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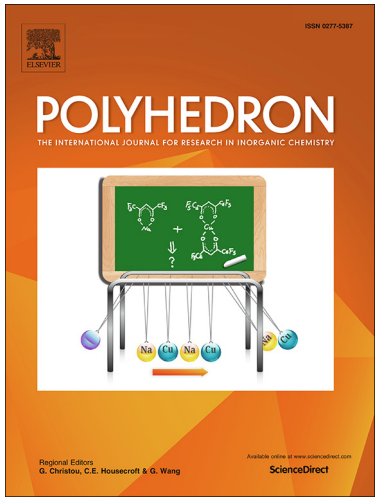

Kinetic and Biocompatibility Investigation on the Catalytic Ring Opening Polymerization of L-Lactide in Bulk Using Cyclic Bu_2Sn Initiators Derived from Ethylene Glycol, Pentaerythritol and Cloisite 30B

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Kinetic and Biocompatibility Investigation on the Catalytic Ring Opening Polymerization of L-Lactide in Bulk Using Cyclic Bu_2Sn Initiators Derived from Ethylene Glycol, Pentaerythritol and Cloisite 30B

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ABSTRACT

In the present work, considering a green approach, PLLA was synthesized by the ring-opening polymerization of L-LA using various cyclic initiators (2,2- dibutyl-2-stanna-1,3-dioxacyclo ethane (**1**), spirocyclic tin (**3**) and cloisite modified tin (**5**)). PLLA was characterized by size exclusion chromatography, differential scanning calorimetry, ^{1}H and ^{13}C NMR, XRD and MALDI-TOF. The molecular weight distribution was narrow (< 1.5) for both low and high molecular weights (> 85,000 g/mol). An X-ray study showed the crystalline nature of PLLA, irrespective of the different types of initiators and polymerization conditions. A kinetic investigation showed that all polymerizations were first order with respect to the monomer and no termination reactions occurred during the polymerization. MALDI-TOF spectra of PLLA chains doped with Na^+ and K^+ cations show that the PLLA prepared using initiators **1** and **3** have hydroxyl and carboxyl end groups

without incorporation of tin. The MALDI-TOF spectrum of PLLA prepared using initiator **5** also enabled the simultaneous detection of the linear and cyclic structure of PLLA without tin. Biocompatible and biodegradable PLLA was obtained, which could be used for biomedical applications.

Keywords: Poly (L-Lactide); cyclic tin initiator; spirocyclic; cloisite modified tin; MALDI-TOF

Introduction

In recent years, environmentally friendly polymers, such as Poly (L-Lactide) (PLLA), have attracted tremendous attention because of their biocompatibility, biodegradability and permeability. They also aid reduction of carbon dioxide emissions which induce global warming. PLLA is also produced from renewable resources [1,2], which is an alternative to the exhaustion of petroleum resources. PLLA is widely used for biomedical applications, such as in surgery, drug delivery systems, surgical sutures, implants (internal bone fixation) and packaging [3]. PLLA is derived from biomass and is being explored as a potential alternative to petroleum-derived polymers such as polyolefin, polyester and polystyrene [4-7]. Efforts have been made to synthesize PLLA through catalyst development and initiator modification [8]. However, there are still great challenges to modify and enhance the properties of the resulting materials.

Cyclic initiators prepared from dibutyltin oxide and various alcohols have been reported as initiators in the ring opening polymerization (ROP) of various lactones and lactides [9-12]. It is observed that the polymerization mechanism involves Sn-O bonds as active species. Again, the reactivity of the initiator increases with the number of attached alkoxide groups to the tin atom and decreases with the increasing bulkiness of the alkoxide groups [13]. The literature reports demonstrate that six-member cyclic dibutyltin alkoxides are interesting initiators for β-D, L-butyrolactone or ε-caprolactone [14,15]. The insertion of lactones into both Sn-O bonds produces macrocyclic polylactones in high yields, and the variation of the monomer/initiator ratio allows easy control of the average ring size. Kricheldorf et al [16] have shown that 10-membered rings containing tin initiate the ROP of L-Lactide (L-LA) and racemic D, L-Lactide (D, L-LA) at 120 °C. The resulting molecular weights are observed to be higher than expected from the monomer/initiator ratio and are not parallel to it. The key aspect of this polymerization is the formation of macrocycles and the absence of

a back-biting reaction. As demonstrated in the literature reports [17], cyclic initiators allow the synthesis of macrocyclic lactones, telechelic linear polylactones with two hydroxyl end groups, A-B-A triblock copolymers and random copolyesters.

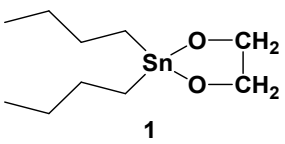
The ROP of L-LA has been initiated with cyclic tin alkoxide, where the microstructure and stereo sequences of poly L-lactic acid are discussed [18]. Homo and copolymers of (D, L)-β-butyrolactone and ϒ-butyrolactone or β-valerolactone have been synthesized using cyclic tin alkoxide [19]. Biodegradable cyclic polyesters and tadpole-shaped polyesters have been synthesized in the presence of cyclic tin alkoxide [20]. Ring expansion polymerization of β-D, L-butyrolactone or Ɛ-caprolactone has been initiated with 2,2-dibutyl-2-stanna-1,3-dioxapane and results in polylactones which are toxic for biomedical applications [21]. L-LA macromonomers have been successfully synthesized using functionalized cyclic tin alkoxides in order to obtain brush-like structures [22]. Dihydroxy terminated PLLA has been obtained by controlled ROP and the control of the polymerization mechanism has also been investigated [23]. The aggregation of active centers in metal alkoxide initiated lactones or lactide in solution is a commonly reported phenomenon. The reactivity of the aggregated and non-aggregated species differs, and as a result, the kinetics of the polymerization are influenced. The propagation commonly proceeds via the non-aggregated species while the aggregated complex is temporarily terminated and thus inactive towards polymerization.

In the literature, it has not been ascertained whether the broad distribution occurred due to low solubility or the reactivity of these initiators. There is also a large difference between solution studies and melt polymerization studies.

The objective of this study was to examine in depth, the ring opening polymerization of L-LA with 1,1,6,6-tetra-*n*-butyl-1,6-distanna-2,5,7,10-tetraoxacyclodecane (**1**/**2**), spirocyclic tin (**3**/**4**) and Cloisite modified tin (**5**) as water-tolerant initiators in bulk polymerization

(green route). The advantageous properties of these initiators are: inexpensive, non-hygroscopic, non-explosive in nature, free from impurities such as water and organic acids, thermally stable, can be stored for long periods without adopting any stringent conditions, easy to handle and non-aggregation in bulk ring opening polymerization. Detailed characterization of PLLA was performed using various techniques, such as MALDI-TOF MS, quantitative ^{13}C NMR analysis, size exclusion chromatography (SEC), wide-angle X-ray diffraction (XRD) analysis and DSC. The nature of the end groups of PLLA was determined with MALDI-TOF MS and ^{13}C NMR spectroscopy. A detailed kinetic study and the efficacy of these initiators for the ring opening polymerization of L-LA in bulk were explored. The synthesized PLLA can be used as a biocompatible and biodegradable polymer in biomedical applications.

STRUCTURES



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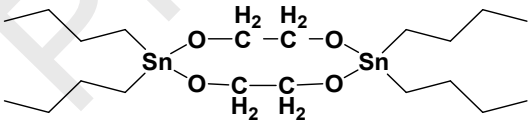

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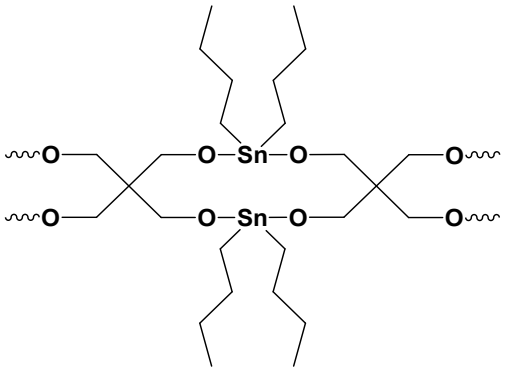

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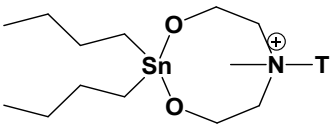


5

Mehrkhodavandi et al. prepared a highly active indium catalyst for living lactide polymerization, where they showed the functional group tolerant polymerization and also catalyst recovery [24]. The spiro polymer has been synthesized, characterized and found show a lack of solubility, melting etc [25]. The mono and bifunctional spiro orthoesters have been synthesized using a cationic ROP technique [26]. Organic spirocyclic initiators have been used for the ring-expansion polymerization of β-lactones [27].

Materials and methods

Materials. Dibutyltin oxide (98 %) and pentaerythritol (99 %) were purchased from Aldrich. Ethylene glycol was purchased from Spectrochem. Cloisite 30B was purchased from Southern Clay. All the materials were used without further purification. L-LA was purchased from Purac and recrystallized once from ethyl acetate. The monomer (L-LA) was dried and stored in a dry glove box.

Preparation of the initiators

1,1,6,6-Tetra-*n*-butyl-1,6-distanna-2,5,7,10-tetraoxacyclodecane (1/2) was prepared using dibutyltin oxide (4.05 g, 0.0163 mol) and ethylene glycol (0.92 mL, 1.021, 0.0163 mol, 1.0 equiv.). The reactants were taken in a three-neck flask containing dry toluene (100 mL) equipped with a Dean and Stark moisture trap. The reaction mixture was stirred under reflux conditions (dibutyltin oxide dissolves) until a constant volume of 0.3 ml liquid had collected in the trap.

The flask containing the product (a clear yellow toluene solution) was gradually cooled to room temperature. The solution deposited white crystals which were isolated by filtration, washed with toluene and dried under vacuum; yield 4.579 g (96%). These were recrystallized from methylene chloride. The M.p. is 223-226.5 °C (lit. 223-229). Exposure of the product to air, overnight, did not affect the M.p. Found: C, 41.36; H, 7.45; Sn,

40.45%; mol.wt. in $CHCl_3$, 650. $C_{20}H_{44}O_4Sn_2$ Cald.: C, 40.99; H, 7.57; Sn, 40.52%; mol. wt. 586). The ^{119}Sn NMR spectrum of initiator **1** was recorded and the structure was confirmed.

3,3,9,9-Tetrabutyl-2,4,8,10-tetraoxa-3,9-distannaspiro[5,5]undecane (3/4) was prepared according to the literature [14,23-25]. Dibutyltin oxide (2.48 g, 9.962 x 10^{-2} mol) and pentaerythritol (0.68 g, 4.981 x 10^{-2} mol dried over P_4O_{10}) were suspended in dry toluene (100 mL) and refluxed until the theoretical amount of by-product water was removed by azeotropic distillation over a period of 24h. When the clear solution was cooled, the product precipitated. The crude product was isolated by filtration. It was dissolved in hot toluene, the insoluble fraction was removed by filtration over dry Celite and the product was isolated by cooling (in the refrigerator overnight) and filtration. Yield: 1.988 g (88%). M.p. : 183-185 °C. Anal. Cald. for $C_{21}H_{44}O_4Sn_2$ (597.96): C, 42.18; H, 7.42. Found: C, 41.56; H, 7.83. The ^{119}Sn NMR spectrum of initiator **3** was recorded and the structure was confirmed.

Cloisite 30B modified tin (5) was prepared by condensing (1.443 g) cloisite 30B, where T is Tallow (65% C_{18}; 30% C_{16}; 5% C_{14}) and (1 g) dibutyltin oxide in dry toluene at 110 °C for 7h. The reaction mixture was cooled at room temperature and filtered. The crude product was washed with *n*-hexane several times and dried using a vacuum to obtain a constant weight. The yield was 2.229 g (95 %). The ^{119}Sn NMR spectrum of the modified cloisite 30B initiator **5** was recorded and the structure was confirmed. No M.p. was observed. The TGA curve of the modified Cloisite 30B catalyst shows a first decomposition temperature at 293 °C.

Polymerization

L-LA (1g, .0069mol) and the requisite mole of initiators were weighed using a dry box (model No-UniLabMBroun-MB-OX-SE-1, S.L.-7120) into a reactor ampoule which had silanized glass walls (pre-treated with Me_2SiCl_2). The break seal technique was used for all polymerization reactions. The sealed ampoule was completely immersed into a preheated fluidized sand bath reactor. All other polymerizations catalyzed by tin modified initiators were performed analogously. The reaction mixture was cooled to room temperature and 100 mL of chloroform were added. The resultant solution was filtered to remove the residual initiator. The filtrate was poured into 400 mL of *n*-hexane for precipitating the polymer. The resultant polymer was collected by filtration and further purified by repeated dissolution and precipitation. A similar procedure was followed to remove the cloisite modified tin initiator.

Analysis

The molecular weights (M_n and M_w) and dispersity were determined with respect to polystyrene standards by size exclusion chromatography (SEC) on a Waters 150C machine at 25 °C by eluting the PLLA solutions (10 mg/ mL in $CHCl_3$), with toluene as an internal standard, through a series of μ-Styragel columns (30 cm length) of pore sizes 10^5, 10^4, 10^3, 500 and 100 Å respectively. Chloroform was used as the mobile phase (flow rate 1 mL/ min) and a refractive index. detector (spectra series RI-150) was used for the detection of the different molecular weight fractions. The correction factor is known in the literature to be 0.58 [28].

Samples for ^{1}H NMR spectroscopy were prepared in $CDCl_3$ in 5 mm diameter NMR tubes at room temperature. 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 a Bruker DRX 500 MHz NMR spectrometer in 10 mm diameter

NMR tubes. $CDCl_3$ was used as the solvent and TMS as an internal standard for all ^{13}C NMR measurements. The relative peak areas were proportional to the number of carbon atoms. The peak areas were calculated by the deconvolution method using the WIN-NMR software. ^{119}Sn NMR was also studied for the cloisite modified initiator.

The thermal stability was analyzed using a Perkin-Elmer TGA-7, by heating the samples from 50 to 700 °C with a heating rate of 10 °C/ min under a nitrogen atmosphere and a flow rate of 50 mL/ min.

Differential scanning calorimetric (DSC) measurements were performed on a Perkin-Elmer thermal analyzer model DSC-7 in a nitrogen atmosphere. The measurements were made from -40 to 200 °C at a heating rate of 10 °C/ min and a cooling rate of 100 °C/ min. The samples were further heated from -40 to 200 °C at a heating rate of 10 °C/ min. The melting temperature(T_m) and glass transition temperature (T_g) were calculated from the second heating curves. Representative second heating curves of PLLA-5, PLLA-10 and PLLA-14 are shown in Figs. 11a-c.

