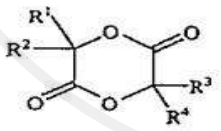
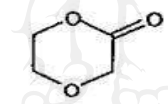
CHAPTER 1
INTRODUCTION

1.1 Cyclic Esters [1-6]

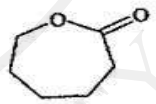
Polyesters can be synthesized from many cyclic ester monomers such as glycolide (G), L-lactide (LL), caprolactone (CL), trimethylene carbonate (TMC), *p*-dioxanone (PD), 2-methyl glycolide (MG), 2,2-dimethyl glycolide (DMG), 1,5-dioxepan-2-one (DOX-5), 1,4-dioxepan-2-one (DOX-4), 3,3-dimethyltrimethylene carbonate (DMTMC), glycosalicylate (GS), and morpholine-2,5-dione (MD). Figure 1.1 shows the structures of these monomers [1] of which L-lactide (LL), glycolide (G) and ε-caprolactone (CL) are the most commonly used in ring-opening polymerisation (ROP).



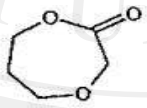
(G) : $R^1 = R^2 = R^3 = R^4 = H$
(MG) : $R^1 = CH_3 : R^2 = R^3 = R^4 = H$
(L) : $R^1 = R^3 = CH_3 : R^2 = R^4 = H$
(DMG) : $R^1 = R^2 = CH_3 : R^3 = R^4 = H$



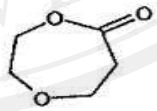
(PD)



(CL)



(DOX-4)



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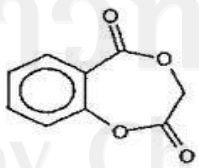
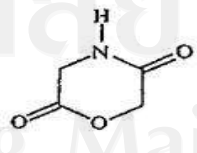


(GS)

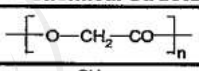
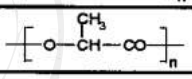
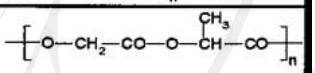
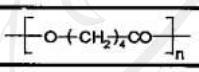
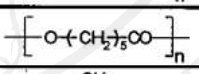
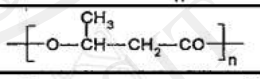
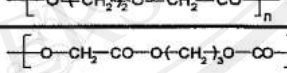


(MD)

Figure 1.1 : Chemical structures of some cyclic ester monomers [1].

Aliphatic polyesters, prepared by the ring-opening polymerisation (ROP) of cyclic ester-containing monomers, are versatile polymers having good mechanical properties, hydrolysability, and biocompatibility. These attributes make them leading candidates in biomedical and pharmaceutical applications such as absorbable sutures, nerve guides, bone fixation devices and drug delivery matrices [2,3,6], some examples of which are given in Table 1.1. An important advantage of synthetic polymers, including these polyesters, is that their physical and chemical properties can be varied over a wide range by, for example, advanced macromolecular architecture and copolymerisation [4].

Table 1.1 : Some biodegradable polyesters used in medicine [5].

Polymer Name	Trade Name	Application	Chemical Structure
Poly(glycolic acid)	DEXON	SS	
Poly(DL-lactic acid)	-	DRM	
Poly(glycolic-co-lactic acid)	VICRYL	SS	
Poly(δ-valerolactone)	-	DRM	
Poly(ε-caprolactone)	-	DRM	
Poly(hydroxy butyrate)	BIOPOL	DRM	
Poly(p-dioxanone)	PDS	SS	
Poly(glycolic acid-co-trimethylene carbonate)	MAXON	SS	

<u>Application</u> :

SS = surgical suture

DRM = drug release matrix

1.2 Ring-Opening Polymerisation [4,7]

Ring-opening polymerisation (ROP) can be used to prepare polymers which cannot easily be prepared by other methods, such as poly(phosphene)s and polyesters. The driving force for the ring-opening of cyclic monomers is the relief of bond-angle strain and/or steric repulsion between atoms crowded into the centre of the ring. Therefore, as for other types of polymerisation, the enthalpy change for ring-opening is negative. Relief of bond angle strain is most important for 3- and 4-membered rings, whereas for 8- to 11-membered rings it is the relief of steric crowding that matters. The enthalpic effects are much smaller for 5-, 6- and 7-membered rings and such monomers are more difficult to polymerise. Usually, ring-opening is initiated by acids, bases or coordination-insertion type initiators and polymer molecules are formed by chain polymerisation mechanisms which most commonly involve sequential additions of monomer to the active centres. However, the precise mechanism of polymerisation depends greatly upon the initiator, monomer and polymerisation conditions. Polylactones and polylactides can be prepared by two difference approaches: (a) by the polycondensation of hydroxycarboxylic acids or (b) by the ROP of cyclic esters. The polycondensation technique is less expensive than ROP but it is difficult to obtain high molecular weight polymers, to achieve specific end-groups, and to prepare well-defined copolyesters. Hence, ROP is the more widely used technique for the synthesis of these polymers. The ROP of lactones and lactides has been thoroughly investigated during the last 40 years due to its versatility in producing a variety of biomedical polymers in a controlled manner. It was Carothers and co-workers who first extensively explored the ROP technique for lactones, anhydrides, and carbonates [4]. Since then the method has been applied to a diversity of monomers to produce all types of polymers and a wide range of initiator and catalyst systems have been developed. In many cases, the resulting polymers exhibit useful properties as engineering materials.

There are several reasons for studying the ROP of cyclic esters: first, to exploit the potential of synthetic polymer chemistry to prepare a variety of polymers with control of the major variables affecting polymer properties. Experimental conditions have to be optimized in order to find the best polymerisation system for

a desired technical or industrial process. Factors such as economy, toxicology, and technical apparatus development are also important. A second reason for studying ROP is to enable various advanced macromolecules including homopolymers with well-defined structures or end-groups to be prepared, as well as copolymers with different architectures such as block graft, or star copolymers. The physical, mechanical, and degradation properties of these various macromolecules are studied to determine the underlying structure-property relationships. The third reason for studying these kinds of systems is that they are valuable models for the examination of the kinetics and mechanisms of elementary reactions in polymerisation.

Polylactones and polylactides of high molecular weight are exclusively produced by the ROP of the corresponding cyclic ester monomers. A polyester is formed when the cyclic ester is reacted with a suitable initiator, as shown for example in Figure 1.2.

Figure 1.2 : ROP of a cyclic ester monomer using a metal alkoxide (M-OR´) as the initiator [4].

Each macromolecule formed generally contains one chain end terminated with a functional group originating from the termination reaction and one terminus end-capped with a functional group originating from the initiator. By altering the initiator and the termination reaction, the nature of the functional groups can be varied to fit the application of the polymer. Functional groups accessible to post-polymerisation reactions can also be introduced into the polymer structure in this way. The ring-opening reaction can be performed either as a bulk polymerisation or in solution, emulsion, or dispersion. Problems associated with condensation polymerisation, 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.

Depending on the initiator, the polymerisation proceeds according to three main types of reaction mechanisms, namely: cationic, anionic, and coordination-insertion. However, radical, zwitterionic and active hydrogen initiation are also possible but such reactions are not used to any great extent. Since this present thesis is concerned specifically with tin(II) alkoxide type initiators, which initiate ROP via the coordination-insertion mechanism, this particular mechanism is described in more detail in the following sections 1.2.3 and 1.3.

