CHAPTER 1

INTRODUCTION

1.1 Biodegradable Polymers

Biodegradation polymers are receiving increasing attention for their use in a wide variety of surgical and pharmaceutical applications as well as in disposable packages. Novel synthetic polymer materials may provide considerable improvement in medical applications due to their tailored thermal and mechanical properties and their decomposition to non-toxic products. Among various families of biodegradable polymer, aliphatic polyesters have a leading position since hydrolytic and/or enzymatic chain cleavage yields hydroxyl carboxylic acid, which in most case are ultimately metabolized. [1]

Aliphatic polyesters such as polylactide (PL), poly(ε-caprolactone) (PCL) and polyglycolide (PG) are widely used in medical applications because of these polymers can be degraded within the human body *via* a simple hydrolysis and the by-products are either metabolizable or excretable from the human body without any adverse toxicological effects. In the theory, ester group will be hydrolysable, degradable and absorbable. The methylene group and ester bond in the polymer structure will increase the main chain flexible. [2]

The application using “biomedical” polymers range from the long-term, as with a pacemaker casing, to a short-term like a suture. Because of the wide spectra of applications, the rate and extent of degradability of a polymeric biomaterial must be predetermined for each assigned function. Factors influencing the degradability are,

for example, chemical structure, copolymer composition, architecture, molecular weight, morphology, surface area and medium character. Tailoring an implant for controlled degradation and transfer of stress to the surrounding tissue as it heals at an appropriate rate is one of the greatest challenges facing researchers today.

1.2 Biodegradable Polymers for Use in Biomedical Applications

Over the last few decades, synthetic biodegradable polymers have been developed for a wide range of biodegradable sutures, stapes, fixation rods, screws and clips. In addition to biocompatibility, the other properties of these polymers that make them uniquely suitable for these and other applications: biodegradability, high strength, permeability, controlled hydrophilicity and non toxicity. Other potential medical uses include bone plates and other orthopedic applications, ear vent tubes, nerve growth tubes and wound dressing. These applications are divided into three major functional areas: surgical sutures, tissue repair and regeneration and drug delivery as described below. [3]

1.2.1 Surgical Sutures

The primary purpose of wound closure material is to bind tissue planes rapidly and assure a tight and strong closure unit heating is completed. In addition, a surgical suture must be biocompatible and, since it has not to interfere with the healing process, it has to gradually degrade as required. [4]

The synthetic biodegradable sutures are divided into braided and monofilament categories. Braided suture are typically more pliable than monofilament and exhibit better knot security when the same type of knot is used.

Monofilament suture are wirier and may require a more secure knot. [5] The first synthetic biodegradable suture (Dexon®) was prepared from PG (Figure 1.1(a)). [6] This is highly crystalline polymer provides a high-strength suture. A second biodegradable suture (Vicryl®) made from 90:10 copolymer of glycolide (G) and L-lactide (LL). [7] Both sutures have supplied as multifilament braids. To provide monofilament sutures with these properties as well as the flexibility normally associated with braided sutures, have been developed. Of these new polymers, the polyglyconate (glycolide/ trimethylene carbonate copolymer) sutures as Maxon® (Figure 1.1(b)) and the polyglecaprone 25 (glycolide/ε-caprolactone copolymer) sutures as Monocryl® have been used successfully. Copolymers 50/50 mixture of D,L-lactide (DLL) and G (Lactel®), rather than LL and G, are preferred because they are amorphous when DLL is a major component, as opposed to semicrystalline when LL is a major component. This property decreases the degradation time of the polymer. [8-9]

One of the first biodegradable polymers to be used for surgical clips and staples was a copolymer of LL and G marketed by the U.S. Surgical Corporation as Lactomer®. Similar products prepared from poly(*p*-dioxanone) have been marketed by Ethicon as Absolok®. In Biomedical Polymers Technology Unit, Department of Chemistry, Faculty of Science, Chiang Mai University the possibility of using novel polyesters based on LL, ε-caprolactone (CL) and G for use as absorbable suture is being studied (Figure 1.2). [10]

(a) (b)

Figure 1.1 Biodegradable monofilament sutures: commercial product (a) Dexon® and (b) Maxon®. [5, 6]

Figure 1.2 Synthetic biodegradable monofilament suture, poly(lactide-*co*-*ε*-caprolactone-*co*-glycolide), poly(LL-*co*-CL-*co*-G) prototype, from Biomedical Polymers Technology Unit. [10]

1.2.2 Tissue Repair and Regeneration

The materials and devices described aid in tissue repair by maintaining the alignment of tissue, by serving as scaffolding for tissue regeneration, or by serving as a barrier to the growth of undesired tissue. LL/G/CL copolymers have been utilized

to provide one or more of these functions in orthopedic, dental, cardiovascular, neurological and dermatological applications. [3]

Many new applications are being developed for the use of biodegradable polymers in nerve tissue regeneration. Nerves are one of the first tissues for which the method of guided tissue regeneration has been tried. Direct reconnection by suturing of the proximal and distal nerve stumps is the first choice in the repair of a nerve gap as shown in Figure 1.3 (a). However, tension at the suture site is a very unfavorable factor. Transplantation of autologous nerve grafts is now a standard method when the nerve gap is large as shown in Figure 1.3 (b). The donor nerve is usually obtained from nerves which are functionally less important such as the sural nerve and superficial cutaneous nerves. The results of nerve grafts are not entirely satisfactory either because of the limited availability of donor nerves, morbidity at the donor site, mismatch between nerve and grafts and additional operation time. [11-12] Both techniques are time-consuming, give rise to complication and do not lead to optimal nerve function recovery. Artificial nerve guides, where a tube bridges the nerve gap, offer a promising alternative to peripheral nerve repair as shown in Figure 1.3 (c).

The idea behind the use of a biodegradable nerve conduit is that the nerve guide directs the outgrowing nerve fibers towards the distal nerve stump, while preventing neuroma formation and in growth of fibrous tissue into the nerve gap. After the nerve function has been restored, the nerve guide is gradually degraded without inducing scar tissue formation. The absorbable nerve guide should be flexible, but relatively strong and easy to handle in microsurgery. It should have an internal diameter large enough to overcome problems when telescoping the nerve

stumps into the lumen of the nerve during the implantation procedure. It should also have a thin wall that swells minimally during degradation and causes no nerve compression. However, this nerve guide tube needs to porous to prevent swelling due to excessive fluid accumulation and it is totally absorbed as the nerve are regenerates.

