Ring Opening Copolymerization of ε-Caprolactone, γ-(Triethylsilyloxy)-ε-Caprolactone and γ-Ethylene Ketal-ε-Caprolactone: a Route to Hetero-Graft Copolyesters

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Abstract : ε-Caprolactone (ε-CL) has been copolymerized with two precursors of γ-hydroxy-ε-CL, i.e., γ-ethylene ketal-ε-caprolactone (TOSUO) and γ-(triethylsilyloxy)-ε-caprolactone (TeSCL). The triethylsilyloxy pendant groups can be selectively deprotected into hydroxyl groups followed by the deprotection of the acetal substituents. Each series of hydroxyl groups can be used to initiate the polymerization of cyclic monomers so leading to hetero-graft copolyesters with, for instance, poly-ε-CL and polylactide grafts.

Introduction

Aliphatic polyesters have received steadily increasing attention for applications in medicine and surgery over the past 20 years. The availability of functional pendant groups is highly desirable for extending the range of their potential applications, e.g., by attaching drugs, improving biocompatibility and promoting bioadhesion. Although functional monomers are known [1-14], either tedious synthesis and/or polymerization out of control limit their potential. Recently, a particular attention has been paid to the synthesis of hydroxyl substituted poly-ε-caprolactone (PCL-OH). In this respect, some of us have reported on the synthesis and controlled polymerization of 1,4,8-trioxa[4,6]spiro-9-undecanone (TOSUO) [15] and ε-caprolactone (ε-CL) leading to well-defined random [16] and block [17] copolymers. These copolymers have been converted into hydroxylated versions, i.e., poly(ε-CL)-*co*-poly(ε-CL-OH) and poly(ε-CL)-*b*-poly(ε-CL-OH). The deprotection is a two-step process, i.e.,

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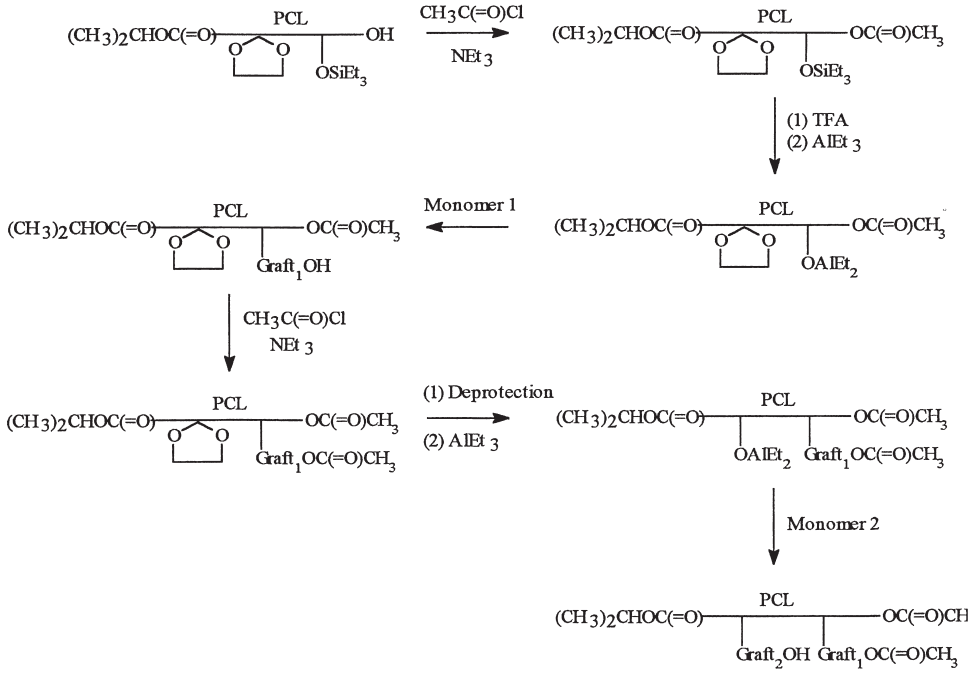
deacetalisation into ketone by triphenylcarbenium tetrafluoroborate and reduction of the ketone into alcohol by sodium borohydride.[17] It has been shown that the hydroxyl pendant groups can be reacted with triethylaluminum (Et_3Al) and converted into aluminum alkoxides, which are very well-known initiators for the living Ring Opening Polymerization (ROP) of lactones. Grafted copolymers [18] and more complex architectures such as dendri-graft [19] or hyperbranched structures [18,20] have accordingly been prepared.

