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SYNTHESIS OF NOVEL BIODEGRADABLE POLY(ESTER-ANHYDRIDE)S

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ABSTRACT

Poly(ε-caprolactone)s containing one and variable numbers of anhydride functions along the polymer backbone were synthesized and characterized. The inclusion of a single anhydride unit involved the coupling of monofunctional carboxylic acid-terminated prepolymers using diphenyl chlorophosphate. The prepolymers were produced using stannous octoate as catalyst and ethanol as the initiator, yielding monofunctional hydroxyl-terminated intermediates which were reacted with succinic anhydride in the presence of 1-methylimidazole. Diphenyl chlorophosphate was then added to a solution of the carboxylic acid-terminated prepolymer and triethylamine in 1,2-dichloroethane, and the reaction was carried out for 5 hours at room temperature to yield a polyester containing a single anhydride unit. The synthesis of polymers containing a variable number of anhydride linkages per chain was carried out in a similar manner using difunctional carboxylic acid-terminated prepolymers as chain-extending segments, and monofunctional carboxylic acid-terminated prepolymers as end-capping units. The difunctional hydroxyl-terminated poly(ε-caprolactone) prepolymers were produced using diethylene glycol as the initiator, and then reacted with succinic anhydride to form difunctional carboxylic acid-terminated prepolymers.

INTRODUCTION

Aliphatic polyesters have been widely used in the area of biomaterials for implantable drug delivery devices [1–3], sutures [4, 5], and general tissue supports [6, 7] after injury or surgery. The ester linkages in these aliphatic polyesters are hydrolytically and/or enzymatically labile and render the polymers degradable in aqueous media. The polyesters traditionally of greatest interest in the area of biomaterials are derived from lactide, glycolide, and ε-caprolactone monomers, with a fairly broad range of degradation profiles accessible through various termonomer combinations. However, in many cases it is desirable to produce unique degradation profiles outside of this range by incorporating functional units along the polymer backbone that are more readily or less readily degradable than ester functional units. Typically, more rapid initial degradation, or specific degradation profiles such as surface erosion, are desired, and in these cases anhydride linkages have been used instead of ester linkages along with hydrophobic modifications of the polymer chain to prevent bulk degradation [8].

Synthesis of various polyanhydrides for use in biomedical applications have been reported in the literature. Aromatic polyanhydrides have been prepared by first converting dibasic acids into mixed anhydrides by reaction with acetic anhydride, followed by melt polycondensation with elimination of acetic anhydride [9]. Langer and coworkers produced polyanhydrides at ambient temperature using a one-step polymerization with phosgene or diphosgene as the coupling agent [10]. Poly(anhydride-*co*-imides) have been synthesized and characterized extensively [11, 12]. Unsaturated poly(anhydrides) have been prepared to be used to form crosslinked networks [13]. Virtually all prior investigations of polyanhydrides have involved high molecular weight homopolymers and copolymers produced using condensation polymerization of monomeric dicarboxylic acids.

In the present work, polyesters containing one and variable numbers of anhydride functions along the polymer backbone were synthesized by the condensation polymerization of linear, aliphatic polyester prepolymers carrying terminal carboxylic acid groups. In these systems, the placement of the anhydride function along the polymer backbone was controlled by the molecular weight of the polyester prepolymer. Very mild reaction conditions were used for the formation of the anhydride linkages so as not to destroy the polyester backbone. Poly(ε-caprolactone) prepolymers were used to model the anhydride-forming, chain extension reaction due to the simplicity of their ^{13}C-NMR spectra and the fact that they have been characterized extensively with regard to end groups and initiator residues using gated decoupling ^{13}C-NMR [14]. ^{13}C-NMR and FT-IR were used to confirm the presence of a single anhydride functional group in the interior of the poly(ε-caprolactone) chain and along the polymer backbone in the poly(ester-anhydrides) containing a variable number of anhydride units. In addition, gel permeation chromatography was used to monitor the relative molecular weights of the carboxylic acid-terminated prepolymers and their anhydride-containing polycondensates.

EXPERIMENTAL

Materials

The following reagents were used without further purification: chloroform-*d* (99.8 atom%, 1% TMS) (Aldrich), ε-caprolactone (Union Carbide), 1,2-dichlo-

roethane (DCE) (Aldrich), diethylene glycol, 99% (DEG) (Aldrich), diphenyl chlorophosphate, 99% (DPCP) (Aldrich), ethanol (EtOH), 100% (AAPER Alcohol and Chemical Co.), hexanes (Fisher), hydrochloric acid (HCl) (Fisher), magnesium sulfate (Fisher), methylene chloride (Fisher), 1-methylimidazole 99+% (NMIM) (Aldrich), sodium sulfate (Fisher), stannous 2-ethylhexanoate (stannous octoate) (Sigma), succinic anhydride 97% (Aldrich), tetrahydrofuran (THF) (Fisher), and triethylamine, 99% (TEA) (Aldrich).

Hydroxyl-Terminated Polyesters

Polymerizations of ε-caprolactone (20–40 g) were carried out in the bulk under nitrogen using stannous octoate as catalyst at a concentration of 1.4×10^{-4} mole per mole of monomer. Glassware was dried at 145–155°C for 24 hours, fitted with rubber septa, and cooled under a flow of dry nitrogen. Table 1 lists the initiator, monomer/initiator ratio, and reaction time and temperature for each polymerization. In Table 1 and throughout this paper, specific polymer samples are designated by two numbers separated by a hyphen; the first number (bold) indicates the generic type of polymer, and the second number is the sequential sample number. When reference is made to a generic type of polymer, only the bold, first number is used. Type **1** polymers are monohydric poly(ε-caprolactone)s initiated with ethanol; type **4** polymers are dihydric poly(ε-caprolactone)s initiated with the diethylene glycol.

