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Polylactones 36. Macrocyclic Polymerization of Lactides with Cyclic Bu_2Sn Initiators Derived from 1,2-Ethanediol, 2-Mercaptoethanol, and 1,2-Dimercaptoethane

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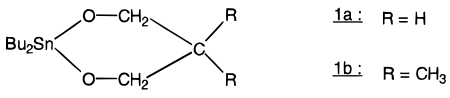
ABSTRACT: Three cyclic initiators were prepared from dibutyltin oxide and 1,2-ethanediol, 2-mercaptoethanol, and 1,2-dimercaptoethane. Mass spectra demonstrated in agreement with literature data that the tin compounds obtained from 1,2-ethanediol and 2-mercaptoethanol form dimeric 10-membered rings. Polymerizations of L-lactide and racemic D,L-lactide were conducted in bulk at 120 °C. The resulting molecular weights were higher than expected from the monomer/initiator (M/I) ratio and do not parallel it. ^{1}H NMR spectra also proved that the lactides exclusively react with the Sn−O bonds. Consequently the 2,2-dibutyl-2-stanna-1,3-dithiolane is an extremely poor initiator. ^{1}H NMR spectra of reaction mixtures showed that the propagation is more rapid than the initiation. The macrocyclic polylactides resulting from the initiation with the ethanediol-based stannadioxolane can be cleaved with 1,2-dimercaptoethane, so that the dibutyltin group is selectively removed. GPC measurements before and after this ring cleavage suggest that the macrocyclic polylactides are mainly monomeric, although the initiator itself is mainly a dimeric (10-membered) ring.

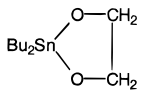
Introduction

Butyltin alkoxides and phenyltin alkoxides have been reported to be efficient initiators of the ring-opening polymerization of various lactones and lactides.[1−8] In the case of L-lactide, polymerization is feasible in bulk at 150 °C without racemization in contrast to typical cationic or anionic polymerizations of L-lactide. This observation and other results[2] have made clear that the polymerization mechanism involves Sn−O bonds as active species and no ions. The scheme of such an insertion mechanism is outlined in eq 1.[2] The reactivity of the initiators increases with the number of alkoxide groups attached to the tin atom, and it decreases with increasing bulkiness of the alkoxide groups.[3] Butyltin alkoxides not only react as initiators with the cisoid ester groups of lactones but they are also efficient transesterification catalysts for noncyclic ester groups and may cause intensive back-biting degradation of polylactones at elevated temperature.[2] Quite recently we found that six-membered cyclic dibutyltin alkoxides suhc as **1a**,**b** are interesting initiators of β-D,L-butyrolactone or ϵ-caprolactone.[9,10] The insertion of lactones into both Sn−O bonds produces macrocyclic polylactones in high yields, and the variations of the monomer/initiator ratio allow an easy control of the average ring size. The present work continues our research on the macrocyclic polymerization of lactones with cyclic tin alkoxide initiators. The reactivity of the dibutyltin derivatives **2**−**4** toward L-lactide and racemic D,L-lactide was studied.



1a : R = H

1b : R = CH_3



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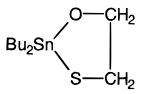

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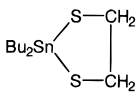

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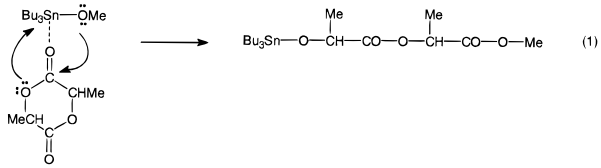

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Experimental Section

Materials. Dibutyltin oxide, 1,2-ethanediol, and 2-mercaptoethanol were purchased from Aldrich Co (Milwaukee, WI) and used without further purification. 1,2-Dimercaptoethane was purchased from Fluka AG (Neu Ulm, FRG). L-Lactide and D,L-lactide were purchased from Boehringer AG (Ingelheim, Rhein, FRG) and recrystallized once from ethyl acetate. The monomers were dried and stored in a desiccator over P_4O_{10}.

1,1,6,2-Tetra-*n*-butyl-1,6-distanna-2,5-dithia-5,10-dioxacyclodecane (3/7). Dibutyltin oxide (20.25 g, 0.08 mol) and 2-mercaptoethanol (5.67 mL 6.32 g, 0.08 mol, 1.0 equiv) were added to a flask containing distilled toluene (500 mL). The flask was fitted with a Dean and Stark trap and condenser, and then the contents were slowly heated to reflux, upon which the dibutyltin oxide dissolved. Reflux was continued for 6 h, after which time the theoretical volume of water had collected in the trap (1.5 mL). Removal of solvent in vacuo to a volume of ~50 mL and addition of ligroin (20 mL) caused the formation of a white solid. The flask was stored at 0 °C for 24 h, after which a copious supply of the solid had formed. This was collected by filtration and subsequently recrystallized from toluene to afford the product as a white solid. Yield 88.3%. Anal. Calcd for $C_{20}H_{44}Sn_2O_2S_2$ (618.12): C, 38.86; H, 7.17; S, 10.38. Found: C, 38.57; H, 7.01; S, 10.05. ^{1}H NMR ($CDCl_3$/TMS): δ 0.91 (6H, t, J = 6.5 Hz), 1.17−1.42 (4H, m), 1.52−1.67 (4H, m), 2.79 (2H, t, J = 5.5 Hz), 3.63 (2H, t, J = 5.5 Hz). ^{119}Sn NMR ($CDCl_3$/Me_3Sn): δ −32 ppm.

