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Ring-opening polymerization of L-lactide catalyzed by a biocompatible calcium complex

Hsuan-Ying Chen, Hui-Yi Tang, Chu-Chieh Lin*

Department of Chemistry, National Chung Hsing University, 250 Kuo Kuang Road, Taichung 402, Taiwan, ROC

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Abstract

A novel calcium complex, $[(DAIP)_2Ca]_2$ (where DAIP-H = 2-[(2-dimethylamino-ethylimino)methyl]phenol), is prepared in a one flask reaction by condensation of $Ca(OMe)_2$ with DAIP-H in toluene/THF. Experimental results show that in the presence of various alcohols, $[(DAIP)_2Ca]_2$ efficiently initiates the ring-opening polymerization of L-lactide in a controlled fashion, yielding polymers with expectative molecular weight and low polydispersity indexes. Furthermore, kinetic studies show a first-order dependency on both [LA] and [BnOH].

Keywords: Calcium; Catalysis; L-Lactide

1. Introduction

Biodegradable, biocompatible and permeable aliphatic polyesters have drawn intensive attention due to their medical and environmental applications [1–3]. Many of these polyesters can be obtained by the ring-opening polymerization (ROP) of cyclic esters using an effective initiating system via metal alkoxide [4–9]. Since complete removal of catalyst residues from the polymer is often impossible, it is highly preferable to use non-toxic or low toxic metals for biomedical purpose. Therefore, a variety of biocompatible metal catalysts such as Li [10], Zn [11], Mg [11], and Fe(II) [12] have been studied extensively. Among all, calcium is one of the most suitable metals for this purpose. Recently, ROP of L-lactide with calcium-based catalysts has been reported [13], but the main drawback with the use of these catalysts is poor control in molecular weight and with broad polydispersity (PDI) due to high reactivity towards most organic solvents and the collocation ligands lack the protective obstacle. Most recently, several other calcium complexes [14] have shown good molecular weight control of PLA with low PDI. However, the reaction rate was slow. We describe herein the preparation of a novel calcium complex, $[(DAIP)_2Ca]_2$ (where DAIP-H = 2-[(2-dimethylamino-ethylimino)methyl]phenol), which is capable to effectively catalyze polymerization of L-lactide with narrow molecular weight distribution by increasing initiator efficiency with the help of fine-tuning the molar ratio of the reactants.

2. Experimental section

2.1. General

All manipulations were carried out under a dry nitrogen atmosphere. Solvents and reagents were dried by refluxing for at least 24 h over sodium/benzophenone (hexane, toluene, tetrahydrofuran (THF)), anhydrous magnesium sulphate (benzyl alcohol), or over phosphorus pentoxide (CH_2Cl_2). L-Lactide was recrystallized from a toluene solution prior to use. *N*,*N*-Dimethylethane-1,2-diamine and 2-hydroxybenzaldehyde were purchased from Showa and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova-600 (600 MHz for ^1H and 150 MHz for ^{13}C) or a Varian Mercury-400 (400 MHz for ^1H and 100 MHz for

* Corresponding author. Tel.: +886 4 22840412; fax: +886 4 22862547.
E-mail address: cchlin@mail.nchu.edu.tw (C.-C. Lin).

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^{13}C) spectrometer with chemical shifts given in parts per million from the internal TMS or center line of $CHCl_3$. Microanalyses were performed using a Heraeus CHN-O-RAPID instrument.

2.2. Synthesis of 2-[(2-dimethylamino-ethylimino)-methyl]phenol (DAIP-H)

2-[(2-Dimethylamino-ethylimino)methyl]phenol (DAIP-H) was prepared by acid-catalyzed condensation according to literature procedures [15]. A mixture of *N*,*N*-dimethylethane-1,2-diamine (8.8 g, 100 mmol), 2-hydroxybenzaldehyde (12.2 g, 100 mmol), and $HCl_{(aq)}$ (35%, 0.30 mL) was stirred in absolute THF (30 mL) for 1 day. Volatile materials were removed under vacuum to give yellow oil. Yield: 18.2 g (95%).

