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Synthesis of Stereoregular Cyclic Poly(lactide)s via "Thiol−Ene" Click Chemistry

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The control over polymer architecture has been an area of fundamental research for decades.[1] Star-shaped, dendritic, and brush polymeric architectures display greatly altered physical properties to their linear counterparts leading to novel behavior. While conceptually the constrainment of polymer chain ends to produce a cyclic polymer is simple, in practice the synthetic inaccessibility of cyclic polymers has led to a limited ability to study the physical and self-assembly properties of pure cyclic polymers.[2−4] Poly(lactide) (PLA) and its copolymers are biocompatible and biodegradable polymers that have found many uses in biomedicine. By judicious choice of catalyst, access to these polymers via the ring-opening polymerization (ROP) of lactide (LA) enables a high level of control over a variety of molecular and hence physical characteristics to be achieved.[5−7] The living nature of many of these polymerizations enable facile control over the chain end functionality and molecular weight with a narrow molecular weight distribution. Architectural effects, especially the constraints of cyclic polymers, result in significant differences in the polymer properties; this is especially highlighted with degradable polymers where a single degradation would lead to ring-opening resulting in a linear polymer.[8]

The increased recent interest in the synthesis of pure cyclic polymers has led to many improved synthetic methodologies. These have primarily been focused around two routes: restriction of chain ends during polymer growth and postpolymerization connection of polymer chain ends. Several groups have reported syntheses of cyclic polymers including the application of surface initiated techniques, taking advantage of trans-esterification reactions to selectively cleave macrocycles of oligo(esters) that while effective leads to a loss of stereopurity of the polymers,[9,10] and ring-expansion strategies such as those reported by Grubbs,[11−13] Kricheldorf,[14−17] Jérôme,[18,19] Waymouth and Hedrick,[20,21] and their co-workers. While these methods are excellent for the synthesis of cyclic polymers, the application of sensitive reagents in the polymerization and cyclization steps, lack of reported stereoregular polymerizations, and/or access to block copolymers led us to examine other synthetic methods.

The alternate route involving the cyclization of linear prepolymers offers much greater versatility in polymer design although the efficiency of the cyclization step is critical to the purity of the resultant macrocycles. This approach is exemplified by the report of Laurent and Grayson in which α-alkyne-ω-azido-poly(styrene)s were cyclized using the copper-catalyzed Huisgen-1,3-dipolar cycloaddition "click" reaction under pseudo-high-dilution conditions.[22,23] This "AB" approach has been adopted in several other studies using both the α-alkyne-ω-azido polymer cyclization[8,24,25] and a comparable "$A_2 + B_2$" approach in which an α,ω-alkyne-functional polymer is cyclized by addition of a bis-azido functional molecule[26,27]—an approach that requires extremely efficient coupling chemistry to be applied. A range of alternative click reactions have been reported to be highly efficient for the tranformation of polymer materials.[28−32] Among these, the range of "thiol−ene" reactions has been well studied to provide strategies for polymer modification without the need for toxic copper catalysts.[33−36] Having shown that Michael addition thiol−ene click chemistry provides a mild and highly effective tool to effect poly(lactide) functionalization with a complete absence of degradation,[37,38] we chose to investigate its efficiency for the synthesis of cyclic stereoregular poly(lactide)s.

