Ring-Opening Polymerization of Cyclic Monomers by Complexes Derived from Biocompatible Metals. Production of Poly(lactide), Poly(trimethylene carbonate), and Their Copolymers

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ABSTRACT: Tridentate Schiff base calcium derivatives have been prepared and shown to be very effective catalysts for ring-opening polymerization of both lactides and trimethylene carbonate to produce high molecular weight polymers with narrow polydispersity. Optimization of the calcium catalyst was achieved changing the imine backbone, initiator, and substituent on the phenolate ring of the calcium complex. Turnover frequencies were obtained up to 1124 h^{-1} for a melt polymerization of L-lactide carried out at 110 °C. Solution studies in $CDCl_3$ demonstrated the polymerization reaction is first order in [monomer] and [catalyst], with $k = 19.9$ M^{-1} h^{-1} for lactide polymerization and $k = 500.0$ M^{-1} h^{-1} for trimethylene carbonate polymerization at ambient temperature. The activation parameters for the ring-opening polymerization of L-lactide using catalyst **1a** were determined to be $\Delta H^{\ddagger} = 73.5 \pm 3.8$ kJ/mol and $\Delta S^{\ddagger} = -42.5 \pm 12.6$ J/(mol K), and catalyst **1a** was shown to produce heterotactic polylactide from *rac*-lactide with a Pr value of 0.73. It was also found that the ring-opening polymerization of trimethylene carbonate is a lower energy process than that of lactide polymerization as revealed by its activation parameters, which were determined to be $\Delta H^{\ddagger} = 37.9 \pm 3.1$ kJ/mol and $\Delta S^{\ddagger} = -135.1 \pm 11.4$ J/(mol K). Furthermore, this class of catalysts afforded from biocompatible metals is very effective at producing diblock copolymer from trimethylene carbonate and lactides. Kinetic studies of the copolymerization of trimethylene carbonate and L-lactide are presented as a function of the feed ratio of the two cyclic monomers.

Introduction

Worldwide research efforts to explore effective catalysts for synthesizing biodegradable polymers for use in medical applications such as sutures, dental devices, orthopedic fixation devices, drug delivery systems, and tissue engineering are currently receiving much attention.[1,2] Specifically, the focus of these undertakings is to develop methods for producing biodegradable polymers of this type in a controlled manner where it is possible to tune their mechanical properties and degradation profiles. Among these polymers, polymeric biomaterials derived from lactic acid have numerous applications, originating with biodegradable sutures. Lactide is a cyclic dimer produced from the dehydration of lactic acid, which can be obtained on the basis of renewable starch-containing resources (e.g., corn, wheat, or sugar beet) by fermentation or by chemical synthesis. Lactide has the three isomers, L-lactide, D-lactide, and *meso*-lactide, where L- and D-lactide are enantiomers that comprise the *rac*-lactide. Pure L- or D-lactide forms crystalline isotactic polymer (Figure 1) while *rac*-lactide without control of stereocenters forms amorphous atactic polymer which is inappropriate for the commercial application (Figure 2).

Poly(lactide) as a biodegradable polymer has been intensively studied with wide range of applications, and ring-opening polymerization of lactides has been investigated using Sn,[3a–f] Ge,[3g] Y,[4] Ln,[5] Fe,[6] Ti/Zr,[7] Ta,[8] Mg,[9] Al,[10] Zn,[11a] Na,[11b] Li,[11c] and Ca[12] complexes. Among these studies, the control of stereoregularity in polymers by catalysts is an important feature for applications since the tacticity of the polymer leads to different properties.[13] The selectivity for lactide polymerization has been studied. Spassky et al. reported chiral binaphthyl Schiff base aluminum methoxide for stereoselectivity in the polymerization of *rac*-lactide where the aluminum methoxide complex demonstrated a preference for D-lactide over L-lactide to produce an optically active isotactic poly(D-lactide)

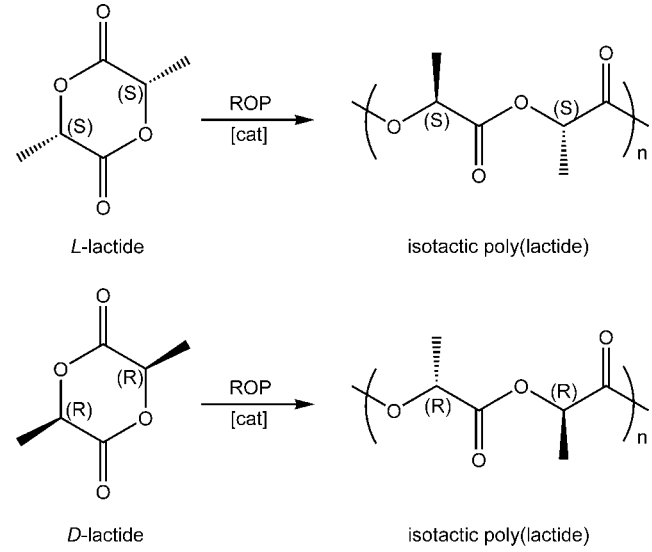

Figure 1. Isotactic poly(lactide) from ring-opening polymerization of L- or D-lactide.

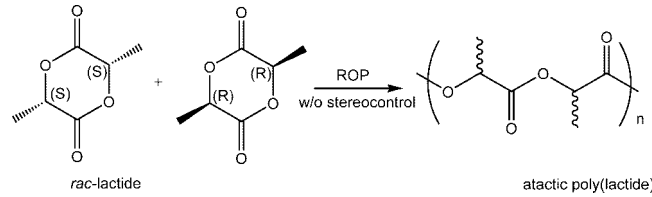

Figure 2. Atactic poly(lactide) from ring-opening polymerization of *rac*-lactide without stereocontrol.

from *rac*-lactide in toluene at 70 °C at low conversion of polymerization.[14] Similar chiral aluminum alkoxide by Coates et al.[15] produces highly syndiotactic polylactide from *meso*-lactide, and Feijen et al. employed chiral salen ligand to

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aluminum which demonstrated the polymerization of L-lactide to be faster than that of D-lactide ($k_L/k_D = 14$) and mostly yields isotactic poly(L-lactide) from *rac*-lactide with a selectivity factor of 5.5.[10a] 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.[12b,c]

However, the brittle nature of poly(lactide) should be modified to be used as biomedical materials. Important among these materials are thermoplastic elastomers obtained from lactides and trimethylene carbonate (1,3-dioxan-2-one or TMC).[16] The composite material derived from these rigid and elastic polymers provides implants with the necessary properties and degradation profiles appropriate for the specific clinical application. These latter copolymers are prominently used as biodegradable internal fixation devices for repair of fractures to small bones and joints, such as feet/hands or ankles/wrists.[17] 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. Copolymerization reactions of cyclic carbonate and cyclic ester have been studied using Sn,[3] Y,[4] and Ln[5] catalysts. These catalysts do not necessarily afford ideal copolymers, often resulting in random or block copolymer with low molecular weight and broad or bimodal molecular distributions. Because of the difficulty to control copolymer's composition and molecular weight, these catalysts yield copolymer with poor mechanical properties and biodegradability. Furthermore, because of the use of poly(TMC) and its copolymers with lactides as biomaterials, it is highly desirable to design effective catalysts for these processes derived from biocompatible materials. Indeed, we have previously shown that calcium salen catalysts in the presence of anionic initiators such as azide ions are very efficient at the ring-opening polymerization of trimethylene carbonate.[18] Other studies aimed at producing poly(TMC) in the absence of toxic catalyst residues include reports of the use of metal-free or organocatalysts[19,20] as well as lipase enzyme as catalysts.[21] Of importance, kinetic or mechanistic studies for the copolymerization process have rarely been reported although these studies are very important to control copolymer's composition and molecular weights which affect mechanical properties and biodegradation of these potential biomaterials.

At this time we wish to describe our studies of the ring-opening polymerization and copolymerization of lactides and trimethylene carbonate utilizing complexes derived from biocompatible metals. That is, calcium complexes with tridentate Schiff base ligands (Figure 3) have been synthesized and characterized and demonstrated to be effective catalysts for the polymerization of both lactides and trimethylene carbonate. Herein, we report investigations of the optimization of the catalysts along with kinetic and mechanistic studies of the homo- and copolymerization of these two monomers.

