Cyclic Polylactides by Imidazole-Catalyzed Polymerization of L-Lactide

Hans R. Kricheldorf,* Nino Lomadze, and Gert Schwarz

Institut für Technische and Makromolekulare Chemie der Universität Hamburg, Bundesstrasse 45, D-20146 Hamburg, Germany

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ABSTRACT: Heating of L-lactide with imidazole to 98−100 °C resulted in complete polymerization within 48 h. Even-numbered cycles resulting from end-to-end cyclization were the only reaction products after 4 h, but the polymerization process was accompanied by intensive racemization. Longer reaction times favored equilibration reactions with formation of odd-numbered cycles. Variation of the monomer−initiator ratio at 120 °C had little influence on the molecular weight. After 8 h at 150 °C, equal quantities of odd- and even-numbered cycles were found, indicating complete equilibration. Other protic heterocycles such as 1,2,4-triazole, benzimidazolyl acetonitrile, uracile, or hypoxanthine were not active as initiators/catalysts at 120 °C. However, the tertiary amine *N*-methylimidazole also catalyzes the formation of cyclic polylactides together with several byproducts. The reaction mechanisms are discussed.

Introduction

The term "ring-opening polymerization" (ROP) is usually understood as a process yielding linear polymers by a sequence of reaction steps involving the ring-opening of a cyclic monomer. This view is certainly correct for the majority of ROPs, but it is based on two requirements. First, the initiation step produces a stable (dead) endgroup, and, second, formation of cycles by "back-biting" equilibration is absent or inefficient. Three scenarios may yield cyclic oligomers and polymers as the endproducts of a ROP. The first is ROPs involving rapid equilibration reactions including back-biting. According to the theory of Jacobson and Stockmayer,[1,2] such a process should mainly yield linear chains with a small weight fraction (e.g., 2.5%) of cycles,[1,3,4] when conducted in bulk, but 100% cycles at low concentration. Yet, according to the theory of Kricheldorf, an efficient ring equilibration should mainly yield cyclic oligomers and polymers with a small percentage of linear chain (depending on the monomer−initiator ratio, if an initiator was used at all) at all concentrations. The second scenario (II) is based on a kinetically controlled ROP involving a cyclic initiator, that is, a ring expansion polymerization. Numerous examples illustrating this scenario have recently been published,[5−9] and the vast majority of such polymerizations were summarized in a review article.[8] The third scenario (III), which is particularly relevant for the present work, is based on kinetically controlled ROPs generating linear chains with two different reactive endgroups. Quite analogous to a step-growth polymerization,[10] these chains have the choice to continue the chain-growth by intermolecular reactions or to undergo cyclization. Several examples of ROPs yielding cyclic polymers via a kinetically controlled chain-growth process involving end-to-end cyclization have recently been published.[11−15] For L- or D,L-lactide as monomers, Culkin et al.[15] have shown that initiation with a nucleophilic carbene yields cyclic polylactides, but due to intensive equilibration it was not clear if the cycles were mainly the consequence of a thermodynamically controlled back-biting process (scenario I) or of a kinetically controlled process according to scenario III.

The purpose of the present work was to study imidazole-initiated ROPs of L-lactide. In contrast to most other amide groups, imidazolides are so electrophilic that they react with amino groups at low temperature or with alcohol groups at higher temperatures. Therefore, it was found that imidazole-initiated polymerizations of α-amino acid NCAs produce cyclic polypeptides.[12] In this case, equilibration reactions are excluded, due to the stability of peptide groups below 100 °C. The present work should answer three questions. First, does imidazole indeed initiate a relatively clean polymerization process? Second, are cyclic polylactides formed via a kinetically controlled polymerization with end-to-end cyclization (e.g., according to Scheme 1)? Third, are cyclic polylactides formed via thermodynamically controlled equilibration reactions?

Experimental Section

Materials. L-Lactide (S-grade) was kindly supplied by Boehringer GmbH & Co. (Ingelheim, Germany). It was twice recrystallized from dry ethyl acetate and stored over P_4O_{10} in a desiccator. Imidazole, *N*-methyl imidazole, 1,2,4-triazole, benzimidazolyl acetonitrile, hypoxanthum, and uracil were purchased from Alpha Aesar (Karlsruhe, Germany). Imidazole was distilled in vacuo and stored over P_4O_{10}. All other heterocycles were used after drying over P_4O_{10}. *N*-Methylimidazole was distilled over freshly powdered calcium hydride in vacuo.

