

Highly Selective *O*-phenylene Bisurea Catalysts for ROP: Stabilization of Oxyanion Transition State by a Semi-flexible Hydrogen Bond Pocket

Jia Zhang[†], Kai Hin Lui[†], Rachele Zunino^{‡,§}, Yuan Jia[†], Romain Morodo[†], Niklas Warlin[†], James L. Hedrick[§], Giovanni Talarico^{‡,§} and Robert M. Waymouth^{*,†}

[†]Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

[‡]Scuola Superiore Meridionale, Largo San Marcellino 10, 80138 Napoli, Italy

[§]Dipartimento di Scienze Chimiche, Università di Napoli Federico II, Complesso Monte S. Angelo, Via Cintia, I-80126 Napoli, Italy

[§]IBM Research-Almaden, 650 Harry Road, San Jose, California, 95120, United States

*Email: waymouth@stanford.edu

J.Z.; K.H.L. and R.Z. contributed equally to this paper

ABSTRACT

Organocatalyzed ring-opening polymerization (ROP) is a versatile technique for synthesizing biodegradable polymers, including polyesters and polycarbonates. We introduce *o*-phenylene bisurea (OPBU) (di)anions as a novel class of organocatalysts that are fast, easily tunable, mildly basic, and exceptionally selective. These catalysts surpass previous generations, such as thiourea, urea, and TBD, in selectivity (k_p/k_{tr}) by 8 to 120 times. OPBU catalysts facilitate the ROP of various monomers, achieving high conversions (>95%) in seconds to minutes, producing polymers with precise molecular weights and very low dispersities ($\bar{M}_w/\bar{M}_n \approx 1.01$). This performance nearly matches the ideal distribution expected from living polymerization (Poisson distribution). Density functional theory (DFT) calculations reveal that the catalysts stabilize the oxyanion transition state via a hydrogen bond pocket similar to the "oxyanion hole" in enzymatic catalysis. Both experimental and theoretical analyses highlight the critical role of the semi-rigid *o*-phenylene linker in creating a hydrogen bond pocket that is tight yet flexible enough to accommodate the oxyanion transition state effectively. These new insights have provided a new class of organic catalysts whose accessibility, moderate basicity, excellent solubility, and unparalleled selectivity and tunability open up new opportunities for controlled polymer synthesis.

INTRODUCTION

The renaissance in organocatalysis has spawned new strategies for the enantioselective synthesis of small molecules¹⁻⁸ and the rapid and selective synthesis of synthetic macromolecules⁹⁻¹¹ of defined structure and function. The origins of organocatalysis extend back to the last century.¹²⁻¹³ It has long been appreciated¹³ that the design of efficient organocatalysts can benefit from our evolving understanding of Nature's strategies for assembling the appropriate arrays of functional groups at enzymatic active sites to enhance the rate and selectivity of catalytic reactions. The extraordinary advances in the development of chiral organocatalysts for enantioselective synthesis¹⁻⁷ have led to new catalysts, processes, and mechanistic insights. While the enantioselectivities of chiral organocatalysts¹⁻⁷ have approached that of enzymes, synthetic organocatalysts have yet to match their rates and turnover numbers.¹⁴⁻¹⁵

Advances in organocatalytic ring opening polymerization (ROP) have provided new potent, metal-free strategies for synthesizing a wide range of polymers, including polyesters, polycarbonates, polysiloxanes, polyacrylates, and polyolefins.^{9-11,16-20} Early generations of organocatalysts for ring-opening polymerization (ROP) were capable of catalyzing chain growth at high rates, but the high basicity and nucleophilicity of some of these early active catalysts were often accompanied by unwanted side reactions such as competitive initiation, monomer enolization, epimerization and chain-transfer reactions.^{10,16,18,21-23}

More selective catalysts were discovered based on hydrogen bonding motifs,^{10,24} but while the thiourea/amine binary systems were able to generate polymers with narrow dispersities, the rates were low, taking days to achieve high conversions.²⁴⁻²⁵ This sluggishness limits its practicality for polymerizing most cyclic lactones or carbonates, as ROP of these monomers proceed even more slowly than lactide polymerization.²⁶⁻²⁷

A major advancement for organocatalytic ROP came with development of (thio)urea anion catalysts. Anionic catalysts derived from deprotonated thioureas²¹ and ureas²⁶⁻²⁷ are a class of highly active and tunable catalysts for ring-opening polymerization reactions, not only offering a substantial increase in polymerization rates compared to thiourea/amine systems, but also managing to preserve good selectivity. The urea anion bifunctional catalysts facilitate ring-

opening both by nucleophilic activation of the alcohol by the urea anion and association of the lactone by N-H hydrogen bonding (Fig. 1a).^{21,26-27} The activity of these urea anions is strongly dependent on the pK_a of the urea: the most reactive urea anions are the most basic, but retain a single N-H bond as an H-bonding donating site (Figure 1a).

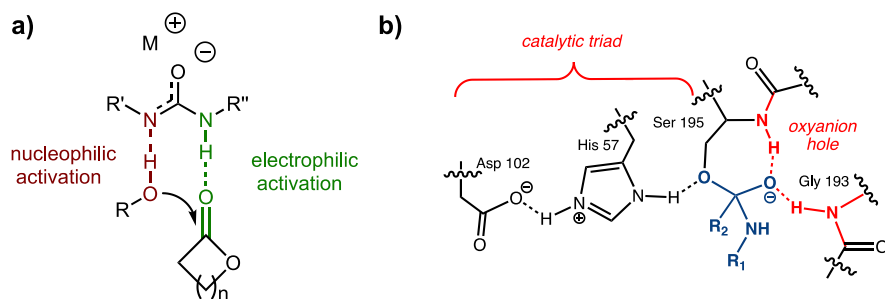


Figure 1. Activation mechanisms for (a) urea anion systems and (b) catalytic triad in serine proteases.

Inspired by the activity of serine proteases,²⁸⁻²⁹ we targeted catalyst designs that might provide better functional mimics³⁰ of these enzyme active sites. Suitably positioned histidines and glutamates (or aspartates) constitute the 'catalytic triad' of serine proteases to activate the serine to facilitate nucleophilic attack on the carbonyl substrate; multiple hydrogen-bond donors from adjacent peptidic sequences form the 'oxyanion hole'²⁹ that stabilizes the key tetrahedral intermediate in amide hydrolysis (Figure 1b).

Herein we report a series of bisurea catalysts with rigid structural linkages (Figure 2b,c) where the relative positioning of the ureas was varied to test whether the appropriate positioning of H-bonding motifs might lead to cooperative stabilization of the key tetrahedral transition states and intermediates proposed in carbonyl substitution reactions. To test for the role of electronic communication between the ureas, we prepared conjugated (BU-1~4) and non-conjugated linkers (BU-5,6) that separated the ureas (BU-5) or positioned them closely in space (BU-1,2,3,6). While other bisurea motifs, particularly those with flexible linkers, have been investigated previously,³¹⁻³⁴ here we sought to specifically test the role of conjugation and spatial positioning of the ureas to generate urea anion catalysts with enhanced activity without introducing excessive basicity.