A typical polymerization procedure was as follows: to a 250-mL boiling flask were added ε-caprolactone (32.43 g, 2.84×10^{-1} mole), ethanol (3.29 g, 7.14×10^{-2} mole), and stannous octoate (0.02 g). The flask was purged with nitrogen, sealed with a ground-glass stopper wrapped with Teflon tape, and placed in an oil bath for 5 hours at 65°C followed by 15 hours at 115°C. The polymerization was quenched by chilling the flask in an ice-water bath, and the polymer was dissolved in methylene chloride 25–35% (w/v), followed by precipitation into a tenfold excess of stirred hexanes. The hexanes layer was decanted, and the polymer was washed with hexanes (3 × 100 mL). The isolated polymer was then redissolved, transferred to a specimen jar, dried for 24 hours in an 80°C oven, and then for 24–48 hours at 80°C in vacuo.

TABLE 1. Initiator, Monomer/Initiator Ratio, and Reaction Time and Temperature for ε-Caprolactone Polymerizations

Sample	Initiator [I]	[M]/[I]	Temperature, °C	Reaction time, hours
1-1	EtOH	8	65	5
			115	15
1-2	EtOH	10	65	5
			115	15
1-3	EtOH	17	65	5
			115	15
4-1	DEG	8	135	20

Carboxylic Acid-Terminated Polyesters

The hydroxyl end groups of poly(ε-caprolactone)s were converted to carboxylic acid end groups by reaction with succinic anhydride. Type **2** polymers were derived from ethanol-initiated, type **1** polymers and carry one carboxylic acid end group; type **5** polymers were derived from diethylene glycol-initiated, type **4** polymers and carry two carboxylic acid end groups. A typical procedure was as follows: to a 250-mL boiling flask equipped with a condenser, hot oil bath, magnetic stirrer, and nitrogen purge were added ethanol-initiated poly(ε-caprolactone) (11.28 g, 2.26 $\times 10^{-2}$ eq), succinic anhydride (3.39 g, 3.38 $\times 10^{-2}$ mole), 1,2-dichloroethane (250 mL), and 1-methylimidazole (1.27 mL). The reaction mixture was heated for 15 hours at 65–70°C. After cooling, the solution was transferred to a separatory funnel and washed with 10% aqueous HCl (2 $\times$ 200 mL) and water (3 $\times$ 250 mL). The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure.

Poly(Ester-Anhydrides) (Single Anhydride Function)

Anhydride formation was carried out using a modification of the procedure of Mestres and Palomo [15]. Diphenyl chlorophosphate (0.22 mL, 1.07 $\times 10^{-3}$ mole), at 25°C, was added to a 250-mL boiling flask containig a solution of EtOH-initiated, carboxylic acid-terminated poly(ε-caprolactone) (2.35 g, 2.15 $\times 10^{-3}$ eq) and triethylamine (0.30 mL, 2.15 $\times 10^{-3}$ mole) in DCE (15 mL) at 0°C. The mixture was allowed to warm to room temperature and was stirred for 5 hours. The solution was then washed with cold water (3 $\times$ 100 mL), and the organic layer was separated and dried over sodium sulfate. Solvent was removed under reduced pressure, and the product was stored in a freezer. The reaction was also carried out by the addition of a solution of prepolymer and TEA to a solution of DPCP.

Poly(Ester-Anhydrides) (Variable Number of Anhydride Functions)

A solution of EtOH-initiated, carboxylic acid-terminated poly(ε-caprolactone) (1.75 g, 1.75 $\times 10^{-3}$ eq) and TEA (0.24 mL, 1.75 $\times 10^{-3}$ mole) in DCE (25 mL) was added slowly to a 250-mL boiling flask containing a solution of DPCP (0.36 mL, 1.75 $\times 10^{-3}$ eq) in DCE (15 mL) at 0°C. To a separate 250-mL boiling flask containing a solution of DPCP (0.73 mL, 3.50 $\times 10^{-3}$ eq) in DCE (15 mL) at 0°C was slowly added a solution of DEG-initiated, carboxylic acid-terminated poly(ε-caprolactone) (5.65 g, 8.76 $\times 10^{-3}$ eq) and TEA (1.22 mL, 8.76 $\times 10^{-3}$ mole) in DCE (25 mL). Both mixtures were stirred at room temperature for 1 hour, at which time they were rechilled to 0°C and mixed together by pouring the solution of the difunctional polymer into that of the monofunctional polymer. The resulting mixture was allowed to warm to room temperature and stirred for 5 hours. The final solution was then washed with cold water (3 $\times$ 150 mL), and the organic layer was separated and dried over sodium sulfate. Solvent was removed under reduced pressure and the product was stored in a freezer.

Measurements

^{13}C-NMR spectra of the model polymers were obtained on a Bruker AC-200 spectrometer using 5 mm o.d. tubes. Sample concentrations were approximately 25% (w/v) in chloroform-*d* containing 1% TMS as an internal reference. FT-IR

spectra were obtained on a Perkin-Elmer 1600 Series FT-IR spectrometer. Polymer samples were cast as thin films from 0.5% (w/v) methylene chloride solutions on sodium chloride plates and analyzed.

Gel permeation chromatography was used to determine relative molecular weights and polydispersities, M_w/M_n, of the polymer samples with respect to polystyrene standards (Polysciences Corporation). Sample concentrations were approximately 0.5% (w/v) in distilled THF.

RESULTS AND DISCUSSION

A poly(ester-anhydride) containing a single anhydride function within the interior of an otherwise all-polyester backbone has been synthesized. Poly(ε-caprolactone) was used as a model polyester backbone due to the simplicity of its ^{13}C-NMR spectrum and the availability of extensive analysis of its end groups [14]. Figure 1(a) depicts the initial step in the overall synthesis in which ethanol was used to initiate the polymerization of ε-caprolactone in the presence of stannous octoate to produce monohydric poly(ε-caprolactone) (**1**). The polymerization temperature was kept low initially to eliminate evaporation of ethanol, thus producing poly(ε-caprolactone) with the correct target molecular weight. The next step shown in Fig. 1(b) involved the reaction of the single hydroxyl group of **1** with succinic anhydride in the presence of NMIM to form the carboxylic acid-terminated prepolymer (**2**). It was necessary to convert the end group from hydroxyl to carboxylic acid in preparation for the coupling reaction to form an anhydride. Lastly, Fig. 1(c) shows the anhydride formation reaction which involved the reaction of **2** (1 eq carboxylic acid) with 0.5 mole of diphenyl chlorophosphate (0.5 eq phosphoroyl chloride) to produce the corresponding anhydride-containing polymer (**3**). The DPCP reagent, at room temperature, was added to a solution of **2** and TEA in DCE which was initially at 0°C; upon mixing the reaction was allowed to warm to ambient temperature for the balance of the reaction. These mild conditions for anhydride formation proved to be suitable for reaction with polyesters.

