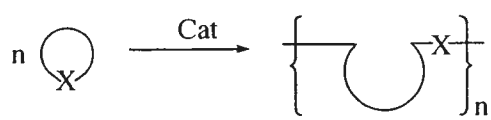
# CHAPTER II

# THEORY AND LITERATURE REVIEW

## 2.1 Ring-Opening Polymerization [21]

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). Ring-opening polymerizations are fundamentally different from condensation polymerizations in that no small molecule by-products are formed during polymerization, even though the polymerization products can contain a wide variety of functionalities.




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

Ring-opening polymerization is a chain polymerization, consisting of a sequence of initiation, propagation, and termination, nevertheless the polymerization reactions do not involve the exothermic driving force of conversion of multiple bonds to single bonds, as in olefin polymerization. Only monomer adds to the growing chains in propagation. Unlike step polymerization, monomer does not react with monomer and larger sized species do not generally react with other in ROP.

The growth process in ROP usually differs from chain polymerizations of carbon-carbon double-bond monomer in an important aspect. The propagation rate constants ring-opening polymerizations are generally similar to the rate constants in most step polymerizations, which make them several orders of magnitude lower than those in typical polymerizations. Thus, the buildup of polymer molecular weight is slower for ROP compared to chain polymerizations. In chain polymerizations, high

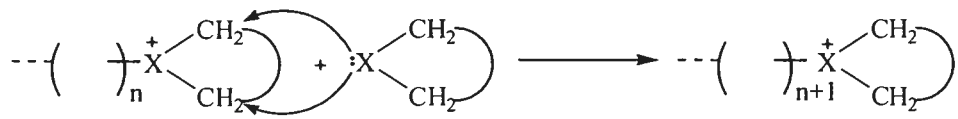
molecular weights are achieved at all conversions, including very low conversion. High polymer is formed throughout the course of a chain polymerization in contrast to the slow building of polymer molecular weight in step polymerization. Most, but not all, ROPs behave as step polymerizations in that 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.

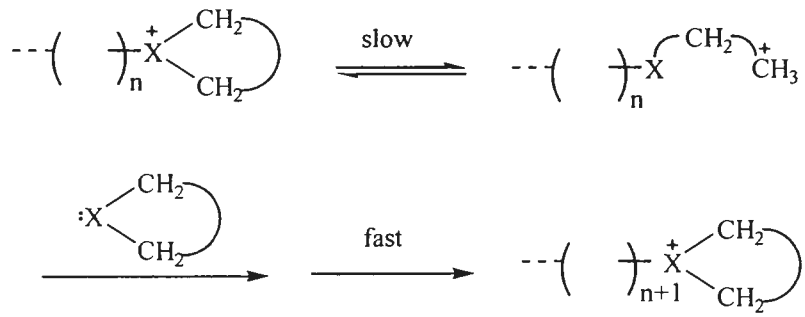
### 2.1.1 Cationic Ring-Opening Polymerization (CROP)

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. In the former the new bond is formed and the old bond is broken simultaneously. In the letter the old bond in the active species (onium ion) is broken first, in the rate-determining step, with the formation of a carbenium ion, which then reacts fast with a monomer. These two general instances are shown in Scheme 2.2.

$S_N2$:



$S_N1$:




**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).

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).

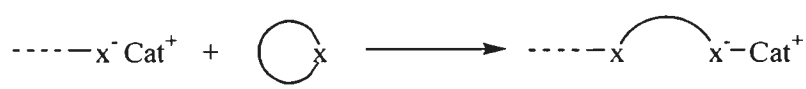
**Scheme 2.3** The activated monomer mechanism (AM) in propagation step of CROP.

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. In the CROPs with active species at the chain end, the major driving force of the reaction is the ring opening of the active species. The monomer provides only the nucleophlilic heteroatom and its contribution to the negative reaction enthalpy is due to the conversion from a neutral to a charged species, whereas the cyclic onium ion converts into a linear species and contributes to the negative enthalpy by release of ring strain.

