

# Anionic Ring-Opening Polymerization of Adipic Anhydride Initiated by Potassium Poly(ethylene glycol)ate

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**ABSTRACT:** Poly(adipic anhydride) (PAA) was prepared by the ring-opening polymerization of adipic anhydride (AA) initiated by potassium poly(ethylene glycol)ate. The effects of various factors, such as the amount of initiator, concentration of the monomer, reaction time and temperature, and polarity of the solvent on the polymerization were investigated. The crude polymerized product was a mixture of PAA homopolymer and poly(ethylene glycol)-poly(adipic anhydride) block copolymer, as confirmed by  $^1\text{H-NMR}$  and gel permeation chromatography. Chain-transfer reactions occurred intensively for the AA polymerization in both

the nonpolar solvent toluene and the polar solvents  $\text{CHCl}_3$  and tetrahydrofuran, which predominantly determined the molecular weight and the monomer conversion for the polymerized product. The lower monomer conversion in toluene was ascribed to a lower livingness for the initiator in the nonpolar solvent when compared with other two, polar solvents. © 2003 Wiley Periodicals, Inc. *J Appl Polym Sci* 88: 2194–2201, 2003

**Key words:** ring-opening polymerization; block copolymers

## INTRODUCTION

Polyanhydrides are well known for their biodegradability, biocompatibility, and nontoxicity.<sup>1–3</sup> Polyanhydrides are mainly used as carriers for drug-delivery systems because they display surface erosion and because their degradation rates can be altered over 1000-fold by simple changes in the backbone.<sup>4</sup> For example, polyanhydrides containing 1,3-bis(*p*-carboxyphenoxy)propane are currently used as implantable devices to control the delivery of chemotherapeutic drugs to treat brain cancer.<sup>5–7</sup>

Generally, polyanhydrides are prepared by the traditional polycondensation method reported by Hill and Carothers,<sup>8,9</sup> which has many disadvantages including a high vacuum, high reaction temperature, and long reaction time. Domb and Langer reported on the synthesis of high-molecular-weight polyanhydrides by an improved melt polycondensation process with mixed anhydrides of diacids and acetic acid and heterogeneous coordination catalysts, such as cadmium acetate, barium oxide, calcium oxide, and calcium carbonate.<sup>5–7</sup> Domb and Langer also used the previously mentioned improved melt polycondensation method to prepare unsaturated polyanhydrides,

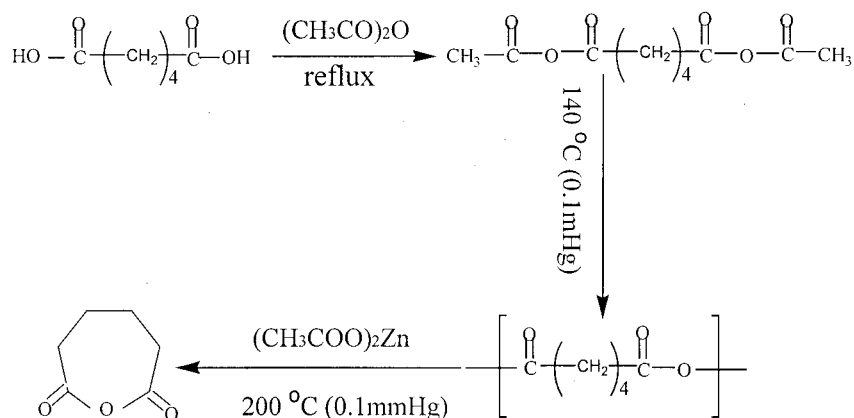
which could be further crosslinked.<sup>10</sup> However, well-defined and drastic conditions are usually required. Comparatively, the ring-opening polymerization of alicyclic anhydrides provides direct access to the related polyanhydrides and is most likely the best way to avoid all the disadvantages of the traditional polycondensation method. Albertsson and Lundmark studied the ring-opening polymerization of adipic anhydride (AA) in bulk in the presence of stannous 2-ethylhexanoate.<sup>11,12</sup> As an extension of the bulk polymerization of AA, Albertsson and Lundmark also studied the ring-opening polymerization of AA in solution with three kinds of catalysts and proposed the acyl-oxygen cleavage mechanism for all cases.<sup>13</sup> However, the polymers they obtained had a broad molecular weight distribution because of the side intermolecular and intramolecular transacylation reactions, which rapidly perturbed chain propagation. Teyssie et al. synthesized high-molecular-weight homopolymer and block copolymers of AA with  $\epsilon$ -caprolactone that had a narrow molecular weight distribution in the presence of aluminum alkoxide.<sup>14,15</sup>

