Living Polymerization and Selective End Functionalization of ε-Caprolactone Using Zinc Alkoxides as Initiators

Introduction. Due to a set of unique properties, such as biocompatibility, biodegradability, and permeability to many drugs, poly(ε-caprolactone) (PCL) and polylactides are receiving an increasing attention for applications in the biomedical field, e.g., as biodegradable sutures, artificial skins, and implantable carriers for drug delivery systems.[1]

The ring-opening polymerization of ε-caprolactone (ε-CL) and lactides provides a direct access to these aliphatic polyesters in a large range of molecular weight. Many metallic compounds have been reported as potential initiators: metal halides, oxides, carbonates, carboxylates, and alkoxides.[2] Among them, aluminum alkoxides deserve special interest because they provide the ring-opening polymerization with a living character.[3,4] Moreover, the great versatility of their structure has opened the way to the macromolecular engineering of the parent polyesters. For instance, the on-purpose synthesis of functional aluminum mono- and trialkoxides has proven to be very effective in selective and functionalization to the point where telechelic polymers,[5] macromonomers,[6] and diblock copolymers[7] have been made available in a very well-controlled way.

This paper aims at stating whether zinc alkoxides, and particularly (functional) zinc mono- and dialkoxides, are also effective in initiating the ring-opening polymerization of ε-CL in such a way that no transfer or termination reactions occur. From the biomedical point of view, this is a valuable target since the use of synthetic polymers requires an extremely high purity and particularly the absence of any toxic compounds. In this regard, if some initiator residue is left in the polymeric material, the substitution of Al by Zn would have a favorable effect, since Zn is an oligoelement which can be present in the human body at a level of 1.36–2.32 g.[8]

Experimental Part. Materials. A 1.1 M solution of diethylzinc in toluene was purchased from Aldrich. ε-Caprolactone (Janssen Chimica) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. 2-Bromoethanol (Aldrich) was washed with a saturated aqueous sodium carbonate solution, dried over P_2O_5, and distilled under reduced pressure. 4-Penten-1-ol (Aldrich) was dried over calcium hydride and distilled under reduced pressure.

Initiators. Ethylzinc alkoxide was prepared by slowly adding a toluene solution of the selected alcohol (0.5 M) into a Pyrex flask containing an equimolar amount of $ZnEt_2$ (1.1 M solution in toluene) and thermostated at −78 °C. The glass reactor was equipped with a rubber septum connected to a gas buret through an oil valve and previously flamed and purged with nitrogen. The solution was then allowed to warm up to room temperature under stirring and kept at 25 °C until no gas evolution was observed. Zinc alkoxide was prepared according to the same procedure except that the alcohol/Zn molar ratio was 2 instead of 1 as before.

Polymerization Procedure. Polymerization took place under stirring in toluene, in a previously flamed and nitrogen-purged glass reactor. Solvent and initiator solutions were added first, followed by the monomer. All these liquid compounds were introduced into the reactor with syringes or stainless steel capillaries through a rubber septum.

Polymerization was stopped by adding an excess (relative to the initiator) of 2 N HCl solution. Initiator residues were extracted with an aqueous EDTA solution. The remaining organic layer was then washed with water up to a neutral pH, and the polymer was precipitated into an excess of heptane, filtered, and dried under vacuum to a constant weight.

Molecular Weight Determination. 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, 10^3, 500, and 100 Å. Molecular weight and molecular weight distribution were calculated from a calibration curve built up with polystyrene standards.

Results and Discussion. Functional aluminum alkoxides have proven to be very successful in the synthesis of end-reactive PCL.[4,5] These functional initiators can actually be comprised of 1–3 (p) functional alkoxide groups, associated to 2–0 ($3-p$) inactive alkyl groups, respectively

$$(C_2H_5)_{3-p}Al(OCH_2X)_p$$

where X is a functional group, e.g., CH_2Br, $(CH_2)_2$-$CH{=}CH_2$, $(CH_2)_2NEt_2$.

