

Synthesis and Characterization of Highly Branched Poly(anhydride-co-glycol) with Glycerin as Branching Agent

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ABSTRACT: A novel branched poly(anhydride-co-glycol) was synthesized by introducing glycerin into a poly(sebacic anhydride-co-ethylene glycol) system via melt condensation without catalyst. The nuclear magnetic resonance spectroscopy (NMR) analysis showed that the reaction between the hydroxyl group on glycerin and the sebacic anhydride pre-polymer was completed without any hydroxyl group remaining. In addition, with more glycerin introduced, intramolecular chain reaction became more remark-

able. This resulted in the production of more cyclic chains and lower molecular weight species that hinder the crystal growth of sebacic anhydride chain segments. This in turn decreases melting temperature of sebacic anhydride chain segments in these synthesized materials. © 2003 Wiley Periodicals, Inc. *J Appl Polym Sci* 90: 886–893, 2003

Key words: glycerin; nuclear magnetic resonance; intramolecular chain reaction; crystal; melting temperature

INTRODUCTION

Biodegradable polymeric materials recently have been increasingly adopted in drug delivery, bone and cartilage repair, and other tissue engineering applications. Polymers, such as poly(α -hydroxy acids), poly(aliphatic esters), poly(orthoesters), poly(phosphate esters), polypeptides, and polysaccharides, have been developed for all of these applications, and their interactions with host tissues have also been extensively investigated.^{1,2} This work is concerned with a particular type of biodegradable polymers, branched polyanhydrides. Several investigations have demonstrated that for drug delivery uses, polyanhydrides exhibit surface erosion behavior, providing sustained and long-term drug release.^{1–5} Polyanhydrides and their degradation products are also highly biocompatible, as established by tissue responses and toxicological studies.^{1,6} Other developments in polyanhydride materials include the use of poly(amino acids)^{7–9} and poly(ethylene glycol) (PEG)¹⁰ to modify the properties of biomaterial systems, where these materials are used in the forms of pre-polymer or copolymers.

Previous studies synthesized poly(sebacic anhydride-co-ethylene glycol) (PSAEG) with various ratios of poly(sebacic anhydride) (PSA) to PEG, using a sebacic anhydride pre-polymer and commercial PEG,

obtained via melt condensation without catalyst.¹¹ The introduction of PEG molecules can adjust the rate of release and hydrophilic properties of the controlled drug delivery system. Additionally, this manufacturing process involving PEG introduction can also maintain the biocompatibility of synthesized polymers and their depolymerized products. This work attempted to introduce trihydroxyl groups containing glycerin to provide a branch structure to the polyanhydride-PEG copolymer system. These synthesized materials were investigated using nuclear magnetic resonance spectroscopy (NMR) to determine their structures. Furthermore, the materials were examined using gel permeation chromatography (GPC) and differential scanning calorimetry (DSC) to determine variations in molecular weight and melting point. These measurements can provide information on the occurrence of intramolecular chain reaction and its influence on the physical properties of material.

EXPERIMENTAL

Materials

Sebacic acid and acetic anhydride were purchased from Riedel-de Haën (Seelze, Germany). Poly(ethylene glycol) (PEG, MW = 2000) and glycerin (anhydrous) was obtained from Merck (Darmstadt, Germany). Additionally, dichloromethane (HPLC grade, Fisons Scientific Eq., Loughborough, UK), toluene (Mallinckrodt, Paris, KY), petroleum ether (anhydrous, J. T. Baker), and ethyl ether (anhydrous, J. T. Baker, Philipsburg, NJ), were all high performance

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TABLE I
Feed Compositions of the Synthesized Materials

Synthesized polymeric materials ^a	Feed compositions (g)		
	pre-SA	PEG	Glycerin
PSAEG	2.5000	0.5000	0.0000
PSAEG-20×	2.5000	0.4000	0.0031
PSAEG-40×	2.5000	0.3000	0.0062
PSAEG-60×	2.5000	0.2000	0.0092
PSAEG-100×	2.5000	0.0000	0.0154

pre-SA, prepolymer of sebacic anhydride.

