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Unimolecular Anion-Binding Catalysts for Selective Ring-opening Polymerization of *O*-carboxyanhydrides

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Abstract: Anion-binding can regulate anion transport in chloride channels via dynamic non-covalent interactions, which gives insights into the designing of new organocatalytic transformations, but is surprisingly unexplored in polymerization catalysis. Herein, we describe an effective unimolecular anion-binding organocatalysis where 4-(dimethylamino)pyridine is anchored to a thiourea for ringopening polymerization of O-carboxyanhydrides (OCAs), which well addresses the formidable challenge of synthesizing high molecular weight (MW) stereoregular polyesters. Ring-opening polymerization of PheOCA (OCA from phenylalanine) mediated by unimolecular anion-binding organocatalyst generates highly isotactic poly(phenyllactic acid) (Ph-PLA) with MW up to 150.0 kDa. Specifically, high MW Ph-PLA exhibits 30-fold increase in the elongation at break in comparison to its low MW congener. Moreover, active species of the polymerization are moisture-tolerant and can be conducted in unpurified solvent, facilitating facile synthesis of high MW stereoregular polyesters with pendant functional groups. Calculations and experiment studies indicate a dynamic cooperative anion-binding mechanism where the dynamic anion-binding interaction of thiourea moiety to propagating species facilitates efficient chain propagation and the synergetic decarboxylation retains high selectivity for OCA ring-opening over side reactions (e.g., cyclization, epimerization and transesterification).

Introduction

The development of novel catalytic techniques and polymerization processes continues to drive innovation in polymer chemistry.^[1] Ring-opening polymerization (ROP) is a powerful and widespread polymerization method.^[2] It has proven especially useful for the furnishing of biodegradable polymers, starting from lactones and related monomers. Recently, ROP of O-carboxyanhydrides (OCAs) has emerged as a promising route towards functionalized polyesters (Figure 1A).^[3] The key advantage of this process over the ROP of lactones and lactides for the generation of polyesters is the large number and diversity of functional monomers that are easily synthesized from amino acid precursors which inherently possess abundant pendant functionality.^[4] For example, OCA prepared from phenylalanine (PheOCA) is extremely attractive, as ROP of PheOCA can generate poly(phenyllactic acid) (Ph-PLA), a phenyl-substituted PLA analogue, where the aromatic ring should lead to degradable polymers with enhanced hydrophobic interactions and rigidity.[5]

So far, a variety of organic and metal-based catalysts have been found capable of catalyzing of the ROP of OCAs.^[6] However, the synthesis of high MW stereoregular polyesters via ROP of OCA still faces formidable challenges, including the trade-off between minimal epimerization and efficient chain propagation 1A). (Figure For instance. 4-(dimethylamino)pyridine (DMAP), a typical organocatalyst, have recently been employed for ROP of OCA.^[6f] However, these organobases inevitably results in epimerization of the α -methine hydrogen in OCAs accompanied by the simultaneous chain transfer or termination, and thus diminishes control over MW and stereoregularity.^[61] The weakly basic catalysts typically epimerization, but the polymerization activity is suppress significantly reduced.^[6g] In this premise, most polyesters obtained from the organocatalytic ROP of OCAs have relatively low MWs (< 50.0 kDa).^[6h] Metal-based catalysts, such as Zn complex with β -diiminate ligands, have been applied for the controlled OCA polymerization.^[7] However, they are also subject to a compromise between minimal epimerization and efficient chain propagation, thus still cannot efficiently produce polyesters with high MW. It is considered that metal-based catalysts typically exhibit strong coordination ability to the carbonate anion of growing chain, thereby beneficial to overcoming significant epimerization but resulting in inefficient decarboxylation and inactive metal-carbonate during the chain propagation (Figure 1A), especially at high degree of polymerization.^[6h] Until recently, Tong et al. utilized photoredox Ni/Ir catalysis for OCA polymerization, which has been used for photoredox decarboxylation of anhydrides, and obtained high MW (> 140.0 kDa) polyesters without epimerization.^[8] However, the metal residues impede the applications of these polyesters in optoelectronic and biomedical materials.^[11, 9] It has no doubt that devising a viable organocatalyst that can catalyze well-controlled ROP to generate high MW, isotactic functionalized polyesters is the ideal yet challenging.