1.2.1 Cationic Mechanism [4]

Among the cyclic esters, 4-, 6- and 7-membered rings form polyesters when reacted with cationic initiators [22–25]. Cationic ROP involves the formation of a positively charged species which subsequently attacks a monomer resulting in ring-opening through an S_N2-type process, as shown in Figure 1.3.

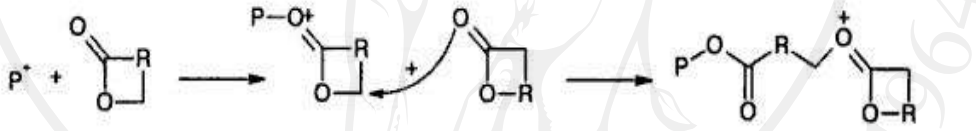


Figure 1.3 : Reaction pathway for the ROP of a cyclic ester by cationic initiation [4].

However, cationic ROP is difficult to control and often only low molecular weight polymers are formed. When the bulk and solution polymerisation of 1,5-dioxepan-2-one (DXO) with cationic initiators were studied, the highest molecular weight achieved was about 10,000 [23]. More detailed reviews on cationic ROP have been published by Penczek and co-workers [26, 27].

1.2.2. Anionic Mechanism [4]

Anionic ROP of cyclic ester monomers takes place by the nucleophilic attack of a negatively charged initiator species on the carbonyl carbon or on the carbon atom adjacent to the acyl oxygen, resulting in a linear polyester, as shown in Figure 1.4 [28, 29]. The propagating species is negatively charged and is counter-balanced with

a positive ion. Depending on the nature of the ionic propagating chain end and the solvent, the reacting complex varies from completely ionic to almost covalent.

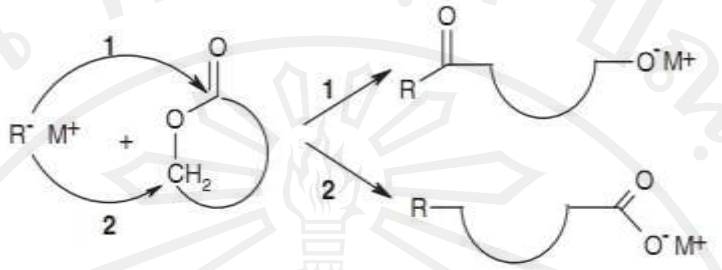


Figure 1.4 : Reaction pathway for the ROP of a cyclic ester by anionic initiation [4]. Ring-opening of monomer by (1) acyl-oxygen bond cleavage and (2) alkyl-oxygen bond cleavage

One of the best controlled methods leading to high molecular weight polymers is anionic ROP carried out in a polar solvent. The Jedlinski group developed living anionic ROP methods for 4- and 5-membered ring lactones and have reported well-defined polymers and copolymers of high molecular weight [30]. The anionic ring-opening of 4-membered rings (β-lactones) occurs through alkyl-oxygen or acyl-oxygen cleavage giving a carboxylate or alkoxide [31]. Larger lactones, such as ε-caprolactone (ε-CL) or lactide, react only by an attack of the anion on the carbonyl carbon atom with acyl-oxygen scission and the formation of an alkoxide as the growing species [32, 33]. A problem often associated with anionic ROP is the extensive back-biting such that, in some cases, only polyesters of low molecular weight are obtained.

1.2.3 Coordination-Insertion Mechanism [4,6,7]

Pseudo-anionic ROP is often referred to as coordination-insertion ROP. It has been extensively used for the preparation of aliphatic polyesters with well-defined structures and architectures. Among this group of initiators, the following compounds are the most common: metal halide and alkyls and metal alkoxides, mostly those of aluminium, zinc, magnesium, titanium, zirconium, tin and combinations of bimetallic alkoxides. The most widely used initiators are various

aluminium and tin alkoxides and carboxylates with vacant "*d*" orbitals. These initiators are capable of producing stereoregular polymers of narrow molecular weight distribution 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., alcohols) as coinitiators. If no active hydrogen compound is added, the actual coinitiating species may be hydroxy-containing impurities.

The first step of the coordination-insertion mechanism occurs when one of the exocyclic oxygens of the cyclic ester becomes temporarily coordinated with the metal atom of the initiator, increasing the nucleophilicity of the alkoxide part of the initiator as well as the electrophilicity of the monomer's carbonyl group. In the second step, the acyl-oxygen bond (between the carbonyl group and the endocyclic oxygen) of the monomer is broken and the monomer is inserted into the metal-oxygen bond of the initiator. A schematic presentation of this coordination-insertion mechanism is shown in Figure 1.5. The alkoxide end of the initiator becomes a dead chain end while the chain growth of this "living" polymerisation continues as additional monomer molecules are opened and inserted into the M-O bond between the metal atom and its adjacent oxygen atom. The reaction is terminated by hydrolysis forming a hydroxyl end group. With functional alkoxy-substituted initiators, macromers with end-groups active in post-polymerisation reactions are produced.

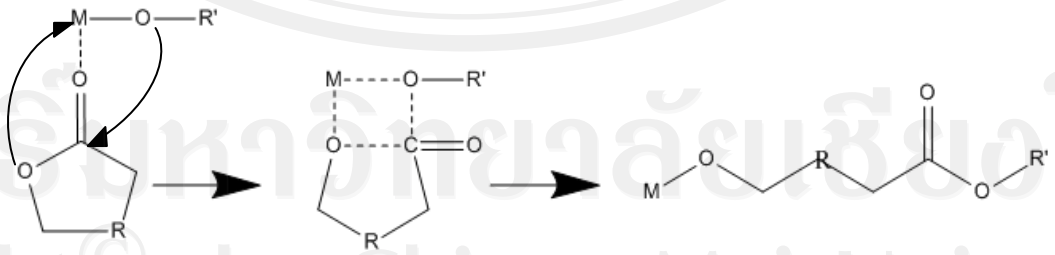


Figure 1.5 : Reaction pathway for the ROP of a cyclic ester by the coordination-insertion mechanism [3].

1.3. Coordination-Insertion Initiators [4, 21]

The synthesis of novel initiators and the ROP of existing or new monomers and macromers substituted with functional groups provide a very interesting and promising strategy for producing structurally advanced macromolecules. A large variety of organometallic compounds such as metal alkoxide and metal carboxylates have been studied as coordination-insertion initiators in order to achieve effective polymer synthesis. Examples the most widely used of some of initiators for the ROP of lactones and lactides are shown in Figure 1.6.

