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SYNTHESIS OF POLY(L-LACTIDE)-BLOCK-LINEAR-POLYGLYCIDOL

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A Thesis Submitted in Partial Fulfillment of the Requirements
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Thesis Title	SYNTHESIS OF POLY(L-LACTIDE)-BLOCK-LINEAR-POLYGLYCIDOL
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Field of Study	Chemistry
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แสงชัย ประพฤติประยูร: การสังเคราะห์พอลิ(แอล-แลกไทด์)-*บล็อก*-*ลิเนียร์*-พอลิไกลซิดอล (SYNTHESIS OF POLY(*L*-LACTIDE)-*BLOCK*-*LINEAR*-POLYGLYCIDOL) อ. ที่ปรึกษา: ผศ. ดร.วราวุฒิ ตั้งพสุธาดล,115 หน้า.

ได้สังเคราะห์บล็อกโคพอลิเมอร์ระหว่างลิเนียร์พอลิไกลซิดอลและพอลิ(แอลแลกไทด์) จากโคพอลิเมอร์ไรเซชันแบบเปิดวงของมอนอเมอร์แอล-แลกไทด์ โดยหมู่ไฮดรอกซีที่ปลายสายโซ่ของพอลิ(1-เอทอกซีเอทิลไกลซิดิลอีเทอร์) โดยใช้ทินออกโทเอทเป็นตัวเร่งปฏิกิริยา และตามด้วยการกำจัดหมู่ปกป้อง เอทอกซีเอทิลออก อัตราส่วนระหว่างโมลของพอลิ(1-เอทอกซีเอทิลไกลซิดิลอีเทอร์) และ แอล-แลกไทด์ แปรเปลี่ยนเป็น 1:10, 1:20 และ 1:30 ทำการสังเคราะห์ที่อุณหภูมิ 110-120 องศาเซลเซียสเวลา 24 ชั่วโมง ได้พอลิเมอร์สองประเภทซึ่งมีการละลายในเมทานอลแตกต่างกัน ผลวิเคราะห์ด้วยเอ็นเอ็มอาร์ และ มัลดิทอฟ เอ็มเอ็สระบุว่าส่วนที่ละลายในเมทานอลคือ พอลิ(1-เอทอกซีเอทิลไกลซิดิลอีเทอร์) -*บล็อก*-พอลิ(แอล-แล็กไทด์)ที่มีโครงสร้างสอดคล้องกับ *tert*-BuO-PG_p-*b*-$PLLA_n$ และ HO-PG_p-*b*-$PLLA_n$ รวมไปถึงพอลิเมอร์อื่นที่ไม่ทราบโครงสร้างที่แน่นอน การกระจายตัวของน้ำหนักโมเลกุลของพอลิเมอร์ดังกล่าวค่อนข้างกว้าง แสดงว่ากระบวนการโคพอลิเมอไรเซชันที่ใช้เป็นแบบนอนลิฟวิ่ง ส่วนที่ไม่ละลายในเมทานอลประกอบด้วยพอลิ(แอล-แลกไทด์) เป็นส่วนใหญ่และพอลิเมอร์ที่ไม่สามาถระบุโครงสร้างได้ ทั้งนี้พบว่า *ลิเนียร์*-พอลิไกลซิดอล-*บล็อก*-พอลิ(แอล-แล็กไทด์)ที่ได้นั้นละลายไม่หมดในน้ำตามที่ได้คาดไว้เดิม

ภาควิชา เคมี ลายมือชื่อนิสิต แสงชัย ประพฤติประยูร

สาขาวิชา เคมี

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KEYWORD: POLYLACTIDE/ LINEAR POLYGLYCIDOL/ RING OPENING POLYMERIZATION/ LINEAR BLOCK COPOLYMER

SANGCHAI PRAPREDTIPRAYOON: SYNTHESIS OF POLY(*L*-LACTIDE)-*BLOCK-LINEAR*-POLYGLYCIDOL. THESIS ADVISOR: ASST. PROF. VARAWUT TANGPASUTHADOL, Ph.D.,115 pp.

Linear polyglycidol-*b*-poly(L-lactide) or PG-*b*-PLLA was prepared from ring opening copolymerization of LLA monomers by the hydroxyl chain end of poly(1-ethoxyethyl glycidyl ether) (PEEGE) by using $Sn(oct)_2$ catalyst, followed by ethoxy ethyl deprotection. The mole ratio of PEEGE and LLA was varied from 1:10, 1:20, to 1:30. The copolymerization was performed at 110-120°C for 24 hours. Two types of polymer products with difference in MeOH solubility were obtained. By NMR and MALDI-TOF-MS, the methanol-soluble part were PEEGE-*b*-PLLA copolymer with structures that matched *tert*-BuO-PG_p-*b*-$PLLA_n$ and HO-PG_p-*b*-$PLLA_n$ as well as other polymers with undefined structure. The molecular weight distribution of the methanol-soluble copolymer was rather wide, indicating the non-living nature of the copolymerization process. The methanol-insoluble parts were found to consist of mostly homo PLLA and polymers with undefined structures. Nevertheless the obtained PG-*b*-PLLA was not completely soluble in water as initially expected.

Department Chemistry Student's signature

Field of study Chemistry

Academic year 2007 Advisor's signature

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AROP	Anionic ring opening polymerization
DBLT	Dibutyltin dilaurate
DCM	Dichloromethane
DSC	Differential scanning colorimetry
EEGE	1-ethoxyethyl glycidyl ether
EEO	1-ethoxy ethyl ether
ESI-MS	Electrospray ionization mass spectroscopy
FT-IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GPC	Gel permeation chromatography
$I_{\text{XX ppm}}$	Integrated proton at chemical shift xx ppm
LLA	L-lactide
MALDI-TOF-MS	Matrix-assisted laser desorption ionization time of flight mass spectrometry
MeOH	Methanol
NMR	Nuclear magnetic resonance
oct	1-ethyl hexanoate
PDI	Polydispersity index
PEEGE	Poly(1-ethoxyethyl glycidyl ether)
PEEGE-*b*-PLLA	Poly(1-ethoxyethyl glycidyl ether)-block-poly(L-lactide)
PG	Polyglycidol
PG-b-PLLA	Poly(glycidol)-block-poly(L-lacide)
PLLA	Poly(L-lactide)
THF	Tetrahydrofuran
$ZnEt_2$	Diethyl zinc

CHAPTER I

INTRODUCTION

1.1 Statement of Problem

The behavior of amphiphilic block copolymers in solvent is one of the most interesting topics in polymer science. They can form particles with various shapes depending on solvent polarity, pH, concentration and temperature [1]. Structure design can be utilized in drug or gene encapsulation application. In addition, the micelle shape in solution can be varied from spherical shape, connected rod by pH change [2]. Micelle formation having hydrophilic block on the shell and inner hydrophobic polylactide blocks occurs in aqueous solution.

Amphiphilic block copolymers having biocompatible and biodegradable hydrophobic aliphatic polyester blocks have received the attention and are promising materials for medical applications such as controlled release polymer vehicle, gene delivery carrier, self-assembled micro and nanoparticle and polymeric micelle [3]. Poly(L-lactide) or PLLA (Figure 1.1) is a biodegradable and biocompatible polyester which has high mechanical strength, high crystallinity, hydrophobicity and excellent molding properties. To construct the structure of amphiphilic PLLA-based copolymer, a number of hydrophilic polymers were introduced such as polyethylene glycol (PEG) and poly(N-isopropyl acrylamide).

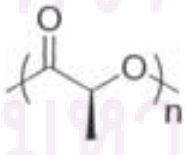


Figure 1.1 Poly(L-lactide) or PLLA.

Highly hydrophilic and hydroxyl-functional linear polyglycidol is among the interesting blocks to introduce in polylactide. The copolymer from the combination

of linear polyglycidol (PG) and PLLA was first reported by Sunsaneeyametha [4]. At that time, linear PG was synthesized through benzyl protected glycidol and copolymerized with PLLA before catalytic hydrogenation to deprotect the benzyl group. The resulted copolymer had very low molecular weight. An improvement of methodology to synthesize PLLA-PG block copolymer was therefore needed.

1.2 Objective

The aim of this thesis was to synthesize linear di and triblock copolymers of linear PG and PLLA. The copolymer structure was determined by NMR, GPC, MS and DSC. Dissolution behavior of the copolymers was also studied in order to evaluate their possible amphiphilic properties.

1.3 Scope of the Investigation

Sequential investigation was carried out as follows.

1. To synthesize linear poly(ethoxyethyl glycidyl ether) (PEEGE) from 1-ethoxyethyl glycidyl ether (EEGE) using potassium tert-butoxide as an initiator.

2. To synthesize the block copolymer of PEEGE and PLLA by ring opening polymerization using PEEGE as initiator and stannous (II) 2-ethylhexanoate as catalyst.

3. To deprotect ethoxy ethyl ether at the EEGE group in PEEGE block

4. To determine structure of the resulting polymers by nuclear magnetic resonance spectroscopy (NMR), differential scanning calorimetry (DSC) and molecular weights determination by matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) and gel permeation chromatography (GPC)

5. To study dissolution behavior of the copolymer in solvent by monitoring visual changes at various temperature.

CHAPTER II

THEORY AND LITERATURE REVIEW

2.1. Block copolymer synthesis of polyester [5]

Up to now, there are several methods to synthesize block copolymer. One simple method is a reactive extrusion that two homopolymers are mixed at high temperature. Intermolecular transesterification reaction is subjected in the block structure production. However, this way is limited to the extent of polymer due to an amount of intermolecular transesterification.

The second method is sequential addition of monomer. When monomer A is run out after polymerization completion, then a monomer B is added to continue polymerization. Consequently, AB or BAB block copolymer is received. The extent of this method are the reaction condition, the nature of monomer and the addition order. The reaction must undergo "living" polymerization condition. It means the initiation step is sufficiently faster than the propagation step and propagation step is required to be faster than termination. So, growing chain of polymer associates with initiator and further continue propagation step when more monomer is added. Moreover, those two monomers must have similar reactivities so that the later monomer must react in propagation step. In addition, the addition order must be considered. For example, in case of ε-caprolactone (ε-CL) and LLA block copolymer with tin (II) octoate ($Sn(oct)_2$) as catalyst and ethanol as initiator, ε-CL was polymerized first. Otherwise, the copolymer formed randomly if LLA is synthesized first.

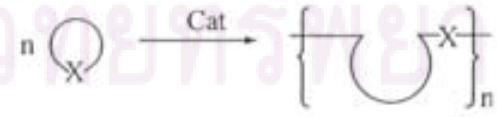
The third method is atom transfer radical polymerization (ATRP). ATRP has been used to prepare AB diblock, ABA triblock and most recently ABC triblock copolymers. To date, the technique has been used to create block copolymers based on polystyrene and various polyacrylates. However, it is possible to synthesize a so-

called macroinitiator by other polymerization mechanism (anionic, cationic, etc.) and use this in the ATRP of vinyl monomers. Some examples are poly(N-(2-hydroxypropyl)methacrylamide)-*b*-poly(D,L-lactide)-*b*-poly(N-(2-hydroxypropyl) methacrylamide [6], poly(N-isopropyl acrylamide)-*b*-poly(D,L-lactide) [7], poly(2-hydroxyethylmethacrylate)-*b*-poly(D,L-lactide) [8]

An alternative method is a combination or condensation reaction of two telechelic polymers, that is prepolymers or macromers with functional end groups. The functional end groups are introduced by either functional initiator or end-capping of living polymers or both. The outstanding advantage of this method are two monomers that are not able to copolymerize can be incorporated in a copolymer. The structure and end groups of prepolymers can be quantitatively and qualitatively controlled. Some examples are polyethylene-*b*-poly(D,L-lactide-co-glycolide) [9], methoxy-poly(ethylene glycol)-*b*-poly(caprolactone-*b*-lactide) [10].

2.2. Ring opening polymer synthesis (ROP)

Ring opening polymerization is an ionic chain polymerization consisting of initiation, propagation and termination. The outstanding characteristic is only monomer adds to the growing chains in propagation. Unlike step polymerization, monomer does not react with monomer and species larger than monomer do not react with each other.



Scheme 2.1 Ring-opening polymerization (X is a heteroatom such as oxygen).

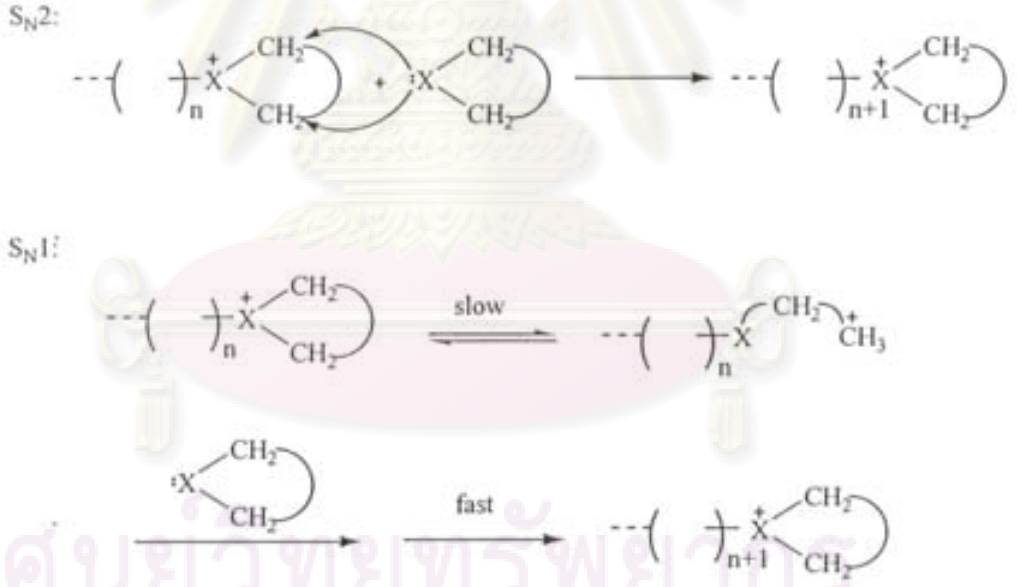
The ring opening reaction can be performed either as a bulk polymerization or in solution, emulsion , or dispersion. A catalyst or initiator is necessary to start the polymerization. Under rather mild condition, high-molecular weight aliphatic polyester of low polydispersity can be performed in short periods of time. Problem

associated with condensation polymerization, such as the need of exact stoichiometry, high reaction temperature, and the removal of low molecular weight by-products are excluded in ROP.

Depending on initiator, the polymerization proceeds according to three different major reaction mechanisms, viz, cationic, anionic, or "coordination-insertion" mechanisms.

2.2.1 Cationic ring opening polymerization

Cationic ROP involves the formation of a positively charged species which is subsequently attacked by a monomer. The attack results in a ring-opening of the positively charged species through an SN2 type process. The cationic polymerization is difficult to control and often only low-molecular weight polyesters are formed.



Scheme 2.2 S_N1 and S_N2 mechanism in propagation step of CROP or active chain end mechanism (ACE) (counter ion omitted; X is a heteroatom).

2.2.2 Anionic ring opening polymerization

Anionic ROP of cyclic ester monomers takes place by the nucleophile attack of a negatively charged initiator on the carbonyl carbon or on the carbon atom adjacent to acyl oxygen, resulting in a linear polyester.

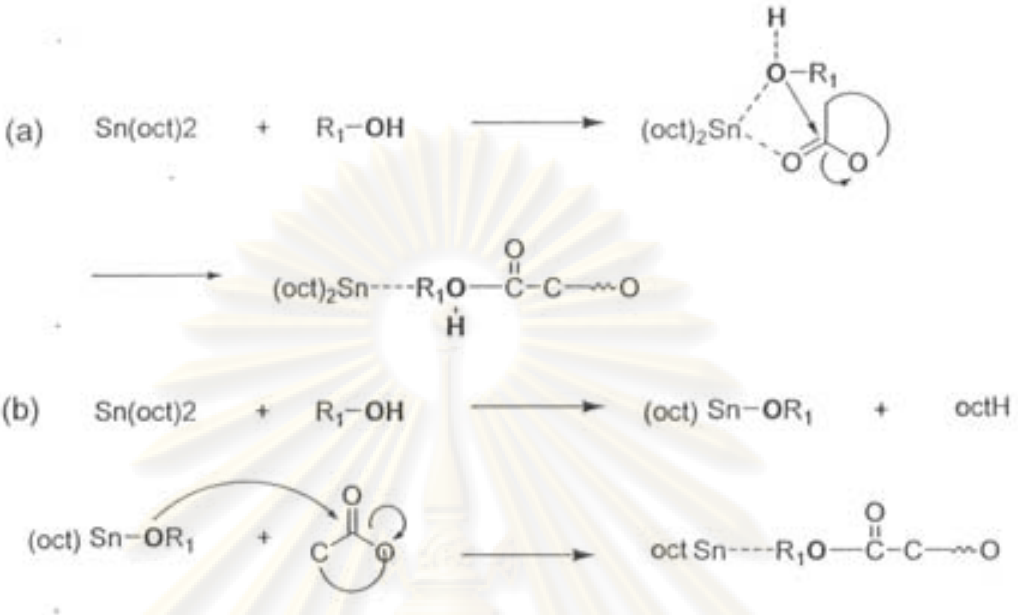
Scheme 2.3 AROP, X denotes heteroatom (e.g., X=O or S) or group including heteroatoms (e.g., C(O)O); cat^+ means the monovalent metal (e.g., Li^+, Na^+, K^+, Cs^+) or onium (e.g., R_4N^+ , R_4P^+) cations.

The propagating species is negatively charged and is counter-balanced with a positive ion. Depending on the nature of the ionic propagating chain end and the solvent, the reacting complex varies from completely ionic to almost covalent. Some examples are poly(N-vinyl-2-pyroolidone)-*b*-poly(D,L-lactide) [11].

One of the best controlled methods leading to high molecular weight polymer is anionic polymerization carried out in a polar solvent. A problem associated with the anionic ROP is the extensive back-biting, and in some cases only polyesters of low molecular weight are achieved.

2.2.3 Coordination insertion ring opening polymerization

The pseudo-anionic ROP is often referred to as coordination-insertion ROP, since the propagation is thought to proceed by coordination of the monomer to the active species, followed by insertion of the monomer into the metal-oxygen bond by rearrangement of the electrons. The growing chain remains attached to the metal through an alkoxide bond during the propagation. The reaction is terminated by hydrolysis forming a hydroxyl end group. With functional alkoxy-substituted initiators, macromers with end group active in post-polymerization reactions are produced.



Scheme 2.4 The main ROP mechanism proposals with $Sn(Oct)_2$ as catalyst, (a) complexation of a monomer and alcohol prior to ROP, and (b) formation of a tin-alkoxide before ROP of lactone.

The coordination insertion type of polymerization has been thoroughly investigated since it may yield well-defined polyesters through living polymerization. When two monomers of similar reactivity are used, block copolymer can be formed by sequential addition to the "living" system.

2.3. Catalyst: Tin (II) 2-ethyl hexanoate

Tin (II) 2-ethyl hexanoate, (Figure 2.1), commonly referred to as stannous octoate [$Sn(oct)_2$], is a frequently used catalyst in the ROP of lactides. It has been approved as a food additive by the American Food and Drug Administration (FDA). The $Sn(oct)_2$ is not the actual initiator since the molecular weight does not depend on the monomer-to-$Sn(oct)_2$ molar ratio. The most promising mechanism is a coordination-insertion mechanism where a hydroxyl functional group is thought to coordinate to $Sn(oct)_2$, forming the initiating tin alkoxide complex.

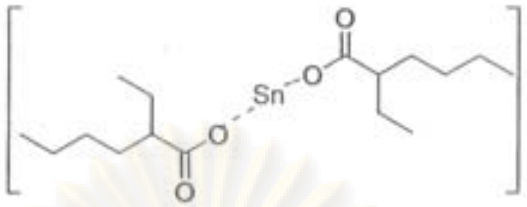


Figure 2.1 Chemical structure of stannous octoate, $Sn(oct)_2$.

Investigations of the coordination-insertion mechanism have resulted in two slightly different reaction pathways. Kricheldorf and coworkers [12] have proposed mechanism where the co-initiating alcohol functionality and the monomer are both coordinated to the $Sn(oct)_2$ complex during propagation. Penczek and coworkers [13] have presented a mechanism where the $Sn(oct)_2$ complex is converted into a tin alkoxide before complexing and ring opening of the monomer.

The $Sn(oct)_2$ catalyst is a strong transesterification agent, and the resulting copolymers normally have a randomized microstructure. An increasing in reaction temperature or reaction time increases the amount of transesterification reactions.

The ROP of lactide with $Sn(oct)_2$ is fairly slow and it is desirable for economic and commercial reasons to increase the rate of polymerization. The addition of an equimolar amount of triphenylphosphine increases the rate and, as an additional advantage, this compound delays the occurrence of the undesirable back-biting reactions.

2.4. Linear polyglycidol

Glycidol is a highly reactive monomer bearing both epoxy and hydroxyl functional groups. Both its composition and structure favor the primary to secondary transitions of the alkoxide active sites, as well as the intermolecular transfers during base-initiated polymerization. The polymerization of glycidol has attracted considerable research interest in the past decade. The propagation may evoke side

reactions. Both the anionic and cationic polymerizations of this monomer lead to hyper-branched polyethers with low polydispersity.

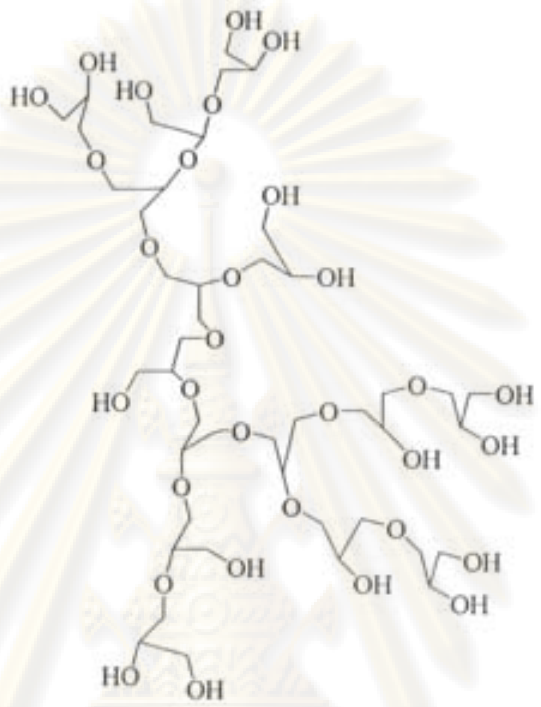
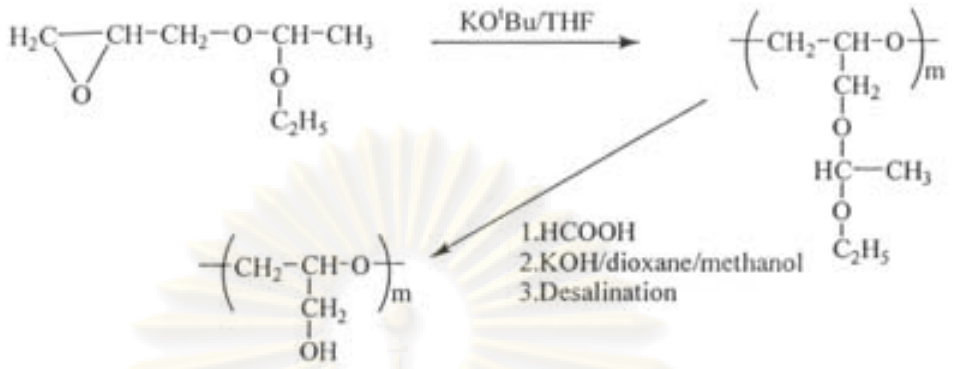


Figure 2.2 Hyperbranched polyglycidol.

In order to obtain linear polymers of glycidol, its hydroxyl group has to be protected by suitable protecting groups. Vandenberg [14] used silylation or etherification of the hydroxyl group of the monomer.

Spassky et al. [15] has shown that ethoxy ethyl glycidyl ether obtained in a reaction of glycidol with ethyl vinyl ether can be polymerized by an anionic mechanism. The protective ethoxy ethyl group can then be easily removed thus yielding a linear polyglycidol, which is a highly hydrophilic water-soluble polymer due to the polyether structure with a hydroxyl group in each repeat unit. They obtained linear polyglycidol with M_n up to 30,000 Da.



Scheme 2.5 Synthesis of linear polyglycidol.

Dworak et al. [16] synthesized linear polyglycidol by firstly anionic polymerization of 1-ethoxyethyl glycidyl ether using potassium tert-butoxide in THF as initiator and secondly acidic hydrolysis. The result showed that the degree of polymerization corresponded well to the initial monomer to initiator ratio as well as narrow the molecular mass. For higher molecular weight, even though broader molecular mass distribution [17], coordination polymerization of 1-ethoxy ethyl glycidyl ether by using partially hydrolyzed $ZnEt_2$ as catalyst was applied, followed by acidic hydrolysis using 3 M HCl.

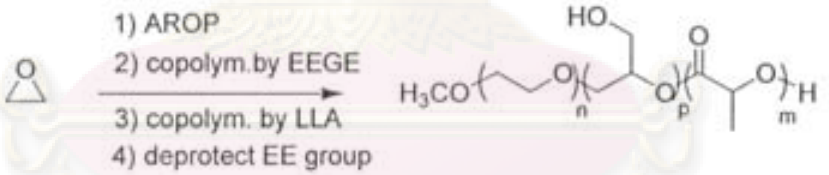
Bong Soo Kim el al. [18] also synthesized linear polyglycidol through 1-ethoxy ethyl glycidyl ether by using sodium ethoxide or potassium ethoxide as initiator. After acidic hydrolysis of acetal polymer, linear polyglycidol was obtained.

2.5. Block copolymers in solution [19]

In a solvent, block copolymer phase behavior is controlled by the interaction between the segments of the polymers and the solvent molecules as well as the interaction between the segments of the two blocks. If the solvent is unfavorable for one block, this can lead to micelle formation in the dilute solution. Lamellar, hexagonal-packed cylinder, micellar cubic and bicontinuous cubic structures have all been observed (these are all lyotropic liquid-crystal phase, similar to those observed for nonionic surfactants).

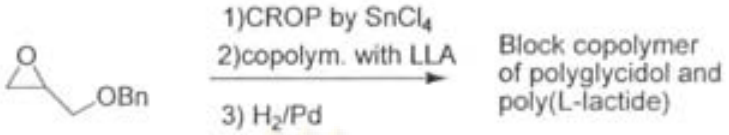
Like surfactant, block copolymers form micelles above a critical concentration. The critical micelle concentration can be located by a variety of techniques, the most commonly used being surface tensiometry where the cmc is located as the point at which the surface tension becomes essentially independent of concentration.

Gadzinowski and Sosnowski [20] reported the synthesis of biodegradable/ biocompatible poly(ethylene oxide)-*b*-polyglycidol-*b*-poly(L,L-lactide) triblock copolymer. Firstly, PEO-b-poly(1-ethoxyethylglycidol)-*b*-PLLA was synthesized by a successive anionic ring opening copolymerization of ethylene oxide, 1-ethoxyethyl glycidyl ether and L,L-lactide initiated with potassium 2-methoxyethanolate. Secondly, the 1-ethyoxyethyl blocking groups of 1-ethoxyethyl glycidyl ether were removed at weakly acidic conditions leaving other blocks intact. The PEO-*b*-PGly-*b*-PLLA copolymers with a molecular weight of PLLA blocks below 5,000 were water soluble. Above the critical micellar concentration (ranging from 0.05 to 1.0 g/L, depending on the composition of copolymer), copolymers formed macromolecular micelles with a hydrophobic PLLA core and hydrophilic PEO shell.



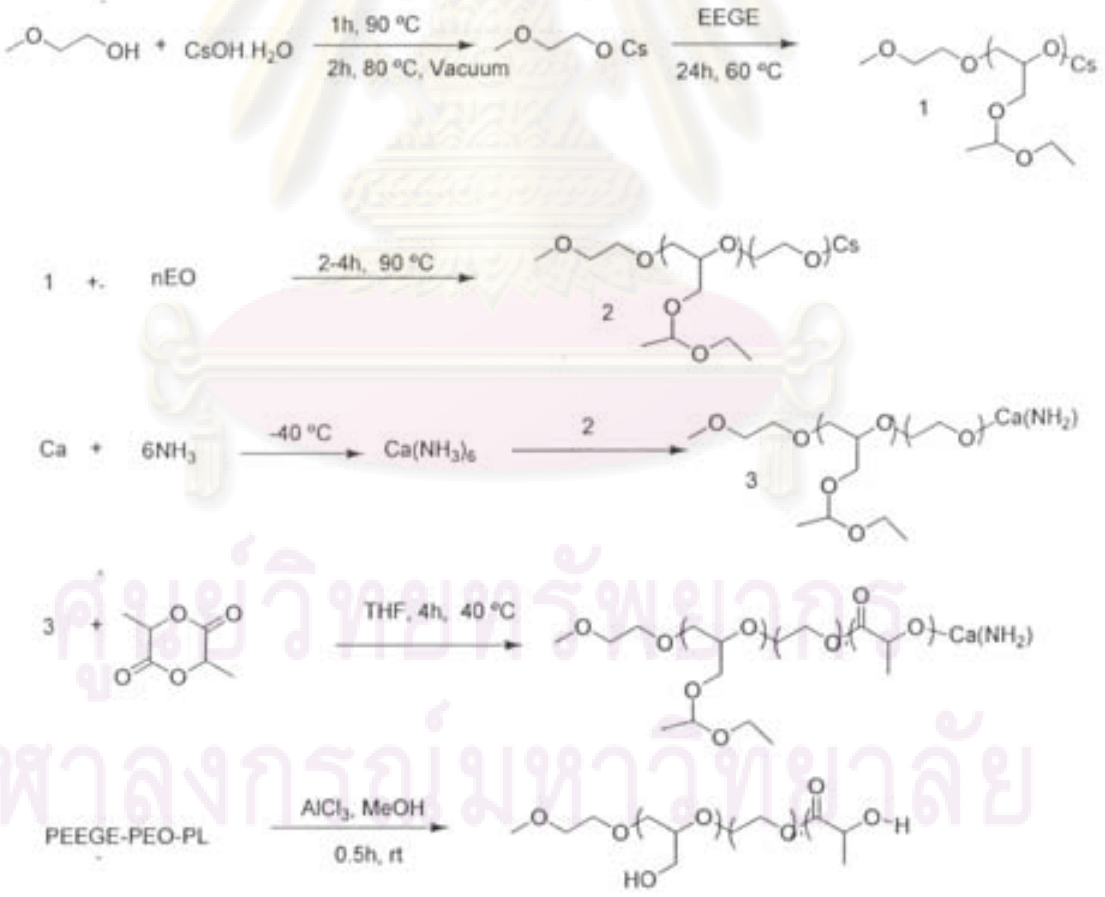
Scheme 2.6 Synthesis of poly(ethylene oxide)-*b*-poly(glycidol)-*b*-poly(L,L-lactide).

Sunsaneeyametha [4] had synthesized linear block copolymer of PLLA and PGly by cationic polymerization of benzyl glycidyl ether using tin (IV) chloride and copolymerization with L–lactide using $Sn(oct)_2$, following by catalytic hydrogenation for benzyl cleavage. NMR spectroscopy revealed the esterification linkage between two blocks. However, the resulting copolymer had low molecular weight.



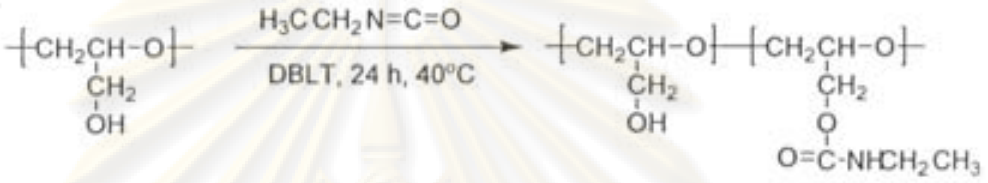
Scheme 2.7 Synthesis of linear block copolymer of PLLA and PGly.

Dimitrov et. al. [21] reported synthesis of PGly-*b*-PEO-*b*-PDLLA. First, PEEGE was polymerized using cesium 1-methoxyethanoate as initiator. The reaction was carried out further with ethylene oxide, before converting to PEEGE-*b*-PEO-$CaNH_2$ as a macroinitiator. Next, ROP of DL-lactide was followed. And finally, the copolymer was obtained after the acidic cleavage of ethoxy ethyl ether. The cloud point of 2% aqueous solution of copolymer was not observed from 0-100 °C at wavelength of 500 nm.



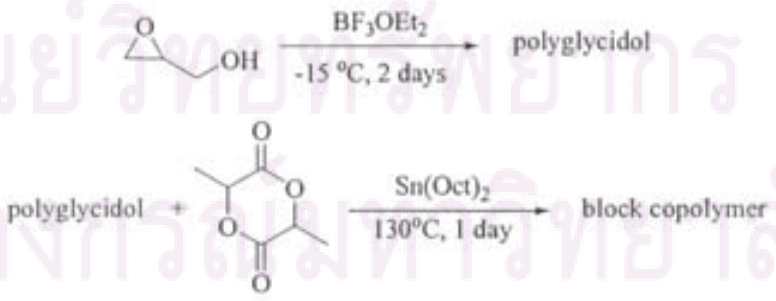
Scheme 2.8 Synthesis of PG-*b*-PEO-*b*-PLA.

Jamroz-Piegza et al. [17] synthesized thermo-sensitive water-soluble polymers, poly(glycidol-co-ethyl glycidyl carbamate), by the hydrophobic modification of hydroxyl groups of polyglycidol chain with ethyl isocyanate. The influence of copolymer composition and polymer concentration on the cloud point was investigated. The cloud point was easily controlled in a range from 22 to 81 °C by changing the degree of modification.



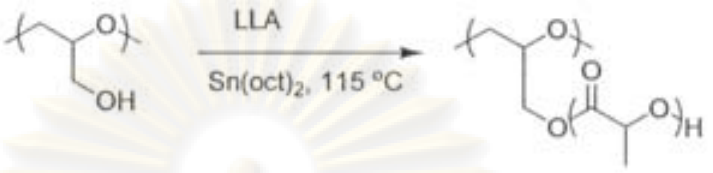
Scheme 2.9 Modification of linear PG.

