Synthesis, Characterization, and Catalytic Activity of Titanium Iminophenoxide Complexes in Relation to the Ring-Opening Polymerization of L-Lactide and ε-Caprolactone

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ABSTRACT: This study synthesized a series of titanium iminophenoxide complexes and investigated their suitability as catalysts for the ring-opening polymerization of L-lactide (L-LA) and ε -caprolactone (CL). Complexes with bidentate ligands demonstrate higher catalytic activity than their tridentate counterparts since the third coordination atom needs to contend with L-LA and CL. Differences in the geometric framework of bidentate ligands also influence the catalytic activity. Type II

INTRODUCTION Ligands are crucial to organometallic catalysis, like olefin polymerization and asymmetric synthesis, due to their ability to improve reactivity and selectivity. Schiff base ligands are commonly selected due to their diversity and simplicity of preparation, and Schiff base metal-supported complexes can be found in a wide range of applications.¹ Schiff base complexes such as Zn² Mg³ Ca⁴ and alkali metals⁵ have been used in the ring-opening polymerization (ROP) of cyclic esters, such as rac-lactide (rac-LA) and *ɛ*-caprolactone (CL) and the effectiveness of Schiff base ligands in protecting the catalytic center from trans-esterification and enhancing reactivity has been widely demonstrated. Biodegradable polyesters are commonly employed in the encapsulation and delivery of proteins, the formation of hydrogels, and various medical applications including the development of microspheres and drug delivery systems.⁶ Metal residing within the polymer must be taken into consideration in applications involving biomaterials. As a result, non-cytotoxic metal complexes such as titanium complexes⁷ have been widely researched in connection with lactide (LA) and CL polymerization. In the following, we provide a recent survey of cyclic ester polymerization using Ti complexes with a Schiff base.

Gibson et al.⁸ synthesized salen ligated titanium alkoxide complex using two ferrocene molecules [Fig. 1(a)], which

ligands (*N, N-trans* form of Ti complex) prevent the coordination of monomers to Ti thereby decreasing the initiation rate. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 51: 327–333, 2013

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could be reversibly oxidized/reduced. The reduced form demonstrated a propagation rate 30-fold greater than that of the oxidized form, following the addition of AgOTf. The electron-donating substituent within the salen structure increases the rate of LA propagation.

The same group synthesized 1,1'-ferrocenediyl salicylaldimine ligands and their titanium alkoxide complexes [Fig. 1(b)]. The Ti complex with *N*-2,6-diisopropylphenyl-substituted ligand showed slightly greater activity than with *N*phenyl-substituted ligand in *rac*-LA polymerization. The Ti complex supported with 1-phosphino-1'-hydroxyferrocene demonstrated greater activity than 1,1'-ferrocenediyl salicylaldimine due to the relatively low coordination number of the titanium in this complex.

Do and coworkers¹⁰ synthesized chiral tridentate Schiff base ligands and their chlorotitanium complexes [Fig. 1(c)]. Their results demonstrated a high degree of activity in the controlled polymerization of L-LA, despite the lack of normal initiators such as alkoxides or amides. Titanium complex supported by the *tert*-butyl-substituted ligand was more active than the hydrogen-substituted ligand and trichlorotitanium complex showed slightly greater activity than dichlorotitanium complex.

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FIGURE 1 Titanium or zirconium alkoxide complexes supported by Schiff base ligands. (a) Salen ligand with two ferrocene molecules.⁸ (b) 1-Phosphino-1'-hydroxyferrocene and 1,1'-ferrocenediyl salicylaldimine.⁹ (c) chiral tridentate Schiff base ligands.¹⁰ (d) chiral bi- and tridentate Schiff base ligands.¹¹

Davidson and coworkers¹¹ synthesized chiral bidentate Schiff base ligands and their titanium and zirconium complexes [Fig. 1(d)] The titanium complexes were inactive for the ROP of *rac*-LA; however, the zirconium complexes demonstrated a high degree of activity in toluene at both 20 °C and 80 °C.

Polymerization is insensitive to ligand substitution and chirality. In a solvent-free system, both the titanium and zirconium complexes demonstrated activity; the former displayed greater control in polymerization than the latter, but lacked selectivity.



