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THESIS

SINGLE-SITE CATALYSTS FOR THE RING-OPENING POLYMERIZATION OF *rac*-LACTIDE

SITTICHOKE TABTHONG

A Thesis Submitted in Partial Fulfillment of
the Requirements for the Degree of
Master of Science (Chemistry)
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Achiral *Bis*(pyrrolidene) Schiff base Aluminum complexes were synthesized. In the first step, ligands **59-64** were synthesized by the condensation reaction between 2-carboxaldehyde and cooresponding diamine. All ligands were obtained in high yield. Then, ligands were reacted with trimethylaluminium to obtain desired aluminum catalysts. All ligands and complexes were characterized by ^{1}H-NMR spectroscopic technique. Aliminum complexes **1-6** in the presence of 2- propanol were used for polymerization of *rac*-lactide. Resulting polymers from polymerization using complexes **3** and **5** are isotactic polymers ($P_m \approx$ 0.8), while resulting polymers from polymerization using other complexes are atactic polymers ($P_m \approx 0.5$).

Aluminum methoxide based on *N,N'*-bis(1H-pyrrole-2-ylmethylene)-1,2-ethylenediamine was used as a catalyst for the theoretical study. The ring-opening mechanism of *D*- and *L*-LA has investigated using a B3LYP density functional theory employing a 6-31G(d,p) basis set. The ring-opening of lactide occurs *via* a coordination insertion mechanism with two transition states (TS1 and TS2). From the energy profiles it found that the second transition state (TS2), the state that the lactide ring-opening can be readily activated through the octahedral transition that involves the $C_{carbonyl}$-O_{acyl} and Al-$O_{carbonyl}$ bond dissociation, is rate determining step for both *D*- and *L*-LA. In comparison, the ring-opening of *L*-lactide occurs more readily than that of *D*-lactide.

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Student's signature Thesis Advisor's signature

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Sittichoke Tabthong

April, 2009

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LIST OF ABBREVIATIONS

Ar	=	gereric acryl group
Et	=	ethyl
GPC	=	gel permeation chromatography
Hz	=	hertz
i	=	isotactic
^{i}Pr	=	isopropyl
k_{app}	=	apparent rate of polymerisation
LA	=	lactide
m	=	*meso*
Me	=	methyl
M_n	=	number average molecular weight
M_w	=	weight average molecular weight
M_n/M_w	=	molecular weight distribution
NMR	=	nuclear magnetic resonance
PDI	=	polydispersity index
Ph	=	phenyl
PLA	=	polylactide
PLLA	=	poly(*D*-lactide)
PLLA	=	poly(*L*-lactide)
P_m	=	probability of *meso* linkages between monomer units
ppm	=	parts per million
P_r	=	probability of r*acemic* linkages between monomer units
r	=	*racemic*
ROP	=	ring-opening polymerisation
s	=	syndiotactic
T_g	=	glass temperature
THF	=	tetrahydrofuran
T_m	=	melting temperature
δ	=	chemical shift

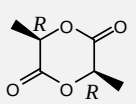
SINGLE-SITE CATALYSTS FOR THE RING-OPENING POLYMERIZATION OF *rac*-LACTIDE

INTRODUCTION

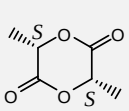
Over the past few decades, polyesters, especially polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL), and their copolymer, are among the most well known synthetic biodegradable polymers due to their biomedical and pharmaceutical applications such as sutures, stints, time release control drugs and tissue polymer matrices (K.E. Uhrich *et al*., 1999). In this work, PLA is found interested as it can be derived from agricultural products which are major products of our country such as corn, beets, and sugar cane. In addition, PLA benefit is increasingly important for a sustainable future as the depletion of petrochemical feedstock comes near (R.E. Drumright *et al*., 2000).

1. Lactide and Polylactide

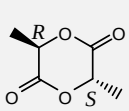
Lactide (LA) is a six-membered cyclic-diester monomer, which can be synthesised from reaction between two molecules of lactic acid. As lactide monomer has two stereogenic centers, it exists as three different stereoisomers (Figure 1). The *R,R*-LA is referred to *D*-LA, while the *S,S*-LA is referred to *L*-LA. The *R,S* isomer is called *meso*-LA. In general, the cyclisation of lactic acids results in an equimolar mixture of *D*- and *L*-LA which is called *racemic* lactide (*rac*-LA).



D-LA



L-LA



meso-LA

Figure 1 Stereoisomers of lactide (LA).

Polylactide can be obtained either by polycondensation of lactic acids or by the ring-opening polymerization (ROP) of the lactide (LA). Polycondensation pathway is known to be the equilibrium of polymer chain and water, which being difficult to remove in condition of polymerization. This generally limits the molecular weight of the polymer and polymer microstructure from polycondensation is random (O. Dechy-Cabaret *et al*., 2004). On the other hand, the ROP of lactide by organometalic initiators is the most widely used method for the synthesis of well-defined polylactide. The reason is the method allows the polymerization to be controlled in terms of molecular weight, polydispersity index (DPI), polymer microstructure, and the rate of polymerization.

Due to lactide monomer has three different stereoisomers, consequently, PLA can be formed in different stereoforms (Figure 2) (T.M Ovitt *et al*., 2002). In case of enantiomerically pure *L*-LA or *D*-LA polymerization, polymer will be polymerized without epimerization at chiral centres. Optically pure *L*-LA or *D*-LA is formed. In other case, *meso*-LA will be polymerized to two stereoisomer polymers. If the enantiomorpic acyl-oxygen bond is preferentially opened, syndiotactic PLA will be obtained, whereas in the absence of stereocontrol, an atactic polymer is produced. For the polymerization of *rac*-LA, if the propagation center of the catalyst preferentially polymerizes one enantiomer faster than the other, an isotactic stereoblock copolymer is formed. On the other hand, if the propagation species polymerizes selected enantiomers in an alternating manner, then heterotactic PLA is produced. As same as *meso*-LA, in the absence of stereocontrol, an atactic polymer is produced.

The microstructure of PLA can be characterized using homonuclear decoupled ^{1}H NMR and proton decoupled ^{13}C NMR spectroscopy at the tetrad level (K.A.M. Thakur *et al*., 1997a, 1997b, 1998a, 1998b). Stereoregular tetrad components are shown in Figure 3 (M.H. Chisholm *et al*., 1997).

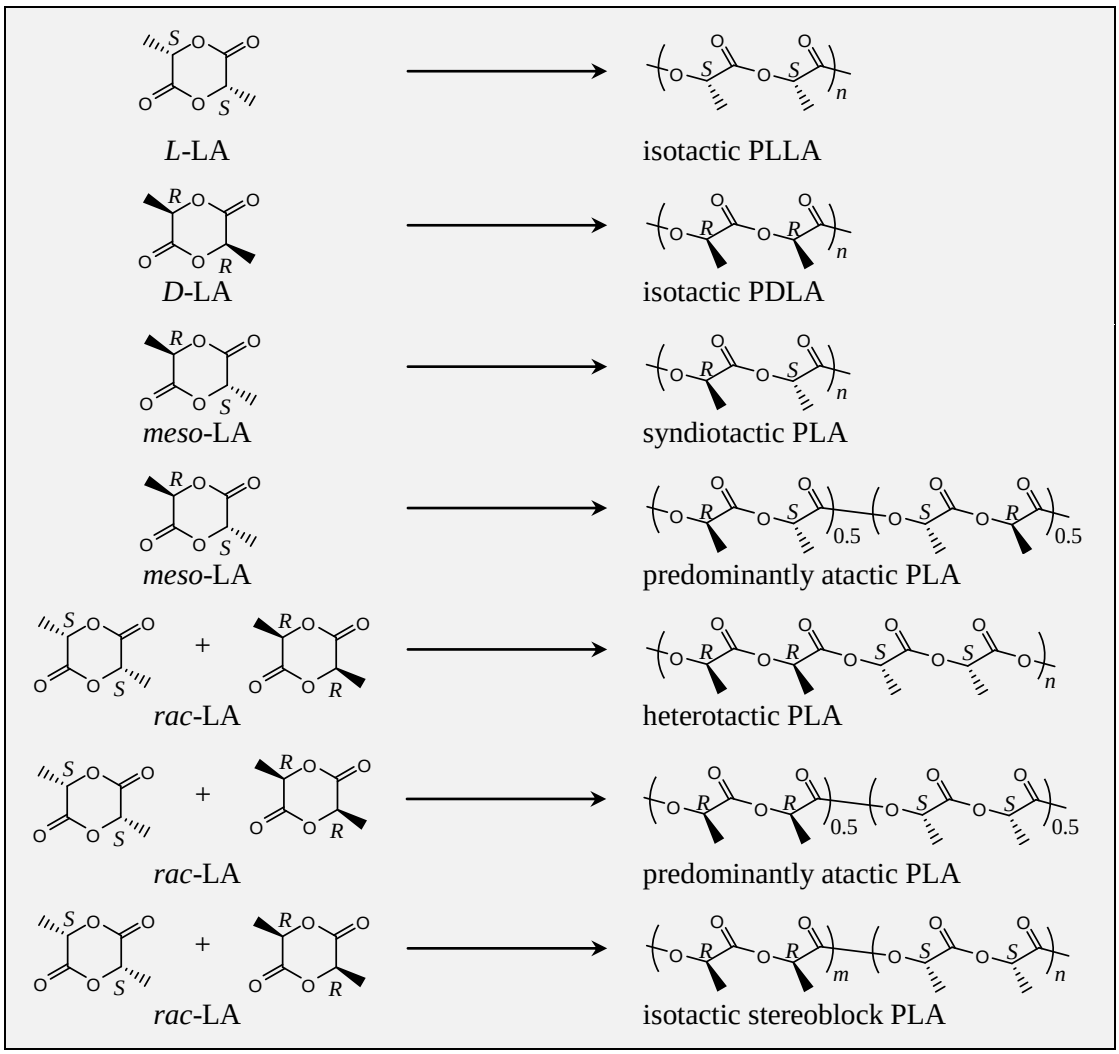


Figure 2 PLA microstructure.

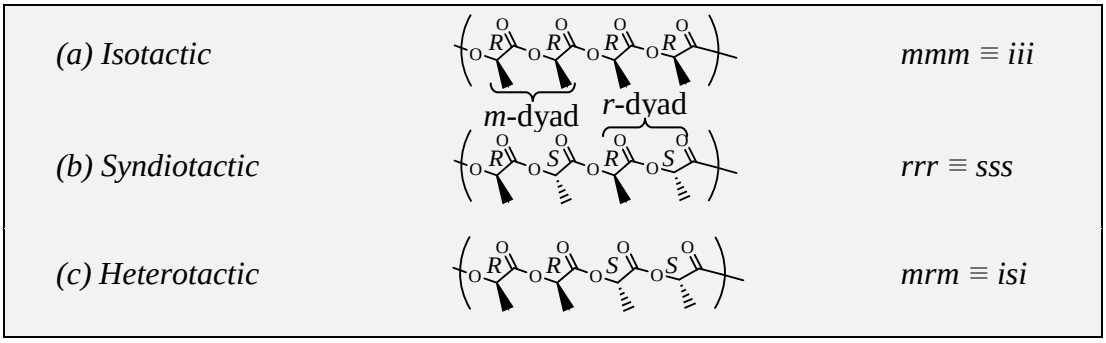


Figure 3 The microstructure of PLA at tetrad level (*m* = *meso*, {*m* ≡ *i*, isotactic}; *r* = *racemic*, {*r* ≡ *s*, syndiotactic}).

2. Ring-Opening Polymerization (ROP) Mechanism

The general mechanism of ROP consists of two steps, coordination-insertion and ring opening polymerization, as illustrated in Figure 4 (H.R Kricheldorf *et al*., 1996; W.M. Stevel *et al*., 1997; P. Dubois *et al*., 1991; A. Kowalski *et al*., 1998, 2000). The polymerization proceeds *via* acyl-oxygen cleavage of LA with insertion of the new monomer into metal-oxygen bond. After that, ester bond is broken. Lactide has changed from cyclic to aliphatic ester. However, the most common side-reaction, transesterification, may occur during the polymerization (Figure 5) (J. Baran *et al*., 1997; S. Penczek *et al*., 1998). Transesterification results from the nucleophilic attack of the propagation metal alkoxide at the carbonyl carbon in the same chain (Intramolecular transesterification) and/ or the other chain (Intermolecular transesterification). Intramolecular transesterification is the cause of cyclic oligomer formation and shorter propagating chain while intermolecular transesterification is the cause of redistribution of polymer chain to both low and high molecular weight. This is the reasons of a loss of control over the stereochemistry, molecular weight and molecular weight distribution.

