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Polylactones: 32. High-molecular-weight polylactides by ring-opening polymerization with dibutylmagnesium or butylmagnesium chloride

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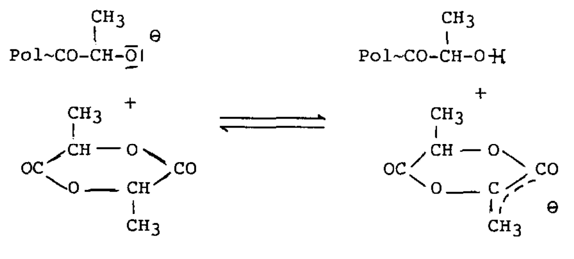
The dibutylmagnesium (Bu_2Mg)-initiated polymerizations of L-lactide at 120°C in bulk yielded poly(L-lactide) of low molecular weights ($\eta_{inh} \leqslant 0.4\,dl\,g^{-1}$ in CH_2Cl_2), regardless of reaction time and initiator concentration. Higher molecular weights were obtained in solution when carried out in the presence of ethers. The addition of crown ethers to polymerizations conducted in toluene at 0°C gave the best results, with η_{inh} values up to $3.0\,dl\,g^{-1}$ (in CH_2Cl_2), corresponding to number-average molecular weights (M_ns) of the order of $3 \times 10^5\,g\,mol^{-1}$. These high-molecular-weight poly(L-lactide)s possess almost complete optical purity and show melting temperatures of ~170°C. Relatively high-molecular-weight poly(D,L-lactide)s were also obtained by the Bu_2Mg-initiated polymerizations of racemic- or *meso*-D,D-lactides, with η_{inh} values up to $1.4\,dl\,g^{-1}$ (in CH_2Cl_2), corresponding to $M_n = 10^5$, being found. The Grignard reagent, BuMgCl, gave somewhat better results than Bu_2Mg when used as an initiator for L-lactide in bulk. However, BuMgCl is not reactive enough to initiate satisfactory polymerizations in solution at temperatures $\leqslant$ 25°C.

(Keywords: polylactones; ring-opening polymerization; dibutylmagnesium initiator)

INTRODUCTION

High-molecular-weight poly(L-lactide) is of interest as a biodegradable thermoplastic and fibre forming material. Medical sutures based on poly(L-lactide) are commercially available, and the fixation of bone fractures by means of bars, rods or pins made of poly(L-lactide) has been evaluated by many research groups. Amorphous and transparent poly(D,L-lactide)s are of interest as matrices for drug-delivery systems and as films or foils for wound treatment and other applications in medicine and agriculture. The standard catalyst for the synthesis of high-molecular-weight polylactides is Sn(II) (2-ethylhexanoate)[1–9]. This catalyst has several advantages, such as solubility in organic solvents and molten lactides, stability on storage, and formation of optically pure poly(L-lactide)s by polymerization in bulk at temperatures of ~120°C. However, for medical and pharmaceutical applications polylactides free of heavy metal ions are desirable, and a purification procedure for Sn-containing polylactides has been patented[10].

Therefore, several attempts were made to replace the Sn-based catalyst by less poisonous initiators. One approach consists of anionic polymerizations initiated with sodium or potassium alkoxides[11–13]. The anionic polymerization of lactides proceeds via alkoxide anions, and these anions are basic enough to deprotonate the monomer (*Scheme 1*)[13]. This deprotonation involves racemization and represents a chain transfer to the monomer with the consequence of reduced molecular weights[12]. In other words, anionic polymerizations are not suited for the preparation of a high-molecular-weight poly(L-lactide) with full optical purity. Nonetheless they may be useful for the synthesis of poly(D,L-lactide)s, in as much as for drug-delivery systems extreme molecular weights are not always necessary, or not even desirable. Even less favourable results were obtained when hemin or hematin was used as initiator[14]. The Al^{3+} ion is a rather harmless ion in low concentrations, and high-molecular-weight poly(D,L-lactide)s were reported for methylalumoxane-initiated polymerizations[15]. However, methylalumoxane is not stable on storage and its properties are difficult to reproduce. In this connection it is the purpose of this present work to study the Bu_2Mg- and BuMgCl-initiated polymerizations of L- or D,L-lactides. Mg^{2+} ions are required by the metabolism of



Scheme 1

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every living organism, including the human body, and thus small amounts of Mg^{2+} ions are certainly not poisonous. Furthermore, $Mg(OEt)_2$ was shown[16] to initiate an insertion mechanism and not an anionic polymerization. Therefore, the risk of racemization was expected to be low. Furthermore, successful Bu_2Mg-initiated polymerizations of a cyclic carbonate and ε-caprolactone have recently been described by another research group[17]. Yet, to the best of our knowledge, the BuMgCl-initiated polymerization of lactones or cyclic carbonates has not been studied so far.

