Polylactones: 30. Vitamins, hormones and drugs as co-initiators of $AlEt_3$-initiated polymerizations of lactide

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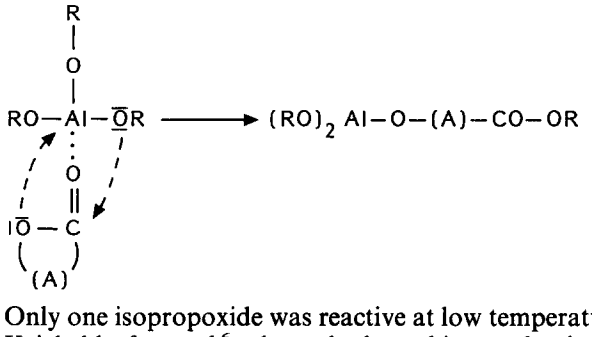
The polymerization of L-lactide with triethylaluminium and alkylaluminium alkoxides was studied in detail. It was found that commercial triethylaluminium is often contaminated with aluminium ethoxide groups resulting from the rapid oxidation of triethylaluminium. The ethoxide group is a far more reactive initiator than the aluminium–carbon bond. Therefore reactive initiators can be prepared *in situ* by the reaction of pure triethylaluminium with vitamins, hormones or drugs containing hydroxyl groups. Polymerization of L-lactide with these *in situ* prepared initiators yields oligo- or poly(L-lactide) with covalently bound vitamins, hormones or drugs. The bioactive co-initiators used in this study were geraniol, stigmasterol, tocopherol, testosterone, pregnenolone, ergocalciferol, cortisone and quinine. It is demonstrated by ^{13}C n.m.r. spectroscopy that the keto groups of steroids do not undergo redox reactions during the polymerization process.

(Keywords: polymerization; L-lactide; initiator)

INTRODUCTION

The first attempts of Tsuruta and co-workers[1,2] to polymerize ε-caprolactone or lactide with triethylaluminium were surprisingly not successful. When Cherdron *et al.*[3] studied the polymerization of ε-caprolactone with triethylaluminium as initiator, they observed that the addition of small amounts of water enhanced the reactivity of the initiator, and high yields and high molecular weights were obtained. These results indicated for the first time that Al–O bonds may be more reactive in the polymerization of lactones than the Al–C bond. Later, Teyssié and co-workers[4,5] demonstrated that aluminium triisopropoxide polymerizes ε-caprolactone at temperatures $\leqslant 20°C$ in such a way that the CO–O bond is cleaved and polyesters with isopropylester end-groups are formed:



(1)

Only one isopropoxide was reactive at low temperatures. Kricheldorf *et al.*[6] showed that this mechanism is operating for all kinds of lactones (in contrast to anionic polymerizations), and all three isopropoxide groups are active at elevated temperatures. Furthermore, Hofman *et al.*[7] showed that diethylaluminium methoxide enables the polymerization of ε-caprolactone at room temperature via an insertion mechanism analogous to equation (1) without back-biting degradation and without interference of redox reactions of the Al–Et groups. More recently Kricheldorf and co-workers[8,9] prepared reactive intiators *in situ* by mixing equimolar amounts of $AlEt_3$ and various alcohols or phenols. Upon addition of L-lactide these co-initiators, which may be biologically active compounds such as α-tocopherol[8] or (+)menthol[9], are incorporated as covalently bound end-groups into the resulting oligo- or polylactides. The aim of the present work was to elaborate this synthetic approach in more detail.

EXPERIMENTAL

Materials

Solutions (1 M) of $AlEt_3$ in toluene or cyclohexane were purchased from Aldrich (Milwaukee, WI, USA). Pure neat $AlEt_3$ was received from Schering AG (Bergkamen, Germany). All handling of $AlEt_3$ solutions was conducted in an atmosphere of pure nitrogen dried over P_4O_{10}. L-Lactide was a gift of Boehringer GmbH (Ingelheim/Rhein, Germany). It was recrystallized twice from ethylacetate/ligroin and dried over P_4O_{10} *in vacuo*. Geraniol, tocopherol, stigmasterol, pregnenolone, cortisone, testosterone and quinine were purchased from Sigma

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Co. (München, Germany) and dried over P_4O_{10} *in vacuo*. Toluene or benzene were distilled twice over P_4O_{10}; dioxane was refluxed twice and distilled over sodium.

