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SYNTHESIS OF POLYMERS AND COPOLYMERS OF LACTIDE THROUGH TITANIUM INITATORS

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To

My Family and Allan Amass

Thanks for helping me to pursue my dream.

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LIST OF ABBREVIATIONS

d: Doublet.
° C: Degrees centigrade.
Conv: Monomer conversion.
ε-CP: ε-Caprolactone.
Dp: Degree of polymerisation.
Dp_{exp}: the calculated degree of polymerisation for any given reaction at any given time.
Dp_{th}: the theoretical degree of polymerisation for any reaction if four alkoxy groups were active
Da: Dalton.
DEFRA: Department of Environment, Food and Rural Affairs.
DIBT: Di-isobutyl tartrate.
DSC: Differential scanning calorimeter.
δ: Solution parameter
E: Young's modulus
FDA: Food and Drug Administration.
FTIR: Fourier transformed infrared spectroscopy.
g: Grams.
G: Shear modulus,
GPC: Gel permeation chromatography.
Hz: Hertz.
I: Initiator.
J: Coupling constant.
K: Reaction rate constant.
I_{OH}: Number of initiating OH groups,
I_{OH th}: Maximum number of initiating OH groups
F: functionality
Ln: Natural logarithm
LAc: Lactic acid.
L-LA: L-Lactide.
L,D-LA: D,L-Lactide.
m: Multiplet
min: Minutes.
M_n: Number average molecular weight.
M_nGPC: Number average molecular weight obtained by GPC
M_n*_{GPC}: Corrected number average molecular weight obtained by GPC. The M_nGPC value has been multiplied by 0.55.
M_nNMR: Number average molecular weight obtained by NMR spectroscopy.
M_nTh: Theoretical number average molecular weight obtained from conversion values if 4 arms of the catalyst were active.
M: Monomer
M_w: weight average molecular weight.
NMR: Nuclear magnetic resonance.

NU: Number of units.
 PAMAM: Amine-terminated poly(amidoamine).
 PCL: poly(ϵ -caprolactone)
 PD: Polydispersity.
 PEG: Poly(ethylene glycol).
 PEG₄₀₀: Poly(ethylene glycol)
 PEG₃₅₀: poly(ethylene glycol) methyl ether.
 PEGNH₂: *O,O'*-Bis(3-aminopropyl)polyethylene glycol
 PE: Polyethylene.
 PET: Poly(ethylene terephthale)
 P(3HB): Poly3(hydroxybutyric) acid,
 PHB Poly(hydroxybutyrate).
 PHBV: Poly(hydroxybutyrate-valerate)
 PGA: polyglycolid acid.
 PLA: Poly(lactic acid)
 PLLA: Poly(L-lactic acid)
 PLDLA Poly(D,L-lactic acid)
 P(LA-co- ϵ -CL): copolymer of lactide and ϵ -caprolactone
 PLA-co-PCL: copolymer of lactide and ϵ -caprolactone
 P(LLA-co- ϵ -CL): copolymer of L-lactide and ϵ -caprolactone
 PLLA-co-PCL: copolymer of L-lactide and ϵ -caprolactone
 PLLA-block-PCL: Block copolymer of L-lactide and ϵ -caprolactone.
 P(LLA-block- ϵ -CL): Block copolymer of L-lactide and ϵ -caprolactone
 PP: Polypropylene.
 PP₂₇₀: Pentaerythritol ethoxylate (3/4 EO/OH)
 ppm: Parts per million.
 PS: Polystyrene.
 PVL: Poly(valerolactone)
 s: Singlet
 sept: Septet
 SEC: Size exclusion chromatography.
 t= Time
 t=Triplet
 T: temperature.
 T_c: Temperature of crystallisation.
 T_g: Glass transition temperature.
 T_m: Melting Point.
 TIBC: Tri-isobutyl citrate.
 THF: Tetrahydrofurane.

SYNTHESIS OF POLYMERS AND COPOLYMERS OF LACTIDE THROUGH TITANIUM INITATORS

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A thesis submitted for the degree of Doctor of Philosophy of Aston University

SUMMARY.

The research described in this thesis explored the synthesis and characterisation of biocompatible and biodegradable polymers of lactide through non-toxic titanium alkoxide initiators. The research objectives focused on the preparation of polylactides in both solvent and solventless media, to produce materials with a wide range of molecular weights. The polylactides were fully characterised using gel permeation chromatography and ^1H and ^{13}C NMR spectroscopy. NMR spectroscopy was carried out in the study the reaction mechanisms. Kinetic studies of the ring opening polymerisation of lactide with titanium alkoxide initiators were also conducted using NMR spectroscopy.

The objectives of this research were also focused on the enhancement of the flexibility of the polymer chains by synthesising random and block copolymers of lactide and ϵ -caprolactone using $\text{Ti}(\text{O}-i\text{-Pr})_4$ as an initiator. This work involved extensive characterisation of the synthesised copolymers using gel permeation chromatography and ^1H and ^{13}C NMR spectroscopic analysis. Kinetic studies of the ring opening polymerisation of ϵ -caprolactone

and of the copolymerisation of lactide and ϵ -caprolactone with $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator were also carried out.

The last section of this work involved the synthesis of block and star-shaped copolymers of lactide and poly(ethylene glycol) [PEG]. The preparation of lactide/PEG block copolymers was carried out by ring opening polymerisation of L-lactide using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator and hydroxyl-terminated PEG's with different numbers of hydroxyl groups as co-initiators both in solution and solventless media. These all-in-one polymerisations yielded the synthesis of both lactide homopolymer and lactide/PEG block copolymer. In order to selectively synthesise copolymers of lactide and PEG, the experiment was carried out in two steps. The first step consisted of the synthesis of a titanium macro-initiator by exchanging the iso-propoxide ligands by PEG with different numbers of hydroxyl groups. The second step involved the ring opening polymerisation of lactide using the titanium macrocatalyst that was prepared as an initiator. The polymerisations were carried out in a solventless media. The synthesis of lactide/PEG copolymers using polyethylene glycol with amino terminal groups was also discussed. Extensive characterisation of the lactide block copolymers and macro-initiators was carried out using techniques such as, gel permeation chromatography (GPC), NMR spectroscopy and differential scanning calorimeter (DSC).

KEYWORDS: Polylactic acid, ring opening polymerisation, lactide, titanium alkoxides, copolymers of lactide, titanium macro-initiators,

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CHAPTER 1

TITLE: LITERATURE REVIEW

1.1-PROS AND CONS OF OIL-BASED POLYMERS

Plastics were the materials of the 20th century and it seems they will continue to be of enormous importance in the near future. During the last 50 years, usage of plastics in the UK has grown dramatically and is now over 4.7 million tonne per annum¹. The major use of plastics is in packaging, where they are used to wrap almost half of all packaged goods. Consumption is continuing to grow at a rate of about 1% per year in the UK. Just over a-third of plastics are used in packaging¹, and a further quarter in the construction industry. Other major uses include electronic goods and vehicles. They also play important roles in medical applications, information technology and communications and their use often offers environmental benefits. For example, plastics are lightweight, and their use in vehicles has resulted in fuel savings. Plastic packaging helps keep some food fresh for longer and prevents contamination. Conversely, plastics also present some disadvantages: the majority are long lived and fly-tipping causes problems in the environment and in waste management.

Despite the major advances in the synthesis, processing and manufacture of these materials there are two major problems that still confront the industry, the use of non-renewable oil-based chemicals and the ultimate fate of waste materials

In reference to the latter, the main concern is related to the increasingly 'throw-away' style of life in our society. 4.5 Million Tonne of plastic waste are produced in the UK¹ each year, much of which is packaging (60 %). The materials most commonly found, such as PE, PP, PS, PVC and PET are recyclable, although non-degradable, polymers and represent 67 % of plastic materials used in the UK. At the end of their lives, most of these materials are landfilled. Based on the last figures released by DEFRA (Department of Environment, Food and Rural Affairs) for 2003/04, 80 % of municipal solid waste was landfilled, and only 16% recycled. These figures are still far from the government waste strategy target of 25% recycled by 2005/06 and even far below other European countries such as Austria or Belgium where 60 % and 50%, respectively, of the waste is recycled. The UK plastic recycling rate of 3% is unacceptably low compared to the 70% achieved by Germany. Optimistically, the latest figures released by DEFRA have shown that the set target of recycling or composting of 25% of household waste for 2005/2006 has been achieved, with 27 % of household waste being recycled or composted.

The main barriers to greater recycling have been identified as low landfill costs, insufficient information available on plastic recycling, difficult to add plastics due to use of kerbside sort vehicles (not enough compartments available), poor demand for recycled compounds and the negligible price difference between virgin polymer and recyclate. Dirty or contaminated plastic waste requires special treatment (collection, separation), which makes it even more expensive. Consequently, the recycling facilities for England and Wales are not as well distributed, which would be desirable and have been mainly focused and developed to recycle mainly plastic bottles. However the percentage of recycling plastic bottles increases every year is still low of reaching 13 % in 2005. At this level of performance, planned activity

could generate close 30% recycling of plastic bottles in the UK household waste stream by the end of 2007.

The use of plastics in packaging and the associated waste produced has considerable environmental impact because of the low densities and large volumes of most commodity polymers causing persistent and hazardous debris. However, the removal of plastics from packaging is not yet a viable option, since there will be a dramatic increase in weight and volume using non-plastic alternatives. There is an environmental need to overcome the disadvantages of plastics derived from oil. "Bioplastics", derived from plants rather than from oil and gas, represent one approach towards "greener" plastics. They present the possibility of producing plastics using renewable resources. Thus, these polymers may provide ecologically attractive technologies, provided the prices of these materials can compete with those of conventional plastics. However, a full life cycle analysis should be carried out on materials to determine their relative "greenness", since some bioplastics may use more fossil fuels in their production than conventional plastics.

1.2. AN ATTRACTIVE ALTERNATIVE: BIODEGRADABLE POLYMERS OR “BIOPLASTICS”.

1.2.1 Introduction and definitions

The world has now accepted the advances in the quality of life brought about by the discovery of polymeric materials in the plastic, rubber, adhesive, paint and electronic industries. However, there is an increasing realisation that the legacy of the progress brought about by this first generation of materials has come at a cost to the environment and this cost is beginning to impinge on the quality of life. If the environmental problems created by the first generation of polymers are to be addressed in a meaningful way, it is essential to develop other materials that have the advantages of the first generation materials, but will not bring with them the environmental disadvantages. A category of materials that will address these problems is that of biodegradable polymers.

One must not confuse degradable plastics and bio-plastics or biodegradable polymers. Degradable plastics can either contain a small percentage of a non oil-based material, such as corn starch, that degrades under certain conditions after a predetermined length of time or contain light sensitive functional groups, which promote break down when exposed to sunlight. Degradable plastics are already being used successfully in Austria and Sweden, where McDonalds has been using degradable cutlery for three years. Carriers for packs of beer cans, that photo-degrade in six weeks, have also been manufactured recently. There are a number of concerns over the use of degradable plastics. Firstly, these plastics will only

degrade if disposed in appropriate conditions. For example, a photodegradable plastic product will not degrade if it is buried in a landfill site where there is no light. Secondly, the mixture of degradable and non-degradable plastics may complicate plastics sorting systems.

Bio-plastics can be an alternative to degradable plastics. The term bio-plastic is applied to polymers derived from plant sugars or plastics grown inside genetically modified plants or micro-organisms^{2,3}. Albertson and Karlsson⁴ define the process of biodegradation as an event that takes place through the action of enzymes and/or chemical decomposition associated with living organisms (bacteria or fungi, etc) or their secretion products.

1.2.2 Classes of biodegradable polymers.

Over the past 20 years, biodegradable polymers, based commonly on esters, have been developed. Examples of such materials are listed in table 1.1.

TYPE	EXAMPLES OF POLYMERS
Polyesters	Poly(α -esters): $-(O-C(R)H-CO)_n-$ Poly(glycolic acid) PGA ($R=H$) Poly(lactic acid) PLA $R=CH_3$
	Poly(β -esters): $-(O-C(R)H-CH_2-CO)_n-$ Poly(3-hydroxybutanoate) P3HB $R=CH_3$ Poly(3-hydroxyvalerate) P3HV $R=C_2H_5$
	Poly (γ -esters): $-(O-C(R)H-(CH_2)_2-CO)_n$ Poly(4-hydroxybutanoate) P4HB $R=H$
	Others polyesters or polylactones: $-(O-C(R)H-(CH_2)_m-CO)_n$ Poly(ϵ -caprolactone), PCL $R=H$ and $m=5$ Poly(valerolactone) PVL $R=H$ and $m=4$
Polyamides	Hydroxylated nylon
Polyurethane	Hydrophilic ether urethanes
Polyethers	Polyethers: $-(O-(CH_2)_x-)_n$ Polyethene oxide, PEG $x=2$
Polyanhydrides	Poly(bis(p-carboxyphenoxy), alkane anhydride or PCPX
Polyorthoesters	Poly(3,9-bis(ethylenedine-2,4,8,10-tetraoxaspiro[5.5]undecane-co-hexanediol or DETOSHU-HD.
Polypeptides and proteins	collagen, gelatine: $-(CH(R)-CO-NH-)_n$ (with different ends groups and chain lengths)..
Polysaccharides	Naturally occurring starches and different forms of cellulose

Table 1.1: Commercially available biodegradable polymers.

Polyesters (e.g. PLA, PCL), polyamides or polyurethanes are among the more interestingly and commercially available polymers.

1.2.3. Commercial applications of biodegradable polymers

The interest of current research in biodegradable polymers is connected to the fact that these polymers can offer a solution to managing packaging waste, besides providing a wide range of different and interesting applications such as glues, productions of fibres, agriculture uses (controlled release of fertilisers and pesticides), surfactants and biomedical applications (drug delivery, surgical implants).

1.2.3.1. Biomedical applications

The most widely researched biodegradable polymers are poly(α - esters), such as poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) and the microbial poly(hydroxyalkanoates) (e.g., P3HB, P3HV and P3HBHV). These have been shown to be non-toxic and biocompatible, both as polymers and with regards to their degradation products. These polymers have a range of pharmaceutical and biomedical uses based on their characteristics and physical and chemical properties. Such uses include as surgical fixation, controlled drug delivery and more recently, tissue-engineering-scaffolds, a relatively new field still to be developed.

Surgical fixation includes sutures, clips, bones pins and membranes. Materials such as PLA and PGA have been used since the 1960's as absorbable synthetic sutures because of their high rate of degradation in the body and the ease of manufacture of these types of materials as strong filaments⁵. One of the first commercially available bioresorbable sutures made of polyglycolid acid (PGA) in the 60's was Dexon. Copolymers of glycolide in combination with lactide (Vicryl⁶) and ϵ -caprolactone (Monocryl⁶) were developed later in order to tailor physical properties and degradation rates. Different types of biodegradable polymers and copolymers are currently used as alternatives to metal implants, which themselves present serious disadvantages regarding the sensitivity of the patient to metals and the need for a removal operation. Some of these commercial materials are ⁷: Phusiline (Phusis Materiaux Bioresorbables SA), EndoFIX (Acufex (Smith + Nephew)) and Bioscrew (Linvatec (Zimmer))

Controlled delivery is the most important and versatile application of these polymers, which has applications not only in medicine but also in veterinary and agricultural fields. Micro- and nanoparticles of poly(esters) (e.g. PCL, PLA & PVL), poly(orthoesters) and polyanhydrides as well as their blends⁵ form an important category of delivery systems because of their hydrolytic degradations and low toxicities. The most important properties of these particles are the release rate of the drug and the degradation rate of the matrix⁸, which can be tailored as desired.

Poly(hydroxyl butyrate) (PHB), commercially known as Biopol, and Poly(hydroxyl butyrate-valerate) (PHBV) copolymers are both used for agricultural and veterinary applications. Holmes⁹ recognised PHBV as a potential polymer for the release of insecticides

into soil. Monsanto has commercialised this type of polymer as a matrix to control the release of weed killer.

1.2.3.2. Packaging applications

Applications of biopolymers in packaging are very recent, the main constraint being the high cost of lactic acid and lactide (lactic acid dimer) from non-petrochemical routes. Advances in the bacterial fermentation of D-glucose have reduced the cost of the raw materials from corn, so that the polymers can compete price-wise with oil-based plastics. The main polymer used for packaging applications is PLA. Cargill currently markets a wide range of packaging products with the name of "Nature Works". Among these products are plastic cups, cling-film, food containers, cutlery, plastic bottles, etc.

1.2.3.3. Production of fibres

One of the latest uses of biodegradable polymers is the production of fibres for applications such as carpets, clothing and bedding. Nature Works uses PLA, which has been branded as Ingeo PLA. Similarly, Dupont has already marketed and patented Sorona®, a polyester made from two monomers or ingredients, one of which is 1,3 propanediol or PDO. DuPont pioneered a way to produce the 1,3 propanediol from renewable resources, namely corn sugar. In 2004, DuPont formed a joint venture with Tate & Lyle, a major corn-based products company with expertise in fermentation processes, to produce Bio-PDO. The Bio-PDO™ will be used in the manufacturing of Sorona® in early 2007.

1.2.3.4. Detergent applications

Biodegradable detergents were initially introduced in the 1980's, in combination with zeolites as partial replacements for phosphates. Waste water treatment plants are unable to remove phosphates and these salts promote plant growth in rivers leading eventually to environmental imbalance. Freeman¹⁰ proved that poly(aspartic) acids show rapid and complete removal of plant microorganisms by municipal treatment.

1.2.3.5. Glues and melt adhesives applications

Biodegradable adhesives is a potential market for poly(lactides), which has developed a great interest in the last ten years. The majority of research has been carried out on tissue adhesives¹¹ in the biomedical sector, and on hot melt adhesives^{12,13} in the packaging industry. Biomedical tissue adhesives represent a preferred alternative to sutures or stapling. Lactide/ ϵ -caprolactone low molecular weight copolymers are biocompatible and biodegradable and can be tailor-made as desired. These represent a good alternative to cyanoacrylates (one of the strongest adhesives), which are forbidden for use in applications in internal organs because of the toxicity of the monomer. In addition, research was carried out by Viljanmaa^{12,13} and co-workers on the use of lactide/ ϵ -caprolactone copolymers as hot melt adhesives in the industrial lamination process. Viljanmaa reported that the thermal stability of these adhesives was sufficient for the standard application process. The adhesion was compared for these copolymers with that of commercial EVA, showing good results if the open time (the time after an adhesive is applied during which a serviceable bond can be made) of the adhesive was not exceeded. However, lactide/ ϵ -caprolactone copolymers should be chemically stabilised

with acetic anhydride in order to achieve a thermal stability comparable with commercial EVA copolymers.

1.3 A SUCCESSFUL BIODEGRADABLE POLYMER:

POLYLACTIC ACID.

1.3.1 Introduction.

The building block of these novel materials is *lactic acid* –an environmentally benign material found in living organisms and in everyday products such as meat, milk and corn. Under adequate humidity and temperature conditions, the resultant polymer, polylactic acid (PLA) degrades in a short period of time generating non-toxic waste. Originally pioneered by Carothers in 1932 ¹⁴, this polymer had a low molecular weight and poor mechanical properties. Further work by DuPont resulted in a higher-molecular-weight product that was patented in 1954 ¹⁵. Its main application was in the medical field until the late 1980s, when lactic acid prices started to drop and other applications such as packaging, fibres production and the controlled release of fertilizers and pesticides were developed.

1.3.2 Polymer and monomer structures

Lactic acid, an organic acid found in many products of natural origin, is one of the simplest chiral molecules and exists as the two stereo- isomers, L(*S*)- and D(*R*)-lactic acid. The L(*S*) form differs from the D(*R*) form in its effect on polarised light. For L(*S*)-lactic acid,

the plane is rotated in a clockwise (laevo) direction, whereas the D(R) form rotates the plane of polarisation in an anticlockwise (dextro) direction. Figure 1.1 illustrates these two forms.

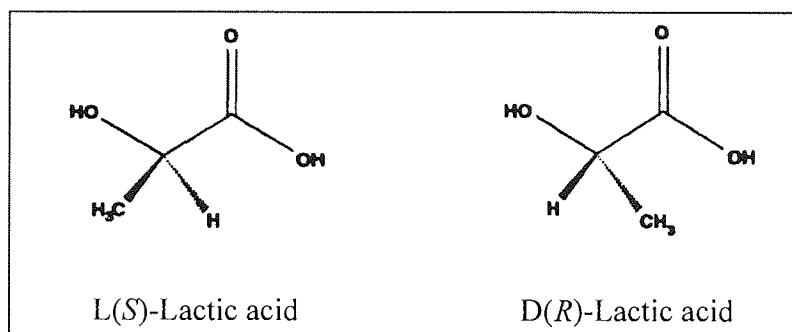


Figure 1.1: Lactic acid stereoforms.

Lactide is the cyclic dimer of lactic acid and presents three different stereo forms as seen in figure 1.2. These three stereo structures enable the production of different types of optically active polylactic acid, isotactic and syndiotactic and atactic polylactides as explained in detail in the next section.

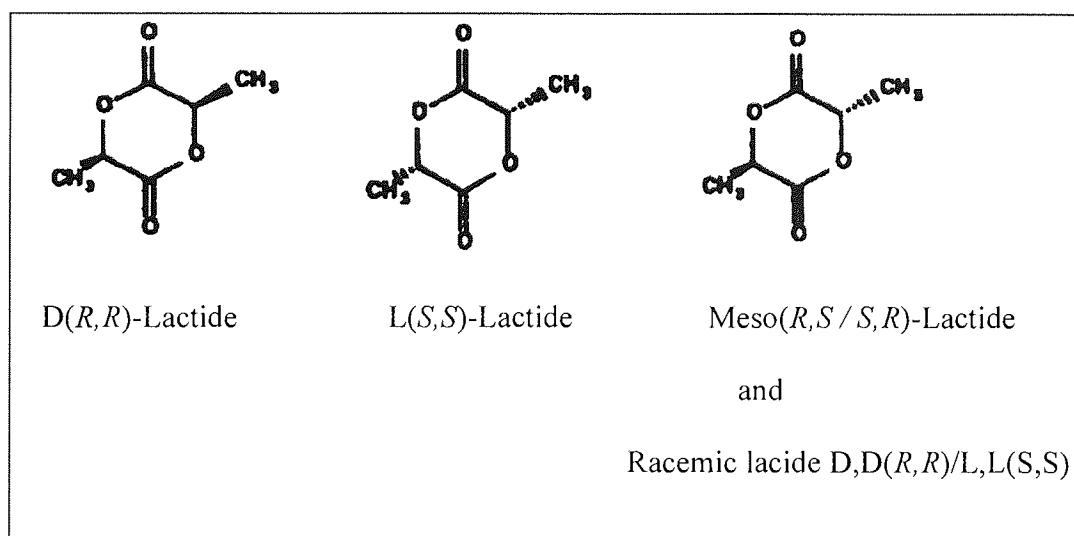


Figure 1.2: Lactide stereoforms.

L-lactic acid is the stereoisomer present in mammalian systems and both stereoisomers are found in bacterial synthesis. Lactic acid can be prepared by bacteria fermentation and is preferably made by the group of lactic acid bacteria capable of converting hexoses into lactic acid. Fermentation can be performed in batch or continuous processes by fine-tuning important parameters such as pH, temperature, atmosphere and in some cases agitation. Lactic acid obtained by fermentation has to be purified in order to be usable for polymerisation processes.

Lactide is commonly produced in two steps. Firstly, low molecular weight PLA is synthesised by polycondensation of lactic acid. The second step involves the depolymerisation of PLA in order to obtain lactide. Lactide monomer is generally used in industry and research to produce medium and high molecular weight poly(lactides) with controlled architecture, which cannot be obtained from lactic acid. Several different approaches to produce polylactic acid from lactic acid or its dimer, lactide, were discussed in section 1.4.

Polylactic acid also shows 3 different stereo structures isotactic or heterotactic PLA (fig 1.3), syndiotactic PLA (fig 1.4) and atactic (fig 1.5). Both, lactic acid and lactide, can be used in the synthesis of PLA. The stereostructure of the produced PLA will depend on the stereo structure of the monomer used, as shown in table 1.2.

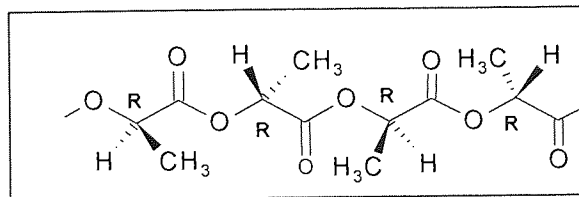


Figure 1.3: Isotactic PLA

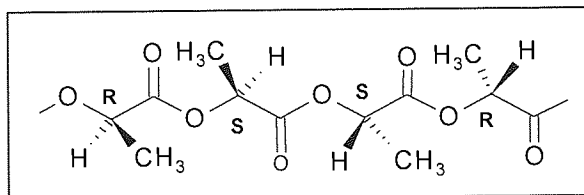


Figure 1.4: Syndiotactic PLA

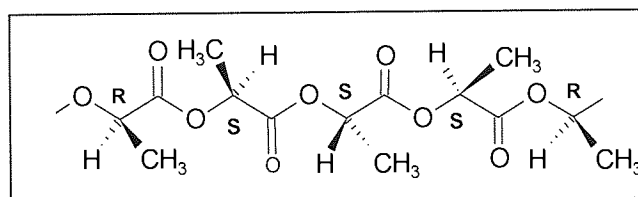


Figure 1.5: Atactic PLA

Monomer stereo structure	Final polymer stereo structure
D(R) lactic acid	Isotactic P(DLA)
L(S)lactic acid	Isotactic P(LLA)
D,D(R,R)-lactide	Isotactic P(DLA)
L,L(S,S) lactide	Isotactic P(LLA)
D,L (R,S/S,R) lactide	Syndiotactic P(D,L)LA
Racemic mixture of D,D(R,R)/L,L(S,S)-lactide	Isotactic P(D,L)LA

Table 1.2: Different PLA stereo-structure depending on the monomer used.

1.3.3 PLA properties

The optical composition of the polymer significantly affects properties such as crystallisation kinetics, the extent of crystallinity ¹⁶, glass transition temperature and the melting point. For instance, L-PLA and D-PLA are highly crystalline, isotactic materials, with a glass transition temperature (T_g) between 50-60 °C and a melting point (T_m) of 180 °C. T_g and T_m may vary slightly depending on the molecular weight of the polymer. On the contrary D,L-PLA is an amorphous polymer with a T_g between 45-50 °C and a T_m of 130 °C.

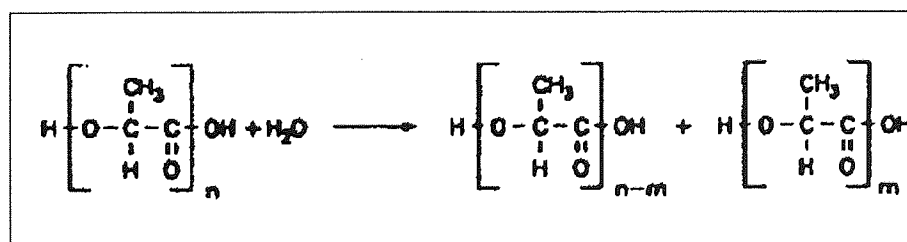
- Polymer properties noteworthy of mention include:
- Biodegradability
- Biocompatibility
- Resistance to fatty foods and dairy products equivalent to PET.
- Excellent flavour and aroma barrier.
- Good heat sealability.
- High stiffness
- For amorphous and biaxial films, clarity and gloss exceeds PET.
- High surface energy allowing easy printability.
- Tensile strength 60 MPa and tensile modulus 3 GPa.
- Flexural modulus 5 GPa > polystyrene.

- However the percentage of elongation at break of 3% is very low. It is still brittle and it has poor melt elasticity. Therefore it is difficult to process.

1.3.4 Degradation of PLA polymers

1.3.4.1 Biodegradation of PLA polymers

PLA polymers are aliphatic polyesters. Carothers *et al.*¹⁷ observed its susceptibility to moisture in 1932, pointing to it as the primary cause of the degradation. Cleavage of the ester linkages by absorbed water produces a successive reduction in molecular weight. The rate of this hydrolytic degradation is temperature and humidity dependent. In the primary degradation phase, abiotic hydrolysis, no microorganisms are involved (scheme 1.1). This is a useful characteristic, particularly for product storage and in applications requiring food contact.



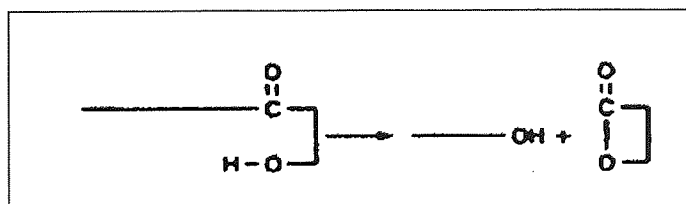
Scheme 1.1: Hydrolysis of a hydroxyacid.

When the microorganisms present in soil begin to digest the lower-molecular-weight lactic acid oligomers, carbon dioxide and water are produced. This two-stage mechanism is distinctly different to many other biodegradable products presently on the market. Typically, biodegradable polymers degrade by a single-step process, involving bacterial attack on the polymer itself. For biodegradable applications, the preferred disposal route is by composting.

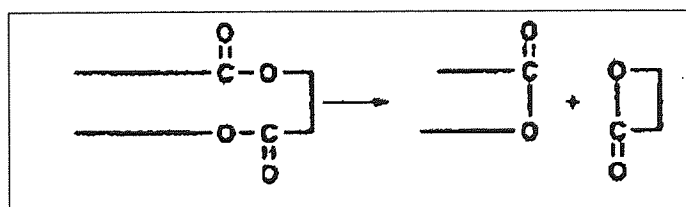
In this environment of high humidity and temperature (55—70°C), PLA polymers degrade rapidly. However, at lower temperatures (room temperature and below) and/or lower humidity, the storage stability of PLA products is considered to be acceptable¹⁸.

1.3.4.2 Thermal degradation.

The relatively rapid decrease of molar mass during processing in the melt is a well-known property of PLA. PLA undergoes degradation when it is heated above its melting temperature. The degradation products and the reactions involved during processing in the melt were studied by Jamshidi¹⁹ *et al* and Zhang *et al.*²⁰. They point to inter- and intramolecular transesterifications as causes for the reduction of the molar mass. Intramolecular transesterification from the end of the chain, also referred to as backbiting (scheme 1.2), or in the middle of the chain (scheme 1.3) lead to the formation of cyclic oligomers and linear polyesters.

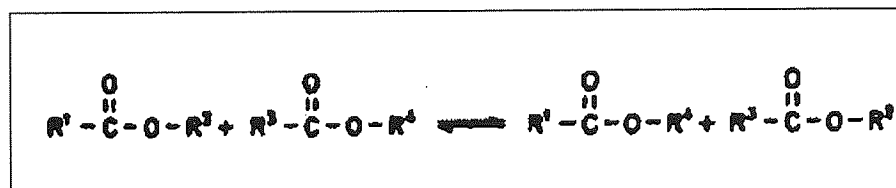


Scheme 1.2: Intramolecular transesterification backbiting reaction



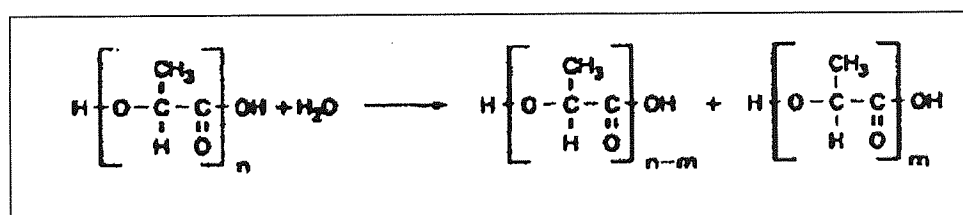
Scheme 1.3: Intramolecular transesterification from the middle of the chain.

Intermolecular transesterification (scheme 1.4) with short molecules present in the medium cause a decrease in the average mass of the molar mass distribution.

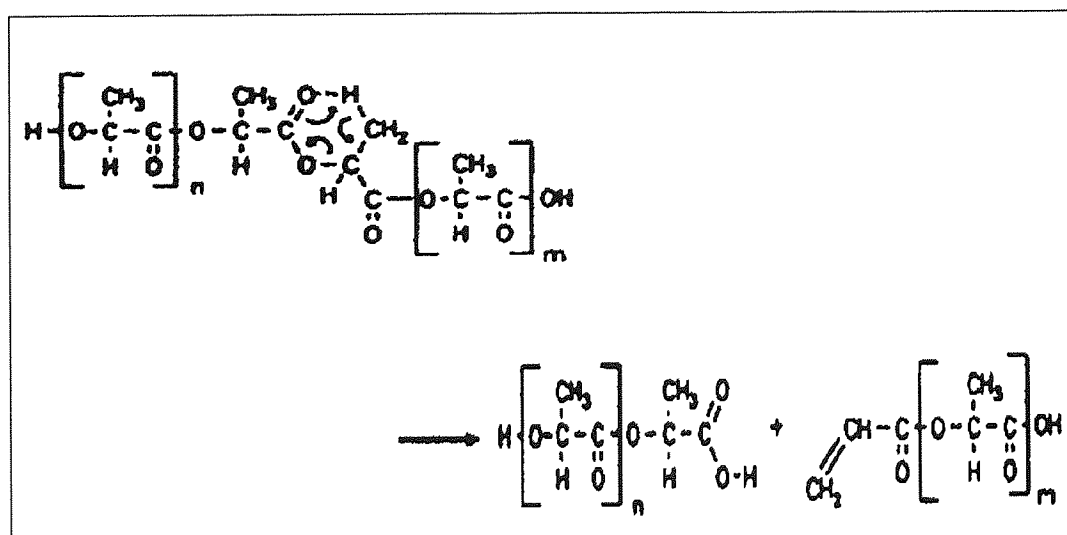


Scheme 1.4: Intermolecular transesterification.

Dahlmzrn.J ²¹ and Tighe ²² also reported that hydrolysis (scheme 1.5) and thermal pyrolytic eliminations (scheme 1.6) by formation of olefinic end groups can also lead to a decrease in molar mass.



Scheme 1.5: Hydrolysis of PLA.



Scheme 1.6: Thermal pyrolytic elimination

The authors (Dahlnmzrn.J ²¹ and Tighe²²) showed that purification of the polylactide before heating increased the thermal stability by removing molecules with low molar mass and residual catalyst. Viljanmaa¹² and co-workers also demonstrated that chemical stabilisation of PLA, such as acetylation of the end groups, led to an increase of thermal stability during processing. However, the drying of the samples before processing or the use of nitrogen as a protective gas during processing seemed to have no effect on the stability of the PLA during processing. The depolymerisation of PLA at high temperature is shown to be caused especially by the presence of residual metal compounds which catalyse the chain transfer, intra- and inter-transesterification reactions ²³.

1.4. SYNTHETIC ROUTES FOR THE PRODUCTION OF PLA

1.4.1 Synthesis of polyesters

Polyesters can be synthesised by three different methods:

- Microbial synthesis
- Polycondensation of the hydroxyacid
- Ring opening polymerisation of the lactone, dilactone, anhydrocarboxylate or anhydrosulfite.

1.4.1.1 Microbial synthesis

Some polyesters, mainly poly(hydroxyalkanoates), which are produced in plant cells, can be synthesised biochemically by bacterial synthesis. The production of these polymers by some microorganisms, such as *Alcaligenes Eutrophus*, is increased by cultivating them under certain conditions: sufficient carbon sources and lack of nitrogen, oxygen and phosphorous. Among the bacterial polyesters, poly3(hydroxybutyric) acid, P(3HB) is the most popular and it is produced by various kinds of microorganism ². P(3HB) (figure 1.6), a crystalline and brittle material, was first discovered by Lemoigne ³ more than 70 years ago but it was only in the late 1950's that it was recognised as a polymeric substance.

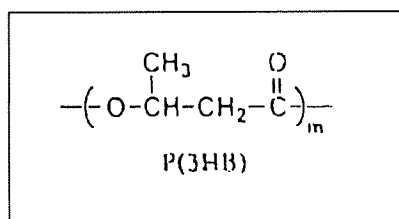


Figure 1.6: P(3HB) structure.

A variety of copolyesters of 3-hydroxybutyrate (3HB) are produced by bacterial fermentation. They include the copolyesters with 3-hydroxyvalerate (3HV), 4-hydroxybutyrate (4HB) and 3-hydroxypropionate (3HP), figure 1.7 and figure 1.8.

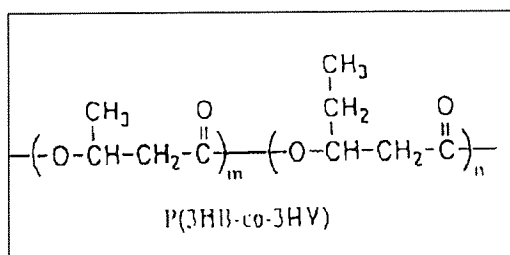


Figure 1.7: Structure of P(3HB-co-3HV)

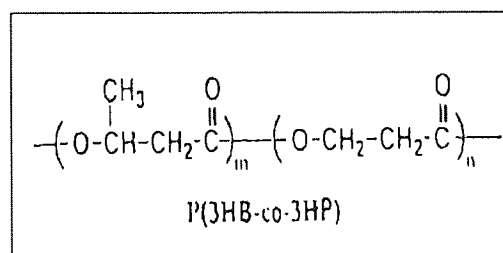


Figure 1.8: Structure of P(3HB-co-3HP)

Other natural biodegradable polymers of great biological and commercial importance are starch (figure 1.9) and cellulose (figure 1.10).

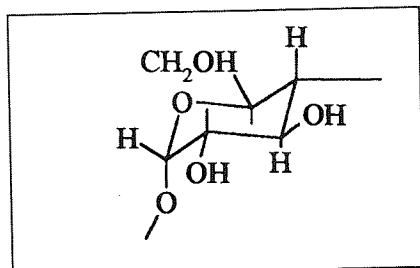


Figure 1.9: Starch

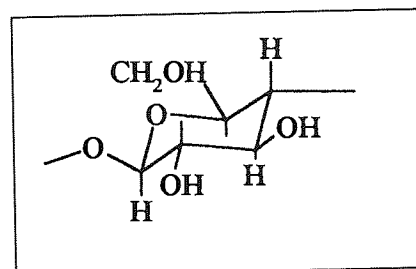


Figure 1.10: Cellulose

Starch is a polymer of glucose in which monosaccharide units are linked by 1,4'- α -glycoside bonds. It is used as an energy source in plants, such as potatoes, rice and corn. Cellulose consists of a repeat unit of D-glucose linked via 1,4'- β -glycoside. It has usually high molecular weight and is used by plants as a structural material to impart rigidity.

1.4.1.2 Polycondensation of the hydroxyacid

Direct polycondensation of L-lactic acid has been known to produce molecular weights in the order of $\approx 10^4$ g/mol because of the unfavourable equilibrium constant for the reaction. High molecular weight polymers²⁴ are difficult to obtain because of the presence of cyclisation reactions. Intermolecular cyclisation is very likely for carboxylic acids as well as other side reactions, such as interchange reactions (inter-trans-esterifications reactions). Broad molecular weight distributions can be a consequence of side reactions (cyclisation and interchange reactions).

This pathway presents various disadvantages such as, high molecular weight polymers can only be produced at very high conversions ($\geq 98-99\%$). In order to obtain high molecular weights long reaction times, high purity reactants and exact stoichiometry are required, since a slight excess of one of the reactants can reduce the final conversion considerably. In addition, equilibrium considerations are also of prime importance. Thus, to displace the equilibrium in the direction of the polymer product a range of factors have to be considered and implemented^{24,25}.

- Reactions should be carried out at high concentrations to minimise cyclisation and maximise the reaction rate.
- Continual removal of water or other small molecules by distillation is required to achieve high conversions.
- Large volumes of solvents of high boiling point are needed for the removal of the dissociated water by azeotropic distillation techniques.
- Multiple reactors and complex facilities are needed for this process and thus raise the production cost.
- Extreme conditions are needed: high temperatures usually in the range of 150-200°C are needed to obtain high conversions.

Some attempts were carried out recently to improve PLLA molecular weights by the direct bulk condensation polymerisation using titanium butoxide as a catalyst²⁵. However, the reaction was carried out at a very low pressure of 1 Torr and 7 hours were necessary to

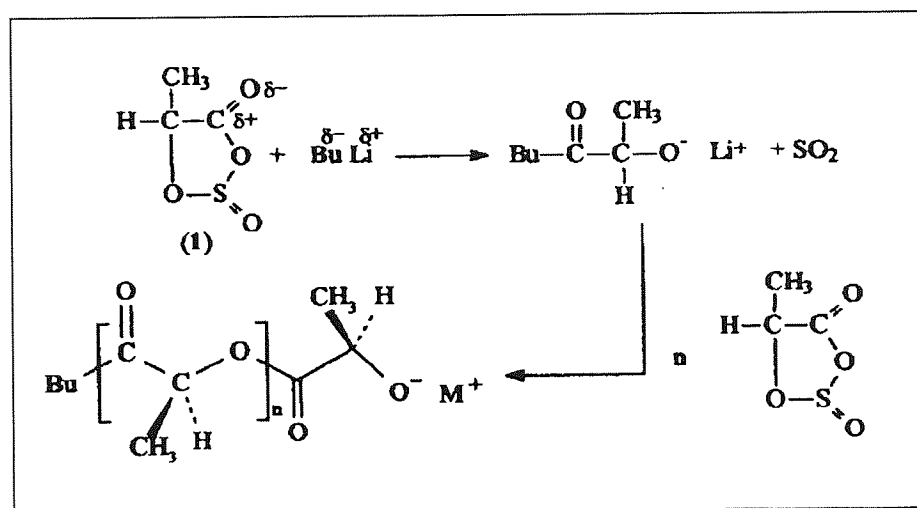
decompress the reactor. Molecular weights obtained are in the range of $3\text{--}4 \cdot 10^4$ g/mol and broad polydispersities are obtained (Pd: 3-4).

1.4.1.3 Ring opening polymerisation

The ring open polymerisation of the lactone/dilactone is the preferred method to obtain high molecular weight polyesters. The advantage of this route is that a wide range of polymers is available. Living ring opening polymerisation is an extraordinary method to produce tailor-made polymers and copolymers with desirable characteristics. Such polymers can only be obtained through a living type process characterised ²⁷ by:

- Good stability of propagating active centres.
- Good correlation between calculated and experimental molar masses.
- High molecular weights can be obtained ($M_n \approx 5 \cdot 10^5$).
- Narrow molar mass distribution (if the rate of initiation is much faster than the rate of propagation).
- Highly optically pure poly(lactides)
- The absence of termination and transfer reactions.
- Bulk polymerisations can be carried out, reducing cost and the use of toxic or expensive solvents.
- The use of specific initiators. Currently, a wide range of systems is available; this topic will be expanded in section 3.4.2.

Alternatively, the anhydrosulfite or anhydrocarboxylate can be synthesised from α -hydroxy acids²⁶ and then the heterocycles can be polymerised thermally or using nucleophilic or base-catalysed reactions over which there is a close control of molecular weight and molecular weight distribution. The anhydrosulfites are more susceptible to ring opening polymerisation than anhydrocarboxylates and its mechanism is shown in Scheme 1.7.

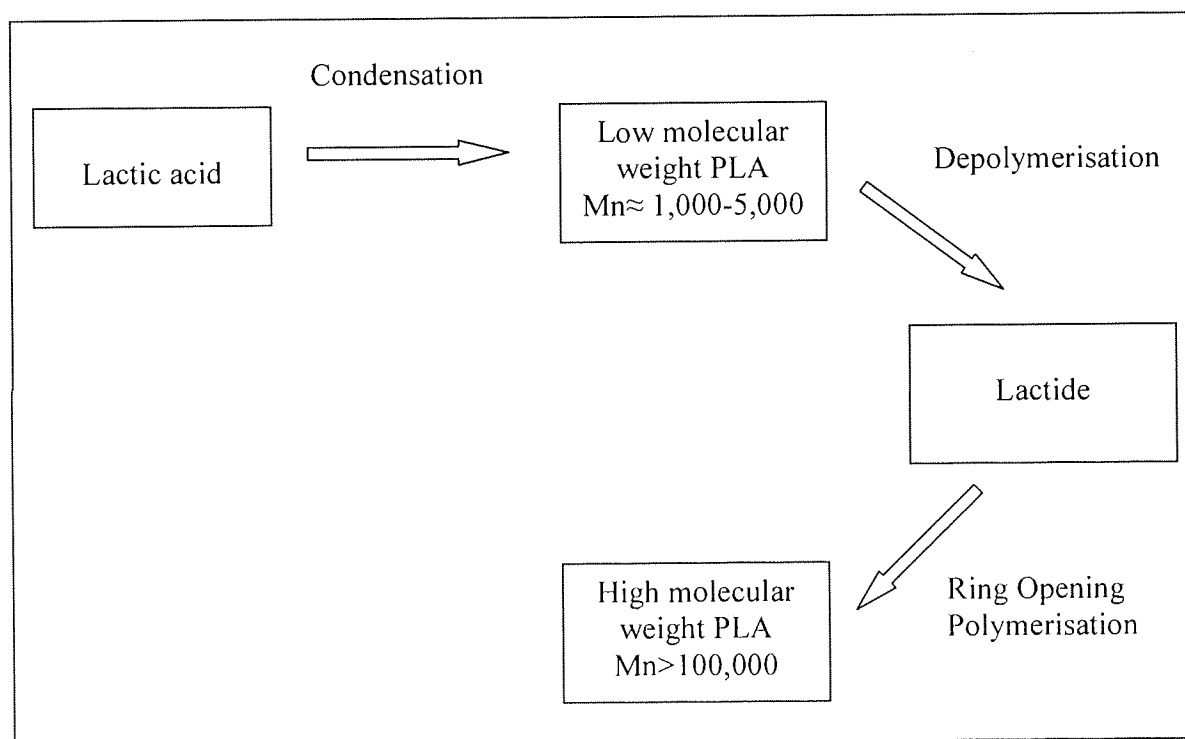


Scheme 1.7: Mechanism for the anionic polymerisation of lactic acid anhydrosulfite.

1.4.2 Industrial manufacture of polylactic acid

Two routes achieve the conversion of lactic acid to high-molecular-weight PLA. Cargill uses a solvent-free process to produce the polymer (NatureWorks PLA) and a novel distillation process for preparation of the monomer in order to manufacture a range of polymers⁵⁷. The process for making NatureWorks PLA begins when a renewable resource such as corn is milled, separating starch from the raw material. Unrefined dextrose, in turn, is processed from the starch. The unrefined dextrose is turned into lactic acid using a fermentation process similar to that used by beer and wine producers. The novelty of the

process lies in the ability to convert lactic acid to a low-molecular-weight polylactic acid, followed by controlled depolymerisation to produce the cyclic dimer (commonly known as lactide). The last step involves the ring opening polymerisation of the lactide in the bulk, using tin octanoate as a catalyst, resulting in the production of PLAs with controlled molecular weights. On average, approximately 2.5 kg of corn (at 15% moisture) are required per kg of PLA (or 2.5 lbs/lb of PLA). This process is described in scheme 1.8.

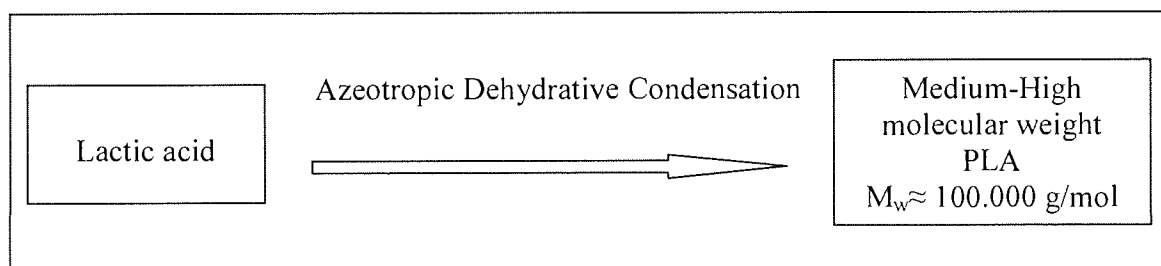


Scheme 1.8: Cargill commercial manufacture process.

Producing the cyclic dimer (lactide) introduces the potential to tailor molecular architecture in the final product. By controlling residence time and temperatures in combination with catalyst type and concentration, it is possible to control the ratio and sequencing of D- and L-lactic acid units in the final polymer. Future technology enhancements

may eliminate the milling step and allow for the use of even more abundant agricultural by products.

In contrast, Mitsui Toatsu⁵⁸ utilises a solvent-based process, in which a medium-high molecular weight polymer is produced by direct condensation, using azeotropic distillation to remove the water of condensation continuously (scheme 1.9). Consequently, synthesised the poly(lactides) have molecular weights much lower than those obtained in the multi-step process develop by Chargill.



Scheme 1.9: Mitsui Toatsu commercial PLA manufacture process.

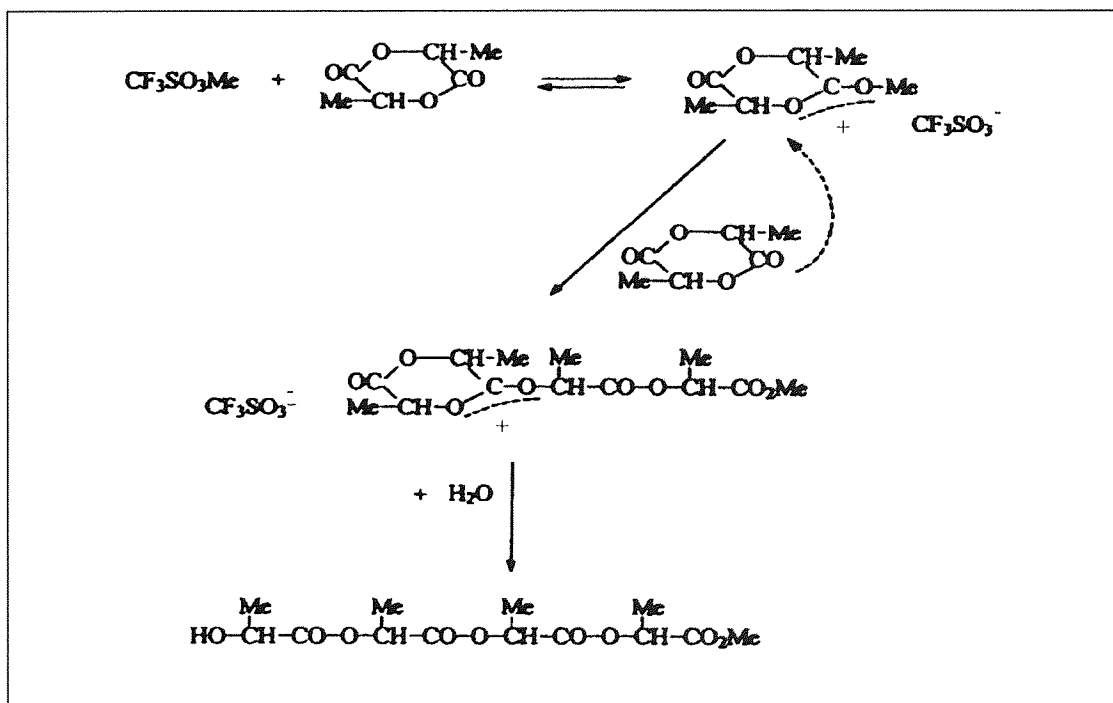
1.4.3 Polymerisation methods of lactide.

The polymerisation of lactides can be classified based on the reaction mechanism of the initiator used, as shown below:

- Cationic polymerisation,
- Anionic polymerisation,
- Coordination-insertion mechanism

1.4.3.1. Cationic polymerisation.

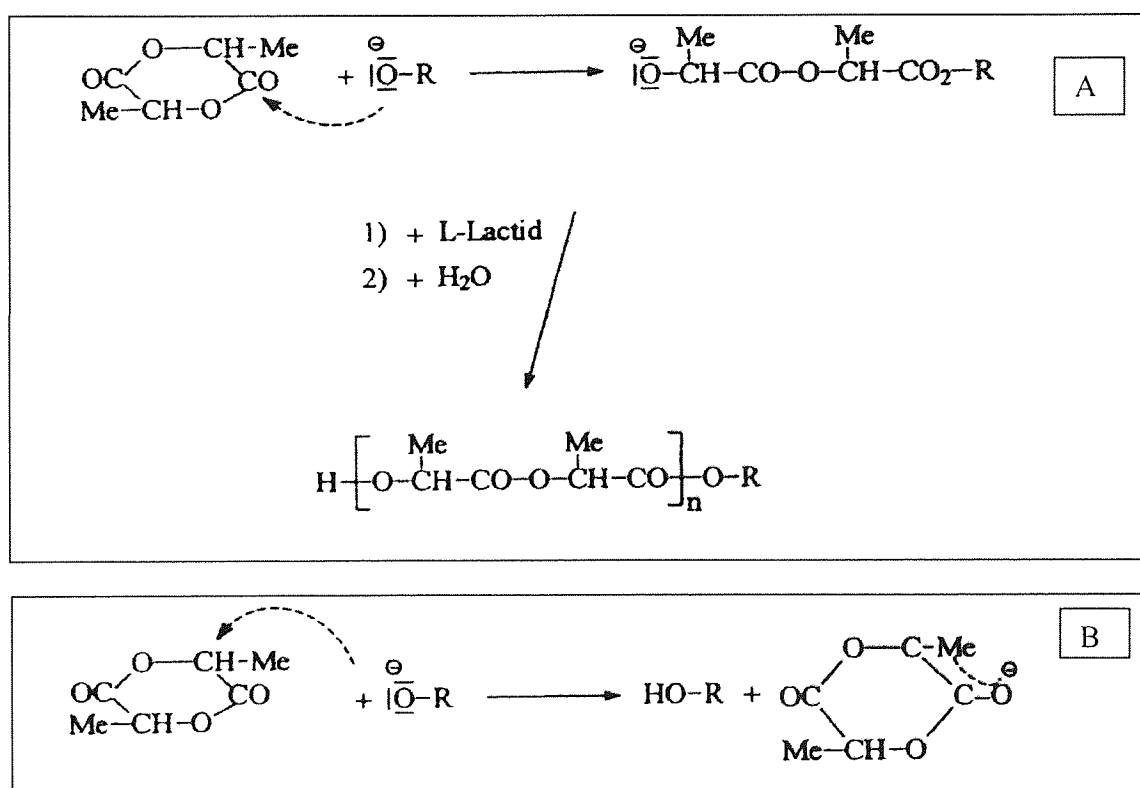
Cationic polymerisation (scheme 1.10) consists of a protonation or alkylation of the carbonyl O-atom of the monomer with the consequence of an electrophilic activation of the O-CH bond. This bond is then cleaved by nucleophilic attack of another monomer, a process which is repeated in every propagation step until a monofunctional nucleophile causes termination. Extensive studies, carried out by Dittrich²⁸ and Kricheldorf,^{29, 30 & 31} have shown that only a few acids or carbenium ion donors are capable of initiating the cationic polymerisation of lactide. This method has the disadvantage that optically pure poly(lactides) can be only prepared at temperatures ≤ 50 °C. At higher temperatures cationic polymerisation causes racemisation since this mechanism involves a nucleophilic substitution at the chiral carbon.



Scheme 1.10: Cationic mechanism of lactide polymerisation.

1.4.3.2. Anionic polymerisation.

Anionic polymerisation of lactide is generally initiated by metal alkoxides^{32,33}. Phenoxides and carboxylates are also active at high temperatures. Both the initiation and propagation steps consist of nucleophilic attack of an anion on the carbonyl carbon of the lactide, follow by the cleavage of the CO-O bond (Scheme 1.11 (A)).



Scheme 1.11: (A) Anionic mechanism of lactide polymerisation with a metal alkoxide initiator. (B) Transfer reactions occurred in the polymerisation of lactide *via* deprotonation of the monomer in α position.

However, because of the highly basic character of many alkoxides, initiation can also proceed by deprotonation of monomer in the α -position *via* an acid base reaction. Owing to

the planarity of the delocalised anion, this deprotonation/reprotonation reaction involves racemisation. Consequently, transfer reactions can take place since the lactide anion is capable of initiating new chains, *via* deprotonation of the monomer (scheme 1.11 (B)). As a result, broad polydispersities and low to medium molecular weights are obtained.

For instance, Kricheldorf and co-workers^{34,35} reported that the yield of poly(L-lactide) from polymerisation of L-lactide initiated with potassium tert-butoxide or butyl lithium in toluene, or dioxane at variable temperatures, does not exceed 75%. The polylactides showed partial polymerisation of lactide and broad molar mass distribution, attributed to the occurrence of side transesterification reactions. Better results were achieved with lithium alkoxides formed from butyl-lithium and primary alcohols³⁶. Primary alcohols are weaker bases than secondary or tertiary alcohols, which could explain why high yields and molar masses of poly (L-lactides) were found and racemisation was minimised. However, the polymerisation does not exhibit living characteristics as is evident from an important discrepancy between experimental and calculated degrees of polymerisation.

