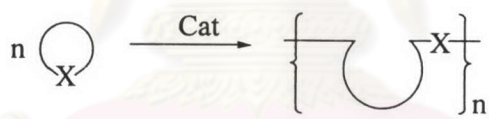
CHAPTER II

THEORY AND LITERATURE REVIEW

2.1 Ring-Opening Polymerization [18]

Ring-opening polymerization (ROP) constitutes one of the most important fields of polymer chemistry. Along with step and chain mechanisms for the formation of polymers, ring-opening reaction provides an important methodology for polymer formation (Scheme 2.1). In ROP, no small molecule by-products are formed during polymerization as in condensation polymerization. It also does not involve the exothermic driving force of conversion of multiple bonds to single bonds, as in olefin polymerization.



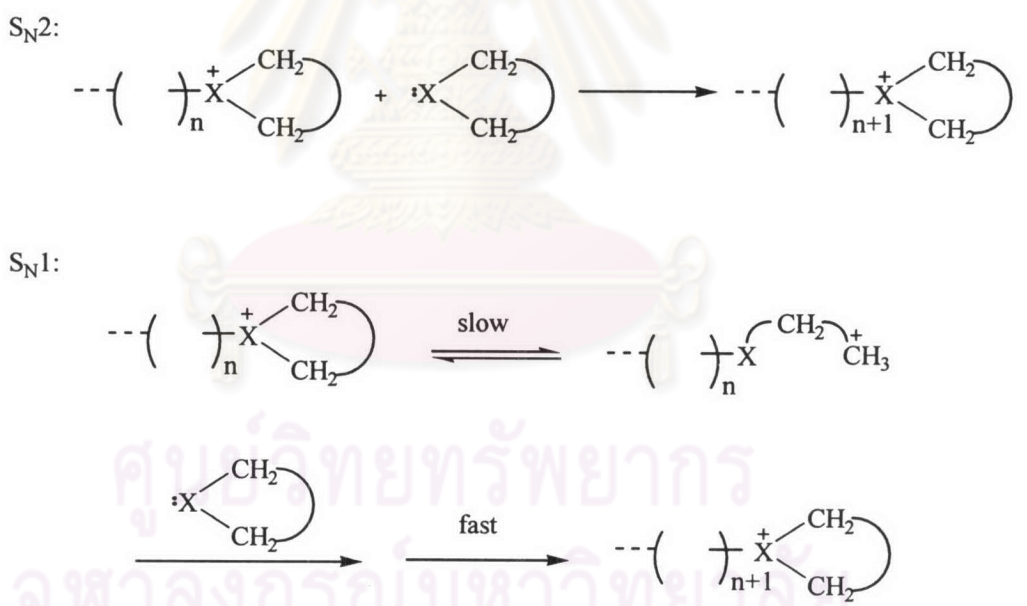
Scheme 2.1 Ring-opening polymerization (X is heteroatom such as oxygen).

The growth process in ROP has some of the characteristic of chain polymerization. Only monomer adds to the growing chains in a propagation step. Species larger than monomer do not react with each other. The classification of a ring-opening polymerization as a chain or step polymerization can be made on the basis of two criteria: (1) the experimentally observed kinetic laws and (2) the relationship between polymer molecular weight and conversion. The second criterion is the prime characteristic that distinguishes chain and step polymerizations. High polymer is formed throughout the course of a chain polymerization in contrast to the slow building of polymer molecular weight in step polymerization. Most, but not all, ROPs behave as step polymerizations in that the polymer molecular weight increases relatively slowly with conversion. This is because the rate constants for ring-opening polymerization of cyclic monomers, such as ethers, amines, siloxanes,

amides, and esters, have values much closer to those for the reactions of step polymerization (*e.g.*, esterification, amidation) than for chain polymerization (addition of radical, carbocation, or carbanion to C=C).

The ring-opening reaction was achieved either by anionic or cationic processes. In many cases, ring-opening polymerization by a "living" mechanism is possible. That is, the initiation step is sufficiently faster than the propagation step, such that each molecule of initiator becomes associated with a growing chain of polymer. In addition, propagation steps are required to be faster than termination reactions, so that chains continue to grow until all the monomer is depleted.

2.1.1 Cationic Ring-Opening Polymerization (CROP)



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).

In CROP the propagation reaction can be described as a nucleophilic reaction, in which the positively charged active species is the electrophile and the monomer is the nucleophile. Their interaction can be classified as the S_N2 type or as the S_N1 type process. These two general instances are shown in Scheme 2.2.

The S_N1 mechanism is favored if the structure of the monomer is such that the resulting carbenium ion is stabilized and if the monomer is a weak nucleophile. This is the case of, *e.g.*, some cyclic acetals and cyclic orthoesters.

In the polymerization mechanisms described above, ions are located at the end of macromolecules, thus, the process is called *active chain end polymerization* (ACE). More recently a new mechanism of propagation has been postulated, for termed *activated monomer polymerization* (AM). In this polymerization, the growing end of the molecule is (*e.g.*, for cyclic ethers) an –OH group. The positive charge is located on the monomer molecules (Scheme 2.3).

Scheme 2.3 The activated monomer mechanism (AM) in propagation step of CROP.

In CROP, proceeding by the ACE mechanism, the bond breaking in the active chain end (onium ion) has been shown to be the decisive factor, determining the rate constant of propagation for a given monomer. It is well known that carbon-onium bonds provide better leaving groups compared with the corresponding carbon-heteroatom bonds (*e.g.*, ammonium *vs.* amine, oxonium *vs.* ether). Therefore, it is not surprising that more heterocycles can be polymerized by a cationic mechanism than by an anionic mechanism.

2.1.2 Anionic Ring-Opening Polymerization (AROP)

Typically, in an anionic ring-opening polymerization each propagation step involves a nucleophilic attack of the anionic active center, located at the end of the growing macromolecule, on the heterocyclic monomer (Scheme 2.4). This attack results in an extension of the length of the polymer chain with regeneration of the active center at the terminal position.

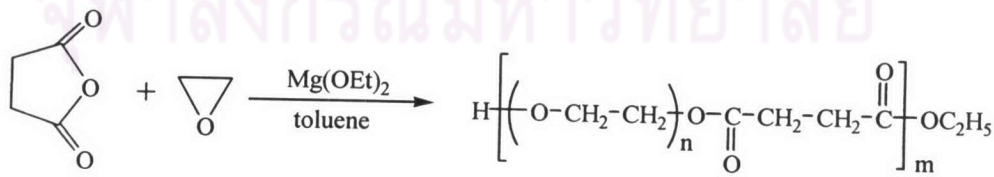
X denotes heteroatom (e.g., X=O or S) or group including heteroatoms (e.g., C(O)O); cat$^+$ means the monovalent metal (e.g., Li^+, Na^+, K^+, Cs^+) or onium (e.g., R_4N^+ , R_4P^+) cations.

