Contrasting Roles of Counterions in Anionic Ring-Opening Polymerization Mediated by Heterocycle Organocatalysts

Jia Zhang[†], Kai Hin Lui[†], Caleb N. Jadrich[†], Yuan Jia[†], Pedro L. Arrechea[‡], James L. Hedrick[‡] and Robert M. Waymouth[†,*]

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

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

ABSTRACT: A library of structurally related heterocycles containing N-H motifs are explored as ring-opening polymerization (ROP) pre-catalysts. Upon deprotonation of these heterocycles with appropriate bases, corresponding salts are formed, which catalyze the ROP of various lactones and cyclic carbonates, affording polymers with dispersity values ranging from 1.01 to 1.12. These catalysts exhibit a wide range of catalytic activities, spanning over seven orders of magnitude (>10^7), with their relative rates generally correlating to the pKa of the N-H group in the neutral heterocycle. Despite apparent structural and electronic similarities, these heterocycle catalysts display markedly different kinetic behaviors regarding the identity of different cations. Kinetic and NMR studies have revealed two distinct sets of mechanisms: small alkali metal cations such as Li^+ and Na^+ reduce the activity of imidazol(in)e derived catalysts due to their tendency to associate with the alkoxide chain-end, thus inhibiting its propagation; conversely, these cations form robust cation-π assemblies with indolocarbazole anions, simultaneously binding and activating monomer carbonyls towards the nucleophilic attack, resulting in a significant rate enhancement. This distinctive activation motif of the indolocarbazole sets it apart from other catalysts by utilizing cations as a potent handle for modulating polymerization reactivity. Coupled with its high availability, good solubility, high activity, moderate basicity, and high selectivity, the indolocarbazole heterocycle emerges as one of the most versatile organocatalysts for ring-opening polymerization.

Key words: *Ring-opening polymerization, cation- π interaction, heterocycle, indolocarbazole, alkali metal, pKa, anionic polymerization*

INTRODUCTION: Organocatalytic ring-opening polymerization (ROP) is a powerful method for generating polyesters and polycarbonates with exquisite control over the molecular weight and molecular weight distribution.[1-5] Guanidine and (thio)urea/base catalyst systems were among the first highly selective organocatalysts, demonstrating good control over molecular weight and dispersity.[6-9] The development of anionic catalysts based on deprotonated (thio)ureas marked a significant advance, as these catalysts retained the high selectivity of the (thio)urea / base catalysts, but were significantly more active. Moreover, their activities can be tuned by over three orders of magnitude by altering substituents on the (thio)ureas.[10-13] Due to the versatility of the anionic (thio)urea catalysts, they have been widely adopted for the ROP of various monomers.[14-22] Mechanistic and computational studies[10-13] indicate that the activity of the anionic (thio)urea catalysts derive from a bifunctional activation mechanism where the negatively charged nitrogen activates the propagating (or initiating) alcohol and the adjacent N-H hydrogen bond binds and positions the lactone to facilitate nucleophilic attack and formation of the tetrahedral intermediate (Figure 1a).[10-13]

We recently reported that salts derived by deprotonation of 2,2'-bisindole[23] are also effective catalysts for ring-opening polymerization, where a strong counterion effect implicated a mechanism involving activation of the lactone by the cation (Figure 1b). This activation motif allows convenient modulation of the polymerization rate by changing the cation. Nevertheless, the 2,2'-bisindole is not readily commercially available and challenging to prepare,[24,25] limiting its general applicability as an ROP catalyst.

To assess the generality of this uncommon activation motif and to uncover the fundamental principles that trigger such a mechanism, we expanded our investigation to include a wider range of heterocycles bearing appropriately positioned N-H motifs. Herein we describe investigation of new classes of heterocycle organocatalysts derived from the deprotonation of a range of imidazole, indole/carbazole, or imidazoline heterocycles (Figure 1c). Mechanistic investigations reveal that the indolocarbazole anions [5^-] are able to position small alkali metal cations (Li^+ and Na^+) through cation-π interactions in a geometry suitable for monomer activation.

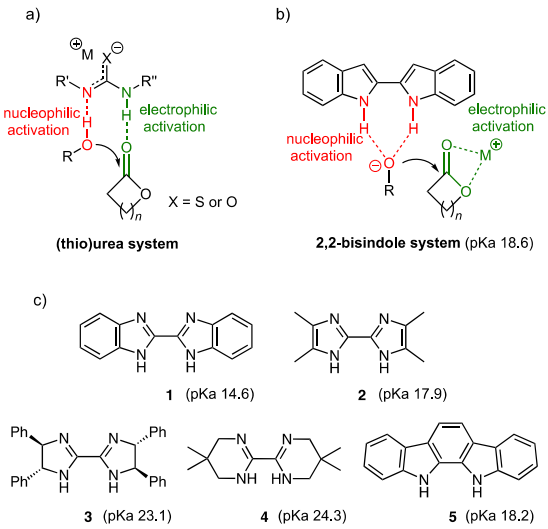

Figure 1. Proposed activation mechanisms for (a) (thio)urea anion systems[10-13] and (b) 2,2'-bisindole systems.[23] Heterocycles examined in this study are shown in (c). All pKa values are measured by UV-Vis titration techniques in DMSO. (Supporting Information)

