimidate formation is not a

prominent mechanism of action for these catalyst pairs. These experiments are corroborated by previous studies performed by our group that show strong H-bonding (no proton transfer) between cocatalyst pairs of thiourea and base,²⁸ but evidence of proton transfer is observed between urea and base.¹⁷ Previous studies have shown that 1:1 mole ratios of H-bond donor and base are optimal for ROP (in solution) no matter how many H-bond donating moieties are present in the donor molecule.^{28,35,36}

ROP of Macrolactones. The TCC/BEMP cocatalyzed ROP of macrolactones, ethylene brassylate and pentadecalactone, under solvent-free conditions proceeds at 80°C. The TCC/BEMP (0.06 mmol) cocatalyzed ROP of EB (2.95 mmol) at room temperature and solvent-free is exceedingly slow (16 h, 60% conversion), but the same ROP at 80°C proceeds in hours to full conversion, Table 5.3. The ROP reactions in Table 5.3 display moderate control of M_n by $[M]_0/[I]_0$ and broad $M_w/M_n \sim 1.5$; however, the M_n evolves linearly with conversion and M_w/M_n remains narrow early in the ROP (Figure 5.8). These observations are consistent with previous reports of the entropically-controlled ROP of macrolactones, which often require heating to favor the formation of polymer,^{22,24,25,37} although enzymatic catalysts do not require excessive heating.^{3,24,26} The results with TCC/BEMP stand in stark contrast to the ROP of EB (0.4 g, 1.47 mmol) mediated by **1-S**/BEMP (0.03 mmol each) from benzyl alcohol (0.03 mmol) which achieves only 25% conversion to polymer in 10 hours. When combined with the **1-S** vs TCC result for the ROP of VL (see ROP of Strained Lactones), these results suggest that ureas are generally more effective than thiourea H-bond donors for ROP.

H-bonding catalysts are effective and thermally stable at 80°C. The ROP of macrolactones are usually conducted at elevated temperatures so that the entropically

controlled enchainment favors the formation of polymer.^{22,37} Hence, the H-bond mediated, solvent-free ROP of macrolactones presents a distinct challenge over that of VL or CL because the H-bonding interactions of thiourea and urea mediated ROP weaken at high temperature.³⁸ Further, organic catalysts are susceptible to charring/decomposition at high temperature.³⁹ However, neither deactivation nor decomposition appear to be a concern for TCC/base cocatalyzed ROP at 80°C (Table 5.3). TCC/BEMP were also applied for the solvent-free ROP of PDL from benzyl alcohol (Table 5.3). Versus EB, the polymerization times (6-8 h) and M_w/M_n (> 2) are attenuated, which may be due to the elevated viscosity of the PDL and PPDL vs EB and PEB.

ROP of Lactide. Contrary to other lactones, thiourea catalysts are more active than their urea analogues in the solvent-free ROP of L-LA conducted at 100°C. L-LA and isotactic PLA are crystalline which requires elevated temperatures to melt the monomer ($T_m = 97^\circ\text{C}$) and, ostensibly, polymer ($T_m = 180^\circ\text{C}$, PLLA). Several H-bond donors with PMDTA cocatalyst (0.0277 mmol each, see Table 5.4) were evaluated for the solvent-free ROP of L-LA (0.40 g, 2.77 mmol) from benzyl alcohol (0.055 mmol) at 100°C. As opposed to the (thio)urea mediated ROP of VL or CL, weak base cocatalysts are optimal for the ROP of LA.^{13,40} Every thiourea H-bond donor is more active for the ROP of LA than its corresponding urea H-bond donor. Indeed, the only urea that stands out in the series is TCC, which is more active in the ROP than the other urea H-bond donors. A similar trend has been observed in solution where TCC is more active than **1-O**,¹⁷ and ureas with fewer electron withdrawing substituents have been observed to be more active.¹⁶

A screen of base cocatalysts with **2-S** showed PMDTA cocatalyst to exhibit a good combination of high rate and control (Table 5.7). The reaction solution solidifies during

the course of the polymerization, ~80% conversion, Figure 5.9, and the first order evolution of concentration of monomer exhibits deviation from linearity that may be associated with limited molecular mobility in the crystalline polymer. However, the other characteristics of a living polymerization persist: M_n predictable from $[M]_0/[I]_0$, linear evolution of M_n vs conversion, and narrow M_w/M_n (Figure 5.9). When initiated from pyrenebutanol, the **2-S**/PMDTA cocatalyzed ROP in solvent-free conditions produces PLA that exhibits overlapping UV and RI traces in the GPC (Figure 5.2), which suggests that the polymer chains are initiated from the fluorescent alcohol. Certainly, the results in Table 5.4 suggest that conducting the H-bond mediated ROP of LA in the polymer melt (i.e. $>180^\circ\text{C}$) is not necessary to retain the high level of control associated with a living organocatalytic ROP.

The solvent-free ROP of LA mediated by **2-S**/PMDTA remains active at elevated temperatures. Solution ROPs of LA (0.694 mmol, 0.25 M) from benzyl alcohol (0.0025 M) using **2-S**/PMDTA (0.0063 M each) were conducted in toluene. At 50°C , the ROP proceeds to 24% conversion in 125 min ($k_{\text{obs}} = 0.0021$, Figure 5.10), but at 80°C and above, the reaction proceeds to polymer very slowly (2% conversion at 60 min). Analogous solvent-free ROP remains active up to 180°C (the highest temperature examined), and the ROPs of macrolactones do not experience deactivation at elevated temperature (see ROP of Macrolactones). The low concentrations required to fully dissolve LA in toluene is not the source of the catalyst deactivation at high temperature. A solvent free ROP of LA (6.244 mmol) catalyzed by **2-S**/PMDTA at reduced catalyst loadings (0.006 mmol each) from benzyl alcohol (0.125 mmol) at 100°C achieves 90% conversion in 24 h. Further, the solution ROP in CDCl_3 (1 M LA; 0.025 M; 0.010 M benzyl alcohol) allows for higher reagent concentrations, but a ROP at 40°C in this solvent is not appreciably faster than the

low concentration toluene run discussed above ($k_{\text{CDCl}_3}/k_{\text{toluene}} = 2$). Even these reaction conditions experience reduced activity at elevated temperatures. These observations suggest greater synthetic flexibility in the solvent-free (versus solution) ROP of LA.

For the ROP of lactide, the effects of reaction conditions on polymer tacticity must also be considered. For each polymerization in Table 5.4, the percent isotacticity was determined from the isolated polymer by ^1H decoupled ^{13}C NMR using previously established tacticity-dependent chemical shifts (Experimental Section).^{13,41,42} A small temperature screen was conducted, and running the **2-S**/PMDTA (0.028 mmol each) cocatalyzed ROP of L-LA at or below $\sim 97^\circ\text{C}$ (the melting point of LA) results in drastically reduced polymerization rates, and reaction temperatures at or above 140°C erode stereochemistry. In the ROP of L-LA, the retention of stereochemistry is important due to the highly tacticity-dependent material properties of PLA.³⁹ The **2-S**/PMDTA cocatalyst system (Table 5.4, entry 1) is not only the most active catalyst of the systems examined, but it exhibits the highest isotacticity (0.94). This observation suggests that **2-S** is highly selective for chain extension vs non-productive reactions and begs for the further optimization of this platform, which will be the focus of future work. In a recent touchstone on the challenges of solvent-free ROP of LA,³⁹ it was noted that commercial samples of PLA are ideally >0.97 isotacticity. This suggests that **2-S**/PMDTA at 0.94 isotacticity is not a ready-made solution to the problem that is the solvent-free, organocatalytic ROP of LA; however, our results suggest that these H-bond mediated catalysts may be able to provide the answer upon further optimization. Indeed, in a comparable solution experiment (c.f. Table 5.4, entry 1), the **2-S**/PMDTA (0.05 mmol) cocatalyzed ROP of L-LA (1 mmol, 1 M) from benzyl alcohol (0.01 mmol) in CDCl_3 at room temperature yields highly isotactic

polymer (%iso = 0.97; T_m = 169°C). In addition to tacticity, the introduction of color to PLA samples from catalyst (or decomposition) impurities can be a concern.³⁹ The **2-S**/PMDTA cocatalyzed ROP (Table 5.4, entry 1) produces an off-white, yellow color at high conversion, but the discoloration is very minimal if freshly-distilled PMDTA is used. Future catalysts with enhanced thermal stability or augmented activity (i.e. lower catalyst loadings) may prevent discoloration, but the color is easily removed by washing the polymer with methanol. Last, the comparable TBD-catalyzed (0.014 mmol) ROP of L-LA (0.40 g, 2.78 mmol) from benzyl alcohol (0.028 mmol) was conducted under solvent-free conditions (at 100°C) resulting in 90% conversion to polymer in 4 h and yielding PLLA that exhibits lower isotacticity (%iso = 0.78) than the **2-S**/PMDTfA cocatalyzed reaction (TBD polymer: M_n = 19,900; M_w/M_n = 1.30). These results suggest that **2-S**, and indeed most thioureas, plus amine base cocatalysts are more effective than TBD for the solvent-free ROP of LA.

Unlike other monomers examined, thioureas (vs ureas) are superior catalysts – in terms of both activity and control – for the H-bond mediated ROP of lactide. We conducted a rate comparison for the **1-S** vs **1-O** (with PMDTA) mediated ROP of L-LA in acetone- d_6 , and the thiourea catalyst is the more active of the two: k_{1-S}/k_{1-O} (acetone- d_6) = 4.4. Contrary to LA, ureas are always more active and controlled than the corresponding thioureas for the ROP of VL and CL regardless of the reaction solvent.^{17,36} This suggests that the relative activity of urea vs thiourea is not dictated by solvent, and the various monomers seem to exhibit a preference for urea vs thiourea. Our group previously described the activity of thiourea/amine base cocatalysts in the ROP of LA as being related to the nature of cocatalyst binding (i.e. enthalpic vs solvophobic binding),³⁴ and

understanding the preference exhibited by LA for thioureas vs ureas may require a full study of the solution interactions at play during an ROP catalyzed by the various catalysts. We are unable to measure a urea/LA binding constant due to poor solubility in non-hydrogen bonding solvents.