Polymerizations. *A. With Imidazole (Nos. 1−4, Table 1).* L-Lactide (40 mmol) and imidazole (2 mmol) were weighed under dry argon into a 25 mL Erlenmeyer flask having silanized glass walls (pretreated with Me_2SiCl_2). The reaction vessel was closed with a glass-stopper and steel spring. The closed reaction vessel was almost completely immersed into a preheated oil bath. Finally, the cold reaction product was characterized.

All other polymerizations catalyzed by imidazole or other protic heterocycles were performed analogously.

B. With N-Methylimidazole (Nos. 5−8, Table 1). L-Lactide (40 mmol) was weighed under dry argon into a 25 mL Erlenmeyer flask having silanized glass walls. After injection of *N*-methylimidazole (2 mmol), the reaction vessel was closed with a glass-stopper and steel spring and immersed into a preheated oil bath.

Measurements. The inherent viscosities were measured in CH_2Cl_2 with an automated Ubbelohde viscometer thermostatted at 20 °C. The 400 MHz ^{1}H NMR spectra and the 100.4 MHz ^{13}C NMR spectra were recorded with a Bruker "Avance 400" FT NMT spectrometer in 5 mm o.d. sample tubes. $CDCl_3$ containing TMS served as solvent. The MALDI-TOF mass spectra (MT) were measured with a Bruker Biflex III mass spectrometer equipped with a nitrogen laser (λ = 337 nm). All spectra were recorded in the

* To whom correspondence should be addressed. E-mail: kricheld@chemie.uni-hamburg.de.

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Table 1. Imidazole- and *N*-Methylimidazole-Catalyzed Polymerizations of L-Lactide at 100 °C in Bulk: Monomer−Catalyst Ratio = 20/1

					even/odd ratio of MALDI-TOF peaks		
expt. no.	catalyst	time (h)	conversion[a]	η_{inh}[b] (dL/g)	below 2 kDa	above 2 kDa	mp[c] (Da)
1	imidazole	4	24		10/0	10/1	41 000
2	imidazole	8	35		10/2	10/1	53 000
3	imidazole	24	90	0.40	10/3	10/5	65 000
4	imidazole	48	99	0.32	10/5	10/7	60 000
5	*N*-methylim.	4	14				
6	*N*-methylim.	8	22				
7	*N*-methylim.	24	90	0.26			
8	*N*-methylim.	48	99	0.25			

[a] ^{1}H NMR spectroscopy of the virgin reaction products. [b] Virgin reaction products measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [c] Peak of SEC elution curve.

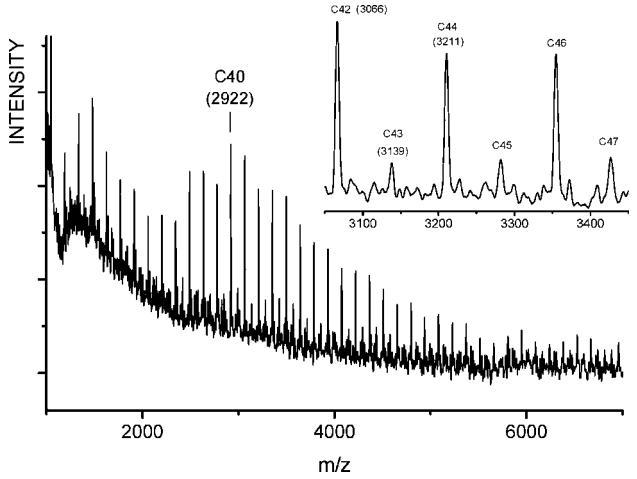


Figure 1. MALDI-TOF mass spectrum of the polylactide no. 2, Table 1 (imidazole as catalyst).