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

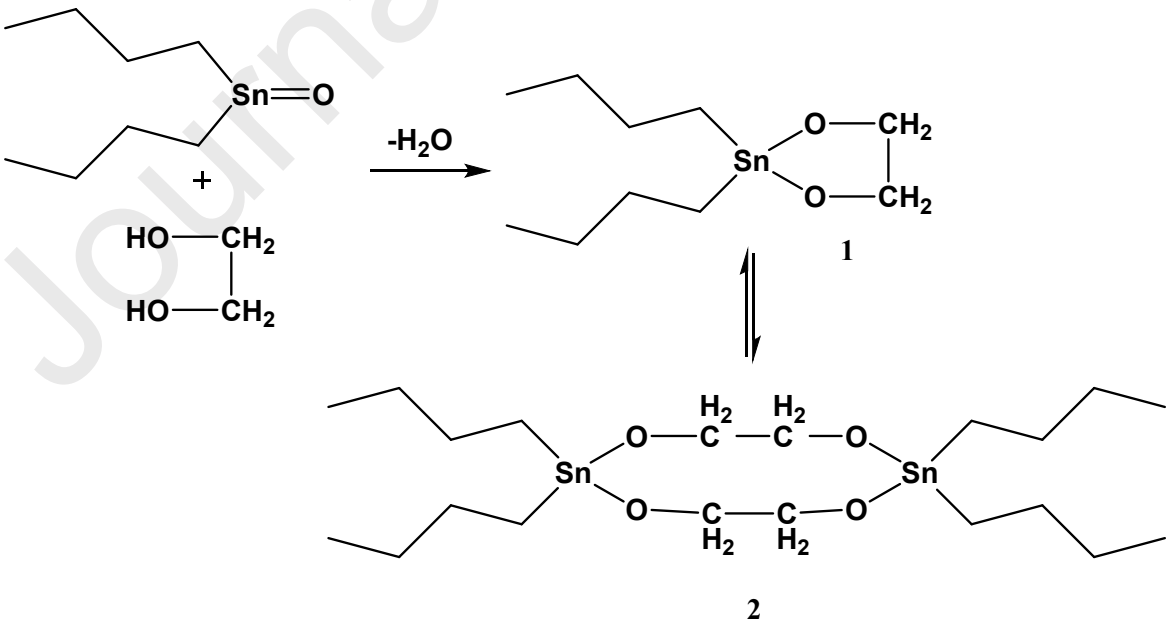
MALDI-TOF MS analysis was performed on a Kratos Kompact MALDI-IV spectrometer equipped with 0.7 m linear and 1.4 m reflection flight tubes as well as a 337 nm nitrogen LASER of pulse width 3 ns. All experiments were carried out at an accelerating potential of 20 kV. In general, mass spectra from 200 shots were accumulated to produce the final spectrum. 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 (~10^{-5} Pa).

Results and discussion

The initiators **1, 3** and **5** have been synthesized by several research groups using three different synthetic methods [12,17,29]. In the present work, all three methods were applied to synthesize these initiators. The reaction of dibutyltin oxide with ethylene glycol was found to be useful for the synthesis of initiator **1**. The product obtained from ethylene glycol and the dibutyltin derivatives is mainly the 10 membered ring dimer **2** and not the monomeric form **1**, as shown in Scheme 1. **1** was used as an initiator for the polymerization of L-LA. The structure was confirmed by ^{1}H NMR (Fig. 1). The signal appearing at δ 1.66 ppm is due to the methylene group attached to the Sn atom.

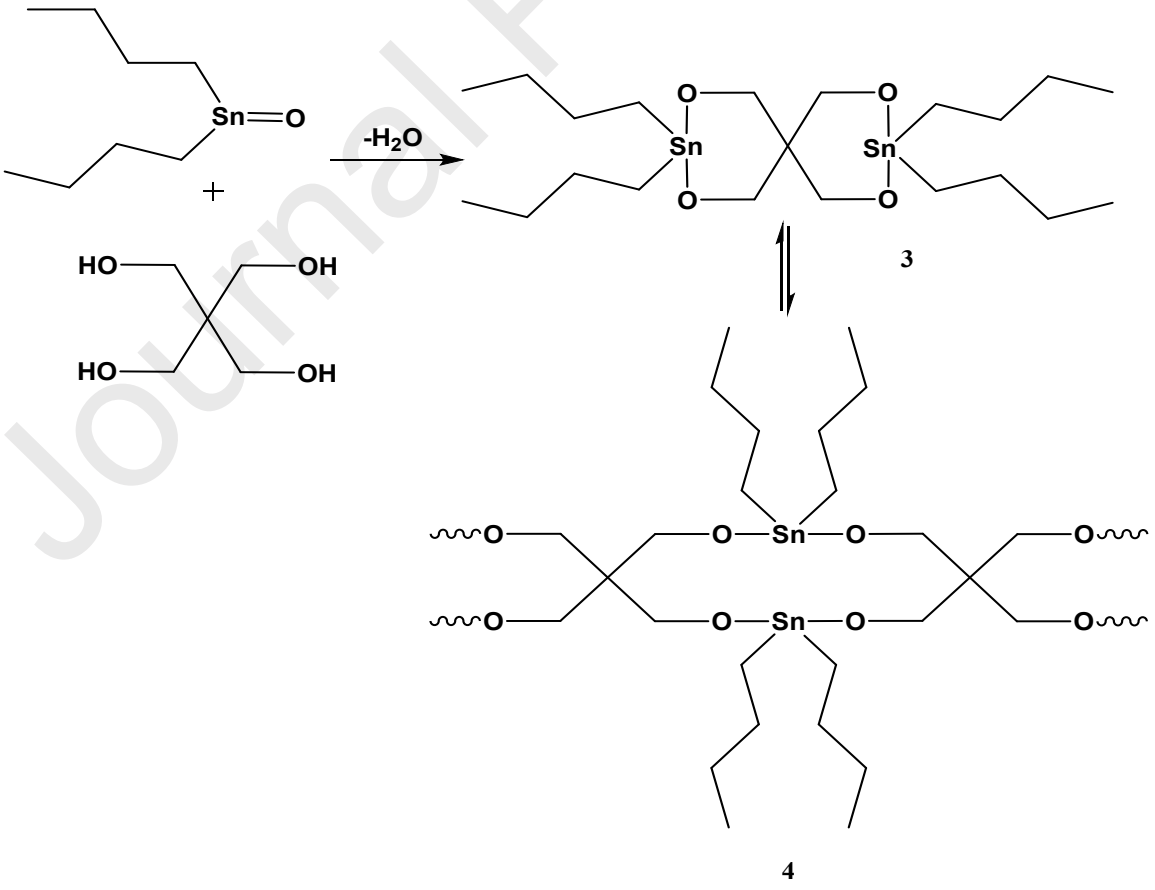
Scheme 1. Synthesis of 1,1,6,6-tetra-*n*-butyl-1,6-distanna-2,5,7,10-tetraoxacyclodecane (1/2)



The ^{119}Sn NMR spectrum in $CDCl_3$ solution exhibited two signals. The experimental results showed a sharp signal at δ -176.74 ppm (relative to internal $(CH_3)_4Sn$). The ^{119}Sn NMR measurement also suggested that the concentrated solution of initiator **1/2** in chloroform involved an association equilibria in addition to the dimerization because of the ^{119}Sn signal was unusually broad, as shown in Fig. 3a. There was no significant line broadening found in the ^{1}H NMR spectra.

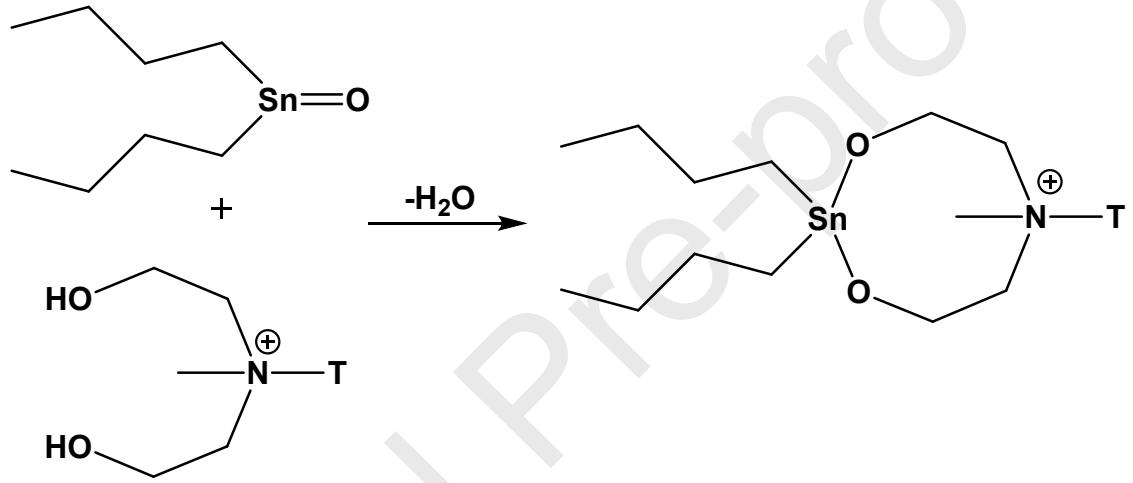
The solid spiro compound **3** was used as an initiator for polymerization of L-LA (Scheme 2). The intermediate formation of the spirocycle **4** and its structure were confirmed by ^{1}H NMR spectroscopy, as shown in Fig. 1B. A signal appeared at δ 1.67 ppm due to the methylene group attached to the Sn atom. The ^{119}Sn NMR spectrum (Fig. 3b) depicted a sharp signal at δ -172.47 ppm, which confirmed the structure of initiator **3/4**.

Scheme 2. Synthesis of spirocyclic initiator (**3/4**)



Clay plays an important role in the improvement of mechanical, thermal and barrier properties. However, the focus here is to study its catalytic activity in the ring opening polymerization of L-LA. Therefore, clay modified compound **5** was prepared by condensing cloisite 30B, where T is Tallow (65% C_{18}; 30% C_{16}; 5% C_{14}), and dibutyltin oxide in toluene as shown in Scheme 3. Initiator **5** was characterized by ^{13}C NMR CP/MAS spectroscopy and is shown in Fig. 2.

Scheme 3. Clay modified tin initiator prepared from dibutyltin oxide and Cloisite 30B (**5**)



The reaction of the cyclic tin alkoxides with 1, 3-dithion-2-one has been studied [30]. 1, 3-Dithion-2-one allows the selective removal of the dibutyltin group from the macrocycle, keeping the ring closure non-toxic, and forms the biodegradable macrocyclic ester. The cyclic tin alkoxides **1, 3** and **5** have also been mentioned in the literature.

Initiator **5** was characterized by ^{13}C NMR CP/MAS spectroscopy and is shown in Fig. 2. The peaks at δ 23.65, 25.28, 27.28 ppm are attributed to the presence of dibutyl groups attached to the tin atom. The disappearance of the peak at ~ δ 70 ppm due to a hydroxyl group and the appearance of methylene and methyl groups at δ 23.65 and 16.04 ppm, confirmed the structure of the initiator. The ^{119}Sn NMR spectrum of the modified clay initiator **5** was recorded (Fig. 3c). The high field signal at δ -176.15 ppm was attributed to

the Sn atom coordinated by two oxygen atoms and two butyl groups. The compound showed an unusually low field signal (δ -86.82 ppm) which might be attributed to the presence of anionic species coordinated with the tin atom. Thermal gravimetric analysis (TGA) was used to obtain information regarding the thermal stability and the results are depicted in Figs. 4a-c. The initiators **1**, **3** and **5** were found to be thermally stable up to ~280 °C.

