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POLYLACTONES. 34. POLYMERIZATIONS OF *meso*- AND *rac*-D,L-LACTIDE BY MEANS OF GRIGNARD REAGENTS

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ABSTRACT

Meso- and *rac*-D,L-lactide were polymerized in bulk at 120°C by means of BuMgCl or EtMgBr. With *rac*-D,L-lactide yields up to 83%, number-average molecular weights (M_n) up to 71,000 and weight-average molecular weights (M_w) up to 108,000 were obtained. Attempts to polymerize *meso*-D,L-lactide in bulk at 60°C gave very low yields. All attempts to polymerize *rac*-D,L-lactide in toluene at 60°C failed completely regardless if crown ethers or benzyl alcohol were added as coinitiators. $MgBr_2$ proved to be useless as an initiator even for polymerizations at 120°C in bulk. Furthermore, copolymerizations of glycolide and *rac*-D,L-lactide initiated with EtMgBr or nBu$_2$Mg were conducted in bulk at 120 and 150°C. Low molecular weights were found in most cases due to side reactions of the glycolide. The molecular weights increased with the molar fraction of *rac*-D,L-lactide.

INTRODUCTION

Polylactides are attracting more and more interest as biodegradable materials based on renewable resources. The most widely used and most versatile method for the preparation of polylactides is the ring-opening polymerization of L- or *rac*-D,L-lactide. In principle, a broad variety of catalysts can be used to initiate the polymerization which may obey a cationic, an anionic, or an insertion mechanism.

The most widely used initiator for the preparation of high molecular weight poly(L-lactide) is Sn(II)2-ethylhexanoate [1–10] because of its efficiency and because it is admitted as food additive by the FDA [11]. For the future technical production of poly(L-lactide), complexes of lanthanides may play a role [12, 13]. However, all these heavy metals are not desirable in polylactides designed for pharmaceutical and medical applications.

Acceptable as "impurities" for any application of polylactides in the human body are metal ions which play a role in human metabolism, i.e., Na, K, Mg, Ca, Zn, or Fe. We consider magnesium compounds to be attractive as potential initiators. The reason for this evaluation is the fact that the metal—oxygen bond which forms the active chain end should be covalent rather than ionic to avoid side reactions. Typical side reaction of an anionic polymerization are partial racemization and chain transfer to the monomer [14, 15]. Also, magnesium salts (and even more calcium salts) bear the risk of such side reactions [16, 17]. However, in a recent study we showed that Bu_2Mg-initiated polymerizations of L-lactide may yield high molecular weight poly(L-lactide) without significant racemization.

In the present work the usefulness of Grignard reagents as initiators for *rac*-D,L-lactide is studied. Previous studies based on L-lactide have shown that BuMgCl is not reactive enough as an initiator in solution at temperatures $\leq 25°C$. Polymerizations conducted in bulk at 120°C resulted in partial racemization. Since racemization is no problem when a D,L-lactide is used, "Grignard reagents" may be still useful initiators for these monomers.

EXPERIMENTAL

Materials

Meso- and *rac*-D,L-lactide were gifts of Boehringer KG (Ingelheim/Rhein, FRG). They were recrystallized from ethyl acetate. The melting point of *rac*-D,L-lactide was 125–126°C after one recrystallization and did not change after a second recrystallization. The melting point of recrystallized *meso*-D,L-lactide was 45–47°C. Glycolide was purchased from Boehringer KG and recrystallized from dry ethanol. (mp 85–87°C). *n*BuMgCl (2 M) in THF and EtMgBr (1 M) in THF were purchased from Aldrich Co. (Milwaukee, WI, USA). Toluene was distilled over P_4O_{10} under nitrogen.

Polymerizations

In Bulk

The D,L-lactide (25 mmol) was weighed under an atmosphere of dry nitrogen into a 50-mL Erlenmeyer flask with silanized glass walls and the initiator solution was injected by means of a syringe. The reaction vessel was closed with a glass stopper and steel spring and immersed into a thermostated oil bath. When the reaction time was over the product was dissolved in methylene chloride (40 mL) and precipitated into cold diethyl ether. The precipitated polylactide was isolated by filtration and dried at 40°C in vacuo.

