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

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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 been 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 temperature 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.

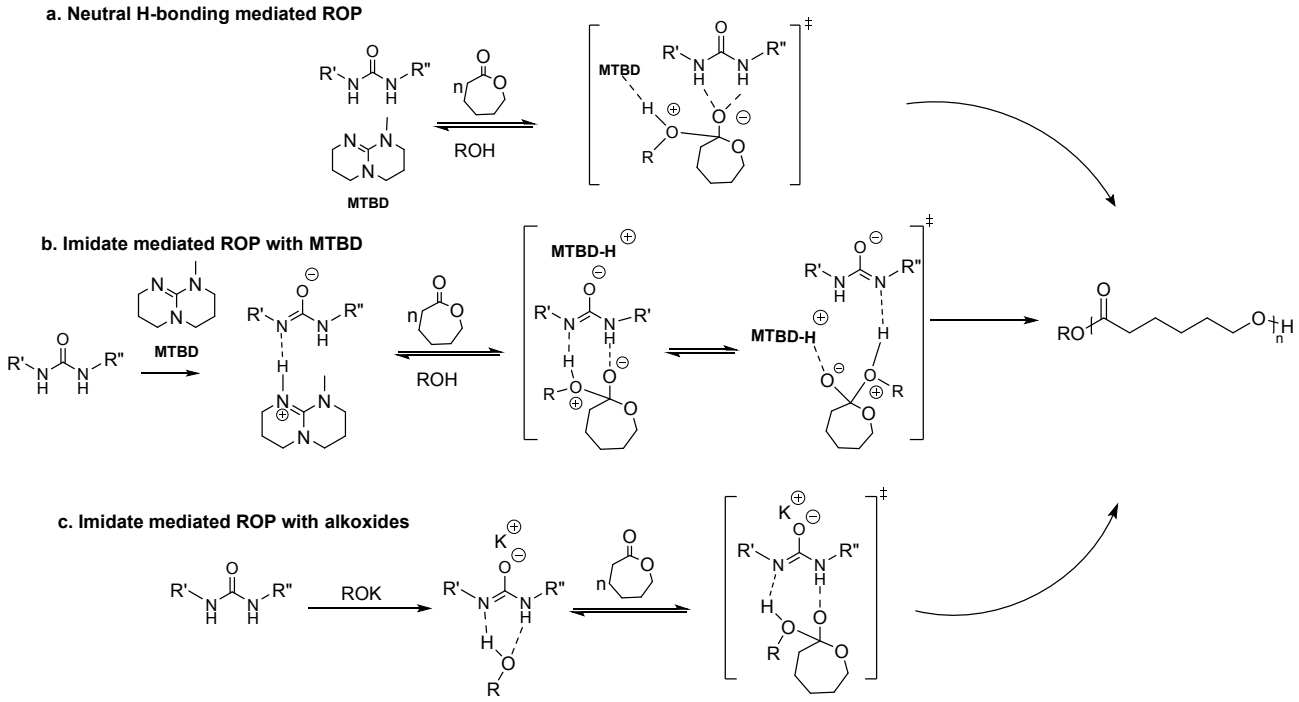
INTRODUCTION

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 (dispersity= Đ = M_w/M_n) and are capable of yielding polymers with well-defined architectures.[1,2,12] The selectivity of catalysts towards ROP versus non-enchainment reactions is vital to minimizing 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 temperature[11,25–29] and pressure, [30,31] and a variety of solvents and solvent-free conditions[32] 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.[1,2,12,33] 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] Although 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.