By analogy, the use of functional zinc mono- and dialkoxides might be considered for the end functionalization of PCL. The synthesis of these compounds has been carried out by reacting $ZnEt_2$ with an equimolar amount and a 2-fold molar excess of a selected functional alcohol, respectively (eq 1).

$$ZnEt_2 + pHORX \rightarrow Et_{2-p}Zn(ORX)_p + pC_2H_6 \quad (1)$$

where $p = 1$ or 2. The reaction equilibrium is favorably displaced by formation and elimination of ethane. Two functional alcohols have been purposely used, i.e., 2-bromoethanol and 4-penten-1-ol. The structure of the expected zinc alkoxides has been ascertained by ^1H NMR analysis as illustrated by Figure 1 for ethylzinc 4-pentenyl 1-oxide. Signals characteristic of the ethyl and 4-pentenyl radicals are clearly observed, and their assignment and intensity are given in Figure 1. From the relative intensity of the signals observed, e.g., at $H_f = 0.31$ ppm and $H_a = 5.02$ ppm, there are as many ethyl as 4-pentenyl radicals within the limits of the experimental errors, which is in agreement with the expected structure. That conclusion is general whatever p and X are in eq 1.

When the ε-CL polymerization is initiated by either $EtZnO(CH_2)_2Br$ or $Zn(O(CH_2)_2Br)_2$, in toluene at 25 °C, the experimental molecular weight as measured by size-exclusion chromatography increases linearly with the monomer conversion (Figure 2). This observation is generally consistent with the living character of the chain propagation. Figure 3 definitely gives credit to that hypothesis, since there is a very close agreement between the experimental degree of polymerization at total conversion and the monomer to initiator molar ratio. It is worth noting that the molecular weight distribution of PCL as initiated by $Et_{2-p}Zn(OCH_2CH_2Br)_p$ is still more narrow (1.05–1.1) than when initiated by functional aluminum alkoxides (1.05–1.3).[4–6]

When the ε-CL polymerization is initiated by an aluminum alkoxide, polymerization proceeds through the coordinative insertion of the monomer into the Al–O bond of the initiator and involves the selective cleavage of the oxygen–carbonyl bond of the ε-CL. As a result, one end group of PCL is systematically an alcohol (after the hydrolysis of the growing species) and the second extremity

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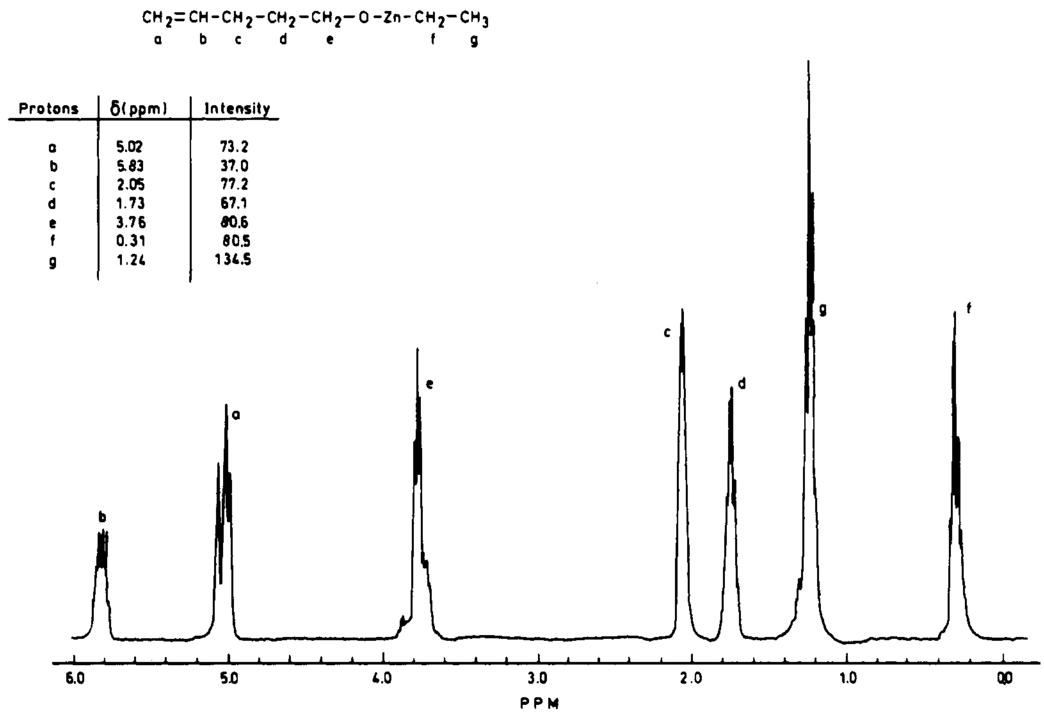