EXPERIMENTAL

Materials

L-Lactide, racemic-D,L-lactide and *meso*-D,L-lactide were gifts of Boehringer GmbH (Ingelheim/Rhein, Germany). All lactides were twice recrystallized from ethyl acetate immediately before use and dried and stored over P_4O_{10} *in vacuo*. Crown ethers were purchased from the Aldrich Co. (Milwaukee, WI, USA) and dried over P_4O_{10} *in vacuo*. Toluene was distilled over P_4O_{10}, and tetrahydrofuran or dioxane was distilled over sodium wire. Solutions of Bu_2Mg in heptane (1 M) and BuMgCl in diethyl ether (2 M) were purchased from the Aldrich Co.

Polymerizations

In bulk. L-Lactide (40 mmol) was weighed into a 25 ml Erlenmeyer flask with freshly silanized glass walls (treatment with Me_2SiCl_2). The initiator was injected by means of a syringe in the form of a 1 M solution. The reaction vessel was closed with a glass stopper and steel spring and then immersed in an oil bath which had been preheated to 120°C. When the reaction time was complete (*Tables 1* and *2*), the cold reaction product was dissolved in CH_2Cl_2 (40–50 ml), precipitated into cold diethyl ether and then dried at 40°C *in vacuo*.

In solution. L-Lactide (40 mmol) was weighed into a 25 ml Erlenmeyer flask with silanized glass walls. Toluene or dioxane (10 ml) were added and the initiator was injected with a syringe in the form of a 1 M solution. The reaction vessel was closed with a glass stopper and steel spring and then thermostated at 50 ± 1, 25 ± 1 or 0–2°C. Finally, the product was dissolved in CH_2Cl_2, precipitated into cold diethyl ether and dried at 40°C *in vacuo*.

Table 1 Bu_2Mg-initiated polymerizations of L-lactide in bulk at 120°C

Experiment no.	Ratio of monomer to initiator	t (h)	Yield (%)	η_{inh} [a] ($\mathrm{dl\,g^{-1}}$)	$[\alpha]^{20}$ [b]
1	100/1	8	85	0.21	−132
2	100/1	24	90	0.19	−140
3	100/1	48	81	0.18	−148
4	100/1	72	77	0.15	−135
5	200/1	24	82	0.30	−137
6	200/1	48	99	0.41	−145
7	200/1	72	65	0.35	−140
8	400/1	24	28	0.28	−135
9	400/1	48	39	0.33	−143
10	400/1	72	68	0.45[c]	−146

[a] Measured at 20°C with a concentration of $2\,\mathrm{g\,l^{-1}}$ in CH_2Cl_2
[b] Measured at 20°C with a concentration of $10\,\mathrm{g\,l^{-1}}$ in $CHCl_3$ at 578 nm
[c] For molecular weight values see *Table 11*

Table 2 BuMgCl-initiated polymerizations of L-lactide in bulk at 120°C

Experiment no.	Ratio of monomer to initiator	t (h)	Yield (%)	η_{inh} [a] ($\mathrm{dl\,g^{-1}}$)	$[\alpha]^{20}$ [b]
1	100/1	8	66	0.15	−118
2	100/1	24	69	0.16	−127
3	100/1	48	76	0.18	−130
4	100/1	72	83	0.45	−133
5	100/1	96	91	0.35	−140
6	200/1	24	80	0.33	−144
7	200/1	48	81	0.52	−142
8	200/1	72	80	0.55	−138
9	200/1	96	78	0.61[c]	−141
10	500/1	72	41	0.38	−124
11	500/1	96	54	0.45	−145
12	500/1	192	70	0.56	−140
13	1000/1	72	16	0.17	−140
14	1000/1	96	41	0.32	−143
15	1000/1	240	47	0.27	−130

[a] Measured at 20°C with a concentration of $2\,\mathrm{g\,l^{-1}}$ in CH_2Cl_2
[b] Measured at 20°C with a concentration of $10\,\mathrm{g\,l^{-1}}$ in $CHCl_3$ at 578 nm
[c] For molecular weight values see *Table 11*

Racemic- or *meso*-D,L-lactides were polymerized in an analogous manner. All reaction mixtures were prepared under dry nitrogen.

Measurements

The viscosities were measured with an automated Ubbelohde viscometer thermostated at 20°C. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at a wavelength of 578 nm, using 1 ml cuvettes with a length of 10 cm. Gel permeation chromatography (g.p.c.) measurements were conducted by using a Kontron HPLC-420 instrument equipped with a Waters differential refractometer (Model 410). A combination of four Ultrastyragel® columns, with pore sizes of 10^2, 10^3, 10^4 and 10^5 Å, was employed.

