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Stannous octoate- versus zinc-initiated polymerization of racemic lactide

Effects on configurational structures

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Summary

Racemic lactide (D,L-lactide) was bulk-polymerized comparatively using stannous octoate and zinc metal as initiators. A two-level fractional factorial design was used to assess the influence of selected experimental variables with respect to intermolecular transesterification, whose extent in the resulting high molecular weight poly(D,L-lactide)s (PLA50) was investigated by ^{13}C NMR. Five variables, namely polymerization temperature, monomer-to-initiator ratio, polymerization time, nature of the initiator and monomer degassing-time, were found significant and were ranked according to their average effect on transesterification. A significant interaction of polymerization temperature and polymerization time was also detected. Zinc led to lower stereoregularity than stannous octoate.

Introduction

High molecular weight poly(lactic acid)s are of great interest in the biomedical and pharmaceutical fields because of their biocompatibility and bioresorbability (1). They are now marketed for applications in human bone surgery and in antitumoral therapy. They can be obtained by ring-opening polymerization (ROP) of D-, L- and/or D,L-lactide, using various initiators, in solution or in the bulk. Whenever polymers are designed for therapeutic applications, bulk polymerization is preferred. However, the synthesis and the characteristics of these polymers are still far from being under control (2). In particular, differences between polymers prepared under different conditions are still unexplained.

Therefore, we have undertaken a systematic study of D,L-lactide ROP in the bulk, using two standard initiator systems, namely stannous octoate and zinc metal. A two-level fractional factorial experimental design $\{2^{11-7}\}$ (3) was set up, in which we investigated possible effects of eleven variables on several characteristics of the resulting PLA50s, including the extent of intermolecular transesterification reactions. Factorial analysis of the original design showed that only five of the selected variables significantly influenced the extent of intermolecular transesterification. Consequently, the original design was reanalyzed as a 2^{5-1} design. In this paper, we wish to report results of this analysis, in an attempt to classify the effects of these variables : nature of the initiator (A), monomer-to-initiator ratio (B), polymerization temperature (C), polymerization time (D), and monomer degassing-time (E) on the configurational structure of the resulting polymers, as determined by ^{13}C NMR.

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Experimental

Materials

D,L-lactide, which was kindly supplied by PHUSIS Matériaux Biorésorbables (Le Versoud, France), was recristallized once in acetone. The monomer feed was degassed ($p \leq 1Pa$) prior to polymerization. Zinc powder (analytical grade, Merck) and tin ethyl-2 hexanoate (stannous octoate) (analytical grade, Sigma) were used as received. Typically, 20g D,L-lactide were polymerized under vacuum in a sealed flask. After cooling, the flask was opened and the polymer was dissolved in acetone. The resulting solution was then filtrated. The crude PLA50 was recovered by solvent evaporation and purified by precipitation, using acetone/ethanol as solvent/non solvent pair.

Methods

Weight-average molecular weights (M_w) and polydispersity indices $I=M_w/M_n$ of PLA50s were determined by size exclusion chromatography (SEC) in dioxane, using a Waters apparatus equipped with a PL-gel column. Data were expressed with respect to polystyrene standards.
^{13}C NMR analyses were performed on solutions of purified PLA50 in $CDCl_3$ (100mg/2cm^3) with a 200 MHz Bruker spectrometer, operated at 50.323 MHz. Spectra were recorded after 1,591 scans.

Factorial analysis of the results was performed with the Statgraphics® software (STSC).

Results and discussion

Polymerization

Table 1 shows the variables which were retained for factorial analysis, together with their selected levels. When entering the field of PLA/GA polymers, we selected zinc as a convenient initiator because of its presence in biochemical pathways and its lack of toxicity. Stannous octoate was retained for comparison because, in the meantime, it has been accredited by the US Food and Drugs Administration. Levels of the other variables were chosen from literature data and self expertise. Factor B was varied by changing the amount of initiator while keeping the amount of monomer constant. Sixteen polymerizations were carried out at random, as well as two replicate runs (n°17 and n°18) (table 2.). Results of PLA50 characterization appear in table 3. Values of the degree of conversion were determined from integrations of the methyl hydrogen ^1H NMR signals of the residual monomer and of the polymer, located at 1.60ppm and 1.50ppm, respectively.