1,1,6,6-Tetra-*n*-butyl-1,6-distanna-2,5,7,10-tetraoxacyclodecane (2/5) was prepared analogously. Yield 76%. Anal. Calcd for $C_{20}H_{44}Sn_2O_4$ (585.95): C, 40.99; H, 7.57. Found: C, 40.65; H, 7.31. ^{1}H NMR ($CDCl_3$/TMS): δ 0.92 (6H, t, J = 6.5 Hz), 1.20−1.37 (4H, m), 1.48−1.75 (4H, m), 3.63 (4H, s). ^{119}Sn NMR ($CDCl_3$/Me_4Sn): δ −179 ppm.

Dibutyl-2-stanna-1,3-dithiolane (4) was prepared analogously. Yield 71%. Anal. Calcd for $C_{10}H_{22}SnS_2$ (325.10): C, 36.95; H, 6.82; S, 19.73. Found: C, 36.71; H, 6.91; S, 19.43. ^{1}H NMR ($CDCl_3$/TMS): δ 0.92 (6H, t, J = 7.5 Hz), 1.27−1.42 (4H, m), 1.48−1.74 (4H, m), 3.03 (4H, s). ^{119}Sn NMR ($CDCl_3$/Me_4Sn): δ 196 ppm.

Polymerizations. L-Lactide (40 mmol) was weighed into a 25 mL Erlenmeyer flask with silanized glass walls, and the initiator was added in the form of a 0.5 M solution in chloroform. The reaction vessel was closed with a glass stopper and steel spring and thermostated at 120 °C. Finally, the cold reaction product was dissolved in CH_2Cl_2 (~50 mL), precipitated into cold methanol, and dried at 40 °C in vacuo after isolation.

GPC Analyses and Selective Ring Opening. The crude reaction product of a polymerization conducted with 100 mmol of lactide and with a M/I ratio of 50:1 was dissolved in CH_2Cl_2 (150 mL) was subdivided into four portions. The first portion was immediately precipitated into cold diethyl ether. 1,2-Dimercaptoethane (0.4 mmol) was added to the second portion, 0.6 mmol to the third, and 0.8 mmol to the fourth. After a reaction time of 20 h, the reaction mixtures were precipitated into dry diethyl ether and the isolated polylactides were dried at 40 °C in vacuo.

All these experiments were repeated several times to check their reproducibility, and in some cases, the conditions were slightly altered. It was found that good reproducibility requires that the four portions of one polylactide sample are worked up on the same day with solvents of the same batch and dried together under identical conditions. Furthermore, the reaction mixtures of DME should be magnetically stirred under nitrogen.

Measurements. The viscosities were measured with an automated Ubbelohde viscometer thermostated at 20 °C.

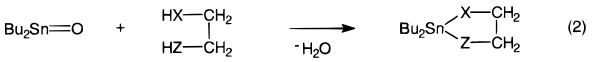
The 100 MHz ^{1}H NMR spectra were recorded with a Bruker AC-100 FT NMR spectrometer in 5 mm o.d. sample tubes. The 360 MHz ^{1}H NMR spectra were obtained on a Bruker AM 360 FT NMR spectrometer in 5 mm o.d. sample tubes. TMS served as internal standard.

The ^{119}Sn NMR spectra were recorded with a Varian Gemini 200 in 5 mm o.d. sample tubes.

The GPC measurements were conducted on a Kontron HPLC apparatus equipped with a Waters Md 410 differential diffractometer. A combination of four Ultrastyragel columns with pore sizes of 10^2, 10^3, 10^4, and 10^5 Å was used, and tetrahydrofuran served as eluent. The mass spectra were performed on a VG 70 SE high-resolution mass spectrometer.

Results and Discussion

Initiators. The initiators **2** and **4** were synthesized by several research groups,[11−16] and three different synthetic methods were used. In the present work, all three methods were applied to the synthesis of initiator **3**. The reaction of dibutyltin oxide with 2-mercaptoethanol was found to be the most convenient and efficient approach, and it was also found to be useful



(2)

for the synthesis of **2** and **4**. Because the ^{1}H NMR spectra of all three Bu_2Sn derivatives have never been compared before, they are displayed in Figure 1, in as much, as a comparison with the oligolactones prepared from them was needed for the elucidation of the polymerization mechanism.

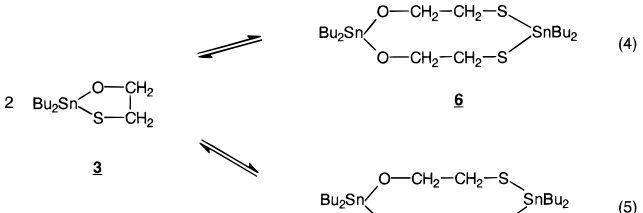
The ^{1}H NMR spectra of all three initiators display the expected signals, and variation of the temperature between −60 and +60 °C did not show any significant change, suggesting a slow equilibration with the corresponding dimeric heterocycles (eq 3). This aspect is of

(3)

2 **5**

interest, because several authors[11−16] have demonstrated that the reaction product resulting from 1,2-ethanediol and dibutyltin derivatives is mainly the 10-membered ring of the dimer (**5**) and not the monomeric form **2**. In contrast, the predominance of the five-membered monomeric ring was confirmed for reaction product obtained from 1,2-dimercaptoethane (**4**).

