Kinetics of ring-opening polymerization of *d,l*-lactide catalyzed by functional Zn–guanidine complex with biphenyl-4-methanol activator

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A combination of Zn–guanidine complex catalyst and biphenyl-4-methanol activator was used as a biofriendly system for the synthesis of poly(*d,l*-lactide). Kinetic curves of the polymerization were measured by differential scanning calorimetry at various temperatures and concentrations of the activator. Due to an inclusion of guanidine ligands into the polymer chains, the synthesized polylactide is capable of fluorescing.
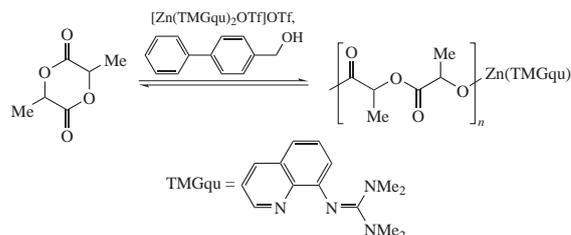
Excellent biocompatibility, controllable structure and wide range of biodegradation rates make lactide polymers good candidates for use in medical devices, drug delivery systems and in production of ecofriendly packaging materials.[1–4] Stannous octoate [BuCH(Et)COO]$_2$Sn was found to be one of the most active catalysts for the ring-opening polymerization (ROP) of lactide, although the requirements of the ASTM standards (for example ASTM F1925-09) for the tin concentration in the polylactide-based materials are rather strict. Hence, search for effective tin-free catalysts is topical. A promising group of biofriendly catalysts for the polymerization of lactide are Zn-based compounds.[5,6] Particularly high conversions and molecular weights were observed in case of the Zn complexes with the hybrid guanidine-pyridine ligands.[5] However, the reaction was rather slow and the conversion of 93–95% was achieved only after 24 h of the polymerization. Although the quality of the polymer was high enough, the reaction time was not appropriate for industrial production of polylactide.

To make the Zn–guanidine catalytic system industrially applicable, a suitable activator can be added to accelerate the polymerization. Hydroxyl-containing compounds are normally used as activators in ROP of lactones.[7] Particularly, a perspective activator is biphenyl-4-methanol being a monoalcohol with the melting temperature close to that of lactide. It was previously successfully used in ROP of trimethylene carbonate catalyzed by methanesulfonic acid.[8] Here we report an efficient lactide polymerization in bulk catalyzed by the Zn-based complex with the biphenyl-4-methanol activator. We focus on the study of the reaction kinetics at various temperatures and catalyst concentrations providing the optimal industrially applicable polymerization conditions. Another attractive feature of the Zn-based complexes as a catalyst is the fluorescence of the synthesized polylactide, which is an alluring property for the visualization of the material in medical devices and drug delivery systems.

The zinc-based complex stabilized by 1,1,3,3-tetramethyl-2-(quinolin-8-yl)guanidine (TMGqu) ligands and the triflate ions, ([Zn(TMGqu)$_2$OTf]OTf), was synthesized and used as a catalyst for ROP of *d,l*-lactide. To confirm the chemical structure of synthesized catalyst, it was studied by ^{1}H NMR spectroscopy (see Figure S1, Online Supplementary Materials). The spectrum of the catalytic complex is similar to that reported by Borner[5] except for the triplets around 7.69 ppm which were presented as doublets. The thermal behavior and the stability of the [Zn(TMGqu)$_2$OTf]OTf catalyst were studied by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) (Figure S2). The upper limit of the reaction of lactide polymerization catalyzed by this compound was found to be not higher than 210 °C.

We employed DSC in the isothermal mode to compare the kinetics of the lactide polymerization in the presence of the proposed catalytic system with that for the case of stannous octoate.[9] Several long-lasting reactions were conducted in the flask as well. The kinetic curves of the *d,l*-lactide polymerization at 150 °C catalyzed by [BuCH(Et)COO]$_2$Sn and [Zn(TMGqu)$_2$OTf]OTf in the equal concentrations of 1000 mol ppm are depicted in Figure 1. It is clear that stannous octoate shows higher activity than pure [Zn(TMGqu)$_2$OTf]OTf. The conversion of 50% was reached in 17 and 25 min, respectively, which is rather close. However, after 4 h of the reaction, the monomer conversion in the presence of stannous octoate was 96%, while for the Zn–guanidine complex it was still far from the equilibrium value and reached only 76%. Polymerization under the same conditions carried out in the flask
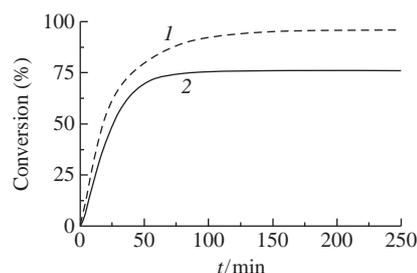
Figure 1 Kinetic curves of *d,l*-lactide polymerization at 150 °C catalyzed by (*1*) stannous octoate and (*2*) [Zn(TMGqu)$_2$OTf]OTf in concentration of 1000 mol ppm.

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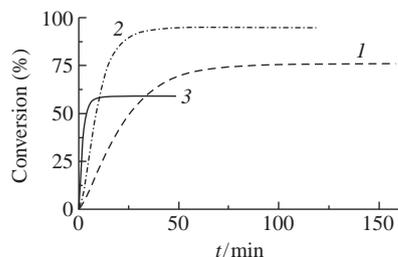
Figure 2 Kinetic curves of *d,l*-lactide polymerization catalyzed by [Zn(TMGqu)₂OTf]OTf (1000 mol ppm): (*1*) without activator at 150 °C, and with biphenyl-4-methanol (2000 mol ppm) activator at (*2*) 150 and (*3*) 180 °C.

