

Kinetic Investigation of the Polymerization of *D,L*-Lactide and Glycolide via Differential Scanning Calorimetry

N. G. Sedush^{a,*}, Yu. Yu. Strelkov^a, and S. N. Chvalun^{b,*}

^a National Research Centre—Kurchatov Institute, pl. Akademika Kurchatova 1, Moscow, 123182 Russia

^b Enikolopov Institute of Synthetic Polymer Materials, Russian Academy of Sciences,
Profsoyuznaya ul. 70, Moscow, 117393 Russia

*e-mail: nsedush@gmail.com

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Abstract—The kinetics of polymerization of *D,L*-lactide and glycolide are studied via differential scanning calorimetry at different temperatures and concentrations of the catalyst tin octanoate. For the polymerization of *D,L*-lactide and glycolide, the enthalpies are determined to be -17 ± 1.5 and 16.5 ± 1.5 kJ/mol, respectively. The time to attain reaction equilibration decreases from 300 to 100 min with an increase in temperature from 200 to 220°C. The time of reaction at 200°C decreases from 280 to 100 min as the concentration of the catalyst is increased from 500 to 830 ppm. When the polymerization of glycolide is conducted at temperatures below 200°C, the reaction is accompanied by crystallization of polyglycolide and an increase in the total enthalpy of the process.

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INTRODUCTION

Poly lactide and its copolymers with glycolide are biocompatible and biodegradable materials that are widely applied in medicine [1, 2]. Owing to excellent physicochemical and mechanical properties, as well as the ability to degrade in the body without the formation of toxic products, they are used to manufacture surgical sutures, pins for bone union, implants, and scaffolds for regenerative medicine. Recently, systems for the targeted delivery and controlled release of drugs have been developed on the basis of these polymers. The supermolecular structure and, consequently, the properties and degradation times of materials based on poly lactide and poly glycolide may be controlled through the synthesis of polymers and copolymers of various structures with different molecular masses [3].

The most widespread method to synthesize lactide- and glycolide-based polymers is ring-opening polymerization in the presence of tin-containing catalysts [4]. A highly efficient catalyst used in industry is tin octanoate, which makes it possible to prepare high-molecular-mass poly lactides with high monomer conversions and low degrees of transesterification over relatively short times (up to 5 min) [5]. However, very few papers are available on the kinetic investigation of homopolymerization and copoly-

merization of lactides at various temperatures and catalyst concentrations.

As was shown in the first papers devoted to the polymerization of lactide, the reaction is of the first order with respect to the monomer and catalyst [6]. In the kinetic study of cationic copolymerization of glycolide with *L*- and *D,L*-lactides with the use of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ as a catalyst, the consumption of the monomers was investigated via NMR spectroscopy [7]. The same authors measured thermodynamic parameters for the polymerization of *D,L*-lactide through the study of polymer destruction [8]. The calculated values of enthalpy and entropy were $\Delta H = -27$ kJ/mol and $\Delta S = -13$ J/(mol K). The kinetics of *L*-lactide polymerization in the condensed state at 103–130°C in the presence of tin octanoate was first investigated in [9]. The authors calculated the activation energy and the rate constant of polymerization in terms of the model of irreversible polymerization of the first order with respect to the monomer and catalyst. A. Duda and S. Penczek investigated the kinetics of the polymerization of *L*-lactide in solution through estimation of the equilibrium concentration of lactide and determined thermodynamic parameters of the reaction at 80–133°C; these parameters were extrapolated to the case of polymerization in melt [10]. The calculated enthalpy and entropy of polymerization were $\Delta H = -22.9$ kJ/mol and $\Delta S = -25.03$ J/(mol K),

respectively. In [11], the model of reversible *L*-lactide polymerization was suggested; it satisfactorily described the experimental dependences. Measurements of the equilibrium concentration of the monomer as a function of polymerization temperature (130–220°C) performed within the framework of the above model made it possible to obtain the following values: $\Delta H = -23.3 \pm 1.5$ kJ/mol, $\Delta S = -22.0 \pm 3.2$ J/(mol K), and $E_a = 70.9 \pm 1.5$ kJ/mol. However, in all the cited papers, the enthalpy of polymerization was calculated indirectly, rather than measured via direct calorimetric methods.

