Macromolecular Engineering of Polylactones and Polylactides. 22. Copolymerization of ϵ-Caprolactone and 1,4,8-Trioxaspiro[4.6]-9-undecanone Initiated by Aluminum Isopropoxide

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ABSTRACT: Novel biodegradable and biocompatible polyesters have been prepared by random copolymerization of ϵ-caprolactone (ϵ-CL) and 1,4,8-trioxaspiro[4.6]-9-undecanone (TOSUO) initiated by Al(O^iPr)$_3$. Copolyesters of molecular weight ($\bar{M}_n$) up to 10^4 and containing up to 90 mol % TOSUO repeating units have been prepared. The copolymer molecular weight is controlled by the molar ratio of the consumed comonomers and the initiator. The TOSUO constitutive units have been quantitatively deacetalized into ketones, which have also been efficiently reduced into hydroxyl groups without any apparent chain degradation. Therefore, poly(ϵ-caprolactone) (PCL) with well-defined content of ketone or hydroxyl pendent groups have been made available. The ϵ-CL and TOSUO comonomer units are randomly distributed within the copolymers, as assessed by the ^{13}C-NMR sequence analysis. Indeed, the reactivity ratios (r_C and r_T) have been calculated from the average length of the ϵ-CL sequences (L_C) and the TOSUO sequences (L_T) and found to be 1.3 (r_C) and 1.0 (r_T), respectively. There is an interesting parallelism between the crystallinity and the average length of the ϵ-CL sequences. Copolyesters containing a molar fraction of TOSUO units smaller than 0.15 are semicrystalline, whereas the incorporation of larger amounts of TOSUO units results in amorphous copolyesters. Conversion of the ethylene acetal pendent groups into ketones and ultimately into hydroxyl pendent groups results in increasing glass transition temperature (T_g), melting temperature (T_m), and melting enthalpy (ΔH_m). The thermal stability depends on the copolyester composition, since it decreases as the molar fraction of TOSUO units is increased.

Introduction

Aliphatic polyesters are well-known examples of biodegradable and biocompatible polymers, as extensively reported and discussed in the scientific literature.[1] These homo- and copolyesters are most efficiently synthesized by ring-opening polymerization of the parent cyclic monomers, such as ϵ-caprolactone (ϵ-CL), lactides (LA), and glycolide (GL). Random copolymerization is known to provide new materials, whose properties are the average of those of the parent homopolymers. This is a valuable method to finely tune one property to the value needed for a specific application. Copolymerization of ϵ-CL with LA or GL yields biodegradable and biocompatible polyesters with a large range of chemical and physical properties.[2−11] The biodegradable sutures, commercially available under the trademark Vicryl, are nothing but random copolymers of PGL and PLA. In the recent past, increasing attention has been paid to some synthetic aliphatic polyesters bearing functional pendent groups because they provide the unique opportunity of attaching drugs, regulating cell function, and improving the desirable hydrophilicity. Copolymerization of functional monomers with ϵ-CL or LA is a typical pathway toward functional polyesters. The functional group of the comonomer is commonly protected, and it needs to be deprotected after copolymerization. Although several polyesters bearing functional pendent groups have been synthesized,[12−25] a series of problems are pending, such as complex and time-consuming procedures for the synthesis of functional comonomers within low yields, limitation in the functional groups available, and copolymerization reactions out of control.

Several years ago, some of us reported that the living polymerization of ϵ-CL could be promoted by bimetallic (Zn, Al) μ-oxo alkoxides.[26] Later on, aluminum trialkoxide and alkylaluminum alkoxides were successfully used for the same purpose.[27−30] More recently, the selective end functionalization of PCL and PLA has been investigated by using aluminum alkoxides carrying functional alkoxy groups as initiators.[10,31] The ring-opening polymerization proceeds through a "coordination-insertion" mechanism that involves the insertion of the monomer into the "Al-O" bond of the initiator. The acyl−oxygen bond of the cyclic monomer is cleaved in a way which maintains the growing chain attached to aluminum through an alkoxide bond. Hydrolysis of the active aluminum alkoxide bond leads to the formation of a hydroxyl end group, the second chain extremity being capped with an ester carrying the alkoxy radical of the initiator.

In a short paper[32] we have reported a very direct and efficient pathway for the synthesis of a new functional monomer, i.e. 1,4,8-trioxaspiro[4.6]-9-undecanone (TOSUO), which is prone to controlled homopolymerization and copolymerization with ϵ-CL and lactide. In this paper, the random copolymerization of ϵ-CL and TOSUO is detailed (copolyester A, Scheme 1). The subsequent deacetalization of the pendent ethylene acetals into ketones (copolyester B, Scheme 1) and the reduction of ketones into hydroxyl pendent groups (copolyester C, Scheme 1) are also discussed. The copolyesters have been characterized by ^{1}H-NMR (monomer conversion, molar composition), ^{13}C-NMR (sequence analysis), size exclusion chromatography (molecular weight distribution, apparent molecular weight), DSC (glass transition