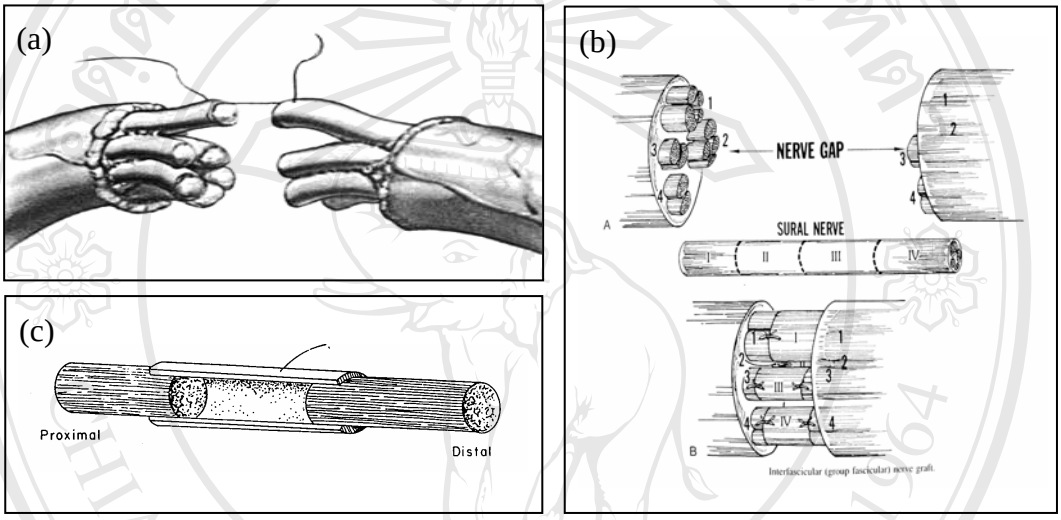
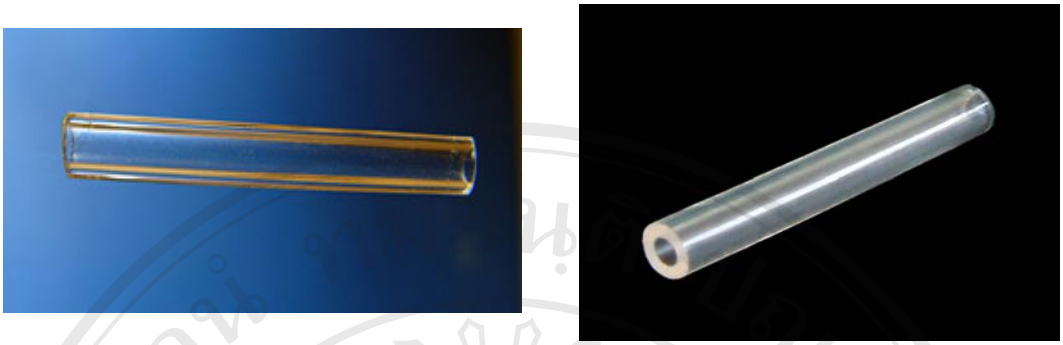


Figure 1.3 Nerve repair methods (a) nerve suture (b) nerve graft and (c) nerve guide.

Various types of biodegradable nerve conduits have been developed. GEM Neurotube® (Synovis Micro Companies Alliance, Bermingham, AL, USA) and Neurolac® (Polyganics BV, The Netherlands) (Figures 1.4(a)) [13] have been approved by the American Food and Drug Administration (FDA) as commercial bioabsorbable nerve conduits made from PG acid and poly(DL-*co*-CL) respectively. [14] In Biomedical Polymers Technology Unit, Department of Chemistry, Faculty of Science, Chiang Mai University the possibility of using novel polyesters based on LL, CL and G for use as absorbable nerve guide is being studied as shown in Figure 1.4(b). [15]



(a) (b)

Figure 1.4 Synthetic biodegradable nerve guide tubes of (a) poly(DL-*co*-CL) from Neurolac® [13] (b) poly(LL-*co*-CL-*co*-G) from Biomedical Polymers Technology Unit. [15]

1.2.3 Drug Delivery Systems

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled-release systems can respond to changes in the biological environment and delivery or cease to delivery drugs based on these changes. In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered. [16]

Originally, PL and PG were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways.

The continuous release of drugs from the polymer matrix could occur either by diffusion of the drug from the polymer matrix, or by the erosion of the polymer (due to degradation) or by a combination of the two mechanisms. In an initial phase, release occurs predominantly by pore diffusion through an interconnecting network formed by the dissolving drug substance itself. The second release phase is governed by polymer degradation. For parenteral delivery systems it is necessary to carefully adjust drug release and polymer degradation rates. In general all hydrolytically degradable polymers rate depends on chemical composition, hydrophilicity and crystallinity. [17]

The molecular architecture of biodegradable polymers can be exploited in another way to adjust polymer degradation and erosion. By incorporation of multifunctional polyols into the polyester chain, branched structures are obtained in suitable solvents ranging from star-branched. In the respective delivery systems this architecture does not compromise the thermo-mechanical properties and accelerates the to star-branched polymer degradation rate by providing preformed break-point in the polymer chain with short chain length, after swelling of the device. The star geometry should, therefore, promote erosion-controlled drug release. [18]

1.3 Ring-Opening Polymerization of Cyclic Esters

Aliphatic polyesters of high molecular weight are exclusively produced by the ring-opening polymerization (ROP) of the corresponding cyclic monomers. Polyesters are formed when cyclic esters are reacted with a catalyst or initiators. Figure 1.5 presents the reaction pathway for the ROP of a cyclic ester. [19]

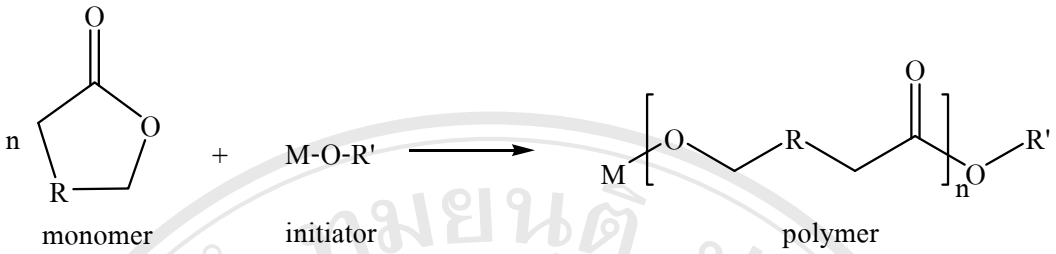


Figure 1.5 Equation representing the ROP of a cyclic ester. (R = $(CH_2)_{0-3}$ and/or CHR", M = metal).

The ROP can be performed either as a bulk polymerization or in solution, emulsion, or dispersion. [20-21] A catalyst or initiator is necessary to start the polymerization. Under mild conditions, high molecular weight aliphatic polyesters of low polydispersity can be prepared in short periods of time. Problems associated with condensation polymerization, such as the need for exact stoichiometry, high reaction temperature, and the removal of low molecular weight by-products (e.g., water) are excluded in ROP. Depend on the initiator, the polymerization proceeds according to one of three different major reaction mechanisms, *viz*., cationic, anionic, or coordination-insertion mechanisms. [22-23] In addition, radical, zwitterionic and active hydrogen [19] initiation is also possible, although such techniques are not used to any great extent.

