Lactide Polymerization

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A Highly Active Chiral Indium Catalyst for Living Lactide Polymerization**

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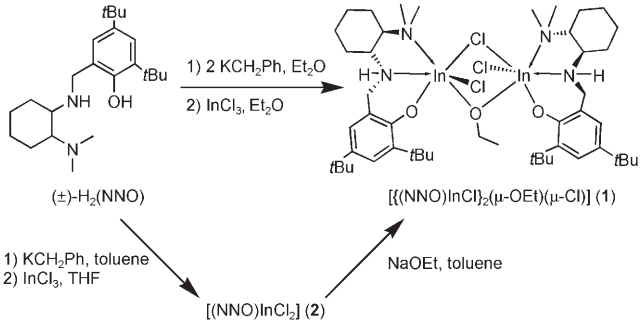
Poly(lactic acid) (PLA), produced by ring-opening polymerization (ROP) of lactide (LA),[1,2] is a leading biodegradable and biocompatible polyester with wide-ranging applications.[3] Several well-defined Lewis acid catalysts have been developed for this reaction; prominent among them are metal alkoxides based on aluminum,[4–8] zinc,[9–11] and rare-earth metals,[12–14] as well as organocatalysts.[15–18] Known systems have successfully addressed one or more important factors in the ROP of LA, such as activity[9] and catalyst toxicity.[19] Enantioselectivity, in particular, has garnered much attention, and catalysts with exquisite control over PLA tacticity have been reported.[20,21] Two modes of selectivity have been explored, enantiomorphic site control and chain-end control. These modes are not independent of each other; chain-end control can play an important role in systems that exhibit site control.[22] Nevertheless, in most cases examples of highly selective catalysts that exhibit site control remain confined to aluminum salen complexes,[23] which have low reactivity and functional-group tolerance. Investigation of new, active, and functional-group-tolerant chiral Lewis acidic catalysts that promote enantiomorphic site control is necessary to expand our understanding of tacticity control in PLA.

Herein we report the synthesis, reactivity, and polymerization behavior of a chiral indium catalyst capable of rapid and living ROP of lactide. Although aluminum compounds have been used extensively as lactide polymerization catalysts, to our knowledge this is the first example of an indium catalyst for the ROP of lactide.[24] We chose indium as the metal center because of the proven functional-group tolerance of indium(III) catalysts in a myriad of organic transformations, some of which have been carried out in water.[25,26] Preliminary studies show that our chiral ligand platform, based on asymmetrically substituted *trans*-diaminocyclohexane, contributes to site control of PLA tacticity. The ligand was inspired by the exceptionally active achiral zinc catalysts for LA ROP reported by Hillmyer, Tolman, and co-workers which generate exclusively atactic PLA.[9] The synthesis of the proligand H_2(NNO) (see Scheme 1) is based on a report by Mitchell and Finney.[27]

Our catalyst is an unusual alkoxy-bridged dinuclear indium complex. Reaction of a racemic mixture of (±)-H_2(NNO) with two equivalents of KCH_2Ph forms (±)-KH(NNO) and KOEt,[28] which are not separated and upon addition to $InCl_3$ form [{(NNO)InCl}$_2$(μ-OEt)(μ-Cl)] (**1**) in a one-pot route (Scheme 1). Alternatively, the reaction



Scheme 1. Different routes for the synthesis of **1**.

between (±)-KH(NNO) and $InCl_3$ gives [(NNO)$InCl_2$] (**2**), which can be converted into **1** by reaction with NaOEt (see the Supporting Information). The molecular structure of **1**, determined by single-crystal X-ray crystallography, shows two octahedral indium centers, asymmetrically bridged with chloride and ethoxy ligands (Figure 1). Interestingly, the crystal structure shows only one enantiomer of the complex, (*RR*,*RR*)-**1**. The dinuclear nature of **1** is maintained in solution; only one set of ethoxide and NNO signals is observed by ^{1}H NMR spectroscopy, and the ratio of ethoxide to NNO methylene protons is 1:2, indicating the persistence

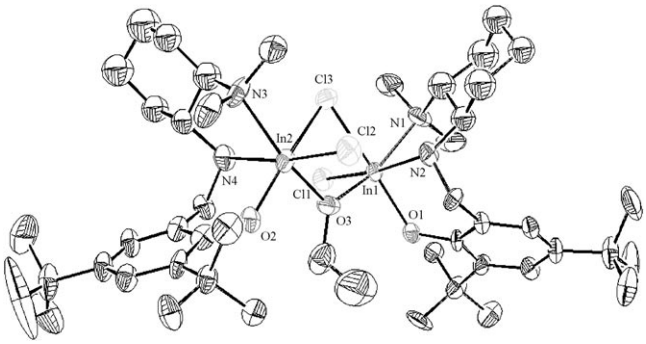


Figure 1. Molecular structure of **1** with thermal ellipsoids set at 35% probability. Hydrogen atoms are omitted for clarity.

