

# Kinetics of D,L-Lactide Polymerization Initiated with Zirconium Acetylacetonate

Kirill T. Kalinin,\* Nikita G. Sedush, Petr V. Dmitryakov, and Sergei N. Chvalun<sup>[a]</sup>

The kinetic of D,L-lactide polymerization in presence of biocompatible zirconium acetylacetonate initiator was studied by differential scanning calorimetry in isothermal mode at various temperatures and initiator concentrations. The enthalpy of D,L-lactide polymerization measured directly in DSC cell was found to be  $\Delta H = -17.8 \pm 1.4 \text{ kJ mol}^{-1}$ . Kinetic curves of D,L-lactide polymerization and propagation rate constants were determined for polymerization with zirconium acetylacetonate

at concentrations of 250–1000 ppm and temperature of 160–220 °C. Using model or reversible polymerization the following kinetic and thermodynamic parameters were calculated: activation energy  $E_a = 44.51 \pm 5.35 \text{ kJ mol}^{-1}$ , preexponential constant  $\ln A = 15.47 \pm 1.38$ , entropy of polymerization  $\Delta S = -25.14 \text{ J mol}^{-1} \text{ K}^{-1}$ . The effect of reaction conditions on the molecular weight of poly(D,L-lactide) was shown.

## 1. Introduction

Poly(lactide) (PLA) is a biodegradable and biocompatible aliphatic polyester which can be derived from renewable resources. Currently, polylactide is used for production of medical implants for orthopedics such as screws, pins and other fixation devices; in tissue engineering for manufacturing of scaffolds<sup>[1]</sup>. Linear and star-shaped copolymers, mostly with glycolide are promising materials for development of nano- and microparticles-based drug delivery systems.<sup>[2,3]</sup>


One of the most popular initiator for lactide polymerization is stannous octoate.<sup>[4]</sup> However, polymers synthesized with this initiator cannot be considered as fully biocompatible due to the high toxicity of the tin ion. Complete elimination of the highly toxic tin compounds from the synthesized polymers is almost impossible. Therefore, biocompatible initiators for lactone polymerization are attracting considerable interest. Recently, many biocompatible initiators have been studied, mainly complexes and salts of various metals: lithium tert-butoxide;<sup>[5]</sup> calcium,<sup>[6]</sup> magnesium and zinc isopropoxide;<sup>[7]</sup> zinc complexes<sup>[8,9]</sup> and others. The transition metal complexes of groups 4 and 5: aluminum, titanium and zirconium showed excellent biocompatibility.<sup>[10]</sup> Zirconium complexes are excelled from this series, which showed not only high activity, but also in some cases stereocontrolled polymerization.<sup>[11]</sup> Zirconium acetylacetonate is the most promising from a series of zirconium complexes, which was effective for lactone polymerization.<sup>[11–13]</sup> This initiator is stable, commercially avail-


able and does not require additional purification before use. Piotr Dobrzynski et al. synthesized poly(L-lactide) with a conversion close to 100% and molecular weight of up to 100 kDa in 72 hours at 120 °C.<sup>[14]</sup> Arkadiusz Orchel et al. studied lactide copolymerization with various comonomers and obtained samples with a molecular weight from 42 to 63 kDa.<sup>[15]</sup> Recently, zirconium acetylacetonate was used as initiator for one-step synthesis of functional low molecular weight poly(lactide-co-trimethylene carbonate) copolymers and high molecular weight poly(L-lactide) with  $M_w$  of 230 kDa and  $PD_i$  of 2.<sup>[16]</sup> It was successfully implemented for synthesis of L-lactide, 1,3-trimethylene carbonate and glycolide terpolymers with shape-memory properties.<sup>[17]</sup>

In the aforementioned papers polymerization was studied at rather low temperatures (100–130 °C) mainly in solution, therefore the reaction time was at least 24 hours. We believe that  $Zr[Acac]_4$  is a promising replacement for  $Sn(Oct)_2$ , but for industrial application it is necessary to study kinetics and thermodynamics of polymerization and to determine the optimal conditions for fast and controlled synthesis of high molecular weight polymer in melt.