Copolymerizations. The generation of copolymers is possible through a one-pot, solvent-free approach. In the one-pot ROP of VL (3.99 mmol) and CL (3.99 mmol) from benzyl alcohol (0.016 mmol) (solvent-free, room temperature), the TCC/MTBD (0.02 mmol) cocatalyst system fully converts VL to polymer in 10 min, but the homopolymer precipitates from CL solution prior to conversion of the slower opening monomer. The TCC/BEMP system, however, allows for the full conversion to PVL-co-PCL ($M_n = 94,000$; $M_w/M_n = 1.41$) in 5 h. The first order evolution of [monomer]s versus time suggests the formation of a gradient-block copolymer (Figure 5.11). The successful formation of block-copolymer with TCC/BEMP versus TCC/MTBD which does not produce copolymer suggests that the former cocatalysts are able to conduct ROP of the slower monomer on a time scale that is competitive with precipitation of the homo-PVL from CL solvent. Copolymerizations were also performed with VL/EB (3.99 mmol/3.99 mmol) and CL/EB (3.5 mmol/3.5 mmol) employing the TCC/BEMP (2 mol%) cocatalysts. In these ROPs, conducted entirely at room temperature and solvent free (see Experimental Section) VL and CL quickly achieve full conversion in 5 min and 6 min, respectively, and the EB blocks grow slowly over the next ~11 h to give PVL-co-PEB ($M_n = 27,000$; $M_w/M_n = 1.60$) and PCL-co-PEB ($M_n = 28,700$; $M_w/M_n = 1.48$). The relative kinetics (Figure 5.12) suggest the formation of block copolymers. This same approach was used to generate a one-pot triblock copolymer: VL (3.99 mmol), CL (3.99 mmol) and EB (3.99 mmol) were grown

from benzyl alcohol (0.1197 mmol) using TCC/BEMP (0.1197 mmol each). The conversion versus time of this ROP suggests a gradient-block polymer (see SI, the previous VL/CL copolymerization produced a gradient-copolymer), and ^1H and ^{13}C NMR of the isolated polymer (see Figure 5.13) indicate that all blocks are present ($M_n = 40,000$, $M_w/M_n = 1.53$).

A solvent-free approach to the copolymerization of LA and VL allows for the one-pot synthesis of block copolymers. In the one-pot synthesis of diblock copolymers of LA and VL in solution, the ROP has been observed to proceed to full conversion of LA when reaction progress halts, resulting in the incorporation of no comonomer.¹¹ To confirm this report, a copolymerization of LA (0.33 mmol, 0.66 M) and VL (0.99 mmol, 2 M) from benzyl alcohol using trimethyl-1,4,7-triazacyclononane (t-TACN, see Table 5.7)/TCC cocatalysts (0.0265 mmol each) was attempted in C_6D_6 .^{34,40} The LA achieved full conversion to polymer in 18 h, but the VL does not convert over the next 24 hours; the expected result. Under solvent-free conditions, however, the copolymerization under otherwise same conditions results in full conversion of both monomer portions in 3.5 h yielding a single peak in the GPC trace ($M_n = 27,600$; $M_w/M_n = 1.57$) and two phase transitions (DSC: $T_m = 52^\circ\text{C}$ and 148°C). First order evolution of [monomer]s vs time suggests the formation of a block copolymer (Figure 5.14). When the one-pot copolymerization of LA and CL is attempted, the LA achieves full conversion in 2 min, but the CL does not undergo any enchainment over the next 24 h. Typically, alkylamine base cocatalysts are not effective for the ROP of VL or CL, but these results suggest that solvent-free, reaction conditions may provide new opportunities in catalyst development as well as materials synthesis.

CONCLUSION

Thiourea and urea catalysts have been shown to be effective for the solvent-free ROP of lactones at ambient and elevated temperatures. The urea class of H-bond donors facilitates solvent-free ROP for most monomers (VL, CL and EB), the thioureas being exceedingly slow in the ROP of these highly polar lactones. Solvent polarity is not the primary determining factor, however, as thioureas (not ureas) are more effective for the ROP of LA in solvent and the monomer melt. The ROPs retain the characteristics of a living polymerization despite solidifying prior to full conversion, and copolymers can be accessed in a variety of combinations. For those seeking to employ organocatalysts of this class in polymer synthesis, we offer a succinct summation: 1) urea (vs thiourea) H-bond donors plus base are the most active and most controlled organocatalysts for ROP under any reaction conditions (lactide excluded); 2) TCC/BEMP is the most active, most controlled organocatalytic system but TCC/MTBD is almost as active and probably more readily available; 3) for the ROP of lactide, the bithiourea **2-S** plus PMDTA is the most active and controlled organic cocatalyst system that we are aware of. In catalyst development, the community has come a long way in terms of catalytic activity from **1-S** (PLA: 0.7/min; PVL: 0.2/min) to more active H-bond donors (PLA: 18.2/min (**2-S**); PVL: 63/min (TCC)), but catalyst productivity has so far been limited by catalyst deactivation at reduced loadings. Further, there is no ostensible cost – in terms of reaction control – for employing more active (thio)urea H-bond donors. For (thio)urea ROP catalysts under solvent-free conditions and in solution,^{35,36} more active catalysts are generally more controlled.

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Entry	Base	[M] ₀ /[I] ₀	Time (min)	Conv. ^a (%)	<i>M</i> _n ^b (g/mol)	<i>M</i> _w / <i>M</i> _n ^b
1	DBU	500	65	97	99,500	1.12
2	BEMP	500	3	95	108,000	1.04
3	MTBD	500	31	99	100,500	1.08
4		200	15	96	43,900	1.07
5		100	15	98	22,000	1.16
6		50	10	98	10,300	1.10
7 ^c	TBD	500	27	99	115,500	1.21

Table 5.1. TCC plus base cocatalyzed ROP of VL. Reaction conditions: VL (3.99 mmol, 1 equiv, neat), TCC and base (0.02 mmol, each). a) monomer conversion was monitored via ¹H NMR. b) *M*_n and *M*_w/*M*_n were determined by GPC (CH₂Cl₂) vs polystyrene standards. c) no TCC, only TBD (0.02 mmol).

Entry	Donor	Time (min)	Conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
1	1-S	1,200	94	71,500	1.29
2	1-O	440	96	97,800	1.17
3	2-S	1,420	96	82,300	1.17
4	2-O	30	97	101,000	1.13
5	3-S	1,900	99	85,700	1.19
6	3-O	6	98	94,500	1.07

Table 5.2. H-bond donor plus base cocatalyzed ROP of VL. Reaction conditions: VL (3.99 mmol, 1 equiv, solvent-free), benzyl alcohol (0.008 mmol) and (thio)urea/MTBD (0.02 mmol each). a) monomer conversion was monitored via ^1H NMR. b) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) vs polystyrene standards.

Entry	Mon.	[M] ₀ /[I] ₀	Time (min)	Conv. ^a (%)	M _n ^b (g/mol)	M _w /M _n ^b
1	EB	50	90	99	28,200	1.64
2		100	130	97	42,800	1.62
3		200	330	96	51,000	1.60
4	PDL	50	360	96	24,800	2.23
5		100	900	97	33,000	2.46

Table 5.3. TCC plus base cocatalyzed ROP of macrolactones. Reaction conditions: EB and PDL (2.95 and 1.66 mmol respectively, 1 equiv, solvent free), benzyl alcohol, TCC/BEMP (0.06 (for EB) and 0.033 (for PDL) mmol). a) monomer conversion was monitored via ¹H NMR. b) M_n and M_w/M_n were determined by GPC (CH₂Cl₂) vs polystyrene standards.

Entry	Base loading (mol%)	Time (min)	Conv. (%) ^a	M_n (g/mol) ^b	M_w/M_n ^b
1	0.1	60	95	100,500	1.21
2	0.2	10	99	103,200	1.12
3	0.4	8	99	114,500	1.06
4	0.5	3	96	108,400	1.04
5	0.6	2	98	113,200	1.23

Table 5.5. Solvent free ROP of VL with TCC/BEMP. a. Conversion determined by ¹H NMR. b. M_n and M_w were obtained by GPC.

Entry	Base	Base loading (mol%)	Time (min)	Conv. (%) ^a	M_n (g/mol) ^b	M_w/M_n ^b
1	BEMP	0.1	47	160	n/a	n/a
2		0.2	95	142	83,000	1.17
3		0.3	98	60	85,000	1.22
4		0.4	98	40	89,100	1.20
5		0.5	97	30	82,500	1.20
6	MTBD	0.1	9	450	n/a	n/a
7		0.3	40	240	n/a	n/a
8		0.5	98	300	92,000	1.28

Table 5.6. TCC plus MTBD or BEMP cocatalyzed ROP of CL. a. Conversion determined by ¹H NMR. b. M_n and M_w/M_n were obtained by GPC.

Entry	Base	Time (min)	Conv. (%) ^a	Isotacticity ^b	M_n^c	M_w/M_n^c
1	<i>t</i> -TACN	1	95	0.82	12,500	1.06
2	Me ₆ TREN	2	87	0.88	13,900	1.04
3	PMDTA	5	90	0.94	10,600	1.07
4	(+)-sparteine	10	87	0.89	12,600	1.16
5	DMAP	40	93	0.72	16,500	1.30
6	TMEDA	90	90	0.76	13,800	1.10
7	pyridine	24 h	3	-	-	-

Table 5.7. Base Screen in the **2-S** Mediated ROP of L-LA. a. Conversion determined by ¹H NMR. b. Isotacticity determined by selectively decoupled ¹H NMR at 50 °C. M_n and M_w/M_n were obtained by GPC.

Scheme 5.1. Mechanism for the urea or thiourea plus base cocatalyzed ROP.

Figure 5.1. (upper) First order evolution of [monomer] versus time and (lower) M_n and M_w/M_n versus conversion for the TCC/MTBD cocatalyzed ROP of VL. Conditions: VL (3.99 mmol), TCC (0.02 mmol), MTBD (0.02 mmol) and benzyl alcohol (0.008 mmol) at room temperature.

Figure 5.2. RI and UV GPC traces of the ROP initiated from pyrenebutanol for (top) PVL (TCC/BEMP) and (bottom) PLA (**2-S**/PMDTA).