In the case of the product derived from 2-mercaptoethanol, no information was available as to what extent the dimers **6** and **7** coexist with the monomeric species



(4) (5)

3 **6** **7**

3. Because molecular weight measurements in solution may be affected by association equilibria, we have preferred to record mass spectra.

For comparison, the mass spectra of **2**/**5** and **4** were recorded first. In the case of **2**/**5** the mass peaks of both the monomeric and the dimeric species were indeed found along with peaks of typical fragments (e.g., loss of a C_4H_9 group) (Figure 2A). In contrast, only peaks of the monomeric species were found in the case of **4** (Figure 2C). The mass spectrum of the system **3**/**7** displays the mass peaks of both monomeric and dimeric species (Figure 2B) quite analogous to the spectrum of

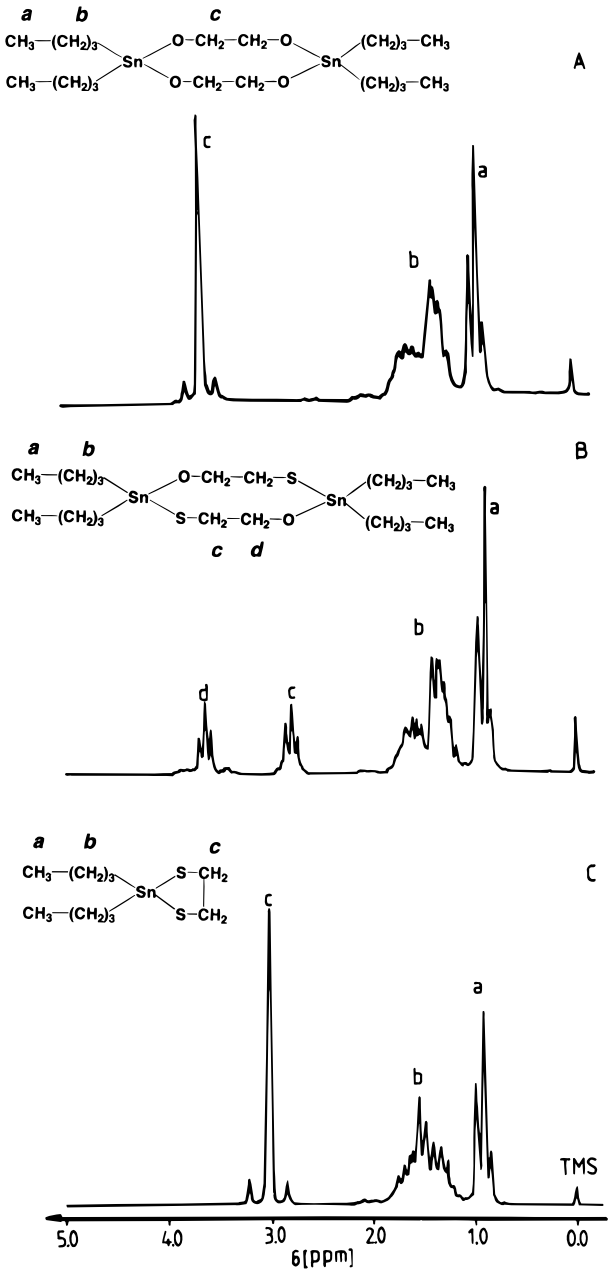


Figure 1. 100 MHz ^{1}H NMR spectra (in $CDCl_3$) of (A) initiator **2**/**5** (B) **3**/**7**, and (C) **4**.

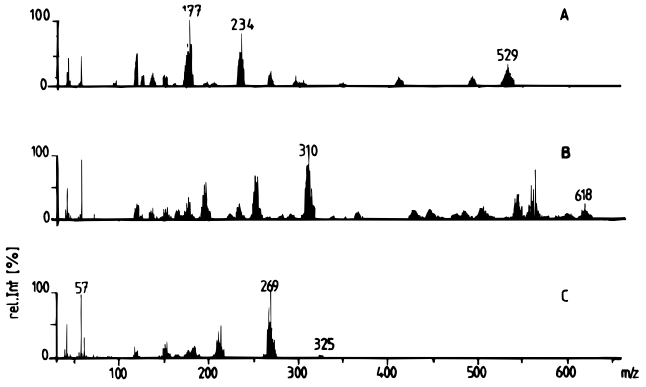


Figure 2. Mass spectra of (A) initiator **2**/**5**, (B) initiator **3**/**7**, and (C) initiator **4**.