Polyethers, especially poly(ethylene glycol) (PEG), have superior properties of nontoxicity, flexibility, hydrophilicity, and biocompatibility. The introduction of PEG into polyanhydrides can improve their hydrophilicity and thus adjust the degradation rate of obtained materials.<sup>16,17</sup> Kim and Langer synthesized degradable networks of poly(ether anhydride) from PEG-bis(carboxymethyl)ethers by photopolymerization. The strong hydrophilicity of the networks made the degradation ways change from surface erosion to bulk

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Scheme 1 Reaction scheme for the synthesis of AA.

hydrolysis.<sup>16</sup> Previously,<sup>18–21</sup> we reported the polymerization of  $\epsilon$ -caprolactone and lactide initiated by potassium poly(ethylene glycol)ate (PEGOK). As an extension of our past work, this study mainly dealt with the ring-opening polymerization of AA initiated by a PEGOK macroinitiator.

## EXPERIMENTAL

### Materials

Adipic acid analytic reagent (AR), acetic anhydride (AR), petroleum ether (AR), and ether (AR) were used as received. Poly(ethylene glycol) 2000 (PEG-2000) was purified by precipitation from chloroform solution into ether and was dried to constant weight under vacuum at 30°C. Toluene and tetrahydrofuran (THF) were dried over sodium and distilled under a nitrogen atmosphere before use. Chloroform ( $\text{CHCl}_3$ ) was dried over  $\text{P}_2\text{O}_5$  and distilled under a nitrogen atmosphere before use.

### Characterization

$^1\text{H-NMR}$  spectra of the copolymers were recorded on a Unit-Inova-400 (Varian, USA) spectrometer at room temperature with  $\text{CDCl}_3$  as solvent and tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Nicolet MX-1 IR spectrometer (WI). The molecular weight and its distribution were determined by gel permeation chromatography (GPC) with a Water Associates model ALC/GPC 2410 apparatus (USA) operating with chloroform and calibrated with polystyrene standards. For differential scanning calorimetry (DSC), we used a Seiko Exstar6000 (Cuiba-shi, Japan) thermal analysis apparatus at a heating rate of 10°C/min and a cooling rate of 20°C/min.

### Preparation of the macroinitiator

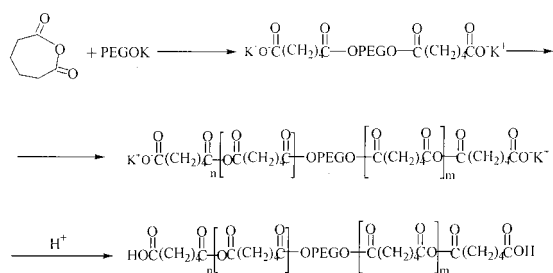
PEG-2000 (1 g) and fresh potassium particles (over stoichiometry) were placed in a previously flamed and nitrogen-purged glass reactor equipped with magnetic stirring bar and reflux condenser. THF (25 mL) was added through rubber septa with a syringe. The reaction mixture was refluxed for 24 h and filtered. The concentration of the initiator was measured by titration with 0.04% aqueous HCl. The results indicate that two terminal hydroxyl groups of PEG were converted into alcoholate.

### Monomer synthesis

AA was prepared as described elsewhere (Scheme 1).<sup>8–15</sup> In a typical reaction, a solution of 30 g of adipic acid in 300 mL of acetic anhydride in a dry reaction vessel equipped with a reflux condenser and a magnetic stirrer was heated for 4 h while nitrogen was continuously bubbled through the solution. The acetic acid formed and the excess acetic anhydride were distilled off under reduced pressure (0.1 mmHg). The residue was transferred into a Claisen flask and distilled in the presence of depolymerization catalyst (zinc acetate  $\cdot$  2 $\text{H}_2\text{O}$ ) under vacuum (0.1 mmHg). The monomer was characterized by  $^1\text{H-NMR}$  in  $\text{CDCl}_3$ , which exclusively showed two signals at 2.74 and 1.98 ppm at a 1:1 ratio corresponding to, respectively, the methylene groups in the  $\alpha$  and  $\beta$  positions of carbonyl functions and in agreement with the expected structure.<sup>12–15</sup> Fourier transform infrared spectroscopy showed a doublet at 1800 and 1756  $\text{cm}^{-1}$ , which is characteristic of a cyclic anhydride, and a second doublet characteristic of a cycle at 961 and 986  $\text{cm}^{-1}$ .