Figures 2 and 3 show the changes in the ^{13}C-NMR spectra during anhydride formation for the carbonyl, and ε-, α-, and δ-carbon regions, respectively, of the poly(ε-caprolactone) repeat unit. Figure 2(a) depicts the carbonyl carbon region of monohydric poly(ε-caprolactone) (**1**). The more intense signal at 173.3 ppm (a) was assigned to the main-chain carbonyl carbons, and the companion signal at 173.5 ppm (b) was attributed to the terminal carbonyl carbon nearest to the hydroxyl end group. These assignments are typical for hydroxyl-terminated poly(ε-caprolactone) [14]. Surprisingly, the carbonyl carbon adjacent to the terminal ethanol group was indistinguishable from the main-chain carbonyl carbons. Figure 2(b) depicts the carbonyl region of the carboxylic acid-terminated prepolymer (**2**) which resulted from endcapping of the hydroxyl-terminated prepolymer with succinic anhydride. The signal for the main-chain carbonyl carbons (a) remained at 173.3 ppm; however, it was no longer accompanied by a separate resonance due to the carbonyl carbon nearest to the hydroxyl end of the chain. Instead, two new signals appeared which are characteristic of the carbonyl carbons of the succinic acid moiety. The upfield signal at 171.9 ppm (c) was attributed to the carbonyl carbon adjacent to the terminal ε-caprolactone repeat unit, and the downfield signal at 176.0 ppm (d)

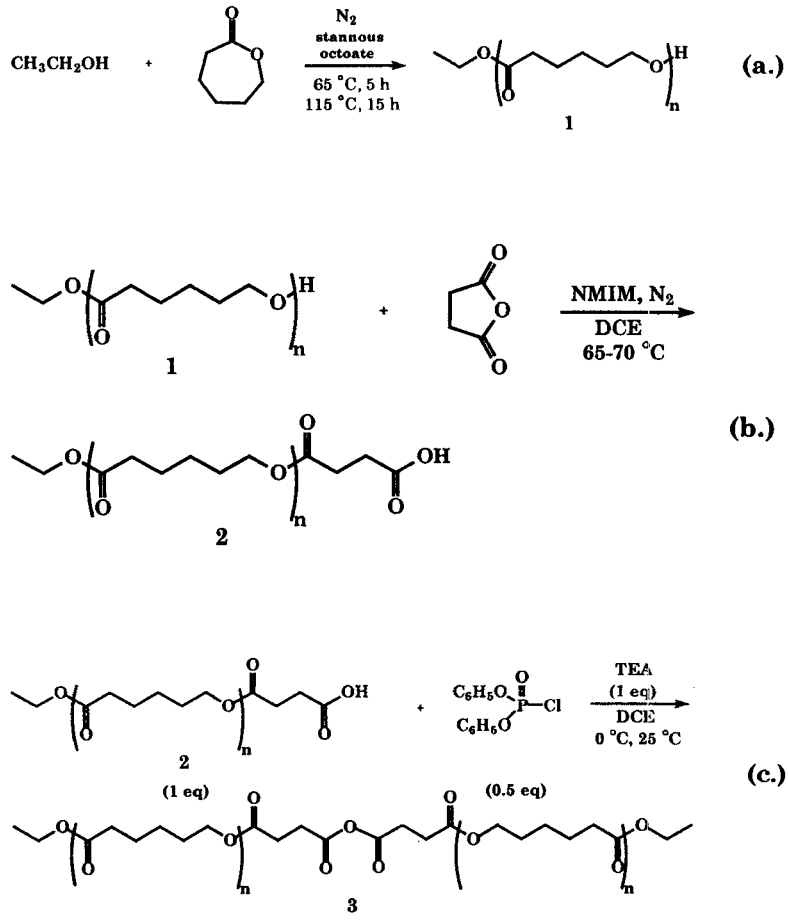

FIG. 1. Reaction schemes for (a) ethanol-initiated polymerization of ε-caprolactone, (b) succinic acid termination of ethanol-initiated poly(ε-caprolactone), and (c) reaction of succinic acid-terminated poly(ε-caprolactone) with diphenyl chlorophosphate.

was assigned to the carbonyl carbon of the carboxylic acid end group. Lastly, Fig. 2(c) depicts the carbonyl region of poly(ε-caprolactone) containing a single anhydride unit (**3**). Again, the signal for the main-chain carbonyl carbons remained virtually unchanged at 173.2 ppm (a). However, the signal for the carbonyl carbon adjacent to the terminal ε-caprolactone moiety shifted 0.5 ppm to 171.4 ppm (c), and this shift is consistent with the loss of hydrogen bonding with the terminal carboxylic acid proton. The most significant shift was displayed by the carbonyl carbon of the acid end group, from 176.0 to 167.7 ppm (d) upon formation of the anhydride functional group. This large upfield shift is characteristic for the conversion of acid carbonyl to anhydride carbonyl groups, and is partially due to the elimination of any hydrogen bonding effects.

