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DIRECT SYNTHESIS OF LACTIDE FROM LACTIC ACID

Miss Kullapornphat Boonpok

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Thesis title	DIRECT SYNTHESIS OF LACTIDE FROM LACTIC ACID
By	Miss Kullapornphat Boonpok
Field of Study	Petrochemistry and Polymer Science
Thesis Advisor	Assistant Professor Yongsak Sritana-anant, Ph.D.
Thesis Co-advisor	Assistant Professor Varawut Tangpasuthadol, Ph.D.

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

……………………………….Dean of the Faculty of Science
(Professor Supot Hannongbua, Dr.rer.nat.)

THESIS COMMITTEE

....Chairman
(Professor Pattarapan Prasassarakich, Ph.D.)

....Thesis Advisor
(Assistant Professor Yongsak Sritana-anant, Ph.D.)

....Thesis Co-advisor
(Assistant Professor Varawut Tangpasuthadol, Ph.D.)

……………………………….Examiner
(Associate Professor Mongkol Sukwattanasinitt, Ph.D.)

……………………………….External Examiner
(Assistant Professor Khamphee Phomphrai, Ph.D.)

กุลพรภัสร์ บุญปก : การสังเคราะห์แล็กไทด์โดยตรงจากกรดแล็กทิก (DIRECT SYNTHESIS OF LACTIDE FROM LACTIC ACID) อ. ที่ปรึกษาวิทยานิพนธ์หลัก : ผศ.ดร. ยงศักดิ์ ศรีธนาอนันต์, อ. ที่ปรึกษาวิทยานิพนธ์ร่วม: ผศ.ดร. วราวุฒิ ตั้งพสุธาดล, 56 หน้า

ได้ทำการสังเคราะห์แล็กไทด์โดยตรงจากกรดแล็กทิก 3 วิธี วิธีแรกได้สังเคราะห์แล็กไทด์แต่ไม่สามารถกลั่นผลิตภัณฑ์ออกมาได้ด้วยไอน้ำ การเติม โทลูอีนมิได้ช่วยให้กระบวนการดีขึ้นโดยปริมาณแล็กไทด์สูงสุดที่ได้จาก วิธีนี้คือ 3 % วิธีที่สองใช้ซิลิกาเจลเป็น ตัวเร่งปฏิกิริยาที่มีความสามารถในการกำจัดน้ำ โดยได้ศึกษา ผ่านการสกัดให้ตัวทำละลายที่เดือด และการอบให้ความร้อนแก่กรดแล็กทิกและซิลิกาเจล พบว่าปริมาณแล็กไทด์สูงสุดที่ได้คือ 9 % เมื่อให้ความร้อนแก่กรดแล็กทิกและซิลิกาเจล ในสัดส่วน 1:1 ในโทลูอีน ที่อุณหภูมิรีฟลักซ์ เป็นเวลา 12 ชั่วโมง วิธีที่สาม เป็นการสังเคราะห์แล็กไทด์ แล้วแยกผลิตภัณฑ์ โดยวิธีการกลั่นลดความดัน ในขั้นตอนเดียวโดยใช้ตัวเร่งปฏิกิริยา ที่เป็น กรดหรือโลหะ ซึ่งจากการทดลองพบว่าแมกนีเซียมซัลเฟตเป็นตัวเร่งปฏิกิริยาที่มีประสิทธิภาพดีที่สุด ในการ สังเคราะห์แล็กไทด์ โดยกลั่นลดความดันที่อุณหภูมิ 180-200 องศาเซลเซียส ระยะเวลา 1 ชั่วโมง ได้ผลิตภัณฑ์ที่มีความบริสุทธิ์ในปริมาณ 20 % วิธีนี้สามารถผลิตแล็กไทด์ได้โดยไม่ต้องมีขั้นตอนการแยกและทำสารให้บริสุทธิ์หลังการผลิตมากนัก

สาขาวิชา ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์ ลายมือชื่อนิสิต……………….……………...……...
ปีการศึกษา……………2554……………....ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก…...…...……..
ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม……………...

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KEYWORDS: LACTIC ACID / LACTIDE / DIRECT SYNTHESIS / REDUCED PRESSURE DISTILLATION

KULLAPORNPHAT BOONPOK: DIRECT SYNTHESIS OF LACTIDE FROM LACTIC ACID. THESIS ADVISOR: ASST. PROF. YONGSAK SRITANA-ANANT, Ph.D., CO-ADVISOR: ASST. PROF. VARAWUT TANGPASUTHADOL, Ph.D., 56 pp.

L-lactide was directly synthesized from L-lactic acid solution through 3 methods. In the first method, L-lactide was synthesized under steam distillation, but could not be isolated via steam distillation. Addition of toluene did not improve the process. The highest yield of L-lactide from this method was 3 %. In the second method, silica gel was used as dehydrating catalyst. The extraction with boiling solvent and baking L-lactic acid with silica gel were investigated. The highest yield of lactide was 9 % when 1:1 ratio of L-lactic acid and silica gel were boiled in toluene at reflux for 12 hours. In the third method, L-lactide was synthesized and isolated via the reduced pressure distillation in the presence of acid or metal catalyst. Magnesium sulfate was found to be the most effective catalyst for L-lactide production, giving pure product in 20 % yield at distillation temperature of 180-200 °C for 1 h. This simple method enables the production of L-lactide without numerous subsequent separation and purification steps.

Field of Study: Petrochemistry and Polymer Science Student's Signature…………….
Academic Year: …………2011…………………..... Advisor's Signature……………
Co-advisor's Signature…………

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LIST OF ABBREVIATION

ROP : Ring-opening polymerization

PC : Polycondensation

PLA : Polylactic acid or polylactide

PLLA : Poly(L-lactide)

PDLA : Poly(D-lactide)

PDLLA : Poly(DL-lactide)

M_w : Weight-average molecular weight

GC : Gas Chromatography

FID : Flame Ionization Detector

NMR : nuclear magnetic resonance spectroscopy

$CDCl_3$: deuterated chloroform

TMS : tetramethylsilane

min : minute

mL : milliliter

ppm : parts per million (unit of chemical shift)

CHAPTER I
INTRODUCTION

1.1 Statement of Problem

Poly(lactic acid) or polylactide (PLA) is one of the most well-known biodegradable and bioabsorbable polymer. It is an attractive raw material which produced from renewable resources, such as corn, potato, garbage and other agricultural products. Because of its good properties, such as mechanical strength, transparency, compostability and safety, the use of PLA in medical, pharmaceutical, and environmental applications has been rapidly increasing over the past two decades.

There are two generally methods for PLA synthesis. The first method is polycondensation of lactic acid. The other method which is currently produced commercially high molecular weight PLA polymer is ring-opening polymerization of lactides (ROP). The key step of PLA production is to prepare high purity monomer.

Lactide is a cyclic dimer of lactic acid which is an intermediate in PLA production. It has three separable optical isomers: the meso-, D-, and L-lactides. For the production of polymers, L- and D, L-lactide (The racemic 1:1 mixture of L and D is generally called D, L-lactide) are used almost exclusively [1]. A Previous research on lactide production has focused on thermal degradation (depolymerisation) of PLA to obtain lactide. This process is in fact comprise many reaction steps a multistep including the self-esterification of lactic acid by heating and driving off water under vacuum to obtain a pre-polymer. Tin compound is then added as catalyst in thermal depolymerisation to obtain lactide. The tin catalyst performed best compared to other catalysts and showed the lowest levels of racemization. Tin octoate (stannous 2-ethylhexanoate) is the most effective catalyst [2]. However, the lactide production by thermal depolymerisation of PLA is considered to be difficult and rather complex.

In this research, therefore, focused on the attempts to produce L-lactide directly from L-lactic acid in one step procedure. Three methods: steam distillation, adding dehydrating catalysts (silica gel), and distilling off the product at reduced pressure using various acid catalysts were investigated. All three methods postulated the concept of the direct condensation of L-lactic acid and concurrent removal of the L-lactide product out of the equilibrium among various oligomers of L-lactic acid.

1.2 Objective

Investigate the production of L-lactide directly from L-lactic acid in one pot reaction by three methods. Steam distillation, adding dehydrating catalysts (silica gel) and distilling off the product at reduced pressure using various acid catalysts were studied here. The effects of reaction temperature and type and amount of catalysts on the yields of L-lactide were investigated as the major parameters.

1.3 Scope of Investigation

1. Synthesis of L-lactide directly from L-lactic acid in one step by three methods: steam distillation, adding dehydrating catalysts (silica gel) and distilling off the product at reduced pressure using acid catalysts.
2. The catalysts of L-lactide production were silica gel (column chromatography grade), PTSA, Li_2SO_4, Na_2SO_4, $MgSO_4$, Mg-lactate, $FeSO_4$, $CuSO_4$, $ZnSO_4$, Zn-lactate, $SnCl_4$, Sb_2O_3, eicosane and hexatriacontane.
3. The effects of reaction temperature and type of catalysts on the yields of L-lactide were two major parameters.
4. The amount and the purity of L-lactide were analyzed using gas chromatography (GC) and nuclear magnetic resonance spectroscopy (NMR).

CHAPTER II

THEORY AND LITERATURE REVIEW

2.1 Lactic acid

Lactic acid (2-hydroxypropionic acid), CH_3-CHOHCOOH, is a naturally occurring organic acid that can be produced by chemical synthesis or fermentation. In contrast to other acids, lactic acid is nonvolatile, odorless, and colorless and has a mild acidic taste (Table 2.1)

Table 2.1 Physical Properties of Lactic acid [2]

Property	Value
CAS number	General: 50-21-5 (S)-Lactic acid: 79-33-4 (R)-Lactic acid: 10326-41-7
Molecular weight (g/mol)	90.08
Formula	$C_3H_6O_3$
Melting point (°C)	18(racemic) 53(chiral pure)
Crystal structure	(S)-Lactic acid
Solid density (g/mL)	1.33 (solid, 20°C)
Liquid density(g/mL, 20°C)	1.186 (80.8% solution in water)
Solubility in water (wt %)	86 (20°C, monomeric (S)-lactic acid)
Boiling point (°C)	122 (at 14 mmHg)
Viscosity (mPas)	28.5 (85.3% solution in water)
pK_a	3.86

Recently, the fermentative production of lactic acid has increased due to the prospects of environmental friendliness and of using renewable resources such as potato, cane, cassava, whey and barley. During fermentation, a suitable carbohydrate is converted to lactic acid by microorganisms. The chemical structure of lactic acid contains an asymmetric carbon atom or a chiral carbon, thus it has two optically active enantiomers, namely L(+)- and D(-)- forms (Figure 2.1). The L(+)-form is the natural and most common form of lactic acid, but D(-)- form can also be produced by microorganisms or through racemization [4].

Figure 2.1 Two enantiomeric forms of lactic acid: L(+)- and D(-)-lactic acid.

2.2 Poly(lactic acid) or polylactide (PLA)

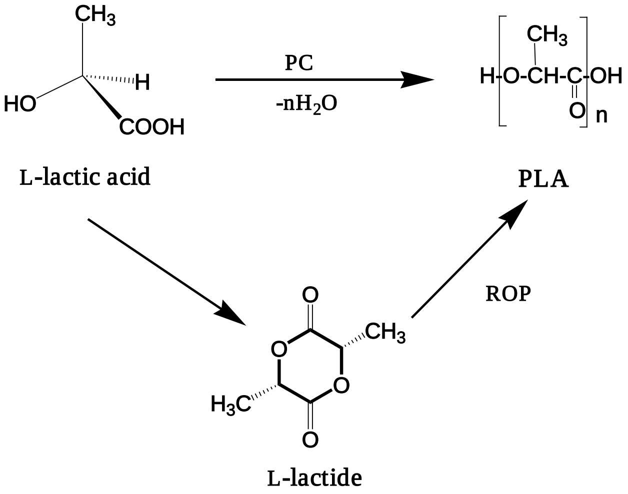
Poly(lactic acid) or Polylactide (PLA) is a well-known biodegradable aliphatic polyester which have become very important material due to the combination of their bioresorbable, biocompatible, biodegradable and mechanical properties such as mechanical strength and transparency. PLA is an attractive thermoplastic material because it can be derived from renewable resources such as potato, corn, and other agricultural products. PLA can degrade back to lactic acid which is a non toxic and naturally occurring metabolite through hydrolysis of ester bond without the need for enzyme catalysis. End uses of PLA are in rigid packaging, flexible film, cold drink cups, cutlery, and bottles. Moreover, PLA is also used in biomedical application such as tissue engineering, surgical sutures, orthopedic implants, and drug delivery system [5]. From the chiral nature of lactic acid, polylactide can exist in three stereochemical forms: poly(L-lactide) (PLLA), poly(D-lactide) (PDLA), and poly(DL-lactide) (PDLLA). This stereochemical structure of PLA can be modified by copolymerization of mixtures of L-lactide and *meso*-, D-, or *rac*-lactide(50% D- and 50% L-lactide) resulting in high molecular weight amorphous or semicrystalline polymers. PLLA homopolymer which comprising only L-lactide is a semicrystalline material with the highest melting point, while PLA copolymers with higher D-isomer content exhibit lower melting points and dramatically slower crystallization behavior, until they finally become amorphous at D-contents higher than 12-15% (Table 2.2) [2,9]. Processing, crystallization, and degradation behavior of PLA all depend on the structure and composition of the polymer chains.

