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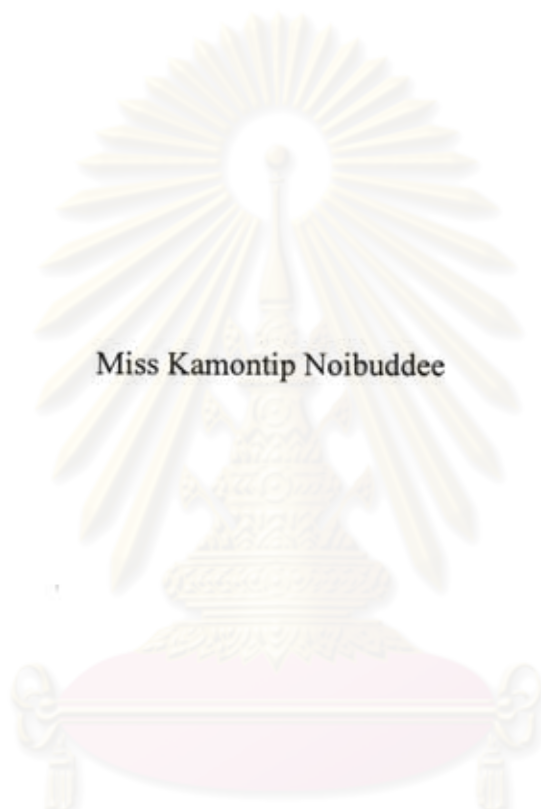
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ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย



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MOLECULAR WEIGHT ENHANCEMENT BY CHAIN EXTENSION OF POLY(LACTIC  
ACID) DERIVED FROM POLYCONDENSATION



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ศูนย์วิทยทรัพยากร

A Thesis Submitted in Partial Fulfillment of the Requirements  
for the Degree of Master of Science Program in Petrochemistry and Polymer Science

Faculty of Science

Chulalongkorn University


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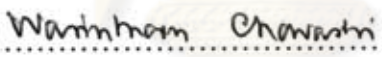
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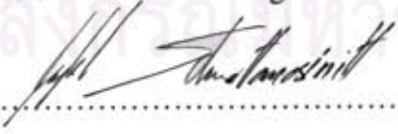
  
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ได้ใช้วิธีการแบบ 2 ขั้นตอนในการเตรียมพอลิแลกติกแอซิดที่มีน้ำหนักโมเลกุลสูง ขั้นตอนแรกได้สังเคราะห์พอลิแลกติกแอซิดขึ้นก่อนจากวิธีพอลิเมอไรเซชันแบบควบแน่นโดยตรง น้ำหนักโมเลกุล ( $\bar{M}_n$ ) ที่ได้อยู่ในช่วง 4,000-40,000 ดาลตัน ขั้นตอนที่สองเป็นการขยายสายโซ่ของพอลิแลกติกแอซิด โดยการเชื่อมพอลิแลกติกแอซิดสองสายเข้าด้วยกันผ่านหมู่ไฮดรอกซิลที่ปลายสายโซ่ โดยใช้ตัวเชื่อมต่อ ได้แก่ 1,1'-คาร์บอนิลไดอิมิดาโซล (CDI), ไดเอทิลคาร์บอนเนต (DEC), ไดฟีนิลคาร์บอนเนต (DPC) และ อีพิกลอโรไฮดริน (EC) ทำปฏิกิริยาทุกปฏิกิริยาในสารละลายโดยใช้โซลีนเป็นตัวทำละลาย สำหรับพอลิแลกติกแอซิดที่มี  $\bar{M}_n$  ต่ำกว่า 10,000 ดาลตันนั้น สามารถขยายความยาวสายโซ่ให้เพิ่มขึ้นได้สูงถึง 107% เมื่อใช้ปริมาณของ CDI มากเกินพอ (10 เท่าของจำนวนโมลของพอลิแลกติกแอซิด) ซึ่งทำที่อุณหภูมิ 110 °C เป็นเวลา 3 ชั่วโมง การขยายสายโซ่โดยใช้ CDI กลับไม่ประสบผลสำเร็จเมื่อ  $\bar{M}_n$  เริ่มต้นของพอลิแลกติกแอซิดมากกว่า 10,000 ดาลตัน ความสามารถในการทำปฏิกิริยาของ DEC และ DPC ต่ำกว่าของ CDI การใช้ EC (3 เท่าของจำนวนโมลของพอลิแลกติกแอซิด) ร่วมกับตัวเร่งปฏิกิริยาโซเดียมคาร์บอนเนตในการขยายสายโซ่เป็นผลให้  $\bar{M}_n$  ของพอลิแลกติกแอซิดที่น้ำหนักที่ต่ำกว่า 10,000 ดาลตันเพิ่มขึ้น 45% และเพิ่มขึ้น 29% เมื่อพอลิแลกติกแอซิดมี  $\bar{M}_n$  18,000 ดาลตัน ในบางกรณีน้ำหนักโมเลกุลลดต่ำลงซึ่งคาดว่าเนื่องมาจากการแตกของสายโซ่โดยปฏิกิริยาที่ไม่พึงประสงค์กับผลิตภัณฑ์พลอยได้ และได้รายงานข้อมูลรายละเอียดโครงสร้างของพอลิเมอร์จากผลการวิเคราะห์ด้วยโปรตอน-เอ็นเอ็มอาร์ สเปกโทรสโกปีด้วย

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ปีการศึกษา 2553

ลายมือชื่อนิสิต กมลทิพย์ น้อยบุตดี

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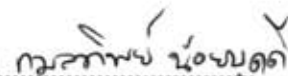
KEYWORDS: POLY(LACTIC ACID)/ 1,1'-CARBONYL DIIMIDAZOLE (CDI)/  
EPICHLOROHYDRIN/ CHAIN EXTENSION/ COUPLING AGENT

KAMONTIP NOIBUDDEE: MOLECULAR WEIGHT ENHANCEMENT  
BY CHAIN EXTENSION OF POLY(LACTIC ACID) DERIVED FROM  
POLYCONDENSATION. ADVISOR: ASST. PROF. VARAWUT  
TANGPASUTHADOL, Ph.D., CO-ADVISOR: ASST. PROF. YONGSAK  
SRITANA-ANANT, Ph.D., 57 pp.

High molecular weight PLLAs were prepared by a two-step method. In the first step, PLLA was synthesized via direct condensation polymerization. The molecular weight ( $\bar{M}_n$ ) obtained was in the range of 4,000-40,000 Da. In the second step, the PLLA chains were extended by joining two PLLA chains together via the terminal hydroxyl groups using chain extender i.e. 1,1'-carbonyldiimidazole (CDI), diethyl carbonate (DEC), diphenyl carbonate (DPC), and epichlorohydrin (EC). All reactions were performed in solution using xylene as the solvent. For PLLA with  $\bar{M}_n < 10,000$  Da, their chain lengths could be increased by as high as 107% when an excess amount of CDI (10 times the moles of PLLA) was used in the extension reaction performed at 110 °C for 3 h. The chain extension by CDI was, however, not as successful when the  $\bar{M}_n$  of starting PLLA were higher than 10,000 Da. The reactivity of DPC and DEC was found to be lower than that of CDI. The use of EC (3 times the moles of PLLA) in combination of Na<sub>2</sub>CO<sub>3</sub> as catalyst in the chain extending reaction resulted in 45% increase of  $\bar{M}_n$  for PLLA with molecular weight of < 10,000 Da and up to 29% increase for the PLLA with  $\bar{M}_n$  about 18,000 Da. In some cases, the decreases of molecular weight were presumably due to chain fragmentation caused by the undesired reaction with by-products. Detailed investigation on polymer structure by proton-NMR spectroscopy was also reported.

Field of Study : Petrochemistry and Polymer Science

Student's Signature :



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Co-Advisor's Signature :



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## LIST OF ABBREVIATIONS

ROP	: Ring-opening polymerization
PC	: Polycondensation
LLA	: L-lactic acid, L-lactide
DLA	: D-lactic acid, D-lactide
PLLA	: Poly(L-lactic acid), poly(L-lactide)
TNBT	: Titanium(IV) butoxide
CDI	: 1,1'-Carbonyl diimidazole
DEC	: Diethyl carbonate
DPC	: Diphenyl carbonate
EC	: Epichlorohydrin
P-CDI	: PLLA reacted with CDI
P-DEC	: PLLA reacted with DEC
P-DPC	: PLLA reacted with DPC
P-EC	: PLLA reacted with EC
NMR	: Nuclear magnetic resonance spectroscopy
GPC	: Gel permeation chromatography
FTIR	: Fourier transform infrared
$\overline{M}_n$	: Number-average molecular weight
$\overline{M}_w$	: Weight- average molecular weight
PDI	: Polydispersity index



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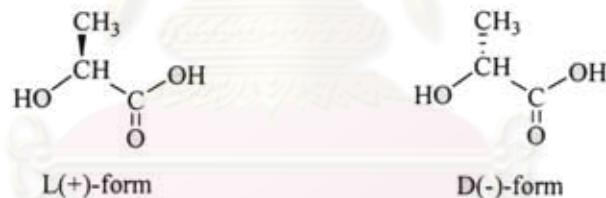
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## CHAPTER II

### THEORY AND LITERATURE REVIEW

#### 2.1 Lactic acid

Lactic acid or 2-hydroxy propionic acid can be produced by fermentation from renewable resources such as milk and carbohydrate such as potato, cane, and cassava. The chemical structure of lactic acid contains an asymmetric carbon atom or a chiral carbon, thus it has two optically active configurations, namely D(-)- and L(+)-isomers (Figure 2.1). The L(+)-isomer is predominate since it can be produced in animals and human being [2-3].

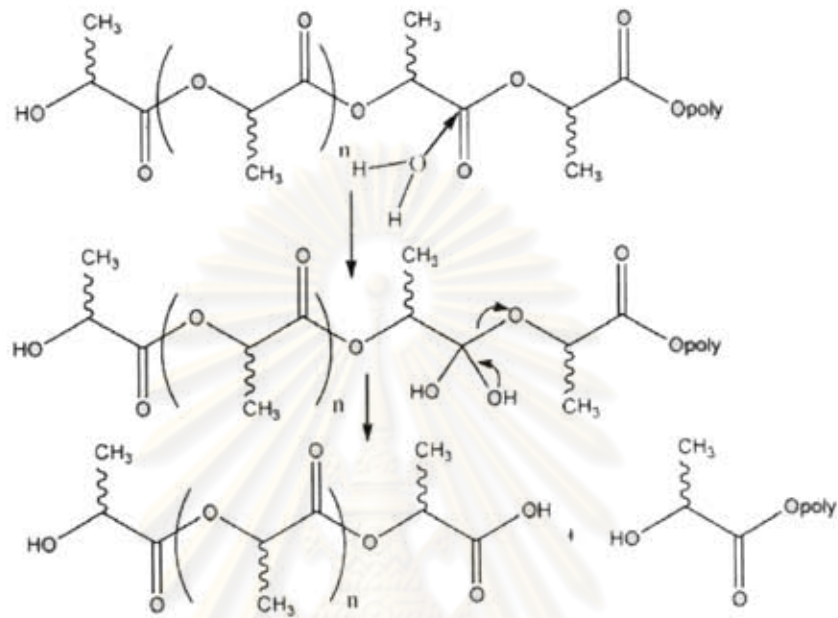


**Figure 2.1** Two configurations of lactic acid: D(-)-isomer and L(+)-isomer

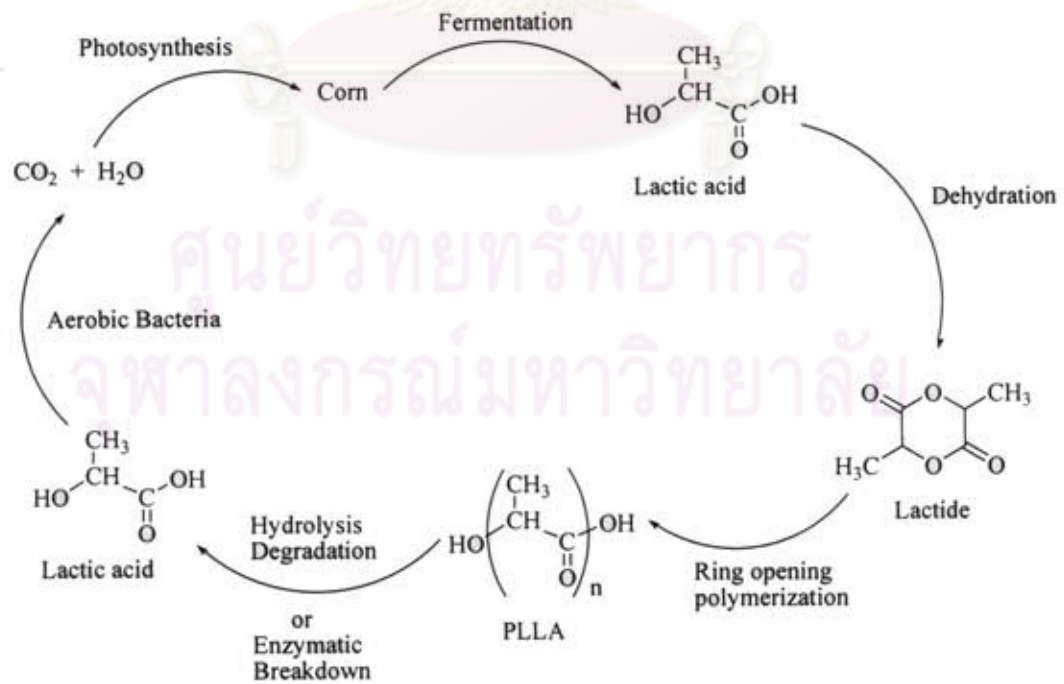
#### 2.2 Poly(lactic acid)

Poly(lactic acid) or Polylactide (PLA) is aliphatic polyester which contain lactide repeating unit. PLA is a biodegradable, biocompatible polymer, derived from renewable resources such as corn, potato, and cassava. PLA is considered an environmentally friendly thermoplastic which it can be recycled back to lactic acid which is a non toxic and naturally occurring metabolite through hydrolysis (Scheme 2.1) [3]. Its physical and mechanical properties can be tailored through the modification of its architecture [4-5]. Most of PLA is used in biomedical such as tissue engineering, orthopedic implants, surgical sutures, and drug delivery system.

Moreover, PLA has promising application in fiber and packaging. Figure 2.2 shows a closed life cycle of the PLA in the environment [6-7].



**Scheme 2.1** Hydrolysis of PLA



**Figure 2.2** The cycle of PLA in the environment



From the chiral nature of lactic acid, polylactide has various structural configurations such as poly(L-lactide), poly (D-lactide), and poly(D,L-lactide). Polymerization of L-lactide will give poly(L-lactide) and polymerization of D-lactide will give poly(D-lactide). Poly(L-lactide) and poly(D-lactide) will have identical properties. However, its racemic mixture (50% D- and 50% L-lactide) will give poly (D,L-lactide), which it is an amorphous polymer. PLA with varying fractions of L- & D-lactic acid can also be produced. Enantiomeric purity of the lactic acid stereocopolymers is an important feature that influences the physical properties of polylactide. The high D- or L-lactide copolymers and homopolymers poly(D-lactide) or poly(L-lactide) have regular structures and form a crystalline phase [8].