We have previously reported the synthesis of linear, telechelic, and star-shaped stereoregular PLAs with maleimide groups at each chain end utilizing the versatile range of aluminum complexes bearing salen/salan ancillary ligands[39] and subsequently demonstrated the availability of these groups for further reactions with thiols.[37,38] In this manner, α,ω-maleimido-functional poly(lactide)s were prepared by initiation of postpolymerization quenching of the aluminum-catalyzed ROP of lactide initiated from 4-(2-hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione, **1**, in toluene at 70 °C with pentanedioyl chloride mono-[2-(3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl)ethyl] ester, **2** (Scheme 1); initially, ROP of L-lactide to yield isotactic PLAs was investigated. Cyclization of the telechelic PLAs by concurrent slow addition (∼0.4 mL h^{-1}) of a precisely measured dichloromethane solution of the telechelic maleimide-functional PLA (∼7 mM) and an equal molarity dichloromethane stock solution of 1,2-ethanedithiol to a stirred solution of triethylamine in dichloromethane (∼200 equiv in 500 mL) that was saturated with sodium metabisulfite in order to suppress thiol reduction, at ambient temperature, provided mild conditions for the cyclization of PLA under pseudo-high-dilution conditions. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), ^{1}H NMR, and gel-permeation chromatography (GPC) analysis of the resultant polymers unambiguously show that the cyclization has occurred in an efficient manner. The loss of the vinyl resonance (δ = 6.8 ppm) in the ^{1}H NMR spectra is observed upon cyclization of the polymer which indicates that the thiol−ene reaction has occurred. Examination of the MALDI-TOF spectra of the linear and cyclic polymers (Figure 1) reveals an increase in molecular weight of 94 Da upon cyclization, corresponding to the addition of a single 1,2-ethanedithiol group per polymer chain (linear polymer $M_{n,MALDI}$ = 3070 g mol^{-1}, PDI_{MALDI} = 1.03; cyclic polymer $M_{n,MALDI}$ = 3250 g mol^{-1}, PDI_{MALDI} = 1.03); no higher molecular weight linear oligomers were observed. Finally, GPC analysis (Figure 2) revealed an increase in the retention time and therefore reduction in the measured molecular weight of the cyclized polymer (in comparison to the linear precursor) while retaining a low polydispersity index which provides compelling evidence for cyclization (linear polymer $M_{n,GPC}$ = 5770 g mol^{-1}, PDI_{GPC} = 1.08; cyclic polymer $M_{n,GPC}$ = 3990 g mol^{-1}, PDI_{GPC} = 1.07). This observation is consistent with the reduced hydrodynamic volume of cyclic polymers resulting from the constrainment of their chain ends; again, no high molecular weight impurity is observed.

The versatility of this approach allows a potential wide range of catalytic methodologies and polymers to be cyclized in this manner. To demonstrate this versatility, we prepared a range of poly(lactide)s with different tacticities. As previously described, simple alteration of the ligand structure of the salen/salan catalysts (**3**−**5**, Figure 3) enables the synthesis of a range of

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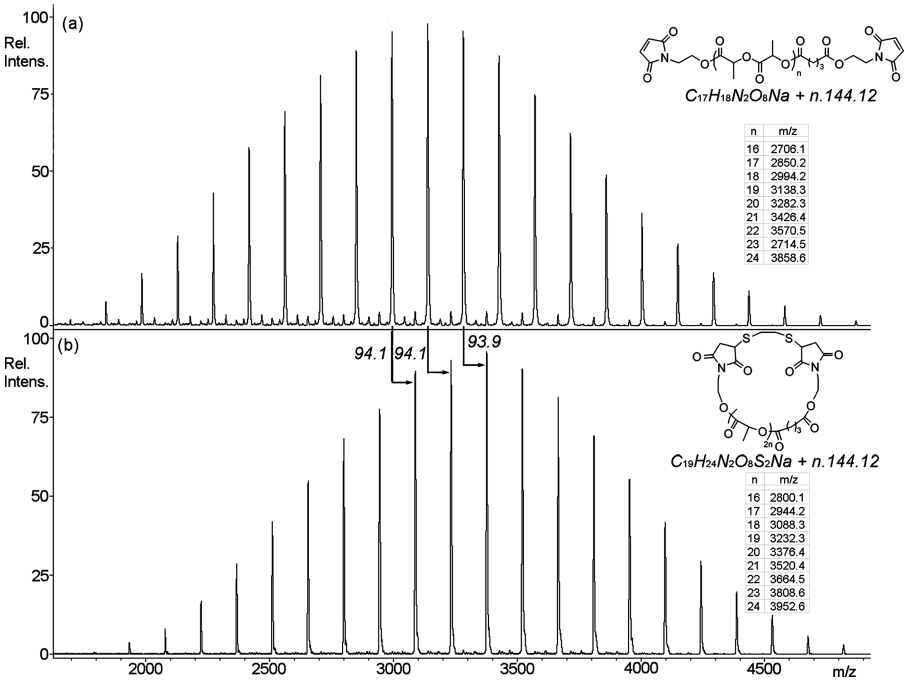
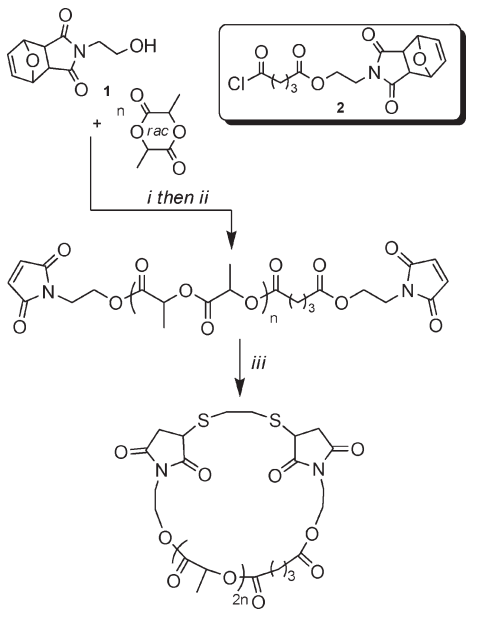