Polymerizations

With triethylaluminium alone. L-Lactide (25 mmol) was dissolved in dioxane (20 ml) and a freshly prepared 1 M solution of pure $AlEt_3$ in toluene (1.0 ml) was added by means of a syringe. The reaction vessel was closed with a glass stopper and steel spring and thermostated to 60°C for 90 h. Afterwards the reaction mixture was poured into 300 ml of cold methanol and the precipitated polylactide was isolated by filtration.

In a parallel experiment the freshly prepared reaction mixture was allowed to stand in dry air for 1 min before heating to 60°C.

Polymerizations with bioactive co-initiators. A 0.5 M solution of a bioactive co-initiator in dry dioxane was added in equimolar amounts to a freshly prepared 2 M solution of $AlEt_3$ in toluene under magnetic stirring. When the evolution of ethane had ceased the reaction mixture was immediately used as initiator.

L-Lactide (50 mmol) was dissolved in dioxane (30 ml) and the freshly prepared initiator solution was added by means of a syringe. The reaction vessel was closed with a glass stopper and steel spring and thermostated at 20°C or 60°C. Finally the oligo- or poly(L-lactide) was precipitated by means of cold methanol.

All polymerizations were conducted in Erlenmeyer flasks with ground glass joints. The glass walls were freshly silanized by means of dimethyldichlorosilane and dried in hot air until free of HCl. All reactants were handled in a glove box under pure nitrogen dried over P_4O_{10}.

Measurements

The 100 MHz ^1H n.m.r. spectra were obtained on a Bruker AC-100 in sample tubes (5 mm o.d.). The 300 MHz ^1H and 75.4 MHz ^{13}C n.m.r. spectra were measured with a Bruker MSC-300 FF-Spectrometer. A repetition time of 4 s and a pulse width of 25–30° was used in the case of ^{13}C n.m.r. spectra.

The inherent viscosities were measured with an automated Ubbelohde viscometer thermostated at 25°C.

Gel permeation chromatography (g.p.c.) measurements were conducted in dichloromethane at 25°C. For the separation, a combination of four Ultrastyragel columns with molecular ranges of 50–1.5×10^3, 10^2–10^4, 2×10^2–30×10^3 and 5×10^3–600×10^3 were used. The detection was carried out with a differential refractometer (Waters Md 410).

RESULTS AND DISCUSSION

Polymerizations with pure and oxidized triethylaluminium

Prior to polymerizations initiated with bioactive co-initiators, the reactions of pure and contaminated $AlEt_3$ with lactide should be studied. A first check of reaction conditions and catalyst systems was made in such a way that a commercial solution of triethylaluminium ($AlEt_3$) was combined with an equimolar amount of neopentanol as co-initiator. When the evolution of ethane had ceased, the resulting initiator solution was added to a solution of L-lactide in toluene to such an extent that a monomer/initiator ratio (M/I) of 50 was obtained. After 48 h at 20°C the reaction mixture was poured into methanol and the isolated poly(L-lactide) was examined by ^1H n.m.r. spectroscopy. In agreement with the mechanism of equations (2) and (3) and previous results[9], the presence of neopentylester end-groups was found in the expected quantity (*Figure 1*). Furthermore, the quadruplet of the lactide OH end-group was observable at 4.2 ppm. Yet surprisingly a triplet (1.2 ppm) and a doublet of doublets (4.2 ppm), indicating an ethylester group, were also detectable (*Figure 1*). When the same $AlEt_3$ solution was combined with L-lactide in toluene without addition of a 'cocatalyst', slow polymerization took place, and the poly(L-lactide) isolated after 48 h contained an ethylester end-group.