### Polymerization

The solution polymerization of AA was carried out in the following manner. To a previously flamed and



**Scheme 2** Anionic ring-opening polymerization of AA initiated by potassium poly(ethylene glycol-2000)ate.

nitrogen-purged glass reactor equipped with a magnetic stirring bar, the monomer was added, followed by solvent and initiator. Polymerization was stopped by the addition of a large volume excess of petroleum ether, and the precipitated polymer [a mixture of poly(adipic anhydride) (PAA) homopolymer and PEG-PAA block copolymer] was recovered by filtration. The obtained product was dissolved in a small volume of chloroform and repeatedly extracted with 0.1*N* aqueous HCl. The previous solution was washed with distilled water until it reached a neutral pH, was concentrated under a reduced pressure, and was then precipitated by petroleum ether. The precipitated product was dried in a vacuum at room temperature until no change in weight was observed. The crude products could be separated by fractionation because of the limited solubility of PAA. The products had to be stored in an anhydrous environment because of the inherent instability of aliphatic polyanhydrides toward moisture and depolymerization.

## RESULTS AND DISCUSSION

PAA with bifunctional carboxyl groups can be formed by the ring-opening polymerization of AA initiated by PEGOK (Scheme 2). Table I shows the effect of initiator amount on molecular weight and monomer conversion in the THF solvent. The molecular weight was lower than the theoretical value and did not increase linearly but only showed a slight change with the increase of initiator amount. The synthesized polymers precipitated from the solvent for all of the investigated polymerization cases in the THF solvent. The active center may have lost the ability to induce further polymerization if its attached chain precipitated from the reaction solvent. Thus, the far lower value of the molecular weight for the synthesized polymers compared with theoretical value may be ascribed to the previously mentioned precipitation effect.

Table I also shows that the monomer conversion increased with increasing initiator amount. However, this increase did not parallel the monomer/initiator ratio. The conversion was higher than the value calculated based on the molecular weight if only the effect of precipitation was considered. This fact indicates that another factor, chain-transfer reactions, may have dominated the polymerization more than the precipitation effect. Figure 1 shows the <sup>1</sup>H-NMR spectrum of the copolymer. Peaks at 1.73, 2.49, 2.40, and 2.35 were assigned to  $\alpha$ ,  $\beta$  methylene protons in PAA units,  $\alpha$ -carboxyl methylene end groups, and  $\alpha$ -methylene anhydride, respectively. The formation of copolymer was confirmed by the appearance of a sharp singlet, a triplet, and a multiplet at 3.64, 3.70, and 4.23 ppm, respectively, because of the methylene protons

**TABLE I**  
Polymerization of AA Initiated by Potassium Poly(ethylene glycol-2000) ate in THF at 20°C for 24 h

No.	AA (g)	AA/PEGOK (w/w)	Conversion (%) <sup>a</sup>	$M_n^{\text{exp}}$	$M_n^{\text{theo}}$ ( $\times 10^6$ )	Polydispersity
1	2.11	5	100	4222 <sup>b</sup>	0.012	—
2	3.54	10	98	4718 <sup>b</sup>	0.022	—
3	3.53	40	92	5710 <sup>c</sup>	0.075	1.30
4	2.90	80	87	5725 <sup>c</sup>	0.141	1.35
5	2.84	100	85	5760 <sup>c</sup>	0.172	1.25
6	2.56	400	85	5670 <sup>c</sup>	0.682	1.37
7	3.20	600	85	5819 <sup>c</sup>	1.022	1.41
8	3.68	800	80	5770 <sup>c</sup>	1.282	1.31
9	9.66	1000	78	5690 <sup>c</sup>	1.562	1.45
10	2.51	1500	78	5687 <sup>c</sup>	2.342	1.36
11	3.17	2500	74	5762 <sup>c</sup>	3.701	1.29

[AA]<sub>0</sub> = 10% (w/v).  $M_n^{\text{exp}}$  = experimental number-average molecular weight;  $M_n^{\text{theo}}$  = theoretical number-average molecular weight.

<sup>a</sup> Conversion was measured by gravimetry.

<sup>b</sup>  $M_n^{\text{exp}}$  was calculated from <sup>1</sup>H-NMR.

<sup>c</sup>  $M_n^{\text{exp}}$  and polydispersity were determined by GPC in chloroform.

<sup>d</sup>  $M_n^{\text{theo}} = 2000[\text{AA}]X/[\text{PEGOK}]100$ , where  $X$  is the monomer conversion.

