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Tailor-Made Stereoblock Copolymers of Poly(lactic acid) by a Truly Living Polymerization Catalyst

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S *Supporting Information*

ABSTRACT: Poly(lactic acid) (PLA) is a biodegradable polymer prepared by the catalyzed ring opening polymerization of lactide. An ideal catalyst should enable a sequential polymerization of the lactide enantiomers to afford stereoblock copolymers with predetermined number and lengths of blocks. We describe a magnesium based catalyst that combines very high activity with a true-living nature, which gives access to PLA materials of unprecedented microstructures. Full consumption of thousands of equivalents of L-LA within minutes gave PLLA of expected molecular weights and narrow molecular weight distributions. Precise PLLA-*b*-PDLA diblock copolymers having block lengths of up to 500 repeat units were readily prepared within 30 min, and their thermal characterization revealed a stereocomplex phase only with very high melting transitions and melting enthalpies. The one pot sequential polymerization was extended up to precise hexablocks having "dialed-in" block lengths.

Poly(lactic acid) (PLA) is a degradable aliphatic polyester having broad commodity and biomedical applications,[1,2] which is prepared by the catalyzed ring-opening polymerization (ROP) of lactide (LA).[3,4] The two lactide enantiomers, L-LA and D-LA and their mixtures, may be employed for producing PLA, whose properties are determined by its microstructural regularity. Isotactic PLA, composed of identical repeat units of either L-LA or D-LA, is a crystalline polymer. PDLA and PLLA, the two enantiomeric homochiral strands, cocrystallize as a stereocomplex (SC) phase whose properties are superior to those of the homochiral (HC) crystal phase.[5,6] However, this crystallization tendency diminishes for higher molecular weight PLA.[7] To retain the stereocomplex crystallization tendency and to access sophisticated PLA architectures, isotactic stereoblock-PLA composed of covalently bound PDLA and PLLA blocks has been targeted. Possible strategies for obtaining stereoblock-PLA include the stepwise building of blocks on prepolymers, the attachment of presynthesized PDLA and PLLA strands having end-group linkers, and the polymerization of *racemic*-LA by isoselective catalysts.[8–14] These strategies pose limitations on the preciseness and complexity of the desired polymer architecture in terms of the integrity, the lengths and the number of the blocks. A more direct strategy for attaining stereoblock-PLA would be the one-pot sequential addition of the lactide enantiomers to a truly living polymerization catalyst,

namely, a catalyst lacking a termination step.[15] If successful, it should give rise to tailor-made copolymers having predetermined number and lengths of blocks, herein referred to as stereo-*n*-block PLA. Yet, this strategy has been of limited scope, because of unavailability of appropriate catalysts.[16–18] Herein, we describe a highly active and truly living magnesium based polymerization catalyst, and a preliminary account of the precise stereo-*n*-block PLA architectures (*n* = di, tri, tetra, penta, etc.,) it can afford in a one-pot synthesis.

Following our recent introduction of the family of zinc ROP catalysts supported by sequential tetradentate monoanionic ligands,[19] we turned to investigate the chemistry of the corresponding magnesium complexes.[20,21] Our preferred ligand, whose zinc−ethyl complex was the most active catalyst of its family, featured the bipyrrolidine backbone. Attempts to synthesize the corresponding magnesium−alkyl complexes by reacting the ligand precursor with various dialkyl magnesium complexes gave mixtures of products that decomposed readily in solution. Attempting an alternative entry, we reacted the ligand precursor with benzyl magnesium chloride and obtained the {ONNN}Mg−Cl complex as a yellow crystalline solid in high yield. ^{1}H NMR analysis revealed that {ONNN}Mg−Cl had formed as a single rigid stereoisomer, and X-ray diffraction measurements revealed a pentacoordinate mononuclear magnesium complex resembling the corresponding zinc complex (Figure 1).
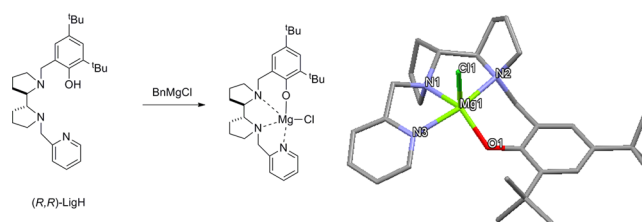

Figure 1. Synthesis and crystallographic structure of {ONNN}Mg−Cl.

