CHAPTER I

INTRODUCTION

1.1 Biodegradable polymers

1.1.1 Background

Polymer is a large molecule (macromolecule) composed of a number of small repeating units. Many (poly-) parts (-mer) are linked together by chemical covalent bonds. The repeating units or "mers" differ from the small molecules which were used in the original synthesis procedure, the monomer, in the loss of unsaturation or the elimination of a small molecule. In a polymer, the molecular size can comprise over 100,000 monomer units, with molecular weights (MW) of up to millions of g/mol [1].

The individual parts, or monomer segments, of a polymer can all be the same. In such a case, a homopolymer exists as illustrated in Figure 1.1a. If the parts of a polymer are different, it is termed a copolymer. These differences in chemical structure are also illustrated in Figure 1.1a, with generic symbols (A, B) for the monomers. Polymers can be either linear or branched as illustrated in Figure 1.1b. The tendency for a polymer to exhibit branching is governed by its synthesis conditions. Keep in mind that the conceptual models of polymer structure illustrated in Figures 1.1a and 1.1b have been highly simplified. For example, it is possible for a copolymer to have a wide range of substructural elements giving rise to an impressive range of possibilities [1, 2].

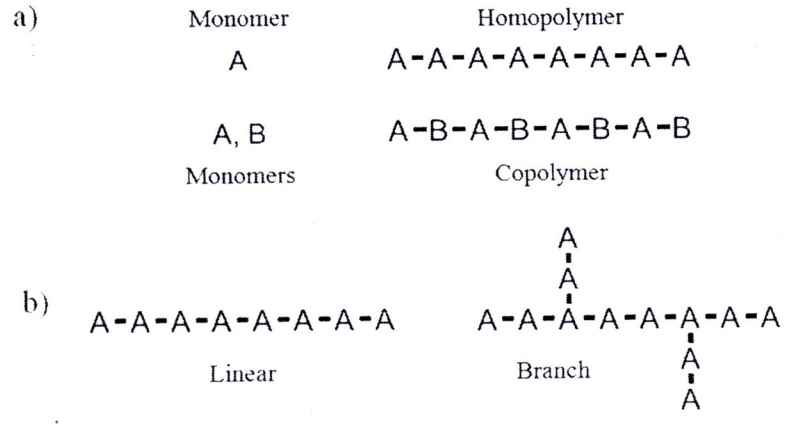


Figure 1.1 Scheme of polymer classification

Although the term polymer is sometimes taken to refer to plastics, it actually encompasses a large class of natural and synthetic materials with a wide variety of properties. The wide variety of polymers includes such as natural materials as cellulose, starches, natural rubber and deoxyribonucleic acid (DNA), the genetic material of all living creatures. While these polymers are undoubtedly interesting and have seen wide-spread use in numerous applications, they are sometimes eclipsed by the seemingly endless variety of synthetic polymers that are available today [2].

Because of the extraordinary range of properties of polymeric materials, polymers play an essential and ubiquitous role in everyday life. In recent year, the worldwide consumption of polymers has increased from 14 million kg in 1996 to an estimated 68 million kg in 2001 and so on. Thus, the polymer industrials were rapidly prospering for balancing demand. However, the wrong development and enormous expansion of polymer cause many environmental problems such as garbage pollution, global warming from dishonestly burning and wastes from production and destruction processes. These problems would dramatically increase. Therefore, the green chemistry is applied to solve these problems using "Biodegradable polymer" [3].

1.1.2 The definition of biodegradable polymers

Between October 1990 and June 1992, confusion as to the true definition of "biodegradable" led to lawsuits regarding misleading and deceitful environmental advertising. Thus, it became evident to The American society for testing of materials (ASTM) and the international standards organization (ISO) that common test method and protocols for degradable polymer were needed [4].

The term "biodegradable" refer to the ability to decompose by natural biological process. However, the term "biodegradable polymer" is widely used in the meaning of a polymer that degrades in the human body or removes from the implanted site by physiologic processes. Generally, a polymer that loses its weight over time in the living body is called an absorbable, resorbable or bioabsorbable, as well as a biodegradable polymer. Biodegradable polymer undergoes degradation from the action of naturally occurring microorganisms such as bacteria, fungi, and algae. Polymer may also be designated as photodegradable, oxidatively degradable, hydrolytically degradable, or those which may be composted [4-7].