Figure 3 Emission spectra of acetone solutions of (*1*) poly(*d,l*-lactide) and (*2*) [Zn(TMGqu)₂OTf]OTf. Inset: optical microphotograph (UV-mode) of synthesized poly(*d,l*-lactide).
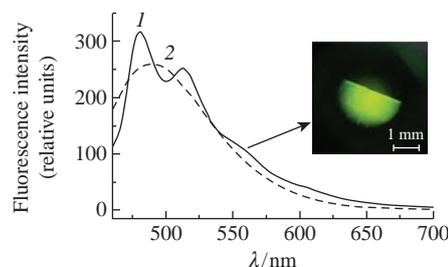
requires much longer time (sample 1, Table S1), and the maximum conversion of 94% (NMR) was reached after 24 h.

Based on these data, we suggest that after 2 h of the reaction at 150 °C with 1000 mol ppm of the Zn–guanidine catalyst the rate of the polymerization was extremely low. The heat effect of such a slow reaction cannot be detected using DSC, and the thermogram levels off after 2 h (see Figure 1). Raising the polymerization temperature up to 200 °C accelerated the reaction, however, the product turned brown with poor molecular weight characteristics (M_w = 48 kDa, PDI = 2.4). Moreover, only 92% conversion was achieved after 6 h (sample 2, Table S1).

To increase the rate of the reaction catalyzed by the Zn–guanidine complex, biphenyl-4-methanol was added as an activator. It is clear from the kinetic curves measured at 150 °C (Figure 2) that polymerization was significantly accelerated by the addition of 2000 mol ppm of biphenyl-4-methanol. The maximum conversion of 95% was reached in less than 1 h. The poly(*d,l*-lactide) sample synthesized under the same conditions in the flask was colourless with M_w = 87 kDa and PDI = 2.25 (sample 3, Table S1). Even faster reaction was observed at higher polymerization temperature of 180 °C, however, the reaction slowed down after 20 min at only 59% conversion. The reason of such a sharp deceleration can be found in the instability of the catalytic complex at high temperatures, although the results of TGA [Figure S2(*b*)] showed that [Zn(TMGqu)₂OTf]OTf is stable up to 270 °C. Apparently, partial decomposition or structural rearrangements in the Zn–guanidine activated catalytic complex could proceed at lower temperatures leading to the decrease in catalytic activity. The enthalpy of the *d,l*-lactide polymerization ΔH_{100} = 17.7 ± 0.9 kJ mol⁻¹ was calculated as an average polymerization enthalpy in different experiments, extrapolated to 100% monomer conversion. This result is close to our previous one[10] being ΔH_{100} = 17.0 ± 1.5 kJ mol⁻¹. The value of the *d,l*-lactide polymerization enthalpy ΔH_{100} = = 27 kJ mol⁻¹ was calculated from the measured heat effect of the polymer combustion.[11] The higher value can be explained by the indirect method of enthalpy determination.

Such a significant acceleration of the polymerization can be rationalized considering the lactide polymerization mechanism in the presence of the similar Zn–guanidine complex.[12] The mechanism of the reaction both with and without activator is described in detail in Online Supplementary Materials (Scheme S1).

Both the [Zn(TMGqu)₂OTf]OTf catalyst and the synthesized polylactide samples were studied by fluorescent spectrometry. To determine the optimal excitation wavelength, spectrophotometry was used. In the absorption spectra of the catalyst and the poly(*d,l*-lactide) solutions (Figure S3), the wavelength of 365 nm corresponds to the maximal absorption of the catalyst solution, whereas the absorption maximum for the polymer solution moves to the higher wavelengths where two small peaks at 444 and 470 nm can be detected. The difference in the absorption spectra is probably due to the structural changes in the catalytic complex during the synthesis, which are caused by scission of the catalyst molecule. Based on the results of spectrophotometry, the wave-

lengths of 365 and 444 nm were chosen as the optimal excitation ones for the catalyst and poly(*d,l*-lactide), respectively. The emission spectra of the catalyst and the polymer solutions (Figure 3) reveal the maximum at 490 nm for the catalyst solution and two peaks for the poly(*d,l*-lactide) solution at 481 and 513 nm. Fluorescence of the synthesized poly(*d,l*-lactide) is clearly observed using microscopy in the UV-mode (inset in Figure 3).

The positions of the maxima in the excitation spectra of the poly-(*d,l*-lactide) and catalyst solutions (Figure S4) coincide with those in the absorption spectra (Figure S3) confirming that the excitation wavelengths of 365 and 444 nm are optimal. Thus, poly(*d,l*-lactide) synthesized in the presence of the [Zn(TMGqu)₂OTf]OTf catalyst contains guanidine fragments whose fluorescence intensity is sufficient for visualization of the material by the fluorescent techniques.

In summary, the kinetic curves of the *d,l*-lactide polymerization in the presence of the [Zn(TMGqu)₂OTf]OTf catalyst and the biphenyl-4-methanol activator were measured directly in the DSC cell under different reaction conditions. Upon the addition of the activator, poly(*d,l*-lactide) with high molecular weight and the conversion of 95% can be synthesized in bulk in less than 1 h. Such optimal conditions allow one to use the proposed catalytic system for the polylactide synthesis at semi-industrial scale. The fluorescence of the obtained poly(*d,l*-lactide) makes it a perspective material for biomedical applications.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.05.021.

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