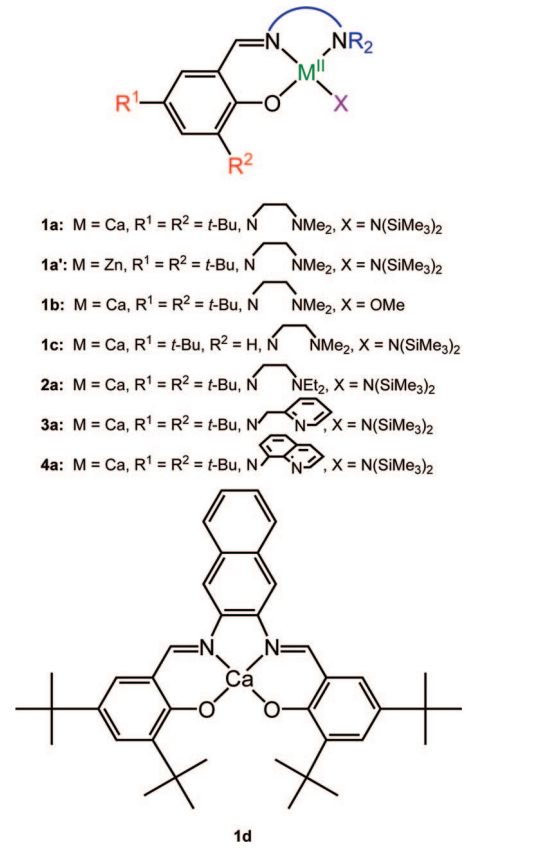


Figure 3. Structures of tridentate Schiff base biocompatible metal complexes utilized as catalysts for the ring-opening polymerization of cyclic monomers.

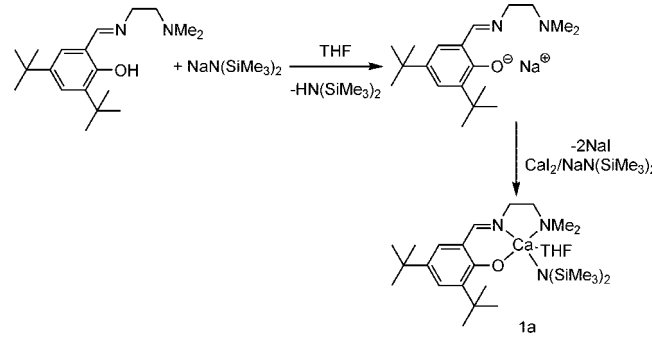


Figure 4. Reaction scheme for the preparation of complex **1a**.

Results and Discussion

Synthesis and Characterization of Calcium Complexes. Calcium complexes containing various tridentate Schiff base ligands have been synthesized by salt metathesis in a one-pot reaction from the Schiff base ligand in the presence of 2 equiv of $NaN(SiMe_3)_2$ and 1 equiv of CaI_2 in THF. Modifications of the Schiff base ligands were readily achieved by varying the aldehyde and diamine starting reagents.[22] Figure 4 illustrates the reaction sequence specifically utilized for the preparation of complex **1a**. The complexes were characterized by analytical/spectroscopic techniques, and in the case of complex **1a** the solid-state structure was established by single-crystal X-ray diffraction. All isolated calcium derivatives were found to contain two to three bound molecules THF in $CDCl_3$ solution by ^1H NMR spectroscopy.

Crystals of complex **1a** suitable for X-ray crystallographic analysis were obtained by slow diffusion of pentane into a saturated benzene solution of the complex at 5 °C. The solid-state structure of complex **1a** shows the calcium center to be five-coordinate and of approximately square-pyramidal geometry with a THF molecule occupying the axial site. There are several $Si-CH_3\cdots Ca$ distances within van der Waals contact of 3.8 Å. The two shortest distances to H25C and H25A on Si(2) of 2.736(3) and 2.766(1) Å are directed at the "vacant" site of the 5-coordinate calcium center (see Supporting Information). Figure 5 contains a thermal ellipsoid representation of complex **1a**, along with pertinent bond distances and angles. As an aside, it should be noted that the analogous calcium derivative containing

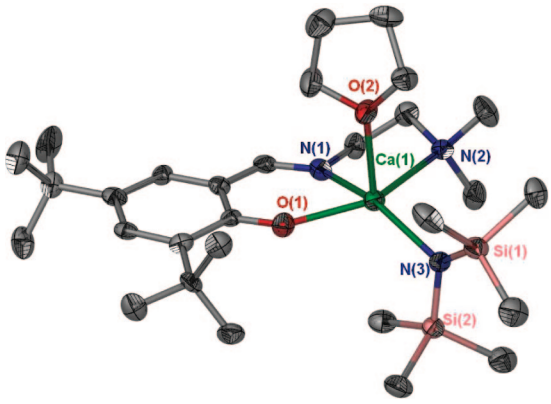


Figure 5. Perspective thermal ellipsoid drawing of the molecular structure of complex **1a** at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Ca(1)−O(1) 2.1914(16), Ca(1)−N(1) 2.474(2), Ca(1)−N(2) 2.600(2),Ca(1)−N(3)2.3512(19),Ca(1)−O(2)2.3494(18);O(1)−Ca(1)−N(1) 74.50(6), N(1)−Ca(1)−N(2) 69.02(7), N(2)−Ca(1)−N(3) 101.02(7), O(1)−Ca(1)−O(2) 93.86(6), O(1)−Ca(1)−N(3) 112.16(7), O(2)−Ca(1)−N(3) 108.93(7), O(1)−Ca(1)−N(3) 112.16(7), Si(1)−N(3)−Si(2) 125.75(11).

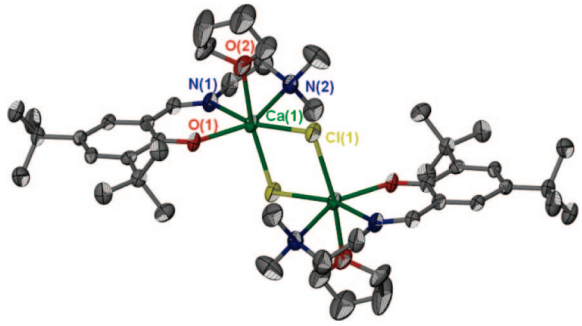


Figure 6. Perspective thermal ellipsoid drawing of the dimeric chloro derivative at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Ca(1)—Cl(1) 2.7345(17), Ca(1)—Cl(1)$^{\#}$ 2.7248(16), Ca(1)···Ca(1)$^{\#}$ 3.9971(19); Cl(1)—Ca(1)—Cl(1)$^{\#}$ 85.86(5).

the (2-methylbenzyl)$_2$N−amido group in the presence of CH_2Cl_2 afforded the dimeric pseudooctahedral complex displayed in Figure 6. That is, this dichloro derivative was obtained upon recrystallization of the amido derivative by the slow diffusion of pentane into a saturated dichloromethane solution of the complex at −15 °C. In general, these amide derivatives of calcium react with chlorinated hydrocarbon solvents leading to chloro−metal complexes, presumably via initial deprotonation of the acidic protons of CH_2Cl_2 or $CHCl_3$ by the strong amide base. Nevertheless, it should be noted here that this reaction is not very fast (vide infra). Chisholm and co-workers have similarly reported that amide derivatives of calcium β-diiminates are reactive toward chlorinated solvents such as CH_2Cl_2.[23a]

Melt Ring-Opening Polymerization Studies. Initially, the effectiveness of the calcium complexes was examined for the ring-opening polymerization of L-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 (**1d**) with bis(phosphoranylidene)ammonium azide ([PPN]N_3) as a cocatalyst is much less active than calcium with tridentate

Table 1. Polymerization of L-Lactide Catalyzed by Biocompatible Metal Complexes[a]

entry	M	conversion (%)[b]	TOF[c]
1	**1a**	80	1124
2	**1a′**	16	22.3
3	**1b**	59	826
4	**1c**	64	891
5[d]	**1d**	35	227

[a] Each reaction was performed in melt maintaining a monomer:initiator ratio as 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] Reaction carried out for 6 h at 110 °C.