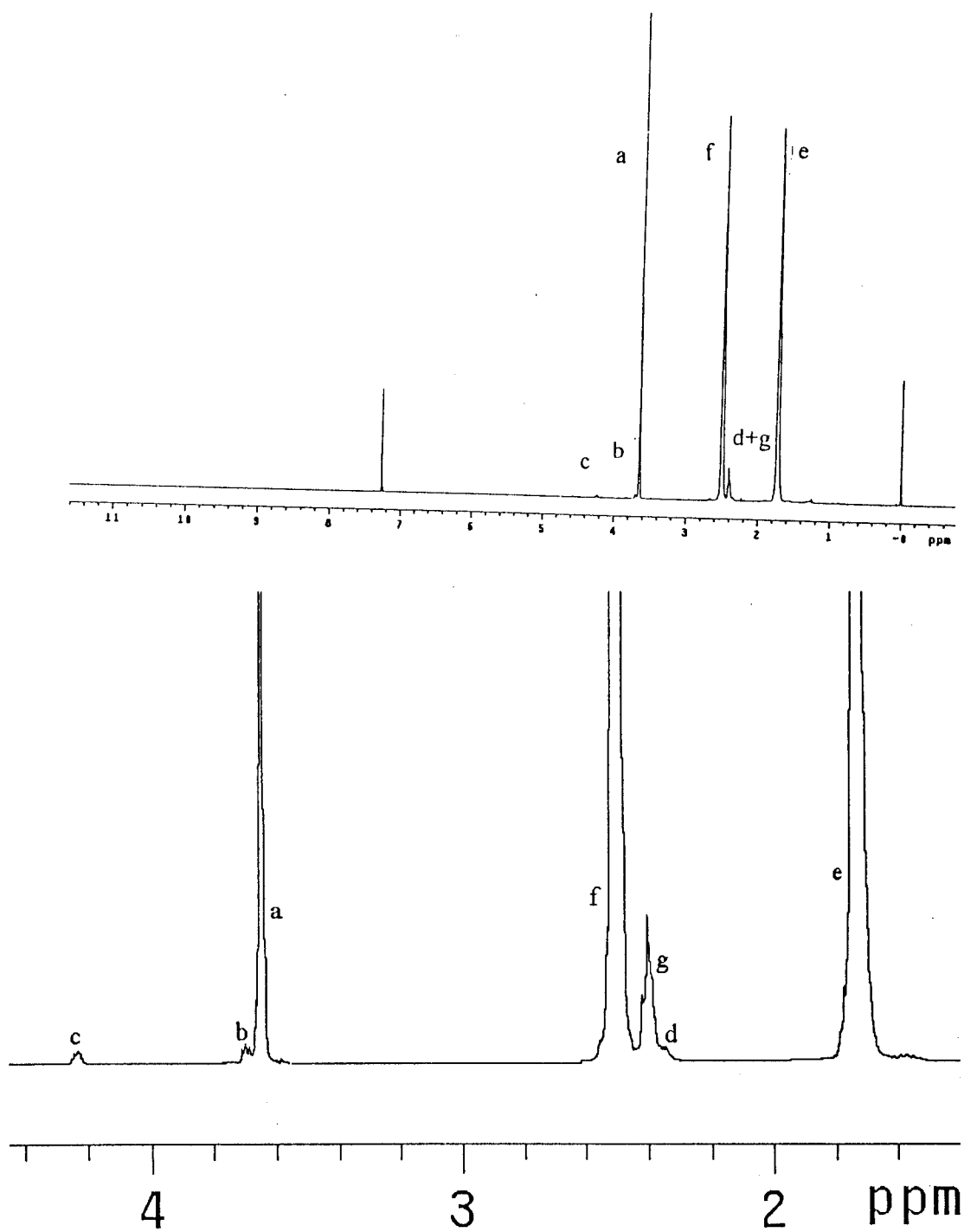
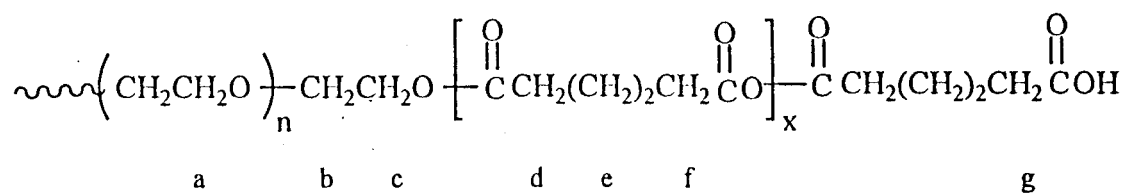


Figure 1  $^1\text{H-NMR}$  spectrum of PAA initiated by potassium poly(ethylene glycol-2000)ate (the solvent was  $\text{CDCl}_3$ ).