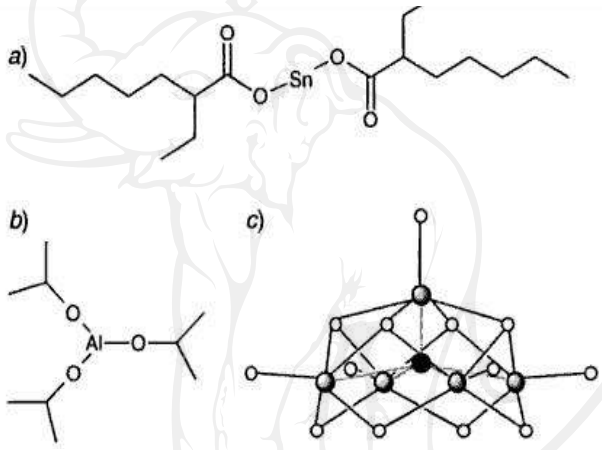


Figure 1.6 : Chemical structures of some coordination-insertion initiators used in the ROP of lactones and lactides [4].
(a) stannous octoate, (b) aluminium isopropoxide, (c) lanthanide isopropoxide (where the lanthanum atoms are represented by gray circles and the oxygen atoms by white circles; the black circle represents the bridging oxygen atom connecting all of the lanthanum atoms; alkyl groups are omitted for clarity)

1.3.1 Tin(II) 2-Ethylhexanoate (Stannous Octoate) [4]

Tin (II) 2-ethylhexanoate, commonly referred to as stannous octoate, $Sn(Oct)_2$, is a frequently used initiator in the ROP of lactones and lactides [6]. It is a very effective and versatile initiator which is easy to handle and is soluble in common

organic solvents and lactones. It also has the advantage, as far as its use in the preparation of biomedical polymers is concerned, that the American Food and Drug Administration (FDA) has approved it as a food additive. The mechanism of polymerisation has been widely discussed. Despite several proposals over a long period of time, it is only recently that the ROP mechanism has been elucidated. When using $Sn(Oct)_2$ in conjunction with an added alcohol, $Sn(Oct)_2$ is not the actual initiator since the molecular weight does not depend on the monomer-to-$Sn(Oct)_2$ molar ratio. Instead, the widely accepted mechanism is a coordination-insertion mechanism where the OH group from the alcohol is thought to coordinate to the $Sn(Oct)_2$ forming the initiating tin alkoxide complex. Investigations of the coordination-insertion mechanism have resulted in two basic types of reaction pathways being proposed. Since $Sn(Oct)_2$ is also a strong transesterification agent, copolymers normally have a randomized microstructure. An increase in reaction temperature or reaction time increases the amount of transesterification. The ROP of lactide with $Sn(Oct)_2$ is fairly slow and it is desirable for economic and commercial reasons to increase the rate of polymerisation.

1.3.2 Aluminium Tri-isopropoxide [4]

ROP initiated with aluminium tri-isopropoxide has been extensively investigated by several research groups since it yields well-defined polymers through living polymerisation. A living polymerisation is a chain polymerisation which proceeds in the absence of the kinetic steps of termination or chain transfer. Polymerisation with aluminium tri-isopropoxide is assumed to proceed through the coordination-insertion mechanism. The mechanism leads to cleavage of the acyl-oxygen bond of the monomer and the metal-oxygen bond of the propagating species. Propagation is characterised by the almost total absence of side-reactions such as transesterification, the main rearrangement of the polymer occurring when the monomers are completely comsumed. The initiator is active at low temperatures and is preferentially used in solution.

Most metal alkoxides are aggregated both in their pure state and in solution and, as a result, an induction period during which the initiator is rearranged to form

the active species often characterises the polymerisation. The type and size of the aggregates depend on the solvent polarity, the nature of the alkyl substituent and the presence of coordinative ligands such as amine and alcohol. The groups involved in coordinative aggregation are not active in propagation.

Recently, systems have been developed where the aluminium alkoxide is covalently bonded to solid porous silica. This system takes advantage of the exchange reaction between the alkoxide and the hydroxy-terminated free molecule to produce a catalytic process, i.e., to produce a larger number of polymer chains than aluminium complexes present. The initiator used can easily be recovered by filtration and recycled. Moreover, the polymers obtained are free from metal residues.

1.3.3 Lanthanum Alkoxides [4]

The ROP of lactones and lactides using lanthanum alkoxide-based initiators is a relatively recent discovery. In general, the activity of these initiators is much higher than that determined for aluminium alkoxides, especially in lactide polymerisation, giving polymers of relatively high molecular weight and narrow molecular weight distribution.

1.3.4 Tin Alkoxides [21]

Tin alkoxides have also been preformed and used as ROP initiators. Alkyl-substituted tin(IV) alkoxides have been more commonly used than their tin(II) counterparts. Compared with tin(IV) monoalkoxides (R'_3SnOR), tin(IV) dialkoxides ($R'_2Sn(OR)_2$) are preferred because of their higher reactivity. One drawback of tin(IV) alkoxides compared with the aluminum alkoxides is the broader molecular weight distribution of the polyester formed. Several phenomena contribute to this effect depending on the structure of the alkoxide, the monomer and the experimental conditions used such as: (1) slow initiation, (2) slow equilibrium between differently aggregated species, and (3) transesterification reactions. As a rule, tin alkoxides are efficient transesterification catalysts and they are less selective in ROP than aluminium alkoxides [19]. Nevertheless, the molecular weight is still predetermined by the monomer/initiator molar ratio. The control of ROP initiated by tin(IV)

alkoxides is maintained in environmentally friendly supercritical carbon dioxide [20]. The extraction of monomer and tin residues by this supercritical fluid is a further advantage, particularly for the production of biomedical-grade aliphatic polyester.

The ROP of ε-caprolactone or lactide initiated by tin(II) butoxide is considered to be a "living" polymerisation and proceeds via the coordination-insertion mechanism. The higher activity of tin(II) alkoxides ($Sn(OR)_2$) compared with tin(IV) alkoxides ($(C_4H_9)_2Sn(OR)_2$) is consistent with the lower steric hindrance of tin at the benefit of the monomer coordination and with the positive induction effect of the R (butyl) groups which decrease activity towards nucleophiles. The higher activity of tin(II) dialkoxides compared with aluminium trialkoxides results from the difference in the ionic radii of the two metals and the accordingly stronger polarization of the tin-oxygen bond.

Therefore, in recent years, attention has tended to focus on using tin(II) alkoxides directly as the initiator in the ROP of cyclic esters. However, although they are effective, they too have their problems, in particular their difficult solubility in cyclic ester monomers and common organic solvents and their instability on contact with air and moisture. This is caused by their solid-state molecular aggregation, as shown below in Figure 1.7. Consequently, it is the aim of this work to prepare soluble and stable tin(II) alkoxide-based macroinitiators which can overcome these difficulties.

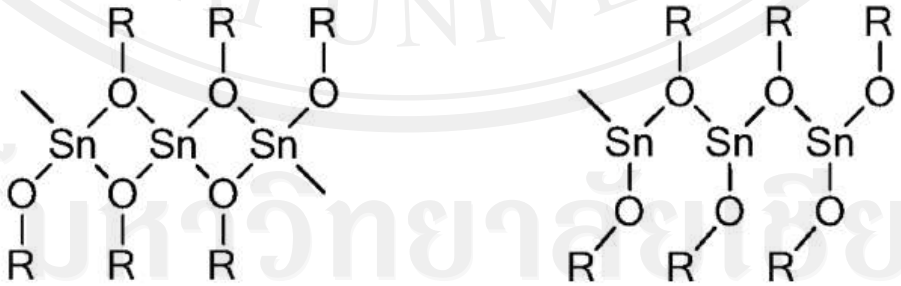


Figure 1.7 : Molecular aggregation in tin(II) alkoxides.