Scheme 2.4 Propagation step of AROP.

For polymerizations with active centers bearing multivalent metal atoms (*e.g.*, Cd, Zn, Mg, Al, and Sn), the propagation step can be written in a way similar to Scheme 2.4. However, there are indications that such active centers are not ionized, and thus, in contrast to polymerizations with alkali metal counter ions. In this system, propagation proceeds on covalent active species, called "pseudo-anionic polymerization".

In spite of the substantial progress made within the last two decades anionic ring-opening polymerization cannot be considered a closed field. Although the number of cyclic monomers known to polymerize anionically is rather limited, the anionic ring-opening polymerization often creates unique possibilities of the controlled synthesis of macromolecules with various regularly repeated carbon and hetero atoms.

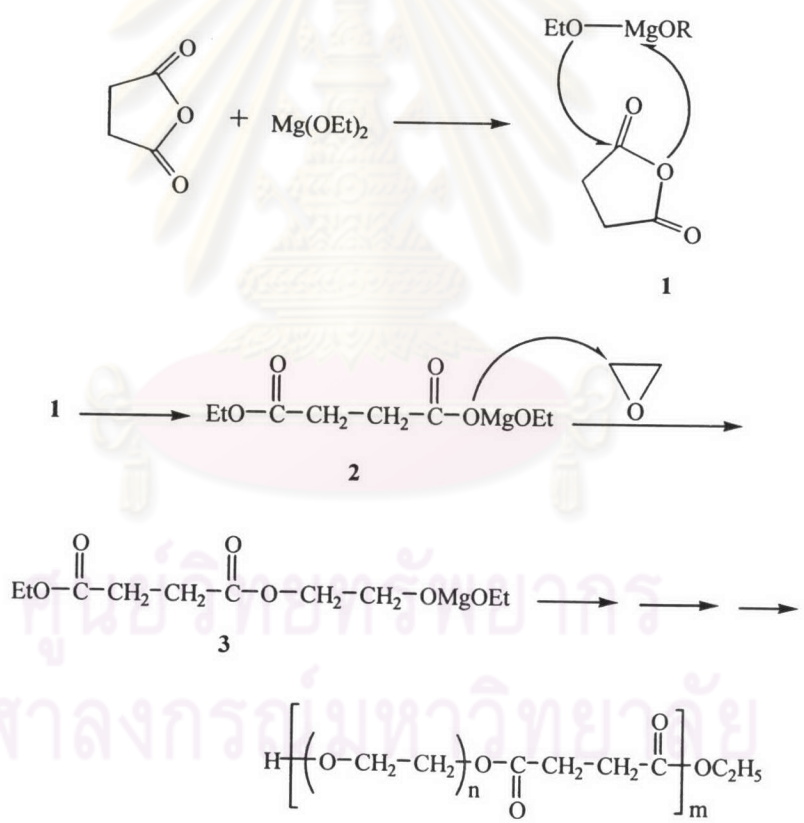
2.1.3 ROP in Copolymer Synthesis



Scheme 2.5 Copolymerization of SA and EO initiating by $Mg(OEt)_2$.

The reactivity of initiators and monomers is the important factor to determine the structure of copolymers. Some of the related works are given below.

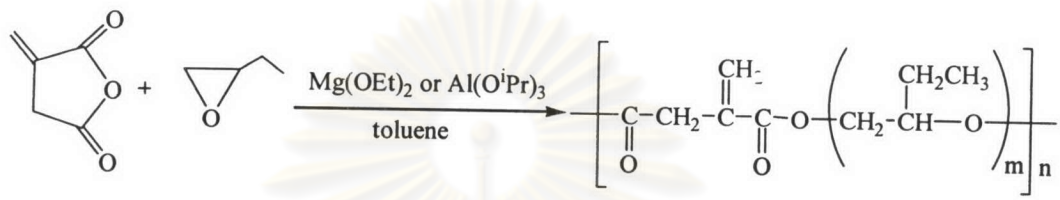
Maeda *et al.* [19] reported the ring-opening copolymerization of succinic anhydride (SA) and ethylene oxide (EO) initiated by $Mg(OEt)_2$. The structure of the copolymer (Scheme 2.5) was found to be alternating, independent of the feed monomer molar ratio. In this work, the copolymerization mechanism was described as show in Scheme 2.6. By cleavage of acyl-oxygen bond of SA (1), an active species **2** is produced, followed by the insertion of EO to O-Mg bond of **2**. Next SA is inserted into O-Mg bond. In this manner, such insertions of monomers are alternately repeated. After polymerization, the copolymerization is stopped by a trace amount of water or ethyl alcohol containing solvents used at the work-up of the polymerization.



Scheme 2.6 Coordination-insertion mechanism of copolymerization of SA and EO initiating by $Mg(OEt)_2$.

Moreover, Takasu *et al.* [20] reported copolymerization of itaconic anhydride (IAn) with 1,2-epoxybutane (EB), using $Al(O^iPr)_3$ or $Mg(OEt)_2$ as an initiator (Scheme 2.7). The copolymer was found to be either alternating or block, depending

on the catalyst used. When using $Al(O^iPr)_3$ the copolymer contains homosequences of EB, *i.e.*, copolyesterethers, while those produced by $Mg(OEt)_2$ were alternating copolymers, *i.e.*, polyesters, irrespective of various feed monomer ratios. The IR, and NMR spectra showed that no peak ascribed to homosequence of EB could be observed in copolymers produced by $Mg(OEt)_2$.



Scheme 2.7 Copolymerization of IAn and EB initiating by $Mg(OEt)_2$ or $Al(O^iPr)_3$.

2.2 Glycidol

2.2.1 Branched Polyglycidol

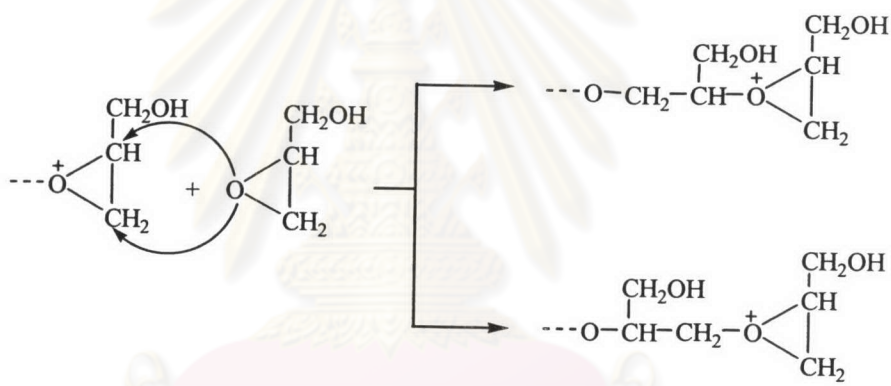
Glycidol, a commercially available and highly reactive hydroxy epoxide, represents a latent AB_2 monomer that can be polymerized to hyperbranched structure by both cationic and anionic polymerization method. The polymerization of glycidol has been the subject of several studies. The formation of branches arises from the presence of the hydroxyl group next to the oxirane group in the monomer molecule.