2.3. Synthesis of [(DAIP)$_2$Ca]

The mixture of DAIP-H (1.92 g, 10 mmol) with $Ca(OMe)_2$ (0.51 g, 5 mmol) was stirred in toluene/THF (20/5 ml) at 100 °C for 3 days in a sealed tube and subsequently surplus $Ca(OMe)_2$ was removed by filtration. Volatile materials were removed under vacuum to yield yellow powder. The powder was washed with hexane (30 mL) twice to remove excess ligand and the yellow powder was obtained after filtration. Yield: 1.27 g (60%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, s, *H*C═N), 7.03, 6.40 (1H, t, $J = 6.8$ Hz, ArH), 6.99, 6.76 (1H, d, $J = 6.8$ Hz, ArH), 3.50 (2H, b, C═NC*H*$_2$), 2.40 (2H, b, C*H*$_2$NMe$_2$), 1.86 (6H, s, N(C*H*$_3$)$_2$) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 173.16 (*C*═N), 169.28 (*C*OH), 135.41, 133.07, 122.40, 122.07, 112.64 (Ar), 60.19 (C═N*C*H$_2$), 57.92 (C═NCH$_2$*C*H$_2$NMe$_2$), 45.21 (N(*C*H$_3$)$_2$) ppm; Anal. Calcd (found) for $C_{22}H_{30}N_4O_2Ca$: C 60.85 (61.00), H 7.10 (6.50), N 12.75 (12.70)%.

2.4. Typical polymerization procedure

A typical polymerization procedure was exemplified by the synthesis of PLA-100 (the number 100 indicates the designed $[LA]_0/[BnOH]$) at room temperature. The conversion yield (98%) of PLA-100 was analyzed by ^1H NMR spectroscopic studies. A mixture of [(DAIP)$_2$Ca]$_2$ (0.021 g, 0.025 mmol), BnOH (0.5 μL, 0.05 mmol) and L-lactide (0.72 g, 5 mmol) in toluene (10 mL) was stirred at room temperature for 55 min. Volatile materials were removed in vacuo, and the residue was redissoved in THF (5 mL). The mixture was then quenched by the addition of an aqueous acetic acid solution (0.35 N, 10 mL), and the polymer was precipitated on pouring into *n*-hexane (40 mL) to give white crystalline solids. Yield: 0.5 g (69%).

2.5. GPC measurements

The GPC measurements were performed on a Hitachi L-7100 system equipped with a differential Bischoff 8120 RI detector using THF (HPLC grade) as an eluent. The chromatographic column was Phenomenex Phenogel 5μ 10^3 Å and the calibration curve is obtained by polystyrene standards to calculate M_n (GPC). A typical GPC measurements' description was exemplified by the measurement of PLLA-50 (the number 50 indicates $[M]_0/[I]_0$). PLLA-50 (0.025 g) was dissolved in 3.975 g THF (HPLC grade) and filtered through a filter (13 mm Millex-HN Filter 0.45 μm NY Nonsterile). The solution (25 μL) was then injected into the GPC and the flow eluent rate was 1 mL/min. The results were calculated by SISC chromatography data solution 1.0 edition.

2.6. X-ray crystallographic studies

Single crystals of [(DAIP)$_2$Ca]$_2$·THF were obtained on slow cooling of a CH_2Cl_2/THF (5/20 ml) solution. Suitable crystals were sealed in thin-walled glass capillaries under nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing ω (width of 0.3° per frame). The absorption correction was based on the symmetry equivalent reflections using SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences, and was confirmed using the structure solution. The structure was solved by direct methods using a SHELXTL package. All non-H atoms were located from successive Fourier maps and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms.