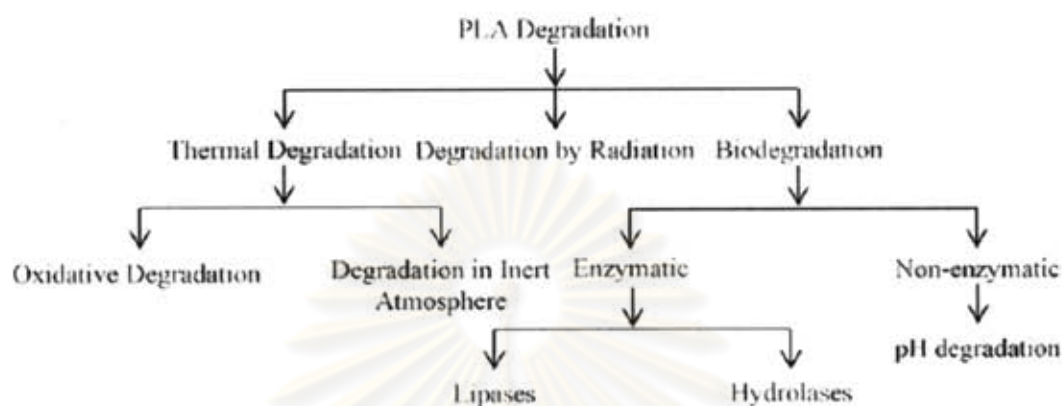
The property of PLA such as melting point, crystallinity, and mechanical strength depend on its molecular weight.  $T_g$  and  $T_m$  of PLA are dependent on the amount of L- and D-lactide repeat unit in PLA. The  $T_g$  and  $T_m$  of PLA is shown in Table 2.1 [9-12].

**Table 2.1** Glass transition temperature and melting temperature of selected PLA copolymer

Copolymer ratio	Glass transition temperature ( $T_g$ ) ( $^{\circ}\text{C}$ )	Melting temperature ( $T_m$ )( $^{\circ}\text{C}$ )
100/0 (L/D,L)-PLA	63	178
95/5 (L/D,L)-PLA	59	164
90/10 (L/D,L)-PLA	56	150
85/15 (L/D,L)-PLA	56	140
80/20 (L/D,L)-PLA	56	125

Different degradation of PLA was shown in Figure 2.3. The polymer degradation rate is mainly determined by polymer reactivity with water and catalysts. The factor affects reactivity such as particle size and shape, temperature, moisture,

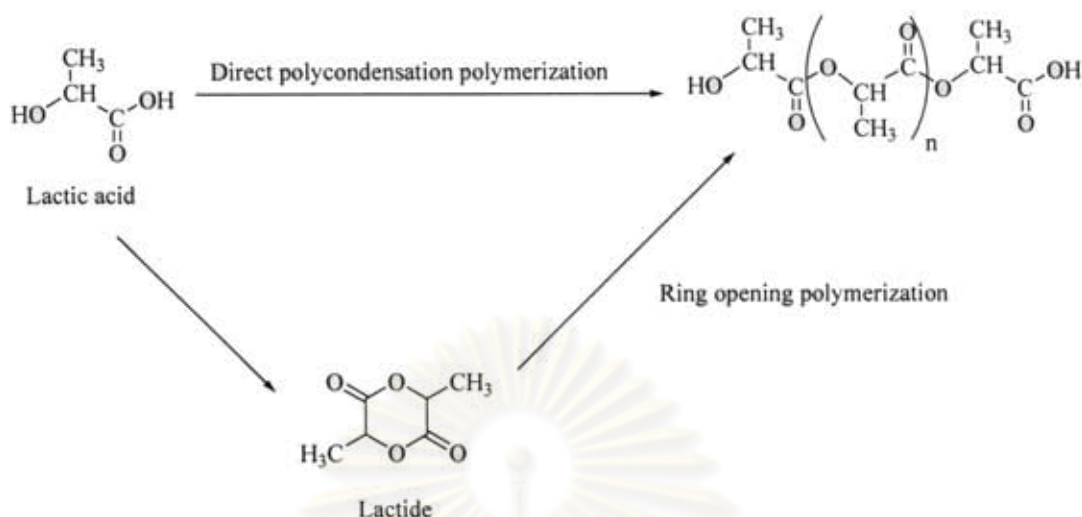
crystallinity, % isomer, molecular weight, water diffusion which all factors will affect the polymer degradation rate [4, 13-16].



**Figure 2.3** Degradation pathways of PLA

For example, thermal degradation of PLA that were considered to have highly concentrated ester bonds on the main chain. The reactions include thermohydrolysis, depolymerization, intermolecular transesterification resulting in formation of monomer and oligomeric ester, and in formation of monomer and oligomeric lactide of low molecular weight occurred by intramolecular transesterification. However, hydroxyl end groups of the main chain will display important role in lowering the molecular weight at high temperatures [3,9].

Generally, PLA is synthesized by two methods: ring-opening polymerization of lactide, a cyclic dimer of lactic acid, and direct polycondensation of lactic acid. Scheme 2.2 shows the two synthesis routes of PLA [3].



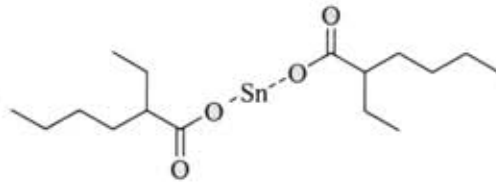
**Scheme 2.2** Synthesis of PLLA via direct polycondensation polymerization and ring-opening polymerization

### 2.2.1 Ring-opening polymerization (ROP)

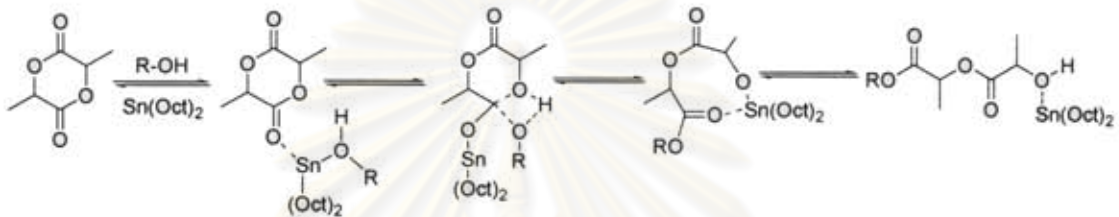
In ROP method, a cyclic dimer of lactic acid or 'lactide' is used as the monomer to synthesize PLA. Lactide is obtained by decomposition of low molecular weight PLA by heat. The polymerization can be controlled accurately, and the properties of resulting polymer can be varied to suit the application [3,17]. Importantly, the molecular weight of PLA obtained by this method was reported to be quite high in the range of 20,000-600,000 Da depending on catalyst types. The reaction mechanisms involved in this system can be either cationic, anionic, or coordination-insertion mechanisms [18-19].

For example, stannous octoate ( $\text{Sn}(\text{Oct})_2$ ) or tin(II) bis-2-ethylhexanoic acid (Figure 2.3) is the catalyst used for bulk polymerization for lactide because of its solubility in lactide. This catalyst gives low levels of racemization and provides high molecular weight PLA [20-21]. The ROP in the presence of  $\text{Sn}(\text{Oct})_2$  takes place via coordination-insertion mechanism (Scheme 2.3).





**Figure 2.4** Chemical structure of stannous octoate ( $\text{Sn}(\text{Oct})_2$ )

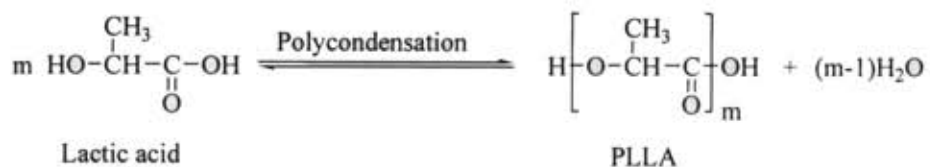


**Scheme 2.3** Coordination–insertion mechanism of lactide to PLA by using  $\text{Sn}(\text{Oct})_2$  as catalyst; R = growing polymer chain [15]

Despite the high molecular weight PLA obtained by ROP, disadvantage of this method is its high cost of monomer production due to the complicated purification process of the lactide monomer [3].

### 2.2.2 Direct polycondensation (PC)

Lactic acid is the monomer used in this method. PC of lactic acid is usually performed in bulk by distillation off the water under vacuum while temperature are progressively increased (Scheme 2.4). Molecular weight of PLLA obtained from this method is in range of 10,000-100,000 Da which is relatively lower than the molecular weight obtained by the ROP method.

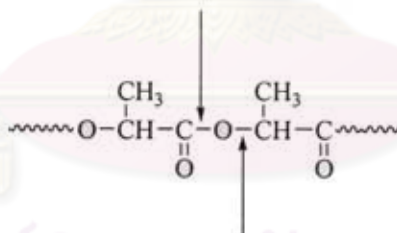


**Scheme 2.4** Polycondensation reaction of lactic acid to give poly(lactic acid)



A number of catalysts for PLA synthesis by PC method were reported. In 1997, Hiltunen *et al.* [22] studied the synthesis of PLLA by PC method. All polymerizations were carried out in the melt using different catalysts such as phosphoric acid ( $H_3PO_3$ ), zinc chloride ( $ZnCl_2$ ), aluminium acetylacetonate ( $Al(acac)$ ), tin(II) octoate ( $Sn(II)oct$ ), dibutyltin dilaurate (DBTL), antimony(III) oxide ( $Sb_2O_3$ ), titanium(IV) butylate ( $Ti(IV)bu$ ), titanium(IV) isopropylate ( $Ti(IV)iso$ ), and sulfuric acid ( $H_2SO_4$ ). The temperatures being studied were 180, 200, and 220 °C. They reported that sulfuric acid was the best catalyst at every temperature, providing PLA with molecular weight about 30,000 Da. Moreover, this research explained that the amount of catalyst and temperature was the key factors that affected racemization. It was found that racemization occurred at high temperature and when the amount of catalyst was increased. Scheme 2.5 shows two positions on the PLLA chains where the ester bond can break. Only the cleavage at the bond connecting the oxygen and  $\alpha$ -carbon can result in racemization.

If this bond is broken during tranesterification  
the no racemization is observed.



If this bond is broken during tranesterification  
the racemization would happen.

**Scheme 2.5** Bond cleavage positions during tranesterification of PLLA [22]

Other catalyst systems being investigated in order to achieve high molecular weight PLLA are as follows. Stannous(II) chloride dihydrate/*para*-toluene sulphonic acid monohydrate ( $SnCl_2/TSA$ ) is a binary catalyst that was found to be more effective than  $Sn(Oct)_2$  a single catalyst performed as the same condition (at 180 °C, 10 Torr and reaction time 12 h). The molecular weight obtained was 30,000 Da, as reported by Lee *et al.* [17]. Next, scandium trifluoromethanesulfonate ( $Sc(OTf)_3$ ) was studied by Takasu *et al.* in 2006 [23]. The reaction condition was at 170°C and 0.3 torr, the resulting in

PLLA with molecular weight as high as 73,000 Da. In 2006, Chen, G. X. *et al.* [24] studied the synthesis of high molecular weight PLLA by using titanium(IV) butoxide (TNBT) as a catalyst at 180 °C. Time of the esterification at 760 Torr was 3 h. The duration of air decompression from 760 to 1 Torr was 7 h, and polymerization at 1 Torr was 40 h. The resulting PLLA had a molecular weight of 130,000 Da. In the same year, Kim *et al.* [25] tried to produce high molecular weight PLLA-based copolymers which were synthesized through direct condensation polymerization of LA with succinic acid (SA) and 1,4-butanediol (BD). In this reaction, catalysts such as titanium(IV)-2-ethyl(hexoxide), indium acetate, indium hydroxide, antimony acetate, antimony trioxide, dibutyl tin oxide, stannous(II) 2-ethyl 1-hexanoate, and titanium(IV) butoxide (TNBT) were investigated. The molecular weight of Poly(l-lactic acid-*co*-succinic acid-*co*-1,4-butanediol) (PLASB) was 210,000 Da at the ratio of LA/SA/BD of 100/0.5/0.5 and using TNBT as the catalyst.

In general, ROP method results in high molecular weight PLLA but this method involves an extra step of lactide synthesis. While PC is a one-step synthesis method for PLLA from lactic acid, but the molecular weight of PLLA obtained is somewhat lower than the ROP method, because the process involves a vigorous water removal. Accordingly, molecular weight of PLLA can be increased by two methods i.e. solid-state polycondensation and chain extension.

### 2.3 Solid-state polycondensation

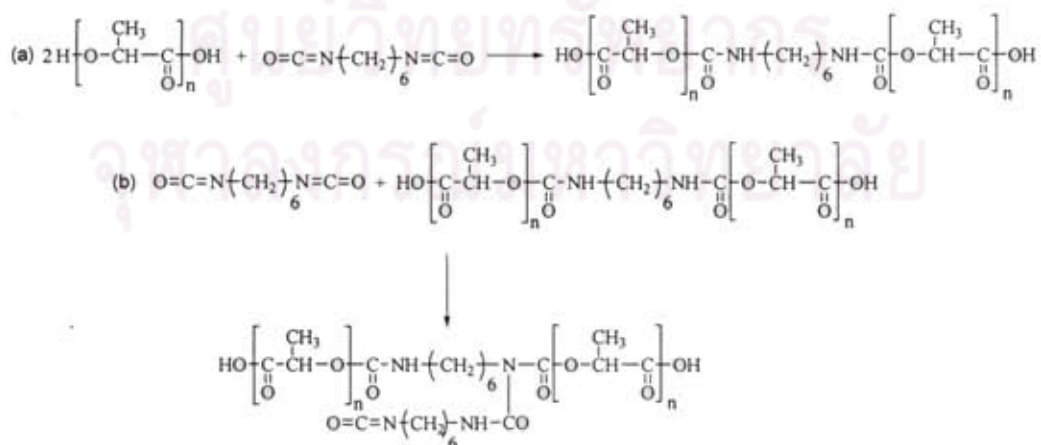
In 2001, Moon *et al.* [26-27] studied melt/solid-state polycondensation for increasing molecular weight of PLLA. In the first step, PLLA was synthesized by melt polycondensation at 180 °C, using tin chloride dihydrate/*p*-toluenesulfonic acid (SnCl<sub>2</sub>/TSA) as catalyst at 10 Torr for 5 h. The molecular weight obtained was 13,000-20,000 Da. In the second step, this obtained product was preheated at 105 °C which at this temperature, PLLA chain will occur arrangement for promoting crystallization. Then it was heated at 140–150 °C, 0.5 Torr for 10–30 h for further polycondensation. A high molecular weight of PLLA was obtained in high yield in a relatively short



reaction time and its molecular weight exceeded 500,000-600,000Da which had never been obtained by the simple melt-polycondensation of L-lactic acid.