Figure 5.3. (upper) First order evolution of [monomer] versus time; and (lower) M_n and M_w/M_n versus conversion for the TCC/BEMP cocatalyzed ROP of VL. Conditions: VL (3.99 mmol), TCC (0.019 mmol), BEMP (0.019 mmol) and benzyl alcohol (0.008 mmol) at room temperature.

Figure 5.4. (upper) First order evolution of [monomer] versus time and (lower) M_n and M_w/M_n versus conversion for the TCC/BEMP cocatalyzed ROP of CL. Conditions: CL (3.50 mmol), TCC (0.018 mmol), BEMP (0.018 mmol) and benzyl alcohol (0.007 mmol) at room temperature.

Figure 5.5. Percent conversion to polymer of VL solutions of MTBD, BEMP and TCC plus benzyl alcohol (0.5 mol%, 0.02 mmol for all catalysts) at (upper) -10°C and (lower) room temperature. Conversions were determined via aliquot by ^1H NMR (CDCl_3).

Figure 5.6. Solvent-free ROP allows for the direct-from-monomer creation of a negative mold in seconds. Above, the hollow, PVL negative mold is of a polypropylene reaction vial. Conditions: 10 mmol VL, 0.049 mmol TCC/BEMP (each), 0.020 mmol benzyl alcohol (see Experimental Section).

Figure 5.7. 400 MHz ^1H NOESY in acetone- d_6 of (upper) TCC/MTBD (0.05 mmol each), and (lower) TCC/BEMP (0.05 mmol each). **1-S**/MTBD show no cross peaks in acetone- d_6 or C_6D_6 at 0.05 mmol.

Figure 5.8. M_n and M_w/M_n vs conversion for the TCC/BEMP cocatalyzed ROP of EB.

Conditions: EB (2.95 mmol), TCC (0.059 mmol), BEMP (0.059 mmol) and benzyl alcohol (0.015 mmol) at 80°C.

Figure 5.9. (upper) First order evolution of [LA] vs time, and (lower) M_n and M_w/M_n vs conversion. Reaction conditions: L-LA (400 mg, 2.77 mmol), benzyl alcohol (1mol%, 0.028 mmol), **2-S** (1 mol%, 0.028 mmol), PMDTA (1 mol%, 0.028 mmol) at 100°C.

Figure 5.10. First order evolution of $[LA]$ vs time for the **2-S**/PMDTA (2.5 mol% each) cocatalyzed ROP from benzyl alcohol (1 mol%) in (upper) toluene at 50°C (0.25 M, 0.694 mmol), and (lower) CDCl₃ at 40°C (1 M, 0.694 mmol).

Figure 5.11. First order evolution of [VL] and [CL] vs time for the one-pot copolymerization catalyzed by TCC/BEMP. Conditions: VL (3.99 mmol), CL (3.99 mmol), TCC (0.02 mmol), BEMP (0.02 mmol) and benzyl alcohol (0.016 mmol)

Figure 5.12. First order evolution of [monomer] vs time for the copolymerization of: (upper) VL and EB. Conditions: VL (3.99 mmol), EB (3.99 mmol), TCC (0.079 mmol), BEMP (0.079 mmol) and benzyl alcohol (0.16 mmol). VL had reached full conversion by first interrogation. (middle) CL and EB. Conditions: CL (3.99 mmol), EB (3.99 mmol), TCC (0.070 mmol), BEMP (0.070 mmol) and benzyl alcohol (0.140 mmol). CL had reached full conversion by first interrogation. (lower) VL and LA. Conditions: VL (3.99 mmol), L-LA (1.33 mmol), TCC (0.133 mmol), t-TACN (0.133 mmol) and benzyl alcohol (0.0532mmol).

Figure 5.13. ^1H and ^{13}C NMR (400 MHz ^1H , CDCl_3) of the poly(VL-co-CL-co-EB). ^1H NMR suggests a mole ratio of the monomers in the polymer to be 1:1 (VL+CL:EB).

Figure 5.14. First order evolution of [monomer] vs time for the copolymerization of VL and L-LA. Conditions: VL (3.99 mmol), L-LA (1.33 mmol), TCC (0.133 mmol), t-TACN (0.133 mmol) and benzyl alcohol (0.053mmol).

Figure 5.15. Percentage conversion of EB vs time for the copolymerization of VL, CL and EB. Conditions: VL (3.99 mmol), CL (3.99mmol), EB (3.99 mmol), TCC (1 mol%, 0.119 mmol), BEMP (1 mol%, 0.119 mmol) and benzyl alcohol (1 mol%, 0.119 mmol). VL had reached full conversion by first interrogation (at 2 min) and CL by third interrogation (at 5 min).

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**UREA AND THIOUREA H-BOND DONATING CATALYSTS FOR RING-OPENING
POLYMERIZATION: MECHANISTIC INSIGHTS VIA (NON)LINEAR FREE
ENERGY RELATIONSHIPS**

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ABSTRACT

Hammett-style free energy studies of (thio)urea/MTBD mediated ROP of δ -valerolactone reveal the complicated interplay of reagents that give rise to catalysis through one of two mechanisms. The operative mechanism depends most greatly on the solvent, where polar solvents favor a (thio)imidate mechanism and non-polar solvents favor a classic H-bond mediated ROP. Data suggest that the transition state is only adequately modeled with ground state thiourea-monomer interactions in the H-bonding pathway, and elusive urea/reagent ground state binding interactions may be irrelevant and, hence, not worth pursuing. However, neither relationship is robust enough to be predictive in the absence of other data. Isotope effects suggest that the base/alcohol binding event is directly observable in the ROP kinetics. New opportunities for catalysis emerge, and a reason for the observed mechanism change is proposed.

INTRODUCTION

For more than a decade, the remarkable selectivity of thiourea plus base cocatalysts for monomer (vs polymer) in the ring-opening polymerization (ROP) of lactones has been applied to the formation of highly-adorned and precisely tailored macromolecules.^{1–3} In the last several years, this class of catalyst has received new attention from several research groups as efforts have been undertaken to increase the activity of these systems without sacrificing their high level of reaction control.^{4–9} One method of devising improved catalysts structures is through mechanistic investigations. Thiourea/base cocatalysts are believed to operate through H-bond activation of monomer/polymer chain end, and this model has been widely corroborated with ¹H NMR titration experiments.^{10–12} A newer model attributes the activity of a thiourea/base system to the nature of the binding between the cocatalysts.^{13–16} The nascent class of urea/base cocatalysts complicates the picture by introducing yet another mechanism.^{4–7} These urea/base cocatalysts have been proposed to form an imidate which functions as a discrete catalyst by dual H-bond activation of monomer and chain end; the epitome of this catalyst architecture is the ‘hyperactive’ urea imidates – formed by the treatment of urea with strong bases – which are incredibly active catalysts for ROP.⁴ However, the imidate formed by the reaction of urea and organic base seems to exist along a continuum with a classic H-bond mediated ROP pathway, Scheme 6.1,^{6,17} and developing a comprehensive mechanistic basis upon which new catalysts can be developed became a daunting goal for our group. Studying urea and thiourea catalysts can be difficult because of the complicated and sensitive interplay of interactions that give rise to catalysis. H-bonding catalysts are known to bind to monomer, base, each other and other species to a lesser extent (i.e. polymer).^{11,14,16} Additionally, ureas and thioureas are

susceptible to proton transfer to base cocatalyst which generates a new mechanism,^{4,5} and we now have the new ability to conduct ROP in polar solvent.^{6,17} ‘Simple’ structural modification of the H-bond donor catalyst modulates all of these interactions. Added to the difficulty in studying these systems is that ground state interactions (e.g. binding constants) are used to model catalytic interactions, which are only *presumed* to persist at the transition state. We believed that Hammett analysis would be uniquely suited to a big picture approach that is required to illuminate the many, dramatic changes that (thio)urea structure modification have upon ROP.

EXPERIMENTAL SECTION

General Considerations. All chemicals were purchased through Fisher Scientific and used as received unless stated otherwise. Benzene- d_6 and chloroform- d were purchased from Cambridge Isotope Laboratories, distilled from calcium hydride and stored under N_2 . Acetone- d_6 was purchased from Cambridge Isotope Laboratories, distilled from calcium sulfate and stored under N_2 . δ -valerolactone (VL) and benzyl alcohol were distilled under high vacuum from calcium hydride prior to use. Dry CH_2Cl_2 was obtained from an Innovative Technology solvent purification system. Aniline, and 3,5-dimethoxyphenyl isocyanate were purchased from Sigma Aldrich. Phenyl isothiocyanate and cyclohexyl amine, 4-nitrophenyl isocyanate, 3,5-bis(trifluoromethyl)phenyl isocyanate, 3,5-dichloromethylphenyl isocyanate were purchased from Acros Organics. 4-nitrophenyl isothiocyanate was purchased from Tokyo Chemical Industry. 4-chlorophenyl isothiocyanate, 4-fluorophenyl isothiocyanate, 4-methoxyphenyl isothiocyanate, 4-methylphenyl isothiocyanate, 4-chlorophenyl isocyanate, 4-fluorophenyl isocyanate, 4-methylphenyl isocyanate, 4-trifluoromethylphenyl isocyanate, 3,5-dimethyl isocyanate were purchased from Alfa Aesar. 4-(trifluoromethyl)phenyl isothiocyanate, 3,5-dichlorophenyl isothiocyanate, 3,5-dichlorophenyl isothiocyanate, 3,5-difluorophenyl isothiocyanate, 3,5-bis(trifluoromethyl)phenyl isothiocyanate, 3,5-dimethoxyphenyl isothiocyanate, 3,5-dimethylphenyl isothiocyanate were purchased from Oakwood Chemicals. All experiments were conducted in an MBRAUN or INERT stainless-steel glovebox or using a Schlenk line under nitrogen atmosphere with pre-dried (in an oven) glassware. NMR experiments were performed on a Bruker Avance III 300 or 400 MHz spectrometer. Urea and thiourea H-bond donors were prepared by established methods.¹²

Syntheses and characterization of ureas have been provided below. Gel Permeation Chromatography (GPC) was performed with an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm $\times$ 300 mm (5 μ m, pore sizes: 10³, 10⁴, 50 Å) using dichloromethane eluent (HPLC grade) at 30 °C with a flow rate of 1 mL/min. M_n and M_w/M_n were obtained against polystyrene standards (500 g/mol-3150 kg/mol, Polymer Laboratories). The GPC samples were prepared at 1 mg/mL by dissolving polymer (cleaned by washing with methanol) in dichloromethane.