Gonil [22] synthesized hyperbranched block copolymer of polyglycidol (PG) and PLLA, and studied degradation of the copolymer in buffer solution pH 7.4. It was found that molecular weight, polydispersity and percentage yield of the copolymer depended on reaction temperature, reaction time and feeding ratio and not the amount of $Sn(oct)_2$ from 2 to 10 percentage mole of hydroxyl mole in PG. The suitable condition of ROP of LLA with PG macroinitiator was carried out at 130°C for 1 day in bulk, using 5 mol% of $Sn(Oct)_2$. The obtained PLLA-*b*-PG showed lower T_g than PLLA homopolymer. The T_g value was in the range of 14 to 48 °C. The copolymer was more hydrophilic than homo PLLA. The hydrophilicity was found to decrease with the increasing of LLA content in the copolymer



Scheme 2.10 Synthesis of hyperbranched PG-*b*-PLLA.

Branched PLLA synthesized by ROP of LLA in bulk using linear polyglycidol as a macrointiator was reported in 2006 [23].



Scheme 2.11 Synthesis of branched PLLA using linear polyglycidol.

CHAPTER III

EXPERIMENTALS

3.1. Materials

All chemicals were used as received without further purification. Commercial-grade solvents were distilled before use. Anhydrous tetrahydrofuran was prepared by refluxing with sodium metal and benzophenone. Chemicals and their manufacturers are L-lactic acid 88% solution (Carlo Erba), *p*-toluene sulfonic acid monohydrate (Fluka), antimony (III) oxide (Fluka), glycidol (Fluka), ethyl vinyl ether (Fluka), sodium hydrogen carbonate (Fluka), sodium sulfate anhydrous (Fluka), potassium *tert*-butoxide (Fluka), stannous (II) 2-ethyl hexanoate (Aldrich), tetrahydrofuran (Labscan Asia), diethyl ether (Merck), acetic acid (Merck), chloroform-d (Aldrich), ethanol-d4 (Wilmad), ethyl acetate (commercial grade), methanol (commercial grade), and dichloromethane (commercial grade).

3.2. Instruments

3.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

Proton (1H), carbon (13C), COSY nuclear magnetic resonance analysis were carried out by using Varian Mercury-400 spectroscopy operating at 400 MHZ for 1H and 100 MHZ for 13C in selected deuterated solvent. Chemical shift (δ) are reported in part per million (ppm) relative to tetramethylsilane (TMS) by using residual protonated solvent signal as a reference.

3.2.2 Gel Permeation Chromatography (GPC)

Gel permeation chromatograms of PLLA and copolymer of LLA and G were obtained from Waters 600 controller chromatograph equipped with three HR

(Waters) columns (HR1, HR3, 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.

3.2.3 Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS)

Mass spectra of PEEGE, PLLA and copolymers were acquired using Brucker Microflex MALDI-TOF mass spectrometer. Spectra were acquired in positive-ion mode using reflectron. Sample was dissolved in THF and mixed with matrix solution prepared from dissolving α-hydroxycyanocinnamic acid (CCA) for PEEGE or dithranol for PLLA and copolymer in THF. PEG 2000 was used as a external standard.

3.2.4 Differential Scanning Colorimetry (DSC)

Measurements were carried out on a Perkin Elmer DSC7 and measured under atmosphere environment. Heating rate 0.7 °C /min from 70 °C to 120 °C.

3.3. Experimental sections

3.3.1 Synthesis of 1-ethoxyethyl glycidyl ether [24]

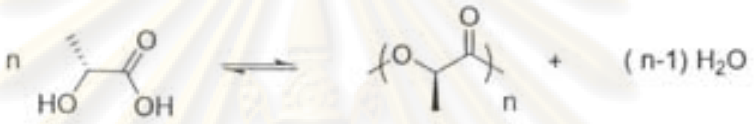
Glycidol (38.0 g, 0.513 mol) and ethyl vinyl ether (150 mL, 1.57 mol) were stirred on water bath at temperature no higher than 40 °C. Then, *p*-toluenesulfonic acid monohydrate (0.75 g, 3.9 mmol) was added portionwise to prevent overheating and bumping. The reaction was kept for 3 hours. Then, 75 mL of 10% aqueous sodium hydrogen carbonate solution was added and transferred to a separating funnel. Aqueous layer was removed. The organic layer was re-extracted again with $NaHCO_3$ solution. Trace of water in the organic layer was removed by adding sodium sulfate anhydrous. The crude product was concentrated using rotary evaporator and distilled under reduced pressure. The collected portion was

determined by (^{1}H, ^{13}C, COSY, HSQC) NMR and kept in a closed bottle in desiccator before use.

3.3.2 Synthesis of L-lactide monomer [25]

L-lactide, a six-memberred ring dimer of L-lactic acid, was synthesized by a two-step method as follows.

Polycondensation



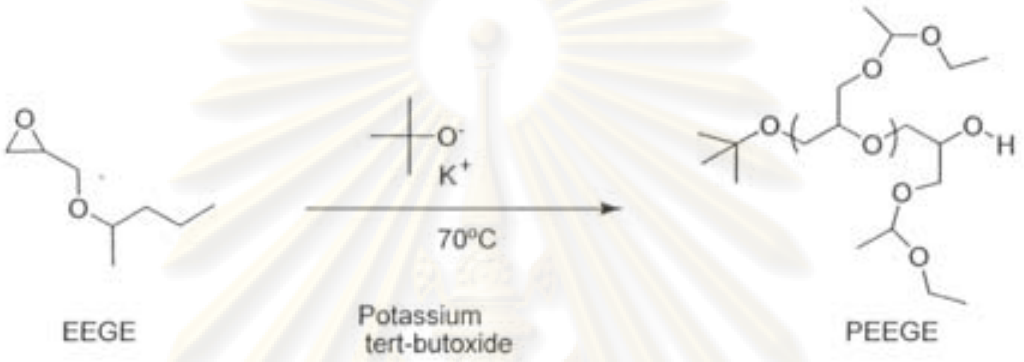
Lactic acid 88% (568 g) and *p*-toluenesulfonic acid monohydrate (5.6 g) was placed in a two-necked 1L round bottom flask equipped with reduced pressure distillation apparatus and a thermometer. Then, the temperature was raised to 140 °C under nitrogen atmosphere within 2 hours. Once the temperature reached 140 °C, heating was continued to 160 °C. The temperature was maintain at to 160 °C until water stopped distilling (approx. 3 hours). Next, apply vacuum to reduce pressure down to 50-100 mbar and maintain the condition until no more water distilled (approx. 3 hours). The residue was called low molecular weight PLLA.

Thermal decomposition

The low molecular weight PLLA from the previous step and antimony (III) oxide (1% by weight) was added into the round bottom flask equipped with reduced pressure distillation apparatus and an air condenser. The mixture was rapidly heated up to 160 °C within 30 minutes under nitrogen atmosphere. Once the temperature reached 160 °C, high vacuum was applied and heating was continue to 220 °C. Stop heating when no more crude product was formed at the air condenser. The crude

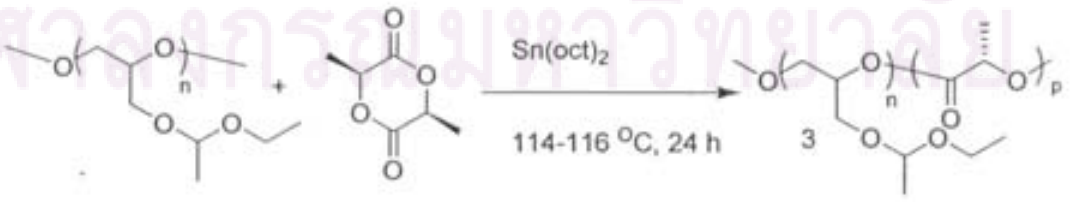
LLA was recrystallized 3 times in ethyl acetate. The product purity was analyzed by ^{1}H NMR and DSC following ASTM E 928-03. LLA was kept in a closed cool dry container.

3.3.3 Synthesis of poly(1-ethoxyethyl glycidyl ether) [16]



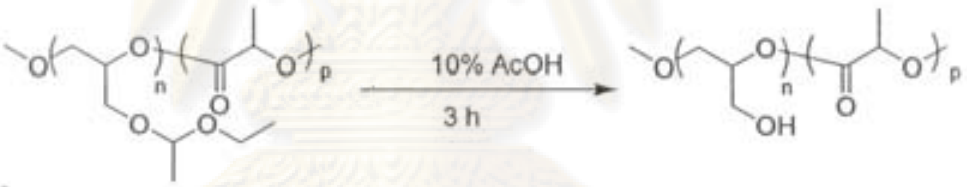
All glasswares and accessories, for example, septum and magnetic bar, were pre-dried under reduced pressure for 1 day before setting up the reaction. 1-Ethoxyethyl glycidyl ether (32.0 g, 0.22 mol) and potassium *tert*-butoxide (0.49 g, 2% mol initiator) were transferred into a round bottom flask in a nitrogen glove box. The reaction was performed at 72 °C under nitrogen atmosphere until the product turned viscous liquid. The percent conversion was determined by 1H NMR. Crude product was purified by dissolving in a large volume of diethyl ether. Insoluble solid residue was separated by centrifugation. The organic solution was evaporated under reduced pressure using rotary evaporator. Product characterization was carried out by NMR, GPC and MALDI-TOF-MS.

3.3.4 Ring opening copolymerization of L-lactide using PEEGE as initiator



All substances, glasswares, and accessories were pre-dried under vacuum for 1 day before setting up the reaction. A pre-weight amount of PLLA was introduced into each PEEGE flask under nitrogen glove box. A precisely amount of freshly prepared $Sn(oct)_2$ solution in anhydrous THF (250 μL + 1 mL THF) was introduced into the flasks. After the mixture was stirred, THF was removed under reduced pressure. Then, the reaction was performed at 114-116 °C for 24 hours. The percent conversion was determined by ^1H NMR. Crude product was purified by dissolving in methanol. Insoluble solid residue was separated by centrifugation and washed several time by methanol. Methanol was evaporated from the organic soluble and insoluble residue under reduced pressure using rotary evaporator. Product characterization was carried out by NMR, GPC and MALDI-TOF-MS.

3.3.5 Deprotection of acetal block on poly(1-ethoxyethyl glycidyl ether)-b-poly(L-lactide) [26]

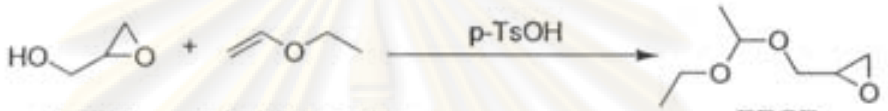


The methanol soluble portion of poly(1-ethoxyethyl glycidyl ether)-b-poly(L-lactide) was dissolved in methanol (56 times the weight of PEEGE in the copolymer). This was followed by dropwise addition of 10% aqueous acetic acid (28 times the weight of PEEGE in the copolymer). The reaction was performed for 3 hours. All solvents were then evaporated under reduced pressure of a rotary evaporator. The sample was dried under reduced pressure for 2 days. Product characterization was carried out by NMR, GPC and MALDI-TOF-MS.

CHAPTER IV

RESUL TS AND DISCUSSION

4.1 Synthesis of 1-ethoxy ethyl glycidyl ether (EEGE)



glycidol ethyl vinyl ether EEGE

Scheme 4.1 Synthesis of 1-ethoxy ethyl glycidyl ether (EEGE).

The synthesis of 1-ethoxyethyl glycidyl ether (EEGE) was carried out by following Fitton's procedure [24] (Scheme 4.1). The portionwise addition of p-Toluene sulfonic acid was critical point in the preparation in order to prevent the mixture overflow and high volatile ethyl vinyl ether loss. Distilled EEGE is clear and colorless liquid with strong unpleasant odor.

^{1}H NMR of EEGE (Figure 4.1 and 4.2) in $CDCl_3$, δ (ppm): 4.71 (2q, J_{HH} = 5.3 Hz, -OC**H**(O)CH_3), 3.76 (dd, J_{HH} = 3.1, 11.5 Hz, -**H**HC-C(O)-C, epoxide ring of diastereoisomer A), 3,66 (dd, J_{HH} = 3.3, 11.6 Hz, -**H**HC-C(O)-C, epoxide ring of diastereoisomer B), 3.61 (qd, J_{HH} = 2.3, 7.4 Hz, **H**HC-CH_3 of diastereoisomer A), 3.59 (qd, J_{HH} = 1.7, 7.1 Hz, **H**HC-CH_3 of diastereoisomer B), 3.45 (qd, J_{HH} = unmeasureable, 7.0 Hz, **H**HC-CH_3 of diastereoisomer A) , 3.43 (qd, J_{HH} = unmeasureable, 7.0 Hz, **H**HC-CH_3 of diastereoisomer B), 3.49 (dd, J_{HH} = 5.4, 6.1 Hz, -**H**HC-HC(O)-CH_2, of diastereoisomer B), 3.36 (dd, J_{HH} = 5.4, 6.1 Hz, -**H**HC-HC(O)-CH_2, of diastereoisomer A), 3.09 (m, J_{HH} = n/a Hz, HHC(O)-C**H**-, epoxide ring), 2.75 (2dd, J_{HH} = 1.0, 4.6 Hz, **H**HC(O)-CH-, epoxide ring), 2.59 (dd, J_{HH} = 2.6, 5,0 Hz, H**H**C(O)-CH-, epoxide ring of diastereoisomer A), 2.55 (dd, J_{HH} = 2.7, 4.9 Hz, H**H**C(O)-CH-, epoxide ring of diastereoisomer B), 1.27 (2d, J_{HH} = 5.6, 6.0 Hz,CH_3CH(O)-O-), 1.15 (2t, J_{HH} = 1.0, 7.0 Hz, CH_3-CH2-O-)

^{13}C NMR of EEGE (Figure 4.3) in $CDCl_3$, δ (ppm):99.59, 99.57 (-$OCH(O)CH_3$), 65.7 (-O-CH_2-CH(O)-(O)CH_2 epoxide ring of diastereoisomer A), 65.0 (-O-CH_2-CH(O)-(O)CH_2 epoxide ring of diastereoisomer B), 60.9, 60.8 (-CH_2-CH_3), 50.7, 50.8 (HC(O)-CH_2, epoxide ring), 44.5, 44.4 (CH_2(O)-C, epoxide ring), 19.7, 19.6 (CH_3-CH(O)O-), 15.2 (CH_3-CH2-)

FT-IR (cm^{-1}) (Figure 4.4): 2983 (s, epoxy ring C-H stretching), 1386 (m, CH_3, symmetrical bending), 1440 (w, CH_3, asymmetrical bending), 1253 (w, cyclic C-O-C symmetrical stretching), 1137-1058 (str, non cyclic C-O-C asymmetrical stretching), 855 (m, cyclic C-O-C asymmetrical stretching)

ESI-MS (positive ion) (Figure 4.5) solvent: methanol, m/e (relative intensity): 133.014 (100), 315.96 (52), 147.075 (30), 169.114 (20), 100.890 (15), 347.217 (7), 201.119 (5)

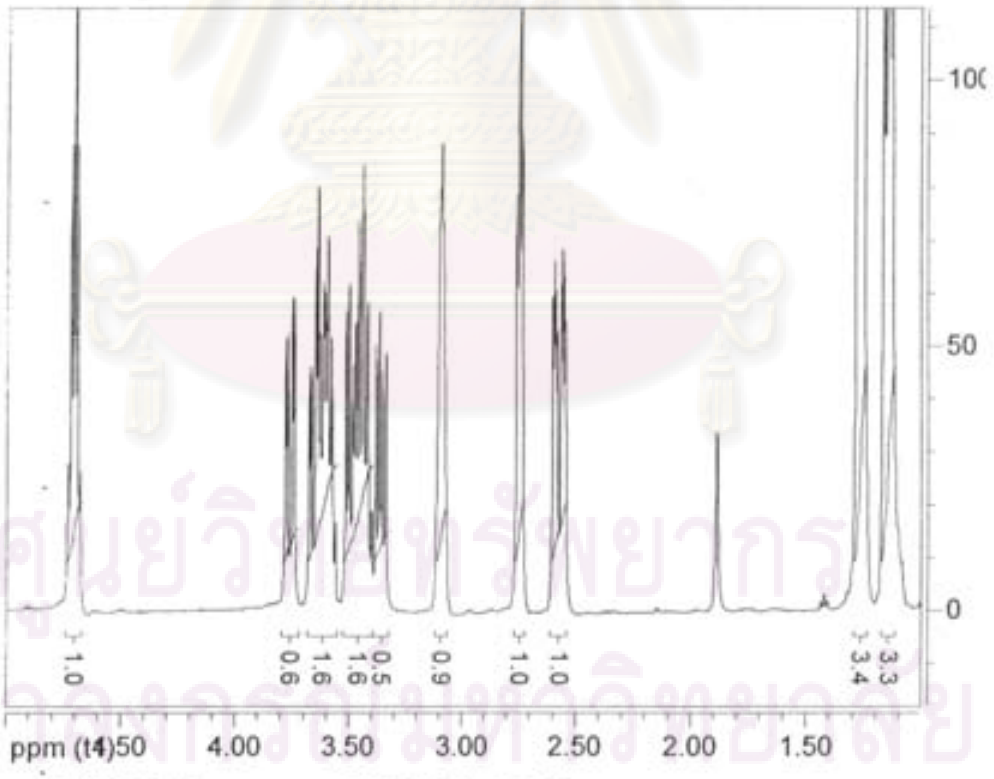


Figure 4.1 ^1H NMR spectrum of EEGE in $CDCl_3$.

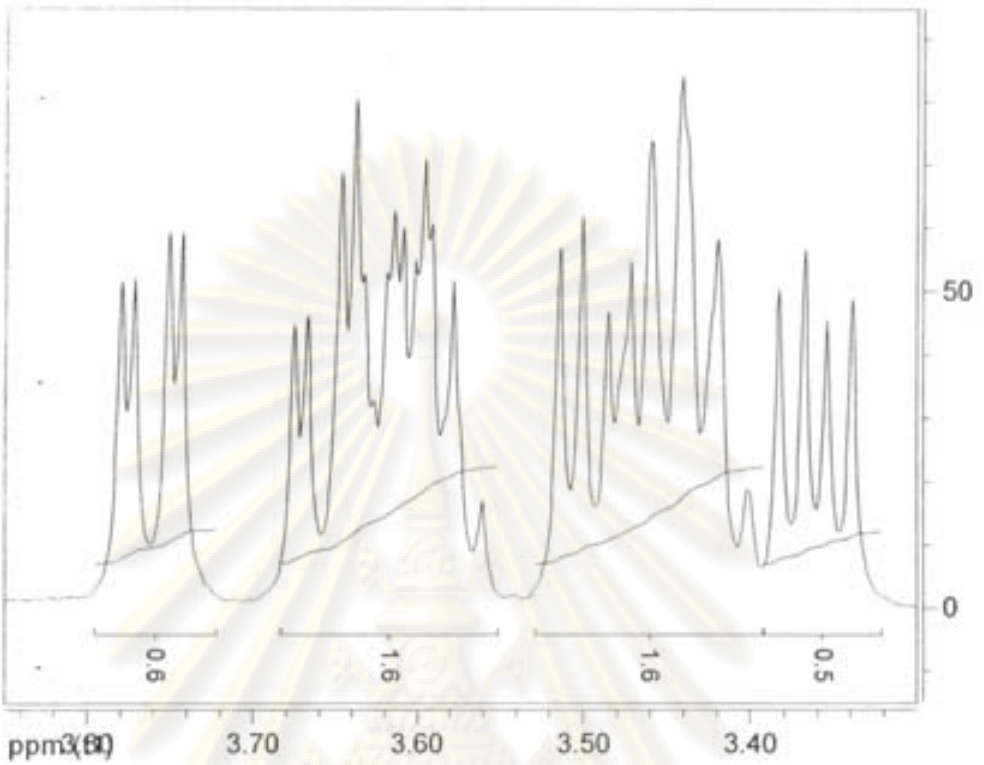


Figure 4.2 Expanded ^{1}H NMR spectrum (3.85-3.30 ppm) of EEGE in $CDCl_3$.

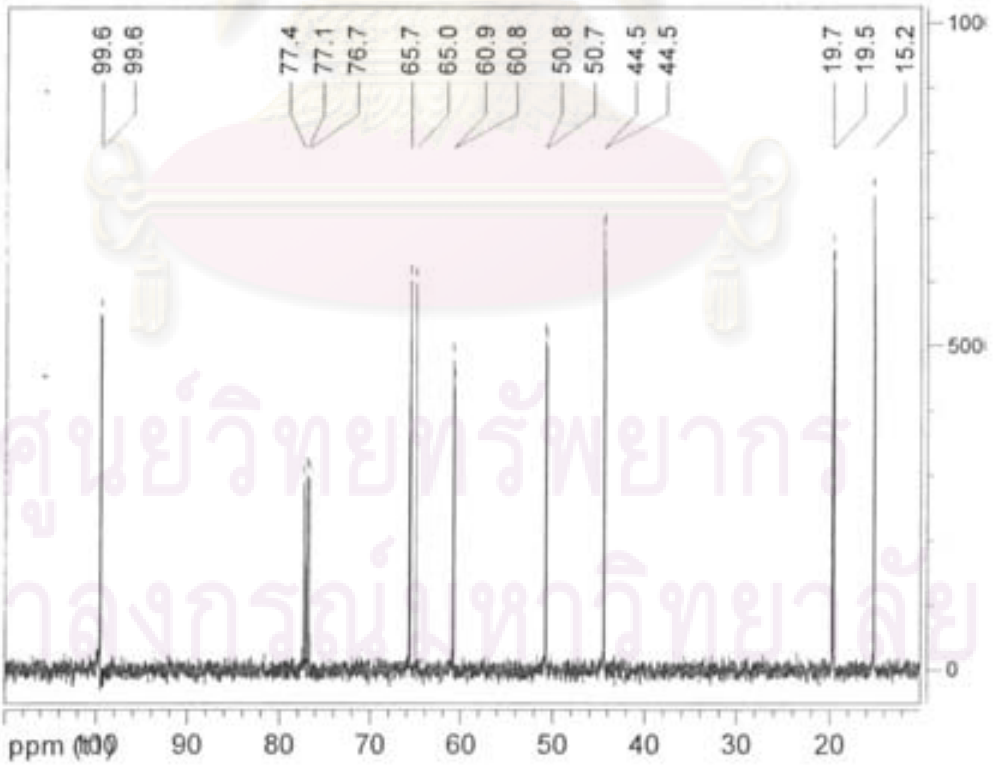


Figure 4.3 ^{13}C NMR spectrum of EEGE in $CDCl_3$.

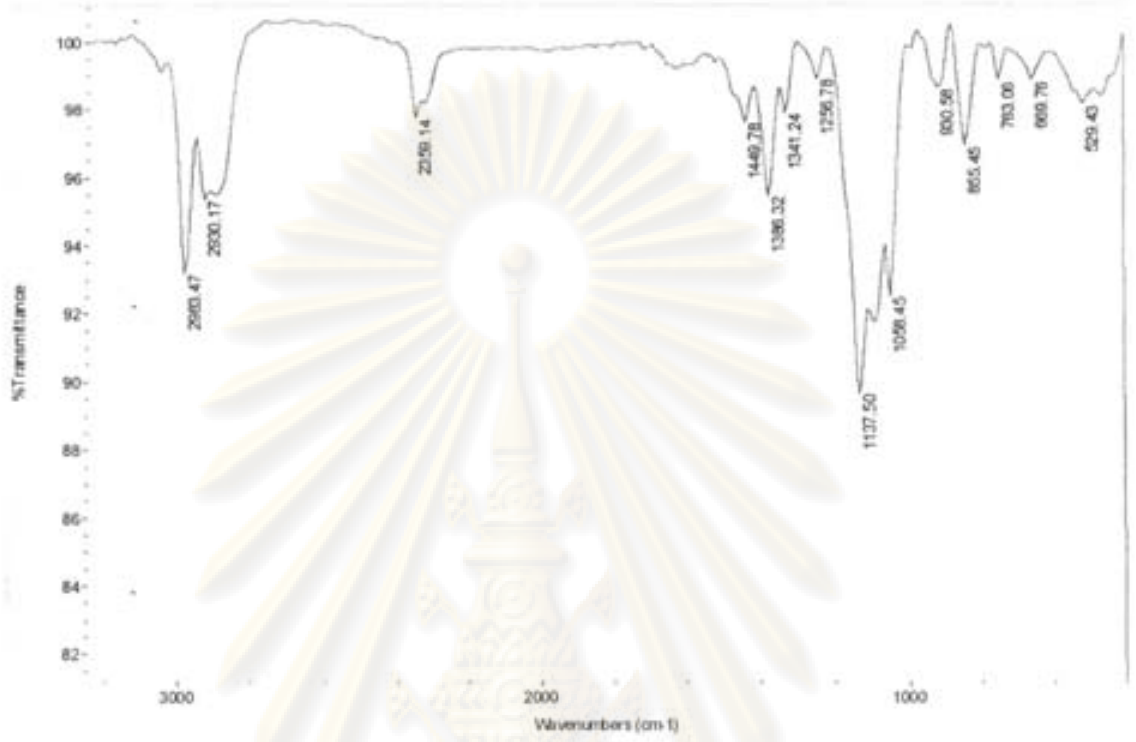


Figure 4.4 FT-IR spectrum of EEGE.

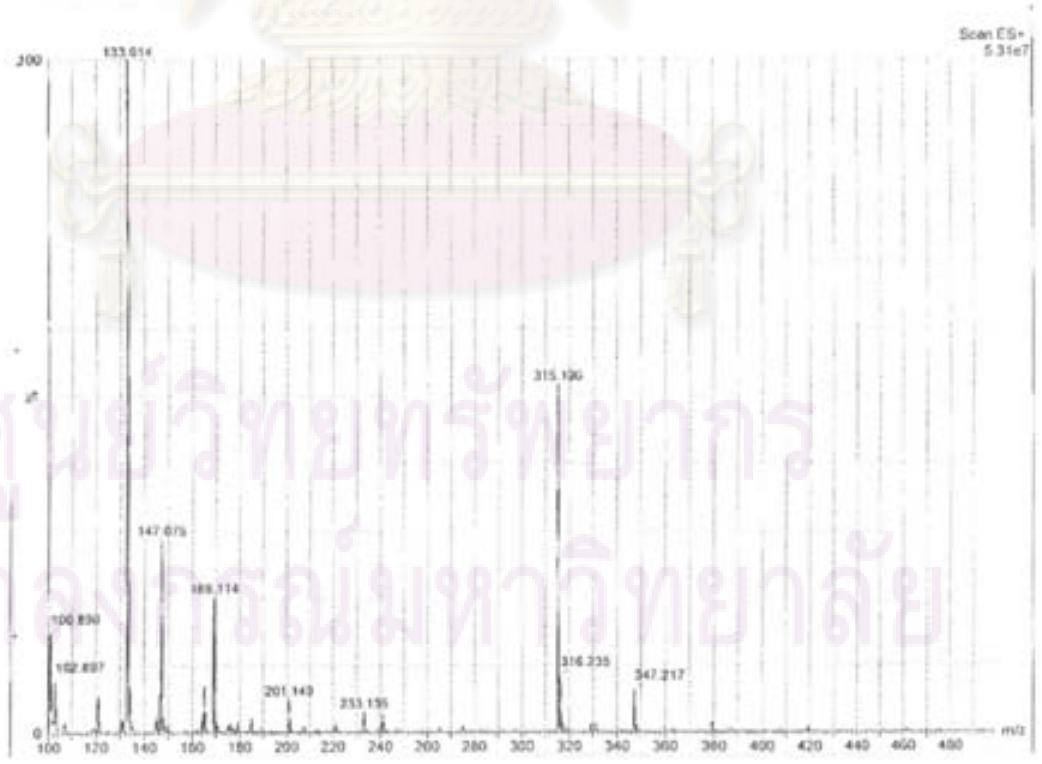
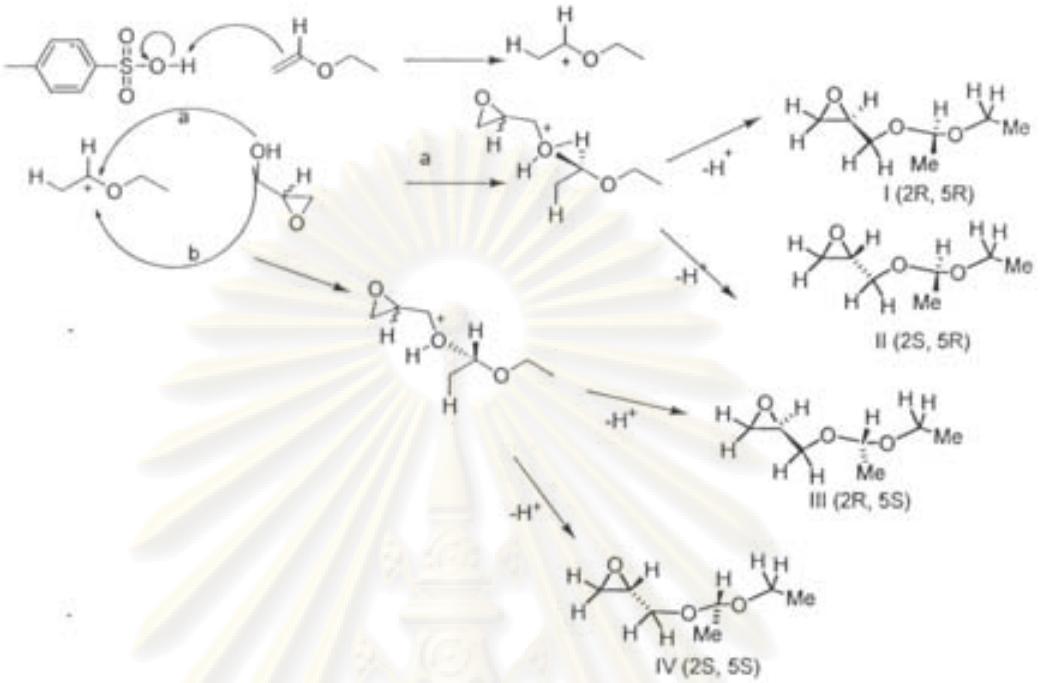


Figure 4.5 ESI-MS of EEGE (solvent: methanol).

All signals in the ^{1}H NMR spectrum was found to match all protons of EEGE [18, 24]. However, the splitting patterns of some signals were not as expected from the chemical structure. For example, the signal at 1.27 ppm appears as a triplet with area ratio of 1:2:1 instead of a doublet; the signal at 4.7 ppm appears as pentet with area ratio of 1:3.2:5.2:3.2:1 instead of a set of quatet. This observation suggested that two sets of doublet signals overlapping each other at 1.27 ppm and two sets of quartets overlapping each other at 4.7 ppm. In addition, the number of proton signals from 3.8-3.3 ppm were more than those present in the EEGE structure. This observation suggested that two EEGE molecules having slightly different structures might be present in the product, resulting in two sets of signals overlapping each other. In addition, the number of carbon signals from ^{13}C NMR spectra were more than those present in the structure, as reported by Kim *et al.* [18]. For example, carbon signals at 99.59 and 99.57 ppm were identified as carbon atoms that coupled with the same proton having a chemical shift at 4.7 ppm from the proton NMR.

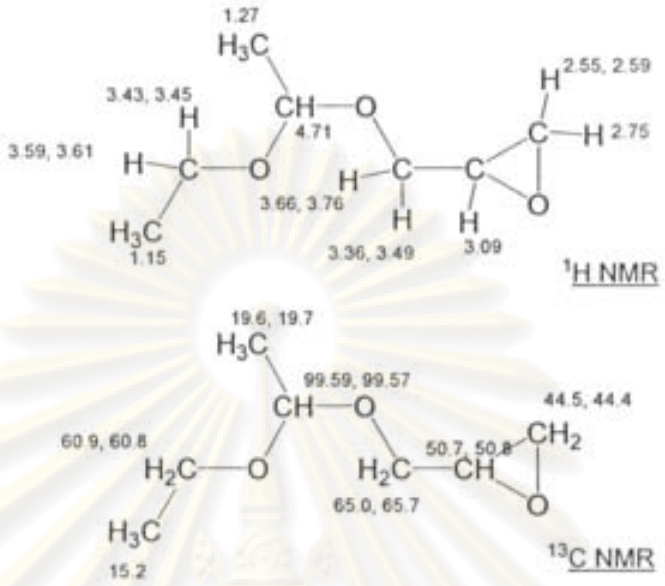
This is most likely due to the formation of diastereoisomers of EEGE during synthesis. The formation of the diastereoisomers is shown in Scheme 4.2. The reaction started when vinyl group was protonated becoming a planar carbocation. Hydroxyl group of glycidol, a stronger nucleophile than the oxygen atom of epoxide ring, can attack equally upper or lower side of the carbocation plane. This attacked carbon will become a new chiral center for the molecule, that already possesses a chiral carbon at the epoxide ring in either *S*- or *R*- form. The obtained EEGE, therefore, has 2 chiral carbons, consequently a mixture of 4 stereoisomers are formed.

As shown in Scheme 4.2, structure I and IV are an enantiomer pair and structure II and III are the other enantiomer pair. So, the structure I and II are diastereoisomers that, in general, give slightly different chemical shifts in NMR analysis, leading to two sets of overlapping signals. The same situation is also applied to structure III and IV.



Scheme 4.2 Reaction mechanism of EEGE synthesis from glycidol and ethyl vinyl ether.

^{1}H-H COSY NMR spectrum (Figure A-1) indicated proton signals coupled, i.e., 4.71 and 1.27; 3.43, 3.45 and 1.15; 3.59, 3.61 and 1.15; 2.59, 2.55 and 2.75; 2.59, 2.55 and 3.09; 2.75 and 3.09; 3.36 and 3.09; 3.49 and 3.09; 3.66 and 3.09; 3.76 and 3.09 ppm. H-C HQSC NMR (Figure A-2) spectrum indicated proton signals coupled carbon signals ,i.e. 4.71 and 99.59, 99.57; 3.36, 3.76 and 65.7, 3.49, 3.66 and 65.0; 3.45, 3.43, 3.61, 3.59 and 60.9, 60.8; 3.09 and 50.8, 50.7; 2.75 and 44.5, 44.4; 2.59, 2.55 and 44.5, 44.4; 1.27 and 19.7, 19.6; 1.15 and 15.2 ppm. All proton and carbon signals are labeled in the EEGE structure as illustrated in Scheme 4.3.



Scheme 4.3 Structure of EEGE labeled with NMR chemical shift.