RESULTS AND DISCUSSION

To investigate how electronic conjugation and structural proximity influences the cooperativity between the urea motifs, we synthesized a series (Figure 2 b-c) of *o*-phenylene bisureas (OPBU, BU-1~3) and other bisureas (BU-4~6) from the corresponding (di)amines and (di)isocyanates (Figure S1, Supporting Information). Bisureas BU-1 to BU-3 possess an *o*-phenylene linkage, positioning the ureas in close proximity and electronic conjugation. Related *o*-phenylene bisureas had been investigated as anion binding agents.³⁵⁻⁴⁰ BU-4 bears a similar substitution pattern to BU-2, but positions the ureas farther away through a meta-phenylene linkage. The meso BU-6 positions the ureas in proximity but lacks the conjugation of BU-1, and BU-5 was designed with a linker that spatially and electronically separates the two ureas.

As prior studies had revealed a correlation between the acidity (pK_a in DMSO) of the urea and the rate of polymerization of the urea anions,²⁷ we measured the pK_a 's of the bisureas in DMSO through UV-Vis titration studies (Figure 2. a-c, see Supporting Information, pK_a determination).⁴¹ Although the catalytic reactions are carried out in THF, DMSO was chosen as a solvent for the pK_a measurements to allow for correlations with pK_a 's of other ureas⁴¹⁻⁴⁴ and to avoid potential complications from ion-pairing effects, which can influence the experimental measurements of pK_a in THF.⁴⁵

The pK_a measurements demonstrated that the *o*-phenylene bisureas (OPBUs) are quite acidic, with BU-1 (pK_{a1} = 12.5) and BU-2 (pK_{a1} = 13.2) displaying higher acidity than the monourea U-1 (pK_a = 13.8).⁴¹⁻⁴² The *o*-phenylene bridged bisureas (BU-1~3) are more acidic than the meta-substituted bisurea BU-4, and the non-conjugated bisureas BU-5 or BU-6. We attribute the higher acidity of OPBUs to the conjugation provided by the *o*-phenylene linkage, which stabilizes these bisurea anion conjugate bases.

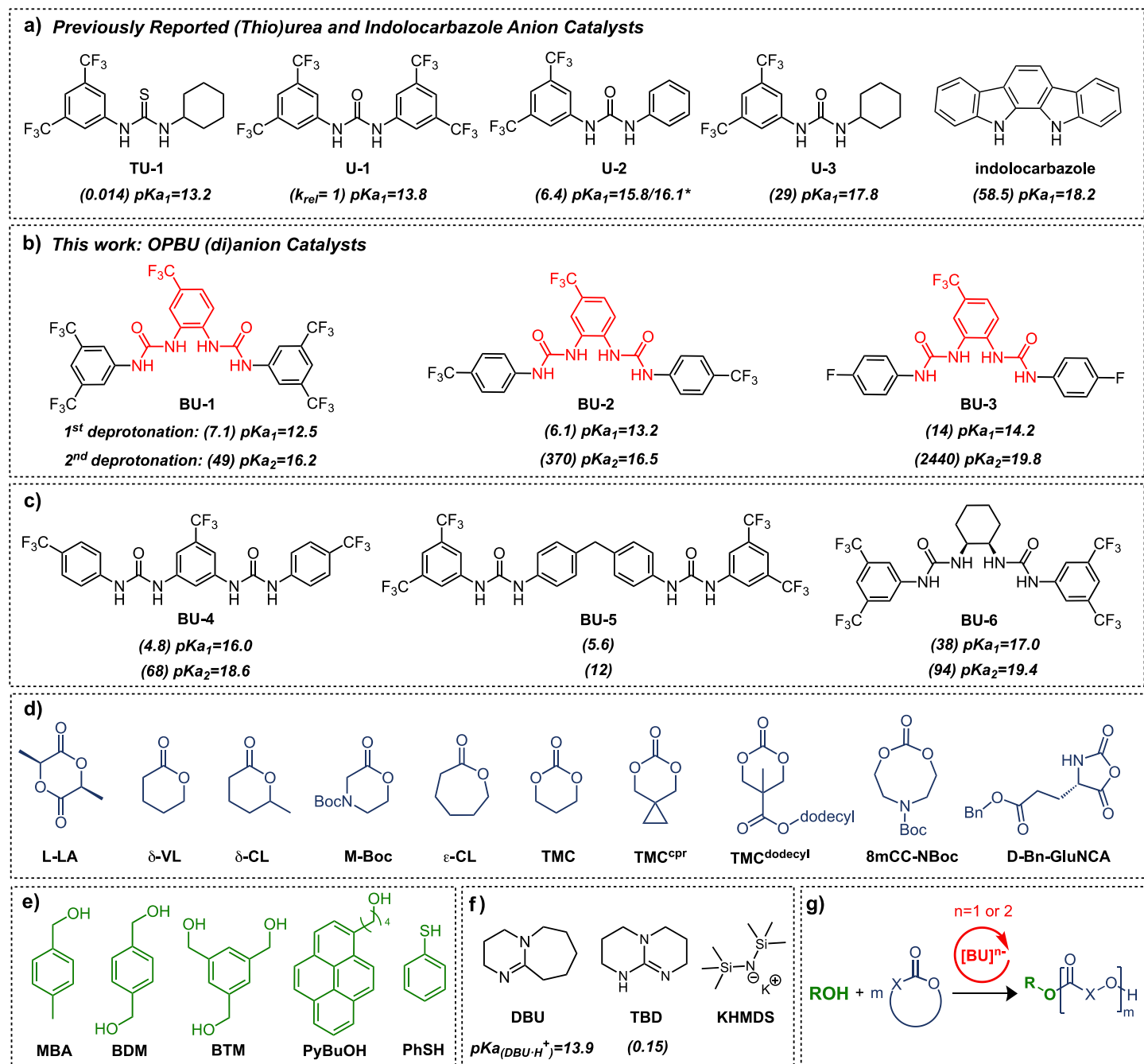


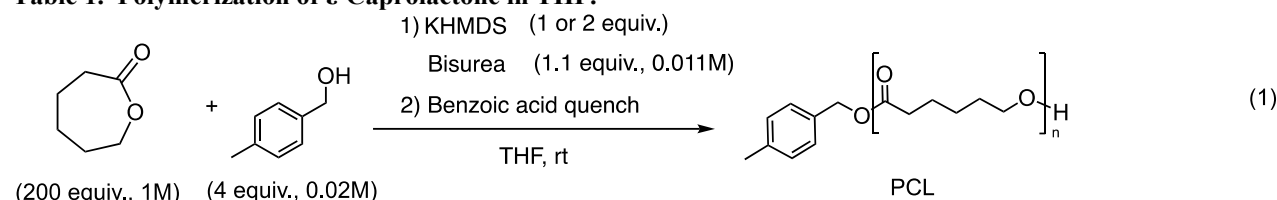
Figure 2. (a) Previously reported (thio)urea anion and indolocarbazole anion catalysts tested (in parentheses are the relative k_p for the polymerization of ϵ -CL initiated with 4-methylbenzyl alcohol (MBA) normalized with respect to U-1) *pK_a of U-2 in DMSO reported by Schreiner is 16.1, our lab measured a similar value of 15.8^{41,46} (b) *O*-phenylene bisurea (OPBU) catalysts for this study (in parentheses are the relative k_p normalized to U-1 after single or double deprotonation). pK_{a1} and pK_{a2} are measured by UV-Vis titration experiments in DMSO, corresponding to the 1st and 2nd deprotonation from neutral bisurea to form mono/dianionic potassium salts respectively. (c) Bisurea catalysts with different linkers studied. (d) Monomers used in this study. (e) Initiators used in this study. (f) Bases used in this study to generate (bis)urea (di)anion, or as a (co)catalyst along with bisurea. (g) General reaction scheme for ROP catalyzed by bisurea (di)anion catalysts.

