

# Stability and Depolymerization of Poly(sebacic anhydride) Under High Moisture Environment

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**ABSTRACT:** Polyanhydrides are found to be useful in drug delivery systems; however, these aliphatic polyanhydrides are also unstable under humidity and temperature (greater than 0°C) for their low toxicity and surface eroding mode of drug release. In this research, poly(sebacic anhydride) was synthesized for a stability and depolymerization study in high humidity a surrounding temperature of 35°C. According to the results from gel permeation chromatography, IR spectrophotometry, and differential scanning calorimetry investigations, it was found that both self-depoly-

merization and hydrolysis mechanisms existed during the depolymerization process for poly(sebacic anhydride) and they can be monitored directly. These results were further compared with previous research in a depolymerization study of polyanhydrides in a vacuum and in buffer solution. © 2003 Wiley Periodicals, Inc. *J Appl Polym Sci* 89: 1423–1429, 2003

**Key words:** polyanhydrides; stability; depolymerization; gel permeation chromatography; differential scanning calorimetry

## INTRODUCTION

In recent years, biodegradable polymeric materials have attracted many research efforts, because of their possible use in drug delivery systems to achieve better pharmacological effects. Hence, a large number of novel materials including polyesters, poly(aliphatic esters), poly(orthoesters), poly(phosphate esters), synthetic peptide-based polymers, and polysaccharides have been synthesized and applied as biodegradable matrices for this purpose.<sup>1–4</sup>

Among these materials, the interest in a class of polymers termed polyanhydrides for biomedical applications has grown remarkably. The syntheses of these polymers were reported, as was their use for the controlled delivery of drugs with surface eroding behavior, thereby providing a sustained release rate over long periods of time.<sup>3–12</sup> It is shown that these materials are not only degradable but also highly biocompatible, as are their degradation products, which has been demonstrated by tissue response and toxicological studies.<sup>3</sup>

However, drawbacks still remain for polyanhydrides. It is well known that these materials are unstable in moisture, which may result in hydrolysis and the forming of carboxyl acid molecules [Scheme 1(a)]. This is the reason that polyanhydrides were aban-

doned for applications in the textile industry in the early years. Furthermore, as indicated in previous research,<sup>13–15</sup> these materials not only eroded in humidity but were also unstable in surroundings with a higher temperature and depolymerized into smaller cyclic polyanhydrides [Scheme 1(b)]. This is a really serious problem that may change the properties of materials and the erosion rates. Therefore, it may result in a significant influence when put into applications.

In this study poly(sebacic anhydride) (PSA) was synthesized from sebacic acid via melt condensation. This material was placed into a humidity chamber to study the depolymerization process. We employed gel permeation chromatography (GPC), IR spectrophotometry, and differential scanning calorimetry (DSC) for an examination of the erosion behavior and to elucidate the mechanisms of depolymerization. It can be found that both of the depolymerization mechanisms (self-depolymerization and hydrolysis) can be monitored directly; moreover, they can be recognized in the GPC and DSC profiles for PSA in these high humidity surroundings.