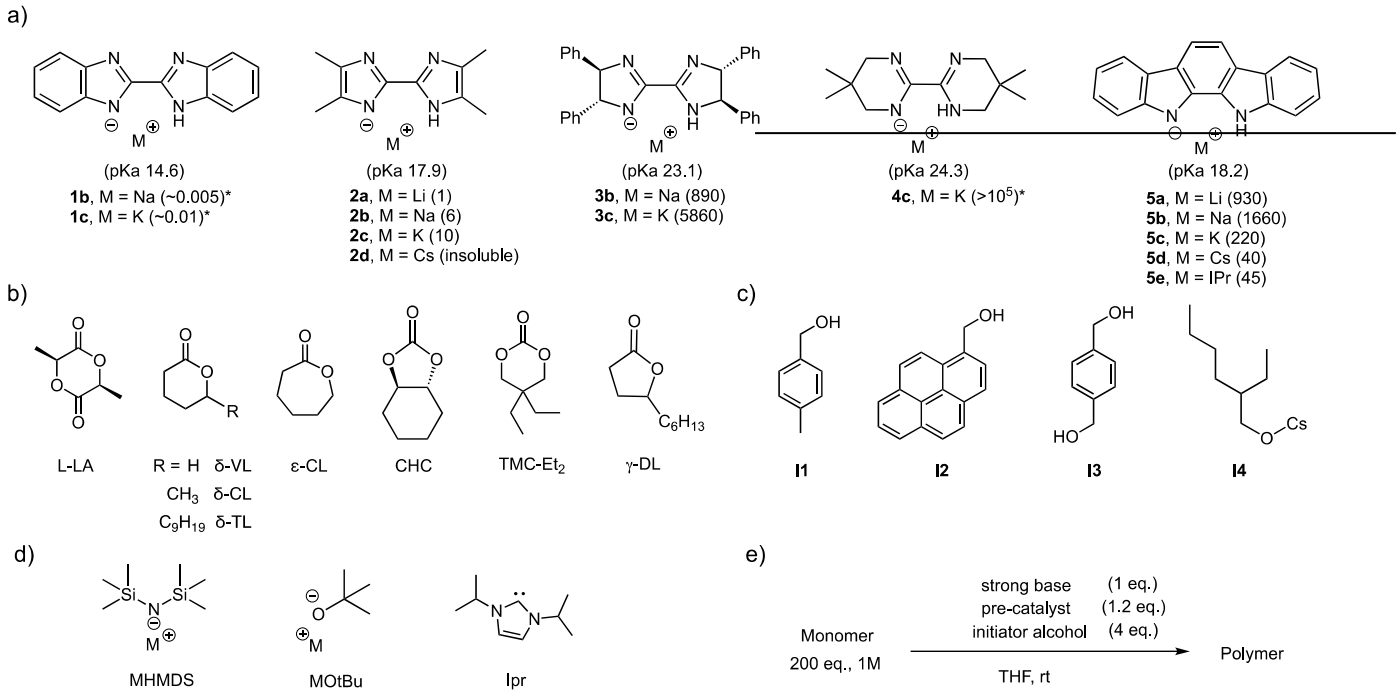

Figure 2. (a) Heterocycle catalysts tested, numbers in parenthesis are relative initial rates for polymerization of ε-CL in THF normalized to k_{rel}(**2a**)=1. *k_{rel} for **1b**, **1c**, and **4c** are extrapolated by ROP of L-lactide or δ-VL. (b) Monomers used in this study.(γ-DL is a non-polymerizable lactone) (c) Initiators used. (d) Strong bases used to deprotonate heterocycles. (e) Typical reaction conditions for ROP.

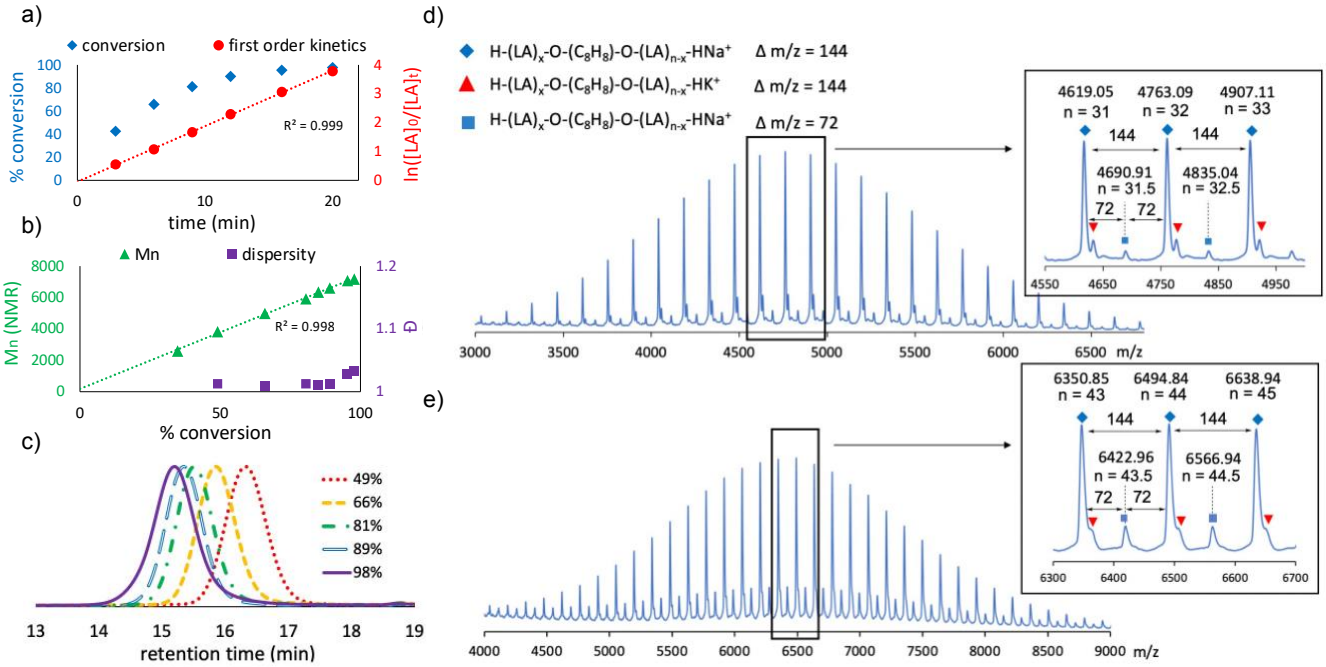

Figure 3. Polymerization of L-lactide (L-LA) with [**1**$^-$][K$^+$] and **I3**. Reaction conditions: [KHMDS]$_0$:[**1**]$_0$:[**I3**]$_0$:[L-LA]: = 1:1.2:4:200, [L-LA]$_0$ = 1 M for (a)~(e). (a) conversion vs time and first order monomer decay plot. (b) $M_{n,\,NMR}$ and dispersity (Đ) vs conversion, (c) GPC traces of the polymerization at different conversions, (d) MALDI-TOF of a poly(L-lactide) sample (66% conv., DP_{target}=50, Đ = 1.02), and (e) MALDI-TOF of a poly(L-lactide) sample (89% conv., DP_{target}=50, Đ = 1.02).

RESULTS AND DISCUSSION: Heterocycles **1**, **2** and **5** were purchased from commercial sources; heterocycles **3** and **4** were prepared in one step by reacting dithiooxamide with appropriate diamines.(Scheme S1 in Supporting Information) To evaluate the catalytic behaviors of these heterocycle anions with various cations, we generated a range of different salts (Figure 2a) by treating 1.2 molar equivalents of the respective heterocycle pre-catalyst with a strong base(Figure 2d, e). Their polymerization of a range of monomers was monitored in THF at 25°C.

As an example, the polymerization of L-lactide (1M in THF) catalyzed by bibenzimidazole potassium ([**1**$^-$][K$^+$]) was monitored until 98% conversion. The active catalyst was generated by deprotonation of **1** with 0.83 equivalents (relative to **1**) of KHMDS (Table 1, entry 1. Figure 2d,e). Under these conditions, the rate of polymerization is first order in lactide concentration (Figure 3a). A linear increase in polymer molecular weight (M_n) with conversion, and narrow dispersity ($Đ$ < 1.03) were observed throughout the course of polymerization (Figure 3b, c). These results are consistent with living polymerization behavior. The narrow dispersity indicates infrequent chain trans-esterification reactions, which was further corroborated by MALDI-TOF analysis on the same sample. A single population of ion distributions are predominantly observed, where the major ions corresponding to the sodium adducts are separated by 144 Daltons; ions associated with minor amounts of transesterification of the PLA chains (m/z = 72) are scarcely detectable at 66% but slightly more pronounced at 89% conversions. Additionally, no hexamethyldisilazane (HMDS) byproducts were observed in the ^{1}H-NMR spectra of worked up polymers, suggesting that HMDS does not function as a competitive initiator. Due to the mild basicity of [**1**$^-$][K$^+$] (pKa$_{(DMSO)}$ 14.6), no epimerization reactions were observed in the homonuclear decoupled ^{1}H-NMR spectrum. A clean, single peak at 5.16 ppm suggests the absence of racemic dyads, indicating a high degree of tacticity in the poly-L-lactide sample (Figure S1 in Supporting Information).