## 2.4 Polymer chain extension

Chain extension of polymer is an alternative way to achieve high molecular weight polyesters. The principle of this method is to join two polymer chains together by using a bi-functional low-molecular weight compound, called a chain extender. In the polyester chains, the hydroxyl end-group usually coexists with the carboxyl end-group [28]. However, hydroxyl-reactive chain extenders can be more effective in increasing the molecular weight of polyesters [28-32]. Examples of chain extender used with most polyester are diisocyanate [1,33-39], bis(2-oxazolines) [40-43]. In 1995, Woo *et al.* [1] reported the preparation of high molecular weight PLA. First, PLA was prepared by direct polycondensation of lactic acid. Its molecular weight was then increased by adding hexamethylene diisocyanate (HMDI) as a chain extender at the last stage of polycondensation. The HMDI reacted with the hydroxyl terminal group (-OH) of polymer. Molecular weight of PLA was obtained as 75,900 when the ratio of [NCO] to [OH] is 4.11 at 160 °C after 10 min of reaction time. A linear structure occurred when the ratio of [NCO] to [OH] was low (Scheme 2.6a). However, the excess amount of HMDI can react with the other end group such as the carboxylic group (-COOH) or the urethane group (allophanate reaction is the reaction of -NCO with urethane) which will form a branch structure (Scheme 2.6b).



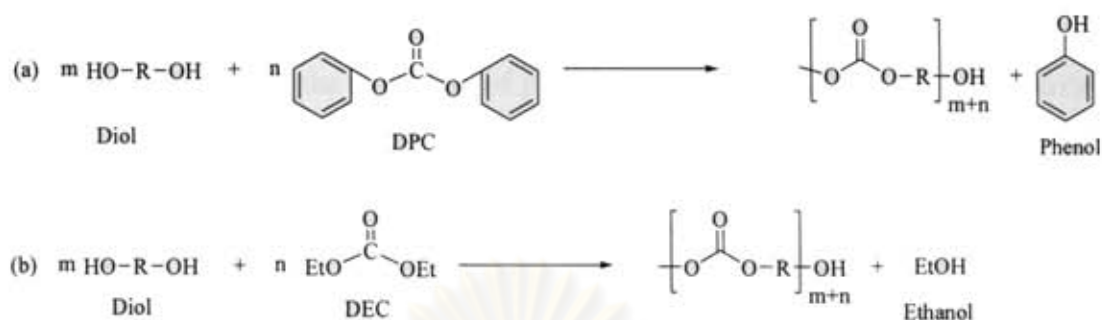
**Scheme 2.6** The reaction of hydroxyl terminal group (-OH) of PLA with HMDI (a) and branch structure of PLA with HMDI (b)

Afterward, Hiltunen *et al.* and Zeng *et al.* studied the synthesis poly(ester-urethane) by using 1,6-hexamethylene diisocyanate (HMDI) as a chain extender. Hiltunen *et al.* [44] used PLLA hydroxyl terminal group (-OH) reacting with HMDI at 180 °C for 15 min. Molecular weight of poly(ester-urethane) as high as 390,000 Da was obtained when the ratio of OH/NCO was 1:1. This ratio seemed to be optimum for linear polymer. Zeng *et al.* [36] used poly(L-lactic acid)-diol (PLLA-OH) (Mw= 10,700 Da) and poly(ethylene succinate)-diol (PES-OH) (Mw= 12,700 Da) reacting with HMDI at 160 °C for 1 h. Molecular weight of poly(ester-urethane) obtained was more than 200,000 Da when the ratio of HMDI to total prepolymer was 1:1. In addition, many types of diisocyanate were used as chain extenders such as; Cooper *et al.* [34] studied the synthesis polyurethane by using linear poly(lactic acid) (BHMBA-PLA) with L-lysine diisocyanate methyl ester (LDI) or dicyclohexylmethane 4,4'-diisocyanate (H<sub>12</sub>MDI) as chain extender which this reaction was proceeded at 40 °C, for 25 h, and toluene as solvent. BHMBA-PLA was synthesized via ring-opening polymerization (ROP) of lactide by using bis(hydroxymethyl) butyric acid (BHMBA) as initiator formed hydroxyl-terminated prepolymers containing a single pendent carboxylic acid group. Molecular weight of chain extended BHMBA-PDLLA was 206,000 Da at the mole ratio of NCO/OH of 1.02. Then *et al.* [37] synthesized high molecular weight aliphatic–aromatic copolyesters from poly(ethylene-co-1,6-hexenetereph-thalate) (PEHT-OH) and poly(L-lactic acid) (PLLA-OH) by chain extension, using toluene-2,4-diisocyanate (TDI) as a chain extender. This reaction proceeded at 160 °C, reaction time of 1 h, the mole ratio of NCO/OH of 1:1. High molecular weight of copolyesters (more than 300,000 Da) could be easily synthesized via chain extension.

In addition, many coupling agents such as diphenyl carbonate (DPC), diethyl carbonate (DEC), 1,1'-carbonyl diimidazole (CDI), and epichlorohydrin (EC) were studied for the purpose of increasing the molecular weight of polymer and, hence, its property improvement.

Polycondensation of DPC with diol monomers will obtain phenol as a by-product (Scheme 2.7a). Polycondensation of DEC with diol monomer will obtain ethanol as a by-product (Scheme 2.7b).

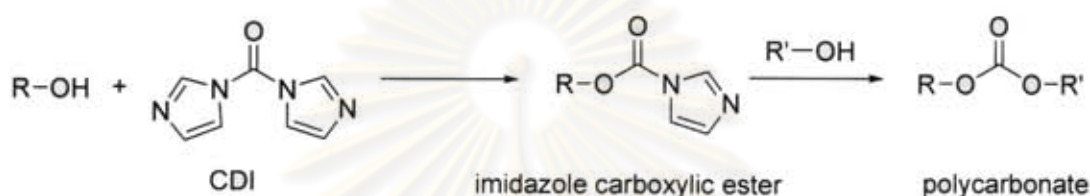




**Scheme 2.7** The synthesis of polycarbonate from DPC (a) and DEC (b) with diol compound

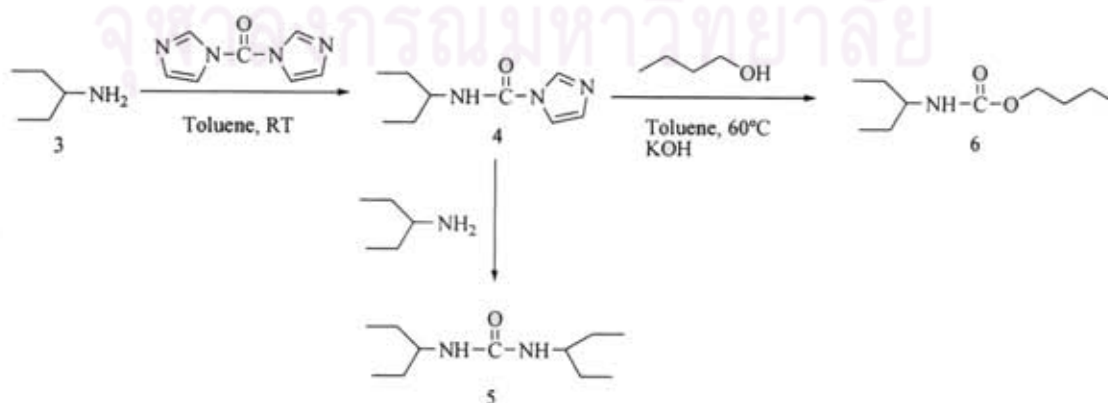
Kim *et al.* [45] prepared polycarbonates by melt transesterification and polycondensation of bisphenol A (BPA) with DPC or DMC at temperature 150-300 °C and different catalyst. The molecular weight of polycarbonates synthesized from DPC was higher ( $M_w = 16,000-50,000$  Da) than the one prepared from DMC ( $M_w = 25,000$  Da). This was because MeOH, the by-product from DMC, was a stronger nucleophile than phenol. From this information, an efficient chain extender should be the one that resulted in a by-product having very low nucleophilicity to avoid transesterification of the polymer. Then, Chandure *et al.* [46] synthesized poly(ester carbonate)s by polycondensation and transesterification process by using adipic acid, 1,3-propanediol and DEC with TNBT as catalyst. The mole ratio of adipic acid:DEC:1,3-propanediol was varied as 0.9:0.1:1.1, 0.8:0.2:1.1, 0.7:0.3:1.1, 0.6:0.4:1.1. Molecular weight of poly(ester carbonate)s increased with increasing DEC from 0.1 to 0.4. Subsequently, Jiang *et al.* [47] synthesized high molecular weight poly(hexamethylene carbonate) ( $M_w > 25,000$  Da) via copolymerization of DEC with 1,6-hexanediol. The process was catalyzed by immobilized *Candida antarctica* Lipase B (CALB). The reactions were performed by using a pressure-varied two-stage process for removing only ethanol by-product and preventing premature volatilization of DEC. First stage oligomerization occurred at low vacuum (600 mmHg pressure) and the second stage polymerization took place under high vacuum (1-5 mmHg pressure).

For 1,1'-carbonyl diimidazole (CDI), it is a coupling agent that can be used to form carbonates, esters, ureas, urethanes, and amides [48]. In 1999 and 2000, Rannard *et al.* [49-50] studied the synthesis of polycarbonate in which imidazole carboxylic esters was synthesized as an intermediate by the reaction of CDI with alcohols at 60 °C in the presence of KOH and toluene as solvent. Then, another alcohol was added, resulting in polycarbonate as the final product (Scheme 2.8).

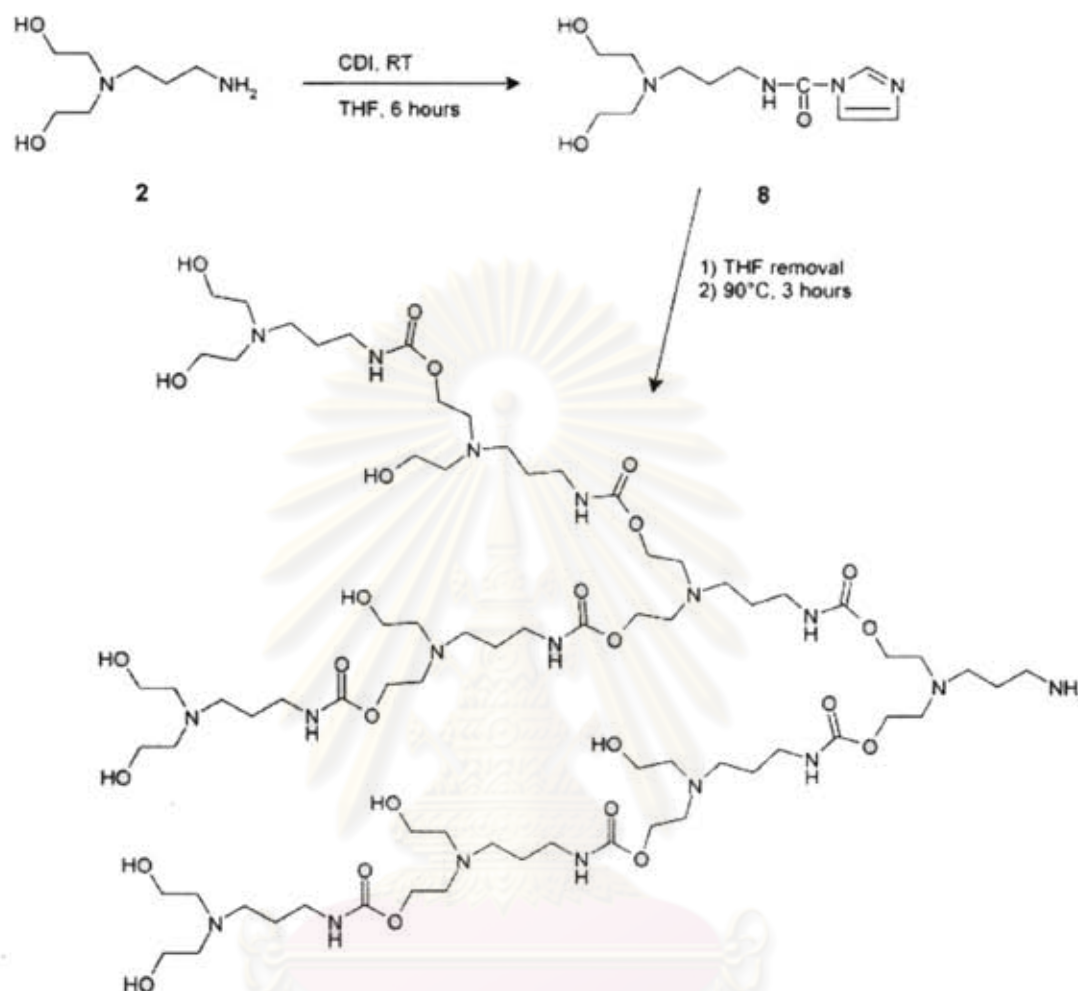


**Scheme 2.8** The synthesis of polycarbonate from CDI

In 2004, Rannard *et al.* [48] synthesized a novel water-soluble hyperbranched polyurethane. The formation urea and urethane is shown in Scheme 2.9. When the molar ratio of EPA (3) to CDI was 1:1, the reaction formed isolated carboxamide (4) in high recovered yield. If the molar ratio of EPA to CDI was increased to 2:1, the symmetric urea (5) was obtained. The hyperbranched polyurethane (Scheme 2.10) was prepared by using an excess amount of CDI. If the molar ratio of CDI to APDE (2) was close to 1:1, very high conversion of amine to carboxamide was obtained. If the residual amine was present after CDI consumption, the symmetrical urea was formed.

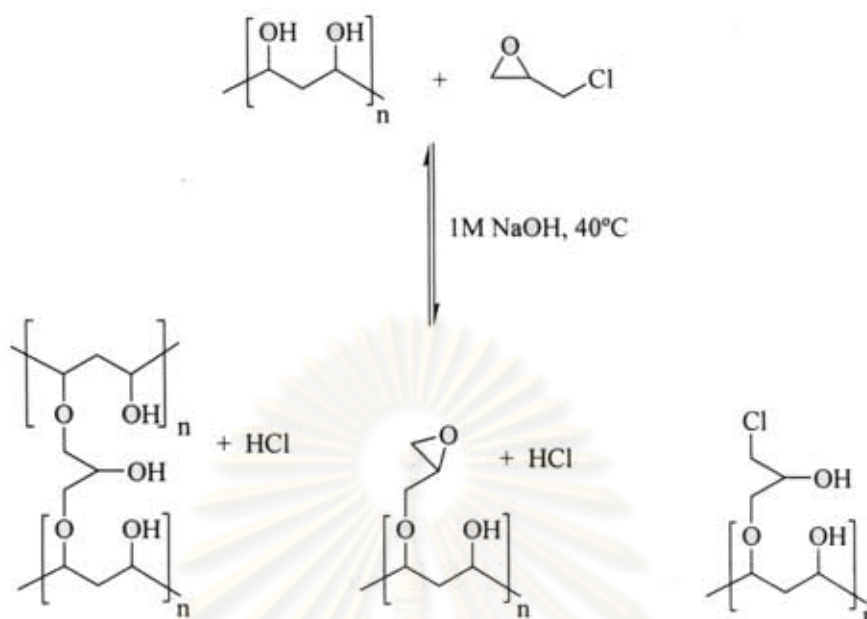


**Scheme 2.9** The formation urea (5) and urethane (6) via carboxamide (4) [48]



**Scheme 2.10** The formation hyperbranched polyurethane by *N*-(3-aminopropyl)-diethanolamine (APDE)(2) with imidazole [48]

Epichlorohydrin (EC) is a highly reactive compound. It was used as a crosslinking agent in the synthesis macroporous poly(vinyl alcohol) foam [51], polysaccharides [52], cross-linked starch/poly(vinyl alcohol) green films [53], poly(vinyl alcohol) resins [54], hydrogel based on poly(vinyl alcohol) [55], and hydrogels of cellulose [56]. The crosslinking reaction of epichlorohydrin and hydroxyl-containing polymers was generally carried out in the basic condition as shown in Scheme 2.11



**Scheme 2.11** The reaction of PVA crosslinking reaction with EC [51]

In this work, the focus was on investigating four chain extending compounds; DPC, DEC, CDI, and EC, to increase the chain length of PLLA that was pre-synthesized from L-lactic acid. All reactions were carried out in solution so that the temperature used would not be too high to cause any thermal degradation of the PLLA.