1.4 Homopolymers [54]

Several factors are known to affect the ring-opening polymerisation 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 4-, 7- and 8-membered rings polymerise, whereas the 5-membered rings generally do not. In the case of 6-membered rings, the polymerisability depends on the substituents.

1.4.1. Poly(ε-caprolactone) [4, 76]

Poly(ε-caprolactone) 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. It is also of interest as a packaging material and in biomedical applications since it is biodegradable and its biodegradation products are non-toxic.

Poly(ε-caprolactone) has a long biodegradation time, which is usually a disadvantage in medical applications except in, for example, long-term drug delivery systems. The *in vivo* degradation of poly(D-lactide) was 2.8 times faster than that of poly(ε-caprolactone) under the same conditions [55]. Different approaches have been used to copolymerise ε-caprolactone to increase the degradation rate. Copolymers of ε-caprolactone and D- and L-lactide of all compositions degrade much more rapidly than their component homopolymers [55]. This observation has been attributed to morphological differences, specifically a reduction in crystallinity and a lowering of the glass transition temperature.

1.4.2 Polylactide [4]

The most efficient way of preparing polylactides is by ROP using coordination-insertion initiators [70]. This method usually allows a controlled synthesis leading to a quite narrow molecular weight distribution. Polymerisation of the different stereoforms results in materials with different properties. The polymers derived from the pure L-lactide or D-lactide monomers are semi-crystalline, relatively hard materials with melting temperatures of around 175-178 ^{o}C

[71] and a glass transition temperature of about 55 ^{o}C [72]. In contrast, polymerisations of meso-lactide and racemic D,L-lactide result in amorphous materials but with a glass transition similar to that of their semi-crystalline counterparts. Polylactides are highly sensitive to heat, especially at temperatures higher than 190 ^{o}C. Heating these materials above this temperature results in a noticeable decrease in the weight-average molecular weight due to intra- and intermolecular transesterification reactions.

1.5 Kinetics of Ring-Opening Polymerisation [4, 76]

The kinetics of ROP have been investigated in order to study the coordination-insertion mechanism and, in particular, to understand the action of the initiator in more detail.

1.5.1 Kinetic Models [4, 76]

ROP reactions initiated with a metal alkoxide initiator are generally characterised by an equilibrium between the free and the aggregated metal alkoxide [57, 58], as shown in equations 1.1 and 1.2 :

$$(P^{*}_{n})_{m} \underset{}{\overset{K_{da}}{\rightleftharpoons}} mP^{*}_{n} \qquad (1.1)$$

$$P^{*}_{n} + M \xrightarrow{k_{p}} P^{*}_{n+1} \qquad (1.2)$$

where P^{*}_{n} , $(P^{*}_{n})_{m}$ and M are non-aggregated active centers, aggregated active centers and monomer repectively, K_{da} is the aggregation equilibrium constant, k_{p} is the propagation rate constant, and m is the degree of aggregation. Aggregation causes a temporary termination of the growing species since the chain ends propagate only if they are non-aggregated. Due to the difference in reactivities between the aggregated compounds, the kinetics of polymerisation are influenced.

In order to solve the kinetic equations corresponding to this system, Penczek and co-workers [45] have recently proposed a method to determine the degree of aggregation in the tin(II) alkoxide initiator from the curved plots of $\ln(k_{app})$ versus $\ln[I]_0$. The solution for the general case of m-aggregate formation is :

$$(k_{app})^{1-m} = - m / k_{da} (k_P)^{m-1} + k_p[I]_0(k_{app})^{-m} \quad (1.3)$$

which, in logarithmic form, becomes

$$\ln (k_{app}) = (1/m) \ln[I]_0 + C \quad (1.4)$$

where k_{app} = apparent rate constant

and $[I]_0$ = initial initiator concentration

This equation allows a straight line interpretation of the experimental data. When $\ln(k_{app})$ is plotted versus $\ln[I]_0$ the slope of the line gives the external order in the initiator. The equation is valid for polymerisations in which a fast reversible aggregation of the active centers takes place.

1.5.2 Dilatometry [59-61]

Dilatometry has been a classical technique for the study of the kinetics of polymerisation for many years [62]. Dilatometry utilizes the volume change that occurs upon polymerisation to follow conversion versus time. The conversion is conveniently followed in a dilatometer whose volume includes a capillary region. The dilatometer is placed in a constant temperature bath and the volume change of the polymerising system, which is quantitatively related to the percent conversion, is followed with time. As the dilatometer is placed into the constant temperature bath, initial meniscus movement is due to both thermal expansion of the monomer and contraction due to polymerisation. However, after a short time (usually not more than 10 mins), the effects due to thermal expansion become negligible. If the capillary cross-section area is determined, usually in terms of volume as a function of length, the change in height of the monomer in the capillary may be expressed as a

volume change. Thus, the slope of a plot of meniscus height versus time gives $\Delta h/\Delta t$ which can easily be converted to a volume to give $\Delta V/\Delta t$. Some dilatometers have the capillary calibrated in volume increments, in which case $\Delta V/\Delta t$ is directly accessible.

The total fractional change in volume corresponds to complete conversion to polymer of density d_2 from W_1 grams of monomer of density d_1. The weight of the polymer would also be W_1, since in an addition or ring-opening polymerisation, no weight is gained or lost. For the total fractional change in volume, this gives:

$$\Delta V_{\text{total fraction}} = \frac{\left(\frac{W_1}{d_1}\right) - \left(\frac{W_1}{d_2}\right)}{\left(\frac{W_1}{d_1}\right)} \tag{1.5}$$

which simplifies to :

$$\Delta V_{\text{total fraction}} = \frac{d_2 - d_1}{d_2} \tag{1.6}$$

The degree of monomer conversion would then be :

$$\frac{\Delta[M]}{[M]} = \frac{\left(\frac{\Delta V}{V_o}\right)}{\left(\frac{d_2 - d_1}{d_2}\right)} \tag{1.7}$$

where $\Delta[M]$ is the incremental change in monomer concentration [M] and ΔV is the change in volume from the initial volume V_o. This is valid since the term $(d_2-d_1)/d_2$ is the fractional volume change which would occur at 100% conversion and $\Delta V/V_o$ is the fractional volume change at any time Δt. The ratio of these two quantities should give the fraction of conversion. It should be noted that the ratio is dimensionless, so that $\Delta[M]$ and [M] could be in units of grams, moles, or molar quantities since they cancel out. If both sides of equation (1.7) are divided by Δt, incremental time, and rearranged, then :

$$\frac{\Delta[M]}{[M]} = \frac{\left(\frac{\Delta V}{\Delta t}\right) \times \left(\frac{[M]}{V_0}\right)}{\left(\frac{d_2 - d_1}{d_2}\right)} = \frac{[M]\, d_2}{V_0\,(d_2 - d_1)} \frac{\Delta V}{\Delta t} \qquad (1.8)$$

and

$$\left(\frac{\Delta[M]}{[M]}\right)_{\lim_{\Delta t \to 0}} = \frac{d\,[M]}{dt} \qquad (1.9)$$

The value of $-d[M]/dt$ has been previously defined as the overall rate of polymerisation, R_p.

$$R_p = - \frac{d[M]}{dt} \qquad (1.10)$$

The % conversion is simply calculated from :

$$\% \text{ Conversion} = \frac{\text{Weight of polymer obtained x 100\%}}{\text{Initial weight of monomer}}$$

This equation assumes no loss of weight due to any by-product formation, as was the case in the ROP reactions studied in this work.