By employing similar methods, the potassium salts of heterocycles **2**-**5** were generated, evaluated, and compared as catalysts for a series of lactone and carbonate polymerization reactions (Table 1, Figure S2-S5 in Supporting Information). As shown in Table 1, excellent control is achieved across the library of heterocycle catalysts, affording a range of molecular weights, predictable degrees of polymerization (DP = 20 to 600) and narrow molecular weight distributions (Đ = 1.01~ 1.1). Compared to urea anion systems, alkali salts of **3**-**5** have exceptional solubility in THF, making them versatile catalysts for low temperature (Table 1, entry 10) and/or bulk (Table 1, entry 19, 20) polymerization conditions. These properties are crucial for controlled polymerization of thermodynamically challenging monomers such as δ-CL.[26] Unlike anionic thioureas where an excess of thiourea (3-10 eq. relative to base) is used to achieve high selectivity,[10] the use of only slight excess (1.2 eq) of heterocycle is sufficient, improving atom economy without compromising control.

The activities of the heterocycle anion catalysts span a wide range. Catalysts derived from imidazoles ([**1**$^-$][K$^+$], ([**2**$^-$][K$^+$]) exhibit the lowest activities, while those derived from cyclic amidines ([**3**$^-$][K$^+$], ([**4**$^-$][K$^+$]) exhibit the highest activities. The indolocarbazole-based catalyst ([**5**$^-$][K$^+$]) exhibits intermediate activity, comparable to the previously reported 2,2'-bisindole potassium complex.[23] For the structurally-related heterocycles **1**-**4**, the relative reactivity generally correspond to the pKa of the N-H of the pre-catalyst (Figure 1c, pKa values measured by UV-Vis titration in DMSO, Supporting Information), where the more basic potassium salts of heterocycles **3** (pKa$_{(DMSO)}$ 23.1) and **4** (pKa$_{(DMSO)}$ 24.3) lead to faster polymerization rates. Although catalysts derived from **3** and **4** exhibit faster rates than those of **1**, **2**, and **5**, the high basicity of the anions derived from **3** and **4** can lead to undesired side reactions. For example, when the potassium salt [**3**$^-$][K$^+$] was employed as a catalyst under the condition of a 1:1 ratio of initiating alcohol and base for the ROP of ε-CL, a bimodal molecular weight distribution was obtained (Figure S3 in Supporting Information), which we attribute to competitive initiation by enolization of the lactone monomer.[27] This competitive enolization could be minimized by employing a 20:1 ratio of alcohol to base (base: pre-catalyst: ROH: monomer = 1: 1.2: 20: 1000, Table 1, entries 8-11). The activity of [**4**$^-$][K$^+$] for the polymerization of δ-VL was so high that it could only be controlled by employing a continuous flow reactor, achieving reaction times as short as 100 milliseconds (Table 1, entry 11. Figure S4 in Supporting Information).

Among the heterocycles investigated as catalysts, the indolocarbazole[28] (**5**) behaves very differently from heterocycles **1**-**4** and is the most versatile in this series: it is commercially available, exhibits high solubility, high activity, moderate basicity, and high selectivity. The activity of indolocarbazole **5** does not follow the general trend with pKa; the pKa$_{(DMSO)}$ of indolocarbazole **5** (pKa$_{(DMSO)}$ 18.2) is similar to that of **2**(pKa$_{(DMSO)}$ 17.9), but its potassium salt ([**5**$^-$][K$^+$], k_{init} = 0.24 M min^{-1}) exhibits a much higher rate for ε-CL polymerization than that of the biimidazole anion ([**2**$^-$][K$^+$], k_{init} = 0.011 M min^{-1}) (Table S1 in Supporting Information). Moreover, as described in more detail below, the activities of the deprotonated indolocarbazole **5** span over two orders of magnitude, depending on the nature of the counterion. The tunable rates and excellent control observed across the library of [**5**$^-$][M$^+$] highlight the versatility of this catalyst system as a practical counterion-tunable organocatalyst suitable for a wide variety of cyclicesters and carbonates like δ-VL, ε-CL, δ-CL, CHC, and TMC-Et$_2$ (Figure 2b, Table 1, entry 12-22).

We investigated the influence of different cations on the activity of heterocycles **1**-**5** activated with different alkali metal amide or alkoxide bases ([Li,Na,K]$^+$[N(TMS)$_2$]$^-$, [Li,Na,K]$^+$[OtBu]$^-$, or CsOR). For heterocycles **1**-**4**, the nature of the cation had a moderate influence on the rate of polymerization, with the potassium salts faster than the sodium salts (by an approximate factor of 2-6x) and lithium salts (by an approximate factor of 10x) (Figure S6 in Supporting Information). These trends (ie., K$^+$>Na$^+$>Li$^+$) are similar to those observed in anionic ring-opening polymerization where small and hard cations such as Li$^+$ tend to inhibit anionic chain ends from efficient propagation by forming strong ion pairs or aggregates,[29,30]

even though the rates are slower than those initiated by, for example, $[M^+][^-N(TMS)_2]$ and alcohol.[31]

Contrasting the trends seen for heterocycle **1-4**, the activities of the indolocarbazole anions $[\mathbf{5}^-][M^+]$ exhibit a pronounced dependence on the identity of the cation (Figure

Table 1. Ring-Opening Polymerization with heterocycles 1~5 and bases[a]

Entry	Catalyst/Initiator	Monomer$_{(DPtarget)}$[b]	Time (min)	Conversion[c] (%)	DP$_{(theory/actual)}$[d]	$Đ$[e]
1	**1c/ I3**	L-LA$_{(50)}$	20	98	49/50	1.03
2	**1b/ I3**	L-LA$_{(50)}$	20	89	45/50	1.01
3[f]	**1c/ I3**	L-LA$_{(380)}$	80	>99	380/385	1.10
4	**1c/ I3**	ε-CL$_{(50)}$	120	0	-	-
5	**2c/ I2**	L-LA$_{(50)}$	0.017	80	40/41	1.02
6	**2c/ I1**	δ-VL$_{(50)}$	20	88	44/45	1.04
7[g]	**2c/ I2**	δ-VL$_{(580)}$	35	90	522/468	1.05
8[h]	**3c/ I2**	ε-CL$_{(50)}$	2.5	92	46/47	1.07
9[h]	**3b/ I2**	ε-CL$_{(50)}$	4	55	-	-
10[i]	**3c/ I2**	δ-TL$_{(18)}$	210	82	15/14	1.04
11[j]	**4c/ I2**	δ-VL$_{(50)}$	0.0017	89	45/45	1.04
12[k]	**5e/ I1**	ε-CL$_{(50)}$	40	89	45/44	-
13	**5d/ I4, I1**	ε-CL$_{(50)}$	36	83	42/56	-
14	**5c/ I1**	ε-CL$_{(50)}$	12	94	47/52	1.12
15	**5b/ I1**	ε-CL$_{(50)}$	0.58	98	49/47	1.07
16	**5a/ I1**	ε-CL$_{(50)}$	1.17	90	45/46	1.04
17	**5c/ I1**	δ-VL$_{(50)}$	0.5	89	45/46	1.02
18[l]	**5c/ I3**	δ-VL$_{(500)}$	1.83	94	470/488	1.10
19[m]	**5c/ I2**	δ-CL$_{(100)}$	10	87	87/91	1.03
20[n]	**5b/ I3**	δ-CL$_{(750)}$	140	83	613/600	1.01
21	**5c/ I3**	CHC$_{(50)}$	1	82	41/40	1.16
22	**5c/ I3**	TMC-Et$_{2(50)}$	0.1	73	37/40	1.03