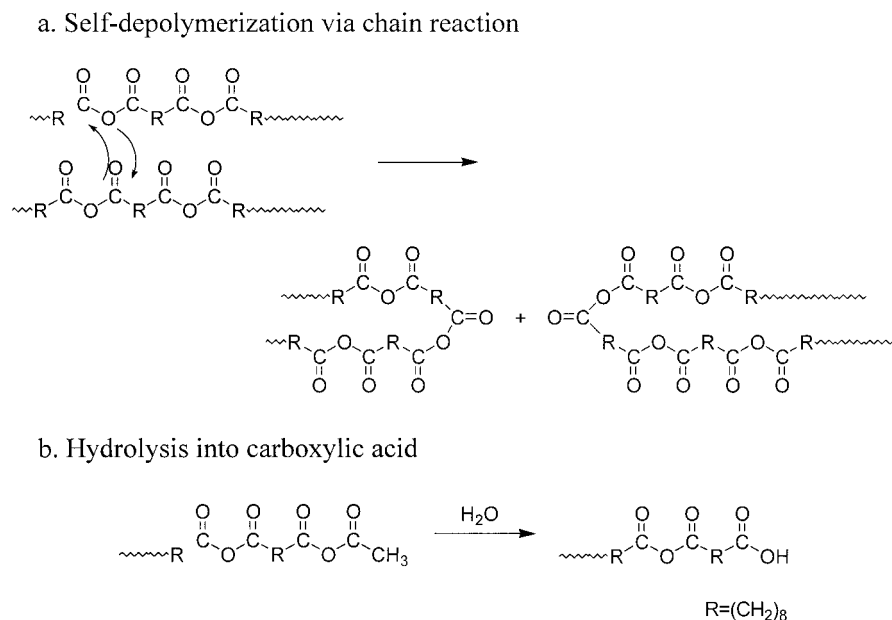
## EXPERIMENTAL

### Materials

Sebacic acid and acetic anhydride were purchased from Riedel-de Haën. Dichloromethane (HPLC grade, Fisons Scientific Eq.), toluene (Mallinckrodt), petroleum ether (anhydrous, J. T. Baker), and ethyl ether (anhydrous, J. T. Baker) were all HPLC grade and were used as received without further purification.

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**Scheme 1** The formation of carboxylacid molecules.

### Synthesis of PSA

After raising the temperature to 140°C, 24 g of sebacic acid and 248 g of acetic anhydride were charged into a dry nitrogen purged reactor. The reaction was processed with rigorous mixing for 20 min. The mixture was then placed in a rotary evaporator to remove the acetic acid and unreacted acetic anhydride. The crude prepolymer was recrystallized from dry toluene. Subsequently, the crystals were immersed in the solvent (1:1 dry petroleum ether and ethyl ether) to extract the traces of acetic anhydride and toluene. After drying under a vacuum, refined prepolymer is obtained.<sup>6</sup>

The refined prepolymer (3.0 g) was then placed in an oil bath reactor at 180°C under a vacuum for 120 min to carry out the melt-condensation process.<sup>3,6</sup> The final product was dissolved in dichloromethane first, and it was purified by precipitation in dry petroleum ether. The precipitate was further purified by extraction with anhydrous ethyl ether.

### Characterization of depolymerization process

After synthesis and purification of PSA, the samples were immediately ground into powder. Subsequently, the sample for depolymerization study was placed in the 35°C temperature controlled humidification chamber with a relative humidity of 100%. At each time point the molecular weight distribution, crystalline behavior, and IR spectrum for degraded products were analyzed with the following instrumental analyses.

The molecular weights of the synthesized PSA and depolymerized products were determined by GPC equipment, which was constructed with a pump

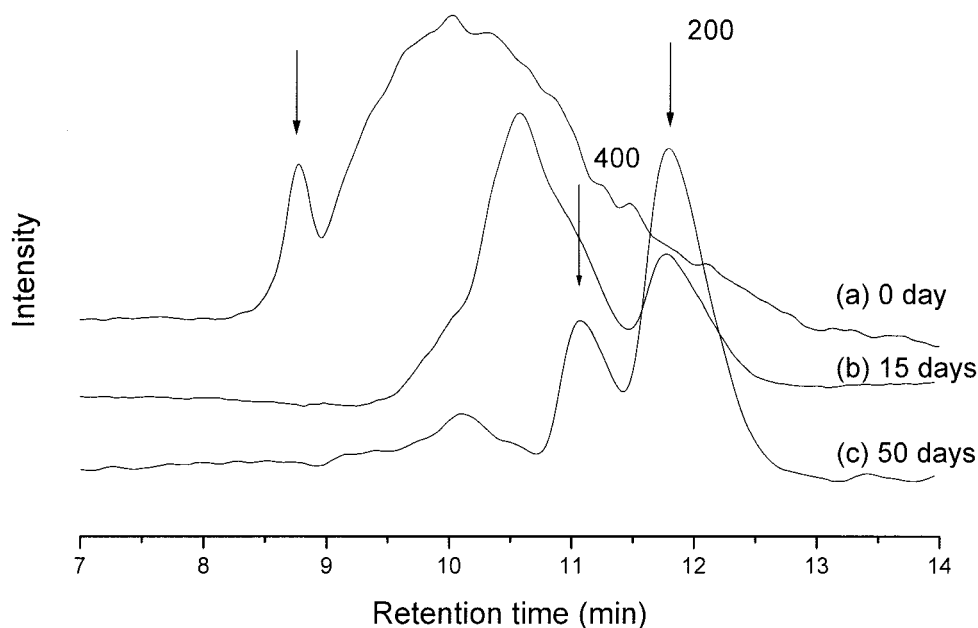
(Jasco PU-1580) and a detector (Jasco RI-1530); polystyrene (Shodex standard SL-105, Showa Denko) was used as the standard. Chloroform was used as an eluent at a rate of 1.5 mL/min. In addition, the IR spectra of these materials were obtained from a Fourier transform IR spectrophotometer (Nicolet Avatar 320) at a 2 cm<sup>-1</sup> resolution with 64 scans in a spectral range of 4000–400 cm<sup>-1</sup>.