In Solution

Under an atmosphere of dry nitrogen, *rac*-D,L-lactide (25 mmol) and the coinitiator were weighed into a 50-mL Erlenmeyer flask with silanized glass walls and dissolved in dry toluene (25 mL). The initiator solution was injected by means of a syringe. The reaction vessel was closed with a glass stopper and steel spring and immersed into a thermostated oil bath. When the reaction time was over the cold reaction product was dissolved in CH_2Cl_2 (40 mL) precipitated into cold diethyl ether and dried at 40°C in vacuo.

Measurements

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

The 100 NH_2 ^{1}H-NMR spectra were recorded with a Bruker AC-100 FT NMR spectrometer in 5 mm o.d. sample tubes.

The GPC measurements were conducted in tetrahydrofuran on a Kontron HPLC 420 equipped with Waters differential refractometer Md 410. A combination of four Ultra-Styragel columns with pore sizes of 10^2, 10^3, 10^4, and 10^5 Å was used.

RESULTS AND DISCUSSION

Homopolymerizations

Several BuMgCl-initiated polymerizations of L-lactide in bulk at 120°C suggested that these reaction conditions might also allow the polymerization of *meso*- and *rac*-D,L-lactide. In a first series of experiments *n*BuMgCl-initiated polymerizations of *rac*-D,L-lactide were conducted in bulk with variation of the monomer/initiator (M/I) ratio and reaction time. The results, compiled in Table 1, allow the

TABLE 1. *n*BuMgCl-Initiated Polymerizations of *rac*-D,L-Lactide in Bulk at 120°C

Experiment	M/I	Time, hours	Yield,[a] %	η_{inh},[a,b] dL/g	Yield,[c] %	η_{inh},[c,b] dL/g
1	100:1	24	48	0.45	54	0.40
2	100:1	72	64	0.53	68	0.45
3	200:1	48	67	0.65	83	0.53
4	200:1	96	58	0.59	80	0.65
5	400:1	72	55	0.50	81	0.60
6	400:1	192	59	0.45	80	0.55
7	600:1	192	42	0.42	72	0.53
8	800:1	192	13	0.43	50	0.48

[a]The *rac*-D,L-lactide was recrystallized once from ethyl acetate.
[b]Measured at 20°C with c = 2 g/L in CH_2Cl_2.
[c]The *rac*-D,L-lactide was recrystallized twice.

following conclusions. The molecular weights do not parallel the M/I ratio. This result and the broad molecular weight distributions discussed below clearly demonstrate that these polymerizations do not obey the pattern of a classical "living polymerization." The highest yields and viscosities were obtained at a M/I ratio of 200/1. The reaction time has little influence.

All polymerizations of this first series were conducted with a *rac*-D,L-lactide recrystallized once from ethyl acetate (footnote a in Table 1). In order to see if the purity of the monomer is crucial for the yields and molecular weights under the given reaction conditions, a second series of analogous polymerizations was conducted with a *rac*-D,L-lactide recrystallized twice from ethyl acetate. In a previous study [18] using $SnBr_4$ as initiator of L,L-lactide, it was found that repeated recrystallization of the monomer has a significant influence on molecular weight. However, in the present work only the yields increase whereas the viscosities had the same order of magnitude regardless of the extent of purification (footnote c in Table 1). These results suggest that side reactions and not the purity of the monomer is decisive for the limitation of the molecular weight. This suggestion has been confirmed by other observations discussed below.