The effect of reaction conditions on polymerization kinetics must be studied in order to control the reaction and characteristics of synthesized polylactide. We have previously shown that differential scanning calorimetry can be successfully applied to study L-lactide<sup>[18]</sup> and D,L-lactide<sup>[19]</sup> polymerization in presence of tin octoate. In this paper, this method is used to study polymerization of D,L-lactide in presence of zirconium acetylacetonate. The enthalpy of the reaction is determined and the activation energy, preexponential factor and entropy of the reaction are calculated.

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## Experimental Section

### Materials

Initiators for lactide polymerization – zirconium acetylacetonate (97%) and tin 2-ethyl hexanoate (95%) were purchased from Sigma-Aldrich (USA) and were used without further purification. D,L-lactide (99%) was purchased from Corbion (Netherlands) and was purified by recrystallization from dry butyl acetate and dried in vacuum at room temperature. Hexane “extra pure” grade was purchased from Komponent-reaktiv (Russia) and was used for preparation of the initiator solution.

### Measurements

Kinetics of D,L-lactide polymerization was investigated in the Mettler DSC 30 calorimeter in isothermal mode in an inert gas flow. The reaction mixture was prepared as follows. The flask was dried before use at 120 °C in vacuum. From 4.2 to 16.6 mg (250–1000 ppm) of zirconium acetylacetonate was dissolved in 3 ml of hexane and this solution was added to a 5 g of D,L-lactide. Similarly, a reaction mixture with tin octoate was prepared. Tin octoate (14.0 mg) was dissolved in 3 ml of hexane and added to a 5 g of D,L-lactide. The reaction mixture was dried under vacuum until complete removal of hexane. The DSC pan (nominal volume of 40  $\mu$ l) was filled with about 20–30 mg of the reaction mixture and sealed. The pan was placed in the preliminary heated DSC cell and recording of the thermogram was started. No weight loss was observed in the pan after experiment.

Molecular weight characteristics of the synthesized polymers were determined by GPC. We used a Knauer chromatographic complex (Germany) equipped with a refractometric detector, a 10<sup>4</sup> Å Agilent PLgel column and tetrahydrofuran as an eluent. The experiments were carried out at a temperature of 40 °C and an eluent flow rate of 1 ml/min. The column was calibrated using polystyrene standards. To process the results, the Claritychrom software was used.

<sup>1</sup>H NMR was used to determine the final monomer conversion. After the end of the experiment a DSC pan was cut and the polymer was dissolved dried deuterated chloroform. The NMR spectra of the received samples were recorded at room temperature with a Bruker DPX-300 spectrometer. The conversion was determined by the ratio of the integral intensity of the polymer methine group ( $\delta = 5.09$ – $5.21$ ) ppm to the sum of the integrated intensities of the polymer and the monomer methine groups 4.99–5.04 ppm:

$$\alpha = \frac{I_{\text{Polymer}}^{\text{CH}}}{I_{\text{Polymer}}^{\text{CH}} + I_{\text{Monomer}}^{\text{CH}}} \quad (1)$$

The thermal stability of zirconium acetylacetonate was studied by thermogravimetric analysis with a Mettler TA 3000 instrument in an inert gas flow, in the temperature range of 25–700 °C and heating rate of 10 °C/min. Isothermal analysis was conducted in inert atmosphere at 180 °C for 80 min.