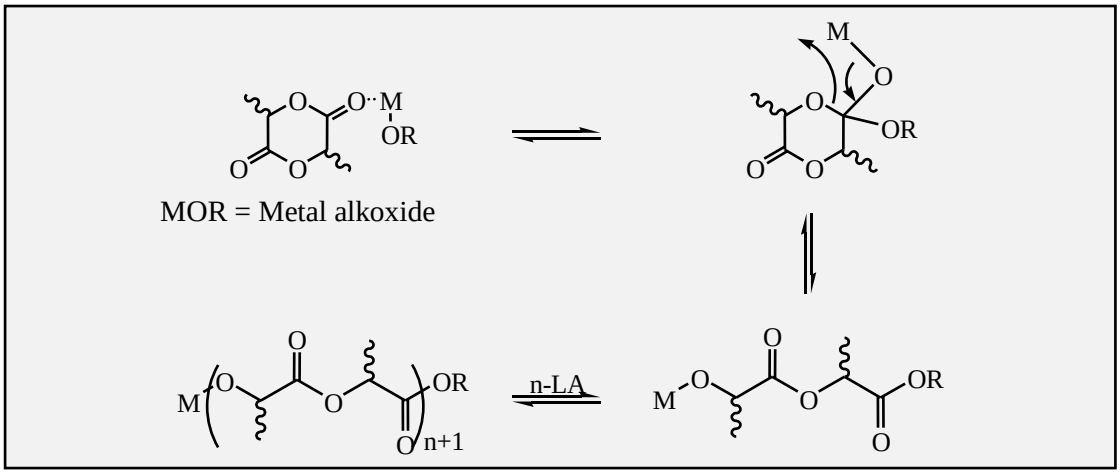


Figure 4 General method for the ring-opening polymerization of lactide by metal initiators.

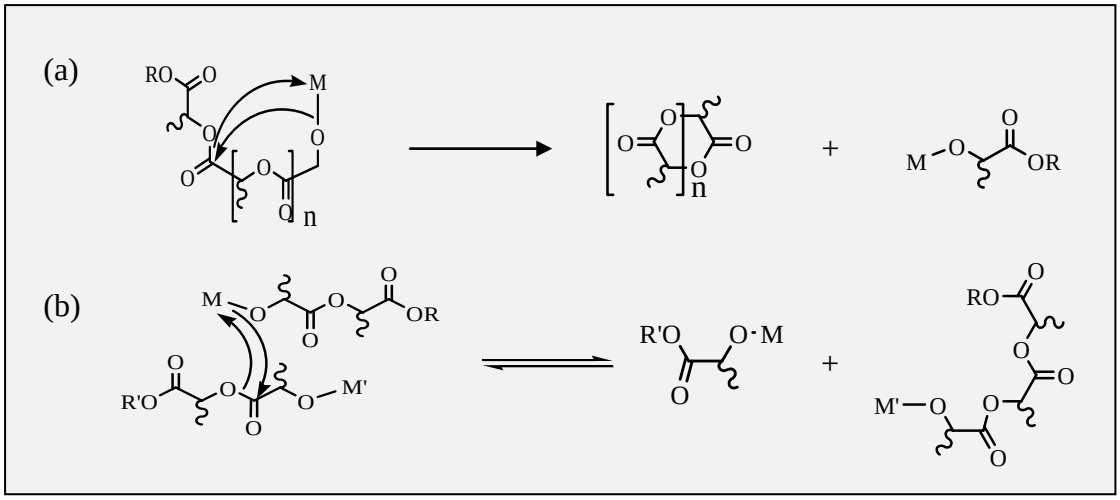


Figure 5 (a) Intramolecular transesterification (b) Intermolecular transesterification.

3. Aluminum Catalysts

In practical, the ROP of lactide requires a suitable initiator to control the properties of polymers such as the physical and mechanical as well as the degradable properties which strongly depend on the microstructure of the polymer chain (M.S Reeve *et al.*, 1994; J.R. Sarasua *et al.*, 1998). Homogeneous single-site catalysts have found to be effective for the ROP of lactide (G.W. Coates, 2000). L_nMOR is a common notation form of the initiator where L_n is the ligand, M is the metal center, and OR is the initiating group. Metals commonly used for the polymerization of lactides are Zn, Al, Mg, Sn, Ca and Fe. The ligand remains attach throughout the polymerization reaction and allows modulation of the activity of the metal center. Through variation in the properties of the metal center and the ligand framework, a number of initiators will be prepared and evaluated. Aluminum is only one element in group 13 metals which displays good catalytic activity toward ring-opening of lactide. Single-site aluminum alkoxide complexes are more active than other aluminum initiators. Most of them can initiate ring opining polymerization of $\mathcal{E}$-caprolactone and lactide at moderate condition.

4. Description of work

In this work, the aluminum alkoxides supported by tetradentate *bis*-pyrrole Schiff-base were studied. The structures of initiators are shown in Figure 6. The work in this study is separated into two main parts which are experimental and theoretical studies.

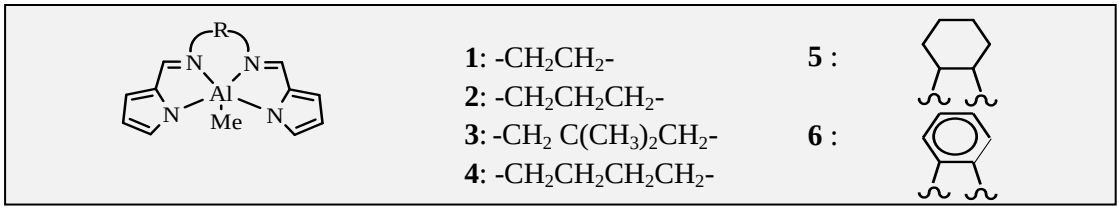


Figure 6 The formulae of initiators **1-6**.

In the experimental part, it focused on the synthesis and characterization of the aluminum complexes using nuclear magnetic resonance (NMR) spectroscopy technique. After that, all complexes were evaluated as the initiators for the polymerization of *rac*-LA. The polymerization activity in term of the polymer microstructure was investigated.

For the theoretical studies, to account for the ring-opening mechanism of LA using aluminum alkoxides supported by tetradentate *bis*-pyrrole Schiff base, the BTLYP6-31G(d,p) method is employed. The information obtained from the theoretical studies was used to explain the effect of catalyst on polymerization process over *D*-LA and *L*-LA.

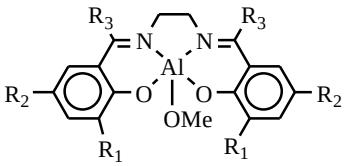
LITERATURE REVIEW

Over the past few decades, the single-site aluminum complexes have received much attention as catalysts/initiator for the ring-opening polymerization of cyclic ester monomer, in particular lactide (O. Dechy-Caberet *et al*., 2004; B. J. O' Kefee *et al*., 2001; J. Wu *et al*., 2006). Among the variety of catalysts for the ROP of lactide, aluminum complexes supported by tetradentate Schiff base ligands have shown to be efficient catalyst systems that exhibit a good control especially over the stereoselectivity. The tetradentate Schiff base ligands prepared from salicyladehyde derivatives and diamine compounds (so called "Salen" ligands) are the most ligand system studied to date due to the electronic and steric properties of the catalyst can be fine turned by changing the substituents on the phenoxy rings and the backbone of the catalysts.

In 1993, Spassky and co-worker reported the first achiral aluminum Schiff base methoxide complex called Al(Salen)OMe (**7**) as an initiator for the polymerization of *rac*-LA (Figure 7) (A. Le Borgne *et al*., 1993). This complex was found to be dimeric in the solid state. Kinetic studies using **7** at 70 ˚C showed that the polymerization was first order in LA and in catalyst, with the rate being twice as fast in toluene as in CH_2Cl_2. The resulting polymers were found to be a predominantly isotactic bias. However, in this processes, transesterifications were observed at lower monomer concentrations (G. Montaudo *et al*., 1996).

The introduction of electron-withdrawing groups on the phenoxy ring, Al(5-Cl-Salen)OMe (**8**) was found to polymerize *L*-LA and *rac*-LA at ambient temperature (P. A. Cameron *et al*., 1999). No esterification reactions were observed as indicated by the constantly narrow molecular weight distribution of polymers up to full conversion. The increase in the reactivity may result from an enchancement of the aluminum electrophilicity or an increase of the polymerization of the initiating propagating Al-X bond. In 2000, Spassky and co-worker reported a new initiator called Al(Hapen)OMe (**9**) which is the Schiff-base complex derived from 2-hydroxy acetophenone and ethylene diamine (A. Bhaw-Luximon *et al*., 2000). Compared to

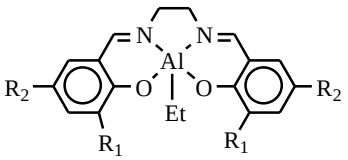
complexes **7** and **8**, the higher polymerization rate was observed. The polymerization was also shown to be a living process in both CH_2Cl_2 at 25 ˚C and toluene at 70 ˚C. Moreover, the polymerization proceeded quickly to highly conversion without significant occurrence of transesterification reactions.



7: $R_1 = R_2 = R_3 = H$

8: $R_1 = H$, $R_2 = Cl$, $R_3 = H$

9: $R_1 = R_2 = H$, $R_3 = Me$



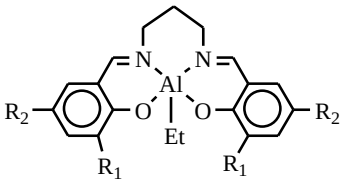
10: $R_1 = R_2 = H$

11: $R_1 = R_2 = Me$

12: $R_1 = {}^{i}Pr$, $R_2 = H$

13: $R_1 = Ph$, $R_2 = H$

14: $R_1 = R_2 = {}^{t}Bu$



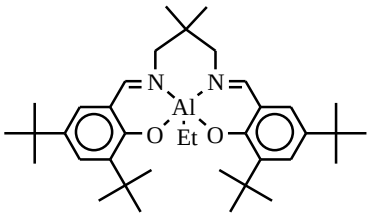
15: $R_1 = R_2 = H$

16: $R_1 = R_2 = Me$

17: $R_1 = {}^{i}Pr$, $R_2 = H$

18: $R_1 = Ph$, $R_2 = H$

19: $R_1 = R_2 = {}^{t}Bu$



20.

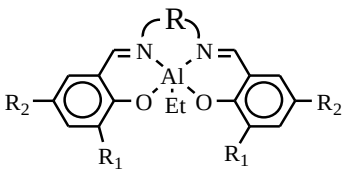
Figure 7 The structure of complexes **7**-**20**.

In 2002, Nomura and co-workers reported two series of achiral aluminum ethyl complexes, **10**-**19** (N. Namura *et al*., 2002). Polymerizations were carried at by *in situ* alcoholysis of the complexes in the presence of one equivalent of benzyl alcohol in toluene at 70 ˚C. Polylactide of notably high isotacticity can be obtained from *rac*-LA using **19** (P_m = 0.91, T_m = 192 ˚C). The polymerization rate and the

tacticity of polymer were found to depend strongly on the substitutes of phenol rings and diimino backbone.

In 2004, Namura (R. Ishii *et al*., 2004) and Chen (Z. Tang *et al*., 2004) independently reported the synthesis of a monoethyl aluminum Schiff-base complex **20**. Polymerization of *rac*-LA using **20** afforded polylactide with P_m of 0.90 and a high T_m of 201 ˚C in the presence of 2-propanol. The polymerization was first order in *rac*-LA concentration. The relationship between the *rac*-LA conversion and molecular weights of the polymer was linear indicating of a well controlled polymerization.