In order to obtain at least a crude estimation of the maximum molecular weights resulting from the experiments in Table 1, the two samples with the highest inherent viscosities [0.65 dL/g (No. 4) and 0.60 dL/g) (No. 5)] were characterized in two ways. First, GPC curves were recorded in tetrahydrofuran, and the maxima of the elution curves were calibrated with commercial polystyrene standards according to the universal calibration method. In this way, viscosity-average molecular weights (M_w) of 100,000 (No. 4) and 85,000 (No. 5) were obtained. Second, the elution curves were evaluated by means of the K and a values of the Mark–Houwink Eq. (1) which was published for solutions of polystyrene in tetrahydrofuran [19]. In this way an M_n of 71,000 and an M_w of 108,000 were found for No. 4. An M_n of 57,000 and an M_w of 90,000 were obtained for No. 5. Thus, in both cases a polydispersity of 1.5–1.6 was the result.

$$[\eta] = 5.49 \times 10^{-4} \times M_n^{0.639} \quad (1)$$

A third series of polymerizations was conducted with *rac*-D,L-lactide as monomer and a commercial solution of EtMgBr in THF as initiator (Table 2). In this third series, yields comparable with those of Table 1 were found, but the inherent viscosities were systematically lower. In a fourth series of polymerizations, *meso*-D,L-lactide was initiated with *n*BuMgCl at 120°C (Table 3). This series of polymerizations gave somewhat lower yields (relative to those of Table 1) whereas the inherent viscosities were comparable. In order to reduce the influence of side reactions which are obviously responsible for the relatively low yields and viscosities, it was desirable to lower the reaction temperature. Unfortunately, the high melting point of *rac*-D,L-lactide (125–127°C) prevents its polymerization in bulk below 120°C. For this purpose the relatively low melting point of *meso*-D,L-lactide (43–45°C) is an advantage. Thus, attempts were made to polymerize *meso*-D,L-lactide in bulk at 60°C with *n*BuMgCl as initiator. Yet, regardless of reaction time and M/I ratio, all experiments failed to yield poly(D,L-lactide). When an analogous series of experiments was conducted with EtMgBr, low yields of poly(D,L-lactide) were obtained (Table 4).

TABLE 2. EtMgBr-Initiated Polymerizations of *rac*-D,L-Lactide in Bulk at 120°C

Experiment	M/I	Time, hours	Yield,[a] %	η_{inh},[b] dL/g
1	100:1	24	61	0.38
2	100:1	72	68	0.35
3	200:1	48	64	0.49
4	200:1	96	44	0.33
5	400:1	72	47	0.45
6	400:1	192	17	0.34
7	600:1	192	1	—
8	800:1	192	0	—

[a]After precipitation into Et_2O.
[b]Measured at 20°C with c = 2 g/L in CH_2Cl_2.

In order to reduce the reaction temperature for *rac*-D,L-lactide, numerous attempts were made to polymerize this monomer in concentrated solutions in toluene at 60°C. Both *n*BuMgCl and EtMgBr were used as initiators, and the M/I ratio and the reaction time were varied. Furthermore, various crown ethers were added. Despite the variation of all these parameters, all experiments failed to yield poly(D,L-lactide). Finally, a series of polymerizations was conducted in such a way that EtMgBr was reacted with an equimolar amount of benzyl alcohol prior to the addition of lactide. Furthermore, crown ethers were added to the reaction mixture in toluene. However, all these experiments conducted in toluene at 60°C failed to produce poly(D,L-lactide).

TABLE 3. BuMgCl-Initiated Polymerizations of *meso*-D,L-Lactide in Bulk at 120°C

Experiment	M/I	Time, hours	Yield,[a] %	η_{inh},[b] dL/g
1	100:1	24	44	0.29
2	100:1	72	44	0.40
3	200:1	24	53	0.57
4	200:1	72	53	0.54
5	400:1	24	47	0.53
6	400:1	72	25	0.50
7	800:1	24	25	0.50
8	800:1	72	14	0.43

[a]After precipitation into Et_2O.
[b]Measured at 20°C with c = 2 g/L in CH_2Cl_2.