1.5.3 First-Order Rate Plots [4, 76]

It is now widely accepted in the research literature that the bulk polymerisation of cyclic esters using coordination-insertion-type initiating systems is kinetically first-order (n=1) with respect to monomer, i.e.,

$$-d[M]/dt = k_1[M] \qquad (1.11)$$

which, when integrated between the limits of $[M]_0$ at time t = 0 and [M] at time t = t, gives the familiar first-order rate equation of :

$$\ln([M]_0/[M] = k_1t \quad (1.12)$$

where k_1 = first-order propagation rate constant

Give the correspondence from dilatometry that

$$\ln([M]_0/[M]) = \ln[(h_0-h_\infty)/(h-h_\infty)] \quad (1.13)$$

where h_0 and h_∞ are the initial and final (constant) meniscus heights respectively, the first-order rate equation can be expressed in terms of the primary data (h, t) as

$$\ln[(h_0-h_\infty)/(h-h_\infty)] = k_1t \quad (1.14)$$

Thus, for a first-order reaction, a semi-log plot of $\ln[(h_0-h_\infty)/(h-h_\infty)]$ against time t should yield a straight line graph of slope = k_1 = the first-order rate constant.

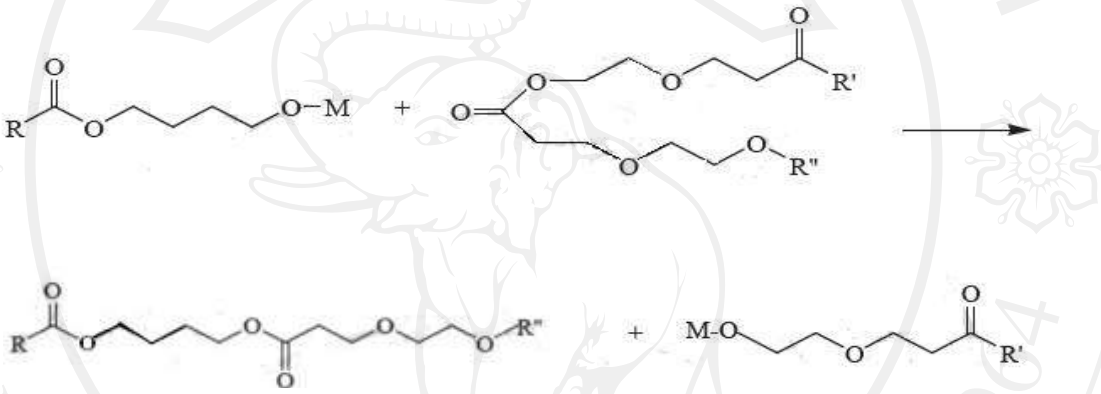
1.6. Transesterification Reactions [6]

The ROP of lactones with organometallic initiators at high temperatures or long reaction times leads to both inter- as well as intramolecular transesterification reactions. Both types of transesterification reactions lead to an increase in the polydispersity of the polyester product.

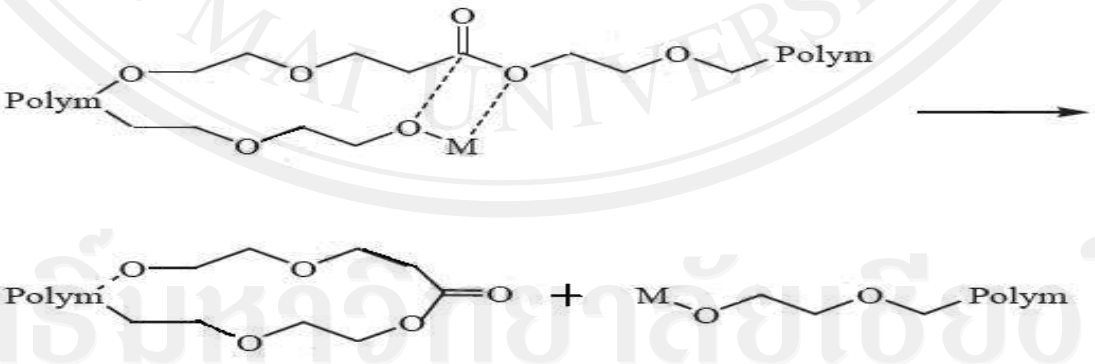
The reaction parameters that influence these transesterification reactions are temperature, reaction time, the type and concentration of initiator, and the nature of the lactone or lactide [6,63]. For example, in the polymerisation of caprolactone or lactide initiated with $SnOct_2$/BuOH or $ZnOct_2$/BuOH, the end-groups in the originally formed macromolecules changed to fully esterified chains [64] on increasing the duration of polymerisation. Certain initiators decompose at elevated temperatures, thereby influencing the rate of ROP and increasing the side-reactions. Furthermore, Kricheldorf *et al.* [65] observed the formation of octanoic acid when $Sn(Oct)_2$ was

heated above 100 ^{o}C. The acid thus liberated may bring about the esterification of alcohol (active hydrogen co-initiator) leading to the formation of water which may react with $SnOct_2$ to form stannoxanes and tin hydroxides. Under such conditions, it would be difficult to control the molecular mass and side-reactions because the presence of water or other hydroxyl compounds is likely to initiate polymerisation and/or act as chain transfer agents.

Intermolecular transesterification



Intramolecular transesterification (back-biting)



Ficgure 1.8 : Intermolecular and intramolecular transesterification reactions in the metal alkoxide (M-OR) initiated ROP of cyclic esters.

1.7. Recent Developments Relevant to This Project

Kricheldorf *et al.* [13,14] proposed the activated monomer mechanism for coordination-insertion using $Sn(Oct)_2$ in which the monomer is coordinated with the $Sn(Oct)_2$ (as catalyst) and is activated. The ROP then proceeds via a nucleophilic attack of the alcohol (as initiator) leading to the insertion of monomer into the metal-oxygen bond by rearrangement of the electrons. The alcohol group and the monomer are both coordinated to the $Sn(Oct)_2$ complex during propagation. Termination occurs by hydrolysis forming a hydroxyl end-group. They also reported that Bu_4Sn catalyzed the ROP of ε-caprolactone at 100 ^oC and that the reaction was accelerated by the addition of benzyl alcohol, but a coordination-insertion mechanism was not definitely proven. In contrast, it was found that Bu_4Sn is sensitive to oxidation by oxygen (air), a process which yields mainly Bu_2SnO and a trace of Bu_3SnOBu. Hence, it was thought that the Bu_2SnO dissolved in Bu_4Sn was the main initiator with added benzyl alcohol acting as a coinitiator yielding benzyl ester chain ends [35]. In addition, Kricheldorf and Thieben [37] studied and compared the reactivities of Bu_3SnOEt, $Bu_2Sn(OEt)_2$ and $BuSn(OEt)_3$ as initiators for the ROP of ε-caprolactone. It was found that the reactivity of the initiator increased with the number of alkoxy groups attached to the Sn atom. MALDI-TOF mass spectra of the polyesters isolated after 98-99% conversion indicated the presence of small amounts of cyclic oligomers (up to 2000 Da) even at reaction temperatures as low as 30°C. Broad molecular weight distributions were also found and were attributed to transesterification reactions.