FT-IR spectra (Figure 4.4) indicated C-H stretching of epoxy ring at 2,983 cm^{-1} [24, 26]. It confirmed the presence of ring in EEGE. Gas chromatography equipped with a chiral column was utilized to check the product purity and the occurrence of those stereoisomers. As shown in Figure 4.6 and Table 4.1, the chromatogram showed 3 peaks at 6.26, 6.43 and 6.49 min with the area ratio of 2:1:1 and tiny two peak signals of racemic glycidol at 2.5 and 2.6 min. Under this GC condition, the 4 stereoisomers were separated into 3 peaks. The first peak was a mixture of two stereoisomers. Although the EEGE purity were so high as 99.4-100%, they looked slightly pale yellow. The discoloration was possibly from contaminated *p*-toluene sulfonic acid. So, EEGE distillation was a must.

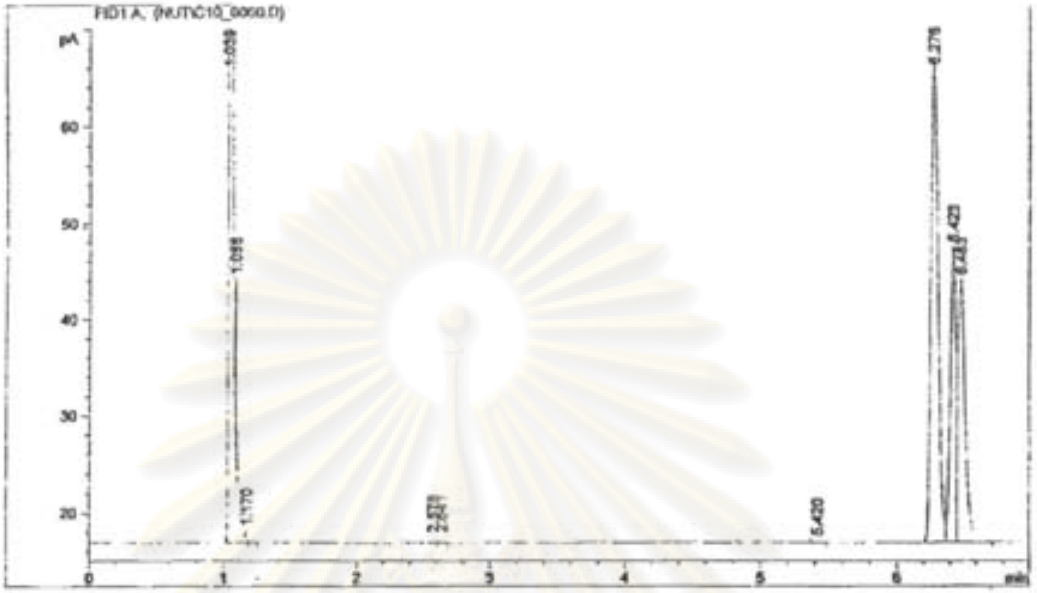


Figure 4.6 Gas chromatogram of EEGE, E3.

Table 4.1 Purity analysis of EEGE[1] by GC[2]

Entry	Peak area at retention time				% Purity
	6.28 min	6.43 min	6.49 min	Other(s)	
E1	0.657	0.321	0.364	0.0054	99.6
E2	0.482	0.244	0.257	-	100
E3	0.638	0.305	0.360	0.0084	99.4
E4	0.461	0.224	0.255	0.0020	99.8

[1]undistilled EEGE was measured.

[2]GC condition: Isothermal (90 °C), manual inject, spilt ratio 100:1, Column No 10 (cyclodextrin derivatives) 29.6 m × 0.25 mm × 250 mm, column velocity = 53 cm/sec at 140 °C, FID detector 250 °C

Moreover, ESI-MS spectrum (Figure 4.5) was determined. A mass peak of 147.075 that matched the protonated mass of EEGE, $C_7H_{15}O_3^+$ (calculated mass = 147.0732) was found. Other peaks were identified as follows, 169.114 $[M+Na]^+$, 315.96 $[2M+Na]^+$, 100.890 $[M-OC_2H_5]^+$, 347.217 $[2M+CH_3OH+Na]^+$, 201.119 $[M+CH_3OH+Na]^+$. The solvent combined mass peak was able to be found in low polar to high polar substance [27]. It is unusual that the mass peak at 133.014 was

also found because $[M-13]^+$ was not existed in mass spectrometry. It might be an impurity from sample preparation.

In conclusion, the obtained EEGE was identified by NMR, FT-IR, and ESI-MS and was used as the starting material for the polymerization of EEGE.

4.2 Synthesis of L-lactide (LLA)

^{1}H NMR of L-lactide (Figure 4.7) in $CDCl_3$, δ (ppm): 5.04 (q, J_{HH} = 6.6 Hz, -C**H**CH_3), 1.64 (d, J_{HH} J_{HH} = 6.6 Hz, -CHC**H$_3$**)

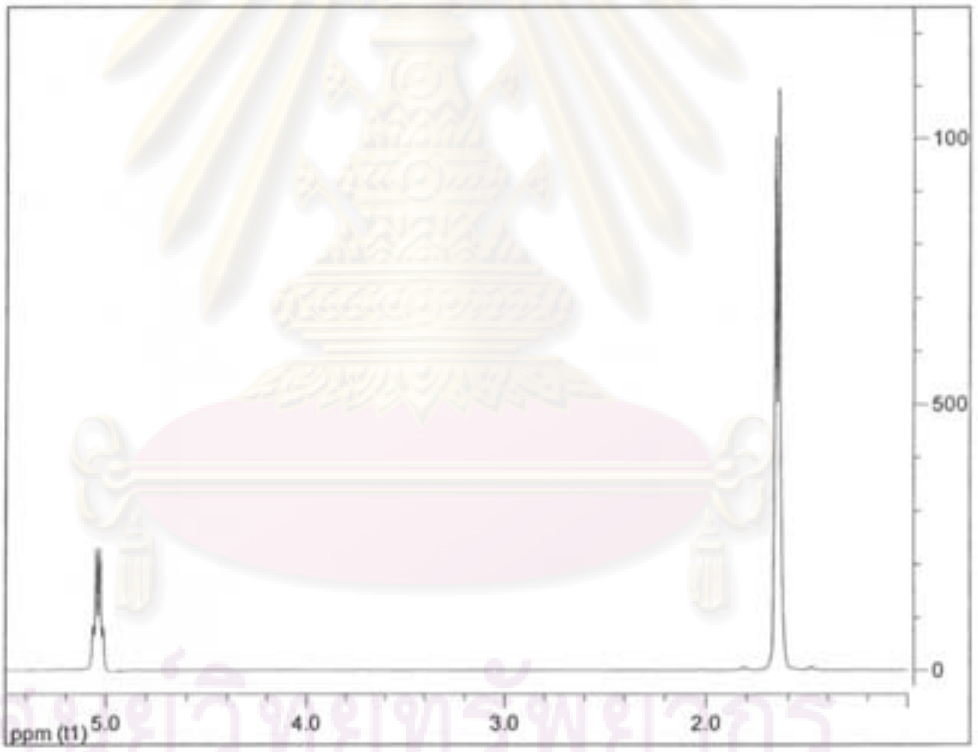


Figure 4.7 ^{1}H NMR spectrum of L-Lactide in $CDCl_3$.

L-Lactide (LLA) was synthesized from 88 % aqueous solution of L-lactic acid. After polycondensation and thermal decomposition steps, crude LLA was obtained as a mixture of pale yellowish to dark brown solid.

Table 4.2 Yield of L-lactide synthesis

Entry	%Mass loss in polycondensation step	%Crude yield	%LLA yield
L1	29.5	56.2	26.0
L2	26.4	43.0	23.1
L3	29.3	57.0	22.5

From Table 4.2, the mass loss in polycondensation step was found to relate with the percent crude yield. The high mass loss brought about the high percentage of crude yield. The percent mass loss in polycondensation step was mainly water from 2 sources. The first one was water from 88% lactic acid solution. The second was by-product water from the acid-catalyzed condensation reaction of L-lactic acid. It meant that the more percent of the L-lactic acid converted to low PLLA, the more by-product water occurred and the more percent mass loss was measured. The obtained 43-57 % crude yield and 22.5-26 % yield of LLA were much lower than the reported value of 70 % crude yield and 41 % yield of LLA [25b]. The lower yield was possibly because of the air condenser design. An extent of distilled LLA were noticeably condensed at air condenser and fallen back to the reactor.

LLA was recrystallized three times in ethyl acetate to become colorless fine needle of LLA and then was characterized by ^{1}H NMR, optical rotation measurement and purity analysis by DSC. The optical rotation of commercial available 98% LLA at a concentration of 1 g/L in toluene at 20 °C and a wavelength of 589 nm ($[\alpha]^{20}_{589nm}$) is -285 ±10 [28]. One batch of recrystallized LLA, L1, was measured by optical rotation for purity determination. The result was -285.49, which was the range of the specification.

Differential scanning colorimetry (DSC) was a standard measurement to determine the purity of LLA following ASTM E928-03: The principle is based on

van't Hoff equation that melting temperature range of a compound broadens when the impurities level rises.

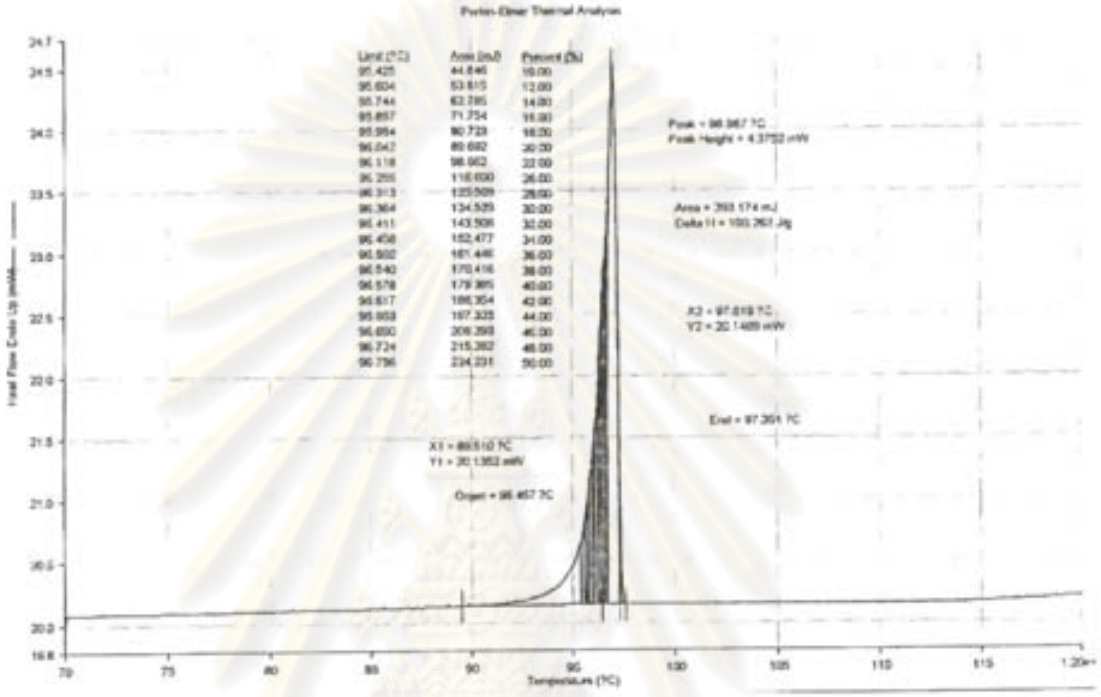


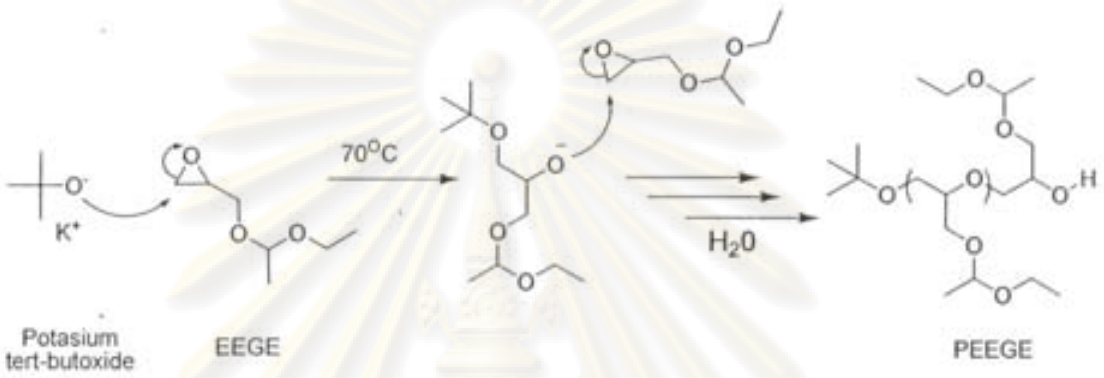
Figure 4.8 A thermogram of purity analysis of LLA (L3) obtained from DSC.

The purity calculation was done manually because the DSC instrument used had no function to calculate the sample purity. The purity of L-lactide, L3 as high as 99.72 % was obtained as shown in Figure 4.8 and Table B-1. The required purity of LLA, however, should not be lower than 99.9% [25a] to obtain a polymer with high molecular weight. The obtained LLA was therefore tested for polymerization as discussed in section 4.4.

4.3 Synthesis of poly(1-ethoxyethyl glycidyl ether)

Poly(1-ethoxyethyl glycidyl ether) was synthesized by ring-opening polymerization of EEGE monomer by using *t*-butoxide as an initiator (Scheme 4.3). The appearance of polymerized product varied from yellowish to brown viscous liquid. It was noticed that all experiments gave discoloration in the reaction mixture after the initiator, potassium *tert*-butoxide, was introduced into EEGE in both bulk

and solution polymerization conditions. The reason of their discoloration phenomena was in doubt. A possible explanation was that *tert*-butoxide ion was a strong base and might initiate side reaction to form unsaturated species in the reaction mixture. The discoloration remained in EEGE even though it was purified with diethyl ether.



Scheme 4.4 Anionic ring opening polymerization of PEEGE.

During the polymerization, the reaction mixture changed from light to viscous liquid. The percentage of monomer conversion was determined from ^{1}H NMR (Figure 4.9) by correlating the peak area of the methine protons at 4.65 ppm in the product and the proton of epoxide functionality in the starting material at 2.76 ppm as shown in equation

$$\%\text{Conversion} = \frac{I_{4.68\ ppm} \times 100}{\left(I_{4.68\ ppm} + I_{2.76\ ppm}\right)}$$

After polymerization, the methine proton signals at 3.09 ppm and methylene protons at 2.75, 2.59 and 2.55 ppm of epoxide ring monomer disappeared. The signals for those protons shifted to the region between 3.68-3.42 ppm. In ring opening polymerization, *tert*-butoxyl group initiated polymerization by attacking the CH_2 of the epoxide ring. In order to identify the *tert*-butoxy end group on the polymer product, an NMR signal at around 1.22 ppm of the nine butyl protons was expected. Unfortunately that signal was shielded by the methyl signal of ethoxy ethyl pendant group at 1.24 ppm. Therefore calculation of the PEEGE molecular weight by end group analysis was not possible. Moreover it should be noted here that, in this synthesis step, no evidence of acetaldehyde signal was detected. It suggested that no

occurrence of acetal cleavage was present during polymerization which corresponds to the fact that the protected acetal group was tolerant to basic condition.

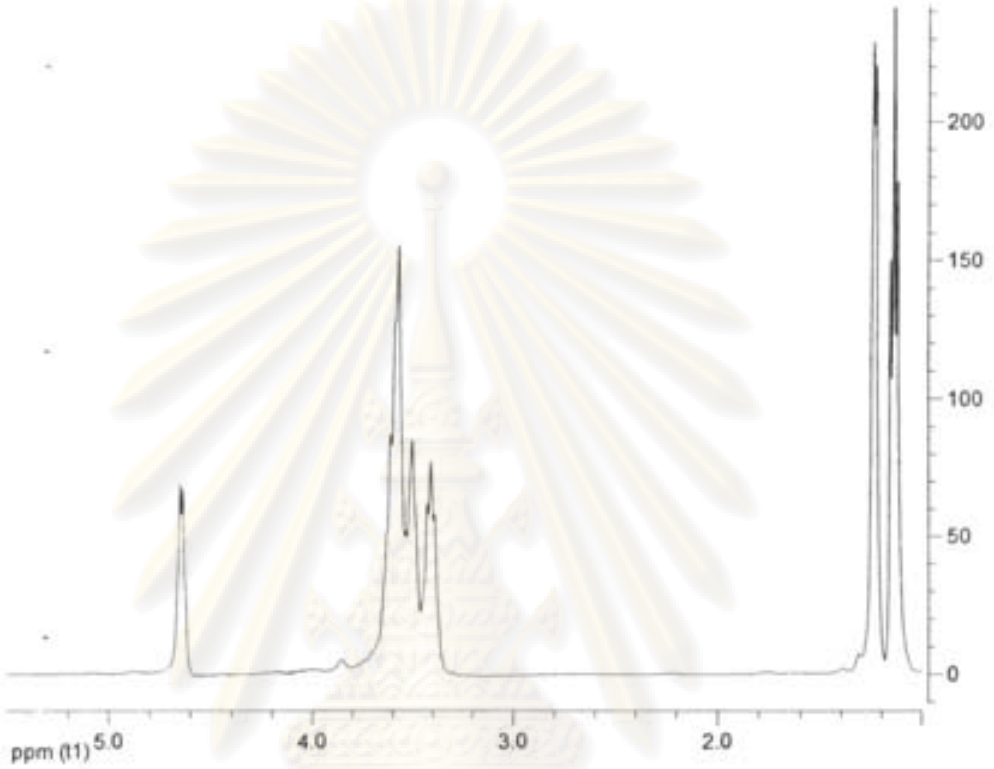


Figure 4.9 ^{1}H NMR spectrum of PEEGE (PE7) in $CDCl_3$.

^{1}H NMR of PEEGE (Figure 4.10) in $CDCl_3$,δ (ppm): 4.65 (-OC**H**CH_3-O), 3.68-3.42 (-CH_2-CH(O)-CH_2-, -O-CH_2-CH3), 1.24 (CH_3-C(O)H-O-), 1.11 (CH_3-CH_2-O-)

Table 4.3 shows the reaction conditions and the molecular weights of PEEGE. The effect of initiator amount on the polymerization was studied by varying the initiator from 0.9-3% mole of the monomer as in entry PE1-PE5. The monomer conversions of all PEEGEs were calculated from NMR spectra (Figure 4.10). In case of PE1, the conversion was only 14% when the initiator was as low as 0.9%. Theoretically lowering the % mole initiator will result in a polymer with higher molecular weight, because the number of initiating species are higher when increasing the initiator in the system. However in this work, it was found that no polymer was obtained when the initiator amount was 1.5% and lower. The polymers were obtained when the initiator was more than 1.5% as shown in Entries PE3 to

PE8. The molecular weights of PEEGE were rather low at around 4,000-6,000 Da, and did not depend on the %initiator from 1.5-3%. An earlier study by Dworak [16] reported that the polymerization of EEGE at 65°C with % mole of the initiator as low as 0.7 %mol gave PEEGE with molecular weight of 13,400 Da. In this work, it seems that there might be some moisture in potassium *tert*-butoxide. Trace of water was able to destroy the catalyst activity and convert potassium *tert*-butoxide to potassium hydroxide and *tert*-butanol which were weaker nucleophiles than butoxide ion. Therefore at low initiator content (~1%), there was probably no potassium *tert*-butoxide to initiate the polymerization. The purification of potassium *tert*-butoxide can be carried out by sublimation at 180°C/0.05 mmHg [29], but the initiator was used as received and not purified before use.

The presence of solvent had some influences on the polymerization. In this study, anhydrous THF was used as solvent for EEGE polymerization. The entry PE3 which was prepared from solution polymerization (Table 4.3) had a lower molecular weight (4,008 Da) than the entry PE6 (5,859 Da) in which no solvent was used in the polymerization. The polymerization of both entries were carried out by using the same 2%mole of initiator. This result was accounted to moisture coming from the solvent. So, in this experiment, neat "bulk" polymerization of EEGE was performed in order to eliminate any moisture within the solvent.

Reaction temperature had significant influence on the polymerization performance. In case of PE6 and PE7, raising the reaction temperature from 68 to 72 °C resulted in higher percentage of conversion from 95% to more than 99%. The reason was that, at higher temperatures, the reactant molecule had higher potential energy and energy barrier was lower. Consequently, the polymerization occurred more than the operation at low temperature.

Reaction time had influence in the polymerization. For, example, in case of PE8, its molecular weight after 184 h of reaction was lower than that of PE6, for which the polymerization time was only 23 h. The reason was the occurrence of chain transfer reaction when the reaction time was too long. As a result, a large number of short chain polymers were generated.

Table 4.3 Polymerization condition and results of EEGE

Entry	%Mole initiator	Temp, °C	Time, hr	%Con-version	$\overline{M}_n$ (Theo)[1]	$\overline{M}_n$ by GPC	PDI by GPC	$\overline{M}_n$ by MS
PE1	0.91	70	>7 d	14	16,064	-	-	-
PE2	1.5	66	68	n.p.[2]	14,199	-	-	-
PE3[3]	2.02	70	86	84	7,231	4,008	1.36	1,810
PE4	2.46	68	94	91	5,937	4,584	1.20	2,296
PE5	3.02	69	69	88	4,836	4,552	1.25	2,145
PE6	1.98	68	23	95	7,374	5,859	1.22	2,235
PE7	1.99	72	45	>99	7,340	6,162	1.25	3,296
PE8	1.91	68	160	85	7,647	4,278	1.22	-
			184	88		4,260	1.21	1,690

[1]calculated from $\frac{100 \times 146.19}{\%initiator\ mole}$

[2]no polymerization as analyzed by ^{1}H NMR

[3]solution polymerization, using anhydrous THF

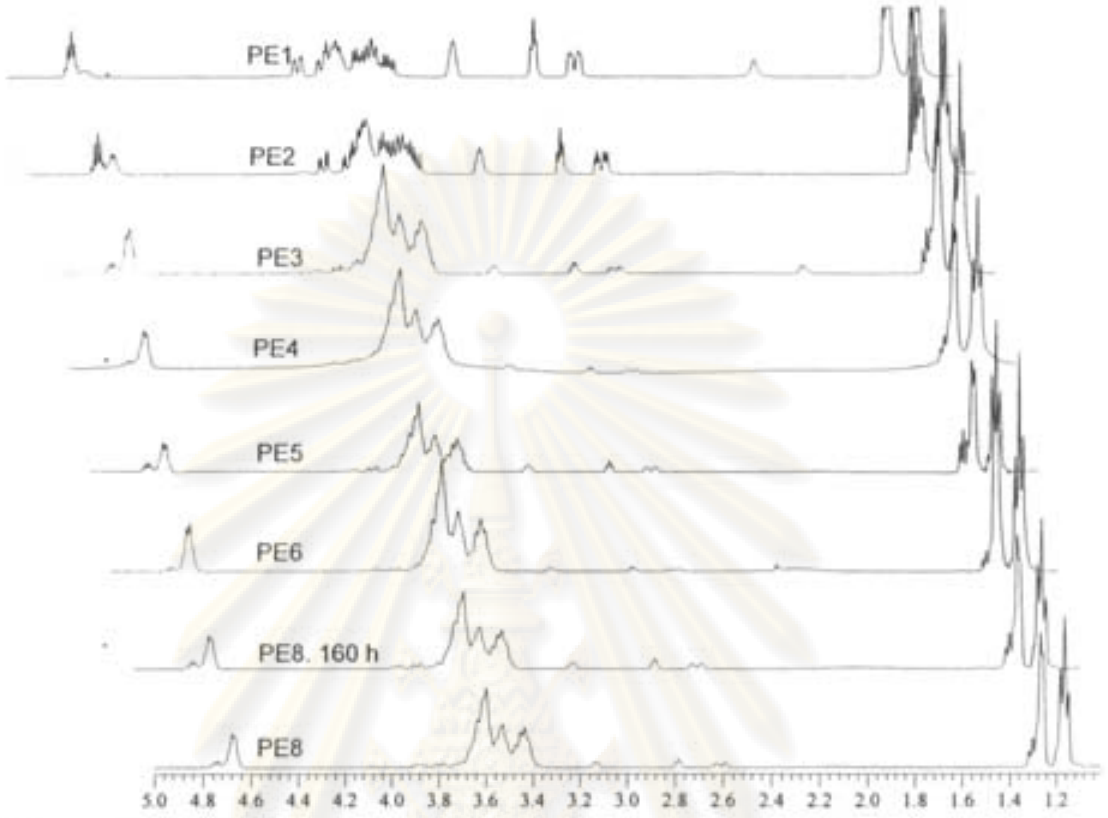


Figure 4.10 ^{1}H NMR spectra of PEEGE at stop reaction in $CDCl_3$.

Molecular weight Analysis-The expected molecular weight of PEEGE was calculated by

$$\text{Expected molecular weight} = \frac{100 \times 146.19}{\%\textit{initiator mole}}$$

For example, the expected molecular weight of PE10 from which 1.99% mol initiator was used, should be 7,340 Da. The expected and obtained molecular weights of PEEGE are listed in Table 4.3. It was found that all molecular weights from GPC were lower than the theoretical values.

The shapes of all PEEGE from GPC, except PE7, were unimodal with back tailing and the PE7 showed unimodal with small front hill as shown in Figure 4.11. The facts were that all polymerization of EEGE were prepared in small batches while in case of PE7, it was done in big batch. The possibly reason was the

polymerization of PE7 was prepared by severe pre-drying all involved glassware to minimize any moisture. Consequently, the conversion of EEGE was so high and high molecular weight of PPEGE was obtained.

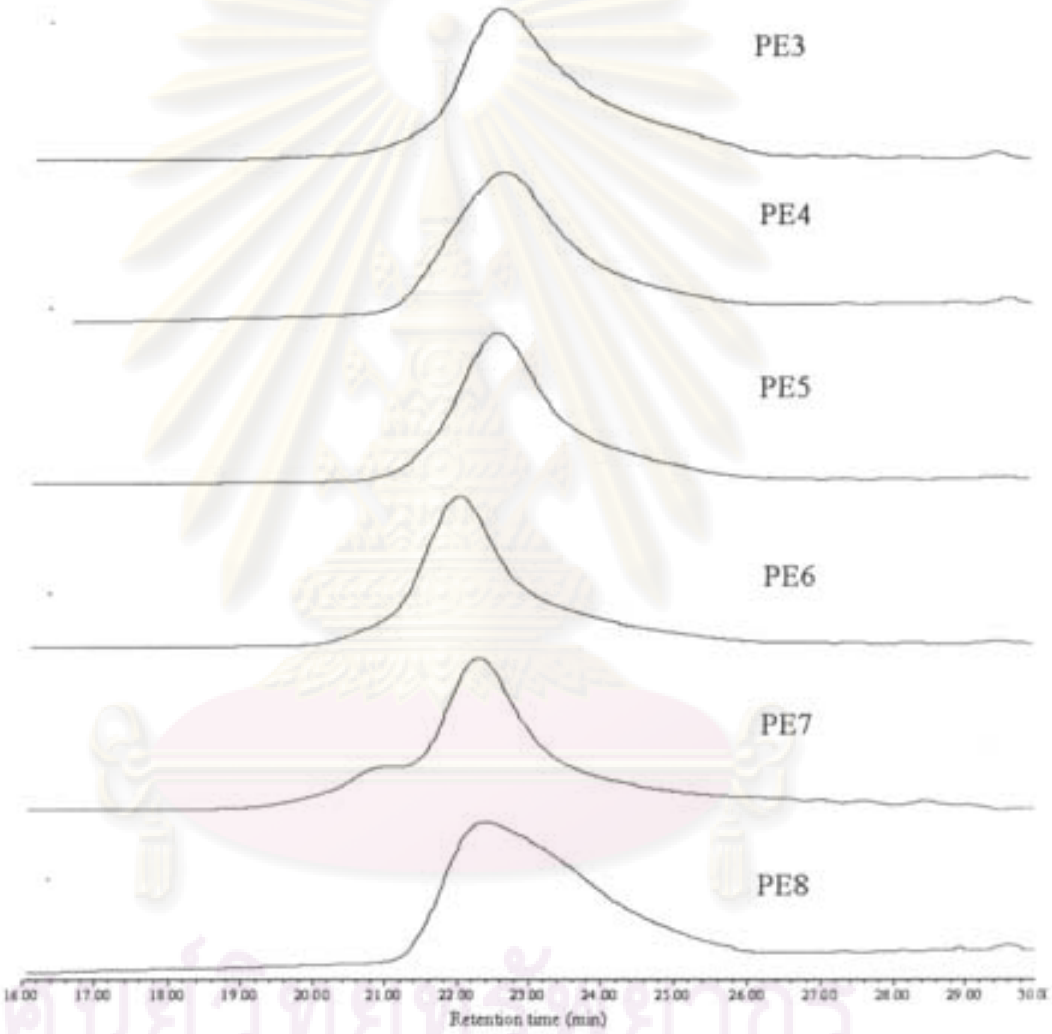


Figure 4.11 Chromatograms of PEEGE analyzed by GPC in THF.

MALDI-TOF mass spectrometry was also used to determine the molecular weight and the functional end group of the polymer chain. Because the mass peak of CCA matrix interfered with the sample peak at low m/z region, only the mass peaks higher than 600 were shown (Figure 4.12). A set of peaks with an interval of 146, equaled to the repeat unit of EEGE, were obtained.

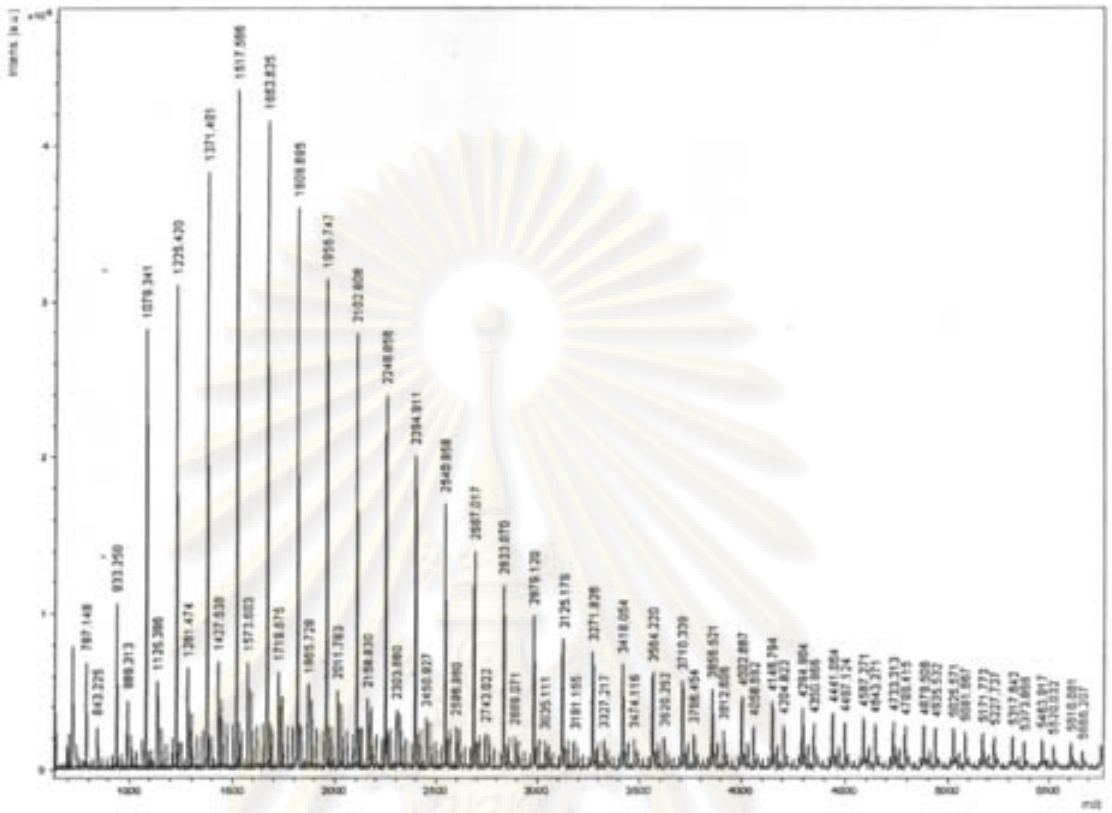


Figure 4.12 MALDI TOF MS of PEEGE, PE5.

Attempt to determine the polymer structure from the mass spectrum revealed that all PE entries, except for PE7, were mostly a series of PEEGE having two hydroxyl end groups with a few amounts of series of $(CH_3)_3CO\text{-}(C_7H_{14}O_3)_n\text{-}H$ plus a potassium ion. For example, in Figure 4.12, the m/z of 1,079.404 matched the molecular weight of PEEGE having two hydroxyl end groups plus a potassium ion while the m/z of 1,573.6 matched the molecular weight of PEEGE having one tert-butoxy end group plus potassium ion as shown below:

Structure $HO\text{-}(C_7H_{14}O_3)_n\text{-}H\ K^+$

m/z calc = mass H_2O + n × mass $C_7H_{14}O_3$ + mass K

= 18.0106 + 146.0943 n + 38.9637

= 1,079.634 where n = 7

Structure $(CH_3)_3CO\text{-}(C_7H_{14}O_3)_n\text{-}H\ K^+$

m/z calc = mass $C_4H_{10}O$ + n × mass $C_7H_{14}O_3$ + mass K

= 74.0732 + 146.0943 n + 38.9637

= 1,573.98 where n = 10

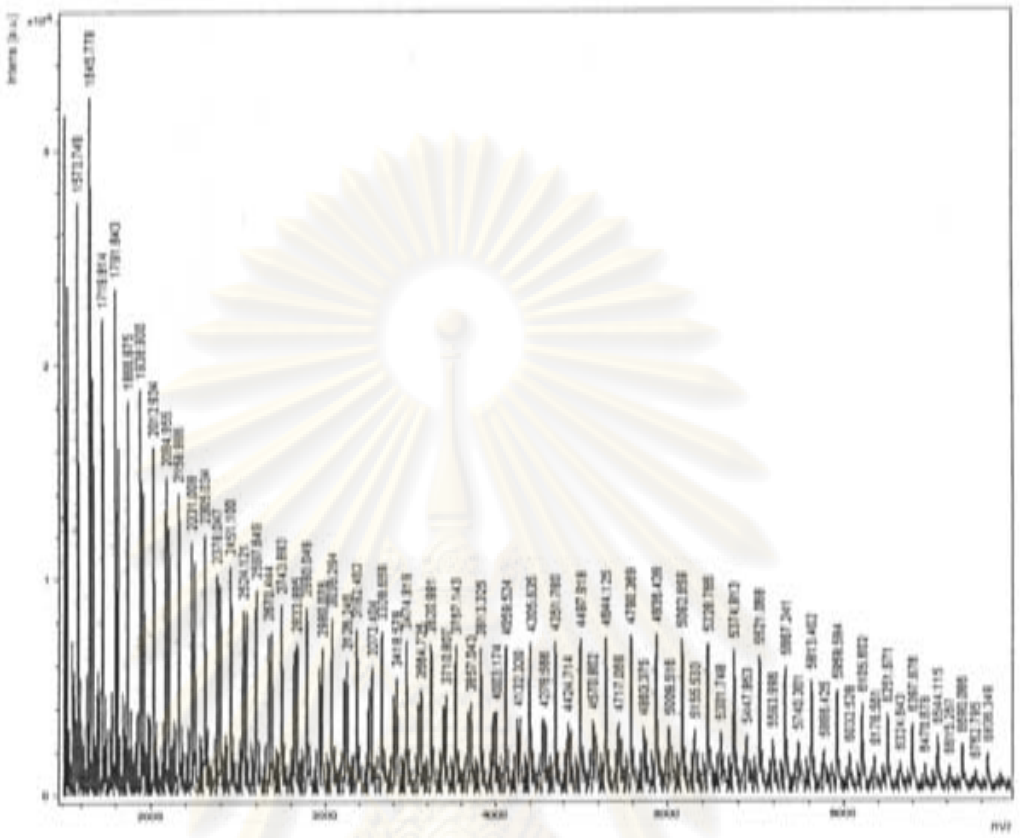


Figure 4.13 MALDI TOF MS of PEEGE, PE7.

