

A Cation-Dependent Dual Activation Motif for Anionic Ring-Opening Polymerization of Cyclic Esters

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ABSTRACT: A new organocatalyst for the ring-opening polymerization of lactones has been identified. Under the tested conditions, the anions of 2,2'-bisindole promote fast, living polymerizations (as short as 10 ms) which are selective for chain elongation over transesterification ($\bar{D} \leq 1.1$). While structurally related to (thio)urea anion catalysts, anions of 2,2'-bisindole activate the monomer via the counterion rather than through hydrogen bonding. This new activation motif enables modulation of the polymerization rate by 2 orders of magnitude by changing the counterion.

Organocatalytic ring-opening polymerization (ROP) is an important strategy for synthesizing polyesters and polycarbonates under mild conditions with high atom economy.^{1–5} Several organic ROP catalysts have been shown to exhibit a high degree of control over molecular weight, dispersity, end group fidelity, and stereoselectivity^{1–4} and can generate a wide array of challenging and unique macromolecular architectures^{5,6} not available through step growth polymerization. Such polymers are useful as biodegradable materials^{6,7} and drug delivery vehicles.^{8–10}

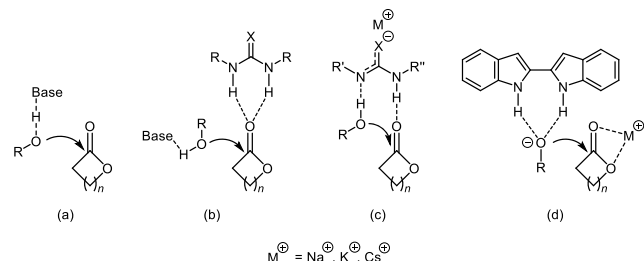
Among the simplest and most well-studied organocatalysts for the ROP of lactones and cyclic carbonates are alkoxide bases (Scheme 1).^{11–19} While alkoxide base-promoted ROP

retained their exceptional control over selectivity and dispersity.^{25–28} Due to these favorable characteristics, (thio)urea anion catalyst systems have attracted significant attention for ROP of a variety of cyclic esters.^{29–39}

We sought to test the generality of the deprotonated (thio)urea motif as one strategy to illuminate the structural and electronic features responsible for their high activities and selectivities.^{25–28,35,38,39} Significant gains in performance and scope may be realized through a fundamental understanding of the relationships and trends between catalyst structures, their effectiveness as ROP catalysts, and their mechanism of polymerization. To assess these factors, we targeted the anions of 2,2'-bisindole (**1**) as potential catalysts for ROP to test whether the disposition of nitrogen-based hydrogen bond donors in **1** might function analogously to those of (thio)ureas. Herein, we report the deprotonation of **1** affords very active organocatalysts aided by alkali metal ions for ROP; mechanistic and computational studies implicate counterion binding rather than H-bonding as the predominant mode of activation of the carbonyl monomers.

Anions of **1** were investigated as organocatalysts for the anionic ROP of lactones initiated by a primary alcohol (Scheme 2). Under the tested reaction conditions, **1b** (Chart 1) catalyzed the polymerization of L-lactide (L-LA), δ -valerolactone (VL), and ϵ -caprolactone (CL), to high monomer conversion with narrow molecular weight distributions (Table 1). In all cases, an excess of **1** was used relative to base in order to prevent initiation by the base and to improve the solubility of the active catalyst. By utilization of a continuous flow reactor, the polymerization of L-LA was

Scheme 1. Proposed Activation Mechanisms for Organocatalytic ROP by (a) Strong, Hindered Bases,^{17,20} (b) (Thio)urea/Base Combination,^{27,38,39} (c) (Thio)urea Anions,^{25,28,37} and (d) 2,2'-Bisindole Anion (This Work)



can be used to generate polyesters with low dispersity, their extreme rate and lack of selectivity can only be controlled using continuous flow conditions.²⁰ To promote selectivity for chain elongation over transesterification, thiourea/ R_3N and guanidine catalyst systems were developed to polymerize lactones and carbonates quickly and selectively.^{21–24} A major improvement for organocatalytic ROP came with the deprotonation of these (thio)urea catalysts, which dramatically increased the polymerization rates relative to thiourea/ R_3N catalysts, yet

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Scheme 2. Conditions for ROP by Potassium 2,2'-Bisindole Anion