Figure 3 shows ^{13}C-NMR spectra of the ε-, α-, and δ-carbon regions of poly(ε-caprolactone)-based prepolymers **1**, **2**, and **3**. The characteristic ε-, α-, and δ-carbon

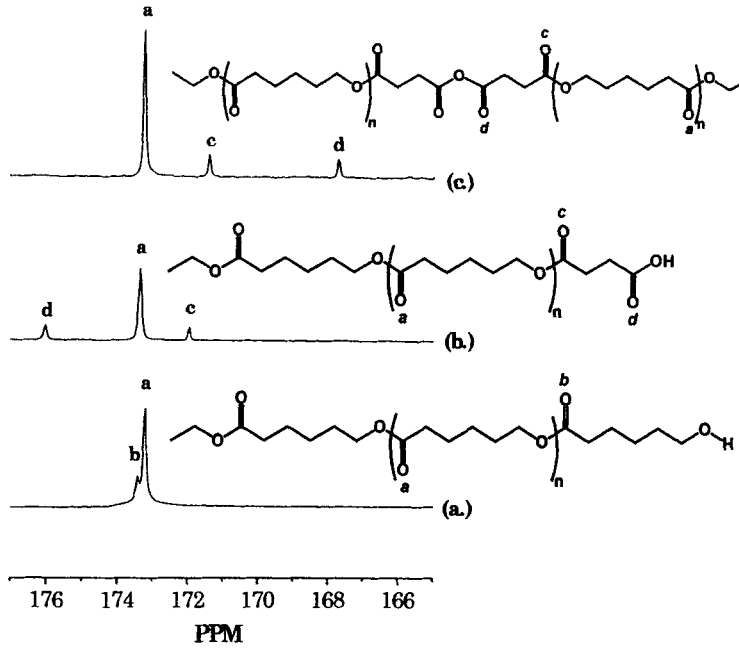

FIG. 2. ^{13}C-NMR spectra of the carbonyl region for (a) ethanol-initiated, hydroxyl-terminated poly(ε-caprolactone), (b) carboxylic acid-terminated poly(ε-caprolactone), and (c) poly(ε-caprolactone) containing a single anhydride function.

main-chain resonances of poly(ε-caprolactone) are located at 63.9, 33.8, and 28.1 ppm, respectively, and do not change significantly from one prepolymer to the next. The signal at 60.0 ppm (a) for all prepolymers was ascribed to the methylene carbon of the ethanol initiator. The carbon resonances of greatest importance are the end group resonances for the ε- and δ-carbons because they offer the most information about reaction at the polymer chain end. Figure 3(a) depicts the ^{13}C-NMR spectrum of prepolymer **1**. Characteristic hydroxyl end group resonances (ε^{OH}) and (δ^{OH}) are visible at 62.0 and 32.0 ppm, respectively, as described previously [14]. In the spectrum of the carboxylic acid-terminated prepolymer (**2**), Fig. 3(b), the ε^{OH}-carbon peak has disappeared and a new resonance (ε′) has appeared at 64.3 ppm. The ε′ resonance is due to the carbon, formerly adjacent to the hydroxyl group, which is adjacent to the newly formed ester function. This 2.3 ppm downfield shift is consistent with esterification of the terminal hydroxyl group. The spectrum also shows two new carbon resonances at 28.6 ppm (b) and 28.7 ppm (c), which were ascribed to the succinyl methylene carbons of the terminal succinic acid moiety. The downfield resonance (c) was logically assigned to the methylene carbon adjacent to the carboxylic acid group. The δ^{OH}-carbon signal disappeared upon succinic acid termination, presumably becoming indistinguishable from that of the main-chain δ-carbons. Thus, addition of the succinic acid moiety to the chain end replaces the hydroxyl group with an ester group and causes the adjacent ε-carbons, and especially δ-carbons, to become more chemically similar to their main-chain counterparts. Finally, Fig. 3(c) depicts the ^{13}C-NMR spectrum of the anhydride-containing poly-

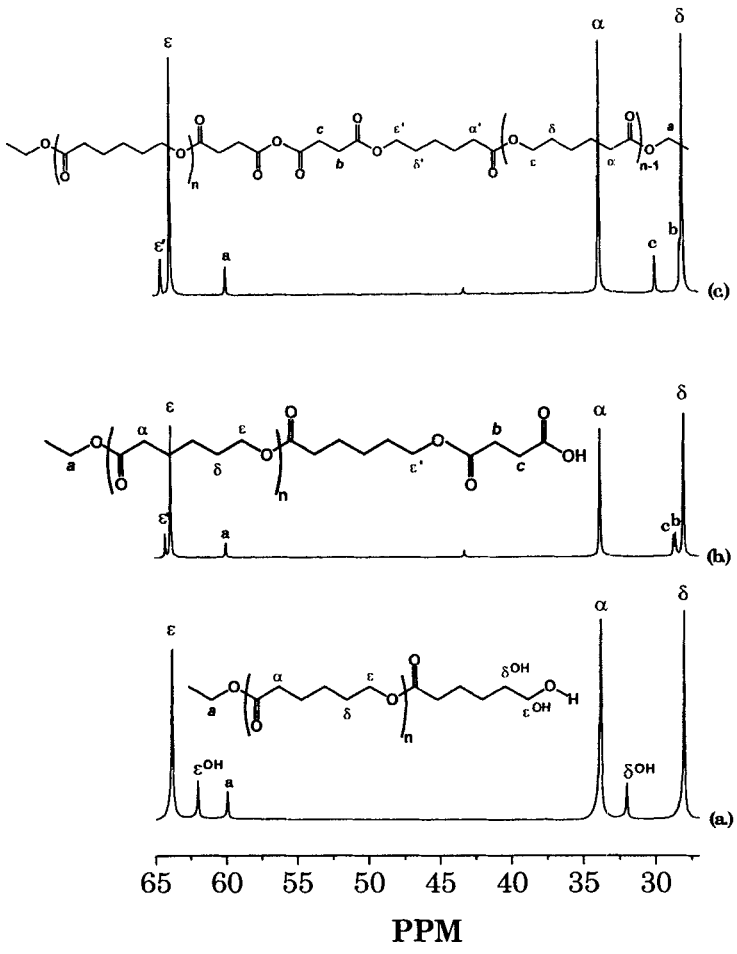

FIG. 3. ^{13}C-NMR spectra of the ε, α, and δ regions for (a) ethanol-initiated, hydroxyl-terminated poly(ε-caprolactone), (b) carboxylic acid-terminated poly(ε-caprolactone), and (c) poly(ε-caprolactone) containing a single anhydride function.

mer (3). The succinyl methylene carbon farther from the anhydride linkage was observed at 28.2 ppm (b), reflecting a 0.4 ppm upfield shift, and the one closer to the anhydride linkage at 30.0 ppm (c), representing a downfield shift of 0.3 ppm. The ε′ signal at 64.5 ppm was shifted slightly downfield from its previous position of 64.3 ppm, which was attributed to the loss of cyclic hydrogen bonding upon anhydride formation.