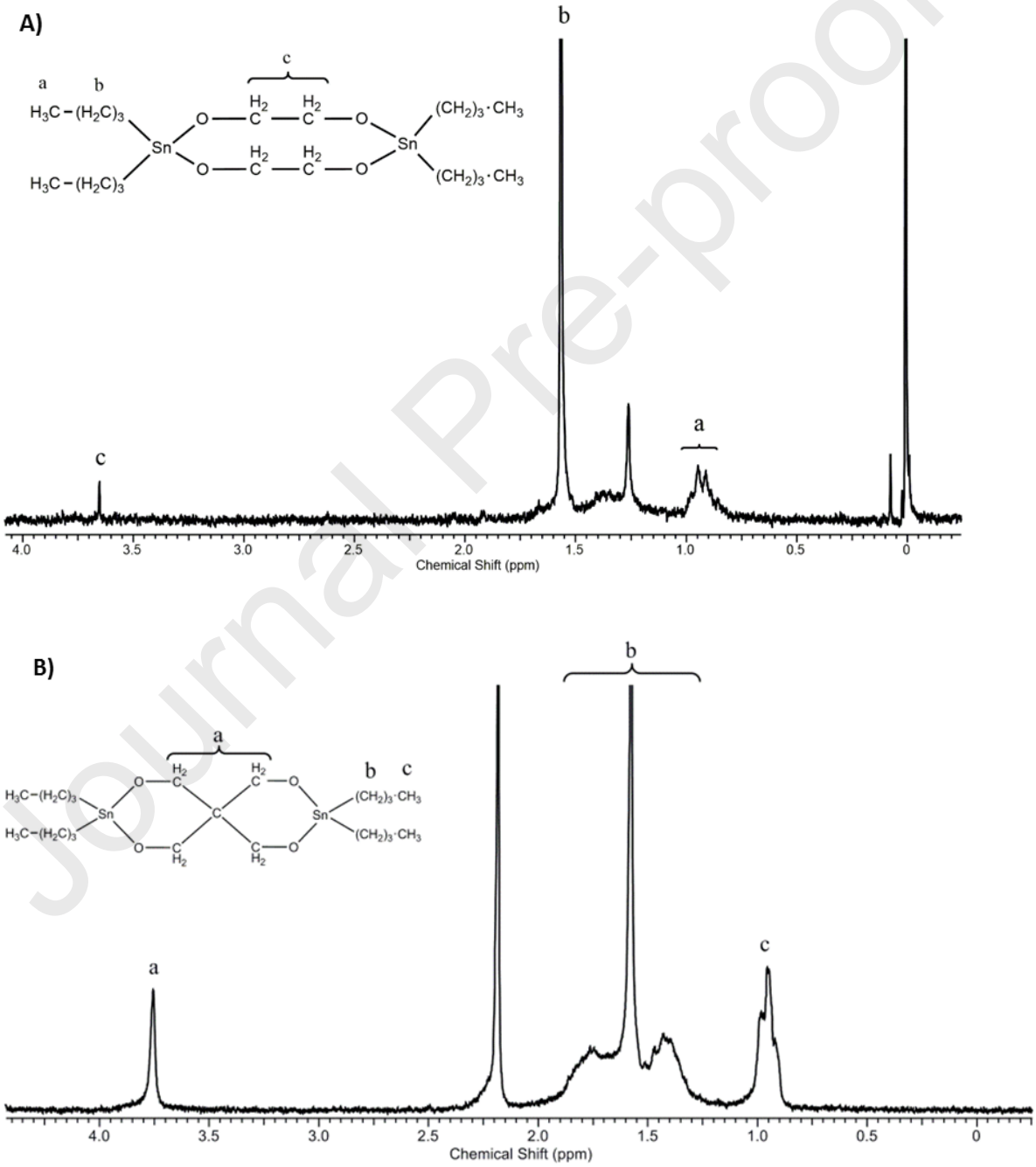


Fig. 1. ^{1}H NMR spectra of the initiators: A) **1**; B) **3**

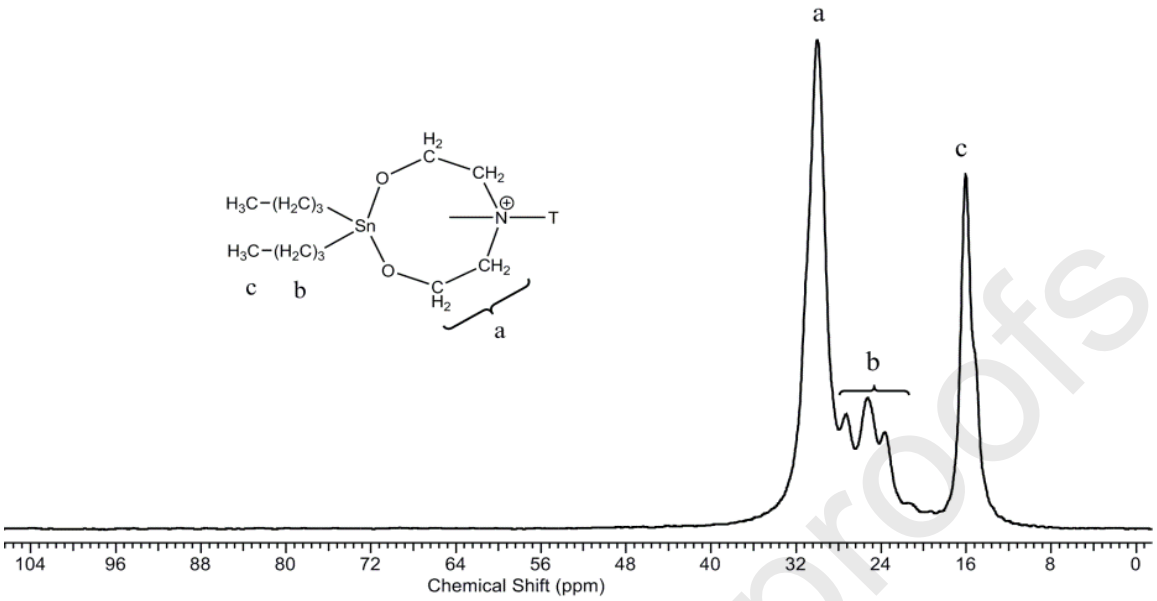
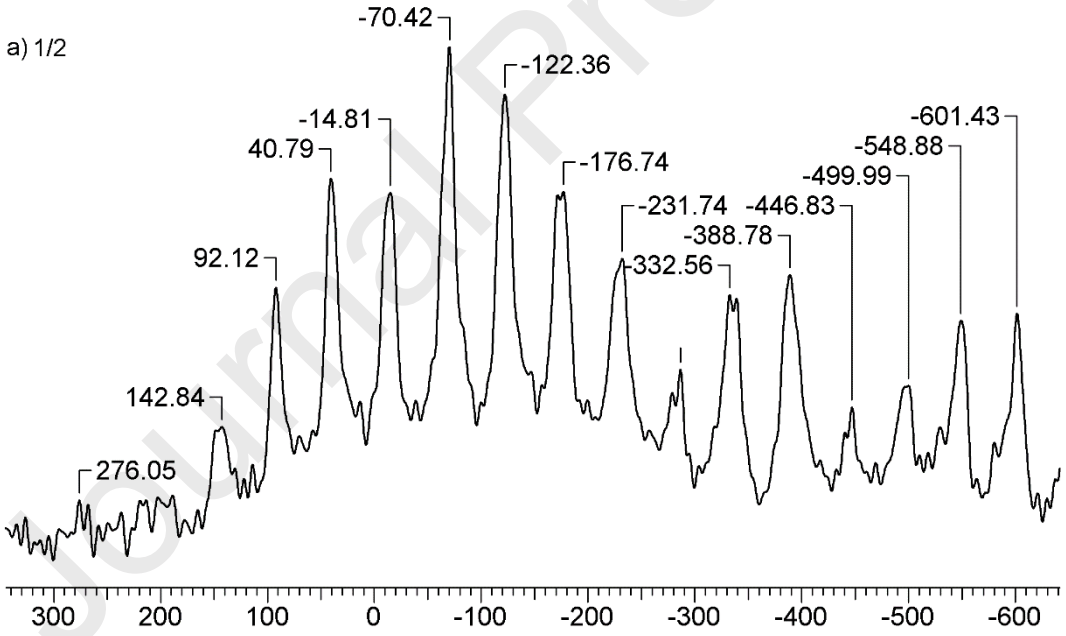


Fig. 2. ^{13}C NMR spectrum of initiator **5**



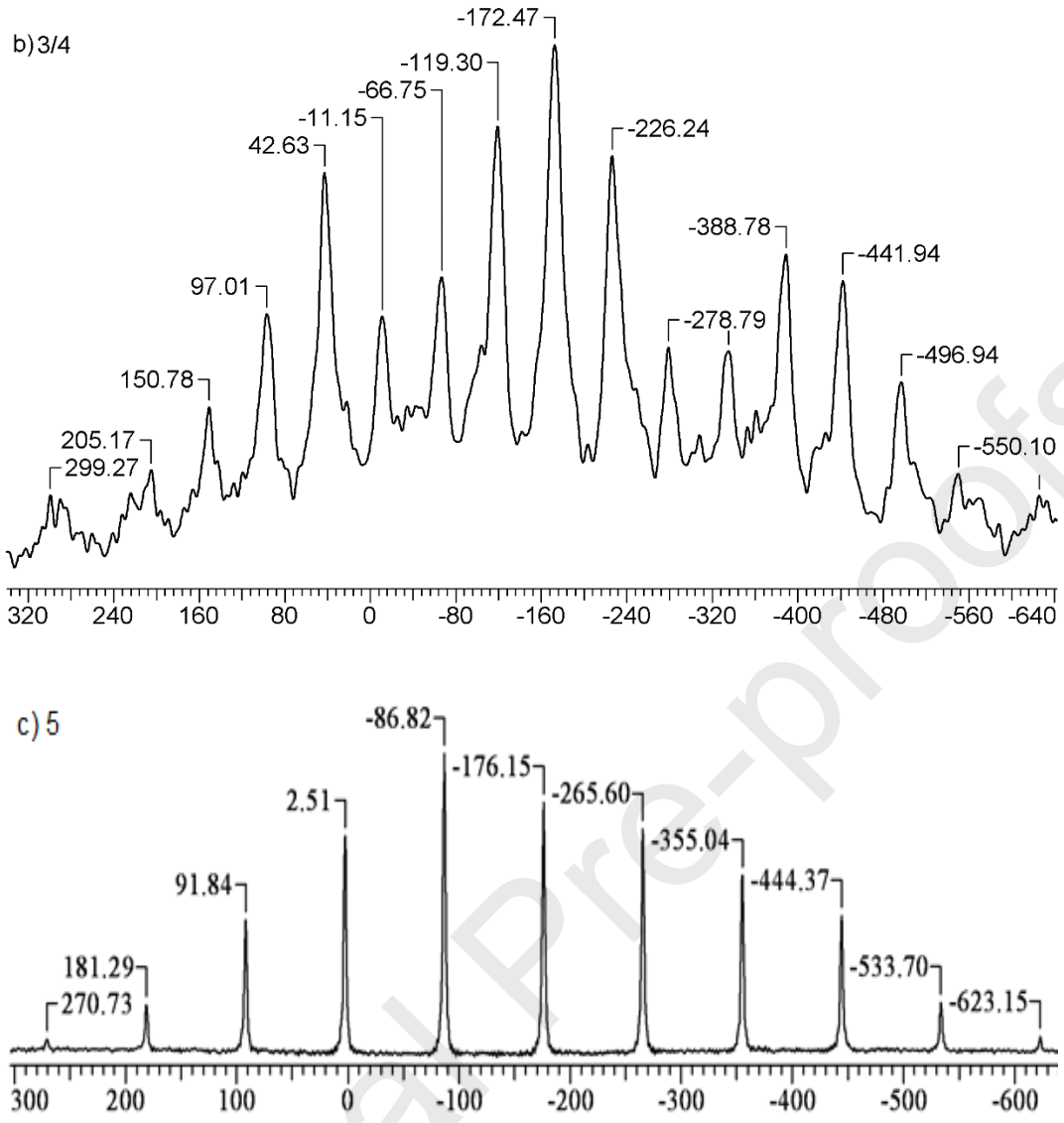
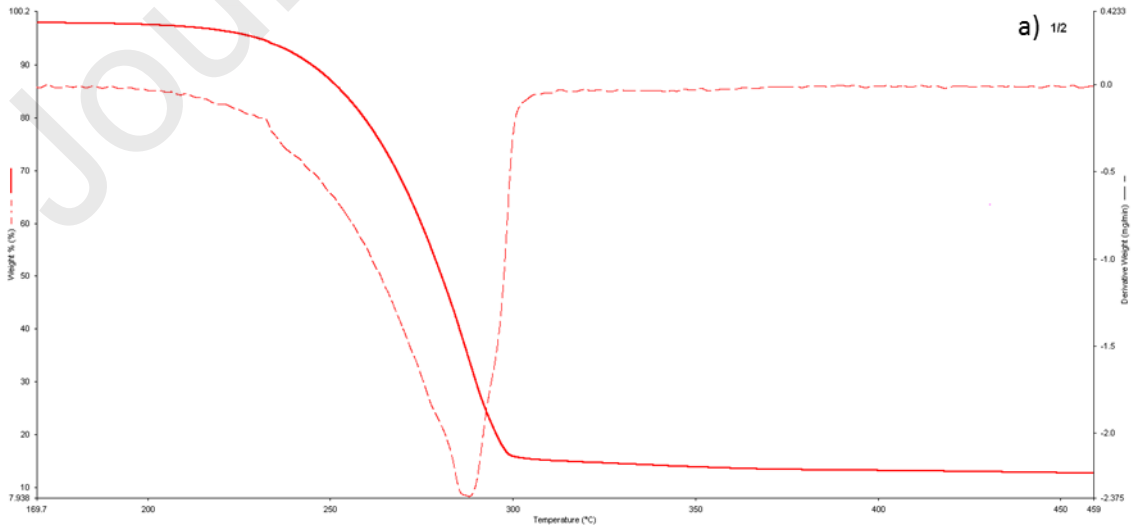


Fig. 3. ^{119}Sn NMR spectra of a) **1**; b) **3** and c) **5**



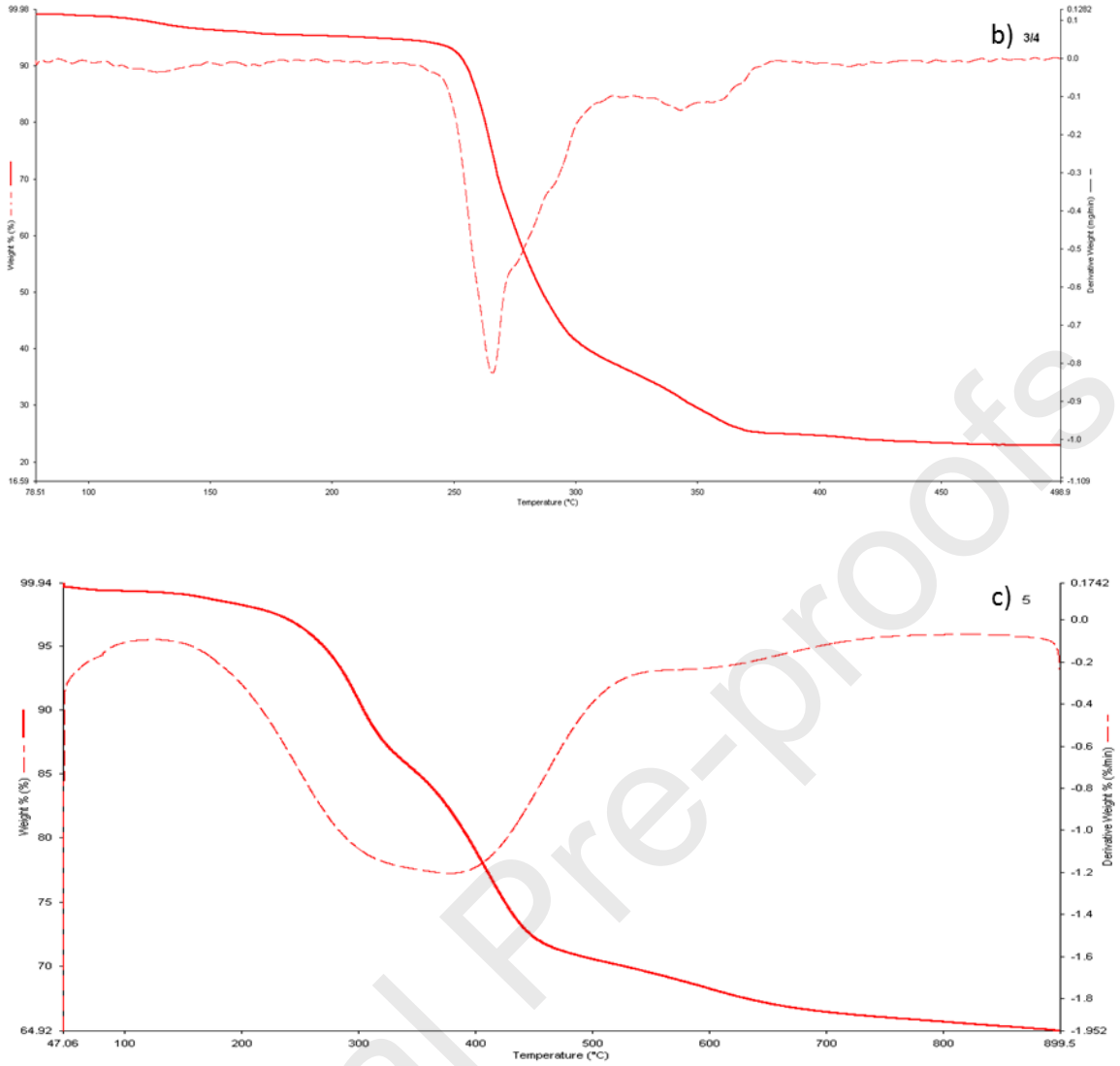


Fig. 4. TGA graphs of initiators a) **1/2**; b) **3/4**) and c) **5**.