In the cationic process the activated monomer (AM) mechanism engages the hydroxyl groups and is responsible for branching. In the anionic processes the hydroxyl groups are in equilibrium with the alcoholate active centers of the chain growth, thus leading to the multiplication of active centers and chain branching. In both cases highly branched chains are obtained. Frey and coworkers [23] have shown that, in the anionic polymerization if the free monomer concentration is kept low (by slow monomer addition), hyperbranched structures with a degree of branching of 60 % result.

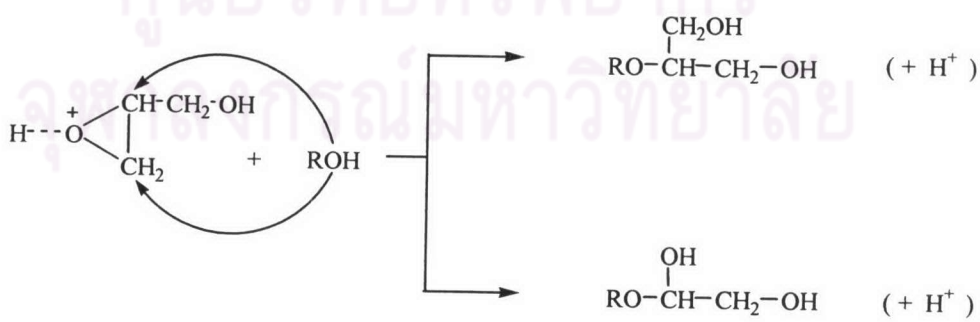
In 1994 Tokar *et al.* [21] synthesized branched-polyglycidol by CROP and suggested that, glycidol is very well suited for studying the competition between the active chain end (ACE) and activated monomer (AM) mechanism of propagation.

Polymerization of glycidol proceeding by the ACE mechanism (Scheme 2.8) would lead to the backbone composed exclusively of $-CH_2-CH(CH_2-OH)-O-$ repeating units; only primary hydroxyl ($-CH_2-OH$) groups are present as substituents of the polyether chains:

On the other hand, propagation by the AM mechanism can lead to two types of repeating units (Scheme 2.9), primary and secondary hydroxyl groups were formed.



Scheme 2.8 The active chain end mechanism (ACE) in propagation step of polymerization of branched-polyglycidol.



Scheme 2.9 The activated monomer (AM) mechanism in propagation step of polymerization of branched-PG.

Therefore two types of repeat units are present in branched PG. One is the "three-atom" (1-3 units) polymer units formed by the ACE mechanism. The other is "four-atom" (1-4 units), formed by the AM mechanism (Fig. 2.1).

1-3 atom units 1-4 atom units

Figure 2.1 Repeating units of branched-polyglycidol, 1-3 atom units and 1-4 atom units.

In a subsequent attempt to analyze the contributions of the AM and ACE mechanisms during the polymerization of glycidol, it was observed that the structure of the polymer formed depends to some extent on the nature of the catalyst. When protic acids (CF_3COOH, CF_3SO_3H) and Lewis acids ($BF_3{\cdot}OEt_2$, $SnCl_4$) (generating protic acids in the reaction with –OH groups) were used as catalysts, the content of 1-3, 1-4 and branched units was observed by ^{13}C and ^{29}Si NMR [22]. The following contribution of the AM mechanism was estimated $SnCl_4$ (80 %) > $BF_3{\cdot}OEt_2$ (50-70 %) > CF_3SO_3H (50 %).

Hyperbranched polyglycidol with controlled molecular weights and narrow molecular weight distribution have been prepared via anionic polymerization of glycidol. TMP or 1,1,1-Tris(hydroxymethyl)propane was partially deprotonated (10%) and used as an initiator for the anionic polymerization carried out under slow monomer addition, to minimize polymerization without initiator as well as cyclization [23].

A schematic structure of the hyperbranched polyglycerol macromolecules prepared by using TMP as initiator is shown in Fig. 2.2. Since all hydroxyl groups remain potentially active in the course of the polymerization, the resulting structure is hyperbranched and consists of perfect dendritic (D), linear (L), and terminal (T) units.

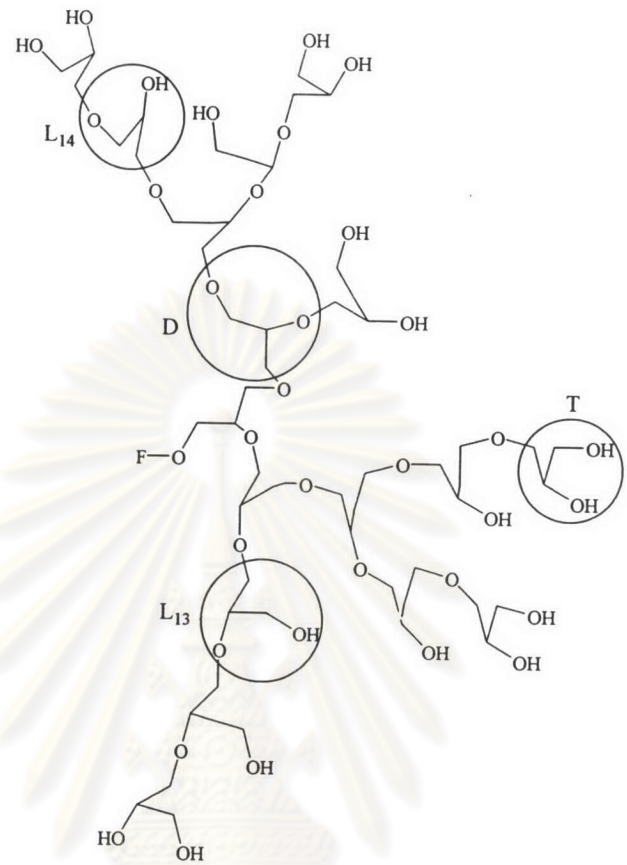
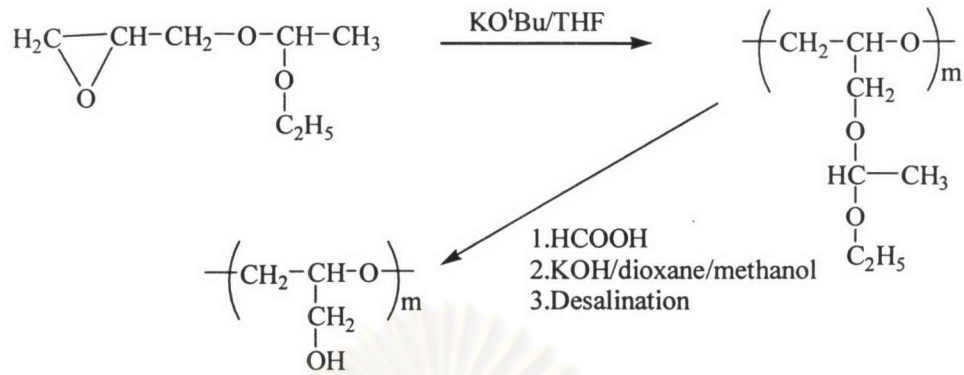


Figure 2.2 Schematic structure of a hyperbranched polyglycidol. Examples of terminal (T), dendric (D), linear 1,3 ($L_{1,3}$), and linear 1,4-units ($L_{1,4}$) are in the cycles, F indicates the core unit attached to the focal monomer unit.