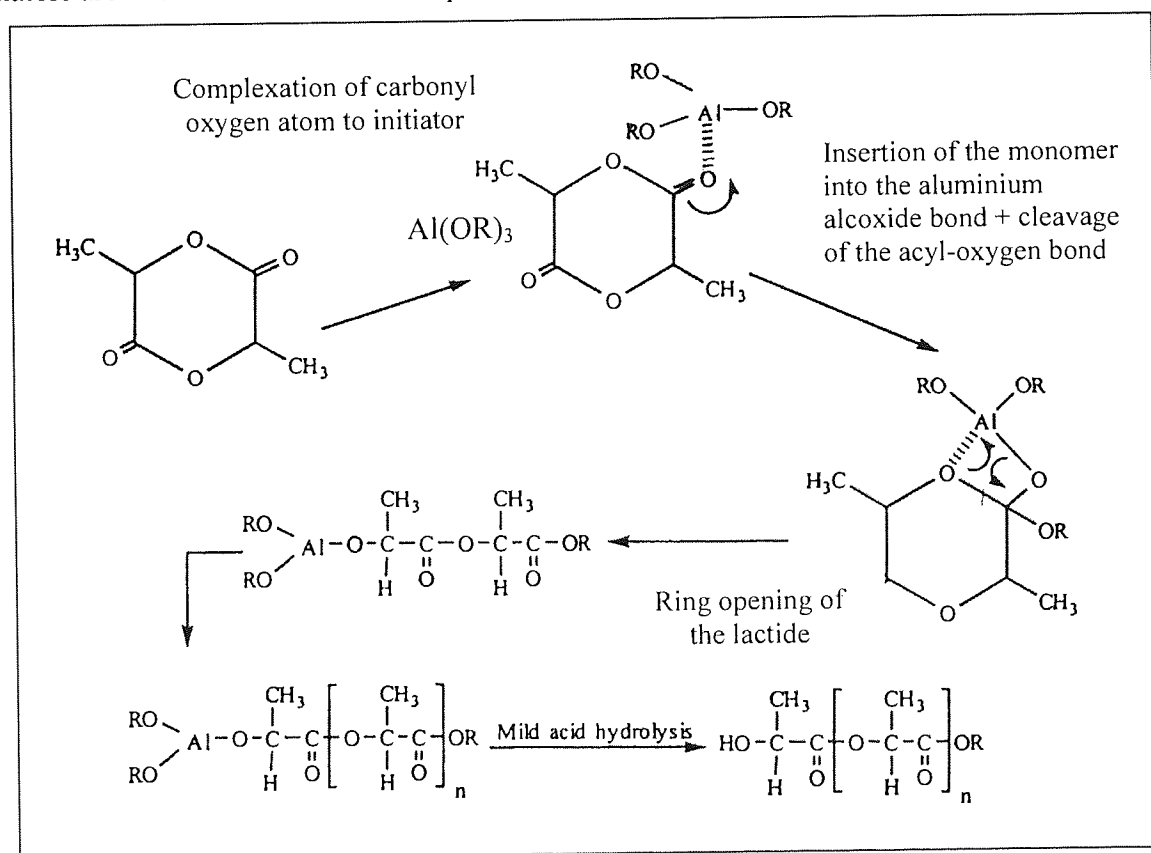
In contrast to the lithium alkoxides, Jedlinski et al.³² studied the polymerisation of L- and D-lactides using potassium methoxide in THF at room temperature. The use of this initiator allowed narrow molar mass distributions as well as a good correlation between experimental and predicted molecular weights. The polymerisation was found to be quite fast and a quantitative yield was reported. Minimisation of transesterification reactions was also observed. High molecular weight poly(lactides) were obtained with dibutyl magnesium and butyl magnesium chloride³⁷. However the rates were very slow and racemisation reactions took place above 25 °C.

1.4.3.3. Coordination-insertion mechanism

Coordination-insertion mechanism is based on metal alkoxides having a covalent metal-oxygen bond and the character of weak Lewis acid initiator such as aluminium alkoxides or zinc compounds. The lactide coordinates temporarily to the metal as a ligand *via* the carbonyl O-atom (Scheme 3.10). This coordination enhances the electrophilicity of the CO-group and the nucleophilicity of the OR-groups, so that an insertion of either lactide or more generally lactones into the metal O-bond may occur. Multivalent metal (Al, Fe, Ti, Sn(IV), Y, Zr, Zn) alkoxides and covalent metal carboxylates such as tin (II) 2-ethylhexanoate are the two main classes of initiators currently utilized for the synthesis of biodegradable aliphatic polyesters and their copolymers⁷². Tin and aluminum alkoxides are the most widely used initiators for the preparation of well-defined aliphatic polyesters of controllable molar mass and narrow molar mass distributions⁷³.

Another advantage of covalent initiators is the easy control over the molecular weight *via* varying the monomer/initiator molar ratio. Much higher molecular weights are obtained and fewer transfer reactions are observed in comparison to cationic or anionic initiators. Racemisation is also reduced, even at high temperatures.

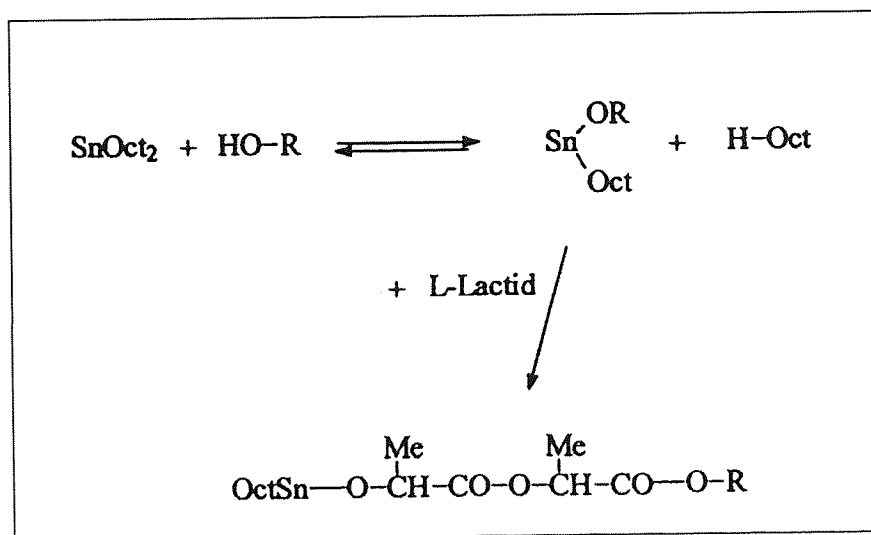
Aluminium alkoxides, such as $\text{Al}(\text{O}^i\text{Pr})_3$ and Al-Shiff's base initiators, have been proved to be effective promoters of the ring opening polymerisation of lactide. Aluminium is electron deficient and readily forms complexes with electron rich substrates. The coordination-insertion mechanism (scheme 1.12) leads to a polymerisation where the chemical nature of the chain end functional group can be controlled and the polymer shows narrow polydispersity and no side reactions [38-41]. Aluminium compounds are toxic, which is the reason why these initiators are not used for medical and pharmaceutical applications.



Scheme 1.12: Coordination-insertion mechanism of lactide polymerisation when aluminium alkoxide is used as an initiator.

The initiators generally used for the polymerisation of lactide such as aluminium alkoxides or Al-Shiff's bases are commonly prepared and applied as neat and pure compounds. However, in the case of tin octanoate ($\text{Sn}(\text{II})$ 2-ethyl-hexanoate) and diethyl zinc,

the initiators are prepared *in situ* by reaction with alcohols and phenols. Both tin octanoate and diethyl zinc should be truly considered as co-initiators or catalysts. Tin octanoate^{42, 43} is the most widely used initiator for synthesis of homopolymers and copolymers of lactides. In its pure state tin octanoate does not contain reactive alkoxide groups. Recent mechanistic studies by several research groups proved that the alcohol that is usually added as an initiator substitutes at least one octanoate group in a rapid equilibrium and the resulting tin alkoxides then the true initiator of the polymerisation process (Scheme 1.13).



Scheme 1.13: Rapid equilibrium between tin octanoate and an alcohol.

However, although tin octanoate has the FDA approval (Sn(IV) more so than Sn(II)) it does have some disadvantages. Tin compounds are toxic and recently there have been claims of its cytotoxicity⁴⁴ for human health. Therefore, its use is not recommended for medical, pharmaceutical or food applications.

Despite the good performance of some of the previously mentioned catalysts, in recent years the demand for non-toxic covalent initiators has been high. Especially since applications

of polymer in the pharmaceutical and medical fields have grown and potential uses of PLA have been extended to areas such as food packaging, where PLA free of heavy metals is desirable. Since complete removal of the catalyst from the finished polymer is not always achievable, and in many of their applications are in contact with the human body, new catalytic routes based on the use of non toxic initiators, such as Ca, Fe, Ge and Zn, have been studied and the results are discussed below.

Of the non-toxic catalysts, *in situ* generation of a calcium alkoxide initiator from bis(tertahydrofuran)calcium bis[bis(trimethyl silyl)amide] and an alcohol reported by Feijen⁴⁵ is worthy of mention. The solution polymerisation in THF, at room temperature, shows fast living ring-opening polymerisation of both ϵ -caprolactone and L-lactide and the absence of racemisation. Polyesters and block copolyesters of expected molecular weight and tailored chain structure can be readily prepared. However, molecular weights reported are not as high as those obtained with tin octanoate. More recently, studies carried out using organic amino calcium catalysts²³ showed the same results as those obtained with *in situ* calcium alkoxides.

A number of iron compounds have also been studied. For instance, iron oxide⁴⁶ was used as a catalyst for the melt polymerisation of lactide. However, the catalyst proved to be useful only at high temperatures (180 °C) and the long reaction times necessary to obtain high conversions, caused racemisation. In other studies, hematin related porphyrine complexes and iron lactate were used in the polymerisation of lactide^{47, 48} under similar conditions. Unfortunately, the poly(lactides) obtained had relatively low molecular mass and were formed in low yields. More recently, further studies were carried out using iron lactate⁴⁹ and monocarboxylic iron derivatives⁵⁰. Although, higher molecular weights were obtained they were not comparable with molecular weights produced by tin octanoate or zinc compounds. In

addition, high polymerisation temperatures are required in order to obtain high yields, and racemisation and broad polydispersity is observed.

Studies carried out by Kricheldorf⁵¹ using germanium alkoxides clearly demonstrates that these initiators are far less reactive than tin alkoxides or tin octanoate. Reaction times exceeded 4 days.

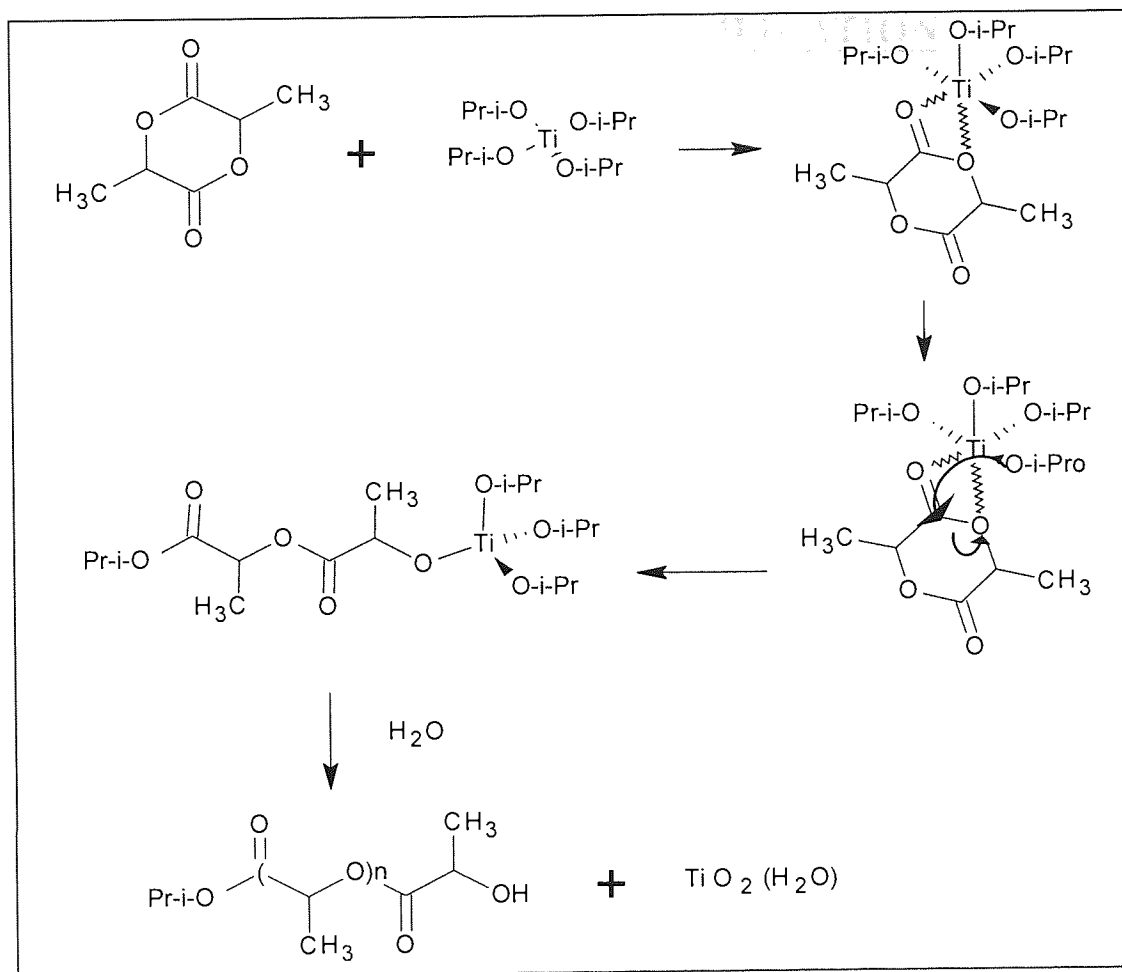
Zn metal and Zn lactate were introduced industrially in France by Phusis to produce lactide homopolymers and copolymers with glycolide⁵². Zn metal is efficient, configuration-respecting but leads to rather slow polymerisations. Studies carried out with Zn complexes⁵³ ($\text{LZn}_2\text{Cl}_2\text{OEt}$, where L: $\text{C}_{23}\text{H}_{43}\text{N}_2\text{O}_2$) showed similar results. However, maximum molecular weights obtained ($M_n \approx 5 \times 10^4 \text{ g.mol}^{-1}$) were not as high as those obtained with Zn metal ($M_n \approx 2 \times 10^5 \text{ g.mol}^{-1}$).

Lanthanide alkoxides show a very high reactivity in the polymerisation of lactide. Lanthanum derivatives are the most reactive initiators, allowing high conversions and narrow polydispersities in solution at room temperature in short times^{54,55}. Yttrium and samarium derivatives are less reactive than those of lanthanum. Maximum molecular weights obtained with these metals do not exceed $5 \times 10^4 \text{ g.mol}^{-1}$, still well below those obtained with tin octanoate.

1.4.4 Development of non toxic catalytic routes.

High molecular weight poly(lactides) are necessary for applications such implants, sutures, fibres and food packaging. On the other hand, low molecular weights are required for drug delivery and adhesives applications. Thus, development of a non-toxic catalyst that can produce a wide range of molecular weights is one of the main aims of this research.

A range of titanium alkoxides have been selected to be tested for the ring opening polymerisation of lactide, in order to produce lactide homopolymers and copolymers. Titanium is perhaps the most biocompatible material known^{69, 70}. Titanium shows non-toxicity and good compatibility towards organisms and mucosa when used as body implants. It also is present in plants and in the human body. Ti (IV) shows some resemblance to Sn (IV). It has a similar covalent radius to Sn (IV); they both have isomorphous oxides, TiO_2 and SnO_2 and similar halides (TiCl_4 & SnCl_4), which can be readily hydrolysed. Little research has been conducted on the use of titanium catalysts for the polymerisation of lactide. However, these initiators have been very successful for the synthesis of polyolefines. $\text{Ti}(\text{O-Bu})_4$ was first used by Kricheldorf³⁰ for the bulk polymerisation of lactide and ϵ -caprolactone. $\text{Ti}(\text{O-Bu})_4$ was shown to be a very active initiator for the ring opening polymerisation of lactide, yielding polylactides with controlled molecular weights but reaction times required to achieve high conversions were high. Recently, $\text{Ti}(\text{O-Bu})_4$ was successfully used for synthesis of PEG spirocycles and the subsequent use of these macro-initiators in the preparation of lactide copolymers⁵⁶. The use of $\text{Ti}(\text{OR})_4$ as an initiator for the ring opening polymerisation of LA will generate TiO_2 as a safe by-product as shown in scheme 3.14.



Scheme 1.14: Coordination-insertion mechanism of lactide polymerisation using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator.

1.5. ROUTES TO PLA MODIFICATION

As mentioned previously, PLA has remarkable physical properties. Those of note include; good resistance to fatty foods and dairy products, equivalent to PET, excellent flavour and aroma barrier, high clarity and gloss. These properties make it an excellent material for amorphous and biaxially oriented films. PLA also shows greater tensile modulus and a flexural modulus greater than commodity plastics such as PS. However, the flexural modulus of PLA is still far below more flexible commercial polymers such as PE and PP. Certain potential applications of PLA such as adhesive or plastic bags require this property to be improved. In an attempt to overcome these problems, a variety of modification techniques have been applied to biodegradable polymers to improve their physical characteristics. These include:

- Addition of plasticisers
- Blending with other polymers
- Copolymerisation

1.5.1 Modification via additives: Plasticisers

1.5.1.1 *Plasticiser requirements*

In addition to the inherent properties of PLA, technologies have been developed to flexibilise PLA using renewable-resource based plasticisers. Plasticisers are used to impart properties such as flexibility, resilience, and softness to polymers. These materials can best be described as a solvent for a polymer, and as such, it is usually a liquid, although in some cases can be solid. In order to function effectively a plasticiser should meet the following requirements:

- It should be a substance with a low volatility and have a high molecular weight, usually greater than 300 Da.
- Have a similar solution parameter (δ) to that of the polymer.
- If a polymer has a tendency to crystallise, the plasticiser should have a specific interaction with the polymer. For these interactions to happen, polymer and plasticiser should have functional groups that can afford mutual attraction. Such groups should be located in relation to each other, so as to permit attractive forces to function. The plasticising molecules should be of the correct shape.
- It should be compatible with the polymer and not migrate to the surface of the polymer.
- It should be chemically and thermally stable.

Plasticisers have a number of effects on mechanical properties:

Tensile strength is generally reduced, because the plasticiser weakens the intermolecular bonds holding the polymer molecules together.

Both the **Young's modulus**, E , and the **shear modulus**, G , of a polymer drop under the influence of a plasticiser.

% of elongation at break usually increases, apparently because the plasticiser permits polymer molecules to slide freely past each other, rather than breaking apart during extension.

Tear strength: is the force required to tear a material under specific conditions. The use of plasticisers usually causes a decrease in the tear strength. The viscous layer of plasticiser can cause a decrease in tear strength, as it cannot withstand the tearing force. Plasticisers have to be selectively chosen to avoid a decrease in tear strength and, therefore, weakening the mechanical properties of the materials. The decrease in the tear strength sometimes can be overcome by the addition of reinforcing fillers.

Creep test provide a measure of the tendency of the polymer to deform after a polymer has been subjected to a constant stress for a period of time. Therefore creep could be defined as a progressive increase in strain, over a period of time, in a polymer subjected to a constant stress. Creep, under long-term load, generally becomes greater, because the plasticiser reduces the number of polymer-polymer bonds available to resist it.

The friction coefficient, which is the ratio of the force that maintains contact between an object and a surface and the frictional force that resists the motion of the object, is generally enhanced by the appropriate choice of plasticiser. The plasticiser increases the mobility of the polymer sufficiently to permit it to penetrate into the microscopic irregularities in the surface over which, it would otherwise slide.

Plasticisers also have an effect on thermal mechanical properties. Fundamentally, addition of plasticiser shifts the entire modulus temperature having an effect on mechanical and physical properties:

Glass transition temperature is lowered, making the polymer soft and flexible. A decrease in T_g to values below or near room temperature will provide the polymer with the desired flexibility.

Melting and flow temperatures also decrease, and melt viscosity at any given temperature is lower, thus improving processability of both flexible and rigid plastics.

1.5.1.2. Plasticising theories

Three theories have been developed in an attempt to explain the plasticisation mechanism⁶⁰:

1.5.1.2.1 Lubrication theory

In the lubrication theory the plasticiser is viewed as a lubricant, where the plasticiser molecules ease the movement of the polymer chains by pushing them further apart and reducing intermolecular friction. Lubricants exhibit no bonding forces with the polymer. They lower the inter-molecular forces and, therefore, only cause partial plasticisation. Lubricants also cause a decrease in the melt viscosity, thereby facilitating processing while generally affecting the properties of a polymer insignificantly. Whilst attractive in its simplicity, the theory does not explain either the efficiency of plasticisers in lowering the glass transition temperatures of polymers or the success of some plasticisers and the failure of others.

1.5.1.2.2 The solvation theory

The solvation theory is based on concepts of colloid chemistry. The polymer/plasticiser system is regarded as a lyophilic colloid, in which the plasticiser will act as a solvating agent. The solvating or swelling power of a plasticiser depends on its molecular weight and on its functional groups. Whether or not a plasticiser is effective as a solvent depends on three intermolecular forces: plasticiser/plasticiser, plasticiser/polymer and polymer/polymer.

1.5.1.2.3 The gel theory (the thermodynamic theory)

The gel theory is an extension of the lubricity theory. It uses solution and swelling as an explanation of gelling but views plasticisation as the reduction the polymer attachments or intermolecular interactions. The gel theory attempts to interpret the intermolecular forces in the plasticiser/polymer system by a model based on the resistance to deformation of a three-dimensional gel. The gel is formed by bonding forces, which are effective along the polymer chains. As an example, in a stiff, brittle polymer the intermolecular separations are small compared with an elastomer and every deformation causes internal stresses, which the molecules cannot accommodate, consequently, elasticity of this polymer is very low (hard rubber). The effect of a plasticiser is now treated as that of reducing the molecular forces much as possible and loosening the bonding of polymer molecules to each other. The gel theory, by itself, is insufficient to explain a completely plasticised system since while a certain concentration of plasticiser molecules will provide plasticisation by this process the remainder will act more in accordance with the lubricity theory, with unattached plasticiser molecules swelling the gel and facilitating the movement of plasticiser molecules, thus imparting flexibility. Molecules acting by this latter action may, on the basis of molecular size measurements, constitute the bulk of plasticiser molecules. If plasticisation took place exclusively by this method it would not be possible to explain the ability of PVC polymers to accept their own weight in plasticiser without exudation i.e. large amounts of additional space ("free volume") are created which other plasticiser molecules can occupy.

1.5.1.2.4 The free volume theory

The free volume theory extends the above ideas and also allows a quantitative assessment of the plasticisation process. Free volume, V_f , is defined as the unoccupied space in a sample, arising from the inefficient packing of disordered chains in the amorphous region of a polymer sample. The equation (equation 1.1) that described the free volume of a polymer is shown below:

$$V_f = V_t - V_o, \text{ Equation 1.1}$$

In the above equation V_t represents the observed specific volume of a sample and V_o the volume occupied by the polymer molecules and the free volume the equation. Each term is temperature dependant. Free volume is a measure of the internal space available in a polymer to undergo rotation and translation, which imparts flexibility to the material. A plasticiser acts in a way that imparts a greater free volume per volume of material since (i) there is an increase in the proportion of end groups and (ii) it has a glass transition temperature (T_g) lower than that of the polymer itself. Therefore plasticisers act so as to increase the free volume of the polymer and also to ensure that free volume is maintained as the polymer-plasticiser mixture is cooled from the melt.

Clearly, the use of a given plasticiser in a certain application will be a compromise between the above ideas and physical properties such as volatility, compatibility, high and low temperature performance, viscosity etc. This choice will be application dependent and therefore there is no ideal plasticiser for every application.

1.5.1.3. Plasticisers for PLA

The effect of citrate and tartrate ester plasticisers, such as tri-isobutyl citrate (TIBC) and di-isobutyl tartrate (DIBT), on the mechanical properties of PLA was studied by Burford⁵⁹. All plasticisers tested caused a significant modification in both the tensile strength and the percentage of elongation at break compared to unmodified PLA. Percentage elongation at break increased dramatically from 3% for unmodified PLA to values over 200% for modified PLA with ester plasticisers. As expected, the tensile strength of modified PLA showed a decrease of roughly 50%, as an average, compared to unmodified PLA.

Addition of 17% by weight of ester plasticisers such TIBC and DIBT lowered the glass transition temperature (T_g) of unmodified PLA from 53.4 °C to 27 °C and 32.5 °C respectively. Crystallisation temperature (T_c) and the melting point (T_m) of PLA also dropped significantly. In the case of T_c a decrease from 95 °C to 78.3 °C and 72.9 °C was observed for TIBC and DIBT respectively. In the same way, T_m also dropped from 175 °C for unmodified PLA to 153.5 °C and 164.8 °C when TIBC and DIBT, respectively, were added. However, the use of plasticisers is not strongly recommended when the polymer is to be used for packaging or medical applications because of the possible migration of the plasticiser to the surface of the polymer. Migration of the plasticiser to the surface will cause a change in the physical and mechanical properties of the material and in the case of food application the plasticiser may cause food contamination.

1.5.2 Modification by blending

1.5.2.1 Definition

The physical characteristics of a polymer can sometimes be modified by blending with another suitable polymer. A polymer blend is simply a mixture of two or more polymers. For instance, if a hard crystalline material is blended with a soft flexible one, the combined blend could achieve intermediate physical properties. However, in many cases, the thermodynamics of mixing prevent the formation of completely miscible blends and phase separation occurs. This results in worsening of the properties of the system and consequently a desire to generate homogeneity of the phases is preferred. Consequently, the two phase system blend exhibit two T_g 's corresponding to each of the two different phases. In contrast, the more uncommon finely dispersed polymer blends may however display only one glass transition. Some polymer blends exhibit partial miscibility. They have a mutual, limited solubility indicated by a shift in the two T_g 's accompanying a change in the phase composition of the blend. The level of homogeneity mainly depends on the solubility parameters (δ) of the components and their concentrations in the blend. The solubility parameter provides as systemic description of the miscibility behaviour of the blend components. It also may be influenced by the method of blending used. A good example of miscibility is found in PLLA and PEO blends⁶¹. High molecular weight PEO and PLLA are miscible in the amorphous state. A single T_g , intermediate between the T_g of the pure components, can be observed. The location of the T_g of the blend appears to be proportional to the blend composition. In the same way, the melting point of PLLA also decreases from 196 °C to 190 °C when PLLA is blend with PEO at PEO concentrations of 18 %. Blending PLLA with PEO, at concentrations higher than 18 % by

weight, significantly influences the mechanical properties of the compression-moulded PLLA. The elongation at break shows a strong increase from 4% for the PLLA homopolymer up to 170% for PLLA/PEO blends containing 18% concentration of PEO, while the tensile strength decreases by half. However, blends of PLLA and PEO with concentrations of PEO over 20 % show phase separation¹⁰¹

There are many advantages of blending, ranging from improvement in physical properties to reduction in cost. However, in many cases the thermodynamics of mixing prevent the blends from being compatible.

1.5.3 Modification through co-polymerisation (internal plasticisation)

1.5.3.1 General characteristics.

Copolymerisation, also known as internal plastisation, is a useful method to modify physical and mechanical properties and also to improve processing. It is based on the modification of the polymer chains by reacting with a flexible and softened monomer (without bulky groups) to reduce the rigidity of the polymer (T_g) and in some cases the melting temperature. Reduction of the polymer melting point will aid reduction of the processing temperature and, therefore, to reduce degradation of the polymer during processing.

There are numerous categories of copolymers which are divided into classes based upon the arrangement of the monomer units within the polymer chain. Considering the

simplest case, that of the copolymerisation of two monomers (A and B), a variety of structures can be obtained as described below;

Alternating copolymers are obtained when each monomer is distributed within the chain in a regular alternating fashion (ABABABAB). This monomer distribution is commonly formed when step growth polymerisation of two monomers, A and B, is carried out.

Random (statistical) copolymers are produced when irregular propagation takes place and the two monomers are distributed within the chain in a statistical fashion (ABABAAAABABBA). This is the most common encountered configuration.

Block copolymers are formed by sections within the polymer chain contains long sequences of one monomer joint to another sequence or block of the other monomer (AAAABBBB). Other combinations are also possible such triblock (AAAAABBBBBBAAAAA) or alternating block (AAABBBAAABBBAAA).

Tapered copolymers consist of small monomer blocks sequences, which have been randomised by secondary reactions or by the different reactivity of each monomer (AAABAABBABBB).

Graft copolymers, branch or non-linear copolymers can be produced by attaching long or short chains of one monomer to the main chain of another homopolymer.

Stereoblock copolymers have a special structure that can be formed by having one monomer with a distinctive feature "tacticity". The regular or irregular distribution of the monomer that possesses atactic centres will generate different type of copolymers.

The monomer distribution within the polymer chain will affect the mechanical and physical of the final material.

1.5.3.2 Copolymers of lactide

1.5.3.2.1 Copolymers of lactide with glycolide.

The most utilised co-monomers for the medical and pharmaceutical applications of lactide polymers are glycolide and ϵ -caprolactone. Both monomers have a low immunogeneity and an exceptionally low toxicity. The resulting polymers are also biodegradable, which makes them ideal materials to be used as sutures, implants, drug delivery components or food packaging. Glycolide generates polymers which are highly crystalline with a high melting point around 219 °C. Although poly(glycolide) is not a very flexible material (T_g: 39 °C), it has satisfactory mechanical properties and a higher degradation rate than lactide. On the other hand, poly(caprolactone) is a more flexible material, with a glass transition temperature (T_g) of -60 °C and a melting point of 56 °C. Unlike poly(glycolide), poly(ϵ -caprolactone) shows a slower biodegradation rate than poly(lactide). The combination of these monomers with lactide to form co-polymers allows a good control over the final mechanical properties of the modified poly(lactide) and its biodegradation rate.

Lactide/glycolide copolymers were investigated by Bero⁶² using calcium acetylacetonate as an initiator in the bulk. All-in-one copolymerisation of lactide and glycolide resulted in copolymers containing long glycolide blocks. Long reaction times and temperatures around 200 °C were needed in order to obtain high conversions. The average length of the lactidyl and glycolidyl blocks were very close to those of the respective blocks obtained when zinc lactate⁶³ was used as an initiator under the same conditions. However, these blocks were almost twice the length of the corresponding blocks obtained with tin octanoate⁶⁴. This suggests that less trans-esterification took place when initiators such as calcium acetylacetonate and zinc lactate were used. Conversely, the use of tin octanoate as an initiator allows a monomer sequence distribution that is closer to those of tapered or random copolymers. Iron compounds⁶⁵, in particular iron acetylacetonate, were also used to produce high molecular weight copolymers of lactide and glycolide with molecular weights comparable to those obtained with tin octanoate. However, reaction times exceeded 5 days. Copolymerisation of lactide and glycolide showed Tg's in between those of the parent homopolymers, in some cases, even lower than the Tg obtained for both homopolymer.

1.5.3.2.2 Copolymers of lactide with ϵ -caprolactone.

Copolymerisation of lactide with a flexible monomer, such as ϵ -caprolactone, has been widely investigated by various research groups. Copolymers of lactide and ϵ -caprolactone combine the permeability and flexibility of the PCL with the rapid biodegradation of the PLA¹¹. This strategy is useful to modify the biodegradation rate of the final material, to improve phase morphology and interfacial adhesion. Copolymers of lactide and ϵ -

caprolactone (block and random) can be tailor made using tin octanoate as an initiator. Their adhesion and reological properties have made them very attractive as tissue ¹¹ and hot melt adhesives ^{12, 13}. AB and ABA block copolymers of lactide and ϵ -caprolactone were successfully synthesised using aluminium alkoxides ⁶⁶ and bimetallic aluminium-zinc alkoxides ⁶⁷ as initiators. Block copolymers can be precisely engineered to provide various controllable periods of biodegradation and controlled release by varying the block length. However, the co-polymerisation rate and conversion were somewhat low.

1.5.3.2.3 Copolymers of lactide with PEG.

A third category of lactide copolymers correspond to materials that possess blocks of poly(ethylene glycol) and lactide. Poly(ethylene glycol), also known as PEG, is a polyether with properties such as, excellent biocompatibility and flexibility, its non-toxic and hydrophilic. Introduction of a hydrophilic and flexible PEG chain into hydrophobic polylactones leads to a new family of biomaterials, with a hydrophilicity/hydrophobicity balance and degradability dependent on its precise composition.

Branched polymers exhibit significantly different physiochemical properties than their linear counterparts of the similar molar mass.^{74, 75, 76} For instance, the presence of a large degree of branching in the backbone of a polymer provides enhanced solubility, lower viscosity and lower crystallinity. Biocompatible polymers with branched architectures are also needed to avoid drawbacks of linear biodegradable polymers such as excessive brittleness and lower thermal stability, which reduces their utilization in high temperature processing applications ⁷⁷. Consequently, the potential use of branched polymers for packaging and as biodegradable adhesives is very attractive. Additionally, polymers with macromolecular

architectures such as star and hyperbranched are advantageous due to their well-defined structures and ease of surface functionality⁷⁸. Therefore, recent efforts are now focused on the synthesis and their copolymers for various biomedical applications.

The preparation of these polymers is similar to that of the preparation of the homopolyester. Ring-opening polymerisation of lactones has been widely used in the preparation of block copolymers of PEG using catalyst such as metal oxides, tin octanoate⁴²,⁶⁸ and potassium alkoxides^{48, 32, 43} and PEG with different number of hydroxy groups as co-initiators. The copolymerisation proceeds according to a 'coordination-insertion' or an anionic mechanism, in most cases. A few other methods for example, catalyst-free and polycondensation, have been also used but they could not compete with the methods described above.

The use of amines as co-initiators in the synthesis of star-shaped biodegradable polyesters is also receiving considerable interest. The polymerization of ϵ -CL or LLA using $\text{Sn}(\text{Oct})_2$ and a primary amine does not differ mechanistically from alcohol initiated ROP.¹³⁷ Furthermore, Lui et al. showed that the amino group of amino acids initiated the polymerization of ϵ -caprolactone through the rupture of the acyl-oxygen bond of the amino group in amino acid to form $-\text{NH}-\text{CO}-$ linkage⁷⁹. Schnabelrauch et al. synthesized star-shaped PLLA using a series of initiators including amino acid esters such as glycine ethylester, L-lysine ethylester, p-Aminobenzoic acid and ethylester⁸⁰. In another study, Wang et al. prepared star-shaped PLAs using an amine-terminated poly(amidoamine) (PAMAM) dendrimer with eight terminal amine groups.⁸¹ However, characterization of the polymers using size exclusion chromatography (SEC) revealed multi-modal SEC profiles at low monomer conversions

which reflected the formation of oligomers with different molar mass at different initiating sites (amine and amido groups) due to steric hindrance.

One of the most important goals of almost all copolymerisations of lactide is the synthesis of block, and random copolymers. Ideally, the ability to produce both as well as branched copolymers is desired. Block copolymers of lactide are normally crystalline and random copolymers amorphous. The crystalline or amorphous nature is commonly characterised by differential scanning calorimeter. The synthesis of block and random copolymer of lactide and caprolactone as well as the synthesis of block copolymers of lactide and PEG using titanium alkoxides as initiators was one the proposed goals for this thesis.

CHAPTER 2

TITLE: EXPERIMENTAL TECHNIQUES

2.1 MATERIALS

2.1.1- Solvents

Toluene was purchased from Fisher as standard lab grade. Prior to use as a polymerisation solvent, toluene was dried over calcium anhydride and distilled under nitrogen.

Ethyl acetate was purchased from Fisher as HPLC grade, dried over calcium hydride and distilled under nitrogen, before it was used to recrystallise lactide.

Chloroform and methanol were obtained from Fisher as HPLC grade and used as received.

Distilled water was purchased from Fisher as HPLC grade.

2.1.2- Catalyst

Titanium (IV) iso-propoxide was bought from Aldrich as 99.999 % purity. It was stored in the glove box and used as supplied.

Titanium (IV) propoxide was purchase from Aldrich as 95% purity. It was stored in the glove box and used as received.

Titanium (IV) n-butoxide was purchase from Aldrich as 98% purity. It was stored in the glove box and used as received.

Titanium (IV) tert-butoxide was supplied by Aldrich as 95% purity. It was stored in the glove box and used as received.

Titanium (IV) 2-ethyl-hexoxide was also purchased from Aldrich as 97% purity. It was stored in the glove box and used as received.

2.1.3- Monomers

L-Lactide (laboratory grade) was supplied by Purac and recrystallised under inert conditions in dried ethyl acetate prior to use, as explained in section 2.2.1.3. Finally, it was dried under vacuum for two hours and stored under argon in a glove box.

D,L-lactide (industrial grade) was supplied by Chargill and recrystallised under inert conditions in dried ethyl acetate prior to use, as explained in section 2.2.1.3. Finally, it was dried under vacuum for two hours and stored under argon in a glove box.

ϵ -Caprolactone was purchased from Aldrich as 99% purity. Prior to use ϵ -caprolactone was dried over calcium hydride and distilled under vacuum, as explained in section 2.2.2. Once purified it was stored in the glove box.

2.1.4-Polymers

Polyethylene glycol 400 (di-hydroxy terminated, Mn: 400 g/mol.), **Pentaerythritol ethoxylate** (3/4 EO/OH, Mn: 270), ***O,O'*-Bis(3-aminopropyl)polyethylene glycol** (Mn: 1500) and **di-hydroxy terminated polycaprolactone** (Mn:1250) were bought from Aldrich and stored in the argon box prior to use.

Methoxy polyethylene glycol 350 (Mn, is 350 g/mol) was purchased from Aldrich. It was dried under argon by using molecular sieves and stored in the argon box. Methoxy polyethylene glycol was dried prior to use since it was not stored in the argon box when bought.

2.1.5- Drying agents

Calcium hydride 97% was purchased from Avocado chemicals and used as supplied.

Molecular sieves 3Å was purchased from Aldrich and dried in the oven at 200 °C prior to use.

Phosphorous pentoxide was supplied by Aldrich and used as received.

2.2- TECHNIQUES TO HANDLE AIR AND MOISTURE

SENSITIVE MATERIALS

Living polymerisations are by nature extremely sensitive to impurities including oxygen and moisture. Solvent and reactants were distilled or recrystallised, depending on the nature of the chemical, prior to use. They were also handled on every occasion under an inert atmosphere. The different purification techniques used are explained in detail in section 2.2.1. All glassware used for polymerisation and synthesis of macro-catalysts was thoroughly cleaned in a KOH/EtOH bath and rinsed with acetone to remove any organic or polymer residues. Finally they were dried in an oven at 200 °C for at least 24 hours.

2.2.1-Purification techniques

2.2.1.1-Solvent distillation technique

Both toluene, used in the solution polymerisations, and ethyl acetate, used for the re-crystallisation of lactide, were dried over calcium hydride for 24 hours before distillation. The distillation apparatus used for this purpose is described below in figure 2.1. Distillation of the solvents took place under a nitrogen atmosphere. A nitrogen flow flushed the distillation apparatus for at least 1 hour to ensure that all the air was eliminated.

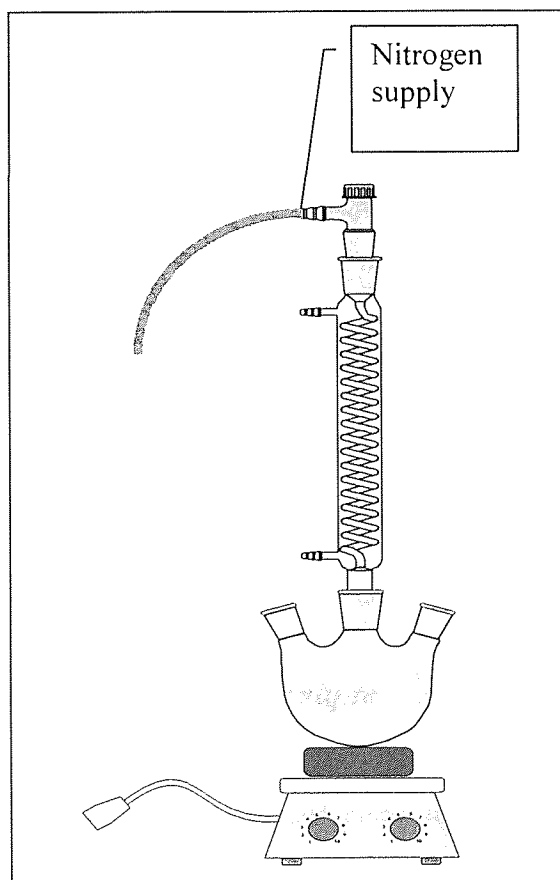


Figure 2.1: Solvent distillation set up.

2.2.1.2- Monomer distillation technique

ϵ -caprolactone was dried over calcium hydride under an inert atmosphere for 24 hours before it was distilled. An apparatus like the one shown in figure 2.2 was used to distill it under reduced pressure.

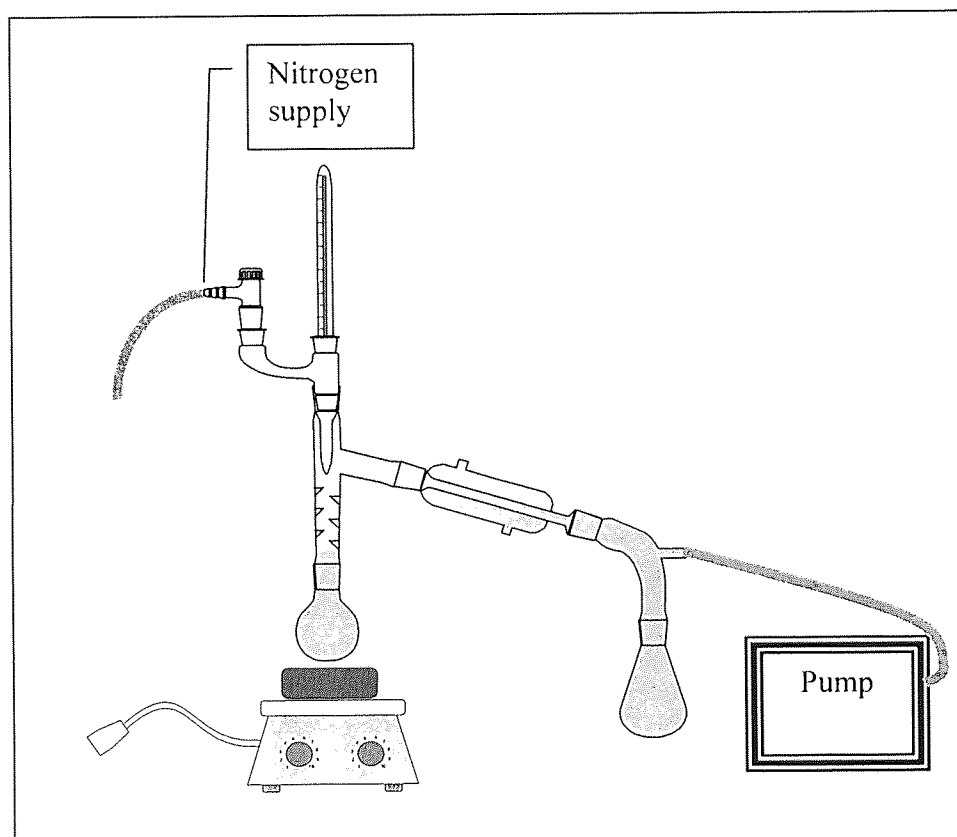


Figure 2.2: ϵ -Caprolactone distillation apparatus

2.2.1.3- Lactide re-crystallisation technique

Lactide was dissolved in dried ethyl acetate under inert atmosphere in the glove box. Once mixed it was placed in an oil bath and heated up to 60 °C until it dissolved completely. Crystals started to appear after 3 hours. When re-crystallisation was finished, lactide

2.2.2- Vacuum line techniques

The vacuum line, illustrated in fig 2.5, is made of pyrex glass and consisted of a single manifold (A) with a series of B 19 ground glass joints connected to this by PTFE greaseless taps. The manifold was connected to a mercury diffusion pump and a vacuum pump via a main tap. One liquid nitrogen cold trap was present to prevent vapours generated in the system from entering and contaminating the vacuum pump. The mercury diffusion pump and the rotary vacuum pump were used in combination to reduce the internal pressure of the system to approximately 10^{-4} mm Hg, which was measured using a mercury "vacustat" gauge. Nitrogen supplied was also connected to the system to allow manipulation of the material under an inert atmosphere. To avoid the glass freezing, vacuum grease must be used.

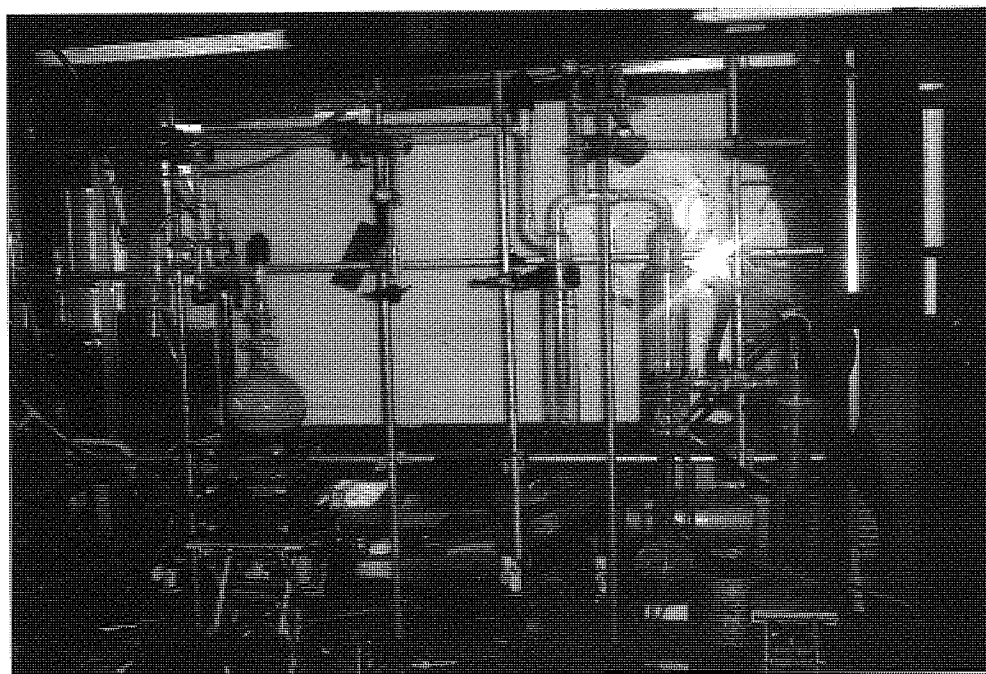


Figure 2.3: Vacuum line.

2.2.3- Argon glove box

A dry-box supplied by Halco Engineering Ltd was utilised to allow storage and manipulation of materials under an inert atmosphere. The apparatus consisted of a main compartment with access gloves and a double-door posting port. The main compartment was maintained under an argon atmosphere, which was constantly re-circulated through moisture absorbant columns containing 3Å molecular sieve. The double-door posting port allowed equipment and materials to be transferred to and from the port without breaching the atmosphere within the main compartment. Transfer of materials into the main compartment was achieved by sealing the door connecting the main compartment and the port, placing the desired articles in the port, sealing the outer door of the port and then subsequently subjecting the port to three cycles of evacuation and filling with argon. The door connecting the main compartment to the port was then opened and the articles transferred from the port into the main compartment. The removal of articles from the main compartment was achieved by the reverse of this procedure.

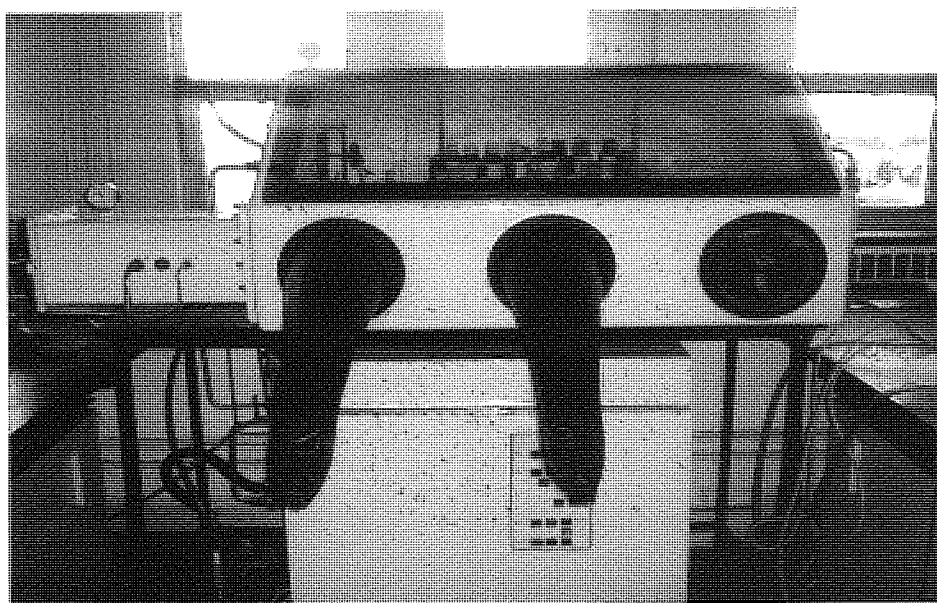


Figure 2.4: Argon Box.

2.3-INSTRUMENTAL METHODS

2.3.1-Gel Permeation Chromatography (GPC)

2.3.1.1- Introduction.

Gel Permeation Chromatography (GPC), also known as Size Exclusion Chromatography (SEC), is by far the most widely used method of determining molecular weight distributions of synthetic polymers. The method is based upon the fractionation of the sample into its constituent molecules according to their hydrodynamic volume (different sizes of the molecule). The separation is achieved by passing the polymer sample solution through a series of columns containing a stationary phase of a highly cross-linked polystyrene polymer. The cross-linked polymer, which swells in the presence of solvent, THF, and the resultant gel, contains pores of different sizes, into which the polymer molecules may permeate. Thus the molecules that have a greater hydrodynamic volume (high molecular weight) will remain in the column for a short period of time and therefore being eluted from the columns more rapidly than molecules with lower hydrodynamic volume, which will be retained for a longer period of time in the pores of the column.

The presence of polymer in the eluent is monitored by a differential refractometer, which compares the refractive index of the eluent with the one of the pure solvent in the reference cell. Any change in the refractive index is proportional to the concentration of the polymer at any time.

2.3.1.2- Apparatus.

A schematic illustration of the gel permeation chromatograph used is shown in figure 2.5.

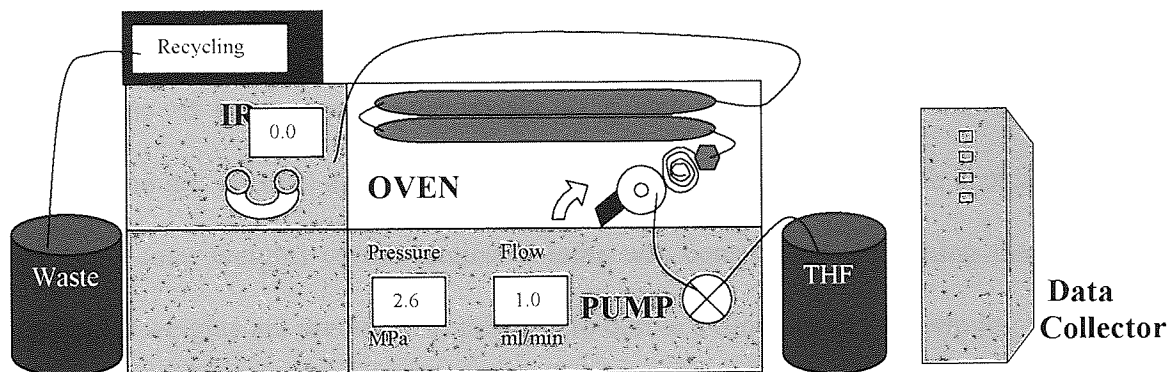


Figure 2.5: Scheme of a gel permeation chromatograph

A Knauer HPLC pump was used to pump the mobile phase, HPLC grade THF, through the system at a rate of 1 ml min^{-1} . 1 % w/v THF polymer solutions were prepared and filtered through nylon membrane filters of $0.45 \mu\text{m}$ pore size and introduced into the system via a reodine valve injector. The column set was supplied by Polymer Laboratories and consisted of a pre-column filter and two Mixed C columns. These columns are made of highly cross-linked polystyrene and cover a range of molecular weights from 200-2,000,000. The columns were contained in a thermostatically controlled oven, at 40°C , to circumvent errors due to fluctuations in temperature. The chromatograph has a Knauer differential refractometer detector. The outputs of the detector were passed to a Polymer Laboratories DCU and analysed using PL Caliber software.

2.3.1.3- Apparatus Calibration

GPC is a relative method, and to achieve results to within a useful level of accuracy the columns must firstly be calibrated. A popular method of calibration is by using a series of polystyrene of known molecular weight as a standard. In this case narrow standards of polystyrene are injected and the elution volumes were recorded for each standard. A plot of \log (molecular weight) versus elution volume was constructed. Assuming that the standard molecular weights are precise, it is possible to derive a function in the form $\log (M) = f (V)$ so that the molecular weight corresponding to any elution volume can be calculated. This resulting curve is called a calibration curve and it is shown in figure 2.6. The equation associated to it, equation 2.1 is the one shown below:

$$140.2 - 43.39X^1 + 5.602X^2 - 0.36X^3 + 0.0114X^4 - 0.0001431X^5, \text{ Equation 2.1}$$

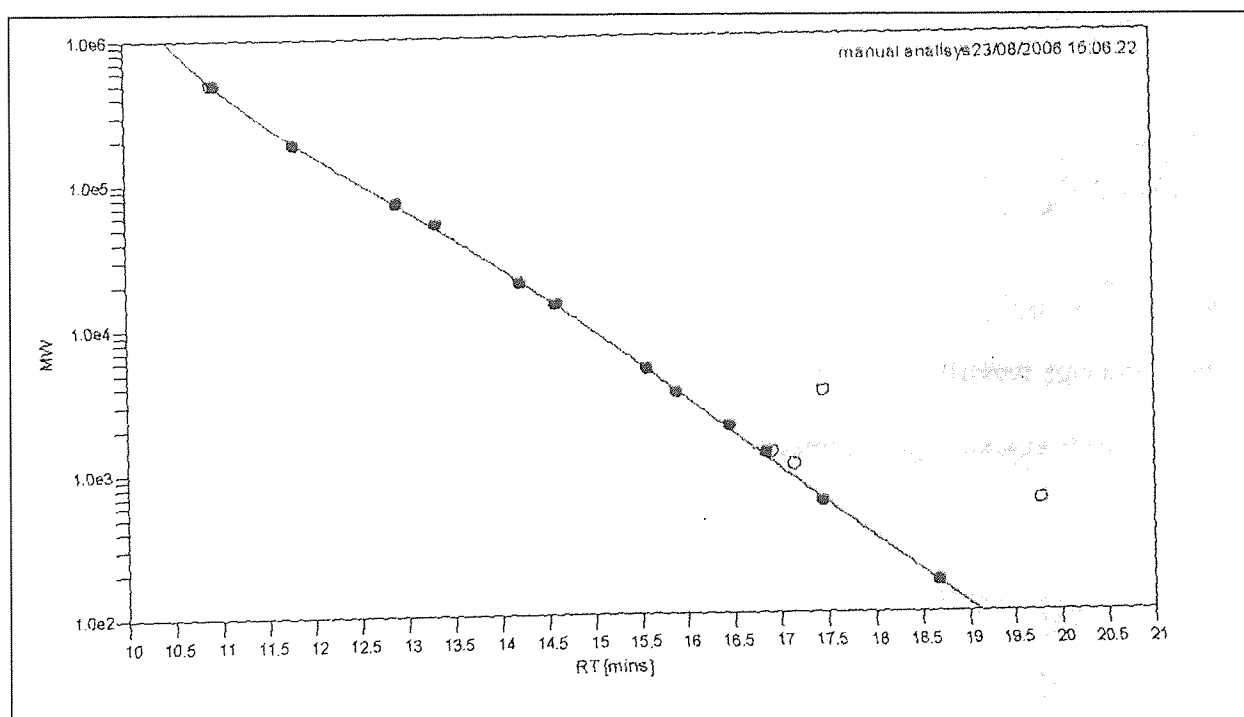


Figure 2.6: Calibration curve using polystyrene standards.

GPC was calibrated using polystyrene standards but because of different polymers swell differently in a given solvent caused by their different properties (hydrodynamic volume, chemical attractions), calculated polymer molecular weights are not exactly the same as those of the polystyrene. To overcome this problem the compensation relies upon the fact that the hydrodynamic volume of a polymer molecule in solution is proportional to its intrinsic viscosity and molecular weight. Therefore, two polymers eluting at the same elution time must have the same hydrodynamic volume as shown below in equation 2.2.

$$[\eta_1]M_1 = [\eta_2]M_2, \text{ Equation 2.2}$$

In the above equation $[\eta_1]$ and $[\eta_2]$ are the intrinsic viscosities of the two polymers and M_1 and M_2 their molecular weights.

