Synthesis of Poly(ester-anhydride)s Based on Poly(ϵ-Caprolactone) Prepolymer

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ABSTRACT: The objective of this study was to prepare high molecular weight poly(ester-anhydride)s by melt polycondensation. The polymerization procedure consisted of the preparation of carboxylic acid terminated poly(ϵ-caprolactone) prepolymers that were melt polymerized to poly(ϵ-caprolactone)s containing anhydride functions along the polymer backbone. Poly(ϵ-caprolactone) prepolymers were prepared using either 1,4-butanediol or 4-(hydroxymethyl)benzoic acid as initiators, yielding hydroxyl-terminated intermediates that were then converted to carboxylic acid-terminated prepolymers by reaction with succinic anhydride. Prepolymers were then allowed to react with an excess of acetic anhydride, followed by subsequent polycondensation to resulting high molecular weight poly(ester-anhydride)s. Upon coupling of prepolymers, size exclusion chromatography analyses showed an increase from 3600 to 70,000 g/mol in number-average molecular weight (M_n) for the 1,4-butanediol initiated polymer, and an increase from 7200 to 68,000 g/mol for the 4-(hydroxymethyl)benzoic acid-initiated polymer. 4-Hydroxybenzoic acid and adipic acid were also used as initiators in the preparation of poly(ϵ-caprolactone) prepolymers. However, with these initiators, the results were not satisfactory. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 81: 176–185, 2001

Key words: poly(ϵ-caprolactone); poly(anhydride); poly(ester-anhydride)

INTRODUCTION

Polylactide, polyglycolide, and poly(ϵ-caprolactone) are widely studied biodegradable polymers that have hydrolytically labile ester linkages and display bulk erosion. Although the degradation kinetics of these bulk-eroding polymers can largely be modified by copolymerizing, unique degradation profiles could be achieved if part of the functional groups incorporated along the polymer backbone were more or less labile than ester linkages.

Poly(ϵ-caprolactone) is a semicrystalline polymer that fulfils many of the demands of a drug-release matrix: it is highly biocompatible, the melting temperature is low enough (~ 60 °C), and it is highly permeable for many drugs.[1] However, poly(ϵ-caprolactone) displays slow degradation kinetics and it is therefore most suitable for long-term drug-delivery systems.[1] The target of the current study was to prepare poly(ϵ-caprolactone)s containing anhydride linkages along the polymer backbone. Incorporation of anhydride linkages into the backbone of poly(ϵ-caprolactone) should have a considerable effect on the rate of degradation because hydrolysis of anhydride linkages is known to be more rapid than hydrolysis of ester linkages.

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The synthesis of poly(ϵ-caprolactone-anhydride)s has been reported by Storey and co-workers.[2] They prepared carboxylic acid-terminated prepolymers that were then converted to higher molecular weight poly(ester-anhydrides). The prepolymers were produced using ethanol or diethylene glycol as the initiators, yielding hydroxyl-terminated intermediates that were then reacted with succinic anhydride in the presence of 1-methylimidazole. The anhydride linkage formation was carried out in a solution of carboxylic acid-terminated prepolymer, diphenyl chlorophosphate, and triethylamine in 1,2-dichloroethane. The polymers displayed a two-stage degradation profile in which the decrease in molecular weight was governed by a very rapid degradation of anhydride linkages followed by a slower degradation of poly(ϵ-caprolactone) oligomers. Hence, it was concluded that the rate of degradation is dependent on the concentration of anhydride linkages and the composition of the original polyester prepolymer.

In their study, Storey and co-workers[2] used solution polymerization and they prepared only low molecular weight polymers. However, high molecular weights are essential if good mechanical properties are required. Because melt polycondensation is typically used in the polymerization of high molecular weight polyanhydrides, our interest was to investigate whether melt polycondensation can also be used in the preparation of high molecular weight poly(ϵ-caprolactone-anhydride)s.

Melt polycondensation involves carboxylic acid-terminated poly(ϵ-caprolactone) prepolymer. In the current study, two alternative methods for preparing prepolymers with carboxylic acid end groups were investigated. One route was to prepare hydroxyl-terminated prepolymer and then convert the hydroxyl end groups to carboxylic acid end groups via the reaction with succinic anhydride. Similar kinds of system have been used earlier to produce carboxylic acid-terminated poly(ethylene glycol)[3, 4] and poly(ϵ-caprolactone).[2] The reactions have been carried out in the presence of pyridine or 1-methylimidazole. An alternative method for preparing carboxylic acid-terminated prepolymer has been reported by Zhang and co-workers.[5] They used succinic acid as an initiator in the polymerization of poly(ϵ-caprolactone) at 225 °C. According to their results, it seems that polymerization is more difficult to control with this initiator and initiation is less effective than with initiators having hydroxyl end groups. However, acid initiators would allow a straightforward route to acid-terminated prepolymers, which is why this kind of initiation system is attractive.

Also, modification of the structure of the prepolymer using aromatic initiators was in our interest. This method should allow modification of the degradation rate of anhydride linkages because aromatic anhydride linkages are known to be more stable than aliphatic anhydride linkages.[6,7] To obtain aromatic anhydride linkages in our poly(ϵ-caprolactone-anhydride) system, 4-hydroxybenzoic acid and 4-(hydroxy-methyl)benzoic acid were used as initiators in the preparation of poly(ϵ-caprolactone) prepolymers.

