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Poly(lactic acid) Synthesis in Solution Polymerization

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Summary: The step-growth polymerization of L-lactic acid in solution was studied in this work. In order to attain a polymer with high molecular weight, the water formed during the polymerization must be continuously removed. The use of organic solvents with high boiling point, drying agents and reduced pressure led to poly(lactic acid) (PLA) with high molecular weight, directly from the monomer. Tin (II) chloride dihydrate, $SnCl_2.2H_2O$, was the best of the catalysts tested as it allowed achieving PLA with a molecular weight close to 80 000 g.mol^{-1}. However, the stereoregurarity control is a severe problem in PLA synthesis by step-growth due to transesterification reactions, which lead to an inversion of the conformation and a decrease of the optical purity of the polymer. Specific rotation measurements were used in this work and showed to be a powerful technique to evaluate the racemization extent. The thermal stability of the PLA samples was evaluated by DSC which exhibits a thermal behaviour similar to the commercial Polylactide.

Keywords: biodegradable polymer; poly(lactic acid) (PLA); solution polycondensation; step-growth polymerization; transesterification reactions

Introduction

The development of sustainable alternatives to petrochemical origin materials has registered an increasing effort in recent years. One of the most promising substitutes is the Poly(lactic acid) (PLA), a synthetic biodegradable polymer obtained from a 100% renewable raw material, the lactic acid. The properties of PLA allow a wide range of applications, from biomedical and pharmaceutical to the conventional large scale polymer uses[1]. The great number of publications on PLA synthesis and its applications demonstrates the tremendous potential of this polymer. Although it is already synthesized at industrial scale, new improvements on PLA synthesis are frequently available. These approaches comprise new catalysts, such as enzymes, new reaction media, such as ionic liquids or supercritic carbon dioxide, and new energy sources, such as microwave.[2]

PLA can be synthesized by two reaction mechanisms: ring opening polymerization (ROP) of the intermediate lactide or step-growth polymerization,[1] also called polycondensation. Nowadays, ROP is the most used method, implemented at large scale production by Cargill Dow LLC Company in the USA. This is an effective but quite complex process that requires several purification steps of the lactide[1] contributing to the high price of PLA comparing to the petrol based thermoplastics.[3] The latter method allows obtaining PLA polymers directly from the monomer, lactic acid. However, to achieve high molecular weight polymers it is essential to ensure the water withdrawal. Due to the difficulty in removing water from a highly viscous medium, Ajioka *et al.*[4] developed the polycondensation of lactic acid in solution. This method has proved to be effective allowing to achieve high molecular weight polymers, up to 250 000 g.mol^{-1}, by continuous removal of

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water, avoiding expensive purification steps, but the information on kinetics or process conditions is scarce.

In this work, aiming to develop an alternative route to ROP, we have been studying the direct polycondensation of lactic acid in solution.[5] This methodology employs a high boiling point solvent which helps removing the byproduct, water. Our attention is focused on the influence of the operating conditions (solvent, pressure, catalyst and drying agent) on the final polymer's properties, such as molecular weight distribution and optical purity. The synthesized PLA polymers were characterized by size exclusion chromatography (SEC), ^{1}H NMR spectroscopy, polarimetry and differential scanning calorimetry (DSC).

Polymerization Mechanism of Lactic Acid

Lactic acid, HO-CH(CH_3)-COOH, is an alpha-hydroxy acid, which comprises two functional groups that undergo a condensation reaction by releasing water. This feature is particularly relevant, as it ensures stoichiometric concentration of both carboxyl, –COOH, and hydroxyl, –OH, end groups.[6]

The polymer grows in a stepwise manner and, along the reaction, the mixture will have entities with different sizes. The kinetic studies usually assume that the reactivity of a functional group is independent of molecule size. This assumption is referred in the literature[6] as the concept of equal reactivity of functional groups, which was introduced by Flory[10] and proved to be valid when the functional groups are more than three atoms apart. When functional groups are separated by less than three atoms, as in the monomer and dimmer, the reactivity differs greatly. However, according to Roger and Long[7] the difference in reactivity diminishes rapidly with the increase in polymer length.

