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# Zn lactate as initiator of DL-lactide ring opening polymerization and comparison with Sn octoate

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## Summary

Zn lactate, $3H_2O$ and dehydrated Zn lactate were used as initiator to polymerize DL-lactide under various conditions. It is shown that the latter does polymerize DL-lactide up to high molecular weight at a slower rate than Sn octoate. Zn lactate being formed when lactic acid is allowed to react with Zn metal, it is believed that the active species in Zn metal initiation is Zn lactate. Comparison was made of the two poly(DL-lactide) initiated with Zn metal and Sn octoate respectively and selected to have almost similar characteristics. It is shown that degradation characteristics of the two polymers are different, especially water uptake and rate of heterogeneous degradation. It is further shown that residual Sn concentrated within the matrix remnants whereas the content in Zn remained constant according to degradation controlled release.

## Introduction

Many initiator systems have been proposed to polymerize lactide cyclic dimers and synthesize a wide variety of poly(lactides) with different configuration structure, depending on the composition of the feed, the extent of racemization during the polymerization, and the occurrence of transesterification rearrangements of stereosequences [1-3]. Among these initiators, two have been used industrially for many years, namely stannous octoate worldwide and Zn metal in France, the former having been approved for surgical and pharmacological applications by the US Food and Drug Administration. Zn metal was selected as an alternative because Zn is an oligoelement which is daily required by the normal metabolism of mammalian bodies. Recently, it was found that in the case of the polymerization initiated by Zn metal, residual traces of lactic acid can attack the Zn metal to yield Zn lactate [4].

In this paper, we wish to report preliminary results of the ring opening polymerization of DL-lactide using Zn lactate as the initiator. The polymerization reaction was conducted in the melt at 140°C under various conditions. The main characteristics of the obtained poly(DL-lactides) are presented. We wish also to report preliminary data on the comparison of two poly(DL-lactides) obtained by ring opening polymerization of DL-lactides with Sn octoate and Zn metal respectively, the latter proceeding actually through initiation by Zn lactate. Although it was impossible to match all the characteristics of the resulting polymers, compromises were made for the sake of minimizing the differences. The comparison was based on water uptake, changes of molar masses, weight loss, crystallinity, contents in residual initiators, identification of degradation by-products and lactic acid formation in the aging aqueous medium.

## Experimental

*DL-lactide :* DL-lactide was obtained from PURAC and was recrystallized once in acetone prior to polymerization. Typically, 30 g DL-lactide were dissolved in 51 ml of acetone (analytical grade) at 50°C. The hot solution was filtrated using a warmed sintered glass filter. The solution was allowed to crystallize at room temperature for 12 hours. The recovered crystals were crushed and further dried under vacuum for 24 hours. The lactide had 0.07±0.02 % residual water as determined by the Karl-Fisher method.

*Zn DL-lactate :* Zn metal in powder form (< 60µm, purity >95% according to MERCK) was dried overnight at 120°C before use. 0.65 g of dried Zn powder were mixed with DL-lactic acid (1.44 g; 98% from SIGMA) and the mixture was allowed to stir 24 h at 140°C. After filtration on sintered glass, a powder clearer than the Zn starting one was recovered. This powder was treated with hot water (20 ml) and the residual Zn metal was separated by filtration. The filtrate was evaporated up to dryness and the resulting solid was washed with acetone and finally filtrated. A white powder (900 mg; 74% yield) was recovered and dried under vacuum at 40°C. Commercial Zn DL-lactate, 3 $H_2O$ (98% purity) was obtained from SIGMA.

*Zn DL-lactate-initiated polymerization of DL-lactide :* Typically, 40 g of recently recrystallized DL-lactide were mixed with Zn-lactate, the monomer/initiator ratio being 5,000. The mixture was separated in four parts, each being placed in a 100 ml round bottom flask. After careful degassing through vacuum/argon cycles, the flasks were sealed under dynamic vacuum by glass melting. The feeds were allowed to polymerize at 140°C for various periods of time. When the desired polymerization time was passed, the polymer was recovered by dissolution in acetone, filtration through a n°5 sintered glass filter and evaporation of the solvent under vacuum for several days at 40°C up to complete dryness.