Figure 1. MALDI-TOF MS of (a) linear and (b) cyclic PLA.

Scheme 1. Synthesis of Stereoregular Cyclic Poly(lactide)[a]



[a] Conditions: (i) [Al], toluene. 70 °C, 4 h; then **2**, 70 °C, 120 h; (ii) vacuum, 100 °C, 24 h; (iii) $HSCH_2CH_2SH$, CH_2Cl_2, NEt_3, $Na_2S_2O_5$.

PLA microstructures (Table 1).[40,41] To this end we have demonstrated the application of these catalysts to produce α,ω-maleimido-functional stereoregular poly(lactide)s that have been cyclized using this simple thiol−ene reaction to complete cyclizations of polymers with various tacticities as well as a range of different chain lengths. To date, we have prepared heterotactic, isotactic, atactic, and stereoblock PLAs with molecular weights up to ~7500 g mol^{-1} and narrow molecular weight distributions (Table 1).

The synthetic versatility offered by this route also provides the opportunity to incorporate a single functional group within the polymeric macrocycle via the synthesis of telechelic PLAs initiated from a bifunctional alcoholic initiator. To this end, we chose to incorporate a single group within the polymer chain that upon response to an external stimulus would selectively cleave to yield a linear polymer, both providing further evidence for initial

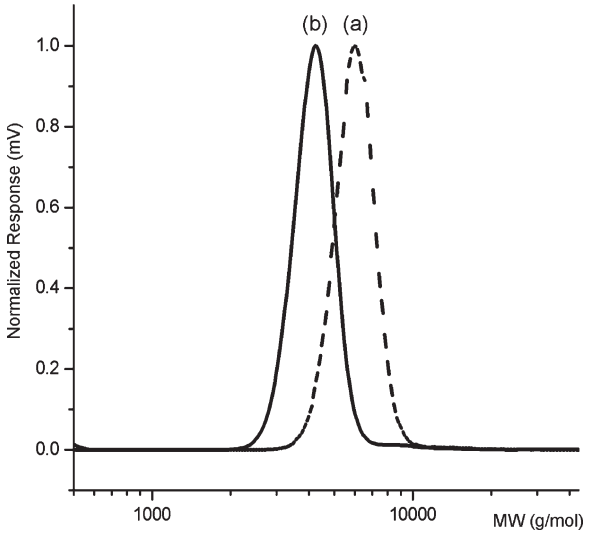


Figure 2. GPC traces of (a) linear and (b) cyclic PLA.