## 2. Results and Discussion

### 2.1. Mechanism

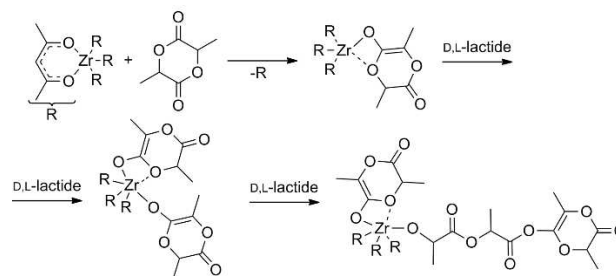
The mechanism of D,L-lactide polymerization in the presence of zirconium acetylacetonate was studied previously.<sup>[13]</sup> Piotr Dobrzynski et al. proposed a coordination-insertion mechanism,

which is described in Scheme 1. Briefly, the lactide molecule coordinates through oxygen of the carbonyl group on the zirconium atom of the initiator. As a result of the disturbances of the charge distribution of methine carbon of lactide, the zirconium acetylacetonate ligand cycle opens, lactide is deprotonated and a hydroxyl group is formed at the end of the ligand. At the same time, the Zr–O bond forms, the unsaturated bond in the lactide ring and the acetylacetonate ligand is released in enol form. The coordination of the next lactide molecule on the zirconium atom occurs through a pair of free electrons of carbonyl oxygen. As a result of the formation of the nine-coordinate complex the lactide ring opens and lactidyl chain is formed ending with a deprotonated lactide attached to the zirconium atom through a Zr–O bond. Chain growth proceeds after the coordination of the next lactide molecule, which is simplified due to coordinatively unsaturated (coordination number 7) form of the complex.

### 2.2. Effect of the Temperature on the Polymerization Rate

D,L-lactide ring-opening polymerization is an exothermic reaction, each act of ring opening and propagation is accompanied by the heat release, which allows one to study the reaction by differential scanning calorimetry. Thermograms of D,L-lactide polymerization in presence of zirconium acetylacetonate were obtained in the temperature range of 160–220 °C with initiator concentration of 250–1000 ppm in isothermal mode. Thermograms and kinetic curves at various temperatures and initiator concentration of 1000 ppm are shown in Figure 1. Kinetic curves were obtained by integration of thermograms taking into account the final conversion of each reaction determined by NMR.

Figure 1a shows the values of the enthalpy of reaction at temperatures of 160–220 °C, which decreases with decreasing polymerization temperature from  $-17.3$  to  $-13.8$  kJ mol<sup>-1</sup>, although the conversion is the same for all samples. The decrease of thermal effect is probably due to the insufficient sensitivity of the DSC sensor, which is crucial at latter stages of slow reactions. The polymerization enthalpy  $\Delta H_{100}$  (corresponding to 100% conversion) was calculated by assigning the thermal effect of the reaction to the measured conversion by NMR. For the D,L-lactide polymerization by averaging the enthalpy  $\Delta H$  of several reactions with the medium rate, a value



**Scheme 1.** Mechanism of lactide polymerization in presence of zirconium acetylacetonate.

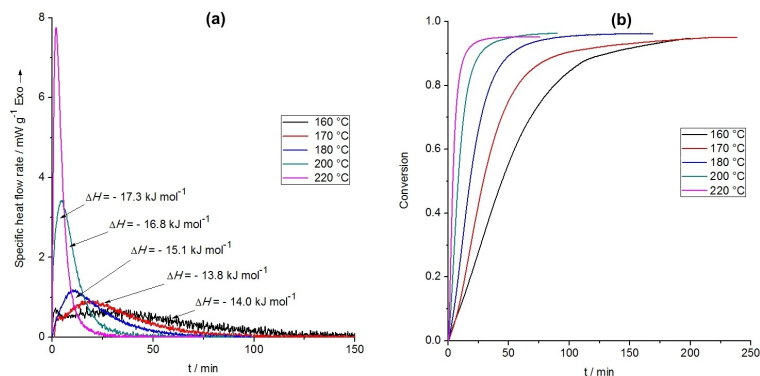


Figure 1. Thermograms (a) and kinetic curves (b) of D,L-lactide polymerization at 160–220 °C and zirconium acetylacetonate concentration of 1000 ppm.