^a Branch ratio is indicated by the code of synthesized materials.

liquid chromatography (HPLC) grade and were used as received without further purification.

Synthesis of desired polymers

After the temperature was raised to 140°C, 24 g sebacic acid and 248 g acetic anhydride were charged into a dry nitrogen purged reactor. The reaction was performed with rigorous mixing for 20 min. The mixture was then placed in a rotary evaporator to remove acetic acid and unreacted acetic anhydride. Next, the crude pre-polymer was recrystallized from dry toluene. The crystals were subsequently immersed in the solvent (1:1 dry petroleum ether to ethyl ether) to extract traces of acetic anhydride and toluene. Refined pre-polymer was obtained by drying in a vacuum.³

To examine the influence of the trifunctional group containing glycerin, feeding composition was adjusted to provide identical hydroxyl group content for all the materials. Additionally, the code for the synthesized materials is the branch ratio, which indicates the proportion of the hydroxyl group provided by glycerin. The desired quantity of refined pre-polymer, PEG, and glycerin (tabulated in Table I) was then placed in the reactor in an oil bath at 180°C, in a vacuum for 120 min, to perform melt condensation.^{1,3} The final product was first dissolved into dichloromethane, and then purified by precipitation in dry petroleum ether. The precipitate was further extracted using ethyl ether anhydrous to yield a purified polymer product.

Characterization of the synthesized polymers

The molecular weight of the synthesized copolymers was determined by GPC, which was constructed with pump (JASCO PU-1580) and detector (JASCO RI-1530), using chloroform as the eluent (flow rate of 1.0 mL/min was used) and polystyrene as the standard. ¹H-NMR spectra were recorded with a 500 MHz instrument (Varian unity INOVA 500NMR spectrometer) using CDCl₃ as a solvent and tetramethylsilane as an internal standard for examining the synthesized materials. Finally, a DSC (TA 2010) was used to study

TABLE II
Molecular Weights of the Synthesized Materials

Synthesized polymeric materials	\bar{M}_n	\bar{M}_w	PDI
PSAEG	3200	7300	2.28
PSAEG-20×	3200	7400	2.31
PSAEG-40×	3300	7700	2.33
PSAEG-60×	3400	8100	2.38
PSAEG-100×	2600	5900	2.27

PDI, polydispersity index.

crystalline behavior, and DSC thermoscans were conducted in a dry nitrogen atmosphere at a heating rate of 10°C/min from 0 to 150°C.

RESULTS AND DISCUSSION

Molecular weight measurement

This study used GPC to determine the average molecular weight and polydispersity index of the synthesized materials. Table II summarizes these results of GPC investigation, while Figure 1 displays the GPC profiles. Table II indicates that the number average and weight average molecular weights of PSAEG were 3200 and 7300 g/mol, respectively. Both values increased as the branch ratio of synthesized materials increased from 0 to 60%. In Figure 1, the main peak of the GPC profile for all these synthesized materials occurs at a retention time of 10.6 to 10.4 min. Additionally, low molecular weight species can also be observed at a retention time of 16.3 min in the GPC profiles (indicated by an arrow in the figure). As indicated in the previous research,³ this low molecular weight species resulted from cyclic anhydride dimers. These results indicate that a branching structure can be developed without increasing low molecular weight species under a branch ratio of 0–60%.