Ring opening polymerization of L-Lactide

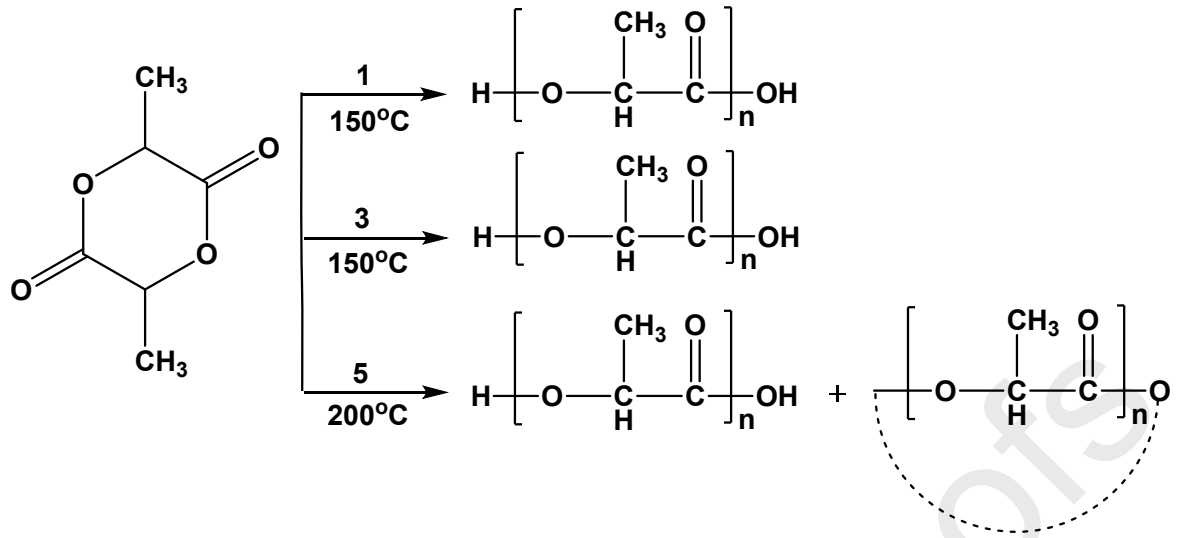
The usefulness of the synthesized three initiators was evaluated in a series of polymerizations with L-LA (Scheme 4a). The mechanism of the L-LA polymerization has been clearly described and is also presented in Scheme 4b. In the bulk polymerization, the reaction temperatures have to be above the melting point of the monomers. In our case, L-LA at just above its melting point (~98 °C), i.e. in the range 110-115 °C, has a tendency to induce crystallization in the newly prepared PLLA. This crystallization makes the remaining melt monomers insoluble in high molecular weight PLLA. This issue may lead to a

reduction of the conversion rate of the monomer; in this regard, we have carried out ROP at different temperatures, ranging from 130-180°C [31].

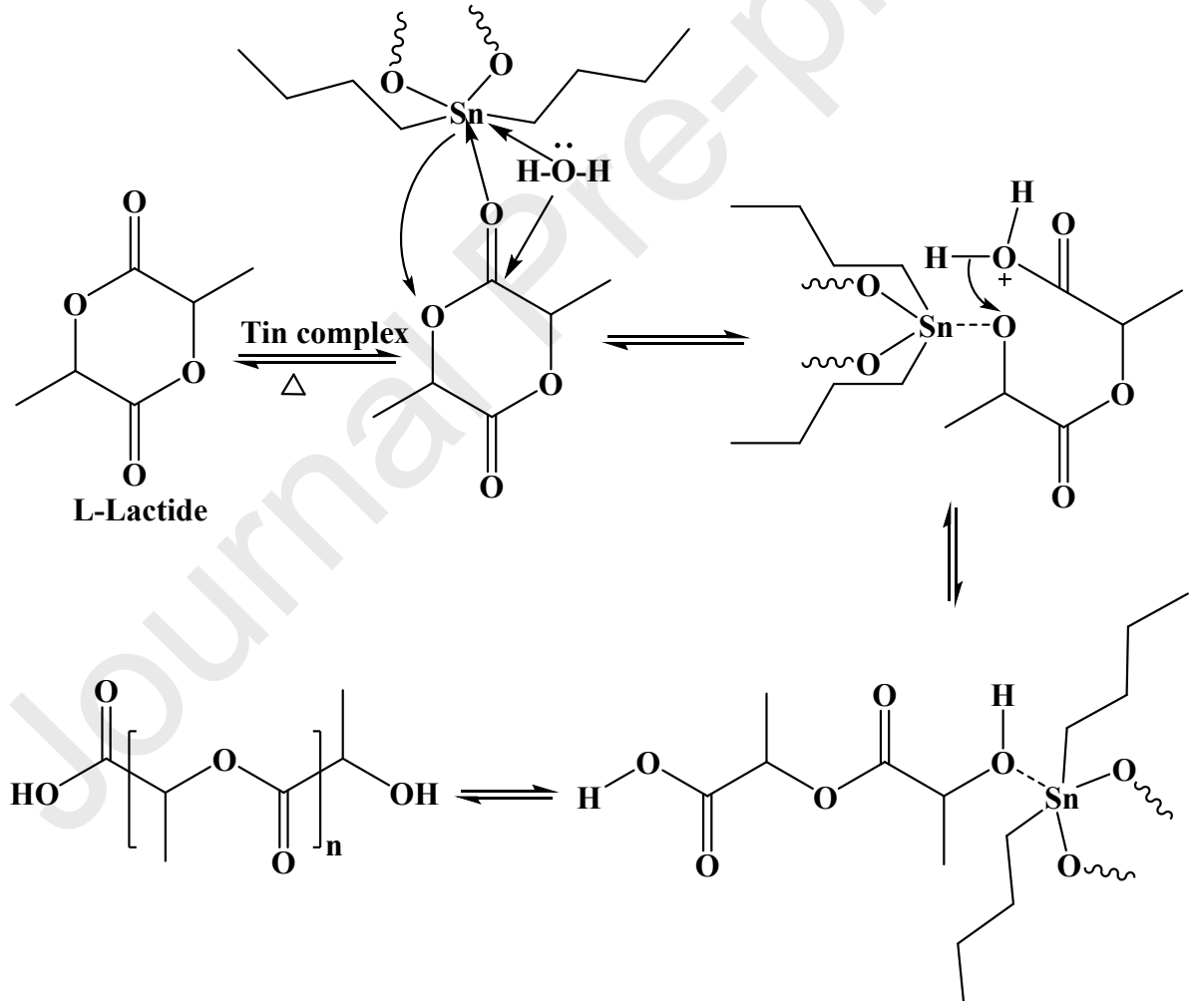
The tin initiators **1**, **3** and **5** show solubility in the monomer melt. A moderate reaction temperature was chosen to avoid all problems connected to the phase separation of the reagents and to limit the number of transesterification reactions. Due to the good solubility of the initiators at the polymerization temperatures, reproducible results have been observed for three consecutive reactions. The molecular distribution of PLLA also supports the strong ability of these initiators [32].

The reaction pathway for the formation of PLLA was enabled by the tin initiators **1**, **3** and **5**. The proposed mechanism is shown in Scheme 4b, where L-LA is coordinated with the initiator via a nucleophilic attack of the hydroxyl group of a trace amount of water present in the system, leading to the insertion of L-LA into the metal-oxygen bond by rearrangement of the electrons [33, 34]. It is assumed that the trace amount of water plays the role of a co-initiator in combination with the normal coordination insertion mechanism, allowing the essential interpretation of all the experimental observations. The prepared PLLA retains its stereochemistry [33]. Further, these initiators in the ROP of L-LA were used in order to gain insight into the kinetics of the reaction and the influence of the initiator structure and polymerization conditions on the initiator activity and polymer properties.

Scheme 4a. Polymerization of L-lactide with cyclic Bu_2Sn initiators derived from ethylene glycol, pentaerythritol and Cloisite 30B



Scheme 4b. Proposed reaction mechanism for PLLA using a tin complex



Kinetics of the L-LA polymerization reactions

The kinetics of the L-LA polymerization reactions were investigated for initiators **1**, **3** and **5** by monitoring the reactions using ^{1}H NMR spectroscopy. The percentage of conversions from L-LA to PLLA was determined by comparing the intensity of the PLLA peak at δ 5.16 ppm to that of the L-LA monomer at δ 5.0 ppm.

The polymerizations were conducted for various times to reach a plateau value in the conversion ratio curve, as shown in Fig. 5. The maximum conversion was obtained after 1h for all three initiators and therefore the reaction time of 1h was kept constant. From the conversion curve, it was established that the initiation was instantaneous.

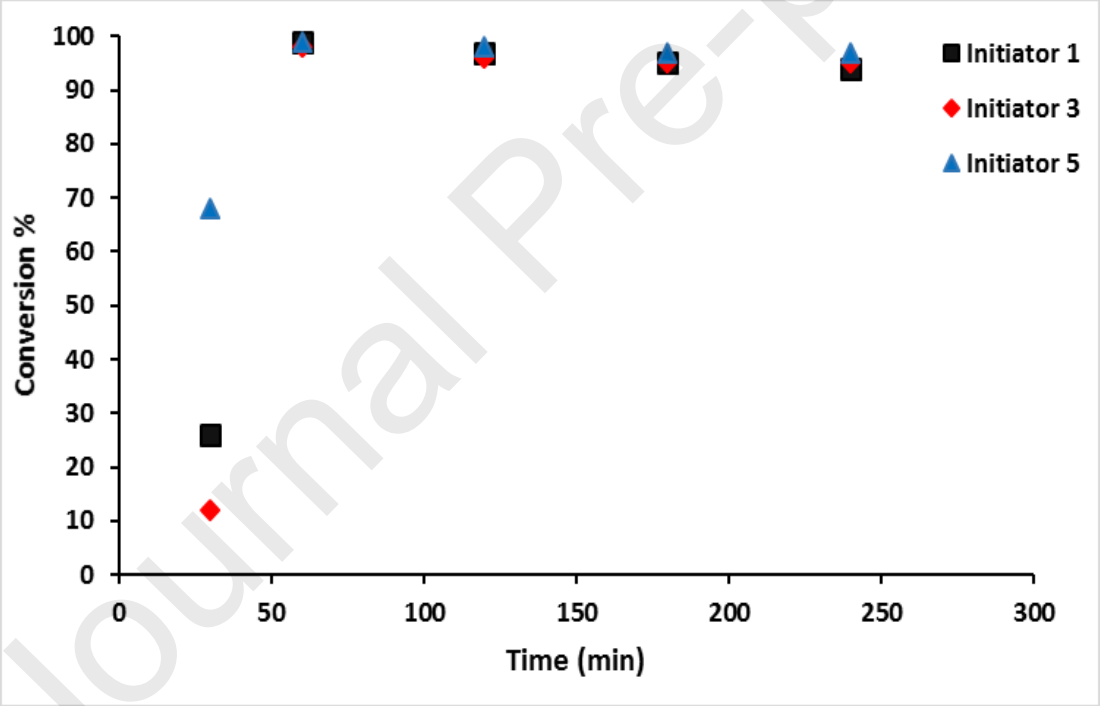


Fig. 5. Conversion of L-LA as a function of reaction time, for polymerizations initiated with the initiators **1**, **3** and **5**.

The effects of the polymerization temperature on the ROP of L-LA using initiators **1**, **3** and **5** are shown in Tables 1, 2 and 3. All polymerizations were initiated with cyclic initiators (**1**,

3 and **5**) and conducted in bulk because all attempts to initiate the polymerization of L-LA below 130 °C resulted in oligomers. Initiators **1** and **3** are reactive enough to catalyze quantitative polymerizations of L-LA in bulk. With relatively short times and low temperatures, a kinetically controlled polymerization takes place.

The effect of temperature on the polymerization kinetics of L-LA was examined for initiators **1** and **3** by comparing the activity over the temperature range 130-150 °C. In presence of initiator **1,** the [M]/ [I] ratio was 500 and conversion ≥ 90%. Initiator **3** showed a similar trend where the [M]/ [I] ratio was 550 and conversion ≥ 85%. In both cases, the molecular weights (M_n and M_w) increased up to 150 °C [31]. Initiator **5** decomposes at approximately 250 °C, therefore polymerization was possible up to 220 °C. The polymerization temperatures were varied from 140 to 220 °C, where the [M]/ [I] ratio was 350 and conversion ≥ 90%.

Table 1. Effect of polymerization temperatures on the ROP of L-LA using initiator **1**

Polymer No.	**Temp. (°C)**	**Conversion[a)] (%)**	**M_n[b)]**	**$M_n$cald.[c)]**	**M_n[d)]**	**PDI**	**T_g (°C)**	**T_m[e)] (°C)**
1	130	86	61920	26332	45400	1.17	49	161
2	135	89	64080	27086	46700	1.20	50	163
3	140	90	64800	27724	47800	1.21	50	167
4	145	92	66240	28130	48500	1.20	54	166
5	150	93	66960	28420	49000	1.23	58	172

L-LA Polymerization run in bulk for 1h and [M]/ [I] = 500; [a)] Conversion determined from ^{1}H NMR spectra of the product [b)] Calculated from the molecular weight of L-LA x [M]/ [I] x conversion; [c)] The calibration value of M_n calculated according to formula $M_n = 0.58M_n$(GPC); [d)] Obtained from GPC analysis and calibrated against polystyrene standard; [e)] T_m calculated from DSC.

Table 2. Effect of polymerization temperatures on the ROP of L-LA using initiator **3**

Polymer No.	Temp. (°C)	Conversion[a)] (%)	M_n[b)]	$M_n$cald.[c)]	M_n[d)]	PDI	T_g (°C)	T_m[e)] (°C)
6	130	84	66528	26738	46100	1.21	46	162
7	135	86	68112	27956	48200	1.21	47	162
8	140	86	68112	29638	51100	1.21	50	164
9	145	89	70488	31494	54300	1.20	56	163
10	150	90	71280	33060	57000	1.21	60	175

L-LA Polymerization run in bulk for 1h and [M]/ [I] = 550; [a)] Conversion determined from ^{1}H NMR spectra of the product; [b)] Calculated from the molecular weight of L-LA x [M]/ [I] x conversion; [c)] The calibration value of M_n calculated according to formula $M_n = 0.58M_n$(GPC); [d)] Obtained from GPC analysis and calibrated against polystyrene standard; [e)] T_m calculated from DSC.

Table 3. Effect of polymerization temperatures on the ROP of L-LA using initiator **5**

Polymer No.	Temp. (°C)	Conversion[a)] (%)	M_n[b)]	$M_n$cald.[c)]	M_n[d)]	PDI	T_g (°C)	T_m[e)] (°C)
11	140	50	25200	12992	22400	1.13	49	167
12	150	57	28728	19952	34400	1.14	55	178
13	180	74	37296	22098	38100	1.16	54	169
14	200	99	49896	26448	45600	1.20	54	172
15	220	99	49896	30740	53000	1.22	60	162

L-LA Polymerization run in bulk for 1h and [M]/ [I] = 350; [a)] Conversion determined from ^{1}H NMR spectra of the product; [b)] Calculated from the molecular weight of L-LA x [M]/ [I] x conversion; [c)] The calibration value

of M_n calculated according to formula $M_n = 0.58M_n(GPC)$; [d] Obtained from GPC analysis and calibrated against polystyrene standard; [e] T_m calculated from DSC.