In 2006, Gibson and co-worker synthesised a series of aluminum salen-type complexes bearing ligands that differ in their steric and electronic properties, **21-27** (P. Hormnirun *et al*., 2006). Both the phenoxy substituents and the backbone linker have a significant influence over the polymerization. Electron withdrawing groups attached to the phenoxy donor generally gave an increased polymerization rate, whereas large *ortho* substituents generally slowed down the polymerization.



a. $R_1 = R_2 = H$

b. $R_1 = R_2 = Cl$

c. $R_1 = R_2 = {}^tBu$

d. $R_1 = Cl$, $R_2 = H$

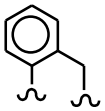
e. $R_1 = R_2 = Br$

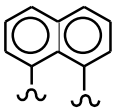
21(**a-d**) : R = $-(CH_2CH_2)-$

22(**a-c**) : R = $-(CH_2C(CH_3)_2)-$

23(**a-c**) : R = $-(CH_2CH_2CH_2)-$

24(**a-c**,**e**) : R = $-(CH_2C(CH_3)_2CH_2)-$

25(**a-c**) : R = 

26(**c**) : R = 

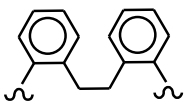
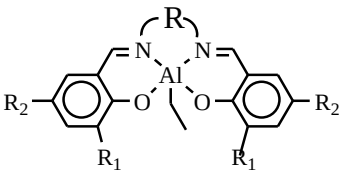
27(**a-c**) : R = 

Figure 8 The structure of complexes **21-27**.

In 2007, Chen and co-workers reported a series of aluminum ethyls and isopropoxides based on tetradentate Schiff base framework, as shown in Figure 9 (H. Du *et al*., 2007). All complexes were monomereric species with a five-coordinated central aluminum in their solid structure. The substituents and the mode of bridging part between the two nitrogen atoms both exerted significant influences upon the progress of the *rac*-LA polymerization , influencing either the tacticity of isolated polymer or the rate of polymerization.



Schiff-base aluminum ethyls

28. (**a**-**c**), **29**. (**a**-**g**), **30**. (**a**,**b**)

28a : R = -(CH_2CH_2)-, $R_1 = R_2 = H$

28b : R = -($CH_2CH_2CH_2$)-, $R_1 = R_2 = H$

28c : R = -(CH_2CH_2 CH_2CH_2)-, $R_1 = R_2 = H$

28d : R = -($CH_2C(CH_3)_2CH_2$)-, $R_1 = R_2 = H$

28e : R = -($OC_6H_3CH_2$)-, $R_1 = R_2 = H$

29a : R = -(CH_2CH_2)-, $R_1 = R_2 = {}^t$Bu

29b : R = -($CH_2CH_2CH_2$)-, $R_1 = R_2 = {}^t$Bu

29c : R = -(CH_2 $CH_2CH_2CH_2$)-, $R_1 = R_2 = {}^t$Bu

29d : R = -($CH_2C(CH_3)_2CH_2$)-, $R_1 = R_2 = {}^t$Bu

29e : R = -($OC_6H_3CH_2$)-, $R_1 = R_2 = {}^t$Bu

29f : R = -($(CH_3)_2CCH_2$)-, $R_1 = R_2 = {}^t$Bu

29g : R = -(OC_6H_4)-, $R_1 = R_2 = H$

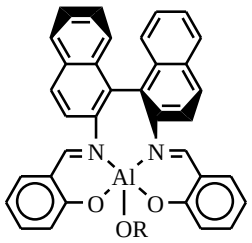
30a : R = -(CH_2CH_2)-, $R_1 = R_2 = Cl$

30b : R = -($CH_2C(CH_3)_2CH_2$)-, $R_1 = R_2 = Cl$

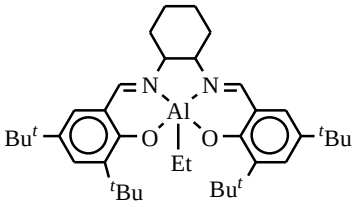
Figure 9 The Schiff base aluminum ethyls complexes **28-30**.

In the case of chiral aluminum Schiff base complexes, the most important breakthrough was the discovery of the enantiomerically pure chiral aluminum complex, (*R*)-(SalBinap)-AlOMe, (*R*)-**31**, by Spassky *et al*. in 1996 (N. Spassky *et al*., 1996). At low conversion, (*R*)-**31** exhibited a 20:1 preference for the polymerization of *D*-LA over *L*-LA ($k_D/k_L = 20$). The polymerization proceeded in a living mechanism, as indicated by the narrow PDIs and control of the resultant polymer

molecular weight by the monomer/initiator ratio. The resulting polymer has a tapered stereoblock microstructure which exhibits a melting temperature (T_m) of 187 ˚C.



(SalBinap)AlOR
(*R*)-**31**, R = Me
(*R*)-**32**, R = ^{i}Pr
(*rac*)-**33**, R = ^{i}Pr



(cyclohexylsalen)AlO^{i}Pr
(*R*)-**34**
(*rac*)-**34**

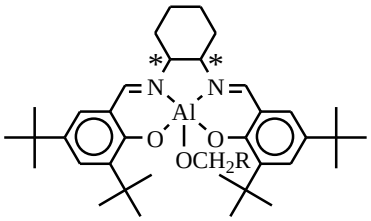
Figure 10 The structure of complexes **31-34**.

In 1999, Coates *et al.* reported the synthesis of syndiotactic PLA from *meso*-LA using the (*R*)-**32** catalyst (T. M. Ovitt *et al*., 1999). The results shown the selectivity of the reaction is P_r = 0.96 when the polymer was produced at 70 ˚C in toluene for 40 hours. Due to the high degree of stereoregularity, the samples of syndiotactic PLA were found to be crystalline with T_g value of *ca*. 45 ˚C and a T_m value of 153 ˚C. The *racemic* catalyst, *rac*-(salBiNap)AlO^{i}Pr ((*rac*)-**33**), was synthesised independently by two different groups (C. P. Radano *et al*.,2000; T. M. Ovitt *et al*., 2002). The polymerization of *rac*-LA using *rac*-**33** resulted in the formation of an isotactic stereoblock PLA (T. M. Ovitt *et al*., 2000). A polymer exchange mechanism was proposed to account for the formation of this polymer. The resulting polymer has a much higher melting temperature (109 ˚C) than isotactic PLLA.

In 2002, Feijen *et al.* showed that the cyclohexylsalen aluminum isopropoxide, (*R*)-**34** and (*rac*)-**34**, provided a high isospecificity and excellent control in both solvent-based and solvent-free polymerizations (Y. Z. Zhong *et al*., 2002, 2003). It was found that (*R*)-**34** polymerized *L*-LA significantly faster than *D*-LA. (*rac*)-**28**

yielded isotactic stereoblock PLA (P_m = 0.93) with a high T_m = 183.5 ˚C and the high degree of crystallinity.

In 2008, Chrisholm and co-workers reported the preparation of a series of chiral Salen aluminum complexes, (*R*,*R*) and (*S*,*S*)-SalenAl(OR), where R= Et, $CH_2{}^{i}Pr$, $CH_2{}^{i}Bu$, and $CH_2CH(S)MeCl$, as shown in Figure 11 (M. H. Chisholm *et al*., 2008). This work describes the complexities in the ROP of LA which are the various competing reactions (*e.g*. interchaintransferification, chain transfer and epimerization) which occur along with the polymerization process.



(*R*,*R*)-**35**, R = Me

(*R*,*R*)-**36**, R = ^{i}Pr

(*R*,*R*)-**37**, R = ^{t}Bu

(*R*,*R*)-**38**, R = CH(*S*)MeCl

(*R*,*R*)-**39**, R = Me

(*R*,*R*)-**40**, R = ^{i}Pr

(*R*,*R*)-**41**, R = ^{t}Bu

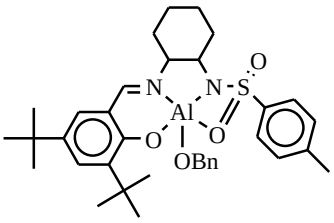
(*R*,*R*)-**42**, R = CH(*S*)MeCl

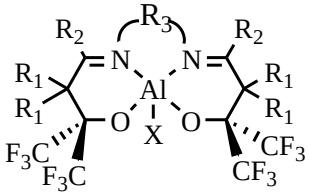
Figure 11 The structure of complexes **35-42**.

Very recently, the various aluminum complexes supported by Salen-like ligands have been reported, as shown in Figure 12 (J. Wu *et al*., 2007; M. Bouyahyi *et al*., 2008; A. Alaaeddine *et al*., 2009). The aluminum complex supported by a sulfonamide/ Schiff base ligand (**43**) was found to be an efficient initiator for the ROP of lactide. In this system, the predominantly isotactic PLA was obtained from *rac*-LA (P_m = 0.60) (J. Wu *et al*., 2007). In 2008, Carpentier *et al*. reported the preparation of new aluminum complexes supported by original di(*β*-hydroxy- *β*-bis(trifluoromethyl))-diimine ligand, **44-51** (M. Bouyahyi *et al*.). These tetradentate fluorinated dialkoxy-diimino ligands related to Salen-type ligands in the nature of the

heteroatoms and their overall ONNO disposition/structure. The Al-O^{i}Pr complexes **46** and **49** were found to be effective initiators for the ROP of *rac*-LA, giving polymers with high molecular weights and relatively narrow PDIs. The polymers produced by these complexes have a highly isotactic-enriched stereoblock microstructure (P_m = 0.87). Very recently, work from the same group revealed the preparation of an original unsymmetrical Schiff base pro-ligand, which combines a phenol and a fluorous alcohol residue (A. Alaaeddine *et al*., 2009). Aluminum complexes supported by this mixed tetradentate ligand were synthesised, **52** and **53**. Complex **52** is an effective initiator for the ROP of *rac*-LA, giving polymers with a highly isotactic-enriched microstructure (P_m = 0.87), molecular weights that agree well with the calculated values and narrow PDIs (M_n/M_w = 1.04-1.18).

43.





{ON^{Et}NO}AlX, R^1 = H, R^2 = Me, R^3 = C_2H_4

{ON^{Cy}NO}AlX, R^1 = H, R^2 = Me, R^3 = trans-1,2-cyclohexyl

{^{Me}ON^{Et}NO}AlX, R^1 = H, R^2 = ^{i}Pr, R^3 = C_2H_4

{ON^{Et}NO}AlX : **44** : X = Me

45 : X = Cl

46 : X = O^{i}Pr

{ON^{Cy}NO}AlX : **47** : X = Me

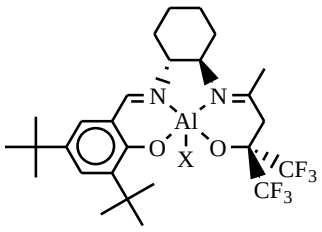
48 : X = Cl

49 : X = O^{i}Pr

{^{Me}ON^{Et}NO}AlX : **50** : X = Me

51 : X = Cl

Figure 12 The structure of complexes **43-53**.

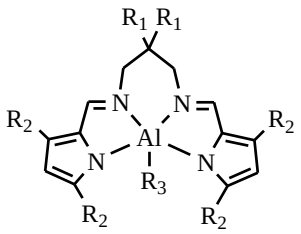


52 : X = Cl

53 : X = O^{i}Pr

Figure 12 (Continued) The structure of complexes **43-53**.

In 2009, Feigen and co-workers reported the synthesis of a series of aluminum ethyls and isopropoxide based on a bis(pyrrolidene) Schiff base ligand, **54-58** (H. Du *et al*., 2009). NMR studies show all complexes have systematic structure with monomeric, and five-coordinated aluminum center core. Aluminum ethyls (**54-56**) in presence of 2-propanol and aluminum isopropoxide (**51-52**) were used as initiator for lactide polymerization. The narrow PDIs and good fit between calculated and actually number-average molecular weights of the isolated polymer were shown all polymerization are living. All complexes are act as single-site catalysts for the polymerization of *R*-LA to isotactic PLA, *rac*-LA to predominant isotactic PLA, and *meso*-LA to atactic PLA. The study of kinetics indicated that the activity of the complexes **54-58** toward LA polymerization decreases on the order of *R*-LA, *rac*-LA and *meso*-LA. Both methyl substituents on the diimine bridge or on pyrrole rings exert significant influence on the cause of polymerization, affecting both the stereoactivity and the polymerization rate. Kinetic studies using **55**/2-propanol and **57** indicated that the polymerization are both first order with respect to *rac*-LA monomer and catalyst. In comparison between **55** and **57**, the *in situ* alcoholysis of **55** is the cause of lower overall polymerization rate.



R_3 = Et : **54** : $R_1 = R_2 = H$

: **55** : R_1 = Me, $R_2 = H$

: **56** : $R_1 = R_2$ = Me

R_3 = O^{i}Pr : **57** : R_1 = Me, $R_2 = H$

: **58** : $R_1 = R_2$ = Me

Figure 13 The structure of complexes **54-58**.

