Communications to the Editor

Living (Co)polymerization of Adipic Anhydride and Selective End Functionalization of the Parent Polymer

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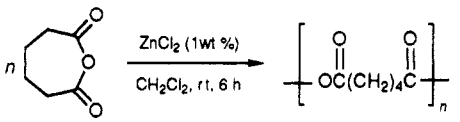
Introduction. The availability of erodible and biocompatible materials, such as aliphatic polyanhydrides, is also of great interest for controlling the kinetics of the release of drugs.[1,2]

Polycondensation of mixed anhydrides is the traditional method[3-5] of synthesis of polyanhydrides, which has all the drawbacks of a step-growth polymerization.

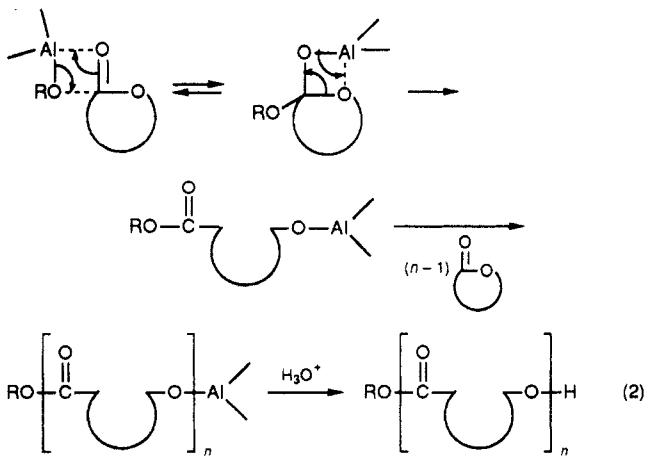
Although the ring-opening polymerization of alicyclic anhydrides is most likely the best way of avoiding these drawbacks, some previous publications[6,7] have reported that the ring-opening polymerization of adipic anhydride (AA or oxepan-2,7-dione) is not under complete control of molecular mass and polydispersity (eq 1).



(1)

$\bar{M}_n$ = 1700; $\bar{M}_w/\bar{M}_n$ = 1.7; yield = 75%

This paper aims at reporting preliminary results on the living polymerization of adipic anhydride as initiated by aluminum alkoxides. Aluminum isopropoxide has proven to be very effective in the formation of poly(ε-caprolactone) (PCL)[8] and polylactides (PLA)[9] with a predictable molecular mass. The "coordination-insertion" mechanism which is operative is schematized by eq 2. One end group



(2)

of the polyester is systematically an alcohol (after hydrolysis of the growing species), and the second extremity is quantitatively capped by an ester, the alkoxy radical of which is nothing but the alkoxy group of the initiator.

Similarly, functional aluminum alkoxides have proven to be very successful in the synthesis of end-reactive PCL[10] and PLA.[11] This paper will also report the polymerization of AA as initiated by functional aluminum alkoxides, the structure of which is schematized below.

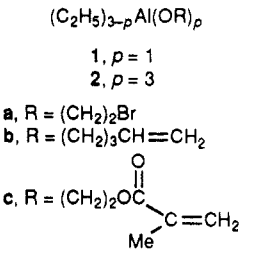


Table I
Polymerization of AA Initiated by $Al(O^iPr)_3$ in Toluene at 20 °C. Dependence of Experimental $\bar{M}_n$ on Reaction Time ([AA] = 0.6 M; $[AA]/[Al]_0$ = 21)

x (%)	time (h)	M_n(theor) (n = 1)	M_n(exptl) (RMN)
29	3	780	700
36	4	969	850
87	24	2338	2250

Experimental Part. Oxepan-2,7-dione was prepared as described elsewhere.[12] ε-Caprolactone was dried over calcium hydride for 48 h at room temperature. The preparation of diethylaluminum alkoxides and aluminum trialkoxides has been described in detail previously.[10,13]

Polymerization was carried out under stirring in toluene, in a previously flamed and nitrogen-purged glass reactor. Polymerization was stopped by adding a large excess of petroleum ether, and the precipitated PAA was recovered by filtration. The polymer was dissolved in a small volume of chloroform and added with an aqueous EDTA solution in order to remove the catalyst residues by repeated extractions. The polymer solution was washed with water up to neutral pH, concentrated under reduced pressure, and finally poured into ether (or heptane) with precipitation of PAA.