Table 1. Selected variables and levels

Variables	Levels
A : Initiator	Stannous octoate or zinc powder
B : Monomer-to-initiator ratio (w/w)	1,000 or 10,000
C : Polymerization temperature (°C)	130 or 160
D : Polymerization time (hr)	24 or 120
E : Monomer degassing-time (min)	15 or 30

Table 2. Design matrix

Run	Initiator	Time (h)	Temp. (°C)	M/I (w/w)	Degassing time (min)
1	Zn powder	24	130	10,000	30
2	Sn octoate	24	130	10,000	15
3	Zn powder	120	130	10,000	30
4	Sn octoate	120	130	10,000	15
5	Zn powder	24	160	10,000	30
6	Sn octoate	24	160	10,000	15
7	Zn powder	120	160	10,000	30
8	Sn octoate	120	160	10,000	15
9	Zn powder	24	130	1,000	15
10	Sn octoate	24	130	1,000	30
11	Zn powder	120	130	1,000	15
12	Sn octoate	120	130	1,000	30
13	Zn powder	24	160	1,000	15
14	Sn octoate	24	160	1,000	30
15	Zn powder	120	160	1,000	15
16	Sn octoate	120	160	1,000	30
17 (8bis)	Sn octoate	120	160	10,000	15
18 (6bis)	Sn octoate	24	160	10,000	15

Table 3. Response matrix

N°	M_W (g/mol)	I	Conv. (%)	TEC (%)
1	11,000	2.0	4.7	9.7
2	216,000	3.4	80.0	0.0
3	216,000	9.2	77.7	28.9
4	162,000	2.4	93.7	0.0
5	146,000	5.6	44.4	26.1
6	120,000	2.8	94.7	8.3
7	110,000	5.6	95.3	81.4
8	364,000	5.7	97.9	16.4
9	231,000	5.4	58.6	21.6
10	137,000	3.0	98.7	23.9
11	75,000	3.9	69.2	15.1
12	328,000	6.6	96.7	33.4
13	127,000	6.4	95.3	71.7
14	254,000	7.5	95.6	43.4
15	172,000	5.8	95.6	89.0
16	85,000	5.2	96.7	92.5
17 (8bis)	229,000	3.1	93.9	27.2
18 (6bis)	231,000	3.1	95.2	0.0

^{13}C *NMR spectra*

All spectra showed the same pattern (fig.1). Carbonyl carbon resonances were detected at ca 169.3ppm, whereas methine and methyl ones resonated at ca 69.1ppm and 16.7ppm respectively. Beside carbonyl and methine carbon fine structures, which have been previously reported (4), methyl carbon lines also appeared stereodependent. Identification of these fine structures remains controversial (4,5).

Because of the pair addition mechanism previously described by Lillie (6), samples of PLA50 were expected to be predominantly isotactic ("i"). This was indeed observed on all spectra. In some instances, however, depending on the experimental conditions, new lines were found to broaden the fine structures in the carbonyl, methine and methyl resonances, whose stereodependences are shown in figure 1, in terms of hexads for the first one and tetrads for the other two, on the basis of Bero's assigments (4), tetrad effects being proposed to account for the two peaks observed for the methyl. The new lines observed at 69.44 ppm, 69.34 ppm and 69.11 ppm were respectively.assigned to iss, sss and ssi tetrads, where one can find successive syndiotactic ("s") dyads, a feature which could not result from the pair addition mechanism only. These theoretically forbidden "ss" sequences were reported earlier, and ascribed to intermolecular transesterification occuring during the polymerization (4,5).

The extent of transesterification was evaluated from the "syndiotactic transesterification coefficient", TEC (4). TEC was defined as the ratio ISS over ISS_{max}, where ISS stands for the intensity of the iss tetrads and ISS_{max} for the maximum intensity of iss tetrads in the single addition Bernoullian statistics ($ISS_{max} = 0.125$). TEC values were calculated from measurements of the area under the methine carbon lines, because of better resolution.

Calculated values of TEC (table 3) ranged from 0.0% to 92.5% (average : 35%). This clearly shows the sensitivity of this response to the selected levels of the experimental variables. It is noteworthy that we have found experimental conditions under which one can obtain high molecular weight PLA50 differently initiated but with similar TEC values and good yields (e.g. runs 7 and 16, 3 and 12).