These results indicated that the commercial $AlEt_3$ solutions used for the present work were contaminated with small amounts of Al–O–Et groups resulting from oxidation. In order to obtain a better understanding of the reactivity of $AlEt_3$, the following experiments were conducted. Pure $AlEt_3$ was purchased, and the ^1H n.m.r. spectrum was measured in benzene-d_6 (*Figure 2A*). Dry air was then introduced for 30 s and the solution was measured again. *Figure 2B* shows evidence of the rapid formation of ethoxide groups.

$$AlEt_3 + HO\text{–}CH_2\text{–}CMe_3 \xrightarrow[-C_2H_6]{} Et_2Al\text{–}O\text{–}CH_2\text{–}CMe_3 \qquad (2)$$

$$Et_2Al\text{–}O\text{–}CH_2\text{–}CMe_3 \longrightarrow \text{(+ } n\text{-lactide)}$$

$$Et_2Al\left[\text{–O–CH(CH}_3\text{)–CO–O–CH(CH}_3\text{)–CO–}\right]_n O\text{–}CH_2\text{–}CMe_3 \qquad (3)$$

When pure triethylaluminium was used as initiator in dioxane at 20°C, no poly(L-lactide) could be precipitated after 48 h. However, after 96 h at 60°C a yield of 29% was obtained. The ^1H n.m.r. spectrum of this sample displays numerous weak signals (*Figure 3A*) which are obviously the result of redox reactions between $AlEt_3$ and the ester groups of lactide. These redox reactions (see equations (4)–(6)) generate Al–O bonds which are the true initiators. This conclusion is supported by a parallel experiment.

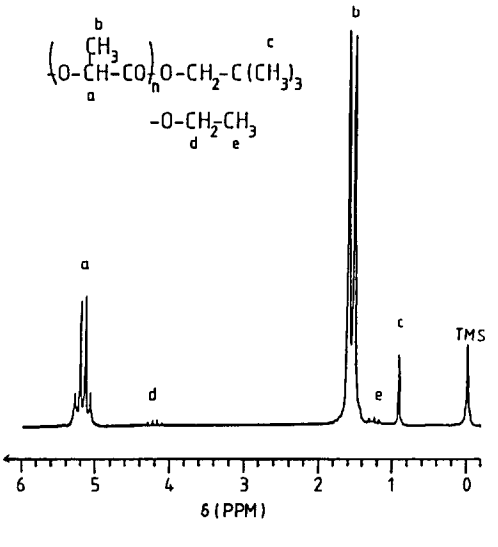


Figure 1 ^1H n.m.r. spectrum (100 MHz) of a poly(L-lactide) in $CDCl_3$ polymerized with $AlEt_3$/neopentanol (1/1) in toluene at 20°C (M/I = 50)

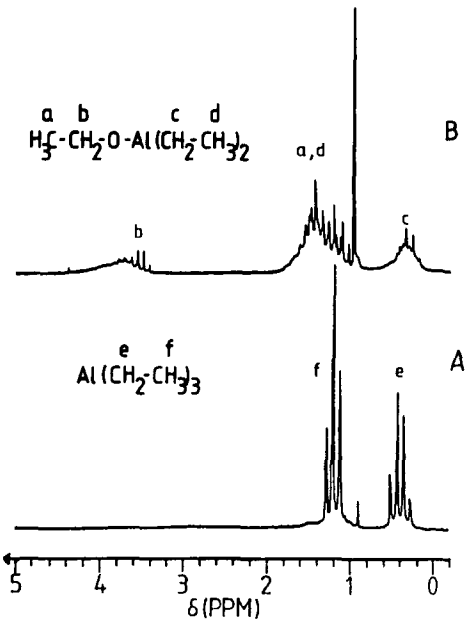


Figure 2 ^{1}H n.m.r. spectra (100 MHz) of (A) pure triethylaluminium in benzene-d_6 and (B) the same solution after introduction of dry air for 30 s at 20°C

