Ring-Opening Polymerization of Cyclic Monomers by Biocompatible Metal Complexes. Production of Poly(lactide), Polycarbonates, and Their Copolymers

Donald J. Darensbourg,* Wonsook Choi, and Casseday P. Richers

Department of Chemistry, Texas A&M University, College Station, Texas 77843

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Polymeric biomaterials derived from lactic acid have numerous medical applications, originating with biodegradable sutures. Important among these materials are thermoplastic elastomers obtained from lactides and trimethylene carbonate.[1] These latter copolymers are prominently used for heart tissue engineering,[2] drug delivery,[3] and as biodegradable internal fixation devices for repair of fractures to small bones and joints, such as feet/hands or ankles/wrists.[4] The aforementioned orthopedic fixation devices afford a natural healing process, where the copolymers degrade at a rate to progressively transfer the load from the device to the broken bone to aid in bone regeneration, at the same time eliminating the need for a second surgery. The ring-opening polymerization of lactides has been investigated using various metal catalysts, including complexes of Sn,[5] Y,[6] Ln,[7] Fe,[8] Ti,[9] Mg,[10] Al,[11] and Zn.[12] Recently, special attention has been given to exploring biocompatible metal catalysts, e.g., calcium complexes for the ring-opening polymerization of cyclic esters or cyclic carbonates.[13] Lactide is a cyclic dimer produced from the dehydration of lactic acid, which can be obtained from renewable starch containing resources (e.g., corn, wheat or sugar beets) by fermentation or by chemical synthesis. Pure L-lactide or D-lactide forms crystalline isotactic polymer while *rac*-lactide in the absence of control of stereocenters forms amorphous atactic polymer.[14] Of importance, the physical properties of poly(lactides) are strongly dependent on their stereochemical composition.

Therefore, there is a need for catalysts that can produce these biodegradable polymeric materials with novel microstructures and/or properties. Pertinent to the above overall objective, we have established that calcium salen complexes in the presence of anionic initiators exhibit a high activity for the ring-opening polymerization of trimethylene carbonates.[13a] However, this system has shown rather low catalytic activity for the ring-opening polymerization of lactides. Herein, we report calcium complexes with tridentate Schiff base ligands for the effective polymerization of both lactides and trimethylene carbonate. The general structure of the calcium complexes employed in these studies is depicted in Figure 1, where modifications of the Schiff base ligands are readily achieved by variations of the aldehyde and diamine starting reagents.[15−17] We have utilized for the most part bis(trimethylsilyl)amide as an initiator, which is very air- and moisture-sensitive, and can be replaced with alkoxide by adding alcohol.[13b,d] These calcium derivatives were found to contain two or three bound molecules of THF by ^{1}H NMR measurements (see Supporting Information for the details of their synthesis).[18]

* Corresponding author: e-mail djdarens@mail.chem.tamu.edu; Fax (979) 845-0158.

Initially, we examined the effectiveness of the calcium complexes for the ring-opening polymerization of L-lactide or D-lactide. Melt polymerizations were performed at a monomer:catalyst ratio of 350:1 at 110 °C for 15 min under an argon atmosphere. The results of these melt polymerization runs are summarized in Table 1, where TOFs (mol of L-lactide consumed)/(mol of catalyst·h)) were determined by precipitating the polymers from dichloromethane, 5% hydrochloric acid, and methanol followed by drying in vacuo and weighing. As indicated in Table 1, a calcium salen catalyst, where salen = *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-napthylenediimine, with bis(phosphoranylidene)ammonium azide ([PPN]N_3) as a co-catalyst is much less active than calcium with tridentate Schiff base ligands. Furthermore, the analogous zinc complex (**1a**′) is also significantly less active than calcium complex (**1a**). Changing the initiator to methoxy displayed similar activity to bis(trimethylsilyl)amide. Less hindered and less donating hydrogen substituent as R_2(**1c**) resulted in similar activity to its bulky *tert*-butyl analogue (**1a**) but less stereoselectivity (Figure S8). However, more significant changes in TOFs were noted upon altering the nature of the imine backbone. The calcium complex containing the more donating and less bulky dimethyl imine backbone resulted in the most active catalyst (**1a**), which is 2.2 times more active than that containing the more electron-withdrawing and bulky aminoquinoline imine backbone (**4a**).

The molecular weight and polydispersity of poly(L-lactide) obtained in these studies were measured by gel permeation chromatography (GPC). The melt polymerizations were carried out at 110 °C using catalyst **1a** depending on M/I ratios. As indicated in Table 2 and Figure 2, the molecular weights increase with increasing M/I ratios maintaining narrow polydispersity indices (PDI, M_w/M_n), thus demonstrating that the level of polymerization control is high.

