

Synthesis and Properties of Biodegradable Copolymers Based on Polyether Oligomers and Fatty Diacids

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ABSTRACT: Polyether oligomers ($M_n = 200\text{--}2000$) were respectively esterified by succinic anhydride and fatty sebacoyl chloride to synthesize corresponding intermediate diacids, and experimental results of melt polycondensations based on these two kinds of intermediates were compared. The reasons for affecting higher molecular weight products to be achieved in polymerization with prepolymers based on succinic anhydride esterification were theoretically analyzed. Light scattering measurements showed that copolyanhydrides with higher molecular weights exceeding 8×10^4 (weight-average) were synthesized from the intermediate diacids prepared by a new method using fatty diacid chlorides to undergo esterification with polyether. Synthesized intermediates were characterized by $^1\text{H-NMR}$ and infrared spectroscopy. Intrinsic viscosity of the polymers were measured to display the advancement of polymerization. The properties of polymers were investigated by X-ray diffraction and differential scanning calorimetry analysis as well. © 1997 John Wiley & Sons, Inc. *J Appl Polym Sci* **66**: 1891–1898, 1997

Key words: biodegradable polyanhydrides; succinic anhydride; sebacoyl chloride; esterification; polycondensation

INTRODUCTION

Because of the potential important application in drug delivery systems, aliphatic polyanhydride has become an attractive polymer.¹ This polymer regarded as an excellent biodegradable material is due mainly to the hydrolytic instability of anhydride linkages, as well as its high biocompatibility. Synthesis, characterization, and degradation both *in vivo* and *in vitro* of this polymer have been extensively investigated in some literatures.^{2–6}

Aliphatic homopolyanhydrides such as poly(sebacic anhydride) (PSA), poly(adipic acid) (PAA), and poly(dodecanoic anhydride) (PDA) generally possess much higher crystallinity, leading to poor fiber–film forming and undesirable mechanical properties. In the mean time, the high crystallin-

ity proved to affect the polymer degradation rates.^{4,5,7} So, though homopolyanhydrides with high molecular weight exceeding 2×10^5 (weight-average) have been synthesized successfully,^{2,5} their practical utilization was limited.

Copolymerization of aliphatic polyanhydrides has been reported to be a very effective way in lowering crystallinity. According to earlier research, a remarkable decrease in polymer crystallinity was brought about when the aliphatic polyanhydride copolymerized with aromatic polyanhydride, and the content of aromatic component affecting fiber–film forming and mechanical property (e.g., tensile strength) of the copolymer was further discovered.^{2,4} Another type of nonlinear copolyanhydride synthesized from prepolymers based on natural fatty diacids was recently reported to possess desired physicochemical properties because of the introduction of fatty branched chains to the molecular structure causing a decrease of the polymer crystallinity.^{5,6}

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Besides the copolyanhydrides mentioned above, copolyanhydrides of aliphatic polyanhydrides and polyethers, such as poly(ethylene glycol) (PEG), have been synthesized in literature⁷ through the three following reactions: (1) polyether oligomer was esterified by succinic anhydride to synthesize intermediate diacid, (2) intermediate diacid reacted with ketene to obtain mixed anhydride of diacid and acetic anhydride, and (3) mixed anhydride underwent melt polycondensation under reduced pressure to form copolyanhydride. According to the literature, these copolymers were proven by differential scanning calorimetry (DSC) analysis to show a decrease in crystallinity, with the polyether segments being introduced into the macromolecular structure. Unfortunately, the molecular weight of synthesized copolymers was relatively lower ($1 \sim 2 \times 10^4$ weight-average), and the influence of polyether segments to polycondensation hasn't been discussed either. On the other hand, reaction (1) was quite slow (lasting for 48 h) and complicated in operation; in the meantime, a large quantity of solvent was used in reactions (2) and (3).

For the purpose of developing aliphatic copolyanhydrides with higher molecular weight from polyether oligomers and fatty diacids, we report here a new way of preparing copolymers in comparing with the reported method above; and we will discuss, for the first time, the influence of polymer composition on polycondensation from the point of reaction mechanism. Some properties of these synthesized copolymers will also be investigated in this article.