The intrinsic viscosity of a polymer can be related to its molecular weight by the equation 2.3:

$$[\eta_1] = KM^a, \text{ Equation 2.3}$$

“K” and “a” are the Mark-Houwink constants for polymers in different solvents. Thus substituting equation 2.3 in equation 2.2 the following expression, equation 2.4 is obtained.

$$K_1M_1^a M_1 = K_2M_2^a M_2, \text{ Equation 2.4.}$$

If the Mark-Houwink constants are known for both the calibrant standard and the polymer under study, applying logarithms, equation 2.5, the accurate molecular weight of the polymer will be known.

$$\text{Log}M_2 = \frac{(1 + \alpha_1)}{(1 + \alpha_2)} \log M_1 + \frac{1}{(1 + \alpha_2)} \log \left(\frac{K_1}{K_2} \right), \text{Equation 2.5.}$$

Therefore molecular weight will be expressed as polystyrene equivalent molecular weights

2.3.1.4- Molecular weight determination

When a differential refractometer is used as detector the difference in refractive index between the solvent reference and the eluted mobile phase, containing polymer sample, are recorded at any given time. The difference in refractive index is dependent on the concentration of the polymer in the eluent and the weight fraction of the polymer at that elution volume. These differences are proportional to the height, h , on the chromatograph (figure 2.7) at that point. $\Delta n \propto h$ and $W_i \propto \text{Elution volume}$

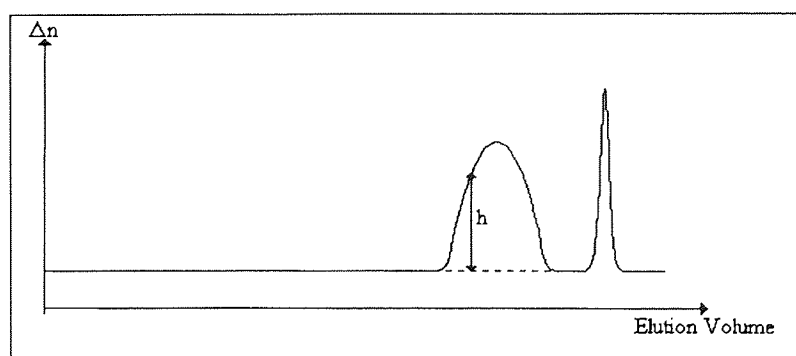


Figure 2.7: A typical gel permeation chromatogram in illustrated in.

Conventionally, the breadth of distribution can be defined in terms of two averages, as a number average molecular weight (M_n) and as the weight average molecular weight (M_w). The number average molecular weight of a polymer sample, also referred as M_n in equation 2.6, is the arithmetic mean representing the total weight of the molecules divided by the total number of molecules.

$$\bar{M}_n = \frac{\sum N_i M_i}{\sum N_i}, \text{ Equation 2.6; where } N_i = \text{number of molecules of molecular weight } M_i$$

M_i

The probability factor in a weight-average considers the mass of the molecules so that the heavier molecules of the polymer segment are more important. The formula to calculate the weight average molecular weight, M_w , is shown in equation 2.7,

$$\bar{M}_w = \frac{\sum N_i M_i^2}{\sum N_i M_i}, \text{ Equation 2.7}$$

Both average numbers would be the same if all the chains had the same length but it is a well known fact of any polymerization process that it is virtually impossible for all growing polymer chains to terminate at the same size. Therefore M_w is always higher than M_n because the molecular weights are more important when you work out the average per gram than per molecule.

Another important factor to describe a molecular weight distribution of a polymer is by using the ratio between M_w and M_n . This ratio, equation 2.8, is known as polydispersity

index, PD, of a given polymer sample and is a measure of the width of the polymer molecular weight distribution.

$$PD = \frac{M_w}{M_n}, \text{ Equation 2.8}$$

If W_i is the weight fraction of polymer at molecular weight M_i then; $W_i \propto N_i M_i$ and $N_i \propto W_i / M_i$. Therefore M_n can also be expressed as shown below in equation 2.9:

$$\bar{M}_n = \frac{\sum W_i}{\sum \frac{W_i}{M_i}}, \text{ Equation 2.9.}$$

Given the above relationships the molecular weights can be calculated from the GPC trace by equations 2.10 and 2.11;

$$\bar{M}_n = \frac{\sum h_i}{\sum \frac{h_i}{M_i}} \text{ Equation 2.10 and } \bar{M}_n = \frac{\sum h_i M_i}{\sum h_i} \text{ Equation 2.11;}$$

In the equations shown above h_i is the GPC curve height at the i th volume increment and M_i the molecular weight of the species eluted at the i th retention volume.

2.3.2 Nuclear Magnetic Resonance (NMR)

Fourier transform high-resolution ^1H and ^{13}C were conducted using Bruker spectrometers. The associated error of this technique is 2%. Homopolymers and commercial catalyst were characterised using Bruker 250 MHz, whereas synthesised macro-catalyst and copolymer were analysed on a Bruker 300 MHz spectrometer. The extra resolution achieved from the 50 MHz difference between Bruker 250 and 300 MHz is desirable for the characterisation of copolymers and macro-catalyst in order to separate some peaks which chemical shifts are almost overlapping. Sample solutions were prepared in deuterated solvents such as chloroform, toluene and di-methyl sulfoxide depending on the solubility of each sample, placed in a Bruker spectrometer and run at room temperature. The following acquisition parameters were used for ^1H NMR, relaxation delay 3 sec, pulse length 11 μs and pulse angle of 30° . In the case of the ^{13}C NMR, the PENDANT (signal enhancement by polarization transfer and attached nucleus testing) sequence was used⁹⁹ for homopolymers, copolymers and commercial catalyst. The PENDANT pulse technique was utilised for ^{13}C analysis and thus methyl and methane carbons appear as positive peaks and methylene and quaternary carbons appear as negative peaks.

Gaussian multiplication analysis was also performed to resolve the overlapping of methyl peaks in the cases of the homopolymers obtained from titanium iso-propoxide. This technique applies an optimum resolution enhancement¹⁰⁰. The FID is multiplied by a two term exponential of the form $\exp(at - bt^2)$, where "a" is negative and "b" is positive. The FID has originally the Lorentzian form $\exp(-t/T_2)$, so that if $a = -1/T_2$ a Gaussian line shape $\exp(-bt^2)$ will result. Since the Gaussian line shape has much less extensive wings as compared to a

Lorentzian, resolution of resonance is greatly improved the constants have the form: $a = \pi \cdot LB$ (LB=line broadening) and $b = -a/2 \cdot GB \cdot AQ$ (GB= Gaussian broadening, AQ= acquisition time)

All the spectra were analysed using winNMR software supplied by Bruker.

2.3.3-Differential Scanning Calorimeter (DSC)

The samples were analysed using a Polymer Laboratories PL STA 625+ differential scanning calorimeter. Differential scanning calorimeter, DSC, is a technique which measures the rate of heat that flows into a sample, with respect to the reference of known heat capacity, as it heated to maintain it at a constant heating rate over a fixed temperature range. Therefore the heat flow required keeping the sample at a fixed constant heating rate. If the sample undergoes and exothermic process, the equipment will supply less heat flow; similarly for endothermic reactions more heat flow will be supplied. On heating, a sample can undergo phase transitions (crystallisation, melting and glass transition) or chemical reactions, which occur at certain temperatures, depending on the material. These transitions will be able to be observed in the tested samples.

DSC is a standard technique for studying thermal behaviour in semicrystalline samples of pure polymers, copolymers and blends to determine enthalpy changes during melting. The process can be used to identify glass transition (T_g), melting temperatures (T_m) and crystallinity processes of homopolymers and copolymers.

The instrument was entirely computer controlled. The oven could be cooled manually using liquid nitrogen delivered from a low pressure Dewar flask. The equipment consists of a hang down balance with space for two aluminium pans (sample and reference) capable of weighing to an accuracy of $\pm 0.01\text{mg}$. Each is under a nitrogen flow and connected to a thermocouple in order to monitor the temperature differences between the pans. A vertically movable oven surrounds the whole assembly. During heating, the thermal changes in the sample pan are monitored with respect to the reference so that the heat input can be adjusted that the temperatures are always identical. In this way endothermic and exothermic peaks are measured. The analysis is displayed as a plot of energy change with time and since the temperature is scanned at a constant rate it is possible to measure the heat.

Each sample is preheated up to its melting point in order to get rid of remaining water or solvents used during the synthesis process. Small amounts of solvent remaining within the sample could modify slightly the glass transition temperature, T_g , of the polymer giving a false reading. Additionally mass changes are also monitored to ensure that samples are free of solvent.

CHAPTER 3

TITLE: SOLUTION POLYMERISATION OF LACTIDE WITH TITANIUM TETRA-COORDINATED ALKOXIDES.

3.1 MATERIALS

L-Lactide was purchased from Purac and stored under an inert atmosphere in a glove box. It was re-crystallized from ethyl acetate before used as described in section 2.2.1.3.

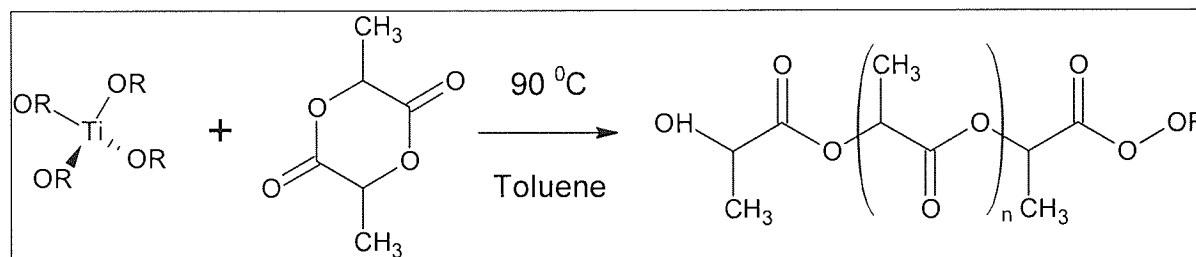
Toluene and ethyl acetate were purchased from Fisher dried over calcium anhydride and distilled as explained in section 2.2.1.1.

The following initiators were stored under an inert atmosphere in a glove box and used as received without any further treatment: titanium(IV) *iso*-propoxide 99.999%, titanium(IV) propoxide 95%, titanium (IV) *n*-butoxide 98%, titanium(IV) *tert*-butoxide 95%, titanium (IV) 2-ethyl-hexoxide 97%.

3.2 L-LACTIDE POLYMERISATIONS IN SOLUTION

Polymerisations of L-lactide were carried out using a constant lactide concentration of $[0.78] \text{ mol/dm}^3$ in toluene, and varying the catalyst concentration. Monomer, initiator and solvent were transferred and mixed in a glove-box under an argon atmosphere. Once the reactor was sealed, it was moved from the argon box and connected to a vacuum line where a continuous nitrogen flow was supplied as shown in figure 2.3. The vessel was then placed in an oil bath to maintain a reaction temperature of 90°C and magnetic stirring was provided throughout the polymerisation as summarized in scheme 3.1. In order to study the evolution of molecular weight and conversion, samples were taken during the course of the reaction. These were quenched with water and were precipitated in methanol, in order to obtain a fine smooth white powder, which could be easily dissolved in common organic solvents, such THF and chloroform. A hard pale yellow solid was obtained if the solvent was evaporated and the obtained product was not precipitated in methanol. This hard solid showed a poor solubility in organic solvents. ^1H NMR analysis of the crude product (unpurified product) was used to calculate monomer conversion at any given time during the reaction. Since the white solid precipitate had not been filtered out, both monomer and polymer were present in the sample. ^1H NMR analysis was also used to calculate the degree of polymerisation (Dp) and the number average molecular weight (M_n) of the polymer. For the calculation of Dp and M_n , the dried product was re-dissolved in toluene, precipitated with methanol and filtered in order to separate the synthesized polymer from any remaining un-reacted monomer or catalyst, which dissolve in methanol. The calculation of Dp, and consequently M_n , is more accurate when the product is free of any unreacted catalyst, since the chemical shift of the reacted and unreacted initiator are slightly overlapped in the ^1H NMR spectrum. The calculation of M_n and Dp will

be explained in detail in section 3.4. Finally the precipitated white solid was dried, without being filtered, at atmospheric pressure and kept under vacuum at 40 °C for 24 h.



Scheme 3.1: Formation of polylactic acid using titanium alkoxide initiators.

The first sign of a successful reaction was the absence of any crystalline lactide as well as an augmentation of viscosity as the reaction progressed. In some cases the reaction was finished in a matter of minutes, although as the concentration of the initiator decreased in this series the reaction time increased. The absence of detectable lactide signals in the ^1H NMR spectra indicated that the monomer conversion was complete.

3.3 PRODUCT CHARACTERISATION.

The extent of the reaction was confirmed by ^1H NMR of the reaction mixture where the methine hydrogen of the lactide (at 5.03 ppm) is shifted down field (5.13 ppm) on polymerisation. A typical ^1H NMR of PLLA is shown in figure 3.1. The NMR evidence of these types of polymer has been widely reported by Zell⁸².

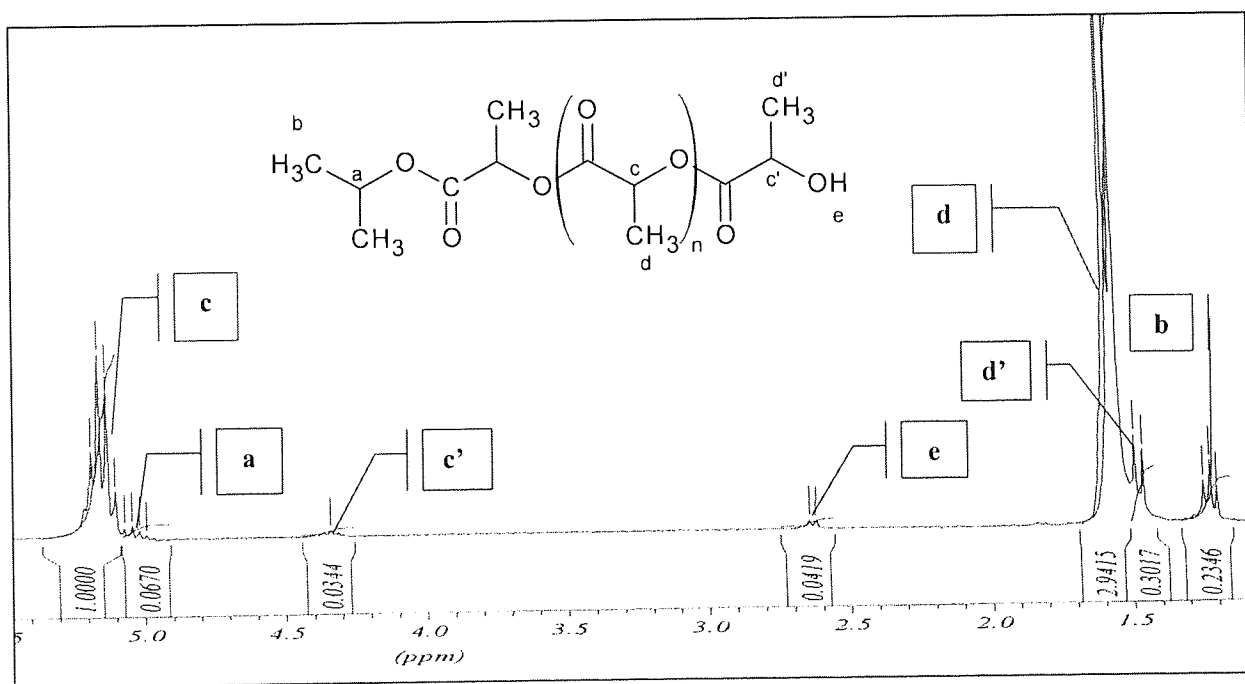


Figure 3.1 ^1H NMR spectrum of a typical polylactic acid bearing an iso-propoxide end group.

A list of PLLA ^1H and ^{13}C NMR chemical shift frequencies is shown in table 3.1.

Group	^1H NMR δ in ppm	End group	^{13}C NMR δ in ppm
$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	5.13 (q)	$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	69 (s)
$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	1.55 (d)	$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	16.6 (s)
		$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	169.6 (s)

Table 3.1: ^1H and ^{13}C NMR chemical shifts δ for PLLA measure in CDCl_3

Each of the tested catalysts successfully initiated the ring opening polymerisation of L-lactide, incorporating the alkoxide ligand as an ester end group within the polymer. The chemical shift frequencies that correspond to the end of the polymer chain for the alcolate are listed in table 3.2.

End group	^1H NMR δ in ppm	End group	^1H NMR δ in ppm
$\text{OCO}-\text{CH}-(\text{CH}_3)_2$	5.06 (sept)	$\text{OCO}-\text{CH}-(\text{CH}_3)_2$	1.22 (t)
$\text{OCO}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	4.08 (t)	$\text{OCO}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	0.91(t)
$\text{OCO}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	4.05(t)	$\text{OCO}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	0.90 (t)
		$\text{OCO}-\text{C}-(\text{CH}_3)_3$	1.43 (s)
$\text{OCO}-\text{CH}_2\text{CH}(\text{CH}_2-\text{CH}_3)(\text{CH}_2)_4-\text{CH}_3$	4.04 (m)	$\text{OCO}-\text{CH}_2\text{CH}(\text{CH}_2-\text{CH}_3)(\text{CH}_2)_4-\text{CH}_3$	0.86 (m)

Table 3.2: ^1H NMR chemical shifts for different end groups.

Although the multiplet of the methyl group of the iso-propoxide chain end (1.22 ppm) appears in the ^1H NMR as a triplet, it is in fact the result of the overlapping of the two doublets, produced by non-equivalent methyl groups. At first sight, one might expect the methyl groups to be chemically identical, especially when one allows for the free rotation of the side chain. However, the two methyl groups become non-equivalent when the iso-propoxide group reacts with the lactide because of the chiral carbon atom of the lactide. This peak can be easily resolved by ^1H NMR using a Gaussian multiplication experiment concentrated in the area where the so-called peak appears. Once the peak was resolved two doublets were observed as shown in figure 3.2.

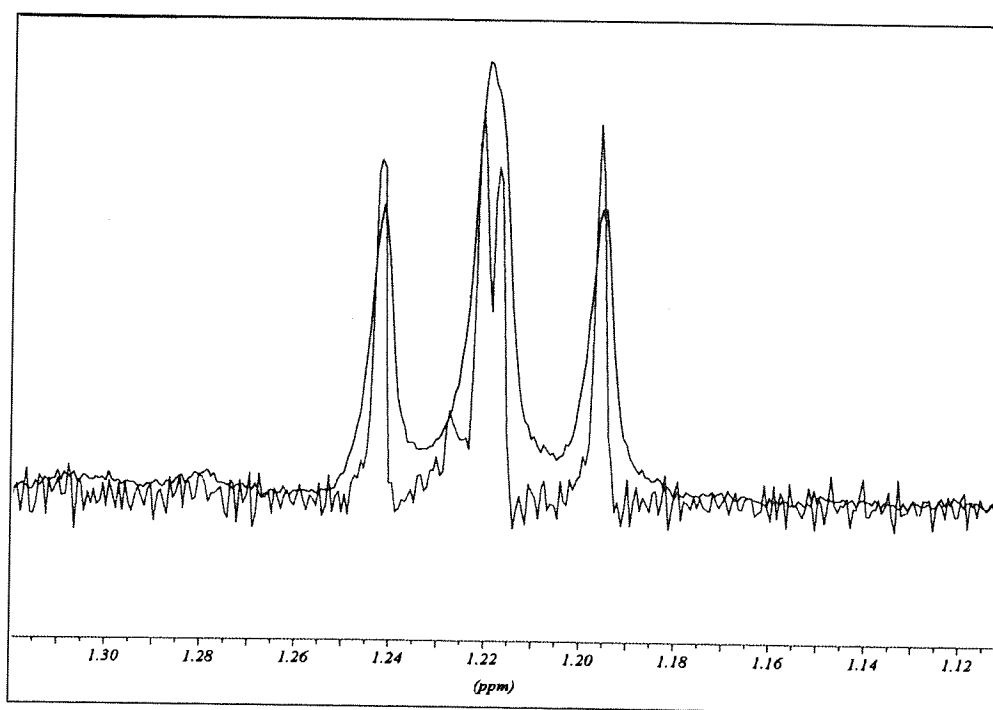


Figure 3.2: Gaussian multiplication experiment for a PLLA containing an iso-propoxide end group.

PENDANT ^{13}C NMR is an invaluable technique for the characterisation of polymers. It is not a quantitative technique, but a good method of analysis to study racemisation of the lactide asymmetric carbon through the carbonyl group, as well as to detect end groups in the

case of low and medium molecular weight polymers. A typical ^{13}C NMR of polylactide is shown below in figure 3.3. All the polymers gave similar spectra composed of three lines located at $\delta = 16.69$, 69.03 and 169.6 ppm. These three lines correspond to the methyl, the methine and the carbonyl carbon atoms respectively. Iso-propoxide end groups have been assigned based on literature published by Kowalski⁸³.

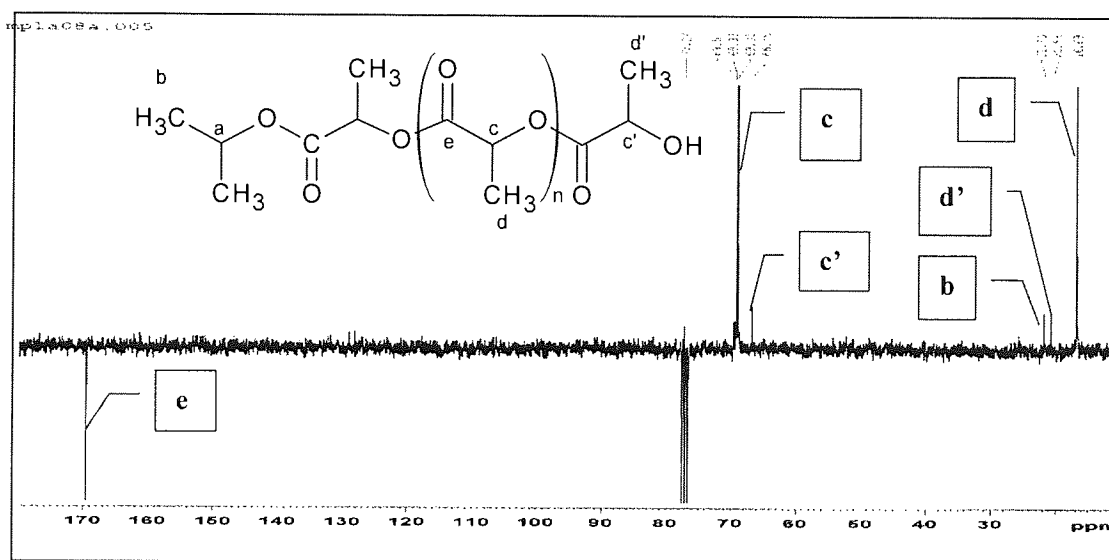


Figure 3.3: ^{13}C NMR spectrum of a typical polylactic acid synthesised using $\text{Ti}(\text{O}-i\text{-Pr})_4$ as an initiator.

^{13}C NMR is an effective technique to observe and assign stereosequences combinations in the polymer. However, why the different chemical shifts arise is still unknown⁸⁴. Polymers with high stereoregularity can form highly crystalline materials, whereas amorphous materials will be formed when polymers have poor stereoregularity. It is very important to determine the correct stereosequence distribution in order to understand the stereoselectivity of the catalyst. There are three possible configurations of lactide, *SS*, *RR* and *RS*. An *SS* configuration is referred to as L-lactide, *RR* as D-lactide and *RS* as *meso*-lactide. The number and distribution of R and S stereocentres in the polymer chain will influence the

physical and mechanical properties of PLA. The distribution is established by the relative probability that a specific sequence of stereocenters will be present in the polymer (i.e., RRRR, RRSS, RSRS, etc.). RR combinations generate an isotactic centres “i”, whereas combinations of RS generate syndiotactic centres “s”. Therefore the combination of triads, such as iii, iis, iss, sii and sis could be present in the polymer. PENDANT ^{13}C NMR is an adequate technique to analyse in detail the methine region of the polylactic acid spectrum, because the polarisation transferred from the hydrogen atom of the methine functional group to the carbon atom of the same group reduces significantly the relaxation time of the carbon atom. Consequently, the relaxation time of the methine carbon is hydrogen dependent and less scans are necessary to obtain a well resolve spectrum. An expansion of the methine region on the ^{13}C NMR spectra of a polylactide (figure 3.4) showed the presence of a main peak at 69.0 ppm associated with the chemical shift of the triads iii, iis, sii and sis and two small peaks at 69.2 and 69.4 ppm associated with the sequences isi and ssi respectively.

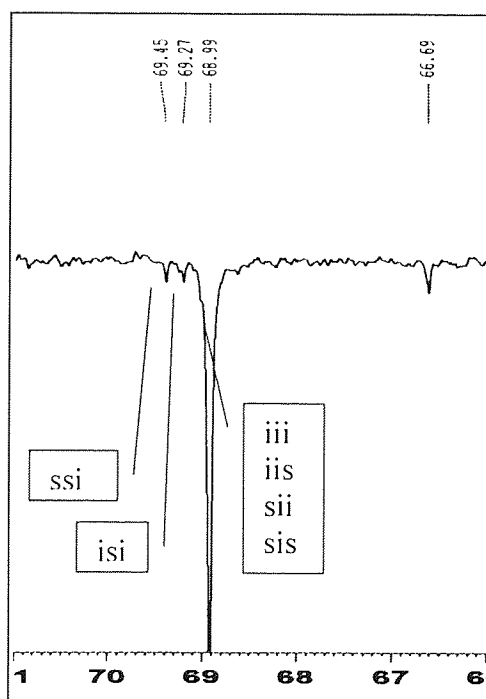


Figure 3.4: Expanded ^{13}C NMR spectrum of a typical polylactic acid synthesised using $\text{Ti}(\text{O-}i\text{-Pro})_4$ as an initiator.

The assignment of these lines to the configurational frequencies (figure 3.4) was based on the previous publications by Kasperczyk ⁹⁸. However the areas of the peaks associated with the configurations the iii, iis, sii and sis triads are overlapped, therefore it was impossible to calculate precisely the average length of the isotactic blocks. ¹³C NMR evidence suggests that racemisation of the chiral carbon atom takes place to only a small extent.

The product was also characterised by gel permeation chromatography, GPC, as shown in figure 3.5, where a mono-disperse curve is observed as well as no sign of oligomers being produced during the course of the polymerization. The majority of these syntheses gave polymers of narrow polydispersities as measured by GPC. It is important to highlight that the small peak, labelled as 2, before the flow rate marker corresponds to a small amount of impurities present in THF-toluene mixture used to prepare the GPC samples. This was proven by running a blank sample. Molecular weights obtained from GPC were corrected by multiplying the GPC experimental value obtained using polystyrene standards by a factor of 0.55 (at least up to $M_n \approx 3 \cdot 10^4$). This correcting factor was calculated by comparing M_n obtained by ¹H NMR with M_n calculated by GPC as described in chapter 4. The calculated correcting factor agrees with literature values published by Penzkec ⁸³ and Soum ⁸⁵.

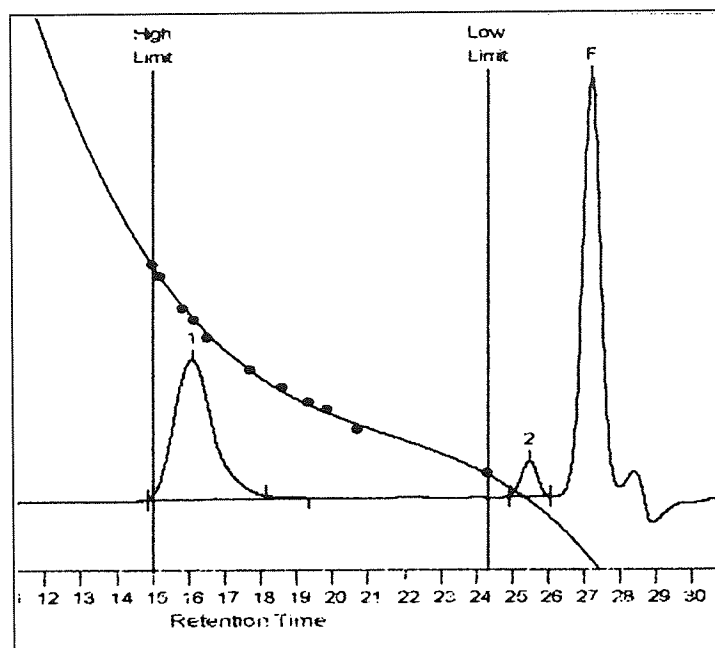


Figure 3.5: GPC of a PLA obtained using $\text{Ti}(\text{O-}i\text{-Pro})_4$ as an initiator and toluene as a solvent.

It was also observed that the polydispersity tends to increase as the reaction came close to completion. Trans-esterification reactions became predominant when the monomer concentration decreased and conversion reached values over 95%. During the reaction trans-esterification reactions are in constant competition with propagation. Early in the reaction the rate of trans-esterification reactions was much slower than propagation. Only when the monomer concentration decreased to values around 5% of the initial concentration did the rate of trans-esterification reactions become significant. At this stage, the rate of propagation slowed down to such an extent that the two rates were similar and competed with one another. Transesterification reactions of intermolecular nature were responsible for broadening significantly the polydispersity, as reported by Jamshidi¹⁹ and Zhang²⁰. The obtained molecular weights, as well as their polydispersities, are shown and explained in detail in section 3.5.

3.4 DETERMINATION OF MONOMER CONVERSION AND

THE DEGREE OF POLYMERISATION USING ^1H NMR

SPECTROSCOPY

Both the degree of polymerisation and monomer conversion were determined by ^1H NMR spectroscopy, by comparing the relative peak areas, representative of each of the constituents of the molecule. In the case of the monomer conversion, the peaks compared were the methyl protons of the lactide at 1.65 ppm and the methyl protons of the PLLA at 1.54 ppm. Similarly the degree of polymerisation, D_p , was calculated by comparing the area under the peak of the methine group, at 5.13 ppm, in the PLLA and the area of the methyl end group of each catalyst used. The equation associated to the degree of polymerisation, equation 3.1, is shown below:

$$D_p = \frac{[I_{\text{PLLA}} / 2]}{[I_{\text{InCH}_3} / N_H]}, \text{ Equation 3.1.}$$

In the above equation I_{PLLA} represents the area (integration) of the methine group in PLLA, I_{InCH_3} is the area of methyl end group of each alkoxide initiator and N_H the number of protons associated with the methyl group or groups of each alkoxide. For instance, in the case of the propoxide end group, N_H is 3 (because of the presence of only one methyl group) although in the case of the iso-propoxide N_H is equal to 6 (because of the presence of two methyl groups). In the case of the titanium (IV) 2-ethyl-hexoxide, the methyl of the 2-ethyl and the methyl protons of the main chain appear overlapped. Therefore the area of this peak will be divided by 6.

Number average molecular weights were calculated by using equation 3.2 below:

$$Mn = Dp_{LA} \times Mw_{LA} + Mw_{endG} + Mw_H, \text{ Equation 3.2;}$$

where Dp_{LA} represents the degree of polymerisation of lactide Mw_{LA} the molecular weight of a lactide unit and Mw_{endG} is the molecular weight associated to the alkoxide end group. Finally, Mw_H is the molecular weight of the molecular weight of the proton (1 g/mol) the polymer gains after been quenched

3.5 RESULTS AND DISCUSSION

Two sets of reactions were carried out, in which the monomer/initiator molar ratio were different, the first one being 50/1 and the second 200/1. In this experiments the concentration was kept constant throughout all polymerisations at [0.78] M. The performance of the different initiators is shown in Table 3.3 for comparison purposes.

The initiators, tetra-alkyltitanates, are highly active towards polymerisation of L-lactide in solution and produce polymers of relatively narrow polydispersity. As can be observed from table 3.3, as well as, figure 3.6, all four alkoxy groups were active in the polymerisation except for the case of $Ti(O-2-Et-Hex)_4$ and $Ti(O-t-Bu)_4$. In the case of $Ti(O-Pr)_4$ is not clear whether each arm of the initiator is active. For the 50/1 ratio the observed degree of polymerisation, Dp , of 11 is very close to the theoretical value, Dp_{th} , of 12.5. Whereas for the 200/1 ratio Dp , 70, is considerably higher than the theoretical Dp expected if

all four alkoxide ligands are involved in the polymerisation. This case will be explained in detail in section 3.8 of this chapter.

The theoretical number average molecular weight, Mn_{th} , shown in table 3.3 is calculated taking into account the conversion of the reaction and the theoretical degree of polymerisation if four arms of the catalyst were active. The values of the theoretical average molecular weight, Mn_{th} , were calculated using the equation 3.3:

$$Mn_{th} = Dp_{th} \times Conv \times Mw_{LA} + Mw_{endG}, \text{ Equation 3.3.}$$

Entry	Initiator	[M]/[I]	Reaction time/ min	% Conversion	Dp	Dp _{th} *	PD	M _n GPC/ g mol ⁻¹	M _n * _{GPC} / g mol ⁻¹	M _n NMR/ g mol ⁻¹	M _n Th/ g mol ⁻¹
1	Ti(O-Pr) ₄	50/1	5	95	11	12.5	1.28	1800	990	1650	1770
2	Ti(O- <i>i</i> -Pr) ₄	50/1	20	98	12.3	12.5	1.13	2100	1200	1730	1820
3	Ti(O-Bu) ₄	50/1	20	100	11.6	12.5	1.37	2600	1500	1750	1870
4	Ti(O-2-Et-Hex) ₄	50/1	30	99	24	12.5	1.33	4700	2600	3620	1840
5	Ti(O- <i>t</i> -Bu) ₄	50/1	180	94	46	12.5	1.97	7600	4200	6650	1750
6	Ti(O-Pr) ₄	200/1	90	96	70	50	1.5	12500	6900	10200	6910
7	Ti(O- <i>i</i> -Pr) ₄	200/1	120	98	41	50	1.47	10800	5900	5900	7120
8	Ti(O-Bu) ₄	200/1	180	98	48	50	2.77	7700	4300	7040	7130
9	Ti(O-2-Et-Hex) ₄	200/1	120	91	33	50	1.19	7900	4300	4860	6630
10	Ti(O- <i>t</i> -Bu) ₄	200/1	300	90	66	50	1.56	18700	10300	9550	6540
L-lactide, [M]=0.78 mol/dm ³ , T=90 °C											

Table 3.3: L-Lactide polymerisation with different titanium alkoxides initiators.

Dp_{th}*: Theoretical degree of polymerisation if four arms of the initiator are active.

M_n*_{GPC}: Corrected number average molecular weight after applying correcting factor 0.55. See section 4.4.

M_nTh: Theoretical number average molecular weight obtained from conversion values if 4 arms of the initiator were active.

In the reactions carried out with $\text{Ti}(\text{O-}t\text{-Bu})_4$ as an initiator the degree of polymerisation is 46 for 50/1 M/I molar ratio and 66 for the 200/1 ratio. Therefore the initiator efficiency is 26% and 68% respectively, which means that either there is only one chain being activated per alkoxide moiety or that some kind of aggregation between the catalysts prevents a fraction of them from reacting. The efficiency of the catalyst has been calculated by applying equation 3.4:

$$Effc = \frac{\text{Con} \times \text{Dp}_{\text{th}}}{\text{Dp}_{\text{exp}}} \times 100, \text{ Equation 3.4.}$$

In the above equation, Con represents % monomer conversion for any given reaction at any given time; Dp_{th} is the theoretical degree of polymerisation for any reaction if four alkoxy groups were active and Dp_{exp} the calculated degree of polymerisation for any given reaction at any given time.

Very high conversions 94-99%, figure 3.7, and polymers of relatively narrow polydispersity, as measured by GPC, have been obtained in all homopolymerisations except when broad polydispersities were obtained using $\text{Ti}(\text{O-}t\text{-Bu})_4$ as initiator. In this case polydispersities up to 2.0 were obtained, which was ascribed to the bulkiness of the *tert*-butoxide group of the initiator causing slow initiation of polymerisation, as illustrated in table 3.2, and therefore broadening of the polydispersity. Since the behaviour of $(\text{O-}t\text{-Bu})_4$ appears to be different from other titanium alkoxides, an extensive study of its reactivity was carried out and is discussed in chapter 4.

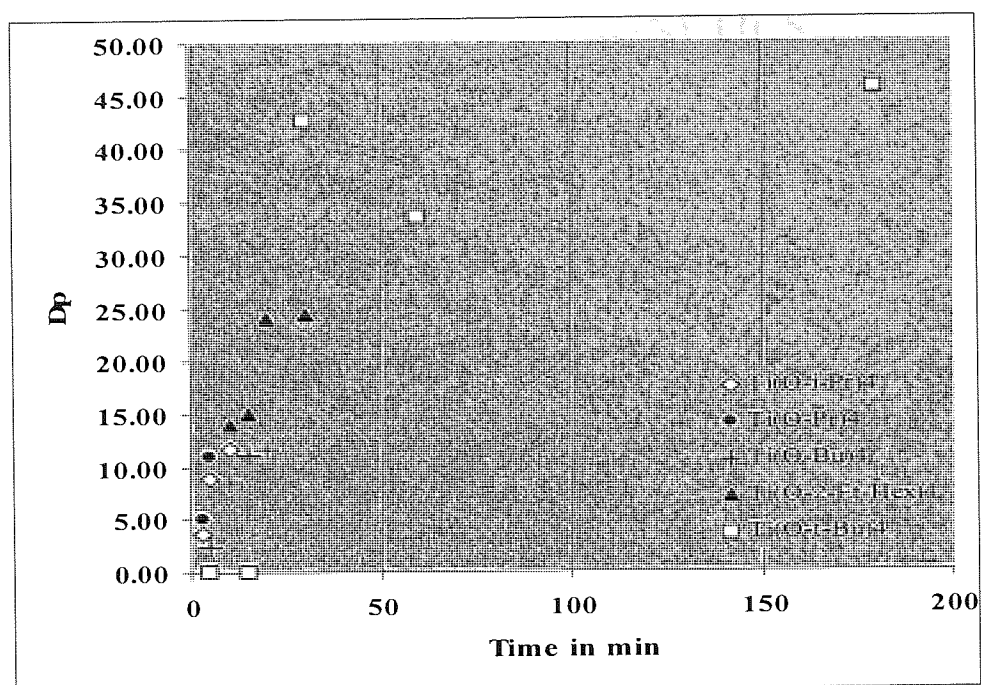


Figure 3.6: Dp of L-lactide versus time for different titanium alkoxide initiator, $[M]/[I]=50/1$.

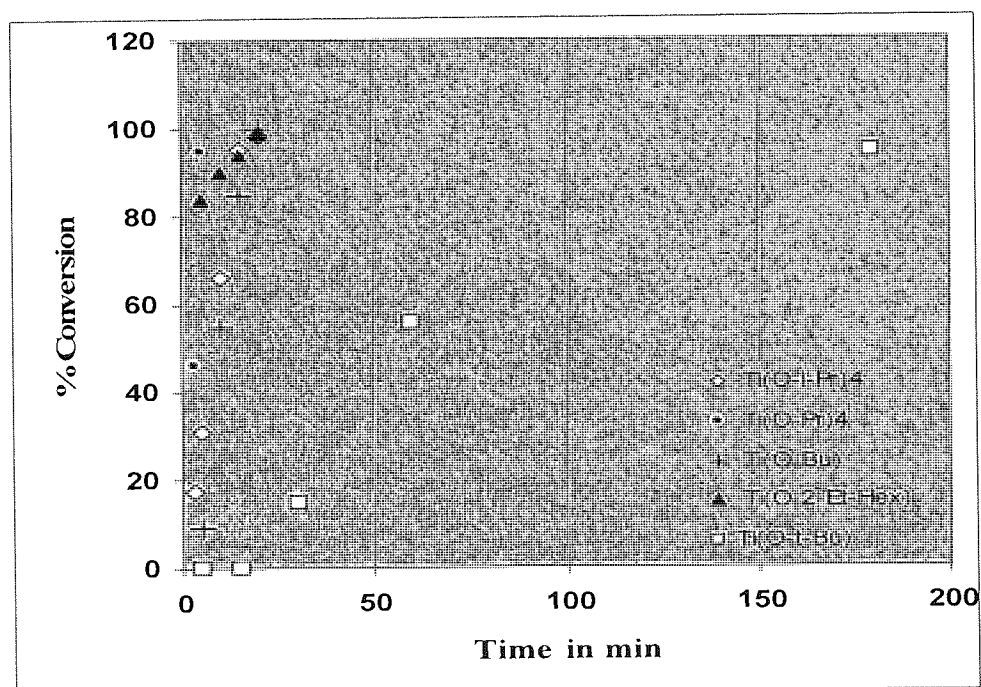


Figure 3.7: Conversion of L-lactide versus time for different titanium alkoxide initiator, $[M]/[I]=50/1$.

3.6 LIVING POLYMERISATION KINETICS

When a living polymerisation⁸⁶ takes place in the absence of transfer reactions, the degree of polymerisation can be defined as equation 3.5:

$$Dp_n = \frac{([M]_0 - [M]_t)}{[I]_0}, \text{ Equation 3.5.}$$

This assumes a rapid initiation where $[M]_0$ is the initial monomer concentration, $[M]_t$ the monomer concentration at time t and $[I]_0$ is the initial initiator concentration, equivalent to the concentration of growing species $[I^*]$.

If the consumption of the monomer is first order, the monomer concentration at any time t can be expressed as equation 3.6 below,

$$[M]_t = [M]_0 \cdot e^{-kt}, \text{ Equation 3.6;}$$

where k is the apparent rate constant (also sometimes written as k_{app}). By substituting equation 3.6 into 3.5, the number average degree of polymerisation will be obtained and expressed as equation 3.7.

$$Dp_n = \frac{([M]_0 - [M]_t) \cdot e^{-kt}}{[I^*]}, \text{ Equation: 3.7.}$$

Rearranging equation 3.7, D_p can also be expressed as equation 3.8 below:

$$Dp_n = \frac{\{[M]_0(1 - e^{-kt})\}}{[I^*]}, \text{ Equation: 3.8.}$$

When the polymerisation is complete, $t=\infty$, the degree of polymerisation can be expressed as a function of the initial monomer concentration and the concentration of active species as shown in equation 3.9.

$$Dp_{n\infty} = \frac{[M]_0}{[I^*]}, \text{ Equation: 3.9.}$$

Therefore if equation 3.9 is substituted in equation 3.8 the following expression, equation 3.10, will be obtained;

$$Dp_n = Dp_{n\infty}(1 - e^{-kt}), \text{ Equation: 3.10,}$$

If the above equation is rearranged equations 3.11 and 3.12 will be obtained;

$$\frac{Dp_n}{Dp_{n\infty}} = (1 - e^{-kt}), \text{ Equation: 3.11,}$$

$$\frac{Dp_{n\infty} - Dp_n}{Dp_{n\infty}} = e^{-kt}, \text{ Equation: 3.12.}$$

Taking natural logarithms of the expression above, equation 3.12, the following expression, equation 3.13 was obtained:

$$Ln(Dp_{n\infty} - Dp_n) = Ln(Dp_{n\infty}) - kt, \text{ Equation: 3.13.}$$

Therefore if $\ln(Dp_{\infty} - Dp_n)$ is plotted versus time for a living polymerisation with a fast initiation reaction, a linear plot with a negative gradient k and an intercept $\ln(Dp_{\infty})$ should be obtained. This plot, figure 3.7, allows the calculation of k , the apparent rate constant of propagation, which will be the gradient of the plot. In this particular case, k is the apparent rate constant of propagation for the synthesis of PLA using $Ti(O-i-Pro)_4$ as an initiator.

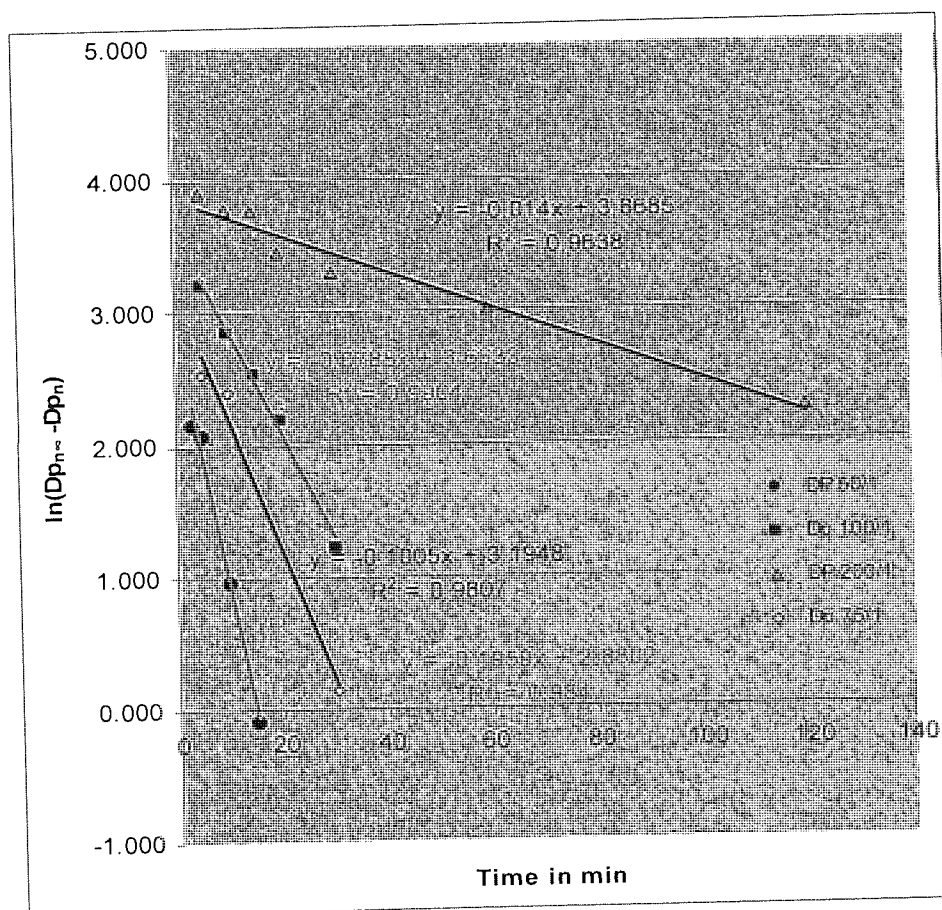


Figure 3.8: Plot of $\ln(Dp_{\infty} - Dp_n)$ against time for the polymerisation of L-lactide in toluene at 90 °C using $Ti(O-i-Pro)_4$.

Plots of $\ln(Dp_{\infty} - Dp_n)$ versus time shown in figure 3.8 have been constructed from degree of polymerisation data obtained from 1H NMR analysis. In all polymerisations carried out for the L-lactide polymerisation using titanium iso-propoxide as initiator, these plots are linear, indicating that the concentration of growing species is constant and providing strong evidence for the polymerisation being living.

The calculated values of the apparent rate constant, k , obtained from these plots are shown below in table 3.4. $[I_0]$ represents the initial initiator concentration.

$[M/I]$	$[I_0]/\text{mol.dm}^{-3}$	$k/(\text{s}^{-1})$
50/1	0.016	0.20
75/1	0.0105	0.10
100/1	0.008	0.079
200/1	0.004	0.014

Table 3.4: Calculated apparent rate constant for different $[M]/[I]$ ratios in the ring opening polymerisation of L-lactide in toluene solution with titanium iso-propoxide at 90 °C.

Comparison of k versus the initial concentration of the initiator, $[I_0]$ (figure 3.9), shows a linear dependence. The line of best fit does not pass through the origin since when, as is common in many ring opening polymerisations, the monomer initiator ratio is increased above a threshold level, conversion falls below 100 %. This affects the maximum degree of polymerisation obtained, and therefore, k . Consequently, k reaches zero before the initiator concentration is zero. This arises from the presence of small amount of impurities.

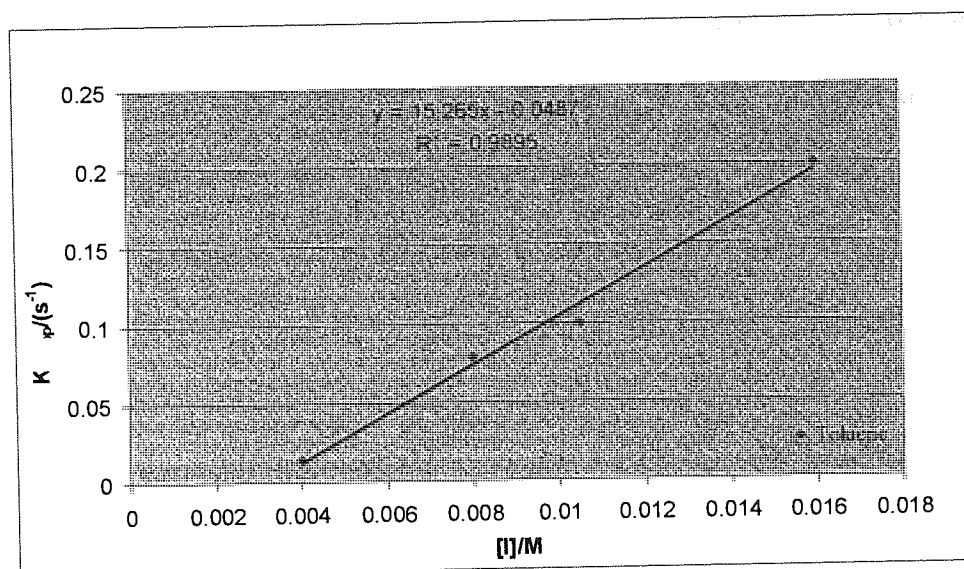


Figure 3.9: Comparison of apparent rate constant versus initiator concentration in toluene as a solvent.

3.7 LIVING CHARACTER OF LACTIDE

POLYMERISATION

A more detailed study on the polymerisation of l-lactide with titanium alkoxides was carried out in order to confirm some of the features that characterise a living system. $\text{Ti}(\text{O-}i\text{-Pr})_4$ was chosen from the catalysts previously tested since it gave high conversions as well as an experimental degree of polymerisation equal to the theoretical degree of polymerisation if 4 arms were equally active in the ring opening polymerisation of lactide. $\text{Ti}(\text{O-}i\text{-Pr})_4$ gives predictable and controllable ring opening polymerisation of L-lactide.

A good test of a living system is a plot of the molar mass of the polymers formed against the percentage of monomer conversion, in which case a straight line passing through the origin should be obtained. Therefore, three reactions were carried out, in

which the monomer/initiator molar ratios were different, 50/1, 100/1 and 200/1. A linear relationship in figure 3.10 was confirmed, of M_n plotted against monomer conversion. In addition a linear dependence of the degree of polymerisation on the $[M]/[I]$ ratio was also observed, as shown in figure 3.11, which allows a good control over the molecular weight as monomer/initiator molar ratio is varied. The linear relationship between molecular weight and monomer conversion indicates an absence of termination and transfer reactions as the monomer is consumed. If termination and transfer reactions occurred the gradient of the plot would change as the concentration of species decreased. Intermolecular transesterification reactions were only detected at very high conversions broadening slightly the polydispersity.

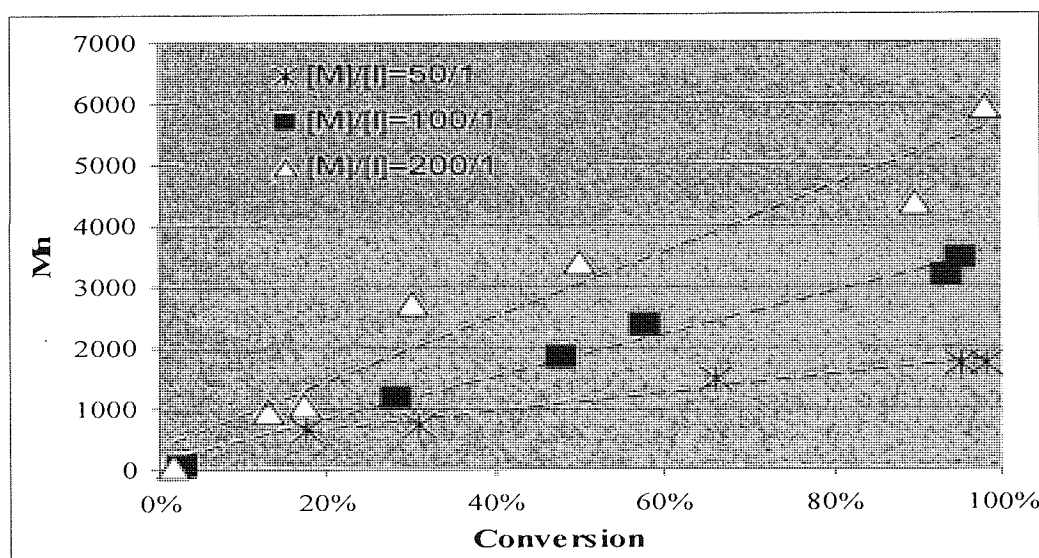


Figure 3.10: M_n versus conversion for different $[M]/[I]$ using $Ti(O-i-Pro)_4$ as an initiator.

Molecular weights up to 32,000 have been achieved so far for a $[M]/[I]$ of 1200/1. When $[M]/[I]$ ratio was increased up to 1600/1, initiation did not take place. The monomer concentration was doubled and quadrupled for this $[M]/[I]$ ratio and the reaction still showed no sign of polymer being produced. It is very probable that the small amount of initiator was deactivated by impurities during the initiation step, since this step becomes very slow at such low catalyst concentrations, preventing the polymers from being produced.

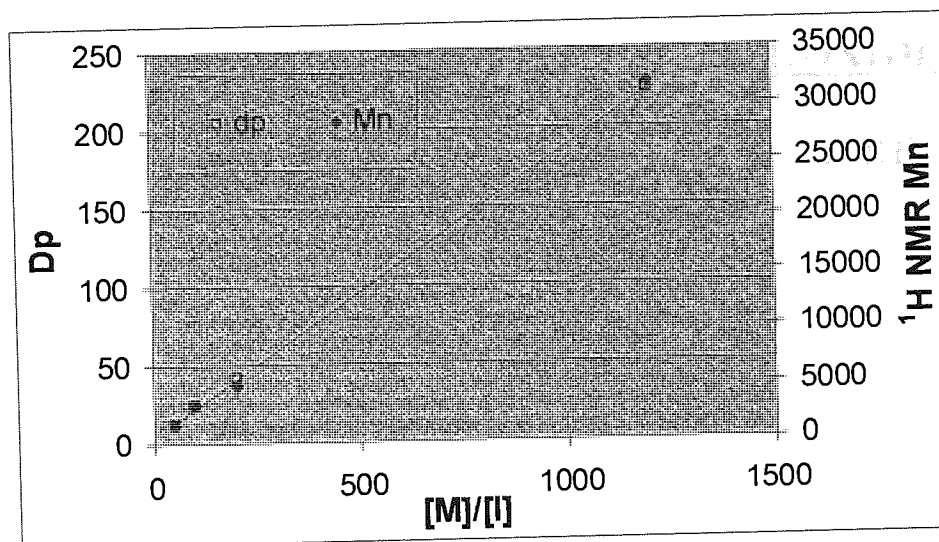


Figure 3.11: Dp versus $[M]/[I]$ for the polymerisation of L-lactide in toluene solution using $Ti(O-i-Pr)_4$ as an initiator at 90 °C.

Another feature of a living system is the absence of termination reactions. Thus it is also imperative to know whether the growing PLA-O-Ti intermediate will continue reacting when more monomer is fed into the reaction vessel after all of the initial monomer has been consumed. By adding 1 g of LA to a completely polymerised PLA system it was found that the polymerisation continues, reaching a monomer conversion of 99.9 % and an increase of molecular weight, measured by 1H NMR, from 1642 up to 2261.

3.8 EFFECT OF THE STRUCTURE OF THE ALKOXIDE GROUP ON THE POLYMERISATION OF L-LACTIDE.

It can be seen from table 3.3 that both the length and the steric bulk of the alkoxy group considerably influence the rate of the polymerisation, the fastest being initiator titanium propoxide. Similar reaction times are required for complete conversion of the monomer when titanium *iso*-propoxide and titanium butoxide are used as initiators for the lactide polymerisation. The initiators can be placed in order of decreasing activity based on their rate of reaction; $\text{Ti}(\text{O-Pr})_4 > \text{Ti}(\text{O-}i\text{-Pr})_4 = \text{Ti}(\text{O-Bu})_4 > \text{Ti}(\text{O-2-Et-Hex})_4 > \text{Ti}(\text{O-}t\text{-Bu})_4$.

It can also be seen that both the length and the steric bulk of the alkoxy group affect the degree of polymerisation. Polymerisations carried out with $\text{Ti}(\text{O-}i\text{-Pr})_4$ and $\text{Ti}(\text{O-Bu})_4$ as initiators show that in each case the same degree of polymerisation is obtained, which correspond to the theoretical degree of polymerisation expected if four arms were active. Degrees of polymerisation greater than those expected, for 4 active arms, are obtained in the case of $\text{Ti}(\text{O-Pr})_4$, $\text{Ti}(\text{O-2-Et-Hex})_4$ and $\text{Ti}(\text{O-}t\text{-Bu})_4$. This feature could arise from either the fact that fewer than four alkoxide groups are active in the polymerisation or by a decrease in efficiency of these initiator.

In order to clarify if either the efficiency of the initiator or the number of active arms were responsible for the degree of polymerisation obtained in the polymerisation of lactide with $\text{Ti}(\text{O-Pr})_4$, multizg ^1H NMR studies were carried out. The multizg technique consists of continuous ^1H NMR analysis of the evolution of the polymerisation as it takes

place in the NMR machine. 0.1 g of lactide and 25 μ l of a 0.78 mol/L solution of $\text{Ti}(\text{O-Pr})_4$ in deuterated toluene (which corresponds to a M/I of 400), were placed in a NMR tube. Deuterated chloroform was used as solvent. In order to mimic previous polymerisation in solution, some attempts were made using deuterated toluene as the solvent for both the analysis and polymerisation. Unfortunately, the solubilities of the lactide and the PLLA synthesised *in-situ* were not sufficient to obtain a properly resolved NMR spectrum. Therefore, the reactions were carried out in deuterated chloroform at 60 °C, slightly below the boiling point of the chloroform, 63 °C.

In order to avoid confusion of the end group signal with signals of un-reacted initiator, the ^1H NMR spectra of the initiators used in this work were measured and listed in table 3.5.

