Copolymerization

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Controlled Ring-Opening Polymerization of *O*-Carboxyanhydrides Using a β-Diiminate Zinc Catalyst

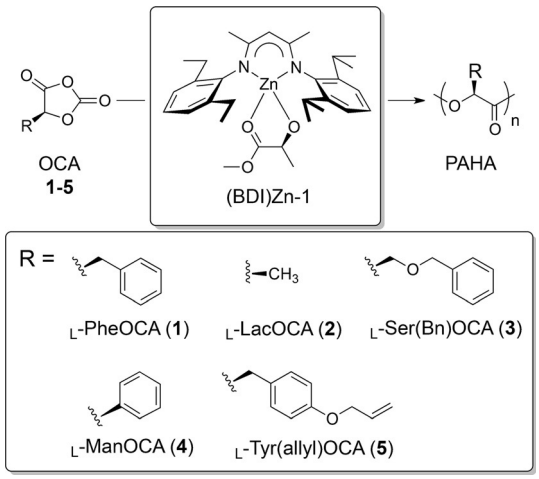
Ruibo Wang, Jiawei Zhang, Qian Yin, Yunxiang Xu, Jianjun Cheng, and Rong Tong**

Abstract: *Recently O-carboxyanhydrides (OCAs) have emerged as a class of viable monomers which can undergo ring-opening polymerization (ROP) to prepare poly(α-hydroxyalkanoic acid) with functional groups that are typically difficult to achieve by ROP of lactones. Organocatalysts for the ROP of OCAs, such as dimethylaminopyridine (DMAP), may induce undesired epimerization of the α-carbon atom in polyesters resulting in the loss of isotacticity. Herein, we report the use of (BDI-IE)Zn(OCH(CH$_3$)COOCH$_3$) ((BDI)Zn-1, (BDI-IE) = 2-((2,6-diethylphenyl)amino)-4-((2,6-diisopropylphenyl)imino)-2-pentene), for the controlled ROP of various OCAs without epimerization. Both homopolymers and block copolymers with controlled molecular weights, narrow molecular weight distributions, and isotactic backbones can be readily synthesized. (BDI)Zn-1 also enables controlled copolymerization of OCAs and lactide, facilitating the synthesis of block copolymers potentially useful for various biomedical applications. Preliminary mechanistic studies suggest that the monomer/dimer equilibrium of the zinc catalyst influences the ROP of OCAs, with the monomeric (BDI)Zn-1 possessing superior catalytic activity for the initiation of ROP in comparison to the dimeric (BDI)Zn complex.*

Poly(α-hydroxyalkanoic acid) (PAHA), including polylactide (PLA), are an important class of polymers that can be used in many applications ranging from biomedical devices to packaging materials.[1] These polymers are traditionally synthesized through the ring-opening polymerization (ROP) of lactones such as lactide (LA) or glycolide. Most PAHAs, however, lack side chain functionality, which prevents facile side-chain modification, limiting subsequent applications. While these issues can be addressed through the ROP of functional LA derivatives, such as hydroxy-[2] and norbornene-lactide,[3] these monomers require multistep synthesis, and the ROP lacks control.[4] Over the last ten years, *O*-carboxyanhydrides (OCAs) have emerged as an alternative class of highly active monomers for the synthesis of PAHAs that are readily available from amino acid precursors which inherently possess rich side-chain functionality,[5] including aromatic rings,[6] carboxylic acids,[7] alcohols,[8] phenols,[9] and amines.[10] OCAs thus provide significant potential for building complex PAHA structures for various applications including drug delivery,[6,9b,11] gene delivery,[9a] and tissue engineering.[8]

OCAs are mostly polymerized using pyridine-based organocatalysts, such as dimethylaminopyridine (DMAP), into the corresponding PAHAs through a non-covalent basic/alcohol activation mechanism.[12] One drawback of these base catalysts is deprotonation of the α-methine hydrogen of OCAs during the ROP process.[8,13] This results in epimerization of the α-carbon atom, and loss of stereoregularity in the PAHA backbone, which leads to changes in the properties of the final polymers.[14] It is therefore crucial to develop a viable catalyst that has enhanced control over the ROP of OCAs leading to PAHAs with controlled molecular weights (MWs) and stereoregularity. An alternative to the use of organocatalysts for the ROP of OCAs involves the use of organometallic catalysts,[6,15] such as metal alkoxides that have been shown to polymerize lactones in a living, highly controlled manner.[16] Herein, we report the first systemic study of single-site organometallic catalyst ((BDI-IE)Zn(OCH(CH$_3$)COOCH$_3$), (BDI)Zn-1) for highly controlled ROP of OCAs.

