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Titanium Complexes Bearing 2,6-Bis(*o*-hydroxyalkyl)pyridine Ligands in the Ring-Opening Polymerization of *L*-Lactide and *ɛ*-Caprolactone

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Abstract

A series of titanium (Ti) compounds bearing 2,6-bis(*o*-hydroxyalkyl)pyridine ligands were synthesized and investigated as catalysts for the ring-opening polymerization of ε -caprolactone (CL) and *L*-lactide (LA). The Ti complexes with electron-withdrawing groups in pyridine rings or steric bulky groups in hydroxymethyl groups reduced the catalytic activity in CL and LA polymerizations, and ^{Me}L^{Ph}-TiOPr₂ exhibited the highest catalytic activity ([CL] = 0.5 M, [CL]:[Cat] = 100:8, 60 °C, 7.5 h, conversion = 93%; [LA] = 0.5 M, [LA]:[Cat] = 100:8, 60 °C, 3.5 h, conversion = 98%). The density functional theory calculation results revealed that CL interacted with the ligand through weak hydrogen bonds, and then approached the Ti center. After being attacked by isopropyl oxide, the carbonyl group of CL bonded to the Ti center. After the rearrangement and ring opening of CL ring, CL was converted to poly- ε -caprolactone.

Keywords: Titanium complex, *E*-Caprolactone, *L*-Lactide, Ring-opening polymerization

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1.0. Introduction

Ligands are essential in organometallic catalysts because they improve the catalytic reactivity and selectivity for catalysis through steric, electronic, and chelating effects. Pincer ligands,^[1-6] a common type of ligand, bond securely to three neighboring coplanar sites in a meridional configuration. The rigidity of the pincer-metal interaction results in high thermal stability in the resultant complexes. Pincer complexes are used in catalytic applications such as addition to olefins, [7, 8] C-C[9-14] and C-S[15] cross-coupling, cycloisomerization, [16, 17] hydrogenation of ketones and aldehydes, [18, 19] hydrogenation of ester and amide, [20-22] hydrophosphination, [23, 24] hydrosilylation of acetophenone, [25, 26] olefin polymerization, [27-29] and ring opening-polymerization of cycloesters.[30] Recently Zaitsev[30] reported the synthesis of pincer Al complexes bearing pyridine-substituted alcohols (Figure 1a) and their application in ε -caprolactone (CL) and L-lactide (LA) polymerization and revealed that Al complexes were moderately active in a controlled or an immortal LA polymerization and that steric bulky substituents on the ligands increased the catalytic activity. Suzuki²⁹ reported the synthesis of pincer Ti complexes bearing pyridine-substituted alcohols (Figure 1b) and their application in ethylene polymerization. The polymerization results revealed that the order of the activity was R = i-Pr > t-Bu > Et, and the molecular mass of the polymer was in the order R = i-Pr > Et > t-Bu. In addition to Al catalysts, Ti complexes[31-42] were used as catalysts in polymerization of cyclic esters. According to these reports, Ti complexes bearing 2,6-bis(hydroxyalkyl)pyridines ligands should be effective in CL and LA polymerizations, and substituents (R) should influence the controllability of Ti catalysts. Herein, we synthesized a series of 2,6-bis(hydroxyalkyl)pyridines ligands and their titanium alkoxide complexes (Figure 2). The ROP of CL and LA were studied to investigate the steric effect on ROP.



Figure 1. Pincer metal complexes bearing pyridine-substituted alcohols: (a) Al complexes³⁰

for ROP and (b) Ti complexes²⁹ for olefin polymerization



Figure 2. Preparation of 2,6-bis(hydroxyalkyl)pyridines ligands and associated Ti compounds

2.0. Results and Discussion

2.1. Synthesis and Characterization of 2,6-bis(hydroxyalkyl)pyridines ligands and

associated Ti Complexes.

^HL^{Me}-H [43, 44] and ^HL^{Ph}-H³⁰ were prepared according to techniques provided in the literature. ^{Me}L^{Ph}-H was synthesized using a method similar to that of the synthesis of ^HL^{Ph}-H. In this case, 2,4,6-collidine was used to replace 2,6-lutidine. ^HL^{Me}O-H was synthesized from the reaction of ^HL^{Me}O-H and H₂O₂ in acetic acid. In the reaction, ^HL^{Me}-H, ^HL^{Ph}-H, and ^{Me}L^{Ph}-H reacted with a stoichiometric quantity of titanium isopropoxide in toluene to produce a moderate yield of Ti compounds (^HL^{Me}-TiOPr₂, ^HL^{Ph}-TiOPr₂, and ^{Me}L^{Ph}-TiOPr₂, respectively) (Figure 2). Furthermore, ^HL^{Me}O-H reacted with a stoichiometric quantity of titanium isopropoxide in toluene to produce (^HL^{Me}Ti-O)₄. Another method of producing (^HL^{Me}Ti-O)₄ is through the reaction of ^HL^{Me}-TiOPr₂ with a stoichiometric quantity of H₂O. According to the ¹H and ¹³C nuclear magnetic resonance (NMR) spectra and elemental analysis (EA) data, when two equivalents of titanium isopropoxide reacted with one equivalent of ^HL^{Me}-H, the resulting product was ^HL^{Me}₂-Ti.

The X-ray structure of ${}^{\mathbf{H}}\mathbf{L}^{\mathbf{Ph}}$ -**TiOPr**₂ (CCDC 2005807, **Figure 3**) revealed the distorted trigonal bipyramidal geometry ($\tau = 0.84$)[45] with two terminal isopropoxides. The axial angle of N(1)-Ti(1)-O(3) was 172.59(8)^o and the equatorial angles between O(1)-Ti(1)-O(2), O(2)-Ti(1)-O(4), and O(4)-Ti(1)-O(2) were 115.06(9)^o, 121.88(10)^o, and 118.24(10)^o, respectively. The bond of Ti(1)-O(3) in the axial position was 1.8392(19) Å, and the bonds of Ti(1)-O(1), Ti(1)-O(2), and Ti(1)-O(4) (in the equatorial position) were 1.8366(19) Å, 1.8394(18) Å, and 1.783(2) Å). The structure of (${}^{\mathbf{H}}\mathbf{L}^{\mathbf{Me}}\mathbf{Ti}$ -O)₄ (CCDC 2005806, **Figure 4**) comprises a tetramer of five coordinated Ti complexes with distorted trigonal bipyramidal geometry ($\tau = 0.94$) and four bridging oxygen atoms connected with four Ti atoms, which form an eight-membered ring structure.