On the other hand, with branch ratios exceeding 60%, the number average and weight average molecular weights of PSAEG-100× declined to 2600 and

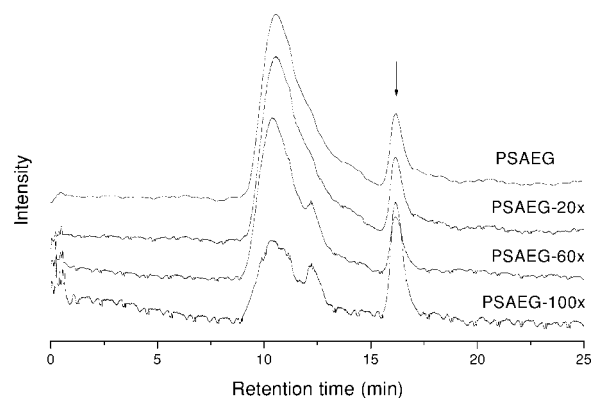


Figure 1 GPC profiles of synthesized materials. Designated peak denoted by arrow was at retention time of 16.2 min.

5900 g/mol, respectively. The ratio of low molecular weight species at retention time of 16.3 min in GPC profiles increased significantly at branch ratios between 60 and 100%. This phenomenon indicates that the formation of cyclic anhydride dimers was induced at branch ratios exceeding 60%, indicated by the increase in the lower average molecular weight species. These findings suggest that the introduction of glycerin may enhance the development of copolymer growth, as well as inducing the formation of anhydride dimers following melt condensation under high glycerin content.

NMR spectra

After copolymer synthesis and purification, NMR spectra were obtained to determine the molecular structures of the final products. Figures 2 and 3 illustrate these results.

Figure 2 displays the ^1H -NMR spectrum of the synthesized polymer: PSAEG. For qualitative analysis, distinct chemical shifts were also assigned. This figure reveals well-resolved chemical shifts at $\delta = 1.3, 1.6, 2.2,$ and 2.4 ppm, which belong to the hydrogen atoms of individual functional groups on poly(sebacic anhydride). Introducing PEG to the polymer causes the other chemical shifts at $\delta = 3.6$ and 4.2 ppm, confirming the existence of the segments of ethylene glycol. The introduction of PEG to the polymer can also confirm the reaction between sebacic anhydride pre-polymer and PEG.¹¹

Figure 3 illustrates the ^1H -NMR spectra of the synthesized branched PSAEG-100x [Fig. 3(a)] and PSAEG-60x [Fig. 3(b)] with chemical shifts assigned. The figure displays new chemical shifts at $\delta = 4.1, 4.3,$ and 5.2 ppm, which correspond to the hydrogen atoms of methylene (4.1 and 4.3 ppm) and methine (5.2 ppm) groups on reacted glycerol. The chemical shifts of distinct hydrogen atoms on glycerin were at $\delta = 3.5, 3.6,$ and 3.7 ppm. After reacting with sebacic anhydride pre-polymer, these chemical shifts vanished and appeared in low field (higher ppm values) as presented in Figure 3. This behavior indicates the variation of electron environments, which was occurred owing to the reaction between glycerin and sebacic anhydride pre-polymer. Increased PEG content allows the chemical shifts at $\delta = 3.6$ and 4.2 ppm to be observed, meaning that PEG and glycerin were both completely reacted with sebacic anhydride pre-polymer during melt condensation so that no hydroxyl group was left.

On the other hand, the intensity of the chemical shifts at $\delta = 2.2$ ppm (denoted by "d") reduced with the introduction of glycerin into the material system. This phenomenon indicates the reduction of the anhydride-terminated molecular chains. From GPC investigation, this phenomenon was thought to be caused

by the formation of cyclic dimers, in which no end group can be found.

