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Resorbable Initiators for Polymerizations of Lactones

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SUMMARY: Numerous nontoxic (resorbable) salts were prepared from cations and anions belonging to the human metabolism, such as Na, K, Mg, Ca, Zn and Fe in combination with chloride, iodide, hydroxide, carbonate, acetate, stearate, glycolate, L-lactate, D-mandelate and various N-substituted α-amino acids. All these salts were used as initiators for polymerizations of L-lactide in bulk at 100 - 180°C. Furthermore, Grignard reagents, hemin and hematin were included in this study. Zn L-lactate was found to be the most useful initiator in terms of reactivity, maximum molecular weight of the isolated poly(L-lactide) and its optical purity. Zn L-lactate initiated copolymerizations of L-lactide and glycolid or L-lactide and ε-caprolactone were also studied. Finally, first studies of the polymerization mechanism of zinc stearate and zin 2-ethylhexanoate were performed. They suggest that zinc carboxylates combined with an alcohol as coinitiator form reactive zinc alkoxides which are the true initiators at temperatures < 150°C.

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Introduction

Biodegradable polymers (mainly polyesters) have recently attracted increasing interest for a variety of applications. The broadest interest and usefulnees is attributed to polylactides and copolyesters of lactic acid. These polyesters can be produced either by ring-opening polymerization of lactides (four stereoisomers are known) or by direct polycondensation of lactic acid.

Regardless of the procedure good transesterification catalysts are needed to obtain sufficiently high molecular weights. The most widely used transesterification catalysts are tin salts particularly Sn(II)2-ethylhexanoate ($SnOct_2$)[1,2]. This catalyst is attractive because it is highly reactive, and because it yields high molecular weight polylactides without racemization. Furthermore, it has been accepted as food additive by the American FDA. The reason for this application is its cytotoxicity (which is typical for most tin compounds) against almost any kind of microorganism, so that it plays the role of a food stabilizer. The now envisaged production of several hundred thousands tons of polylactide per year raises the concern that the delivery of larger quantities of poisonous tin compounds to the environment and to the human body (in the case of medical or pharmaceutcal applications) is not tolerable.

Another frequently used group of initiators are aluminum alkoxides or complexes. Aluminum ions are certainly less toxic than tin ions, but they do not belong to the human metabolism and are suspicious to support the Alzheimer desease. This situation prompted us 15 years ago[3-12] to start a systematic search for a non-toxic, resorbable initiator, and the present paper provides a short review of our results.

Results and Discussion

The strategy used for finding a resorbable initiator is based on the simple consideration that they should consist of components (e.g. cations and amions) familiar to the human metabolsm. The cations meeting this requirements are:

$$Na^{\oplus}, K^{\oplus}, Mg^{2\oplus}, Ca^{2\oplus}, Zn^{2\oplus}, Fe^{2\oplus}$$

The human body also contains traces of $Mn^{2\oplus}$, but manganese salts show a significant toxicity and were found to be poor polymerization catalysts[5)]. Therefore, this review does not pay further attention to $Mn^{2\oplus}$ salts.

The number of species in the human body which can play the role of counterons (anions) is far higher than the number of cations. The most important examples are:

chloride and iodide
oxide, hydroxide and carbonate
acetate and higher fatty acids
lactate, tartrate, citrate
α-amino acids and peptides

Numerous salts and complexes were prepared (or purchased) from the aforementioned cations and anions, and evaluated with regard to their usefulness as initiators. Most experiments were conducted in such a way that the dry and finely powdered initiators were mixed with recrystallized L-lactide and heated in bulk to temperatures in the range of 100 - 180°C. The usefulness and efficiency of the potential initiators were defined by the reactivity, the maximum molecular weights and the optical purity of the isolated poly(L-lactide)s.
The results of a large number of experiments were compiled in Tables 1 - 3.