A variety of natural, synthetic, and biosynthetic polymers are bio and environmentally degradable. A polymer based on a C-C backbone tends to resist degradation, whereas heteroatom-containing polymer backbones confer biodegradability. Biodegradability can, therefore, be engineered into polymers by the judicious addition of chemical linkages such as anhydride, ester, or amide bonds, among others. The usual mechanism for degradation is by hydrolysis or enzymatic cleavage of the labile heteroatom bonds, resulting in a scission of the polymer backbone. Macroorganisms can eat and, sometimes, digest polymers, and also initiate a mechanical, chemical, or enzymatic aging [3].

Biodegradable polymers with hydrolyzable chemical bonds are researched extensively for biomedical, pharmaceutical, agricultural, and packaging applications. In order to be used in medical devices and controlled-drug-release applications, the biodegradable polymer must be biocompatible and meet other criteria to be qualified as biomaterial-processable, sterilizable, and capable of controlled stability or degradation in response to biological conditions. The chemical nature of the degradation products, rather than of the polymer itself, often critically influences biocompatibility. Poly(ester) based on aliphatic polyester, and their copolymers have been extensively employed as biomaterials. Degradation of these materials yields the corresponding hydroxy acids, making them safe for *in vivo* use [4].

1.1.3 Degradation mechanism of biodegradation polymer

The notable property of this polymer is friendly environmental and bio-decomposed of degradation. Many degradation mechanisms involved about biodegradation such as solubilization, ionization followed by solubilization, enzymatically-catalyzed hydrolysis and simple hydrolysis [8, 9].

Solubilization: The solubilization is applicable to polymers that are water-soluble. The degradation process involves diffusion of water on the polymer matrix, followed by continuous salvation and swelling until either fragmentation or dissolution occurs.

Ionization followed by solubilization: Utilization of an ionization mechanism for bringing about water-solubility allows materials being designed that are relatively hydrophobic prior to ionization, However, when these polymers are placed to an

environment which causes them to become ionization, their surfaces absorb water, swell and final dissolve, causing the surface to erode.

Enzyme-catalyzed hydrolysis: Enzyme-catalyzed biodegradation is perhaps the classical mechanism by which implants are removed from the body and has more impact on natural polymers than synthetic biodegradable polymers. Enzyme-catalyzed biodegradation was controlled suitable temperature and pH for each enzyme that catalyzed different biodegradable polymers such as collages enzyme can be catalyzed hydrolysis of collagen in maximum pH 7-8.

Simple hydrolysis: Simple hydrolysis is the depolymerization process which can be seen as the reverse of polymerization. Its occurrence is feasible in the aqueous extra cellular fluid such as the polymer has to contain hydrolytically unstable bonds or the hydrolysis has to take place at the physiological pH and temperature. 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 1.2 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.

