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Mechanistic Study of the Stereoselective Polymerization of D,L-Lactide Using Indium(III) Halides

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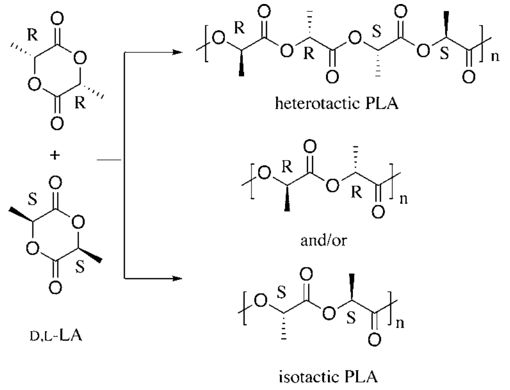
Abstract: We report the results of a comprehensive investigation of the recently discovered stereoselective and controlled polymerization of racemic lactide (D,L-LA) using an initiator prepared *in situ* from indium(III) chloride ($InCl_3$), benzyl alcohol (BnOH), and triethylamine (NEt_3). Linear relationships between number-average molecular weight (M_n) and both monomer to alcohol concentration ratio and monomer conversion are consistent with a well-controlled polymerization. Studies on polymerization kinetics show the process to be first-order in $[InCl_3]_0$ and zero-order in both $[BnOH]_0$ and $[NEt_3]_0$. The rate of D,L-LA conversion is also dependent on the indium(III) halide (i.e., $t_{1/2}(InCl_3) \approx 43$ min versus $t_{1/2}(InBr_3) \approx 7.5$ h, 21 °C, CD_2Cl_2, $[\text{D,L-LA}]_0/[BnOH]_0 \approx 100$, $[\text{D,L-LA}]_0 = 0.84$ M, $[InX_3]_0/[BnOH]_0 = 1$) and lactide stereoisomer (i.e., $k_{obs}^{\text{D,L-LA}} \approx k_{obs}^{meso\text{-LA}} > k_{obs}^{\text{L-LA}}$). A model system that polymerizes D,L-LA with the same high degree of stereoselectivity was developed using 3-diethylamino-1-propanol (deapH) in lieu of BnOH and NEt_3. The product of the reaction of deapH with $InCl_3$ was identified as $[InCl_3(deapH)(H_2O)]_2$ by elemental analysis, X-ray crystallography, and NMR and FTIR spectroscopies. An anhydrous version of the complex was also isolated when care was taken to avoid adventitious water, and was shown by pulsed gradient spin−echo (PGSE) NMR experiments to adopt a dinuclear structure in CD_2Cl_2 solution under conditions identical to those used in its stereoselective polymerization of D,L-LA. The combined data suggest that the initiating species for the $InCl_3$/BnOH/NEt_3 system is similar to $[InCl_3(deapH)(H_2O)]_2$ and of the type $[InCl_{(3-n)}(OBn)_n]_m$. With this information we propose a mechanism that rationalizes the observed stereocontrol in D,L-LA polymerizations. Finally, in an exploration of the scope of the $InCl_3$/BnOH/NEt_3 system, we found this system to be effective for the polymerization of other cyclic esters, including ε-caprolactone and several substituted derivatives.

Introduction

Developing biodegradable materials from biorenewable resources is a crucial step in future sustainable polymer technologies.[1] Of particular interest is polylactide (PLA), a biodegradable and biocompatible polyester,[2] which due to its mechanical and physical properties is suitable for a variety of applications such as product packaging,[3,4] sutures,[2,5,6] and artificial tissue matrices.[7,8] Since the properties of PLA can be tailored by tuning its tacticity, molecular weight, and molecular weight distribution, interest in developing initiators that carry out the stereoselective and controlled ring-opening polymerization of D,L-lactide (D,L-LA) has flourished (Scheme 1).[9] To date, most strategies have focused on developing discrete metal complexes that rely on the steric bulk and/or chirality of an ancillary ligand to impart stereochemical selectivity, a process that is exerted through chain-end and/or enantiomorphic site control.[10,11] This approach provides synthetic avenues to improve activity and stereoselectivity through fine-tuning the structural and electronic architectures of the supporting ligands.[12]

Scheme 1. Heterotactic and Isotactic Microstructures of PLA Prepared from D,L-LA



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Recently, we discovered the stereoselective polymerization of D,L-LA using an initiator prepared *in situ* from indium trichloride ($InCl_3$), benzyl alcohol (BnOH), and triethylamine (NEt_3).[13,14] This system affords PLA with a highly heterotactic microstructure (P_r values as large as 0.97, where P_r is the probability of racemic placement of monomer stereoisomers), an extraordinary finding given the absence of an "added" directing ancillary ligand that has been required for most systems.[15] In addition, preliminary studies showed that this convenient route affords PLA with narrow polydispersity indices (PDIs) and shows excellent molecular weight control using readily available reagents at ambient temperature. Herein we provide a detailed description of the polymerization behavior of this new catalytic system. In particular, we discuss molecular weight control experiments and kinetic investigations, with emphasis on new studies that probe the reaction order with respect to $[InCl_3]_0$, $[BnOH]_0$, and $[NEt_3]_0$, and the polymerization rate dependence on both indium(III) halides and monomer stereoisomers (i.e., *meso*-LA, L-LA, and/or D-LA). We also discuss the structural characterization of an indium(III) complex prepared from 3-diethylamino-1-propanol, a ligand comprising both alkoxide and amine components. This complex polymerizes D,L-LA with a similar degree of stereoselectivity as the $InCl_3$/BnOH/NEt_3 system and thus provides inspiration for mechanistic proposals. Finally, we explore the scope of the $InCl_3$/BnOH/NEt_3 system through studies of other cyclic ester polymerizations.

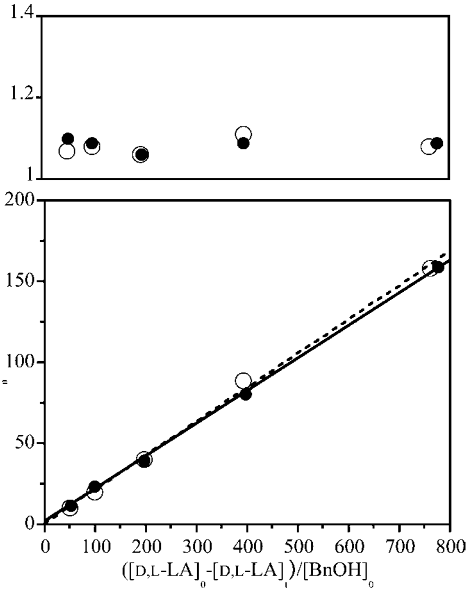

Figure 1. Plot of M_n and PDI vs $([D,L\text{-}LA]_0 - [D,L\text{-}LA]_t)/[BnOH]_0$ using $InCl_3$ (●) and $InBr_3$ (○), with linear fits shown as solid and dashed lines, respectively. Conditions: $[BnOH]_0/[InX_3]_0 \approx 1$, $[D,L\text{-}LA]_0 \approx 0.8-1$ M, CH_2Cl_2, 25 °C. M_n determined by SEC (relative to polystyrene in $CHCl_3$).

Results

Molecular Weight Control and Stereochemistry. Polymerization experiments were performed at ambient temperature by adding BnOH (1 equiv) and NEt_3 (2 equiv)[16] to a stirring suspension of InX_3 (1 eq, X = Cl, Br, or I) in a 1 M D,L-LA solution (CH_2Cl_2). The degree of molecular weight control was evaluated by plotting apparent M_n (SEC vs polystyrene, in chloroform) versus (a) converted monomer to initial alcohol concentration ratio (i.e., $([D,L\text{-}LA]_0 - [D,L\text{-}LA]_t)/[BnOH]_0$, Figure 1)[13] and (b) percent monomer conversion at fixed initial monomer to alcohol ratio ($[D,L\text{-}LA]_0/[BnOH]_0 = 400$; Figure 2). The linear relationships in these plots combined with the low PDI values (<1.1) illustrate excellent molecular weight control. A similar level of control (and stereoselectivity; see Figure 1 and Table S1 and Figure S2 in the Supporting Information) was also achieved using $InBr_3$, although the reactions required longer periods of time to reach near complete conversion (*ca.* > 95%). In the absence of BnOH, InX_3, or NEt_3, polymerizations of D,L-LA did not proceed, indicating that the catalytic species is derived from all three components. Polymer was produced with similar molecular weight and stereocontrol when NBu_3, $NHBu_2$, or 1,8-bis(dimethylamino)naphthalene (Proton Sponge) was substituted for NEt_3 (Figure S1, Table S2 in the Supporting Information), in support of the idea that this additive is acting merely as a base and is not an integral part of the catalytically active species. Molecular weight control was not evaluated for InI_3 due to its catalytic inefficiency.

