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Note

# Lactide Cyclopolymerization by an Alumatrane-Inspired Catalyst

Jonathan Weil,<sup>†</sup> Robert T. Mathers,<sup>‡</sup> and Yutan D. Y. L. Getzler<sup>\*,†</sup>

<sup>†</sup>Department of Chemistry, Kenyon College, Gambier, Ohio 43022, United States

<sup>‡</sup>Department of Chemistry, The Pennsylvania State University, New Kensington, Pennsylvania 15068, United States

**Supporting Information** 

# ■ INTRODUCTION

Control of molecular structure is an enduring motivation for chemists. From total synthesis<sup>1</sup> to self-assembly<sup>2</sup> to crystal growth,<sup>3</sup> the pursuit continues unabated. Polymer synthesis, in particular, has seen a revolution in control. It is now possible to precisely predetermine chain length, extent of cross-linking, comonomer incorporation, block length, stereochemistry and topology.<sup>4</sup> There has even been success in sequence control,<sup>5</sup> previously achieved only in biological systems. The difficulties inherent in the synthesis of pure macrocycle<sup>6</sup> have limited their availability, despite their compelling predicted properties. A variety of strategies have been employed but only two avoid linear material at all stages: catalyst-free ring equilibration and ring-expansion polymerizations (REP).<sup>7</sup> Our general catalyst design has been influenced by a recent example of the latter strategy wherein Grubbs used a ring-opening metathesis polymerization (ROMP) catalyst modified with a permanently tethered initiating group to polymerize cylcooctene yielding high-molecular-weight rings free of any linear contaminants.<sup>8,9</sup> Taking a cyclic catalyst and a cyclic monomer as our design criteria, we focused on cyclic poly(lactic acid)(cPLA) as a target. PLA architectures are interesting due to their degradation profiles and because they can be renewably sourced, and the cyclic architecture of cPLA in particular may be advantageous in drug delivery.<sup>10</sup> Whereas cyclic lactide oligomer have been synthesized,<sup>11–13</sup> we sought to produce high-molecular-weight cPLA.<sup>10</sup> N-Heterocyclic carbenes,<sup>14,15</sup> organotin compounds<sup>16</sup> and imidazoles<sup>17</sup> have previously been reported as effective catalysts for lactide REP to form cPLA. Herein we report an alumatrane-inspired catalyst, (N,N-bis(3,5di-tert-butyl-2-benzyloxy)-2-(2-aminoethoxy)ethoxy)aluminum [(<sup>t</sup>Bu-SalAmEE)Al, 1], that is active for controlled cPLA synthesis by lactide REP.

Metallatranes, the trigonal bipyramidal complexes of tripodal tetradentate ligands,<sup>18</sup> have been widely used<sup>19–21</sup> and continue to be an area of active research.<sup>22–28</sup> Of particular relevance to this work are recent examples of monomeric alumatranes.<sup>29–31</sup> Alumatranes are most commonly dimeric, and the alumatrane dimers which have been examined for lactide polymerization are inactive.<sup>32,33</sup> However, a monomeric alumatrane-isopropanol adduct capable of lactide polymerization in the melt has been reported.<sup>32</sup> Further inspiration was drawn from ligand hemilability where changes in hapticity<sup>34</sup> or denticity<sup>35</sup> can stabilize reactive catalytic intermediates or allow substrate coordination.

# RESULTS AND DISCUSSION

**Catalyst Synthesis.** The synthesis of catalyst 1 is straightforward and uses inexpensive materials (Scheme 1).

Scheme 1. Ligand and Catalyst Synthesis<sup>a</sup>



 $^{a}$ Key: (a) C<sub>7</sub>H<sub>8</sub>, reflux. (b) 0.01 M 2, AlMe<sub>3</sub>, THF, reflux, N<sub>2</sub>, 5 days.

Ligand 2 was produced via Mannich condensation of the relevant phenol and aminoalcohol in toluene under Dean-Stark conditions. Although related ligand syntheses are frequently driven by precipitation of the product,<sup>36,37</sup> 2 remained soluble, limiting yields. Despite this, 2 has been isolated on >15 g scale. Metalation was more challenging as initial attempts using known proceures<sup>29-33</sup> yielded an intractable and complex mixture of products that, remarkably, included unreacted aluminum alkyls. Success required dilution in THF and an extended (five day) reflux. The necessity of both the relatively high dilution and lengthy reaction time were verified separately. Characterization by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopies revealed a highly symmetric compound. However, given the frequent dimerization of alumatranes noted above, our representation of 1 as monomeric must be taken as tentative. Detailed characterization of 1 is underway and will be reported elsewhere.

**Polymerization Activity and Polymer Characterization.** Catalyst 1 was active for the polymerization of lactide in the melt and in solution and produced polymers with high molecular weights and narrow polydispersities (Table 1). At constant concentration of monomer and catalyst with increasing reaction time, the conversion of monomer to polymer steadily increased, consistent with a well-defined catalyst (Table 1, entries 1–3). The system also clearly

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Table	1.	Solution	and	Melt	Pol	lymerizations	of	Lactide	with	Catalyst	1"
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								MHS values <sup>d</sup>	
entry	solvent	[monomer]/ [catalyst]	time (h)	convn $(\%)^b$	$M_{\rm w} ~({\rm g/mol})^c$	$M_{\rm w}/M_{\rm n}^{\ c}$	$[\eta](\mathrm{mL/g})^d$	α	K (mL/g)
1	toluene	62	2	24	4080	1.8	4.1	0.29	0.383
2	toluene	62	4	39	6130	1.2	5.8	0.37	0.243
3	toluene	62	8	64	7380	1.2	8.7	0.81	0.006 74
4	toluene	52	12	79	9200	1.2	9.5	0.39	0.290
5	toluene	250	12	34	12 680	1.1	10.6	0.71	0.0135
6	toluene	416	12	21	16 320	1.1	9.7	0.91	0.002 47
7	melt	104	2	79	31 880	1.2	21.8	0.44	0.239
8	melt	165	2	66	33 760	1.4	22.9	0.46	0.201
9	melt	407	2	39	38 820	1.2	26.1	0.53	0.109