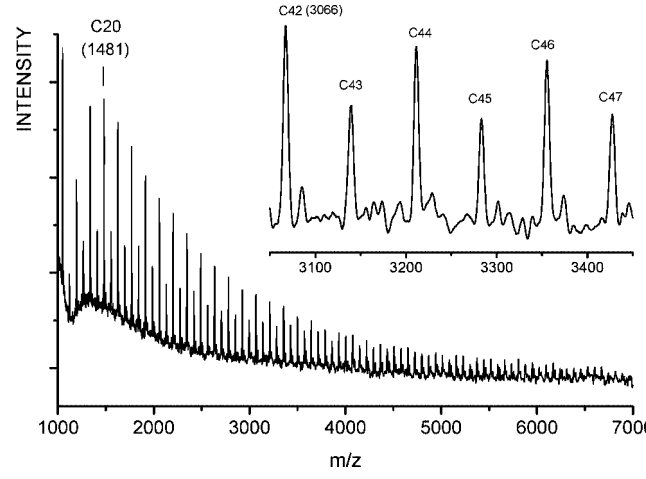


Figure 2. MALDI-TOF mass spectrum of the polylactide no. 4, Table 1 (imidazole as catalyst).

reflection mode with an acceleration voltage of 20 kV. The irradiation targets were prepared from chloroform solutions with dithranol as matrix (weight ratio 1/20) and potassium trifluoroacetate as dopant. The SEC measurements were performed with an apparatus of Polymer Laboratories equipped with a RI detector Shodex RS 101. A combination of three PC mixed-bed columns was used with chloroform as eluent (flow rate 1.0 mL/min). Commercial polystyrene standards served for calibration.

Results and Discussion

Because the melting point of L-lactide amounts to 95−96 °C, the lowest temperature applicable to a polymerization is 96−97 °C. For imidazole as initiator or catalyst, a rather low reactivity was expected, and thus a first "test experiment" with a high concentration of imidazole (monomer/catalyst = 10/1) was conducted at 96−98 °C. After 24 h, an almost complete polymerization was found. Therefore, a series of four experiments was performed at 98−100 °C using a M/C ratio of 20/1. As indicated by the data summarized in Table 1 (experiments 1−4), the conversion steadily increased over a period of 48 h, so that quantitative conversion was reached after 48 h. The MT mass spectra revealed interesting results. After 4 h, only peaks of even-numbered cycles were detectable. After 8 h, weak peaks of odd-numbered cycles had appeared as illustrated in Figure 1. The intensities of their peaks increased with time, but even after 48 h the fraction of odd-numbered cycles was still clearly lower than that of the even-numbered ones (Figure 2). A comparison of experiment no. 3, Table 1, with the first "test polymerization" based on a M/C ratio of 10/1 revealed that the higher concentration of imidazole produced a higher fraction of odd-numbered cycles, or, in other words, it favored a more intensive equilibration. Experiment no. 6, Table 2, finally proved that the higher temperature of 150 °C resulted in complete equilibration as demonstrated by the MT mass spectrum of

Table 2. Imidazole-Catalyzed Polymerizations of L-Lactide in Bulk at 120 or 150 °C

expt. no.	lactide imidazole	temp (°C)	time (h)	conversion[a]	η_{inh}[b] (dL/g)
1	3/1	120	4	96	0.16
2	10/1	120	4	95	0.29
3	30/1	120	24	91	0.27
4	50/1	120	48	93	0.27
5	100/1	120	48	98	0.30
6	30/1	150	8	95	0.20

[a] ^{1}H NMR spectroscopy of the virgin reaction products. [b] Virgin reaction products measured at 20 °C with $c = 2$ g/L in CH_2Cl_2.

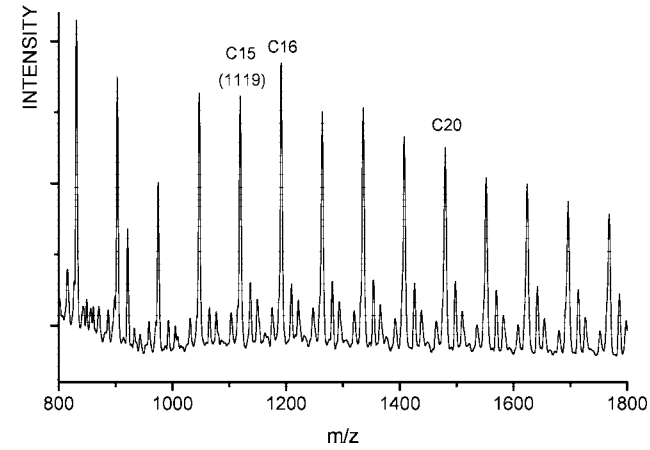
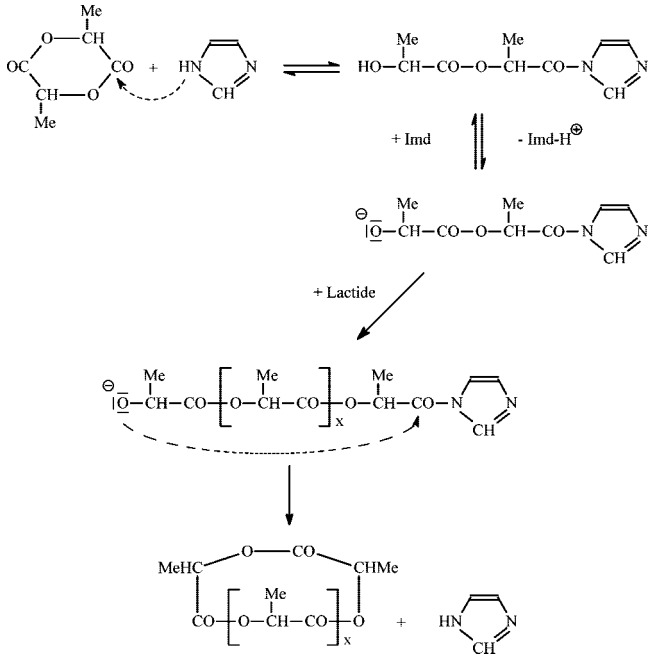