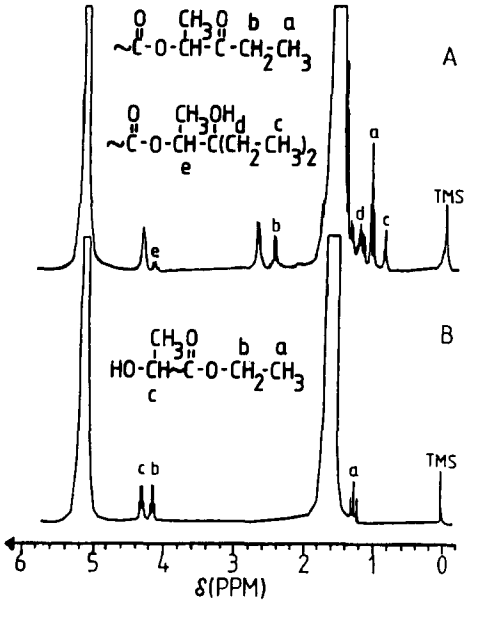
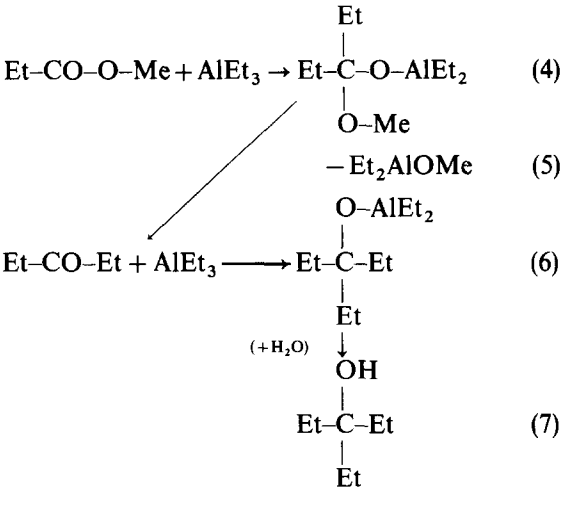


Figure 3 ^{1}H n.m.r. spectra (300 MHz) of poly(L-lactide) in $CDCl_3$: (A) polymerized with pure $AlEt_3$ in toluene for 96 h at 60°C; (B) polymerized with $AlEt_3$ in toluene for 96 h at 60°C after exposure to air for 1 min

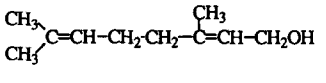
After mixing pure $AlEt_3$ and L-lactide in toluene, the reaction was exposed to dry air for 1 min and then polymerized for 96 h at 60°C. The ^{1}H n.m.r. spectrum of the resulting poly(L-lactide) exclusively exhibits the signals of ethylester end-groups (*Figure 3B*) and the yield was higher (51%).

Finally, a series of model reactions with methyl propionate were conducted in toluene-d_8 at 20, 50 and 80°C. Pure $AlEt_3$ (50 mol%) was used as reaction partner and the reactions were monitored by ^{1}H n.m.r. spectroscopy. After 24 h significant redox reactions were only observed at 50 and 80°C. The ^{1}H n.m.r. signals suggested the formation of diethylketone and triethylmethanol. A similar redox reaction was repeated in benzene at 60°C on a larger scale, and after hydrolytic work-up the reaction mixture was analysed by gas chromatography. In addition to unreacted methyl propionate, small amounts of diethylketone and large amounts of triethylmethanol were identified by comparison with commercial products. Furthermore, a separate reaction of diethylketone with $AlEt_3$ was conducted in toluene-d_8, indicating that the ketone is more reactive than methyl propionate. These redox reactions (equations (4)–(7)) clearly support the conclusions drawn from polymerizations of L-lactide. Finally, it is worth noting that the model reactions with methylpropionate were repeated with diethyl zinc, and qualitatively identical results were obtained.



Polymerizations with bioactive co-initiators

The bioactive alcohols or phenols used as co-initiators in this work are geraniol (**1**), quinine (**2**), α-tocopherol (**3**), testosterone (**4**), pregnenolone (**5**), stigmasterol (**6**) and ergocalciferol (**7**). All polymerizations were conducted in



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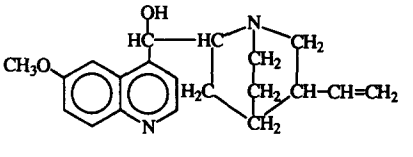

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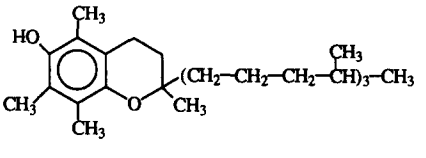