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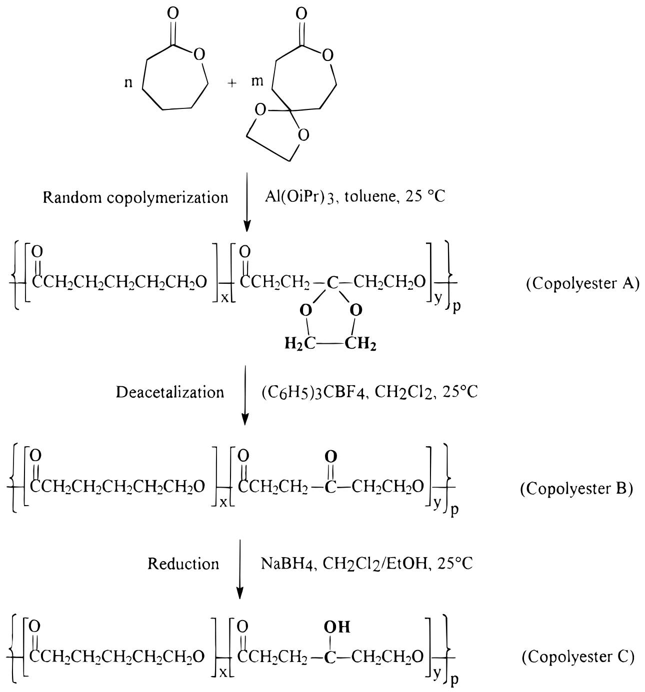
Scheme 1



temperature, melting temperature, and melting enthalpy), and thermogravimetric analysis (TGA, thermal stability).

Experimental Section

Materials. Synthesis of 1,4,8-trioxaspiro[4.6]-9-undecanone (TOSUO) was described elsewhere.[32] Triphenylcarbenium tetrafluoroborate (Acros), sodium borohydride (Janssen), and ethanol (Riedel-de Haën) were used as received. ϵ-Caprolactone (Janssen) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. Toluene (Acros) was dried by refluxing over calcium hydride and distilled under nitrogen. Dichloromethane (Acros) was dried by molecular sieves (Aldrich) and distilled just before use. Aluminum isopropoxide [$\text{Al(O}^i\text{Pr)}_3$] (Aldrich) was twice sublimated and then dissolved in toluene under nitrogen.

Polymerization Techniques. Copolymerization was carried out at 25 °C in toluene under stirring, in a previously flamed and nitrogen-purged glass reactor. 1,4,8-Trioxaspiro-[4.6]-9-undecanone (5-ethylene ketal ϵ-caprolactone) was dried by repeated (three times) azeotropic distillation of toluene just before polymerization. Solvent, ϵ-caprolactone, and initiator [$\text{Al(O}^i\text{Pr)}_3$] were successively added into the reactor through a rubber septum with syringes or stainless steel capillaries. After polymerization, an excess of 1 N HCl was added and the copolymer (A) was recovered by precipitation in cold heptane and filtration.

Deacetalization of the TOSUO/ϵ-CL Copolymer. The random copolymer (A) of TOSUO/ϵ-CL (3.2 mmol of TOSUO) and triphenylcarbenium tetrafluoroborate (TPFB) (3.4 mmol) were dissolved in 280 mL of dichloromethane under stirring for 30 min. The copolymer (B) was recovered by precipitation in cold methanol.

Reduction of Ketone Pendent Groups into Hydroxyl Pendent Groups. Copolymer (B) (2.4 mmol of ketones) and sodium borohydride (2.9 mmol) were dissolved in 294 mL of CH_2Cl_2/EtOH (5:2 vol/vol) under stirring for 30 min. Then copolyester (C) was recovered by precipitation in cold methanol.

Characterization. Copolymer composition was determined by ^{1}H-NMR from the relative intensity of the methylene signal of PCL at 1.65 ppm and the methylene signal of polyTOSUO at 2.00 ppm. Spectra were recorded in $CDCl_3$ at 25 °C, using a Bruker AM400 apparatus operating at 400 MHz. ^{13}C-NMR spectra were recorded in $CDCl_3$ at 25 °C, using the same equipment operating at 100 MHz. The "INVGATE" sequence was used for the analysis of the comonomer distribution within the copolymers. ^{13}C-NMR measurements proved to be quantitative with a pulse width of 30°, an acquisition time of 0.7 s, and a delay of 3 s between pulses. The molecular weight was calculated by ^{1}H-NMR from the relative intensity of the signals of the isopropyl ester end group ($\delta = 5.01$ ppm) and the methylene groups ($\delta = 1.65$ and 2.00 ppm). Size exclusion chromatography (SEC) was performed in THF, by 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). Apparent molecular weight and molecular weight distribution were calculated by reference to a universal calibration curve set up with polystyrene standards and the PCL viscosimetric relationships.[33] Differential scanning calorimetry (DSC) was carried out with a DuPont 9900 DSC thermal analyzer and calibrated with indium. The melting temperature (T_m) and melting enthalpy (ΔH_m) were measured after cooling the sample to −120 °C and heating it to 100 °C (heating rate = 20 °C/min). For the measurement of the glass transition temperature (T_g), the sample was premelted at 100 °C for 1 min, then quenched to −120 °C, and finally heated at a 20 °C/min rate. Thermogravimetric analysis was carried out with a DuPont 51 thermogravimetric analyzer over the 25−600 °C temperature range at a 10 °C/min rate under a nitrogen flow (10 mL/min).