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(16) While 2 equiv of NEt_3 were used in the polymerization of D,L-LA reported herein (unless otherwise noted) to help facilitate the dissolution of $InCl_3$ in the reaction medium, PLA samples with similar M_n and P_r values are afforded using only 1 equiv.

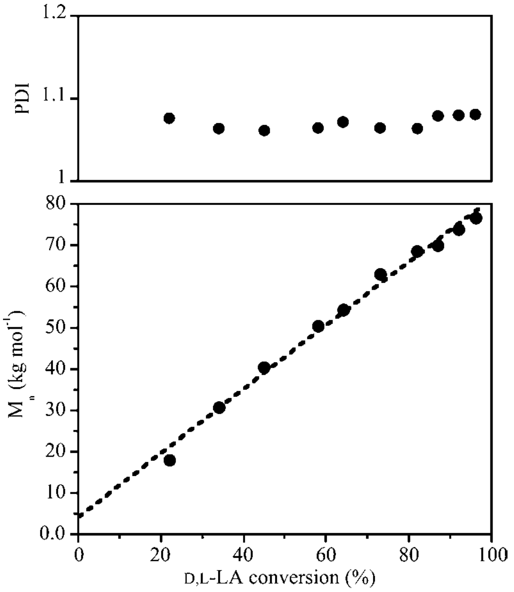

Figure 2. Plot of M_n (●) and PDI vs D,L-LA conversion for the production of heterotactic PLA using the $InCl_3/BnOH/NEt_3$ system. Conditions: $[\text{D,L-LA}]_0 = 0.84$ M, $[\text{D,L-LA}]_0/[BnOH]_0 = 400$, $NEt_3/BnOH/InCl_3 = 2{:}1{:}1$, 25 °C, CH_2Cl_2.

In addition to analyzing the products by ^1H NMR spectroscopy and SEC, a sample of oligomers isolated from an aliquot of a polymerization reaction ($[\text{D,L-LA}]_0/[BnOH]_0 = 46$) was characterized by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Figure 3). As an example, the molecular ion $m/z = 2581.9$ is consistent with a PLA chain terminated with a BnO− group and having a degree of polymerization (DP) of 17 plus a sodium ion (calculated $m/z = 2581.2$). Analysis of the same sample by ^1H NMR spectroscopy indicated the reaction proceeded to 42% monomer conversion corresponding to an average DP = 19 if every BnOH molecule gives rise to a polymer chain. Using every polymer peak in the MALDI mass spectrum in Figure 3, we calculate an average DP = 17.6. The major peaks in the mass spectrum are separated by a lactide unit (*ca.* 144 g/mol) and correspond to polymers with DP values in the range of 9−29. A second set of peaks of lower intensity is offset from the primary peaks by approximately half a lactide unit (*ca.* $m/z = 70-74$)

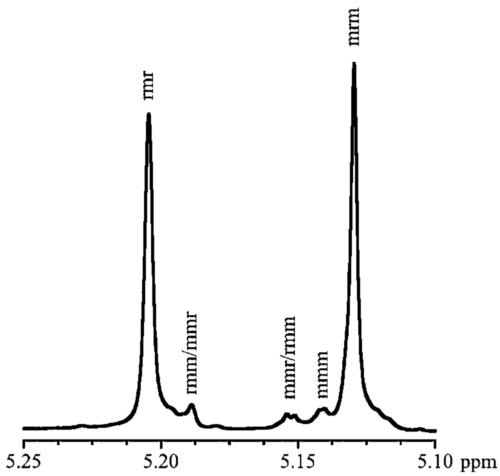

Figure 4. Homonuclear decoupled ^1H NMR spectrum of the methine region of heterotactic PLA prepared with the $InCl_3/BnOH/NEt_3$ system at 25 °C (500 MHz, $CDCl_3$, $P_r = 0.94$).

suggesting some level of transesterification during polymerization, albeit not enough to compromise the narrow molecular weight distributions described above to any significant extent.

The tacticity of the PLA produced from D,L-LA or *meso*-LA using $InCl_3/BnOH/NEt_3$ was assessed by analyzing the methine proton resonances in homonuclear decoupled ^1H NMR spectra.[12o,17] The NMR spectrum for a highly heterotactic microstructure with a probability of racemic enchainment $P_r = 0.94$ is shown in Figure 4.[13] The level of heterotacticity was dependent upon polymerization temperature and ranged from $P_r = 0.97$ at 0 °C, to $P_r = 0.86$ at 60 °C, to essentially that of atactic polylactide ($P_r = 0.6$) produced from solvent-free reactions at 140 °C (in "perfectly atactic" samples, $P_r = 0.50$). The level of stereocontrol exhibited by this simple $InCl_3/BnOH/NEt_3$ system at 0 °C and ambient temperature compares favorably to those reported for other catalysts bearing sterically hindered and/or chiral supporting ligands, such as the (BDI)ZnOEt system (cf. $P_r = 0.94$ at 0 °C) in which the β-diketiminate (BDI) ligand is thought to be responsible for chain-end control of product tacticity.[12o,x] Interestingly, PLA produced from polymerizations of *meso*-LA at temperatures between 0 and 70 °C was essentially atactic ($P_r \approx 0.56$). This result is in contrast to the findings reported for (BDI)ZnOEt complexes whereby moderately syndiotactic

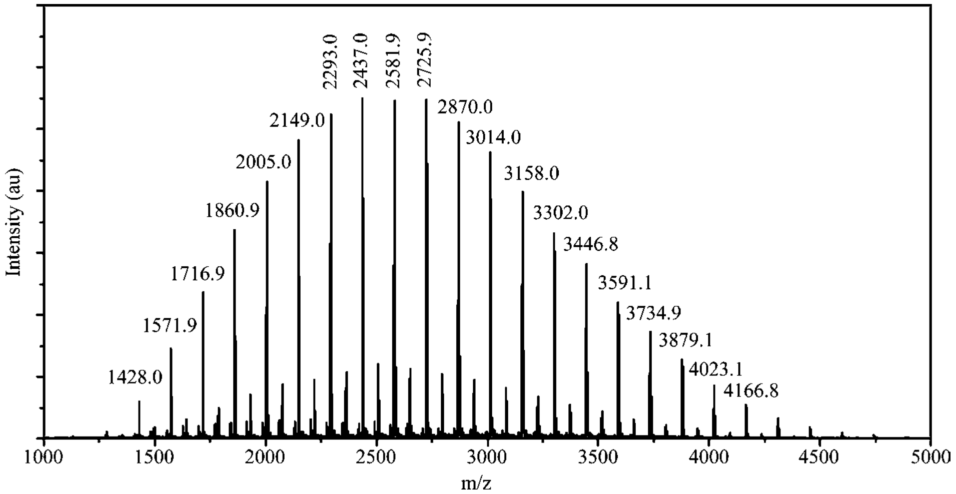

Figure 3. MALDI-TOF mass spectrum of the product isolated from a polymerization of D,L-LA by the $InCl_3/BnOH/NEt_3$ system quenched at 42% monomer conversion (^1H NMR). Conditions: $[\text{D,L-LA}]_0 = 0.84$ M, $[\text{D,L-LA}]_0/[BnOH]_0 = 46$, $NEt_3/BnOH/InCl_3 = 2{:}1{:}1$, 25 °C, CH_2Cl_2.