EXPERIMENTAL

Materials

Adipic acid and sebacic acid were purified by recrystallization from ethanol. A series of PEG with various molecular weights (M_n from 200 to 2000) were dried under vacuum at 25°C overnight. Succinic anhydride was of analytical grade.

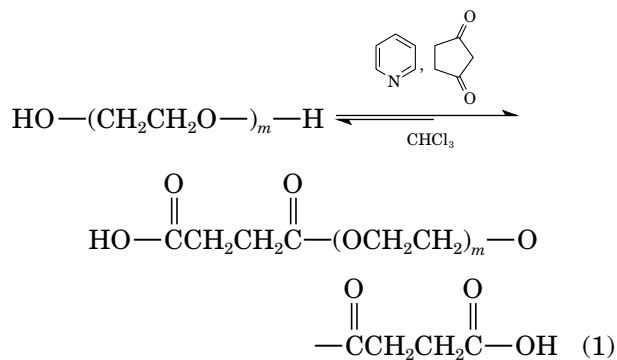
Sebacoyl chloride was prepared by refluxing sebacic acid in thionyl chloride and then distilling under reduced pressure, as described in Baumgarten.⁸ Cadmium acetate dihydrate and calcium acetate hydrate were ground to a particle size of less than 30 μ and were used as catalysts in polymerization.

All solvents were of analytical grade and were dried before being used.

Synthesis of Intermediate Diacids from Polyether Oligomers

Intermediate Diacids Based on Succinic Anhydride Esterification

As reported in Albertsson and Lundmark,⁷ intermediate diacids were synthesized by the following reaction of polyether and succinic anhydride (1 : 2 molar ratio) in catalysis of basic pyridine:



After purification, the resulting product was dissolved in tetrahydrofuran (THF). Then using phenolphthalein as an indicator, the solution was titrated with 0.1M NaOH to determine the average carboxyl number, which reflected the advancement of esterification of polyether.

Intermediate Diacids Based on Sebacoyl Chloride Esterification

Typically, polyether oligomer (1 mol) and sebacoyl chloride (2 mol) were added to a round-bottomed flask with a magnetic stirrer. The flask was immersed into a 50°C glycerin bath, and a vacuum of 667 Pa was supplied. The reaction mixture was stirred until gas evolution ceased. Sebacic acid (2 mol) was added, and the reaction temperature was raised to 80°C. The reactants were again stirred until there was no gas emerging. The crude product was recrystallized from acetone and then purified by precipitation to ethyl ether from acetone solution. Finally, a white candlelike product was obtained.

Prepolymer Synthesis

The mixed anhydride prepolymers of diacid and acetic anhydride were prepared referring to a lit-

erature report² using acetic anhydride (instead of ketene) to react with intermediate diacids.

The intermediate diacid reacted with excess acetic anhydride at 180°C for 20 min, then excess anhydride was removed by vacuum distillation. The crude product was purified by precipitating to a 1 : 1 mixture of dry petroleum ether and ethyl ether (v/v) from chloroform solution.

Polymer Synthesis

All polymers were synthesized by melt polycondensation. In general, prepolymer and reaction catalyst were added to a carefully dried glass reaction tube with a side arm, then the tube was immersed in a 200°C oil bath to undergo polymerization. During the reaction, the melt was swept with nitrogen gas for 1–2 min every 15 min. The crude polymer was dissolved in chloroform, then the catalyst was removed by filtration, and polymer was finally obtained by precipitation in dry petroleum ether.

Measurements

Intermediates were characterized by infrared (IR) and ¹H-NMR spectroscopy. The Fourier transform infrared (FTIR) spectroscopy used was a Perkin-Elmer 1600, and solid samples were pressed into KBr pellets. The ¹H-NMR spectra were obtained on a EM-360 (60 MHz) and a Varian-200 using tetramethylsilane (TMS) as an internal reference; intermediate diacids and prepolymers were dissolved, respectively, in deuterioacetone and deuteriochloroform. Molecular weights of polymers were determined at 25°C by means of light scattering employing Zimm plotting was done on a DLS-700 and a differential refractometer RM-102, and all samples were dissolved in dried chloroform and stored below 0°C before measurements. A Perkin-Elmer DSC-7 calibrated with In was used to analyze the thermal properties of polymers at a heating rate of 10°C min. Crystallinity of polymer was measured on a D/MAX-RB X-ray diffractometer (Japan). Intrinsic viscosity of polymers in chloroform solution were measured in a Ubbelodde viscosimeter (2 mL, 0.39 mm).