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## **CHAPTER III**

### **EXPERIMENTAL**

#### **3.1 Materials**

Lactic acid (minimum assay as lactic acid total 88% by weight) was purchased from Carlo Erba Reagent (France). Titanium(IV) butoxide (TNBT, reagent grade 97%), 1,1'-carbonyl diimidazole, diphenyl carbonate, diethyl carbonate and epichlorohydrin were purchased from Sigma-Aldrich (USA). Pyridine, sodium hydrogencarbonate ( $\text{NaHCO}_3$ ), sodium carbonate ( $\text{Na}_2\text{CO}_3$ ), and methanol ( $\text{MeOH}$ ) were purchased from Merck (Germany). Chloroform ( $\text{CHCl}_3$ ), tetrahydrofuran (HPLC grade), and xylene (assay 98% min.) were purchased from RCI Labscan Limited (Thailand). Calcium carbonate ( $\text{CaCO}_3$ ) was purchased from Asia Pacific Specialty Chemicals Limited (Australia).

#### **3.2 Equipments**

##### **3.2.1 Nuclear Magnetic Resonance (NMR) Spectroscopy**

$^1\text{H}$  NMR spectra were recorded in solution of  $\text{CDCl}_3$  using a Varian, model Mercury-400 nuclear magnetic resonance spectrometer (USA) operating at 400 MHz. Chemical shifts were reported in part per million (ppm) relative to tetramethylsilane (TMS) or using the residual protonated solvent signal as a reference.

##### **3.2.2 Fourier Transform -Infrared Spectroscopy (FT-IR)**

IR spectra were collected using a Nicolet 6700 FT-IR spectrometer. All samples were prepared as KBr pellets.

### 3.2.3 Gel Permeation Chromatography (GPC)

Gel permeation chromatograms of PLLA were obtained from Waters 600 controller chromatograph equipped with two HR (Waters) columns (HR1 and HR4) (MW resolving range = 100-500,000) at 35 °C and a refractive index detector (Waters 2414). Tetrahydrofuran (HPLC grade) was used as an eluent with the flow rate of 1.0 mL/min. Sample injection volume was 50 µL. Polystyrenes (996-188,000 Da) were used as standards for calibration.

## 3.3 Methods

### 3.3.1 Synthesis of PLLA by condensation polymerization

Synthesis of PLLA followed the procedure reported by Chen et al. in 2006 [24], in which the reaction temperature was set 180 °C, 1 Torr, and reaction time of 40 h. In this work, however, the temperature used for all direct condensation polymerization of PLLA was at 178 °C, in order to avoid over heating which could result in racemization.

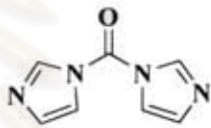
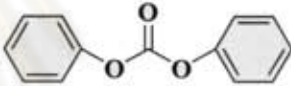
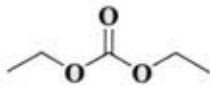



L-lactic acid (88% solution, 10 g, 111 mmole) was added to a three-neck round-bottom flask. In the first step the reaction flask was immersed in 110 °C oil bath under slow nitrogen purging for 4 h to remove water. In the second step, the reaction flask was heated to 178 °C, and then was added TNBT (0.11 mmole). The reaction mixture was stirred under nitrogen atmosphere for 1 h. After that, the pressure was reduced gradually to a full vacuum within 2 h. The reaction was left with slow stirring in vacuum for 5, 7, 20, 30, 40, or 50 h. Finally, the resulting polymer was dissolved in chloroform and precipitated by pouring the polymer solution into an excess volume of methanol (10 times of chloroform). The appearance of synthesized PLLA is white solid.

### 3.3.2 Chain extension of PLLA by chain extender compound

In this step, various types of the chain extender, i.e. 1,1'-carbonyl diimidazole (CDI), diethyl carbonate (DEC), diphenyl carbonate (DPC), and epichlorohydrin (EC), were used to act as coupling agent of the two PLLA chains. Table 3.1 shows the chemical structure of the chain extender investigated in this work.

**Table 3.1** Chemical structure of chain extender

Chain extender	Chemical structure
1,1'-Carbonyl diimidazole (CDI)	
Diphenyl carbonate (DPC)	
Diethyl carbonate (DEC)	
Epichlorohydrin (EC)	

#### 3.3.2.1 CDI as chain extender

PLLA prepolymer (0.15 mmole,  $\overline{M}_n = 4,000-7,300$ ), CDI and xylene (1 mL) were put into the flask which was purged with nitrogen. The mole ratios of PLLA prepolymer to CDI were varied as shown in Table 3.2. Then the reaction flask was immersed in a 110 °C silicone oil bath in which the polymer dissolved at this temperature and stirred for 0.5-20 h. After the reaction, the polymer was dissolved in chloroform and precipitated by pouring the polymer solution into an excess of methanol (10 times of chloroform) in which unreacted CDI was removed in this step. The appearance of resulting PLLA is white solid.



**Table 3.2** Variation of mole ratio of PLLA prepolymer:CDI

Sample name	$\overline{M}_n$ of PLLA prepolymer (Da)	Mole ratio of PLLA/CDI	Temperature (°C)	Reaction time (h)
P-CDI3	7,396	1:0.5	110	3
P-CDI4	4,033	1:1	110	3
P-CDI5	4,033	1:2	110	3
P-CDI6	4,033	1:3	110	3
P-CDI7	4,033	1:4	110	3
P-CDI2	5,366	1:5	110	3
P-CDI8	6,839	1:6	110	3
P-CDI9	5,928	1:8	110	3
P-CDI10	4,962	1:10	110	3

### 3.3.2.2 DPC as chain extender

PLLA prepolymer (0.15 mmole,  $\overline{M}_n = 4,600\text{Da}$ ), DPC (0.75 mmol, the mole ratio of PLLA prepolymer to DPC was 1:5), and xylene (1 mL) were put into the flask which was purged with nitrogen. Then the reaction flask was immersed in a 110 °C silicone oil bath and stirred for 3 h. The polymer was dissolved in chloroform and precipitated by pouring the polymer solution into an excess of methanol (10 times of chloroform) in which DPC was removed in this step. The appearance of resulting PLLA is white solid.

### 3.3.2.3 DEC as chain extender

PLLA prepolymer (0.15 mmole,  $\overline{M}_n = 4,600$  Da), DEC (0.75 mmol, the mole ratio of PLLA prepolymer to DEC was 1:5) and xylene (1 mL) were put into the flask which was purged with nitrogen. Then the reaction flask was immersed in a 110 °C silicone oil bath and stirred for 3 h. The polymer was dissolved in chloroform and precipitated by pouring the polymer solution into an excess of methanol (10 times of chloroform) in which DEC was removed in this step. The appearance of resulting PLLA is white solid.

### 3.3.2.4 EC as chain extender

PLLA prepolymer (0.15 mmole,  $\overline{M}_n = 5,600-7,300$  Da), EC (varied mole), base (varied types) and xylene (1 mL) were put into the flask which was purged with nitrogen. Then the reaction flask was immersed in a 110 °C silicone oil bath and stirred for 3-10 h. The polymer was dissolved in chloroform, filtered (to eliminate base particle that is insoluble in the reaction solution). The resulting PLLA was then precipitated by pouring the polymer solution into an excess of methanol (10 times of chloroform) in which EC was removed in this step. The appearance of resulting PLLA is white solid. The mole ratios of PLLA prepolymer to EC to base, reaction time, and base type were varied as shown in the Table 3.3 and 3.4.

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**Table 3.3** Variation of the mole ratio of PLLA:EC:Na<sub>2</sub>CO<sub>3</sub> and reaction time (h)

Sample name	$\overline{M}_n$ of PLLA prepolymer (Da)	Mole ratio of PLLA/EC/Na <sub>2</sub> CO <sub>3</sub>	Temperature (°C)	Reaction time (h)
P-EC6	5,760	1:0.5:0.5	110	3
P-EC7	6,552	1:1:1	110	3
P-EC2	6,552	1:3:3	110	3
P-EC8	6,300	1:5:5	110	3
P-EC9	6,693	1:8:8	110	3
P-EC2	6,552	1:3:3	110	3
P-EC10	5,921	1:3:3	110	5
P-EC11	5,928	1:3:3	110	7
P-EC12	7,396	1:3:3	110	10
P-EC13	6,552	1:3:1.5	110	3
P-EC2	6,552	1:3:3	110	3
P-EC14	5,664	1:3:5	110	3
P-EC15	5,928	1:3:5	110	5
P-EC16	5,664	1:3:7	110	5
P-EC17	7,396	1:3:10	110	5



**Table 3.4** Variation base type in the reaction between PLLA and EC

Sample name	$\overline{M}_n$ of PLLA prepolymer (Da)	Mole ratio of PLLA/EC /Base	Base	Temperature (°C)	Reaction time (h)
P-EC2	6,552	1:3:3	Na <sub>2</sub> CO <sub>3</sub>	110	3
P-EC3	6,925	1:3:3	pyridine	110	3
P-EC4	6,552	1:3:3	NaHCO <sub>3</sub>	110	3
P-EC5	6,552	1:3:3	CaCO <sub>3</sub>	110	3

After the chain extension reaction, molecular weight change (%) of PLLA was calculated by the following equation:

$$\text{Molecular weight change (\%)} = \frac{\overline{M}_n \text{ of PLLA} - \overline{M}_n \text{ of PLLA prepolymer}}{\overline{M}_n \text{ of PLLA prepolymer}} \times 100$$

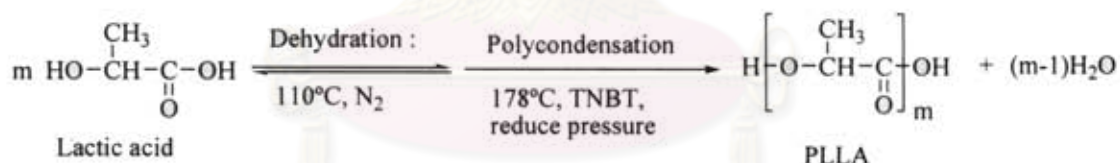
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## CHAPTER IV

### RESULTS AND DISCUSSION

This chapter was divided into two parts. The first part focused on the synthesis and characterization of PLLA which was synthesized through polycondensation polymerization. In this part, the influences of temperature, amount of catalyst, and reaction time were investigated. In the second part, chain extension of the resulting PLLA was studied through the reactions between PLLA and a selected coupling agent in solution. The influences of coupling agent, temperature, mole ratio of reaction, and reaction time were investigated.

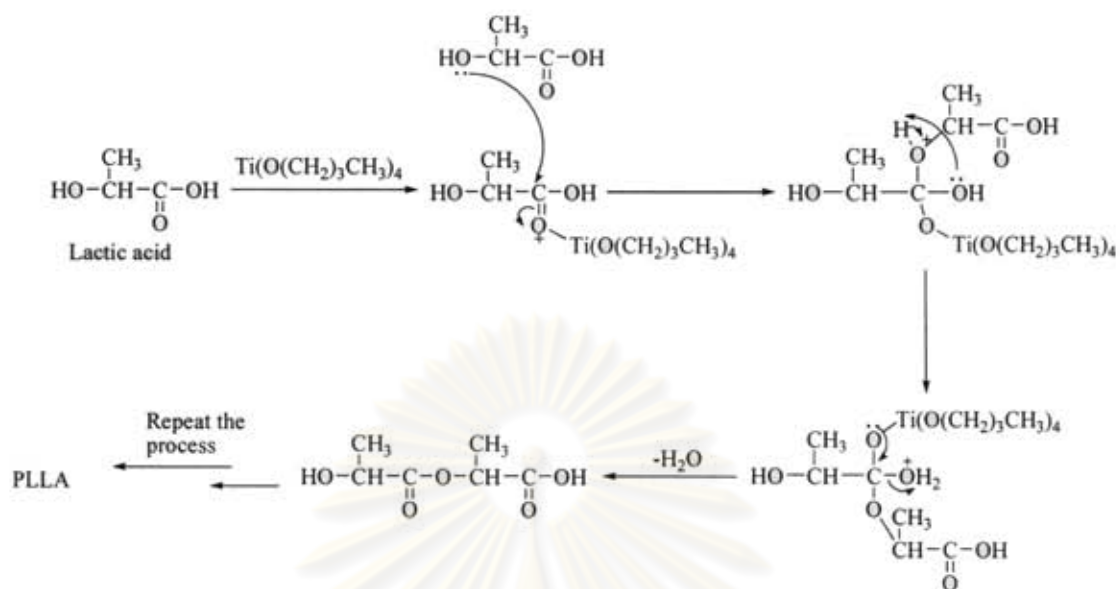
#### 4.1 Synthesis of PLLA by polycondensation polymerization



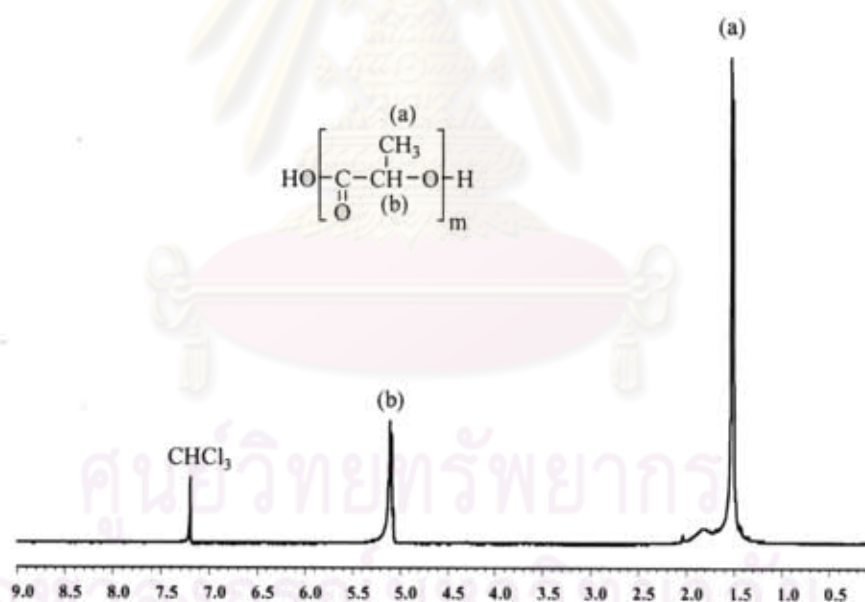
**Scheme 4.1** Synthesis of PLLA from lactic acid

In this part, reaction temperature, amount of TNBT, and reaction time were studied for polycondensation of lactic acid to produce PLLA (Scheme 4.1). This method followed the work reported by Chen *et al.* in 2006 [24]. The mechanism of PLLA synthesis in the presence of TNBT is shown in Scheme 4.2.