γ-(t-butyldimethylsilyloxy)-ε-caprolactone (SCL) that has been synthesized by Pitt et al., is another version of protected γ-hydroxyl-ε-CL.[22] It has been copolymerized with ε-CL, δ-valerolactone and various amounts of 2,2-bis(ε-caprolactone-4-yl)propane at 140 °C in the presence of stannous octoate with formation of elastomers.

This paper aims at reporting on the terpolymerization of ε-CL, TOSUO and TeSCL, so leading to polyesters substituted by two types of protected hydroxyl groups. The sequential deprotection of the silanolate groups followed by the acetal ones will be carried out, with the purpose to graft from the backbone two types of chains, both of them being initiated by aluminum alkoxides, as illustrated by scheme 1.



Scheme 1 : Strategy for the synthesis of hetero-graft copolymers starting from terpolymer of ε-CL, TOSUO and TeSCL

Experimental Section

Materials. Synthesis of γ-ethylene ketal-ε-caprolactone(TOSUO) was described elsewhere.[15] γ-(t-butyldimethylsilyloxy)-ε-caprolactone (SCL) was synthesized according to the experimental procedure reported by Pitt et al.[22] The synthesis pathway for the γ-(triethylsilyloxy)-ε-caprolactone (TeSCL) will be detailed in the next section. Prior to polymerization, SCL, TeSCL and TOSUO were dried by repeated (three times) azeotropic distillations of toluene under reduced pressure (10^{-2} mmHg). ε-CL (Acros) was dried over CaH_2 (Aldrich) for 48 h and then distilled under reduced pressure prior to use. Aluminum isopropoxide (Aldrich) was purified by distillation under reduced pressure and dissolved in dry toluene. Concentration of this solution was measured by complexometric titration of Al by standard solution of EDTA according to previously reported procedure.[23]

Triethylaluminum (Fluka) was used as received and dissolved in dry toluene, the solution concentration being also determined by complexometric titration of Al by EDTA.

Trifluoroacetic acid (Aldrich), triphenylcarbenium tetrafluoroborate (Acros) and sodium borohydride (Aldrich) were used as received. Toluene (Acros) and acetyl chloride (Aldrich), THF (Acros) and triethylamine (Acros) were dried by refluxing over, respectively, CaH_2, sodium in the presence of benzophenone, and KOH, and distilled under nitrogen prior to use. Cyclohexane-1,4-diol (Aldrich), chlorotriethylsilane (Aldrich), imidazole (Aldrich), m-chloroperoxybenzoic acid (Aldrich) and CH_2Cl_2 (Acros) were used as received.

Synthesis of γ-(triethylsilyloxy)-ε-caprolactone (TeSCL). 4-Hydroxycyclohexanone was prepared from cyclohexane-1,4-diol in 78% yield by oxidation with Jones reagent.[25] Chlorotriethylsilane (16.7g, 0.111 mol) was dropwise added to a solution of 4-hydroxycyclohexanone (10.2g, 0.089 mol) and imidazole (18.9g, 0.0278 mol) in dry DMF (60 ml) at 0°C. After addition, the reaction was allowed to stand at 35°C for 24 h. The solution was diluted with ether (150 ml), washed with water (5x50ml), dried (Na_2SO_4) and concentrated under vacuum. Pure γ-(triethylsilyloxy)cyclohexanone (70% yield) was recovered by fractional distillation under vacuum. 3-Chloroperoxybenzoic acid (13.8 g, 0.056 mol) was added to a solution of this compound (11.6 g, 0.05 mol) in CH_2Cl_2 (80 ml) for 40 min under stirring. The mixture was refluxed for 24 h, filtered, cooled down to 5°C, filtered again and concentrated. CH_2Cl_2 was added and the solution was washed with aq. K_2CO_3, dried (over Na_2SO_4) and concentrated. The fractional distillation under vacuum gave γ-

(triethylsilyloxy)-ε-caprolactone with 50% yield. NMR ($CDCl_3$) (0.55 (q, 6H, $SiCH_2$), 0.91 (t, 9H, $SiCH_2CH_3$), 1.77-1.95 (m, 4H, 3-CH_2 and 5-CH_2), 2.35 (m, 1H, $COCH_2$), 3.04 (m, 1H, $COCH_2$), 4.02 (m, 1H, CHOCO), 4.08 (m, 1H, CHOSi), 4.53 (m, 1H, CHOCO). FT-IR (cm^{-1}) : 742, 1002, 1082, 1150, 1237, 1289, 1457, 1741, 1775, 2875, 2953.