Polyesterification is a slow reaction and, in order to reach high molecular weight products, an external catalyst is required. Moreover, to continuously shift the equilibrium towards polymer production, an efficient removal of water, a reaction byproduct, must be accomplished. Under these experimental conditions the polymerization can be considered irreversible[6] leading to the rate of polymerization (r):

$$r = K[COOH]\,[OH]\,[cat] \tag{1}$$

Considering that the concentration of external catalyst, $[cat]$, remains constant throughout the polymerization, $K' = K[cat]$ and, as the concentration of the end groups is the same, $[COOH] = [OH]$, the rate of polymerization can be written as:

$$r = K'[COOH]^2 \tag{2}$$

In this batch polymerization the concentration of the carboxyl (or hydroxyl) groups will be:

$$\frac{1}{[COOH]} = K't + \frac{1}{[COOH]0} \tag{3}$$

Where $[COOH]_0$ represents the initial concentration of carboxyl groups. Considering the extent of reaction, p, at time t, $p = \frac{[COOH]_0 - [COOH]}{[COOH]_0}$, equation (3) becomes:

$$\frac{1}{1-p} = 1 + K'[COOH]_0 t \tag{4}$$

The concentration of carboxyl groups in the initial mixture and in the collected samples is measured by titration, allowing the determination of the extent of reaction. Another important relationship is the Carothers equation,[6] which defines the average degree of polymerization (DP):

$$DP = 1/(1-p) \tag{5}$$

Experimental Part

Reagents

Reagents were ordered from Sigma-Aldrich and used as received: Monomer – aqueous solution of L(+)-lactic acid (80%); Solvents – anisole (96%), *m*-xylene (96%) and chloroform HPLC grade; Catalysts – tin (II) chloride dihydrate ($SnCl_2.2H_2O$) (98%), tin (II) octoate (Sn(II)Oct) (98%), titanium (IV) butoxide

(Ti(IV)Bu) (98%), dibutyltin dilaurate (DBTL) (95%) and 4-dodecylbenzenesulfonic acid (DBSA) (90%); Drying agent – molecular sieves, 3 Å beads, 8–12 mesh, adsorption capacity of 21%. Polylactide grade 2002D was purchased from Cargill Dow and exhibits an average molecular weight of 160 000 g.mol^{-1} obtained by SEC.

Polycondensation of Lactic Acid in Solution

The polymerization of lactic acid in solution was carried out using two high boiling point organic solvent, anisole or *m*-xylene. The initial concentration of the monomer in the mixture was 20% (v/v). The reaction was performed in a 2 L volume flask, equipped with a Dean-Stark trap and a mechanical stirrer. The first reaction step was the distillation of the aqueous solution of monomer, which took *ca.* 8 hours. Then, the catalyst was introduced (0.1% mol) and the Dean-Stark trap was replaced by a tube packed with molecular sieves as drying agent. The polymerization was performed for several hours at the boiling point of the solvent, using a bath to keep the temperature constant, and under inert atmosphere (N_2). Some of the experiments were performed at reduced pressure, by decreasing the pressure step by step till reaching the set-point. In order to avoid oil contamination, a cold trap was placed between the reactor and the vacuum pump. The final polymer was recovered as a white powder after dissolution in chloroform and precipitation in ethanol. The reaction yield was near 30%.

