

Direct condensation of lactic acid in the presence or absence of supported zirconium sulfate

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ABSTRACT: Direct condensation of L-lactic acid was studied, aiming at highly crystalline and enantiopure high molecular weight (MW) products. Catalyst-free polylactic acid (PLA) with weight average MW of $80,000 \text{ g mol}^{-1}$, based on PLA standards, and a crystallinity of 75% is synthesized at 140°C in a fixed-bed reactor under vacuum or nitrogen purging. Supported zirconium sulfate is found to be an efficient and enantioselective catalyst for the melt and solid-state post-condensation of short-chain prepolymers. Small-molecule monohydroxy alcohols, aldehydes, di- and monocarboxylic acids (e.g., acrylic acid [1,700 ppm], propionic acid [1,800 ppm]) are detected in the lactic acid and prepolymers by high performance liquid chromatography, electron spray ionization, and electron impact mass spectroscopy. Thermal degradation of polymer chains, the crystallinity of the prepolymer, and the presence of monofunctional impurities are crucial parameters for the limitation of the MW of the resulting product. © 2015 Wiley Periodicals, Inc. *J. Appl. Polym. Sci.* **2015**, *2015*, 42444.

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INTRODUCTION

In the last years, medical applications of polylactic acid (PLA) have gained enormous interest due to the totally body absorbable nature of PLA. PLA can be synthesized by the melt condensation of lactic acid.^{1–9} Removal of water, formed by condensation reaction, from the bulk material is necessary either by evaporation under reduced pressure or by driving it away by a carrier gas (e.g., nitrogen). In the literature, the use of strong and weak acids such as sulfuric acid and phosphoric acid as well as numerous organometallic compounds based on germanium, antimony, tin, iron, aluminum, titanium, or zinc has been investigated.^{1,2} Especially sulfuric acid, tin(II) octoate, tin(II) chloride, and titanium(IV) butoxide have exhibited satisfactory catalytic reactivity.^{1,2} Generally, maximum number average molecular weights (MWs) have been reached after 30–90 h at $180\text{--}200^\circ\text{C}$ depending on the catalyst ($M_n \sim 2,300\text{--}90,000 \text{ g mol}^{-1}$).^{2–4} The use of Sn(II) catalysts activated by sulfonic acids can increase the MW of PLA.^{5–9} 1,3-propanedisulfonic acid and 1,5-naphthalene disulfonic acid have been found to successfully synthesize high MW PLA.⁶ A problem faced during the melt condensation is the discoloration of the reaction mixture caused by the high reaction temperature, long reaction time, byproducts, and catalysts. The use of *p*-toluene sulfonic acid or triphenylphosphane as co-catalysts are effective

for hindering color formation and depressing racemization in the melt condensation process.^{8,9} An increasing degree of polymerization is strongly dependent on removal of water formed by condensation reaction. The thicker the melting layer, the harder the diffusion of water is. Solid-state post-condensation (SSP) is a simple and efficient process to increase the MW of PLA. The direct condensation of lactic acid seems an easy way to obtain highly crystalline products. Moon *et al.*¹⁰ reported SSP of PLA reaching high MW PLA for the first time in 2001. Today, several SSP studies of PLA exist^{10–29} including the synthesis of nanocomposite PLA.²⁰ Most SSP articles refer exclusively to weight average MWs based on polystyrene standards (PS). SSP temperatures are selected from a reaction temperature range between the glass transition and melting temperatures of PLA. Usually, small PLA particles are subjected to a previous annealing process lower²⁶ or even at their cold crystallization temperature.^{10,22–25,27} It is assumed that functional end groups, as well as homogeneous catalysts, are accumulated in the amorphous phase of the polymer.^{30,31} Due to an increased accumulation of functional end groups in the amorphous part of the polymer, condensation takes place at an enhanced rate. In this article, the effect of prepolymer treatment and crystal properties of prepolymers on SSP are studied

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since the crystallinity of the prepolymer and the SSP product influences the esterification rate, affecting the mobility of chain end groups and the water diffusion.^{26,27} Too high crystallinity is considered to decrease end group mobility and by-product diffusion.²⁷ Literature results indicate that there is a linear^{14,15,26} or an exponential relationship²⁷ between the reaction time and MW at an early stage of the SSP reaction. Generally, the time of post-condensation is much longer than in the melt since the mobility of end groups is restricted and slower compared to higher reaction temperatures.³² It is surprising that a 14–25 times higher MW after 10–20 h of SSP has been described in the literature.^{10,12,14,22,26}

Lactic acid produced by fermentation includes impurities, especially organic acids (such as citric, glyceric, succinic, malic, formic, propionic, fumaric, pyruvic, and acetic acid), monohydroxy alcohols (methanol, ethanol, butanol), lactates (methyl, ethyl and butyl lactates), amino acids, and protein fragments.^{33–37} The available information about the amount and effect of monofunctional impurities on the direct condensation reaction of lactic acid is scarce.³⁸ Oxalic acid (28 ppm), pyruvic acid (174 ppm), acetic acid (1717 ppm), and succinic acid (388 ppm) were found in lactic acid purchased from Purac and used for ring opening polymerization of lactide.³⁷ Few calculations of MW limitation by the amount of end terminators are available.^{31,39} The total amount of monofunctional impurities should preferably be smaller than 0.01 mol % before condensation reaction.³¹ Without a removal of impurities, the presence of unremoved chain end terminators becomes an important factor in the MW limitation of PLA.

Literature results indicate that there is a relationship between the concentration of catalysts and MW of post-condensed polymers.¹³ In our previous studies, supported zirconium sulfate (ZS) was found to be an active and selective polycondensation catalyst.⁴⁰ It is not yet proven if ZS is an efficient catalyst for the post-condensation of lactic acid prepolymers. Since a catalyst-free PLA is relevant to medical applications, we implemented an easy procedure for obtaining a catalyst-free prepolymer with particle diameters at μm levels and for the removal of free available small molecule impurities and low MW oligomers, reducing self-sticking prepolymer particles. The available information about the absence of catalyst and the presence of Brønsted acids during the post-condensation reaction of PLA is rare.

The results of SSP with supported ZS as catalyst as well as the properties of the obtained PLA are discussed together with limiting factors for the condensation rate and MW of the polymer. Some of the results are consistent with those obtained by other authors. The presence of this work is still justified in terms of Brønsted acid catalysis and different reaction conditions since Lewis acids have been used in other experiments.^{10–27,29} Supported ZS is found to be an efficient and enantioselective catalyst for the SSP of short-chain prepolymers. A maximum MW ($M_w \sim 160,000 \text{ g mol}^{-1}$ based on PS) is obtained in the presence and absence of supported ZS.

EXPERIMENTAL

Materials

A 90 wt % aqueous solution of L-lactic acid (LAPGL90, Galactic) was supplied by Uhde Inventa-Fischer (2013) with an optical

purity (OP) of at least 99% according to the manufacturer. ZS tetrahydrate (ZST, 99.99%) was purchased from ABCR. Silica support SIPERNAT[®] 310 was received from Evonik. The following materials were used without further treatment: chloroform (>99.8%) from Acros, phosphoric acid (85%) and anhydrous copper monosulfate from Merck, acetone (>99.7%), *n*-heptane (>99%), and nitric acid (65%) from ROTH, oxalic acid (>99%), propionic acid (>99.5%), and acrylic acid (>99%) from Sigma-Aldrich. Other organic acids, for example, acetic acid (>96%), pyruvic acid (>98%), and formic acid (>98%), were purchased from ROTH. ROTISOLV[®] HPLC-grade solvents water, acetonitrile, and chloroform with 1 vol % ethanol were supplied by ROTH. Tetrahydrofuran (THF) was used as applied at BAM (Bundesanstalt für Materialforschung und -prüfung).

