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Polylactones
6. Influence of Various Metal Salts on the Optical Purity of Poly(L-Lactide)

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SUMMARY

L,L-lactide was polymerized in bulk at 120°C, 150 or 180°C by means of various metal oxides, carbonates or carboxylates. Yield, viscosities and optical rotation were measured and compared. Several catalysts enable a nearly complete conversion even at 120°C indicating rapid diffusion of the monomer in the solid reaction mixture. At 180°C only SnO and Sb_2O_3 proved to be useful catalyst, because they gave within 12 h yields > 80% along with an optical purity around 97%. Longer reaction times lead at 180°C to substantial racemization in all cases.

INTRODUCTION

In the past twenty years poly(L-lactide) and copolyesters of L-Lactide acid found increasing interest as non-immunogenic, non-toxic and biodegradable materials for medical and pharmaceutical applications. In numerous patents and papers dealing with the polymerization of L,L-lactide or other lactones, various metaloxides, carbonates and carboxylates are claimed as potential initiators [1-8]. To the best of our knowledge, any comparative investigation of these metal salts with respect to their effectiveness as initiator is lacking. In particular, the influence of both initiator and reaction conditions on the optical purity of poly(L-lactide) has never been studied on a broad basis. In the preceding paper it was reported that all magnesium salts used as initiators of L,L-lactide cause partial racemization even at 150°C. On the one hand, high reaction temperature, eg. $\geq$ 180°C, are necessary for extrusion of the molten poly(L-lactide) ($T_m \approx 175$°C). On the other hand, optically pure poly(L-lactide) is desired, if good mechanical properties are required (e.g. for medical sutures), because only as fully isotactic polylactide possesses a high degree of crystallinity, and thus, sufficient mechanical strength. Therefore, it was the purpose of the present work to compare the catalytic efficiency of various metal salts along with their influence on the optical purity of poly(L-lactide).

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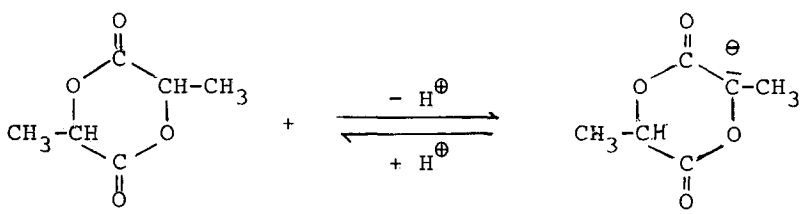
RESULTS and DISCUSSION

All polymerizations were conducted with recrystallized L,L-lactide in bulk at three different temperatures. The highest reaction temperature (180°C) was chosen, because this is the lowest temperature which allows one to keep the resulting poly-(L-lactide) in the molten state; lower temperatures (150 and 120°C) were chosen to minimize racemization. Preliminary experiments with organometallic initiators (published elsewhere) had shown that the monomer can diffuse in the solid reaction mixture to such an extent that complete conversions are obtainable at 150°C.

Various metal oxides were used as initiators for the first series of polymerizations. The result listed in Table 1 may be summarized as follows:

1) Titanium, germanium and tin(IV)oxides are rather ineffective catalysts.
2) In contrast tin(II) and lead(II)oxide rank among the most effective catalysts. PbO is particularily remarkable because it gave a yield > 90% even at 120°C. SnO is remarkable because it yielded the highest optical purity at 180°C.
3) Increasing reaction temperature may cause a conspicious increase of conversion, e.g. in the case of Fe_2O_3 the yield increased from 0 to 91%.
4) Increasing temperature causes stronger racemization. This effect is best seen in the case of PbO.

The results obtained with metalcarbonates (Table 2) indicate that alkalimetal carbonates are reactive initiators; yet they cause considerable racemization even at the lowest reaction temperature. The comparison of the four metal carbonates, the comparison of calcium oxide with magnesium oxide or of calcium oxide with calcium carbonate clearly indicate that extent of racemization increases with increasing basicity of the catalyst. This result suggests that deprotonation of the monomer is the main source of racemization. The monomer is more sensitive to racemization because the delocalization of the negative charge in a cyclic molecule is favoured by entropy:



The polymerizations conducted with metal acetates, stearates or 2-ethyl hexanoates (octoates) are summarized in Table 3. In agreement with the afore-discussed racemization mechanism the sodium salts caused stronger racemization than all other carboxylates, and the extent of racemization increases in the order.