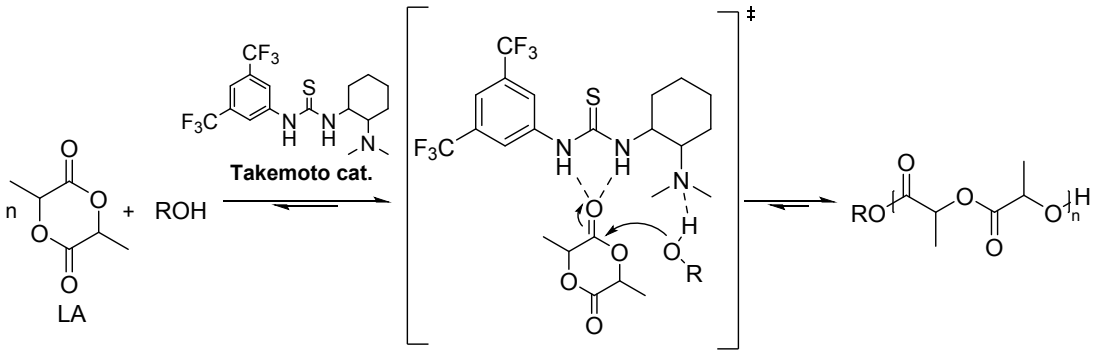


Scheme 1. Neutral versus Imidate Mediated ROP of Lactones

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

The naissance of H-bond mediated ROP occurred in 2005 when the Takemoto thiourea (Figure 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 2), yielding, in addition to typical 'living' behavior, highly selective ROP with minimum broadening of M_w/M_n even at monomer conversions ≥ 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** plus *N,N*-dimethylcyclohexylamine ($NCyMe_2$) 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]



Scheme 2. Proposed activation pathway of covalently linked bifunctional thiourea in ROP of LA

For H-bond mediated ROP, strong organic base cocatalysts are required with 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 ($[M]_o/[I]_o$ = 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 $[M]_o/[I]_o = 200$ 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]

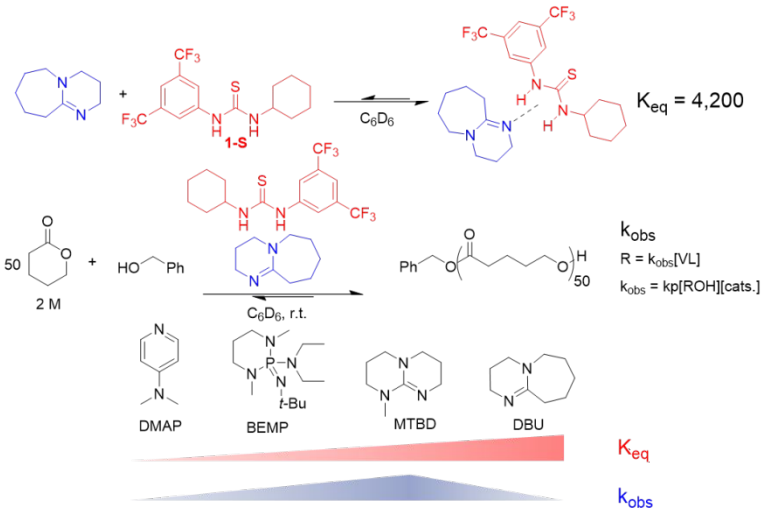


Figure 1. Strength of cocatalyst binding is predictive of catalytic activity.

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 $[\mathbf{1\text{-}S}]_o$; a mechanistic account was proposed.[44] As a direct result, the bisthiourea **2-S** was synthesized and applied with base cocatalysts for the ROP of lactide, which resulted in enhanced rates ($k_{2\text{-}S}/k_{1\text{-}S} \sim 12$).[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 (Rate = $k_{obs}[M]$; $k_{obs} = [\mathbf{2\text{-}S} + \text{base}]_o[\text{initiator}]_o$) which suggests that

2-S is acting as a discrete catalyst (one bisthiourea per base per monomer in the transition state).[34,37] Buttressed by computational studies[37] and indirect evidence,[34] an *activated-TU* mechanism was proposed, whereby the 'extra' thiourea stabilizes the catalytic thiourea via H-bond activation, Figure 2. The ROP of cyclic lactones in the presence of **2-S** and base proceeded with lower catalyst loadings and enhanced rates compared to mono-thiourea **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 tristhiourea?* However, the tristhiourea **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 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.