Table 2.2 Physical properties of PLA* [10]

Property	L-PLA	DL-PLA
Glass transition temperature (T_g)	60-65 °C	50-60 °C
Melting point (T_m)	184 °C	Amorphous
Specific gravity	1.24	1.25
Tensile strength (MPa)	55.2-82.7	27.6-41.4
Elongation (%)	5-10	3-10
Modulus (MPa)	2758-4137	1379-2758
Inherent viscosity (dl/g)	0.90-1.2	0.55-0.75

*Produced by DURECT Corporation, Birmingham Polymers, AL, USA

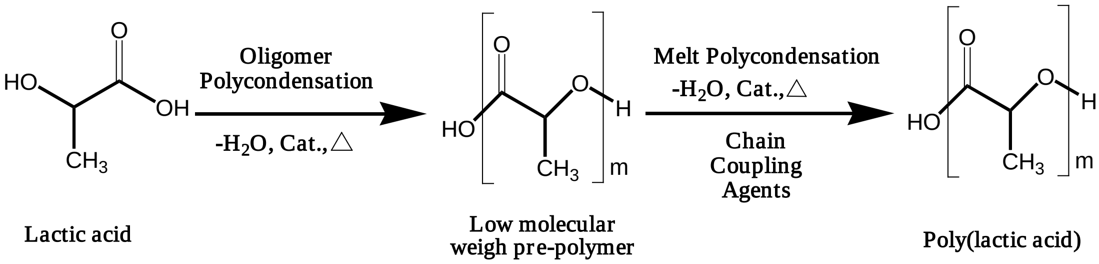
Generally, PLA can be produced by two methods, one is polycondensation (PC) of lactic acid has been known to produce low to moderate molecular weight PLA. High-molecular weight PLA is produced commercially by the ring-opening polymerization (ROP) of L-lactide, which obtained through dimerization of lactic acid (Scheme 2.1).



Scheme 2.1 Production of PLA through PC and ROP

2.2.1 Direct Condensation Polymerization

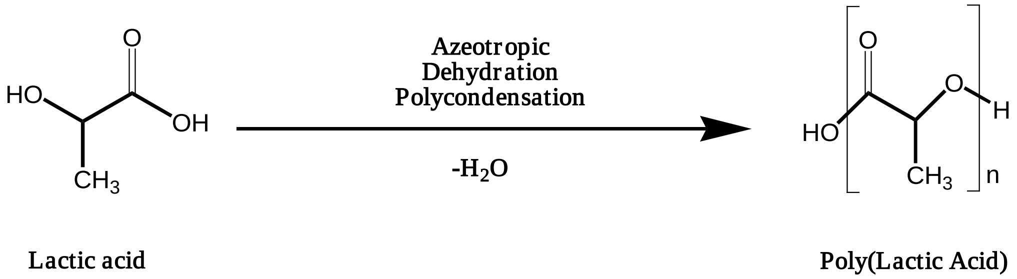
Lactic acid is polymerized in this method in the presence of a catalyst at reduced pressure for removal water produced in the condensation. Direct condensation polymerization includes bulk (solution) polycondensation and melt condensation. The polymer obtained has a low molecular weight, because it is hard to remove water completely from the highly viscous mixture as well as the equilibrium among free acid, oligomers, and the water produced. The low-molecular weight polymer is the main disadvantage of this method and it restricts its use. The condensation polymerization produce oligomers with average molecular weights several tens of thousands and other side reactions also can occur, such transesterification, resulting in the formation of ring structures as lactide. Moreover, the streoregularity cannot be controlled during the polymerization. The condensation polymerization is the least expensive route and employed only if the polymer of low molecular weight is required. However, the high-molecular weight polymer can be obtained by the use of chain coupling agents such as isocyanates, epoxides or peroxide [7]. The coupling agent joins the polymer chain of low molecular weight to the chain of high molecular weight (Scheme 2.2)



Scheme 2.2 Direct Condensation Polymerization of Poly(Lactic Acid) [12]

Direct condensation of lactic acid is carried out in three stages: removal of free water, oligomer polycondensation, and melt condensation of high molecular weight PLA. The direct condensation of lactic acid in bulk is not applied on a large scale, because of the competitive reaction of lactide formation. In the sequential melt/solid-state polycondensation, besides the three mentioned steps is utilized an additional fourth stage. The fourth stage, the melt-polycondensated PLA is cooled below its melting temperature, followed by particle formation which then subjected to a crystallization process [2]. Moon *et al.* successfully obtained high molecular weight PLA through the melt/solid polycondensation catalyzed by a tin chloride dehydrate/p-toluenesulfonic acid binary system [17-18].

The azeotropic condensation polymerization is a direct method used to obtain high molecular weight PLA without the use of chain extenders or adjuvents and associated drawbacks. In this route, the removal of water formed from the reaction medium becomes relatively easier and a higher molecular weight of the PLA is achievable (Scheme 2.3). Mitsui Chemicals (Japan) has commercialized a process wherein lactic acid and a catalyst are azeotropically dehydrated in a refluxing, high boiling, aprotic solvent under reduced pressures to obtain high molecular weight PLA ($M_w \geq 300000$) [7]. This polymerization gives considerable catalyst residues because of its high concentration needed to reach an adequate reaction rate. This can cause many drawbacks during processing, such as degradation and hydrolysis. For most biomedical applications, the catalyst toxicity is a highly sensitive issue.



Scheme 2.3 Azeotropic Dehydration Polycondensation of PLA [7]

Rahul *et al*. [47] studied the role of silica gel in polycondensation of lactic acid in organic solvent. Poly(lactic acid) was made through enzyme-catalyzed direct polycondensation in non polar solvent with the addition of silica gel. The addition of silica gel appeared to greatly enhance the lactic acid conversion (up to 98%). Further investigations, the silica gel itself was found to catalyze the polycondensation due to it has a large number of surface hydroxyl groups and an isoelectric point of about pH1 which may catalyze the reversible esterification and hydrolysis reaction, in addition to the role of water removal.

2.2.2 Ring-Opening Polymerization (ROP)

Ring-Opening Polymerization (ROP) is the most commonly route to achieve pure high molecular weight PLA due to the possibility of accurate control of the chemistry and thus varying the properties of the resulting polymers in a more controlled manner. In ROP method involves three separate steps: polycondensation of lactic acid, lactide formation, which is a cyclic dimer of lactic acid used as the monomer to synthesize PLA, and ring-opening polymerization.

The preparation of PLA by ring-opening polymerization has been carried out in the melt polymerization, bulk polymerization, solution polymerization and suspension polymerization. The ring-opening polymerization of lactides can be classified by their three different reaction mechanisms and initiator types: anionic polymerization, cationic polymerization, coordination-insertion mechanisms depending on catalyst used. The ROP of lactide requires the use of transition metal catalyst, such as tin [17, 18, 20, 36, 54], aluminum [31, 32,], zinc [28, 33, 53], bismuth [53], lithium [29], and yttrium [55]. Tin (II) 2-ethylhexanoate or stannous octoate ($Sn(Oct)_2$) is the most common used catalyst in the ring-opening polymerization of lactides (Figure 2.2). Because of its high catalytic efficiency, low toxicity, food and drug contact approval and ability to give low levels of racemization and provide high molecular weight PLA [3]. Stannous octoate is preferred for the bulk polymerization due to their solubility in molten lactide. The ROP in the presence of stannous octoate is generally thought to occur via a coordination-insertion mechanism (Scheme 2.4).

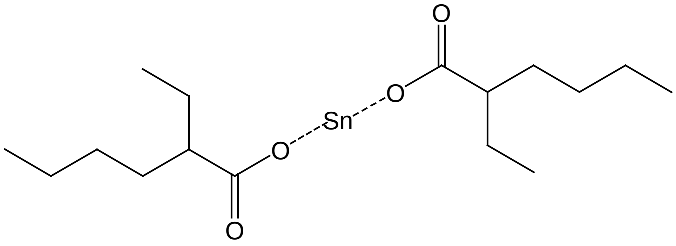
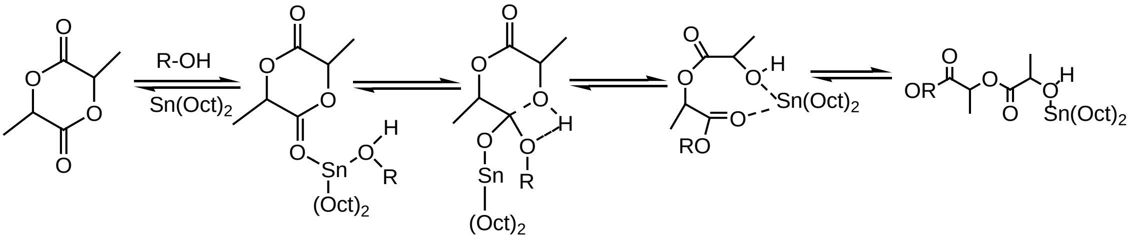


Figure 2.2 Stannous octoate ($Sn(Oct)_2$) [3]

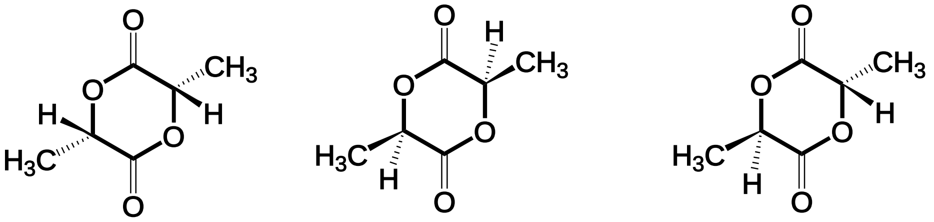


Scheme 2.4 Generalized coordination-insertion chain growth mechanism of lactide to PLA (R, growing polymer chain) [3]

To ensure a good PLA polymer with high optical purity and molecular weight to use in some specific applications such as, food packaging and medical system, the monomers must be extremely pure and essentially free of water and acids. That is, preparation of lactide monomer has become the key steps of the synthesis PLA by ring-opening polymerization method.

2.3 Lactide

Lactide (3, 6-dimethyl-1, 4-dioxane-2, 5-dione) is the common name for the cyclic di-esters of lactic acid [2]. Since lactic acid is found in two different optically active stereoisomeric forms therefore lactide is formed in three different stereoisomeric forms: L(-)-lactide (S,S), D(+)-lactide (R,R) and the optically inactive meso-lactide (R,S) (Figure 2.3). The racemic 1:1 mixture of L and D is generally called D, L-lactide. The reaction steps necessary to produce and purify these monomers are described in detail for the L-lactide. The physical and chemical properties of lactide show in Table 2.3.



L-lactide **D-lactide** **meso-lactide**

T_m=95-99 °C **T_m=95-99 °C** **T_m=53-54 °C**

Figure 2.3 Structures of Lactides [42]

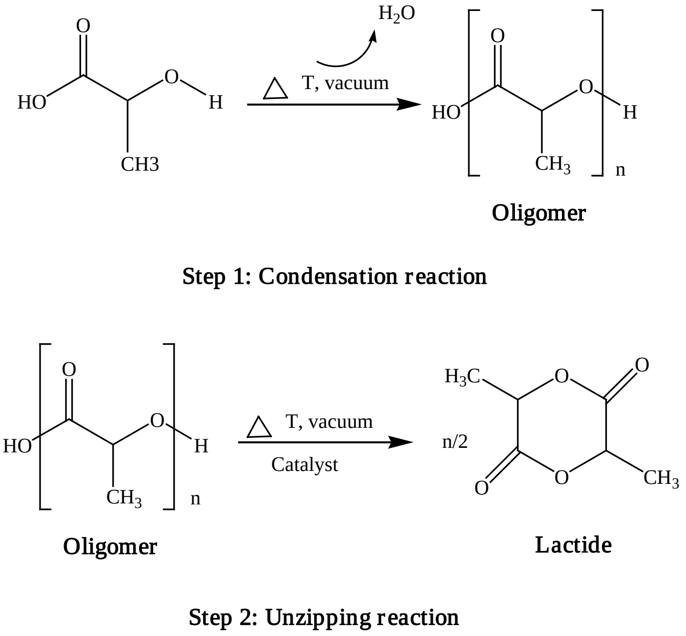
Table 2.3 Physical and chemical properties of lactide [2]

Properties	value	Isomer
Molecular weight	144.13	D
	144.13	L
	144.13	meso
Melting point (°C)	97	D
	97	L
	53	meso
Boiling point (°C)	255	L
Optical rotation in degrees	-260	L
	+260	D

Lactide is miscible with benzene, toluene, xylene, methylene chloride, chloride, chloroform, tetrahydrofuran, ethyl acetate, methanol, isopropanol, acetone, and butanone. Lactide will hydrolyze to lactic acid in water at room temperature, and the rate of hydrolysis of meso-lactide is much higher than that of D, L-lactide.

The lactide must be as pure as possible in order to be able to carry out the ring-opening polymerization leading to corresponding PLA with high molecular weights. The preparation of lactide is usually conducted in two distinct steps involving first preparing an oligomer of lactic acid, then added catalyst and heating the oligomer under reduced pressure to generate the desired lactide after the oligomer decomposes.