Effects of selected experimental variables on the transesterification coefficient

Main effects and interaction effects of all the experimental variables on TEC, were calculated and tested for significance. For that purpose, an estimation of the pure-error standard deviation of an effect (S) was obtained from replicate runs. Reduced effects, defined as ratios of average effects over S, were calculated. They were considered significant whenever their absolute value exceeded the relevant significance limit t ($t = 4.30$) (3). In a first approximation, interaction effects were assumed negligible in 3 cases : firstly, when they involved more than 2 factors; secondly, when they were confounded with main effects; thirdly, when they involved variables whose main effects were not significant. Calculated main effects and interaction effects of the variables on TEC are reported in table 4 along with corresponding reduced effects ($S \cong 3.30\%$).

Beside main effects of the five selected experimental variables, the temperature-time interaction was found to be significant too (table 4). Interaction effects AE, BE and AB were confounded with B, A and E main effects respectively, and were therefore not considered in the present analysis.

Figure 1. Transesterification extent in PLA50s synthesized with (A) zinc powder and (B) stannous octoate (curve numbers refer to experimental runs in table 2; the symbols "i" and "s" stand for isotactic and syndiotactic dyads)

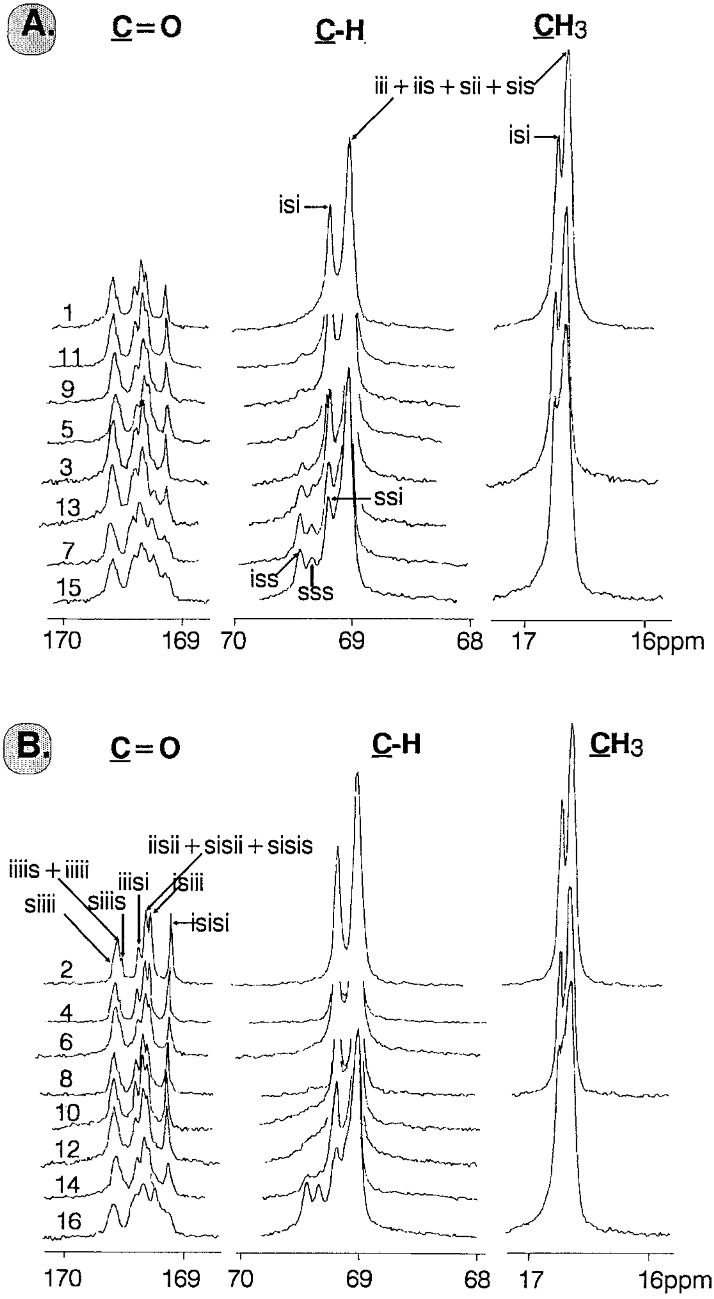
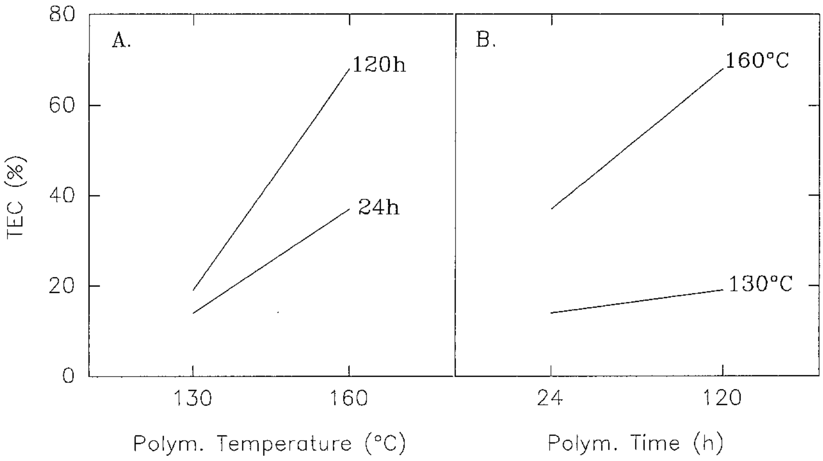


