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Macromolecular engineering of polylactones and polylactides

I. End-functionalization of poly ε- caprolactone

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SUMMARY

Aluminum alkoxides carrying functional alkoxy groups are effective initiators for the ε-caprolactone polymerization in toluene and tetrahydrofuran. The coordination-insertion type of polymerization is living and yields exclusively linear polyesters of a predictable molecular weight with a narrow molecular weight distribution within the period of time required for the total monomer conversion. The functional group associated to the active alkoxy group of the initiator is selectively attached to one chain-end, and the second end-group is systematically a hydroxyl function resulting from the hydrolysis of the living growing site. Asymmetric telechelic polyesters are thus obtained in a perfectly controlled way, including macromonomers. Beside (meth)acrylic double bond, the functional end-group derived from the initiator can be, for instance, an unsaturation, a halogen and a tert-amine. Coupling the asymmetric telechelic polymer via the OH end-group (or the precursor Al alkoxide end-group) is a direct way to the related symmetric telechelic of a twofold increased molecular weight.

INTRODUCTION

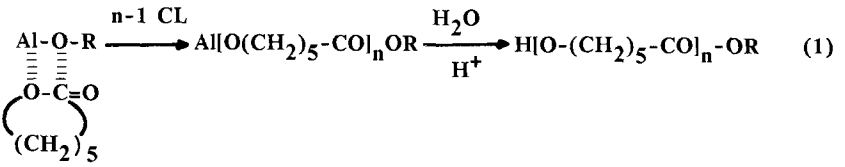
Poly ε-caprolactone (PCL) is of major interest due to the industrial availability of its monomer (CL) and a set of unique properties. Let us recall an original combination of biocompatibility, permeability and biodegradability that makes PCL a synthetic biomaterial and a container for the sustained release of low molecular weight drugs [1,2]. PCL has also a unique ability to blend with a variety of other polymers and to improve some of their deficient properties, e.g. poor stress-crack resistance and lack of dyeability, gloss and adhesion [3]. The discovery that some organometallic compounds are very effective in the synthesis of high molecular weight PCL [4] has promoted an extensive investigation of the ring-opening polymerization of CL as initiated by alkylmetals and metal alkoxides [5-8]. In most cases the polymerization course is perturbed by side intra- and intermolecular transesterification reactions leading to a mixture of linear and cyclic molecules [9,10]. As a rule, a decrease in the nucleophilicity of the initiator, by modification of the counterion for example, is favorable to the propagation of linear chains compared to the macrocyclization process [11]. In previous papers, we have reported that the living polymerization of CL could be promoted by aluminum alkoxide functions, such as trialkoxyaluminum [12] and bimetallic μ-oxoalkoxides [13-15]. The living polymerization of CL has also been reported by Inoue [16,17] and Penczek [18] using α,β,γ,δ-tetraphenylporphinatoaluminum derivatives and diethylaluminum methoxide, respectively, as initiator.

This paper aims at reporting preliminary results on the living polymerization of CL as initiated by aluminum alkoxides, the alkyl group of which bears a well defined functional group. As schematized below, the initiators used in this study comprise a number of functional alkoxide groups ranging from 1 to 3 and correspondingly 2 to 0 alkyl groups :

$$(C_2H_5)_{3-p}\ Al(O\text{-}CH_2\text{-}X)_p$$

1 : p = 1 a : X = $-CH_2-Br$
2 : p = 2 with b : $-(CH_2)_2-CH=CH_2$
3 : p = 3 c : $-(CH_2)_2-NEt_2$

As documented previously [19], the CL monomer can be inserted into aluminum-alkoxide bond followed by the acyl-oxygen cleavage of the lactone in a way which maintains the binding of the growing chain to the aluminum through an alkoxide link. Under strictly anhydrous conditions, alkyl aluminum bonds are inactive in the lactone polymerization [12]. The hydrolysis of the active aluminum-alkoxide link leads to a hydroxyl group at one end of PCL. The second end-group is nothing but an ester carrying the R radical of the initial alkoxide function (equ. 1).