Polymerization Procedure. Terpolymerization of ε-CL, TeSCL and TOSUO was carried out in toluene at 25°C. Toluene, monomers and initiator [$Al(OiPr)_3$ in toluene] were successively added to the reactor through a rubber septum with a syringe or stainless steel capillary. Polymerization was stopped by adding an excess of 1N HCl. The terpolymer was recovered by precipitation in cold heptane.

Selective deprotection of the silanolate groups. 1.5 equivalent trifluoroacetic acid with respect to the silanolate groups were added to 6wt% terpolymer solution in THF/water (6/1 v/v). The reaction was carried out at room temperature for 1.5 h and, after concentration, the polymer was precipitated in cold heptane.

Deprotection of the ketal pendant groups into hydroxyl ones. 1.1 equivalent of triphenylcarbenium tetrafluoroborate with respect to the ketal groups was added to 1wt% solution of terpolymer in CH_2Cl_2. After 30 min of reaction, the ketone containing polyester was precipitated in cold methanol. 10 equivalents of sodium borohydride with respect to the ketone groups were added to 1.7wt% solution of the recovered terpolymer in CH_2Cl_2/EtOH (5/2 v/v). The reaction was allowed to stand at room temperature for 45 min, before the polyester was precipitated in cold methanol.

Graft copolymerization. The required amount of hydroxyl containing terpolymer was added to a previously flamed and nitrogen purged glass reactor. It was dried by two azeotropic distillations of toluene. Dry toluene was then added through a rubber septum with a stainless steel capillary, and cooled down to –78 °C. 1.2 equivalent of $AlEt_3$ with respect to the hydroxyl groups of the terpolymer was added and reacted at room temperature for 2-3h. Then, the reaction mixture was heated to 40 °C for 30 min. The monomer was added to the reaction mixture at room temperature and polymerization was carried out under vigorous stirring and stopped by adding HCl (0.1 M HCl solution) in excess with respect to the initiator. The polymer was precipitated into cold methanol and the crude polymer was dried under vacuum at 40 °C until constant weight.

Acetylation of the hydroxyl groups of the terpolymer. 10 equivalents with respect to the hydroxyl groups of dry triethylamine and acetyl chloride were added to a 10 % terpolymer solution in dry THF. The reaction was carried out at room temperature for 50 h. Finally, the solution was filtered and the polymer was precipitated in methanol.

Characterization. Size exclusion chromatography (SEC) was performed in THF, by using a Hewlett-Packard 1090 Liquid Chromatogram equipped with four columns (10^5, 10^3, 500 and 100 Å) and a Hewlett-Packard 1037A refractive index detector. Polystyrene standards were used for calibration and the number (Mn) and weight (Mw) average molecular weights were accordingly calculated. Nuclear magnetic resonance spectroscopy was performed with a Bruker AM400 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal reference. IR spectra were recorded by using a Perkin-Elmer 106 FTIR.

Results and discussion

In a preliminary study, the selective hydrolysis of the silanolate groups of poly(ε-CL-*co*-TOSUO-*co*-SCL) terpolymers was investigated. However, the stability of these protecting groups is such that too much reactive agents, e. g. HF, $LiBF_4$, Ph_3CBF_4 have to be used, which is detrimental to the selectivity of the deprotection and also to the polymer stability. In order to increase the propensity of the silanolate ε-CL units to hydrolysis, the t-butyldimethylsilyloxy protecting groups have been substituted for triethylsilyloxy ones. Therefore, γ-(triethylsilyloxy)-ε-caprolactone (TeSCL) has been synthesized according to a two-step reaction. Indeed, 4-hydroxycyclohexanone has been firstly reacted with chlorotriethylsilane with formation of 4-(triethylsiloxy)-cyclohexanone, that has then been converted into TeSCL by oxidation with m-chloroperbenzoic acid within a 50% yield. The molecular structure has been confirmed by ^1H NMR and FT-IR (see experimental part). The high purity (> 99%) of the final monomer has been assessed by GC.

