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Cooperative Hydrogen-bond Pairing in Organocatalytic Ring-Opening Polymerization

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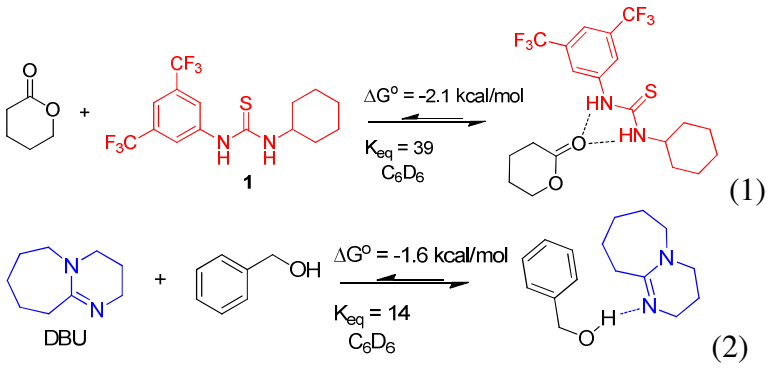
ABSTRACT

Thiourea (TU)/amine base co-catalysts 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 co-catalyst pairs are shown by ^{1}H-NMR binding studies to be highly associated in solution, dominating all other known non-covalent 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 is attributed to the strong binding between the two co-catalysts, and the predictive utility of these binding parameters is applied for the discovery of a new, highly active co-catalyst pair.

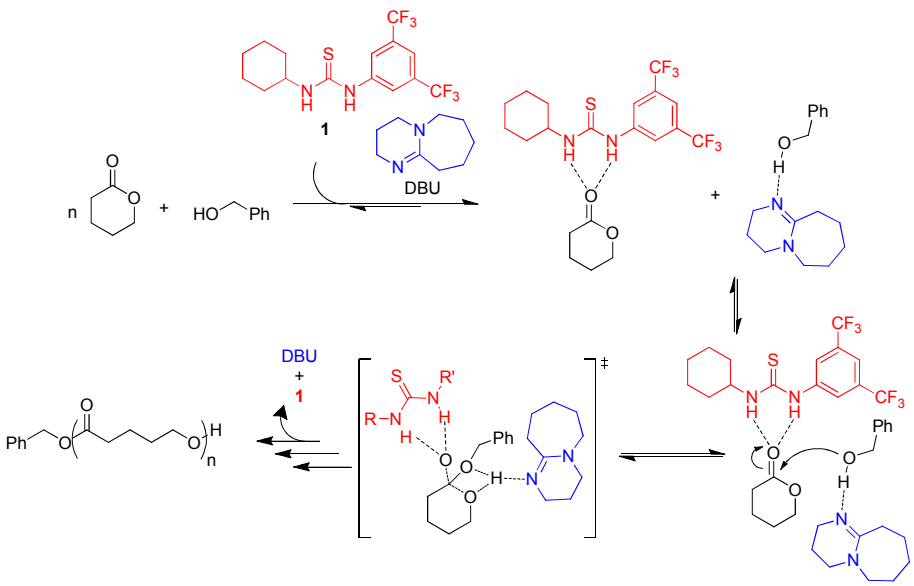
INTRODUCTION

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 co-catalysts (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 co-catalysts 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 co-catalysts 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 co-catalyst pair for ROP.



Scheme 1: H-bonding mechanism for the ROP of δ-valerolactone



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 (2M, 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 (SI). The resulting plot, Figure 1, of observed rate constant, k_{obs}, versus ([**1**] + [DBU]), where [**1**] = [DBU], is linear which describes an ROP reaction that is first order in co-catalysts: 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 co-catalyst system that behaves as a discrete catalyst species, yet the role of the individual co-catalyst moieties is unclear.