Polymer Characterization

The average molecular weight (*Mw*), number molecular weight (*Mn)* and polydispersity index (*PD*) were determined by Size Exclusion Chromatography (SEC), which was calibrated with narrow polystyrene standards (4 000, 10 050, 19 880, 30 300, 66 350, 96 000 and 200 000 g.mol^{-1}). The column set consists of a Polymer Laboratory 5 μm guard column (50 × 7.5 mm) followed by two PLgel 5 μm MIXED-D columns (300 × 7.5 mm) connected in series. The HPLC pump was set with a flow rate of 1 mL.min^{-1} and the eluent was Chloroform HPLC grade. The measurements were carried out at 25 °C with a concentration of ≈ 2 mg.mL^{-1} of polymer sample after precipitation. Before the injection (≈ 50 μL), the samples were filtered through a PTFE membrane with a 0.45 μm pore. After column exclusion, the samples were analysed in an evaporative light scattering detector, PL-EMD 960. Data processing was carried out with GPC Clarity software from DataApex.

The ^{1}H NMR spectra of PLA were recorded on a Varian 500-MHz spectrometer at 25 °C, using deuterated chloroform, $CDCl_3$, as solvent containing 1% (v/v) of tetramethylsilane as internal standard.

The specific rotation of PLA polymers, $[\alpha]_\lambda^T$, was measured on a Optical Activity AA-5 electrical polarimeter at 25 °C, with a wavelength of 589 nm and a concentration of 1 g.dL^{-1} in chloroform. The percentage of optical purity of PLA polymers (*OP%*) was calculated using the following relationship: $OP\% = [\alpha]_{589}^{25} \Big/ (-156) \times 100$, where -156 is the specific rotation of PLA with only L stereoisomer in its composition.[5]

The carboxyl end groups disappearance was followed by chemical titration. The collected samples after solvent evaporation, 1 g, were dissolved in 20 mL of a mixture ethanol:chloroform (1:1 v/v) and titrated with a solution of KOH in ethanol (0.05 mol.L^{-1}). This procedure was repeated 3 times. The concentration of carboxyl groups in the sample, [*COOH*], is defined as the number of *COOH* moles per g of polyester.[7]

The melting point (*Tm*), decomposition temperature (*Td*) and fusion enthalpy (*ΔHm*) were measured using a differential scanning calorimetry equipment, SDT Q600 from TA Instruments, under nitrogen atmosphere, with a heating rate of 10 °C.min^{-1}. The samples were analyzed in the range of temperatures 30 °C to 450 °C. The percentage of crystalinity (*Xc%*) was calculated using the following relationship: $Xc\% = (\Delta Hm/93) \times 100$. The fusion enthalpy of a PLA crystal of infinite size is 93 J.g^{-1}.[8]

Results and Discussion

The process starts with the thermal dehydration of the 80% lactic acid solution. Figure 1 enables to compare the broad molecular weight distribution of the mixture of lactic acid oligomers with different sizes, obtained by distillation of the aqueous solution of L-LA, to the narrow molecular weight distribution of the final polymer. The ^{1}H NMR spectrum of the PLA polymer is shown in Figure 2. The bands of the –CH_3 and –CH groups appear at 1.6 and 5.2 ppm, respectively, confirming the successful synthesis of PLA. The band at 7.3 ppm refers to the solvent used in the analysis, $CDCl_3$.

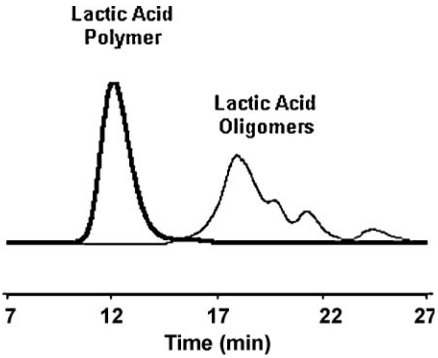


Figure 1.
SEC curves of the mixture of oligomers and PLA.

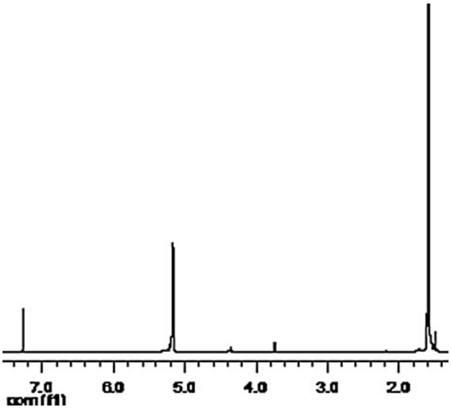


Figure 2.
^{1}H NMR spectrum of PLA.