A TA 2010 DSC apparatus was utilized for the crystalline behavior study of the synthesized PSA and its depolymerized products. DSC thermoscans of these materials were conducted under dry nitrogen at a heating rate of 10°C/min. After a 5-min isothermal process at a temperature higher than that for complete melting of the crystals, a subsequent cooling scan was carried out at a cooling rate of 5°C/min to acquire the information on the crystalline behavior.

## RESULTS AND DISCUSSION

### GPC study for molecular weight variations

The GPC measurements of the depolymerized products are shown in Figure 1. There is a main peak at 10.1 min on the GPC profile for the synthesized PSA (Fig. 1, spectrum a). A relatively high molecular weight peak also exists at a retention time of 8.8 min on the same profile as the arrow indicates. In previous research presented by Domb and Langer,<sup>6</sup> they pointed out that polyanhydride is a mixture of longer and shorter molecular chains, where the intramolecular or intermolecular chain reaction may occur during the melt-condensation process. In addition, the intramolecular reaction may result in the formation of larger rings and may possibly continue to react via the



**Figure 1** The molecular weight distribution of PSA (Spectrum a) and the samples depolymerized in the surrounding humidity with depolymerization times of 15 (spectrum b) and 50 days (spectrum c). The designated peaks denoted by arrows are at retention times of 8.8, 11.1, and 11.8 min.

same mechanism to produce smaller rings with a reaction time greater than 90 min. Hence, it can be confirmed that the high molecular weight species found on the GPC profile in this study resulted from the formation of high molecular weight rings via the melt-condensation process at high temperature, and it also raised the polydispersity index of PSA.

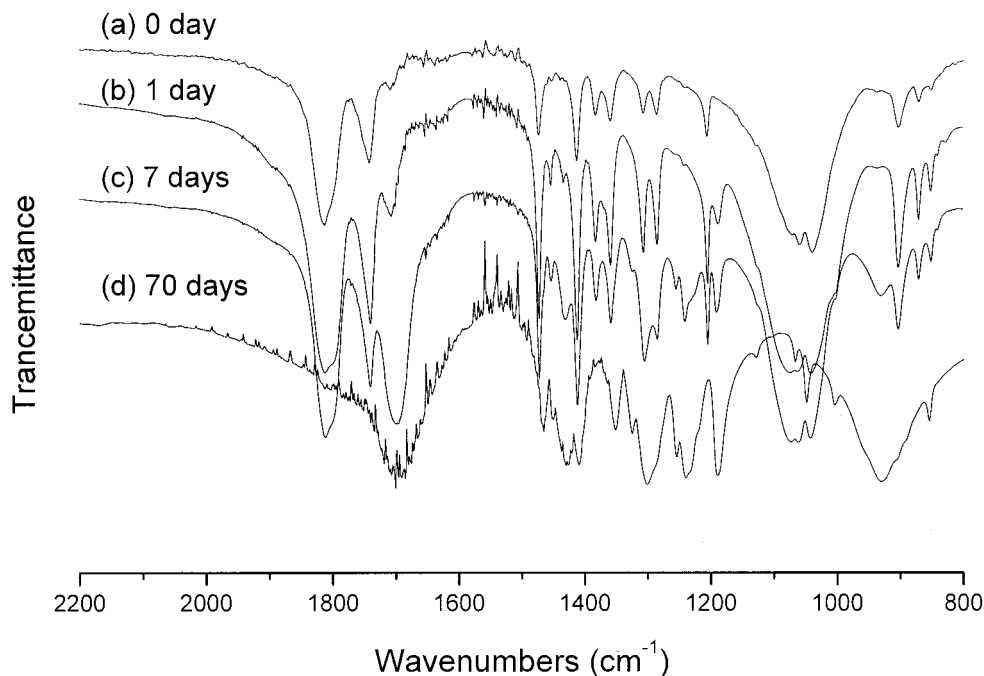
On the other hand, there are obvious peaks at retention times of 10.6 and 11.8 min that can be found for PSA with a depolymerization time of 15 days (Fig. 1, spectrum b). On the same GPC profile, two shoulders existed on the side of the eluent peak at 10.6 min, which were located at retention times of 10.1 and 11.1 min. After depolymerization for 50 days, the main peak at 10.6 min disappeared and the two shoulders with retention times of 10.1 and 11.1 min developed into two distinct peaks (Fig. 1, spectrum c, arrows). Moreover, the amount of species increased at a retention time of 11.8 min, which exhibited much more than that with a depolymerization time of only 15 days. This peak was identical to that of the monodispersed GPC profile for a sebacic acid monomer (molecular weight =  $\sim 200$ ). The peaks at retention times of 11.1 and 11.8 min indicate the formation of dimers and monomers, respectively.