RESULTS AND DISCUSSION

Intermediate Diacids and Prepolymers

Succinic Anhydride Esterification

According to the description mentioned in the literature, a kind of intermediate diacid was synthesized by esterification of polyether and succinic anhydride.

The average molecular carboxyl numbers (AMCN) of achieved products determined by titration in solution of THF with 0.1M NaOH were shown in Table I.

All products possessing higher average molecular carboxyl numbers approaching to theoretical maximum of two indicated sufficient esterification of polyether and succinic anhydride.

Through these intermediate diacids reacting with acetic anhydride, mixed anhydride prepolymers were synthesized.

The IR spectra of prepolymers showed characteristic absorption at 1740 and 1810 cm⁻¹ due to the symmetrical and asymmetrical stretching absorption of anhydride carbonyl. The ¹H-NMR spectra showed typical peak at 2.30 ppm from the end group methyl protons, as shown in Figure 1.

Sebacoyl Chloride Esterification

Based on sebacoyl chloride esterification, we synthesized another kind of intermediate diacids by the following reactions.

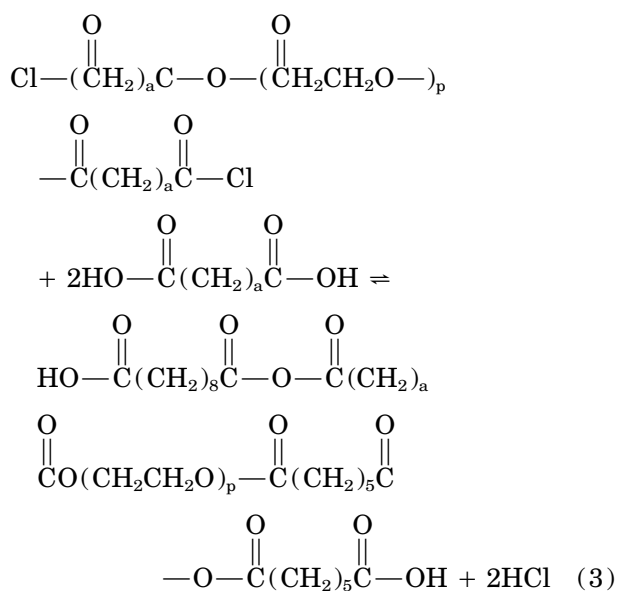
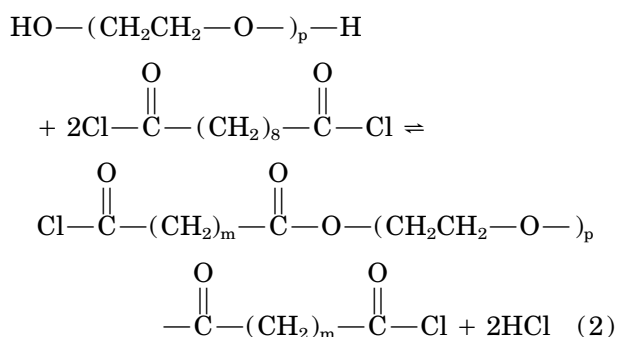
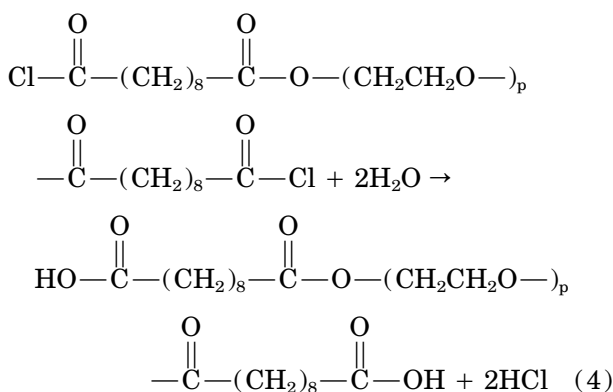