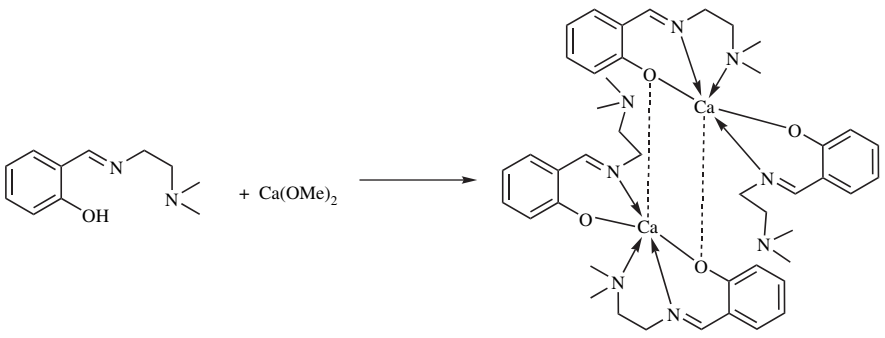
3. Results and discussion

3.1. Syntheses and crystal structure determination

The ligand, 2-[(2-dimethylamino-ethylimino)methyl]phenol (DAIP-H) was prepared by the condensation of *N*,*N*-dimethylethane-1,2-diamine with 2-hydroxybenzaldehyde in the presence of HCl according to literature procedures [15]. The catalyst, [(DAIP)$_2$Ca]$_2$ (**1**) was obtained by the reaction of DAIP-H (10 mmol) with $Ca(OMe)_2$ (5 mmol) in toluene/THF (20/5 ml) in a sealed glass tube at 100 °C for 3 days as shown in Scheme 1. Surplus $Ca(OMe)_2$ was removed by filtration and the filtrate was then dried under vacuum to yield yellow powder. The powder was washed with hexane (30 mL) twice to remove excess ligands. Single crystals suitable for X-ray determination of [(DAIP)$_2$Ca]$_2$·THF (**1**·THF) were obtained by slow cooling of a CH_2Cl_2/THF (5/20 ml) solution. The molecular structure of **1**·THF (Fig. 1) reveals a dinuclear feature in which two nonequivalent calcium atoms are bridged through two phenoxy oxygen atoms. One of them is six-coordinated and another is seven-coordinated with an extra coordinated THF. The coordination of THF on the Ca^{2+} provides us the information of probable mechanism for ring-opening polymerization of L-lactide.

3.2. Ring-opening polymerization of L-lactide

ROP of L-lactide (LA) catalyze by compound **1** employing benzyl alcohol (BnOH) as an initiator has been systematically



Scheme 1.

examined in toluene at room temperature as shown in Table 1. Experimental results indicate that compound **1** is an efficient catalyst for ring-opening polymerization of L-lactide in the presence of BnOH. The conversion can reach to >96% within 40–60 min at room temperature when $[M]_0/[I]_0$ ratio is ranging from 50 to 125 (Table 1). The good polymerization control is demonstrated by the linear relationship between M_n and $[M]_0/[I]_0$ (Fig. 2) and the polymers with low PDIs, ranging

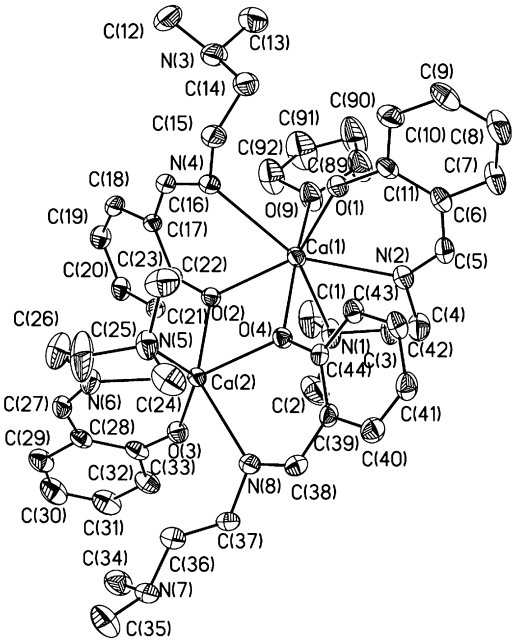
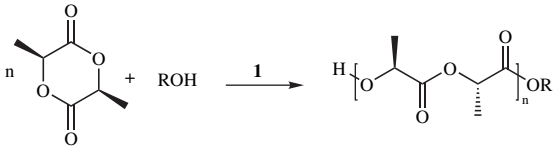