Figure 3. Molecular structure of ${}^{H}L^{Ph}$ -**TiOPr**₂ with 20% probability ellipsoids (all hydrogen atoms were omitted for clarity). Selected bond lengths (A) and bond angles (deg): Ti(1)–O(1) 1.8366(19), Ti(1)–O(2) 1.8394(18), Ti(1)–O(3) 1.8392(19), Ti(1)–O(4) 1.783(2), Ti(1)–N(1) 2.355(2); O(3)–Ti(1)–N(1) 172.59(8), O(4)–Ti(1)–O(1) 121.88(10), O(4)–Ti(1)–O(2) 118.24(10), O(1)–Ti(1)–O(2) 115.06(9), Ti(1)–O(3)–C(14) 127.61(17), Ti(1)–O(4)–C(39) 164.5(2).



Figure 4. Molecular structure of $({}^{H}L^{Me}Ti-O)_{4}$ with 10% probability ellipsoids (all hydrogen atoms were omitted for clarity). Selected bond lengths (A) and bond angles (deg): Ti(1)–O(1) 1.8433(17), Ti(1)–O(2) 1.8351(17), Ti(1)–O(3) 1.8392(19), Ti(1)–O(4) 1.783(2), Ti(1)–N(1) 2.363(2); O(4)–Ti(1)–N(1) 175.71(7), O(3)–Ti(1)–O(1) 119.49(8), O(3)–Ti(1)–O(2) 119.46(8),

O(1)-Ti(1)-O(2) 115.27(8), Ti(1)-O(3)-Ti(2) 162.95(11), Ti(1)-O(4)-Ti(2A) 169.66(10).

2.2. Polymerization of CL and LA.

In this experiment, the polymerizations of CL and LA using Ti complexes as an initiator in toluene were investigated under nitrogen (Tables 1 and 2). As observed from entries 1-5 in Table 1, the catalytic order of Ti complexes for CL polymerization was ${}^{Me}L^{Ph}$ -TiOPr₂ > ${}^{H}L^{Me}$ -TiOPr₂ > ${}^{H}L^{Ph}-TiOPr_{2} > {}^{H}L^{Me}{}_{2}-Ti > ({}^{H}L^{Me}Ti-O)_{4}.$ The results revealed that ${}^{Me}L^{Ph}-TiOPr_{2}$ had a higher catalytic activity than ^HL^{Me}-TiOPr₂ because the electron donating substituents in the pyridyl ring, such as the methyl group, enhanced catalytic activity, whereas ${}^{H}L^{Ph}$ -TiOPr₂ with the bulky substituents in the hydroxyethan-1-olate group, such as the phenyl group, reduced catalytic activity compared with ^HL^{Me}-TiOPr₂. Electron donating substituents can enhance pyridine coordination and weaken the Ti-isopropyl oxide bond to ease monomer initiation by isopropyl oxide. The steric bulky substituent in the hydroxyethan-1-olate group can block monomer coordination and reduce catalytic activity. (^HL^{Me}Ti-O)₄ exhibited the lowest catalytic activity because of a crowded catalytic Ti center and weak initiators (BnOH) with lower nucleophilicity than isopropyl oxide. The LA polymerization results (Table 2) from using these Ti complexes were similar to those of CL polymerization, with the exception of ^HL^{Me}₂-Ti, which had the lowest catalytic activity. $^{Me}L^{Ph}$ -TiOPr₂ with the highest catalytic activity was used as a catalyst to test the controllability of PLA and PCL. Polymerization with various ratios of monomers catalyzed by ^{Me}L^{Ph}-TiOPr₂ was studied to identify the properties of these polymers (entries 6-11 of Table 1, and 6-12 in Table 2, and Figure 5). The results revealed that ^{Me}L^{Ph}-TiOPr₂ exhibited higher controllability with similar values of Mn_{Cal} , Mn_{NMR} , and Mn_{GPC} and narrow dispersity (D, less than 1.26). The ¹H NMR spectrum of PCL (Figure S23) and PLA (Figure S24) revealed that isopropyl oxide initiated the monomers to form the polymer end chain.