2/**5**. Hence it is obvious that **3** favors the dimeric form in solution in contrast to **4**. Obviously the reactivity of the Sn−O bond is responsible for this difference. However, neither the ^{1}H NMR nor the mass spectra allow a

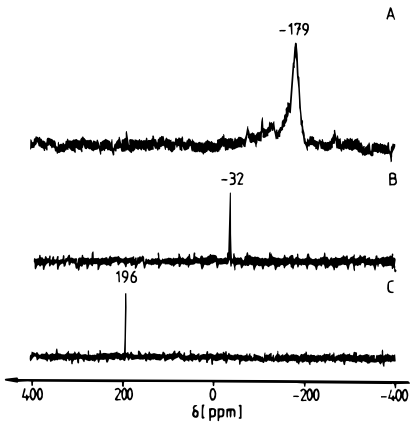


Figure 3. ^{119}Sn NMR spectra (in $CDCl_3$) of (A) **2**/**5**, (B) **3**/**7**, and (C) **4**.

differentiation between the isomeric dimers **6** and **7**. Therefore, a ^{119}Sn NMR spectrum was measured in $CDCl_3$ solution, which should exhibit one signal in the case of **7**, but two signals similar two those of **2**/**5** and **4** in the case of **6**. The experimental result was one sharp signal at −32 ppm (relative to internal $(CH_3)_4Sn$), a chemical shift in between the signals of **2**/**5** and **4** (Figure 3). This result clearly demonstrates the predominance of **7** (or **3**) over **6**. The ^{119}Sn NMR measurements also suggest that a concentrated solution of initiator **2**/**5** in chloroform involves association equilibria in addition to the dimerization, because the ^{119}Sn signal is unusually broad. Surprisingly, no significant line broadening was found in the ^{1}H NMR spectra. A more detailed study of this phenomenon was not intended in this work.

Finally, the role of ring size and temperature needs a short discussion. It has been demonstrated by molecular weight measurements in solution that even the six-membered 2-stanna-1,3-dioxane **1** prefers to form a 12-membered dimer at moderate temperatures.[16] A mass spectrum recorded in the present study confirms the formation of a rather stable dimer. In contrast, the exclusive formation of the monomeric seven-membered ring was reported for the reaction product of 1,4-butanediol.[16] In other words, a greater distance between the OH groups of the diol favors monomeric stannoxanes. For thermodynamic reasons this trend is reasonable, because the energetically unfavorable conformations (and bond angles) of the smaller rings disappear when the ring size of the monomers increases, whereas the gain in entropy favors the monomeric species at the expense of the dimeric ones. For the same reason, higher temperatures favor the monomeric rings, and experimental evidence for this tendency has indeed been reported.[16]

Polymerizations. Preparative Aspects. All polymerizations of this work were conducted with L-lactide or D,L-lactide in bulk at 120 °C. This temperature was selected, because the melting point of L-lactide is ∼95 °C and that of racemic D,L-lactide around 125−126 °C. Therefore, a temperature of 120 °C is the lowest temperature that allows polymerization and comparison of both monomers.

A first series of polymerizations was conducted with L-lactide and initiator **2**/**5**. The results compiled in Table 1 allow the following conclusions. First, these polymerizations are rather rapid and yields of ∼90% can be obtained within 2−4 h. Second, variation of the reaction time between 4 and 24 h in the case of M/I =

Table 1. Polymerizations of L-Lactide with Initiator 2/5 in Bulk at 120 °C (Variation of the M/I Ratio)

expt no.	M/I	time (h)	yield (%)	η_{inh}[a] (dL/g)	$[\alpha]_D^{20}$[b]	M_n[c] ($\times 10^3$)	M_n[d] ($\times 10^3$)
1	50	2	89	0.26	−150.0	6.8	16
2	100	2	88	0.41	−151.0	14.0	28
3	200	4	95	0.56	−153.5	27.0	38
4	400	4	91	0.73	−150.0	55.0	
5	400	8	92	0.77		55.0	
6	400	24	94	0.71	−149.0	55.0	54
7	800	8	88	0.82	−146.5	109.0	
8	800	24	95	0.86		109.0	72

[a] Measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [b] Measured at 20 °C with $c = 10$ g/L in $CHCl_3$ at 578 mm. [c] Calculated from eq 6 by assuming 95% conversion. [d] Determined by viscometry via eq 7.

400 has little influence on yield and molecular weight. There is no indication of back-biting degradation at the longer reaction times. Third, the extent of racemization is low and falls into the range of 2−6% (100% optical purity corresponds to an $[\alpha]_D^{20}$ value of 157 ± 2% in $CHCl_3$). Fourth, the molecular weights (M_n) increase with the M/I ratio, but they do not parallel the M/I ratio. Whereas the M/I ratio varies by a factor of 16, the M_n values vary only by a factor of 5. Two effects contribute to this discrepancy. The experimental M_n's are too high at low M/I ratios (50 or 100) and they are too low at high M/I ratios (e.g., 800).

Fractionation resulting from the precipitation into methanol certainly contributes little to the higher M_n's found at low M/I ratios, because the difference between the yield and the maximum conversion is rather low (3−6%). In this connection it should be remembered that for thermodynamic reasons conversions of L-lactide are not allowed to exceed 96%, when the polymerizations are conducted at temperatures of ≥120 °C. As discussed below, the main reason for molecular weights higher than expected on the basis of eq 6 seems to be a slow initiation step with incomplete conversion of the initiator.

$$\mathrm{DP} = \frac{M}{I}\,\frac{100}{\%\ \text{conversion}}$$

DP = average degree of polymerization (6)

The lower than expected molecular weights found at an M/I of 800:1 may have two explanations. First, the precipitation into methanol results in methanolytic cleavage of the polylactide chains, even when the methanol is cold and filtration rapid. The methanolytic cleavage was detected by a weak singlet signal at 3.8 ppm in the 360 MHz ^{1}H NMR spectra of the isolated polylactide samples. Furthermore, the determination of M_n values from intrinsic viscosities and the Mark−Houwink equation (7) is certainly not highly accurate.