The copolymerization of ε-CL, TOSUO and TeSCL in the 90/5/5 molar ratio has been initiated by $Al(O^iPr)_3$ in toluene at 25 °C and left overnight. After precipitation in heptane, the terpolymer has been recovered with a quantitative yield and then characterized by ^1H NMR. In agreement with the well-known addition-insertion mechanism for aluminum isopropoxide initiated ROP, the polyester chains are selectively end-capped by a hydroxyl group and an isopropyl ester, respectively. The number-average degree of polymerization

has been calculated for each comonomer by ^1H NMR from the relative intensity of the isopropyl end group at 5.0 ppm (coming from the initiator) and the typical protons for each comonomer (at 0.5 ppm and at 0.95 ppm for TeSCL, at 3.9 ppm for TOSUO and at 4.1 ppm for ε-CL) (Figure 1). An average-number molecular weight of 9,500 for the terpolymer has been accordingly calculated and is in close agreement with the theoretical value of 10,000 calculated from the comonomer over initiator molar ratio, as reported in Table 1. Furthermore, the size-exclusion chromatogram shows that the elution peak is symmetrical and relatively narrow ($M_W/M_n = 1.3$) (Figure 2). These experimental observations are in line with a living polymerization. The distribution of each comonomer along the polymer backbone has not been analyzed, being out of the scope of this study. The main attention has actually been paid to the selective deprotection of the alcohol groups from the silanolates and the acetals, respectively, which is the prerequisite to prepare hetero-graft copolyesters.

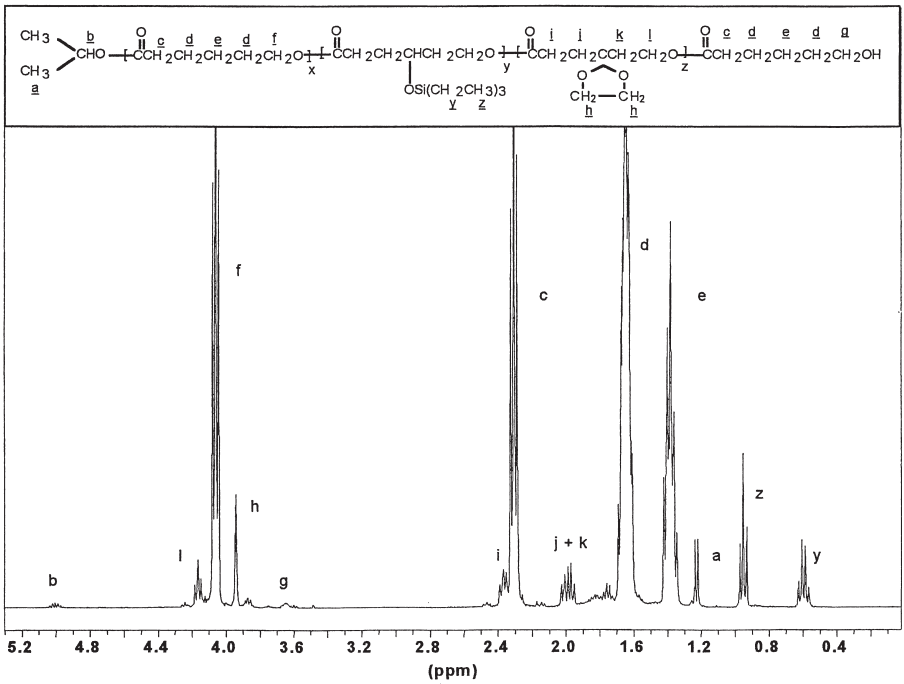


Figure 1 : ^1H NMR spectrum of the ε-CL, TOSUO and TeSCL terpolymer

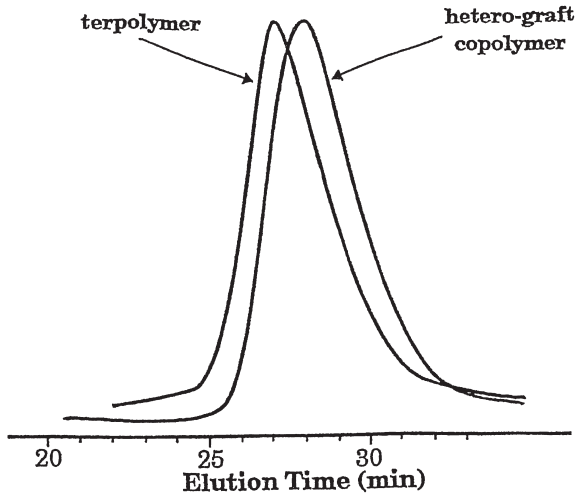


Figure 2 : Comparison of the SEC-chromatograms for the terpolymer and the hetero-graft copolyester.