The chloride channels, found throughout biology, catalyze the rapid flow of chloride anions across cell membranes, thus adjusting electrical excitation in skeletal muscle and the flow of salt and water across epithelial barriers.^[10] Anion-binding plays a considerable role in chloride channels, in which anion-binding site are constructed by bringing together specific amino acids from four separate regions (Figure 1B).^[11] A prominent feature of anion-binding is that it does not form tight ion pairs *via* direct

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Figure 1. (A) ROP of OCAs and side reactions commonly observed in the polymerization. (B) Anion-binding in nature chloride channel. (C) Representative examples of anion-binding concept for organocatalytic transformations. (D) This work: Unimolecular anion-binding for ROP.

charge-charge contact; instead, the chloride anion is dynamic stabilized through non-covalent hydrogen bonding thus promotes rapid flow of ions, which leads to the development of molecular recognition, sensors and transporters for anionic species in supramolecular chemistry,^[12] further gives insights into the designing of new organocatalytic transformations.^[13] For instance, Jacobsen et al. has exploited a variety of chiral anionbinding catalysts derived from urea and thiourea for enantioselective nucleophilic ring-opening of episulfonium (Figure 1C, a),^[13a] Pictet-Spengler Cyclization,^[13b] and alkylation R-arylpriopionaldehdyes.^[13c] Similarly, Seidel et al. of demonstrated the enantioselective O to C acyl transfer of azlactones (Steglich rearrangement, Figure 1C, b)^[13d] and kinetic resolution of amines^[13e] using chiral thiourea-based anionbinding catalysts. While the anion-binding concept has been applied to great success in organic chemistry, it remains surprisingly unexplored in polymer synthesis and/or in polymerization catalysis. Considering that ionic intermediates or reagents are ubiquitous in numerous polymerization processes, it is extraordinarily worthy of pursuing anion-binding catalysis to address the unresolved challenges in polymerizations.

Inspired by the unique anion-binding concept, we envisioned the cooperative use of DMAP and a thiourea catalyst might allow for the controlled ROP of various OCAs to afford high MW isotactic polyesters (Figure 1C). Specifically, the thiourea bonding moiety is not only expected to activate the monomers by classical H-bonding interactions with carbonyl groups,^[11, 9, 14] but also to form noncovalent interactions with carbonate anion of the propagating polymer chain *via* anion-binding. In this anionbinding catalytic mode, stabilization of the carbonate anion of growing chain end by the thiourea should serve to maintain the livingness of propagating chains, while this type of anion-binding is less stronger than the metal-carbonate, which facilitate the efficient decarboxylation during the chain propagation, a process similar to the chloride anion transport in chloride channels. In addition, the thiourea moiety may potentially serve as a Lewis acid capable of modulating the basicity of DMAP moiety or propagating chain ends to enable minimal competitive epimerization reactions.^[21, 6g]

Herein, we document an unprecedented unimolecular anionbinding organocatalysis for ROP of OCAs, leading to efficient chain propagation and high selectivity for ring-opening over side reactions (*e.g.*, epimerization and cyclization), delivering high MW (reached 150.0 kDa) isotactic polyesters bearing diverse functionality. We believe this unimolecular anion-binding organocatalysis strategy not only paves the way for synthesis of high MW isotactic polyesters but also opens novel avenues for the advance of chemoselective ROP.

Results and Discussion

We used L-PheOCA (L-1) as a model monomer, which was readily prepared from L-phenylalanine through a simple two-step procedure (Figure 2A). At the outset, an anion-binding organocatalyst 3a, featuring a thiourea moiety in the metaposition of DMAP (Figure 2B), was prepared in a six-step procedure requiring purification by recrystallization (Scheme S1, detailed synthesis procedure, see Supporting Information). NMR and MS analysis revealed the desired 3a structure (Figures S9-10). Since 3a was both an initiator and a catalyst, for convenience, we termed 3a as organocatalyst in the following studies. 3a was initially tested in the polymerization of enantiomerically pure L-1 at 25 °C in dichloromethane (DCM) at different monomer to 3a ratios ([_L-1]₀/[3a]₀) ranging from 100:1 to 500:1 (Table 1, entries 1–3). Reaction carried out at a lower [$_{L}$ -1]₀/[3a]₀ ratio of 100:1, led to 100% _L-1 conversion in 1 h and formation of poly(L-1) with a number average molecular weight (M_n) of 16.6 kDa and a molecular weight distribution $(D = M_w/M_n)$ of 1.24 (entry 1). However, at a higher $[_L-1]_0/[3a]_0$ ratio of 500:1, uncontrolled polymerization occurred, generating poly(L-1) with a $M_{\rm n}$ of 49.0 kDa, much lower than the targeted one ($M_{\rm n,calcd.}$ = 74.4 kDa) (entry 3). To synthesize high MW polymers with nucleophilic initiators, Waymouth had suggested that the initiating nucleophile should exhibit relatively poor leaving group ability (low nucleofugality).^[15] This fact indicated that metasubstituted catalyst 3a might exhibit strong nucleofugality, which was detrimental to the synthesis of high MW polymers.