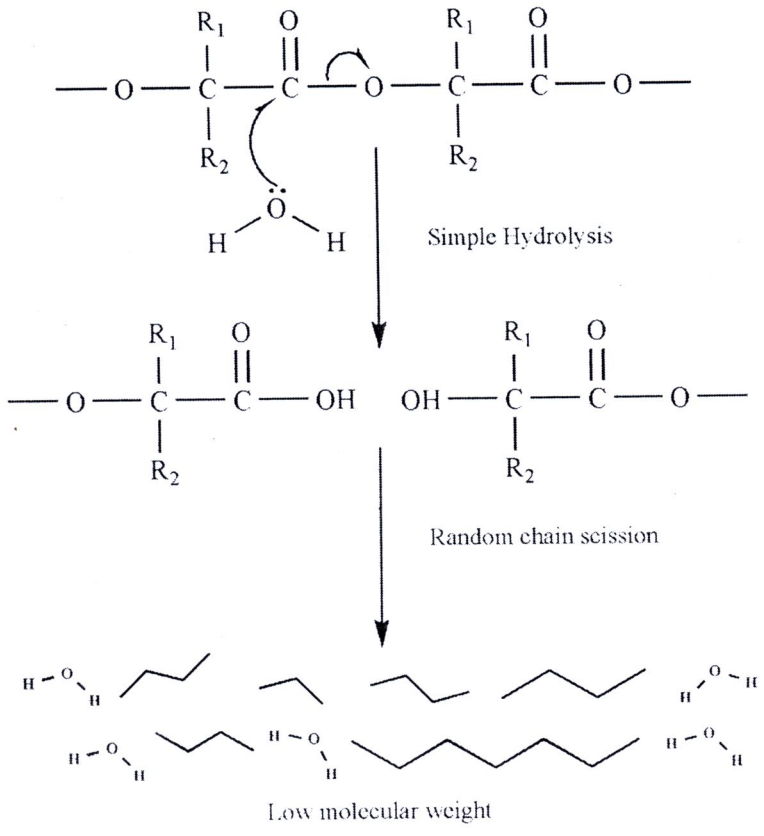


Figure 1.2 Simple hydrolysis of aliphatic polyester

1.1.4 Aliphatic polyester as biodegradable polymer

Among the various families of degradable polymers, aliphatic polyesters have a leading to position. They are most effectively derived from ring-opening polymerization (ROP) and they have long been considered as degradable materials for medical application. The interest has been high since the hydrolytic and/or enzymatic chain cleavage yield ω-hydroxyacids [10, 11].

Aliphatic polyesters are biodegradable polymer consisting of many ester bonds in the chains. These chains are very weak and can be reacted with water in hydrolysis process. So, these biodegradable can be degraded to smaller molecules. Recently, productions of this kind of biodegradable polyester are shown in the Figure 1.3. Most of them are aliphatic polyester because the chain is appropriated to break

bonding. Aliphatic polyester consists of 4 families such as polybutylene succinate (PBS), polycaprolactone (PCL), polyhydroxyalkanoates (PHA), polylactic acid (PLA). The PBS and PCL produced from monomers in petrochemistry, PHA need alternative raw materials but it depends on polymerization in chemical reaction. Whereas, the PHA is the same family as synthetic process as well as reaction found in microorganism [11].

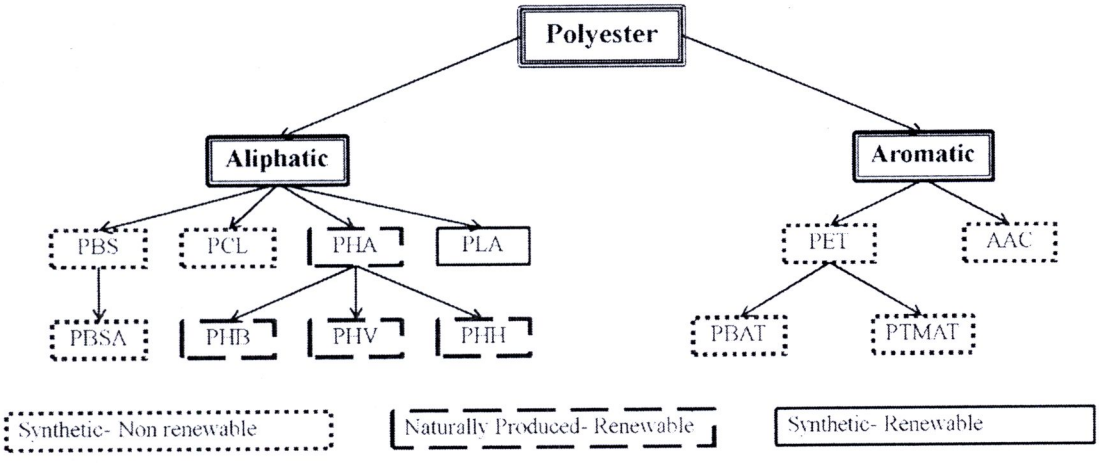


Figure 1.3 The classification and example of polyesters

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 (if used) and reaction temperature, and also the ring size of the monomer and the substituents on the monomer ring. Cyclic esters of four-, seven-, and eight-membered rings polymerize, whereas the five-membered rings generally do not. In the case of six-membered rings, the polymerisability depends on the substituents [9, 12]. In aliphatic polyester in which of cyclic ester, PCL is widely used and popular for biomedical polymer. Many reports and patents of both polymers were published and registered.

Because of the specific properties and valuable applications of this polymer, so the details properties of PCL are described in next section.