TABLE 4. EtMgBr-Initiated Polymerizations of *meso*-D,L-Lactide in Bulk at 60°C

Experiment	M/I	Time, hours	Yield,[a] %	η_{inh},[b] dL/g
1	200:1	24	6	0.22
2	200:1	48	20	0.26
3	200:1	72	20	0.30
4	200:1	96	22	0.30
5	200:1	192	3	0.41

[a]After precipitation into Et_2O.
[b]Measured at 20°C with c = 2 g/L in CH_2Cl_2.

Copolymerizations

Copolymers of lactide, particularly copolymers of glycolide and D,L-lactide, are of interest for pharmaceutical applications, such as the microencapsulation of drugs. Therefore, it was of interest to study the copolymerization of glycolide and *rac*-D,L-lactide initiated by Grignard reagents. In a previous study [20] based on more than 20 different initiators, it was found that glycolide is more reactive than lactide regardless of the polymerization mechanism. Random or nearly random sequence can only be obtained when reaction temperatures ≥150°C are applied. The high temperatures reduce the difference of the reactivities and favor the equilibration of sequences by transesterification.

All nine EtMgBr-initiated copolymerizations of glycolide and *rac*-D,L-lactide were conducted in bulk either at 150°C or at 180°C. The results, compiled in Table 5, show that the yields of the precipitated copolyesters were low in all cases. These low yields are partially a consequence of fractionation because the oligomers and low molecular weight polymers are soluble in methanol. Yet this fractionation is only effective because the average molecular weight of all samples was low. The most interesting aspect of these copolyesters is the finding that all samples are soluble in a mixture of CH_2Cl_2 and trifluoroacetic acid. This good solubility indicates that long blocks of glycolide are absent, because polyglycolide and copolymers with long blocks of glycolide are insoluble in all common inert solvents with the exception of hexafluoroisopropanol.

The relatively good solubility of all copolyesters listed in Table 5 does not mean that the sequences are perfectly random. The degree of blockiness can be seen (and quantified) from the CO-signals of the ^{13}C-NMR spectra (Fig. 1). The assignments of these signal patterns has been discussed previously [20, 21]. The ^{13}C-NMR spectra demonstrate that the blockiness of the sequences decreases with increasing reaction temperature and time. A second series of 1:1 copolymerizations of glycolide and *rac*-D,L-lactide was conducted in bulk at 120°C with *n*BuMgCl as initiator. It was hoped that lower temperature would reduce the frequency of side reactions and yield higher molecular weights. However, all copolyesters obtained in this way were so heterogeneous with regard to their block length distribution that a considerable fraction was insoluble in CH_2Cl_2/trifluoroacetic acid. Since copolyes-

TABLE 5. EtMgBr-Initiated Copolymerizations of Glycolide and *rac*-D,L-Lactide (mole ratio 1:1) in Bulk at 150°C (Nos. 1-6) or at 180°C (Nos. 7-9)

Polymer	Temperature, °C	M/I[a]	Time, hours	Yield,[a] %	Composition[b]	η_{inh},[c] dL/g
1	150	200/1	24	18	0.89:1	0.17
2	150	200/1	48	15	0.86:1	0.19
3	150	200:1	72	17	1.00:1	0.16
4	150	400:1	24	30	0.92:1	0.15
5	150	400:1	48	32	0.61:1	0.19
6	150	400:1	72	36	1.10:1	0.20
7	180	200:1	1	39	0.50:1	0.15
8	180	200:1	4	49	0.89:1	0.18
9	180	200:1	8	15	0.95:1	0.15

[a]Initial molar-feed ratio.

[b]Molar composition of the precipitated copolyesters as determined by ^{1}H-NMR spectroscopy.

[c]Measured at 20°C with c = 2 g/L in CH_2Cl_2/trifluoroacetic acid (volume ratio 4:1).

ters of such a broad heterogeneity are useless for any potential application, a detailed characterization of these samples was not conducted for this work.