of  $\Delta H = -17.8 \pm 1.4 \text{ kJ mol}^{-1}$  was calculated. Previously determined value<sup>[18]</sup> is rather close –  $\Delta H = -17.3 \pm 1.5 \text{ kJ mol}^{-1}$ . The conversion for samples synthesized at 160–220 °C is 0.95–0.96. At temperatures of 160 and 170 °C a peak appears at the beginning of the thermogram, which is absent at higher temperatures. It can be associated with a slower of formation of active centers. As can be seen from the kinetic curves (Figure 1b), the reaction rate increases with increasing temperature. The time to reach maximum conversion at 180 °C is about 100 minutes. Raising the temperature to 200 and 220 °C accelerates the reaction and maximum conversion was achieved in 70 and 45 minutes, respectively.

Comparison of catalytic activity of zirconium acetylacetonate and tin octoate were conducted at 180 °C and initiator concentration of 1000 ppm. It can be seen from the graphs in Figure 2 that the catalytic activity of zirconium acetylacetonate is lower than that of tin octoate. The time to achieve maximum conversion is 120 minutes for the reaction initiated by  $\text{Zr}[\text{Acac}]_4$  and 60 minutes in presence of  $\text{Sn}(\text{Oct})_2$ . The weight average molecular weight of the polylactide synthesized in the presence of  $\text{Zr}[\text{Acac}]_4$  is 108 kDa and 130 kDa with  $\text{Sn}(\text{Oct})_2$ . The reaction rate in case tin octoate is higher, but the lack of catalytic activity of zirconium acetylacetonate can be compensated by an increased concentration, which is impossible when using tin octoate due to its toxicity.

Decreasing the initiator concentration to 750 ppm at the same temperatures (Figure 3) leads to a decrease of polymerization rate of D,L-lactide. The conversion values of the samples were 0.95–0.96. Reducing the initiator concentration from 1000 to 500 ppm weakly affects the kinetics of the reaction. The reaction rate noticeably decreases at a temperature of 170 °C (equilibrium conversion achieved in 370 minutes) in comparison to polymerization at 180–220 °C.

A similar pattern is observed at the initiator concentration of 500 ppm. As in the case of 750 ppm, the kinetic curves at high temperature are similar, while the kinetic curve at 180 °C is noticeably distinguished. The conversion of the samples is 0.95–0.96 and the reaction time at 180, 200 and 220 °C is 190, 140 and 90 minutes, respectively.

A significant decrease in the polymerization rate occurs at the initiator concentration of 250 ppm. The half-time of conversion at 200 and 220 °C is rather close – 30 and 12 minutes, but the time to achieve the equilibrium is very different – 320 and 80 minutes, respectively. At temperatures of 160 and 170 °C the equilibrium conversion was not achieved even in 450 minutes of the reaction, the maximum value is 0.91 and 0.89, respectively. An induction period appears, which may be associated with a slow stage of the formation of active centers. A significant slowdown in polymerization at temperatures below 170 °C can be explained as follows. In the

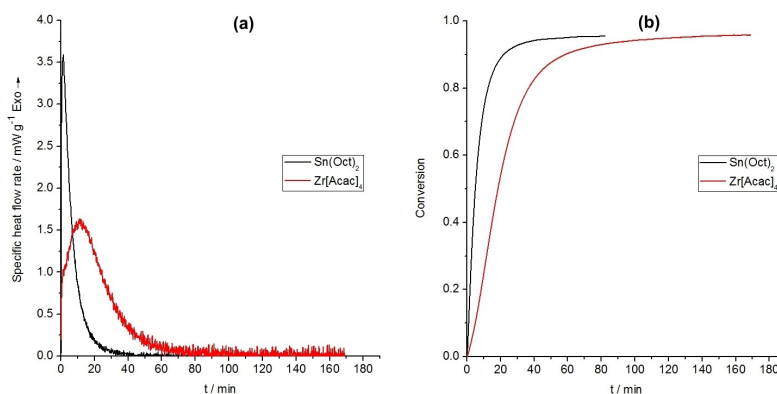


Figure 2. Thermograms (a) and kinetic curves (b) of the D,L-lactide polymerization at a temperature of 180 °C and initiator concentration of 1000 ppm.