EXPERIMENTAL

Materials

ϵ-Caprolactone (Solvay) was dried over molecular sieves and the following products were used without further treatment: Sn(II) octoate (Sigma), 1,4-butanediol (Fluka), 4-hydroxybenzoic acid (Fluka), 4-(hydroxymethyl)benzoic acid (Fluka), adipic acid (Merck), and acetic anhydride (Fluka). Chloroform stabilized with 1% ethanol (Riedel-de Haen) was used for determination of the molecular weights of prepolymers, and chloroform stabilized with 0.006% of amylene (Fluka) was used for determination of the molecular weights of polymers containing anhydride linkages. Chloroform-d_1 (Fluka), deuteration degree not less than 99.5%, was used for nuclear magnetic resonance (NMR) measurements.

Characterizations

Molecular weights (number-average molecular weight, M_n, and weight-average molecular weight, M_w) and molecular weight distribution (M_w/M_n) were determined with respect to polystyrene standards by size exclusion chromatography (SEC). The Waters Association system that was used was equipped with a Waters 700 Satellite wisp injector, a Waters 510 HPLC solvent pump, four linear PL gel columns (10^5, 10^4, 10^3, and 100 Å) connected in series and a Waters 410 differential refractometer. All samples were analyzed at room temperature. Chloroform was used as the eluent. The eluent was delivered at a flow rate of 1.0 mL/min. The samples were dissolved in chlo-

Table I Adipic Acid-Initiated Prepolymers, Polymerization at 160°C for 6 h

Polymer	ε-CL, mol %	AA, mol %	SnOct, mol %	M_n[a], g/mol	M_w[a], g/mol	Conversion, %
PCL-A 1	95	5	0.01	15,200	18,600	Low[c]
PCL-A 2	97.5	2.5	0.01	19,300	24,600	Low[c]
PCL-A 3	99	1	0.01	19,600	34,900	Low[c]
PCL-A 4	97.5	2.5	0.03	29,600	43,800	Low[c]
PCL-A 5	97.5	2.5	0.05	34,400	53,500	43[b]

[a] Determined by SEC.
[b] Determined by ^{1}H NMR.
[c] Indicated by a very high monomer peak at SEC slope.

roform at a concentration of 1.0% (w/v). The injection volume was 200 μL.

Proton decoupled ^{13}C NMR spectra with nuclear Overhauser effect (NOE) were obtained with a Varian Gemini 2000 300 MHz spectrometer working at 75.452 MHz. Sample concentrations in 5-mm tubes were 10% by weight in $CDCl_3$.

In hydrolysis analyses, rectangular test specimens (2 × 4 × 10 mm) were immersed in phosphate buffer solution of pH 7.0 at 37 °C. Test specimens were prepared by melt pressing at 70 °C. Before SEC analyses, test specimens were vacuum-dried for 2 days at 40 °C.

Synthesis

Adipic Acid-Initiated Prepolymers

An overview of the synthesized prepolymers is given in Table I. All the polymerizations were carried out in a 2.5-L batch reactor. The reactor was equipped with two intersecting blades that intermesh throughout the conical envelope of the bowl. The stirring rate was 60 rpm in all the polymerizations. The polymerization procedure was as follows: ε-caprolactone, adipic acid, and Sn(II) octoate were weighted into a reactor and the temperature was raised over a period of 0.5 h to 160 °C for 6 h. Polymerizations were carried out under a nitrogen atmosphere. After cooling, the physical appearance of the prepolymers varied between liquid and waxy solids.

1,4-Butanediol-Initiated Prepolymers

An overview of the 1,4-butanediol initiated prepolymers is given in Table II. The prepolymers were prepared in two steps. The first step was the preparation of hydroxyl-terminated prepolymers. In the second step, the terminal hydroxyl groups of the prepolymer were converted to carboxylic acid end groups via the reaction with succinic anhydride. Hydroxyl-terminated prepolymers were prepared as follows: 1,4-butanediol, ε-capro-

Table II Hydroxyl-Terminated Prepolymers Initiated by 1,4-Butanediol, 4-Hydroxybenzoic Acid, and 4-(Hydroxymethyl)benzoic Acid

Polymer	Initiator	Initiator, mol %	Polymer	M_{theor}, g/mol	M_n[a], g/mol	M_w[a], g/mol	M_{NMR}[c] g/mol
PCL-OH 6	1,4-BD	3	160°C/6 h	3800	5900	11,500	—[b]
PCL-OH 7	1,4-BD	5	160°C/6 h	2300	3600	6100	2500
PCL-OH 8	4-HBA	5	160°C/6 h	2300	13,800	37,000	—[b]
PCL-OH 9	4-HBA	10	180°C/6 h	1200	13,000	29,900	—[b]
PCL-OH 10	4-HBA	10	140°C/24 h	1200	17,700	40,100	—[b]
PCL-OH 11	4-HBA	5	200°C/6 h	2300	16,200	36,100	—[b]
PCL-OH 12	4-(HM)BA	3	160°C/6 h	3800	7200	13,500	3900

[a] Determined by SEC with respect to polystyrene standards.
[b] Not determined.
[c] Determined by ^{1}H NMR via the ratio of methylene proton peaks locating at 3.4 and 4.1 ppm.

lactone, and Sn(II) octoate (0.01 mole %) were weighted into a reactor and polymerization was carried out at 160 °C for 6 h. In the second step, the molar equivalent of succinic anhydride in relation to hydroxyl groups was added to the reactor and the reaction was continued for 1 h at 160 °C. The resulting prepolymers were used without purification.