Table I Average Molecular Carboxyl Numbers for Esterification Products

Reactants	PEG-200	PEG-400	PEG-800	PEG-2000
AMCN	1.95	1.85	1.86	1.89

Reaction in conditions as described in Albertsson and Lundmark.⁷

A small portion of the product of reaction (2) was taken out of the reaction system to undergo following hydrolysis at 0°C:



Chloride of carboxylic acid was very easy to react with water, even at low temperature (e.g. 0°C); so reaction (4) finished within a short reaction time of several minutes. In this reaction condition, hydrolysis of ester bonds could be ignored. The reaction mixture was extracted with chloroform, dried with anhydrous Na₂SO₄, and filtered. Then chloroform was removed from the extract by vacuum distillation. The resulting diacid product (about 70% yield) was dissolved in THF and ti-

trated with 0.1M NaOH to determine the average molecular carboxyl number. Results were shown in Table II.

The purified product of reaction (4) possessing high AMCN indicated that the esterification of polyether and sebacoyl acid, namely reaction (2), was sufficient in given reaction condition. In fact, reaction (4) showed a method to obtain intermediate diacid from the product of reaction (2), but the purification of hydrolysis diacid product was difficult. So another reaction (3) with higher product yield was finally employed to synthesize the goal intermediate diacid products.

Comparing with succinic anhydride esterification to synthesize intermediates from polyether oligomers, the means of sebacoyl chloride esterification was obviously more advantageous, due mainly to much shortened reaction time, higher product yield, and more simple reaction operation.

Corresponding mixed anhydride prepolymers were prepared with intermediate diacids synthesized in reaction (3) by reacting with acetic anhydride. The IR spectra of prepolymers showed characteristic bands at 1735 and 1810 cm⁻¹, attributed to the symmetrical and asymmetrical stretching absorption of anhydride carbonyl. The ¹H-NMR spectra showed typical peak at 2.30 ppm from the end group methyl protons, as shown in Figure 2.

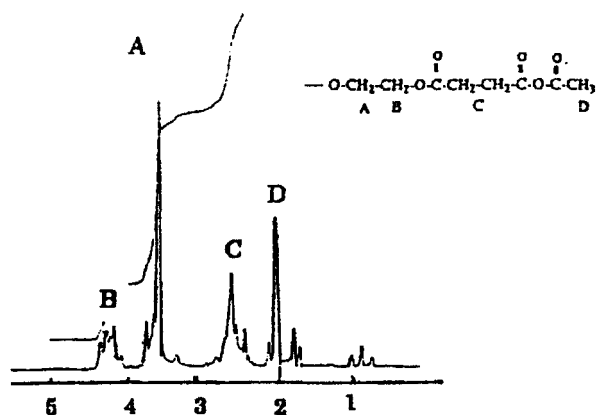


Figure 1 A 60 MHz ¹H-NMR spectrum of prepolymer from PEG-200 (based on succinic anhydride esterification).

Polymer Synthesis

Investigation of Reaction Conditions

By melt polycondensation, corresponding polymers were synthesized, respectively, from two different kinds of prepolymers discussed above. As a comparison, PSA was also synthesized.

The same regulations on reaction conditions as reported² were applied so that all polymerizations of prepolymers synthesized in this article were affected by reaction time and temperature, as well as accelerated by acetate catalysts of Ca and Cd (Figs. 3 and 4).

Table II Average Molecular Carboxyl Number of the Purified Product of Reaction

Basic Reactant	PEG-200	PEG-400	PEG-800	PEG-2000
AMCN	1.97	1.92	1.92	1.90

See Mathiowitz et al.⁴

The optimized reaction condition for polymerization of prepolymers based on esterification of polyether and sebacoyl chloride was discovered to be reacting for 90 min at 200°C in the presence of acetates of Ca or Ca as the catalysts for the reaction.

Comparison of Polymerization of Various Kinds of Prepolymers

According to the reports in the literature,^{2,5} though homopolymers with higher molecular weights exceeding 1×10^5 (weight-average) based on long-chain fatty diacids such as sebacic acid and dodecanoic acid have been successfully synthesized by melt polycondensation, the molecular weights of copolymers from polyethers and fatty diacids were relatively lower.