Methods

With respect to PS, number (M_n) and weight average MWs (M_w) were determined by gel permeation chromatography (GPC) with two PLgel 5 μm Mixed D columns ($300 \times 7.5 \text{ mm}$) and a refractive index detector. One milliliter of chloroform for 1 min was used as eluent flow rate whereas 200 μL of the sample solution (3 mg mL^{-1} chloroform) was injected. The analyses were done at room temperature, doubly replicated. Owing to an error of graphical evaluation, the divergency of number average MWs came to 10%. All MW presented in this work were based on PLA standards. The conversion of the MW was done using the eq. (1).⁴¹ A close correlation between ¹H-NMR spectroscopy and data based on eq. (1) was established for lactic acid oligomers.⁴⁰

$$\log M(\text{PLA}) = 0.95922 \times \log M(\text{PS}) - 0.1592 \quad (1)$$

PLA surface area was studied by a five point BET analysis. Samples were degassed at 100°C and 300 mbar for 3 h. Adsorption of nitrogen was done at -196°C using a Gemini 2375 V5.00 device (Micromeritics).

Zirconium and sulfur contents were detected by an inductively coupled plasma optical emission (ICP-OE) spectrometer Varian 715-ES using standard calibration (wavelength $\lambda_{Zr} = 344 \text{ nm}$, $\lambda_S = 182 \text{ nm}$). Samples were dissolved in nitric acid to get a concentration of 5 wt % PLA.

Differential scanning calorimetric (DSC) measurements were done on a Perkin-Elmer DSC-7 between 25 and 200°C with a heating rate of 10°C min⁻¹. Crystallinity, related to the reference value 93.6 J g⁻¹ of poly-L-lactic acid,⁴² was given by the area difference of the melting and cold crystallization peaks from the first scan, calculated by the program Pyris Series.

OP of PLA was determined by chiral high performance liquid chromatography (HPLC). Chiral HPLC analyses (method 1) were performed using a guard column ($30 \times 4.6 \text{ mm}$) and a chiral Daicel CHIRALPAK[®] MA(+) column ($50 \times 4.6 \text{ mm}$). Hydrolysis of PLA was done as presented in a previous work.⁴⁰ A solution of 10 mg sample and 1 mL HPLC-grade chloroform was filtrated by a membrane with a pore diameter of 0.45 μm . 20 μL of that solution were injected into the HPLC system. The flow rate of the mobile phase water/3 mM copper monosulfate was 1.5 mL min⁻¹. Chiral HPL chromatograms were recorded at 238 nm and 30°C (method 1). For the method 2 of the reversed-phase (RP) HPLC, a guard column ($30 \times 4.6 \text{ mm}$)

and an Eurospher 100-5 C18 column (250 × 4.6 mm) from Knauer were used at 40°C. An isocratic mode was used. The mobile phase was a mixture of acetonitrile and water. Phosphoric acid (0.2 vol %) were added to the mobile phase obtaining a higher efficiency of the column.⁴³ Ten microliter of the sample solution with a concentration of 10 mg mL⁻¹ acetonitrile were filtrated by a membrane (0.20 μm pore diameter) and inserted into the HPLC system. UV-Vis detector with 206 nm was used.

OP was also calculated from the eq. (2) based on the fact that the value of the specific optical rotation of pure lactic acid is +3.2.⁴⁴ Specific optical rotation of the sample is the number of degrees of rotation caused by a solution of 0.1 g of the compound per mL of chloroform (*c*) in a sample tube 1.0 dm long (*l*), denoted as deg cm³ g⁻¹ dm⁻¹.

$$OP = \frac{\text{specific optical rotation of the sample}}{\text{specific optical rotation of the pure enantiomer}} \quad (2)$$

The observed rotation α was measured using a Disc Polarimeter WXG-4 (HINOTEK) at 20°C and a wavelength of 589 nm. Specific optical rotation was given by the eq. (3).⁴⁵

$$[\alpha]_D^{20} = \frac{\alpha}{l \times c} \quad (3)$$

Crystallite size was calculated from Scherrer equation [eq. (4)].⁴⁶ Values were given by wide-angle X-ray diffraction measurements carried out on an X' Pert PRO MPD diffractometer (PANalytical) in reflection mode using Cu K α primary radiation ($\lambda = 0.154$ nm). Diffractograms were recorded from 5 to 40° with a step scan of 0.013°. Baselines were corrected manually.

$$L = \frac{k \times \lambda}{\cos \Theta \times \sqrt{\text{FWHM}(\text{PLA})^2 - \text{FWHM}(\text{apparatus})^2}} \quad (4)$$

[*k*: shape factor (*k* = 0.9 for spherulitic crystals); FWHM: full width half maximum of diffraction peak at corresponding diffraction angle 2θ , FWHM (apparatus) = 0.01°]

Matrix-assisted laser desorption/ionization (MALDI) measurements were carried out on an Autoflex III time-of-flight (TOF) mass spectrometer (Bruker). Samples were dissolved in THF (2–3 mg mL⁻¹) and prepared with a 2,5-dihydroxybenzoic acid (DHB) matrix (10 mg mL⁻¹ THF) in such a way as to deposit a mixture of 50 μL (DHB) and 20 μL (sample) onto a target. A smart-beam-LASER (356 nm) was used to produce laser desorption. Two thousand shots were summed for each spectrum. Samples were calibrated using reflector method.

For mass spectrometry (MS) using electron impact (EI), samples were analyzed on a Finnigan MAT 95 S sector field MS (Thermo Fisher Scientific). Primary electron energy of 70 eV was used. MS using electrospray ionization (ESI) was carried out on a LTQ Orbitrap XL (Thermo Fisher Scientific) using negative ion mode. Molecules would not be detected if their mass to charge ratio was smaller than 50. Since the response of a molecule measured by ESI depended on the surface activity, the polarity and the composition of the mixture, a 1 : 1 mixture of lactic acid and monocarboxylic impurities (acetic acid, acrylic acid, propionic acid, oxalic acid, and pyruvic acid) as well as a mixture of impurities in concentration of the expected level (0.001–0.100 mol %) and lactic acid were prepared for calibration. A sample concentration of 0.3 mg mL⁻¹ acetonitrile was used. 300 μL min⁻¹ of this solution were injected

into the system. Molecular formulas were determined using the program Thermo Xcalibur Qual Browser.

Catalyst Preparation

ZST was supported on silica SIPERNAT[®] 310 by diffusion-controlled impregnation method described in a previous work.⁴⁰ Supported catalysts with 30% loading were calcined at 300°C for 1 h in air, showing highest activity.⁴⁰ Loading is based on ZS and defined as mass ratio $m(\text{ZS})/m(\text{ZS} + \text{support})$.

Synthesis of Prepolymer by Melt Condensation of L-Lactic Acid

Water of aqueous L-lactic acid solution was removed under reduced pressure (50 mbar) at 80°C for 0.5 h. Condensation of dehydrated L-lactic acid was performed at 180°C and 0.5 mbar from 5 h to more than 60 h. More details were presented in a previous work.⁴⁰ Using 0.3 wt % ZS and a loading of 30% was found to be an appropriate choice for getting enantiopure PLA.⁴⁰ The rotation speed of the rotary evaporator was changed from 100 rpm down to 30 rpm after 20 h of reaction. After this procedure, the reaction mass was usually cooled by pouring the molten reaction mixture onto an aluminum foil.

Treatment of Prepolymer for SSP

Grinding of Prepolymer. RETSCH Ultra Centrifugal Mill ZM 100 was used for the grinding of melt condensates. To avoid thermal chain degradation, the samples were frozen in liquid nitrogen before grinding. A medial particle diameter of 250 μm was obtained.

Reprecipitation of Prepolymer. For removal of low MW oligomers⁴⁷ and for obtaining a prepolymer with particle diameters smaller than 100 μm, the melt condensate was dissolved in chloroform, dried over 4 Å molecular sieves, to get a concentration of 10 wt % product. The solution was filtered through a membrane (0.20 μm pore diameter). Catalyst support material and black carbon as decomposition product were separated. The solution was added into an anhydrous solution of *n*-heptane/acetone (2 : 1 vol %) under vigorous stirring at room temperature. The solvent was removed by vacuum filtration. Reprecipitated PLA was washed by 20 mL of anhydrous *n*-heptane/acetone (2 : 1 vol %) and dried under vacuum at 30°C and 8 mbar for 24 h. The white powder was sieved (100 or 250 μm mesh size) and showed a BET area of 2 m² g⁻¹.