1.2 Poly(ε-caprolactone)

In this present work, PCL which is cyclic polyester and its beneficial properties such as biodegradable polymer is focused. Poly(ε-caprolactone), PCL, or simply polycaprolactone as it usually referred to, is a synthetic biodegradable aliphatic polyester, notably in the specialist biomedical areas of controlled release drug delivery systems and 3D scaffolds for using in tissue engineering [13]. Since biomedical applications have a very stringent property requirement, the demand for polymers with controlled microstructures and MW is constantly increasing. This requires a detailed understanding of the mechanisms and kinetics of the polymer-forming reactions involved [14-16].

1.2.1Property of poly(ε-caprolactone)

PCL is a hydrophobic, semi-crystalline polymer having a low Tm ~ 58-65 °C and a Tg ~ -60 °C. The repeating molecular structure of PCL consists of five nonpolar methylene groups and a single relatively polar ester group. This structure gives PCL some unique properties. Because it is tough and flexible thus, PCL is in the rubbery state and exhibits high permeability to low molecular species at body temperature [9]. The mechanical properties of PCL are similar to polyolefins because of its high olefinic content, while the presence of the hydrolytically unstable aliphatic ester linkage causes the polymer to be biodegradable. The example structure and properties of ε-caprolactone (CL) and PCL are shown in Figure 1.4 in many styles a)

2D stereo structure of CL, b) 3D tube structure of CL in boat form view and c) 3D ball and stick structure of CL in side view [17].

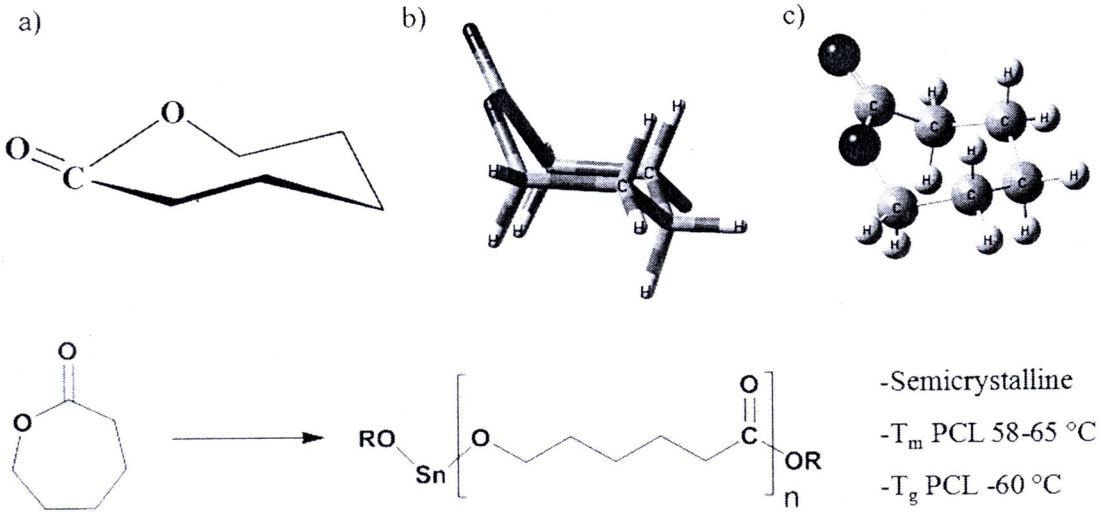


Figure 1.4 Structures and properties of ε-caprolactone (CL) and PCL

The toxicology of PCL has been extensively studied as part of the evaluation of Capronor. Based on a large number of tests, CL and PCL are currently regarded as nontoxic and tissue-compatible materials. In Europe, PCL is already in clinical use as a degradable staple (for wound closure), and it stands to reason that PCL, or blends and copolymers containing PCL, will find additional medical applications in the future [2].

1.2.2 Ring-opening polymerization of poly(ε-caprolactone)

PCL is prepared by the ROP of a cyclic ester monomer. And the monomer is CL, a seven-membered ring in which a single ester moiety is linked together with five methylene group units (Figure 1.5). The ROP temperatures for PCL are in the range of 100-150°C with the polymerization again being normally initiated by $Sn(Oct)_2$.