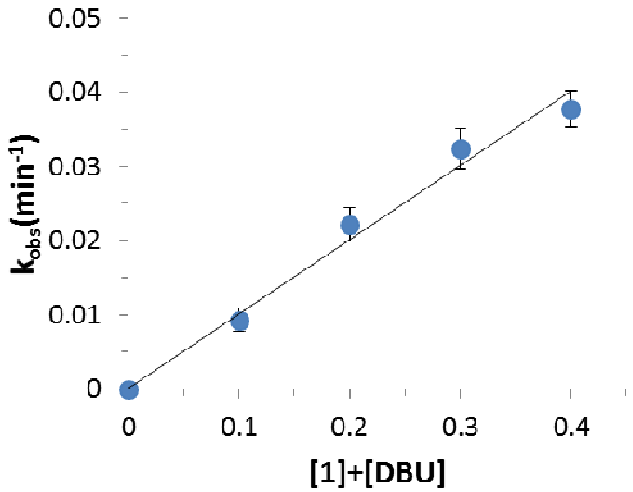


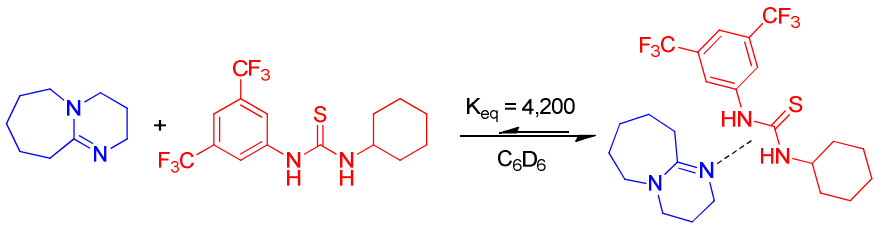
Figure 1. For the ROP of VL, observed rate constant (k_{obs}) vs [**1**]+[DBU]. Conditions: VL (2M, 100 mg):benzyl alcohol 50:1 in C_6D_6. Rate= k_{obs} [VL]; where $k_{obs} = k_P$([**1**] +[DBU])[benzyl alcohol].

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 SI). 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 SI. The fact that both co-catalysts 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.

Co-catalyst Binding. Inhibitory interactions by amine base co-catalysts upon **1** have been suggested by other researchers to decrease ROP rate.[5] In an illuminating study of several co-catalysts, 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 co-catalysts 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 mM to 0.125 mM) reveals a strong **1**●DBU binding constant of K_{eq} = 4,200 ± 170 (eq 3), see SI. Such strong interactions have previously been posited (*vide infra*) between coulombically tethered co-catalysts,[14] and strong co-catalyst binding is not necessarily inhibitory to ROP. All binding processes are reversible and rapid on the NMR timescale, 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 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 co-catalysts can be cooperatively interrupted by VL and alcohol to result in a reaction turnover, Scheme 2.



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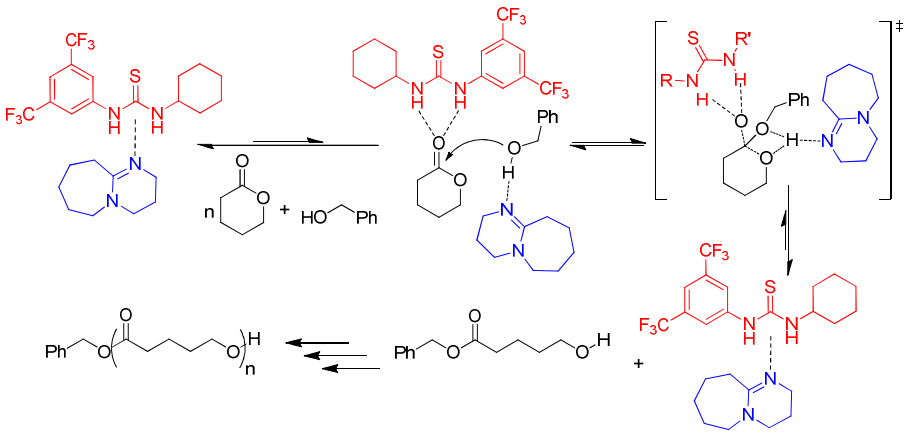
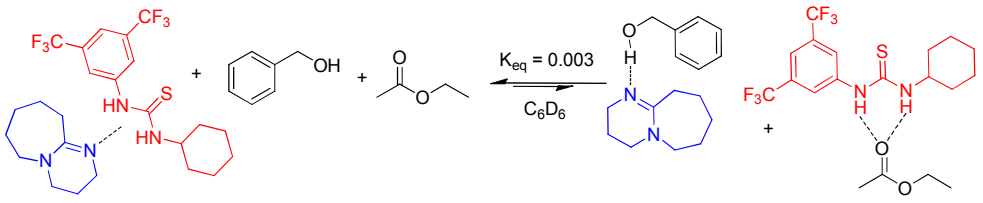
Scheme 2. Proposed Co-catalyst Binding Mechanism for the ROP of VL



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 post-polymerization transesterification upon the identity of the base co-catalyst suggests that factors other than the **1**•ester binding constants control ROP selectivity. Indeed, the identity of the base co-catalyst dominates the equilibria which describe the ability of ethyl acetate (a surrogate for polymer, which exhibits a small but non-zero binding to **1**)[4] to interrupt the **1**•DBU pair (eq 4) versus that of VL (eq 5). These values (K_{eq} = 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 co-catalyst would be expected to drastically alter the co-catalyst selectivity for monomer, as empirically observed.[1-3,23]



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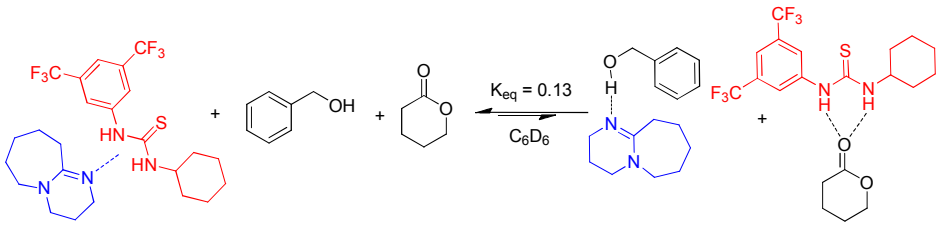