FIGURE 2 Titanium alkoxide complexes supported by various bi- and tri-dentate Schiff base ligands.



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FIGURE 3 Preparation of $(L^1 - L^6)_2 TiO^i Pr_2$ compounds.

Johnson et al.¹² synthesized a variety of bidentate and tridentate Schiff base ligands and their titanium alkoxide complexes. It was revealed that four types of titanium alkoxide complexes are dependent on the steric effect of ligands (Fig. 2). However, the author did not report the ROP of CL or LA using these complexes as catalysts.

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Researchers have demonstrated that the various steric effects of Schiff base ligands can alter the coordinated form of titanium alkoxide complexes; however, no studies have dealt with the relationship between the rate of ROP and these coordinated forms. Gibson and coworkers9 indicated that coordination numbers can influence the activity of LA ROP; however, the evidence was inconclusive because not all of the ligands were Schiff base ligands. This study synthesized six Schiff base ligands and their titanium alkoxide complexes, and investigated the influence of the coordinated forms and coordination numbers on the ROP of CL and LA (Fig. 3).

RESULTS AND DISCUSSION

Synthesis and Characterization of Ti Complexes

All L¹-H to L⁶-H ligands were prepared according to the procedures outlined by Johnson et al.¹² L¹-H to L⁶-H reacted

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with a stoichiometric quantity of titanium isopropoxide in toluene to produce a moderate yield of Ti compounds (Fig. 3). According to Johnson's description,¹² the titanium alkoxide complexes of $L^1 - L^5$ are Type I and $(L^6)_2 Ti(O^i Pr)_2$ is Type II.

Polymerization of &-Caprolactone and L-Lactide

This study investigated the polymerizations of LA and CL in toluene using Ti complexes as initiators. The experiments were conducted under nitrogen at 100 °C (Table 1). Table 1 illustrates the degree of catalytic activity in the polymerization of LA and CL associated with various Ti complexes and their related ligands. As shown in Table 1 Ti complexes with bidentate ligands (Entries 3 and 9) demonstrated the greater activity than tridentate ligands (Entries 1, 2, 7, and 8) and complexes with N-alkyl-substituted tridentate ligands were more active than N-aryl-substituted tridentate ligands (Entry 1 vs. 7, 2 vs. 8, and 3 vs. 9). The molecular weight (NMR) of polymers catalyzed using these Ti complexes was lower than the expected value and Ti complexes with bidentate ligands (entries 3 and 9) demonstrated poor controllability with the broad polydispersity index (PDI). The reason that bidentate ligands demonstrated a less pronounced chelation effect may be due their lack of a third coordinated atom, which

TABLE 1 Polymerization of &-Caprolactone and L-Lactide Using Each of the Ti Complexes as an Initiator at 100 °C

Entry	Cat. L=	Time (h)	Conv.ª (%)	$M_{n(Cal)}^{b}$	$M_{n(NMR)}^{a}$	<i>M</i> _{n(GPC)} ^c	P ^d	PDI ^c
1 ^e	L ¹	64.33	93	5,400	5,400	2,700	0.16	1.17
2 ^e	L ²	39.75	92	5,300	3,200	4,100	0.26	1.23
3 ^f	L ³	0.30	93	5,400	2,000	6,300	35.34	1.72
4 ^g	L ³	0.33	95	5,500	1,200	4,700	32.81	1.69
5 ^h	L ³	0.58	89	5,100	3,700	4,900	17.49	1.40
6 ⁱ	L ³	0.75	91	5,200	1,300	5,700	13.83	1.28
7 ^e	L^4	7.00	89	5,100	4,600	6,000	1.45	1.17
8 ^e	L ⁵	2.55	90	5,200	4,100	6,300	4.02	1.25
9 ^e	L ⁶	1.00	92	5,300	4,300	6,000	10.49	1.46
10 ^j	L1	68.00	90	6,500	k	2,100	0.19	1.26
11 ^j	L ²	71.67	62	4,500	k	2,000	0.13	1.27
12 ^j	L ³	0.33	90	6,500	k	5,500	39.27	1.19
13 ^j	L^4	7.50	87	6,300	k	6,900	1.67	1.26
14 ^j	L⁵	2.25	91	6,600	k	7,600	5.82	1.26
15 ^j	L ⁶	1.75	89	6,500	k	15,800	7.32	1.39