We have initiated kinetic measurements of the ring-opening polymerization of L-lactide in solution in the presence of catalyst **1a**. The rate of polymerization in the coordinating solvent tetrahydrofuran was found to be much faster than in the chlorinated solvent, since the complexation of calcium ion by coordinating solvents enhances the nucleophilicity of the initiator.[13b,19] The kinetic studies were conducted in $CDCl_3$ and monitored by ^{1}H NMR spectroscopy. The polymerization reaction was found to be first order in monomer (L-lactide) and catalyst concentrations with $k = 19.9\ M^{-1}\ h^{-1}$ at ambient temperature. Table 3 summarizes the determined rate constants (k_{obsd}) for the ring-opening polymerization of L-lactide as a function of the catalyst concentration and temperature. We have similarly observed that the ring-opening polymerization of trimethylene carbonate catalyzed by complex **1a** in $CDCl_3$ is first order in monomer and catalyst concentrations. In this instance, the rate is much faster than that for L-lactide with a rate constant at ambient temperature determined to be 500 $M^{-1}\ h^{-1}$. As previously reported for calcium salen complexes initiated by an external nucleophile, the ring-opening polymerization of trimethylene carbonate by complex **1a** was found to have a high level of polymerization control.[13a] That is, the product polymers exhibited a linear increase in M_n with conversion and possessed low polydispersity indices. Catalyst **1a** efficiently produces both random and block copolymers from lactides and trimethylene carbonate. Interestingly, it was observed that the rate of enchainment of trimethylene carbonate monomer is much slower than that of lactide during random

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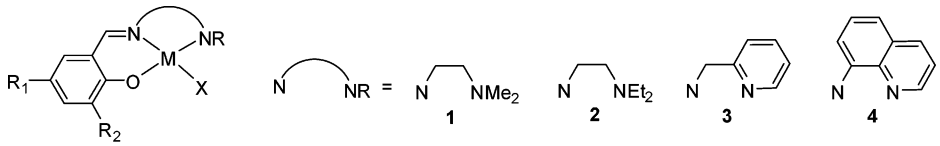

catalyst	M	R_1	R_2	R	X
1a	Ca	^{t}Bu	^{t}Bu	1	$N(SiMe_3)_2$
1a′	Zn	^{t}Bu	^{t}Bu	1	$N(SiMe_3)_2$
1b	Ca	^{t}Bu	^{t}Bu	1	OMe
1c	Ca	^{t}Bu	H	1	$N(SiMe_3)_2$
2a	Ca	^{t}Bu	^{t}Bu	2	$N(SiMe_3)_2$
3a	Ca	^{t}Bu	^{t}Bu	3	$N(SiMe_3)_2$
4a	Ca	^{t}Bu	^{t}Bu	4	$N(SiMe_3)_2$

Figure 1. General structure of calcium complexes with tridentate Schiff base ligands.

Table 1. Polymerization of L-Lactide Catalyzed by Calcium Complexes with Tridentate Schiff Base Ligands[a]

entry	catalyst	conversion (%)[b]	TOF[c]
1	**1a**	80	1124
2	Ca(salen)	35[d]	22.3
3	**1a′**	16	227
4	**1b**	59	826
5	**1c**	64	891
6	**2a**	54	753
7	**3a**	41	519
8	**4a**	39	502

[a] Each reaction was performed in melt maintaining a monomer:initiator ratio of 350:1 at 110 °C for 15 min. [b] Obtained from ^{1}H NMR. [c] The TOFs were determined by weighing the polymer after precipitating in 5% HCl and MeOH and drying in a vacuum oven and is reported as mol of L-LA consumed/(mol of Ca·h). [d] For 6 h.

Table 2. Molecular Weights of Poly(lactide) Depending on M/I[a]

		M_n		
entry	M/I	theoretical[b]	GPC	PDI
1	350	40 481	65 005	1.022
2	450	45 360	82 362	1.048
3	500	50 400	94 529	1.035
4	700	69 552	110 624	1.039

[a] Each reaction was performed in melt at 110 °C for 30 min using catalyst **1a**. [b] Theoretical M_n = (M/I) × (% conversion) × (M_w of lactide).

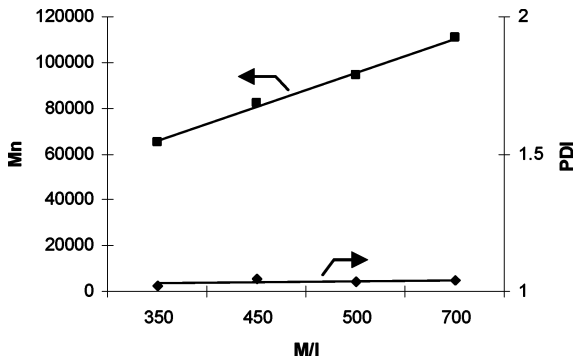

Figure 2. Plot of the dependence of molecular weight of poly(L-lactide) on M/I ratios.

copolymerization reactions. The molecular weight of a block copolymer produced from trimethylene carbonate and L-lactide (45:55 composition) was determined to be 18 000. The thermal properties of this block copolymer were investigated by TGA and DSC, and it was found to be stable up to 250 °C with a T_m of 150 °C.