### 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.

## 2.2 Branched Polyglycidol

Glycidol, a commercially available and having in the molecule two functions, namely the oxirane ring and hydroxyl group, represents a latent $AB_2$ monomer that can be polymerized to hyperbranched polyethers with numerous hydroxyl end groups. Glycidol was synthesized 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.

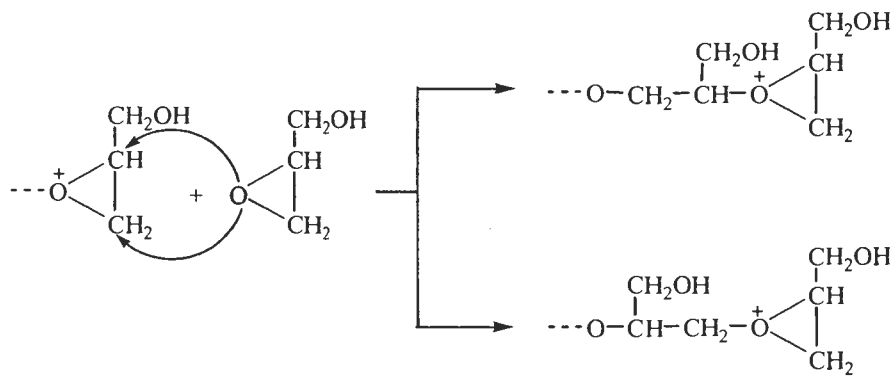
In the cationic process the activated monomer (AM) mechanism engages the hydroxyl groups and is responsible for branching. In the anionic processes the hydroxyl groups are in equilibrium with the alcoholate active centers of the chain growth, thus leading to the multiplication of active centers and chain branching. In both cases highly branched chains are obtained. Frey and coworkers [22] 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.* [23] 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.

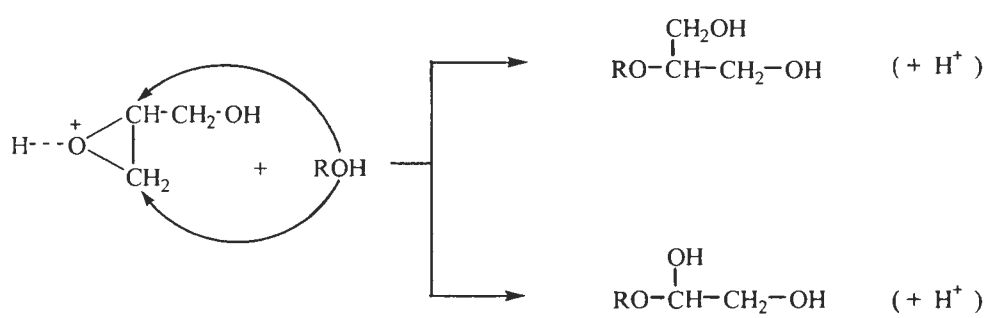
Polymerization of glycidol proceeding by the ACE mechanism (Scheme 2.5) would lead to the backbone composed exclusively of $-CH_2-CH(CH_2-OH)-O-$

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 2.6), primary and secondary hydroxyl groups were formed.



**Scheme 2.5** The active chain end mechanism (ACE) in propagation step of polymerization of branched-polyglycidol.



**Scheme 2.6** 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 [24]. 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 [22].

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.