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of a dinuclear species in solution. The solution structure is further corroborated by ^{13}C and correlation NMR experiments (see the Supporting Information). Since we are using (±)-H_2(NNO) for the formation of **1**, we expect both (*RR*,*RR*)-**1** and (*SS*,*SS*)-**1** to form; however, these enantiomers have the same NMR pattern at room temperature. Homochiral **1** forms exclusively; we have found no evidence for the formation of (*RR*,*SS*)-**1**. An enantiopure version of the catalyst prepared from (+)-H_2(NNO), **1***, has identical NMR features to **1**.

Complex **1** is an active catalyst for the ROP of lactide. In reactions monitored to 90% conversion by ^1H NMR spectroscopy (25°C, CD_2Cl_2), 200 equivalents of *rac*-LA were converted into PLA in 30 min. This result is comparable to the most active reported catalysts and is significantly faster than aluminum salen complexes, which usually require several hours at elevated temperatures to convert LA under otherwise similar conditions.[5,21] Polymerization of *rac*-LA catalyzed by **1** is living. We observed an initiation phase with subsequent first-order conversion of 100 equivalents LA up to 90% conversion, at which time the polymerization rate decreases exponentially until 100% conversion ($k = 0.56(18)\ s^{-1}M^{-1}$). Addition of a further 100 equivalents *rac*-LA to this reaction mixture results in full conversion with similar polymerization kinetics ($k = 0.59(18)\ s^{-1}M^{-1}$). In reactions where the concentration of *rac*-LA is held constant and the concentration of **1** is changed, polymerization is first order in [**1**], giving an overall second-order rate law for LA consumption (rate $= k$[**1**][LA]).[29] Polymerization reactions were also carried out in the temperature range of −5 to 32°C, and activation parameters were obtained from the resulting Eyring plot ($\Delta H^{\ddagger} = 49(2)\ kJ\,mol^{-1}$, $\Delta S^{\ddagger} = -140(12)\ J\,K^{-1}\,mol^{-1}$; see the Supporting Information). These values are in agreement with reported values and indicate an ordered transition state in a coordination insertion mechanism.[30,31]

Gel permeation chromatography (GPC) data corroborate our mechanistic investigation. In reactions taken to complete conversion, yields of isolated polymer are between 85 and 100%. The plot of observed M_n value versus added monomer for greater than 200 equivalents *rac*-LA follows closely the values expected for involvement of one indium center in ROP (Figure 2). The PDI values for these samples are between 1.09 and 1.14 and, along with the kinetics data, confirm a living polymerization system. At lower monomer concentrations the observed M_n value is significantly higher than expected and the PDI value increases to 1.2. The high M_n value indicates that at low monomer concentration a reduced number of active catalyst sites are available for polymerization, and the higher PDI value indicates a range of available catalyst sites.

Equilibrium between dinuclear and mononuclear species plays an important role in this system and provides an explanation for the above observations (Scheme 2). We know that at room temperature the dinuclear complex **1** is not prone to dissociation in the absence of a coordinating species, while in the presence of a donor such as pyridine the breakup into mononuclear species occurs (see the Supporting Information). Thus, dissociation of **1** upon addition of LA

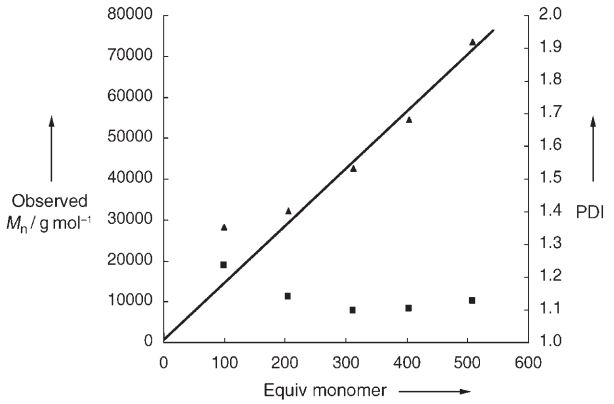
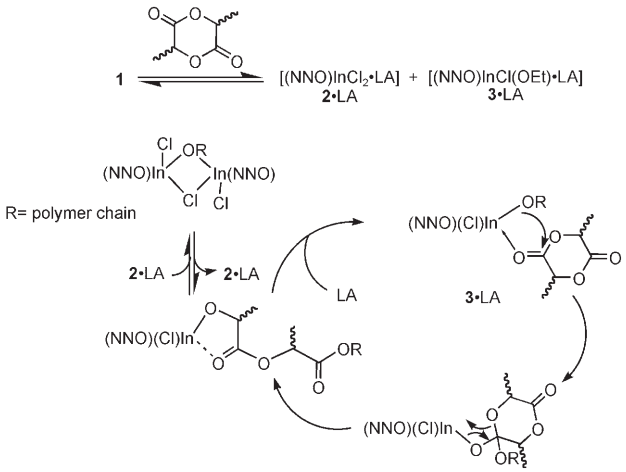


Figure 2. Plot of observed PLA M_n (▲, left-hand axis) and molecular weight distribution (■, right-hand axis) as functions of added monomer (M_n = number-averaged molecular weight, PDI = polydispersity index). The line indicates calculated M_n values based on monomer added.