4-Hydroxybenzoic Acid- and 4-(Hydroxymethyl)benzoic Acid-Initiated Prepolymers

The polymerizations are summarized in Table II. Sn(II) octoate (0.01 mol%), 4-hydroxybenzoic acid or 4-(hydroxymethyl)benzoic acid , and ϵ-caprolactone were weighted into a reactor and the temperature was raised to 140 °C for 24 h (PCL-OH 10), 160 °C for 6 h (PCL-OH 8, PCL-OH 12), 180 °C for 6 h (PCL-OH 9), or 200 °C for 6h (PCL-OH 11). To convert the terminal hydroxyl groups to carboxylic acid end groups, the molar equivalent of succinic anhydride in relation to hydroxyl groups of 4-hydroxybenzoic acid was added to the polymer melt and the reaction was then carried out for 1 h at 160 °C. The addition of succinic anhydride was carried out when the temperature of the polymer melt had reached the temperature of 160 °C if another polymerization temperature was used. The resulting prepolymers were used without purification.

Poly(ϵ-caprolactone-anhydride)s

The polymerizations were carried out in batch reactor equipped with a double helix agitator and distillation column. The "one-pot" procedure was used in polymerizations: 500 g of prepolymer was first refluxed for 1 h in 350 mL of acetic anhydride, a vacuum was then applied to remove acetic acid and the excess of acetic anhydride, and finally polymerization was continued under high vacuum (1 mbar) to remove the condensation product (acetic anhydride) evolved from anhydride linkage formation. To prevent the foaming of the reaction mixture, the applying of vacuum to 1 mbar was gradually done over a period of 45 min at 150 °C. The temperature was raised to 180 °C after applying of vacuum because the viscosity of the reaction mixture rapidly began to rise, indicating the formation of anhydride linkages. Polymerizations were then continued at 180 °C for 1 to 2 h, depending on how long the viscosity build-up continued. The increase in viscosity was monitored via the stirring torque. The final products were slightly yellowish, semicrystalline polymers with melting temperature of ~50 °C.

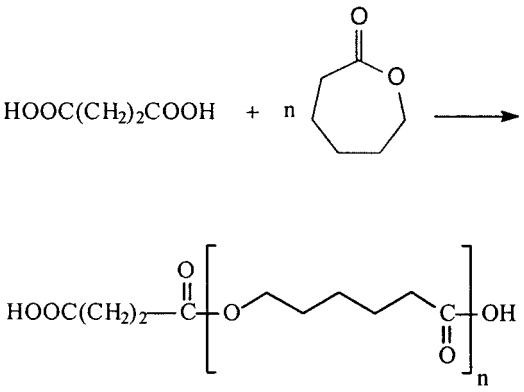

Figure 1 Reaction scheme for succinic acid initiated polymerization of ϵ-caprolactone.

RESULTS AND DISCUSSION

Polyanhydrides are most commonly prepared by the melt polycondensation technique. The dicarboxylic acid monomers are reacted with an excess of acetic anhydride to form acetyl-terminated anhydride prepolymers. The prepolymers then undergo melt polycondensation under vacuum. In our system, poly(ϵ-caprolactone) prepolymer bearing carboxylic acid terminal end groups was used instead of dicarboxylic acid monomers.

Prepolymer Synthesis

Zhang et al.[5] have studied the polymerization of ϵ-caprolactone in the presence of succinic acid. They reported that ϵ-caprolactone alone does not polymerize rapidly when heated to 220 °C for 1.5 h, but in the presence of succinic acid, ϵ-caprolactone can easily be polymerized under the same conditions. They proposed that the polymerization of ϵ-caprolactone in the presence of succinic acid can be described as shown in Figure 1.

To prepare poly(ϵ-caprolactone) prepolymer bearing carboxylic acid terminal end groups, we first tried the acid-initiator method that would allow a straightforward route to the desired prepolymer. In the polymerizations, Sn(II) octoate was used as a catalyst and adipic acid as an initiator. Because ϵ-caprolactone easily polymerizes at 160 °C with hydroxyl-containing initiators, the polymerization temperature of 160 °C was

used to compare the effectiveness of the acid-initiation method with the method using hydroxyl-containing initiators.

An overview of the polymerizations is shown in Table I. Prepolymers PCL-A 1, PCL-A 2, and PCL-A 3 remained in the liquid state after cooling. Because high monomer peaks at SEC slopes revealed that conversions were very low, the concentration of Sn(II) octoate was increased to 0.03 mol% in the polymerization of PCL-A 4 and to 0.05 mol% in the polymerization of PCL-A 5. With increasing catalyst concentration, more viscous reaction mixtures were obtained. However, conversions were still low because, after cooling, only a part of the reaction mixture turned to a waxy polymer whereas the rest remained in the liquid state. Quantitatively, the conversion of 43% was measured by ^{1}H NMR for the prepolymer PCL-A 5. The conversions of other prepolymers were not analyzed but, according to physical appearance and high monomer peaks at SEC slopes, they were obviously lower than for PCL-A 5.