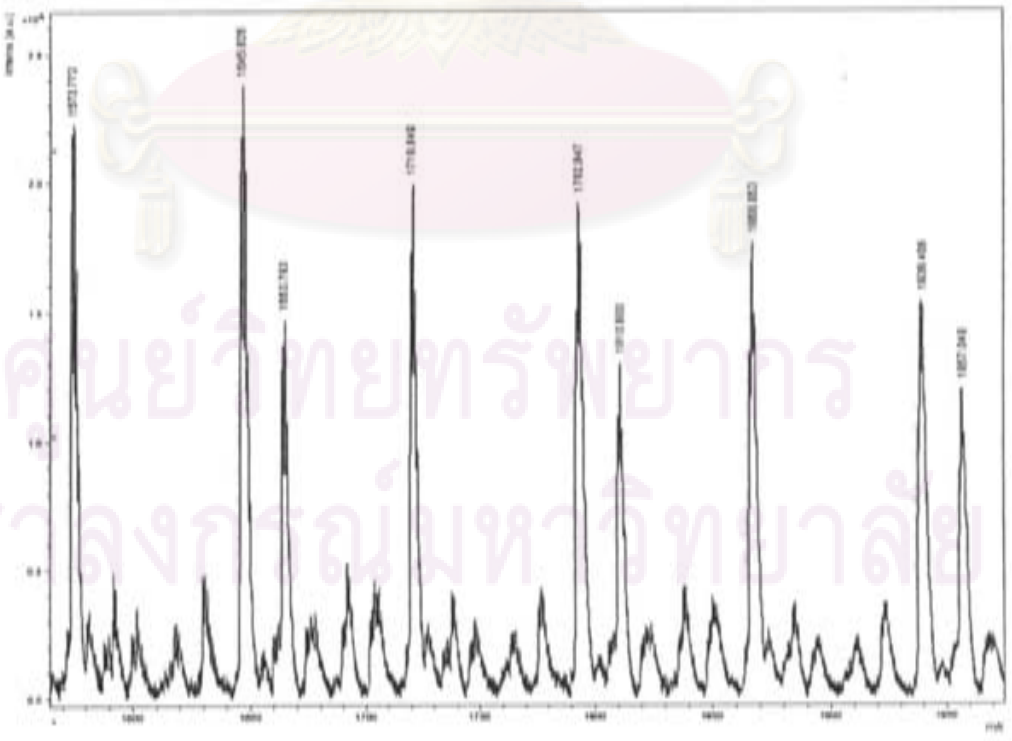


Figure 4.14 Expanded MALDI TOF MS of PEEGE, PE7.

In case of PE7 (Figure 4.13-4.14), three series of mass peaks were observed. The peak intervals of both mass series were equaled to 146, the same as other product entries. Structure elucidation of each series, however, resulted in two different polymer structures. The structure of series 1 were $(CH_3)_3CO$-$(C_7H_{14}O_3)_n$-H plus a potassium ion. The structure of series 2 and 3 were HO-$(C_7H_{14}O_3)_n$-H plus a sodium ion and a potassium ion, respectively. The intensity of series 1 and 2 was about 3:2, meaning that the mole ratio of polymer having one chain end as tert-butoxy group to the one with dihydroxy end groups was about 3:2.

Table 4.4 Mass peaks series of PEEGE, PE7

Series 1	Series 2	Series 3
1573.748	1,645.8	1,663.8
1719.814	1,791.8	1,810.8
1866.875	1,938.9	1,957.5

The mass spectra of PE7 was a significant evidence showing that tert-butoxide was able to initiate the polymerization of EEGE. Unexpectedly, the hydroxide ion also existed in the system and resulted in PEEGE having two hydroxyl end groups.

PE7 was used as polyether block for copolymerization with LLA. The molecular weight used for calculation was 6,162. Because PE8 composed of two types of the polyether, i.e., mono tert-butoxy and dihydroxy types, the structure of dihydroxy PEEGE was used as a representative model structure for PEEGE entry PE10 for copolymerization setting up.

The solubility test of crude PEEGE was studied in order to purify the product. Diethyl ether was one proper solvent to purify PEEGE. The precipitated solid was believed to be potassium hydroxide

Table 4.5 Solubility test of crude PEEGE

Solvent	Result	Result after centrifuge
Acetone	Cloudy light yellow solution	-
Dichloromethane	Cloudy light yellow solution	Cloudy solution with precipitate solid
Methanol	Clear colorless solution	-
Diethyl ether	Cloudy light yellow solution	Cloudy solution with precipitate solid

4.4 Homopolymerization of LLA

Homopolymerization of LLA was carried out in order to evaluate polymerization condition and the characteristic of PLLA.

^{1}H NMR of PLLA (Figure 4.15) in $CDCl_3$, δ (ppm): 5.16 (-CO(O)C**H**(CH_3)- of PLLA repeating unit), 4.34 (-CO(O)C**H**(CH_3)OH end group of PLLA), 1.58 (CO(O)CH(C**H$_3$**)- of PLLA repeating unit), 1.47 (-CO(O)CH(C**H$_3$**)OH end group of PLLA).

PLLA was obtained as white solid. All signals obtained from NMR confirmed the structure of PLLA. [30]. From Table 4.6, it was found that polymerization of LLA was achieved by potassium *tert*-butoxide initiator as well as $Sn(oct)_2$.

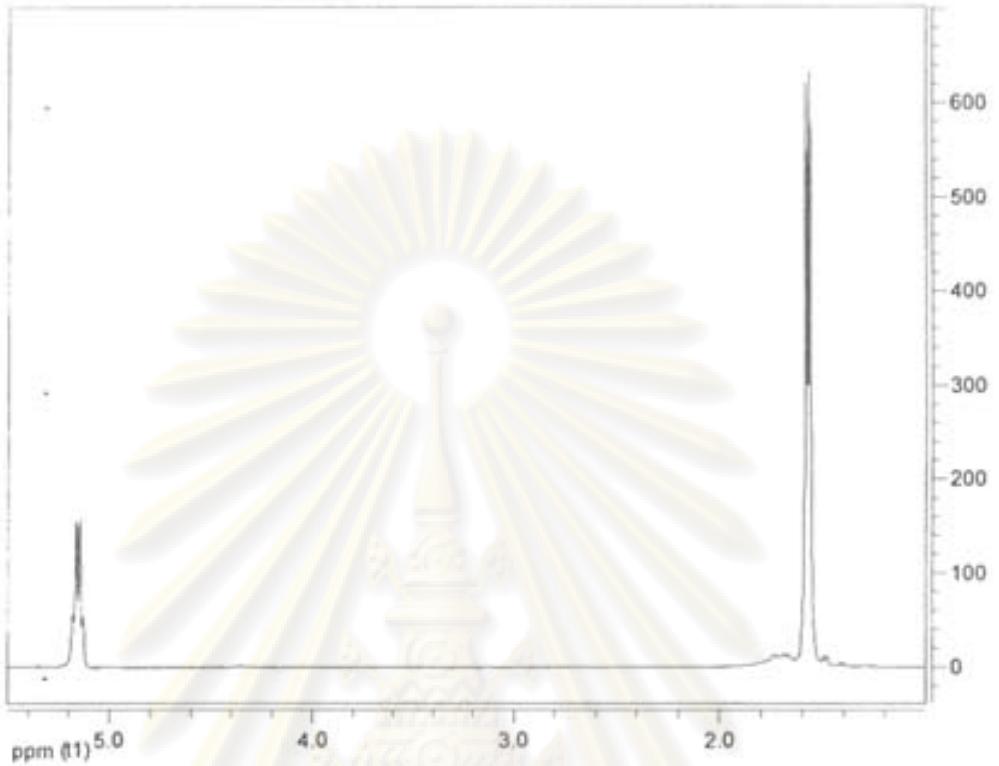


Figure 4.15 ^{1}H NMR spectrum of PLLA in $CDCl_3$.

Table 4.6 Homopolymerization of LLA with different initiator

Entry	%Mol initiator to LLA	Temp, °C	Time, hr	Yield, %	$\overline{M}_n$ (GPC)	PDI (GPC)	$\overline{M}_n$ (MS)	$\overline{M}_n$ (NMR)
PL1	0.704[1]	120	17	41.2	10,805	1.08	5,937	5,787
PL2	0.47[2]	115	24	78.6	17,999	1.69	-	6,175

[1]Initiator: potassium *tert*-butoxide

[2]Initiator: $Sn(oct)_2$

Molecular weight of PLLA can be performed by ^{1}H NMR by correlating the methine signal of PLLA chain end at 4.34 ppm [31] and that of methine unit at 5.16 ppm.

$$\overline{M}_n \text{ (Da) of PLLA by NMR} = \frac{\left(I_{5.16\ ppm} + I_{4.34\ ppm}\right) \times 72.0211}{I_{4.34\ ppm}}$$

For example, MW of PL2 calculated by NMR was

$$= \frac{(100 + 1.18) \times 72.0211}{1.18}$$

$$= 6{,}175 \text{ Da}$$

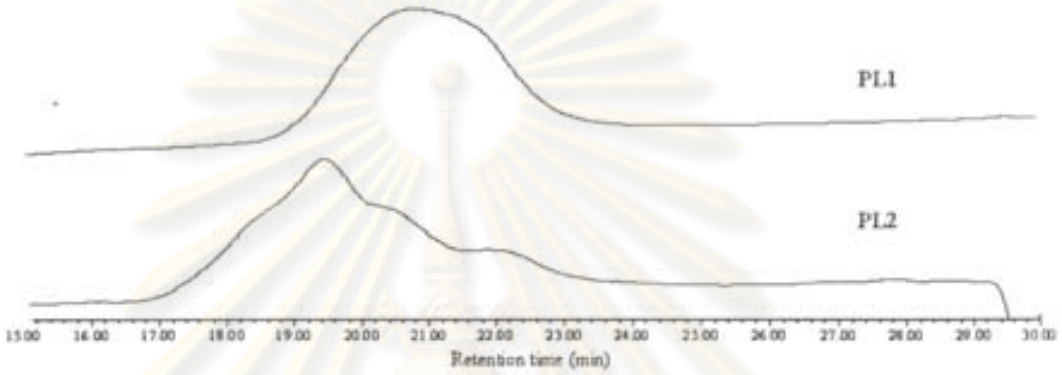


Figure 4.16 GPC of PLLA entry PL1 and PL2.

The GPC chromatogram of PL1 and PL2 are shown in Figure 4.16. To define the end groups of PL1, the distribution of mass peaks from MALDI-TOF-MS (Figure 4.17) spectra were used. For example, m/z of the PL1 at 2489.201 matched either *tert*-butoxyl end and potassium ion or hydroxyl end group with sodium ion,

m/z calc for butoxyl end group = mass $C_4H_{10}O$ + n × mass $C_3H_4O_2$ + mass K

= 2,489.733 for n = 33

m/z calc for hydroxyl end group = mass H_2O + n × mass $C_3H_4O_2$ + mass Na

= 2,489.718 for n = 34

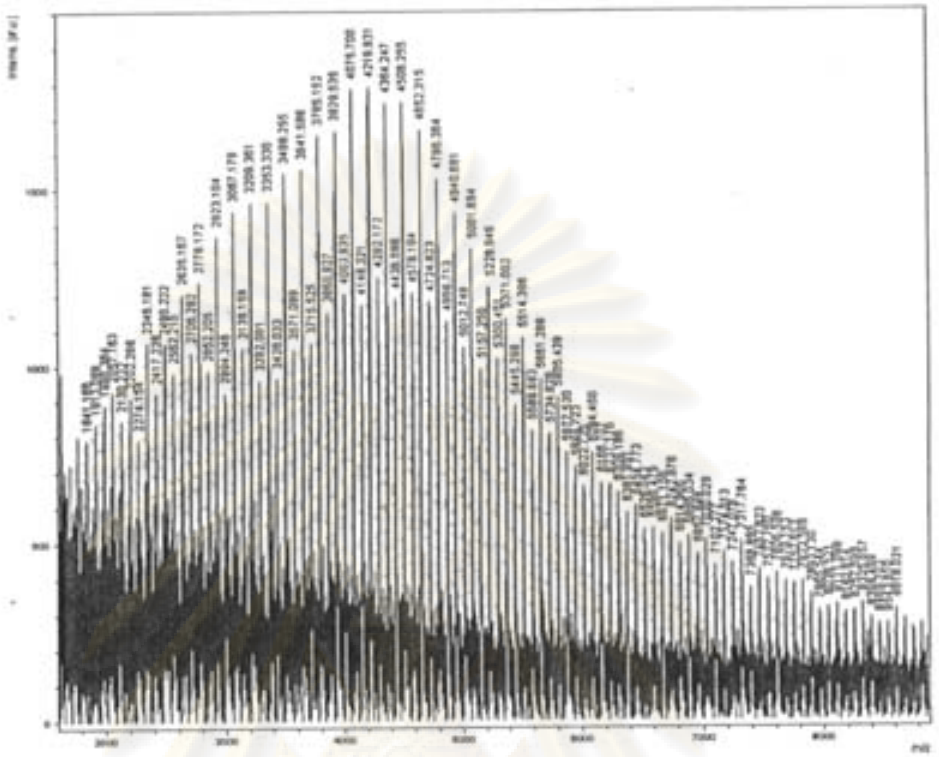


Figure 4.17 MALDI-TOF MS of PLLA., PL1.

Doping polymer with alternative ionizing agent [32, 33] was used to distinguish either of both possible structures. As shown in Figure 4.18, the mass peak of sodium and potassium doping are different. The dominant mass peak observed from spectra was matched to PLLA structure having hydroxy groups at both ends with potassium ion. For example, m/z observed at 4,236.7 matched the PLLA structure having two hydroxy end groups plus potassium ion (m/z of 4,234.2 when n=58), while PLLA structure having tert-butoxy end group with potassium ion should have been presented at a calculated m/z of 4,218.2. Therefore, the PL1 was mostly PLLA with hydroxy at both end groups.

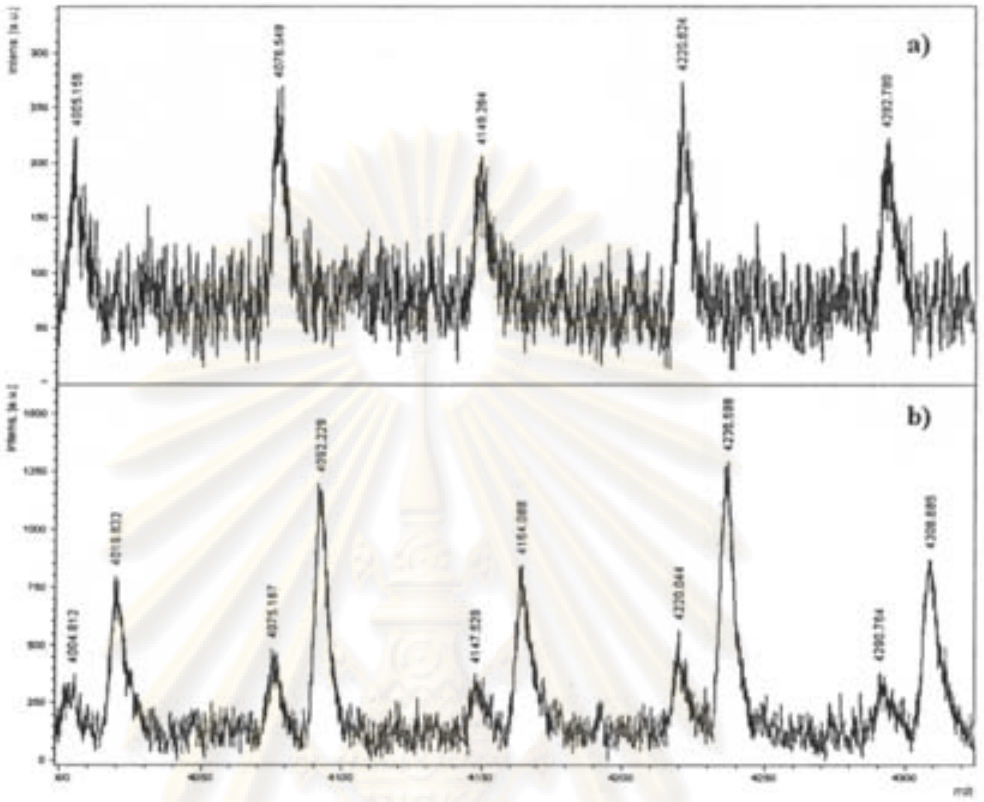
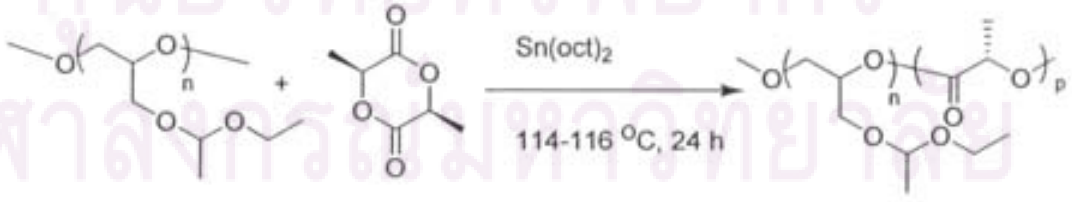


Figure 4.18 MALDI-TOF MS of PLLA (PL1) with different doping agents; a)doped with Na^+ and b)doped with K^+.

PLLA PL2 was analyzed by MALDI-TOF MS several times, but it gave disordered mass peaks. The reason was probably improper matrix/sample preparation for high molecular weight sample.

4.5 Synthesis of poly(1-ethoxyethyl glycidyl ether)-*b*-poly(L-lactide)



PEEGE LLA PEEGE-*b*-PLLA

Scheme 4.5 Ring opening polymerization of LLA with PEEGE as initiator.

This copolymerization (Scheme 4.5) was designed such that in each copolymerization batch, L-lactide was fixed at 7.42 mmol while the fed amount of PEEGE was varied to be 0.12, 0.18 and 0.35 mmol. The amounts of LLA monomers were therefore 10, 20 and 30 folds of the dihydroxy end groups in PEEGE. Moreover, the amount of $Sn(oct)_2$ was also varied to be 5, 10 and 15 % mole of the hydroxyl end group of PEEGE. Each entry was named, for example, as 1/10/10, meaning that the reaction mixture composed of 1 mole of hydroxyl of dihydroxy PEEGE, 10 mole of L-lactide and $Sn(oct)_2$ in the amount of 10% mole of hydroxyl of hydroxy PEEGE.

Because $Sn(oct)_2$ was highly viscous liquid, the catalyst was prepared as solution in order to reduce error in quantitative measurement. The reported solvent for PLLA polymerization in the literature was anhydrous toluene [25a] or anhydrous THF [23]. Although toluene is non-hygroscopic, its toxicity and high boiling point may cause problem during polymer synthesis (toluene b.p.111 °C, THF b.p.66 °C). So, THF was chosen for preparing $Sn(oct)_2$ solution

As shown in Table 4.7, three samples, 1/20/05, 1/20/10 and 1/30/10, were partially soluble in DCM, THF and methanol at room temperature. The sample entry 1/20/10 and 1/30/10 swelled up in THF while the 1/20/05 swelled up in all three solvents. After repeating the copolymerization of 1/20/05, 1/20/10 and 1/30/10, the same results were obtained. The swelling behavior of these three samples suggested that cross-linking might take place in the polymer structure. A possible explanation for this occurrence was that the EE protecting groups in PEEGE were cleaved, exposing pendant hydroxyl group which were able to react with LLA monomer to form branched or networking structure. Consequently, the solubility of the resulting copolymer was altered. The occurrence of EE cleavage was in fact observed in a trial experiment in which PEEGE and 10%mol of $Sn(oct)_2$ were placed in the same reaction condition as the copolymerization step. It was suspected that trace of water might be present in the copolymerization step, and was the cause of deprotection especially in the presence of a Lewis acid $Sn(oct)_2$.

Table 4.7 Polymerization condition and results of PEEGE-*b*-PLLA

Entry	mole ratio (OH of PEEGE:LLA)	%mole Sn:OH of PEEGE	Appearance	% Acetal cleavage	Solvent solubility[1]		
					DCM	THF	MeOH
1/10/05	1:10	5	Orange solid	0	+	+	+
1/10/10	1:10	10	Brown viscous liquid	4.2	+	+	0
1/10/15	1:10	15	Yellow viscous liquid	12.3	+	+	0
1/20/05	1:20	5	Yellow gum	n/a[2]	0	0	0
1/20/10	1:20	10	Brown gum	n/a[2]	0	0	0
1/20/15	1:20	15	Yellow viscous liquid	0	+	+	0
1/30/05	1:30	5	Pale yellow viscous liquid	43.4	+	+	0
1/30/10	1:30	10	Brown gum	n/a[2]	0	0	0
1/30/15	1:30	15	Pale yellow viscous liquid	12.0	+	+	0

[1] + = soluble, 0 = partial soluble, - = insoluble

[2] not analyzed

The rest 6 entries, that were soluble in THF, were analyzed by NMR to determine the copolymerization conversion as shown in Figure. 4.19. The NMR signals of methine and methyl of L-lactide monomer at 5.04 ppm and 1.64 ppm were not observed. It meant that all monomers were completely converted into connecting LLA chains, in which the methine and methyl signals were shifted to 5.14 and 1.56 ppm, respectively. However, there were signals at 9.88 ppm (aldehyde, O=C**H**) and

2.2 ppm ($CH_3C=O$) from 1/10/10, 1/10/15, 1/30/05 and 1/30/15, indicating partial acetal cleavages in these samples during the copolymerization. The percentage of acetal cleavage was determined by comparing the hydrogen of aldehyde (9.88 ppm) with hydrogen of acetal groups (4.67 ppm) as follows:

$$\% \text{ Acetal cleavage} = \frac{I_{9.88\ ppm} \times 100}{\left(I_{4.67\ ppm} + I_{9.88\ ppm}\right)}$$

As shown in Table 4.7, the percentage of acetal cleavage had no relation with the feeding monomer and initiator ratios.

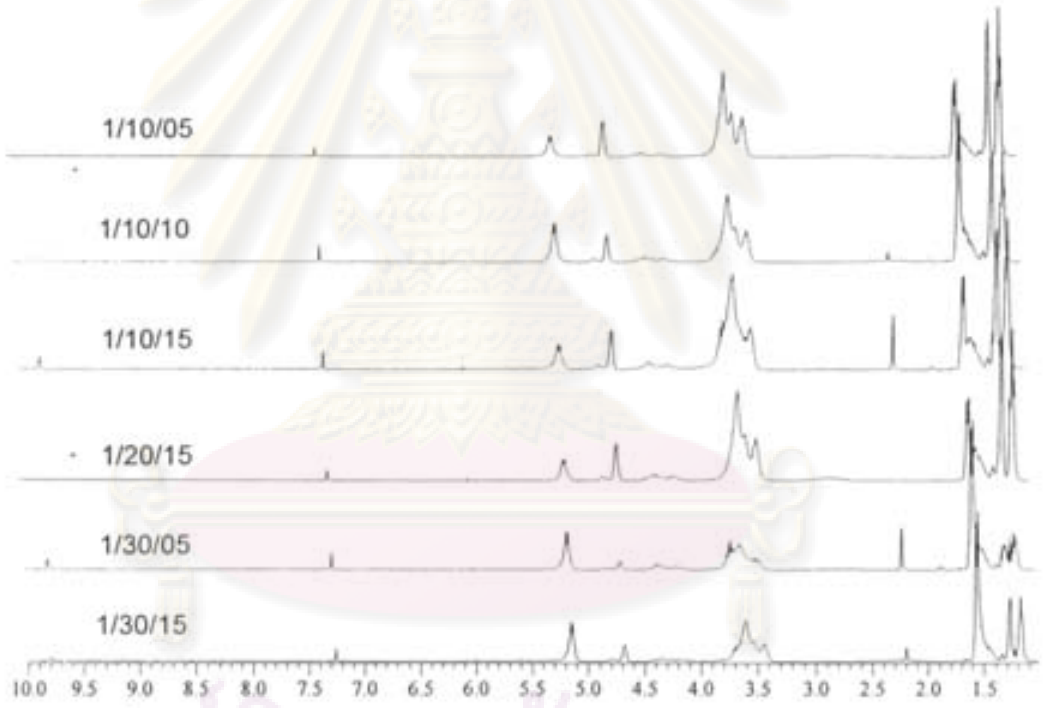


Figure 4.19 ^1H NMR spectra of copolymers at stop reaction in $CDCl_3$.

After polymerization, methanol was used to purify the crude products. In each batch, it was separated into two parts; methanol soluble and methanol insoluble parts.

4.5.1 Methanol-soluble part

Characteristic NMR signals of the copolymers are shown in Figure 4.20-4.28 and Table B-2.

^{1}H NMR of PEEGE-*b*-PLLA (Figure 4.20-4.28) in $CDCl_3$, δ (ppm): 5.14 (-CO(O)C**H**(CH_3)- of LLA repeating unit), 4.79 (-OC**H**(CH_3)-O of chain end PEEGE), 4.67 (-OC**H**(CH_3)-O of PEEGE repeating unit), 4.4 and 4.2 (pending group -C**H**$_2$-O- CO(O)CH(CH_3)-), 4.34 (-CO(O)C**H**(CH_3)OH end group of PLLA), 3.68-3.42 (-C**H**$_2$-C**H**(C**H**$_2$-O-)-O-, -O-C**H**$_2$-CH3 of PEEGE), 1.56 (CO(O)CH(C**H**$_3$)- of LLA repeating unit), 1.41 (CO(O)CH(C**H**$_3$) of end group of LLA), 1.3 (OCH(C**H**$_3$)-O of chain end PEEGE), 1.26 (C**H**$_3$-C(O)H-O- of PEEGE), 1.16 (C**H**$_3$-CH$_2$-O- of PEEGE)

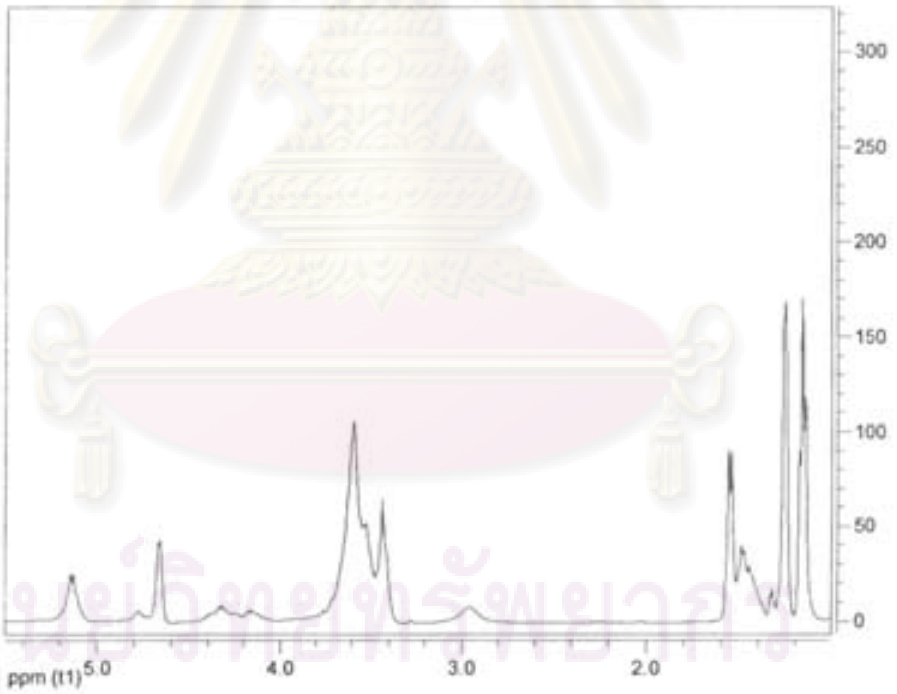


Figure 4.20 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:10, with $Sn(oct)_2$ 5% mol) in $CDCl_3$ •

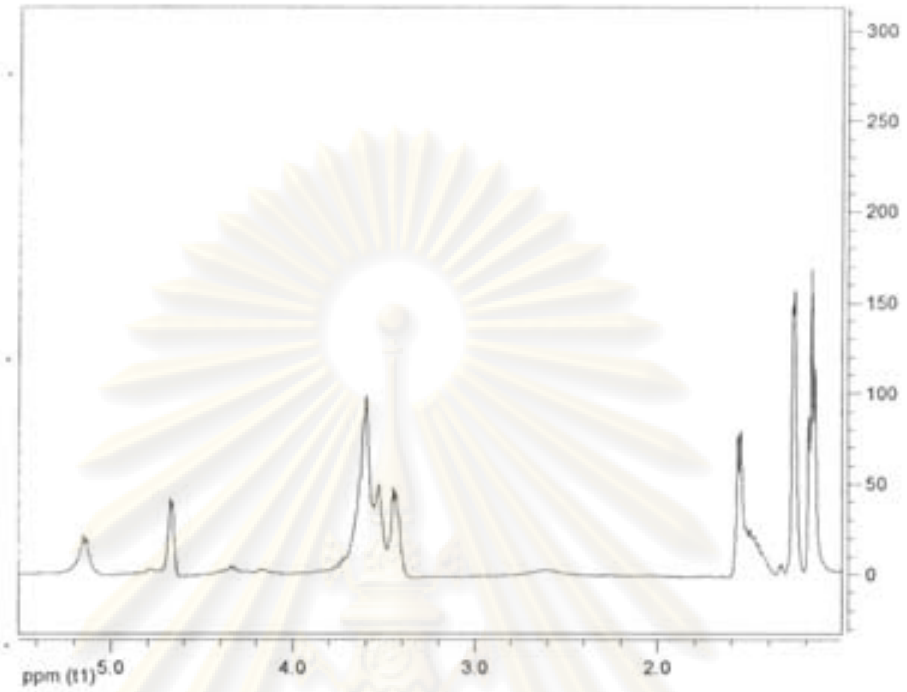


Figure 4.21 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:10, with $Sn(oct)_2$ 10% mol) in $CDCl_3$.

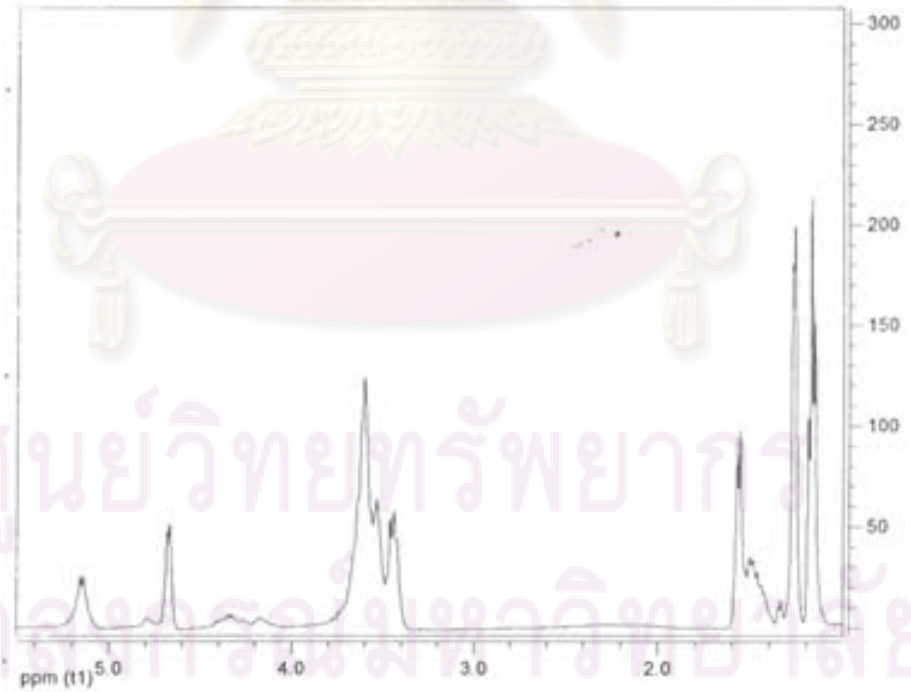


Figure 4.22 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:10, with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

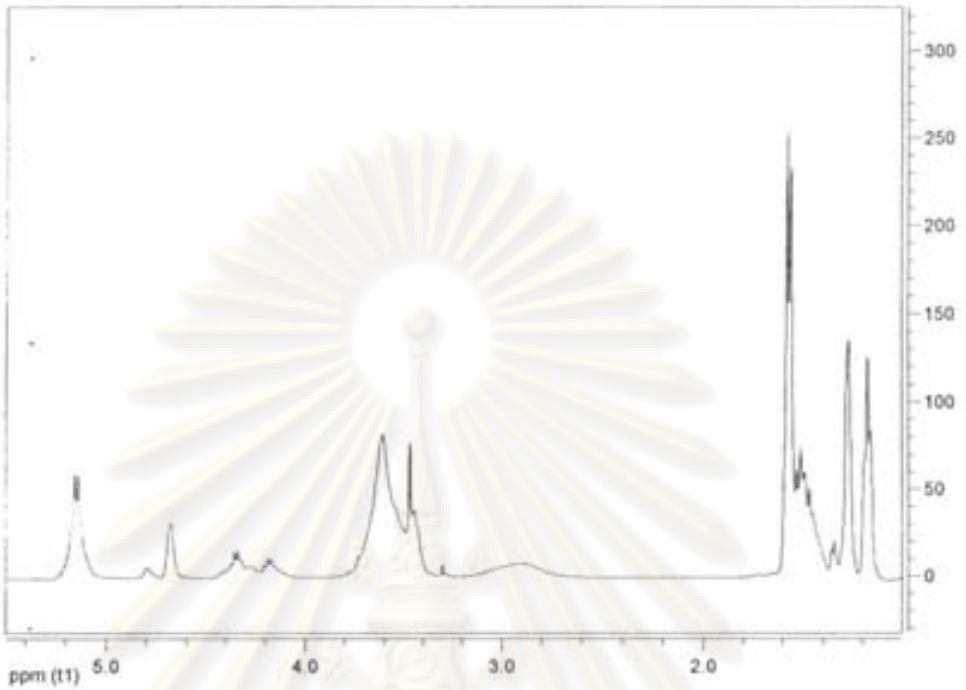


Figure 4.23 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:20, with $Sn(oct)_2$ 5% mol) in $CDCl_3$.