^a Obtained from ¹H NMR analysis.

 b Calculated from the molecular weight of monomer \times [monomer]_0/ 2[Cat]_0 \times conversion yield + $M_{w(O}\textit{I}_{Pl})$

^c Obtained from GPC analysis and calibration based on the polystyrene standard. Values in parentheses are the values obtained from GPC times 0.58 for PLA¹³ and 0.56 for PCL.¹⁴

^d The productivity = the polymer weight/mol of cat. \times time (kg/mol h).

increased the space available for the monomer to associate with the metal center. However, this also made it easier for the polymer chain to backbite to the metal causing transesterification with broad PDI. This situation was resolved by reducing the concentration of the catalyst and CL (Entries 4, 5, and 6). Results similar to those of LA polymerization by Ti complexes are shown in Entries 10-15; however the PDI of the polymers can only be controlled up to less than 1.39. The molecular weights of polymers catalyzed by Ti complexes with N-aryl-substituted ligands (Entries 10, 11, and 12) were higher than those of N-alkyl-substituted ligands (Entries 13, 14, and 15). L³H and L⁶H are both stereo-bulky bidentate ligands; however, the Ti complex with L³ showed greater activity than the complex with L⁶. This is probably due to the framework of Ti complexes. $(L^3)_2 Ti(O^i Pr)_2$ is Type I whereas $(L^6)_2 Ti(O^i Pr)_2$ is Type II, as shown in Figure 4. The middle structure in Figure 4 is the $L_2Ti(O^iPr)_2$ model, in which three positions are available for the monomer to coordinate to Ti. However, OⁱPr initiators are unable to initiate the monomer in position 3; therefore, it is of no benefit to the polymerization. ^tButyl groups are capable of blocking positions 2 and 3 in $(L^3)_2 Ti(O^i Pr)_2$, while isopropyl groups are capable of blocking positions 1 and 2 in $(L^6)_2 Ti(O^i Pr)_2$. This decreases the effectiveness with which the monomer coordinates to Ti, which reduces catalytic activity. The ¹H NMR spectra of PCL and PLA are shown in Supporting Information Figures S6 and S7.

To compare the polymerization control using these Ti complexes, polymerization using various ratios of CL and catalysts were studied, respectively, to identify the properties of e Conditions: toluene (5 mL), [CL] = 4.0 M, [CL]:[Cat] = 100:1.

 $^{\rm f}$ Conditions: toluene (20 mL), [CL] = 1.0 M, [CL]:[Cat] = 100:1. $^{\rm g}$ Conditions: toluene (25 mL), [CL] = 0.8 M, [CL]:[Cat] = 100:1.

^h Conditions: toluene (20 mL), [CL] = 0.5 M, [CL].[Cal] = 100.1.

ⁱ Conditions: toluene (50 mL), [CL] = 0.4 M, [CL]:[Cat] = 100:1.

^j Conditions: toluene (5 mL), [LA] = 2.0 M, [LA]:[Cat] = 100:1.

^k Unavailable

the resulting polymers (Supporting Information Table S1 and Fig. S1). The results showed that the Ti complexes with L^1 and L^2 provide better control with narrow PDI (less than 1.21) than other Ti complexes; however, this is accompanied by a drop in catalytic activity. It appears that ligands with multi-dentate atoms are capable of protecting the metal center against the trans-esterification. N-alkyl-substituted ligands are more flexible than N-aryl-substituted ligands in their ability to coordinate to the metal; however, this decreases the likelihood of monomer coordination.

The control of LA polymerization using $(L^4)_2 Ti(O^i Pr)_2$ is evident in the linear relationship between Mn(GPC) and



FIGURE 4 Spatial structure of Type I and Type II Ti complexes.



FIGURE 5 Linear plot of Mn(GPC) vs. $[LA]_0 \times \text{conv.}/$ $[(L^2)_2\text{Ti}(O^{j}\text{Pr})_2]_0$, with polydispersity indexes indicated by closed circles (Table 2Entries 5–8).