In view of these results, we decided to prepare and explore unimolecular anion-binding catalyst with low nucleofugality for the synthesis of isotactic high MW polyesters. Given the sterichindrance effect of ortho-substituent groups, we foresaw that DMAP with thiourea attached to the ortho-position should display low nucleofugality (Figure S40).^[16] Thus, a new unimolecular anion-binding catalyst 3b, where thiourea was anchored into ortho-position of DMAP, was prepared by the route described in Figure 2C (for detailed procedures see Supporting Information). Next, 3b was investigated for the polymerization of L-1 in DCM at 25 °C (Table 1). Surprisingly, when the $[M]_0/[3b]_0 = 800:1$, high MW polyesters with M_n up to 150.0 kDa and a low *D* of 1.20 were achieved by unimolecular anion-binding organocatalyst for the first time (Table 1, entry 8), which was approximately 3 times as much as that of polyesters from ROP mediated by DMAP.^[6h] Importantly, neither DMAP nor thiourea/DMAP bicomponent system could mediate controlled ROP of L-1 under similar conditions to furnish high MW polyesters (Table 1, entry 9-14, and Table S1, entry 18), thus pointing to the importance of the covalent-linking between DMAP and thiourea for high MW. Moreover, no epimerization of the α -methine hydrogen occurred even for high MW sample, as evidenced by homodecoupled ¹H NMR analysis (Table 1, entry 8; Figure 3A and Figure S21-23), indicating that the thiourea moiety could modulate the basicity of propagating anions to enable minimal competitive epimerization reactions.

With the base unit identified, we have further examined the effect of different H-bond groups on the ROP (Figure 2B). Both **3c** with one CF₃ substituent and **3d** with zero CF₃ substituent resulted in high MW polyesters with $M_n > 50.0$ kDa (Table 1, entry 15-16), indicating that the *ortho*-substituent of DMAP is critical to produce high MW polyesters. However, polymerization with **3c** and **3d** demonstrated slower polymerization activities than **3b** (see Figure S42). Moreover, ROP did not efficiently

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occur when applying less acidic urea 3e (Table 1, entry 17). Obviously, polymerization activity exhibits a remarkable correlation with the acidity of the thiourea (urea) moiety: polymerization is faster with higher acidity of the thiourea (3b > b)3c > 3d > 3e). This reactivity trend suggests that the activation of the monomer through H-bonding to the thiourea (urea) moiety plays a key role in influencing the polymerization activity. More acidic thiourea moiety is more effective for activating the monomer toward nucleophilic attack, and hence the chain propagation. Overall, the above results suggested that the Hbond donor unit could also contribute to the MW outcomes as as the ROP activities and that the 3,5well bis(trifluoromethyl)phenyl thiourea unit was optimal.

Having confirmed 3b as the best catalyst for 1-1, the polymerization was further explored in details. ROP of 1-1 by the unimolecular anion-binding catalyst 3b displays several characteristics of controlled polymerization. $Poly(_L-1)$ with varied $M_{\rm p}$ can be successfully prepared by regulating $[_{L}-1]_{0}/[3b]_{0}$ ratio. The $M_{\rm p}$ values of obtained poly($_{L}$ -1) increased from 10.9 kDa to 150.0 kDa as [1-1]0/[3b]0 ratio increased from 25:1 to 800:1 (Figure 3B, Table 1 entry 4-8, and Table S1 entry 11-15). SEC traces showed unimodal distributions with low D (D, around 1.05-1.22) at different [L-1]/[3b] ratios (Figure 3C). Meanwhile, the evolution of $M_{\rm n}$ exhibited a linear correlation with monomer conversion while *D* (1.05-1.17) remains low (Figure 3D). Importantly, the SEC curves of poly(L-1) after 100% L-1 conversion and prolonged reaction times exhibited a very similar peak profile, indicating minimal transesterification and formation of carbonate instead of alkoxide propagating species (Figure S43A). Together the data suggested that 3b-mediated polymerization of L-1 showed a controlled characteristic. However, the 3b-mediated ROP exhibit some deviations from an ideal "living" behavior ^[17] Plots of the M_n versus monomer conversion extrapolate to a nonzero intercept (Figure 3D); the observed MWs do not conform to the $[{}_{\it L}\mbox{-}1]_{\it o}/[3b]_{\it 0}$ ratio and are significantly higher than the predicted value (Figure 3B).

We further explored the chain extension reaction with $_L-1$ ([$_L-$ 1]₀/[3b]₀=50:1). Upon 100% conversion of the initial _L-1, an additional 50 equiv of L-1 were added, and the polymerization was allowed to continue to completion. SEC plots (Figure S43B) indicated an ascend of poly(L-1) M_n from 20.6 to 39.8 kDa mol⁻¹ and a change in *Đ* from 1.10 to 1.06 (Table S1, entry 17). The latter values were consistent with those for polyesters independently synthesized from а 100:1 [L-1]0/[3b]0 polymerization (M_n = 41.1 kDa, D = 1.07). These results also indicated a controlled manner of 3b-mediated OCA polymerization.