Protons	δ(ppm)	Intensity
a	5.02	73.2
b	5.83	37.0
c	2.05	77.2
d	1.73	67.1
e	3.76	80.6
f	0.31	80.5
g	1.24	134.5

Figure 1. ^{1}H NMR spectrum of ethylzinc 4-pentenyl 1-oxide in $CDCl_3$.

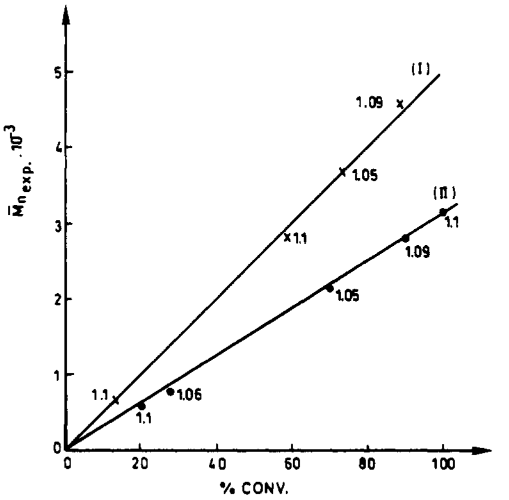
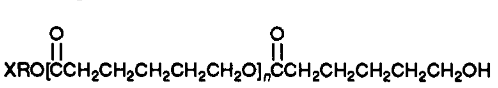


Figure 2. Relationship between $\bar{M}_n$(exptl) and monomer conversion (%) for ε-CL polymerization in toluene at 25 °C. Initiators: (I) $EtZnOCH_2CH_2Br$ (M/C = 45; $[M]_0$ = 0.79 mol·L^{-1}) and (II) $Zn(OCH_2CH_2Br)_2$ (M/C = 53; $[M]_0$ = 0.76 mol·L^{-1}). Polydispersity ($\bar{M}_w/\bar{M}_n$) is mentioned in front of each relevant sample.

is quantitatively capped by an ester, the alkoxy radical of which is nothing but the alkoxy group of the initiator. If that mechanism is also operative in the ε-CL polymerization as initiated by functional zinc alkoxides, the formation of an α-hydroxyl, ω-X functional polyester (where X is the organic function associated to the alkoxide) would occur. ^{1}H NMR is certainly the best tool to investigate the PCL chains as initiated by $Et_{2-p}Zn(ORX)_p$ compounds (where R–X = $(CH_2)_2Br$ and $(CH_2)_3CH{=}CH_2$) are of the expected structure



$$XRO[\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2CH_2O]_n\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2CH_2OH$$

Figure 4 completely supports that expectation in the particular case where the ε-CL polymerization has been initiated by $EtZnO(CH_2)_2Br$. In addition to the assignment of the methylene protons of the chain, Table I reports