2.2.2 Linear Polyglycidol

In order to obtain linear polyglycidol, the hydroxyl group of the monomer must be protected. Previously Spassky *et al.* [24] and Walach *et al.* [25] showed that, if the hydroxyl group of the monomer is converted into an acetal group, the obtained protected monomer may easily be polymerized via anionic polymerization under conditions very close to living one by using the protecting groups were easily removed under mild conditions (Scheme 2.10).

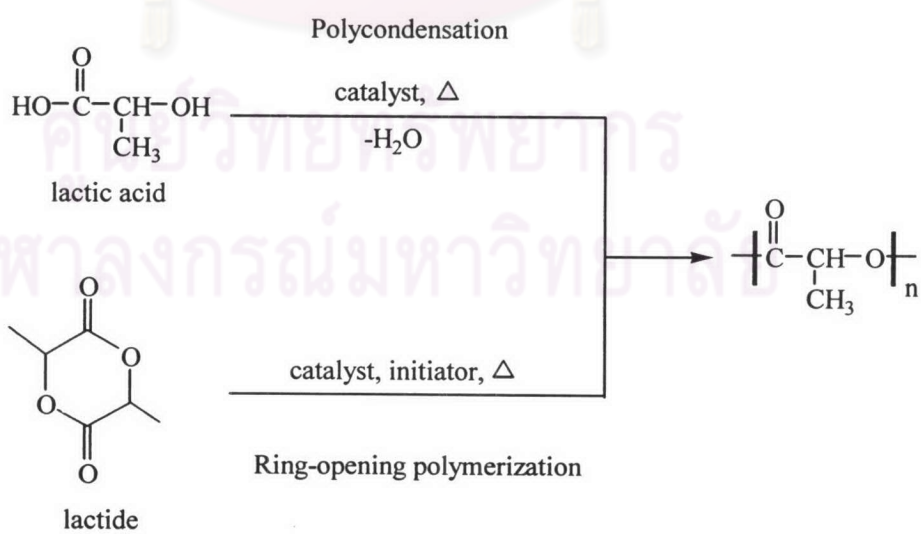


Scheme 2.10 Synthesis of linear polyglycidol.

2.3 Polylactide

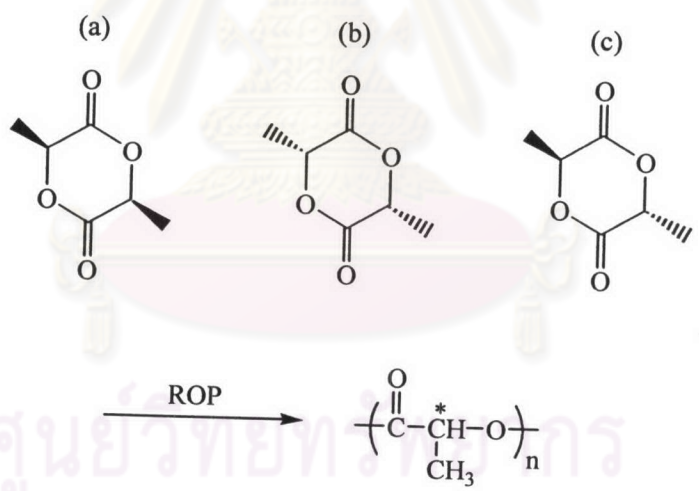
2.3.1 Properties and Applications of Polylactide

Polylactide or poly(lactic acid) (PLA) is the aliphatic polyester, containing lactide (LA) repeating units. PLA can be synthesized by two methods [26]: polymerization of lactic acid and ring-opening polymerization (ROP) of lactides, they are schematically illustrated in Scheme 2.11.



Scheme 2.11 Polycondensation of lactic acids and ring-opening polymerization of LAs.

The most efficient way of preparing polylactides is ROP [27], by coordination initiators such as aluminum alkoxide or stannous alkoxide. This method usually allows a controlled synthesis leading to a narrow molecular weight distribution (MWD). Polymerization of PLA is highly sensitive to heat, especially temperatures higher than 190 °C. Heating these materials above this temperature results in a noticeable decrease of molecular weights. Polymerization of the different stereoforms results in materials with different properties (Scheme 2.12). The polymers derived from the pure L-LA or D-LA monomer are semi-crystalline, relatively hard materials with melting temperatures around 184 °C, and the glass transition temperatures of about 55 °C. The pure enantiomeric PLLA is naturally occurring. Polymerization of the rac-(D,L)-lactide and meso-lactide results in an amorphous material with a glass transition similar to that of the semicrystalline counterparts.



Scheme 2.12 Structure of the different stereoforms of the lactide monomer and the resulting repeating unit, the chiral center marked with *, (a) L,L-lactide, (b) D,D-lactide, and (c) mesolactide.

Early reports of the biomedical use of poly(lactic acid) are dated back to the 1960s [27]. Since then PLA had gained wide spread application in the medical field, for use in sutures, drug delivery devices, prosthetics, scaffolds, vascular grafts, and bone screws, pins and plates for temporary internal fracture fixation. Good mechanical properties and the fact that it degrades into non-toxic products explain

the popularity of PLA. A good number of studies agree that PLA is completely resorbable, triggering no or very mild and transient adverse tissue responses. In addition, PLA has been approved by The American Food and Drug Administration (FDA) for medical use and is commercially available in a variety of grades. Hydrolytic degradation of PLLA eventually generates the monomer lactic acid, which is metabolized via the tricarboxylic acid cycle and subsequently eliminated as CO_2 via the respiratory system (Fig. 2.3).