Table 1 . Polymerization of CL using various Ti complexes as catalysts.										
Entry	Catalyst	Time	Conv. ^a	Mn_{Cal}^{b}	$Mn_{\rm NMR}^{a}$	Mn _{GPC} ^c	Ð ^c	k _{obs} (h ⁻¹)		
	[CL]:[Cat]:[BnOH]	<mark>(h)</mark>	<mark>(%)</mark>					[error] ^k		
1^d	HL ^{Me} -TiOPr ₂	<mark>11</mark>	<mark>93</mark>	<mark>800</mark>	<mark>1100</mark>	<mark>900</mark>	<mark>1.11</mark>	<mark>0.238 [6]</mark>		
	<mark>100:8:0</mark>									
2^d	HLPh-TiOPr2	<mark>20</mark>	<mark>94</mark>	<mark>800</mark>	<mark>1000</mark>	<mark>900</mark>	<mark>1.12</mark>	<mark>0.141 [5]</mark>		
	<mark>100:8:0</mark>									
3 ^d	MeLPh-TiOPr2	<mark>7.5</mark>	<mark>93</mark>	<mark>800</mark>	<mark>1200</mark>	<mark>900</mark>	<mark>1.08</mark>	<mark>0.356 [8]</mark>		
	<mark>100:8:0</mark>									
4 ^e	(^H L ^{Me} Ti-O) ₄	<mark>14</mark>	<mark>53</mark>	<mark>900</mark>	<mark>1100</mark>	<mark>1000</mark>	<mark>1.31</mark>	<mark>0.062 [2]</mark>		
	100:2:8									
5 ^e	^H L ^{Me} ₂ -Ti	<mark>5.5</mark>	<mark>50</mark>	<mark>800</mark>	<mark>1200</mark>	<mark>1100</mark>	<mark>1.34</mark>	<mark>0.117 [7]</mark>		
- c	100:8:8									
<mark>6⁷</mark>	^{Me} L ^{Pn} -TiOPr ₂	<mark>8</mark>	<mark>99</mark>	<mark>5800</mark>	<mark>5800</mark>	<mark>6400</mark>	<mark>1.09</mark>	<mark>_ </mark>		
<u>-a</u>	100:1:0							;		
<mark>7</mark> 8	$^{\text{Me}}L^{\text{H}}-\text{TiOPr}_2$	8	<mark>99</mark>	<u>11500</u>	11300	<mark>11900</mark>	<mark>1.23</mark>	- ⁷		
<mark>oh</mark>	200:1:0	0	70	10500	12000	14000	1.10	i		
<mark>8.</mark>	$^{110}L^{11}-110Pr_2$	<mark>8</mark>	<mark>/3</mark>	12500	<mark>13000</mark>	<mark>14000</mark>	<mark>1.16</mark>	- ⁷		
o ⁱ	300:1:0	0	50	11500	12200	12200	1.02	i		
7	$\frac{1}{400.1.0}$	<u>o</u>	30	<mark>11300</mark>	12000	<mark>15500</mark>	1.23	-		
10^{h}	Met Ph Tiopr	16	00	17200	17300	18000	1.25	j		
	$\frac{2}{300\cdot1\cdot0}$	10	//	17200	17500	10700	1.43			
11 ⁱ	Mel Me-TiOPr-	16	99	<mark>22900</mark>	23400	23000	<mark>1.26</mark>	_ j		
11	$\frac{1011}{400.1.0}$		~ /	22700	<u>23</u> -100	23000	1.20			

^{*a*} Obtained from ¹H NMR analysis. ^{*b*} Calculated from the molecular weight of monomer × $[CL]_0/2[Cat]_0$ × conversion yield + Mw(Pr'OH) (entries 1-3 and 6-11). Calculated from the molecular weight of monomer \times [CL]₀/ [BnOH]₀ \times conversion yield + Mw(BnOH) (entries 4-5).^c Obtained from GPC analysis and calibrated using the polystyrene standard. Values of Mn_{GPC} are the values obtained from GPC times 0.56 for PCL.^d Reaction condition: toluene (5 mL), [CL] = 0.5 M, [CL] : [Cat] = 100 : 8, 60 °C. ^e Reaction condition: toluene (5 mL), [CL] = 0.5 M, [CL] : [Cat] : [BnOH] = 100 : 2 : 8, 60 °C. ^{*f*} Reaction condition: no solvent, ${}^{Me}L^{Ph}$ -TiOPr₂ = 0.1 mmol, CL = 10 mmol, 100 °C. ^{*g*} Reaction condition: no solvent, ${}^{Me}L^{Ph}$ -TiOPr₂ = 0.1 mmol, CL = 20 mmol, 100 °C. ^hReaction condition: no solvent, ^{Me}L^{Ph}-TiOPr₂ = 0.1 mmol, CL = 30 mmol, 100 °C. ⁱReaction condition: no solvent, $^{Me}L^{Ph}$ -TiOPr₂ = 0.1 mmol, CL = 40 mmol, 100 °C. ^{*j*} k_{obs} do not be calculated. ^{*k*} k_{obs} is obtained by the first-order rate law for the consumption of [CL]. [error] is standard deviation from the kinetic study.

<mark>Entry</mark>	<mark>Catalyst</mark>	Time	Conv. ^a	Mn_{Cal}^{b}	Mn _{GPC} ^c	Ð ^c	k _{obs} (h ⁻¹)
	[LA]:[Cat]:[BnOH]	<mark>(h)</mark>	<mark>(%)</mark>				[error] ^l
1 ^d	^H L ^{Me} -TiOPr ₂	<mark>4</mark>	<mark>96</mark>	<mark>900</mark>	<mark>1200</mark>	<mark>1.17</mark>	<mark>0.924 [27]</mark>
	<mark>100:8:0</mark>						
2^d	^H L ^{Ph} -TiOPr ₂	<mark>6</mark>	<mark>96</mark>	<mark>900</mark>	<mark>1100</mark>	<mark>1.11</mark>	<mark>0.564 [12]</mark>
	100:8:0						
3 ^d	MeLPh-TiOPr2	<mark>3.5</mark>	<mark>98</mark>	<mark>1000</mark>	<mark>1100</mark>	<mark>1.11</mark>	<mark>1.262 [44]</mark>
	<mark>100:8:0</mark>						
4 ^e	(^H L ^{Me} Ti-O) ₄	<mark>4</mark>	<mark>80</mark>	<mark>1500</mark>	<mark>1400</mark>	<mark>1.12</mark>	<mark>0.431 [7]</mark>
	<mark>100:2:8</mark>						
5 ^e	HL ^{Me} 2-Ti	<mark>14</mark>	<mark>51</mark>	<mark>1000</mark>	<mark>1100</mark>	<mark>1.10</mark>	<mark>0.070 [1]</mark>
.	100:8:8						
<mark>6[†]</mark>	^{Me} L ^{Ph} -TiOPr ₂	1	<mark>99</mark>	<mark>7300</mark>	<mark>8100</mark>	<mark>1.03</mark>	- ^k
	100:1:0						7
7 ⁸	^{Me} L ^{Pn} -TiOPr ₂	<mark>3</mark>	<mark>99</mark>	<mark>14500</mark>	<mark>16600</mark>	<mark>1.10</mark>	<mark>- ^k</mark>
1.	200:1:0						1.
<mark>8</mark> "	^{Mc} L ^{rn} -TiOPr ₂	1	<mark>72</mark>	<mark>15600</mark>	<mark>19900</mark>	<mark>1.11</mark>	- ^
ai	300:1:0	-		10000			ŀ
<mark>9'</mark>	$^{\text{MCL}^{\text{III}}-\text{TiOPr}_2}$	3	<mark>84</mark>	<mark>18200</mark>	<mark>21100</mark>	<u>1.23</u>	<mark>- ^</mark>
1 oh	400:1:0		00	21700	01700	1.05	k
<u>10</u> "	$^{11}L^{11}-11OPr_2$	0	<mark>99</mark>	<mark>21700</mark>	<mark>21700</mark>	1.25	- 1
11 ^{<i>i</i>}	300:1:0 Met Me T:ODr	12	00	20000	20000	1.22	k
11	$\frac{1}{400\cdot1\cdot0}$	12	<mark>77</mark>	<mark>28900</mark>	<mark>26900</mark>	1.22	-
1.0 ^j		10	00	<mark>36100</mark>	36500	1.21	k
14	$\frac{500.1.0}{500}$	12	<mark>77</mark>	30100	<u>30300</u>	1.41	-