1.3.1 Homopolymers

Several factors are known to affect the ROP of cyclic esters. The main factors are the reaction conditions, i.e., the nature of the initiator, type of solvent and reaction temperature, and also the ring size of the monomer used and the substituent on the

monomer ring. Cyclic esters of four-, seven-, and eight-membered rings polymerize, whereas the five-membered ring esters do not. In the case of six-membered rings, the polymerizability depends on the substituent. [1]

1.3.1.1 Polylactide, PL

Due to the presence of two chiral centers, there are three forms of the lactide monomer as shown in Figure 1.6. Repeating units with different configurations have been used to produce stereocopolymers where the physical and mechanical properties and the rate of degradation are easily adjusted. [1]

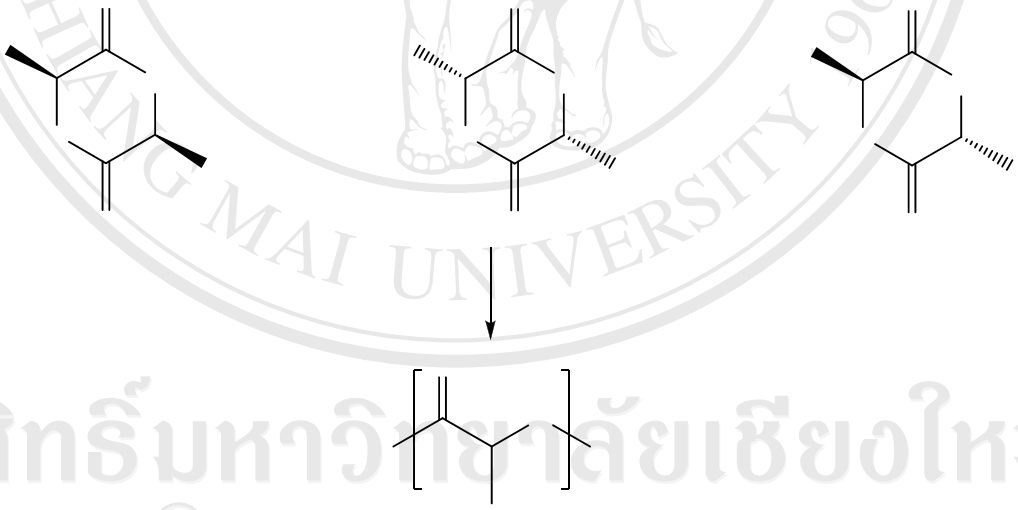


Figure 1.6 Structures of the different stereoforms of the lactide monomer and the resulting polymer repeating unit, with the chiral center marked with *. (a) L-lactide (LL), (b) D-lactide (DL) and (c) *meso*-lactide.

The most efficient way of preparing PL is *via* ROP using coordination-insertion initiators. [24] This method usually allows a controlled synthesis leading to a quite narrow molecular weight distribution. Polymerization of the different stereoforms results in materials with different properties. The polymers derived from the pure LL or DL monomers are semi-crystalline, relatively hard materials with melting temperatures around 175-178°C [25] and glass transition temperatures (T_g) of about 55°C. [26] Polymerization of the *rac*-(D,L)-lactide and *meso*-lactide results in an amorphous material with a T_g similar to that of the semi-crystalline counterparts. PLs are highly sensitive to heat, especially temperatures higher than 190ºC. Heating these materials above this temperature results in a noticeable decrease in the weight-average molecular weight ($\overline{M}_w$).

1.3.1.2 Poly(*ε*-caprolactone), PCL

PCL has been investigated thoroughly because of the possibility of blending this aliphatic polyester with a number of commercial polymers such as poly(vinyl chloride) and bisphenol a polycarbonate. [27] It is of interest as a packaging material and in biomedical applications since it is biodegradable and its degradation products are non-toxic.

PCL crystallizes readily due to the regular structure and has a melting temperature of 61°C. It is tough and flexible. The T_g of PCL is low (-60°C). Thus, PCL is in the rubbery state and exhibits high permeability to low molecular species at body temperature. PCL degradation proceeds through hydrolysis of backbone ester bonds. The hydrolysis of PLL was faster than that of PCL. [1] These properties,

combined with documented biocompatibility, make PCL a promising candidate for controlled releases applications. Different approaches have been used to copolymerize CL to increase the degradation rate. Copolymers of CL and LL of all compositions degraded much more rapidly than their component homopolymers. [28] This observation has been attributed to morphological differences, specifically a reduction in crystallinity and a lowering of the glass transition temperature.

1.3.2 Coordination-Insertion Ring-Opening Polymerization

Coordination-insertion ROP has been extensively used for the preparation of aliphatic polyesters with well defined structures and architectures. The most widely used initiators are various aluminum and tin alkoxides and carboxylates with vacant "*d*" orbitals. These initiators are capable of producing stereoregular polymers of narrow molecular weight distribution (MWD) and controlled molecular mass, with well-defined end-groups.

The carboxylates are weaker nucleophiles in comparison to the alkoxides and are considered to behave more like a catalyst rather than an initiator. Metal carboxylates are therefore used together with an active hydrogen compound (e.g., an alcohol) as coinitiator. The polymerization proceeds *via* acyl-oxygen cleavage of the cyclic ester with insertion of the monomer into the metal-oxygen bond of initiator. The coordination of the endocyclic oxygen to the metal results in the polarization and makes the carbonyl carbon of the monomer more susceptible for nucleophilic attack as shown in Figure 1.7.

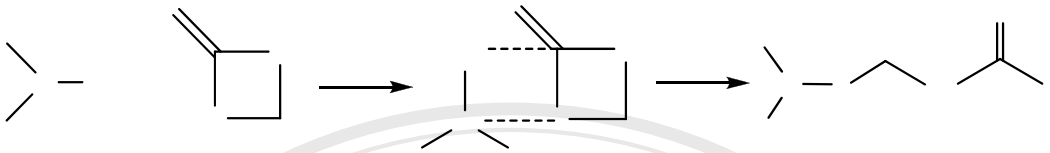
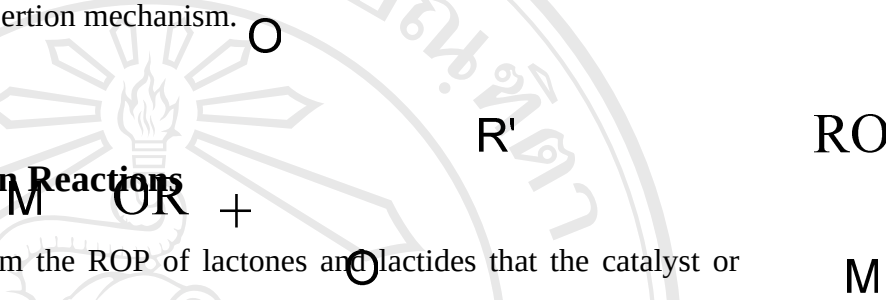


Figure 1.7 The reaction pathway for the ROP of a cyclic ester by the coordination-insertion mechanism.