[a]Unless otherwise specified, $[base]_o$:$[pre\text{-}catalyst]_o$: $[initiator]_o$: $[monomer]_o$ = 1:1.2:4:200 and $[monomer]_o$ = 1 M in THF at room temperature (reactions run in batch and quenched with benzoic acid). [b]DP_{target} = $[monomer]_o/[initiator]_o$. [c]Conversion determined by integrating monomer peaks against polymer peaks in ^{1}H NMR. [d]Actual DP determined by end group analysis in ^{1}H NMR. [e] $Đ$=M_w/M_n calculated by GPC analysis. [f]$[KHMDS]_o$:$[\mathbf{1}]_o$: $[\mathbf{I3}]_o$: $[L\text{-}LA]_o$ = 1:1.2:1.5:570 and $[L\text{-}LA]_o$ = 3 M in 1:5 THF/DCM mixture. [g]$[KHMDS]_o$:$[\mathbf{2}]_o$: $[\mathbf{I2}]_o$: $[\delta\text{-}VL]_o$ = 1:1.2:1:580 and $[\delta\text{-}VL]_o$ = 3 M in THF. [h]$[Na/KHMDS]_o$:$[\mathbf{3}]_o$: $[\mathbf{I2}]_o$: $[\varepsilon\text{-}CL]_o$ = 1:1.2:20:1000 and $[\varepsilon\text{-}CL]_o$ = 1 M in THF. [i]$[KHMDS]_o$:$[\mathbf{3}]_o$: $[\mathbf{I2}]_o$: $[\delta\text{-}TL]_o$ = 1:1.2:20:360 and $[\delta\text{-}TL]_o$ = 3 M in THF at -35^{o}C. [j]Experiment conducted in a continuous flow system, $[KOtBu]_o$:$[\mathbf{4}]_o$: $[\mathbf{I2}]_o$: $[\delta\text{-}VL]_o$ = 1:1.2:20:1000 and $[\delta\text{-}VL]_o$ = 1 M in THF. [k]$[CsOR]_o$:$[\mathbf{5}]_o$:$[\mathbf{I1}]_o$:$[\varepsilon\text{-}CL]_o$ =1:1.2:3:200. [l]$[KHMDS]_o$:$[\mathbf{5}]_o$: $[\mathbf{I3}]_o$: $[\delta\text{-}VL]_o$ = 1:1.2:1.6:800 and $[\delta\text{-}VL]_o$ = 2 M in THF. [m]$[KHMDS]_o$:$[\mathbf{5}]_o$: $[\mathbf{I2}]_o$: $[\delta\text{-}CL]_o$ = 1:1.2:2:200 and $[\delta\text{-}CL]_o$ = 6 M in THF. [n]$[NaHMDS]_o$:$[\mathbf{5}]_o$: $[\mathbf{I3}]_o$: $[\delta\text{-}CL]_o$ = 1:1.2:1.6:1200 and $[\delta\text{-}CL]_o$ = 6 M in THF.

S7-S10 in Supporting Information), following the order $Na^+ > Li^+ > K^+ > Cs^+$, Ipr^+ (1,3-diisopropylimidazolium). The pattern is at odds with what was observed in the anionic polymerization of lactones by alkoxides, while bearing resemblance to the behavior seen for 2,2'-bisindole.[23] For instance, polymerization of ε-CL with $[\mathbf{5}^-][Na^+]$ reaches 98% conversion in just 35 seconds, compared to over 40 minutes required to achieve 89% conversion with $[\mathbf{5}^-][Cs^+]$ (Table1, entry 13, 15). These differences in overall activity are reflected both in the initial rates and the observed rate laws. The initial rate for the catalyst derived from $[\mathbf{5}^-][Na^+]$ is 7.8 times faster than that of $[\mathbf{5}^-][K^+]$, and 26 times faster than those of $[\mathbf{5}^-][Cs^+]$ or $[\mathbf{5}^-][Ipr^+]$. Furthermore, the enhancement of reactivity was also accompanied by a change in the rate law. While the polymerization rate of ε-CL with ($[\mathbf{5}^-][K^+]$, $[\mathbf{5}^-][Cs^+]$ or $[\mathbf{5}^-][Ipr^+]$) is first order in [ε-CL], that with ($[\mathbf{5}^-][Na^+]$) is zero-order in [ε-CL]. The lithium salt ($[\mathbf{5}^-][Li^+]$) exhibits intermediate activity (k_{init} = 1.02 M min^{-1}) between ($[\mathbf{5}^-][Na^+]$ k_{init} = 1.83 M min^{-1}) and ($[\mathbf{5}^-][K^+]$ k_{init} = 0.24 M min^{-1}) and a rate law intermediate between 0 and 1st order for $[\varepsilon\text{-}CL]_o$ = 1M. Notably, the ROP of ε-CL with $[\mathbf{5}^-][Li^+]$ exhibits higher rate than that of the much more basic $[RO^-][Li^+]$ system[31], while demonstrating much better control, as the dispersity stays narrow during the polymerization ($Đ([\mathbf{5}^-][Li^+])$= 1.04, $Đ([RO^-][Li^+])$= 1.22 at ~90% conversion) (Table 1, entry 16).[31]

The unusual counterion dependence (Na^+>Li^+> K^+> Cs^+) of the polymerization rate with [**5**$^-$][M^+] is similar to that of the 2,2'-biisindole anions, in which strong ion-dipole interactions between the cation and the lactone carbonyl group was implicated by DFT computations.[23]

To test the cation-dipole interactions between [**5**$^-$][M^+] and lactone monomers under simulated catalytic conditions (with ROH in THF, 25°C) without initiating ring-opening polymerization reactions, we employed γ-DL, a lactone that does not readily polymerize under these conditions. The ^{13}C NMR signal of γ-DL was monitored both in the presence and absence of various [**5**$^-$][M^+] salts with initiator alcohol in deuterated THF. As shown in Table 2, the ^{13}C NMR signal of γ-DL carbonyl group shifts downfield by 0.4 ppm upon addition of neutral heterocycle **5** (Table 2, entry 1,2), likely due to the hydrogen bonding interactions between N-H motif and the γ-DL carbonyl group. Introducing an equimolar of [Li,Na,K]$^+$[$N(TMS)_2$]$^-$ to **5** led to the formation of salt ([**5**$^-$][Li,Na,K]$^+$); in the presence of this salt, the γ-DL carbonyl ^{13}C NMR signal shifts downfield by 0.27-0.81 ppm (relative to 176.73 ppm, Table 2, entry 3, 5, 7), indicative of an interaction between [Li,Na,K]$^+$ and γ-DL carbonyl group. On the other hand, [**5**$^-$][Cs^+] bearing a large and soft cesium cation did not induce additional shifts of the γ-DL carbonyl signal compared to neutral heterocycle **5** (Table 2, entry 9). The addition of crown ethers[32] (benzo-12-crown-4 (B12C4) to [**5**$^-$][Li^+] and benzo-15-crown-5 (B15C5) to [**5**$^-$][Na^+]) substantially mitigated the downfield shifts triggered by [**5**$^-$][Li^+] and [**5**$^-$][Na^+]. In the presence of crown ethers, the γ-DL carbonyl ^{13}C NMR shifts closely resembled those observed with neutral **5** or [**5**$^-$][Cs^+], suggesting that the employed crown ethers are potent ligands that compete favorably with γ-DL in binding to given alkali metal cations.