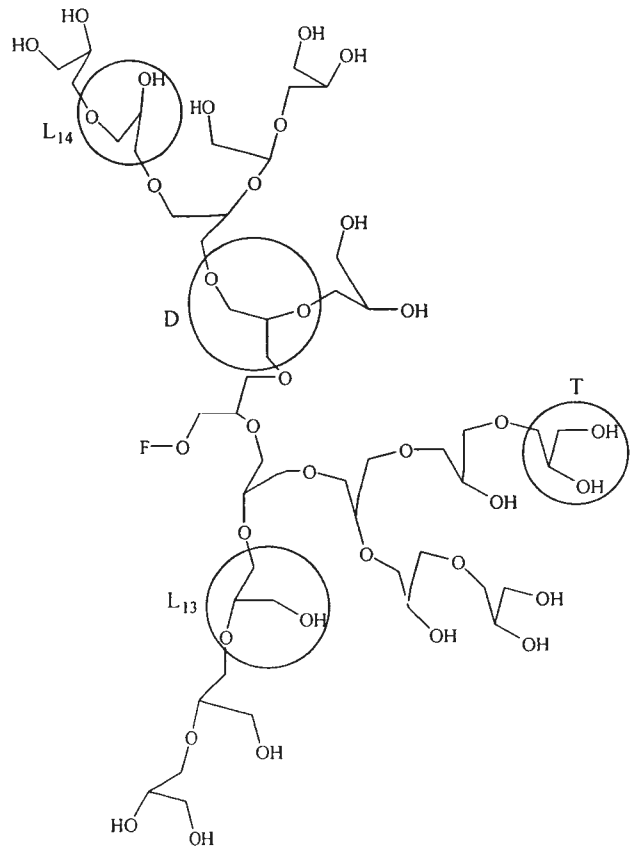
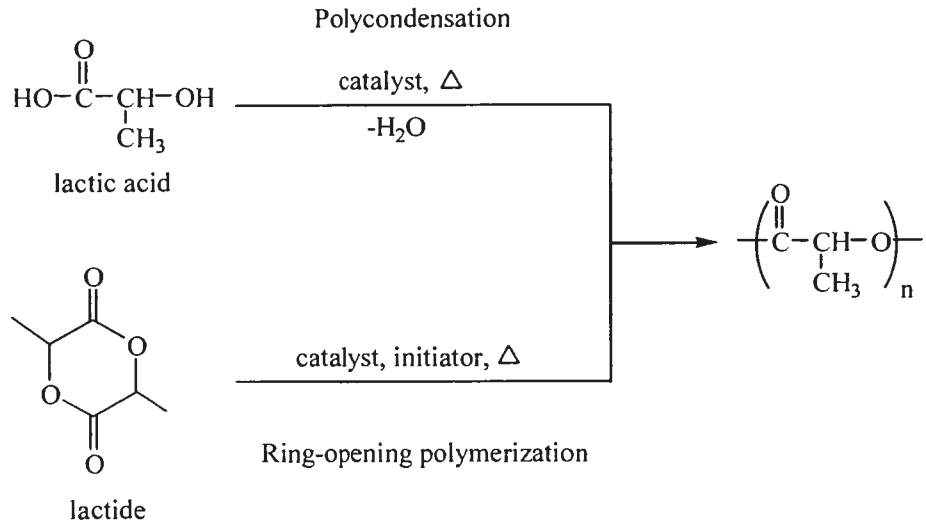



**Figure 2.2** Schematic structure of a hyperbranched polyglycidol. Examples of terminal (T), dendric (D), linear 1,3 ($L_{1,3}$), and linear 1,4-units ($L_{1,4}$) are in the cycles, F indicates the core unit attached to the focal monomer unit.

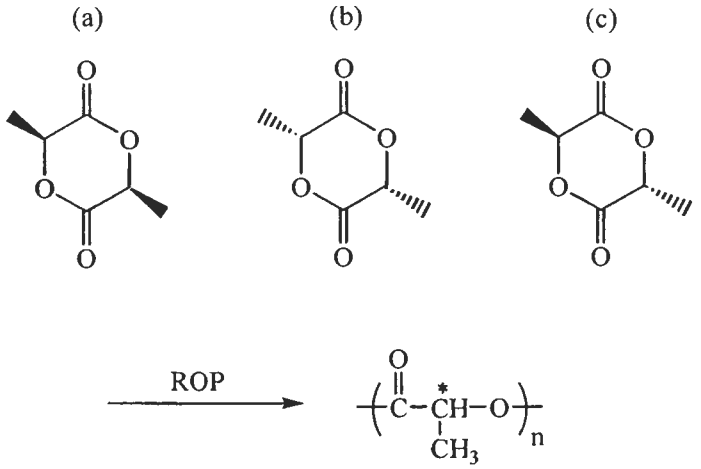
## 2.3 Polylactide

Polylactide or poly(lactic acid) (PLA) is the aliphatic polyester, containing lactide (LA) repeating units. Polylactides can be prepared by two different approaches, by the polycondensation of lactic acid, which is carried out in bulk or in solution or by the ring-opening polymerization of cyclic ester (lactide), they are schematically illustrated in Scheme 2.7 [25]. The polycondensation technique is difficult to obtain high molecular weight polymers. Polylactide of high molecular weight are exclusively produced by the ROP of the corresponding lactide monomers. The ring-opening reaction can be performed either as a bulk polymerization, or in solution.