Figure 3 presents the evolution of carboxyl end groups, (◆), and reaction extent, (■). As expected for a step-growth polymerization, at the beginning of the reaction a steep decrease in carboxyl end groups concentration is registered, which corresponds to an increase in reaction extent. The initial lactic acid molecule contains a carboxyl and a hydroxyl group, which are responsible for the high polarity of the initial reaction mixture. Whilst the initial monomer is converted into small oligomers, the concentration of carboxylic groups decreases as well as the polarity of the reaction.[9] This was reported by Moon *et al.*,[9] who related polarity change to catalytic activity. While the initial thermal dehydration is self-catalysed by the carboxyl group of the monomer an external catalyst must be added after oligomerization in order to further carry out the polymerization.

Table 1 summarizes the experimental conditions used in this study: solvent, catalyst, pressure and reaction time. The average molecular weight (*Mw*), polydispersity index (*PD*) and optical purity (*OP*) of the PLA samples are also shown.

The experimental programme used for the step-growth polymerization of lactic acid enabled screening catalysts and solvents and studying the influence of process variables on the quality of the final polymer. It is well-known that PLA for commodity applications should exhibit high molecular weight and high stereoregularity, since they have a strong influence on the mechanical properties and degradation rate. Thus, the molecular weight and optical purity were chosen for evaluating the performance of the experiments.

Experiments 1 and 2 (PLA1 and PLA2, Table 1) were carried out at atmospheric pressure without removing the water during the polymerization. The results obtained by SEC technique show that the polymers synthesized under these experimental conditions have the lowest average molecular

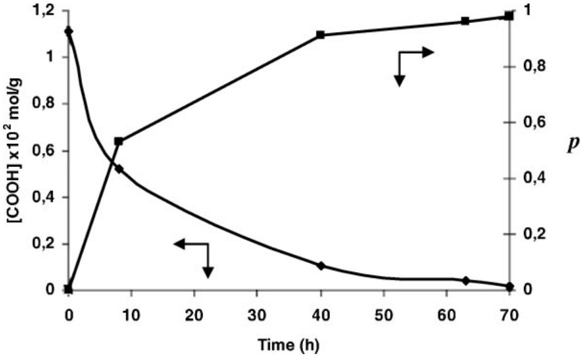


Figure 3.
Evolution of carboxyl end groups concentration, [*COOH*], and reaction extent, *p*, during the experiment 6 (◆– represents the [*COOH*]; ■ – represents the *P*).

weight among the polymers analysed. To achieve high molecular weight polymers, it is essential to ensure an efficient water removal, as mentioned before. In order to increase the molecular weight, different strategies to control water content in the reacting mixture were tested in the subsequent experiments.

In the remaining set of experiments (3 to 10), after the initial distillation step, the Dean-Stark Trap was replaced by a tube packed with molecular sieves, synthetic zeolites, which has the ability to adsorb small molecules such as water. This new set-up allowed the vapour solvent containing the water formed during the polymerization to pass through the molecular sieves bed, the water was remover and the dry solvent was reintroduced into the reactor vessel. This approach allowed a considerable increase in the molecular weight of the final polymer (PLA3 and PLA4, Table 1), however, not enough for the intended target. In order to promote a more effective water adsorption by the drying agent, in the set of experiments 5 to 10, the pressure in the reaction vessel was gradually reduced through the course of the polymerization, leading to higher molecular weight polymers (Table 1).

As already mentioned, the esterification processes have a slow reaction rate and therefore an external catalyst is required. Proton acids, such as H_2SO_4 or H_3PO_3, are often used. However, metal ions, such as Lewis acids, can be more efficient than hydrogen ions.[7] According to the data shown in Table 1, the catalyst has a great

Table 1.
Lactic acid polycondensation - experimental conditions and results.