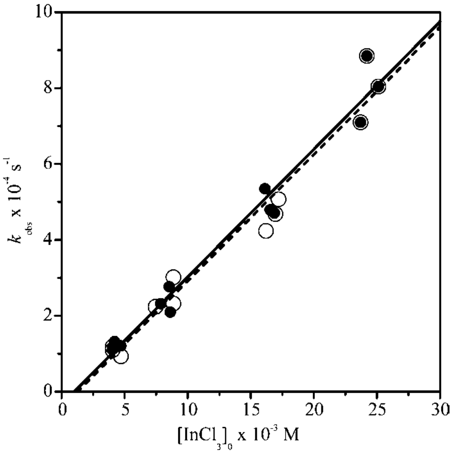

Figure 5. Kinetic plot of k_{obs} vs $[InCl_3]_0$ for the polymerization of D,L-LA. Conditions: (a) $[D,L\text{-}LA]_0 \approx 0.84$ M, $[BnOH]_0 \approx 25$ mM, $[NEt_3]_0 \approx 50$ mM, 21 °C, CH_2Cl_2 (●) and (b) $[D,L\text{-}LA]_0 \approx 0.84$ M, $NEt_3/BnOH/InCl_3 = 2:1:1$, 21 °C, CH_2Cl_2 (○) with linear fits shown as solid and dashed lines respectively.

($P_r = 0.76$) or heterotactic ($P_r = 0.37$) PLA is produced in polymerizations of *meso*-LA,[18] depending on the nature of the BDI ligand.[12o] For the indium-based system reported herein, we infer that the difference in stereocontrol exerted in polymerizations of D,L-LA and *meso*-LA indicates that both stereocenters in LA are important in controlling monomer enchainment and thus the tacticity of the resultant polymer.

Polymerization Kinetics. Rates of D,L-LA polymerization were analyzed at 21 °C using fixed monomer, alcohol, and amine concentrations (*ca.* $[D,L\text{-}LA]_0 \approx 0.84$ M, $[BnOH]_0 \approx 25$ mM, $[NEt_3]_0 \approx 50$ mM, CD_2Cl_2) while $[InCl_3]_0$ was varied between 4 and 25 mM. All experiments were monitored *in situ* by ^1H NMR spectroscopy to at least four half-lives, and observed rate constants (k_{obs}) were extracted from exponential monomer decay curves (Figure S3 and Table S4 in the Supporting Information). In each case, a first-order dependence on monomer concentration was observed. The reaction order in $[InCl_3]_0$ was determined from a plot of k_{obs} versus $[InCl_3]_0$ (solid circles, Figure 5). The linear relationship indicates a first-order rate dependence on $[InCl_3]_0$.

Polymerization rates were also analyzed by fixing $[D,L\text{-}LA]_0$ (≈ 0.84 M) and adjusting alcohol and amine concentrations such that $NEt_3/BnOH/InCl_3 = 2:1:1$ (○, Figure 5). This variation of the reaction conditions has little effect on the rate of polymerization, indicating a zero-order dependence on $[BnOH]_0$ and $[NEt_3]_0$ over the range of concentrations tested when the idealized ratio is used. Fixing $[D,L\text{-}LA]_0$, $[InCl_3]_0$, and $[NEt_3]_0$ ($[D,L\text{-}LA]_0 \approx 0.84$ M, $[InCl_3]_0 \approx 16$ mM, $[NEt_3]_0 \approx 33$ mM, CH_2Cl_2, 25 °C) while varying $[BnOH]_0$ (*ca.* 16−197 mM, $NEt_3/BnOH/InCl_3 = 2:1:1$ to $2:12:1$) has little effect on the rate of polymerization (see Figure S4).[19] Alternatively, fixing $[D,L\text{-}LA]_0$, $[InCl_3]_0$, and $[BnOH]_0$ ($[D,L\text{-}LA]_0 \approx 0.84$ M, $[InCl_3]_0 \approx 16$ mM, $[BnOH]_0 \approx 16$ mM, CH_2Cl_2, 25 °C) while varying $[NEt_3]_0$ (*ca.* 16−197 mM (i.e., $NEt_3/BnOH/InCl_3 = 1:1:1$ to $12:1:1$) results in only a slight increase in polymerization rate (see Figure S5).[20] These data collectively support a polymerization process that is zero-order in $[BnOH]_0$ and $[NEt_3]_0$ when these reagents are used in and above the idealized ratio of $NEt_3/BnOH/InCl_3 = 2:1:1$. Thus, we propose the rate expression $-d[D,L\text{-}LA]/dt = k_p[D,L\text{-}LA]_0[InCl_3]_0$ with the propagation rate constant $k_p \approx 0.3$ M^{-1} s^{-1} (calculated from the slopes of the plots in Figure 5). This value is similar to that observed in another indium(III) system, $[\{(NNO)InCl\}_2(\mu\text{-}OEt)(\mu\text{-}Cl)]$[14b] ($k_p \approx 0.56$ M^{-1} s^{-1}), but is more than an order of magnitude smaller than that for one of the fastest known lactide polymerization catalysts, L^1ZnOEt ($k_p \approx 2.2$ M^{-1} s^{-1}, L^1 = 2,4-di-*tert*-butyl-6-{[(2′-dimethylaminoethyl)methylamino]methyl}phenolate).[21] Interestingly, polymerization is impeded when $InCl_3$ was used in excess of alcohol (i.e., $[InCl_3]_0/[BnOH]_0 > 1$).[13] Thus, in experiments where $[D,L\text{-}LA]_0/[BnOH]_0 \approx 100$, reactions proceeded to 96%, 89%, and 60% conversion after 2.5 h when $[InCl_3]_0/[BnOH]_0 \approx 1$, 2, and 3, respectively ($[NEt_3]_0 = 2[BnOH]_0$). Although the product polymers from these runs possessed similar molecular weights, the PDI values increased with increasing $[InCl_3]_0/[BnOH]_0$ ratio. We surmise from the kinetic results that the nature of the catalytic species is perturbed by the "excess" indium(III) at $[InCl_3]_0/[BnOH]_0 > 1$, resulting in a decrease in activity.

Additional reactions were performed using $InCl_3$, $InBr_3$, or InI_3 under identical conditions (21 °C, CD_2Cl_2, $[D,L\text{-}LA]_0/[BnOH]_0 \approx 100$, $[D,L\text{-}LA]_0 = 0.84$ M, $[InX_3]_0/[BnOH]_0 = 1$, $[NEt_3]_0 = 2[BnOH]_0$). Experiments employing $InBr_3$ afforded PLA with $k_{obs} \approx 2.6 \times 10^{-5}$ s^{-1} ($t_{1/2} \approx 7.5$ h), approximately an order of magnitude less than that observed in reactions using $InCl_3$ ($k_{obs} \approx 2.7 \times 10^{-4}$ s^{-1}, $t_{1/2} \approx 43$ min). Polymerizations were retarded further still with InI_3, where reactions proceeded only to *ca.* 10% conversion after 4 h before reaching a plateau of *ca.* 27% after 29 h. Taken together, these data showing the significant rate effects of halide variation, as well as other stereochemical data discussed below, suggest that the halide is bound to the indium(III) center in the catalytically active species.

Polymerizations of L- and *meso*-LA were compared to D,L-LA polymerizations (21 °C, CD_2Cl_2, $[LA]_0 \approx 0.84$ M, $[LA]_0/[BnOH]_0 \approx 100$, $NEt_3/InCl_3/BnOH = 2:1:1$). From the exponential monomer decay curves (Figure 6), a first-order dependence on monomer concentration was observed. Under near identical conditions, $k_{obs}^{meso\text{-}LA}$ (2.5×10^{-4} s^{-1}, $t_{1/2} \approx 46$ min) was similar to $k_{obs}^{D,L\text{-}LA}$ (2.3×10^{-4} s^{-1}, $t_{1/2} = 50$ min). These values were approximately 12 times larger than $k_{obs}^{L\text{-}LA}$ (2.1×10^{-5} s^{-1}, $t_{1/2} \approx 9$ h). Similar rate disparities were reported for the (BDI)ZnOR system and are consistent with the preference for alternating incorporation of D- and L-LA isomers to yield highly heterotactic PLA in polymerizations of D,L-LA.[12o] Polymerization of a mixture of LA stereoisomers was also monitored by ^1H NMR spectroscopy to determine if the consumption of a single LA diastereomer is influenced by the presence of another. Here, BnOH (1 equiv) and NEt_3 (2 equiv) were added to a stirring suspension of $InCl_3$ in a *ca.* 0.84 M solution of LA stereoisomers (52 equiv of L-LA and 48 equiv of *meso*-LA, CD_2Cl_2). The results (Figure S6, Supporting Information) confirm that *meso*-

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(17) Zell, M. T.; Padden, B. E.; Paterick, A. J.; Thakur, K. A. M.; Kean, R. T.; Hillmyer, M. A.; Munson, E. J. *Macromolecules* **2002**, *35*, 7700–7707. Bernoullian integration percentages for a given P_r and illustrative integration data are provided in the Supporting Information.