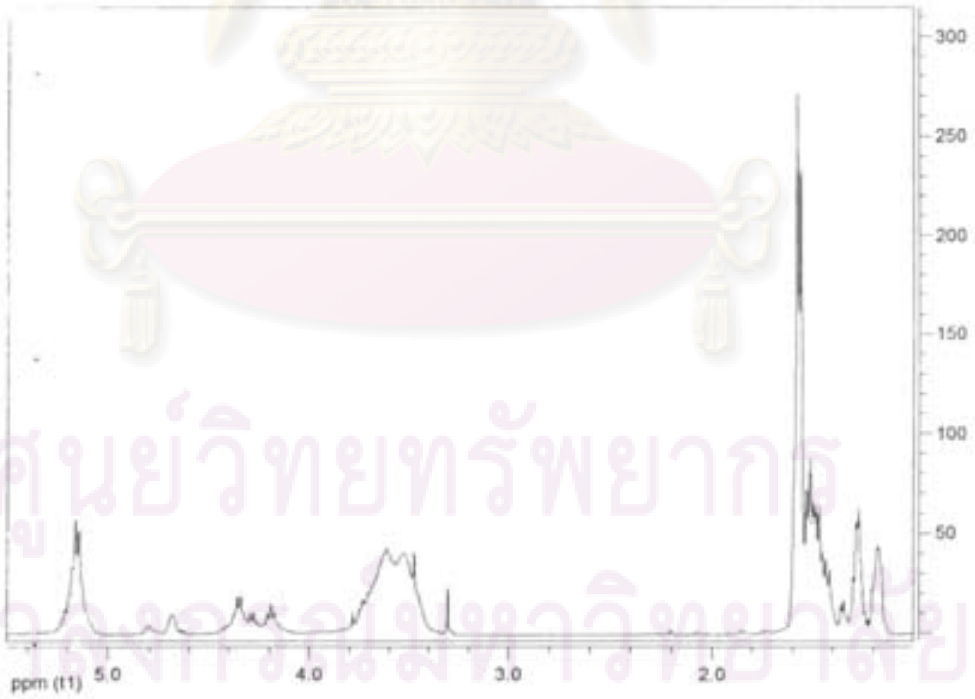


Figure 4.24 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:20, with $Sn(oct)_2$ 10% mol) in $CDCl_3$.

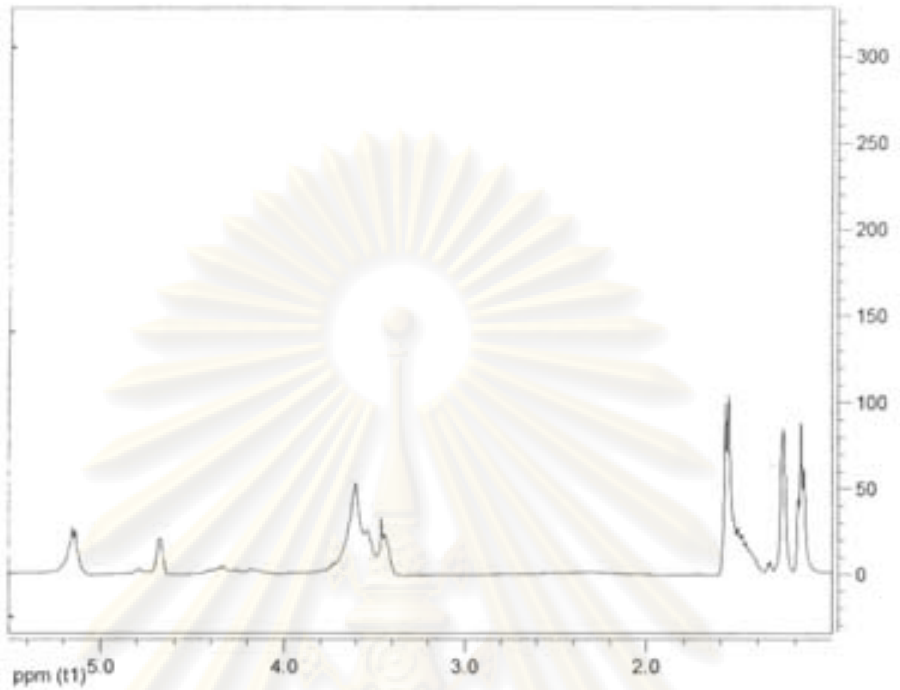


Figure 4.25 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:20, with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

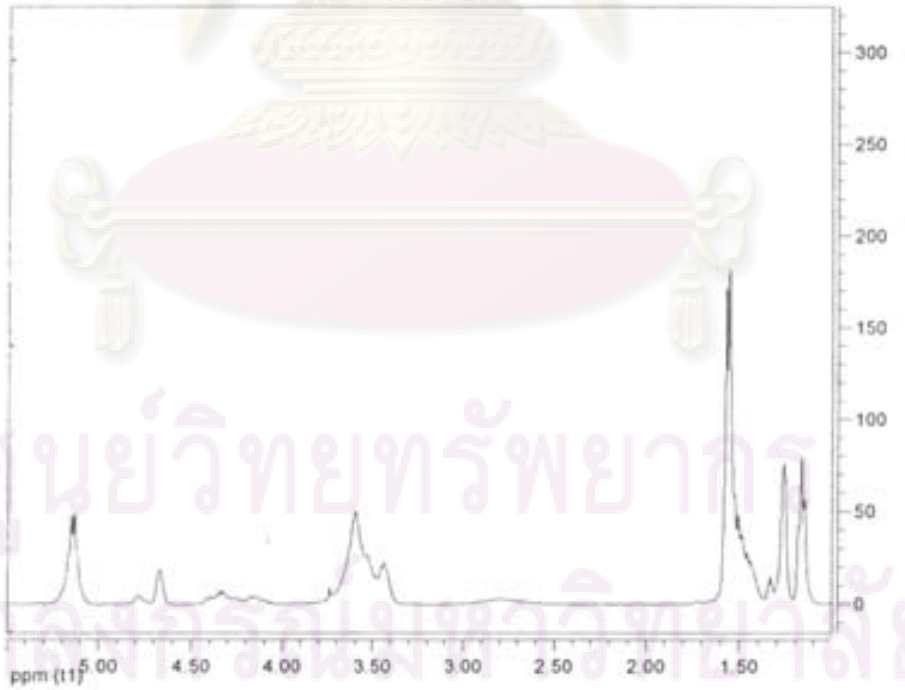


Figure 4.26 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:30, with $Sn(oct)_2$ 5% mol) in $CDCl_3$.

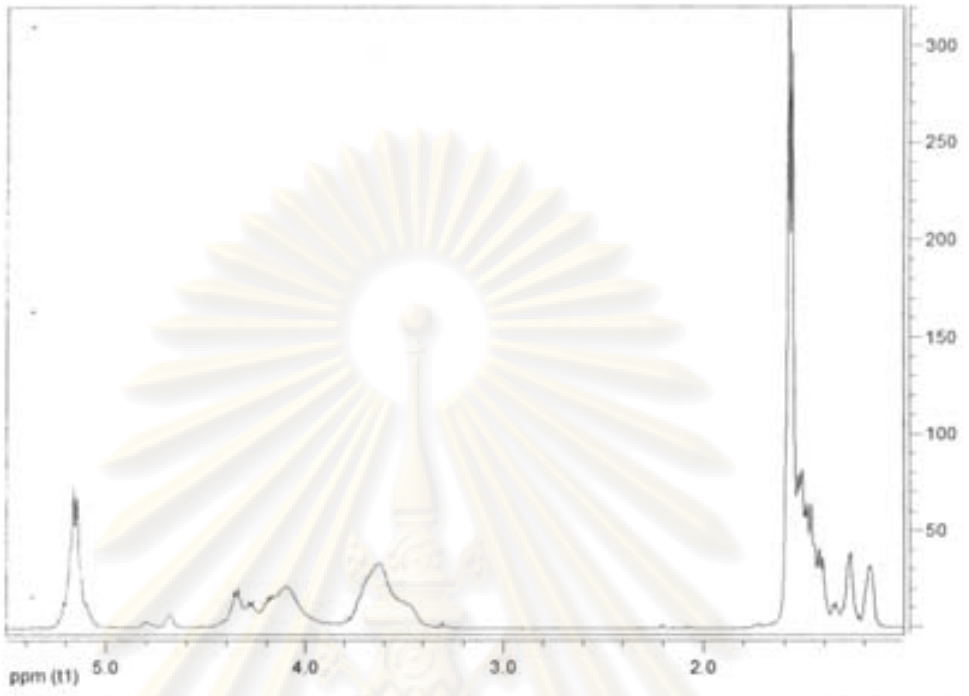


Figure 4.27 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:30, with $Sn(oct)_2$ 10% mol) in $CDCl_3$.

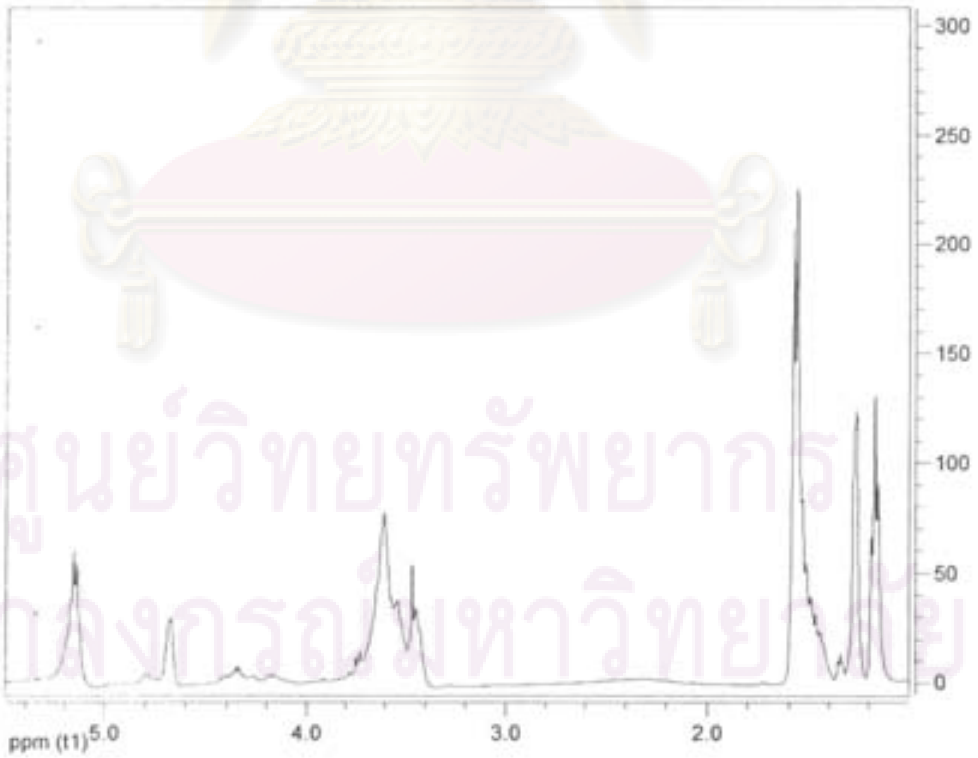


Figure 4.28 ^{1}H NMR spectrum of methanol-soluble part copolymer (OH of PEEGE: LLA = 1:30, with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

From the NMR, PEEGE and PLLA, were found in the methanol-soluble portion of the copolymerization product. This meant that it composed of PEEGE and PLLA. If the two blocks are connected, there will be a signal shift caused by changing of a chain end "ether" proton of EEGE from 3.3-3.7 ppm to an "ester" proton at 5.1 ppm (Figure 4.29). The esterified CH of PEEGE chain end must couple to a neighbour CH_2 when analyzed by COSY technique. The H–H COSY analysis of the methanol-soluble copolymer revealed faint coupling between signals at 5.09 and 3.70 ppm as shown in Figure A-1 to A-9. This is a significant evidence of the success of the ROP of LLA monomer by the chain end hydroxyl group of PEEGE block [4]. In addition, two peaks at 4.2 and 4.4 ppm were also found and defined as methylene group (-CH_2-) that connected to the lactide unit via ester linkage as reported by Dworak [34]. These terminal methylene groups could be found at two positions. One was the methylene chain end unit that was generated by ring-opening polymerization of the epoxide monomer by hydroxide ion. The other was possibly pendent methylene group that was formed after the partial cleavage of ethoxy ethyl protecting group discussed earlier. The formation of methylene hydroxy groups from both positions was able to initiate the ROP of lactide monomer. The structure of two possible CH_2 esterified were shown in Figure 4.30. Moreover, the signal at 4.8 ppm was found and coupled with 1.3 ppm (Figure A-3-A-11). These two signals were defined as CH and CH_3 of the acetal in the protecting group of chain end PEEGE unit, respectively.

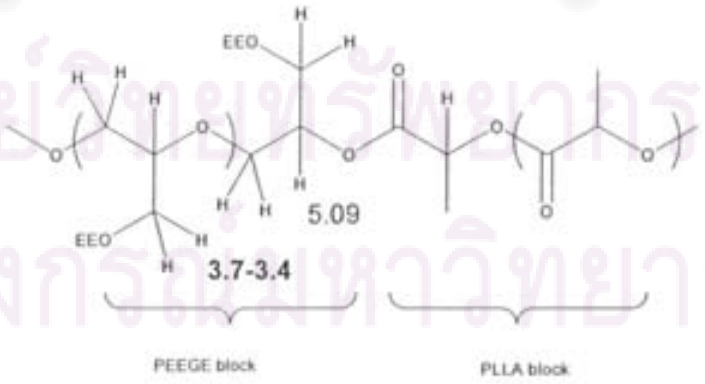


Figure 4.29 Assignment of chemical shift (δ) from ^{1}H NMR of esterified linkage between PEEGE and PLLA.

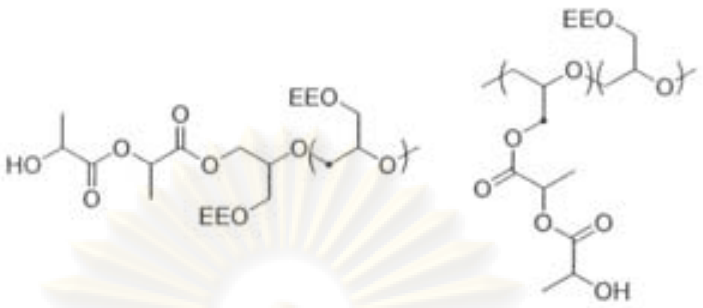


Figure 4.30 Two possible structure of CH_2 esterified.

In polymerization principle, molecular weight of product increases when percent mole of $Sn(oct)_2$ decreases or mole ratio of feeding LLA increases. However, the molecular weight of methanol-soluble parts did not follow the principle as shown in Table 4.8. At fixed mole ratio of feeding LLA, the molecular weight decreased when mole $Sn(oct)_2$ changed from 5% to 10% but rebounded at 15% as shown in Figure 4.31.

Table 4.8 Characterization results of methanol-soluble part PEEGE-*b*-PLLA

Entry	% weight	Appearance	$\overline{M}_n$		PDI	$\overline{M}_n$
			Theo[1]	(GPC)	(GPC)	(MS)
1/10/05	98.1	Slightly brown cloudy viscous liquid	8,940	8,300	3.93	1,116
1/10/10	93.83	Slightly orange cloudy viscous liquid	8,940	5,947	1.79	1,255
1/10/15	97.73	Slightly yellow cloudy viscous liquid	8,940	7,281	2.22	1,421
1/20/05	47.52	Transparent yellow gel	11,820	4,908	27.9	-
1/20/10	35.23	Transparent yellow gel	11,820	2,430	4.22	-
1/20/15	86.44	Slightly orange cloudy viscous liquid	11,820	8,564	2.65	1,314
1/30/05	87.60	Slightly orange viscous liquid	14,702	11,749	7.70	1,197
1/30/10	52.31	Transparent yellow gel	14,702	2,762	3.84	-
1/30/15	72.05	Slightly yellow cloudy viscous liquid	14,702	7,205	3.03	1,386

[1]calculated from feed ratio as in the equation;

$$= \overline{M}_n \text{ of PEEGE} + \frac{mole\ LLA \times 144.04}{mole\ PEEGE}$$

For example, the expected molecular weight of entry 1/10/05 was

$$= 6{,}162 + \frac{2 \times 10 \times 144.04}{1} \qquad = 8{,}940 \text{ Da}$$

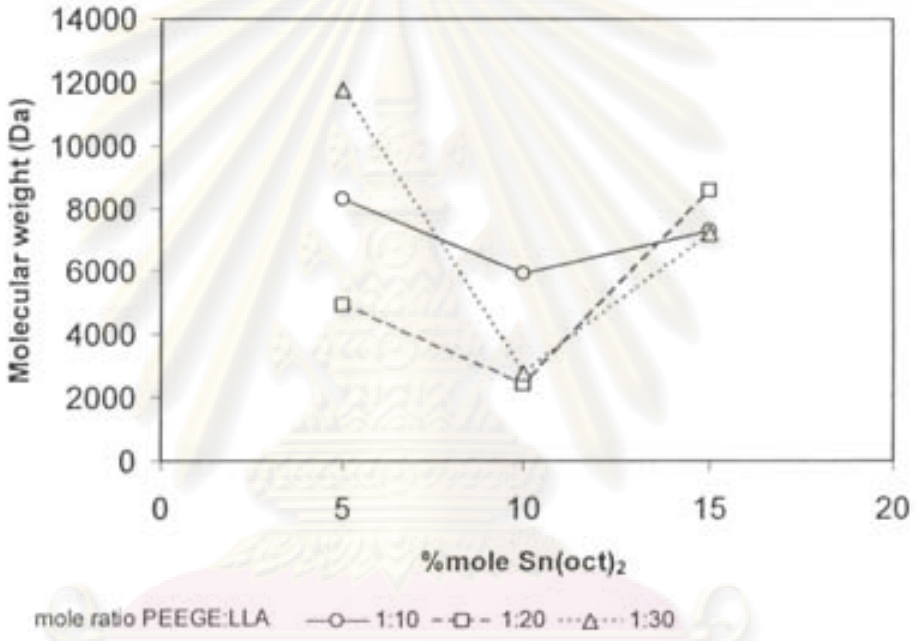


Figure 4.31 Relationship between molecular weight and %mole Sn(oct)2 at various mole ratio PEEGE:LLA.

To evaluate the copolymerization performance by using NMR as a tool, degree of acetal cleavage, H ratio of PEEGE:LLA, average PLLA chain length, and mass increase due to PLLA block are listed in Table 4.9. In PEEGE blocks, the area ratio of the acetal proton (4.7 ppm) to the ether proton (3.68-3.42 ppm) must be 1:7. However, as shown in Table 4.8, the acetal proton values of all entries were lower than they should be (1:7). It meant that cleavage of the ethoxy ethyl protecting group in PEEGE block segment indeed occurred in the MeOH-soluble product. It was most likely that trace of water and $Sn(oct)_2$ were accounted for this cleavage.

The mole ratio of PEEGE:LLA in the product was determined and compared with the feeding mole ratio. As in the previous paragraph, an extent of acetal cleavage was observed, so the acetal proton at 4.7 ppm was not represented for the PEEGE content in the copolymer. Instead, the protons at 3.68-3.42 belonging to the methine and methylene of backbone EEGE units were used to calculate the PEEGE content in the product. The amount of LLA was identified by the methine proton of PLLA at 5.14 ppm.

For example, the entry 1/10/5 to 1/10/15 (feeding ratio PEEGE:LLA =1:10)

Repeating unit of PEEGE determined from $\overline{M}_n$ (GPC) was

= 6,060/146

= 41

Therefore, the average number of H in the backbone (3.68-3.42 ppm) of PEEGE was

= 7 × repeating unit of PEEGE

= 7 × 41

= 287 protons

Because the structure of PEEGE was assumed to contain two hydroxyl end groups, the methine proton amount of LLA was

= 2 × 20 protons

So, the theoretical proton ratio of PEEGE:LLA = 287/40 = 7.2

The mole ratio of PEEGE:LLA found in the copolymers were lower than the theoretical value shown in blanket. This suggested that the methanol-soluble parts contained lower amounts of LLA units than that of the added content. In fact, homo PLLA was found in the methanol-insoluble part, as discussed in the next section.

The integration values of the methine protons of LLA in the repeating unit (5.14 ppm) and in the terminal unit (4.34 ppm) were used to calculate average PLLA chain length. As a result, PLLA lengths in the copolymer were rather short. For these experiments, there was no relation or trend between the PLLA chain length and the feeding mole ratio.

Table 4.9 Characteristics of methanol-soluble part from copolymerization of PEEGE and LLA as evaluated by ^{1}H NMR

Entry	Acetal proton ratio in PEEGE[1]	% Acetal cleavage[2]	H ratio PEEGE:LLA[3] (feeding ratio PEEGE:LLA)	Average PLLA chain length[4]	Mass increase due to PLLA segment[5]
1/10/5	0.80:7	12.9	7.2:0.80 (7.2:1)	3.7	266
1/10/10	0.91:7	6.8	7.2:0.81 (7.2:1)	6.6	475
1/10/15	0.89:7	9.7	7.2:0.77 (7.2:1)	4.3	309
1/20/5	0.61:7	12.1	3.6:0.94 (3.6:1)	5.1	367
1/20/10	0.29:7	27.1	3.6:0.72 (3.6:1)	3.8	274
1/20/15	0.80:7	11.2	3.6:0.78 (3.6:1)	13.3	958
1/30/5	0.72:7	20.7	2.4:0.92 (2.4:1)	7.8	561
1/30/10	0.29:7	27.9	2.4:0.62 (2.4:1)	4.3	310
1/30/15	0.78:7	12.2	2.4:0.75 (2.4:1)	9.6	691

[1] $I_{4.7\ ppm}/I_{3.3\text{-}3.8ppm}$

[2] $I_{4.8\ ppm} \times 100/(I_{4.8\ ppm}+ I_{4.7\ ppm})$

[3] $I_{3.3\text{-}3.8\ ppm}/I_{5.14ppm}$

[4] $I_{5.14\ ppm}/I_{4.34\ ppm}$

[5] $I_{5.14\ ppm} \times 72/I_{4.34\ ppm}$

From GPC analysis, all entries gave broad and multimodal signals as shown in the chromatograms (Figure 4.32). However, all entries except 1/20/10 and 1/30/10 had maximum peak at retention times shorter than PEEGE starting polymers, meaning that they had higher molecular weight than that of PEEGE. The increase of polydispersity index and multimodal distribution obtained from the GPC indicated that the copolymerization process in this experiment condition were 'non-living.' This, therefore, led to a variety of molecular chain length and possibly, homo PLLA.

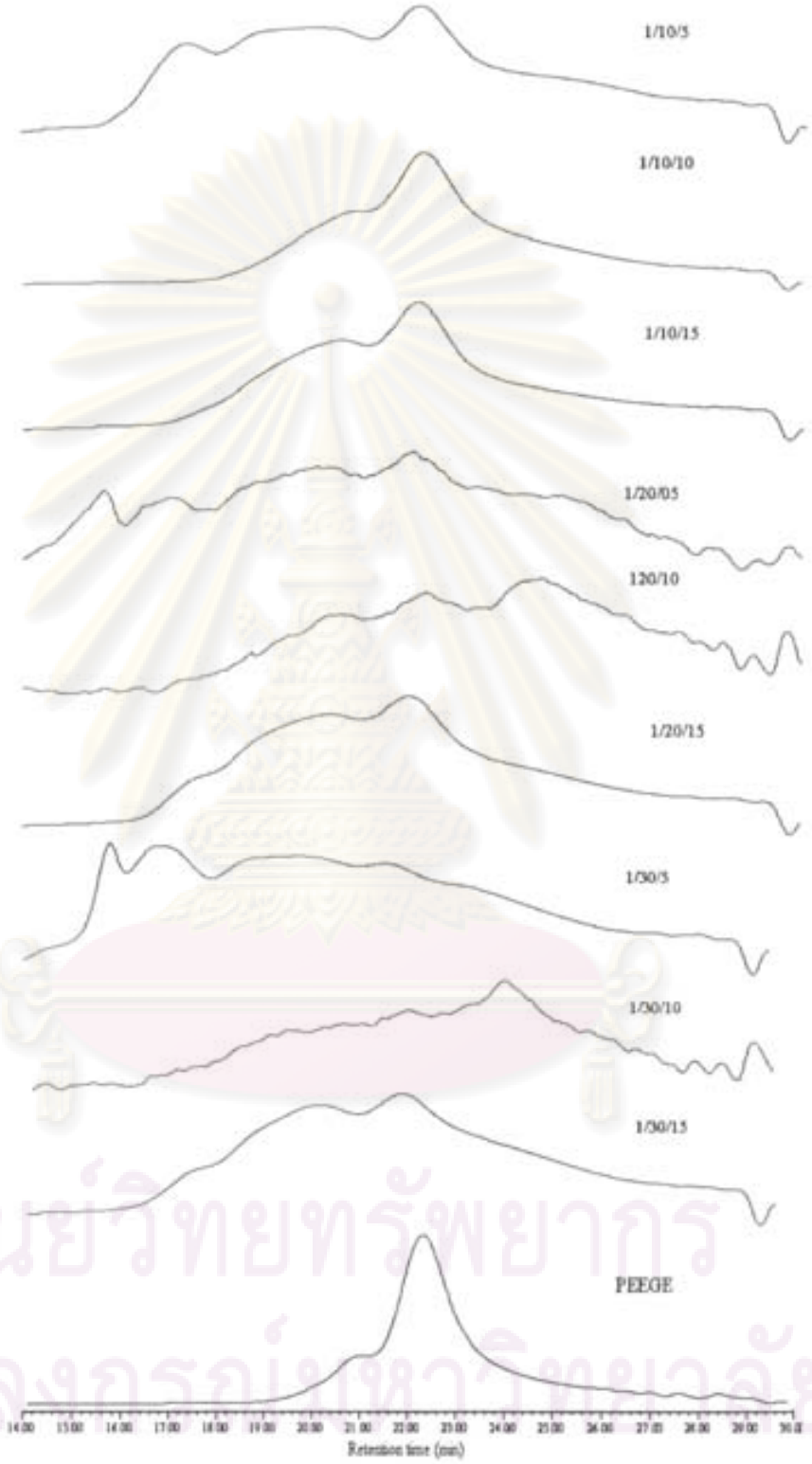


Figure 4.32 GPC of methanol-soluble part from the copolymerization between PEEGE and LLA. The chromatogram of PEEGE was also presented for comparison.

MALDI-TOF analysis of the methanol-soluble parts (Figure 4.33-4.38) gave a series of peaks that had 72 m/z mass interval, equal to a repeating unit of lactic acid, e.g., m/z at 2,029.5, 1,957.4, 1,885.3, 1,813.4, 1,741.4, 1,670.4 and 1597.3.However, the mass peaks did not exactly match the structure of PLLA or PEEGE-*b*-PLLA copolymer. The methanol-soluble parts possibly contained PEEGE-*b*-PLLA with some acetal cleavage discussed earlier from the NMR analysis. The reason that the structure was not identified because partial acetal cleavage in PEEGE block of the copolymer was random.

The mass peaks from MALDI-TOF analysis were categorized in three group as shown in Table 4.10. The first group was match a series of tert-BuO-PEEGE-*b*-PLLA plus a potassium ion. The second group was match a series of HO-PEEGE-*b*-PLLA plus a potassium ion. The last group was seven series of undefined structure polymer that possibly contained PEEGE-*b*-PLLA with an extent of acetal cleavage discussed earlier from NMR analysis.

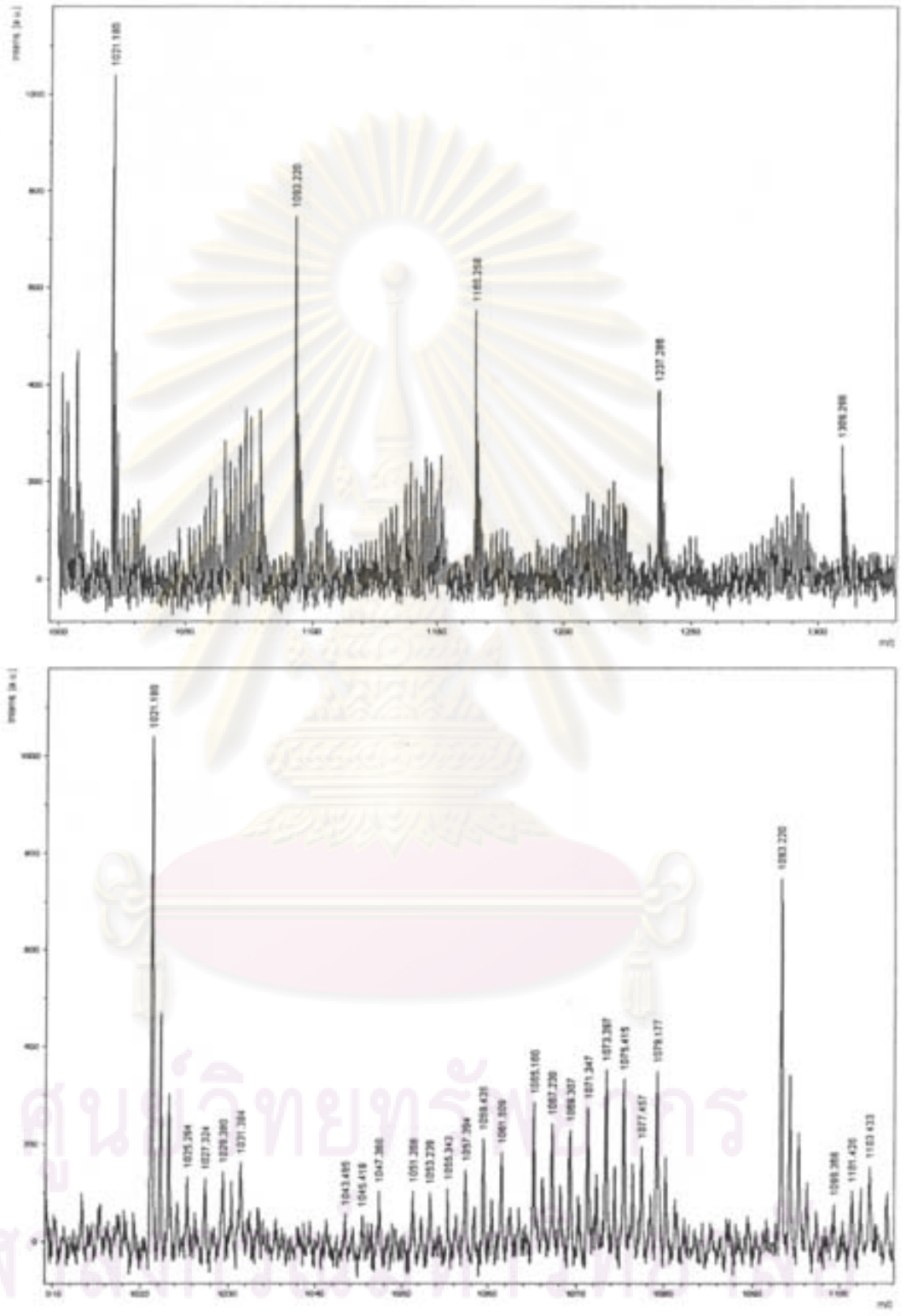


Figure 4.33 MALDI-TOF MS spectra of methanol soluble part copolymer (OH of PEEGE: LLA = 1:10, with $Sn(oct)_2$ 5% mol) [bottom-expanded spectrum].