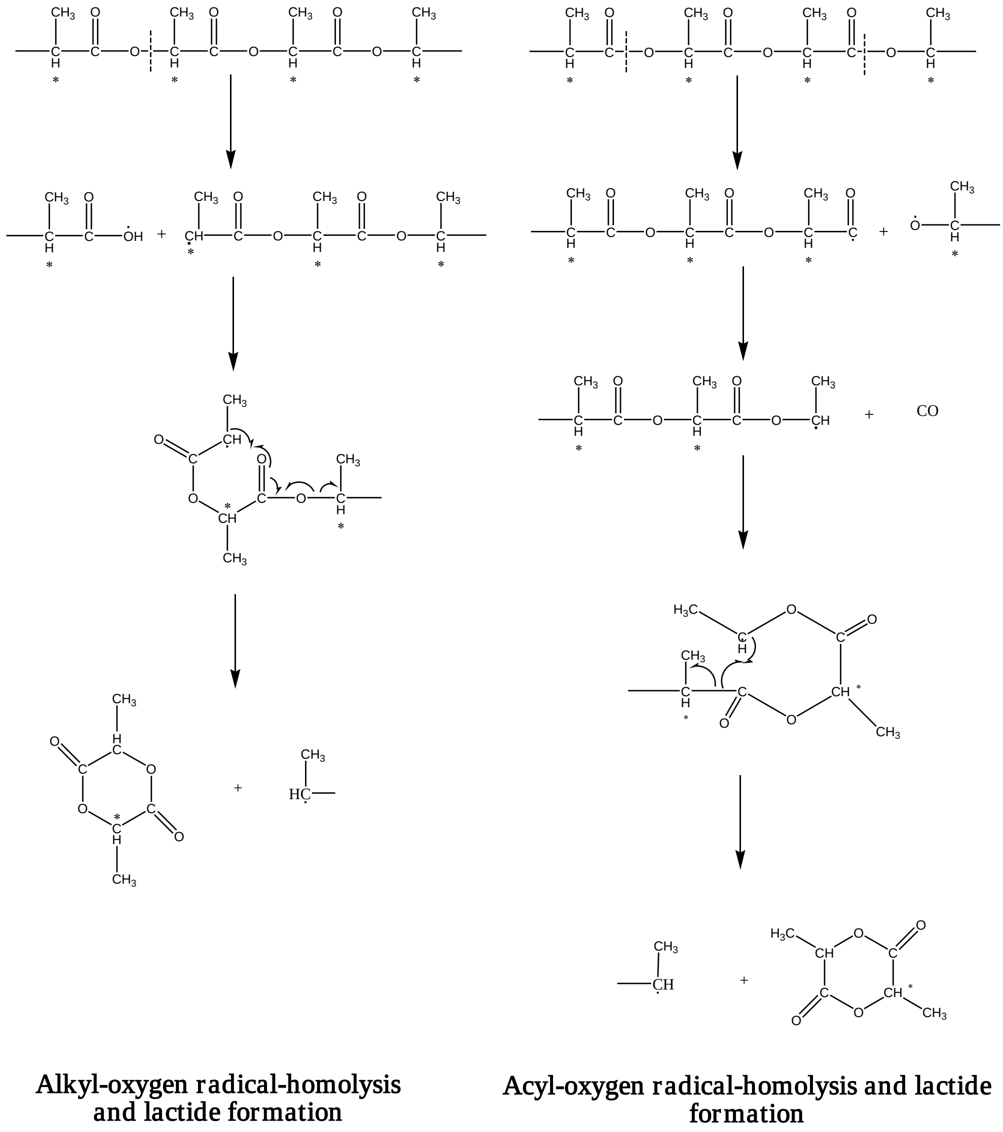
The synthesis of lactide was first described by Pelouze in 1845 [2]. He investigated the self-esterification of lactic acid by heating and driving off water and obtained a pre-polymer. He noticed that some nice crystals were formed. He gave the name “lactid” to the substance. In the past two decades, several catalyst used for lactide synthesis were reported. In 1997, Bendix [1] studied the synthesis of polylactide and its copolymers for medical applications. L-lactide production has been described in two steps: the first step in the synthesis is the direct condensation of L-lactic acid to an oligomer by the removal of water, appling heat and vacuum. The next step is a thermal unzipping reaction, metal oxide are used as a reaction catalyst in a temperature range of 200-300 °C in a good vacuum. Finally, the crude lactide was obtained and purified (Scheme 2.5).



Scheme 2.5 Synthesis of lactide [1]

Zhang *et al*. [43-44] studied the preparation of monomer of degradable biomaterial poly (L-lactide). L-lactide was prepared under the atmospheric pressure and low-pressure, including three stages. At the first stage, under the atmospheric pressure, the L-lactic acid was dehydrated at 135-150 °C for 3-4 h. At the second, under low pressure (2.5-8.0 kPa) the L-lactic acid was heated and reflowed at 150-160 °C for 2-3 h. At the third stage, under reduced pressure (0.027 kPa), stannous octoate (1% mass fraction) was used to depolymerization of oligomer (180-220 °C) to produce a lactide monomer.

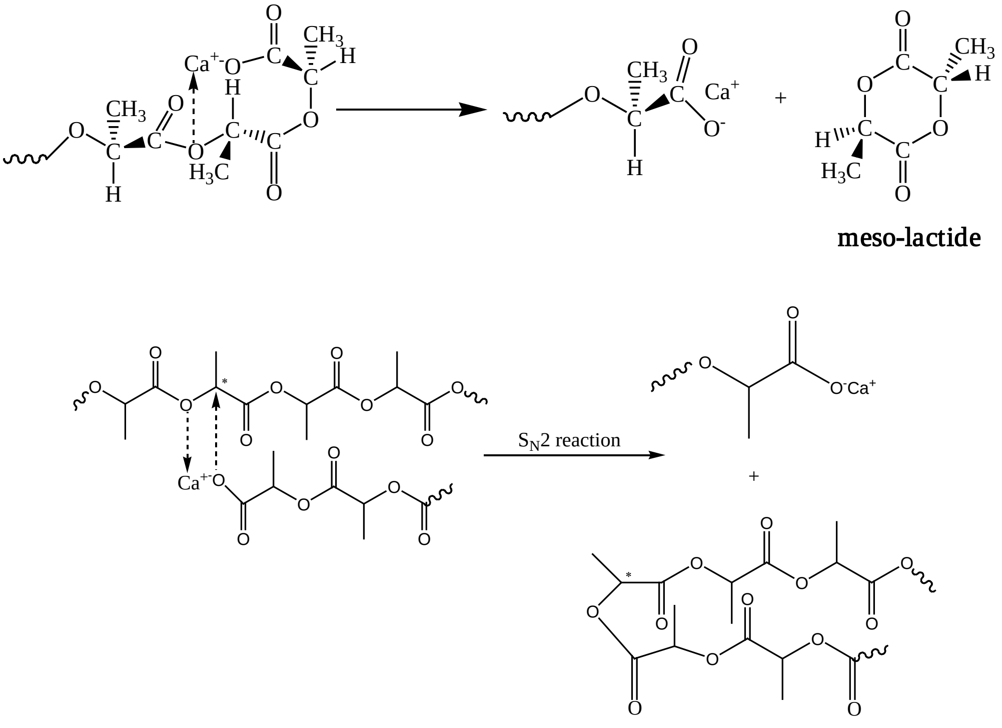
Hyo-Hyon *et al.* [37] synthesized lactide monomers through depolymerization of the oligomers catalyzed by inorganic metal salts. Antimony trioxide powder (Sb_2O_3) 0.1%wt were added to oligomer. Depolymerization of the oligomer to produce a lactide monomer was carried out under reduced pressure (~2 mmHg) in a temperature range of 180-220 °C. The yield of lactides was about 75%. In 2003, Tsuji *et al.* were investigated the formation of lactide in a closed system by thermal degradation of poly(L-lactic acid)(PLLA) [42]. PLLA films were sealed in a test tube under reduced pressure below 3 mmHg and the sealed films were thermally degraded in an oven controlled at constant temperatures in the range of 250-290 °C. This research elucidated the effects of degradation temperature and time on the yield of lactides and the fractions of L-lactide, D-lactide and meso-lactide, and to explore the mechanism of formation of D-lactide and meso-lactide (Scheme 2.6). They reported that the highest yield of lactides and L-lactide at 270 °C and 10 h were as low as 14 and 8%, respectively. It was found that the fractions of L-lactide and of D-lactide and meso-lactide respectively decreased and increased with increasing degradation temperature and time. Moreover, the low yield of L-lactide such as 8% is attributable to the formation of high amounts of meso-lactide and D-lactide.


Alkyl-oxygen radical-homolysis and lactide formation

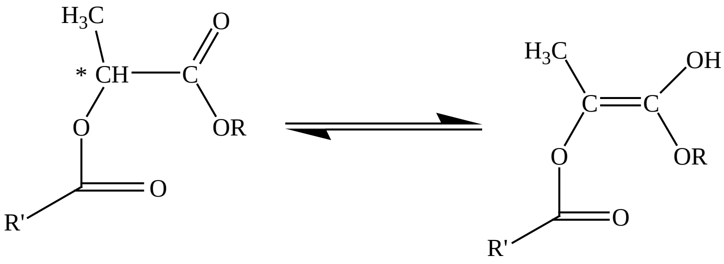
Acyl-oxygen radical-homolysis and lactide formation

Scheme 2.6 Probable pathways for the racemization at asymmetric carbon atoms in PLLA [42]

Fan *et al.* [39] studied L-lactide recovery through the pyrolysis of poly(L-lactide) with calcium salt end structure (PLLA-Ca), which is a promising material for PLLA recycling because of the ease of lactide recovery through the unzipping depolymerization process. Racemization and its control in the pyrolysis of PLLA-Ca were also investigated. This research suggested that racemization took place in the two temperature ranges of lower than 250 °C and higher than 320 °C, meso-lactide was formed. At a temperature lower than 250 °C, the reaction by a nucleophilic attrack by a carboxylate anion end on an electrophilic carbon in polymer chain occurred accompanying the Walden's inversion at an asymmetrical center, resulting in predominant meso-lactide formation (Scheme 2.7). On the other hand, at temperatures over 320 °C, by-reactions, such as the enolization reaction, cause meso-lactide to form, but not dominantly (Scheme 2.8).

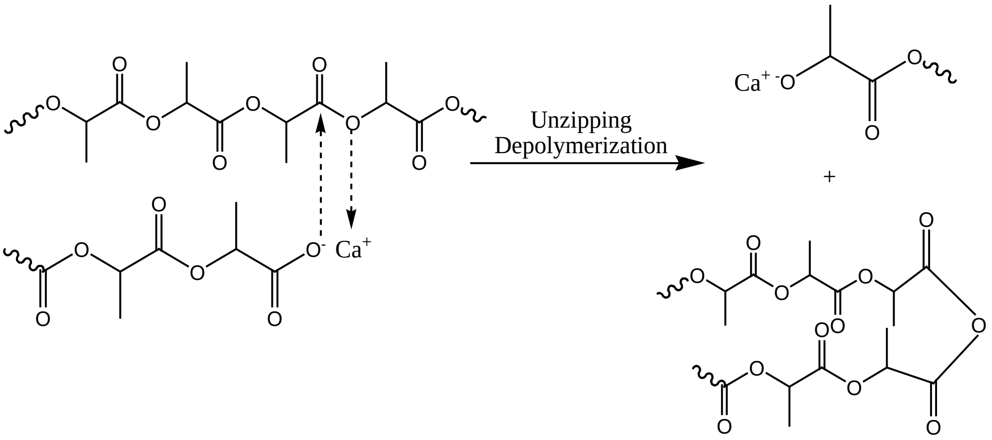


Scheme 2.7 Meso-lactide formation by the S_N2 reaction on a symmetrical methyne carbon at temperature below 250 °C [39]



Scheme 2.8 Enolization in lactate unit [39].

Moreover, they found a special range (250-320 °C) with almost no meso-lactide formed within this temperature range, L-lactide formation was predominant. Because in this temperature range, almost all carboxylate anion ends were changed into the alkoxide anion ends, and the unzipping depolymerization as main reaction proceeded predominantly (Scheme 2.9).