1.3.3 Transesterification Reactions

It is well known from the ROP of lactones and lactides that the catalyst or initiators cause transesterification reactions at high temperatures, or at long reaction times as shown in Figure 1.8. Intermolecular transesterification reactions modify the sequences of copolylactones and prevent the formation of block copolymers. Intramolecular transesterification reactions, *i.e.*, back-biting caused degradation of the polymer chain and the formation of cyclic oligomer. Both types of transesterification reaction broaden the molecular weight distribution.

As displayed in the proposed scheme, each intramolecular transesterification randomly breaks the polymer chain. In this way, an attack on the polymer chain leads to a free residual polymer and new randomized, modified polymer. Consequently, an original copolymer with a block like-structure would be converted to a randomized copolymer after undergoing transesterifications.

Parameters that influence the number of transesterifications are temperature, reaction time, and type and concentration of catalyst or initiator. Depending on the metal used, the initiator is more or less active towards side-reactions such as transesterification reactions. [1]

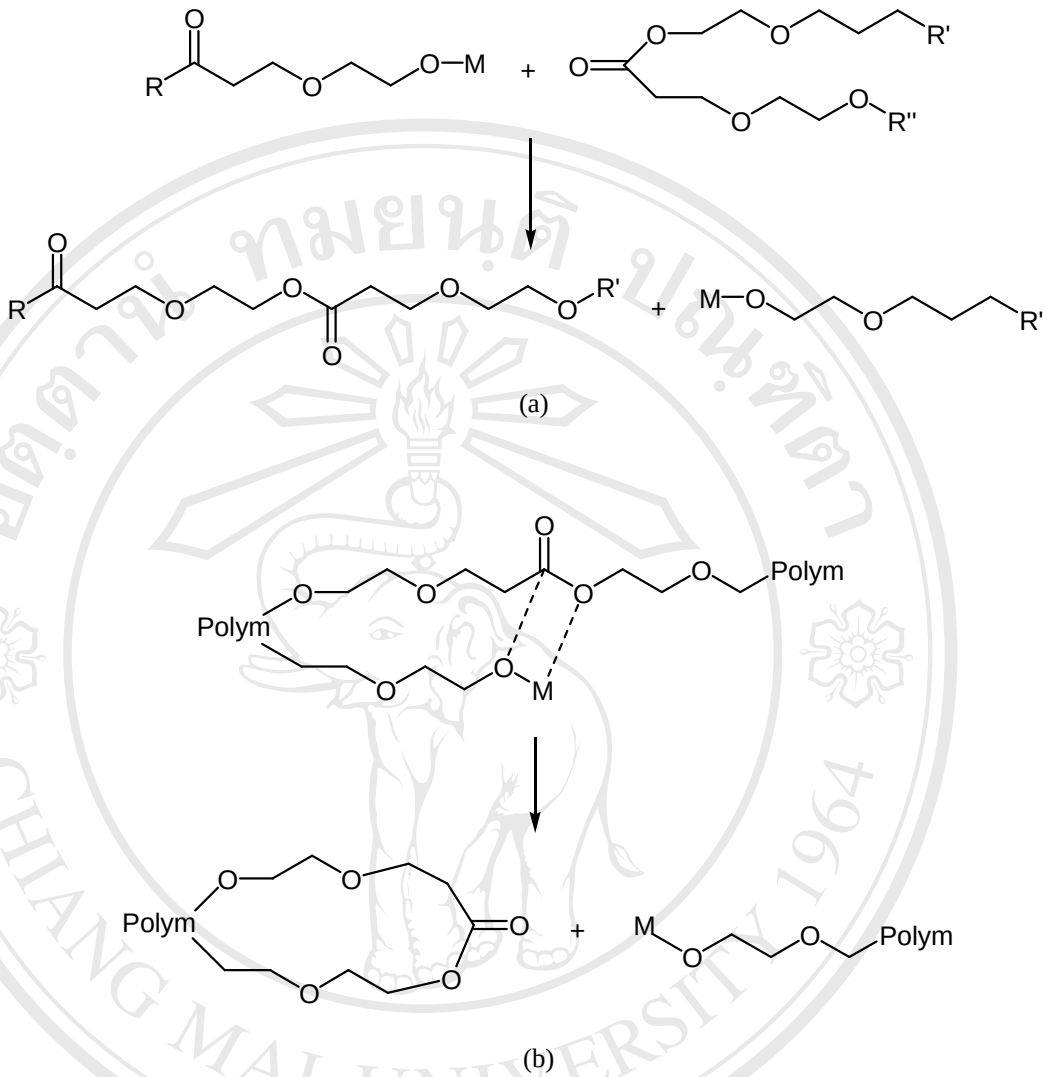


Figure 1.8 Reaction schemes for transesterification reaction; (a) intermolecular transesterification and (b) intramolecular transesterification (back-biting).

1.3.4 Initiators/Catalysts for the Ring-Opening Polymerization

The most widely used catalyst for coordination-insertion polymerization of aliphatic polyesters is tin (II) 2-ethylhexanoate. It is also known as stannous octoate ($SnOct_2$) in the industry and exists in the form seen in Figure 1.9. It is a very effective

and versatile catalyst, which is easy to handle and is soluble in common organic solvents and cyclic ester monomer. The Food and drug Administration (FDA) has approved it is a food additive. [29-33]

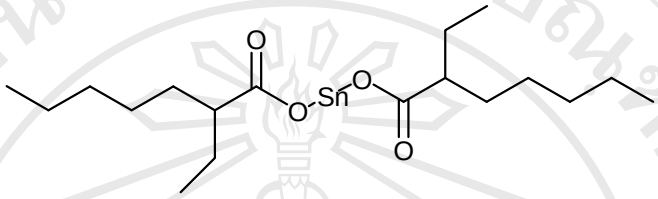


Figure 1.9 Tin (II) 2-ethylhexanoate or stannous octoate ($SnOct_2$).

The mechanism of polymerization has been widely discussed. The $SnOct_2$ is not thought to be the actual initiators since the molecular weight dose not depend on the monomer to $SnOct_2$ molar ratio. The most promising mechanism is a coordination-insertion mechanism where a hydroxyl functional group is thought to coordinate to $SnOct_2$, forming the initiating tin alkoxide complex. Investigations of the coordination-insertion mechanism have resulted in two slightly different reaction pathways. Recently, the generally accepted "coordination-insertion" mechanism for $SnOct_2$ catalyzed ROP of lactones and lactides has been demonstrated by Kricheldorf *et al.* [34-35] and Penczek *et al.* [36-38] although there are still some debates.