^{1}H NMR spectra of PAA were recorded in $CDCl_3$ using a Bruker AM 400 apparatus. IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR apparatus.

Results and Discussion. Monomeric Adipic Anhydride Synthesis. Depolymerization of poly(adipic anhydride) was reported by Hill[14] as an effective way to prepare oxepan-2,7-dione. Adipic acid was converted with acetic anhydride into a "mixed adipic anhydride" (MAA), which was then step-polymerized (eq 3). The formed polyanhydride was depolymerized under vacuum in the presence of zinc acetate.[12] The yield was on the order of 70% as compared to 50% in the absence of catalyst.

The ^{1}H NMR spectrum of the monomer in $CDCl_3$ shows a triplet at 2.8 ppm and a multiplet at 2.0 ppm in a 1:1 ratio, which is in agreement with the expected structure.[6] The infrared spectrum shows a doublet at 1800 and 1753

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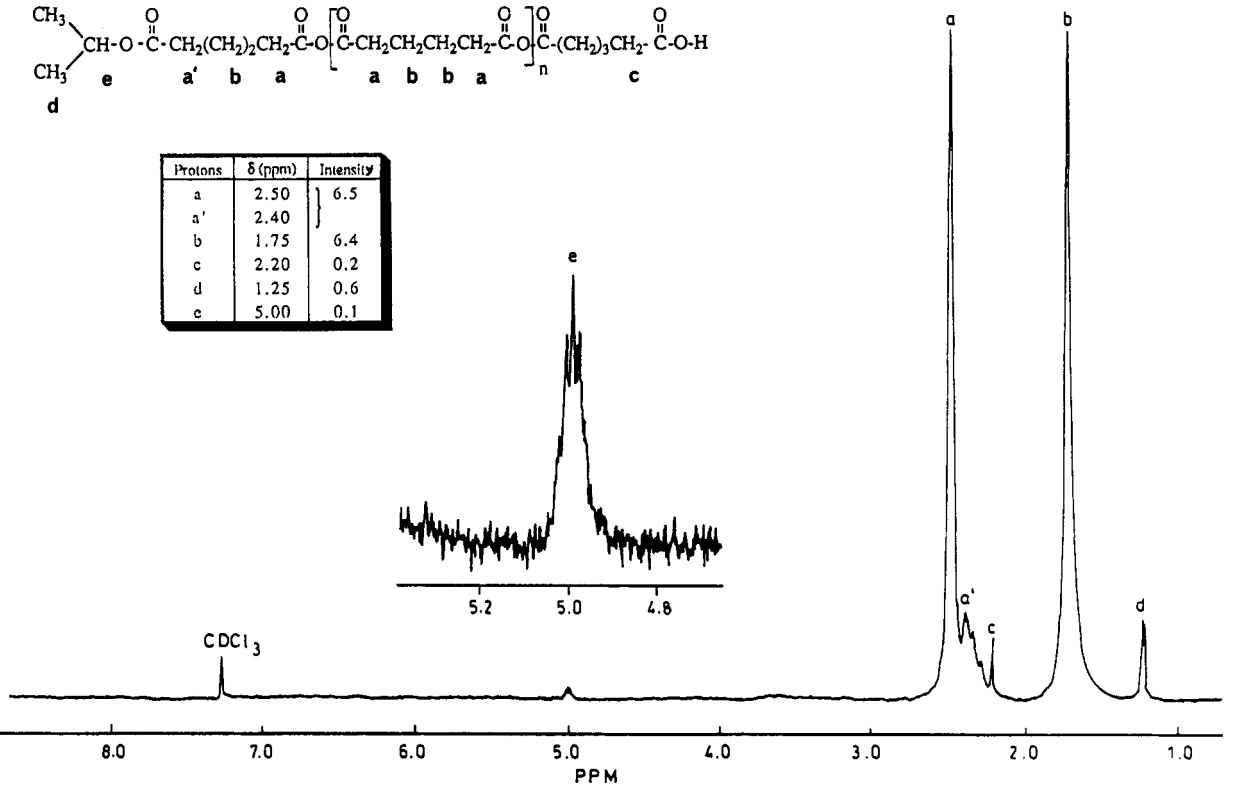
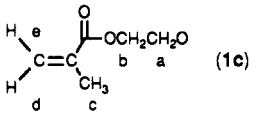
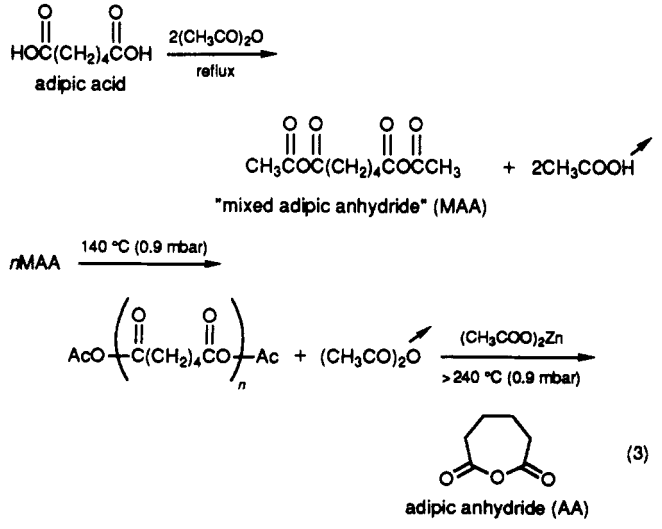