Table 2. Polymerization Results on Varying the Backbone Where the Substituents in the 3,5-Positions of the Phenolate Ring Are *tert*-Butyl Groups[a]

entry	NR_2	conversion (%)[b]	TOF[c]
1	dimethylamine (**1a**)	80	1124
2	diethylamine (**2a**)	54	753
3	pyridine (**3a**)	41	519
4	aminoquinoline (**4a**)	39	502

[a] Each reaction was performed in melt maintaining a monomer:initiator ratio as 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).

Schiff base ligands. Furthermore, the analogous zinc complex (**1a′**) is also less active than calcium complex (**1a**). Changing the initiator to methoxy (complex **1b**) displayed similar activity to bis(trimethylsilyl)amide. Less hindered and less donating hydrogen substituent on R^2 (**1c**) resulted in similar activity to bulky *tert*-butyl group, but with less stereoselectivity (vide infra). However, more significant changes in TOFs were noted upon altering the nature of the imine backbone (Table 2). 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. Hence, we will utilize this derivative for kinetic studies of the polymerization of L-lactide in solution.

The melt polymerization of L-lactide was carried out at 110 °C using complex **1a** as catalyst as a function of the monomer:initiator ratio. As indicated in Table 3 and shown graphically in Figure 7, 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. Because of the experimental design of these melt polymerization reactions, some of the lactide sublimed from the reaction medium, resulting in the process being limited to about 80% of the monomer being consumed. For example, when entry 1 in Table 3 was carried out for longer periods (1.5 and 16 h), 80% conversion was observed as well, or 100% of the available monomer was consumed. In the latter instances, a decrease in M_n to ∼53 000 with a concomitant increase in PDI of ∼1.6 were observed due to transesterification of the polymer chain. The molecular weights and polydispersities of poly(L-lactide) were determined by gel permeation chromatography (dual RI and light scattering detectors) in tetrahydrofuran using polystyrene as standard.

Solution Kinetic Studies of Ring-Opening Polymerization of L-lactide. Kinetic measurements of the ring-opening polymerization of L-lactide in solution were performed in the presence of catalyst **1a**. These studies were conducted in $CDCl_3$ and monitored by ^{1}H NMR spectroscopy. It should be noted here that the lactide monomer and calcium catalyst were introduced to the reaction vessel prior to the addition of $CDCl_3$. In this manner initiation of the polymerization of lactide by the

Table 3. Dependence of Poly(lactide) Molecular Weight on M/I[a]

entry	M/I	conversion (%)[b]	M/I × monomer conversion	M_n theoretical[c]	M_n GPC	PDI
1	350	80	280	40 481	65 000	1.02
2	450	70	315	45 360	82 400	1.05
3	500	70	350	50 400	94 500	1.04
4	700	69	483	69 552	110 600	1.04

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

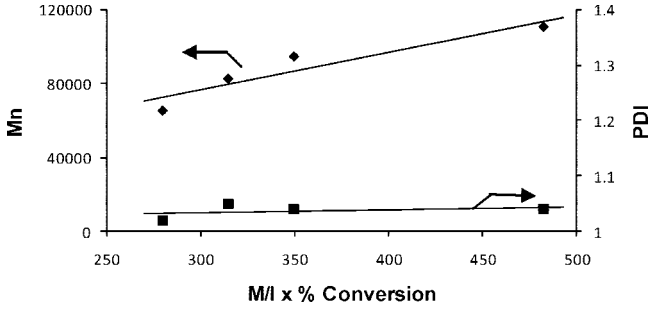


Figure 7. Plot of the dependence of molecular weight of poly(L-lactide) on M/I ratios.

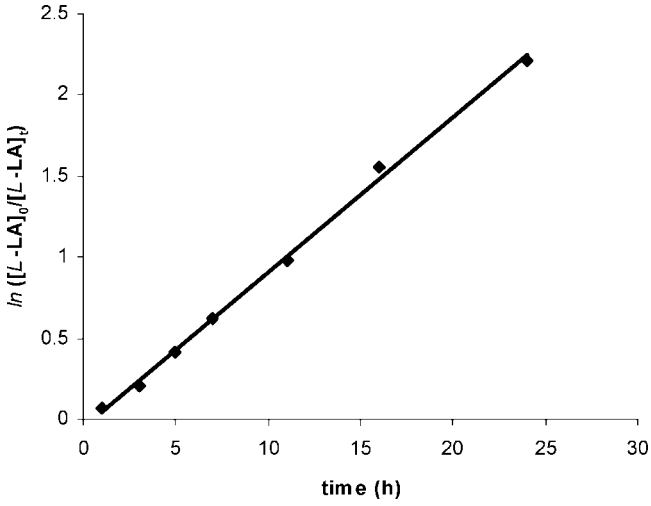


Figure 8. ln([L-LA]$_0$/[L-LA]$_t$) vs time plot depicting a reaction order of unity with respect to monomer concentration (R^2 = 0.997).

amide group was faster than the transformation of the calcium amide derivative to its chloro derivative (vide supra).[24] The polymerization reaction was found to be first order in monomer (L-lactide) (Figure 8) and catalyst concentrations with k = 19.9 M^{-1} h^{-1} at ambient temperature (Figure 9). Table 4 summarizes the determined rate constants (k_{obsd}) for the ring-opening polymerization of L-lactide as a function of the catalyst concentration and temperature.

The activation parameters for the ring-opening polymerization of L-lactide catalyzed by **1a** in $CDCl_3$ were found to be $\Delta H^{\ddagger}$ = 73.5 ± 3.8 kJ/mol and $\Delta S^{\ddagger}$ = −42.5 ± 12.6 J/(mol K). These values were calculated from the temperature-dependent second-order rate constants determined from k_{obsd} divided by [Ca] values as provided in Table 4 and the Eyring plot in Figure 10. A $\Delta G^{\ddagger}$ value of 86.1 kJ/mol was calculated for the ring-opening polymerization of L-lactide catalyzed by the calcium catalyst (**1a**) at 25 °C.

Of significance, the rate of polymerization of L-lactide in the presence of catalyst **1a** was found to be appreciably faster in the coordinating solvent tetrahydrofuran than in chloroform. As illustrated in Figure 11, the rate of polymerization at ambient temperature in chloroform solution was found to increase with

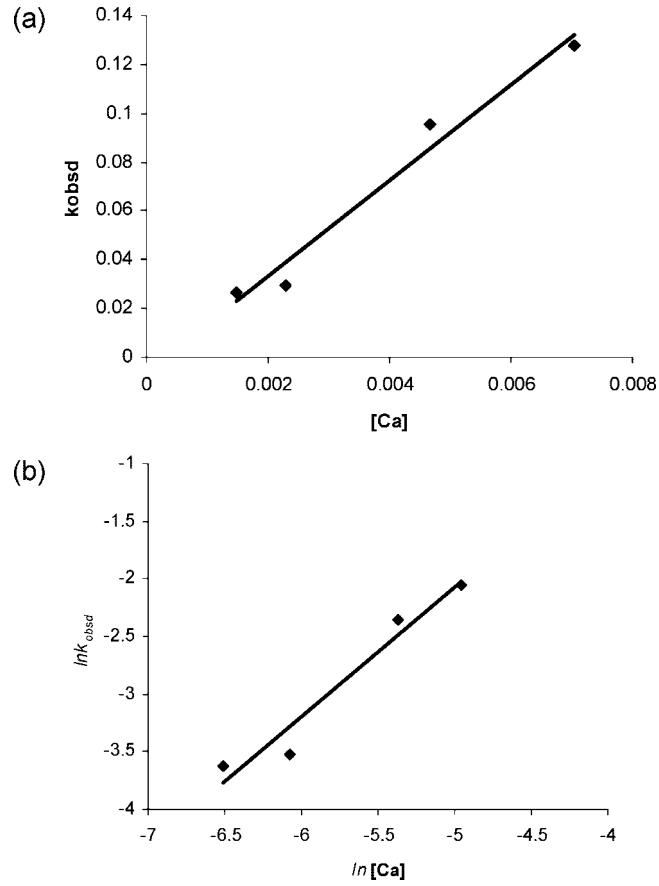


Figure 9. (a) Plot of k_{obsd} vs [Ca] with slope = 19.9 and R^2 = 0.971. (b) Plot of ln k_{obsd} vs ln[Ca] with slope = 1.12 with R^2 = 0.949.