Table 2. ^{13}C NMR shifts of γ-DL carbonyl in *d*^{8}-THF[a]

Entry	[5$^-$][M$^+$]	Crown ether	δ ^{13}C $_{(C=O)}$ (ppm)	Δ {δ ^{13}C $_{(C=O)}$} (ppm)
1	-	-	176.33	-0.4
2	5	-	176.73	0
3	[5$^-$][Li$^+$]	-	177.00	+0.27
4	[5$^-$][Li$^+$]	B12C4	176.80	+0.07
5	[5$^-$][Na$^+$]	-	177.54	+0.81
6	[5$^-$][Na$^+$]	B15C5	176.64	-0.09
7	[5$^-$][K$^+$]	-	177.12	+0.39
8[b]	[5$^-$][K$^+$]	DB18C6	-	-
9[c]	[5$^-$][Cs$^+$]	-	176.72	-0.01

[a]Unless otherwise specified, conditions were:[γ-DL]=0.03M, [(5^-)(M^+)]=0.17M, [I1]=0.17M, [crown ether]=0.34M in *d*^{8}-THF at 25°C. [b] Addition of DB18C6 to [5$^-$][K^+] led to precipitation at this concentration. [c][γ-DL]=0.03M, $[5]_0$=0.17M, $[I4]_0$=0.17M in *d*^{8}-THF at 25°C.

To further evaluate the unusual counterion dependence on the rate of ε-CL polymerization with [**5**$^-$][M^+], we investigated the influence of added crown ethers and γ-DL on the polymerization rate. As indicated in Table 3, introducing benzo-15-crown-5 (5 eq. vs Na^+) to a ε-CL polymerization with [**5**$^-$][Na^+]/**I1** not only significantly inhibited the initial rate (k_{init} (no additive)= 1.83 M min^{-1} compared to k_{init}(B15C5) = 0.49 M min^{-1}), but also shifted the reaction kinetics from zero-order in [ε-CL] to first-order. (Table 3, entry 4-5. Figure 4b). Similarly, the addition of γ-DL (126 eq. vs Na^+) to ε-CL polymerization with [**5**$^-$][Na^+]/**I1** led to a decrease in rate (k_{init}(γ-DL) = 0.43 M min^{-1}) and a change in the rate law to near first-order, indicating the presence of strong competition between the non-polymerizable γ-DL and the polymerizable ε-CL (Table 3, entry 6. Figure 4b). Similar rate inhibitions were observed upon the addition of B12C4 or γ-DL to [**5**$^-$][Li^+] (Table 3, entry 1-3). However, the addition of crown ethers or γ-DL had little effect on the rate of polymerization with the potassium salts [**5**$^-$][K^+] (Table 3, entry 7-9. Figure S11 in Supporting Information).

These data indicate that: (1) the mechanisms of enchainment for anions derived from heterocycles **1-4** differ from that of **5**, and (2) that for the [**5**$^-$][M^+] salts, the Na^+ and Li^+ counterions behave differently than the K^+ or Cs^+ counterions. For catalysts derived from **1-4**, the strong dependence of the activity on the basicity of the heterocycle anions suggests that alcohol activation by hydrogen bonding to the anion is the most significant contributor to the rate.[10-13] This mechanism is consistent with that proposed for serine activation in the catalytic triad in serine proteases.[33,34] The cation dependence with [**1-4**]$^-$[M^+] is similar to that of the anionic polymerizations[29-31] and implicates that for these catalysts, the cation primarily functions as an inhibitor during the catalytic process.

For indolocarbazole **5**, the strong influence of counterion on the polymerization rate (Na^+ >Li^+> K^+ > Cs^+, Ipr^+) is indicative of a different mechanism from that of **1-4**. In the presence of small and hard cations such as Li^+ and Na^+ within the [**5**$^-$][M^+] complex, we propose that activation of the monomer and stabilization of the tetrahedral intermediate is facilitated by a direct ion-dipole interaction with the cation, which is suitably positioned by a cation-π interaction[35-38] with the aromatic system of indolocarbazole (Figure 4a, Path A). The ^{13}C NMR experiments and the pronounced rate inhibition observed with the addition of crown ethers or γ-DL both support this hypothesis. The zero-order kinetics in these cases is consistent with the rate-determining formation of the tetrahedral intermediate (INT1) from the reaction complex (RC) (Figure 4a, Path A); in the saturation regime where binding of the alkali cation to the indolocarbazole is favorable, an increase in monomer concentration will not influence the steady-state concentration of RC, leading to zero order kinetics in monomer. Indolocarbazoles such as **5** have been extensively investigated as anion-binding agents;[28,39-43] crystallographic studies of TBA^+Cl^- adducts indicate that the halide anion binds to the N-H bonds, while the associated TBA^+ cations coordinate above the π-system of the indolocarbazole through a cation-π interaction.[39] This is analogous to the interaction depicted in Figure 4a, Path A. For the K^+ counterions, the rate's insensitivity to added crown ether or γ-DL is inconsistent with Path A. Catalysts derived from

anions of **5** with K^+, Cs^+, Ipr^+ counterions all exhibit first-order dependence on monomer concentration. For these counterions, it is likely that the propagation occurs through a complex series of equilibria between ion pairs and solvent-separated ion pairs (Path B).[29-30,44-46]

While the mechanism depicted in Figure 4a provides a reasonable rationale for the results reported here, the situation is likely more complex. Counterion effects have been the subject of intensive studies in the field of anionic polymerization; for alkali metal alkoxide-mediated polymerization reactions, these effects have been attributed to complex equilibria between alkoxide aggregates, ion pairs, separated ion pairs and free alkoxide anions.[29-30,44-46] For the deprotonated heterocycle anion catalysts here, hydrogen bonding between the alcohol and the heterocycle anion both solubilizes and modulates the nucleophilicity of the propagating alcohol/alkoxide. The crucial role of the cation-π interaction in optimally positioning the alkali metal cation

Table 3. Kinetic studies of [5⁻][M⁺] with cation sequestration ligands[a]