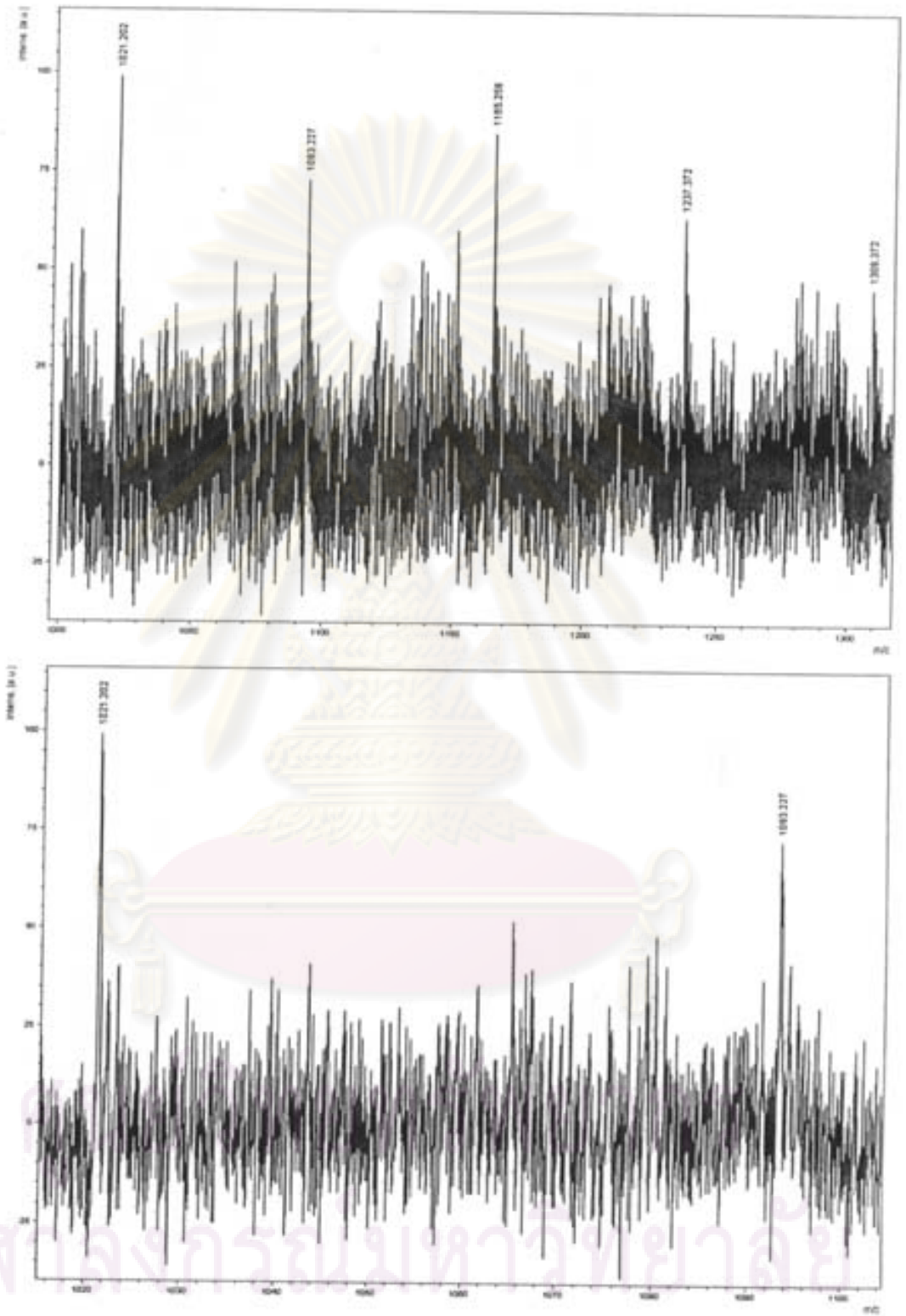


Figure 4.34 MALDI-TOF MS spectra of methanol soluble part copolymer (OH of PEEGE: LLA = 1:10, with $Sn(oct)_2$ 10% mol) [bottom-expanded spectrum].

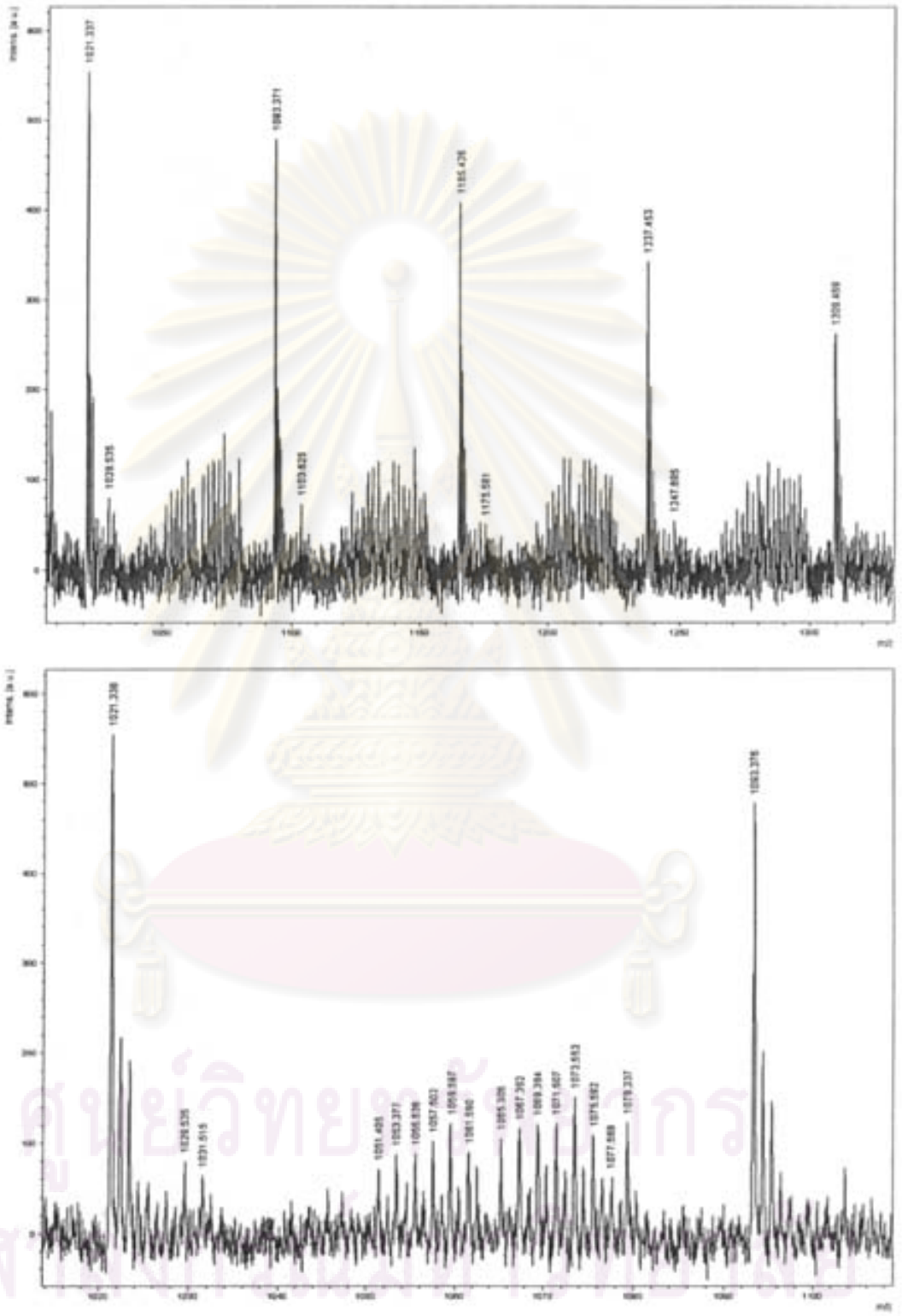


Figure 4.35 MALDI-TOF MS spectra of methanol soluble part copolymer (OH of PEEGE: LLA = 1:10, with $Sn(oct)_2$ 15% mol) [bottom-expanded spectrum].

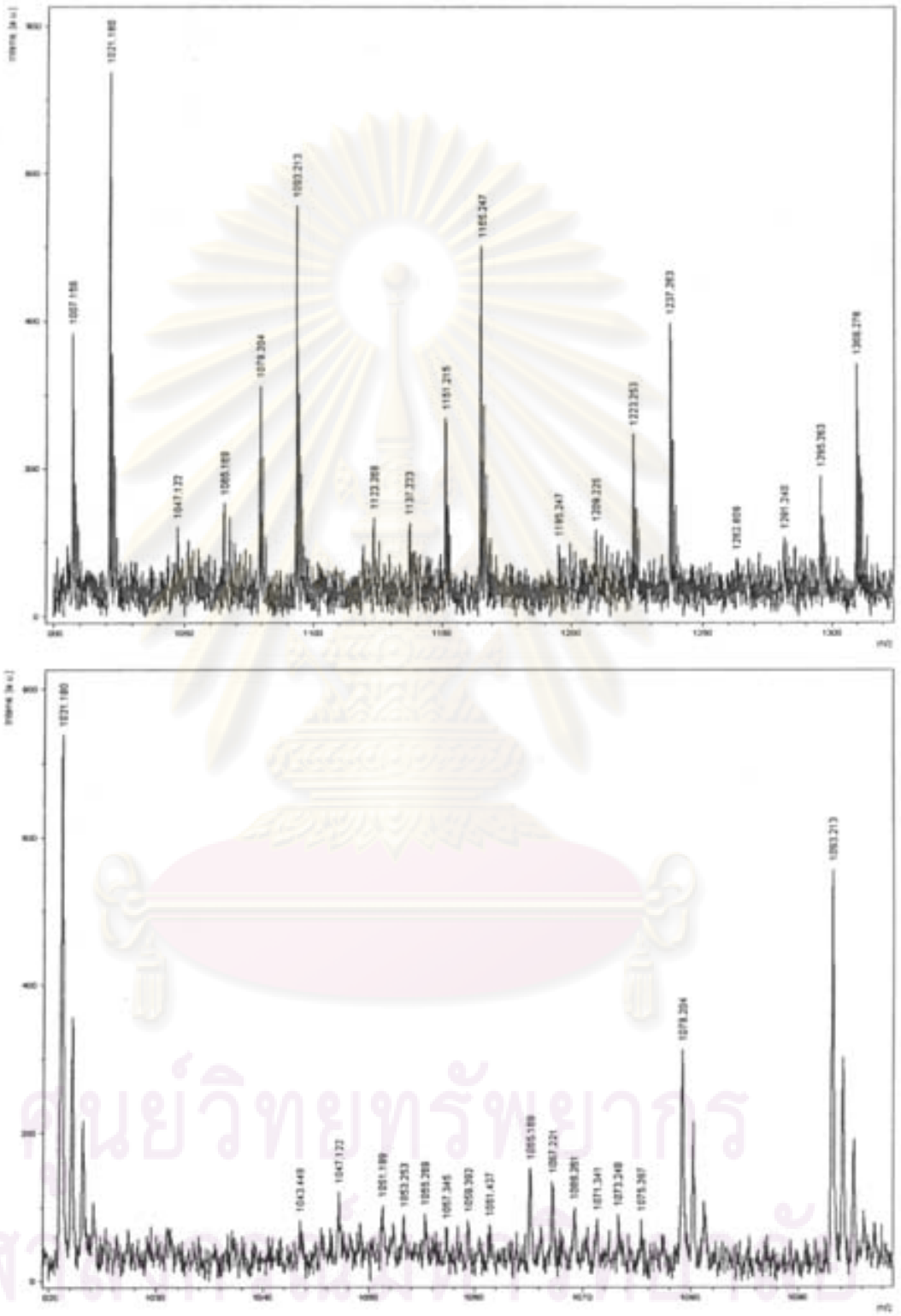


Figure 4.36 MALDI-TOF MS spectra of methanol soluble part copolymer (OH of PEEGE: LLA = 1:20, with $Sn(oct)_2$ 15% mol) [bottom-expanded spectrum].

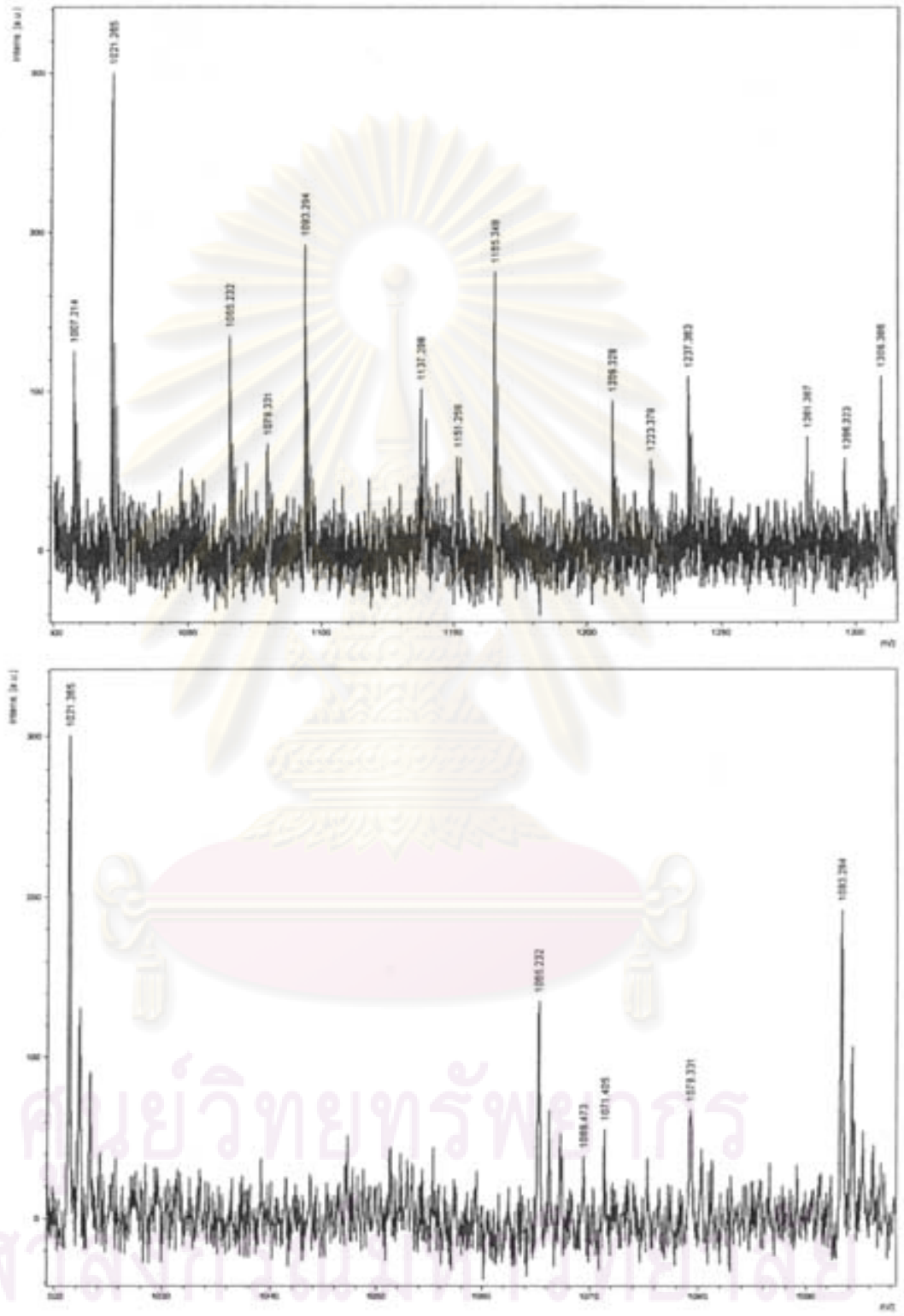


Figure 4.37 MALDI-TOF MS spectra of methanol soluble part copolymer (OH of PEEGE: LLA = 1:30 with $Sn(oct)_2$ 5% mol) [bottom-expanded spectrum].

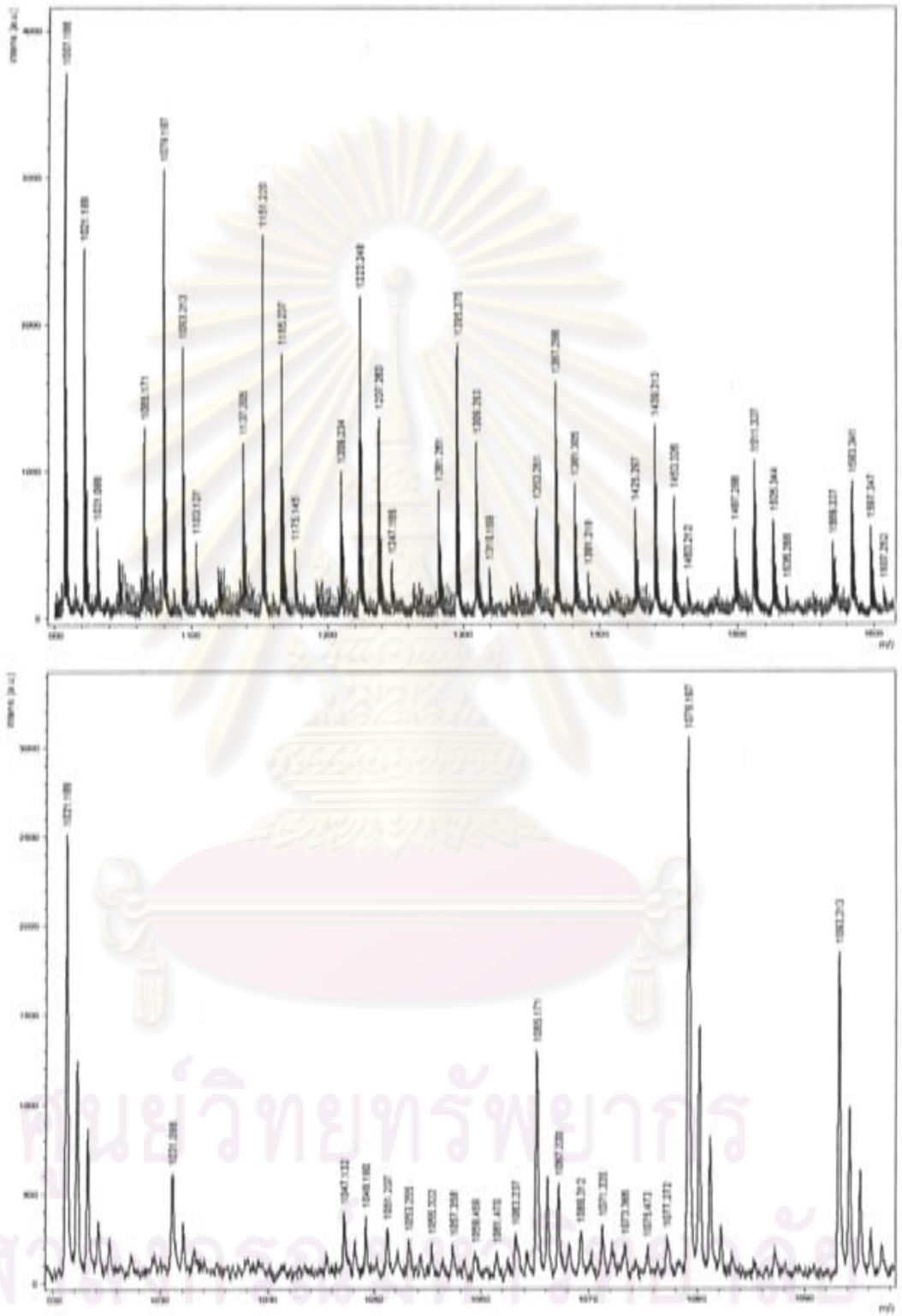


Figure 4.38 MALDI-TOF MS spectra of methanol soluble part copolymer (OH of PEEGE: LA = 1:30, with $Sn(oct)_2$ 15% mol) [bottom-expanded spectrum].

Table 4.10 Interpretation mass peak of methanol-soluble PEEGE-*b*-PLLA

Mass peak	Interpretated structure
Group 1	
1,053.2, …	tert-BuO-PEEGE$_2$-*b*-PLLA$_p$ plus a potassium when p = 9, 10, …
1,055.3, …	tert-BuO-PEEGE$_3$-*b*-PLLA$_p$ plus a potassium when p = 7, 8, …
1,057.4, …	tert-BuO-PEEGE$_4$-*b*-PLLA$_p$ plus a potassium when p = 5, 6, …
1,059.4, …	tert-BuO-PEEGE$_5$-*b*-PLLA$_p$ plus a potassium when p = 3, 4, …
1,061.5, …	tert-BuO-PEEGE$_6$-*b*-PLLA$_p$ plus a potassium when p = 1, 2, …
Group 2	
1,067.2, …	HO-PEEGE$_1$-*b*-PLLA$_p$ plus a potassium when p = 12, 13, …
1,069.2, …	HO-PEEGE$_2$-*b*-PLLA$_p$ plus a potassium when p = 10, 11, …
1,071.3, …	HO-PEEGE$_3$-*b*-PLLA$_p$ plus a potassium when p = 8, 9, …
1,073.4, …	HO-PEEGE$_4$-*b*-PLLA$_p$ plus a potassium when p = 6, 7, …
1,075.4, …	HO-PEEGE$_5$-*b*-PLLA$_p$ plus a potassium when p = 4, 5, …
1,077.5, …	HO-PEEGE$_6$-*b*-PLLA$_p$ plus a potassium when p = 2, 3, …
Group 3	Undefined structure polymer
1,021.2, …	1,025.3, … 1,027.3, …
1,029.3, …	1,031.3, … 1,065.2, …
1,079.2, …	

4.5.2 Methanol-insoluble part

Characteristic NMR signals of the copolymers are shown in Figure 4.39-4.42 and Table B-3.

^{1}H NMR of PEEGE-*b*-PLLA (Figure 4.39-4.42) in $CDCl_3$, δ (ppm): 5.14 (-CO(O)C**H**(CH_3)- of repeating unit PLLA), 4.79 (-OC**H**(CH_3)-O of chain end PEEGE), 4.67 (-OC**H**(CH_3)-O of repeating unit PEEGE), 4.4 and 4.2 (pending , 3.68-3.42 (-C**H**$_2$-C**H**(C**H**$_2$-O-)-O-, -O-C**H**$_2$-CH3 of PEEGE), 1.56 (CO(O)CH(C**H**$_3$)-

of repeating unit PLLA), 1.41 (CO(O)CH(**CH$_3$**)- of repeating unit PEEGE),1.3 (-OCH(**CH$_3$**)-O of chain end PEEGE), 1.26 (**CH$_3$**-C(O)H-O- of PEEGE), 1.16 (**CH$_3$**-CH$_2$-O- of PEEGE)

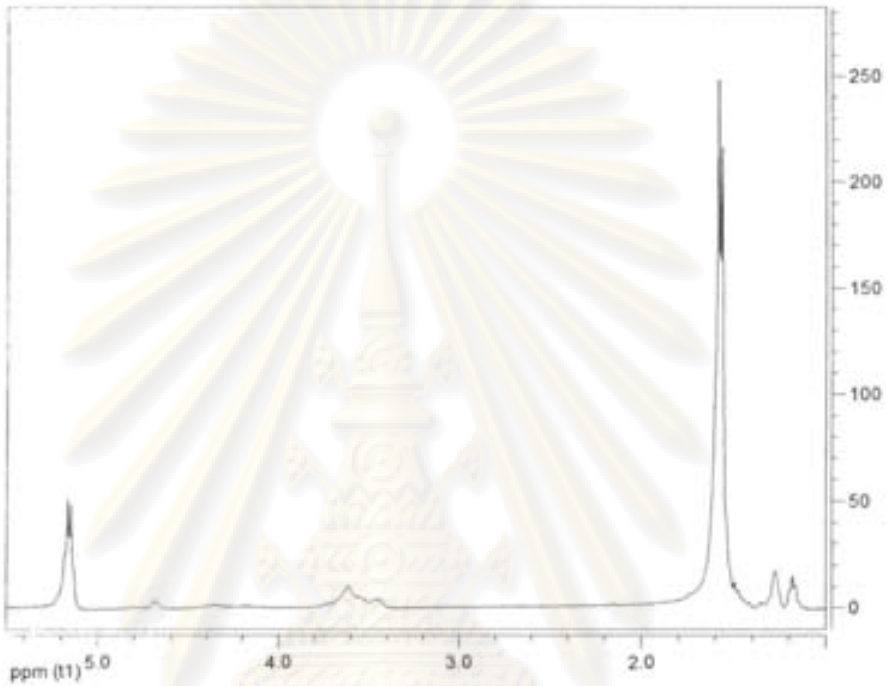


Figure 4.39 ^{1}H NMR spectrum of methanol-insoluble part copolymer (OH of PEEGE: LLA = 1:10 with Sn(oct)$_2$ 10% mol) in $CDCl_3$.

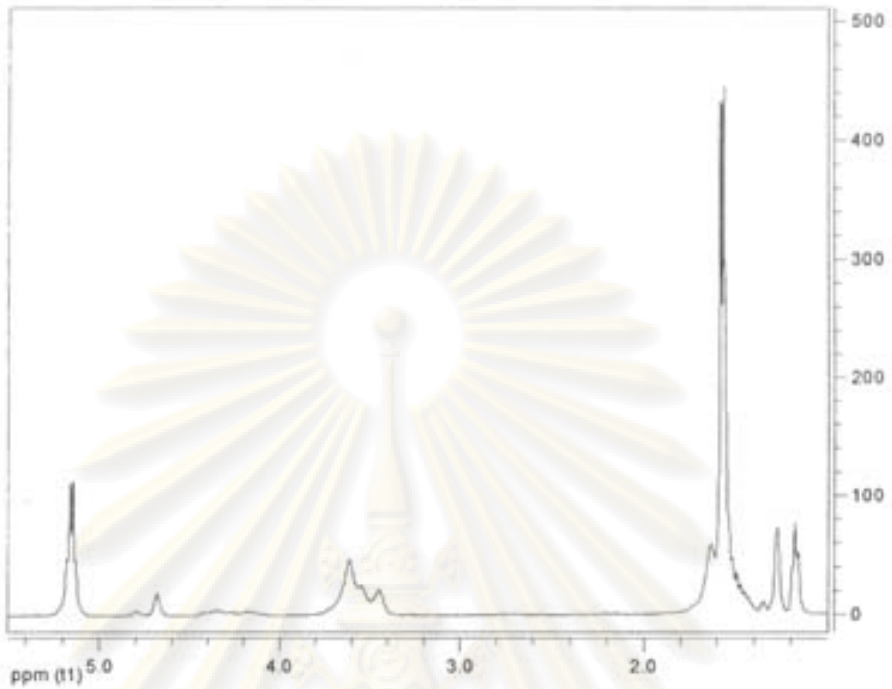


Figure 4.40 ^{1}H NMR spectrum of methanol-insoluble part copolymer (OH of PEEGE: LLA = 1:20 with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

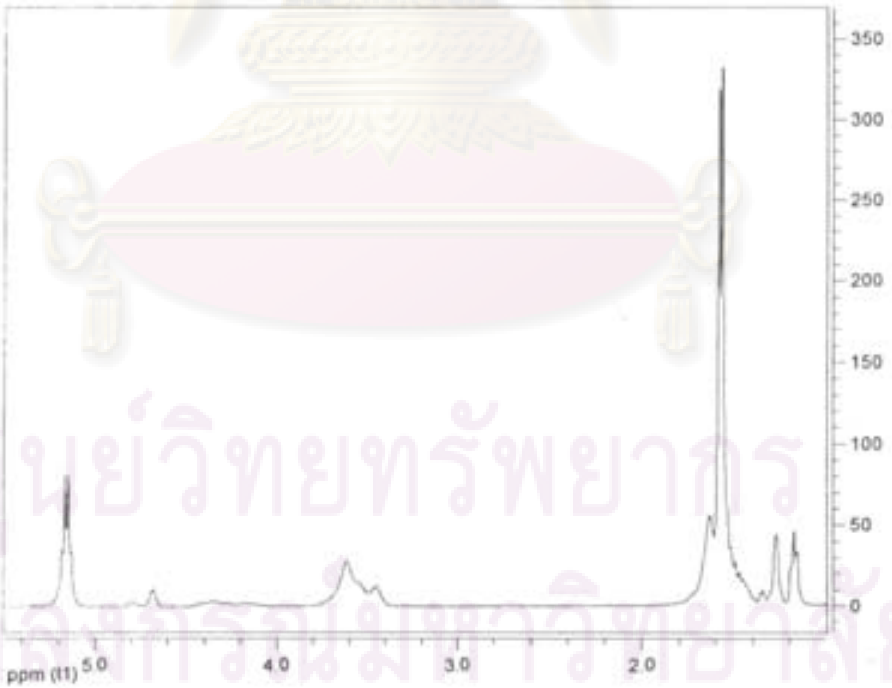


Figure 4.41 ^{1}H NMR spectrum of methanol-insoluble part copolymer (OH of PEEGE: LLA = 1:30 with $Sn(oct)_2$ 5% mol) in $CDCl_3$.

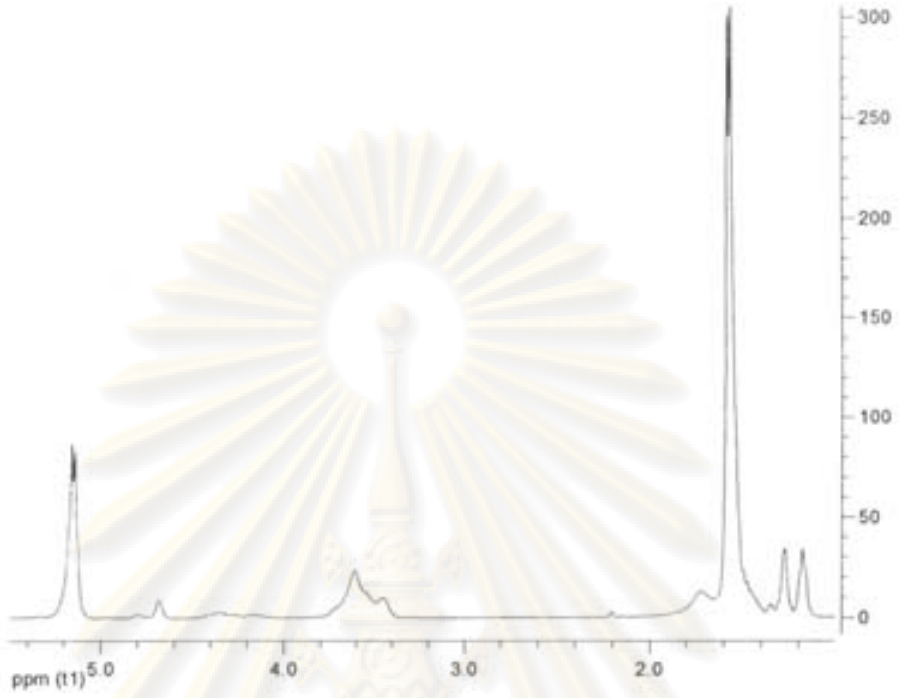


Figure 4.42 ^{1}H NMR spectrum of methanol-insoluble part copolymer (OH of PEEGE: LLA = 1:30 with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

Characterization results of methanol-insoluble part of obtained polymers are presented in Table 4.11. The methanol-insoluble part of the copolymerization product was most likely homo PLLA because of its methanol-insoluble properties. However, signals of PEEGE found in NMR spectra suggested that these solid part contained PEEGE and PLLA or its copolymer having long PLLA block. H-H COSY NMR (Figure A-12-A-15) gave a couple signal between 5.1 and 3.6 ppm in entry 1/30/15 but were not noticeable in the others.

Table 4.11 Characterization results of methanol-insoluble part PEEGE-*b*-PLLA

Entry	%Weight	Appearance	$\overline{M}_n$ (GPC)	PDI (GPC)	$\overline{M}_n$ (MS)
1/10/05	-[1]	-			
1/10/10	0.75	Grey solid	10,064	2.62	2, 025
1/10/15	-[1]	-			
1/20/05	54.28	Brown gum	-	-	-
1/20/10	59.40	Brown gum	-	-	-
1/20/15	0.95	Brown Solid	10,245	2.42	-
1/30/05	5.25	White solid and brown solid	10,924	7.53	-
1/30/10	41.87	Brown gum	-	-	-
1/30/15	10.43	Yellow solid	13,098	2.31	2,109

[1]Reddish brown solid residue in 1/10/05 and white fine solid residue in 1/10/15 that were insoluble in methanol were observed. However, they were not analyzed because of their small amount.

As shown in Table 4.12, the acetal proton value of all entries were lower than it should be (1:7). It meant that cleavage of ethoxy ethyl protecting group in PEEGE block segment somewhat occurred.

Table 4.12 Characteristics of methanol-insoluble part from copolymerization of PEEGE and LLA as evaluated by ^{1}H NMR

Entry	Acetal proton ratio in PEEGE[1]	% Acetal cleavage[2]	H ratio PEEGE:LLA[3] (feeding ratio PEEGE:LLA)	Average PLLA chain length[4]	Mass increase due to PLLA segment[5]
1/10/10	0.62:7	13.3	7.2:11.90 (7.2:1)	29.2	2,105
1/20/15	0.75:7	10.6	3.6:2.82 (3.6:1)	27.4	1,973
1/30/5	0.64:7	17.9	2.4:2.09 (2.4:1)	21.3	1,532
1/30/15	0.64:7	15.9	2.4:2.92 (2.4:1)	31.6	2,278

[1] $I_{4.7\ ppm}/I_{3.3\text{-}3.8ppm}$

[2] $I_{4.8\ ppm} \times 100/(I_{4.8\ ppm} + I_{4.7\ ppm})$

[3] $I_{3.3\text{-}3.8\ ppm}/I_{5.14ppm}$

[4] $I_{5.14\ ppm}/I_{4.34\ ppm}$

[5] $I_{5.14\ ppm} \times 72/I_{4.34\ ppm}$

GPC chromatograms (Figure 4.43) of the methanol-insoluble parts had the highest peak at a retention time shorter than that of the methanol-soluble part. It meant that these insoluble parts had a greater amount of high molecular weight chains than methanol-soluble one did.

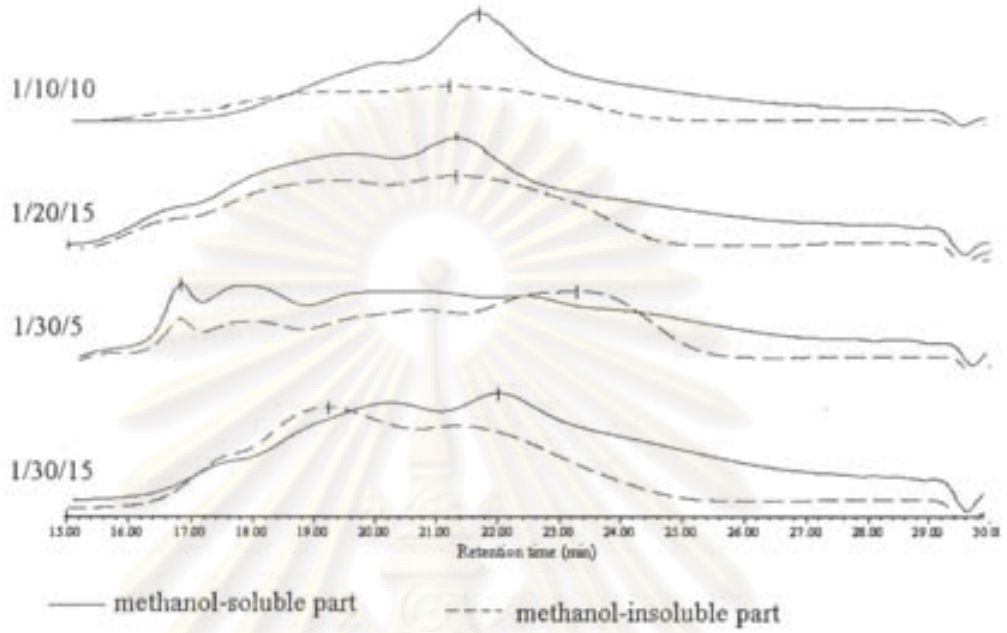


Figure 4.43 GPC of methanol-insoluble part from the copolymerization between PEEGE and LLA.

