CHAPTER 2

POLY(L-LACTIDE)

2.1 INTRODUCTION [10-11, 13]

Polylactide (PL) in its various stereoisomeric forms is a biodegradable aliphatic polyester which is finding increasing use in medical and industrial applications. Polylactide has the advantages of being not only biodegradable but also renewable since the raw material, lactic acid, is produced by microbial fermentation of biomass. Therefore, nowadays PL is one of the polymers widely accepted to play a major role as a future packaging material.

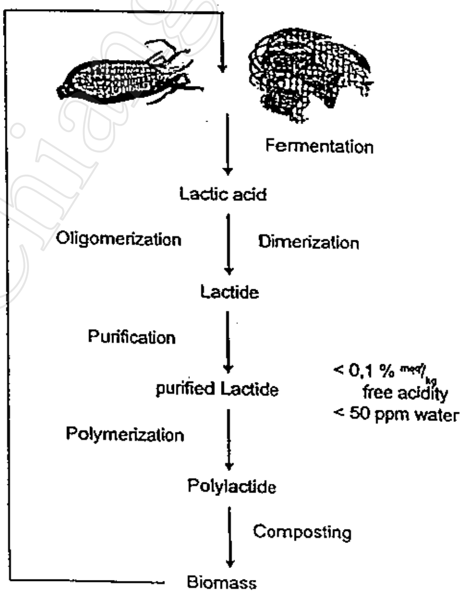
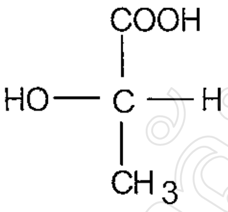
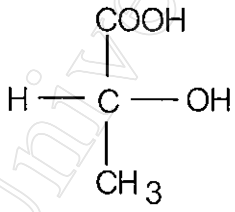


Figure 2.1 Nature cycle for the production of polylactide.

Lactic acid is a α-hydroxy acid which possesses one asymmetric carbon and exists in two optically active enantiomeric forms, referred to as L-(+)- and D-(-)-lactic acid, and as an optically inactive racemic mixture of the two, referred to as DL-lactic acid. The two enantiomeric forms are represented in the Fischer projection formulae shown below:

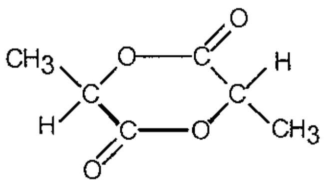


L-(+)-lactic acid

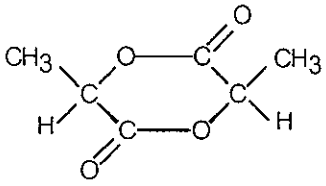


D-(-)-lactic acid

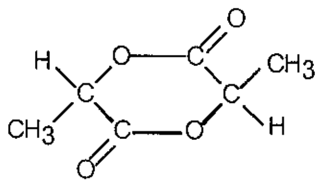
Lactide, the cyclic ester of lactic acid, has four stereoisomeric forms: L(-)-lactide, D(+)-lactide, *meso*-lactide, and DL-Lactide. The L(-) and D(+) forms are optically active while the less common *meso* form, which has both L(-) and D(+) chirality within the same molecule, is optically inactive. The DL form is a racemic mixture of the D(+) and L(-) forms and is therefore also optically inactive.



L(-)-Lactide

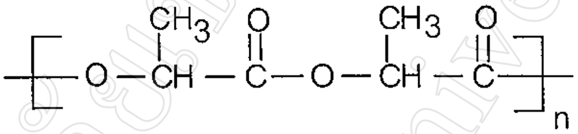


D(+)-Lactide



meso-Lactide

Consequently, polylactide can be found in three stereoisomeric forms: poly(L-lactide) (PLL), poly(D-lactide) (PDL) and poly(D,L-lactide) (PDLL). The polymers derived from the optically active L- and D- monomers are semi-crystalline, whereas the optically inactive poly(D,L-lactide), from a racemic mixture of the L- and D- monomers, is always amorphous [10,13].