Mass spectrometry experiments were performed using a Thermo Electron (San Jose, CA, USA) LTQ Orbitrap XL mass spectrometer affixed with electrospray ionization (ESI) interface in a positive ion mode. Collected mass spectra was averaged for at least 50 scans. Tune conditions for infusion experiments (10 μ L/min flow, sample concentration 5 μ g/mL in 50/50 v/v water/ methanol) were as follows: ion spray voltage, 5000 V; capillary temperature, 275°C; sheath gas (N₂, arbitrary units), 11; auxiliary gas (N₂, arbitrary units), 2; capillary voltage, 21 V; and tube lens, 90 V; multipole 00 offset, -4.25 V; lens 0 voltage, -5.00; multipole 1 offset, -8.50 V; Multipole RF Amplitude, 400 V; Ion trap's AGC target settings for Full MS was 3.0e4 and FT's 2.0e5 (with 3 and 2 averaged microscans, respectively). Prior to analysis, the instrument was calibrated for positive ions using Pierce LTQ ESI positive ion calibration solution (lot #PC197784).

An example of determining observed rate constant (k_{obs}) for ROP of VL. A 7 mL vial was charged with 4-nitrophenyl cyclohexylthiourea (13.9 mg, 0.049 mmol), VL (100 mg, 0.998 mmol) and benzene-*d*₆ (237 mg, 249.7 μ L) and agitated to make a homogeneous solution. Another 7 mL vial was charged with MTBD (7.65 mg, 0.049 mmol), benzyl alcohol (1.08 mg, 0.009 mmol) and benzene-*d*₆ (237 mg, 249.7 μ L) and shaken to mix. The

contents of the second vial were transferred to the other by a Pasteur pipette, shaken to mix, and transferred to an NMR tube. Reaction progress was monitored using ^1H NMR. Observed rate constants (k_{obs}) were extracted from a first order evolution of $[\text{VL}]$ versus time (min), where k_{obs} is:

$$\text{Rate} = -d[\text{VL}]/dt = k_{\text{obs}}[\text{VL}]$$

$$k_{\text{obs}} = k_{\text{p}}[\text{cats}][\text{alcohol}]$$

and

$$\ln([\text{VL}]_0/[\text{VL}]) = k_{\text{obs}} t$$

The (thio)urea plus base cocatalyzed ROP was previously shown to be first order in $[\text{thiourea} + \text{base}]_0$ as opposed to $[\text{thiourea}]_0[\text{base}]_0$.¹⁴ Observed rate constants in the benzene- d_6 Hammett Plots are the average of at least 2 runs, and k_{obs} are given in min^{-1} . A tabulation of errors is given below (Tables 6.1 to 6.4).

Example binding study of a thiourea to VL. Stock solutions were prepared in benzene- d_6 of VL (500 mM) and phenyl cyclohexylthiourea (10 mM). To a NMR tube, 100 μL of the thiourea stock solution and varying amounts of VL stock solution were added, and the final volume of solution was taken to 500 μL with benzene- d_6 . The final concentrations of VL in the NMR tubes were varied between $400 \text{ mM} \geq [\text{VL}]_0 \geq 0 \text{ mM}$, and the concentration of the thiourea was $[\text{phenyl cyclohexylthiourea}] = 2 \text{ mM}$. ^1H NMR spectra (referenced to residual benzene-H) were acquired for each solution at 300 K, and the chemical shift of the *ortho*-protons of phenyl thiourea was determined. The binding was determined by a line fitting method,³⁰ and the values match those obtained by Lineweaver-Bruker method.³¹ The errors on the binding constants were calculated by

linear regression of the linear method, and a tabulation of errors is given in the Tables 6.1 and 6.4.

Example of binding study of a thiourea to MTBD. Stock solutions were prepared in benzene- d_6 of MTBD (500 mM) and phenyl cyclohexylthiourea (10 mM). To a NMR tube, 100 μ L of the thiourea stock solution and varying amounts of MTBD stock solution were added, and the final volume was taken to 500 μ L with benzene- d_6 . The final concentrations of MTBD in the NMR tubes were varied between 400 mM $\geq$ [MTBD] $\geq$ 0 mM, and the concentration of the thiourea was [phenyl cyclohexylthiourea] = 2 mM. ^1H NMR spectra (referenced to residual benzene-H) were acquired for each solution at 300 K, and the chemical shift of the *ortho*-protons of phenyl thiourea was determined. The binding was determined by a line fitting method,³⁰ and the values match those obtained by Lineweaver-Bruker method.³¹ The errors on the binding constants were calculated by linear regression of the linear method, and a tabulation of errors is given in Tables 6.3 and 6.4.

Example Isotopic Effect study. A 7 mL vial was charged with 4-(trifluoromethyl)phenyl cyclohexylthiourea (15.1 mg, 0.049 mmol), benzyl alcohol (1.08 mg, 0.009 mmol), VL (100 mg, 0.998 mmol) and C_6D_6 (249.7 μ L) and agitated to make a homogeneous solution. Another 7 mL vial was charged with MTBD (7.6 mg, 0.049 mmol) and CDCl_3 (249.7 μ L), and the contents of the second vial were transferred to the other by a Pasteur pipette followed by transfer of the reaction mixture into a NMR tube. The progress of reaction was monitored by ^1H NMR. This was repeated with varying portions of CHCl_3 in the chloroform portion of the solvent: 75 %, 67 %, 25% and 16.6%. The k_{obs} of each reaction were plot against the percentage of CDCl_3 , and the line was extrapolated

to obtain rate at 100 % CHCl_3 with which the $k_{\text{H}}/k_{\text{D}}$ value was calculated. The errors on the $k_{\text{H}}/k_{\text{D}}$ were calculated by linear regression of the k_{obs} vs %D line, and a tabulation of errors is given in Tables 6.1 to 6.4. ^1H NMR spectra of benzyl alcohol in these solvent mixtures indicates that the alcohol adopts the same isotopic ratio as the $\text{CDCl}_3/\text{CHCl}_3$ portion of the solvent, see Figure 6.11. The (thio)urea NHs also undergo H/D exchange and adopt the isotopic ratio of the chloroform feed. While we presume that the IE of the OD bond makes up the majority of the IE, we cannot rule out an IE from the D-bonding catalyst.

Synthesis of thiourea H-bond donors

1,3-diphenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (20-25 mL), phenyl isocyanate (1 g, 8.39 mmol) and aniline (0.766 mL, 8.39 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 0.9231g, 62%. Characterization matches literature.³²

4-chlorophenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 4-chlorophenyl isocyanate (1 g, 6.511 mmol) and aniline (0.59 mL, 6.51 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 1.12 g, 70%. Characterization matches literature.³³

4-fluorophenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 4-fluorophenyl isocyanate (1 g, 7.29 mmol) and aniline (0.66 mL, 7.29 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 1.31 g, 78%. Characterization matches literature.³⁴

4-nitrophenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 4-nitrophenyl isocyanate (1 g, 6.093 mmol) and aniline

(0.567 mL, 6.093 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 1.33 g, 85%. Characterization matches literature.³⁵

4-methylphenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 4-methylphenyl isocyanate (1 g, 7.51 mmol) and aniline (0.699 mL, 7.51 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 1.17 g 68%. Characterization matches literature.³⁶

4-(trifluoromethyl)phenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 4-trifluoromethylphenyl isocyanate (0.786 g, 5.34 mmol) and aniline (0.29 mL, 0.98 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 0.67 g, 74%. NMR spectra given below. HRMS : m/z exp. = 281.0900 ($C_{14}H_{12}F_3N_2O+H$)⁺, (calc. = 281.0896). ¹H NMR (400 MHz, Acetone-*d*₆) δ 8.22 (s, 1H), 8.12 (s, 1H), 7.66 – 7.48 (m, 9H), 7.39 – 7.22 (m, 9H), 7.07 – 6.94 (m, 2H).

3,5-dichlorophenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-dichlorophenyl isocyanate (1 g, 5.31 mmol) and aniline (0.724 mL, 5.31 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 1.32 g, 89%. NMR spectra given below. HRMS : m/z exp. = 281.0243 ($C_{13}H_{11}Cl_2N_2O+H$)⁺, (calc. = 281.0245). ¹H NMR (400 MHz, Acetone-*d*₆) δ 8.40 (s, 1H), 8.22 (s, 1H), 7.69 – 7.45 (m, 8H), 7.31 (t, J = 7.8 Hz, 4H), 7.05 (dd, J = 15.6, 8.2 Hz, 3H).

3,5-bis(trifluoromethyl)phenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-bis(trifluoromethyl)phenyl isocyanate (1 g, 3.91 mmol) and aniline (0.35 mL, 3.91 mmol). The solution was stirred

overnight, and the solvent was removed under reduced pressure. Yield: 1.31 g, 96%. NMR spectra given below. HRMS : m/z exp. = 349.0770 ($C_{15}H_{11}F_6N_2O+H$)⁺, (calc. = 349.0774). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.57 (s, 0H), 7.44 (t, J = 7.8 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.26 (d, J = 7.5 Hz, 0H), 6.79 (s, 1H), 6.49 (s, 1H).

3,5-dimethoxyphenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-dimethoxyphenyl isocyanate (1 g, 5.58 mmol) and aniline (0.50 mL, 5.58 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 1.46 g, 97%. NMR spectra given below. HRMS : m/z exp. = 273.1234 ($C_{15}H_{17}N_2O_3+H$)⁺, (calc. = 273.1239). ¹H NMR (300 MHz, Acetone-*d*₆) δ 8.03 (s, 0H), 7.55 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.29 – 6.03 (m, 1H).

3,5-dimethylphenyl-3-phenyl urea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-dimethylphenyl isocyanate (1 g, 6.79 mmol) and aniline (0.62 mL, 6.79 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. Yield: 1.08 g, 64%. NMR spectra given below. HRMS : m/z exp. = 241.1335 ($C_{15}H_{17}N_2O+H$)⁺, (calc. = 241.1343) ¹H NMR (400 MHz, Acetone-*d*₆) δ 7.54 (d, J = 8.0 Hz, 4H), 7.28 (t, J = 7.8 Hz, 4H), 7.18 (s, 4H), 6.98 (t, J = 7.4 Hz, 2H), 6.65 (s, 2H).