As these bisureas contain two acidic ureas that can be deprotonated, we measured both the first (pK_{a1}) and second (pK_{a2}) dissociation constants in DMSO, corresponding to the deprotonation of the neutral bisurea (pK_{a1}) and the monoanion form (pK_{a2}), respectively. The substitution patterns on the aryl-rings affect both pK_{a1} and pK_{a2} of OPBUs as expected, where electron-withdrawing substituents on the N-aryl-rings (3,5-bis(CF₃)phenyl > 4-(CF₃)phenyl > 4-fluorophenyl) lead to lower

pK_a values. The influence of the *o*-phenylene linkage is also evident in comparisons of BU-2 with its isomer BU-4, where the meta-phenylene linkage separates the urea motifs, resulting in significantly higher pK_a values for BU-4 ($pK_{a1,2}$ (BU-2) = 13.2, 16.5; $pK_{a1,2}$ (BU-4) = 16.0, 18.6).

ROP Screen of Bisureas. The catalytic behaviors of both the mono- and di- deprotonated forms of the bisureas BU-1-6 were assessed by the ring-opening polymerization of ϵ -caprolactone (ϵ -CL) in THF at room temperature with bisurea catalysts loadings of 0.55 mol% and base loadings of 0.5 or 1.0 mol%. The polymerization behavior of the bisurea complexes was compared with those of other organic catalysts TBD,⁴⁷⁻⁴⁸ (thio)urea^{21, 26-27} anions and indolocarbazole⁴⁹ potassium complexes (Eq. 1, Table 1).

Table 1. Polymerization of ϵ -Caprolactone in THF.



entry	cat./base	cat. pK_a^b	[I] ₀ : [base]: [cat.]: [M] ₀	time (min)	conv. ^c (%)	k_{obs}^d (min ⁻¹)	$k_{p(rel)}^e$	k_p/k_{tr}^f	SP _(rel) ^g	DP _{cal/NMR} ^h	$\bar{D}^i$
1	BU-1/KHMDS	12.5	4:1:1.1:200	92	90	0.028	7.1	5700	5.6	45/44	1.02
2	BU-1/ 2 KHMDS	16.2	4:2:1.1:200	17	97	0.22	49	8500	8.3	49/49	1.02
3	BU-2/KHMDS	13.2	4:1:1.1:200	280	100	0.024	6.1	3400	3.3	50/51	1.03
4	BU-2/ 2 KHMDS	16.5	4:2:1.1:200	3	99	1.63	370	4000	4	50/51	1.02
5	BU-3/KHMDS	14.2	4:1:1.1:200	45	94	0.068	14	3800	3.7	47/48	1.03
6	BU-3/ 2 KHMDS	19.8	4:2:1.1:200	0.33	96	10.0	2440	6700	6.5	48/46	1.03
7	BU-4/KHMDS	16.0	4:1:1.1:200	180	97	0.02	4.8	350	0.34	48/52	1.09
8	BU-4/ 2 KHMDS	18.6	4:2:1.1:200	12	96	0.29	68	1700	1.7	48/50	1.05
9	BU-5/KHMDS	-	4:1:1.1:200	160	97	0.022	5.6	-	-	49/55	1.05
10	BU-5/ 2 KHMDS	-	4:2:1.1:200	48	91	0.049	12	-	-	46/48	1.11
11	BU-6/KHMDS	17.0	4:1:1.1:200	15	93	0.15	38	4500	4.4	47/49	1.04
12	BU-6/ 2 KHMDS	19.4	4:2:1.1:200	12	98	0.38	94	980	1	50/51	1.07
13 ^j	TU-1/KHMDS	13.2	4:4:4.4:200	11040	90	0.00022	0.014	190	0.19	45/48	1.06
14	U-1/KHMDS	13.8	4:1:1.1:200	1100	99	0.0041	1	1000	1	50/46	1.10
15	U-2/KHMDS	15.8	4:1:1.1:200	30	54	0.026	6.4	1000	1	-	-
16	U-3/KHMDS	17.8	4:1:1.1:200	26	99	0.12	29	360	0.35	50/49	1.19
17 ^k	2 U-3/ KHMDS	17.8	4:1:2:200	20	76	0.073	18	-	-	-	-
18	TBD	-	4:1:0:200	5400	96	0.00063	0.15	70	0.07	48/44	1.34
19	indolocarbazol e/KHMDS	18.2	4:1:1.1:200	12	95	0.24	59	650	0.64	48/55	1.12

^aAll reactions in this table were run with $[\epsilon\text{-CL}]_0 = 1$ M in THF at room temperature (reactions run in batch and quenched with benzoic acid). ^b pK_a values were either measured by UV-Vis titration method in DMSO at room temperature or obtained from literature. ^cConversion determined by integrating monomer peaks against polymer peaks in ¹H NMR. ^d k_{obs} was obtained by extracting the first order rate constant from fitting $\ln([\epsilon\text{-CL}]_0/[\epsilon\text{-CL}]_t)$ versus reaction time (min). ^e $k_{p(rel)}$ was obtained by calculating k_p from k_{obs} for each catalyst according to rate law and normalizing to $k_{p(rel)}\text{U-1} = 1$. ^fSP (selectivity parameter) = k_p/k_{tr} was measured as described in Supporting Information. ^gSP_(rel) was obtained by normalizing to SP_(rel) U-1 = 1. ^hDP determined by ¹H NMR end group analysis by integrating initiator methylene singlet peak at 5.06ppm against polymer triplet peak at 4.05ppm.(Figure S3, Supporting Information) ⁱ $\bar{D}=M_w/M_n$ obtained by size exclusion chromatography (SEC) in THF using polystyrene standard, $\bar{D}$ was measured with uncertainty of ± 0.01 . ^jReaction was run with higher catalyst loading due to slow kinetics. ^kReaction was run with 1 equiv. excess neutral urea U-3.