Early work by Waymouth has demonstrated that the polymer MWs can be regulated by alcohol initiators, during the ROP of lactones catalyzed by nucleophilic catalysts, such as NHC and DBU.^[11, 15] In stark contrast, when benzyl alcohol (BnOH) was used and [$_L$ -1]₀/[BnOH]₀ ratios were systematically varied between 50:1 and 200:1, reactions carried out with the unimolecular anion-binding catalyst **3b**, afforded polyesters whose MWs did not differ markedly and were substantially close to that in the absence of BnOH (Table 1, entries 5, 18-20). These results indicated that competitive side reactions (*e.g.*, alcohol-initiated chain propagation, chain transfer to alcohol) were significantly suppressed due to the reduced nucleofugality of 3b and rapid polymerization kinetics.

It is challenging to carry out OCA polymerizations in the presence of water and impurities, which induce unwanted side

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Figure 2. (A) Scope of OCAs. (B) Screening of anion-binding catalysts. (C) Typical synthesis route of catalyst 3b.

Entry	Catalyst	[1] ₀ /[cat] ₀ /[alcohol] ₀	Time (h)	M _{n,calcd.} (kDa) ^b	M _{n,SEC} (kDa) ^c	${\cal D}(M_{\rm w}/M_{\rm n})^c$
1	3a	100:1:0	1	15.2	16.6	1.24
2	3a	200:1:0	1	30.0	26.9	1.34
3	3a	500:1:0	8	74.4	49.0	1.35
4	3b	50:1:0	0.5	7.8	23.3	1.09
5	3b	100:1:0	1	15.2	41.1	1.07
6	3b	200:1:0	2	30.0	72.7	1.14
7	3b	500:1:0	24	74.4	123.2	1.22
8	3b	800:1:0	24	118.8	150.0	1.20
9	DMAP	100:1:0	1	14.9	19.0	1.28
10	DMAP	200:1:0	1	29.7	32.7	1.34
11	DMAP	500:1:0	8	74.1	45.0	1.33
12	DMAP+4	100:1:0	1	14.9	6.6	1.37
13	DMAP+4	200:1:0	1	29.7	15.3	1.34
14	DMAP+4	500:1:0	2	74.1	48.2	1.31
15	3c	100:1:0	2	15.2	55.8	1.12
16	3d	100:1:0	2	15.1	54.0	1.15
17 ^d	3e	100:1:0	2	15.2		
18 ^e	3b	100:1:0.5	1	29.7	41.0	1.07
19 ^e	3b	100:1:1	1	14.9	40.4	1.08
20 ^e	3b	100:1:2	1	7.5	40.0	1.10
21 ^{<i>t</i>}	3b	50:1:0	0.5	7.8	26.6	1.09
22 ^{<i>t</i>}	3b	100:1:0	1	15.2	44.5	1.08
23 ^f	3b	800:1:0	24	118.8	148.8	1.19

Table 1. Screening of unimolecular anion-binding catalysts for controlled ROP of L-1 ^a

^aThe polymerizations of *L*-1 were performed in dry DCM (water contents, 20ppm) at 25^oC with [*L*-1]₀=0.5M. All of polymerizations (except for entry 17, in which no obvious polymerization was observed for 2 h) were terminated after achieving 100 % monomers conversion, which were measured by ¹H NMR. ^{*b*}*M*_{n,calcd.} = 148×[*L*-1]₀/[cat]₀ ×Conv.+*M*_{cat}. ^aMeasured by SEC (DMF, 0.02M LiBr, 50 °C), PMMA calibration. The samples were measured without purification, except for entries 8, and 23, that were measured after precipitating into methanol, facilitating subsequent mechanical properties tests. ^{*d*}Only trace conversion of monomers was observed. ^aBnOH was added as initiator, *M*_{n,calcd.} = 148×[*L*-1]₀/[BnOH]₀ ×Conv.+*M*_{BnOH}. ^{*f*}Polymerizations were performed in unpurified DCM (water contents, 465ppm).

120

0

0

20

40

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Conversion (%) Elution time (min) Figure 3. ROP of OCAs mediated by unimolecular anion-binding catalyst. (A) Homodecoupling ¹H NMR spectrum of the α-methine region of poly (L-1) (B) Plots of M_n(square, black) and M_w/M_n (circle, red) vs [_L-1]₀/[3b]₀ ratio. (C) SEC chromatograms of poly (_L-1) in panel B. (D) M_n and M_w/M_n vs conversion of _L-1. (E) SEC chromatograms of poly (l-1) $([l-1]_0/[3b]_0=50/1$, black), the block copolymer poly (l-1)-b-poly $(l-1)_0/[l-1]_0/[3b]_0=50/50/1$, blue), and the random copolymer poly (l-1)-b-poly $(l-1)_0/[l-1]_0/[3b]_0=50/50/1$, blue), and the random copolymer poly $(l-1)_0/[3b]_0=50/50/1$, blue). (L-1)-co-poly (L-4) ([L-1]₀/[L-4]₀/[3b]₀=50/50/1, red). (F) Kinetic plots of In([M]₀/[M]₁) vs time with [L-1]₀=0.5 M and different [L-1]₀/[3b]₀.