According to the SEC results, solidified parts in the reaction mixture exhibited much higher molecular weights than they should have if all adipic acid molecules in the mixture had initiated the polymerization of ϵ-caprolactone. This result indicates, together with low conversions, that adipic acid does not initiate the polymerization effectively. Because the results of the acid-initiator method were very unsatisfactory, we did not investigate the method further.

The second synthetic route surveyed for the carboxylic acid-terminated prepolymer was basically similar to that of Storey et al.[2] First, ϵ-caprolactone was polymerized in the presence of Sn(II) octoate and hydroxyl-containing initiator. The terminal hydroxyl groups of the prepolymer were then converted to carboxylic acids in the reaction with succinic anhydride. The initiators that were used in the polymerizations were either 1,4-butanediol, 4-hydroxybenzoic acid, or 4-(hydroxymethyl)benzoic acid. The assumed reaction schemes of 1,4-butanediol and 4-hydroxybenzoic acid-initiated polymerizations are presented in Figure 2.

The results of the polymerizations are given in Table II. It is well known that hydroxyl-containing initiators allow variation in the molecular weight via the monomer/initiator ratio. The molecular weights of samples PCL-OH 6 and PCL-OH 7 were near the theoretical values. This result reveals that initiation is fast for 1,4-butanediol-initiated polymerization. Note that the difference between SEC and ^{1}H NMR results is due to calibration of SEC with respect to polystyrene standards. When 4-hydroxybenzoic acid was used as an initiator, the measured molecular weights were much higher than the theoretical values, suggesting that propagation is more rapid than initiation. The polymerization temperature did not affect the rate ratio of initiation to propagation because polymerizations carried out at 140, 160, 180, or 200 °C yielded all to the M_n of ~15,000 g/mol. Probably, the less nucleophilic nature of the aromatic hydroxyl group prevents the effective initiation. However, the initiator bearing one methylene group between the aromatic ring and hydroxyl group allowed more successful polymerization because polymerization initiated by 4-(hydroxymethyl)benzoic acid yielded a molecular weight near theoretical (PCL-OH 12). The result was predictable because benzyl alcohol has a similar hydroxyl group position and it has been used without problems as an initiator in the polymerization of lactide.[8]

The next step was to convert the terminal hydroxyl groups of prepolymers to carboxylic acids. The reaction of succinic anhydride with hydroxyl end groups has been used before to produce carboxylic acid-terminated poly(ethylene glycol)[3,4] and poly(ϵ-caprolactone).[2] The reactions have been carried out in solution in the presence of pyridine or 1-methylimidazole. To avoid several purification steps of the reported methods, we tried the method in which only the molar equivalent of succinic anhydride in relation to the hydroxyl groups was added to the polymer melt when the polymerization of hydroxyl-terminated poly(ϵ-caprolactone) intermediate was complete. The conversion reaction was then carried out at the polymerization temperature of 160 °C for 1 h. Figure 3a shows the ^{1}H NMR spectrum of the polymer before the addition of succinic anhydride and Figure 3b shows the spectrum after the reaction with succinic anhydride. The disappearance of hydroxyl peaks at 3.6 ppm and the appearance of new peaks at 2.6 ppm indicate the conversion of hydroxyl groups to carboxylic acids. ^{13}C NMR analyses also showed this reaction pathway to be promising because the spectrum of the sample prepared by this method was identical to carboxylic acid-terminated poly(ϵ-caprolactone) reported by Storey and co-workers.[2]

The simple reaction pathway was used for the preparation of prepolymers that were used in the subsequent melt polycondensations. In the syntheses, a small excess of succinic anhydride