Fig. 1. ORTEP drawing of $[(DAIP)_2Ca]_2 \cdot THF$ (**1**·THF) (non-hydrogen atoms) with thermal ellipsoids drawn at the 20% probability level. Selected bond lengths [Å] and bond angles (°): Ca(1)–O(1) 2.251(4), Ca(1)–O(2) 2.334(3), Ca(1)–O(4) 2.391(4), Ca(1)–O(9) 2.457(5), Ca(1)–N(1) 2.752(5), Ca(1)–N(2) 2.550(5), Ca(1)–N(4) 2.676(5), Ca(2)–O(2) 2.294(4), Ca(2)–O(3) 2.477(5); O(4)–Ca(1)–O(9) 166.61(15), O(1)–Ca(1)–O(9) 86.65(16), O(2)–Ca(1)–O(4) 74.57(12), O(4)–Ca(1)–N(2) 86.92(14), O(4)–Ca(1)–N(4) 106.42(14), O(4)–Ca(1)–N(1) 85.99(17), O(3)–Ca(2)–O(2) 96.27(13), O(3)–Ca(2)–O(4) 134.97(14), O(2)–Ca(2)–O(4) 76.54(12), O(3)–Ca(2)–N(8) 84.90(15), O(2)–Ca(2)–N(8) 141.90(15), O(4)–Ca(2)–N(8) 76.08(14), O(3)–Ca(2)–N(6) 74.03(16), O(2)–Ca(2)–N(6) 98.67(15), O(4)–Ca(2)–N(6) 150.63(16), N(8)–Ca(2)–N(6) 117.98(17), O(3)–Ca(2)–N(5) 138.32(17), O(2)–Ca(2)–N(5) 107.23(18), O(4)–Ca(2)–N(5) 84.73(15), N(8)–Ca(2)–N(5) 96.08(19), N(6)–Ca(2)–N(5) 68.83(18).

Table 1
Polymerization of L-lactide catalyzed by **1** in the presence of [ROH] at room temperature



Entry	[LA]:[**1**]:[ROH][a]	Time (min)	M_w/M_n	M_n[b] (GPC)	M_n[c] (calcd)	M_n[d] (NMR)	Conv[d] (%)
1[e]	50:0.5:1	40	1.26	12 500	7100	7800	97
2[e]	75:0.5:1	50	1.11	19 400	10 800	11 200	99
3[e]	100:0.5:1	55	1.20	23 900	14 200	15 100	98
4[e]	125:0.5:1	60	1.22	32 400	17 400	17 700	96
5[f]	40:0.5:1	30	1.26	11 000	5900	6200	99
6[f]	75:0.5:1	60	1.19	21 900	10 800	11 500	99
7[g]	25:0.5:1	30	1.28	6600	3700	3700	99

[a] [ROH] = 5 mM.
[b] Obtained from GPC analysis and calibrated by polystyrene standard.
[c] Calculated from the molecular weight of L-lactide × $[M]_0/[ROH]_0$ × conversion yield plus M_w (ROH).
[d] Obtained from ^{1}H NMR analysis.
[e] ROH = benzyl alcohol.
[f] ROH = (3-hydroxy-propyl)-carbamic acid methyl ester.
[g] ROH = 2-(2,5-dinitro-phenylsulfanyl)-ethanol.

