DECLARATION

Certified that the work incorporated in this thesis **“Synthesis of Biodegradable Poly(Lactic Acid) Polymers”** submitted by Mr. Subarna Shyamroy was carried out by the candidate under my supervision. Such materials as have been obtained from other sources have been duly acknowledged.

(S. Sivaram)
Research Supervisor

Acknowledgement

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(SUBARNA SHYAMROY)

PUBLICATIONS

1. S. Shyamroy, B. Garnaik and S. Sivaram
   Formation of macrocycles of lactic acid by dehydro-polycondensation with tetraphenyltin and terabutyl dichlorodistannoxane catalysts
   Macromolecules
   (Manuscript under preparation)

2. S. Shyamroy, B. Garnaik and S. Sivaram
   Room temperature post-polycondensation of L-lactic acid oligomers
   Macromolecules
   (Manuscript under preparation)

3. S. Shyamroy, B. Garnaik and S. Sivaram
   High molecular weight poly(lactic acid) from telechelic oligomers using bis-lactone and bis-carbonate coupling agents,
   J. Polym. Sci., Part A: Polym. Chem. ed.
   (Manuscript under preparation)

4. S. Shyamroy, B. Garnaik and S. Sivaram
   Copolymerization of L-lactic acid with 12-hydroxystearic acid by dehydro-polycondensation reaction, **Chemistry of Materials**
   (Manuscript under preparation)

ABSTRACT

The thesis presents the results of dehydropolycondensation of L-lactic acid into poly(lactic acid) (PLA) oligomers, followed by postpolymerization by several means. The dehydropolycondensation was achieved under different reaction conditions of temperature and solvents and using Lewis acid catalysts. The oligomeric products of such dehydropolycondensation were characterized for their thermal and crystalline properties as well as for molecular weight and end groups, using SEC, DSC, powder XRD, NMR and MALDI-ToF spectroscopy. It has been found that properties of PLA oligomers as well as molecular weights can be controlled by varying these reaction parameters. The identity of end groups is of importance for the success of any postpolymerization process.

Formation of macrocylcic oligomers was identified under certain reaction conditions. The probability of macrocycles formation was found to increase with increasing reaction temperature and with the use of solvent in performing the dehydropolycondensation reaction. Reactions done either at temperatures below 150 °C or at higher temperatures but without solvent were found to result in linear oligomers with both hydroxyl and carboxylic acid end groups. Dehydropolycondensation performed at 190 °C was found to give rise to racemizaiton of the chiral carbon of the L-lactic acid unit, though at lower reaction temperatures there was no racemizaiton. The amount and sequence distribution of the isomeric repeating units along the backbone of the polymer was found to be a function of the catalyst employed. The overall crystallinity of the PLA oligomer is a result of both racemizaiton and macrocycles formation. A linear polymer with no racemizaiton has higher crystallinity, which increases with molecular weight.

The oligomers, which possess both hydroxyl and carboxylic acid end groups and which are semicrystalline with T_m > 140 °C, were subjected to postpolycondensation by solid state polymerization (SSP) with and without a plasticizer. It was found that a depression of T_g of the oligomers due to plasticization does not improve the rate of the SSP reaction.

The PLA oligomers were also subjected to postpolymerization via acylation of the hydroxyl end group by the carboxylic acid end group derivatized in-situ with the help of a condensing agent. Derivatization of the carboxylic acid end group into a O-acylurea using diisopropyl carbodiimide increased the esterification rate several folds and PLA

oligomers with weight average molecular weight (by SEC) greater than 80,000 have been obtained at room temperature.

Diol-terminated PLA oligomers with secondary hydroxyl groups at both ends were prepared by dehydropolycondensation of L-lactic acid in presence of a small amount of a suitable diol. This oligomer is chain extended using μ-isopropylbis-(ε-caprolactone) and diphenyl carbonate as coupling agents. Although the chain extension reactions resulted in the formation of a copolyester and a copolyester-carbonate, respectively, their coupling efficiency was found to be limited by transesterification reactions.

L-lactic acid was copolymerized with a ω-hydroxycarboxylic acid, namely 12-hydroxystearic acid (12-HSA), which is a fatty acid derived from castor oil. Copolymers with 1, 3 and 5 mol% incorporation of 12-HSA with L-lactic acid were synthesized by a melt polycondensation reaction between lactic acid and 12-HSA at 150 – 200 °C under reduced pressure. Such copolymers were found to be internally plasticized with a T_g close to 60 °C. A homopolymer of the 12-HSA failed to plasticize the PLA oligomer externally because of incompatibility and immiscibility problems.

GLOSSARY

LA	Lactic acid
LLA	L-Lactic acid
PLA	Poly(L-lactic acid)
TPT	Tetraphenyltin
CLD	Tetra-n-butyl dichlorodistannoxane
ROP	Ring opening polymerization
SSP	Solid state polymerization
DIPC	Diisopropyl carbodiimide
DMAP	Dimethylaminopyridine
PTSA	p-Tolune sulphonic acid
DPTS	Dimethylaminopyridinium p-toluene sulphonate
12-HSA	12-Hydroxystearic acid
PHSA	Poly(12-hydroxystearic acid)
PEG	Polyethylene glycol
$\bar{M}_n$	Number average molecular weight
$\bar{M}_w$	Weight average molecular weight
$\bar{M}_v$	Viscosity average molecular weight
MWD	Molecular weight distribution
$[\eta]$	Intrinsic viscosity
T_g	Glass transition temperature
T_m	Melting point (of polymer)
m.p.	Melting point (of an organic compound)
b.p.	Boiling point

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CHAPTER - 1

CHAPTER – 1: SYNTHESIS, CHARACTERIZATION AND APPLICATION OF POLYLACTIC ACID AS A BIODEGRADABLE POLYESTER

1.1. Introduction

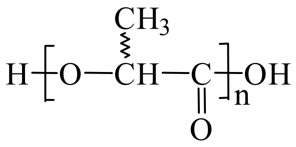
Because of ever-increasing amount of plastic wastes worldwide considerable research and development efforts have been devoted towards making a single-use, biodegradable substitute of conventional thermoplastics. Biodegradable polymers are classified as a family of polymers that will degrade completely - either into the corresponding monomers or into products, which are otherwise part of nature - through metabolic action of living organisms. They should offer a possible alternative to traditional, non-degradable polymers if the recycling of the latter is impractical or hazardous to the environment or not economical.

International organizations such as the American Society for Testing and Materials (ASTM), the Institute for Standards Research (ISR), the European Standardization Committee (CEN), the International Standardization Organization (ISO), the German Institute for Standardization (DIN), the Italian Standardization Agency (UNI), and the Organic Reclamation and Composting Association (ORCA), are all actively involved in developing definitions and tests of biodegradability in different environments and compostability [1,2]. Although a standard, global definition for biodegradable plastics has so far not evolved, each available definition (ASTM, CEN, ISO) correlates the degradability of a material with a specific disposal environment and to a specific standard test method.

Biodegradability must be looked at as a supplementary property for a thermoplastic product whose primary characteristic has to be a material, which is stable during its first use and then, after a certain induction time, becomes degradable until its complete assimilation in the biological cycle of nature.

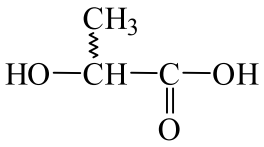
Poly(lactic acid)s (PLA, **1**) consist of aliphatic ester linkages, which are prone to both chemical and enzymatic hydrolysis. PLA is hydrolyzed by many enzymes such as protease, proteinase K, bromelain, esterase and trypsin [3]. But these ester linkages start hydrolyzing only when in contact with water and under certain specific conditions of pH and temperature. The primary degradation phase is purely hydrolytic, where no microorganisms are involved. Only after the weight average molecular weight decreases below approximately 10,000, micro-organisms begin to digest the lower molecular weight lactic acid oligomers, producing carbon dioxide and water.

This two-stage mechanism of degradation is a distinct advantage of PLA over other biodegradable polymers, which typically degrade by a single-step process involving bacterial attack on the polymer itself. This is a useful attribute, particularly for product storage and in applications requiring food contact. PLA degrades rapidly in the composting atmosphere of high humidity and temperature (55 - 70 °C). But, at lower temperatures and / or lower humidity, the storage stability of PLA products is considerably high.



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

1.1



$$HO-\overset{CH_3}{CH}-\underset{\overset{\|}{O}}{C}-OH$$

1.2

The building block of poly(lactic acid)s is lactic acid or 2-hydroxypropanoic acid (**2**), in which the carbon in between the carboxylic acid and hydroxyl functional groups is chiral, which gives rise to the possibility of diastereoisomeric (isotactic, syndiotactic and hetero- or atactic) polymer chains of PLA, depending on the direction of the methyl group with respect to the direction of propagation of the chain. PLA polymers range from amorphous glassy polymers with a glass transition temperature of about 50 – 60 °C to semicrystalline products with melting points ranging from 130 to 180 °C, depending on the sequence of enantiomeric repeating units (L and D) in the polymer backbone. A careful selection of stoichiometry of repeat units coupled with judicious plasticizer selection, therefore, allows flexible blown and cast film products to be successfully manufactured. Nucleated crystalline products of PLA are essentially opaque, whereas stress-induced crystalline materials are transparent. In summary, the basic properties of PLA lie between those of crystalline polystyrene and PET. In particular, certain properties worth noting include:

- Flexural modulus > polystyrene
- Fat barrier properties, comparable to PET
- Excellent gas barrier properties
- Good heat stability

- Clarity and gloss of amorphous and biaxial films exceeding those of PET and PP
- High surface energy allowing easy printability.

In 1997, the potential market for biodegradable polymers was evaluated by the European Union to be 1,145 million tons [4] and PLA was clearly among the most promising ones. In an attempt to figure out its potential in near future, one may reasonably extrapolate a PLA-only share of 400,000 tons by year 2008, with a progressive drop in sales price down to EUR 1.75 /kg [5].

Poly(lactic acid)s marked its beginning when Carothers made it in 1932 [6], although with a low molecular weight and poor mechanical properties. Further work by the DuPont chemical company resulted in a high molecular weight product that was patented in 1954 [7]. Activity in this field, however, subsided again because of the products' susceptibility to hydrolytic degradation until in 1972 Ethicon introduced the high-strength, biocompatible fibers for resorbable sutures, which were copolymers of lactic acid and glycolic acid [8]. But till the late 1980s the application of PLA polymers could not be conceived outside the area of costly, medical products mainly because of the high cost of the monomer. The commodity application of PLA polymers was envisaged only after cheap methods of lactic acid production started developing.

In the subsequent years research and development activity on lactic acid production has come a long way. The present global market for lactic acid itself (exclusive of PLA and lactide) has crossed well over the 100,000 tons/year mark and is showing an annual growth rate of 15 % [5]. The major companies dealing in lactic acid are listed in the Table 1.

Table 1.1: Lactic Acid Production: Global Scenario

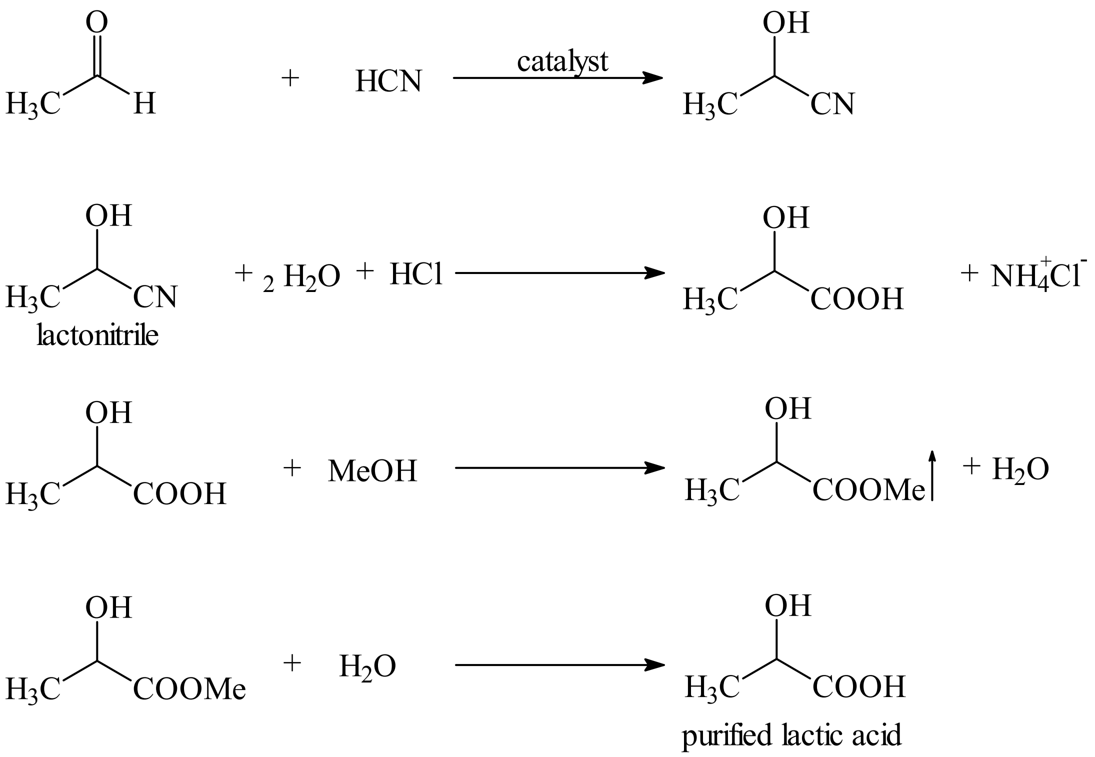
Company	Plant location	Capacity (in tons)
Purac	Holland, Spain, Brazil	80,000
Cargill-Dow LLC	USA	180,000
Galactic	Belgium	15,000
ADM	USA	10,000
Musahino	Japan	8000

1.2. Source of monomer

Lactic acid or 2-hydroxypropanoic acid ($C_3H_6O_3$), which is the monomer for poly(lactic acid), is present in almost every form of organized life. Its most important function in animals and humans is related to the supply of energy to muscle tissues. This is a water soluble and highly hygroscopic aliphatic acid, and exists in two enantiomeric forms. Almost all the lactic acid found in natural sources is dextrorotatory L(+), the D(-) form, on the contrary, being very uncommon.

Lactic acid can be obtained in large, commercial scale from two different sources. One is the petrochemical source (**Scheme 1.1**), in which lactic acid is chemically synthesized by hydrolysis of lactonitrile and results in a 50/50 or racemic form. On the contrary, lactic acid from the second source, that is fermentation broth of sugar and starch using different lactic acid bacteria (LAB), exists almost exclusively as the dextrorotatory (d or L(+)) form. Of the 100,000 tons of lactic acid that is produced worldwide every year about 90 % is made by lactic acid bacterial fermentation and the rest is produced synthetically. Presently, Musahino, Japan, is the sole producer of the synthetic variety.

Scheme 1.1: The synthetic route to lactic acid monomer through lactonitrile



Fermentative source has the advantage that by choosing a strain of lactic acid bacteria (LAB) producing only one of the isomers, an optically pure product can be obtained. The ability to produce an enantiomerically pure lactic acid has important ramifications in the ultimate structure-property relationship of the PLA. Besides, Cellulose, hemicellulose and starch are abundantly available in nature, and when hydrolyzed to mainly glucose they are fermentable by a number of microorganisms [9] to produce lactic acid. On top of that these resources, unlike the limited oil- and fossil-fuel-based sources, do not give any net contribution of carbon dioxide to the atmosphere because they necessitate uptake of carbon dioxide for their own photosynthesis and growth.

1.3. Production of lactic acid

In view of the discussion above, only the production of lactic acid from renewable natural resources is significant from the industrial and economic as well as environmental point of view.

1.3.1. Enzymatic, fermentation route to lactic acid:

Lactic acid is produced in the metabolic cycle of a group of bacteria, which are called the Lactic Acid bacteria (LAB). Lactic acid bacteria (LAB) consist of the following genera: *Carnobacterium*, *Enterococcus*, *Lactobacillus*, *Lacticoccus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Tetragenococcus*, *Vagococcus* and *Weissella* [10].

LAB are unable to synthesize ATP (adenocine triphosphate); instead produce lactic acid as the major end product from anabolic (energy-conserving) fermentation of sugars. Most of them are facultative anaerobes and are highly acid-tolerant (down to Ph. 5 and lower). Their optimal temperature for growth varies from 20 to 45 °C (from genera to genera) [11,12]. Most of them are considered GRAS (**g**enerally **r**egarded **a**s **s**afe), but some strains, e.g. streptococci, are pathogenic. Another common and very important characteristic of all the LAB is that they do not synthesize vitamins-B and amino acids [13], which renders them able to grow in a complex nutrient environment and metabolize many different carbohydrates [14].

Depending on the pH and temperature and also depending on the sugar which is fermented, LAB may produce either lactic acid only (Homofermentation, for example, by *Lactobacillus delbrueckii*), or an equimolar mixture of lactic acid, carbon dioxide and ethanol or acetate (Heterofermentation), or a mixture of lactic acid, ethanol, acetate and formate (Mixed acid fermentation) [15–29]. All other LAB except *lactrobacilli* of type I [19] (e.g. *lactobacillus casei*) are facultative heterofermenters. Homofermenters start carrying out mixed acid fermentation when the sugar is other than glucose or when glucose is in short supply.

In search of a new large-scale fermentation process for lactic acid, much effort has been put in to utilize cheaper medium components. For the carbon source to be converted to lactic acid, most of the attention has been paid to renewable glucose and lactose available from cheese whey permeate [30–35].

However, the fastidious nature of lactic acid bacteria is still the main impediment to the economical feasibility of the fermentation process. Most lactic acid bacteria require a wide range of growth factors including amino acids, vitamins, fatty acids, purines and pyrimidines for their growth and biological activity [36,37]. It has been found from a number of studies worldwide that the more supplemented the medium, the higher the productivity of lactic acid. Among various complex nitrogen sources, yeast extract (YE) is generally considered to be the best choice for both microbial growth and lactic acid production [38–41]. However, for the production of lactic acid as a source for commodity chemicals and materials, YE is not cost effective. YE is found to contribute over 30 % to the total cost of lactic acid or further downstream materials [42,43], which suggests an obvious need for a cheaper alternative.

There have been a number of efforts to utilize other nitrogen sources from industrial byproducts as growth factors to achieve a partial or complete replacement of YE [44–47]. Barley malt sprout has been found to be a feasible, partial replacement [48]. Besides, a newly screened strain similar to *Lactococcus lactis* has been found to provide with a clear advantage of replacing YE by utilizing dairy sewage (whey) protein as a measure for cost-effectiveness [49]. Soybean hydrolyzate has been found to be capable of being used as the sole source of nitrogen by *Lactobacillus rhamnosus*, giving a complete replacement of YE. Further enhancement of lactic acid production using this nitrogen source has also been found by supplementation with 7 specific vitamins as additional growth factors, and the process has been found to more cost-effective than the YE process by 41 % [50].

Direct conversion of starch into enantiopure L-(+)-lactic acid has been achieved with the help of certain strains, for example of *Lactobacillus amylophillus* GV6 and *Rhizopus oryzae* [51–53].

Maintaining pH by neutralizing lactic acid with NaOH is generally found to improve the growth, glucose consumption and lactic acid production by *Lactobacillus casei*. But maintaining pH with $CaCO_3$ is found to be effective also at high glucose concentration, which is generally found to impose a decrease in the growth rate [54].

1.3.2. Isolation of monomer:

the basic protocol is to extract the lactic acid from the fermentation broth by reactive extraction with a suitable extracting agent at a particular pH. Over 50 % yield of lactic acid was obtained from in a single extraction step, when using tertiary amine Hostarex A327 as the extractant, 1-decanol as the diluent and trimethylamine (TMA) as the stripping solution [55]. Mixtures of tripropylamine (TPA) and tripctylamine (TOA) dissolved in 1-octanol/n-heptane have been found to be successful in rective extraction of L(+)-lactic acid I aqueous solution [56]. Maximum distribution coefficients were obtained in the range from 6:4 to 8:2 weight ratio of TPA/TOA at 5 % (w/w) lactic acid in aqueous phase and their extraction efficiencies were above 90 %.

Another extracting agent is poly(vinyledene fluoride)-supported liquid membrane containing 40 vol. % trialkyl phosphine oxide (TRPO) in kerosine as a carrier [57]. Alumina ceramic filters with mean pore diameter of 1.6 μm have also been successfully applied for continuous removal of lactic acid form the culture broth [58].

Controlling pH is essential to keep the productivity high. One way is to add basic materials. But the other viable alternative is to continually isolate the lactic acid from the fermentation broth by means of extraction, adsorption or electro-dialysis. The optimum pH for lactic acid production varies between 5 and 7, but a pH necessarily below 5.7 is optimal for lactobacillus strains, which are more acid tolerant than the other LAB [59].

1.4. Purity and impurities in lactic acid

1.4.1. Chemical purity:

Chemical purity of the lactic acid is of utmost importance from the viewpoint of polymerization. Total impurities above a limit of about 100 ppm limit the maximum attainable molecular weight very drastically. A detailed study on this subject is reported in the literature [60]. The lactic acid obtained by working up the fermentation product has 98 % or more of optical (enantiomeric) purity. But the product still contains, besides residual sugars and various biological impurities, certain alcohols like methanol and ethanol, mono and dicarboxylic acids like acetic, pyruvic, oxalic and succinic acids and esters of lactic acid such as methyl and ethyl lactate. This product is yellow in color, turns black on heating, and is absolutely unsuitable for polymerization.

1.4.1a. Purification of fermentation-produced lactic acid:

Complete esterification is a viable means of purification. But that reduces the enantiomeric purity due to associated racemization of various extents. Besides, traces of the esterifying alcohol remain as impurity. Various other methods, largely physical, have been reported, including solvent extraction, steam distillation, electro-dialysis and fractional crystallization [61–67].

Industrial effort of lactic acid purification has quite a long history, dating back to as early as the 1930s. The oldest reference discusses purification by a fractional crystallization from a concentrated lactic solution obtained through thin film evaporation and distillation followed by fractional crystallization under high vacuum [68]. But the process is applicable only for small amounts to avoid large material loss and is too tricky to be industrially viable.

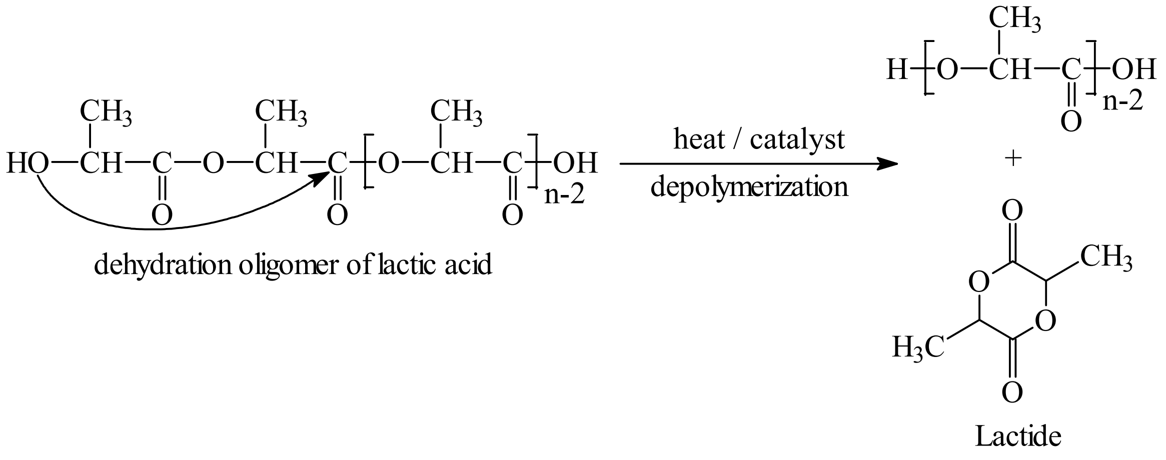
Enantiomerically pure, crystalline L-lactic acid with more than 99 % purity and less than 1 % moisture content, and with solved crystal structure has been known only in the early 1990s and has been marketed on a commercial scale by Fluka and Sigma chemical companies [69–72].

By now the best processes of industrial scale purification of fermentation-derived lactic acid have been known, which can give a crystalline lactic acid, which is colorless, chemically pure as well as enantiomerically pure. The processes are basically distillation under reduced pressure followed by crystallization. Oligomers and possible anhydrides are saponified completely into the monomer before concentration and distillation. The lactic acid thus obtained is reported more than 99 % chemically pure and 99.8 % enantiopure (99.6 % enantiomeric excess), having alcohol < 250 ppm, $N_2 < 5$ ppm, sugar < 100 ppm and other COOH < 250 ppm [67]. The basic technique of crystal formation that is followed is adiabatic cooling. These lactic acid crystals are immediately dissolved in water and commercially exploited in the form of 80 – 90 % aqueous solutions.

1.4.1b. Lactide production and purification:

Another viable – and sometimes more popular – means of lactic acid purification has been to prepare its dilactone, which popularly is called the lactide or the dilactide. The basic technique is to depolymerize a lactic acid oligomer at high temperature in presence of certain catalysts (**Scheme 1.2**). The process is equilibrium one and necessitates constant or phased removal of the product. Its synthetic feasibility, thermodynamic stability and properties have been thoroughly discussed and studied as long back as in the 1930s [73–75], while detailed studies of reaction parameters, of different possible catalysts and their relative effectiveness and of racemization processes yielding varying percentages of L,L-, D,L- and D,D- lactides have been carried out relatively recently [76]. Favorable depolymerization temperatures are 190 – 260 °C and catalysts are various, for example zinc octoate, zinc oxalate, Sn-phthalocyanin, Sn-acetate, Zn (II) oxide, stannous octoate, dibutyltin oxide, Zinc (IV) oxide, Zn-powder and zinc lactate. The lactides are all volatile solids, which are to be condensed as sublimate between 20 and 35 °C.

Scheme 1.2: Production of lactide from lactic acid oligomer



Industrial response towards this material remained scant for a long time in its total history, which is but as old as having its first reference dating back to the first decade of the last century [77]. Although there have been passing references here and there to this nice organic compound [78], heightened activity with this as a material for polymerization started only as recently as in the 1980s [79–94]. Various aspects of lactide synthesis have seen competitive amounts of research activity by each passing day. Fluorocarbon compounds have been mixed with the de-polymerizing oligomer [85] and thin film evaporation technique has been employed [86] to increase the interfacial area between the lactide and the oligomer in order for better stripping of the lactide from the oligomer. NaOH as a catalyst [90] yielded an isomeric lactide ratio of DL : LL : DD = 36 : 32 : 32, whereas Sn-powder [81,82] gave exclusively L,L-lactide with high enantiomeric purity (enantiomeric excess > 99 %) from L-lactic acid. Other tin compounds like $SnCl_2.2H_2O$ and $Sn(OH)_2$ have also been used as catalysts (enantio-purity not reported) [89]. Rare earth metals, for example $La(OAc)_3$, have also been employed as catalysts to improve enantiomeric purity [87].

The first process disclosure to make commercially viable, polymer grade lactide with chemical as well as enantiomeric purity, from crude unpurified lactic acid came from Cargill, Inc. [91], which brought in a continuous process for large-scale production, where the crude lactic acid could be any ester of lactic acid or mixtures of several esters including self-esters, where racemization was taken care of and oxidation was prohibited by use of phosphite-containing organic compounds and hindered phenols as thermal stabilizers, and where diastereoisomeric impurities were removed by fractional distillation in the production line itself instead of fractional crystallization off-line. To date, Cargill, Inc. manufactures, utilizes and sells the largest volume of polymer grade dilactide.

1.4.1c. Analytical methods for purity determination:

Purity of the LAB strain is an important parameter in controlling production and purity of the lactic acid. FTIR has been found to be a potentially suitable tool for identifying LAB in dairy products. 20 species and 9 subspecies altogether of the LAB *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Weissella* and *Streptococcus* have been identified in soft cheese, with good correlation with other methods. A more complete database of all LAB is in process of making [95]. Next comes the question of determining the purity of the lactic acid that is produced. In a broad survey of different analytical methods including titration, photometry, fluorometry and enzymic assays, an HPLC method, using a Sepharon SGX-C18 column, mobile phase of 2 % $(NH_4)_2HPO_4$ / H_3PO_4 pH 3.5 and differential refractometric detector, was proved more suitable and a practical one [96]. This method is also suitable for on-line monitoring the course, rate and completion of the fermentation process. Other columns, mobile phases and detectors have also been exploited for HPLC analysis of aqueous lactic acid solutions [97]. Packed column gas-liquid chromatography [98], indirect polarography based on the inhibition of the catalytic wave of Mo (IV) reduction in presence of sodium nitrate [99] and capillary electrophoresis [100] have also been reported as nice processes of simultaneous qualitative as well as quantitative determination of lactic acid in presence of other impurities especially other carboxylic acids. The indirect polarographic method is reported to be particularly sensitive for quantitative detection with detection limits down to 2 x10 $^{-8}$ moles/100 mL.

1.4.2. Optical purity:

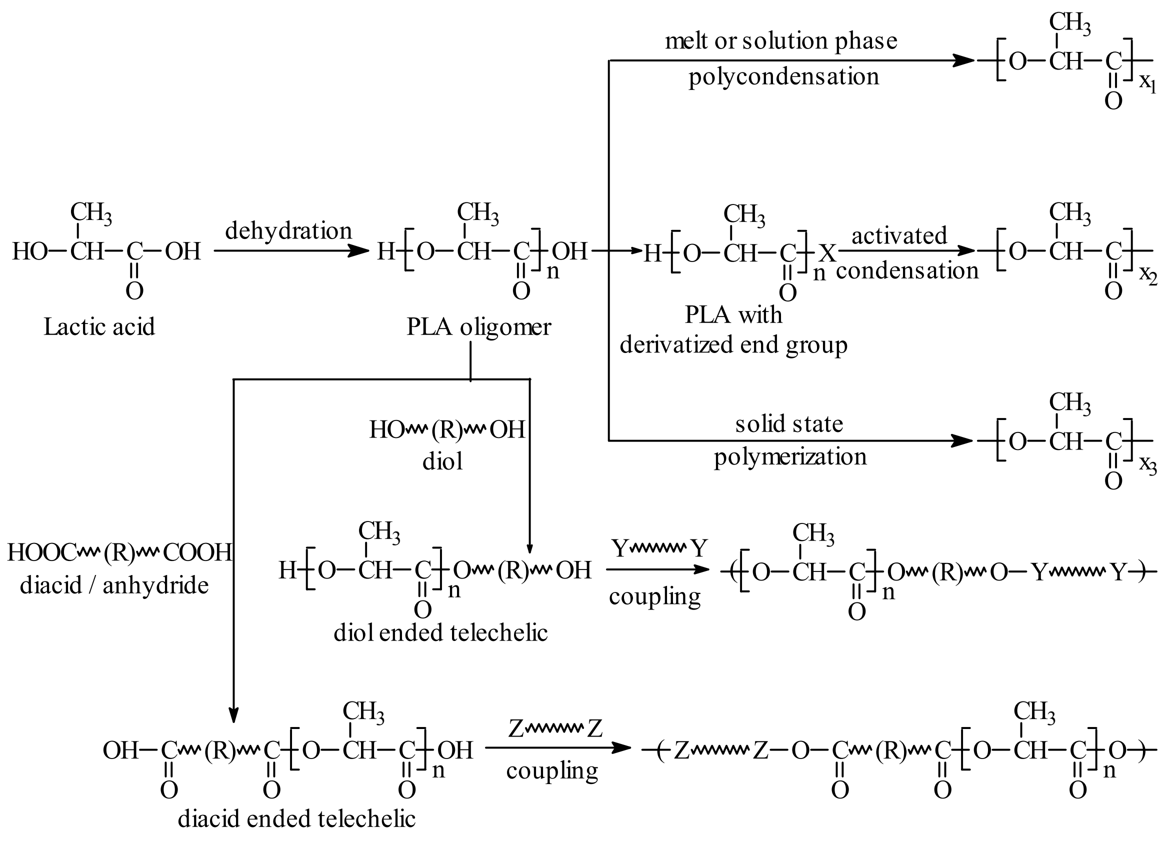
Optical purity of the monomer has a great deal to do with the structure property relationship in the final polynmer. For example, pure poly(L-lactic acid) (PLLA) and pure poly(D-lactic acid) (PDLA), which are isotactic, are semicrystalline, poly(D,L-lactic acid) (PDLLA) is amorphous.

Chiral resolution of D- and L-lactic acids has been performed by capillary electrophoresis using 2-hydroxypropyl-β-cyclodextrin as a chiral selector in a 90 mM phosphate buffer (pH 6.0) [101 a,b]. Another novel and recently developed method for enantiomeric purification of lactic acid is chiral recognition by macrocyclic receptors [102]. A chiral HPLC technique [103] has also been reported for identification of lactic acid isomers. In fact, this technique has been employed to investigate the chiral selectivity of an enzyme-catalyzed lactic acid polymerization.

1.5. Synthesis and Characterization of Poly(Lactic Acid)s

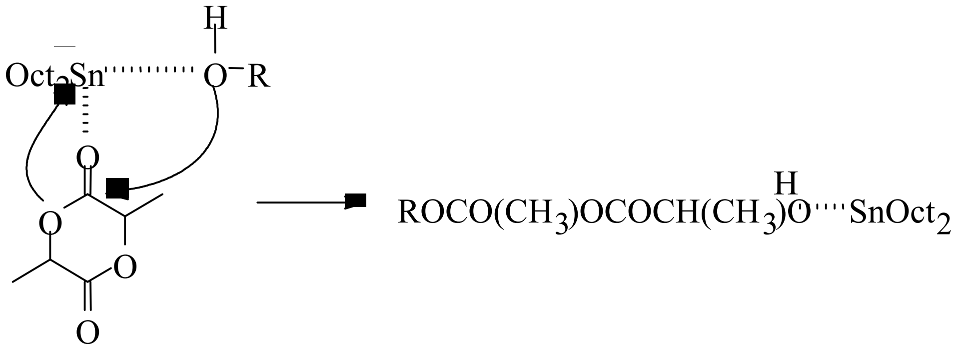
PLA is synthesized mostly in two ways. One is direct dehydropolycondensation in melt or solution phase to from oligomers followed by various postpolymerization processes (**Scheme 1.3**), for example (i) melt or solution phase polycondensation, which basically means extension of the process of oligomer synthesis itself, (ii) solid state polymerization (SSP), where postpolycondensation between the carboxylic acid and hydroxyl end groups is performed inside the amorphous region of the polymer/ oligomer at a reaction temperature above the glass transition temperature and below the melting point of the polymer, (iii) condensing agent-promoted postpolycondensation, where the strategy is to derivatize the carboxylic acid terminal so that its reactivity towards the acylation of the hydroxyl terminal will increase, and (iv) chain extension by coupling the chains through the chain end groups which are made to react with some multi-functional coupler or chain extender molecule (that is molecules bearing two or more similar functional groups capable of reacting with at least one of the chain end groups. In case of such chain extension by coupling, the general strategy is to react the PLA oligomer of dehydropolycondensation with either a dicarboxylic acid or a diol to prepare a dicarboxylic acid-terminated or a diol-terminate telechelic prepolymer, respectively. Stoichiometric amounts (with respect to the corresponding end group concentration) of a coupler molecule is then reacted with the telechelic to achieve maximum degree of coupling.

Scheme 1.3: Dehydropolycondensation of lactic acid and postpolymerization processes



The other means is to perform cationic, anionic or co-ordination (Lewis acidic) ring opening polymerization (ROP) of the lactide. Although studies on lactide polymerization with cationic and anionic initiators such as triflic acid/ methyl triflate initiators and potassium alkoxide intiators (strong nucleophiles yet weak base) initiators, respectively, have been done from an academic viewpoint, they have been found to be plagued by high degrees of racemization and transesterification because of very high reactivity of the lactide in presence of such initiators. These mechanisms are also relatively highly susceptible to impurity levels. On the contrary, bulk melt polymerization of lactides in presence of non-ionic, Lewis acidic initiators (also called catalysts) through a coordination insertion mechanism (**Scheme 1.4**) are free of the above problems, while the reactions are relatively slow. Less reactive metal carboxylates, oxides and alkoxides fall in this category of initiator.

Scheme 1.4: Coordination-insertion mechanism of Lewis acid-initiated ring opening polymerization (ROP) of lactide in presence of a hydroxyl-containing co-initiator



A summary of patent literature on the synthesis of PLA is shown in Table 1.2, placed at the end of this chapter.

1.5.1. Dehydro-polycondensation of lactic acid:

One of the ways of producing poly(lactic acid) at least up to the level of oligomers is direct dehydropolycondensation of chemically pure lactic acid. The subject has seen extensive amount of research and development activity, but the literature is mostly scattered in numerous patents, some representative samples of which has been shown in a later part of this discussion in Table 2. Number of published literature is relatively few.

The process is basically an acid-catalyzed intermolecular esterification of the hydroxyl and carboxylic acid groups of lactic acid, in which numerous Lewis acids as well as protonic acids have been used for trials. Ajioka et al [104] have accumulated results of lactic acid dehydropolycondensation with various catalysts and compared the results. They have synthesized poly(L-lactic acid) (PLLA) by dehydropolycondensation of L-lactic acid in biphenyl ether solvent at different temperatures using various catalysts and compared weight average molecular weights, to find that higher the temperature of reaction higher the molecular weight, in case all other parameters were kept constant. The effect of normal boiling point of the solvent used and effect of negative pressure (to make the solvent reflux at a desired temperature) on the dehydropolycondensation rate were observed. Results of characterization of molecular weights by GPC and thermal degradation leading to cyclic oligomers by MALDI-ToF spectroscopy and results of characterization of thermal as well of mechanical properties have been gathered.

A number of Lewis acids and different reaction conditions were investigated also by Seppala and coworkers [105] for the direct dehydropolycondensation of L-lactic acid to make PLLA, and the polymers prepared thereof were characterized for molecular weight as well as conversion, cyclic dimer formation and racemization by proton NMR and for crystallinity by thermal analysis. 98 % H_2SO_4 was found to be the best polycondensation catalyst, which yielded a PLA of number average molecular weight 31,000, and minimum or no racemization. $Sn(Oct)_2$, which is a good Lewis acid and widely used in the coordination ring opening polymerization of the cyclic dimer of lactic acid, yielded a number average molecular weight of 30,000 in dehydropolycondensation, but racemization with this catalyst was high (about 48 mol%) and the product polymer consequently completely amorphous.

Sn(II) Lewis acid catalysts such as SnO, $SnCl_2.2H_2O$ etc., which are commonly used as catalysts for dehydropolycondensation of lactic acids are found to be activated by various proton acids [106]. Such activated catalysts have been found to produce PLLA with high weight average molecular weight of about 100,000 in relatively short reaction time (15 h), compared to reactions catalyzed by non-activated catalysts as mentioned above, which produce weight average molecular weight of around 30,000 in 20 h. Such activated catalysts are also reported to give less racemization.

High molecular weight poly(lactic acid) with number average molecular weight of about 67,000 has been achieved by direct dehydropolycondensation of lactic acid using dipentaerythritol as a chain branching agent [107].

Hydroxyl-terminated telechelic lactic acid oligomers have been prepared easily by direct dehydropolycondensation of lactic acid several diols and different Lewis acid catalysts [108, 109].

Direct polycondensation of lactic acid using condensing agents such as 1,1-carbonyldiimidazole (CDI), N, N, N',N'-tetramethylchloroformamidium chloride (TMCFAC) and N,N'-dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP) has been carried out and their comparative effectiveness as condensing agents was studied [110]. Similar polycondensation using condensing agents has been patented [111].

The lactic acid dehydropolycondensation, like any other esterification reaction, is an equilibrium-controlled process, in which both esterification of the alcohol and carboxylic group and hydrolysis of the ester linkages by water, which is a by-product of esterification, proceed simultaneously, thereby limiting the attainable molecular weight unless the by-product water is removed from the system very efficiently. A new type of tin-based Lewis acid catalyst, tetrabutyl distannoxane, which can retard the hydrolysis has been exploited for lactic acid dehydropolycondensation reaction by Ottera, J. et al [112], where a maximum weight average molecular weight of 75,000 has been attained.

1.5.2. Solid state polymerization (SSP):

Relatively less information is available in the field of solid state polymerization (SSP) of poly(lactic acid)s. Oligomer preparation is important for the success of a SSP reaction because an optimum amount of crystallinity and sufficient diffusivity of the by-product (water) through the bulk of the substrate oligomer out on to the surface are vital to a good reaction rate and a resultant progress of the reaction in the forward direction. Use of crystal nucleating agents, for example magnesium stearate and titania, for bringing about a required amount of crystallinity to the PLA oligomer [113] and making a solid solution of the PLA oligomer with biphenyl ether to effect a more efficient removal of water b-product are known to improve the progress of SSP reaction [114].

Generally the same Lewis acid catalysts, which are used for dehydropolycondensation of L-lactic acid, are used for SSP of PLLA prepolymers, although some report of SSP of PLA without catalysts can also be found [115]. SSP of PLLA prepolymers using a binary catalyst system of tin dichloride hydrate and p-toluenesulphonic acid (PTSA) is reported to result in high molecular PLLA, generally not achievable by other condensation polymerization methods [116a,b].

1.5.3. Coupling of telechelic oligomers

Coupling of hydroxyl-terminated telechelic oligomers of poly(lactic acid) using diisocyanate type chain-extenders have been reported quite frequently. High molecular weight poly(lactic acid) has been achieved using hexamethylene diisocyanate as chain extender with Sb_2O_3, Zn-acetate and dibutyltin oxide as catalysts. Molecular weight of the resultant poly(ester-urethane) polymer is found to increase with increasing isocyanate to OH molar ratio [117].

Poly(ester-urethane)s with long chain branches, whose mechanical properties are comparable with polylactides, have also been made by joining hydroxyl-terminated telechelics of PLA with diisocyanate chain extender in excess of hydroxyl groups present as the chain ends of the telechelic oligomer. Large excess of the diisocyanate extender gives rise to cross-linking, while an isocyanate to OH molar ratio much less than unity (1) gives rigid and brittle poly(ester-urethane)s, which are of low molecular weight [118a,b].

Poly(ester-urethane) from poly(lactic acid), in which the ester component is a telechelic copolymer of lactic acid (LA) and ε-caprolactone (CL) condensation-polymerized in presence of 1,4-butanediol , is also reported [119]. Such poly(ester urethane)s were all amorphous, but with varying glass transition temperatures and tensile strengths depending on the comonomer ratio (LA to CL). CL rich polymers were highly elastomeric, while polymers with small amounts of CL are rigid.

Aliphatic poly(ester-carbonate)s or multiblock poly(ester-ether-carbonate)s can be achieved by joining lactic acid based polyester (PLA or PLGA, poly(lactic acid-glycolic acid)) telechelics with bis-chloroformates of either simple diols or of poly(ethylene glycol)s. Different physicochemical properties, including varying hydrolytic degradability result from varying length of the diol of which the bis-chloroformate is made and also by varying the LA to GA ratio [120].

Poly(ester-amide) copolymers made from carboxyl-terminated poly(lactic acid) telechelic oligomers using 2,2'-bis(2-oxazoline) as chain extender have been reported recently, resulting in copolymers having improved mechanical properties compared to those of some biopolymers and thermoplastics [121].

1.5.4. Ring opening polymerization of lactides:

Poly(lactic acid) can be obtained from an entirely different route, that is ring opening polymerization (ROP) of the cyclic dilactone of lactic acid, called dilactide or lactide, in presence of an initiator (also called catalyst). The lactide is prepared from lactic acid oligomers by a thermal depolymerization process using certain catalysts, as discussed elaborately in a previous section.

The lactide is a molecule with two chiral carbon centers, thereby giving rise to three diastereoisomers of LL, DD and LD (meso) configurations respectively. A 50-50 mixture of the LL and DD enantiomers is called the racemic lactide. Therefore depending on the choice of stereo-comonomers in the feed and the initiator, different sequences can result, giving rise to different tacticities of the polymer.

Stereoselective and living ring opening of meso-dilactide with enantiomerically pure aluminium alkoxide initiator has yielded purely syndiotactic poly(lactic acid) with narrow polydispersity and controlled molecular weight [122].

Ring opening polymerization of racemic dilactide using single-site zinc alkoxide.β-diimine complex has yielded heterotactic polylactide [123], in comparison with which, an ytrium alkoxide initiator yielded a polylactide from the same, racemic dilactide with less heterotacticity [124].

Stannous octoate gave a ring opening polymerization of L-lactide resulting high molecular weight and narrow polydispersity, but depolymerization started beyond a conversion of about 80 % that takes 72 hours at 130 °C in a bulk (solventless) polymerization. Depolymerization starts sooner if the reaction temperature is higher [125].

A method for evaluation, computation and prediction of favored diastereoisomeric sequence in the ring opening polymerization of racemic dilactide using stannous octoate and Zn metal initiators in absence of transesterification has been discussed on the basis of equivalent reactivity and stereo-dependent reactivity between LL and DD pairs generated from the racemic mixture of DD and LL dilactide diastereoisomers, which indicates that LL/DD heterotactic junctions are formed preferentially [126].

A “coordination insertion” mechanism of $Sn(Oct)_2$-initiated ROP of lactones has been proposed and demonstrated separately by both Penczek et al [127a - c] and Kricheldorf [128] et al. The mechanism is generally accepted for all lactones including the lactides and glyolides.

Kricheldorf et al has also shown that $Sn(Oct)_2$-catalyzed ROP of lactones and lactides do not entail transesterification reactions below 120 °C [129,130].

Six different acetylacetonato complexes ($M(AcAc)_n$, M = Nd, Y, Zn, Zn, Fe, Co, Ni) as initiators have been found to give ring opening polymerization of D,L-dilactide with close to 99 % conversion in all cases, the conversion for the rare earth metal complexes being higher and decreasing remarkably with increase in reaction temperature and time [131].

Aluminium alkoxides are also another class of ROP catalysts that proceeds through the co-ordination-insertion mechanism and give living polymerization, controllable molecular wrights and low molecular weight distribution (1.1 – 1.4) of PLA [132,133] and also give rapid polymerization with high conversion, low transesterification and zero racemization, when ROP is carried out below 150 °C [134,135]. Dubois et al. have done thorough studies of the ROP of lactones (especially, lactides) catalyzed by aluminium isopropoxide, $Al(OiPr)_3$, and confirmed the coordination-insertion mechanism, involving three active sites per aluminum atom, no aggregation of catalyst and insertion of the lactide into the aluminium-alkoxide bond with lactide acyl-oxygen cleavage, similar to the Sn-octoate mechanism [136-138].

Lanthanum and yttrium based ring-opening catalysts, studied in detail separately by McLain and coworkers [139-144] and Feijan and coworkers [145-147], also go by similar coordination-insertion mechanism, but they give very fast reactions (100 % conversion in as less as 15 minutes) at room temperature and the turnover frequencies of these catalysts for the ROP of lactides at 25 °C are more than 30 times as much as the turnover frequency of $Al(OiPr)_3$ for the same reaction at 70 °C.

1.6. Structure and Properties of Poly(Lactic Acid)s

1.6.1. General structure-property relationships:

Pure poly(L-lactic acid) (PLLA) and pure poly(D-lactic acid) (PDLA) are semicrystalline, with spherulites composed of crystalline lamellae and amorphous regions located between lamellae and between spherulites [148–150]. Within the lamellae the polymer adopts a 10_3 helical structure [151–153]. The degree of crystallinity and melting point of PLLA are affected by the stereo-irregularity in the polymer [154,155]. Incorporation of the other isomer in a primarily stereo pure PLA reduces both the degree of crystallinity and the spherulite size, with a concomitant decrease in the ΔH value of the crystalline melting endotherm related to one another by a best-fitting straight-line equation [154] of the form

$$y = 1.63 + 1.27x,$$

Where y is %-crystallinity and x is ΔH (in J/g) of the crystalline melting at T_m.

While de’Santis and Kovacs [152] propose a 10/3 helix, ten Brinke and coworkers [153] have shown that another helical structure, a 3/1 helical structure called the beta-structure (the 10/3 helix being called the alpha-structure henceforth) is also possible for PLLA isotactic polymers. Only hot drawing of PLLA fibers at high temperature and under high stress (high draw ratios) can make a alpha to beta-structure transformation possible. Besides, they have also calculated the relative atomic positions in a chemical unit of PLLA.

Shikinami and coworkers [156] have experimentally validated both the propositions, but held the view that the previous report on the relative positioning of two helical chains were in error. They have determined the correct positions. The second chain rotates by 2.46 degrees with respect to the first chain. Besides, the gyration tensor components of solid PLLA fibers along the helical axis was found to be extremely large, which corresponded to a high rotatory power, about two orders of magnitude higher than those of ordinary crystals. This is the first experimental evidence that helical polymers like PLLA will produce enormous optical activity in solid state.

The stereochemical composition of the PLA polymer significantly affects the crystallization kinetics, spherulite size and ultimate extent of crystallinity [157]. Both spherulitic size and the percentage crystallinity are particularly influential in determining the crystalline melting point of the polymer. A completely pure PLLA has a melting point of 180 °C, which can go down to as low as 130 °C with increasing stereo-irregularity. Although crystallinity is necessary for certain end application of the PLA polymer, which require properties such as high mechanical strength, high heat resistance, stiffness, high chemical resistance and permeability, a lower crystalline melting point benefits by allowing lower melt-processing temperatures. Reduction in processing temperature in turn reduces hydrolytic and oxidative degradation as well as lactide reformation.

Although essentially structure dependent, crystallinity can be developed in two ways, namely the nucleating agent-driven, solvent-induced, quiescent crystallization, which is but a slow process, and the fast, stress-induced crystallization. The former process gives an opaque material while the latter gives transparent material.

In contrast to polyolefins, PLA polymer has relatively poor melt elasticity, thereby leading to problems in extrusion processes typically used for cast film, paper coating and blown film manufacture. The poor melt elasticity results from poor degree of entanglement in linear PLA chains. This problem of low elasticity can be taken care of by introducing a low amount of branching during the polymerization process, which is achieved by utilizing low levels of epoxidized natural oil [158]. Another viable alternative for increasing melt elasticity can be introduction of small amount of cross-linking by cross-linkers such as peroxides, though at the cost of a slight increase in melt viscosity. Essentially any process that increases the polydispersity increases the melt elasticity [159].

Analysis by small and wide angle -ray scattering together throws some light on the lamellar stack parameters and on the degree of crystallinity during heating of a quenched sample of polylactic acid up to the melting and subsequent cooling. The two processes differed very significantly as far as crystallization mechanism is concerned. During heating there was a sudden crystallization at around 80 °C and then there was not much change in the lamellar and amorphous layer thickness till the melting. But while cooling, two different crystallization mechanisms operated, the first one involving lamellar thickening and the second one the formation of new lamellae in the stacks [160].