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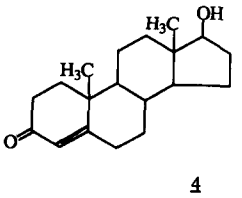

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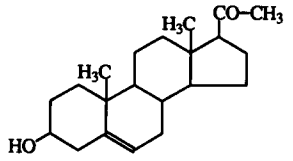

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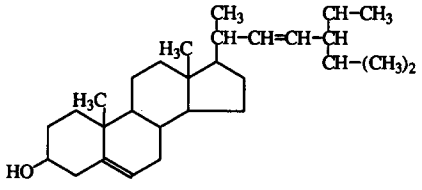

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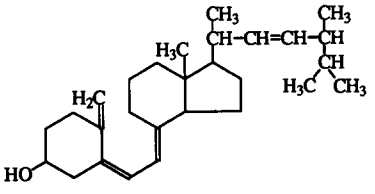

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such a way that equimolar amounts of the co-initiator and pure $AlEt_3$ were mixed in dry dioxane, and a solution of L-lactide was added after the evolution of ethane had ceased. All oligo- or polylactides were finally isolated by precipitation into cold methanol. The results obtained with co-initiators **1**, **2** and **3** are summarized in *Table 1*, and all polymerizations initiated with steroid hormones are compiled in *Table 2*.

The reaction temperature of 60°C was selected because in the case of α-tocopherol no polymerization took place at 20°C. $AlEt_3$/α-tocopherol proved to be the least reactive initiator, in accordance with the fact that this co-initiator possesses a sterically hindered phenol group as the only reactive site. For steric and electronic reasons the alcohol groups of all other co-initiators are more nucleophilic and (after treatment with $AlEt_3$) polymerizations of lactide are feasible at room temperature. However, for the sake of comparison all polymerizations were conducted at 60°C. In the case of alcoholic initiators the reaction time was shortened compared to that of α-tocopherol. Two separate model polymerizations conducted with geraniol and testosterone in deuterated dioxane were evaluated by 360 MHz ^1H n.m.r. spectroscopy. The n.m.r. spectra proved that in both cases the conversion was above 90%, even at an M/I ratio of 100. This result indicates almost complete polymerization, because the thermodynamic polymerizability of L-lactide is relatively low[10,11]. L-Lactide is a relatively stable double-substituted six-membered ring, and in solution or at higher temperatures in the melt, conversions above 95% are thermodynamically impossible. Therefore the

Table 2 $AlEt_3$-initiated polymerizations of L-lactide in dioxane at 60°C co-initiated with **4–7**

Co-initiator	M/I[a]	Yield (%)	η_{inh}[b] (dl g^{-1})	Elution time[c] (min)	DP[d]
Testosterone (**4**)	10	68	0.12	33.7	30
Testosterone (**4**)	20	77	0.14	32.6	42
Testosterone (**4**)	50	87	0.19	30.7	72
Testosterone (**4**)	100	86	0.20	30.6	120
Pregnenolone (**5**)	10	53	0.11	33.8	20
Pregnenolone (**5**)	20	82	0.14	32.8	40
Pregnenolone (**5**)	50	85	0.16	31.8	90
Pregnenolone (**5**)	100	88	0.21	30.4	130
Stigmasterol (**6**)	10	65	0.08	34.5	–
Stigmasterol (**6**)	20	81	0.11	33.6	–
Stigmasterol (**6**)	50	85	0.19	30.8	–
Stigmasterol (**6**)	100	84	0.23	30.0	–
Ergocalciferol (**7**)	10	47	0.08	34.3	30
Ergocalciferol (**7**)	20	63	0.10	33.8	50
Ergocalciferol (**7**)	50	70	0.17	31.0	95
Ergocalciferol (**7**)	100	72	0.24	29.9	240

[a] Molar monomer/initiator ratio
[b] Inherent viscosity measured at 25°C with $c = 2\,g\,l^{-1}$ in CH_2Cl_2
[c] G.p.c. measurements at 25°C in tetrahydrofuran
[d] Determined by ^1H n.m.r. spectroscopic end-group analysis