Table 2. Polymerization of LA using various Ti complexes as catalysts.

^{*a*} Obtained from ¹H NMR analysis. ^{*b*} Calculated from the molecular weight of monomer × $[LA]_0/ 2[Cat]_0$ × conversion yield + $Mw(Pr^iOH)$ (entries 1-3 and 6-12). Calculated from the molecular weight of monomer × $[LA]_0/ [BnOH]_0$ × conversion yield + Mw(BnOH) (entries 4-5). ^{*c*} Obtained from GPC analysis and calibrated using the polystyrene standard. Values of Mn_{GPC} are the values obtained from GPC times 0.58 for PLA. ^{*d*} Reaction condition: toluene (5 mL), [LA] = 0.5 M, [LA] : [Cat] = 100 : 8, 60 °C. ^{*e*} Reaction condition: toluene (5 mL), <math>[LA] = 0.5 M, [LA] : [Cat] : [BnOH] = 100 : 2 : 8, 60 °C. ^{*f*} Reaction condition: no solvent, ^{Me}L^{Ph}-TiOPr₂ = 0.1 mmol, LA = 10 mmol, 130 °C. ^{*g*} Reaction condition: no solvent, ^{Me}L^{Ph}-TiOPr₂ = 0.1 mmol, LA = 30 mmol, 130 °C. Reaction condition: no solvent, ^{Me}L^{Ph}-TiOPr₂ = 0.1 mmol, LA = 50 mmol, 130 °C. ^{*k*} k_{obs} do not be calculated. ^{*l*} k_{obs} is obtained by the first-order rate law for the consumption of [CL]. [error] is standard deviation from the kinetic study.



Figure 5. Linear plot of (A) M_{nGPC} versus ([CL]₀ × conv. / [^{Me}L^{Ph}-TiOPr₂]₀) and (B) M_{nGPC} versus ([LA]₀ × conv. / [^{Me}L^{Ph}-TiOPr₂]₀) with polydispersity indexes indicated by blue closed square [entries 3, 6-11 for (A); entries 14, 17, 20-23 for (B), Table 1]

Kinetic Studies of the Polymerization of CL and LA catalyzed by ^HL^{Me}-TiOPr₂

Kinetic studies were performed at 100 °C with respect to the ratio of $[M]_0/[^{H}L^{Me}-TiOPr_2]$ ([CL] = 0.5 M and [LA] = 0.5 M in CDCl₃ [1 mL] in a sealed NMR tube), as depicted in **Tables S3-S4** and **Figures S2-S5**. The preliminary results indicated a first-order dependency on [CL] and [LA] (**Figures S2** and **S4**). By plotting k_{obs} versus [$^{H}L^{Me}$ -**Ti**(**OPr**)_2] with $^{H}L^{Me}$ -**Ti**(**OPr**)_2 order of 1, k_{app} values of 0.072 and 0.354 (M⁻¹min⁻¹) were discovered for CL and LA (**Figures S3** and **S5**), respectively. The polymerizations of CL and LA using $^{H}L^{Me}$ -**Ti**(**OPr**)₂ at 100 °C demonstrated the following rate law:

$$d[CL]/dt = 0.072 \times [CL][^{H}L^{Me}-Ti(OPr)_{2}]$$
$$d[LA]/dt = 0.354 \times [LA][^{H}L^{Me}-Ti(OPr)_{2}]$$

Density Functional Theory Study of the Polymerization Mechanism Catalyzed by

^HL^{Ph}-Ti(OPr)₂

The reaction mechanism of cyclic ester ROP catalyzed by titanium catalysts was studied using density functional theory (DFT) calculation under the B3LYP level. The basis set for Ti was LanL2DZ, and that for H, C, N and O atoms was 6-31G(d). The structures of reaction intermediates and transition states in the calculation were based on the X-ray structure of ^HL^{Ph}TiOPr₂. CL was selected as the monomer in the theoretical study.

To initiate the ROP reaction, a monomer molecule must be bounded on the catalyst to activate its ester group or to draw the group close to the alkyl oxide initiator. On the base of this consideration, the catalyst can activate CL through three reaction pathways (**Figure 6**). In the first pathway, CL approaches the complex from the space above the ${}^{H}L{}^{Ph}$ ligand, which generates intermediate **I**. In the second pathway, axial isopropyl oxide is reorganized to equatorial positions, and CL coordinates on the axial position trans to ${}^{H}L{}^{Ph}$ pyridine to form intermediate **II**. In the third pathway, the monomer enters the equatorial sites trans to hydroxyethan-1-olate groups of ${}^{H}L{}^{Ph}$ to form intermediate **D**.