MALDI-TOF MS spectra of the methanol-insoluble part from 1/10/10 and 1/30/15 were representatively analyzed (Figure 4.44-4.45). They showed two series of mass peaks at higher mass than that found in the methanol-soluble part. The mass intervals were 72 equal to the lactic acid unit. The first series matched PLLA having both hydroxyl end chain with potassium ion, for example, m/z at 1929.303 matched PLLA with potassium ion where n = 26 (calculated m/z = 1929.5). The second series, such as 1,957.4 and 1,885.6, had mass peaks the same as those found in the methanol-soluble part and did not exactly match the structure PEEGE-*b*-PLLA copolymer. The reason that the structure was not identified was from the fact that partial acetal cleavage in PEEGE block of the copolymer occurred. In conclusion, the methanol-insoluble part consisted of PLLA homopolymer and undefined polymer structure.

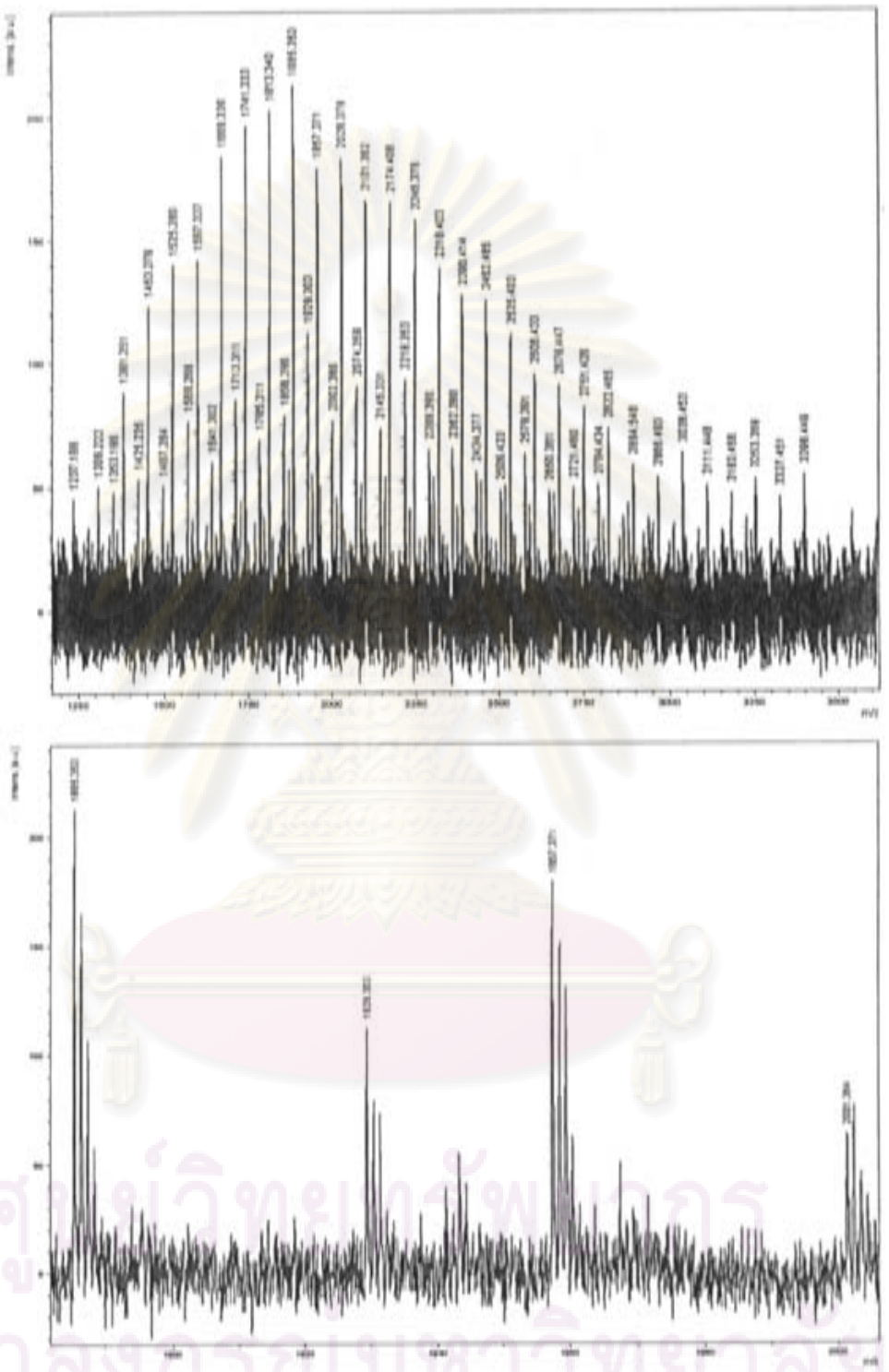


Figure 4.44 MALDI-TOF MS spectra of methanol-insoluble part copolymer (OH of PEEGE: LLA = 1:10, with $Sn(oct)_2$ 10% mol) [bottom- expanded spectrum].

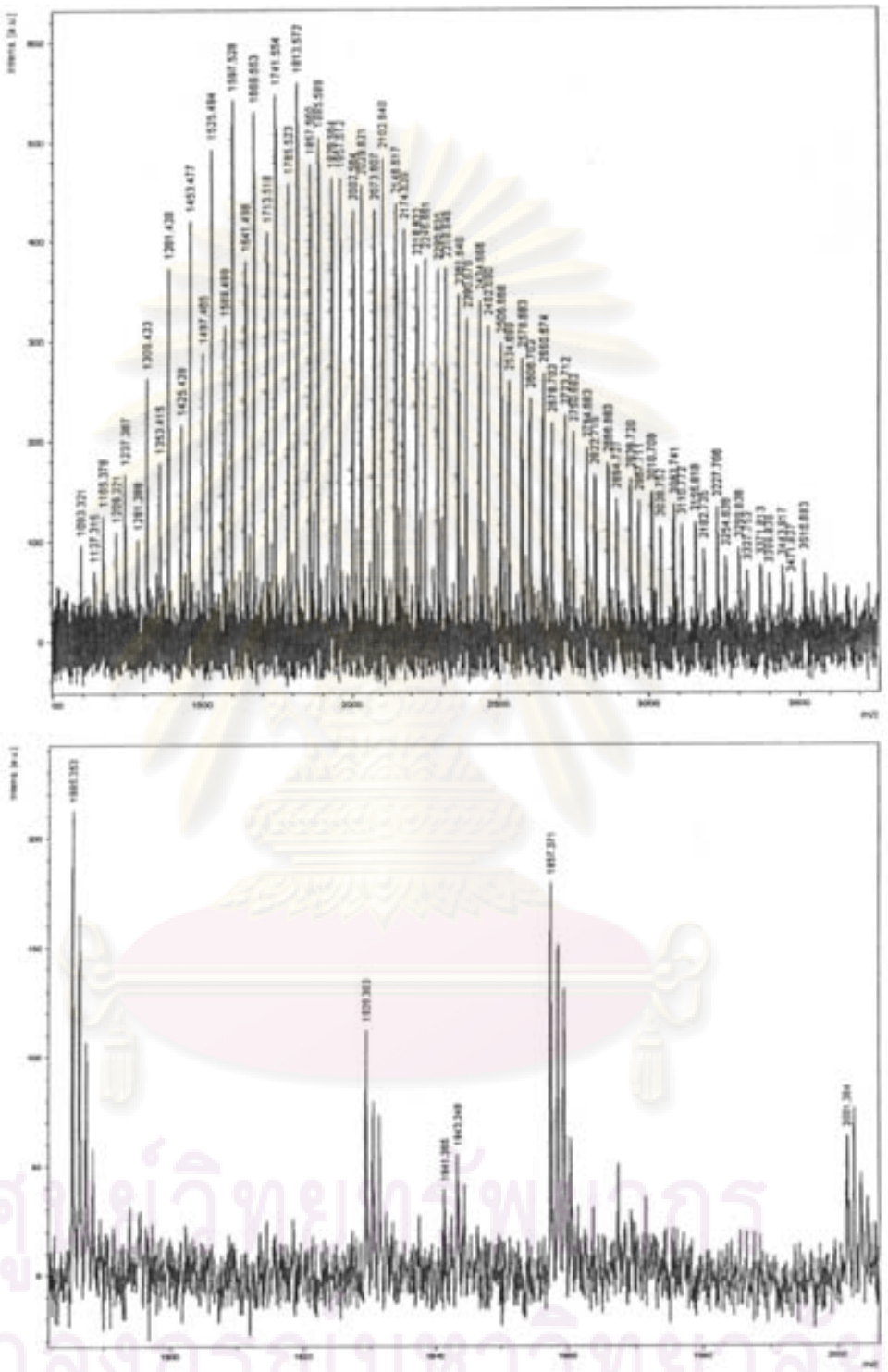


Figure 4.45 MALDI-TOF MS spectra of methanol insoluble part copolymer (OH of PEEGE: LLA = 1:30, with $Sn(oct)_2$ 5% mol) [bottom- expanded spectrum].

4.6 Acetal deprotection of PEEGE

Acetal deprotection of linear PEEGE was carried out in order to determine the reaction condition and the characteristic of linear PG.

^{1}H NMR of linear poly(glycidol) (Figure 4.46) in CD_3OD, δ (ppm): 3.76-3.50 (-CH_2-CH(CH_2-O-)-O-of PG repeating unit), 1.98 (**OH** of PG repeating unit), 1.19((CH_3)$_3$-C-O, chain end)

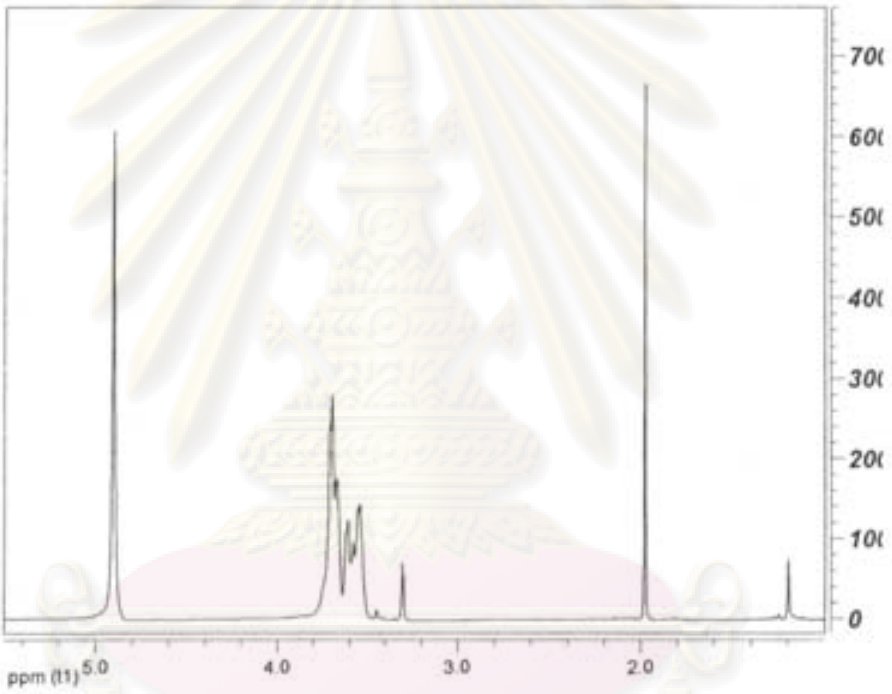


Figure 4.46 ^{1}H NMR spectrum of linear poly(glycidol) in CD_3OD.

The obtained linear PG was yellow liquid. It was insoluble in THF but soluble in water and methanol. The coupling between signals at 3.7 and 1.98 ppm was observed from H-H COSY NMR analysis (Figure. 4.47). This confirmed the presence of methylene –CH_2- (3.7 ppm) that was adjacent to the hydroxyl –OH (1.98 ppm). Moreover, it was found a coupling between peaks at 3.50 ppm and 1.19 ppm. These two signals were thought to be caused by trace amount of methanol, a by-product of deprotection, in the polymer.

Figure 4.47 ^{1}H-H COSY spectrum of linear poly(glycidol) in CD_3OD.

Because linear PG was insoluble in THF, its molecular weight was not determined by our GPC at which THF was used as a mobile phase. MALDI-TOF MS was therefore used to determine its molecular weight. A series of peaks that had mass interval of 74, a repeating mass of PG, were observed as shown in Figure 4.48 and interpreted in Table 4.13. The number average molecular weight was 1,866 with PDI of 1.15.

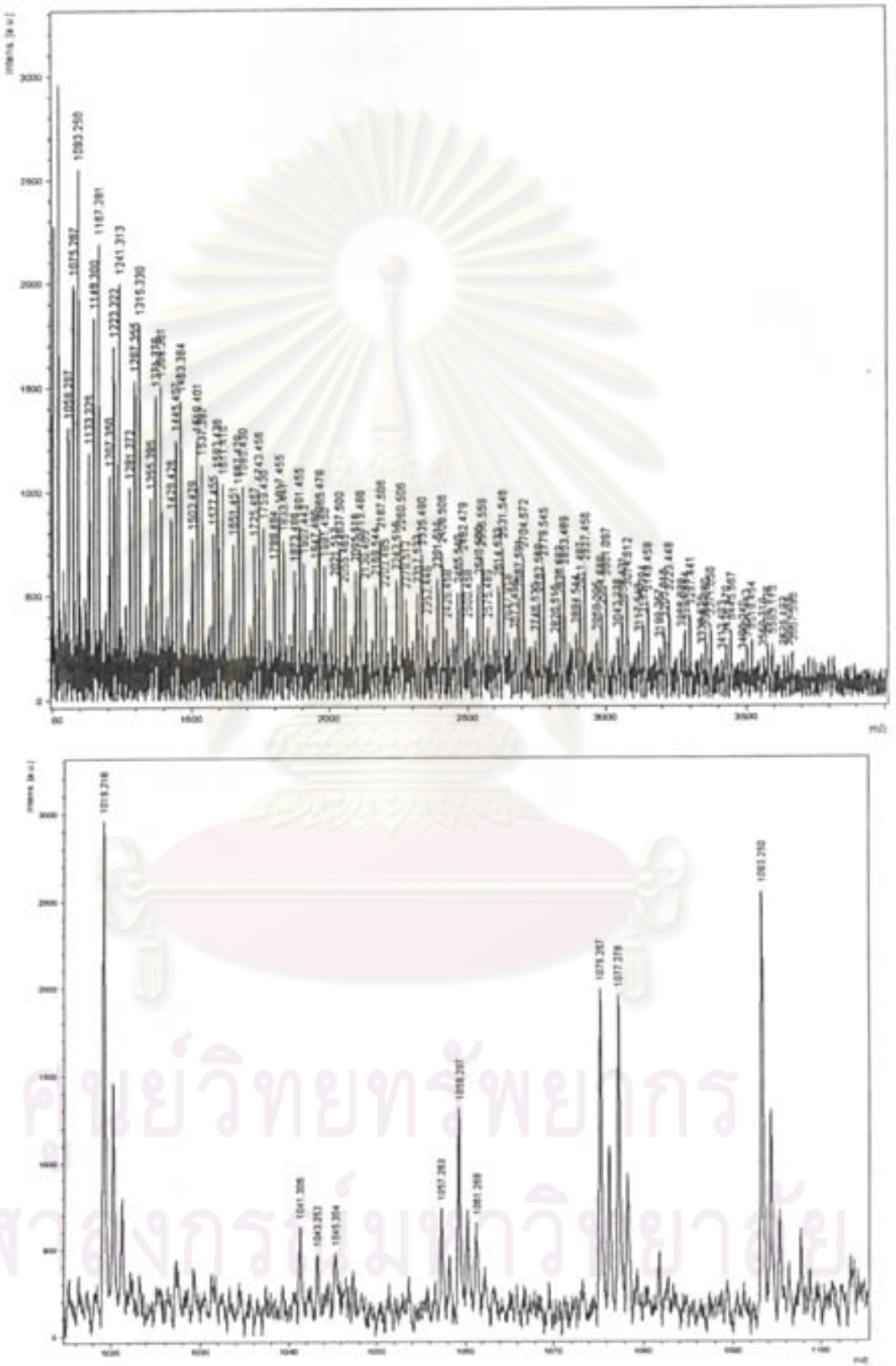
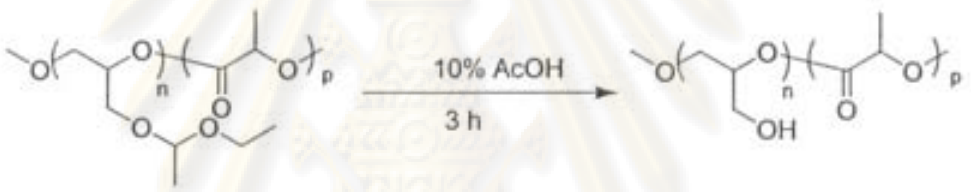


Figure 4.48 MALDI-TOF MS spectra of linear poly(glycidol) [bottom-expanded spectrum].

Table 4.13 Mass peaks interpretation of PG

tert-BuO-PG + Na	tert-BuO-PG + K	HO-PG + Na	HO-PG + K
1,059.3	1,075.3	1,079.3	1,093.3
1,133.3	1,149.3	1,151.3	1,167.3
1,207.4	1,223.3	1,225.3	1,241.3

4.7 Acetal deprotection of methanol-soluble PEEGE-*b*-PLLA to PG-*b*-PLLA



Scheme 4.7 Acetal deprotection of PEEGE-*b*-PLLA.

The deprotection of acetal protecting group was carried out as shown in Scheme 4.6. Because 10% aqueous acetic acid solution was used to remove the acetal protecting group in PEEGE blocks in the copolymers, a large volume of methanol was needed to homogenize organic and aqueous phases. The amounts of methanol and aqueous acetic acid solution required were based on the weight of PEEGE in the copolymers. The weight ratio of PEEGE in the copolymer was estimated from the feeding ratio. The obtained products were pale yellow viscous liquid.

As shown in Figure 4.49, the NMR signal of methine at 4.7 ppm indicated the present of acetal group remained in the product after the deprotection of methanol-soluble PEEGE-b-PLLA. It was found that only two entries, 1/10/05 and 1/10/10 were successfully deprotected while entries 1/10/15, 1/20/15, 1/30/05 and 1/30/15 were not. The reason for incomplete removal was accounted for the high PLLA weight ratios in the copolymers. Because the copolymer entries 1/20/15, 1/30/05 and 1/30/15 had high ratios of PLLA in the copolymer, the methanol-water

mixed solvent was not able to solubilize the two components completely. Consequently, acetal deprotection was not completed.

The percent of acetal deprotection was determined by

$$= \frac{I_{3.7-3.4\,ppm} \times 100}{5 \times \left(I_{3.7-3.4\,ppm} + I_{4.65\,ppm}\right)}$$

And the results were shown in Table 4.14

Table 4.14 Characteristics of deprotection of methanol-soluble PEEGE-*b*-PLLA

Entry	% Yield	Appearance	%deprotection
d1/10/5	86.1	Transparent yellow viscous liquid	>99
d1/10/10	82.3	Cloudy yellow viscous liquid	>99
d1/10/15	90.1	Slightly cloudy yellow viscous liquid	23.6
d1/20/15	83.8	Cloudy yellow viscous liquid	19.8
d1/30/5	81.4	Transparent orange viscous liquid	29.4
d1/30/15	93.4	Slightly cloudy yellow viscous liquid	28.8

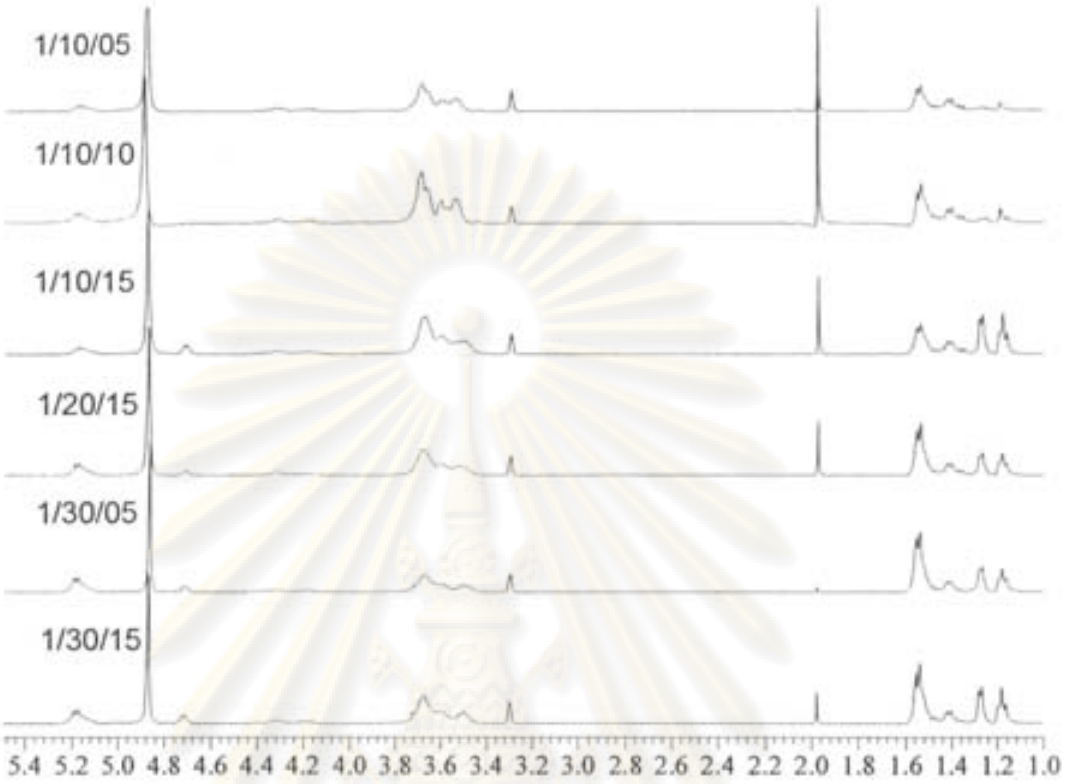


Figure 4.49 ^{1}H NMR spectrum of deprotected copolymer (PG-*b*-PLLA) in $CDCl_3$.

^{1}H NMR of PG-*b*-PLLA in CD_3OD, δ (ppm): 5.18 (-CO(O)C**H**(CH_3)- of LLA repeating unit), 4.91 (CD_3OD, solvent), 4.32 (-CO(O)C**H**(CH_3)OH end group of PLLA), 3.8-3.5 (-C**H**$_2$-C**H**(C**H**$_2$-O-)-O-of PG repeating unit), 3.30 (CD_3OD, solvent), 1.98 (**OH** of PG repeating unit), 1.55 (CO(O)CH(C**H**$_3$)- of LLA repeating unit), 1.41 (CO(O)CH(C**H**$_3$) of end group of LLA), 1.19((C**H**$_3$)$_3$-C-O, chain end)

Molecular weight of PG-*b*-PLLA were determined by NMR spectroscopy by integrating end chain CH of PLLA possessed δ 4.34 ppm as one proton. Then, molecular weight was calculated by

$$\text{Molecular weight of PG block} = \frac{I_{3.8\text{-}3.5\ ppm} \times 74.0368}{5}$$

$$\text{Molecular weight of PLLA block} = \frac{I_{5.18\ ppm} \times 72.0211}{I_{4.34\ ppm}}$$

The results as well as those from MALDI-TOF-MS are shown in Table 4.14.

Table 4.15 Characterization of deprotected methanol-soluble PEEGE-b-PLLA copolymer

Entry	% Yield	$\overline{M}_n$ of each block (NMR), (Da)		$\overline{M}_n$ (NMR) of PG-*b*-PLLA (Da)	$\overline{M}_n$ (Da) (MS)	PDI (MS)
		PG	PLLA			
d1/10/05	86.1	321	187	508	1.241	1.07
d1/10/10	82.3	524	252	776	1,206	1.08

^{1}H-H COSY NMR analysis (Figure 4.50-4.51) of entry d1/10/05 and d1/10/10 revealed a low-intensity coupled signal between the peak at 5.05 and 3.7 ppm which were the evidences of conjugation between the LLA and EEGE blocks.

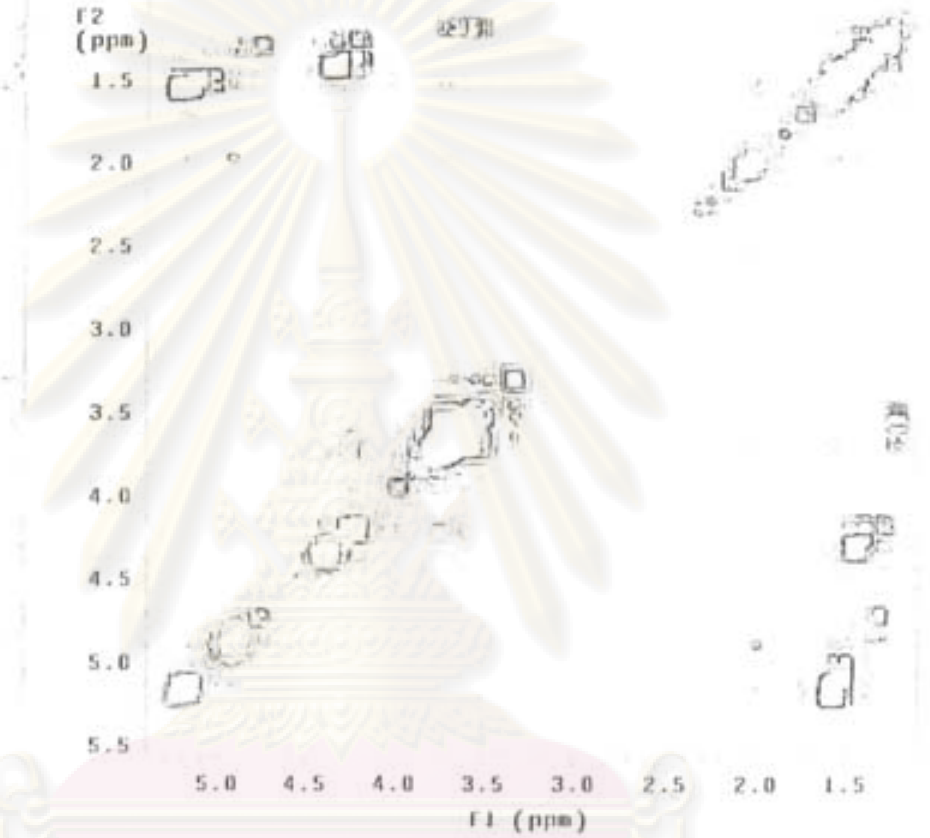


Figure 4.50 ^{1}H-H COSY spectrum of PG-*b*-PLLA, entry 1/10/5 in CD_3OD.

Figure 4.51 ^{1}H-H COSY spectrum of PG-*b*-PLLA, entry 1/10/10 in CD_3OD.

Solubility test for entries d1/10/5 and d1/10/10 was carried out. Results are shown in Table 4.15. PG-*b*-PLLA entries d1/10/5 and d1/10/10 were partially soluble in water. Their solutions looked turbid and some white solid settled at the bottom of the solution. Their solubilities in THF were different, however. Entry d1/10/5 was partially dissolved in THF, but entry d1/10/10 was not soluble in THF. The water-soluble components were probably homo PG and PG-*b*-PLLA copolymer. The water-insoluble solid was most likely the homo PLLA, discussed in the earlier section. More purification steps is in fact needed in order to separate the homo PLLA from other copolymer identities. The PG can be removed from the copolymer mixture by precipitation in THF, while homo PLLA can be precipitated by MeOH.

Due to the time limit and small amount of sample residue, the mentioned purification steps were not, however, performed.

Table 4.16 Solubility test of deprotected copolymer at room temperature (30 °C)

Entry	Solubility	
	Water	THF
d1/10/05	Partially soluble[1]	Partially soluble
d1/10/10	Partially soluble[2]	Insoluble

[1] water-soluble = 86.1%, water-insoluble = 13.9%

[2] water-soluble = 85.6%, water-insoluble = 14.4%

Molecular weight of THF-soluble part of the polymer entry d1/10/5 was 2,268 Da. (PDI=2.15), determined by GPC for preliminary investigation. Molecular weight distribution of THF-soluble PG-*b*-PLLA entry d1/10/05 (Figure 4.52) was uni-modal. The molecular weight was found to be lower than methanol-soluble part of PEEGE-*b*-PLLA entry d1/10/5. However, the obtained molecular weight was the result of THF-soluble part of polymer entry 1/10/5.

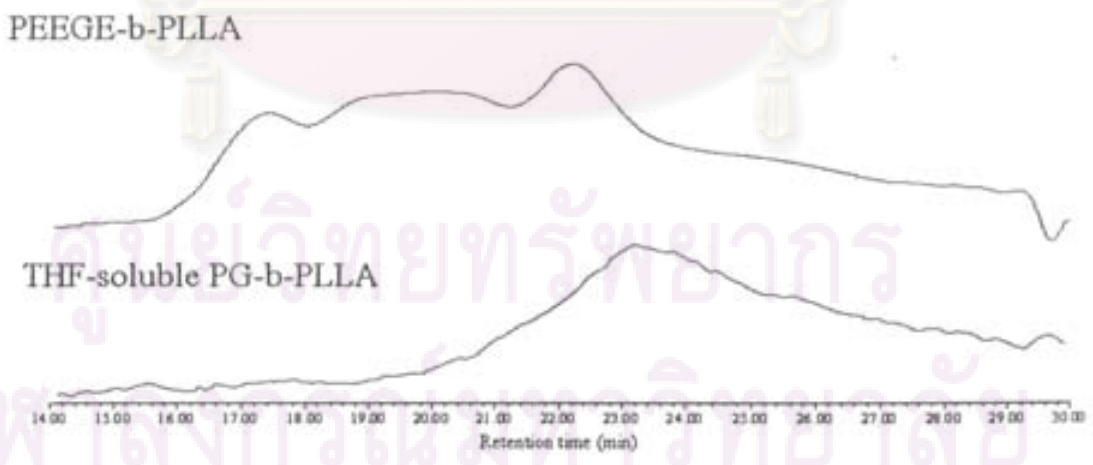


Figure 4.52 GPC of PEEGE-*b*-PLLA and THF-soluble part of PG-*b*-PLLA of entry d1/10/05.

PG-*b*-PLLA entry 1/10/05 and 1/10/10 were characterized by MALDI-TOF to determine the structure (Figure. 4.53-4.54), in which three series groups were obtained in both entries. Three series groups were presented in Table 4.16. The mass interval in each series was 72 which matched the mass of lactic acid.

Table 4.17 Interpretation mass peak of PG-*b*-PLLA

Mass peak	Interpreted structure
1,065.1, …	tert-BuO-PG_8-*b*-$PLLA_p$ plus a potassium when p = 5, 6, …
1,067.1, …	tert-BuO-PG_9-*b*-$PLLA_p$ plus a potassium when p = 4, 5, …
1,069.1, …	tert-BuO-PG_{10}-*b*-$PLLA_p$ plus a potassium when p = 3, 4, …
1,071.1, …	tert-BuO-PG_{11}-*b*-$PLLA_p$ plus a potassium when p = 2, 3, …
1,073.1, …	tert-BuO-PG_{12}-*b*-$PLLA_p$ plus a potassium when p = 1, 2, …
Group 2 :	
1,077.1, …	HO-PG_6-*b*-$PLLA_p$ plus a potassium when p = 8, 9, …
1,079.1, …	HO-PG_7-*b*-$PLLA_p$ plus a potassium when p = 7, 8, …
Group 3 :	Undefined structure polymer
1,021.1, …	1,023.1, …
1,025.1, …	1,031.0, …

In conclusion, the obtained polymers contained tert-BuO-PG_n-*b*-$PLLA_p$, HO-PG_n-*b*-$PLLA_p$ and polymers with undefined structure.

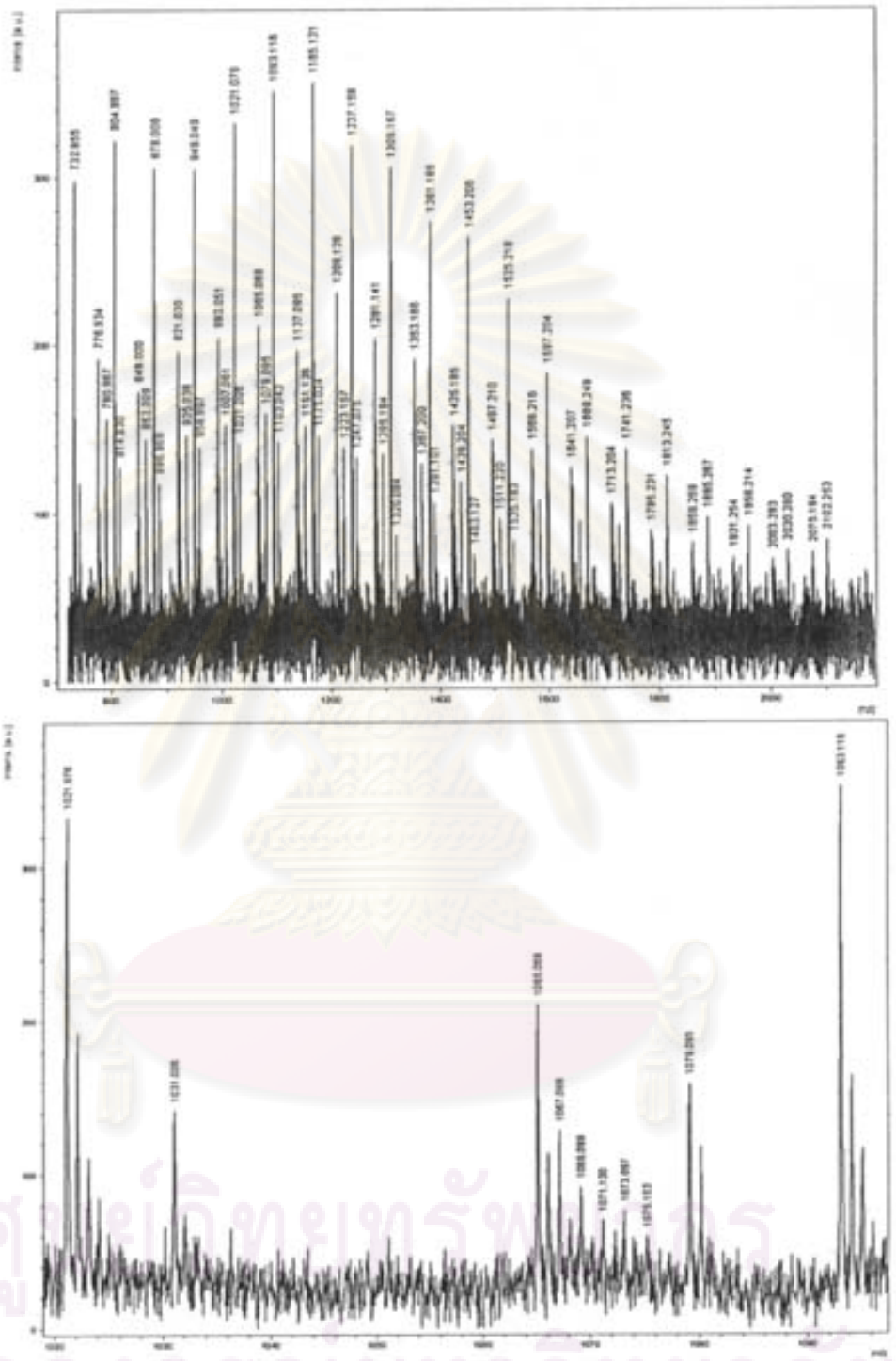


Figure 4.53 MALDI-TOF MS spectra of copolymer PG-*b*-PLLA d1/10/05 [bottom-expanded spectrum].