RESULTS AND DISCUSSION

Polymerization of L-lactide in bulk

The synthesis of high-molecular-weight polylactides with Sn(II) (2-ethylhexanoate) is usually conducted in bulk, because this initiator is rather inactive at low temperatures (≤25°C) in solution. Due to the high melting point of *rac*-D,L-lactide (124–126°C), a temperature of 120°C is the lowest possible reaction temperature which enables polymerizations of all isomeric lactides in bulk. Therefore, this temperature was also selected for this present study. In order to determine how serious the problem of racemization is in bulk and in solution, L-lactide was preferentially used as monomer under both reaction conditions.

The results obtained from the Bu_2Mg-initiated polymerizations of L-lactide in bulk are summarized in *Table 1*. It is obvious, that regardless of reaction time and monomer/initiator (M/I) ratio, low-molecular-weight polylactides were always obtained. Furthermore, all polymerizations involved slight racemization, because the $[\alpha]^{20}_{578}$ value for 100% optical purity amounts to 158 ± 2° when measured in $CHCl_3$.

Table 3 Polymerization of L-lactide with Bu_2Mg in toluene

Experiment no.	T (°C)	Ratio of monomer to initiator	t (days)	Yield (%)	η_{inh}[a] ($\mathrm{dl\,g^{-1}}$)	$[\alpha]^{20}$[b]
1	25	200/1	4	87	1.43	−149
2	25	400/1	4	59	0.80	−155
3	25	400/1	8	81	1.05	−158
4	25	800/1	4	56	0.85	−161
5	25	800/1	8	58	1.00	−161
6	0	200/1	4	66	0.95	−151
7	0	200/1	8	76	1.30	−154
8	0	400/1	4	51	0.90	−159
9	0	400/1	8	62	1.00	−158
10	0	800/1	8	58	0.80	−156

[a] Measured at 20°C with a concentration of $2\,\mathrm{g\,l^{-1}}$ in CH_2Cl_2
[b] Measured at 20°C with a concentration of $10\,\mathrm{g\,l^{-1}}$ in $CHCl_3$ at 578 nm

Table 4 Bu_2Mg-initiated polymerizations of L-lactide in toluene containing 10 vol % tetrahydrofuran

Experiment no.	T (°C)	Ratio of monomer to initiator	t (days)	Yield (%)	η_{inh}[a] ($\mathrm{dl\,g^{-1}}$)	$[\alpha]^{20}$[b]
1	25	100/1	4	97	1.20	−146
2	25	100/1	8	98	1.25	
3	25	200/1	4	94	1.00	−152
4	25	200/1	8	85	1.20	
5	25	400/1	8	80	1.10	−156
6	0	100/1	4	92	1.35	−151
7	0	100/1	8	97	1.20	
8	0	200/1	4	96	1.75	−152
9	0	200/1	8	89	1.25	
10	0	400/1	8	81	1.90[c]	−156

[a] Measured at 20°C with a concentration of $2\,\mathrm{g\,l^{-1}}$ in CH_2Cl_2
[b] Measured at 20°C with a concentration of $10\,\mathrm{g\,l^{-1}}$ in $CHCl_3$ at 578 nm
[c] For molecular weight values see *Table 11*

A similar series of polymerizations was conducted with BuMgCl as the initiator (*Table 2*). In this case somewhat higher viscosity values were obtained, but the extent of racemization was not improved. Low initiator concentrations ($M/I \geqslant 400$) are certainly favourable with respect to higher molecular weights and for reducing the risk of racemization, but high conversion was never obtained at high M/I ratios. Taken together, Bu_2Mg- or BuMgCl-initiated polymerizations in bulk are far from attractive for the synthesis of high-molecular-weight, optically pure poly(L-lactide).

Polymerization of L-lactide in solution

A series of Bu_2Mg-initiated polymerizations of L-lactide were conducted in four solvents of different polarity, namely toluene, toluene containing 10 vol % tetrahydrofuran, neat tetrahydrofuran and neat 1,4-dioxane. In order to minimize the risk of racemization the reaction temperature was lowered to ±25°C, and finally to 0°C. The reaction times, M/I ratios and results obtained in neat toluene are compiled in *Table 3*. No conspicuous difference is observable between the experiments conducted at 25 or at 0°C. However, when compared to the polymerizations in bulk (*Tables 1* and *2*) two significant improvements are noteworthy. First, higher molecular weights were obtained and secondly almost complete optical purity is achieved (with exception of experiment no. 1). In other words, these reaction conditions represent an attractive way for the syntheses of poly(L-lactide)s.