The value of M_n and M_w monotonously increases with a rise in temperature. At lower temperatures, a large number of very low-molecular-weight oligomeric species predominate. An increase in the temperature beyond 180 °C resulted in high molecular-weight species [35]. A similar observation has been made for PLA macrocycles containing tin atoms in their chains. The maximum M_n and M_w were obtained at 220 °C as 53,000 and 100,000 Da respectively. However, the M_w/M_n value is also increased. This is presumably due to the presence of macrocycles. The reaction temperature was selected as 200 °C on the basis of the low molecular weight distribution and a higher melting temperature.

Ring-opening polymerization of L-LA was carried out using initiators **1** and **3** at 150 ^oC and **5** at 200 ^oC. The reaction time was varied from 0 to 60 minutes. The first series of polymerizations were conducted with L-LA and initiator **1**. The results are compiled in Tables 1, 4 and 6. These polymerization reactions are rapid and yield more than 90% within an hour. There is no indication of backbiting degradation with longer reaction times. The molecular weights, M_n increase with the M/I ratio, but do not parallel the [M]/ [I] ratio.

The kinetics of the L-LA polymerization reactions was compared to earlier literature results. The reaction conditions and the results are summarized in Tables 1 and 2. For initiators **1**, **3** and **5**, the monomer-to-initiator ratio [M]/ [I] was varied from 100/1 and 800/1. The linearity showed that no termination occurred during the polymerization, i.e. the number of propagating chains was constant throughout the reaction, and that the initiation was fast [36].

The polymerization proceeded easily, and high monomer conversions were achieved under the conditions used, as illustrated in Tables 4-7. Mild reaction conditions resulted in good control of the molecular weights and molecular weight distribution of the polymer chains.

Table 4. Ring-opening polymerization of L-LA in bulk with initiator **1** at 140 °C[a)]

Polymer no.	[M]/[I][b)]	Conversion[c)] (%)	M_n[d)]	$M_n$cald.[e)]	M_n[f)]	PDI	T_g (°C)	T_m (°C)
16	100	97	13968	8990	15500	1.10	47	161
17	200	96	27648	16298	28100	1.16	51	163
18	400	98	56448	28942	49900	1.16	53	171
19	800	94	108288	57536	99200	1.17	60	172

[a)] The reaction was conducted for 1h at 140 °C; [b)] Molar feed ratio M=L-LA, I=1; [c)] Conversion determined from ^{1}H NMR spectra of the product; [d)] Calculated from the molecular weight of L-LA x [M]/ [I] x conversion; [e)] The calibration value of M_n calculated according to formula $M_n = 0.58M_n$(GPC); [f)] Obtained from GPC analysis and calibrated against polystyrene standard.

Table 5. Ring-opening polymerization of L-LA in bulk with initiator **3** at 140 °C [a)]

Polymer no.	[M]/[I][b)]	Conversion[c)] (%)	M_n[d)]	$M_n$cald.[e)]	M_n[f)]	PDI	T_g (°C)	T_m (°C)
20	100	97	13968	17864	30800	1.10	59	163
21	200	93	26784	21692	37400	1.11	55	164
22	400	97	55872	29174	50300	1.14	56	165
23	800	96	110592	48894	84300	1.13	56	172

[a)] The reaction was conducted for 1h at 140 °C; [b)] Molar feed ratio M=L-LA, I=1; [c)] Conversion determined from ^{1}H NMR spectra of the product; [d)] Calculated from the molecular weight of L-LA x [M]/ [I] x

conversion; [e] The calibration value of M_n calculated according to formula $M_n = 0.58M_n(GPC)$; [f] Obtained from GPC analysis and calibrated against polystyrene standard

Table 6. Ring-opening polymerization of L-LA in bulk with initiator **1** at 150 °C[a]

Polymer no.	[M]/[I][b]	Conversion[c] (%)	M_n[d]	$M_n$cald.[e]	M_n[f]	PDI	T_g (°C)	T_m (°C)
24	100	98	14112	6612	11400	1.14	49	152
25	200	95	27360	11136	19200	1.23	50	161
26	400	94	54144	21286	36700	1.22	52	163
27	800	93	107136	40426	69700	1.19	60	168

[a] The reaction was conducted for 1h at 150 °C; [b] Molar feed ratio M=L-LA, I=1; [c] Conversion determined from ^{1}H NMR spectra spectrum of the product; [d] Calculated from the molecular weight of L-LA x [M]/ [I] x conversion; [e] The calibration value of M_n calculated according to formula $M_n = 0.58M_n(GPC)$; [f] Obtained from GPC analysis and calibrated against polystyrene standard.

Table 7. Ring-Opening Polymerization of L-LA in bulk with initiator **3** at 150 °C [a]

Polymer no.	[M]/[I][b]	Conversion[c] (%)	M_n[f]	$M_n$cald.[e]	M_n[d]	PDI	T_g (°C)	T_m (°C)
28	100	97	13968	12876	22200	1.08	51	147
29	200	97	27936	18212	31400	1.12	53	156
30	400	94	54144	26622	45900	1.15	54	157
31	800	96	110592	47038	81100	1.14	61	158

[a] The reaction was conducted for 1h at 150 °C; [b] Molar feed ratio M=L-LA, I=3; [c] conversion from ^{1}H NMR of the product; [d] Calculated from the molecular weight of L-LA x [M]/ [I] x conversion; [e] The calibration

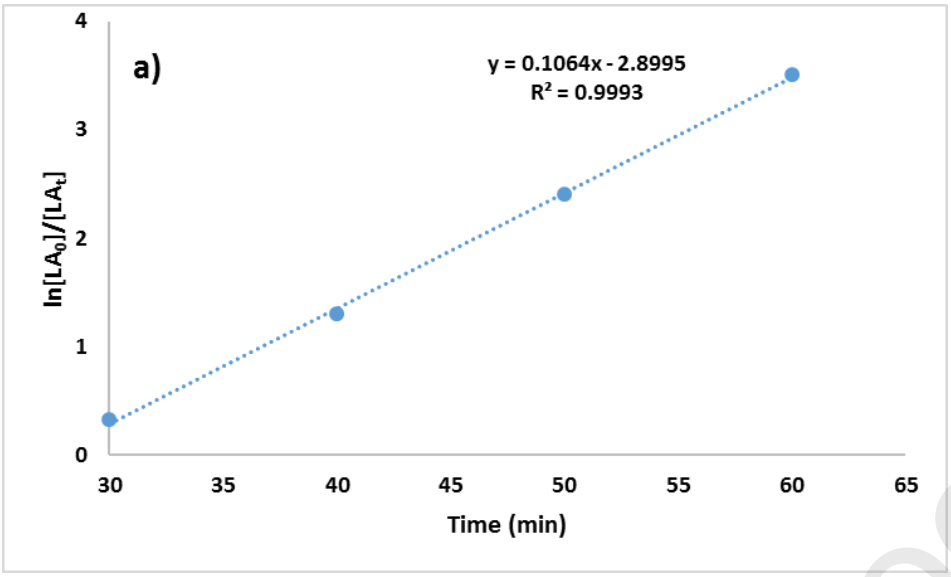
value of M_n calculated according to formula $M_n = 0.58M_n(GPC)$; [f] Obtained from GPC analysis and calibrated against polystyrene standard.

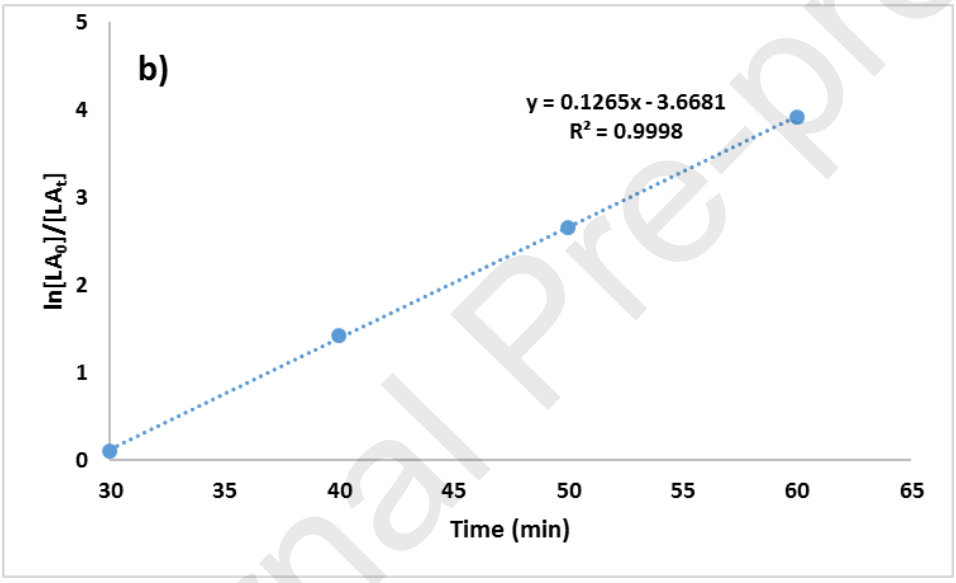
The kinetics of the L-LA polymerization reaction for all three initiators proceeded according to simple pseudo first order kinetics, as shown in equation 1.

$d[LA]/dt=k[LA]$……eq. 1

where $k = k_p [I]^x$, k_p = rate of chain propagation, I = initiator and x = order of reaction. The plot shows a linear relationship with pseudo first-order kinetics with respect to L-LA for all the initiators.

The plots of $\ln[LA_0]/ [LA_t]$ versus the reaction time for the polymerization reaction using the three different initiators **1**, **3** and **5** are shown in Figs. 6a-c, where $[LA_0]$ is the initial monomer concentration and $[LA_t]$ is the monomer concentration at reaction time t. The plot shows straight lines, at least up to 97 % monomer conversion in all three cases. However, the polymerization temperature in the case of initiators **1** and **3** was 150 °C, whereas the polymerization temperature of initiator **5** was 200 °C. These results show that the polymerizations are first order reactions with respect to the monomer, when initiated at 150 (**1** and **3**) and 200 °C (**5**). The negative intercept with the x-axis may be due to initiation by a trace amount of moisture present in L-LA (Fig. 2c). A similar negative intercept with the x-axis has been observed in the ring opening polymerization of L-LA in the presence of N.O Guanidine Catalysts [37,38].The rate constants for initiators **1**, **3** and **5** were obtained from Fig. 6 as 0.106, 0.126 and 0.113 min, respectively. The higher activity observed for **3** is consistent with a literature report [35].





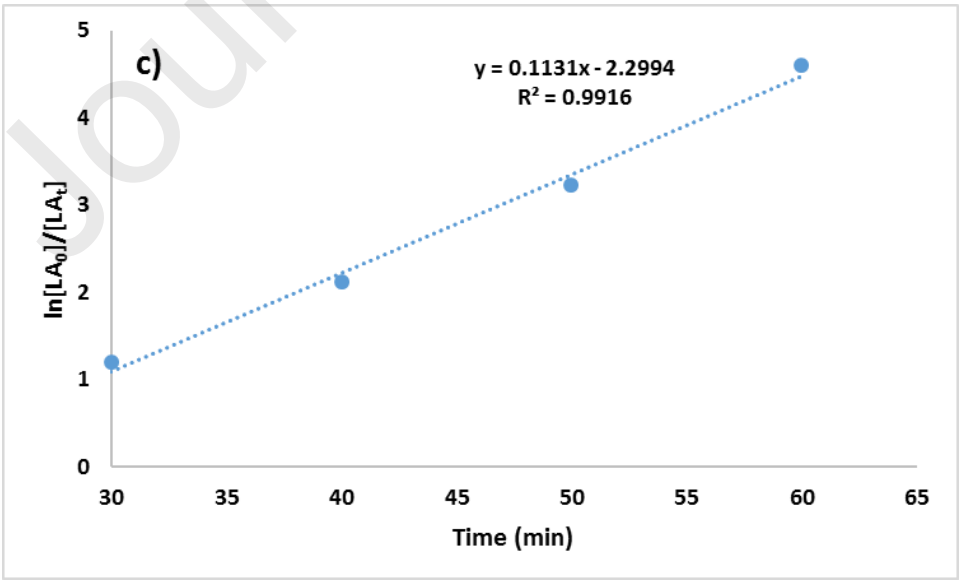
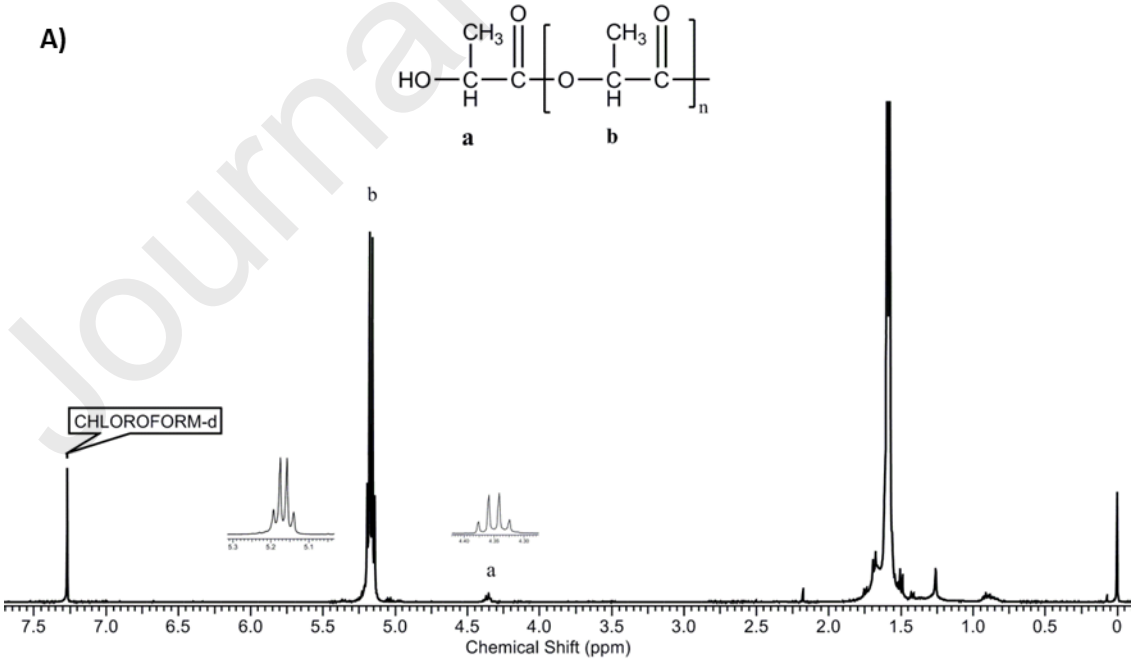


Fig. 6. Semi-logarithmic plots of L-LA monomer with various initiators: a) **1**; b) **3**; c) **5**.