Table 4. Rate Constants Dependence on the Concentration of the Catalyst (1a) and Temperature[a]

entry	[Ca] (mM)	temp (°C)	k_{obsd} (h^{-1})
1	1.49	25.0	0.0266
2	2.30	25.0	0.0295
3	4.66	25.0	0.0955
4	7.03	25.0	0.1277
5	4.66	0.0	0.0047
6	4.66	41.0	0.4731
7	4.66	51.0	0.8083

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

the addition of increasing quantities of THF. That is, the rate constant (k) for lactide enchainment reached a maximum value of 69.4 M^{-1} h^{-1} at 25 °C at greater than 1.0 M THF or more than 3 times its corresponding value in pure chloroform. This is explained by the coordination of the calcium center by THF molecules which enhance the nucleophilicity of the X initiator or the alkoxide ligand of the growing polymer chain. A similar observation has been reported by Feijen and co-workers, as well as Chisholm and co-workers, for the polymerization of L-lactide initiated by calcium alkoxides.[23] This kinetic result suggests the lactide ring-opening event to be proceeding via a simple

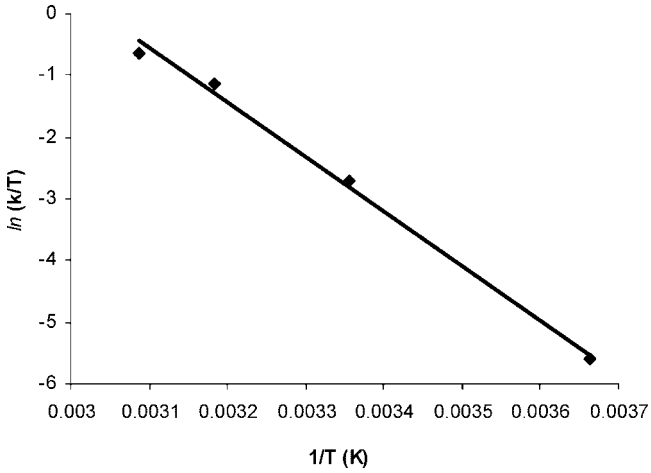


Figure 10. Eyring plot of ROP of L-lactide in the presence of catalyst **1a** in $CDCl_3$. Slope = −8836 with $R^2 = 0.995$.

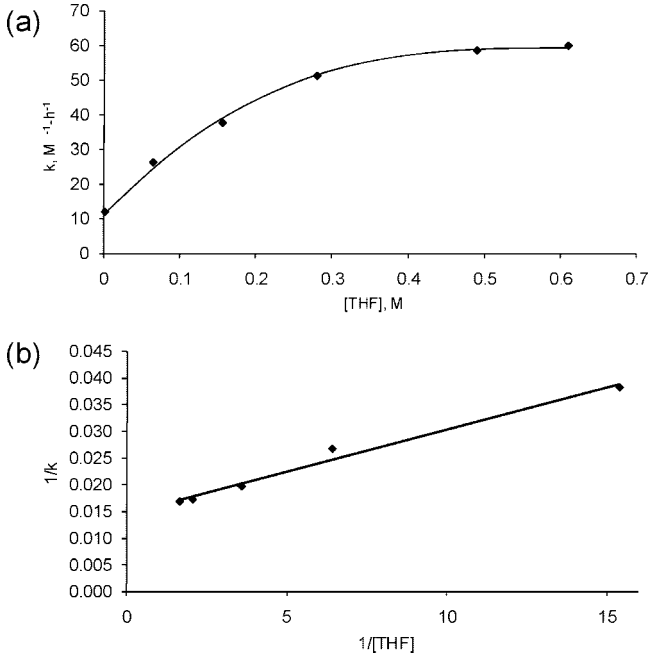
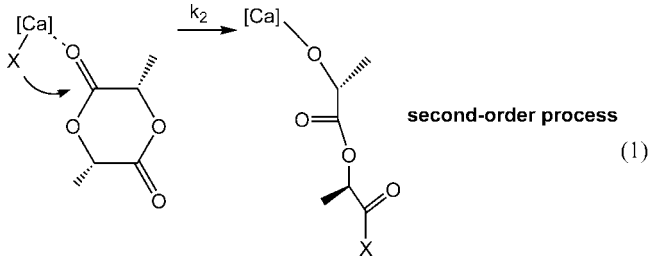


Figure 11. Dependence of rate constant for L-lactide enchainment on the THF concentration in chloroform at 25 °C. (a) Second-order rate constant, k, as a function of [THF]. (b) Double reciprocal plot of $1/k$ vs 1/[THF], affording an intercept of $1/k$ of 0.0144 or $k_{max} = 69.4\ M^{-1}\ h^{-1}$, $R^2 = 0.984$.

second-order process (eq 1), which does not require lactide coordination at the calcium metal center prior to ring opening.



(1)

Because the physical and degradation properties of poly(lactides) are highly dependent on the polymers' stereochemistries, it is imperative that the polymerization of *rac*-lactide is stereoselective. In this regard the catalytic polymerization of *rac*-lactide utilizing complex **1a** and the closely related

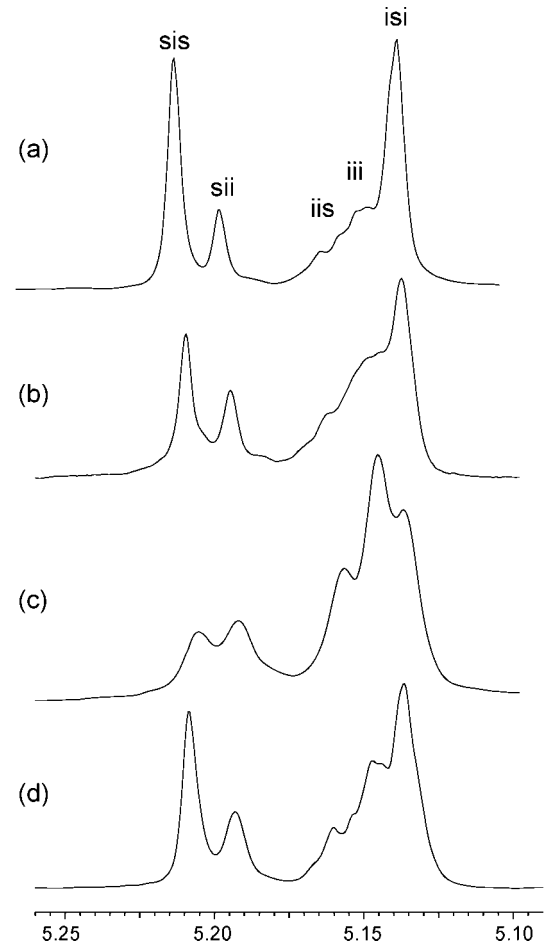


Figure 12. Homonuclear decoupled ^1H NMR ($CDCl_3$, 500 MHz) spectra of the methine region of poly(lactide) prepared from *rac*-lactide with **1a** (a) in THF at −33 °C (Pr = 0.73), (b) in THF at 0 °C (Pr = 0.57), (c) in THF at room temperature (Pr = 0.52), and (d) in $CDCl_3$ at room temperature (Pr = 0.66).