Table 1 : Number-average degree of polymerization for each comonomer in the terpolymer.

	DP_{th}	DP_{exp}
ε-CL	73	73
TOSUO	4	3.5
TeSCL	4	2.5

The hydroxyl end-groups have then been converted into acetates by reaction with acetyl chloride in THF in the presence of triethylamine, in order to prevent them from participating to further reaction ,e.g., with Et_3Al. The conversion is quantitative as confirmed by ^1H NMR based on the relative intensity of the isopropyl end-group at 5.0 ppm and of the acetyl end-group at 2.05 ppm.

The silanolate pendant groups have been selectively hydrolyzed with trifluoroacetic acid, as shown by the disappearance of the Et_3SiO- peaks at 0.58 and 0.95 ppm (Figure 3). The unchanged relative intensity of the signal at 3.95 ppm typical of the acetal groups is evidence for their stability. Furthermore, the short reaction time prevents the copolymer from being degraded under the acidic conditions used, as confirmed by SEC and ^1H NMR analysis.

In order to prepare the graft copolymer (first step), the pendant hydroxyl groups have been reacted with Et_3Al in order to form aluminum alkoxides, able to initiate the ROP of ε-CL in

toluene at 25 °C. The proton on the methine carbon to which the PCL graft is expected to be attached, proton q in fig. 3, is not significantly shifted.

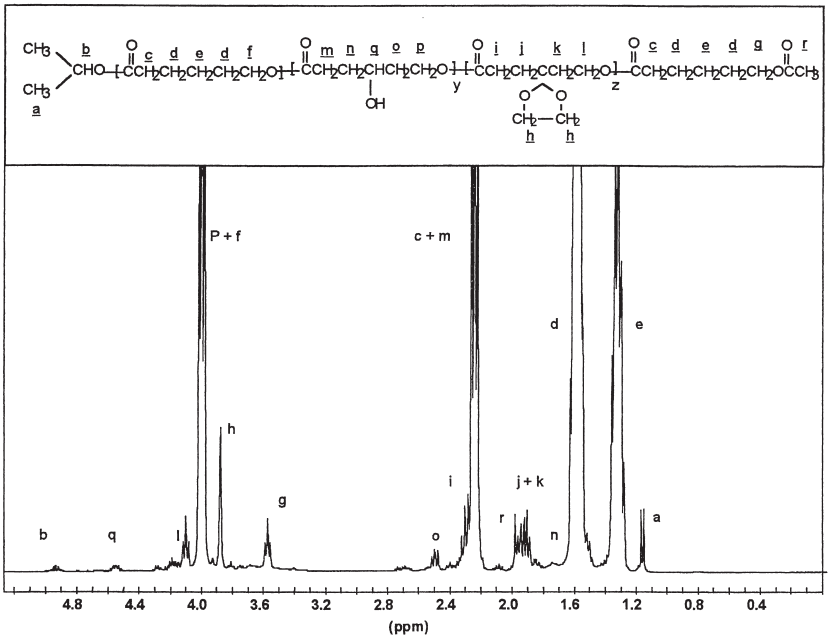


Figure 3 : ^{1}H NMR spectrum of the terpolymer after acetylation of the alcohol end-group and hydrolysis of the silanolate groups.

The copolymer recovered after the first grafting step has been mixed on purpose with ca. 50wt% of the original macroinitiator (before conversion into alkoxide) and the mixture has been reacted with α-naphthalenylisocyanate in order to convert the hydroxyl groups into carbamates. The ^{1}H NMR spectrum shows two multiplets centered at 4.45 ppm for the reaction of the macroinitiator with the isocyanate (-CH_2-C<u>H</u>(O-CO-NH-)-CH_2-) and at 4.49 for the grafting site (-CH_2-C<u>H</u>(O-CO-CH_2-)-CH_2-), as shown in Figure 4. This observation is an additional and more convincing evidence that graft copolymer has actually been formed as result of the first grafting step.