**Scheme 2.7** Polycondensation of lactic acids and ring-opening polymerization of lactide.

The most efficient way of preparing polylactides is ROP [26], 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 2.8). 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 2.8** 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.

A catalyst or initiator is necessary to start the polymerization. Depending on the initiator, the polymerization proceeds according to three different major reaction mechanisms, cationic, anionic, or coordination-insertion mechanisms.

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 [26]. 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. The catalytic systems for coordination polymerization will be presented.

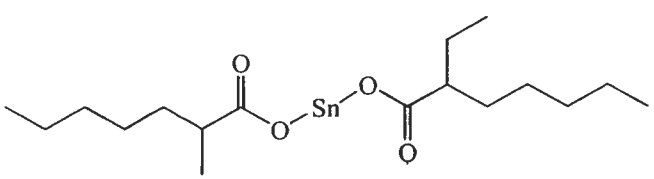
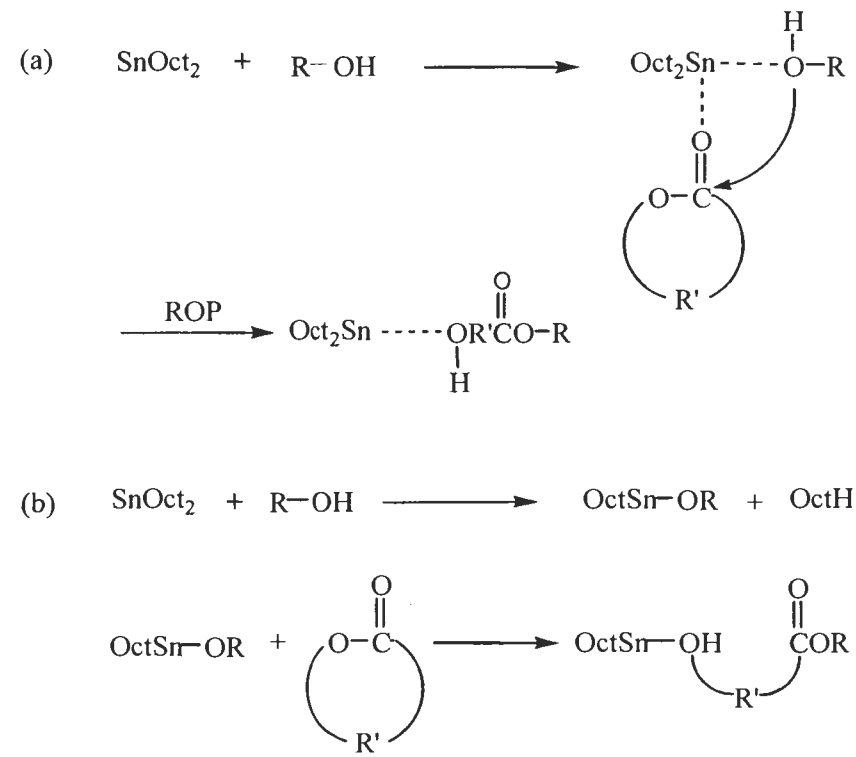



**Figure 2.3** Chemical structure of stannous octoate ($Sn(Oct)_2$).

The most widely used complex for the industrial preparation of PLA is undoubtedly Tin(II) 2-ethylhexanoate (Figure 2.4). This derivative, usually referred

to as tin(II) octoate or stannous octoate ($Sn(Oct)_2$), is commercially available, easy to handle, and soluble in common organic solvents and in melt monomers. $Sn(Oct)_2$ 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.