MATERIALS AND METHOD

The work in this study is focused on the study of the ring-opening polymerization of *rac*-LA using aluminum complexes supported by tetradentate ligands featuring pyrrole units. The study is divided into two parts; the experimental studies and the computational studies. For the former part: it is focused on the polymerization studies, *i.e*. the synthesis of ligands, the synthesis of aluminum complexes, and the evaluation of the catalysts as initiators for the ROP of *rac*-LA whereas the latter part is concentrated on the study of the ring-opening mechanism using the computation calculation.

1. Experimental studies

All reactions with air- and/or water-sensitive compounds were carried out under dry nitrogen using a Mbraun drybox or standard Schlenk line techniques.

NMR spectra were recorded on Varian 400 MHz spectrometer. ^{1}H NMR spectra were referenced internally to the residual protio impurity peaks in the deuterated solvent (^{1}H: $CDCl_3$, δ 7.24; d_6-DMSO, δ 2.49). ^{13}C NMR spectra were referenced to the solvent as follow: ^{13}C: $CDCl_3$, δ 77.0; d_6-DMSO, δ 40.0. The following abbreviations have been used for multiplicities: s (singlet); d (doublet); t (triplet); q (quartet); sept (septet); dd (doublet of doublets); dt (doublet of triplets); td (triplet of doublets); m (unresolved multiplet); br (board).

1.1 Materials

Toluene and isopropyl alcohol were dried over calcium hydride and then freshly distilled onto activated 3 Å molecular sieves under nitrogen atmosphere. Both solvents were degassed prior to use unless started otherwise. NMR solvents were dried over 3 Å molecular sieves and degassed prior to use. *rac*-LA was sublimed and

then stored under nitrogen atmosphere. All other reagents are commercially available and were used without purification.

1.2 Synthesis of Ligands

The bis(pyrrole) Schiff-base compounds **59-64** were prepared by the condensation reaction between two equivalents of pyrrole-2-carboxaldehyde and one equivalent of appropriate diamine in ethanol at room temperature as shown in Figure 14. All of compounds were recrystallized from a mixture of methanol and hexane. In all cases, the desired products were obtained in quantitative yield.

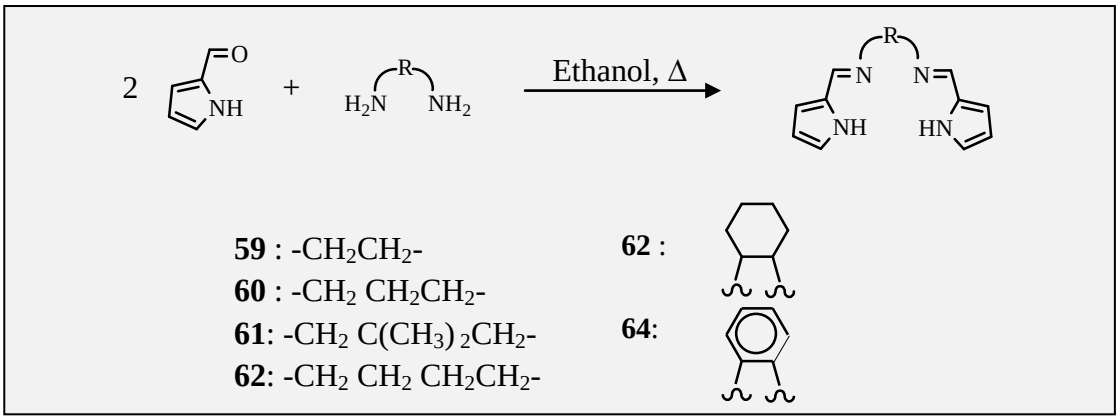


Figure 14 Synthetic pathway for the preparation of ligandss **59-64**.

1.2.1 Preparation of *N,N'*-bis(1H-pyrrole-2-ylmethylene)-1,2-ethylenediamine (**59**)

To a stirred solution of pyrrole-2-carboxaldehyde (2.00 g, 21 mmol) in ethanol (20 ml) was slowly added 1,2-ethylene diamine (0.63 g, 10 mmol). Formic acid (0.05 ml) was then added. The reaction mixture was stirred at 90˚C overnight. After cooling to the room temperature, pale brown crystals formed in 1.41 g (54%) yield (van den Ancker *et al*., 2006; Bhowon *et al*., 2004; Yang *et al*., 2004, 2003; Bacchi *et al*., 2003; Srivastava and Kalam, 2002; Jones *et al*., 2001a, 2001b).

1.2.2 Preparation of *N,N'*-bis(1H-pyrrole-2-ylmethylene)-1,3-propylenediamine (**60**)

To a stirred solution of pyrrole-2-carboxaldehyde (2.00 g, 21 mmol) in ethanol (20 ml) was slowly added 1,3-propylene diamine (0.78 g, 10 mmol). To this reaction mixture was added formic acid (0.05 mL). The reaction mixture was stirred at 90˚C overnight. After cooling to the room temperature, pale brown crystals formed in 1.80 g (65%) yield (Bhowon *et al*., 2004; Yang *et al*., 2004; Datta *et al*., 2003; Bacchi *et al*., 2003; Jones *et al*., 2001; Mueller-Westerhoff and Swiegers, 1994).

1.2.3 Preparation of *N,N'*-bis(1H-pyrrol-2-ylmethylene)-2,2-dimethyl 1,3-propylene diamine (**61**)

To a stirred solution of pyrrole-2-carboxaldehyde (2.00 g, 21 mmol) in ethanol (20 ml) was slowly added 2,2-dimethyl-1,3-propylene diamine (1.07 g, 10 mmol). To this reaction mixture was added formic acid (0.05 mL). After the mixture was stirred for 3 hours, a yellow solid precipitated. The product was obtained in 2.88 g (94%) yield (Yang *et al*., 2007).

1.2.4 Preparation of *N,N'*-bis(1H-pyrrol-2-ylmethylene)-1,4-butylene diamine (**62**)

To a stirred solution of pyrrole-2-carboxaldehyde (2.00 g, 21 mmol) in ethanol (20 ml) was slowly added 1,4-butylene diamine (0.93 g, 10 mmol). To this reaction mixture was added formic acid (0.05 mL). The reaction mixture was stirred overnight, a white solid precipitated. The product was obtained in 2.55 g (87%) yield (Yang *et al*., 2003,2004)

1.2.5 Preparation of *N,N'*-bis(1H-pyrrol-2-ylmethylene)-1,2-cyclohexenediamine (**63**)

To a stirred solution of pyrrole-2-carboxaldehyde (2.00 g, 21 mmol) in ethanol (20 ml) was slowly added 1,2-cyclohexenediamine (1.20 g, 10 mmol) and formic acid (0.05 mL). The reaction mixture was stirred overnight, a white solid precipitated. The product was obtained in 2.55 g (87%) yield (Bhowon *et al*., 2004; Bacchi *et al*., 2003; Shan *et al*., 2007; Chen *et al*., 2007; Wang *et al*., 2007; van den Ancker *et al*., 2006; Hechavarria Fonseca *et al*., 2003).

1.2.6 Preparation of *N,N'*-bis(1H-pyrrol-2-ylmethylene)-1,2-phenylenediamine (**64**)

To a stirred solution of pyrrole-2-carboxaldehyde (2.00 g, 21 mmol) in ethanol (20 ml) was slowly added 1,2- phenylenediamine (1.13 g, 10 mmol) and formic acid (0.05 mL). The reaction mixture was reflux overnight at 90˚C t. After cooling to the room temperature, pale brown crystals formed in 1.95 g (62%) yield (Bhowon *et al*., 2004; Bacchi *et al*., 2003; Srivastava and Kalam, 2002; Munro *et al*., 2006; Berube *et al*., 2003; Franceschi *et al*., 2001).

1.3 Synthesis of Aluminum Schiff-Bases Complexes

The aluminum complexes **1-6** were prepared by treating the relevant tetradentate Schiff-base with trimethylaluminum. All tetradentate Schiff-base and trimethylaluminum were dried and free of oxygen using standard Schlenk line (vacuum-nitrogen) techniques. The reactions were carried out in toluene at 110 °C overnight, according to Figure 15.

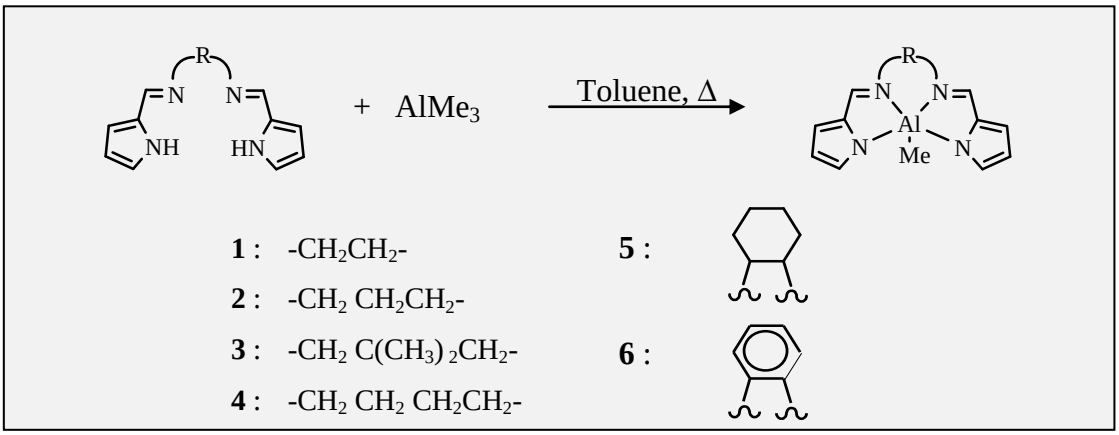


Figure 15 Synthetic pathway for the preparation of aluminum complexes **1-6.**

1.3.1 Preparation of Complex **1**

To a stirred solution of ligand **59** (1.00 g, 4.7 mmol) in toluene (30 ml) was slowly added $AlMe_3$ (2.33 ml of a 2.0 M solution in toluene, 4.7 mmol). The reaction mixture was stirred at 110 °C overnight. Removal of the solvent under reduced pressure afforded a red solid which was then recrystallised from hot toluene. A red crytallinesolid was obtained in 0.72 g (60%) yield.

1.3.2 Preparation of Complex **2**

To a stirred solution of ligand **60** (1.00 g, 4.4 mmol) in toluene (30 ml) was slowly added $AlMe_3$ (2.19 ml of a 2.0 M solution in toluene, 4.4 mmol). The reaction mixture was stirred at 110 °C overnight. After cooling to room temperature, a brown solid precipitate was isolate by filtration and dry under reducing pressure. The product was obtained in 0.61 g (52%) yield.

1.3.3 Preparation of Complex **3**

To a stirred solution of ligand **61** (1.00 g, 3.9 mmol) in toluene (30 ml) was slowly added $AlMe_3$ (1.95 ml of a 2.0 M solution in toluene, 3.9 mmol). The reaction mixture was stirred at 110 °C overnight. After cooling to room temperature, red-brown crystals formed which was then isolated by filtration and dried under reduced pressure. The product was obtained in 0.52 g (45%) yield.

1.3.4 Preparation of Complex **4**

To a stirred solution of ligand **62** (1.00 g, 4.1 mmol) in toluene (30 ml) was slowly added $AlMe_3$ (2.06 ml of a 2.0 M solution in toluene, 4.1 mmol). The reaction mixture was stirred at 110 °C overnight. After cooling to room temperature, a red-brown solid precipitated which was then isolated by filtration and dried under reduced pressure. The product was obtained in 1.16 g (74%) yield.

1.3.5 Preparation of Complex **5**

To a stirred solution of ligand **63** (1.00 g, 3.7 mmol) in toluene (30 ml) was slowly added $AlMe_3$ (1.86 ml of a 2.0 M solution in toluene, 3.7 mmol). The reaction mixture was stirred at 110 °C overnight. After cooling to room temperature, a red solid precipitated which was then isolated by filtration and dried under reduced pressure. The red-brown solid was obtained in 1.00 g (88%) yield.

1.3.6 Preparation of Complex **6**

To a stirred solution of ligand **64** (1.00 g, 3.8 mmol) in toluene (30 ml) was slowly added $AlMe_3$ (1.91 ml of a 2.0 M solution in toluene, 3.8 mmol). The reaction mixture was stirred at 110 °C overnight. After cooling to room temperature, a black solid precipitated which was then isolated by filtration and dry under reducing pressure. The product was obtained in 1.04 g (91%) yield.