Mechanism of chain reaction

Interestingly, the main elution peak in the GPC profile splits into two distinct peaks when the branch ratio is increased (Fig. 1). A previous work by Domb and Langer³ indicated that polyanhydride is a mixture of longer and shorter molecular chains, in which the intramolecular or intermolecular chain reaction may occur during the melt condensation process. Additionally, intramolecular reaction may result in the formation of larger rings; the same reaction may continue to produce smaller rings when reaction time exceeds 90 min. In this study, the split peaks did not belong to the extremely high molecular weight species as the product from the synthesis of neat poly(sebacic anhydride) during melt condensation process.³ These peaks are owing to intramolecular chain reaction between two anhydride molecular chains extended from the same glycerin molecule (Scheme 1). Although both intramolecular and intermolecular chain reactions can occur, only the intramolecular chain reaction mechanism results in the formation of relatively low molecular weight species, namely cyclic molecular chains, thus reducing the weight average molecular weight of the synthesized materials. As discussed in the above GPC results, the ratio of low molecular weight species did not increase when branch ratio increased to 60%. This phenomenon suggests that intramolecular chain reaction intensifies with a branch ratio of over 60% in these synthesized materials.

Crystalline behavior

Figure 4 illustrates DSC thermoscan curves of the synthesized materials. All of the synthesized materials exhibited a single melting point at ca. 79°C , because they were composed of crystals of sebacic anhydride chain segments. However, closer observation revealed that melting temperature of materials decreased with increasing branch ratios. As Figure 4 indicates, the melting temperature of PSAGE was 79.7°C . However, the melting temperature decreased to 79.0°C when the branch ratio was increased to 60%. Additionally, melting temperature was further decreased to 78.3°C when PEG was completely replaced by glycerin (branch ratio: 100%). Reduced crystal layer thickness is well known to reduce melting point.¹² Consequently, the crystal growth of sebacic anhydride chain segments can be judged to be hindered by the introduction of glycerin (trihydroxyl groups) to replace PEG (dihydroxyl groups). This caused an intramolecular chain reaction that produced rings and low molecular weight species that hinder the crystal growth of sebacic anhydride chain segments.