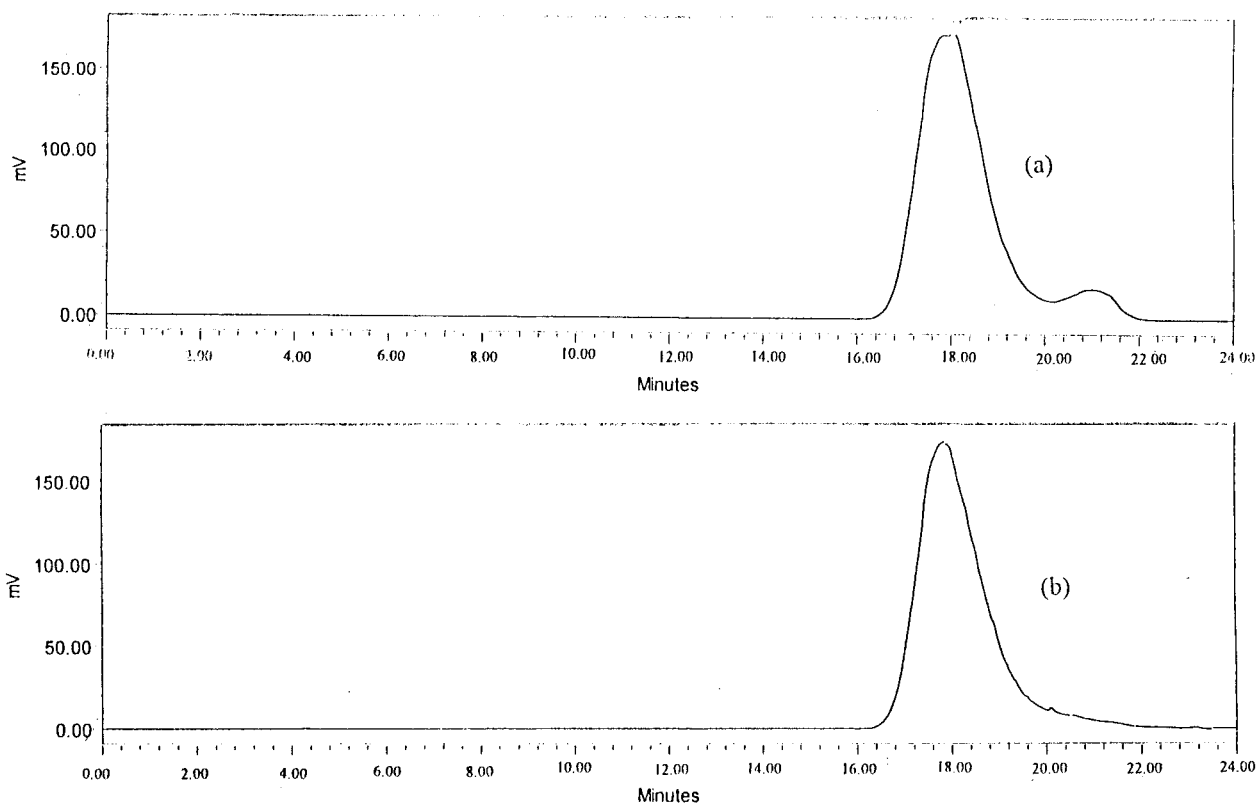


Figure 2 GPC traces of (a) crude polymerized product and (b) purified polymer.

of the homosequences of PEG oxyethylene units and the terminal oxyethylene group. However, the signal intensity of the  $\alpha$ -carboxyl methylene end group

( $-\text{CH}_2\text{COOH}$ , 2.40 ppm) was stronger than that of  $\alpha$ -methylene anhydride ( $\text{PEGOCCH}_2-$ , 2.35 ppm) and the terminal oxyethylene group of PEG