SSP of Prepolymer

After annealing prepolymers below or even at their cold crystallization temperature (70–110°C, 0.5–2.5 h), post-condensation of these products was performed at 120–155°C (isothermal or non-isothermal) in the solid phase under reduced pressure (0.05–8.00 mbar) or nitrogen flow (0.04 L g⁻¹ min⁻¹). A tubular fixed-bed reactor was preheated to the SSP reaction temperature using BÜCHI GKR-50 oven. Finally, prepolymer particles were filled into the reactor. Dry nitrogen gas was preheated in a coiled pipe before entering the reactor. In the case of vacuum condensation, a drying oven and a thin layer technique of prepolymer particles were used. There had not been a reprecipitation process before the analysis of the final product was done.

RESULTS AND DISCUSSION

Analysis of Lactic Acid Used

The commercial lactic acid is a mixture of lactic acid, short-chain oligomers,⁴⁸ and carboxylic acid impurities identified by

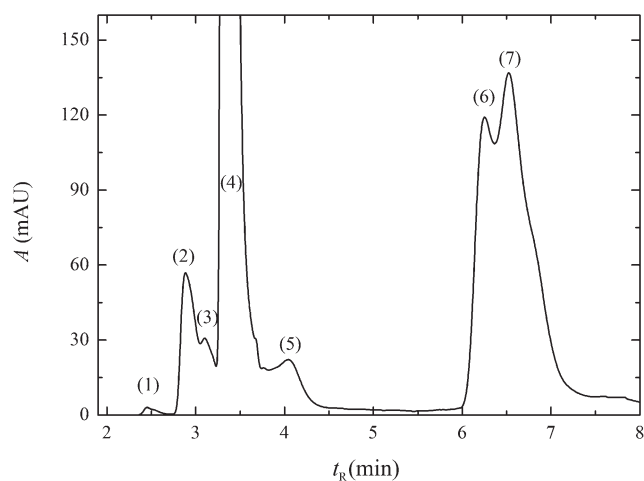


Figure 1. RP chromatogram of lactic acid as received (Method 2: Euro-spher 100-5 C18 column, acetonitrile/water: 10/90, 0.8 mL min⁻¹, 206 nm): oxalic acid (1), formic acid (2), pyruvic acid (3), lactic acid (4), acetic acid (5), acrylic acid (6), propionic acid (7).

recording HPL chromatograms of carboxylic acid standards (Figure 1). The concentrations of the impurities were determined by ESI-MS internal standard calculation. Acrylic acid (1,700 ppm, 5.3×10^{-3} mol %) and propionic acid (1,800 ppm, 5.5×10^{-3} mol %) are considered to be potential chain end terminators. The oxalic acid and pyruvic acid contents are negligible. Under the given melt condensation conditions, acrylic acid and propionic acid seem to be volatile. A MW limitation assigned to the effect of monofunctional impurities cannot be excluded since the concentrations of monocarboxylic acid impurities were too low to be detected in the reaction mixture. According to Uhde Inventa-Fischer, raw lactic acid solutions of varied composition rates are the consequence of different production units. It is possible that other scientists have successfully produced high MW PLA via direct condensation of lactic acid using similar raw material from Galactic.

Characterization of Prepolymer

Molecular Weight. All MW presented in this work are based on PLA standards. The results are almost synonymous with halving of GPC PS results.⁴¹ Melt condensation using 0.3 wt % ZS was stopped after different times at 180°C and 0.5 mbar, obtaining a product with M_n of 1,000–11,000 g mol⁻¹ (Figure 2). A pressure of 0.5 mbar showed a yield of 50%. Prolonging the period of condensation to 60 h allows no further significant increase in M_n and \mathcal{D} (constant dispersity of 2) since the MW is mainly limited by mass transfer of water out of the highly viscous reaction mass.

Crystallinity and OP. Prepolymers show a crystallinity of 38% after 5 h of melt condensation. In the case of 30 h melt condensates, the degree of crystallinity is up to 35% depending on the cooling rate of the melt (Figure 3). The use of a mill has no influence on MW (10,300 g mol⁻¹) and crystallinity (35%) of the untreated product shown in Figure 3. Prolonging the period of condensation to 60 h, no change in crystallinity is observed. The reason for this effect can be seen in the high OP all over the reaction time (Figure 2). The OP was determined by chiral

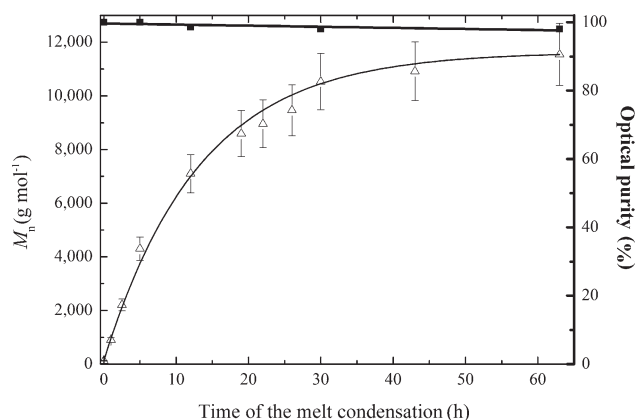


Figure 2. Number average MW (Δ), based on PLA standards, and OP (\blacksquare) of lactic acid prepolymers depending on reaction time. [Synthesis: 180°C, 0.5 mbar, 0.3 wt % ZS].

HPLC and optical rotation measurements. A prepolymer sample is a mixture of lactic acid (Figure 4), cyclic oligomers (Figure 5), and linear prepolymers. L-lactic acid shows a positive specific optical rotation.⁴⁴ Since the specific optical rotation of cyclic lactic acid oligomers is much higher than the specific optical rotation of linear PLLA,⁴⁴ it is not possible to calculate the OP of prepolymers based on the specific optical rotation of PLLA. Therefore, prepolymers were hydrolyzed as described in a previous work.⁴⁰ As shown in Table I, there are good agreements between the optical rotation and chiral HPLC experiments.

Impurities. HPLC measurements determined carboxylic acid impurities present in prepolymer samples (Figure 4). As a result of the 5 h condensation reaction, the concentration of acrylic acid was lower than 200 ppm (ESI-MS). Prepolymer samples were also measured using EI ionization after 30 and 60 h of melt condensation at 180°C and 0.5 mbar; decomposition

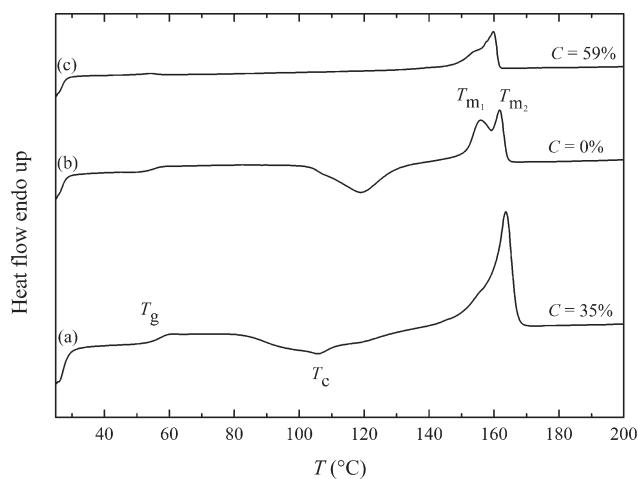


Figure 3. DSC heating curves (10°C min⁻¹) of lactic acid prepolymer. [Synthesis: 30 h, 180°C, 0.5 mbar, 0.3 wt % ZS; (a) melt cooled at room temperature; (b) melt cooled by liquid nitrogen directly after reaction; (c) melt cooled and reprecipitated at room temperature; T_g : glass transition temp.; T_c : cold crystallization temp.; T_{m1} , T_{m2} : melting temp.; C : crystallinity].