Would the radical of the alkoxide carry a functional group (-R=$-CH_2-X$) and an asymmetric telechelic polyester can be prepared in a straightforward way, as previously pointed out [13]. Consideration will be given to the living polymerization of CL and the actual end functionalization of PCL in connection with the nature of the functional group of the initiator.

EXPERIMENTAL

Materials :

CL (Janssen Chimica) was dried over calcium hydride for 48 hours at room temperature and distilled under reduced pressure just before use. Triethylaluminum (Fluka) and aluminumisopropoxide (Aldrich) were purified by distillation under reduced pressure. 4-penten-1 ol (Aldrich) and 3-diethylamino-1 propanol (Aldrich) were dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. 2-bromoethanol (Aldrich) was repeatedly treated with saturated aqueous K_2CO_3, dried over phosphorus pentoxide and freshly distilled under reduced pressure. Toluene and tetrahydrofuran (THF) were dried by refluxing over calcium hydride and benzophenone Na complex, respectively.

Preparation of the initiators :

- Diethylaluminum alkoxides 1 were prepared by reaction of triethylaluminum with the corresponding alcohol (equ. 2). 1,0 mmol of the required alcohol in 10 ml of toluene was slowly added into a carefully dried pyrex flask equipped with a rubber septum, connected through an oil valve to a gas burette and containing an equimolar amount of $AlEt_3$ in 90 ml of toluene. The reaction proceeded under nitrogen and a vigorous stirring at room temperature. When the evolution of ethane stopped, the catalyst solution was kept under stirring at room temperature for an extra hour.

- Aluminumtrialkoxides 3 were synthesized by reaction of aluminum triisopropoxide with the appropriate alcohol (equ. 3) in a carefully dried and nitrogen purged distillation apparatus. 3,0 mmol of the required alcohol in 10 ml of toluene was added dropwise into an aluminum triisopropoxide (1,0 mmol) solution in 90 ml of toluene at 110°C. The toluene/isopropanol azeotrope was then distilled off continuously.

Polymerization procedure :

- CL polymerization was carried out under stirring in toluene solution in a flask previously dried, purged with nitrogen, and kept at constant temperature for a suitable period of time. The reaction was stopped by adding a tenfold excess of 2N HCl solution with regard to Al.

- The catalyst residues were removed by repeated extractions with an aqueous EDTA solution (0,1 mol.l^{-1}) and the polymer solution was washed with water up to neutral pH. 2/3 of the initial toluene was removed under reduced pressure and the polymer was further recovered from toluene by precipitation. It was finally dried for 24 hours at room temperature under reduced pressure.

$$(CH_3CH_2)_3Al + HO\text{-}CH_2\text{-}X \rightarrow (CH_3CH_2)_2Al\text{-}O\text{-}CH_2\text{-}X + C_2H_6 \uparrow \quad (2)$$

$$(iPrO)_3Al + 3\ HO\text{-}CH_2\text{-}X \xrightarrow{\text{toluene}} (X\text{-}CH_2\text{-}O)_3Al + 3\ iPrOH \quad (3)$$

with X = $-CH_2-Br$
$-(CH_2)_2CH=CH_2$
$-(CH_2)_2N(CH_2CH_3)_2$

Characterization

^{1}H-NMR spectra of PCL were recorded in $CDCl_3$ using a Bruker AM400 apparatus. Gel Permeation Chromatography (GPC) was performed in tetrahydrofuran using a Hewlett-Packard 1090 liquid Chromatograph equipped with a Hewlett-Packard 1037A Refractometer Index Detector and a set of columns : pore size 10^5 Å, 10^3 Å, 500 Å and 100 Å. Molecular weight and molecular weight distribution were calculated from a calibration curve built up from polystyrene standards. Low molecular weights ($\overline{M}_n$ < 15000) were also estimated by ^{1}H-NMR from the comparison of the signal intensities of the α-hydroxymethylene end-group ($-C\underline{H}_2-OH$) and the ester methylene ($-C(O)O-C\underline{H}_2-$) in the polyester chain. The molecular weights calculated from ^{1}H-NMR spectroscopy were in close agreement with the values obtained by GPC.