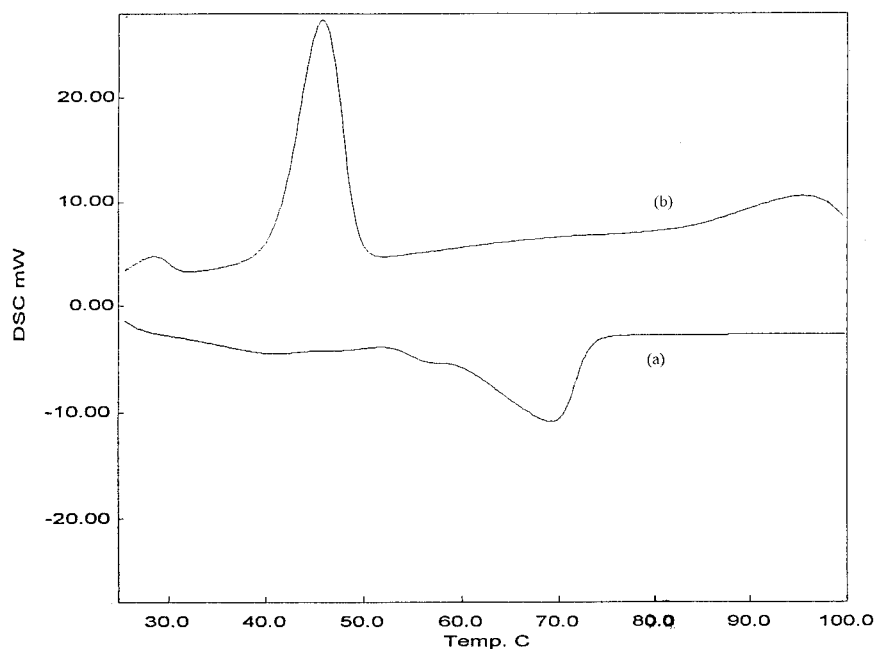
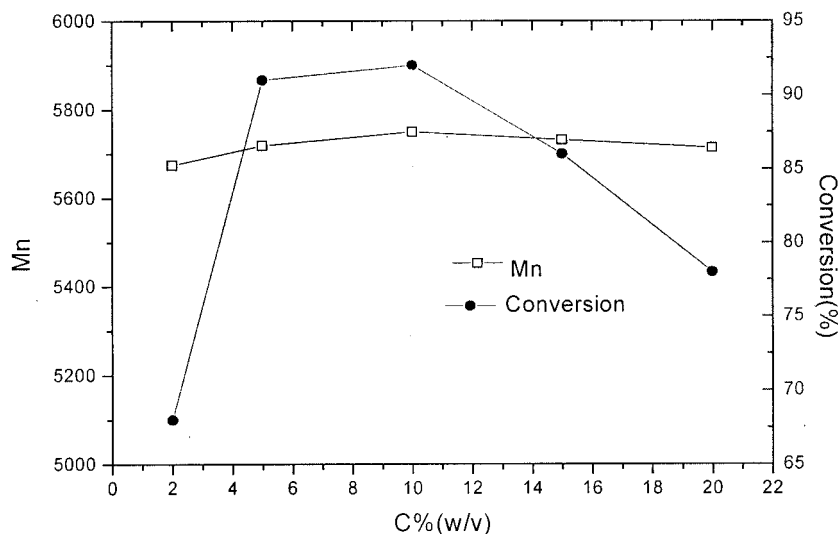


Figure 3 DSC curves of block copolymer recorded at the (a) first heating and (b) cooling process (sample weight = 9.99 mg, heating rate =  $10^\circ\text{C}/\text{min}$ , cooling rate =  $20^\circ\text{C}/\text{min}$ ,  $\text{N}_2$  = 50 mL/min).



**Figure 4** Effect of monomer concentration on polymerization [AA/PEGOK = 1500 (w/w) at 20°C for 24 h].  $M_n$  = number-average molecular weight.

(—OCH<sub>2</sub>CH<sub>2</sub>OOC—, 3.70 and 4.23 ppm). This fact indicates that the crude polymerized product in the THF solvent was not a pure poly(ethylene glycol)-poly(adipic anhydride) (PEG-PAA) block copolymer but a mixture containing PAA homopolymer. This could be confirmed by the appearance of double peaks in GPC [Fig. 2(a)]. The crude product had a broader molecular weight distribution when compared with the purified polymer [Fig. 2(b)]. These results confirm the formation of PAA homopolymer and the previously mentioned hypothesis that chain-transfer reactions were the more dominating factor controlling the molecular weight for the AA polymerization in the THF solvent when compared with the precipitation effect.