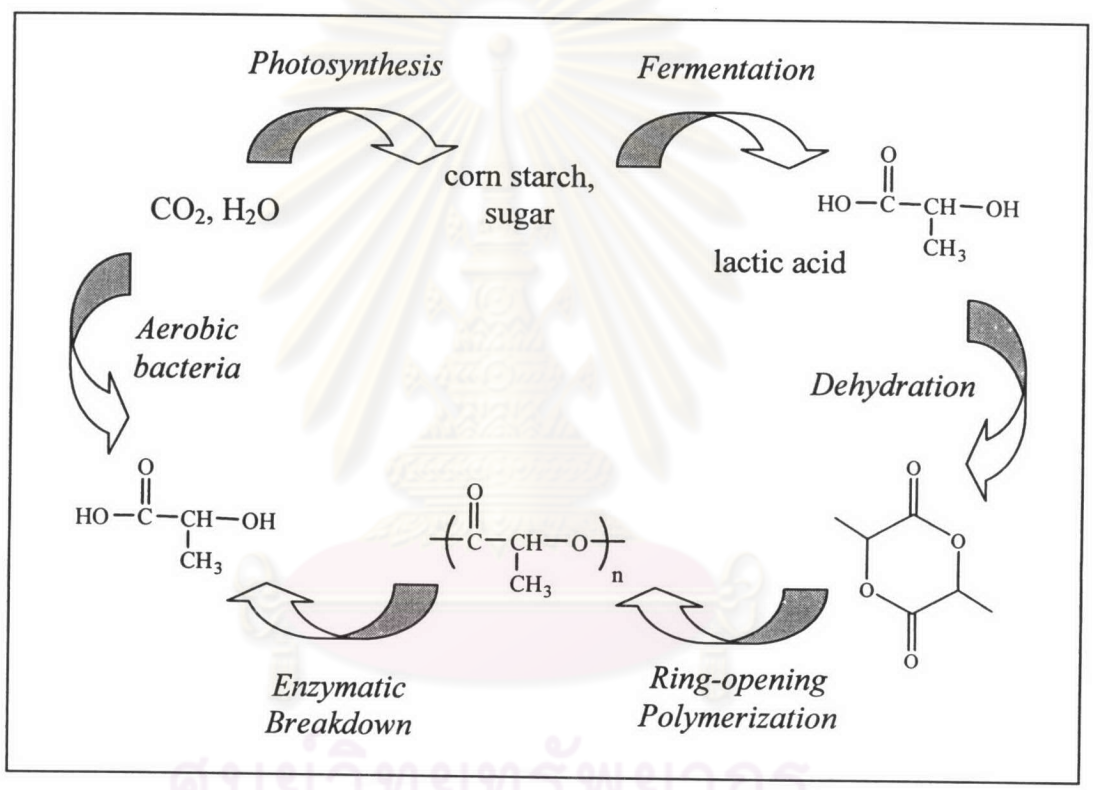


Figure 2.3 The cycle of PLA in environmental.

The commercial interested PLA is continuously growing. This is governed by the recent advances in processing and engineering of the product properties, but most of all by the recent developments in manufacturing the monomer from renewable resources. Up until the mid 1990s, PLA was produced from a petrochemical feed stock and the high product price limited its applicability. Now, the monomer can be economically obtained by bacterial fermentation of D-glucose from corn and the lowered market price of PLA opens up a range of new applications, including packaging and other disposable items.

2.3.2 Initiators for Polylactide Synthesis

A large variety of organic compounds, *e.g.*, metal alkoxides and metal carboxylates, has been studied as an initiator or a catalyst in order to achieve effective polymer synthesis [27]. Many reactions catalyzed by metal complexes are highly specific and, by careful selection of metal and ligands, reactions can be generated to form a desired polymer structure. The covalent metal alkoxides with free *p* or *d* orbitals react as coordination initiators and not as anionic or cationic initiators. Figure 2.4 show two frequently used initiators (or catalysts) for lactone monomers.

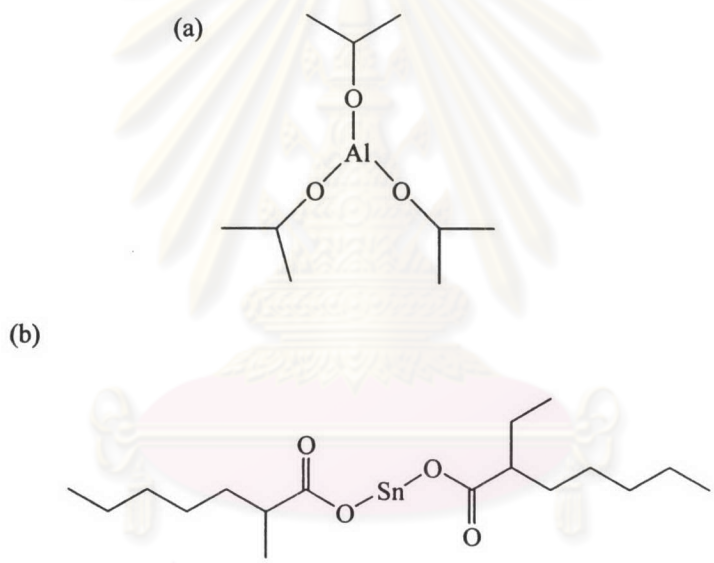
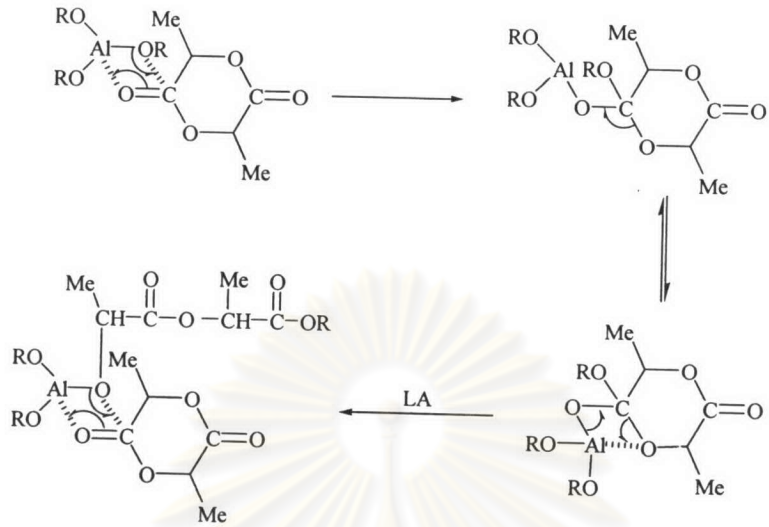


Figure 2.4 Chemical structure of initiators used in ROP of lactones, (a) aluminium isopropoxide-Al(O^iPr)$_3$, and (b) stannous octoate-Sn(Oct)$_2$.