We used **1** as a model monomer, which was conveniently prepared from L-phenylalanine using a simple two-step synthesis (Scheme 1).[6] Because of the excellent control of lactone-type of monomer polymerization by Coates catalysts,[16b,17] we prepared a number of Zn catalysts with varying degrees of bulkiness in the ancillary ligand or initiating



Scheme 1. ROP of OCAs catalyzed by (BDI)Zn-1.

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alkoxide groups (Table S1) and found that (BDI)Zn-1 provided exceptional polymerization results, outperforming the other (BDI)Zn catalysts tested. (BDI)Zn-1 contains a bulky asymmetric BDI ligand, and a (−)-methyl lactate moiety as the initiating group. The polymerization initiated by (BDI)Zn-1 in anhydrous THF at room temperature was highly active; immediate gas generation was observed when **1** was added into the solution of (BDI)Zn-1 at different monomer-to-initiator ratios ranging from 25 to 200 (Table 1, entries 1–4). Consumption of monomers for all reactions was complete within 5 minutes as determined by the disappearance of the 1812 cm^{-1} anhydride peak by FT-IR. Analysis via gel permeation chromatography (GPC) of polymers resulting from **1** showed narrow polydispersity (PDI < 1.1) with number-average molecular weights (M_n) close to the expected M_n, suggesting a highly controlled ROP process (see Figure S1 in the Supporting Information). The matrix-assisted laser desorption/ionization mass spectra (MALDI-MS) of poly(**1**) revealed methyl lactate as the predominant end group (Figure S2), suggesting the initiation from (BDI)Zn-1.

Table 1: Controlled ROP of OCAs mediated by (BDI)Zn-1.[a]

Entry	OCAs	[OCA]/[Zn]	M_n (exp.) [kDa][b]	M_n (cal.) [kDa]	PDI[b]
1	**1**	25	3.7	3.8	1.06
2	**1**	50	8.3	7.5	1.05
3	**1**	100	16.4	14.9	1.07
4	**1**	200	33.1	29.7	1.02
5	**2**	50	4.6	3.7	1.15
6	**3**	50	7.9	9.0	1.15
7	**4**	50	8.0	6.8	1.17
8	**5**	100	26.5	20.4	1.29
9	**1/2**	50/50	10.9	11.1	1.10
10	**1/3**	50/50	16.1	16.4	1.09
11	**2/3**	50/50	16.5	12.6	1.10

[a] Representative results of homopolymers and block copolymers initiated by (BDI)Zn-1 (2 mM) in THF at room temperature. Abbreviations: M_n (exp.): experimental number-average molecular weight; M_n (cal.): calculated molecular weight according to the feeding ratio between the monomer and (BDI)Zn-1; PDI: polydispersity index. [b] Determined by the GPC analysis in DMF (0.1 M LiBr) using dn/dc values in Table S2.

We then expanded the monomer scope to other OCAs with various side chains, including methyl (L-LacOCA, **2**), benzyl protected hydroxyl (L-Ser(Bn)OCA, **3**), phenyl (L-ManOCA, **4**), and allyl groups (L-Tyr(allyl)OCA, **5**, Scheme 1). Under similar polymerization conditions, (BDI)Zn-1 was able to initiate and polymerize all four OCAs. The GPC analysis of those PAHAs showed excellent polymerization control, similar to poly(**1**) and the M_n of the resulting polymers matched the calculated M_n well, with PDIs lower than 1.3 (Table 1, entries 5–8). We also synthesized diblock copolymers from two different OCAs (Table 1, entries 9–11). These block copolymers had remarkable control of MWs and MWDs (PDI < 1.1).

Enantiomerically pure OCAs were used to study the stereo-retention of the ROPs catalyzed by (BDI)Zn-1.[5] PAHAs initiated from isopropanol (^{i}PrOH) under the catalysis of DMAP ([OCA]/[^{i}PrOH]/[DMAP] = 50:1:1) were used as control. Poly(**1**) and poly(**2**) polymerized by DMAP showed good stereoregularity judged by NMR (Figure S17, 19). However, poly(**3**) and poly(**4**), with relatively acidic α-hydrogens, showed significant epimerization and atactic polymer features with broad and multiple peaks around methine regions in NMR spectra (Figure 1, Figures S17–25), consistent with previous literature reports.[8,13] On the other hand, all PAHAs mediated by (BDI)Zn-1 showed perfect stereoregularity. Narrow singlets for backbone α-methine hydrogens were observed in the homonuclear decoupled ^{1}H NMR spectra, revealing > 95% isotacticity[16a] for all PAHAs (Figure 1, Figures S4, S7, and S15). Additionally, ^{13}C NMR spectra showed narrow singlets corresponding to α-carbons, further suggesting excellent stereo-control (Figures S5, S8, S11, S13, and S16). Our results suggest that the catalysis of (BDI)Zn-1 does not affect the chiral centers of OCAs with high tolerance of side-chain functionalities, presumably due to the high catalytic activity and different ROP mechanism of (BDI)Zn-1 compared to DMAP.