RESULTS AND DISCUSSION

Living character of the polymerization

A perfectly "living" character has been observed for the polymerization of ϵ-caprolactone as initiated by the functional aluminum alkoxides of the series 1a,b,c, and 3a,b,c. As an example, Fig. 1 shows that the molecular weight of PCL increases linearly with the monomer conversion when the aluminum alkoxides 1a and 3a are used as an initiator. This behavior is also supported by the accurate correspondence between the mean degree of polymerization ($\overline{D.P.}$) at total conversion (^{1}H-NMR and/or GPC) and the monomer/initiator mole ratio (Fig. 2). This relationship holds even for the synthesis of very high molecular weight polyester. For instance, the CL polymerization by 1a in toluene at 25°C leads to PCL of 110,000 $\overline{M}_n$ quite consistent with the actual $[CL]_0/[Al]$ ratio of 880. These results are in agreement with the polymerization of CL by diethylaluminum methoxide as reported recently by Penczek [18]. PCL samples prepared in this first series of experiments display a rather narrow molecular weight distribution ($\overline{M}_w/\overline{M}_n$ = 1.05 to 1.20).

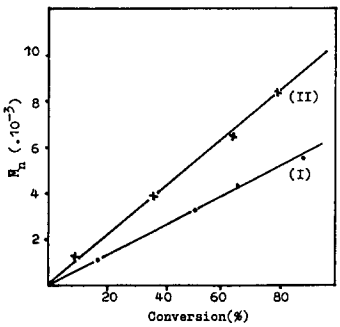


Fig. 1 : Relationship between $\bar{M}_n$ (GPC) and conversion (%) for the polymerization of CL in toluene at 25°C, initiated by
(I) 3a : $Al(O\text{-}CH_2\text{-}CH_2\text{-}Br)_3$; $[CL]_0/[Al]$ = 167; [Al] = $5{,}15.10^{-3}$ mol.l^{-1}
(II) 1a : $Et_2Al\text{-}O\text{-}CH_2\text{-}CH_2\text{-}Br$; $[CL]_0/[Al]$ = 88; [Al]= $12{,}1.10^{-3}$ mol.l^{-1}

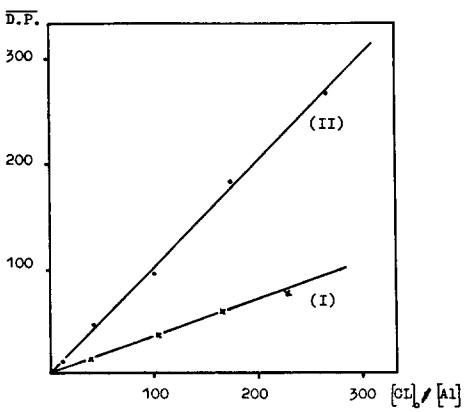


Fig. 2 : Dependence of $\overline{D.P.}$ on the [monomer]/[initiator] mole ratio in the polymerization of CL in toluene at 25°C, initiated by
(I) 3a : $Al(O\text{-}CH_2\text{-}CH_2\text{-}Br)_3$; $[CL]_0 = 8{,}6.10^{-1}$ mol.l^{-1}
(II) 1a : $Et_2Al\text{-}O\text{-}CH_2\text{-}CH_2\text{-}Br$; $[CL]_0 = 10{,}6.10^{-1}$ mol.l^{-1}

Since the slope of the $\overline{D.P.}$ vs $[CL]_0/[Al]$ mole ratio linear plot (fig. 2) is 1 and 1/3 for the initiators 1a and 3a, respectively, it is clear that each alkoxide group initiates the CL polymerization at 25°C in toluene. The molecular weight of PCL can thus be predicted, using equ. 4 :

$$\bar{M}_{n(theoretical)} = \frac{[CL]_0.M_{CL}}{[Al].p} \qquad (4)$$

where M_{CL} = 114,14 (M.W. of the monomer) and p is the number of alkoxide groups per aluminum molecule. However, this equation is not valid at lower temperatures. At 0°C for instance, all alkoxides are not active to initiate the growth of one polymer chain [12]. This phenomenon which results from the coordinative aggregation of the initiator will be studied in more details in a forthcoming paper.