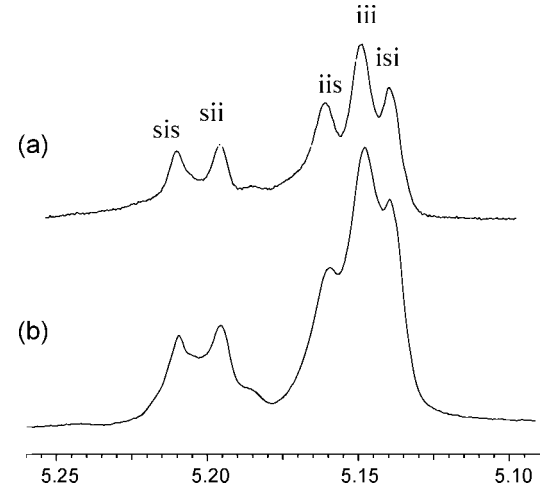


Figure 13. Homonuclear decoupled ^1H NMR ($CDCl_3$, 500 MHz) spectra of the methine region of poly(lactide) prepared from *rac*-lactide with **1c** (a) in THF at room temperature (Pr = 0.48) and (b) in $CDCl_3$ at room temperature (Pr = 0.54).

but sterically less crowded complex **1c** was examined in both $CDCl_3$ and THF at ambient temperature. The tacticity of the produced polymers was assigned using the methine proton signals with homonuclear decoupling as described by Hillmyer and co-workers.[25] Pr values were calculated from the

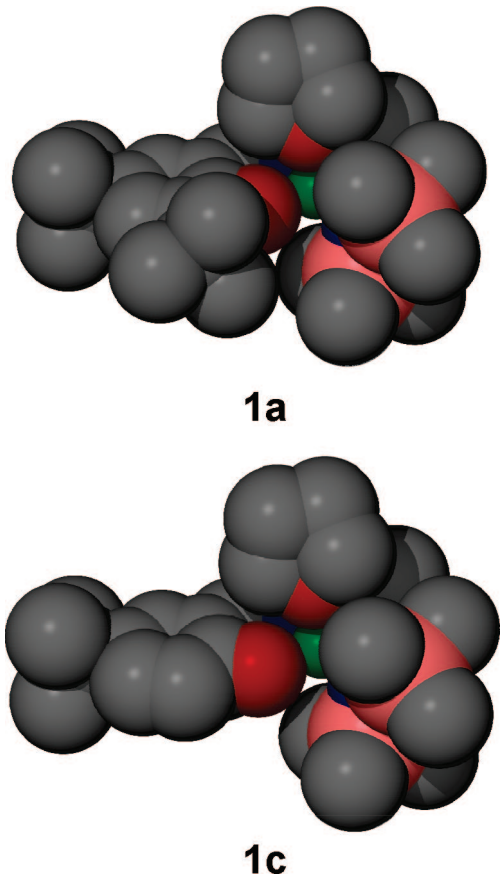


Figure 14. Space-filling models of complexes **1a** and **1c** illustrating the greater access to the metal center in the sterically less crowded complex **1c**. Complex **1c** is presented as a model structure where the ^{t}Bu substituent was removed from complex **1a**.

ratio of the (area of isi and sis)/(total area in methine proton region) from the decoupled ^{1}H NMR spectra shown in Figures 12 and 13. As evident from the proton NMR spectra in Figure 12, the polymer produced employing complex **1a** as catalyst provided poly(lactide) with a moderate degree (Pr = 0.73) of heterotacticity in THF at low temperature (−33 °C), with stereoselectivity decreasing with increasing polymerization reactions temperature (Pr = 0.52 at 25 °C). On the other hand, complex **1a** as catalyst in $CDCl_3$ at ambient temperature provided a polymer from *rac*-lactide with a Pr value of 0.66. In stark contrast utilizing complex **1c** as catalyst, where R_2 = *tert*-butyl in complex **1a** is replaced by the sterically nonencumbering H atom, afforded completely atactic poly(lactide) from *rac*-lactide, as shown in Figure 13.[11a] Figure 14 illustrates the difference in steric crowding about the metal centers in complexes **1a** and **1c**.

Solution Kinetic Studies of Ring-Opening Polymerization of Trimethylene Carbonate. The ring-opening polymerization of trimethylene carbonate catalyzed by complex **1a** in $CDCl_3$ was shown to similarly be first order in monomer (Figure 15) and catalyst concentrations (Figure 16). Table 5 lists the determined rate constants (k_{obsd}) for the ring-opening polymerization of trimethylene carbonate as a function of the catalyst concentration and temperature. In this instance, the rate of polymerization of TMC is much faster than that for L-lactide with a rate constant parameter at ambient temperature of 500 M^{-1} h^{-1}. Since TMC is known to readily form adducts with calcium complexes, it is not possible to define this rate constant parameter as a simply second-order rate constant (k_2) or the product of a rapid equilibrium of **1a** and TMC followed by a first-order rate constant for TMC ring-opening or enchainment

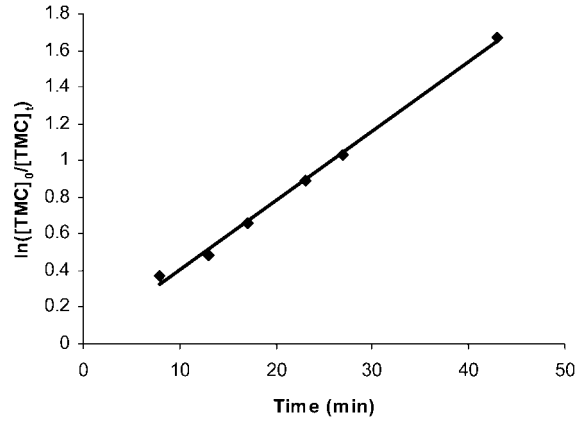


Figure 15. $\ln([TMC]_0/[TMC]_t)$ vs time plot depicting a reaction order of unity with respect to monomer concentration (R^2 = 0.996).

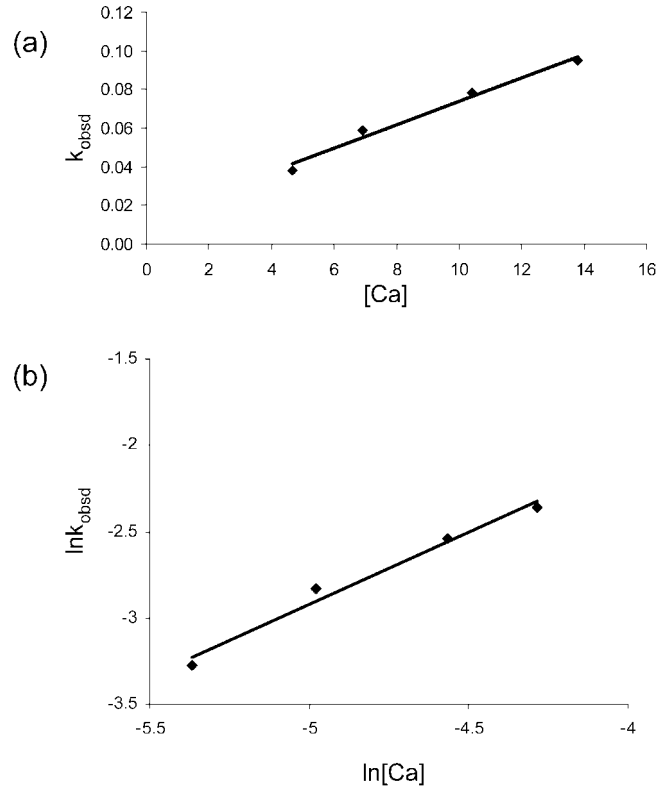


Figure 16. (a) Plot of k_{obsd} vs [Ca], illustrating a linear dependence of k_{obsd} on catalyst construction, R^2 = 0.9797. (b) Plot of ln k_{obsd} vs ln[Ca] with slope = 0.83 with R^2 = 0.984.