The PLLA molecular weight depends on the monomer-to-initiator ratio. With monomer-to-initiator ratios from 100 to 800, the conversions were high and a low molecular weight distribution (MWD) was observed in all polymerizations.

Nuclear magnetic resonance

The polymers were characterized using ^{1}H NMR spectroscopy. Representative ^{1}H NMR spectra of PLLA-2, PLLA-7 and PLLA-14, prepared using initiators **1**, **3** and **5**, are shown in Figs. 7A-C. The methine and methyl peaks of PLLA appear at δ 5.16 and 1.56 ppm in all cases, as reported for linear PLLA [2]. The end group is assigned to the –CHOH group, which appears at δ 4.30 ppm in all cases. The peaks at δ 1.6 (doublet) and 5.0 ppm (quartet) are due to the methyl and methine groups of L-LA which appear because of incomplete conversion of L-LA to PLLA (PLLA-2 and PLLA-7). However, these peaks are absent in the case of PLLA-14, indicating the complete conversion of L-LA to PLLA.



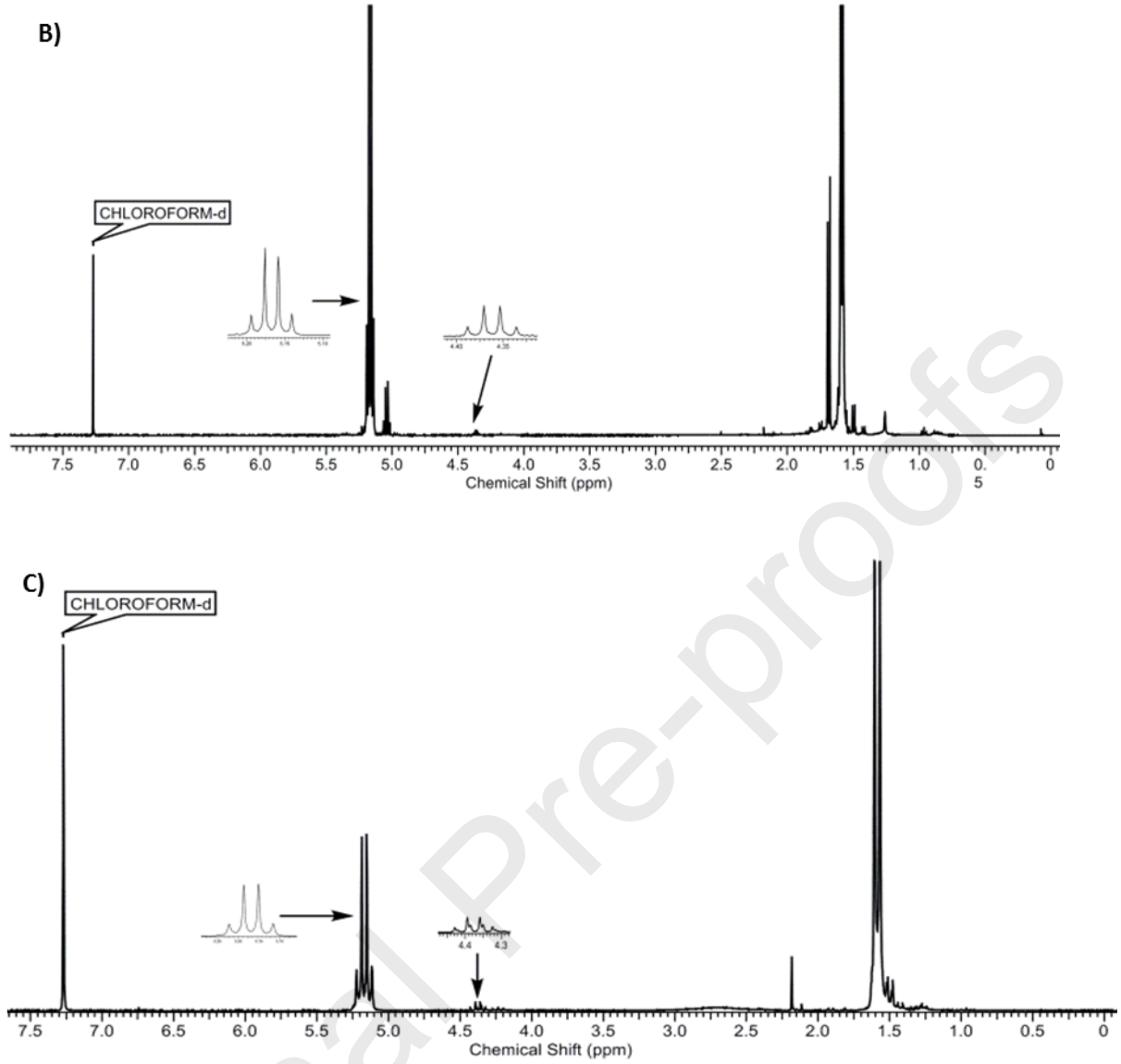


Fig. 7. ^{1}H NMR spectra of A) PLLA-2; B) PLLA-7; C) PLLA-14

Size exclusion chromatography

Size exclusion chromatography was used to analyze all these polymers and commercial narrow polystyrene standards were used for calibration. Representative elugrams of PLLA in the presence of initiators **1**, **3** and **5** are shown in Figs. 8a-c. The results are presented in Tables 1-4. The number-average molecular weight M_n, obtained from the SEC measurements, is plotted versus the [M]/ [I] ratio for the L-LA polymerizations initiated by **1** and **3**. The molar masses with initiator **3** in Fig. 4 show a strong deviation because the Sn-

O bonds are less stable and might not have undergone a clean stoichiometric insertion into the cyclic tin initiator **3**. Relatively narrow PDI values were reported and supported better control of the ROP reactions. A possible explanation could be rapid chain transfers of the growing polymer chains at the expense of chain propagation. Similar results have been reported for bridged bis(amidinate) ytterbium alkoxide systems employed in the ROP of ε-CL and LA [36, 37]. There is a linear relationship over the entire range of [M]/ [I] ratios and the M_n value is proportional to the [M]/ [I] ratio at 140 °C, as shown in Fig. 9. These results confirm that the M_n value of PLLA can be controlled by adjusting the [M]/ [I] ratio in the polymerization of L-LA. There is also a linear relationship over the entire range of [M]/ [I] ratios and the M_n value is proportional to the [M]/ [I] ratio at 150 °C initiated by initiators **1** and **3** (Fig. 10). The M_n value of the PLLA obtained at 150 °C was controlled by adjusting the [M]/ [I] ratio in the polymerizations of L-LA initiated with **1** and **3**.

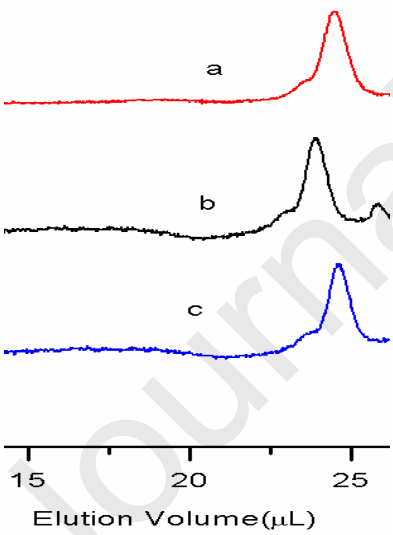


Fig. 8. Representative SEC elugrams of PLLA: a) prepared using initiator **1**; b) prepared using initiator **3** and c) prepared using initiator **5**.

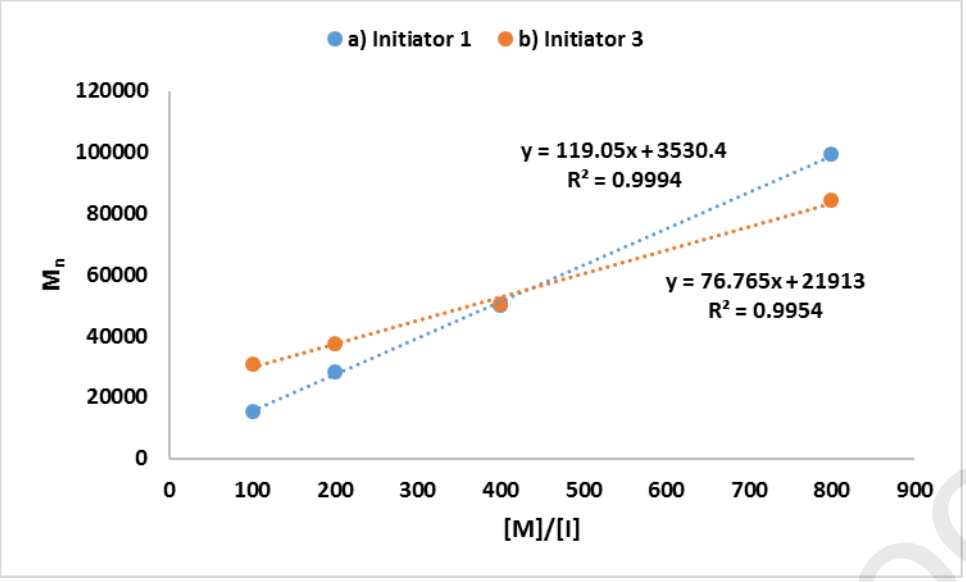


Fig. 9. [M]/ [I] versus M_n graph at 140 °C a) initiator **1**; b) initiator **3**

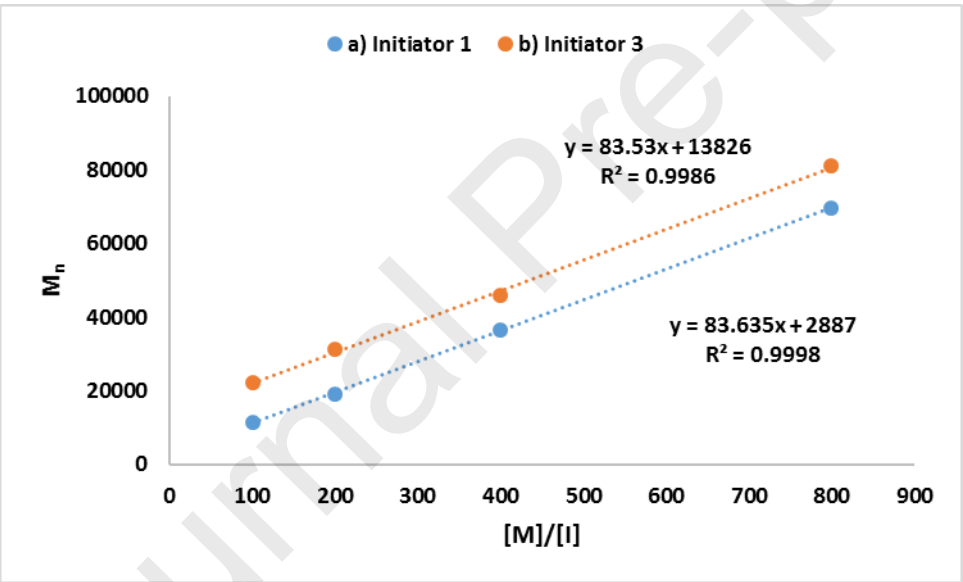


Fig. 10. [M]/ [I] versus M_n graph at 150 °C a) initiator **1**; b) initiator **3**

Thermal characterization

The results of the thermal characterization are shown in Tables 1-7. T_g varies from 46 to 60 °C for the polymers prepared with initiators **1**, **3** and **5** at various temperatures (Tables 1-3). The maximum melting temperature (T_m) of PLLA-5 (red curve) prepared at 150 °C with

initiator **1** is 172.50 °C. Similarly, the maximum melting temperatures (T_m) of PLLA-10 (green curve) and PLLA-14 (blue curve) are 175.81 and 172.02 °C, respectively, as shown in Fig. 11.

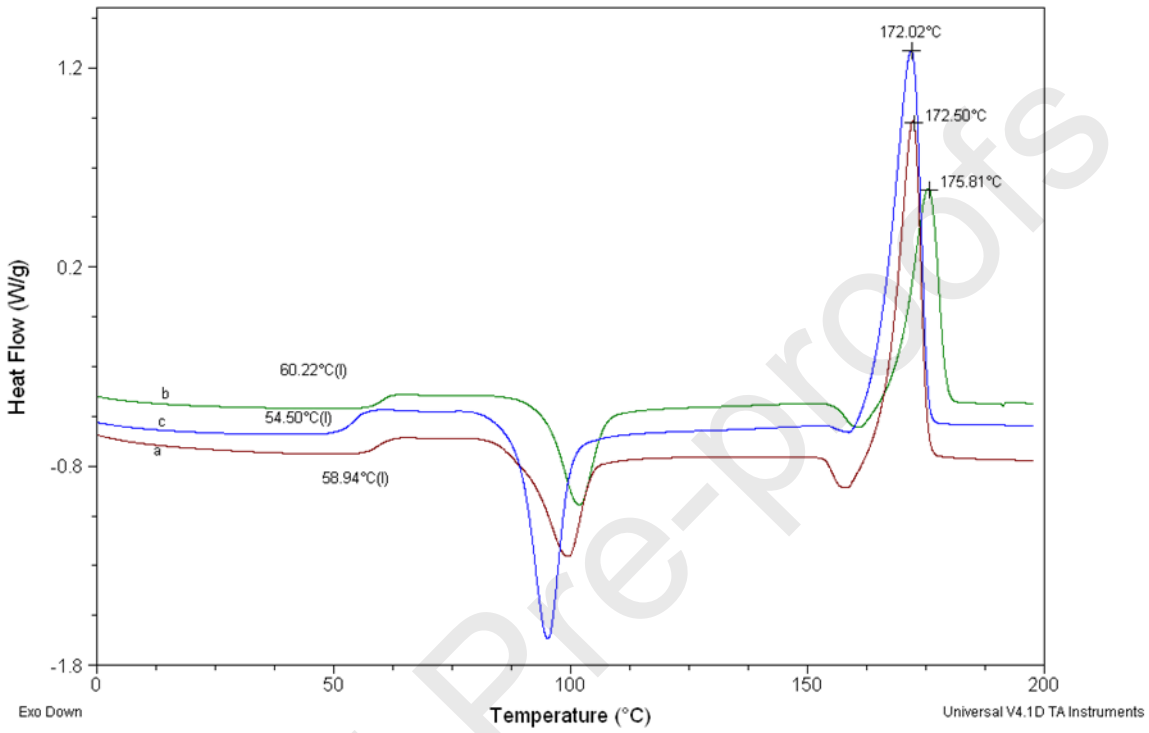


Fig. 11. Differential scanning calorimetry graphs of: a) PLLA-5; b) PLLA-10; c) PLLA-14

X-ray powder diffraction

The degree of crystallinity was calculated from a powder XRD pattern, as shown in Fig. 12. Typically, the degree of crystallinity was between 80 and 85%. The observation can be attributed to racemization of L-LA to D-LA and its incorporation into the polymer chain. The percentage of crystallinity as determined by DSC was lower than that determined by XRD [35,41]. A similar observation was reported for PLLA prepared by ring-opening polymerization in the presence of tin initiators [35]. The samples PLLA-5 (blue curve), PLLA-10 (black curve) and PLLA-14 (red curve) shows some diffraction peaks at 2θ values of 12.5, 15.2, 19.9 and 23.3°.