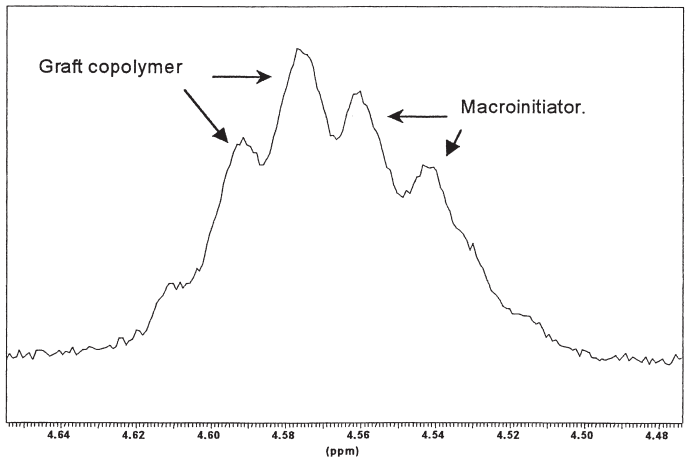


Figure 4 : ^{1}H NMR evidence for the effective grafting.

The number-average molecular weight ($M_{n,NMR}$=21,000) has been calculated from the relative intensity of the isopropyl end-group and the typical protons for each comonomer. The comparison of the degree of polymerization of ε-CL before and after the grafting allows to calculate the molecular weight of the PCL grafts (M_n= 4,500) on the assumption that all the hydroxyl groups have initiated the ε-CL grafting. The apparent M_n calcultated by SEC (polystyrene standards, $Mn_{app,SEC}$=5,600) is much smaller than the value measured by ^{1}H NMR ($M_{n,NMR}$=21,000) which might indicate some contraction of the hydrodynamic volume as result of the grafting. This is only a tentative conclusion, since $M_{n,SEC}$ has no absolute meaning being referred to a polystyrene calibration. The polydispersity index has not changed significantly.

In order to graft the second monomer, the alcohol end-capped grafts have been converted into acetyl end-groups (CH_3COCl, pyridine, NEt_3, 30 °C). The acetal groups along the backbone have then been deprotected into alcohols under the previously reported experimental conditions (i: Ph_3CBF_4 ; ii: $NaBH_4$).[17] The disappearance of the peak at 3.95 ppm assigned to these acetal groups is witness to the quantitative deprotection (Figure 5).

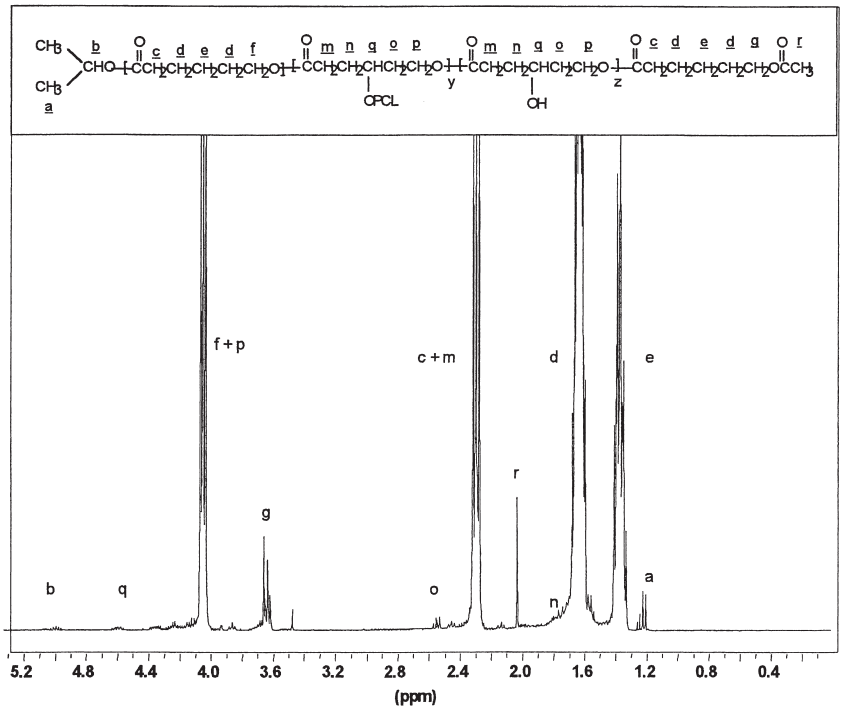


Figure 5 : ^{1}H NMR spectrum for the homo-graft copolymer after acetylation of the alcohol groups and deprotection of the acetal groups.