$$[\eta] = 7.4 \times 10^{-5} \times M_n^{0.87} \quad (CHCl_3,\ 20\ °C^{17}) \quad (7)$$

$$[\eta] = 2.21 \times 10^{-4} \times M_n^{0.77} \quad (CHCl_3,\ 30\ °C^{18}) \quad (8)$$

Nonetheless this method was selected because (as discussed previously[20]) the results of eq 7 agree largely with those of eq 8, and both equations together are based on calibrations with three different independent methods. All three calibration methods yielded number-average molecular weights, and they were applied to nonfractionated polylactide samples with M_w/M_n ratios of ∼2. Therefore, the determination of molecular weights via eq 7 or 8 yields molecular weights close to M_n. Direct GPC measurements of the poly(L-lactide) samples were not feasible, because they are insoluble in tetrahydrofuran, and a GPC apparatus working with $CHCl_3$ or CH_2Cl_2 as eluent was not available. Furthermore, it should be taken into account that M_n measurements of polylactides calibrated with polystyrene standards are not necessarily more accurate then the application of eq 7 or 8.

Table 2. Polymerizations of L-Lactide with Initiator 3/7 in Bulk at 120 °C (Variation of the Reaction Time)

expt no.	M/I	time (h)	yield (%)	η_{inh}[a] (dL/g)	$[\alpha]_D^{20}$[b]
1	400	4	93.3	0.98	−154.7
2	400	8	91.8	1.07	−155.7
3	400	24	96.0	0.97	
4	400	48	96.0	0.92	−157.4
5	400	72	93.9	0.90	
6	400	96	97.1	0.98	−158.0

[a] Measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [b] Measured at 20 °C with $c = 10$ g/L in $CHCl_3$.

Table 3. Polymerizations of L-Lactice with Initiator 3/7 in Bulk at 120 °C (Variation of the M/I Ratio)

expt no.	M/I	time (h)	yield (%)	η_{inh}[a] (dL/g)	$[\alpha]_D^{20}$[b]	M_n[c] ($\times 10^3$)	M_n[d] ($\times 10^3$)
1	50	2	90.5	0.53	−155.0	6.8	42
2	100	2	94.0	0.68	−157.0	14.0	54
3	200	4	92.5	0.92	−157.0	27.0	77
4	400	4	92.5	0.94		55.0	
5	400	8	92.0	0.98	−153.5	55.0	
6	800	8	80.0	0.98	−150.0	109.0	54

[a] Measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [b] Measured at 20 °C with $c = 10$ g/L in $CHCl_3$. [c] Calculated from eq 6 by assuming 95% conversion. [d] Determined by Viscometry via eq 7.

When L-lactide was polymerized with initiator **3**/**7**, the results (listed in Tables 2 and 3) largely resembled those obtained with initiator **2**. Most yields were on the order of 90%. Nearly 100% optical purity was found in all but one experiment. The maximum molecular weights were slightly higher than in the case of initiator **2**, and the variation of M_n with the M/I ratio was even less pronounced (by a factor 2.5). Furthermore, six polymerizations were conducted at an M/I ratio of 400:1 with variation of the reaction time (Table 2). No decrease of the viscosities was detectable at the longest reaction time. This means that no back-biting degradation occurred under these reaction conditions.

When initiator **4** was used, a completely different picture emerged. Low yields (<10%) of poly(L-lactide) were only obtained at the longest reaction times of 8 h, whereas not significant conversion took place at shorter reaction times. These negative results fit in with the well-known fact that the Sn−S bond is more stable than the Sn−O bond (provided that the substituents are identical). Obviously, the initiation step of **4** and lactide is for kinetic and thermodynamic reasons unfavorable.

Due to the failure of **4** to initiate satisfactory polymerizations of L-lactide the polymerizations of *rac*-lactide were exclusively conducted with the initiators **2**/**5** (Table 4) and **3**/**7** (Table 5). The results obtained with both initiators largely parallel those found for polymerizations of L-lactide (Tables 1 and 2). Yields above 90% were obtained in both series. The molecular weights increase with the M/I ratios for M/I = 50−200, but level off at higher M/Is. Once again the molecular weights are too high for M/I = 50 or 100 and too low for M/I = 800. Because the poly(D,L-lactide)s obtained in this work were soluble in tetrahydrofuran, GPC mea-

Table 4. Polymerizations of *rac*-Lactide with Initiator 2/5 in Bulk at 120 °C

expt no.	M/I	time (h)	yield (%)	η_{inh}[a] (dL/g)	M_n[b] ($\times 10^3$ g/mol)	M_n[c] ($\times 10^3$)	M_w/M_n[d]
1	50	2	47	0.25	6.8 (3, 6)[e]	13	2.7
2	100	2	62	0.35	14.0		2.5
3	100	4	91	0.40	14.0	25	
4	200	4	89	0.72	27.0	50	
5	200	8	93	0.75	27.0	56	3.0
6	400	4	90	0.68	55.0		2.5
7	400	8	94	0.80	55.0	63	
8	800	8	80	0.65	109.0		2.7
9	800	24	92	0.82	109.0	65	3.0

[a] Measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [b] Calculated from eq 6 by assuming 95% conversion. [c] Determined from viscosity measurements in combination with eq 7. [d] GPC measurements (calibrated with polystyrene) and eq 9. [e] Calculated from eq 6 by assuming 50% conversion.