Effect of structure, especially that of the amorphous region, on the deformation behavior of poly(lactic acid) has been study by Raman spectroscopy [161]. Ikada and coworkers [162] have determined the experimental dependence of both glass transition and melting point of PLLA on molecular weight and found that both of them reach a maximum or saturation value at high molecular weights. The maxima of glass transition and melting points were found to be at 58 and 184 °C respectively, while the heat of fusion at the melting point per mole of repeating unit was found to be 3.5 kcal/mole, which is comparable to the value of 3 kcal/mole for poly(caprolactone) (PCL).

Both crystallinity and molecular weight have considerable impact on the properties of poly(lactic acid). The amorphous polymer is soluble in most common organic solvents such as ketones, THF, benzene, acetonitrile, dioxane and chlorinated solvents, whereas a highly crystalline PLA material will dissolve only in chlorinated solvents or benzene at elevated temperatures. Poly(L-lactic acid) (PLLA) showed more interesting mechanical properties than poly(DL-lactic acid) (PDLLA) and its behavior significantly improves with increase in crystallinity. Annealed specimens possess higher values of tensional and flexural modulus of elasticity, Izod impact strength and heat resistance. The plateau region of flexural strength as a function of molecular weight appears around $\overline{M}_v$ = 35,000 for PDLLA and amorphous PLLA and at higher molecular weight around 55,000 for crystalline PLLA [163]. Table 1.3 shows somewhat of a correlation of crystallinity with certain mechanical properties.

Table-1.3: Effect of stoichiometry and crystallinity on mechanical properties

Properties	PLA		
	L-PLA	Annealed L-PLA	D,L-PLA
Yield strength (MPa)	70	70	53
Tensile strength (MPa)	59	66	44
Flexural strength (MPa)	106	119	88
Notched Izod impact ($J.m^{-1}$)	26	66	18
Vicat penetration (°C)	59	165	52

Melt rheological properties of star polymers of poly(lactic acid) are completely different from those of linear poly(lactic acid). Branch entanglement starts at a much lower molecular weight (around 3500) and zero shear viscosity of the star is also higher than that of linear poly(lactic acid) [164]. Zero shear viscosity of the star is a function of the number of arms.

1.6.2. Stereocomplex:

Stereo pure PLA polymers show another remarkable property called stereocomplex formation. Polymer-polymer complexation is known, when two different polymers with different chemical structures complex between themselves upon simple mixing because of favorable interactions existing between the different polymer chains. The well-known inter-polymer complexes include (1) a poly-electrolyte complex between poly-anion and poly-cation [165], (2) a hydrogen-bonding complex between a poly(carboxylic acid) and a polyol or polyether [166] and (3) a charge-transfer complex polymeric donor and acceptor [167].

But stereocomplexes are complexes between two polymers of same chemical structures but different stereochemical configurations. This is comparable to two enantiomeric compounds forming a racemic crystal if their molecular affinity is sufficiently strong. For example, both L,L-dilactide (cyclic monomer of PLLA) and D, D-lactide (that of PDLA) possess a melting point of 97.5 °C each, while their racemic mixture crystallizes differently to give a new crystalline melting point of 124 °C.

A stereocomplex differs from a racemic mixture of the two, stereopure polymers in the sense that the stereocomplex, unlike a racemic mixture, should have a new crystalline packing pattern. Racemates of optically active D- and L- polymers are well known, but among them only a few are stereocomplexes [168–170].

Stereocomplex between separately prepared, pure poly(L-lactic acid) and poly(D-lactic acid) was first synthesized and reported by Ikada and coworkers [171]. They got the stereocomplex by mixing equal moles of the two polymers, both taken as dichloromethane solutions, together and precipitating into methanol and drying under vacuum. While the individual PLAs showed a single crystalline melting point of 180 °C each, the stereocomplex showed a single, new melting endotherm at 230 °C. Wide angle X-ray diffraction patterns also showed peaks at completely new positions for the 50-50 mixtures. All physical and material properties of the stereocomplex are different from the individual poly(lactic acid). An interesting property, for example, is that it forms gel in a concentrated solution [172].

Stereocomplexes are generally made from a 50-50 mixtures of stereo pure PLAs in solution. But in-situ stereocomplex has also been reported of late. There are mainly two different strategies. One is synthesizing a stereo pure poly(lactic acid) from an enantiopure lactide in presence of poly(lactic acid) of the opposite configuration [173]. The other strategy is in-situ stereocomplex formation by polymerizing a racemic lactide in presence of a suitable chiral catalyst [174].

The stereocomplex has found use in the industry as a new poly(lactic acid) material because of its high crystallinity, good processability and good moldability [175,176].

1.6.3. Properties of copolymers:

The ability to make PLA polymers in two different ways, namely polycondensation and ring opening polymerization, leads to a wide variety of copolymers for improving or changing the final properties. The use of direct condensation leaves open the use of any hydroxy-acid, diol, or diacid, with which to form random or nearly random copolymers, mostly with increased flexibility and modified solubility. The use of ROP yields the ability the form random, block, or pseudoblock copolymers to produce polymers with a wide range of mechanical properties.

However, beginning of a discussion of properties of poly(lactic acid) copolymers can as well be made with the aliphatic copolyesters of lactic acid, which in many cases have been found to be more processable – due to lower glass transition temperatures – and more thermally stable.

For example, copolyesters of L-lactic acid/ethylene glycol/adipic acid and L-lactic acid/1,4-butanediol/succinic acid were been prepared by direct dehydropolycondensation, yielding linear polyesters whose molecular weights were less than 30,000, while addition of a polyol such as pentaerythritol produced multibranched with a little higher molecular weights (>50,000) [177]. The glass transition temperatures of linear and branched copolyesters were in the ranges form -17 to 43 °C and from 10 to 23 °C respectively, both of which are lower than that of linear poly(L-lactic acid), which is close to 60 °C. Initial thermal decomposition temperatures (T_D) of the linear and branched copolyesters were in the ranges from 205 to 272 and from 194 to 228 °C respectively, both of which are higher than that of linear PLLA, which is about 170 °C.

High molecular weight copolyesters of L-lactic acid and ε-caprolactone were prepared using Sb_2O_3 as catalyst and dipentaerythritol (DIP) as initiator [178]. In this process short chain polycaprolactone (PCL) oligomers were produced by ROP, which simultaneously co-polycondensed with the lactic acid, thereby yielding copolyesters that were mostly amorphous. The T_g was in the range of -48 and 43 °C and decreased with increasing caprolactone content. The initial thermal decomposition temperature (T_D) was in the range of 212 and 289 °C, while that of PLA homopolymer was 168 °C.

The most frequently synthesized and most largely exploited copolyesters of lactic acid, as far as material application is concerned, are the copolyesters of lactic and glycolic acid, prepared by both dehydropolycondensation of lactic and glycolic acids as well by ring opening polymerization of the lactides with dilactone of glycolic acid, called glycolide [179–187]. The higher (than PLA) melting point of 228 °C and a lower T_g of 37 °C for polyglycolic acid leads to a range of amorphous polymers, depending on the sequence of glycolic and lactic blocks in the backbone of the copolymer, with lower glass transition temperature yet more toughness than pure PLA. Increasing glycolic acid content also reduces the hydrophobicity of and copolyesters with 30 mol% or more glycolic acid content are insoluble in non-polar aprotic solvents and more easily degradable than pure PLA.

Introduction of mandelic acid comonomer in a poly(lactic acid) synthesized by dehydropolycondensation improved thermal and mechanical properties, in spite of randomness of the incorporation and consequent destruction of crystallinity [188]. As amount of comonomer feed increased, the molecular weight of the copolymer decreased linearly. But the glass transition and decomposition temperature shifted higher, indicating improved thermal stability with increased mandelic acid content. Tensile strength of cast films also improved in copolymers with 5 - 10 wt% of mandelic acid.

Direct dehydropolycondensation of bis-carboxyl-terminated PLA with PEG yielded multiblock copolymers, in which PLA and PEG blocks were phase separated and the properties of one block were affected by the block length of the other [189]. The longer the PLA block the lower the crystallinity and melting temperature of the PEG block. These copolymers were having different crystallization behavior in melt and solution casting crystallization process, even though the chemical structures and molecular weights were the same in both cases. The crystallizability of the PLA block was more affected by the crystallization method than that of the PEG block. Such alternating multiblock copolymers formed interesting hydrogels, which are thermoplastic in nature [190]. They offer potential for application in drug delivery and various other biomedical projects.

Di- ad triblock copolymers of telechelic PEG with aliphatic polyesters like PLA showed thermo-reversible gelation because of the hydrophilicity-hydrophobicity balance between the two block components [191a,b]. Such block copolymers formed micelle in water at lower concentrations while at higher concentrations the gel to sol transition was observed as temperature was increased up to a certain temperature beyond which the polymer precipitated. With increasing block length of the hydrophobic aliphatic ester block, the gel to sol transition is observed at lower concentrations and with a broad temperature range from 0 °C to 90 °C. Such properties are worth exploitation in the drug delivery industry.

Aqueous solutions of triblock copolymers, poly(ethylene glycol-b-(DL-lactic acid-co-glycolic acid)-b-ethylene glycol) (PEG-PLGA-PEG), coupled with hexamethylene diisocyanate, have shown even more interesting thermo-reversing gelation, where there is a sol-to-gel transition at lower temperature and a gel-to-sol transition at a higher temperature [192]. It is the lower transition, sol-to-gel, which is more important because the polymer will flow as a solution at room temperature while gel inside the body at body temperature. Such polymers are worth exploitation in the drug delivery industry as "injectable gel".

Investigation of surface topography of PLA-PEO diblock copolymer submerged in water by AFM visualized the apices of the PEO chains extending into the aqueous environment from the surface, corresponding to visualization of polymer brushes at molecular level and anticipated resistance to protein interactions [193].

Linear and star stereoblock copolymers of lactic acid are prepared by sequential polymerization of isomeric lactides in presence of diol or polyol. The most important message is that the block copolymers crystallize even at 35mol% concentration of the D-isomer in a preponderance of the L-units, in contrast to the amorphous nature of random steerocopolymers similar and less incorporation of the stereoisomer [194]. The Crystallinity of the stereoblock copolymer is a function of annealing temperature and time.

PLA has a very crucial hydrophile-lipophile balance that is severely affected, rather altered, by block-copolymerization with PEO. At the same time, fine-tuning the relative block lengths of PEO and polylactide, its stability against rupture of microscopic liquid film and nanoemulsions can be controlled [195].

The onset of weight loss during hydrolytic degradation of poly(lactic acid) is generally found to become more rapid when block-copolymerized with PEO, but with time the difference almost vanishes [196]. This is explained in terms of initial rapid diffusion of water in to the copolymer due to miscibility of the PLA and PEG blocks and greater water solubility of the PEG-PLA copolymer. But as water intake increases and chain scission of PLA blocks occurs there occurs a gradual phase separation between the PLA and PEG blocks, that makes the chain rates of the PLA blocks similar to that in a pure PLA homopolymer.

Copolymers of itaconic anhydride and methacrylate terminated PLLA macromonomer was made with 15 – 85 mol % incorporation of the itaconic anhydride and retention of the cyclic anhydride structure in order to provide a new set of biodegradable polymers prepared from natural resources and with a wide range of properties [197]. The copolymers showed a range of glass transition temperatures from 31 to 73 °C, increasing with increase in the itaconic anhydride incorporation. No residue of crystallinity of the parent PLLA is restored in these copolymers.

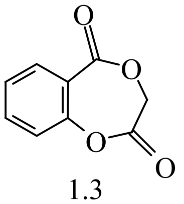
Comonomers that impart lower glass transition temperatures and flexibility have been increasingly researched in order to improve the low temperature properties and ductility of PLA. The work has been driven mainly by the need for biocompatible ingredients that would that would improve the properties of implantable medical devices and drug delivery systems. Extensive studies have been done on more common and commercial monomers to elucidate reactivity ratios and sequence formation during melt and/ or solution copolymerization.

The ring opening copolymerization of lactide and ε-caprolactone give polymers with wider spectrum of properties than the polymers synthesized by copolycondensation of the corresponding hydroxy acids, which have been discussed earlier. Such ring opened copolymers yield tough polymers with properties ranging form rigid thermoplastics to elastomeric rubbers [198,199], with tensile strengths ranging from 80 to 7000 psi (0.6 – 48 MPa), and elongations over 400 % [200]. The larger reactivity of lactide over ε-caprolactone leads to copolymers that are blocky, where the block lengths depend on the starting comonomer composition, catalyst [201] and polymerization temperature. Poly(ε-caprolactone) (PCL) itself has a T_g of –60 °C with a melting point of 59 – 60 °C, which when the monomer is ring open polymerized with pure L-lactide yields a copolymer with flexibility because of the caprolactone segment and high crystalline melting points from the L-PLA blocks. These blocks must be sufficiently large to allow rapid crystallization. Grijpma has synthesized a copolymer with 1:1 monomer molar ratio, which crystallized at room temperature very quickly, in contrast to a similar copolymer with average block lengths of 8.5, which exhibited crystallinity only after weeks of annealing at room temperature and the former polymer with longer block lengths had a T_g of –39 °C, both PLA and PCL block melting points, a tensile strength of 18.2 MPa, and elongation at break of 480 % [202].

Poly(lactic acid) is one of the highest glass transition temperature-possessing polymers among aliphatic polyesters and polyethers.. Only a few monomers, including the mandelic as mentioned before, have been found to increase the glass transition temperature of PLA when copolymerized into the backbone. Lactones of salicylic acid are reported to have homopolymer glass transition temperatures of 73 – 110 °C and polymerize slowly with lactide to give copolyesters with higher T_g values than PLA homopolymers [203,204].

The size and chemistry of the rings and the variety of comonomers, which can be ring-open polymerized with lactides to form different block or random block copolymers, is thus largely dependent on their mode of propagation, reactivity and initiation. **3 – 19** are some of the monomers that have been studied extensively with regards to ring opening copolymerization with lactides Thus, besides lactones and epoxides, morpholinediones are another important class of cyclic compounds that have been copolymerized with the lactides. Morpholinediones, which are half α-hydroxyacid and half α-aminoacid type cyclic molecules, which were found to copolymerized with lactide to yield high molecular weight yet random copolyester-amides, with glass transition temperature close to the arithmetic mean of those of the corresponding homopolymers of lactic acid, the other α-hydroxyacid and the α-aminoacid. Morpholinediones made up of glycine and lactic acid when copolymerized with L-lactide gave T_g of 109 and 71 °C for 50 and 75 mol% lactic acid, respectively, in the polymer backbone. Morpholinediones have been synthesized using lactic or glycolic acid and most of the simpler amino-acids such as glycine, alanine, leucine and valine, with the monomers containing glycolic cid giving the fastest rate of polymerization [205–211]. Use of functional aminoacids in the synthesis of the morpholinedione has thus become an effective way of incorporating functional pendant groups into the polymer. Comb-like graft copolymers of lactic acid, poly(L-lactic acid-co-L-lysine), with L-lysine side chains, of degree of polymerization ranging from 10 to 100, have been reported, with the overall L-lysine content in the copolymer varying from 7 to 72 % [212]. L-lysine residues of such poly(L-lactic acid-co-L-lysine) copolymers were further modified with an RGD(arginine-glysine-aspartic acid) cell adhesion promoting peptide, the modified copolymer being useful for tissue engineering [213]. Its degradation rate was faster than poly(L-lactic acid) due to disruption of crystallinity by the lysine residues in the copolymers.

Boury and coworkers [214] have investigated the interfacial behavior of PLA in comparison with influence of lactic acid and glycolic acid proportion in copolymers by studying on monolayer spreading at air/water interface, using Langmuir-Blodgett films. The pure poly(L-lactide) gave a more rigid film and had higher surface pressure than the film of the copolymer. The extent of orientation decreases with increasing incorporation of the glycolide unit, while the parent pure poly(L-lactide) film is highly oriented, which is the cause of high surface pressure. The high surface area is attributed to strong lateral interaction between lactic groups, which form microdomains in small areas. Glycolic acid units disrupt this interaction and do not allow formation of the microdomains. In condensed state, the major contribution to the surface free energy was non-polar, although small polar component of the force, due to O atoms was measured. The lactic acid groups, particularly the Me groups, are oriented towards the air phase.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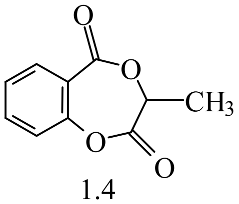
Glycosalicylide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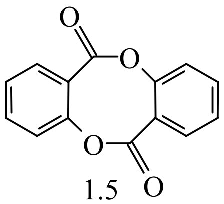
Lactosacylide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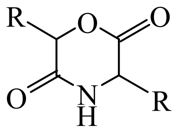
Disalicylide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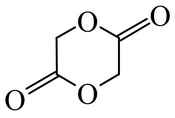
Morpholinedione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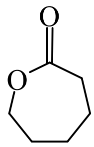
Glycolide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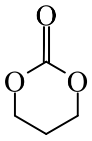
ε-Caprolactone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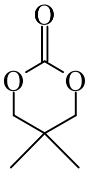
Trimethylene carbonate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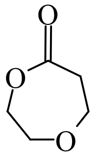
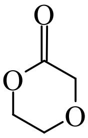
Dimethyltrimethylene carbonate


1.11
1,5-Dioxepane-2-one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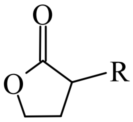
p-Dioxanone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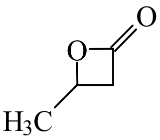
γ-Butyrolactone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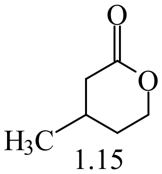
β-Butyrolactone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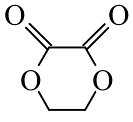
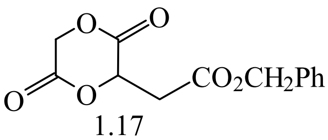
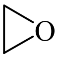
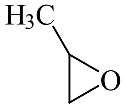
β-Methylene -δ-valerolactone


1.16
Ethylene oxalate


1.17
3-[(Benzyloxycarbonyl)methyl] -1,4-dioxane-2,5-dione


1.18
Ethylene oxide


1.19
Propylene oxide

1.6.4. Modification of properties by blending, compositing and plasticization:

Nakafuku and coworkers [215a–c] have extensively studied the melting and crystallization behaviors of PLA/PEO binary mixtures. Mixing with PEO of mol. wt. 100, 000 changes the melting and crystallization behavior of PLA drastically under high pressure. Melting and crystallization were both affected by mixing of PEO with PLA (a binary mixture). While crystallized from a melt, mixing of PEO reduced the melting point of PLA and the extent of reduction increased with increasing proportion of PEO. But while crystallizing from a chloroform solution, there was no melting point depression at all, irrespective of the proportion of PEO in the binary mixture. WAXD indicated co-crystallization does not occur while cooling from the melt, but does occur while evaporating chloroform. Ringed spherullites are formed in the binary mixture, though non-ringed spherullite are characteristic of both of pure PLA and pure PEO. Ringed spherullite is made up of lamellae of both components of the mixture.

Melting and crystallization of PLLA in a binary mixture of PLLA and PEG depends on the molecular weight of both, but the nature of dependence is very much different in cases of high and low molecular weight PLLAs. Melting temperature of the low molecular weight PLLA decreases drastically only when the weight fraction of PLLA in the mixture is brought down to below 0.2 (that is 20 %) and the decrease is not a function of the molecular weight of the PEG component. Melting temperature of high molecular weight PLLA decreases considerably with increasing low molecular weight PEG content in the mixture, while there is no drastic fall in the T_m of PLLA with increase in the fraction of high molecular weight PEG in the mixture. Blends of PEG and PLLA, both of high molecular weight, are incompatible showing two melting temperatures one each for the two components [216]. While the T_m of PEG decreases constantly as more PLLA is added, there is not much effect on that of PLLA with variation of the PEG fraction. The change in the stretching vibration of the carbonyl group is also negligible. But AB type and ABA type copolymers were found to be good compatibilizers of the two phases, decreasing the size of PEG domains, increasing the tensile strength and depressing the PLLA melting point. The effects were more pronounced in case of diblock compatibilizers than triblock ones. Whenever one component is present in more than 20 wt % proportion in a PLA/PEG blend, the major component is able to crystallize, which is the fundamental driving force of the phase separation in these blends [217].

Blends of aliphatic polyesters and copolyesters are interesting from the point of view of degradation (hydrolytic). In a ternary blend of poly(ε-caprolactone) (PCL) and poly(L-lactic acid) (PLLA) with poly(glycolic acid-co-L-lactic acid) (PGLA) all three component affected one another's degradability. The rate of random chain scission of PGLA was decreased and that of PCL and PLLA increased [218].

Artificial (synthetic) bone materials have been made out of porous composites of calcium hydroxyapatite with biodegradable and/or bioresorbable aliphatic polyesters such as poly(lactide), poly(lactide-co-glycolide), poly(ε-caprolactone-co-lactide) and poly(vinyl alcohol) [219a–g]. Morphology of such materials can be controlled by variation in the blending conditions such as temperature of firing.

Poly(lactic acid) has been flexibilized with various plasticizers, namely poly(propylene glycol) dibenzoate [220], low molecular weight poly(lactic acid)s [221], untreated or stearic acid terminated poly(ethylene glycol) [222], epoxidized soybean linseed oils [223], tributyl and acetyl tributyl citrates [224a,b] and samples useful for films, fibers and containers have been processed. with plasticizers resulting good transparency and dynamic storage modulus. PEG plasticizers yielded compositions with good impact resistance also. Hydrolytic and enzymatic degradation rates have also been found to be affected differently by different plasticizers.

1.7. Degradation Mechanisms and Degradability

1.7.1. Hydrolytic / Enzymatic:

A sort of quantitative correlation can be drawn among the degree of crystallinity, orientation and enzymatic degradability of poly(lactic acid), the rate of enzymatic degradation decreased with increase in Crystallinity [225]. A threshold was observed when the heat of fusion was less than 20 J/g. Effects of temperature, pH, molecular weight an copolymerization on the hydrolysis rate of poly(lactic acid) have been studied [179, 226–231].

Impurities and residual monomer increase the hydrolysis rate [232,233]. Peroxide modification increases the hydrolysis rate [234]. In larger size devices of PLA, the rate of hydrolytic degradation is higher inside than at the surface of the material because of the autocatalyzing effects of the carboxylic acid groups trapped inside the device [235a – c].

Whether there are microorganisms in nature that are able to biodegrade PLA polymers of any molecular weight is still under discussion and investigation. There have been only a few studies where PLA or its oligomers have been subjected to selected microorganisms. In general, these studies tell us that the molecular weight is initially decreased by abiotic hydrolysis, but after the initial abiotic degradation, the molecular weight of samples aged in a biotic medium goes down faster than samples aged in an abiotic medium [236a–d]. Presence of certain enzymes such as pronase, proteinase K and bromelain decreases the degradation rate of PLA [237,238], but effect of certain other important and likely enzymes such as esterase and lactate dehydrogenase is yet to be ascertained.

Presence of easily assimilated lactic acid and lactoyllactic acid was not only important for an enhanced degradation of poly(lactic acid) in biotic media, but was also a prerequisite for the initial growth of microorganisms on the surface of the material [239].

The effects of physical aging is profound on crystallinity and consequently on degradation also. The enzymatic degradation rate decreases as a function of physical aging that is excess enthalpy relaxation, the change of which is fast at the beginning of heating and slows down with time [238].

In the acid catalyzed hydrolysis of PLA, the chain end scission is the predominant pathway, in contrast to hydrolysis of poly(ε-caprolactone) (PCL) which occurs predominantly by random scission of backbone ester linkages [240]. Blocking the free carboxylic acid function of PLA, for example by esterification, gives good hydrolysis resistance and enhances shelf-life [241].

1.7.2. Thermo-oxidative:

When examined by heating under nitrogen within a temperature range of 180 and 240 °C, PLA showed thermal instability and loss of mass even at temperatures as low as 190 °C. There may be several reasons for its poor thermal stability: (1) hydrolysis by trace amounts of water catalyzed by hydrolyzed monomer (lactic acid); (2) depolymerization in unzipping fashion resulting lactide molecules, catalyzed by residual polymerization catalyst; (3) oxidative, random main chain-scission and (4) intermolecular transesterification with monomer and oligomeric esters [242] The dominant reaction pathway is an intramolecular transesterification giving rise to formation of cyclic oligomers. In addition, acrylic acid from cis-elimination as well as oxides of carbon and acetaldehyde from fragmentation reactions were detected [243].

Thermal degradation of PLA in air involves an initial rapid decrease in molecular weight and high rate of loss of mass, accompanied by an initial decrease of the melting point and then increase with time die to chain stiffening [244].

Thermal decomposition of PLA forms cyclic oligomers, which are detected by pyrolysis mass spectroscopy accompanied with positive and negative chemical ionization, but unstable under electron impact ionization method [245].

1.8. Conclusion and Future Directions

High molecular weight poly(lactic acid)s have been synthesized starting with lactic acid by a number of routes, which include dehydropolycondensation, post-polycondensation and coupling of low molecular weight chains, or ring opening of lactide. PLA is a thermoplastic, high strength, high modulus polymer. A minimum weight average molecular weight of 50,000 is required for mechanical properties suitable to material application. PLA is a stiff thermoplastic like polystyrene because of its high glass transition temperature. Different approaches have been taken to modulate the mechanical properties of PLA, especially the improvement of flexibility with retention of impact strength, for example by plasticization and blending. Moreover, tremendous enlargement of the available range of properties, form a brittle thermoplastic to a rubbery polymer, has been achieved through random and block copolymerization with a number of monomers in general and with glycolide/ glycolic acid, PEG/ PEO/ epoxides and ε-caprolactone in specific. Lactic acid itself being a non-toxic constituent of the human metabolic cycle, gives absolute biocompatibility to the PLA polymer, making it a safe polymer for human body-contact applications such as biomedicals and textiles. It is also a truly hydrolysable/ biodegradable polymer, which can be composted and degraded through the mechanism of ester hydrolysis to return lactic acid, which is naturally consumed to yield carbon dioxide, water and biomass.

However, in spite of the fact that PLA is now in the shape of a technical preparedness to sell as numerous materials such as non-woven fibers, oriented films, extrusion coating, flexible film, cast sheet, injection molding and foam, the prohibitive cost is one factor that has kept its application still mainly confined to the high-value, speciality applications.

Table 1.2: Synthesis of Poly(Lactic Acid)s: Summary of Patent Literature

PATENT NO.	C. A. N.	SUBSTRATE	PRODUCT	KEY PROCESS	HIGHLIGHTS
DEHYDROPOLYCONDENSATION, DEPOLYMERIZATION AND ROP					
JP 224392 A2	135:179808	D,L-lactic acid	Poly(lactic acid)	Dehydropolycondensation with enzyme catalysis	Poly(lactic acid) is manufd. by reacting lactic acid with hydrolases. DL-lactic acid was treated with Pseudomonas cepacia lipase at 130° for 4 days to give poly(lactic acid)
JP 213949 A2	135:137866	Lactic acid	High-molecular-weight poly(lactic acid)	Reactor design for lactic acid dehydropolycondensation	The polymer is manufd. by feeding a soln. contg. lactic acid monomer, corn starch, and monobutyltin oxide and stirring the soln. at 160-220° under 0.01-9 kPa in the absence of solvents. Byproduct lactide and other low-mol.-wt. oligomers are refluxed with the cylinder at 30-80° under 0.01-9 kPa, while byproduct H2O is discharged to atm. Poly(lactic acid) with Mw 480,000 was manufd
JP 031746 A2	134:131985	Lactic acid	High-molecular-weight poly(lactic acid)	Reactor design for lactic acid dehydropolycondensation	The height of the gas-liq. countercurrent phase in formed between the tower and the reactor is regulated by the flow rate so that evapn. of water and

					reflux of lactide are ppropriately performed for polycondensation of lactic acid.
JP 273164 A2	133:252906	Lactic acid	Poly(hydroxy-carboxylic acid)	Dehydro-polycondensation of L-lactic acid with instrumentation to recycle the vaporized lactide back to the reaction.	Lactic acid was polymd. in the presence of Sn powder at 160° and 30 mmHg for 10 h in o-dichlorobenzene with removing H2O and recycling the dimer and the solvent to give PLA with Mw 10,000 contg. <300 ppm residual solvent.
JP 204144 A2	133:105501	Lactic acid	Poly(lactic acid)	Dehydro-polycondensation of L-lactic acid with instrumentation to recycle the vaporized lactide back to the reaction.	polycondensation of lactic acid under reduced pressure with removal of water, wherein produced lactide is refluxed with water with reflux app. and flow rate of gaseous lactide in the reflux app. is adjusted by detecting hight of gas-liq. countercurrent contact layer.
CN 1208740 A1	132:335039	Lactic acid	Poly(lactic acid)	By heating lactic acid in the presence of 0.02-0.2 mol% catalysts contg. monobutyltin trioxide (sic) or dialkyltin oxides at 150-220°.	Diethyltin oxide, dipropyltin oxide, dibutyltin oxide, dipentyltin oxide, dihexyltin oxide, diheptyltin oxide, dioctyltin oxide, dinonyltin oxide, didecyltin oxide, diundecyltin oxide, didodecyltin oxide and ditetradecyltin oxide
JP 086749	132:223363	Low molecular	High molecular	Irradiation by UV light	Polylactic acid is irradiated by

A2		weight poly(lactic acid)	weight poly(lactic acid)		UV light of >120 mW/cm2 in strength and <400 nm in wave length to give polylactic acid with high mol. wt.
JP 015107 A2	132:108448	Lactic acid oligomers	Lactides	Lactides are prepd. by thermal degrdn. of lactic acid oligomers under reduced pressure in the presence of compds. Zn(O2CR1)(O2CR2) (R1, R2 = C£19 alkyl, alkenyl, aryl) or ZnX1X2 (X1, X2 = halo)	Tungstosilicate, tungstophosphate, Al and Zr compds. are also used as catalysts. Thus, heating L-lactic acid oligomer in the presence of Zn 2-ethylhexanoate gave LL-lactide with optical purity 99.58%.
JP 11255877 A2	131:229188	Lactide	Poly(lactic acid)	Dehydro-polycondensation of L-lactic acid with instrumentation to recycle the vaporized lactide back to the reaction.	The method improves polymn. efficiency. Thus, poly(lactic acid) with wt.-av. mol. wt. 145,000 was manufd. in 20 h with 98% yield.
JP 11035663 A2	130:168818	L-lactide or D-lactide	Racemized lactic acid-based polyesters	ROP of L-lactide or D-lactide (and optional other monomers) in the presence of (A) polymn. catalysts and (B) 0.005-0.2 mol% alkali metal compds. and/ alk. earth metal compds. as racemizing agents	10.0 g L-lactide was polymd. in the presence of 3 mg Sn octylate and 24 mg Ca acetylacetonate under N at 190° for 2 h to give poly(lactic acid) having |L - D| = 78%, hsp/C = 0.446 dL/g, and av. mol.-wt. 42,000.
JP 10231358 A2	129:189815	Lactide	Poly(lactic acid)	Dehydro-polycondensation of L-lactic acid with instrumentation to recycle the vaporized lactide back to the reaction.	90% aq. L-lactic acid was charged in a reactor, dehydrated at 60°, mixed with SnCl2 at 170° at 5 mm-Hg, and polymd. to give PLA of Mw 37,000.

JP 10120772 A2	129:5010	Lactide	Polylactic acid	ROP of lactide with total catalyst content per the monomers is controlled in £50 ppm and (ii) the catalysts are intermittently or continuously added in reactors little by little while making the stirring power higher in stages or continuously as the thickness of the reaction liqs. increases.	Thus, PLA with av. mol. wt 235,000 was prepd. by ring-opening polymn. of 10-kg/h lactide at 180-200° in the presence of 0.1 g/h (10 ppm) Sn octylate by using 3 polymn. reactors and an extruder. The resulting poly(lactic acid) had catalyst content £50 ppm.
JP 10017653 A2	128:102572	Lactide	Poly(lactic acid)	Dehydro-polycondensation of L-lactic acid with instrumentation to recycle the vaporized lactide back to the reaction.	Poly(lactic acid) is manufd. by ring-opening polymn. of lactide (I) with capturing vaporized unreacted lactide by H2O to prevent clogging of ejector
JP 09216940 A2	127:191227	lactic acid polymers		Condensation polymn. of lactic acid, bases are added during the polymn. The bases prevent lactide formation during polymn.	Thus, L-lactic acid was polymd. at 120-170° in the presence of Zn(OAc)2 to give oligomers with Mw 10,940, which was then polymd. at 170° in the presence of 0.05 part HIS to give a polymer with Mw 78,400 contg. remaining lactide 2.4% without discoloration.

P 09165441 A2	127:66320	L-lactic acid	Poly(lactic acid), silane caoupled	One-pot preparation of biodegradable poly(hydroxy-carboxylic acids) by using water-stable distannoxane catalysts and silane couplers	L-Lactic acid was mixed with 1,3-dichloro-1,1,3,3-tetrabutyl-distannoxane in a glass tube oven, the inner pressure reduced to 1 mmHg to remove H2O, and the mixt. was treated at 190° for 20 h to give poly(L-lactic acid) with Mw 22,000, which was treated with Si(OBu)4 at 150° for 8 h to show mol. wt. 30,000.
JP 09031182 A2	126:238819	L-lactic acid	Poly(lactic acid)	Dehydro-polycondensation using distannoxane catalyst	100 mmol I was polymd. at 200° for 20 h in the presence of 0.01 mmol 1,3-dichloro-1,1,3,3-tetrabutyldistannoxaneto to give a polymer with Mw 12,000.
JP 08311176 A2	126:118359	Lactide	Polylactic acid	ROP of lactide	1.0 g L-lactide (optical purity 99.0%) was polymd. at 140° for 1 h and crystd. at 120° for 9 h in the presence of Sn octylate to give 98% poly(lactic acid) having wt.-av. mol. wt. 149,000.
JP 08259676 A2	126:31856	Lactide	Polylactic acid	ROP of lactide with special reactor design	L-Lactide was polymd. as above to give a polymer with low residual monomer content.
JP 08193127 A2	125:222817	Lactide	Lactic acid-based polymers	by ring-opening polymn. of lactides in the presence of catalysts comprising (A) thermal condensates of Al alkoxides, Si halides, and phosphate esters and	5 g 30%-L-lactide CH2CL2 soln. was treated at 60° for 8 days in a sealed ample in the presence of 38 mg 3%-AlEt3 soln. in hexane and 38 mg

				(B) C1-4 trialkylaluminum and/or dialkylaluminum chloride with the ratio of Al in B based on that in A 0.02-0.35.	condensates obtained from Al isopropoxide, SiCl4, and Bu3PO4 to give a polymer with sp. viscosity 0.42 dL/g.
WO 9528432 A1	124:57097	L-lacctic acid	Poly(lctic acid)	Dehydropolycondensation using synthetic alumino silicate	Poly(L-lactic acid) with wt.-av. mol. wt. 98,000 was prepd. by heating 150 g a 90% aq. soln. of L-lactic acid at 120° for 5 h while stirring under vacuum, adding 2.1 g a synthetic Al silicate contg. 17% Al oxide, heating to 220°, evacuating to 20 mm-Hg over 30 min, and mixing for 30 min at 220°C
JP 07173264 A2	123:341384	Methyl lactate	Poly(lactic acid)	Dehydro-polycondensation in presence of Sn powder catalyst	Heating 37.4 g Me lactate with 0.125 g Sn at 140-160° for 12 h with distn. of MeOH and further treatment with 53.9 g Ph2O at 165° for 3 h in a vessel equipped with Dean-Stark trap and with a mol. sieve in a reflux condenser at 160°/20 mm for 36 h gave a polyester with Mw 61,000.

JP 07173265 A2	123:314950	L-lactic acid	Poly(lactic acid)	Dehydro-polycondensation with Sn powder catalyst, with solubilization of Sn in lactic acid and removal of insoluble Sn prior to condensation	0.5 g Sn was dissolved in 100 g 90% L-lactic acid at 80° for 3 h under N and then insol. Sn was removed by filtration to obtain a soln. contg. 3000 ppm Sn. It (36.0 g) was treated in 75.6 g Ph2O at 130-140° under reduced pressure in a vessel equipped with Dean Stark trap, and then with mol. sieve in a reflux condenser at 130°/15 mmHg for 20 h to give 83% poly(lactic acid) with Mw 200,000.
JP 07102053 A2	123:257882	Poly(lactic acid) with more than 500 ppm Sn	Poly(lactic acid) with less than 5 ppm Sn	Removal of Sn catalyst from poly(lactic acid) synthesized by dehydro-polycondensation by contacting with mineral acid	Thus, poly(L-lactic acid) with logarithmic viscosity 1.50 dL/g contg. 560 ppm Sn (catalyst) was stirred with 0.5 N HCl/EtOH at 35° to give polymer with 4 ppm Sn, which showed 5% wt. loss temp. 320° and retention of tensile strength (as film) ^{3}95% after 400-h weathering test.

JP 07053684 A2	123:170656	L-lactide	Poly(lactic acid)	ROP of lactide with instrumentation for continuous feed of substrate and continuopus removal of the polymer	Thus, 120 g/min cyclic dimer of lactic acid and 0.036 g/min a 3% Sn octoate (PhMe soln.) were continuously supplied with stirring under N in autoclave at 200° and 20 min (av.) retention time with taking out the product [melt viscosity 250 P, reduced viscosity (h) 0.78] at a rate of 120 g/min from the bottom of the autoclave into a twin-kneader and polymg. the product at 20 min (av.) retention time to obtain PLA (100% recovery).
JP 06306149 A2	122:214894	L-lactic acid	Poly(lactic acid)	Melt dehydro-polycondensation using membrane type evaporator for removal of by product, SnCl2 catalyst	Thus, 100 parts 90% L-lactic acid was stirred at 130°/50 mm for 3 h with removal of H2O and then stirred with 0.8 part SnCl2 at 130°/15 mm for 5 h to obtain medium-mol. wt. poly-L-lactic acid (I; wt.-av. mol. wt. (Mw) ~40,000), which was heated to 100° and passed through a membrane-type evaporator at 170°/15 mm and 30 min retention with H2O sepn. to obtain PLA (Mw 150,000).

JP 06298913 A2	122:161781	L-lactic acid	Poly(lactic acid)	Dehydro-polycondensation in an azeotroping solvent, with reactor design to recycle the solvent after drying to reaction, Sn powder catalyst	90% L-lactic acid (I) 112.5, powd. Sn 0.405, and di-Ph ether (II) 236 kg were stirred at 130° and 160-130 mmHg for 6 h to remove H2O, I was oligomerized at 140° and 110-100 mmHg for 25 h then polycondensed at 130° and 20-15 mmHg for 30 h to obtain a ~25% soln. of poly(L-lactic acid) (av. mol. wt. 126,000) in II, wherein II was recovered by cooling the distg. azeotropic mixt. contg. H2O, dried through a mol. sieve-filled tower, vaporized through a heat exchanger, and returned into the reaction system.

JP 93-89676	122:161782	L-lactic acid	Poly(lactic acid)	Melt dehydro-polycondensation with reactor design for high viscosity, SnCl2 catalyst	100 parts 90% L-lactic acid was stirred at 130° and 50 mmHg for 3 h with removal of H2O and then stirred with 0.8 part stannous chloride at 130° and 15 mmHg for 5 h to obtain poly(L-lactic acid) [I; wt.-av. mol. wt. (Mw) ~40,000], which was heated to 100° and fed into a twin horizontal high-viscosity reactor at 170° and 15 mmHg at 60 min retention time while removing H2O to obtain white powd. I (Mw 280,000).
JP 06279577 A2	122:134232	L-lactic acid	Poly(lactic acid)	Dehydro-polycondensation in azeotroping solvent in presence of acetaldehyde, Sn powder catalyst	L-lactic acid contg. 0.05 mol % AcO in Ph2O in the presence of Sn and mol. sieve 3A at 130°/15 mm gave 96.1% poly(lactic acid) with specific viscosity 1.18.
US 5357034 A1	122:11005	Lactic acid	High molecular weight poly(lactic acid)	Depolymerization of poly(lactic acid) prepolymer into lactide followed by purification by means of melt crystallization and ROP of lactide in melt condition or in solution	Process for poly(lactic acid) preparation and avoids problems associated with equilibrium between lactic acid, low and high molecular weight PLA, lactide and water.

WO 9403522 A1	122:106763	L-lactic acid	Poly(lactic acid) and lactide	Polymerization of lactic acid in presence of iron ions	Poly(lactic acid) with mol. wt. >25,000 and lactide are obtained as the principal products in the polycondensation of lactic acid using Fe ions (e.g., ferrous lactate) as the catalyst.
JP 06172502 A2	121:257090	L-lactic acid	Poly(lactic acid) and lactide	Choice of solvents for dehydro-polycondensation	polymers are prepd. by dehydration-polycondensation of hydroxycarboxylic acids or their oligomers in ethers ROR1 (R = C1-5 alkyl, halophenyl, C1-5-alkylphenyl, C1-5-alkoxyphenyl; R1 = Ph, halophenyl, alkylphenyl, etc.), followed by cooling to ppt. the polymers. Polymg. 75.0 g 90%-L-lactic acid at 130° in anisole in the presence of Sn with water removal and cooling to 50° gave 55 g polymer.

WO 9318021 A1	120:165229	Alpha-Hydroxyacids	Poly(hydroxy-carboxylic acid)s	Rare-earth-metal-catalyzed oligomerization of alpha-hydroxycarboxylic acids and conversion to dimeric lactones	alpha-Hydroxy acids or their heat-dissociable amine salts are oligomerized in the presence of rare-earth metal compd., and the oligomers are degraded by to cyclic dimer esters by further heating in the presence of the rare-earth metal compd. Thus, L-lactic acid was polymd. 2 h at 185° in the presence of La(OAc)3 hydrate (I) to give liq. polymer (II) with d.p. 11, and II contg. I was passed into the top of a column at 210° while N at 200° was countercurrently passed into the column so that L-lactide was vaporized and collected at the top of the column at 56% yield.
JP 05287056 A2	120:77984	L-lactic acid	Lactide and poly(lactide)	Depolymerization of poly(lactic acid) prepolymer followed by ring oprning polymerization (ROP) of lactide	Thus, aq. L-lactic acid was polymd., heated in 1-dodecanol, thermally depolymd. to a cyclic dimer, and polymd. in the presence of stannous octanoate.

WO 92-JP1638	120:9195	L-lactic acid	Poly(lactic acid)	Dehydro-polycondensation in an azeotroping solvent, Sn powder catalyst	A mixt. of 40.2 g 90% L-lactic acid and 0.5 g Sn in 85 mL anisole was heated at 154° for 2 h with removal of water by azeotropic distn. then further heated at 154° for 45 h with removal of water by azeotropic distn., while the distillate was passed through a 40-g Mol. Sieve 3A tube to remove water to residual water content 1 ppm and returned to the reaction mixt The reaction mixt. was then concd., taken up in 300 mL methylene chloride, filtered, and washed with MeOH to give 24.4 g polymer with inherent viscosity 0.84 and mol. wt. 100,000.
JP 05105745 A2	119:204147	L-lactic acid	Poly(lactic acid) and pure lactide.	Thermal dehydro-polycondensation of L-lactic acid in the presence of tin trifluoroacetate (I), then the polymer is heated in the presence of same catalyst to obtain lactide.	Stirring 100 g 90% L-lactic acid with 0.36 g I at 200°/30 mmHg for 3 h then at 200°/10 mmHg for 1 h gave 51 g poly(lactic acid) with mol. wt. 7000. Stirring 634 g poly(lactic acid) of mol. wt. 460 with 2.26 g I at 150°/30 mmHg for 1 h increased the mol. wt. to 800-850, and distn. at 175-230°/5 mmHg gave 505 g pure lactide.

JP 320033	109:150334	Racemic lactic acid	Lactic acid polymer and stereo-copolymers.	Depolymerization of poly(lactic acid) prepolymer into lactide followed by purification by solvent extraction and ring oprning polymerization (ROP) of lactide	Mixing 3295 g 90% racemic lactic acid with 16.4% Zn owder at 200° in vacuo to get lactide, dissolving the crude lactide in 100 mL CH2Cl2, extracting against 40 g NaCl in 150 mL H2O and 4.74 g NaHCO3 in 70 mL H2O, and polymg. the pure lactide (20 g) with 4.0 mg Sn octanoate (as 5% PhMe soln.) gave poly(lactide) with relative viscosity 1.78 (0.5 g/100 mL CHCl3, 30°).
POLYCONDENSATION THROUGH DERIVATIZATION OF END GROUP					
WO 060891 A1	137:125523	Ammonium lactate obtained by lactic acid fermentation	Lactide and poly(lactide)	Depolymerization of poly(lactic acid) prepolymer followed by ring oprning polymerization (ROP) of lactide	Synthesis of prepolymer poly(lactic acid) of Mw 15,000 by condensation of ammonium lactate and depolymerizing the prepolymer to give lactide. Polylactic acid is prepared by ring-opening polymn. of lactide.
JP 213875	136:119297	Low molecular weight poly(lactide)	Higher molecular weight poly(lactide)	Chain extension by reactive blending in presence of a carboxylic acid activating agent	Blending of 99.28% 50:50 poly(L-lactide) and poly(D-lactide) mixt. and 0.72%N,N'-bis(2,6diisopropylphenyl)carbodiimide, spinning, and stretching gave fibers with good heat resistance.
US 6326458	136:20374	Ester of lactic	Lactide and	Depolymerization of poly(lactic	Poly(lactide) was prepared from

B1		acid	poly(lactide)	acid) prepolymer followed by ring oprning polymerization (ROP) of lactide	a purified lactide mixt. of 80% L- and 20% D,L-lactide in THF in presence of tin(II) 2-ethylhexanoate catalyst
JP 053758 A2	132:152357	Lactic acid or lactic acid based oligomer	Polyhydroxycarboxylic acid	Dehydration condensation of hydroxycarboxylic acids and polycondensation in the presence of haloimine salts	The reaction of polydroxycarboxylic acids and/or their oligomers in the presence of a haloiminium salt and an org. base. The polymer is isolated by adding an aliph. alc. into the soln. to ppt. the polymer. The remaining soln. contg. a mixt. of the org. solvent, the aliph. alc., the salt of the org. base, and amides and/or urea derivs. and/or imidazolidinones (which is converted back to the haloiminium salt by treating with agent such as phosgene).
JP 026589 A2	132:108494	L-lactic acid	High-quality poly(hydroxycarboxylic acids)	Dehydration condensation of hydroxycarboxylic acids and polycondensation in the presence of haloimine salts	L-lactic acid was oligomerized, polymd. in the presence of 2-chloro-1,3- dimethyl-imidazolinium chloride and pyridine in xylene, mixed with iso-PrOH, crystd., and washed with iso-PrOH to give poly(lactic acid) contg. £10 ppm 1,3-dimethylimidazolidinone and pyridine hydrochloride and

					showing yellowing index 2.0 after molding.
JP 007774 A2	132:79025	Lactic acid	Polyhydroxycarboxylic acid	Dehydration condensation of hydroxycarboxylic acids and polycondensation in the presence of haloimine salts	Refluxing 90% lactic acid 300, SnO 0.216, and chlorobenzene 30 g while removing water for 15 h, stirring the polylactic acid oligomer (82.5%) with 221 g chlorobenzene, 5.12 b-picoline, and 3.88 g 2-chloro-1,3-dimethylimidazolinium chloride (DMC) at 80°, adding 480 g iso-PrOH and cooling gave 78.9 g polylactic acid with Mw184,000, no byproducts, and no DMC and picoline residues.
JP 11181075 A2 and JP 11181074	131:59269, 131:59267	Lactic acid oligomers	Hydroxycarboxylic acid polymers	By polymn. of (oligomeric) hydroxycarboxylic acid chlorides in presence of base	Thus, treating L-lactic acid oligomer in 1,2-dichloroethane in the presence of 2-chloro-1,3-dimethylimidazolinium chloride and b-picoline (II), adding dropwisely the soln. in a water and xylene mixt., heating at 50° gave a PLA of Mw 120000.
JP 11021342 A2	130:182905	Lactic acid	Hydroxycarboxylic acid polymers	By polymn. of (oligomeric) hydroxycarboxylic acid chlorides in the presence of tertiary amines	90% lactic acid was condensation polymd. at 160° for 8 h, followed by reaction with 2-chloro-1,2-dimethyl-imidazolinium chloride to give oligomers terminated with acid

					chloride (Mw 5700, Mn 1500, acid chloride group concn. 6.67 ´ 10-4 mol/g), 10 g of which was polymd. at 40° for 2 h in 50 g CH2Cl2 contg. 2.45 g quinoline to give polylactic acid with Mw 172,000, Mn 4,000, and 2-chloropropionic acid content £100 mol-ppm.
JP 08073573 A2	125:34415	L-lactic acid and acetic anhydride	Poly(lactic acid)	Acetylation of oligomers, deacetylation and polycondensation	Lactic acid was dehydrated to form oligomers and acetylated in presence of acetic anhydride and the acetylated oligomer was polycondensed by de-acetylation to yield PLA of wt. av. mol. wt. 13,000.
JP 08027255 A2	124:290626	Methyl lactate	Poly(lactic acid)	Reactive extrusion	7.8 kg Me lactate was polycondensed at 85-110° for 8 h with removal of MeOH and further polycondensed at 140-160° for 9 min in screw extruders to give polymer with wt. av. mol. wt. 14,500.
SU 852889 A1	96:35891	α-Chloropropionic acid	Poly(lactic acid)	Condensation by means of de-hydrochlorination with the help of alkali (NaOH/ KOH), instead of dehydration of lactic acid	a-Chloropropionic acid reacted with an equimolar amt. of alkali and heating for 40-50 min at 185-195°.The polymer was prepd. using dry NaOH and KOH or a 1:1:2.6 mixt. of

					NaOH, KOH, and H2O, Me2CO, or an alcohol
SOLID STATE POLYMERIZATION					
JP 192444 A2	135:93397	L-lactic acid	High molecular weight poly(lactic acid)	Dehydro-polycondensation followed by crystallization of oligomer followed by SSP	Thus, 88% L-lactic acid was polymd. in the presence of p-toluenesulfonic acid, crystd. in H2O, and polymd. at 120° for 10 h and at 140° for 120 h to give a polyester with Mw 140,000 and catalyst content 914 ppm.
WO 078840 A1	134:57139	Low molecular weight poly(hydroxy-carboxylic acid)	High molecular weight poly(hydroxy-carboxylic acid)	Crystallization of oligomer followed by SSP	A polyhydroxycarboxylic acid having a wt.-av. mol. wt. of 50,000 to 1,000,000 is prepd by (A) a step in which pellets of a polyhydroxycarboxylic acid having a wt.-av. mol. wt. of 2,000 to 100,000 obtained by liq.-phase polycondensation are heated with stirring at a temp. not lower than the glass transition point but not higher than the m.p., followed by (B) SSP
JP 212425 A2	133:136073	Low molecular-weight poly(lactic acid)	High molecular-weight poly(lactic acid)	SSP of lactic acid oligomer in presence of phenyl ether (as solid solution)	Title process with low thermal degrdn. comprises (A) ranulation of the solid soln. contg. low-mol. wt. compd. of lactic acid 100 and di-Ph ether 2-100 parts (based on lactic acid monomer)

					at a temp. ^{3}10° lower than the m.p. of poly(lactic acid), and (B) polymn. in the solid state.
JP 11279267 A2	131:272369	Lactide	Poly(lactic acid)	2-step polymn. (melt polymn. followed by solid-phase polymn.) using a twin screw-type stirrer.	Thus, poly(L-lactic acid) of wt.-av. mol. wt. 110,000 was manufd.
JP 11106499 A2	130:325513	Lactide	Poly(lactic acid)	(1) Melt polymerization of a lactide, with instrumentation to reflux vaporized lactide back to reaction, followed by (2) solid-state polymerization (SSP) of the polylactic acid obtained in the first step	Thus, 7500 g L-lactic acid was dehydrated at 100° for 4-5 h, melt-polymd. in the presence of 0.5% stannous chloride at 160° and 10-30 torr for 10-15 h, cooled to 130°, and solid-state polymd. for 10-12 h at 130° and 0.1-2 torr to give a polymer of wt. av. mol. wt. 110,000.
JP 08269175 A2	126:31857	L-lactide	High molecular weight poly(lactic acid)	(1) Melt polymerization of a lactide followed by (2) solid-state polymerization (SSP) of the polylactic acid obtained in the first step	The poly(lactic acid) is prepd. The reactions are typically carried out at 100-190° for the 1st step in the presence of a catalyst (tin octylate) and 80-175° for the 2nd step polymn.
JP 08193123 A2	125:248878	Lactide	Lactic acid-based polymers	(1) Melt polymerization of a lactide, contg. 0.01-1.0% inorg. microparticles or org. components as nucleating agents for crystn., followed by (2) solid-state polymerization (SSP) of the polylactic acid	Thus, 1000 parts L-lactide was polymd. at 200° for 3 h in the presence of 1 part CaCO3 and Sn octylate, cooled down to 140° in 1 h, kept for 1 h, and then at 130° for 5 h to give a polymer with wt.-av. mol. wt. 150,000,

					low mol.-wt. component 1.5%, m.p. 183°, and Tg 65°.
JP 08151436 A2	125:168988	L-lactide	High molecular weight poly(lactic acid)	(1) Melt polymerization of a lactide followed by (2) solid-state polymerization (SSP) of the polylactic acid obtained in the first step	Thus, L-lactide was polymd. at 180° using Sn octanoate catalyst and further polymd. at 110° for 50 h to give I with av. mol. wt. 140,000. catalyst is added more than twice during the 1st polymn.
EP 664309 A2	123:257904	Lactide	Poly(lactide)	(1) Melt polymerization of a lactide followed by (2) solid-state polymerization (SSP) of the polylactic acid obtained in the first step	The reactions are typically carried out at 120-190° (for the first step) and 100-175° (for the second step). Catalyst added once in the first step and again in the second step
EP 500098 A2	118:22831	Low molecular weight lactic acid polymers	High molecular weight lactic acid polymers	SSP of low mol. Wt. Lactic acid homo- or co-polymer, especially stereocopolymer, without catalyst	Solid-state polymerization (SSP) in the absence of catalysts by heating a low mol. wt. L(+) and/or D(-) lactic acid homopolymer or copolymer having crystallinity ^{3}10% in an inert atm. or vacuum.