Results and Discussion

Copolymerization of ϵ-CL and TOSUO. Copolymerization of ϵ-CL and TOSUO has been initiated in toluene with aluminum isopropoxide, which is the most efficient catalyst known for the living polymerization of ϵ-CL.[1c] The molar fraction of TOSUO in the mixtures with ϵ-CL has been changed from 0.13 to 0.91. The (co)monomer-to-initiator molar ratio has been calculated in order to reach a ca. 10 000 molecular weight on the assumption of a living polymerization. Under these conditions, the analysis of the chain end groups remains reliable. Copolymerization conditions and results are summarized in Table 1. In all the experiments, the comonomer conversion has been quantitative. The number average degree of polymerization (DP) is directly controlled by the ($[\epsilon\text{-CL}]_o + [\text{TOSUO}]_o)/3[\text{Al(O}^i\text{Pr)}_3]_o$ molar ratio, as assessed by the good agreement between values calculated from eq 1 which holds for a living system, and the experimental values calculated by ^{1}H-NMR (Table 1).

$$M_n = (114[\epsilon\text{-CL}]_o + 172[\text{TOSUO}]_o)/3[\text{Al(O}^i\text{Pr)}_3]_o + 60 \quad (1)$$

M_n measured by size exclusion chromatography with the universal calibration curve valid to PCL is as less consistent with values calculated from ^{1}H-NMR data as the TOSUO content is high. Actually, the elution volume in THF tends to decrease with respect to that of PCL of the same molecular weight as the TOSUO content of the copolymer rises.

Since the application of eq 1 accounts for the experimental DP, three chains are growing per $\text{Al(O}^i\text{Pr)}_3$ molecule, as is the case for the ϵ-CL homopolymerization.[34−36] The molecular weight distribution (M_w/M_n) of the copolymers remains narrow when the chains are deactivated as soon as the monomer conversion is complete. This explains why the molecular weight distribution of copolymer D (Table 1) is broader, in relation to a polymerization time longer than requested for a quantitative monomer conversion and partial transesterification reactions. When the molar fraction

Table 1. Random Copolymerization of ϵ-CL and TOSUO in Toluene at 25 °C Initiated by Al(O^{i}Pr)$_3$

entries	[ϵ-CL]$_o$/ 3[Al(O^{i}Pr)$_3$]$_o$	[TOSUO]$_o$/ 3[Al(O^{i}Pr)$_3$]$_o$	F_T[a]	time (h)	conversion (%)	$10^{-3}M_n$[b] (th)	DP (^{1}H-NMR) ϵ-CL	DP (^{1}H-NMR) TOSUO	F_T[c]	$10^{-3}M_n$ (^{1}H-NMR)	$10^{-3}M_n$[d] (SEC)	M_w/M_n
A	78.4	0	0	0.25	100	9.0	76.8	0	0	9.0	9.0	1.20
B	63.1	9.2	0.13	2.0	100	8.8	64.9	9.0	0.12	9.0	7.0	1.15
C	71.1	11.7	0.14	2.1	100	10.2	66.7	11.4	0.15	9.5	7.6	1.15
D	51.3	24.8	0.33	15.7	100	10.2	54.8	21.2	0.28	10.0	7.4	1.35
E	26.4	28.2	0.52	14	100	7.9	25.7	25.8	0.50	7.5	6.0	1.25
F	19.3	45.4	0.70	15.3	100	10.1	19.9	45.8	0.70	10.0	5.5	1.25
G	5.6	54.4	0.91	17.3	100	10.1	5.7	50.4	0.90	9.5	4.5	1.20

[a] Molar ratio of TOSUO in the feed F_T = [TOSUO]$_o$/([ϵ-CL]$_o$ + [TOSUO]$_o$). [b] Theoretical molecular weight: M_n = [ϵ-CL]$_o$/3[Al(O^{i}Pr)$_3$]$_o$ × 114 + [TOSUO]$_o$/3[Al(O^{i}Pr)$_3$]$_o$ × 172 + 60. [c] Molar fraction of the TOSUO repeating units in the ϵ-CL/TOSUO copolymers. [d] M_n (SEC) calculated with a universal calibration for PCL.[33]

of TOSUO in the comonomer feed is higher, the time for a 100% copolymerization reaction is also longer.

The molar composition of the copolyesters has been calculated from the ^{1}H-NMR spectrum of the purified products. Figure 1A illustrates the ^{1}H-NMR spectrum of copolymer B (Table 1). The TOSUO content (F_T) is calculated by eq 2 from the relative intensity (I) of the appropriate resonances (see Figure 1A).

$$F_T = \frac{I_{d1+d2}}{I_d + I_{d1+d2}} = \frac{I_{c1}}{I_c + I_{c1}} = \frac{I_{f1}}{I_f + I_{f1}} \qquad (2)$$

F_T values are listed in Table 1, and they are expectedly in agreement with the molar fraction of the comonomer feed since the comonomer conversion is quantitative.