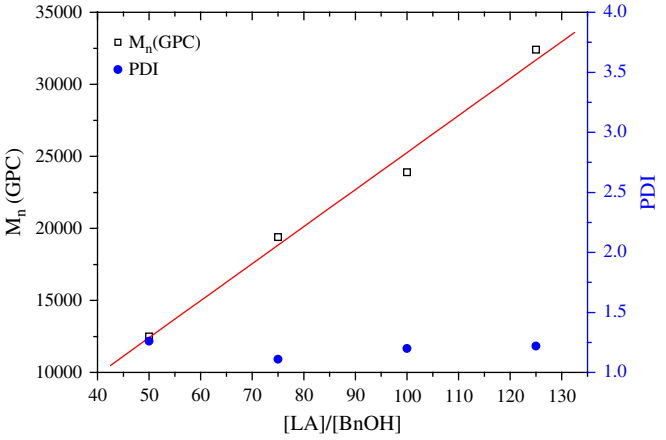


Fig. 2. Linear plot of M_n (GPC) vs. [LA]/[BnOH], with polydispersity indexes indicated by closed circles (GPC).

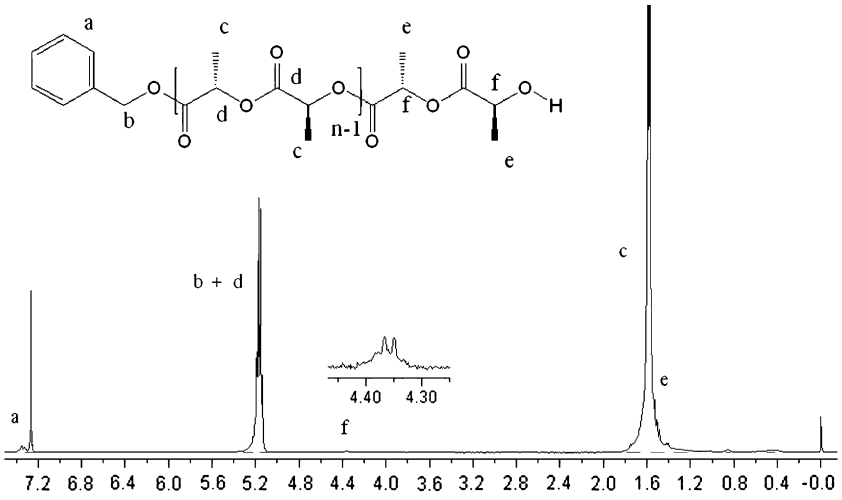


Fig. 3. ^{1}H NMR spectrum of PLLAOBn-50 (50 indicates [LA]/[BnOH] = 50).

from 1.11 to 1.26. The ^{1}H NMR spectrum of PLLA indicates that the polymer chain should be capped with one benzyl ester and one hydroxyl end with the integration ratio between $PhCH_2O-$ and $-CHCH_3OH$ of 5:1 (Fig. 3). By comparison with the other Ca complexes, compound **1** reveals higher reactivity and better PDI control.

Initiating activities do not drastically change with the change of alcohols and the synthesized polylactides with diverse functional groups also have expected molecular weight and low PDIs (Table 1, entries 5–7). The diverse functional groups on the polylactide end such as $PLLAOCH_2CH_2CH_2NHCOOMe$ (Fig. 4) and $PLLAOCH_2CH_2SC_6H_3(NO_2)_2$ (Fig. 5), which are verified by the ^{1}H NMR spectrum of PLLA, have been prepared. After deprotection, these polymers, $PLLAOCH_2CH_2CH_2NH_2$ and $PLLAOCH_2CH_2SH$, can potentially be used as macroinitiators for the preparation of functionalized polypeptide-*b*-polylactide copolymers [16]. The applications of these diverse functionalized PLLA are undertaken.

3.3. Kinetic studies of polymerization of L-lactide catalyzed by compound 1 in the presence of BnOH

Because the polymerization rate at room temperature is so fast and when the concentration of $[(DAIP)_2Ca]_2$ is smaller than [BnOH], the reaction is so slow and the conversion is low. The kinetic studies were performed at 0 °C with respect to the ratio of $[LA]_0$/[BnOH] in which an excess of $[(DAIP)_2Ca]_2$ related to [BnOH] is used and the concentration of $[(DAIP)_2Ca]_2$ is regarded as constant. Therefore, it is incorporated into k_{app}. Preliminary results indicate a first-order dependency on [LA] (Fig. 6, $k_{app} = 0.012\ s^{-1}$). Moreover, a first-order dependency in [BnOH] is indicated of k_{app} vs. [Initiator], with a slope equal to the second-order rate constant $k_{prop} = 1.95\ M^{-1}\ s^{-1}$ (Fig. 7). The rate law can be shown as $d[LA]/dt = k_{prop}[LA][BnOH]$. In agreement with kinetic and structural data, the ROP mechanism fits a "coordination-insertion" mechanism, commonly referred to as "pseudoanionic"