Synthesis of thiourea H-bond donors

1-cyclohexyl-3-phenylthiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), phenyl isothiocyanate (200 mg, 1.48 mmol) and

cyclohexyl amine (168.87 μ L, 1.48 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The crude solid was purified by recrystallization in methanol. Yield: 242 mg, 70%. Characterization matches literature.^{37,38}

1-cyclohexyl-3-(4-nitrophenyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 4-nitrophenyl isothiocyanate (200 mg, 1.11 mmol) and cyclohexyl amine (125.8 μ L, 1.11 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in DCM. Yield: 285 mg, 92%. Characterization matches literature.^{38,39}

1-(4-chlorophenyl)-3-cyclohexylthiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 4-chlorophenyl isothiocyanate (200 mg, 1.18 mmol) and cyclohexyl amine (134.4 μ L, 1.18 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in DCM. Yield: 282 mg, 89%. Characterization matches literature.^{38,40}

1-cyclohexyl-3-(4-fluorophenyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 4-fluorophenyl isothiocyanate (200 mg, 1.31 mmol) and cyclohexyl amine (129.5 μ L, 1.31 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in DCM. Yield: 300 mg, 91%. Characterization matches literature.^{38,41}

1-cyclohexyl-3-(4-methoxyphenyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 4-methoxyphenyl isothiocyanate

(200 mg, 1.21 mmol) and cyclohexyl amine (138.0 μ L, 1.21 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in methanol. Yield: 240 mg, 75%. Characterization matches literature.⁴⁰

1-cyclohexyl-3-(p-tolyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 4-methylphenyl isothiocyanate (200 mg, 1.34 mmol) and cyclohexyl amine (152.9 μ L, 1.34 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in methanol. Yield: 226 mg, 68%. Characterization matches literature.⁹

4-(trifluoromethyl)phenyl cyclohexyl thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 4-(trifluoromethyl)phenyl isothiocyanate (200 mg, 0.98 mmol) and cyclohexyl amine (112.2 μ L, 0.98 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in DCM. Yield: 266 mg, 90%. Characterization matches literature.^{40,42}

1-cyclohexyl-3-(3,5-dichlorophenyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 3,5-dichlorophenyl isothiocyanate (200 mg, 0.98 mmol) and cyclohexyl amine (111.7 μ L, 0.98 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in DCM. Yield: 264 mg, 89%. NMR spectra given below. HRMS : m/z exp. = 303.0488 ($C_{13}H_{16}Cl_2N_2S + H$)⁺, (calc. = 303.0484). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.12 (d, *J* = 1.8 Hz, 2H), 5.93 (s, 1H), 4.23 (s,

1H), 2.09 (dt, $J = 12.8, 3.5$ Hz, 2H), 1.81 – 1.58 (m, 3H), 1.52 – 1.30 (m, 2H), 1.28 – 1.10 (m, 3H).

1-cyclohexyl-3-(3,5-difluorophenyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 3,5-difluorophenyl isothiocyanate (200 mg, 1.17 mmol) and cyclohexyl amine (133.2 μ L, 1.17 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in DCM. Yield: 269 mg, 85%. NMR spectra given below. HRMS : m/z exp. = 271.1078 ($C_{13}H_{16}F_2N_2S + H$)⁺, (calc. = 271.1075). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 6.78 – 6.67 (m, 3H), 6.04 (s, 1H), 4.25 (s, 1H), 2.08 (dt, $J = 12.3, 4.0$ Hz, 2H), 1.67 (ddt, $J = 29.0, 12.9, 3.9$ Hz, 3H), 1.48 – 1.34 (m, 2H), 1.18 (tdq, $J = 15.5, 8.4, 4.3, 3.9$ Hz, 3H).

1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (200 mg, 0.74 mmol) and cyclohexyl amine (84 μ L, 0.74 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in DCM. Yield 216 mg, 79%. Characterization matches literature.^{40,43}

1-cyclohexyl-3-(3,5-dimethoxyphenyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 3,5-dimethoxyphenyl isothiocyanate (200 mg, 1.02 mmol) and cyclohexyl amine (116.8 μ L, 1.02 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in methanol. Yield: 219 mg, 73%. NMR spectra given below. HRMS : m/z exp. = 295.1485 ($C_{15}H_{22}N_2O_2S + H$)⁺, (calc. = 295.1475). ¹H

NMR (400 MHz, Chloroform-*d*) δ 7.47 (s, 1H), 6.36 (t, $J = 2.2$ Hz, 1H), 6.30 (d, $J = 2.2$ Hz, 2H), 6.13 (s, 1H), 4.28 (s, 1H), 3.78 (s, 6H), 3.78 (s, 6H), 2.06 (dt, $J = 12.5, 4.0$ Hz, 3H), 1.73 – 1.58 (m, 3H), 1.49 – 1.31 (m, 2H), 1.15 (qd, $J = 11.8, 11.4, 3.3$ Hz, 3H).

1-cyclohexyl-3-(3,5-dimethylphenyl)thiourea. A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (10-15 mL), 3,5-dimethylphenyl isothiocyanate (200 mg, 1.22 mmol) and cyclohexyl amine (139.7 μ L, 1.22 mmol). The solution was stirred overnight, and the solvent was removed under reduced pressure. The resulting crude solid was purified by recrystallization in methanol. Yield: 251 mg, 78%. NMR spectra given below. HRMS : m/z exp. = 263.1579 ($C_{15}H_{22}N_2S + H$)⁺, (calc. = 263.1576). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.69 (s, 1H), 6.90 (s, 1H), 6.78 (d, $J = 1.6$ Hz, 2H), 5.94 (s, 1H), 4.26 (s, 1H), 2.31 (s, 6H), 2.04 (dq, $J = 12.4, 3.8$ Hz, 2H), 1.70-1.54 (m, 3H), 1.46-1.32 (m, 2H), 1.25 – 1.00 (m, 3H).

RESULTS AND DISCUSSION

Thioureas in Non-polar Solvent. Cyclohexyl aryl thioureas with variable aryl substitution display Hammett behavior in the rate of polymerization they exhibit for the thiourea/MTBD (0.049 mmol, 0.099 M each) (MTBD = 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene, Scheme 6.1) cocatalyzed ROP of δ -valerolactone (VL) (2 M) from benzyl alcohol (0.02 M) in benzene- d_6 . A series of thiourea H-bond donors were synthesized with systematic variation at the *m*- and *p*- positions (see Experimental Section), Scheme 6.1, and the observed rate constants (k_{obs} in min^{-1}) they exhibit in the ROP of VL were measured by ^1H NMR from the first order evolution of [VL]. These ROP have previously been shown to be first order in [monomer], [benzyl alcohol] $_o$ and [catalysts] $_o$.^{10,13,14} The plots of $\log k_{\text{obs}}$ versus σ_m or σ_p are linear, Figure 6.1, which suggest that changing the electronics of the aryl ring is felt at the H-bond donating thiourea moiety. The rates exhibited by the *m*-X-S series ($\sigma_m = 1.9$) are more sensitive to a change in group, X, than the *p*-X-S series ($\sigma_p = 0.9$), and this may be attributed to the two functional groups per H-bond donor in the former. The extent of reaction control, as measured by M_w/M_n , is similar across both series: *p*-NO₂-S, $M_w/M_n = 1.041$; *m*-CF₃-S, $M_w/M_n = 1.048$; H-S, $M_w/M_n = 1.050$ (90% conversion for all). ^1H NMR titration experiments between X-S and MTBD (discussed below) suggest that all X-S undergo *H-bonding* to the base cocatalyst in benzene- d_6 (vs deprotonation)^{6,14}, and that the Hammett (k_{obs}) behavior is due to modulation of the H-bond acidity in the transition state occurring in a *H-bond mediated ROP*, Scheme 6.1. Previous, truncated, Hammett studies on thiourea H-bond donors for ROP have observed a similar effect,¹¹ and Hammett correlations on catalysts (versus substrate), while not classic, are well-documented.^{18,19}

The strength of thiourea binding to monomer, K_{VL} , and base, K_{MTBD} , have both been suggested to be indicative of the reaction rate, but while these values can reasonably be predicted by σ , they have low correlation to observed rate constant, k_{obs} . Both *m*-X-S and *p*-X-S exhibit a good Hammett correlation to the thiourea/VL binding constant, K_{VL} . Thiourea H-bond donors have previously been shown via 1H NMR titration to bind to monomer, and this binding has been used as a model for the catalytic mechanism for thiourea-mediated ROP and to account for the high selectivity exhibited by thioureas for monomer vs polymer. The binding constants of the thioureas to VL, K_{VL} , were measured in benzene- d_6 using established methods, see experimental section, and these values display Hammett behavior, especially for those H-bond donors with electron withdrawing groups ($\sigma > 0$), Figure 6.2. These plots suggest that the electron withdrawing groups (EWGs) and electron donating groups (EDGs) groups directly affect the monomer binding ability of the thiourea. The $\log k_{obs}$ vs $\log K_{VL}$ plots (for both *m*- and *p*-) show a weak correlation (Figure 6.25), suggesting that the binding of monomer to thiourea can *reasonably* predict catalytic activity (i.e. k_{obs}), and that, while ground state thiourea-monomer interactions provide *an approximate model* of the transition state, these models should be applied with caution.

