醫工學會誌 : 第 13 卷 第 2 號, 1992
J. of KOSOMBE : Vol. 13, No. 2

研 究 論 文
92-13-2-08

Synthesis and Physical Properties of New Biodegradable Polyester-Polypeptide Copolymer

Yong Kiel Sung, Chul Hyun Park, Dae Kyung Song, and Jae Hee Jung

=Abstract=

Poly(glycolic acid-co-glycine-L-lactic acid) has been prepared by ring opening polymerization. The monomer 6-methyl morpholine-2, 5-dione was synthe-sized by bromopropionylation of 2-bromopropionyl bromide with glycine. Glycolide and 6-methyl morpholine-2, 5-dione have been used as starting materials for polydepsipeptides. The synthesized copolymers have been identified by NMR and FT-IR spectrophotometer. The Tg value of poly(glycolic acid-co glycine-L-lactic acid) is increased with increasing mole fraction of 6-methylmorpholine-2, 5-dione(60－84℃). The glass trasition temperature of poly(glycolic acid-co-glycine-L-lactic-acid) (62－86℃) is lower than that of poly(L-lactic acid-co-glycine-L-lactic acid). The thermal degradation of poly(L-lactic acid-co-glycine-L-lactic acid) is decreased with increasing mole fraction of L-lactide. The thermal degradation of poly(glycolic acid-co-glycine-L-lactic acid) is increased with increasing mole fraction of glycolide.

Ⅰ. INTRODUCTION

Biodegradable polymeric materials are frequently used in medicine and surgery[1－2] for example as surtures[3], drug delievery systems [4] fo the controlled realease of drugs or as resorbable prosthesis in orthopedic surgery[5]. Two important classes of synthetic biodegradable polymers are poly(α-amino acid)s and poly(α-hydroxy acid)s. Important requirements for the use of biodegaradable polymers are a predictable rate of biodegradation, suitable mechanical properties and lack of formation of toxic products[6－11].

Specially, copolymers of α-amino acids and α-hydroxy acids, which are called polydepsipeptides, contain both ester and amide functional groups so that their biodegradation behavior will be different from the homopolymers[12－13]. Shalaby and Koelmel[14] described the formation of polymers of p-dioxanone containing 1 to 15% of morpholine-2, 5-dione or its 3-methyl and N-methyl derivatives. Helder and Feijen et. al.[15] reported the copolymerization of D, L-lactic acid and glycine. Yonezawa et. al. [16] reported the copolymerization of 6-isopropyl-2, 5-morpholinedione and 6-isopropyl-4 methyl-2, 5-morpholinedione with D, L-lactic acid. The polymerization yields were rather low and extensive characterization of the polymers was not described. Hwang et. al.[17] reported the synthesis of unsubstituted morpholine-2, 5-dione. Sung et. al.[18,19] reported the synthesis and characterization of poly(glycine-co-lactic acid), poly(glycine-co-glycolic acid), poly(L-

〈접수 : 1992년 4월 8일〉

Department of Chemistry, Dongguk University, Seoul 100－715, Korea

lactic acid-co-glycine-L-methyl lactic-acid) and poly(L-lactic acid-co-glycine-L-lactic acid).

In this work, we have studied on synthesis and physical properties of copolymers of glycolide with 6-methyl morpholine-2, 5-dione in order to control its mechanical properties and degradation rate. Poly(glycolic-acid-co-glycine-L-lactic acid) and degradation rate. Poly(glycolic-acid-co-glycine-L-lactic acid) was prepared by ring opening polymerization of 6-methyl morpholine-2, 5-dione and glycolide. The glass transition temperature and themal degradation of poly(glycolic acid-co-glycine-L-lactic acid) have been compared with those of poly(L-lactic acid-co-glycine-L-lactic acid).

Ⅱ. EXPERIMENTAL SECTION

1. Materials and Instruments

1) Materials

L-lactide(Aldrich Co.), glycine(Tokyo kasei Co.), bromopropionyl bromide(Aldrich Co.), glycolide(Polyscience Co.), and stannous octoate (E. Merk Co.) were used for the experiments. All reagents and solvents were used as reagent grade and used without further purification.