The bisurea anions all exhibit living polymerization behavior⁵⁰ (Figures S4 – S16, Supporting Information), with rates that are first order in monomer, linear increases of M_n with conversion that correspond to the monomer/initiator ratio, and narrow dispersities ($\bar{D}$ = 1.02-1.11 at conversions > 91%). The activities of the bisurea mono- and di-anions span a large range of reactivities with rate constants spanning 4 orders of magnitude relative to a benchmark urea anion U-1 (Table 1, entry 14, $pK_{a(\text{DMSO})}$ 13.8) and the guanidine TBD (Table 1, entry 18). From the first order rate constants, relative rates can be readily compared for the bisurea mono-anions and dianions, relative to benchmark mono-urea anions and TBD.⁴⁷⁻⁴⁸ Several interesting trends emerge from these comparisons. As previously reported,²⁷ the mono urea anion catalysts exhibit a linear free energy relationship between the log of the polymerization rate constant and the pK_a of the urea, where reactivity increases with increasing pK_a of the urea conjugate acids (anions of the less acidic ureas are more active (Figure 3)). The *o*-phenylene bisureas (BU-1~3) do not exhibit such a clear linear relationship (Figure 3) and are more active than the corresponding monourea anions of comparable pK_a . For example, the BU-3 mono-anion (Table 1, Entry 5) is 14 times more active than the U-1 mono-anion (Table 1, entry 14), despite having comparable acidity. Moreover, the mono-anions of BU-1 and BU-2 are more active than U-1, even though they are more acidic. In contrast, the meta-phenylene bisurea (BU-4) mono-anion exhibits lower activity than the isomeric BU-2 despite having much higher pK_a . Instead, the BU-4 shares a comparable rate to the mono-urea U-2, which also has a similar pK_a . These comparisons show that ortho positioning of the H-bond donors leads to an enhancement in rate for the bisureas while lowering their pK_a 's. These data suggest a cooperative interaction between the H-bonding provided by the ortho-positioned urea and alcohol activation by the deprotonated urea. As seen in figure 3, OPBU (di)anion catalysts in general are more active than any other classes of catalysts studied while possessing milder basicity.

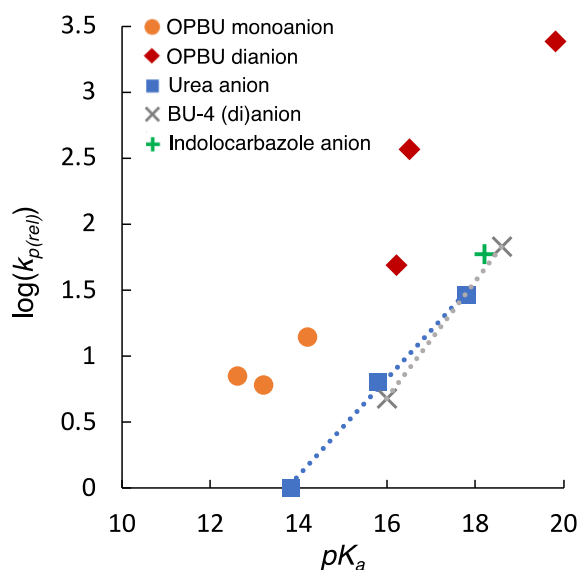


Figure 3. Plot of $\log(k_{p(\text{rel})})$ vs pK_a (DMSO) for OPBU (di)anion catalysts, urea anion catalysts, and indolocarbazole anion catalysts (counterion = K^+).

Another attribute of the bisurea complexes is that both mono-anionic and dianionic catalysts are readily prepared simply by changing the ratio of the base / bisurea. Both mono-anionic and dianionic forms are active and exhibit living behavior. In all cases the dianionic catalysts are more active than their mono-anionic congeners (Figure 4), but some surprising trends are evident. For bisureas BU-5 and BU-6, the dianions are approximately twice as active as the mono-anions, consistent with a doubling of active sites. In contrast, the dianion of BU-3 is approximately 170 times faster than the BU-3 mono-anion. For BU-2 and BU-1, the dianions are approximately 70 or 8 times more active than the mono-anions, respectively. The differences in pK_a 's can partially, but not fully explain this behavior, as the $\delta_{pK_a} = (pK_{a2} - pK_{a1})$ for BU-2 ($\delta_{pK_a} = 3.3$) is smaller than that of BU-1 ($\delta_{pK_a} = 3.7$), but the relative rates of the dianions/monoanions are much larger for BU-2 relative to BU-1. Nevertheless, large rate differences between mono/dianionic forms of OPBU afford a convenient handle for tunability and can be exploited to easily accommodate different monomers' kinetic behaviors.

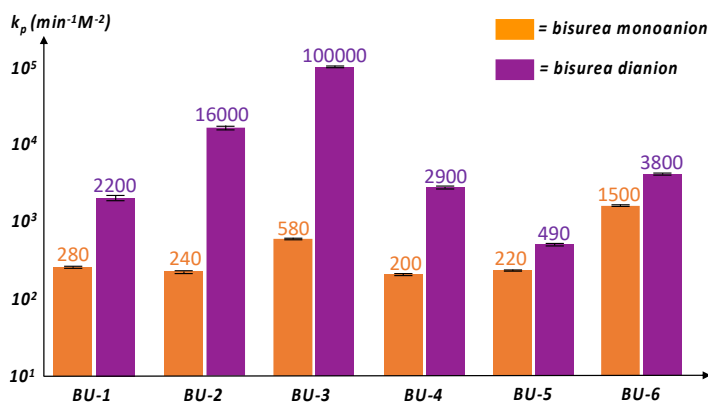


Figure 4. Bar graph of polymerization rate constants (k_p) for BU-1-6 monoanions and dianions.

Selectivity of BU-1~6. The *o*-phenylene bisurea catalysts BU-1~3 not only exhibit higher activities than other organocatalysts, but also are significantly more selective, as evidenced by the very narrow dispersities ($\bar{D} \leq 1.03$) observed with the resulting polymers, even at high conversions (Table 1). For example, the polymerization of ϵ -CL with BU-2 (monoanion, Table 1, entry 3) was carried out for over 10 half-lives ($\sim 100\%$ conversion and the dispersity was only slightly higher than that predicted for an ideal Poisson distribution of $\bar{D} = 1.02$ ($DP = 50$). This is also evident in Figure 5a, where the dispersities for the PCL polymers generated with the dianion of BU-1 (Table 1, entry 2, red diamonds in Figure 5a) do not increase, even at 97% conversion.

Transesterifications between polymer chains will broaden the dispersity, even for living ring-opening polymerization reactions; this is generally manifested as an increase in dispersity at high conversions when the concentration of monomer decreases to the point where inter-chain transesterifications compete with propagation. The higher selectivity (for propagation over inter-chain transesterification) of OPBU catalysts compared to the mono-urea U-3, or the guanidine TBD is evident in Figure 5a, where the dispersities of polymers made by TBD and U-3 at high conversions increase much more significantly than that of the more active BU-1 dianion.