CHAIN EXTENSION OF TELECHELIC OLIGOMERS					
JP 08027256 A2	124:318147	Lactic acid oligomers	Lactic acid based polyurethane	Condensation of lactic acid oligomers and diols to synthesize diol-terminated lactic acid telechelic oligomers followed by chian with di-isocyanate by reactive extrusion	Lactic acid prepolymers with no. av. mol. wt. (Mn) 500-5000 and diols, poly(ethylene glycol,) are copolymd. to give polylactic acid diols, which are chain-extended by reactive extrusion with di-isocyanates (HMDI) to give biodegradable polymers having polyurethane structure and Mn 50,000-150,000.
JP 08003262 A2	124:290612	Lactic acid oligomers	Lactic acid based polyurethane	Condensation of lactic acid oligomers and diols to synthesize diol-terminated lactic acid telechelic oligomers followed by chian with di-isocyanate by reactive extrusion	Lactic acid prepolymers with no. av. mol. wt. (Mn) 18,000 and diols, polycaprolactone-diol are copolymd. to give polylactic acid diols, which are chain-extended by in refluxing dichlorobenzene with di-isocyanates (HMDI) to give PLA having polyurethane structure and Mn 39,000.
US 835166	124:118366	Telechelic poly(lactic acid) prepolymer	High molecular weight poly(lactic acid)	Coupling telechelics through end groups using chain extenders	Biodegradable poly(lactic acid) with wt. av. mol. wt. 25,000-100,000 manufactured by coupling dicarboxylic- or diol-ended telechelics of a lower mol. wt with diisocyanates, diepoxides, bisoxazolines, or bis-ortho esters.

COPOLYMERIZATION, CROSS-LINKING AND REACTIVE BLENDING					
JP 097350 A2	136:280176	Lactide and an aliphatic polyester	Lactic acid-based aliphatic copolyester	Ring opening polymerization (ROP) of lactide in a medium already containing the aliphatic polyester	Lactic acid-based random-block copolyester with good impact resistance and biodegradability, but having a micro phase separated structure consisting of (A) a continuous phase of aliph. polyester units, (B) polylactic acid units dispersed as islands in the continuous phase, and (C) spherical particles of the aliphatic homopolyester in-situ blended with the copolyester
JP 262667	136:233002	Poly(lactic acid)	Crosslinkable soft lactic acid polymers	Poly(lactic acid) heated along with alkylene oxides and cross-linkers was heated in extruder	Aliph. polyesters contg. lactic acid, terminal-reactive alkylene oxides, and radical initiators are heated under N to prep. the title polymers. Thus, Lacty 9000 80, Kayahexa AD40C 0.3, and Uniox AA 800 (polyethylene glycol diallyl ether) 20 parts were mixed, melted, extruded, cut, and molded.

WO 079315 A1	135:332062	Poly(lactic cid)	Polylactide-dextran graft copolymers for tissue engineering	Cross-linking by transesterification	A copolymer is prepd. from crosslinking a polylactic acid with a polysaccharide such as dextran by transesterification. The resulting copolymer is a biodegradable hydrogel or solid having both hydrophobic and hydrophilic properties and provides for a mechanism in which biol. active agents may be covalently bonded to the dextran prior to incorporation of the dextran into a copolymer, and the subsequent release of the biol. active agents as the copolymer degrades.
US 6211325 B1	134:267041	Poly(lactic acid)	Starch modified poly(lactic acid)	Reactive blending with starch	Dried starch (moisture 1%), polylactic acid and MDI, 45:55:0.5 wt.%, were blended at 190° and compression molded into test pieces having tensile strength 66.6 ±3.3 MPa, elongation 4.4 ±0.3%, and modulus 1972 ±161 MPa.
JP 10087796 A2	128:230866	Lactide	Polylactic acid and polylactic acid resin	dehydration polymn. of lactic acid or ring-opening polymn. of lactide in the presence of amides of (poly)carboxylic acids or (poly)amines.	L-Lactide was polymd. using tin octoate catalyst in the presence of 2,6-naphthalenedicarboxylic acid dicyclohexyl amide.

EP 796881 A1	127:278615	Lactide	Polylactic acid	Heating a lactide, a cyclic imide compd., e.g. succinimide, and a polymn. catalyst, e.g. Sn octylate at 100-190°C with stirring under N(g) flow.	It is preferred that the amt. of the cyclic imide compd. is 1-35 mol.% based on the lactide. Even if an amt. of the polymn. catalyst is small, e.g. 0.00001-0.1 mol.%, based on the lactide, polylactic acid can be efficiently prepd. It is possible to avoid remains of the catalyst in the polymer and coloring of the polymer.
EP 778306 A2	127:82591	Aliphatic polyester, especially poly(lactic acid)	poly(lactic acid)-co-polycarbonate block copolyester	Transesterification between polyester and polycarbonate polymers	The copolymer is prepd. by reacting an arom. polycarbonate with an aliph. polyester in the presence of a catalyst. The copolymer films has better degradability than arom. polycarbonate, transparency equal to polycarbonate, better thermal resistance than aliph. polyester, and melt flowability superior to arom polycarbonates.
EP 96-114321	126:268544	Lactide	Triblock copolymer	Sequential ROP of dimeric lactones of lactic acid and glycolic acid and of caprolactone	bioabsorbable, ternary block copolymer consisting of (A) polylactic acid segment, (B) poly(e-caprolactone) segment and (C) polyglycolic acid segment, useful for biomedicals.

JP 09031179 A2	126:238836	Lactide	Lactic acid-based polyester-polyether resins	ROP of lactide with a polyether macro-initiator	A linear ethylene oxide-propylene oxide block copolymer (wt.-av. mol. wt. 4050) 20, L-lactide 76, and D-lactide 4 g were polymd. to give a polymer with no.-av. mol. wt. 25,000, wt.-av. mol. wt. 35,000, Tg 53°, m.p. 153°, and tensile strength 290 kg/cm2.
EP 712880 A2	125:88094	Poly(lactic acid) + poly(butylene succinate)	Degradable block copolyester	Copolymerization by mutual transesterification	Polylactic acid and oly(butylenes succinate) refluxed together in a solvent with b.p. higher than 180° and and with capacity of water removal by azeotroping (ethers, alkylaryl ethers, and di-Ph ether), using metals of group II, III, IV, and V and oxides or salts thereof as catalysts, singly or as a mixture, to give co-polymer with high transparency in addition to strength and elongation as well as very good heat resistence.

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CHAPTER - 2

CHAPTER – 2: SCOPE AND OBJECTIVE OF THE PRESENT WORK

2.1. Objectives of the present thesis

The present investigation concerns dehydropolycondensation followed by postpolymerization of L-lactic acid into poly(L-lactic acid)s polymer (PLA). considerable work has been carried out in the past in the field of dehydropolycondensation. They deal with aspects of molecular weight, yield, racemization and cyclic dilactone formation using different catalysts [1-3]. However, an in-depth study of the nature of the end groups has generally been lacking. For any successful postpolymerization of lactic acid oligomers, existence of appropriate end groups is a key requirement. The end groups, however, may or may not be retained in these forms if there are side reactions, for example cyclization, or dehydration of the hydroxyl terminal giving rise to olefinic double bonds, or if there are impurities in the monomer that can derivatize the end groups and consequently stop further condensation. But these possibilities have not so far been studied thoroughly.

Among postpolymerization processes of L-lactic acid oligomers, solid state polymerization (SSP) has been one that has attracted much industrial attention. SSP of L-lactic acid has, however, been found to be slow. Several attempts to increase the reaction rate of L-lactic acid via SSP are found in the literature. These include enriching the crystallinity and increasing the melting point by thermal curing [4], and using crystal-nucleating agents like magnesium stearate, titania etc. [5], using a solid solution of granular PLA oligomer and biphenyl ether for obtaining better diffusion of by-product by increasing the porosity of the prepolymer [6]. Increasing the mobility of the reactive end groups residing in the amorphous region of the semicrystalline PLA prepolymer can be another approach for increasing the rate of SSP.

Condensation of oligomers after activation of end groups by derivatization and chain extension of oligomers by reacting with coupling agents are also common modes of postpolymerization of L-lactic oligomers. Dialkyl carbodiimides are good activating agents of the carboxylic acid end group, thereby promoting condensation by acylation of the hydroxyl terminal [7a-d]. But the reaction is limited by certain side reactions. The protocol has been reportedly used for postpolymerization of L-lactic acid oligomer [8a,b], but no attempts to study the effect of parameters like solvent, temperature and catalyst on the side reaction and on the progress of reaction and build-up of molecular weight has been made. Coupling reactions using telechelic L-lactic acid oligomers are reported to result in chain-extended polyester-urethanes, polyester-amides and polyester-carbonates. A new class of coupling agent was targeted, which would result in aliphatic copolyester from lactic acid oligomer. Synthesis of aliphatic polyester-carbonate from lactic acid oligomer without incorporation of any extra aliphatic moiety in the backbone was also intended with the use of a suitable coupling agent.

Copolyesters and copolyester-amides of L-lactic acid have been prepared with ring opening polymerization of L,L-dilactide (L-lactide) with small lactones and lactams like caprolactone, valerolactone, butyrolactone and caprolactam. Copolymerizations with macrocylic lactones and lactams have not been achieved. Such copolymers of lactic acid are therefore limited to incorporation of only short-chain aliphatic moieties as comonomeric units. Copolymerization by simultaneous dehydro-polycondensation with hydroxy-acid derivatives of long chain fatty acids can easily remove this limitation and increase the potential of property variation by incorporation of long aliphatic moieties in the backbone of PLA. Such copolymers have not been reported thus far.

2.2. Approaches:

Synthesis of L-lactic acid oligomers and characterization of end groups: L-lactic acid oligomers would be synthesized by dehydro-polycondensation using Lewis acid catalysts, their carboxylic end groups would be determined using ^{13}C-NMR spectroscopic technique. The validity of the NMR technique for determination of carboxylic acid end groups would be established by preparing model L-lactic acid oligomers having known number average molecular weight through controlled ring opening polymerization of L-lactide. The existence of carboxylic acid and hydroxyl end groups as such would also be checked using MALDI-ToF, which would also show derivatization, if any, of the end groups due to either side reactions or impurities.

Postpolymerization of poly(L-lactic acid) oligomers by solid state polymerization in presence of a chemically inert plasticizer in order to increase the reaction rate: A suitable plasticizer for poly(L-lactic acid) would be found, which would neither react with the end groups nor attack the ester linkages in the backbone. Solid state polymerization would be performed in presence of such a plasticizer, in order to see if the enhancement of mobility of the end groups in the amorphous region could bring about an increase in the rate of the postpolycondensation. The plasticizer would be so chosen as to be non-volatile at the reaction temperature.

Detailed study of effect of different reaction parameters on the progress of postpolymerization in presence of a carboxylic acid activating agent: Diisopropyl carbodiimide was chosen as the carboxylic acid derivatizing agent, which would enhance the acylation of the hydroxyl end group through an irreversible reaction forming an alkylurea by-product, which was non-reactive.

Use of new coupling agents for chain extension: Diol-terminated telechelic poly(L-lactic acid)s would be synthesized by using a small percentage of an aliphatic diol, namely 2,5-hexanediol, along with the lactic acid monomer during dehydropolycondensation. The particular diol was chosen so that all the end groups remain secondary hydroxyl, like that in lactic acid itself, in order to avoid a mixture of primary and secondary hydroxyl end groups, which are widely different in reactivity as nucleophiles. μ-isopropylbis-(ε-caprolactone) and diphenyl carbonate would be chosen as coupling agents, to prepare a chain-extended copolyester and a chain-extended copolyesr-carbonate, respectively, by coupling the telechelic through the hydroxyl terminals.

Synthesis of new copolyesters material having long aliphatic (alkylene) group: 12-Hydroxy stearic acid was chosen as the co-monomer and would be co-polycondensed with L-lactic acid, in order to synthesize a copolyester of lactic acid having long aliphatic moieties at various places of the backbone. At the same time each repeating unit due to the co-monomer would contribute one 6-carbon aliphatic pendant that was expected to internally plasticize the resultant polyester.

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CHAPTER - 3

CHAPTER 3: ANALYSIS OF L-LACTIC ACID AND POLY(L-LACTIC ACID)S

3.1. Introduction

In the dehydropolycondensation of L-lactic acid (LLA) to poly(L-lactic acid) (PLA), small amounts of impurities are expected to play a major detrimental role. LLA prepared by fermentation of biomass may contain impurities derived either from the fermentation step itself or from the separation and purification steps after fermentation. Several impurities, for example, methanol, ethanol, acetic acid, pyruvic acid, some dicarboxylic acids like oxalic, fumaric and succinic acids etc. have been reported to occur in the fermentation derived L-lactic acid [1]. The level as well as nature of impurities in the polymerization is believed to have a large effect on the final molecular weight by end capping either the hydroxyl or the carboxylic acid terminal of the growing polymer chain and thereby limiting the chain growth. It has been found that total level of interfering impurities should be less than 100 ppm [2] for obtaining high molecular weight PLA.

This chapter describes the effort to analytically detect and quantitate the level of impurities in the LLA to be used for all polymerization reactions in the subsequent chapters. The LLA obtained as an aqueous solution was esterified with ethyl alcohol to form ethyl L-lactate. Both the LLA aqueous solution and the ethyl lactate were analyzed by gas liquid chromatography (GC).

Controlled ring opening polymerization (ROP) of L,L-dilactide (the dilactone of LLA, alternatively called L-lactide) was also performed with stannous 2-ethylhexanoate (stannous octoate, $Sn(Oct)_2$) catalyst and measured amount of water as co-initiator, to produce linear PLA oligomers of well-defined number average molecular weight with carboxylic acid and hydroxyl end groups. These polymers were desired as model PLA oligomers for any LLA that would be prepared in the work described in subsequent chapters. The carboxylic end groups were also quantitatively determined using ^{13}C NMR spectroscopic technique, which in turn, was used to calculate the $\overline{M}_n$.

3.2. Materials and methods:

Materials: L-lactic acid (LLA) was obtained from PURAC Chemical Company, Holland, in the form of 88 % aqueous solution and was used as such, without any purification.

Ethanol and benzene were both obtained from S. D. Fine Chemicals, India. Ethanol was purified by distillation and dried on fused calcium chloride followed by magnesium ethoxide before use. Benzene was purified (freed of thiophene) by stirring with 98 % H_2SO_4, washed with sodium bicarbonate and water, followed by drying first over fused calcium chloride and then over sodium metal. THF was dried over fused calcium chloride followed by calcium hydride (CaH_2). Trimethylsilyl chloride (TMSCl), acetone, 98 % H_2SO_4, sodium carbonate, fused calcium chloride and sodium metal were all obtained from S. D. Fine Chemicals, India, and used without purification. CaH_2 was procured from Aldrich Chemicals and was also used without any purification. L,L-dilactide was procured from Aldrich Chemicals and was used after recrystallization from dry THF. Doubled distilled and de-ionized water was used as co-initiator of ROP reactions. $Sn(Oct)_2$ catalyst was procured from Aldrich Chemicals and freshly distilled before use.

Preparation of ethyl lactate from L-lactic acid: L-lactic acid was azeotropically dried with benzene (thiophene-free) without any catalyst, followed by removal of benzene under reduced pressure of 0.1 mbar at 60 °C (5 h). The dry, waxy solid (10 g) was esterified by refluxing in dry ethanol (50 mol/ mol of LLA) with a few drops of 98 % H_2SO_4 as catalyst for 20 hours, with intermittent (azeotropic) distilling out of ethanol and by-product water at every 4 hours. After 20 h the whole reaction mixture was distilled up to dryness, so that all ethanol together. Further fractional distillation at the boiling point of ethanol and under atmospheric pressure removed ethanol and yielded 9.87 g (86 %) pure ethyl lactate (b.p. observed 155 °C, lit. 154 °C).

General procedure for ROP of L-lactide: To 2.20 g (0.015 mol) L-lactide (recrystallized and dried) taken in single-neck, 250 mL volume round bottomed flask, previously passivated with 30 % acetonic solution of TMSCl followed by drying, maintained under inert (argon) atmosphere, was added $Sn(Oct)_2$ catalyst (0.1214 g, 2 mol% of lactide) and de-ionized water (0.008 mL, 0.03 mol/ mol of lactide) was added subsequently using a hypodermic syringe. The mixture was stirred at room temperature for 5 h, followed by evacuating and sealing under vacuum and then heating at 120 °C for 12 h.

3.3. Analysis:

Gas liquid chromatography (GC): GC-analysis of L-lactic acid was done on Perkin Elmer GC Auto System XL-200 by injecting 0.1, 1 and 10 microliter injection volumes of the LLA 88 % aqueous solution as such to a Perkin-Elmer BP-20 (polyethylene oxide, terephthalic acid treated) capillary column of 25 meter length by means of on-column injection procedure and comparing with the chromatograms of aqueous solutions of 4, 9 and 19 ppm (that is below 5, 10 and 20 ppm, respectively) concentrations each of methanol, ethanol, acetic acid, and pyruvic acid. The split ratio was 1:60, the detector was FID, the carrier gas was nitrogen with a pressure of 7 psi and the fuel for FID was hydrogen. Oven was isothermal at 50 °C for 30 min, followed by heating with a ramp rate of 5 °C/ min from 50 °C till another 30 min. The injector and detector were kept at 250 and 280 °C, respectively. Dicarboxylic acids, namely oxalic, fumaric and succinic, did not elute through this column.

Ethyl lactate was analyzed under the same conditions, except that the column was Perkin-Elmer BP-21 (polysiloxane) and the injection was done in normal injection mode, where the sample evaporated inside the injector and went into the column in a gaseous form. Ethyl lactate chromatograms (corresponding to 0.1, 1 and 10 microliter injection volumes) were compared with chromatograms of ethanolic solutions of 4, 9 and 19 ppm (that is below 5, 10 and 20 ppm, respectively) concentrations each of diethyl oxalate and diethyl succinate.

Molecular weights: Molecular weights (relative, $\overline{M}_n$ and $\overline{M}_w$) and polydispersity ($\overline{M}_w/\overline{M}_n$) were determined with respect to polystyrene standards by size exclusion chromatography on a Thermo Finnigan Spectra Series AS300 machine at 25 °C by eluting PLLA solutions of 10 mg/ mL concentration in $CHCl_3$, with toluene as internal standard, through a series of five μ-Styragel columns of pore sizes 10^5, 10^4, 10^3, 500, and 100 A°, respectively, and length 30 cm each. $CHCl_3$ was used as the mobile phase (flow rate 1 mL/ min) and a refractive index detector (Spectra Series RI-150) was used for detection of different molecular weight fractions. Molecular weights were calculated with respect to polystyrene calibration. Number average molecular weights and intrinsic viscosities were determined with the help of a KNAUER K-7000 Vapor Pressure Osmometer (25 °C) and a 3-arm Ubbelohde viscometer (SCHOTT GERATE) at 30 °C in chloroform.

Quantitative ^{13}C-NMR spectroscopic analysis: For NMR measurements, the samples were dissolved in Chloroform-d in 5 mm dia. NMR tubes at room temperature. The chemical shifts in parts per million (ppm) were reported up field with reference to internal standard chloroform-d at 7.25 ppm. The sample concentration for ^{13}C NMR measurements was 10 % by weight. Proton decoupled ^{13}C NMR spectra with NOE were recorded on a Bruker DRX 500 MHz NMR spectrometer working at 125.577 MHz for Carbon-13. $CDCl_3$ served as solvent and TMS as internal standard for all ^{13}C-NMR measurements. Relative peak areas were proportional to the number of carbon atoms. Peak areas were calculated by deconvolution method using WIN-NMR software.

Thermal analysis: Differential scanning calorimetric (DSC) measurements were made on a Perkin-Elmer thermal analyzer model DSC-7 in a nitrogen atmosphere. The measurements were run from –40 to 200 °C at a heating rate of 10 °C/ min and a cooling rate of 100 °C/ min. The glass transition temperature (T_g) and the crystallinity data were recorded from the second and first heating curves, respectively. Crystallinity values for different polymers were calculated from the heat of fusion. By integrating the normalized area of the melting endotherm, determining the heat involved, and rating it to the reference 100 % crystalline polymer (93.6 J/ g) [9], the relative crystallinity of the polymer was assessed. In the present work, the relative degree of crystallinity is referred to as crystallinity, and T_m is the melting temperature.

X-ray analysis: Wide angle X-ray scattering (WAXS) pattern of the samples was obtained in reflection mode using a Rigaku Dmax 2500 diffractometer and Ni filtered copper radiation. The sample was scanned in the range $2\theta = 10 - 35\ °$ and the generator was operated at 40 kV and 150 mA. The FWHM of the 110 peak was determined by peak fitting software available with the Rigaku diffractometer.

3.4. Results and discussion:

3.4.1. Impurity detection and analysis in the L-lactic acid and ethyl L-lactate

L-lactic acid: Individual levels of different impurities as shown in Table-3.1. Presence of L-lactide was also detected, but its quantification was not attempted because its formation inside the GC column was also possible, since LLA is a thermally labile material. Although methanol, ethanol, acetic acid and pyruvic acid were individually detectable up to 4 ppm level from respective aqueous solutions, they were not found in the LLA sample when injected. So it was thus concluded that pyruvic acid was present in less than 5 ppm level in the LLA sample.

Table-3.1: Detection limits of different alcoholic and monocarboxylic acid impurities in LLA

Impurity type	Methanol	Ethanol	Acetic acid	Pyruvic acid
Impurity level (ppm)	<5	<10	<10	<5

Ethyl lactate: No impurities peaks were found in the ethyl lactate sample when injected (cut off time of 4 min given for ethanol). Impurities with boiling points less than that of ethanol had presumably been removed at the time of removal of ethanol. However, any impuritiy with a boiling point higher than ethanol should remain in the sample after esterification. But the fact that no impurities were found implied that the peaks found after the LLA peak during elution of the LLA aqueous solution sample might be due to small oligomers of LLA. The detection level of diethyl oxalate, diethyl fumarate and diethyl succinate was about 4 ppm, under the specified condition of anaysis. Thus it can be inferred that these impurities were present in less than 5 ppm concentration in the ethyl lactate sample.

Table-3.2: detection limits of different dicarboxylic acid impurities in LLA

Impurity type	Oxalic acid	Fumaric acid	Succinic acid
Impurity level (ppm)	<5	<5	<5

The GC analysis thus unambiguously ascertained the total level of interfering impurities to be less than 30 ppm. Traces of L-lactide that was found could be either due to its presence as an impurity in the sample or its formation during the elution through the heated GC column, or both.

3.4.2. Synthesis and characterization of linear PLA oligomers of controlled number average molecular weight and with both carboxylic and hydroxyl end groups

Synthesis, by ROP of L-lactide: $Sn(Oct)_2$-catalyzed (or, -initiated) ring opening polymerization (ROP) of lactonic monomers, including L-lactide, in presence of alcoholic co-initiators proceeds via a coordination-insertion mechanism of initiation and propagation [4-6], (Scheme-3.1).

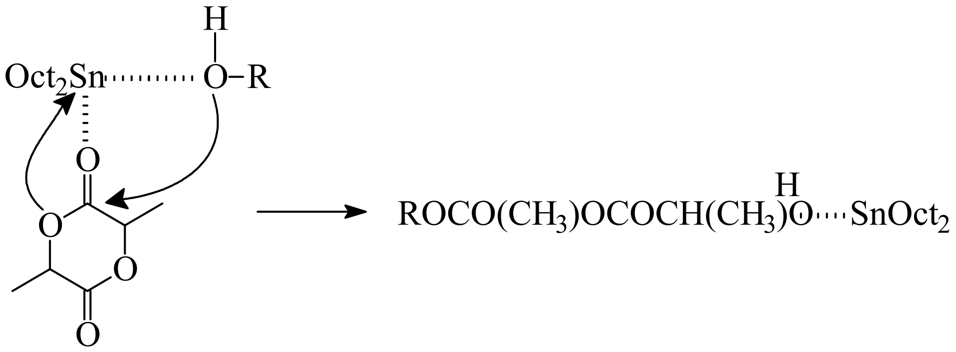
In the present work, L-lactide was thoroughly dried under vacuum and all precautions were taken to avoid ingress of moisture during the reactions. Water was used as the co-initiator, so that carboxylic acid end groups instead of ester end groups as found in the Scheme-3.1 could be generated at the terminal of each PLA oligomer chain.

The number average molecular weight and degree of polymerization, $\overline{M}_n$ and $\overline{DP}_n$, respectively, of PLA oligomers thus prepared were calculated as:

$$\overline{M}_{n,} = ([M] / [I]) \text{ x } M_{CL} \text{ x conversion \%}$$

$$\text{and } \overline{DP}_n = ([M] / [I]) \text{ x conversion \%}$$

Scheme-3.1: Coordination-insertion mechanism of ROP of L-lactide



Where [M] = moles of monomer, [I] = moles of co-initiator (water) and M_L = molecular weight of L-lactide. Conversion was determined from yield of PLA oligomer.

Determination of molecular weights of oligomers: The achieved degree of polymerization and number average molecular weight was determined from the ratio of integral of the ester carbonyl carbon to that of the carboxylic acid carbonyl carbon in the 13C-NMR spectrum, as shown in Fig. 3.1. Number average molecular weights of these oligomers were also determined by vapor pressure Osmometry (VPO). Both theoretically calculated and experimentally obtained values of these parameters are organized in the data shown in Table-3.3.

The theoretically calculated and experimentally obtained values of these parameters were found to be in very good agreement, thereby indicating successful use of water as a co-initiator in the ROP of L-lactide.

Table-3.3: Number average molecular weights of the PLA oligomers synthesized by ROP of L-lactide with water as co-initiator and $Sn(Oct)_2$ as initiator.

PLA sample	[Lactide]/ [$Sn(Oct)_2$]	[Lactide]/ [H_2O]	Conv. (%)	$\overline{DP}_{n, Calc}$	$\overline{DP}_{n, NMR}$	$\overline{M}_{n, NMR}$	$\overline{M}_{n, VPO}$
3.1	200	32	86	55	60	4320	4400
3.2	400	45	87	79	77	5544	5692

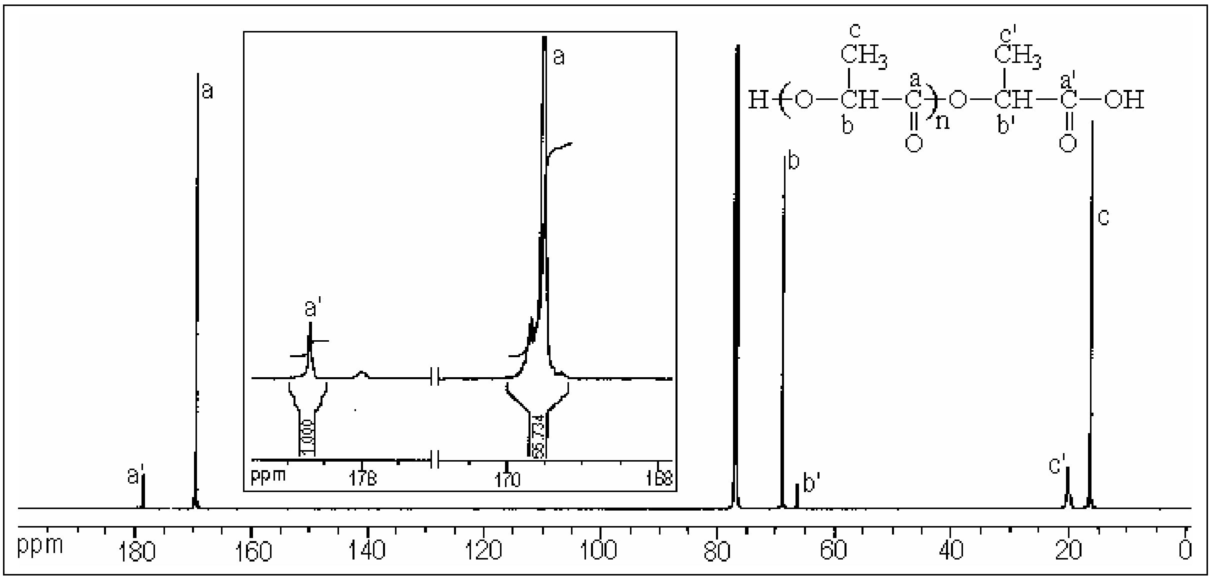


Fig. 3.1: ^{13}C-NMR spectrum (500 MHz) of PLA oligomer 3.1 synthesized by ROP of L-lactide: inset showing ester carbonyl region (ester as well as carboxylic acid) as enlarged.

Thermal characterization (DSC) and powder XRD of oligomers: the thermal characterization data (melting point, T_m, and glass transition temperature, T_g) of the two oligomer samples 3.1 and 3.2 are shown in Table-3.2, as well as in Fig. 3.4. Both oligomers had similar values of T_m and T_g. effect of $\overline{DP}_n$ on T_m is also evident from the result. Anomalous appearance of more than one melting points in the second heating cycles might be due to presence of different crystallites corresponding to widely varying chain lengths of PLA in the sample.

Table-3.4: Thermal characterization and crystallinity values of PLA oligomers synthesized by ROP of L-lactide

PLA samples	T_g (°C)	T_m (°C)	$\Delta H_{melting}$ ($J.g^{-1}$)	% Crystallinity from powder XRD
3.1	48	141	53.4	85
3.2	51	162	59.7	85

The powder XRD patterns of the two oligomers are shown in Fig. 3.3, where it can be found that the two polymers had almost identical patterns, as expected. The % crystallinity values of the oligomers calculated from these XRD patterns are shown in Table-3.3, and they were also found to be similar.

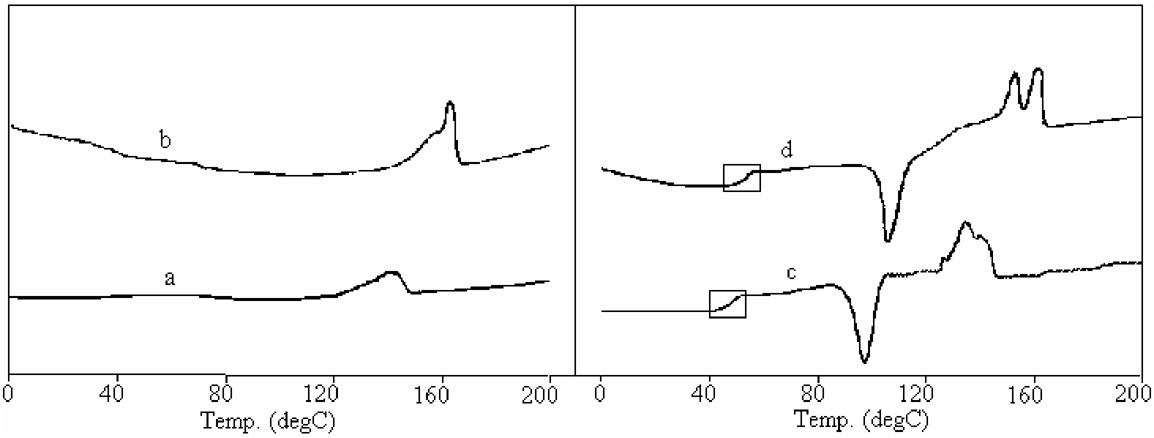


Fig. 3.2: Thermal characterization (DSC) first and second heating showing T_m and T_g, respectively of PLA oligomers: (a) 3.1, first heating; (b) 3.2, first heating; (c) 3.1, second heating and (d) 3.2, second heating.

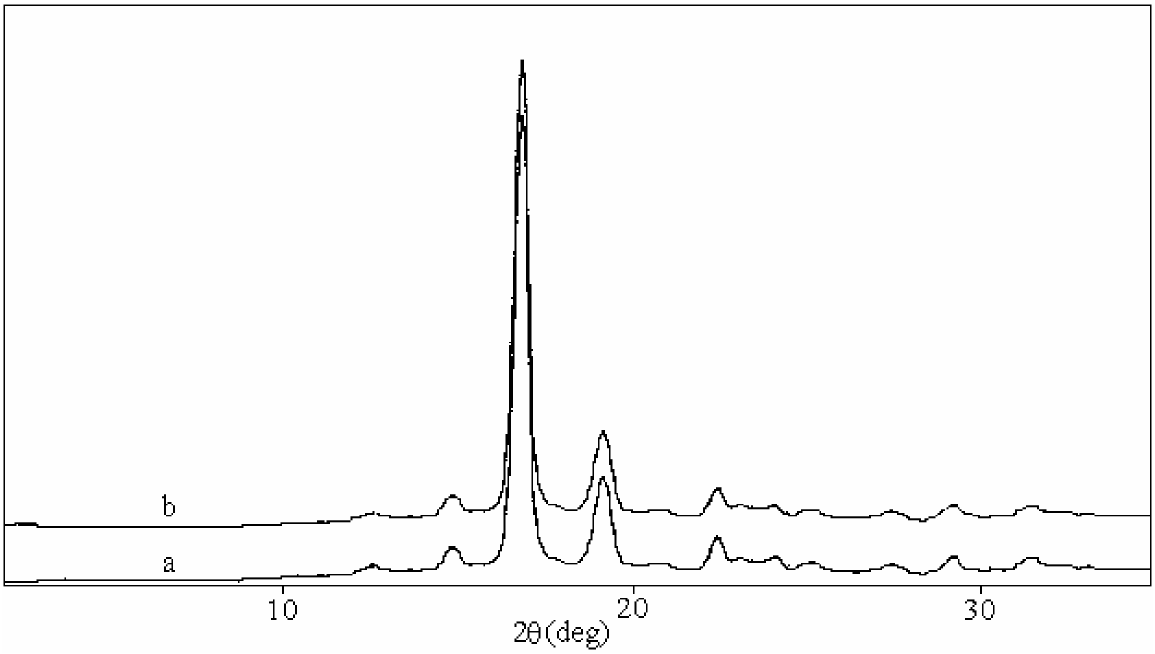


Fig. 3.3: Powder XRD patterns of PLA oligomers: (a) 3.1 and (b) 3.2.

3.5. Conclusion:

Impurities such as ethanol and acetic acid were detected to be present in less than 10 ppm level in the PURAC L-lactic acid sample, while the other impurities such as methanol, pyruvic acid, oxalic acid, fumaric acid and succinic acid were present in less than 5 ppm level each. Thus, the total impurities detected was less than 30 ppm.

Linear PLA oligomers of controlled molecular weight were successfully prepared for the first time using ring opening polymerization (ROP) of the L-lactide using water as the co-initiator. These polymers were terminated by carboxylic acid at one end and hydroxyl at the other. The molecular weights ($\overline{M}_n$) as determined by ^{13}C-NMR technique were in good agreement with those determined by VPO.

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CHAPTER - 4

CHAPTER – 4: DEHYDROPOLYCONDENSATION OF L-LACTIC ACID TO POLY(L-LACTIC ACID) OLIGOMERS

4.1. Introduction:

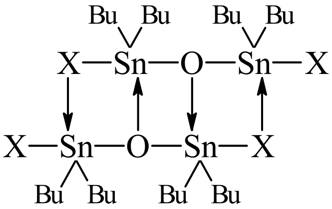
The shift in the interest concerning poly(lactic acid) (PLA) from a specialty biocompatible, medical-use polymer to environmentally friendly, commodity, low-end consumer thermoplastic is of a recent origin [1]. The driver behind this shift is the increasing consumer need for a biodegradable polymer and the substantial improvement in the biotechnology of fermentation processes for the production of L-lactic acid (LLA). Significant efforts have been invested in recent years in studies concerning the effect of catalyst on the properties of PLA. Catalysts such as $SnCl_4$ [2], coordination catalysts (containing Zn and Al) [3], aluminium isopropoxide [4], and various other Lewis acid catalysts [5, 6] have been used in the ring opening polymerization (ROP) of L-lactide. Catalysts used in ROP define the microstructure, stereosequence and molecular weights of the polymer, which in turn, determine the properties of the polymer.

On the contrary, direct dehydropolycondensation of L-lactic acid (LLA) has received relatively less attention. The commercially available LLA produced by fermentation contains ca. 12 % water, which requires the polycondensation catalyst to be water-tolerant. To avoid such difficulties, in most commercial processes, LLA is initially converted to the corresponding dilactide, which is isolable in an anhydrous form. This dilactide is subjected to ring opening polymerization (ROP).

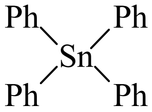
Yamaguchi and co-workers [7] studied the direct condensation of LLA using various Bronsted and Lewis acid catalysts through continuous azeotropic dehydration where the recycled solvent is passed through a tube packed with molecular sieves to maintain the amount of water in the solvent to less than 3 ppm. Otera et al [8] showed that distannoxanes, which are already known to be good esterification and transesterification catalysts, are also effective catalysts for the direct dehydropolycondensation of L-lactic acid to poly(L-lactic acid). Appropriately substituted distannoxane catalysts are themselves hydrophobic in nature because of bulky alkyl groups around the tin atoms, which are the catalytic centers, and are able to retard the hydrolysis of ester linkages to some extent. Based on a study of variation of the substituents (**4.1**, R = n-Bu, X = Cl, OH, NCS) on the distannoxane ladder structure, it was concluded that the molecular weights of the obtained polymers are relatively insensitive to the nature of the substituents.

This chapter reports the preparation of a number of 1,3-disubstituted tetraalkyldistannoxanes (**4.1**: R = n-Bu and X = OC_6H_5 (**4.1a**), $OCOCH_3$ (**4.1b**), Br (**4.1c**), Cl (**4.1d**)) and a study of their effect on the molecular weight of the PLLA polymer obtained by dehydro-polycondensation of LLA. The catalysts were fully characterized and model dehydro-polycondensation reactions were carried out to obtain low molecular weights polymers/ oligomers.

	X
a	OC_6H_5
b	$OCOCH_3$
c	Br
d	Cl



4.1



4.2

Tetraphenyltin (**4.2**), another tin Lewis acid, has also been widely used in ROP of lactonic monomers, especially lactides. However, there is no report of use of tetraphenyltin as a catalyst for direct dehydropolycondensation. Therefore, tetraphenyltin was explored as a catalyst for the synthesis of PLLA oligomers from LLA by the direct dehydropolycondensation technique. Besides, tetraphenyltin is a catalyst approved by FDA and, therefore, can be used safely for the synthesis of polymers targeted for biomedical applications.

The dehydropolycondensation of LLA was studied in solution as well as in bulk using tetraphenyltin and the distannoxane as catalysts. The PLA oligomers were analyzed by using various techniques, namely Matrix-Assisted Laser Desorption/ Ionization – Time of Flight Mass Spectrometry (MALDI-ToF MS), quantitative ^{13}C NMR analysis, size exclusion chromatography (SEC), wide angle X-ray diffraction analysis (WAXRD), and vapor pressure osmometry (VPO). While SEC and VPO give the weight average and number average molecular weights, respectively, the determination of end groups (carboxylic acid) of the PLLA polymers by acid-base titration method is rather erroneous and not quantitative because of the hydrolysis of aliphatic ester linkages. However, the identification and quantification of end groups is necessary and important to ascertain the suitability of the oligomer for any postpolymerization process, such as, solid state polymerization, chain extension and coupling reactions. The identification of end groups of PLLA oligomers prepared by dehydropolycondensation has not been previously reported either by MALDI-ToF MS or 13C NMR spectrometry. Properties of oligomers obtained by solution- and bulk, melt-phase dehydropolycondensation polymerization using **4.2** and **4.1d** as catalysts are also reported in this chapter.

4.2. Materials and Methods:

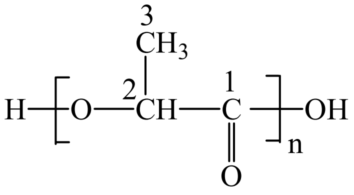
Materials: L-lactic acid was obtained form PURAC as 88 % (w/w) aqueous solution and was used without further purification. Tetraphenyltin, dibutyltin oxide, dibutyltin acetate, dibutyltin dibromide, and dibutyltin dichloride, all obtained from Aldrich, were used without further purification. p-Xylene, mesitylene and decalin (mixture of isomers of decahydronaphthalene) from Aldrich were also used without further purification. Phenol was obtained from S. D. Fine Chemicals and was recrystallized from hot water.

Synthesis of distannoxane catalysts: Catalyst **4.1d** was prepared by condensing 1.5192 g (0.5 mmol) n-butyltin dichloride and 1.2446 g (0.5 mmol) di-n-butyltin dioxide in benzene for 10 h. Crude product was obtained by evaporating benzene and purified by crystallization form a minimum amount of hot n-hexane. The other three tetra-n-butyl distannoxane catalysts, **4.1c**, **4.1b** and **4.1a**, were prepared by similarly condensing 1.13 mL (0.5 mmol) dibutyltin dibromide, 1.33 mL (0.5 mmol) dibutyltin diacetate and 0.47 g (0.5 mmol) phenol, respectively, with equimolar amount of dibutyltin oxide. Pure catalysts were identified by melting points and gravimetric analysis (Table-4.1).

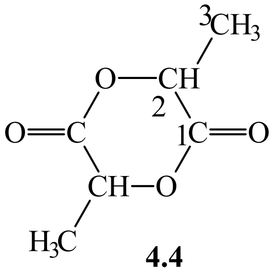
Passivation of glass surface: Inner surface of glass reactors whenever required were passivated by treating with TMSCl (30 % w/v acetone solution), washed with methanol, dried at 150 °C in an oven and cooled immediately before polymerization reaction.

General procedure for synthesis of PLLA by direct dehydropolycondensation: Using a reaction flask equipped with a Dean & Stark type condenser, 40.2 g of 88 % L-lactic acid was azeotropically dehydrated using 40 mL of a non-polar, aprotic, organic solvent for 6 h at the reflux temperature of the corresponding azeotrope without any catalyst. After removal of water in the trap of the Dean & Stark condenser the reaction vessel was cooled to 50 °C. For bulk polymerization, this azeotroping step was performed with the help of a efficient yet low boiling solvent like benzene and the waxy material obtained after azeotrope was dried under high vacuum (0.1 mbar) at about 50 °C for 5 h.

Subsequently, catalyst (0.01 mol% **4.1d** or 0.02 mol% **4.2**) was added followed by heating of the reaction mixture slowly up to the refluxing temperature of the solvent under mild stirring with the help of a magnetic stir bar. The reaction time was 15 h in all cases. After 15 h of stirring the reaction mixture was cooled to room temperature and 100 mL of chloroform was added. The resultant mixture was poured into 400 mL of n-hexane. The precipitated polymer, PLLA (**4.3**) was collected by suction filtration. The catalyst was removed by repeated dissolution and precipitation, and the polymer was finally washed



4.3



4.4

with further amount of n-hexane and dried under reduced pressure. ^{1}H-NMR (Fig.-4.1) δ (ppm, $CDCl_3$) 5.20 – 5.05 (q, 1H, H-2), 4.45 – 4.25 (q, 1/n H, H-2 at the last repeating unit) and 1.7 – 1.45 (d, 3H, H-3), where n was the number average degree of polymerization. A portion of the product volatilized during the reaction and condensed as a solid in the collector part of the Dean & Stark apparatus. This was identified as L-lactide (**4.4**) by comparison with the ^{1}H-NMR of pure, recrystallized L-lactide and also by melting point (m.p. 124 °C). ^{1}H-NMR δ (ppm, $CDCl_3$) 5.15 – 4.95 (q, 1H, H-2) and 1.60 – 1.45 (d, 3H, H-3) (Fig. 4.2).

4.3. Analysis:

Melting point determination: Melting points were recorded on a Thermonik Campbell melting point apparatus. All melting points are uncorrected and are recorded on the Celsius scale.

Microanalysis of carbon and hydrogen percentage: Elemental analyses (C, H) were obtained on a Carlo-Erba 1100 automatic CHN analyzer.

Gravimetric determination of tin: Gravimetric determination of tin (Sn) in the synthesized distannoxane catalysts was done by digestion of 10 mg catalyst in a mixture of 50 mL

2(N) sulfuric and 2 mL concentrated nitric for 30 minutes on a Guch (silica) crucible followed by repetition of a cycle of charring, washing with de-ionized water, drying in the oven and cooling in desiccators till constant weight and weighing as SnO_2.

Molecular weights: Were performed as described in chapter 3.

Nuclear magnetic resonance: For NMR measurements, the samples were dissolved in Chloroform-d in 5 mm dia. NMR tubes at room temperature. ^1H NMR spectra were recorded on a Bruker AC 200 Spectrometer at 200 MHz with 4 % w/v concentrations of solutions. The chemical shifts in parts per million (ppm) are reported up field with reference to internal standard chloroform-d at 7.25 ppm. The sample concentration for ^{13}C NMR measurements was 10 % by weight. Proton decoupled ^{13}C NMR spectra with NOE were recorded on a Bruker DRX 500 MHz NMR spectrometer working at 125.577 MHz for Carbon-13. ^{13}C-NMR spectroscopy was also performed on the Bruker DRX 500 MHz NMR spectrometer in 10 mm o.d. sample tubes. A digital resolution of 32 K data points/ 18,000 Hz spectral width was used, a pulse angle of about 30 ° along with a relaxation delay of 2s, and $10^3 - 10^4$ transients were accumulated. $CDCl_3$ served as solvent and TMS as internal standard for all ^{13}C-NMR measurements. Relative peak areas were proportional to the number of carbon atoms. Peak areas were calculated by deconvolution method using WIN-NMR software.

Thermal analysis: Were performed as described in chapter 3.

X-ray analysis: Were performed as described in chapter 3.

MALDI-ToF MS analysis: MALDI-ToF MS analysis was performed on a Kratos Kompact MALDI IV spectrometer equipped with 0.7 m linear and 1.4 m reflection flight tubes as well as a 337 nm nitrogen LASER of pulse width 3 ns. All experiments were carried out at an accelerating potential of 20 kV. In general, mass spectra from 200 shots were accumulated to produce a final spectrum. The obtained data were smoothened to reduce the spikiness by the “average” method, where smoothening filter moves along the collected data channels adding together a number of channels and dividing by that number to give an average signal. This smoothening, however, does not eliminate or hide minor signals distinct form baseline noise. The samples were dissolved in tetrahydrofuran (1 mg/ mL) and mixed with the matrix (15 mg/ mL of THF) before drying on the sample plate. 2,4,6-trihydroxyacetophenone (THAP) was used as the matrix. The sample plate was inserted into the apparatus under high vacuum ($\sim 10^{-5}$ Pa).

4.4. Results and discussion:

4.4.1. Characterization of distannoxane catalysts: All four distannoxane catalysts were found to be pure after synthesis. The melting point values matched with reported values and elemental analysis of Sn, C and H agreed well with calculated values according to chemical formula (Table-4.1).

4.4.2. Choice of reactor material: Dehydropolycondensation of L-lactic acid was carried out in bulk and in decalin solvent for 15 h using 98 % sulphuric acid and using the catalyst 4.1d (0.1 mol%) in a round bottom flask. Three types of glass vessel were chosen, namely, borosilicate glass, borosilicate glass passivated with trimethylsilyl chloride and quartz.

The results are shown in Table-4.2 the polycondensation proceeded with greater efficiency in a quartz reactor and passivated glass reactors than untreated borosilicate glass reactors. Hence, all subsequent reactions were carried out in a quartz round bottom flask.