Table 5. Rate Constants Dependence on the Concentration of the Catalyst and Temperature for ROP of TMC[a]

entry	[Ca] (mM)	temp (°C)	k_{obsd} (min^{-1})
1	4.66	22.0	0.0379
2	6.90	22.0	0.0588
3	10.4	22.0	0.0787
4	13.8	22.0	0.0948
5	6.90	6.0	0.0146
6	6.90	0.0	0.0101
7	6.90	−33.0	0.00112

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

(k_2K_1) (eq2). As previously reported for calcium salen complexes initiated by an external nucleophile,[18] the ring-opening polymerization of trimethylene carbonate by complex **1a** was found to have a high level of polymerization control. That is, the

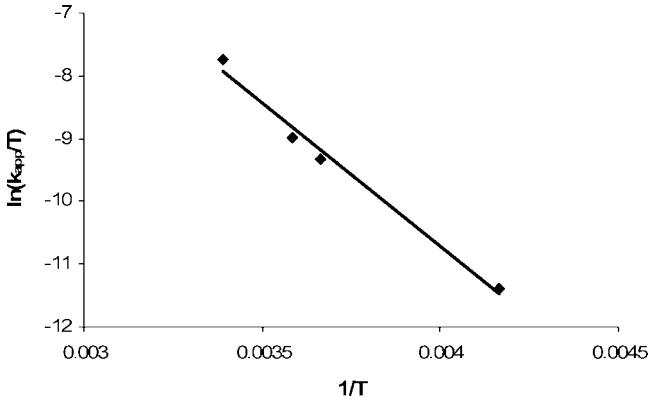
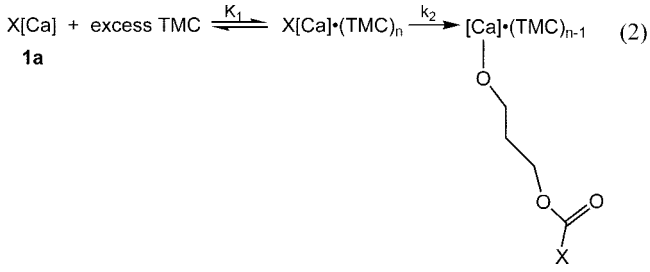


Figure 17. Eyring plot of ROP of TMC in the presence of catalyst **1a** in $CDCl_3$. Slope = −4557 with R^2 = 0.987.

product polymers exhibited a linear increase in M_n with conversion and possessed low polydispersity indices.



(2)

Activation parameters ($\Delta H^{\ddagger}_{app}$ = 37.9 ± 3.1 kJ/mol, $\Delta S^{\ddagger}_{app}$ = −135.1 ± 11.4 J/(mol K)) for the ROP of TMC were determined from the Eyring plot in Figure 17, where k_{app} may be k_2K_1 or k_2. In either instance a plot of $\ln(k_{app}/T)$ vs $1/T$ is linear; however, for the preequilibrium process $\Delta H^{\ddagger}_{app}$ and $\Delta S^{\ddagger}_{app}$ would have components due to $\Delta H°$ and $\Delta S°$ for the preequilibrium reaction. The apparent $\Delta G^{\ddagger}$ is calculated at 25 °C to be 78.2 kJ/mol, which is consistent with the ring-opening polymerization of TMC being a less energetic process compared to lactide, where $\Delta G^{\ddagger}$ was found to be 86.1 kJ/mol at 25 °C.

Copolymerization of L-Lactide and Trimethylene Carbonate. Catalyst **1a** was shown to effectively copolymerize lactides and trimethylene carbonate in solution. These reactions were carried out at ambient temperature in $CDCl_3$ and were monitored by ^{1}H NMR spectroscopy. A tapered poly(lactide)−poly(TMC) copolymer, where the lactide monomer conversion was initially high, was afforded during the simultaneous polymerization of lactides and trimethylene carbonate, whereas a diblock copolymer was obtained following the completion of polymerization of TMC by the addition of a solution of lactide monomer. Copolymers were purified by precipitation from 5% HCl and methanol and dried in vacuo. A purified diblock copolymer possessing a composition 55:45 (mol of PLLA:mol of PTMC) as revealed by ^{1}H NMR and a M_n value of 18 000 (PDI = 1.73) was shown to be stable up to 250 °C with a T_m of 150 °C (Figure 18). Diblock copolymers with other compositions and molecular weights exhibited thermal properties as indicated in Table 6. Thus far, we have not established whether a diblock copolymer of L-lactide and TMC can be obtained by first polymerizing L-lactide with these calcium complexes. However, Höcker et al. have demonstrated that although an A−B block copolymer was isolated by first polymerizing 2,2-dimethyltrimethylene carbonate (DTC) with a Et_2Zn initiator and then L-lactide, a statistical diad distribution in the copolymer was obtained upon first polymerizing L-lactide.[26] On the other hand, Duda and coworkers have show that when employing an aluminum alkoxide initiator, an A−B block copolymer of L-lactide and ϵ-caprolactone was obtained starting from a living poly(L-lactide).[27]

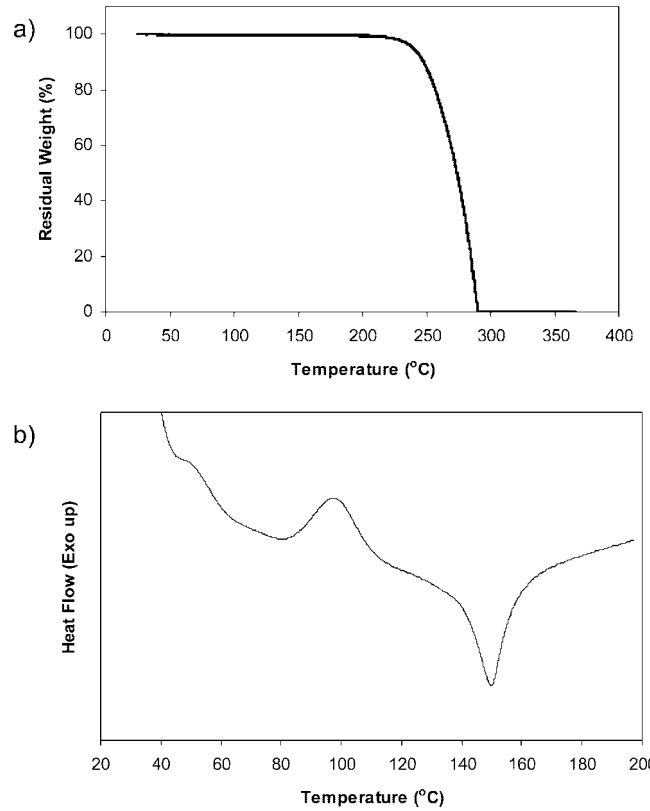


Figure 18. (a) TGA and (b) DSC curves (second heating run) of TMC-*block*-LLA copolymer (composition = 45:55 (mol:mol) by ^{1}H NMR after purification).

Table 6. Physical and Thermal Properties of Diblock Copolymers of Poly(TMC) and Poly(L-lactide)

composition[a] (TMC:L-lactide)	M_n (PDI)	decomposition temp (°C)	T_m[b] (°C)
45:55	18 000 (1.73)	250	150
47:53	41 500 (1.84)[c]	300	155
37:63	22 000 (2.49)[c]	300	144

[a] Determined by ^{1}H NMR spectroscopy on purified copolymer. [b] Determined from second heating run. [c] Theoretical molecular weight values in close agreement with M_n observed, i.e., 45 000 and 22 000, respectively.

A solution kinetic study of the copolymerization reaction of TMC and L-lactide catalyzed by **1a** has been investigated monitoring the rate of enchainment of trimethylene carbonates as well as that of lactide during copolymerization. As mentioned earlier, it was observed that the rate of enchainment of trimethylene carbonate monomer is much slower than that of lactide during the copolymerization reactions, thereby affording a tapered poly(lactide)−poly(TMC) copolymer. As might be anticipated, it was also noted that the rate of enchainment of trimethylene carbonate is increased after ROP of lactide is completed, which means that the two reactions of ring-opening polymerization of cyclic monomers compete with each other and influence the other's reactivity. In order to investigate the kinetics in detail, the concentration of catalyst and feed ratio of trimethylene carbonate and lactide were varied.

The polymerization reaction was found to be first-order in each monomer (trimethylene carbonates and L-lactide) concentration (Figure 19) and catalyst (Figure 20). Table 7 summarizes the determined rate constants (k_{obsd}) for the copolymerization of trimethylene carbonate and L-lactide as a function of the catalyst concentration and temperature when the feed ratio is 50:50 (mol:mol).