It was found earlier that these materials are unstable in surrounding humidity, which may result in the hydrolysis from anhydride into smaller diacid molecules. In addition, as indicated in previous research,<sup>14</sup> the self-depolymerization mechanism indeed plays an important role in the depolymerization process at this high temperature (35°C in a vacuum) and this may

result in the smooth shifting of the GPC profile of the polymers with time. Hence, from these results an inference can be made that more than one depolymerization route existed, which incurred a peculiar profile during the GPC investigation in this heterogeneous erosion research (compare to the erosion study in a well-mixed solution). One route degrades the PSA continuously to low molecular weight products (peak at 11.8 min, Fig. 1, spectrum a) and the other to products of a certain molecular weight (as the peaks at retention time of 10.1 and 11.1 min), and these two routes have different depolymerization rates. This may have resulted from a different mechanism or depolymerization route. More evidence is presented and discussed in the following sections.

#### IR analysis for PSA and its depolymerization products

The variation of the IR absorptions of PSA provides indications of the structural changes during the depolymerization process. Figure 2 shows the IR spectra of PSA and PSA with depolymerization products for 7 and 70 days of incubation. In this figure the absorptions at 1090–1030  $\text{cm}^{-1}$  were due to the stretching vibration for the C—O—C group on acid anhydrides.<sup>16</sup> In addition, all the absorption peaks at about 1814, 1739, and 1697  $\text{cm}^{-1}$  were well resolved, which were related to asymmetric stretching for the carbonyl group on anhydride, symmetric stretching for the carbonyl group on anhydride, and stretching vibration for the carbonyl group on carboxylic acid, respective-



**Figure 2** The IR absorption of PSA (spectrum a) and the samples depolymerized in the surrounding humidity with depolymerization times of 1 (spectrum a), 7 (spectrum c), and 70 days (spectrum d).

ly.<sup>16</sup> It is obvious that the carbonyl absorption for carboxylic acid (at  $1697\text{ cm}^{-1}$ ) was increased and the absorptions for carboxylic anhydride (at  $1814$  and  $1739\text{ cm}^{-1}$ ) were diminished as depolymerization proceeded. Combining the vanishing of the absorption peaks at  $1090\text{--}1030\text{ cm}^{-1}$ , it can be proposed that the hydrolysis effect is important during depolymerization under the high humidity in this study. This confirms the conclusions made from the GPC investigation.