14

16

18

12

1.0

8

10

100

60

80

		Table 2. Controlled	d polymerization of	OCAs mediated by	3b ^a	
Entry	Monomer	[M] ₀ /[3b] ₀	Time (h)	M _{n,calcd.} (kDa) ^b	M _{n,SEC} (kDa) ^c	$D(M_{\rm w}/M_{\rm n})^{\rm c}$
1	L -2	100:1	2	16.3	49.0	1.15
2	L -2	200:1	5	33.2	73.5	1.18
3	2	500:1	24	81.4	139.2	1.22
4	L -3	100:1	2	23.1	54.9	1.20
5	L -3	200:1	5	45.8	81.5	1.17
6	3	500:1	24	113.9	145.3	1.21
7	4	100:1	1	7.6	27.9	1.10
8	4	200:1	2	14.8	43.8	1.22
9	L -4	500:1	24	36.4	50.0	1.22
10 ^{<i>d</i>}	<i>⊾</i> -1+ <i>⊾</i> -4	50:50:1	0.5/0.5	7.8/11.4	23.0/37.7	1.14/1.16
11 ^e	L-1+ L-4	50:50:1	1	11.4	38.0	1.14

^aThe polymerizations of OCAs mediated by 3b were performed in dry DCM at 25°C with [M]₀=0.5M. All of polymerizations were terminated after achieving 100% monomers conversion, which were measured by ¹H NMR. ${}^{b}M_{n,calcd} = (M(OCA) - M(CO_2)) \times [M]_0/[cat]_0 \times Conv. + M_{cat}$. ^cDue to the poor solubility in DMF, these samples were measured by SEC in THF (35°C, PS calibration). ^dBlock copolymerization of L-1 and L-4 via sequential monomer addition. ^eRandom copolymerization of L-1 and _-4.

reactions that result in ill-defined polyestes. Therefore, these polymerizations are generally carried out applying a Schlenk line or a glovebox to maintain stringent water-free polymerization conditions. $\ensuremath{^{[7-8]}}$ Encouraged by the aforementioned findings, we propose that the low nucleofugality of 3b and rapid polymerization kinetics might also minimize water-induced side reactions. Therefore, we examined the 3b-mediated ROP of L-1 using unpurified DCM as solvent. It was found that high MW (M_n = 26.6-148.8 kDa) polyesters with narrow distributions (D = 1.08-1.19) were obtained, in analogy to that produced under stringent anhydrous conditions (Table 1, entry 21-23). Moreover, similar well-controlled polymerization behavior was observed when titrated amounts of water were added to the dry DCM (Table S1, entry 19). These results are vital because it will be more convenient to implement ROP of OCAs if a glove box or Schleck line is not available.

0.0

0

40

80

Time (min)

To evaluate the versatility of our unimolecular anion-binding catalyst, we applied the 3b for ROP of three other OCAs, including para-tolyl (L-MePheOCA, L-2), bromophenyl groups (L-BrPheOCA, L-3), and methyl (L-LacOCA, L-4), (Figure 2A). Under similar conditions, 3b was able to initiate and polymerize all three OCAs. The SEC result displayed high MW polyesters with a low \mathcal{D} (\mathcal{D} < 1.25) were obtained (Table 2, entries 1-9). Particularly, when [M]₀/[3b]₀ was 500:1, we were pleased to observe poly($_{L}$ -3) with a $M_{\rm p}$ = 145.3 kDa, and a D value of 1.21 was achieved. No epimerization of the a-methine hydrogen occurred (Figures S24-S32). Block copolymer could also be synthesized via one pot sequential ROP of L-1 and L-4, achieving controlled M_n and D values (Figure 3E, Table 2, entry 10, and

Figure S35-37). We also found the random copolymerization of $_{L}$ -1 and $_{L}$ -4 (50/50) led to full monomers consumption and formation of a random copolymer with a M_{n} of 38.0 kDa and a D of 1.14, close to the corresponding diblock copolymer (Figure 3E, Table 2, entry 11, and Figure S38-39).

To elucidate the OCA ROP mechanism mediated by unimolecular anion-binding organocatalyst **3b**, we carried out several kinetic experiments by varying initial $[_L-1]_0/[3b]_0$ ratios between 100:1 and 300:1 and monitoring the monomer conversion by ¹H NMR. Analysis of a plot of $\ln([M]_0/[M]_1)$ vs time revealed that the ROP was first-order dependence on $_L$ -1 concentration (Figure 3F). The polymerization orders with respect to **3b** were 1.14 ± 0.08 (Figures 3F and S46). The above data demonstrated that the overall rate law can be described as follows:

$$-d[_{L}-1]/dt = k_{p}[\mathbf{3b}]^{1.14}[_{L}-1]_{t}$$
(1)

where k_p is the propagation rate constant. Meanwhile, initiation was comparable to propagation, also confirmed by the linear dependence of $\ln([M]_0/[M]_t)$ on time. A slow initiation relative to enchainment would lead to curved profiles with gradually ascending slopes.^[18] In addition, the kinetics results revealed that the monomer activation in current system was weaker than that in Lewis pairs catalytic systems,^[1k] where the kinetics obeyed zero-order of monomer concentrations due to the strong monomer activation. The theoretical deduction of the chain propagation rate law was also in keeping with the above rate law and had first-order dependence on [**3b**] and [M]_t (see Figure S47 and Derivation of the propagation rate law).