Table-4.1: Characterization of distannoxane catalysts prepared in laboratory

Distannoxane catalyst		m. p. (°C)	%C	%H	%Sn
4.1a	Determined value	137 – 140	50.45	6.82	36.21
	Reported/ calculated	137 – 139	50.34	6.89	35.57
4.1b	Determined value	58 – 60	39.38	6.26	40.01
	Reported/ calculated	No report	40.04	7.00	39.61
4.1c	Determined value	106 – 108	30.12	5.63	37.52
	Reported/ calculated	107 – 108	29.04	5.61	37.03
4.1d	Determined value	109 – 111	33.62	6.93	43.47
	Reported/ calculated	110 – 112	34.75	6.52	42.98

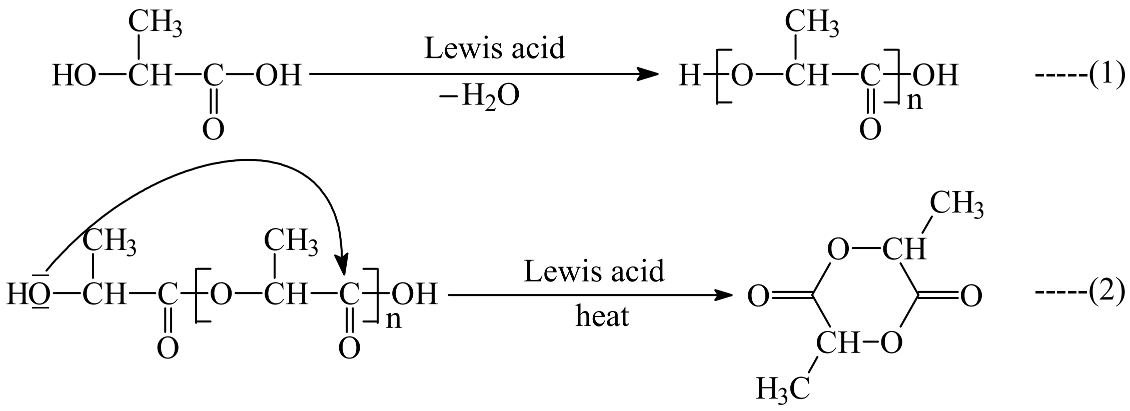
Dehydropolycondensation is a reversible reaction, where the ultimate molecular weight is dependent on the relative rates of forward (chain growth) and reverse reaction (hydrolysis). The reverse reaction is normally catalyzed by basic or acidic surfaces. Borosilicate glass surfaces are known to be mildly basic. Hence it is likely that in unpassivated borosilicate glass surface, the reverse hydrolysis process may become favorable leading to lower molecular weight of the polymer.

Table-4.2: Choice of reactor materialfor L-lactic acid dehydropolycondensation

Catalyst	Solvent	Catalyst	Time	[η] (dL/g) bare glass	[η] (dL/g) passivated	[η] (dL/g) quartz
98 % H_2SO_4	Nil	190 °C	10 h	0.16	0.25	0.29
4.1d	Nil	190 °C	10 h	0.17	0.25	0.32
4.1d	Decalin	190 °C	10 h	0.22	0.29	0.36

4.4.3. Effect of catalyst concentration: Since Lewis acid-catalyzed dehydropolycondensation is a reversible equilibrium reaction and PLA is known to undergo an irreversible, thermal unzipping, back-biting side reaction (Scheme-4.1), which is also Lewis acid-catalyzed, giving rise to reduction of molecular weight and simultaneous formatoin of L-lactide, the amount of catalyst used is, therefore, expected to play a critical role. Dehydropolycondensation was therefore performed in decalin solvent for 15 h using both **4.2** and **4.1d**, at different catalyst concentrations. The results of which are summarized in Table-4.3.

Scheme-4.1: Dehydropolycondensation of L-lactic acid and back-biting side reaction



The results show that 0.01 mol% of the dichlorodistannoxane (**4.1d**) catalyst and 0.02 mol% tetraphenyltin (**4.2**) gave rise to the highest molecular weight oligomers as well as lowest amounts of L-lactide. Any increase in concentration of either catalyst resulted in lower molecular weight of the obtained PLA oligomer and higher amount of lactide.

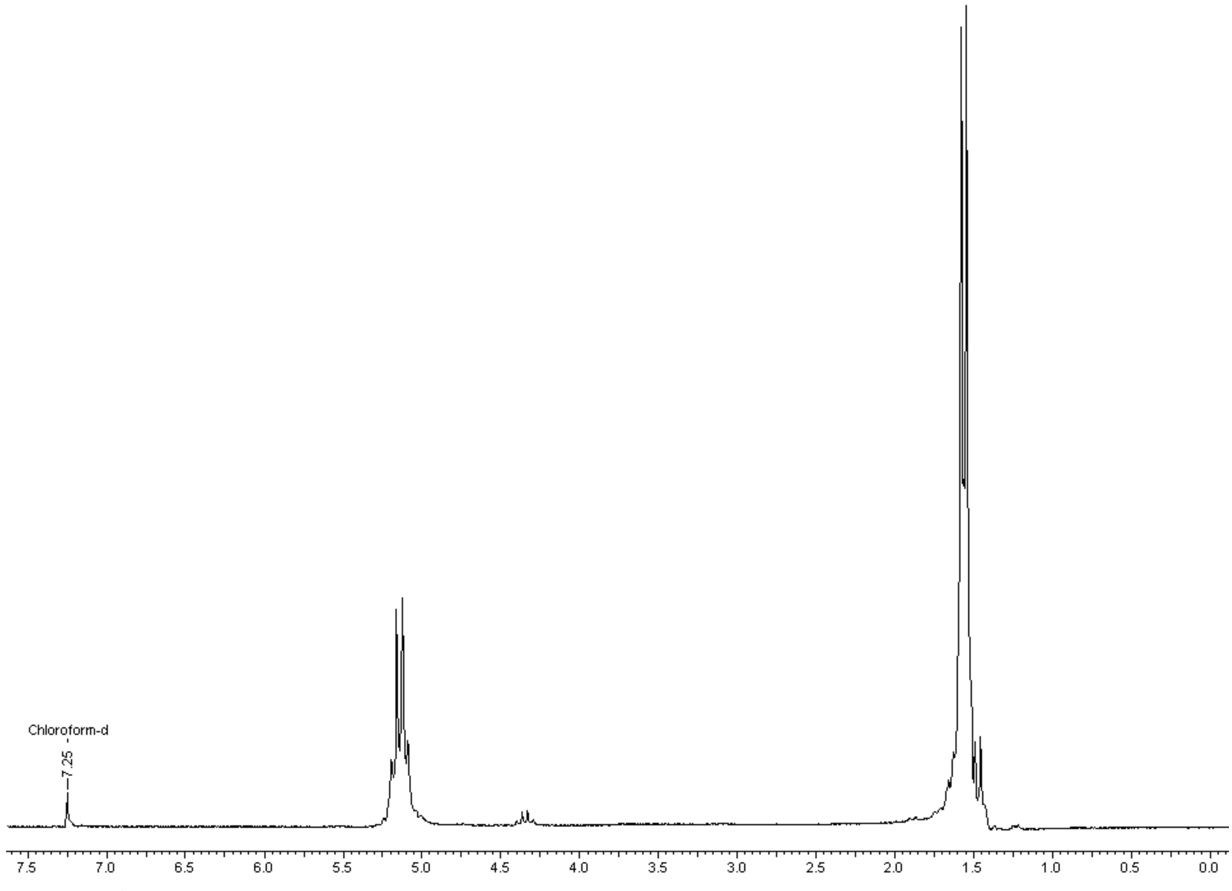


Fig. 4.1: ^{1}H NMR spectrum of poly(L-lactic acid) oligomer 4.3.1

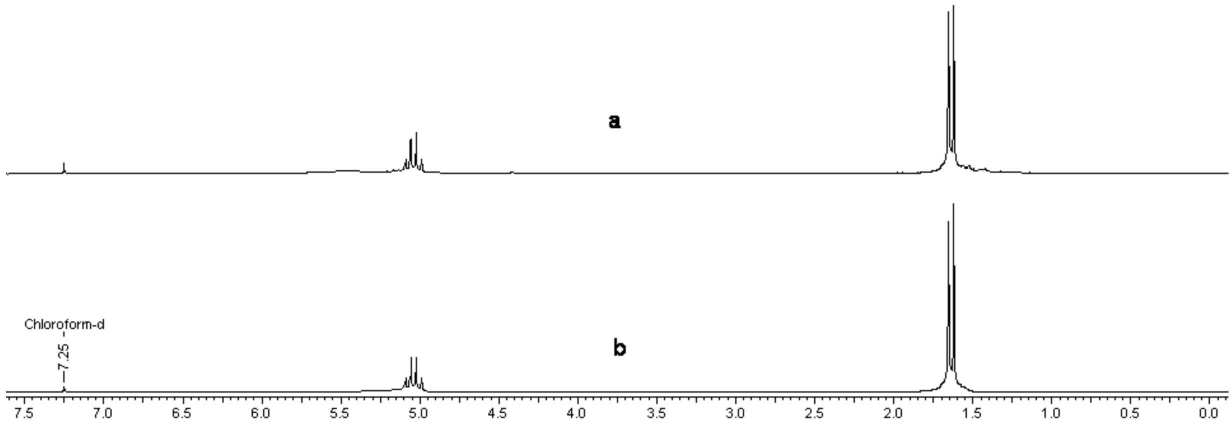


Fig. 4.2: ^{1}H NMR spectrum of L,L-dilactide (lactide) sample (a): produced as a volatile material and condensed as solid during dehydropolycondensation of L-lactic acid and (b): commercially availed from Aldrich and purified by recrystallization from THF.

Table-4.3: Effect of catalyst concentration on L-lactic acid dehydropolycondensation

Catalyst	Catalyst concn. (mol% of monomer)	[η] (dL/g)	Yield (%)	Isolated lactide (%)
4.1d	0.10	0.35	78	21
	0.02	0.33	70	28
	0.01	0.45	82	15
4.2	0.10	0.40	70	27
	0.05	0.49	70	28
	0.02	0.65	90	06

Therefore, all further dehydropolycondensation reactions were done with 0.01 mol% and 0.02 mol% concentration of distannoxane and tetraphenyltin catalysts with respect to number of moles of L-lactic acid monomer initially taken.

4.4.4. Effect of substitution on the distannoxane catalysts: Results of variation of substitution on the distannoxane catalyst and its effect on L-lactic acid dehydropolycondensation are summarized in Table-4.4. Otera et al [8] suggested that there is no effect of substituent variation of the distannoxane catalyst on the dehydropolycondensation, especially at low catalyst concentration (0.1 mol% and lower).

Table-4.4: Results of L-lactic acid dehydropolycondensation using different distannoxane catalysts

Distannoxane catalyst	Catalyst concn. (mol% of monomer)	[η] (dL/g)	Yield (%)	Isolated lactide (%)
4.1c	0.01	0.30	78	19
4.1b	0.01	0.30	76	24
4.1a	0.01	0.33	71	25
4.1d	0.01	0.45	82	15

But, different intrinsic viscosities of PLLA oligomers were obtained for different distannoxane catalysts in the present study, when dehydropolycondensation was performed in decalin at 190 °C for 15 h. The bromo-, acetylato- and phenolato-distannoxanes resulted in almost similar intrinsic viscosities of oligomers. But the dichlorodistannoxane resulted in significantly higher intrinsic viscosity as well reduced amount of lactide formation. The difference is likely to be due to the difference in the Lewis acidity of the various distannoxane catalysts.

4.4.5. Material balance: For a model reaction of dehydropolycondensation in decalin solvent at 190 °C using the dichlorodistannoxane (4.1d) catalyst for 15 h, the material balance was checked. The results are shown in Table-4.5. The substrate LLA, the 12 % water in that L-lactic acid sample, the weight of solvent, weight of catalyst, weight of synthesized oligomer in the reactor before work up, the weight of volatilized L-lactide that solidified and collected in the Dean & Stark apparatus and weight of any possible voltile products that would be trapped in a previously weighed amount of chilled methanol were taken into account. Formation of lactide due to thermal decomposition or degradation of low molecular weight L-lactic acid polymers, as shown in Scheme-4.1, is well discussed [10]. Good material balance was found with a loss of less than 5 wt% of starting material. A gas chromatographic analysis of the chilled material in the trap confirmed the absence of any volatile material.

Table-4.5: Material balance of a dehydropolycondensation reaction of L-lactic acid

Time	Inside the reactor		Outside the reactor	
	Material	Weight (g)	Material	Weight (g)
Before reaction	Lactic acid	35.36	Chilled MeOH	51.66
	Catalyst (0.01 mol%)	0.02		
	Decalin (solvent)	35.12		
	Total	**70.50**		
After reaction	Material inside reactor	64.51	Chilled MeOH	52.03
			L-lactide	5.28
			Total	**57.31**
Balance		***5.99***		***5.65***

4.4.6. Reproducibility: For similar model reactions of dehydropolycondensation in decalin solvent at 190 °C for 15 h and also in bulk at 190 °C for 15 h, reproducibility of results was checked using both 4.2 and 4.1d as catalysts (0.2 and 0.1 mol%, respectively), the results of which are summarized in Table-4.6.

Table-4.6: Reproducibility of results under different conditions (190 °C, 15 hrs)

Reaction medium	Catalyst	Catalyst concn. (mol%)	[η] (dL/g)	Yield (%)	Isolated lactide (%)
Decalin solvent	4.1d	0.01	0.45	82	15
		0.01	0.44	95	06
	4.2	0.02	0.63	80	20
		0.02	0.65	90	06
Bulk	4.2	0.02	0.40	72	25
		0.02	0.42	70	25
	4.1d	0.01	0.25	79	20
		0.01	0.27	83	18

The results were found to be reasonably reproducible. Only in the isolated lactide data there were a few discrepancies, which can be attributed to variable degree of volatilization of the formed lactide depending on small differences in the reflux rate. Yield of polymer in all the reactions was found to be complementary to the lactide formation. Reaction temperature of 190 °C and reaction medium of either bulk or solvent were chosen in all experiments described in discussions from Section 4.4.2 to Section 4.4.6.

4.4.7. Elucidation of structure and property of oligomers synthesized under different sets of reaction conditions:

Molecular weights: The SEC elugrams of poly(L-lactic acid) oligomer samples are all shown in Fig. 4.3. PLA oligomers **4.3.1**, **4.3.2** and **4.3.3** were prepared by dehydropolycondensation method using tetraphenyltin as a catalyst but using various solvents namely p–xylene, mesitylene and decalin, respectively, as shown in Table-4.7. Oligomer **4.3.4** was prepared by bulk polymerization using the same catalyst.

Oligomer **4.3.1** (Fig. 4.3a) showed a broad peak, whereas a bimodal peak was observed in case of oligomer **4.3.2** (Fig. 4.3b). Oligomers **4.3.3** (Fig. 4.3c) and **4.3.4** (Fig. 4.3d) showed a single monomodal peak each. The number average ($\overline{M}_n$) and weight average ($\overline{M}_w$) molecular weights for PLA oligomer **4.3.1** were 900 and 2100 respectively, while those for PLA **4.3.2** were 3400 and 6400 (first peak) and 600 and 700 (second peak), respectively. $\overline{M}_n$ and $\overline{M}_w$ of PLA **4.3.3** were 12,000 and 43,300, respectively, while those of PLA **4.3.4** were 6000 and 23,500.

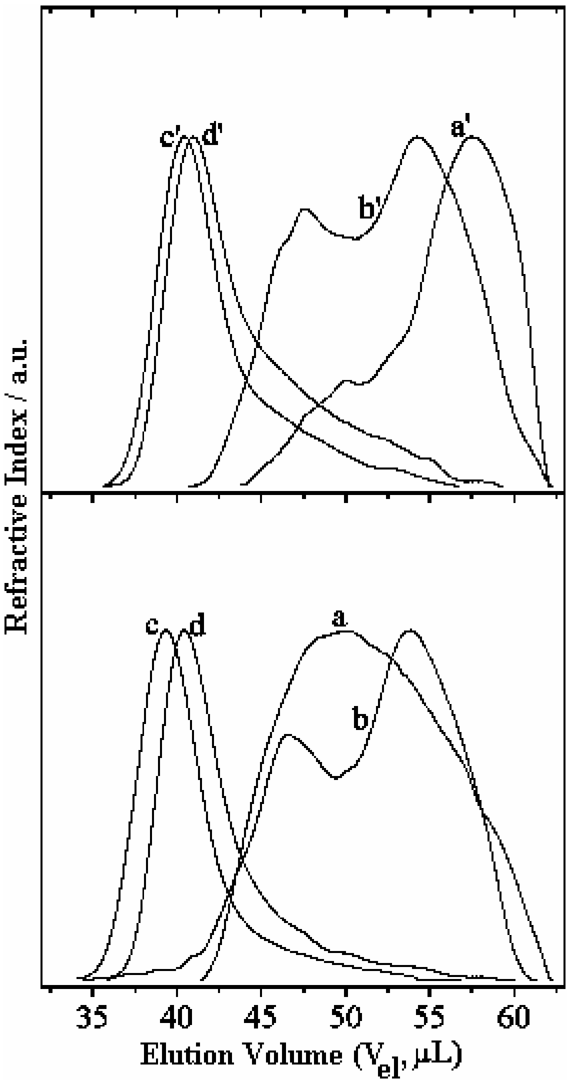


Fig. 4.3: Size Exclusion Chromatography (SEC) elugrams of PLA oligomer samples (a): 4.3.1, (b): 4.3.2, (c): 4.3.3, (d): 4.3.4, (a′): 4.3.1a, (b′): 4.3.2a, (c′): 4.3.3a and (d′): 4.3.4a.

Similar observations were made in the case, where catalyst was 1,3-dichloro-1,1,3,3-tetra-n-butyldistannoxane and all other parameters were constant. The corresponding PLA oligomers are represented as **4.3.1a**, **4.3.2a**, **4.3.3a** and **4.3.4a**, respectively, in Table-4.7. The PLA **4.3.1a** (Fig. 4.3a′) showed a broad peak corresponding to $\overline{M}_n$ 500 and $\overline{M}_w$ 900. PLA **4.3.2a** (Fig. 4.3b′) showed a bimodal distribution, the first peak corresponding to $\overline{M}_n$ 2600 and $\overline{M}_w$ 3600 and the second peak corresponding to $\overline{M}_n$ 500 and $\overline{M}_w$ 600. PLA **4.3.3a** (Fig. 4.3c′) showed a single peak corresponding to $\overline{M}_n$ 6400 and $\overline{M}_w$

24,700, while in case of PLA **4.3.4a** (Fig. 4.3d′), the $\overline{M}_n$ and $\overline{M}_w$ values were 3600 and 17,000, respectively. It is apparent that variation of polymerization temperature has a major influence on molecular weights. The molecular weights increased with increase in temperature, in case of both catalysts. Moreover at 165 °C a bimodal distribution of molecular weight appeared, indicative of two widely different kinds of molecular weights, while at 140 °C the peak shape was broad. This is indicative of a large number of very low molecular weight oligomeric species in equilibrium with each other. Further increase in temperature beyond 165 °C, however, gave rise to single peak of relatively high molecular weight species as seen in cases of reactions carried out at 190 °C. Similar observations have been made by Yamaguchi et al [7]. Table-4.7 shows that there was a monotonous increase in the intrinsic viscosity values as well as in the number average molecular weights values calculated by VPO with increase in reaction temperature.

Thermal characterization: Results of thermal characterization are shown in Table-4.8 and thermograms are all shown in Figs. 4.4a and 4.4b. The glass transition temperature, T_g, of the polymers varied from 44 to 60 °C in case of polymers prepared with the help of **4.2** catalyst, while it varied from 42 to 59 °C in case of polymers prepared using the **4.1d** catalyst.

T_g increased with increasing $\overline{M}_n$ (VPO) and was independent of the nature of the catalyst. T_m of the polymers prepared using tetraphenyltin catalyst was between 146 and 149 °C. The polymer **4.3.1a** to **4.3.3a**, prepared using the distannoxane catalyst, showed a monotonic increase in melting temperature from 142 to 162 °C.

The degree of crystallinity calculated from powder XRD patterns are shown in Figs. 4.5a and 4.5b and is given in Table 4.7. Typically, the degree of crystallinity was found between 70 and 80 %, except in case of **4.3.3** and **4.3.3a**, which were abnormally low. These could be due to racemization of L-LA to D-LA and its copolymerization. This aspect will be further discussed in the following paragraphs.

Table-4.7: PLA oligomers by dehydropolycondensation: Effect of reaction condition

Polymer sample	Solvent for azeotrping	Temp. (°C)	Catalyst	Yield (%)	Lactide volatilized (%)	Lactide in polymer (%)	[η] (dL/ g)	$\overline{M}_n$ (NMR)	$\overline{M}_n$ (VPO)	$\overline{M}_n$ (SEC)	$\overline{M}_w$ (SEC)	% cryst (powder XRD)
4.3.1	p-Xylene	143	4.2	97	nil	nil	0.11	1100	1200	900	2100	79
4.3.1a			4.1d	96	nil	nil	0.07	900	800	500	900	79
4.3.2	Mesitylene	165	4.2	70	27	1.6	0.27	3300	2500	3400, 600	6400, 700	85
4.3.2a			4.1d	76	20	nil	0.18	n.d.	1800	2600, 500	3600, 600	67
4.3.3	Decalin	190	4.2	90	06	0.5	0.65	n.d.	8900	12,000	43,000	37
4.3.3a			4.1d	82	15	0.4	0.45	n.d.	5600	6400	24,700	50
4.3.4	No solvent (bulk)	190	4.2	72	25	nil	0.40	1600	4100	6000	23,500	70
4.3.4a			4.1d	79	20	nil	0.25	1920	2200	3600	17,000	80

n.d. – not determined

Table-4.8: Thermal characterization results of poly(L-lactic acid) oligomers

Polymer sample	T_g (°C)	T_m (°C)	ΔH_f (j/ g)
4.3.1	44	146	42
4.3.1a	42	142	48
4.3.2	42	144	44
4.3.2a	55	154	37
4.3.3	60	149	25
4.3.3a	59	162	47
4.3.4	57	153	47
4.3.4a	55	145	40

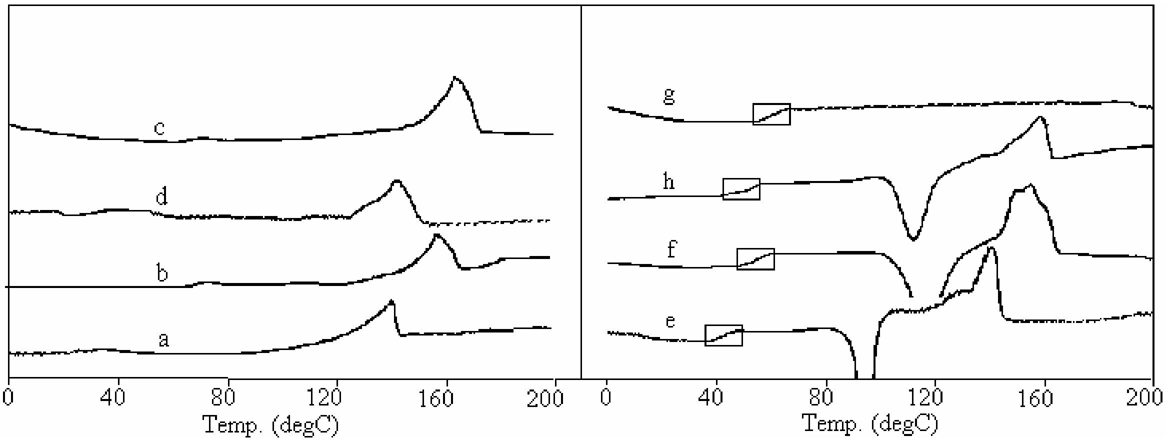


Fig. 4.4a: Differential Scanning Calorimetry (DSC) first and second heating thermograms showing melting points and glass transition temperatures, respectively, of PLA oligomers synthesized using catalyst 4.1d: (a) 4.3.1a, first heating; (b) 4.3.2a, first heating; (c) 4.3.3a, first heating; (d) 4.3.4a, frist heating; (e) 4.3.1a, second heating; (f) 4.3.2a, second heating; (g) 4.3.3a, second heating and (h) 4.3.4a, second heating.

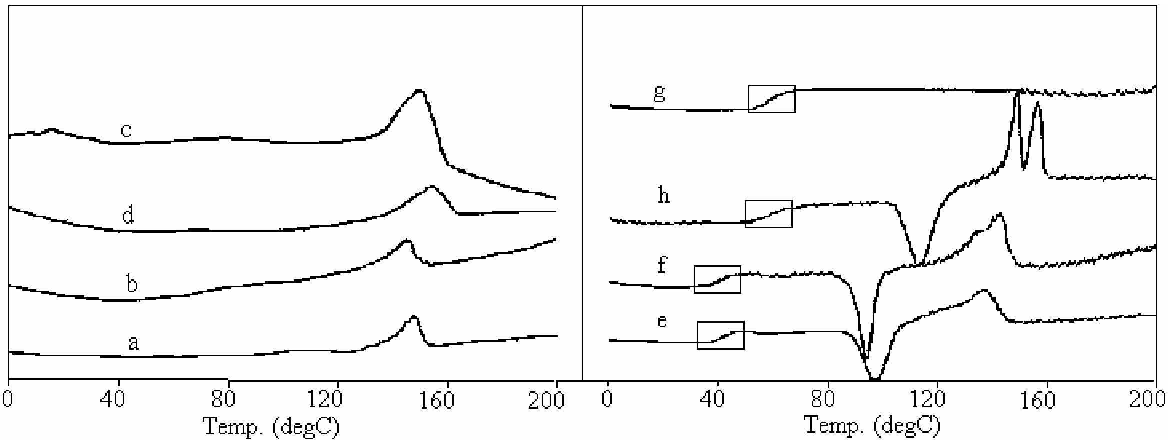


Fig. 4.4b: Differential Scanning Calorimetry (DSC) first and second heating thermograms showing melting points and glass transition temperatures, respectively, of PLA oligomers synthesized using catalyst 4.2: (a) 4.3.1, first heating; (b) 4.3.2, first heating; (c) 4.3.3, first heating; (d) 4.3.4, frist heating; (e) 4.3.1, second heating; (f) 4.3.2, second heating; (g) 4.3.3, second heating and (h) 4.3.4, second heating.

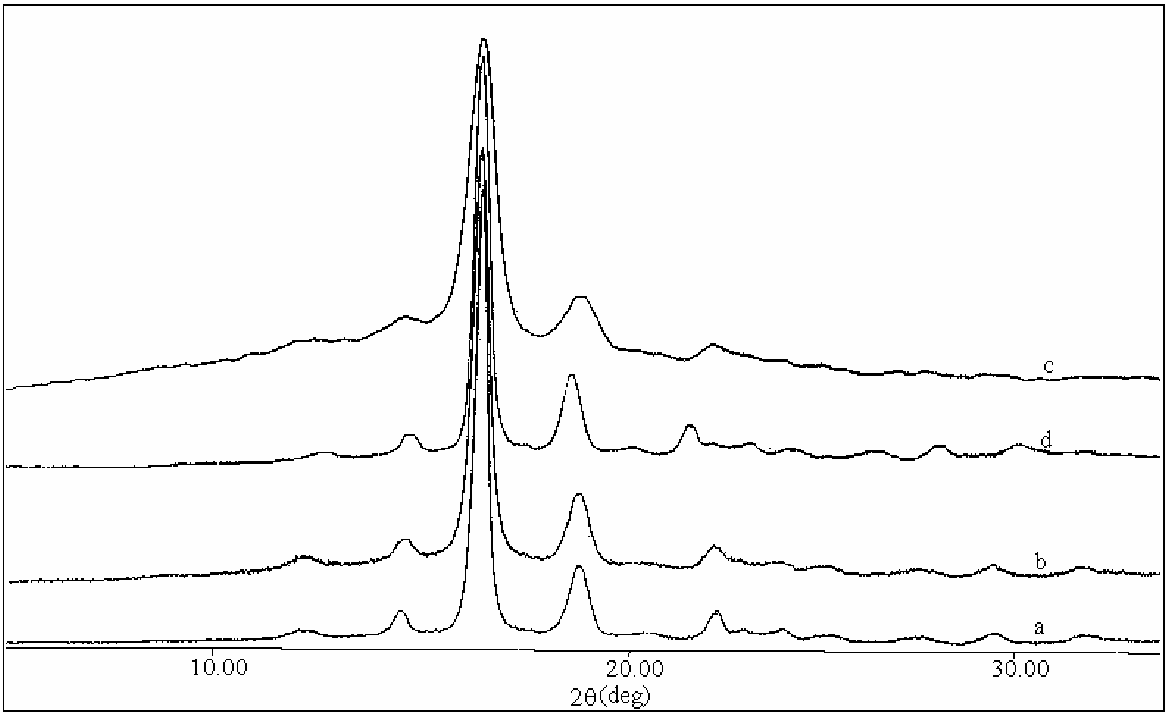


Fig.-4.5a: Powder X-Ray Diffraction (XRD) patterns of PLA oligomers synthesized using catalyst 4.1d: (a) 4.3.1a, (b) 4.3.2a, (c) 4.3.3a and (d) 4.3.4a

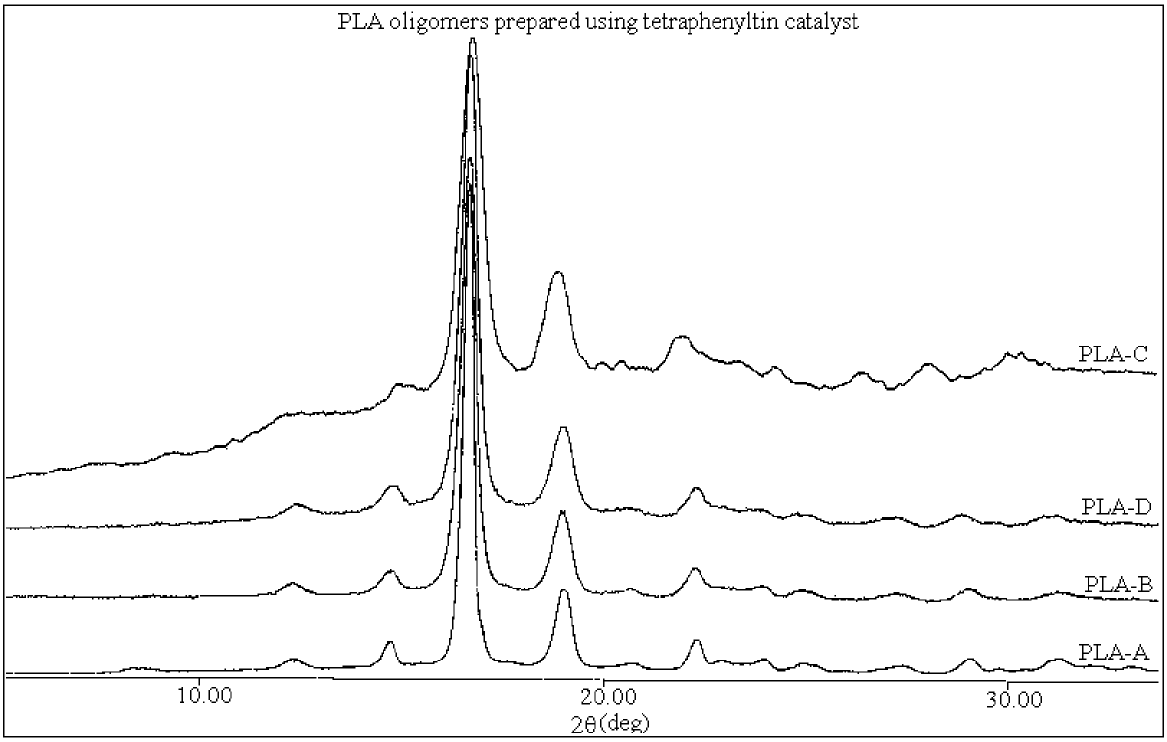


Fig.-5b: Powder X-Ray Diffraction (XRD) patterns of PLA oligomerssynthesized using catalyst 4.2: (a) 4.3.1, (b) 4.3.2, (c) 4.3.3 and (d) 4.3.4

End group analysis by ^{13}C NMR: ^{13}C NMR has been utilized as a useful tool for determining the number average molecular weight, $\overline{M}_n$, quantitatively. Besides end group determination, this technique has also been utilized in other quantitative analyses for determination of residual L-lactic acid, lactide formed due to unzipping of chain ends [10], as shown in Scheme-4.1, and for determining the optical purity of the polymer.

^{13}C NMR has also been used to study the crystallinity and morphology of poly(L-lactide) [11]. And for the direct observation of stereodefects in poly(L-lactide) [12]. There is, however, no proper report of end group analysis and determination of presence of residual lactic acid and lactide in the PLA polymer prepared by dehydropolycondensation using tetraphenyltin and distannoxane type catalysts.

In the present study, NMR was used to determine the effect of catalysts and temperature on poly(L-lactic acid) (PLA) end groups and presence of lactide and residual amount of lactic acid in the PLA samples. For this purpose, PLAs were prepared using the two different catalysts, tetraphenyltin and dichlorodistannoxane and varying the temperature through 143, 165 and 190 °C as described in Table-4.7. Fig. 4.6 shows the spectra corresponding to PLA oligomers **4.3.1** (a), **4.3.2** (b), **4.3.3** (c) and **4.3.4** (d), the oligomers synthesized using the tetraphenyltin catalyst, as listed in Table 4.7, and also the spectra of the PLA oligomers **4.3.1a**, **4.3.2a**, **4.3.3a** and **4.3.4a**, the oligomers synthesized using the dichlorodistannoxane catalyst, are shown in Fig. 4.6 as a′, b′, c′ and d′, respectively.

In the spectrum of PLA **4.3.1** (Fig. 4.6a), the peaks appearing from 168.5 to 169.7 ppm are due to ester carbonyl group and peaks arising from 172.9 to 173.1 ppm are due to carboxylic acid end functional group. The accuracy of the $\overline{DP}_n$ estimate, which was based on the relative integral ratio of these groups of signals was determined and found same in two consecutive NMR measurements. There are no peaks due to lactide in this polymer. The calculated $\overline{DP}_n$ and $\overline{M}_n$ were 16 and 1100, respectively.

In the spectrum of PLA **4.3.2** (Fig. 4.6b), the peaks for ester carbonyl group and the carboxylic acid end group appear once again, as in case of 4.3.1, from 168.5 to 169.7 ppm and from 172.9 to 173.1 ppm, respectively. The $\overline{DP}_n$ and $\overline{M}_n$ were calculated in the same way by taking the ratio of these two integrals and the values were found to be 45 and 3300 respectively. The peak at 167.6 ppm is due to the lactonic carbonyl group of the L-lactide. The proportion of formed lactide in the sample was determined by taking the integral ratio of peaks for the lactone carbonyl to ester carbonyl and the value was found 1.6 mol%.

In the spectrum of PLA **4.3.3** (Fig. 4.6c), the ester carbonyl peak appears between 168.9 to 169.6 ppm, but there was no peak due to the carboxylic end groups. The other peak at 167.3 ppm is due to the carbonyl group of the lactide. The absence of any peak due to carboxylic acid end groups indicates possibility of formation of macrocyclic oligomers of PLLA. The proportion of formed lactide in this sample was calculated to be 1 mol%.

Spectrum of PLA **4.3.4** (Fig. 4.6d) shows the peaks between 169.2 and 169.8 ppm and between 173.0 to 173.3 ppm for ester carbonyl and carboxylic acid end functional groups, respectively. The $\overline{DP}_n$ and $\overline{M}_n$ were found to be 23 and 1600, respectively. There were no peaks corresponding to the lactonic carbonyl carbon.

A comparison of spectra (a – c) with (d) indicates that, when tetraphenyltin is used as the dehydropolycondensation catalyst, linear oligomers are formed exclusively at 143 °C, whereas cyclic oligomers are formed exclusively at 190 °C in decalin solvent. But at same same 190 °C, when the dehydropolycondensation is performed in bulk (without solvent), linear polymers are formed.

In case of PLA **4.3.1a** (Fig. 4.6a′), the ester carbonyl and the carboxylic acid end group peaks arise between 169.5 and 169.7 ppm and at 173.3 ppm, respectively. The values of $\overline{DP}_n$ and $\overline{M}_n$ were found to be 40 and 2900, respectively. The percentage of formed lactide in this sample was nil, since there was no peak corresponding to the lactonic carbonyl. In spectrum of polymer 4.3.2a (Fig. 4.6b′), the ester carbonyl peak appears between 169.2 and 169.5 ppm. No peak was found corresponding to the carboxylic acid end group. Therefore, formation of macrocyclics is implied. There was no peak for the lactide carbonyl.

PLA oligomer **4.3.3a** (Fig. 4.6c′) was also found to comprise completely of macrocyclics, since the spectrum shows only the ester carbonyl peaks between 169.2 and 169.6 ppm, and no peak for the carboxylic acid end group. The lactide was found to be present in 0.5 mol% concentration.

PLA oligomer **4.3.4a** (Fig. 4.6d′) was once again found to be a mixture of linear and cyclic oligomers, since the spectrum contains peaks arising due to both ester carbonyl and the carboxylic acid end groups, between 169.3 and 169.7 ppm and between 173.7 and 173.8 ppm, respectively. The calculated $\overline{DP}_n$ and $\overline{M}_n$ were 18 and 1300, respectively.

Once again, a comparison of spectra (a′ – c′) with (d′) bring out a conclusion for oligomers synthesized using the distannoxane catalyst similar to that in case of oligomers synthesized using tetraphenyltin. Both solvent and temperature have profound effect on the end groups of the oligomers. While the oligomers prepared at 143 °C and 165 °C showed presence of carboxylic acid end groups, the oligomers synthesized at 190 °C and in decalin solvent showed an absence of such end groups, indicating a probability of exclusive formation of cyclic oligomers. However, at 190 °C oligomers with carboxylic acid end groups are formed when the reaction is performed in bulk.

Effect of temperature on racemization of LLA: As discussed before, it was found that polymerization using two different catalysts, namely **4.2** and the **4.1d** produced reasonably highly crystalline oligomers at 143 °C, but when the polymerization reaction temperature was raised to 190 °C, the crystallinity decreased from 79 % to 37 %.

The extent of racemization at 143 and 190 °C was examined using ^{13}C NMR. The spectrum for oligomer **4.3.3**, synthesized at 190 °C using tetraphenyltin catalyst, showed five characteristic signals at 169.20, 169.21, 169.31, 169.39 and 169.54 ppm (Fig. 4.7a). According to the theoretical stereosequence distributions, the signal at 169.54 ppm (isotactic (i, mm)) was assigned to the sequence of carbonyl carbon atom of successive L-lactic acid units. The peaks in the region between 169.31 and 169.39 ppm were tentatively assigned as heterotactic in nature (h, rm) and the peak at 169.20 ppm was assigned as syndiotactic (s, rr). ^{13}C NMR spectra of copolymers of copolymers of L-lactide and D-lactide have been studied by Chabot and Vert [13] and the fine structures in the carbonyl region have been discussed. Considering the different components, they have divided the carbonyl spectrum into three regions. The unique peak at downfield has been considered to correspond to the isotactic triad. The peaks in the up field have ben assigned to heterotactic and syndiotactic triads, respectively. The extent of D-lactic acid units in the backbone was to be about 22.0 %.

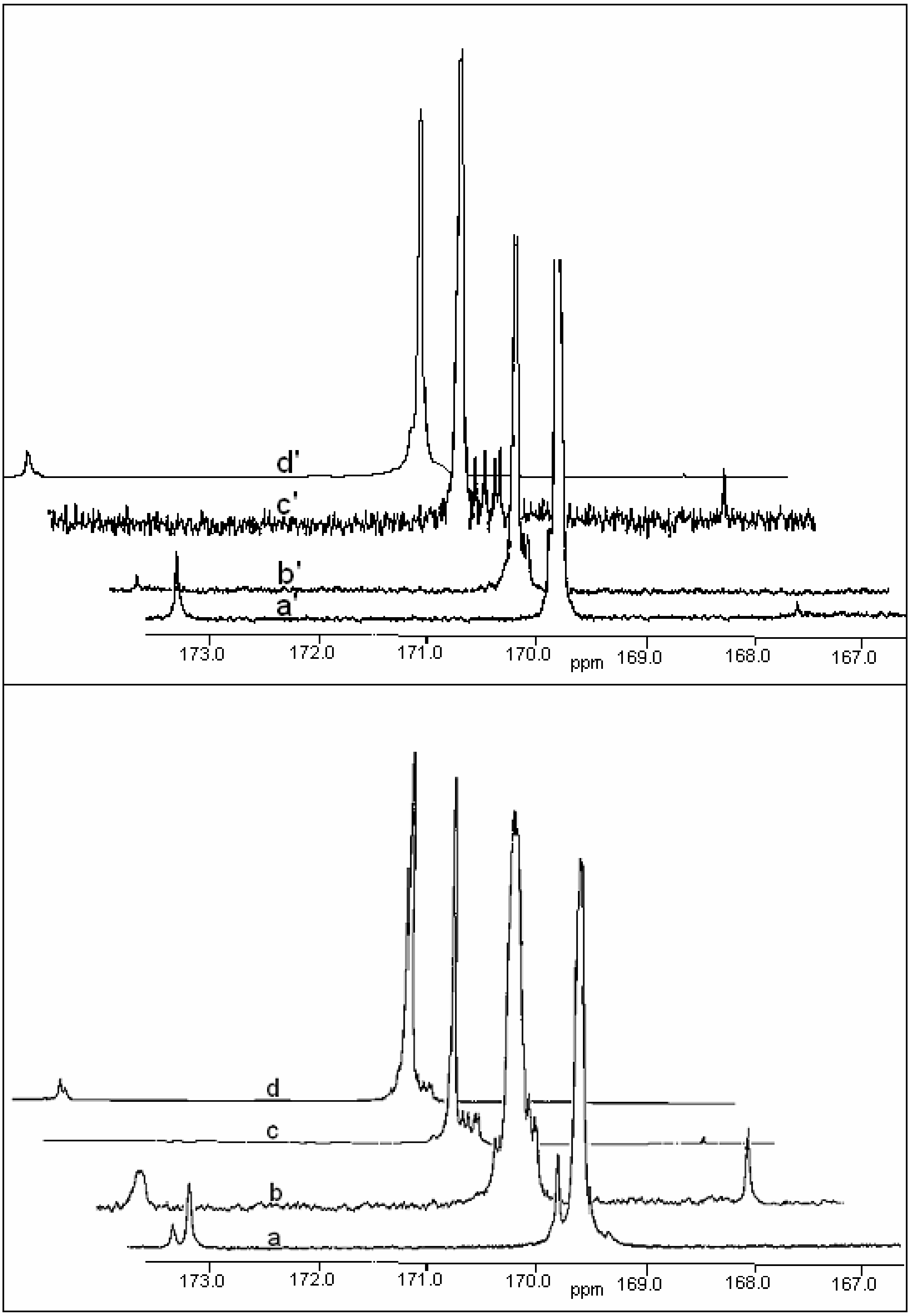


Fig. 4.6: 500 MHz ^{13}C NMR spectra around carbonyl (ester), carbonyl (acid) and carbonyl (lactone, lactide) area of PLA oligomer samples: (a) 4.3.1, (b) 4.3.2, (c) 4.3.3, (d) 4.3.4, (a) 4.3.1a, (b) 4.3.2a, (c) 4.3.3a and (d) 4.3.4a.

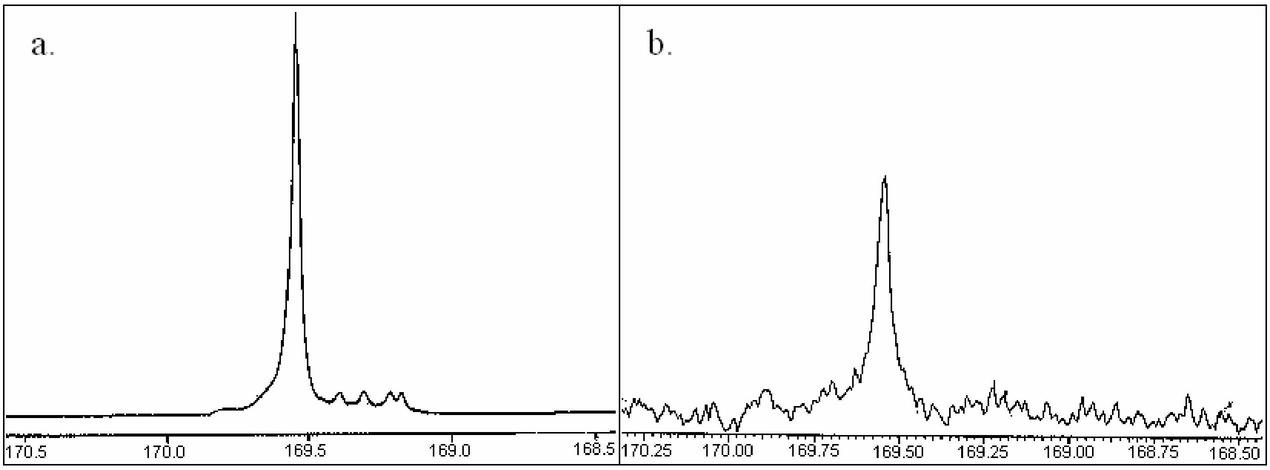


Fig. 4.7: ^{13}C NMR spectra of PLA oligomers: (a) 4.3.3 with 22 % D-lactic acid content and (b) 4.3.3a with 12 % D-lactic acid content

The spectrum obtained from **4.3.3a**, the oligomer synthesized at 190 °C using the dichlorodistannoxane catalyst, also showed five characteristic signals at 169.20, 169.23, 169.30, 169.46 and 169.55 ppm, as shown in Fig. 4.7b. According to the theoretical stereosequence distribution, the signal at 169.55 ppm is assigned to the sequence of carbonyl carbon of the successive L-lactic acid units by virtue of large intensity. The other four smaller signals are attributed to carbonyl carbons influenced by different D-lactic acid unit sequences along the polymer backbone. The percentage of D-lactic acid units is thereby calculated as 12 mol%. PLA oligomers prepared at lower temperatures, 143 and 165 °C, did not show any amount of D-lactic acid incorporation.

The racemization reactions were most likely due to a dynamic equilibrium of ester interchange reactions happening between the polymer chains. The L-lactic acid that was used for polymerization is more than 99 % enantiomerically pure. Under the Lewis acid catalyzed condition of the dehydropolycondensation, whatever be the temperature, the probability of deprotonation-protonation equilibrium at the chiral methane carbon of the lactic acid is virtually nil. But during the ester interchange reactions there are two ways the ester linkage between successive lactic acid units could break. One is the acyl-oxyen cleavage, which would not involve the chiral carbon in question. The other is the alkyl-oxygen cleavage, where the covalent bond between oxygen and the chiral carbon would break and subsequently reforms. That is when an inversion of configuration is possible and likely.

Form the results of racemization analysis by NMR technique, it is apparent that the ester interchange reactions occur mostly in the acyl-oxygen cleavage fashion. However, when the temperature is raised the probability of alkyl-oxygen cleavage increases significantly. What is worth noting is that tetraphenyltin as a catalyst encouraged more alkyl-oxygen cleavage than dichlorodistannoxane. In the dehydropolycondensation reaction catalyzed by tetraphenyltin, the D-lactic acid units seem to get incorporated in the backbone in a purely random manner, whereas in case of the dichlorodstannoxane-catalyzed reaction, the L-lactic acid and D-lactic acid isomers are introduced in the polymer chain as small blocks apart from each other and separated from the large peak obtained due to isotactic L-lactic acid units. The splitting pattern of these signals is identical to the earlier report shown in the literature [13]. In the literature, the D- and L- lactide isomers are found to have introduced into the polymer chain in pairs due to ring opening polymerization. But, in the present case, the D- and L-lactic acid units are introduced not in pairs but in small blocky segments.

These observations on the nature of polymerization using catalysts **4.1d** and **4.2** can be understood based on the difference between the electron-cloud densities around the tin (Sn) atoms in the two catalysts. **4.1d** is a harder Lewis acid in comparison to **4.2**. The acid-catalyzed esterification or transesterification, irrespective of whether by acyl-oxygen cleavage or by alkyl-oxygen cleavage, involves polarization of the electron cloud of an oxygen atom of the carboxyl moiety by the Sn atom of the Lewis acid catalyst. This O-Sn partial bonding in turn helps in the delocalization or polarization of the electron cloud over the C-O bond of the carboxyl moiety, thereby facilitating nucleophilic attack by the O of an alcohol. The mechanism of transesterification by distannoxane catalysts in general is well discussed in literature [14], while the reaction pathway of tetraphenyltin is yet unknown. There is a possibility of hydrolysis or alcoholysis of one, two, three or all four of the Sn-C linkages of tetraphenyltin in presence of water and lactic acid in the system, leading to alkoxy-tin, hydroxy-tin, or tin-carboxylate covalent linkage [15]. Some Sn-O-Sn linkages are also possible by ways of condensation of two hydroxy-tin moieties. Thus, only a more in-depth knowledge about the mechanism of the catalysis mechanism of tetraphenyltin could explain why one catalyst introduced D-lactic acid units in the PLLA backbone in a completely random sequence, while the other incorporated them in small blocks of two or three units.

MALDI-ToF MS analysis: Recently, MALDI-ToF MS technique has been employed for the determination of molecular weights of synthetic polymer chains as well as determination of their end groups [16]. Using dehydropolycondensation reaction, only low molecular weight oligomers can be prepared. Such oligomers are amenable to analysis by MALDI-ToF. The identification and quantification of end groups becomes very important if the prepolymer has to be further chain extended by any of the well known methods namely solid state polymerization, melt polymerization and coupling. There are several analytical tools for end group identification/ determination of polymers, such as, NMR titration etc. NMR is an accurate as well as quantitative technique. However, it is the limited by the sensitivity of detectors. Titration (of carboxylic acid end groups) is not feasible for aliphatic polyesters, which can undergo main chain hydrolysis under these conditions. MALDI-ToF MS can detect all end groups and impurities (chemically borne of the polymer chain as end groups) with a high level of sensitivity. However, quantification is difficult using this technique. We, therefore, subjected all the oligomers prepared using catalysts **4.1d** and **4.2** to MALDI-ToF MS analysis.

The results of the analysis are shown in Figs. 4.8a to 4.8d and Figs. 4.9a to 4.9d. Fig. 4.8a reports the MALDI-ToF mass spectrum of PLA **4.3.1**. The oligomer was found to contain chains terminated by OH on one side and COOH on the other. The MALDI spectrum is dominated by a series of intense peaks ranging from mass 500 to mass 1500 Da, corresponding to sodiated adduct molecular ions of type $H\text{-}[O\text{-}CH(CH_3)CO]_n\text{-}OH\text{----}Na^+$, (mass 72.0n + 18 + 23), where n is found to be ranging from 7 to 20, 23 being the mass number of the sodium (Na) ion that formed the adduct molecular ion. The five most intense peaks belonging to this series corresponding to oligomers with n = 9 to 13 are labeled in the spectrum and reported as enlarged in the inset. The spectrum also displays other peaks of lower intensities, which desorbed and flew as potassiated ions (K^+ adduct molecular ions, mass = 72.0n + 18 + 39, see peaks at 705, 777, 849, 921 and 992 Da, respectively, in the inset).