(18) In the case of *meso*-LA polymerization, P_r is the probability of *r*-dyad placement between monomer units.

(19) When $[BnOH]_0 \approx 8$ (i.e., $NEt_3/BnOH/InCl_3 = 2:0.5:1$) the rate of polymerization was found to decrease, a phenomenon that we cannot currently explain.

(20) We attribute this minor effect to the dissolution of $InCl_3$ in the reaction medium that appears to become more rapid as $[NEt_3]_0$ increases. This phenomenon would result in faster catalyst formation *in situ* and a larger k_{obs}.

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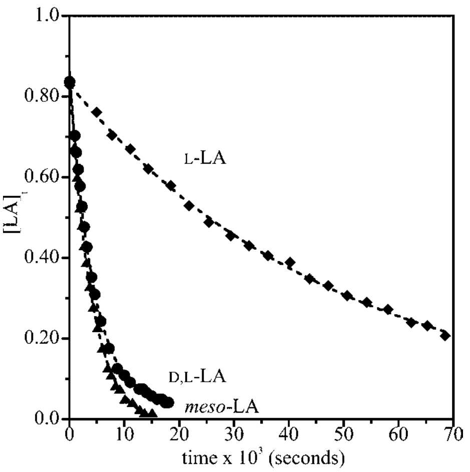

Figure 6. Illustrative kinetic data for polymerizations of D,L-LA, L-LA, and *meso*-LA by the $InCl_3$/BnOH/NEt_3 system with best fits to the first order decay equation ($[\text{D,L-LA}]_t = [\text{D,L-LA}]_0 \exp(-k_{obs}t)$). Conditions: $[LA]_0 \approx 0.84$ M, $[LA]_0/[BnOH]_0 \approx 100$, $NEt_3/InCl_3/BnOH = 2:1:1$, 21 °C, CD_2Cl_2. (▲) *meso*-LA, (●) D,L-LA, (◆) L-LA.

LA is consumed faster than L-LA in a competitive polymerization situation.

With this knowledge in hand, we set out to exploit the difference in monomer consumption rates as a means of purifying one isomer of LA contaminated with the others, an important issue when LA or PLA of high optical purity is required.[22] Here, an isomeric mixture of D-, L-, and *meso*-LA (90:5:5) with a specific rotation $[\alpha]^{25}_{D} = +228$ (*c* 5.1, $CHCl_3$) was polymerized for 2 h (25 °C, CH_2Cl_2, $[LA]_0/[BnOH]_0 \approx 130$, $[NEt_3]_0 = 2[BnOH]_0$) and quenched at 30% total monomer conversion. After solvent removal, the product was vacuum sublimed (50 °C, 100 mTorr) affording LA (50% yield) with $[\alpha]^{25}_{D} = +279$ (*c* 5.1, $CHCl_3$), a value consistent with our pure-stock D-LA ($[\alpha]^{25}_{D} = +276$ (*c* 5.1, $CHCl_3$)). Thus, through partial polymerization of the D-, L-, and *meso*-LA mixture (90:5:5), removal of L- and *meso*-LA 'impurities' was accomplished. ^1H NMR analyses of the sublimate revealed no trace of *meso*-LA while the remaining unsublimed residue was found to be comprised of 70% atactic PLA and 30% unreacted monomer. In a control experiment, vacuum sublimation of the 90:5:5 isomeric mixture prior to polymerization (50 °C, 100 mTorr) afforded LA with $[\alpha]^{25}_{D} = +232$ (*c* 5.1, $CHCl_3$), proving that the process of sublimation has a negligible effect on stereoisomer separation. In sum, although the protocol is not optimized, the aforementioned experiments illustrate a facile and convenient route for purifying L-LA (or D-LA) contaminated with small amounts of stereoisomeric impurities.

Synthesis and Structure of an Initiator Complex. Multiple attempts to isolate crystals of a coordination complex from solutions of $InCl_3$, BnOH, and NEt_3 were unsuccessful. In an alternative strategy, 3-diethylamino-1-propanol (deapH) was used in lieu of BnOH and NEt_3 to exploit the propensity of ammonium salts to crystallize. In a typical experiment, deapH (1 equiv) was added to a stirring suspension of $InCl_3$ in CH_2Cl_2. After stirring overnight, an amorphous solid was precipitated upon dropwise addition of the reaction solution to vigorously stirring pentane. Crystals were grown over a period of 2 months by slow diffusion of pentane vapor into a solution of the product in CH_2Cl_2.

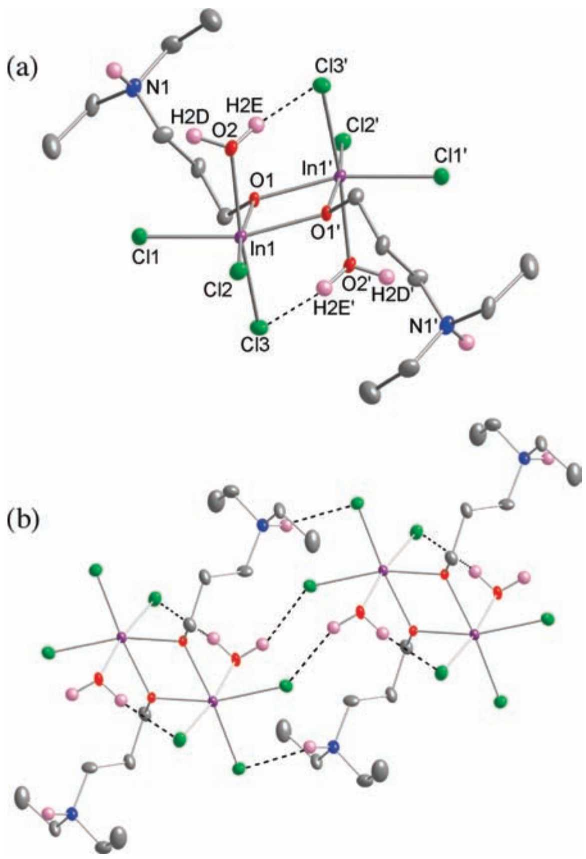

Figure 7. Representations of the X-ray crystal structure of $[InCl_3(deapH)(H_2O)]_2$ as 50% thermal ellipsoids (except H atoms). (a) A single molecule is shown with selected nonhydrogen atoms labeled and hydrogen atoms on C atoms omitted for clarity. (b) View showing adjacent molecules and hydrogen bonds (dashed lines), without atom labels and hydrogen atoms on C atoms for clarity. Key: In = purple, Cl = green, C = gray, N = blue, O = red, H = pink spheres. Selected bond distances (Å) and angles (deg): In1−O1, 2.158(3); In1−O1′, 2.160(3); In1−O2, 2.290(4); O1−In1−O1′, 74.77(14); In1−O−In1′, 104.23(14).

X-ray crystallographic analysis revealed the product to be a dinuclear indium complex with the structural formula $[InCl_3(deapH)(H_2O)]_2$ (Figure 7). The indium(III) ions are bridged by two alkoxides forming a planar In_2O_2 ring motif similar to that found in various organoindium alkoxides and aryloxides.[23] The coordination sphere of each indium(III) ion is completed by three chloride ligands and a water molecule (presumably introduced during the crystallization process) to yield a six-coordinate distorted octahedral geometry, with *cis*- and *trans*-angles about the metal centers with ranges of *ca.* 76°−99° and 164°−172°, respectively. The coordinated water molecules participate in hydrogen bonds, one intramolecular (to Cl3 and Cl3′, Figure 7a) and the other to Cl1/Cl1′ in an adjacent

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(22) (a) Yamaguchi, Y.; Arimura, T. European Patent 0 657 447 B1, 1995. (b) Ohara, H.; Okuyama, H.; Ogaito, M.; Fujii, Y.; Kawamoto, T.; Kawabe, T.; Horibe, Y. U.S. Patent 6,313,319 B1, 2001. (c) O'Brien, W. G.; Sloan, G. J. U.S. Patent 6,310,218 B1, 2001.