DSC is a direct method that makes it possible to determine thermodynamic parameters of chemical reactions. This method is distinguished from the other calorimetric methods by high accuracy and speed, thereby allowing fast reactions to be studied. In 1957 [12], thermal analysis was first used for the kinetic investigation of the chemical reaction between *N,N*-dimethylaniline and methyl iodide. Later, this method was used to study polymerization reactions [13–19]. Recently, an attempt has been made to apply DSC to the kinetic investigation of the polymerization of *D,L*-lactide and glycolide in the presence of ZnOct_2 as a catalyst [20]. Experiments were performed in both the dynamic regime and the isothermal regime, and the data obtained in a DSC cell were compared with the results of polymerization in a reactor. Because of a poor reproducibility of the results, it was inferred that this method is inapplicable to the kinetic investigation of *D,L*-lactide polymerization because the reaction proceeds rapidly and that the enthalpy of melting of lactide is superimposed on the heat effect of polymerization. In the case of glycolide polymerization, the results of the two methods coincided. It is noteworthy that the experiments were conducted at high concentrations of the catalyst and in the presence of an activator; as a result, noticeable acceleration of the process was observed.

In this study, the DSC method was found to be efficient for the kinetic investigation of the polymerization of *D,L*-lactide and glycolide at various temperatures and concentrations of tin octanoate used as a catalyst.

EXPERIMENTAL

D,L-Lactide (Aldrich, United States) and glycolide (Sigma, United States) were used for polymerization experiments. The residual content of acidic groups in the monomers was found spectrophotometrically with the use of the dye Rhodamine 6G [21]. For *D,L*-lactide and glycolide, these values were 3×10^{-5} and 4×10^{-6} mol/g, respectively. The melting temperatures were determined via DSC as 126 and 84°C for *D,L*-lactide and glycolide, respec-

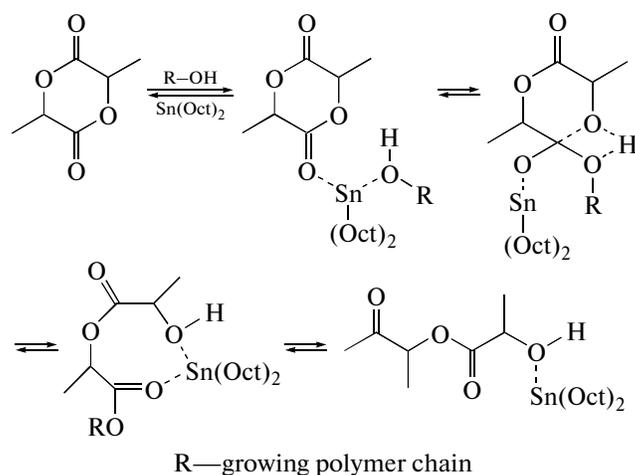
tively. Various optical forms of lactide have different melting temperatures: 54°C (meso form), 96°C (*L* and *D* forms), and 126°C (*D,L* form) [22, 23]. Thus, the absence of other melting peaks except that at 126°C is evidence for the optical purity of the used lactide. Tin octanoate (95%, Aldrich, United States) was used as a catalyst. Chemically pure petroleum ether dried over calcium hydride was used to prepare the catalyst solution.

Polymerization mixtures for DSC measurements were prepared as follows. A monomer (3–4 g) was weighed, and the catalyst solution in petroleum ether with the required concentration was prepared (so that the solution volume completely covered the weighed amount of the monomer). The solution was poured onto this weighed amount, and the solvent was removed at a reduced pressure. The resulting mixture was sampled (25–30 mg) and placed in an aluminum cup that was hermetically sealed and placed into the cell of a Mettler-30 differential scanning calorimeter at room temperature. After programming, the calorimeter cell was heated to the experiment temperature for about 20 s. Well before the recording started, the instantaneous heat flow was monitored on the device screen. Melting of the monomer accompanied by the endothermic effect occurred within ~1 min. In order to exclude this effect from the thermograms, recording was started only after the heat flow became equal to zero. Experiments were performed at 180, 200, and 220°C. Recording was stopped after the curve attained a horizontal baseline. Control experiments with the monomer and without any catalyst showed that the baseline was horizontal. After an experiment, the sample was weighed. Each experiment was performed at least three times, and the differences in the measured enthalpies defined the statistical error in the determination of ΔH .

The degree of monomer conversion was determined via NMR spectroscopy on a Bruker AV-300 spectrometer at room temperature; the working frequency was 300 MHz. Conversion of the monomer was calculated from the integral intensities of the signals due to CH groups of the monomer ($\delta = 5.06$ – 5.13 ppm) and the polymer ($\delta = 5.19$ – 5.30 ppm) on the spectra (Fig. 1).