**Scheme 2.9** 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.

Investigation of the coordination-insertion mechanism have resulted in two slightly difference reaction pathways. Kricheldorf 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 2.9) [26]. 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 2.9) [26]. Direct observation of tin alkoxide complex has been reported by using MALDI-TOF spectroscopy for both lactide and ε–CL polymerization.

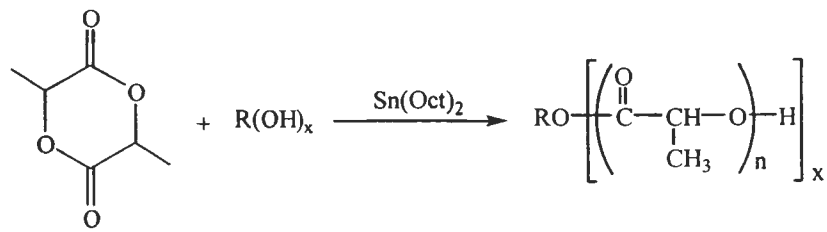
It is highly active (typical reaction times in bulk at 140-180 °C range from minutes to a few hours) and allows for the preparation of high molecular weight polymers (up to $10^5$ or even $10^6$ Da in the presence of an alcohol). Hence, the use of alcohols as a co-initiator increases the reaction rate 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 Synthesis of Polylactides Using $Sn(Oct)_2$

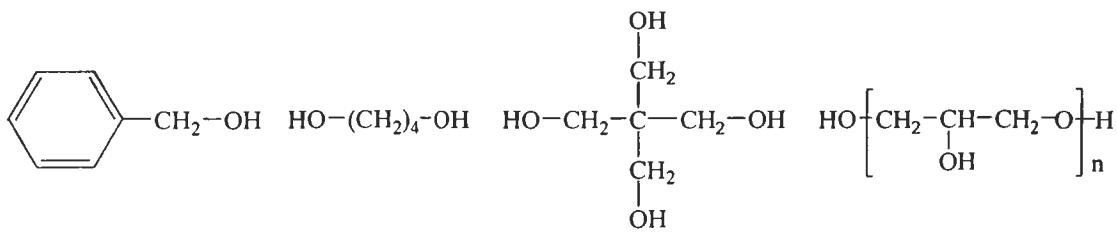
Polylactide is known for the applications in the biomedical field. Most applications require high molecular weight polymers, and the preferred route for the synthesis of such polylactides is bulk ROP of lactide in the presence of $Sn(Oct)_2$. According to the most recent results, $Sn(Oct)_2$ reacts with compounds containing hydroxyl groups to form a tin alkoxide that acts as an actual initiator in the polymerization.

In 2001, Korhonen *et al.* [18] 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 2.10). 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 2.10** Reaction scheme for the polymerizations of PLA by various $Sn(Oct)_2$-alcohol initiating systems.

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 [27], sorbitol [28], aminopropanediol, and aminohydroxymethylpropanediol [29] (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 2.11.