Table 1 $AlEt_3$-initiated polymerizations of L-lactide in dioxane at 60°C co-initiated with **1–3**

Co-initiator	M/I[a]	Time (h)	Yield (%)	η_{inh}[b] (dl g^{-1})	Elution time[c] (min)	DP[d]	M_n (v.p.o.)
Geraniol (**1**)	10	96	48	0.10	34.0	23	1500
Geraniol (**1**)	20	96	74	0.14	32.3	40	2800
Geraniol (**1**)	50	96	86	0.22	30.8	110	–
Geraniol (**1**)	100	96	88	0.31	30.0	210	–
Quinine (**2**)	10	96	23	0.07	35.0	15	1200
Quinine (**2**)	20	96	82	0.17	32.0	45	3000
Quinine (**2**)	50	96	84	0.27	30.5	95	–
Quinine (**3**)	100	96	85	0.32	29.5	210	–
α-Tocopherol (**3**)	10	120	14	0.05	35.5	15	–
α-Tocopherol (**3**)	20	120	46	0.09	34.0	23	–
α-Tocopherol (**3**)	50	120	60	0.16	31.3	70	–
α-Tocopherol (**3**)	100	120	67	0.25	29.7	130	–

[a] Molar monomer/initiator ratio
[b] Inherent viscosity measured at 25°C with $c = 2\,g\,l^{-1}$ in CH_2Cl_2
[c] G.p.c. measurements in tetrahydrofuran
[d] Determined by ^1H n.m.r. spectroscopic end-group analysis

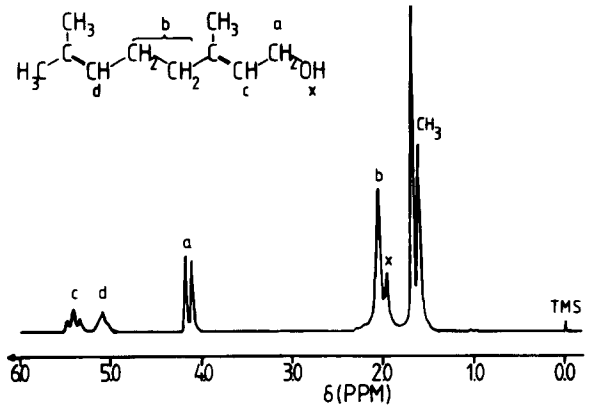

Figure 4 ^{1}H n.m.r. spectrum (100 MHz) of poly(L-lactide) ($DP \approx 22$) initiated with geraniol/$CDCl_3$

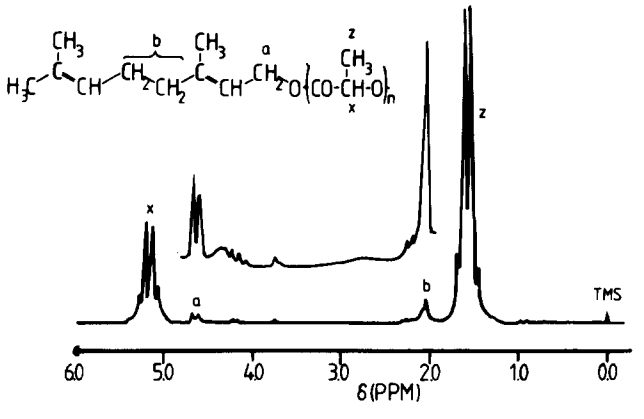

Figure 5 ^{1}H n.m.r. spectrum (100 MHz) of poly(L-lactide) ($DP \approx 22$) initiated with geraniol/$AlEt_3$

low yields found for low M/I ratios (*Tables 1* and *2*) result from fractionation, due to the solubility of low oligomers in methanol.