The two dominant diffraction peaks at 15.2 and 19.9° are attributed to 110/200 and 203 reflections and small diffraction peaks at 12.5 and 23.3° have been assigned to the reflection of the 010 and 016 planes [42, 43].

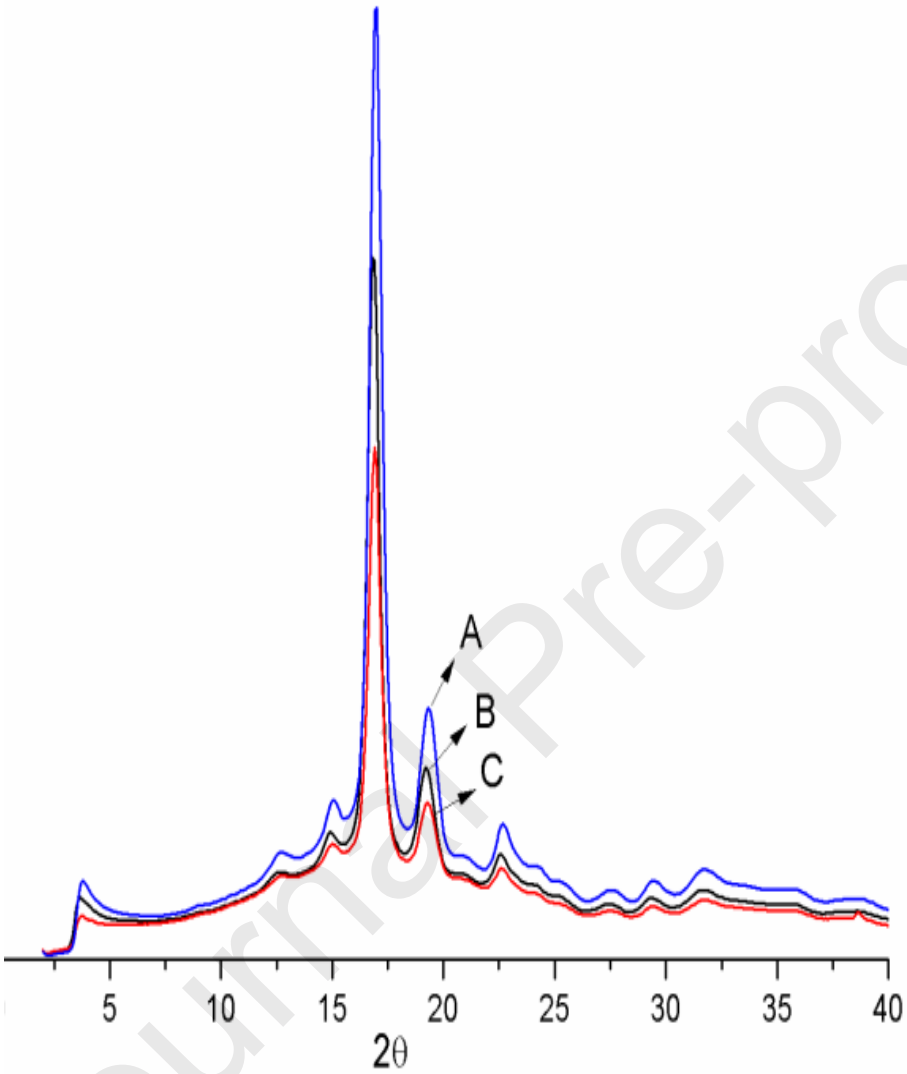


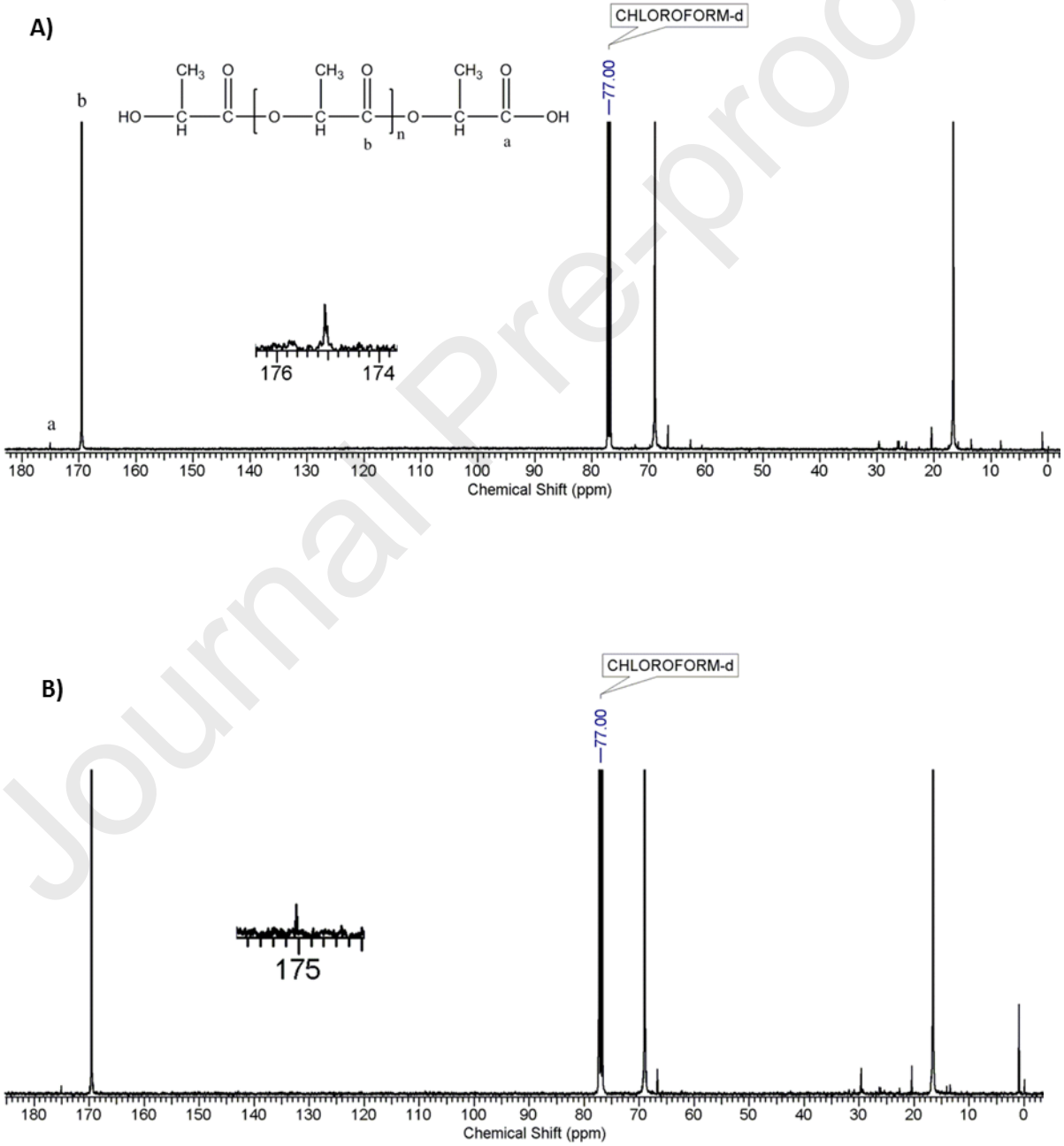
Fig. 12. XRD curves of: A) PLLA-5; B) PLLA-10; C) PLLA-14.

End-group analysis by ^{13}C NMR spectroscopy

^{13}C NMR spectroscopy is a useful tool for determining M_n. Besides end-group determination, this technique has also been used for the determination of residual L-LA, the lactic acid formed by unzipping of chain ends and the optical purity of the PLLA polymer.

However, in this case, the method proved to be inadequate because the DP of PLLA was in a higher range.

In this study, the NMR technique was used to determine the effect of initiators on the end groups and to estimate the amount of L-LA in the PLLA samples. The ^{13}C NMR spectra corresponding to PLLA-2, PLLA-7 and PLLA-14, from initiators **1**, **3** and **5**, are shown in Fig. 13A-C.



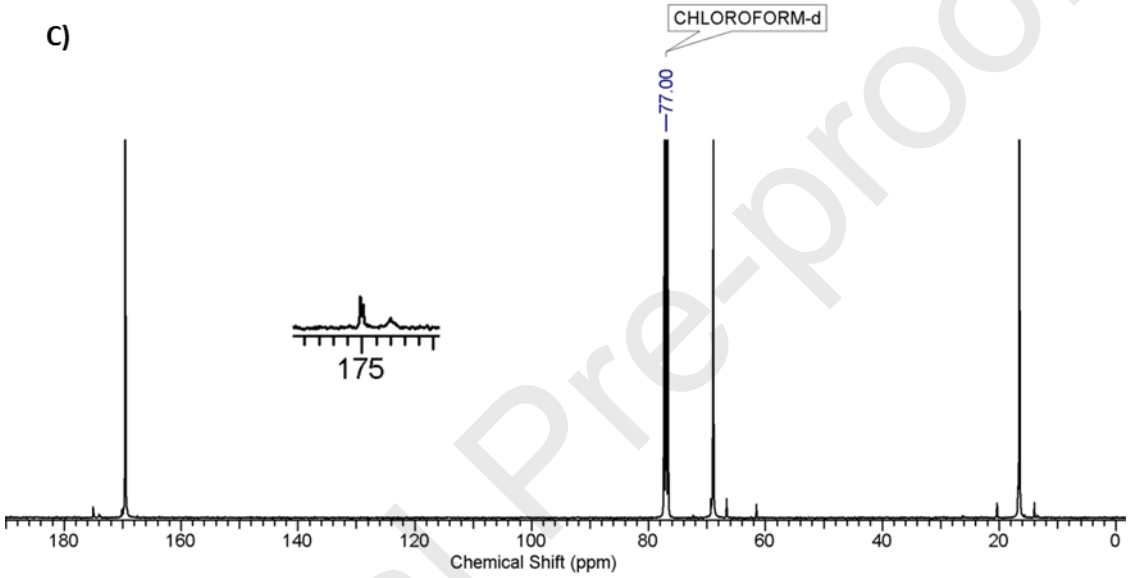


Fig. 13. Quantitative ^{13}C NMR spectra of A) PLLA-2; B) PLLA-7; C) PLLA-14

In the ^{13}C NMR spectrum of PLLA, the peaks appearing from δ 168.5 to 170 ppm are due to ester carbonyl groups, and the peaks at δ 174 to 175 ppm are due to carboxylic end functional groups. The greatest influence on the chemical shift of the end units of PLLA is the long-distance interaction, and this suggests a particular conformation and arrangement of the stereoisomers [31]. The degree of polymerization (DP) was estimated from the relative integral ratio of these groups' signals. The accuracy of the DP estimate was determined and found to be the same in two consecutive NMR experiments [44]. The small amount (< 1%)

of the cyclic fraction (unreacted L-LA appears at δ 5.0 ppm) was not taken into account for calculating M_n by NMR spectroscopy. There were no peaks due to L-LA in this polymer.

MALDI-TOF MS

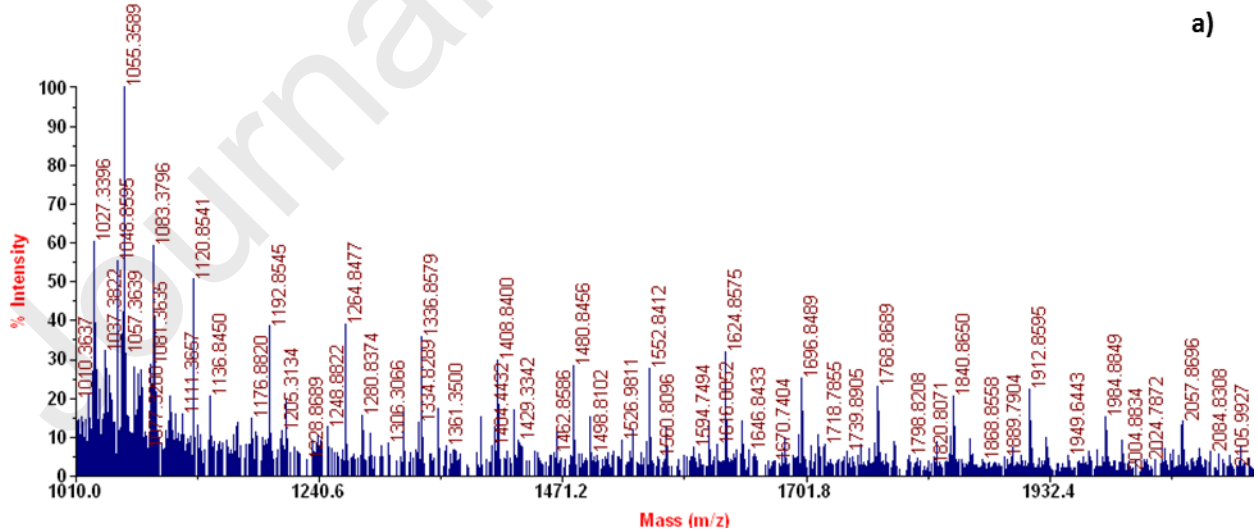
MALDI-TOF MS analysis has been employed for the determination of molecular weights and the nature of the end groups, as shown in Scheme 4a [45,46].

The MALDI-TOF MS of PLLA-2 is shown in Fig. 14a and the most intense peaks belonging to this series correspond to polymers with n = 15 to 25, in the region of 1000 to 2000 Da. The polymer contained chain is terminated by hydroxyl (-OH) on one side and carboxyl (-COOH) on the other. This is dominated by a series of intense peaks in the region ranging from 1000 to 2870 Da, corresponding to an empirical formula of HO-(CO-$CH(CH_3)$-O)$_n$-H-----Na^+, and formula weight (72n +18+23), where n ranges from 16 to 38. A particular peak appears at 1192 Da, which corresponds to the empirical formula OH-(CO-$CH(CH_3)$-O)n-H-----Na^+ and formula weight (72n+18+23), where n is 16. The spectrum also displays other peaks of lower intensity, which are desorbed polymers doped with K^+ ions (K^+ adduct molecular mass = 72n+18+39; see the peaks in the region from 1000 to 2000 Da corresponding to polymers with n = 15 to 26).

The MALDI spectrum of PLLA-7 is shown in Fig. 14b and the most intense peaks belonging to this series correspond to polymers with n = 15 to 25, in the region of 1000 to 2000 Da. The most intense peaks belonging to this series, corresponding to polymers with n values of 17 to 63, are labelled in the spectrum. The spectrum also displays other peaks, which are desorbed polymers doped with K^+ ions (K^+ adduct molecular ions, mass = 72n+18+39; see the peaks in the region 1064 to 2361 Da corresponding to polymers with n = 14 to 32). The spectrum shows the chemical homogeneity, which consists of linear polymers.