Table 5. Polymerizations of *rac*-Lactide with Initiator 3/7 in Bulk at 120 °C

expt no.	M/I	time (h)	yield (%)	η_{inh}[a] (dL/g)	M_n[b] ($\times 10^3$)	M_n[c] ($\times 10^3$)	M_w/M_n[d]
1	50	2	86	0.22	6.8	11	3.3
2	100	2	88	0.39	14.0	20	2.6
3	200	4	97	0.59	27.0	30	3.0
4	400	4	97	0.89	55.0	54	2.9
5	400	8	95	0.85	55.0		
6	800	8	93	0.87	109.0	59	3.0

[a] Measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [b] Calculated from eq 6 by assuming 95% conversion. [c] From viscosity measurements in combination with eq 7. [d] From GPC measurements (calibrated with polystyrene) and eq 9.

surements were conducted using commercial polystyrene standards for calibration. These GPC measurements were used to obtain at least crude information on the polydispersity. For the calculation of M_n and M_w, the *a* and *k* values of eq 9 were used, which were

$$[\eta] = 1.25 \times 10^{-4} \times M_n^{0.717} \quad \text{(THF, 30 °C}^{19}\text{)} \quad (9)$$

published for solutions of polystyrene in tetrahydrofuran.[19] To the best of our knowledge, no Mark–Houwink equation is known for poly(D,L-lactide)s in tetrahydrofuran. The M_w/M_n ratios obtained from GPC measurements and the *a* and *k* values of eq 9 are all on the order of 2.5–3.5, indicating broad molecular weight distributions (Tables 4 and 5). When the *k* and *a* values of eq 8 were used despite the different solvent, the M_w/M_n ratios were even higher. These high polydispersities are qualitatively in good agreement with the finding that the rates of the propagation are higher than those of the initiation regardless of whether **2**/**5** or **3**/**7** are used as catalyst (see below). Taken together, it may be said that both initiator systems allow the preparation of polylactides in high yields with number-average molecular weights (M_n's) above 50×10^3 and without significant racemization.

Polymerizations. Mechanistic Aspects. The polymerizations of lactide initiated with the **2**/**5** and **3**/**7** raise the following interesting questions: (I) Why are the molecular weights higher than the M/I ratios at low M/I? (II) Does the insertion of lactides occur at one Sn–O bond of **2**/**5** (structure **8**) or at both Sn–O bonds (**9** and **10**)? (III) Does the insertion exclusively occur at the Sn–O bond of **3**/**7** or is the Sn–S bond likewise involved? (IV) Are the macrocyclic polylactides monomeric (structures **9** and **12**) or dimeric (structures **10** and **13**)?

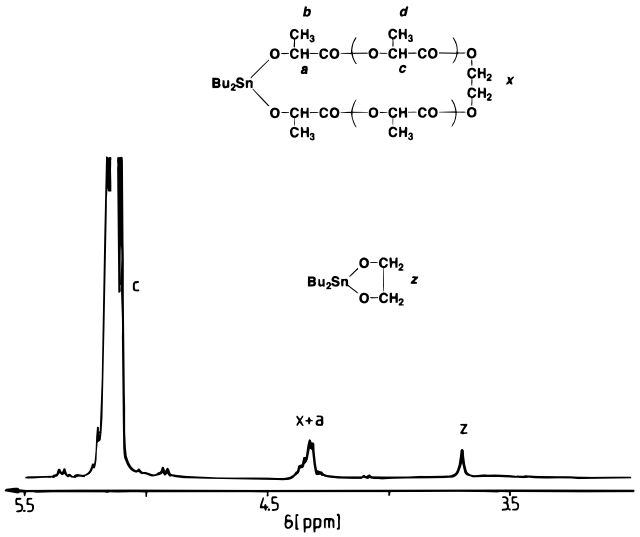


Figure 4. 360 MHz ^{1}H NMR spectrum of the reaction mixture of a **2**/**5**-initiated polymerization of L-lactide in bulk (M/I = 100) recorded after 2 h at 120 °C.

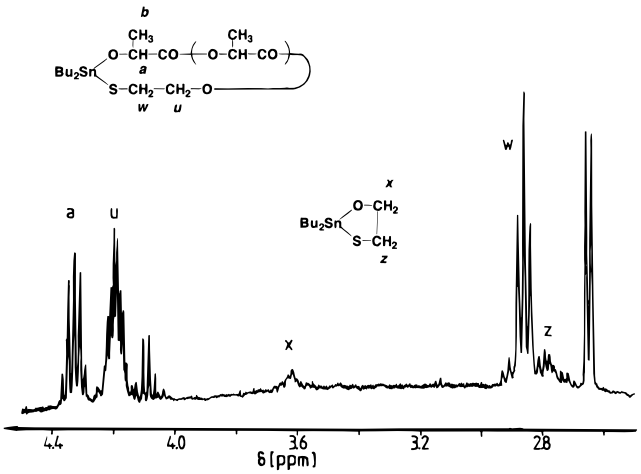


Figure 5. 360 MHz ^{1}H NMR spectrum of the reaction mixture of a **3**/**7**-initiated polymerization of L-lactide in bulk (M/I = 100) recorded after 1 h at 120 °C.