The central Ti of the optimized structure of intermediate **I** (Figure S16) exhibited a trigonal bipyramidal geometry, which is similar for that of ${}^{H}L^{Ph}TiOPr_{2}$, in which one OPr ligand and ${}^{H}L^{Ph}$ pyridine ligands coordinated on the axis positions, and two ${}^{H}L^{Ph}$ hydroxyethan-1-olate ligands and the other OPr are on the equatorial positions. CL bounded above ${}^{H}L^{Ph}$ through weak interactions with the phenyl rings of ${}^{H}L^{Ph}$. The distance between the CL carbonyl oxygen (O^{carb}) and the central Ti atom was 4.422 Å, which was considerably longer than those of Ti-O^{carb} bonds of other Ti-ester complexes (2.02 to 2.10 Å), indicated that CL did not directly coordinate on the Ti atom.[46-48] However, the distances between O^{carb} and two ortho hydrogen atoms (H^{ortho}) of the two equatorial phenyl rings of ${}^{H}L^{Ph}$ were 2.496 and 2.497 Å, respectively, and the distance between ester oxygen (O^{ring}) and H^{ortho} of an axial phenyl ring of ${}^{H}L^{Ph}$ was 2.644 Å. These three distances were smaller than the sum of the van der Waals radii of hydrogen and oxygen atoms (approximately 2.9 Å), which indicated that these H^{ortho} atoms had direct attraction interaction with O^{carb} and O^{ring}.[49]

These three interactions are regarded to be the major forces that bind CL to the catalyst. Moreover, the distance between the carbonyl carbon atom (C^{carb}) of CL and the oxygen atom (O^{Pr}) of the axial alkoxide ligand was 3.728 Å, and C^{carb} directly faced axial O^{Pr}. This conformation facilitated the addition reaction of axial O^{Pr} to C^{carb} . The free energy of intermediate I was 18.2 kcal mol⁻¹, assuming the sum of the free energy of ${}^{H}L^{Ph}TiOPr_{2}$ and free CL was 0 kcal mol⁻¹. (Figures 7 and 8) The optimized intermediate II has an octahedral coordination geometry for titanium (Figure S17). All four alkoxide ligands were in the equatorial plane. The CL coordinated on the axial site opposite to the pyridine ligand. The Ti-O^{carb} bond length was 2.220 Å and the Ti-O^{carb}-C^{carb} angle was 135.78°. The bond length was approximately 0.1 Å longer and the bond angle was approximately 15° smaller than those of other Ti-ester complexes (2.02 to 2.1 Å, 149 to 153°), which indicated that this Ti-O^{carb} bond was slightly weaker than those of other Ti-ester complexes.[46-48] The structure of **II** was different from that of **I** such that no OPr ligands directly faced the carbonyl group, which smoothened the addition reaction. Although a stable optimized structure of intermediate II occurred in this pathway, its free energy was 34.7 kcal mol⁻¹, which is considerably higher than that of **I** because all bulky ligands were reorganized to crowded equatorial sites, which created high repulsive forces. In the third pathway, CL did not bond on an equatorial coordination site or have any weak interaction with the catalyst because of the crowding of the equatorial space. After CL bonded to the catalyst, OPr reacted with C^{carb} to form a hemiacetalate (2-isopropoxyoxepan-2-olate) ligand and then produced intermediate III (Figure S18). This additional reaction can start from intermediate I or II. From I, the CL is drawn close to the titanium center to generate a Ti-O-C-O four membered ring transition structure (TS1; Figure 6, left). In this transition structure, the Ti-O^{carb} bond length was 2.282 Å, which was longer than that of Ti-O^{Pr} (1.978 Å) in the ring. Moreover, the O^{carb}-C^{carb} bond length was 1.270 Å, which was slightly longer than that of the C=O bond of free CL (1.208 Å) but considerably shorter than the C-O single bond, which indicated that it still has high double-bond characteristics. The O^{Pr}-C^{carb} bond (1.781 Å) was longer than that of O^{Pr}-C^{hemi} (1.417 Å) of intermediate **III**. Thus, **TS1** has a structure that resembles

intermediate **I**. The free energy of this transition structure was 43.1 kcal mol⁻¹ and the activation energy of the addition reaction from intermediate **I** to **III** was 24.9 kcal mol⁻¹. This relatively high activation energy can explain why this catalytic ROP progressed smoothly when the temperature was higher than 60 $^{\circ}$ C.



Figure 6. The ball and stick models of TS1 and TS2.

Direct transformation from **II** into **III** did not occur in our DFT calculation. When the distance between CL and isopropyl oxide was shortened to initiate the addition reaction, the octahedral structure of the catalyst became unstable and one equatorial isopropyl oxide was forced back to the axial position to reform intermediate **I** and no stable and achievable transition structure was possible between intermediates **II** and **III**.

After forming intermediate **III**, the hemiacetalate ligand rotated to draw O^{ring} close to central Ti to dissociating O^{ring} from C^{hemi} (**Figure 6**, right). The complex then underwent the second transition state (**TS2**) to open the seven-membered CL ring. In **TS2**, the O^{ring}-Ti and O^{carb}-Ti bond length were 2.006 and 2.188 Å, respectively. The bond lengths of O^{ring}-C^{carb} and O^{Pr}-C^{carb} were 1.737 and 1.295 Å, respectively. Thus, the transition structure had considerably higher ester characteristics than hemiacetalate did. The free energy of **TS2** was 38.4 kcal mol⁻¹, and the activation energy of the ring opening was 12.2 kcal mol⁻¹ from **III** to **IV**, which was considerably lower than that of **TS1** (**Figure 8**). This indicated that the rate determining step of this catalytic reaction was the alkyl oxide

addition reaction through TS1.

After ring opening, the complex formed intermediate **IV** with the new ester group weakly bonded to the open pocket of CL (**Figure S19**). The free energy of **IV** was 7.7 kcal mol⁻¹, slightly higher than the sum of those of ${}^{\rm H}{\rm L}^{\rm Ph}{\rm TiOPr}_2$ and CL because separated molecules have greater freedom. Although its free energy was slightly higher than that of the starting materials, the activation energy of the reverse reaction from **IV** to **III** (30.7 kcal mol⁻¹) was higher than the forward reaction from **I** to **III** (23.9 kcal mol⁻¹). Thus, its recyclization reaction was slower than ring opening. Moreover, the considerably higher concentration of monomers compared with polymers drove the forward reaction. Finally, the ester group was dissociated from the open pocket for binding monomers to form intermediate **V** (**Figure S20**). Although the ester group has an almost identical structure with intermediate **VI**, the chain of the polymer in the ester group was not folded on the surface of the catalyst to cover the active site; rather, it was released in the open space. The free energy of **V** was 9.9 kcal mol⁻¹, which was only slightly higher than that of **VI** and indicated that this conformation change progressed smoothly. After the monomer pocket was opened, the catalytic cycle restarted through the acceptance of another CL molecule.