Figure 1. ^{1}H NMR spectrum of PAA as initiated by Al(O^{i}Pr)$_3$ (solvent = $CDCl_3$).

Table II
^{1}H NMR Chemical Shifts of Functionalized PAA As Initiated by Al(O^{i}Pr)$_3$, 2a, 1b, and 1c

X-R-O	chemical shift δ (intensity) H_a	H_b	H_c	H_d	H_e	CH_2COOH	M_n(exptl)
$(CH_3)_2CHO$	4.9	1.2				2.2	2032
b a	(0.1)	(0.6)				(0.2)	
$BrCH_2CH_2O$ (2a)	4.39	3.52				2.2	2430
b a	(0.25)	(0.3)				(0.3)	
$CH_2{=}CHCH_2CH_2CH_2O$ (1b)	4.06		2.15	5.8	5.02	2.25	2410
e d c b a	(0.7)		(0.4)	(0.2)	(0.4)	(0.55)	
 (1c)	4.35		1.95	5.65	6.15	2.2	2550
	(12)		(9.9)	(3.1)	(2.8)	(6.0)	

cm^{-1}, which is characteristic of a cyclic anhydride, and a second doublet characteristic of the cycle at 961 and 985 cm^{-1}.



(3)

Adipic Anhydride Homopolymerization Initiated by Al(O^{i}Pr)$_3$. The polymerization of oxepan-2,7-dione initiated by aluminum isopropoxide was first studied in toluene at 20 °C.

The experimental molecular weight as measured by ^{1}H NMR (from comparison of the signal intensity of the α-carboxyl methylene end group [-CH_2COOH] and the α-anhydride methylene in the polyanhydride chain [-CH_2C(O)OC(O)-]) increases linearly with monomer conversion (Table I). A very close agreement is also observed between the experimental and the theoretical molecular weight calculated as

$$\bar{M}_n(\text{theor}) = \frac{[M](128x)}{[Al](100n)} \qquad (4)$$

where x = degree of conversion (%), n = number of active sites per aluminum molecule, [M]/[Al] = monomer to initiator molar ratio, and 128 = molecular mass of AA. When n is supposed to be 1, the relationship between M_n(theor) and M_n(exptl) is linear and goes through the origin (least-squares linear regression coefficient, 0.997). All these observations are consistent with the living character of the chain propagation.