End group	^1H NMR δ in ppm	End group	^1H NMR δ in ppm
$\text{Ti}(\text{O-CH}-(\text{CH}_3)_2)_4$	4.45 (sept)	$\text{Ti}(\text{O-CH}-(\text{CH}_3)_2)_4$	1.21 (d)
$\text{Ti}(\text{O-CH}_2\text{-CH}_2\text{-CH}_3)_4$	4.24 (t)	$\text{Ti}(\text{O-CH}_2\text{-CH}_2\text{-CH}_3)_4$	0.87(t)
$\text{Ti}(\text{O-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3)_4$	4.20(t)	$\text{Ti}(\text{O-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3)_4$	0.85(t)
		$\text{Ti}(\text{O-C}-(\text{CH}_3)_3)_4$	1.27 (s)
$\text{Ti}(\text{O-CH}_2\text{-CH}(\text{CH}_2\text{-CH}_3)(\text{CH}_2)_3\text{CH}_3)_4$	4.13 (m)	$\text{Ti}(\text{O-CH}_2\text{-CH}(\text{CH}_2\text{-CH}_3)(\text{CH}_2)_3\text{CH}_3)_4$	0.89 (m)

Table 3.5: ^1H NMR Chemical shifts of metal alkoxide initiators.

From the ^1H NMR spectrum, figure 3.12, it can be seen that the methylene and methyl protons of the propoxide ligand, at 4.24 ppm and 0.86 ppm respectively, shift to 4.07 ppm (named “a” in figure 3.11) and 0.91 ppm (named “c”) when they are incorporated into the polymer chain as an ester end group. The multiplet at 4.07 ppm is the result of the overlapping of the two triplets produced by non-equivalent methylene groups. The two methylene groups become non-equivalent when the propoxide ligand reacts with the lactide because of the chiral carbon atom of the lactide. This feature is also observed in the case of the $\text{Ti}(\text{O-Bu})_4$ and $\text{Ti}(\text{O-2Et-Hex})_4$ and in the methyl group of the $\text{Ti}(\text{O-}i\text{-Pr})_4$, as mentioned previously.

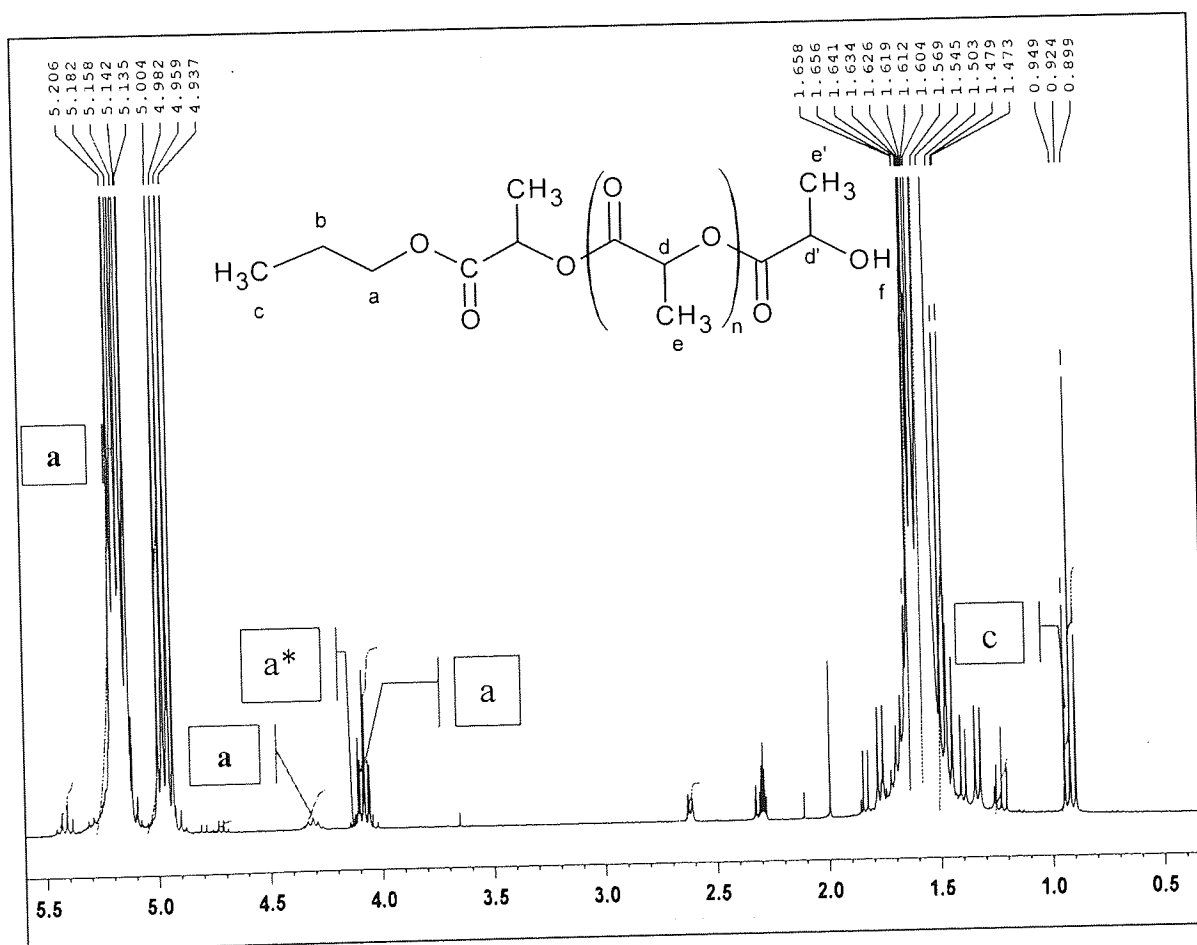


Figure 3.12: ^1H NMR spectra of a L-LA polymerisation *in-situ* using $\text{Ti}(\text{O-Pro})_4$ as initiator.

A small peak at 4.10 ppm (named "a*") can also be observed, slightly overlapped with the propoxylate end group at 4.07 ppm. It is believed that this peak is associated with the methylene group of a small percentage of propoxide ligands that have not reacted with the lactide and therefore remain bound to the titanium. The chemical shift at 4.10 ppm, is slightly different from the chemical shift of the completely unreacted $\text{Ti}(\text{O-}i\text{-Pr})_4$ at 4.24 ppm. This effect could be explained by the altered chemical environment of the titanium that is created by the active polymer chains, which are also bound to the titanium during the propagation step. The majority of the four alkoxy groups of the initiator were active in the polymerisation and only a very small percentage of alkoxy groups remained probably unreacted. The small difference in M_n obtained by GPC for a PLLA obtained using $\text{Ti}(\text{O-}i\text{-Pr})_4$, M_n : 6020 and a PLLA obtained with $\text{Ti}(\text{O-}i\text{-Pr})_4$ M_n : 7000 can be explained.

In the case of $\text{Ti}(\text{O-2-Et-Hex})_4$, the degree of polymerisation obtained for a $[\text{M}]/[\text{I}]$ of 50/1 (entry N 4) is 24, which is twice the expected value if all four arms were active. This result suggests that only two alkoxide groups are active in the polymerisation. A $[\text{M}]/[\text{I}]$ of 200/1 (entry N 9) on table 3.3, also shows some unusual characteristics regarding its degree of polymerisation. A D_p of 33 is obtained, which is much lower than the theoretical degree of polymerisation expected for a conversion of 91%. One reasonable explanation could result from the method used to calculate D_p from ^1H NMR. Since both methyl end-groups in the 2-ethyl hexoxide ligand are overlapped in the NMR spectrum, the area involving these peaks does not fully correspond to the real area of these 6 protons. There is a percentage of error by using this area, which could explain why such low D_p 's are obtained. The number average molecular weight obtained by GPC 7900 seems to be in accordance with the M_n s obtained from GPC for $\text{Ti}(\text{O-Bu})$ 7300 and $\text{Ti}(\text{O-}i\text{-Bu})$ 7600 when the degrees of polymerisation are close to 50. It has been observed through the

experiments that this catalyst is more sensitive to impurities than other titanium alkoxides, since this reaction (reaction N 9) had to be performed 4 times. In the previous attempts no polymer or polymers of very low molecular weight were obtained. Small amounts of impurities could have prevented the polymerisation either from starting or being completed. The sensitivity of this catalyst to water and impurities makes this polymerisation less reproducible.

In-situ Multizg ^1H NMR studies were carried out in the case of $\text{Ti}(\text{O}-2\text{-Et-Hex})_4$. The sample consisted of 0.1 g of lactide and 56 μl of a 0.93 mol/L solution of $\text{Ti}(\text{O}-2\text{-Et-Hex})_4$ in deuterated toluene giving a $[\text{M}]/[\text{I}]$ of 200/1. The ^1H NMR *in-situ* spectrum (figure 3.12) shows that not all of the $\text{Ti}(\text{O}-2\text{-Et-Hex})_4$ moieties are active in the ring opening polymerisation of the lactide. The chemical shift of remaining unreacted alkoxy groups will depend on the structure of the titanium moiety. As the number of propagating groups attached to titanium increases the chemical shifts of the remaining unreacted alkoxy groups would change progressively. In this case, a percentage $\text{Ti}(\text{O}-2\text{-Et-Hex})_4$ moieties remained unreacted (labelled as "a*" in figure 3.13), approximately 33% by comparison to polymer end-group alkoxy ligands (labelled as "a"). This caused a considerable increase in the Dp compared to those obtained with $\text{Ti}(\text{O}-i\text{-Pr})_4$ where four arms were active. The percentage of un-reactive ligands has been calculated by comparing the respective areas obtained from ^1H NMR analysis. In conclusion, the higher Dp observed in the ring opening polymerisation of lactide with $\text{Ti}(\text{O}-2\text{-Et-Hex})_4$ is caused by a poorer efficiency of the initiator compared to those shown by titanium alkoxides with smaller alkoxy ligands.

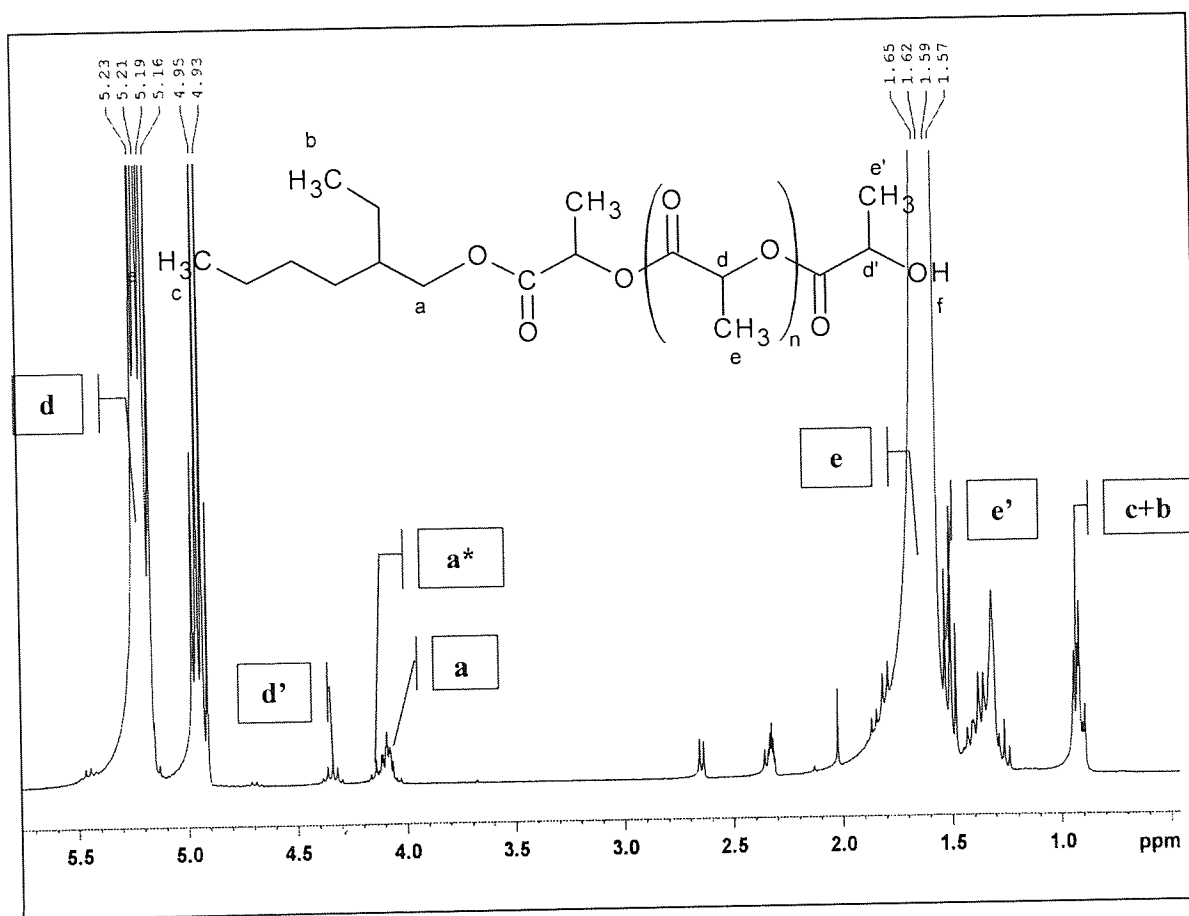


Figure 3.13: ^1H NMR spectra of a L-LA polymerisation *in-situ* using $\text{Ti}(\text{O}-2\text{-Et-Hex})_4$ as initiator.

In the case of the titanium *tert*-butoxide, a slow initiation is observed in both monomer initiator ratios of [200/1] and [50/1], which gives rise to a broadening of the polydispersity as well as a more inconsistent degree of polymerisation. The behaviour of this initiator will be reported in detail in chapter 5.

The broad polydispersity of reaction N 8 (table 3.3) occurred in a system that was left for a relatively long reaction time. It is quite probable that trans-esterification reactions were responsible for this feature since it was also observed for titanium tetra *iso*-propoxide when the reaction was allowed to continue after almost all of the monomer was consumed.

In order to calculate apparent rate constant, k , of each initiator, plots of $\ln(Dp_{\infty} - Dp_n)$ versus time are plotted in figure 3.14. This plot has been constructed from the degree of polymerisation data obtained from ^1H NMR analysis.

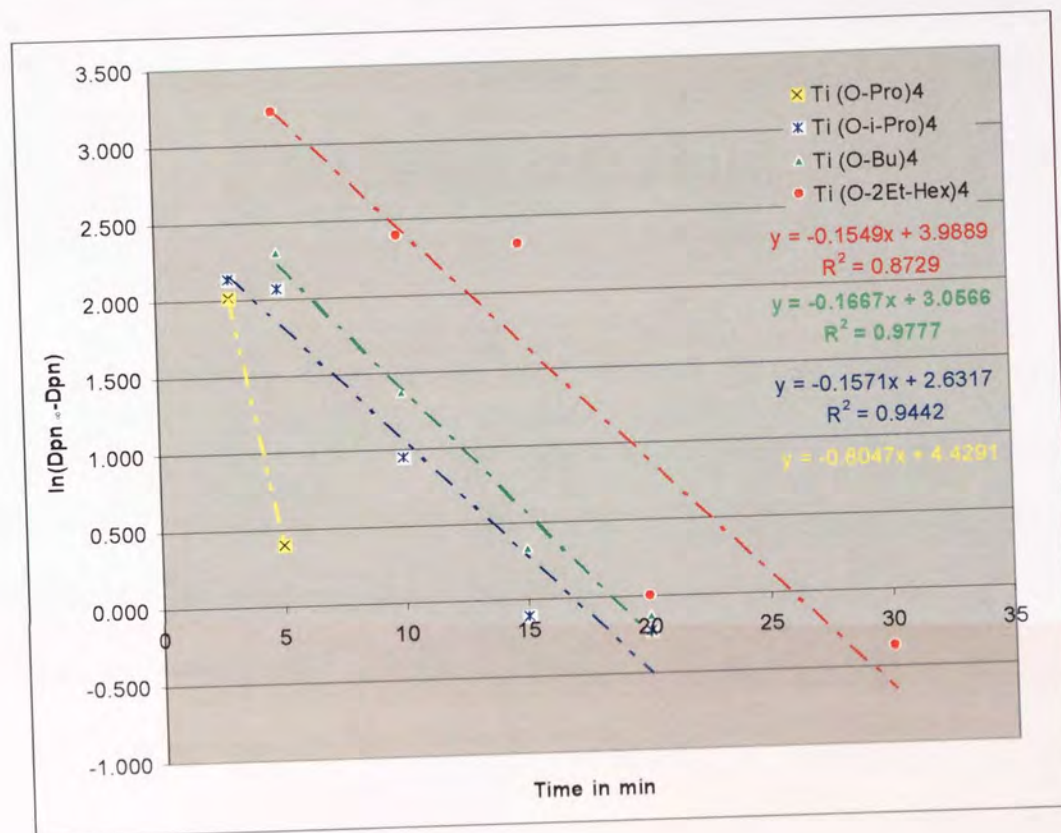


Figure 3.14: Plot of $\ln(Dp_{\infty} - Dp_n)$ versus time for the polymerisation of L-lactide with a $[M]/[I]=50$ in toluene at $90\text{ }^{\circ}\text{C}$, using different titanium alkoxides.

The calculated apparent rate constants, k 's, are shown below in table 3.5.

Titanium catalyst $[M/I]=50/1$	$k/(s^{-1})$
Ti(O-Pr) ₄	0.8*
Ti(O- <i>i</i> -Pr) ₄	0.157
Ti(O-Bu) ₄	0.167
Ti(O-2-Et-Hex) ₄	0.155**

Table 3.6: k for different $\text{Ti}(\text{OR})_4$ for the ring polymerisation of L-lactide in toluene solution at $90\text{ }^{\circ}\text{C}$.

* The calculated k_p app for $\text{Ti}(\text{O-Pr})_4$ is an estimated value since only two points were recorded due to very rapid reaction.

** The accuracy of k_p app is not is limited by errors associated with the ^1H NMR technique.

CHAPTER 4

TITLE: MELT POLYMERISATION OF LACTIDE WITH TITANIUM ALKOXIDES.

High molecular weight poly(L-lactide) is of interest as a biodegradable thermoplastic and fibre forming material. Medical sutures based on poly(lactides) such as Vicryl⁶, are commercially available. Number average molecular weights for these applications are above 60,000 g/mol. About 40 different biodegradable polymers and copolymers are currently used as alternatives to metal implants, which themselves present serious disadvantages such as: the sensitivity of the patient to metals, particularly nickel, and the need for a removal operation. Some of these commercial polymers and copolymers are ⁷: Phusiline (Phusis Materiaux Bioresorbables SA, Fixsorb (by Takiron) and Bioscrew (Linvatec (Zimmer). Number average molecular weights required for these applications are in the range of 1 and 3×10^5 . The synthesis of high molecular weight poly(lactic acid) is usually achieved by the ring polymerisation of lactide in the melt. The most widely used initiator for this purpose is tin octanoate ¹⁶⁻²³. Tin octanoate can be used to reach M_n 's up to 5×10^5 . However, the complete removal of highly toxic tin compounds is practically impossible⁸⁷. To avoid this issue, several attempts have been carried out to synthesise high molecular weight poly(lactides) with the use of less toxic initiators. As mentioned in chapter 1, only zinc and magnesium compounds have been successful in producing high molecular weight poly(lactides). However, the melt polymerisation of lactide with

magnesium compounds, such as di-butyl magnesium and butyl magnesium chloride, requires several days and results in low yields³⁷.

The aim of the work reported in this chapter was the study the performance of titanium iso-propoxide and titanium propoxide in the melt polymerisation of L-lactide in order to determine the reaction conversion, polydispersity and the maximum Mn that could be produced. $\text{Ti}(\text{O-Pr})_4$ and $\text{Ti}(\text{O-}i\text{-Pr})_4$ have been used, along with other titanium alkoxides as initiators for the polymerisation of lactide in solution reported in chapter 3. Both initiators show good control over the polymerisation and give fast reactions. Based on these characteristics they were selected to be used in the melt polymerisation of L-lactide.

4.1 MATERIALS

L was purchased from Purac stored under inert atmosphere in a glove box. It was re-crystallized from ethyl acetate before used, as described in section 2.2.1.3.

Ethyl acetate was purchased from Fisher, dried over calcium anhydride and distilled, as explained in section 2. 2.1.1.

$\text{Ti}(\text{O-Pr})_4$ and $\text{Ti}(\text{O-}i\text{-Pr})_4$ were used as received without any further treatment.

4.2 HOMO-POLYMERISATIONS IN THE MELT.

Monomer and initiator were transferred into a round bottom flask and mixed under an argon atmosphere in a glove-box. Once the reactor was sealed, it was moved from the glove box and placed in an oil bath to maintain the reactions at 105°C, a few degrees above the melting point of the L-lactide (92° C). Magnetic stirring was provided throughout the polymerisation but the formation of a hard, white solid as the reaction came to completion prevented the magnetic flea from working. At that point, the round bottom flask was taken out off the oil bath and the product obtained was dissolved in ethyl acetate. In previous publications⁶, PLA obtained by melt polymerisation of tin octanoate was dissolved in chloroform. In order to improve the green character of these polymerisations ethyl acetate was chosen since it is one of the mildest organic solvents (in terms of toxicity) in which the polymers of lactide dissolved. The dissolution of the product in ethyl acetate took place at 60° C, since solubility of the product in ethyl acetate is not as high as in chloroform. The presence of small amounts of water in the ethyl acetate was responsible for quenching the polymerisation. Once the dissolution was finished, methanol was added in order to precipitate the polymer. Ethyl acetate and methanol were evaporated by gentle heating with a hot-air gun and the remaining solid was dried under vacuum at 40° C for 24 h. Monomer conversion was calculated by ¹H NMR spectroscopic analysis of the crude product, referred to as unpurified product (since it is a mixture of the synthesised PLA and any unreacted monomer).

4.3 PRODUCT CHARACTERISATION.

The product was characterised by gel permeation chromatography (GPC) as shown in figure 4.1. The majority of these syntheses gave polymers of narrow polydispersities, as obtained by GPC, without oligomer formation. The product was characterised before it was washed with methanol and the remaining un-reacted monomer was removed. Molecular weights obtained from GPC were corrected by multiplying the GPC experimental value obtained using polystyrene standards by a factor of 0.55 (at least up to $M_n \approx 3 \times 10^4$). This correcting factor was calculated and explained in section 4.4, by comparing M_n obtained by ^1H NMR with M_n calculated by GPC.

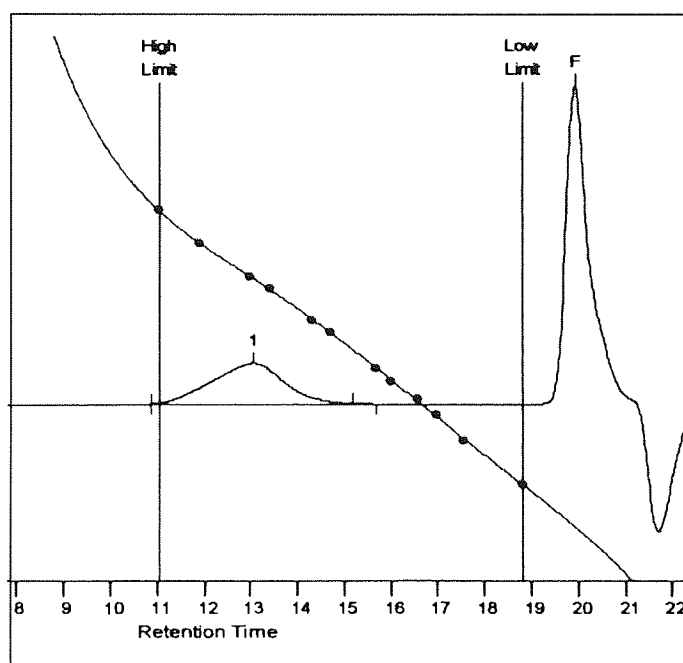


Figure 4.1: GPC of a PLLA obtained using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator in the absence of solvent.

In addition to GPC studies the characterisation of the product was carried out by ^1H NMR spectroscopy. The ^1H NMR spectrum of the reaction mixture was used to determine conversion the relative intensities of the monomer and polymer methine quartets at 5.03 ppm and 5.13 ppm respectively. ^1H NMR spectrum of a melt polymerisations with $\text{Ti}(\text{O-}i\text{-}$

Pr)₄ is shown below in figure 4.2. No difference was observed between the ¹H NMR spectra obtained from solution polymerisations and melt polymerisations.

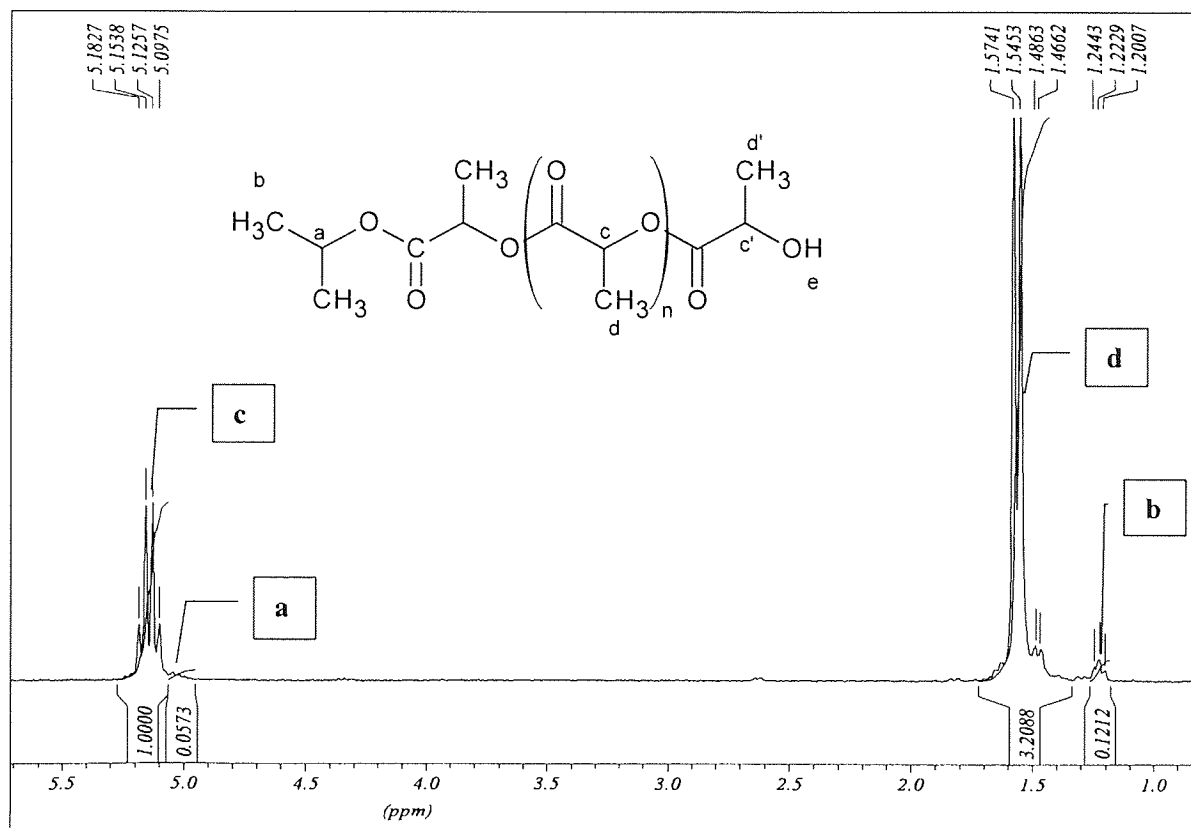


Figure 4.2: ¹H NMR spectrum of the PLLA obtained through the melt polymerizations of L-lactide with Ti(O-*i*-Pr)₄.

Spectroscopic end-group analysis was shown by Kricheldorf and co-workers³⁰ to be an accurate means to establish the method for the determination of the degree of polymerisation and, therefore, the number average molecular weight. Dp and Mn will be calculated as previously explained in section 3.4. A quantitative evaluation of the end-group signal should clarify whether all alkoxide groups of the initiators under study participate in the initiation process.

4.4 RESULTS AND DISCUSSION

To determine the influence of the catalyst concentration on the molecular weight, two sets of reactions were carried out, in which the monomer/initiator molar ratio was varied and the monomer concentration kept constant at [8.6] M throughout all polymerisations. In the first set of reactions, $\text{Ti}(\text{O-}i\text{-Pr})_4$ was used as an initiator, whereas $\text{Ti}(\text{O-Pr})_4$ was employed in the second set. Polymerisations were carried out with monomer to initiator molar ratios varying from 50 to 3000. The results of the lactide polymerisation with both $\text{Ti}(\text{O-}i\text{-Pr})_4$ and $\text{Ti}(\text{O-Pr})_4$ in the melt are shown below in tables 4.1 and 4.2.

$[\text{Ti}(\text{O-}i\text{-Pr})_4]$	$[\text{M}]/[\text{I}]$	Reaction time (min)	% Conversion	Dp	PD	$M_{n\text{GPC}}/$ g/mol	$M_{n\text{GPC}}^*/$ g/mol	$M_{n\text{NMR}}/$ g/mol	$M_{n\text{Th}}/$ g/mol
0.0043	2400/1	180	99	NA	1.9	74800	74800	NA	85250
0.0054	1600/1	120	>99	NA	1.54	59100	59100	NA	57660
0.0086	1000/1	120	>99	280	1.7	39700	39700	40380	36060
0.017	600/1	60	>99	145	1.58	35300	19400	20940	21660
0.043	200/1	60	98	46	1.74	16500	9100	6680	7110
0.086	100/1	25	98	26	1.5	8800	4800	3780	3590
0.17	50/1	35	>99	14	1.21	5600	3100	2110	1880
0.86	10/1	20	>99	2.7		800	440	450	420
L-lactide, $[\text{M}]=8.6 \text{ mol/dm}^3$, $T=105^\circ\text{C}$									

Table 4.1: L-Lactide polymerisation with in the melt $\text{Ti}(\text{O-}i\text{-Pr})_4$

$M_{n(\text{GPC})}^*$: Molecular weights obtained from GPC within the range of $(100\text{-}3 \times 10^4)$ were corrected by applying a correcting factor of 0.55.

[Ti(O-Pr) ₄]	[M]/[I]	Reaction time (min)	% Conversion	Dp	PD	M _n GPC / g/mol	M _n GPC* / g/mol	M _n NMR / g/mol	M _n Th / g/mol
0.0043	3000/1	180	70	NA	1.63	53600	53600	NA	75660
0.0054	2400/1	120	99	NA	1.58	72000	72000	NA	86460
0.0086	1600/1	120	99	NA	1.99	57900	57900	NA	57660
0.017	600/1	75	99	130	1.41	28000	15400	18780	21660
0.043	200/1	40	>99	52	1.75	16600	9100	7550	7260
L-lactide, [M]=8.6 mol/dm ³ , T=105 °C									

Table 4.2: L-Lactide polymerisation with Ti(O-Pr)₄ in the melt.

It should be noted that the calculation of the number average molecular weight by NMR end group analysis was not possible for monomer/initiator molar ratio above 1000 since the area of the end group was lower than the detection limit and the error associated with it very high. This limitation is represented in tables 4.1 and 4.2 by the abbreviation N.A, which stands for not applicable.

Melt polymerisations of lactide with both Ti(O-*i*-Pr)₄ and Ti(O-Pr)₄ show very short reaction times ranging from 25 min up to 3 hours depending on the monomer/initiator molar ratio used. Conversions were, in each case, virtually quantitative, as shown in figure 4.3. In the case of Ti(O-*i*-Pr)₄, conversions are very high, up to a monomer/initiator molar ratio of 2400. However, conversion drops to 70 % for M/I of 3000/1. When very high molecular weights are produced, the rate of the reaction becomes dependent on the diffusion rate of the monomer from the monomer phase to the polymer phase. Therefore, increased reaction times may be required to achieve higher conversions under these conditions.

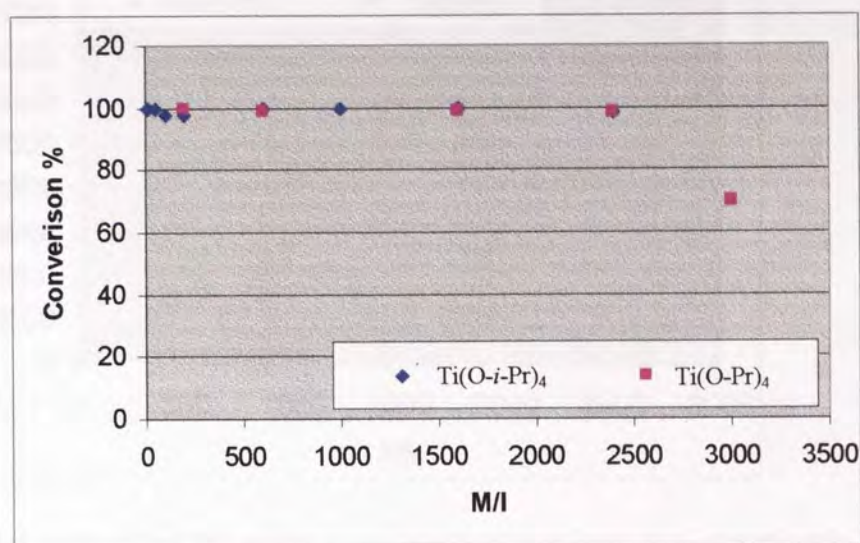


Figure 4.3: Evolution of conversion and Mn as monomer/initiator ratio is varied for the melt polymerisation of lactide with Ti(O-*i*-Pr)₄ and Ti(O-Pr)₄.

Polymerisations of lactide, with both Ti(O-*i*-Pr)₄ and Ti(O-Pr)₄, required similar reaction times and produced the same number average molecular weight for the same monomer/initiator ratio. The maximum Mn_{GPC} obtained by both initiators was very similar, reaching molecular weights in the range of 72,000 to 75,000 for a monomer/initiator ratio of 2400/1. Higher [M]/[I] molar ratios were not tested, but could be investigated in subsequent work. Likewise, the influence of the reaction time in the number average molecular weight should also be studied to confirm if the maximum conversion has been achieved for the highest [M]/[I] molar ratio. This will indicate if conversion and the number average molecular weight can be further increased or if a plateau has been reached.

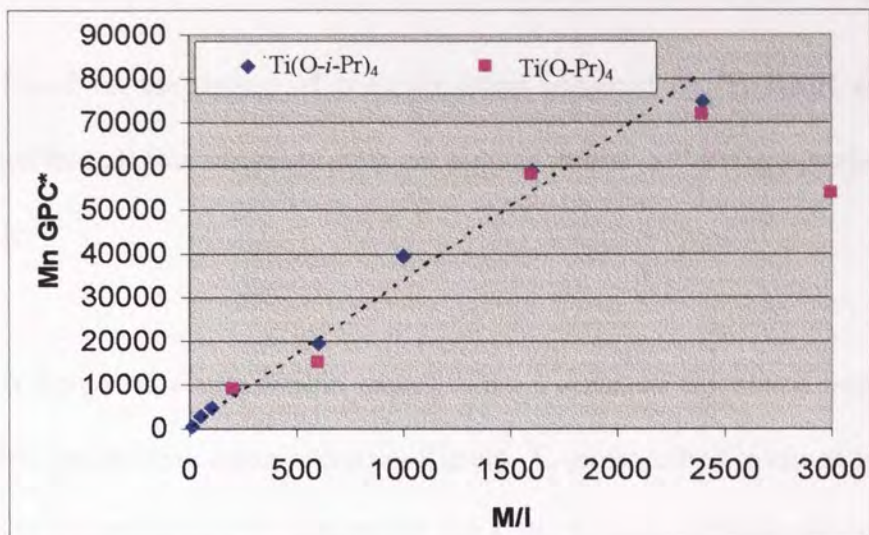


Figure 4.4: Evolution of Mn as the monomer/initiator ratio is varied for the melt polymerisation of L-lactide with Ti(O-*i*-Pr)₄ and Ti(O-Pr)₄ at a 105 °C.

Dp of PLLA synthesised using Ti(O-*i*-Pr)₄ (calculated by spectroscopic end-group analysis), shows a linear dependence with the monomer/initiator molar ratio for a [M/I] up to 1000/1, as shown in figure 4.5. The same behaviour was also observed when the polymerisation was carried out in solution.

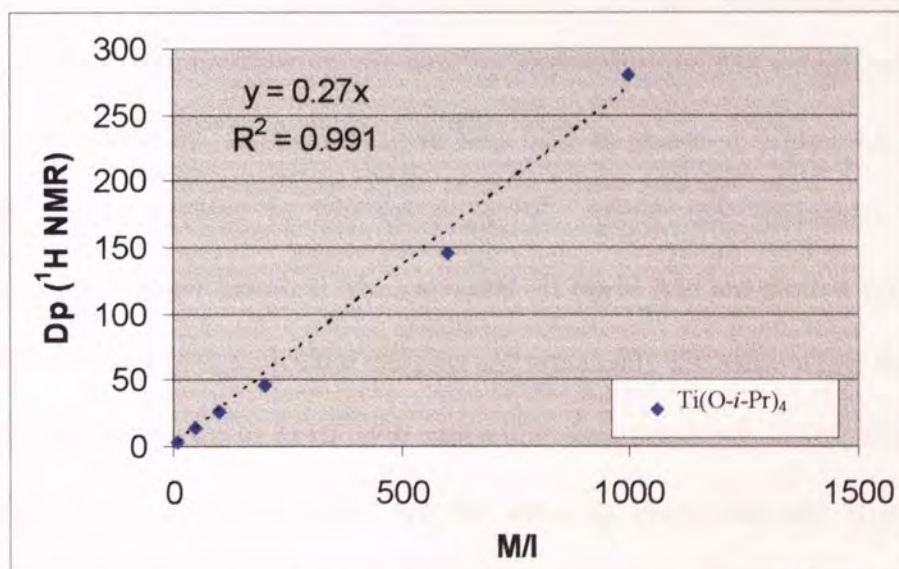


Figure 4.5: Dp versus [M]/[I] for the melt polymerisation of L-lactide using Ti(O-*i*-Pr)₄ as an initiator at 105 °C.

Based on the degree of polymerisation obtained by ^1H NMR analysis it can be confirmed that all four alkoxide arms are equally active in the ring opening polymerisation of lactide.

Average molecular weight values, $M_n(\text{GPC}^*)$ can be calculated from the polystyrene calibration curve using a correcting coefficient, X , as described in equation 4.1 below. This coefficient is calculated by comparing the GPC values to those obtained for the same polymers by several other techniques such as vapour pressure osmometry, MALDI-TOF MS and ^1H NMR analysis.

$$M_n(\text{GPC}^*) = X \times M_n(\text{GPC}), \text{ Equation 4.1.}$$

The average reported values of the correcting coefficient for poly(D,L-LA)¹⁰² and poly(ϵ -CL)¹⁰³ are 0.58 and 0.56 respectively. The average value of the correcting coefficient that was obtained for poly(L-LA) by comparing the M_n calculated from GPC and the M_n calculated by ^1H NMR analysis was 0.55 as shown in figure 4.6. This linear relationship can be applied to M_n up to 3×10^4 . Above this molecular weight the relationship is no longer linear. If $M_n(\text{GPC}^*)$ and ^1H NMR M_n are plotted versus $[\text{M}]/[\text{I}]$, it can be observed that both molecular weights are practically the same when the correcting factor is applied for M_n up to 3×10^4 . For molecular weights above 3×10^4 , M_n 's obtained directly from polystyrene calibrations are the same as those obtained from ^1H NMR analysis. It can be assumed that for high molecular weights above 3×10^4 , M_n obtained from GPC and M_n obtained from ^1H NMR analysis are essentially the same as seen in figure 4.7.

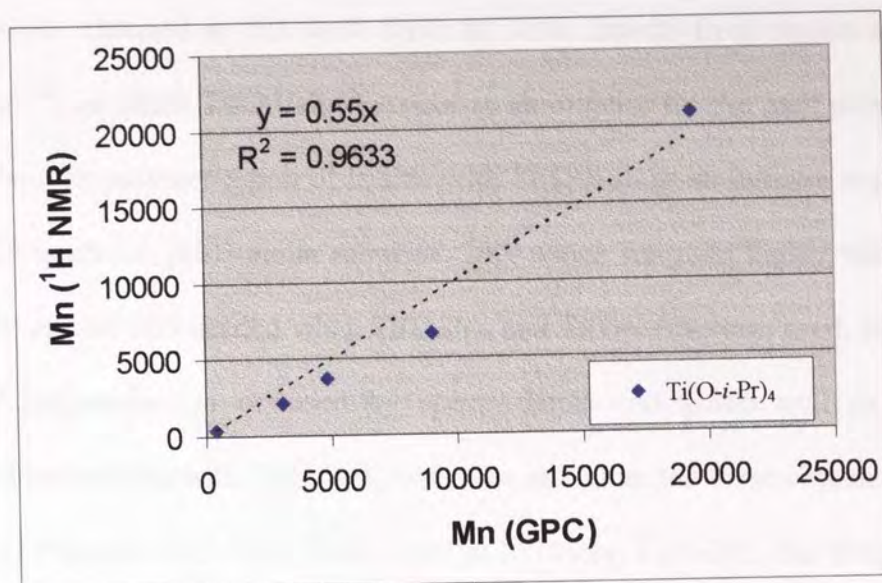


Figure 4.6: Mn obtained from GPC versus Mn obtained from ¹H NMR spectra for the melt polymerisation of L-lactide using Ti O-*i*-Pr)₄ as an initiator at 105 °C.

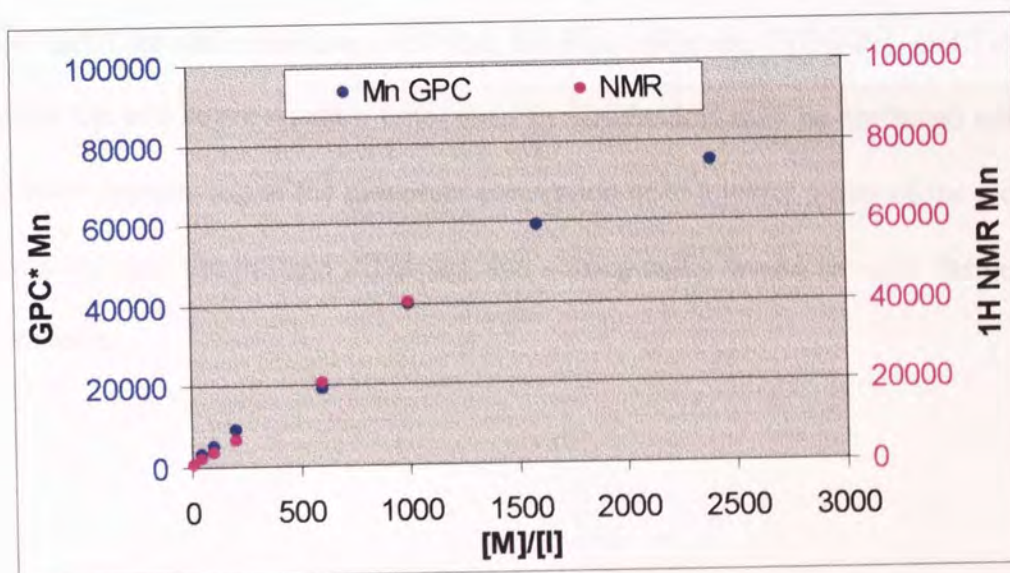
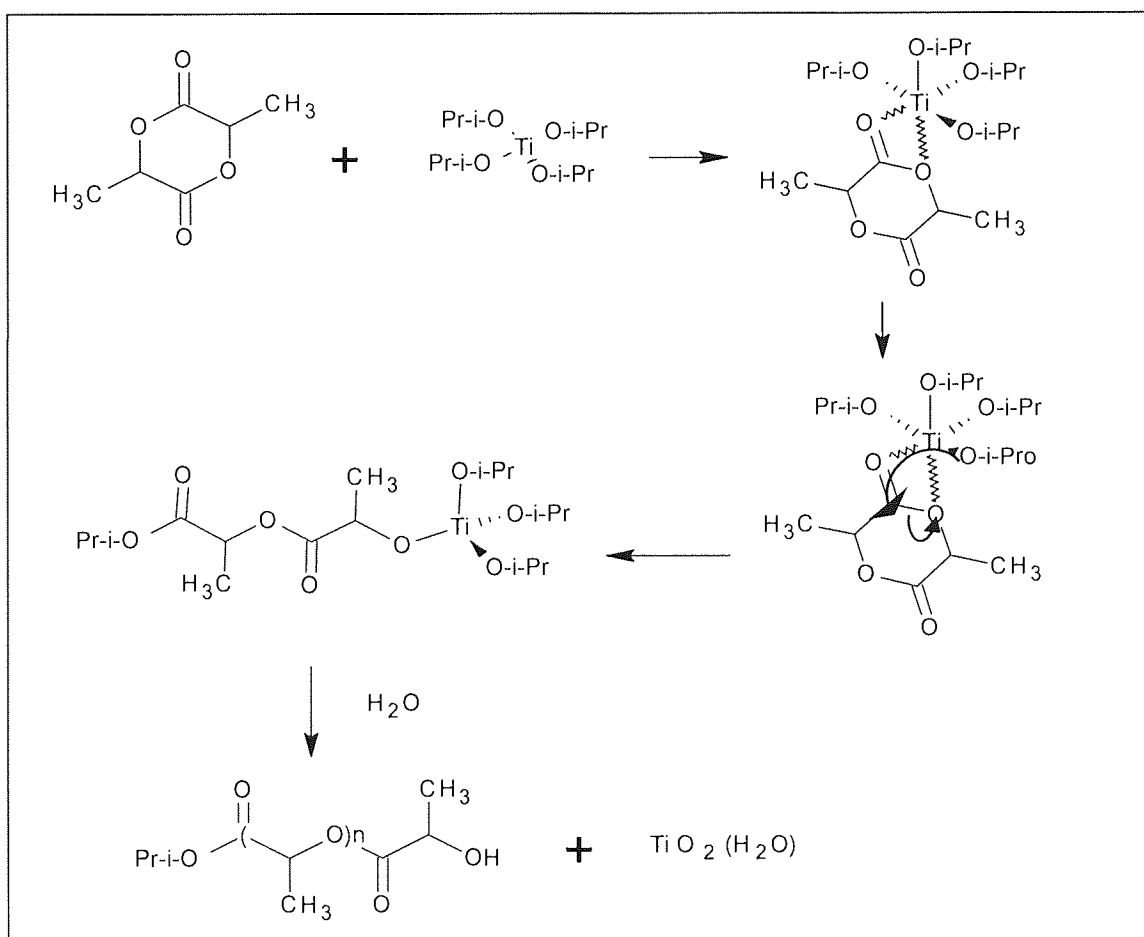


Figure 4.7: Similarities of the corrected Mn obtained from GPC and Mn obtained by ¹H NMR analysis versus monomer initiator molar ratio.

Results obtained in this work differ in some aspects from studies carried out by Kricheldorf³⁰, in which $\text{Ti}(\text{O-Bu})_4$ was used as an initiator for the melt polymerisation of lactide. The melt polymerisation of lactide with $\text{Ti}(\text{O-Bu})_4$ as an initiator required reaction times of 24 hours for $[\text{M}/\text{I}]$ molar ratios of 200, which contrasts highly with the reaction times of 40 and 60 min needed when $\text{Ti}(\text{O-Pr})_4$ and $\text{Ti}(\text{O-}i\text{-Pr})_4$ were used. In addition, the degree of polymerisation obtained by spectroscopic end group analysis of the melt polymerisation product with $\text{Ti}(\text{O-Bu})_4$ was twice as high as the those obtained in this work when $\text{Ti}(\text{O-Pr})_4$ and $\text{Ti}(\text{O-}i\text{-Pr})_4$ were used as initiators. $\text{Ti}(\text{O-Bu})_4$ has been discussed in the previous chapter for the polymerisation of lactide in solution and shows a similar behaviour to $\text{Ti}(\text{O-}i\text{-Pr})_4$, where the same conversion and D_p are obtained for a given $[\text{M}/\text{I}]$ molar ratio. Therefore, similar degrees of polymerisation and reaction times would be expected under the same reaction conditions for both initiators, $\text{Ti}(\text{O-}i\text{-Pr})_4$ and $\text{Ti}(\text{O-Bu})_4$. The higher D_p and larger reaction times seen by Kricheldorf may be attributed either to a less extensive monitoring of the monomer conversion or to a lower purity of the monomer, which would lower the initiator efficiency and consequently would increase the degree of polymerisation.

In conclusion, the ring opening polymerisation of the lactide, using $\text{Ti}(\text{O-Pr})_4$ or $\text{Ti}(\text{O-}i\text{-Pr})_4$ as initiators, can be described as the nucleophilic attack of the alcoholate active species on the monomer ester group, followed by the acyl-oxygen bond scission. Ions are presumably not involved in these polymerisations and the monomer addition proceeds *via* the concerted insertion into the metal-oxygen bond. This mechanism can be applied to both solution and bulk polymerisations. An illustration of the mechanism is shown below (scheme 4.1).



Scheme 4.1: Coordination-insertion mechanism of lactide polymerisation using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator.

CHAPTER 5

TITLE: POLYMERISATION OF LACTIDE WITH TITANIUM *TERT*-BUTOXIDE.

Lactide polymerisation with titanium alkoxides has not been studied in great depth in the past. Kricheldorf³⁰ investigated the polymerisation of lactide with $\text{Ti}(\text{O-Bu})_4$ in the melt. In addition to these studies, melt polymerisation of lactones, such as D,L- β -butyrolactone and ϵ -caprolactone, and solution polymerisation of β -propiolactone were also carried out using $\text{Ti}(\text{O-Bu})_4$ as an initiator³⁰.

Series of polymerisations, both in solution and in the melt, were carried out in order to comprehend fully the effect of the $\text{Ti}(\text{O-}i\text{-Bu})_4$ on the degree of polymerisation obtained in the solution polymerisation of lactide in toluene is described in chapter 3. The polymerisations were carried out either using a constant concentration of lactide and varying the catalyst concentration or *vice versa*.

5.1 MATERIALS.

L-Lactide was purchased from Purac, stored under an inert atmosphere in a glove box and re-crystallised from ethyl acetate before used, as described in section 2.2.1.3.

Toluene and ethyl acetate were purchased from Fisher. They were dried over calcium anhydride and distilled as explained in section 2.2.1.1.

Ti(O-*t*-Bu)₄ (95%) was purchased from Aldrich and stored in the glove box. It was used as received without any further treatment.

5.2 L-LACTIDE POLYMERISATIONS IN SOLUTION.

Monomer, catalyst and solvent were transferred and mixed under an argon atmosphere in a glove-box. Once the reactor was sealed, it was removed from the glove box and connected to a vacuum line. The polymerisation was carried out as described in section 3.2. Analysis of the crude product (unpurified product) was used to calculate monomer conversion at any given time during the reaction. ¹H NMR analysis was also used to calculate the degree of polymerisation (Dp) and the number average molecular weight (Mn). Calculation of conversion, Dp and Mn was carried out as explained in section 3.2 and 3.4.

5.3 PRODUCT CHARACTERISATION.

Products obtained from this polymerisation were characterised by gel permeation chromatography (GPC) and ^1H and ^{13}C NMR. Analysis by GPC of the crude products showed that the majority of these syntheses gave polymers of broader polydispersities than those described in chapter 3, ranging from 1.4 to 2. The absence, in every single case, of oligomer formation was also shown. A list of polymer polydispersities and molecular weights is given in tables 5.1 and 5.2. A chromatograph of a PLA synthesised using $\text{Ti}(\text{O}-t\text{-Bu})_4$ is shown in figure 5.1.

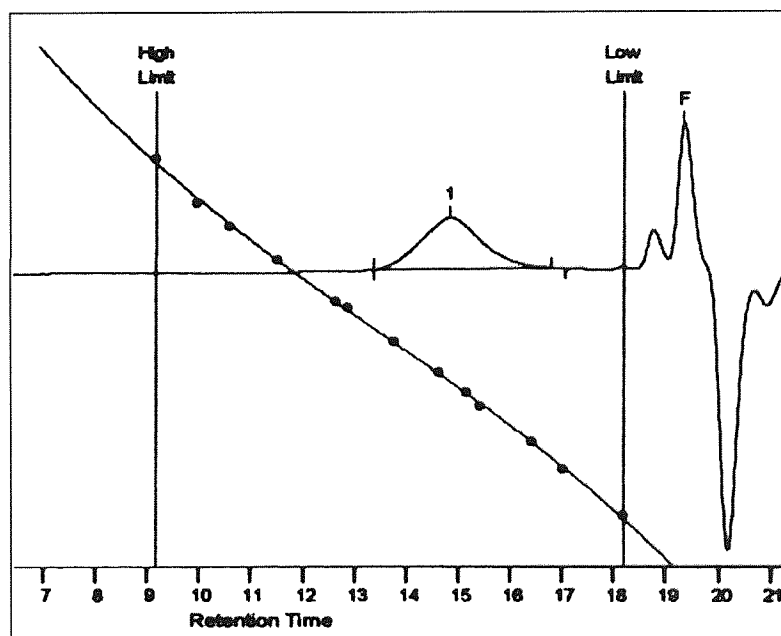


Figure 5.1: GPC of PLA synthesised in toluene solution at 90 °C using $\text{Ti}(\text{O}-t\text{-Bu})_4$ as an initiator.

A small peak can be observed in figure 5.1, just before the flow marker peak labelled as F, which corresponds to the presence of some impurities in the THF, the mobile phase. This has been proved by recording the chromatograph of the solvent containing no sample, as shown below in figure 5.2.

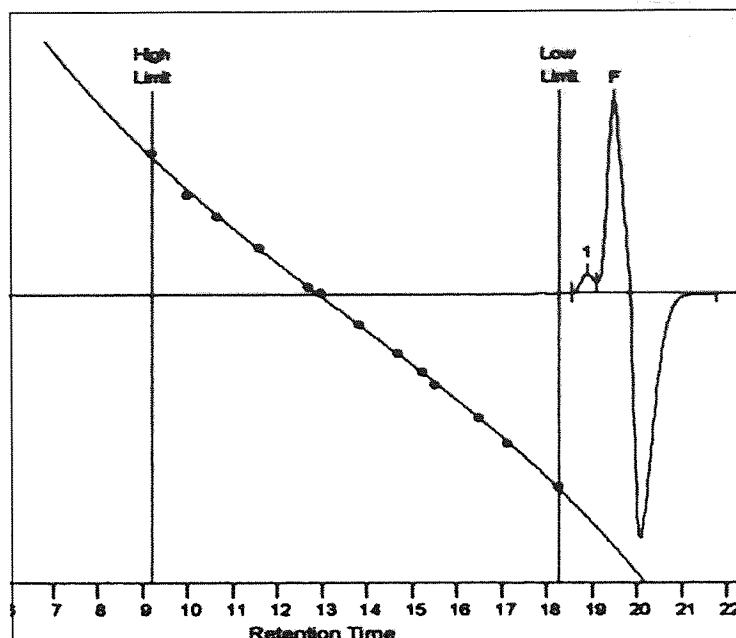


Figure 5.2: GPC of a blank sample of solvent.

^1H NMR spectroscopy of the purified product (figure 5.3) confirms the presence of the methine and methyl protons of the lactide at 5.13 and 1.55 ppm respectively, as well as the incorporation of the *tert*-butoxide ligand as an ester end group within the polymer by the presence of the methyl protons of the *tert*-butyrate group at 1.43 ppm. The chemical shift of the *tert*-butyrate was confirmed against a model ester, *tert*-butyl formate, the chemical shifts of which are listed in table 5.1. The ^1H NMR chemical shift frequencies of PLA, as well as the alcoholate end group, are listed in table 5.1.

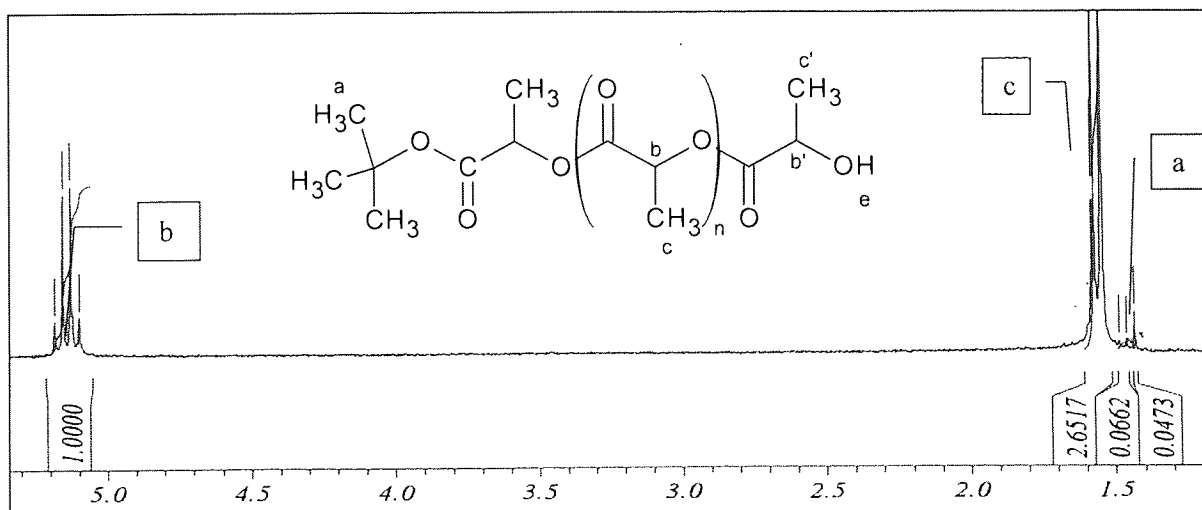


Figure 5.3: ^1H NMR of a typical polylactic acid bearing a *tert*-butoxide as an end group.