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molecule in the unit cell (Figure 7b). The ammonium proton is also hydrogen bonded to a chloride in the adjacent molecule (Cl2/Cl2′).

The complex was also obtained in bulk form as an amorphous solid, which can be isolated in anhydrous and hydrated forms that are distinguishable on the basis of NMR and FTIR spectroscopy. Thus, when initially isolated from the reaction mixture and kept under an inert atmosphere, ligand peaks in the ^{1}H NMR spectrum (*ca*. δ 4.01, 3.25, 1.90, and 1.25 ppm) are observed to be broadened and shifted relative to free deapH (CD_3CN, 25 °C, Figure S7, Supporting Information), but no vibrational frequency ν(OH) is seen in the FTIR spectrum (Figure S8, Supporting Information). Exposure of the amorphous solid to air prior to dissolution in CD_3CN gives rise to a slightly different set of ligand-based chemical shifts in the ^{1}H NMR spectrum (*ca*. δ 3.71, 3.16, 1.86, and 1.25 ppm) and the appearance of a broad absorption band at 3500 cm^{-1} attributable to ν(OH) in the solid-state FTIR spectrum. Importantly, the ^{1}H NMR spectrum of the crystals analyzed by X-ray crystallography matches that of the latter species. These results, in combination with elemental analysis data, are consistent with assignment of the bulk amorphous material exposed to air as the hydrated complex $[InCl_3(deapH)(H_2O)]_2$. Critically, the complex in anhydrous form[24] was found to polymerize D,L-LA to PLA with a highly heterotactic microstruture ($P_r = 0.92$) and M_n (19.1 kg/mol, SEC vs polystyrene, $CHCl_3$) that compares favorably with PLA prepared using the $InCl_3$/BnOH/NEt_3 system ($P_r = 0.94$, $M_n = 23.8$ kg/mol, SEC vs polystyrene, $CHCl_3$) under the same reaction conditions ([D,L-LA]$_0$ = 0.84 M, [D,L-LA]$_0$/[ROH] = 100, 25 °C, CH_2Cl_2). However, the rate of polymerization was observed to be slower in the former case (i.e., $t_{1/2}$ = 155 min versus 43 min). In view of the similar degree of stereocontrol exhibited by $[InCl_3(deapH)]_n$ and the $InCl_3$/BnOH/NEt_3 system, we are led to postulate that similar structures for the catalytically active species are adopted, with the X-ray structure of $[InCl_3(deapH)(H_2O)]_2$ serving as a reasonable model.

In order to ascertain if the structure in the solid state is retained in solution under conditions like those used in polymerizations, pulsed gradient spin−echo (PGSE) NMR spectroscopy experiments[25] were performed on solutions of the anhydrous $[InCl_3(deapH)]_n$ species in CD_2Cl_2 at ∼21 °C. This technique enables measurement of the translational diffusion coefficient (D_t) of a molecule, which can be used to evaluate its hydrodynamic radius (r_H) by using the Stokes−Einstein equation.[26] Values of D_t were obtained for deapH and $[InCl_3(deapH)]_n$ as the slope of each best fit line in Figure S9 (Supporting Information) while r_H was calculated according to methods outlined by Macchioni and co-workers[25b] using tetramethylsilylsilane (TMSS) as an internal standard (see Supporting Information for details). From the experimental PGSE data, diffusion coefficients of 18.3×10^{-10} m^2 s^{-1} (deapH), 13.4×10^{-10} m^2 s^{-1} (TMSS), and 8.5×10^{-10} m^2 s^{-1} ($[InCl_3(deapH)]_n$) were determined in CD_2Cl_2 at a concentration (*ca.* 5 mM) similar to that employed for D,L-LA polymerizations. The fact that the D_t value for the ligand is approximately double that of $[InCl_3(deapH)]_n$ is consistent with the latter being dinuclear ($n = 2$). Furthermore, inserting the D_t values into the modified[25b] Stokes−Einstein equation allowed values of r_H for $[InCl_3(deapH)]_n$ and deapH of 5.8 and 3.4 Å, respectively, to be calculated (Supporting Information). For comparison, the hydrodynamic radii values were estimated from the X-ray crystal structure ($r_{X\text{-ray}}$) of $[InCl_3(deapH)(H_2O)]_2$, a hypothetical monomer $InCl_3(deapH)(H_2O)$, and deapH and found to be 5.9, 3.9, and 3.3 Å, respectively.[27,28] The close agreement between the r_H and $r_{X\text{-ray}}$ values for deapH as well as between $r_{X\text{-ray}}$ for $[InCl_3(deapH)(H_2O)]_2$ and r_H for its anhydrous form in CD_2Cl_2 supports a dinuclear structure for the latter. This conclusion is further corroborated by (a) the similarity between the D_t values for the indium complex and a similarly sized bis(phenolato)amine zinc(II) complex reported previously[29] (*ca.* 7.2×10^{-10} m^2 s^{-1}) and (b) comparison of these D_t values and those reported previously for molecules of varying sizes (Figure S10, Supporting Information). In sum, the PGSE data are consistent with retention of a dinuclear $[InCl_3(deapH)]_2$ structure in solution under similar conditions (∼5 mM CD_2Cl_2, 21 °C) to those used in LA polymerizations.

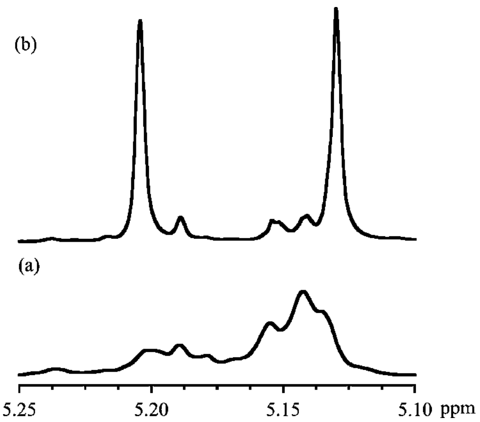

Figure 8. Homonuclear decoupled ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of the methine region of PLA prepared from D,L-LA and (a) $[In(OCH_2CH_2OCH_3)_3]_n$ and (b) a 1:0.5 mixture (molar) of $[In(OCH_2CH_2OCH_3)]_n$ and $InCl_3$.

To further test our ideas on the importance of the halide ligand in the $InCl_3$/BnOH/NEt_3 system, we examined the catalytic behavior of the indium alkoxide complex $[In(OCH_2CH_2OCH_3)]_n$[30] and 0.5 mol equiv of that complex and $InCl_3$. While the homoleptic alkoxide effectively polymerizes D,L-LA, the product PLA is atactic (Figure 8a, [D,L-LA]$_0$ = 1 M, CH_2Cl_2/THF = 86:14). In contrast, the mixture with $InCl_3$ yielded highly heterotactic PLA ($P_r = 0.91$, Figure 8b). Taken

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(24) The hydrated form of the complex polymerized D,L-LA, but at a slower rate and with slightly decreased stereocontrol. Thus, for [D,L-LA]$_0$/$[[InCl_3(deapH)H_2O]_2]_0$ = 110 and [D,L-LA]$_0$ = 0.7 M, polymerization proceeded to 30% conversion with the polymer having a predominantly heterotactic microstructure ($P_r = 0.82$), reaching 50% conversion after 27 h ($P_r = 0.86$), and reaching a conversion plateau of 60% after 100 h ($P_r = 0.82$).

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(26) Edward, J. T. *J. Chem. Educ.* **1970**, *47*, 261–270.

(27) Price, W. S. In *New Advances in Analytical Chemistry*; Atta-ur-Rahman, Ed.; Hardwood Academic Publishers: Singapore, 2000; pp 31−72.

(28) The values of $r_{X\text{-ray}}$ for $[InCl_3(deapH)(H_2O)]_2$ and the hypothetical $InCl_3(deapH)(H_2O)$ were calculated using the equation $r_{X\text{-ray}} = (ab^2)^{1/3}$, where *a* and *b* are the semiaxes of a hypothetical prolate ellipsoid estimated from the space-filling diagram of $[InCl_3(deapH)(H_2O)]_2$. For deapH, the equation $r_{X\text{-ray}} = (a^2b)^{1/3}$ was used, where *a* and *b* are the semiaxes of a hypothetical oblate ellipsoid estimated from the space-filling diagram of $[InCl_3(deapH)(H_2O)]_2$.