N°	Solvent	Catalyst	Pressure	Time	*Mw*	*PD*	*OP*
			[bar]	[h]	[g.mol^{-1}]		[%]
PLA1	*m*-Xylene	$SnCl_2.2H_2O$	1	30	3 200	1.5	83
PLA2	Anisole	$SnCl_2.2H_2O$	1	24	1 800	1.9	79
PLA3	*m*-Xylene	$SnCl_2.2H_2O$	1	24	7 900	1.0	83
PLA4	*m*-Xylene	$SnCl_2.2H_2O$	1	48	23 200	1.3	87
PLA5	*m*-Xylene	$SnCl_2.2H_2O$	0.3	40	45 400	–	54
PLA6	*m*-Xylene	$SnCl_2.2H_2O$	0.3	70	80 000	1.3	–
PLA7	*m*-Xylene	Sn(II)Oct	0.1	48	35 800	1.6	0
PLA8	*m*-Xylene	Ti(IV)But	0.1	40	40 800	3.2	–
PLA9	Anisole	$SnCl_2.2H_2O$	0.4	64	47 200	1.5	48
PLA10	*m*-Xylene	DBSA[a]	0.3	48	17 500	1.5	83

[a] 0.2% v/v.

influence on molecular weight and optical purity of the final product. The obtained polymers (PLA1 to PLA10) have an optical purity lower than 100%, suggesting the occurrence of some racemization reactions. At reduced pressure the optical purity of the polymers was drastically lower than that exhibited by the polymers synthesized at atmospheric pressure, experiments 1 to 4. Most probably, this result was due to a leak in the set-up, which may have allowed oxygen in, promoting the ester interchange reactions. These kind of reactions have also been reported for tin chloride ($SnCl_2.2H_2O$) used as catalyst in bulk/melt lactic acid polycondensation.[9] However, tin chloride was the most effective catalyst tested and allowed to achieve the highest molecular weight, near 80 000 $g.mol^{-1}$ (PLA6, Table 1).

Sn(II)Oct, a Lewis acid catalyst, is ranked as an efficient catalyst for reaching high molecular weight PLA by ring opening polymerization.[1] However, Table 1 shows that for direct esterification of lactic acid tin chloride is more efficient. Sn(II)Oct was used for experiment 7. For this polymer an optical purity of 0% was measured (Table 1), *i.e.*, the polymeric chain of PLA7 contains the same amount of L- and D- estereoisomers; one can refer that Sn(II)Oct is a strong ester interchange catalyst promoting high levels of racemization.

Titanium(IV) butoxide, (Ti(IV)but), is also a Lewis acid and proved to be an efficient polyesterification catalyst, although the final polymer exhibits a wider molecular weight distribution which should be avoided.

Table 1 illustrates that reduced pressure improves the polymerization rate but this was not enough for 4-dodecylbenzenesulfonic acid, DBSA, a weak proton acid, to enable achieving a high molecular weight. Nevertheless, according to the data it could be used to control the polymer stereoregularity. Dibutyltin dilaurate, DBTL, were also tested but did not lead to encouraging results, data not shown.

Regarding the solvents used, the *m*-xylene seems to be a better solvent for PLA synthesis than anisole, producing less racemization reactions and, additionally, it has a lower boiling point requiring a lower reaction temperature.

Figure 4 shows the average molecular weight, (▲), obtained by SEC, and the polymerization degree, (◆), obtained with equation 5, against reaction time measured during experiment 6 ($SnCl_2.2H_2O$; 0.3 bar).