The further reaction of the alcohols with Et_3Al leads again to the formation of aluminum alkoxide, i.e., the initiator for the ROP of lactide used as the second monomer in toluene at 70 °C. The experimental conversion of lactide has been measured by ^{1}H NMR from the relative intensity of the peaks for the monomer at 5.0 ppm and for the P(D,L)LA grafts at 5.1 ppm (Figure 6).

The SEC chromatogram shows some shift toward lower elution volume ($M_{n,SEC}$=6,000), and the molecular weight distribution is somewhat increased (M_W / M_n =1,5) (Figure 2). As expected, the total $M_{n,NMR}$ has increased (32,000) as shown by the peaks at 5.1 ppm from P(D,L)LA and at 1.2 ppm for the isopropyl end-groups (Figure 6). Assuming again that the alcohol pendant groups have been quantitatively converted into alkoxides, a number-average molecular weight of 3,000 can be calculated for the P(D,L)LA grafts.

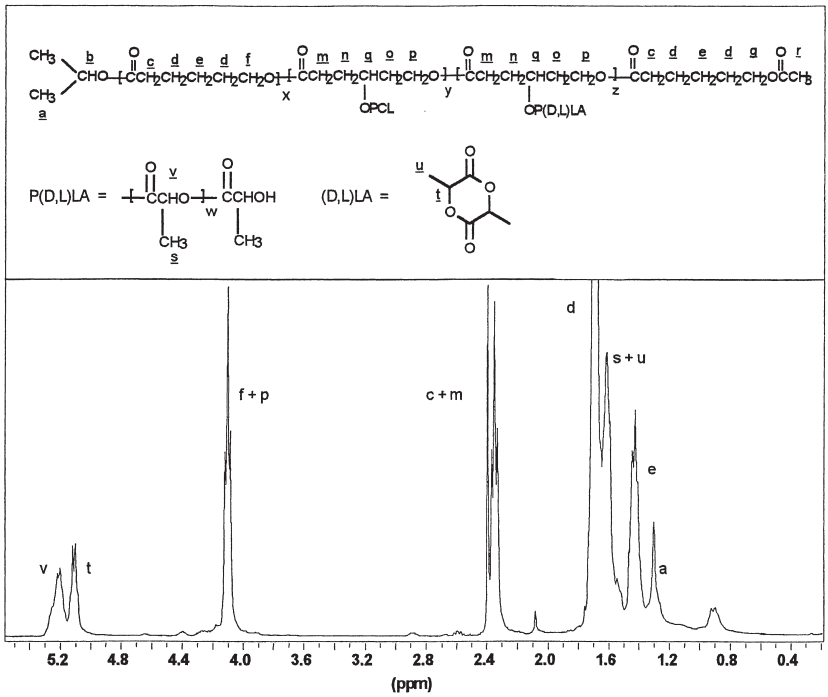


Figure 6 : ^{1}H NMR spectrum for the hetero-graft copolyester.

Conclusion

ε-CL has been copolymerized with two derivatives substituted by two differently protected hydroxyl groups, TOSUO and TeSCL. The sequential deprotection of the TeSCL comonomer units followed by the deprotection of the TOSUO units is a valuable strategy to prepare hetero-graft polyesters containing e.g. PCL and PLA grafts. Indeed, the hydroxyl groups which are released in this sequential fashion are converted into aluminum alkoxides, i. e., efficient initiators for the ROP of cyclic esters or diesters.

The one-step hydrolysis of the pendant triethyl silanolate groups is efficient and selective in the presence of the acetal protecting groups and compatible with the stability of the polyester backbone. Therefore, the use of TeSCL rather than TOSUO as protected hydroxyl containing monomer is more advantageous, since the conversion of TOSUO units into the parent alcohol derivatives is a two-step reaction. A forthcoming paper will report on the contribution of TeSCL to the macromolecular engineering of aliphatic polyesters.

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