1.4 Lactide polymerization studies

Aluminum complexes **1-6** were examinined as initiators for the ROP polymerization of *rac*-LA. In nitrogen filled glove box, *rac*-LA (720 mg, 5.0 mmol) and isopropyl alcohol ($(CH_3)_2CHOH$) (3.82 μL, 0.05 mmol) were place in a Schlenk tube. To this Schlenk tube were added a solution of initiator (0.05 mmol) in toluene (6.00 ml) ($[LA]_0/[Al] = 100$; $[LA]_0 = 0.83$ M; [Al] = 8.33 mM). The aluminum alkoxide species were generated *in situ* by alcoholysis of the aluminum methyl complexes with isopropyl alcohol, according to Figure 16. Polymerizations were stirred and carried out at 70°C in toluene. Reactions were allowed to proceed to high conversion (> 90%). Small amount of methanol (2 to 3 drops) were used to quenched the reaction. The polymer was precipitated from excess methanol, collected by filtration and dried *in vacuo* to constant mass.

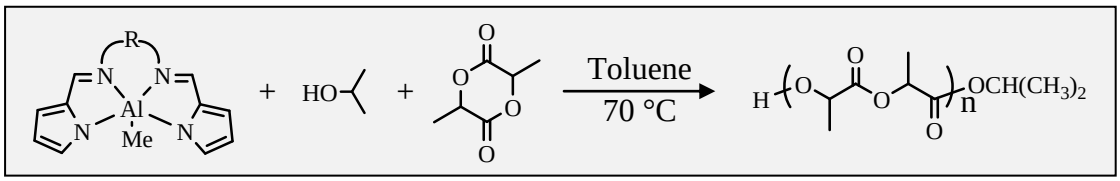


Figure 16 The LA polymerization procedure using complexes **1-6**.

2. Computational Studies

The ring-opening polymerization of *rac*-LA using an aluminum methoxide initiator supported by *N,N'*-bis(1H-pyrrole-2-ylmethylene)-1,2-ethylenediamine ligand , as shown in Figure 17, was studied.

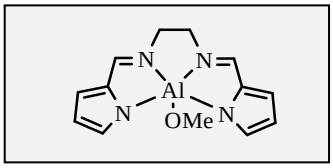


Figure 17 The structure of the aluminum complex using in the computational study.

In the detail of calculations, geometries of all reactants, adsorptions, transition states, and intermediates involving in the ROP process were optimized using B3LYP density functional theory employed 6-31G(d,p) basis set. The ring-opening of the LA molecule dictates the study of up to 52 atoms. Energy of each geometries in comparison with total energy of reactants was used to construct an energy diagram.

RESULTS AND DISCUSSION

The work in this study, as mentioned previously, was divided into two parts: experimental and computational studies. The details of each part were discussed as follow:

1. Experimental Studies

1.1 Ligand syntheses

The bis(pyrrolidene) Schiff-base ligands **59-64** were prepared by the well established condenzation reaction between two equivalents of pyrrole-2-carboxaldehyde and one equivalent of diamine in ethanol as shown in Figure 18. All compounds were obtained in good yields. Ligands **59** and **60** were isolated as a brown powder whereas ligand **61** was obtained as a yellow crystalline solid. Ligands **62-64** were obtained as a white powder.

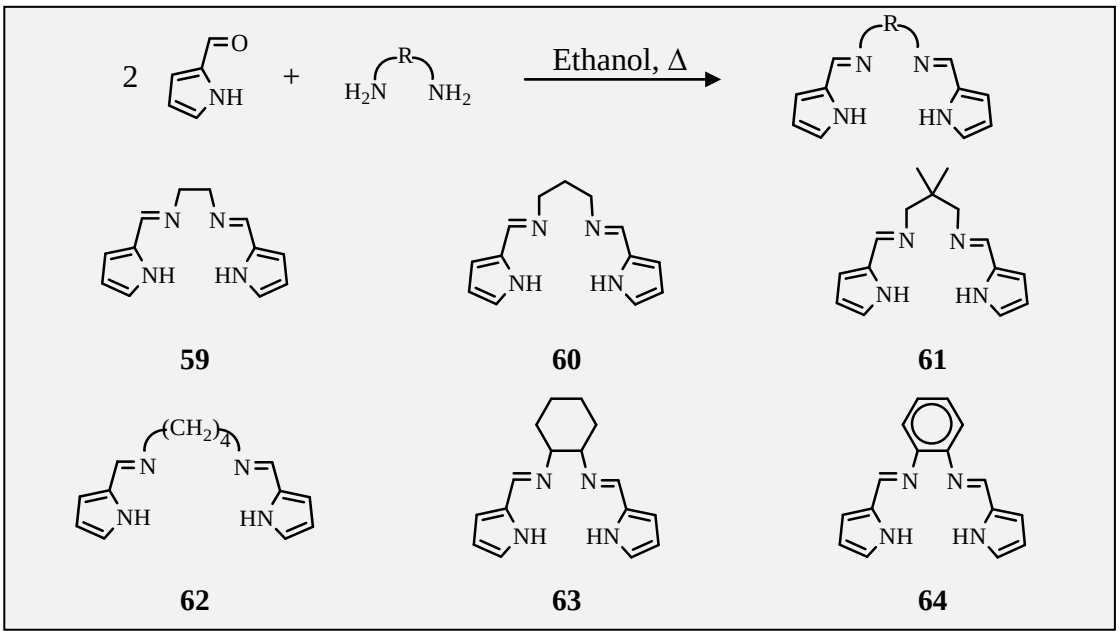


Figure 18 Synthetic pathway for the preparation of ligands **59-64**.

The ^{1}H NMR spectra of ligands **59-64** with full assignments are shown in Figure 19-24, respectively, and their spectroscopic data are consistent with the formulation shown in Figure 18. All ligands in this work exhibit characteristic resonances in their ^{1}H-NMR spectra arising from the imine proton at *ca*. 8 ppm..

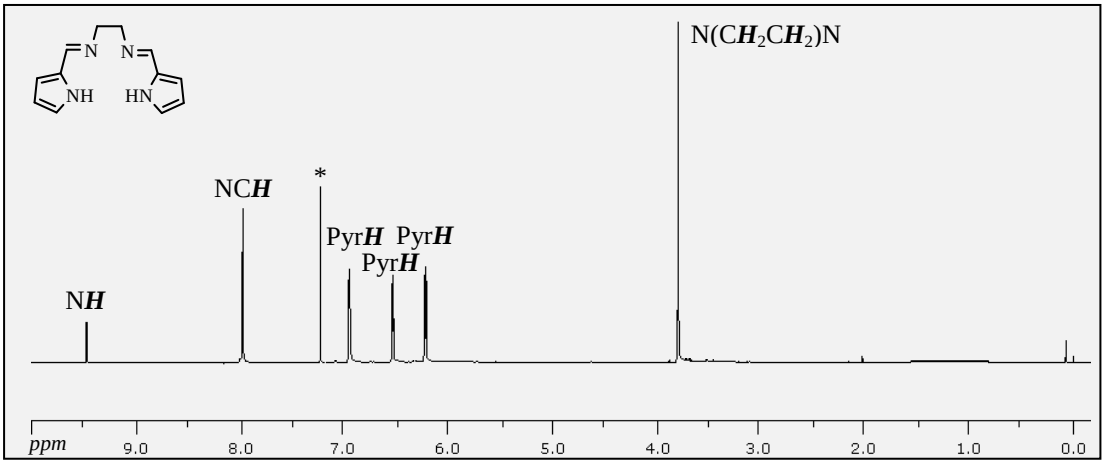


Figure 19 400 MHz ^{1}H NMR spectrum of ligand **59** in $CDCl_3$ (* = solvent signal).

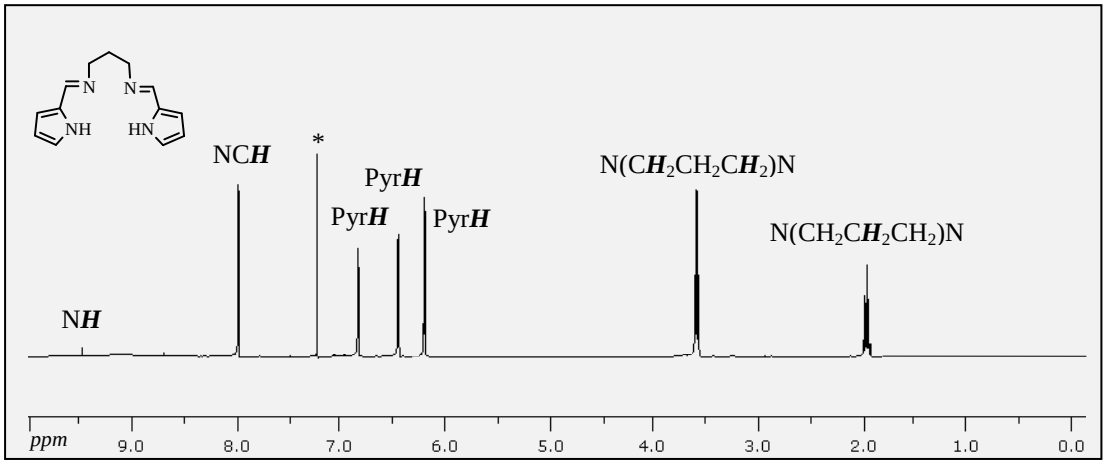


Figure 20 400 MHz ^{1}H NMR spectrum of ligand **60** in $CDCl_3$ (* = solvent signal).

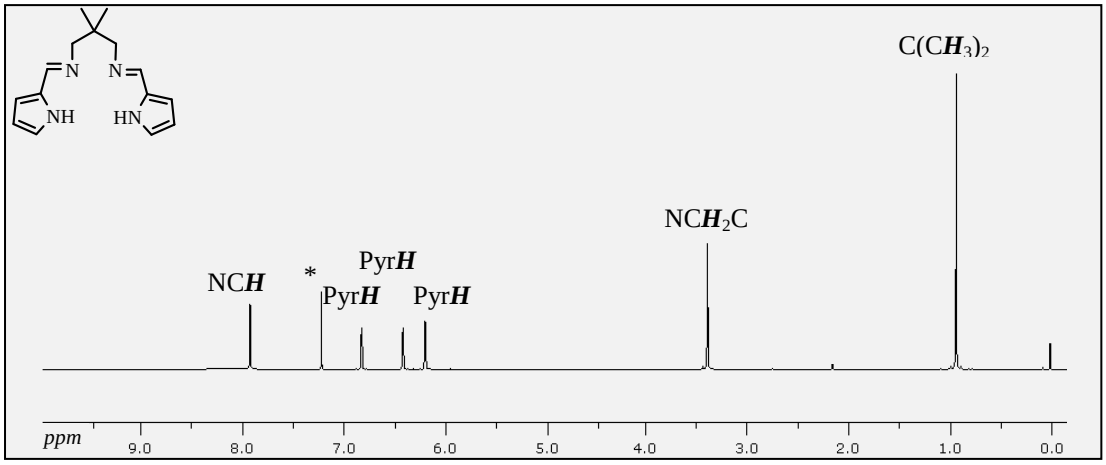


Figure 21 400 MHz ^{1}H NMR spectrum of ligand **61** in $CDCl_3$ (* = solvent signal).

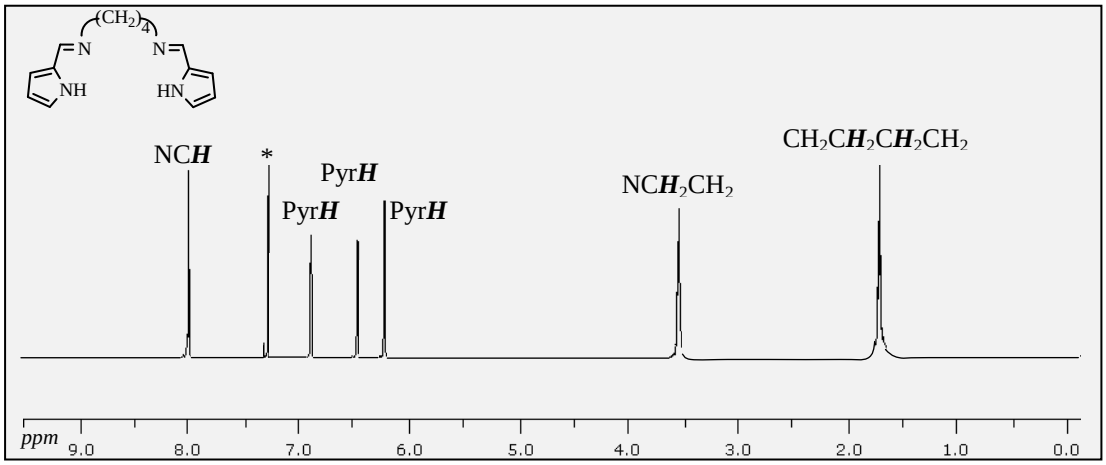


Figure 22 400 MHz ^{1}H NMR spectrum of ligand **62** in $CDCl_3$ (* = solvent signal).