It was found in our research, using the new way of sebacoyl chloride esterification to synthesize intermediate diacids, that copolymers with higher molecular weight (also reflected by higher

intrinsic viscosity) were obtained from polyethers and fatty diacids in comparison to the reported method (Fig. 5). However, during polymerization of copolymers at optimized conditions, it was still difficult to reach high molecular weights as in the polymerization of PSA according to the following results of light scattering measurements: $M_{w(\max)}(\text{copolymers}) = 0.5 \sim 1 \times 10^5$; $M_{w(\max)}(\text{PSA}) = 2.4 \times 10^5$.

To the polymerization in Figure 5, light scattering measurements showed that the highest molecular weights of copolymers A and B, respectively, were as follows: $M_{w(A)} = 1.82 \times 10^4$; $M_{w(B)} = 8.33 \times 10^4$.

From the experimental results mentioned above, it is conceivable that the segments of polyether affected the polymerization of prepolymers from polyether oligomers and fatty diacid.

The following reaction mechanism of polymerization of polyanhydride, which has been given before,⁷ should be accepted:

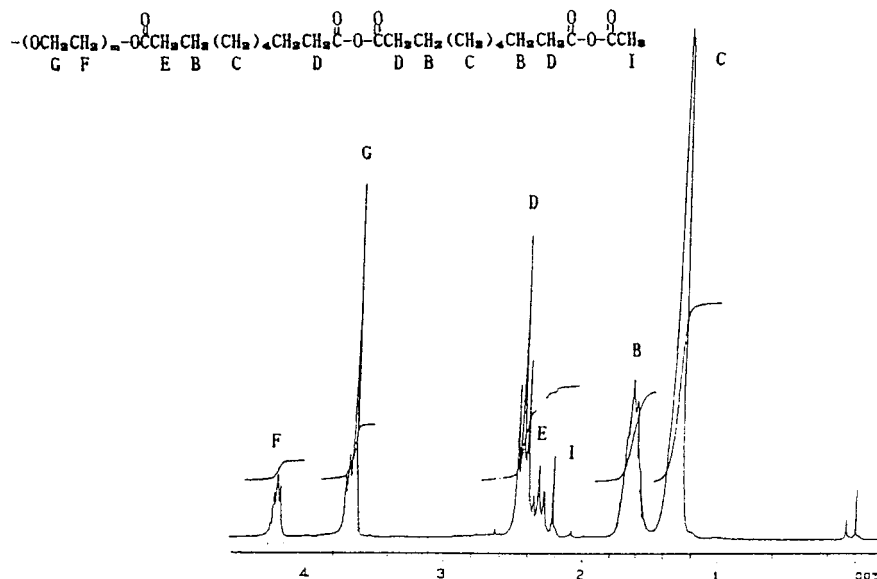
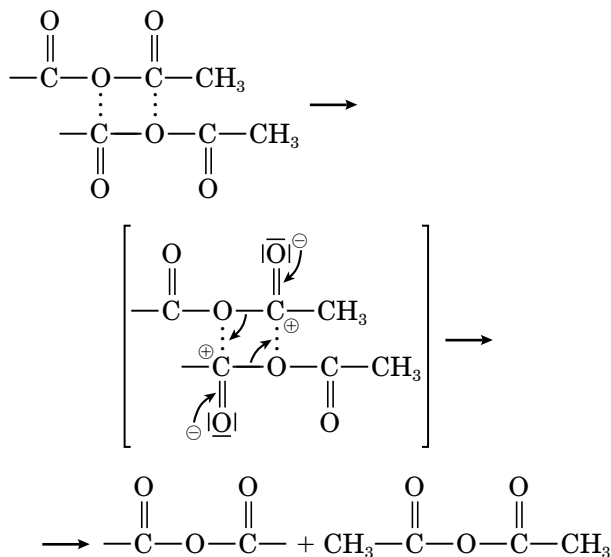


Figure 2 A 200 MHz ¹H-NMR spectrum of prepolymer from PEG-200 (based on sebacoyl chloride esterification).



It is thus clear that the polymerization is an anhydride interchange between the mixed anhydride end group that essentially involves a nucleophilic attack on the positive carbonyl carbon by the nucleophilic etheric oxygen from the end reaction group of another molecule.