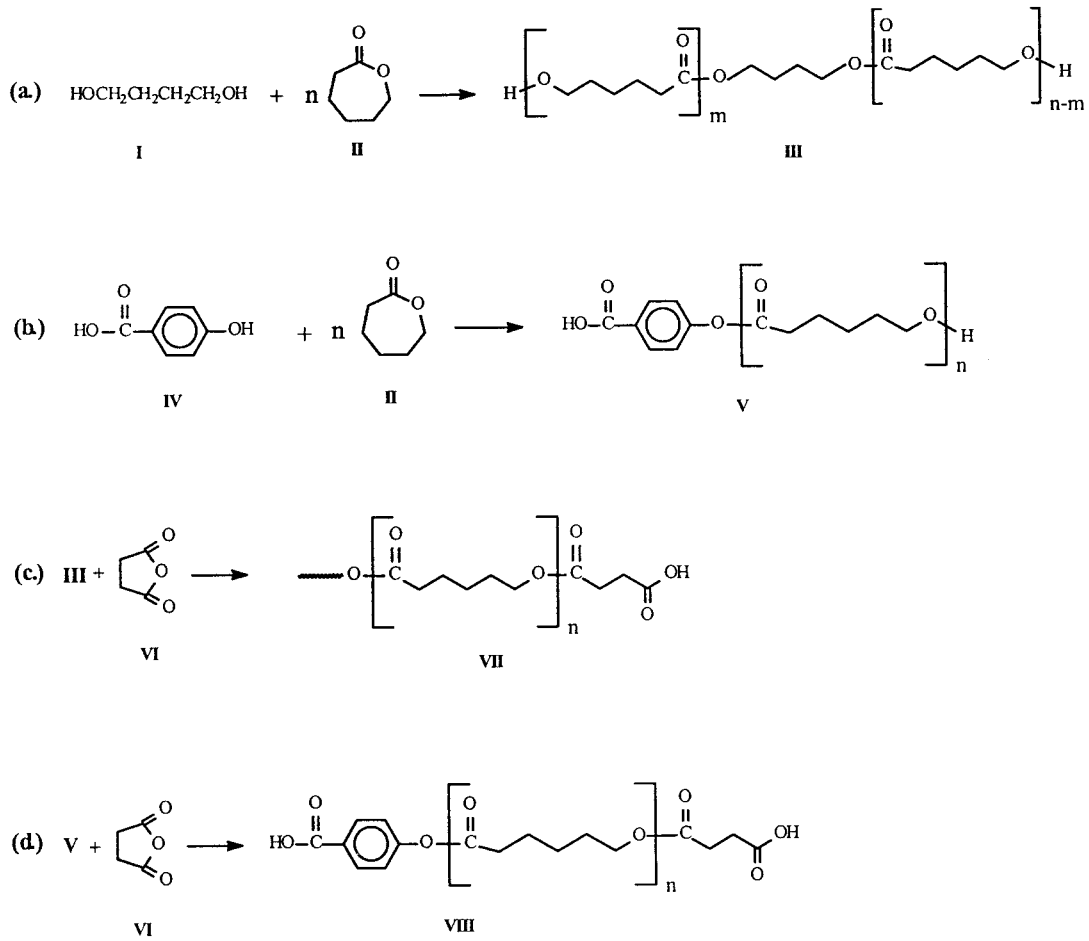

Figure 2 Reaction schemes for: (a) 1,4-butanediol-initiated polymerization of ϵ-caprolactone, (b) 4-hydroxybenzoic acid-initiated polymerization of ϵ-caprolactone, and (c) and (d) conversion of terminal hydroxyl groups to carboxylic acids.

(1.05:1 mole ratio of succinic anhydride to hydroxyl groups) was used to compensate for the loss of succinic anhydride via sublimation to the cover of the reactor. The resulting prepolymers were used without purification.

Preparation of Poly(ϵ-caprolactone-anhydride)s

The assumed reaction scheme of melt polycondensation for prepolymers initiated by 1,4-butanediol is shown in Figure 4. When high molecular weight polyanhydrides are prepared by melt polycondensation, the critical factors affecting polymer molecular weight are monomer purity, temperature of polymerization, time of reaction, and the removal of the condensation product.[9] In the synthesis of polyanhydrides, monomers are usually purified separately after refluxing in acetic anhydride. In purification, the excess of acetic anhydride is vaporized at mild temperature under vacuum. Monomers are then recrystallized, and traces of acetic anhydride are removed by extracting. In contrast to the typical system, we did not have the separate purification step, but, after refluxing, the excess of acetic anhydride was quickly removed at high temperature. The polycondensation step then followed immediately after the removal of excess acetic anhydride. The simplification of polymerization procedure was tried for two reasons. First, we believed that the separate purification step is mainly needed to decrease undesirable oligomerization of monomers during the removal of the excess acetic anhydride. Polyanhydrides are often copolymers, and oligomerization of monomers may cause blockiness or other undesired properties in the resulting copolyanhydride.[9] In our case, the formation of anhydride linkages before the polycon-

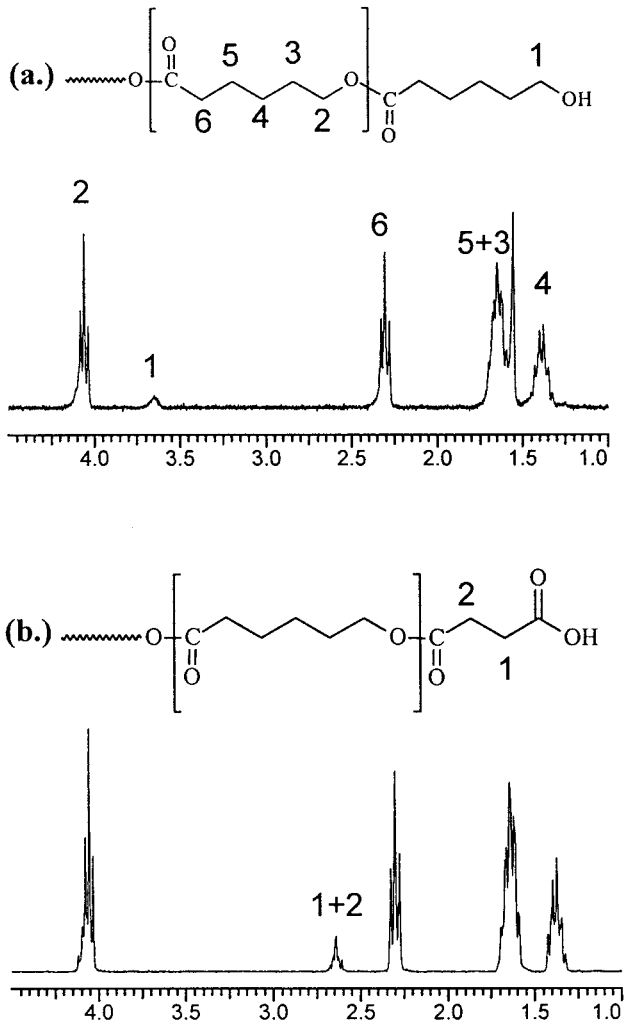

Figure 3 ^{1}H NMR spectra for: (a) hydroxyl-terminated poly(ϵ-caprolactone) (PCL-OH 7), and (b) carboxylic acid-terminated poly(ϵ-caprolactone) (PCL-A 7).

densation step is not crucial because it does not have an effect on the structure of the resulting poly(ester-anhydride). Second, the condensation product is acetic anhydride, and we did not feel it necessary to remove all traces of acetic anhydride in a separate purification step because in subsequent polycondensation, some acetic anhydride is present in the reaction mixture whether the prepolymer is purified or not.

