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Cooperative Hydrogen-Bond Pairing in Organocatalytic Ring-Opening Polymerization

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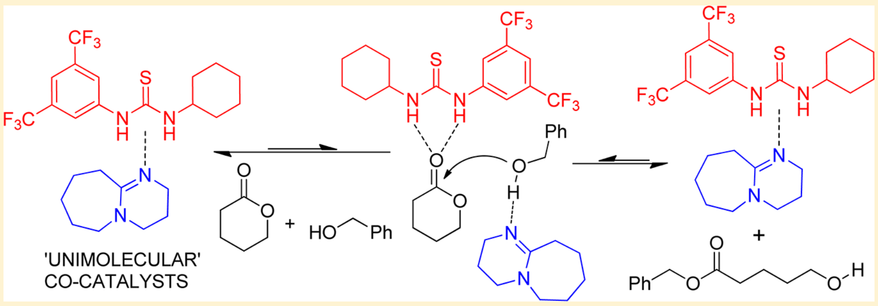
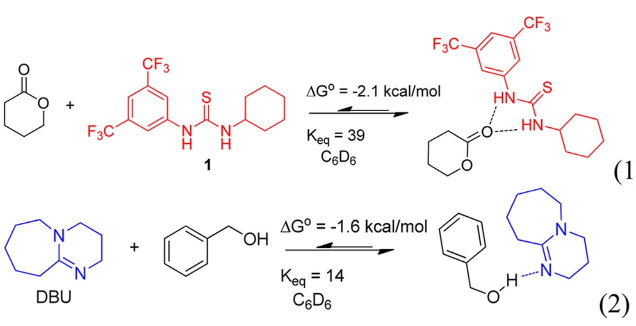
Supporting Information



ABSTRACT: Thiourea (TU)/amine base cocatalysts are commonly employed for well-controlled, highly active "living" organocatalytic ring-opening polymerizations (ROPs) of cyclic esters and carbonates. In this work, several of the most active cocatalyst pairs are shown by ^{1}H NMR binding studies to be highly associated in solution, dominating all other known noncovalent catalyst/reagent interactions during ROP. One strongly binding catalyst pair behaves kinetically as a unimolecular catalyst species. The high selectivity and activity exhibited by these ROP organocatalysts are attributed to the strong binding between the two cocatalysts, and the predictive utility of these binding parameters is applied for the discovery of a new, highly active cocatalyst pair.

INTRODUCTION

The multitude of polymer architectures and constructs that can be generated via organocatalytic ring-opening polymerization (ROP) is largely driven by the precise level of reaction control engendered by the catalysts.[1−3] The asymmetrical thiourea, **1** in Scheme 1, is believed to selectively activate cyclic esters and carbonates for ROP (eq 1);[4] it is conveniently synthesized,



highly active, and has become a preferred hydrogen bond donor for ROP.[4−10] A more varied slate of base cocatalysts (H-bond acceptors) is used to activate the initiating/propagating alcohol for nucleophilic attack (eq 2)[4,6,8] and stronger bases are generally more active as cocatalysts for ROP.[11] The imine bases, particularly 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU in Scheme 1), have found common implementation in ROP.[1,3,4,7,12] The preponderance of experimental[4,10,13,14] and computational[13,15,16] evidence suggests that bimolecular hydrogen bond activation of lactone and initiating/propagating alcohol facilitates the rapid ROP of lactone monomers exhibited by **1**/DBU (Scheme 1).[3,4,17] The exact balance of interactions that must exist for a "living" ROP to occur is impressive,[5] and deep mechanistic insights into the robust and diverse set of H-bonding ROP organocatalysts will be the driving force for the development of the improved catalysts which precede new materials. In the following, we present evidence that **1** and amine base cocatalysts are highly associated in solution and that this binding is productive rather than inhibitory toward the high activity and selectivity of these **1**/amine base systems. This increased mechanistic understanding is applied to the discovery of a new cocatalyst pair for ROP.