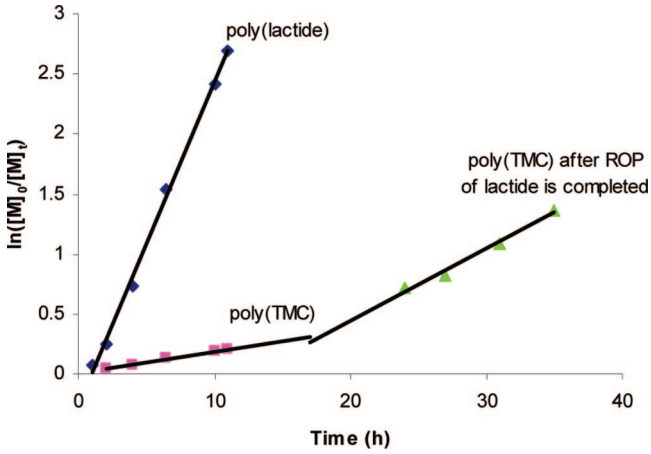


Figure 19. $\ln([M]_0/[M]_t)$ vs time plot depicting a reaction order of unity with respect to each monomer concentration ($R^2 = 0.997$ for poly(lactide) and $R^2 = 0.993$ for poly(TMC)).

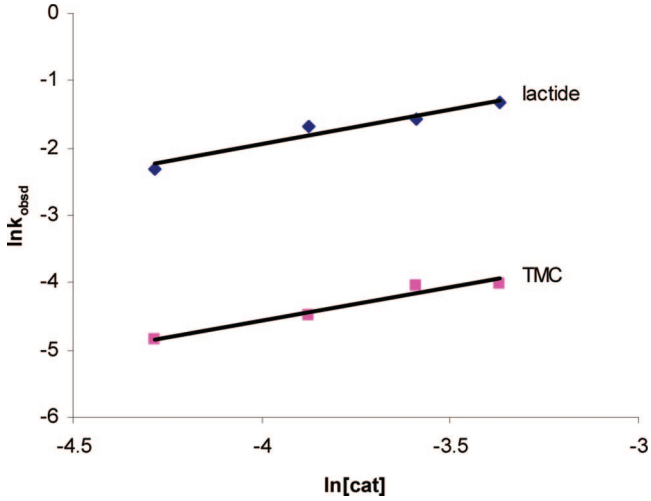


Figure 20. Plot of ln k_{obsd} vs ln [cat.] to determine the order of the polymerization reaction with respect to the concentration of catalyst. Slope = 1.04 with $R^2 = 0.956$ for lactide. Slope = 0.983 with $R^2 = 0.956$ for TMC.

Table 7. Rate Constants Dependence on the Concentration of the Catalyst and Temperature in Copolymerization[a]

entry	[cat.] (mM)	temp (°C)	k_{obsd} (lactide) (h^{-1})	k_{obsd} (TMC) (h^{-1})
1	13.8	25	0.0997	0.0078
2	20.7	25	0.185	0.0113
3	27.6	25	0.211	0.0175
4	34.5	25	0.268	0.0180
5	13.8	0	0.0125	0.00106
6	13.8	41	0.873	0.0672
7	13.8	51	n.d.[b]	0.0918

[a] Each monomer concentration held constant at 0.69 M and reactions carried out in $CDCl_3$. [b] n.d. = not determined because the reaction was too fast.

On the basis of these kinetic results, the copolymerization rate can be expressed as indicated in eq 3. Activation parameters have been determined from Eyring plots, and these are compared with activation parameters for the homopolymerization of L-lactide or trimethylene carbonate (Table 8). $\Delta H^{\ddagger}$ for ROP of lactide in copolymerization is lower than that in homopolymerization while $\Delta H^{\ddagger}$ for ROP of TMC in copolymerization is higher than that of its homopolymerization. From these kinetic parameters for the ring-opening polymerizations of L-lactide and TMC, it was observed that L-lactide has a higher $\Delta H^{\ddagger}$ than that of TMC and less negative $\Delta S^{\ddagger}$ than that of TMC in both homopolymerization and copolymerization process.

Table 9. Rate Constants Dependence on the Monomer Feed Ratio in Copolymerization[a]

entry	L-lactide:TMC (mol:mol)	k_{obsd}(lactide) (h^{-1})	k_{obsd}(TMC) (h^{-1})	k_{obsd}(TMC)[b] (h^{-1})
1	1:99	n.d.[b]	0.2115	0.6450
2	5:95	0.3453	0.0620	0.5270
3	25:75	0.1971	0.0150	0.0158
4	50:50	0.1847	0.0113	0.0465
5	75:25	0.1722	0.0101	0.0360
6	95:5	0.1685	n.d.[c]	0.0029
7	99:1	0.1540	n.d.[c]	n.d.[c]

[a] Reactions carried out in $CDCl_3$ at room temperature; [cat.] = 0.0207 M. [b] Determined rate constant after lactide polymerization is completed. [c] n.d. = not detected because of too small amount of monomer.

$$\text{rate} = [\text{cat.}](k_{LA}[\text{L-lactide}] + k_{TMC}[\text{TMC}]) \quad (3)$$

The feed ratios were also changed in order to investigate the influence of the other monomer, and Table 9 lists the determined rate constants (k_{obsd}) for the various feed ratios. Rate constants for L-lactide polymerization or TMC polymerization in a copolymerization process have been plotted depending on the fraction of the other monomers (Figure 21). According to these results, the rate to grow poly(lactide) is increased with increasing amounts of TMC (vide infra),[23] while the rate to grow poly(TMC) is decreased with increasing amounts of lactide. Rate constants were found to change significantly between 0.0 and 0.1 of monomer fraction and little between 0.25 and 0.75, and the rate drops more dramatically in TMC polymerization, even in the presence of small quantities of lactide.

The average copolymerization rate is expressed in eq 4, and the average rate constant is plotted as a function of the fraction of TMC (Figure 22), where the average rate was calculated from eq 5 and $\bar{k}$ is an average rate constant for copolymerization.[28] The average rate constant for copolymerization is decreased with the fraction of TMC between 0.0 and 0.75 and increased very dramatically between 0.95 and 1.0.

$$\text{rate} = \bar{k}[\text{cat.}]([\text{L-lactide}] + [\text{TMC}]) \quad (4)$$

$$\text{total \% conversion} = \frac{\%\ \text{conv(L-lactide)} \times \text{g of L-lactide} + \%\ \text{conv(TMC)} \times \text{g of TMC}}{\text{g of L-lactide} + \text{g of TMC}} \quad (5)$$

Binding Studies between Monomers and Calcium Complexes. Pertinent to $\Delta S^{\ddagger}$ values for ROP of lactide and TMC, binding studies between these two monomers and the metal complex have been investigated using the (salen)Ca azide adduct in tetrachloroethane which exist as an equilibrium mixture of (salen)Ca and (salen)CaN_3^- (eq 6). The equilibrium processes for the reaction in eqs 6 and 7 were determined by monitoring the ν_{N_3} vibrational modes in the metal bound and free azide species. For ROP of TMC, upon addition of excess trimethylene carbonate all the azide ligand is free in solution.[18] The infrared spectra showed the free ν_{N_3} absorption was not increased much with the addition of an equivalent quantity of lactide (Figure 23) compared to that upon addition of TMC. The better binding ability of TMC to Ca(II) metal is consistent with the larger negative $\Delta S^{\ddagger}$ value for ROP

Table 8. Comparison of Activation Parameters in Homopolymerization and Copolymerization

	homopolymerization		copolymerization	
	lactide	TMC	lactide	TMC
$\Delta H^{\ddagger}$ (kJ/mol)	73.5 ± 3.8	37.9 ± 3.1	68.8 ± 8.3	63.9 ± 6.7
$\Delta S^{\ddagger}$ (J/(mol K))	−42.5 ± 12.6	−135.1 ± 11.4	−62.0 ± 28.3	−100.3 ± 22.4
$\Delta G^{\ddagger}$ (kJ/mol) at RT	86.1	78.2	87.3	93.8