The results of melt polycondensations are summarized in Table III. The preparation method proved to be successful for the synthesis of aliphatic poly(ester-anhydride)s because the considerable increase in molecular weight was measured for 1,4-butanediol initiated polymers (PCL-AH 6, PCL-AH 7). In fact, a lot of higher molecular weights than those obtained (M_w 223,000 g/mol for PCL-AH 7) are difficult to obtain via the polycondensation method. The highly viscous reaction mixture prevents effective mixing, and thus the removal of the condensation product becomes more hindered. The synthesis of poly(ester-anhydrides) containing aromatic anhydride linkages was successful when 4-(hydroxymethyl)benzoic acid-initiated prepolymer was used. On coupling, SEC analysis showed an increase from 7200 to 68,000 g/mol in molecular weight (M_n). By contrast, the coupling of 4-hydroxybenzoic acid-initiated prepolymers yielded only to the M_n of ~39,000 g/mol, even though the molecular weights of prepolymers were as high as 15,000 g/mol. This result is obviously due to problems in the preparation of 4-hydroxybenzoic acid-initiated prepolymers.

^{13}C NMR Analyses

The ^{13}C NMR peak assignments of aliphatic poly(ester-anhydride)s have been thoroughly reported by Storey et al.[2,10] The peak identifications were carried out according to their results. The changes in the ^{13}C NMR spectra of 1,4-butanediol-initiated poly(ester-anhydride)s are presented in Figure 5. The spectrum of hydroxyl-terminated prepolymer (PCL-OH 6) is seen in Figure 5a. In the spectrum, characteristic hydroxyl group resonances are located at 62.5 and 32.3 ppm. Figure 5b shows the spectrum of prepolymer (PCL-A 7) after the reaction with succinic anhydride. The disappearance of hydroxyl peaks and the appearance of two new peaks at 176.1 and at 172.2 ppm proves the conversion of hydroxyl end groups to carboxylic end groups. The spectrum of the polymer after the melt polycondensation step (PCL-AH 7) is shown in Figure 5c. The signal of carboxylic acid carbonyl carbon at 176.1 ppm has disappeared and a new signal appears at 168.0 ppm. This shift is characteristic for the conversion of acid carbonyl to anhydride carbonyl groups.

In the spectrum of 4-(hydroxymethyl)benzoic acid-initiated poly(ester-anhydride), four anhydride carbonyl shifts appeared. The peak at 168.0 ppm was also seen in the spectrum of 1,4-butanediol-initiated poly(ester-anhydride) and it indicates tail-to-tail configuration. The new peaks indicating head-to-tail and head-to-head configurations located at 163.0, 164.7, and 169.2 ppm. The concentration of anhydride linkages was too low to reliably analyze the ratio of the three different configurations.