Finally, a third series of copolymerizations was conducted in bulk at 120°C but with variations of the glycolide/lactide ratio. Again, *n*BuMgCl served as initiator (Table 6). As mentioned above, the copolyester resulting from a 1:1 molar ratio was partially insoluble in most inert solvents. However, higher lactide/glycolide ratios yielded samples completely soluble in CH_2Cl_2. The most interesting result is the observation that the inherent viscosities increase with the lactide/glycolide ratio. Obviously the glycolide causes more termination steps than the lactide. A hypothetical explanation of this result is discussed below.

Mechanistic Aspects

Albeit this work had not the purpose of mechanistic studies, the mechanistic aspects of the results need a short discussion. Since both anionic polymerizations and insertion mechanisms of lactides involve a cleavage of the acyl—oxygen bond, it is obvious that the chain growth proceeds via a magnesium-alkoxide endgroup (Eq. 2). $MgEt_2$-initiated polymerizations of β-lactones discussed previously [22] suggest that the Mg—alkoxide bonds have a covalent rather than an ionic nature. However, higher temperatures and a polar environment will certainly favor the ionic character of the Mg—O bond. The results of this work (e.g., Table 4) show that *n*BuMgCl and EtMgBr possess somewhat different reactivities. Furthermore, it was found previously [23] that nBu$_2$Mg is much more reactive than both Grignard reagents. Since the alkyl groups disappear from the reaction mixture in the form of alkanes, it is obvious that the "counterion" is permanently associated with the magnesium and somehow controls the reactivity of the active chain end. Therefore,

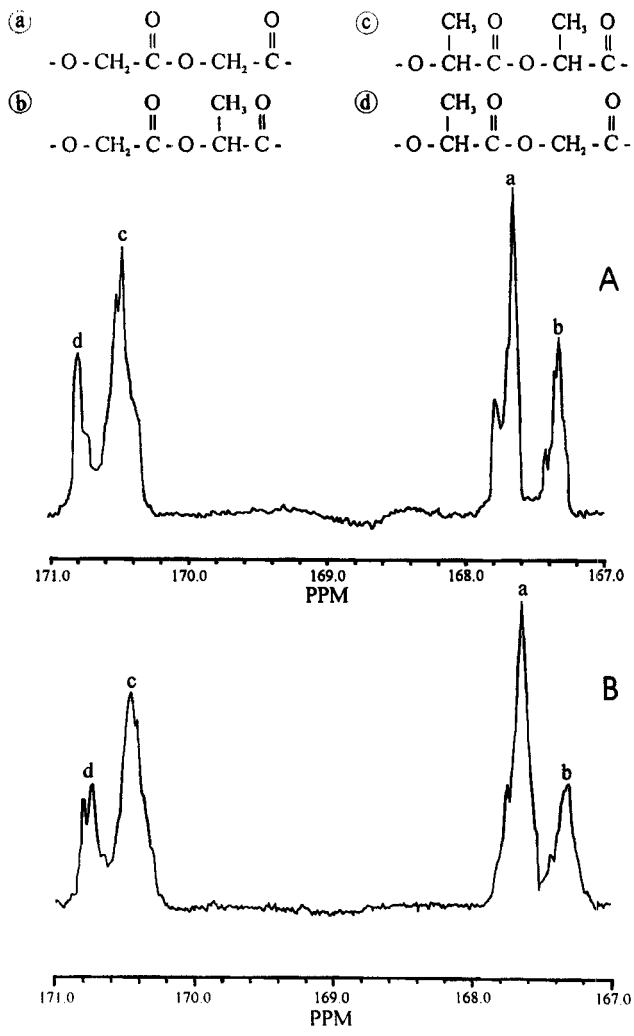


FIG. 1. 25.4 MHz ^{13}C-NMR spectra (measured in hexafluoroisopropanol) of (A) Polymerization 6, Table 5; (B) Polymerization 8, Table 5.

it should be emphasized that Eq. (2) gives only a schematic illustration of the insertion mechanism under discussion. The formation of aggregates involving two or more Mg ions and "counterions" is highly probable.