Figure 7. Reaction mechanism of the polymerization reaction catalyzed by ^HL^{Ph}TiOPr₂.



Reaction Coordinate

Figure 8. Energy diagram of all intermediates and transition structures.

According to our DFT study, the most influential step of the reaction rate is that from intermediate **I** to **III** through **TS1**. This can explain the reactivity difference between the three catalysts, ^HL^{Me}TiOPr₂, ^HL^{Ph}TiOPr₂, and ^{Me}L^{Ph}TiOPr₂ because the higher activity of ^HL^{Me}TiOPr₂ compared with ^HL^{Ph}TiOPr₂ was attributed to the less bulky ^HL^{Me}. This resulted in a larger open pocket site for the monomer, which facilitated the monomer approach to the axial OPr ligand. This reduced the activation energy of the addition reaction and increased the reaction rate. Because of the substituted group difference between these two ligands, we cannot completely exclude the possibility of other reaction mechanisms for ^HL^{Me}TiOPr₂ to reduce its activation energy for the catalytic reaction. The reactivity of ^{Me}L^{Ph}TiOPr₂ was higher than ^HL^{Me}TiOPr₂ because of the electron-donating effect of the 4-methyl group on the pyridine ring. Favorable electron-donating ligands in Ti (IV) complexes can reduce the strength of the bond trans to them and increase their bond length.[50] Therefore, the Ti-O^{Pr} bond trans to the pyridine ligand in ^{Me}L^{Ph}TiOPr₂ becomes weaker, and the activation energy of **TS1** state can be reduced efficiently. This explanation is also proved by our DFT calculation results. The energy barrier of TS1 for ^{Me}L^{Ph}TiOPr₂ is 0.12 cal mol⁻¹ lower than that of ^HL^{Me}TiOPr₂. Moreover, in the first transition structures, the Ti-O bond trans to pyridine of ${}^{Me}L^{Ph}TiOPr_2$ (1.981 Å) is slightly longer than that of ${}^{H}L^{Me}TiOPr_2$ (1.978 Å).

3.0. Conclusions

In this study, a series of 2,6-bis(*o*-hydroxyalkyl)pyridine ligands and associated titanium complexes were synthesized and used as catalysts for the ROP of CL and LA. The Ti complexes with electron-withdrawing groups in pyridine ring or steric bulky groups in hydroxymethyl groups reduced the catalytic activity in CL and LA polymerizations, and ^{Me}L^{Ph}-TiOPr₂ exhibited the highest catalytic activity. The mechanism of CL polymerization by the DFT calculation results revealed that CL first formed a weak hydrogen bond with the ligand, and then approached the Ti center. After being attacked by isopropyl oxide, the carbonyl group of CL coordinated to the Ti center. After the rearrangement and ring opening of CL ring, CL was converted to poly-ε-caprolactone.

Experimental Section

General

Standard Schlenk techniques and a N₂-filled glove box were used throughout the isolation and handling of all the compounds. Solvents, *L*-lactide, and deuterated solvents were purified prior to use. 2,6-Dimethylpyridine, 2,4,6-trimethylpyridine, acetone, benzophenone, *N*,*N*,*N*',*N*',-tertamethylethylenediamine, *n*-butyllithium, and titanium (IV) isopropoxide was purchased from Sigma-Aldrich. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini2000-200 (200 MHz for ¹H and 50 MHz for ¹³C) 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. GPC measurements were performed on a Jasco PU-2080 PLUS HPLC pump system equipped with a differential Jasco RI-2031 PLUS refractive index detector using THF (HPLC grade) as an eluent (flow rate 1.0 mL/min, at 40 °C). The chromatographic column was JORDI Gel DVB 10^3 Å, and the calibration curve was made by primary polystyrene standards to calculate Mn_{GPC} . ^HL^{Me}-H³⁰ were prepared following literature procedures.

X-ray Crystallographic Studies. Single crystals of complexes ${}^{H}L^{Ph}$ -TiOPr₂ and (${}^{H}L^{Me}$ -TiO)₄ were obtained from a saturated dichloromethane solution in NMR tube. Suitable crystals were immersed in FOMBLINY under a N₂ atmosphere and mounted on an Oxford Xcalibur Sapphire-3 CCD Gemini diffractometer employing graphitemonochromated Mo K α radiation ($\lambda = 0.710$ 73 Å), and the intensity data were collected with ω scans.

General Procedures for the Polymerization of LA and CL. A typical polymerization procedure was exemplified by the synthesis of entry 1 (Table 1) using complex ${}^{H}L^{Me}$ -TiOPr₂ as an initiator. The polymerization conversion was analyzed by ${}^{1}H$ NMR spectroscopic studies. The 5 mL of toluene was added to a mixture of CL (0.285 g, 2.5 mmol) and complex ${}^{H}L^{Me}$ -TiOPr₂ (0.2 mmol). After the solution was mixed and then stirred for 11 h at 60 °C, the reaction was then quenched by adding a drop of ethanol; the polymer was precipitated by pouring the solution into n-hexane (30.0 mL) to give white solids. The oil was dissolved in CH₂Cl₂ (200 mL) and the solution was washed with water (200 mL) and the solvent removed at reduced pressure to give the white powders. Yield: 0.55 g (76%)

Synthesis of 2,2'-(pyridine-2,6-diyl)bis(1,1-diphenylethan-1-ol) (^HL^{Ph}-H).