FT-IR spectroscopy was also very useful in confirming the presence of an anhydride function in the interior of the poly(ε-caprolactone) backbone. Figures 4(a) and 4(b) depict prepolymers **2** and **3**, respectively. The most signficant evidence for anhydride formation is the appearance in spectrum (b) of a new carbonyl stretch at 1823 cm^{-1}, indicative of an anhydride carbonyl group.

Gel permeation chromatography (GPC) provided further compelling evidence for anhydride formation. GPC was used to monitor the relative number-average

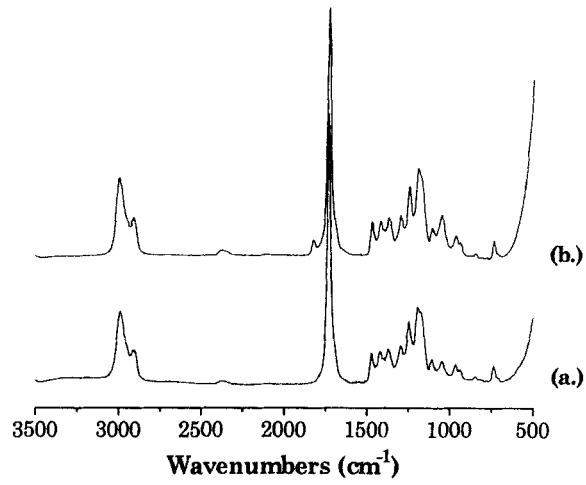

FIG. 4. FT-IR spectra for (a) carboxylic acid-terminated poly(ε-caprolactone) and (b) poly(ε-caprolactone) containing a single anhydride function.

molecular weights (M_n) and molecular weight distributions (MWD) of the poly(ε-caprolactone) prepolymers. Table 2 lists the GPC data for all carboxylic acid-terminated prepolymers and their anhydride containing analogues. Figure 5 depicts the chromatograms of a monofunctional carboxylic acid-terminated poly(ε-caprolactone) (**2**-1), its anhydride-coupled product (**3**-1), and the latter polymer after being hydrolyzed for 72 hours in buffered saline solution at 37°C (**3**-1-D). The M_n

TABLE 2. Molecular Weights and Molecular Weight Distributions for Carboxylic Acid-Terminated Polymers and Their Anhydride-Containing Analogues

Sample	M_n	MWD
1-3	2,400	1.71
2-1	1,200	1.22
2-2	1,500	1.28
5-1	1,600	1.33
3-1	2,000	1.25
3-2	3,000	1.27
6-1	4,700	2.33
1-3-D[a]	2,600	1.59
3-1-D	1,100	1.37
3-2-D	1,400	1.41
6-1-D	1,600	1.40

[a]D = degraded for 72 hours at 37°C in buffered saline solution.

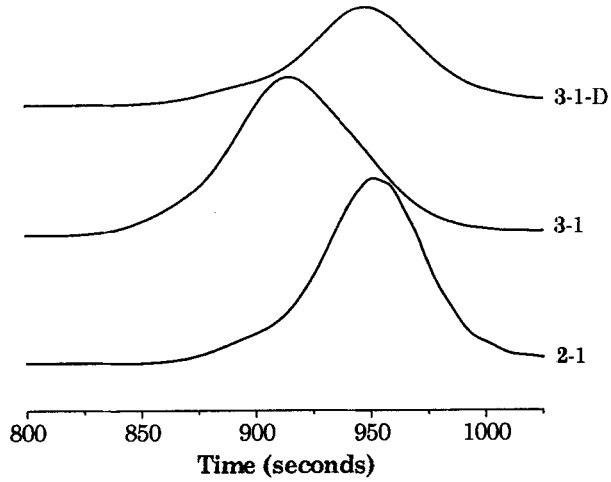

FIG. 5. Gel permeation chromatograms for carboxylic acid-terminated poly(ε-caprolactone) (2-1), poly(ε-caprolactone) containing a single anhydride function (3-1), and poly(ester-anhydride) after degradation in 37°C buffered saline solution for 72 hours (3-1-D).

for 2-1 relative to poly(styrene) standards was 1200 g/mol, with MWD = 1.22. Upon coupling of 2-1 via anhydride formation to form 3-1, GPC analysis yielded M_n = 2000 g/mol and MWD = 1.25. The fact that the M_n nearly doubled offers strong evidence for the success of the anhydride-forming reaction. Upon degradation of 3-1 in buffered saline for 72 hours at 37°C, GPC analysis indicated M_n = 1100 g/mol and MWD = 1.37, showing that the polymer had completely degraded back to its original carboxylic acid-terminated analogue, with only a slight broadening of the MWD. As expected, the poly(ε-caprolactone) backbone remained intact due to its stability in buffer solution over short periods of time. The anhydride reaction was repeated using a different monofunctional carboxylic acid-terminated prepolymer (2-2) and a change in the order of addition of reactants in the reaction procedure. In this case, a solution of 2-2 (M_n = 1500 g/mol and MWD = 1.28) and TEA was added to a solution of DPCP, instead of the reverse. This change in protocol yielded an anhydride-coupled product (3-2) with a number-average molecular weight exactly equal to theoretical (M_n = 3000 g/mol and MWD = 1.27). After 3-2 was subjected to a 37°C buffered saline solution for 72 hours (3-2-D), the resulting M_n was 1400 g/mol (MWD = 1.41).