Fig. 4.8b shows the MALDI spectrum of the PLA **4.3.2**. The most intense peaks belonging to this series corresponding to oligomers with n = 14 to 27 are labeled in the spectrum and reported as enlarged in the inset. The spectrum shows the chemical heterogeneity, which consists of linear and cyclic oligomers. Macrocyclic structures with n = 14 to 27 (mass = 72.0n + 23) were observed. The macrocyclic structures are formed by intramolecular transesterification or esterification between chain ends. The spectrum also shows the potassiated ions (mass = 72.0n + 39, see peaks 1048 to 1983 Da), which overlap with the sodiated molecular ions of the linear polymers of masses ranging from 1050 to 2000. The potassiated molecular ions of these linear chains show as peaks 1568, 1640 and 1712 Da, respectively (see inset).

Fig. 4.8c shows the MALDI mass spectrum of polymer **4.3.3**. The spectrum is dominated by a series of intense peaks of masses ranging from 600 to 3000 (within n = 10). In this region, the spectrum also shows two mass series of higher intensity, which can be assigned to poly(L-lactic acid) cyclic oligomers that appear as sodiated and potassiated molecular ions having masses (72.0n + 23) and (72.0n + 39), respectively. The intensity of peaks due to cyclics falls off sharply at higher molecular masses. No peaks corresponding to either sodiated or potassiated molecular ions of linear polymers were found.

Fig. 4.8d shows MALDI-ToF mass spectrum of PLA **4.3.4**. The spectrum is dominated by a series of intense peaks ranging from 800 to 2000 Da with n = 10. In the region between 800 and 1100 Da, this spectrum shows one series of higher intensity and two mass series of lower intensity. The peaks at higher intensities ranging from 800 to 1100 Da correspond to sodiated molecular ions of cyclic polymers and also overlap with peaks of the potassiated ions of linear oligomers at lower intensities. The sample expected to be formed by oligomers bearing $–COCH_3$ and OH as terminal groups, corresponding to a general formula $CH_3CO\text{-}[O\text{-}CH(CH_3)\text{-}CO]\text{-}OH\text{----}Na^+$, shows peaks in the region between 800 and 1020 Da, from where the molecular mass of each oligomer can be calculated as (72.0n + 60 + 23). The peaks ranging from 1200 to 1450 Da correspond to two different formulas namely $HO\text{-}Sn(O)\text{-}O\text{-}CH(CH_3)\text{-}CO\text{-}OCH(CH_3)\text{-}COOCH_2CH_3$ and $CH_3O\text{-}[CO\text{-}CH(CH_3)\text{-}O]_n\text{-}Sn(O)\text{-}[O\text{-}CH(CH_3)\text{-}CO]\text{-}OCH_3$. These peaks appeared in the MALDI spectrum because of presence of impurities such as methanol, ethanol and acetic acid, which reacted with and formed chain ends of poly(L-lactic acid). GC analysis results of the L-lactic acid monomer also showed the presence of these impurities. Such chains also have residual catalysts attached at the end in different forms, though in small concentrations. Cyclic oligomers varying from n = 10 to n = 16 were also found.

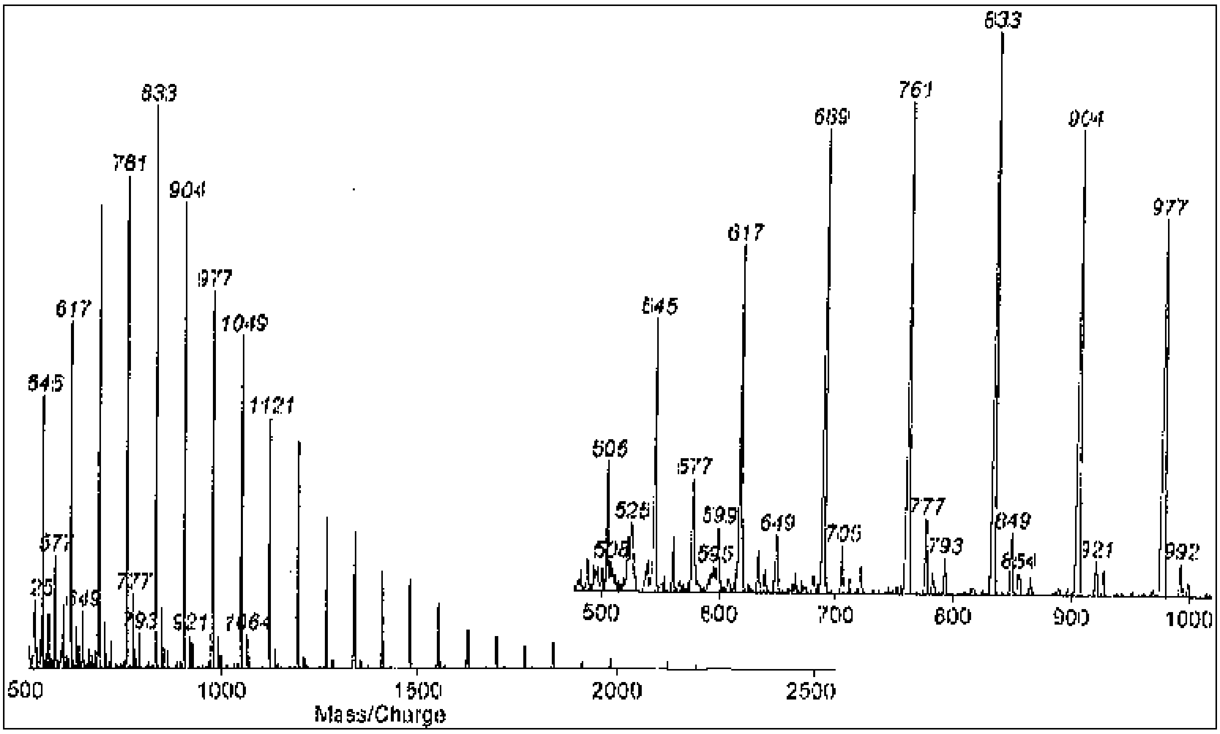


Fig. 4.8a: MALDI-ToF MS of the poly(L-lactic acid) 4.3.1

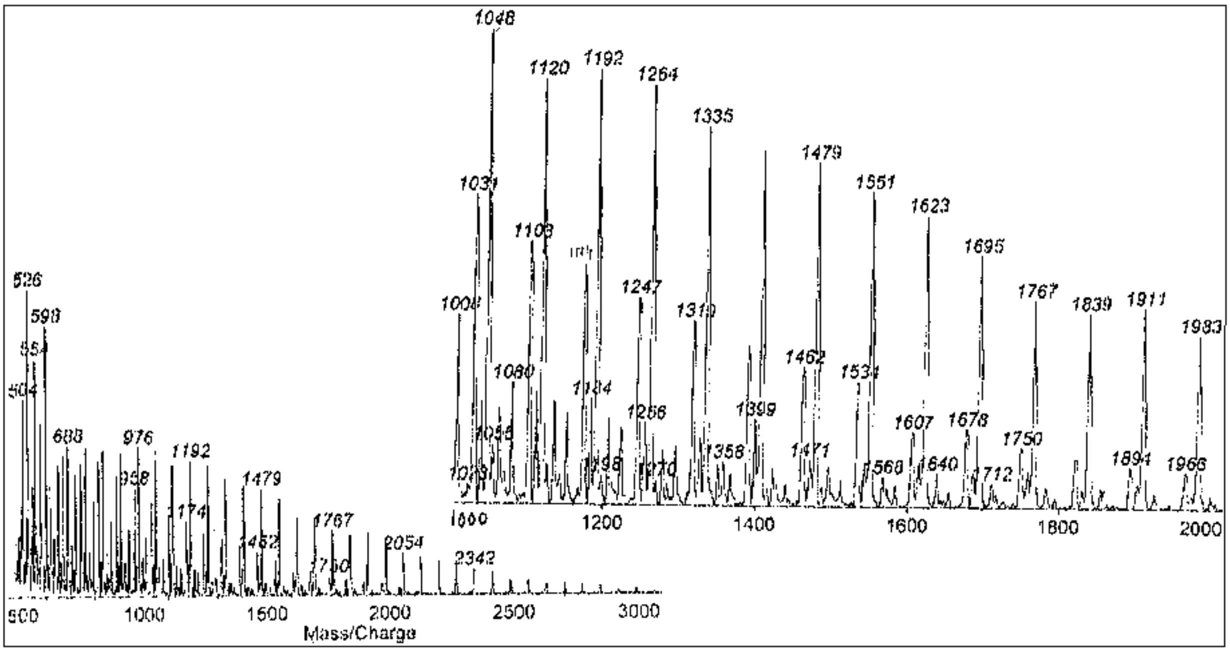


Fig. 4.8b: MALDI-ToF MS of the poly(L-lactic acid) 4.3.2

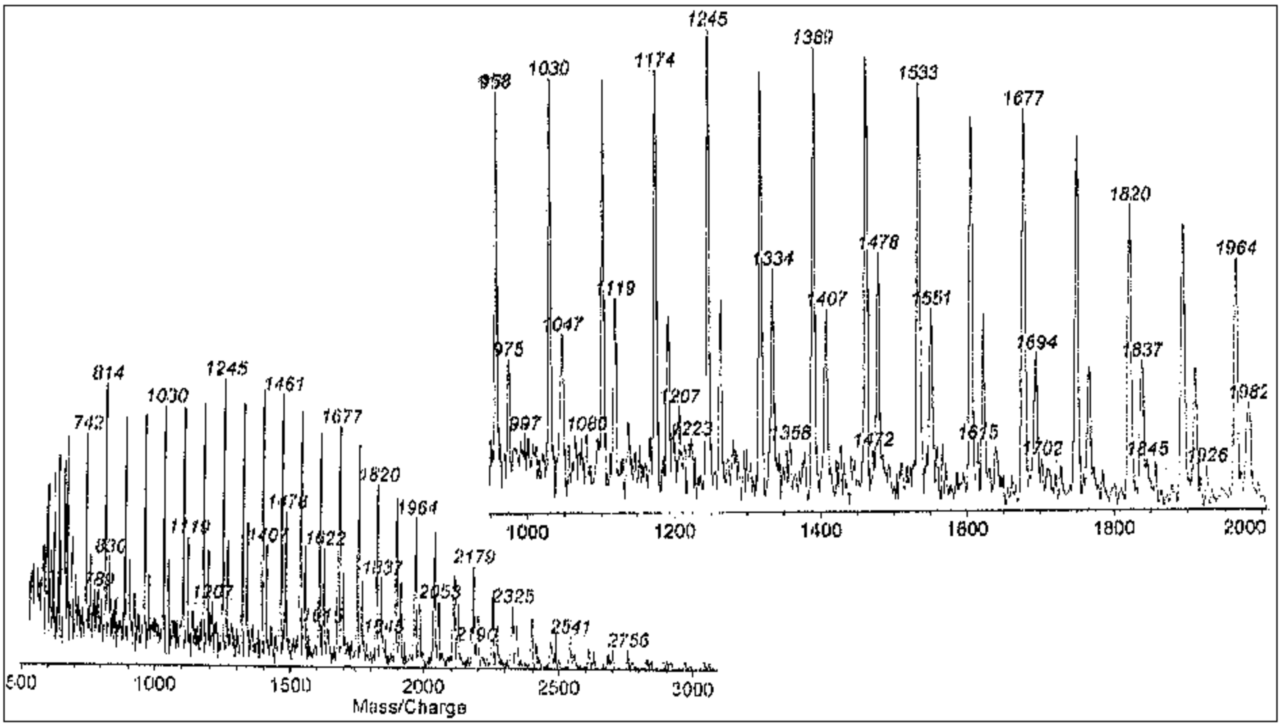


Fig. 4.8c: MALDI-ToF MS of the poly(L-lactic acid) 4.3.3

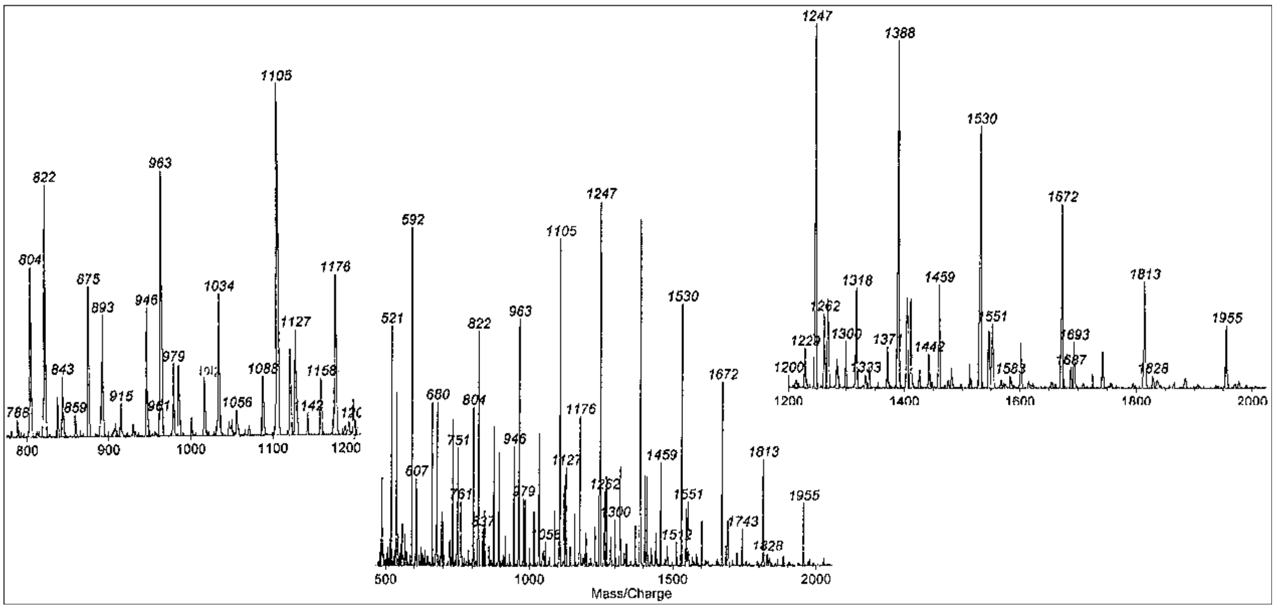


Fig. 4.8d: MALDI-ToF MS of the poly(L-lactic acid) 4.3.4

Fig. 4.9a depicts MALDI-ToF mass spectrum of PLA **4.3.1a**. As expected, the MALDI-ToF mass spectrum of this sample in Fig. 4.9a shows a series of intense molecular ion peaks ranging from mass 500 to 2900 Da that are assigned to sodiated adducts of the oligomers, denoted by the structure $H\text{-}[O\text{-}CH(CH_3)\text{-}CO\text{-}]_nOH\text{-----}Na^+$. In the region 1200 to 1400 Da, the MALDI spectrum also shows some other mass series of lower intensity. These peaks are assigned to $CH_3CO\text{-}[O\text{-}CH(CH_3)\text{-}CO\text{-}]_nOH$ oligomers desorbing without forming any adduct with either sodium or potassium. The peaks ranging from 1600 to 2700 Da show a mass series of higher intensity. These peaks correspond to oligomers of the structure $H\text{-}[O\text{-}CH(CH_3)\text{-}CO\text{-}]_nOCH3$, with molecular mass (72.0n + 32), once again desorbing without adduct formation. Such Desorption of smaller molecular ions without adduct formation is neither very unusual or unknown [15] In the region 1700 to 2400 Da, the lower intensity peaks correspond to sodiated oligomers terminate with OCH_3 and H, most likely generated from the impurities present in L-lactic acid.

The MALDI spectrum of PLA **4.3.2a** is shown in Fig. 4.9b. The most intense peaks ranging from 700 to 2100Da correspond to sodiated cyclic oligomers of mass (72.0n + 23), where n varies from 10 to 28. The corresponding potassiated ions of the cyclic oligomers are also seen as peaks of mass (72.0n + 39). These potassiated molecular ions peaks of cyclic oligomers overlap with a series of peaks of sodiated molecular ions of linear oligomers of mass (72.0n + 18 + 23). The result therefore indicates a mixture of linear and cyclic oligomers in the PLA **4.3.2a**.

Fig. 4.9c depicts the MALDI spectrum of the PLA **4.3.3a**. The most intense peaks arising in the region from 600 to 2000 Da correspond to the sodiated molecular ions of cyclic oligomers, where n ranges from 9 to 40. The potassiated ions that appear in the same region are also of the cyclic oligomers. This confirms that exclusively macrocyclic oligomers are present in this sample, just like in the sample of PLA **4.3.3** oligomer discussed before.

Similarly, MALDI spectrum of PLA **4.3.4a** is shown in Fig. 4.9d. The spectrum is dominated by a series of intense peaks ranging from 500 to 3000, corresponding to sodiated molecular ions of linear oligomers (mass = 72.0n + 18 + 23), where n ranges between 9 and 30. The most intense peaks in this series are reported enlarged in the inset, showing peaks in the region between 600 and 1500 Da.

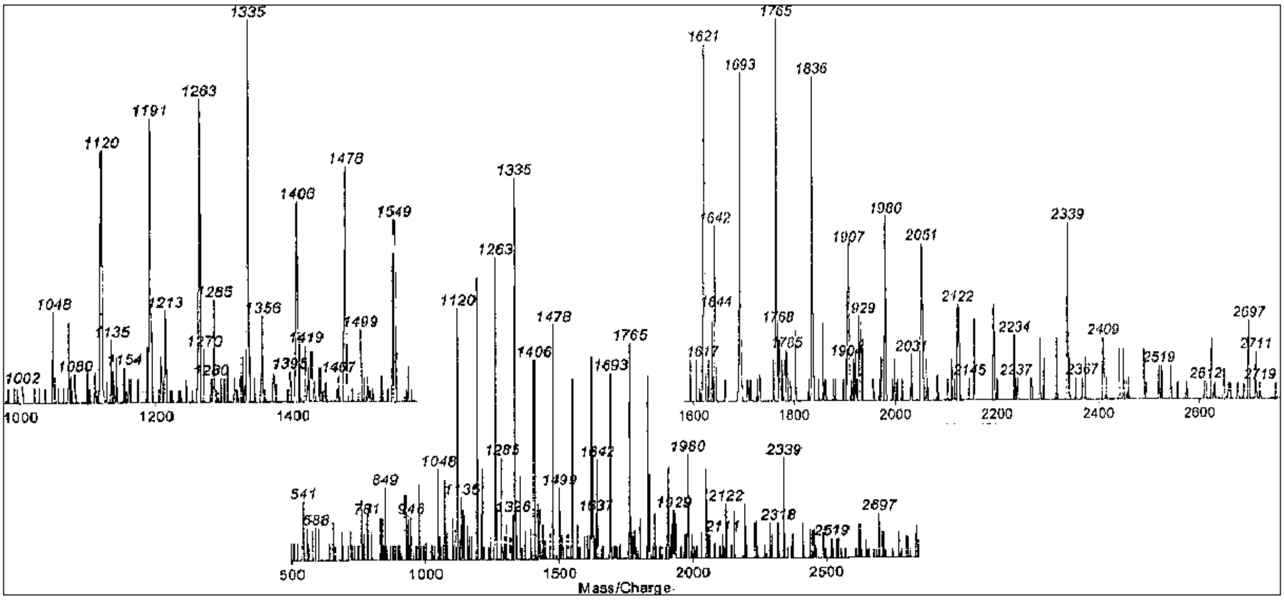


Fig. 4.9a: MALDI-ToF MS of the poly(L-lactic acid) 4.3.1a

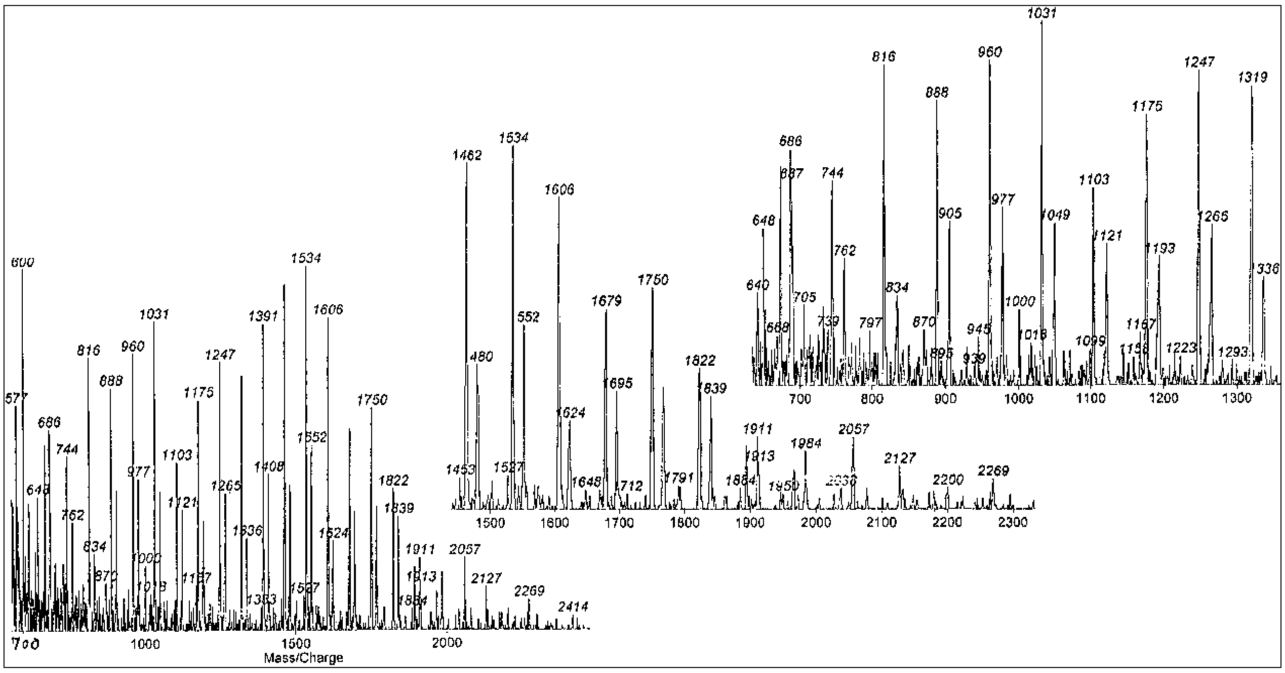


Fig. 4.9b: MALDI-ToF MS of the poly(L-lactic acid) 4.3.2a

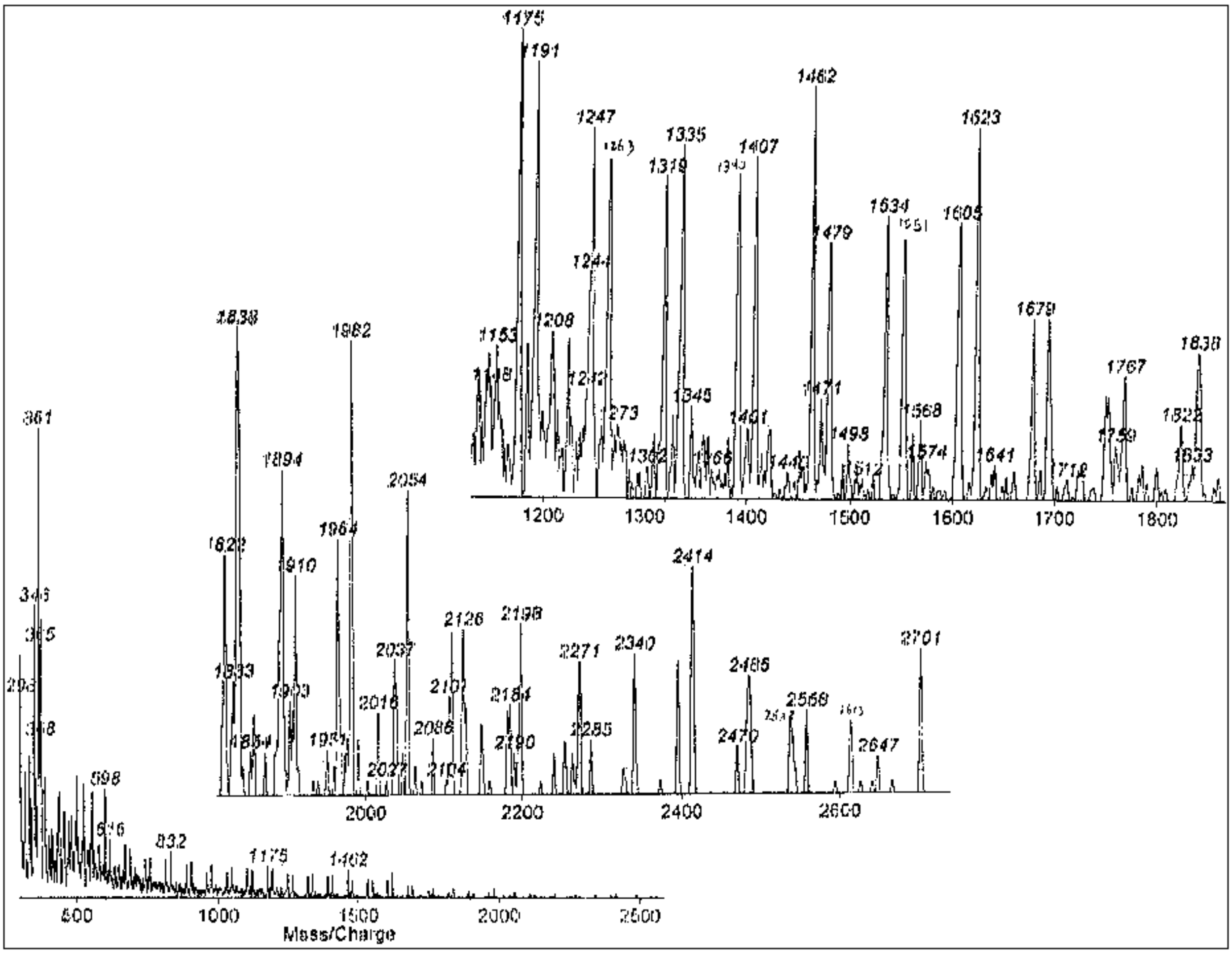


Fig. 4.9c: MALDI-ToF MS of the poly(L-lactic acid) 4.3.3a

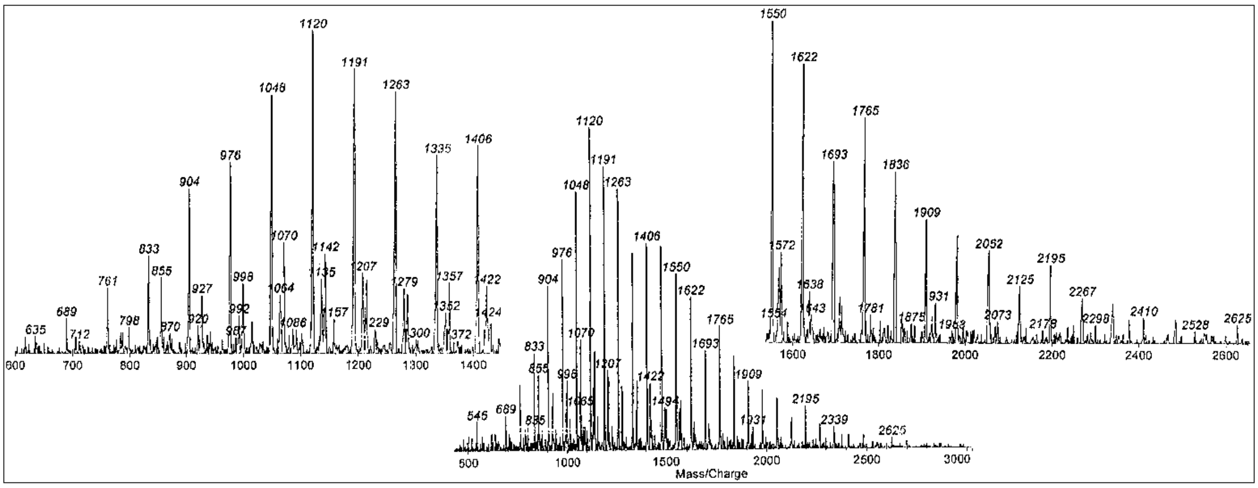
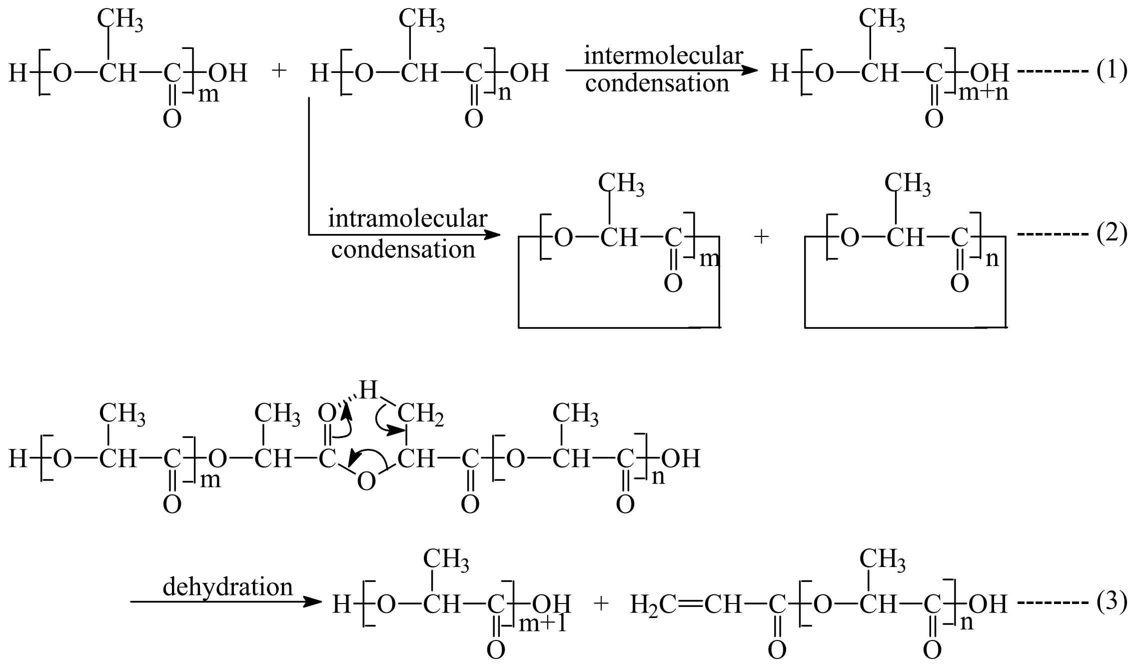


Fig. 4.9d: MALDI-ToF MS of the poly(L-lactic acid) 4.3.4a

The sodiated adduct molecular ion peaks in the region from 600 to 1800 Da overlap with the sodiated molecular ion peaks of the type H-[O-CH(CH_3)-CO-]OCH_3-----Na^+, that is linear polymer molecules with a methyl ester end group instead of carboxylic acid (again, mass = 72.0n + 34 + 23). The potassiated molecular ions corresponding to this series are also seen clearly in the mass region between 600 and 1900 Da. The molecular ion peaks in the region between 1600 and 2400 Da correspond to the potassiated adduct ion peaks of cyclic oligomers, where n ranges from 21 to 30.

Scheme-4.2: Formation of macrocyclic PLA oligomers and linear oligomers with acrylic end groups



Effect of temperature solvent: The MALDI-ToF results were strongly supported by the results of 13C-NMR spectra, which are discussed earlier. For both sets of oligomers prepared using the two different catalysts, it was found that formation of cyclic oligomers is a function of both temperature and solvent. At 143 °C reaction temperature and in xylene solvent there were only linear oligomers, at 165 °C in mesitylene solvent there were mixtures of linear and cyclic oligomers and at 190 °C in decalin solvent there were only cyclic oligomers. But when the dehydropolycondensation is done without solvent, the relative population of cyclic oligomers decreases and some linear oligomers are also formed even at 190 °C. Macrocyclic poly(L-lactic acid)s with a degree of polymerization as high as 40 could be identified.

4.5. Conclusion: The properties of low molecular weight lactic acid polyesters are determined by the nature of catalyst and the polymerization temperature. Results show that PLA oligomers with $\overline{M}_n$ 8900 cabn be obtained using tetraphenyltin catalyst, whereas oligomers with $\overline{M}_n$ 5600 using the dichlorodistannoxane catalyst. The failure to obtain high molecular weight polymers either in bulk, or in presence of solvent, is attributed to the competitive formation of macrocycles. The structure of oligomers changes form linear to macrocyclic as the reaction temperature is increased. When dehydropolycondensation is performed in absence of solvent, some linear polymer is also obtained. The probability of cyclization in polycondensation reaction increases with reaction temperature. Oligomer crystallinity varied between 37 and 85 % depending on the nature of catalyst and solvent. Absence of racemization reactions at temperatures of 165 °C or below was confirmed by ^{13}C-NMR. However, the D-lactic acid incorporation was calculated as 12 and 22 wt% for oligomers synthesized using the dichlorodistannoxane and tetraphenyltin catalysts, respectively, at 190 °C. The anomalous variation of crystallinity of the different oligomers over a wide range of values may be due to the incorporation of D-lactic acid units along the predominantly L-lactic acid polymer backbone as well as the presence of macrocyclic structures. The T_g and T_m of the polymers varied from 42 to 60 °C and from 142 to 162 °C, respectively, because of the same reason. The presence of traces of impurities such as methanol, ethanol and acetic acid in the starting L-lactic acid monomer was also identified by MALDI-ToF as end groups of PLA. MALDI-ToF also showed exclusively linear structures of oligomers at 143 °C, a heterogeneous mixture of linear and macrocyclics, at 165 °C and predominantly macrocyclic structures at 190 °C. The molecular ion peaks of macrocyclic structures, either sodiated or potassiated adduct form, observed in MALDI-ToF might however overlap with linear oligomers with acrylic end groups, which could be formed by intramolecular dehydration as shown in Scheme-2 [10]. But ^{13}C-NMR confirmed the absence of such acrylic end groups in any of the oligomers.

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CHAPTER - 5

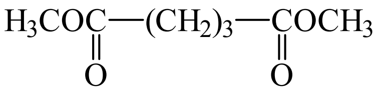
CHAPTER 5: SOLID STATE POLYMERIZATION

5.1. Introduction:

Solid state polymerization (SSP) is a well-established method of postpolycondensation for many aromatic polyesters and polyamides, for example PET, PBT and different nylons, respectively [1a-g]. This process consists in heating a semi-crystalline, solid prepolymer (of relatively low molecular weight) in powder, pellet, chip or fiber form up to a temperature below the melting temperature with simultaneous removal of the by-product of condensation from the surface of the material (after it diffuses out from the bulk) either (by volatilizing) under reduced pressure or with a carrier, for example blowing air or some inert gas. Solid state polymerization is performed on semicrystalline oligomers (oligomers). An optimum amount of crystallinity is required to prevent agglomeration of particles in the reactor [1b,1f,2]. But the reaction essentially takes place in the amorphous region of the polymer, where all the reactive end groups reside. Therefore the solid state polymerization reaction has to be performed at a temperature above the glass transition temperature (to allow mobility of the end groups to react) and below the melting temperature. Since solid state reactions actually start at much lower temperatures, compared to molten or solution state [3], the reaction temperature can range from sufficiently below the melting temperature [4] to just 5-15 °C below the melting temperature [1g]. Because of the restriction of mobility, however, the time needed to each a particular molecular weight is generally much longer than that in melt or solution [4]. Use of solid state polymerization methods reduces discoloration and degradation associated with high temperature melt polymerization in molten state. That is what makes this process a useful and widely accepted one in the polyester and polyamide synthesis industry. Besides, although SSP takes longer time, yet very high molecular weights can be achieved, which is not generally possible to accomplish in melt or solution because of viscosity restrictions and hydrolytic, thermal and oxidative degradations [5-7]. Almost all catalysts for melt and solution phase polycondensation are catalysts for solid state polymerization [8.9].

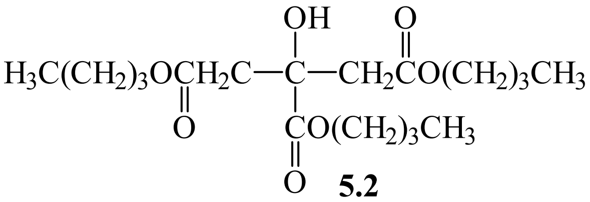
Poly(L-lactic acid) (PLA) oligomers are semicrystalline (as in Chapter 4) and thus can undergo post-polycondensation by solid state polymerization (SSP) with suitable catalyst. Prior literature references to SSP of poly(L-lactic acid) (PLA) prepolymers are relatively few in number and most of them have not achieved weight average molecular weights more than the range of 5000 to 10,000 [10-13]. SSP of PLA prepolymers using a binary catalyst system of $SnCl_2.2H_2O$ and PTSA has, however, been reported to result in number average molecular weight of 50,000, which is generally not achieved by other polycondensation methods [14a,b].

This chapter describes the SSP on PLA oligomers employing the same catalysts as used for the melt and solution phase dehydropolycondensation of LLA described in Chapter 4. We have explored the use of plasticizers with a view to increasing the mobility of the end groups in the amorphous region and consequently increasing the rate of the SSP reaction. Polyethylene glycols (PEG) of two different number average molecular weights were chosen as plasticizers [15]. Although dimethyl adipate (**5.1**), tributyl citrate (**5.2**) and acetyl tributyl citrate (**5.3**), are reported as biodegradable plasticizers for PLA polymers [16], they have not been chosen because they have aliphatic alcohol and ester groups which can undergo transesterification with the PLA chain ends.



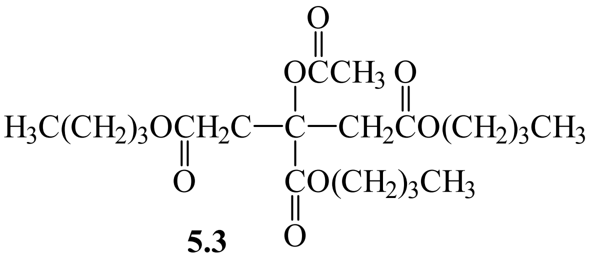
$$\mathrm{H_3CO\underset{\overset{\|}{O}}{C}-(CH_2)_3-\underset{\overset{\|}{O}}{C}OCH_3}$$

5.1



$$\mathrm{H_3C(CH_2)_3O\underset{\overset{\|}{O}}{C}H_2C-\overset{\overset{OH}{|}}{\underset{\underset{\underset{\overset{\|}{O}}{C}O(CH_2)_3CH_3}{|}}{C}}-CH_2\overset{\overset{O}{\|}}{C}O(CH_2)_3CH_3}$$

5.2



$$\mathrm{H_3C(CH_2)_3O\underset{\overset{\|}{O}}{C}H_2C-\overset{\overset{O\overset{\overset{O}{\|}}{C}CH_3}{|}}{\underset{\underset{\underset{\overset{\|}{O}}{C}O(CH_2)_3CH_3}{|}}{C}}-CH_2\overset{\overset{O}{\|}}{C}O(CH_2)_3CH_3}$$

5.3

$H_3C\left[OCH_2CH_2\right]_nOCH_3$

5.4

Contrary to the common notion that only small organic molecules with flexible and compatible moieties can act as plasticizers for a glassy polymer, polycaprolactone (PCL) is also a well-known plasticizer for PLA [17a-g]. But PCL being another aliphatic polyester will also have the potential to undergo transesterification with PLA under the SSP condition. It has been reported that upto 20 %(w/w) loading of PEG in PEG-PLA blends, there is no microphase separation [16]. PEG loading of up to 50 wt%, in spite of some microphase separation, has been found to improve properties like tensile strength and elongation at break of PLA [18a, b]. The incorporated PEG also remains enzymatically degradable upto a 30 wt% loading. The improvement of elongation and tensile properties are, however, better accomplished with lower molecular weight PEG (number average molecular weight upto about a few thousands) than by high molecular weight [19]. As an extra benefit, blending with PEG also gives an amount of anti-static property to PLA [20]. End-capping hydroxyl end groups as methyl ether renders PEG non-reactive with PLA. So considering all these aspects two different low molecular weight PEG samples, both end-capped as dimethyl ether (**5.4**), of number average molecular weights 500 and 1000 (**5.4a** and **5.4b**, respectively), have been used as plasticizers for PLA in the present work. Each of them has been incorporated in the linear PLA oligomer at 5, 10 and 20 wt% loading and SSP was performed separately on each plasticized oligomer thus obtained.

5.2. Materials and methods:

Materials: Polyethylene glycol dimethyl ether oligomers of number average molecular weights 500 and 100 (**5.4a** and **5.4b**, respectively) were obtained from Aldrich and dried azeotropically with toluene before use. Toluene and p-xylene were obtained from S. D. Fine Chemicals and were made sulphur (thiophene) free and dreied over sodium using standard techniques before use. Dichloromethane (DCM), methanol and n-hexane were also procured from S. D. Fine Chemicals and while DCM was distilled over K_2CO_3 to free it from any residual HCL impurities, methanol and n-hexane were used as such without further purification. Tetraphenyltin was obtained from Aldrich and was used as such without further treatment.

General method for synthesis of PLA oligomer: Two PLA oligomers, namely **5a** and **5b** were synthesized according to the similar procedure described for the synthesis of the PLA oligomer namely 4.3.1 using tetraphenyltin catalyst and for different reaction times. The synthesis conditions of these oligomers result in linear oligomers with carboxylic acid and hydroxyl end groups, according to discussion already made in Chapter 4 .

General method of plasticization of PLA: The PEG plasticizer (each of **5.4a** or **5.4b**, 50 mg, 100 mg and 200 mg of each) was taken in a 100 mL round bottomed flask along with the PLA prepolymer (950, 900 and 800 mg, respectively) and 1000 ppm tetraphenyltin catalyst (as the plasticization was ultimately targeted towards sample preparation for the SSP reaction), dissolved together in 50 mL DCM, stirred magnetically for 5 h for good mixing and then poured on flat petry dishes. Films were cast by aerial evaporation of

DCM over a period of 10 h, followed by drying under reduced pressure. Unplasticized PLA was also cast into film, along with equivalent amount of the catalyst, in exactly the same way for the sake of comparative studies.

General method for sample preparation for SSP: All PLA samples, plasticized and unplasticized, were crushed into powders with the help of a small-scale, table-top grinding mill, at room temperature. SSP was performed on the powdered samples.

General method of carrying out solid state polymerization reaction: The SSP reactor was basically a vertically placed quartz tube longitudinally divided into two halves by a quartz sintered disc of pore size G-1. The sintered disc acted as the bed, on which the sample was placed. The lower end of the tube was connected to a gas inlet and the upper end connected to a gas outlet. After placing sample on the bed, the reactor tube was dipped inside a sand bath previously set at the required reaction temperature and heated for the specified amount of time, with intermittent checking of rise in the melting point of the sample, so that the reaction temperature was raised accordingly to reach just 5 °C below the onset of melting. Before placing the reactor in the heating bath, the gas inlet is closed by stopcock while the outlet is connected to vacuum and the pressure was reduced slowly to 0.1 mbar, in case of reactions under reduced pressure (static bed SSP reaction). In case of reactions under purge of dry argon gas (inert gas), the inlet was connected to an argon flow of specified number of liters per minute and the outlet was left open to air via a reflector bulb that was able to reflect any powder that flew off back to the reactor tube. The argon gas was made to reach the reactor gas inlet via a spiraling duct placed in the same heating bath, so that the incoming gas was at the same temperature and there was no local cooling effect due to the purging. The samples after SSP reactions were characterized after freeing from PEG plasticizer by repeated cycles of dissolution in DCM and precipitation into methanol, in which PEG dimethyl ether plasticizers were freely soluble, followed by drying under reduced pressure.

5.3. Characterization methods:

Molecular weights: Were performed as described in Chapters 3 & 4.

Nuclear magnetic resonance, ^{13}C: Were performed as described in Chapters 3 & 4.

FTIR spectroscopy: IR spectra were recorded as KBR pellets, on a Perkin-Elmer Infrared Spectrometer Model 16-PC FT-IR, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).

Thermal analysis: Were performed as described in Chapters 3 & 4.

5.4. Results and Discussion:

According to the synthesis procedure, the PLA oligomers **5a** and **5b** were linear with both carboxylic acid and hydroxyl terminals, which is a pre-requisite for any post-polycondensation of PLA including SSP. The molecular weights and thermal characterization data of both the oligomers are summarized in Table-5-1 below.

Table-5.1: Properties of the PLA oligomers used for solid state polymerization (SSP)

Prepolymer	T_g (°C)	T_m (°C)	[η] (dL.g^{-1})	$\overline{M}_{n, VPO}$	$\overline{M}_{n, NMR}$	$\overline{M}_{n, SEC}$	$\overline{M}_{w, SEC}$
5a	43	145	0.11	1200	1100	900	2100
5b	48	146	0.24	2200	2100	2300	4200

Solid state polymerization of unplasticized PLA prepolymer: SSP was performed on both the unplasticized prepolymers, **5a** and **5b**. The SSP was carried out either under reduced pressure or under argon flow. SSP was performed for 15 h, starting with a temperature of 125 °C, which was sufficiently below the melting temperature of the prepolymer and then increasing the temperature every 5 h following the rise of melting temperature, so that the reaction temperature always remained 5 °C below the onset of melting and the final reaction temperature for the last leg of 5 h was 140 °C. The results are summarized in Table-5.2.

A few important observations can be made form this set of results. The extent of postpolycondensation achieved was very small in the case of both oligomers of different intrinsic viscosities. Because of very low molecular weight (intrinsic viscosity) of the prepolymers their melting points were also quite low and increased only to a small extent with progress of reaction, so that reaction rates could not be enhanced by increasing temperature [1e]. The progress of the postpolycondensation was also found to be almost independent of whether the reaction was done under vacuum (static bed, reactant un-agitated) or under a flow of argon gas (dynamic bed, reactant agitated) [21]. The gas flow rate was varied within the range usually followed in SSP reactions [4, 1e]. A gas flow rate below 2 liters per minute was found to be ineffective in maintaining a dynamic bed by giving sufficient agitation to the reactant, but an increase of gas flow beyond 4 liters per minute was also not useful since a doubling of gas flow rate from 2 to 4 liters per minute did not bring about improvement. The kinetics of SSP is driven by three parameters: one, rates of reaction with respect to the reactive end groups and secondly, the diffusion of by-product through the reactant up to the surface of the reactant and finally, removal of by-product from the surface of the reactant. While any of the first two parameters could be rate-determining depending on the particular type of reaction being carried out, the third one, which was performed with the help of either reduced pressure or purging with a carrier gas, did not control the rate. Only if the by-product was not effectively removed or the heat transfer was not proper, for example in case of reaction being carried out under reduced pressure and in absence of a carrier gas with sufficient flow rate, the reverse reaction might start occurring thereby limiting the resultant forward progress of the reaction and molecular weight of the final polymer [1d, 4]. Thus, since ther was no apparent rate-enhancement effect of a prepolymer of higher intrinsic viscosity and a higher flow rate of the carrier gas, the oligomer **5a** of intrinsic viscosity 0.11 dL.g $^{-1}$ and a flow rate of 2 lit.min $^{-1}$ of the carrier gas argon were chosen for all further studies.

Table-5.2: Postpolycondensation of unplasticized PLA oligomers by solid state polymerization under reduced pressure and under flow of inert carrier gas argon

Oligomer	Initial [η] (dL.g $^{-1}$)	Reaction temp. (°C)	Time (h)	Pressure	Final [η] (dL.g $^{-1}$)
5a	0.11	125 – 140	15 h	Reduced to 0.1 mbar	0.26
				Argon flow 2 L.min $^{-1}$	0.29
				Argon flow 4 L.min $^{-1}$	0.28
5b	0.24	125 – 140	15 h	Reduced to 0.1 mbar	0.34
				Argon flow 2 L.min $^{-1}$	0.36
				Argon flow 4 L.min $^{-1}$	0.36

Plasticization of PLA prepolymer with polyethylene glycol (PEG) dimethyl ethers: PEGs (dimethyl ether end capped) of two different number average molecular weights, 500 and 100 (**5.4a** and **5.4b**, respectively) was solution-blended with the PLA oligomer **5a**. Reduction of glass transition temperature (Table 5.3) provided the proof of plasticization. The dependence of T_g on the plasticizer amount is shown in Fig.-5.1.

It is observed that both the PEGs were equally good plasticizers that brought down the glass transition temperatures sharply from 43 °C to almost 25 °C. Besides, the melting temperature of the PLA oligomer remained unchanged. This indicates that there may not be any microphase separation up to 20 wt% loading of either PEG plasticizer [15]. Such plasticized PLA prepolymer samples were further subjected to postpolycondensation by SSP.

Table-5.3: Thermal properties (T_g and T_m) of PLA oligomer 5a plasticized by PEG dimethyl ether oligomers

Plasticizer used	Loading (wt%)	Thermal properties of plasticized PLA	
		T_g (°C)	T_m (°C)
5.4b	05	36	143
	10	31	141
	20	26	144
None	00	43	145
5.4a	05	36	143
	10	32	147
	20	27	143

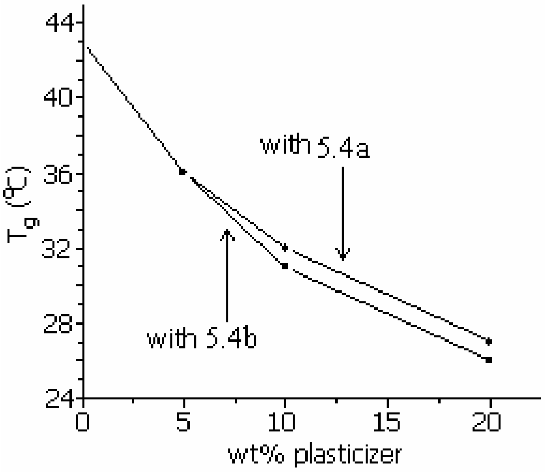


Fig. 5.1: Decrease in the glass transition temperature of 5a oligomer upon blending with different amounts of plasticizers 5.4a and 5.4b.

Postpolycondensation by solid state polymerization of plasticized PLA prepolymer: All the plasticized prepolymer samples were subjected to postpolycondensation by SSP for 15 h with an initial reaction temperature of 125 °C, which was stepwise (every 5 h) increased to a final reaction temperature of 140 °C following the increase in the melting point of the prepolymer, and with a carrier (argon) gas flow of 2 lit.min^{-1}. The results are shown in Table-5.4. It is observed that plasticization did not improve the rate of SSP, indicating that incorporation of plasticizer molecules in the amorphous region had no effect on the reaction rates. Plasticizers were expected to increase the mobility of the reactive end groups in the amorphous region by reducing the glassiness of the PLA polymer at a given temperature and thereby expected to increase the reaction rates of the reactive end groups. The SSP reaction proceeded by esterification between different chain end groups (hydroxyl and carboxylic acid terminals), between chain ends and ties and loops and anchors of consecutive crystalline regions of the semicrystalline PLA prepolymer.