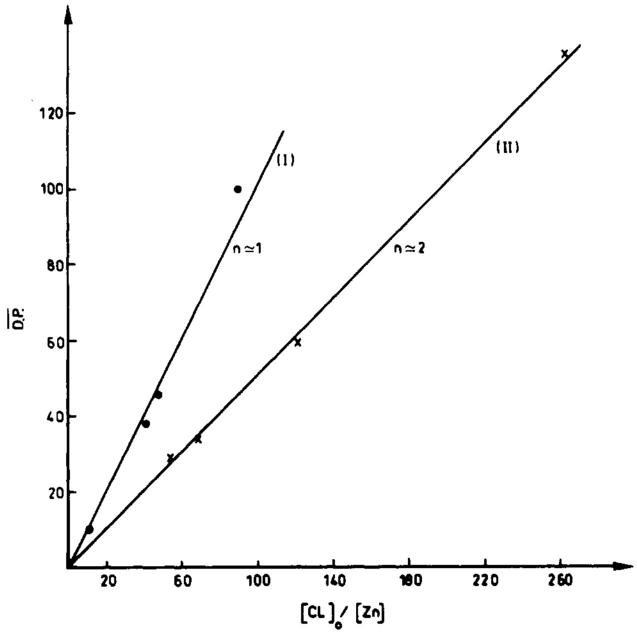


Figure 3. Dependence of $\overline{DP}$ on the monomer/initiator molar ratio for the polymerization of ε-CL initiated by (I) $EtZnOCH_2CH_2Br$ ($[CL]_0$ = 0.79 mol·L^{-1}) and (II) $Zn(OCH_2CH_2Br)_2$ ($[CL]_0$ = 0.76 mol·L^{-1}) in toluene at 25 °C. *n* is the average number of active alkoxides per Zn atom.

the chemical shift and intensity of the α-methylene protons and those characteristic of the bromoethyl and 4-pentenyl end groups, respectively. The close agreement between the theoretical molecular weight (as calculated from the monomer to initiator molar ratio and the observation (Figure 3) that each alkoxy group is active) and the experimental values determined by size-exclusion chromatography and ^{1}H NMR (integrations of signals at 3.64 and 4.06 ppm, respectively) unambiguously shows that the functional group associated to the active alkoxy groups on Zn is selectively attached to one chain end. That conclusion holds for both functional zinc mono- and dialkoxides, since bromo-terminated PCL has been initiated

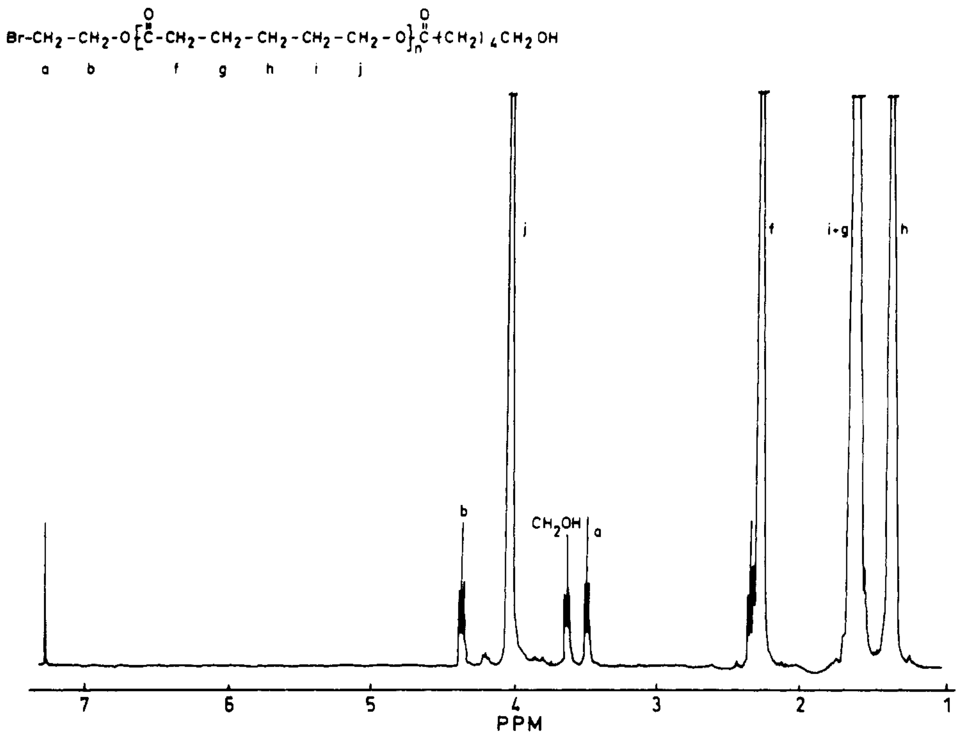
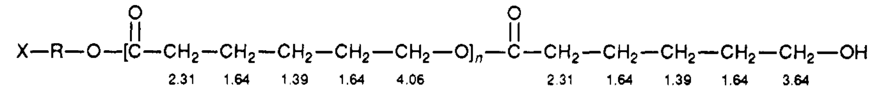


Figure 4. ^{1}H NMR spectrum of the PCL α-bromo, ω-hydroxyl as recovered after hydrolysis of the PCL initiated by $EtZnOCH_2CH_2Br$ (solvent, $CDCl_3$).