Entry	[5⁻][M⁺]	Additive[b] (eq. vs M⁺)	Time (min)	Conversion[c] (%)	Initial rate ($M \cdot min^{-1}$)	Dependence on [monomer]
1	[5⁻][Li⁺]	-	1.17	90	1.02	Near 0th order
2	[5⁻][Li⁺]	B12C4 (5 eq.)	3	91	0.53	1st order
3	[5⁻][Li⁺]	γ-DL (126 eq.)	2	96	0.67	Between 0th and 1st order
4	[5⁻][Na⁺]	-	0.58	98	1.83	0th order
5	[5⁻][Na⁺]	B15C5 (5 eq.)	4	95	0.48	1st order
6	[5⁻][Na⁺]	γ-DL (126 eq.)	2	96	0.43	Between 0th and 1st order
7	[5⁻][K⁺]	-	12	95	0.24	1st order
8	[5⁻][K⁺]	DB18C6 (3 eq.)	12	95	0.26	1st order
9	[5⁻][K⁺]	γ-DL (126 eq.)	12	88	0.19	1st order

[a]Unless otherwise specified, $[MHMDS]_0$:$[\mathbf{5}]_0$: $[\mathbf{I1}]_0$: $[\varepsilon\text{-CL}]_0$ = 1:1.2:4:200 and $[\varepsilon\text{-CL}]_0$ = 1 M in THF at room temperature, total reaction volume is 4mL.[b]Additives (benzo-12-crown-4 (B12C4), benzo-15-crown-5 (B15C5), dibenzo-18-crown-6 (DB18C6), gamma-decalactone (γ-DL)) are noted in molar equivalence compared to alkali metal cations. [c]Conversion determined by ^1H NMR.

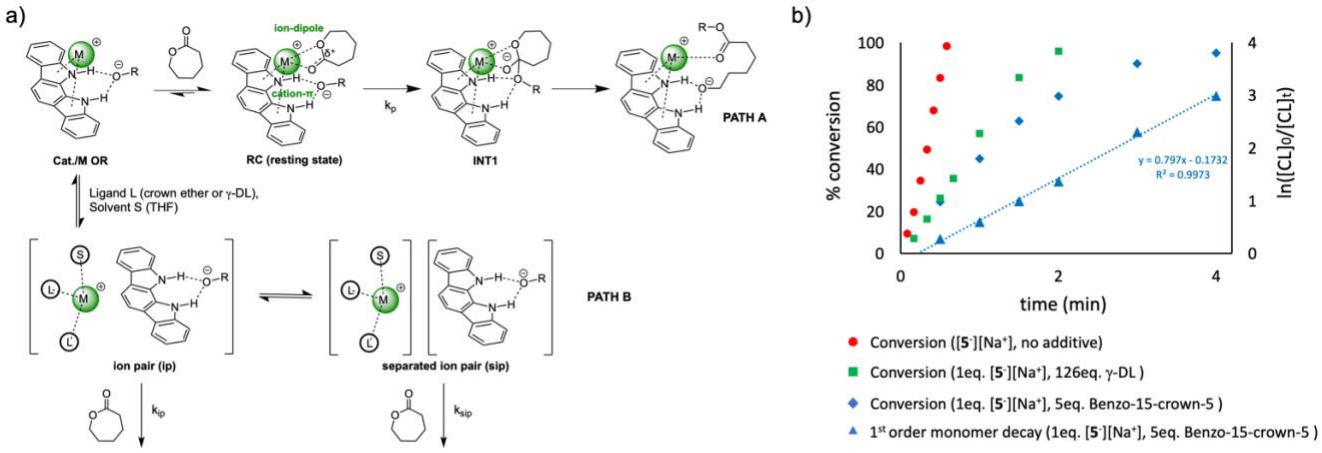

Figure 4. (a) Proposed mechanism for ROP catalyzed by indolocarbazole salts [5⁻][M⁺]. Path A: ring-opening of ε-CL mediated by cation-π assemblies of indolocarbazole anion and counterions (Na^+, Li^+). Path B: Ion-pair mechanism mediated by alcohol activation by indolocarbazole anion (K^+, Ipr^+, Cs^+). (b) Conversion vs time and first order monomer decay plot of [5⁻][Na⁺] with and without additives. Red circles: $[CL]_0$ = 1M; total volume = 4 mL in THF, $[NaHMDS]_0$:$[\mathbf{5}]_0$:$[\mathbf{I1}]_0$:$[\varepsilon\text{-CL}]_0$: = 1:1.2:4:200. Green squares: $[CL]_0$ = 1M; total volume = 4 mL in THF, γ-DL = 0.5mL, $[NaHMDS]_0$:$[\mathbf{5}]_0$:[γ-DL]:$[\mathbf{I1}]_0$:$[\varepsilon\text{-CL}]_0$: = 1:1.2:126:4:200. Blue diamonds and blue triangles: $[CL]_0$ = 1M; total volume = 4 mL in THF, $[NaHMDS]_0$:$[\mathbf{5}]_0$:[benzo-15-crown-5]:$[\mathbf{I1}]_0$:$[\varepsilon\text{-CL}]_0$: = 1:1.2:5:4:200.

for monomer activation is further corroborated by the counterion inhibition observed with heterocycles **1-4**, where cation-π interactions would not be significant, due to the electron poor nature of the imidazole ring[47] and cyclic amidine's lack of an aromatic π system.

This dual activation of the monomer and propagating alcohol chain-end offers a novel design motif for ring-opening polymerization. This unique approach allows for the optimization of both the nature of the cation and the heterocycle, positioning both the alcohol and Lewis-acidic counterion in the optimal position for the key nucleophilic attack step. Within this framework, the [**5**$^-$][M$^+$] system demonstrates its unique ability to transform small alkali metal cations from chain-end inhibitors into monomer activators. This remarkable capability of indolocarbazole **5** is best elucidated when compared to heterocycle **2,** which shares a similar pKa (pKa$_{(DMSO)}$ 18.2 vs 17.9). With larger cations such as K^+ or Cs^+, the activity of [**5**$^-$][M$^+$] and [**2**$^-$][M$^+$] differ only by a factor of 4 (k_{rel}([**5**$^-$][Cs^+])=40, k_{rel}([**2**$^-$][K^+])=10, Figure 2a), and the activity in these cases is predominantly governed by the nucleophilic activation provided by similarly basic anions. The scenario changes dramatically when small and hard cations such as Li^+ and Na^+ come into play: these cations become increasingly inhibiting for the [**2**$^-$][M$^+$] system due to strong alkoxide binding, while becoming more activating for [**5**$^-$][M$^+$] due to strong monomer activation and cation-π interactions. As a result, [**5**$^-$][Li^+] exhibits an initial rate that is 930 times faster than that of [**2**$^-$][Li^+] (Figure 2a. Table S1 in Supporting Information) despite their comparable basicities.

CONCLUSION: In this study, we present the development, characterization, and mechanistic investigations of a new class of heterocycle organocatalysts for ring-opening polymerization reactions. Despite sharing some structural and electronic attributes, these heterocycle catalysts demonstrate drastically different kinetic behaviors regarding the nature of cations. Mechanistic investigations implicate different mechanisms for these heterocycles: for anions derived from imidazol(in)e **1-4,** small alkali metal cations like Li^+ and Na^+ inhibit the rate of polymerization, whereas for indolocarbazole anions these counterions bind and activate the monomer for the nucleophilic attack. The indolocarbazole anions are versatile organocatalysts for polymerization of a wide array of monomers under diverse conditions; their ability to position small alkali metal cations (Li^+ and Na^+) through cation-π interactions in a geometry suitable for monomer activation reveals a new motif for monomer activation. This insight may pave the way for new methods to exploit counterion effects in anionic polymerizations and other organic transformations.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

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

Author Contributions

All authors have given approval to the final version of the manuscript.