The binding constant of the H-bond donors to MTBD, K_{MTBD} , show Hammett behavior, yet the magnitude of K_{MTBD} is only weakly correlated to k_{obs} . The binding constant of each H-bond donor to MTBD, K_{MTBD} , was measured in benzene- d_6 by 1H NMR titration, see experimental section, and these values show good Hammett correlations, Figure 6.3. These data reinforce the K_{VL} observations that EWG/EDG modulation directly influences H-bond acidity of the thiourea. The possibility of a coincidental relationship

should not be discounted as a stronger H-bond acid would be expected to bind to all H-bond acceptors more strongly. However, the influence of changing σ on K_{MTBD} is stronger than upon K_{VL} ($\rho_{\text{MTBD}} > \rho_{\text{VL}}$), and the relationship is more robust (better fit for K_{MTBD}). This highlights a difficulty of catalyst modification, as thiourea binding to base – which is known to be inhibitory to catalysis^{13,14} – will outpace increased binding to monomer. Our group has previously proposed that the activity of a cocatalyst system in the H-bond mediated ROP of lactones arises from the cooperative interruption of the thiourea•base adduct by initiator/chain-end and monomer.¹⁴ Indeed, plots of $\log k_{\text{obs}}$ vs $\log K_{\text{MTBD}}$ (Figures 6.25 and 6.26) show weak correlation but suggest that the binding of thiourea to MTBD *influences* the rate exhibited by these cocatalysts and may exhibit a maximum rate. These observations suggest that the binding of thiourea to cocatalyst and monomer are important measures of catalyst efficacy and *adequately* describe catalytic (transition state) interactions. In this case, the cocatalyst binding constants could influence rate by forming the thiourea•base adduct which has previously been suggested by our group to be important to catalysis (i.e. $k_{\text{obs}} = k_{\text{p}}[\text{initiator}]_0[\text{thiourea}+\text{base}]_0$).^{13,14}

Isotope effects (IEs) of propagating alcohol H/D substitution on ROP rate were conducted and suggest 1) that ground state binding is an adequate model for the transition state of the H-bonding mechanism, and 2) that rate dependencies of some reagents in the ROP rate equations may arise from binding events prior to enchainment. The $k_{\text{H}}/k_{\text{D}}$ of ROP were measured for the thiourea/MTBD cocatalyzed (0.099 M each) ROP of VL (0.99 mmol, 2 M) from benzyl alcohol (0.02 M) in a mixture of $\text{C}_6\text{D}_6/\text{CDCl}_3/\text{CHCl}_3$ (50% benzene, 50% chloroform), where the H/D ratio in the chloroform blends is adopted by the benzyl alcohol, see experimental section. The *m*-X-S H-bond donors exhibit very small

($k_H/k_D \sim 1$), normal IEs that do not vary with σ_m , and the *p*-X-S with EWG exhibit the same trend, Figure 6.4. For the thioureas with EDGs in the *p*-X-S series, the IEs are inverse. The small magnitude of the IEs, particularly the inverse IEs, suggests that we are observing equilibrium isotope effects rather than small KIEs.^{18,20} An inverse, primary KIE is impossible for an elementary reaction.²² D-bonds have been observed to be stronger than H-bonds which implicates the MTBD/alcohol binding event as the source of the inverse IE.²³ This implies that the first order dependence upon [initiator]_o in the H-bond mediated ROP is due to an equilibrium step prior to the enchainment event that shifts towards MTBD•alcohol + thiourea•VL adducts upon D for H substitution.¹⁴ We presume that the inverse IEs are observed only for EDG-bearing thioureas because thiourea/MTBD binding for these compounds is comparably small (see Figure 6.3, lower). This renders apparent any minute change in alcohol/MTBD binding which occurs upon H/D substitution. In this interpretation, the rate dependencies of the ROP, which is first order in [base + thiourea]_o, [alcohol]_o and [monomer],^{10,13,14} could arise from the assembly of the reagents prior to the enchainment step, reinforcing the concept of thiourea/base catalysts functioning as an entropy trap.²¹ We should note that the energy surface of this ROP is very shallow, and binding events occur with a similar energy to enchainment.²¹ Hence, the observed effects should also be consistent with an enchainment rate determining step exhibiting a very small KIE characteristic of a reactant-like transition state with a mostly intact OH/OD bond. Further study will be necessary to elucidate these suggestions, but we believe this is the first evidence for these systems of a binding event being directly measurable in the ROP kinetics. The touchstone analysis of thiourea/base mediated ROP (using *m*-CF₃-S/MTBD for the ROP of VL) predicted that reagent/catalyst binding events would be evident in ROP

kinetics, and the Arrhenius analysis in that publication shows an entropy of activation consistent with a bimolecular reaction.¹⁰ If the present suggestions prove to be true, they imply new opportunities for catalyst development based on isotopic substitution.

Thioureas in Polar, H-bonding Solvent. Hammett analysis of thiourea/MTBD mediated ROP of VL in acetone-*d*₆ provides detailed mechanistic insight of two competing ROP mechanisms. Thiourea/base mediated ROP is traditionally run in non-polar solvent, but recent advances have favored the application of polar solvent.^{4,17} Particularly, the development of thiourea anions allowed for the rapid ROP of lactones in polar solvent, and these reactions were proposed to proceed through a thioimide mechanism, Scheme 6.1.⁵ Hammett analysis is an ideal tool to probe the dueling mechanisms available to thiourea/base cocatalyzed ROP in polar solvent. Binding constants of either MTBD or VL to the thioureas are too small in acetone-*d*₆ to be accurately measured by ¹H NMR due to the competitive binding with solvent, so our Hammett analysis is limited to rate.

For thioureas with EDGs and weak EWGs in acetone-*d*₆, an H-bonding mechanism of ROP is favored, but thioureas with strong EWGs operate via a thioimide mechanism. In the Hammett plot of log *k*_{obs} vs σ (acetone-*d*₆), both *m*-X-S and *p*-X-S exhibit a nonlinear plot with a maximum at $\sigma \sim 0.2$, Figure 6.5. The thioureas with substituents of $\sigma \leq \sim 0.2$ show a positive ρ value and those with $\sigma \geq \sim 0.2$ possess a negative ρ value. ¹H NMR spectra of the various thioureas plus one equivalent MTBD (0.099 M each) in acetone-*d*₆ reinforce a mechanism change at $\sigma \sim 0.2$. The NMR spectra of the positive ρ range indicate H-bonding (a downfield shift of the thiourea cyclohexyl methine resonance vs free thiourea) where the stronger EWGs presumably facilitate stronger H-bond activation of substrate (and faster rates) just as in benzene. The NMR spectra of thioureas with and without

MTBD in the negative ρ range indicate thioimide formation (an upfield shift, cyclohexyl methine). One explanation for this change is that the less-acidic thioureas (smaller σ) generate more basic anions which yield faster rates. This explanation is consistent with the initial reports of (thio)imide mediated ROP.^{4,5,17} We infer that the thioimide mechanism appears to ‘turn on’ at $\sigma \sim 0.2$ because the pK_a of MTBD (pK_a (DMSO) MTBD- $H^+ \sim 14$ -16)^{24,25} may be the same as that of a thiourea at that σ value (e.g. pK_a (DMSO) m -CF₃-S = 13.2 < pK_a m -Cl-S, presumably)²⁶. The pK_a MTBD- H^+ in DMSO is not known, but is expected to be between that of DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, pK_a DBU- $H^+ = 13.9$) and BEMP (BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, pK_a BEMP- $H^+ = 16.5$).^{24,25} However, we prefer to view the mechanism as a continuum (vs an ‘on/off’ phenomenon) where the gradual change in acidity of the thioureas is the presumed source of the V-shaped Hammett plots²⁰ (Figure 6.5) as the mechanism gradually shifts from H-bonding to thioimide with increasing σ . Treating p -CF₃-S with 0.5 equivalent MTBD in acetone- d_6 results in one set of ¹H NMR resonances for p -CF₃-S, which indicates that proton transfer is dynamic on the NMR timescale. This suggests that quantitative proton transfer is not required to effect thioimide mediated ROP. In a continuum point of view, the reduction of basicity of thiourea anions (with increasing σ) is outpacing the formation of a higher [thioimide] (Scheme 6.1) past $\sigma \sim 0.2$. However, in the case of strong base cocatalysts (e.g. KH or potassium *tert*-butoxide) where proton transfer is ‘irreversible’, an on/off mechanism seems irrefutable.^{4,5}

We would like to propose an alternative explanation for the V-shaped Hammett plots (Figure 6.5) that is reminiscent of a more classic Hammett-based argument that

attributes the portions of the Hammett plots with negative ρ to the formation of positive charge during the transition state. In an imidate mechanism, the ‘formation of positive charge’ is tantamount to the thioimide becoming ‘less negative’ and could arise from the donation of electron density from the thioimide to the alcohol that is resisted by the stronger EWGs. This Hammett-based explanation seems inconsistent with the thioimide acting as both H-bond donor and acceptor, as dual activation would not be expected to dramatically change the charge at the thioimide at the transition state. This implicates the base- H^+ as the H-bond donor (activating monomer) during ROP in an imidate mechanism. These roles are similar to those proposed in the DBU/benzoic acid mediated ROP of lactide.²⁷ Ultimately, the two points of view are complementary and may be identical; a more acidic thiourea with strong EWGs will produce a weaker base thioimide (acid/base argument) and the strong EWGs will resist H-bond accepting (Hammett argument). The change in mechanism is not associated with a substantial change in alcohol k_H/k_D (versus Figure 6.4, benzene): *m*-CF₃-S, $k_H/k_D = 1.6$; *p*-NO₂-S, $k_H/k_D = 1.5$ (acetone-*d*₆:CDCl₃/CHCl₃, 50:50). While both mechanisms have been suggested previously,^{4,5,17} we believe this the most systematic and controlled observation of the mechanism shift; with a V-shaped Hammett plot, a mechanism continuum becomes difficult to refute.

Ureas in Polar and Non-polar Solvent. The urea/MTBD cocatalyzed ROP of VL from benzyl alcohol undergoes ROP via solvent-determined H-bonding (benzene-*d*₆) or imidate (acetone-*d*₆) mechanisms. The Hammett plots of log k_{obs} (both *m*- and *p*-) show positive slopes in acetone-*d*₆ and benzene-*d*₆, Figure 6.6. Any number of equilibria (e.g. binding to VL or cocatalyst, proton transfer to form imidate, etc.) which are superimposed on the observed rate constant will result in a linear Hammett plot except in the case of a change

in mechanism (i.e. X-S in acetone, Figure 6.5).^{20,28} The positive slopes of the Hammett plots suggest that negative charge is building during the transition states and are consistent with either mechanism but arise through different phenomena. ¹H NMR spectra of *m*-CH₃-O or *m*-CF₃-O with and without MTBD indicate H-bonding (downfield shift with MTBD) in benzene-*d*₆ and imidate (upfield shift with MTBD) in acetone-*d*₆ (Figure 6.14). *In the H-bonding path*, higher σ values would be associated with stronger H-bonding to monomer in the transition state. This explanation is identical to that for the thiourea mediated ROP in C₆D₆ (Figure 6.1).