2) Instruments

Proton nuclear magnetic resonance(^{1}H-NMR) spectra were taken at 60MHz(Varian T-60A spectrometer). Chemical shifts were reported in part per million(δ) downfield from tetramethylsilane(δ0.00) as an internal standard. FT-IR spectra were recorded on a Nicolet 5-MX as a KBr pellet. Melting points were determined by Thiele apparatus and were uncorrected. Thermal properties were obtained by the differential scanning calorimeter(Perkin Elmer DSC4) and the thermogravimetric analyzer(Perkin Elmer TGS-2).

2. Synthesis of Poly(glycolic acid-co-glycine-L-lactic acid)

Polymerization tubes(10ml) were silanized using dichlorodimethylsilane (23 wt.% in toluene) and subsequently dried in an oven at 120 ℃ for at least 12hrs. 6-Methyl morpholine-2, 5-dione[19] and glycolide were placed in the polymerization tube and the corresponding amount of stannous octoate, dissolved in a small quantity of dry toluene, was added. Stannous octoate(tin bis 2-ethyl hexanoate) was used as initiator using a molar ratio of monomer(s) and initiator(M:I) of 2500. After evaporation of the solvent in vacuum, the tube was purged several times with dry nitrogen. The tube was sealed in vacuum and placed in an oil bath at 130℃. After the time indicated(Table 1) the tube was cooled and opened. The glassy-like, yellow-brown materials was washed several times with DMF and ethyl acetate.

(IR (KBr) : 3,400(ν_{N-H}), 1,7500($\nu_{C=O}$), 1,670 (amide Ⅰ), 1,540cm^{-1}(amide Ⅱ) : NMR (d^6-DMSO) : δ 5.0(q, 1H, C-H, s, 2H, $-CH_2$), 4.0 (s, 2H, $-CH_2$), 8.5(s, 1H, N-H), 1.5(d, 3H, $-CH_3$).

3. Thermal Properties

1) Differential scanning calorimetry

The glass transition temperatures of poly(glycine-L-lactic acid), poly(L-lactic acid), poly (glycolic acid) and their copolymers were measured by differential scanning calorimeter in the sealed aluminium pan under the helium purge gas. The temperature range was 0—150℃ C ; the weights of the samples were 5mg ; and the rate of heating was 10℃/min.

2) Thermogravimetry

The thermal degradations of poly(glycine-L-lactic acid), poly(L-lactic acid), poly(glycolic

Table 1 Melt polymerization of 6-methyl morpholine-2.5-dione(MMD) and glycolide(GL)

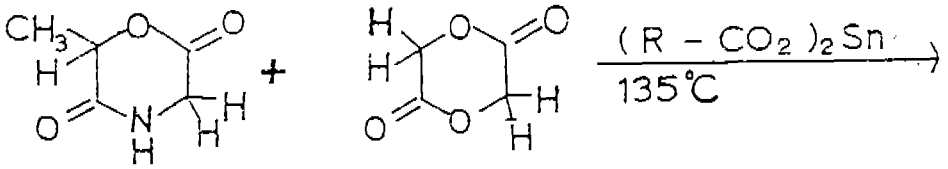
Polymers	Mole fraction in feed		Polymerization	Polymers
	MMD	GL	time(hrs)	yield(%)
PGL	1.00	0.00	52	62
PGGL 1	0.75	0.25	48	70
PGGL 2	0.50	0.50	45	79
PGGL 3	0.25	0.75	35	85
PGA	0.00	1.00	30	86

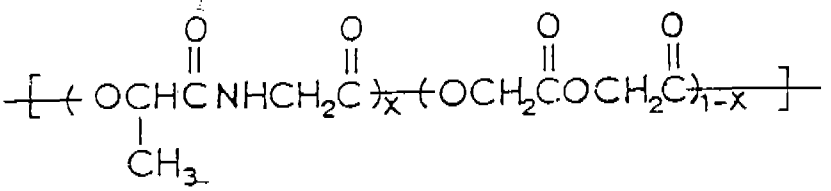
acid) and their copolymers were measured by thermogravimetric analyzer in a nitrogen atmosphere. The temperature range was 50—500℃ ; the weights of the samples were 5—7mg ; and the rate of heating was 20℃/min.

Ⅲ. RESULTS AND DISCUSSION

1. Identification of Copolymer

Poly(glycolic acid-co-glycine-L-lactic acid) was synthesized by ring opening polymerization with 6-methyl morpholine-2, 5-dione[19] and glycolide[6]. stannous octoate was used as initiator.