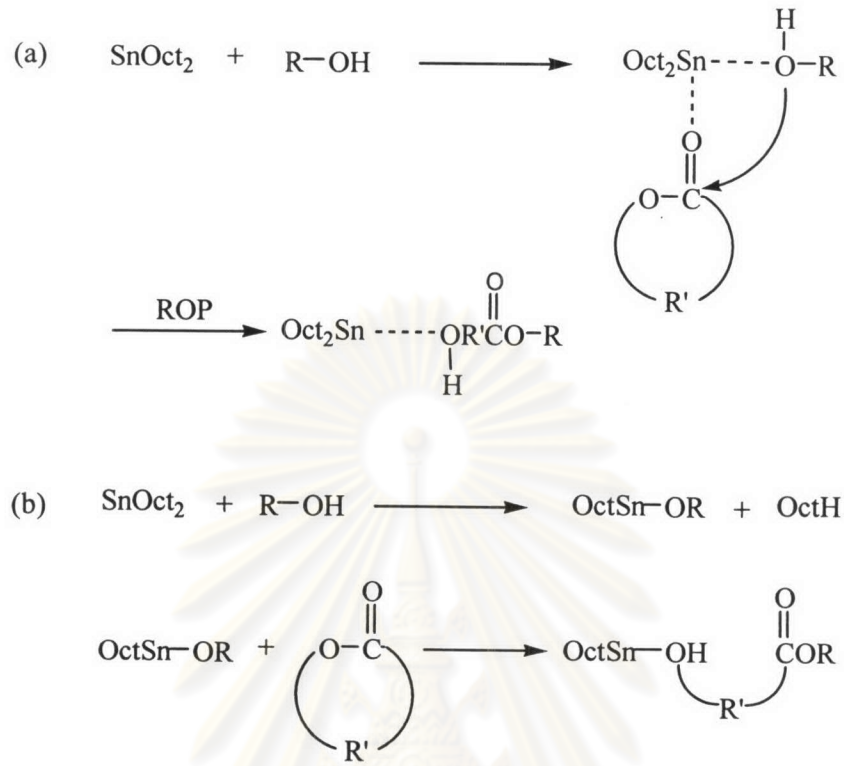
Aluminium-alkoxide-initiated polymerization of lactide proceeds according to a "coordination-insertion" mechanism, which involved acyl-oxygen bond cleavage of the monomer and insertion into the aluminium-oxygen bond of the initiator. The coordination of the exocyclic oxygen to the metal results in polarization and this makes the carbonyl carbon of the monomer more susceptible to nucleophilic attack (Scheme 2.13) [28].



Scheme 2.13 Aluminium isopropoxide initiated polymerization of lactide.

Tin(II) 2-ethylhexanoate, commonly referred to as stannous octoate [$Sn(Oct)_2$], is a frequently used catalyst in the ROP of lactones and lactides. $Sn(Oct)_2$ has been approved as a food additive by the American Food and Drug Administration (FDA). The $Sn(Oct)_2$ is not thought to be 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 hydroxy functional group is thought to coordinate in $Sn(Oct)_2$, forming the initiating tin alkoxide complex.

Investigation of the coordination-insertion mechanism have resulted in two slightly difference reaction pathways. Kricheldor and coworkers have proposed a mechanism where the co-initiating alcohol functionality and the monomer are both coordinated to the $Sn(Oct)_2$ complex during propagation (Eq. a in Scheme 2.14) [27]. Penczek and coworkers have presented a mechanism where the $Sn(Oct)_2$ complex is converted into a tin alkoxide before complexing and ring-opening of the monomer (Eq. b in Scheme 2.14) [27]. Direct observation of tin alkoxide complex has been reported by using MALDI-TOF spectroscopy for both lactide and ε–CL polymerization.



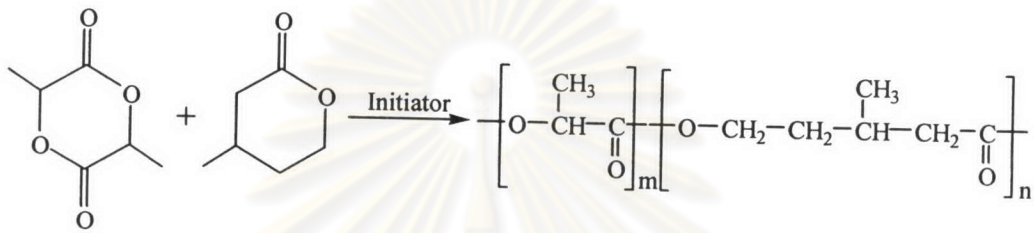
Scheme 2.14 The main ROP mechanism proposals with $Sn(Oct)_2$ as catalyst, (a) complexation of a monomer and alcohol prior to ROP, and (b) formation of a tin-alkoxide before ROP of lactone.

According to the mechanisms above, $Sn(Oct)_2$ reacts with compounds containing hydroxyl groups to form a tin alkoxide that acts as an actual initiator in the polymerization. Hence, the use of alcohols as a co-initiator increases the reaction rate of polymerization. The propagation is stopped via a chain transfer with another alcohol molecule, which causes the polymerization to yield hydroxyl-terminated polymers with molecular weight depending on the ratio of monomer to co-initiator.

2.4 Polylactide Copolymers

In order to improve properties such as impact strength, biodegradability and hydrophilicity of PLA, many approaches to overcome these problems have been reported.

A long methylene chain promotes biodegradability by imparting flexibility to the polymeric chain. Nakayama *et al.* achieved poly(D,L-β-methyl-δ-valerolactone-co-L-lactide) containing the attractive features of valerolactone's flexibility and LLA's hydrolysability (Scheme 2.15) [29]. The copolymer was easily hydrolyzed with lipase and the hydrolysis rates of the copolymers were faster than that of PLLA.



Scheme 2.15 Synthesis of poly(D,L-β-methyl-δ-valerolactone-co-L-lactide).

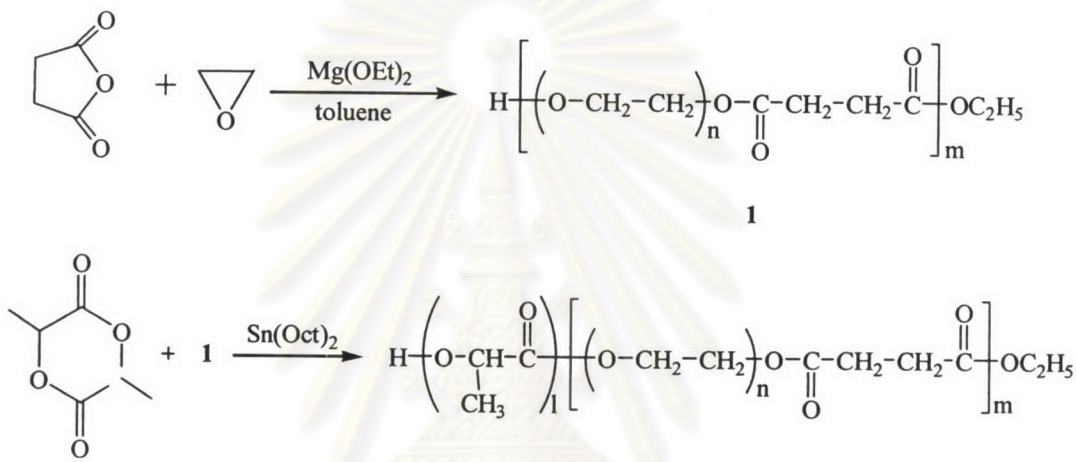
Copolymers containing hydrophobic segment of PLLA and hydrophilic segments of polyethers are widely studied. Because of the C-O-C bonds of polyether, both flexibility and hydrophilicity of PLLA copolymers increase. The ring-opening copolymerization of these polymers was successfully carried out through coordination-insertion mechanism, using various initiators. To achieve structures and properties of the copolymers supporting various biomedical applications, the copolymerization conditions were widely studied and reported by many research groups.