Kricheldorf *et al.* [34-35] have proposed a mechanism where the initiating alcohol functionality and the monomer are both coordinated to the complex during propagation. The reaction is terminated by hydrolysis forming a hydroxyl end group as shown in Figure 1.10.

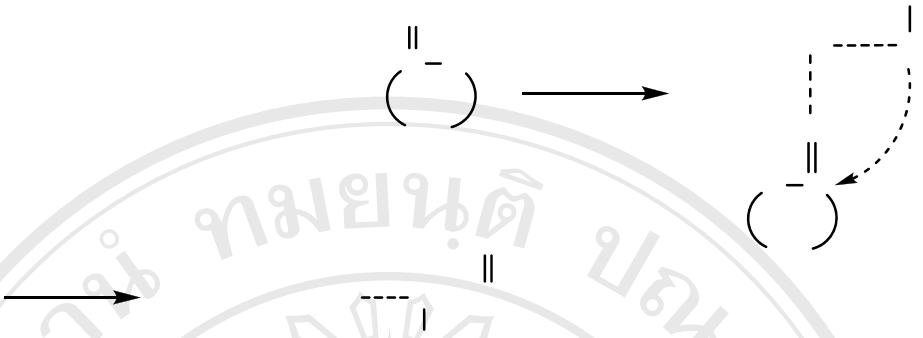


Figure 1.10 The main ROP mechanism proposals with $SnOct_2$ as catalyst that the complexation of a monomer and alcohol prior to ROP.

Penczek *et al.* [36-38] proposed the alternative mechanism suggesting that when $SnOct_2$ mixed with an alcohol an initiating complex is formed prior to polymerization. The establishment of equilibrium between $SnOct_2$ and alcohol results in the liberation of acid from the catalyst. The tin alkoxide complex thus formed then initiates the polymerization. The presence of tin alkoxide complex has recently been reported by using MALDI-TOF spectroscopy for both lactide and CL polymerization. Figure 1.11 shows the $SnOct_2$ catalyst is a strong transesterification agent, and the resulting copolymers normally have a randomized microstructure. [39]

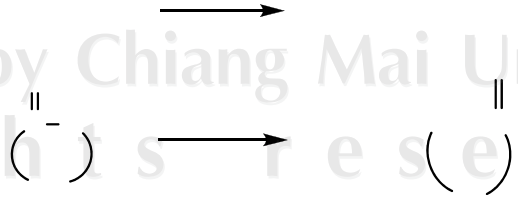


Figure 1.11 The main ROP mechanism proposals with $SnOct_2$ as catalyst that the formation of a tin alkoxide before ROP of cyclic ester.

1.4 Controlled Molecular Architecture

Many recent advances in polymer synthesis have involved the development of new controlled polymerization systems proceeding *via* a variety of mechanisms. A number of architectures may be produced as a result of the great versatility of the ROP of cyclic esters. Different strategies have been applied for the design of new polymeric materials. [40] In recent years, the branched and star-shaped biodegradable aliphatic polyesters have gained widespread attention due to their unique properties, often differing significantly from their linear counterparts. Structure-property studies have shown that variations in the macromolecular architecture can have substantial effects on the morphological, thermal, rheological and physico-mechanical properties and also on the biodegradability of biomedical materials.

Star-shaped polymers are one of the simplest forms of branched polymers. They consist of a core molecular onto which linear polymers are coupled or grafted form. Among various attempts to synthesize polyesters with this architecture, there are two methods that are most widely used and can be classified and distinguished into two patterns:

1. Core first, living polymerization with a multifunctional initiator [41-42]
2. Arm first, coupling reaction of linear living polymers with a multifunctional coupling agent [43-44]

Synthesis can be divided into two general approaches described in Figure 1.12. The first route is the core-first method where polymer chains are grown outwards from a multifunctional core (route a). The second route is the arm-first method, where preformed linear polymers are linked to a multifunctional coupling agent or a diene (route b and c).