Deacetalization of poly(ϵ-CL-*co*-TOSUO). Consistently with the sensitivity of the aliphatic polyesters to hydrolysis, attempts to convert the acetal pendent groups into ketones under the usual acidic conditions have resulted in chain degradation. Pyridinium tosylate (PPTS) is a known catalyst for acetalization and deacetalization reactions of acid sensitive compounds due to a low pK_a.[38,39] However, the deacetalization of poly(ϵ-CL-*co*-TOSUO) catalyzed by PPTS is far from being complete even after reaction at 25 °C for 168 h followed by refluxing (56.5 °C) for 72 h. The oxidation of ketone acetals by hydride transfer[40] is another method of irreversible deacetalization under neutral conditions. Triphenylcarbenium tetrafluoroborate (TPFB) has proved to be a useful and efficient reagent for the deacetalization of ketone acetals.[40,41] This efficiency has been confirmed in this work by the complete deacetalization of poly(ϵ-CL-*co*-TOSUO) samples. As an example, Figure 1B shows the ^{1}H-NMR spectrum for copolymer B (Table 1) after deacetalization. The acetal protons at δ = 3.94 ppm have completely disappeared, whereas correspondingly, the multiplets at δ = 2.00 (H_{d1+d2}) and triplets at δ = 2.38 (H_{c1}), 3.77 (H_{g1}), and 4.18 (H_{f1}) of the original copolyester (Figure 1A) have been shifted to lower fields (δ = 2.76 ($H_{d1'}$), 2.81 ($H_{d2'}$), 2.61 ($H_{c1'}$), 3.89 ($H_{g1'}$), and 4.35 ($H_{f1'}$)) which is clear evidence for the completeness of the deacetalization reaction.

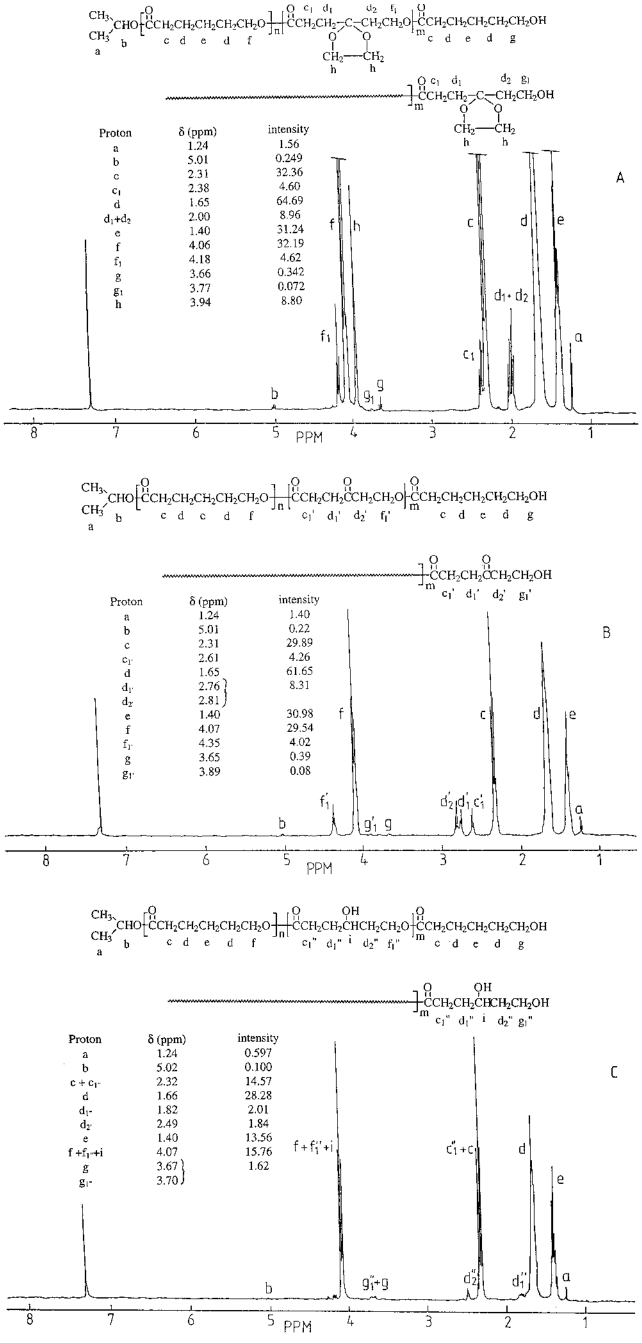


Figure 1. ^{1}H-NMR spectrum of poly(ϵ-CL-*co*-TOSUO) (copolymer B in Table 1) (A) before deacetalization, (B) after deacetalization, and (C) after reduction.

Reduction of Ketones into Hydroxyl Pendent Groups. Sodium borohydride is well-known as a very mild reducing agent. In hydroxylic solvents (i.e., H_2O and alchols), aldehydes and ketones are rapidly and selectively reduced at 25 °C, in contrast to other functional groups, such as esters.[42] The copolyesters under consideration are insoluble in alcohols in which sodium borohydride is readily soluble. It has thus been a problem to find out a common solvent for the copolymer and sodium borohydride. Finally, these two compounds have been successfully solubilized in a solvent mixture, i.e. CH_2Cl_2/EtOH (5:2 vol/vol). Ethanol has the twofold advantage of allowing the reduction to be carried out under homogeneous conditions and reacting slowly enough with sodium borohydride to minimize the loss of the reducing agent.[43] Figure 1C shows that the