RESULTS AND DISCUSSION

Chemical Kinetics. Kinetic studies were undertaken to help elucidate the roles of **1** and DBU in the ROP of δ-valerolactone (VL). While holding the concentration of VL (2 M, 1.00 mmol) and benzyl alcohol (0.04 M, 0.020 mmol) constant in C_6D_6, the concentrations of **1** and DBU were varied from [**1**] = [DBU] = 0.05 to 0.20 M (see Supporting Information). The resulting plot (Figure 1) of observed rate constant, k_{obs}, versus

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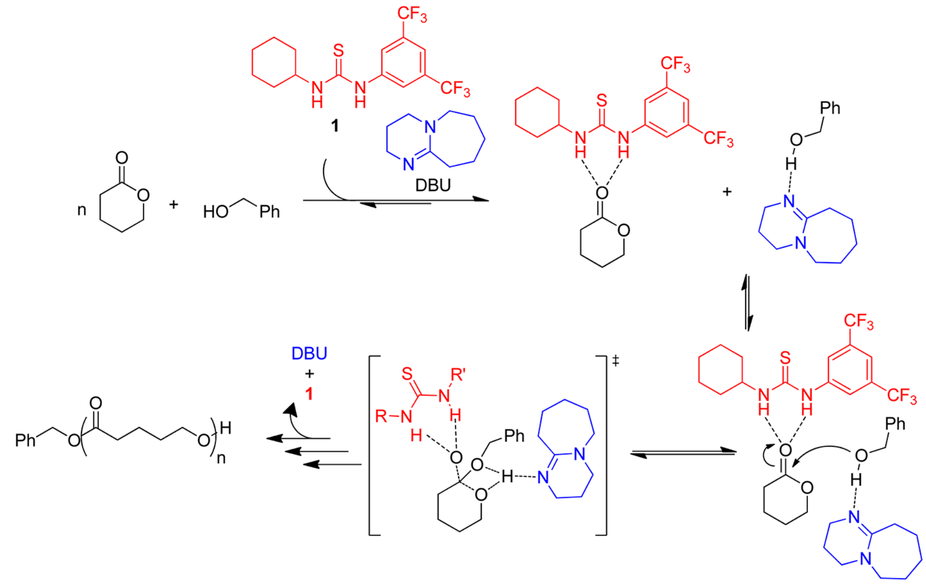
Scheme 1. H-Bonding Mechanism for the ROP of δ-Valerolactone



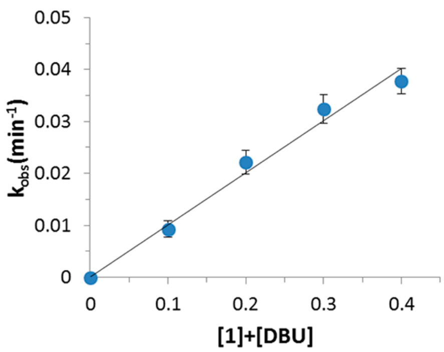


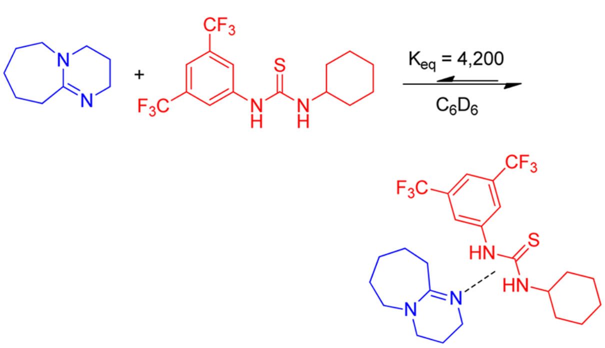
Figure 1. For the ROP of VL, observed rate constant (k_{obs}) vs [**1**] + [DBU]. Conditions: VL (2 M, 100 mg):benzyl alcohol 50:1 in C_6D_6. Rate = k_{obs}[VL], where k_{obs} = k_P([**1**] + [DBU])[benzyl alcohol].

([**1**] + [DBU]), where [**1**] = [DBU], is linear, which describes an ROP reaction that is first order in cocatalysts: Rate = k_{obs}[VL], where k_{obs} = k_P([**1**] + [DBU])[benzyl alcohol], and k_P is the polymerization rate constant. This observation is in contrast to a previous report which assumed for purposes of kinetic fitting that rate is proportional to both [**1**] and [base] (i.e., k_{obs} = k_P[**1**][base][benzyl alcohol]).[4] The ROP rate being proportional to ([**1**] + [DBU]) suggests a cocatalyst system that behaves as a discrete catalyst species, yet the role of the individual cocatalyst moieties is unclear.