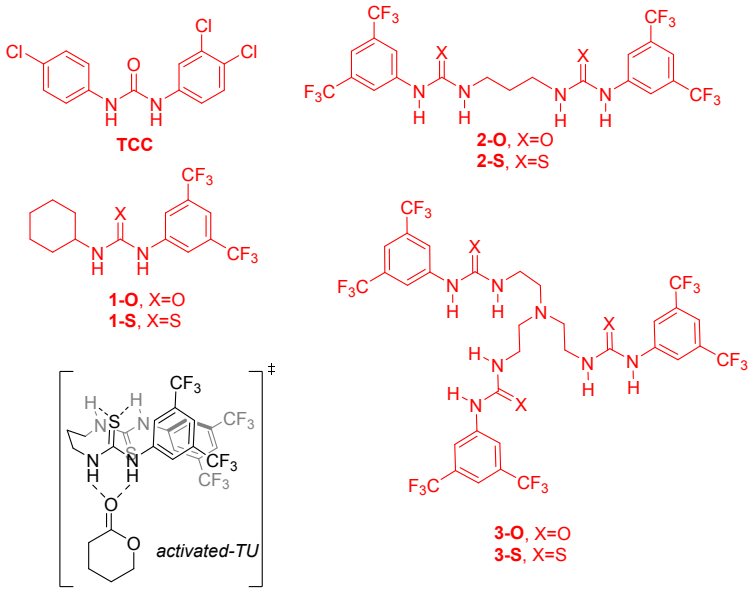


Figure 2. Representative (thio)ureas in red and proposed *activated*-TU mode activation for multi-donors.

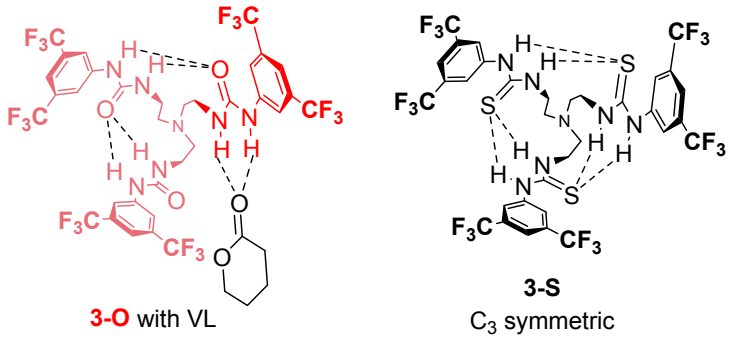
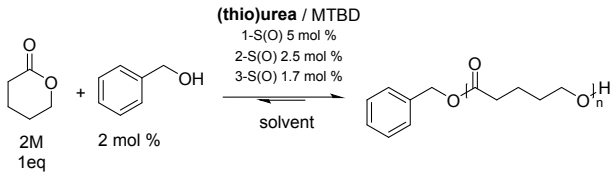


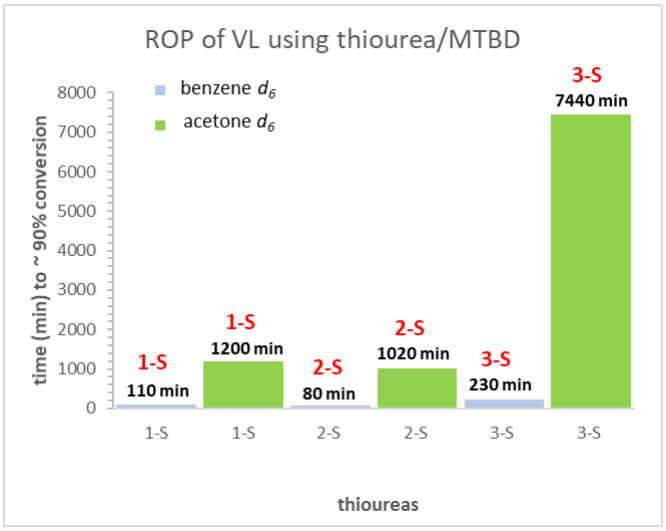
Figure 3. Monomer activation by *activated*-**3-O** and intramolecular deactivation of **3-S**.

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 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.