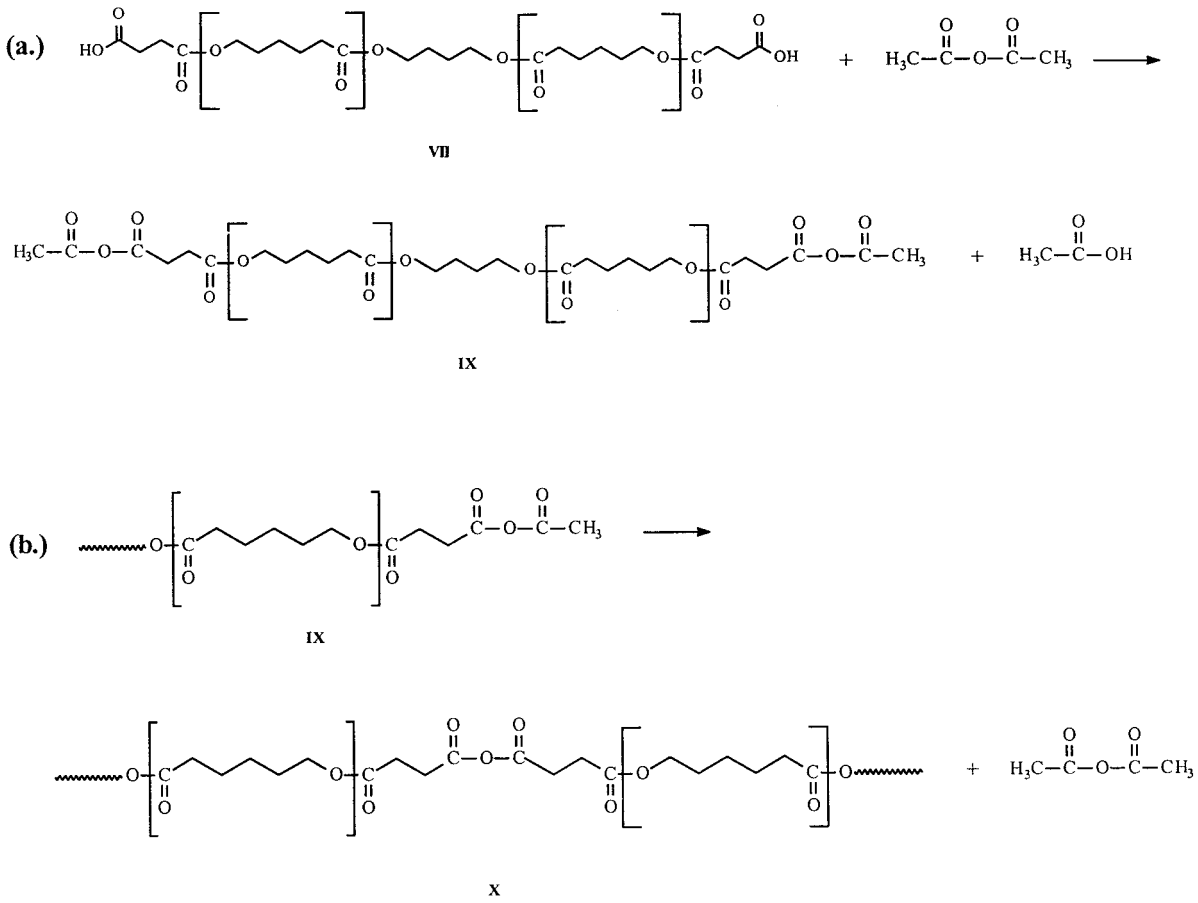

Figure 4 Reaction scheme for the melt polycondensation of poly(ϵ-caprolactone-anhydride)s.

Hydrolysis

The hydrolysis slopes of poly(ester-anhydride)s containing aliphatic (PCL-AH 6) or aromatic (PCL-AH 12) anhydride linkages are shown in Figure 6. Both poly(ester-anhydride)s have a two-stage degradation profile consisting of a very rapid hydrolysis of anhydride linkages, followed by a slower hydrolysis of the remaining poly(ϵ-caprolactone). There was no clear difference between the degradation rates of aliphatic and aromatic anhydride linkages because both polymers degraded almost completely back to poly(ϵ-caprolactone) prepolymers within 3 days. In future studies, a higher concentration of anhydride link-

Table III Molecular Weights of Poly(ester-anhydride)s

	Molecular Weights before Linking			Molecular Weights after Linking		
Sample	M_n, g/mol	M_w, g/mol	M_w/M_n	M_n, g/mol	M_w, g/mol	M_w/M_n
PCL-AH 6	5900	11,500	1.95	53,400	133,300	2.50
PCL-AH 7	3600	6100	1.69	70,000	223,000	3.19
PCL-AH 8	13,800	37,000	2.69	39,400	75,200	1.91
PCL-AH 9	13,000	29,900	1.99	45,900	103,000	2.24
PCL-AH 12	7200	13,500	1.88	68,300	154,700	2.27