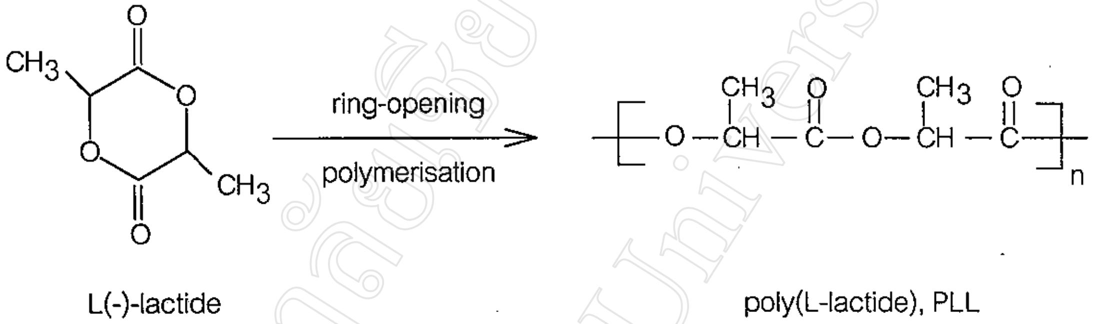
$$\left[-O-\overset{CH_3}{\overset{|}{C}H}-\overset{O}{\overset{||}{C}}-O-\overset{CH_3}{\overset{|}{C}H}-\overset{O}{\overset{||}{C}}- \right]_n$$

polylactide

The name ' polylactide' is therefore a general name which defines only the chemical structure of the repeating unit but not the stereochemistry of the polymer chain. In this project, attention is focussed especially on poly(L-lactide), PLL, synthesized from L-(+)-lactic acid via L-(-)-lactide.

2.2 PROPERTIES OF POLY(L-LACTIDE), PLL [8,15]

Poly(L-lactide) is synthesized from L(-)-lactide monomer via ring-opening polymerization with a suitable initiator.



PLL is a biodegradable polymer having a melting point (T_m) of approximately 175-178 °C and a glass transition temperature (T_g) of approximately 60-65 °C. The value of the heat of fusion of 100% crystalline PLL is 93.7 J/gram, while the heat of fusion for commercial products has been reported as low as 30 J/gram (% crystallinity $\approx$ 35%). The polymer's specific gravity is approximately 1.2-1.3 and it is easily soluble in a range of common organic solvents such as chloroform, benzene and tetrahydrofuran. In its more highly crystalline form, PLL has a very high tensile strength and low elongation, and consequently has a high modulus that makes it suitable for load-bearing biomedical applications such as in orthopaedic bone fixation. The biodegradation time of PLL is much slower than that of amorphous PDLL, requiring more than 2 years to be completely absorbed in the human body.

In the polymerization of L-lactide, temperatures in the range of 105-185 °C are typical. When polymerization temperatures are less than the melting point of the polymer (~175 °C), crystallization of the polymerisate occurs, resulting in solid-state polymerization, which has been useful in forming very high-molecular-weight polymers with molecular weights of ~1,000,000 Daltons. The polymerization reaction is normally catalyzed by an organotin compound such as stannous octoate or stannic chloride dihydrate. However, other catalysts can also be used.

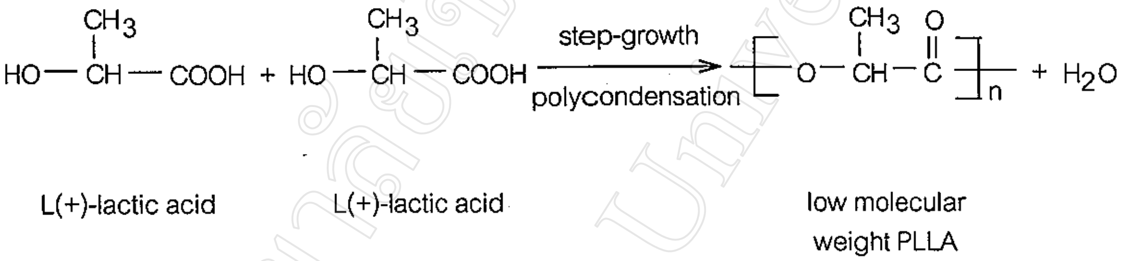
2.3 SYNTHESIS OF POLY(L-LACTIDE) [11,16]

The polymerization of L(-)-lactide has been successfully carried out using bulk polymerization, solution polymerization and suspension polymerization techniques. Each of these methods has its advantages and disadvantages, but generally bulk polymerization is considered to be the simplest and most reproducible method, even though the high temperatures used may cause some thermal degradation of the polymer to occur during the reaction.