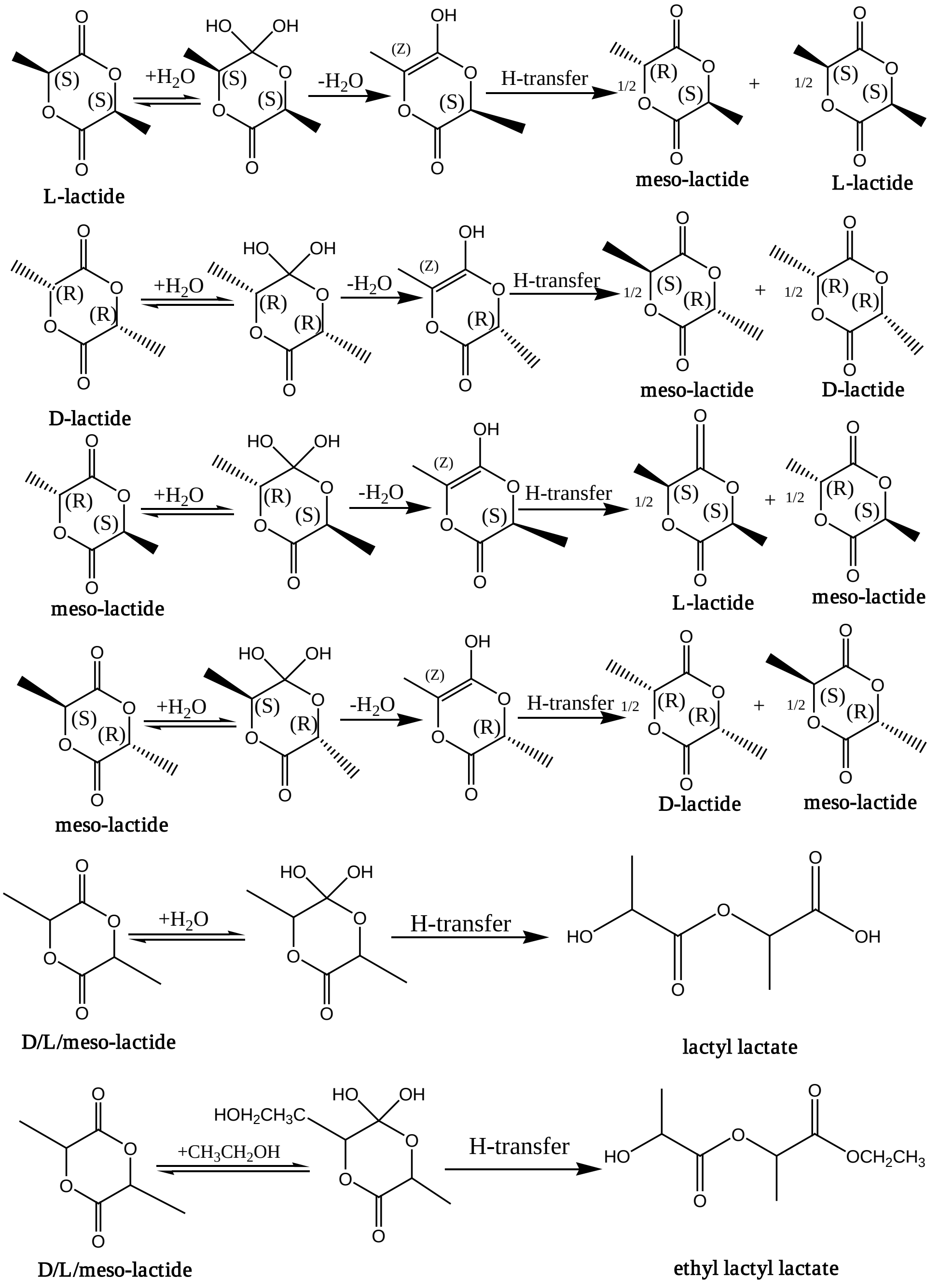


Scheme 2.9 The unzipping depolymerization in PLLA-Ca pyrolysis [39].

Other metal used for the PLLA depolymerization reported by Nishida *et al.* [36]. They studied the effect of residual Sn on the PLLA pyrolysis, PLLA samples with different Sn contents from 20-607 ppm were prepared maintaining a similar level in both molecular weight and distribution. The pyrolysis of PLLA Sn-607 (Sn content: 607 ppm) in the temperature range of 40-400 °C selectively produced lactides. On the other hand, the pyrolysis of PLLA Sn-20 (Sn content: 20 ppm) was accompanied by the production of cyclic oligomers. The increase in Sn content moved the degradation temperature to a lower range and a decrease in activation energy (E_a). Moreover, PLLA/aluminum hydroxide {$Al(OH)_3$} composite was investigated. PLLA/Al(OH)$_3$ makes the melt processing of composite easier and acts as the effective depolymerization of PLLA proceeded without any racemization reaction to selectively convert into L,L-lactide [35-36].

Magnesium oxide (MgO) was used in the depolymerization of poly-L-lactic acid (PLLA) into L,L-lactide by Motoyama *et al*. [38]. MgO is considered the effectively depolymerization of PLLA due to it used only a small amount of MgO (<5 wt %) and it functions only as a depolymerization catalyst. In 2007, Tsukegi *et al*. [40] also studied the racemization behavior of L,L-lactide during heating with the presence of MgO as a catalyst. They found that in the absence of a depolymerization catalyst, the conversion to meso-lactide increased with increase in the heating temperature and time at a high rate than the conversion into oligomers. The resulting high composition of meso-lactide suggests that the direct racemization of L,L-lactide had occurred in addition to the know racemization mechanism that occurs on the oligomer chains. In the presence of MgO, the oligomerization rapidly proceeded to reach equilibrium state between monomers and oligomers. The equilibrium among L,L-, meso-, and D,D-lactides was found to be a convergent composition ratio L,L-: meso- : D,D-lactides = 1:1.22:0.99 (wt/wt/wt) after 120 min at 300°C. This composition ratio also indicates that in addition to the known racemization reaction on the oligomer chains, direct racemization among the lactides is also a frequent occurrence.

The reactions of lactide racemization, hydrolysis, or alcoholysis in the presence of water or anhydrous alcohol have been investigated by Feng *et al*. in 2011[45-46]. They found that a small amount of water leads to lactide racemization and hydrolysis, the two reactions form a pair of parallel competitive reactions. When the water level is less, water acts as a catalyst for the conversion between meso- and D/L-lactides. The reaction of lactide with anhydrous alcohol is mainly its alcoholysis rather than its racemization. The reaction mechanisms for lactides in the presence of water or alcohol shows in Scheme 2.10.



Scheme 2.10 The reaction mechanisms for lactides in the presence of water or alcohol [45]

Direct syntheses of lactide have also been disclosed. A number of catalysts for L-lactide production were reported. Selman *et al*. [49] reported the preparation of lactide by heating lactic acid at a temperature of 100 °C to 250 °C in the presence of titanium alkoxide. This process seems to be advantageous in view of the classical polymerization/depolymerization process but the yield is still quite limited, being of only 60%. Furthermore, titanium alkoxide is consumed and thus cannot be recycled in a process [32].

Benecke *et al*. [50] showed the synthesize lactide by azeotropic distillation of a diluted solution of lactic acid in an organic solvent. This method has the main drawback to require the use of a huge amount of organic solvents such as benzene, toluene and acetonitrile, which is not compatible with an environmental friendly process. Samuel *et al*. [51] has disclosed a process for the synthesis of lactide by reacting the calcium or magnesium salt of the lactic acid with a strong acid. This process requires the first step to prepare the lactic acid metal salt. Then, by reacting the lactic acid metal salt with a strong acid, a huge amount of salts is formed, such as calcium sulfate ($CaSO_4$) that needs to be treated or destroyed. Another disadvantage of this process is its low yield, below 50%.

In 2012, Wautier *et al*. [48] has studied the process for the preparation of lactide comprising heating lactic acid in the presence of hygroscopic salt, wherein the hygroscopic salt is present in an amount of at least 1 mol per mol of lactic acid, lactic acid readily forms the corresponding lactide, which can be easily separated from the reaction. The instance selected of the hygroscopic salt such as magnesium oxide (MgO), calcium chloride ($CaCl_2$), magnesium sulfate ($MgSO_4$), calcium sulfate ($CaSO_4$) [41], in particular zinc sulfate. They believed that the lactic acid will be dispersed into the hygroscopic salt which will isolated the lactic acid molecules from one another, and thus favor dimerisation and cyclisation of the lactic acid molecules to form lactide, rather than oligomerization of lactic acid. In this process, lactic acid is typically heated in the presence of hygroscopic salt at temperature from 120-220 °C under the reduced pressure less than 200 mbar. Water can be added to the reaction and heated to favor the solubilization of the hygroscopic salt. A first heating step may be conducted to first remove at least part of the water initially present in the reaction and the hygroscopic salt is presented in a dehydration state. The reaction may be conducted in a still or in a distillation apparatus which allows the removal of water from the reaction mixture and which allows subsequent separation of the lactide from the reaction. The lactide can be removed from the reaction and recovered progressively, as it is formed, especially by vacuum distillation. The lactide may also be removed from the reaction mixture by extraction using toluene, acetone, tetrahydrofurane or methylene dichloride. The highest yield of lactide from this process is 51%.

In this work, the focus was on the direct synthesis of L-lactide from L-lactic acid to produce a high purity and a high yield of L-lactide through the easier and simpler method. Three methods and various catalysts used in L-lactide production were investigated.

CHAPTER III

EXPERIMENTAL

3.1 Chemicals

All chemicals were purchased as AR grade from various venders unless indicate atherwise: 85% Aqueous L-(+)-lactic acid, the standard (3*S*)-cis-3,6-dimethyl-1,4-dioxane-2,5-dione (L-lactide standard), magnesium L-lactate hydrate ($C_6H_{16}O_6Mg.xH_2O$), eicosane ($C_{20}H_{42}$) and hexatriacontane ($C_{36}H_{74}$) were purchased from Sigma-Aldrich (USA). Magnesium sulfate anhydrous was from Panreac (EU). Iron (II) sulfate heptahydrate ($FeSO_4.7H_2O$), Copper (II) sulfate pentahydrate ($CuSO_4.5H_2O$), Sodium hydrogen carbonate ($NaHCO_3$) and Sodium sulfate anhydrous (Na_2SO_4) were from Merck (Germany). Zinc sulfate heptahydrate ($ZnSO_4.7H_2O$) was from RIEDEL-DE HAËN. Lithium sulfate ($Li_2SO_4.H_2O$) was from AnalaR (England). Antimony (Ш) oxide (Sb_2O_3) and p-toluene sulfonic acid monohydrate were from Acrōs Organics (USA). Tin metal granulated was from Ajax Chemicals (Australia). Zinc dust was from Mallinckrodt (USA). Acetone was from Burdick & Jackson (Korea). Xylene, toluene, ethyl acetate, hexane, and dichloromethane were from RCI Labscan Limited (Thailand). Tin lactate was the mixture of 2 mL of L-lactic acid solution and 0.5 g of tin metal, which was stirred at room temperature for 7 days. Tin mesylate was the mixture of 2 mL of methanesulfonic acid and 0.5 g of tin metal which was stirred at room temperature for 7 days. Tin tosylate was the mixture of 0.5 g of L-lactic acid solution, 0.2 g of PTSA and 10 mL of toluene, which was stirred at room temperature for 7 days. Antimony lactate was the mixture of 3 mL of L-lactic acid solution and 0.3 g of $Sb_2O_{3,}$ which was stirred at room temperature for 7 days. Antimony tosylate was the mixture of 0.3 g of Sb_2O_3, 0.6 g of PTSA and 10 mL of toluene, which was stirred at room temperature for 7 days. $SbCl_3$ was the mixture of 5 mL of conc. HCl and 1 g of Sb_2O_3, which was stirred at room temperature for 7 days.

3.2 Equipments

3.2.1 Gas Chromatography (GC)

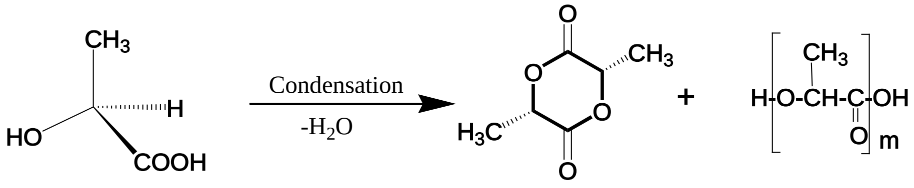
Gas Chromatograms were obtained from Varian CP-3800 with a flame ionization detector (FID), equipped with the SUPELCO capillary column, sil-8 (0.25 mm i.d. × 30 m). The GC operating conditions were as follows: the temperatures of the injector, the detector, and the column oven were 250, 250 and 200 °C, respectively. The flow rate of the carrier gas (N_2) was 8.0 mL/min. The split ratio was 50/1. The temperature programs of GC operating conditions (for entries 13-14 of the synthesis L-lactide by reduced pressure distillation) were as follows: both of temperatures of the injector and the detector were 250 °C. The column oven was set 100 °C for 4 min; then to 200 °C at a rate of 50 °C/min and then held for 4 min. The flow rate of the carrier gas (N_2) was 8.0 mL/min. The split ratio was 100/1.

3.2.2 Nuclear Magnetic Resonance (NMR) Spectroscopy

^{1}H-NMR spectra were recorded on 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. The samples were prepared in chloroform-*d* solution.

3.3 Synthesis

3.3.1 L-lactide synthesis from L-lactic acid with steam distillation



L-lactic acid L-lactide PLLA

L-lactic acid (85% aqueous solution, 50 mL) was heated to boiling for 3 h. Water was then distilled and checked for the presence of lactide.

Next, L-lactic acid (85% aqueous solution, 50 mL) and 100 mL of toluene were mixed and heated to reflux for 3 h. The organic layer was separated and removed the solvent to obtain a mixture of light yellow oil with a little amount of white solid.

Using a Dean stark trap, 50 mL of 85% solution of L-lactic acid was mixed with 100 mL toluene and heated to reflux for 6 h. After removed distilled water from the Dean stark trap, the organic layer was separated and removed the solvent to obtain a mixture of light yellow oil with a little amount of white solid.