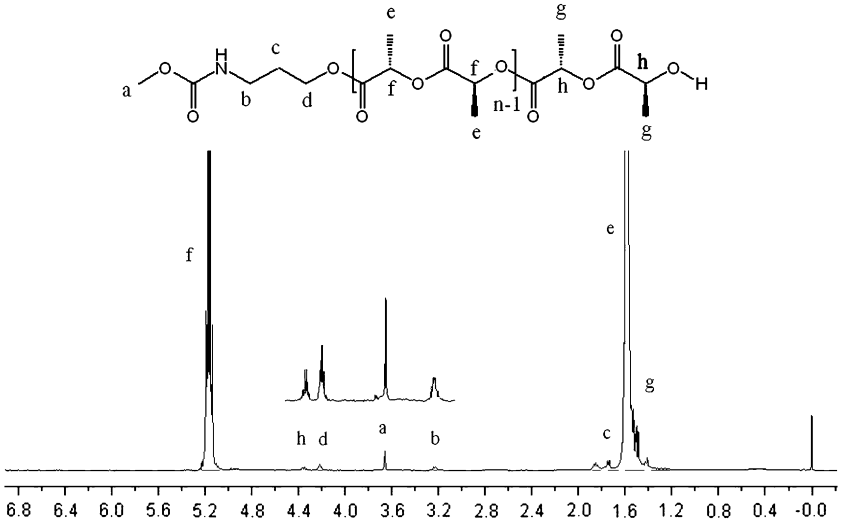


Fig. 4. ^{1}H NMR spectrum of $PLLAOCH_2CH_2CH_2NHCOOMe$-40 (40 indicates [LA]/[$HOCH_2CH_2CH_2NHCOOMe$] = 40).

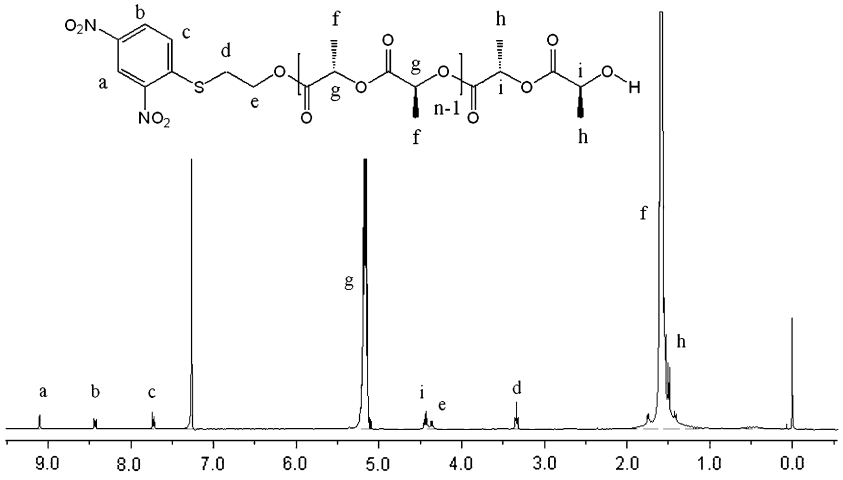


Fig. 5. ^{1}H NMR spectrum of PLLAOCH$_2$CH$_2$SC$_6$H$_3$(NO$_2$)$_2$-25 (25 indicates [LA]/[HOCH$_2$CH$_2$SC$_6$H$_3$(NO$_2$)$_2$] = 25).