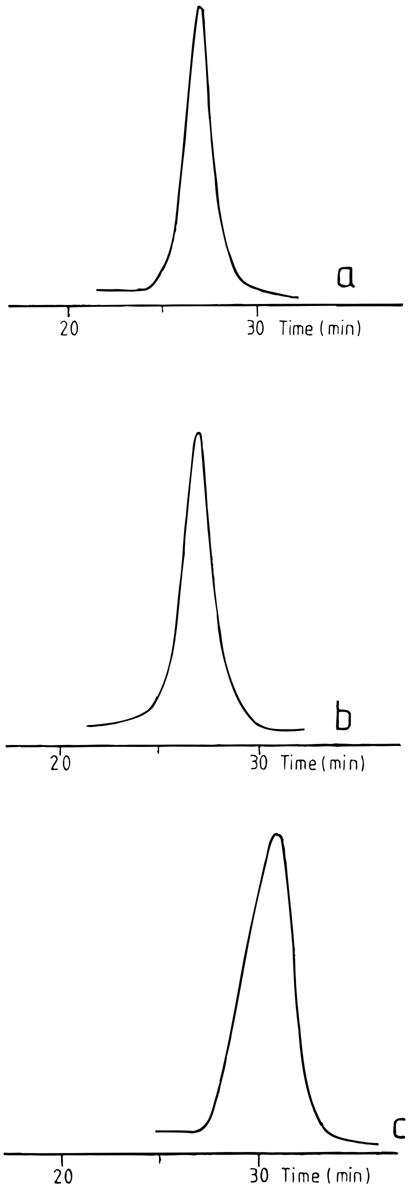


Figure 2. SEC traces for copolymer B in Table 1 (a) before deacetalization, (b) after deacetalization, and (c) after reduction.

ketone pendent groups of copolymer B are completely reduced to hydroxyl pendent groups by sodium borohydride in the dichloromethane/ethanol mixture at 25 °C. The triplets at $\delta = 2.76$ ($H_{d1'}$), 2.81 ($H_{d2'}$), 2.61 ($H_{c1'}$), 3.89 ($H_{g1'}$), and 4.35 ($H_{f1'}$) in Figure 1B are indeed shifted back to high fields, resulting in some overlapping with the signals of PCL protons.

The molecular weight for the copolyesters B (Table 1) has been calculated from the ^{1}H-NMR spectrum for the hydroxyl-containing copolymer (Figure 1C: from the relative intensity of the H_b and H_d, $H_{d2''}$ protons), on one hand, and for the precursor ketone-containing copolymer (Figure 1B: from the relative intensity of the H_b and H_d, $H_{d1'+d2'}$ protons), on the other hand. The calculated values are in agreement within the limits of experimental errors ($9.0 \times 10^3 \pm 10\%$) and fit the molecular weight for the original ethylene acetal-containing copolymer (Table 1 and Figure 1A). This observation strongly supports that the ethylene acetal pendent groups have been quantitatively converted firstly into ketone groups, and finally into hydroxyl pendent groups, and that the polyester chains have not been degraded at all.

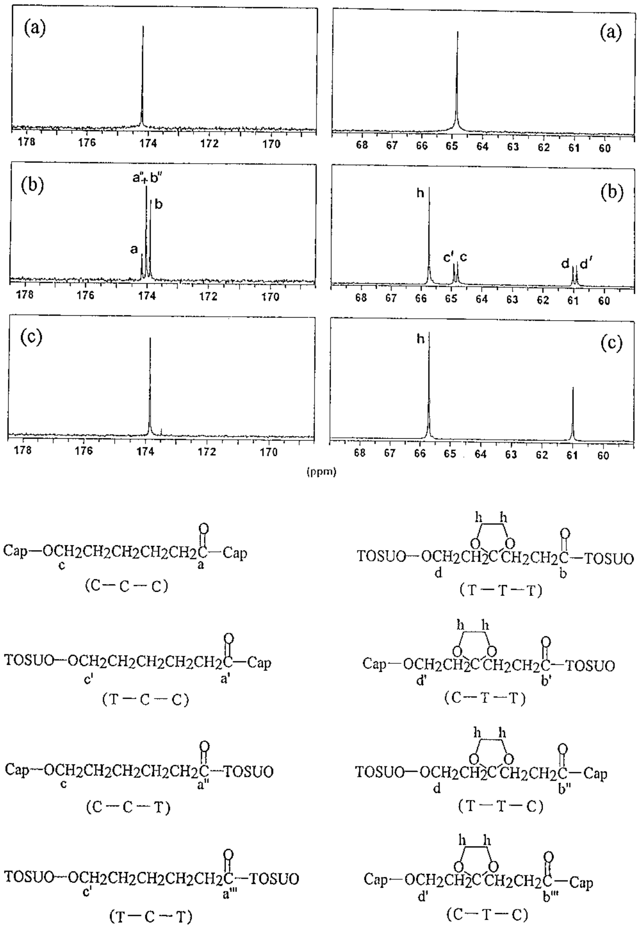


Figure 3. Expanded ^{13}C-NMR spectra for (a) PCL, (b) copolymer E in Table 1, and (c) polyTOSUO.

The molecular weight distribution of the original copolyesters is not significantly modified by the deacetalization and reduction reactions, as shown by SEC analysis. For example, the molecular weight distribution of copolymer B (Table 1) is slightly increased from 1.15 to 1.20 upon deacetalization, and to 1.25 after reduction. The SEC traces are shown in Figure 2. Clearly, both ^{1}H NMR analysis and SEC analysis provide convincing evidence that the PCL chains are not degraded by the two derivatization reactions and the final formation of hydroxyl groups.