The MALDI spectrum of PLLA-14 is shown in Fig. 14c. The spectrum is dominated by three series of intense peaks with masses ranging from 687 to 2129 Da (n > 9), 759 to 1984 Da (n > 10) and 631 to 1784Da (n > 8). In this region, the spectrum also shows three mass series and a mass series of higher intensity that can be assigned to cyclic polymers of PLLA, which appear as polymers doped with potassium ions with masses of 72n+39. There are equal quantities of even and odd no of cycles with more than C9. Similar findings have been observed previously [36].

There are two distinct series of intense peaks ranging from 759 to 1984 Da and from 631 to 1784 Da, corresponding to linear PLLA polymers doped with sodium ions (mass = 72_n+18+23, where n ranges from 10 to 27) and potassium ions ((mass = 72_n+18+39, where n ranges from 8 to 24). These two series are expected to be formed by oligomers bearing –COOH and –OH as terminal groups, corresponding to the general formula H[(-O-CH(CH_3)-CO)]-OH-Na^+ and H[(-O-CH(CH_3)-CO)]-OH-K^+. The spectrum shows the chemical heterogeneity, consisting of linear and cyclic polymers.



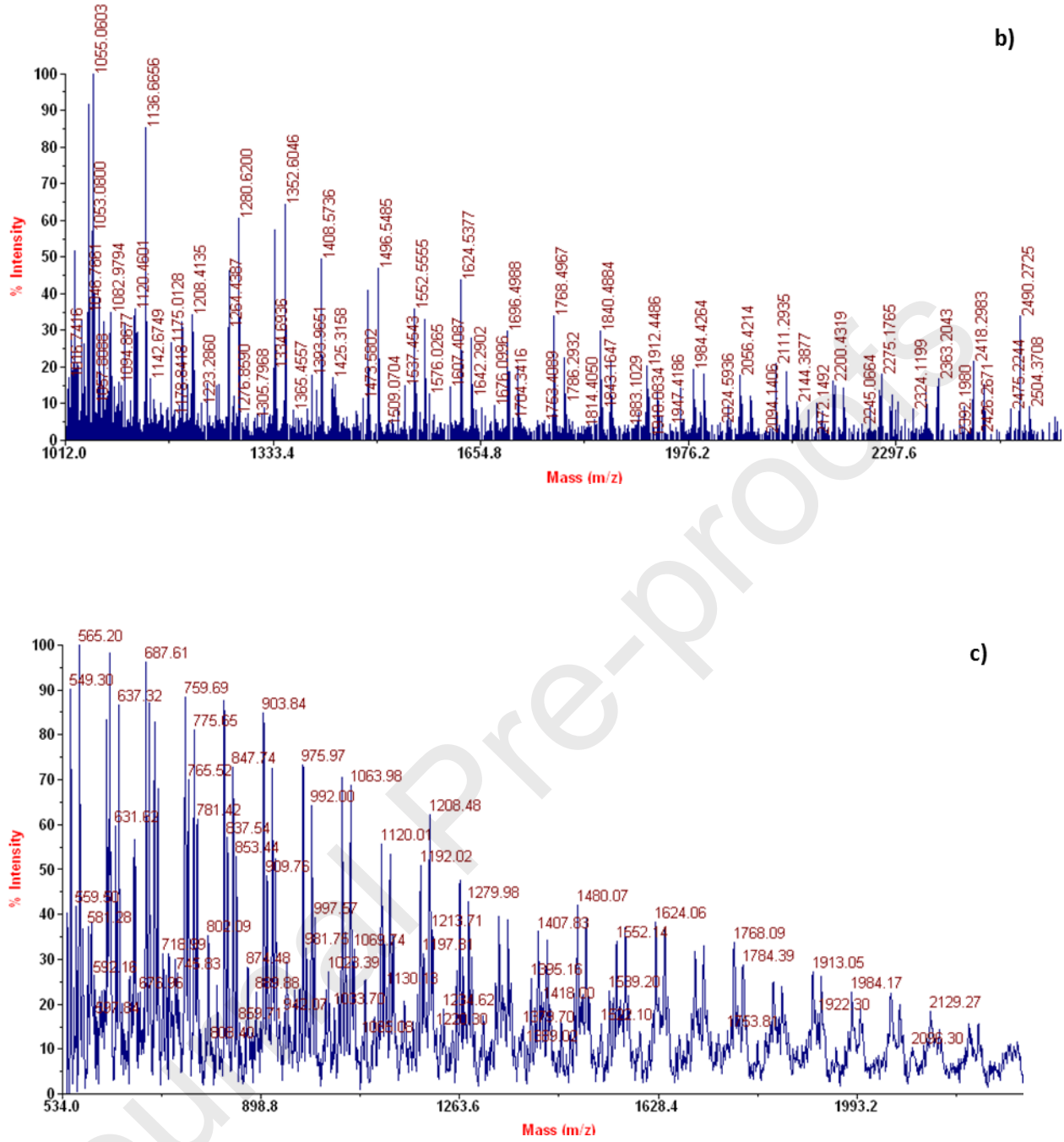


Fig. 14. MALDI-TOF spectra of a) PLLA-2; b) PLLA-7; c) PLLA-14.

Biocompatibility and cytotoxicity evaluation

PLLA is a biocompatible and non-toxic polymer, but toxicity arises due to the presence of residual initiator in the polymer. Because of this toxicity, PLLA refrains itself from biomedical applications. A number of purification steps are involved to remove the initiator.

In bacterial cell adhesion assay, there was no zone of inhibition observed around the PLLA solution in the presence of both bacteria *Staphylococcus aureus ATCC 6538* and *Escherichia coli ATCC 8739* in MH agar plates (Fig. 15). PLLA is an excellent substrate which shows efficient bacterial adhesion because it is a highly hydrophobic polymer, retaining in bacterial cells. Similar bioadhesive properties for eukaryotic cells have also been observed [47]. Bacterial adhesion assays showed that PLLA-2, PLLA-7 and PLLA-14 are good substrates which could not inhibit bacterial growth.

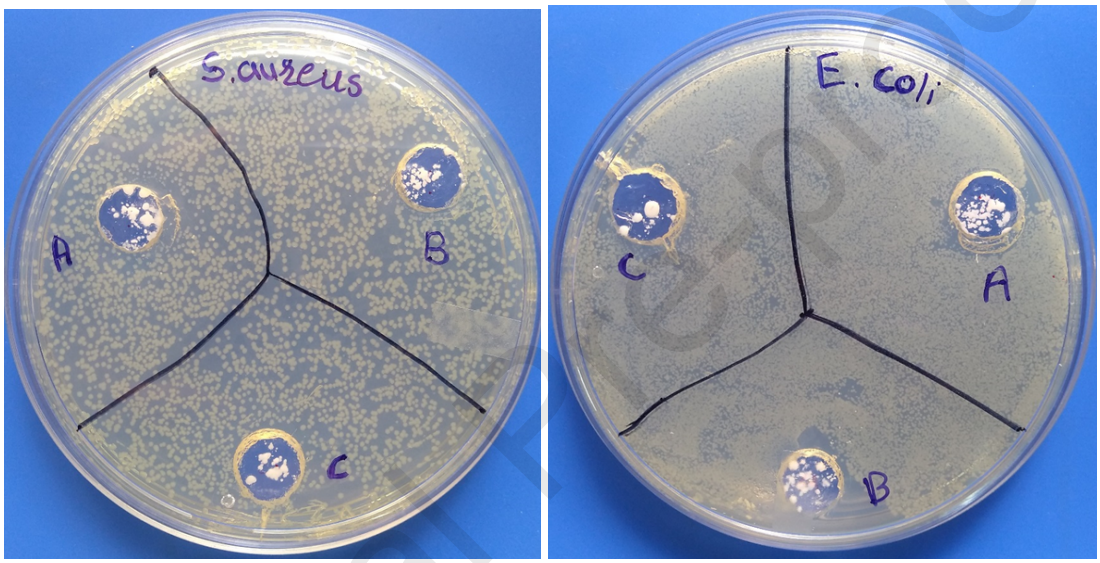


Fig. 15. Antimicrobial activity against *S.aureus* and *E.coli* of A) PLLA-2; B) PLLA-7; C) PLLA-14

Conclusions

The results obtained in the present work show that three tin initiators have been successfully synthesized. ^{1}H, ^{13}C and ^{119}Sn NMR spectra have confirmed the structures of the initiators and the assignments agree well with those published in the earlier literature reports for similar compounds and they are thermally stable up to 280 °C. These initiators were used in the solvent-free polymerization (Green Route) of L-LA to overcome the proportion of aggregated and non-aggregated species present in solution. The results are very good on

using polymerization reaction temperatures such as 140 and 150 °C. For initiator **5**, a higher polymerization temperature (200 °C) was required. Thermodynamically controlled polycondensation tends to end up with a ring-ring equilibrium and not with the formation of a net giant chain in equilibrium with a few cycles. The molecular weight distribution is narrow and the molecular weight can be controlled by the monomer to initiator ratio. The conversion is >95%. There is no induction period for polymerization. Initiator **3** showed higher reactivity in comparison to initiators **2** and **5**. The PLLA polymers show high T_g and T_m values of 60 and 175 °C, respectively. XRD results show that all PLLA polymers are crystalline in nature. ^{13}C NMR and MALDI-TOF spectra confirm that these PLLA polymers are linear, containing hydroxyl and carboxyl end groups (initiators **1** and **3**), or mixed type structures such as linear PLLA with hydroxyl and carboxyl end groups and macrocyclic compounds without containing tin (initiator **5**). The NMR and MALDI-TOF characterizations confirmed the absence of tin. A toxicity study was also carried out and the results showed that the prepared PLLA is safe for biomedical applications. The results confirmed that the PLLA is non-toxic in nature, irrespective of using cyclic tin initiators. This contributes an additional property to PLLA. From these results, it is evident that these three initiators are a very attractive class of functionalized tin alkoxides for solvent-free polymerization process of L-LA.

Notes

Conflicts of interest

There are no conflicts of interest to declare.

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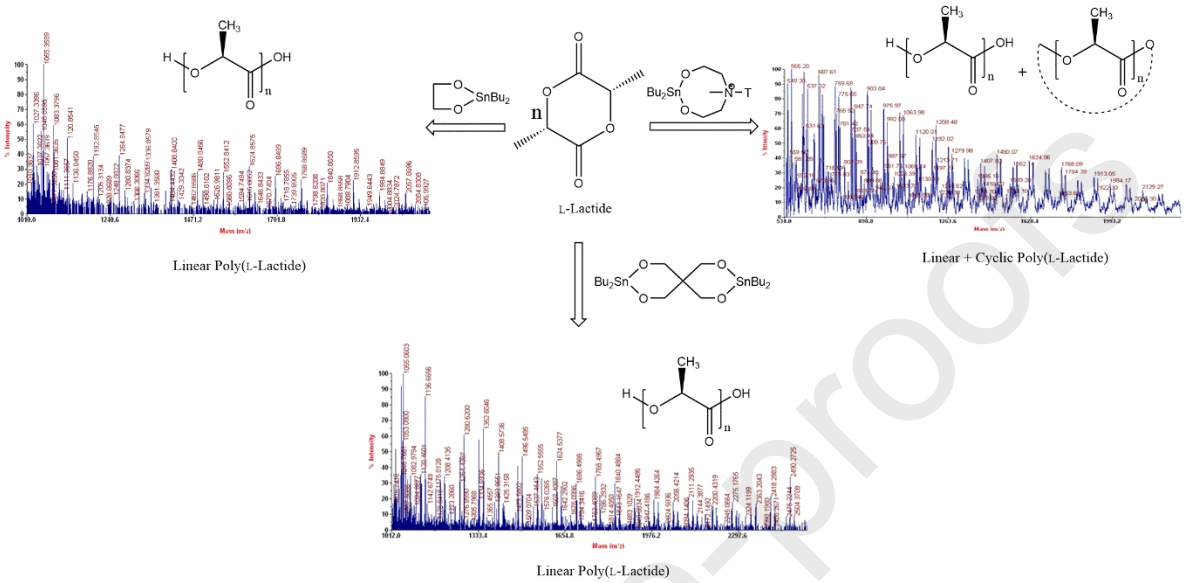
Biocompatible PLLA prepared using tin complexes

TOC



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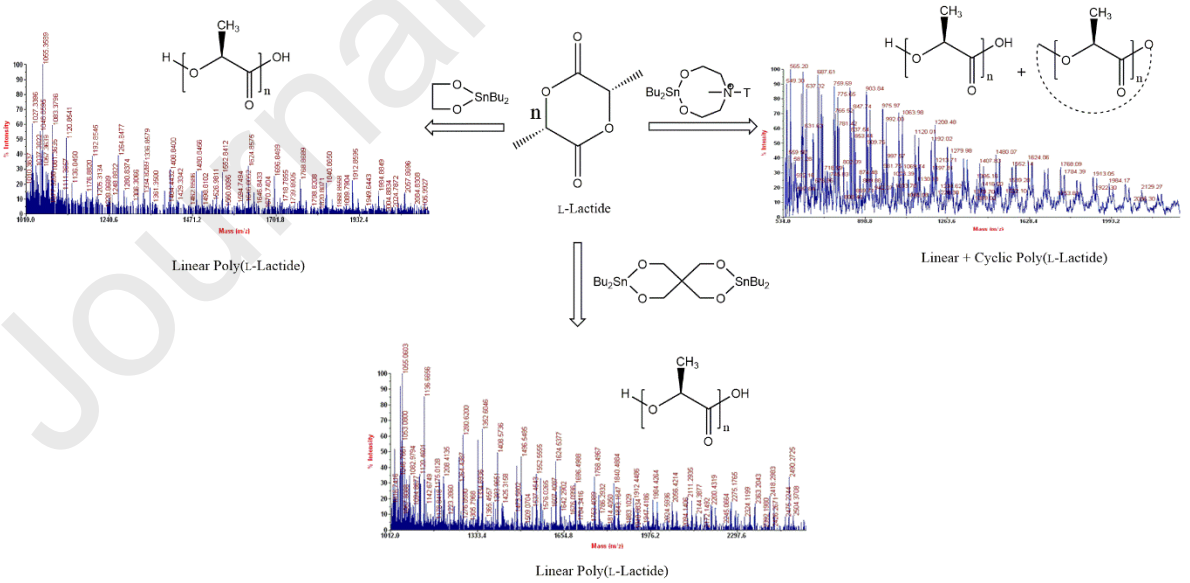

- ✓ ROP of L-lactide in bulk using cyclic Bu_2Sn initiators through a green route
- ✓ Initiators are inexpensive, non-hygroscopic, non-explosive and easy to handle
- ✓ High molecular weight PLLA was obtained in all cases
- ✓ A kinetic study showed good control over molecular weight
- ✓ These initiators performed polymerization at higher temperatures
- ✓ PLLA was proved to be biocompatible against S. aureus and E. coli