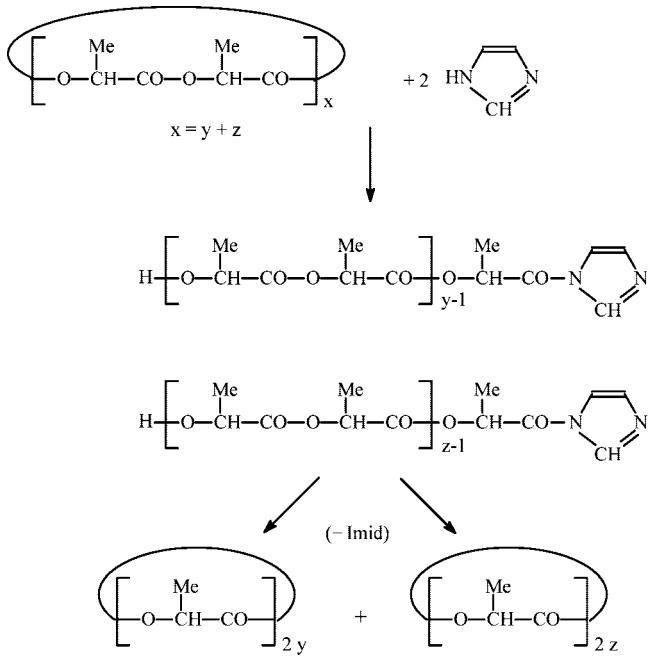
Figure 3. MALDI-TOF mass spectrum of the polylactide no. 6, Table 2 (imidazole as catalyst).

Figure 3, which indicates equal quantities of even- and odd-membered cycles at least above C16. All of these findings together allow the following conclusions. First, imidazole is

Scheme 1. Hypothetical Mechanisms of the Imidazole-Catalyzed Formation of Cyclic Polylactides



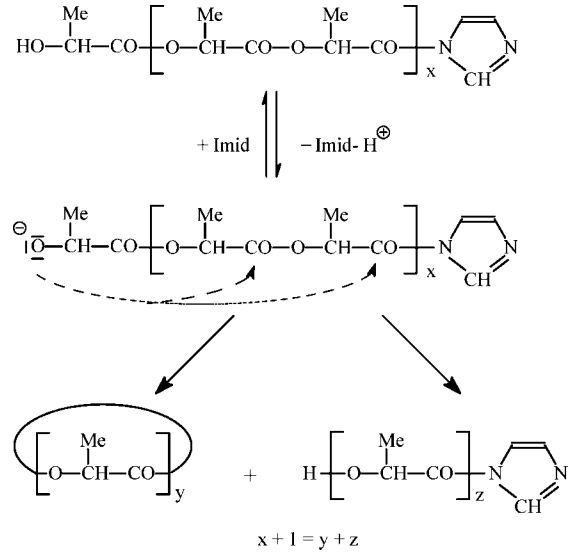
Scheme 2. Formation of Odd-Numbered Cyclic Polylactides by Random Cleavage of Even-Numbered Cycles



reactive enough to catalyze quantitative polymerizations of L-lactide in bulk. Second, at relatively short times and low temperatures, a kinetically controlled polymerization takes place, and all cycles result from end-to-end cyclization according to Scheme 1. Third, temperatures ≥150 °C and reaction times ≥24 h generate a thermodynamically controlled ring−ring equilibration.