^HL^{Ph}-H were prepared following literature procedures.^{13a} To a solution of 2,6-dimethylpyridine (2.14 g, 20 mmol) in tetrahydrofuran (25 mL, THF), *n*-butyllithium (2.5 M hexane solution, 20 mmol) was added dropwise at -78 °C over 1 h. Benzophenone (3.64 g, 20 mmol) in THF (20 mL) was added. The mixture was warmed up to room temperature and stirred overnight. Then the

solution was again cooled at -78 °C, and additional *n*-butyllithium (20 mmol) was added dropwise. The solution was warmed up to room temperature with stirring over 4 h. Then an additional benzophenone (3.64 g, 20 mmol in THF 20 mL) was added, and the mixture was stirred overnight. Hydrochloride acid (1 N) was added, and the mixture was stirred for 1 h, and then neutralized with aqueous sodium carbonate, extracted twice with dichloromethane. Organic layers were washed with water, and dried over magnesium sulfate and filtered. Volatile materials were removed under vacuum to give yellow solid. Yield: 8.39 g (89%). ¹H NMR (CDCl₃, 200 MHz): δ 7.36-7.15 (m, 21H , Ar-H), 6.65 (d, *J* = 6.0 Hz, 2H, *m*-Py-*H*), 5.24 (br, 2H, O*H*), 3.64 (s, 4H, Py(C*H*₂Ph₂OH)₂). ¹³C NMR (CDCl₃, 50 MHz): δ 157.45, 146.60, 136.91, 127.95, 126.61, 126.12, 122.85 (Ar-C), 78.15 (Ph₂COH), 48.13 (Ph₂CCH₂Py). Elemental anal. calcd for C₃₃H₂₉NO₂(471.6): C, 84.05; H, 6.20; N, 2.97%. Found: C, 84.16; H, 6.38; N, 2.85%. Mp: 106 °C.

Synthesis of 2,2'-(4-methylpyridine-2,6-diyl)bis(1,1-diphenylethan-1-ol) (^{Me}L^{Ph}-H).

Using a method similar to that for ^HL^{Ph}-H expect 2,4,6-trimethylpyridine was used in place of 2,6-dimethylpyridine. Yield: 7.96 g (82%). ¹H NMR (CDCl₃, 200 MHz): δ 7.36-7.15 (m, 21H , Ar-H), 6.48 (s, 2H, *m*-Py-*H*), 5.33 (br, 2H, O*H*), 3.59 (s, 4H, Py(C*H*₂Ph₂OH)₂) 2.02 (s, 3H, 4-C*H*₃-Py). ¹³C NMR (CDCl₃, 50 MHz): δ 157.05, 148.30, 146.68, 127.90, 126.54, 126.11, 123.87 (Ar-C), 78.07 (Ph₂COH), 47.87 (Ph₂CCH₂Py), 20.73 (4-CH₃-Py). Elemental anal. calcd for C₃₄H₃₁NO₂(485.6): C, 84.09; H, 6.43; N, 2.88%. Found: C, 84.15; H, 6.51; N, 2.77%. Mp: 110 °C.

Synthesis of 2,6-bis(2-hydroxy-2-methylpropyl)pyridine 1-oxide (^HL^{Me}O-H).

To a solution of, was added dropwise at room temperature. A mixture of ${}^{H}L{}^{Ph}$ -H (2.23g, 10 mmol) and H₂O₂ (10 mL) in acetic acid (50 mL) was stirred and heated at 100 °C over a week. And then the solution was warmed up to room temperature, neutralized with aqueous sodium hydroxide, and extracted twice with dichloromethane. Organic layers were washed with water, and dried over magnesium sulfate and filtered. Volatile materials were removed under vacuum to give brown oil.

Yield: 1.31 g (55%). ¹H NMR (CDCl₃, 200 MHz): δ 7.39 (t, J = 8.0 Hz, 1H, p-Py-H), 7.25 (d, J = 8.0 Hz, 2H , m-Py-H), 6.45 (br, 2H, OH), 3.25 (s, 4H, Py(CH₂Me₂OH)₂), 1.28 (s, 12H, Py(CH₂(CH₃)₂OH)₂). ¹³C NMR (CDCl₃, 50 MHz): δ 150.19, 128.41, 126.84, (Ar-C), 71.91 (Me₂COH), 44.79 (Me₂CCH₂Py), 29.79 ((CH₃)₂CCH₂Py). Elemental anal. calcd for C₁₃H₂₁NO₃(293.3): C, 65.25; H, 8.85; N, 5.85%. Found: C, 65.16; H, 8.68; N, 5.51%.

Synthesis of ^HL^{Me}-TiOPr₂

A mixture of ^HL^{Me}-H (2.23 g, 10 mmol) and Ti(OPr)₄ (2.84 g,10 mmol) in THF (20 mL) was stirred for one day. Volatile materials were removed under vacuum to give yellow powder and then it was washed with hexane (30 mL) and white powder was obtained. Yield: 2.51 g (64%). ¹H NMR (CDCl₃, 200 MHz): δ 7.64 (t, *J* = 8.0 Hz, 1H, *p*-Py-*H*), 7.05 (d, *J* = 8.0 Hz, 2H , *m*-Py-*H*), 4.65 (m, 2H, OC*H*(CH₃)₂), 3.07 (s, 4H, Py(CH₂C(CH₃)₂), 1.20-1.14 (m, 24H, Py(CH₂C(CH₃)₂), OCH(CH₃)₂). ¹³C NMR(CDCl₃, 50 MHz): δ 158.08, 137.69, 123.15, 78.83 (Py(CH₂C(CH₃)₂), 75.73 (Py(CH₂C(CH₃)₂), 51.59 (OCH(CH₃)₂), 30.03 (Py(H₂C(CCH₃)₂), 25.97 (OCH(CH₃)₂). Elemental anal. calcd for (C₁₉H₃₃NO₄Ti): C, 58.92; H, 8.59, N, 3.62%. Found: C, 59.01; H, 8.68, N, 3.33%. Mp: 180 °C.