Generally, L(-)-lactide is synthesized in a two-step process: (1) step-growth polycondensation of L(+)-lactic acid, followed by (2) thermal decomposition of the resulting low molecular weight poly(L-lactic acid) to the cyclic diester lactide.

2.3.1 Step-growth Polycondensation of L(+)-Lactic Acid [11, 17-18]

The step-growth polycondensation of L(+)-lactic acid yields only low molecular weight ($\overline{M}_n < 5000$) poly(L-lactic acid), PLLA. Therefore, high molecular weight poly(L-lactide), PLL, which has the same chemical structure as PLLA, has to be synthesized via L(-)-lactide as the monomer rather than directly from L(+)-lactic acid.



$$HO-\overset{CH_3}{\overset{|}{CH}}-COOH + HO-\overset{CH_3}{\overset{|}{CH}}-COOH \xrightarrow[\text{polycondensation}]{\text{step-growth}} \left[O-\overset{CH_3}{\overset{|}{CH}}-\overset{O}{\overset{\|}{C}} \right]_n + H_2O$$

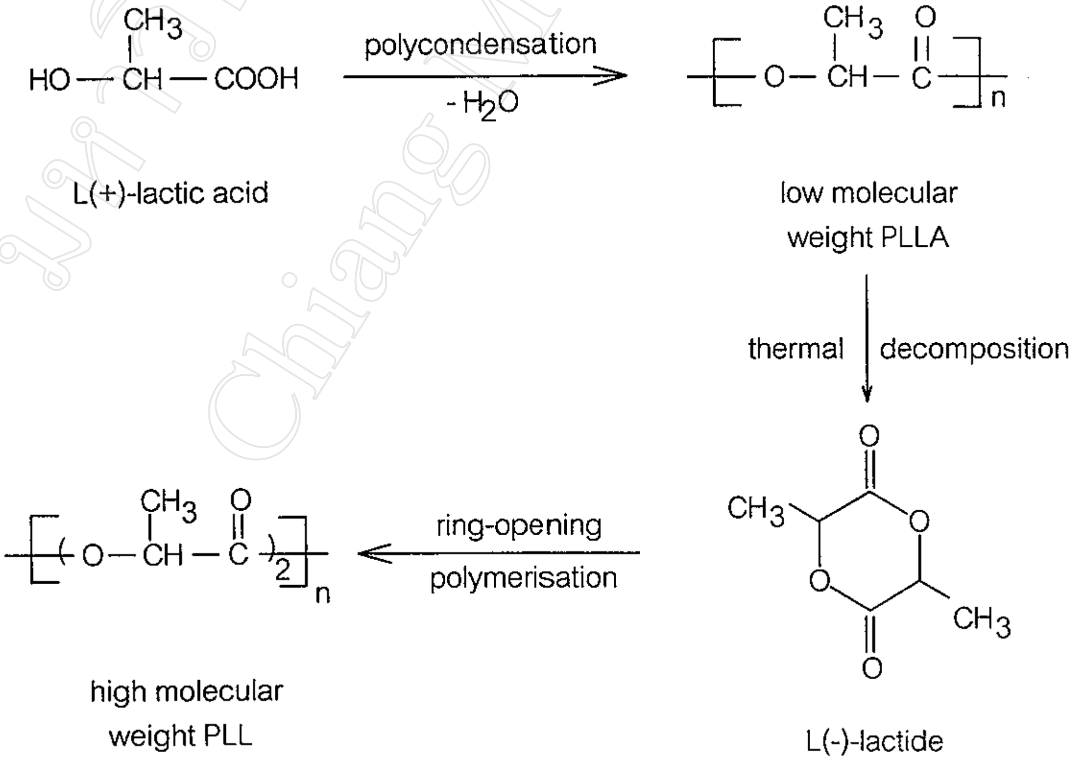
The practical drawbacks of polycondensation are well known: high temperatures, long reaction times and the continuous removal of water are required to produce high molecular weight chains. Even though conversion of the hydroxyl and acid groups is close to completion, any departure from the reaction stoichiometry has a detrimental effect on the chain length. Therefore, the final polymer molecular weight is generally low and the mechanical properties of the polymer are correspondingly poor.