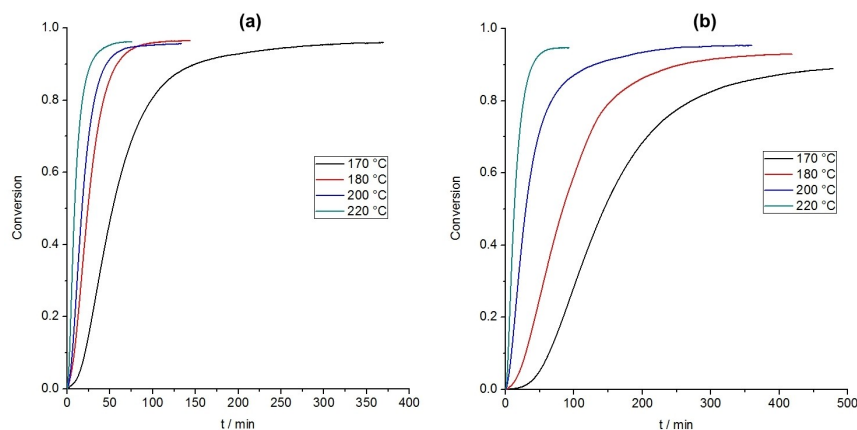


Figure 3. Kinetic curves of D,L-lactide polymerization in the temperature range 170–220 °C and initiator concentration of 750 ppm (a) and 250 ppm (b).

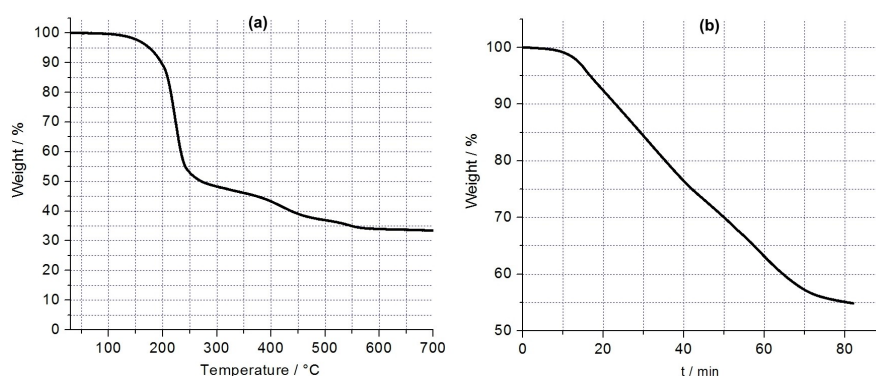


Figure 4. Thermogravimetric curves of zirconium acetylacetonate in dynamic 10 °C/min (a) and isothermal 180 °C (b) modes.

polymerization mechanism described above, the replacement of one zirconium acetylacetonate ligand with a deprotonated lactide molecule is required to form an initiating complex. At temperatures above 170 °C spontaneous separation of zirconium acetylacetonate ligands occurs (the higher the temperature, the more intense the separation), which results in an acceleration of the formation of the initiating complex and acceleration of the reaction. This statement is indirectly confirmed by thermogravimetric analysis: in the temperature range 120–250 °C. A loss of 45 % of the initiator mass attributed to release of organic initiator ligands occurs (Figure 4a). Isothermal TGA experiment (Figure 4b) demonstrates that linear weight loss over time occurs even at temperatures as low as 180 °C.

It should be noted that in contrast to mechanism with tin octoate, where additional hydroxyl-containing compounds are needed to initiate the polymerization, zirconium acetylacetonate acts both as catalyst and initiator. Therefore, by varying the concentration of zirconium acetylacetonate it is possible to control the molecular weight of the synthesized polylactide. Table 1 and Figure S2 show that with increasing concentration of the zirconium acetylacetonate the molecular weight decreases. An increase in the polymerization temperature is also accompanied by the decrease in the molecular weight, which could be explained by the higher effective concentration of the

Table 1. Effect of reaction conditions on the molecular weight characteristics of polylactide.