#### Variation of crystalline behavior of PSA

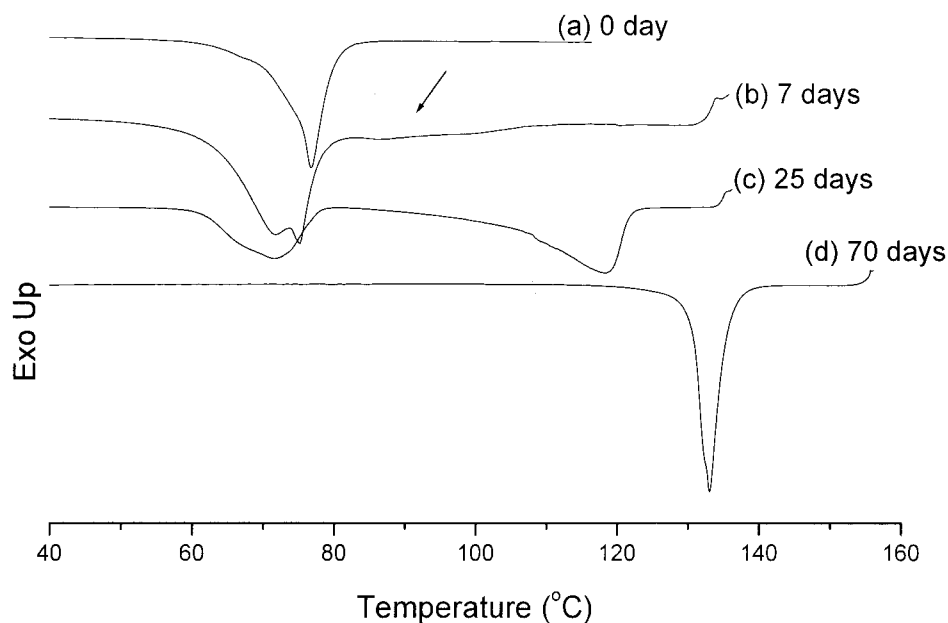
At the desired time points after depolymerization, the crystalline behavior of these products was investigated using DSC. The curves of DSC thermoscan are sketched in Figures 3 and 4 for heating scans and cooling scans, respectively. In Figure 3, the thermoscan curve of the synthesized PSA has only a single endothermic peak and the melting point is  $76.8^\circ\text{C}$  (Fig. 3, spectrum a). In addition, after PSA was depolymerized, the endothermic peak at about  $75^\circ\text{C}$  was diminished and a second endothermic peak was observed at  $85\text{--}105$  (arrow) and  $118.2^\circ\text{C}$  for the samples with depolymerization times of 7 and 25 days, respectively. This new peak increased and shifted to a higher temperature region as the time passed in the depolymerization process. After depolymerization for 70 days, a single melting point was found again, but at the relatively high temperature of  $133.3^\circ\text{C}$  (Fig. 3, spectrum d). On the other hand, in the DSC cooling profiles (Fig.

4) it can also be found that an apparent shoulder existed beside the main exothermic peak at  $51.6^\circ\text{C}$  (arrow) for the sample with a depolymerization time of 7 days; furthermore, a distinct peak was also found at  $95.1^\circ\text{C}$  for the sample with a depolymerization time of 25 days. In addition, there was also a single exothermic peak found (at  $119.8^\circ\text{C}$ ) in the cooling scan for the sample with 70-day depolymerization.

As shown in Figure 5, the sample depolymerized under anhydrous conditions (in a vacuum) does not exhibit two endothermic peaks in the DSC thermoscan as it depolymerized in the surrounding humidity; only a single peak and a shifting to a lower temperature region can be observed. In general, when the crystallites of polymers break down into smaller species, the crystallinity of the system may be decreased and the size of the crystallites may also be diminished. Thompson and Gibbs suggested an equation to predict a linear relationship between the melting point and the reciprocal of the crystal thickness for distinct components<sup>17</sup>:

$$T_m = T_m^0 \left( 1 - \frac{2\sigma}{L_c \rho_c \Delta h^0} \right) \quad (1)$$