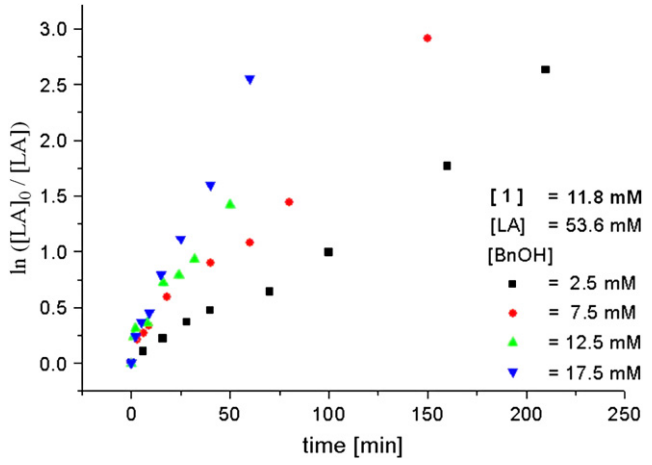


Fig. 6. First-order kinetic plots for L-lactide polymerizations with time in CH_2Cl_2 at 0 °C with different concentrations of [BnOH] as an initiator producing high molecular weight poly(L-lactide) with narrow molecular weight distributions.

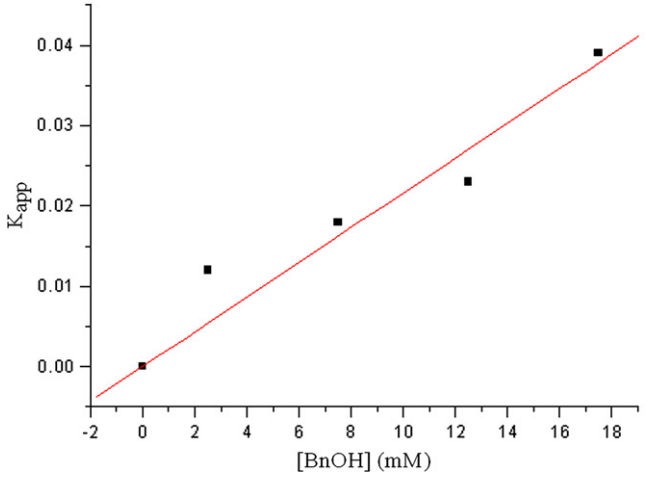


Fig. 7. Linear plot of k_{app} vs. [BnOH] in [LA] = 53.6 mM and [**1**] = 11.8 mM.

polymerization consistent with the monomer insertion into an active "Ca–O" bond with sufficient reactivity and then an acceptable control in the ring-opening polymerization of L-lactide could be achieved. The induction period of time for ROP of lactides clearly depends on the ability of the monomer to coordinate with the initiator.

3.4. Proposed mechanism for polymerization of L-lactide

Based on the molecular structure of [(DAIP)$_2$Ca]$_2$·THF, featuring a dimeric structure with both hexa- and hepta-coordinated calcium ions in solid state, and the kinetic studied results, it is believed that compound **1** exists as equilibrium with THF association and dissociation in solution state, and the place will be substituted by L-lactide for ROP (**A**) (Scheme 2). Then, dimethylamino group maybe dissociated from calcium ion to accept benzyl alcohol giving intermediate **B**. Due to hydrogen bonding between phenoxide or dimethylamino groups and benzyl alcohol, which has been observed in several occasions [17], benzyl alcohol becomes more basic and easier to attack L-lactide. Followed by the ring opening of lactide, a new alcohol (PhCH$_2$OC(O)CH(CH$_3$)OC(O)CH(CH$_3$)OH) is produced which becomes a new initiator to keep the polymerization to go on.

4. Conclusion

In conclusion, a novel calcium complex has been prepared and structurally characterized. The calcium complex has shown great reactivity for the controlled polymerization of LA in the presence of different kinds of alcohols to produce polymer with defined macromolecular architecture, high molecular weight and narrow polydispersities. This catalyst system is very promising in the synthesis of polymers intended for biomedical and pharmaceutical applications.