Although SEC measurements do not yield accurate number average (M_n) or weight average (M_w) molecular weights of polylactides as discussed below, molecular weight data were added to experiment nos. 1−4 in Table 1. These data represent the peaks of the elution curve and indicate qualitatively that the molecular weights slightly increase with the conversion in

Scheme 3. Formation of Even- and Odd-Numbered Cyclic Polylactides by Anionic "Back-Biting" Degradation



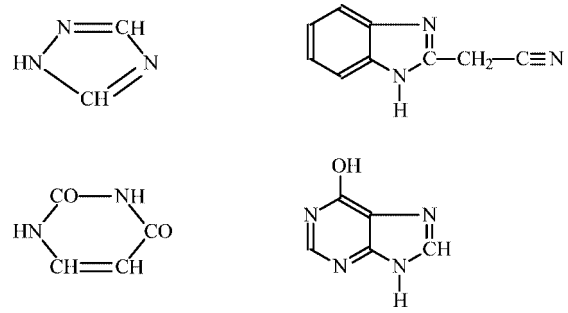
experiment nos. 1−3. This finding agrees with the polymerization mechanism outlined in Schemes 1−3, because cyclizations prevent a steady chain-growth paralleling the conversion.

In agreement with a strong influence of equilibration reactions, experiment nos. 2−5 of Table 2 demonstrate that the average molecular weights do not significantly depend on the M/C ratio, whereas a strong dependence is expected for kinetically controlled polymerizations. Three reaction mechanisms may account for the odd-numbered cycles. First is a random cleavage of the even-membered cycles by at least two imidazoles (as outlined in Scheme 2), so that two odd-numbered linear chains are formed as reactive intermediates. Second is cleavage of linear chains (which may be present in small amounts in the high molar mass part of a sample) by one or more imidazole molecules, so that odd-numbered fragments result. Both mechanisms lead to a reduction of the average molecular weight and agree with the observation that inherent viscosity and molar mass (M_p) of sample no. 4, Table 1, are lower than those of sample no. 3. However, it must also be taken into account that in the course of the polymerization odd-numbered chains can react with even-numbered ones, generating a longer odd-numbered chain that upon cyclization yields a larger cycle. The third equilibration mechanism results from a partial and reversible deprotonation of the OH-chain ends followed by anionic back-biting degradation (Scheme 3). A partial deprotonation of the OH-groups is not unlikely, because the rapid racemization (discussed below) indicates that imidazole is basic enough to deprotonate the CH-group at temperature ≥100 °C. The acidity of the OH-group is certainly not much lower than that of the CH-group. Both mechanisms are not alternation, but may occur simultaneously in the reaction mixture, but certainly not at the same rate.

A third series of experiments was conducted in such a way that the heterocycles presented in Scheme 4 were added to L-lactide at 120 °C in a M/C ratio of 50/1. None of these heterocycles catalyzed a polymerization. The L-lactide remained unchanged, which proves that the catalytic effect of imidazole is not a triviality that can be copied by numerous heterocycles of similar structure.

To find out if the N-proton of imidazole is decisive for the catalytic activity and for the entire course of the polymerization, a series of four experiments was conducted at 100 °C with *N*-methyl imidazole (MeIm) as catalyst (nos. 5−8, Table 1). This aprotic amine catalyzed indeed polymerizations that were

Scheme 4. Heterocycles Tested as Potential Catalysts of the Ring-Opening Polymerization of L-Lactide in Bulk at 120 °C



not much slower than the imidazole-catalyzed ones. Yet, the MT mass spectra revealed a largely different and more complex composition of the reaction mixture. Several mass peaks of polylactides having difficult to interpret endgroups were found together with weak peaks of cyclic oligo- and polylactides (Figure 4). The formation of cyclic polylactides may be explained by a zwitterionic mechanism as outlined in Scheme 5. The tertiary amine-catalyzed formation of cyclic polysarcosine,[13] poly(thioglycolide),[14] and poly(α-hydroxyisobutyrate)[16] via zwitterionic polymerizations was recently reported.