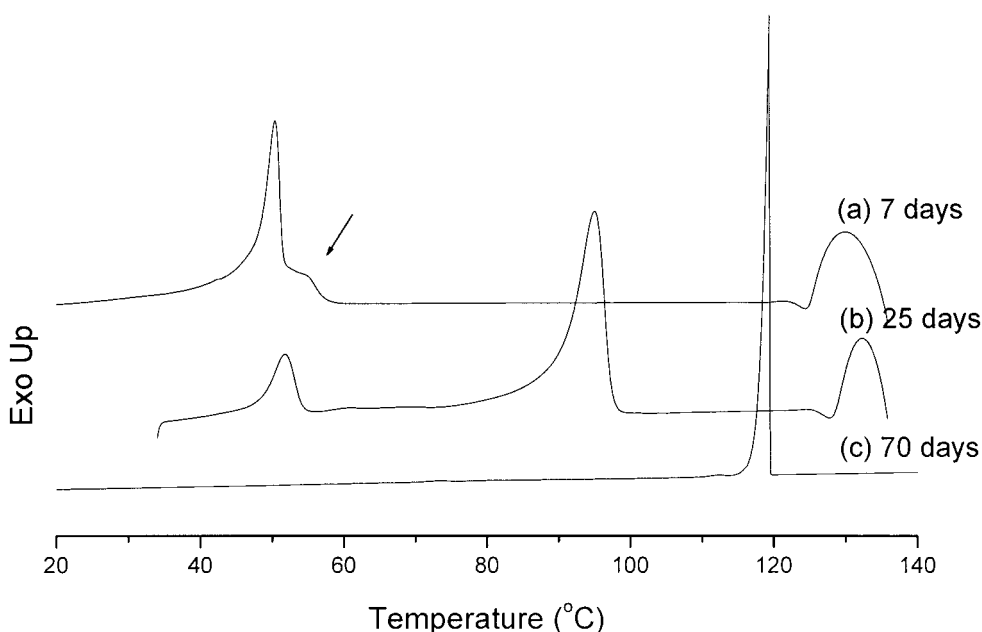
where  $\sigma$  is the specific fold surface energy;  $L_c$  is the thickness of the crystals;  $\rho_c$  is the density;  $\Delta h^0$  is the heat of fusion of the crystalline component; and  $T_m$  and  $T_m^0$  are the melting point and the equilibrium melting point (for infinite crystal thickness), respectively.



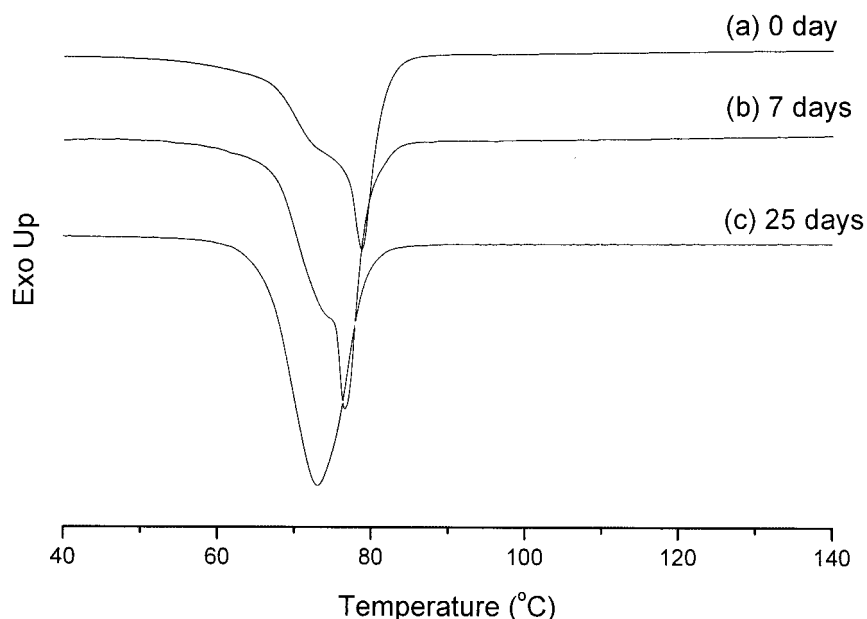
**Figure 3** The DSC thermogram curves of PSA (spectrum a) and the samples depolymerized in the surrounding humidity with depolymerization times of 7 (spectrum b), 25 (spectrum c), and 70 days (spectrum d) in the first heating scan.

Therefore, from this equation the decrease of the crystallinity and the size of the crystallites would result in the reduction of the melting enthalpy and the melting temperature. In addition, the melting temperature of the sebacic anhydride prepolymer was also slightly lower than that of PSA. From these results it is obvious that the endothermic peak of the DSC thermogram at about 75°C in Figure 3 resulted from the melting of PSA crystals. In addition, the melting points of sebacic anhydride or PSA oligomer were also proximate to

this temperature. Hence, the second endothermic peak in the heating scans or the exothermic peaks in the cooling scans observed in the higher temperature region is due to the other crystalline behavior from the depolymerized product. However, the appearance of a newly endothermic peak in the DSC thermogram was at a higher temperature region than the synthesized PSA. Moreover, it shifted continuously to a much higher temperature of 133.3°C after the PSA sample was depolymerized for 70 days, so that the



**Figure 4** The DSC thermogram curves of the PSA samples depolymerized in the surrounding humidity with depolymerization times of 7 (spectrum a), (b) 25 (spectrum b), and 70 days (spectrum c) in the cooling scan.