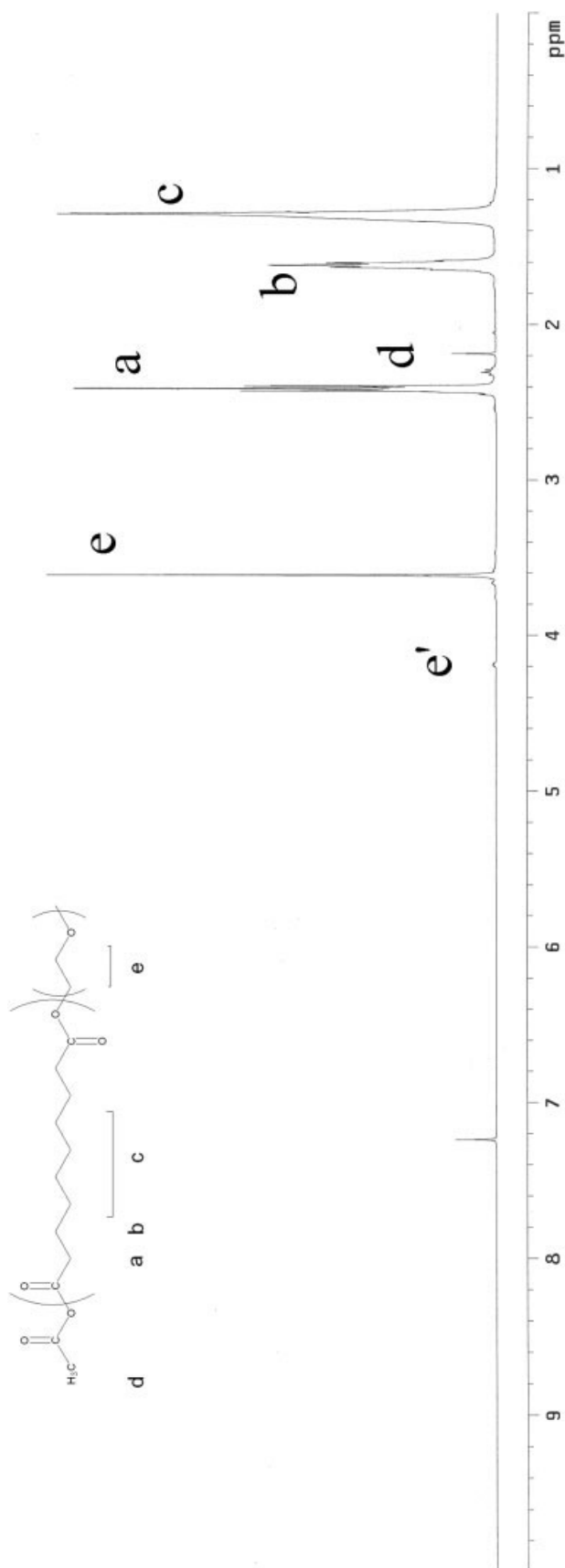


Figure 2 $^1\text{H-NMR}$ spectra of PSAEG. The assignments for distinct hydrogen atoms are on the figure.