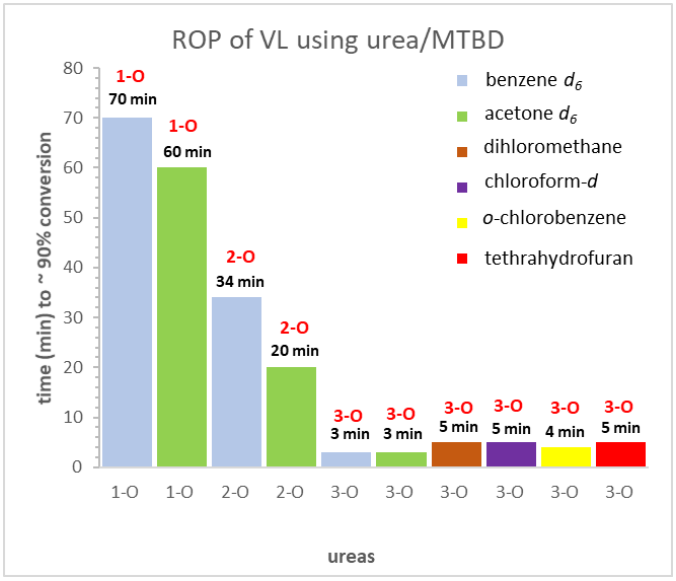
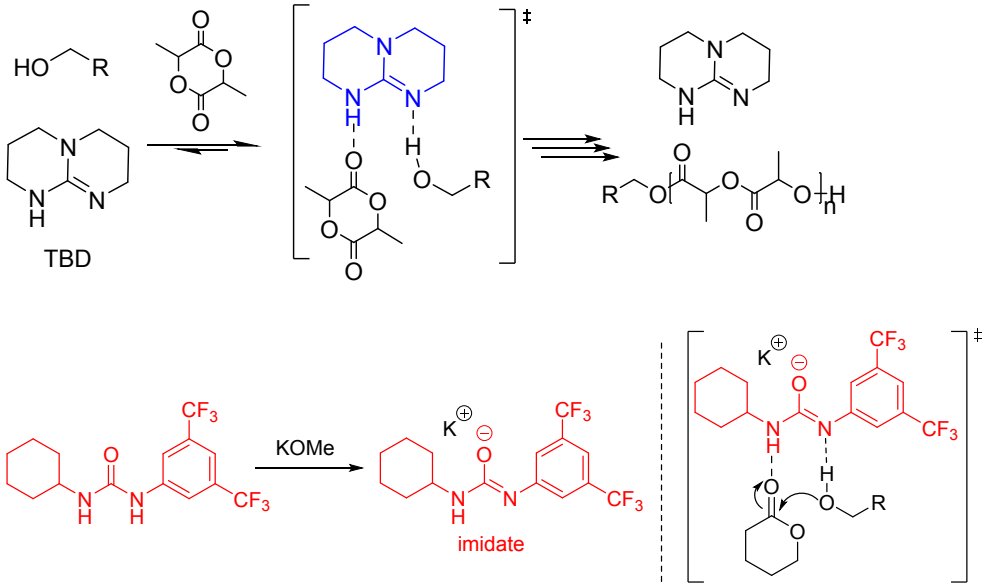


Figure 4. The thiourea/base mediated ROP of lactones slows in polar solvent while urea/base mediated ROP remain active.

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 3).[1,2,49,50] The mode of activity displayed by TBD serves a as an analogy to the advance made by Waymouth and coworkers whereby a thiourea is treated with a strong base to form a thioimidate species, which is highly-active for ROP, Scheme 3.[35,51] The treatment of a thiourea with strong bases like sodium and potassium methoxides form the thioimidate salt and an alcohol which can be used as catalyst/initiator systems for the ROP of lactones. The thioimidate (anionic thiourea) can function both as an H-bond donor and acceptor similar to TBD (Scheme 3).[51] When the ROP of LA ($[LA]_o/[NaOCH_3]_o = 200$) 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 3. The larger association constant for the binding of TU^-K^+/HO^tBU to VL (24±4 M^{-1}) versus ethyl acetate (5±2 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]



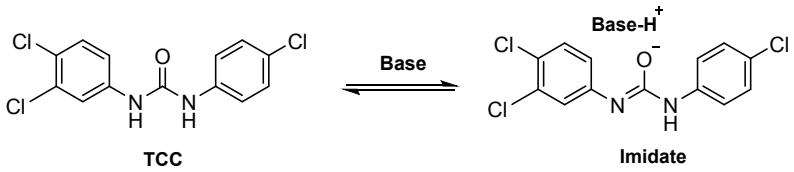
Scheme 3. (upper) Bifunctional activation of monomer and initiator/chain end by TBD (lower) Formation of imidate catalyst and suggested activation modality.