We propose that the simplest explanation of the positive, linear slopes of the σ_m or σ_p vs log k_{obs} plots (Figure 6.6, acetone-*d*₆) is the formation of more imidate character (higher [imidate]) with stronger EWGs. This explanation assumes that the imidate is in equilibrium with the neutral urea in acetone-*d*₆, just as proposed for thioureas in acetone-*d*₆. Indeed, a reversible imidate formation would be expected to result in a more controlled ROP (versus all imidate) as the imidate ion pair reverts to a relatively-inert H-bond donor/acceptor pair, as appears to be the case.^{4,6} In a purely imidate mechanism, which occurs upon the treatment of urea H-bond donors with strong bases (e.g. KH), published studies have shown the opposite effect where more EWGs (CF₃ groups) on the urea resulted in slower ROP (an implied negative ρ).⁴ For the published study, the slower rates were attributed to a reduced basicity of the imidate with increase number of CF₃ groups which was suggested to reduce H-bond accepting ability. This observation is analogous to the negative ρ portion of Figure 6.5, the treatment of *thioureas* with MTBD in acetone-*d*₆. Because ureas are less acidic than thioureas,²⁹ we propose that the data in Figure 6.6 (acetone-*d*₆) is analogous to the low ρ portion of Figure 6.5. That is, the ureas are not acidic

enough to become fully deprotonated and result in a change in mechanism. We predict that ROP rate in Figure 6.6 may eventually reach a maximum value if extended to higher sigma. This appears to be the only explanation that is consistent with, 1) the published report,⁴ 2) the ¹H NMR studies of urea with and without MTBD, 3) the Hammett behavior in Figure 6.6, and 4) a unified mechanism for both urea and thiourea cocatalysts. Controllably modulating the position of the H-bonding vs imidate equilibrium – or possibly developing true on/off abilities – could yield impressive control in the ROP

Kinetic isotope studies on observed rate constant for the *m*-X-O/MTBD catalyzed ROP of VL show a later transition state versus the thiourea cocatalyzed ROPs. The H/D substitution studies were performed by conducting the ROPs in CDCl₃/CHCl₃ blends which are adopted by the benzyl alcohol, see experimental section. The KIEs range from $k_H/k_D = 4.5$ for electron donating methyl- to $k_H/k_D = 2.09$ for electron withdrawing CF₃, Figure 6.7. The larger IEs versus thioureas (Figure 6.4) suggests that the present values are indeed *kinetic* isotope effects. It is possible that the large KIEs (vs thioureas) represent a change in mechanism, but this would not be consistent with ¹H NMR spectra of ureas in nonpolar solvent in the presence and absence of MTBD which indicate an H-bonding mechanism. Further, the KIEs measured in chloroform solvent match those performed in benzene/chloroform blends, which suggests that the H-bond mediated mechanism dominates in chloroform. Rather, the larger KIEs suggest a later transition state characterized by more equal sharing of the H/D in an H-bond mediated ROP. These results also suggest that catalyst/reagent interactions are not very similar to those at the transition state. Hence, the community might not be too concerned with the inaccessibility of urea/reagent binding constants as they may not be as meaningful as thiourea/reagent

binding constants. Under the present conditions, stronger EWGs are associated with lower KIEs, which suggests that the more active catalysts feature a transition state closer to the reagents. If electronic changes to H-bond donating catalyst (urea) result in a KIE at the H-bond donating substrate (alcohol), the urea-dependent KIE reinforces the complicated interplay of the (thio)urea/base cocatalysts acting as a single system. When the KIE experiment is repeated in acetone/chloroform (50:50) solvent mixtures (which is associated with imidate formation), the KIE for the *m*-MeO-O/MTBD cocatalyzed ROP of VL drops to $k_H/k_D = 2.02$.

CONCLUSION

Linear and nonlinear free energy studies of (thio)urea/MTBD mediated ROP of VL reveal the complicated interplay of reagents that give rise to catalysis through one of two mechanisms. Which mechanism is operative depends most greatly on the solvent, where polar solvents favor a (thio)imide mechanism and non-polar solvents favor a classic H-bond mediated ROP. For thiourea H-bond donors in acetone, the mechanism is observed to change from H-bonding for thioureas with weak EWG (and EDGs) to a thioimide mechanism for strong EWGs. The change in mechanism may occur when resistance to increased electron donation from thioimide to alcohol caused by strong EWGs ($\rho < 0$) outweighs increased [imide] ($\rho > 0$), which would occur in the regime that [imide] is not a function of σ . We predict that the enhanced control of (thio)urea/base cocatalyzed ROP versus other highly-active systems may be shown to arise from this mechanistic duality, and advanced, switchable catalysts may further improve selectivity. Despite the large amount of information that has been discovered about these catalysts over that last decade, hints at new opportunities emerge through the present studies. Particularly, the isotope studies tease at new catalysts and provide evidence of binding events in the rate determining step.

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<i>meta-substituted diphenyl urea</i>						
	K_H/K_D	Standard Error for (K_H/K_D)	k_{obs} (C₆D₆) (min⁻¹)	Standard Error for k_{obs} (C₆D₆) (min⁻¹)	k_{obs} (acetone-<i>d</i>₆) (min⁻¹)	Standard Error for k_{obs} (acetone-<i>d</i>₆) (min⁻¹)
<i>CF</i>₃	2.09	0.0014	0.1538	0.005	0.2201	0.005
<i>Cl</i>	2.31	0.0018	0.0688	0.0016	0.2147	0.006
<i>OMe</i>	3.12	0.0004	0.016	0.0003	0.0529	0.002
<i>H</i>	-	-	0.0116	0.0002	0.0385	0.001
<i>Me</i>	4.5	8.90E-05	0.0079	0.0001	0.021	0.001

Table 6.1. Tabulation of Errors for meta-substituted diphenyl urea. See Experimental Section for the methods of error determination.

<i>para-substituted diphenyl urea</i>				
	k_{obs} (C₆D₆) (min⁻¹)	Standard Error for k_{obs} (C₆D₆) (min⁻¹)	k_{obs} (acetone-<i>d</i>₆) (min⁻¹)	Standard Error for k_{obs} (acetone-<i>d</i>₆) (min⁻¹)
<i>CF</i>₃	0.0346	0.0006	0.1599	0.0076
<i>Cl</i>	0.0221	0.0006	0.1127	0.0065
<i>F</i>	0.0225	9.00E-05	0.057	0.0026
<i>H</i>	0.0116	0.0002	0.0385	0.0014
<i>NO</i>₂	0.1608	0.0016	0.1353	0.0057
<i>Me</i>	0.0073	1.70E-05	0.0266	0.0009

Table 6.2. Tabulation of Errors for para-substituted diphenyl urea. See Experimental Section for the methods of error determination.

<i>meta-substituted cyclohexyl thiourea</i>										
	K_{eq} to VL	Standard Error of K_{eq}	K_{eq} to MTBD	Standard Error for K_{eq}	K_H/K_D	Standard Error for (K_H/K_D)	k_{obs} (C_6D_6) / min^{-1}	Standard Error for k_{obs} (C_6D_6)	k_{obs} (acetone- d_6) / min^{-1}	Standard Error for k_{obs} (acetone- d_6) / min^{-1}
<i>CF₃</i>	41	0.3	1500	100	1.0977	0.0001	0.0119	0.0070	0.0023	0.00003
<i>Cl</i>	6.8	0.5	533	8	0.9716	0.0005	0.0073	0.0014	0.0024	0.0002
<i>F</i>	7.2	0.6	319	15	1.0293	0.0003	0.0100	0.0003	0.0024	0.0002
<i>OMe</i>	1.8	0.1	40.2	2.4	1.1811	0.0003	0.0022	0.0001	0.0039	0.0001
<i>H</i>	1.2	0.04	58.5	3.6	1.2188	0.0001	0.0017	0.0001	0.0032	0.0001
<i>Me</i>	1.6	0.04	21.8	1.0	1.0514	0.00003	0.0011	0.00004	0.0023	0.0001

Table 6.3. Tabulation of Errors for meta-substituted cyclohexyl thiourea. See

Experimental Section for the methods of error determination

<i>para-substituted cyclohexyl thiourea</i>										
	K_{eq} to VL	Standard Error of K_{eq}	K_{eq} to MTBD	Standard Error for K_{eq}	K_H/K_D	Standard Error for (K_H/K_D)	k_{obs} (C_6D_6) / min^{-1}	Standard Error for k_{obs} (C_6D_6) / min^{-1}	k_{obs} (acetone- d_6) / min^{-1}	Standard Error for k_{obs} (acetone- d_6) / min^{-1}
<i>NO₂</i>	7.8	0.04	803	8	1.264	0.0003	0.0088	0.0007	0.0012	0.00001
<i>CF₃</i>	5.3	0.98	461	76	1.118	0.00003	0.0063	0.0006	0.0038	0.0001
<i>Cl</i>	3.5	0.07	79	4	1.245	0.0002	0.0041	0.0001	0.0055	0.0001
<i>F</i>	1.6	0.08	94	2	1.146	0.0001	0.0036	0.0001	0.0041	0.0002
<i>H</i>	1.2	0.04	58	4	1.219	0.0001	0.0017	0.0001	0.0032	0.0001
<i>Me</i>	1.6	0.08	57	4	0.951	0.0001	0.0018	0.00002	0.0038	0.0001
<i>OMe</i>	1.6	0.13	72	11	0.827	0.00004	0.0009	0.00001	0.0023	0.0001

Table 6.4. Tabulation of Errors for para-substituted cyclohexyl thiourea. See Experimental

Section for the methods of error determination.

Scheme 6.1. The two mechanisms for (thio)urea plus base cocatalyzed ROP are proposed to exist along a continuum of reactivity from imidate- to H-bond-mediated ROP.

NON-POLAR SOLVENT FAVORS NEUTRAL H-BONDING MECHANISM

POLAR SOLVENT FAVORS (THIO)IMIDATE MEDIATED MECHANISM

Scheme 6.2. Summary of the observations and competing mechanisms discussed in this study.