RESULTS AND DISCUSSION

The polymerization of *D,L*-lactide and glycolide catalyzed by tin octanoate proceed via the coordination–insertion mechanism [5].



The scheme shows the act of monomer addition to the growing polymer chain (R). OH groups necessary for activation of the catalyst may be provided by both compounds specially introduced into the reaction and admixtures contained in the monomer and catalyst. Because every act of lactide or glycolide ring opening and its addition to the growing polymer chain is accompanied by heat release, the kinetic curve of

polymerization can be easily built and the enthalpy of the reaction can be measured from the heat-flow dependence measured in the DSC cell. The evolved heat is proportional to monomer conversion, the integral of the time dependence of heat flow is the kinetic curve of polymerization, and the value of this integral is the enthalpy of polymerization. On the basis of the collected data, the activation energy, rate constant,

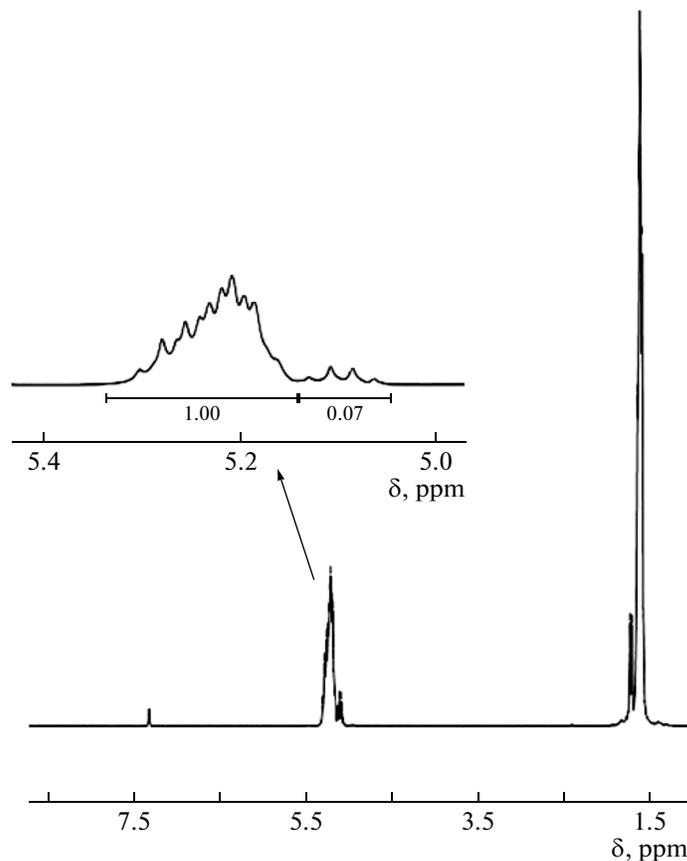


Fig. 1. ^1H NMR spectrum of a poly(*D,L*-lactide) sample synthesized in the DSC cell at 220°C and a catalyst concentration of 500 ppm. Conversion is 93%.

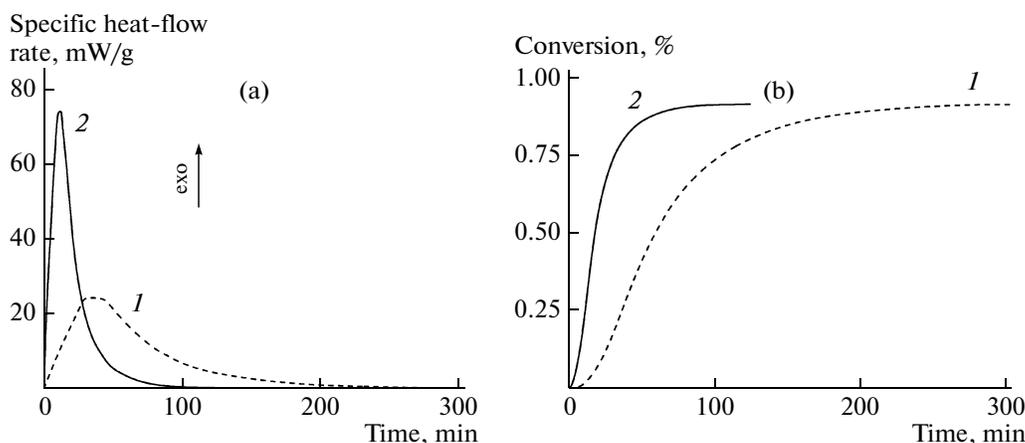


Fig. 2. (a) Thermograms and (b) kinetic curves of *D,L*-lactide polymerization at (1) 200 and (2) 220°C. The catalyst concentration is 500 ppm.