Table 1. Efficiency of metal halides as polymerization catalyst for L-lactide

Cation	Cl	Br	I	Comment
Na	---	---	---	inactive
K	---	---	---	inactive
Mg	---	---	---	inactive
Ca	---	---	---	inactive
Fe	+	+	+	active
Zn	+	+	+	active

Table 2. Efficiency of basic metal salts as polymerization initiators for L-lactide

Cation	O^{2-}	OH-	CO_3^{2-}	Comment
Na	---	---	---	
K	---	---	---	Strong
Mg	---	---	---	Racemiz.
Ca	---	---	---	and
Fe	---	---	---	Chain
Zn	---	---	---	Transfer

Table 3. Efficiency of zinc salts of falty acid and hydroxy acids as polymerization initiators for L-lactide

Cation	Acetate	Stearate	Glycolate	Lactate	Comment
Na	---	---	---	---	Deprot.
K	---	---	---	---	Racem.
Mg	---	---	---	---	Chain
Ca	---	---	---	---	Transfer
Fe	---	---	---	---	
Zn	+	+	+	+	useful

In connection with the evaluation of magnesium and calcium halides[4,5] (Tab. 1) it should be mentioned that also alkyl Grignard reagents were tested[8]. Due to the elimination of alkanes (resulting from the deprotonation of lactide) even Grignard reagents may be classified as resorbable initiators. However, they only showed a moderate performance in terms of reactivity and molecular weight. When used in bulk polymerizations, they caused racemization. $Zn^{2\oplus}$, $Fe^{2\oplus}$ and $Mn^{2\oplus}$ halides proved to be reactive enough to initiate polymerizations of L-lactide at temperatures $\geq 150°C$[9,10], but only $ZnBr_2$ gave satisfactory results. When compared to Zn lactide ($ZnLac_2$), $ZnBr_2$ has the short-comings of a greater hygroscopicity, and the bromide ion is not part of the human metabolism, even though the toxicity of small amounts is extremely low.

When the oxides, hydroxides and carbonates were studied (Tab. 2) it was found that all these basic salts are useless regardless of the cation. The reasons for this classification are low to moderate molecular weights and signifcant racemization. Both effects are interconnected. Lactides are relatively acidic monomers having pK_a values of the α-protons around 17 ± 2. The deprotonation (eq. 1) generates a planar anion due to delocalization of the negative charge. The reprotonation of this anion can occur from both sides of the ring resulting in racemization. Furthermore, the lactide anion can initiate a new chain growth, so that deprotonation produces high conversion but low molecular weights. Therefore, it is an important result of this study that those initiators favoring racemization also tend to yield lower molecular weights. The influence of $FeLac_2$ on the optical purity of unreacted L-lactide recovered from incomplete polymerizations is documented in Table 4. The influence of various organic and inorganic bases on the racemization of L-lactide was also studied in ref.[13].

Table 4. Influence of $FeLac_2$ on the optical purity of L-lactide upon polymerization in bulk at 150°C (M/I = 1000/1)[a)]

Characterized product	Reaction time h		
	8	24	48
Polylactide isolated after precipitation in Et_2O at 20°C	Yield 10 %	48 %	75 %
Oligolactides isolated from the filtrate after extraction with Et_2O	Yield 65 %	26 %	15 %
Monomer obtained by evaporation of the Et_2O extract	Yield 21 % $[\alpha]_D^{20}$ - 250	18 % - 226	18 % - 188
Starting material: $[\alpha]_D^{20}$	---	---	---

a) The optical rotations were measured in $CHCl_3$ at 20°C with c = 1 g/dL

Table 5. $ZnLac_2$ initiated polymerization of L-lactide in bulk at 150°C

Mon Init.	Time (h)	Yield (%)	η_{inh}[a)] dL/g	$[\alpha]_D^{20}$ [b)]
500	96	91	0.46	-
500	192	90	0.48	- 155
1000	96	90	0.51	-
1000	192	88	0.51	- 157
2000	96	92	0.82	-
2000	192	90	0.66	- 160
4000	96	88	0.89	-
4000	192	91	0.70	- 159
8000	96	81	0.90	-
8000	192	85	0.81	- 158