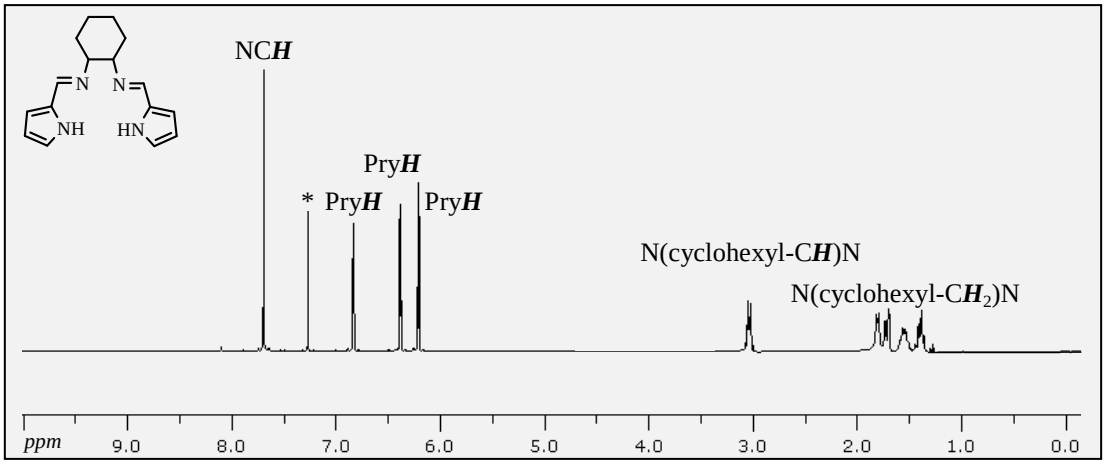


Figure 23 400 MHz ^{1}H NMR spectrum of ligand **63** in $CDCl_3$ (* = solvent signal).

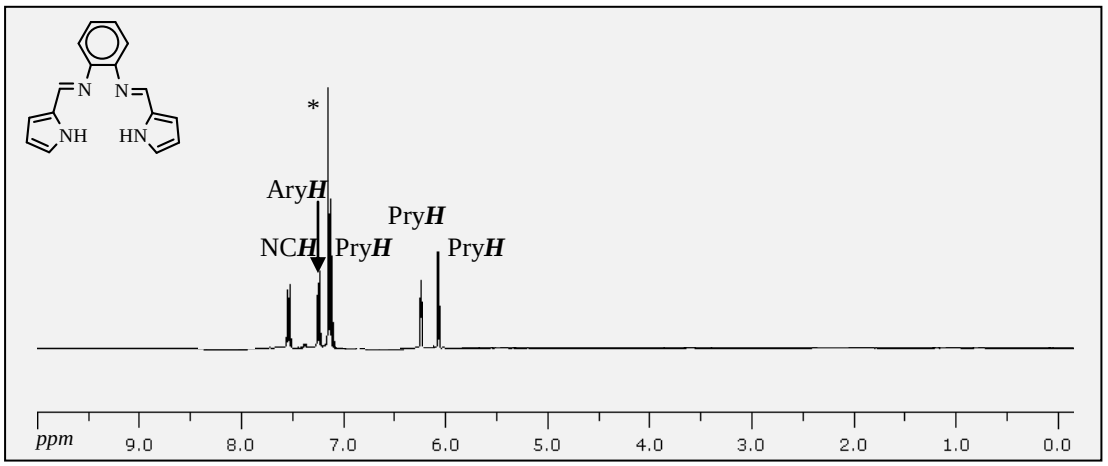


Figure 24 400 MHz ^{1}H NMR spectrum of ligand **64** in $CDCl_3$ (* = solvent signal).

1.2 Synthesis of aluminum complexes

The desired aluminum methyl complexes **1-6** were synthesized by treatment of trimethylaluminum with appropriate ligands in toluene at 110 ^{o}C, according to Figure 25. Complex **1** was obtained after recrystallising from hot toluene

whereas the other aluminum complexes (**2-6**) precipitated from the reaction mixture after cooling to room temperature.

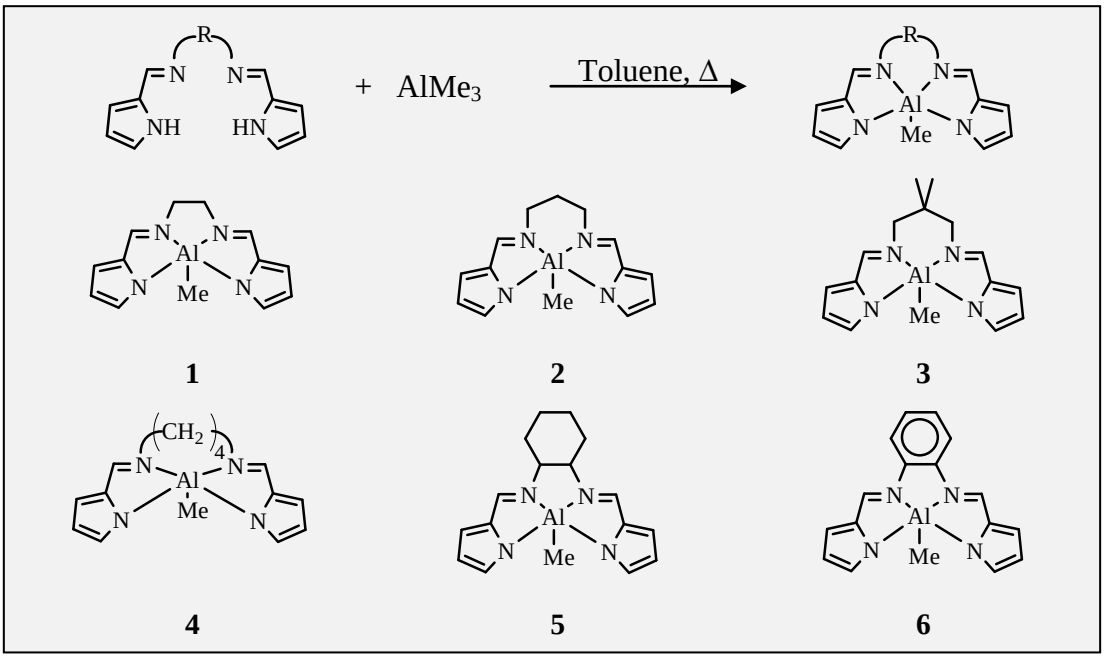


Figure 25 Synthetic pathway for the preparation of aluminum complexes **1-6**.

Figure 26 shows the ^{1}H NMR spectrum of complex **3** with full assignment. The signals at δ 7.40 , δ 6.69 and δ 6.34 correspond to the pyrrolic proton, and the imine proton occurs at δ 7.83. Signals due to the diastereotopic methylene protons from the backbone occur as two doublets centered at δ 4.61 and δ 3.48. The aluminum-methyl resonance is apparent at high field (δ -0.82).

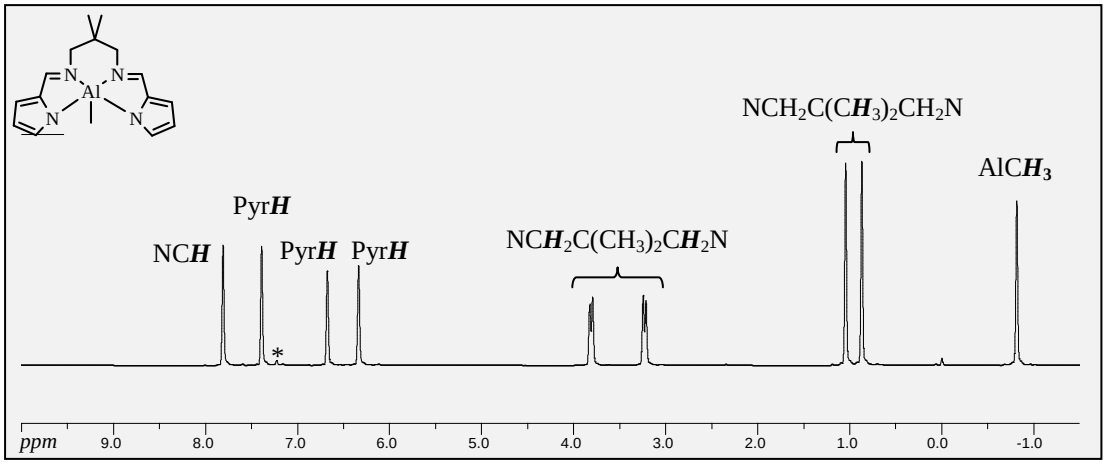


Figure 26 400 MHz ^{1}H NMR spectrum of aluminum complex **3** in $CDCl_3$ (* = solvent signal).

1.3 LA Polymerization Studies

Complexes **1-6** were examined as initiators for the polymerization of *rac*-LA. The aluminum alkoxide species were generated *in situ* by alcoholysis of the aluminum methyl complexes with one equivalent of isopropyl alcohol, according to Figure 27.

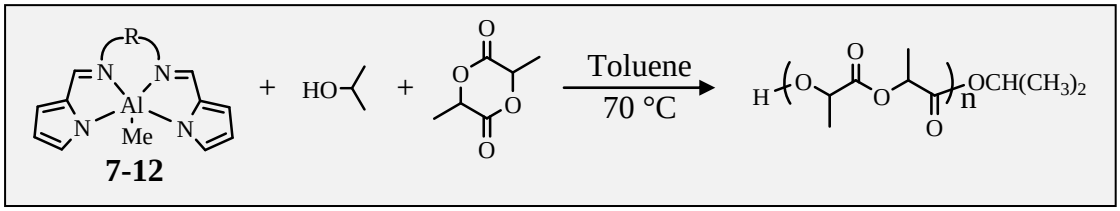


Figure 27 The LA polymerisation procedure using complexes **1-6**.

In the first phase of this work, the experiments were carried out in toluent at 70 ˚C, and the molar ratio of *rac*-LA to initiator was fixed at 100:1 ($[LA]_0/[Al] = 100$; $[LA]_0 = 0.83$ M; [Al] = 8.33 mM). Polymerizations were allowed to proceed for 24 hours. It was found that all aluminum complexes are active intiators for the ROP of rac-LA. The results are summarised in Table 1.

Table 1 LA polymerization result for aluminum complexes **1-6** ([a] As determined *via* integration of the methine resonances (^{1}H NMR) of LA and PLA ($CDCl_3$, 400 mHz)).

Complex	Time (h)	Conversion[a] (%)
7	24	98
8	24	97
9	24	99
10	24	98
11	24	98
12	24	97

The tacticity of the polymers prepared by aluminum complexes **1-6** was determined by ^{1}H NMR spectroscopy. In comparison with ^{1}H NMR spectra for isotactic, atactic and hightly heterotactic PLA, the approximate tacticity of the polymers prepared by complexes **1-6** were shown in Figure 28.

2. Computational Studies

Since the ring-opening of lactide monomer is believed to occur *via* a coordinative-insertion polymerization, as shown in Figure 4. The ring-opening polymerization proceeds *via* acyl-oxygen cleavage of LA with insertion of the new monomer into the *meta*-oxygen bond. Here we investigated a DFT study into the ring-opening of the first monomer (*D*-LA and *L*-LA) using an aluminum methoxide supported by *N,N,N',N'*-bis(pyrrole)-1,2-ethylenediamine ligand.

The reaction mechanism for the ring-opening of the lactide monomer was modeled to proceed consecutively as shown in Figure 29.