Mg stearate < Ca stearate < Ba acetate.

It is also obvious that increasing temperature considerably accelerates the racemization.

The most effective initiators (of Table 3) with respect to both yield and viscosity are Sn(II), Sb and Bi octoate. The highest viscosity of all poly(L-lactide)s prepared in this study was obtained with Sn(II) octoate at 120°C. However, this catalyst also caused considerable racemization at 180°C although it was patented for the synthesis of medical sutures from L,L-lactide at temperature ≥ 180°C [4]. Bi octoate is noteworthy, because it caused little racemization even at 180°C. Nonetheless, it must be emphasized that no catalyst yielded a 100% opticaly pure poly(L-lactide) $[\alpha]_D^{20}$ -158±1° at 180°C, whith a reaction time of 48h. However, the results of Table 4 demonstrate that a reaction time of 12 h suffices at 180°C to obtain yields ≥ 95%, when the most effective catalysts are used. Under these conditions at least Sn(II) and Bioctoate yield 100% optically pure poly(L-lactide). Also noteworthy are the high viscosities. They suggest that the best initiators are also good transesterification catalysts which cause degradation due to backbiting of the active chain ends. Hence the best reaction conditions are temperatures between 120 and 150°C at reaction times > 24h in combination with initiators such as Sn(II), Sb and Bioctoate. Heating above 180°C for extrusion should be limited to the shortest possible time.

EXPERIMENTAL

Materials: L,L-lactide was a gift of Boehringer-Ingelheim, it was recrystallized from ethyl acetate and dried at room temperature in vacuo over P_2O_5. Most metal salts were purchased from Merck & Co (Darmstadt, W.Germany) as purum analyticum grade. Antimony and bismuth octoate(2-ethylhexanoate) were gifts of Hoechst AG (W.Germany). Tin(II)octoate and magnesium stearate were purchased from Ventron GmbH (7500 Karlsruhe, W.Germany).

Polymerizations: 40 mmol L,L-lactide and 0,4 mmol of the initiator were successively weighed under nitrogen in a 50 ml Erlenmeyer flask with silanized glass walls. The reaction vessel was closed with a glass stopper and steel spring. It was completely immerzed into the thermostated oil bath to avoid sublimation of L,L-lactide. After completion of the reaction time, the reaction product was dissolved in methylene chloride and precipitated from cold methanol containing 10% (by volume) of water. The yield was determined after drying of the precipitated poly(L-lactide) at 60°C/12 mbar. For viscosity and optical rotation measurements part of the crude polymer was again dissolved in methylene chloride, filtered from insoluble catalyst and precipitated from cold methanol.

Table 1: Bulk polymerizations of L,L-lactide by means of various metal oxides (M/I = 100; reaction time = 48 h)

No	Initiator	Temperature (°C)	Yield (%)	η_{inh}	$[\alpha]_D^{20}$	Appearence of product
1	MgO	120	22	0,15	-153	white solid
2	MgO	150	71	0,36	-122	white solid
3	MgO	180	91	0,35	-103	coloured solid
4	CaO	120	25			white solid
5	CaO	150	78	0,24	- 86	white solid
6	CaO	180	82	0,18	- 48	brown sirup
7	Al_2O_3	120	0	-	-	-
8	Al_2O_3	150	0	-	-	-
9	Al_2O_3	180	15	0,09	-146	white solid
10	GeO_2	120	0	-	-	-
11	GeO_2	150	0	-	-	-
12	GeO_2	180	11	0,10	-127	white solid
13	SnO	120	13	0,15	-154	white solid
14	SnO	150	94	0,55	-155	white solid
15	SnO	180	92	0,34	-142	white solid
16	SnO_2	120	0	-	-	-
17	SnO_2	150	0	-	-	-
18	SnO_2	180	15	0,11	- 96	white solid
19	PbO	120	95	0,34	-157	white solid
20	PbO	150	96	0,38	-151	white solid
21	PbO	180	89	0,14	- 75	brown sirup
22	Sb_2O_3	120	0	-	-	-
23	Sb_2O_3	150	43	0,23	-156	white solid
24	Sb_2O_3	180	88	0,22	-142	white solid
25	ZnO	120	65	0,36	-153	white solid
26	ZnO	150	90	0,37	-144	white solid
27	ZnO	180	90	0,34	-130	white solid
28	TiO_2	120	0	-	-	-
29	TiO_2	150	0	-	-	-
30	TiO_2	180	1	-	-	white solid
31	Fe_2O_3	120	0	-	-	-
32	Fe_2O_3	150	21	0,17	-158	white solid
33	Fe_2O_3	180	91	0,36	-133	pink solid