In order to verify that none of the degradation of 3-2 was contributed by poly(ε-caprolactone) main-chain degradation, an ethanol-initiated hydroxyl-terminated poly(ε-caprolactone) (M_n = 2400 g/mol and MWD = 1.71) (1-3) was subjected to a 37°C buffered saline solution for 72 hours (1-3-D). As can be seen by the GPC traces in Fig. 6, it is apparent that no degradation of poly(ε-caprolactone) occurred in the time frame of the degradation experiment.

A chain-extended poly(ester-anhydride) containing a variable number of anhydride units along the polymer backbone was synthesized following the reaction scheme shown in Fig. 7. The molar ratio, $2/n$, of EtOH-initiated, monofunctional

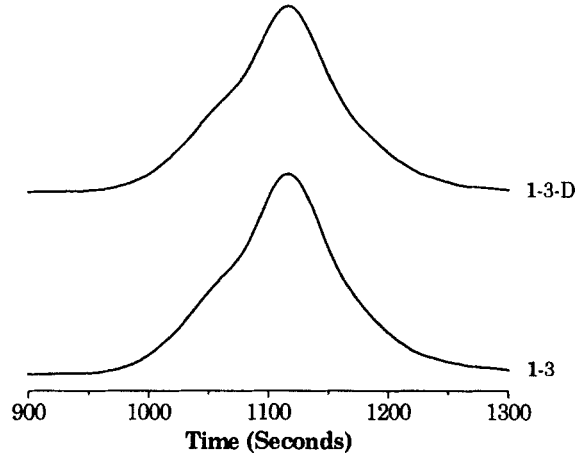

FIG. 6. Gel permeation chromatograms for ethanol-initiated, hydroxyl-terminated poly(ε-caprolactone) (1-3) and ethanol-initiated, hydroxyl-terminated poly(ε-caprolactone) after degradation in 37°C buffered saline solution for 72 hours (1-3-D).

carboxylic acid-terminated poly(ε-caprolactone) (2) to DEG-initiated, difunctional carboxylic acid-terminated poly(ε-caprolactone) (5) determined the average number of anhydride units per chain, $n + 1$. The polymer produced, with $n = 5$, was analyzed extensively using ^{13}C-NMR. Figures 8, 9, and 10 show the ^{13}C-NMR spectra of the carbonyl region, the ε region, and the α and δ regions, respectively, of the prepolymers and the chain-extended product. Figure 8(a) shows the carbonyl carbon region for DEG-initiated, carboxylic acid-terminated poly(ε-caprolactone) (5). Figure 8(b) shows the EtOH-initiated prepolymer (2), which was discussed in detail earlier in Fig. 2(b). The only difference in the two spectra is that 5 shows a resonance (a), slightly upfield from the main-chain carbonyl carbons, that is due

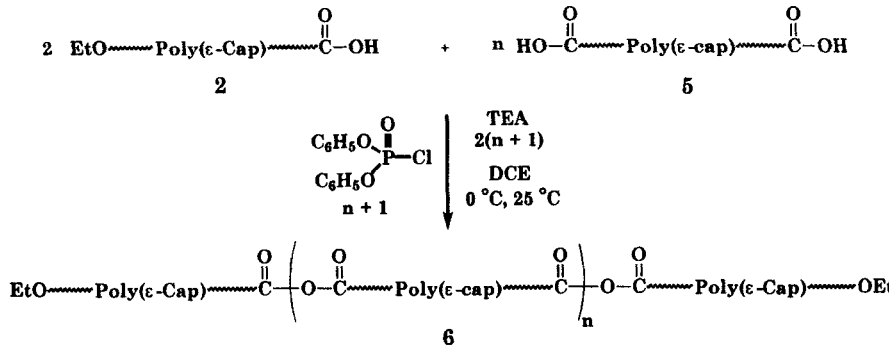

FIG. 7. Reaction of monofunctional carboxylic acid-terminated poly(ε-caprolactone) (2) and difunctional carboxylic acid-terminated poly(ε-caprolactone) (5) with diphenyl chlorophosphate.

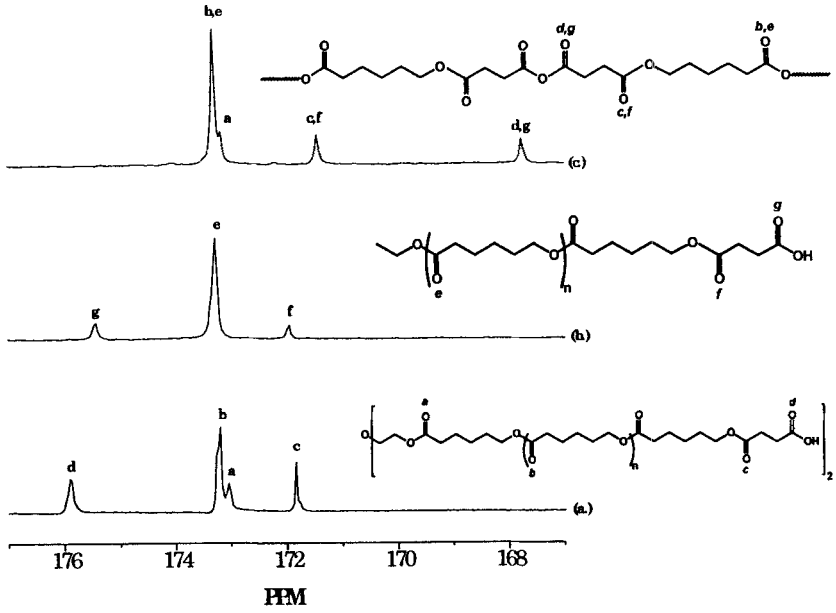

FIG. 8. ^{13}C-NMR spectra of the carbonyl region for (a) difunctional carboxylic acid-terminated poly(ε-caprolactone), (b) monofunctional carboxylic acid-terminated poly(ε-caprolactone), and (c) chain-extended poly(ester-anhydride).