Chain ends, ties, loops and anchors basically inter-converted into one another by such esterification and transesterification reactions, which is called "chemical migration" that is kinetically very similar to physical migration or translational motions of different such segments, but not really physical, translational motions of such reactive segments toward one another resulting in reactive collisions [22-25]. A physical transnational motion of end groups is unlikely because thermal motions of chain ends are very restricted in the solid state compared to the molten state and more so because the relative motions of different chain segments are severely restricted by anchoring of almost all of them to the crystallites of the semicrystalline polymer. Plasticizers could not interfere with the chemical migration of the end groups to a significant extent and, therefore, could not affect the reaction rate.

Table-5.4: comparison of results of SSP reaction of PLA oligomer 5a in both plasticized and unplasticized conditions.

Plasticizer used	Loading (wt%)	Reaction temp. (°C)	Argon flow	PLA prepolymer		PLA after SSP	
				T_m (°C)	[η] (dL.g^{-1})	T_m (°C)	[η] (dL.g^{-1})
5.4b	05	125 - 140	2 lit.min^{-1}	143	0.11	163	0.30
	10			141		158	0.28
	20			144		151	0.27
None	00	125 - 140	2 lit.min^{-1}	145	0.11	163	0.29
5.4a	05	125 - 140	2 lit.min^{-1}	143	0.11	166	0.27
	10			147		173	0.31
	20			143		149	0.27

Thus the effect of plasticization, if any, was expected to be manifested into the vibrational frequency of the reactive segments. The C=O stretching vibration of the PLA oligomer in the FTIR was, therefore, examined with and without plasticizer. The 20 wt% blends of both PEGs **5.4b** and **5.4a** with the PLA oligomer **5a** was examined by FTIR at 30, 70, 100 and 140 °C, to observe the changes in the frequency of this particular vibration with increasing temperature. The observations are all shown in the Figs. 5.2a, 5.2b and 5.2c.

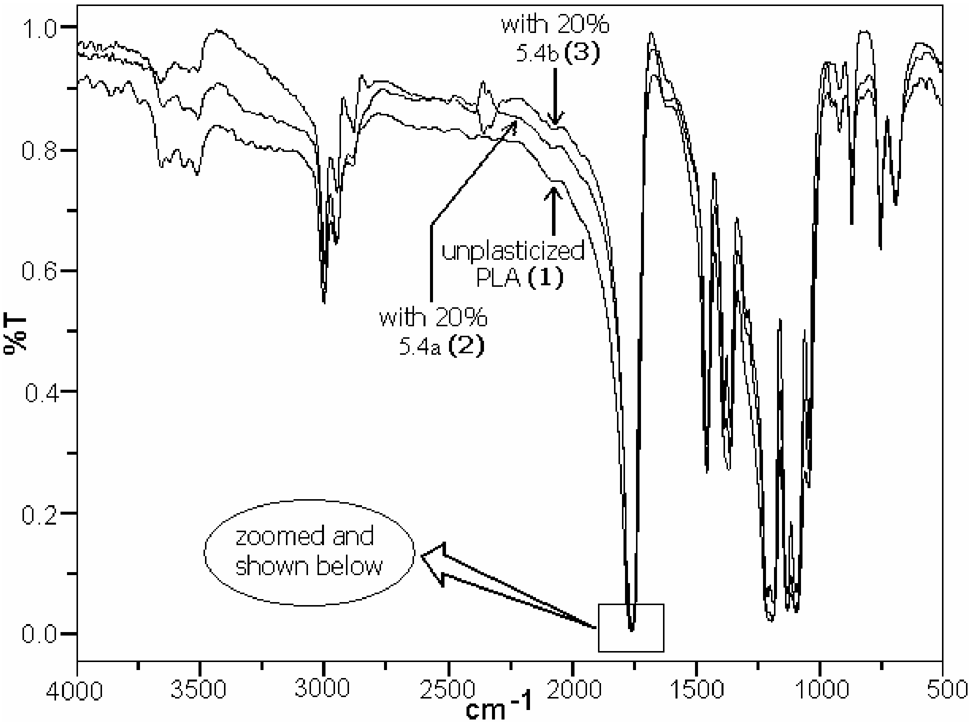


Fig. 5.2a: Overlaying FTIR spectra of (1) un-plasticized 5a oligomer against the same plasticized (2) with 20 wt% 5.4a and (3) with 20 wt% 5.4b plasticizer at 30 °C, showing the C=O stretching vibration as selected for enlargement

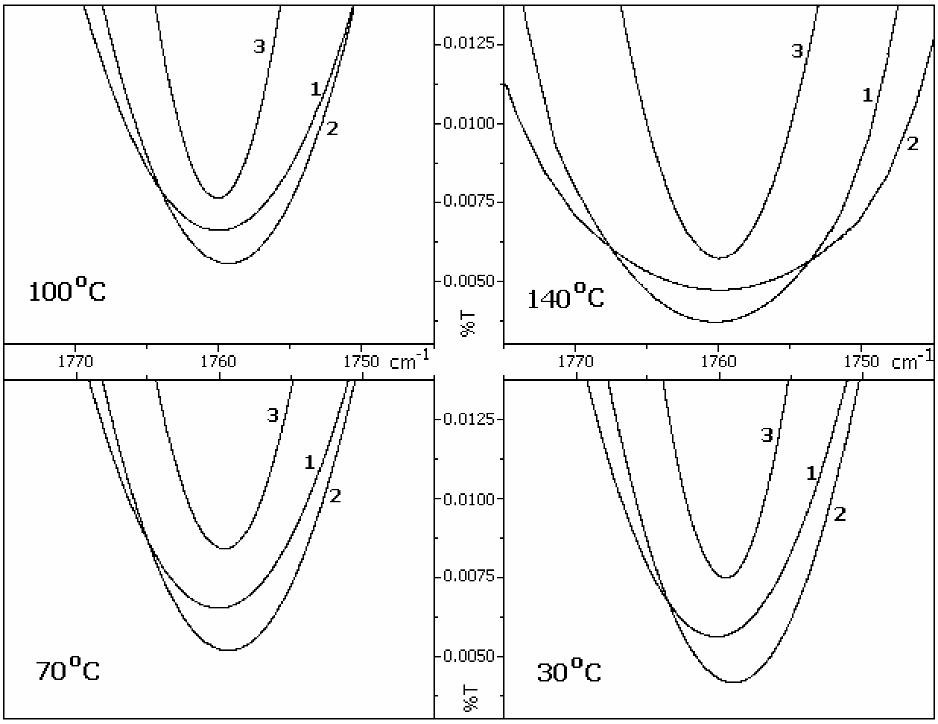


Fig. 5.2b: Enlargement of the C=O stretching vibrational region, as selected in Fig. 5.2a, showing the relative shifts of the same stretching peak minima due to (1) un-plasticized 5a oligomer, (2) same oligomer with 20 wt% 5.4a and (3) with 20 wt% 5.4b plasticizer at 30, 70, 70 and 140 °C, respectively (clockwise).

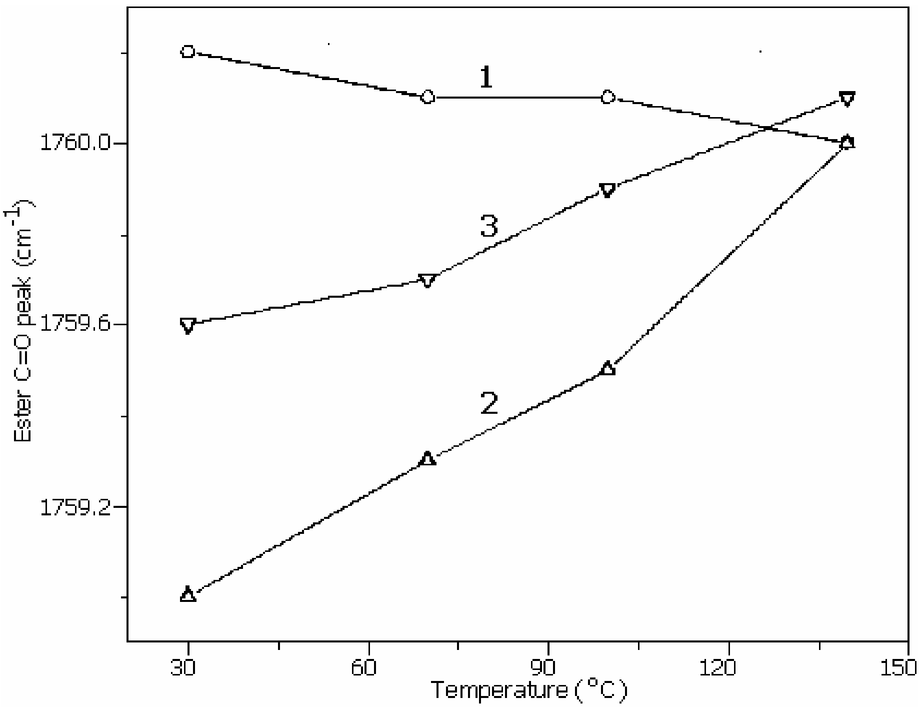


Fig. 5.2c: Changes in the positions of minima of the C=O stretching peaks of (1) un-plasticized 5a oligomer, (2) same oligomer with 20 wt% 5.4a and (3) with 20 wt% 5.4b plasticizer, as determined form the enlarged regions of the corresponding FTIR spectra shown in Fig. 5.2b, along with increase in temperature from 30 to 140 °C.

From the enlarged regions around the peak minima due to C=O stretching vibration of the different polymers (plasticized and Unplasticized, Fig. 5.2b), it could be found that the position of the peak minima shifted due to plasticization. The numbers of cm^{-1} of shift in all cases were also found from the FTIR spectra, as shown in Table-5.5 and were all plotted together in Fig. 5.2c.

Table- 5.5: Shifts in the minima of the FTIR peak due to C=O stretch of (1) un-plasticized 5a oligomer, (2) same oligomer with 20 wt% 5.4a and (3) with 20 wt% 5.4b plasticizer at different temperatures from 30 to 140 °C

Temperature (°C)	Ester C=O peak position (cm^{-1})		
	Unplasticized PLA	With 20 % PEG-500	With 20 % PEG-1000
30	1760.2	1759.0	1759.6
70	1760.1	1759.3	1759.7
100	1760.1	1759.5	1759.9
140	1760.0	1760.0	1760.1

It is, thus, observed that, at 30 °C, there were significant shifts in the minima from (1) un-plasticized **5a** oligomer to (2) same prepolymer with 20 wt% **5.4a** plasticizer to (3) with 20 wt% **5.4b** plasticizer, but the differences in the minima positions gradually minimized as the temperature increased from 30 to 140 °C, indicating that the plasticization effect on the mobility of the reactive segments minimized with increase in temperature. Since the SSP reactions also took place in the temperature range of 125 – 140 °C, the presence of the supposed plasticizer molecules in the prepolymer was not perhaps able to impart any effect on the mobility of the reactive segments at that temperature. That explained why no significant change was found in the progress of the SSP reaction (in terms of increase in the value of intrinsic viscosity, [η]) even by adding the plasticizers. The presence of plasticizers thus made no difference at an elevated temperature required for the SSP reaction to occur. There were, however, small depressions in the extents of increment of both melting point and intrinsic viscosity with 20 wt% loading of either plasticizer, meaning less efficient progress of the SSP reaction than in the other cases. This could be because of less diffusion of the by-product water from the core of the reactant to the surface as the core of the reactant became somewhat more hydrophilic because of the presence of significant amount of PEG molecules.

5.5. Conclusion:

Unplasticized, linear poly(L-lactic acid)s did not undergo any efficient postpolycondensation by solid state polymerization using tetraphenyltin catalyst, which was also used for the dehydropolycondensation of L-lactic acid in solution and in bulk, and only a small increase in the intrinsic viscosity could be achieved in 15 h of SSP reaction. Polyethylene glycol dimethyl ethers of number average molecular weights 500 and 1000 were found to be good plasticizers for the PLA prepolymer at room temperature (30 °C). However, depression of T_g did not improve the rate of SSP.

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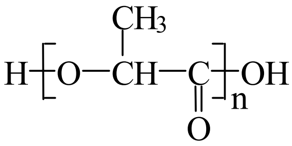
CHAPTER - 6

CHAPTER 6: POST-POLYMERIZATION OF PLA OLIGOMERS BY ACTIVATED POLYCONDENSATION AND CHAIN EXTENSION.

6.1. Introduction:

The first part of the present chapter discusses post-polycondensation of poly(L-lactic acid)s oligomer (PLA, **6.1**) with a condensing agent. The aim was to prepare high molecular weight aliphatic polyesters based on PLA oligomers by using a diisopropylcarbodiimide (DIPC. **6.2**) as the condensing agent.



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

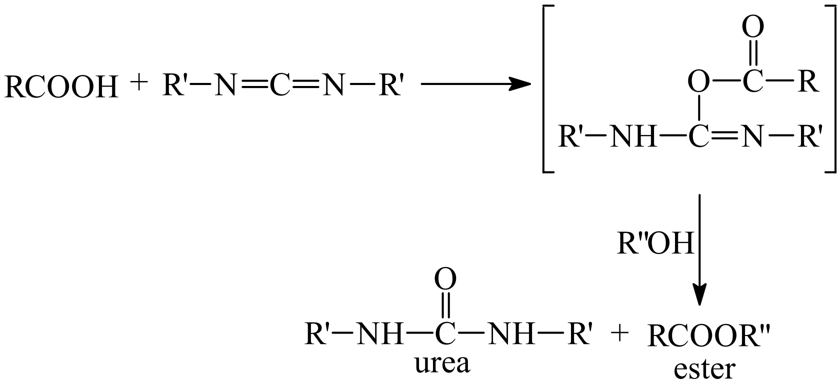
6.1

$(CH_3)_2HC-N=C=N-CH(CH_3)_2$

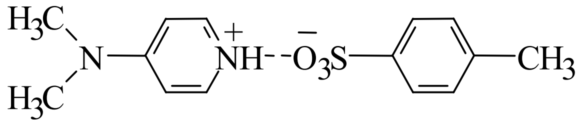
6.2

Direct esterification of organic compounds have been explored using carbodiimides as the condensing agent [1,2], (Scheme-6.1) and polyesterification reactions have been carried out with aromatic acids and alcohols or phenols [3]. Maximum $\overline{M}_w$ upto 15,000 has been reported in this reactions. Direct condensation of lactic acid to make PLA using dicyclohexyl carbodiimide (DCC) as the condensing agent has also been attempted [4] and the polyesterification of aliphatic hydroxyacids in general has been patented using several condensing agents, namely dicyclohexyl carbodiimide (DCC), triphosgene and carbonyl diimidazole (CDI) [5].

Scheme-6.1: Activated esterification using a carbodiimide adjuvant



Since carbodiimides do not react with aliphatic alcohols or phenols except under drastic conditions, therefore one expects selective activation of the carboxylic acid terminal in the case of a hydroxyacid [1]. There is no need for a separate pre-activation. Traces of moisture can also be tolerated, since any ester linkage that undergoes hydrolysis can also be regenerated in-situ. However, there are certain side reactions, which cause low molecular weight polyesters to form in such reactions. There is no report available in the prior literature about the use of DIPC as the condensing agent for postpolymerization. More importantly, suppression of side reactions, and consequent improvement of molecular weight by varying reaction parameters, for example temperature, solvent and catalyst, has also not been documented. In the present work, DIPC-mediated post-polycondensation of PLA oligomers was studied using a mixture of a strongly basic, super-acylation catalyst, 4-(dimethylamino)-pyridine (DMAP) and a strongly acidic (protonic) catalyst p-toluene sulphonic acid (PTSA) [6]. A 1:1 adduct, namely 4-(dimethylamino)-pyridinium p-toluene sulphonate (DPTS, **6.3**) was employed [3].

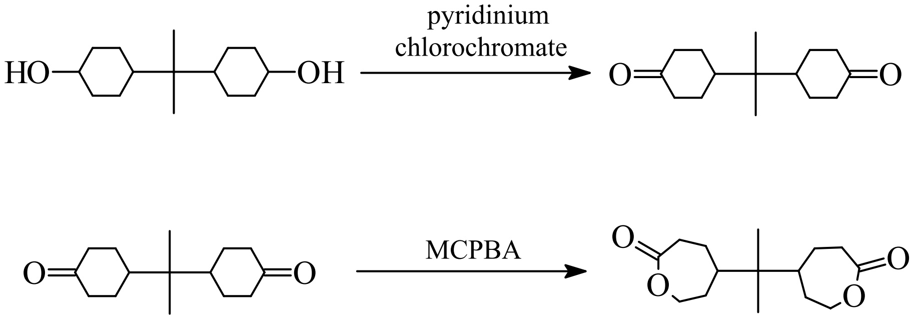


6.3

The second part of this chapter, describes results of an attempt to increase the molecular weight of a low molecular weight PLA oligomer by first synthesizing a telechelic PLA prepolymer followed by coupling through the end groups with the help of suitable coupling agents (chain extenders). Coupling of telechelic PLA oligomers through chain extenders is well known. Coupling reactions between diol-ended telechelic PLA prepolymers and diisocyanate chain extenders have been performed to make copoly(ester-urethanes) [7a –d]. Diol ended PLA telechelics have also been coupled through bis-chloroformate type chain extenders [8] to yield aliphatic copoly (ester-carbonate)s. But in such reactions, the by product is a hydrochloride salt of the corresponding HCl-abstracting base that is essentially required to drive the equilibrium between the hydroxyl and chloroformate groups towards complete formation of the carbonate linkage. Synthesis of dicarboxylic acid-terminated PLA prepolymer followed by coupling through bis-oxazoline chain extender to make copoly(ester-amide)s have also been reported recently [9]. Telechelics of PLA have been made from direct condensation of L-lactic acid, ε-caprolactone and 1,4-butanediol and such telechelics have been coupled to yield copoly(ester-urethane)s [7d]. Copolymerization of L-lactide and other lactones, especially ε-caprolactone (CL), by means of ring opening polymerization (ROP) using various hydroxyl-terminated molecules as initiators is also well documented [10a-g]. Block copolymerization of LLA and CL using hydroxyl-terminated poly(ε-caprolactone) (PCL) chains as macro-initiators for the ROP of the L-lactide has also been explored by Kricheldorf et al and others [11a-e]. Cross-linked poly(ether-lactone)s have been prepared by simultaneous ROP of 1,5-dioxepan-2-one (DXO) in presence of bis(ε-caprolactone) molecules [11f]. But use of a bis-lactone type molecule as a chain extender for a diol-ended PLA telechelic prepolymer to obtain a linearly coupled, high molecular weight copolyester of LLA has not been explored; neither a direct condensation between a diol-terminated PLA telechelic and a diaryl carbonate to synthesize an aliphatic copoly(ester-carbonate) has been studied.

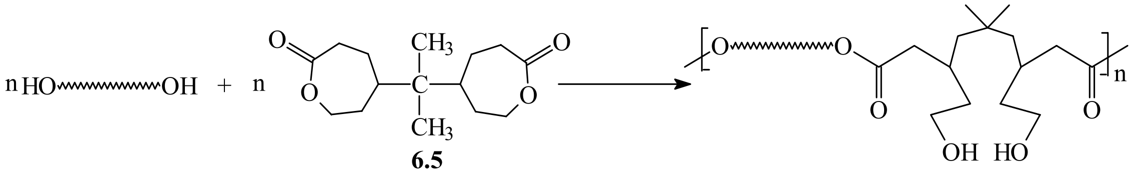
In the present study, coupling of telechelic PLA was examined using a suitable bis-lactone and a diaryl carbonate chain extenders. Since the opening of ε-caprolactone ring with alcohol functional groups is well known, a bis-(ε-caprolactone) molecule, namely μ-isopropylbis-(ε-caprolactone) (**6.5**), was synthesized as shown in Scheme 62. A diol-ended PLA telechelic was then coupled as shown in Scheme-6.3. Since polycaprolactone itself is known to be a biodegradable polyester, such a copolyester was also expected to retain the biodegradability properties of PLA.

Scheme- 6.2: Synthesis of μ-isopropylbis-(ε-caprolactone)



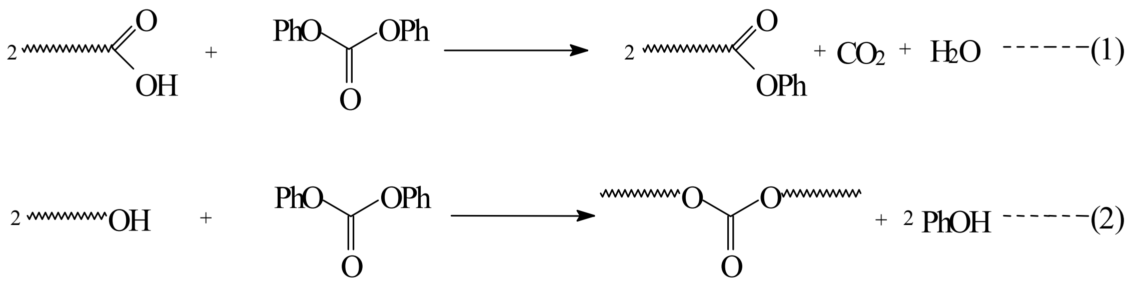
6.4 **6.5**

Scheme-6.3: Coupling of diol-ended PLA with μ-isopropylbis-(ε-caprolactone)



Attempt was also made to couple a diol-ended PLA telechelic oligomer using diphenyl carbonate as chain extender. Diphenyl carbonate (DPC, **6.6**) is known to participate in ester exchange reactions with both carboxylic acids and alcohols [12a, b], as shown in Scheme-6.4. The diol-ended PLA telechelic was, therefore, expected to undergo coupling via carbonate linkages with DPC acting as the chain extender, like in reaction (2) of Scheme-6.4.

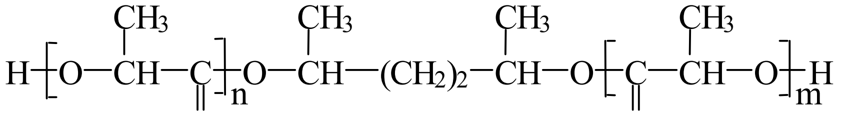
Scheme-6.4: Possible ester exchange reactions of diphenyl carbonate (DPC)



6.6

Such reactions are known to take place under both Lewis acidic as well as basic catalysis [13-15]. Basic, especially quaternary phosphonium and ammonium salt, catalysts have been reported to be better as well as having less energy requirement than acidic catalysts in general for such reactions [16, 17]. Alcoholic OH groups can react with DPC at 210 – 220 °C [13-15], the temperature requirement for the aliphatic carboxylic acids to react is about 50 °C higher [18, 19]. In the present work, chain extension by DPC was performed on the diol-ended PLA telechelic

The telechelic PLA prepolymer (**6.7**) was prepared form dehydropolycondensation of L-lactic acid (LLA) in presence of small amount of 2,5-hexanediol, so that both ends of the telechelic contained similar, secondary hydroxyl groups.



$$H\left[O-\underset{}{\overset{CH_3}{\overset{|}{CH}}}-\underset{\underset{O}{\|}}{C}\right]_n O-\overset{CH_3}{\overset{|}{CH}}-(CH_2)_2-\overset{CH_3}{\overset{|}{CH}}-O\left[\underset{\underset{O}{\|}}{C}-\overset{CH_3}{\overset{|}{CH}}-O\right]_m H$$

6.7 ($0 \leqslant m \leqslant n$)

6.2. Materials and methods:

Materials: L-lactic acid was obtained form PURAC as 88 % (w/w) aqueous solution and was used without further purification. Tetraphenyltin and DMAP, obtained from Aldrich, were used without further purification. M-Chloroperbenzoic acid (MCPBA) was obtained from S.D. Fine Chemicals, India and used without further purification. PTSA was obtained from Aldrich, but was freshly dried azeotropically with benzene and recrystallized from petroleum ether followed by vacuum drying before use. Benzene, p-xylene, dichloromethane (DCM), ethylene dichloride (EDC), chlorobenzene and toluene were also obtained from Aldrich and while benzene and p-xylene were used without further purification/ drying, DCM, EDC and chlorobenzene were dried over CaH_2 and toluene dried over metallic sodium. Diisopropylcarbodiimide (DIPC) was obtained from Aldrich and was used without further purification. 2,5-hexanediol (HDO) was also obtained from Aldrich, but was freshly distilled under reduced pressure before use. Stannous 2-ethyl hexanoate (alternatively called, stannous octoate, $Sn(Oct)_2$) was freshly vacuum-distilled before use and titanium isopropoxide ($Ti(OPr^i)_4$) was used as a 30 % solution in dry DCM. All liquids, except benzene and p-xylene, were transferred through canula.

Passivation of glass surface: Was performed as described in Chapter 4.

Synthesis of PLA oligomers with both carboxylic acid and hydroxyl end groups: The oligomer **6.1a** was synthesized in the same procedure (ROP of lactide) as PLA oligomer **3.1** and the oligomer **6.1b** was synthesized in the same procedure as PLA oligomer **4.3.1**, synthesized by dehydropolycondensation of L-lactic acid.

Synthesis of DPTS (**6.3**)*:* Equi-molar amounts of DMAP and dry PTSA were stirred together in hot benzene while they first dissolved and then formed a white suspension. The suspension was stirred for further 1 hour and cooled, followed by filtering, washing, recrystallization from saturated and chloroform solution, washing with n-hexane and drying. DPTS was collected as needle shaped white crystals, which were inert to moisture or air.

Synthesis of μ-isopropylbis-(ε-caprolactone) (**6.5**)*:* Hydrogenated bisphenol-A (HBPA), obtained from Aldrich chemicals was purified by recrystallization from hot toluene. HBPA was dissolved in DCM and oxidized with the help of pyridinium chlorochromate supported on 100-200 mesh silicagel by stirring for 4 h at room temperature [20a, b] to obtain the corresponding μ-isopropylbis-cyclohexanone (**6.4**). The black mud was filtered off and the colored solution was run through a column of silica gel supported on celite to get a colorless solution, which was then washed with dilute $NaHCO_3$ solution to remove any carboxylic acid, followed by washing with water. The crude product was collected as white powder by evaporating the DCM. A portion of the bis-ketone was taken in DCM solution and stirred with 4 equivalents of m-chloroperbenzoic acid (MCPBA) at room temperature to achieve Bayer-Villiger oxidation [21] of **6.4** into **6.5** in 12 h. Washing the DCM solution resulted in the desired product with 95 % yield. FTIR (KBR pellet): peaks due to ketonic and lactonic carbonyls at 1714 (**6.4**) and 1726 cm^{-1} (**6.5**), respectively (Fig. 6.4). ^{1}H-NMR of **6.4** (Fig. 6.5a) δ (ppm, $CDCl_3$ 7.25): 2.50 – 1.25 (m, 9H, CH and all CH_2) and 0.90 – 0.75 (s, 3H, CH_3); and characteristic ^{1}H-NMR of the bis-lactone (Fig. 6.5b) δ (ppm, $CDCl_3$ 7.25): 4.35 – 3.95 (t + t, axial-equatorial splitting, $1H_a + 1H_e$, OCH_2), 2.70 – 1.10 (m, 7H, CH and rest CH_2) and 0.80 – 0.65 (s, 3H, CH_3). The bis-lactone **6.5** decomposed without melting.

Synthesis of diol-ended telechelic PLA prepolymer (**6.7**)*:* In a reactor vessel of glass, passivated as mentioned above and fitted with a Dean & Stark type condenser, L-lactic acid (20 g, 0.196 mol), as 88 % aqueous solution obtained from PURAC and 2,5-hexanediol (HDO) (2.3 g, 0.0196 mol) were simultaneously with p-xylene for 6 h and cooled to 50 °C under argon atmosphere, following which tetraphenyltin (0.0855 g, 0.04 mmol, 0.02 mol% of L-lactic acid) was added and refluxed in p-xylene for 15 h. The xylene was finally evaporated and obtained polymer was dissolved in DCM (50 mL), precipitated into petroleum ether (250 mL), filtered, washed with petroleum ether and dried under reduced pressure at room temperature, and characterized. ^{1}H-NMR (500 MHz, Fig. 6.6): δ (ppm, $CDCl_3$ at 7.25) 5.20 – 5.05 (qt, CH-a attached to ester in the repeating unit, extra shoulders due to different environments and/ or different degrees of polymerization), 4.65 – 4.60 & 4.55 (m &m, CH-b attached to ester, different environments), 4.25 – 4.12 (m, CH-b attached to terminal hydroxyl and CH-b attached to penultimate ester linkage, for those chains where HDO was at the end), 4.36 – 4.29 (qt, CH-a attached to terminal hydroxyl), 1.87 – 1.78 (m, CH_2-CH_2 due to HDO), 1.61 – 1.49 (d, CH_3-a), 1.22 – 1.49 (double d, CH_3-b + CH_3-b′).

Postpolycondensation of PLA prepolymer with the help of DIPC (**Entry No. 2, Table-6.2**)*:* To a dry glass reactor previously passivated and fitted with septum adaptor, PLA oligomer **6.1a** (100 mg), previously dried under reduced pressure at 50 °C, and DPTS (90 mg) were poured [3]. To this was added dry DCM 1 mL, followed by addition of DIPC (0.8 mL) and stirring for an appropriate length of time at an appropriate temperature. The final polymer was recovered by precipitating from the reaction solution into 5 times by volume of petroleum ether, filtering and drying under reduced pressure at room temperature, and characterized by SEC and VPO for weight average and number average molecular weights, respectively, and compared with those of the starting PLA prepolymer.

Coupling of diol-ended telechelic PLA by μ-isopropylbis-(ε-caprolactone) (**Entry No. 1, Table- 6.6**)*:* In a glass reactor passivated and dried as discussed above and maintained under inert (dry argon) atmosphere, telechelic PLA (**6.7**, 100 mg) was taken and μ-isopropylbis-(ε-caprolactone) (**6.5**, 10 mg) and DPTS catalyst (9 mg) were added. Dry DCM was added to it for proper mixing. DCM was evaporated under reduced pressure and the reaction mixture was dipped into a sand bath previously set at an appropriate temperature and heated under inert atmosphere for different lengths of time. The final polymer was recovered by dissolving in DCM and precipitating into petroleum ether, followed by drying under reduced pressure at room temperature, and was characterized by SEC for both weight average and number average molecular weights.

Coupling of PLA by DPC (**Entry No. 1, Table- 6.7**)*:* In a glass reactor passivated and dried as discussed above and maintained under inert (dry argon) atmosphere, either the diol ended telechelic PLA (**6.7**, 100 mg) was taken and DPC (5 mg) and DPTS catalyst (9 mg) were. Similarly as above, dry DCM was added for mixing and evaporated under reduced pressure, following which the reactor was dipped in a sand bath previously set at the required reaction temperature and was heated for a different lengths of time under reduced pressure of 1 mbar only. In the particular case of coupling by DPC, the reactor taken was of a long tube type and only the bottom of the tube where the reactants resided was dipped in the sand bath, so that among the by-product phenol and a portion of the DPC, both of which volatilized, only the phenol condensed at the upper part of the tube while DPC came back in liquid form to the bottom of the reactor [22]. Similarly as above, the final polymer was recovered by dissolving in DCM and precipitating into petroleum ether, followed by drying under reduced pressure at room temperature, and was characterized by SEC for both weight average and number average molecular weights.

6.3. Analysis:

Molecular weights: Molecular weights ($\overline{M}_n$ and $\overline{M}_w$) were determined using SEC, ^{13}C NMR, VPO and intrinsic viscosity as described in Chapters 3 & 4.

Nuclear magnetic resonance, ^{1}H *and* ^{13}C*:* were performed as described in Chapters 3 & 4.

Determination of hydroxyl end groups concentration by ^{31}P-NMR spectroscopy: The hydroxyl terminals of the diol-terminated telechelic PLA oligomer (prepolymer) were derivatized into O-P linkage using 1,2-phenylenephosphorochloridite (PPC) at room temperature using $CDCl_3$ and 2,4,6-trichlorophenol as solvent and internal standard, respectively and ^{31}P-NMR data were acquired on a 500 MHz NMR spectrometer [23]. Typical acquisition parameters included a 30-degree flip angle and collection of 32K data points. A pulse delay was chosen so that the total recycle time was 3 sec. The number of scans was 800. The peak due the internal standard showed up at 130.68 ppm in the spectrum, as shown in Fig. 6.7. The peak appearing at 128.63 ppm (a) and the other small peak in between (a′) were both due to derivatization of hydroxyl terminals of the telechelic that contained two different types of hydroxyl terminals (**6.7**). The peak at 121.39 ppm was due to the traces of moisture present in the system being derivatized by PPC. The concentration of PLA hydroxyl terminal in unit of meq/ kg was obtained as their total integration divided by the number of mg of polymer used in the reaction, with respect to 10,000 value assigned to integration of the peak due to internal standard.

MALDI-ToF MS analysis: Was performed as described in Chapter 4.

FTIR spectroscopy: Was performed as described in Chapter 5.

6.4. Results and Discussion:

6.4a. Postpolycondensation of PLA prepolymer with condensing agent DIPC

According to the established mechanism of the reaction [3,23] (Scheme-6.4), the acylation of an alcohol (both primary and secondary are reactive) or by carboxylic acid occurs through the formation of an in-situ anhydride (**6.11**), which in turn is formed via O-acylurea (**6.9**) of the carboxylic acid. The by-product of the anhydride formation reaction is the corresponding alkylurea whose formation is an irreversible process. The final step of the reaction is acylation of the alocohol by the anhydride which is also irreversible. Therefore, the overall process is not limited by equilibrium, although the formation of the O-acylurea occurs in a reversible way. The formation of the alkylurea, therefore, acts as the driving force of the whole reaction, resulting in quantitative yield and high molecular weight of the polyester. Both strongly basic (for example, 4-(dimethylamino)-pyridine, DMAP) and strongly acidic (for example, p-toluene sulphonic acid, PTSA) catalysts are required [6]. Linear PLA oligomers **6.1a** and **6.1b** were subjected to the DIPC mediated post-polycondensation (Table 6.1).

Scheme-6.4: Mechanism of acylation of hydroxyl by carboxylic acid activated by DIPC

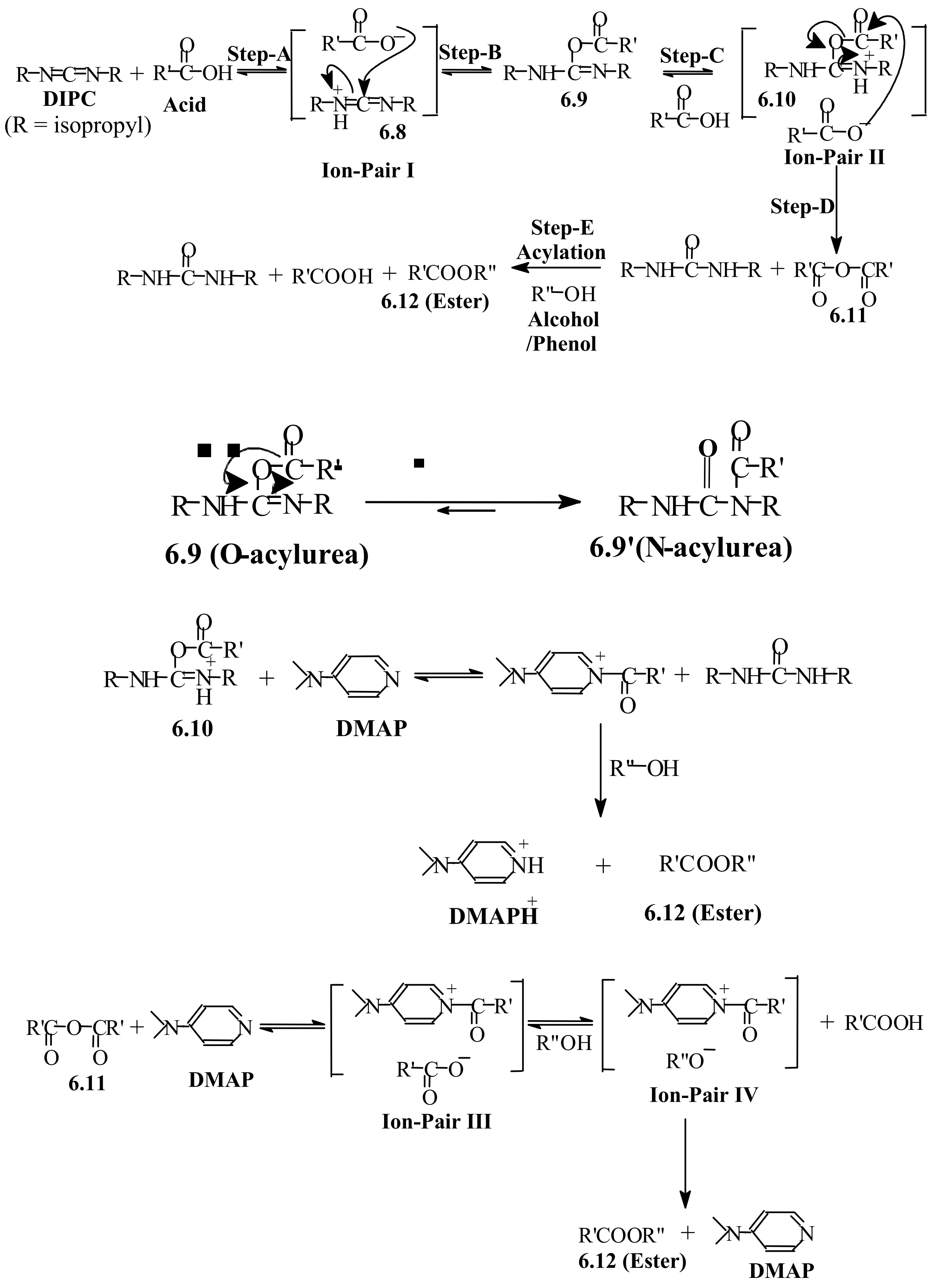


Table-6.1: PLA oligomers used for postpolycondensation using DIPC

Oligomer	Synthesis method	[η] (dL/g)	$\overline{DP}_{n,\ NMR}$	$\overline{M}_{n,\ NMR}$	$\overline{M}_{n,\ VPO}$	$\overline{M}_{n,\ SEC}$	$\overline{M}_{w,\ SEC}$
6.1a	ROP of L,L-dilactide	0.20	60	4320	4400	n.d.	n.d.
6.1b	Dehydropolycondensation	0.11	15	1100	1200	900	2100

n.d. not determined

Model postpolycondensation reaction with DIPC up on PLA prepolymer with controlled number average molecular weight: Model PLA oligomer **6.1a** with controlled $\overline{M}_n$ value was subjected to postpolycondensation with DIPC condensing agent in presence of DPTS catalyst in DCM solvent and at 30 °C, in order to see the feasibility of the reaction on PLA polymer. The results of such reactions are shown in Table-6.2 below.

Table-6.2: Postpolymerzation of PLA oligomer 6.1a using DIPC and DPTS

Entry No.	Eqv. of DIPC	Temp. (°C)	Time (h)	$\overline{M}_{n,\ NMR}$	$\overline{M}_{n,\ VPO}$
1	1.0	30	12	5900	5300
2	1.2	30	12	8400	8600

The DPTS concentration was maintained at 1 equivalent with respect to the equivalence of carboxyl terminals in the PLA oligomer **6.1a** [3]. It was found that 1.2 equivalent of DIPC with respect to the carboxyl-equivalence gave better. The excess was perhaps needed to take care of traces of moisture present in the system. Therefore, for all subsequent reactions the equivalence of DIPC was kept at 1.2 and the other parameters varied.

*Postpolycondensation of PLA oligomer **6.1b**:* Postpolymerization was performed on the other PLA oligomer **6.1b** with 1.2 equivalent DIPC. Different non-polar aprotic solvents [3] were used for the purpose of variation of reaction temperature. Different catalyst concentrations were also used to see the effect on the achievable molecular weight. The results are all summarized in Table-6.3.

Effect of solvent, temperature, time and catalyst concentration: It can be observed from these data is that reduction in catalyst DPTS concentration from a stoichiometric equivalent of carboxylic acid end group to 0.1 equivalent resulted in higher molecular weights of the final polymers. Reaction in DCM solvent at room temperature and reduced DPTS concentration resulted in high molecular weights. A maximum weight average molecular weight of 88,000 was thereby achieved in 12 h. Role and effect of catalyst in postpolycondensation of PLA with DIPC condensing agent will be discussed in more detail in a later section of this chapter.

Table-6.3: Postpolymerzation of PLA oligomer 6.1b using DIPC and DPTS

Solvent	Eqv. of DPTS	Temp. (°C)	Time (h)	Entry No.	[η] (dL/ g)	SEC	
						$\overline{M}_n$	$\overline{M}_w$
Dichloromethane	1.0	30	12	1	0.33	7,500	17,400
	0.1	30	03	2	0.57	18,600	36,200
			06	3	0.72	32,400	49,700
			12	4	1.09	45,600	88,200
			24	5	0.92	39,900	70,100
Ethylene dichloride	1.0	30	12	6	0.39	13,500	21,400
	0.1	30	03	7	0.49	11,500	29,800
			06	8	0.50	11,900	30,000
			12	9	0.51	15,400	31,200
			24	10	0.43	8,700	24,500
		45	03	11	0.39	11,400	21,600
			06	12	0.52	15,600	31,900
			12	13	0.42	8,800	23,500
			24	14	0.33	8,000	17,500
		80	03	15	0.27	8,600	11,500
			06	16	0.27	8,200	11,400
			12	17	0.18	4,800	6,300
			24	18	0.13	1300	2700
Toluene	0.1	30	03	19	0.36	9,500	19,600
			06	20	0.50	12,900	30,300
			12	21	0.53	13,200	33,100
			24	22	0.47	13,000	27,500
Chlorobenzene	0.1	30	03	23	0.36	6,500	19,300
			06	24	0.44	10,900	25,800
			12	25	0.44	11,400	25,600
			24	26	0.45	11,700	26,000

What is noteworthy at this point is that in any solvent and at any temperature the average molecular weight and intrinsic viscosity [η] leveled off after a certain period of time. According to the overall mechanism of this postpolycondensation (activated acylation), a number of equilibria between conjugate protonic acid-base pairs are involved in the reaction. So non-polar aprotic solvents should be most appropriate for this reaction since they will not interfere with these equilibria by acting as either proton donor or acceptor [1]. Non-polarity and low dielectric constant were important, so that the ion-pairs should be tightly caged and not dissociated or solvated separately. It is evident form the data in Table-6.3 that DCM was the best solvent for this reaction. This is more clearly visible from Figs. 6.1-A and 6.1-B. Increasing reaction temperature reduced the maximum achievable molecular weight and in certain cases accelerated the leveling off of the molecular weight.

Role of catalyst in regulating occurrence of side reactions and/ or degradation: Both DMAP and PTSA components play crucial role in this acylation mechanism as shown in Scheme-6.4. DMAP forms adducts with different protonated intermediate species, as shown in the mechanism, thereby accelerating the conversion of O-acylurea to alkylurea and the ester as well as acylation by the anhydride once that is formed. On the other hand, PTSA causes a depression of an important reaction involving conversion of the O-acylurea (**6.8**) to an N-acylurea (**6.8'**), which does not take part in the final acylation mechanism. This conversion is thermodynamically very facile particularly in a weekly acidic system. The conversion from **6.8** to **6.8'** needs migration of the lone pair of the imine nitrogen to the carbonyl carbon. But the spatial disposition of the lone pair is away from the carbon, so a rotational inversion of the already existing C-N double bond is necessary. A weak acid causes a protonation-deprotonation equilibrium with the basic imine nitrogen, so that sp^3 character of the C-N double bond increases and existing sp^2 character decreases. Then the rotation becomes freer and the rearrangement is also easier.

But with a strong acid like PTSA (which is a very strong acid in non-polar solvents like benzene or dichloromethane because of the conjugate anion PTS being very stable by delocalization and having very low basicity), the nitrogen is strongly protonated. Thus the rearrangement is inhibited. DMAP and PTS (conjugate base of PTSA) being comparably strong bases, PTSA tends to protonate DMAP, thereby decreasing the equilibrium concentration of free DMAP. A 1:1 molar ratio of DMAP and PTSA has been found to be the best catalyst composition [3].

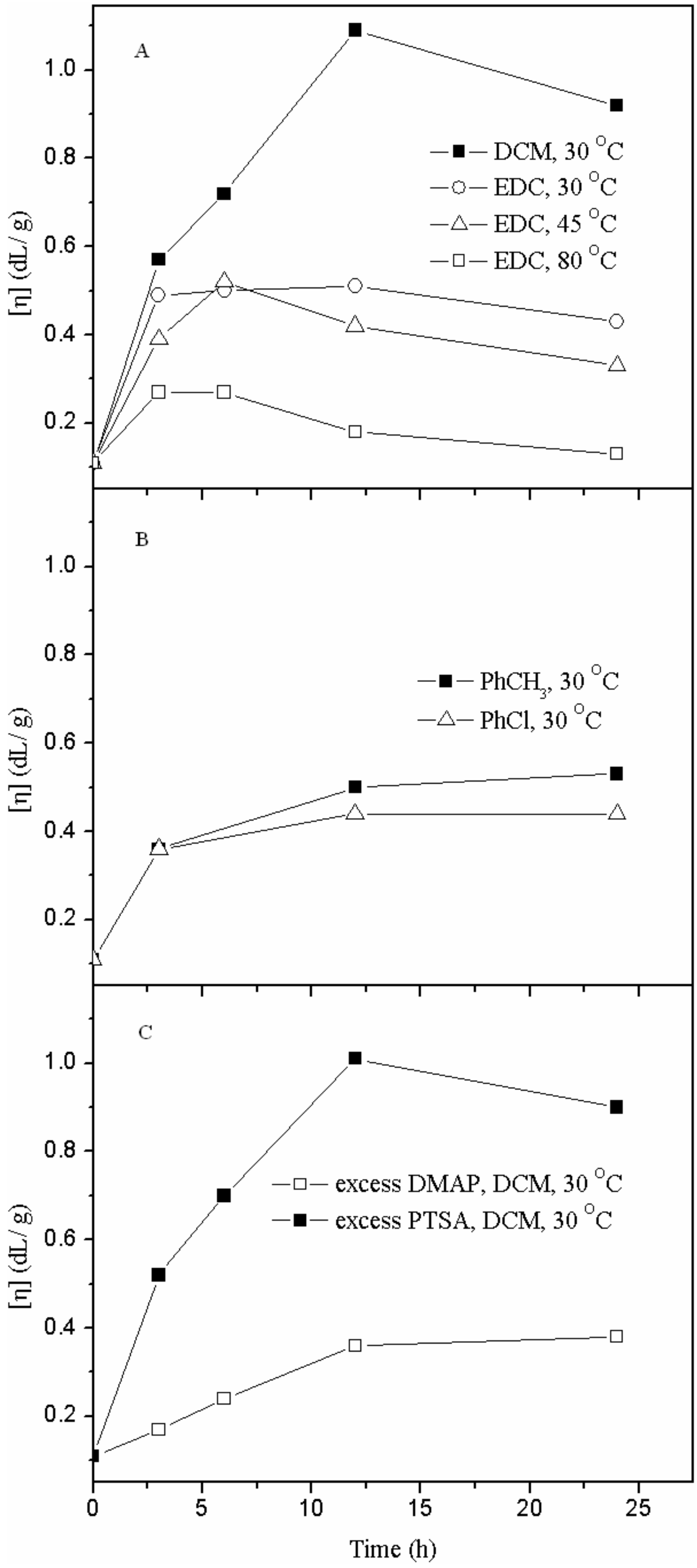


Fig. 6.1: (A) Effect of temperature, (B) effect of solvent (dipole moment) and (C) effect of excess DMAP and excess PTSA on the build up of molecular weight in the DIPC-mediated post-polycondensation of PLA oligomers using DPTS catalyst.

In the present study, the effect of a small variation of DMAP to PTSA ratio was also studied and the results are shown in Table-6.4. It can be clearly found that while a small excess of DMAP along with DPTS reduced the maximum achievable intrinsic viscosity or average molecular weight to a large extent, an excess of PTSA did not have such prominent effect. The same is clearly understandable from Fig. 6.1-C.

Table-6.4: Effect of excess DMAP and excess PTSA on the postpolycondensation of PLA oligomer 6.1b with condensing agent DIPC and DPTS catalyst

Solvent	Eqv. of DPTS		Temp. (°C)	Time (h)	Entry No.	[η] (dL/ g)	GPC	
							$\overline{M}_n$	$\overline{M}_w$
Dichloromethane	0.1	+ 0.05 eqv. DMAP	30	03	1	0.17	4,100	6,600
				06	2	0.24	6,400	11,200
				12	3	0.36	10,300	19,000
				24	4	0.38	10,100	20,200
		+ 0.05 eqv. PTSA	30	03	5	0.52	17,800	32,200
				06	6	0.70	26,600	48,300
				12	7	1.01	40,100	79,700
				24	8	0.90	37,800	68,300

This clearly indicated that the DMAP component of the DPTS catalyst had a distinct role in either degradation or some side reaction that was responsible for the reduction of molecular weight. An increase in the concentration of DMAP over that of PTSA prompted protonation of more DMAP by PTSA, so that more conjugate base of PTSA and less PTSA itself was available for trapping of the O-acylurea intermediate by protonation. That allowed more O-acylurea to be converted to the N-acylurea, which did not take part in further reaction. This was one reason why the molecular weight could not increase sufficiently. The reduction of molecular weight due to overall increase in the DPTS concentration can be explained based on a degradation mechanism involving traces of moisture in the system. The likelihood of a DMAP-catalyzed hydrolytic degradation of the growing PLA chain cannot be ruled out. Such side reactions and possible degradation processes generate many different types of chains in the growing PLA sample, which was visible as emergence of shoulders towards lower molecular weights in the SEC elugrams with time and with increased DPTS concentration (Fig. 6.2).