 $[monomer]_0 \times conv./[(L^2)_2Ti(O^iPr)_2]_0$ (Table 2 Fig. 5), as well as the polymers with low PDIs, ranging from 1.22 to 1.34.

Kinetic Studies of the Polymerization of CL and LA Catalyzed by $(L^4)_2 Ti(O^iPr)_2$

Kinetic studies were performed at 100 °C using the following ratios: $[M]_0/[(L^4)_2\text{Ti}(O^i\text{Pr})_2]$ ([CL] = 4 M in toluene 5 mL and [LA] = 2 M in CDCl₃ 1 mL) shown in Supporting Information Tables S2 and S3 and Figures S2 and S4. Preliminary results indicate a first-order dependency on [CL] and [LA] (Supporting Information S2 and S4). By plotting $\ln k_{obs}$ vs. ln $[(L^4)_2\text{Ti}(O^i\text{Pr})_2]$, $(L^4)_2\text{Ti}(O^i\text{Pr})_2$ orders of both 1, kappa values of 7.51 and 3.41 were discovered for CL and LA (Supporting Information Fig. S3 and S5), respectively. The polymerization of CL and LA using $(L^4)_2\text{Ti}(O^i\text{Pr})_2$ at 100°C demonstrated the following rate law:

$$d[\text{CL}]/\text{d}t = 7.51 \times [\text{CL}]^1 [(\text{L}^4)_2 \text{Ti}(\text{O}^i \text{Pr})_2]^1$$
$$d[\text{LA}]/\text{d}t = 3.41 \times [\text{LA}]^1 [(\text{L}^4)_2 \text{Ti}(\text{O}^i \text{Pr})_2]^1$$

TABLE 2 Controlled L-Lactide Polymerizations of Using $(L^4)_2 Ti(O'Pr)_2$ as an Initiator at 100 °C.

Entry	[M]/[Ti]	Time (h)	Conv.ª (%)	$M_{n(Cal)}^{\rm b}$	Mn _(GPC) °	P ^d	PDI ^c
1 ^e	100/1	7.50	87	5,000	6,000	1.67	1.22
2 ^e	150/1	13.33	91	7,800	9,200	2.16	1.25
3 ^e	200/1	17.33	92	10,600	11,100	1.53	1.32
4 ^e	250/1	17.33	90	13,000	14,000	3.6	1.34

^a Obtained from ¹H NMR analysis.

 b Calculated from the molecular weight of monomer \times [monomer]_0/ 2[Cat]_0 \times conversion yield + $M_{w(O}i_{Pr).}$

^c Obtained from GPC analysis and calibrated using the polystyrene standard. Values in parentheses are the values obtained from GPC times 0.58 for PLA.

 $^{\rm d}$ The productivity = the polymer weight / mol of cat. \times time (kg/mol h).

^e Condition: toluene (5 mL), $[(L^4)_2 Ti(O^i Pr)_2] = 0.02$ M.





FIGURE 6 Possible mechanisms underlying the polymerization by hexa-coordinated Ti complex.

Mechanistic Studies of Polymerization

According to the kinetic characteristics, one monomer is consumed in every polymerization cycle and the Ti complexes retain a mononuclear form because the order of the monomer and Ti complex is 1. There are two possible polymerization mechanisms. One involves a monomer associating at the position of dissociation of nitrogen in the ligand forming the hexa-coordinated form (Mechanism A in Fig. 6). The other is a monomer bonding to Ti from position 1 or 2 (the middle structure in Fig. 4), forming the hepta-coordinated form (Mechanism B in Fig. 6). Assuming that Mechanism A is the correct, the left side of Figure 6 shows the intermediates of $(L^3)_2 Ti(O^i Pr)_2$ and $(L^6)_2 Ti(O^i Pr)_2$ during polymerization. $(L^{6})_{2}Ti(O^{i}Pr)_{2}$ should have greater catalytic activity than $(L^3)_2 Ti(0^i Pr)_2$ because there are two isopropoxide groups in the *cis*-position of the monomer in $(L^6)_2 Ti(O^i Pr)_2$, which determines the ring-opening rate. However, data related to polymerization returned the opposite result, thereby disqualifying Mechanism A as a candidate. The actual mechanism is most likely Mechanism B, as previously reported.¹⁵ The crowded situation enhanced the initiation of isopropoxide to monomer, releasing in the unstable energy of repulsion, the repeated coordination of monomers, and the initiation of alkoxide to produce the polymer. L¹, L², L⁴, and L⁵ Ti complexes displayed low activity due to the coordination of the monomer having to compete against the third coordinated atom of the ligand, which decreased the polymerization rate.