Ryner *et al.* [34] presented a theoretical study of the ROP mechanism of 1,5-dioxepan-2-one (DXO) and L-lactide (LL) with $Sn(Oct)_2$ as initiator. Their results supported a coordination-insertion mechanism initiated by a tin alkoxide species formed prior to the ROP. The rate-determining step 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 as 19.8 kcal/mol and for L-lactide as 20.6 kcal/mol. The mechanism predicted facile (reversible) chain transfer in the system and this was said to explain the relatively narrow molecular weight distribution obtained. Penczek *et al.* [10,15,16] later replaced this mechanism with an alternative

mechanism in which the $Sn(Oct)_2$ and ROH reacted together to form a tin alkoxide (the true initiator) before complexing and ring-opening of the monomer. Figures 1.9 (a) and (b) compare these two different mechanisms.

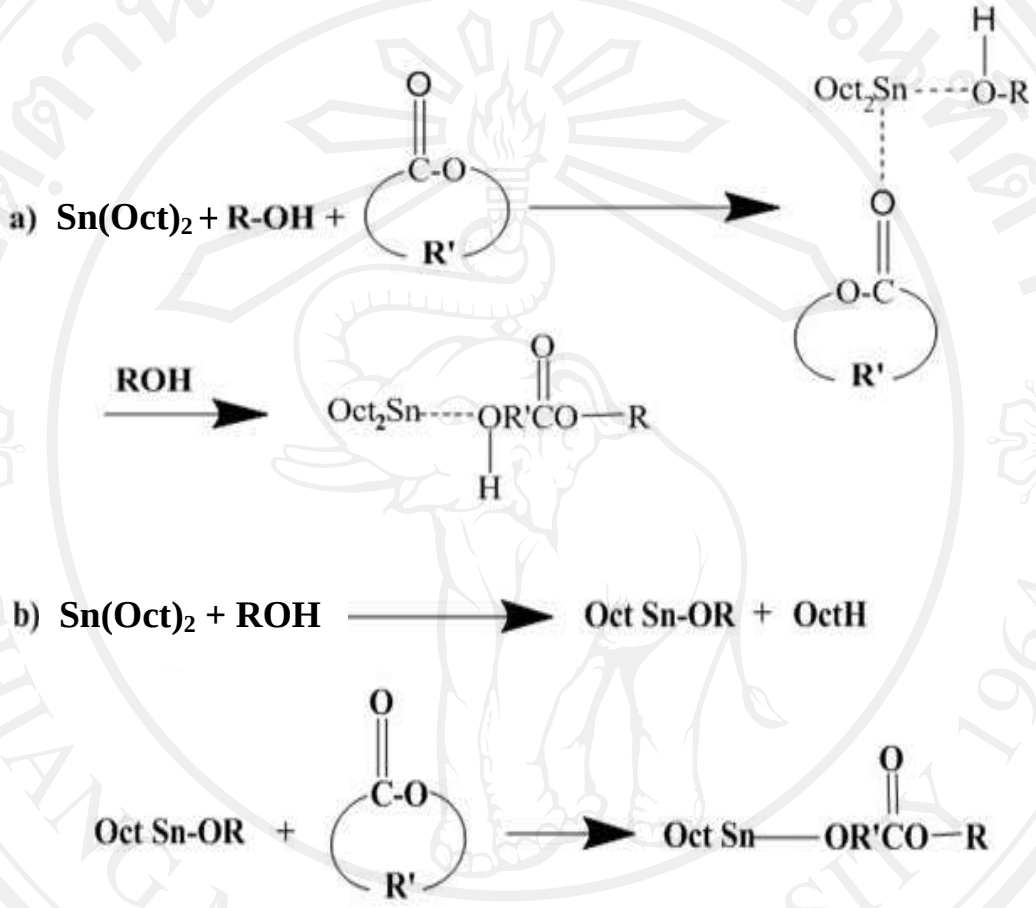


Figure 1.9 : The main ROP mechanistic proposals using $Sn(Oct)_2$ as catalyst/initiator
(a) as catalyst : complexation of the monomer and alcohol prior to ROP
(b) as initiator : formation of a tin alkoxide before ROP [11]

Storey and Sherman [8] presented evidence that the bulk ROP of ε-caprolactone conducted at 130 ^{o}C displays the characteristic kinetic features of a polymerisation that propagates through an active tin(II) alkoxide centre generated by the reaction between $Sn(Oct)_2$ and a purposely-added alcohol. This reaction, in the early stages of the polymerisation, is responsible for the formation of the "true"

initiating species, subsequent ring-opening, and formation of the active, propagating chain end. Prior to the beginning of polymerisation, adventitious hydroxyl-functional impurities (e.g., water) or a purposely-added alcohol first complex and subsequently react with $Sn(Oct)_2$ producing a stannous alkoxide species (1) and free 2-ethylhexanoic acid (3), as shown in reaction B in Figure 1.10. Adventitious water, meanwhile, serves mainly as an initiator deactivator via a reversible reaction with 1 or 2 thereby decreasing the concentration of active initiator and producing a stannous alcohol derivative (4), such as shown in reaction C, which is more thermodynamically stable than the stannous dialkoxide and is less efficient as an initiator. Reaction of 2 with monomer (reaction D) by means of coordination-insertion generates the first actively propagating chain end (5, 1-mer) consisting of not only the initiating alcohol fragment but also the active propagating center derived from the first monomer unit and stannous alkoxide. The 1-mer species may either propagate or undergo rapid intermolecular exchange of the stannous alkoxide moiety for a proton from either the hydroxyl groups of the initiator (if remaining) or another hydroxyl chain end, either 1-mer or polymeric in nature. This rapid exchange of protons and stannous alkoxide moiety results in a dynamic equilibrium between activated chain ends as depicted in reaction E, where ROH = unreacted alcohol initiator or hydroxyl chain-end generated *in situ*. This process eventually consumes the remaining unreacted alcohol initiator not involved in the initial formation of 2.