Other initiators which have been used include various Lewis acids, metal alkyls and organic acids. MW is controlled by the addition of chain control agents. These chain control agents are usually water, primary alcohols, amines, or some other active hydrogen compound [18].

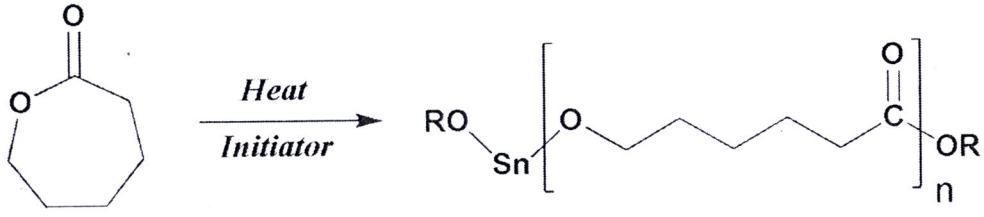


Figure 1.5 Principle reaction of PCL synthesizing

The most widely used technique for synthesizing these polymers is ROP. Indeed, this process allows quite good control of the polymer characteristics and is particularly well-suited for macromolecular engineering with the production of homo- and copolymers of various architectures [19]. In the literature, two major ROP mechanisms were proposed: the activated monomer mechanism and the coordination-insertion mechanism. Both mechanisms are thought to be alcohol-initiated, since the degree of polymerization is clearly dependent on the monomer-to-alcohol ratio and the end groups of the polymer have hydroxy functionalities. However, The coordination-insertion mechanism provides an explanation of the highly stereoregular polymers obtained with $Sn(Oct)_2$ [20-22].

ROP has been widely studied and many efficient initiators have been developed. Three methods of ROP mechanism are cationic, anionic and coordination-insertion [23]. The coordination-insertion is the best method due to its advantages such as easy control of the MW, the lower risk of side reactions and the higher

molecular weight obtained [24]. The most common catalyst used in coordination-insertion is metal alkoxides, such as tin, aluminium, trivalent lanthanide, magnesium, zinc derivatives, group IV metals and iron [25-28]. These metal alkoxides have been reported to be effective initiators that initiate ROP of cyclic esters. Among them, tin alkoxide is suitable for the ROP catalyst because of its solubility and ease of handling. In particular, tin(II) 2-ethylhexanoate, commonly known as stannous octoate ($SnOct_2$), is the most widely used in both scientific research and industrial production. It is the only catalyst that has been accepted by the U.S. Food and Drug Administration (FDA) [29]. The polymerization mechanism with this initiator is rather complex and several mechanisms have been proposed in the past [30-33]. In the polymerization process, $Sn(Oct)_2$ acts as an initiator in the presence of an alcohol (ROH) coinitiator before carrying to actual initiating species. So, $Sn(Oct)_2$ is not the true initiator.

In the coordination-insertion mechanism, a compound containing a hydroxide group is believed to react with $Sn(Oct)_2$ to form the actual initiator, an alkoxide covalent bond to tin. A comparative study between two initiating systems, $Sn(Oct)_2$ with butanol and Sn(II)butoxide, showed that the growing polymer chain in these systems could be identical [32]. Recent investigations on $Sn(Oct)_2$ systems have actually confirmed the presence of a tin-alkoxide complex by Matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF). The reaction pathway proposed by Penzcek *et al.* [33-36] involved the dissociation of at least one 2-ethylhexanoate group from the metal complex in the form of the corresponding acid. Recent studies by Kricheldorf *et al.* [37] supported the dissociation of 2-ethylhexanoic acid. The presence of carboxylic acids decreases the reaction rate. This

effect was proposed as a blocking of the coordination site or more recently explained as a shift in the equilibrium between $Sn(Oct)_2$ and Sn(Oct)-alkoxide species [32].

For this reason many years ago, many researchers tried to study and identify the true initiator of the coordination insertion mechanism on ROP in order to understand the exact mechanism. And to date, it is widely accepted that the $Sn(Oct)_2$ initiator and ROH as a co-initiator react together *in situ* to form the corresponding tin(II) monoalkoxide, [Sn(Oct)(OR)], and dialkoxide, $[Sn(OR)_2]$ which are the "true initiator" [13] as shown in Figure 1.6.