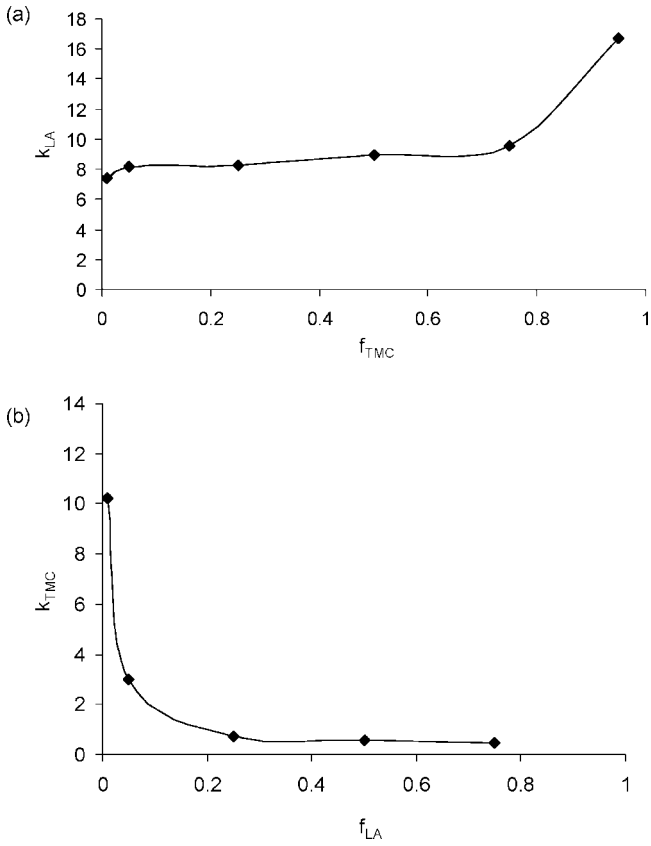


Figure 21. Rate constants as a function of fraction of monomers in copolymerization of lactide and TMC: (a) rate constant for lactide polymerization vs fraction of TMC; (b) rate constant for TMC polymerization vs fraction of lactide.

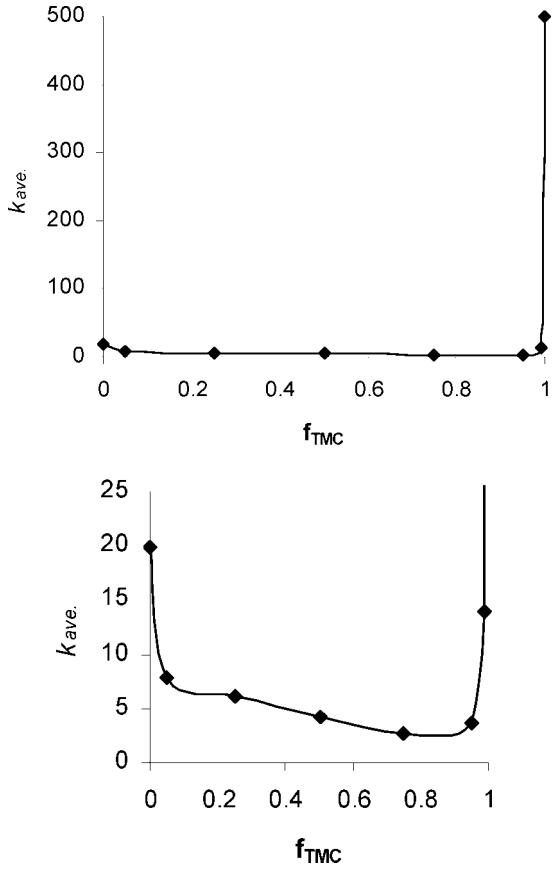


Figure 22. Average rate constants as a function of fraction of TMC monomers in copolymerization of lactide and TMC.

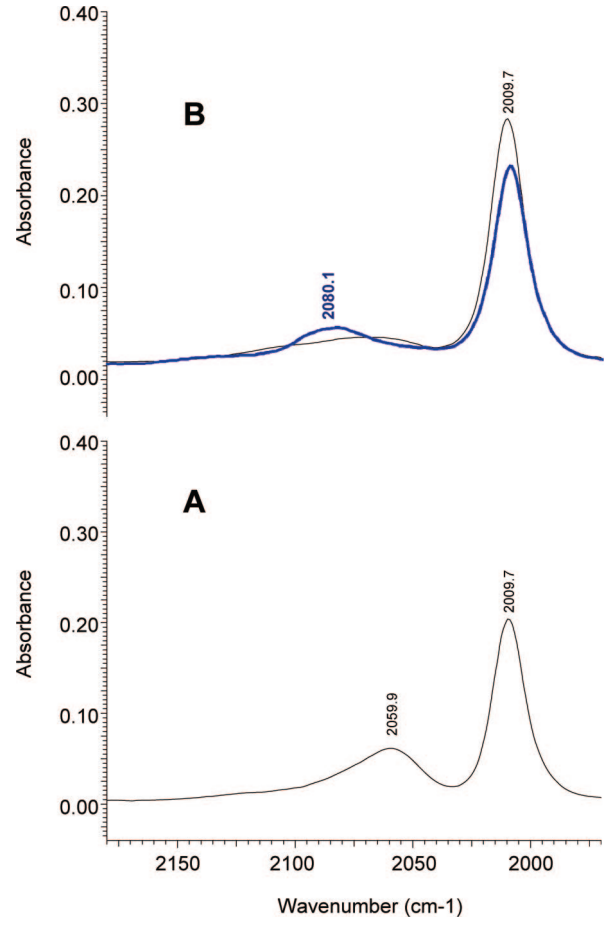
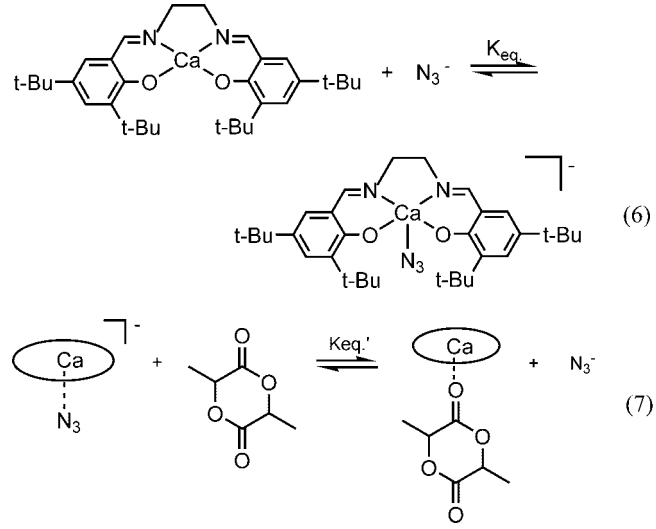


Figure 23. Infrared spectra in ν_{N_3} stretching region in tetrachloroethane. (A) 0.025 M Ca(salen) and 1 equiv of n-$Bu_4N^+N_3^-$ at ambient temperature, 2009.7 cm^{-1} peak for free N_3^- and 2059.9 cm^{-1} peak for calcium bound N_3^-. (B) After addition of 50 equiv of lactide to the solution in (A) (thick blue line) and after addition of 50 equiv of TMC to the solution in (A). Note that free ν_{N_3} absorption has increased less with addition of lactide than that with TMC.

of TMC vs lactide and supports the role of TMC in enhancing the catalytic activity of the calcium derivative (complex **1a**) during the copolymerization of TMC and lactide.



(6)

(7)

Summary

Herein we have reported on the use of tridentate Schiff base derivatives of biocompatible metals as catalysts for the ring-opening polymerizations of the cyclic monomers. Among these

metal derivatives, calcium complexes have shown 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 copolymerize these two monomers. Solution kinetic studies revealed the polymerization reaction to be first order in both [monomer] and [catalyst]. The polymerization reactions were shown to be quasi-living as illustrated by a linear relationship between M_n and % conversion and a low polydispersity index, clearly demonstrating that the level of polymerization control was high. From stereoselectivity studies of *rac*-lactide polymerization, the polymer tacticity under various polymerization conditions have been investigated, and it was shown that catalyst **1a** produced heterotactic poly(lactide) with a Pr value of 0.73 from *rac*-lactide at −33 °C in THF.

Activation parameters for trimethylene carbonate and lactides homopolymerization have been determined, and it was found that ring-opening polymerization of TMC has a lower $\Delta G^{\ddagger}$ at 25 °C than that of lactide. Activation parameters for copolymerization of lactide and trimethylene carbonate have also been determined and compared with those for homopolymerization. It was observed that the feed ratios influence not only polymer properties and degradation but also the copolymerization rates.

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Supporting Information Available: Experimental details for the synthesis and polymerization reactions; X-ray crystallographic file in CIF format for the structure determination of complex **1a** and its dimeric chloro derivative. This material is available free of charge via the Internet at http://pubs.acs.org.

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