Scheme 2. Proposed mechanism for ROP of LA with **1**.

to form adducts [(NNO)$InCl_2$·LA] (**2**·LA), presumably inactive, and [(NNO)InCl(OEt)·LA] (**3**·LA), the active catalyst, constitutes the initiation phase of polymerization. Chain-end analysis by ^1H NMR spectroscopy shows ethoxy groups and confirms the reactivity of **3** (see the Supporting Information). At high LA concentrations, propagation occurs through a coordination–insertion mechanism. However, at low LA concentrations polymerization is slow, likely owing to formation of a new dinuclear complex that removes active sites from the catalytic cycle, effectively decreasing the concentration of the catalyst. Formation of this dinuclear species is reversible, and, as with **1**, upon addition of more LA it can dissociate and re-enter the reaction cycle.

Complex **1**, formed from (±)-H_2(NNO), shows modest isoselectivity for the polymerization of *rac*-LA ($P_m = 0.53$–0.62; see the Supporting Information).[32] As discussed above, **1** most likely exists as a pair of enantiomers, (*RR*,*RR*)-**1** and (*SS*,*SS*)-**1**. Polymerization of L-LA with **1** results in entirely isotactic PLA and rules out intermolecular transesterification as a scrambling mechanism. Significantly, preliminary reactions indicate that site control is an important mechanism for

tacticity control in this system. When a sample of **1** derived from (+)-H_2(NNO), **1***, is used as a catalyst, a marked *decrease* in polymerization activity and in P_m values is observed. The k_{obs} value for ROP of *rac*-LA with a 2.7 mM solution of **1*** (2.1×10^{-4} s^{-1}) is roughly an order of magnitude less than that obtained with **1** (1.5×10^{-3} s^{-1}) and the P_m value for **1*** is 0.43 (0.59 for **1**). The rate of ROP of L-LA with **1*** is yet slower ($k_{obs} = 4.4 \times 10^{-5}$ s^{-1}).

Chain-end control alone cannot account for such a drastic change in activity and tacticity upon using an enantiopure catalyst; however, significant decreases in rate have been observed in the kinetic resolution of racemic monomers through enantiomorphic site control.[33] Thus, in reactions with **1*** that are taken to 100% conversion the catalyst may be reacting with mismatched monomer units, which would result in the significantly lower observed rates. The decreased tacticity may be due to a conflict between chain-end and site-control mechanisms at higher conversions, which has been observed in olefin polymerization.[34] In experiments with mixtures of **1** and **1*** the dependence of polymerization isoselectivity and activity on the optical purity of the ligand was nonlinear (see the Supporting Information).[35] Further mechanistic studies are underway to study these nonlinear effects and elucidate the extent of enantiomorphic site control in the selectivity of the system.

In conclusion, we have developed the first indium catalyst for rapid, living lactide polymerization as demonstrated by kinetics studies and GPC data. This unique, asymmetrically bridged, chiral dinuclear indium complex can be easily synthesized in one step from the deprotonated ancillary ligand to form a pair of enantiomers selectively. The racemic catalyst **1** shows modest isoselectivity in LA polymerization. Interestingly, the enantiopure catalyst **1*** shows significantly *decreased* enantioselectivity in LA ROP, thus highlighting the importance of a site-control mechanism. To understand the mode of selectivity we are developing mononuclear versions of this system and are changing the ligand design to accommodate more bulky substituents.

Finally, with an indium system there is a possibility of functional-group-tolerant polymerization and catalyst recovery. Preliminary data show that in the presence of dry ethanol (5 equiv) the polymerization rate ($k = 0.71(11)$ $s^{-1}M^{-1}$), molecular weight distribution (1.2), and PLA tacticity ($P_m = 0.57$) remain unchanged, although molecular weights are significantly decreased (M_n(calcd) = 28054 g mol^{-1}, M_n(obs) = 13080 g mol^{-1}). In the presence of water, complex **1** is transformed quantitatively to a well-defined hydroxy-bridged dimer (see the Supporting Information).