2.4.1 Block Copolymers of PLLA and Polyether

Block copolymers may serve as emulsifiers for the blend of 2 or more biodegradable homopolymers. Therefore, the study of such copolymers is of great interest. Diblock copolymers can be used to decrease the size of the blend component domains and interfacial tensions and improve the mechanical properties of immiscible polymer blends.

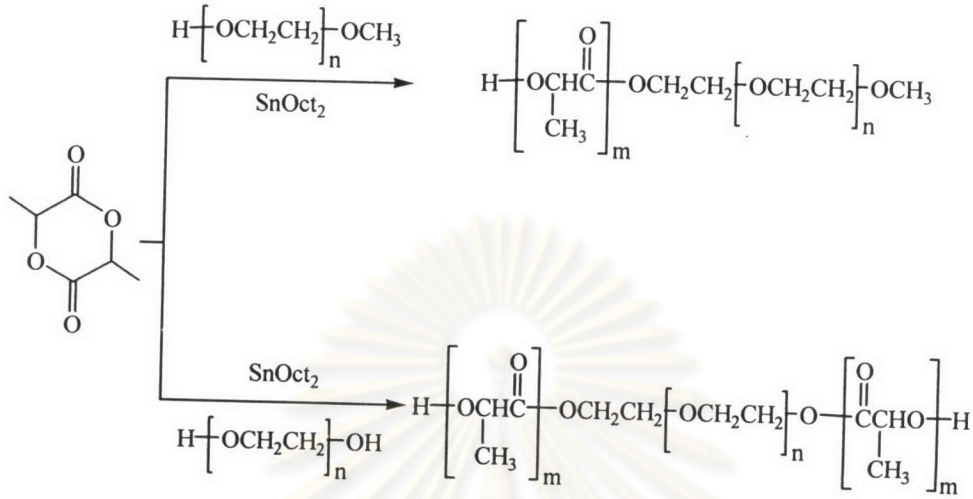
Sn(Oct)$_2$ as an Initiator

The copolymerization of LLA was carried out in the presence Sn(Oct)$_2$ and copoly(succinic anhydride-ethylene oxide), which have a hydroxyl end group [30]. The block copolymers could be hydrolyzed with or without lipase and bio-degraded by enzymes from microorganisms in activated sludge. Hydrolyzability decreased with increase in LLA content in the block copolymers (Scheme 2.16).



Scheme 2.16 Synthesis of copoly(SA-EO)-poly(L-lactide) using Sn(Oct)$_2$ as catalyst.

Recently, much attention has been paid to the block copolymers involving PLLA and poly(oxyethylene) (PEG) [31] as hydrophobic and hydrophilic block, respectively, because of their wide applications in the biomedical field. For example, versatile drug-delivery systems and temperature-dependent sol-gel systems have been developed with these PLLA-PEG copolymers having different block lengths. ROP of PLLA-PEG block copolymer using Sn(Oct)$_2$ as a catalyst was driven from hydroxy tail of PEG, in the case of diblock (PLLA-PEG) and triblock PLLA-PEG-PLLA) copolymers using poly(oxyethylene)-monomethyl ether (PEGMe) and PEG with dihydroxy end groups, respectively (Scheme 2.17).



Scheme 2.17 Synthesis of PLLA-PEG and PLLA-PEG-PLLA using $Sn(Oct)_2$ as a catalyst.

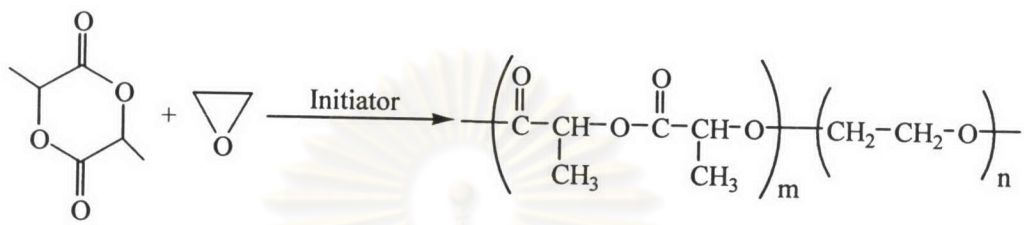
Other Initiators

An alternative route to ester-ether block copolymers is living anionic ring-opening polymerization by the sequential addition of cyclic ether and lactide monomers. Indeed, a number of catalysts have been used to prepare polyester-polyether di- and tri-block copolymers by living polymerizations.

Aluminium tetraphenylporphyrin [(TPP)AlZ] [32] is a representative initiator, which effectively brings about living polymerization of various epoxides such as ethylene oxide, propylene oxide, 1,2-epoxybutane, and epicholrohydrin, affording the corresponding polyethers with a narrow molecular weight distribution. Sequential polymerizations of living polyethers with lactones or lactides give the corresponding AB and ABC type block copolymers with controlled block length.

L-lactide/ethylene oxide (EO) multiblock copolymer were successfully synthesized (Scheme 2.18) by using various catalysts including isobutylaluminoxane (IBAO), *in situ* $AlR_3 \cdot 0.5H_2O$ systems (R = ethyl, isobutyl) and Sn-Al bimetallic-catalysts. The multiblock segment length and molecular weight of the copolymers were regulated by a variation in the reaction temperatures, reaction time, reaction

medium and the catalyst structures. An increase in the reaction temperature was used to obtain shorter segment block lengths. The idea explored was that the multiblock copolymers would be expected to leach into aqueous environments at a slower rate than PEGs.



Scheme 2.18 Synthesis of poly(LLA-co-EO) multiblock copolymer.

2.4.2 Star-Branched Copolymers of PLLA and Polyether

In the field of orthopaedic applications of PLLA require a high molecular weight, its high melt viscosity (for linear PLLA) results in degradation during melt processing for fibers, bone plates and screws. Star-branched polymers could yield high-molecular-weight PLLA but with significantly lower melt viscosities than the linear PLLA.