Polymerizations of the homochiral L-LA were run in dichloromethane at room temperature by adding benzyl alcohol to {ONNN}Mg−Cl followed by addition of the lactide.[22] Preliminary runs showed that the addition of 300 equiv of L-LA to a solution including {ONNN}Mg−Cl and 1 equiv of benzyl alcohol led to full consumption of the monomer within 1 min.

This corresponds to one of the highest activities ever reported for lactide polymerization.[23,24] Gel permeation chromatographic (GPC) analysis of the polymer samples revealed exceptionally narrow molecular weight distributions with typical PDI (polydispersity index: M_w/M_n) values of ≤1.05, and number-average molecular weights (M_n) that coincided with the monomer/initiator molar ratio. Significantly, {ONNN}Mg−Cl was found to act as an "immortal polymerization" catalyst as well,[25,26] namely, it enabled the growth of more than a single polymer chain by every magnesium center by simply employing more than a single equivalent of benzyl alcohol. The PLA samples obtained under the immortal conditions retained very narrow PDI values, and the measured M_n values were consistent with the calculated values of monomer/benzyl alcohol molar ratio. The activity of the {ONNN}Mg−Cl complex was examined up to L-LA loading of 4300 equiv (and 2 equiv of benzyl alcohol). Full monomer consumption was reached in 6 min and the PLLA produced was monodisperse and of very high M_n (Tables 1 and S1). [1]H

Table 1. Homopolymerization of L-LA[a]

|	[I]/[BnOH]/[LA]	time (min)	conv.[b]	M_n[c]	PDI
3	1/1/300	1	>0.99	44340	1.04
4	1/2/600	1	>0.99	41360	1.05
5	1/4/600	1	>0.99	23420	1.05
6	1/2/4300	6	>0.99	266000	1.07

[a]Polymerizations performed in CH_2Cl_2 (5 mL) at RT employing 10 μmol of catalyst. [b]Determined by ^{1}H NMR spectroscopy (500 MHz). [c]Determined by GPC analysis calibrated with polystyrene standards and multiplied by a correction factor of 0.58. Values are given in g mol⁻¹.

NMR and HRMS characterization of a mixture of {ONNN}-Mg−Cl and benzyl alcohol in dichloromethane revealed that no reaction had taken place. Namely, the ROP catalysis probably follows an activated-monomer mechanism in which the lactide coordinates to the magnesium rather than a coordination−insertion mechanism which would require an {ONNN}Mg−OBn type complex. Consistently, the {ONNN}Mg−Cl complex was found to be highly active even in the absence of alcohol (see Table S1).[21,26]

Next, we attempted the synthesis of stereodiblock copolymers by adding L-LA to a mixture of {ONNN}Mg−Cl and benzyl alcohol in dichloromethane, followed by addition of D-LA several minutes later and eventual workup after an identical interval (Scheme 1). We found that PLLA−PDLA diblock copolymers having identical block lengths each of 100 (2 × 5 min), 300 (2 × 10 min), and even 400 or 500 (2 × 15 min) repeat units could be readily prepared by this one-pot synthesis (Tables 2 and S3). The two lactide enantiomers were fully consumed, and the polymer samples featured a perfectly isotactic stereodiblock microstructure (rather than a gradient microstructure that would result from an incomplete consumption of the first enantiomer) according to the sharp *mmm* tetrad in their homodecoupled (HD) ^{1}H NMR spectra (Figure 2).