Group	^1H NMR δ (ppm)	End group	^{13}C NMR δ (ppm)
$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	5.13 (q)	$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	69 (s)
$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	1.55 (d)	$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	16.6 (s)
$\text{OCO}-\text{C}-(\text{CH}_3)_3$	1.43 (s)	$-\text{OCO}-\text{CH}(\text{CH}_3)\text{O}-$	169.6 (s)
$\text{Ti}(\text{O}-\text{C}-(\text{CH}_3)_3)_4$	1.27 (s)	$\text{OCO}-\text{C}-(\text{CH}_3)_3$	27.82 (s)
$\text{CH}_3\text{OCO}-\text{C}-(\text{CH}_3)_3$	1.45 (s)	$\text{CH}_3\text{OCO}-\text{C}-(\text{CH}_3)_3$	27.5 (s)

Table 5.1: ^1H and ^{13}C NMR chemical shifts, δ , for PLLA, $\text{Ti}(\text{O}-t\text{-Bu})_4$ and end groups measured in CDCl_3 .

^{13}C NMR spectroscopy also confirms the presence of the methyl carbon of the *tert*-butyrate end group at 27.82 ppm (figure 5.4). The presence of the quaternary carbon is not detectable, due to its low abundance. ^{13}C NMR chemical shift frequencies of the PLA and the alcoholate end group are listed in table 5.1.

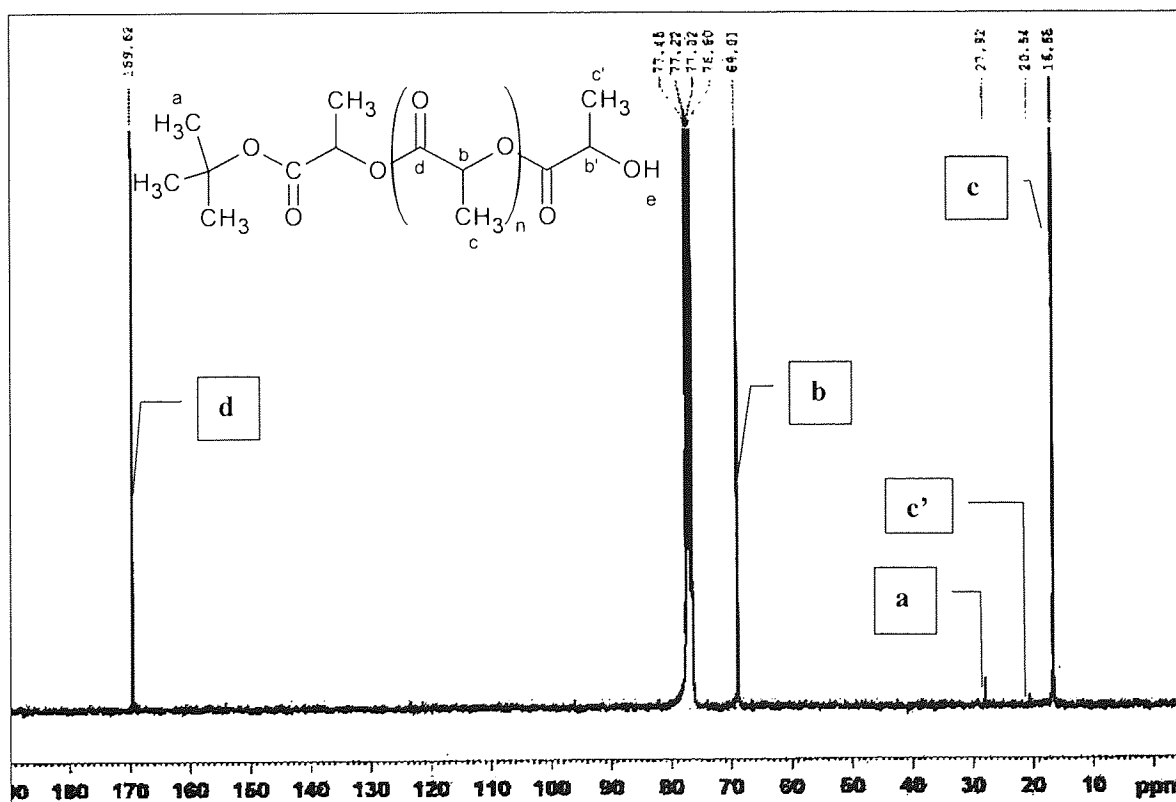


Figure 5.4 ^{13}C NMR of a typical polylactic acid bearing a *tert*-butoxide as an end group.

5.4 RESULTS AND DISCUSSION

An initial set of reactions was carried out in which the monomer concentration was kept constant and the catalyst concentration was varied. The results obtained for this series are summarised in table 5.2. High conversions were obtained in all experiments, as well as relatively broad polydispersities, which were ascribed to the bulkiness of the *tert*-butoxide group of the initiator causing slow initiation of the polymerisation. The degree of polymerisation was, in each case, higher than expected if four arms of the initiator were active. Although D_p increased as the monomer/initiator molar ratio increased, it did not follow a linear relationship with the ratio of monomer to initiator used giving uncontrolled polymerisations.

[M] /[Mol/dm ³]	[Ti(O- <i>t</i> -Bu) ₄] /[Mol/dm ³]	[M]/[I]	Reaction time/ min	Conversion /%	D_p	PD	M_{nGPC} /(g/mol)	M_{nNMR} /(g/mol)	I.E. /%
0.78	0.098	8	60	100	28	1.5	6000	4090	7
0.78	0.031	25	120	94	25	1.6	8800	3720	24
0.78	0.016	50	180	94	46	1.97	7600	6650	26
0.78	0.0078	100	240	94	75	1.41	9500	10840	31
0.78	0.0039	200	300	90	66	1.56	18700	7400	68

Table 5.2: L-Lactide polymerisation in solution with different titanium *tert*-butoxide concentrations.

M: Monomer (L-lactide)

IE: Initiator efficiency. Error in the calculation of the initiator efficiency is a maximum of 4%

It can be seen from figure 5.5 that the efficiency of the catalyst increases exponentially as the catalyst concentration decreases. This is likely to occur because as the concentration of the initiator is raised, a decrease of solubility of titanium *tert*-butoxide in the toluene is observed making the catalyst less efficient. Therefore, when a high initiator concentration is used, only a small percentage of catalyst molecules are active.

Two solutions of titanium *tert*-butoxide in toluene were carried out at room temperature. Concentrations of 0.13 and 0.05 mol/dm³ were used. Crystals were observed 24 hours after both, initiator and solvent, were mixed. The solubility of the initiator is clearly the cause of the drop in the efficiency of the initiator at initiator concentrations above 0.004 mol/dm³.

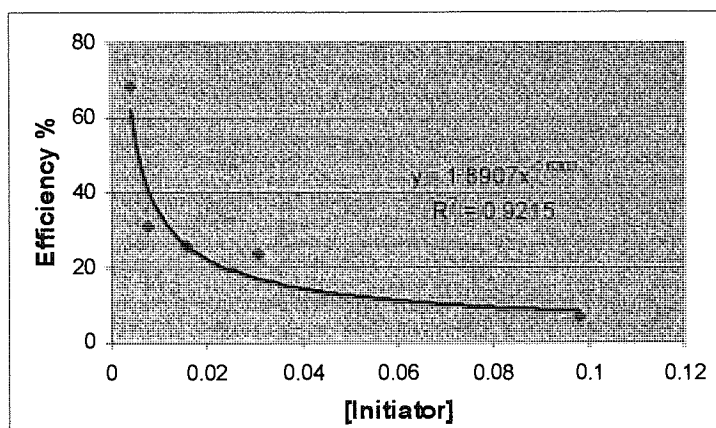


Figure 5.5: Efficiency of the initiator in solution polymerisations of L-lactide as a function of the initiator concentration for $[M]=0.78 \text{ mol.dm}^{-3}$.

Consequently, the efficiency also increased as the monomer initiator ratio increased, as seen in figure 5.6.

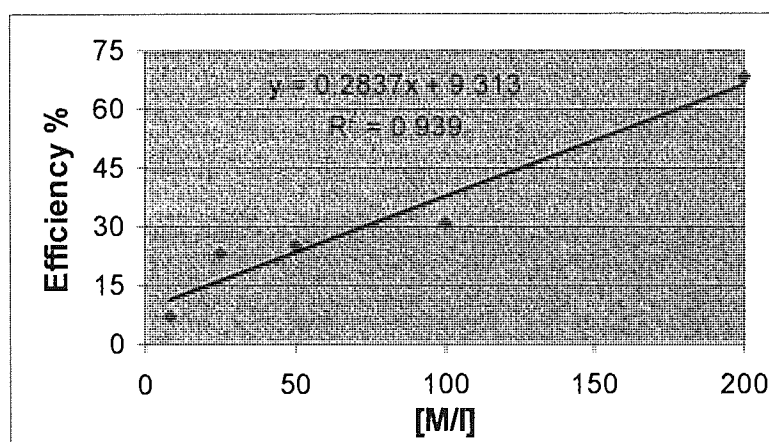


Figure 5.6: Efficiency of the initiator in solution polymerisations of L-lactide at 90 °C as a function of M/I for $[M]=0.78 \text{ mol.dm}^{-3}$.

A second set of reactions was carried out, in which the monomer concentration was varied and the initiator concentration was kept constant. Results obtained from this series (table 5.3) show that conversions were high. The increase of Dp with the monomer initiator ratio does not follow a linear relationship, as in the previous set of reactions.

[M] /[Mol/dm ³]	[Ti(O- <i>t</i> - Bu) ₄] /[Mol/dm ³]	[M]/[I]	Reaction time/ min	Conversion /%	Dp	PD	M _n GPC /(g/mol)	M _n NMR /(g/mol)	I.E. / %
0.14	0.017	8	120	98	14			2130	14
0.4	0.016	25	150	92	41	1.35	5300	6000	14
0.78	0.016	50	180	94	46	1.97	7600	6650	26
1.59	0.016	100	180	100	62	1.31	16100	9030	40

Table 5.3: L-Lactide polymerisation in solution with titanium *tert*-butoxide at 90 °C varying monomer concentration.

It can be seen from figure 5.7 that, for a constant initiator concentration, the efficiency of the initiator increased linearly with monomer concentration. This relationship is attributed to the increased probability of a molecule of monomer coming into contact with a molecule of initiator as the monomer concentration increases. A similar linear relationship was observed between the efficiency and the monomer initiator ratio (figure 5.8).

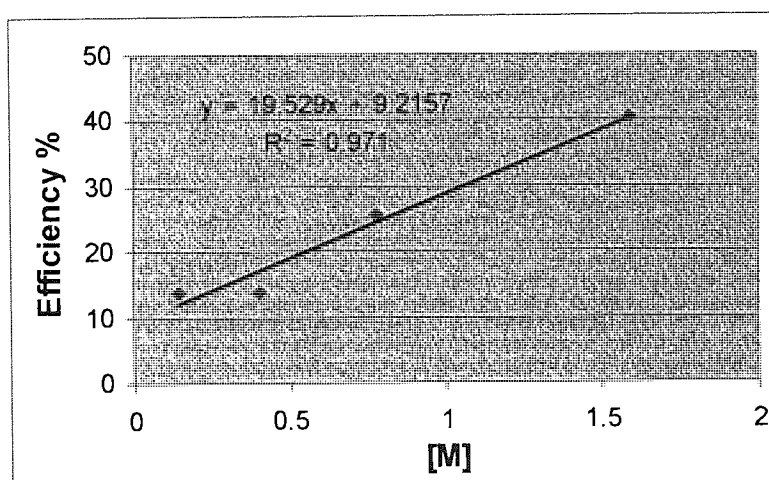


Figure 5.7: Efficiency of the initiator in solution polymerisation of L-lactide at 90 °C as a function of [M] for a [I]=0.016 mol.dm⁻³

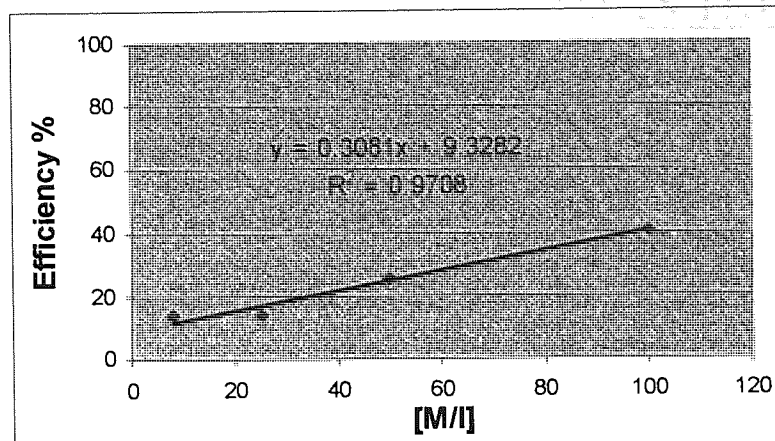


Figure 5.8: Efficiency of the initiator in solution polymerisations of L-lactide at 90 °C as a function of $[M/I]$ for $[I]=0.016 \text{ mol.dm}^{-3}$

The concentration of the initiator, $\text{Ti}(\text{O-}i\text{-Bu})_4$, plays an important role in controlling the reaction and allows the degree of polymerisation to be predicted. Molar concentrations of initiators above 0.004 M are preferable to obtain higher efficiencies and better control of the polymerisation. The high D_p 's obtained from these two series of experiments suggest that only one alkoxide ligand per molecule of initiator was active in the ring opening polymerisation of lactide. This was likely to occur because of the bulkiness of the *tert*-butoxide ligand.

5.4 L-LACTIDE POLYMERISATIONS IN THE MELT.

As industrial polymerisations are often carried out in the melt, it is also important to explore the behaviour of this catalyst under this condition. Thus, a series of reactions was carried out varying the monomer to initiator ratio and, therefore, the initiator concentration in order to study the evolution of the degree of polymerisation and the efficiency of the initiator. Monomer and initiator were transferred into a round bottom flask and mixed in a glove-box under an argon atmosphere. The description of the lactide polymerisation in the melt follows as described in section 4.

5.4 RESULTS AND DISCUSSION

Monomer conversion was calculated by ^1H NMR spectroscopy analysis of the crude product. The purified product, polymer, was used to calculate the degree of polymerisation by ^1H NMR spectroscopy. Results of the analysis carried out for this series (table 5.3) show that conversions reach 100 %, slightly higher than those obtained in solution polymerisations. Only when high monomer initiator ratios are used, 400 or greater, did conversion drop significantly. As expected, melt polymerisations were faster than polymerisations in toluene solution. Polymerisation times were short, ranging from 15 minutes for the 50/1 ratio up to 3 hours for the 400/1 ratio.

As seen in previous series of experiments within this chapter, the degree of polymerisation did not follow a linear relationship with monomer conversion. In addition to this, it can be seen in table 5.4 that there is a very significant difference between the number average molecular weights obtained by GPC and by ^1H NMR. These differences

could be explained from the fact that some branching may take place during the polymerisation, which will affect the hydrodynamic volume of the synthesised polymers. An increase in the hydrodynamic volume will affect the time the polymer is retained in the column and, therefore, the molecular weight obtained by GPC, increasing this value significantly. However, branching should not affect the average number molecular weight obtained by ^1H NMR, since the number of active sites remains constant.

$[\text{M}]$ /[Mol/dm ³]	$[\text{Ti}(\text{O}-t\text{-Bu})_4]$ /[Mol/dm ³]	$[\text{M}]/[\text{I}]$	Reaction time/ min	Conversion /%	Dp	PD	$M_{n\text{GPC}}$ /(g/mol)	$M_{n\text{NMR}}$ /(g/mol)	I.E. / %
8.61	1.08	8	15	100	18	1.5	6300	2650	11.1
8.61	0.54	16	15	100	22	1.63	8300	3200	18
8.61	0.17	50	15	100	46	1.4	22700	6841	27
8.61	0.043	200	50	100	58	1.36	26600	8400	86
8.61	0.022	400	180	83	77	1.26	23500	11100	108*

*The efficiency should not be higher than 100%, the slightly increase above 100 % due to experimental error. Experimental error in the calculation of the initiator efficiency is maximum of 4%

Table 5.4: Melt polymerisation of L-Lactide with $\text{Ti}(\text{O}-t\text{-Bu})_4$ at 105 °C varying initiator concentration.

As seen previous series, the % efficiency of the initiator increases exponentially as the initiator concentration decreases, as shown in figure 5.9.

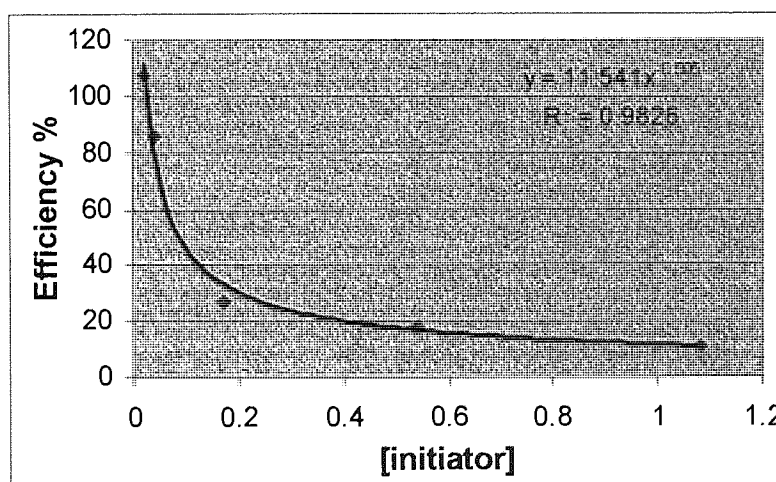


Figure 5.9: Efficiency of the initiator in the melt polymerisation of L-lactide with $\text{Ti}(\text{O}-t\text{-Bu})_4$ at 105 °C as a function of M/I for $[\text{M}] = 8.6 \text{ mol} \cdot \text{dm}^{-3}$.

An increase of the monomer initiator ratio (or the initiator concentration) results in a considerable decrease in the polydispersity. As observed in solution polymerisations as the initiator concentration decreases the efficiency of the catalyst improves, generating polymer chains of similar size and therefore reducing polydispersity. The reduction of polydispersity as the efficiency increases is shown below, in figure 5.10.

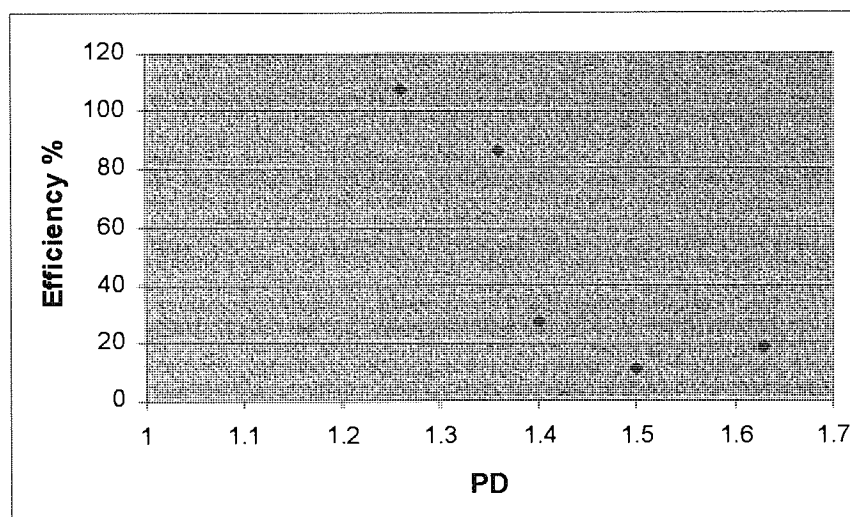


Figure 5.10: Effect of the efficiency of the initiator in the polydispersity for the melt polymerisation of L-lactide with $\text{Ti}(\text{O-}i\text{-Bu})_4$ at 105 °C.

CHAPTER 6

TITLE: COPOLYMERISATION OF LACTIDE AND ε-CAPROLACTONE IN SOLUTION WITH TITANIUM ISO-PROPOXIDE.

Co-polymerisation is a method that can be used to obtain polymer materials with properties that the individual homopolymers do not possess and has been widely used for lactic acid based polymers. The most utilised co-monomers for lactide are glycolide and ε-caprolactone. The co-monomer units can be organised in block sequences or appear in a random way. This is a valuable method to adjust the properties of the polymers that are required for a particular application. For instance, monomers such as ε-caprolactone can be incorporated into the polymer backbone to provide the polyester chains with enhanced flexibility allowing fine tuning of the glass transition temperature of the polymer being formed. Random polymerisation is known to provide new materials with properties intermediate between those of the parent homopolymers. Random copolymers have successfully been used as biodegradable sutures. A well known example of this type of copolymer, commercialised as Vicryl, is based on a random copolymer of glycolide and lactide. This strategy is useful to improve phase morphology and interfacial adhesion. In contrast to random copolymers, block copolymers are more often multiphase materials that provide for additivity of the phase materials. As an example, block copolymers of lactide and caprolactone combine the permeability and flexibility of PCL with the rapid biodegradation of PLA¹¹.

Another interesting application of biodegradable lactide copolymers is as tissue adhesives¹¹. Tissue adhesives represent a better alternative to sutures or stapling, provided they bind tissue planes rapidly and assure a tight and strong closure until healing is complete. Low molecular weight copolymers of lactide and ϵ -caprolactone, both random and block, have shown outstanding adhesive behaviour under *in vitro* conditions^{11, 88}. However, as discussed with the homopolymers, the synthesis of these materials has been carried out using tin octanoate as an initiator. Therefore, the aim of this work described in this chapter was to synthesise a range of molecular weight lactide and ϵ -caprolactone copolymers using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator. Based on the results described in the previous chapter, it can be concluded that both $\text{Ti}(\text{O-}i\text{-Pr})_4$ and $\text{Ti}(\text{O-Pr})_4$ offer similar reactivity. Therefore, only one of them was tested for further co-polymerisations. $\text{Ti}(\text{O-}i\text{-Pr})_4$ has been selected because of its commercial availability as a high purity compound. The synthesis was carried out in toluene solution. Although, the use of toluene is not ideal in order to improve the greenness of the synthesis, it allows us to compare the results obtained from these co-polymerisations with those obtained in the previous homo-polymerisations in solution.

6.1 MATERIALS.

The monomers and initiators used in this chapter were; L-lactide, D,L-Lactide, ϵ -Caprolactone 99% and $\text{Ti}(\text{O-}i\text{-Pr})_4$ 99.99%. The solvents used were, toluene, ethyl acetate, methanol and distilled water. The purity of each material and their treatments prior to use were described in section 2.1 and 2.2.

6.2 SOLUTION POLYMERISATION OF **ϵ -CAPROLACTONE.**

To study the reaction mechanism and the characterisation of copolymers of lactide and ϵ -caprolactone in solution, it is essential to study the behaviour of each of these monomers individually when they polymerise in the presence of titanium iso-propoxide. The homo-polymerisation of lactide has already been reported in chapter 3. Therefore, section 6.2.1 will be focused on the synthesis in solution of ϵ -caprolactone homo-polymer using titanium iso-propoxide as an initiator.

6.2.1 Homo-polymerisation in toluene solution.

Ring opening polymerisation of ϵ -caprolactone with titanium iso-propoxide was carried out in toluene using a monomer to initiator molar ratio of 50/1. Monomer and initiator concentrations were 0.78 M and 0.016 M respectively. Monomer, initiator and solvent were transferred and mixed within a glove-box under an argon atmosphere. Once the reactor was sealed, it was moved from the argon box and connected to a vacuum line, where a continuous nitrogen flow was supplied, as shown in figure 2.3. The vessel was then placed in an oil bath to maintain reactions at 90°C and magnetic stirring was provided throughout the polymerisation as summarised in scheme 3.1. In order to study the evolution of molecular weight and conversion, samples were taken during the course of the reaction, always maintaining the reaction vessel under a nitrogen atmosphere. These were quenched with water and then precipitated in methanol. Finally, the precipitated transparent gel was dried, without being filtered, at atmospheric pressure and kept under vacuum at 40 °C for 24 h. ^1H NMR analysis of the crude product obtained (un-purified

product) was used to calculate monomer conversion at any given time during the reaction. Since the precipitated gel was not filtered out, both monomer and polymer were present in the sample. ^1H NMR analysis was also used to calculate the degree of polymerisation (Dp) and the number average molecular weight (M_n).

6.2.2 Characterisation and Results

The extent of the reaction was confirmed by ^1H NMR of the reaction mixture where the methylene proton near the ester group of the ϵ -caprolactone at 4.21 ppm is shifted to a higher field 4.04 ppm on polymerisation. A typical ^1H NMR of PCL is shown in figure 6.1. The NMR characterisation of this type of polymer has been widely reported by Duda and Penczek

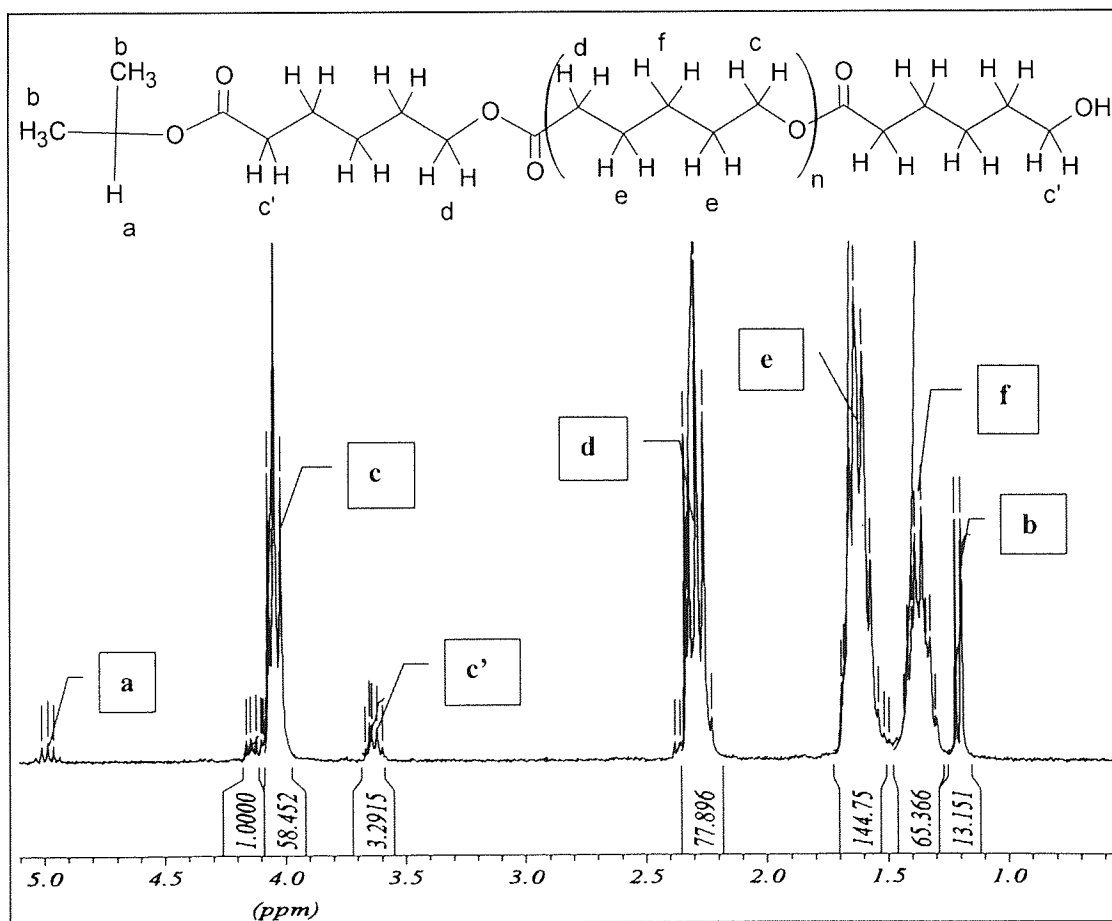


Figure 6.1: ^1H NMR of a PCL synthesised using $\text{Ti}(\text{O}-i\text{-Pr})_4$ as an initiator and toluene as a solvent at 90 °C.

Unlike the ring opening polymerisation of lactide, the chemical shift of the methyl group of the iso-propoxide chain end (1.20 ppm) appears in the ^1H NMR as a doublet. This arises because ϵ -caprolactone has no any chiral carbon atoms. Consequently, the two methyl groups of the iso-propoxide are equivalent when the iso-propoxide group reacts with the ϵ -caprolactone, producing only one doublet.

Both the degree of polymerisation as well as monomer conversion were determined using ^1H NMR spectroscopy by comparing the relative peak areas, representative of each of the constituents of the molecule. Monomer conversion was determined by comparing the areas under the peaks of the methylene protons of the PCL ("c" protons in figure 6.1) at 4.04 ppm and methylene protons of the ϵ -caprolactone at 4.21 ppm.

The degree of polymerisation, D_p , was calculated by comparing the area under the peak of the methylene protons of the PCL ("c" protons in figure 6.1) at 4.04 ppm and the area of the methyl end group of the initiator ("b" protons in figure 6.1). The equation associated with the degree of polymerisation, equation 6.1, is shown below:

$$D_p = \frac{\left[\frac{I_{Hc} + I_{Hc'}}{2} \right]}{\left[I_{HbCH_3} / 6 \right]}, \text{ Equation 6.1.}$$

In the above equation, I_{Hc} and $I_{Hc'}$ represent the area of the methylene protons in PCL ("c" protons in figure 6.1) and the area of the terminal PCL methylene protons, HOCH_2 , ("c'" protons in figure 6.1) respectively. I_{HbCH_3} is the area of methyl end group of each alkoxide initiator ("b" protons in figure 6.1) and 6 is the number of protons associated with the methyl groups of the iso-propoxide.

The ring opening polymerisation of ϵ -caprolactone gives polymers that show slightly broader polydispersity, 1.52, than polylactide, 1.20. They also show backbiting of the polymer chain, leading to oligomer formation as seen in figure 6.2. The peak observed in figure 6.1, right before the flow marker peak labelled as 6, corresponds to the presence of some impurities in the THF used to prepare the sample solution. This feature was explained previously in section 5.3.

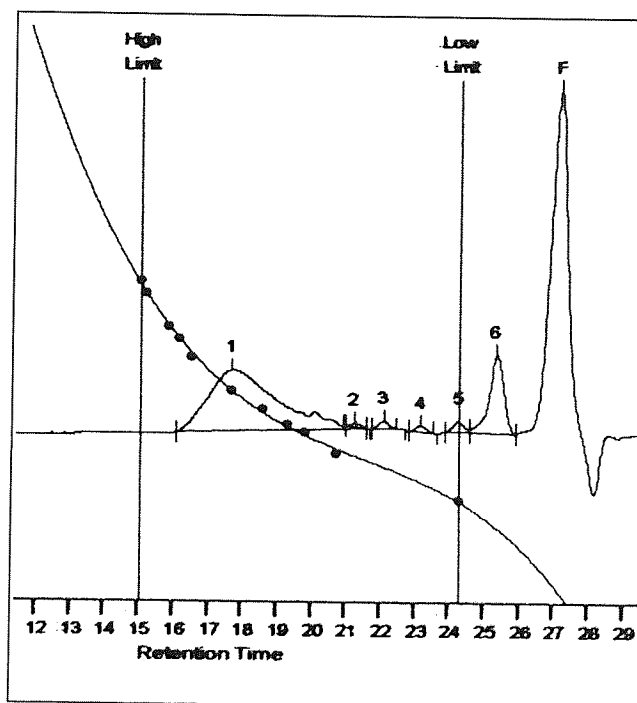


Figure 6.2: GPC of a PCL synthesised using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator and toluene as a solvent at 90 °C.

As seen in figure 6.3, the initiator titanium iso-propoxide is also highly active towards the polymerisation of ϵ -caprolactone in solution, reaching a maximum conversion of 93% after only 15 min. Four alkoxy groups were active in the polymerisation obtaining a degree of polymerisation of 13 for a monomer to initiator molar ratio of 50/1.

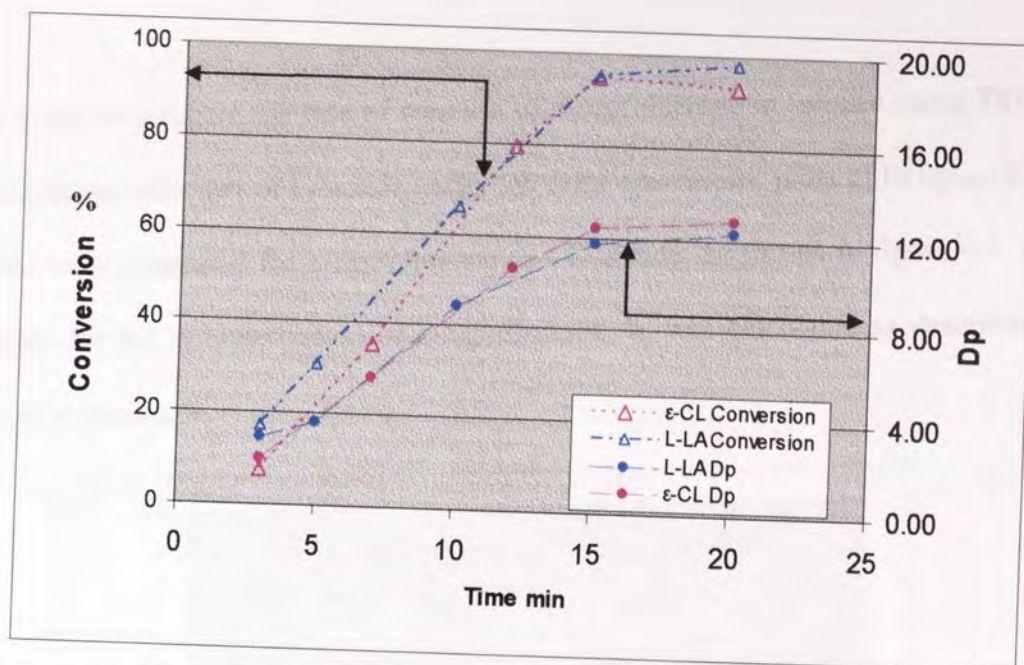


Figure 6.3: Conversion and molecular weight evolution for the homo-polymerisation of L-lactide and ϵ -caprolactone in toluene solution at 90 °C versus time when $\text{Ti}(\text{O-}i\text{-Pr})_4$ is used as a initiator, $[\text{M}]/[\text{I}]=50/1$.

As seen in figure 6.3, solution polymerisation of ϵ -caprolactone with titanium isopropoxide shows a similar behaviour from that of L-lactide. ϵ -caprolactone needed a slightly shorter time than lactide to reach maximum conversion.

In order to compare the rate of reaction of ϵ -caprolactone in toluene using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator with that of L-lactide under the same conditions, plots of $\ln(\text{Dp}_{\infty} - \text{Dp}_n)$ versus time were generated for ϵ -caprolactone and L-lactide, as shown in figure 6.4. The rate constant for the polymerisation of ϵ -caprolactone, k , was calculated as described in Section 3.6 of chapter 3.

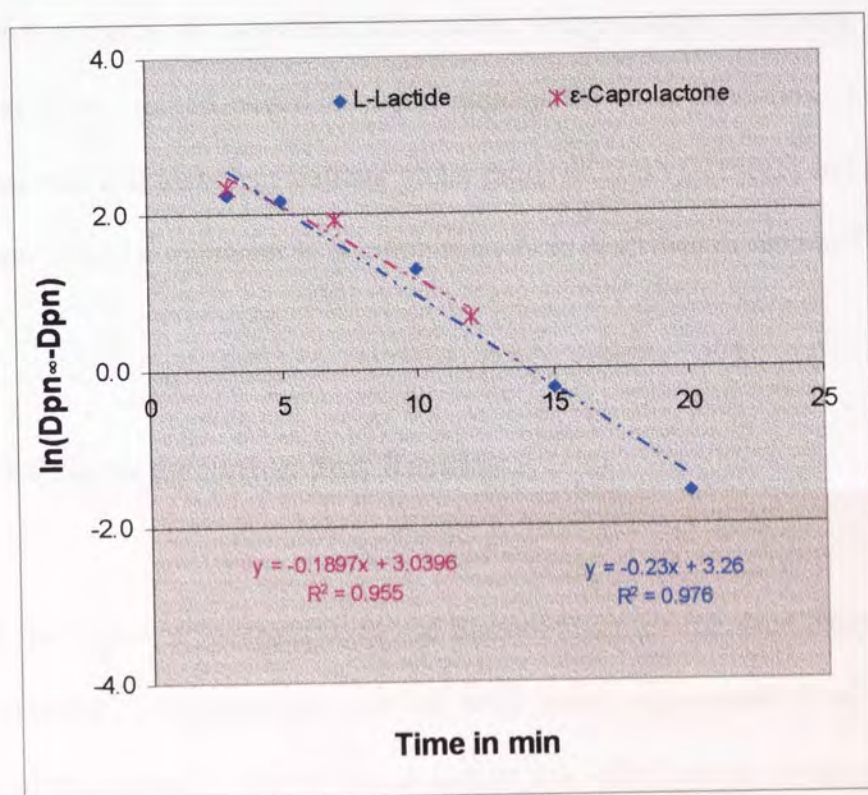


Figure 6.4: Plot of $\ln(\text{Dp}_{\infty} - \text{Dp}_n)$ versus time for the polymerisation of ϵ -caprolactone with a $[\text{M}]/[\text{I}]=50$ in toluene at 90°C , using $\text{Ti}(\text{O-}i\text{-Pr})_4$.

The calculated k for L-lactide and ϵ -caprolactone polymerisation in toluene solution using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator ($[\text{M}]/[\text{I}]=50/1$ are 0.23 s^{-1} and 0.19 s^{-1} respectively.

6.3 ALL-IN-ONE CO-POLYMERISATIONS OF LACTIDE

AND E-CAPROLACTONE.

6.3.1 Co-polymerisation in solution.

Weighed amounts of L-lactide, D,L-lactide, ϵ -caprolactone, initiator and solvent were transferred and mixed under an argon atmosphere in a glove-box. Titanium isopropoxide was added at monomer/initiator molar ratios of, [50/1], [160/1] and [400/1]. The polymerisation of cyclic monomer in solution follows as described in section 3.2.

6.3.2 Characterisation and Results

Both the degree of polymerisation and monomer conversion were determined by ^1H NMR spectroscopy, comparing the relative peak areas, representative of each of the constituents of the molecule. Conversion of lactide was calculated by comparing the areas under the peaks of the methine protons of the lactide at 5.05 ppm and the methine protons of the PLLA at 5.13 ppm. Similarly, conversion of ϵ -caprolactone was calculated by comparing the areas under the peaks of the methylene protons of the PCL at 4.04 ppm and methylene protons of the ϵ -caprolactone at 4.21 ppm. The ^1H NMR spectrum of poly (L-lactide-co- ϵ -caprolactone) obtained with use of $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator and a monomer/initiator molar ratio of 25/25/1, is shown in figure 6.5. Chemical shifts in the ^1H NMR were assigned as: δ 5.13 (s, Ha), 1.55 (d, Hb), 2.27 (t, Hc), 4.04 (t, Hd), 1.65 (m, Hg + Hh), 1.37 (m, Hf). A triplet at δ 3.63 ppm is due to the $-\text{CH}_2\text{CH}_2\text{OH}$ end group. The signals at δ 4.11 and 2.37 have been assigned to Hd' and Hc' respectively. Hd'

corresponds to methylene hydrogens (Hd) of the PCL, when ϵ -CL monomer is coupled to a lactide monomer unit. The same concept is applied to the methylene protons, Hc, of the PCL when they are adjacent to a lactide monomer. The same phenomenon occurs in the case of the methine protons of the PLLA when a LA monomer is adjacent to a ϵ -CL monomer. The methine protons at 5.13 ppm shift up field to 5.07 ppm because of a slight difference in chemical environment.

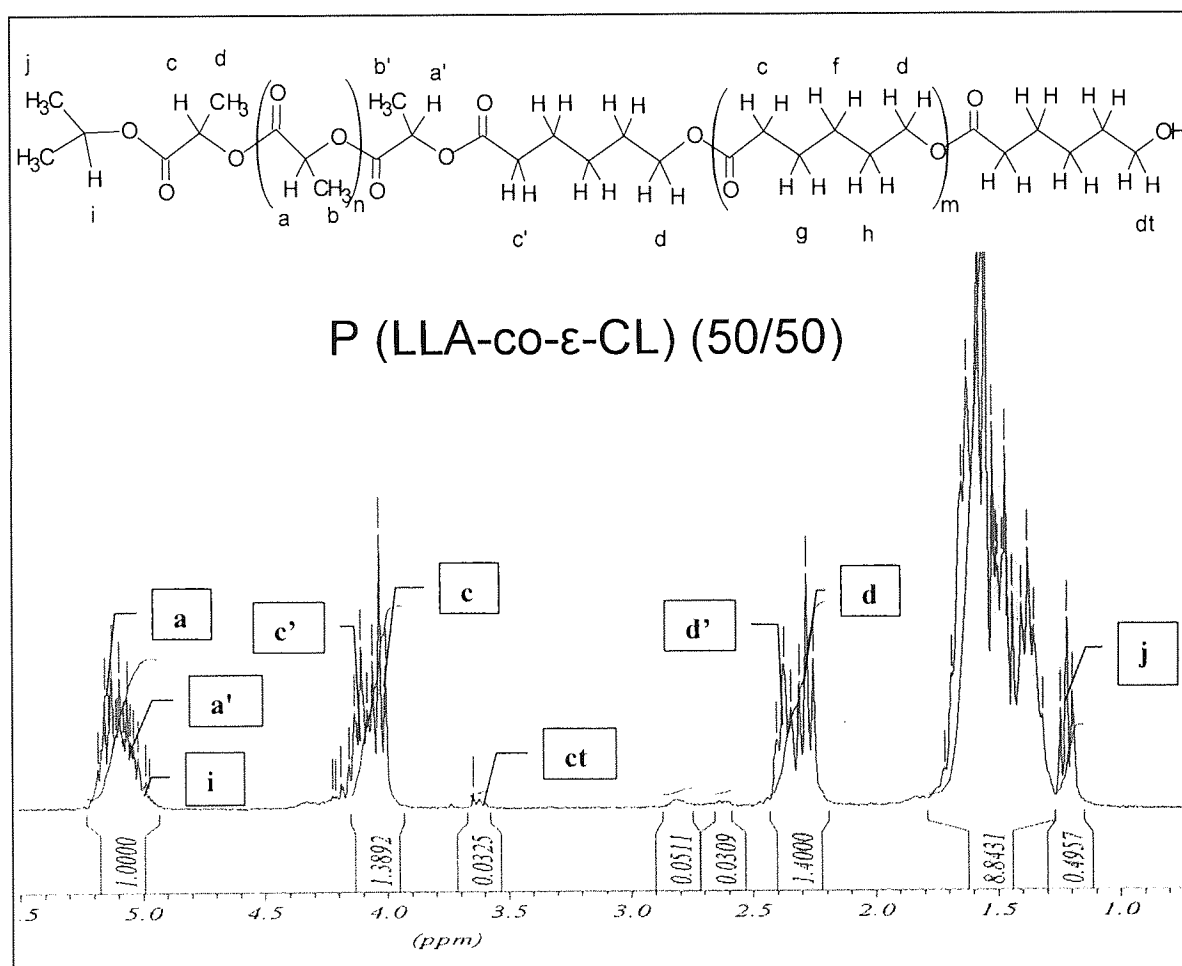


Figure 6.5: ^1H NMR spectrum of poly (L-lactide-co- ϵ -caprolactone) obtained using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator for a monomer/initiator molar ratio of [25/25/1] at 90 °C.

The number of ϵ -CL units per chain, NU_{CL} , was calculated by comparing the area under the peak of the methylene protons of the PCL at 4.04 (Hc) and 4.11 (Hc') ppm and the area of the methyl end group of the initiator. Similarly the number of L-lactide units per chain, NU_{La} was calculated by comparing the peaks of the methine protons of the

PLLA at δ 5.13 (Ha) and δ 5.07 (Ha'). The equations to calculate the number of lactide and ϵ -caprolactone units per chain, equation 6.2 and equation 6.3 respectively, are shown below.

$$NU_{CL} = \frac{\left[\frac{I_{HcPCL} + I_{Hc'PCL} + I_{HctPCL}}{2} \right]}{\left[\frac{I_{HjCH3}}{6} \right]}, \text{ Equation 6.2.}$$

$$NU_{La} = \frac{\left[\frac{I_{HaPLLA} + I_{Ha'PLLA} + I_{Hat}}{2} \right]}{\left[\frac{I_{HjCH3}}{6} \right]}, \text{ Equation 6.3.}$$

In the above equations, I_{HaPLLA} and $I_{Ha'PLLA}$ represent the areas of the methine protons in a PLLA block and the area of the methine in a LA monomer adjacent to a ϵ -CL unit respectively. I_{HjCH3} is the area of methyl end group of the alkoxide initiator. There being six such protons in each iso-propoxide. Finally, I_{Hdt} represents the area of the methine protons of a lactyl end group.

Number average molecular weights (Mn_{end}) based on end-group analysis were calculated by using NU_{La} and NU_{CL} obtained by 1H NMR using equation 6.4 below:

$$Mn_{end} = NU_{CL} \times Mw_{CL} + NU_{La} \times Mw_{La} + 60 \quad \text{Equation 6.4;}$$

where Dp_{CL} and Dp_{LA} represent the degree of polymerisation of ϵ -caprolactone and lactide respectively. 60 is the molecular weight associated to the iso-propoxide end group (59 g/mol) plus the molecular weight of the proton (1 g/mol) the copolymer gains after been quenched

Number average molecular weights based on conversion (Mn_{conv}) were calculated by using conversion values of each monomer obtained from 1H NMR spectra as shown in equation 6.5 below:

$$Mn_{conv} = \left[Mw_{LA} \cdot Conv_{LA} \cdot \frac{[LA]_0}{\frac{[Ti(O-i-Pr)_4]_0}{4}} \right] + \left[Mw_{CL} \cdot Conv_{CL} \cdot \frac{[CL]_0}{\frac{[Ti(O-i-Pr)_4]_0}{4}} \right] + 60$$

, Equation 6.5.

In the above equation, the abbreviations Mw and Conv represent the molecular weight and conversion respectively of each monomer involved in the co-polymerisation, in this case lactide and ϵ -caprolactone.

As mentioned previously, several all-in-one co-polymerisations of lactide and caprolactone were carried out with varying monomer/initiator molar ratios, ranging from 50/1 up to 400/1. A list of the co-polymerisations and their results are shown in table 6.1

M1	[M]/[I]	[M1]/[M2]	Reaction time/min	Conv M1	Conv M2	LA Length	ϵ -CL Length	M_{hend} /g.mol ⁻¹	M_{hconv} /g.mol ⁻¹	M_{hGPC} /g.mol ⁻¹	PD	Entry
L-lactide	50/1	80/20	20	>99	80	5.4	1.5	1710	1730	2120	1.4	1
L-lactide	50/1	50/50	15	>99	98	3.3	2.3	1740	1670	1760	1.4	2
L-lactide	50/1	20/80	10	>99	>99	2.5	5.4	2120	1560	1820	1.7	3
L-lactide	160/1	50/50	75	>99	99	4.3	2.5	4570	5090	6700	3	4
D,L-lactide	160/1	50/50	60	>99	98	3.2	2.2	3270	5650	5600	1.9	5
L-lactide	400/1	50/50	180	>99	81	2	2	7880	11880	16000	1.9	6
D,L-lactide	400/1	50/50	240	>99	98	2.5	2	7180	12850	16700	1.8	7
Lactide and ϵ -caprolactone all-in-one solution polymerisations in toluene with Ti(O- <i>i</i> -Pro) ₄ as an initiator at 90 °C												

Table 6.1: L-lactide and ϵ -caprolactone all-in-one polymerisations with Ti(O-*i*-Pro)₄ as an initiator.

LAc: abbreviation for lactic acid.

M_{hend} : Number average molecular weight obtained by using end group analysis.

M_{hconv} : Number average molecular weight calculated using conversion values.

Co-polymerisations with $\text{Ti}(\text{O-}i\text{-Pr})_4$ show very short polymerisation times, ranging from 10 min up to 3 hours, increasing directly as the monomer/initiator molar ratio rises. It is also evident that, in general, high conversions are achieved by both monomers, lactide giving slightly higher conversions. Only in the case of entries N 1 and N 6 are caprolactone conversions lower than usual values. These conversions may have increased if more time was allowed for the reaction.

Several polymerisations involving a $[\text{M}]/[\text{I}]$ molar ratio of 50/1 were performed with different monomer feed ratios in order to see the effect of the monomer feed ratio on conversion, PD, oligomer formation and the type of copolymer produced. As shown in table 6.1, the following monomer, LA/ ϵ -CL, feed ratios were used: L-LA(80)/ ϵ -CL(20) , L-LA(50)/ ϵ -CL(50) & L-LA(20)/ ϵ -CL(80). The ^1H NMR spectra of the copolymers obtained are shown in figures 6.5, 6.6, 6.7.

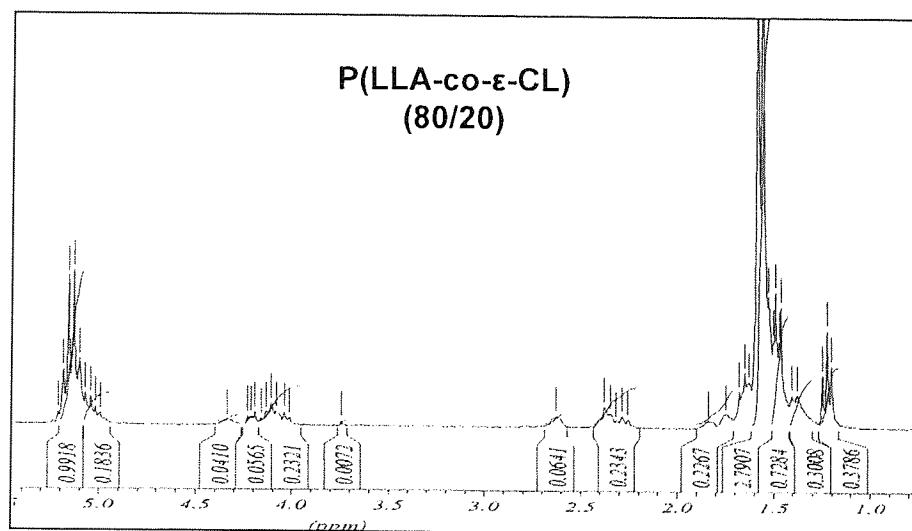


Figure 6.6: ^1H NMR spectrum of poly (L-lactide-co- ϵ -caprolactone) obtained using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator for a monomer/initiator molar ratio of 40/10/1 at 90 °C.

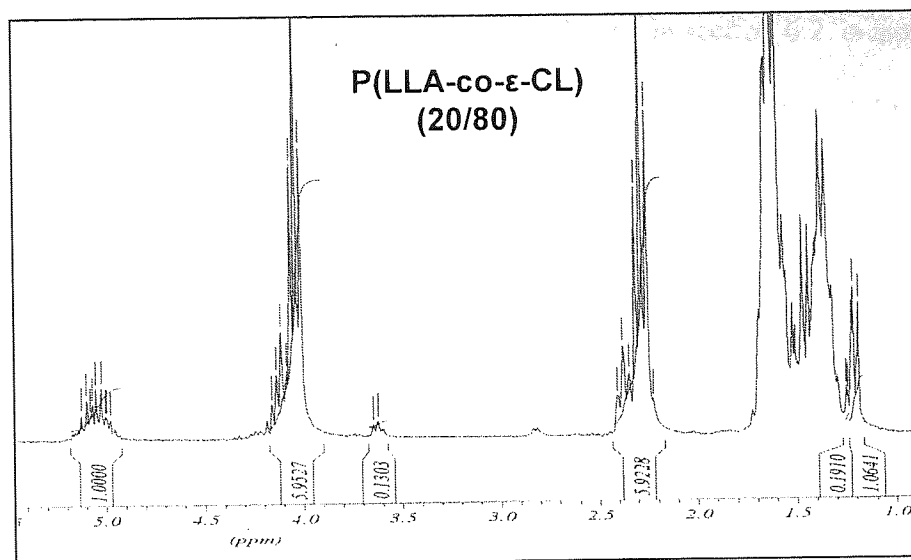


Figure 6.7: ^1H NMR spectrum of poly (L-lactide-co- ϵ -caprolactone) obtained using $\text{Ti}(\text{O}-i\text{-Pr})_4$ as an initiator for a monomer/initiator molar ratio of 10/40/1 at 90 °C.

It can be seen from the ^1H NMR spectra of these copolymers that lactide was the main initiated specie when the initial concentration of lactide was equal or greater than 50%, as shown by the triplet at 1.21 ppm, associated with the methyl protons of the isopropoxide end group. Only when the L-LA/ ϵ -CL molar ratio decreases to 1/4 is the doublet, associated to the methyl protons adjacent to a ϵ -CL unit, at 1.20 ppm observed. However, the area generated by the triplet at 1.21 ppm was still greater than the area generated by the methyl protons adjacent to a ϵ -CL unit. Therefore, lactide is still reacting faster than ϵ -caprolactone at this low ratio.

The evolution of the monomer consumption over time for each monomer feed ratio was studied and is displayed in figure 6.8, 6.9 and 6.10. For each monomer/feed ratio, L-LA always reacts faster than ϵ -CL. For the 50/50 molar ratio, L-lactide reacts only slightly faster. The fact that the L-LA reacts faster than ϵ -CL may be contrary to what one may have predicted, bearing in mind that ϵ -caprolactone is a more strained ring than lactide and

also has a greater rate of polymerisation than lactide under homo-polymerisation conditions with $\text{Ti}(\text{O-}i\text{-Pr})_4$. As previously explained in section 6.2, ϵ -caprolactone requires shorter reaction times than lactide to reach maximum conversion, but on the contrary, L-lactide reached higher conversions than ϵ -caprolactone at an early stage in the co-polymerisation. The faster rate of the lactide consumption over ϵ -caprolactone, observed in an early stage of the homo-polymerisation, must surely contribute to the preference of Ti to coordinate to lactide rather than to ϵ -caprolactone in the initiation and propagation steps. This preferred coordination of the lactide could arise because of two reasons. Firstly, lactide is a smaller size monomer than ϵ -caprolactone, which will be an advantage when coordinating to a small metal like titanium (which is already tetra-coordinated). Secondly, the carbon atom of the carbonyl group of the lactide monomer has a higher δ^+ charge than that of the ϵ -caprolactone monomer, which may make the lactide monomer more readily reactive with the active centres.

A small amount of oligomer formation (around 1%) was found by GPC, similar to the homo-polymerisations of ϵ -caprolactone. In addition, a bi-modal distribution was observed for a LA/ ϵ -CL molar feed ratio of 20/80.

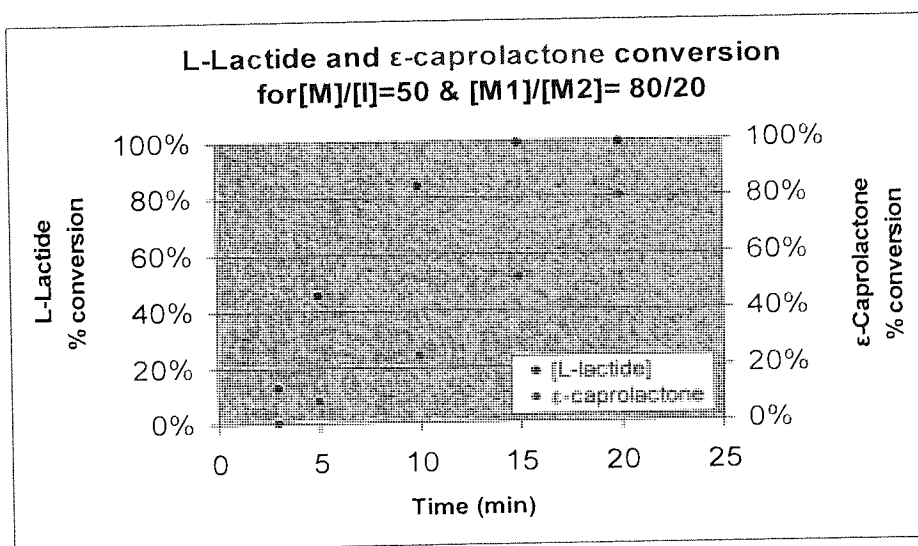


Figure 6.8: The evolution of the monomer consumption over time for a L-LA/ ϵ -CL monomer molar feed ratio of 80/20.