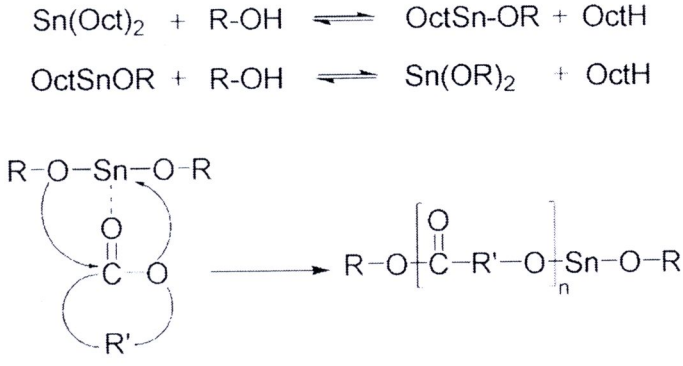
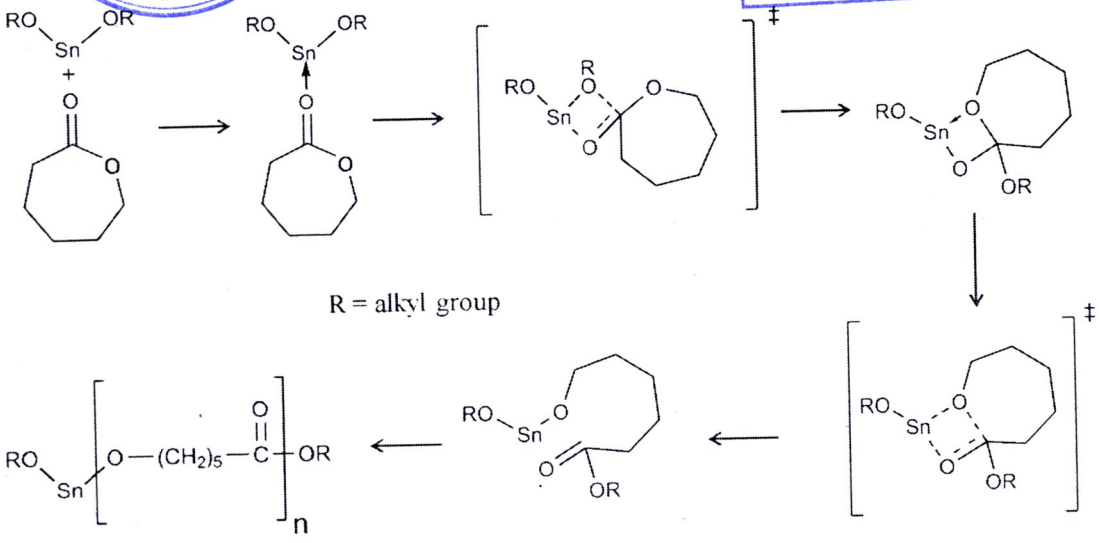


Figure 1.6 The coordination-insertion mechanism for the ROP of a cyclic ester using the $Sn(Oct)_2$/ROH as initiator/co-initiator and alkoxide formation (old mechanism)

Moreover, many researchers and also Winita's group [13, 14, 38] showed that the good method to synthesize the PCL with high percent yield was achieved by coordination-insertion mechanism of ROP method in bulk of the CL using novel tin(II) alkoxide initiators [13]. And the new mechanism was also proposed clearly (step-by-step) in Figure 1.7.



R = alkyl group

Figure 1.7 Scheme of new purpose mechanism for ROP of CL initiated by tin(II) alkoxide

1.2.3 Degradation phenomena and application of poly(ε-caprolactone)

The degradation of polyesters generally involves random hydrolysis of their ester bonds. PLA and PCL degrade to form lactic 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 PLA have been reported in any of the vital organs.

PCL degrades at a much lower rate than PLA 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, MW, morphology, stresses, amount of residual monomer, porosity and site of implantation [9].

In enzyme degradation, the degradation of PCL is assumed to contain four steps: (1) the adsorption of enzyme on polymer substrate. (2) formation of transition complex between polymer and enzyme. (3) specific chain scission of the polymer. And (4) interaction of the polymer enzyme adsorbed complex and polymers. Figure 1.8 shows the chemical structure of PCL and the point of attack of the enzyme [39].