These results point out a linear molecular weight increase along reaction time. On the other hand, the polymerization degree *(DP)* shows a steep increase late in the polymerization. This is consistent with the results presented in Figure 3, confirming that to reach high molecular weight PLA polymers, the conversion of carboxyl end groups must be very close to 100%. Experimental results for esterification

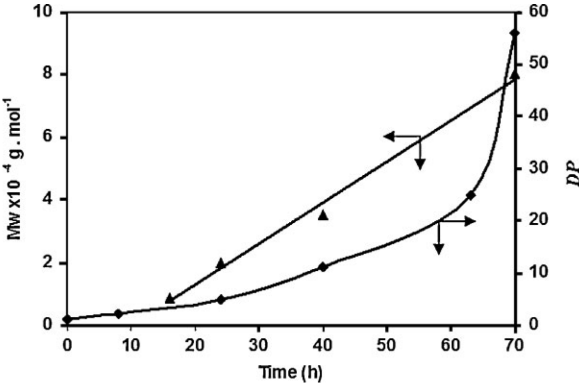
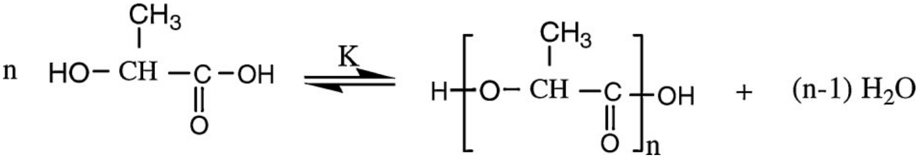


Figure 4.
Average molecular weight, *Mw*, and degree of polymerization, *DP*, against reaction time for PLA6 (▲– represents the *Mw*; ◆– represents the *DP*).



Scheme 1.
Dehydration reaction of lactic acid.

reactions presented in the literature show that the plot of 1/(1-p) *vs* reaction time is linear in the high conversion range[6] and Figure 4 confirms this pattern. The non-linearity in the low conversion region is attributed by Flory[10] to the changes in reaction medium, mainly, the polarity decrease.

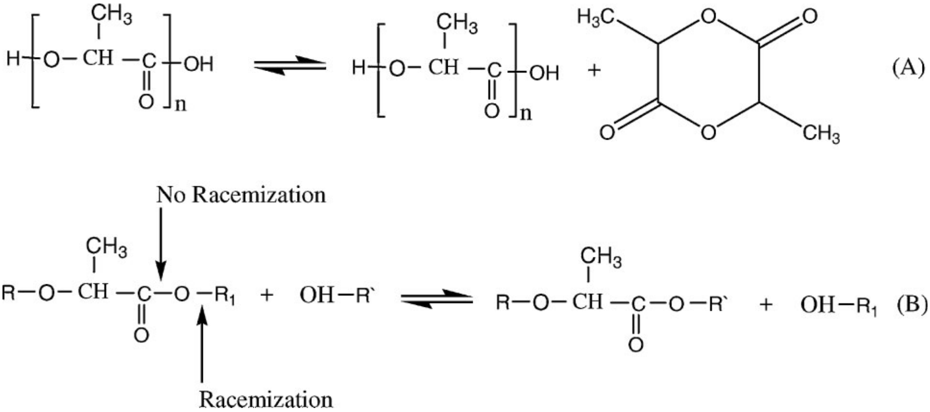
The lactic acid polymerization by step-growth involves several reversible reactions and, according to Hiltunen *et al.*,[11] the main ones are represented in Schemes 1 and 2.

Dehydration, Scheme 1, has the major contribution to achieving a high molecular weight polymer and the equilibrium must privilege the direct reaction.[11] The key to obtain a high molecular weight polymer is to promote an efficient water removal, which comprises the use of drying agents, vacuum and high temperature.

The ring-chain equilibrium, reaction (A) in Scheme 2, involves the depolymerization of PLA into lactide. The organic solvent has an important role to control the extent of this reaction as it allows reintroducing the lactide into the reaction medium during the polymerization. Other cyclization reactions producing macrocyclic polymers, also called back-biting, have been identified in PLA synthesis.[12] It is well known that commercial grades of polyesters have a 0.25–2.0% weight content on cyclic polymers.[13] Unfortunately, it was not possible to assess the synthesis of this kind of compounds.