Because the etheric oxygen of polyether is also a nucleophilic agent, it is not difficult to understand that, as the introduction of polyether segments to macromolecular structure, these polyether segments will affect the reactivity of car-

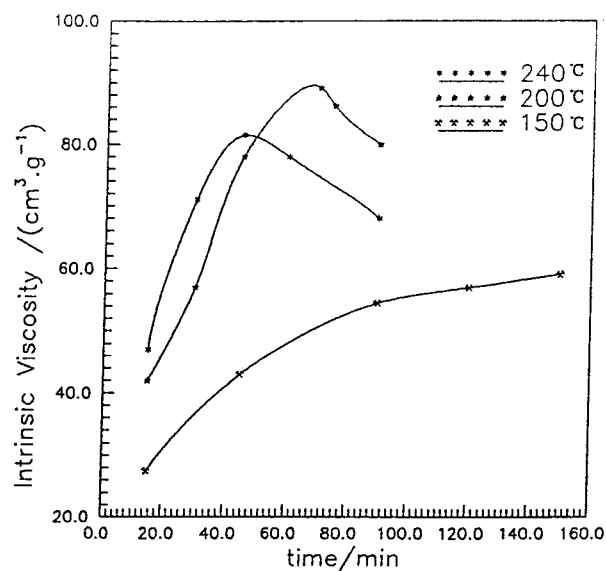


Figure 3 Relationship between polymer intrinsic viscosity and reaction time-temperature in the polymerization of a prepolymer from PEG-800 (sebacoyl chloride esterification).

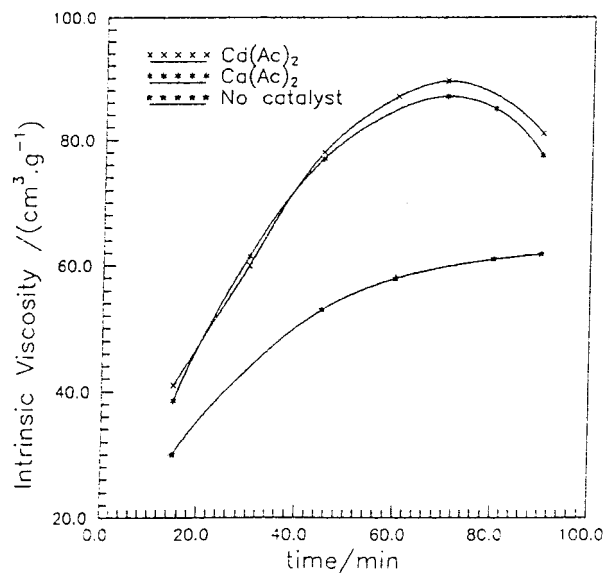


Figure 4 Relationship between polymer intrinsic viscosity and reaction time in 200°C polymerization of a prepolymer from PEG-800 (sebacoyl chloride esterification).

bonyl carbon, especially when these segments are very close to the mixed anhydride end group (see Fig. 6).

Obviously, in the prepolymer molecules based

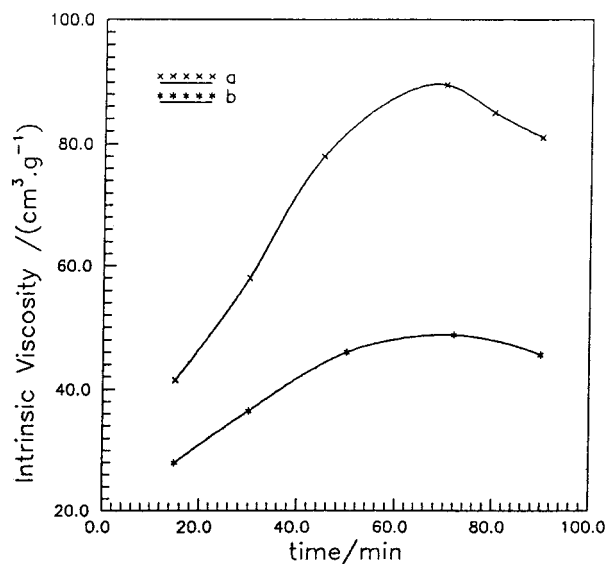


Figure 5 Polymer intrinsic viscosity-reaction time curves of polymerization (200°C; cadmium acetate dihydrate as catalyst): (a) copolymer from PEG-800 based on succinic anhydride esterification, and (b) copolymer from PEG-800 based on sebacoyl chloride esterification.