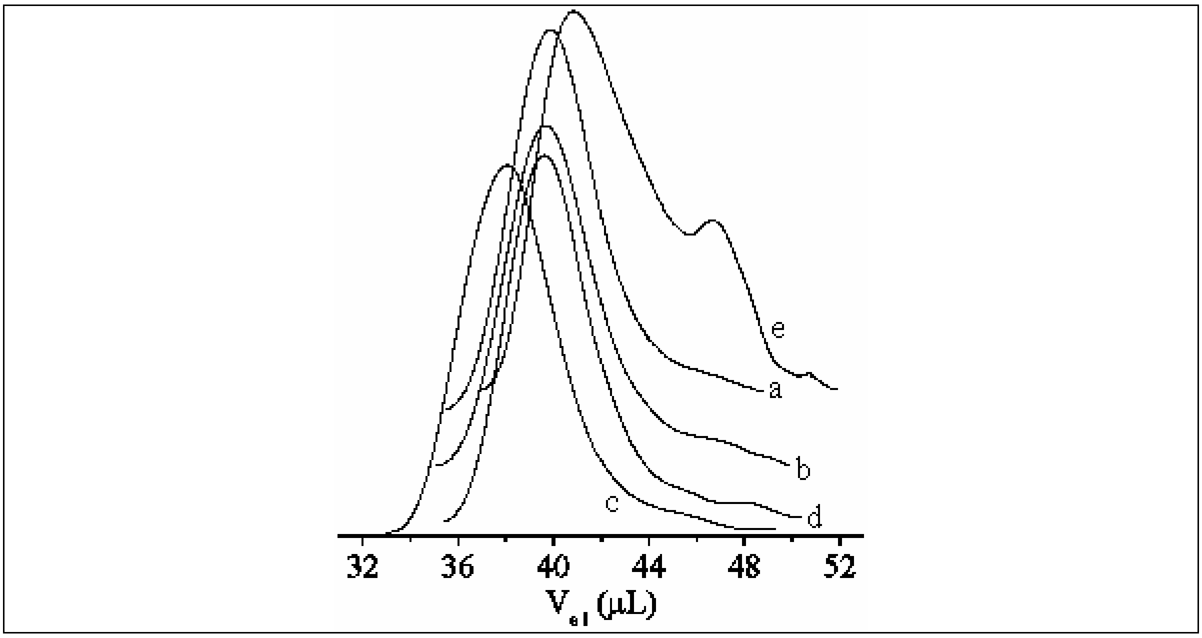


Fig. 6.2: Carbodiimide reactions SEC elugrams characteristic of side reactions in DCM solvent at 30 °C corresponding to product samples according to : (a) Entry No.2, (b) Entry No. 3, (c) Entry No. 4, (d) Entry No. 5 and (e) Entry No. 1, respectively, of Table- 6.3.

Weight average molecular weight increased monotonically with time up to 12 h (Fig. 6.2a to c) and then levels off and falls (Fig. 6.2d) in case of 0.1 equivalent DPTS being used, while the tailing and emergence of new mode in the elugram towards lower molecular weight became more prominent, indicating perhaps more side reactions or simple hydrolytic degradation. Emergence of new modes in the lower molecular weight side of the elugram was very prominent in case of an overall increased amount of DPTS (1.0 equivalent) being used and the maximum molecular weight achieved was also much less.

Evidence of side reactions from MALDI-ToF MS analysis: The occurrence of lower molecular weight shoulders in the SEC elugram was also examined further by MALDI-ToF spectroscopy. Fig. 6.3 shows the MALDI-ToF spectrum of the sample 6.1b-1, which showed the most prominent emergence of shoulders in the SEC elugram. The whole MALDI spectrum (Fig. 6.3a) is found dominated by a series of intense peaks in the region of 1000 to 3000 Da corresponding to an empirical formula of $(CH_3)_2CH\text{-}NH\text{-}CO\text{-}N(CH(CH_3)_2)\text{-}(CO\text{-}CH(CH_3)\text{-}O)_n\text{-}H\text{-----}Na^+$, and formula weight (72n + 143 +23), where n ranges from 15 to 41. The most intense peaks belonging to this series, corresponding to oligomers with n = 15 to 25 in the region from 1000 to 2000 Da are reported enlarged in Fig. 6.3b. In this region, the MALDI spectrum of corresponding potassium adducts were also seen (mass = 72n + 143 + 39). There was another set of peaks in the region ranging from 2000 to 3600 Da, which corresponded to an empirical formula $(CH_3)_2N\text{-}C_5H_{10}NH^+$ $^-O\text{-}(CO\text{-}CH(CH_3)\text{-}O)\text{-}H\text{-----}Na^+$ and formula weight (72n + 51 + 23), where n ranged from 27 to 34.

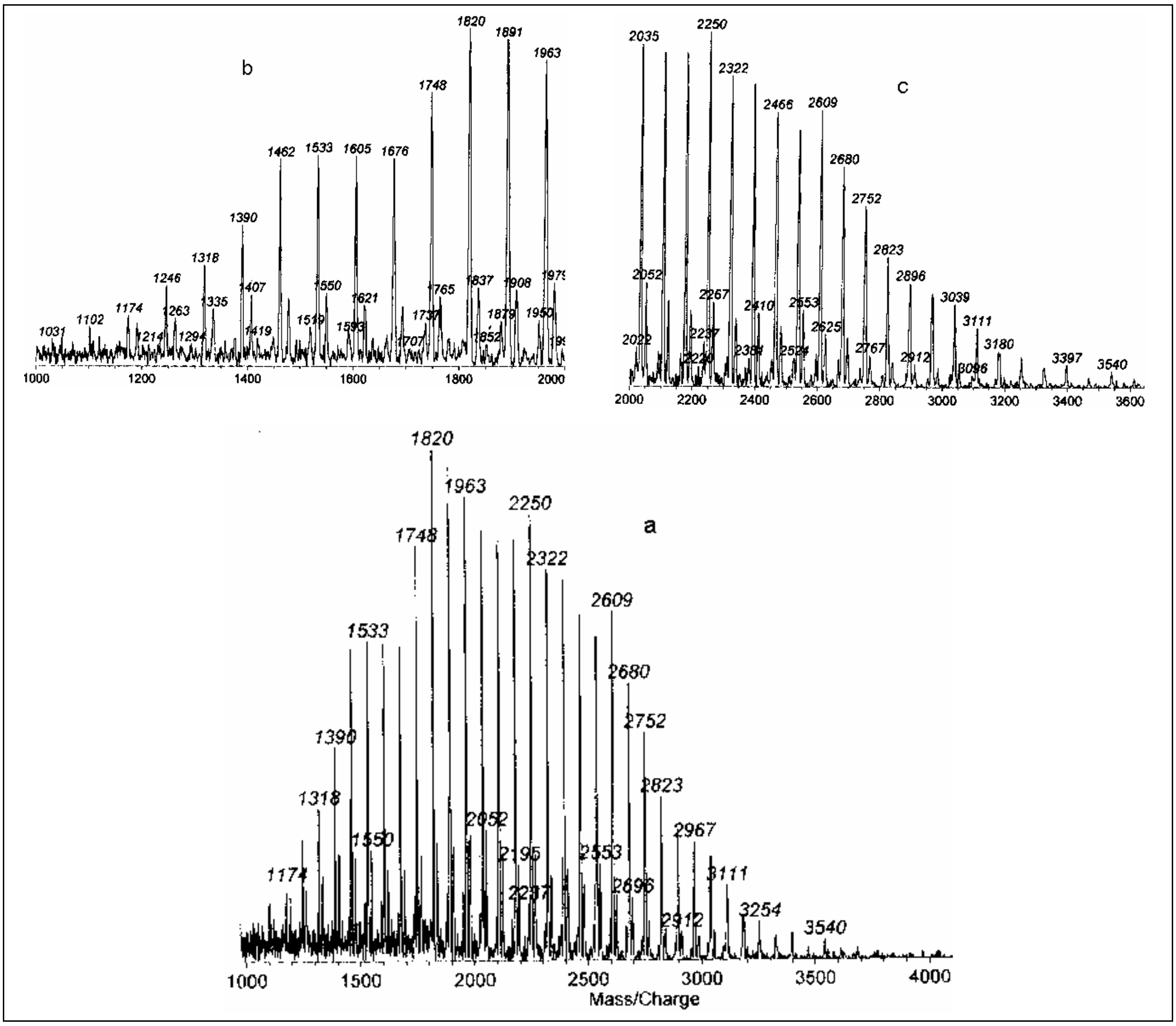


Fig. 6.3: MALDI-ToF MS of PLA sample according to Entry No.1, Table- 6.3, obtained after post-polycondensation using DIPS and 1.0 equivalent DPTS, solvent DCM, 30 °C, 12 h.

It was therefore evident that in presence of large amount of DMAP, the carboxylic terminals of the PLA chains were largely capped as either N-acylurea derivative or salt of DMAP, both of which prevented the chain to further react and grow. Presence of significant amount of N-acylurea derivative meant that under such conditions PTSA failed to trap the O-acylurea derivative by protonation. The detrimental effect of DMPA as was found in the molecular weight data in Table-6.3 was thus supported by MALDI-ToF spectral evidence. The shoulders in the SEC elugram of the corresponding sample were also due to such end-capped, low molecular weight PLA chains.

6.4b. Chain extension of the diol-terminated telechelic PLA prepolymer with the bis-caprolactone type coupler:

The structure of the synthesized μ-isopropylbis-(ε-caprolactone) chain extender (**6.5**) was confirmed with the help of both FTIR (Fig. 6.4) and ^{1}H-NMR (Fig. 6.5), while structure of the diol-ended PLA telechelic was confirmed by ^{1}H-NMR (500 MHz) spectrum alone (Fig. 6.6)

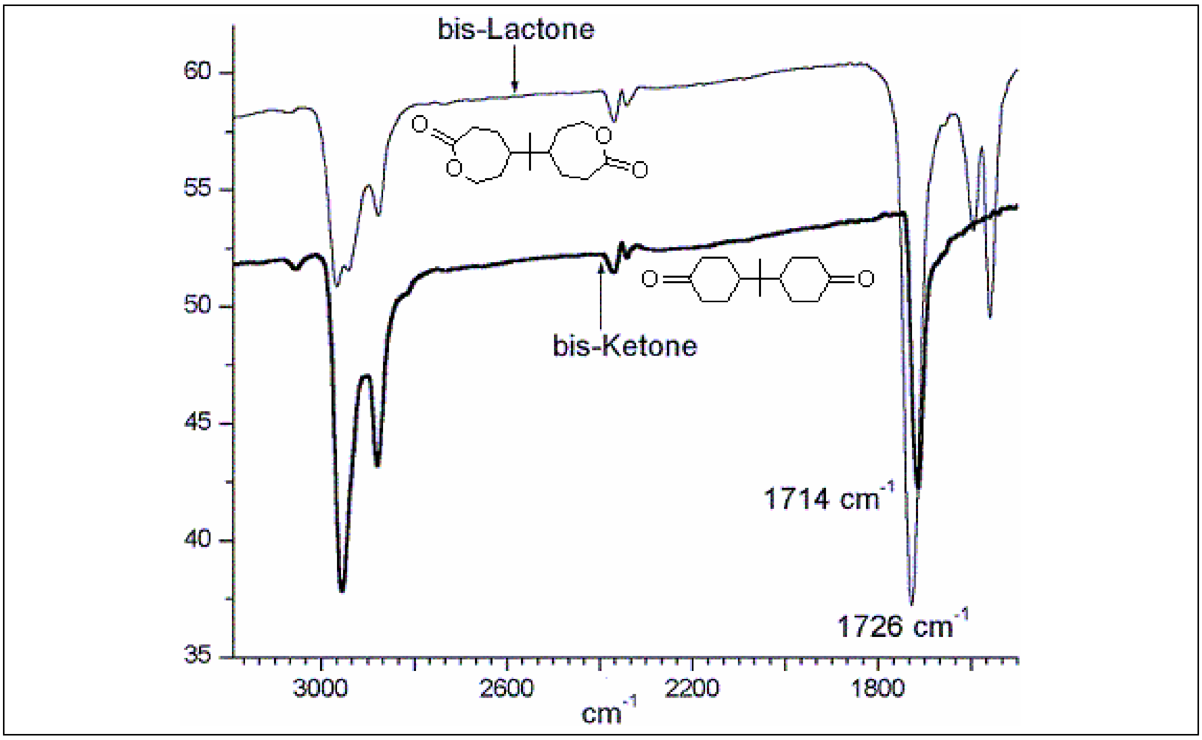


Fig. 6.4: FTIR spectra of the precursor bis-cyclohexanone (**6.4**) and bis-caprolactone (**6.5**)

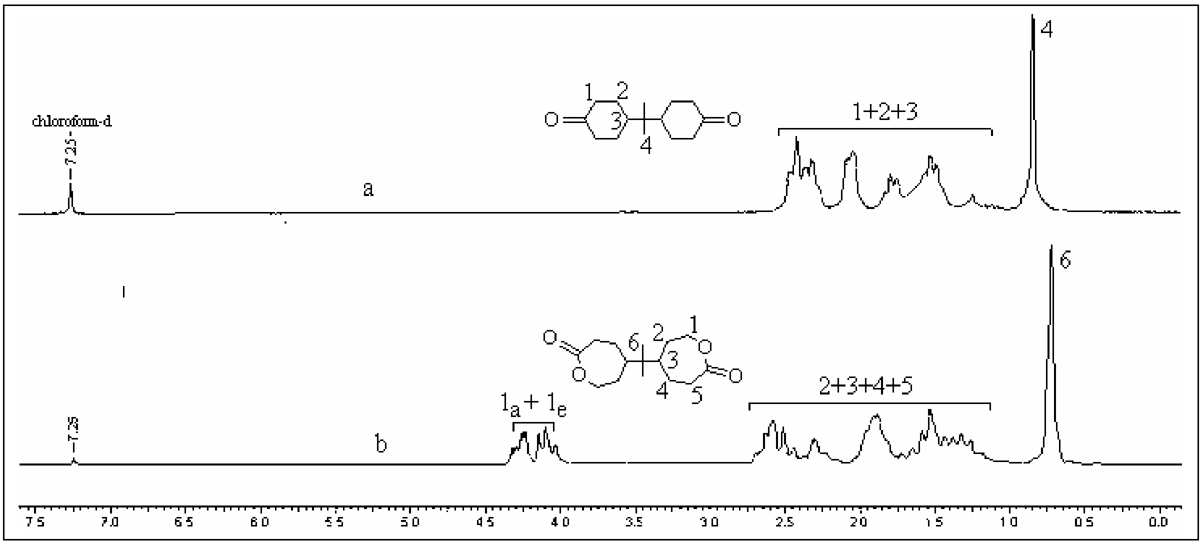


Fig. 6.5: ^{1}H-NMR spectra of (a) precursor bis-cyclohexanone (**6.4**) and (b)bis-caprolactone (**6.5**)

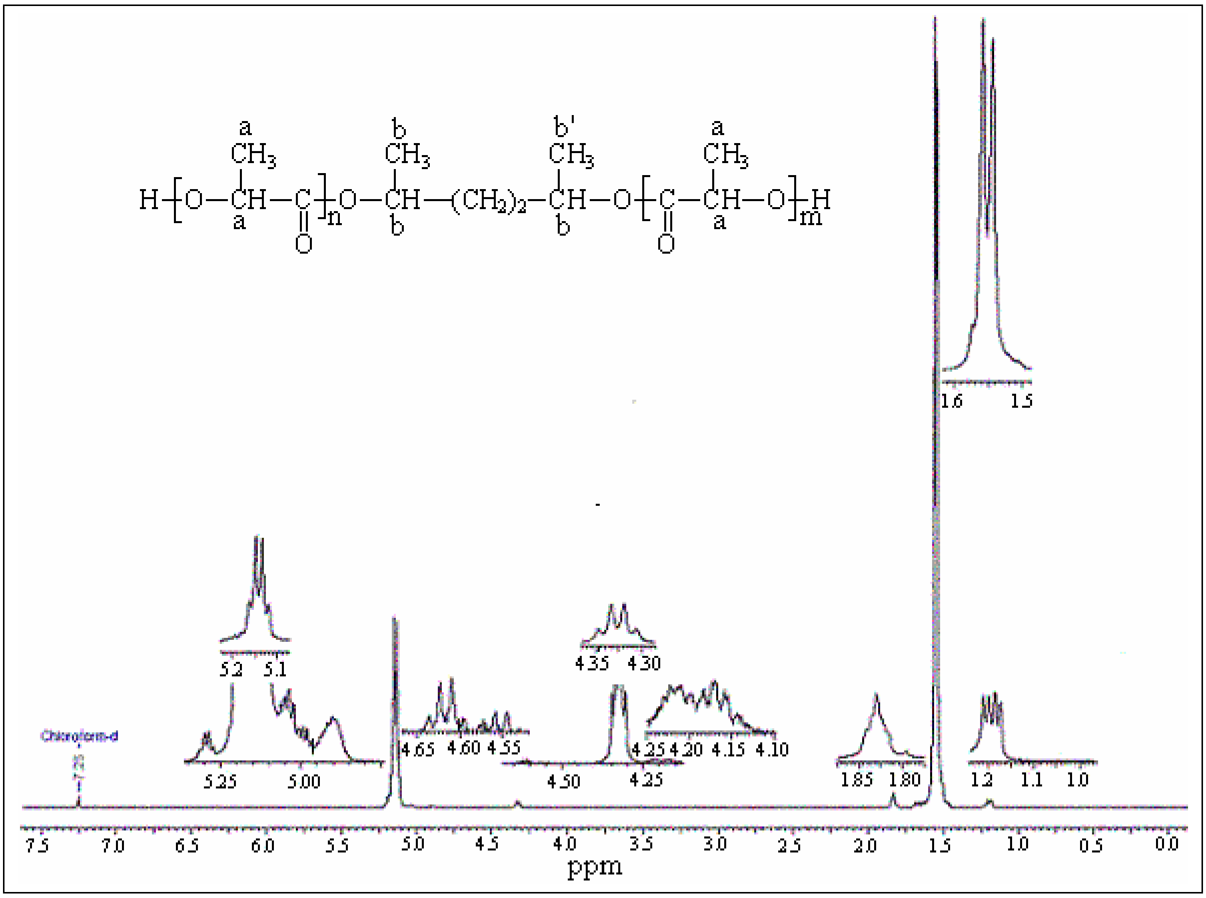


Fig. 6.6: ^{1}H-NMR spectrum (500 MHz) of the diol-terminated telechelic, 6.7.

The OH end group concentration of the telechelic PLA prepolymer was determined by ^{31}P-NMR (Fig. 6.7) and was found to be 2.49 x 10^{-3} moles/g. The number average molecular weight calculated based on the OH end group was 820, which agreed closely with the values determined by SEC and VPO, as shown in Table-6.5.

Table-6.5: Analysis of diol-ended PLA telechelic polymer used for coupling

Telechelic oligomer	Synthesis method	[η] (dL/g)	$\overline{M}_{n,}$ NMR	$\overline{M}_{n,}$ VPO	$\overline{M}_{n,}$ SEC	$\overline{M}_{w,}$ SEC
6.7	Co-condensation of LLA with HDO	0.085	820	830	900	1200

Choice of catalyst for the coupling reaction: Since a lot of work has been reported on the ROP of ε-caprolactone using hydroxyl-terminated molecules as initiators and with the help of various Lewis acid catalysts [10a-g], an attempt was first made in the present work to utilize the telechelic PLA as a diol-type macro-initiator for opening of each ring of the μ-isopropylbis-(ε-caprolactone) (**6.5**) chain extender molecule. Lewis acid catalysts, namely aluminium isopropoxide [Al(OPr^{i})$_3$], stannous-2-ethylhexanoate

[Sn(Oct)$_2$] and titanium isopropoxide [Ti(OPr^i)$_4$] were used and reactions performed at a temperature of 150 °C, the minimum at which the polymer melted. Catalyst concentrations were all kept at 0.1 mol% of the number of moles of the chain extender.

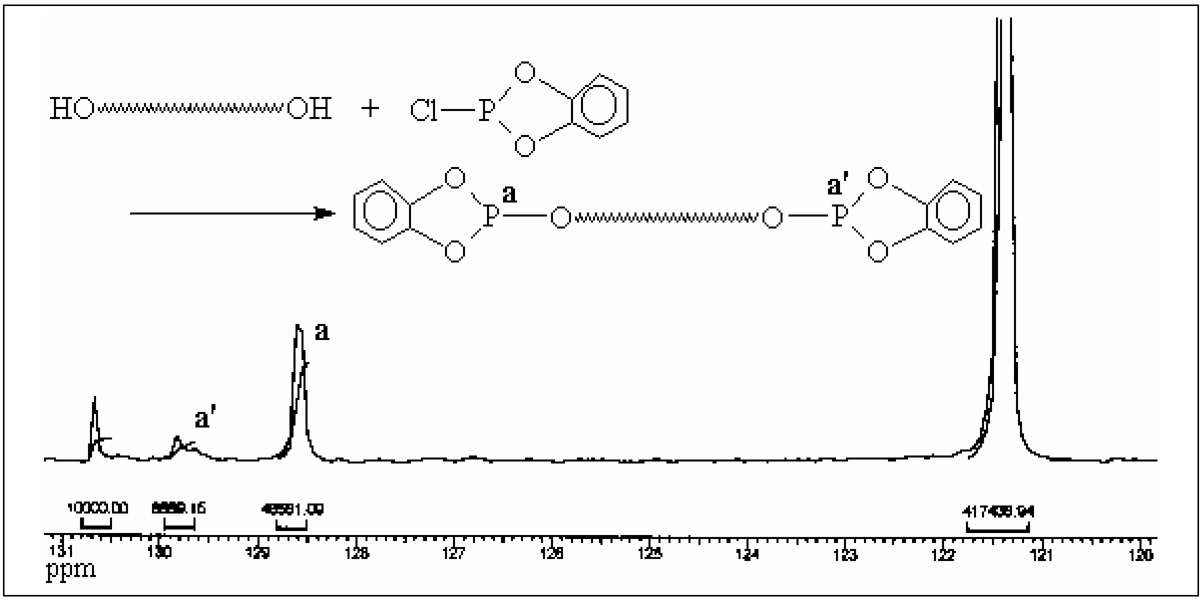


Fig. 6.7: ^{31}P-NMR spectrum of the diol-terminated telechelic (PLA-TEL, **6.7**)

The degree of polymerization of the caprolactone ring by ROP was expected to be proportional to the ratio of the concentration of monomer (the bis-lactone in the present case) to the concentration of the initiator (macro-initiator diol-ended PLA telechelic in the present case) and, in fact, equal to the ratio if conversion is complete [24]. So the mole ratio of the telechelic (determined by the hydroxyl end group concentration) to the bis-lactone in the present study was maintained at 1.1, which is just greater than unity, so that the degree of self-polymerization of individual caprolactone rings should be confined to the value of 1. That was the ideal case of chain extension of the PLA telechelic, where each individual caprolactone ring would be opened by one hydroxyl terminal of each PLA telechelic but further ring opening polymerization would not occur, since there would be no un-initiated caprolactone ring left. But in all the cases of attempted acid-catalyzed chain extension, insoluble materials resulted. They were, therefore, not characterized.

These results indicated that the PLA telechelics did not act as macro-initiator, and self-polymerization of each caprolactone ring proceeded uncontrolled. It is also worth noting that in all the works of ε-caprolactone/ L-lactide ring opening block copolymerization, the macro-monomer of polycaprolactone (PCL) has been used to open the lactide and never the reverse [11d]. This perhaps is because a secondary alcohol cannot initiate the opening of ε-caprolactone ring. A similar argument can be advanced for the present observation also, since the telechelic had both the hydroxyl terminals secondary. On the contrary, cross-linking of linear PLA prepolymer by small amounts of bis-caprolactone molecules is well documented [25].

Transesterification of lactones, including ε-caprolactone, by alcohol with the help of basic catalysts is well known. Attempts were, therefore, made to transesterify both the ε-caprolactone rings from either side with the telechelic and, thereby, achieve chain-extension. Base catalyzed transesterification reactions are generally fast. Under such base catalyzed transesterification conditions, no ROP should occur. Only strong alkalis that can generate alkoxides can promote or catalyze anionic ROP. DMAP is an excellent acylation/ transesterification catalyst and was employed for the present purpose. The reaction temperature was again kept as low as possible (for melting the polymer) and fixed at 150 °C, in order to minimize hydrolysis of ester linkages.

Molecular weights of PLA polymers obtained by coupling of the telechelic using the bis-caprolactone chain extender: Table-6.6 shows molecular weights of all polymers obtained by coupling of telechelic PLA using the bis-caprolactone chain extender. It was found that the reaction was indeed rapid and was completed within 5 to 10 minutes. With a longer reaction time, the molecular weight (as represented by intrinsic viscosity) decreased sharply. The possible reason for this was the obvious transesterification of existing and newly generated ester linkages by the pendant OH moieties that was created due to the opening of the caprolactone rings (see Scheme-6.2). This reason for the fall in intrinsic viscosity of the coupled polymer again is also supported by the fact that samples of longer reaction times (all 15 minute samples) contained some amount of insoluble material, which could only arise due to cross-linking generated by such undesired transesterification reaction as mentioned above.

Although undesired side reactions could not be avoided because of the use of basic catalyst, yet considerable efficiency of chain extension was achieved, as a nearly 10-fold increase in the weight average molecular weight was observed under certain reaction conditions (Entriy Nos. 2, 4 and 7 of Table-6.6).

Table-6.6: Chain-extension of diol-ended PLA telechelic polymer 6.7 by coupler 6.5

Entry No.	Reaction time	Telechelic to extender ratio	[η] (dL/ g)	$\overline{M}_{n, SEC}$	$\overline{M}_{w, SEC}$
1	05 min	1 : 1.0	0.48	7700	10,800
2	10 min		0.51	9500	12,400
3	15 min		0.20[a]	n.d.	n.d.
4	05 min	1 : 1.2	0.55	9400	12,800
5	10 min		0.52	8300	12,100
6	15 min		0.25[a]	n.d.	n.d.
7	05 min	1 : 1.5	0.50	8600	11,500
8	10 min		0.50	8300	11,400
9	15 min		0.21[a]	n.d.	n.d.
10	05 min	1 : 2.0	0.30	2000	5500
11	10 min		0.27	1700	4800
12	15 min		0.20[a]	n.d.	n.d.

a: portion of the material became insoluble, n.d. not determined

A 1.2 times molar excess of the extender resulted in the highest molecular weight as well as intrinsic viscosity. A further increase in the proportion of feed of the chain extender however resulted in reduced chain efficiency as number of hydroxyl terminal available for coupling in such a case was reduced because of end capping by excess extender molecules.

Characterization of the chain extended PLA by NMR spectroscopy: ^{1}H NMR spectrum of the sample namely 6.6a-7, which was having the highest intrinsic viscosity as well as weight average molecular weight, was examined (Fig. 6.8). Different types of protons, especially those borne on the ring opened bis-caprolactone moiety, could be assigned satisfactorily. A comparison of Fig. 6.8 with the NMR spectrum of the uncoupled telechelic (Fig. 6.6) and that of the coupler **6.5** (Fig. 6.5b) also supported the peak assignment. Presence of the peaks due to the a, b and c type protons in this Fig. 6.8 proved the attachment of the (ring-opened) chain extender molecule with the PLA telechelic.

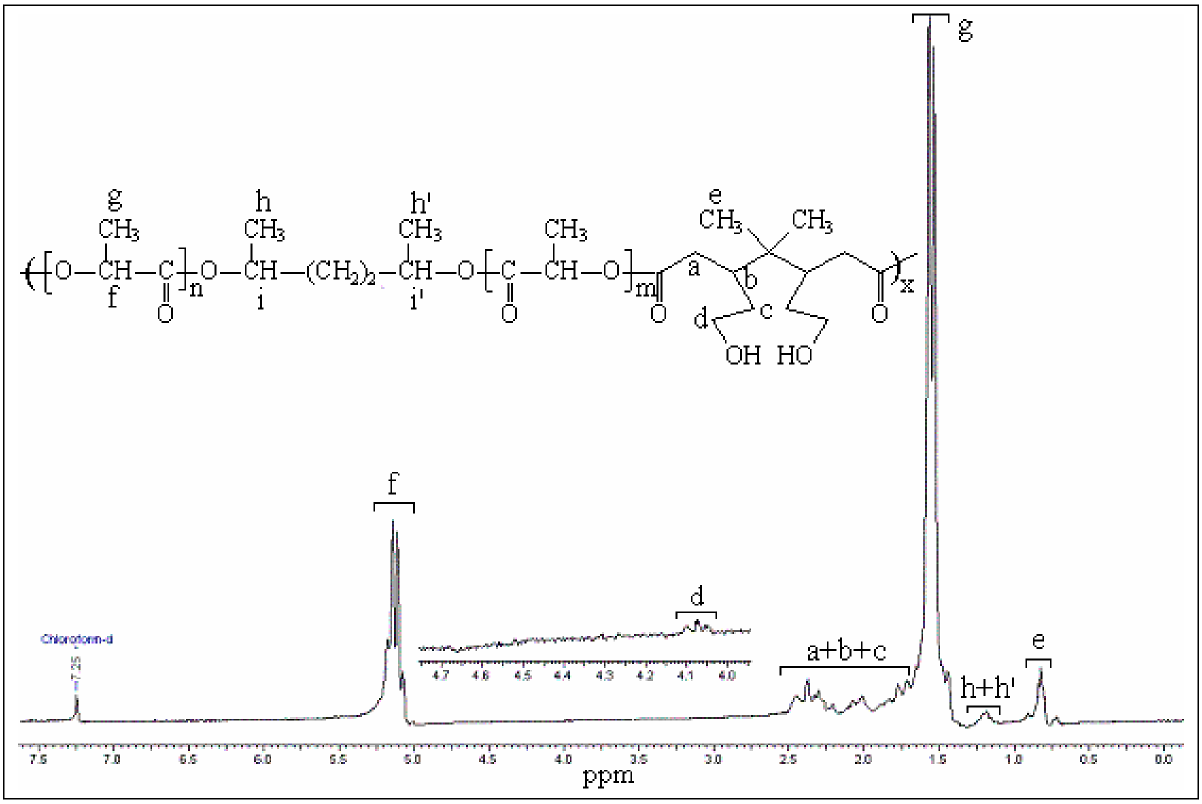


Fig. 6.8: ^{1}H NMR (500 MHz) of a PLA oligomer chain extended by the bis-caprolactone extender using basic, DPTS, catalyst (Entry No. 7, Table- 6.6)

Also, the absence of the axial-equatorial split triplet due to the OCH_2 (found in Fig. 6.5b) of the caprolactone moiety from Fig. 6.8 proved the opening of the caprolactone rings. That is again supported by the emergence of unsplit triplet due to H-d near 4.1 ppm in Fig. 6.8. Absence of protons due to the methine protons (i and i′) of the HDO moiety, from the ^{1}H NMR sepctrum was due perhaps to their overall less population in the chain extended polymer. Absence of methine protons attached to hydroxyl terminals indicated the absence or considerable reduction of such end groups, which was due to occurrence of the coupling reaction.

6.4c. Coupling of the diol-terminated telechelic PLA prepolymer with diphenyl carbonate: The telechelic prepolymer, 6.6 (Table-6.5) was reacted with diphenyl carbonate at a temperature of 200 °C for different time periods between 5 and 10 hours. Although the reactions between DPC and diols are reported to be done at 210 – 220 °C [13-15], reaction temperatures had to be limited to a maximum of 200 °C, as PLA was found unstable (charred to brown in less than 1 h, even under high vacuum or inert argon atmosphere) at temperatures beyond that. All reactions were, therefore, done at 200 °C, using the DPTS catalyst, which was a quaternary ammonium salt.

Molecular weights of PLA polymers obtained by coupling of the telechelic using DPC: Table-6.7 shows molecular weights of all polymers obtained by coupling of telechelic PLA using the diphenyl carbonate chain extender.

Table-6.7: Chain-extension of diol-ended PLA telechelic 6.7 using DPC and DPTS

Entry No.	Reaction time	Telechelic to extender ratio	[η] (dL/ g)	$\overline{M}_{n, SEC}$	$\overline{M}_{w, SEC}$
1	05 h	1 : 1.0	0.22	2300	3700
2	08 h		0.24	2800	4300
3	10 h		0.27[a]	4200	5100
4	05 h	1 : 1.5	0.31	3300	5900
5	08 h		0.35	4800	7100
6	10 h		0.28[a]	4000	5200
7	05 h	1 : 2.0	0.51	9000	12,000
8	08 h		0.48	7300	10,800
9	10 h		0.38[a]	5100	7900
10	05 h	1 : 2.5	0.53	9500	12,600
11	08 h		0.45	7900	9900
12	10 h		0.33[a]	3900	6500
13	05 h	1 : 3.0	0.32	4300	6500
14	08 h		0.21	1900	3500
15	10 h		0.13[a]	1100	1850

a: material became brown colored

First of all, no reaction was carried out beyond 10 h because of considerable discoloration (due to degradation and/ high temperature side reactions). The degradation with time is also clearly visible from the intrinsic viscosity data as shown in this table. Further, it can be observed that a much larger than stoichiometric equivalent amount of DPC was required for the most efficient coupling. This was because the equilibrium concentration of DPC in the reaction was much less than the feed concentration, as DPC was also volatile [22], though less than the by-product, phenol. A portion of the volatilized DPC came back to the reactor, due to its appropriate placing in the heating bath, as already discussed, but a portion evaporated beyond recovery. Besides, at a temperature lower than

200 or 210 °, the conversion of DPC might also be less than complete. Although, side reactions could not be fully avoided, considerable coupling was, however, achieved as once again more than 10 fold increase in the number average as well as weight average molecular weight could be achieved under certain reaction condition. But the molecular weight and intrinsic viscosity dropped due to side reactions with increasing reaction time.

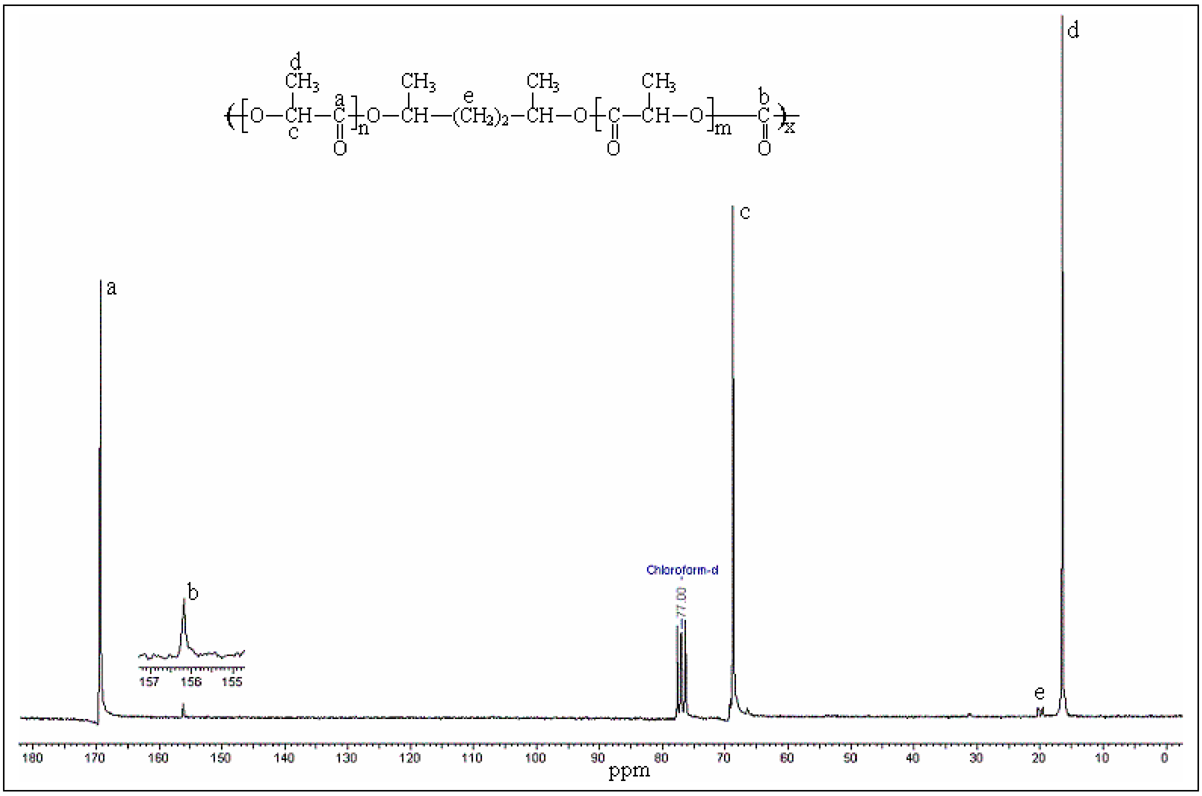


Fig. 6.9: ^{13}C-NMR (500 MHz) spectrum of the telechelic PLA after chain extension by DPC (Entry No. 10, Table- 6.7)

Spectroscopic characterization of the PLA polymer chain extended with DPC: Both ^{13}C and ^{1}H NMR spectra of the sample according to Entry No. 10 of Table-6.7, which attained the highest number and weight average molecular weights, were examined. The ^{13}C NMR spetrum (Fig. 6.9) clearly shows a carbonate carbonyl at 156.20 ppm beside the ester carbonyl of the PLA segment. The small peaks close to the noise level at about 20 ppm were due to methylene carbons of the HDO segment of the original telechelic. Methyl and methine carbon peaks due to the HOD segment either did not show up due to less population or merged with similar peaks due to the PLA segment.

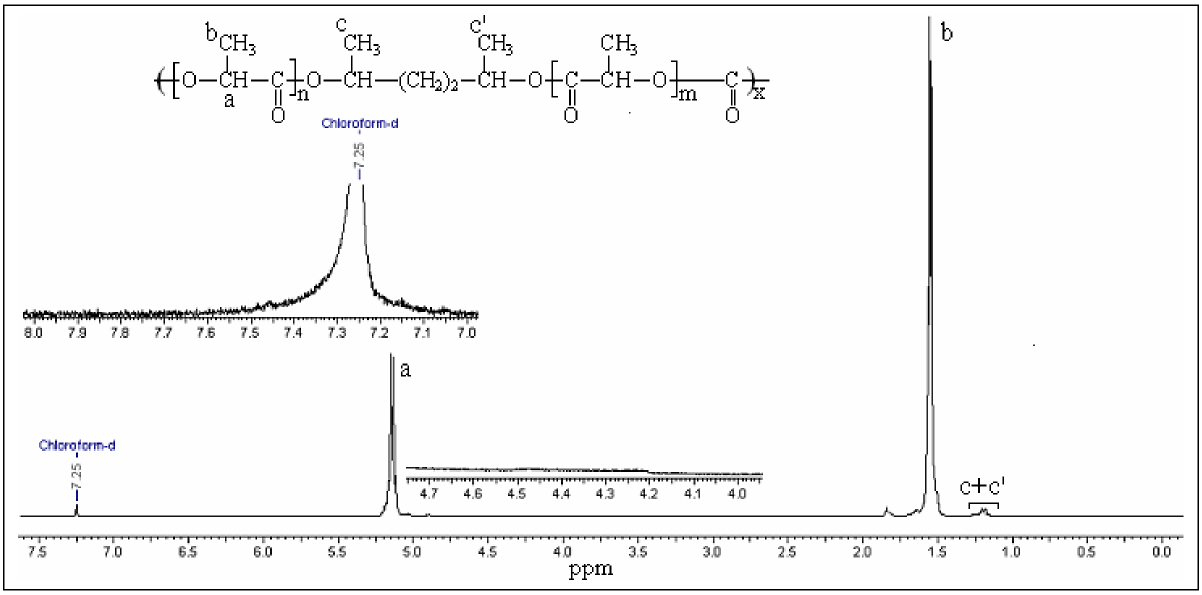


Fig. 6.10: ^{1}H-NMR (500 MHz) spectrum of the telechelic PLA after chain extension by DPC (Entry No. 10, Table- 6.7)

^{1}H-NMR spectrum of the same sample (Fig. 6.10) further assisted in ascertaining that the carbonate carbon peak at 156.2 ppm seen in Fig. 6.9 had been only due to the carbonate linkage in the coupled polymer and not due to the carbonate linkage of DPC. Upon magnification of appropriate regions, the Fig. 6.10 did not show any peaks due to aromatic protons, thereby confirming absence of either any by-product phenol or any unreacted DPC in the NMR sample. Thus it not only confirmed that the earlier peak at 156.2 ppm in the ^{13}C NMR of the same spectrum was not due to any residual DPC, but also proved that the peak was not due to C-1 carbon of the phenyl moiety of the DPC, which might also show up in the same region. Therefore, the peak at 156.2 ppm in the ^{13}C NMR was correctly assigned to the carbonate linkage between two telechelic segments after the coupling. This confirmed, along with the molecular weight data, that the desired coupling reaction had indeed taken place.

6.5. Conclusion:

The highest molecular weight linear PLLA (M_v = 88,200) was obtained by using diisopropyl carbodiimide as a condensing agent. The most important factors were: use of DPTS catalyst at lower concentration (0.1 equivalent) and DPTS catalyst preparation. The DPTS catalyst was prepared from a 1:1 equivalence reaction of DMAP and PTSA. However, employment of PTSA catalyst in slight excess of the 1:1 ratio had little effect on the post-polycondensation of PLA oligomers because it only decreased the equilibrium concentration of free DMAP for the reaction. But a slight excess DMAP had detrimental effect in terms of molecular weights because the excess DMAP meant less available protons from PTSA for trapping the O-acylurea by protonation and stopping its conversion into the N-acylurea side product.

Starting with a diol-terminated PLA telechelic of $\overline{M}_w$ 1200 and using the bis-caprolactone chain extender at 150 ^{0}C and the basic catalyst DMAP, a maximum molecular weight $\overline{M}_w$ of 12,000 of the PLA polymer was obtained. An aliphatic copoly(ester-carbonate) was also achieved by using the same diol-terminated PLA telechelic and diphenyl carbonate as a chain extender at 200 ^{0}C and the quaternary ammonium salt catalyst DPTS. The two chain extension reactions were however limited by simultaneous degradation. Especially, the former was associated with simultaneous transesterification by the newly generated primary hydroxyl groups from the opening of caprolactone rings. The nucleophilicity of a primary hydroxyl being greater than that of a secondary (the end groups of the PLA telechelic), there reached an equilibrium beyond which the transesterification by the primary alcohol superceded the opening of lactone rings. It is a situation, which cannot be avoided, especially in the base-catalyzed pathway, so that the chain extension reaction could not be carried out beyond a limit. The free primary hydroxyl groups remained in such chain extended PLA polymer, which had the potential of causing the same, undesired transesterification, and consequent degradation and/ or cross-linking, during processing. This problem can, however, be taken care of by end-capping the free hydroxyl groups, for example, by acetylation.

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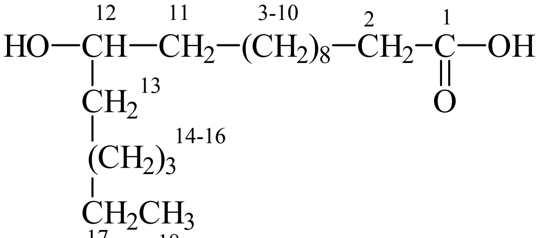
CHAPTER - 7

CHAPTER 7: COPOLYMERIZATION OF 12-HYDROXYSTEARIC ACID WITH L-LACTIC ACID

7.1 Introduction:

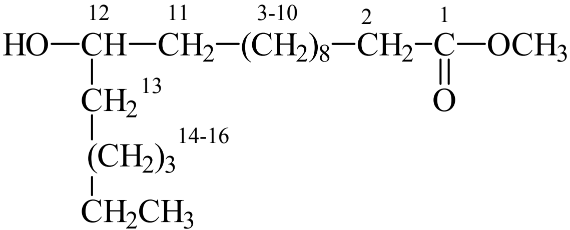
12-hydroxystearic acid (12-HSA) or 12-hydroxyoctadecanoinc acid (**7.1**), which is an aliphatic hydroxy-carboxylic acid, has been polymerized into aliphatic polyester by self-condensation. The dehydropolycondensation of 12-HSA was performed in bulk polymerization at 160 °C under vacuum, using p-toluene sulphonic acid (PTSA) as a catalyst. A polymer with $\overline{M}_n$ up to 3500 – 4000 was obtained in 5 hours [1]. Its structure was confirmed by showing, with the help of titration methods, that equal number of hydroxyl and carboxylic acid end groups were present. The homopolymer of 12-HSA, that is poly (12-HSA) (PHSA), is a colorless, viscous liquid. The presence of n-hexyl pendant (side chain) affects any parallel arrangement of the backbone polymer chains, which is essentially required for crystallization, although a similar polyester, poly(11-hydroxyundecanoate), which does not have such an aliphatic pendant is considerably crystalline even at low number average molecular weight [1]. This is clear evidence of the fact that softness and amorphous property of PHSA is due to the n-hexyl side chain. Copolyester-amides from 12-HSA have been reported as new materials. They have been prepared by two different ways. Linear, carboxylic acid-terminated polyester telechelics ($\overline{M}_v$ = 1600) were prepared by condensing 12-HSA oligomers and adipic acid in presence of $Ti(Obu)_4$ catalyst at 190 °C under vacuum without solvent for up to 25 hours, followed by reacting dimaines (for example an 80 : 20 mixture of 1-methyl-3,5-diethyl-2,4-diaminobenzene and 1-methyl-3,5-diethyl-2,6-diaminobenzene) with the telechelic again for up to 25 hours [2]. Copolyester-amides of 12-HSA has also been prepared by directly condensing 12-HSA with polyamines at temperatures ranging from 150 – 220 °C, even without using any catalysts. The polyester-amides thus prepared, especially above 170 °C, showed long blocks (DP = 10 to 22) of PHSA [3]. Only a few references of macrolactonization of ω-hydroxycarboxylic acids, especially macrocyclic lactone formation from 12-HSA in presence of distannoxane type of catalysts, are available [4,5]. Such lactonization is, however, reported to occur only in dilute systems or emulsions or microemulsions with or without the help of detergents. The low molecular weight homopolymers of 12-HAS ($\overline{M}_n$ 5000 – 50,000) have found application as an adhesion tuner and carrier material in ink-compositions [6], as a softener in styrene-butadiene rubber [7], and as a surface active agent in finished cotton-polyester mixed fabric and leather treatment [8]. The copolyester-amides of derived of 12-HSA, depending on molecular weight and chemical structure, have been found useful for manufacture of polyurethanes and polyureas as well as dispersing agents for solid particles, for example, pigments and dyes, in organic solvents [2,3]. Poly(12-hydroxystearic acid)-poly(ethylene oxide)-poly(12-hydroxystearic acid) triblock copolymer has been observed to be a very efficient polymeric surfactant for preparing oil-in water microemulsions [9].

There is no report in the literature, however, on the synthesis of copolymers of 12-HSA with L-lactic acid (LLA) or poly(L-lactic acid) (PLA) oligomers. 12-HSA is a component of castor oil, which is a cheap and abundant natural product. 12-HSA is isolated from castor oil in commercial scale with a purity of 80 – 90 wt%.



$$HO-\underset{\substack{|\\CH_2\\|\\(CH_2)_3\\|\\CH_2CH_3}}{CH}-CH_2-(CH_2)_8-CH_2-\underset{\substack{||\\O}}{C}-OH$$

7.1



$$HO-\underset{\substack{|\\CH_2\\|\\(CH_2)_3\\|\\CH_2CH_3}}{CH}-CH_2-(CH_2)_8-CH_2-\underset{\substack{||\\O}}{C}-OCH_3$$

7.2

An objective of the present work was to prepare homopolymer of 12-HSA and its copolymer with LLA and to examine the properties of those homo- and copolymers. Since the new ester linkages being incorporated are also aliphatic, the hydrolytic and enzymatic degradability properties were not expected to be affected because of the presence of the 12-HSA units in the PLA polymer. In order to obtain 12-HSA of monomer of high purity, 12-HSA was converted to the corresponding methyl ester (**7.2**) and separated from the other fatty acidic impurities by means of column chromatography.

7.2. Materials and methods:

Materials: L-lactic acid was obtained from Purac Chemical Co. as a 88 %(w/w) aqueous solution with total impurities less than 100 ppm (detected by gas liquid chromatography, discussed in Chapter 2), and was used as such for polymerization. 12-hydroxystearic acid was obtained from Jayant Oil Mills Ltd. as light pink colored, waxy solid flakes with reported impurities upto 15 % (w/w). It was converted into methyl ester and purified by column chromatography. The purified methyl ester of 12-hydroxystearic acid, which was a white, waxy solid, contained total impurities less than 50 ppm as detected by gas liquid chromatography. This was used for polymerization. Hydrochloric acid (12N) was obtained from S. D. Fine Chemicals Ltd. and was used as such. Dichloro-tetra-n-butyl-distannoxane (4.1d) was prepared as described in Chapter 4, and tetraphenyltin (4.1) was purchased from Aldrich Chemical Co. All solvents were dried using standard procedures, for example benzene by distilling over metallic sodium and methanol by distilling over magnesium cake (methyl magnesium iodide). All liquids were transferred by syringe under dry argon atmosphere.

Synthesis of methyl 12-hydroxystearate: 17.65 g (0.05 mol) of 12-HSA (85 % w/w purity) was refluxed under dry argon atmosphere with 50 mL (1.56 mol) dry methanol and 0.0276 g (0.05 mmol) catalyst **4.1d** inside a two-neck, 100 mL reactor flask fitted with reflux condenser for 2 h, following which all the methanol along with the by-product water was distilled off under reduced pressure and reflux restarted with a fresh charge of 50 mL dry methanol. The process was further repeated twice. Finally, the reaction product was dissolved in minimum amount of dichloromethane, after removing both methanol and water under reduced pressure. Methyl 12-hydroxystearate (Me-12-HSA) was purified by column chromatography (20 % v/v ethyl acetate/ petroleum ether) using a flash silica gel column (yield 90 %).

^{1}H NMR (Fig. 7.2) δ (ppm, $CDCl_3$) 3.64 (s, 3H, OCH_3), 3.58 – 3.52 (m, 1H, H-12), 2.28 (t, 2H, H-2), 1.80 – 1.45 (m, 4H, H-11 & H-13), 1.25 (broad peak, 24H, H-3 to H-10 and H-14 to H-17), and 0.86 (t, 3H, H-18); GC (Fig. 7.1): total impurity more than 15 wt% (as per supplier), comprising of fatty acids namely stearic, oleic and palmitic acids and 12-ketostearic acid, before purification and less than 50 ppm after purificaiton.

Synthesis of poly(12-HSA) homopolymer (PHSA): 1 g (3.18 mmol) of Me-12-HSA and 0.0014 g (0.003 mmol) tetraphenyltin catalyst were melted together under magnetic stirring and under dry argon atmosphere in each of three single neck, 10 mL reactor flasks, previously passivated, dried at 150 °C in an oven, cooled under dry argon atmosphere and tared. Pressure in each flask was then gradually reduced to 1.0 mbar while temperature was increased to 150, 200 and 250 °C respectively and finally, polymerization in each flask was continued for 15 h. All polymers were transparent, colorless and viscous liquids, soluble in both chloroform and petroleum ether and were characterized without any work-up. The monomer and polymer being soluble in the same solvents (both chloroform and methanol), any residual monomer could not be separated and the homopolymer in this form was subjected to analysis.