Sn octoate and Zn metal initiated polymerization's were conducted under vacuum at monomer/initiator (M/I) ratios = 1,000 and 10,000 and at 160 and 130°C for 24 and 120 hours respectively.

*Residual solvents :* Residual solvents were assayed by Head Space liquid/gas GC using a HS 6/8500 PERKIN-ELMER chromatograph equipped with a flame ionization detector and using a 20 meshes Carbowax static phase, the mobile phase being helium. The polymer was dissolved in N-methyl pyrrolidone prior to head space GC analyses.

*Molecular weights :* MW values were determined by Size Exclusion Chromatography (SEC) using a Waters equipment fitted with 30 cm long $10^4$ Å ultrastyragel column, the mobile phase being dioxane. Data were expressed according to polystyrene standards.

*Transesterification coefficient :* TC was determined from the proportion of iss tetrad components of the methine resonances in $^{13}C$ NMR spectra according to the method previously reported [5].

*Water absorption :* WA was determined by weighing the specimens before and after vacuum drying as usual [6].

*Lactic acid assay :* LA was assessed enzymatically using a SGI Microzym-L analyzer and sodium lactate solutions as standards.

*Crystallinity :* Crystallinity was determined from X-ray diffraction patterns obtained with a diffractomer equipped with a CuKα ($\lambda$=1.54 Å) source.

*Specimen processing :* 10x10x2 mm parallel-sided specimens were obtained by machining from larger plates processed by compression molding at 160°C under 200 bars for 10 min. [7].

*Degradation :* Hydrolytic degradation assays were performed in a standard isoosmolar phosphate buffer solution (0.13 M, pH = 7.4). Each specimen was allowed to age in a 30mL flask loaded with 25 ml phosphate buffer and placed in a thermostated oven set at 37.5°C.

## Results and discussion

DL-lactide ring opening polymerization was attempted with both commercial Zn lactate trihydrate and homemade dehydrated Zn lactate for 24 hours at 140°C under air or under vacuum atmospheres, and for various values of the monomer/initiator ratio M/I (Table 1).

The use of rather large amounts of initiator was selected because we wanted to limit the molar masses and have the possibility to identify chain ends.

According to Table 1, two factors seem to be important, namely the presence of crystallization water and the atmosphere. Under air and for M/I = 1 or 2, no polymerization was observed in the presence of hydrated Zn lactate. It is likely that only thermal opening of lactide occurred since IR spectra were typical of lactyllactic acid with a C=O band at 1741 $cm^{-1}$. The absence of the vibration band in the 1600 cm-1 range which is typical of C=O in a carboxylate group suggested that no anion exchange occurred between lactate and lactyllactic acid in agreement with the lower acidity of the latter. The dehydrated Zn lactate was more efficient, especially under vacuum since the conversion reached ~ 94% whereas $\overline{M}w/\overline{M}n$ decreased very much. These findings suggested that moisture played a role in the polymerization of DL-lactide by Zn lactate. Under vacuum, values of the SEC relative number average degree of polymerization appeared much larger than theoretical ones assuming that each Zn lactate molecule initiated one macromolecule. Values of the Mw/Mn ratio reflected rather high polydispersity and thus ruled out the occurrence of fast initiation with respect to propagation. Finally, dehydrated Zn-lactate appeared as a rather efficient initiator since Mw in the range of 150,000 daltons were obtained after 96 hours (run 7).

Figure 1 shows that ln(Mo/M) varied linearly with time. The polymerization kinetics was thus first order in monomer and the apparent rate constant was 0.045 $h^{-1}$, i.e. 8 times slower than when Sn octoate was used as initiator, under similar conditions [4]. Furthermore, an induction period of 1.5 h was observed for Zn lactate which was never detected for Sn octoate. The variation of relative Mn as determined by SEC was not proportional to the degree of monomer conversion under the selected conditions and indicated that more chains were formed than the number expected from a fast initiation and slow propagation.