Kinetic studies were also undertaken when [**1**] ≠ [DBU]. For the case where **1** is in excess, the observed rate constant is insensitive to [**1**] (within error) for the concentration range examined (see Supporting Information). The thiourea, **1**, is known to self-bind at high concentrations,[5] and any increased monomer activation may be attenuated by catalyst self-inhibition (due to **1**·**1**) at [**1**] > 0.2 M. In the case of [DBU] > [**1**], the data describe a reaction that is inverse first order in [DBU] for the entire concentration range examined (100 mM < [DBU] < 400 mM; [**1**] = 50 mM) (see Supporting Information). The fact that both cocatalysts must be present for ROP to occur suggests that DBU facilitates catalysis. However, the empirical rate dependences upon [**1**] and [DBU] imply an inhibitory role for DBU which would occur upon a strong binding interaction between **1** and DBU.

Cocatalyst Binding. Inhibitory interactions by amine base cocatalysts upon **1** have been suggested by other researchers to decrease ROP rate.[5] In an illuminating study of several cocatalysts, it was found via ^{1}H NMR binding studies that **1** and sparteine, an erstwhile favorite catalyst pair for the ROP of lactide,[9] exhibit a moderate binding constant of $K_{eq}(CDCl_3)$ = 6 ± 1.[5,18] This magnitude of binding constant was not thought to be inhibitory to catalysis, but the same study ascribed the reduced activity of some more strongly binding cocatalysts to an undesirable H-bond equilibrium that reduces the effective concentration of catalyst through self-inhibition.[5,7] The potent H-bonding ability of DBU[19] and high activity of **1**/DBU for ROP belie this concept.

A ^{1}H NMR binding study[20] conducted in our laboratory by serial dilution of a 1:1 mixture of DBU and **1** (from 5 to 0.125 mM) reveals a strong **1**·DBU binding constant of K_{eq} = 4200 ± 170 (eq 3) (see Supporting Information). Such strong



(3)

interactions have previously been posited (*vide infra*) between Coulombically tethered cocatalysts,[14] and strong cocatalyst binding is not necessarily inhibitory to ROP. All binding processes are reversible and rapid on the NMR time scale, and the ROP is determined by the approach to the equilibrium monomer concentration, $[VL]_{eq}$. The strong **1**·DBU binding constant may simply act in concert with other known interactions (**1**·VL and DBU·benzyl alcohol; eqs 1 and 2) to

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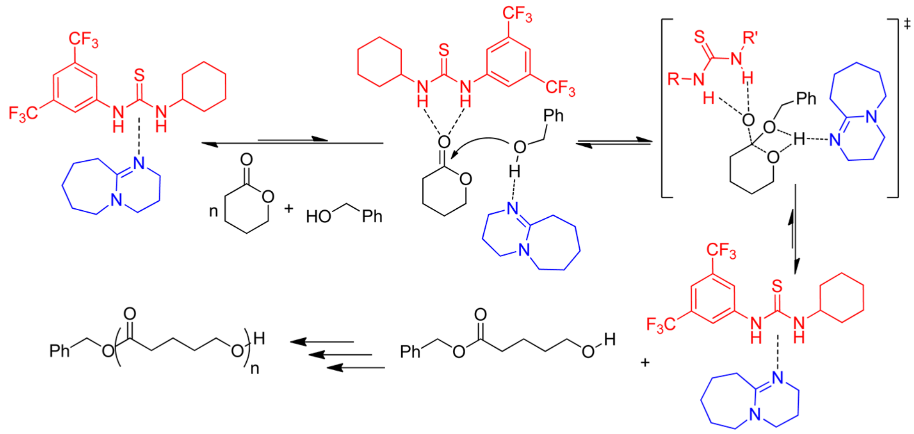
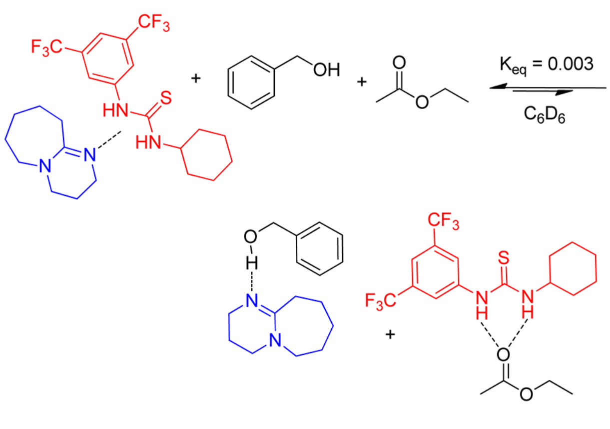
Scheme 2. Proposed Cocatalyst Binding Mechanism for the ROP of VL