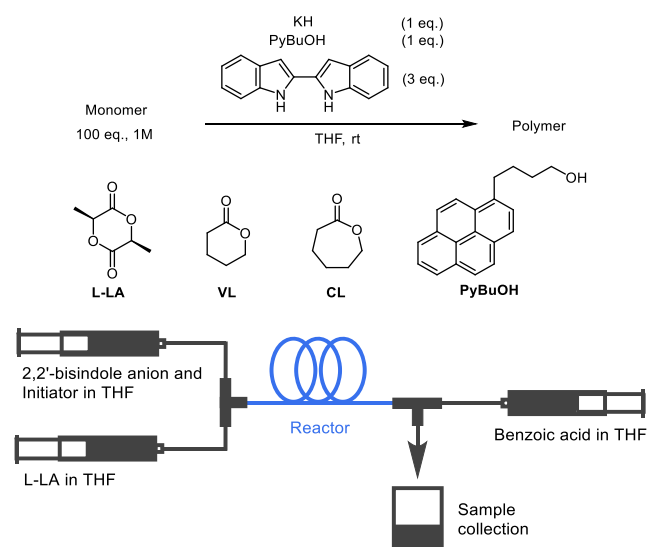
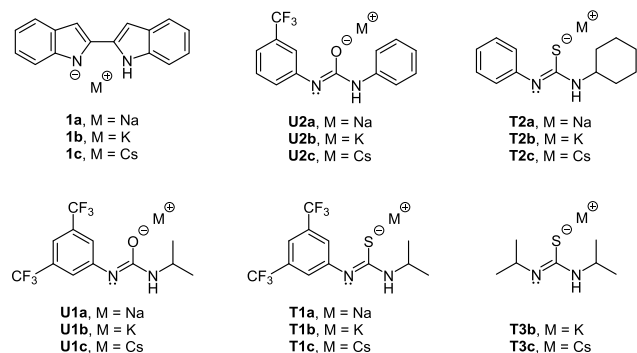


Chart 1. Catalysts for DFT Calculations and Counter Ion Studies



achieved with a residence time of 97 ms. With CL, **1b** displays characteristics of living polymerization, providing poly(CL) with M_n values matching those predicted from the starting monomer/initiator ratios ($M_{n,theor}$, Figure 1b,c) and first order kinetics with respect to monomer (Figure 1a). MALDI-TOF analysis of poly(L-LA) made by **1b** (Table 1, entry 1) shows that transesterification is minimal until reaching very high conversions (>95%), when the rate of transesterification becomes competitive with chain elongation (Figure 2). This observation is consistent with the appearance of a high molecular weight shoulder appearing in the GPC traces at high conversion (>90%). Due to the fast polymerization rate and the slight broadening of the molecular weight distribution at high conversion, narrow molecular weight poly(L-LA) could only be prepared with **1b** under continuous flow conditions.

Table 1. Polymerizations with Potassium 2,2'-Bisindole Anion (1b**)^a**

entry	monomer	time (s)	conversion (%)	$M_{n,theor}$ (kDa)	$M_{n,NMR}$ (kDa)	$M_{n,GPC}$ (kDa)	$\bar{D}$
1 ^b	L-LA	0.097	86	6.5	6.8	9.3	1.10
2 ^c	VL	13	88	8.9	8.5	10.0	1.07
3 ^d	CL	360	91	10.7	11.2	11.0	1.05

^a[M]₀ = 1.0 M for all reactions. $\bar{D} = M_w/M_n$. ^bPerformed under continuous-flow conditions. [KH]₀:**1**:**PyBuOH**:**L-LA**₀ = 1:2:5:250. ^cPerformed in a batch reactor, [KOME]₀:**1**:**VL**₀ = 1:3:100. ^dPerformed in a batch reactor, [KH]₀:**1**:**PyBuOH**:**CL**₀ = 1:3:1:100. PyBuOH = 1-pyrenebutanol; KH = potassium hydride; KOME = potassium methoxide.