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Table 1. Polymerization of CL in CH_2Cl_2[a]

Entry	$[CL]_0/[BnOH]_0$	$[InCl_3]_0/[BnOH]_0$	T (°C)	t (h)	% Conv[b]	M_n (kg mol^{-1})	PDI[c]
1	24	1	25	8	96	6.5	1.07
2	50	1	25	18	99	16.6	1.09
3	100	1	25	24	99	32.0	1.16
4	100	2	25	25	95	30.1	1.34
5	100	3	25	25	95	31.9	1.40
6	196	1	25	48	99	56.7	1.09
7[d]	392	1	60	50	98	83.7	1.65

[a] $[CL]_0 \approx 0.7-1$ M. $NEt_3/BnOH/InCl_3 = 2{:}1{:}1$. [b] Determined by ^1H NMR spectroscopy. [c] Determined by SEC (relative to polystyrene in $CHCl_3$). [d] $[CL]_0 \approx 7$ M.

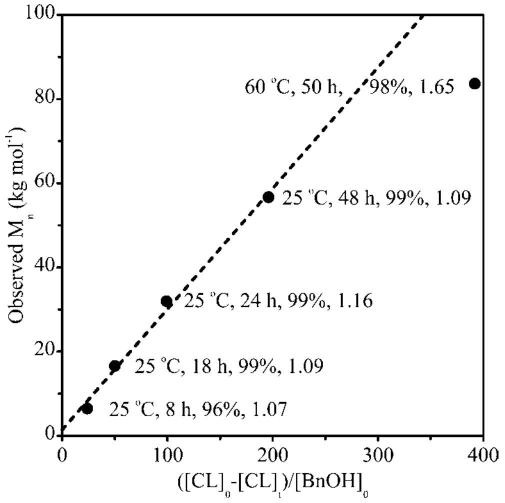
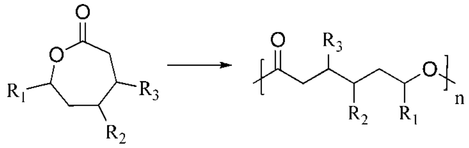


Figure 9. Plot of M_n vs $([CL]_0 - [CL]_t)/[BnOH]_0$ for the polymerization of CL by $InCl_3/BnOH/NEt_3$ (1:1:2). Conditions: $[CL]_0 \approx 0.7-1$ M, CH_2Cl_2, 25 °C. Listed with each data point are temperature, reaction time, conversion, and PDI. M_n determined by SEC (relative to polystyrene in $CHCl_3$).

together, the combined data show that the nature of the ligands on the indium(III) center has a major affect on the polymerization rate and tacticity, with the presence of chloride being essential for observation of significant stereocontrol. Moreover, the data are consistent with the hypothesis that the initiating species in the $[In(OCH_2CH_2OCH_3)]_n/InCl_3$,[31] $[InCl_3(deapH)]_2$, and $InCl_3/BnOH/NEt_3$ systems are structurally analogous complexes of the type $[InCl_{(3-n)}(OR)_n]_m$.

Polymerization of *ε*-Caprolactone and Other Cyclic Esters. In an exploration of the scope of the $InCl_3/BnOH/NEt_3$ system, polymerizations of a variety of cyclic esters were examined. For example, when ε-caprolactone (CL) (100 equiv) was added to a stirring solution of $InCl_3$ (1 equiv), BnOH (1 equiv), and NEt_3 (2 equiv) in CH_2Cl_2 ($[CL]_0 \approx 0.84$ M), poly(ε-caprolactone) (PCL) with $M_n = 32.0$ kg/mol and PDI = 1.16 was produced (entry 3, Table 1). After 6.5 h at 25 °C, the reaction proceeded to 48% conversion, reaching 99% conversion after 24 h. This polymerization is slower compared to that of D,L-LA, which proceeds to 96% conversion in 2.5 h under similar conditions. The PDI values (entries 3−5, Table 1) were found to increase with the $[InCl_3]_0/[BnOH]_0$ ratio, as discussed for the polymerization of D,L-LA using this system as well.[13] At $[InCl_3]_0/[BnOH]_0 = 1$, good control of PCL molecular weight was observed (Figure 9, entries 1−3 and 6, Table 1), but only over a narrow range of monomer/alcohol ratios (*ca.* $([CL]_0 - [CL]_t)/[BnOH]_0 \approx 25-200$). At $[CL]_0/[BnOH]_0 \approx 400$, conversions were found to plateau at *ca.* 40%. These reactions could be driven to near complete conversion when carried out at a higher temperature and concentration (60 °C; entry 7, Table 1).

Scheme 2. Polymerization of Seven-Membered Lactones



CL	$R_1 = H, R_2 = H, R_3 = H$	PCL	$R_1 = H, R_2 = H, R_3 = H$
1	$R_1 = CH_3, R_2 = H, R_3 = H$	poly-**1**	$R_1 = CH_3, R_2 = H, R_3 = H$
2	$R_1 = H, R_2 = CH_3, R_3 = H$	poly-**2**	$R_1 = H, R_2 = CH_3, R_3 = H$
3	$R_1 = i\text{-Pr}, R_2 = H, R_3 = CH_3$	poly-**3**	$R_1 = i\text{-Pr}, R_2 = H, R_3 = CH_3$

Table 2. Polymerizations of Cyclic Esters **1**−**3**[a]

Entry	Monomer (M)	$[M]_0/[BnOH]_0$	T (°C)	t (h)	% Conv[b]	M_n (kg mol^{-1})	PDI[c]
1[d]	**1**	93	60	24	87	19.9	1.05
2[e]	**1**	115	60	24	99	20.2	1.30
3[d]	**2**	100	25	24	97	19.6	1.20
4[d]	**2**	106	60	24	95	20.0	1.62
5[e]	**2**	99	60	24	99	21.8	1.78
6[e]	**3**	102	65	25	99	22.9	1.13

[a] $NEt_3/BnOH/InCl_3 = 2{:}1{:}1$. [b] Determined by ^1H NMR spectroscopy. [c] Determined by SEC (relative to polystyrene in $CHCl_3$). [d] $[M] \approx 0.7-0.9$ M. [e] $[M] \approx 4$ M.

The $InCl_3/BnOH/NEt_3$ system is also effective for the polymerization of 6-methyl-ε-caprolactone (**1**),[32] 4-methyl-ε-caprolactone (**2**),[32,33] and (−)-menthide (**3**)[34] (Scheme 2, Table 2). With the structurally diverse architectures of the monomers (*M*) in mind, three sets of polymerization conditions were used: (a) $[M]_0 \approx 0.7-0.9$ M, CH_2Cl_2, 25 °C; (b) $[M]_0 \approx 0.7-0.9$ M, CH_2Cl_2, 60 °C; and (c) $[M]_0 \approx 4$ M, CH_2Cl_2, 60 °C. Unlike **2**, monomers **1** and **3** did not polymerize under condition (a), which we attribute to steric effects imparted by the alkyl substituents at the 6-position of the lactone. Monomers **1** and **3** polymerize (entries 2 and 6, Table 2) under condition (c) to yield poly-**2** and poly-**3** respectively with relatively low PDIs. The high monomer concentration and temperature required for monomer **3** may be attributed to a combination of the steric effects imparted by the alkyl substituents at the 3- and 6-positions of the lactone.

Summary and Conclusions

A catalytic initiator prepared *in situ* from indium(III) chloride, benzyl alcohol, and triethylamine exhibits excellent stereochemical control in the polymerization of D,L-LA despite the absence of an ancillary "directing" ligand that is typically required in other catalyst systems. We observed linear relationships between M_n and both monomer conversion and monomer to alcohol ratio (*ca.* 50−800) (Figures 1 and 2) that support a controlled polymerization process affording highly heterotactic PLA with narrow PDIs. In addition, this system was also shown to successfully initiate the ring-opening polymerization of a variety

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(31) It is relevant to note that $[InCl_{(3-n)}(CH_2Ph)_n]_2$ complexes may be prepared by appropriate combination of $InCl_3$ and $In(CH_2Ph)_3$. See: Neumueller, B. *Z. Anorg. Allg. Chem.* **1991**, *592*, 42–50.