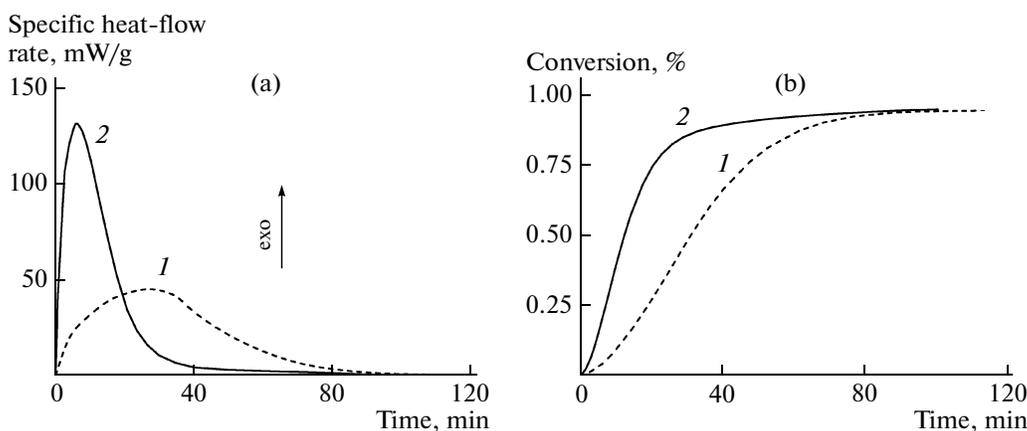


Fig. 3. (a) Thermograms and (b) kinetic curves of *D,L*-lactide polymerization at (1) 200 and (2) 220°C. The catalyst concentration is 830 ppm.

pre-exponential factor, and entropy of the reaction may be calculated in terms of the reversible-polymerization model [6].

Polymerization of D,L-Lactide

The kinetics of polymerization of *D,L*-lactide was investigated at temperatures of 200 and 220°C and catalyst concentrations of 500 and 830 ppm. These values are optimum for registration of polymerization kinetics in the DSC cell because the reaction lasts from 15 to 300 min. The obtained thermograms are shown in Fig. 2a (the heat flow is normalized to the sample weight). The area under the curve is equal to the polymerization enthalpy; it does not depend on polymerization conditions. In both cases, this value is -16 ± 1.5 kJ/mol.

Enthalpy may slightly vary with a change in the temperature of reaction because the equilibrium shifts

toward reagents and the maximum attainable conversion decreases with an increase in temperature. In our case, the conversions are 94 and 93% for samples obtained at temperatures of 200 and 220°C, respectively. These estimates are close to the data reported in [11], where the equilibrium concentration of the monomer increased from 3.5 to 5% as temperature was changed from 200 to 220°C. Thus, the enthalpy of polymerization corresponding to 100% conversion may be determined as $\Delta H_{100} = -17 \pm 1.5$ kJ/mol. The difference in the values of the heat effect that correspond to reaction temperatures of 200 and 220°C lies within the levels of experimental error. Note that the enthalpy of polymerization for *D,L*-lactide is much lower than that for *L*-lactide. In accordance with [24], this value is -20 ± 1.5 kJ/mol.

Figure 2b presents the kinetic curves measured for the polymerization of *D,L*-lactide at a catalyst concentration of 500 ppm and temperatures of 200 and

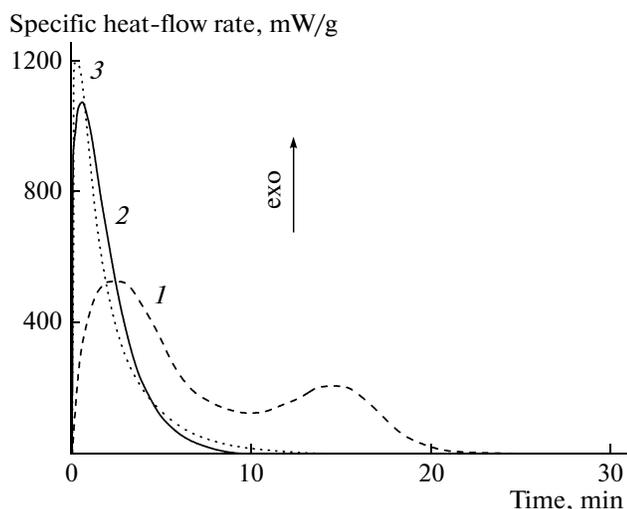


Fig. 4. Thermograms of glycolide polymerization at (1) 180, (2) 200, and (3) 220°C. The catalyst concentration is 500 ppm.