Figure 4.1 shows  $^1\text{H}$  NMR spectrum of the obtained PLLA. The proton signals at 1.58 and 5.18 ppm were assigned to methyl (a) and methine (b) protons of the lactide unit, respectively.



**Scheme 4.2** Mechanism of synthesis of PLLA from lactic acid



**Figure 4.1**  $^1\text{H}$  NMR spectrum of PLLA in  $\text{CDCl}_3$

Table 4.1 shows molecular weight, PDI, and yield of the PLLA synthesized by varying reaction temperature, reaction time, and amount of TNBT. Upon increasing the temperature from 154-178 °C, the molecular weight ( $\overline{M}_w$ ) of PLLA increased from 7,400-25,000 Da. At 204 °C, the resulting product appeared brownish possibly resulted from thermal degradation at this rather high temperature.



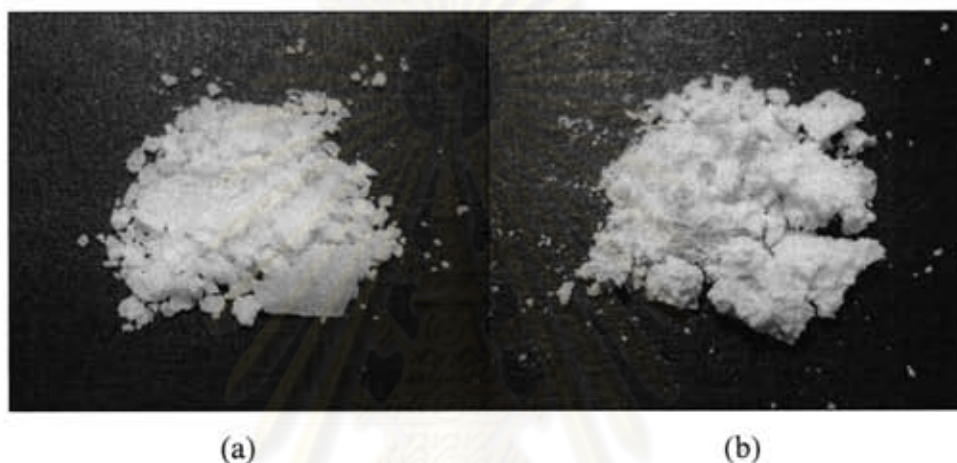
The molecular weight of PLLA was slightly increased when the amount of TNBT was increased from 0.1 to 0.2 mol%, but decreased at 0.3 mol% of TNBT. At 0.3% catalyst, the content of TNBT is probably so high that the titanium atom can coordinate with the oxygen atoms of the carbonyl as well as with the hydroxyl group of the terminal lactic acid. When the hydroxyl group is coordinated by Ti, its nucleophilicity is lowered so the condensation reaction rarely occurs. In addition, TNBT is a weak ester-interchange catalyst [22]. If the amount of TNBT is high, ester interchange would frequently occur. The consequence would be low molecular-weight PLLA. Moreover, an inversion of the configuration from L-isomer to D-isomer occurred when the amount of TNBT was high and the temperature was increased to more than 180 °C [22,24].

The effect of reaction time on the condensation polymerization was found that highest molecular weight of PLLA was obtained at reaction time of 30 h (PLLA6). At 40 and 50 h, molecular weight obtained became low. At high reaction temperature, a process called “transesterification”, or an attack of –OH on the chain ester bond could become dominant causing the molecular weight drop.

**Table 4.1** Molecular weight, polydispersity index, and yield of PLLA synthesized by varying reaction temperature, time, and amount of TNBT

Sample code	Reaction temp (°C)	Reaction time (h)	Amount of TNBT (% mole)	$\bar{M}_n$ (Da)	$\bar{M}_w$ (Da)	PDI	Yield (%)
PLLA1	204	40	0.1	-	-	-	-
PLLA2	178	20	0.1	10,138-18,571	15,375-24,921	1.23-1.52	12-54
PLLA3	154	20	0.1	5,470	7,379	1.35	44
PLLA4	178	20	0.2	20,727	26,844	1.30	33
PLLA5	178	20	0.3	18,175	24,554	1.35	32
PLLA6	178	30	0.1	19,139-40,614	28,388-50,083	1.23-1.48	21-50
PLLA7	178	40	0.1	20,495-26,537	28,332-35,502	1.34-1.42	11-37
PLLA8	178	50	0.1	20,360	26,063	1.28	30

Furthermore, low molecular weight of PLLA was synthesized using 0.1 % TNBT, at 178 °C, and reaction time were limited to 5-7 h. The molecular weights ( $\overline{M}_w$ ) of PLLA obtained were in range of 4,500-9,400 Da ( $\overline{M}_n = 4,000-7,300$  Da). The appearance of PLLA as synthesized by condensation polymerization is white solid as shown in Figure 4.2.



**Figure 4.2** The appearance of PLLA as synthesized by condensation polymerization at 178 °C, reaction time of 5 h (a) and reaction time of 20 h (b)

#### 4.2 Chain extension of PLLA

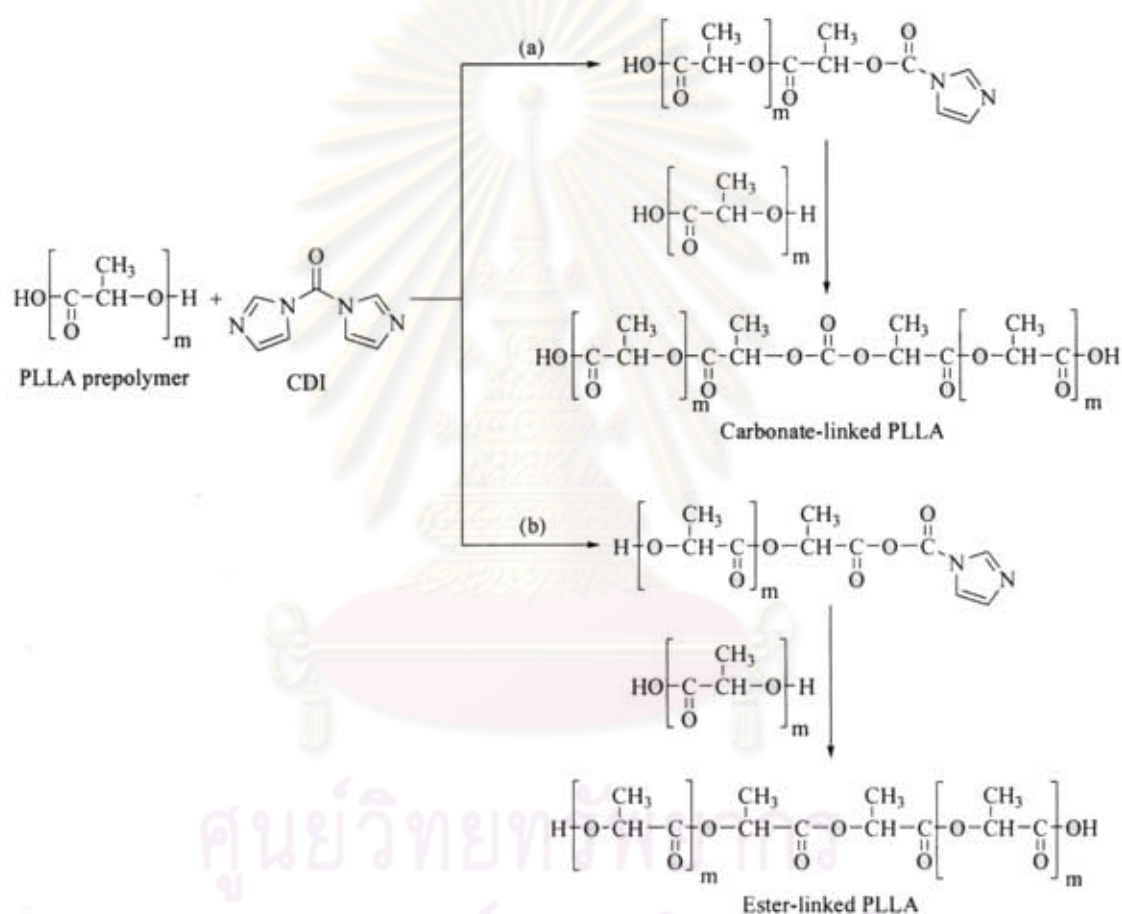
In this section, PLLA was reacted with selected coupling agents in solution as an attempt to increase the PLLA molecular weight. The role of these coupling agents was to join two polymer chains together. A theoretical mole ratio of polymer chain to chain extender is 2:1 or 1:0.5. At this ratio, the molecular weight of PLLA can increase two folds (molecular weight change= 100%). The molecular weight change (%) and % recover were calculated by the following equation (1) and (2):

$$\text{Molecular weight change (\%)} = \frac{\overline{M}_n \text{ of PLLA} - \overline{M}_n \text{ of PLLA prepolymer}}{\overline{M}_n \text{ of PLLA prepolymer}} \times 100 \dots \dots \dots (1)$$

$$\text{Yield (\%)} = \frac{\text{weight of PLLA}}{\text{weight of PLLA prepolymer}} \times 100 \dots \dots \dots (2)$$

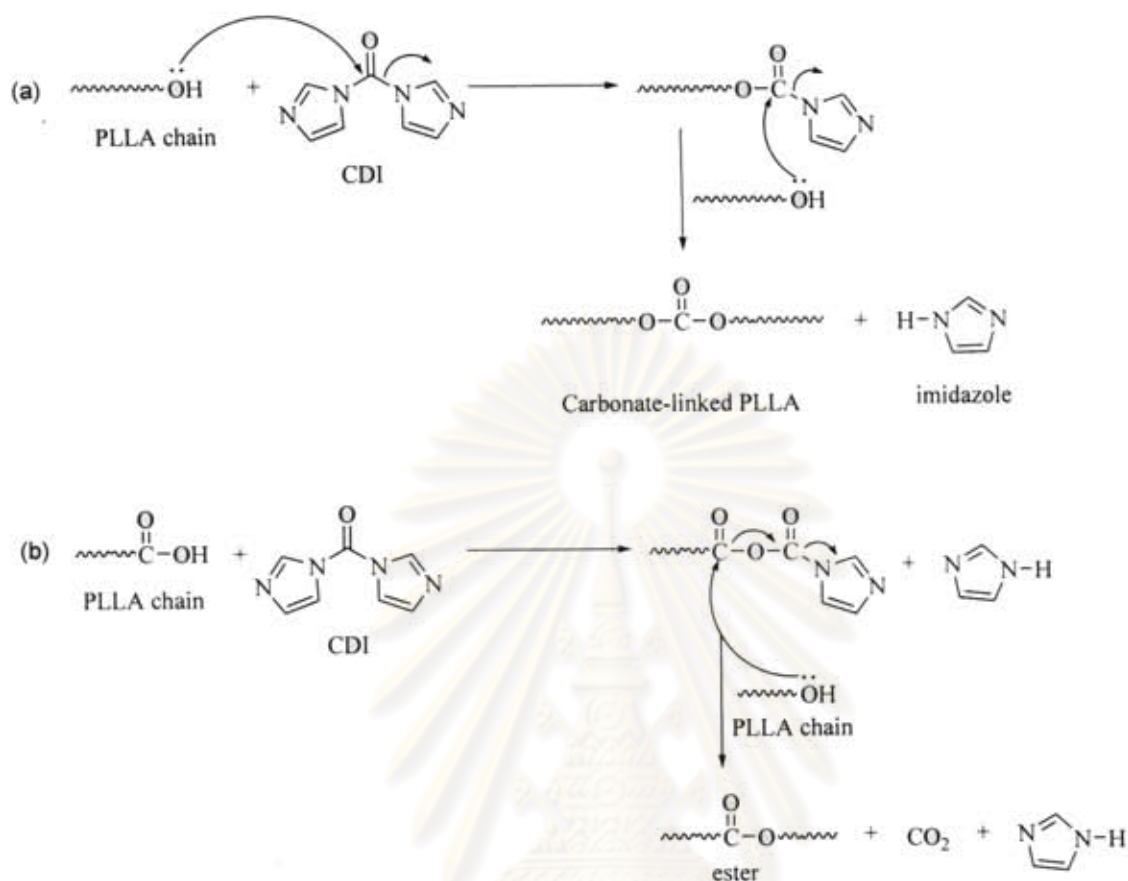
Four types of chain extender molecules were studied, i.e. 1,1'-carbonyl diimidazole (CDI), diphenyl carbonate (DPC), diethyl carbonate (DEC), and epichlorohydrin (EC).

#### 4.2.1 CDI as chain extender



**Scheme 4.3** CDI acts as chain extension by joining the two hydroxyl groups of PLLA chains, forming a carbonate bond (a), and coupling agent by activating ester bond formation between a hydroxyl and carboxylic ends of two PLLA chains (b)





**Scheme 4.4** Mechanism of chain extension reaction by CDI (a) by joining the two hydroxyl group of PLLA chains, (b) ester-linked PLLA from carboxylic acid activated by CDI

Scheme 4.3 shows two possible reactions of PLLA prepolymer and CDI. In the 1<sup>st</sup> reaction (Scheme 4.3a and 4.4a), the CDI molecule joins each hydroxyl group (-OH) of two PLLA chains to form “carbonate-link PLLA”. In the 2<sup>nd</sup> reaction (Scheme 4.3b and 4.4b), the role of CDI was to activate ester bond formation by first changing a terminal carboxylic acid to an anhydride which is more active toward -OH attack than the original -COOH. The resulting product is “ester-linked PLLA” [57].

The effect of temperature was studied by using two solvents. Chloroform was used in the coupling reaction performed at 75 °C, while xylene was used in the reaction at 110 °C. Table 4.2 shows the effect of temperature on molecular weight change of PLLA. It was found that at 110 °C, the molecular weight of PLLA was increased to almost 56 % (P-CDI2), which was higher than the reaction at 75 °C (P-CDI1). Thus, the

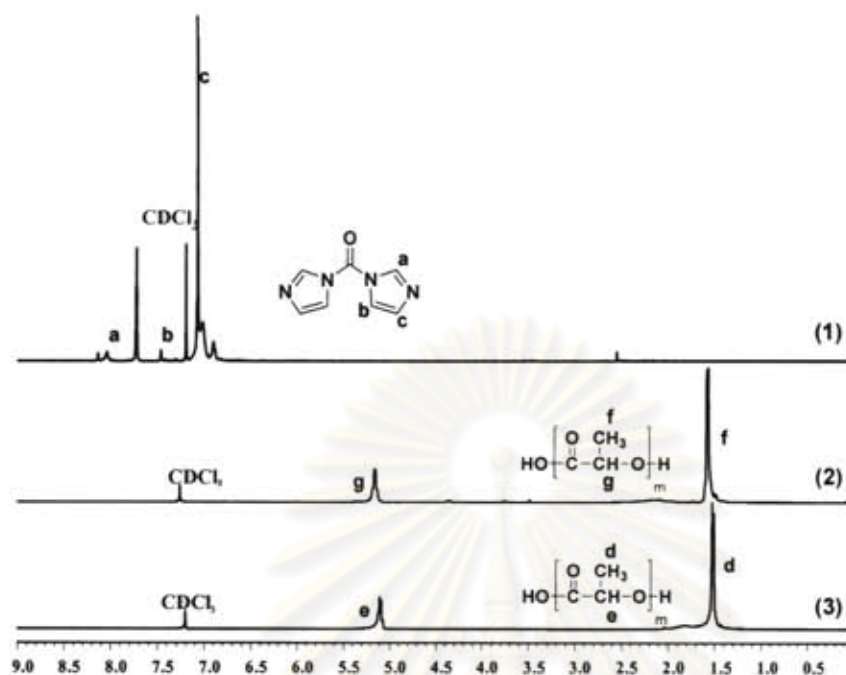
reaction occurred faster at higher temperature. In general, the use of CDI as coupling agent to form carbonates, ureas, amides, urethanes, and ester were achieved at temperature in range of 60-70 °C [48,50]. The high temperature required in this work (110 °C) was probably because one of the reactant was a long chain polymer. Factors include chain mobility and probability of molecular attack (at the chain end) must be taken into account.