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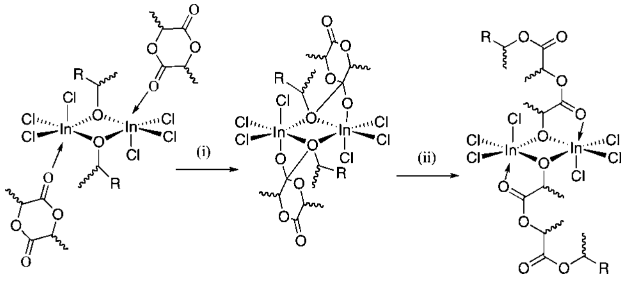
of seven-membered ring lactones. These findings for such a simple catalyst system raise intriguing questions about the polymerization mechanism, particularly pertaining to the nature of the active catalyst, which we addressed through varied experimental approaches.

Combined MALDI-TOF MS and ^{1}H NMR spectroscopic data acquired from PLA oligomers support a polymerization process initiated by BnOH insertion. A series of kinetic experiments revealed the rate of polymerization to be first-order in $[InCl_3]_0$ and zero-order in $[BnOH]_0$ and $[NEt_3]_0$ indicating that the *in situ* generation of initiator is fast with respect to polymerization. Several pieces of data indicate that the halide is a critical structural component in the active catalyst that affects both the rate and stereocontrol of monomer enchainment. Thus, the rate of polymerization of D,L-LA was found to decrease by an order of magnitude upon switching the indium(III) source from $InCl_3$ to $InBr_3$, with reactions using InI_3 being even more sluggish. Polymerizations employing $[In(OCH_2CH_2OCH_3)_3]_n$ were found to initiate the polymerization of D,L-LA, but the product was atactic; highly heterotactic PLA was isolated when $[In(OCH_2CH_2OCH_3)_3]_n$ was mixed with $InCl_3$. Finally, while structural characterization of the species resulting from mixture of $InCl_3$, BnOH, and NEt_3 has been elusive, the X-ray structure of $[InCl_3(deapH)(H_2O)]_2$ was obtained and the dehydrated derivative $[InCl_3(deapH)]_2$ was shown to polymerize D,L-LA with a high degree of stereoselectivity. Moreover, ^{1}H NMR, FTIR, and PGSE spectroscopy results indicate that the dinuclear structure is retained in solution under the same conditions used in polymerizations of D,L-LA. On the basis of these results, we suggest that similar structures are adopted by the catalytically active species generated upon mixing $InCl_3/BnOH/NEt_3$ or $[In(OCH_2CH_2OCH_3)_3]_n/InCl_3$ and that these are complexes of the type $[InCl_{(3-n)}(OR)_n]_m$. The role of the amine in the former system is to act as a base, as evidenced by the presence of a trialkyl ammonium moiety in the X-ray structure of $[InCl_3(deapH)(H_2O)]_2$ and the high degree of heterotacticity observed in PLA polymers prepared using the non-nucleophilic base Proton Sponge in lieu of NEt_3.

The ~12-fold difference between the observed rate constants $k_{obs}^{D,L\text{-}LA}$ and $k_{obs}^{L\text{-}LA}$ illustrates the propensity of the $InCl_3/BnOH/NEt_3$ system to favor racemic enchainment. Also noteworthy is the similarity between $k_{obs}^{meso\text{-}LA}$ and $k_{obs}^{D,L\text{-}LA}$, despite the lack of stereoselectivity observed in the former ($P_r^{exp} \approx 0.56$). These findings support a mechanism where both the rate of polymerization and selectivity of monomer enchainment are dictated by multiple stereocenters of the monomer and/or polymer chain end. Studies on the polymerization kinetics of a diastereomeric mixture of L-LA and *meso*-LA led us to develop a protocol for purifying D-LA spiked with small amounts (*ca*. 5%) of L-LA and *meso*-LA. This purification protocol could be useful when either D- or L-LA of high optical purity is required.

Based on our observations, we propose that LA polymerization occurs via a coordination−insertion mechanism that employs an $[InCl_{(3-n)}(OR)_n]_m$ propagating species (with R_3NH^+ as the counterion), drawn as a dinuclear complex ($m = 2$) in Scheme 3 by analogy to the X-ray structure of the model $[InCl_3(deapH)(H_2O)]_2$. We hypothesize that a lactide molecule coordinates to the Lewis acidic indium center via a carbonyl oxygen, perhaps at the site where water binds in $[InCl_3(deapH)(H_2O)]_2$. Subsequent insertion into the indium−alkoxide bond would occur via nucleophilic attack of the alkoxide on the LA carbonyl carbon (step i) and cleavage of the acyl−oxygen bond (step ii). Rationalizing the stereocontrol exhibited in this system is challenging, and at this juncture we can only speculate on the basis of precedent provided by theoretical analysis of the stereoselective polymerization of D,L-LA to heterotactic PLA by (BDI)MgOMe.[35] As proposed for that system, we hypothesize that energy differences in the environment created by a combination of steric and electronic effects imparted by the halide(s) and multiple stereocenters of the growing polymer chain end during propagation dictate the rate of monomer insertion and stereocontrol. Evidently, the steric effects are substantial despite the absence of a hindered ancillary supporting ligand that is typically required for stereocontrol in polymerizations catalyzed by metal−alkoxide complexes.

Scheme 3. Postulated Mechanism for LA Polymerization



Experimental Section

General Methods and Materials. All experiments were carried out in an inert atmosphere using dry solvents and reagents unless otherwise noted. All indium(III) halide salts, 3-diethylamino-1-propanol, *N*,*N*,*N*,*N*-tetramethyl-1,8-naphthalenediamine (Proton-sponge), tetramethylsilylsilane, and benzyl alcohol were purchased from Aldrich and used as received. Deuterated solvents were purchased from Aldrich and dried over calcium hydride. Triethylamine and ε-caprolactone were purchased from Acros and distilled over calcium hydride. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and degassed 3× using freeze−pump−thaw techniques. Toluene was distilled from sodium and benzophenone and degassed using freeze−pump−thaw techniques. D-Lactide, L-lactide, and D,L-lactide (Purac) were purified by recrystallization from toluene followed by vacuum sublimation. *meso*-Lactide was obtained from NatureWorks and purified by recrystallization from isopropanol (2×) and then toluene (2×) and dried under vacuum for 48 h. Pentane was passed through a purification column (Glass Contour, Laguna, CA) prior to use. Monomers **1**,[32] **2**,[32,33] and **3**[34] were prepared according to literature methods. All reagents were stored in a dinitrogen-filled MBraun UNIlab glovebox.

Physical Methods. All ^{1}H NMR homonuclear spectra were collected on either Varian Inova 500 or Varian Inova 300 spectrometers and referenced to the residual protonated solvent peaks at δ 7.24 for deuterated chloroform ($CDCl_3$) or δ 5.32 for deuterated methylene chloride (CD_2Cl_2). All ^{1}H NMR homonuclear decoupled spectra were collected on a Varian Inova 500 spectrometer and calibrated to the residual protonated solvent at δ 7.24 for deuterated chloroform ($CDCl_3$). All optical rotation experiments were carried out on a Jasco DIP-370 digital polarimeter. Molecular weights (M_n and M_w) and polydispersity indices (M_w/M_n) were determined by size exclusion chromatography (SEC). SEC was performed using a Hewlett-Packard 1100 series liquid chromatograph with chloroform as the mobile phase at 35 °C. The chromatograph was equipped with 3 Varian PLgel Mixed C columns and a PLgel 5 μm guard column. Output was detected with an HP1047A differential refractive index detector using an eluent flow rate of 1 mL/min and a 50 μL injection loop. Molecular weights were determined from a 10-point calibration curve created using

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(35) Marshall, E. L.; Gibson, V. C.; Rzepa, H. S. *J. Am. Chem. Soc.* **2005**, *127*, 6048–6051.

polystyrene standards purchased from Polymer Laboratories. MALDI-TOF mass spectrometry was performed on a Bruker Reflex III MALDI-TOF mass spectrometer equipped with a pulsed nitrogen laser operating at 337 nm with a maximum average power of 6 mW. 2,5-Dihydroxybenzoic acid (DHB) was used as the matrix material, and tetrahydrofuran was used as the solvent. Insulin (from bovine pancreas) was used as the calibration standard. Solid-state IR spectra were obtained on an Avatar 370 FTIR ThermoNicolet spectrometer. PGSE NMR experiments were carried out on a Varian Inova 300 MHz spectrometer equipped with a 4-nucleus pulsed field gradient probe using a bipolar gradient pulse stimulated echo sequence with convection compensation.[36,37] Each experiment was performed at ∼21 °C using a spectral width of 2580 Hz, a 90° pulse width of 17 μs, a diffusion delay time of 0.05 s, and a total diffusion-encoding pulse width of 0.002 s. The diffusion encoding pulse strength was arrayed from 0 to 33.2 G cm^{-2} over 15 increments with four steady-state scans and 16 scans per increment.