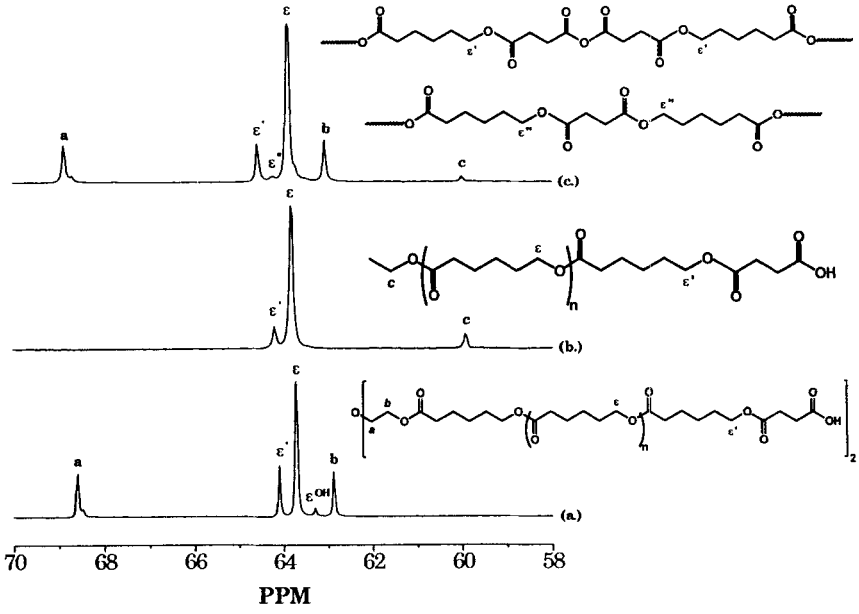

FIG. 9. ^{13}C-NMR spectra of the ε regions for (a) difunctional carboxylic acid-terminated poly(ε-caprolactone), (b) monofunctional carboxylic acid-terminated poly(ε-caprolactone), and (c) chain-extended poly(ester-anhydride).

to the carbonyl carbon nearest the DEG-initiator residue. Figure 8(c) shows the poly(ester-anhydride) product (**6**), and it is clear that the anhydride-forming reaction proceeded to a high extent. The carboxylic acid carbonyl carbons (d and g) have shifted far upfield, consistent with formation of the anhydride linkage. However, the presence of a barely discernible signal between 173.2 and 171.4 ppm indicates that a very small amount of chain extension occurred via the formation of ester linkages. The latter result from incomplete functionalization of the prepolymers (in this case the difunctional prepolymer **5**) with terminal succinic acid moieties. Small amounts of residual hydroxyl end groups readily react with carboxylic acid end groups in the presence of DPCP to form the observed ester linkages.

Figures 9(a), (b), and (c) depict changes occurring in the ε-carbon region during anhydride formation. Figure 9(a) shows signals at 68.6 ppm (a) and 62.9 ppm (b) which were attributed to the methylene units in the DEG initiator moiety in prepolymer **5**. The signals at 63.7 ppm (ε) and 64.1 ppm (ε′) were assigned to ε-carbons in the main-chain and adjacent to the terminal succinic acid moieties, respectively. The signal at 63.3 ppm (ε^{OH}) was attributed to the carbon adjacent to the residual hydroxyl end groups, indicating that the reaction with succinic anhydride was not totally quantitative for this particular prepolymer. The remainder of the assignments in Fig. 9(a) and all of the assignments in Fig. 9(b) are the same as given earlier in Fig. 3(b). Figure 9(c) depicts the ε-carbon region of the chain-extended poly(ester-anhydride) resulting from the reaction of **2** and **5**. The main-chain ε-carbons appear in their normal place at 63.9 ppm. The signals at 68.9 ppm (a) and 63.1 ppm (c), due to the methylene units of the DEG initiator moiety in **5**, showed virtually no change upon anhydride formation. Likewise, the signal at 59.9 ppm (c) that was assigned to the methylene unit of the ethanol initiator moiety in **2** showed essentially no change as well. The signal at 64.6 ppm was assigned to the ε′-carbons of both polymers **2** and **5** upon reaction to form the poly(ester-anhydride). The small signal at 64.4 ppm (ε″) was assigned to ε-carbons adjacent to succinic acid moieties that formed ester linkages with residual hydroxyl end groups in **5**.

Figures 10(a), (b), and (c) depict changes occurring in the α- and δ-carbon regions during anhydride formation. The major signals in Fig. 10(a), at 33.6 and 27.8 ppm, were assigned to the main-chain α- and δ-carbons of **5**. The signal at 33.5 ppm (α″) was assigned to the α-carbon adjacent to the DEG initiator moiety. The two signals at 28.6 ppm (b) and 28.4 ppm (a) were ascribed to the succinyl methylene carbons at the chain end of **5**. The assignments in Fig. 10(b) are identical to those given in Fig. 3(b). Upon chain extension, the α and δ main-chain signals at 33.9 and 28.1 ppm remained virtually unchanged as expected. The signal at 33.7 ppm (α″) for **5** also remained virtually unchanged. The signal at 30.0 ppm (b and d) was ascribed to the succinyl methylene carbons adjacent to the anhydride linkages; the signal at 28.3 ppm was assigned to the other succinyl methylene carbons. These assignments are identical to those given in Fig. 3(c). Additionally, in the 28–30 ppm region, a small signal (ε″) appears that was attributed to the succinyl methylene carbons of ester-linkages within the poly(ester-anhydride) product, found as a result of residual hydroxyl end groups in **5**.