**Table 4.2** The effect of temperature on molecular weight change of PLLA in the presence of CDI as chain extender; mole ratio of PLLA prepolymer/CDI (1:5), reaction time 3 h

Sample code	Before reaction with CDI			After reaction with CDI			
	$\overline{M}_n$ of PLLA prepolymer (Da)	solvent	Rxn. temp (°C)	$\overline{M}_n$ of PLLA (Da)	PDI	Molecular weight change (%)	Yield (%)
P-CDI1	6,441	CH <sub>2</sub> Cl <sub>2</sub>	75	8,207	1.27	27.42	62
P-CDI2*	5,366	xylene	110	8,386	1.27	56.28	37

\* The value shown was averaged from 2 sets of experiments. In the first synthesis of P-CDI2\*, starting molecular weight of PLLA was 4,143 Da after reacting with CDI molecular weight of PLLA increased by 7,063 Da (molecular weight change as 70.48%). In the second synthesis of P-CDI2\*, starting molecular weight of PLLA was 6,589 Da after reacting with CDI molecular weight of PLLA increased by 9,709 Da (molecular weight change as 47.35%).

Figure 4.3 shows the <sup>1</sup>H NMR spectra of PLLA prepolymer, P-CDI2, and CDI. The proton signals at 1.58 and 5.18 ppm were assigned to methyl and methine protons of the lactide unit, respectively. The proton signals of CDI at 7.25, 7.54, and 8.21 ppm were no longer present in the spectrum indicating that CDI and imidazole by-product were removed from the polymer product.

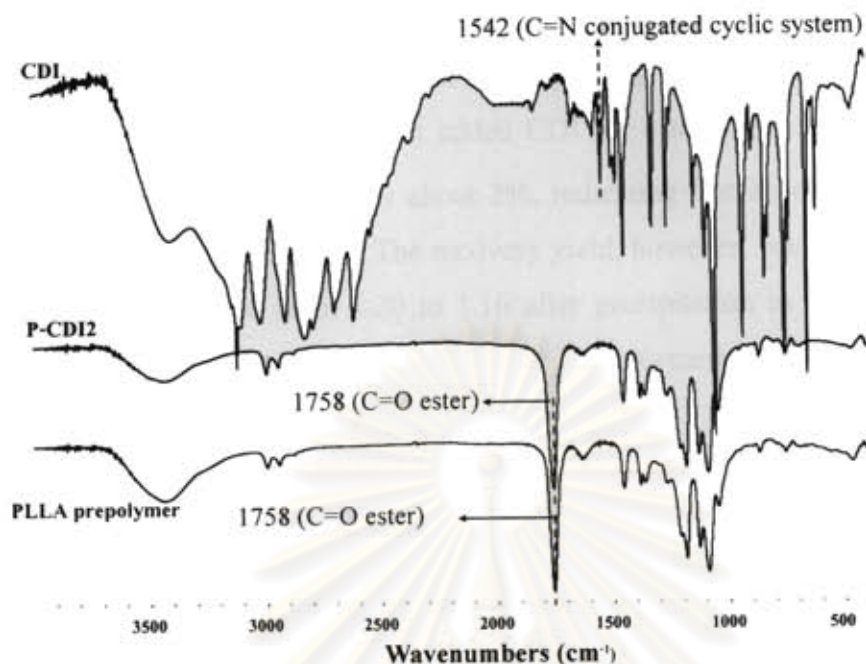


**Figure 4.3**  $^1\text{H}$  NMR spectrum of CDI (1), P-CDI2 (2) (after chain extension reaction), and PLLA prepolymer (3) (before chain extension reaction) in  $\text{CDCl}_3$

FTIR was used to analyze the functional groups in the polymers. Figure 4.4 shows the FTIR spectra of PLLA prepolymer, P-CDI2, and CDI. The appearance of a characteristic peak at  $1758\text{ cm}^{-1}$  assigned to  $\text{C}=\text{O}$  of ester groups of P-CDI2 and PLLA prepolymer. The peak at  $1542\text{ cm}^{-1}$  assigned to  $\text{C}=\text{N}$  conjugated cyclic system of imidazole. From P-CDI2, it shows that the peak attributed to the  $\text{C}=\text{N}$  conjugated cyclic system was not found in the range of around  $1542\text{ cm}^{-1}$ , indicating that imidazole was removed from the resulting polymer consistent with the NMR result.

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**Figure 4.4** FTIR spectra of CDI, P-CDI2 (after chain extension reaction), and PLLA prepolymer (before chain extension reaction).

Table 4.3 shows influence of mole ratio of PLLA prepolymer:CDI and reaction time on chain extension reaction. At the theoretical mole ratio of 1:0.5, the molecular weight of PLLA after coupling with CDI was increased by 21% (P-CDI3) which was rather low. This result suggested that the coupling reaction between two polymer chains by CDI is rather difficult. This is possible due to the fact that one of the reactants is a polymer. The possibility of having two chain ends to react with the chain extender molecule was therefore low. Additionally, this reaction was carried out in solution in which the concentration of the polymer chains was somewhat low, reducing the probability of the successful reaction. Increasing the amount of CDI should increase the chance for reacting the hydroxyl chain ends of PLLA chains with CDI. It was found that molecular weight of PLLA was increased when the amount of CDI was increased excessively from 1:1 to 1:10. At 1:10, the molecular weight of PLLA increased by as high as 107% (P-CDI10). Thus, a large and excess amount of CDI was needed to achieve a large increase or double value of molecular weight. During the course of this study, the author suspected that PLLA would degrade during heating in the coupling

step in which the temperature as high as 110 °C was reached. Therefore PLLA prepolymer was subjected to blank reaction test, by bring the polymer to the same heating condition and solvent but without added CDI for a total time of 3 h. It was found that the  $\overline{M}_n$  in fact decreased by about 2%, indicating that no chain extension took place without the chain extender. The recovery yield, however, was only 54% and the PDI was slightly lowered from 1.20 to 1.16 after precipitation in MeOH. It was believed that a certain amount of low molecular-weight polymers and oligomers were washed away by MeOH during the precipitation step.

The effect of reaction time on chain extension capability of PLLA and CDI (molar ratio = 1:5) was studied (Table 4.3). It was found that the molecular weight of PLLA was increased with increasing reaction time from 0.5 to 5 h. At 10 h, the molecular weight of PLLA was decreased and became even lower than the starting value after 20 h of reaction. At a long reaction time, molecular weight of PLLA was decreased because the imidazole by-product probably acted as a base subtracting a proton of the methyl group in the unit adjacent to the newly formed carbonate bond and methyl group in lactide unit. The mechanism of carbonate cleavage and ester cleavage are proposed in Scheme 4.5 and 4.6.



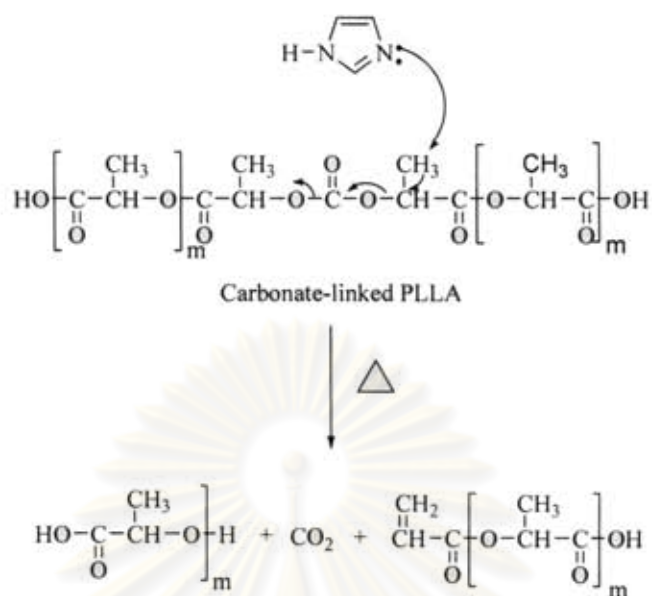
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**Table 4.3** Influence of mole ratio of PLLA prepolymer:CDI and reaction time on molecular weight change of PLLA in the presence of CDI as chain extender; solvent:xylene, T = 110 °C

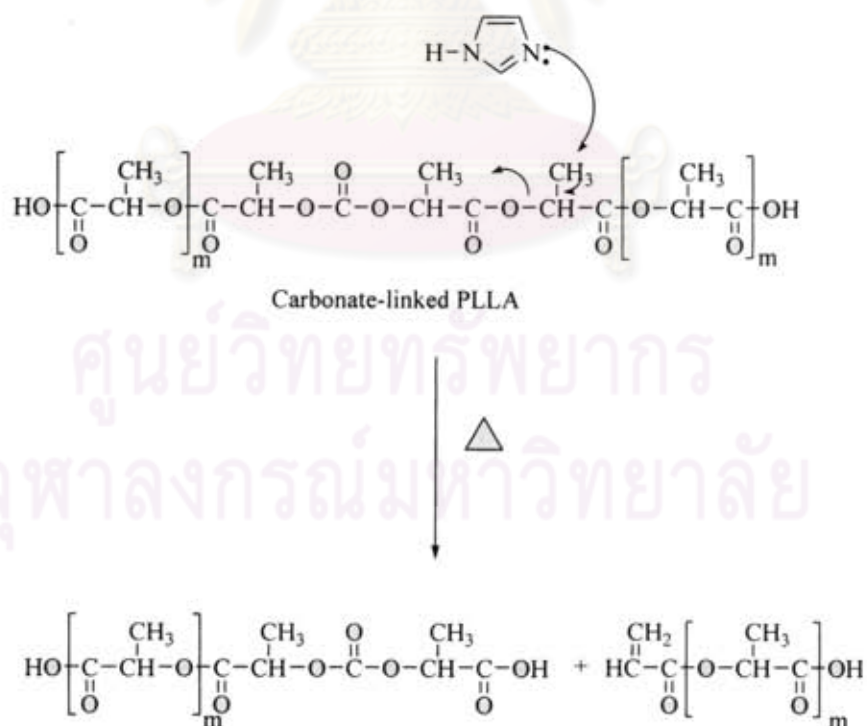
Sample code	Before reaction with CDI			After reaction with CDI			
	$\overline{M}_n$ of PLLA prepolymer (Da)	Molar ratio of PLLA prepolymer/ CDI	Rxn time (h)	$\overline{M}_n$ of PLLA (Da)	PDI	Molecular weight change (%)	Yield (%)
PLLA-pre	4,143	1:0	3	4,229	1.16	2.076	54
P-CDI3	7,396	1:0.5	3	8,975	1.26	21.35	64
P-CDI4	4,033	1:1	3	5,082	1.22	26.01	39
P-CDI5	4,033	1:2	3	5,304	1.25	31.52	44
P-CDI6	4,033	1:3	3	5,835	1.27	44.68	37
P-CDI7	4,033	1:4	3	6,074	1.28	50.61	38
P-CDI8	6,839	1:6	3	9,689	1.31	41.67	23
P-CDI9	5,928	1:8	3	10,545	1.25	77.88	20
P-CDI10*	4,962	1:10	3	10,620	1.33	106.8	25
P-CDI11	4,143	1:5	0.5	6,070	1.27	46.51	46
P-CDI12	4,769	1:5	1	7,183	1.32	50.62	58
P-CDI13	4,769	1:5	5	7,940	1.28	66.49	32
P-CDI14	4,769	1:5	10	5,510	1.30	15.54	6.2
P-CDI15	5,626	1:5	20	5,972	1.23	6.150	10
PLLA-pre	20,909	1:0	3	20,022	1.59	-4.242	79
P-CDI16	22,400	1:10	3	17,020	1.18	-24.02	64
P-CDI17	10,277	1:10	3	9,853	1.44	-4.126	65
P-CDI18	10,277	1:20	3	11,090	1.42	7.911	59
P-CDI19	7,314	1:25	3	13,629	1.43	86.34	45
P-CDI20	10,277	1:30	3	13,014	1.37	26.63	45

\* The value shown was averaged from 2 sets of experiments. In the first synthesis of P-CDI10\*, starting molecular weight of PLLA prepolymer was 4,620 Da after reacting with CDI molecular weight of PLLA increased by 9,934 Da (molecular weight change as 115.0%). In the second synthesis of P-CDI10\*, starting molecular weight of PLLA prepolymer was 5,664 Da after reacting with CDI molecular weight of PLLA increased by 11,307 Da (molecular weight change as 99.63%).





**Scheme 4.5** Fragmentation of PLLA by the abstraction of proton by imidazole at the methyl group in the unit adjacent to the newly formed carbonate bond

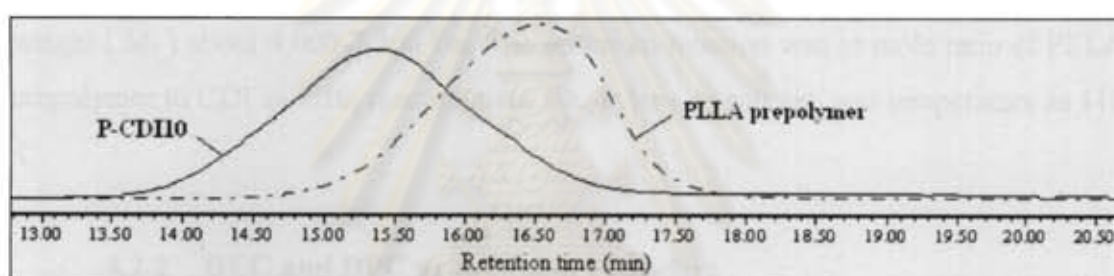


**Scheme 4.6** Fragmentation of PLLA by the abstraction of proton by imidazole at the methyl group in the lactic acid repeat unit

After PLLA was reacted with CDI, the appearance of PLLA at longer reaction time (at 10-20 h) before precipitation gave more viscous product, presumably because at long reaction time, there was a longer amount of salt of PLLA with imidazole formed in the reaction (Scheme 4.7).