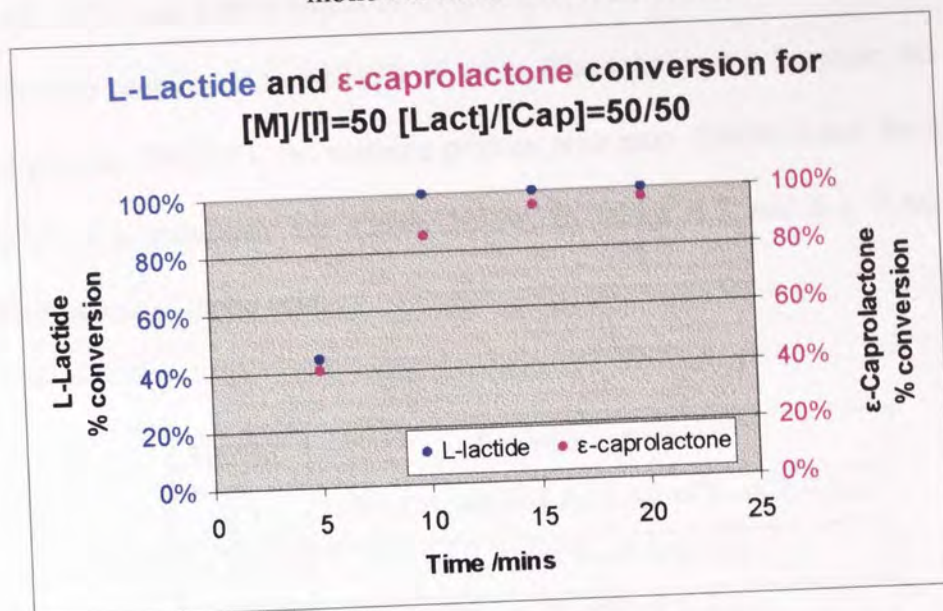


Figure 6.9: The evolution of the monomer consumption over time for a L-LA/ ϵ -CL monomer molar feed ratio of 50/50.

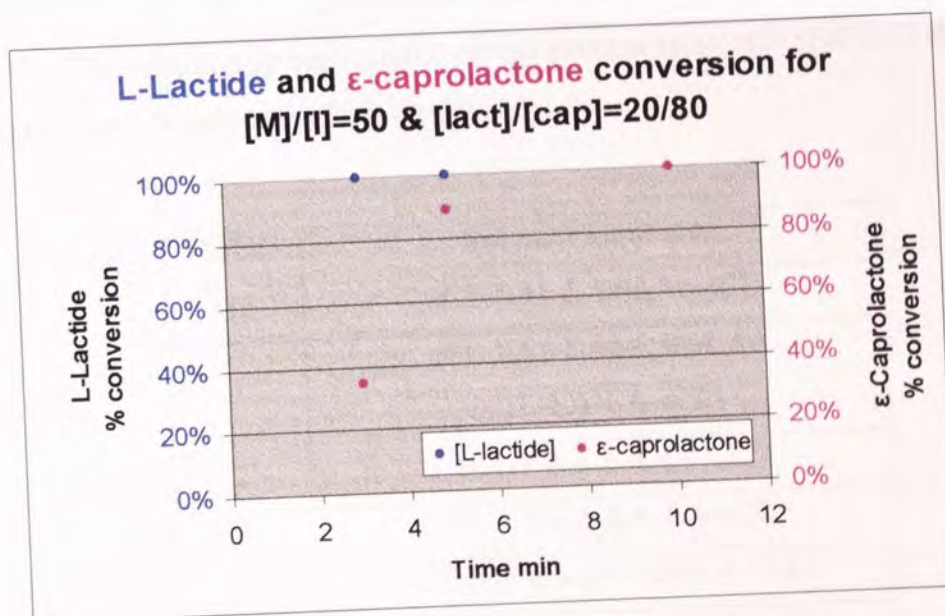


Figure 6.10: The evolution of the monomer consumption over time for a L-LA/ ϵ -CL monomer molar feed ratio of 20/80.

The average length of the ϵ -CL block was calculated from the integral ratios of homo (ϵ CL- ϵ CL- ϵ CL) and hetero sequence signals (ϵ CL- ϵ CL-LAc, LAc- ϵ CL- ϵ CL), corresponding to methylene protons (Hd and Hd') of ϵ -CL. The relationship between the areas of the methyl protons (Hd/Hd'), the methine protons area ratio (Ha/Ha') and the average block length of each monomer are shown below, in tables 6.2 and 6.3. LAc abbreviation represents a unit of lactic acid.

Hd/Hd'	Polymer sequences
0.5	50% LAc- ϵ CL-LAc/LAc- ϵ CL- ϵ CL-LAc
1	LAc- ϵ CL- ϵ CL-LAc
2	LAc- ϵ CL- ϵ CL- ϵ CL-LAc
3	LAc- ϵ CL- ϵ CL- ϵ CL- ϵ CL-LAc
4	LAc- ϵ CL- ϵ CL- ϵ CL- ϵ CL- ϵ CL-LAc
5	LAc- ϵ CL- ϵ CL- ϵ CL- ϵ CL- ϵ CL- ϵ CL-LAc

Table 6.2: The relationship between the methyl protons areas ratio (Hd/Hd') and the average block length of the PCL blocks.

Ha/Ha'	Polymer sequences
0.5	ϵ CL-LAc-LAc-LAc- ϵ CL
1	ϵ CL-LAc-LAc-LAc-LAc (ϵ CL-LA-LA- ϵ CL)
2	(ϵ CL-LA-LA-LA- ϵ CL)
3	(ϵ CL-LA-LA-LA-LA- ϵ CL)
4	(ϵ CL-LA-LA-LA-LA-LA- ϵ CL)
5	(ϵ CL-LA-LA-LA-LA-LA-LA- ϵ CL)

Table 6.3: The relationship between the area ratio of the methine protons (Ha/Ha') and the average block length of the PLA blocks.

The average lengths of the lactide and ϵ -caprolactone, shown in table 6.1, indicated that the copolymers synthesised using a L-LA/ ϵ -CL molar ratio of unity have short average block lengths, diads and triads, which means that these copolymers are very close to being statistical. Instead, they should be classified as tapered co-polymers. Tapered co-polymers consist of short blocks of any monomer, in this case LA and ϵ -CL, which were randomised by either a similar rate of polymerisation of each monomer or transesterification reactions or both.

6.4 BLOCK CO-POLYMERISATIONS OF LACTIDE AND **ϵ -CAPROLACTONE.**

6.4.1 Co-polymerisation in solution.

Weighed amounts of L-lactide, D,L-lactide or ϵ -caprolactone were added and mixed in dry toluene in a glove-box under an argon atmosphere. Titanium iso-propoxide was added at monomer/initiator molar ratios of 50/1 or 160/1. Once the reactor was sealed, it was removed from the argon box and connected to a vacuum line where a continuous nitrogen flow was supplied, as shown in figure 2.3. The vessel was then placed in an oil bath to maintain reactions at 90°C. Magnetic stirring was provided throughout the polymerisation as summarised in scheme 3.1. When PLA blocks were formed initially, the incorporation of ϵ -CL units followed, by reaction of the terminal hydroxyl terminal groups of PLAs with ϵ -caprolactone rings and their subsequent polymerisation. Similarly, when PCL blocks were formed first, the incorporation of LA units followed, by reaction of the terminal hydroxyl terminal groups of PCL's with lactide rings and their subsequent

polymerisation. In order to study the evolution of molecular weight and conversion, samples were taken during the course of the reaction. These were treated as described in section 6.2.1. ^1H NMR analysis was also used to calculate the degree of polymerisation (D_p) and the number average molecular weight (M_n).

6.4.2 Characterisation and Results

Both ϵ -CL and LA can be homo-polymerised in a living manner with $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator in toluene solution. Therefore, the sequential polymerisation of ϵ -CL and LA should lead to the respective block co-polymers. Initially the preparation of block-copolymers of LA and ϵ -CL was investigated by synthesising poly (lactide) as the first block and subsequently copolymerising this PLA pre-polymer with ϵ -caprolactone. The crude polymerisation products were characterised by ^1H NMR, ^{13}C NMR and GPC. Both the degree of polymerisation and monomer conversion were determined by ^1H NMR spectroscopy as explained in section 6.3.2. In the ^1H NMR spectrum of the co-polymerisation product (figure 6.11), the HOCHCH_3 methine proton signals belonging to the lactide pre-polymer ($\delta=4.35$ ppm) has almost disappeared. Furthermore, the presence of a new proton signal at $\delta=4.10$ ppm corresponding to the terminal OCH_2 methylene group of a ϵ -CL adjacent to a LA moiety, clearly demonstrated the formation of PLA-PCL copolymer. The copolymer chains were terminated by a ϵ -CL derived hydroxyl group, as demonstrated by the HOCH_2 methylene proton signals at $\delta=3.65$ ppm. However, the signal of HOCHCH_3 methine proton signals belonging to the lactide pre-polymer ($\delta=4.35$ ppm) should be absent. The presence of this signal may be due to transesterification reactions.

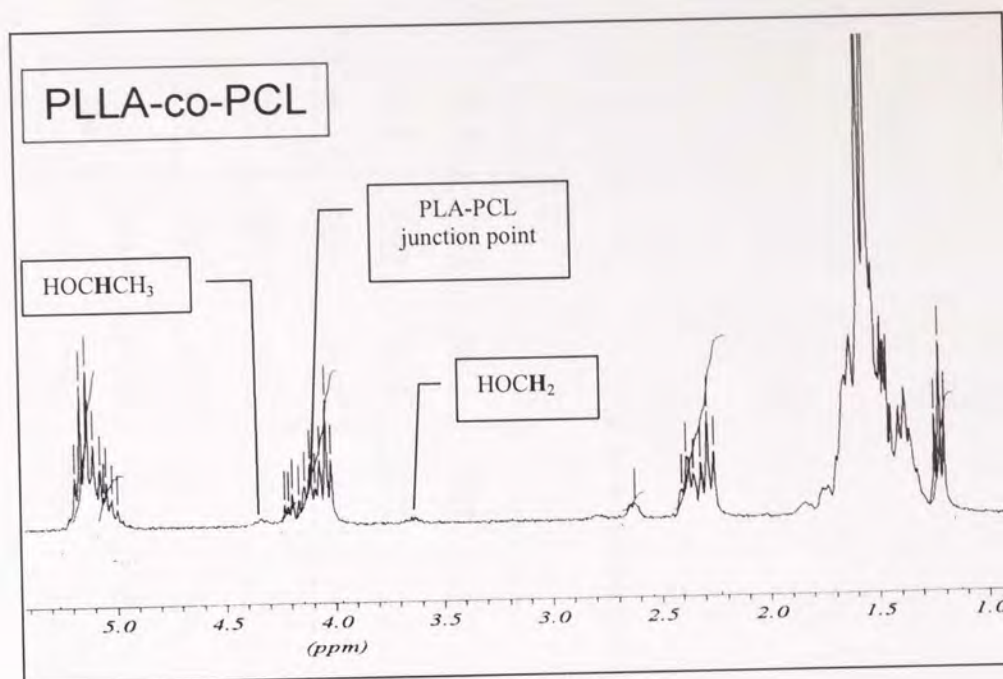


Figure 6.11: Poly(LA-co- ϵ -CL) ^1H NMR synthesised by CL addition to active PLLA using $\text{Ti}(\text{O-}i\text{-Pr})_4$

^1H NMR spectrum of the polymerisation products of the lactide pre-polymer with ϵ -caprolactone showed high conversion of the caprolactone monomer, as well as the formation of a low concentration of ϵ -caprolactone oligomers. The theoretical molecular weights calculated from monomer conversion may differ from those calculated using end group analysis. The reason for this may arise from the fact that, at high lactide conversions the peak of the remaining lactide was overlapped with the peak associated with the methine in a LA monomer adjacent to a ϵ -CL unit. Therefore, when most of the lactide monomer was consumed and the lactide peak disappeared from the GPC chromatograph, a 100% conversion of lactide was assumed.

Analysis of these products by GPC confirmed the generation of low concentration of oligomer and showed a uni-modal distribution curve with rather narrow polydispersities as seen in table 6.4.

M1	[M1]/ Mol/dm ³	[M1]/[I]	[M1]/[M2]	Reaction time (min)	Conv M1	Conv M2	LA Length	ϵ -CL Length	M _n end /g.mol ⁻¹	M _n conv /g.mol ⁻¹	M _n GPC /g.mol ⁻¹	PD	Entry
L-lactide	0.79	50/1	50/0	20	98	NA	11	NA	1650	1770	2120	1.28	8
L-lactide	0.79	50/1	50/50	35	100	93	4	3	1490	1610	2690	1.36	9
L-lactide*	0.79	50/1	50/50	30	97	92.4	5.5	5.6	1650	1590	1830	1.54	10
L-lactide	0.79	160/1	50/50	90	100	94	2.3	2.1	3180	5170	4890	2.03	11
D,L-lactide	0.79	160/1	50/50	85	100	97.4	3	2.2	4480	5130	5880	2.14	12

L-lactide*: Addition of L-lactide to an active poly(ϵ -caprolactone)

Table 6.4: Sequential polymerisations of L-lactide and ϵ -caprolactone using Ti(O-*i*-Pr)₄ as an initiator at 90 °C.

^{13}C NMR spectroscopy is a good technique to give distinctive information on the sequence distribution of the ϵ -hydroxy caproyl and lactyl units. If an AB block copolymer is formed during the polymerisation of lactide pre-polymer and ϵ -caprolactone, only sequences arising from the reaction of lactyl end-groups with ϵ -caprolactone should be present. This implies that, in the ^{13}C NMR spectra of the copolymers, the carbonyl carbon signals belonging to CL-LA-LA (CLL and CCL) sequences should be present. The signals originating from LCL, LLC, CLC and LCC sequences must be absent. The ^{13}C NMR spectra of the copolymers (figure 6.12 (A)) confirmed the formation of a LA/CL copolymer because of the presence of the CLL and CCL carbonyl signals alongside the homo-polymers carbonyl signals, LLL and CCC. In addition, the formation of LCL, LLC, CLC and LCC sequences were also clearly visible indicating the occurrence of trans-esterification reactions.

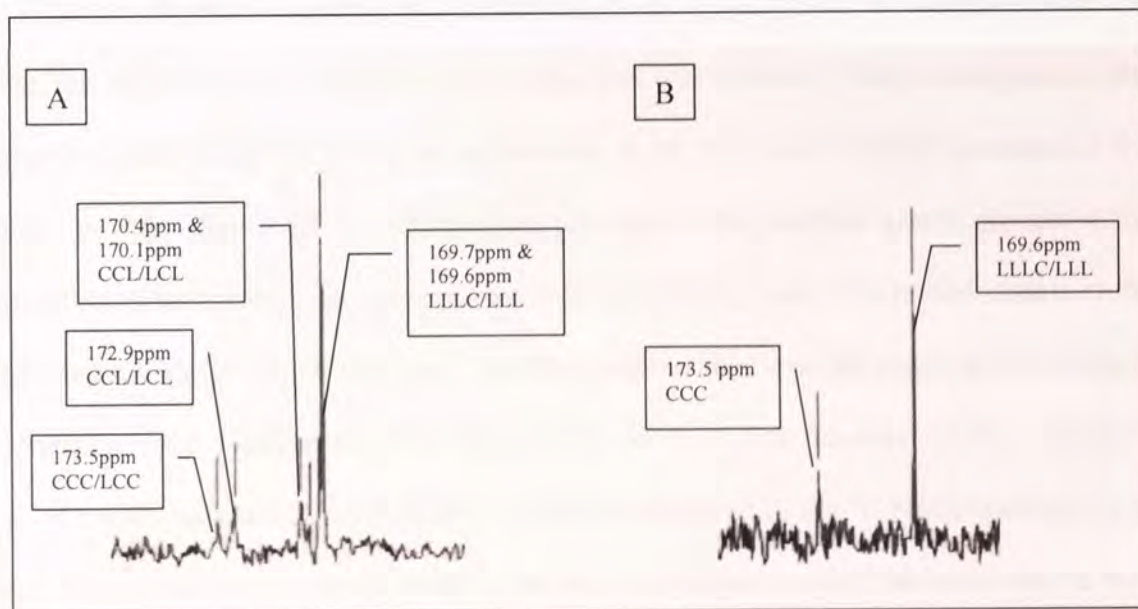


Figure 6.12: (A) ^{13}C NMR spectrum of poly(LA-co- ϵ -CL) prepared by co-polymerisation of L-LA pre-polymer with ϵ -CL using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator. (B) ^{13}C NMR spectrum of poly(ϵ -CL-block-L-LA) prepared by co-polymerisation of ϵ -CL pre-polymer with L-LA using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator.

The presence of transesterification reactions is also very significant in the ^1H NMR spectra, as shown by the low ratio areas of the OCH_2 methylene proton of the PCL blocks and the terminal OCH_2 methylene group of a ϵ -CL adjacent to a LA unit. Apparently, the ϵ -hydroxyl caproyl end groups generated during the co-polymerisation of ϵ -caprolactone with pre-polymers of lactide are reactive towards the ester groups in the polymer chains, generating trans-esterification reactions. This behaviour has been also observed in the synthesis of block co-polymers of CL and LA in the melt with tin octanoate ⁹⁰ and aluminium alkoxides ⁶⁶. In conclusion, lactide pre-polymers successfully initiated the polymerisation of ϵ -caprolactone. Formation of tapered copolymers, rather than block copolymers, occurs due to the presence of trans-esterification reactions.

As an alternative method of synthesising block co-polymers of ϵ -caprolactone and lactide, the polymerisation sequence of the monomers was inverted. Thus ϵ -caprolactone was polymerised first using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator at 90 °C. The ^1H NMR spectrum of the obtained product (figure 6.13) confirmed the presence of the methine proton signals of the hydroxyl lactyl end groups. The disappearance of the HOCH_2 methylene proton signals of the ϵ -caprolactone end group, at 3.65 ppm, provides more evidence of the copolymer formation. The junction point between the PCL-PLA blocks at 4.10 ppm (terminal OCH_2 methylene group of a ϵ -CL adjacent to a LA moiety) cannot be observed in the ^1H NMR spectrum. The area of the junction peak in the ^1H NMR of the block co-polymer should be much smaller than in tapered co-polymer, which could be a reason why it cannot be seen in the ^1H NMR spectrum. Also a peak at 4.13 ppm with a significant area may be overlapped, hiding the junction point peak. The peak at 4.13 ppm corresponds to the presence of a considerable concentration of ϵ -caprolactone oligomers being formed during the synthesis of the PCL pre-polymer. The concentration of oligomers, measured by ^1H NMR, is 7.6 %.

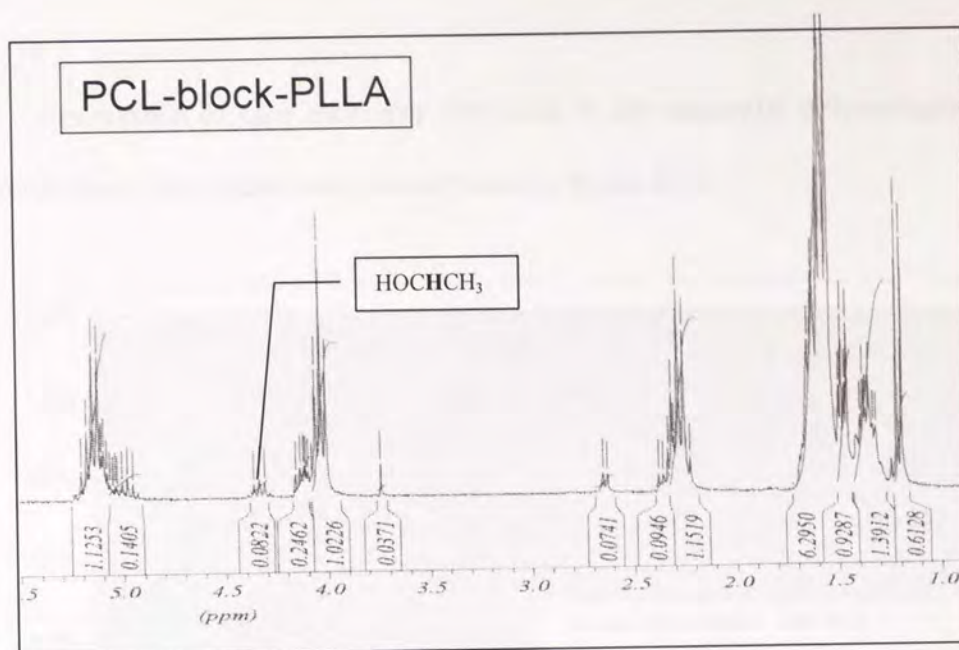


Figure 6.13: Block poly(ϵ -CL-block-L-LA) ^1H NMR synthesised by L-LA addition to active PCL using $\text{Ti}(\text{O-}i\text{-Pr})_4$

In the ^{13}C NMR spectra of the product obtained from the polymerisation of lactide with ϵ -caprolactone pre-polymer (figure 6.12 (B)), only the signals originating from the CCC and LLL sequences can be observed. Trans-esterification reactions are not observed. The lactide hydroxyl derivative is less reactive towards the main chain esters groups than the ϵ -caprolactone hydroxyl derivate. In conclusion, the only way to produce lactide and ϵ -caprolactone block-copolymers using sequential polymerisation techniques is by sequentially synthesising ϵ -caprolactone pre-polymers followed by polymerisation with lactide.

Consumption of each monomer over time in the sequential polymerisation of lactide and caprolactone was studied and plotted below in figure 6.14.

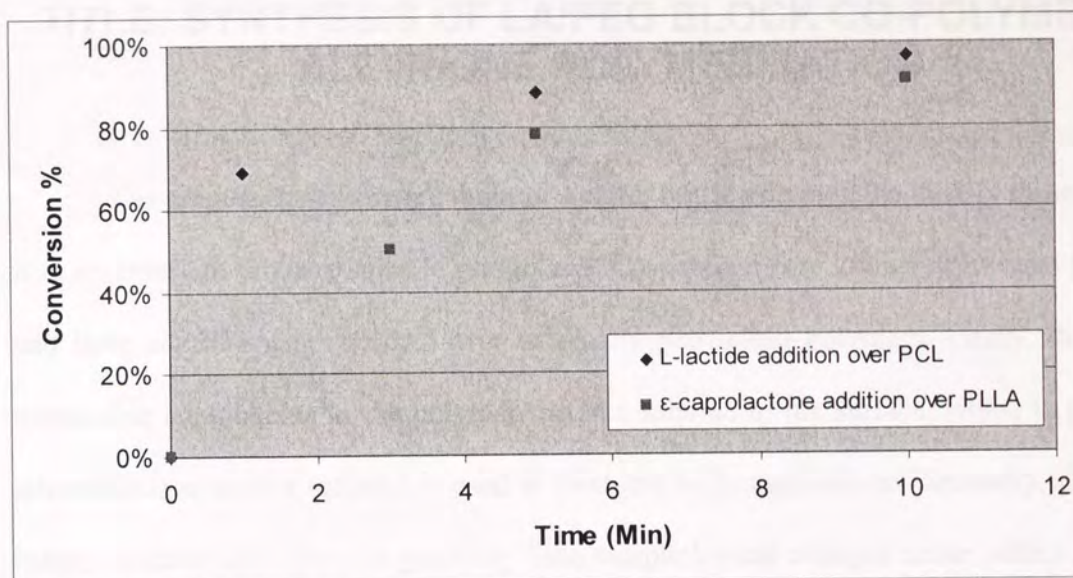


Figure 6.14: Monomer consumption over time for the sequential polymerisations of lactide and ϵ -caprolactone using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator.

Addition of lactide to ϵ -caprolactone pre-polymer occurred more rapidly than the addition of ϵ -caprolactone to lactide pre-polymer. Lactide shows a similar behaviour when copolymerised with ϵ -caprolactone by all-in-one reactions.

CHAPTER 7

TITLE: SYNTHESIS OF LA/PEG BLOCK CO-POLYMER BY ALL-IN-ONE POLYMERISATION

The properties of PLA are those of a rigid, brittle polymer. To modify these properties it is necessary to produce suitable plasticisers. Co-polymers are known as internal plasticisers and have significant advantages over externally plasticised polymers. Firstly, there are no extractable components in the polymer that can migrate to the surface, which is particularly adventitious when the material is used in food and body applications. Secondly, the polymer matrix is stable over time, as generally little morphological changes occur, which can have a detrimental effect on the strength, flexibility or degradation rate of the material. Our concept is to employ an internally plasticised PLA (flexible copolymer of lactide) as an external plasticiser for a lactide homopolymer. The internally plasticised PLA would be a sort of hybrid plasticiser, which because of its size and similarity in composition with PLA will not migrate to the surface of the material and also have a higher compatibility and phase stability with the poly(lactide) than regular blends. The hybrid plasticiser will consist of a block copolymer of lactide and PEG. The lactide copolymer will be made of a rigid region provided by a lactide block and a flexible region provided by the PEG block.

Co-polymers of LA and PEG have been previously studied by Seppala⁶⁸ and Kricheldorf⁴² using $\text{Sn}(\text{Oct})_2$ as an initiator. The idea behind the synthesis proposed in these papers was the use of alcohols with different number hydroxyl groups as initiators. The structure of the polymer depends on the alcohol used as a co-initiator. Mono- and di-functional

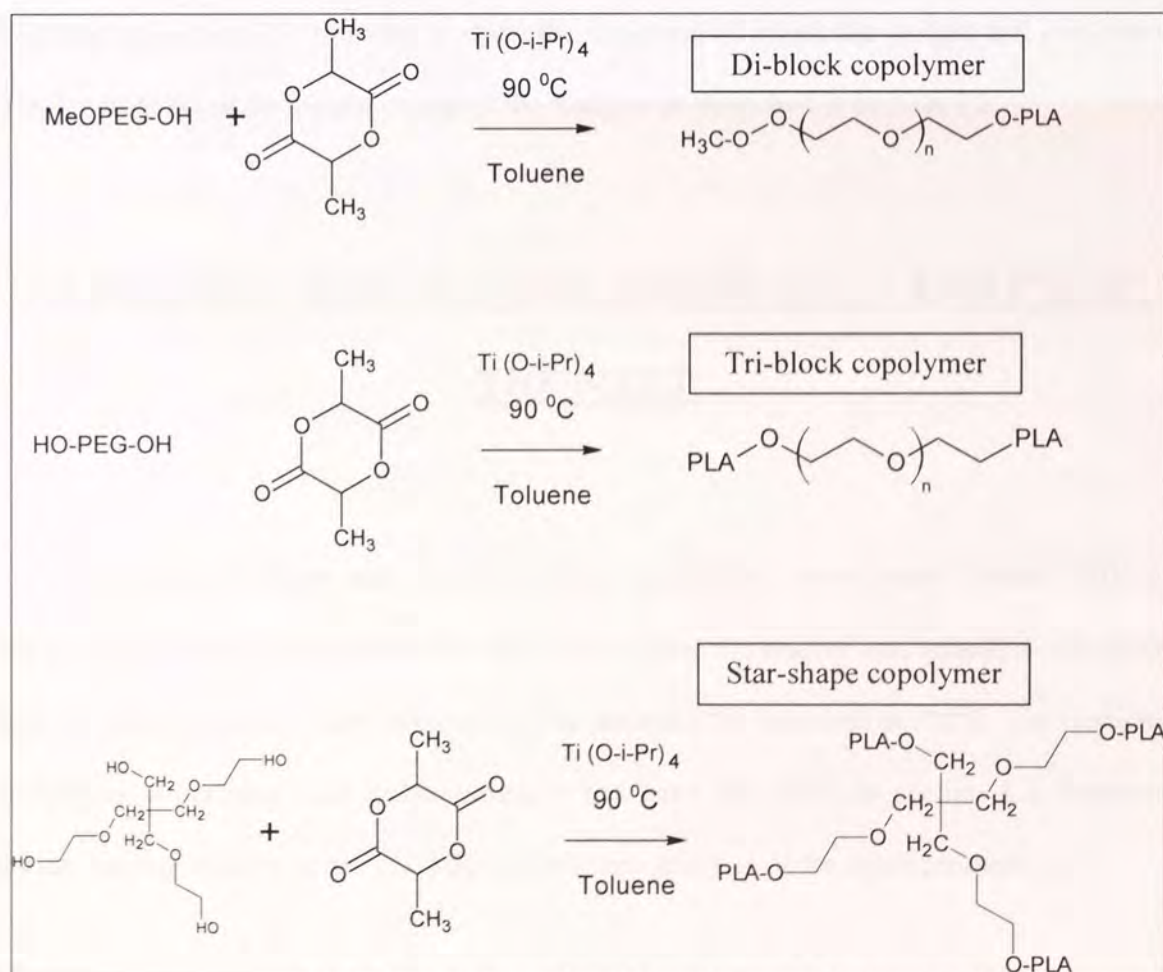
alcohols yield linear copolymers, while alcohols with hydroxyl functionalities higher than two generate star-shaped co-polymers. For example, Pentaerythritol has been used in the preparation of 4 arms polymers and dipentaerythritol or sorbitol has for 6-arm polymers^{91, 92, 93}. Higher molecular weights were achieved for star-shape polylactides with pentaerythritol as co-initiator than for linear ones without co-initiator⁹³, under the same reaction conditions. Since homo-polymerisation of lactide with $\text{Ti}(\text{O-}i\text{-Pr})_4$ showed fast reactions and a good control over the molecular weight, an attractive challenge would be to carry out this approach using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as the main initiator and PEG's as co-initiator.

7.1 MATERIALS

The materials used in the work described in this chapter; L-lactide, $\text{Ti}(\text{O-}i\text{-Pr})_4$ 99.99%, toluene, ethyl acetate, methanol and distilled water. The co-initiators used were: 2-butanol, 2-methyl-2-propanol, poly(ethylene glycol) methyl ether (PEG_{350}), poly(ethylene glycol) (PEG_{400}), pentaerythritol ethoxylate (3/4 EO/OH) (PP_{270}). The purity of each material and their treatments prior to use were described in sections 2.1 and 2.2.

7.2 SYNTHESIS OF COPOLYMERS OF LA AND PEG

A number of co-initiators with different numbers of hydroxyl groups have been selected in order to study its effect on the polymerisation of lactide. Two mono-hydroxy terminated short chain alcohols have been selected, 2-butanol and 2-methyl-2-propanol. In addition, three PEGs with different numbers of hydroxyl-groups have been chosen in order to obtain diblock, triblock and star-shaped co-polymers. PEG₃₅₀ (mono-hydroxy terminated, Mn: 350), PEG₄₀₀ (di-hydroxy terminated, Mn: 400) and PP₂₇₀ (a star-shaped PEG with four arms, which Mn is 270). The reaction scheme assumed for the synthesis of di-block, tri-block and star shape PLLA/PEG copolymers is shown below (Scheme 7.1).



Scheme 7.1: Formation of copolymers of LA and PEG.

7.3 PREPARATION OF COPOLYMERS OF LA AND PEG IN SOLUTION.

Co-polymerisations of L-lactide and PEG were carried out using constant lactide and $\text{Ti}(\text{O-}i\text{-Pr})_4$ concentrations of 0.78 mol/dm^{-3} and $0.016 \text{ mol/dm}^{-3}$ respectively in toluene, and varying the co-initiator concentration. Monomer, initiator, co-initiator and solvent were transferred and mixed under an argon atmosphere in a glove-box. Once the reactor was sealed, it was moved from the argon box and connected to a vacuum line where a continuous nitrogen flow was supplied as shown in figure 2.3. The polymerisation procedure in solution has been described in section 3.2. In order to study the evolution of molecular weight and conversion, samples were taken during the course of the reaction as described in section 3.2.

7.4 PREPARATION OF COPOLYMERS OF LA AND PEG IN THE MELT.

Monomer, initiator and co-initiator were transferred into a round bottom flask and mixed under an argon atmosphere in a glove-box. Once the reactor was sealed, it was moved from the glove box and placed in an oil bath to maintain the reactions at 105°C . The procedure carried out describing melt polymerisations has been described in section 4.2. Monomer conversion was calculated by ^1H NMR spectroscopy analysis of the crude product.

7.5 CHARACTERISATION OF COPOLYMERS OF

LA AND PEG.

The extent of reaction was confirmed by ^1H NMR analysis of the reaction mixture, using the methine hydrogen of the lactide (at 5.03 ppm) which is shifted down field (5.13 ppm) on polymerisation. To prove the existence of a co-polymer it is necessary to show the junction between the two blocks. ^1H NMR spectra were used to determine accurately the junction between the PEG and the PLLA. The ^1H NMR spectra of the reaction products (figure 7.1, figure 7.2) show all the required peaks that constitute a copoly(lactide-block-(polyethylene glycol)) copolymer as well as a complex multiplet center on 4.25 ppm, which contains the protons associated with the lactide-ethylene glycol junction (labeled as "b₁") and those associated with methine protons of the lactide end group (labeled as "c"). It is common for the acylation reaction of the HO-CH₂ end groups of PEGs to cause a down field shift of 0.6 ppm of the proton (from 3.7 to 4.25 ppm). This concept can be applied to PEGs in general regarding the number of hydroxyl groups they may contain. Complete reaction of the initial PEG is observed in each experiment and confirmed by the disappearance of the peak at 3.7 associated to the end group of the PEG. However, initiation via the iso-propoxide ligand is also observed, as proved by the appearance of the multiplet at 1.22 ppm associated to the methyl protons of the iso-propoxide end group. Therefore, initiation of the ring opening polymerisation of the lactide took place through the PEG co-initiator as well as through the iso-propoxide ligand generating the homopolymers alongside the copolymer.

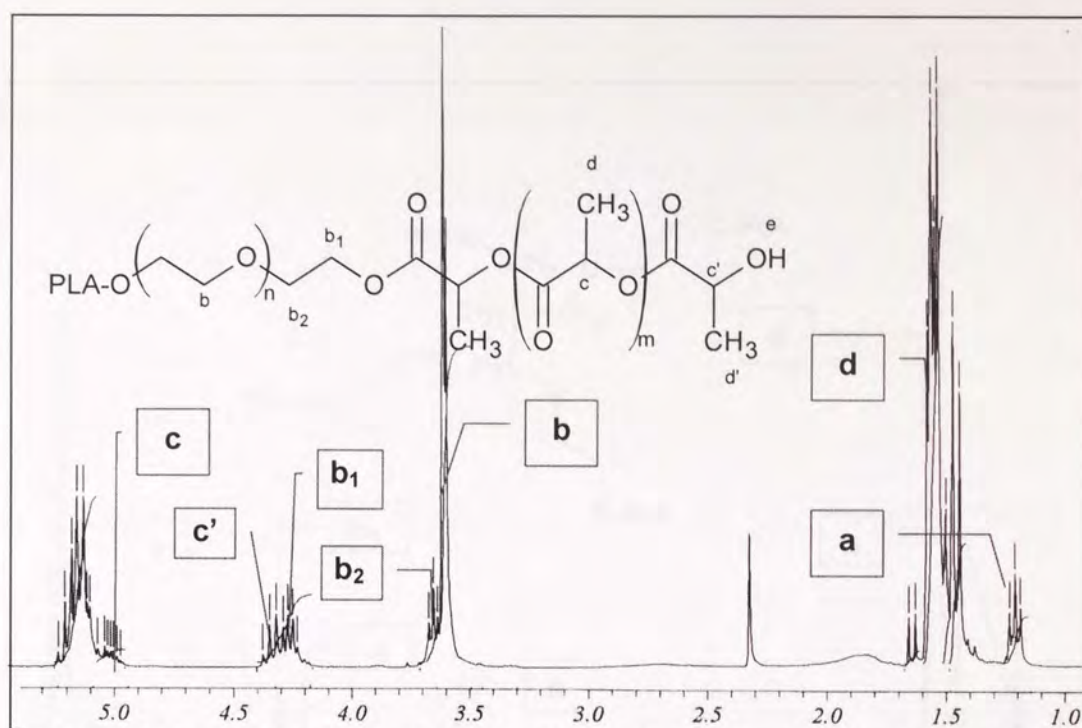


Figure 7.1: ^1H NMR spectrum of the product from the ring opening polymerisation of lactide with $\text{Ti}(\text{O-}i\text{-Pr})_4$ as initiator and di-hydroxy terminated PEG_{400} as a co-initiator.

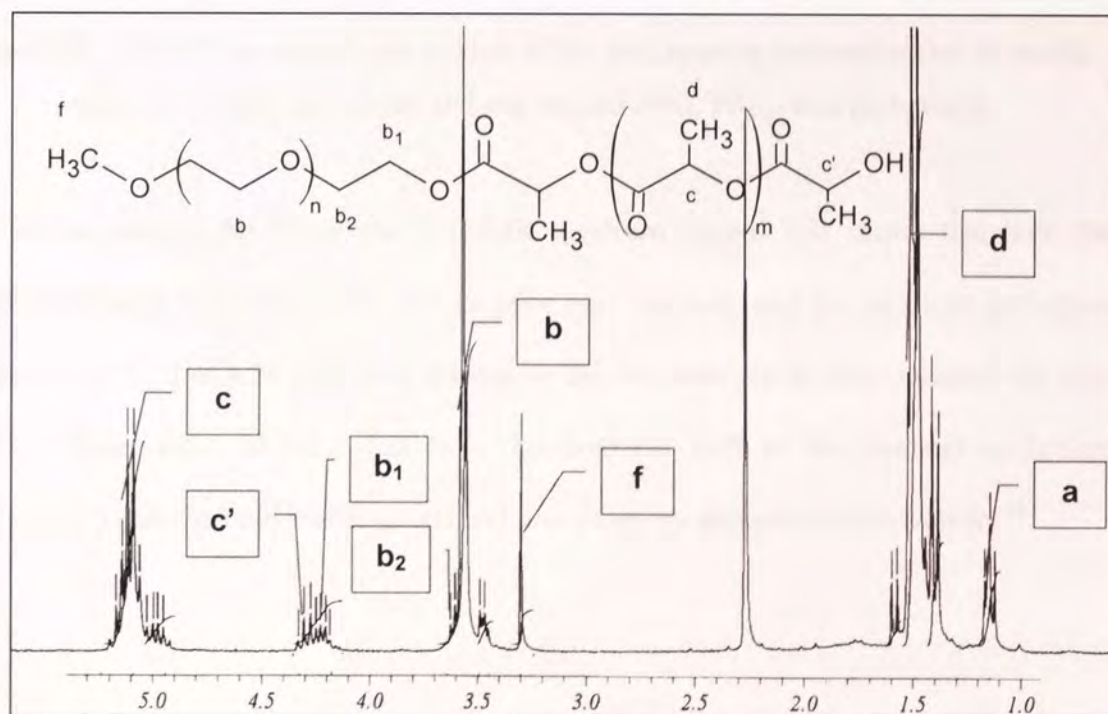


Figure 7.2: ^1H NMR spectrum of the product of the ring opening polymerisation of lactide with $\text{Ti}(\text{O-}i\text{-Pr})_4$ as initiator and mono-hydroxy terminated PEG_{350} as a co-initiator.

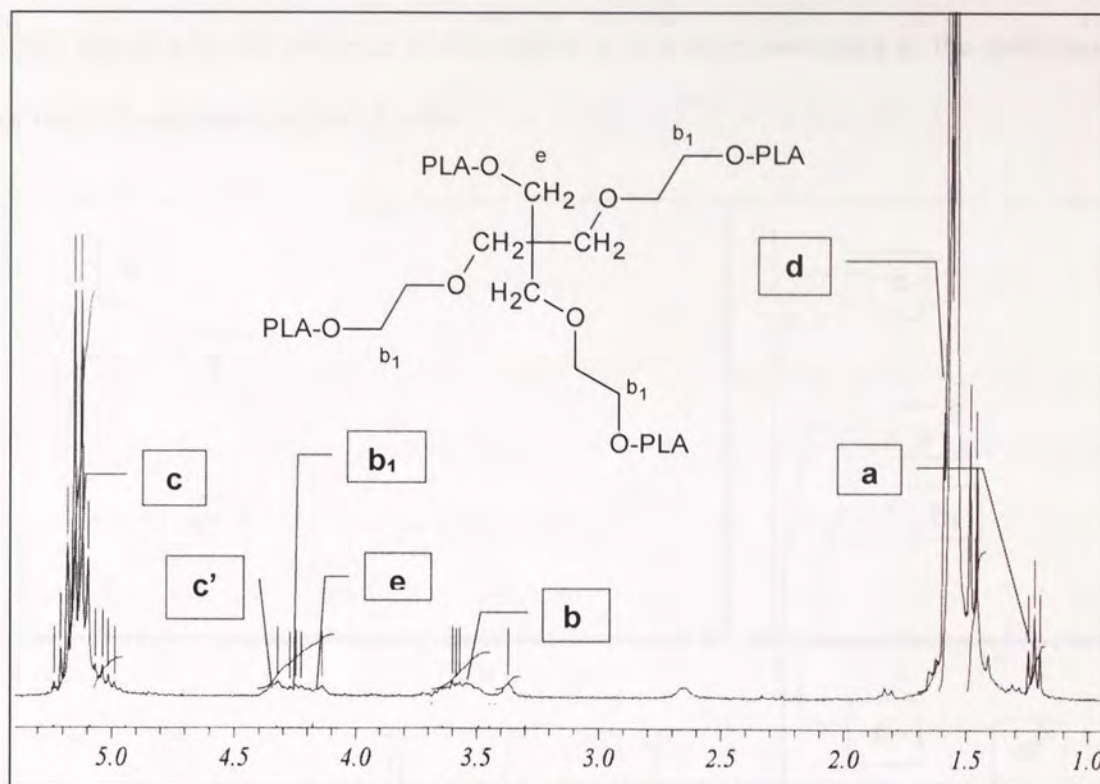


Figure 7.3: ^1H NMR spectrum of the product of the ring opening polymerisation of lactide with $\text{Ti}(\text{O-}i\text{-Pr})_4$ as initiator and star-shaped PEG, PP_{270} , as a co-initiator.

In the case of the PP_{270} , the ^1H NMR spectrum (figure 7.3) shows that both the terminal methylene (HOCH_2- , “e”) at 4.13 ppm near the core and the terminal methylene ($\text{HOCH}_2\text{CH}_2-$, “b₁”) at 4.25 ppm that belongs to the ethylene glycol unit, initiated the ring opening polymerisation of the L-lactide. The chemical shift of the terminal methylene (HOCH_2- , “e”) near the core was characterised previously by Seppala and co-workers⁶⁸.

The ^{13}C NMR spectrum of this product (figure 7.4) also confirmed the existence of the PLLA-PEG junction by the presence of the carbon at 64.4 ppm associated to the methylene group of the PEG adjacent to a lactide unit.

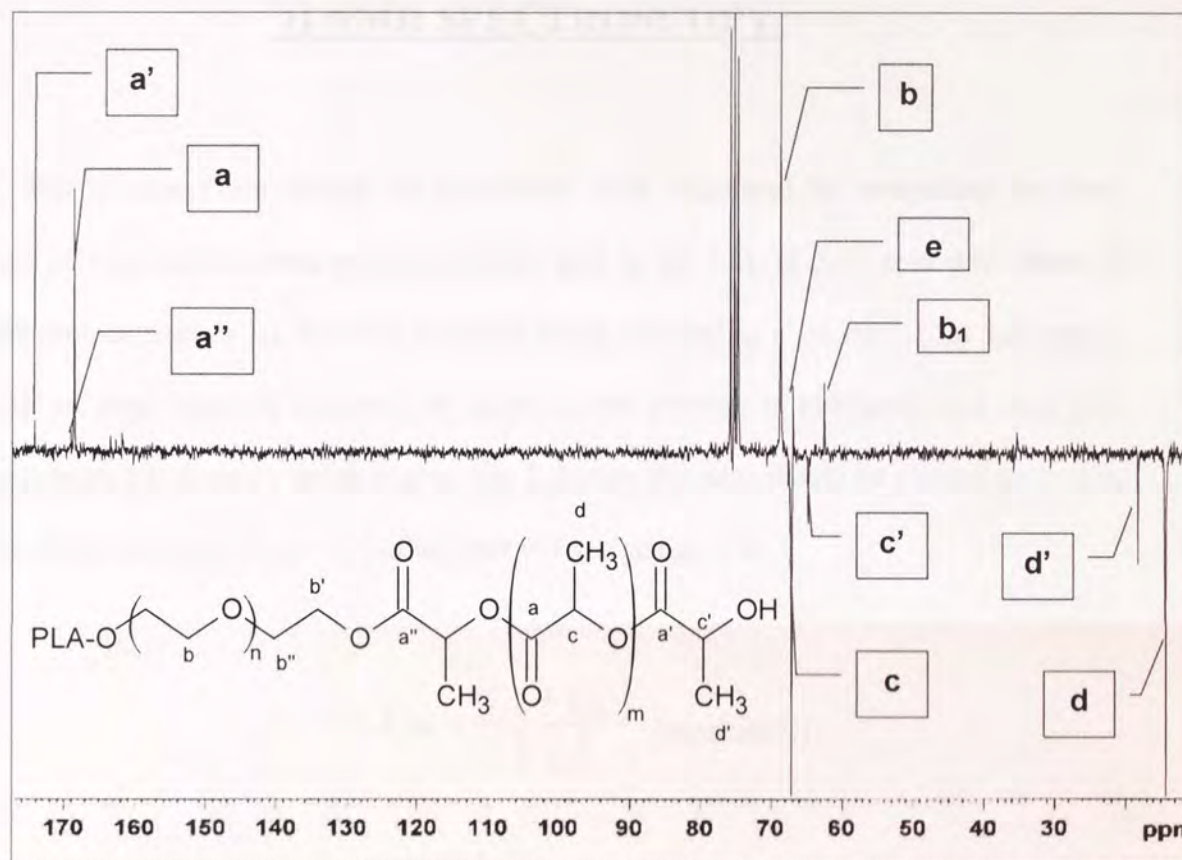


Figure 7.4: ^{13}C NMR spectrum of the ring opening polymerisation of lactide with $\text{Ti}(\text{O}-i\text{-Pr})_4$ as initiator and PEG_{400} as a co-initiator.

The products obtained by all-in-one polymerisations were also characterized by gel permeation chromatography, GPC. The use of co-initiators in the ring opening polymerisation of lactide gave polymers of narrower polydispersities than those obtained in the absence of a co-initiator (table 7.1). GPC analysis also shows the absence of oligomer formation. A list of the molecular weights obtained is shown on table 7.1. Analysis of GPC results is discussed later in section 7.7.

7.6 DETERMINATION OF THE DEGREE OF POLYMERISATION IN COPOLYMERS USING ¹H NMR SPECTROSCOPY.

The average chain lengths of polylactide were calculated by comparing the peak integrals of the chain methine protons (labeled as **c** in fig 7.1), at 5.10 ppm with those of methine protons next to the terminal hydroxyl group (labeled as **c'** in fig 7.1, at 4.35 ppm). The ratio of these integrals evaluates the length of the polymer in polylactic acid units (CL Lac), equation 7.1. Because the monomer was L-lactide the ratio should be divided by two in order to obtain the chain length in lactide units (CL), equation 7.2.

$$\text{CL Lac} = \frac{[I_{Hc} + I_{Hc'}]}{[I_{Hc'}]} \quad \text{Equation 7.1.}$$

$$\text{CL} = \frac{[I_{Hc} + I_{Hc'}]}{[I_{Hc'}] \times 2} \quad \text{Equation 7.2.}$$

¹H NMR can also be used to calculate the average number of OH groups in the co-initiator that participate in the initiation. Calculations can be performed by two methods. The first method compares characteristics peaks of the reacted and un-reacted OH groups of the co-initiators. However, this method is not appropriate for mono-hydroxy terminated, since un-reacted methylene proton end group signals (HO-CH₂-CH₂-) are overlapped with the methylene proton signals (CH₂-CH₂-O-CH₃) near the terminal methoxy group. Therefore in

order to use the same analytical method for every case, the average number of hydroxyl groups that took part in the polymerisation process was determined by comparing the theoretical chain length (CL_{th}) with the chain length determined by 1H NMR (CL), as in equation 7.3.

$$I_{OH}(\text{Initiating OH}) = \frac{CL_{th}}{CL} \bullet F \quad \text{Equation 7.3.}$$

In the equation 7.3 F is an abbreviation of functionality. The functionality represents the maximum number of initiating OH groups, in the ring opening polymerisation of lactide with different co-initiators and it can be calculated using equation 7.4.

$$F = N_{OH \text{ initiator}} + N_{OH \text{ Co-initiator}} \quad \text{Equation 7.4.}$$

In the above equation (equation 7.4) $N_{OH \text{ initiator}}$ represent the number of alkoxy group in the initiator and $N_{OH \text{ co-initiator}}$ the number of OH groups from the co-initiator. The percentage of initiating OH groups from the co-initiator used in each reaction can be calculated using 1H NMR analysis, as show in the equation 7.5.

7.7 RESULTS AND DISCUSSION

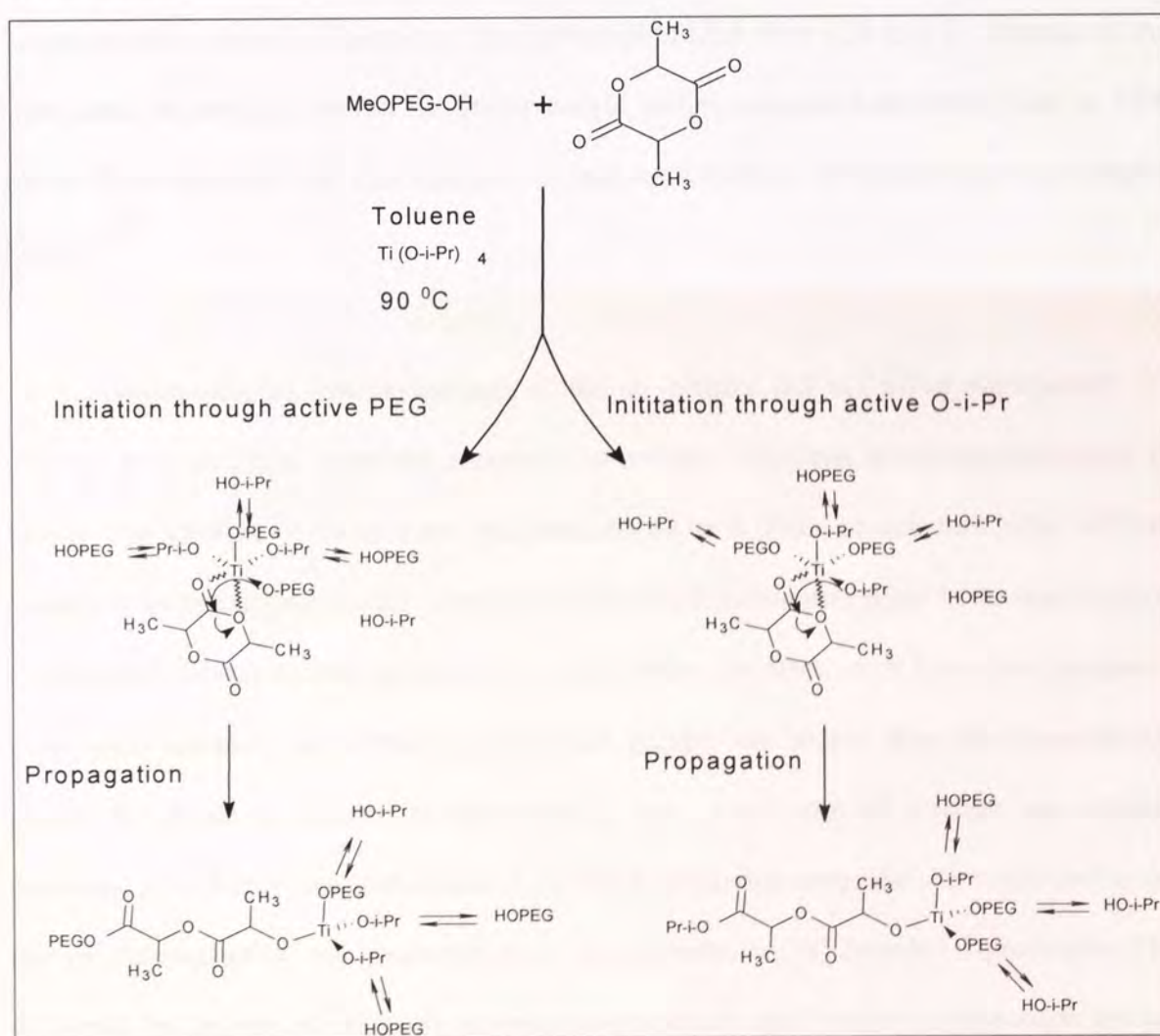
7.7.1 Solution polymerisation.

The solution polymerisation of L-LA with $\text{Ti}(\text{O-}i\text{-Pr})_4$ and co-initiators with different number of hydroxyl groups has been summarised in table 7.1.

Co-initiator	[M]/[CI]/[I]	Reaction time (min)	% Conversion	$M_{n\text{GPC}}/\text{g.mol}^{-1}$	PD	CL	CL_{th}	I_{OH}	$I_{\text{OH th}}$
None	50/0/1	20	98	2500	1.34	11.4	12.3	4.4	4
2-butanol	50/5/1	20	98	1400	1.25	6.8	5.5	7.3	9
2-butanol	50/10/1	20	87.5	1410	1.13	3.6	3.1	12	14
2-methyl-2-propanol	50/5/1	30	94	2650	1.28	8.6	5.2	5.4	9
2-methyl-2-propanol	50/8/1	40	96	2570	1.40	7.3	4.1	6.7	12
PEG ₃₅₀	50/5/1	30	96	1470	1.21	5	5.4	9.7	9
PEG ₄₀₀	50/5/1	30	98	1720	1.16	3.2	3.6	15.5	14
PEG ₄₀₀	50/8/1	20	98	1290	1.08	1.83	2.5	27.3	20
PP ₂₇₀	50/1/1	30	97.2	9880/ 1650	1.07/ 1.25	8.6	6.1	5.7	8
Polymerisation of L-lactide, $[\text{M}] = 0.78 \text{ mol/dm}^3$, in toluene solution at 90°C									

Table 7.1: L-lactide polymerisations in toluene solution in the presence of $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator and co-initiators with different number of hydroxyl groups.

$\text{Ti}(\text{O-}i\text{-Pr})_4$ was a very effective initiator in combination with hydroxy terminated PEG's to produce block copolymers of lactide and PEG. Conversion of the lactide monomer remained very high over 95 % and the polydispersities of the products reasonably narrow ranging from 1.1-1.3. As well as the formation of a lactide/PEG copolymer, lactide homopolymer is also produced. The synthesis of PLA alongside PLA-co-PEG block copolymer can be explained by a rapid exchange that takes place between the hydroxy-terminated PEG and the alkoxy group of the initiator with the titanium metal, as seen in scheme 7.2.



Scheme 7.2: Ring opening polymerisation of lactide using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator and PEG as a co-initiator.

Therefore, initiation of the ring opening polymerisation of lactide took place through the O-CH of the iso-propoxide and the terminal O-CH₂ of the PEG. During the propagation step the growing propagating centres containing either the iso-propoxide or PEG group as a chain end become indistinguishable and therefore should have the same rate of propagation. The rate of exchange during initiation and propagation remained fast, reducing the transesterification reactions and therefore keeping the polydispersity very narrow. For instance, increasing the amount of a mono-hydroxy-terminated, small-chain alcohol as a co-initiator helped to reduce the polydispersity of the synthesised PLLA from 1.34 to 1.13 although, at the same time, the average number molecular weight will be reduced from 2500 g/mol to 1400 g/mol. This behavior was also observed in mono di-hydroxy terminated and star-shaped PEG's.

The number of hydroxyl-groups of the co-initiator did not affect significantly the reaction time to reach complete monomer conversion. Whereas homo-polymerisation of lactide was finished in 20 minutes, polymerisations with PEG co-initiators with different number of hydroxyl groups were completed in 30 min. A substantial effect in the reaction time to complete conversion was observed only when bulky initiators, such 2-methyl-2-propanol, were used. Initiation via 2-methyl-2-propoxide groups was slower than via iso-propoxide groups, as shown in chapter 3. Consequently, the overall rate of reaction was slightly decreased when bulky co-initiators such 2-methyl-2-propoxide were used. This decrease in the rate of polymerisation was proportional to the concentration of 2-methyl-2-propoxide. The difference in the rate of initiation between iso-propoxide and 2-methyl-2-propoxide species broadened the polydispersities when high concentrations of 2-methyl-2-propoxide co-initiator was used.

All co-initiators, with the exception of PP₂₇₀, yielded a uni-modal molecular weight distribution curve suggesting that initiation rates of both co-initiators were very similar and that both co-initiators exchange rapidly enough. In the case of PP₂₇₀, a bi-modal distribution curve is observed. Two different molecular weights are obtained by GPC analysis 9880 and 1650. The lowest molecular weight is in the range of molecular weights obtained when PEG₃₅₀ or 2-butanol were used in the polymerisation of lactide. Therefore, the only way to obtain molecular weights in the range of 10,000 would be if the majority, if not all, of the hydroxy-groups of a PP₂₇₀ moiety were active. However, the number average of hydroxy groups active in the polymerisation was 5.7 out of 8, it was not possible to confirm accurately, which percentage of them belonged to hydroxy groups of PP₂₇₀.

As seen from table 7.1, the number of active hydroxyl groups (I_{OH}), calculated by ¹H NMR analysis, when bulky alcohols were used as co-initiators were always lower than the total available. Sterically hindered co-initiator, 2-methyl-2-propanol, decreased the rate of initiation of lactide and also the rate of alcohol exchange. In comparison, when linear PEG's were used as co-initiators the calculated number of active hydroxy group was higher than the total available. This arises from the fact that the peak at 4.25 ppm, which corresponds to PLA-co-PEG junction, and the peak of the terminal CHCH₃OH at 4.35 ppm overlap. The integration of the overlapped areas is not accurate giving for the CHCH₃OH terminal group a larger area than actual and therefore a smaller degree of polymerisation than expected. A 250 MHz NMR was use to carried out these analysis therefore, a more powerful magnet would be needed in order to resolve the peaks accurately. In the cases of PP₂₇₀, since the molecule is not symmetrical, the chemical shift of the PLA-co-PEG junction differed from the linear PEG's

and was more spread out in the ^1H NMR spectrum. As a result of this, the overlapping of these peaks is minor and the integration of area of the terminal CHCH_3OH more precise.