EXPERIMENTAL

Standard Schlenk techniques and a N₂-filled glovebox were used in all the isolation and treatment of all the compounds. Solvents, CL, L-LA, and deuterated solvents were purified prior to use. Sodium hydride, salicylaldehyde, tert-butylamine, N, Ndimethylethylenediamine, o-anisidine, 2,6-diisopropylaniline, and 2-(methylthio)aniline were purchased from Alfa. 2,2-Dimethoxyethylamine and benzyl alcohol were purchased from Aldrich. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini2000-200 (200 MHz for ¹H and 50 MHz for 13 C) spectrometer with chemical shifts given in ppm from the internal TMS or center line of CDCl₃. Microanalyses were performed using a Heraeus CHN-O-RAPID instrument. The gel permeation chromatography (GPC) measurements were performed on a Waters 1515 Isotratic HPLC pump system equipped with a differential Waters 2414 refractive index detector using THF (HPLC grade) as the eluent. The chromatographic column was a Water Styragel Column (HR4E), and the calibration curve was made by polystyrene standards to calculate Mn(GPC). Ligands of L^{1} -H to L^{6} -H were prepared by acid-catalyzed condensation following literature procedures.⁵ $(L^3)_2Ti(O^iPr)_2$, $(L^4)_2Ti(O^iPr)_2$, and $(L^6)_2Ti(O^iPr)_2$ were prepared following literature procedures.¹²

Synthesis of (L¹)₂Ti(OⁱPr)₂

A mixture of L¹-H (3.845 g, 20 mmol) and Ti(OⁱPr)₄ (2.843 g, 10 mmol) in THF (10 mL), was stirred for 12 h. Volatile materials were removed under vacuum to give red oil and then it was washed with hexane (20 mL) and a deep orange oil was obtained. Yield: 3.890 g (58%). ¹H NMR (CDCl₃, 200 MHz): δ 8.06 (2H, s, CH=N), 7.21–7.39, 6.71–6.85, (8H, m, ArH), 4.68 (sept, 2H, *J* = 5.8 Hz, OCH(CH₃)₂) 3.48 (4H, br, NCH₂CH₂N(CH₃)₂), 2.54 (2H, br, NCH₂CH₂N(CH₃)₂), 2.38 (2H, br, NCH₂CH₂N(CH₃)₂), 2.07 (12H, s, N(CH₃)₂), 1.19 (d, 12H, *J* = 5.8 Hz, OCH(CH₃)₂), 1.19 (d, 12H, *J* = 5.8 Hz, OCH(CH₃)₂), 1.19 (d, 12H, *J* = 5.8 Hz, OCH(CH₃)₂), 59.17 (NCH₂CH₂N(CH₃)₂), 58.18 (NCH₂CH₂N(CH₃)₂), 59.17 (NCH₂CH₂N(CH₃)₂), 58.18 (NCH₂CH₂N(CH₃)₂), 44.66 (NCH₂CH₂N(CH₃)₂), 24.62 (OCH(CH₃)₂). Anal. Calcd (found) for C₂₈H₄₄N₄O₄Ti (548.8): C, 61.31 (60.50); H, 8.08 (7.83); N, 10.21 (10.05)%.