A typical DSC analysis for the purified product is shown in Figure 3. As shown, the melting temperature and crystalline temperature of PAA were positioned at 69.2 and 45.3°C, respectively, and their corresponding endotherm and exotherm were 46.80 and 51.65 J/g, respectively. Furthermore, a broad melting range

due to the different crystalline grade was observed. According to Pearce and Marchessault,<sup>22</sup> such a broad melting range is intimately linked to a melt-recrystallization process. The melting peak for the PEG segments, however, was not observed on the heating curve. This may be ascribed to the hindrance effect of the PAA component on the crystallization of PEG segments.

The influence of monomer concentration on the polymerization is presented in Figure 4. As shown, the proper monomer concentration for polymerization in the THF solvent was 5–10% (g/mL). The monomer conversion increased to some extent (92%) and then decreased with increasing monomer concentration. This decrease was ascribed to the precipitation of polymerized product at high monomer concentration. The polymer slurry formed did not stir well, which led to the decrease in monomer conversion.

To further investigate the polymerization of AA initiated by PEGOK, polymerizations with toluene and CHCl<sub>3</sub> as the solvents were performed, and the

**TABLE II**  
Effects of Solvents on the Polymerization of AA at 30°C for 24 h

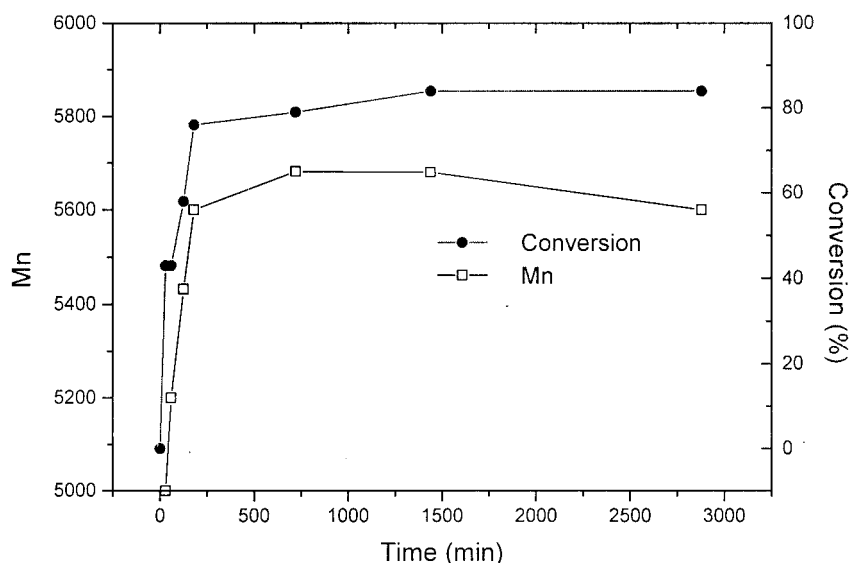
AA/PEGOK (w/w)	Conversion (%) <sup>a</sup>			$M_n^{\text{expb}}$			$M_n^{\text{theo c}} (\times 10^6)$			Polydispersity		
	Toluene	THF	CHCl <sub>3</sub>	Toluene	THF	CHCl <sub>3</sub>	Toluene	THF	CHCl <sub>3</sub>	Toluene	THF	CHCl <sub>3</sub>
600	34	85	87	5910	5819	5600	0.408	1.022	1.046	1.25	1.40	1.98
1000	14	78	84	5987	5690	5720	0.280	1.562	1.682	1.18	1.45	1.78
1500	8	78	80	5600	5687	5814	240	2.342	2.402	1.12	1.35	1.64
2500	8	74	61	—	5762	5602	—	3.701	3.051	—	1.29	1.58

[AA]<sub>0</sub> = 10% (w/v).  $M_n^{\text{exp}}$  = experimental number-average molecular weight;  $M_n^{\text{theo}}$  = theoretical number-average molecular weight.

<sup>a</sup> Conversion was measured by gravimetry.

<sup>b</sup>  $M_n^{\text{exp}}$  and polydispersity were determined by GPC in chloroform.

<sup>c</sup>  $M_n^{\text{theo}} = 2000[\text{AA}]X/[\text{PEGOK}]100$ , where X is the monomer conversion.