<sup>*a*</sup>Melt polymerizations were conducted under nitrogen at 130 °C using monomer and catalyst (3.5 mg). Solutions polymerizations were conducted under nitrogen at 130 °C using monomer (106 mg), catalyst, and toluene (1.1 mL). <sup>*b*</sup>Conversion was calculated from the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>*c*</sup>Weight-average ( $M_w$ ) molecular weights and molecular weight distributions ( $M_w/M_n$ ) were calculated by gel-permeation chromatography using light scattering in tetrahydrofuran (THF). <sup>*d*</sup>Mark–Houwink–Sakarada (MHS) values and intrinsic viscosity ([ $\eta$ ]) were measured in THF at 35 °C using a gel-permeation chromatography system with light scattering and viscometer detectors.

displayed the expected time-dependent increases in both molecular weight and intrinsic viscosity (Table 1, entries 1–3). If reaction time was instead held constant, but catalyst loading decreased, percent conversion displayed a concomitant decline, consistent with fewer active polymerization sites (Table 1, entries 4–6). Fewer active sites should also produce material with higher molecular weights, a trend which was observed in the same data (Table 1, entries 4–6). Melt polymerizations by catalyst 1 responded to decreasing catalyst loadings in an analogous fashion (Table 1, entries 7–9), with decreased conversion of monomer and increased molecular weights.

The polymerization activity of compound 1 was consistent with a well-defined catalyst (Figure 1). Melt polymerizations



**Figure 1.** Conversion of lactide monomer in solution and melt polymerizations as a function of catalyst loading and time. Conversion was calculated from the <sup>1</sup>H NMR spectrum of the crude reaction mixture. Key: (blue  $\Box$ ) 0.7 mmol of lactide, 1.1 mL of toluene, 12 h, 130 °C; (blue  $\bigcirc$ ) 6  $\mu$ mol of 1, 2 h, 130 °C; (red  $\blacksquare$ ) 60:1 monomer:1, 5  $\mu$ mol of 1, 0.55 mL of toluene, 130 °C; (red  $\blacksquare$ ) 190:1 monomer:1, 6  $\mu$ mol of 1, 130 °C.

gave higher conversion with decreasing monomer-to-catalyst ratio as did solution polymerizations. When concentrations were instead held constant but reaction time was varied, conversion increased with time as expected. Unsurprisingly, the much higher concentrations of catalyst in the melt polymerizations resulted in much higher conversions at a given time than the comparable solution polymerizations. The proposed cyclic structure of 1 means that the polymer formed from enchainment of lactide by 1 could also be cyclic. We investigated this possibility by comparing the polymer to authentic linear PLA, synthesized with a bis(2-ethylhexanoate)tin catalyst. When the absolute molecular weights and elution volumes of linear PLA and the polymer produced by 1 were compared, the latter eluted at higher volumes, consistent with the smaller hydrodynamic volume of a cyclic topology



Figure 2. Molecular weight as a function of elution volume for linear PLA (blue -) and the PLA produced by 1(green  $\bigcirc$ ).

(Figure 2). Further evidence for a cyclic topology was found in overlaid Mark–Houwink-Sakurada plots of linear material and the polymer formed by 1 (Figure 3). As expected, for a given molecular weight, the linear material displayed a higher intrinsic viscosity. Cyclic polymer topology is also supported by MALDI–TOF MS data, where the dominant peaks are integer multiples of the monomer (Supporting Information).

A plausible polymerization mechanism for the formation of cPLA by 1 is shown in Scheme 2. Enchainment of lactide could proceed through a coordination—insertion mechanism<sup>38</sup> to generate macrometallacycle 3, which would eventually undergo an intramolecular chain transfer<sup>9</sup> to liberate cPLA (4) and regenerate free catalyst (1). We are interested in more closely examining the kinetics of the system, particularly whether molecular weight and molecular weight distribution can be

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**Figure 3.** Mark–Houwink–Sakurada plot of linear PLA (blue) and PLA produced by 1 (green), each overlaid with their respective linear regressions.





influenced by reaction temperature, as might be expected from the proposed mechanism.

# CONCLUSION

We presented a new catalyst for the ring-expansion polymerization of lactide to cyclic poly(lactic acid). The pseudoalumatrane complex contains a putative initiating group tethered to a permanently bound ligand, analogous to Grubbs' catalyst for ring-expansion polymerization of cyclooctene. Our catalyst is active for polymerization of lactide in solution and in the melt and shows a linear increase in conversion with either catalyst loading or polymerization time under either polymerization condition, consistent with a well-defined active site. The expected trends are also observed for molecular weight and intrinsic viscosity. The polymer produced displays physical characteristics consistent with a cyclic architecture when compared to linear material of equivalent molecular weights including longer elution times when subjected to size exclusion chromatography and lower intrinsic viscosity. This catalyst is a valuable addition to an ever-expanding body of methods for the control of macromolecular structure.

ASSOCIATED CONTENT

#### Supporting Information

Detailed experimental procedures and characterization of new compounds including MALDI–TOF and NMR spectra (two files). This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: getzlery@kenyon.edu.

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