Table I
^{1}H NMR Chemical Shifts δ (ppm, Relative to Internal TMS) of Hydrolyzed Polyesters as Initiated by Functional Zinc Alkoxides

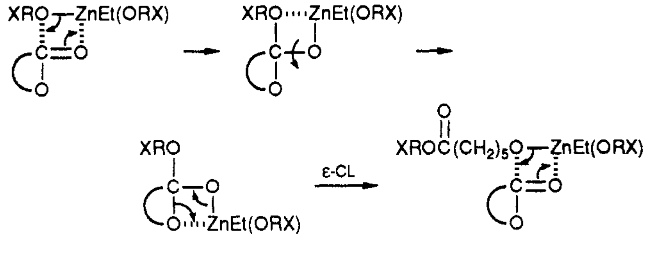

$$X{-}R{-}O{-}[\overset{O}{\overset{\|}{C}}{-}\underset{2.31}{CH_2}{-}\underset{1.64}{CH_2}{-}\underset{1.39}{CH_2}{-}\underset{1.64}{CH_2}{-}\underset{4.06}{CH_2}{-}O]_n{-}\overset{O}{\overset{\|}{C}}{-}\underset{2.31}{CH_2}{-}\underset{1.64}{CH_2}{-}\underset{1.39}{CH_2}{-}\underset{1.64}{CH_2}{-}\underset{3.64}{CH_2}{-}OH$$

	chemical shifts, ppm (intensity)						$\bar{M}_n$			
XRO–	H_a	H_b	H_c	H_d	H_e	CH_2OH	^{1}H NMR	GPC	theor[a]	$\bar{M}_w/\bar{M}_n$
$Br{-}CH_2{-}CH_2{-}O{-}$ a b	3.52 (0.92)	4.39 (0.91)				3.64 (0.95)	5500	5200	5550[b]	1.07
$CH_2{=}CH{-}CH_2{-}CH_2{-}CH_2{-}O{-}$ a b c d e	5.02 (2.50)	5.80 (1.30)	2.15 (2.60)	1.74 (–)[d]	4.06 (–)[e]	3.64 (2.65)	3250	3100	3200[c]	1.05

[a] $\bar{M}_n(\text{theor}) = [CL]_0/[Zn]\cdot 1/n\cdot x$, with x = conversion and n = number of active sites per zinc atom (see Figure 3). [b] Polymerization initiated by EtZnORX. [c] Polymerization initiated by $Zn(ORX)_2$. [d] Superimposed to the signal at 1.64 ppm corresponding to β-ester methylene in the polymer chain ($OC(O)CH_2CH_2$). [e] Superimposed to the signal at 4.06 ppm corresponding to ester methylene in the polymer chain ($CH_2OC(O)$).

by a zinc monoalkoxide, in contrast to the unsaturated counterpart that has been produced by a dialkoxide initiator.

The preliminary results reported in this paper convincingly show that (functional) zinc alkoxides are effective initiators for the ring-opening polymerization of ϵ-CL under very mild conditions. Polymerization is living, and the molecular weight distribution is narrow. ^{1}H NMR analysis of PCL supports the formation of asymmetric telechelic polyesters since one end group is systematically a hydroxyl function and the second extremity is nothing but an ester containing the (functional) alkoxy radical of the initiator. There is thus a complete analogy with the polymerization mechanism accepted for the initiators of the aluminum alkoxide type. That "coordination–insertion" mechanism relies upon the selective cleavage of the acyl–oxygen bond of the monomer. Interestingly enough, Noltes et al.[9] have reported in 1970 that β-propiolactone could be polymerized by $EtZnOCH_3$ according to the same mechanism. Accordingly, the ϵ-CL polymerization initiated by functional zinc alkoxides can be described as follows:



Extension to lactides will be investigated in the near future as well as the kinetic characteristics of the ring-opening polymerization promoted by zinc mono- and dialkoxides (in comparison to aluminum mono- and trialkoxides).

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