In an effort to gain more insight into the polymerization mechanism, **3b** was allowed to react with $_{L}$ -**1** in 1:1 ratio at 25 °C in CD₂Cl₂ ([$_{L}$ -**1**] = 0.025 M). The solution changed from light-green to yellow-green instantaneously. ¹H NMR result of the reaction mixture (Figure S48) revealed the disappearance of the monomers and the appearance broad proton resonances because of low MW poly($_{L}$ -**1**). This result again indicated that initiation was comparable to chain propagation, consistent with the kinetics results. ¹H NMR analysis of purified low MW poly($_{L}$ -**1**) also revealed some information about the nucleophilic ROP of monomers by DMAP moiety (shift of the proton signals of

initiated DMAP moiety in Figure 4C and Figure S50A), resulting in negatively charged carbonate propagating species, which were stabilized by the thiourea moiety of **3b** *via* anion-binding (shift of the proton signals of NH group in Figure 4C and Figure S50A).

FTIR spectrum obtained from the reaction of L-1 and 3b in a 1:1 molar ratio showed four carbonyl peaks in the 1900-1550 cm⁻¹ range (Figure S52A). Three peaks at 1759, 1716, and 1685 cm⁻¹ were due to the ester of the backbone, carbonyl adjacent to DMAP moiety and carbonate end-group, consistent with the proposed carbonate anion propagating species bearing one 3b moiety at one chain end and carbonate at the other (Figure 4C). The band at 1697 cm⁻¹ was presumably originated from the vibrational coupling of carbonate anions due to the anion-binding.

We next end-capped the aforementioned low MW $poly(_{L}-1)$ with electrophiles (e.g., acetylchloride, AcCl) at 25 °C. The ¹H NMR and MALDI-TOF MS results of the afforded product revealed the polymer chain ends contained one 3b and one acetoxycarbonyl or acetyl moiety (Figure S53-54). The generation of acetoxycarbonyl end-groups was also revealed by FTIR analysis, as confirmed by the appearance of the characteristic anhydride peak at 1834 cm⁻¹ (Figure S52B).^[18] The bands assigned to the ester of the backbone and the carbonyl adjacent to DMAP moiety at 1759 and 1716 cm⁻¹ remained unchanged. These findings were consistent with the proposed carbonate anion propagating intermediates (Figure 4C). Importantly, these observations, coupled with the fact that high MWs and successful chain extension experiments involved carbonate ions, reveal that the carbonate anions of growing chain remains dynamically stable and maintains reactive due to the synergetic anion-binding interaction. In addition, the stabilization of reactive carbonate anions by the thiourea moiety of 3b via anion-binding would also be retained in other halohydrocarbon (e.g., CHCl₃ and CICH₂CH₂Cl, see Table S1, entries 5-6), but would be weakened in the presence of interaction between thiourea moiety and solvents (e.g., THF), resulting in slower polymerization and failure to generate high MW polymers (see Table S1, entry 7).



Figure 4. Nucleophilic ROP of OCA by DMAP moiety of **3b** and the generation of carbonate anion propagating species synergistically. (A) ¹H NMR spectrum of $_{L}$ -**1**. (B) ¹H NMR spectrum of **3b**. (C) ¹H NMR spectrum of low MW poly($_{L}$ -**1**) (initial ratio, [$_{L}$ -**1**] $_{0}$ (**3b**)_{0}=10:1, precipitated into *n*-hexane for purification) in CD₂Cl₂.

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Figure 5. Quantum chemical simulations of selective ROP of OCA. (A) Reaction diagram for ROP of OCA by 3b. The structures described here are corresponding to the optimized reaction coordinate (see Figure S64) for the transition states and intermediates. H-bonding interactions are indicated with purple dashed lines. Breaking and forming bonds are indicated with green dashed lines. Grey regions exhibit that the carbonate anion is stabilized *via* anion-binding to the thiourea moiety of 3b. The calculations indicate a dynamic cooperative anion-binding mechanism where the dynamic stability of the carbonate anion propagating intermediate facilitates efficient chain propagation and the synergetic decarboxylation retains high selectivity for monomer ring-opening over side reactions. (B) Energy profile of the mechanism for 3b-mediated ROP of OCA. All energies are relative to the separated reactants in the unit of kcal/mol (red numbers).