Synthesis of $[InCl_3(deapH)]_2$/$[InCl_3(deapH)(H_2O)]_2$. Under a dinitrogen atmosphere, 3-diethylamino-1-propanol (deapH; 100 μL, 0.67 mmol) was added to a stirring suspension of $InCl_3$ (150 mg, 0.68 mmol) in CH_2Cl_2 (9 mL) and the subsequent clear and colorless solution was left to stir for 12 h. An off-white solid was precipitated out of solution by adding the mixture to stirring pentane (30 mL), isolated on a glass frit, and dried in vacuo (96% yield). Single crystals of $[InCl_3(deapH)(H_2O)]_2$ were grown over a period of 2 months by diffusion of pentane vapor into a $[InCl_3(deapH)]_n/CH_2Cl_2$ solution and were isolated from a residual soft solid. **($[InCl_3(deapH]_2$):** ^{1}H NMR (CD_3CN, 500 MHz) δ 4.01 (4H, br s, OCH_2), 3.25 (12H, br s, $CH_2N(CH_2CH_3)_2$), 1.90 (br s, $N(CH_2CH_3)$), 1.25 (12H, t, $^3J_{HH}$ = 7.29 Hz, $N(CH_2CH_3)$). ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 4.18 (4H, br s, OCH_2), 3.36 (12H, br s, $CH_2N(CH_2CH_3)_2$), 2.05 (4H, br s, $N(CH_2CH_3)$), 1.32 (12H, t, $^3J_{HH}$ = 7.20 Hz, $N(CH_2CH_3)$). ^{13}C NMR (CD_3CN, 125 MHz) δ 61.97, 53.33, 47.71, 27.26, 8.79. IR (cm^{-1}): 3059, 1470, 1393, 1063, 936, 829, 793. **($[InCl_3(deapH)(H_2O)]_2$):** ^{1}H NMR (CD_3CN, 500 MHz) δ 3.71 (4H, br s, OCH_2), 3.16 (12H, m, $CH_2N(CH_2CH_3)_2$), 2.14 (4H, s, H_2O), 1.86 (4H, p, $^3J_{HH}$ = 5.72 Hz, $OCH_2CH_2CH_2NEt_2$), 1.25 (12H, t, $^3J_{HH}$ = 7.29 Hz, $N(CH_2CH_3)$). IR (cm^{-1}): 3419, 3066, 1622, 1472, 1389, 1057, 930, 894, 871, 829. Anal. Calcd for $C_{14}H_{38}Cl_6In_2N_2O_4$: C, 22.70; H, 5.17; N, 3.78; Cl, 28.71. Found: C, 22.60; H, 5.39; N, 4.37; Cl, 28.20.

General Procedure for Synthesis of PLA. Polymerizations were performed using ∼1 M monomer solutions (in CH_2Cl_2) prior to addition of the appropriate volumes of BnOH and amine stock solutions (0.276 M in CH_2Cl_2). A typical procedure for the polymerization of LA is as follows: Under an inert atmosphere, BnOH (1 equiv) was added to a stirring suspension of InX_3 (1 equiv) in an LA solution. After 5−10 min of stirring, NEt_3 (2 equiv) was added after which the indium salt began to dissolve. Once the reaction reached near complete conversion (95−98%), the polymer was precipitated out of solution upon dropwise addition to cold wet methanol (0 °C, 20 mL of methanol/1.38 mL of reaction solution). The polymer was isolated and dried under high vacuum for 48 h.

General Procedure for the in Situ Observation of LA Polymerization. Polymerizations were monitored using ^{1}H NMR spectroscopy unless otherwise noted. In a glovebox, appropriate volumes of BnOH and NEt_3 stock solutions (0.276 M in CH_2Cl_2) were added to a scintillation vial charged with LA (∼400 mg), the appropriate amount of InX_3, and CD_2Cl_2. Volumes of CD_2Cl_2 were adjusted so that $[LA]_0 \approx 0.84$ M after the addition of BnOH and NEt_3. Once the suspension dissolved, an aliquot was placed in an NMR tube that was later sealed and placed in the spectrometer probe. In the case of experiments outlined in Figures S4 and S5, polymerizations were monitored by IR spectroscopy using a Mettler Toledo ReactIR iC10 spectrometer. In the glovebox, a reaction flask was charged with appropriate amounts of D,L-LA, CH_2Cl_2, $InCl_3$,and BnOH. The flask was removed from the glovebox and attached to the spectrometer probe using a ground glass joint under a positive pressure of N_2. The appropriate volume of NEt_3 was then injected into the flask through a septum. A peak due to D,L-LA at 938 cm^{-1} was monitored: analysis of [D,L-LA] decay was consistent with results obtained using ^{1}H NMR spectroscopy.

Procedure for Removing Isomeric Impurities from D-LA. An isomeric mixture of LA (500 mg, 3.46 mmol, D-LA/L-LA/*meso*-LA = 90:5:5) dissolved in CD_2Cl_2 (3.5 mL) was added to a scintillation vial charged with $InCl_3$ (6 mg, 0.027 mM), BnOH (100 μL, 0.276 M stock solution, CH_2Cl_2), and NEt_3 (200 μL, 0.276 M stock solution, CH_2Cl_2). After 2 h of stirring at 25 °C, the solvent was removed under reduced pressure. ^{1}H NMR analysis revealed that the reaction proceeded to 30% conversion with no evidence of *meso*-LA present. The crude product (400 mg) was vacuum sublimed (50 °C, 100 mTorr, 3.25 h) affording LA (200 mg, 50% yield) with $[\alpha]_D^{25} = +279$ (*c* 5.1, $CHCl_3$), a value consistent with our pure-stock D-LA ($[\alpha]_D^{25} = +276$ (*c* 5.1, $CHCl_3$)).

General Procedure for Polymerization of CL. ε-Caprolactone was added to a scintillation vial charged with BnOH (100 μL, 0.276 M stock solution, CH_2Cl_2), NEt_3 (200 μL, 0.276 M stock solution, CH_2Cl_2), and $InCl_3$ (∼6 mg, 0.027 mM) in CH_2Cl_2. The volume of CH_2Cl_2 was adjusted such that $[CL]_0$ = 0.7−0.9 M. After the reaction reached near complete conversion (96−98%), the polymer was precipitated out of solution upon dropwise addition to cold wet methanol (0 °C, 20 mL of methanol/1.38 mL of reaction solution). The polymer was isolated on a Buchner funnel and dried for 24 h.

General Procedure for Polymerization of Monomers 1−3. A pressure bomb was charged with $InCl_3$ (∼6 mg, 0.027 mM), BnOH (100 μL, 0.276 M stock solution, CH_2Cl_2), and NEt_3 (200 μL, 0.276 M stock solution, CH_2Cl_2) before appropriate amounts of monomer (and CH_2Cl_2 if necessary) were added. The reactions were left to stir for periods listed in Table 2. A heated oil bath was employed for reactions requiring elevated temperatures. After the reactions were complete, the reaction solutions were concentrated and precipitated in cold methanol (*ca.* 0°). The clear viscous polymers were isolated by decantation and dried *in vacuo* overnight.

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Supporting Information Available: Polymerization, spectroscopic, PGSE, and kinetic data (Tables S1−S4, Figures S1−S8), method used to interpret the PGSE data, and X-ray crystallographic data in cif format. This material is available free of charge via the Internet via http://pubs.acs.org.

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