Sequence Analysis. As reported in the scientific literature, the carbonyl resonances observed by ^{13}C-NMR of the aliphatic polyesters are sensitive to the sequence effect.[4,7] In order to illustrate the assignment of the carbonyl signals of the herein studied copolyesters, the sequence analysis for copolymer E (Table 1) is now discussed. Figure 3 shows the spectra for the carbonyl and the oxymethylene (OCH_2) regions of the homopolyesters and the copolyester E. Although only one resonance is observed for the carbon of the carbonyl in PCL (Figure 3a) and polyTOSUO (Figure 3c), three resonances are clearly distinguished for the copolymer E (Figure 3b). They have been assigned as follows. Let us first consider the triads in which ϵ-CL is the central unit: C—C—C, T—C—C, C—C—T, and T—C—T. By comparison with the carbonyl chemical shift in PCL (Figure 3a), the resonance at 174.15 ppm is typical of the C—C—C triad (resonance a). In the T—C—C triad, the acetal of the TOSUO unit is not very close to the carbonyl of the central ϵ-CL unit (see molecular structures in Figure 3). It may thus be assumed that the influence of the TOSUO unit is negligible and that resonances a and a′ cannot be distinguished. In the C−C−T and T−C−T triads, the acetal of the TOSUO unit is now in such a position that it can trigger an upfield chemical shift of the carbonyl resonance at 174.03 ppm. For the same reason as before, no significant difference is expected for the carbonyl resonance of the central unit in the C−C−T and T−C−T triads, so that resonances a″ and a‴ cannot be distinguished from each other. When the triads containing a central TOSUO unit are concerned, i.e. T−T−T, C−T−T, T−T−C, and C−T−C, the resonance at 173.90 ppm for the copolymer has to be assigned to the T−T−T triad by reference to the resonance (b) observed for polyTOSUO (Figure 3c). In the C−T−T triad, the first unit (c) is far enough away from the carbonyl of the central TOSUO unit to have no significant influence. Only one resonance is thus observed for b and b′. In the case of the triads containing a third ϵ-CL unit instead of a TOSUO one (T−T−C and C−T−C), a downfield shift is expected to occur with the observation of a unique resonance for b″ and b‴. Resonances of the a″ and b″ type appear to coincide, which is not too surprising taking into account the small difference (0.3 ppm) between the extreme resonances a and b.

When the copolyester composition is changed ($0.12 \leq F_T \leq 0.90$), no modification is observed in the number and position of the carbonyl resonances. Only a change in the relative intensity of the three resonances is reported.

The oxymethylene (OCH_2) carbon resonances of ϵ-CL units and TOSUO units in the copolymers show a diad sensitivity and have been assigned accordingly (Figure 3b). By comparison with the chemical shift observed in PCL, peak c for the copolyester has been assigned to the C−C diad. The TOSUO unit in the T−C diad causes a downfield chemical shift and resonance c′ is observed. Similarly, resonance d has been assigned to the T−T diad and resonance d′ results from an upfield chemical shift in the C−T diad. The sequence analysis of the copolyesters based on the carbonyl and the oxymethylene resonances is consistent not only with each other but also with the ring-opening mechanism generally accepted for lactones and lactides.

In binary copolymers (i and j comonomers), the average length of the i-type sequence (L_i) is commonly related to the triad composition according to eq 3,[4]

$$L_i = \frac{n_{iii} + n_{iij}}{n_{jii} + n_{jij}} \tag{3}$$

where $n_{iij} = n_{jii}$ since each sequence of more than one i unit begins with a jii triad and ends up with an iij triad. The average lengths, L_i and L_j, can thus be calculated from the integration of the triad signals in the case of quantitative ^{13}C-NMR. The average lengths of the ϵ-CL sequences (L_C) and TOSUO sequences (L_T) have been calculated from eqs 4 and 5 (Table 2), where I_i is the

$$L_C = \frac{I_a}{(I_{a''} + I_{b''})/2} + 1 = \frac{I_c}{I_{c'}} + 1 \tag{4}$$

$$L_T = \frac{I_b}{(I_{a''} + I_{b''})/2} + 1 = \frac{I_d}{I_{d'}} \tag{5}$$

intensity of peak i characteristic of the corresponding sequence. The molar fraction of TOSUO in each copolymer (F_T) has been calculated by eq 6

$$F_T = \frac{L_T}{(L_T + L_C)} \tag{6}$$

Table 2. ^{1}H-NMR and ^{13}C-NMR Data for Poly(ϵ-CL-*co*-TOSUO)

sample	F_T	F_T (^{1}H-NMR)	L_C	L_T	F_T (^{13}C-NMR)
B	0.13	0.12	10.30	1.40	0.12
D	0.33	0.28	3.40	1.60	0.32
E	0.52	0.50	2.05	2.05	0.50
F	0.70	0.70	1.65	2.85	0.65
G	0.91	0.90	1.30	10.80	0.89

Table 2 shows that the F_T values determined by ^{1}H-NMR and ^{13}C-NMR are in good agreement within the limits of the NMR experimental errors, which confirms the interpretation of the ^{13}C-NMR spectra.