When THF was added even better results were found (*Table 4*), i.e. higher yields and higher viscosities, along with optical purities in the range 97–99%. It is particularly remarkable that in both series of polymerizations (*Tables 3* and *4*) the molecular weights (viscosities) do not significantly depend on the M/I ratios. The improved results obtained by the addition of THF suggested that solvation of the active chain ends by ether groups accelerates the conversion and favours chain growth at the expense of side reactions. However, when an analogous series of polymerizations was conducted in neat THF disappointing results were found (data not given). The extent of racemization increased and the inherent viscosities were all below $0.6\,\mathrm{dl\,g^{-1}}$. The next surprise occurred when polymerizations were conducted in neat 1,4-dioxane. As illustrated by the data summarized in *Table 5* the yields were distinctly higher than those obtained in neat toluene. Furthermore, the molecular weights seemingly parallel the M/I ratios, in contrast to all of the series studied previously.

Table 5 Bu_2Mg-initiated polymerizations of L-lactide in dioxane

Experiment no.	T (°C)	Ratio of monomer to initiator	t (days)	Yield (%)	η_{inh}[a] (dl g^{-1})	$[\alpha]^{20}$[b]
1	25	100/1	4	98	0.60	−148
2	25	200/1	4	98	0.90	−154
3	25	400/1	4	97	1.15	−157
4	25	800/1	4	97	1.20	−155
5	50	100/1	4	97	0.55	–
6	50	200/1	4	98	0.75	–
7	50	400/1	4	98	1.10	–
8	50	800/1	6	97	1.30	–

[a] Measured at 20°C with a concentration of 2 g l^{-1} in CH_2Cl_2
[b] Measured at 20°C with a concentration of 10 g l^{-1} in $CHCl_3$ at 578 nm

Table 6 Bu_2Mg-initiated polymerizations of L-lactide in toluene with addition of crown ethers

Experiment no.	T (°C)	Crown ether[a]	Ratio of monomer to initiator	t (days)	Yield (%)	η_{inh}[b] (dl g^{-1})	$[\alpha]^{20}$[c]
1	25	A	200/1	4	93	2.07	−153
2	25	A	400/1	4	96	2.19[d]	−154
3	25	B	200/1	4	95	1.67	−147
4	25	B	400/1	4	82	2.13	−150
5	25	C	200/1	2	79	0.78	−146
6	0	A	200/1	4	85	3.01[d]	−153
7	0	A	400/1	4	88	2.98	–
8	0	B	200/1	4	91	2.30	−146
9	0	B	400/1	4	83	2.51	−151
10	0	C	200/1	2	77	1.97	–
11	0	C	200/1	4	89	1.80	−156
12	0	C	400/1	2	81	2.31	–
13	0	C	400/1	4	83	2.00	−156

[a] A = 12-crown-4; B = dibenzo-18-crown-6; C = 18-crown-6
[b] Measured at 20°C with a concentration of 2 g l^{-1} in CH_2Cl_2
[c] Measured at 20°C with a concentration of 10 g l^{-1} in $CHCl_3$ at 578 nm
[d] For molecular weight values see *Table 11*

It is possible that the polymerization mechanism was changed in the polar reaction medium, but a detailed mechanistic study was not intended in this present work.

However, polymerizations proved most successful when carried out in toluene with the addition of various crown ethers (see *Table 6*). Three different crown ethers were tested, namely 12-crown-4, dibenzo-18-crown-6, and 18-crown-6 (A, B and C in *Table 6*, respectively). The polymerizations conducted at 25 and 0°C both agree in that 12-crown-4 gives optimum results. The inherent viscosities (~ 3 dl g^{-1}) are the highest values obtained in this present work; the determination of molecular weights is discussed below. In addition to high yields and viscosities almost complete optical purity resulted from these polymerization reactions. The polymerizations with 12-crown-4 were repeated several times with different samples of L-lactide, toluene and Bu_2Mg solutions. It was found that reproducibility of the high molecular weights is sensitive to slight variations in the reaction conditions. Twice-recrystallized L-lactide gave higher viscosities than those found for the once-recrystallized monomer. Freshly recrystallized lactide dried over P_4O_{10} *in vacuo* gave higher viscosities than a lactide which had been exposed to air. Treatment of the reaction vessel with dichlorodimethylsilane (silanization) also favoured a higher-molecular-weight product. Distillation of toluene over P_4O_{10} proved to be more effective than a simple distillation without any drying agent present. Taken together, these observations suggest that the presence of any kind of impurities which contain OH groups or other electrophilic sites affects the formation of high-molecular-weight product.