Acknowledgment

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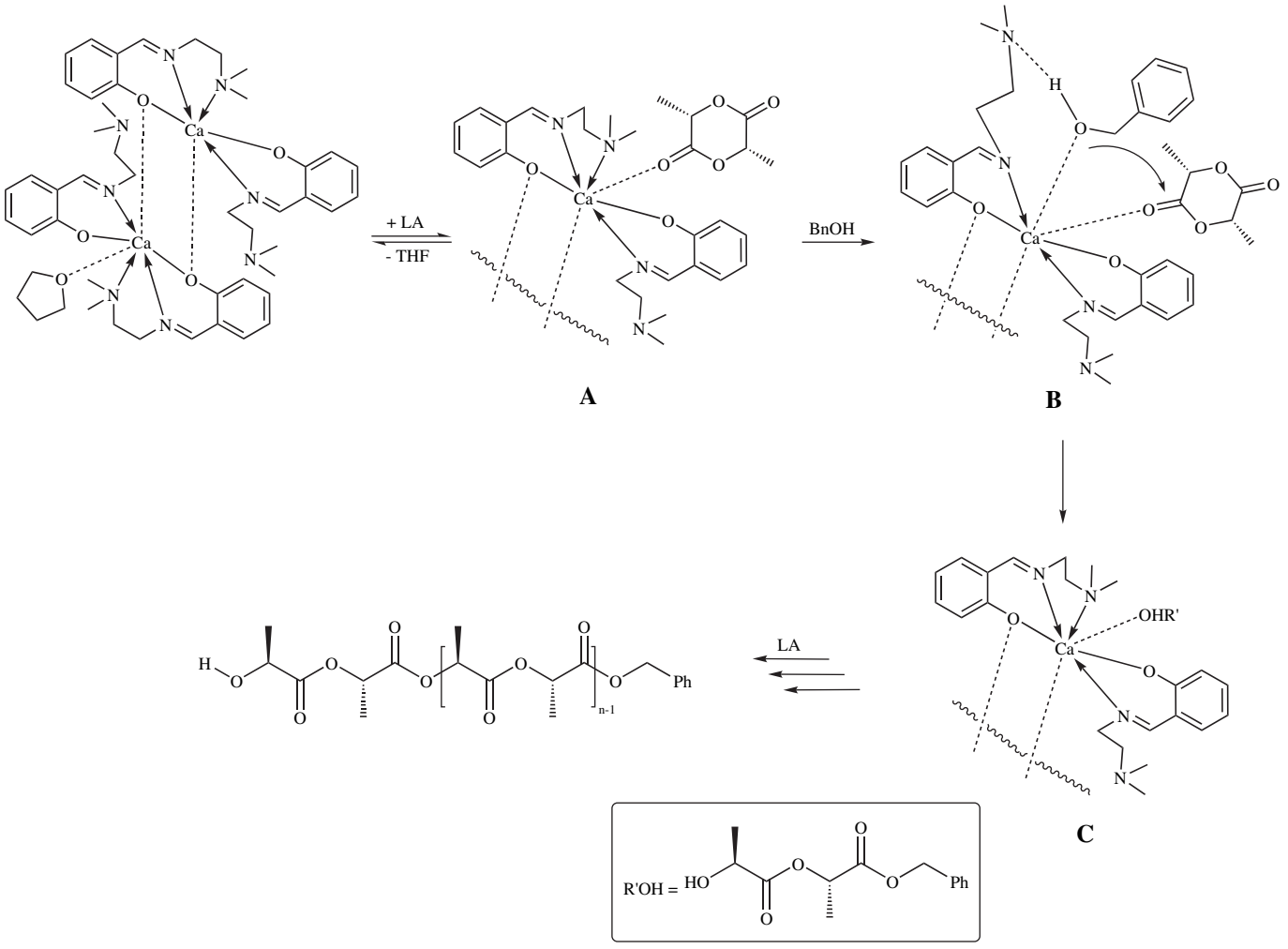

Scheme 2. Proposed polymerization pathways.

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