The NMR spectrum of the small amount of polymer collected from run 8 and dissolved in DMSO-d6 showed the presence of lactyl COOH end units (4.9 ppm) and of lactyl OH end units (4.2 ppm) in agreement with assignment made from the spectra of PLA50 oligomers in resolution-promoting DMSO-d6 [8].

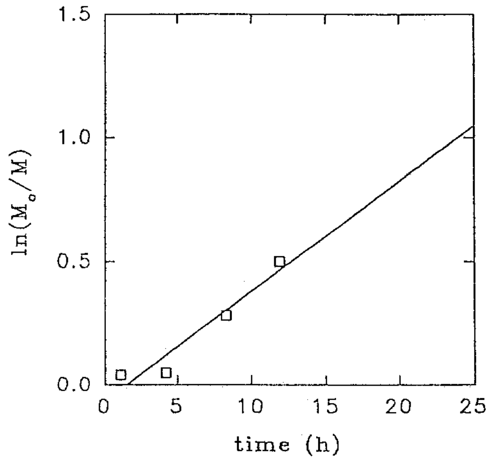

Figure 1 : ln([Mo]/[M]) = f(t) plot in the case of Zn lactate initiated polymerization of DL-lactide at 140°C and for M/I = 5,000

Table 1 : Bulk ring opening polymerization of DL-lactide by Zn lactate at low M/I ratio

| Run | M/I mol/mol | Atmosphere | Time hours | Conversion %[b)] | $DP_n$ (SEC) | $DP_n$ (theor.)[d)] | $\overline{M}w/\overline{M}n$ |
|---|---|---|---|---|---|---|---|
| 1 | 1[a)] | air | 24 | 0 | | | |
| 2 | 10[a)] | air | 24 | 71 | 5.3[c)] | 7 | - |
| 3 | 10 | air | 24 | 79 | 12 | 8 | 7.6 |
| 4 | 1.2 | vacuum | 24 | 95 | 21.5 | 1 | 3.0 |
| 5 | 2.1 | vacuum | 24 | 90 | 26 | 2 | 2.9 |
| 6 | 10.6 | vacuum | 24 | 94 | 14 | 10 | 3.3 |
| 7 | 2,870[e)] | vacuum | 96 | 97 | 646 | 2775 | 1.6 |
| 8 | 5,000 | vacuum | 1.1 | 3.8 | - | 190 | |
| 9 | 5,000 | vacuum | 4.2 | 5.1 | 18 | 255 | 1.5 |
| 10 | 5,000 | vacuum | 8.3 | 24.6 | 541 | 1230 | 1.6 |
| 11 | 5,000 | vacuum | 11.9 | 39.2 | 729 | 1960 | 1.7 |

a) Zn lactate, $3H_20$ ; b) from $^1H$ NMR; c) from $^1H$ NMR ; d) based on lactyllactic repeating unit, e) 150°C

In an attempt to show the possible differences in structures and characteristics between poly(DL-lactide)s prepared through Zn metal and Sn octoate initiations, two polymers were compared. These polymers were selected from a series of compounds polymerized under various conditions and previously investigated from the transesterification coefficient viewpoint [9]. The selection was made on the basis of compromises among the main structural and physical characteristics. The two selected polymers exhibited almost similar molecular weights and polydispersities, differences being reasonably negligible (Table 2). For both, no residual monomer was present within the limits of $^1$H nmr detection. Tg values were comparable. Usually, tin octoate leads to more stereoregular PLA50s than Zn partly because the latter requires higher polymerization temperature and thus generates more transesterification rearrangements [9]. However, molecular weights are usually much too high to allow easy injection molding. In order to minimize the molecular weights in the case of Sn octoate initiation, polymerization temperature was increased and thus transesterification was increased too. Although a slight difference remained, the two polymers were considered as having comparable chain configuration structures. Initiator residues were present in both polymers as shown by Zn and Sn assessments. However, the residual amount of Zn was smaller (40 ppm) than that of Sn, the latter being not removable by the dissolution/precipitation method.