In order to obtain an answer on question I, L-lactide was polymerized with **2**/**5** in bulk at 120 °C, so that the reaction time was varied at a constant M/I ratio of 50:1. Samples were taken from the reaction mixture after 1, 2, and 4 h. These samples were subjected to ^{1}H NMR measurements in chloroform. As illustrated by Figure 4, the singlet signal of the unreacted initiator at 3.6 ppm was detectable even after 4 h. However, as indicated by the result of experiment 1, Table 1, and also by ^{1}H NMR measurements, the conversion of L-lactide is nearly complete after 2 h. Thus, these results clearly demonstrate that the propagation steps are much faster than the initiation step. An analogous polymerization and ^{1}H NMR measurements were conducted with L-lactide and initiator **3**/**7** at 120 °C in bulk. Again, unreacted initiator was detected after 1 or 2 h (Figure 5), despite an almost complete conversion of the monomer. Obviously initiator **3**/**7** is somewhat more reactive than **2**/**5**, but the propagation is again much faster than the initiation. These answers to question I raise the additional question of why the initiators **2**/**5** and **3**/**7** are less reactive than the corresponding macrocycles **9**, **10**, or **11**. Certainly Sn–O bonds derived from lactide units are weaker and more reactive than those of the initiators, because the HO group of lactide

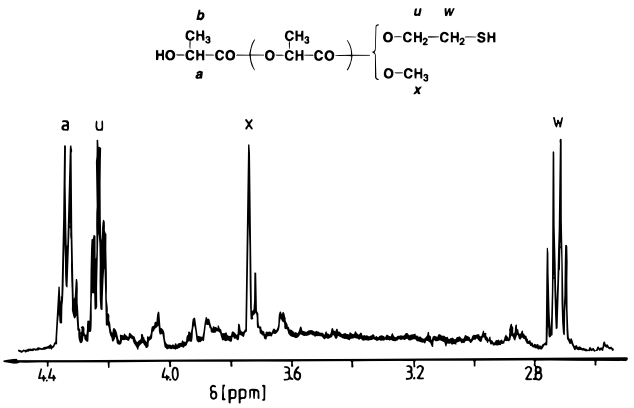
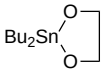
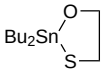


Figure 6. 360 MHz ^{1}H NMR spectrum of a **3**/**7**-initiated poly(L-lactide) polymerized in bulk at 120 °C with M/I = 100 and isolated after precipitation into methanol.

Table 6. GPC Elution Times (mn) of Poly(D,L-Lactide) Prepared in Bulk at 120 °C for 2 h (M/I = 50:1)

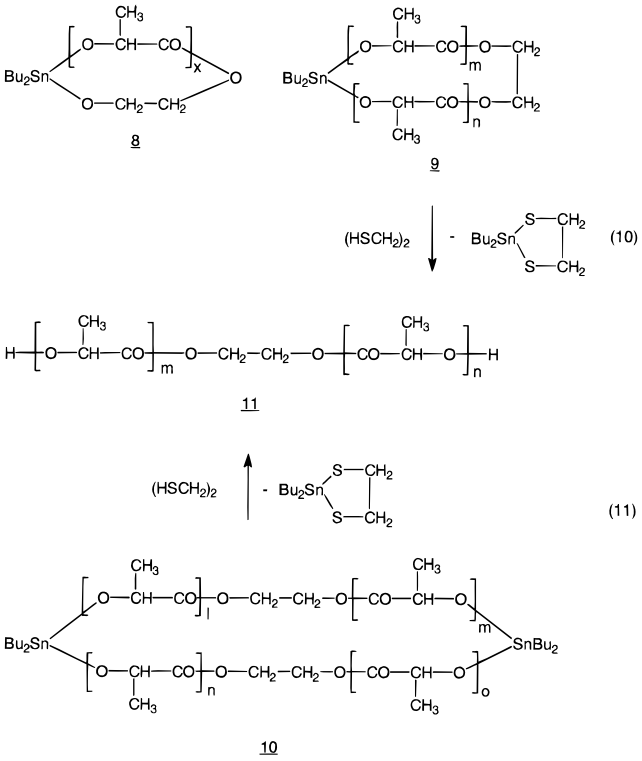
	treatment with DME 24 h at 25 °C			
		mol ratio[b]		
initiator	no DME	1.0:1.0	1.0:1.5	1.0:2.0
$Bu_2Sn(OMe)_2$	32.17	32.91	32.79	31.83
	31.18	31.88	31.81	32.21
	28.58	27.78	27.93	28.41
	29.02	29.35	29.74	29.42
	28.37	27.80	27.98	27.77
	28.51	28.05	28.11	28.15

[a] Treated with dimercaptoethane at 25 °C in CH_2Cl_2 solution and precipitated into Et_2O. [b] Molar ratio of Bu_2Sn to DME.