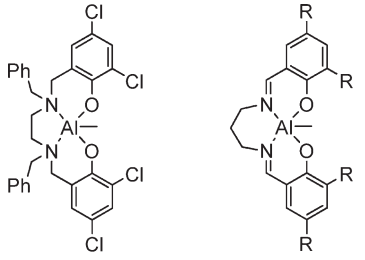


Figure 3. Structures of Salen/salan aluminum complexes **3**−**5** applied in stereospecific ring-opening polymerization of lactide.

chain cyclization and revealing latent functional handles. 2,2′-Dithiodiethanol was chosen and applied as an initiating species in the ROP of L-LA mediated by **2** (target DP = 10). One-pot end-capping, maleimide deprotection, and subsequent cyclization with 1,2-ethanedithiol realized the disulfide-containing cyclic PLA. Data consistent with cyclization were obtained including a reduction in apparent molecular weight by GPC analysis of the cyclic polymer compared to its linear precursor (linear polymer M_n = 5260 g mol^{-1}, PDI = 1.13; cyclic polymer M_n = 3030 g mol^{-1}, PDI = 1.08). Disulfide bridges can be selectively reduced by a range of stimuli including chemical reduction by phosphines. Cleavage of the disulfide bridge in both the linear precursor and cyclic polymer was attempted using 10 equiv of ^{n}Bu$_3$P under an inert atmosphere. Accurate data were unable to be recorded, probably the result of interchain interactions and re-formation of disulfide bridges upon exposure to air during the work-up procedure. In order to overcome these limitations, we attempted to trap the thiol *in situ* by further reaction with a maleimide. Thus, cleavage of the disulfide bridge by ^{n}Bu$_3$P in the presence of *N*-methylmaleimide (10 equiv) and NEt$_3$ (10 equiv) resulted in cleavage and trapping of the *in situ* generated thiols. After precipitation, analysis of the ^{1}H NMR spectra of the cleaved polymers revealed no residual *N*-methylmaleimide as evidenced by the absence of the vinyl resonance at δ = 6.8 ppm. As expected, cleavage of the linear polymer resulted in reduction of the molecular weight as evidenced by both GPC and MALDI-TOF MS (Figure 4A,B) (linear polymer M_n = 5740 g mol^{-1}, PDI = 1.11; cleaved linear polymer M_n = 2430 g mol^{-1}, PDI = 1.14). In contrast, analysis of the cyclized polymer after cleavage revealed a slight increase in molecular weight by MALDI-TOF MS corresponding to the addition of two *N*-methylmaleimides (Figure 4C, D) whereas GPC analysis of the two polymers revealed a notable increase in apparent molecular weight, resulting from the increased hydrodynamic volume of the linear polymer compared to the cyclized precursor (cyclic polymer M_n = 3030 g mol^{-1}, PDI = 1.08; cleaved cyclic polymer M_n = 3750 g mol^{-1}, PDI = 1.11).

Table 1. Preparation of a Range of Cyclic Poly(lactide)s

			linear polymer		cyclic polymer	
tacticity[a]	catalyst	target DP[b]	M_n, g mol^{-1}[c]	PDI[c]	M_n, g mol^{-1}[c]	PDI[c]
heterotactic	**3**	10	2370	1.14	1710	1.16
heterotactic	**3**	20	5280	1.14	3740	1.11
isotatic	**5**	20	5770	1.08	3990	1.06
stereoblock	**5**	20	3060	1.11	2230	1.13
atactic	**4**	20	3930	1.15	3110	1.12
isotactic	**5**	50	11 080	1.08	8120	1.09

[a] Determined by ^{1}H NMR spectroscopy. [b] Targeted degree of polymerization based on [LA]/[initiator]. [c] Determined by GPC analysis.

In conclusion, we have demonstrated the application of thiol−ene click chemistry, specifically the Michael addition of thiols to maleimides, to synthesize and functionalize cyclic poly(lactide)s. Importantly, the mild nature of these reactions enables the retention of stereoregularity, and the versatility of the approach presents a facile methodology for the preparation of more complex biodegradable polymer architectures.