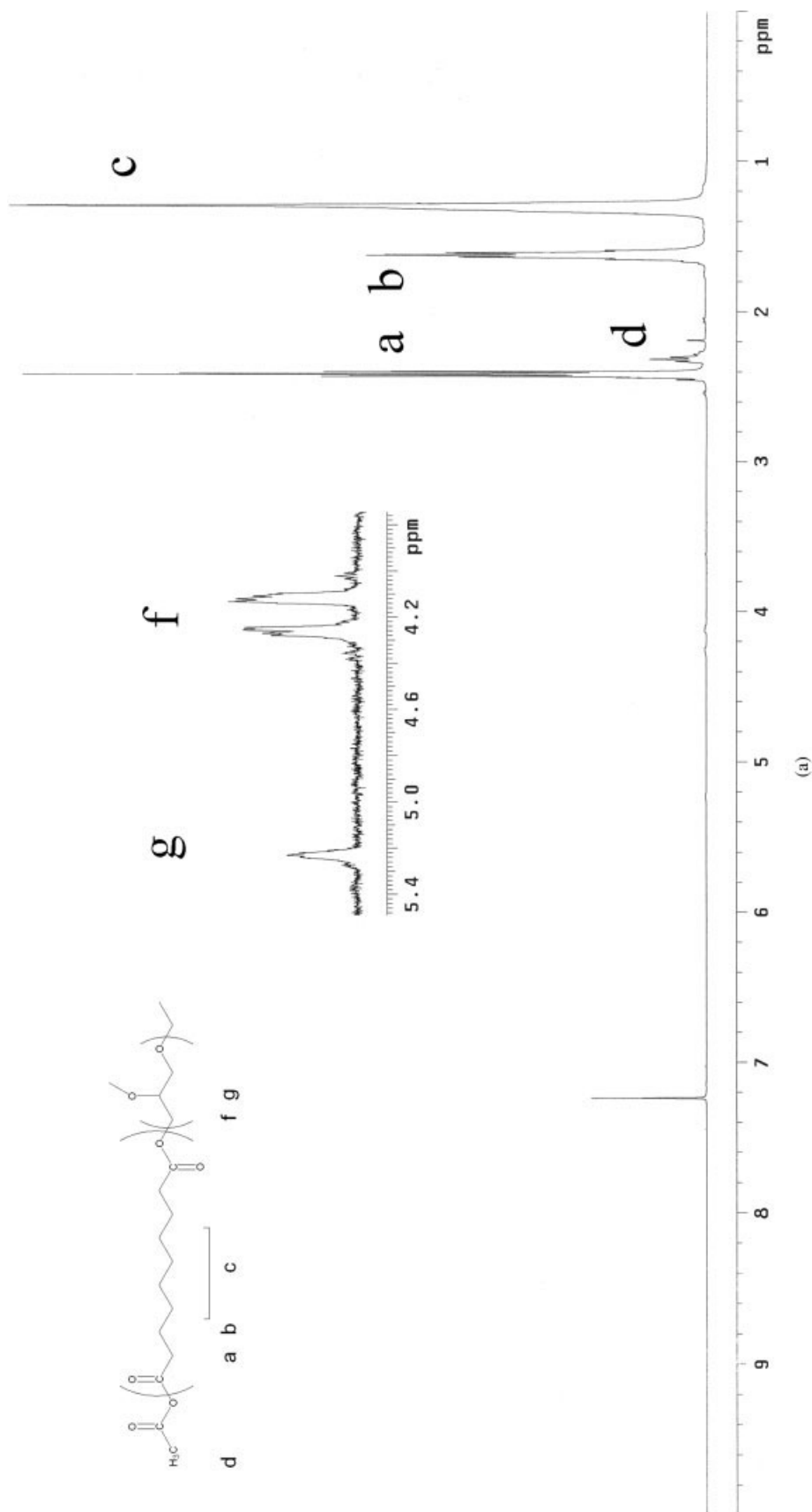


Figure 3 $^1\text{H-NMR}$ spectra of (a) PSAEG-100 \times , (b) PSAEG-60 \times , and (c) PSAEG-20 \times .