hold all reagents in close proximity during a rapid exchange of binding partners, thereby accelerating the reaction.[21] However, the kinetic data suggest that the strong binding could serve to make a distinct catalytic species.[22] The binding and kinetic data collectively describe a reaction process where highly self-associated cocatalysts can be cooperatively interrupted by VL and alcohol to result in a reaction turnover (Scheme 2).

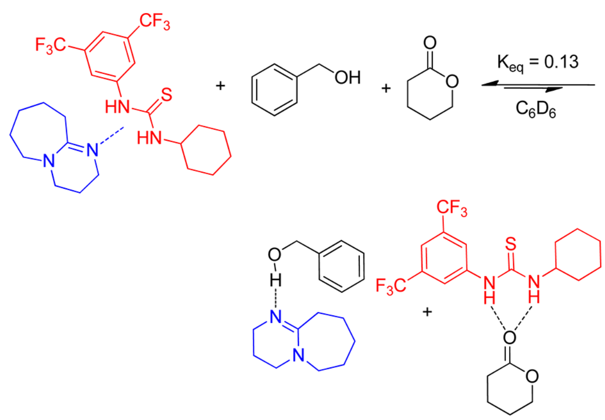
The selectivity of **1**/DBU for monomer in the ROP of VL can be rationalized by the magnitude of the **1**·DBU binding constant. This selectivity has previously been attributed to the preference of **1** to bind to *s*-cis esters (monomers) versus *s*-trans esters (polymer backbone);[4] however, some **1**/amine base combinations result in almost zero transesterification of the resultant polymer after 4 h.[23] The very dependence of postpolymerization transesterification upon the identity of the base cocatalyst suggests that factors other than the **1**·ester binding constants control ROP selectivity. Indeed, the identity of the base cocatalyst dominates the equilibria which describe the ability of ethyl acetate (a surrogate for polymer, which exhibits a small but nonzero binding to **1**)[4] to interrupt the **1**·DBU pair (eq 4) versus that of VL (eq 5). These values (K_{eq} =



(4)

0.003 vs K_{eq} = 0.13, respectively), which can be found through thermodynamic sums, could account for the high selectivity of the ROP reaction. Further, altering the base cocatalyst would be expected to drastically alter the cocatalyst selectivity for monomer, as empirically observed.[1−3,23]

Our study was continued on a variety of base cocatalysts (with **1**) for ROP, and a relationship between cocatalyst binding and ROP activity was discovered. Binding constants to **1** in C_6D_6 were measured by either the dilution or titration



(5)

method[24−27] for bases previously evaluated as cocatalysts in the ROP literature: DBU, MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), pyridine, proton sponge (1,8-bis(dimethylamino)naphthalene), and DMAP (4-(dimethylamino)pyridine). The k_{obs} values were also measured for each of these bases (see Supporting Information) in the **1** (0.1 M, 0.050 mmol) and base (0.1 M, 0.050 mmol) catalyzed ROP of cyclic ester monomers (2 M, 1.00 mmol) from benzyl alcohol (0.04 M, 0.020 mmol); the results of these experiments are shown in Table 1. In general, a strong **1**·base binding constant is associated with rapid ROP, and weakly binding cocatalysts exhibit very low or zero ROP activity.