Synthesis of ^HL^{Ph}-TiOPr₂

Using a method similar to that for ^HL^{Me}-TiOPr₂ expect ^HL^{Ph}-H was used in place of ^HL^{Me}-H. Yield: 5.48 g (86%). ¹H NMR (CDCl₃, 200 MHz): δ 7.45-7.41, 7.25-7.02 (m, 21H , Ar-H), 6.76 (d, *J* = 8.0 Hz, 2H, *m*-Py-*H*), 4.85 (sept, *J* = 6.0 Hz, 2H, OC*H*(CH₃)₂), 3.80 (s, 4H, Py(CH₂Ph₂O)₂), 1.20 (d, *J* = 6.0 Hz, 12H, OCH(CH₃)₂). ¹³C NMR(CDCl₃, 50 MHz): δ 156.52, 146.18, 137.21, 127.61, 127.39, 126.04, 123.74, 84.97 (Py(CH₂CPh₂), 77.63 (Py(CH₂CPh₂), 50.20 (OCH(CH₃)₂), 25.62 (OCH(CH₃)₂). Elemental anal. calcd for (C₃₉H₄₁NO₄Ti): C, 73.70; H, 6.50, N, 2.20%. Found: C, 74.17; H, 6.90, N, 2.56%. Mp: 242 °C.

Synthesis of ^{Me}L^{Ph}-TiOPr₂

Using a method similar to that for ^HL^{Me}-TiOPr₂ expect ^{Me}L^{Ph}-H was used in place of ^HL^{Me}-H. Yield: 4.38 g (67%). ¹H NMR (CDCl₃, 200 MHz): δ 7.42 (s, *J* = 8.0 Hz, 8H, Ar-H), 7.20-7.08 (m, 12H, Ar-H), 6.60 (s, 2H, *m*-Py-*H*), 4.83 (sept, *J* = 6.0 Hz, 2H, OC*H*(CH₃)₂), 3.73 (s, 4H, Py(C*H*₂Ph₂O)₂), 2.07 (s, 3H, 4-C*H*₃-Py), 1.19 (d, *J* = 6.0 Hz, 12H, OCH(C*H*₃)₂). ¹³C NMR(CDCl₃, 50 MHz): δ 156.09, 148.78, 147.86, 127.63, 126.06, 124.91, 120.36, 84.73 (Py(CH₂CPh₂), 77.22 (Py(*C*H₂CPh₂), 50.50 (OCH(CH₃)₂), 26.10 (OCH(CH₃)₂), 20.73 (PyCH₃). Elemental anal. calcd for (C₄₀H₄₃NO₄Ti): C, 73.95; H, 6.67, N, 2.16%. Found: C, 73.64; H, 6.69, N, 1.96%. Mp: 254 °C.

Synthesis of (^HL^{Me}Ti-O)₄

A mixture of ^HL^{Me}O-H (2.39 g, 10 mmol) and Ti(OPr)₄ (2.84 g,10 mmol) in THF (20 mL) was stirred for one day. Volatile materials were removed under vacuum to give yellow powder, and then it was washed with hexane (30 mL), and white powder was obtained. Yield: 1.63 g (57%). ¹H NMR (CDCl₃, 200 MHz): δ 7.50 (t, *J* = 8.0 Hz, 1H, *p*-Py-*H*), 7.18 (d, *J* = 8.0 Hz, 2H , *m*-Py-*H*), 4.33 (d, *J* = 12.0 Hz, 2H, Py(CH₂Me₂O)₂), 2.52 (d, *J* = 12.0 Hz, 2H, Py(CH₂Me₂O)₂), 1.47 (s, 6H, Py(CH₂(CH₃)₂O)₂), 0.77 (s, 6H, Py(CH₂(CH₃)₂O)₂). ¹³C NMR (CDCl₃, 50 MHz): δ 152.22, 132.17, 125.30 (Ar-C), 79.50, 78.43 (Me₂CO), 44.15, 32.18 (Me₂CCH₂Py), 28.57, 24.73 ((CH₃)₂CCH₂Py). Elemental anal. calcd for (C₅₂H₇₆N₄O₁₂Ti₄): C, 54.76; H, 6.72, N, 4.91%. Found: C, 54.54; H, 6.31, N, 4.58%. Mp: 268 °C.

Synthesis of ^HL^{Me}₂-Ti

A mixture of ^HL^{Me}-H (4.46 g, 20 mmol) and Ti(OPr)₄ (2.84 g,10 mmol) in THF (20 mL) was stirred at 40 °C for one day. Volatile materials were removed under vacuum to give white powder, and then it was washed with hexane (50 mL), and white powder was obtained. Yield: 3.23 g (66%). ¹H NMR (CDCl₃, 200 MHz): δ 7.55 (t, *J* = 8.0 Hz, 1H, *p*-Py-*H*), 6.98 (d, *J* = 8.0 Hz, 2H , *m*-Py-*H*), 3.26 (br, 4H, Py(CH₂Me₂O)₂), 1.42-1.10 (m, 12H, Py(CH₂(CH₃)₂O)₂). ¹³C NMR (CDCl₃, 50 MHz): δ 157.94, 137.20, 122.71 (Ar-C), 77.63 (Me₂CO), 51.58 (Me₂CCH₂Py), 30.43 ((CH₃)₂CCH₂Py). Elemental anal. calcd for (C₂₆H₃₈N₂O₄Ti): C, 63.67; H, 7.81, N, 5.71%. Found: C, 63.36; H, 7.91, N, 5.87%. Mp: 202 °C.

DFT calculation. The DFT calculation was carried out using the Gaussian09 program. The structures were built according to the crystal structure of ^HL^{Ph}TiOPr₂. Its geometry optimization was carried out using B3LPY.[51] The LanL2DZ basis set[52, 53] was used for Ti atom, and the 6-31G(d) basis set[54] was for other atoms. The temperature for the calculation was set to 333.15 K. The polarizable continuum model was used for simulate the solvent effect of toluene.[55] The minimum energy stationary points of intermediates and the saddle points of transition states were confirmed by frequency analysis with the same calculation level.

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Ti compounds bearing 2,6-bis(o-hydroxyalkyl)pyridine ligands were synthesized.

LA and CL polymerizations were investigated.

 ${}^{Me}L^{Ph}\text{-}TiOPr_2$ exhibited the highest catalytic activity.

Declaration of interests

■ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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