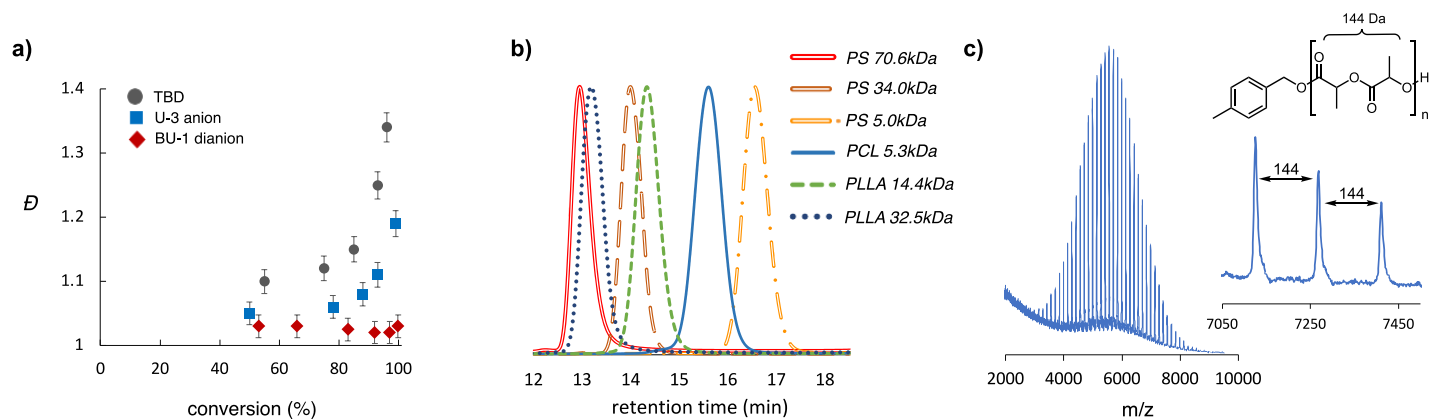


Figure 5. (a) dispersity ($\bar{D}$) vs conversion for polymerization of ϵ -CL using TBD, U-3 anion and BU-1 dianion catalyst. Reaction conditions are presented in Table 1, entry 2, 16 and 18. (b) SEC (RI) traces of commercial polystyrene standards (5.0 kDa, 34.0 kDa, and 70.6 kDa) overlaid with PCL and PLLA samples generated by BU-1 catalyst. (c) MALDI-TOF of a poly(L-lactide) sample (97% conversion, $DP_{\text{target}}=40$). The reaction conditions were $[DBU]_0:[BU-1]_0:[4\text{-methylbenzyl alcohol}]_0:[L\text{-LA}]_0 = 1:1.1:5:200$, $[L\text{-LA}]_0 = 1$ M in THF. Major peaks are separated by 144 m/z, suggesting rare occurrences of chain transfer reactions.

Penczek⁵¹⁻⁵² and Szymanski⁵²⁻⁵³ had shown that the relative rate of propagation to chain-transfer (k_p/k_{tr}) can be estimated by fitting the evolution of dispersity as a function of conversion. However, this analysis is infeasible with the OPBU catalysts as the dispersity increases imperceptibly at high conversion (Figure 5a). To provide a quantitative estimate

of the relative rate of propagation and chain transfer for these highly selective catalysts, we measured the rate of transesterification of polycaprolactone chains (DP = 120) with 4-methylbenzyl alcohol (MBA) as a proxy for the rate of inter-chain transesterification reactions. This was done by monitoring the rate of MBA decay as a function of time upon reaction with PCL chains ($[MBA]_0 = 0.08\text{M}$, $[-CL-]_0 = 1.0\text{M}$, Figure S17-18, Table S1, Supporting Information) to measure the rate constant k_{tr} . The ratio of the rate constants (k_p/k_{tr}) represents a quantitative estimate to compare the selectivity of various catalyst systems and are reported in Table 1.

As shown in Table 1, the selectivity parameters (k_p/k_{tr}) for the OPBU catalysts (BU-1-3) are very high, ranging from 3400 to 8500, which are significantly higher than other systems studied. These values are consistent with the simulations of Szymanski,⁵³ which indicate that for selectivity parameters (k_p/k_{tr}) ≥ 2500 , there should be very little increase in $\bar{D}$ at high conversion. For comparison, the guanidine TBD,⁴⁷⁻⁴⁸ known to be a reasonably active but modestly selective catalyst, exhibits a selectivity parameter of $k_p/k_{tr} = 70$.

We had previously described the (thio)urea anions^{21,26-27} as a class of highly active and selective catalysts. The data of Table 1 indicate that the OPBU anions and dianions demonstrate even greater selectivity (up to 45-fold) than these highly selective mono-(thio)urea catalysts. As shown in Table 1, the anions of the mono-ureas U-1 and U-2 exhibit selectivity parameters $k_p/k_{tr} = 1000$, whereas those of the thiourea anion TU-1 and urea anion U-3 ($k_p/k_{tr} = 190$ and 360 , respectively) are lower than those of U-1 and U-2, but higher than that of TBD ($k_p/k_{tr} = 70$). The BU-1 dianion emerged as the most selective catalyst in our study, with a k_p/k_{tr} ratio of 8500, surpassing TBD by over 120-fold, the U-3 anion by 24-fold despite similar reactivity, and outperforming the recently reported indolocarbazole potassium system by 13-fold.⁴⁹ Comparing OPBU to other bisureas lacking *o*-phenylene linkages, the *o*-phenylene bridged bisurea BU-2 mono-anion is 10 times more selective than its meta-substituted counterpart, BU-4, indicating that the disposition of the ureas in the phenyl ring (ortho- vs. meta-) significantly influences both the activity and selectivity.

We previously attributed the high selectivity of the (thio)urea anion catalysts (TU-1, U-1~U-3) to the preferential binding of the *s-cis* lactone to the (thio)urea anion relative to binding of open chain *s-trans* esters of the polymer chain, favoring propagation over transesterification.^{21,24-27} The preferential binding stems from the stronger dipole resulted from enforced *s-cis* conformation of the lactone,^{21,53} which would enhance hydrogen bond-dipole interactions⁵⁵⁻⁵⁶ relative to the *s-trans* esters of the polymer chain. In addition to electrostatic interactions, steric effects may also contribute to OPBU's high selectivity, as it is likely that *s-cis* lactones are more readily accommodated into the relatively tight hydrogen-bonding pocket of the OPBUs. Further experimental and computational studies are planned to test these hypotheses.

Computational Studies. To gain more insights into OPBU (di)anion's extraordinary catalytic capabilities, DFT calculations were carried out using the dispersion-corrected B3LYP-D3 method with the 6-31+G(d) basis set followed by single point energy calculations with the triple- ζ TZVP basis set in THF. (Supporting Information 'Computational methodology'). We initially assessed the relative stability of monoanion and dianion configurations of bisurea (BU-1~6) compounds, derived by removing protons from the neutral precursors' N-H groups (Figure S2, Supporting Information). For BU-1~3 mono-anions, deprotonation is favored at two central nitrogen atoms. For BU-4 there is little preference among the four N-Hs while for BU-5 and BU-6, deprotonation is favored at the peripheral N-Hs. (Figure S2, Supporting Information). The dianions of conjugated BU-1~4 systems tend to adopt configurations with two anionic nitrogens spaced apart by one N-H unit, where positioning two negative charges on adjacent nitrogen atoms is strongly disfavored (Figure S2, Supporting Information). In contrast, for unconjugated BU-5 and BU-6 species, our calculations found a preference for the double deprotonation of peripheral N-H units.