Star-branched copolymer of LLA were synthesized by reacting LLA with monomer containing multihydroxyl groups using $Sn(Oct)_2$ as an initiator. The alcohols used as co-initiators can be utilized to control the polymer structure. Mono- and difunctional alcohols yield linear polymers, while alcohols with hydroxyl functionality higher than 2 give star-shaped polymers, for example, glycerol [33], sorbitol [34], aminopropanediol, and aminohydroxymethylpropanediol [35] (Fig. 2.5) have been used in the preparation of 3, 6, 2, and 3-arm polymers respectively. The crystallinity of the polyesters was found to depend on the molar ratio of LLA to these monomers *i.e.*, when LLA/SB > 20/1, the polyesters are semicrystalline whereas at molar ratios of LLA to SB which are lower than those mentioned above the polymers become amorphous. The structure of poly(L-lactide-co-glycerol) is showed in Scheme 2.19.

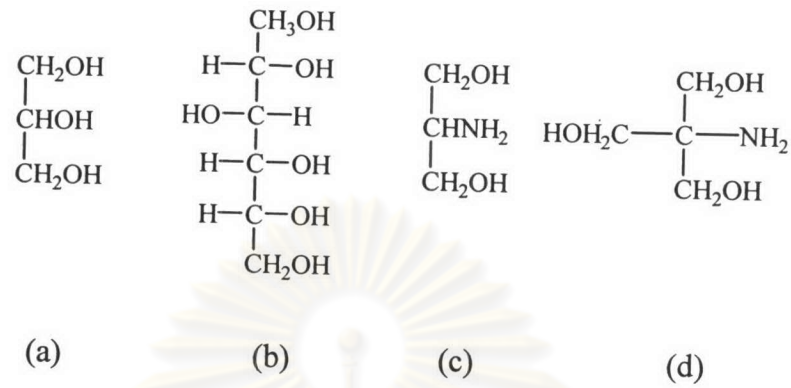
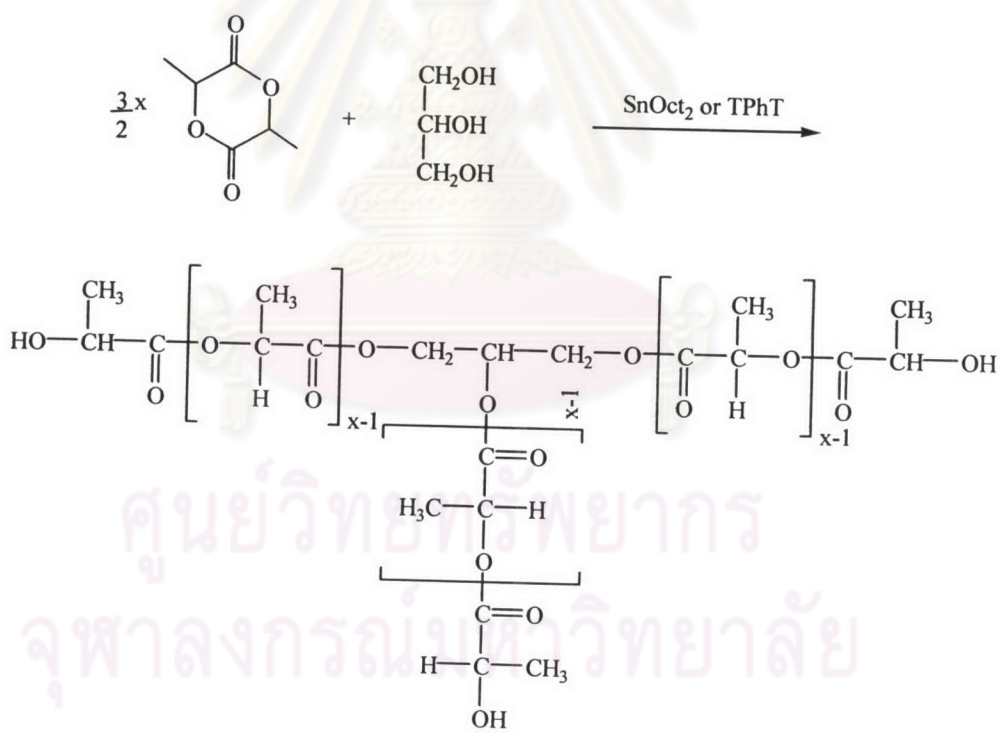


Figure 2.5 Monomers containing multihydroxy groups, (a) glycerol, (b) sorbitol, (c) aminopropanediol, and (d) aminohydroxymethylpropanediol.

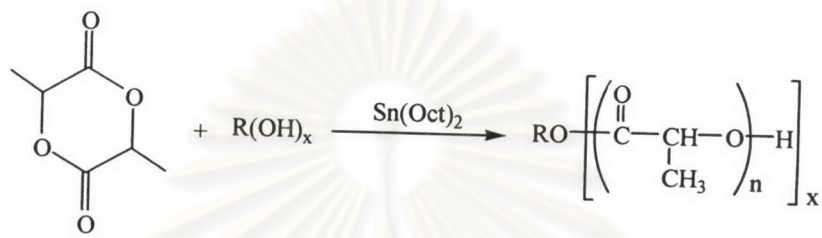


Scheme 2.19 Synthesis of poly(L-lactide-co-glycerol) using $Sn(Oct)_2$ as a catalyst.

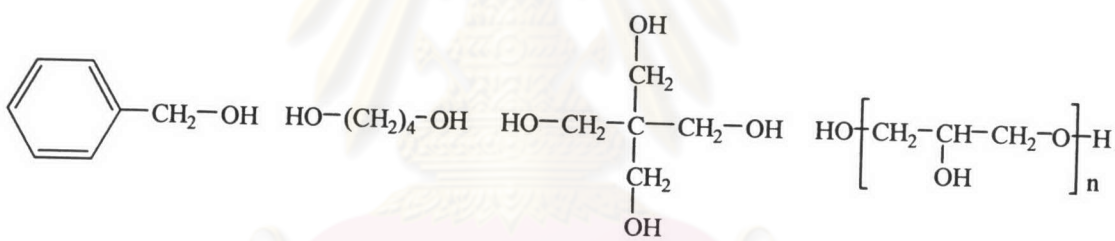
In 2001, Korhonen *et al.* [36] reported the effect of alcohols with different numbers of hydroxyl groups on the polymer structure by preparation of linear and star-shaped high-molecular-weight polylactides using alcohols with different number of hydroxyl group as co-initiators (scheme 2.20). They found that the polymerization

rate increased with the number of hydroxyl groups in the co-initiator, lead to faster polymerization and higher molecular weight. Furthermore, increasing hydroxyl group content did not cause a drop in the maximum conversions or enhanced backbiting during extended polymerization time.

Reaction scheme



Co-initiators



Benzyl alcohol *1,4-butanediol* *pentaerythritol* *n = 06 polyglycerine-06*

n = 10 polyglycerine-10

Scheme 2.20 Reaction scheme for the polymerizations of PLA by various $Sn(Oct)_2$-alcohol initiating systems.