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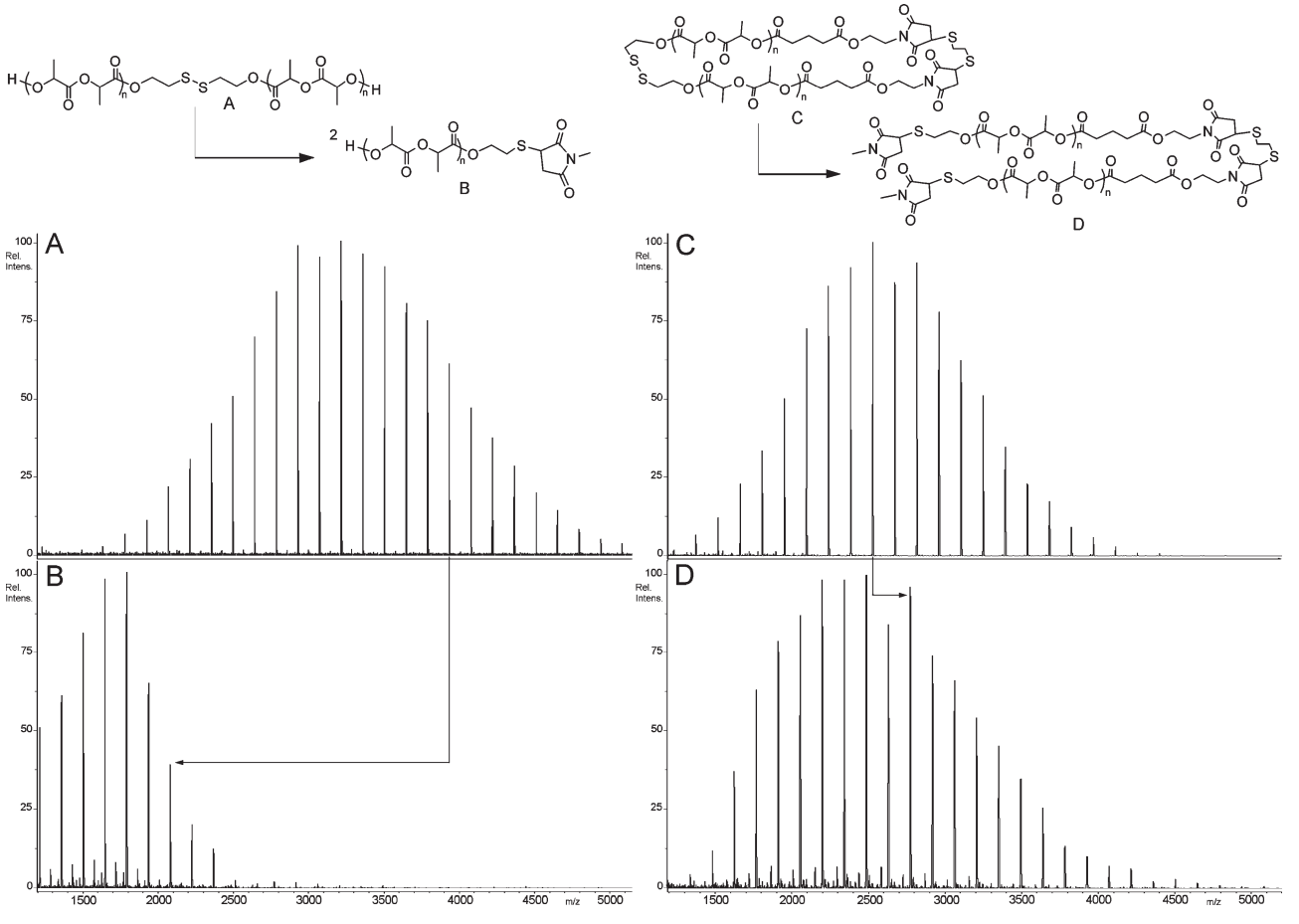

Figure 4. MALDI-TOF spectra of linear and cyclic polymers before and after cleavage of disulfide bridge with ^{n}Bu$_3$P, NEt$_3$, and *N*-methylmaleimide.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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