However, in recent years, it has been reported that high molecular weight PLLA can be synthesized by the one-step polycondensation of L-lactic acid if appropriate azeotropic solvents are employed. Alternatively, chain extenders which connect the OH and COOH end-groups of low molecular weight PLLA can be used to increase the molecular weight. Effective chain extenders in the reaction with polyesters were found to be ethylene carbonate, heterocyclic compounds and diisocyanates, such as hexamethylene diisocyanate (HDI) [19].

2.3.2 Ring-Opening Polymerization of L(-)-Lactide [11, 16-17]

2.3.2.1 Sequence of Reactions

The ring-opening polymerization of L(-)-lactide is the preferred polymerization route for high molecular weight poly(L-lactide) because this method is free from the limitations of polycondensation. Under relatively mild conditions, high molecular weight PLL can be prepared in short periods of time with complete monomer conversion. Provided that propagation is relatively free from competitive transfer and termination reactions, the final polymer molecular weight is predictable from the monomer-to-initiator molar ratio.

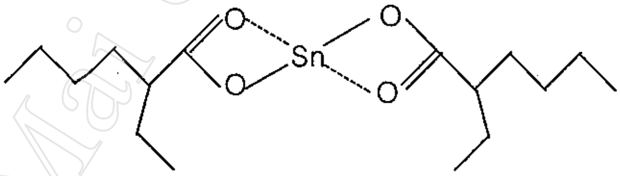


2.3.2.2 Type of Initiator/Catalyst Used [11,16-17,20]

The ring-opening polymerization of L(-)-lactide is known to be promoted by Lewis acid type catalysts such as metals, metal halogenides, oxides, aryls and carboxylates. The main representative of this group of catalysts is tin(II)-bis-(2-ethyl hexanoate), commonly known as stannous octoate, $Sn(Oct)_2$.

Stannous octoate has been used as a standard catalyst mainly because it is highly effective with extremely low toxicity. Indeed, it has been accepted by the FDA (Food and Drug Administration, Washington DC) in the USA as a food additive.

$Sn(OOCC_7H_{15})_2$ =



stannous octoate, $Sn(Oct)_2$ = tin(II)-bis-(2-ethyl hexanoate)

The apparent popularity of $Sn(Oct)_2$ as a coordination-insertion type initiator/catalyst in cyclic ester polymerization is based on a range of advantages, the main ones being that it is:

1. A highly efficient initiator/catalyst that allows almost quantitative conversion even at monomer : catalyst mole ratios as high as 10^4 : 1.
2. As it contains ester groups itself, it is more easily miscible with cyclic ester monomers.
3. Easy to handle with no special storage precautions.

4. Relatively inexpensive.
5. Importantly for biomedical polyesters, it has an extremely low level of human toxicity compared with other heavy metal salts to the extent that it is now a permitted food additive.

On the other hand, $Sn(Oct)_2$ does also have one or two disadvantages, namely that:

1. Commercial $Sn(Oct)_2$, typically 95% pure, commonly contains octanoic acid as an impurity which is difficult to remove.
2. It is hygroscopic in contact with air and can easily hydrolyze to a hydroxy derivative and more octanoic acid, for example as follows:

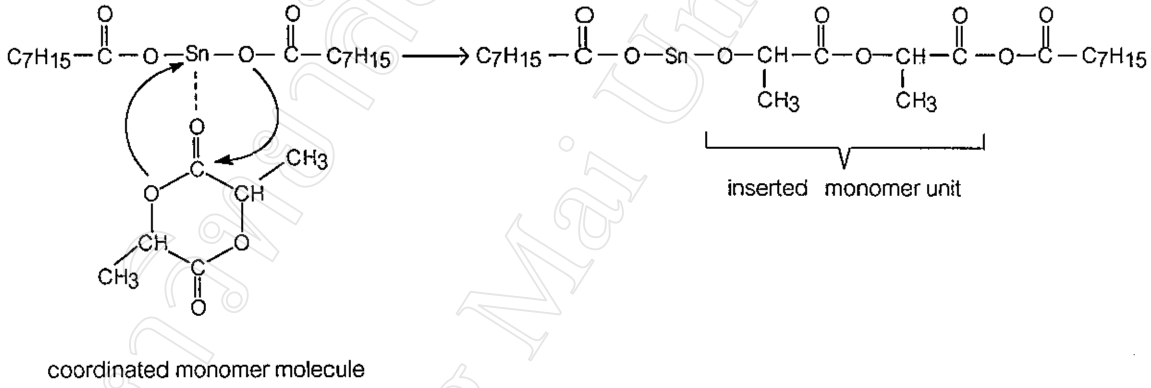
$$C_7H_{15}COO-Sn-OOCC_7H_{15} + H_2O \rightleftharpoons C_7H_{15}COO-Sn-OH + C_7H_{15}COOH$$