Finally, two series of polymerizations based on BuMgCl as the initiator need discussion here. Some preliminary experiments conducted in toluene or dioxane had shown that BuMgCl is not reactive enough as an initiator at temperatures $\leqslant$ 25°C. Therefore, the reaction temperature was raised to 80°C. The results obtained, summarized in *Table 7*, allow two decisive conclusions to be made. First, high molecular weights were never obtained, regardless of whether toluene or dioxane was used as the solvent. The inherent viscosities were even lower than those found for the BuMgCl-initiated polymerizations in bulk (see *Table 2*). Secondly, all

Table 7 BuMgCl-initiated polymerizations of L-lactide in solution at 80°C

Experiment no.	Solvent	Ratio of monomer to initiator	t (h)	Yield (%)	η_{inh}[a] (dl g^{-1})	$[\alpha]^{20}$[b]
1	Toluene	100/1	24	80	0.15	−145
2	Toluene	100/1	48	94	0.30	−146
3	Toluene	100/1	72	95	0.35	−147
4	Toluene	100/1	96	96	0.20	−138
5	Toluene	200/1	96	56	0.30	−146
6	Toluene	500/1	96	47	0.45	−143
7	Dioxane	100/1	48	65	0.18	−147
8	Dioxane	100/1	72	80	0.30	−146
9	Dioxane	100/1	96	86	0.35	−147
10	Dioxane	200/1	72	65	0.35	−142
11	Dioxane	200/1	96	80	0.35	−150
12	Dioxane	500/1	192	0	–	–

[a] Measured at 20°C with a concentration of 2 g l^{-1} in CH_2Cl_2

[b] Measured at 20°C with a concentration of 10 g l^{-1} in $CHCl_3$ at 578 nm

Table 8 Bu_2Mg-initiated polymerizations of racemic-D,L-lactide in toluene

Experiment no.	T (°C)	Crown ether[a]	Ratio of monomer to initiator	t (days)	Yield (%)	η_{inh}[b] (dl g^{-1})	L_i^c
1	25	–	200/1	4	96	1.22	3.4
2	25	–	200/1	8	94	1.17	3.1
3	25	–	400/1	8	98	0.95	–
4	25	A	400/1	8	88	1.14	–
5	25	A	400/1	8	89	1.21	–
6	0	–	200/1	8	57	1.12	3.4
7	0	–	400/1	8	35	1.24	–
8	0	–	400/1	16	94	1.27	–
9	0	A	200/1	16	64	1.38[d]	–
10	0	A	400/1	16	55	1.41	3.3

[a] A = 12-crown-4

[b] Measured at 20°C with a concentration of 2 g l^{-1} in CH_2Cl_2

[c] Average lengths of the isotactic blocks as determined by ^1H and ^{13}C n.m.r. spectroscopy[19]

[d] For molecular weight values see *Table 11*

polymerizations in solution involved slight racemization. Taken together, the results obtained in this work clearly indicate that BuMgCl is not attractive as an initiator in solution.

Polymerization of rac- *and* meso-*D,L-lactide*

A series of Bu_2Mg-initiated polymerizations of *rac*-D,L-lactide was conducted in toluene at 25 and 0°C (*Table 8*). Both the yields and inherent viscosities were slightly higher than those obtained with L-lactide under similar reaction conditions (see *Table 3*). However, an interesting difference concerns those polymerizations conducted with the addition of 12-crown-4 (nos 4, 5, 9, and 10 in *Table 8*). In contrast to analogous polymerizations of L-lactide (see *Table 6*) the crown ether did not cause a significant improvement in the molecular weights of the products. Polymerizations conducted in dioxane at 25 or 50°C (*Table 9*) gave yields and viscosities similar to those found in toluene (*Table 8*), and also similar to those obtained from L-lactide in dioxane (*Table 5*). These results prove that the polymerizability of *rac*-D,L-lactide was identical to that of L-lactide under the reaction conditions used in this study, and the failure of the crown ethers to give higher molecular weights needs a special explanation (see below).

A few Bu_2Mg-initiated polymerizations were conducted with *meso*-D,L-lactide (*Table 10*). The only conspicuous result is again the failure of the crown ether to improve the molecular weights of the resulting polymers. When the polymerizations with the addition of 12-crown-4 were repeated with another batch of *meso*-D,L-lactide that had been stored for some weeks in a desiccator the viscosities were even worse than those listed in *Table 10*. In other words, the ineffectiveness of the crown ether was reproducible.

Last, but not least, the L_i values listed in *Tables 8–10* require a brief comment. These data represent the average length of stereoblocks made up by isotactic diads. These L_i values were calculated from the CH signal of high resolution ^1H and ^{13}C n.m.r. spectra, as described previously[18,19]. An L_i value of ~3.4 indicates, for poly(D,L-lactide) prepared from *rac*-D,L-lactide, that

Table 9 Bu$_2$Mg-initiated polymerizations of racemic-D,L-lactide in 1,4-dioxane

Experiment no.	T (°C)	Ratio of monomer to initiator	t (days)	Yield (%)	η_{inh}[a] (dl g^{-1})	L_i^b
1	25	200/1	4	96	1.05	–
2	25	400/1	4	91	1.40[c]	–
3	25	400/1	8	95	1.20	3.4
4	25	800/1	4	90	0.92	–
5	50	200/1	4	90	0.80	–
6	50	400/1	2	94	1.05	3.1
7	50	400/1	4	98	1.00	–
8	50	800/1	4	98	1.00	3.2