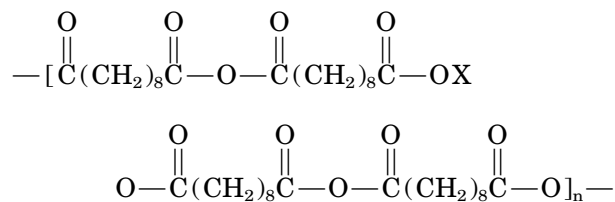
Figure 6 Sketch of the electrostatic shield of polyether segments to carbonyl carbon.

on succinic anhydride esterification of polyether, the mixed anhydride end group $-\text{COOCOCH}_3$ is very close to polyether segment. A very strong electrostatic shield to carbonyl carbon from polyether will intensively affect the reactivity of this reaction center, so copolymers with higher molecular weights were theoretically difficult to achieve from polymerization of prepolymers based on succinic anhydride esterification of polyethers to synthesize intermediate diacids.

In this article, a new kind of intermediate diacids with molecular structure in which the mixed anhydride end group was far away from polyether segment was synthesized using sebacoyl chloride to undergo esterification with polyether. Experimental results consistent with the above theoretical analysis were achieved; copolymers with higher molecular weights than reported before were synthesized based on these prepolymers.

Properties Investigation of Copolymers

Based on sebacoyl chloride esterification of polyether discussed in the preceding section, copolymers were synthesized with the following structure:



where X refers to polyethers with various molecular weights.

Crystallinities of these copolymers were measured by X-ray diffraction (XRD) referring to reports in the literature (Table III).^{4,9}

From Table III, every copolymer possessed much lower crystallinity than the homopolymer PSA, and crystallinity decreased with the increase in the molecular weight of the selected polyether. But when the molecular weight of polyether was raised to a higher number (e.g. 2000), crystallinity of the copolymer showed an opposite trend of increase, perhaps due to further crystallization being induced by the high content of polyether.

Thermal properties of these copolymers were analyzed by DSC (Table IV).

From Table IV, homopolyanhydride PSA didn't show a notable glass transition in the DSC thermogram due to its higher crystallinity, so corresponding glass transition temperature was unable to be detected. However, copolyanhydrides exhibited much lower heats of fusion (ΔH) but obvious glass transitions, indicating lower crystallinities, in comparison to PSA.

Table III Crystallinities of Polymers Measured by XRD

X in Copolymer	Intrinsic Viscosity $[\eta]$ (cm^3/g)	Crystallinity χ_c (%)
PEG-200	97.2	53.40
PEG-400	93.6	31.79
PEG-800	89.2	25.27
PEG-2000	68.4	34.64
Without X (PSA)	112.5	72.54

Table IV Results of DSC Analysis on Thermal Properties of Several Polymers

X in Copolymer	Intrinsic Viscosity [η] (cm ³ /g)	T_g (°C)	T_{peak} (°C)	ΔH (J/g)
PEG-200	97.2	42.2	72.8	47.73
PEG-400	93.6	52.2	69.9	25.88
PEG-800	89.2	45.1	63.6	17.66
PEG-2000	78.8	50.6	71.4	17.25
Without X (PSA)	112.5	not found	86.0	134.5

CONCLUSIONS

Both experimental results and theoretical analysis proved that polymerizations of prepolymers based on fatty diacids and polyether oligomers were affected by the structures of prepolymers and reaction conditions. In this article, sebacoyl chloride underwent esterification with polyether oligomers to synthesize a new kind of intermediate diacids, as well as prepolymers, composed of polyethers and fatty diacids. From these prepolymers, copolymers with higher molecular weights exceeding 8×10^4 (weight-average) were synthesized by vacuum melt polycondensations. DSC analysis and XRD measurement showed that the introduction of polyethers segments to copolymers molecules greatly lowered their crystallinities and improved their thermal properties as well.

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