Previous studies of the anionic polymerization of L-lactide have demonstrated [14] that L-lactide is sensitive to racemization at higher temperatures, even by weak bases such as triethylamine or pyridine. Furthermore, it was found that various magnesium salts [16] and *n*BuMgCl [23] cause partial racemization of L-lactide above 100°C. This anionic racemization proceeds via deprotonation of the rather acidic α-carbon (Eq. 3). The resulting delocalized anion is also capable of initiating chain growth as demonstrated by *n*BuLi [24] or *n*Bu_2Mg-initiated [23] polymerizations of neat L-lactide. Hence, deprotonation does not only cause racemization, it

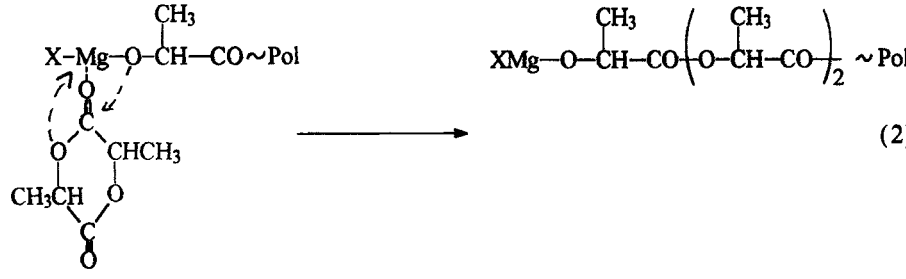
TABLE 6. BuMgCl-Initiated Copolymerization of Glycolide and *rac*-D,L-Lactide in Bulk at 120°C

Polymer	M/I	Time, hours	D,L-Lactide / Glycolide	η_{inh},[a] dL/g
1	200:1	24	1:1	0.17[b]
2	200:1	48	1:1	0.15[b]
3	200:1	24	2:1	0.26
4	200:1	48	2:1	0.22
5	200:1	48	4:1	0.32
6	200:1	48	9:1	0.41
7	200:1	48	39:1	0.50

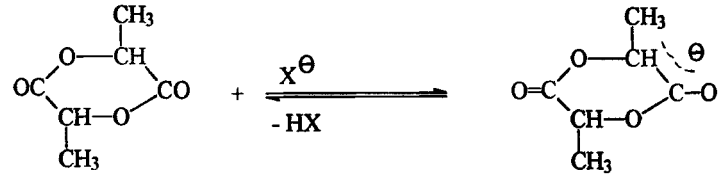
[a]The crude reaction products were measured at 20°C with c = 2g/L in CH_2Cl_2.

[b]Fraction soluble in CH_2Cl_2.

also represents a chain transfer to the monomer. Thus, it is obvious that the racemization observed for nBu$_2$Mg and nBuMgCl-initiated polymerizations of L-lactide and the moderate yields and molecular weights found here for polymerizations of *meso*- and *rac*-D,L-lactide all have the same origine, namely deprotonation of the monomer (Eq. 3) and reinitiation by the resulting anion. Further unknown side reactions may also be involved.



(2)



(3)

This hypothesis is supported by the nBuMgCl and EtMgBr-initiated copolymerizations of lactide with glycolide (Tables 5 and 6). Glycolide is more acidic than lactide, and its presence causes a further reduction of the molecular weight. This effect is more or less proportional to its molar fraction.

CONCLUSIONS

Grignard reagents such as EtMgBr and *n*BuMgCl are far less reactive than Bu_2Mg and cannot be used as initiators for lactides in solution below 100°C. Polymerizations of *rac*- or *meso*-D,L-lactide in bulk at 120°C give moderate yields and molecular weights. A reduction of the reaction temperature does not bring any progress. Copolymerizations with glycolide result in even lower molecular weights. Deprotonations of the monomers catalyzed by the Mg—O group or by the halogenide ions seem to be responsible for the termination steps.

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