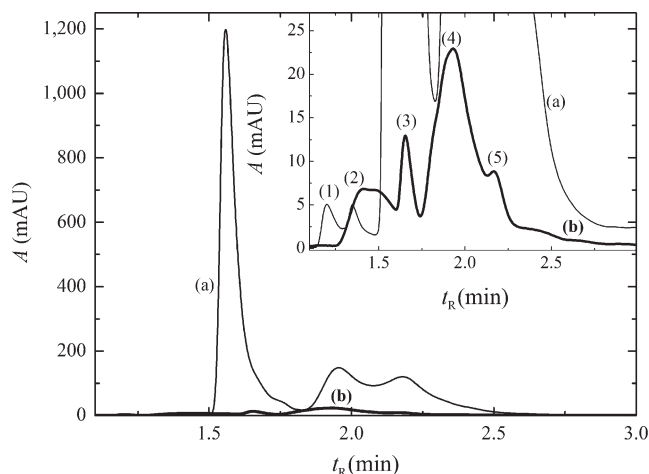


Figure 4. RP chromatograms of (a) lactic acid used and (b) lactic acid prepolymer (Method 2: Eurospher 100-5 C18 column, acetonitrile/water: 20/80, 1.5 mL min⁻¹, 206 nm): oxalic acid (1), formic acid/pyruvic acid (2), lactic acid (3), acrylic acid (4), propionic acid (5). [Synthesis of prepolymer: 5 h, 180°C, 0.5 mbar, 0.3 wt % ZS].

products of C1 and C2 monocarboxylic acids (formic acid, acetic acid), monohydroxy alcohols (methanol, ethanol), and aldehydes (formaldehyde, acetaldehyde) were detected. Using ZS as catalyst for the polycondensation of lactic acid, the concentrations of enclosed formic acid, ethanol, and methanol increase with the time of melt condensation as indicated by increased intensities of the corresponding signals of formic acid, ethanol, and methanol, while the intensities of other detected monocarboxylic acids and aldehydes are unchanged. It is unclear whether these chain end terminators, formed by the catalyst and water at high temperature in the melt phase, will avoid an increased chain prolongation in the further course of the condensation reaction. An increase in the condensation time and catalyst concentration results in a black product, assumedly due to carbon formation. Discoloration caused by the absorption of light energy by chemical bonds, for example, double bonds, is excluded due to the fact that a clear colorless product is obtained after membrane filtration described in the experimental part. Hauser and Herzfeld⁴⁹ has described the formation of sulfuric acid and zirconyl sulfuric acids when ZS has got in contact with water. It is expected that low MW degradation products are formed by strong acidic materials like sulfuric acid.⁵⁰ In the presence of sulfuric acid, the transformation of lactic acid into formic acid and also lactic acid into acrylic acid may take place.³⁶

Table I. OP of Lactic Acid Prepolymers^a Synthesized at Different Reaction Times

Reaction time <i>t</i> (h)	Specific optical rotation $[\alpha]_D^{20}$ (deg cm ³ g ⁻¹ dm ⁻¹)	OP (%)	
		Optical rotation	Chiral HPLC
5	3.20	100.00	100.00
12	3.18 ± 0.01	99.38 ± 0.03	98.60
30	3.14 ± 0.01	98.13 ± 0.03	97.93
63	3.10 ± 0.01	96.88 ± 0.03	97.37

^aMade by melt condensation of lactic acid at 180°C and 0.5 mbar in the presence of 0.3 wt % ZS.

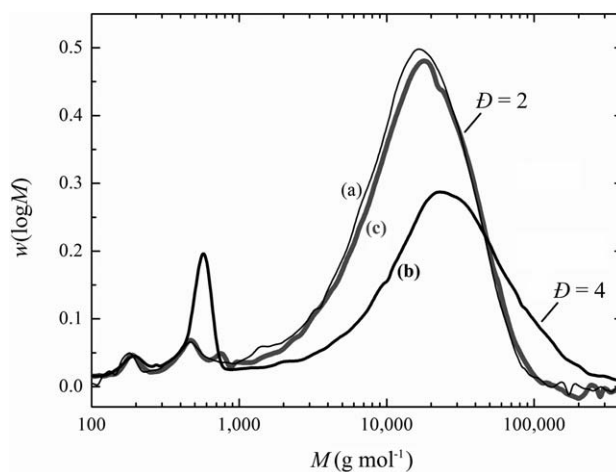


Figure 5. MW distributions of PLA before (a) and after (b,c) SSP based on PLA standards. [Synthesis of prepolymer: condensation of lactic acid with 0.3 wt % ZS at 180°C and 0.5 mbar for 30 h; treatment of prepolymer: reprecipitation; post-condensation: 140°C, 8 mbar, (b) 66 h, (c) 150 h].

Treatment of Prepolymer

Reprecipitation. ICP-OES measurements detected neither zirconium nor sulfur in reprecipitated PLA samples. It can be assumed that all zirconium and sulfur concentrations less than the limit of detection (60 pg L⁻¹ Zr, 30 ng L⁻¹ S) are essentially equal to the absence of zirconium and sulfur. ZS is recovered by a membrane filter (0.20 μm pore diameter), whereas sulfuric acid is removed by washing with *n*-heptane/acetone solution as described in the experimental part. Therefore, a catalyst-free product can be obtained by reprecipitation and membrane filtration. The presence of formic acid, ethanol, and methanol in reprecipitated prepolymers is excluded since the EI-MS response signals are not found out of the signal-to-noise ratio. Particle diameters of prepolymers are smaller than 100 μm directly obtained after reprecipitation and sieving. Crystallinity of prepolymers is increased considerably by reprecipitation; reprecipitated prepolymers, synthesized at different reaction times, show crystallinities of 55–59% (Table II). Drying at 30°C for 24 h has no effect on crystallinity. Based on reprecipitated samples shown in Table II, no cold crystallization peak will be detected by DSC if the product shows a crystallinity of more than 55% (Figure 3). A long crystallization time during the reprecipitation process and a favored orientation of prepolymer chains, resulting in highly crystalline prepolymers, explain the absence of the cold

Table II. Crystallinity of Non-Recrystallized and Recrystallized Prepolymers Depending on Annealing Conditions and Number Average MW

Annealing conditions		M_n^a (g mol ⁻¹)			M_n^a (g mol ⁻¹)		
		C ^b (%) of non-recrystallized prepolymer			C ^b (%) of recrystallized prepolymer		
T (°C)	t (h)	4,300	8,700	10,300	4,300	8,700	10,300
	0	38 ^c	35 ^c	8 ^c	55	56	59
70	1.0	40	35	8	56	56	59
70	2.5	45	35	10	58	56	59
90	0.5	59	38	12	55	56	59
90	1.0	62	40	13	55	57	59
105	0.5	nd ^d	55	45	nd	56	59
105	1.0	nd	56	52	nd	58	60
110	0.5	nd	56	45	nd	56	59
110	1.0	nd	58	53	nd	58	60

^a Number average MW determined by GPC, based on PLA standards.

^b Degree of crystallinity based on DSC measurements (10°C min⁻¹).

^c Crystallinity depending on the cooling rate of the melt (Figure 3).

^d nd: not determined.

crystallization peak. In Figure 3(b), the first melting peak is attributed to the formation of lamellar crystals being accumulated by cold crystallization.⁵¹ According to the work of Wang *et al.*,⁵² the second melting peak at 160°C is caused by the main component of lamellar crystals which have been formed during the cooling of PLA after melt condensation. It is necessary to remove unbound catalysts to keep good polymer quality, for example, thermal stability. Catalyst removal by precipitation has been described in the literature.⁵³

Annealing. Under the optimum crystallization conditions cited in the literature^{26,27} (70°C: 1.0 h; 110°C: 0.5 h), the crystallinities and MW of all recrystallized products do not change with respect to the original value (Table II). This result can be associated to the high crystallinity of the prepolymer (Figure 3). In contrast to literature results,²⁶ non-recrystallized ground prepolymers, showing M_n of 10,300 g mol⁻¹ and a crystallinity of 8%, are largely amorphous when they are annealed at 70°C for 1.0–2.5 h (Table II). As shown in Table II, a significant increase

in the crystallinity is observed when non-recrystallized samples are annealed at their cold crystallization temperature.