[a] Measured at 20°C with a concentration of 2 g l^{-1} in CH$_2$Cl$_2$

[b] Average lengths of isotactic blocks as determined by ^{1}H and ^{13}C n.m.r. spectroscopy[19]

[c] For molecular weight values see *Table 11*

Table 10 Bu$_2$Mg-initiated polymerizations of *meso*-D,L-lactide in toluene with an M/I ratio of 200/1

Experiment no.	T (°C)	Crown ether[a]	t (days)	Yield (%)	η_{inh}[b] (dl g^{-1})	L_i^c
1	25	–	4	86	0.90	–
2	25	–	8	97	0.91	1.47
3	25	A	4	97	0.85	–
4	0	–	8	97	0.94[d]	1.41
5	0	A	4	96	0.78	–
6	0	A	8	97	0.85	1.45

[a] A = 12-crown-4

[b] Measured at 20°C with a concentration of 2 g l^{-1} in CH$_2$Cl$_2$

[c] Average lengths of the isotactic blocks as determined by ^{1}H and ^{13}C n.m.r. spectroscopy[19]

[d] For molecular weight values see *Table 11*

the ring-opening polymerization did not involve any transesterification between chain segments. The same conclusion holds for the L_i values of 1.4 ± 0.1 in the case of *meso*-D,L-lactide. These results agree well with a recent study of Wurm *et al.*[17] who found that in the Bu$_2$Mg-initiated polymerizations of ϵ-caprolactone little or no transesterification was involved.

Determination of molecular weights

Since numerous Mark–Houwink equations have been reported in the literature[20,21] for poly(L-lactide) and poly(D,L-lactide), all of the molecular weight data summarized in *Table 11* are based on viscosity measurements and calculations using equations (1)–(4) (see below). The [η] measurements were all conducted in chloroform, because benzene, the alternative solvent used in previous studies[20], is for health reasons not

Table 11 Molecular weight data obtained for the polylactides

Sample no.	η_{inh}[a] (dl g^{-1})	[η][b] at 20°C	[η][b] at 30°C	M_n[c] (×10^3)	M_n[d] (×10^3)	M_n[e] (×10^3)	M_n[f] (×10^3)
Poly(L-lactide) No. 10, *Table 1*	0.45	0.374	0.334	7	13	18	17
Poly(L-lactide) No. 9, *Table 2*	0.61	0.422	0.383	8	16	21	21
Poly(L-lactide) No. 10, *Table 4*	1.90	2.761	2.186	86	155	179	531
Poly(L-lactide) No. 2, *Table 6*	2.19	2.889	2.676	114	200	190	574
Poly(L-lactide) No. 6, *Table 6*	3.01	4.117	3.730	180	309	285	1057
Poly(D,L-lactide) No. 9, *Table 8*	1.38	1.707	1.539	53	98	104	232
Poly(D,L-lactide) No. 2, *Table 9*	1.40	1.775	1.570	65	100	108	248
Poly(D,L-lactide) No. 4, *Table 10*	0.94	1.039	1.025	31	58	58	98

[a] Measured at 20°C with a concentration of 2 g l^{-1} in CH$_2$Cl$_2$

[b] Measured in chloroform at 20 or 30°C

[c] Calculated from equation (1)

[d] Calculated from equation (2)

[e] Calculated from equation (3)

[f] Calculated from equation (4)

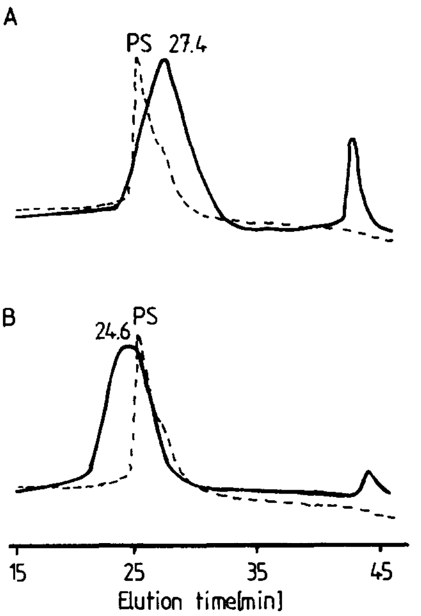


Figure 1 G.p.c. measurements in tetrahydrofuran: (a) poly(L-lactide) no. 10, *Table 3*; (B) poly(D,L-lactide) no. 9, *Table 8*. A polystyrene standard (M_w 120000, $M_w/M_n = 1.05$) is used in both cases

recommended any more. The molecular weights calculated from equations (1)–(4) for selected polylactides are compiled in *Table 11*. The molecular weight data reported in this table show satisfactory agreement between the results obtained from equations (2) and (3). However, the values obtained from equations (1) and (4) do not agree with each other, nor with those obtained from equations (2) or (3), and thus the origin and significance of this set of equations need a short discussion.