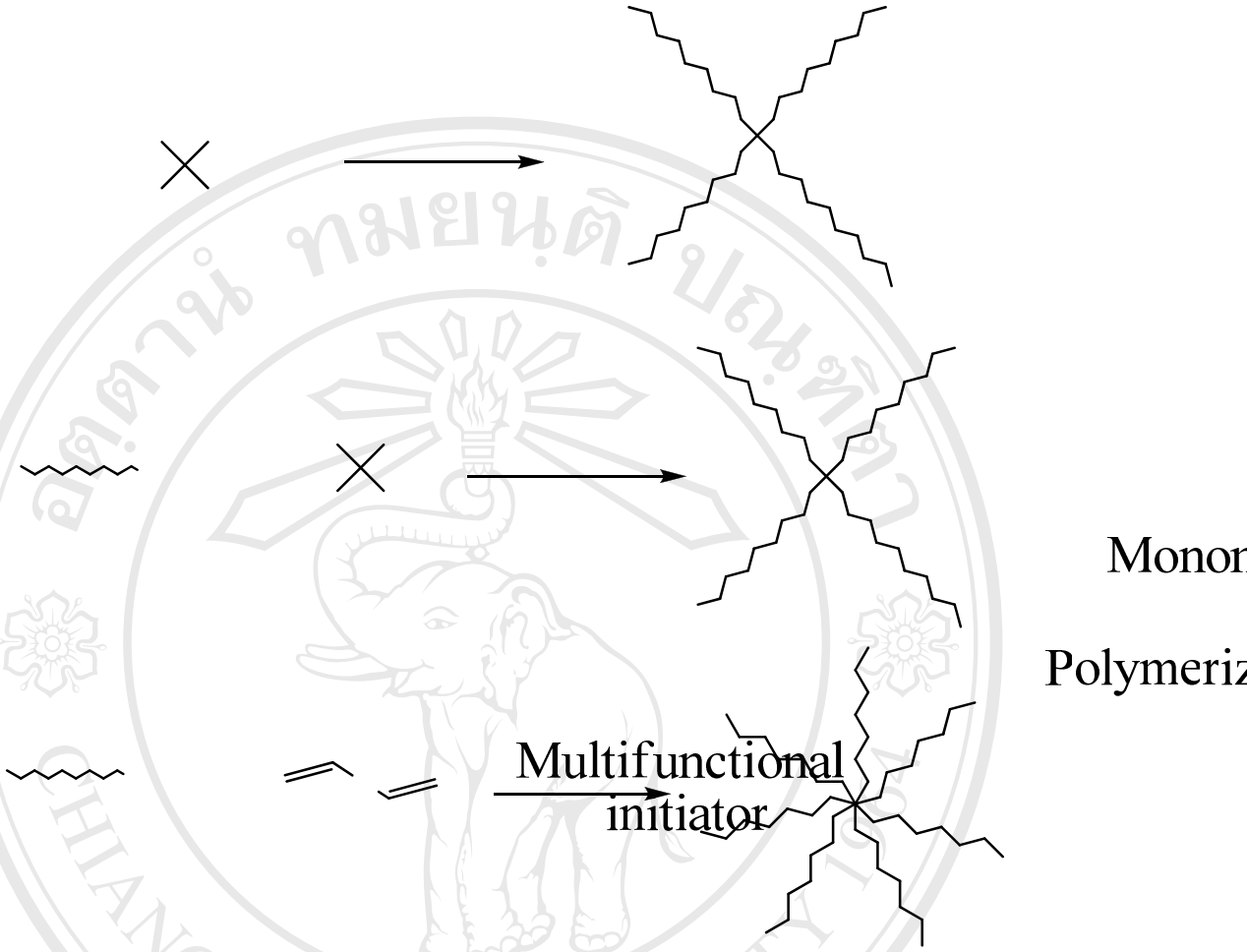


Figure 1.12 Illustrations of the three approaches for the synthesis of a star-branched polymer (a) the core-first method (b) and (c) the arm-first method. [33]

Examples of polymers with different molecular architectures are shown in Figure 1.13. A linear structure may be presented by a chain with one or two ends. There are a many different types of branched polymers. Dendritic, comb and star-branched polymers are just some example. A short-chain branch has an oligomeric nature whereas a long-chain branch is of polymeric length [45].

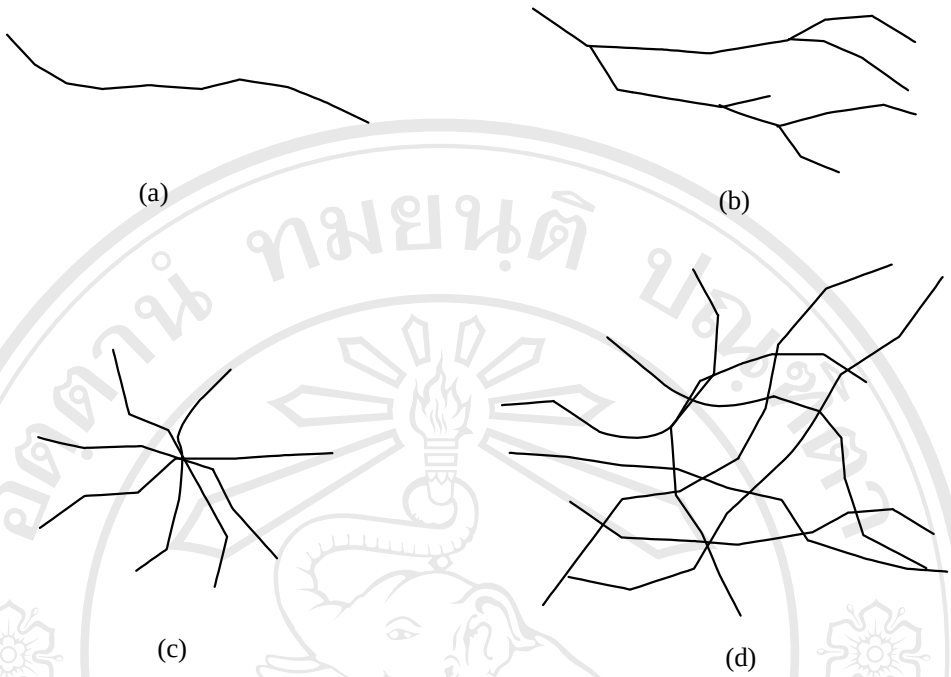


Figure 1.13 Representation of structures of polymers with different molecular architectures: (a) linear, (b) branch, (c) star-branch and (d) network.

The molecular architecture is important for many properties. Branching changed the properties of the biodegradable polymers. Branch polymer contains more chain ends than its linear counterpart of equal molecular weight and the polymer chains are shorter. With the increasing number of terminal groups, their effect on the polymer properties is increased. [46] Short-chain branching tends to reduce crystallinity. Long-chain branches have profound effects to rheological properties. Typical of ladder polymers is a high strength and a high thermal stability. Hyperbranched polymers consist of molecules with an approximately spherical shape, and it has been shown that their linear analogue with the same molar mass. Crosslinked polymers are thermosets, *i.e.* they do not melt. They also show little creep under constant mechanical loading. Due to the complex architecture of branched

polymers have been studied extensively, especially the star polymers where they have served as model to increase the general understanding of branched macromolecules. [47]

1.5 Degradation Phenomena in Biodegradable Polymers

A material that can be used as a scaffold in tissue engineering must satisfy a number of requirements. These include biocompatibility, biodegradation to non toxic products within the time frame required for the application, processability to complicated shapes with appropriate porosity, ability to support cell growth and proliferation, and appropriate mechanical properties, as well as maintaining mechanical strength during most part of the tissue regeneration process.

Among the families of synthetic polymers, the polyesters such as PL, PCL and PG have been attractive for these applications because of their ease of degradation by hydrolysis of ester linkage, degradation products being resorbed through the metabolic pathways in some cases and the potential to tailor the structure to alter degradation rates.

Numerous studies have established a simple degradation mechanism *via* homogeneous erosion. The degradation process occurs in two stages, the first involves the diffusion of water into the amorphous regions of the matrix and simple hydrolytic chain scission of the ester groups. The second stage of degradation involves largely the crystalline areas of the polymer, which becomes predominant when the majority of the amorphous regions have been eroded. Figure 1.14 was shown simple hydrolysis mechanism of polyester reacts with water, then ester bonds

in polymer molecule were broken and gives low molecular weight short chains polymer as by-products.