**Scheme 4.7** Formation of PLLA salt with imidazole



**Figure 4.5** GPC chromatogram of P-CDI10 (after chain extension) and PLLA prepolymer (before chain extension)

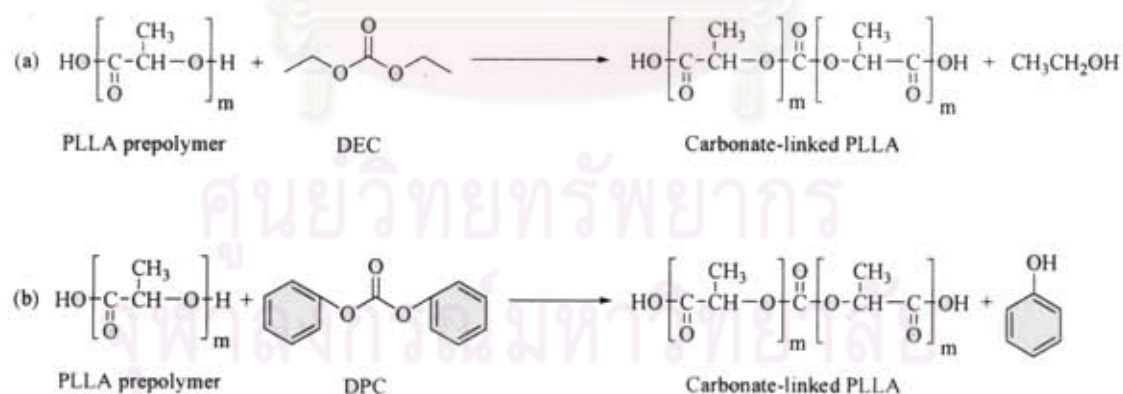
A comparison between GPC chromatograms of P-CDI10 and PLLA prepolymer was made in Figure 4.5. The shape of chromatogram of the prepolymer shows some tailing to the left but, after reacting with CDI, its shape became more symmetrical. The result suggests that the low molecular weight PLLA chains reacted with the CDI more than did the high molecular weight ones.

Moreover, the decrease of molecular weight of PLLA may be because PLLA chain was thermally self-degraded during the reaction. This result agrees with the previous research by Li and co-worker [58]. They reported the synthesis of PLA-co-PGMA copolymer performed in xylene as solvent at a reaction time of 5 h and temperature of 70 °C. The starting number-average molecular weight ( $\bar{M}_n$ ) of PLA was 70,000 Da but after the synthesis of PLA-co-PGMA copolymer, the molecular weight of copolymer decreased to 42,000 Da through self degradation.

The chain extension by CDI of PLLA prepolymer having number-average molecular weight ( $\bar{M}_n$ ) in the range of 10,000-22,000 Da was also studied (Table 4.3). The condition used was the optimum condition for low molecular weight prepolymer; i.e. the mole ratio of PLLA:CDI was 1:10, and the reaction was carried out in xylene at 110 °C for 3 h. It was found that the number-average molecular weight of PLLA in range of 10,000-22,000 Da after reacting with CDI was decreased at this condition. It may be because the starting molecular weight of PLLA prepolymer was very high. The probability of the chain end reacting with CDI became so low, that the fragmentation of PLLA by imidazole became the main reaction.

From all of the results, it can be concluded that chain extension by CDI was achieved only for the PLLA prepolymer with starting number-average molecular weight ( $\bar{M}_n$ ) about 4,000-7,300 Da. The optimum reaction was at mole ratio of PLLA prepolymer to CDI as 1:10, reaction time 3 h, xylene as solvent, and temperature as 110 °C.

#### 4.2.2 DEC and DPC as the chain extenders



**Scheme 4.8** Chain extension reaction by using DEC (a) and DPC (b) as chain extender which two hydroxyl group of PLLA chains joined

Scheme 4.9 shows the coupling reactions between two PLLA prepolymer chains and DEC (Scheme 4.8a) and DPC (Scheme 4.8b). Table 4.4 shows influence of chain extender to chain extension on molecular weight change of PLLA in the

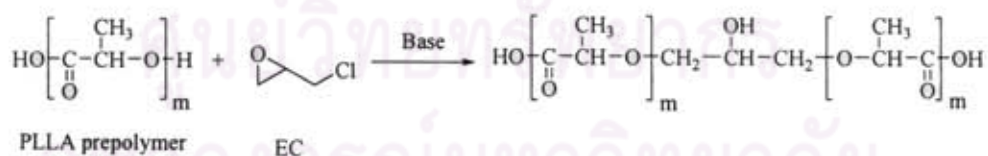


presence of DEC and DPC as chain extender. It was found that both DEC and DPC was able to increase the molecular weight of PLLA by only 8% (P-DEC and P-DPC). At the same reaction condition, the molecular weight of PLLA increased by CDI was higher than those by DEC and DPC. It was likely that imidazole (from CDI) was a better leaving group than ethoxide (from DEC) and phenoxide (DPC) ions.

**Table 4.4** Chain extension on molecular weight change of PLLA in the presence of DEC and DPC as chain extender; mole ratio of PLLA prepolymer/chain extender (1:5), solvent:xylene, T = 110 °C, reaction time 3 h

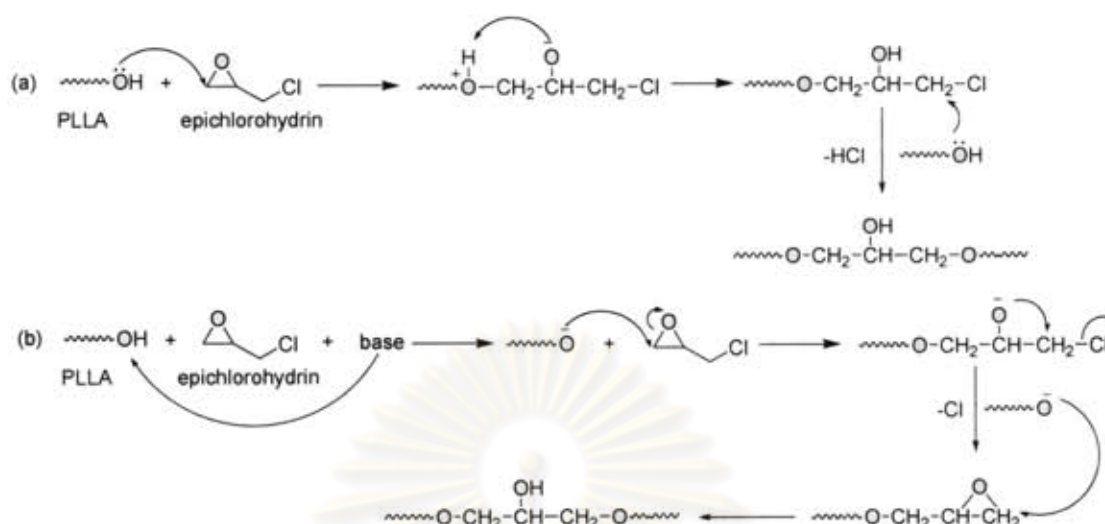
Sample code	Before reaction with chain extender		After reaction with chain extender			
	$\overline{M}_n$ of PLLA prepolymer (Da)	Chain extender	$\overline{M}_n$ of PLLA (Da)	PDI	Molecular weight change (%)	Yield (%)
P-DEC	4,620	DEC	4,999	1.24	8.203	71
P-DPC	4,620	DPC	5,013	1.24	8.506	73

#### 4.2.3 EC as the chain extender



**Scheme 4.9** Chain extension by using EC as chain extender which two hydroxyl end group of PLLA chains joined





**Scheme 4.10** Mechanism of chain extension of PLLA prepolymer with EC by joining two hydroxyl end group of PLLA chains; (a) no added base and (b) with added base

Scheme 4.8 shows chain extension of PLLA prepolymer by EC. Without a base, the reaction proceeded and produced HCl as a by-product that might have retarded reaction (Scheme 4.10a). Therefore a basic compound is added to achieve higher yield and faster reaction rate (Scheme 4.10b). Table 4.5 shows the effect of the added base on chain extension reaction. It was found that if no base was added, the molecular weight of PLLA was increased by only 8% (P-EC1). When an appropriate base was added, molecular weight of PLLA was increased by up to 30% (P-EC2), as expected by the mechanism show in Scheme 4.10b, in which the alkoxide ion was more reactive than the hydroxyl group. Sodium carbonate ( $\text{Na}_2\text{CO}_3$ ) was found to be a more effective catalyst than pyridine (18%) (P-EC3), whereas sodium bicarbonate ( $\text{NaHCO}_3$ ) and calcium carbonate ( $\text{CaCO}_3$ ) were ineffective when the mole ratio of PLLA:EC:base was 1:3:3. It should be noted that among all of base tested only pyridine was soluble in the reaction mixture.

**Table 4.5** Influence of base on molecular weight change of PLLA in the presence of EC as chain extender using xylene as solvent,  $T = 110\text{ }^{\circ}\text{C}$ , reaction time 3 h

Sample code	Before reaction with EC			After reaction with EC			
	$\bar{M}_n$ of PLLA prepolymer (Da)	Mole ratio of PLLA prepolymer /EC/ base	base	$\bar{M}_n$ of PLLA (Da)	PDI	Molecular weight change (%)	Yield (%)
P-EC1	7,058	1:5:0	-	7,592	1.18	7.566	77
P-EC2	6,552	1:3:3	$\text{Na}_2\text{CO}_3$	8,508	1.18	29.85	20
P-EC3	6,925	1:3:3	pyridine	8,176	1.24	18.06	25
P-EC4	6,552	1:3:3	$\text{NaHCO}_3$	6,856	1.20	4.640	57
P-EC5	6,552	1:3:3	$\text{CaCO}_3$	6,508	1.17	-0.672	59

Table 4.6 shows the influence of mole ratio of PLLA:EC: $\text{Na}_2\text{CO}_3$  and reaction time on molecular weight change of PLLA in the presence of EC as chain extender. The mole ratio of PLLA:EC: $\text{Na}_2\text{CO}_3$  was varied (keeping the ratio of EC: $\text{Na}_2\text{CO}_3$ ) from 1:0.5:0.5 to an excess of EC and base. It was found that molecular weight increase of PLLA at 30% (P-EC2, Table 4.5) was already at the optimum (mole ratio of PLLA:EC: $\text{Na}_2\text{CO}_3$  as 1:3:3). The number dropped slightly to 28 (P-EC8) and 23% (P-EC9) when mole ratio of PLLA:EC: $\text{Na}_2\text{CO}_3$  was increased as 1:5:5 and 1:8:8, respectively.

**Table 4.6** Influence of mole ratio of PLLA:EC:Na<sub>2</sub>CO<sub>3</sub> and reaction time on molecular weight change of PLLA using xylene as solvent, T = 110 °C

Sample code	Before reaction with EC			After reaction with EC			
	$\bar{M}_n$ of PLLA prepolymer (Da)	Mole ratio of PLLA/EC /Na <sub>2</sub> CO <sub>3</sub>	Rxn time (h)	$\bar{M}_n$ of PLLA (Da)	PDI	Molecular weight change (%)	Yield (%)
P-EC6	5,760	1:0.5:0.5	3	6,815	1.16	18.32	43
P-EC7	6,552	1:1:1	3	7,603	1.18	16.04	50
P-EC2	6,552	1:3:3	3	8,508	1.18	29.85	20
P-EC8	6,300	1:5:5	3	8,086	1.18	28.35	28
P-EC9	6,693	1:8:8	3	8,225	1.17	22.89	31
P-EC10	5,921	1:3:3	5	8,254	1.17	39.40	37
P-EC11	5,928	1:3:3	7	8,368	1.19	41.16	36
P-EC12	7,396	1:3:3	10	10,716	1.23	44.89	53
P-EC13	6,552	1:3:1.5	3	7,502	1.18	14.50	39
P-EC14	5,664	1:3:5	3	7,379	1.15	30.28	35
P-EC15	5,928	1:3:5	5	8,335	1.20	40.60	32
P-EC16	5,664	1:3:7	5	8,101	1.19	43.03	17
P-EC17	7,396	1:3:10	5	8,357	1.24	12.99	19
P-EC18	20,361	1:5:5	3	22,854	1.57	12.24	69
P-EC19	18,073	1:3:3	5	23,262	1.53	28.71	65
P-EC20	20,216	1:3:7	5	21,610	1.51	6.895	64

In the sample P-EC2, P-EC10, P-EC11, and P-EC12, the reaction time was varied as 3, 5, 7, and 10 h for the reaction having the reagent content of 1:3:3 (Table

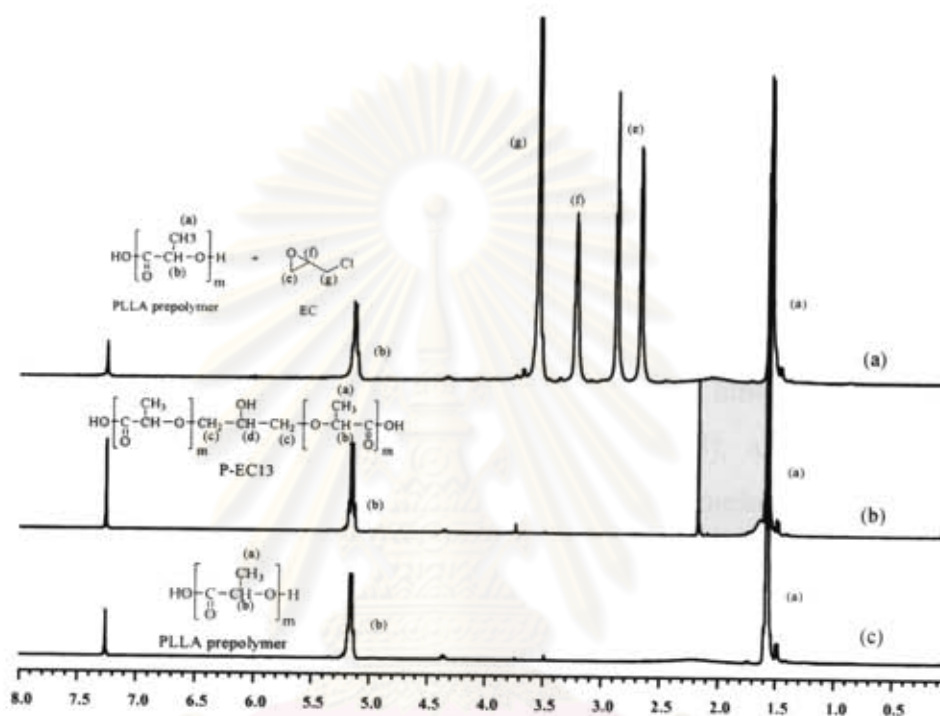


4.6). As a result, the molecular weight of PLLA was increased with increasing the reaction time. At the long reaction time, the chance for PLLA chain to react with EC would increase too. At 10 h, the molecular weight was increased by up to 45% (P-EC12). Moreover, attempts on increasing the base content in the reaction from 5 to 10 times of PLLA were also carried out (sample P-EC15 to P-EC17, Table 4.6). The optimum base amount was achieved in sample P-EC16 (1:3:7), in which the molecular weight increase was 43% with rather low yield of only 17%. Therefore, the mole ratio PLLA:EC:Na<sub>2</sub>CO<sub>3</sub> of 1:3:3, longer reaction time up to 10 h seemed to give the better condition for the chain extension of PLLA by EC in the presence of Na<sub>2</sub>CO<sub>3</sub> base, in which the best ratio of EC:Na<sub>2</sub>CO<sub>3</sub> was later found to be at 3:7 after 5 h of reaction time (P-EC16). When the base content was increased to 10 times of the PLLA, the molecular weight increase was only 13% (P-EC17). It was possible that the based-catalyzed hydrolysis of PLLA chain occurred with the excess amount of base combined with trace amount of MeOH or H<sub>2</sub>O in the reaction mixture.