In the ring opening copolymerization, the polymerization times make a difference because the reactivity of 6-methyl morpholine-2, 5-dione was lower than that of glycolide. We used stannous octoate as an initiator because it was known as non-toxic material in vivo.

The copolymers were identified by FT-IR and ^{1}H-NMR spectra. The FT-IR spectrum(Figure 1) of poly(glycolic acid-co-glycine-L-lactic acid) revealed peaks at 3,400cm^{-1}(N-H stretching), 1,750cm^{-1}(ester carbonyl), 1,670cm^{-1}(amide Ⅰ), and 1,540cm^{-1}(amide Ⅱ). After polymerization, it is observed that the ester ring formation peak of 6-methyl-morpholine-2, 5-dione at 1,130cm^{-1} and the ester ring formation peak of glycolide at 835cm^{-1} were disappeared.

The ^{1}H-NMR spectrum of poly(glycolic acid-co-glycine-L-lactic acid) revealed peaks at δ5.0 (q, 1H,C-H, and s, 2H, -CH_2), δ4.2(s, 4H, -CH_2, -CH_2), δ8.5(s, 1H, N-H) and δ1.5(d, 3H, -CH

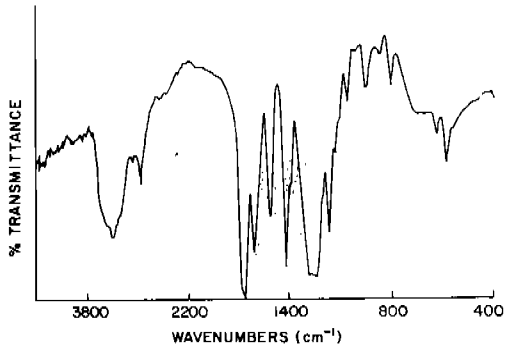


Fig. 1 FT-IR spectrum of poly (glycolic acid-co-glycine-L-lactic acid) (KBr)

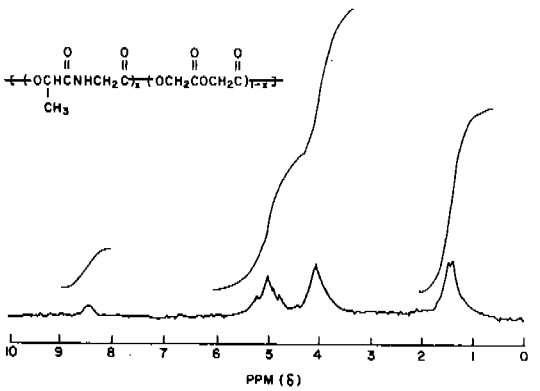


Fig. 2 ^{1}H-NMR spectrum of poly (glycolic acid-co-glycine-L-lactic acid) (6MD : GL=3:1) (D_6-DMSO)

$_3$) (Figure 2). By interpretation for the integration of peaks corresponding to glycolic acid(δ4.2, 4H, $-CH_2$, $-CH_2$) and glycine-L-lactic acid(δ8.5, 1H, -CO-NH-), the composition of the poly (glycolic acid-co-glycine-L-lactic acid) was able to calculate. It was found that the mole ratio of each repeating unit in the poly(glycolic acid-co-glycine-L-lactic acid) was 1:1 when the mole ratio of glycolic acid and 6-methyl-morpholine-2, 5-dione was 1:3.

2. Thermal Properties of Copolymers

The glass transition of the polymers occurs when the glassy amorphous polymers become flexible or rubberlike because of onset of segmental motion. The measured glass transition temperatures of poly(glycolic acid-co-glycine-L-lactic acid) were shown in Table 2.

Table 2 Glass transition temperatures of poly(glycolic acid-co-glycine-L-lactic acid)

Polymers	mole fraction in feed		Tg(℃)
	MMD	GL	
PGL	1.00	0.00	107
PGGL 1	0.75	0.25	84
PGGL 2	0.50	0.50	64
PGGL 3	0.25	0.75	60
PGA	0.00	1.00	32

The glass transition temperatures of poly(L-lactic acid-co-glycine-L-lactic-acid) revealed at the range of 62-86℃[19]. Poly(glycolic acid-co-glycine-L-lactic acid) revealed at the range of 60-84℃. The glass transition temperatures of the homopolymers such as poly(L-lactic acid), poly(glycolic acid) and poly(glycine-L-lactic acid) show at 53℃, 32℃, and 107℃, respectively. The glass transition temperatures of poly(glycolic acid-co-glycine-L-lactic acid) were increased by increasing of mole fraction of 6-methyl morpholine-2, 5-dione[19].