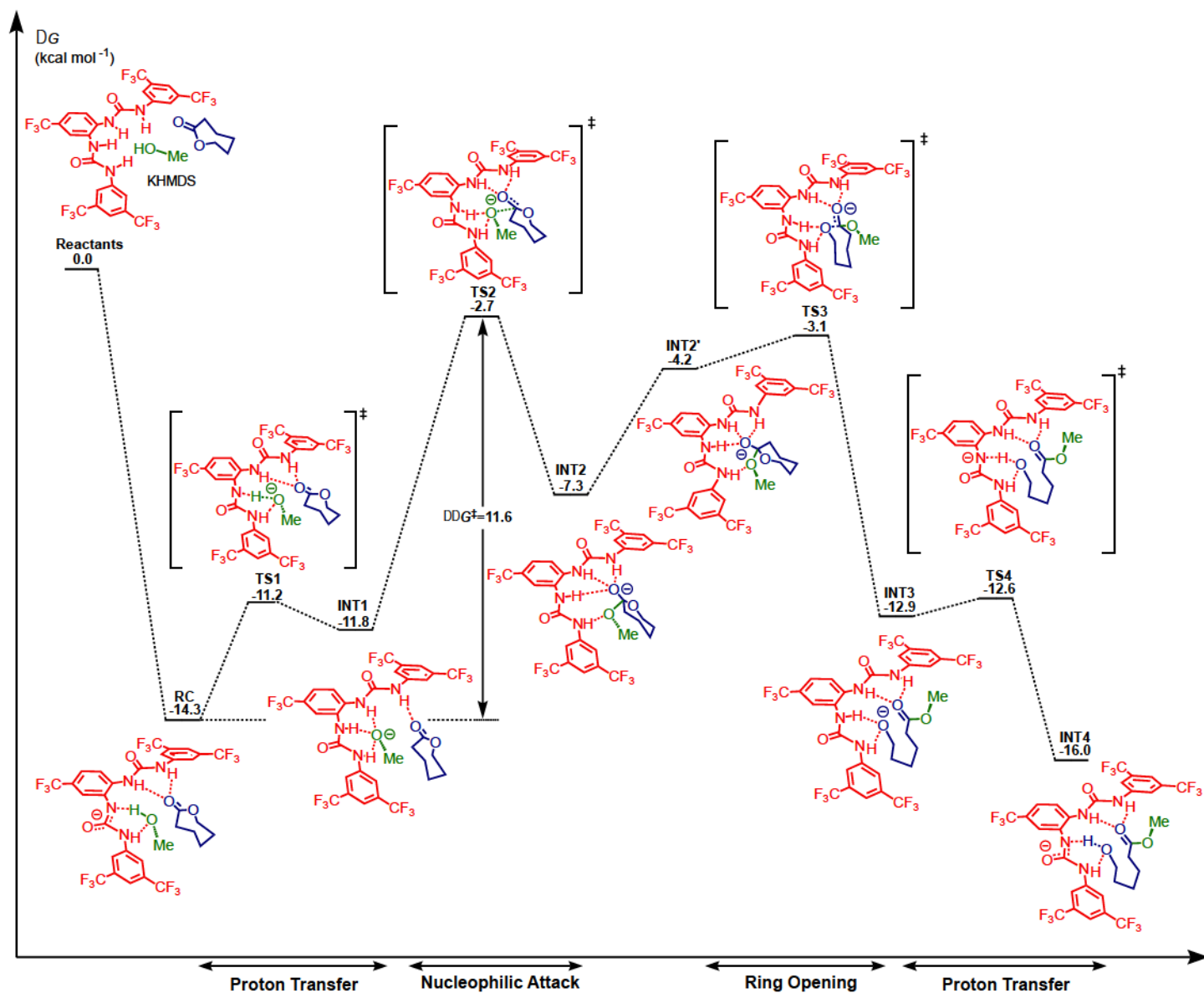


Figure 6. Calculated Gibbs energies (kcal mol⁻¹) and reaction coordinate for the ε-caprolactone ROP promoted by methanol and BU-1⁻. DFT calculations indicate the RDS of the reaction is the nucleophilic attack from methoxide on monomer carbonyl.

The monoanion of BU-1 was selected as the representative system for computational analysis of the reaction coordinate for ring-opening polymerization of ε-CL, using methanol as an initiator. The completed energetic path is reported in Figure 6. The calculated reactant complex (RC) is a tri-molecular assembly of methanol, lactone, and BU-1 anion, interconnected by four hydrogen bonds. The formation of this RC is exergonic by -14.3 kcal mol⁻¹ relative to the reactants, which is a combined result of a highly exothermic acid-base reaction and the favorable hydrogen bond complexation. From RC, we found a two-step mechanism consisting in an endergonic proton transfer from methanol to BU-1⁻ (TS1) and then the nucleophilic attack (TS2) of the resulting hydrogen bond-stabilized methoxide to the ε-CL carbonyl group (Figure 6). The TS2 is the rate-determining step (RDS) where the oxyanion is stabilized through four hydrogen bond interactions, as reflected in the calculated NH...O distances of 1.68 Å, 1.74 Å, 1.83 Å, 1.96 Å (Figure 7a). The resulting tetrahedral intermediates INT2 and INT2' are stabilized by four hydrogen bonds and facilitate the ring opening step (TS3) to yield INT3. Once proton transfer has occurred (TS4) it leads to the formation of the alcohol-terminated open chain lactone (INT4). This energetic path is substantially independent of the computational methods, as different models all yielded similar reaction paths (variabilities are reported in Table S2, Supporting Information). The modest overall activation barrier for the

reaction ($\Delta\Delta G^\ddagger = \Delta G^\ddagger - \Delta G_{RC} = 11.6$ kcal/mol) correlates well with the rapid kinetics experimentally observed at room temperatures.

The calculations performed on BU-1 monoanion indicate that the key transition state (TS2) and the tetrahedral intermediate (INT2) structures are cooperatively stabilized by four hydrogen bonds across the bisurea motifs (Figure 7a). These transition states and intermediates are reminiscent of those proposed in serine proteases,²⁸⁻²⁹ where H-bonding by residues in the oxyanion hole are proposed to provide up to 6 kcal/mol in stabilizing the transition state for nucleophilic attack.²⁸ The felicitous positioning of the two ureas provided by the *o*-phenylene linkage is also important to position these hydrogen bonds appropriately. The calculations reveal that while the *o*-phenylene linker positions the ureas around the key transition state, the ureas retain some flexibility as they rotate slightly during the catalysis process (Figure S24, S25, Supporting Information), adjusting the bisurea's hydrogen bond "pocket" shape to accommodate different substrate configurations along the reaction coordinate.

The positioning of the ureas by the semi-rigid *o*-phenylene linker differs from that of other bis(thio)urea catalysts connected by flexible linkers.^{31-34, 57-59} Bis(thio)urea catalysts with flexible aliphatic linkers tend to self-conjugate instead of simultaneously binding N-H motifs to the key tetrahedral anion transition state (Figure 7b).^{31,33,57}