Finally, *high* molecular weight PLLA prepolymer ranging from 18 to 20 kDa were also studied (Table 4.6). In general, the molecular weight increases were moderate at 7 to 29% for the reaction carried out for 3-5 h. It was possible that at high Na<sub>2</sub>CO<sub>3</sub> content, the chance of Na<sub>2</sub>CO<sub>3</sub> subtracting a proton of the methyl group in lactide unit became high. Therefore, the fragmentations of PLLA could have occurred competitively.

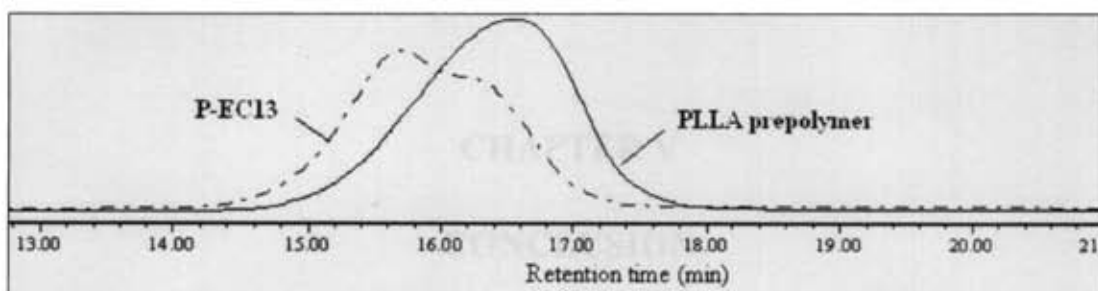
Figure 4.6 shows the <sup>1</sup>H NMR spectra of PLLA prepolymer with EC, P-EC16 (after reacting with EC), and PLLA prepolymer (before reacting with EC). The proton signals at 1.58 and 5.18 ppm were assigned to methyl and methine protons of the lactide unit, respectively (Figure 4.6c). The signal at 4.33 ppm was assigned to the methine protons of PLLA chain end. For EC, the proton signals of unreacted EC were found at 2.67 and 2.89 ppm (-CH<sub>2</sub>- in epoxide ring), 3.23 ppm (-CH-), and 3.55 ppm (-CH<sub>2</sub>-) (Figure 4.6a). For reacted EC, the methine signal (CH-OH) would show up at 3.87, the methylene signal (-CH<sub>2</sub>-O) would shift to 3.52 ppm. Analysis of sample P-EC16 (the resulting product of PLLA and EC) revealed that not a single peak of reacted and unreacted EC was found in the product (Figure 4.6b). The disappearance of unreacted EC suggested that it was completely removed from the polymer product. But the missing signal of reacted EC was somewhat surprising. It was possible that the

mole ratio of EC in the overall product was too low to be detected by NMR method. Also a number of unreacted PLLA remained in the product as reported earlier that the molecular weight of resulting PLLA was only 43%.



**Figure 4.6**  $^1\text{H}$  NMR spectrum (in  $\text{CDCl}_3$ ) of PLLA prepolymer with EC(a), P-EC16 (after reacting with EC) (b), and PLLA prepolymer (before reacting with EC) (c)

Figure 4.7 shows GPC chromatogram of P-EC16 and PLLA prepolymer. It was found that chromatogram of P-EC16 was splitted to two peaks. It suggests that during the reaction with EC, different molecular weight of PLLA prepolymer reacted with EC.



**Figure 4.7** GPC chromatogram of P-EC16 and PLLA prepolymer

In addition, high molecular weight PLLA prepolymer was studied (Table 4.6). It was found that at the mole ratio PLLA:EC:Na<sub>2</sub>CO<sub>3</sub> of 1:3:3 and reaction time of 5 h, the molecular weight of PLLA was increased by up to 29% (P-EC19), but when used the mole ratio PLLA:EC:Na<sub>2</sub>CO<sub>3</sub> of 1:5:5 and the reaction time of 3 h, the molecular weight of PLLA was increased by only 12% (P-EC18), and at the mole ratio PLLA:EC:Na<sub>2</sub>CO<sub>3</sub> of 1:3:7 and reaction time of 5 h, the molecular weight of PLLA was increased by only 7%. It was possible that at high Na<sub>2</sub>CO<sub>3</sub> content, the chance of Na<sub>2</sub>CO<sub>3</sub> subtracting a proton of the methyl group in lactide unit became high. Therefore, the fragmentations of PLLA would have competitively occurred.

From the result, the molecular weight of PLLA could not be doubled from the ring-opening reaction of EC. It was possible that the added base in the reaction mixture withdrew the proton from the hydroxyl end group (-OH) of PLLA to make it more reactive enough to cause transesterification of PLLA chains. In addition, the added base could subtract a proton of the methyl group in lactide unit, causing chain fragmentation. Accordingly, molecular weight increase of PLLA by these processes was limited.



## CHAPTER V

### CONCLUSION

#### 5.1 Conclusions

Chain extension methods were investigated as a way to increase the molecular weight of PLLA, biodegradable and biocompatible polyester. The concept of chain extension was to use a 'coupling agent' to join two polymer chains via the terminal hydroxyl group in each chain, subsequently increase the molecular weight. Four types of coupling agents were studied: diethyl carbonate, diphenyl carbonate, 1,1'-carbonyl diimidazole, and epichlorohydrin. It was found that among the coupling agents studied here, CDI was the most effective chain extender. The molecular weights of PLLA with  $\overline{M}_n$  of 4,000 to 7,300 Da could be increased by as high as 107% (slightly more than double in length) by CDI, in the case when the mole ratio of PLLA to CDI was 1:10 at the reaction temperature of 110 °C for 3 h. DPC and DEC had low reactivity for chain extension of PLLA. They only resulted in about 8% increase of molecular weight whereas up to 56% increase was observed for CDI at the condition where PLLA:coupling agent was 1:5. For the epoxide derivative, EC provided up to 45% increase of PLLA molecular weight in the reaction when the mole ratio of PLLA:EC:Na<sub>2</sub>CO<sub>3</sub> was 1:3:3 at the reaction time 10 h.

It was however observed that chain fragmentation took place during the reaction with the coupling agent as well, especially when the molecular weight ( $\overline{M}_n$ ) of the starting PLLA was more than 10,000 Da. In the case of CDI, imidazole by-product could possibly cause chain cleavage by subtracting protons from the repeating units of PLLA, which subsequently led to cleavage at the ester and the newly formed carbonate bonds. Another explanation for failed attempts in the chain extension of high molecular weight PLLA was that the longer the polymer was, the lower probability of successful

reactions between the terminal hydroxyl groups of polymer and the coupling agents became.

## 5.2 Future Direction

Other types of phosgene derivatives that could behave similarly to CDI could be attempted as potential chain extenders. Although phosgene derivatives exhibit reactive chain extender, the toxicity of these reagents should also be cautiously considered.



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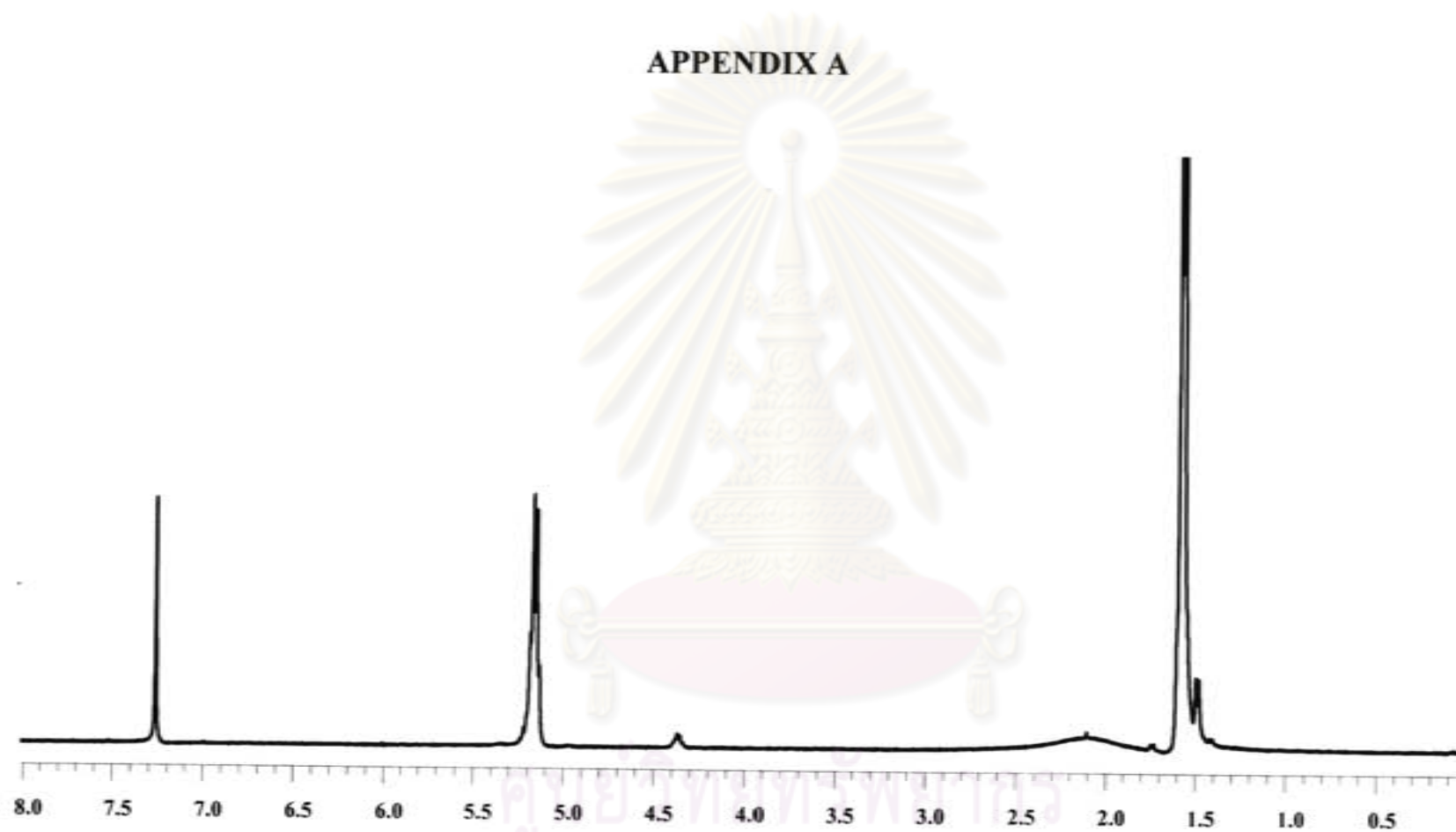


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**Figure A-1**  $^1\text{H}$  NMR spectrum of PLLA in  $\text{CDCl}_3$

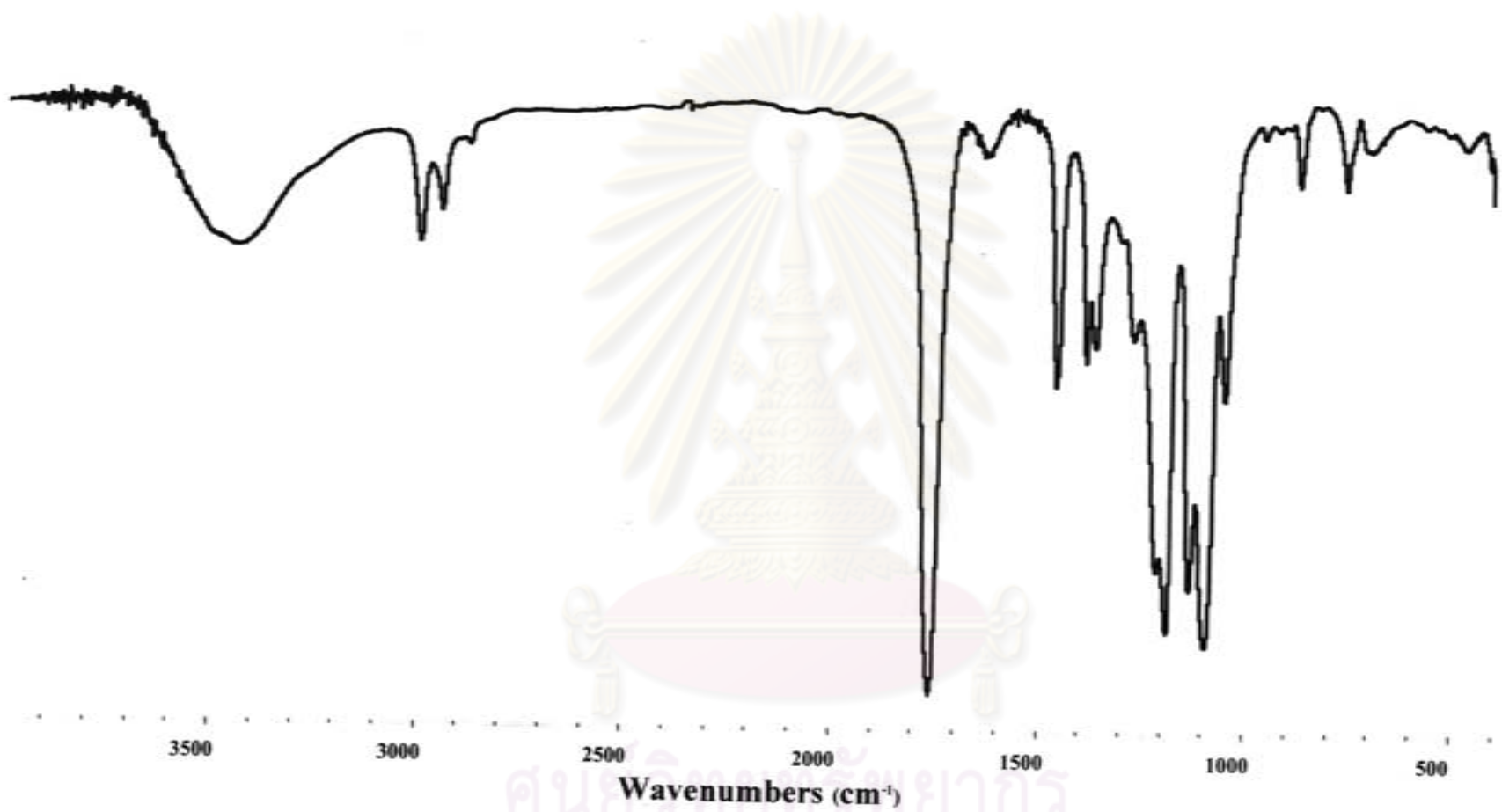


Figure A-2 FTIR spectra of PLLA

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October 7-8, 2010    Poster presentation with proceeding in The 1<sup>st</sup> Polymer Conference of Thailand, Convension Center, Chulabhorn Research Institute, Bangkok.

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