The activation parameters for the ring-opening polymerization of L-lactide catalyzed by **1a** in $CDCl_3$ were found to be $\Delta H^{\neq} = 73.5 \pm 3.8$ kJ/mol and $\Delta S^{\neq} = -42.5 \pm 12.6$ J/(mol·K). These values were calculated from the temperature-dependent rate constants listed in Table 3. A $\Delta G^{\neq}$ value of 86.1 kJ/mol was calculated for the ring-opening polymerization of L-lactide catalyzed by calcium catalyst (**1a**) at 25 °C. This $\Delta G^{\neq}$ value is comparable to that determined for the ring-opening polymerization of TMC catalyzed by **1a** in $CDCl_3$ ($\Delta H^{\neq} = 37.9 \pm 3.1$ kJ/mol, $\Delta S^{\neq} = -135.1 \pm 11.4$ J/(mol·K), and $\Delta G^{\neq} = 78.2$ kJ/mol at 25 °C, which is consistent with the ROP of TMC being faster than that of L-lactide.

Table 3. Rate Constants Dependence on the Concentration of the Catalyst and Temperature for the ROP of L-Lactide[a]

entry	[Ca] (mM)	temp (°C)	k_{obsd} (h^{-1})
1	1.49	25	0.0266
2	2.30	25	0.0295
3	4.66	25	0.0955
4	7.03	25	0.1277
5	4.66	0	0.0047
6	4.66	41	0.4731
7	4.66	51	0.8083

[a] Monomer concentration held constant at 0.69 M and reactions carried out in $CDCl_3$.

As previously noted, the control of stereoregularity in poly(lactide) synthesis by catalysts is an important feature for their applications.[11b,19,20] Spassky and co-workers have reported chiral aluminum alkoxide for stereoselectivity in the polymerization of *rac*-lactide.[21] Similarly, Coates and co-workers have shown chiral aluminum alkoxide produces highly syndiotactic poly(lactide) from *meso*-lactide and highly heterotactic poly(lactide) from *rac*-lactide in the presence of β-diiminate zinc complexes.[22] Feijen and co-workers employing chiral (salen)AlX derivatives have demonstrated that the polymerization of L-lactide is faster than that of D-lactide.[11b] Since these catalysts have chiral centers, an enantiomorphic site control mechanism is possible. Recently, Chisholm and co-workers have shown that calcium complexes containing bulky tris(pyrazolyl) borate ligands and phenolate or $N(SiMe_3)_2$ initiators polymerize *rac*-lactide with a high degree of heteroactivity in THF.[13b] As observed in the zinc analogues,[12a] complex **1a** with the bulky *tert*-butyl substituent in the R_2 position of the phenolate ring produces predominantly heterotactic poly(lactide) from *rac*-lactide (Figure 3). Replacement of the *tert*-butyl group with R_2 = H leads to production of atactic poly(lactide) at ambient temperature. Utilizing complex **1a**, it was observed that polymerization reactions carried out at lower temperatures in THF resulted in enhanced degrees of heteroactivity (see Figure S7). The tacticity of the polymer was assigned using the methine proton signals with homonuclear decoupling as described by Hillmyer and co-workers.[23]

In summary, we report herein calcium complexes with tridentate Schiff base ligands which show excellent catalytic activity for ring-opening polymerization of trimethylene carbonate or lactide to produce high molecular weight polymers with narrow polydispersities. In addition, these catalysts effectively

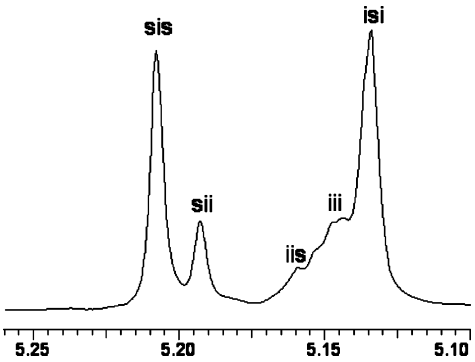

Figure 3. Homonuclear decoupled ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of the methine region of poly(lactide) prepared from *rac*-lactide with **1a** in THF at −33 °C ($P_r = 0.73$).

copolymerize these two monomers. Further studies will investigate the stereoselectivity of the polymer products under various polymerization conditions and activation parameters for the copolymerization of lactides and trimethylene carbonate.

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Supporting Information Available: Syntheses of calcium complexes with tridentate Schiff base ligands, preparation of materials, and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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