3.3.2 Synthesis of L-lactide from L-lactic acid using silica gel

3.3.2.1) Boiling solution

L-lactic acid (85% aqueous solution, 20 g) and silica gel 60 (partical size 0.063-0.200 mm, 20 g) were mixed in various weight ratios (lactic acid: silica = 1:1, 1:2, 1:3, and 1:5). An organic solvent (hexane, ethyl acetate, toluene or xylene) was added and reflux for a certain time (6-12 hours, table 3.1). After that, silica gel was removed by filtration and the resulting filtrate was evaporated to obtain light yellow oil.

Table 3.1 Conditions on L-lactide formation using silica gel in boiling solvents

Entry	Solvent	Reflux Temperature (°C)	Reaction Time (h)	Lactic acid: Silica ratio
1	Hexane	68	6	1:1
2	Ethyl acetate	77	6	1:1
3	Toluene	110	6	1:1
4	Toluene	110	6	1: 2
5	Toluene	110	6	1: 3
6	Toluene	110	6	1: 5
7	Toluene	110	9	1:1
8	Toluene	110	12	1:1
9	Xylene	138	6	1:1

3.3.2.2) Baking

L-lactic acid (85% aqueous solution, 5 g) and silica gel 60 (partical size 0.063-0.200 mm, 5-25 g) were mixed in various weight ratios (lactic acid: silica = 1:1, 1:2, 1:3, and 1:5). Each mixture was baked in an oven temperature controller at 100, 130, 150, 180, 200 °C for 1-6 hours. After the reaction flask cooled down, ethyl acetate and 1 M sodium hydrogen carbonate were added to extract L-lactide. Light yellow oil was obtained after removal of solvent.

3.3.3 Synthesis of L-lactide from L-lactic acid using acid or metal catalysts

3.3.3.1) Boiling solution/ extraction

20 mL of L-lactic acid solution was added into a round-bottom flask. Water was removed at 50 °C until the volume was about 8 mL. Various amount of catalysts (Table3.2, for preparations of some catalyst mixtures, see section 3.1) and 100 mL of toluene were added into the flask. The reaction was refluxed for 6 h. After that, catalyst was removed by filtration and the organic extract was then evaporated to obtain the product.

Table 3.2 Various types and amount of acid catalysts upon lactide synthesis.

Entry	Catalyst	Equivalent of metal
1	Sb_2O_3	0.015
2	$AlCl_3$	0.033
3	$SnCl_4$	0.007
4	Sn metal	0.015
5	MSA (2 mL) + Sn (0.5 g)	0.018
6	PTSA (2 g) + Sn (0.5 g)	0.018
7	Sn (3 g) + Lactic acid (3 mL)	0.110
8	Sn (5 g) + PTSA (2 g) + Toluene (10 mL)	0.180
9	Sb_2O_3 (0.3 g) + Lactic acid (3 mL)	0.005
10	Sb_2O_3 (0.3 g) + PTSA (0.6 g) + Toluene (10 mL)	0.005
11	Sb_2O_3 (1 g) + Conc.HCl (5 mL)	0.015

3.3.3.2) Reduced pressure distillation

From the procedure reported by Zhang *et al.*, [43], L-lactide could be isolated from three steps reaction by distillation at 140-220°C under reduced pressure with stannous octoate as a reaction catalyst. In this work, the reaction was modified into one step using various acid or metal catalysts.

20 mL of 85% L-lactic acid solution with a catalyst (or none, see Table 3.3) were added into a flask equipped with distillation apparatus connected to a vacuum pump. Under reduced pressure, the stirring mixture was heated and distilled off the excess solvated water at 150-160 °C for 30 min. L-lactide was then obtained when the heating temperature was increased gradually from 160 °C to 220 °C. The distillation was continued until there was no more product observed in the receiver and the condenser (about 30 min). The obtained wet L-lactide was dissolved in

dichloromethane and washed with 1 M sodium hydrogen carbonate solution to eliminate L-lactic acid. The white crystalline solid of L-lactide was obtained after removal of the solvent. Alternatively, the distillation was carried on without interserption. (150-220 °C for 1 h)

To test if an in situ extraction could improve this method, in addition to 3 g of $MgSO_4$, 2 g of eicosane or hexatriacontane were added into the reaction flask to provide the organic phase in which L-lactide could be partitioned into this phase and helped divert the equilibrium. The heating and distillation were carried out similarly. The obtained wet L-lactide was isolated by the same procedure above. The residue eicosane or hexatriacontane were recycled by extraction with hexane.

Table 3.3 Various types of acid catalysts used in reduced pressure distillation procedure.

Entry	Catalyst	Amount	Equivalent of metal
1	None	-	-
2	PTSA	0.3 g	0.008
3	$SnCl_4$	0.3 mL	0.005
4	Sb_2O_3	0.3 g	0.005
5	Li_2SO_4	3 g	0.120
6	Na_2SO_4	3 g	0.090
7	$MgSO_4$	3 g	0.110
8	Mg-lactate	3 g	0.055
9	$FeSO_4$	3 g	0.460
10	$CuSO_4$	3 g	0.080
11	$ZnSO_4$	3 g	0.045
12	Zn-lactate	3 g	0.047
13	$MgSO_4$+Eicosane	3 g+ 2 g	0.110
14	$MgSO_4$+Hexatriacontane	3 g+ 2 g	0.110

The remaining residue in the reaction flask after distillation was also studied. 10 g of the remaining residue in the reaction flask was redissolved in chloroform-water mixture (50:10 mL). After that, the inorganic salt was removed by filtration and the organic phase was then evaporated to obtain the product. The presumably oligolactic acid and small amount of L-lactide mixture was obtained.

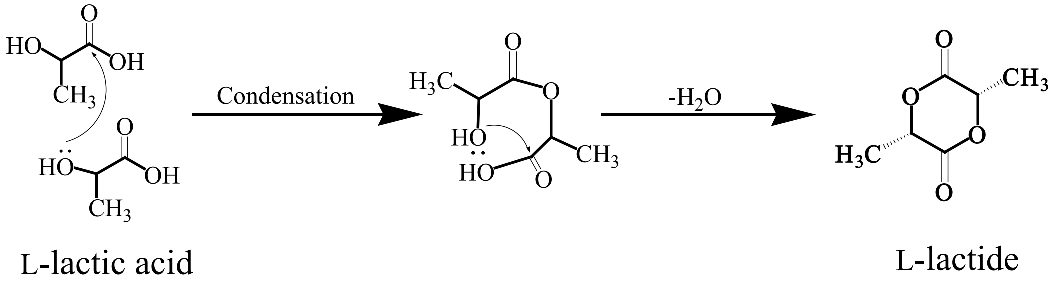
Finally, the stability of synthesized L-lactide upon contact with aqueous solution was investigated. 0.5 g of solid L-lactide was stirred in 5 mL of water, diluted lactic acid solution or 1 M sodium hydrogen carbonate solution for 1-2 hours. The weight of recovered L-lactide was observed and calculated during hour.

CHAPTER IV

RESULTS AND DISCUSSION

This chapter was divided into three parts of methods on L-lactide syntheses. The first part focused on the synthesis and characterization of L-lactide from L-lactic acid with concurrent steam distillation. In this part, the influences of temperature and reaction time were investigated. In the second part, direct synthesis and characterization of L-lactide from L-lactic acid using silica gel as a dehydrating catalyst were studied. The influence of temperature, reaction time, type of solvent and the proportion between L-lactic acid and silica gel were investigated. The third part focused on the direct synthesis and characterization of L-lactide from L-lactic acid using acid or metal catalysts upon distillation. In this part, the effects of temperature, pressure, reaction time, types and amount of catalyst were studied.

4.1 L-lactide synthesis from L-lactic acid with steam distillation



Scheme 4.1 Dehydration of L-lactic acid to L-lactide

In this part, the temperature and the reaction time were the two experimental parameters to be studied (Scheme 4.1). This method postulated the concept of the direct condensation of L-lactic acid and concurrent removal of the L-lactide product out of the equilibrium among various oligomers of L-lactic acid.

Apart from direct visualization of the possible distilled product from steam distillation, the distillate was characterized further by thin layer chromatography

(TLC). The obtained product from steam distillation was characterized by thin layer chromatography (TLC) against L-lactide standard using ethyl with ethyl acetate as a mobile phase. Unfortunately, no product was observed in the receiver or detected in the distillate.

Toluene was added to the reaction anticipating the equilibrium shift more towards L-lactide due to the increase of its miscibility. Figure 4.1 shows ^{1}H-NMR spectrum of the obtained product retrieved from the toluene layer separated out from the reaction flask. The proton signals at 1.54 and 5.12 ppm correspond to methyl and methine protons of L-lactide unit, respectively. On the other hand, no product was found in the distillate mixture. L-lactide was isolated as white solid crystalline from the toluene phase in the reaction flask. The highest yield of the obtained L-lactide from this method was 3%.

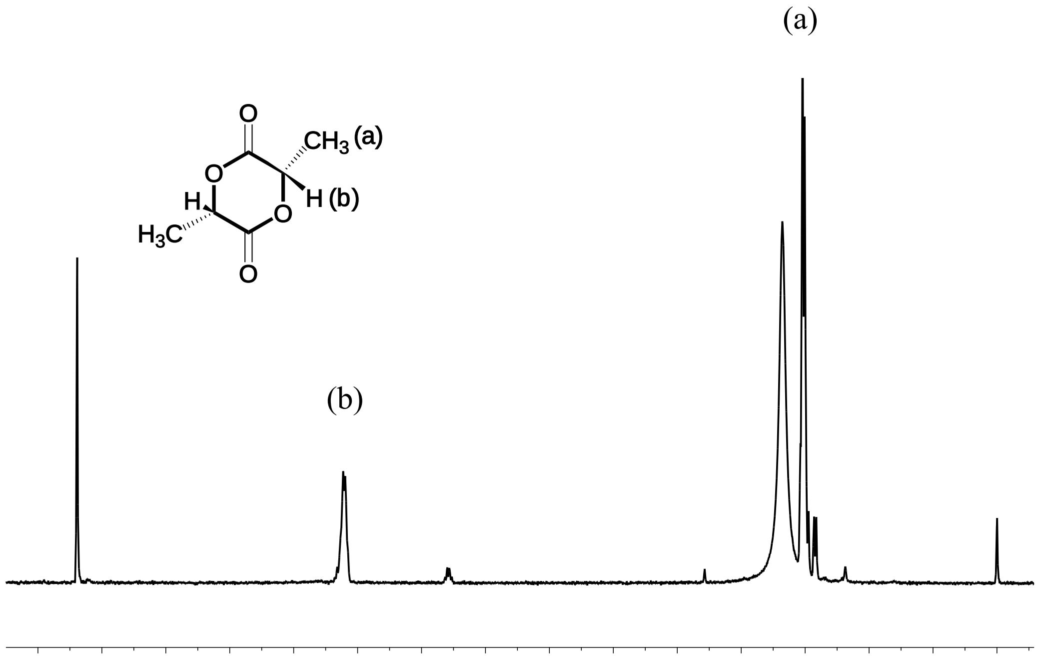


Figure 4.1 ^{1}H-NMR spectrum ($CDCl_3$) of the obtained product from toluene layer

Adding Dean stark trap to help removing water may enhance the formation of L-lactide. Most of the water was distilled out after 6-hour reflux. The product could be isolated out of the organic phase. ^{1}H-NMR spectrum of the obtained product similarly indicated the presence of L-lactide (Appendix A, Figure A). The highest yield of the obtained L-lactide was still only at 5%.

4.2 Synthesis of L-lactide from L-lactic acid using silica gel

4.2.1) Boiling solution

This method reclaimed the concept reported by Sonwalkar *et al.* in 2003 [47] in which silica gel was used as a reaction catalyst of direct polycondensation of lactic acid in boiling organic solvent. In this study, silica gel was used as a catalyst for the attempted synthesis L-lactide from L-lactic acid.

The effect of reaction temperature was studied in four types of solvents at reflux: hexane, ethyl acetate, toluene, and xylene. After filtering off silica gel and evaporating solvent, a light yellow oil mixture with lactic acid was obtained. Pure lactide could be isolated by extraction with ethyl acetate and water and washed with 1 M sodium hydrogen carbonate solution to eliminate L-lactic acid.

Table 4.1 shows the effects of temperature and solvent on L-lactide formation. Refluxing toluene for 6 h gave L-lactide 7% yield (Entry 3). There is no significant difference between toluene and the higher boiling xylene (Entry 9). Only slightly better yield of 9% was obtained with toluene at longer reflux of 12 hours (Entry 8). Ethyl acetate as the solvent could yield L-lactide only 5% (Entry 2). This reaction could be complicated by the residual water in lactic acid solution and possible tranesterification. In the case of hexane, L-lactide formation did not occur at all in this condition (Entry 1).

Upon varying the ratio of the silica to the starting lactic acid, the higher amount of silica catalyst seemed to worsen the yield of the product (Entries 4-6). As the result, the optimum reaction time and the proportion between silica gel and L-lacctic acid were 6 h and 1:1, respectively.