T, °C	Mw, kDa (PD <sub>i</sub> )			
	Initiator concentration, ppm			
	250	500	750	1000
180	187 (1.90)	148 (1.94)	120 (1.81)	113 (1.73)
200	–	103 (1.74)	–	–
220	89 (2.06)	82 (2.00)	34 (2.10)	30 (2.02)

active sites. The lower molecular weight and higher PD<sub>i</sub> at 220 °C can be attributed to a high rate of side reactions. At this temperature the polymer has dark color after 30 minutes of reaction. It has been found that the optimal polymerization temperature is in the range of 180–200 °C. High molecular weight polymer with PD<sub>i</sub> < 2 can be synthesized in short time at these conditions.

### 2.3. Effect of the Initiator Concentration on the Reaction Rate

The effect of the initiator concentration on the polymerization reaction rate was studied in a series of experiments at a temperature of 180 and 220 °C and initiator concentration of 250–1000 ppm (Figure 5).

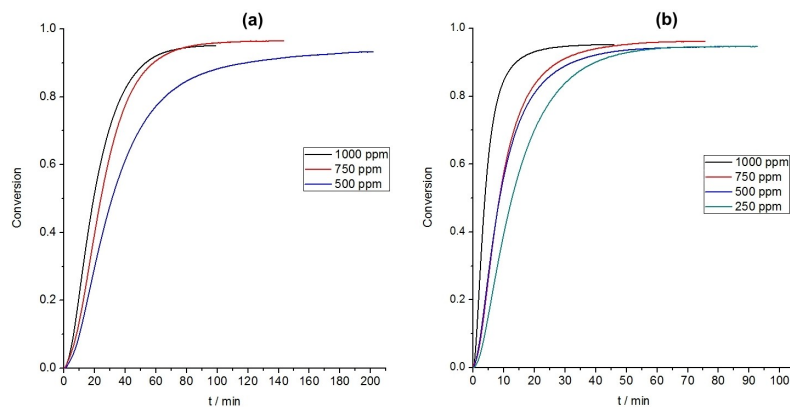


Figure 5. Kinetic curves of D,L-lactide polymerization at 180 (a) and 220 °C (b) and initiator concentration of 250–1000 ppm.

At 220 °C and 250 ppm of initiator the equilibrium conversion is achieved after 85 min of polymerization. At concentration of 500 and 750 ppm there is not much difference, equilibrium is reached after 70 minutes. At 1000 ppm equilibrium conversion is achieved in 45 minutes.

Reducing the polymerization temperature to 180 °C increases the time to reach equilibrium up to 185 minutes at an initiator concentration of 500 ppm. In 105 minutes of reaction, equilibrium is reached at concentration of 750 and 1000 ppm.

#### 2.4. Thermodynamic Parameters of D,L-Lactide Polymerization

The study of the thermodynamic parameters of the reaction is necessary not only for more complete understanding of the process, but also for the possibility of transferring the reaction from laboratory to industrial scale. The polymerization enthalpy was determined by integrating reaction thermograms. The reaction rate constant  $k$ , the activation energy  $E_a$ , and the preexponential factor  $A$  were calculated using the reversible polymerization model proposed and verified by Witzke et al.<sup>[20]</sup>

To calculate the rate constants at different temperatures, the  $-\ln(1-\alpha/\alpha_{\max})$  time dependences were plotted (Figure S1). The rate constants were calculated from the slopes of the linear approximation. The initial portion of the dependence has a deviation from a linearity. This is due to the existence of a transition process with simultaneous initiation and growth of chains. After the formation of all initiating centers the dependence becomes linear and correctly described by the model of reversible polymerization. This fact is confirmed by an increase in the initial deviation for slower reactions. Deviation in the final section of the dependence is associated with a non-exponential equilibrium, unlike the model. To calculate the rate constants a linear section in the region of medium conversions was used. The results are presented in Table 2.