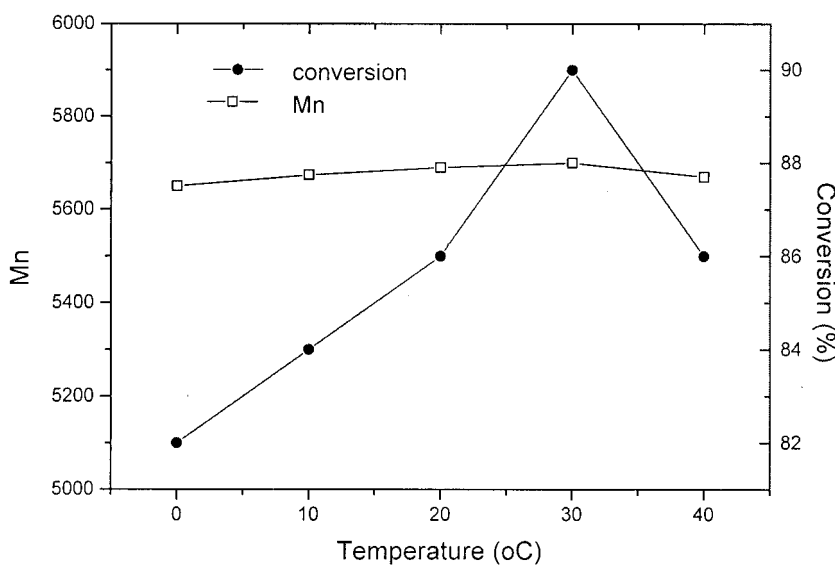


**Figure 5** Influence of the reaction time on the molecular weight of the polymer and the conversion of the monomer. [4.32 g of AA in 44 mL of  $\text{CHCl}_3$ , AA/PEGOK = 1500 (w/w) at  $30^\circ\text{C}$ ].  $M_n$  = number-average molecular weight.

results are listed in Table II. As shown, the molecular weight of the polymers obtained in the  $\text{CHCl}_3$  solvent showed a slight change with monomer/initiator ratio, and the value was almost the same as that in the THF solvent despite the fact that  $\text{CHCl}_3$  was a good solvent for both PAA and PEG-PAA. Furthermore, the experimental monomer conversion was higher than that calculated on the basis of the molecular weight. These facts indicate that the polymerization of AA in the  $\text{CHCl}_3$  solvent was intensively perturbed by the occurrence of chain-transfer reactions at the expense of the control of molecular weight. The previous results

are in close agreement with those obtained from AA polymerization initiated by aluminum triisopropoxide in  $\text{CH}_2\text{Cl}_2$ .<sup>14,15</sup>

Similar to the AA polymerization in THF and  $\text{CHCl}_3$ , the molecular weight of the polymerized product in toluene was also determined by chain-transfer reactions (Table II). However, the monomer conversion in toluene was lower than those obtained in THF or  $\text{CHCl}_3$ . It is well known that anionic polymerization is greatly influenced by the polarity of the solvent. The anionic initiator was more easily associated in the nonpolar solvent of toluene compared with the polar



**Figure 6** Dependence of the molecular weight of the polymer and the conversion of the monomer on the reaction temperature [M/I (monomer/initiator) = 1000 (w/w), C% (concentration) = 10% (w/v),  $\text{CHCl}_3$ , 24 h].  $M_n$  = number-average molecular weight.

solvents THF and  $\text{CHCl}_3$ . The existence of more compact ion pairs decreased the concentration of the active centers of initiators in toluene, thus leading to a lower monomer conversion compared with those in THF and  $\text{CHCl}_3$ .

Figure 5 shows the influence of reaction time on the AA polymerization in the  $\text{CHCl}_3$  solvent. During the initial 3-h polymerization, the monomer conversion increased with increasing reaction time, whereas the molecular weight stayed at almost the same value. This fact further confirmed that chain-transfer reactions controlled the AA polymerization in the  $\text{CHCl}_3$  solvent.

The effect of temperature on the polymerization was also investigated (Fig. 6). The data indicate that a high reaction temperature should not be recommended for AA polymerization in solution and that the optimum temperature for the polymerization is  $30^\circ\text{C}$ . The rate of chain-transfer reactions increased more rapidly than the polymerization rate at elevated temperatures, thus leading to a decrease in the molecular weight of the polymerized product. This result is in close agreement with that reported by Albertsson et al.<sup>11–13</sup>

### CONCLUSIONS

PAA was prepared by the ring-opening polymerization of AA initiated by PEGOK. The polymerized product was a mixture of PAA homopolymer and PEG–PAA block copolymer, as confirmed by  $^1\text{H-NMR}$  and GPC. Chain-transfer reactions occurred intensively for the AA polymerization in either the nonpolar solvent toluene or the polar solvents  $\text{CHCl}_3$  and THF, which predominantly determined the molecular weight and the monomer conversion for the polymer-

ized product. The lower monomer conversion in toluene was ascribed to a lower livingness for the initiator in the nonpolar solvent as compared with other two, polar solvents.

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