Figure 6.1. (upper) Hammett plot ($\log k_{\text{obs}}$) for the *m*-X-S/MTBD (0.099 M each) cocatalyzed ROP of VL (0.99 mmol, 2 M) from benzyl alcohol (0.02 M) in benzene-*d*₆. (lower) Hammett plot ($\log k_{\text{obs}}$) for the *p*-X-S/MTBD (0.099 M each) cocatalyzed ROP of VL (0.99 mmol, 2 M) from benzyl alcohol (0.02 M) in benzene-*d*₆. The $\log (k_{\text{obs}}/k_{\text{H}})$ Hammett plots are in Figure 6.8.

Figure 6.2. (upper) Hammett plot of the binding constant of *m*-X-S to VL, K_{VLm} , in benzene-*d*₆. (lower) Hammett plot of the binding constant of *p*-X-S to VL, K_{VLp} , in benzene-*d*₆. The $\log (K_{VL}/k_{VL,H})$ Hammett plots are in Figure 6.9.

Figure 6.3. (upper) Hammett plot of the binding constant, K_{MTBDm} , of *m*-X-S to MTBD in benzene-*d*₆. (lower) Hammett plot of the binding constant, K_{MTBDp} , of *p*-X-S to MTBD in benzene-*d*₆. The $\log (K_{\text{MTBD}}/k_{\text{MTBD,H}})$ Hammett plots are in Figure 6.10.

Figure 6.4. Plots of k_H/k_D vs σ_p and σ_m . Reaction conditions: VL (0.998 mmol, 2.00 M); X-O/MTBD (0.1 M each); benzyl alcohol (0.02 M) in C₆D₆/CDCl₃/CHCl₃ (varying CDCl₃/CHCl₃ ratio). The k_H and k_D were extracted from plots of k_{obs} vs %D in the chloroform feed.

Figure 6.5. (upper) Hammett plot of $\log k_{\text{obs}}$ of *m*-X-S in acetone- d_6 . (lower) Hammett plot of $\log k_{\text{obs}}$ of *p*-X-S in acetone- d_6 . Conditions: VL (0.99 mmol, 2 M); X-S/MTBD (0.099 M each); benzyl alcohol (0.02 M) in acetone- d_6 . The $\log (k_{\text{obs}}/k_{\text{H}})$ Hammett plots are in Figure 6.12.

Figure 6.6. Hammett plots of k_{obs} for the ROP of VL (0.998 mmol, 2 M) from benzyl alcohol (0.02 M) in acetone- d_6 and benzene- d_6 by (upper) *p*-X-O/MTBD (0.1 M each); and (lower) *m*-X-O/MTBD (0.1 M each). The $\log (k_{\text{obs}}/k_{\text{H}})$ Hammett plots are in Figure 6.13.

Figure 6.7. Plot of $k_{\text{H}}/k_{\text{D}}$ vs σ_m . Reaction conditions: VL (0.998 mmol, 2.00 M); *m*-X-O/MTBD (0.1 M each); benzyl alcohol (0.02 M) in $\text{CDCl}_3/\text{CHCl}_3$. The k_{H} and k_{D} were extracted from plots of k_{obs} vs %D in the chloroform feed.

Figure 6.8. (upper) Hammett plot of the rate constant of *m*-X-S in the ROP of VL, $\log(k_X/k_H)$, in benzene-*d*₆. (lower) Hammett plot of the rate constant of *p*-X-S in the ROP of VL, $\log(k_X/k_H)$, in benzene-*d*₆. Conditions: X-S/MTBD (0.099 M each), VL (0.99 mmol, 2 M) benzyl alcohol (0.02 M) in benzene-*d*₆.

Figure 6.9. (upper) Hammett plot of the binding constant of *m*-X-S to VL, $\log(K_{VLX}/K_{VLH})$, in benzene-*d*₆. (lower) Hammett plot of the binding constant of *p*-X-S to VL, $\log(K_{VLX}/K_{VLH})$, in benzene-*d*₆.

Figure 6.10. (upper) Hammett plot of the binding constant of *m*-X-S to MTBD, $\log(K_{\text{MTBD}_X}/K_{\text{MTBD}_H})$, in benzene- d_6 . (lower) Hammett plot of the binding constant of *p*-X-S to MTBD, $\log(K_{\text{MTBD}_X}/K_{\text{MTBD}_H})$, in benzene- d_6 .

Figure 6.11. ^1H NMR (400 MHz) benzyl alcohol (1.08 mg, 0.009 mmol), MTBD (7.65 mg, 0.049 mmol), benzene- d_6 (249.7 μL), CDCl_3 (124.8 μL) and CHCl_3 (124.8 μL). The ratio of the OH resonance (3.75 ppm): benzylic CH_2 (4.5 ppm) is 1:2, suggesting that the isotopic ratio of the solvent matches the alcohol chain end.

Figure 6.12. (upper) Hammett plot of $\log(k_{\text{obs}}/k_{\text{H}})$ of *m*-X-S in acetone- d_6 . (lower) Hammett plot of $\log(k_{\text{obs}}/k_{\text{H}})$ of *p*-X-S in acetone- d_6 . Conditions: VL (0.99 mmol, 2 M); X-S/MTBD (0.099 M each); benzyl alcohol (0.02 M) in acetone- d_6 .

Figure 6.13. Hammett plots of $\log (k_{\text{obs}}/k_{\text{H}})$ for the ROP of VL (0.998 mmol, 2 M) from benzyl alcohol (0.02 M) in acetone-*d*₆ and benzene-*d*₆ by (upper) *m*-X-O/MTBD (0.1 M each); and (lower) *p*-X-O/MTBD (0.1 M each).

Figure 6.14. (upper) ¹H NMR (acetone-*d*₆, 400 MHz) spectra of select urea H-bond donors in the presence and absence of MTBD (0.098 M each) (referenced to residual acetone-H). (lower) ¹H NMR (C₆D₆, 400 MHz) spectra of select urea H-bond donors in the presence and absence of MTBD (0.0049 M each) (referenced to residual benzene-H).

Figure 6.15. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz) spectrum of 4-(trifluoromethyl)phenyl-3-phenyl urea (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz) spectrum of 4-(trifluoromethyl)phenyl-3-phenyl urea.

Figure 6.16. (Upper) ^1H NMR (acetone- d_6 , 400 MHz) spectrum of 3,5-dichlorophenyl-phenyl urea (Lower) ^{13}C NMR (acetone- d_6 , 100 MHz) spectrum of 3,5-dichlorophenyl-phenyl urea.

Figure 6.17. (Upper) ¹H NMR (CDCl₃, 400 MHz) spectrum of 3,5-bis(trifluoromethyl)phenyl-3-phenyl urea (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz) spectrum of 3,5-bis(trifluoromethyl)phenyl-3-phenyl urea.

Figure 6.18. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz) spectrum of 3,5-dimethoxyphenyl-3-phenyl urea (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz) spectrum of 3,5-dimethoxyphenyl-3-phenyl urea.

Figure 6.19. (Upper) ^1H NMR (acetone- d_6 , 400 MHz) spectrum of 3,5-dimethylphenyl-3-phenyl urea (Lower) ^{13}C NMR (CDCl_3 , 100 MHz) spectrum of 3,5-dimethylphenyl-3-phenyl urea.

Figure 6.20. (Upper) ^1H NMR (CDCl_3 , 400 MHz) spectrum of 3,5-dimethylphenyl cyclohexyl thiourea. (Lower) ^{13}C NMR (CDCl_3 , 100 MHz) spectrum of 1-cyclohexyl-3-(3,5-dichlorophenyl)thiourea.

Figure 6.21. (Upper) ¹H NMR (CDCl₃, 400 MHz) spectrum of 3,5-difluorophenyl cyclohexyl thiourea. (Lower) ¹³C NMR (CDCl₃, 100 MHz) spectrum of 1-cyclohexyl-3-(3,5-difluorophenyl)thiourea.

Figure 6.22. (Upper) ^1H NMR (CDCl_3 , 400 MHz) spectrum of 3,5-dimethoxyphenyl cyclohexyl thiourea. (Lower) ^{13}C NMR (CDCl_3 , 100 MHz) spectrum of 1-cyclohexyl-3-(3,5-dimethoxyphenyl)thiourea.

Figure 6.23. (Upper) ^1H NMR (CDCl_3 , 400 MHz) spectrum of 3,5-dimethylphenyl cyclohexyl thiourea. (Lower) ^{13}C NMR (CDCl_3 , 100 MHz) spectrum of 1-cyclohexyl-3-(3,5-dimethylphenyl)thiourea.

Figure 6.24. ^1H NMR spectra (acetone- d_6 , 400 MHz) of select thiourea H-bond donors in the presence and absence of MTBD (0.099 M each) (referenced to C_6H_6 internal standard). Cyclohexyl methine ~ 4.1 ppm indicates thioimide formation (upfield shift).

Figure 6.25. Plots of $\log k_{\text{obs}}$ vs $\log K_{\text{VL}}$ for *m*-X-S (LEFT) and *p*-X-S (RIGHT). Note that axes do not extend to the origin.

Figure 6.26. Plots of $\log k_{\text{obs}}$ vs $\log K_{\text{MTBDm}}$ and K_{MTBDp} . Note that the axes do not extend to the origin.

Figure 6.27. Plot of $\ln([VL]_0/[VL])$ vs time for *p*-X-S in benzene-*d*₆ (upper) and acetone-*d*₆ (lower). Note: only a selected run of many runs for each catalyst is included; the k_{obs} values in the Hammett plots represent the average of at least 2 runs.

Figure 6.28. Plot of $\ln([VL]_0/[VL])$ vs time for *m*-X-S in benzene- d_6 (upper) and acetone- d_6 (lower). Note: only a selected run of many runs for each catalyst is included; the k_{obs} values in the Hammett plots represent the average of at least 2 runs.

Figure 6.29. Plot of $\ln([VL]_0/[VL])$ Vs time for *m*-X-O in benzene- d_6 (upper) and acetone- d_6 (lower). Note: only a selected run of many runs for each catalyst is included; the k_{obs} values in the Hammett plots represent the average of at least 2 runs.

Figure 6.30. Plot of $\ln([VL]_0/[VL])$ Vs time for *p*-X-O in benzene- d_6 (upper) and acetone- d_6 (lower). Note: only a selected run of many runs for each catalyst is included; the k_{obs} values in the Hammett plots represent the average of at least 2 runs.