Table 4.1 L-lactide formation in various refluxing solvents

Entry	Solvent	Reflux Temperature (°C)	Reaction Time (h)	Lactic acid: Silica gel ratio	Yield (%)
1	Hexane	68	6	1:1	-
2	Ethyl acetate	77	6	1:1	5
3	Toluene	110	6	1:1	7
4	Toluene	110	6	1:2	5
5	Toluene	110	6	1:3	2
6	Toluene	110	6	1:5	<1
7	Toluene	110	9	1:1	6
8	Toluene	110	12	1:1	9
9	Xylene	138	6	1:1	8

^{1}H-NMR spectrum of the obtained product from entry 8 of Table 4.1 was shown in Figure 4.3. The expected proton signals at 1.52 and 5.12 ppm corresponding to protons of lactide unit appeared. However, another set of signals also showed up at 1.58 and 5.0 ppm corresponding to methyl and methine protons of the meso-lactide, respectively, together with the third set at 1.48 and 4.25 ppm corresponding to protons of oligolactides. Long reaction time at high temperature in the presence of acidic silica might have triggered racemization and oligomerization resulting in the observed mixture.

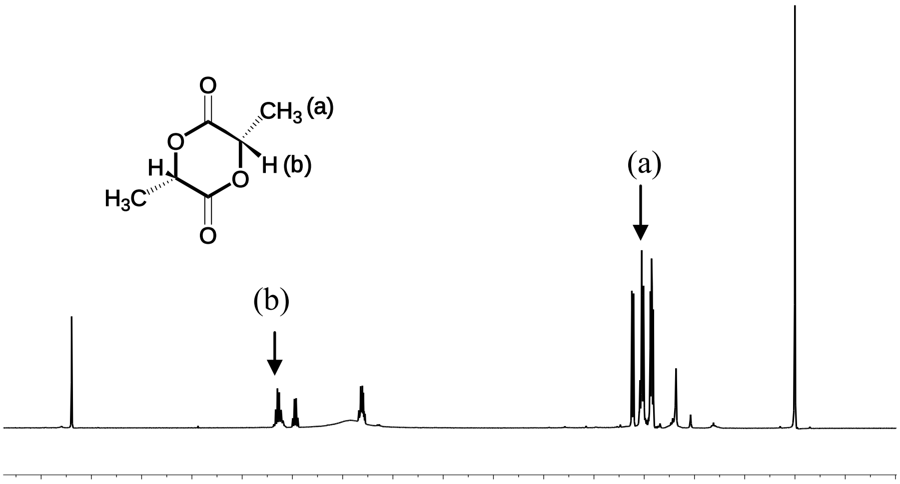


Figure 4.2 ^{1}H-NMR spectrum of the obtained mixture from refluxing L-lactic acid with silica in toluene (12 h).

4.2.2) Baking

The previous solution reaction has the main drawback of requiring the use of huge amount of organic solvents, especially toluene, which is not compatible with an environmentally friendly process. Moreover, the yield of lactide is still quite low. Thus, this baking process, which was modified from the report by Sonwalkar *et al.* in 2003, [47], was intended to improve upon the solution process by excluding solvent use. A 1:1 mixture of silica with L-lactic acid baked in an oven to produce L-lactide after extraction. The effect of reaction temperature was studied using the oven temperature controller. The highest yield of lactide was obtained at high baking temperature of 200 °C for not longer than 3 h (Table 4.2, Entries 25-30). Unfortunately, the yields in most case were still quite low.

At 200 °C, the highest yield of 5.2% was obtained in 1 hour. Higher temperature may have accelerated the dehydration, but most parts of the samples perhaps reacted further towards polymerization and thus lowered the yields of lactides.

It was found that the yields of L-lactide increased slightly during 1 to 3 h. After 3 hours, the yield of L-lactide mostly decreased. At long reaction time, polymerization to PLA became perhaps the major pathway.

The proportions between silica gel and L-lactic acid were also investigated (Table 4.3). The suitable proportion of silica gel and L-lactic acid was found to be 1:1. The high amount of silica gel compared to the lactic acid resulted in small amount of L-lactide probably because of the diluted concentration of lactic acid lowered the chance for dimerization.

Table 4.2 Effect of baking temperature and time on the yields of synthesized lactide

Entry	Oven Temperature(°C)	Reaction Time (h)	Yield (%)
1	100	1	0.5
2	100	2	1.2
3	100	3	1.8
4	100	4	1.7
5	100	5	1.4
6	100	6	1.5
7	130	1	0.6
8	130	2	1.5
9	130	3	1.6
10	130	4	1.4
11	130	5	1.4
12	130	6	0.9
13	150	1	0.9
14	150	2	1.9
15	150	3	1.9
16	150	4	0.7
17	150	5	0.6
18	150	6	0.1
19	180	1	3.0
20	180	2	5.0
21	180	3	4.7
22	180	4	3.5
23	180	5	1.4
24	180	6	0.8
25	200	1	5.2
26	200	2	5.0
27	200	3	4.3
28	200	4	0.4
29	200	5	-
30	200	6	-

Table 4.3 Effect of the proportion of L-lactic acid and silica on the yields of synthesized L-lactide at 180 °C.

Entry	Reaction Time (h)	Lactic acid: Silica gel (weight ratio)	Yield (%)
1	1	1:1	3.0
2	2	1:1	5.0
3	3	1:1	4.7
4	4	1:1	3.5
5	5	1:1	1.4
6	6	1:1	0.8
7	1	1:2	1.5
8	2	1:2	1.7
9	3	1:2	1.2
10	4	1:2	1.4
11	5	1:2	1.5
12	6	1:2	1.1
13	1	1:3	1.0
14	2	1:3	0.3
15	3	1:3	0.3
16	4	1:3	0.2
17	5	1:3	0.2
18	6	1:3	0.1
19	1	1:5	-
20	2	1:5	-
21	3	1:5	-
22	4	1:5	-
23	5	1:5	-
24	6	1:5	-

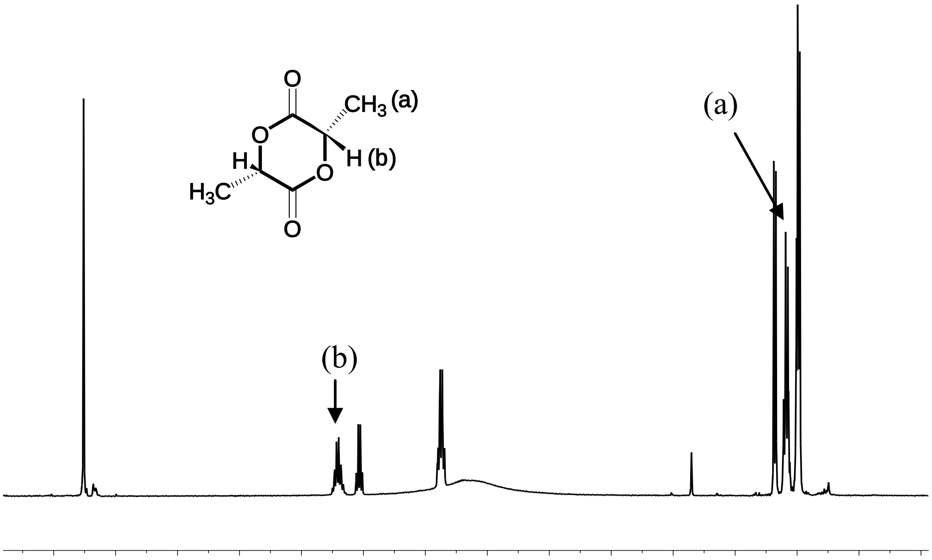
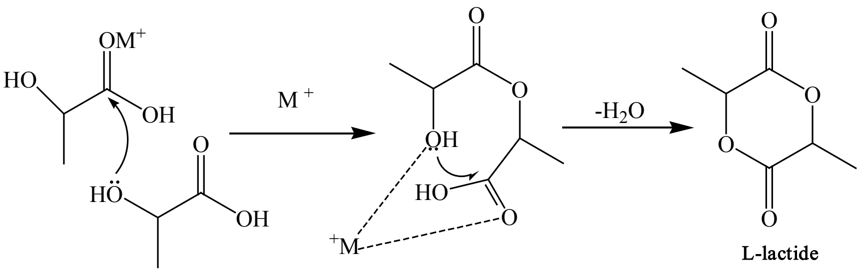


Figure 4.3 ^{1}H-NMR spectrum of the obtained product from baked L-lactic acid with silica (2h).

^{1}H-NMR spectrum of the obtained product from Entry 2, Table 4.3, is shown in Figure 4.3. The mixture of 3 components was found, similarly to those obtained from solution method. Although less solvent was used, the yield of the products was lower while the racemization and oligomerization still occurred.

4.3 Synthesis of L-lactide from L-lactic acid using acid or metal catalysts

There are several successful catalysts for PLA synthesis reported in literature. Since the percent of lactide formation is quite similar mechanistically. This section attempted to apply the types of catalyst for PLA synthesis for L-lactide production.



Scheme 4.2 The mechanism of L-lactide formation in the presence of metal ion catalyst.

4.3.1) Boiling solution/extraction

This method is quite similar to the previous method using silica gel (Section 4.2.1). Toluene was chosen as the extracting solvent because there was a report that polymerization of lactic acid was accelerated in aprotic hydrocarbon solvent when its boiling point is higher than 130 °C. [9]

From Table 4.4, it is quite clear that this method was not a suitable one for lactide synthesis since all of the obtained yields were rather low. Although, in this case, tin lactate could be considered to be the most effective catalyst with the highest yields of 2.8%. These catalysts were primarily chosen for their usages as polymerization catalysts. However, in the present case, they probably gave mostly PLA from the dominated polymerization and only small amount of L-lactide.

Table 4.4 The effect of the catalyst on L-lactide formation

Entry	Catalyst	Equivalent of metal catalyst	Lactide yield (%)
1	Sb_2O_3	0.015	0.4
2	$AlCl_3$	0.033	1.0
3	$SnCl_4$	0.007	1.1
4	Sn	0.015	1.5
5	Sn+ PTSA	0.018	1.0
6	Sn + MSA	0.018	1.7
7	Sn + Lactic acid	0.110	2.8
8	Sn + PTSA + Toluene	0.180	2.3
9	Sb_2O_3 + Lactic acid	0.005	1.2
10	Sb_2O_3 + PTSA + Toluene	0.005	0.3
11	Sb_2O_3 + Conc.HCl	0.015	2.2

4.3.2) Reduced pressure distillation

Synthesis of L-lactide from L-lactic acid here was modified from the procedure reported by Zhang *et al.* [43]. In this method, the L-lactide production from L-lactic acid was combined into one-step reaction, in which the product was distilled at 180-220 °C under reduced pressure using acid or metal catalyst. This method is potentially provide a simple and environmentally friendly procedure that enables the production of L-lactide without numerous subsequent separation and purification steps.

After lactic acid solution was mixed with a catalyst, heated and distilled under reduced pressure, white solid of L-lactide was obtained after extraction procedure in all cases. GC analysis of the product indicated that L-lactide, eluted at the approximate retention time of 3.6-3.7 min, was the only product obtained when either PTSA, $MgSO_4$, $CuSO_4$, $FeSO_4$, $ZnSO_4$, magnesium lactate or zinc lactate was used as the catalyst. In contrast, when the catalyst was Na_2SO_4, Li_2SO_4, $SnCl_4$, Sb_2O_3 or none was used, a byproduct was observed as a broad signal at retention time 6.73 min. This byproduct was presumed to be short-chain oligomers of lactic acid from the competing polymerization process. Large oligomers and polymers were assumably present as the solid residue mixture with the remaining catalyst in the reaction flask in all cases.

The effect of reaction temperature on L-lactide formation was studied. It was found that the highest yield of L-lactide was obtained when the distilling temperature was almost 200 °C. When the temperature was raised above 220 °C to accelerate the distillation, the L-lactic acid or the synthesized L-lactide was unexpectedly isomerized [40, 46]. In this case, the diastereomeric meso-lactide was also obtained as the co-distilled minor product (Figure 4.4).

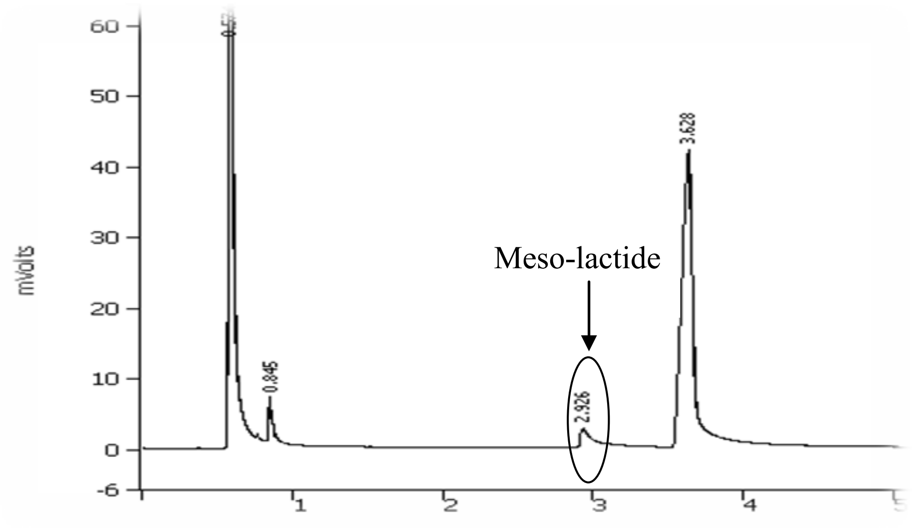


Figure 4.4 The gas chromatogram of the synthesized L-lactide distilled at temperature over 220 °C.