a) measured at 20°C with c = 2 g/L in CH_2Cl_2

b) measured at 20°C with c = 1 g/L in $CHCl_3$

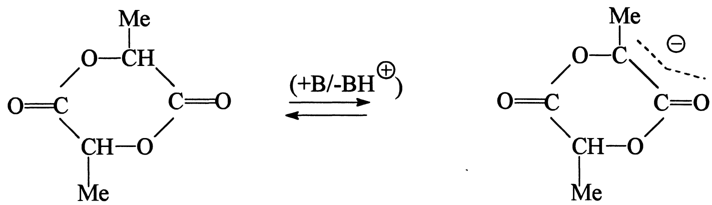
Table 6. Zn aceturate and Zn-L-prolinate-catalyzed polymerizations[a)] of L-lactide with variation of the monomer/catalyst ratio

Polymer No.	Catalyst	Monomer Catalyst	Yield %	η_{inh}[b)] dL/g	$[\alpha]_D^{20}$ [c)]
1	Zn-aceturate	1000/1	87	0.44	- 156
2		2000/1	81	0.48	-
3		4000/1	87	0.52	-
4		8000/1	84	0.65	- 157
5	Zn-prolinate	1000/1	88	0.38	- 144
6		2000/1	84	0.44	-
7		4000/1	79	0.48	-
8		8000/1	75	0.62	- 147

a) all polymerizations were conducted in bulk at 150°C (192 h)

b) measured at 20°C with c = 2 g/L in CH_2Cl_2

c) measured at 20°C with c = 1 g/L in $CHCL_3$

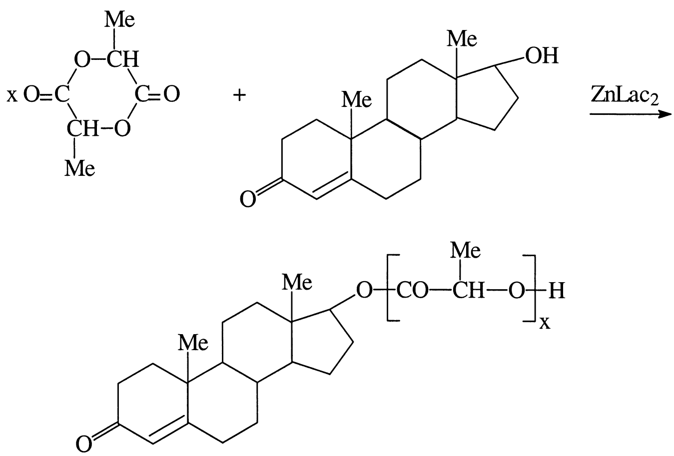


(1)

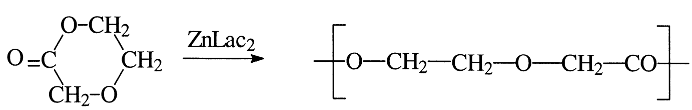
When the acetates and L-lactates of Zn, Fe and Mn were compared, the L-lactates of all three cations gave better results in terms of higher molecular weights and less racemization. Furthermore, the Zn lactate was superior to the Zn glycolate or Zn mandelate[9]. Moreover, the L-lactate of Zn proved to be better than the L-lactates of Fe, Mn, M_g and Ca[14]. Finally, it was found that Zn L-lactate yield slightly higher molecular weights and optical rotation than the Zn salts of N-acetylglycine, N-rosyl-glycine, L-proline, L-pyroglutanic acid or N-acetyl-4-aminobenzoic acid[11]. In other words Zn L-lactate proved to be the most attractive and useful resorbable initiator of all our studies (including hemin and hematin which gave poor results[6] None the less, Zn L-lactate is a relatively sluggish initiator and temperatures above 140°C are required for bulk polymerizations of L-lactide. Some typical results obtained with Zn-L-lactate and Zn amino acid salts were summarized in Tables 5 and 6.