The glass transition temperatures were increased by addition of 6-methyl morpholine-2, 5-dione. It was shown that the bond strength of amide group in 6-methyl morpholine-2, 5-dione was stronger than that of ester group in lactide or glycolide. The molecular stiffness of the copolymers was increased by increasing content of 6-methyl morpholine-2, 5-dione.

Ther thermal degradation of poly(L-lactic acid-co-glycine-L-lactic acid) and poly(glycolic acid-co-glycine-L-lactic acid) was measured by thermogravimetry and their thermograms were shown in Figures 3 and 4, respectively.

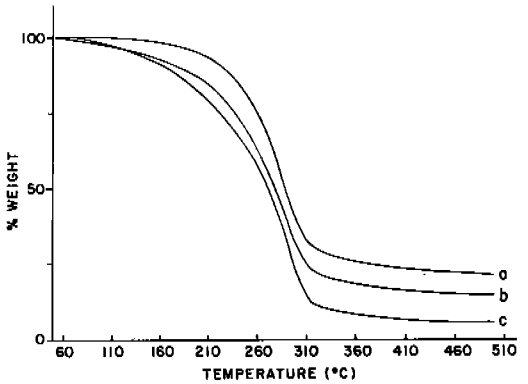


Fig. 3 TGA thermogram of poly(glycine-L-lactic acid) (a), poly(L-lactic acid-co-glycine-L-lactic acid) (b) MMD:LA=1:1, and poly(L-lactic acid) (c)

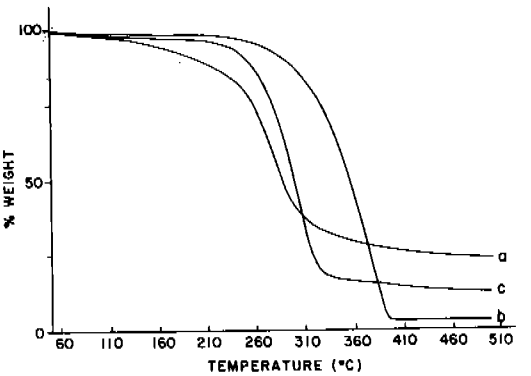


Fig. 4 TGA thermogram of poly(glycine-L-lactic acid) (a), poly(glycolic acid) (b), and poly (L-lactic acid-co-glycine-L-lactic acid) (c) MMD:GL=1:1

The TGA thermogarm of poly(L-lactic acid-co -glycine-L-lactic acid) was varied in the middle range of the poly(glycine-L-lactic acid) and poly(L-lactic acid) thermograms. And the TGA thermograms of poly(glycolic acid-co-glycine-L -lactic acid) was also changed in the middle range of the poly(glycine-L-lactic acid) and poly(glycolic acid) thermograms. The temperature range of thermal degradation and residual weights of the copolymers are shown in Tables 3 and4. The thermal degradation temperature and the residual weights of ply(L-lactic acid-co -glycine-L-lactic acid) were decreased by increasing of mole fraction of L-lactide. Otherwise, the thermal degradation temperatures of poly(glycolic acid-co-glycine-L-lactic acid) were decreased by increasing of mole fraction of glycolide. The degradability of poly(glycolic acid-co-glycine-L-lactic acid) showed the tendency of poly(glycolic acid) at low temperature and the tendency of poly(glycine-L-lactic acid) at high temperature.

Ⅳ. CONCLUSIONS

The copolymers were synthesized by ring opening polymerization with glycolide and 6-methyl morpholine-2, 5-dione. Stannous octoate was used initiator. The synthesized polymers were identified by ^{1}H-NMR spectrometer and

Table 3 The range of degradation temperature and residual weight of poly(L-lactic acid-co-glycine-L-lactic acid)

Polymers	Range of temperature(℃)		D_{max}(℃)	Residual weight(%) (at 350℃)
	Initial	Final		
PGL	220.06	333.25	281.33	23.90
PLGL 1	216.46	326.74	283.19	16.05
PLGL 2	176.11	322.04	282.76	14.80
PLGL 3	171.31	319.52	283.68	9.78
PLA	169.08	316.42	286.94	6.34