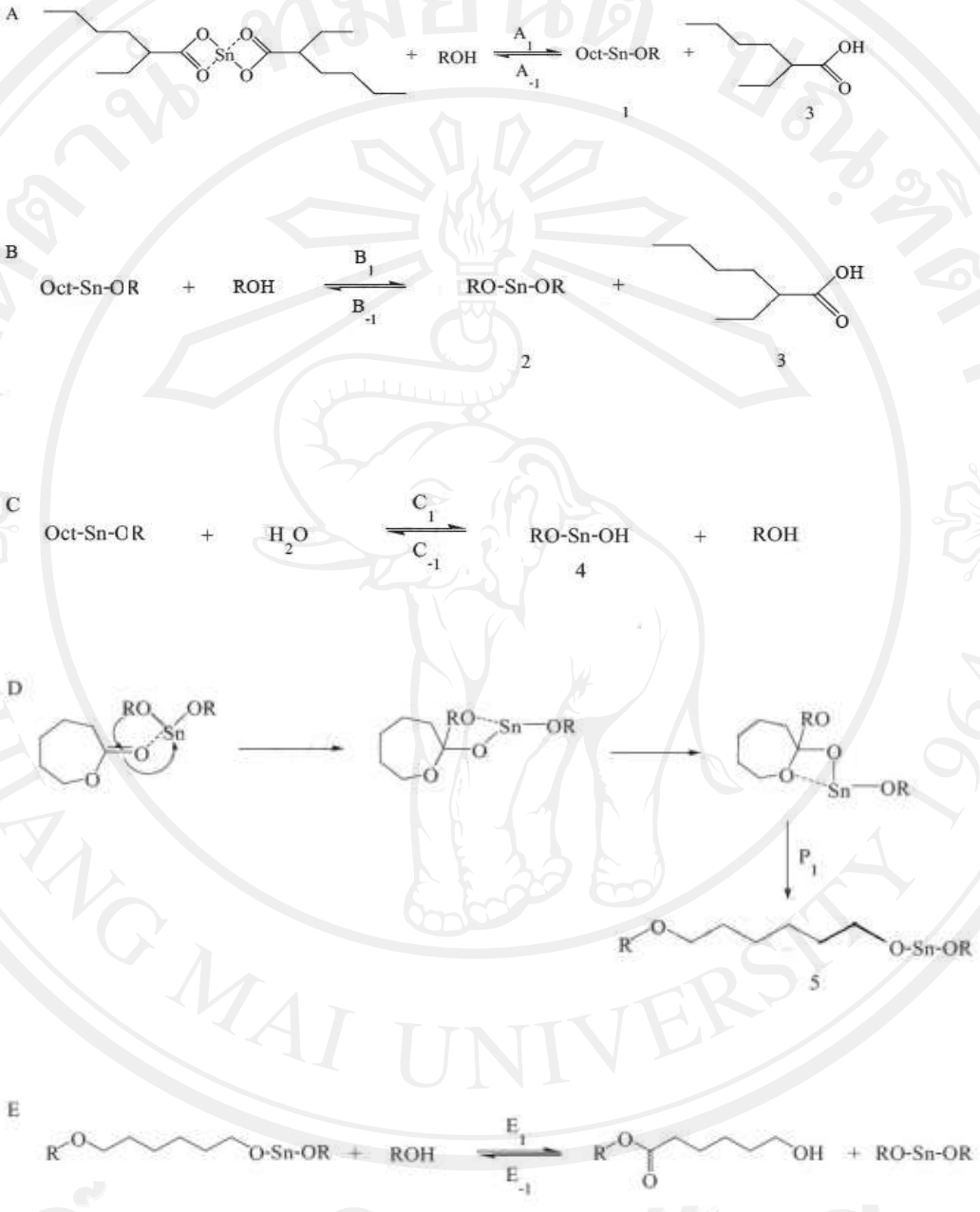


Figure 1.10 : Mechanism of initiation in the stannous octoate initiated polymerisation of ε-caprolactone, including (A,B) formation of stannous alkoxide initiator, (C) deactivation of catalyst with reaction by water, (D) coordination-insertion of monomer into the Sn-O bond generating the 1-mer, and (E) chain transfer of active polymerising center from 1-mer to unreacted alcohol.

Moreover, Storey and Taylor [36] studied the effects of $Sn(Oct)_2$ on the composition, molecular weight, and molecular weight distribution of ethylene glycol-initiated poly(ε-caprolactone). Bulk ROPs of ε-caprolactone (CL) were conducted at 120 ^{o}C with and without ethylene glycol (EG) as initiator and $Sn(Oct)_2$ as catalyst. Polymer molecular weight was determined by the [CL]/[EG] ratio and not by the $[Sn(Oct)_2]$ or the concentration of adventitious water brought into the reactor via the catalyst. It was found that, without EG, molecular weights were higher but decreased as $[Sn(Oct)_2]$ was increased; polymerisation rates were also lower, and the relationship between molecular weight and conversion suggested the participation of both ring-opening and condensation polymerisation.

Zhang *et al.* postulated that the reaction of $Sn(Oct)_2$ with an alcohol, ROH, yielded a tin monoalkoxide (OctSnOR) and/or dialkoxide (ROSnOR) that initiated the polymerisation of lactides and lactones via the classical coordination-insertion mechanism [9]. However, they also believed that $Sn(Oct)_2$, and most probably any other covalent metal carboxylate, also has to be able to initiate polymerisation at the metal-oxygen bond by insertion as with metal alkoxide initiators [10]. Kowalski *et al*. have more recently presented MALDI-TOF and kinetic data supporting Zhang's conclusions [11]. Duda *et al.* [12] compared $Sn(Oct)_2$ and tin(II) butoxide, $Sn(OC_4H_9)_2$, as initiators for the ROP of ε-caprolactone and L-lactide. Whereas the polymerisation initiated by $Sn(Oct)_2$ in the presence of ROH as coinitiator proceeded on the tin(II) alkoxide active centers generated *in situ*, the $Sn(OC_4H_9)_2$ initiator was already the true initiator. Hence, $Sn(OC_4H_9)_2$ initiation was fast and quantitative with every alkoxide group starting the growth of one macromolecule and monomer addition proceeding via acyl-oxygen bond scission. Thus, $Sn(Oct)_2$ did not directly initiate polymerisation. The real initiators were the monoalkoxide and dialkoxide generated in reactions (1.15) and (1.16). Comparison of the polymerisation rates initiated by $Sn(Oct)_2$ and $Sn(OC_4H_9)_2$, assuming similar reactivities of the tin(II) alkoxide active centres derived from $Sn(OC_4H_9)_2$ and $Sn(Oct)_2$/ROH, allowed an estimation to be made of the concentration of the growing species in the polymerisation.

$$Sn(Oct)_2 + ROH \longrightarrow Oct\text{-}Sn\text{-}OR + OctH \quad (1.15)$$

$$Oct\text{-}Sn\text{-}OR + ROH \longrightarrow Sn(OR)_2 + OctH \quad (1.16)$$

where OctH = octanoic acid

From equations (1.15) and (1.16), the exact Sn(Oct)OR and $Sn(OR)_2$ concentrations are unknown throughout the polymerisation which makes it difficult to produce polymers with predictable and reproducible molecular weights. Moreover, the octanoic acid (OctH) by-product plus any OH-containing impurities (e.g., parent hydroxy acid of the cyclic ester monomer, moisture, etc.) present in the system will also interfere with the overall reaction. Hence, the kinetic profile of the polymerisation reaction and the final molecular weight cannot be accurately predicted. Therefore, it has been in an attempt to overcome these uncertainties that attention has turned to the direct use of tin(II) alkoxides, $Sn(OR)_2$, as the true initiator in an accurately known concentration.