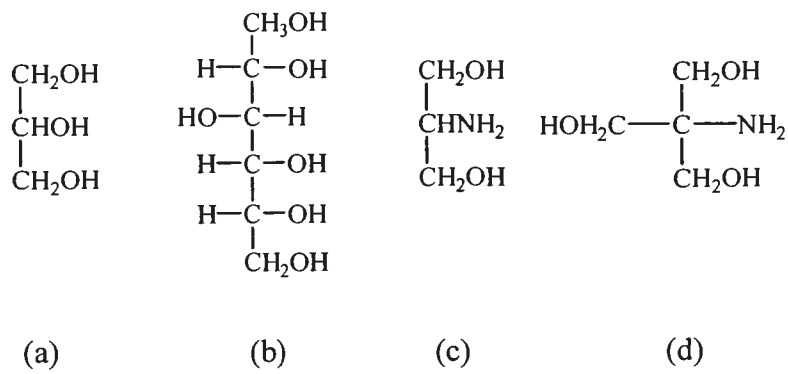
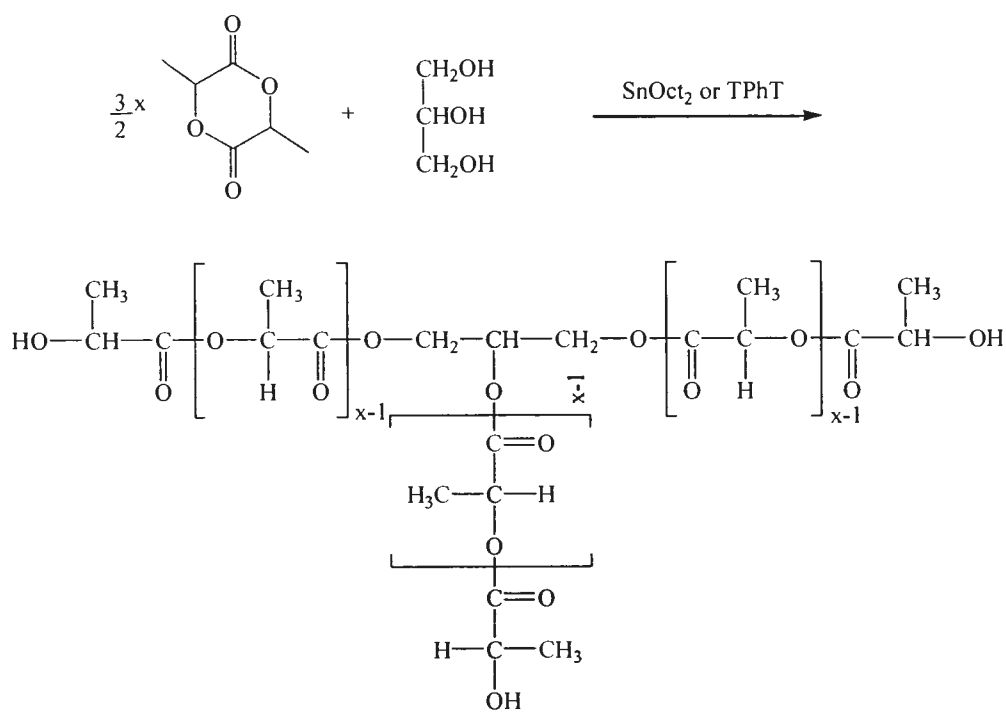


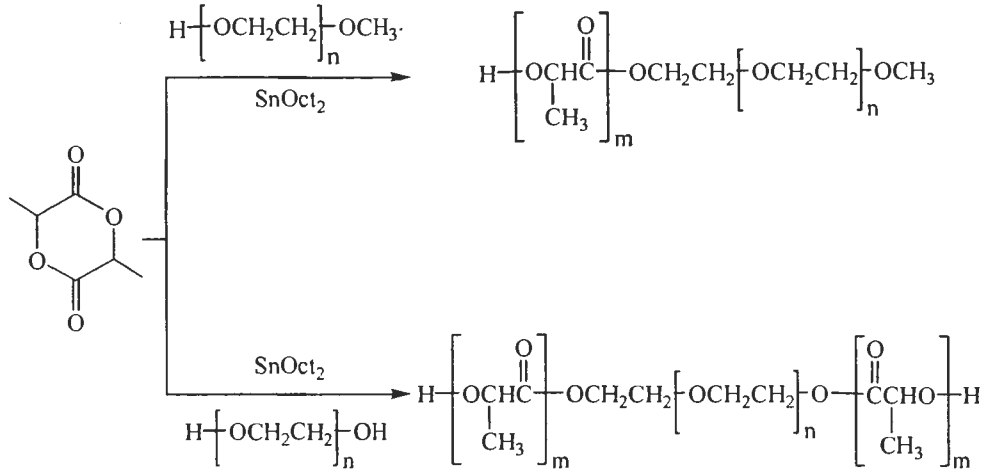

**Figure 2.4** Monomers containing multihydroxy groups, (a) glycerol, (b) sorbitol, (c) aminopropanediol, and (d) aminohydroxymethylpropanediol.