End group structure of the poly-ϵ-caprolactone

According to equ. 1, each PCL chain should be capped at one end by the radical derived from the initiating alkoxide function. In order to state unambiguously that the functional group X associated to the alkoxide is actually attached to the PCL chain, the polyester prepared using $CH_2=CH(CH_2)_3$-O-Al$(CH_2-CH_3)_2$ 1b as an initiator has been characterized by IR (fig. 3) and ^{1}H-NMR spectroscopy (fig. 4). The absorption at 1630 cm^{-1} is consistent with the presence of the olefinic group associated to the initiator (fig. 3). The same qualitative conclusion is supported by the signals observed at δ = 5.02 ppm and 5.80 ppm on the ^{1}H-NMR spectrum of fig. 4.

More interestingly, the theoretical molecular weight as calculated by equ. 4 ($\overline{M}_{nth.}$ = 5,000) is in a very close agreement with the experimental value determined by ^{1}H-NMR (4,980 ± 10%), i.e. from the integration of the signals corresponding to the H_j (δ = 5.80 ppm) and H_e (δ = 2.31 ppm) protons (see formula in fig. 4). The same conclusion emerges when the signal associated to the H_b protons (δ = 3.64 ppm) is compared to that of the H_j protons. These data support that PCL is quantitatively capped by one double bond at one end and by a hydroxyl group at the other end. They fit in very well with the expected insertion of CL into the Al-O bond of the initiator 1b, followed by the selective acyl-oxygen cleavage of the lactone as proposed in equ. 1. Upon hydrolysis of the living polymer, the structure of the recovered PCL is thus as follows :

$$H[O(CH_2)_5\overset{O}{\overset{\|}{C}}]_{44}O(CH_2)_3CH=CH_2$$

The olefinic end-group is due to the attachment of the initiator at the extremity of the growing chain and the second functional end-group (CH_2-OH) results from the hydrolysis of the active species (aluminum alkoxides).

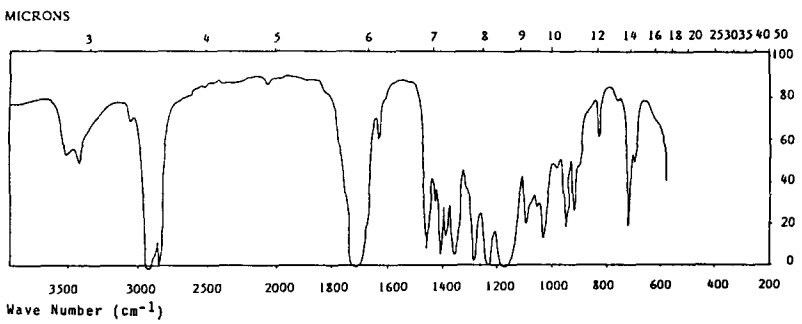


Fig. 3 : I.R. spectrum of PCL as recovered after hydrolysis of the living polymer initiated by $CH_2=CH(CH_2)_3O$-Al$(CH_2-CH_3)_2$ 1b