D_{max} : maximum decomposition temperature

Table 4 The range of degradation temperature and residual weight of poly(glycolic acid-co-glycine-L-lactic acid)

Polymers	Range of temperature(℃)		D_{max}(℃)	Residual weight(%) (at 400℃)
	Initial	Final		
PGL	220.06	333.25	281.33	23.60
PLGL 1	232.06	336.05	293.95	18.68
PLGL 2	249.95	351.10	302.63	11.91
PLGL 3	264.49	358.51	327.64	10.11
PLA	289.28	393.24	372.87	2.73

D_{max} : maximum decomposition temperature

FT-IR spectrophotometer. The glass transition temperatures and thermal properties were measured by differential scanning calorimetry and thermogravimetry. From this study, it has been concluded as follows :

1. The glass transition temperatures of poly(L-lactic acid-co-glycine-L-lactic acid) and poly(glycolic acid-co-glycine-L-lactic acid) are higher than those of poly(L-lactic acid) and poly(glycolic acid), respectively. The glass transition temperature of each copolymer is increased, according o increasing of mole fraction of 6-methyl morpholine-2, 5-dione, showing that its segmemtal motion is decreased by increasing of number of methyl group.
2. The glass transition temperatures of poly (glycolic acid-co-glycine-L-lactic acid) are lower than those of poly(L-lactic acid-co-glycine-L-lactic acid), showing that its segmental motion is increased by decreasing of number of methyl group.
3. The thermal degradation of poly(L-lactic acid-co-glycine-L-lactic acid) and poly(glycolic acid-co-glycine-L-lactic acid) are decreased by increasing of mole fraction of 6-methyl morpholine-2, 5-dione.

Acknowledgement :

This work was financially supported by the Korea Science and Engineering Research Foundation (No-89-04-05-05).

REFERENCES

1) J. Kopecek and K. Ulrich, *Prog. Polym Sci.*, 9, 1 (1983).
2) R. Langer and N. Peppas, *J. Macromol. Sci., Rev. Macromol. Chem. Phys.*, C23, 61(1983).
3) J.W. Hodge, Jr., *U.S. Nat. Inform. Serv.* AD Rep. 742719(1979), Chem, Abstr. 77, 135063m (1979).
4) L.C. Anderson, D.L. Wise and J.F. Howes, *Contraception* 13, 375(1976).
5) R.K. Kulkarni, E.G. Moore A.F. Hegyeli and F. Leonard, *J. Biomed. Mater. Res.*, 5, 169(1971).
6) D.K. Gielding and A.M. Reed, *Polymer*, 20, 1459(1979).
7) D. Nissen, CH. Gilon and M. Goodman, *Macromol. Chem., Suppl.*, 1, 23(1975).
8) M. Goodman, *J. Polym Sci., Polym. Sym*, 62, 173 (1978).
9) B. Ridge, H.N. Rydon and C.R. Snell, *J. Chem. Soc., Perkin Trans.* 1, 2041(1972).
10) F.H.C. Stewart, *Aust. J. Chem.*, 21, 1639(1968).
11) F.H.C. Stewart, *Aust. J. Chem.*, 22, 1291(1968).
12) H. Kunz and K. Lorenz, *Augew. Chem.*, 92, 953 (1980).
13) D.K. Gielding, "*Biodegradable Polymers in Biocompatibility of Clinical Implant Materials*", Ed. by Williams, CRC Press, Boca Raton, Florida, Vol. Ⅱ, 1981.

14) Eur. Pat. Appl. EP 86, 613(1983), Ethicon Inc. ; S.W. Shalaby, D.F. Koelmel, *Chem. Abstr.* 99, 200560p(1983).

15) J. Helder, F.E. Kohn, S. Sato, J.W. van den Berg and Jan Feijen, *Macromol. Chem., Rapid Comm.*, 6, 9(1985).

16) N. Yonezawa, F. Toda and M. Hasegawa, *Macromol. Chem. Rapid Comm.*, 6, 607(1985).

17) S.S. Hawang, S.I. Hong and N.S. Choi, *Hanguk Sumyu Konghakhoe Chi.*, 18, 200(1981) ; *Chem. Abstr.* 98, 143822d 1983.

18) Y.K. Sung and H. Kim, *J. of KOSOMBE*, 9, 215 (1988).

19) Y.K. Sung and K.H. Park, *J. of KOSOMBE*, 9, 225(1988).