In toluene at 20 °C, only one of the three Al-alkoxy bonds of the initiator thus participates in the polymeri-

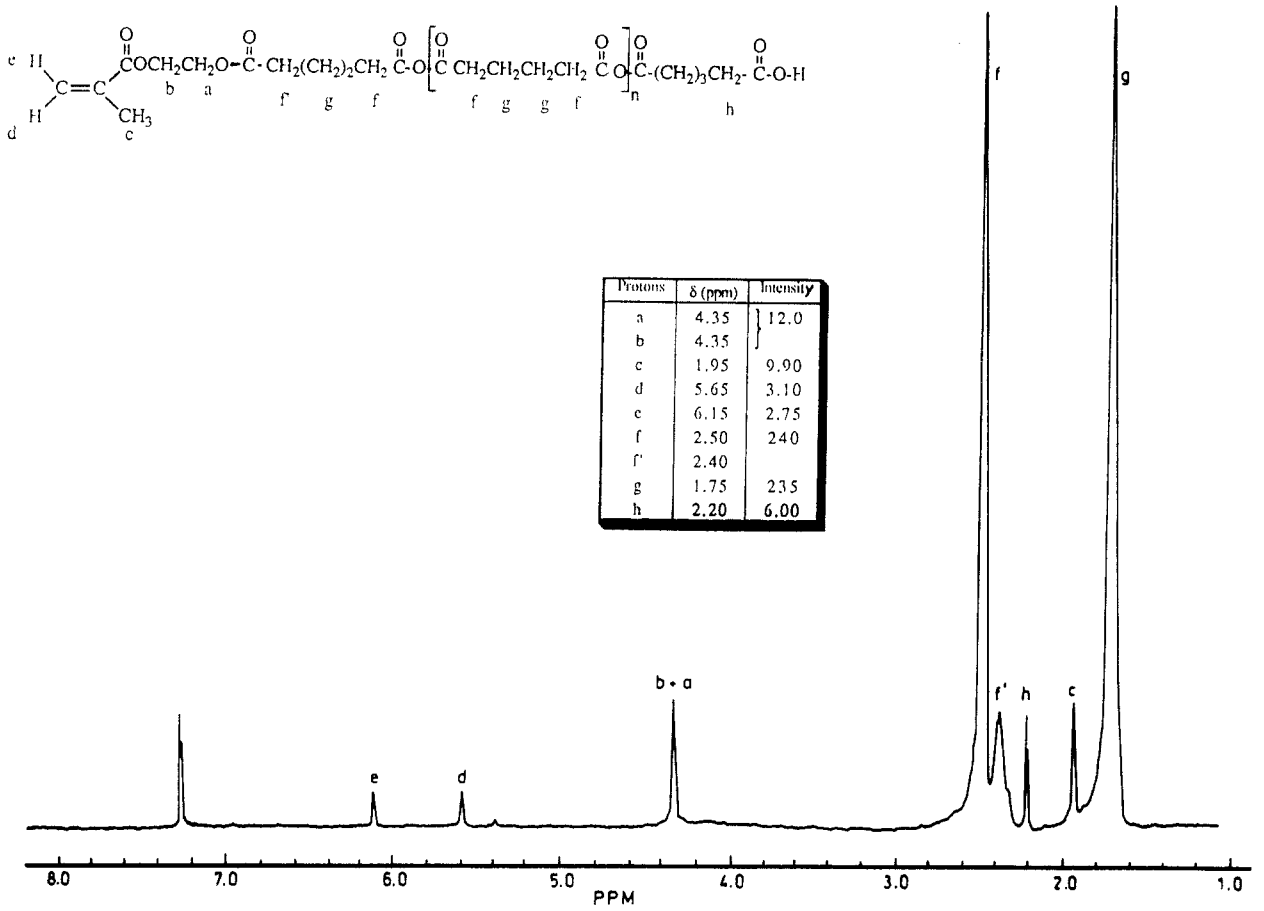
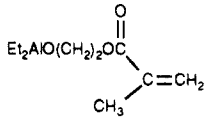