These results further support that the thiourea moiety aids in the activation of the monomers and subsequently stabilizes the carbonate anion propagating species.

To better understand the mechanism of **3b**-mediated selective OCA polymerization, we employed the dispersion corrected B3LYP-D3 density functional in conjunction with the 6-31G (d,p) basis set, to identify structures of the transition states (**TS**) and intermediates (**INT**), and to determine free energies of the reaction pathways (Figure 5, for detailed Methods, Optimized structures and Coordinates, see Computational methodology in SI). For the sake of clarity and simplicity, monomer $_L$ -**4** was used as a model monomer in the computation.

The calculations reveal the initial formation of a reactant complex (**RC**) comprising the thiourea moiety of **3b** hydrogenbonded to both endocyclic and exocyclic oxygen atom of the $_L$ -**4**, which is an exergonic process by 2.9 kcal/mol more stable than the reactants (Figure 5B). Subsequent nucleophilic attack of the DMAP moiety in **3b** onto the hydrogen-bonding activated carbonyl group of $_L$ -**4** occurs *via* transition state **TS1** with an activation barrier of about 16.1 kcal/mol. The resulting carbonate anion intermediate **INT1** is stabilized *via* anion-binding to the thiourea moiety of **3b**, which agrees with ¹H NMR (Figure 4C and Figure S50A) and FTIR studies (Figure S52). The binding of an additional $_L$ -**4** monomer to **3b** facilitates dynamic dissociation

of intermediate INT1 to afford the intermediate INT2. This result implies that the anion-binding interaction is dynamic similarly to the chloride anion transport in chloride channel, in contrast to that of traditional metal-mediated polymerization where the tight metal-carbonate was formed, which is critical for the efficient chain propagation and synthesis of high MW polyesters. The decarboxylation of INT2 and nucleophilic attack of the alkoxy onto the carbonyl group of L-4 proceeds cooperatively (TS2) with an activation barrier of 15.8 kcal/mol to give tetrahedral intermediate INT3. Ring-opening of the tetrahedral INT3 is facile and requires a low barrier of 4.1 kcal/mol (TS3) to produce carbonate anion propagating intermediate INT4 for further enchainment. The calculations also suggest that direct decarboxylation to form the alkoxide anion intermediate (via TS2', Figure 5B and S64C) is energetically less favoured compared to synergetic decarboxylation (activation barrier of TS2 vs TS2', 15.8 kcal/mol vs 33.7 kcal/mol). This result offers a rationale for the high selectivity of the unimolecular anionbinding catalyst system for OCA ring-opening over epimerization. cyclization, and transesterification; the undesired highly basic alkoxide propagating species is avoided due to the synergetic decarboxylation, thereby minimizing extensive side reactions.

Computational studies support the hypothesis of a dynamic cooperative anion-binding mechanism where the dynamic stability of the carbonate anion propagating intermediate facilitates efficient chain propagation and the synergetic decarboxylation retains high selectivity for monomer ringopening over side reactions. This is in contrast to classical thiourea-based organocatalytic polymerization $^{\left[11,\ 2g,\ 2i,\ 9,\ 14\right]}$ and our previous chloropyridine-thiourea system^[6g] where the thiourea moiety is only considered as a H-bonding donor to activate monomers, or the thiourea moiety is deprotonation to yield thioimidate to activate the alcohol. Computational studies also indicate that the abstraction of α -H of $_{L}$ -4 by DMAP moiety is less preferred and the transition state (TS1', Figure 5B and S64B) has a higher barrier than that of initiation and propagation (TS1, TS2 and TS4), further attesting to the disfavour of epimerization side reactions.

This mechanism is reminiscent of that proposed for the polymerization mediated by the N-heterocyclic carbene (NHC), [11, ^{15, 19]} a versatile organic catalyst for ROP. In contrast to widely studied zwitterionic ring-opening polymerization mediated by NHC where the cyclic products were generated, [15, 18, 20] no respective cyclic congeners were obtained via liberating the 3b in our system, as evidenced by MALDI-TOF-MS analysis (Figure S54). This can be attributed to the reduced nucleofugality of 3b and anion-binding interactions (or more specifically synergetic decarboxylation), thus suppressing possible cyclization side reactions and allowing the synthesis of high MW polyesters. Indeed, the calculations also reveal that the synergetic decarboxylation and back-biting of alkoxy of INT4' (Figure 5B and S64D) onto the carbonyl group of initiating acylpyridinium is unfavorable (TS4').^[21] In addition, computational studies verify our previous speculation that the BnOH-initiated chain propagation is significantly suppressed compared to the synergetic decarboxylation and ring-opening propagation (activation barrier of TS2" vs TS2 or TS4, 25.9kcal/mol vs 15.8 kcal/mol or 13.6 kcal/mol, see Figure 5B, S64 and S65). Collectively, the unique dynamic anion-binding interactions is critical for the controlled polymerization behavior and high MW. In addition to facilitating the efficient chain propagation, anionbinding maintained by the thiourea moieties also manage

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potential side reactions (e.g., cyclization, transesterification and epimerization) by reducing the basicity and nucleophilicity of the anionic propagating species *via* the synergetic decarboxylation.