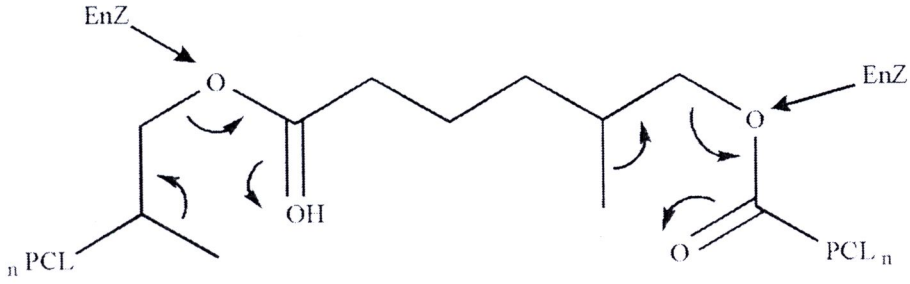


Figure 1.8 The enzyme degradation of PCL

For oxidation degradation, PCL is shown to undergo oxidative degradation at 120 °C under oxygen environment. The mechanism of degradation of PCL is debatable. It was suggested that PCL decomposes by a two-step mechanism, wherein the first step is a polymer chain cleavage at any random point along the chain by pure unzipping of monomer on isothermal heating. The second step is the scission of the monomer at the end of the polymer chain by random chain scissions as well as by unzipping of monomer on non-isothermal heating [40, 41].

Because of the slow rate degradation of PCL, different approaches have been used to copolymerize CL to increase the degradation rate. Copolymers of CL and LL of all compositions are degraded much more rapidly than their component

homopolymers. This observation has been attributed to morphological differences, specifically a reduction in crystallinity and a lowering of the glass transition temperature [9]. PCL has been also 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 [42]. It is also of interest as a packaging material and in biomedical applications since it is biodegradable and its biodegradation products are non-toxic [12]. To reduce manufacturing costs, PCL may be blended with starch-for example, to make trash bags. By blending PCL with fiber-forming polymers (such as cellulose), hydroentangled nonwovens (in which bonding of a fiber web into a sheet is accomplished by entangling the fibers by water jets), scrub-suits, incontinence products, and bandage holders have been produced [3].

1.3 Theoretical study survey of this thesis

Currently, there has been increasing interest in materials derived from biorenewable resources as environmentally sustainable alternatives to petrochemical-derived products. Among the most prominent examples are PLA and PCL which have been studied intensively due to their biodegradability, biocompatibility and permeable properties. Their potential applications have shown in a variety of field such as biomedical and pharmaceutical industries as a resorbable implant material and a vehicle for controlled drug delivery [22, 43, 44].

For example in theoretical study of PCL, in 2009, Liu *et al.* [28] investigated the monomer insertion mechanism of ROP polymerization of CL with yttrium alkoxide initiators using density functional theory at B3LYP method with mix basis set. The mix basis set was assigned by 6-31G(d) for all non-metal atoms and

LANL2DZ for yttrium atom. The results showed that the monomer insertion was completed by CL ring-opening via acyl-oxygen bond cleavage. The rate-determining step was the nucleophilic attack of the alkoxide on the *exo*-ring carbonyl carbon of the monomer. Afterwards, the same group headed by Ling (2009) *et al.* [26] also used the same method as previous work on the investigation of ROP of cyclic esters initiated by scandium-alkoxide. They found that the transition states corresponding to monomer addition indicate a penta-coordinate scandium and have nearly the same energies for all of their interested monomers. The dipole moments of the intermediates and transition states are lower than those of reactants predicting faster reaction rate in low polarity solvents.

For other theoretical studies, Eguiburu *et al.* (1999) [45] studied the ROP of *L*-lactide initiated by aluminum mono/trialkoxides using quantum chemical calculation. The differences of initiator on alkoxide groups were compared by HF and B3LYP method. The results showed that five-fold of aluminum trialkoxides was more catalytic than aluminum monoalkoxide corresponding with the experiment.