This hydroxy derivative may, in turn, conceivably react further with $Sn(Oct)_2$ to yield a further derivative as:

$$\begin{array}{c} C_7H_{15}COO-Sn-OH \quad + \quad C_7H_{15}COO-Sn-OOCC_7H_{15} \\ \upharpoonleft\downharpoonright \\ C_7H_{15}COO-Sn-O-Sn-OOCC_7H_{15} \quad + \quad C_7H_{15}COOH \end{array}$$

These various derivatives of $Sn(Oct)_2$ are probably also active initiating species to greater or lesser extents than the $Sn(Oct)_2$ itself, a complication which tends to obscure the exact nature of $Sn(Oct)_2$-initiated polymerizations.

Consequently, the actual mechanism by which $Sn(Oct)_2$ acts as a coordination - insertion initiator has been the subject of much debate in the polymer literature. As the word 'coordination' suggests, the initiation step involves coordination of the cyclic ester monomer to the Sn atom through the exocyclic (C=O) oxygen atom. This is then followed by ring-opening and monomer insertion into the Sn-O bond accompanied by cleavage of the monomer acyl-oxygen bond. The polymerization proceeds by successive insertions of coordinated monomer molecules into the Sn-O bond. In the case of L(-)-lactide, this initiation step can be written as:



2.3.2.3 Nature of the Reaction Conditions Employed [17]

Amongst the reaction variables which need to be carefully controlled in the ring-opening polymerization of cyclic esters are:

(a) <u>Temperature</u> has a great influence on the reaction rate and on the nature of the products formed. The profile of monomer conversion with time at different temperatures shows that an increase in temperature usually results in an expected acceleration of the polymerization rate and in an increase in $\overline{M}_n$. However, there are exceptions to these trends.

(b) <u>Pressure</u> also has some influence on the reaction rate. For example, γ-butyrolactone cannot polymerize at normal pressure but polymerization can be achieved at 20,000 atm and 160 °C to yield stable polymer of modest molecular weight ($\overline{M}_n$ = 1000 – 3000). Similar results can be obtained with γ-valerolactone although here polymerization is also possible at 1 atm and 60 °C. It is possible that, in this latter case, crystallization of the polymer makes a crucial negative contribution to ΔG_p.

(c) <u>Time</u> obviously influences the reaction rate, % conversion, and molecular weight of the polymer formed, as in any addition-type polymerization mechanism.

(d) <u>Purity of the reagents</u> is a basic prerequisite to achieving a high degree of polymerization. The reagents should not contain any impurities that initiate additional chains or hinder the build up of chains by forming non-reactive end-groups.

(e) <u>Method of Mixing the Monomer and the Initiator</u>: there are two methods for doing this. In the first method, the monomer and the initiator are mixed together at room temperature before heating to the polymerization temperature. This contrasts with the second approach in which the monomer is pre-heated by itself up to the polymerization temperature and the initiator then injected rapidly with efficient stirring. It is often found in practice that these different methods lead to differences in % conversion and molecular weight distribution. It may also have an effect on the monomer sequence distribution in random copolymers. In copolymerization, sequential monomer addition is another procedural variation.

2.4 BIODEGRADABILITY IN THE HUMAN BODY [8, 15, 21]

Once implanted, a biodegradable polymeric device should maintain its mechanical properties until it is no longer needed and then be absorbed and excreted by the body, leaving no trace. Simple chemical hydrolysis of the hydrolytically unstable ester bonds in the polymer backbone is the prevailing mechanism for polyester biodegradation. This occurs in two phases. In the first phase, water penetrates the bulk of the device, preferentially attacking the chemical bonds in the amorphous phase and converting long polymer chains into shorter water-soluble fragments. Because this occurs in the amorphous phase initially, there is an initial reduction in molecular weight without a loss in physical properties, since the device matrix is still held together by the crystalline regions. This reduction in molecular weight is then followed by a reduction in physical properties, as water begins to fragment the device.