A factor that all series, with the seven different co-initiators, have in common is that the inherent viscosities increase with higher M/I ratios. Increasing molecular weights were confirmed by decreasing elution times as determined by g.p.c. Weight-average molecular weights were not determined by g.p.c. because it is not applicable to samples where one end-group may make up 25 wt% of the total molecular weight. Apparent average degrees of polymerization (*DP*) were calculated by ^{1}H n.m.r. spectroscopic end-group analyses. The ^{1}H n.m.r. spectroscopic data were confirmed by ^{13}C n.m.r. measurements. Although the ^{13}C n.m.r. signal intensities are not highly accurate, they allow a clear differentiation between *DP*s of 10, 20, 30 and 40, because the segmental mobility of bulky end-groups and polymer chain is almost identical in the case of oligomers. Furthermore, four samples were subjected to vapour pressure osmometry (v.p.o.) and the resulting molecular weights showed a satisfactory agreement with the n.m.r. spectroscopic *DP*s, taking into account that traces of solvent lower the v.p.o. values (*Table 1*).

When these *DP*s are compared with the M/I ratios, several aspects must be taken into account. Firstly, the M/I ratios are based on lactide—a dimer of lactidyl residues upon which the *DP*s are based. Secondly, the solubility of oligomers in methanol entails the consequence of *DP*s higher than expected from M/I ratios and 95% conversion. This effect is particularly pronounced for polymerizations with M/I = 10 and 20. Thirdly, slight back-biting degradation may have occurred. In this regard, model polymerizations with ε-caprolactone were conducted in dioxane over a period of 16 h with $AlEt_3$/neopentanol as initiator. In contrast to lactide, ε-caprolactone has the advantage that cyclic oligomers are easy to detect by g.p.c. measurements. In agreement with Hofman *et al.*[7] no back-biting degradation was observed at 20°C, whereas cyclic oligomers were detected at 60°C. Furthermore, it has to be taken into account that the initiator solutions do not contain pure diethylaluminium alkoxides. The *in situ*-prepared reaction mixtures also contain smaller amounts of ethylaluminium bisalkoxides, aluminium trisalkoxides and triethylaluminium. Therefore, it is quite normal that relatively broad molecular weight distributions were found ($M_w/M_n \geq 2$) even for the precipitated polylactides.

Direct evidence for a complete, or almost complete, reaction of the co-initiators with lactide was obtained by ^{1}H n.m.r. spectroscopy. In the case of geraniol, the $\underline{CH_2}$–OH group shows a doublet at 4.1 ppm (*Figure 4*).

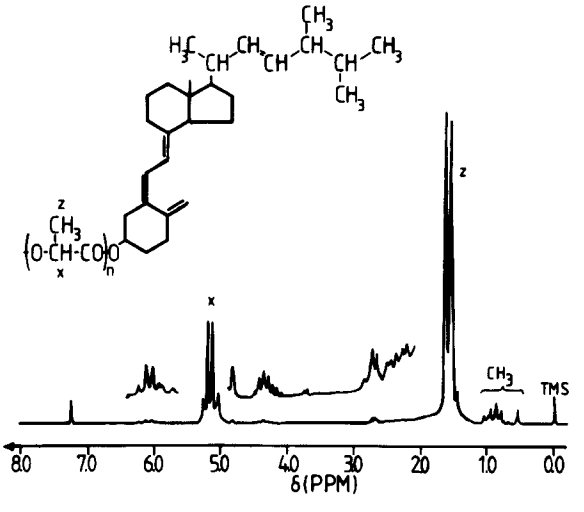

Figure 6 ^{1}H n.m.r. spectrum (100 MHz) of poly(L-lactide) ($DP \approx 23$) initiated with ergocalciferol

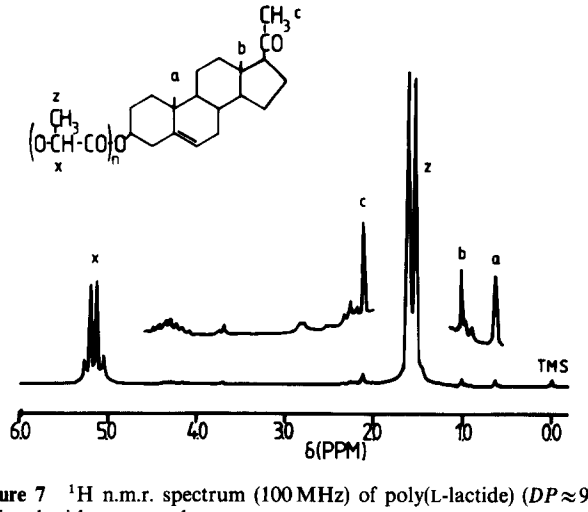

Figure 7 ^{1}H n.m.r. spectrum (100 MHz) of poly(L-lactide) ($DP \approx 90$) initiated with pregnenolone