As can be seen in the wide-angle X-ray diffractograms (Figure 6), the presence of peaks is dependent on the treatment of melt condensates (annealing and recrystallization). Extremely small crystallites can be the reason for the absence of peaks. The average crystallite size increases during the process of annealing at 110°C. It is 37.8 nm for the ground and annealed 5 h melt condensate and 29.0 nm for the recrystallized and annealed sample according to the FWHM of the (110/200) peak. A small crystal size should be favorable to water transport. The integral intensity is dependent on the number of atoms in the lattice plane but is constant in the case of both annealed prepolymers [Figure 6(b)]. The structure of annealed prepolymers, shown in Figure 6, is nearly the same, and only the (110/200) peak is shifted. Peak widening may be due to water being trapped as a consequence of highly crystalline recrystallized prepolymers. Similar 2θ values of major peaks were reported in the literature.^{17,37,54} The position of the peaks presented in Figure 6 indicates the presence of α' -crystals⁵⁵ and is dependent on the annealing temperature.⁵⁴ According to Zhang *et al.*,⁵⁶ the α' -crystal system is less compact than the α -phase.

SSP of Recrystallized Prepolymer

Effect of Reaction Time and MW. MW and crystallinity. With respect to melting temperatures of prepolymers (Figure 3), SSP temperature must be well adapted for successful post-condensation. As presented in Figure 7, an exponential increase in M_n may be observed for recrystallized and post-condensed PLA at 140°C and 8 mbar. The dispersity of 2 and the MW of PLA do not change during the first 30 h of SSP (Figure 7). We assume that a reorientation of prepolymer chain ends occurs during the first 30 h of SSP; hence, active chain ends orient themselves into favorable positions for reaction. A higher concentration of end groups, rejected from the crystalline phase into the amorphous phase, may be caused by an increase of 10% in the crystallinity during the first 20 h of SSP and leads

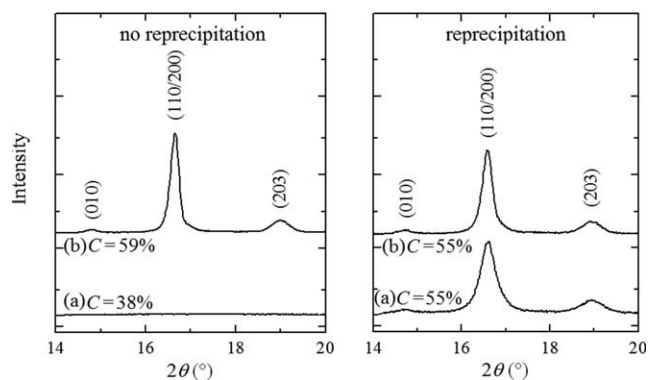


Figure 6. Wide-angle X-ray diffractograms of lactic acid prepolymers depending on heat treatment and recrystallization. [(a) prepolymer synthesized at 180°C and 0.5 mbar with 0.3 wt % ZS for 5 h; (b) prepolymer annealed at 90°C for 0.5 h; peaks according to Peng *et al.*²⁶].

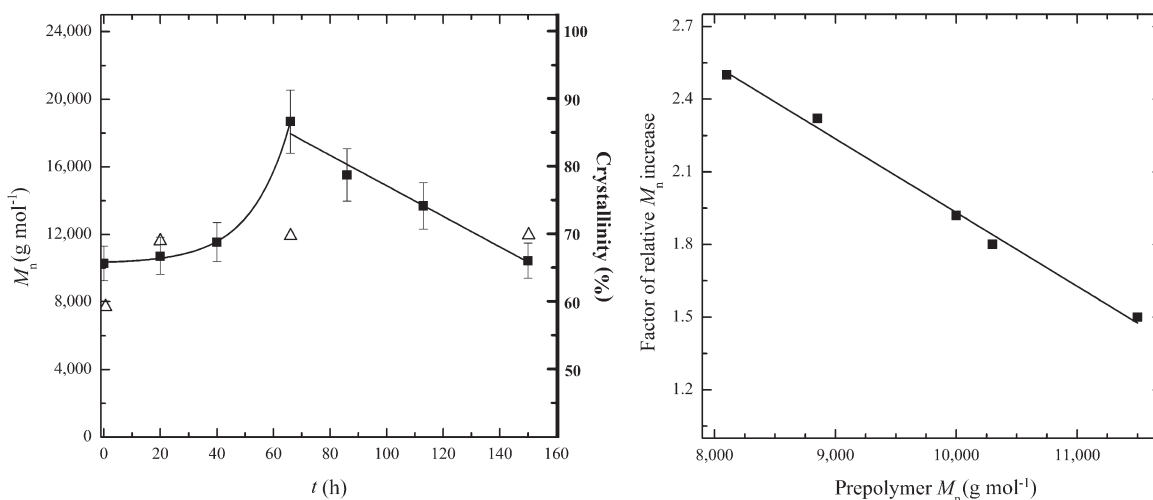


Figure 7. SSP of reprecipitated lactic acid prepolymers: effect of reaction time on crystallinity (Δ) and number average MW (M_n) (\blacksquare) as well as effect of M_n of prepolymer on M_n of post-condensed PLA based on PLA standards. [SSP: 140°C, 8 mbar; on the right: 66 h, 140°C, 8 mbar].

to an increase in the condensation rate. Beyond 20 h of SSP, the increase in the crystallinity is very poor (Figure 7). We suppose that a high PLA crystallinity results in retarded chain end group mobility. As the total number of functional end groups decreases, a decay of esterification rate is expected at longer SSP time. An exponential increase in M_n with time can be explained by a relative increase in the condensation rate of long polymer chains after reorientation of functional end groups. Reorientation of functional end groups is especially required for long prepolymer chains since the concentration of functional end groups decreases with increasing the length of polymer chains. A long SSP time (66 h) is required to increase the number average MW of reprecipitated PLA by more than 80% to around 20,000 g mol^{-1} . The dispersity of PLA changes from 2 to 4; hence, a weight average MW of 80,000 g mol^{-1} is obtained after 66 h of SSP at 140°C and 8 mbar. The conversion of the melt condensation/SSP process was 99.8% with respect to lactic acid, calculated from the amount of water found in the nitrogen trap. As the result of the annealing and crystallization process of the prepolymer, the monomer is segregated in the amorphous region of PLA. This fact allows the SSP yield to reach 99%. The total yield of the whole condensation reaction (melt condensation followed by SSP) is 50%. The use of PLA particle diameters of less than 100 μm or diameters of less than 250 μm has no effect on the MW shown in Figure 7. The smaller the MW of the prepolymer at the beginning of the SSP reaction, the larger the relative increase in the MW is (Figure 7: right side). The reason can be found in the decreased number of functional end groups of long-chain PLA.

As presented in Figure 5, chains undergo intermolecular and intramolecular condensation during SSP. An increase in long-chain formation takes place. MALDI-TOF-MS enables the detection of cyclic lactic acid oligomers (residual mass: 18 u). Especially, the formation of 24-membered rings, consisting of 8 lactic acid units, takes place in the case of 66 h of SSP (Figure 5). The formation of oligocycles will be explained by back-biting of prepolymer chain ends if prepolymer chain ends are flexible in the amorphous part of the prepolymer. The forma-

tion of oligocycles could be favored by an increased crystallinity coupled with a simultaneous increase in the concentration of mobile chain ends in the amorphous phase. An increased fraction of cycles may cause a constant PLA melting temperature of around 160°C since the cycles may act as a plasticizer in the material.

Figure 7 demonstrates a linear decrease in M_n with longer reaction times. We assume that temperature-induced chain degradation dominates chain prolongation beyond 70 h of SSP. As presented in Figure 5, the amount of cycles decreases after 70 h of SSP. In the case of 150 h of SSP, PLA shows a crystallinity of 70% and D of 2 (Figure 5). The decrease in the dispersity can be explained by statistical decomposition of polymer chains since the final dispersity would be equal to 1. The effect of slower kinetics at high crystallinity has been discussed in the literature.¹² A linear decrease in M_n as a result of PLA degradation is consistent with the statistical decomposition model.⁵⁷ Factors such as hydrophilicity, crystallinity, MW of the polymer, and the presence of low MW compounds also influence the rate of degradation.^{58,59} In the literature, intramolecular transesterification resulting in cyclic oligomers has been identified as the main thermal degradation process of PLA.⁶⁰ This effect was not observed due to the low reaction temperature.