Reactivity Ratios. The number average length of the sequence formed by each comonomer (1 and 2) in a binary copolymerization is given by eqs 7 and 8, where

$$L_1 = \frac{1}{1 - P_{11}} \tag{7}$$

$$L_2 = \frac{1}{1 - P_{22}} \tag{8}$$

P_{11} and P_{22} are the probabilities for one comonomer to be added to a chain ended with an active species of the same type. These probabilities have been expressed by Alfrey and Goldfinger,[45,46] as shown by eqs 9 and 10.

$$P_{11} = \frac{r_1[M_1]_o}{r_1[M_1]_o + [M_2]_o} \tag{9}$$

$$P_{22} = \frac{r_2[M_2]_o}{[M_1]_o + r_2[M_2]_o} \tag{10}$$

From the combinations of eqs 7 and 9 and eqs 8 and 10, respectively, a relationship between the reactivity ratio (r) and the average length of the sequence (L) for each comonomer can be extracted (eqs 11 and 12), where $A = [M_C]_o/[M_T]_o$.

$$L_1 = Ar_1 + 1 \tag{11}$$

$$L_2 = \frac{r_2}{A} + 1 \tag{12}$$

Indeed, a linear relationship is observed when the sequence length (L_C or L_T) is plotted against A ($[M_C]_o/[M_T]_o$) or A^{-1} ($[M_T]_o/[M_C]_o$) (Figure 4). Thus, from the slope of the straight line, r_C and r_T are easily calculated as 1.3 and 1.0, respectively. The reliability of the r_C and r_T values is, of course, basically dependent on the accuracy of L_C and L_T. It must also be pointed out that the occurrence of transesterification reactions is a source of errors in L_C and L_T and thus in r_C and r_T. Due to these uncertainties, r_C and r_T will be measured in the future according to the traditional method, which is much more time-consuming.

Thermal Analysis. 1. DSC Study of the Copolyesters. The thermal transitions in the ϵ-CL/TOSUO copolymers have been analyzed by differential scanning calorimetry (DSC). As shown in Figures 5 and 6, copolymerization of ϵ-CL with increasing amounts of TOSUO has a strong effect on the glass transition temperature (T_g), the melting temperature (T_m), and the melting enthalpy (ΔH_m). The unique T_g observed

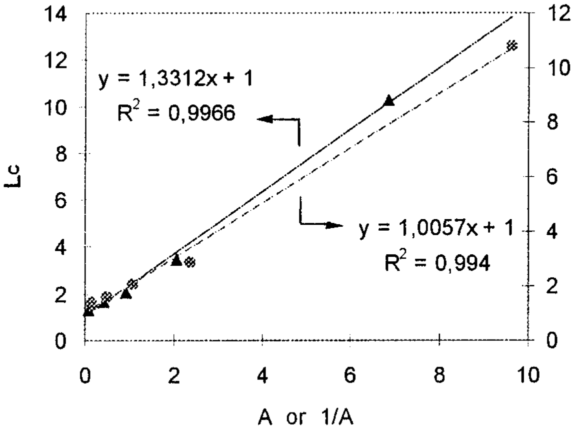


Figure 4. Relationship between sequence lengths (L_C or L_T) and initial comonomer ratio A ($[M_C]_o/[M_T]_o$) or A^{-1} ($[M_T]_o/[M_C]_o$).

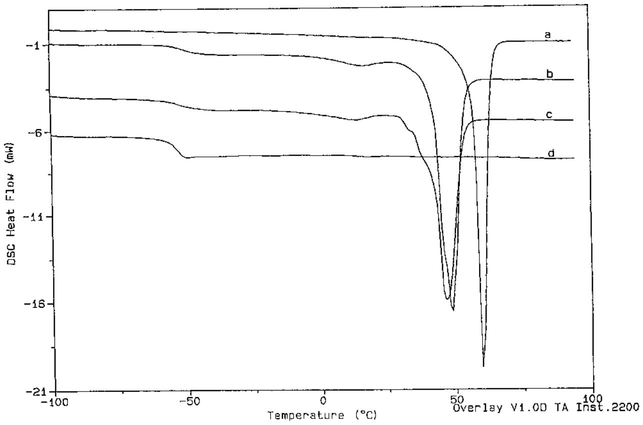


Figure 5. DSC traces for copolyesters of various compositions: (a) $F_T = 0$; (b) $F_T = 0.12$; (c) $F_T = 0.15$; (d) $F_T = 0.28$.

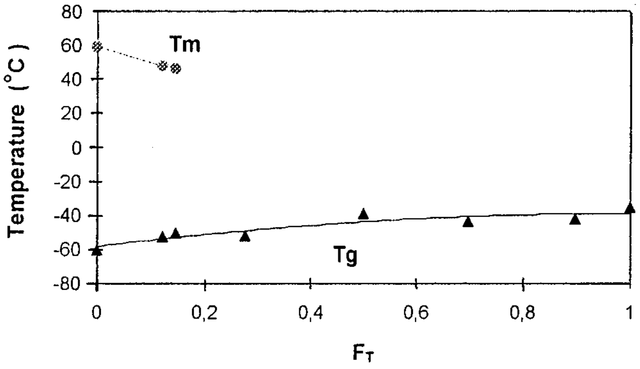


Figure 6. Phase diagram for the poly(ϵ-CL-*co*-TOSUO) copolymers.

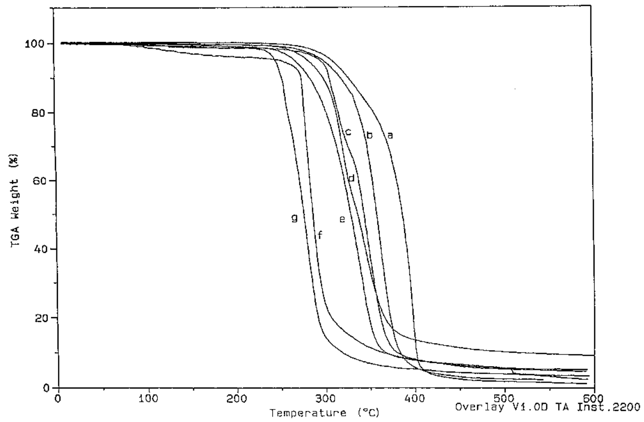


Figure 7. TGA curves of the homopolyester and copolyesters of various TOSUO molar fractions (F_T): (a) 0; (b) 0.12; (c) 0.28; (d) 0.50; (e) 0.70; (f) 0.90; (g) 1.00.