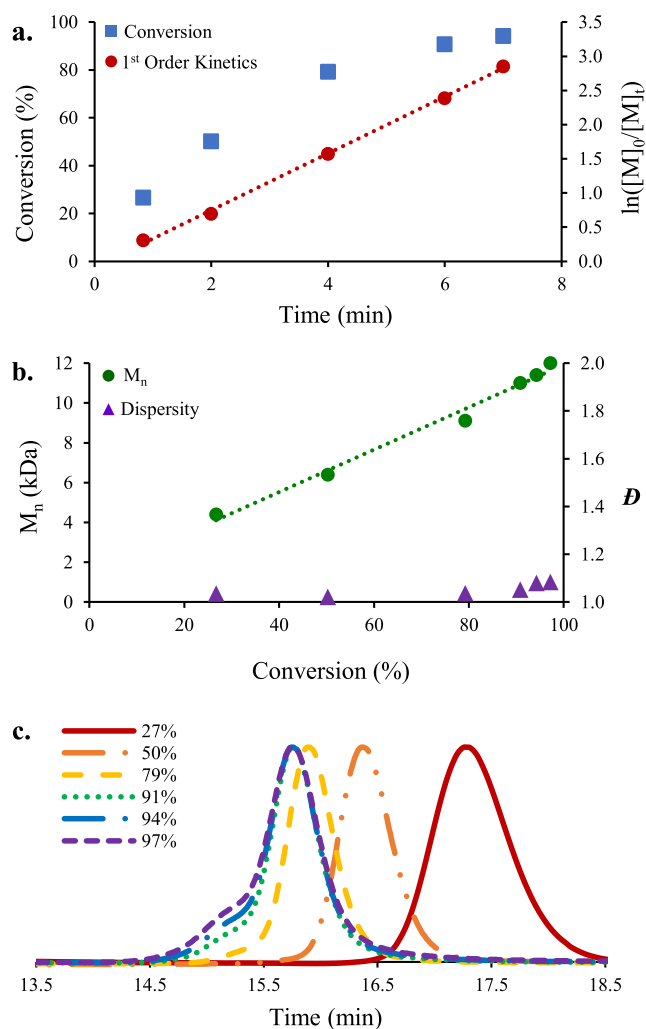


Figure 1. Representative polymerizations of CL with **1b**: (a) conversion vs time and first order monomer decay plot, (b) $M_{n, GPC}$ and dispersity ($\bar{D}$) vs conversion, and (c) GPC traces of the polymerization at different conversions. [KOME]₀:**1**:**CL**₀ = 1:3:100. [CL]₀ = 1 M.

Computational studies performed with the B3LYP-D3 density functional theory (DFT) for the ring-opening of L-LA with anions derived from **1**, 1-(3,5-bis(trifluoromethyl)phenyl)-3-isopropylurea (**U1**), and 1-(3,5-bis(trifluoromethyl)phenyl)-3-isopropylthiourea (**T1**) (Chart 1) suggest the anions of **1** utilize a different mode of activation than (thio)urea anions to accelerate the ROP of L-LA. Previous mechanistic and computational studies indicate that (thio)urea anions activate both the attacking alcohol and the lactone carbonyl via hydrogen bonding (Figures 3 and 4a).^{25,27,28} In contrast, the optimized computed structure of

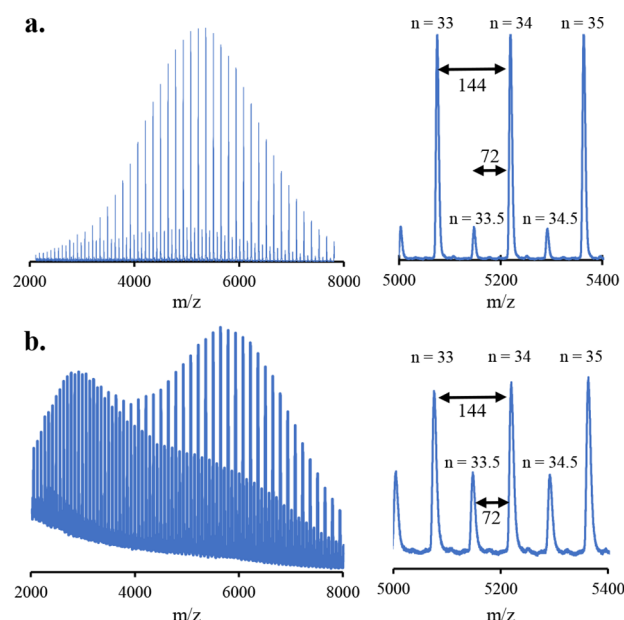


Figure 2. MALDI-TOF of a poly(L-LA) sample target DP = 50 prepared by **1b**, at (a) 85% conversion and (b) 97%.