Table 1. Binding Constants and Observed Rate Constants for the Bases Studied

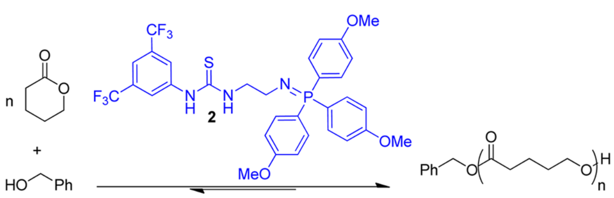
base	K_{eq} [a]	k_{obs} [b] $\times 10^{-3}$, min^{-1}
proton sponge	0	0[c]
pyridine	9 ± 1	0[c]
DMAP	170 ± 30	4.1 ± 0.2[c]
BEMP	1200 ± 40	17.8 ± 0.3
MTBD	1500 ± 100	20.0 ± 0.1
DBU	4200 ± 170	16.2 ± 0.1

[a]Binding constant (at 292 K) for base + **1** in equilibrium with **1**·base as measured with NMR titration/dilution experiments. [b]Observed rate constant, k_{obs}, for the **1**/base catalyzed ROP of VL from benzyl alcohol. Conditions VL:base:**1**:benzyl alcohol:100 (100 mg, 2 M):5:5:2 in C_6D_6. [c]Observed rate constant (at 100 h) for the ROP of LA, same experimental conditions as footnote [b].

In the low binding constant regime, K_{eq} correlates with polymerization rate, and cocatalyst binding constant appears to be a better predictor of catalytic activity than does pK_a. The k_{obs} for the systems that exhibited weak binding (**1** with DMAP, pyridine, or proton sponge) were measured for the **1**/base catalyzed ROP of L-lactide (LA) (Table 1) as they are not active for the ROP of VL. Of these cocatalysts, only **1**/DMAP exhibits ROP activity: $k_{obs}(LA) = 4.1 \times 10^{-3}$ min^{-1}. Both **1**/pyridine and **1**/proton sponge are inactive for the ROP of LA, but **1**·pyridine displays weak binding (**1**·pyridine $K_{eq} = 9 \pm 1$) whereas **1**·proton sponge exhibits none. The binding constant observed for **1**·DMAP was the strongest of the three (**1**·DMAP $K_{eq} = 170 \pm 30$). A pK_a explanation of ROP activity is unsuccessful for the case of DMAP vs proton sponge (in acetonitrile: DMAP-H$^+$$pK_a = 18.2$;[28] proton sponge-H$^+$$pK_a = 18.7$),[29,30] yet their ROP activities correlate well with the strength of their binding to **1**. For the **1**/pyridine system, its moderate binding constant yet lack of ROP activity could indicate that ROP is only feasible when cocatalyst binding becomes competitive with **1**·lactone binding (**1**·VL $K_{eq}(C_6D_6) = 44$;[4] **1**·LA $K_{eq}(CDCl_3) = 2$)[5] such that the cocatalysts are closely associated in solution.

The binding constant between **1** and DBU was the strongest measured, but this catalyst pair is not the most active of those examined for the ROP of VL. **1**/MTBD exhibited a faster rate for the ROP of VL than **1**/DBU, which is reasonably predicted by pK_a: MTBD-H$^+$ $pK_a^{MeCN} = 25.4$;[30] DBU-H$^+$ $pK_a^{MeCN} = 24.3$.[30] As Bibal et al. noted, strong cocatalyst binding is anticipated to be inhibitory to ROP,[5,6] and one interpretation of the **1**/DBU vs **1**/MTBD reactions is that ROP activity (k_{obs}) becomes attenuated due to catalyst inhibition if the cocatalyst binding constant becomes too large, $1500 < K_{eq} < 4200$.

BEMP/1 Catalyzed ROP. One of the most powerful applications of reaction mechanism elucidation is in the discovery of new catalyst species, and we sought to ply our increased understanding of **1**/base catalyzed ROP to this end. While this work was ongoing, Dixon et al. reported the ROP of VL by a phosphazene-inspired bifunctional TU-iminophosphorane catalyst, **2** in eq 6.[31] The bifunctional catalyst **2**



(6)

exhibits "living" ROP behavior, the usual relative monomer reactivity ($k_{LA} > k_{VL} \gg k_{CL}$), and good selectivity for monomer.[31] While the application of phosphazene bases like BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) to the ROP of LA is known,[32] this superbase is not active for the ROP of VL except in neat monomer where reaction control is poor (2 days, 93% conversion, $M_w/M_n = 1.23$).[33]