Table 3. DSC Analysis of PCL Bearing Different Functional Pendent Groups

samples	pendent groups	F_T (^{1}H-NMR)	T_g (°C)	T_m (°C)	ΔH_m (J/g)
A	no	0	−61	59	82.0
B	ethyleneacetal	0.12	−53	46	55.5
B1	ketone	0.12	−42	64	87.5
B2	hydroxyl	0.12	−42	60	104.0

increases with the molar fraction of TOSUO (F_T), which indicates that the amorphous phase is homogeneous, as could be anticipated from the estimated reactivity ratios. Figure 6 shows a melting behavior typical of random copolymers in which only one component (PCL) is able to crystallize. It must indeed be mentioned that a melting endotherm is observed for homoPTOSUO ($F_T = 1$) precipitated from chloroform solution into cold heptane and scanned for the first time. No crystallization from the melt occurs even when cooled from the melt at a rate lower than 2 °C/min and annealed for 1 week under ambient conditions.[47] The T_m of PCL is decreased as the TOSUO content is increased until $F_T = 0.15$ (Figure 6). Figure 5 (curves b and c) shows a small endotherm at a lower temperature than T_m, which might be assigned to poorly crystallized PCL domains as a result of disturbances by TOSUO units. For $F_T > 0.15$, the copolymers are completely amorphous (e.g., curve d in Figure 5).

The DSC measurements are in good qualitative agreement with the sequence analysis by ^{13}C-NMR. Indeed, upon increasing F_T the average block length of the ϵ-CL units (L_C) decreases, which expectedly results in a decreasing T_m. At $F_T > 0.15$, L_C becomes small enough to inhibit the ϵ-CL block crystallization. Thus, both the sequence analysis and the DSC measurements confirm the randomness of copolymers.

Table 3 illustrates how the thermal behavior of poly(ϵ-caprolactone) changes upon modification by a constant molar amount of pendent groups. Ethylene acetal substituents are responsible for some increase in T_g and a dramatic decrease in T_m, although the melting enthalpy becomes smaller. Substitution of ketones for the acetal groups results in a further increase in T_g, T_m, and ΔH_m. Substitution of the ketone groups by hydroxyl ones has no significant effect on T_g and T_m; there is only an increase in ΔH_m.

2. Thermogravimetric Analysis of the Copolyesters. Figure 7 shows the thermogravimetric analysis for each homopolyester ($F_T = 0$ and 1) and the related copolyesters ($F_T = 0.12-0.90$). PCL and PTOSUO experience thermal decomposition at 397 and 279 °C, which indicates a substantially lower thermal stability of PTOSUO compared to PCL. Expectedly, the random copolyesters start to decompose as rapidly as the molar fraction of TOSUO rises (F_T).

Conclusion

Functional biodegradable and biocompatible polyesters have been prepared by ring-opening polymerization of 1,4,8-trioxaspiro[4.6]-9-undecanone and copolymerization with ϵ-caprolactone by using freshly distilled $Al(O^iPr)_3$ as initiator. The copolymer molecular weight is controlled by the $([\epsilon\text{-CL}]_o + [TOSUO]_o/3[Al(O^iPr)_3]_o$ molar ratio, in agreement with a living process. Deacetalization of the copolyesters with formation of ketones and reduction of the ketones into hydroxyl groups can be achieved until completeness, without any degradation of the polyester main chain. Thus, the molar fraction of TOSUO allows the content of the ketone and hydroxyl pendent groups to be finely controlled. The comonomer sequence analysis by ^{13}C NMR and the DSC analysis agree with a random distribution of the ϵ-CL and TOSUO units in the copolyester. From the average sequence length of the ϵ-CL blocks (L_C) and TOSUO blocks (L_T), the reactivity ratios, r_C and r_T, have been calculated as 1.3 (r_C) and 1.0 (r_T), respectively. Only copolyesters containing less than 15 mol % TOSUO are semicrystalline. The thermal stability of the copolyesters under nitrogen decreases with the increasing molar fraction of TOSUO.

The availability of pendent hydroxyl groups on poly(ϵ-caprolactone) has great potential for applications in medicine, surgery, and tissue engineering. These reactive groups also pave the way to novel molecular architecture and materials. For instance, reaction of the pendent hydroxyl groups with an excess of triethylaluminum provides a macroinitiator for the ring-opening polymerization of lactones and lactides with formation of comb-graft copolymers. If the grafts also contain TOSUO units, the release of hydroxyl groups and reaction with AlEt$_3$ allow an additional grafting reaction to be performed, leading to dendritic structures. Furthermore, the low glass transition temperature of the amorphous poly(ϵ-CL-*co*-TOSUO) ($F_T > 0.15$) makes it a valuable rubbery material to be used in combination with semicrystalline PCL to form triblock copolyesters, poly(ϵ-CL-*b*-ϵ-CL/TOSUO-*b*-ϵ-CL), which are potential biodegradable and biocompatible thermoplastic elastomers. All of these opportunities will be studied and reported in forthcoming papers.

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