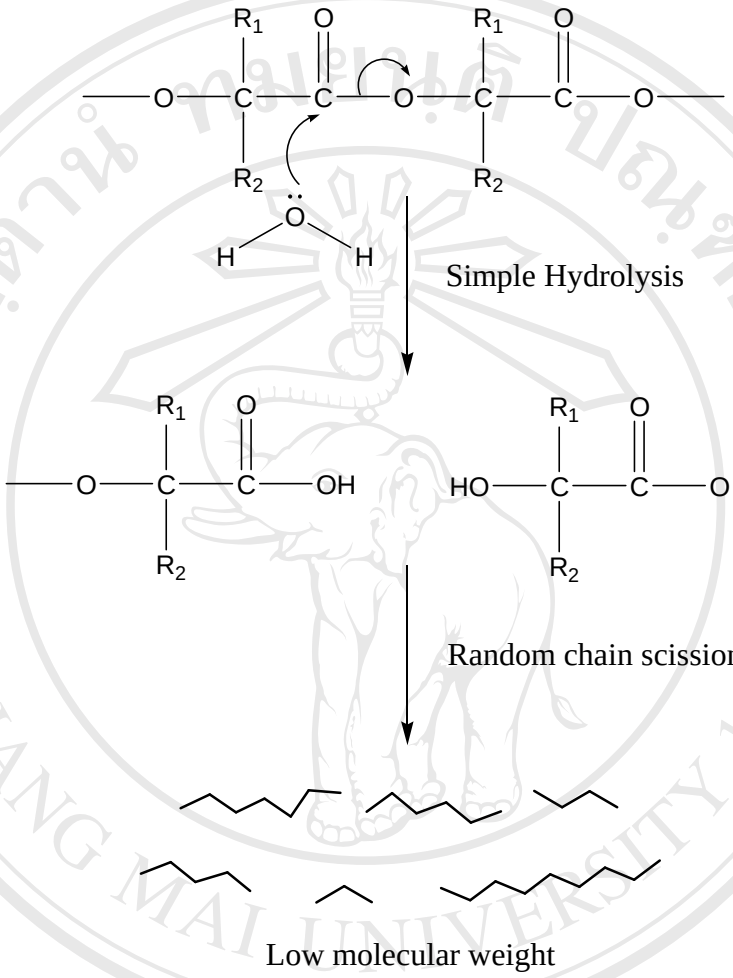


Figure 1.14 Simple hydrolysis of aliphatic polyester.

The degradation of polyesters generally involves random hydrolysis of their ester bonds. PL, PG and PCL degrade to form lactic acid, glycolic acid and caproic acid respectively which are normally present in the body. This acid then enters tricarboxylic acid cycle and is excreted as water and carbon dioxide. No significant amounts of accumulation of degradation products of PL have been reported in any of the vital organs.

PCL degrades at a much lower rate than PL and is a useful base polymer for developing long term, implantable drug delivery systems. The PCL homopolymer has a degradation time of the order of two to three years. PCL with an initial average molecular weight of 50,000 takes about three years for complete degradation *in-vitro*. The rate of hydrolysis can be altered by copolymerization with other polymers, for example a copolymer of LL and CL degrades more readily. The rates of degradation, however is determined by factors such as configurational structure, molecular architecture, copolymer ratio, crystallinity, molecular weight, morphology, stresses, amount of residual monomer, porosity and site of implantation. [48]

1.6 *In Vitro* Hydrolytic Degradation Testing

The testing of materials for biomedical applications involved investigating the biocompatibility and/or the degradability of these materials. *In vitro* was performed by immersing the sample in the phosphate buffer saline (PBS) solution at the physiological pH 7.4 and temperature 37°C. Blood plasma, Krebs solution, citrate-phosphate buffer, boric acid-borax buffer, etc., can be used as the immersion medium. [49]

In order to follow the *in vitro* hydrolytic biodegradation of synthetic polyesters, the following properties were monitored.

1.6.1 Weight Loss

Weight loss resulting from the degradation of a polymer requires the breakage of chemical bonds. Once chemical bonds start to break, reactive chain end and free

radicals are created. Degradation can proceed either by depolymerization or by random chain scission. The dominant degradation mechanism may depend on the details of structure and composition, including the type of end groups terminating, the polymer chain and the presence of structural defect, additive or impurities.

1.6.2 Polymer Morphology

The morphology of the biodegradable polyesters is an important variable in the hydrolytic degradation process. The amorphous phase of the polymer is much more accessible to water than the crystalline phase. Consequently, amorphous polyesters degrade faster than the crystalline polyesters. It is expected that the degree of crystallinity will influence chemical and physical properties, such as swelling behavior and hydrolytic sensitivity of the polymer and its rate of biodegradation. The degree of crystallinity reaches a maximum and starts to decrease as hydrolysis proceeds to the second stage and destroys the crystalline lattice.

1.6.3 pH

pH is one of the most importance factors of hydrolytic polymer degradation. pH changes can modify hydrolysis rate by orders of magnitude. In addition, the degradation products of many degradable polymers change pH by their acid functionality. Substantial pH changes were also found during the erosion of polymers.

1.7 Previous Work Relevant to This Study

In recent years, there has been an increased interest in the synthesized of star-shaped biodegradable aliphatic polyesters, which can be used in biomedical and pharmaceutical applications. One reason for the growing interest in this type of degradable polymers is their physical and chemical properties. The previous related studies are briefly described below.

Dong *et al*. [50-51] synthesized of poly(D,L-lactic acid-*alt*-glycolic acid), poly(*ε*-caprolactone)-*b*-poly(D,L-lactic acid-*alt*-glycolic acid) from the polymerization of D,L-3-methylglycolide, CL and DLL and poly(D,L-3-methylglycolide) *via* the ROP with multifunctional initiators, such as 1,1,1-tris(hydroxymethyl)-propane (TMP) (3-OH) or pentaerythritol (PTOL) (4-OH) and $SnOct_2$ catalyst in bulk at 110°C. ^{1}H-NMR spectra of the resulting polymers obtained show that TMP or PTOL initiator and $SnOct_2$ catalyst produced two types of three-arm or four-arm star-shaped polymers. The studies the effect of monomer to initiator ratio on the molecular weight indicated that the molecular weight of polymer were proportional to the molar ratio of monomer to initiator.

Choi *et al*. [52] synthesized a series of star-branched PCLs with the architectural variation on the arm numbers and length through ROP under bulk condition by using multifunctional initiating core such as TMP, PTOL and dipentaerythritol (DPTOL) (6-OH) and characterized the effects on branching, thermal properties and crystallinity. The melting temperature (T_m) and degradation temperature (T_d) were observed to increase with increasing arm lengths but with constant arm number. However, for star-branched PCLs with equivalent molecular

weight, the degree of crystallinity was found to decrease with increasing arm numbers.

Wang and Dong [53] studies the physical properties and crystallization kinetics of star-shaped poly(*ε*-caprolactone) (sPCL) having four arms (4sPCL) and six arms (6sPCL) and linear poly(*ε*-caprolactone) (LPCL) having one arm (LPCL) and two arms (2LPCL) were synthesized by using PTOL, DPTOL, benzyl alcohol and 1,6-hexanediol as the initiating *via* ROP. The maximal melting point, the cold crystallization temperature (T_c), and the degree of crystallinity of these PCL polymers decrease with the increasing number of polymer arms and they have similar crystalline structure. The isothermal crystallization rate constant (K) is in the order of $K_{2LPCL} > K_{LPCL} > K_{4sPCL} > K_{6sPCL}$. For the linear PCL, the molecular mobility increases with both the increasing arm number and the decreasing molecular weight of each arm, which induced that 2LPCL had a higher value of K than LPCL. However, with the continuous increasing arm number, both the strong hydrogen bond interactions among the arms of star-shaped PCL and the constrained geometry mainly decreased the molecular mobility and rearrangement, suggesting a lower value of K.

