

Notes

Free Acid Effect and NMR Study of Glycolide

Bumchan Min, Seon-Ho Kim, Sang Hern Kim,[†] Soohan Kwon,[‡] Hack-Ju Kim,[§] and Whan-Gi Kim^{*,*}

Samyang group R & D Center, Taejeon 305-717, Korea

[†]Department of Chemical Technology, Taejeon National University, Taejeon 300-717, Korea

[‡]Department of Chemistry, Chungbuk National University, Chongju 361-763, Korea

[§]Department of Environmental Engineering, Shinsung College, Dangjin 343-860, Korea

^{*}Department of Applied Chemistry, Kon-Kuk University, Chungju, Chungbuk 380-701, Korea

Received February 2, 2000

Homo and copolymers of polylactones have been the subject of growing attention because of their numerous applications in biomedical and environmental fields. Polyglycolic acid (PGA), a common biocompatible polymer, is widely utilized to make various kinds of medical device and sustained materials for drug delivery system.¹⁻⁴ Often these various applications require a high molecular weight polymer, depends on the catalyst and polymerization method.^{5,6} The type and quality of monomers are also important in obtaining polymers of high molecular weight and good quality.⁷⁻⁹ The many kinds of impurities in glycolide depend on its manufacturing process and treatment. Water in glycolide is known to have a serious effect on the degree of polymerization.^{10,11}

Kohn *et al.* studied the effect impurities had on polymer molecular weight and molecular weight distribution of D,L-lactide.⁹ They found that impurities in lactide, such as water or ethyl acetate, caused serious reduction in molecular weight. They also studied the aging effect of D,L-lactide. Polymer prepared from old D,L-lactide had a lower molecular weight than polymer prepared from the fresh one. Unfortunately, they did not give any clear characterizations for impurities in the old D,L-lactide. Moreover, in the case of glycolide and PGA, there are no systematic studies of impurities and aging effect on polymerization. It is very important to have this information because it can be the basis of the establishing a method to produce quality polymer.

In this study, we synthesize PGAs from glycolides containing different acid concentration, and their melt viscosities are compared. In addition, we obtain information on the impurities formed in the aged glycolide. We use NMR spectroscopy to identify these impurities and present the results of quantitative analysis of these impurities in glycolide. It is believed that this method provides a more complete analysis.

Experimental Section

Materials and Instrumentation. Glycolide was purchased from PURAC BIOCHEM BV (The Netherlands). Tin octoate and lauryl alcohol were purchased from Sigma Chem. Co. Glycolides of different acid concentration (3-35 meq/kg) were randomly obtained from the purchased glycolide. Free

acid concentrations in glycolide increased as time passed. Rheometrics Dynamic Spectrometer AMES was to determine the melt viscosity at 250 °C, at a frequency of 10 rad/sec. ¹H NMR spectra were taken in acetone-*d*₆ solution on a Bruker AMX-500 NMR spectrometer. The fresh glycolide (sample 1) and the old glycolide (sample 2) were prepared to know the types of impurities. Sample 2 was prepared as follows. Fresh glycolide was stored at room temperature and left for 1 year to determine the aging effect of glycolide. For these two samples, peak assignments and quantitative analysis of the impurities were carried out by NMR experiments with delay of 10 sec using 30° pulse. The integration of the peaks of this proton spectrum was performed as closely as possible. Proton relaxation (*T*₁) experiments of sample 2 were also performed for detailed analysis of compositions. The proton NMR relaxation time (*T*₁) was measured by the standard inversion recovery method.¹² *T*₁ was used for intermediate relaxation with 10 μsec, 90° pulse and different delays in the range from 0.01 to 5. A relaxation delay of 15 sec gave us sufficiently accurate relaxation times for this purpose.