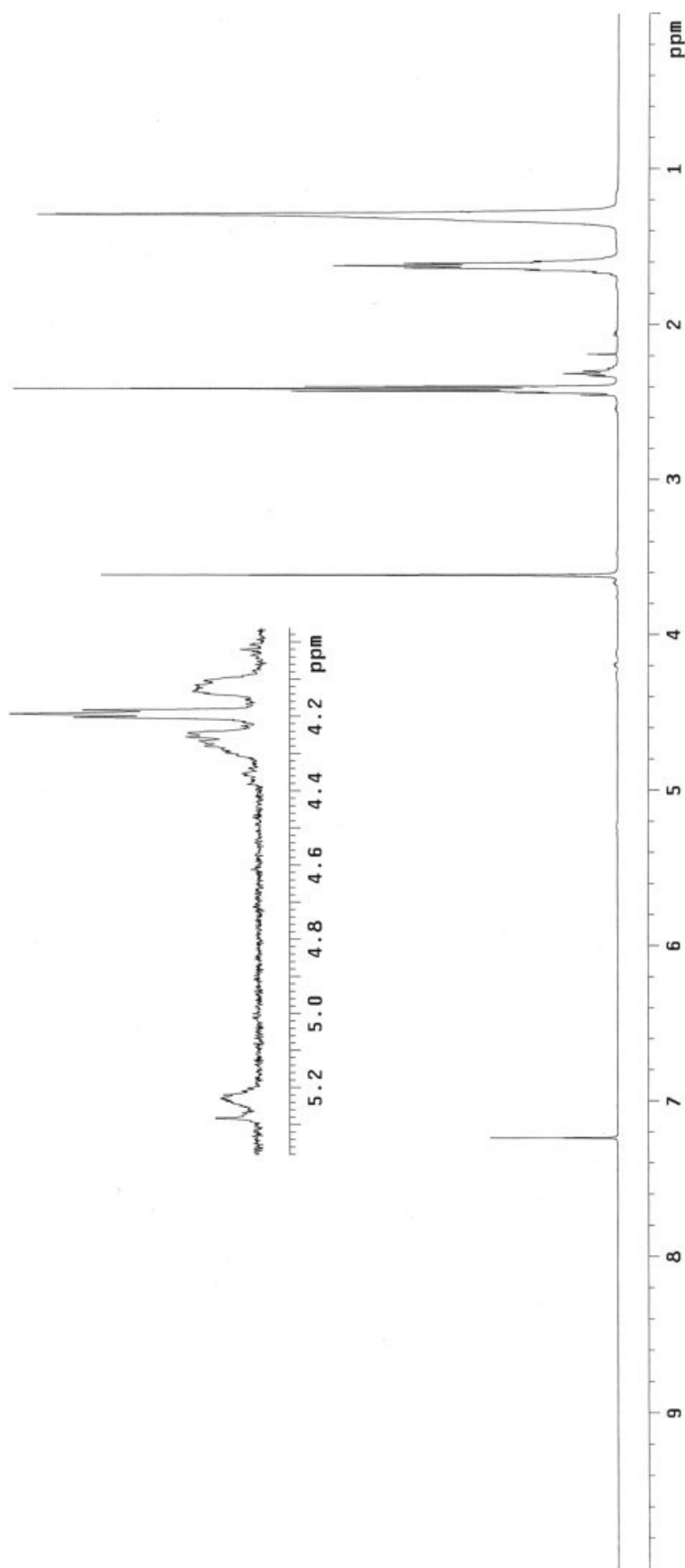


Figure 3 (Continued from the previous page)

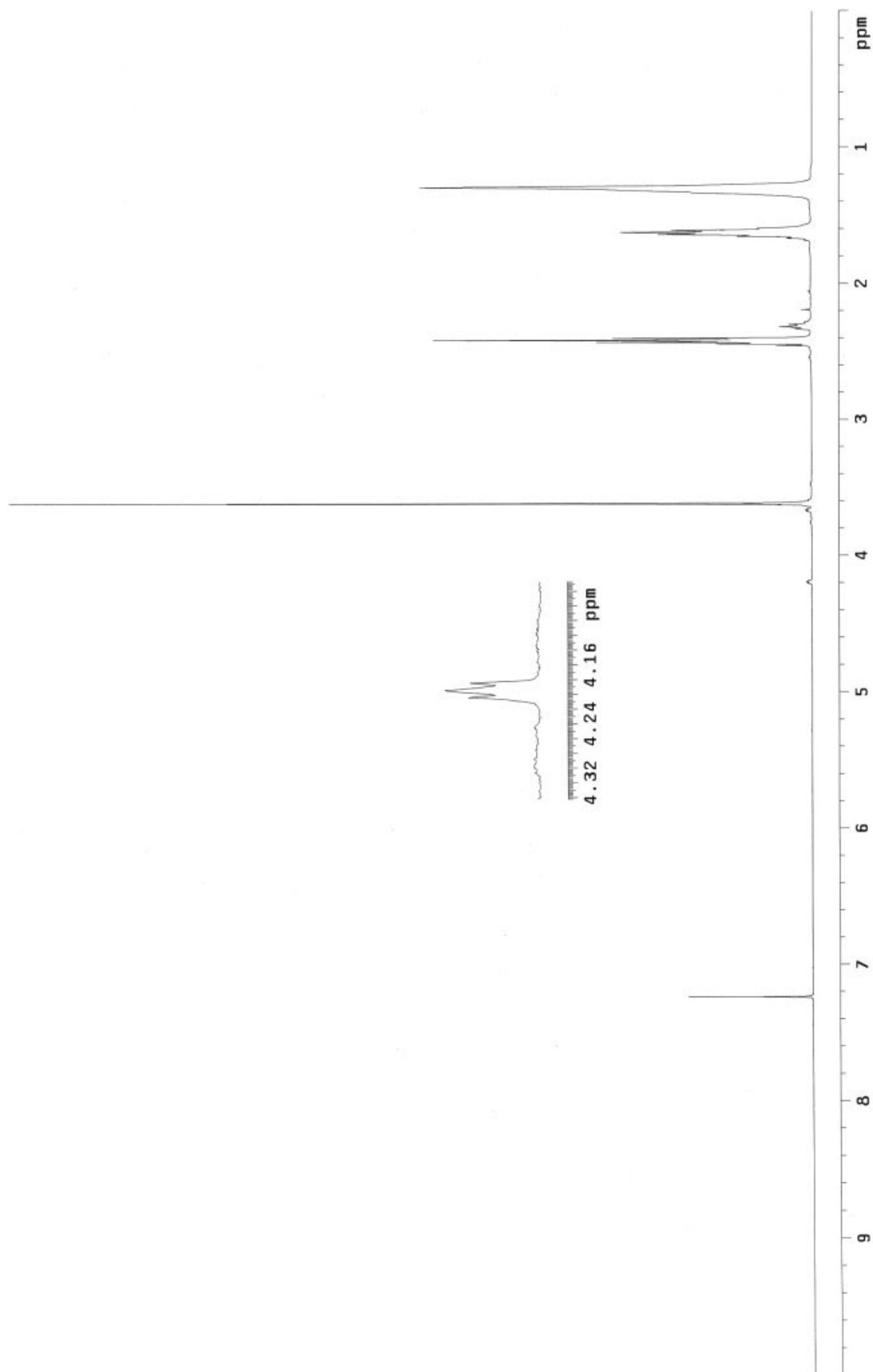
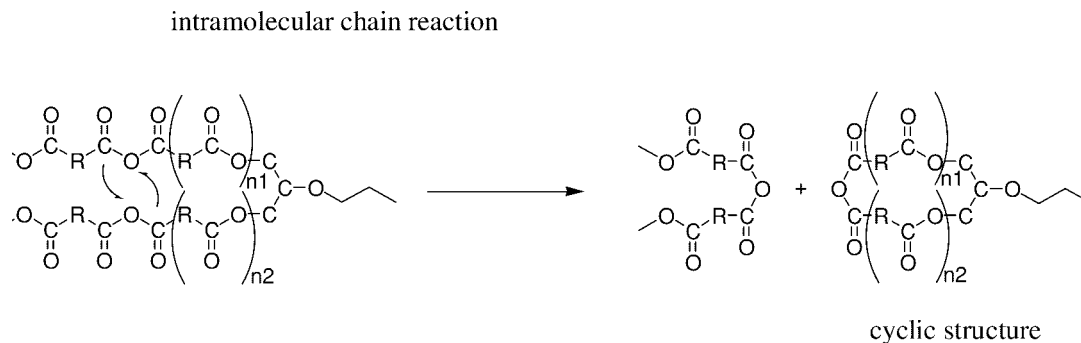