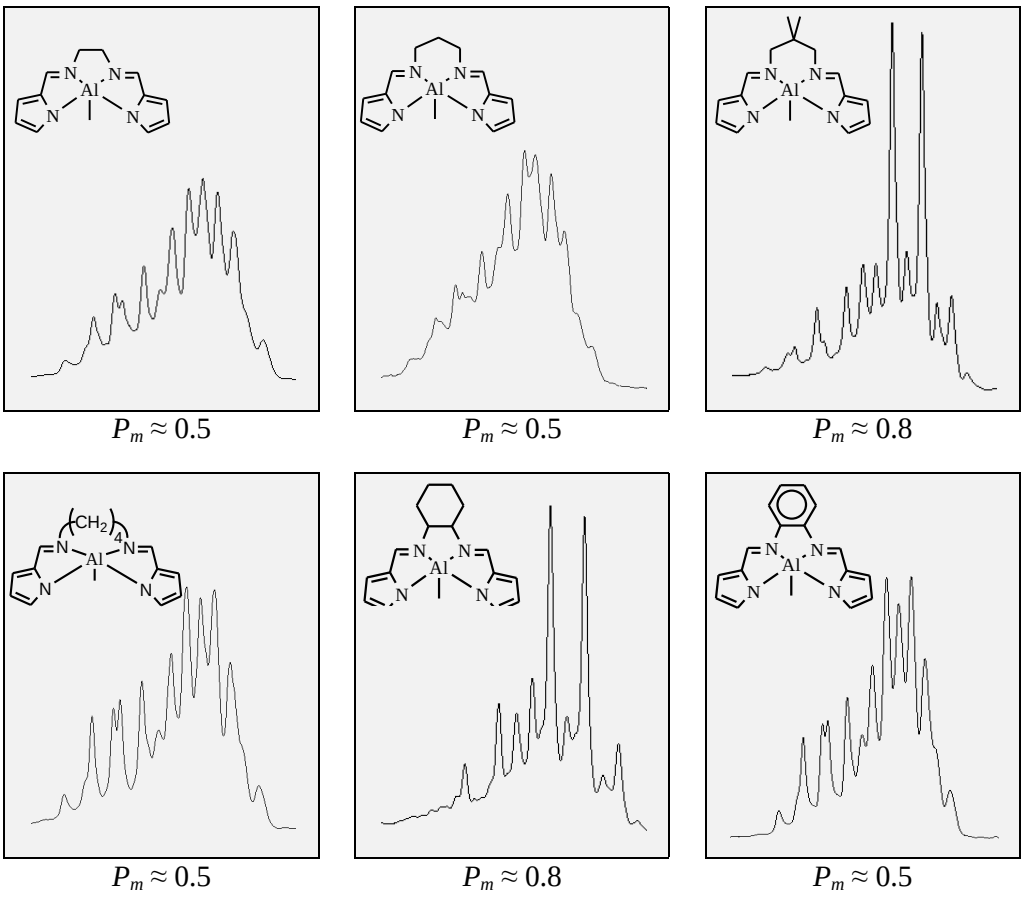


Figure 28 ^{1}H NMR spectra of the methane region of PLA prepared by **1-6** (400 mHz, $CDCl_3$).

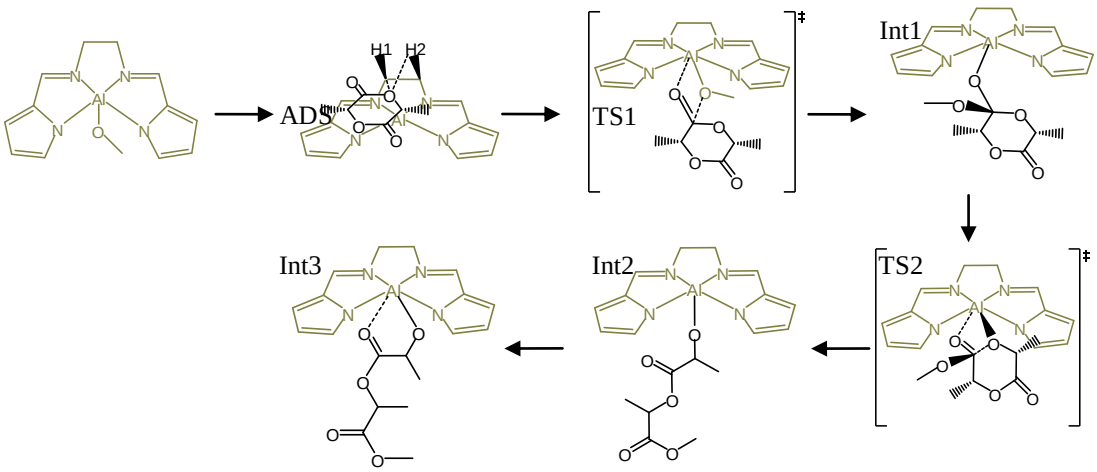


Figure 29 Reaction coordinates for the ring-opening of *L*-lactide.

The geometry at the aluminum center of the initiator was initially best described by a square-pyramidal configuration (τ = 0.02). Only a small change of the aluminum center was observed when it formed an adsorption complex, **Ads** (Figure 30 and 31), with the lactide monomer. This is due to the approaching of the lactide monomer to the aluminum center is restricted at some distances by weak interactions with the ethylene-bridging hydrogens (H1 and H2). The distances between the oxygen atoms of lactide monomer ($O_{carbonyl}$ and O_{acyl}) and the ethylene bridging hydrogens (H1 and H2), thus, can be used to indicate the binding energy of the adsorption complex. The shortest $O_{carbonyl}\cdots H1$ and $O_{carbonyl}\cdots H2$ distances in the adsorption complex of *D*-LA were calculated to be 2.576 and 2.710 Å, respectively, while the shortest $O_{carbonyl}\cdots H1$ and $O_{acyl}\cdots H2$ distances in the adsorption complex of *L*-LA were calculated to be 2.492 and 2.639 Å, respectively.

The corresponding binding energies for *D*- and *L*-LA were evaluated to be 9.43 and 13.00 kcal/mol, respectively (see Figure 42). The insertion of lactide monomer to coordinate with the aluminum center of the initiator, therefore, requires some energy to break down these interactions and to change the symmetry of the aluminum center. It was found that the coordination of lactide monomer at the aluminum center takes place through the octahedral transition state. **TS1** (see Figures 32 and 33), that involves the simultaneously nucleophilic attacks of the lactide carbonyl oxygen at the aluminum center ($O_{carbonyl}\cdots Al$= 2.027 and 2.038 Å for *D*- and *L*-LA, respectively) and of the aluminum methoxide at coordinated carbonyl carbon of lactide monomer ($O_{methoxide}\cdots C_{carbonyl}$ = 1.963 and 1.986 Å for *D*- and *L*-LA, respectively). These resulted in the lengthening of the Al-$O_{methoxide}$ and $C_{carbonyl}$-$O_{carbonyl}$ distances when compared with that in the adsorption complex. The activation energy required for this transition state was calculated to be 14.01 and 13.33 kcal/mol for *D*- and *L*-LA monomer, respectively (see Figure 42).

The tetrahedral intermediate (**Int1**, Figures 34 and 35), at the carbonyl carbon, is the first stable intermediate generated immediately after the lactide monomer is coordinated with the aluminum center. The $O_{carbonyl}$ is now covalently boned to the aluminum center with the Al-$O_{carbonyl}$ distance of 1.774 and 1.770 Å for *D*- and *L*-LA,

respectively. The acyl oxygen bond, $C_{carbonyl}$-O_{acyl}, is lengthened and weakened. The lactide ring-opening can, therefore, be readily activated through the octahedral transition that involves the $C_{carbonyl}$-O_{acyl} (2.290 and 2.211 Å for *D*- and *L*-LA, respectively) and Al-$O_{carbonyl}$ (2.181 and 2.043 Å for *D*- and *L*-LA, respectively) bond dissociation, **TS2** (Figures 36 and 37). The cleavage of these bonds results in the highly negative charge of the acyl oxygen atom which can rapidly from a covalent bond with the highly positive charge aluminum center to be an alkoxide intermediate, **Int2**, with the Al-O_{acyl} distance of 1.758 and 1.773 Å for *D*- and *L*-LA, respectively (Figures 38 and 39). The activation energy required for the lactide ring-opening step was calculated to be 20.21 and 16.42 kcal/mol for *D*- and *L*-LA, respectively (see Figure 42). The interconversion from **Int2** to **Int3** (see Figures 40 and 41) seems very convincing in the *D*-LA. This species was experimentally found to be the stable intermediate in the other closely related initiators. The energy profile for the ring-opening of lactide is shown in Figure 42.

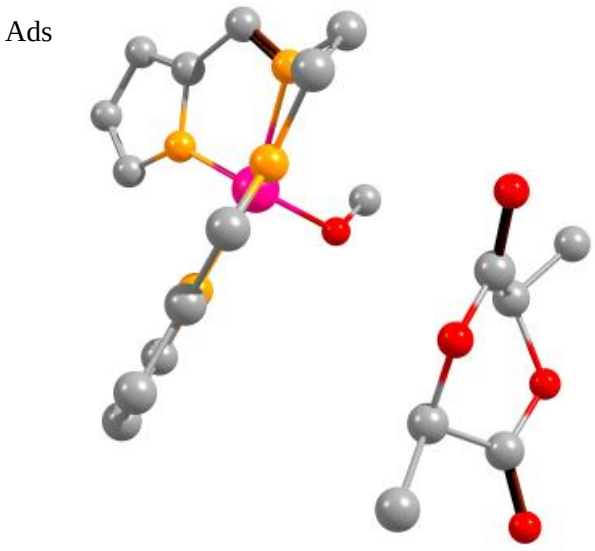


Figure 30 The absorption between an aluminum methoxide complex supported by *N,N,N',N'*-bis(pyrrole)-1,2-ethylene diamine supported on aluminum methoxide as initiator and *D*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

Ads

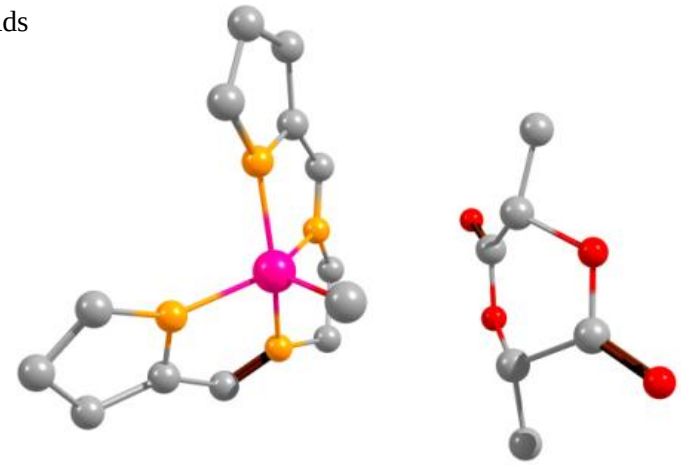


Figure 31 Adsorption species using *N,N,N',N'*-bis(pyrrole)-1,2-ethylenediamine supported on aluminum methoxide as initiator of *L*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

TS1

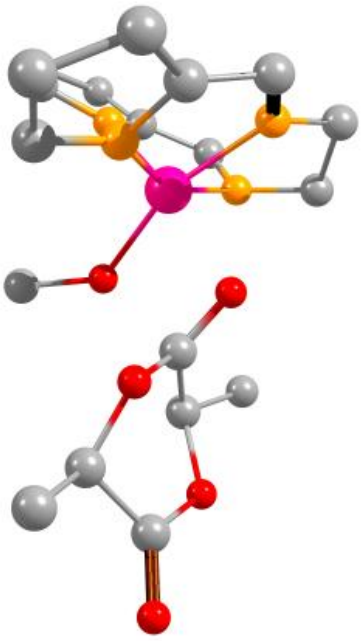


Figure 32 The Transition State 1 for the ring-opening of *D*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

TS1

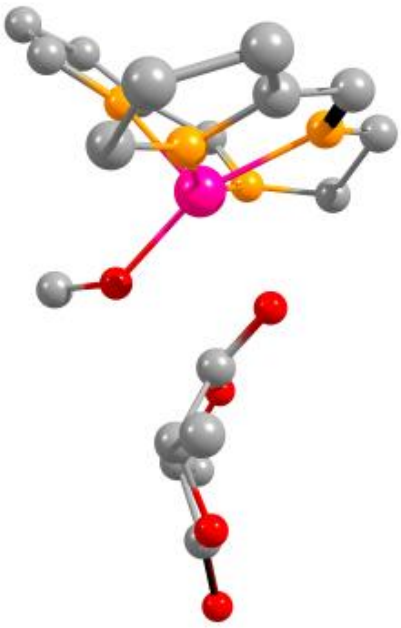


Figure 33 Transition State 1 for the ring-opening of *L*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