It is known that the SSP rate increases in the first few hours of SSP due to the increase in the effective concentration of functional end groups.¹² On the basis of the experimental results of Katiyar *et al.*,¹² we assume that an initial crystallinity of 50% results in a crystallinity of 70% after 20 h of SSP. This effect is also observed in the current study. In contrast to favorable initial crystallinity shown in other SSP articles (Refs. 26 and 27; 25–45%), a high degree of crystallinity of around 70%, formed by solid-state condensation at 140°C, was necessary to induce condensation reaction in the solid phase. We suppose a further reorientation of functional end groups rejected from the crystalline phase into the amorphous phase. In the case of high initial crystallinity (68%), Katiyar *et al.*¹² describe a more rapidly further crystallization (68–90% within 20 h of SSP). Reasons may

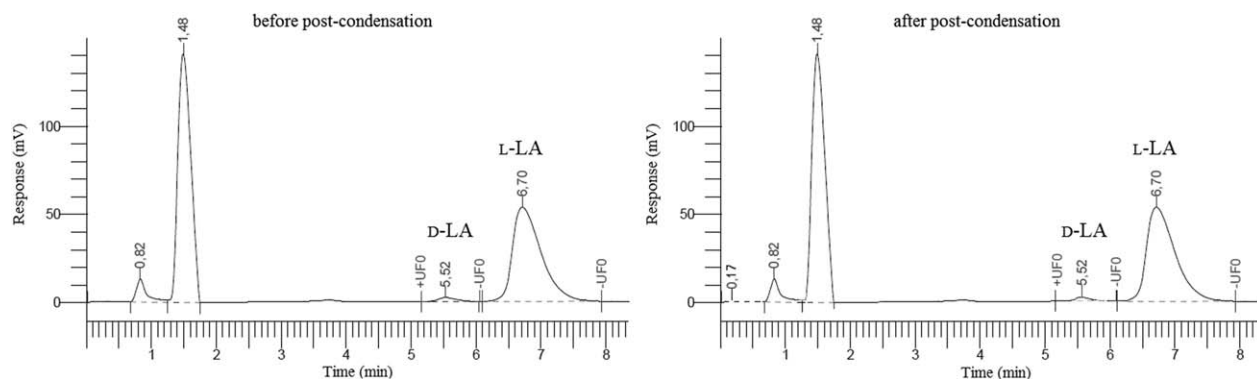


Figure 8. Chiral column chromatograms of precipitated and hydrolyzed lactic acid prepolymer before and after post-condensation showing peaks of D-lactic acid and L-lactic acid. [HPLC, Method 1: CHIRALPAK[®] MA(+) column, 3 mM copper monosulfate/water, 1.5 mL min⁻¹, 238 nm; synthesis of prepolymer: 30 h, 180°C, 0.5 mbar, 0.3 wt % ZS, reprecipitation; post-condensation: 140°C, 8 mbar, 66 h; chromatograms provided by Uhde Inventa-Fischer].

be found in different reaction conditions. The diffusivity is reported to be relatively independent of MW.¹² But the diffusivity reduces significantly with the increase in the initial crystallinity of the lactic acid prepolymer.¹² In byproduct diffusion limited reactions, SSP rate decreases with increasing crystallinity.¹² High values of crystallinity obtained by post-condensation are well known due to the synchronization of the crystallization rate with that of the slower and longer lasting step-growth SSP.¹⁷ Kuran *et al.*⁶¹ have described condensation reactions as a consequence of a high degree of crystallinity due to the fact that large fractions of long polymer chains have been supposed to be immobilized and the attack of by-products should be impossible. Xu *et al.*²⁷ have also implied an exponential relationship between the reaction time and MW, but in this case, the MW has been simply constant for less than 10 h and a relationship between reaction time, crystallinity and MW has not been inquired as in our current work. Other articles have pointed out that there is a strong increase in the MW during the first 20 h of SSP.^{10,12,14,15,22,26,29} Previous works^{10,12,17,22} have used rather small molar masses of the prepolymers whereas other researchers^{26,27} have used nearly the same starting MW and crystallinity²⁶ as described in this article. A high activity of Lewis acids has been taken as a basis of high MW products. This work considers SSP in a much lower temperature range as opposed to that in the Refs. 12, 17, 20, 22 and 26. In the current work, self-sticking particles were observed using higher reaction temperatures. On the other hand, a weight average MW around 160,000 g mol⁻¹, based on PS, is not far from previous literature studies (e.g., $M_w \sim 166,000$ g mol⁻¹ at a constant temperature of 150°C after 20 h²⁶). The long-time interval can be explained by the differences in the process conditions (catalyst, pressure, temperature) between those in the current work and those in the cited literature. The correlation, shown in Figure 7 on the right side, is consistent with the results of Vouyiouka *et al.*²⁸ In contrast to this work, another SSP literature article has pointed out that a high MW of prepolymer results in a high concentration of the reactive chain ends in the reaction area due to the fact that there should be a more effective confinement of the amorphous phase.⁶² Duh has suggested that chains of low MW prepolymers can easily fit into crystal

lattices, thus a high number of functional end groups will be trapped and become inactive.⁶³ Song and Wu²¹ have found that a small increase in M_w of the prepolymer has led to a very large increase in M_w of the final product. Such a multitude of different results shows the importance of scrutinizing the SSP of lactic acid prepolymers.

Optical Purity. Due to the lower reaction temperature in the solid phase condensation, racemization does not take place (Figure 8). PLLA is 98% optically pure. There is also no more discoloration caused by side reactions. Therefore, a short time for pre-condensation in the melt phase and a longer SSP time are beneficial procedures to get enantiopure and relatively uncolored high MW products.

Effect of Reaction Temperature. Isothermal reaction. SSP was performed at 120°C or at 140°C and 8 mbar for 20 h. In both cases, M_n does not change (10,300 g mol⁻¹), \mathcal{D} is 2 and the crystallinity increases by 10% to a crystallinity of 69%.

Stepwise increase in reaction temperature. With regard to M_n of 10,000 g mol⁻¹, a temperature-time program (5 h/140°C, 5 h/150°C, 10 h/155°C and 8 mbar) does not result in any higher M_n than a reaction proceeding constantly at 140°C for 20 h. It does not matter whether an isothermal process or a stepwise increase in the SSP temperature is chosen during the first 20 h of SSP since the orientation process of functional end groups may be independent on temperature. In contrast to this result, it has been reported in the literature that a stepwise increase in the SSP temperature should result in a higher final MW compared to an isothermal process.^{22,26,29}

Effect of Vacuum and Nitrogen Flow. SSP was carried out under vacuum (0.05–8.00 mbar) or nitrogen flow; however, no significant difference in MW of all samples is observed under the same start and reaction conditions (Table III).

SSP of Non-Recrystallized Prepolymer

Effect of Catalyst Concentration. As presented in Table IV, a three times larger MW of the condensate is obtained by tripling the concentration of ZS when low MW prepolymers are used. Side reaction effects resulting in a lower relative increase in M_n

Table III. Effect of Vacuum and Nitrogen Flow on Number Average MW of Post-Condensed Reprecipitated Prepolymers

M_n^a of prepolymer (g mol^{-1})	M_n^a (g mol^{-1}) after post-condensation at 140°C, 66 h		
	0.05 mbar	8 mbar	N_2^b
8,100	20,000	20,300	19,800
8,700	20,100	20,000	20,100
10,300	19,200	18,500	18,400
11,500	19,500	17,300	17,500

^aNumber average MW determined by GPC, based on PLA standards.

^bUsing tubular fixed-bed reactor and nitrogen flow of $0.04 \text{ L g}^{-1} \text{ min}^{-1}$.

are observed at a high catalyst concentration (Table IV). A 30 h melt condensate shows a crystallinity of 45% after grinding and annealing at 110°C for 0.5 h. In comparison to reprecipitated 30 h melt condensates, no difference in M_n ($19,000 \text{ g mol}^{-1}$), dispersity (4), crystallinity (70%), and OP (98%) is observed under the same post-condensation reaction conditions (66 h, 8 mbar, 140°C) using ground 30 h melt product with 0.3 wt % ZS. With regard to ground prepolymers with M_n of $10,000 \text{ g mol}^{-1}$, M_n does not change during the first 20 h of SSP ($19,200 \text{ g mol}^{-1}$). The orientation process of functional end groups seems to be independent on the presence of ZS.