The synthesis of tin(II) alkoxides via the reaction between anhydrous tin(II) chloride, an alcohol and triethylamine, as shown in equation (1.17), was reported over 40 years ago by Morrison and Haendler [17].

$$SnCl_2 + 2\ ROH + 2\ (C_2H_5)_3N \longrightarrow Sn(OR)_2 + 2\ (C_2H_5)_3N.HCl \quad (1.17)$$

This work was followed by Gsell and Zeldin [41] who reported spectroscopic (mass, IR, ^{1}H-NMR and Mossbauer) data for $Sn(OCH_3)_2$, $Sn(OC_2H_5)_2$ and $Sn(OC_4H_9)_2$. Apart from these two papers [17,41], little else seems to have been reported on the synthesis of tin(II) alkoxides, $Sn(OR)_2$, with R > C_4H_9. It has to be concluded therefore that tin(II) alkoxides are a relatively unexplored class of compound which merit further study. The sensitivity of tin(II) alkoxides towards moisture and oxygen makes their elemental analysis difficult. Reliable analytical data for carbon and hydrogen can only be obtained from freshly sublimed samples of tin(II) alkoxides according to the procedure described by Gilman [42]. In this procedure, the tin content is determined as SnO_2 after oxidation of the alkoxide in a mixture of fuming

nitric and sulfuric acids followed by ignition at 800°C. Gsell and Zeldin [41] demonstrated that tin(II) alkoxides are white solids which exhibit an increase in solubility in organic solvents as the length of the alkoxy group increases. The low solubility of $Sn(OCH_3)_2$ is well known and reactions involving this compound are carried out heterogeneously [17]. In comparison, $Sn(OC_2H_5)_2$ is slightly soluble in polar solvents (CH_3CN, CH_2Cl_2), while the butoxide is reported to be readily soluble in these polar solvents and may be purified by recrystallisation from toluene. However, a practical problem with reaction (1.17) is that, as the $Sn(OR)_2$ is formed, it precipitates out of solution as a molecular aggregate, $[Sn(OR)_2]_n$. This molecular aggregation makes the product very difficult to dissolve in cyclic ester monomers or common organic solvents. In order to overcome this solubility problem, the conditions used for reaction (1.17) were modified by Dumklang *et al.* [39], as shown in equation (1.18).

$$SnCl_2 + 2\,ROH + 2\,(C_2H_5)_2NH \xrightarrow{n-\text{heptane}} Sn(OR)_2 + 2\,(C_2H_5)_2NH.HCl \qquad (1.18)$$

In this reaction (1.18), the role of the *n*-heptane is to keep the $Sn(OR)_2$ in solution as it forms, thereby preventing or at least minimizing its molecular aggregation. It is an adaptation of a method described in a U.S. patent for the synthesis of tin(IV) tertiary alkoxides, $Sn(t\text{-}OR)_4$ [18].

Kalmi *et al.* [38] used tetrakis Sn(IV) alkoxides as highly active initiators for the ROP of D,L-lactide. The activities of Sn(IV) tetra-2-methyl-2-butoxide, Sn(IV) tetra-isopropoxide, and Sn(IV) tetra-ethoxide were compared to the $Sn(Oct)_2$/*n*-BuOH initiating system. All polymerisations were conducted at 75 °C in solution in toluene. The activities of the tetrakis Sn(IV) alkoxides grew in order of increasing steric hindrance with the bulky Sn(IV) alkoxides showing a higher activity than the $Sn(Oct)_2$/*n*-BuOH system. The living character of the polymerisation was demonstrated both in the homopolymerisation of D,L-lactide and in the block copolymerisation of L-lactide with ε-caprolactone.

Finally, Storey *et al.* synthesized novel tin(II) macroinitiator adducts containing oligomeric L-lactide (LL), DL-lactide (DLL) and ε-caprolactone (CL) via their ROP with $Sn(OEt)_2$ ([monomer]/[initiator] ≤ 20) [40]. The soluble tin alkoxide macroinitiators obtained gave predictable and quantitative initiation and were stable for up to 1 month on storage at room temperature. It was found that, in contrast to the insoluble $Sn(OEt)_2$, their solubility resulted in polymers with low polydispersities (≤ 1.5) in high conversion (>95%) within relatively short polymerisation times (≤ 2 hrs.). Adjusting the monomer/macroinitiator ratio effectively controlled the molecular weight of the polymer. It is this work which is of particular interest to the work which is now described in this thesis.

1.8. Aims of This Study

The main objectives of this research are to synthesize, characterise and study the initiating efficiencies of some novel tin(II) alkoxide adducts as macroinitiators for the ROP of cyclic ester monomers, such as ε-caprolactone and L-lactide. In particular, it is aimed that the macroinitiators will be readily soluble in cyclic ester monomers and/or common organic solvents and be stable on storage.

This is to be achieved by first synthesizing tin(II) *t*-butoxide, $Sn(O\text{-}t\text{-}C_4H_9)_2$, via the two reactions shown below :

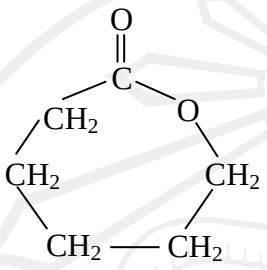
$$SnCl_2 + 2\ t\text{-}C_4H_9OH + 2\ (C_2H_5)_3N \longrightarrow Sn(O\text{-}t\text{-}C_4H_9)_2 + 2\ (C_2H_5)_3N{\cdot}HCl$$

$$SnCl_2 + 2\ t\text{-}C_4H_9OH + 2\ (C_2H_5)_2NH \xrightarrow[n\text{-heptane}]{\text{in}} Sn(O\text{-}t\text{-}C_4H_9)_2 + 2\ (C_2H_5)_2NH{\cdot}HCl$$

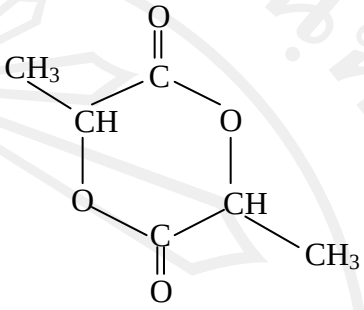
The purified $Sn(O\text{-}t\text{-}C_4H_9)_2$ will then be reacted with ε-caprolactone monomer (M) in molar ratios of 1:10 and 1:20 in order to produce tin(II) *t*-butoxide-oligoester adducts via the reaction :

$$Sn(O\text{-}t\text{-}C_4H_9)_2 + nM \longrightarrow t\text{-}C_4H_9O\text{-}(M)_n\text{-}SnO t\text{-}C_4H_9$$

These adducts will then be used as macroinitiators for the further high molecular weight polymerisation of ε-caprolactone or, indeed, any other cyclic ester monomer such as lactide.



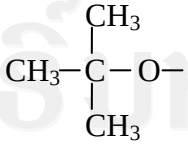
ε-caprolactone



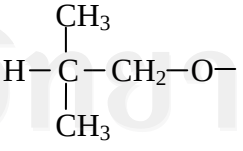
lactide

It is hoped that the M content in the t-C_4H_9O—$(M)_n$—Sn$O$$t$-$C_4H_9$ macronitiator structure will make it readily soluble in cyclic ester monomers for bulk polymerisation in contrast to the original $Sn(O\text{-}t\text{-}C_4H_9)_2$ which is insoluble due to molecular aggregation.

Initially, the *t*-butoxide is chosen in preference to the *n*-butoxide and *i*-butoxide simply because it contains 18 equivalent protons per $Sn(O\text{-}t\text{-}C_4H_9)_2$ molecule which will facilitate t-C_4H_9 end-group detection by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy.



t-butoxide



i-butoxide

n-butoxide

However, the *n*-butoxide, $Sn(O\text{-}n\text{-}C_4H_9)_2$, will also be studied so that the steric effect of the C_4H_9 group on initiator solubility and initiating efficiency can be determined by comparison with the *t*-butoxide.