Synthesis of (L²)₂Ti(OⁱPr)₂

A mixture of L^2 -H (4.185 g, 20 mmol) and Ti(O^i Pr)₄ (2.843 g, 10 mmol) in THF (10 mL), was stirred for 12 h. Volatile materials were removed under vacuum to give yellow powder and then it was washed with hexane (20 mL) and a light yellow powder was obtained after filtration. Yield: 4.11 g (58 %). ¹H NMR (CDCl₃, 200 MHz): δ 8.06 (2H, s, CH=N), 7.25–7.40, 6.72–6.83 (8H, m, ArH), 4.63 (2H, sept, I = 6.0Hz, OCH(CH₃)₂), 4.59 (2H, t, J = 4.4 Hz, CH(OCH₃)₂), 3.47 (4H, d, J = 4.4 Hz, $CH_2CH(OCH_3)_2$), 3.23 (12H, s, $CH(OCH_3)_2$), 1.06 ppm (12H, br, OCH(CH₃)₂). ¹³C NMR (CDCl₃, 50 MHz): δ 164.19 (C=N), 167.92, 134.27, 133.77, 122.05, 119.03, 117.12 (Ar), 103.82 (CH₂CH(OCH₃)₂), 78.21 (OCH(CH₃)₂), (CH₂CH(OCH₃)₂), 55.29 (CH₂CH(OCH₃)₂), 55.10 63.39 (OCH_3) , 25.27 $(OCH(CH_3)_2)$. Anal. Calcd (found) for C₂₈H₄₂N₂O₈Ti (582.78): C, 57.73 (56.90); H, 7.27 (7.36); N, 4.81 (4.98)%. m.p.: 116 °C.

Synthesis of (L⁵)₂Ti(OⁱPr)₂

Using a method similar to that for $(L_2)_2 Ti(O^i Pr)_2$. Yield: 4.55 g (59%). ¹H NMR (CDCl₃, 200 MHz): δ 7.80 (2H, s, CH=N), 7.43, 7.10–6.90 (4H, m, ArH), 6.61 (2H, t, J = 7.4 Hz, ArH), 6.14 (2H, d, J = 7.8 Hz, ArH), 4.90 (2H, sept, J = 6.2 Hz, OCH(CH₃)₂), 2.10 (6H, s, SCH₃), 1.21 ppm (12H, d, J = 6.2 Hz, OCH(CH₃)₂). ¹³C NMR (CDCl₃, 50 MHz): δ 166.77 (COH), 151.43 (C=N), 164.79, 134.09, 125.41, 123.90, 118.85, 116.83 (Ar), 78.22 (OCH(CH₃)₂), 25.50 (OCH(CH₃)₂), 15.85 (SCH₃). Anal. Calcd (found) for C₃₄H₃₈N₂O₄S₂Ti (650.96): C, 63.01 (62.76); H, 5.99 (5.89); N, 4.25 (4.31) %. M.p.: 120 °C.

General Procedures for the Polymerization of ɛ-Caprolactone and L-lactide

A typical polymerization procedure was exemplified by the synthesis of Entry 7 (Table 1) using complex $(L^4)_2 \text{Ti}(O^i Pr)_2$ as a catalyst. The polymerization conversion was analyzed by ¹H NMR spectroscopic studies. Toluene (5.0 mL) was added to a mixture of complex $(L^4)_2 \text{Ti}(O^i Pr)_2$ (0.1238 g, 0.2 mmol) and CL (2.2 g, 20 mmol) at 100 °C. After the solution was stirred for 7 h, the reaction was then quenched by adding to a drop of ethanol, and the polymer was precipitated pouring into *n*-hexane (30.0 mL) to give white solids. The white solid was dissolved in CH₂Cl₂ (5.0 mL) and then *n*-hexane (70.0 mL) was added to give white crystalline solid. Yield: 1.25 g (57%).

CONCLUSIONS

This study synthesized a series of iminophenol ligands (L^{1} -H to L^{6} -H) and their titanium complexes. Changing the coordination number and size of the N-substituted group altered the polymerization of CL and LA. Generally, if a Ti complex with a bidentate ligand is changed to a tridentate one, the degree of activity decreases dramatically, due to the third coordination atom having to contend with the monomer. The geometric framework also influences the catalytic activity for ROP. Compared with the Type I Ti complex, the steric bulky N-substituted group in the Type II Ti complex forms blocks in more positions. This increases the effectiveness in preventing the coordination of monomers to Ti and decreases the initiation rate.

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