In the second phase, enzymatic attack and metabolism of the fragments occurs, resulting in a rapid loss of polymer mass. This type of degradation, where the rate at which water penetrates the device exceeds that at which the polymer is converted into water-soluble materials (resulting in erosion throughout the device), is called 'bulk erosion'. All of the commercially available synthetic polyester devices and sutures degrade by bulk erosion.

A second type of biodegradation known as 'surface erosion' occurs when the rate at which water penetrates the device is slower than the rate of conversion of the polymer into water-soluble materials. Surface erosion results in the device thinning over time while maintaining its bulk integrity. Polyanhydrides and polyorthoesters are examples of materials that undergo this type of erosion, where the polymer is hydrophobic but the chemical bonds are still susceptible to hydrolysis. In general, this process is referred to in the literature as bioerosion rather than biodegradation.

The major route of in the physiological breakdown of poly(L-lactide) is via simple (non-enzymatic) hydrolysis. This occurs at the ester bonds which are a weak point for hydrolysis by water in the extracellular fluid. This leads to random chain scission and generates the low molecular weight products which then can be metabolized through the Krebs Cycle and eventually eliminated through the respiratory and excretory systems. A representation of this simple hydrolysis mechanism for poly(L-lactide) is shown in Figure 2.2 below.

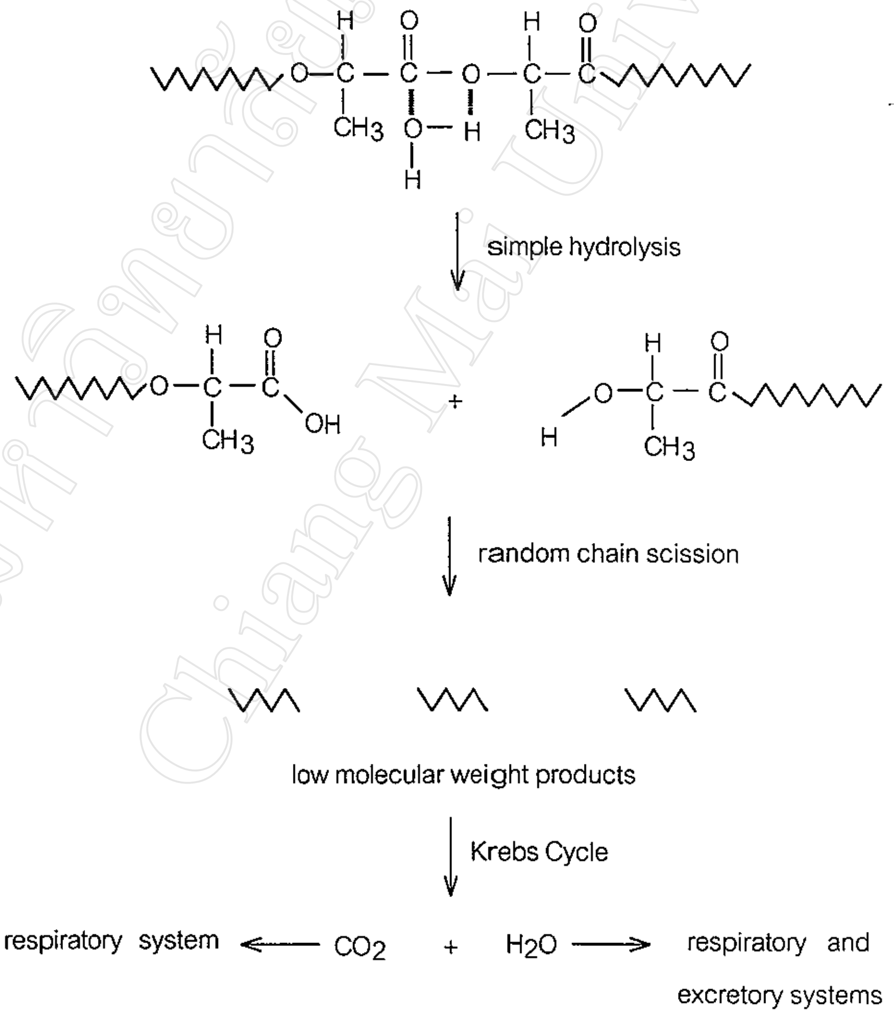


Figure 2.2 Simple hydrolysis of poly(L-lactide) leading to its biodegradation pathway.