Table 2: Bulk polymerizations of L,L-lactide by means of various metal carbonates (M/I = 100, reaction time = 48 h)

No	Initiator	Temperature (°C)	Yield (%)	η_{inh}	$[\alpha]_D^{20}$	Appearence of product
1	Li_2CO_3	120	8	0,11	-144	white solid
2	Li_2CO_3	150	41	0,25	- 85	white solid
3	Li_2CO_3	180	79	0,21	- 30	brown sirup
4	Na_2CO_3	120	84	0,26	- 86	yellow sirup
5	Na_2CO_3	150	92	0,20	- 44	brown sirup
6	Na_2CO_3	180	79	0,10	- 10	brown sirup
7	$CaCO_3$	120	0	-	-	-
8	$CaCO_3$	150	0	-	-	-
9	$CaCO_3$	180	11	0,10	-148	white solid
10	$PbCO_3$	120	62	0,34	-151	white solid
11	$PbCO_3$	150	92	0,30	-142	white solid
12	$PbCO_3$	180	93	0,19	- 91	brown sirup

Table 3: Bulk polymerizations of L,L-lactide by means of various metal carboxylates (M/I = 100, reaction time = 48 h)

No	Initiator	Temperature (°C)	Yield (%)	η_{inh}	$[\alpha]_D^{20}$	Appearence of product
1	Na Acetate	120	76	0,25	- 74	yellow sirup
2	Na Acetate	150	95	0,18	- 31	brown sirup
3	Na Acetate	180	83	0,13	- 8	brown sirup
4	Ba Acetate	120	0	-	-	-
5	Ba Acetate	150	41	0,13	- 67	brown sirup
6	Ba Acetate	180	92	0,14	- 25	brown sirup
7	Na Octoate	120	98	0,30	- 67	white solid
8	Na Octoate	150	96	0,18	- 36	brown sirup
9	Na Octoate	180	86	0,12	- 9	brown sirup
10	Sn Octoate	120	99	0,60	-159	white solid
11	Sn Octoate	150	98	0,50	-147	white solid
12	Sn Octoate	180	93	0,15	-116	coloured solid
13	Sb Octoate	120	91	0,45	-159	greyish solid
14	Sb Octoate	150	94	0,18	-146	coloured solid
15	Sb Octoate	180	88	0,14	-138	coloured solid
16	Bi Octoate	120	98	0,46	-158	white solid
17	Bi Octoate	150	96	0,44	-154	greyish solid
18	Bi Octoate	180	94	0,26	-146	greyish solid
19	Mg Stearate	120	23	0,18	-142	white solid
20	Mg Stearate	150	87	0,17	-102	yellow sirup
21	Mg Stearate	180	91	0,15	- 70	brown sirup
22	Ca Stearate	120	35	0,14	-135	white solid
23	Ca Stearate	150	93	0,16	- 58	brown sirup
24	Ca Stearate	180	94	0,23	- 33	brown sirup
25	Zn Stearate	120	54	0,25	-154	white solid
26	Zn Stearate	150	96	0,41	-143	white solid
27	Zn Stearate	180	97	0,26	-133	coloured solid

Table 4: Bulk polymerizations of L,L-lactide at 180°C with various initiators

No	Initiator	Time (h)	Yield (%)	η_{inh}	$[\alpha]_D^{20}$	Appearence of product
1	SnO	12	92	0,50	-154	white solid
2	Sb_2O_3	12	81	0,30	-154	yellow solid
3	Zn-stearate	12	93	0,34	-146	white solid
4	Sn-octoate	12	91	0,24	-138	white solid
5	Sb-octoate	12	91	0,20	-150	yellow solid
6	Bi-octoate	12	96	0,39	-145	white solid

Measurements: The viscosities were determined in an Ubblehode viscosimeter thermostated at 20°C. A concentration of 2 g/l in dichloromethane was used in all cases; η_{inh} is given in dL/g.

Optical rotations were measured at 20°C on a Perkin Elmer Md. 243 in an 1 ml cell of 10 cm length. A concentration of 10 g/l in dichloromethane was used in all cases.

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