Funding Sources

This work was supported by the National Science Foundation(GOALI NSF CHE-2002933).

Supporting Information

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

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

ACKNOWLEDGMENT

We thank Senjie Ma and Yehao Qiu (UC Berkeley) for engaging helpful discussions regarding the data interpretation of the cation sequestration experiments.

REFERENCES

(1) Kiesewetter, M. K.; Shin, E. J.; Hedrick, J. L.; Waymouth, R. M. Organocatalysis: Opportunities and Challenges for Polymer Synthesis. *Macromolecules* **2010**, 43 (5), 2093–2107.

(2) Walsh, D. J.; Hyatt, M. G.; Miller, S. A.; Guironnet, D. Recent Trends in Catalytic Polymerizations. *ACS Catal.* **2019**, 9 (12), 11153–11188.

(3) Kamber, N. E.; Jeong, W.; Waymouth, R. M.; Pratt, R. C.; Lohmeijer, B. G. G.; Hedrick, J. L. Organocatalytic Ring-Opening Polymerization. *Chem. Rev.* **2007**, 107 (12), 5813–5840.

(4) Zhang, X.; Fevre, M.; Jones, G. O.; Waymouth, R. M. Catalysis as an Enabling Science for Sustainable Polymers. *Chem. Rev.* **2018**, 118 (2), 839–885.

(5) Hu, S.; Zhao, J.; Zhang, G.; Schlaad, H. Macromolecular Architectures through Organocatalysis. *Prog. Polym. Sci.* **2017**, 74, 34–77.

(6) Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. Thiourea-based Bifunctional Organocatalysis: Supramolecular Recognition for Living Polymerization. *J. Am. Chem. Soc.* **2005**, 127, 13798–13799.

(7) Lohmeijer, B. G. G.; Pratt, R. C.; Leibfarth, F.; Logan, J. W.; Long, D. A.; Dove, A. P.; Nederberg, F.; Choi, J.; Wade, C.; Waymouth, R. M.; et al. Guanidine and Amidine Organocatalysts for Ring-Opening Polymerization of Cyclic Esters. *Macromolecules* **2006**, 39 (25), 8574–8583. https://doi.org/10.1021/ma0619381.

(8) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Lundberg, P. N. P.; Dove, A. P.; Li, H.; Wade, C. G.; Waymouth, R. M.; Hedrick, J. L. Exploration, Optimization, and Application of Supramolecular Thiourea-Amine Catalysts for the Synthesis of Lactide (Co)Polymers. *Macromolecules* **2006**, 39 (23), 7863–7871. https://doi.org/10.1021/ma0616070.

(9)Fastnacht, K. V.; Spink, S. S.; Dharmaratne, N. U.; Pothupitiya, J. U.; Datta, P. P.; Kiesewetter, E. T.; Kiesewetter, M. K. Bis- and Tris-Urea H-Bond Donors for Ring-Opening Polymerization: Unprecedented Activity and Control from an Organocatalyst. *ACS Macro Lett.* **2016**, 5 (8), 982–986. https://doi.org/10.1021/acsmacrolett.6b00527.

(10) Zhang, X.; Jones, G. O.; Hedrick, J. L.; Waymouth, R. M. Fast and Selective Ring-Opening Polymerizations by Alkoxides and Thioureas. *Nat. Chem.* **2016**, 8 (11), 1047–1053. https://doi.org/10.1038/nchem.2574.

(11) Lin, B.; Hedrick, J. L.; Park, N. H.; Waymouth, R. M. Programmable High-Throughput Platform for the Rapid and Scalable Synthesis of Polyester and Polycarbonate Libraries. *J. Am. Chem. Soc*. **2019**, 141 (22), 8921–8927. https://doi.org/10.1021/jacs.9b02450.

(12) Lin, B.; Waymouth, R. M. Organic Ring-Opening Polymerization Catalysts: Reactivity Control by Balancing Acidity. *Macromolecules* **2018**, 51 (8), 2932–2938. https://doi.org/10.1021/acs.macromol.8b00540.

(13) Lin, B.; Waymouth, R. M. Urea Anions: Simple, Fast, and Selective Catalysts for Ring-Opening Polymerizations. *J. Am. Chem. Soc*. **2017**, 139 (4), 1645–1652. https://doi.org/10.1021/jacs.6b11864.

(14) Fang, G.; Zhe, W.; Yanyun, Z.; Xiaowu, W. Ionic (Co)Organocatalyst with (Thio)Urea Anion and Tetra- n -butyl Ammonium Cation for the Polymerization of Γ-Butyrolactone. *Macromol. Chem. Phys*. **2020**, 221 (16), 2000172. https://doi.org/10.1002/macp.202000172.

(15) Zhou, L.; Wang, Z.; Xu, G.; Lv, C.; Wang, Q. Structure and Activity Relationship Studies of N-Heterocyclic Olefin and Thiourea/Urea Catalytic Systems: Application in Ring-Opening Polymerization of Lactones. *Polym. Chem*. **2021**, 12 (12), 1806–1815. https://doi.org/10.1039/D0PY01747G.

(16) Jiang, Z.; Zhao, J.; Zhang, G. Ionic Organocatalyst with a Urea Anion and Tetra- n -Butyl Ammonium Cation for Rapid, Selective, and Versatile Ring-Opening Polymerization of Lactide. *ACS Macro Lett*. **2019**, 8 (7), 759–765. https://doi.org/10.1021/acsmacrolett.9b00418.

(17) Cywar, R. M.; Zhu, J-B.; Chen, E. Y. X. Selective or living organopolymerization of a six-five bicyclic lactone to produce fully recyclable polyesters. *Polym. Chem.*, **2019**, 10, 3097-3106.

(18) Shen, Y.; Zhao, Z.; Li, Y.; Liu, S.; Liu, F.; Li, Z. A Facile Method to Prepare High Molecular Weight Bio-Renewable Poly(γ-Butyrolactone) Using a Strong Base/Urea Binary Synergistic Catalytic System. *Polym. Chem*. **2019**, 10 (10), 1231–1237. https://doi.org/10.1039/C8PY01812J.

(19) Zaky, M. S.; Guichard, G.; Taton, D. Structural Effect of Organic Catalytic Pairs Based on Chiral Amino(thio)ureas and Phosphazene Bases for the Isoselective Ring-Opening Polymerization of Racemic Lactide *Macromolecules* **2023**, 56, 3607–3616. https://doi.org/10.1021/acs.macromol.3c00462.

(20) Dharmaratne, N. U.; Pothupitiya, J. U.; Kiesewetter, M. K. The Mechanistic Duality of (Thio)Urea Organocatalysts for Ring-Opening Polymerization. *Org. Biomol. Chem*. **2019**, 17 (13), 3305–3313. https://doi.org/10.1039/c8ob03174f.

(21) Hewawasam, R. S.; Kalana, U. L. D. I.; Dharmaratne, N. U.; Wright, T. J.; Bannin, T. J.; Kiesewetter, E. T.; Kiesewetter, M. K. Bisurea and Bisthiourea H-Bonding Organocatalysts for Ring-Opening Polymerization: Cues for the Catalyst Design. *Macromolecules* **2019**, 52 (23), 9232–9237. https://doi.org/10.1021/acs.macromol.9b01875.