Figure 11 depicts the GPC chromatograms for: monofunctional carboxylic acid-terminated poly(ε-caprolactone) (**2**-2), difunctional carboxylic acid-terminated poly(ε-caprolactone) (**5**-1), chain-extended poly(ester-anhydride) derived from the

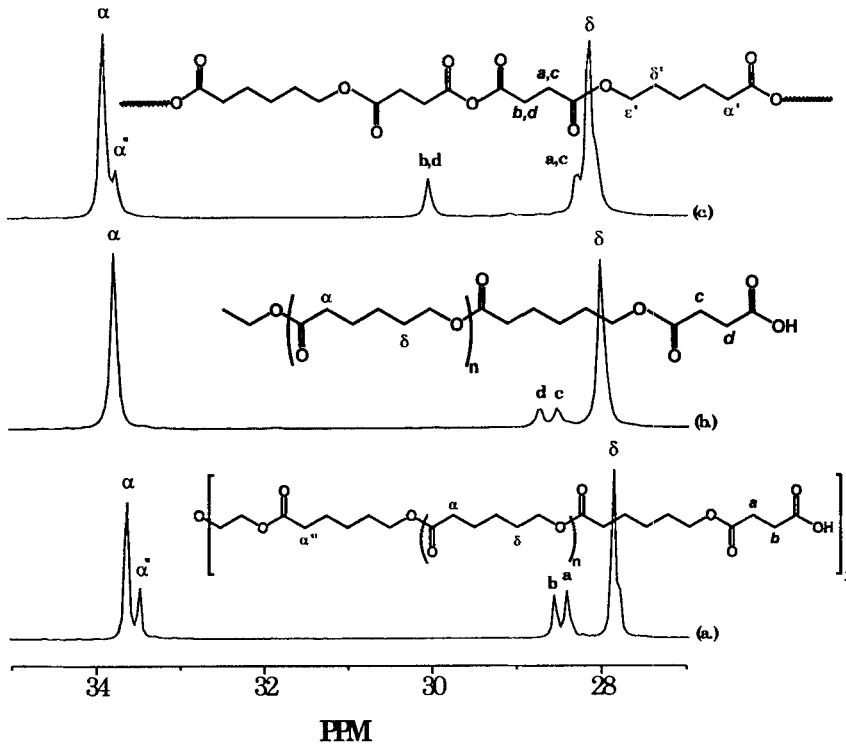

FIG. 10. ^{13}C-NMR spectra of the α and δ regions for (a) difunctional carboxylic acid-terminated poly(ε-caprolactone), (b) monofunctional carboxylic acid-terminated poly(ε-caprolactone), and (c) chain-extended poly(ester-anhydride).

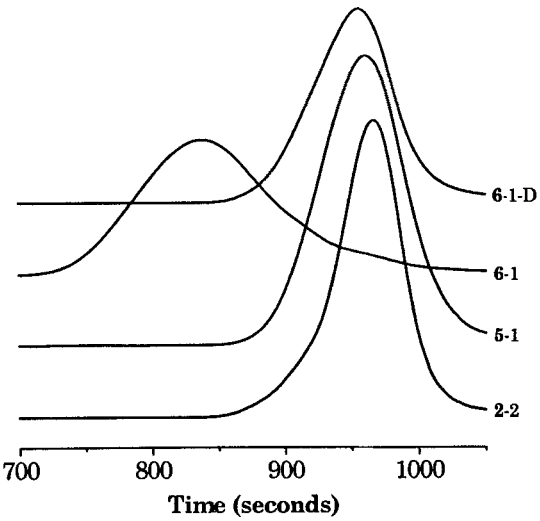

FIG. 11. Gel permeation chromatograms for monofunctional carboxylic acid-terminated poly(ε-caprolactone) (**2-2**), difunctional carboxylic acid-terminated poly(ε-caprolactone) (**5-1**), chain-extended poly(ester-anhydride) (**6-1**), and chain-extended poly(ester-anhydride) after degradation in 37°C buffered saline solution for 72 hours (**6-1-D**).

reaction of **2**-2 and **5**-1 in a molar ratio of 2:5 (**6**-1), and the latter poly(ester-anhydride) after being subjected to 37°C buffered saline solution for 72 hours (**6**-1-D), all of which are listed in Table 2. According to GPC, the M_n for **2**-2 was 1500 g/mol (MWD = 1.28), and the M_n for **5**-1 was 1600 g/mol (MWD = 1.33). Upon reaction of **2**-2 and **5**-1 in a molar ratio of 2:5, the M_n of the poly(ester-anhydride) was 4700 g/mol with MWD = 2.33. Clearly the molecular weight of the prepolymers has increased upon chain extension with DPCP, although not to the extent that was expected (theoretical 10,500 g/mol). In addition, the MWD was considerably broader than the MWDs of the reactants, as would be expected for a polycondensation reaction. Finally, Fig. 11 shows that the hydrolysis reaction produced a product (**6**-1-D) with a M_n of 1600 g/mol and a MWD of 1.40. This GPC data suggest a very rapid degradation of the anydride linkages in the poly(ester-anhydride) polymer. The ester-linked components discussed earlier are either in such small quantities that they are undetectable by GPC in the degraded polymer, or these ester linkages are more susceptible to hydrolysis than the main-chain poly(ε-caprolactone) backbone.

CONCLUSIONS

The complete synthesis of a low molecular weight poly(ε-caprolactone) containing a single anhydride function in the polymer chain interior was successfully demonstrated using ^{13}C-NMR, FT-IR, and GPC analysis. The synthesis was relatively simple, utilizing DPCP initially at 0°C and then at ambient temperature for the quantitative coupling of carboxylic acid-terminated poly(ε-caprolactone) prepolymers via anhydride linkages. GPC yielded the most convincing evidence of coupling, and it showed that the coupled product could be readily hydrolyzed to return the original prepolymers with all ester linkages essentially intact. Synthesis of chain-extended poly(ester-anhydrides) containing variable numbers of anhydride units was also confirmed spectroscopically and by GPC analysis. It was shown that a considerable, but less than theoretical, increase in molecular weight was achieved, and that the chain-extended poly(ester-anhydride) could also be degraded rapidly back to its prepolymer constituents.

This work demonstrates the general concept of degradable polymers that can be designed to display two-stage degradation profiles. The presence of the anhydride linkages allows a relatively rapid decrease in molecular weight, the extent of which is governed by the concentration of the anhydride linkages along the chain, followed by a slower degradation of the remaining oligomers, the rate of which is governed by the composition of original polyester prepolymers. These materials have potential applications in the area of controlled release and surgical devices.

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