Figure 2. ^{1}H NMR of PAA as initiated by $Et_2Al[O(CH_2)_2OCOC(CH_3)=CH_2]$ (1c) (solvent = $CDCl_3$).

Table III
Polymerization of AA As Initiated by Aluminum Alkoxides 2a, 1b, and 1c in Toluene

initiator	polymzn conditions					
	T (°C)	time (h)	(AA)/(Al)(theor)	convn (%)	M_n(theor)	M_n(exptl)
$Al(OCH_2CH_2Br)_3$ (**2a**)	20	24	23	85	2550	2430
$Et_2AlO(CH_2)_3CH=CH_2$ (**1b**)	35	40	23	82	2460	2410
	35	40	23	84	2520	2550

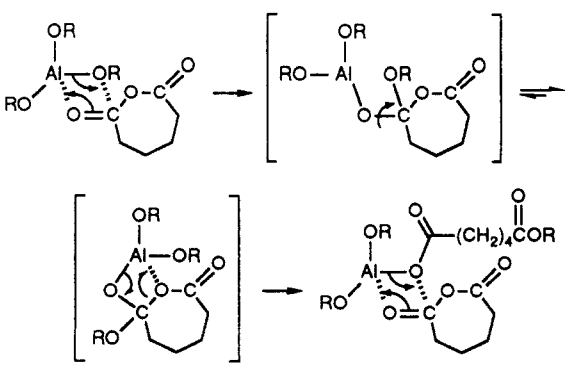
zation (n = 1). In the absence of $Al(O^iPr)_3$, no polymerization occurs.

The obtained poly(adipic anhydride) was characterized by ^{1}H NMR analysis. The spectrum is reported in Figure 1 and shows a triplet at 1.75 ppm and a multiplet at 2.50 ppm. Chemical shifts characteristic of the anhydride are thus shifted to lower ppm values, which is consistent with the ring opening of oxepan-2,7-dione.[6]

When the AA polymerization is initiated by aluminum isopropoxide, one end group of PAA is systematically an acid function which results from the hydrolysis of the growing species ($\delta[CH_2CO_2H]$ = 2.2 ppm), whereas the second extremity is quantitatively capped by an isopropyl ester group ($\delta[COCH(CH_3)_2]$ = 5.0 ppm; $\delta[COCH(CH_3)_2]$ = 1.25 ppm), the isopropyloxy radical of which is nothing but the alkoxy group of the initiator.

The infrared spectrum shows a doublet at 1816 and 1759 cm^{-1}, which is characteristic of an aliphatic anhydride. Furthermore, it confirms the complete disappearance of the doublet centered on 970 cm^{-1} and characteristic of the ring vibration of a cyclic anhydride, supporting the hypothesis that the ring opening of the monomers has occurred.[15]

All these experimental results support a polymerization which proceeds through "coordinative-insertion" of the monomer into the "Al–O" bond of the initiator and involves the selective cleavage of one oxygen–carbonyl bond of the AA (eq 5).