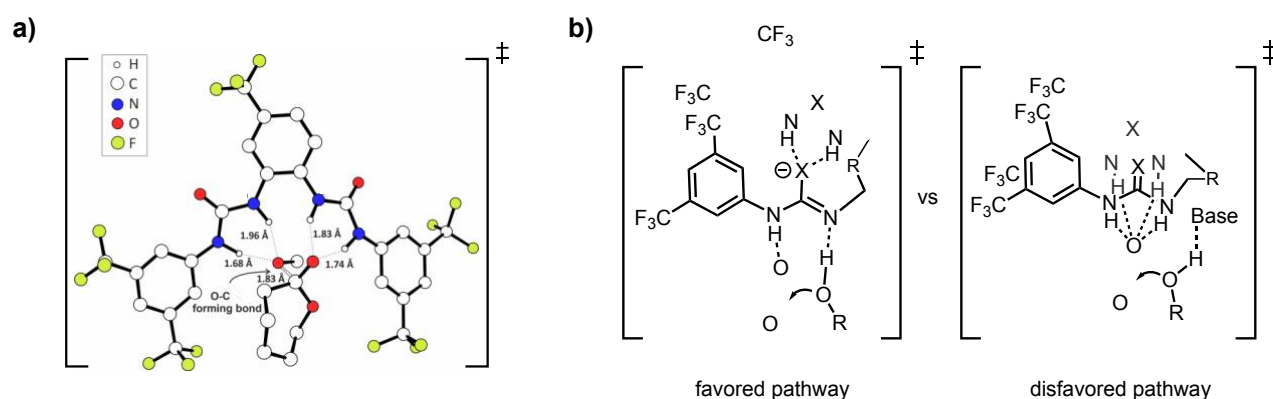


Figure 7. Transition state structures for a) *o*-phenylene bisurea catalyst (BU-1, TS2), (b) bis(thio)urea catalyst^{31,33,57} with flexible aliphatic linkers

O-phenylene bisureas have previously been extensively investigated for their exceptional binding affinity to chloride, bicarbonate, and carboxylate anions, surpassing that of mono-ureas and *m*-phenylenebis(methylene)bisureas.³⁵⁻⁴⁰ The outstanding strength of these anion-OPBU interactions have been leveraged in various applications, ranging from sensing to the extraction of specific anions from complex mixtures, as well as using them as transmembrane anion transporters.³⁵⁻⁴⁰ This enhanced affinity is attributed to a denser network of hydrogen bonds compared to monoureas and the ortho-phenylene linker's reduced degree of flexibility compared to *m*-phenylenebis(methylene)bisurea, offering greater preorganization.^{38,40} Given the electronic and structural similarities between carboxylate or bicarbonate anions and the key tetrahedral intermediates in lactone polymerization, our studies hint the relevance of this high binding affinity extends beyond mere anion recognition.

We also performed calculations on the reaction path catalyzed by the dianion of BU-1, but these studies were more challenging due to the large number of possible intermediates. The calculations reveal that one or two methanol molecules may be involved, leading to two different pathways, as reported in Figure S21-S23 in supporting information. Interestingly, both pathways starting from trimolecular or tetramolecular RC assemblies (Figure S21-S22, Supporting Information) proceed via a concerted TS where the proton transfer from the methanol to the N-deprotonated atom and the nucleophilic attack on the monomer carbonyl group act simultaneously leading to the tetrahedral intermediates INT1 and INT1' (Figure S21-S22, Supporting Information). The concerted TS1 dianion, corresponding to nucleophilic attack, is the RDS of the reaction. For the dianions, the ring-opening and the proton transfer steps (TS2, Figure S21-S22, Supporting Information) to generate the open chain lactone occur through a single TS without any intermediates. The non-covalent interaction analysis performed on the RCs and RDSs of BU-1⁻ and BU-1²⁻ are reported in Figure S26-S27 in Supporting Information.

Monomer Scope of OPBU Catalysts To illustrate the generality and selectivity of OPBU catalysts for different monomers, we investigated the polymerization of a range of lactones, carbonates, and N-carboxyanhydrides (NCAs), with different bases, initiators, and solvents (Figure 2d, e, f, Table 2). Polymerizations of various cyclic esters and carbonates with different substituents and ring sizes yield high conversions with very narrow dispersities within minutes. The polymerization of lactide with BU-1 / DBU was faster than that of the guanidine TBD and yielded PLA with a significantly narrower dispersity (Table 2, entries 1 and 2). The high selectivity of lactide polymerization is further confirmed by MALDI-TOF analysis. A PLA sample produced using BU-1/DBU at 97% conversion displays ions peaks that are separated by 144 m/z, the mass of a lactide unit. The absence of ions at δ 72 m/z (corresponding to lactic acid) signifies the lack of detectable intermolecular chain transfer reactions, even at such high conversions (Figure 5c). Moreover, when comparing the SEC traces of polyesters synthesized with BU-1 catalysts to that of commercial polystyrene standards, the distributions are nearly identical (see Figure 5b). This comparison further highlights the high level of control achieved by OPBU catalysts.

The highly selective OPBU catalysts are operationally advantageous, as the reactions can be run to high conversion without broadening the dispersity (Figure 5a). For instance, the polymerization of the morpholinone M-Boc⁶⁰ with BU-1/DBU in CH₂Cl₂ reached 90% conversion (near equilibrium for M-Boc monomer) in 2 minutes and yielded a dispersity of $\bar{D}$ = 1.04 (Table 2, entry 10). When the same reaction was quenched at 8 min (>15 half-lives), the dispersity of the polymer remained narrow $\bar{D}$ =1.07 (Table 2, entry 11). Compared to previous catalysts where termination between 3-4 half-lives is necessary to achieve high conversion while retaining narrow dispersities (Figure S28, Supporting Information), the high activities and selectivities of the OPBU catalysts allows for reactions to be carried out to high conversion quickly and quenched when convenient, even without a detailed understanding of the reaction kinetics or conversions. Polymerization of D-Bn-GluNCA (Table 2, entry 15) to its corresponding polypeptide was also achieved using BU-1/DBU with thiophenol as initiator; however, the control over NCA polymerization was not as good as observed with lactone or carbonate monomers, nor did it match the precision of recently reported tris-thiourea catalysts⁶¹ for the same monomer, despite being moderately faster.

Table 2. Polymerization of lactones, carbonates with different catalysts, bases and initiators^a