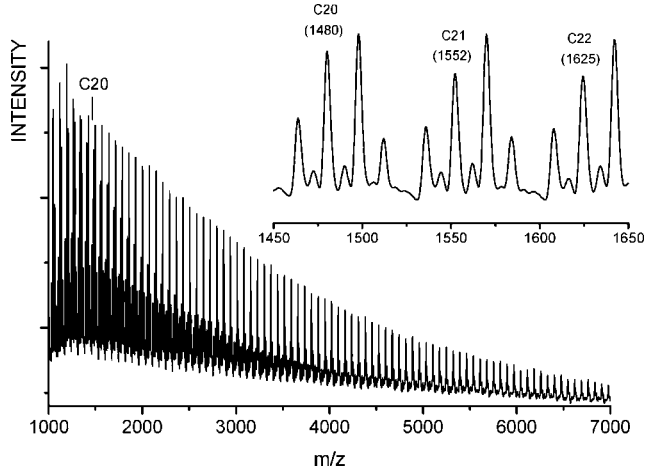
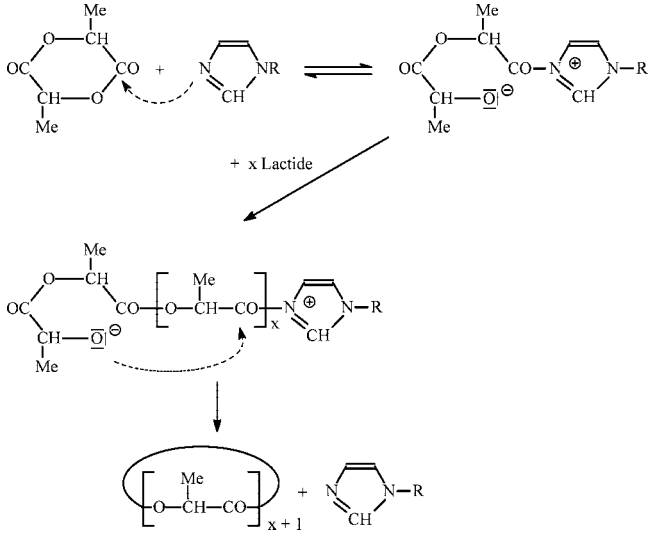


Figure 4. MALDI-TOF mass spectrum of the polylactide no. 7, Table 1.

Scheme 5. *N*-Methylimidazole-Catalyzed Zwitterionic Polymerization of L-Lactide



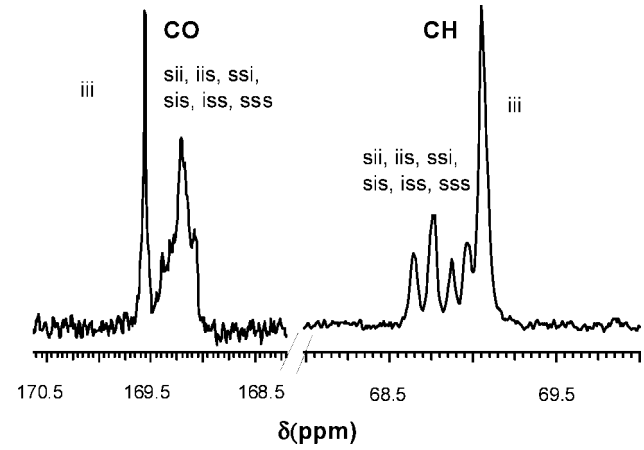
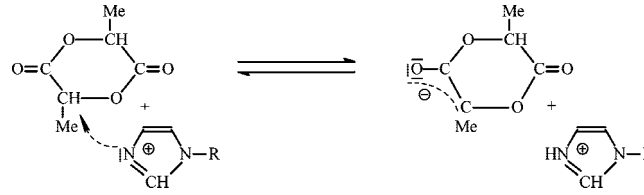


Figure 5. 100.4 MHz ^{13}C NMR signals of the polylactide no. 1, Table 1 (imidazole as catalyst).

Scheme 6. Reversible α-Deprotonation Causing Racemization of L-Lactide



In the case of lactide, a zwitterionic activation was postulated for *N*,*N*-dimethyl-4-aminopyridine-catalyzed and alcohol-initiated polymerizations by several authors.[17] Yet, a clean zwitterionic polymerization with formation of cyclic polylactides was never studied. In other words, the reaction mechanisms catalyzed by MeIm are quite different from that catalyzed by imidazole. The rather clean polymerizations catalyzed by imidazole obviously obey the mechanism formulated in Scheme 1, whereby the N-proton plays an important role.