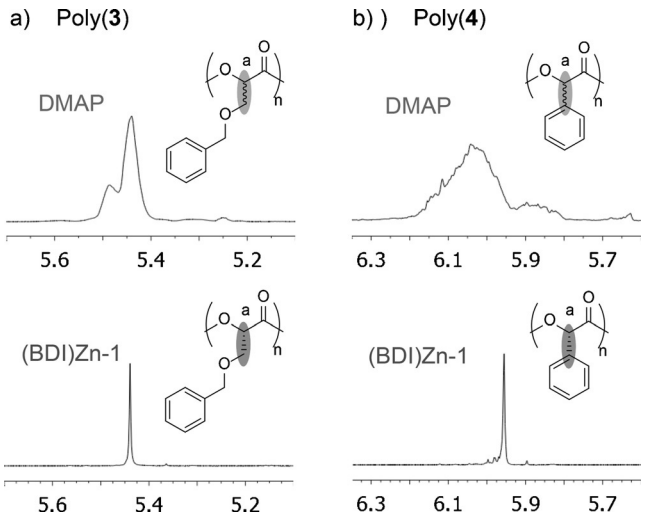

Figure 1. The effect of OCA ROP catalysts on the methine carbon chirality. a) Poly(**3**) and b) poly(**4**) were synthesized with the monomer/catalyst ratio of 50:1. The polymerization mediated by DMAP (^{i}PrOH as initiator) exhibited epimerization of the α-methine hydrogen atom in both ^{1}H NMR spectra of the polymers [homonuclear decoupled ^{1}H NMR spectroscopy for poly(**3**)] while the use of (BDI)Zn-1 retained the isotacticity of the polymers.

We explored if two types of monomers, LA and OCA, could be combined in single catalytic system to build block copolymers (Table 2). As (BDI)Zn-alkoxides—structural analogs of (BDI)Zn-1—are known to polymerize LA,[16b] we hypothesized that (BDI)Zn-1 might also achieve the block copolymerization of both LA and OCA. Of note, DMAP only polymerizes LA at high concentration and is difficult to achieve full conversion,[18] disqualifying it as a suitable catalyst for one-pot ROP of LA and OCAs. We first constructed a poly(**1**) block with a degree of polymerization (DP) of 50 in the presence of (BDI)Zn-1. Upon full conversion of OCA (determined by FT-IR), L-lactide (LLA, 50 equiv to (BDI)Zn-1) was added into the reaction mixture. LLA was fully converted within 4 h, confirmed by FTIR as the

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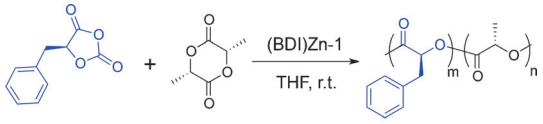
Table 2: Block copolymerization of OCA (**1**) and LLA catalyzed by (BDI)Zn-1.[a]



L-PheOCA (**1**) L-Lactide (LLA) poly (**1**-*b*-LLA)

Entry	Monomers	[Monomer]/[Zn][b]	M_n (exp.) [kDa][c]	M_n (cal.) [kDa]	PDI[c]
1	**1**	50	6.9	7.5	1.07
2	**1**/LLA	50/50	17.4	14.7	1.03
3	LLA/**1**	50/50	13.4	14.7	1.03
4	**1**/LLA/**1**	50/50/100	32.3	29.4	1.05

[a] Representative results of block copolymers initiated by (BDI)Zn-1 (3.0 mM) in THF at room temperature; monomers were added sequentially. [b] (BDI)Zn-1 was set as 1 equiv relative to all of the monomer ratios. [c] Determined by GPC analysis in DMF (0.1 M LiBr) using dn/dc values in Table S2.

peak shift from 1750 cm^{-1} (lactone) to 1760 cm^{-1} (ester). The resulting poly(**1**-b-LLA) block copolymer showed a monomodal peak with a PDI of 1.03 (Figure S26), which completely shifted from 6.9 kDa to 17.4 kDa compared to that of poly(**1**)$_{50}$ in GPC spectra; the M_n of the copolymer agreed well with the calculated value (Table 2, entries 1–2). We also realized identical control upon reversal of the sequence of monomer addition (Table 2, entry 3), as the resulting poly(LLA-b-**1**) showed a monomodal peak with narrow MWD in the GPC (Figure 2) that agreeably overlapped with that of