Characteristic ^{1}H NMR (Fig. 7.4) δ (ppm, $CDCl_3$) 4.87 – 4.82 (m, 1H, H-12), 3.65 (s, (3/n)H = 0.05H, OCH_3 end group), 2.26 (t, 2H , H2), 1.65 – 1.50 (m, 4H, H-11 & H-13), 1.24 (broad peak, 24H, H-3 to H-10 and H-14 to H-17), 0.86 (t, 3H, H-18), where n was the number average degree of polymerization that was calculated from the integration value at δ 3.65 ppm.

Simultaneous polycondensation of LLA and 12-HSA: 0.3072 g (0.9 mmol), 0.9211 g (2.9 mmol) and 1.5354 g (4.9 mmol) of Me-12-HSA was taken in each of three two-neck, 100 mL reactor flasks, previously passivated, dried at 80 °C under 0.1 mbar and cooled under argon atmosphere. White waxy 12-HSA, insoluble in organic solvents as well as water, was obtained in each flask after cooling. To each of them were added 10 g (0.098 mol) L-lactic acid 88 % (w/v) aqueous solution and 0.005 g (0.009 mmol) 4.2 catalyst, azeotroped with benzene for 5 h. Benzene was evaporated under vacuum and then polycondensation was performed just by heating at 150 °C for 15 h under gentle magnetic stirring and in dry argon atmosphere. Polymer in each flask was cooled, dissolved in 10 mL chloroform, precipitated into 100 mL chilled methanol, filtered and dried at room temperature under 0.1 mbar for 5 h. The dry polymers were further extracted with n-hexane in order to remove homopolymer of 12-HSA, if any, since the homopolymer had been found soluble in n-hexane.

^{1}H NMR (Fig. 7.7) δ (ppm, $CDCl_3$) 1.56 (d, 3nH, H-a), 0.86 (t, 3mH, H-a'), where (m/n) x100 was the mol% incorporation of 12-HSA units among L-lactic acid units of the copolymer.

Preparation of PLA films externally plasticized by PHSA: 0.0196 g (0.07 mmol), 0.0586 g (0.21 mmol) and 0.0979 g (0.35 mmol) of PHSA were taken separately in three (3) different flasks, each mixed with 0.5 g (7 mmol of lactic acid repeating units) PLA, and dissolved in dichloromethane. Solvent-cast PLA films plasticized with 1, 3 and 5 mol% of PHSA, respectively were obtained out of the three solutions by spreading on flat surfaces, evaporating the solvent slowly in air and finally drying under 0.1 mbar at room temperature.

7.3. Analysis:

Gas Liquid Chromatogrpahy(GC): GC analyses were performed on a Perkin Elmer Autosystem XL GC, keeping injector at 200 °C and detector at 225 °C, programming the oven from 50 to 180 °C with 2 and 5 deg/ min ramping rates in 50 – 100 °C and 100 – 180 °C temperature ranges, respectively, and using nitrogen and hydrogen as the carrier gas in the column and the fuel in the detector, respectively. Sample solutions of 1g in 10 mL acetone proportion were used for injection into the injector with varying injection volumes from 0.1 to 10 μL, in order to detect impurities present in the samples down to 50 ppm and less.

NMR Spectroscopy: ^{1}H NMR spectra were recorded as described in Chapters 3 & 4.

Molecular weights: Was performed as described in Chapters 3 & 4.

Thermal analysis Was performed as described in Chapters 3 & 4.

X-ray analysis: Was performed as described in Chapters 3 & 4.

MALDI-ToF MS analysis: Was performed as described in Chapter 4.

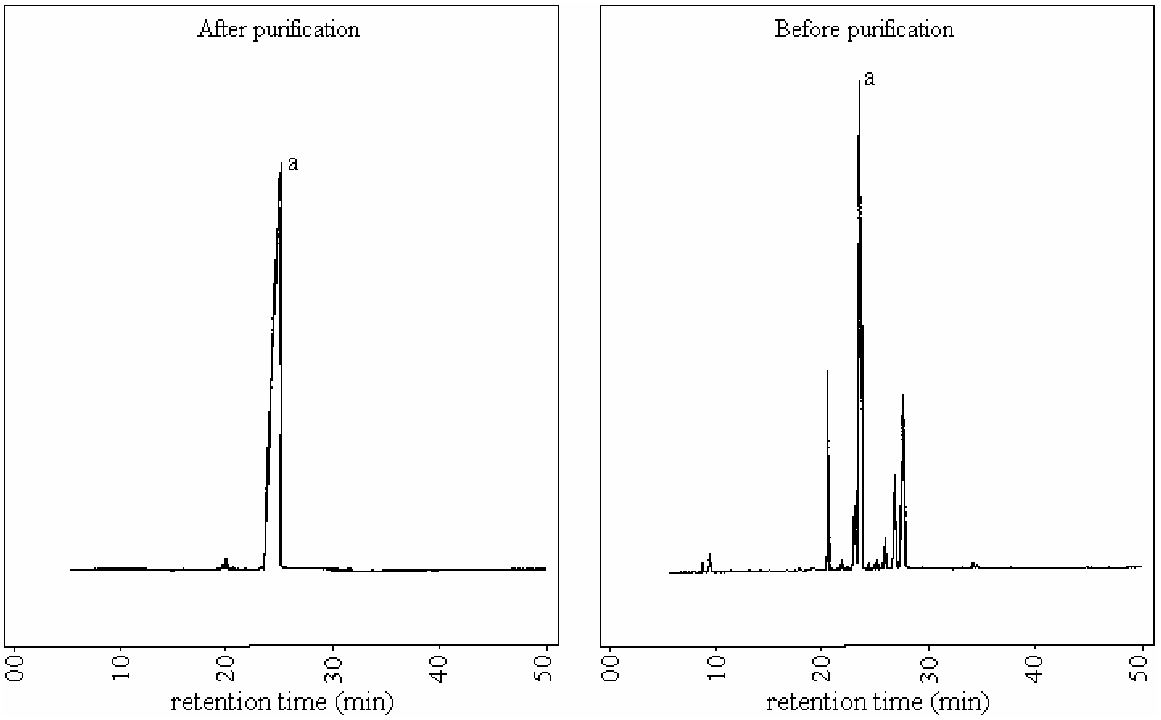


Fig. 7.1: GC chromatogram of pure and impure methyl ester of 12-HSA (a)

7.4. Results and Discussion:

7.4.1. Synthesis of poly(12-HSA) homopolymer (PHSA) and use of PHSA as plasticizer for PLA : The homopolymer PHSA (**7.3**) was found to be a transparent, viscous liquid, which showed a crystalline melting point 20 °C below zero, irrespective of number average molecular weight and showed no glass transition temperature till –40 °C (Fig. 7.3). The glass transition might therefore occur even at some lower temperature, which could not be seen because of analytical limitation. The number average molecular weight of the homopolymer was calculated form ^{1}H-NMR (Fig.-7.4) as well as by vapor pressure osmometry (VPO). From the $\overline{M}_n$ results of PHSA homopolymers synthesized at 150, 200 and 220 °C, as described by sample names **7.3a**, **7.3b** and **7.3c**, respectively, in Table 7.1, it was evident that the homopolymer was thermally unstable at temperatures beyond 200 °C. Attempted polycondensation at 220 °C yielded a discolored product with a lower number average molecular weight than that synthesized at 150 and 200 °C temperatures.

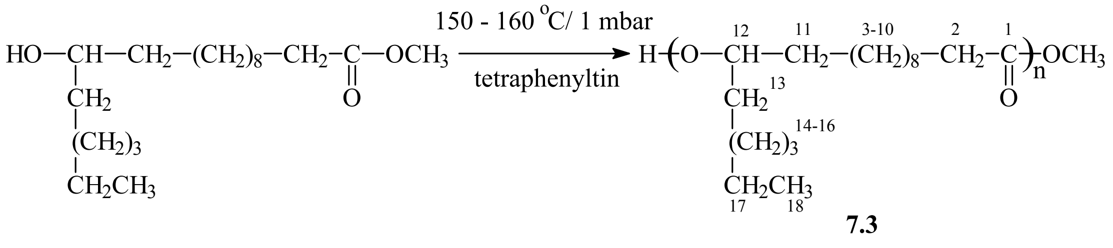
By virtue of its low glass transition PHSA could be expected to impart some flexibility to PLLA, as a plasticizer. Both PLA and PHSA were soluble in the same solvents, namely chloroform and DCM. Homopolymer PHSA was also soluble in n-hexane and methanol, which were non-solvents for the PLLA.

Table 7.1: Characterization of homopolymers of 12-HSA methyl ester

Sample name	Reaction temp. (°C)	Yield (%)	$\overline{DP}_{NMR}$	$\overline{M}_{n, NMR}$	$\overline{M}_{n, VPO}$	T_g (°C)	T_m (°C)
7.3a	150	99	44	12,500	12,200	n.f.	-20
7.3b	200	99	42	12,000	10,800	n.f.	-19
7.3b	220	94	06	1700	2100	n.f.	-20

n.f. not found in the thermal analysis

Scheme 7.1: Synthesis of homopolymer of Me-12-HSA



$$HO{-}CH(CH_2(CH_2)_3CH_2CH_3){-}CH_2{-}(CH_2)_8{-}CH_2{-}C({=}O){-}OCH_3 \xrightarrow[\text{tetraphenyltin}]{150 - 160\,^{o}C/\ 1\ mbar} H{\left(O{-}CH(CH_2(CH_2)_3CH_2CH_3){-}CH_2{-}(CH_2)_8{-}CH_2{-}C({=}O)\right)_n}OCH_3$$

7.3

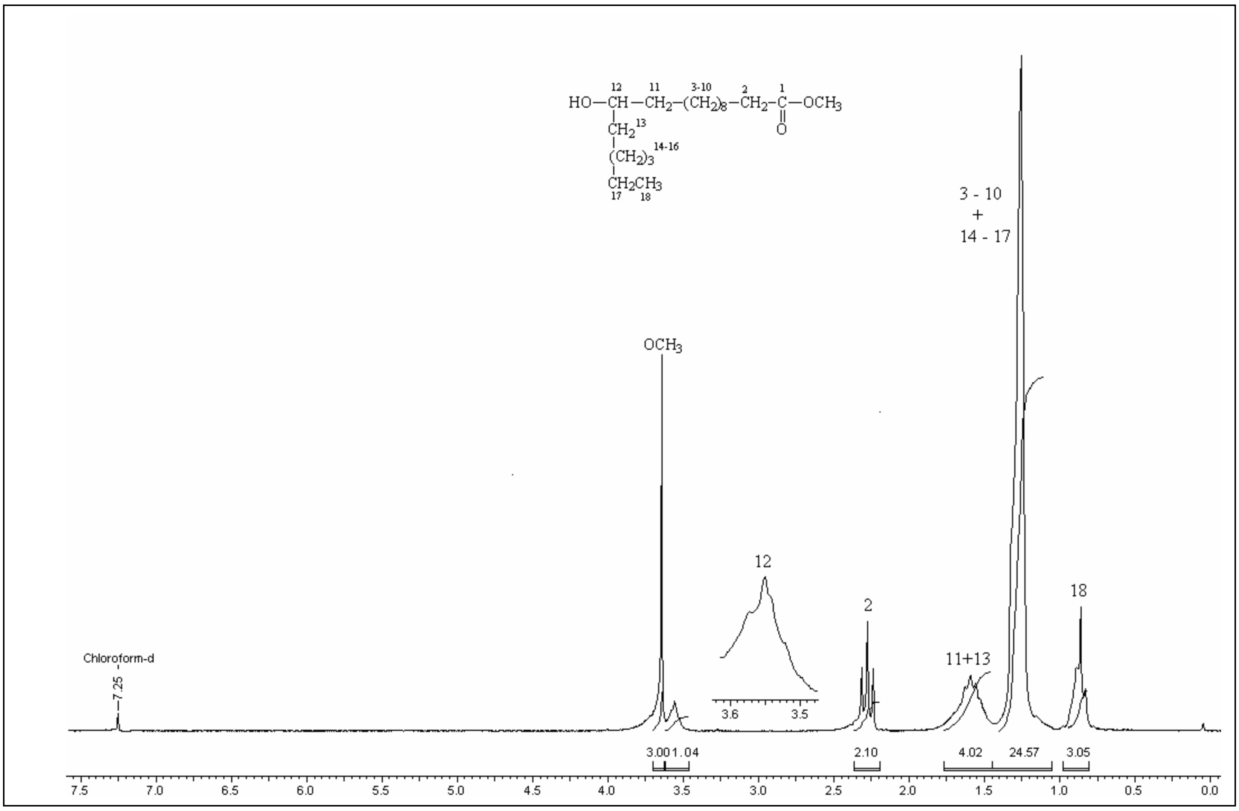


Fig. 7.2: ^{1}H-NMR (500 MHz) spectrum of methyl ester of 12-HSA, purified.

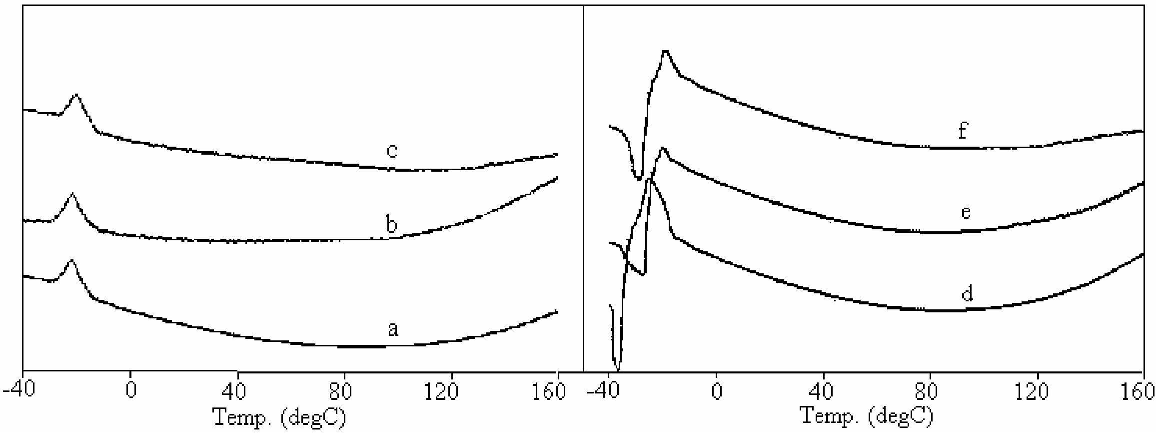


Fig. 7.3: DSC thermograms corresponding to first and second heating of PHSA homopolymer samples (a) 7.3a, (b) 7.3b and (c) 7.3c.

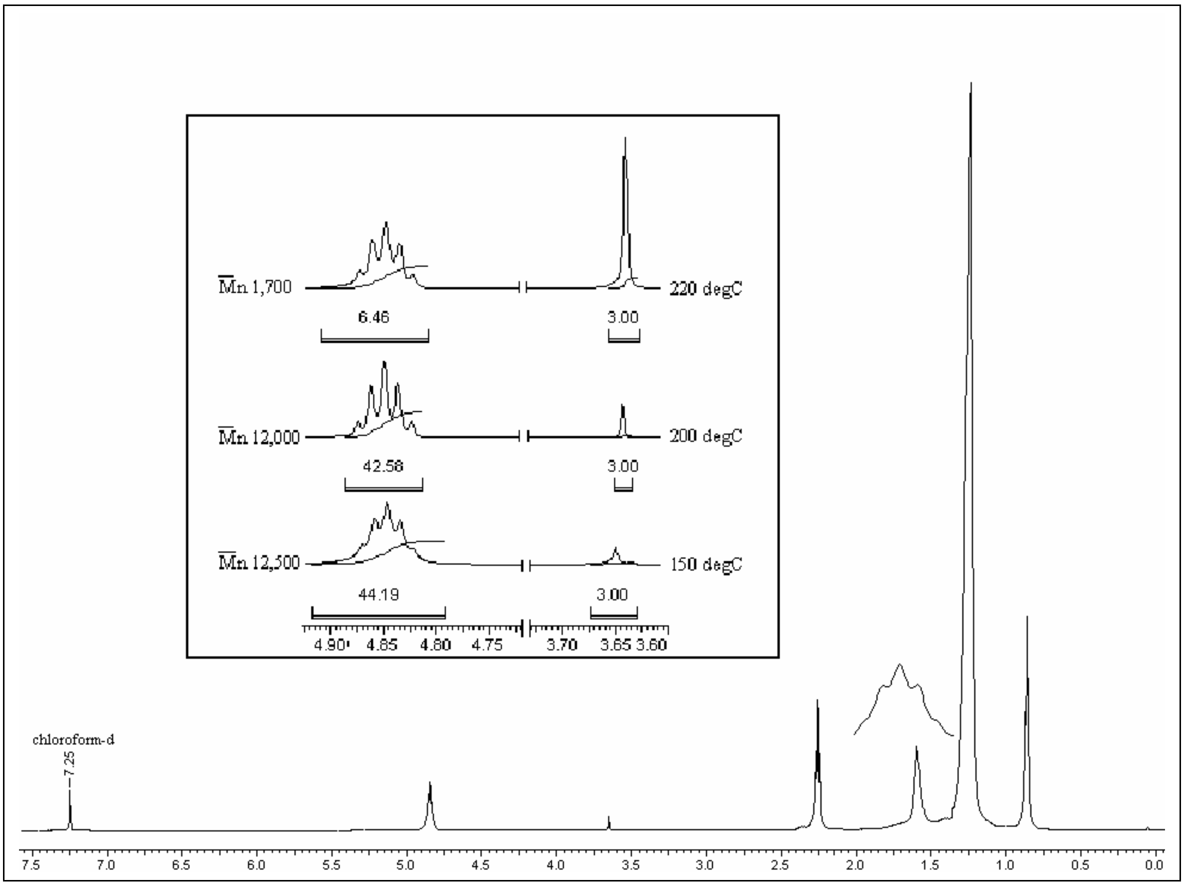


Fig. 7.4: ^{1}H-NMR spectrum (500 MHz) of the PHSA homopolymer

However, no evidence of plasticization was found (Fig.-7.5) as there was no change in the glass transition of the PLLA, when solvent cast PLLA films containing 1, 3 and 5 mol% PHSA were made, which are described as samples **7.4a**, **7.4b** and **7.4c**, respectively in Table-7.2. From the results of thermal characterization as shown in Table-7.2, it can be found that T_gs of the films were all very close to those of the pure PLLA sample from which they were made. In fact, exclusion of PHSA from the PLLA phase was visible even to the naked eye as the films were oily and sticky on the surface. ^{1}H-NMR of the oily material on the surface of the film showed it to be PHSA.

No evidence of existence of two glass transition temperatures characteristic of two different phases from differential scanning calorimetry could, however, be provided because the glass transition of the PHSA was anyway below –40 ºC and undetectable. The thermograms of the film prepared with 3 and 5 mol% PHSA, on the other hand, showed two distinctly different melting peaks, indicative of disturbances in the crystalline growth of the PLA phase (Fig. 7.5).

Table 7.2: Thermal characterization of PLLA homopolymer samples externally plasticized with PHSA homopolymer

Sample no.	mol% PLA	mol% PHSA	T_g (°C)	T_m (°C)
7.4c	95	05	48	51^a, 130
7.4b	97	03	47	30^a, 153
7.4a	99	01	47	156
3.1	100	00	48	142

a: second melting peaks appeared in these cases, b: PLLA synthesized by ROP, considered as standard sample of PLLA homopolymer

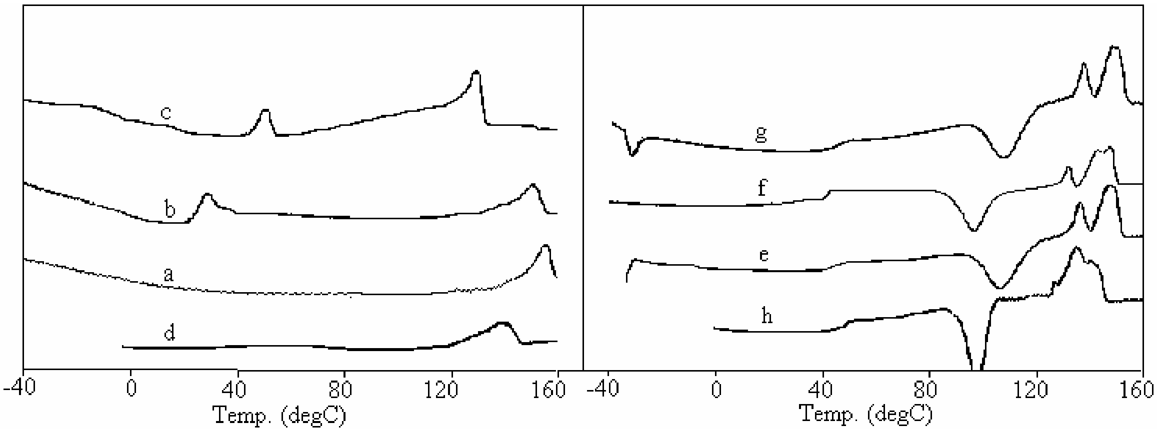


Fig. 7.5: DSC thermograms corresponding to first and second heating of PLA samples externally plasticized with PHSA homopolymer: (a) 7.4a, (b) 7.4b, (c) 7.4c and (d) 3.1 – all first heating thermograms showing T_m and (e) 7.4a, (f) 7.4b, (g) 7.4c and (h) 3.1 – all second heating thermograms showing T_g values.

This indicated that PHSA forced itself in the PLA, if at all, more as an impurity than as a plasticizer. The XRD patters of these films (Fig. 7.6) did not have some of the small peaks that were present in the XRD of the pure PLA homopolymer, indicating once again a disturbance in the crystalline region.

7.4.2. Copolymerization of LLA with 12-HSA: Since the homopolymer PHSA was found to be immiscible and thus ineffective as an external plasticizer to PLA, we attempted the synthesis of a copolymer of 12-HSA with LLA (Scheme 7.2). The three copolymers that were synthesized showed complete incorporation of the comonomer in the PLA backbone. As shown in Table-7.3, where the PLLA samples with 1, 3 and 5 mol% comonomer (12-HSA) incorporation are described as **7.5a**, **7.5b** and **7.5c**, respectively, the mole ratio of comonomers in the feed and that in the product were the same in case of each copolymer. The ^{1}H-NMR spectrum of the three copolymers and the mole ratio of two comonomers in each of the copolymer samples are shown in Fig. 7.7.

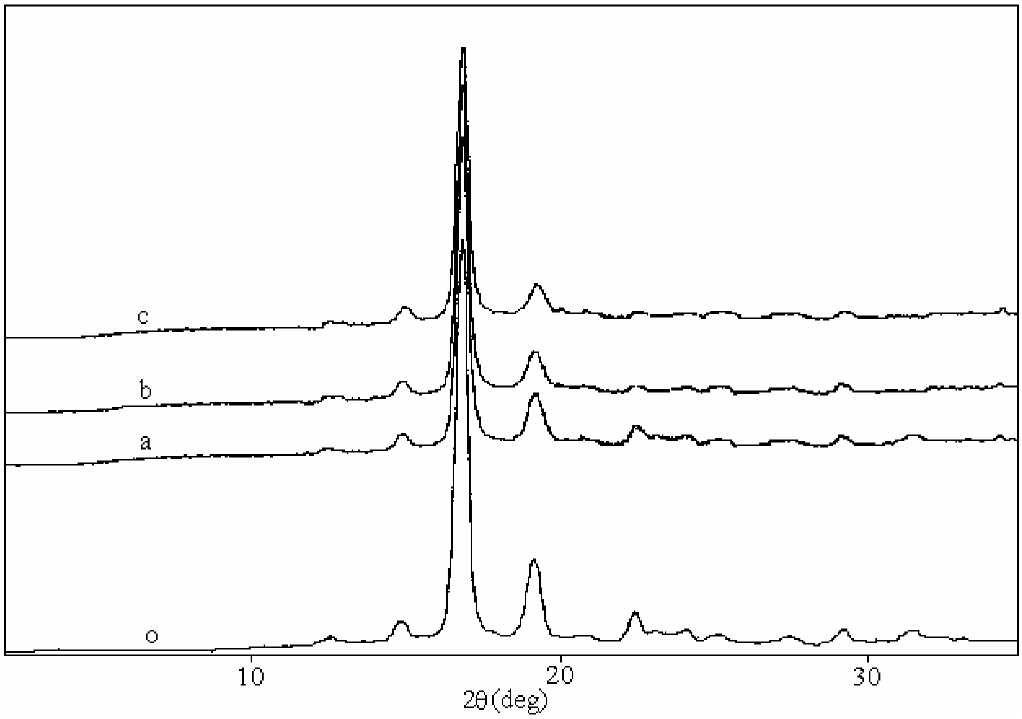


Fig. 7.6: XRD patterns of PLLA samples externally plasticized with PHSA homopolymer: (a) 7.4a, (b) 7.4b, (c) 7.4c and (d) 3.1.

Scheme 7.2: Synthesis of 12-HSA / L-lactic acid random copolymer

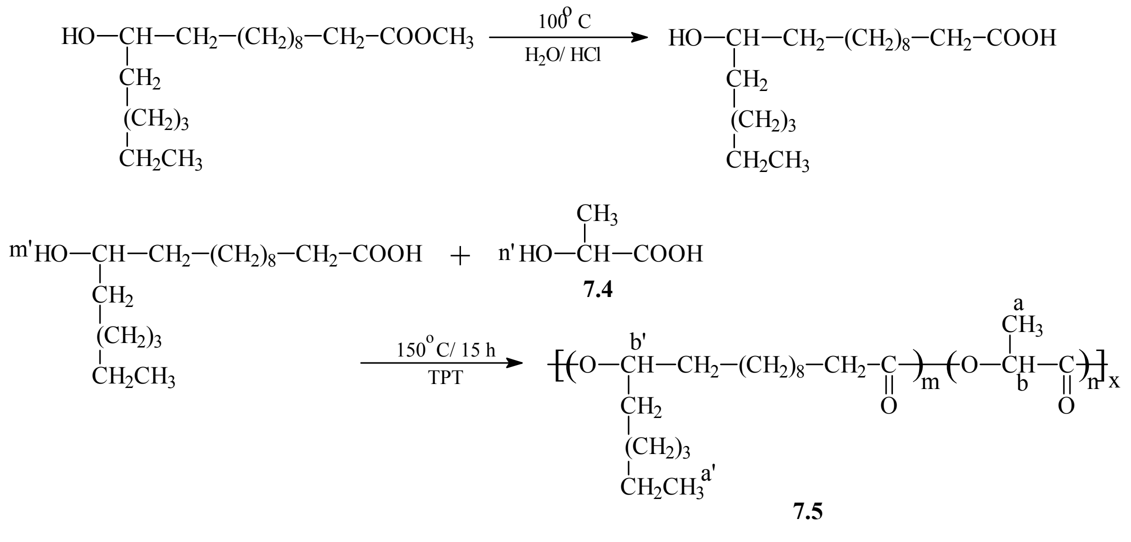


Table 7.3: Thermal characterization of PLA-PHSA copolymers

Sample no.	mol% PLA	mol% PHSA		T_g (°C)	T_m (°C)	$\overline{M}_n$ (VPO)
		Feed	Product[a]			
7.5a	99	01	0.99	38	147	8,800
7.5b	97	03	3.01	28	143	7,600
7.5c	95	05	4.92	22	133	8,100
3.1	100	00		48	142	4,320

a: calculated from ^{1}H-NMR.

Although the completeness of hydrolysis of the methyl ester of 12-HSA into the corresponding carboxylic acid was not ascertained because of the 12-HSA being insoluble – hence equal reactivity of similar functional groups not ensured – before the polycondensation, yet absence of any methoxy proton signal (singlet at about 3.65 ppm) from the ^{1}H-NMR of any of the copolymers indicated that the comonomer was in the carboxylic acid form.

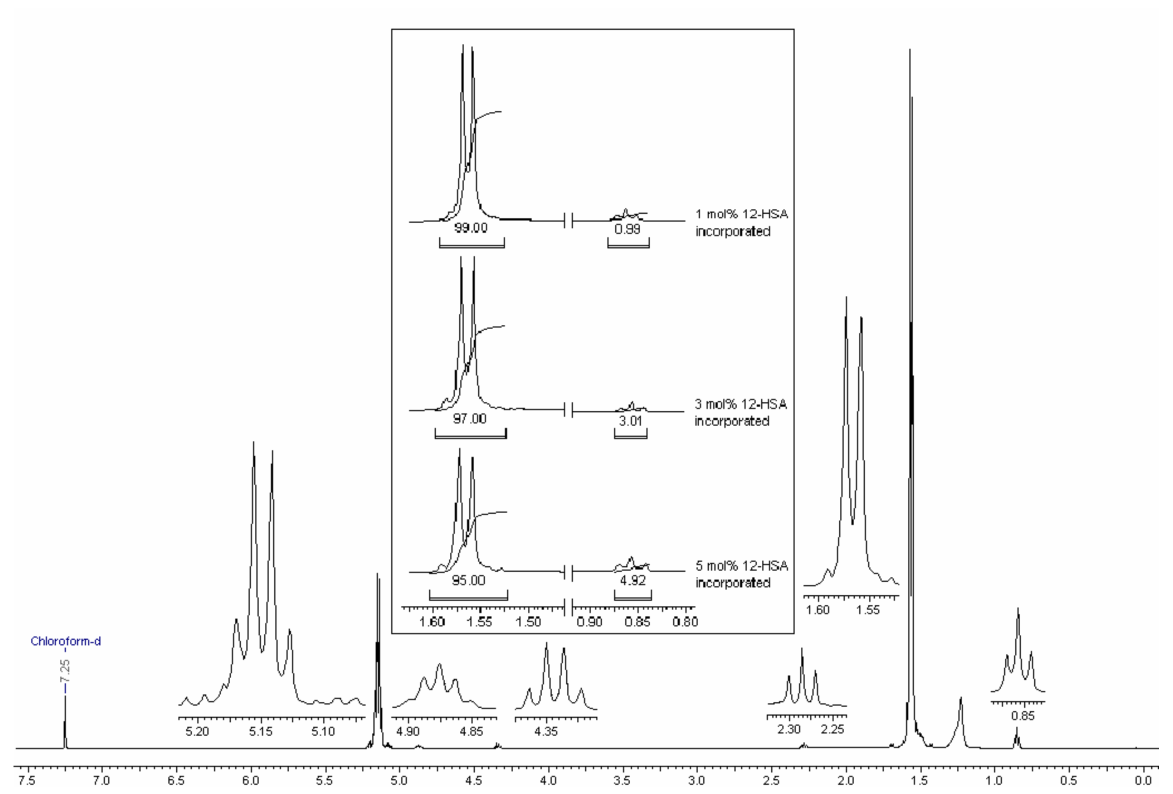


Fig. 7.7: ^{1}H-NMR spectrum (500 MHz) of 12-HSA / LLA copolymers

Determination of comonomer incorporation as well as end groups by MALDI-ToF spectroscopy: The MALDI-ToF spectrum of the copolymer with 5 mol% incorporation is shown in Fig. 7.8. Fig. 7.8a presents the complete MALDI spectrum of the sample, while Fig. 7.8b and c are zoomed pictures of two different regions selected from the full spectrum. The MALDI spectrum showed presence of PLLA homopolymers of different molecular weights as the most intense peaks in the region from 1120 to 1480 Da corresponding to sodiated adduct molecular ions of the empirical formula $H\text{-}(O\text{-}CH(CH_3)\text{-}CO)_n\text{-}OH$ and molecular weight (72n + 18 + 23), where n ranges from 17 to 20. The LLA oligomers that reacted with 12-HSA should still contain OH and COOH as end groups. The empirical formula of such oligomers will be $H\text{-}(O\text{-}CH(CH_2(CH_2)_3CH_2CH_3)CH_2(CH_2)_8CH_2\text{-}CO)_m\text{-}(O\text{-}CH(CH_3)\text{-}CO)_n\text{-}OH$, from where the molecular weight of each copolymer molecular ion (potassiated adduct) can be calculated as (282m + 72n + 18 + 39). The peaks at 1279, 1845, 2125, 2407 etc. are due to such potassiated copolymer adducts, where m varies from 1 to 5 and n is 13 in al the cases. Corresponding sodiated adducts could not, however, be located. Zooming of selected areas did not reveal any further information because of noisy baseline. The desorption of adduct molecular ions of the copolymers seemed difficult. Likewise, the peaks at 1708, 1852, 2140 etc. are also due to copolymers, but of the empirical formula $H\text{-}(O\text{-}CH(CH_3)\text{-}CO)_n\text{-}(O\text{-}CH(CH_2(CH_2)_3CH_2CH_3)CH_2(CH_2)_8CH_2\text{-}CO)_m\text{-}OCH_3$, that is methyl ester ended instead of carboxylic acid, and they desorbed as sodiated adducts, so that the molecular weights can be calculated as (282m + 72n + 32 + 23), where value of n varied from 19 to 25 and m was 1 in all the cases. This means that the methyl ester ended copolymers actually had one unit of methyl ester of 12-HSA at the end, and they did not reacted further. Presence of such methyl ester ended chains also indicated that the hydrolysis of the 12-HSA (methyl ester) monomer into the carboxylic acid was not complete.

MALDI-ToF results thus showed the presence of PLA homopolymer, copolymers with 12-HSA with both hydroxyl and carboxylic acid end groups and also copolymers with hydroxyl and methyl ester end groups. The PLA homopolymer could not be separated from copolymers because both were soluble in chloroform and DCM while n-hexane and methanol were non-solvents for both. The absence of PHSA homopolymer was confirmed by soxhlet extraction using n-hexane, which had been earlier found to be a good solvent for the PHSA homopolymer. MALDI-ToF results also did not detect any PHSA homopolymer.

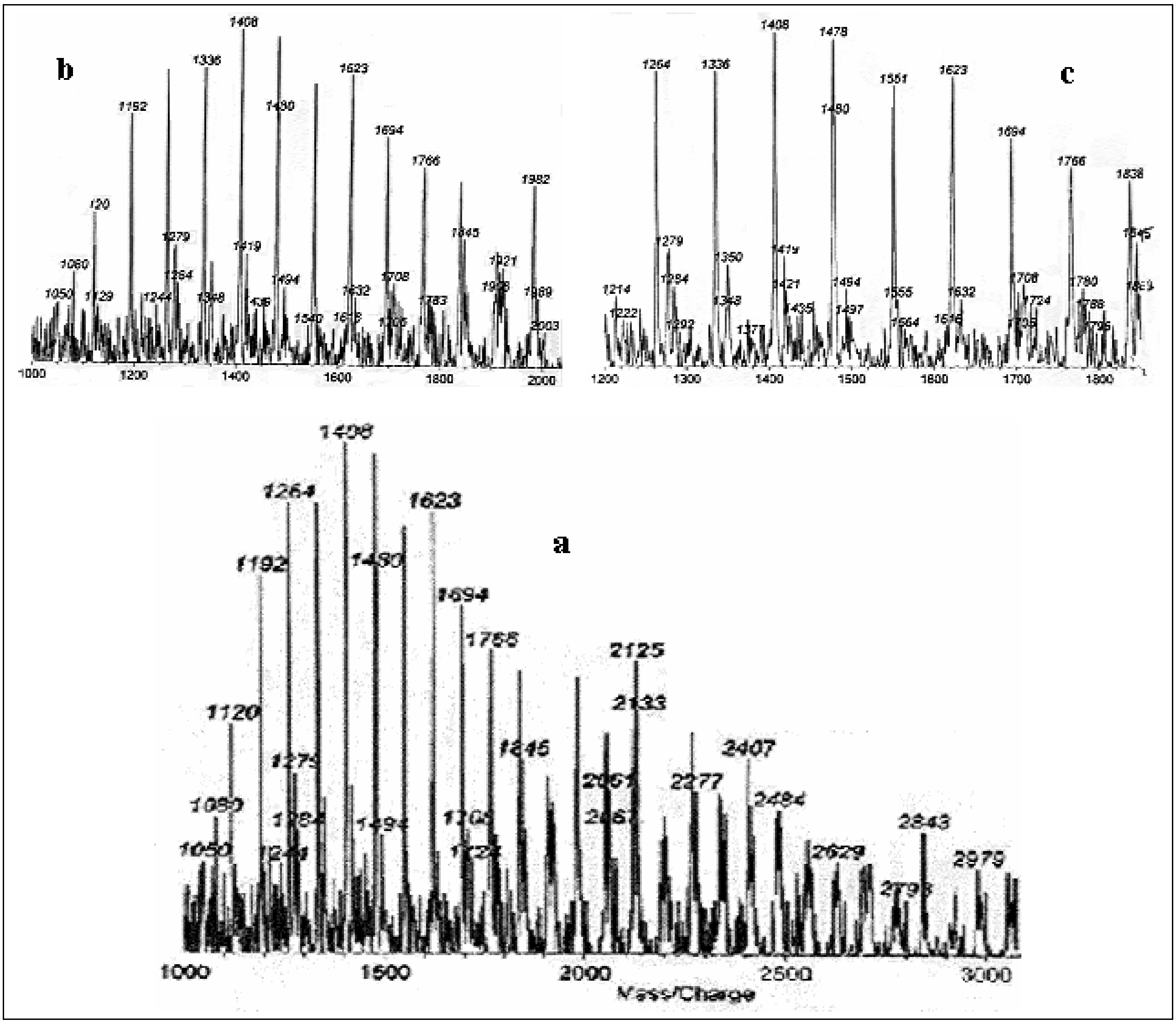


Fig. 7.8: MALDI-ToF spectrum of 12-HSA / LLA copolymer with 05 mol% 12-HSA incorporation: clockwise (a) full spectrum, (b) zoomed region of molecular weight from 1000 to 2000 Da and (c) zoomed region of molecular weight from 1200 to 1800 Da.

The presence of methyl ester ended polymer chains in the MALDI-ToF spectrum might be attributed to incomplete hydrolysis of the methyl ester of 12-HSA monomer. However, ^{1}H-NMR did not find any OCH_3 end groups, probably because of very low population.

7.4.3. Internal plasticization by copolymerization: A gradual reduction in the T_g with increasing comonomer incorporation was found, as shown in both Table 7.3 and Fig. 7.9, thereby indicating increased mobility of the amorphous phase. The crystalline melting point, T_m, of PLLA phase was also found to be disturbed, although only to a small extent, but there was no significant change to be found in the powder XRD pattern in comparison with that of the PLLA homopolymer (Fig.-7.10). This indicated that the effect on the crystalline phase was not very pronounced. What was more important was the depression of the glass transition temperature.

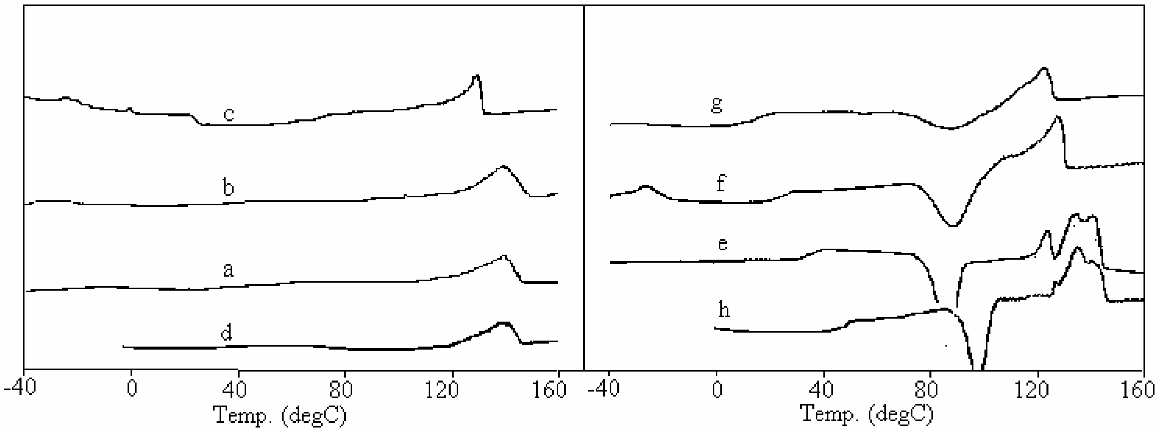


Fig. 7.9: DSC thermograms corresponding to first and second heating of 12-HSA / LLA copolymers showing internal plasticization: (a) 7.5a, (b) 7.5b, (c) 7.5c and (d) 3.1 – all first heating thermograms showing T_m and (e) 7.5a, (f) 7.5b, (g) 7.5c and (h) 3.1 – all second heating thermograms showing T_g values.

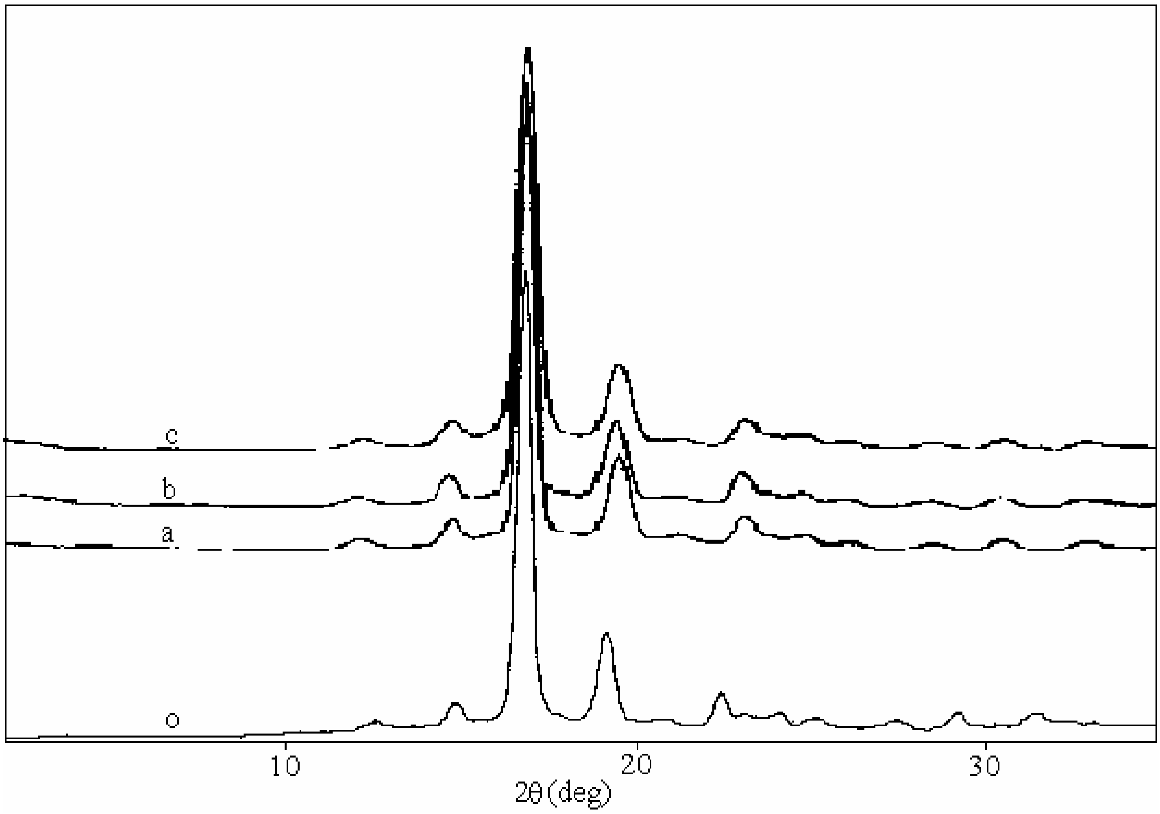


Fig. 7.10: XRD patterns of 12-HSA / LLA copolymers: (a) 7.5a, (b) 7.5b and (c) 7.5c and and (d) 3.1.

Although the absence of a T_g characteristic of PHSA could not be ascertained, yet the absence of a glass transition characteristic of pure homopolymer PLLA was, however, sufficient proof of plasticization. Therefore, the lowering of glass transition temperature of PLLA by a statistical copolymerization with small molar proportions of 12-HSA can indeed be called a case of "internal plasticization".

7.5. Conclusion: PHSA oligomers, although a well-known plasticizer and softener for many materials by virtue of its six carbon-long, aliphatic pendant, failed to plasticize poly(L-lactic acid) externally. A copolymer of 12-HSA with L-lactic acid could be prepared in various molar proportions by means of simultaneous polycondensation of the two comonomers. A comparison of thermal analysis (DSC) results of the homopolymer with copolymers **7.5a**, **7.5b** and **7.5c** showed a monotonic decrease in the T_g values form 48 to 22 °C as the mole percent of comonomer (12-HSA) feed/ incorporation increased from 0 through 1 through 3 to 5. As observed by MALDI-ToF spectrum, the copolymer contained some PLA homopolymer. So, the observed lowering of T_g in the copolymer was actually the resultant of two interactions overlapped up on each other. First incorporation of 12-HSA units in the form of copolymer brought about internal (intramolecular) plasticization of the PLA and lowered the glass transition temperature. But then, there was also intermolecular (external) plasticization between the PLA homopolymer and copolymer. Each copolymer sample (mixed with homopolymer, though) showed single glass transition temperature, which was lower than that of PLA homopolymer. This indicated that the PLA homopolymer and each copolymer were compatible with each other at the molecular level, resulting in miscible blends, showing a single T_g. although the two homopolymers were found immiscible. Thus a small incorporation of the 12-HSA in the backbone of PLA in the form of copolymer enhances the compatibility between two completely immiscible systems, namely PLA and PHSA homopolymers.

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CHAPTER - 8

CHAPTER 8: SUMMARY AND CONCLUSIONS

In the present work, poly(L-lactic acid) (PLA) oligomers were synthesized, starting from an L-lactic acid monomer obtained as 88 % aqueous solution. Monomer purity was determined by gas liquid chromatography and the total amount of impurities such as ethanol, acetic acid, methanol, pyruvic acid, fumaric acid and succinic acid was detected to be less than 30 ppm.

Linear PLA oligomers of controlled number average molecular weight and having both hydroxyl and carboxylic acid end groups were successfully prepared for the first time as model PLA oligomers using ring opening polymerization (ROP) of the lactide using water as the initiator and stannous octoate as the catalyst.

Both linear and macrocyclic PLA oligomers were obtained by dehydropolycondensation of L-lactic acid under various reaction conditions and using Lewis acid catalysts. Properties of the PLA oligomers were found to be a function of catalysts as well as polymerization temperature in the range of 140 to 190 °C. However, only low molecular weight oligomers were obtained. The failure to obtain high molecular weight by dehydropolycondensation either in melt or in solvent has been attributed to the competitive formation of macrocycles. The structure of oligomers changed from linear to macrocyclic as the reaction temperature increased. Incorporation of D-lactic acid units in the backbone due to racemization was also observed at 190 °C.

Postpolymerization of the liner oligomers were performed by different means such as solid state polymerization (SSP), postpolycondensation using condensing agents and chain extension of telechelic oligomers using coupling agents. SSP was performed on both unplasticized and plasticized linear oligomers. Low molecular weight polyethylene glycol dimethyl ethers were found to be good plasticizers for the PLA at room temperature. However, reduction of the glass transition temperature due to plasticization of PLA oligomers did not improve the rate of SSP reaction. Internally platicized copolyesters with single and reduced glass transition temperatures (with respect to T_g of pure PLA oligomer) were also synthesized by simultaneous dehydropolycondensation with 12-hydroxy-stearic acid.

Salient achievements of the present work:

1. Although synthesis of aliphatic polyesters with controlled number average molecular weights by ROP of lactones and lactides using Lewis acid catalysts have been widely studied, the carboxylic acid end groups of these polymers have always been end-capped with the alcohol that is used as co-initiator. **PLA oligomers with controlled and predetermined molecular weights as well as having free carboxylic acid end groups were synthesized for the first time by using water as co-initiator**.
2. Unequivocal identification of end groups as well as linear and macrocyclic PLA oligomers produced via dehydropolycondensation of L-lactic acid was accomplished by the combined use of ^{13}C-NMR and MALDI-ToF spectroscopy. **It was shown that either linear or macrocyclic oligomers can be obtained depending on the temperature of the reaction**.
3. Using an oligomer of weight average molecular weight of 1000, a molecular weight of 88,000 was reached in a few hours by postpolymerization of PLA oligomers using an in-situ derivatization method using DIPC. **Appropriate conditions were defined to minimize undesirable side reactions**.
4. Chain extension of diol-ended PLA telechelic oligomers was achieved using μ-isopropylbis-(ε-caprolactone) and diphenyl carbonate as chain extenders. **An aliphatic copolyester and an aliphatic copolyester-carbonate, respectively, were thus synthesized with a 10 folds enhancement in the molecular weight**. The coupling efficiency was limited by thermal degradation and transesterification upon using extended reaction times.
5. L-lactic acid was copolymerized with a 12-hydroxystearic acid, which is a fatty acid derived from castor oil. Copolymers with 1, 3 and 5 mol% incorporation of 12-HSA into a predominantly L-lactic acid backbone was obtained. **Such copolymers have been found to be internally plasticized with respect to the pure PLA**. A physical mixture of a homopolymer of methyl ester of 12-HSA and PLA was found to be immiscible.

Future directions:

For arriving at a higher molecular weight PLA from direct dehydropolycondensation, the only way is to synthesize higher molecular weight oligomers than achieved in the present work and then perform various postpolymerization reactions. But, higher molecular weight of PLA oligomers can definitely not be achieved through dehydropolycondensation of LLA by increasing the reaction temperature, because of competitive cyclization. The only way is to restrict the reaction temperature below 150 °C and perform repeated dehydropolycondensation reaction on re-precipitated and dried oligomers.

Branched and cross-linked PLA has also been synthesized using multifunctional monomers for increasing molecular weights and altering physical properties. On the other hand, PLA has recently been found to intercalate/ exfoliate silicates and alumino-silicate clays. Synthesis of allyl-terminated PLA followed by hydrosilylation with hydride terminated polysilesesquioxanes (POSS) can be a novel means of incorporation chemically bound silica material into PLA as well as incorporation of branching/ cross-linking.

Silicates and alumino-silicates (clays) have generally been used for compositing with PLA, where PLA is the main matrix and clay is the minor component. Such compositing is expected to bring about changes in mechanical properties of PLA. As an extension from this idea of compositing, the silicious material may be taken as a major component, in which linear, branched or cross-linked PLA can be present as templates. Such composites materials can be calcinated to burn off the polymeric template and then ceramic materials with pores and channels of different sizes can be obtained.

In case of coupling of PLA using μ-isopropylbis-(ε-caprolactone), it has been found (in Chapter 6) that the coupling efficiency is terminated by the reactivity of the primary hydroxyl groups that are originated out of the coupling reaction. Such primary hydroxyl groups can be inhibited from reacting by selective protection in presence of free secondary hydroxyl terminals of the telechelic PLA and thus more efficient coupling can be achieved.