$$[\eta] = 5.45 \times 10^{-4} M_n^{0.73} \text{ (for poly(L-lactide) at 30°C)}^{20} \quad (1)$$

$$[\eta] = 2.21 \times 10^{-4} M_n^{0.77} \text{ (for poly(D,L-lactide) at 30°C)}^{20} \quad (2)$$

$$[\eta] = 7.4 \times 10^{-5} M_n^{0.87} \text{ (for poly(L-lactide) at 20°C)}^{21} \quad (3)$$

$$[\eta] = 1.32 \times 10^{-3} M_n^{0.58} \text{ (for poly(D,L-lactide) at 20°C)}^{22} \quad (4)$$

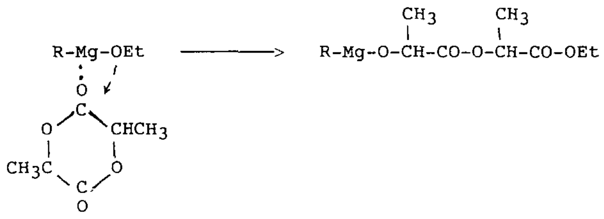
All of the four Mark–Houwink equations have in common the fact that the calibration is based on number-average molecular weights (M_ns). In the case of equations (1) and (2) the M_n values were determined by titration of the carboxyl end groups. This method is risky because the ester bonds of polylactides are sensitive to any kind of basic or hydrolytic cleavage, even at room temperature in (neutral) water. The problem here is the existence of two different Mark–Houwink equations, i.e. for poly(L-lactide) and poly(D,L-lactide). The samples used for calibration were hydrolysed in tetrahydrofuran. However, we found that high-molecular-weight poly(L-lactide) ($\eta_{inh} > 1.0\,\mathrm{dl\,g^{-1}}$) is not completely soluble in this solvent. Incomplete solubility leads to a non-statistical hydrolysis, and therefore to problems with the calibration, as pointed out by Schindler and Harper[20]. These authors explain the different calibration data obtained for poly(L-lactide) and poly(D,L-lactide) for different conformations in both benzene and chloroform solutions, by assuming a greater chain stiffness for poly(L-lactide). They justify this conclusion by citing slightly different chemical shifts of the isotactic tetrads in the ^{1}H n.m.r. spectra of poly(L-lactide) and poly(D,L-lactide).

We have compared the 360 MHz ^{1}H n.m.r. spectra of poly(L-lactide) and poly(D,L-lactide) with different L/D ratios and similar viscosities in chloroform by using homodecoupling of the vicinal protons[19] (apparently not used in ref. 20). We did not find any shift differences of the polylactides under investigation, provided that identical temperatures and concentrations were used. Furthermore, the ^{13}C n.m.r. spectra of poly(L-lactide)s and poly(D,L-lactide)s measured in $CDCl_3$ were compared for this present discussion. Again, no shift differences were found for the isotactic tetrads. In other words, there is no n.m.r. spectroscopic evidence for the largely differing conformations of poly(L-lactide) and poly(D,L-lactide) postulated in $CDCl_3$. Therefore, it is not clear why Schindler and Harper found two different Mark–Houwink equations[20]. Problems with the random hydrolysis of their poly(L-lactide) samples seem to be the most likely source of errors in this previous work.

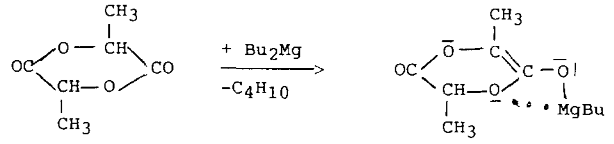
The calibration of equation (3) is based on two different analytical methods. Dahlmann and coworkers[21] found that results obtained from membrane osmosis and g.p.c. measurements of their samples showed good agreement. Taking into account the fact that the molecular weights derived from equations (2) and (3) show satisfactory agreement, these molecular weights are, in fact, based on three different calibration methods, and thus seem to be most reliable. Equation (4) was developed for samples with narrow molecular-weight distributions. However, g.p.c. measurements of poly(L-lactide)s with $\eta_{inh} < 1.0\,\mathrm{dl\,g^{-1}}$, and of several poly(D,L-lactide)s in tetrahydrofuran revealed that most of the polylactides prepared in this present work possess M_w/M_n ratios of ~ 2. Samples with monomodal molecular-weight distributions ($M_w/M_n \sim 2$) were also used for the calibration of both equations (2) and (3). Hence, the molecular weights calculated from both of these equations for samples used in this work clearly represent number average values (M_ns). *Figure 1* shows the molecular weight distribution for samples with low and high molecular weight.