In addition, deviation of the polyester $M_{n,SEC}$ from the theoretical values may be attributed to the unique selfassociation of 3b as evidenced by calculations (see geometry optimizations for 3b, Figure S64A) as well as its broadened and overlapped proton resonances as compared to the methylated counterpart 3f in variable-temperature ¹⁹F and ¹H NMR spectra (Figure S58-61), resulting in significantly reduced initiation efficiency. The initiation efficiency, estimated as the $M_{\rm n, calcd}/M_{\rm n, SEC} \times 100$ %, ascends from 37% to 79% as $[1-1]_0/[3b]_0$ ratio raises from 25:1 to 800 :1 (Figure S62). This result seems reasonable as the lower concentration of 3b disfavored selfassociation behavior and hence promoted high initiation efficiency. Indeed, similar intramolecular self-association was also observed in the typical Takemoto's catalytic system, [22] which was different from the intermolecular association in bicomponent thiourea/amine catalytic systems.[23] It is also postulated that the self-association accounts for the deviation from the ideal "living" behavior in our system.

Poly(phenyllactic acid) (Ph-PLA) is a phenyl-substituted PLA polymer, where the aromatic ring could lead to enhanced hydrophobic interactions and rigidity.^[5] So far, all of the previously reported Ph-PLA are very brittle with a very low elongation at break due to low MW less than 50.0 kDa,[6h] limiting possible commodity and biomedical applications. It is well known that mechanical properties of a polymer increase as the MW increases. In this context, the stress-strain behavior of Ph-PLA with different M_n s were comparatively studied (Figure 6). As expected, the mechanical properties of high MW Ph-PLA $(M_{\rm n}$ = 150.0 kDa) were quite different from those of low MW congener (M_n = 41.1 kDa). The measured tensile strength for high MW Ph-PLA was 4.3-fold higher than that measured for low MW analog. Importantly, the elongation at break of high MW Ph-PLA was approximately 30 times higher than its low MW counterpart. Therefore, it is of importance to obtain high MWs polyesters for improving their mechanical properties.



Figure 6. Stress-strain curves of low MW Ph-PLA (S_A, red curve, *E*=1076 Mpa, σ_b = 5.1MPa, ϵ_b =0.5%, $M_{n,SEC}$ = 41.1 kDa, entry 5 in Table 1) and high MW Ph-PLA (S_B, blue curve, *E*=1370 Mpa, σ_y = 22.3MPa, ϵ_b =15%, $M_{n,SEC}$ = 150.0 kDa, entry 8 in Table 1). Break point indicated by "X". Inset data between 0 and 1.0% strain.

Conclusion

Inspired by the nature of anion-binding, we developed here. an unimolecular anion-binding organocatalysis for the efficient ring-opening polymerization of OCAs, generating high MW isotactic polyesters bearing diverse functionality. High MW polyester shows significantly improved mechanical properties in comparison to the low MW congeners. The experimental and DFT calculations highlighted the key roles played by the unique dynamic anion-binding interaction of thiourea moiety to propagating species and the synergistic decarboxylation for addressing the tradeoff issue between efficient chain propagation and minimal epimerization. The moisture-tolerant of these unimolecular anion-binding catalysts, coupled with their ability to impart potent control on ring-opening polymerization, illustrate their potential to the chemistry community. Organocatalytic ring-opening polymerization via thiourea-based H-bond organocatalysts have been reported previously;^[11, 9b, 14a-c] however, this is the first time that a process based on anionbinding, which represents an advanced binding mode has been used for selective ring-opening polymerization of OCAs, and has potential feasibility for other monomers, such as Ncarboxyanhydrides (NCA) and propiolactones. Furthermore, We believe that the concept of utilizing the dynamic anion-binding to suppress side reactions (e.g., cyclization, transesterification and epimerization) and to facilitate the chain propagation is universal and valuable that is often inaccessible to more conventional organobases or transition metal-based catalysts.

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Conflict of interest

The authors declare no competing financial interests.

Keywords:	Anion-binding	catalysis;	Ring-opening
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stereoregularity			

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Entry for the Table of Contents

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Chloride Channel Channel Channel Channel Channel Channel Channel Channel Cooperative Anion-binding Catalysis Controlled Polymerization Controlled Polymerization Controlled Polymerization	M. Li, ^[a] S. Zhang, ^[a] X. Zhang, ^[b] Y. Wang, ^[a] J. Chen, ^[a] Y. Tao, ^{*(a)} X. Wang ^{*(a)} Page No. – Page No. Unimolecular Anion-Binding Catalysts for Selective Ring-opening Polymerization of O- carboxyanhydrides