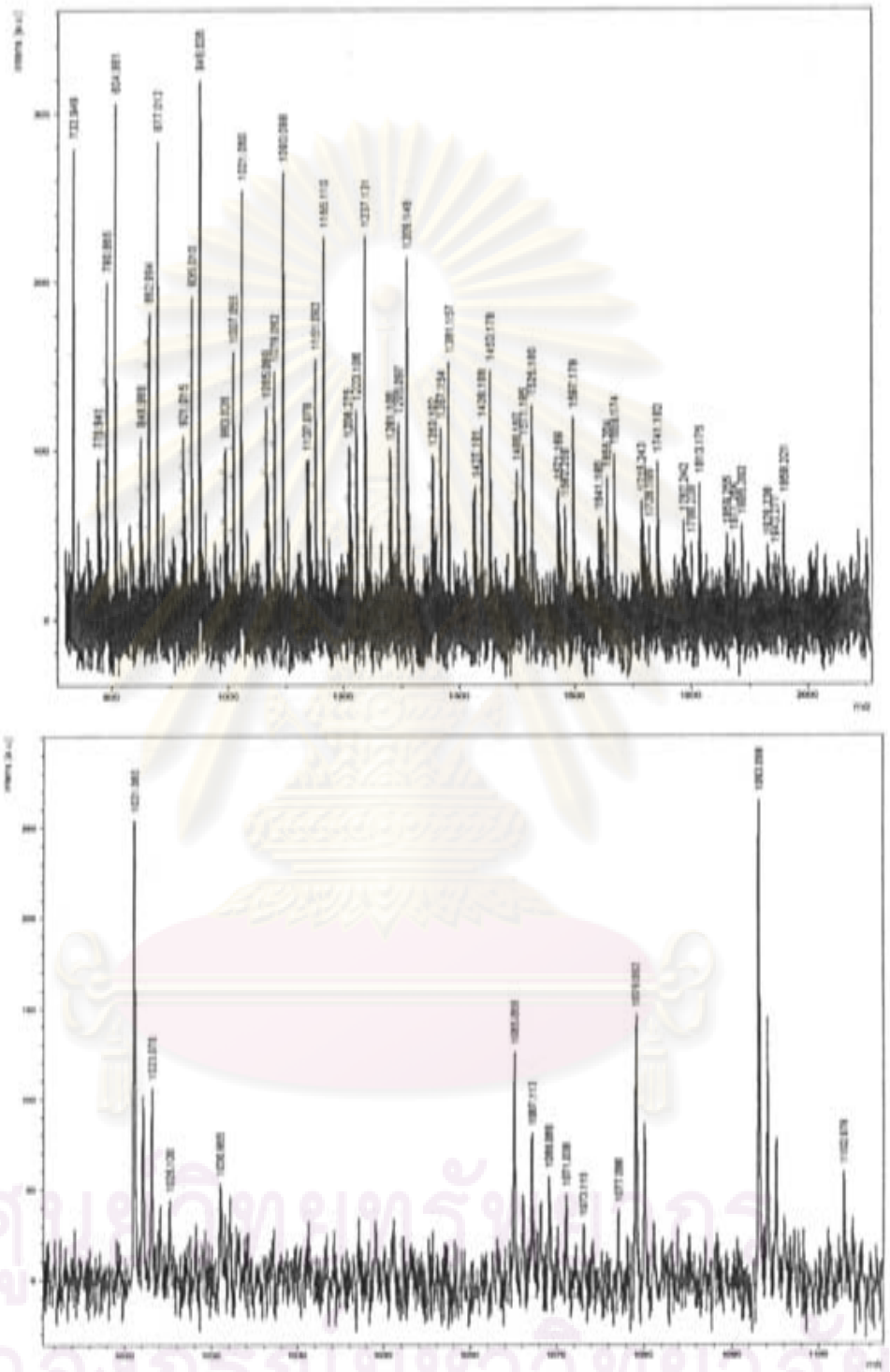


Figure 4.54 MALDI-TOF MS spectra of copolymer PG-*b*-PLLA d1/10/10 [bottom-expanded spectrum].

CHAPTER V

CONCLUSIONS AND FUTURE DIRECTIONS

5.1 Conclusions

Linear polyglycidol-*b*-poly(L-lactide) or PG-*b*-PLLA was prepared from ring opening copolymerization between poly(1-ethoxyethyl glycidyl ether) (PEEGE) and LLA monomers in the presence of $Sn(oct)_2$ catalyst, followed by ethoxy ethyl deprotection. The mole ratio of PEEGE and LLA was varied from 1:10, 1:20, to 1:30. The copolymerization was performed at 110-120°C for 24 hours. Two types of polymer products with difference in MeOH solubility were obtained.

The methanol-soluble part were PEEGE-*b*-PLLA copolymer as characterized by NMR and MALDI-TOF-MS. Esterification between PEEGE chain end and LLA unit was evidently found by the NMR and their MS peak series. The molecular weight of the methanol-soluble copolymer had wide distribution, indicating that the copolymerization was non-living. Mass spectrometer revealed that the number average molecular weight of PG-*b*-PLLA was about 1,200 Da, and pointed out that their structures matched *tert*-BuO-PG_p-*b*-$PLLA_n$ and HO-PG_p-*b*-$PLLA_n$ as well as a number of polymers with undefined structures. The methanol-insoluble parts were found to mostly consist of homo PLLA and undefined structure polymers. Although the obtained PG-*b*-PLLA was soluble in MeOH, it was not completely soluble in water at room temperature (~30°C).

5.2 Future directions

- Investigate the use of alternate catalysts, for example, $Ca(NH_3)_6$, for ring-opening polymerization of LLA that can be used in combination with PEEGE to prepare the block copolymer without the occurrence of acetal protecting group cleavage.

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APPENDICES

APPENDIX A

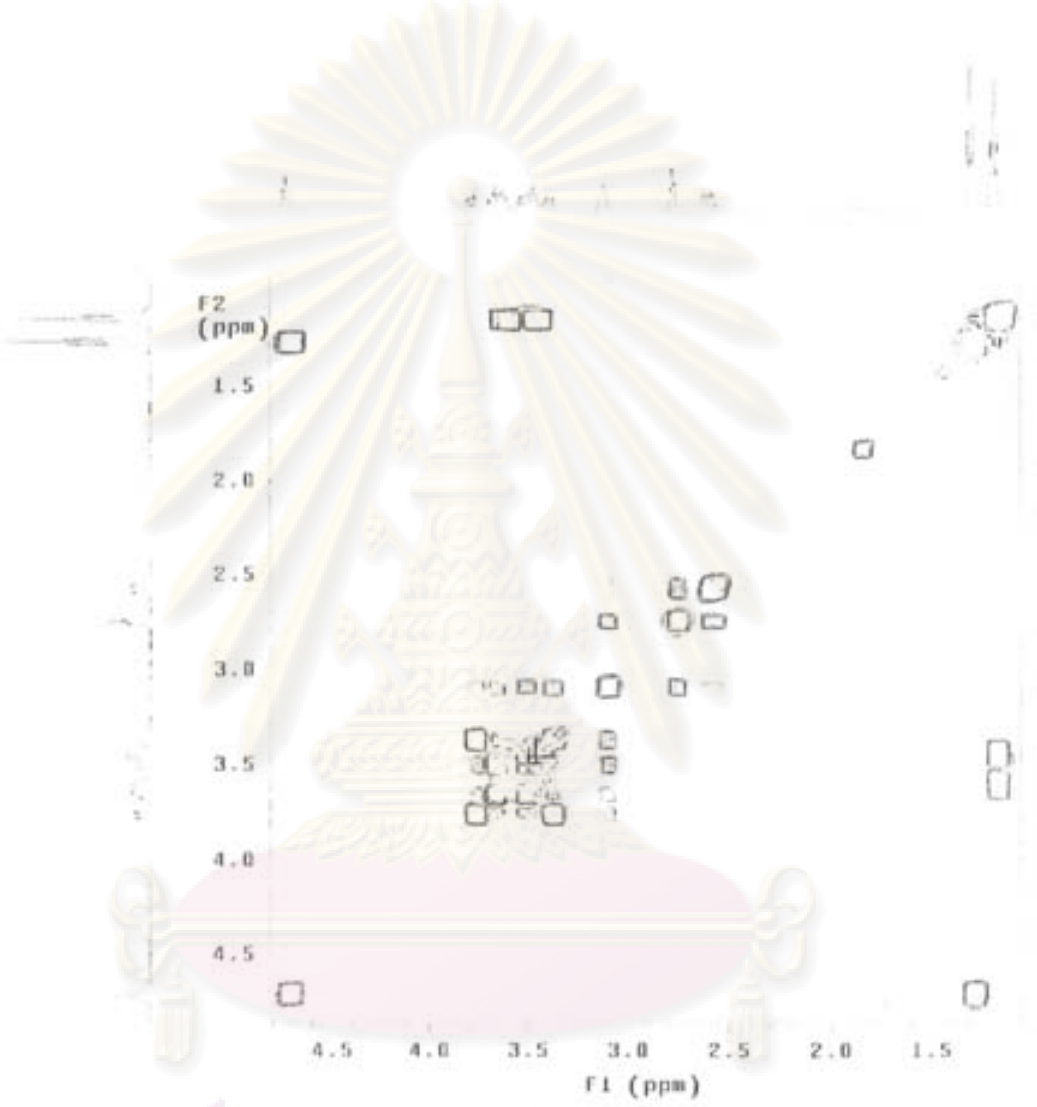

Figure A-1 ^{1}H-H COSY spectrum of EEGE in $CDCl_3$.

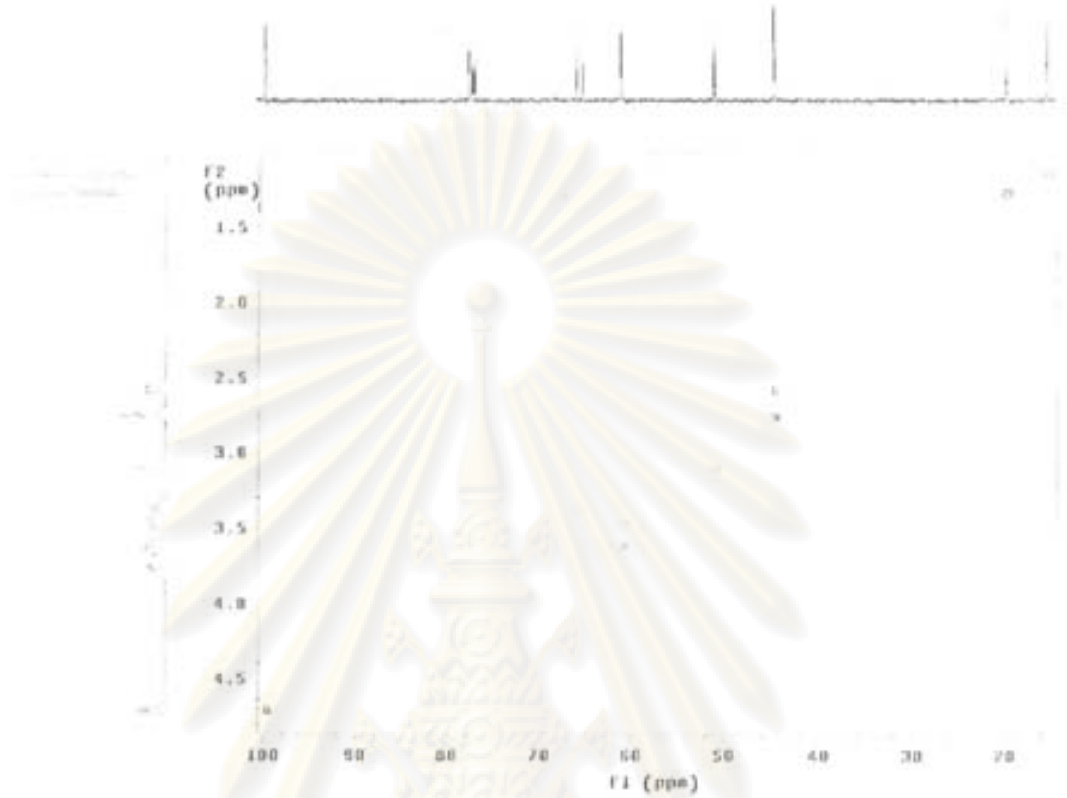

Figure A-2 ^{1}H-C HSQC spectrum of EEGE in $CDCl_3$.

Figure A-3 ^{1}H-H COSY spectrum of Methanol-soluble part copolymer (feeding mole ratio OH of PEEGE :LLA = 1:10 with $Sn(oct)_2$ 5% mol) in $CDCl_3$.

Figure A-4 ^{1}H-H COSY of mleethanol soluble part copolymer (feeding mole ratio OH of PEEGE :LLA = 1:10 with $Sn(oct)_2$ 10% mol) in $CDCl_3$.

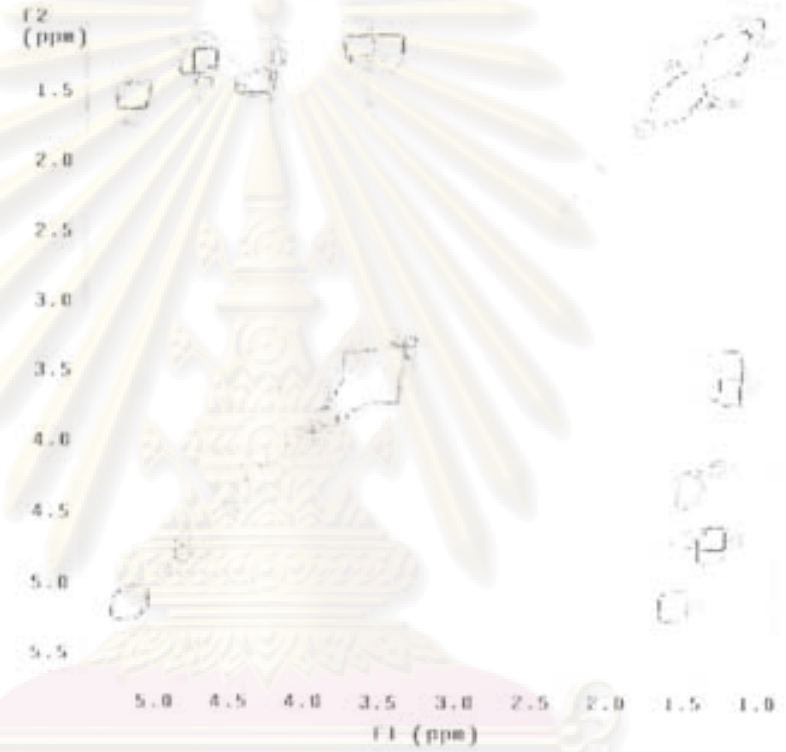

Figure A-5 ^{1}H-H COSY spectrum of Methanol-soluble part copolymer (OH of PEEGE :LLA = 1:10 with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

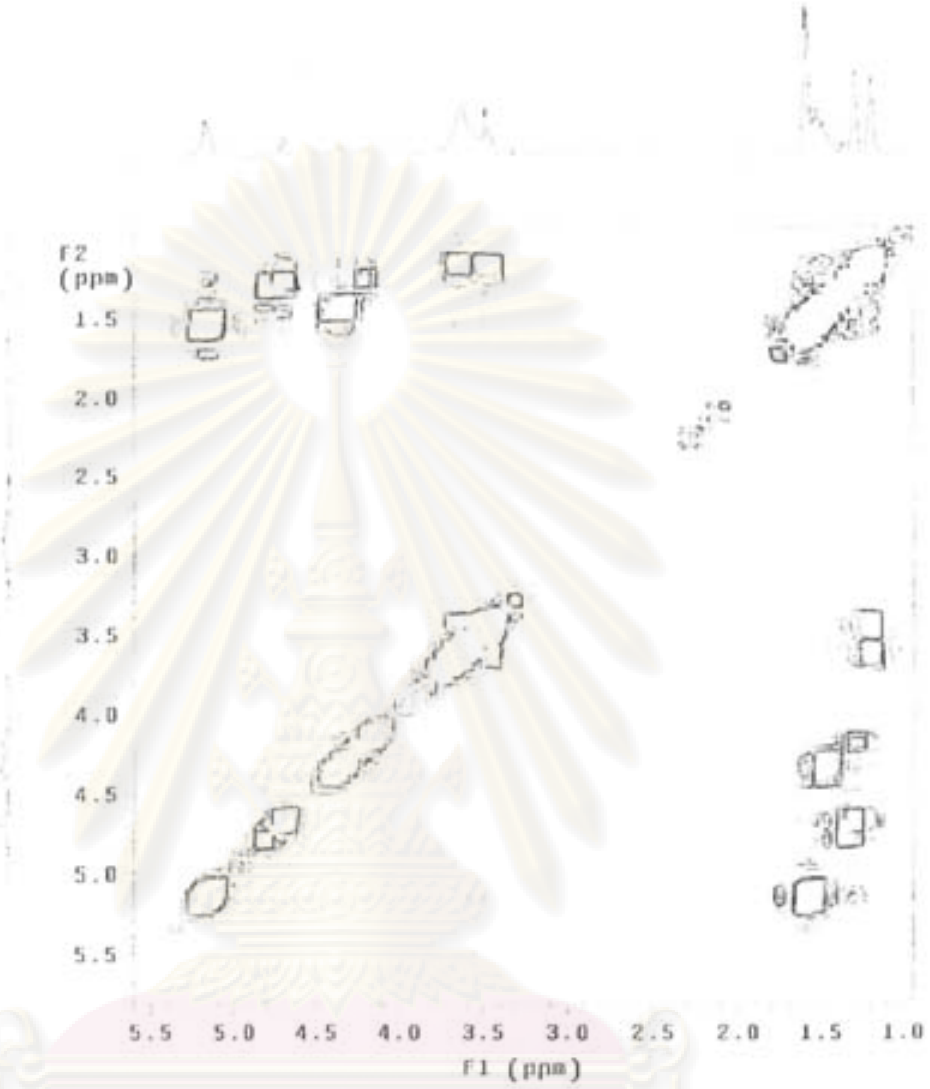

Figure A-6 ^{1}H-H COSY spectrum of methanol-soluble part copolymer (OH of PEEGE :LLA = 1:20 with $Sn(oct)_2$ 5% mol) in $CDCl_3$.

Figure A-7 ^{1}H-H COSY of methanol-soluble part copolymer (OH of PEEGE :LLA = 1:20 with $Sn(oct)_2$ 10% mol) in $CDCl_3$.

Figure A-8 ^{1}H-H COSY spectrum of methanol-soluble part copolymer (OH of PEEGE :LLA = 1:20 with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

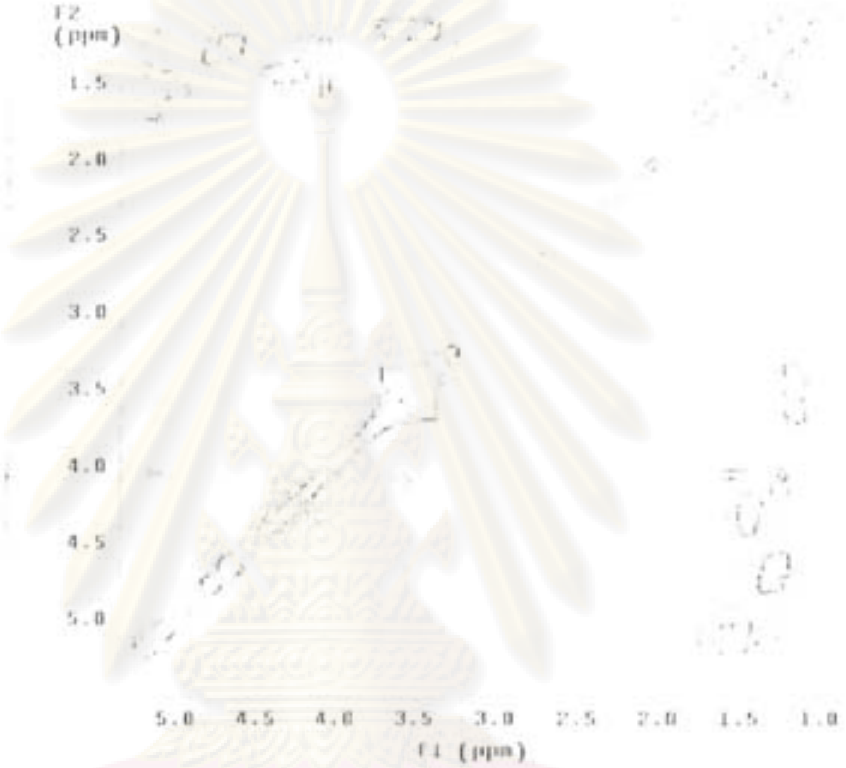

Figure A-9 ^{1}H-H COSY spectrum of methanol-soluble part copolymer (OH of PEEGE :LLA = 1:30 with $Sn(oct)_2$ 5% mol) in $CDCl_3$.

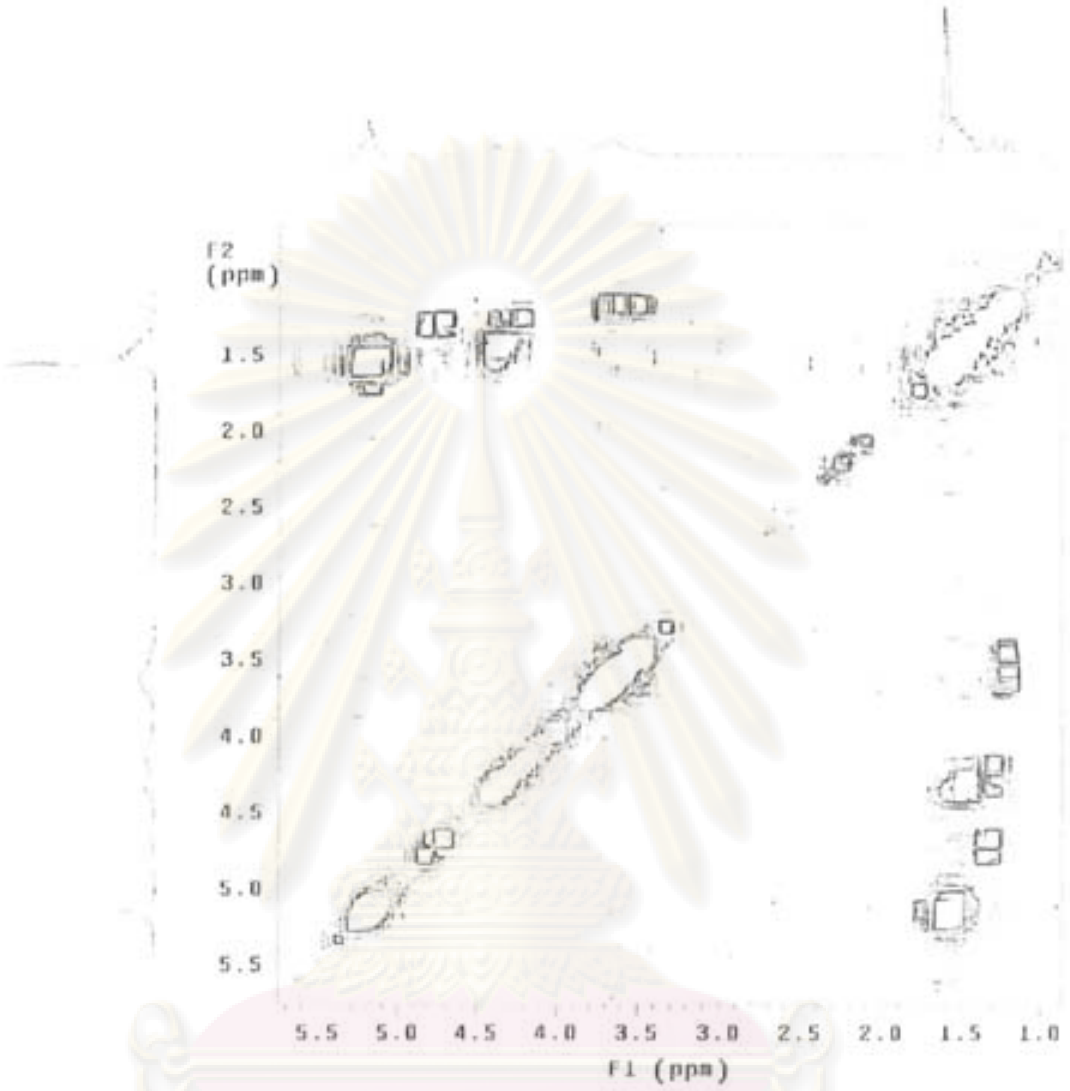

Figure A-10 ^{1}H-H COSY of Methanol-soluble part copolymer (feeding mole ratio OH of PEEGE :LLA = 1:30 with $Sn(oct)_2$ 10% mol) in $CDCl_3$.

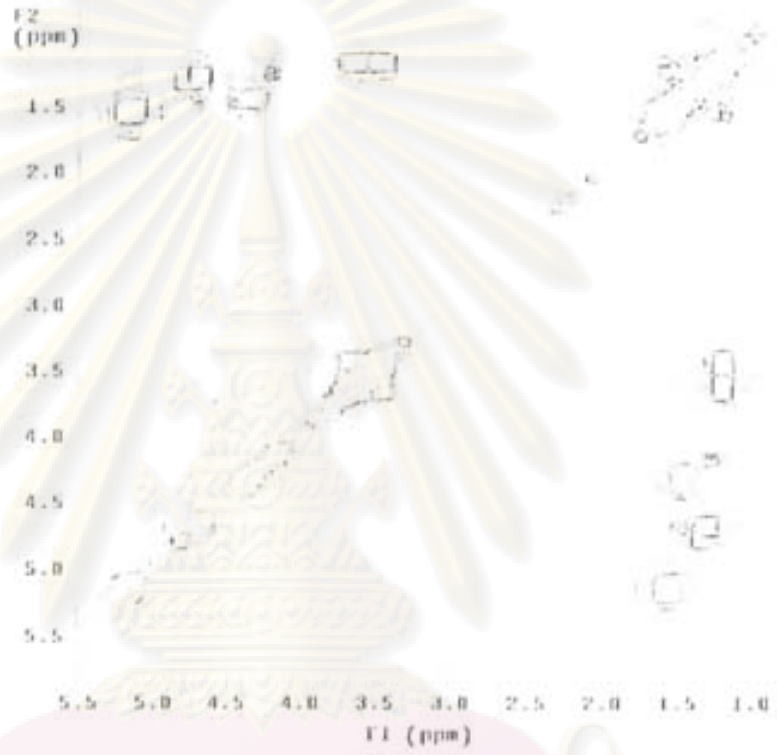

Figure A-11 ^{1}H-H COSY spectrum of methanol-soluble part copolymer (OH of PEEGE :LLA = 1:30 with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

Figure A-12 ^{1}H-H COSY spectrum of methanol-insoluble part copolymer (OH of PEEGE :LLA = 1:10 with $Sn(oct)_2$ 10% mol) in $CDCl_3$.

Figure A-13 ^{1}H-H COSY spectrum of methanol-insoluble part copolymer (OH of PEEGE :LLA = 1:20 with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

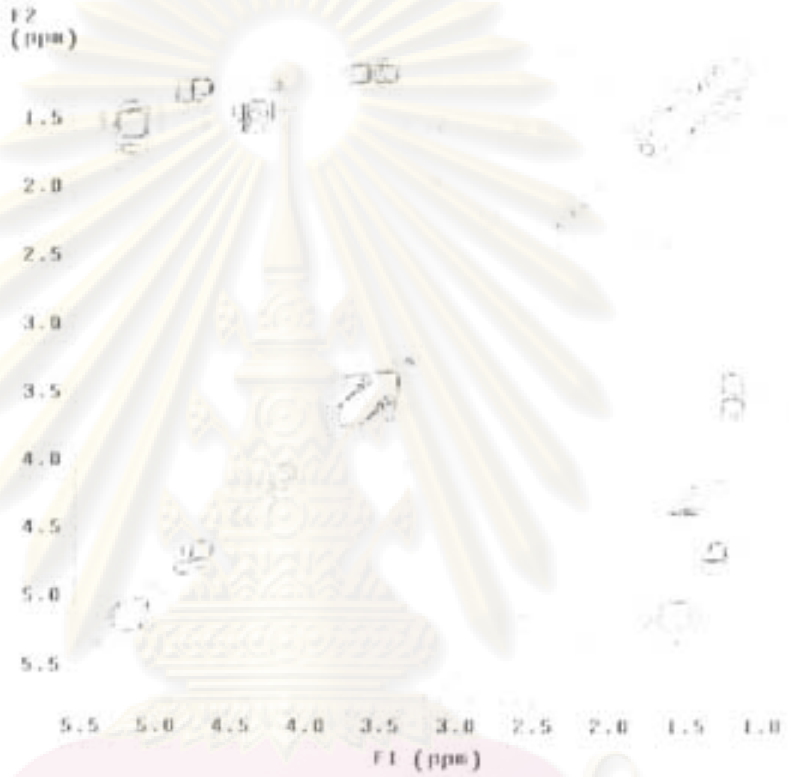

Figure A-14 ^{1}H-H COSY spectrum of methanol-insoluble part copolymer (OH of PEEGE :LLA = 1:30 with $Sn(oct)_2$ 5% mol) in $CDCl_3$.

Figure A-15 ^{1}H-H COSY spectrum of methanol-insoluble part copolymer (OH of PEEGE :LLA = 1:30 with $Sn(oct)_2$ 15% mol) in $CDCl_3$.

APPENDIX B

Table B-1 Purity Calculation of LLA, L3

% Area percent	ADEA (mJ)	Td 'C	de(cm)	DE (mW) =DE×F	TF, K =Td+DE /S	1/F= (ABCA)/ (ADEA)	(ABCA)/ (ADEA)
10	44.846	95.425	2.2	0.4925	368.5567	8.7672	8.7672
12	53.815	95.604	3.05	0.6828	368.7287	7.3060	7.3060
14	62.785	95.744	3.7	0.8284	368.8633	6.2622	6.2622
16	71.754	95.857	4.5	1.0075	368.9697	5.4795	5.4795
18	80.723	95.954	5	1.1194	369.0625	4.8707	4.8707
20	89.692	96.042	5.65	1.2649	369.1451	4.3836	4.3836
22	98.662	96.118	6.3	1.4104	369.2157	3.9851	3.9851
24	107.631	96.189	6.9	1.5448	369.2817	3.6530	3.6530
26	116.6	96.225	7.5	1.6791	369.3128	3.3720	3.3720
28	125.569	96.313	8.45	1.8918	369.3929	3.1311	3.1311
30	134.539	96.364	9.6	2.1493	369.4343	2.9224	2.9224
32	143.508	96.411	10.05	2.2500	369.4776	2.7397	2.7397
34	152.477	96.458	10.35	2.3172	369.5221	2.5786	2.5786
36	161.446	96.502	11.45	2.5634	369.5570	2.4353	2.4353
38	170.416	96.54	12.2	2.7313	369.5888	2.3071	2.3071
40	179.385	96.578	12.3	2.7537	369.6259	2.1918	2.1918
42	188.354	96.617	12.5	2.7985	369.6633	2.0874	2.0874
44	197.323	96.653	12.75	2.8545	369.6972	1.9925	1.9925
46	206.293	96.69	13.3	2.9776	369.7296	1.9059	1.9059
48	215.293	96.724	13.6	3.0448	369.7612	1.8262	1.8262
50	224.231	96.756	14	3.1343	369.7898	1.7534	1.7534

Constant

sample weight (mg) = 3.70

Δ H of sample (J/g) = 100.256

Δ H of standard (J/g) = 121.206

Conversion factor (mW/cm) = 0.2239

S, Slope of indium (mW/K) = -26.98

ABCA = Total area = 393.174

Results

T_0 (° C) = 96.85

%Purity (Method A) = 99.72

Table B-2 Integration proton of methanol-soluble part copolymer PEEGE-b-PLLA

δ, ppm	1/10/51	1/10/10	1/10/15	1/20/5	1/20/10	1/20/15	1/30/5	1/30/10	1/30/15
5.14	100	100	100	100	100	100	100	100	100
4.79	15.4	8.4	12.7	4.6	3.95	6.5	6.9	2.4	5.0
4.67	104.5	115.0	118.3	33.5	10.6	51.4	26.3	6.1	35.9
4.34	27.4	15.2	23.37	19.8	26.1	7.5	12.8	23.34	10.4
3.7-3.4	907.3	883.8	935.4	382.4	257.9	455.3	254.7	150.0	318.9
1.56	349.5	245.3	331.1	313.6	315.1	270.3	312.8	342.9	330.4
1.49	77.0	61.9	79.4	63.4	47.8	64.1	52.2	81.8	42.1
1.26	352.5	366.4	384.8	136.1	65.4	185.3	93.9	37.5	117.8
1.16	377.8	380.31	420.0	134.2	57.8	206.0	103.1	37.6	135.4

Table B-3 Integration proton of methanol-insoluble part copolymer PEEGE-b-PLLA

δ, ppm	1/10/10	1/20/15	1/30/5	1/30/15
5.14	100	100	100	100
4.79	0.82	1.62	2.28	1.42
4.67	5.34	13.68	10.47	7.50
4.34	3.42	3.65	4.70	3.16
3.7-3.4	60.51	128.47	115.10	82.28
1.56	467.44	310.44	339.17	334.70
1.49	35.34	73.14	31.16	23.87
1.26	30/73	54.86	42.21	31.35
1.16	24.80	58.96	46.57	33.70

VITAE

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