A particularly useful property of $ZnLac_2$ as initiator is the combination with an alcohol playing the role of a coinitiator. The coinitiator accelerates the polymerization process slightly and allows a control of the molecular weight via the monomer/coinitiator ratio. In this way each polylactide chains obtain a stable ester endgroup at one chain end, whereas a hydroxy group forms the second chain end after hydrolysis or methanolysis of the Zn-O bond. Such studies were first performed with benzylalcohol as coinitiator[9]. However, an interesting aspect of this strategy is the use of bioactive alcohols or phenols as coinitiator such as geraniol, testosteron, stigmasterol α-tocopherol etc. With low monomer/coinitiator ratios vitamines, hormones or drugs modified with short oligolacitde substitutents were obtained[9] (eq. 2).

In addition to the homopolymerization of L-lactide the homopolymerization of 1,4-dioxane-2-one was studied and high molecular weights were obtained when the polymerizations were performed in bulk at 100°C (eq. 3). However, due to unfavorable thermodynamical properties of this monomers the yields never exceed 70 %[12]. Furthermore, 1:1 copolymerization of L-lactide and glycolide or L-lactide and ε-caprolactone were conducted. When compared to $ZnCl_2$, Zn I_2 or Zn $(stearate)_2$, Zn L-lactate proved to be the most active initiator and transesterifcation catalyst. Although perfectly random sequences were never obtained, the blockiness of the sequences was so low that in all cases copolylactones soluble in CH_2Cl_2 were obtained. Such a good solubility is needed for an application in drug-delivery systems. In summary, Zn L-lactate showed a number of positive properties such as low costs, easy synthesis, good stability on storage, high efficiency as inititor, but it seems to be difficult to achieve number average molecular weights above 10^5.



(2)



(3)

Quite recently mechanistic studies concerning zinc carboxylates as initiators were started. Zinc stearate and zinc 2-ethylhexanoate ($ZnOct_2$) were used as initiators and (for analytical reasons) benzylalcohol served as coinitiator. First model reactions indicated that the zinc carboxylates react with the alcohol at temperatures ≥ 120°C with formation of benzylesters (eq. 4). This esterification is a slow process below 120°C but rapid and nearly quantitative at 180°C a temperature needed for the technical production of poly(L-lactide). The liberation of water generates in the first step Zn-OH groups, but with increasing conversion ZnO precipitates from the reaction mixture of the neat reactants (eqs. (5) + (6)). These results suggest that the intermediately formed zinc hydroxide groups or the zinc-alkoxide groups formed by exchange with an alcohol (eq. (7)) are the active species which react with lactide according to the established coordination-insertion mechanism[15] (eqs. (8)).

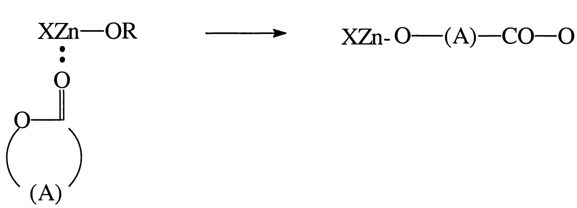
$$Zn(O_2C{-}C_{17}{-}H_{35})_2 + \longrightarrow \begin{matrix} Zn(O_2C\text{-}C_{17}H_{35})\,OH \\ C_6H_5\text{-}CH_2O_2C\text{-}C_{17}H_5 \end{matrix} \qquad (4)$$

$$\begin{matrix} Zn(O_2C\text{-}CH_{17}H_{35})\,OH \\ + \; C_6H_5CH_2OH \end{matrix} \longrightarrow \begin{matrix} C_6H_5\text{-}CH_2\text{-}O_2C\text{-}C_{17}H_{35} \\ + \; Zn(OH)_2 \end{matrix} \qquad (5)$$

$$\downarrow$$

$$ZnO + H_2O \qquad (6)$$

$$\begin{matrix} Zn(OH)_2 + \\ C_6H_5{-}CH_2OH \end{matrix} \xrightarrow[-H_2O]{} Zn(OH)\text{-}O\text{-}CH_2\text{-}C_6H_5 \qquad (7)$$



(8)

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