Supported ZS is an enantioselective catalyst for SSP of prepolymers since the OP of PLA does not change during the SSP. Nearly the same maximum M_n is obtained even for lower and higher catalyst concentrations (0.2 wt %: $19,700 \text{ g mol}^{-1}$; 0.5 wt %: $18,600 \text{ g mol}^{-1}$). The effect of the acidic catalyst on the MW of PLA is not any longer available since side reactions come out on top and a maximum MW of PLA is reached.

Effect of Reaction Time and Temperature. A linear increase in M_n is observed when a short-chain prepolymer is heated up to 90°C for 0.5 h and to 120°C for 10 or 20 h in presence of 0.3 wt % ZS ($M_n(0 \text{ h SSP}) \sim 4,300 \text{ g mol}^{-1}$, $C(0 \text{ h SSP}) = 59\%$, $M_n(10 \text{ h SSP}) \sim 8,700 \text{ g mol}^{-1}$, $C(10 \text{ h SSP}) = 63\%$, $M_n(20 \text{ h SSP})$

Table IV. SSP of Lactic Acid Prepolymers: Effect of Concentration of ZS on MW and Crystallinity

Prepolymer (ground) ^a			Annealed prepolymer ^d C^d (%)	SSP condensate ^e	
C (ZS) (wt %)	M_n^b (g mol^{-1})	C^c (%)		M_n^b (g mol^{-1})	C^c (%)
0.0	1,400	8	45	1,500	48
0.1	2,200	35	55	3,100	60
0.2	3,300	37	56	6,400	63
0.3	4,300	38	59	9,500	65
0.5	5,000	38	59	10,100	66

^aMade by melt condensation of lactic acid at 180°C and 0.5 mbar for 5 h in the presence of ZS.

^bNumber average MW determined by GPC, based on PLA standards.

^cDegree of crystallinity based on DSC measurements ($10^\circ\text{C min}^{-1}$).

^dAnnealed at 90°C (cold crystallization temperature) for 0.5 h.

^eSSP run at 120°C (5 h, 8 mbar) and 125°C (5 h, 8 mbar).

Table V. Number Average MW of Post-Condensed PLA^a Depending on Pre-Treatment (Annealing, Reprecipitation)

Annealing conditions		SSP condensate ^b without previous reprecipitation		SSP condensate ^b with previous reprecipitation	
T (°C)	t (h)	C^c (%)	M_n^d (g mol^{-1})	C^c (%)	M_n^d (g mol^{-1})
	0	8 ^c	10,300	59	18,000
70	1.0	8	10,200	59	18,100
70	2.5	10	10,700	59	18,100
90	0.5	12	10,900	59	18,000
90	1.0	13	11,800	59	18,300
105	0.5	45	19,300	59	18,300
105	1.0	52	19,700	60	17,000
110	0.5	45	19,000	59	18,500
110	1.0	53	19,300	60	17,700
120	0.5	63	16,500	58	18,100

^aPrepolymer made by melt condensation of lactic acid at 180°C and 0.5 mbar for 30 h in the presence of 0.3 wt % ZS.

^bSSP run at 140°C and 8 mbar for 66 h.

^cDegree of crystallinity based on DSC measurements ($10^\circ\text{C min}^{-1}$).

^dNumber average MW determined by GPC, based on PLA standards.

$\sim 13,000 \text{ g mol}^{-1}$, $C(20 \text{ h SSP}) = 63\%$, $D = \text{const.} = 2$). The melting temperatures of this prepolymer are found to be 122 and 142°C. Performing post-condensation of this ground prepolymer by a stepwise increase in the SSP reaction temperature (0.5 h/90°C, 5 h/120°C, 5 h/125°C, 15 h/130°C, 25 h/135°C, 75 h/145°C and 8 mbar), PLA with $22,000 \text{ g mol}^{-1}$ (M_n) and D of 4 is obtained. The listed temperature program results in an increase in M_n by a factor of 5; the melting temperature is 163°C and the crystallinity is in the order of 75%.

Variation of Annealing Conditions

No post-condensation takes place in the case of largely amorphous prepolymers (Table V). We suppose that the number of functional end groups is too low in the amorphous phase where the condensation should take place. As a consequence of the largest mobility of the prepolymer chains, optimum crystallization conditions of ground PLA with M_n of $10,300 \text{ g mol}^{-1}$ are found to be at the cold crystallization temperature of the sample (105–110°C) shown in Table V. Experimental data show no difference in the MW of post-condensates when a pressure of 8 mbar was used. As presented in Table V, an annealing process will be not necessary if the reprecipitation procedure is performed.

CONCLUSIONS

Catalyst-free PLA was synthesized by reprecipitation and SSP of lactic acid prepolymers. One of the most important results of this work is found in an unchanged MW and dispersity of 2 after more than 30 h of SSP at a relatively high reaction temperature. A high degree of crystallinity and a high concentration of end groups, rejected from the crystalline phase into the amorphous phase, were necessary to induce condensation reaction. Reorientation of functional end groups was especially required

for long prepolymer chains since the concentration of functional end groups decreased with increasing the length of polymer chains. In the case of high MW PLA, the dispersity changed to 4. A maximum MW ($M_w \sim 80,000 \text{ g mol}^{-1}$ based on PLA standards) was obtained by the direct condensation process. In comparison to reprecipitated samples, there was no difference in the course of the condensation reaction and in the maximum MW using supported ZS as catalyst and long-chain prepolymers ($M_n \sim 10,000 \text{ g mol}^{-1}$). Supported ZS was found to be an efficient and enantioselective catalyst for the SSP of short-chain prepolymers ($M_n \sim 1,400\text{--}5,000 \text{ g mol}^{-1}$). The same maximum MW was obtained in the presence or absence of catalyst. On the basis of our experimental results, we have thus proven that the present condensation reaction is mainly limited by degradation reactions. The choice of catalyst plays an important role during the SSP of prepolymers. The present work helps to give the best possible overview about MW limitation of post-condensed PLA in the presence and absence of a Brønsted acid catalyst.