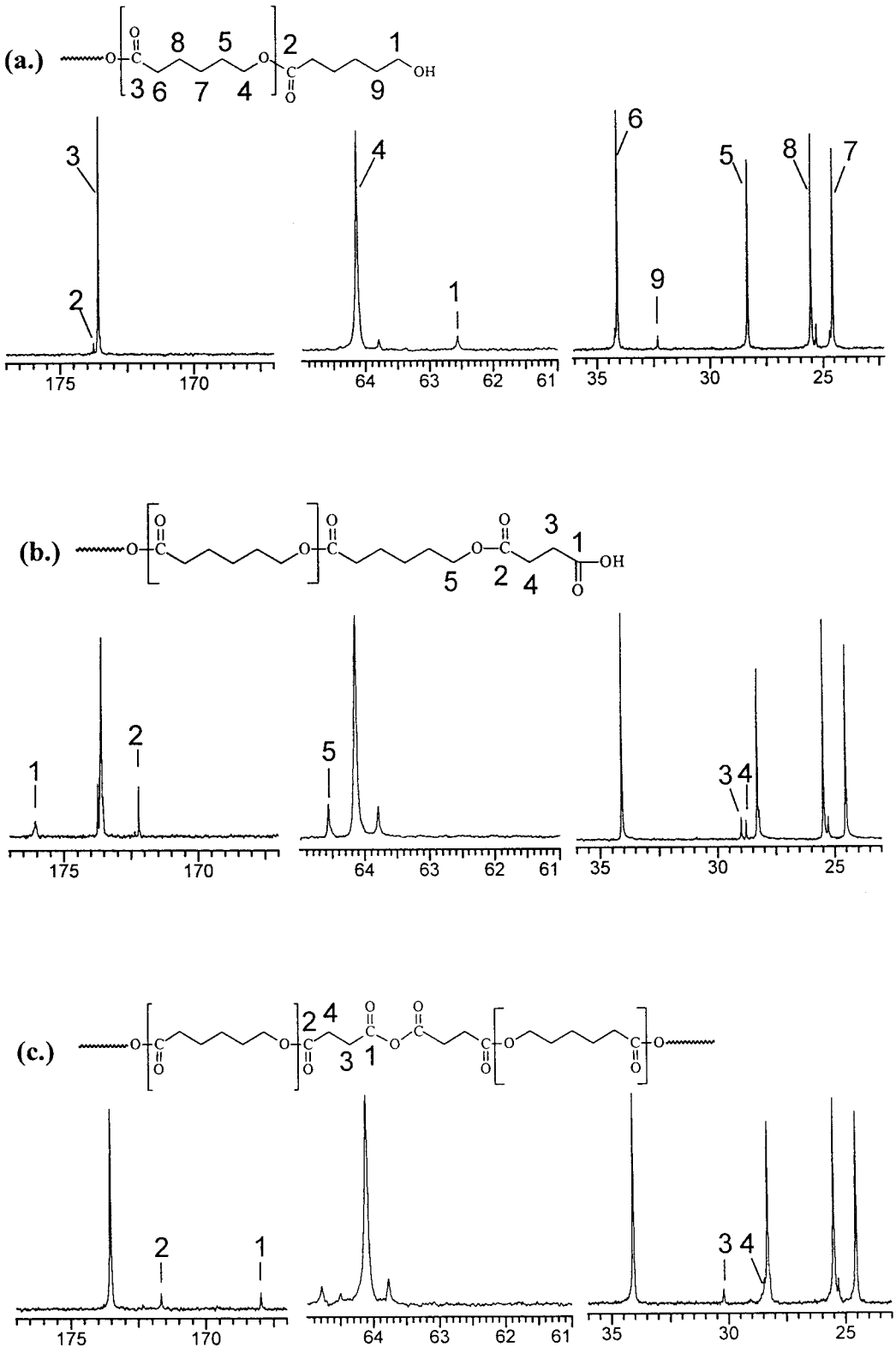

Figure 5 ^{13}C NMR spectra for: (a) hydroxyl-terminated poly(ϵ-caprolactone), (b) carboxylic acid-terminated poly(ϵ-caprolactone), and (c) poly(ϵ-caprolactone) containing anhydride linkages along the polymer backbone.

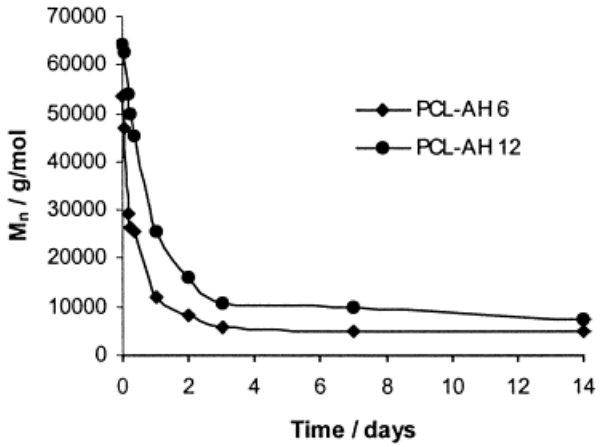

Figure 6 Loss of molecular weight (M_n) at 37 °C for: 1,4-butanediol-initiated poly(ϵ-caprolactone-anhydride) (PCL-AH 6) and 4-(hydroxymethyl)benzoic acid-initiated poly(ϵ-caprolactone-anhydride) (PCL-AH 12).

ages should be used if differences in degradation rates occur.

CONCLUSIONS

High molecular weight poly(ϵ-caprolactone)s containing anhydride linkages along the polymer backbone were prepared. The synthesis consisted of the preparation of carboxylic acid-terminated poly(ϵ-caprolactone) prepolymer and the subsequent melt polycondensation of the prepolymer.

Two alternative methods for preparing prepolymers with carboxylic acid end groups were investigated. The ineffectiveness of adipic acid as an initiator in the ring-opening polymerization of poly(ϵ-caprolactone) prevented a straightforward preparation of carboxylic acid-terminated prepolymer. Another route was to prepare hydroxyl-terminated prepolymer and then convert hydroxyl end groups to carboxylic acid end groups via the reaction with succinic anhydride. The conversion of hydroxyl groups to carboxylic acids was carried out by a simple method of adding the molecular equivalent of succinic anhydride to the polymer melt when polymerization of hydroxyl-terminated poly(ϵ-caprolactone) prepolymer was complete. The preparation of prepolymers was successful when 1,4-butanediol or 4-(hydroxymethyl)benzoic acid were used as initiators. By contrast, 4-hydroxybenzoic acid did not initiate the ring-opening polymerization of poly(ϵ-caprolactone) effectively.

"One-pot" melt polycondensation was used for the coupling of carboxylic acid-terminated poly(ϵ-caprolactone) prepolymers via anhydride linkages. Prepolymers were first refluxed in an excess of acetic anhydride, acetic anhydride was then removed at high temperature, and finally, polycondensation was carried out under high vacuum at 180°C. SEC analyses showed an increase from 3600 to 70,000 g/mol in number-average molecular weight (M_n) on coupling of 1,4-butanediol-initiated prepolymer, and an increase from 7200 to 68,000 g/mol on coupling of 4-(hydroxymethyl)-benzoic acid-initiated prepolymer. The resulting poly(ester-anhydride)s displayed a two-stage degradation profile consisting of a very rapid hydrolysis of anhydride linkages, followed by a slower hydrolysis of the remaining poly(ϵ-caprolactone).

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