7.7.2 Melt polymerisation.

To improve the greenness of the reaction and mimic industrial processes the polymerisation of lactide with $\text{Ti}(\text{O-}i\text{-Pr})_4$ and co-initiators with different numbers of hydroxyl groups was carried out in the melt. The results of the melt polymerisation results are shown in table 7.2. Some of the melt polymerisations were also carried out in solution (entries 4 and 7 in table 7.2) in order to compare both polymerisations more accurately.

PEG	[M]/[P]/[I]	Reaction time/min	% Conversion	$\text{Mn}_{\text{GPC}}/\text{g}\cdot\text{mol}^{-1}$	PD	Dp	Dp_{th}	I_{OH}	I_{OHth}	Entry
None	200/1	90	>99	14900	1.5	44.0	50	4.54	4	1
PEG ₄₀₀	200/2/1	210	>99	8000	2.03	31.0	25	5.2	8	2
PEG ₄₀₀	200/3/1	300	>99	6500	2.3	17.3	20	11.6	10	3
PEG ₄₀₀	200/3/1	90	95	6400	1.4	16.6	19	11.4	10	4*
PEG ₃₅₀	200/4/1	120	>99	7800	1.8	27.6	25	7.2	8	5
PEG ₃₅₀	200/6/1	120	>99	5000	2.6	16.1	20	12.4	10	6
PEG ₃₅₀	200/6/1	120	95	4000	1.4	20.9	19	9.1	10	7*
Melt polymerisations of L-lactide with $\text{Ti}(\text{O-}i\text{-Pr})_4$ and hydroxy terminated co-initiators, $T=105^\circ\text{C}$										

*Polymerisations of L-lactide carried out in toluene solution.

Table 7.2: Melt polymerisations of L-lactide with $\text{Ti}(\text{O-}i\text{-Pr})_4$ using co-initiators with different number of hydroxy groups.

The bulk polymerisation of L-LA with $\text{Ti}(\text{O-}i\text{-Pr})_4$ and PEG as co-initiators showed that conversions in the melt, over 99 %, were slightly higher than in solution, 95 %. Similar observations were made when polymerisation was carried out in solution, partial isopropoxide/PEG exchange is produced leading to the synthesis of both poly(lactide) and poly(lactide-block-(polyethylene glycol)). An increase in the PEG concentration (hydroxyl group content) did not cause a decrease in the maximum conversions or cause backbiting during extended polymerisation times. However, an increase in the PEG concentration increased the required time for the reaction to go to complete conversion as well as the polydispersity. The increase in the polydispersity was a distinctive feature compared to solution polymerisation, entries 4 and 7 in table 7.2. The rate of propagation in the melt was slightly reduced and transesterification reactions became more prevalent. Diffusion of the chain ends of the PEG's in the melt may also be slower giving rise to the greater polydispersity.

Moreover, the number average molecular weight decreased, which suggest that the M_n is controlled by the number of potential chain ends. GPC suggested that the decrease in molecular weight is not due to backbiting, since oligomers were not detected. Since the ratio of the co-initiator to lactide controls the molecular weight of the polymer, the amount of co-initiator must be low when high molecular weight polymers are prepared. However, the total concentration of hydroxyl groups in polymerisation can be augmented by increasing the number of hydroxyl groups in the initiator without having to decrease the molecular weight.

CHAPTER 8

TITLE: SYNTHESIS OF LA/PEG BLOCK CO-POLYMER BY STEP CONTROLLED POLYMERISATION

The ring opening polymerisation of the lactide using $\text{Ti}(\text{O-}i\text{-Pr})_4$ and PEG co-initiators leads to the formation of PLA-co-PEG copolymers alongside lactide homopolymer. In order to avoid the synthesis of the lactide homopolymer and accomplish the selective synthesis of PLA-co-PEG copolymers the reaction was, therefore, carried out in two steps. The first step consists of the condensation of $\text{Ti}(\text{O-}i\text{-Pr})_4$ and co-initiators with different number of hydroxyl groups. The condensation should take place by exchange of alkoxide groups by PEG oligomers. It is known that tin alkoxides, can easily exchange alkoxide groups *via* donor-acceptor interactions⁹⁴. Recently, Kricheldorf⁵⁶ successfully carried out poly-condensations of PEG oligomers with different metal alkoxides, such as $\text{Sn}(\text{O-}t\text{-Bu})_4$, $\text{Ge}(\text{O-Et})_4$, $\text{Zr}(\text{O-Et})_4$ and $\text{Ti}(\text{O-Bu})_4$. The synthesis of these spirocycles was unknown to us when this research was started and, therefore, the reaction conditions used for the synthesis of these titanium macro-catalysts or macro-initiators differ from those used by Kricheldorf. The term macro-catalyst will be used in this chapter instead of spirocycle, since there is not a spectroscopic method (to our knowledge) that can distinguish between a spirocycle or a network.

The second step of the block co-polymer synthesis was the ring opening polymerisation of lactide in the melt using the synthesised titanium macro-catalysts as initiators. Similar reactions were carried out by Kricheldorf⁵⁶ for the ring opening polymerisation of ϵ -caprolactone using spirocycles of metals such as titanium, tin, zirconium and germanium.

8.1 MATERIALS

The materials used in the work described were; L-lactide, D,L-lactide, $\text{Ti}(\text{O-}i\text{-Pr})_4$ 99.99%, ethyl acetate, methanol and distilled water. The co-initiators used were: poly(ethylene glycol) methyl ether (PEG_{350}), poly(ethylene glycol) (PEG_{400}), pentaerythritol ethoxylate (3/4 EO/OH) (PP_{270}), *O,O'*-Bis(3-aminopropyl)polyethylene glycol (PEGNH_2) and di-hydroxy terminated polycaprolactone (PCL_{1250}). The purity of each material and the treatment prior to use were described in section 2.1 and 2.2.

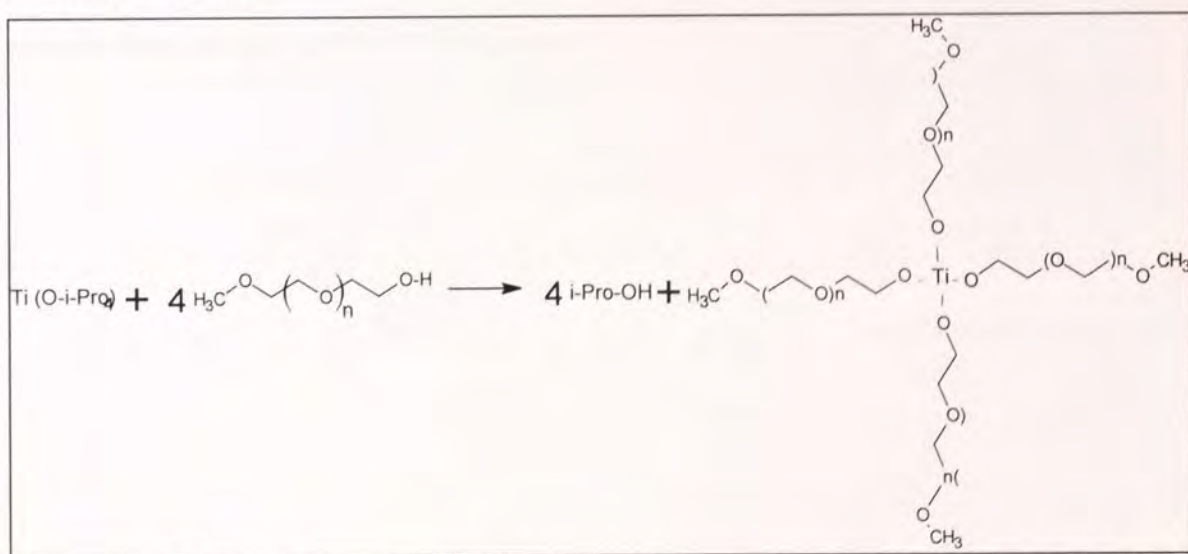
8.2 PREPARATION OF TI MACRO-INITIATORS.

Alcohols with different number of hydroxyl groups were selected to carry out condensation reactions with $\text{Ti}(\text{O-}i\text{-Pr})_4$. PEG_{350} , PEG_{400} and Pt_{270} (used in the previous chapter for the synthesis of lactide/PEG block copolymers) were selected since they have different number of hydroxyl groups but similar molecular weights. A PEG with terminal amino groups (PEGNH_2) was also selected, in order to determine if this two step pathway is also appropriate to the synthesis of PLA-block-PEG co-polymers. A di-hydroxy terminated PCL (PCL_{1250}) was selected in order to synthesise tri-block copolymers of lactide and ϵ -caprolactone (copoly(lactide-block-caprolactone-block-lactide)).

Condensations of the hydroxy terminated co-initiators with $\text{Ti}(\text{O-}i\text{-Pr})_4$ were carried out in toluene under an inert nitrogen atmosphere. $\text{Ti}(\text{O-}i\text{-Pr})_4$, co-initiators and solvent were

weighed and mixed in a glove-box under an argon atmosphere. Once the reactor was sealed, it was moved from the argon box and connected to a vacuum line where a continuous nitrogen flow was supplied, as shown in figure 2.3. The vessel was then placed in an oil bath (still connected to the vacuum line) to maintain a reaction temperature of 105°C. Magnetic stirring was provided throughout the polymerisation as summarized in scheme 3.1. After 16 hours the temperature was raised to 120 °C and the toluene and iso-propanol bi-product distilled and dried under reduced pressure on the vacuum line. The flask was connected to the vacuum line at all times and, therefore, was always under inert conditions. The drying time needed for small molecular weight PEG's was 2 hours. The products generated from PEGNH₂ and PCL₁₂₅₀ needed longer drying times as shown in table 8.1.

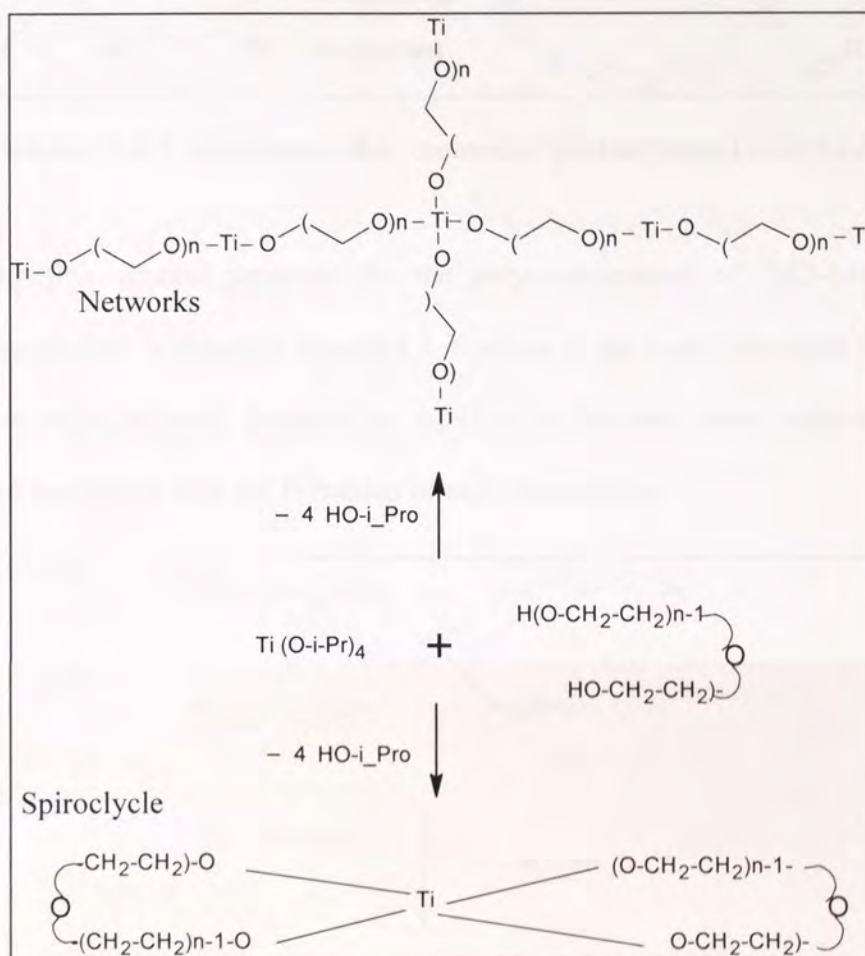
The reaction scheme for the condensation of Ti(O-*i*-Pr)₄ with oligoethers mono-ols, is shown in scheme 8.1.



Scheme 8.1: Condensation of a mono-hydroxyl terminated PEG with Ti(O-*i*-Pr)₄.

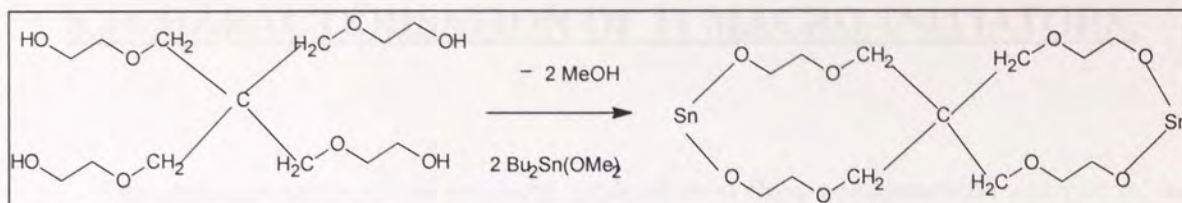
In contrast to alkanes, aliphatic ether groups of polyether diols favour gauche conformation, because the lone pair of electrons of the O-atom interferes with the C-H-bonds in the all-trans conformations, which is, generally, the most stable conformation of alkanes. Therefore, the chances of obtaining thermodynamically stable spirocycles are high in the case of the polyether diols. However, the formation of networks is also possible when the reaction is kinetically controlled and also very likely to be dependent on the length of the diol. Recent publications by Kricheldorf ⁵⁶, on the formation (through a different pathway) of stable spirocycles of titanium with PEG's, showed that, when PEG's with M_n 's above 1000 were used, the product obtained showed syrup consistency and good solubility in chloroform. In contrast, products generated, when PEG's of low M_n (300, 400 and 600) were used, remained stiff gels. This arose from the fact that spirocycles and networks stayed in equilibrium. These results suggested that the equilibrium between network and spirocycles might also be controlled by the length of the PEG oligomer.

The reaction scheme proposed for the condensation of $\text{Ti}(\text{O-}i\text{-Pr})_4$ with oligoether diols, is shown in scheme 8.2



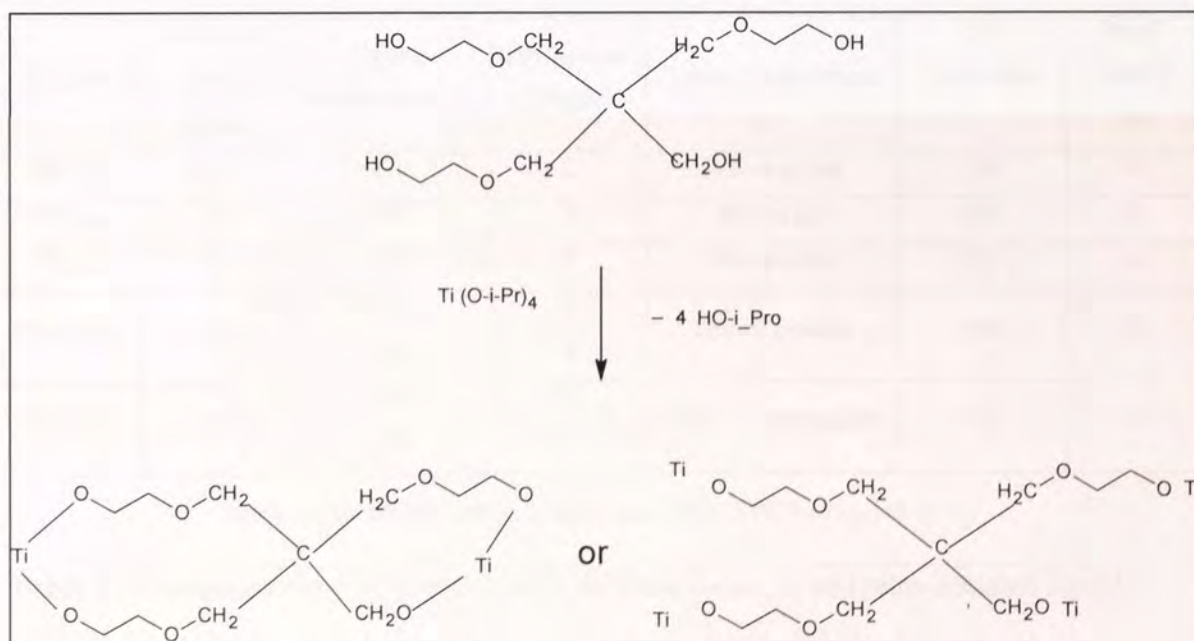
Scheme 8.2: Polycondensation of a di-hydroxyl terminated PEG or PCL with $\text{Ti}(\text{O-}i\text{-Pr})_4$.

Recently, thermodynamically controlled formation of spirocycles, at the expense of networks, has been observed when pentaerythritols were condensed with $\text{Bu}_2\text{Sn}(\text{OMe})_2$, with quantitative elimination of methanol. Spirocycles with structure as shown in scheme 8.3 were produced without any appreciable formation of gel particles.



Scheme 8.3: Condensation of a commercial pentaerythritol with $\text{Bu}_2\text{Sn}(\text{OMe})_2$.

The reaction scheme proposed for the polycondensation of $\text{Ti}(\text{O-}i\text{-Pr})_4$ with the selected pentaerythritol, is shown in scheme 8.4. Because to the small size of the PEG chain, it is believed that either network formation or equilibrium between spirocycles and networks would be more favourable than the formation of only spirocycles.



Scheme 8.4: Condensation of a pentaerythritol with $\text{Ti}(\text{O-}i\text{-Pr})_4$.

8.3 CHARACTERISATION OF TI MACRO-INITIATORS.

The characterisation of the products obtained from these condensations was carried out by ^1H and ^{13}C NMR. Samples were prepared in the glove box using well dried NMR tubes and deuterated solvents. The products obtained, with the exception of $\text{Ti}(\text{PCL}_{1250})_2$, showed a poor solubility in chloroform. Either deuterated DMSO or toluene was therefore used, as the solvent of the products. $\text{Ti}(\text{PP}_{270})$ was dissolved in deuterated toluene. A summary of the appearance of the products and conversions are shown in table 8.1.

Polymer	Reaction time/ Hours	Drying temperature/ °C	Drying time /Hours	Colour + appearance	% Conversion	% of <i>i</i> -PrOH left
PEG ₃₅₀	16	120	2	Brown syrup	100	0
PEG ₄₀₀	16	120	2	Brown gel	100	0
PP ₂₇₀	16	120	2	White solid	91	3
PEG NH ₂	16	120	6	Yellow powder	100	0
		160	3			
PCL ₁₂₅₀	16	120	2	White + soap texture	100	0
		160	8			
Condensation of Ti(O- <i>i</i> -Pr) ₄ , in toluene at 105 C, [Ti(O- <i>i</i> -Pr) ₄]=0.07 M.						

Table 8.1: Condensation of $\text{Ti}(\text{O-}i\text{-Pr})_4$ with different mono, bi and tetra-dentated ligands.

GPC analysis was not carried out because of the tendency of these compounds to hydrolyse.

8.3.1 Characterisation of $\text{Ti}(\text{PEG}_{350})_4$ and $\text{Ti}(\text{PEG}_{400})_2$

When ^1H NMR spectra of $\text{Ti}(\text{PEG}_{350})_4$ and $\text{Ti}(\text{PEG}_{400})_2$ products were recorded, no signals associated with iso-propanol (methyl signal at 1.21 ppm) or $\text{Ti}(\text{O-}i\text{-Pr})_4$ (methyl signal at 1.02 ppm) groups were detected, as seen in figure 8.1(A) and 8.2 (A). The ^1H NMR spectrum also shows a strong signal at 3.55 ppm which corresponds to the methylene groups of PEG, and a down field shift of the methylene HO-CH_2 -end group from 3.6 ppm up to 4.55 ppm when bonded to the titanium.

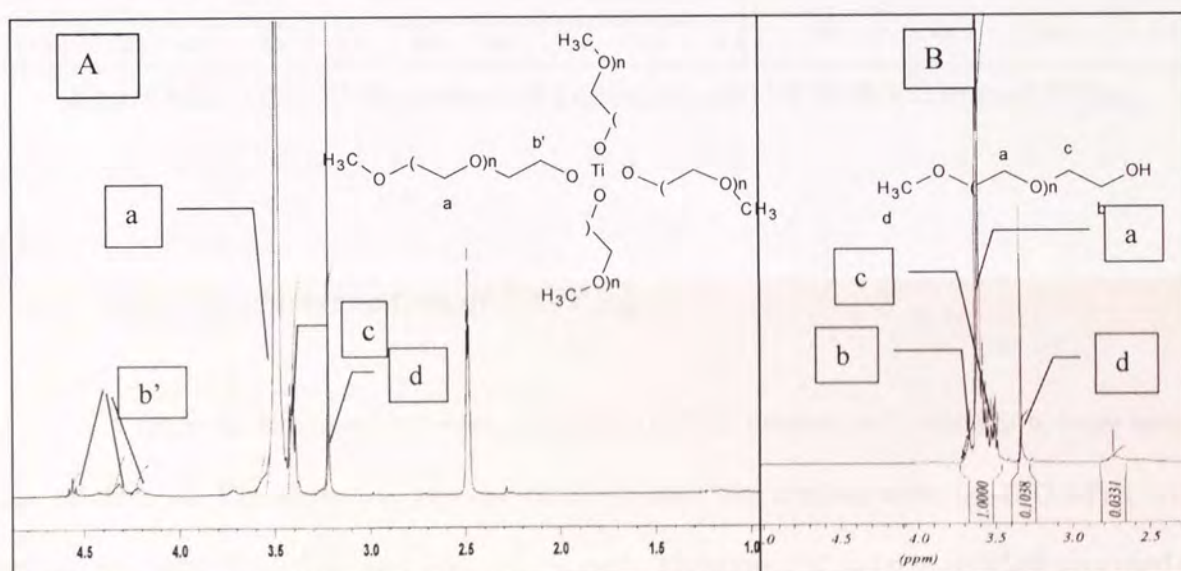


Figure 8.1: (A) ^1H NMR spectrum of $\text{Ti}(\text{O-PEG-OMe})_4$. (B) ^1H NMR spectrum of MeOPEG_{350} .

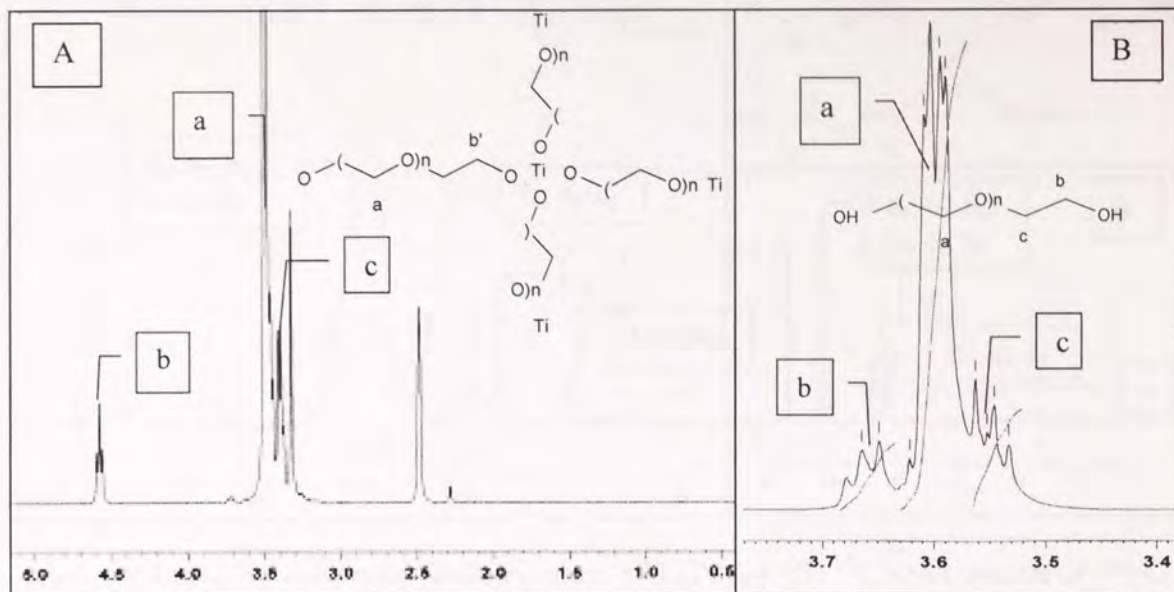


Figure 8.2: (A) ^1H NMR spectrum of $\text{Ti}(\text{PEG}_{400})_2$. (B) ^1H NMR spectrum of PEG_{400} .

8.3.2 Characterisation of $\text{Ti}(\text{PP}_{270})$

A range of deuterated solvents, including DMSO, toluene and chloroform, were tested as solvents for the white fine powder obtained from the condensation of $\text{Ti}(\text{O-}i\text{-Pr})_4$ with PP_{270} . The solubility of this was very poor in each. Therefore, ^{13}C solid state NMR was used to analyse the product rather than solution NMR. Cross polarization technique was used, applying a spin speed of 4500 Hz. Cross polarization techniques are not accurately quantitative, since it is difficult to ensure that the same polarization will be transferred to each carbon, because of difference in the chemical environment. The spin lock (time required for the cross polarisation to take place) has not been optimised. The scale of the transfer polarisation in PENDANT is within the range of μsec , whereas in the cross polarisation is in the range of msec. An error of $\pm 10\%$ is generally accepted for the quantitative estimations carried out.

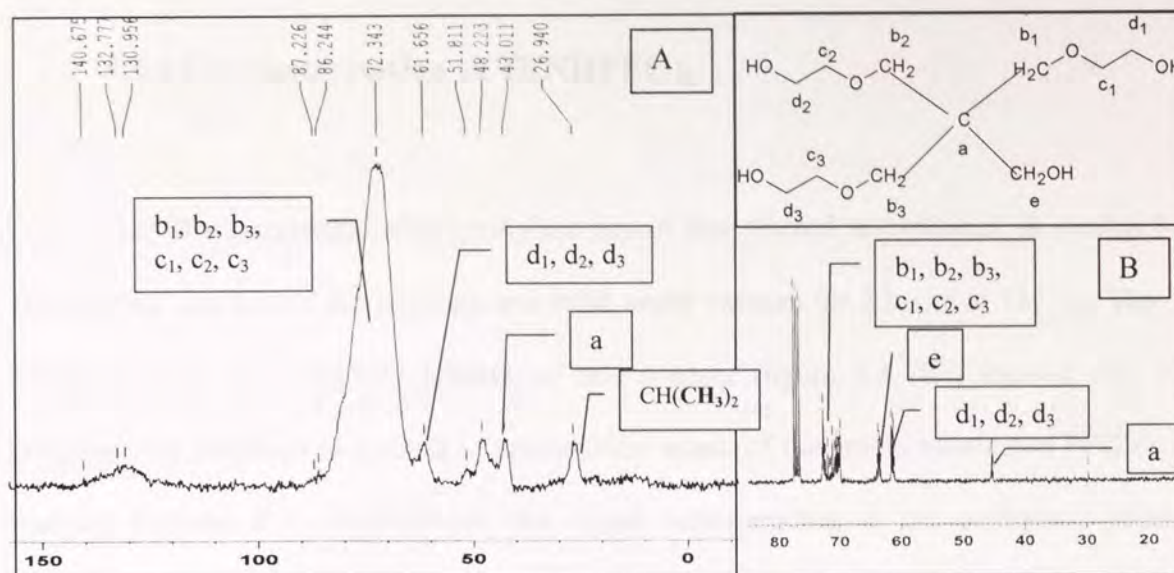
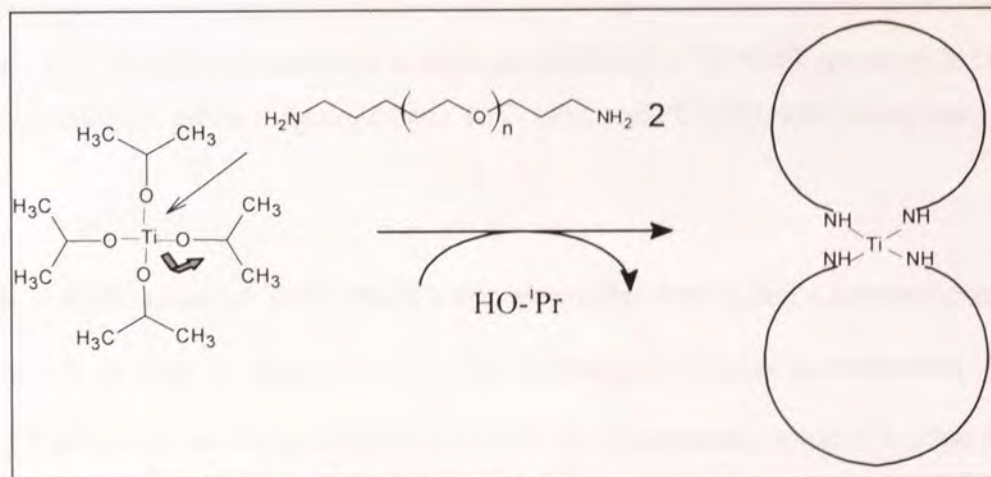


Figure 8.3: (A) ^{13}C solid state NMR spectrum of $\text{Ti}(\text{PP}_{270})$. (B) ^{13}C NMR spectra of PP_{270} .

The solid state NMR spectrum (figure 8.3(A)) confirmed the presence of the pentaerythritol by the existence of a broad peak at 72.34 ppm, which includes the chemical shifts of the methylene carbons b (b_1, b_2 and b_3) and c (c_1, c_2 and c_3), as shown in figure 8.3). The presence of the terminal methylene carbons (d) at 61.67 ppm shows that a fraction of the original groups remained un-reacted. The ratio of the area associated with methylene carbons b' and c' and the area of the un-reacted methylene carbon d shows that conversion reached approximately 91 %. The solid state NMR spectrum also shows the presence of the methylene carbons associated with the iso-propoxide groups still bonded to titanium. More time should be allowed for the reaction to continue, to determine the maximum conversion that can be achieved. The rigidity of the star-shaped co-initiator and the short length of the PEG arms could be an important factor that decreases the rate of the condensation reaction and, therefore, reaction conversion at a given time.

8.3.3 Characterisation of $\text{Ti}(\text{NHPEG})_2$

O,O'-Bis(3-aminopropyl)polyethylene glycol was reacted as explained in section 7.2. The mixture was heated for 16 hours and dried under vacuum for 2 hours at 120 °C. The ^1H NMR spectrum, in deuterated DMSO, of this product (figure 8.4 (B)) showed that isopropanol was produced as a result of nucleophilic attack of the amino terminated PEG on to titanium (scheme 8.5). Furthermore, the signal corresponding to the methylene protons adjacent to the amino group of the unreacted PEGNH_2 at 2.54 ppm (figure 8.4 (A)) are shifted slightly, upon reaction, to 2.59 ppm. The change in chemical shift was not as large as that observed with hydroxyl terminated PEG's, since the methylene group is attached to an NH, which has a smaller electron-withdrawing effect than O.



Scheme 8.5: Nucleophilic attack of the amino terminated PEG onto titanium.

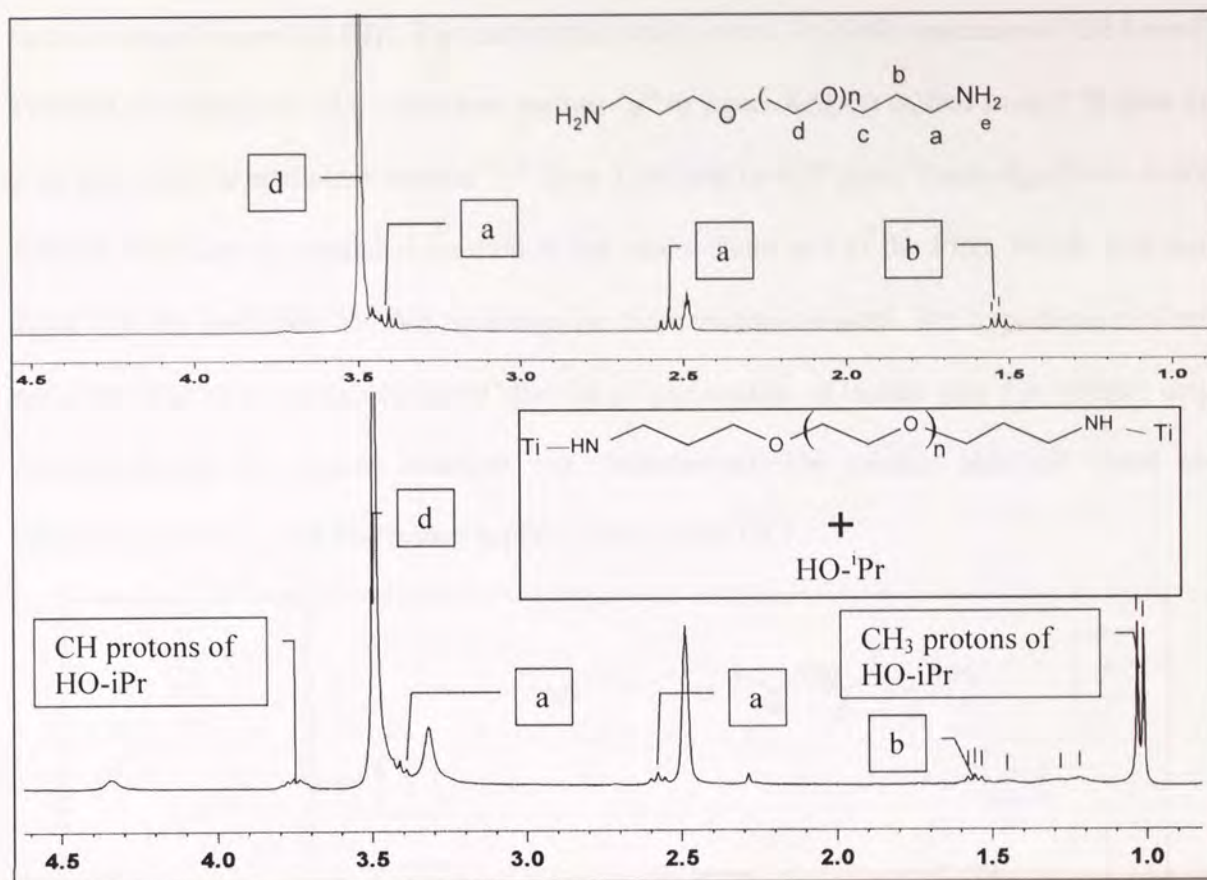


Figure 8.4: (A) ^1H NMR spectrum of PEGNH₂ in DMSO. (B) ^1H NMR spectrum in DMSO of the condensation product obtained from Ti(O-*i*-Pr)₄ and PEGNH₂ after being dried for 2 h.

The ^1H NMR spectrum of the product also shows that there is still a substantial amount of propanol left as seen in figure 8.4 (B). The substantially higher concentration of isopropanol still present in the flask, compared to previous experiments, is likely to arise from a weaker vacuum, as an alternative vacuum line was used for this distillation. To eliminate the substantial amount of remaining iso-propanol, the product was heated further for a period of 8 hours at 160 °C. The ^1H NMR spectrum in deuterated chloroform (the solubility of the product in DMSO was not sufficient to obtain a well resolved spectrum) showed that further changes took place upon heating. The ^1H NMR spectrum of the unreacted PEGNH₂ in chloroform (Figure 8.5 (A)) was compared to the polycondensation product of PEGNH₂ and Ti(O-Pr)₄

upon heating (Figure 8.5 (B)). Two substantial shifts in the ^1H NMR spectrum of the heated PEGNH₂ are observed. The methylene protons "a" in figure 8.5(A)) shifted from 2.78 ppm to 2.30 ppm and the methylene protons "c" from 3.54 ppm to 4.05 ppm. These significant shifts indicate that there is a major disruption in the amine chain end of the PEG, which does not agree with the predicted ^1H NMR spectrum for these macro-initiators. The hypothesis of what occurred upon heating was developed after the polymerisation of lactide with this initiator was carried out and the product obtained was characterised. The product obtained would be referred as Ti(PEG)₂ and this theory explained in section 7.4.1.

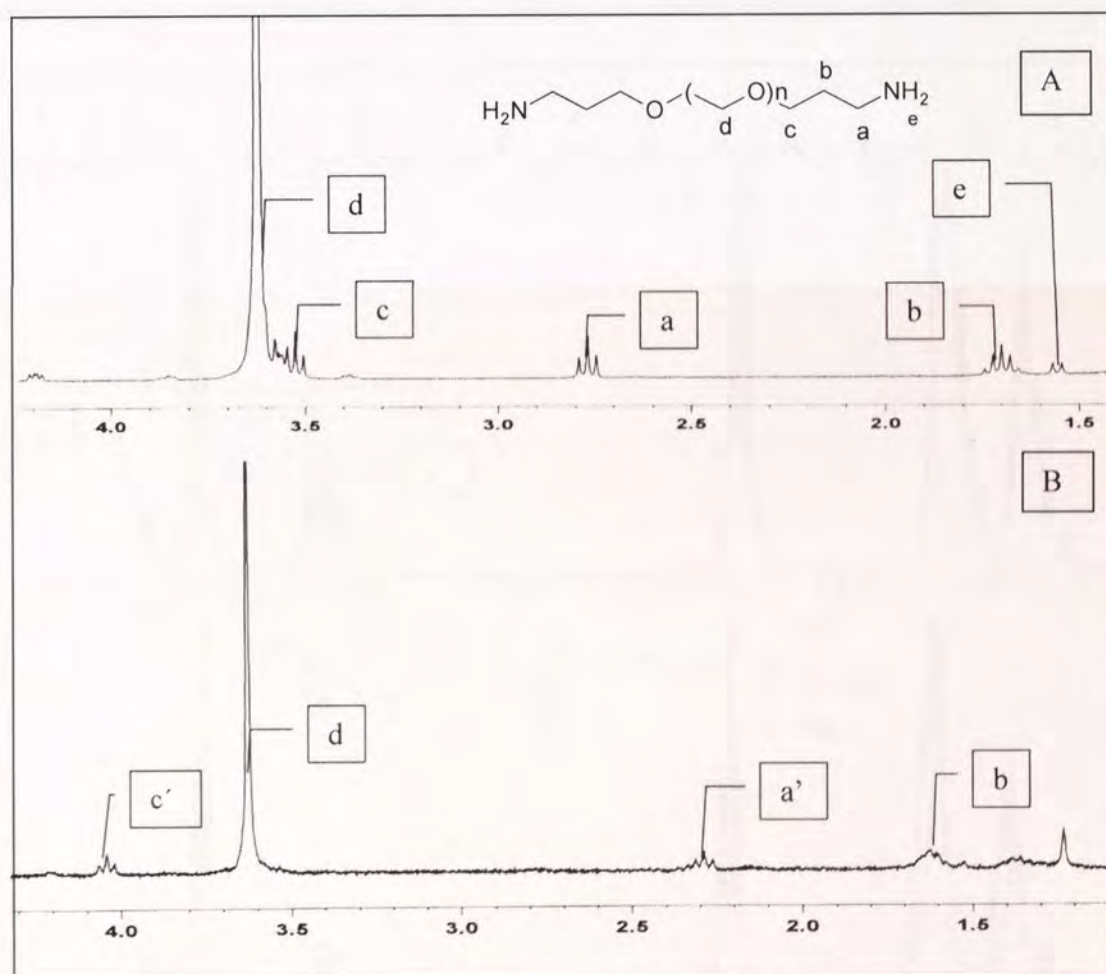


Figure 8.5: (A) ^1H NMR spectrum of PEGNH₂ in chloroform. (B) ^1H NMR spectrum in chloroform of the polycondensation product obtained from Ti(O-*i*-Pr)₄ and PEGNH₂ after being dried for 2 hours.

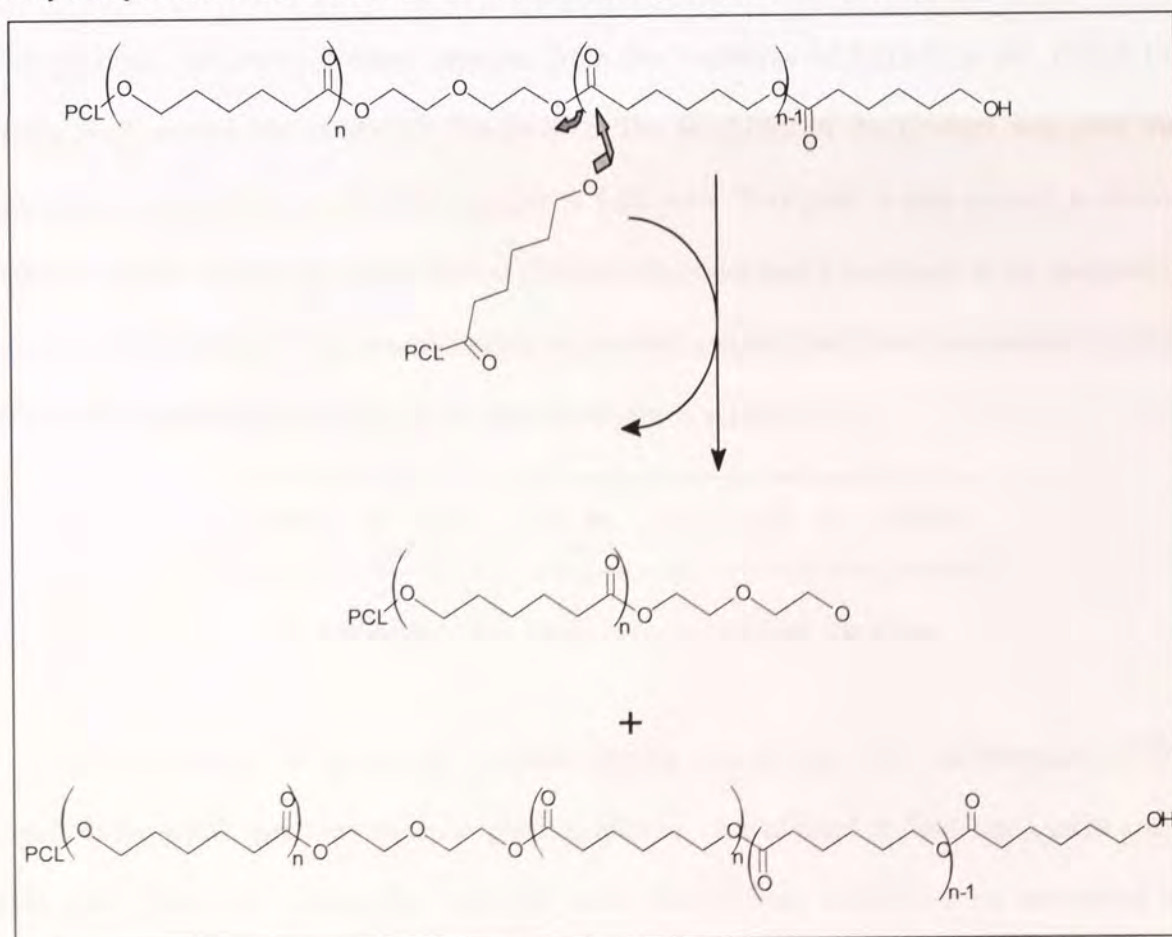
8.3.4 Characterisation of $\text{Ti}(\text{PCL})_2$

Commercial di-hydroxy terminated PCL is manufactured using di-ethylene glycol ($\text{HO}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-\text{H}$) as an initiator. When diethylene glycol is used as an initiator, the ^1H NMR spectrum (figure 8.6 (A)) shows two signals. A triplet at approximately 4.2 ppm (e), as a consequence of the acylation of the terminal $\text{HO}-\text{CH}_2$ end groups and another triplet at approximately 3.65 ppm (f) associated to the other methylene protons, which in this case are equivalent. ^1H NMR spectrum of a commercial PCL is shown in figure 8.6(A). The remaining peaks correspond to methylene protons associated with a standard PCL.



Figure 8.6: (A) ^1H NMR spectra of PCL_{1250} . (B) ^1H NMR spectra of product obtained from the poly-condensation of $\text{Ti}(\text{O}-i\text{-Pr})_4$ and PCL_{1250} .

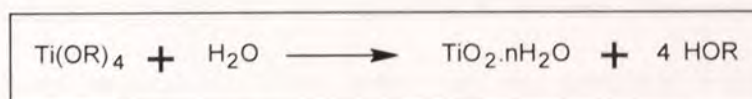
Condensation of the di-hydroxy terminated PCL and $\text{Ti}(\text{O-}i\text{-Pr})_4$ yields a white soft solid. The ^1H NMR spectrum (Figure 8.6 (B)) of the solid produced showed that the ratio of the methyl protons (near the ester group) of the PCL at 4.05 ppm and the methylene protons (near the ester junction) of the initiator at 4.20 ppm were shifted significantly. This may arise from the fact that inter-molecular transesterification reactions between PCL chains took place. Inter molecular transesterification reactions (scheme 8.6) from the end of the PCL chain to the carbonyl ester adjacent to the initiator would decrease the number of methylene protons of the initiator adjacent to an ester group of a CL unit. In addition, PCL chains with higher molecular weights would be generated. A small decrease in the area corresponding to the terminal methylene protons of the PCL is observed, confirming the previous assumption.



Scheme 8.6: Inter-transesterification reactions.

The shift of terminal methylene protons in PEG's after polycondensation with $\text{Ti}(\text{O-}i\text{-Pr})_4$ is of approximately 0.5-0.7 ppm. If a similar shift is expected for the terminal methylene protons of the caprolactone when bonded to titanium, the NMR signal associated with them could easily be overlapped with the signal of the methylene protons (near the ester group) of the PCL. The ^1H NMR failed to show the signal of any terminal methylene protons either from the PCL ($\sim\text{CH}_2\text{-O-Ti}$) or from the terminal product ($\sim\text{O-CH}_2\text{-CH}_2\text{-O-Ti}$), generated from transesterification reactions, bonded to the titanium.

The ^1H NMR spectrum of the condensation product also showed a singlet at 1.22 ppm. This peak is associated with the product generated when a titanium alkoxide is hydrolysed. The ^1H NMR spectra of product obtained from the hydrolyse of $\text{Ti}(\text{O-Bu})_4$ and $\text{Ti}(\text{O-2-Et-Hex})_4$ were carried out in DMSO (figure 8.7). The solubility of the product was poor but sufficient to prove the presence of a singlet at 1.22 ppm. This peak is also present in homopolymerisations carried out with different titanium alkoxides and it decreases as the polymer is washed with methanol. Titanium alkoxides are thermally stable and hydrolyse readily in water to give amorphous titanium dioxide hydrate as shown in scheme 8.7.



Scheme 8.7: Hydrolysis of titanium alkoxides.

The formation of amorphous titanium dioxide hydrate was also confirmed by FTIR. Bands in the FTIR spectrum were assigned as follows: broad band at 3400 cm^{-1} , 2924 cm^{-1} , 2850 cm^{-1} , 2361 cm^{-1} , 1624 cm^{-1} and 550 cm^{-1} . Bands from $3900\text{-}2500$ are associated to hydrogen bonded TiO-H stretching vibrations in different environments^{95, 96}. Two bands at

2924 and 2850 cm^{-1} correspond to hydrocarbon contaminants. Some hydrolysis of the titanium compound could have happened during the reaction due to small amount of impurities present in the polymer or because of a small amount of water impurities present in the NMR tube.

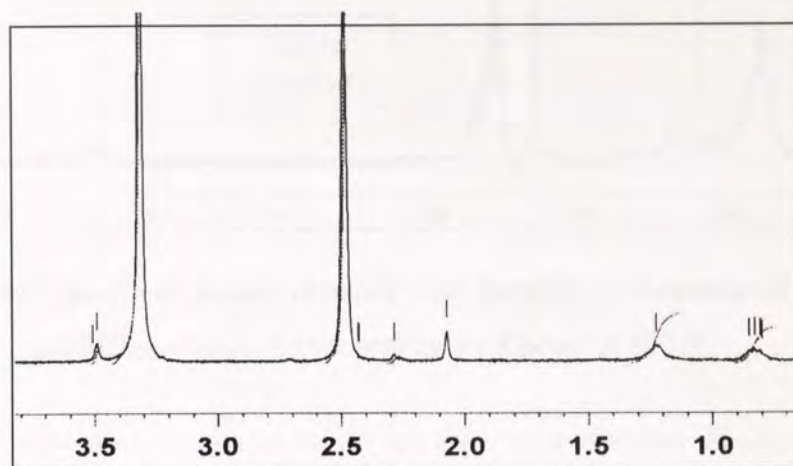


Figure 8.7: ^1H NMR spectrum of product obtained from the hydrolyses of $\text{Ti}(\text{O-Bu})_4$.

The polycondensation product obtained from the $\text{Ti}(\text{O-}i\text{-Pr})_4$ and PCL was heated further in order to eliminate the remaining toluene. The ^1H NMR spectrum of the product (Figure 8.8) showed that intra-transesterification reactions resulting in the formation of undesirable cycle oligomers (scheme 8.8) took place. Oligomer formation is confirmed by the presence of new peaks at 4.15 and 2.62 ppm associated to the methylene protons near the ester group and the carbonyl respectively. These peaks were also present as a side product in the homo-polymerisation of ϵ -caprolactone with $\text{Ti}(\text{O-}i\text{-Pr})_4$.

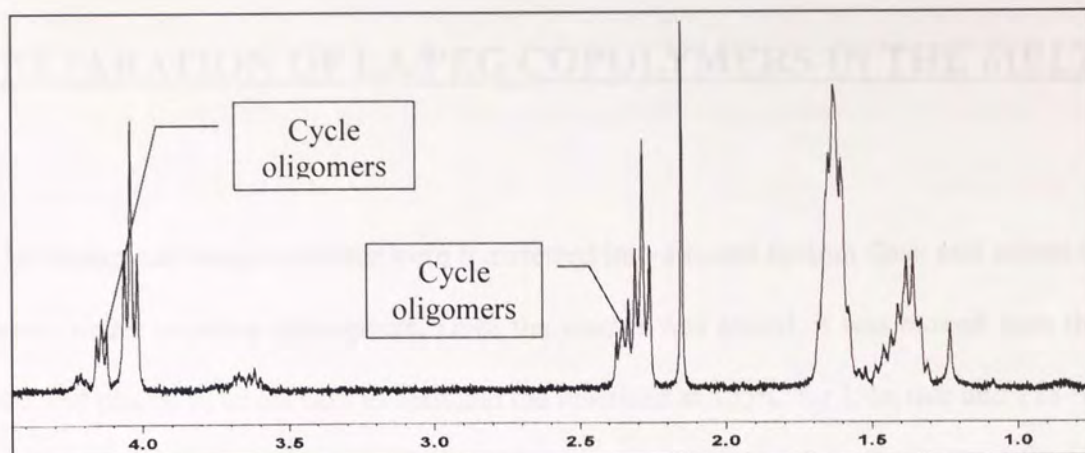
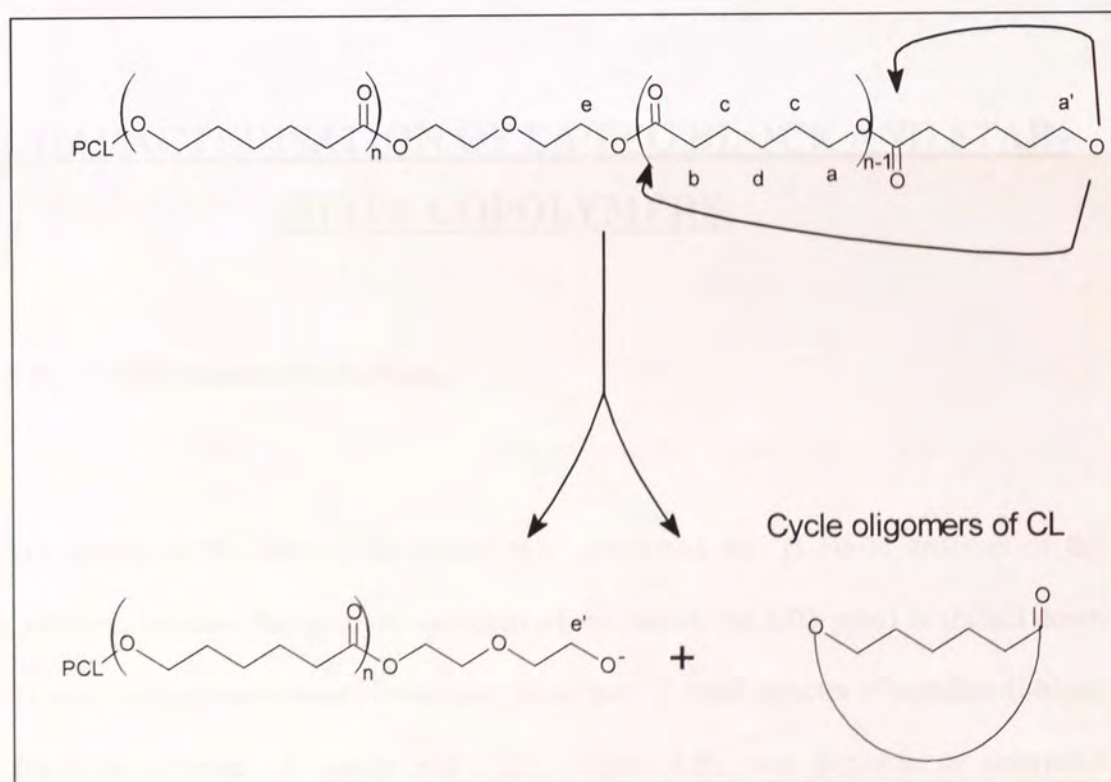


Figure 8.8: ^1H NMR spectra of product obtained from the poly-condensation of $\text{Ti}(\text{O-}i\text{-Pr})_4$ and PCL_{1250} upon further heating for 8 hours at 160°C .



Scheme 8.8: Intra transesterification reactions.

8.4 PREPARATION OF LA/PEG COPOLYMERS IN THE MELT

Monomer and macro-initiator were transferred into a round bottom flask and mixed in a glove-box under an argon atmosphere. Once the reactor was sealed, it was moved from the glove box and placed in an oil bath to maintain the reactions at 105°C for L-lactide and 115 °C in the case of D,L -lactide. The procedure for melt polymerisations has been described in section 4.2. Reaction times till completion were very short in the order of 2 hours for the majority of the reactions that were carried out.

8.5 CHARACTERISATION OF LA/PEG BLOCK AND STAR-SHAPE COPOLYMERS.

8.5.1 NMR characterisation.

The extent of the lactide conversion was confirmed by ^1H NMR analysis of the reaction mixture, because the methine hydrogen of the lactide (at 5.03 ppm) is shifted down field (5.13 ppm) on polymerisation. From analysis of the ^1H NMR spectra of purified di-block and tri-block copolymers of lactide and PEG, (figure 8.9), was possible to determine accurately the junction between the PEG and the PLLA, a resonance at 4.3 ppm, and the peak that contains the protons associated to the methine protons of the lactide end group at 4.35 ppm. As mentioned in chapter 6, the acylation of the HO-CH₂ end groups of PEG's causes a

down field shift of 0.6 ppm in the terminal methyl group from 3.7 to 4.3 ppm. This feature confirms initiation of the ring opening polymerisation of lactide via PEG ligands. Initiation via the iso-propoxide ligand is not observed, as proved by the disappearance of the multiplet at 1.22 ppm associated to the methyl protons of the iso-propoxide end group. The small singlet at 1.23 ppm is due to the presence of some remaining titanium dioxide hydrate.

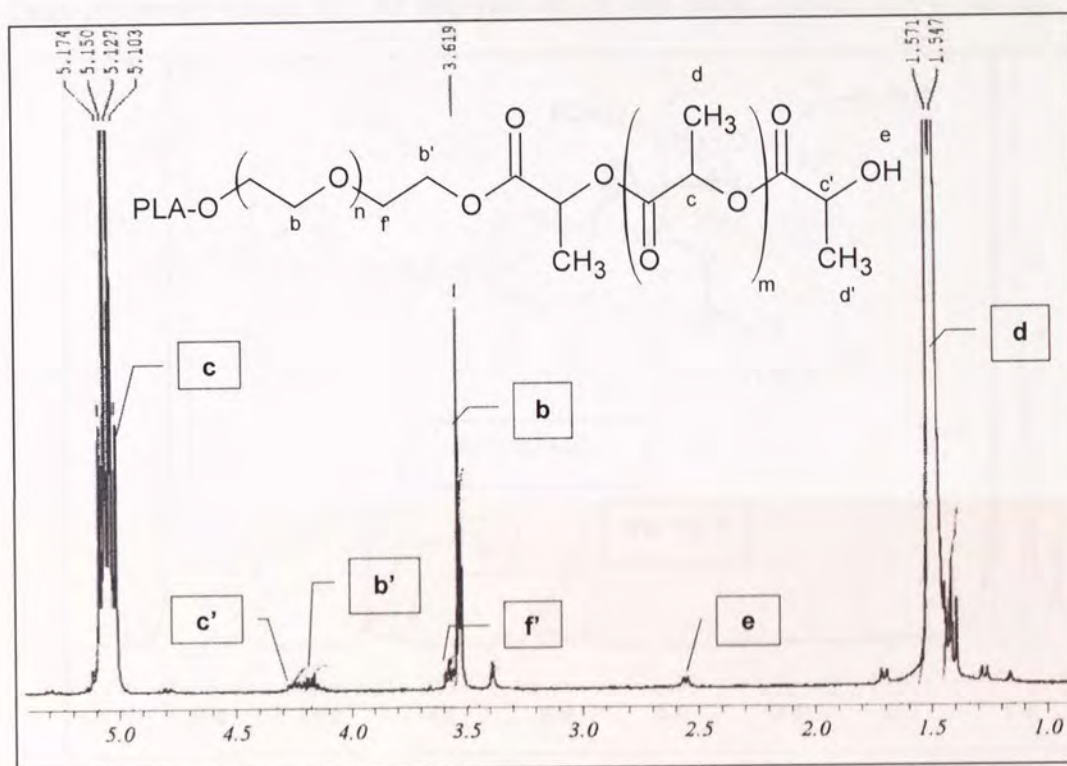


Figure 8.9: ^1H NMR of PLLA-block-PEG-block-PLLA tri-block copolymer.