**Scheme 2.11** Synthesis of poly(L-lactide-co-glycerol) using $Sn(Oct)_2$ as a catalyst.

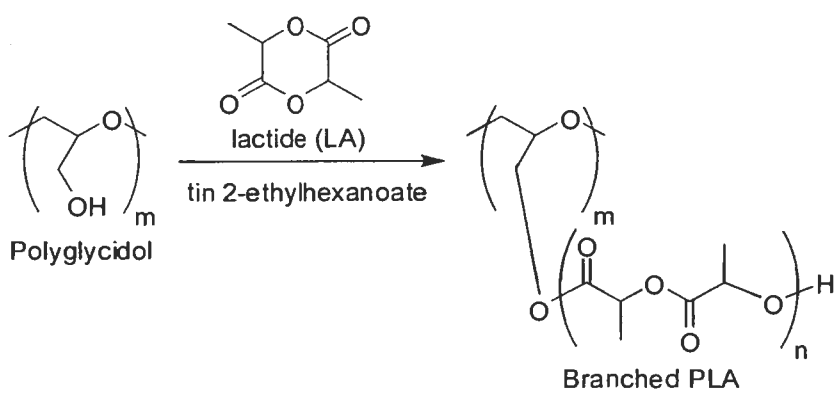
Recently, much attention has been paid to the block copolymers involving PLLA and poly(oxyethylene) (PEG) [30] as hydrophobic and hydrophilic block, respectively, because of their wide applications in the biomedical field. For example, versatile drug-delivery systems and temperature-dependent sol-gel 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 2.12).




**Scheme 2.12** Synthesis of PLLA-PEG and PLLA-PEG-PLLA using $Sn(Oct)_2$ as a catalyst.

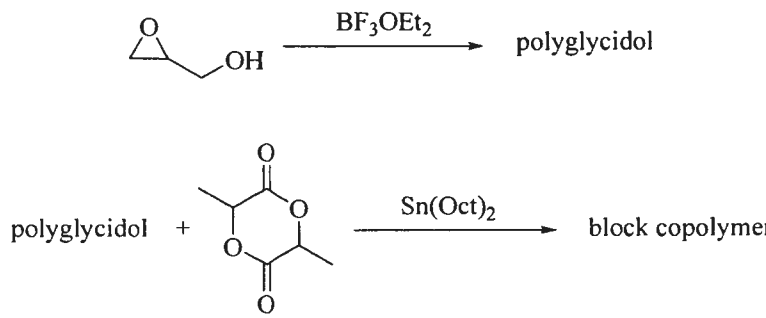
Branched PLLA was synthesized by bulk polymerization of LA in the presence of linear polyglycidol as a macroinitiator using $Sn(Oct)_2$ as shown in Scheme 2.13 [15].




**Scheme 2.13** Synthetic route of branched PLLA

In 2003, Sunsaneeyametha and Tangpasuthadol [20] prepared block copolymers of LLA and G in 2 steps (Scheme 2.14). First, branched polyglycidol (PG) was synthesized using $BF_3{\cdot}OEt_2$ as an initiator. The molecular weight of PG

obtained from MALDI-TOF MS analysis was 800-1,500 Da, with polydispersity index of 1.0-1.3. Second, the hydroxyl group of PG together with $Sn(Oct)_2$ was used to initiate the ring-opening polymerization of LLA.




**Scheme 2.14** Block copolymers of LLA and G using hydroxyl group of PG and $Sn(Oct)_2$ as initiation system.

Sunsaneeyametha reported only the synthesis of the copolymer. More experiments to be completed are to study various properties of the polymers, *e.g.* solubility, degradation profile, thermal, and mechanical properties.

## 2.5 Degradation of Polylactide and Copolymers

Polylactide is mainly degraded by a non-specific hydrolysis to monomer in an aqueous environment. Polylactide undergoes hydrolytic de-esterification into lactic acid. The rate of degradation also varies greatly with different physicals and chemical characteristics, such as molecular weight and the enantiomeric composition of the polymer, the size and shape of the device, and with environmental factors, methods of processing, and sterilization.