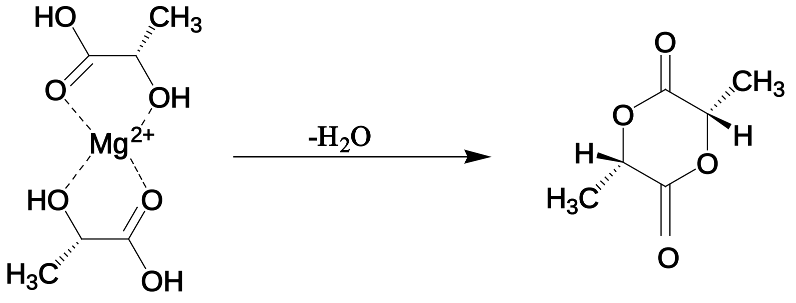
The ^{1}H-NMR spectrum of the purified product indicated the expected doublet and quartet signals at δ 1.65 and 5.00 ppm, corresponding to the methyl and the methine groups of L-lactide, respectively. (Appendix A, Figure A)

Table 4.5 shows influence of the catalyst on the L-lactide formation. In the absence of catalyst, the white crystalline solid of L-lactide was obtained with the yield of 4% (Entry 1). This indicated that L-lactic acid could in general condense to give L-lactide without the catalyst, though with only low yield. Adding protonic acid such as p-toluene sulfonic acid (PTSA) or known polymerization catalysts had no effect on the condensation due to it probably gave mostly PLA from the dominated polymerization and only small amount of L-lactide (Entries 2-4). Large amount of alkali sulfate salts was used anticipating the salting-out effect in this method (Entries 5, 6). However, even less L-lactide was distilled and there seemed to be more polymerization in the reaction instead. The more successful condensations were obtained with the divalent metal catalysts. (Entries 7-12).

Table 4.5 Results of reduced pressure distillation procedure

Entry	Catalyst	Amount	Equivalent of metal	Yield (%)
1	None	-	-	4
2	PTSA	0.3 g	0.008	4
3	$SnCl_4$	0.3 mL	0.005	4
4	Sb_2O_3	0.3 g	0.005	5
5	Li_2SO_4	3 g	0.120	2
6	Na_2SO_4	3 g	0.090	1.5
7	$MgSO_4$	3 g	0.110	20
8	Mg-lactate	3 g	0.055	13
9	$FeSO_4$	3 g	0.460	11
10	$CuSO_4$	3 g	0.080	9
11	$ZnSO_4$	3 g	0.045	13
12	Zn-lactate	3 g	0.047	14
13	$MgSO_4$+Eicosane	3 g + 2 g	0.110	12
14	$MgSO_4$+Hexatriacontane	3 g + 2 g	0.110	16

Magnesium sulfate was found to be the most effective catalyst for L-lactide production in this case, giving the pure L-lactide product in 20% yield (Entry 7). It could be assumed that the mildly acidic property of $MgSO_4$ did not induce the competing polymerization substantially, while its chelating ability (Scheme 4.3) increased the chances for two molecules of L-lactic acid to dimerize and eventually become L-lactide. This chelating effect was also observed with other magnesium salt or divalent metal catalysts in perhaps lesser extent (Entries 8-12). The effect was perhaps absent or relatively weak with the protonic acid and the monovalent alkali metals.



Scheme 4.3 L-lactide production with the chelated magnesium ion catalyst

This result agrees with the latest patent by Wautier [48]. This patent reported heating lactic acid in the presence of hygroscopic salt at 120-220°C under reduced pressure. The hygroscopic salt was believed to isolate the lactic acid molecules from one another, and thus favor dimerization and cyclization to form lactide rather than oligomerization.

Next, with $MgSO_4$ as the catalyst, eicosane or hexatriacontane were added into the reaction to provide in situ organic phase extraction, anticipating the improvement of the L-lactide formation. These long chain alkane, melted upon heating and became an organic solvent phase, which would allow the formed L-lactide to partition into this phase and lower the chance of its hydrolysis back to lactic acid, hence further shifting the equilibrium as L-lactide was distilled off. During the distillation, much larger amount of white solid was observed in the distillate. But it was later identified to be a mixture of L-lactide and eicosane that was codistilled out together (boiling point of eicosane = 220 °C at 30 mmHg). Eicosane was then removed by extraction with hexane. Only 12% yield of the white crystalline solid of L-lactide was obtained after removal of eicosane (Table 4.5, Entry 13).

Figure 4.5 shows ^{1}H-NMR spectrum of the obtained product from the reduced pressure distillation with eicosane. Apart from the proton signals at 1.68 and 5.05 ppm of lactide. The new proton signals of eicosane were clearly present. Figure 4.6 shows gas chromatogram of the product from the reduced pressure distillation with eicosane. Under the isothermal condition used (150 °C), L-lactide and eicosane eluted at the approximate retention time of 0.85 and 17.40 min, respectively.

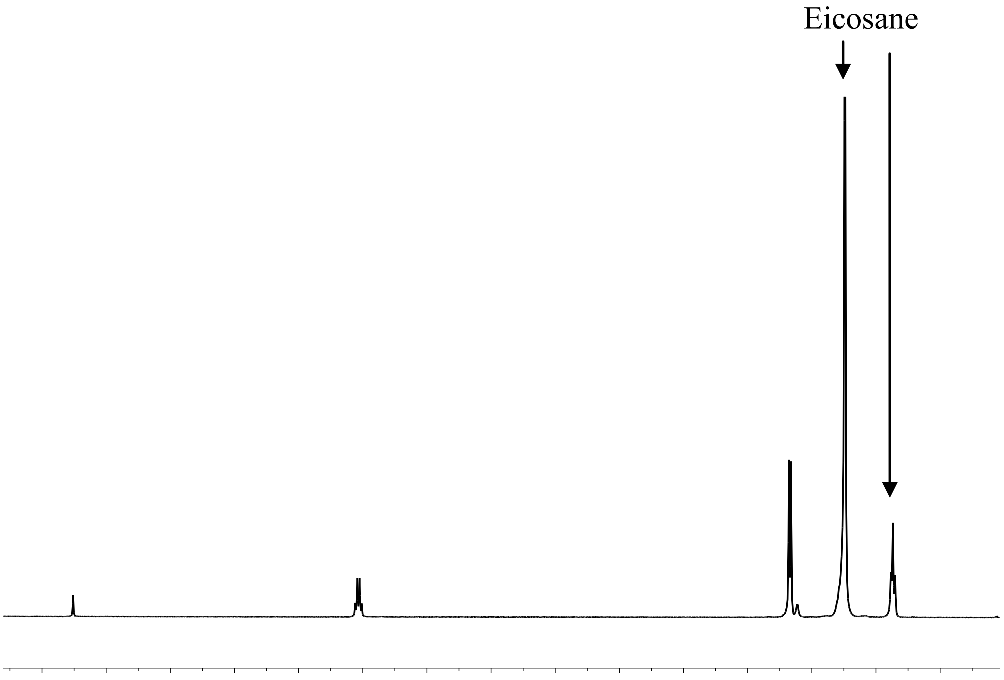


Figure 4.5 ^{1}H-NMR spectrum of the product from the reduced pressure distillation with eicosane

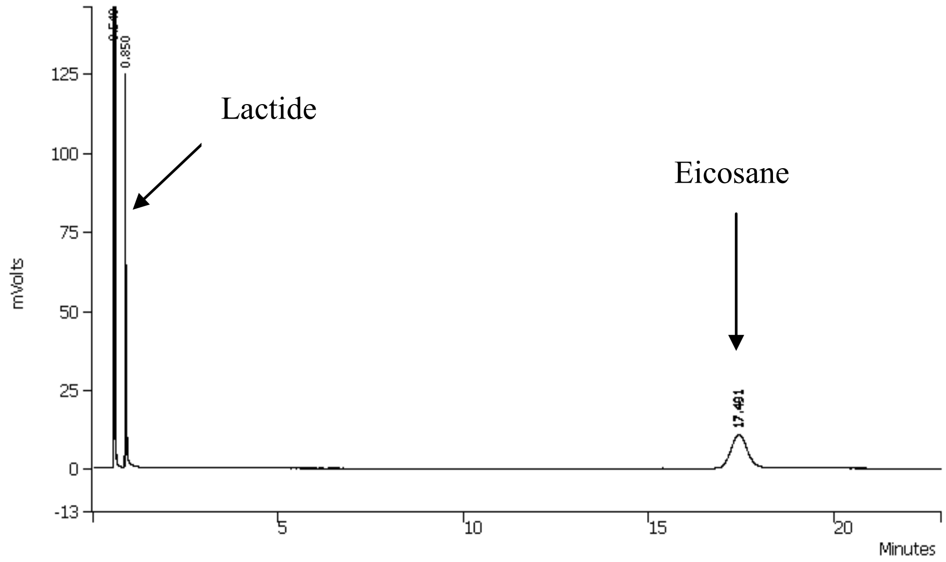


Figure 4.6 The gas chromatogram of the product from the reduced pressure distillation with eicosane (Isothermal 150 °C)

Hexatriacontane ($C_{36}H_{74}$) was used in place of eicosane to prevent the codistillating problem due to its much higher boiling point than eicosane (265°C at 1 mmHg). In the presence of hexatriacontane and magnesium sulfate, 16% yield of the white crystalline solid of L-lactide was obtained after removal of small amount hexatriacontane that was still codistilled out. The result indicated that there was only slightly difference in the use of magnesium sulfate with or without hexatriacontane. In this case, similar to eicosane, hexatriacontane was also obtained as the co-distillate contaminating the L-lactide product and required further separation and purification steps, which may be the reason for lower yield than the experiment using $MgSO_4$ alone.

Figure 4.7 shows ^{1}H-NMR spectrum of the obtained product from the reduced pressure distillation with hexatriacontane. Apart from the proton signals at 1.68 and 5.05 ppm of lactide. The new proton signals of hexatriacontane were clearly present.

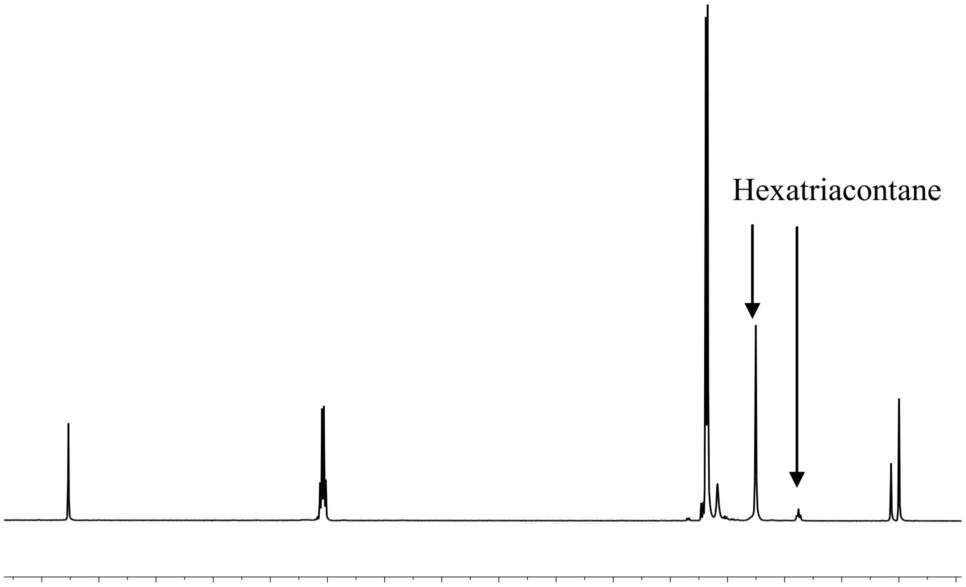


Figure 4.7 ^{1}H-NMR spectrum of the product from the reduced pressure distillation with hexatriacontane

From the results, it appeared that the addition of eicosane or hexatriacontane cannot improve or had no effect on the yield of L-lactide. The ^{1}H-NMR spectra and gas chromatograms of synthesized L-lactide clearly indicated that either eicosane or hexatriacontane was also obtained as the co-distilled minor product and require additional separation and purification steps. This latter procedure would perhaps lower the yields of L-lactide from what has originally produced.

The remaining residue in the reaction flask after distillation was also studied. It was redissolved in chloroform-water mixture. After washing out the inorganic salt and removal of organic solvent, the presumably oligolactic acid and small amount of L-lactide mixture was obtained. The total yield calculated as lactic acid unit was approximately 47%.

Finally, the stability of synthesized L-lactide upon contact with aqueous solution was investigated. The solid L-lactide was stirred in either plain water, lactic acid solution or sodium hydrogen carbonate solution. In the neutral condition, the weight of recovered L-lactide remained approximately constant during the first hour and decreased slightly after prolonged stirring. On the other hand, significant weight decrease of L-lactide was observed during one hour stirring in the acidic or alkaline condition. Prolonged contact with aqueous solutions should be avoided.