(5)

Selective End Functionalization of PAA. According to the previous section one end group of PAA is an acid and the second extremity is capped by an ester, the alkoxy

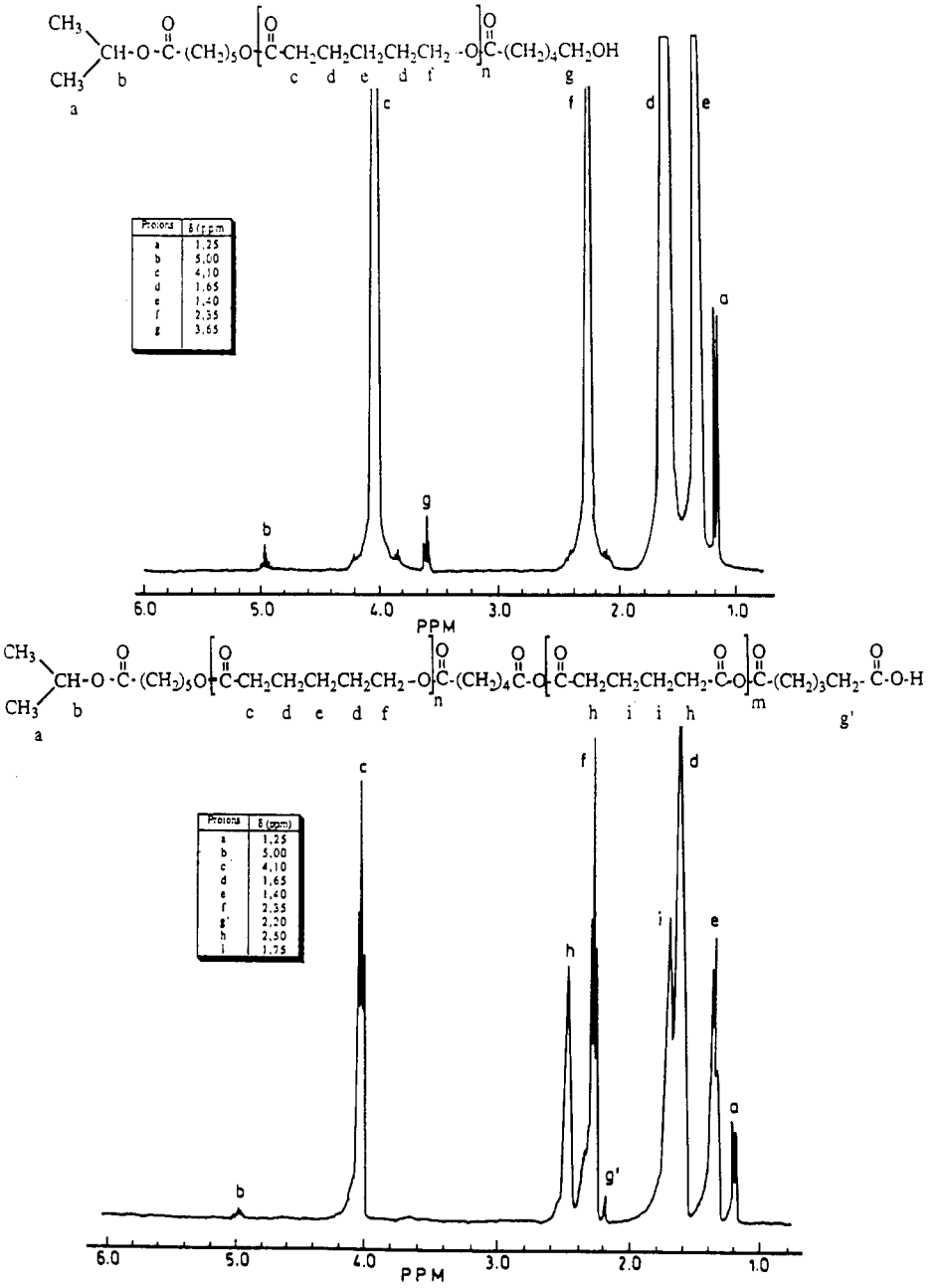


Figure 3. ^{1}H NMR spectra of (a) the ^{i}PrO–PCL–OH block and (b) the block copolymer P[CL-*b*-AA] α-isopropyl ester, ω-carboxylic acid (solvent = $CDCl_3$).

radical of which is the alkoxy group of the initiator. Accordingly, functional aluminum alkoxides (**1** and **2**) are expected to produce α-carboxylic acid, ω-X functional polyanhydrides, X being the organic function associated to the active alkoxide.