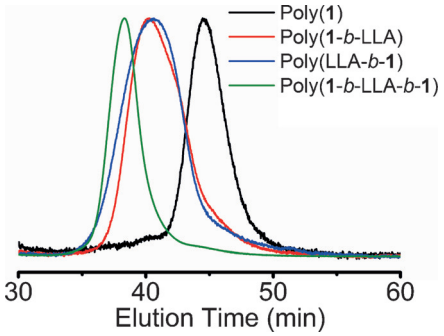


Figure 2. Normalized light scattering GPC traces of the block copolymers synthesized in Table 2.

poly(**1**-b-LLA) (Figure 2). Additionally, a triblock copolymer poly(**1**-b-LLA-b-**1**) was synthesized by adding another potion of **1** (100 equiv to initiator) into the poly(**1**-b-LLA) reaction solution (Table 2, entry 4). The obtained triblock copolymer exhibited a controlled M_n of 32.3 kDa with the low PDI of 1.05, similar to that of diblock copolymer synthesis (Figure 2), which suggests minimal transesterification reactions. Thus the chain ends of poly(**1**) or PLLA are capable of initiating the ROP of the other monomer. It is likely that the ROP of OCAs catalyzed by (BDI)Zn-1 shares the same active chain propagation group as the reported ROP of LA by Zn catalyst, presumably (BDI)Zn-alkoxide.

To further elucidate the OCA ROP mechanism initiated by (BDI)Zn-1, we conducted several kinetic studies to establish reaction orders of the OCA monomer and (BDI)Zn-1. The conversion of **1** ([**1**] was 40 mM initially) was monitored by FT-IR at different catalyst concentrations at room temperature ([(BDI)Zn-1] = 0.17–0.67 mM), and corresponding M_n values were obtained from GPC analysis. The M_n of resulting poly(**1**) showed a linear correlation with the conversion of **1**, agreeing with the expected values (Figure 3a). The PDI remained lower than 1.1 throughout

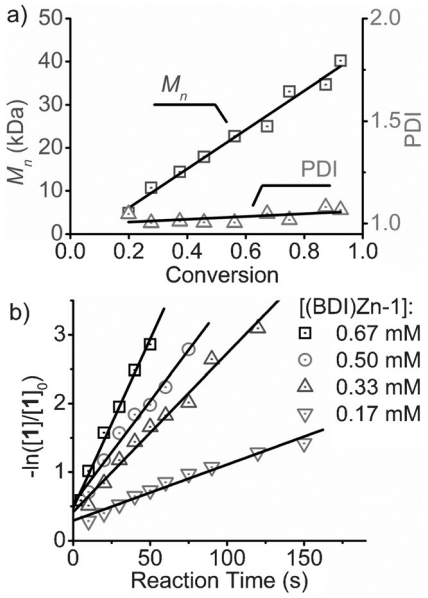


Figure 3. Kinetic study of the polymerization of **1** initiated by (BDI)Zn-1. a) Plot of the M_n and PDI of poly(**1**) versus the monomer conversion. ([**1**] = 30 mM, [(BDI)Zn-1] = 0.10 mM). b) First-order kinetic plot of the polymerization of **1**. ([**1**] = 40 mM, [(BDI)Zn-1] = 0.17, 0.33, 0.50, 0.67 mM, that is, [**1**]/[(BDI)Zn-1] = 240, 120, 80, 60).

the polymerization process. The polymerization proceeded with first-order dependence on OCA concentration (Figure 3b), indicated by the linear relationship between $-\ln([\mathbf{1}]/[\mathbf{1}]_0)$ and reaction time. Derived from the kinetic data of four different concentrations of (BDI)Zn-1, the order in Zn catalyst concentration was determined to be 1.21 from the slope of the fitted lines (Figure S27), indicating that the ROP of **1** likely proceeds through monometallic enchainment step.[19] These data, along with fair agreement between the observed and theoretical values of M_n and the MALDI results, strongly suggest that (BDI)Zn-1 acts as a single-site catalyst wherein the bulky BDI ligand remains bound to the Zn center and the methyl lactate moiety initiates the polymerization.