CHAPTER V
CONCLUSION

Direct synthesis of L-lactide from L-lactic acid solution was proposed as a simpler method than the traditional two-steps oligomerization-depolymerization process. The focus was to search for a suitable catalyst to promote condensation and cyclization over polymerization of lactic acid monomer. Three methods for L-lactide formation and isolation were studied: steam distillation, extraction, and reduced pressure distillation, all in the presence or absence of a catalyst. In the first method, the produced L-lactide could not be distilled off through the steam. Toluene did not help on the process. The highest yield of L-lactide obtained from this method was 3 %. In the second method, L-lactide was directly synthesized from L-lactic acid with the presence of silica gel as a dehydrating catalyst. The extraction with boiling solvent and baking L-lactic acid with silica gel were investigated. The obtained highest yield of lactide was 9% when L-lactic acid aqueous solution and silica gel were boiled in toluene at reflux for 12 hours with the weight ratio of silica gel and L-lactic acid to be 1:1. Better yields were mostly observed when heated to higher temperature with short reaction time. In the third method, L-lactide was synthesized and isolated by reduced pressure distillation in the presence of acid or metal salt catalyst. Magnesium sulfate was found to be the most effective catalyst for L-lactide production, giving the pure product in 20% yield at distillation temperature of 180-200 °C for 1 h. This method is simple and environmental friendly, which enables the production of L-lactide in one-pot setup, without numerous subsequent separation and purification steps.

It was however observed that racemization and polymerization took place during the reactions, especially when the reaction temperature was increased over 220 °C, meso-lactide was observed. The type of catalyst also affected the by-product formation. When the catalyst was Na_2SO_4, Li_2SO_4, $SnCl_4$, Sb_2O_3 or none was used, short-chain oligomers of PLA from the competing polymerization process was observed. The L-lactide was obtained with low yield.

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APPENDICES

APPENDIX A

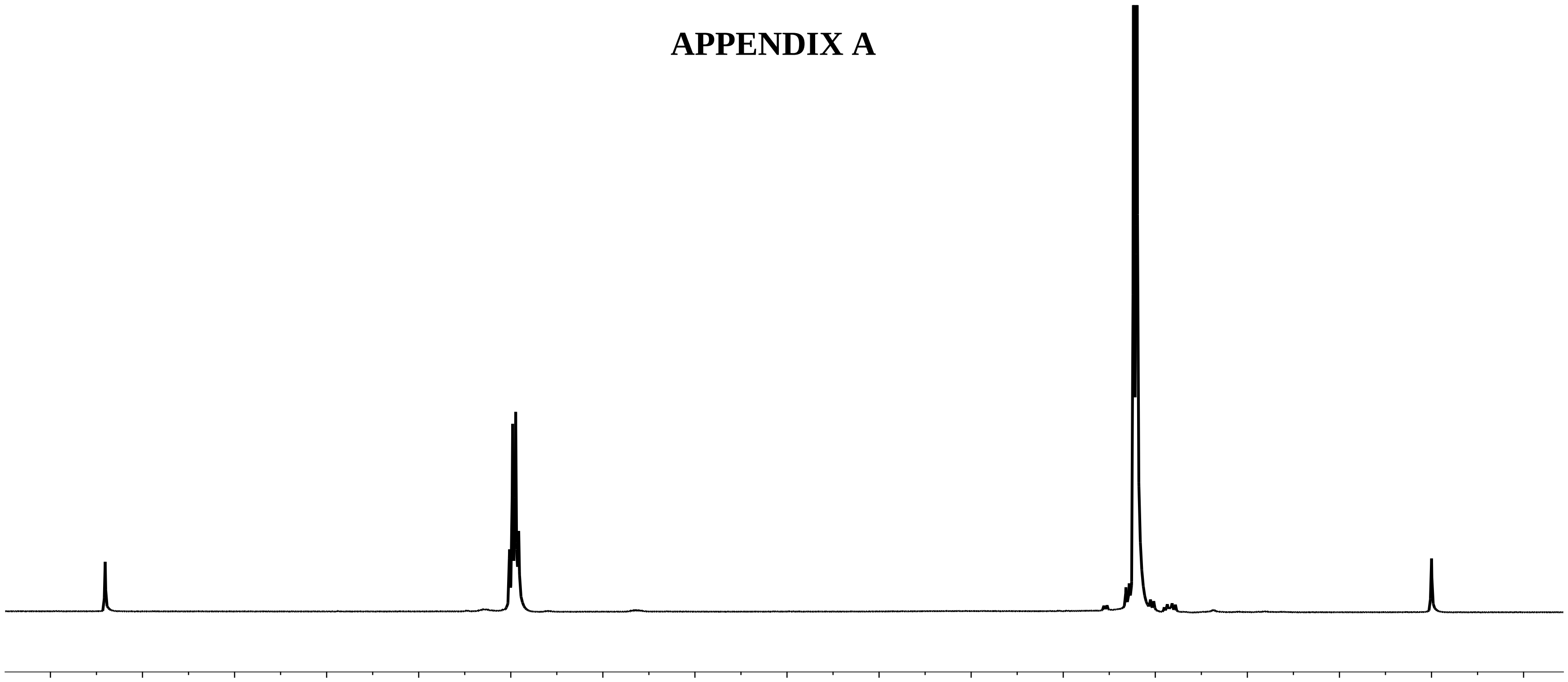

Figure A ^{1}H-NMR spectrum of lactide in $CDCl_3$

APPENDIX B

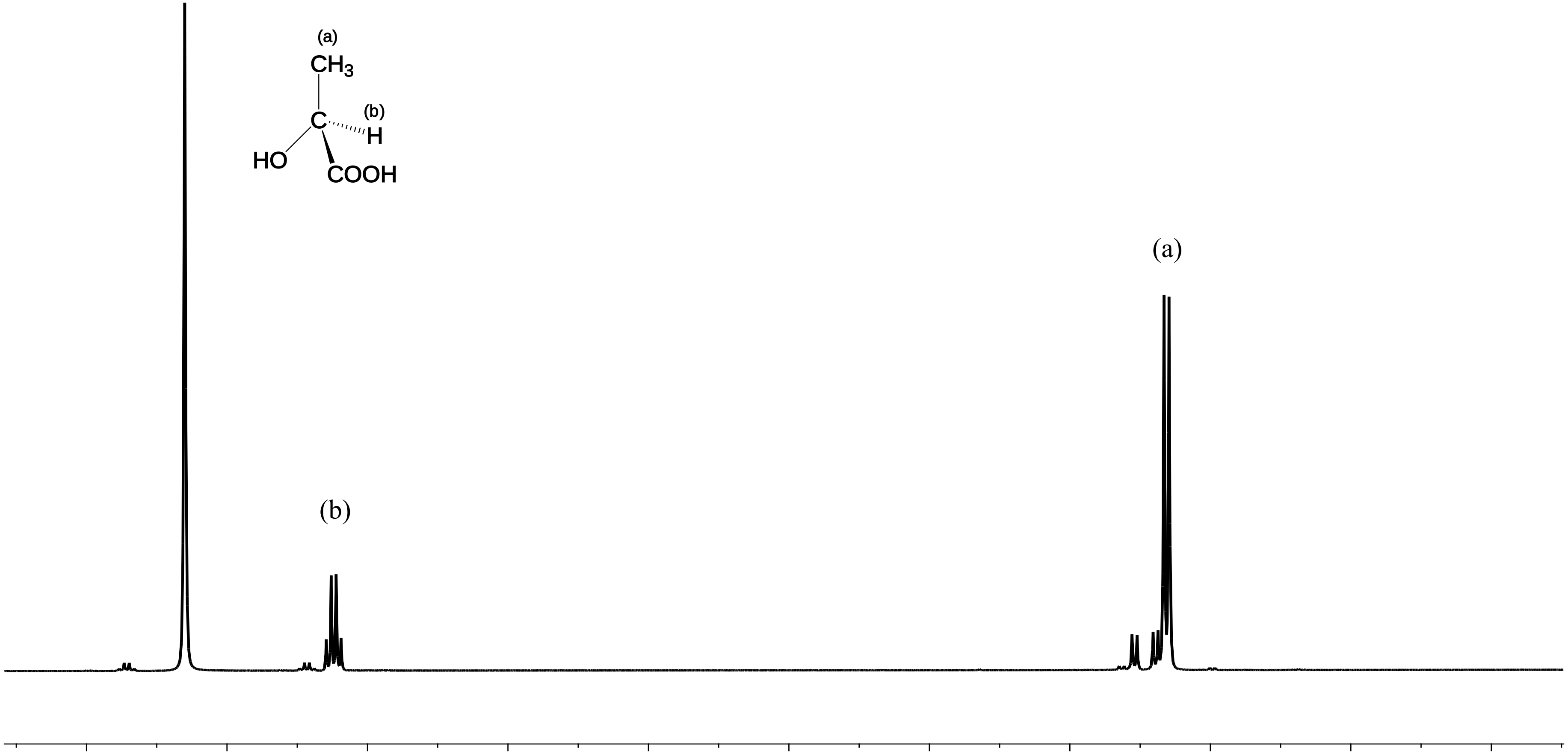

Figure B ^{1}H-NMR spectrum of L-lactic acid (in D_2O).

APPENDIX C

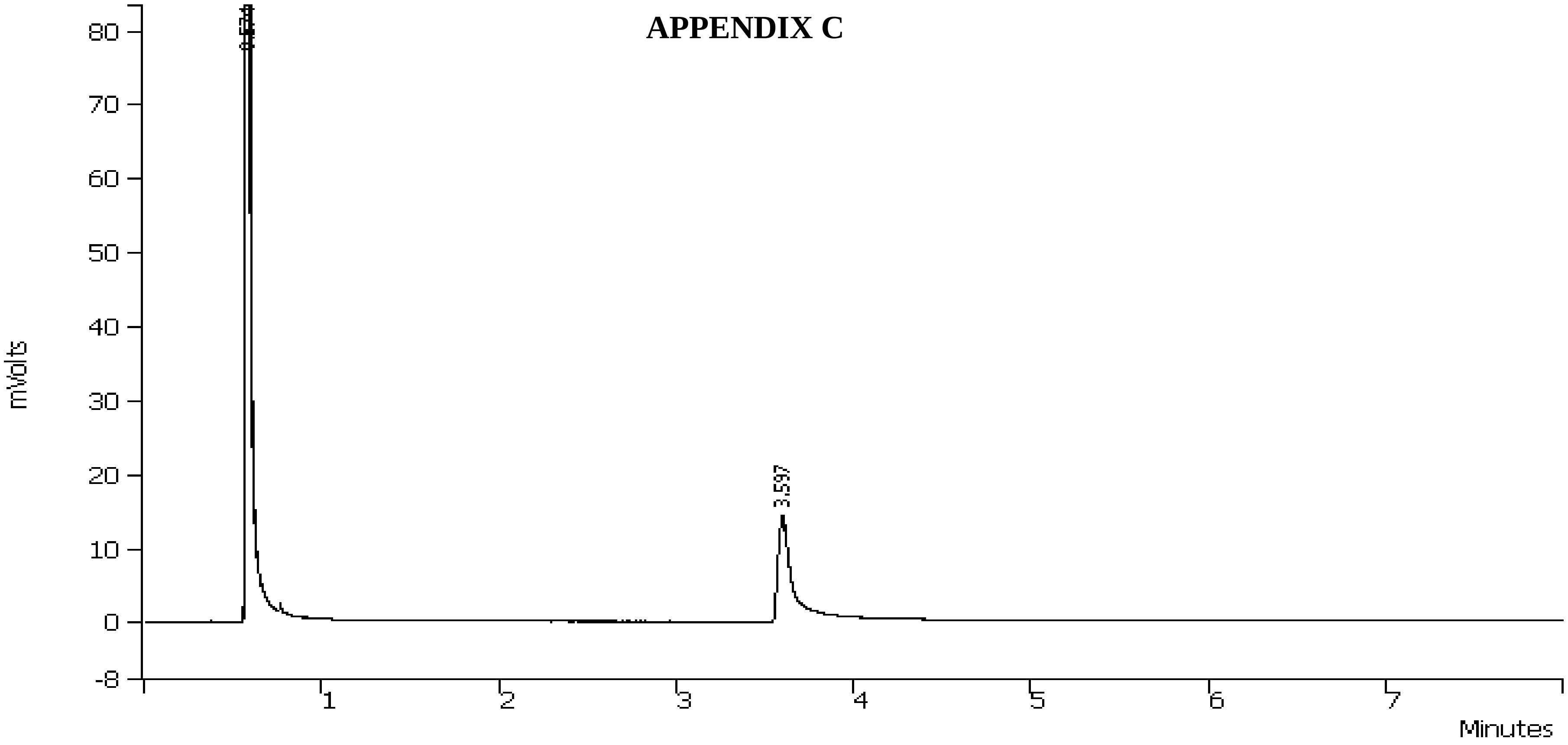

Figure C Gas chromatogram of pure L-lactide

VITAE

Miss Kullapornphat Boonpok was born in Ubonratchathani, Thailand, on March 6th, 1985. She received a Bachelor Degree of Science (Chemistry) from the Department of Chemistry, Faculty of Science, Chulalongkorn University in 2007. The next year, she continued her study as a Master Degree student in the Program of Petrochemistry and Polymer Science, Faculty of Science, Chulalongkorn University, and completed the program in May 2012.

Presentation in Conference:

January 11-13, 2012	Poster presentation in Pure and Applied Chemistry International Conference (PACCON2012), The Empress Chiang Mai Hotel, Chiang Mai.
April 24, 2012	Poster presentation with proceeding in the 3rd Research Symposium on Petrochemical and Materials Technology & The 18th PPC Symposium on Petroleum, Petrochemicals, and Polymers, Queen Sirikit National Convention Center, Bangkok.