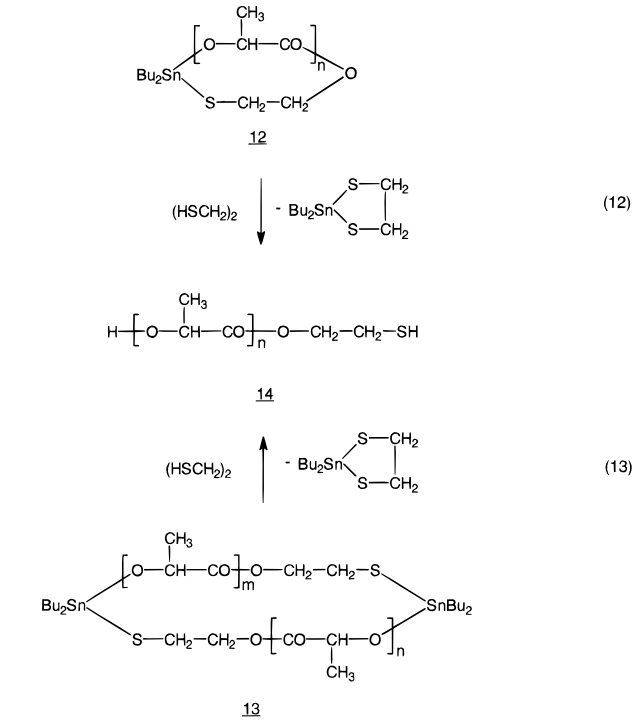
acid is more acidic than that of ethanediol. Furthermore, association equilibria of the initiator blocking the free d-orbitals may play a role, but a clearcut answer cannot be given at this time.

The ^{1}H NMR spectra of Figure 4 also provide the answer to question II. One broad singlet signal appears at 4.3 ppm as expected for double-acylated ethanediol (structure **9** or **10**). The two triplet signals expected for structure **8** were never observed. Thus the ^{1}H NMR spectra clearly indicate that an insertion at both Sn−O bonds of **2**/**5** is highly favored over a "monoacylation" (structure **8**). In the case of initiator **3**/**7** the signal of the O−CH_2 group has experienced a downfield shift of 0.6 ppm (from 3.62 to 4.20 ppm) after reaction with L-lactide. In contrast, a downfield shift of only 0.07 ppm is detectable for the S−CH_2 signal, what means that the Sn−S bond did not react with L-lactide. The ^{1}H NMR spectrum of the same **3**/**7**-initiated poly(L-lactide) recorded after precipitation into methanol (Figure 6) confirms the measurement and interpretation of the reaction mixture. This spectrum (Figure 6) also shows that a longer contact with methanol removes the Bu_2Sn group and entails a methanolytic cleavage of ester linkages with the formation of a methyl ester groups.

In order to find an answer to question IV, six poly(D,L-lactide) samples were prepared (and compared), two of them initiated with $Bu_2Sn(OMe)_2$, two initiated with **2**/**5**, and two initiated with **3**/**7**. All polymerizations were conducted in bulk at 120 °C for 2 h with a M/I ratio of 100:1. The crude product of each polymerization was dissolved in dry CH_2Cl_2 and divided into four portions. One portion was directly precipitated into cold diethyl ether. The other three portions were treated with dimercaptoethane in 1:1, 1:1.5, and 1:2 molar ratios relative to the Bu_2Sn group (Table 6) prior to the precipitation. The purpose of this treatment was to cleave the macrocyclic polylactides selectively at the Sn−O bonds with formation of open chains (eqs 10−13). It has been demonstrated in the preceding part of



this series that DME reacts at room temperature with dibutyldimethoxytin almost quantitatively yielding **4** and methanol (eq 14). Furthermore, it has been dem-



onstrated in the case of macrocyclic poly(β-D,L-butyrolactone) that DME allows as nearly quantitative and highly selective cleavage of the macrocyclic polyesters. In the case of polylactides, a selective ring cleavage at the Sn−O bonds is more risky because the ester bonds of lactide units are more sensitive to any nucleophilic attack.

Nonetheless, the experiments with DME gave some interesting results, which are summarized in Table 6. The treatment of $Bu_2Sn(OMe)_2$-initiated polylactide with DME yields products with higher retention times indicating lower molecular weights, as expected from a bisection of the original sample. In contrast, the treatment of **2**/**5** or **3**/**7**-initiated polylactides with DME yields polymers with slightly lower retention times. This means that the average M_n's did not change upon treatment with DME regardless of whether an equimolar amount of DME or 50 and 100% excess of DME were used. The successful removal of the Bu_2Sn groups according to eqs 10−13 was checked by ^1H NMR spectroscopy of the precipitated polylactides. Therefore, these results demonstrate the following: (1) that both the **2**/**5**-initiated and the **3**/**7**-initiated macrocycles are mainly monomeric and (2) that a regioselective ring opening of monomeric macrocycles took place, yielding open chains with slightly a higher hydrodynamic volume.

It should be emphasized that these results are not only consistent and reproducible (see Table 6), they also agree with the results obtained from ring opening of β-D,L-butyrolactone with the cyclic initiators **1a** or **1b** followed by treatment with DME.[10]

Conclusion

A more detailed characterization of the cyclic initiators used in this work confirmed that the heterocycles derived from 1,2-ethanediol or 2-mercapethanol are mainly dimeric, 10-membered rings. Sufficient reactivity as initiators was only found when the heterocycles contained a Sn−O bond. These cyclic initiators give high yields of medium to high molecular weight polylactides, when the polymerizations are conducted in bulk. An interesting aspect of these polymerizations is the formation of macrocycles and the almost complete absence of back-biting degradation. However, the relatively slow initiation steps make it difficult to control the molecular weight and produce broad molecular weight distributions.

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