Experimental Section

1: A slurry of KCH_2Ph (0.722 g, 5.55 mmol) in Et_2O was added to a stirred solution of (±)-H_2(NNO) (1.000 g, 2.775 mmol) in Et_2O (125 mL total, −34 °C). The resulting mixture was warmed to room temperature and stirred for 48 h. The resulting off-white solid was filtered, dried, and added as a slurry in Et_2O to a slurry of $InCl_3$ (0.608 g, 2.75 mmol) in Et_2O (150 mL total, −34 °C). The mixture was stirred at room temperature for a further period of 48 h. The resulting mixture was vacuum filtered through celite and washed with Et_2O (3 × 50 mL). The filtrate was dried and the resulting residue was taken up in pentane. The white precipitate was isolated by vacuum filtration to yield **1** (0.99 g, 0.90 mmol; 65% yield based on $InCl_3$ as the limiting reagent). X-ray-quality crystals were grown from cold toluene over one week. ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.61$ (1H, d, $J = 2.3$ Hz, ArH), 6.8 (1H, d, $J = 2.2$ Hz, ArH), 5.26 (1H, d, $J = 13.6$ Hz, NH-CH_2-Ar), 4.69 (1 h, m, OCH_2CH$_3$), 3.59 (1H, d, $J = 13.6$ Hz, NH-CH_2-Ar), 2.84 (1H, d, $J = 11.0$ Hz, R_2N-CH-CH$_2$), 2.66 (1H, m, R_2N-CH-CH$_2$), 2.52 (3H, s, N-CH$_3$), 2.42 (1H, br m, CH$_2$ of DACH), 2.20 (1H, d, $J = 4.3$ Hz, CH$_2$ of DACH), 1.95(2H, br m, CH$_2$ of DACH), 1.83 (9H, s, *t*Bu), 1.78 (3H, s, N-CH$_3$), 1.56 (1H, t, $J = 6.7$ Hz, O-CH$_2$-CH_3), 1.40 (9H, s, *t*Bu), 1.20 (2H, br m, CH$_2$ of DACH), 1.06 (1H, d, $J = 11.5$ Hz, CH$_2$ of DACH), 0.61 (2H, br m, CH$_2$ of DACH), 0.16 ppm (1H, br m, CH$_2$ of DACH), DACH = *trans*-diaminocyclohexane; ^{13}C NMR (C_6D_6 100 MHz): $\delta = 163.94, 140.33, 137.36, 127.11, 125.42, 120.01, 65.63, 64.07, 53.27, 51.93, 51.15, 44.85, 39.04, 36.71, 34.91, 32.92, 31.49, 31.36, 25.42, 25.27, 22.19, 20.59$ ppm. Elemental analysis (%) calcd for $C_{48}H_{83}Cl_3In_2N_4O_3$: C 52.40, H 7.60, N 5.09; found: C 51.96, H 7.53, N 5.03.

Crystal data for **1**·C_7H_8: $C_{62}H_{97}N_4O_3In_2Cl_3$, $M_r = 1282.43$, crystal dimensions $0.04 \times 0.08 \times 0.35$ mm^3, monoclinic, space group $P2_1/c$ (no. 14), $a = 16.905(2)$, $b = 20.967(2)$, $c = 18.428(1)$ Å, $\beta = 94.020(4)°$, $V = 6515(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.307$ g cm^{-3}, $F000 = 2680.00$, μ(Mo$_{K\alpha}$) = 8.74 cm^{-1}, λ(Mo$_{K\alpha}$) = 0.71073 Å, $2\theta_{max} = 45.0°$, 42181 reflections collected: unique = 8470 ($R_{int} = 0.062$). Final GooF = 1.10, $R1 = 0.081$, $wR2 = 0.168$, R indices based on 5395 reflections with $I > 2\delta(I)$ (refinement on F).

In situ observation of ROP of *rac*-LA: In a teflon-sealed NMR tube, **1** in CD_2Cl_2 (0.50 mL, 4.8 mM, 0.0024 mmol) was added to a solution of *rac*-LA (66 mg, 0.47 mmol) and 1,3,5-trimethoxybenzene (5 mg, 0.03 mmol) in CD_2Cl_2 (0.48 mL). The resulting solution was immediately frozen in liquid nitrogen, transported to the spectrometer, and was warmed to room temperature before it was inserted into the probe.

Large-scale polymerization of *rac*-LA: In a 20-mL scintillation vial, **1** in CH_2Cl_2 (1.00 mL, 4.6 mM, 0.0046 mmol) was added to a solution of *rac*-LA (129.3 mg, 0.92 mmol) in CH_2Cl_2 (6 mL). The solution was stirred for 16 h at room temperature, and then the volatiles were removed. The residue was dissolved in a minimum amount of CH_2Cl_2 and added to cold wet methanol (7 mL, 0 °C). The polymer precipitated and was isolated by centrifugation. The supernatant was decanted off, and the polymer was dried under high vacuum for 2 h prior to analysis.

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