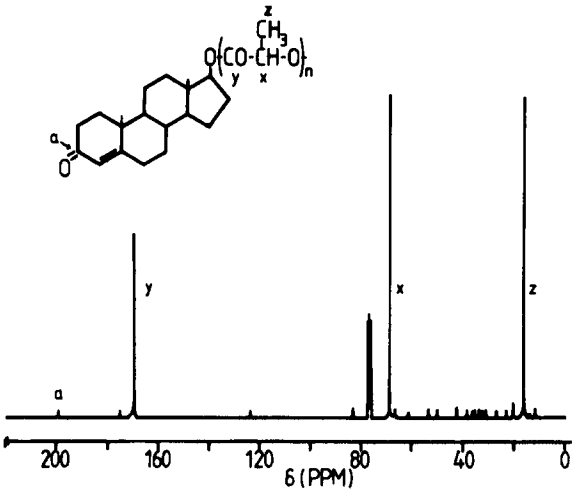

Figure 8 ^{13}C n.m.r. spectrum (75.4 MHz) of poly(L-lactide) ($DP \approx 30$) initiated with testosterone

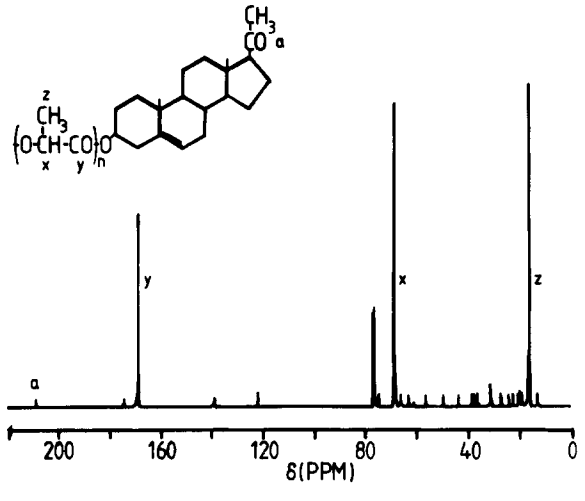

Figure 9 ^{13}C n.m.r. spectrum (75.4 MHz) of poly(L-lactide) ($DP \approx 20$) initiated with pregnenolone

Esterification with lactide results in a downfield shift of the CH_2 protons to 4.7 ppm (*Figure 5*). Analogous downfield shifts were observed for the methine protons of the secondary alcohol groups in co-initiators **2**, **4**, **5** and **6**. The signals of the CH–OH proton of the neat co-initiator appears around 3.7–3.8 ppm (when measured in chloroform against tetramethylsilane) and shifts to 4.4 ppm after esterification with lactide (*Figures 6* and *7*). A quadruplet signal of free CHOH end-groups of the polylactide chain was also found in this position. Hence, the ^1H n.m.r. end-group analyses agree well with the chemical structure expected on the basis of equations (1)–(3). Furthermore, ^{13}C n.m.r. spectra of testosterone and pregnenolone initiated polylactides were recorded. As evidenced by *Figures 8* and *9*, these ^{13}C n.m.r. spectra demonstrate the presence of the keto groups (~205 ppm). This observation means that significant redox reactions with Al–Et groups did not take place.

Taken together, all experimental results of this work agree in that the bioactive co-initiators were incorporated into the oligo- or polylactide chains without significant side reactions. These materials may also be considered as lactide-modified vitamins or hormones which may be useful as components of drug-delivery devices. The acylation with oligo- or polylactides will certainly retard the liberation of free vitamins, hormones and drugs. Furthermore, other bioactive compounds with a synergistic effect might be embedded in these polylactides. All these complex systems need extensive studies *in vivo* prior to a final evaluation.

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