In 2001, Ryner *et al.* [20] studied the ROP mechanism of 1,5-dioxepan-2-one (DXO) and LL initiated by tin(II) 2-ethylhexanoate [$Sn(Oct)_2$] with methanol by density functional theory at B3LYP level. They found that the rate determining step in the ROP was the nucleophilic attack of the alkoxide on the carbonyl carbon of the monomer. The activation energy for the ROP of DXO with $Sn(Oct')_2$ was determined to be 19.8 kcal/mol and for L-lactide 20.6 kcal/mol.

Afterwards in 2002, the same group headed by von Schenck *et al.* [21] demonstrated the theoretical study of ROP mechanism of DXO and glycolide with tin(II) alkoxides ($SnMe_3OMe$, $SnMe_2(OMe)_2$) and Al(III) alkoxide ($AlMe_2OMe$)

initiators using B3LYP method. The results revealed two principle reaction steps of coordination-insertion mechanism. At first step, the alkoxide of the initiators perform a nucleophilic attack on the carbonyl carbon and the carbonyl bond is broken. The second step involves the acyl-oxygen cleavage of the monomer. It was found that the more electrophilic initiators the faster polymerization of cyclic esters.

In 2005, Marshall *et al.* [46] studied the ROP mechanism of *rac*-lactide initiated by single-site-β-diketiminate metal complexes using B3LYP method. They found that the more steric effect of ligand increases, the more reaction barrier height also increases. And In 2006, Dove *et al.* [43] studied the same reaction as their previous work but they changed the metal center from Mg to Sn. The results indicated that the difference of metal center has an effect on rate-determining step in ROP. The insertion of first lactide monomer into the tin(II) alkoxide bond is facile, with the induction period arising from a slower insertion of the second (and possibly third and fourth) monomer unit.

Moreover, the detailed information from quantum chemical calculation can be applied to obtain the rate law and rate constant using transition state theory (TST). In 2008, Khanna *et al.* [47] studied molecular modeling of the polymerization initiation mechanism using different initiators a) H_2SO_4 for polycondensation, b) aluminium isopropoxide for coordination-insertion mechanism, c) methyl triflate for cationic ROP and d) potassium methoxide for anionic ROP by B3LYP method. They found that the enthalpy changes of aluminium isopropoxide initiator matched with Ryner's work [20]. And the rate constants of H_2SO_4 initiator were in good agreement with experimental results reported by Wang *et al.* [48].

From the literatures reviews [20, 21, 26, 28, 43, 45-48], it is shown that the theoretical study is one alternative and important way for understanding chemical reaction. Especially for quantum chemical calculations, it can be used as a powerful tool to obtain detailed information on the ROP of coordination-insertion using metal alkoxides as initiators. Therefore, we decided to use this well-know and well-accepted method for our work.

1.4 Thesis objectives

Because tin(II) alkoxide initiators have an important role for ROP mechanism of cyclic ester, Punyodom *et al.* [13] have developed the true initiators and also proposed the new mechanism. From their experiment, the synthesis was achieved on $Sn(OR)_2$ series where R = *n*-C_4H_9, *i*-C_4H_9, *t*-C_4H_9, *n*-C_6H_{13} and *n*-C_8H_{17}. These new initiators can completely control the ROP polymerization of CL and give the high MW polymers. Moreover, their kinetic study from dilatometry method at 120 °C of ROP showed very interesting results. All initiators performed high reactivity and fast reaction as a first order rate with respected to monomer concentration. However, there is no clear description of the ROP mechanism and the effects of different R group on the initiators are not well understood. For more understanding of this factor, the ROP polymerization mechanism of CL with tin(II) alkoxide initiators will be investigated by quantum chemical calculations.

Geometries, energies and vibrational frequencies of all stationary along the reaction profiles will be calculated using density functional theory at B3LYP level with mixed basis set. The calculated results will be used to predict the energy profile and compare the effects of different of R groups on initiators. Furthermore,

information derived from energy profile will be used to calculate the rate constants of different initiators using transition state theory. The objectives of this thesis are showed below:

I. To theoretically study the ring-opening polymerization (ROP) mechanism of ε-caprolactone with tin(II) alkoxide initiators

II. To compare the reaction barrier heights using different types of tin(II) alkoxide initiators

III. To calculate rate constants of reactions and compare with experimental

The knowledge from this research might be applied and usefulness for the other study especially in the guideline of experiment and the application of industrial catalyst.