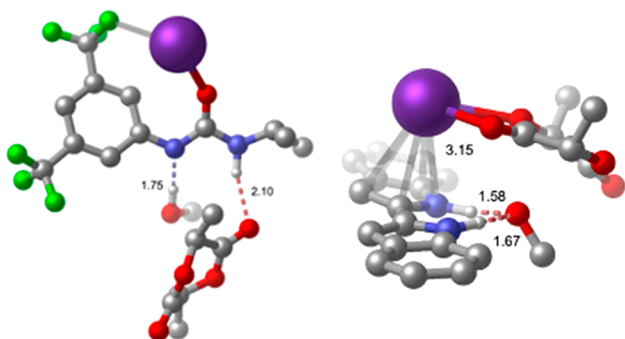


Figure 3. Binding modes for **U1b** and **1b** with L-LA.

the reaction complex of L-LA and **1b**, formed from **1** and potassium methoxide (KOMe), indicates the potassium counterion binds to L-LA through an ion–dipole interaction and to the anion of **1** by cation– π interactions (Figures 3 and 4b). This previously unobserved activation motif suggests the catalytic activity of the anions of **1** would be highly sensitive to the nature of the counterion.

Previous computational investigations²⁵ indicated nucleophilic attack of the bound alkoxide on the carbonyl to form the anionic tetrahedral intermediate (Figure 4) is associated with the highest activation energy along the reaction coordinate for ring-opening of L-LA (Figure S21). The critical intermediates (RC and INT 1) and transition state (TS 1) calculated are shown in Figure 4a and Figure 4b for the anions derived from **U1** and **1**, respectively. The free energy profiles and energies for the formation of the tetrahedral intermediate (INT 1) from the reaction complex (RC) for the **U1b** and **1b** are compared in Figure 4c. These free energy profiles show that the barrier to form INT1 from **1b** (activation free energy of 2.8 kcal/mol) is lower than that involving **U1b** (10.0 kcal/mol).

To investigate the presence of a counterion effect, rates of polymerization of CL with anions derived from **1**, 1-phenyl-3-(3-(trifluoromethyl)phenyl)urea (**U2**), 1-cyclohexyl-3-phenylthiourea (**T2**), and diisopropylthiourea (**T3**) (Chart 1, Scheme

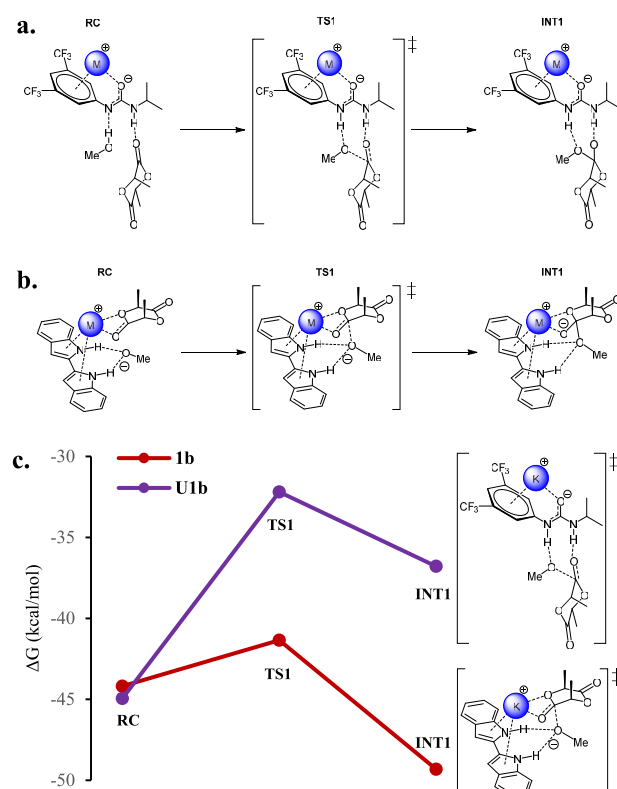
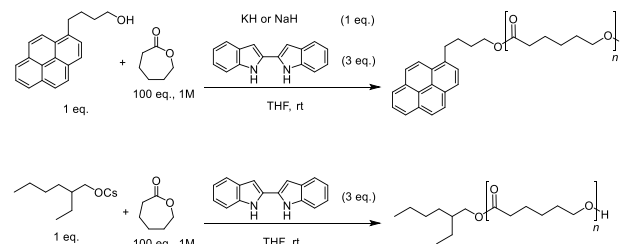


Figure 4. Computed rate-determining steps for formation of tetrahedral intermediate INT 1 for anions of (a) **U1** and (b) **1**. Free energy profiles and energies, in kcal/mol, for the ring-opening of L-LA by (c) **U1b** and **1b** formed from KOMe.