Transesterification reactions, Scheme 2, reaction (B), inter and intramolecular, are important reactions in lactic acid polymerization. It is a dynamic equilibrium of ester interchange reactions occurring between polymer chains. Its occurrence can explain the introduction of D-lactyl units in the polymer chain. The L-lactic acid used as raw material is optically pure and the probability of it undergoes racemization reactions is very small.[11]

Step-growth polymerization of optically pure L-lactic acid should lead to an isotactic



Scheme 2.
Side reactions that can occur during the lactic acid polycondensation: (A) Ring-chain equilibrium; (B) Transesterification equilibrium.

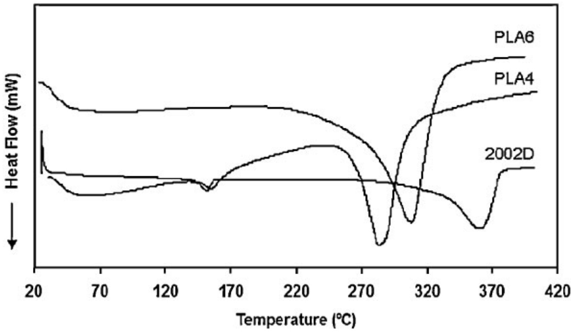


Figure 5.
DSC Traces of PLA4, PLA6 and a commercial Polylactide, 2002D.

chain structure, if no racemization occurs. Therefore, the optical purity results in Table 1 reveal, undoubtedly, the racemization reactions occurrence. The results also show that the racemization reactions are dependent on the reaction conditions and, mainly, on the catalyst used. During the ester interchange reactions there are two ways in which ester linkage can cleave, Scheme 2, reaction (B): by acyl-oxygen cleavage, which does not involve the chiral carbon; by alkyl-oxygen cleave, in which the covalent bond between oxygen and the chiral carbon breaks and subsequently reforms.[11] This leads to a random inversion of the conformation (L- is converted into D-) and, consequently to a decrease of optical purity.

The DSC technique was used to evaluate the thermal properties of some of the polymeric materials synthesized and one commercial Polylactide, PLA 2002D.

Figure 5 shows the DSC traces of PLA4, PLA6 as well as the trace of a commercial Polylactide, PLA 2002D. The commercial PLA exhibits the melting temperature at 151 °C, the decomposition temperature at 360 °C and a crystallinity degree of 30% determined from the heat of fusion. PLA4 has the melting point at 155 °C and a crystallinity of 28%. It decomposes at a much lower temperature than that observed for the commercial polymer, which is due to the lower molecular weight of the former polymer. Among the polymers synthesized, PLA6 is the one with the highest molecular weight (80 000 g.mol^{-1}); thus, it starts to decompose at the highest temperature, 311 °C. However, it is not observed in its DSC trace any peak that could be assigned to the melting transition, suggesting an amorphous structure. This could be attributed to the racemization reactions that can occur during the step-growth polymerization, leading to a polymer with an atactic structure, *i.e.*, there is a random distribution of the L- and D-lactyl units which hinder the polymer chain crystallization.

Conclusion

PLA polymers were successfully synthesized by direct condensation of lactic acid in solution. The use of high boiling point solvents, a drying agent and reduced pressure, shown to be a good strategy to allow an efficient water removal, which is a reaction byproduct, and, consequently, the obtention of high molecular weight polymers. This polymerization method enabled to obtain high molecular weight PLA polymers directly from monomer, instead of the three steps required by the ROP method, which is a great advantage from an economic point of view.

The change of L- to D-lactyl units, supported by the optical purity results, confirmed to be a severe problem in PLA synthesis by polycondensation. Thus, its control is essential and can be attained selecting a suitable catalyst. In order to avoid racemization reaction in PLA polymers, protonic acids proved to be the best catalysts. More research work should be carried out to find the best catalyst that provides an enhanced molecular weight and lower racemization extent.

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