(BDI)Zn catalysts were reported to have monomer-dimer equilibria in solution,[19] which significantly affect the catalytic activity of (BDI)Zn catalysts in the lactone's ROP. We investigated whether such equilibria could also influence the ROP process of OCAs. (BDI)Zn-1 showed a single set of ligand peaks in ^{1}H NMR spectra (Figure S28), indicating a predominant monomeric form in THF solution (less than

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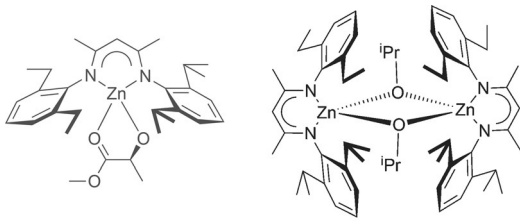

Scheme 2. The structural comparison between (BDI)Zn-1 and (BDI)Zn-2.

5% of dimeric form). We synthesized (BDI)Zn-2 (Scheme 2) with less bulky isopropanol (^{i}PrO-) as the initiator group and the same BDI ligand as (BDI)Zn-1. (BDI)Zn-2 showed two sets of peaks for ethyl and isopropyl groups on the BDI ligand in ^{1}H NMR spectra (Figure S29), indicating a predominant dimeric form in THF solution (about 5% of monomeric form calculated based on the integration of the singlet peak at 4.9 ppm).[20] We observed slower kinetics of OCA **1** polymerization initiated by (BDI)Zn-2 compared with that of (BDI)Zn-1 under the same conditions ([**1**]/[Zn] = 50:1, [Zn] = 1.0 mM). While only 60% of **1** was consumed within 4 hours in the presence of (BDI)Zn-2 (being eventually consumed at 24 h), the rapid ROP of **1** mediated by (BDI)Zn-1 was completed in seconds (Figure 3). The resulting polymer had three times higher M_n than expected value and a high PDI value of 1.33 (Figure S30). The MALDI-MS analysis indicated that all of poly(**1**) had the isopropanol group from (BDI)Zn-2. As (BDI)Zn-1 and (BDI)Zn-2 share the same ligand, the chain propagating species should be identical. In other words, the high MW of poly(**1**) catalyzed by (BDI)Zn-2 was not due to the transesterification. The drastic difference in catalytic behavior likely comes from the initiation step. We thus studied the initiation step of the ROP catalyzed by (BDI)Zn-2 by mixing (BDI)Zn-2 and OCA **1** at 1:1 ratio. The ^{1}H NMR spectrum of the reaction mixture at 4 hours exhibited a distinct quartet peak at 5.25 ppm (α-methine hydrogen in poly(**1**)), indicating the formation of long isotactic poly(**1**) instead of the theoretical (BDI)Zn-(OCH-(Ph)CO)-O^{i}Pr complex (Figure S31). On the contrast, mixing (BDI)Zn-1 and OCA **1** at 1:1 ratio resulted in the 1:1 adduct (the distinguishable quartet peak of α-methine proton at 5.32 ppm) with only a small portion of oligomers (< 20% based on NMR spectroscopy, Figure S32). These results suggest that the dimeric (BDI)Zn-2 complex likely inhibits its coordination to **1** and prevents the initiation of the ROP; only a small portion of monomeric (BDI)Zn complex in (BDI)Zn-2 served as the actual initiating species for the ROP (Scheme 2). A similar phenomenon is observed in the ROP of β-butyrolactone in which the dimeric (BDI)Zn-alkoxide complex is a poor catalyst for ROP.[19]

Combining results from both kinetics and initiation studies, we thus propose a polymerization mechanism of ROP of OCA catalyzed by (BDI)Zn-1 (Figure S33). The ROP process starts with the coordination of the OCA monomer to the Zn center of the monometallic (BDI)Zn-1 complex. Subsequent ring-opening occurs with acyl-oxygen bond cleavage and the removal of CO_2, maintaining the configuration at the α-methine carbon. The active monometallic (BDI)Zn resides at the chain end and mediates the monomer insertion and chain propagation.

In conclusion, we have described a highly reactive single-site catalyst, (BDI)Zn-1, for the controlled ROP of OCAs. The use of (BDI)Zn-1 allows the synthesis of homo- and block co-PAHAs from a variety of OCA monomers, with controlled MW, narrow MWD, retained stereoregularity and no transesterification. One-pot block copolymerization of LA and OCAs can be easily accomplished with the use of (BDI)Zn-1, regardless of the monomer addition sequence. The mechanistic study indicated the monomeric (BDI)Zn-1 complex actively mediates the initiation and chain propagation in the ROP of OCAs. Therefore the ROP of OCAs catalyzed by (BDI)Zn complex represents an efficient and powerful route to prepare functional PAHAs. Ongoing work is directed at employing (BDI)Zn-1 for the synthesis of new polyester materials, as well as a step deeper to investigate metal catalysts for the stereochemistry-controlled polymerization of OCAs.

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