Preparation of Polymers. The method for synthesis was similar to that described by Gilding and Reed.¹⁰ To a 500 L three-neck round-bottom flask, fitted with a nitrogen inlet and a mantle, glycolide (1.293 mol) and lauryl alcohol (0.047 mol) as a catalyst and chain control agent were inserted. The mixture was maintained for 1 hr at 60 °C under 0.1 torr and tin octoate (8.85 × 10⁻⁶ mol) was added. The reaction occurred from 60 °C to 225 °C with the temperature elevated 1.4 °C/min and maintained at 225 °C for 150 min. The polymer was quenched at room temperature and crushed to fine powder. Residual monomer was removed by refluxing the crushed polymer in ethyl acetate, and the insoluble polymer fraction was weighed to obtain 80-95% conversion.

Measurement of Free Acid Concentration. Glycolide (4-5 g) was dissolved in methanol and acetone (25 mL/25 mL). The typical method of potentiometric titration was used. To each collected solution, the typical apparatus (saturated calomel electrode/pH glass electrode with millivolt scale) was fitted. The acid concentration was measured by titration with 0.01 mol/L (M) sodium methoxide solution in a mixed solvent of methanol and acetone (50V/50V).

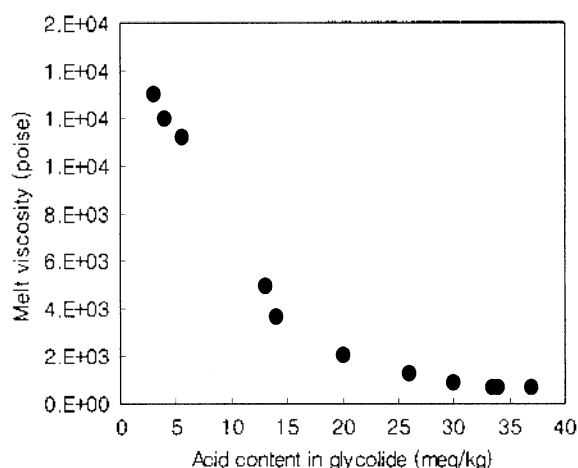


Figure 1. Melt viscosity (poise) as a function of acid content in glycolide.

Approximate equilibrium is indicated when the measured potential ceases to drift by more than a few millivolts. Stirring is frequently effective in hastening the achievement of equilibrium.

Results and Discussion

Several polymerizations of glycolides containing different acid concentration (3–37 meq/kg) were carried out under the same experimental condition and the change of melt viscosity was measured to find the effect of free acid. Figure 1 shows melt viscosity as a function of free acid content in glycolide. The results show that melt viscosity decreases nonlinearly as free acid content increases. Therefore, we proposed that molecular weight could be influenced by the free acid concentration. To get high molecular PGA, fresh glycolide containing a low concentration of free acid should be used.

In the present study, we describe our effort to investigate free acid in glycolide by the aging effect. The result could be obtained by the close examination of proton NMR spectra of two samples: the fresh glycolide (sample 1) and the old one (sample 2). Proton NMR spectra of samples 1 and 2 in normal intensity show significant differences between the two spectra. The spectrum of sample 1 shows pure glycolide at 5.08 ppm (Figure 2(a)), while the various components in the spectrum of sample 2 were observed in the range from 4.0 to 5.2 ppm (Figure 2(b)). In Figure 2(c) is the proton spectrum of sample 1, which was magnified about two hundred times for Figure 2(a). The peaks of impurities, except glycolide, appeared in the same ranges as those of sample 2. Moreover, it can be easily seen that the peak pattern of the impurities is very similar to that of sample 2, except for the spinning side band (ssb) and carbon satellites of glycolide. The structures of the impurities of sample 1 are difficult to identify because of the small quantity. However, for sample 2 detailed structural analyses for the components were performed. The resonance peaks of glycolide is itself, at 5.08 ppm, a major component (Figure 2(a)), and the second major component