entry	monomer/[M] ₀	solvent	cat./base	initiator	[I] ₀ : [base]: [cat.]: [M] ₀	time	% conv. ^b	M _n ^{theo} (kDa) ^c	M _n ^{SEC} (kDa) ^d	$\bar{D}$ ^e
1	L-LA/[1M]	THF	TBD	MBA	1:1:0:100	1.5min	98	14.2	13.1	1.64
2	L-LA/[1M]	THF	BU-1/DBU	MBA	1:1:1.1:100	40s	99	14.4	14.5	1.02
3	L-LA/[1M]	THF	BU-1/DBU	MBA	1:1:1.1:400	4min	91	52.9	56.3	1.01
4	L-LA/[1M]	THF	BU-1/DBU	BTM	1:1:1.1:100	15s	98	14.3	10.5	1.01
5	δ -VL/[2M]	THF	BU-3/KHMDS	MBA	1:1:1.1:100	5min	90	9.1	7.5	1.04
6	δ -VL/[4M]	THF	BU-1/KHMDS	MBA	2:2:1.1:400	1min	92	18.4	13.7	1.03
7	δ -VL/[4M]	THF	BU-1/KHMDS	MBA	2:2:1.1:400	2min	97	19.4	14.2	1.03
8	ϵ -CL/[1.2M]	THF	BU-1/KHMDS	BTM	2:2:1.1:120	5min	87	6.1	5.6	1.02
9	δ -CL/[6M]	THF	BU-3/KHMDS	BDM	1:2:1.1:180	20min	83	17.2	5.7	1.01
10	M-Boc/[1.8M]	CH ₂ Cl ₂	BU-1/DBU	MBA	1:1:1.1:100	2min	90	18.2	5.8	1.04
11	M-Boc/[1.8M]	CH ₂ Cl ₂	BU-1/DBU	MBA	1:1:1.1:100	8min	92	18.6	6.3	1.07
12	TMC/[1M]	THF	BU-1/KHMDS	BDM	1:1:1.1:100	10min	98	10.1	11.5	1.05
13	TMC ^{cpr} /[2M]	CH ₂ Cl ₂	BU-1/DBU	BDM	2:1:1.1:100	10min	93	6.1	-	-
14	8mCC-NBoc/[2M]	CH ₂ Cl ₂	BU-1/DBU	BDM	2:1:1.1:100	50s	98	11.5	-	-
15	D-Bn-GluNCA/ [0.5M]	CH ₂ Cl ₂	BU-1/DBU	PhSH	1:1:1.1:100	30min	91	20	15.0 ^f	1.90 ^f
16	M-Boc- <i>block</i> - TMC ^{dodecyl}	CH ₂ Cl ₂	BU-1/DBU	PyBuOH	7.7:1:1.1:(100/100)	80+40s	92/92	6.6	2.64	1.04
17	M-Boc- <i>block</i> - TMC ^{dodecyl}	CH ₂ Cl ₂	BU-1/DBU	PyBuOH	1.3:1:1.1:(100/100)	200+110 s	92/96	37.8	7.61	1.06
18	M-Boc- <i>block</i> - TMC ^{dodecyl}	CH ₂ Cl ₂	TBD	PyBuOH	1.3:1:0:(100/100)	10+5min	94/96	38.1	7.04	1.14

^aAll reactions in this table were run with under N₂ atm at room temperature (reactions run in batch and quenched with benzoic acid). ^bConversion determined by integrating monomer peaks against polymer peaks in ¹H NMR. ^c $M_n^{theo} = MW_{initiator} + \%conv. \times \frac{[M]_0}{[I]_0} \times MW_{monomer}$. ^dDetermined by SEC in THF using polystyrene standard. For entries 1-8, 12, dn/dc values applied for PLA = 0.05, for PVL = 0.086, for PCL = 0.071 and for PTMC = 0.043.⁶² For entries 9-11, 16-18, M_n values are reported based on polystyrene's dn/dc value of 0.185. For entry 19, dn/dc value of 0.065 (based on a 50/50 copolymer composition of PVL and PLA) was applied.⁶³ ^e $\bar{D} = M_w/M_n$ obtained by SEC in THF using polystyrene standard, $\bar{D}$ was measured with uncertainty of ± 0.01 . ^fDetermined by SEC in DMF with LiBr (1 g/L) using PEG standards.

As shown in Table 1 and entries 2-12 of Table 2, the high activity and selectivity of the OPBU catalysts provide facile access to living polymerizations with narrow dispersities. For many homopolymers, minor amounts of intermolecular chain-transfer and/or narrow dispersities may not be critical to their overall performance and can, in some cases, be deleterious to the processing characteristics.⁶⁴ Nevertheless, for the synthesis of well-defined block copolymers, intermolecular chain-transfer can have a detrimental influence on the block copolymer sequences. For example, as shown for a represented block copolyester, intermolecular chain transfer can lead to not only a broadening of the dispersity, but a scrambling of the block copolymer sequences (Figure 8).

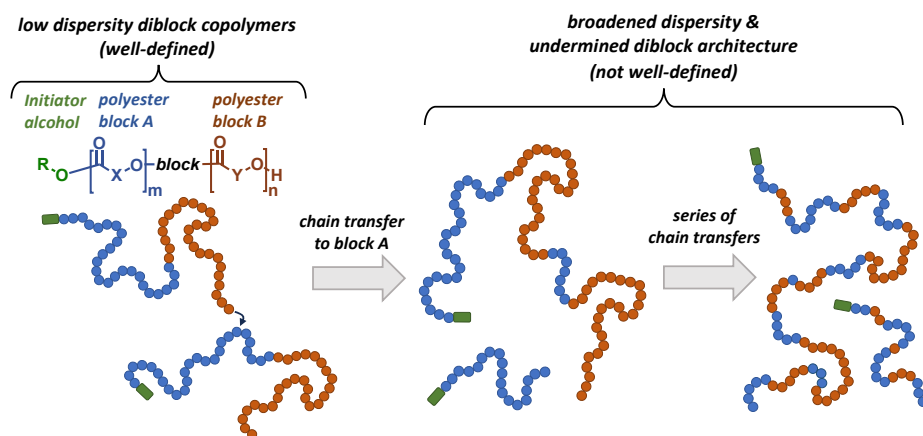


Figure 8. Chain transesterification side reactions undermine copolymer architectures.

The high selectivity of OPBU catalysts allow for the precise synthesis of block copolymer architectures (Table 2, entry 16-17, 19). For example, synthesis of MBoc_m-TMC^{dodecyl}_n block copolymer (precursor to a polymer used for mRNA delivery),⁶⁵ was easily achieved with BU-1/DBU. (Table 2, entry 16, 17) The SEC curve from UV detector showed near-complete agreement with RI and LS detectors, indicating high level of architectural integrity. (Figure S29 a-b, see Supporting Information) In contrast, the same reaction mediated with TBD not only afforded higher dispersity, (Table 2, entry 18) but also showed deviation of the UV-SEC curves from LS or RI detectors, (Figure S29 c-d, see Supporting Information) likely caused by chain transfer reactions that undermined the original architecture.

CONCLUSION

In this study, we report a class of OPBU (di)anions as a mild yet highly efficient catalytic system for fast, tunable, and ultra-selective ROP of various cyclic monomers. Of the various classes of active and selective organic catalysts,^{9-11, 21, 27, 49} the OPBU (di)anions stand out both for their fast and tunable rates and high selectivities. On the basis of our studies to date, the BU-1 anion or dianion are the most versatile for high to moderately reactive monomers; for less reactive monomers (ϵ -CL, δ -CL), the more active BU-3 (di)anions are recommended. However, due to its commercial availability and ease of handling, TBD remains a good choice for ROP of reactive monomers when dispersity or architecture control is not a priority.

Comparisons of bisureas with different linkers reveal that the positioning and electronic communication between the ureas influence both the reactivity and selectivity of anionic bisurea catalysts. Mechanistic and computational studies indicate that both nucleophilic attack and ring-opening oxyanion transition states are simultaneously stabilized by 4 hydrogen bonds in the OPBU's pocket in a manner analogous to the "oxyanion hole" in enzymatic catalysis. These systems offer enhanced selectivity for chain propagation versus chain transfer, as well as high reactivity with milder basicity compared to previously reported ROP organocatalysts. The high activities and selectivities of these catalysts afford narrowly dispersed polyesters, as well as well-defined block copolymer architectures. This study offers new insights to exploit cooperativity to address ongoing challenges in improving the rates and selectivities of polymerizations or organic transformations involving anionic transition states.

AUTHOR INFORMATION

Corresponding Author

* Robert M. Waymouth Email: waymouth@stanford.edu

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, computational details, NMR spectra, SEC chromatograms, kinetic data, and pK_a measurements (PDF)

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