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REFERENCES

- Hiltunen, K.; Seppälä, J. V.; Härkönen, M. *Macromolecules* **1997**, *30*, 373.
- Harshe, Y. M.; Storti, G.; Morbidelli, M.; Gelosa, S.; Moscatelli, D. *Macromol. React. Eng.* **2007**, *1*, 611.
- Achmad, F.; Yamane, K.; Quan, S.; Kokugan, T. *Chem. Eng. J.* **2009**, *151*, 342.
- Chen, G.-X.; Kim, H.-S.; Kim, E.-S.; Yoon, J.-S. *Eur. Polym. J.* **2006**, *42*, 468.
- Moon, S. I.; Lee, C. W.; Miyamoto, M.; Kimura, Y. *J. Polym. Sci. Part A: Polym. Chem.* **2000**, *38*, 1673.
- Peng, B.; Xu, Y.; Hu, J.; Bu, Z.; Wu, L.; Li, B.-G. *Polym. Degrad. Stab.* **2013**, *98*, 1784.
- Kanno, T.; Oyama, H. T.; Usugi, S. *Eur. Polym. J.* **2014**, *54*, 62.
- Marques, D. S.; Gil, M. H.; Baptista, C. M. S. G. *J. Appl. Polym. Sci.* **2013**, *128*, 2145.
- Baick, I. H.; Luciani, C. V.; Park, S. Y.; Lim, T.; Choi, K. Y. *Ind. Eng. Chem. Res.* **2012**, *51*, 16617.
- Moon, S.-I.; Lee, C.-W.; Taniguchi, I.; Miyamoto, M.; Kimura, Y. *Polymer* **2001**, *42*, 5059.
- Kucharczyk, P.; Poljansek, I.; Sedlářik, V. *J. Macromol. Sci. A* **2012**, *49*, 795.
- Katiyar, V.; Shaama, M. S.; Nanavati, H. *J. Appl. Polym. Sci.* **2011**, *122*, 2966.
- Fukushima, K.; Kimura, Y. *J. Polym. Sci. Part A: Polym. Chem.* **2008**, *46*, 3714.
- Kucharczyk, P.; Sedlářik, V.; Junkar, I.; Kreuh, D.; Sáha, P. *Mater. Technol.* **2012**, *46*, 37.
- Steinborn-Rogulska, I.; Parzuchowski, P.; Rokicki, G. *Polym. Chem.* **2014**, *5*, 5412.
- Zhang, W.-x.; Wang, Z.-z. *Chin. J. Polym. Sci.* **2008**, *26*, 425.
- Katiyar, V.; Nanavati, H. *Polym. Eng. Sci.* **2011**, *51*, 2078.
- Pivsa-Art, S.; Niamlang, S.; Pivsa-Art, W.; Pavasupree, S.; Ishimoto, K.; Ohara, K. *Adv. Mater. Res.* **2012**, *418/420*, 1301.
- Huang, W.; Cheng, N.; Qi, Y.; Zhang, T.; Jiang, W.; Li, H.; Zhang, Q. *Polymer* **2014**, *55*, 1491.
- Katiyar, V.; Nanavati, H. *Polym. Compos.* **2011**, *32*, 497.
- Song, F.; Wu, L. *J. Appl. Polym. Sci.* **2011**, *120*, 2780.
- Moon, S.-I.; Taniguchi, I.; Miyamoto, M.; Kimura, Y.; Lee, C.-W. *High Perform. Polym.* **2001**, *13*, 189.
- Fukushima, T.; Sumihiro, Y.; Koyanagi, K.; Hashimoto, N.; Kimura, Y.; Sakai, T. *Int. Polym. Proc.* **2000**, *15*, 380.
- Qian, G.; Zhou, X.-G.; Zhu, L.-B.; Yuan, W.-K. *J. Polym. Eng.* **2003**, *23*, 413.
- Wu, L.; Hou, H. *J. Appl. Polym. Sci.* **2010**, *115*, 702.
- Peng, B.; Hou, H.; Song, F.; Wu, L. *Ind. Eng. Chem. Res.* **2012**, *51*, 5190.
- Xu, H.; Luo, M.; Yu, M.; Teng, C.; Xie, S. *J. Macromol. Sci. B* **2006**, *45*, 681.
- Vouyiouka, S.; Theodoulou, P.; Simeonidou, A.; Papaspyrides, C. D.; Pfaender, R. In *Solid State Polymerization of Poly(lactic acid): Critical Process Parameters*; 7th Conference MoDeSt: Prague, **2012**.
- Ren, J.; Zhang, N.-W.; Wang, Q.-F. *CN Pat.*, 1718607 A, **2004**.
- Meyer, K. *Angew. Makromol. Chem.* **1973**, *34*, 165.
- Södergård, A.; Stolt, M. In *Poly(lactic acid): Synthesis, Structures, Properties, Processing and Applications*; Auras, R., Lim, L.-T., Selke, S. E. M., Tsuji, H., Eds.; Wiley: Hoboken, New Jersey, **2010**; Chapter 3, pp 28–31.
- Chen, F. C.; Griskey, R. G.; Beyer, G. H. *AIChE J.* **1969**, *15*, 680.
- Achmad, F.; Yamanishi, K.; Liu, Z. Y.; Kokugan, T. *J. Chem. Eng. Jpn.* **2009**, *42*, 632.
- Liu, C.; Lievens, J. *US Pat.*, US 20050112737 A1, **2003**.
- Zhang, Z.; Jackson, J. E.; Miller, D. *J. Bioresour. Technol.* **2008**, *99*, 5873.
- Qureshi, M. S.; Bhongale, S. S.; Thorave, A. K. *J. Chromatogr. A* **2011**, *1218*, 7147.
- Pandey, A. K. *IJAPBC* **2013**, *2*, 68.
- Inkinen, S.; Hakkarainen, M.; Albertsson, A. C.; Södergård, A. *Biomacromolecules* **2011**, *12*, 523.
- Flory, P. *J. Chem. Rev.* **1946**, *39*, 137.
- Raase, J. M.; Reichert, K.-H.; Schomäcker, R. *Macromol. Symp.* **2014**, *333*, 216.
- Radke, W. In *Poly(lactic acid) (PLA) for New Biobased Packaging*, Project Number 08 EN (DKI 8801); German National Library, Deutsches Kunststoff-Institut Darmstadt, Annual Report, 2010;

- pp 41–44; Available at: URL: <http://d-nb.info/1011520184>. Last accessed on February 17, 2014.
42. Fisher, E. W.; Sterzel, H. J.; Wegner, G. *Kolloid Z. Z. Polym.* **1973**, *251*, 980.
 43. Codari, F.; Moscatelli, D.; Storti, G.; Morbidelli, M. *Macromol. Mater. Eng.* **2010**, *295*, 58.
 44. Bancroft, W. D.; Davis, H. L. *J. Phys. Chem.* **1931**, *35*, 2508.
 45. Bruice, P. Y. In *Organic Chemistry*; Zalesky, J., Eds.; Prentice Hall, Inc.: Upper Saddle River, New Jersey, **2014**; Vol. 7, Chapter 4, pp 160–164.
 46. Patterson, A. L. *Phys. Rev.* **1939**, *56*, 978.
 47. Kaitian, X.; Kozluca, A.; Denkbaz, E. B.; Piskin, E. *Turk. J. Chem.* **1996**, *20*, 43.
 48. Vu, D. T.; Kolah, A. K.; Asthana, N. S.; Peereboom, L.; Lira, C. T.; Miller, D. *J. Fluid Phase Equilib.* **2005**, *236*, 125.
 49. Hauser, O.; Herzfeld, H. *ZACC* **1919**, *106*, 1.
 50. Kleine, J.; Kleine, H.-H. *Macromol. Chem. Phys.* **1959**, *30*, 23.
 51. Cai, Y. H.; Yan, S. F.; Yin, J. B.; Fan, Y. Q.; Chen, X. S. *J. Appl. Polym. Sci.* **2011**, *121*, 1408.
 52. Wang, B. B.; Zhou, Z. W.; Gu, L. X. *Mater. Res. Bull.* **2003**, *38*, 1449.
 53. Cam, D.; Marucci, M. *Polymer* **1997**, *38*, 1879.
 54. Pan, P.; Kai, W.; Zhu, B.; Dong, T.; Inoue, Y. *Macromolecules* **2007**, *40*, 6898.
 55. Yasuniwa, M.; Sakamo, K.; Ono, Y.; Kawahara, W. *Polymer* **2008**, *49*, 1943.
 56. Zhang, J. M.; Duan, Y. X.; Sato, H.; Tsuji, H.; Noda, I.; Yan, S.; Ozaki, Y. *Macromolecules* **2005**, *38*, 8012.
 57. Lechner, M. D.; Gehrke, K.; Nordmeier, E. H. In *Makromolekulare Chemie: Ein Lehrbuch für Chemiker, Physiker, Materialwissenschaftler und Verfahrenstechniker*; Lechner, M. D.; Gehrke, K., Eds.; Birkhäuser Verlag: Basel, Switzerland, **2010**; Vol. 5, Chapter 7, pp 664–680.
 58. Göpferich, A. *Biomaterials* **1996**, *17*, 103.
 59. Mayer, J. M.; Kaplan, D. L. *Trends Polym. Sci.* **1994**, *2*, 227.
 60. McNeill, I. C.; Leiper, H. A. *Polym. Degrad. Stab.* **1985**, *11*, 309.
 61. Kuran, W.; Dèbek, C.; Wielgosz, Z.; Kuczyńska, L.; Sobczak, M. *J. Appl. Polym. Sci.* **2000**, *77*, 2165.
 62. Gaymans, R. J.; Amirtharaj, J.; Kamp, H. *J. Appl. Polym. Sci.* **1982**, *27*, 2513.
 63. Duh, B. *J. Appl. Polym. Sci.* **2001**, *81*, 1748.