The treatment of a urea H-bond donor with a strong base form 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 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$[initiator]_o$ and inverse first order dependence on urea when $[alkoxide]_o \leq [urea]_o$. 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 TCC/base mediated ROP, and a simple ^{1}H NMR experiment of TCC with and without base cocatalyst proved highly diagnostic. 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 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]



Scheme 4. Equilibrium between neutral versus imidate TCC with base

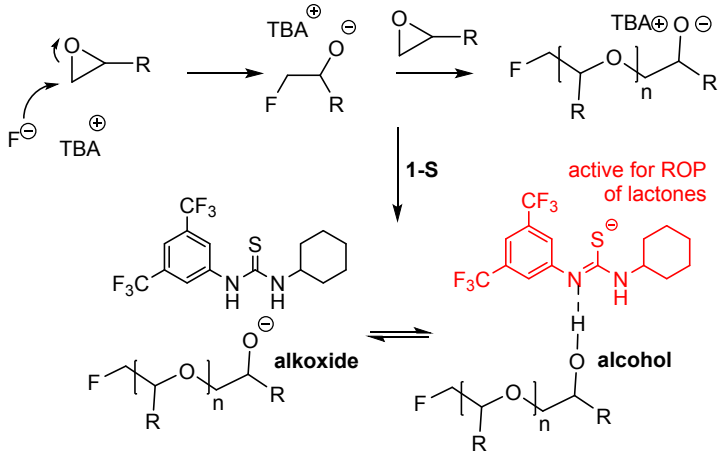
NEW REACTIONS AND ABILITIES

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 mediate 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 (PγBLs) via selective ROP of "nonpolymerizable" γ-butyrolactone (γBL) at -40^{o}C.[28,29] The utility of commercially available phosphazene super bases and (thio)ureas facilitated the formation of linear PγBL initiated by the alcohol species. These species display among the highest activity for the organocatalytic ROP of γBL.[28] The ROP of γBL 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.

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-polylactide 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** thioimidate, which is competent for the controlled ROP of LA, Scheme 5. Hence, the mechanistic duality of the **1-S** system directly facilitates the one pot copolymerization of epoxide and LA.[14,56–58]



Scheme 5. ROP of epoxides and thiourea mediated conversion of alkoxide to alcohol and thioimdate for the ROP of lactones.

CONCLUSION

Since the application of the Takemoto thiourea for ROP and the discovery that covalent 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.

BIOGRAPHIC SKETCHES

Nayanthara U. Dharmaratne was born in 1991 in Colombo, Sri Lanka. Following her BS in chemistry in 2015 from the Institute of Chemistry Ceylon in Sri Lanka, she started her graduate carrier as a synthetic polymer chemist in 2015 at the University of Rhode Island under the guidance of Prof. Matthew Kiesewetter. Her current research focuses on designing and synthesizing organic catalysts for ring-opening polymerizations, synthesizing novel monomers to produce biodegradable, biocompatible polymers and studying the chemistry of non-strained cyclic lactones.

Jinal U. Pothupitiya was born in 1991 in Colombo, Sri Lanka. He received his BS in Chemistry in 2014 from the College of Chemical Sciences, Institute of Chemistry Ceylon in Sri Lanka. He is

currently a PhD candidate at the University of Rhode Island under the advisement of Prof. Matthew Kiesewetter. He is extremely fond of synthesizing and studying novel polymeric materials and developing new applications for them. His current research interests are in the area of polymer chemistry and engineering, materials chemistry, and catalysis.

Matt Kiesewetter was born in 1982 in Normal, Illinois. His initial training was in physical organic chemistry with Professor Cheryl D. Stevenson at Illinois State University where he received his BS in Chemistry in 2004. He conducted his graduate research in polymerization catalysis under the advisement of Prof. Robert M. Waymouth and Dr. Jim Hedrick (IBM) at Stanford University. Following postdoctoral research with Prof. Tim Swager (MIT), he joined the faculty at the University of Rhode Island in 2013 where he is currently Associate Professor of Chemistry. His current research interests are in homogeneous catalysis, supramolecular chemistry and polymerization chemistry.

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