Yuan *et al*. [54-56] studies the thermal and the degradable properties of hexa-arm star-shaped poly(*ε*-caprolactone)-*b*-poly(D,L-lactide-co-glycolide) and PLL and poly(D,L-lactide)s (PDLLs) initiated with hexakis[*p*-(hydroxymethyl)phenoxy]cyclo triphosphazene, as the hydroxyl-terminated cyclotriphosphazene and $SnOct_2$ catalyst in bulk. The terpolymer presented a two-phase structure, namely, PCL crystalline and D,L-LAGA amorphous domains, which made the copolymer different from linear PCL and star-shaped PCL in crystallinity and thermal behaviors. Thermal analysis revealed that the star-shaped PLLs possessed lower T_m, crystallinity and onset T_d but

higher maximum T_d than linear ones. Analysis of hydrolytic degradation of linear and star-shaped PDLL and PLL showed that star-shaped PDLL possessed the best degradability, while linear PLL possessed the poorest degradability. The degradation of star-shaped PLL was divided into two steps, with was different from the degradation process of linear PLL. Ester groups were hydrolysed and PLL chains were cleared randomly and the short PLL chain were detached from cyclotriphosphazene core.

Dorgan *et al*. [57] studied the melt rheological properties of star-branched polyester and compared the properties of the linear material. Rheological measurements of zero shear rate viscosity, η° showed that the star-branched polyester had a considerably lower η° than linear polyester with similar molecular weight ($\overline{M_n}$ <10^6). One describes an expected reduction of η° due to the smaller radius of gyration of gyration and branched polymer. However, viscosities of the high molecular weight stars were higher when comparisons were made at a constant radius of gyration. The enhancement of η° found for branched polymers is thought to be caused by the slowing of the reptation along a backbone contour when long arms are present. The low melt viscosity and the crystallity produced a rheological behaviour suitable for the film formation process for powder coating.

Yuan *et al*. [58] studied controllable drug release of dendritic star-block poly(L-lactide)s-*b*-2-(*N*,*N*′-dimethylamino)ethyl methacrylate (PLLA-*b*-PDMAEMA) which prepared from PLLABr macroinitiator and DMAEMA via transfer radical polymerization (ATRP) at 60°C. The dendritic star-block PLLA-*b*-PDMAEMA copolymer could be expected to become an intelligent carrier in controllable drug release system. Chlorambucil was a kind of alkylating anticancer agent and used as a

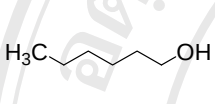
model drug to investigate the controllable release properties of the copolymer. In acidic and neutral solutions, PDMAEMA block presented expanding conformation and chlorambucil could diffuse out from the copolymer. The behavior of model drug chlorambucil release from the copolymer indicated that the rate of drug release could be effectively controlled by alternating pH values of the environment.

Thapsukhon [59] synthesized linear and star-shaped homopolyester of CL and LL and terpolyesters of CL, LL and G with variable numbers of arms by ROP using alcohols with different numbers of hydroxyl groups (1-hexanol, 2,2-dimethyl-1,3-propanediol (DMP), TMP and PTOL) as initiators and the effects of branching on polymer properties were studied. Low molecular weight PCL and PLL with different molecular architectures were synthesized to confirm the structure and evaluate the influence of chain architecture on the properties using ^{1}H-NMR spectroscopy. The ^{1}H-NMR results showed that the average number of OH groups initiating polymerization, as calculated from the average degree of the polymerization per arm (DP_n/arm) was close to the actual OH functionalities. The arm structures as evidenced on the $g^{1/2}/g'$ values, where $g^{1/2}$ and g' denote the ratio of mean-square radius of gyration and intrinsic viscosity of star-shaped to those of linear structure with similar molecular weight.

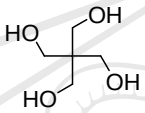
1.8 Aims of This Study

The main aim of this research project is concerned with the synthesis of a novel pentaerythritol tetrakis(6′-hydroxyhexanoate) star-core macroinitiator as initiator for use in the ROP of cyclic esters and studies the polymer properties with different molecular architectures. The structure of the polymer will be controlled by

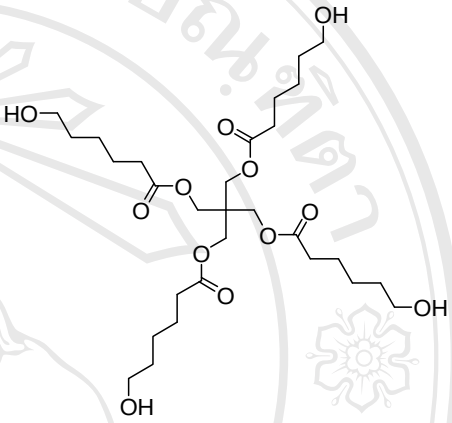
using different number of hydroxyl end group of initiators. 1-Hexanol yields linear polymer, while PTOL and pentaerythritol tetrakis(6′-hydroxyhexanoate) give star-shaped polymers. The structures of initiators used in this research are shown below.



1-hexanol



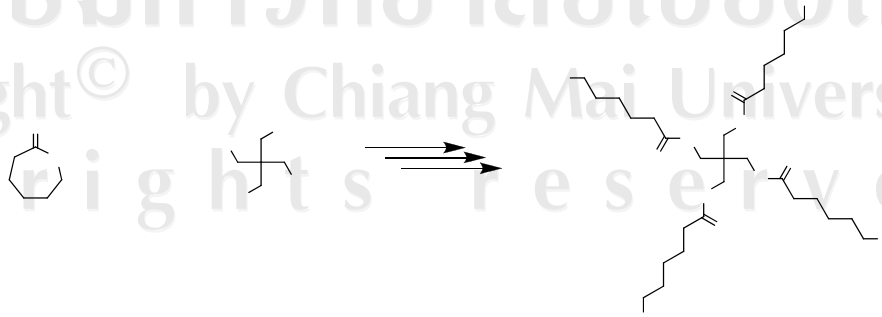
PTOL



pentaerythritol tetrakis(6'-hydroxyhexanoate)

The detail of this study as follow:

1. To synthesize pentaerythritol tetrakis(6'-hydroxyhexanoate), as a novel star-core macroinitiator for use in the ROP of cyclic esters. This star-core macroinitiator is to be prepared by using CL to cap the OH groups of PTOL as shown below.



2. To synthesized low molecular weight polyesters using 1-hexanol, PTOL and novel star-core macroinitiator as initiators and $SnOct_2$ as catalyst *via* ROP in bulk. The low molecular weight polyesters were characterized and confirmed their microstructures.
3. To synthesized high molecular weight polyesters using 1-hexanol, PTOL and novel star-core macroinitiator as initiators and $SnOct_2$ as catalyst *via* ROP in bulk. The effects of different molecular architecture on the thermal, morphological, rheological properties and *in vitro* hydrolytic degradation studies of high molecular weight linear and star-shaped polyesters will be investigated.