3) were compared by changing the counterion of the base employed. For anions of **1**, a dramatic difference in rate was

Scheme 3. Polymerization of CL Using Anions of 2,2'-Bisindole (*t* in Minutes)



observed by changing the counterion from Cs⁺ (**1c**, $k_{\text{rel}} = 1$, initiated from cesium ethylhexoxide) to Na⁺ (**1a**, $k_{\text{rel}} = 51$). When using Na⁺ as the counterion, the rate increase is accompanied by a change in the rate dependence on monomer concentration from first order to zero order (Figure S1). This suggests **1a** polymerizes CL with saturation kinetics under these conditions. Rate modulation by the counterion is also present, but to a much lesser degree, for the selected thiourea anion catalysts and is not apparent for the anion of **U2** (Table 2). For both the anions of **1** and **T2**, there is some evidence of imperfect initiation with Na⁺ counterion, as indicated by multimodal GPC traces observed at low conversion (Figures S4 and S14). These results follow the trends predicted by the computational results with L-LA.

In summary, the 2,2'-bisindole anion is a highly active and selective catalyst for anionic ROP of cyclic esters. Polyesters

Table 2. Counterion Effects on Rate Constant for Polymerization of CL^a

entry	catalyst	k_{obs} (min ⁻¹)	k_{rel} ^b	time (min)	conversion (%)	$M_{n,\text{theor}}$ (kDa)	$M_{n,\text{GPC}}$ (kDa)	$\bar{D}$
1 ^c	1a	1.01 ± 0.02	51	0.833	90	10.5	9.1	1.11
2	1b	0.44 ± 0.03	7.6	6.00	91	10.7	11.0	1.05
3	1c	0.058 ± 0.003	1	40.0	89	10.3	11.0	1.09
4	U2a	0.153 ± 0.006	1.3	12.5	87	10.2	10.1	1.02
5	U2b	0.16 ± 0.01	1.3	12.5	89	10.4	10.8	1.04
6	U2c	0.121 ± 0.006	1	15.0	82	9.5	9.6	1.12
7	T2a	0.0037 ± 0.0001	7.5	600	89	10.4	10.3	1.16
8	T2b	0.00145 ± 0.00003	2.9	1455	92	10.8	10.8	1.09
9	T2c	0.00050 ± 0.00008	1	4420	94	10.9	8.7	1.08
10	T3b	9.64 ± 0.02	5.2	0.217	87	10.2	10.5	1.08
11	T3c	1.87 ± 0.06	1	1.08	89	10.3	9.7	1.08

^aRT in THF. [Base]:[PyBuOH]:[precatalyst]:[CL] = 1:1:3:100. ^bCalculated from the ratio of k_{obs} for a given catalyst to the k_{obs} of cesium catalyst with the same anion. ^c k_{obs} is listed in M·min⁻¹.

produced by the anions of **1** have low dispersities ($\bar{D} \leq 1.1$) and M_n values consistent with those predicted from the initiator to monomer ratio. Despite its structural similarity to previously studied urea anions, calculations suggest catalysts derived from **1** activate monomers via a previously unobserved binding motif, in which the catalyst counterion plays a vital role in lactone activation. Computational studies predicted rate modulation through counterion manipulation, which was confirmed experimentally. This mechanism of activation and counterion rate dependence could have ramifications for other molecular transformations. Furthermore, the activity and selectivity of anions of **1**, alongside (thio)urea anions, suggest deprotonation of bifunctional H-bond donors to yield active catalysts is a generalizable concept that can be applied to other molecular structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c01436>.

Experimental details, NMR spectra, GPC chromatograms, and kinetic data (PDF)

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Notes

The authors declare no competing financial interest.

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