Mechanistic aspects

The results presented in this work demonstrate that the addition of tetrahydrofuran or crown ethers favours the formation of high-molecular-weight poly(L-lactide). Results reported in a future paper in this series will demonstrate that linear oligo- or poly(ethylene glycol)s have a similar influence on the Bu_2Mg-initiated polymerizations of L-lactide. At first glance these findings suggest that the Bu_2Mg-initiated polymerizations have an anionic character, and the crown ethers favour the dissociation, and thus activation, of the ions by 'solvation' of Mg^{2+}. However, several observations contradict an anionic polymerization mechanism. First, it was demonstrated in a previous part of this series[16] that $Mg(OEt)_2$ initiates an insertion mechanism and not an anionic mechanism. As illustrated in *Scheme 2* the two characteristic steps of an insertion mechanism are (a) the reversible association of monomer and covalent initiator



Scheme 2



Scheme 3

or active chain end, and (b) the irreversible 'insertion' of the lactone into the Mg–O–alkyl bond. Secondly, Bu_2Mg-initiated polymerizations of L-lactides proceed without racemization at temperatures $\leqslant 25°C$. In contrast, anionic polymerizations of lactides involve an alkoxide anion as an active chain end, thus causing partial racemization by deprotonation of the monomer[11]. Thirdly, anionic deprotonation of a lactide is also a chain transfer process to the monomer, which severely limits the molecular weights in anionic polymerization. The increased molecular weights obtained by addition of crown ethers to Bu_2Mg-initiated polymerizations are thus in complete contrast to a true anionic polymerization. Fourthly, the Bu_2Mg-initiated polymerizations of lactides and lactones[17] do not involve transesterification.

With regard to the initiation process only one aspect is clear. Addition of Bu_2Mg to a lactide in solution (or vice versa) results in an evolution of butane. Hence, deprotonation of the monomer is clearly the first step, and the resulting lactide magnesium complex (see *Scheme 3*) somehow initiates the polymerization. This hypothesis is supported by the finding that n-butyl end groups were not detectable by ^1H n.m.r. spectroscopy, even when the samples with the lowest viscosities were examined. Furthermore, the molecular weights are not particularly dependent on the M/I ratios. In the non-polar solvent toluene the magnesium–lactide complexes and the active chain ends possibly form larger aggregates. The positive influence of the ethers, particularly crown ethers, might consist of breaking up these aggregates, thus facilitating the access of monomer to the active chain ends. However, this effect should also be valid for Bu_2Mg-initiated polymerizations of *rac*- and *meso*-D,L-lactides, but the crown ethers are not effective in this case.

In this connection the biphasic character of the 'solution polymerizations' conducted in toluene needs discussion. The small amount of toluene used to minimize side reactions of potential impurities (and of the solvent itself) was not sufficient to dissolve all of the lactide. Obviously the polymerization starts in solution, but with the increasing lengths of the poly(L-lactide) chains crystallization tends to occur, thus forming a third phase. The high yields prove that the active chain ends remain located on the surface of the growing crystals. Presumably, crown ethers and oligo(ethylene glycol)s prevent inclusion of the active chain ends in or between the growing crystals and thus facilitate access of the monomers.

In addition, the poly(D,L-lactide) chains form a separate phase in toluene, despite the lack of crystallinity. In this case it is unlikely that most of the active chain ends concentrate on the surface of the amorphous phase. However, most of the *rac*- or *meso*-D,L-lactides may be 'dissolved' in the more polar poly(D,L-lactide) phase and are sufficiently mobile to migrate to the active chain ends. In this case ethers are not required to improve the contact between monomers and active chain ends. Obviously, the different physical aspects of the polymerizations conducted with either L-lactide or D,L-lactide are the reason why crown ethers play a favourable role in the former, but not in the latter case. Further intensive studies are certainly required to elucidate the complex reaction mechanism in more detail.

CONCLUSIONS

The dibutylmagnesium-initiated polymerization of L- or D,L-lactides at low temperatures allows the synthesis of high-molecular-weight polylactides. Number-average molecular weights up to 3×10^5 were obtained. A more rigorous purification of the monomers and deactivation of the surface of the reaction vessel might yield even higher molecular weights. However, the molecular weights reported here are sufficient for most medical and pharmaceutical applications. The presence of crown ethers is only necessary when molecular weights above 10^5 are required; these are easier to remove, by precipitation or washing of the polymer, than hydrophobic and covalently bound tin compounds. Thus, Bu_2Mg is an attractive initiator for the polymerization of L- or D,L-lactides, in as much as Mg^{2+} ions are fully compatible with the metabolism of the human body.

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