Based on the data in Table 2, the Arrhenius plot was obtained (Figure 6). The activation energy  $E_a$  was determined from the slope of the straight line and the pre-exponential

Table 2. Polymerization rate constants of D,L-lactide under various reaction conditions

T, (°C)	[Zr(AcAc) <sub>4</sub> ] [ppm]	k [h mol%init] <sup>-1</sup>	lnk
170	750	23.1	3.14
170	1000	31.7	3.45
180	500	40.0	3.68
180	750	45.4	3.81
180	1000	33.5	3.51
200	500	89.9	4.49
200	750	55.5	4.01
200	1000	72.7	4.28
220	250	72.1	4.27
220	500	103.6	4.64
220	750	88.5	4.48
220	1000	124.5	4.82

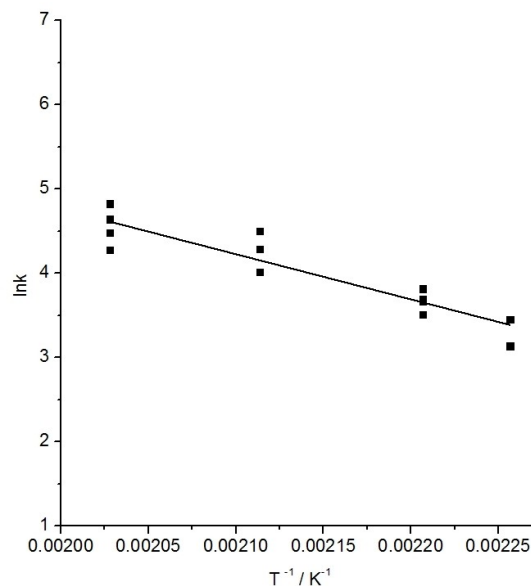


Figure 6. Dependence of the rate constant on temperature in Arrhenius coordinates.

factor  $A$  was determined from its intersection with the ordinate axis.

The values of the activation energy  $E_a$  and the preexponential factor A were found to be:

$$E_a = 44.51 \pm 5.35 \text{ kJ mol}^{-1} \quad \ln A = 15.47 \pm 1.38$$

The activation energy of the polymerization of D,L-lactide initiated by zirconium acetylacetonate was determined for the first time. The calculated kinetic parameters in this work are quite close to the values that we previously determined for the polymerization of L-lactide in presence of tin octoate:<sup>[18]</sup>  $E_a = 50 \pm 5 \text{ kJ mol}^{-1}$ ,  $\ln A = 18 \pm 1$ .

The polymerization entropy of D,L-lactide can be calculated using the following equation:

$$\Delta S = \Delta H/T - R \cdot \ln M_{eq} \quad (2)$$

The average value of entropy at various temperatures is  $\Delta S = -25.14 \text{ J mol}^{-1} \text{ K}^{-1}$ . A close value of entropy was obtained by Penczek<sup>[21]</sup>  $\Delta S = -25.03 \text{ J mol}^{-1} \text{ K}^{-1}$ .

### 3. Conclusions

For the first time, the kinetics of the bulk polymerization of D,L-lactide initiated by zirconium acetylacetonate was studied in the wide range of reaction conditions. The reaction enthalpy  $\Delta H_{100} = -17.8 \pm 1.4 \text{ kJ mol}^{-1}$  was determined. The following parameters were calculated: the activation energy  $E_a = 44.51 \pm 5.35 \text{ kJ mol}^{-1}$ , the preexponential factor  $\ln A = 15.47 \pm 1.38$  and the reaction entropy  $\Delta S = -25.14 \text{ J mol}^{-1} \text{ K}^{-1}$ . It was shown that zirconium acetylacetonate is a perspective biocompatible initiator for synthesis of poly(D,L-lactide) in bulk with predetermined molecular weight up to 187 kDa.

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### Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Acetylacetonate · biodegradable polymers · differential scanning calorimetry · polymerization kinetics, zirconium

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