Both polymers were processed similarly to parallel-sided specimens comparable with those used in previous studies aimed at investigating the mechanism of degradation of large size devices made of different PLA polymers [7]. The same aging medium (0.13 M pH=7.4 phosphate buffer at 37°) was used to investigate water uptake, weight loss and molecular weight changes.

Table 2 : Main Characteristics of the selected racemic polylactides derived from stannous octoate (PLA50-Sn) and Zn metal (PLA50-Zn)

| Characteristics | PLA50-Zn | PLA50-Sn |
|---|---|---|
| morphology | amorphous | amorphous |
| residual lactide | non detectable | non detectable |
| glass transition | 48°C | 50°C |
| $\overline{M}n$ (SEC) | 155,000 daltons | 212,000 daltons |
| $\overline{M}w/\overline{M}n$ | 2.3 | 2.2 |
| Transesterification coef. | 29% | 43% |
| residual metal | Zn = 40 ppm | Sn = 306 ppm |

Water absorption measurements were the first to reveal differences between the behaviors of the two types of PLA50 as shown in Fig. 2 where PLA50-Zn absorbed much more water than PLA50-Sn and at a faster rate. Both types of specimens showed heterogeneous degradation with faster degradation inside than at the surface. Dramatic release of water soluble degradation products were observed after about 1000 hours in the PBS aging medium. However, this release occurred earlier (900 hours) for PLA50-Zn than for PLA50-Sn (1,200 hours) in agreement with the larger amount of absorbed water. Differences were also found at the level of the fate of residual Zn and Sn ions. Whereas the relative content of Zn within the polymer residue remained almost constant and low in agreement with a homogeneous dispersion, the relative content in Sn, which remained also constant until about 1,100 hours, i.e. up to the beginning of the dramatic release of the soluble oligomers, increased all over sudden beyond this time, thus showing that Sn residues did not diffuse out of the degraded matrix remnants. The $^1H$ NMR and elementary analyses of the products formed when lactide was allowed to react stoechiometrically with Sn octoate for 24 hours showed a good agreement with characteristics expected from hydroxy Sn octoate and lactate [4].

## Conclusions

From the results of our preliminary investigations, one can conclude that Zn lactate is a good initiator for lactide ring opening polymerization and that polymers obtained with Zn metal or dehydrated Zn lactate are different insofar as water uptake, weight loss and fate of initiator residues are concerned. It is likely that these features are related to the mechanism of polymerization and to the poor water-solubility of Sn octoate, Sn hydroxyoctoate, Sn hydroxylactate, and octanoic acid which cannot diffuse out of the degrading matrix.

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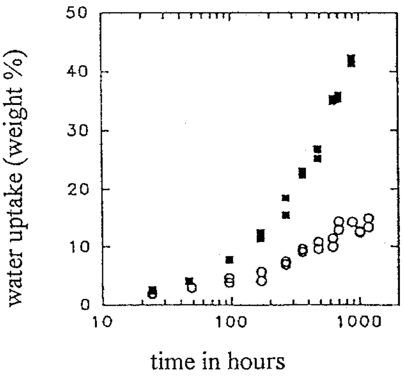

Figure 2 : Water uptake as a function of time
(■) PLA50Zn ; (○) PLA50Sn

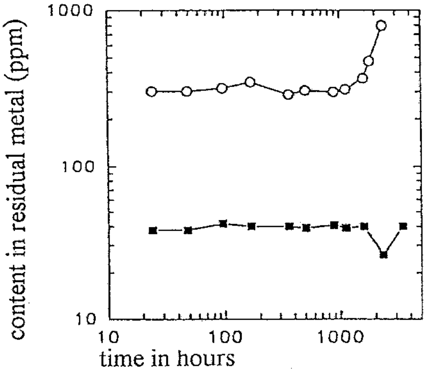

Figure 3 : Variation of the content of residual
Zn (■) and Sn (○) in the matrix remnants