Our study was continued on a variety of base co-catalysts (with **1**) for ROP, and a relationship between co-catalyst binding and ROP activity was discovered. Binding constants to **1** in C_6D_6 were measured either by the dilution or titration method[24–27] for bases previously evaluated as co-catalysts 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-dimethylaminopyridine). The k_{obs} values were also measured for each of these bases (see SI) 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 co-catalysts 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] **x** 10^{-3}**, min**$^{-1}$
proton sponge	0	0[c]
pyridine	9 ± 1	0[c]
DMAP	170 ± 30	4.1±0.2 [c]
BEMP	1,200 ± 40	17.8±0.3
MTBD	1,500 ± 100	20.0±0.1
DBU	4,200 ± 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 (100mg, 2M):5:5:2 in C_6D_6. c) Observed rate constant (at 100 hours) for the ROP of LA, same experimental conditions as b.

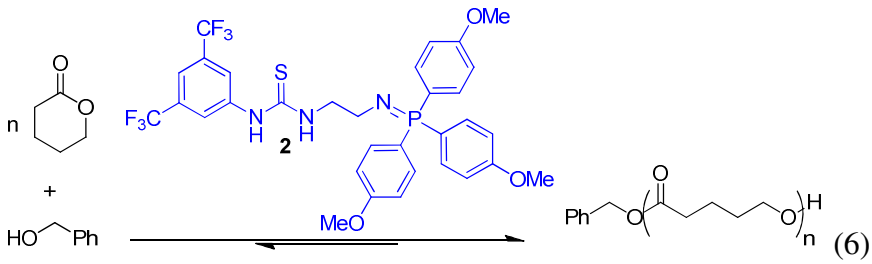
In the low binding constant regime, K_{eq} correlates with polymerization rate, and co-catalyst binding constant appears to be a better predictor of catalytic activity than does pK_a. The k_{obs} for

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 co-catalysts, only **1**/DMAP exhibits ROP activity: k_{obs} (LA)= 4.1 x 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 ± 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 ± 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 co-catalyst 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 co-catalysts 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 co-catalyst 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 co-catalyst binding constant becomes too large, 1,500 < K_{eq} < 4,200.

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** exhibits 'living' ROP behavior, the usual relative monomer reactivity ($k_{LA} > k_{VL} >> k_{CL}$), 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]



(6)

Table 2. The **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	6,200	1.05
VL	100	2	92	14,600	1.03
VL	200	3	83	32,200	1.01
VL	500	5	98	92,600	1.01
CL[b]	50	42	98	8,900	1.03
CL[b]	100	75	94	17,000	1.02
TMC[b]	50	0.2	99	2,800	1.07
TMC[b]	100	0.3	97	7,600	1.03

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

The binding constant of BEMP and **1** was measured in C_6D_6, K_{eq} = 1,200 ± 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 x 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 SI), evidence of end group fidelity (overlapping RI and UV signals by GPC), and M_n that is predictable by $[M]_o/[I]_o$. The evidence of H-bonding for both BEMP-to-alcohol[33] and **1**-to-VL[4] taken with these experimental observations suggest an H-bond mediated 'living' ROP of VL. The ROP activity (for VL) of the co-catalyst systems **1**/BEMP, **1**/DBU and **1**/MTBD is only slightly attenuated in THF.

CONCLUSION

For the organocatalytic ROP co-catalysts examined, the magnitude of the co-catalyst binding constant has been shown to be proportional to the ROP rate. For the bases studied, co-catalyst 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 co-catalyst activity; and 3) the point at which co-catalyst 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. 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 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 a Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm x 300mm (5μm, pore sizes: 10^3 Å, 10^4 Å, 10^5 Å). Molecular weight and M_w/M_n were determined versus PS standards (500 g/mol – 3,150 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 mM 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 SI), 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 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 minutes, the VL solution was transferred via pipette to the vial containing catalysts and initiator. To quench the reaction, benzoic acid (2 mol equivalents 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)$CH_2CH_2CH_2CH_2$O-).

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.

AUTHOR INFORMATION

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Author Contributions

‡These authors contributed equally.

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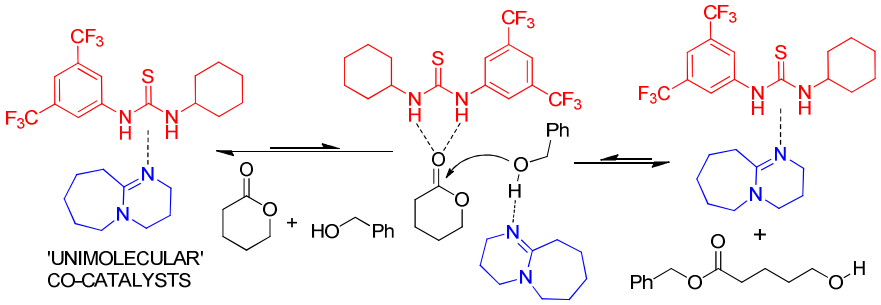
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