The binding constant of BEMP and **1** was measured in C_6D_6, $K_{eq} = 1200 \pm 40$. Within the set of K_{eq} vs k_{obs} data, the strength of the **1**·BEMP binding constant suggests its VL ROP activity should be similar to that of **1**/MTBD. Indeed, the observed rate constant for the **1**/BEMP catalyzed ROP of VL ($k_{obs}(VL) = 17.8 \times 10^{-3}$ min^{-1}) is slightly less than that of **1**/MTBD, as would be expected by the **1**·BEMP K_{eq} value. This result would not be anticipated by a pK_a argument: BEMP-H$^+$ $pK_a^{MeCN} = 27.6$;[34] MTBD-H$^+$ $pK_a^{MeCN} = 25.4$.[30] Further studies show that **1**/BEMP is active for the ROP of VL, ε-caprolactone (CL), and trimethylene carbonate (TMC) but is inactive for β-butyrolactone (BL) (Table 2). The **1**/BEMP catalyzed ROP of VL from pyrenebutanol exhibits the characteristics of a "living" ROP: linear evolution of M_n with conversion (see Supporting Information), evidence of end-group fidelity (overlapping RI and UV signals by GPC), and M_n that is predictable by $[M]_0/[I]_0$. The evidence of H-bonding for both BEMP-to-alcohol[33] and **1**-to-VL[4] taken with these experimental observations suggests an H-bond mediated "living" ROP of VL. The ROP activity (for VL) of the cocatalyst systems **1**/BEMP, **1**/DBU, and **1**/MTBD is only slightly attenuated in THF.

Table 2. 1/BEMP Catalyzed ROP of Cyclic Monomers[a]

monomer	$[M]_0/[I]_0$	time (h)	% conv	M_n(GPC)	M_w/M_n
BL[b]	100	48	0		
VL	50	0.75	88	6200	1.05
VL	100	2	92	14600	1.03
VL	200	3	83	32200	1.01
VL	500	5	98	92600	1.01
CL[b]	50	42	98	8900	1.03
CL[b]	100	75	94	17000	1.02
TMC[b]	50	0.2	99	2800	1.07
TMC[b]	100	0.3	97	7600	1.03

[a]Reaction conditions: monomer (2 M, 100 mg), pyrenebutanol, 5 mol % BEMP and 5 mol % **1**. Reactions conducted in dry toluene in a glovebox (N_2) and quenched at the given time by the addition of 2 mol equiv of benzoic acid to BEMP. [b]Reactions performed in C_6D_6.

CONCLUSION

For the organocatalytic ROP cocatalysts examined, the magnitude of the cocatalyst binding constant has been shown to be proportional to the ROP rate. For the bases studied, cocatalyst binding constant is a far better predictor of catalytic activity than pK_a. The strongly binding **1**/DBU system behaves kinetically as a unimolecular catalyst species, and it could be representative of a hydrogen-bonding analogue of so-called "cooperative ion pairing" in asymmetric organocatalysis.[22] We agree with the conclusion of Bibal et al. that TU/amine base binding can be inhibitory to ROP[5,6] but submit that (1) the phenomenon is much more general than first proposed, (2) the magnitude of the interaction may be a good predictor of cocatalyst activity, and (3) the point at which cocatalyst binding becomes counterproductive to catalysis is significantly higher than once believed. As organocatalysis strives to mimic the awe-inspiring catalytic abilities of nature, it is important to fully understand the catalytic systems being employed. As it would happen, the roles of **1** and DBU in the ROP of VL are not very dissimilar from those of enzyme and cofactor. Further mechanistic studies are ongoing; such studies have already revealed one new catalyst system for ROP (**1**/BEMP), and they are expected to yield dividends in the form of more new catalyst systems.

EXPERIMENTAL SECTION

General Considerations. All manipulations were performed in an MBRAUN stainless steel glovebox equipped with a gas purification system under a nitrogen atmosphere. All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise.

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Toluene and THF were dried on an Innovated Technologies solvent purification system with alumina columns and nitrogen working gas. Benzene-d_6 was supplied by Cambridge Isotope Laboratories and distilled from CaH_2 under a nitrogen atmosphere. δ-Valerolactone (VL; 99%) and ε-caprolactone (CL; 99%) were distilled from CaH_2 under high vacuum. Benzyl alcohol was distilled from CaH_2 under high vacuum. L-Lactide was supplied by Acros Organics and recrystallized from dry toluene prior to use. 1-[3,5-Bis-(trifluoromethyl)phenyl]-3-cyclohexylthiourea (**1**) was synthesized and purified according to literature procedures.[4] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) were purchased from TCI. NMR experiments were performed on a Bruker Avance 300 MHz spectrometer. Size exclusion chromatography (SEC) was performed at 40 °C in dichloromethane (DCM) using an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm × 300 mm (5 μm, pore sizes: 10^3, 10^4, and 10^5 Å). Molecular weight and M_w/M_n were determined versus PS standards (500 g/mol−3150 kg/mol; Polymer Laboratories).