^{1}H NMR analysis supports the expectation in the particular case where the AA polymerization has been initiated by $Al[O(CH_2)_2Br]_3$ (**2a**), $Et_2Al[O(CH_2)_3CH{=}CH_2]$ (**1b**), and $Et_2Al[O(CH_2)_2OC(O)C(CH_3){=}CH_2]$ (**1c**), respectively (Figure 2, with 1c). In addition to the assignment of the methylene protons of the chain, Table II reports the chemical shifts and intensities of the α-carboxylic methylene protons and those characteristic of the 2-bromoethyl, 4-pentenyl, and 2-(methacryloyloxy)ethyl end groups, respectively. The close agreement between the theoretical molecular weights (as calculated from eq 4 where n = 1) (Table III) and the experimental values determined by ^{1}H NMR (integration of signals at 2.2 and 1.75 ppm, respectively) unambiguously shows that the functional group associated to the active alkoxy groups of Al is selectively attached to one chain end. These experimental data are again in favor of the living polymerization of AA under very mild conditions and confirm the formation of asymmetric telechelic polyanhydrides in a perfect analogy with the ϵ-CL and lactide polymerization.[10,11]

Block Copolymerization of ϵ-CL and AA. In block copolymerization experiments, the ϵ-CL polymerization has been first initiated by $Al(O^iPr)_3$ in toluene at 20 °C. After 5 h of polymerization, a sample of PCL is withdrawn from the reactor, and the molecular weight is determined by GPC and ^{1}H NMR ($\bar{M}_n$ = 6000). A carefully dried AA solution is then added to the living polycaprolactone solution, and the temperature is raised up to 80 °C. After 36 h, the polymerization medium is acidified at room temperature and the crude copolymerization product analyzed by SEC and ^{1}H NMR. The size-exclusion chromatogram in THF (a selective solvent of PCL) shows one elution peak with a slight increase of $\bar{M}_n$ and no change in polydispersity ($\bar{M}_w/\bar{M}_n$ = 1.25). The crude copolymerization product has been fractionated by using cold THF (<10 °C) as a nonsolvent of PAA and $CHCl_3$ as a common

solvent. No homopolymer has been separated from the P[ϵ-CL-*b*-AA] block copolymer. $\bar{M}_n$ of the PCL block has been measured by SEC and ^{1}H NMR (6000), and $\bar{M}_n$ of the PAA block (2800) has been calculated by ^{1}H NMR (Figure 3). These figures are in perfect agreement with the expected values ($\bar{M}_n$(PCL) = 6000 and $\bar{M}_n$(PAA) = 3000).

The blocky structure of the copolymer has been ascertained by ^{13}C NMR since no signal intermediate to those of the PCL carbonyl groups and the PAA carbonyl groups is observed.

Conclusions. This study has clearly shown that adipic anhydride can be polymerized by aluminum isopropoxide according to a "coordination-insertion" mechanism which involves the selective opening of the "acyl–oxygen" bond of the monomer. The molecular weight of PAA is predictable on the basis of the monomer/initiator molar ratio and the monomer conversion (at least, for short length chains).

The living polymerization mechanism of adipic anhydride is identical to that reported for ϵ-CL and lactides in the presence of the same initiator. The average number of active sites per aluminum molecule has been calculated to be 1. Furthermore, functional aluminum alkoxides have proven to be very successful in the synthesis of end-reactive PAA. Finally, block copolymers of ϵ-CL and AA can be synthesized in a controlled way.

Mechanistic and kinetic characteristics of the ring-opening polymerization promoted by aluminum alkoxides and zinc mono- and dialkoxides are under current investigation and will be published in a forthcoming paper.

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