(22) Pothupitiya, J. U.; Hewawasam, R. S.; Kiesewetter, M. K. Urea and Thiourea H-Bond Donating Catalysts for Ring-Opening Polymerization: Mechanistic Insights via (Non)Linear Free Energy Relationships. *Macromolecules* **2018**, 51 (8), 3203–3211. https://doi.org/10.1021/acs.macromol.8b00321.

(23) Jadrich, C. N.; Pane, V. E.; Lin, B. H.; Jones, G. O.; Hedrick, J. L.; Park, N. H.; Waymouth, R. M. A Cation-Dependent Dual Activation Motif for Anionic Ring-Opening Polymerization of Cyclic Esters *J. Am. Chem. Soc*. **2022**, 144, 8439-8443. doi: 10.1021/jacs.2c01436

(24) Kumaran, E.; Fan, W. Y.; Leong, W. K. $[Cp^*IrCl_2]_2$ Catalyzed Formation of 2,2′-Biindoles from 2-Ethynylanilines. *Org. Lett*. **2014**, 16, 1342–1345.

(25) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. Synthesis of Polyfunctional Indoles and Related Heterocycles Mediated by Cesium and Potassium Bases *Tetrahedron*, **2003**, 59, 1571.

(26) Li, C.; Wang, L.; Yan, Q.; Liu, F.; Shen, Y.; Li, Z. Rapid and Controlled Polymerization of Bio-sourced δ-Caprolactone toward Fully Recyclable Polyesters and Thermoplastic Elastomers. *Angew. Chem. Int. Ed*. **2022**, 61, https://doi.org/10.1002/anie.202201407

(27) Stukenbroeker, T. S.; Bandar, J. S.; Zhang, X.; Lambert, T. H.; Waymouth, R. M. Cyclopropenimine Superbases: Competitive Initiation Processes in Lactide Polymerization *ACS Macro Lett*. **2015**, 4, 853-856. doi: 10.1021/acsmacrolett.5b00421

(28) Kadam, S. A.; Haav, K.; Toom, L.; Haljasorg, T.; Leito, I. NMR Method for Simultaneous Host–Guest Binding Constant Measurement. *J. Org. Chem*. **2014**, 79, 2501–2513.

(29) Boileau, S.; Deffieux, A.; Lassalle, D.; Menezes, F.; Vidal, B. Reactivities of Anionic Species for the Ring Opening of Ethylene Oxide *Tetrahedron Letters* **1978**, 19, 1767-1770. doi: https://doi.org/10.1016/0040-4039(78)80039-2

(30) Deffieux, A.; Graf, E.; Boileau, S. Anionic-Polymerization of Ethylene-oxide with Cryptates as Counterions: 1. *Polymer* **1981**, 22, 549-552. doi: 10.1016/0032-3861(81)90178-6

(31) Lin, B. H.; Jadrich, C. N.; Pane, V. E.; Arrechea, P. L.; Erdmann, T.; Dausse, C.; Hedrick, J. L.; Park, N. H.; Waymouth, R. M., Ultrafast and Controlled Ring-Opening Polymerization with Sterically Hindered Strong Bases. *Macromolecules* **2020**, 53 (20), 9000-9007

(32) Bajaj, A. V.; Poonia, N. S. Comprehensive Coordination Chemistry of Alkali and Alkaline Earth Cations with Macrocyclic Multidentates: Latest Position *Coord. Chem. Rev*. **1988**, 87, 55.

(33) Simon, L.; Goodman, J. M. Enzyme Catalysis by Hydrogen Bonds: The Balance between Transition State Binding and Substrate Binding in Oxyanion Holes. *J. Org. Chem*. **2010**, 75, 1831-1840. doi: 10.1021/jo901503d

(34) Hedstrom, L. Serine Protease Mechanism and Specificity *Chem. Rev*. **2002**, 102, 4501-4524. doi: 10.1021/cr000033x

(35) Ma, J. C.; Dougherty, D. A. The Cation–π Interaction *Chem. Rev*. **1997**, 97, 1303-1324. doi: 10.1021/cr9603744

(36) Dougherty, D. A. The Cation-pi Interaction *Acc. Chem. Res*. 2013, 46, 885-893. doi: 10.1021/ar300265y

(37) Mahadevi, A. S.; Sastry, G. N. Cation–π Interaction: Its Role and Relevance in Chemistry, Biology, and Material Science *Chem. Rev*. **2013**, 113, 2100-2138. doi: 10.1021/cr300222d

(38) Kennedy, C. R.; Lin, S.; Jacobsen, E. N., The Cation–π Interaction in Small-Molecule Catalysis. *Angew. Chem. Int. Ed*. **2016**, 55 (41), 12596-12624.

(39) Chang, K.-J.; Moon, D.; Lah, M. S.; Jeong, K.-S. Indole-Based Macrocycles as a Class of Receptors for Anions *Angew. Chem. Int. Ed*. **2005**, 44, 7926-7929. doi: https://doi.org/10.1002/anie.200503121

(40) Gale, P. A. Synthetic Indole, Carbazole, Biindole and Indolocarbazole-based Receptors: Applications in Anion Complexation and Sensing *Chem. Commun*. **2008**, 4525 – 454

(41) Brown, A.; Mullen, K. M.; Ryu, J.; Chmielewski, M. J.; Santos,S. M.; Felix, V.; Thompson, A. L.; Warren, J. E.; Pascu, S. I.; Beer, P.D. Interlocked Host Anion Recognition by an Indolocarbazole-Containing [2]Rotaxane. *J. Am. Chem. Soc*. **2009**, 131, 4937–4952.

(42) Chae, M. K.; Lee, J. I.; Kim, N. K.; Jeong, K. S. An Ion Pair Receptor Showing Remarkable Enhancement of Anion-binding Strengths in the Presence of Alkali Metal Cations. *Tetrahedron Lett*. **2007**, 48, 6624–6627.

(43) Suk, J. M.; Jeong, K. S. Indolocarbazole-based Foldamers Capable of Binding Halides in Water. *J. Am. Chem. Soc*. **2008**, 130, 11868–11869.

(44) Penczek, S.; Duda, T.; Szymanski, R.; Biela, T. What We Have Learned in General from Cyclic Esters Polymerization *Macromolecular Symposia* **2000**, 153, 1-15.

(45) Boileau, S.; Illy, N. Activation in Anionic Polymerization: Why Phosphazene Bases are Very Exciting Promoters *Prog. Polym. Sci*. **2011**, 36, 1132-1151. doi: 10.1016/j.progpolymsci.2011.05.005

(46) Penczek, S.; Cypryk, M.; Duda, A.; Kubisa, P.; Słomkowski, S. Living Ring-opening Polymerizations of Heterocyclic Monomers *Prog. Polym. Sci*. **2007**, 32, 247-282. doi: https://doi.org/10.1016/j.progpolymsci.2007.01.002

(47) Gokel, G. W.; Negin, S. 1.05 - The Supramolecular Alkali Metal Cation–π Interaction. *Comprehensive Supramolecular Chemistry II,* **2017**, 103-120