Table 4. Estimated main effects and interaction effects on TEC (%)

Variables and/or interactions	Effects (%)	Reduced effects	Significance
C : Polymerization temperature	37.2	11.3	significant
B : Monomer-to-initiator ratio (+ AE)	-27.3	-8.3	significant
D : Polymerization time	20.2	6.1	significant
A : Initiator (+ BE)	15.5	4.7	significant
CD	14.6	4.4	significant
E : Monomer degassing-time (+ AB)	14.5	4.4	significant
BC	-13.5	-4.1	
DE	13.1	4.0	
AC	11.0	3.3	
BD	2.8	0.9	
AD	1.1	0.3	
CE	-0.3	-0.1	

The largest average effect was due to the polymerization temperature. A 30°C increase in this variable resulted in a 37.2% increase in TEC. However, temperature was found to significantly interact with time (average interaction effect: 14.6%). Increasing the polymerization temperature from 130°C to 160°C resulted in a 25% increase in TEC for a 24hr polymerization-time, whereas for a 120hr polymerization-time, the same increase in temperature resulted in a 50% increase in TEC (fig.2.A).

Figure 2. Interaction plots for polymerization time and polymerization temperature : temperature effect for polymerization times set at 24hr- and 120hr- (A), time effect for -polymerization temperatures set at 130°C-and 160°C (B)



The second largest average effect was ascribed to the monomer-to-initiator ratio, an increase in this variable causing a 27.3% decrease in TEC. The third main effect was due to the polymerization time. Increasing the value of this variable from 24hr to 120hr increased TEC by 20.2%, on the average. However, as noticed previously, time was found to significantly interact with temperature. Increasing the polymerization time from 24hr to 120hr resulted in a 5% increase in TEC only when polymerization took place at 130°C, whereas at 160°C the same increase in polymerization time caused TEC to increase by 35% (fig.2.B). The fourth main effect was ascribed to the initiator type. Switching from stannous octoate to zinc increased TEC by 15.5%. Finally, increasing the monomer degassing-time from 15min up to 30min increased TEC by 14.5%.

Conclusion

In this work, the extent of intermolecular transesterification reactions which affect the stereosequences of PLA50s was monitored by ^{13}C NMR spectroscopy. Within ranges of the selected variables, a hierarchy of average effects was established: polymerization temperature > monomer-to-initiator ratio > polymerization time > initiator > monomer degassing-time. The occurence of the monomer degassing-time as an influential variable is somewhat unexpected. In this particular case, the confounded interaction of monomer-to-initiator ratio and initiator type, which was neglected in the factorial analysis, might be responsible for the observed effect. This point is being further investigated. The temperature vs time-of-polymerization interaction was pointed out for the first time, to the best of our knowledge, and might turn out to be of technological importance. On the other hand, polymers prepared with stannous octoate exhibited lower TEC values, on the average, than those prepared with zinc. Nevertheless, experimental conditions have been found under which PLA50s of similar degrees of transesterification were synthesized, regardless of initiator type. Moreover, stannous-octoate-initiated PLA50s are usually obtained under milder conditions, a situation which further decreases TEC values as compared with zinc-initiated polymers. The significance of these findings is being evaluated with respect to biomedical applications of PLA polymers.

Acknowledgements

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