Int1

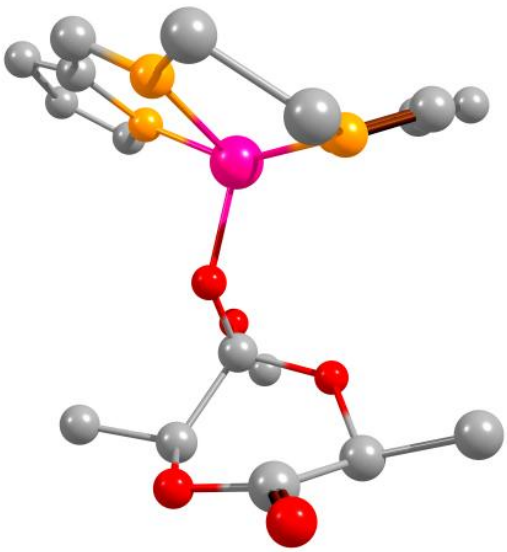


Figure 34 Intermediate **1** for the ring-opening of *D*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

Int1

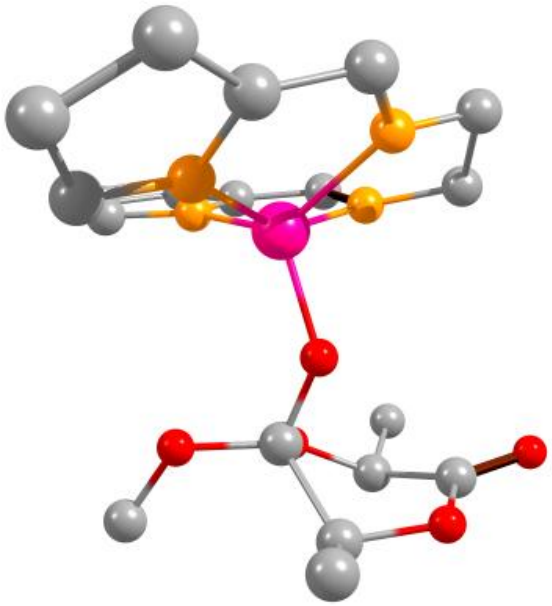


Figure 35 Intermediate **1** for the ring-opening of *L*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

TS2

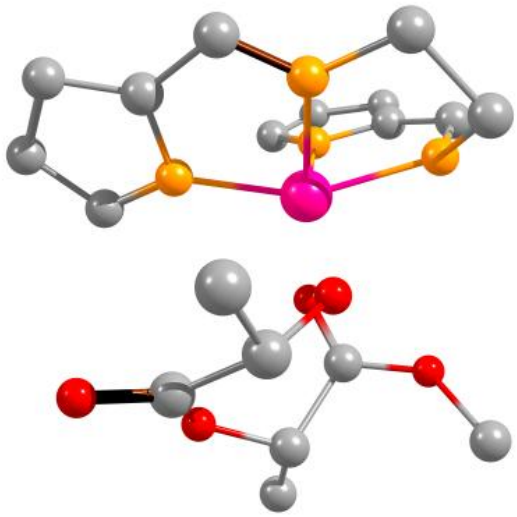


Figure 36 Transition State 2 for the ring-opening of *D*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

TS2

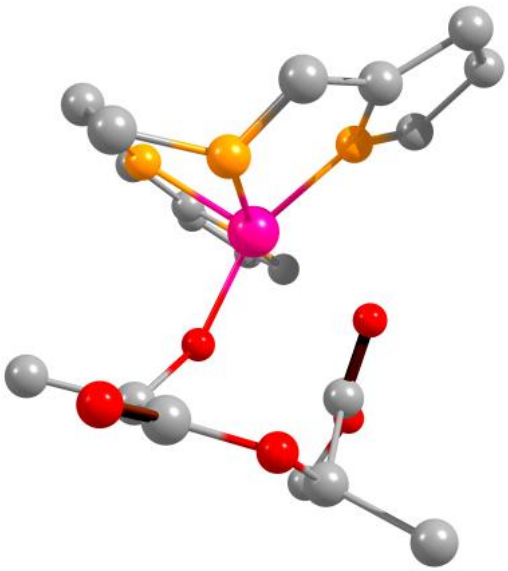


Figure 37 Transition State 2 for the ring-opening of *L*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

Int2

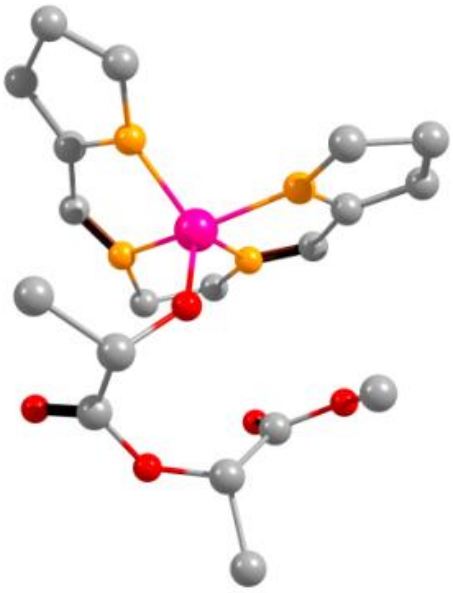


Figure 38 Intermediate 2 for the ring-opening of *D*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon)**.**

Int2

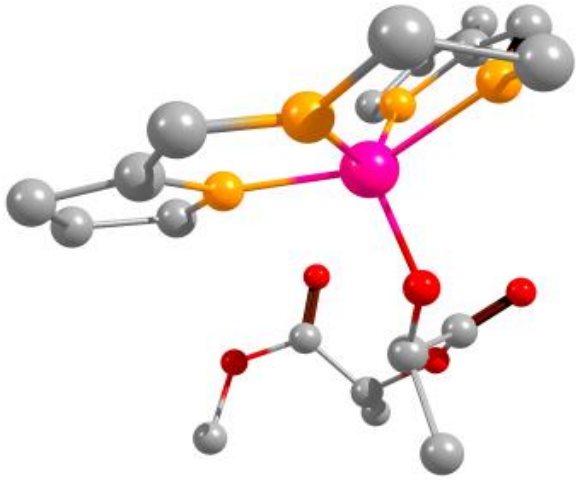


Figure 39 Intermediate 2 for the ring-opening of *L*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

Int3

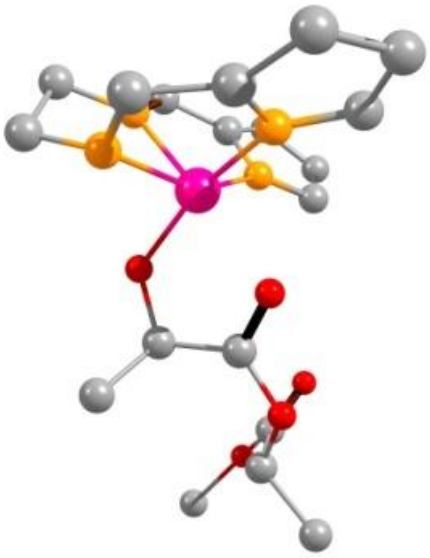


Figure 40 Intermediate 3 for the ring-opening of *D*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

Int3

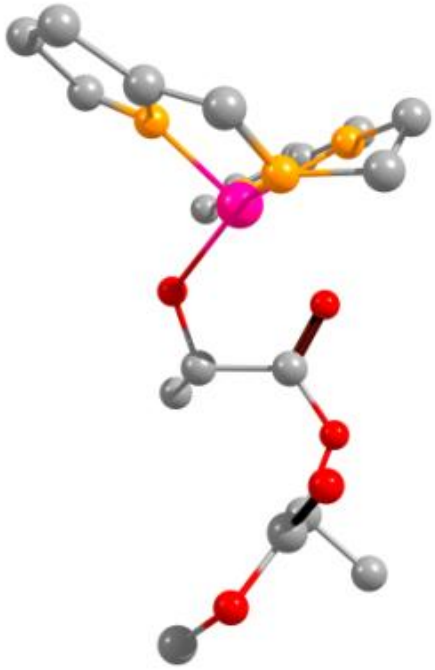


Figure 41 Intermediate 3 for the ring-opening of *L*-LA (pink : aluminum, orange : nitrogen, red : oxygen, gray : carbon).

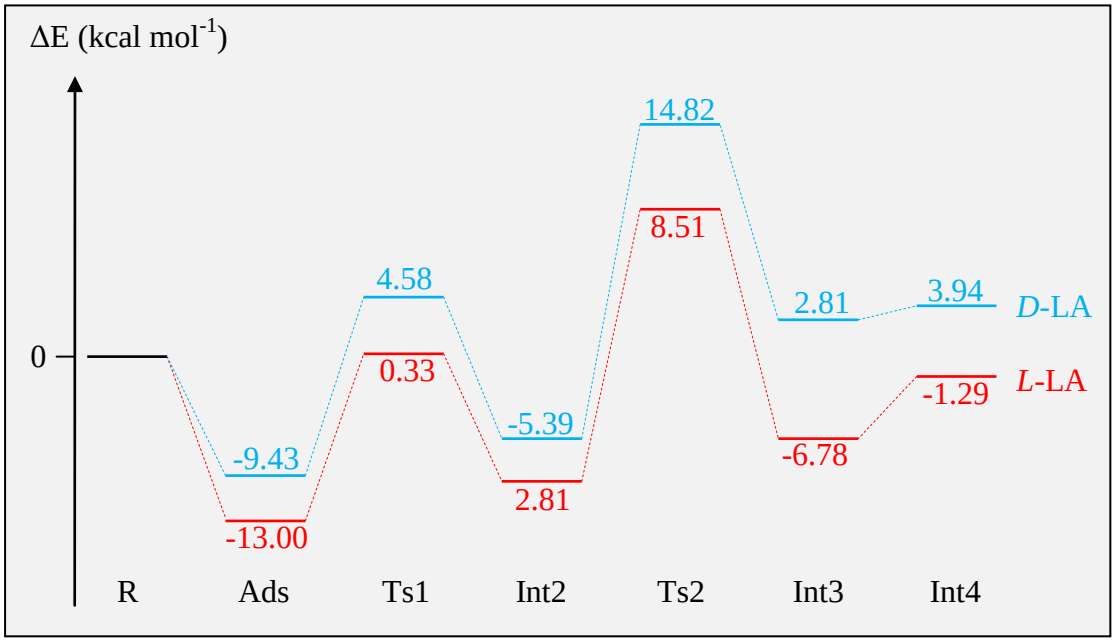


Figure 42 The energy diagrame for the key species: Top *D*-LA, Base *L*-LA.

CONCLUSIONS

A theoretical study into the ring-opening mechanism of lactide (*D*-lactide and *L*-Lactide) by a tetradentate bis(pyrrole) Schiff-base aluminum complex was investigated using a B3LYP density functional theory employing a 6-32G(d,p) basis set. The ring-opening of lactide occurs *via* a coordinative insertion mechanism with two transition states (TS1 and TS2). According to the energy profiles for both *D*-lactide and *L*-lactide, it was found that the rate determining step is the second transition state (TS2), the state of the nucleophilic attack of the aluminum alkoxide at the coordinated carbonyl carbon of lactide monomer. In comparison, the ring-opening of *L*-lactide occurs more readily than that of *D*-lactide.

For the experimental study, ligands **59-64** were successfully synthesized. These ligands was then used for the synthesis of the desired aluminum complexes 7-12. At this stage, only complex **3** was characterized by the NMR spectroscopic technique. All aluminum complexes were evaluated and found that all are effective initiators for the ROP of *rac*-LA. In addition, examination of the microstructure of PLA samples produced by aluminium complexes **1-6** shows that the different backbone structure of the ligand has the effect on the selectivity during the course of polymerization.

Work in the future will be concentrated on the fully characterization of all complexes. In addition, for the polymerization process, the kinetic studies will be carried out and also the determination of the molecular weight of the polymer samples need to be done using Gel Permeation Chromatography (GPC).

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2. Sittichoke Tabthong, Pimpa Hormnirum, Supawadee Namuangruk, Tanin Nanok. **A Theoretical Study of the Ring-Opening Mechanism of Lactide Initiated by a Tetradentate bis(pyrrole) Schiff-base Aluminium Complexes** (Oral). 2nd Pure and Applied Chemistry International Conference, 14-16 January 2008. Phitsanulok, Thailand.