We ran a control experiment that simulates an incomplete first monomer conversion: We polymerized 96 equiv of L-LA and waited for 10 min to ascertain a full conversion, before adding a mixture consisting of 100 equiv of D-LA and 4 equiv of L-LA and letting the polymerization proceed to full conversion. HD ^{1}H NMR of this sample showed stereoerrors

Scheme 1. One-Pot Synthesis of Poly(lactic acid) Homopolymers and Isotactic Stereo-n-block Copolymers[a]
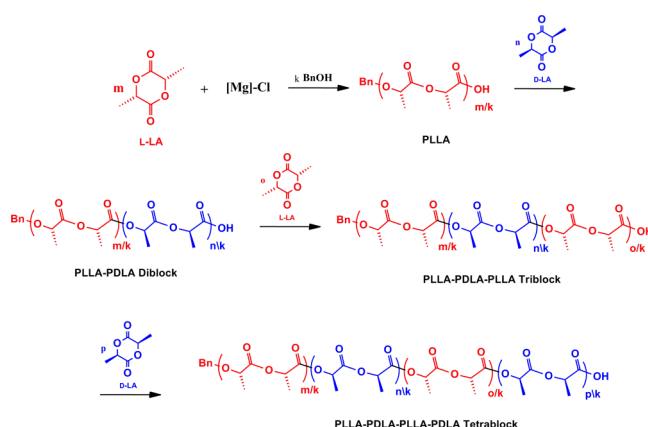
[a]The blocks' length is determined by the lactide/benzyl alcohol molar ratio. Copolymers including up to eight blocks were prepared.

Table 2. Stereoblock Copolymerization of L-LA and D-LA[a]

	type	composition	time[b]	$M_{n,calc}$[c]	M_n[d]	PDI
1	di block	100L-*b*-100D	10	28800	27500	1.07
2	di block	300D-*b*-300L	20	86400	90000[e]	1.13
3	di block	500L-*b*-500D	30	144000	177000[e]	1.11
4	tri block	100L-*b*-100D-*b*-100L	15	43200	45500	1.06
5	tri block	200L-*b*-200D-*b*-200L	25	86400	81500	1.12
6	tri block	300L-*b*-15D-*b*-300L	25	88560	87600	1.14
7	tetra block	100L-*b*-100D-*b*-100L-*b*-100D	25	57600	64300	1.12
8	tetra block	200L-*b*-200D-*b*-200L-*b*-200D	55	115200	122910[e]	1.13
9	penta block	100L-*b*-100D-*b*-100L-*b*-100D-*b*-100L	55	72000	61000	1.12
10	hexa block	50L-*b*-50D-*b*-50L-*b*-50D-*b*-50L-*b*-50D	60	43200	34000	1.10
11	octa block	50L-*b*-50D-*b*-50L-*b*-50D-*b*-50L-*b*-50D-*b*-50L-*b*-50D-*b*-50L	60	57600	50984	1.12

[a]Polymerizations performed in CH_2Cl_2 (5 mL) at RT employing 10 μmol of catalyst and 2 equiv of BnOH. Full conversion was confirmed by ^{1}H NMR (500 MHz) except for the octa-block copolymer (conv = 0.96). [b]Total polymerization time given in minutes. 5−20 min were maintained between each monomer addition, depending on the monomer amount and length of polymer chain. [c]Calculated from monomer conversion assuming full benzyl alcohol participation. Values are given in g mol⁻¹. [d]M_n was determined by GPC analysis calibrated with polystyrene standards and multiplied by a correction factor of 0.58. [e]GPC measurements were performed with $CHCl_3$ as eluent.