**Figure 5** The DSC thermogram curves of PSA (spectrum a) and the samples depolymerized in a vacuum with depolymerization times of 7 (spectrum b) and 25 days (spectrum c) in the first heating scan.

melting temperature was identical to that of neat sebacic acid. Therefore, this elevated peak in the higher temperature region in the DSC thermogram did not result from the crystalline behavior of PSA, nor from depolymerized anhydride-terminated oligomer, but from sebacic acid.

In the previous research presented by Göpferich et al.,<sup>15</sup> they observed a similar phenomenon in a poly-(fatty acid dimer-*co*-sebacic acid) copolymer system during erosion in a phosphate buffer solution. They indicated that the second endothermic peak (higher one) was continuously shifting to a higher temperature. Furthermore, the enthalpy value of the sebacic acid monomer examined in the DSC thermogram was increased before they released it into the buffer. From their results and the information from the IR spectra and DSC investigation in this study, another inference can be made that the molecular structure of the depolymerized product observed in the second endothermic peak in the DSC thermogram was terminated with an acid group, not an anhydride group, which resulted from the hydrolyzation in the humid atmosphere. Moreover, these polymeric molecules and oligomers were continuously decomposed into smaller diacid oligomers with the depolymerization time, thus resulting in the melting point continuously shifting to a higher temperature. Eventually, after the PSA eroded into sebacic acid completely, only a single sharp endothermic peak can be found at 133.3°C in the DSC thermogram. Hence, the elevation and shifting of the second endothermic peak observed in the DSC thermogram can be attributed to the melting of crystallites of variously sized carboxylic acid terminated

oligomers, resulting from the depolymerization of the synthesized material via a hydrolysis mechanism.

#### Depolymerization mechanisms

Nevertheless, the identity of the two peaks found in the GPC profile for PSA with a 50-day depolymerization was not resolved. For this aspect, DSC profiles may provide some indication for the origin of the peaks. Spectrum b in Figure 3 (7-day depolymerization) shows the obvious shoulder at the lower temperature region on the side of the endothermic peaks for PSA crystals in the DSC thermogram. In addition, the width of the endothermic peak was increased for the sample with a depolymerization time of 25 days. This indicates that an unusual PSA structure (anhydride terminated) absolutely existed, which may be sebacic anhydride oligomer or cyclic sebacic anhydride. Previous research indicated that cyclic dimer can be formed during the self-depolymerization process.<sup>14</sup> This can result in the rise of the peak in the GPC profile at a retention time of 11.1 min. According to these results from the peculiar GPC profile, the accumulation of cyclic dimers of sebacic anhydride is confirmed. It can also be noted that the cyclic dimer degraded into sebacic monomer at a much lower rate than did the linear PSA molecules. Without the carboxylic acid group, these species have a completely different degradation rate than the carboxylic acid terminated depolymerized products; thus, this resulted in the heterogeneous depolymerization behavior in the GPC profile. In addition, after being depolymerized for 70 days, the content of these cyclic

PSA or PSA dimers was insufficient to exhibit crystalline behavior; therefore, we found no obvious peak in the DSC thermogram.

### CONCLUSION

In this study PSA was synthesized for a depolymerization study in the humid surroundings with a temperature of 35°C. It was found that was PSA depolymerized not only by self-depolymerization via a chain reaction as it depolymerized in a vacuum but also by the mechanism of being hydrolyzed into diacid molecules in such high humidity surroundings. Furthermore, both of these mechanisms can be monitored directly. From our GPC investigation we also found that the depolymerization of PSA is heterogeneous in humid surroundings at 35°C, in which the abnormal GPC profiles can be observed. This phenomenon is different than the erosion behavior of polyanhydrides in organic or buffer solutions. Both of these depolymerization mechanisms can be easily found and traced in the variation of the profiles in the GPC and DSC investigations during the depolymerization process, in which the elevation and shifting of the second endothermic peak observed in the DSC thermogram is attributed to the carboxylic acid terminated depolymerized products. In addition, the degradation rate for the cyclic dimer of sebacic anhydride is much lower than PSA. This can result in the accumulation of the cyclic dimer of sebacic anhydride and the peculiar profile during the GPC investigation.

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