The effect of molecular weight and small amounts of D-lactide units on the hydrolytic degradation behavior in phosphate-buffered solution at 37 °C of PLLA were investigated by Tsuji and Saha in 2006 [10]. To exclude the effect of crystallinity on the hydrolytic degradation, the PLLA films with different number-average molecular weight ($\overline{M}_n$) and D-lactide unit contents ($X_D$) were made

amorphous. The incorporation of small amounts of D-lactide units drastically enhanced the hydrolytic degradation of PLLA. In the period of 0-32 weeks, the hydrolytic degradation rate constant ($k$) of PLLA films increased with increasing $X_D$, while the k values did not depend on $\overline{M}_n$. This means that the effects of $X_D$ on the hydrolytic degradation rate of the films are higher than those of $\overline{M}_n$. In contrast, in the period of 32-60 weeks neither $X_D$ nor $\overline{M}_n$ was a crucial parameter to determine k values, probably because in addition to these parameters the differences in the amount of catalytic oligomers accumulated in films and crystallinity affect the hydrolytic degradation behavior of the films.

In 1999, Tracy *et al.* [31] was to study the degradation of poly(lactide-co-glycolide) (PLG) microspheres. Four types of PLG 50:50 polymers were used in this experiment to investigate the effects of molecular weight and end group on degradation. The polymer end group is determined by the choice of initiator used in the polymerization reaction. Uncapped (or hydrophilic) PLG has free carboxyl groups at the polymer terminus. Capped PLG has ester linkages at the polymer terminus resulting in a more hydrophobic alkyl end. The effects of PLG chemistry and the effects of encapsulating on the degradation rate were assessed. The different types of PLG were found to degrade at different rates depending on the chemistry of the polymer end group and, to a lesser extent, the molecular weight. Of the polymer chemistry variables tested, the PLG end group had the greatest effect on degradation, with uncapped PLG degrading faster than capped. Though the molecular weight effect was considerably smaller than the end group effect, there was a trend toward faster degradation with the lower molecular weight polymer microspheres.

In 2004, Park and Kim [32] investigated the effect of poly(ethylene glycol) (PEG) segments added to the PLA microcapsules on the degradation. The degradation of PLLA/PEG was much faster than that of PLLA, due to the ester linkage between PLA and PEG being likely to degrade first. Thus the block ratio (PLLA/PEG) was generally observed to increase as the degradation proceeds, because PEG was first solubilized. The pH change in polymer suspensions was utilized as an indication of polymer degradation, since random hydrolytic ester

cleavage produced polymer fragments with carboxylic acid end groups. The buffer pH instantly decreased and further declined with increasing incubation time.

Star-block copolymers containing a hydrophilic 4- or 8-arm branched poly(ethylene oxide) (PEO) central unit and hydrophobic PLLA or poly(L-lactide-co-glycolide) (PLLGA) arms were synthesized [19]. The introduction of hydrophilic PEO block led to rapid swelling in water, resulting in faster degradation rate. The star-block copolymers possessed similar swelling properties in water. But, compared to the fast erosion of linear triblock copolymers, the star-block copolymers show a slower degradation in the first 2-3 weeks. In the case of linear triblock copolymers, the rapid degradation was mainly caused by the fast cleavage of the PEO block by hydrolysis. This leads to a change of the matrix composition of the linear triblock copolymer, decreasing the hydrophilicity of the polymeric matrix.

Hydrolysis of the novel tri-block copolymer poly(l-lactide-*b*-1,5-dioxepan-2-one-*b*-l-lactide) of different compositions was studied in buffered salt solution at 37°C and pH 7.4 by Stridsberg and Albertsson in 2000 [33]. The polymer composition did not influence the rate of degradation. The rate of degradation was influenced only by the original molecular weight. $T_g$ increased with degradation time due to an increased amount of LLA in the polymer matrix. Degradation products formed during hydrolysis were identified as lactic acid and 3-(2-hydroxyethoxy)-propanoic acid, up to 70% of the theoretical amount of 3-(2-hydroxyethyl)-propanoic acid and 10–20% of lactic acid was released after 23 weeks of degradation. The ether bond in the DXO repeat unit was not affected by hydrolytic degradation. The crystalline phase appeared to be very resistant to degradation and resulted in a multi-modal SEC chromatogram and an increase in the LLA content in the remaining polymer films.