In the case of the four-arm star-shaped PLLA copolymer, the ^1H NMR spectrum of product (figure 8.10) shows a more complex multiplet between 4.3 and 4.1 ppm. This is due to the fact that the star-shaped pentaerythritol chosen has asymmetric arms and, therefore, produces more than one signal for the PEG-PLA junction point. This spectrum is in agreement with those obtained by Seppala⁶⁸ for the synthesis of star shaped copolymers of lactide.

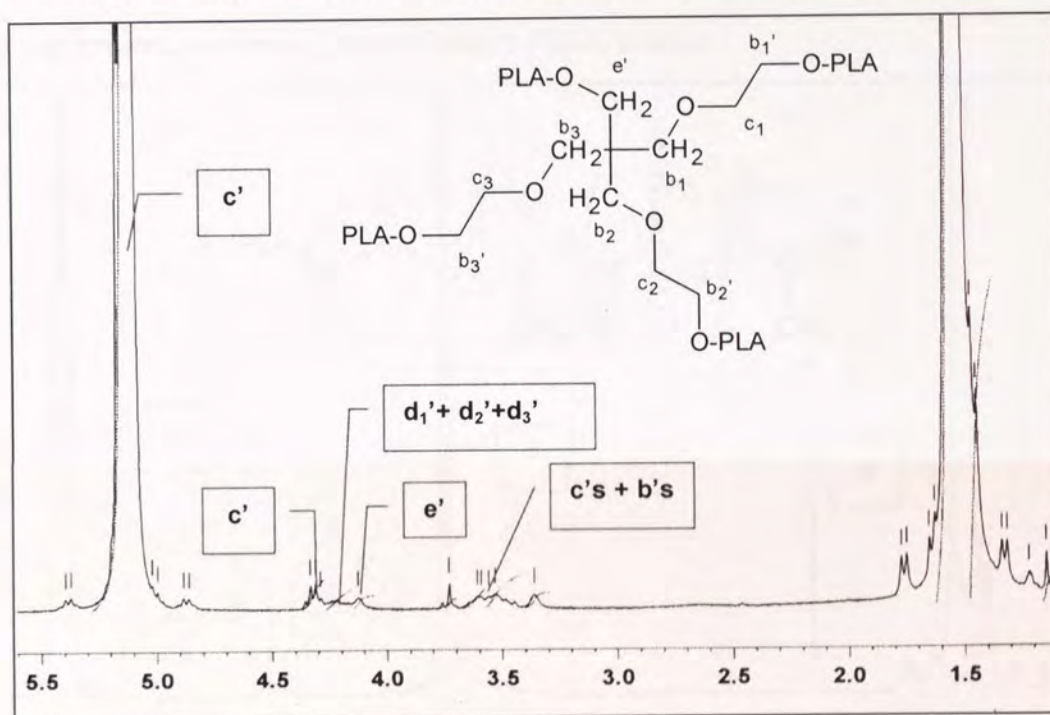


Figure 8.10: ^1H NMR of PLLA-co-PEG star-shape copolymer.

The ^1H NMR spectrum (Figure 8.11) of the purified product obtained from the melt polymerisation of L-lactide and $\text{Ti}(\text{PEG})_2$ confirmed the presence of the main chain methine hydrogen of the L-lactide (at 5.03 ppm) and the presence of the methylene protons of the PEG (at 3.65 ppm), and therefore, indicating the formation of a PLLA-b-PEG block copolymer. In addition, the signal at 4.35 ppm, resulting from the acylation of a terminal $\text{O}-\text{CH}_2-\text{CH}_2\text{-PEG}$ of a PEG, is also present, confirming the PEG-block-PLLA junction.

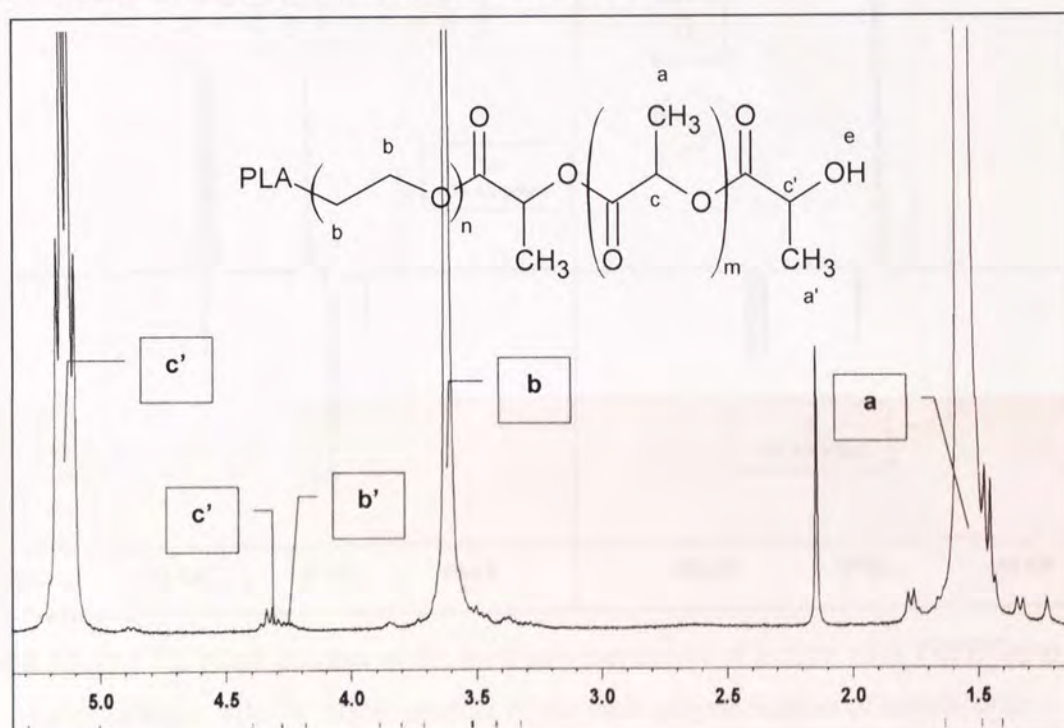


Figure 8.11: ^1H NMR product of the lactide melt polymerisation with the condensation product obtained from PEG_{NH_2} and $\text{Ti}(\text{O}-i\text{-Pr})_4$.

The presence of a methylene carbon at 64.48 ppm, see figure 8.12, belonging to a PEG chain immediately adjacent to a lactide unit, was also observed by comparison of the ^{13}C NMR spectrum of the purified product obtained using $\text{Ti}(\text{PEG})_2$ (figure 8.12 (B)) with a ^{13}C NMR spectrum of a PLLA-co-PEG copolymer generated using $\text{Ti}(\text{PEG}_{400})_2$ as a macro-initiator (figure 8.12 (A)).

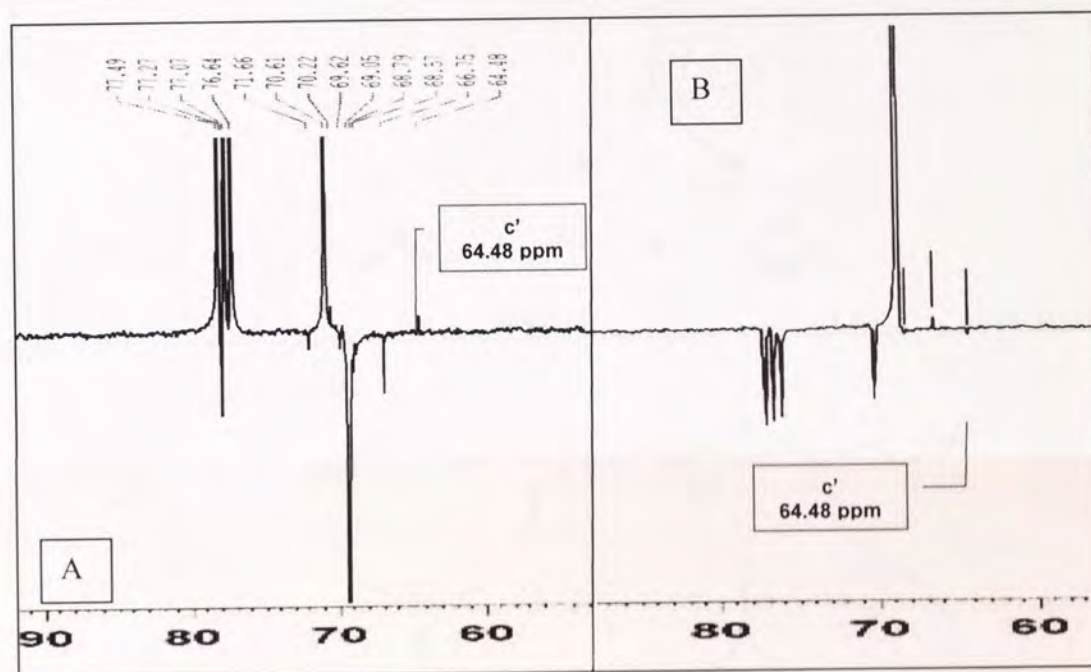
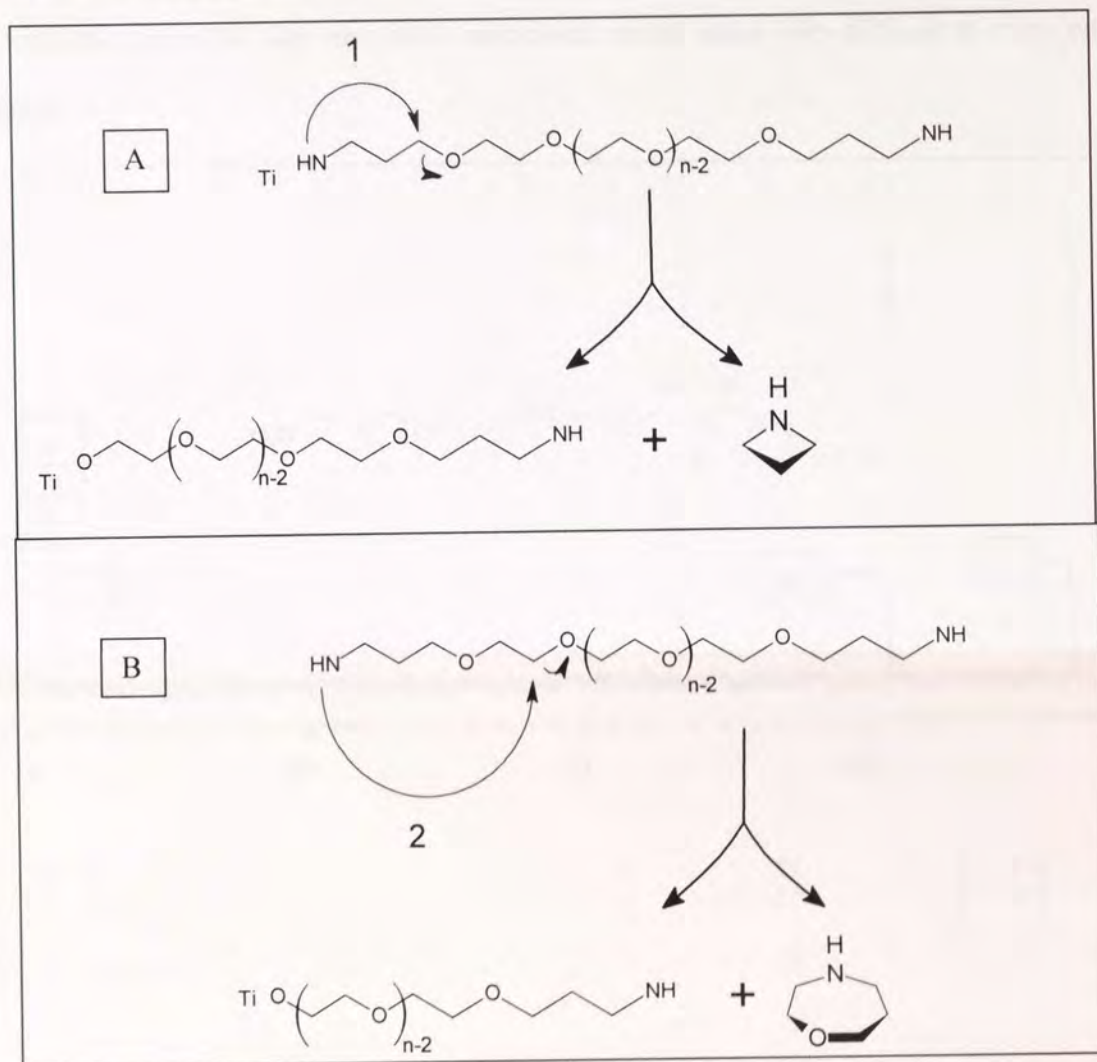


Figure 8.12: (A) ^{13}C NMR product of the melt polymerisation of lactide with $\text{Ti}(\text{PEG})_2$ as a macro-initiator. (B) ^{13}C NMR product of the melt polymerisation of lactide with $\text{Ti}(\text{PEG}_{400})_2$ as a macro-initiator.

The combination of ^1H and ^{13}C NMR spectra proved that the initiation of the ring opening polymerisation of lactide using $\text{Ti}(\text{PEG})_2$ took place *via* the attack of a terminal $\text{O}-\text{CH}_2$ of the PEG at the carbonyl group of the lactide. The initiation of the lactide *via* a terminal $\text{O}-\text{CH}_2$ suggests that either the terminal amino alkyl chain was eliminated or rearranged in the middle of the chain when the $\text{Ti}(\text{PEG})_2$ macro-initiator was heated. Elimination or rearrangement of the amino alkyl chain could have been produced *via* inter or

intra transesterification reactions of the amino terminated PEG onto a CH₂ near an oxygen. The elimination of a terminal alkyl chain would lead to the generation of cyclic by-products, as shown in scheme 8.9 (A) and (B).



Scheme 8.9: (A) Proposed mechanism 1 for the elimination of a terminal alkyl chain of the PEG macro-ligand during the drying period of Ti(PEG)₂ at 160 °C. (B) Proposed mechanism 2 for the elimination of a terminal alkyl chain of the PEG macro-ligand during the drying period of Ti(PEG)₂ at 160 °C.

The generation of these cycles, *via* attack of the lone pair of electrons on the terminal NH on a methylene carbon near an oxygen in the PEG chain, is unlikely, since the signal associated with the methylene carbons of the amino alkyl chain would be absent from the ¹³C

NMR spectrum of the purified product. Three signals associated with methylene alkane carbons at 37.47, 29.68 and 28.99 ppm are present in the ^{13}C NMR spectrum of the purified product, as seen in figure 8.13 (B). The formation of four membered ring cycles, scheme 8.9 (A), is unlikely, since the high ring strain associated would make very difficult to carry out ring closure.

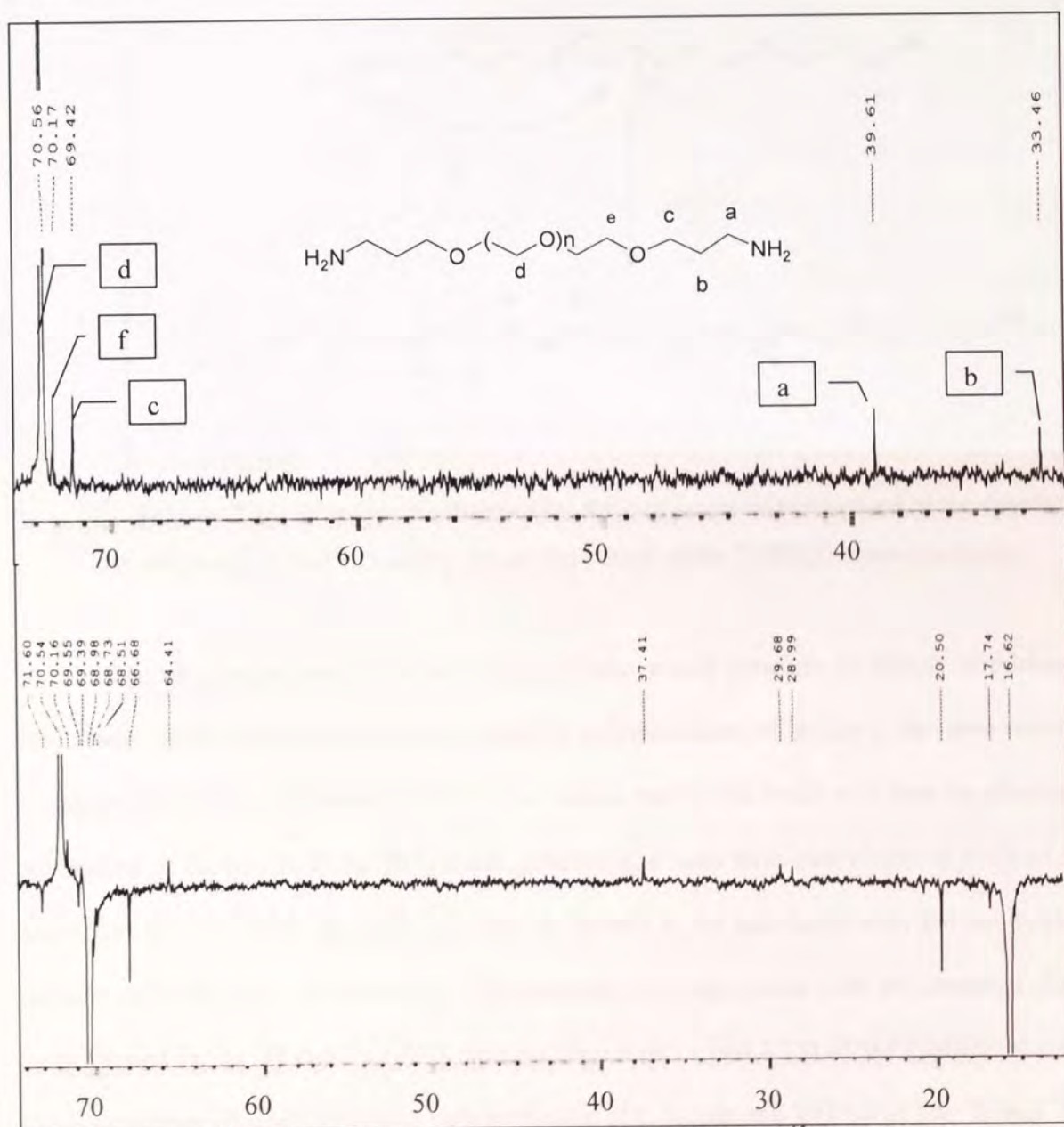
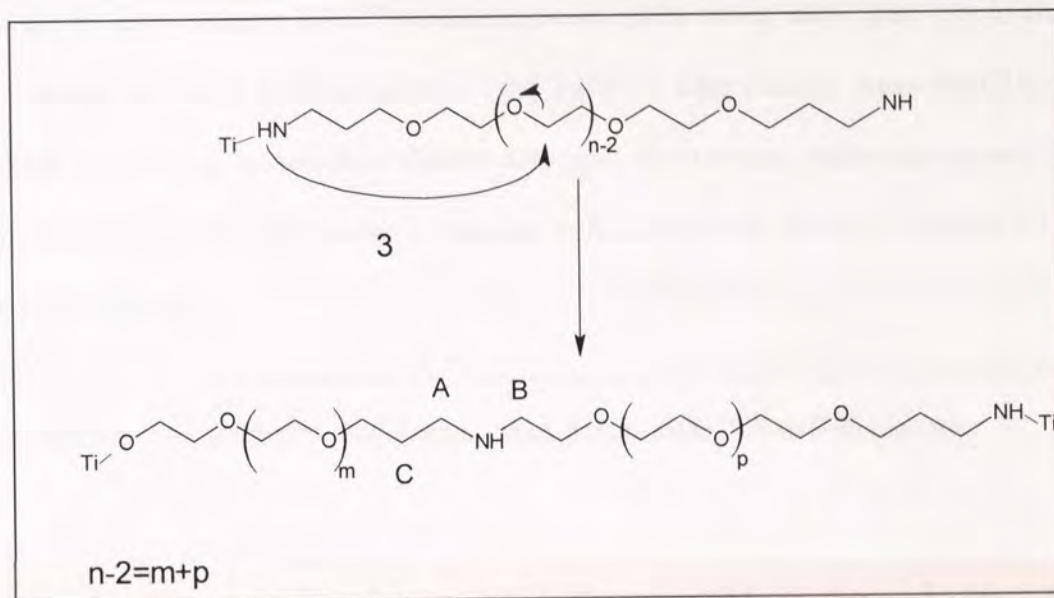


Figure 8.13: (A) ^{13}C NMR spectrum of the unreacted PEGNH_2 . (B) ^{13}C NMR spectrum of the product obtained from the melt polymerisation of lactide with $\text{Ti}(\text{PEG})_2$ as a macro-initiator.

Intra-molecular reactions of the terminal amino group of the PEG chain during heating of the macro-initiator could also cause re-arrangement of the amino alkyl chain within the PEG chain, as shown below in scheme 8.10.



Scheme 8.10: Proposed mechanism for the intra-molecular reactions of the terminal amino group of the PEG during the drying period of the $\text{Ti}(\text{PEG})_2$ macro-initiator.

The re-arrangement of the amino alkyl chain would generate an alkoxy terminated PEG chain, which would initiate the ring opening polymerisation of lactide in the same way as a commercial hydroxyl terminated PEG. The amino part of the chain will then be allocated somewhere in the middle of the PEG chain, generating at least three new chemical shifts (A, B and C) in the ^{13}C NMR spectrum (as seen in scheme 8.10) associated with the methylene carbons near the amino functionality. This postulate is in agreement with the chemical shift values found in the ^1H and ^{13}C NMR spectra (figure (8.11 and 8.13) of the purified PLLA-PEG copolymer obtained from melt polymerisation of L-lactide and $\text{Ti}(\text{PEG})_2$. The ^1H and ^{13}C NMR chemical shifts of the PLLA-co-PEG copolymer were assigned as follows; ^1H NMR, 5.11 ppm (He), 4.35 ppm (He'), 4.25 ppm (Hd'), 3.62 ppm (Hd), 1.55 ppm (Hf), 1.47 ppm

(Hf') and 1.44 ppm (Hf''). ^{13}C NMR, 175.2 ppm (Ch'), 170.09 (Ch''), 169.65 (Ch), 71.76 ppm (Ce''), 70.61 (Cd), 70.22 (Cd1), 69.05 ppm (Ce) 66.75 ppm (Ce'), 66.48 ppm (Cd'), 37.47 ppm (CB), 29.74 ppm (CA), 20.57 ppm (CC), 17.81 ppm (Cf'), 16.69 ppm (Cf). An illustration of the different types of hydrogen and carbon atoms within the PLA-co-PEG copolymer can be seen in figure 8.14. The rearrangement of the amino alkyl chain would also explain the change in the ^1H NMR spectrum of the $\text{Ti}(\text{PEG})_2$ after heating, when the CH_2 of the alkyl chain at 3.50 ppm moved down field to 4.05 ppm. The terminal methylene protons of the PEG shifted down field when bonded to titanium as macro-ligands, as seen in section 7.3.1 with PEG_{350} and PEG_{400} .

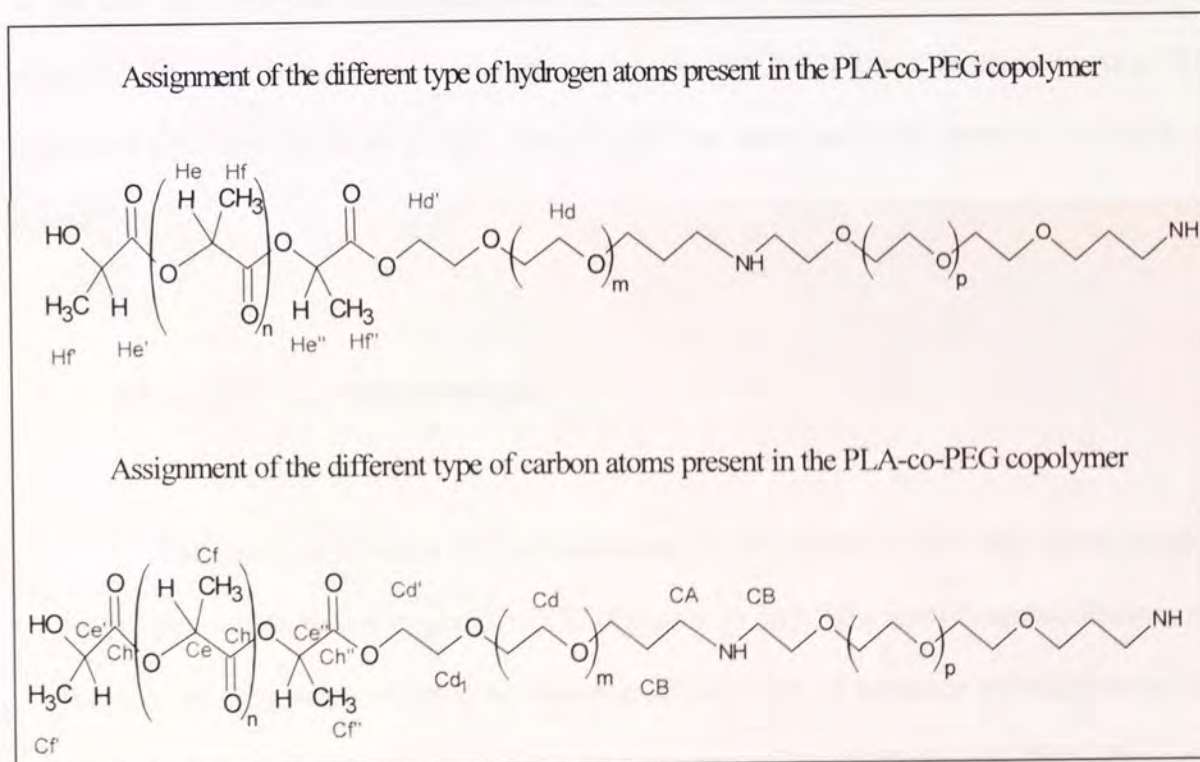


Figure 8.14: Assignment of the different type of hydrogen and carbon atoms present in the PLA-co-PEG copolymer obtained from the melt polymerisation of L-lactide with $\text{Ti}(\text{PEG})_2$.

The re-arrangement of the amino alkyl chain could take place through both terminal ends. The model has been developed for one end in order to facilitate of the mechanism and the structure of the copolymer. It is very likely that both ends undergo similar reactions and therefore initiate the ring opening polymerisation of lactide producing tri-block copolymers of PEG and LA.

Inter-transesterification reactions of the terminal amino group could also occurred when the macro-catalyst was further heated at high temperature. This would cause an increase of the M_n PEG and the incorporation of the amino alkyl chain within the PEG backbone structure. The number average molecular weight of the PEG would increase having NH instead of O-CH₂ as terminal groups. This supposition seems unlikely, however, it is still a possibility.

8.5.2 GPC characterisation

The products obtained by step-controlled polymerisations were also characterized by gel permeation chromatography, GPC (figure 8.15 (A)). The use of macro-initiators in the ring opening polymerisation of lactide gave polymers of narrower polydispersities in the case of di-block, than those obtained by all-in-one polymerisations with Ti(O-*i*-Pr)₄ and PEG₃₅₀ (table 7.1). The opposite effect is observed when tri-block copolymers are synthesised using Ti(PEG₄₀₀)₂ as an initiator. This may arise from the poor solubility that Ti(PEG₄₀₀)₂ shows on the molten lactide. The same feature has been observed when D,L-lactide copolymers are synthesised. L-LA copolymers show in every case narrower P_d 's

than D,L lactide copolymers, possibly because of the different origin of the lactides. Whereas L-lactide, laboratory grade, was purchase from Purac and therefore is highly pure, D,L-lactide, industrial grade, was supplied by Chargill and contain higher amount of impurities. Impurities in lactide can easily broaden the polydispersity, by causing early termination or exchange reactions with the initiator, which then could slow down the rate of propagation.

Star-shaped copolymers of L-lactide showed a bi-modal distribution, as seen in figure 8.15 (B). The reason for this bi-modality could arise from the small amount of remaining iso-propoxide groups, which may act as co-initiators. Bimodality disappears in the case of star shaped D, L-lactides. As the polymerisation proceeded, the shoulder in the MWD curve distribution disappears, probably due to intermolecular transesterification reactions, which gradually randomised chain lengths.

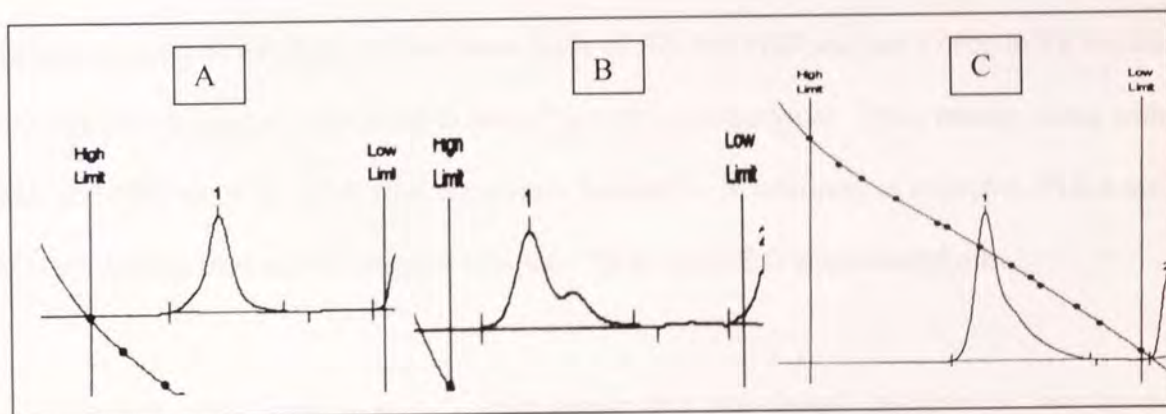


Figure 8.15: (A) GPC chromatogram of a PLLA/PEG di-block copolymer. (B) GPC chromatogram of a star-shaped PLLA. (C) GPC chromatogram of PLLA-co-PEG block copolymer generated from di-amino terminated PEG.

Poly(lactide) block copolymers generated from di-amino terminated PEG showed a unimodal MWD with a presence of a shoulder, as seen in figure 8.15 (C). GPC analysis also shows the absence of oligomer formation. A list of the molecular weights obtained is displayed on table 7.1. Analysis of GPC results is discussed later in section 7.7.

8.5.3 DSC Characterisation

DSC analysis was carried out on some of the PLLA-PEG block copolymers, as described in section 2.3.3. When synthesising block co-polymers, by combining a high melting block A with a low melting block B, a material with a lower T_g for A and higher T_g for B would be obtained. The change in T_g in co-polymers is rather variable and depends on the nature of the monomer used, as well as the arrangements of the blocks³. The thermal data of the co-polymers is shown in table 8.2. The lactide copolymers, linear and star-shaped, synthesised using titanium macro-initiators made of flexible PEG showed a drop in T_g for the more rigid block (lactide) compared to that of lactide homo-polymer. These results, along with NMR and GPC analysis, confirmed copolymer formation. In addition, as expected, PLLA-co-PEG copolymers were semicrystalline whereas PDLLA-co-PEG were amorphous.

Studies carried out by Kim⁹⁷ have shown that star-shaped copolymers have lower melting temperatures and higher cold-crystallisation temperatures than the linear equivalents. In agreement with studies reported by Kim, the melting temperatures of the star-shaped L-lactide copolymer synthesised using titanium macro-initiators is slightly lower than those of linear ones. The small decrease in melting temperature is likely to be related to the much

higher molecular weight of the star-shaped copolymer compared to linear ones. Melting temperatures vary slightly with molecular weight. No crystallisation temperature was shown for linear L-lactide copolymers or homopolymers, besides the semicrystalline nature of L-lactide polymers. However, crystallisation seems to improve for the L-lactide star shaped copolymer since a cold crystallisation temperature of 97 °C was measured.

Monomer	Polymer	[C]/[M]	Mn _{GPC} / g.mol ⁻¹	Mn _{NMR} / g.mol ⁻¹	DSC T _g	DSC T _c	DSC T _m
L-lactide	PLLA	200/1	16600	6900	61		166
l-lactide	PLLA-PEG	200/1	16600	7550	57.8		167.6
l-lactide	PLLA-PEG-PLLA	200/1	11400	14500	39.4		167
l-lactide	PLLA-Pt 270	200/1	35100	26800	48	97	166
D,l-lactide	PLLA				58		amorphous
D,l-lactide	PDLLA-PEG	200/1	15900	7690	42		amorphous
D,l-lactide	PDLLA-PEG- PDLLA	200/1	7120	14200	53		amorphous
D,l-lactide	PDLLA-Pt 270	200/1	34600	28500	47.2		amorphous

Table 8.2: DSC results for PEG-block-PLA co-polymers.

The glass transition temperature of a polymer (T_g) is dependent on its molecular weight. Therefore, since the synthesised copolymers had different molecular weights, a direct relationship between the number of co-initiators arms and T_g of the co-polymer cannot be established.

8.6 CHARACTERISATION OF PLA-BLOCK-PCL

COPOLYMERS.

Synthesis of lactide/caprolactone block copolymers was confirmed by ^1H NMR. The ^1H NMR spectrum (Figure 8.16) established the formation of a lactide/PCL copolymer by the presence of the methine hydrogen of the lactide at 5.03 ppm (labelled as "a" in figure 8.16) and the presence of the methylene protons of the PCL adjacent to the ester group at 4.04 ppm (labelled as "d" in figure 8.16).

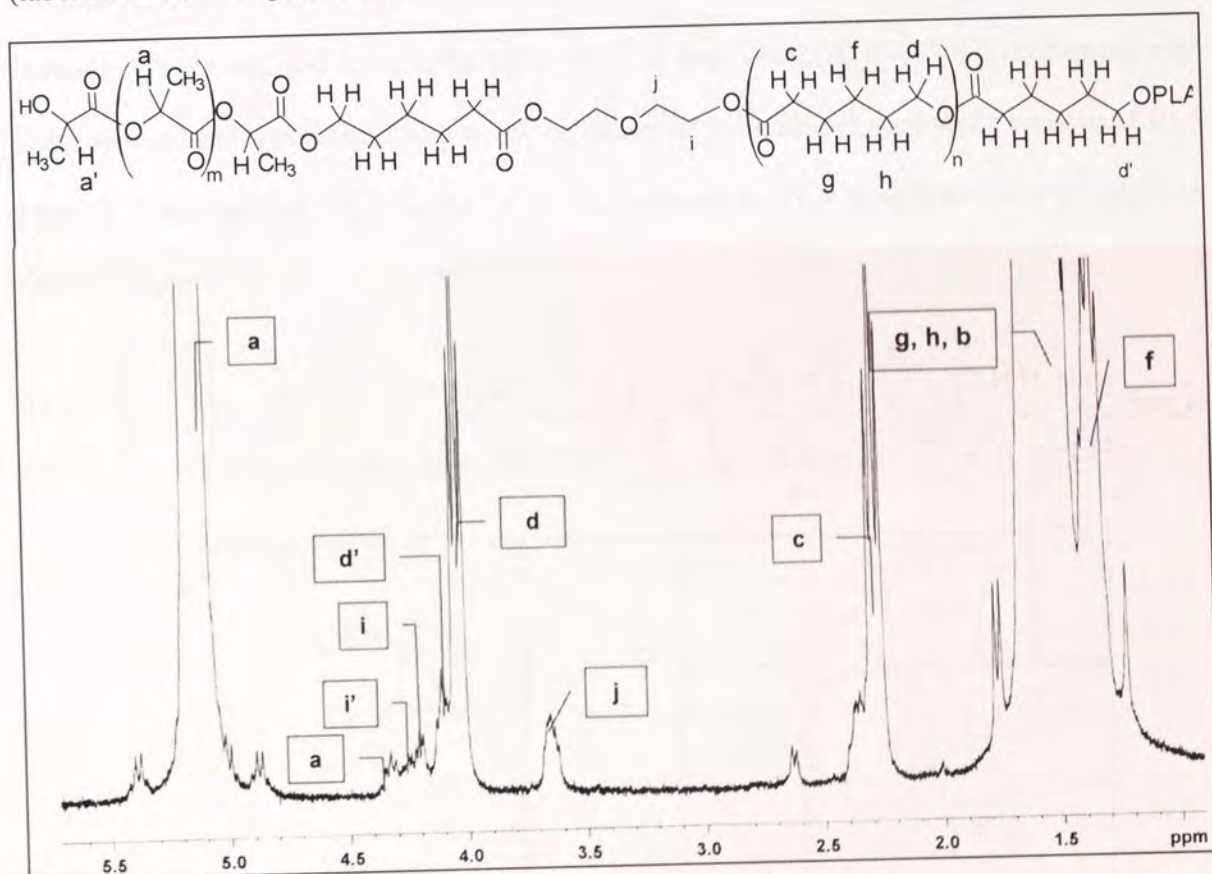


Figure 8.16: ^1H NMR of PLLA-PCL-PLLA.

The presence of a new proton signal at δ 4.10 ppm ("d'" in figure 8.16), corresponding to the terminal OCH_2 methylene group of a ϵ -CL adjacent to a LA moiety, clearly demonstrated the formation of PLA-PCL copolymer. Furthermore, the chemical shifts corresponding to the acylation of the terminal methylene protons of the initiator for the synthesis of the commercial PCL ($\text{PCL-O-CH}_2\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O}$, also labelled as "i'" at 4.24 ppm are also present. The terminal methylene protons were generated due to the intermolecular transesterification side-reactions occurring during the synthesis of the titanium macro-initiator. The formation of a block copolymer was also confirmed by ^{13}C NMR. The ^{13}C NMR spectrum (figure 8.17) showed the chemical shifts of the carbonyl sequences belonging to the CL and LA blocks, CCC at 173.5 ppm and LLL at 169.6 ppm respectively. The chemical shifts corresponding to the acylation of the terminal methylene carbons at 63.5 ppm ("i'") and the methylene carbon of an ϵ -CL adjacent to a LA moiety at 65.2 ("d'") ppm can also be detected.

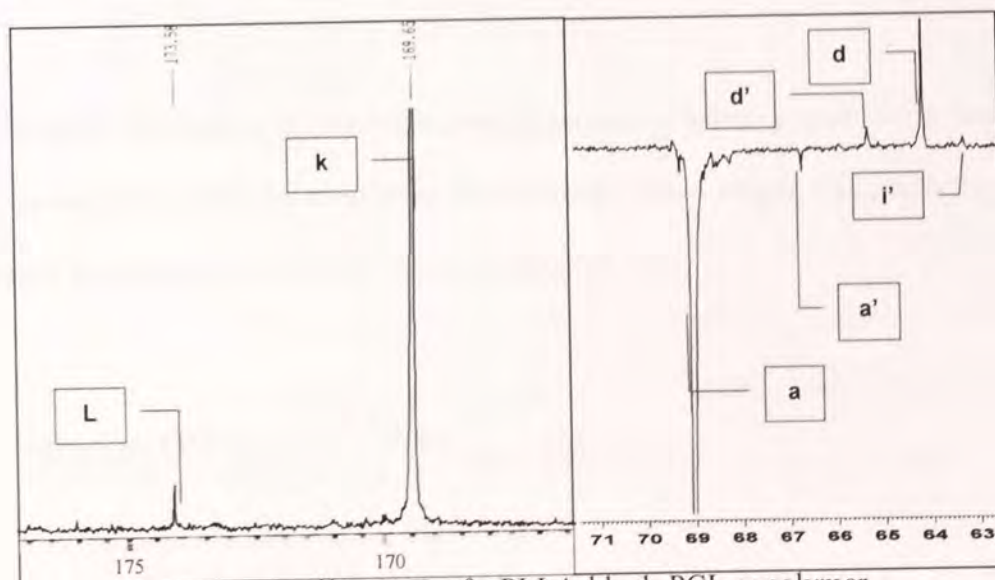
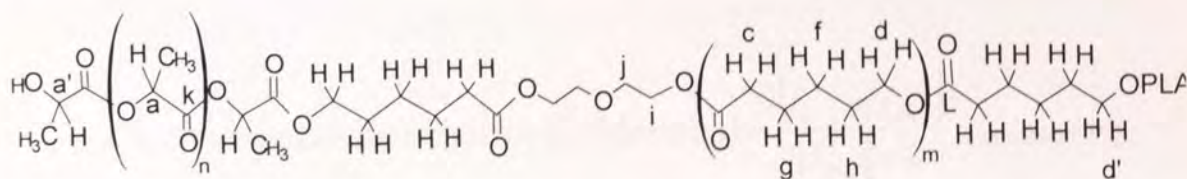


Figure 8.17: ^{13}C NMR of a PLLA-block-PCL copolymer.

8.7 DETERMINATION OF THE DEGREE OF POLYMERISATION FOR LACTIDE COPOLYMERS USING ¹H NMR SPECTROSCOPY.

¹H NMR was used to calculate the average polylactide chain lengths, CL. CL was calculated by comparing the peak integral of chain methine protons (5.10 ppm), with those of methine protons next to the terminal hydroxyl group (4.35 ppm). This gives the length of the polymer in polylactic acid units (equation 7.1). It should be divided by two in order to obtain the chain length in lactide units (equation 7.2).

$$CL_{Lac} \text{ (Average chain length in lactic acid units)} = \frac{[I_{Hc} + I_{Hc'}]}{[I_{Hc'}]}, \text{ Equation 8.1.}$$

$$CL \text{ (Average chain length in lactide units)} = \frac{[I_{Hc} + I_{Hc'}]}{[I_{Hc'}] \times 2}, \text{ Equation 8.2.}$$

¹H NMR was used to calculate the average number of hydroxyl groups that took part in the polymerisation process by comparing the theoretical chain length, CL_{th}, with the average chain length determined by ¹H NMR, CL, as in equation 7.3

$$\text{Initiating OH (I}_{OH}) = \frac{CL_{th}}{CL} \cdot I_{OHth}, \text{ Equation 8.3.}$$

In the equation 8.3, I_{OHth} represents the maximum number of initiating OH groups, which in the case of the ring opening polymerisation of lactide in the melt with different titanium macro-initiators was four.

8.8 RESULTS AND DISCUSSION

The bulk polymerisation of L-LA with titanium alcoholates with different numbers of hydroxyl groups generally gave very high conversions. The only exception was found with the ring opening polymerisation of D,L lactide with $Ti(PEG_{400})_2$, where conversions were low. This may be because of the poor solubility of the macro-initiator in the lactide melt. Polymerisation results are summarised in table 8.3. As observed in solution polymerisation, an increase in the number of arms of the alcoholate did not cause a drop in the maximum conversions or cause backbiting during the extended polymerisation time. Reaction times to reach complete monomer conversion were very short and remained the same as those observed for all-in-one polymerisations of lactide and PEG's in the melt.

The polydispersity of the synthesised block copolymers is relatively narrow although it appeared to increase when the solubility of titanium macro-initiator in the molten D,L-lactide was poor. The MWD also increased when D,L lactide was used instead of L-lactide. This may arise from the presence of a higher concentration of impurities in industrial grade lactides. The broad polydispersity observed when block copolymers of lactide and ϵ -caprolactone are synthesised was caused by intermolecular reactions that took place during the synthesis of the titanium PCL macro-initiator.

Monomer	Macro-initiator	[C]/[M]	Reaction Time/min	% Conversion	PD	Mn _{GPC} /g.mol ⁻¹	Mn _{NMR} /g.mol ⁻¹	CLth	CL	I _{OHth}	I _{OH}
L-lactide	Ti(O- <i>i</i> -Pr) ₄	200/1	60	>99	1.75	16600	6900	50	46	4	4.34
L-lactide	Ti(PEG ₃₅₀) ₄	200/1	150	94	1.20	16600	7550	46.8	52	4	3.6
L-lactide	Ti(PEG ₄₀₀) ₂	200/1	120	90	2.1	11400	14540	45	49	4	3.67
L-lactide	Ti(PP270)	200/1	120	99	1.48	35100	26770	48.1	46	4.12	4.31
L-lactide	Ti(PCL ₁₂₅₀) ₂	200/1	90	95	2.9	36500	24800	47.5	69	4	2.76
L-lactide	Ti(PEG) ₂	200/1	300	77	1.56	9100	NA	NA	26.2	NA	NA
D,L-lactide	Ti(PEG ₃₅₀) ₄	200/1	120	>99	2.06	15900	7690	50	51	4	3.92
D,L-lactide	Ti(PEG ₄₀₀) ₂	200/1	120	40	3.73	7100	14220	20	48	4	1.66
D,L-lactide	Ti(PP270)	200/1	120	>99	2.11	34600	28490	48.1	49	4.12	4.04

Table 8.3: Polymerisation results of lactide with different titanium macro-catalyst.

NA: Not applicable

The number of hydroxy groups active in the initiation of lactide is close to four for the polymerisation of lactide with $\text{Ti(PEG}_{350}\text{)}_4$, $\text{Ti(PEG}_{400}\text{)}_2$ and $\text{Ti(PEG}_{270}\text{)}_2$. In the case of $\text{Ti(PEG}_{270}\text{)}_2$ the theoretical chain length, CL_{Th} , and the theoretical number of active hydroxyl groups, I_{OHth} , were calculated based on results obtained from ^{13}C solid state NMR, a technique which is no as accurate as ^1H NMR. This could be the reason why the number of active hydroxyl groups was slightly higher than the theoretically possible. For the lactide/ ϵ -caprolactone block copolymers the number of active initiating centres was close to three, lower than those obtained with polyglycolates. The solubility of the PCL macro-initiator in the molten L-lactide was poor, which might have prevented some of active PCL from reacting. Finally, the number of theoretically active initiating groups of the Ti(PEG)_2 could not be calculated since it is not known the extend of the intermolecular reactions. It is not possible to confirm whether any remaining amino terminated PEG could have initiated the lactide homopolymerisation. Consequently, the theoretical chain length for the PLLA-co-PEG could not be calculated either.

CONCLUSION AND FURTHER WORK

The catalysts, tetra-alkyltitanates, are highly active towards polymerisation of L-lactide in toluene solution, where monomer conversions over 95% were reached and polymers of relatively narrow polydispersities were produced. No oligomer formation was detected using liquid chromatography (GPC) or NMR spectroscopy. The length and the steric bulk of the alkoxy group considerably influence the rate of the polymerisation, the fastest initiator of those studied being $\text{Ti}(\text{O-Pr})_4$. The initiators can be placed in order of decreasing activity based on their conversion in given reaction time; $\text{Ti}(\text{O-Pr})_4 > \text{Ti}(\text{O-}i\text{-Pr})_4 = \text{Ti}(\text{O-Bu})_4 > \text{Ti}(\text{O-2-Et-Hex})_4 > \text{Ti}(\text{O-}t\text{-Bu})_4$. It can also be seen that both the length and the steric bulk of the alkoxy group affect the degree of polymerisation. Polymerisations carried out with $\text{Ti}(\text{O-}i\text{-Pr})_4$ and $\text{Ti}(\text{O-Bu})_4$ as initiators gives products of the same the same degrees of polymerisation, which correspond to the theoretical degree of polymerisation expected if all four arms were active. Degrees of polymerisation greater than those expected, for four active arms, were obtained in the case of $\text{Ti}(\text{O-Pr})_4$, $\text{Ti}(\text{O-2-Et-Hex})_4$ and $\text{Ti}(\text{O-}t\text{-Bu})_4$. In the case of $\text{Ti}(\text{O-Pr})_4$, the majority of the four alkoxy groups of the initiator are active in the polymerisation of lactide and only a very small percentage of alkoxy groups remained inactive. As seen in the *in situ* ^1H MNR spectrum of the reaction mixture, the chemical shift of the methylene hydrogens of the propoxide ligands in the unreacted $\text{Ti}(\text{O-Pr})_4$ shifted upfield because of the altered chemical environment of the titanium created by the active polymer chains, which were also bound to the titanium during the propagation step.

In the case of the $\text{Ti}(\text{O}-2\text{-Et-Hex})_4$ *in-situ* Multizg ^1H NMR spectroscopic studies showed the higher Dp observed in the ring opening polymerisation of lactide was caused by a poorer efficiency of the initiator. One reasonable explanation of the lower efficiency of this initiator could result from the slow initiation caused by the steric bulk of the alkoxy group. The sensitivity of this catalyst to water and impurities makes this polymerisation less reproducible.

A slightly different behaviour was observed when $\text{Ti}(\text{O}-t\text{-Bu})_4$ was used as an initiator for the polymerisation of L-lactide. The use of $\text{Ti}(\text{O}-t\text{-Bu})_4$ as an initiator yielded polymers with broad polydispersities, which were ascribed to the bulkiness of the *tert*-butoxide group of the initiator causing slow initiation of the polymerisation, as well as a more inconsistent degree of polymerisation. The concentration of the initiator, $\text{Ti}(\text{O}-t\text{-Bu})_4$, played an important role in controlling the reaction and allowed the degree of polymerisation to be predicted. Molar concentrations of $\text{Ti}(\text{O}-t\text{-Bu})_4$ above 0.004 mol/dm^3 were preferable to obtain higher efficiencies and better control of the polymerisation.

A more detailed study on the polymerisation of L-lactide with titanium alkoxides was carried out using $\text{Ti}(\text{O}-i\text{-Pr})_4$ as an initiator in order to confirm some of the features that characterise a living system. A linear relationship of the number average molecular weight (M_n) against monomer conversion was confirmed. In addition, a linear dependence of the degree of polymerisation on the $[\text{M}]/[\text{I}]$ molar ratio was also observed, which allowed the synthesis of poly(lactides) with the pre-determine molecular weight. The linear relationship between molecular weight and monomer conversion indicates an absence of termination and

transfer reactions as the monomer is consumed. Intermolecular trans-esterification reactions were only detected at very high conversions, broadening slightly the polydispersity.

In order to mimic industrial polymerisations, the ring opening polymerisation of lactide was carried out in the melt, using either $\text{Ti}(\text{O-Pr})_4$ or $\text{Ti}(\text{O-}i\text{-Pr})_4$ as initiator. As was seen in the polymerisations carried out in solution, both initiators showed a linear dependence of the number average molecular weight (M_n) with monomer conversion and a linear dependence of D_p on $[\text{M}]/[\text{I}]$ molar ratio, which gives good control over molecular weight. Both initiators, ($\text{Ti}(\text{O-Pr})_4$ or $\text{Ti}(\text{O-}i\text{-Pr})_4$), showed very similar reaction times to a given conversion, which in both cases were a function of the $[\text{M}]/[\text{I}]$ molar ratio used. As expected, the rate of polymerisation of lactide in the melt is faster than that obtained in solution. Molecular weights (M_n) up to 75,000 g/mol can be achieved after 2 hours. Characterisation by GPC confirmed that no oligomer formation was detected and that the polydispersities of the polymers synthesised using $\text{Ti}(\text{O-}i\text{-Pr})_4$ (PD's 1.2-1.5) as an initiator were slightly narrower than those obtained when $\text{Ti}(\text{O-Pr})_4$ was used (PD's 1.4-1.9). The presence of a trace of impurity contained in $\text{Ti}(\text{O-Pr})_4$ could have caused early termination in the propagation step, preventing some alkoxy ligands from reacting or/and generating transfer reactions, which would lead to an increase in the polydispersities of the synthesised polymers.

In conclusion, the ring opening polymerisation of the lactide, using titanium alkoxides as initiators, can be described as the nucleophilic attack of the alcoholate active species on the monomer ester group, followed by the acyl-oxygen bond scission. Ions are presumably not involved in these polymerisations and the monomer addition proceeds *via* the concerted

insertion into the metal-oxygen bond. This mechanism can be applied to both solution and bulk polymerisations as seen in scheme 4.1.

Results obtained in this work differ in some aspects from studies carried out by Kricheldorf ³⁰, in which $\text{Ti}(\text{O-Bu})_4$ was used as an initiator for the melt polymerisation of lactide. The degree of polymerisation obtained by spectroscopic end group analysis of the melt polymerisation product using $\text{Ti}(\text{O-Bu})_4$ was twice as high as the those obtained in this work when $\text{Ti}(\text{O-Pr})_4$ and $\text{Ti}(\text{O-}i\text{-Pr})_4$ were used as initiators. The higher Dp and longer reaction times (up to 48 hours) seen by Kricheldorf may be attributed to a lower purity of the monomer.

All-in-one co-polymerisation of lactide and ϵ -caprolactone with $\text{Ti}(\text{O-}i\text{-Pr})_4$ in solution yielded copolymers of short length blocks, very close to being random. These copolymers are classified as tapered co-polymers and consist of short blocks of any monomer, in this case LA and ϵ -CL, which were randomised by either a similar rate of polymerisation of each monomer, transesterification reactions or both. Sequential polymerisation of lactide and ϵ -caprolactone pre-polymer using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator led to the synthesis of block copolymers of lactide and ϵ -caprolactone. On the contrary, when sequential polymerisation of ϵ -caprolactone with lactide pre-polymer was investigated, formation of tapered copolymers occurs preferentially to block copolymers, due to the presence of trans-esterification reactions. This suggests, the ϵ -hydroxyl caproyl end groups generated during the co-polymerisation of ϵ -caprolactone with pre-polymers of lactide are reactive towards the ester groups in the polymer chains, generating trans-esterification reactions.

The synthesis of lactide/PEG block and star-shaped copolymers was carried out by one step and two step processes. All-in-one polymerisations (one-step process) of lactide using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator and PEG's with different number of hydroxyl groups as co-initiators were carried out. Partial iso-propoxide/PEG exchange is produced leading to the synthesis of both poly(lactide) and poly(lactide-block-(polyethylene glycol)). An increase in the PEG concentration (hydroxyl group content) did not cause a decrease in the maximum conversions or cause backbiting during extended polymerisation times. However, an increase in the PEG concentration caused a decrease in the molecular weight, which suggests that the M_n is controlled by the number of potential chain ends. Since the ratio of the co-initiator to lactide controls the molecular weight of the polymer, the amount of co-initiator must be low when high molecular weight polymers are prepared.

Consequently, a step controlled polymerisation, in this case a two-step process, is necessary to selectively synthesise block and star-shape copolymers of lactide and PEG. In the first step titanium macro-initiators were synthesised by exchanging the iso-propoxide ligands by PEG with different numbers of hydroxyl groups. The titanium macro-initiators were characterised by NMR spectroscopy. The second step involved the ring opening polymerisation of lactide using the titanium macro-initiator that was previously prepared as an initiator. The polymerisations, carried out in a solventless medium, yielded block and star-shaped co-polymers of lactide and polyethylene glycol. The synthesised co-polymers of lactide and PEG showed a drop in T_g for the more rigid block (lactide) compared to that of lactide homo-polymer. As predicted, PLLA-co-PEG copolymers were semicrystalline,

whereas those of PDLLA-co-PEG were amorphous. The rates of reactions of the polymerisation of lactide with titanium macro-initiators bearing PEG ligands was in the order of those obtained for the all-in-one polymerisation of lactide using $\text{Ti}(\text{O-}i\text{-Pr})_4$ as an initiator and hydroxyl-terminated poly(ethylene glycol)s as co-initiators. High monomer conversions were reached with the exception of the reaction carried out using D,L-lactide and $\text{Ti}(\text{PEG})_{400}$ as a macro-initiator.

The same approach was followed to prepare block copolymers of lactide and ϵ -caprolactone. A di-hydroxyl-terminated PCL was used to synthesise titanium macro-initiators containing two PCL polymer chains, following the same procedure that was used with hydroxyl-terminated PEG's. Block copolymers of lactide and ϵ -caprolactone were successfully prepared. However, the polydispersity of the lactide/ ϵ -caprolactone block copolymer remained high because trans-esterification reactions of the PCL chains occurred during the preparation of the $\text{Ti}(\text{PCL})_2$ macro-initiator.

The polydispersities of the lactide co-polymers prepared by sequential polymerisation are variable and seem to be dependent on the miscibility of the monomer with the titanium macro-initiator.

In conclusion, the use of PEG multi-arm co-initiators allowed vast improvements in the molecular weight of the poly(lactides) with values four times greater than those of the homo-polymer prepared using $\text{Ti}(\text{O-}i\text{-Pr})_4$. The decrease in the glass transition temperature of the multi-arm poly(lactide) results in the formation of a more flexible, crystalline material.

Further study of the polymerisation of L-lactide with $\text{Ti}(\text{O-Pr})_4$ or $\text{Ti}(\text{O-}i\text{-Pr})_4$ in the melt using monomer to initiator molar ratios greater than 2400/1 should be conducted as this may also lead to an increase in molecular weight of lactide homopolymers. This would allow the preparation of poly(lactides) with molecular weights as high as those produced using tin octanoate.

The use of lower temperatures in the drying step of the synthesis of the titanium macrocatalyst produced when *O,O'*-bis(3-aminopropyl)polyethylene glycol was used as a ligand may prevent the unwanted side reactions, thereby allowing a more controlled polymerisation in the sequential step.

Physical properties, such as T_g , tensile strength, % of elongation at break and tear strength, of the blends made of homo-polymers and co-polymers of lactide should be investigated and compared to those of the individual polymers to determine any associated benefits.

Other biocompatible hydroxy terminated building blocks could also be tested using either a one-step (all-in-one polymerisation) or two-step (step controlled polymerisation) pathway to prepare lactide copolymers.

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