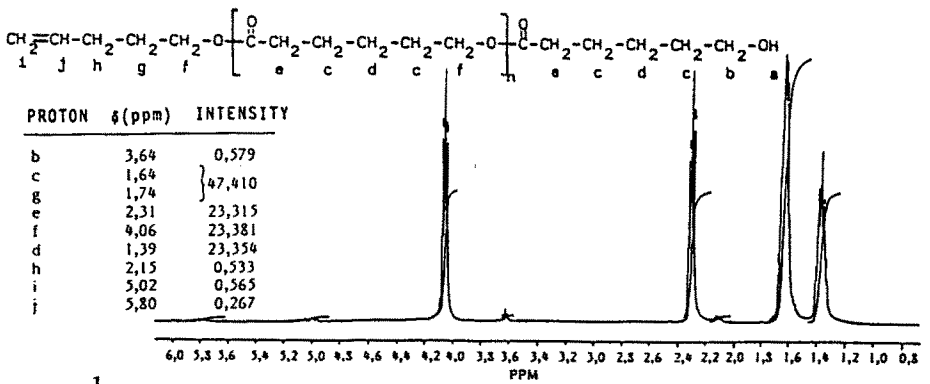


Fig. 4 : ^{1}H-NMR spectrum of PCL as recovered after hydrolysis of the living polymer initiated by CH_2=CH(CH_2)$_3$O-Al(CH_2-CH_3)$_2$ 1b

Table I provides a non-exhaustive list of functional alcohols which can be reacted with alkyls aluminum, alkyl aluminum hydrides or aluminum alkoxides with formation of functional Al alkoxide bonds active in the CL polymerization. It is worth noting that the use of 2-hydroxyethylmethacrylate (HEMA) (code 4) provides a straightforward access to PCL macromonomers and in a further step, to graft copolymers containing PCL branches. These results will be published elsewhere. Would one mole of a diol (code 5) be reacted with 2 moles of $AlEt_3$ and an initiator is made available [Et_2Al-O-CH_2-X-CH_2-O-AlEt_2] for the controlled synthesis of α,ω-dihydroxyl PCL. Similarly, 2,2'-methyliminodiethanol (code 6) is another particular diol that offers the opportunity to insert a tertiary amine in the central position of hydroxy-telechelic PCL.

Table 1 : Polymerization of CL initiated by the reaction product of $AlEt_3$ and a functional alcohol ([Al]/ [OH] = 1) in toluene

Code	Functional Alcohol	T(°C)	Time	$[CL]_0/[Al]$	Conversion (%)	$\bar{M}_w/\bar{M}_n$	$\bar{M}_n$ (1)
1	$HO(CH_2)_2Br$	25	1h 1/3	44	100	1.2	5,500
2	$HO(CH_2)_3CH{=}CH_2$	25	1h 1/2	44	100	1.1	5,500
3	$HO(CH_2)_3NEt_2$	35	8h	88	90	-	9,000
4	$HO(CH_2)_2O_2C$-C(Me)=CH_2	25	2h	13	100	1.2	1,500
5	$HO(CH_2)_4$-OH (2,3)	25	19h	66	96	-	3,500
6	$HO(CH_2)_2N(Me)(CH_2)OH$ (3)	40	4h	53	100	-	3,500

(1) Molecular weight determined by ^{1}H-NMR (± 10%)
(2) Solvent = tetrahydrofuran (THF)
(3) The initiator was prepared by reaction of 2 moles of $AlEt_3$ and one mole of the diol

The preliminary results reported in this paper provide very exciting prospects for the macromolecular engineering of poly ϵ-caprolactone, i.e. predictable molecular weight, absence of side macrocyclization process, rather narrow polydispersity and quantitative control of the nature of the end-groups, including controlled synthesis of macromonomers. This approach can be safely extended to other lactones (β-propiolactone, δ-valerolactone) and lactides, as it will be reported later on. Last but not least, asymmetric α-hydroxy,ω-X functional PCL can be coupled within very high yields (> 95%) by a difunctional agent, such as an aromatic diisocyanate or an aromatic diacid chloride. A symmetric α,ω-X functional PCL of a

twofold increased molecular weight is accordingly obtained. The same coupling reactions can be carried out successfully using the precursor living polymer rather than PCL recovered after hydrolysis and precipitation. It means that symmetric telechelic PCL's (dihalogeno-,di t-amino-, diolefinic, etc) can be easily synthesized in a one pot process. All these opportunities will be reported extensively in the near future as well as the effect of the functional groups X on the kinetics of CL polymerization.

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