Nonetheless, both imidazole and MeIm catalyze one reaction in the same way, racemization of L-lactide. All polylactides isolated in this work were amorphous, transparent materials, properties that are characteristic for poly(D,L-lactide). ^{13}C NMR spectroscopic measurements confirmed this interpretation. As demonstrated in Figure 5, even at the shortest time and at the lowest temperature imidazole caused a nearly complete racemization. After 48 h (no. 4, Table 1), the ^{13}C NMR spectrum was quite similar. As was already discussed in a previous paper[18] dealing with the anionic polymerization of L-lactide, base-catalyzed racemization results from reversible deprotonation of the α-CH group with intermediate formation of a planar delocalized anion (Scheme 6). The rapid racemization of L-lactide by imidazole or MeIm agrees with our previous observation that even the weak base pyridine can racemize L-lactide, when present in high concentration and elevated temperature. The rapid racemization of L-lactide within 4 h at 100 °C in the absence of equilibration suggests that both types of reactions are not directly correlated. This conclusion is supported by the observations of Culkin et al.,[15] who reported that the carbene-catalyzed polymerization of L-lactide at 25 °C involves rapid equilibration with little racemization.

Finally, it should be mentioned that four polylactide samples were characterized by SEC measurements calibrated with polystyrene. The inherent viscosities of these samples covered the full range of viscosity data obtained in this work (Table 3). It is well-known from numerous publications of at least six research groups that polystyrene-calibrated SEC measurements considerably overestimate the real molecular weights of aliphatic

Table 3. Molecular Weight Measurements by SEC in Chloroform

sample	η_{inh}[a] (dL/g)	M_n[b] (SEC)	M_n[c] (correct.)	M_n[d] (correct.)	PD[b]
no. 1, Table 2	0.16	13 000	8900	7500	1.60
no. 3, Table 2	0.27	25 000	17 000	14 500	1.62
no. 3, Table 1	0.40	47 000	32 000	27 000	1.65
no. 4, Table 1	0.33	41 000	28 000	24 000	1.75

[a] Virgin reaction products measured at 20 °C with $c = 2$ g/L in chloroform. [b] Original SEC data resulting from calibration with polystyrene. [c] SEC data multiplied by the factor 0.68 (ref 20). [d] SEC data multiplied by the factor 0.58 (refs 19 and 21).

polyester. Depending on the structure of the polyester and depending on the mass range, this overestimation amounts to 50−100%. For poly(L-lactide), a correction factor of 0.58 was reported by Duda et al. in 1998[19] and a factor of 0.68 in 2000[20] without explanation for this discrepancy. Save et al.[21] reported later a correction factor of 0.58 for poly(D,L-lactide). Therefore, three series of number average molecular weights (M_n's) were listed in Table 3, the original SEC measurements and M_n's calculated with aforementioned correction factors. The use of a correction factor makes sense, because all four samples gave monomodal molecular weight distributions. Regardless of which correction factor is used, the M_n data indicate that imidazole-catalyzed polymerizations of L-lactide may yield rather high molecular weights and not just oligomers. The comparison with the M/C ratios also demonstrates that imidazole reacted as true catalyst and not as initiator fixed to the CO-chain end. From this point of view, the SEC measurements support the mechanism formulated in Scheme 2.

Conclusion

In contrast to various related heterocycles, imidazole catalyzes the polymerization of L-lactide at temperatures above its melting point. At first, a relatively rapid kinetically controlled ring-opening polymerization yielding even-numbered cycles is followed by a slower equilibration process yielding odd-numbered cycles. The formation of cyclic polymers via kinetically controlled end-to-end cyclization should be understood as a special case of a kinetically controlled step-growth polycondensation (KCP). It has been demonstrated by computer simulations[22−24] and numerous experimental results[10,25−27] that a KCP cyclization competes with chain extension at any concentration and at any stage of the polymerizations, and at 100% conversion all reaction products have a circular structure. If a ring-opening polymerization generates a chain with two different reactive endgroups, this polymerization can continue by intermolecular condensation steps or by cyclization quite analogous to a normal KCP. According to the Ruggli−Ziegle dilution principle,[28] a low molar concentration of the reactive chains favors cyclization at the expense of chain extension. The imidazole-catalyzed polymerization of L-lactide at low temperatures and short times therefore represents one more example of the rare case that a polymerization process combines chain-growth and step-growth polymerization.

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