Figure 3 (Continued from the previous page)



Scheme 1

CONCLUSION

This study synthesized poly(anhydride-co-glycerol) by introducing glycerin into a poly(sebacic anhydride-co-ethylene glycol) system via melt condensation without a catalyst. Reaction between hydroxyl group on glycerin and sebacic anhydride pre-polymer was confirmed. Furthermore, synthesized materials were found to be totally free of hydroxyl group. Additionally, the introduction of a high content of glycerin (60% or more) caused the intramolecular chain reaction to become more remarkable. The intramolecular chain reaction can produce cyclic chains and low mo-

lecular weight species to reduce average molecular weight. Furthermore, these cyclic chain structures and low molecular weight species can hinder the crystal growth of sebacic anhydride chain segments, decreasing the melting temperature of sebacic anhydride chain segments in these synthesized materials.

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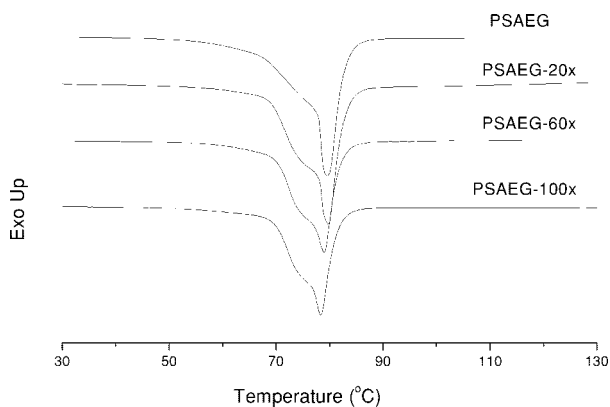


Figure 4 DSC thermogram curves of synthesized materials.