that were practically absent from our original diblock copolymers (Figure 2), signifying that therein the conversion of the L-LA prior to the addition of the D-LA substantially exceeded 96%. GPC analysis of the short diblock copolymers in THF and the less soluble longer diblock copolymers in chloroform[16] revealed that they had all exhibited narrow PDI values of M_w/M_n ≤ 1.13 and as expected M_n values (Tables 2 and S3). To our knowledge, there is but a single precedent for the synthesis of isotactic stereodiblock PLA of comparable
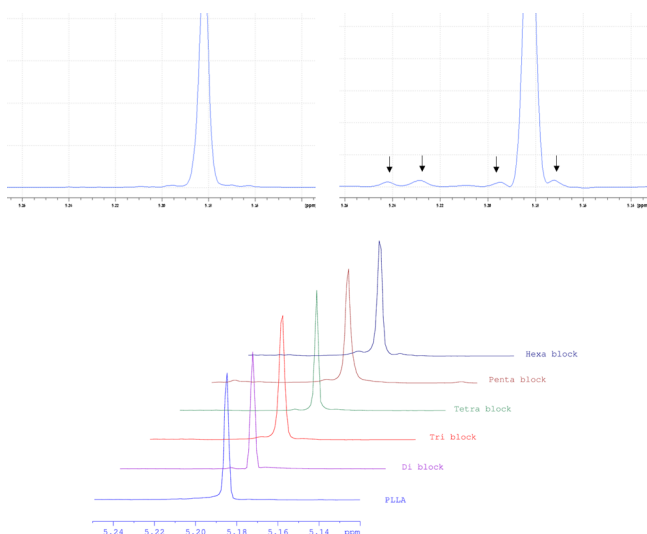
Figure 2. Homodecoupled ^{1}H NMR spectra of PLA samples. Top: Spectrum of a precise isotactic diblock copolymer (150D-*b*-150L) showing no errors (left); spectrum of a gradient isotactic diblock copolymer (96L-*b*-(100D+4L)) clearly showing stereoerrors (right). Bottom: Spectra of PLLA and several isotactic block copolymers bearing different block numbers.

microstructural precision employing a living polymerization catalyst. Two "overnight" periods were required for full monomer consumption by the indium-based catalyst employed therein.[16] Obviously, our one-pot methodology is applicable for the synthesis of precise stereodiblock PLAs of any block lengths' ratio, which are currently prepared by a laborious and less controlled two-step synthesis.[27] Following the evolution of a postpolymerization mixture of a 150L-*b*-150D stereodiblock copolymer by GPC and HD ^{1}H NMR for 1 h after full monomer consumption revealed a very mild PDI broadening (1.05 to 1.08) and no apparent change in the NMR, signifying a negligible postpolymerization trans-esterification.[28] Differential scanning calorimetry (DSC) measurements of the stereodiblock copolymers carried out on dichloromethane-cast films revealed very similar melting transitions of T_m = 215−220 °C for all samples, consistent with a stereocomplex crystal phase, which was confirmed by wide-angle X-ray diffraction analysis (Figures S18, S19 and S26 in the ESI). The crystallinity degree of the samples, estimated by comparing the melting enthalpies ΔH_m (61−85 J/g) to ΔH°_m (melting enthalpy of crystal of infinite size, 142−146 J/g)[29] ranged from 40 to 60%. To our knowledge, these melting enthalpies are the highest ever reported for isotactic stereodiblock PLA copolymers consistent with the high degree of crystallinity of the stereocomplex phase enabled by these precise microstructures.[12,30] All samples were found to completely crystallize from the melt during the DSC cooling run, and the T_m values of the second heating were practically identical to those of the first heating with sample crystallinities remaining high (38−47%). No evidence for homocrystallization was found, even for the longer diblock samples.

Extending this methodology to a three-step sequential addition afforded isotactic stereotriblock PLA copolymers. Full monomer consumption was observed within 15−30 min, giving rise to triblock copolymers of narrow PDIs and as-predicted M_n values, as well as precise isotactic blocks constitution (see Figure 2) that are unprecedented, to our knowledge. Different combinations of blocks could be "dialed

