RESORBABLE INITIATORS FOR POLYMERIZATIONS OF LACTONES

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ABSTRACT

Numerous 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-amiono 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 glycolide or ε-caprolactone were also studied.

INTRODUCTION

Biodegradable polymers (mainly polyesters) have recently attracted increasing interest for a variety of applications. The broadest interest and usefulness 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 thousand 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 pharmaceutical applications) is not tolerable.

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Another frequently used group of initiators are aluminium alkoxides or complexes. Aluminium ions are certainly less toxic than tin ions, but they do not belong to the human metabolism and are suspicious to support the Alzheimer disease. This situation prompted us 15 years ago[3)] to start a systematic search for an absolutely 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 anions) familiar to the human metabolism. The cations meeting these requirements are:

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

The human body also contains traces of Mn2$^{\oplus}$, but manganese salts show a sinificant 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, cetrate
a-amino acids and peptides

Numerous salts 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 "condensed" and listed in the Table 1-3.

Table 1 Efficiency of metal halides

Kation	Cl	Br	I	
Na --	---	---	---	inactive
K	---	---	---	inactive
Mg	---	---	---	inactive
Zn	+	+	+	active
Fe	+	+	+	active

Table 2 Efficiency of basic catalysts

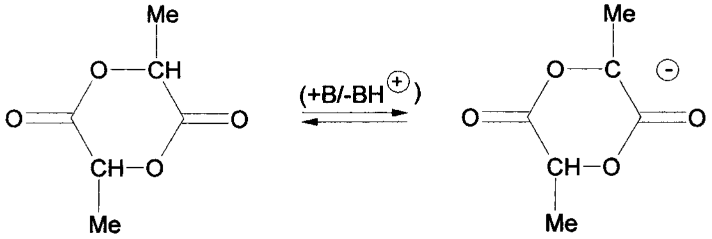
Kation	O^{2-}	OH^-	CO_3^{2-}	
Na	---	---	---	
K	---	---	---	strong
Mg	---	---	---	Racemiz.
Ca	---	---	---	and
Zn	---	---	---	Chain
Fe	---	---	---	Transfer

Table 3 Efficiency of fatty acid and hydroxy acid salts

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

In connection with the evaluation of magnesium and calcium halides$^{4,5)}$ (Table 1) it should be mentioned that also alkyl Grignard reagents were tested$^{7)}$. 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 ≥150°C$^{8,9)}$, but only $ZnBr_2$ gave satisfactory results. When compared to Zn lactide ($ZnLac_2$) it has the shortcomings of a greater hydroscopicity, and the bromide ion is not part of the human metabolism.

When the oxides, hydroxides and carbonates were studied (Table 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 significant racemization. Both effects are interconnected. Lactides are relatively acidic monomers having pK_a values of the α-protons of the order of 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 initnate 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.



(1)

Table 4. ZnI_2-initiated polymerizations of L-lactide in bulk at 120 or 150°C

Temp. in °C	Time in h	Mon. Init.	Yield in %	$\eta_{inh.}$ a) dL/g	$[\alpha]^{20}_{D}$ b)
120	48	200	72	0.32	-
120	96	200	84	0.39	-
120	192	200	94	0.60	- 160
120	48	500	40	0.31	-
120	96	500	65	0.52	- 162
120	192	500	93	0.56	-
120	48	500	92	0.40	-
150	96	500	93	0.53	- 156
150	192	500	93	0.42	- 150
150	48	2000	61	0.28	-
150	96	2000	86	0.26	- 156
150	192	2000	90	0.25	- 154

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

Mon. Init.	Time in h	Yield in %	η_{inh} a) dL/g	$[\alpha]^{20}_{D}$ 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

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

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

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

Polymer No.	Catalyst	Monomer catalyst	Yield %	η_{inh}[b)] dl/g	$[\alpha]_D^{20}$
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/dL in $CHCl_3$

Table 7. 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 in 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 et2O extract	Yield 21 % $[\alpha]^{20)}$ -250 D	18 %	18 %
Starting material: $[\alpha]^{20}$ – 284 D	--	--	--

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

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$^{8)}$. Moreover, the L-lactate of Zn proved to be better than the L-lactates of Fe, Mn, Mg and Ca$^{6)}$. 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$^{10)}$. 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$^{11)}$. Nonetheless, Zn L-lactate is 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 ZnI_2, Zn-L-lactate, Zn amino acid salts and Fe L-lactate were summarized in Table 4-7.

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. However, due to unfavourable thermodynamical properties of these monomers the yields never exceed 70 %. 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 transesterification 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 initiator, but it seems to be difficult to achieve number average molecular weights above 10^5.

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