220°C. The reaction accelerates with the increase in temperature, and the limiting conversions are attained after 100 and 280 min at 220 and 200°C, respectively.

In addition, the effect of temperature on the kinetics of polymerization was investigated at a catalyst concentration of 830 ppm. The corresponding thermograms and kinetic curves at 200 and 220°C are presented in Fig. 3.

At this concentration of the catalyst, an increase in temperature is accompanied by shortening of the reaction time from 100 to 90 min. Thus, the temperature-induced increase in rate is significantly weaker than that observed at a catalyst concentration of 500 ppm. The value of the limiting conversion was unaffected by the catalyst-concentration increment and remained equal to 94%.

The comparison of kinetic curves from Figs. 2 (curve 1) and 3 (curve 1) shows that the reaction noticeably accelerates with the increase in the catalyst concentration and that the time of equilibration drops from 280 to 100 min at a temperature of 200°C. In both samples, conversions were likewise almost the same and equal to 94%. At a polymerization temperature of 220°C, the reaction weakly accelerates with an increase in the catalyst concentration. The time of attainment of the maximum conversion decreases from 100 to 90 min (Fig. 3, curve 2; Fig. 2, curve 2).

Polymerization of Glycolide

In contrast to the polymerization of *D,L*-lactide, whose polymer is incapable of crystallization owing to the absence of chain stereoregularity, the polymerization of glycolide at temperatures below the melting temperature of the polymer (225–230°C) is accompanied by crystallization. The exothermic effect of gly-

colide polymerization is clearly seen on the thermogram obtained at 180°C (Fig. 4, curve 1). At the same time, the thermograms obtained at polymerization temperatures of 200 and 220°C, which are close to the melting temperature of polyglycolide, are classical pictures showing one peak characteristic of the polymerization of *D,L*-lactide (Fig. 4, curves 2, 3).

Note above all that the rate of glycolide polymerization is higher than that of lactide polymerization. At 200°C and a catalyst concentration of 500 ppm, the thermogram levels off to the baseline after 10 min. The enthalpy of polymerization is -20 ± 1.5 kJ/mol. As the temperature of polymerization is decreased to 180°C, a second (likewise exothermic) peak, corresponding to crystallization of the formed polyglycolide, appears in addition to the first exothermic peak. As a result, the total registered heat effect increases to -32 ± 2 kJ/mol. The enthalpy of crystallization of polyglycolide synthesized at 200°C was measured under the isothermal regime at 180°C; this value amounted to -10 ± 1 kJ/mol. Thus, it may be concluded that the difference in the total heat effects of the reactions at 180 and 200°C is associated solely with the contribution of the exothermic effect of the crystallization of the reaction product.

At 180°C, the polymerization of polyglycolide, together with the crystallization of polyglycolide, lasts for about 30 min. When temperature is increased to 200°C, polymerization comes to an end after 15 min. In this case, a small part of polyglycolide has enough time to crystallize; the total heat effect of the process at 200°C is slightly higher than that at 220°C and amounts to -20 ± 1.5 kJ/mol. At 220°C, no crystallization occurs; therefore, the enthalpy of the process is contributed solely by the enthalpy of polymerization and has a minimum value of -16.5 ± 1.5 kJ/mol.

CONCLUSIONS

Our studies have shown that DSC is highly efficient for the kinetic investigation of *D,L*-lactide and glycolide polymerization. This method allows kinetic curves and the enthalpies of reaction to be directly obtained from the experiment. Under similar conditions, the polymerization of *D,L*-lactide proceeds slower than that of glycolide, and the reaction enthalpy for the former process is noticeably lower than that for the latter. If the polymerization of glycolide is performed below the melting temperature of the polymer, the thermograms exhibit an exothermic crystallization peak, which considerably increases the total heat effect. The developed methodology makes it possible to optimize the reaction conditions in order to provide a short reaction time (15 min at most) and a high degree of conversion, a circumstance that is necessary to conduct the synthesis in an extruder [21].

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