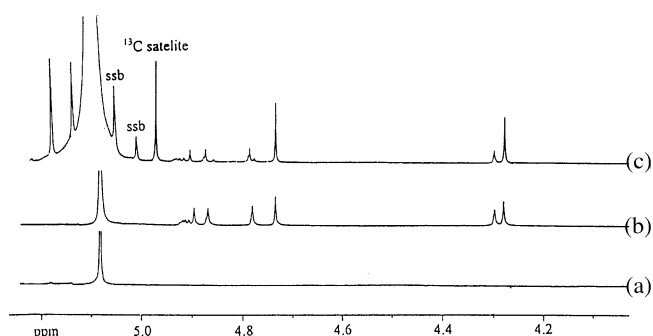


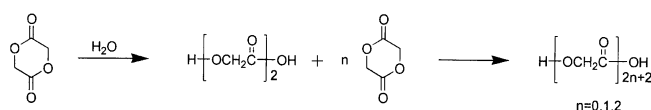
Figure 2. ^1H NMR spectra of glycolide in the range 4.0–5.2 ppm. a: sample 1; b: sample 2; c: 200 magnified spectrum of (a).

of sample 2 is the dimer of glycolic acid ($\text{HO}-(\text{CH}_2\text{COO})_2\text{-H}$), which is observed at the peaks of 4.28 and 4.74 ppm. (Figure 2(b)) It is considered a product of hydrolysis of glycolide as suggested in the study of lactide and PLA.⁹ The integral values of 4 peaks (4.30, 4.78, 4.87 and 4.90 ppm), which have similar intensities, strongly suggest that the third major component of the sample is tetramer of glycolic acid ($\text{HO}-(\text{CH}_2\text{COO})_4\text{-H}$). In addition, there are other 6 minor peaks, including shoulders at 4.30, 4.78 and 4.87 ppm, and 3 peaks from 4.90 to 4.92 ppm. (Figure 2(b)) Keeping with the above reasoning, it could be thought that the hexamer of glycolic acid ($\text{HO}-(\text{CH}_2\text{COO})_6\text{-H}$) was formed.

In addition to the chemical shift and integral value of each peak of the proton 1D spectra, the measured relaxation times (T_1) of the proton give us additional evidence about the above assignment. The proton NMR peak assignment and measured relaxation times (T_1) of the resonance lines of the suggested components of sample 2 are summarized in Table 1. It is well known that the T_1 value of one atom in a small organic molecule in the solution is proportional to the mobility of the given atom. Actually, this corresponds to the extreme narrowing region in the dynamics of molecules, and in that condition T_1 increases as the temperature increases, viscosity decreases and molecular size decreases.^{12,13} Therefore, the order of T_1 values in Table 1 give good proof for the above identification. For example, the relaxation times for the peaks of the suggested hexamer are shorter than those of other suggested components. Finally, from the similarities between the spectra of sample 1 and 2, we may conclude that the main impurities of glycolide, other than water, are dimer, tetramer and hexamer of glycolic acid.

Table 1. The ^1H NMR peak assignment and measured relaxation times (T_1 s) of the resonance lines corresponding suggested components of sample 2

Glycolic acids	Resonance lines (ppm)	Measured relaxation times (sec)
$(\text{CH}_2\text{COO})_2$	5.08	3.07
$\text{HO}-(\text{CH}_2\text{COO})_2\text{-H}$	4.28, 4.74	2.06, 1.77
$\text{HO}-(\text{CH}_2\text{COO})_4\text{-H}$	4.30, 4.78, 4.87, 4.90	1.59, 1.12, 1.11, 1.02
$\text{HO}-(\text{CH}_2\text{COO})_6\text{-H}$	4.30, 4.78, 4.87, 4.90, 4.91, 4.92	not available for 3 peaks, 0.96, 0.95, 0.91



Scheme 1

Interestingly, there are only even number of multimers, such as dimer, tetramer, and hexamer of glycolic acid in glycolide. The newly identified impurities of glycolide are formed during storage. Presumably, the dimer of glycolic acid would be formed by hydrolysis of glycolide, and the following process may happen yielding tetramer from dimer of glycolic acid. Hexamer of glycolic acid may be formed by a similar process between the tetramer and glycolide (Scheme 1). Actually, we found small amounts of precipitation in sample 2, which is considered to be a higher multimer of glycolic acid that is not soluble in acetone.