Determination of Binding Constant by the Dilution Method. A stock solution containing **1** (2.8 mg, 0.0075 mmol) and DBU (0.0011 mL, 0.0075 mmol) was prepared in deuterated benzene (1.5 mL). This solution was distributed to 6−10 NMR tubes, and each NMR tube was diluted with benzene-d_6 to give final concentrations ranging from 5 to 0.313 mM. ^{1}H NMR spectra (referenced to residual benzene-H) were acquired for each tube at multiple temperatures, and the chemical shift of the *ortho*-protons of **1** was noted. The K_{eq} values were determined from the linearized (Lineweaver−Burke) forms of the binding equations (see Supporting Information), which are a powerful means of accurately measuring binding constants with fewer samples (versus curve fitting).[25] The binding constant for each **1**/base pair was determined at elevated temperatures (303−323 K). The enthalpy and entropy of binding were determined by plotting ln K_{eq} versus $1/T$ to conduct a Van't Hoff analysis, and error was determined from linear regression at the 95% confidence interval.

Example Determination of k_{obs}. In a glovebox under a nitrogen atmosphere, one vial (baked at 140 °C overnight) was loaded with a stir bar and δ-valerolactone (VL) (0.0927 mL, 1.00 mmol). A second dried vial was loaded with benzyl alcohol (0.0021 mL, 0.020 mmol), **1** (18.5 mg, 0.050 mmol), and DBU (0.0075 mL, 0.050 mmol). 200 μL of deuterated benzene was added to the first vial, and 300 μL of deuterated benzene was added to the second vial. The solutions were stirred until homogeneous. The reaction was started by transferring the solution of VL into the vial containing catalyst solution and stirred to mix before transferring to an NMR tube. The change in the concentration of the monomer was monitored by ^{1}H NMR. Rate constants were extracted from a plot of $\ln([VL]_0/[VL])$ versus time; the reaction is linear on this plot to 3+ half-lives. The slope of this plot is k_{obs}, and the error was determined by propagation of NMR integration error at ±5%. Only [**1**] and [DBU] were varied between individual kinetic runs.

Example Ring-Opening Polymerization. In a typical polymerization, VL (0.100 g, 0.999 mmol) was added to a 20 mL glass vial containing a stir bar, both of which were baked at 140 °C overnight. In another dried 20 mL glass vial with stir bar, **1** (0.0185 g, 0.499 mmol), BEMP (14.45 μL, 0.499 mmol), and pyrenebutanol (9.96 μmol) were added. Solvent (for C_6D_6 0.4744 g, 2 M in VL) was added to both vials to bring the total mass of solvent to the desired level, approximately equal portions of solvent per vial. After stirring for 5 min, the VL solution was transferred via pipet to the vial containing catalysts and initiator. To quench the reaction, benzoic acid (2 mol equiv to base) was added. The vial was removed from the glovebox, and the polymer solution was treated with hexanes to precipitate the polymer. The hexanes supernatant was decanted, and the polymer removed of volatiles under reduced pressure. Yield, 90%; M_w/M_n = 1.03; $M_{n(GPC)}$ = 16 800. ^{1}H NMR (C_6D_6) δ: 7.22−7.17 (2H, d, benzyl aryls), 7.13−7.05 (3H, m, benzyl aryls), 4.97 (2H, s, benzylic), 3.91 (193H, t, $-C(O)OCH_2-$), 2.04 (193H, t, $-CH_2C(O)O-$), 1.58−1.30 (386H, m, $C(O)CH_2CH_2CH_2CH_2O-$).

ASSOCIATED CONTENT

Supporting Information

Binding equations, binding curves, thermodynamic values, kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

O.I.K. and P.P.D. contributed equally.

Notes

The authors declare no competing financial interest.

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