in" including identical blocks of various lengths, like 100L-*b*-100D-*b*-100L and 200L-*b*-200D-*b*-200L or long−short−long blocks like 300L-*b*-15D-*b*-300L (Table 2). DSC analysis of the triblock enantiomers (LDL and DLD) having block lengths of 100 repeat units revealed that T_m values and ΔH_m values (T_m of 206 °C for both, and ΔH_m of 41 and 51 J/g for LDL and DLD, respectively) were lower than those of the typical diblock copolymers. This behavior supports the notion that crystallization of copolymers having unpaired enantiomeric blocks should be accompanied by defects in the stereocomplex phase.[7] A 1:1 blend of these two enantiomeric triblock copolymers led to enhancement of both the T_m (211 °C) and ΔH_m (65 J/g) (Table S4).[7] Consistently, isotactic stereotetrablock PLA copolymers could be prepared by a four-step sequential addition process in a total polymerization time of less than 60 min, and exhibited all the characteristics of precise copolymer structure. DSC analysis of the stereotetrablock samples revealed that while their Tms were similar to those of the analogous triblock copolymers, their ΔH_m values were higher by 37% than those of triblocks on average (Figures S20, S21). This behavior should be expected for copolymers of equal number of D-LA and L-LA repeat units of identical lengths.

How far can we extend this methodology? We attempted the synthesis of isotactic PLA copolymers of penta-block, hexa-block and even octa-block sequences. Analysis of the conversion of the monomers, and the PDIs, M_n values and stereoregularities of the polymers revealed that the penta-block copolymer (5 × 100) was still of very high precision according to all parameters with a very high degree of isotacticity of $P_m >$ 0.96. Some decrease in isotacticity was noted for the hexa-block copolymers, possibly signifying incomplete conversion of a given lactide enantiomer prior to the addition of the opposite enantiomer. A further decrease of tacticity and incomplete lactide conversion were found for the octa-block copolymer. Optimizing the intervals between monomer additions may lead to even higher microstructural control. The exceptional regularity of these stereo-*n*-block copolymers (100 repeat units per block) is clearly evident in Figure 3, which follows a declining zigzag pattern in the T_m and the ΔH_m as a function of *n*. The lower than expected T_m of the hexablock copolymer probably derives from its less-than-perfect structure. Notably, the imperfect 96L-*b*-(100D+4L) diblock PLA exhibits inferior thermal properties relative to the 100L-*b*-100D counterpart, demonstrating the importance of block integrity. In terms of its
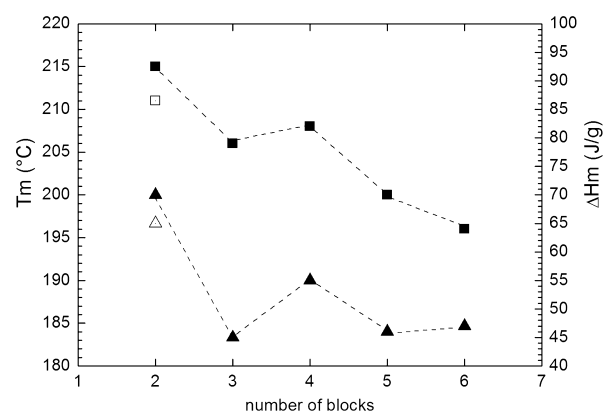

Figure 3. Thermal parameters of stereo-*n*-block PLA copolymers (100 repeat units) vs block number. T_m, full squares; ΔH_m, full triangles; 96L-*b*-(100D+4L), hollow squares and triangles.

ability to create *n-block*-copolymers of such precise microstructures, this {ONNN}Mg−Cl complex is by far the most living catalyst ever described for cyclic ester ring-opening polymerization[31] and is comparable to the highest living catalysts for any polymerization.[32]

Novel poly(lactic acid) materials featuring isotactic stereoblock microstructures of unprecedented precision are now accessible by a one-pot sequential monomer addition to a truly living polymerization catalyst based on the common and nontoxic metal magnesium. The range of tailor-made architectures made possible by this methodology is immense.[33] For example, changing the blocks' character by employing *rac*-LA or related cyclic esters, or synthesizing more elaborate polymeric architectures which consist of more than a single polymeryl branch by employing polyalcohols instead of benzyl alcohol are at hand. We are currently investigating the origins of the exceptional performance of this catalyst, as well as structure−property relationships of these tailor-made PLA-based materials that are expected to find advanced applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07287.

> Experimental material (PDF)
> Data for C$_{30}$H$_{44}$Cl$_3$MgN$_3$O (CIF)

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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