The amount of impurities (dimer, tetramer and hexamer) was estimated through proton NMR spectra. A comparison between integral values of the peaks of the proton spectrum of sample 1 and sample 2 was performed. The results of a quantitative analysis of sample 2 are shown in Table 2. The amounts of impurities shown above are about 1.4 weight %. For sample 1, the relative amount of impurity could be obtained from comparison of the integral values of the NMR peaks of each impurity with that of glycolide (around 5.08 ppm). First, we identified the integrals of the NMR peaks of impurities and that of glycolide. It was difficult to obtain the exact integrals of NMR peaks of all impurities separately because of severe overlap of NMR peaks. Though dimer have isolated peaks in the spectrum (Figure 2), all peaks of tetramer overlapped with those of hexamer, making it impossible to get integral intensities of tetramer directly. Fortunately, two peaks of hexamer were isolated from the other peaks in the range of 4.91 to 4.92 ppm. Careful integration of these two peaks allowed us to estimate the relative integrals of hexamer and tetramer after appropriate subtractions of integrals of hexamer from the overlapped tetramer NMR peaks (from 4.30 to 4.90). Final the wt.% of each impurity was evaluated by simple calculation considering, simultaneously, integral values, molecular structures (particularly number of protons) and molecular weights of all components, including glycolide as well as all impurities. NMR analysis is available to check the purity of glycolide in the production line. We suggest that the glycolide impurities have serious effects on the polymerization of PGA to obtain

Table 2. Quantitative analysis for impurities in glycolide (sample 2) using ¹H NMR integral values

Glycolic acids	Amount/wt%
HO-(CH ₂ COO) ₂ -H	0.76
HO-(CH ₂ COO) ₄ -H	0.48
HO-(CH ₂ COO) ₆ -H	0.16

high molecular weight polymer. When the amount of impurity exceeded 0.1% of the glycolide monomer, the degree of polymerization was significantly reduced. Therefore great care must be taken to treat and evaluate the purity of glycolide.

The effect of free acid in glycolide on melt viscosity was studied. The melt viscosity decreased as the free acid in glycolide increased. The chemical structures of the impurities in glycolide were investigated by NMR spectroscopy. Impurities were identified as dimer, tetramer, and hexamer of glycolic acid, which are inhibitors to the polymerization reaction of glycolide. NMR spectroscopy was used as a simple method for quantitative analysis of these impurities.

Acknowledgment. This paper was supported by Konkuk University (1999).

References

- Carter, B. K.; Wilkes, G. L. *Polym. Prep.* **1983**, *24*, 77.
- Hoffman, A. *Am. Chem. Soc. Sym.* **1984**, *256*, 13.
- Chu, C. C.; Browing, A. *J. Biomed. Mater. Res.* **1988**, *22*, 699.
- Chu, C. C. *J. Appl. Polym. Sci.* **1985**, *30*, 3133.
- Leenslag, J. W.; Pennings, A. *J. Makromol. Chem.* **1987**, *188*, 1809.
- Deasy, P. B.; Finan, M. P.; Meegan, M. J. *J. Microencapsulation* **1989**, *6*, 369.
- Dahlmann, J.; Rafler, G.; Fechner, K.; Mehlis, B. *British Polym. J.* **1990**, *23*, 235.
- Kissel, T.; Brich, Z.; Bantle, S.; Lanerajan, I.; Nimmerfall, F.; Vit, P. *J. Controlled Rel.* **1991**, *16*, 27.
- Kohn, F. E.; Van Den Berg, J. W. A.; Van Den Berg, G.; Feijen, J. *J. Appl. Polym. Sci.* **1984**, *29*, 4265.
- Gilding, D. K.; Reed, A. M. *Polymer* **1979**, *20*, 1459.
- Chujo, K.; Kobayashi, H.; Suzuki, J.; Tokuhara, S. *Die Macromol. Chemie* **1969**, *100*, 267.
- Harris, R. K. *Nuclear Magnetic Resonance Spectroscopy*; Pitman; London, 1983; Chap. 4.
- Rue, J. W. *LUCKY Polymer Technology* **1992**, *23*, 47.