

## Copolymers of D,L-lactic acid and glycine

Janneke Helder, Jan Feijen\*

Department of Chemical Technology, Twente University of Technology,  
P.O. Box 217, 7500 AE Enschede, The Netherlands

Seung Jin Lee, Sung Wan Kim

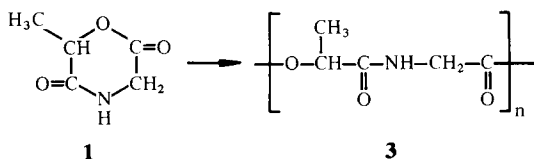
Department of Pharmaceutics, University of Utah, Salt Lake City, Utah 84112, U.S.A.

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### Introduction

Synthetic bioabsorbable polymers, like poly( $\alpha$ -hydroxy acids) and poly( $\alpha$ -amino acids), are of great interest for biomedical applications such as surgical sutures or drug delivery systems<sup>1,2</sup>. Important requirements for the use of bioabsorbable polymers are a predictable rate of biodegradation, suitable mechanical properties and lack of formation of toxic products. For application in drug delivery systems the materials should be suitable to prepare membranes or matrices having the required permeability for drugs.

Since the properties of homopolymers can only be slightly modified by varying the molecular weight or crystallinity, copolymers are required to provide materials with a wider range in properties. Gilding and Reed<sup>3</sup> reported that lactic/glycolic acid copolymers show a wide range of properties depending on their compositions. Copolymers of  $\alpha$ -amino acids and  $\alpha$ -hydroxy acids could be a valuable addition to the existing bioabsorbable polymers. Since these polymers contain both ester and amide groups, their biodegradation behaviour will be different from the homopolymers<sup>4</sup>.



We previously reported on the synthesis of poly(glycine-D,L-lactic acid) (3) by ring-opening polymerization of 6-methyl-2,5-morpholinedione (1)<sup>5</sup>. The polymerization afforded linear, alternating  $\alpha$ -hydroxy and  $\alpha$ -amino acid copolymers. However, polymer 3 showed unfavourable mechanical properties, which probably result from the low molecular weight or which may be due to the intrinsic properties of this polymer. Copolymers with improved mechanical properties and higher molecular weights may be obtained by varying the percentage of either  $\alpha$ -amino acid or  $\alpha$ -hydroxy acid residues.

Shakaby and Koelmel<sup>6</sup> synthesized copolymers of 2,5-morpholinedione derivatives and *p*-dioxanone. It was observed that these copolymers showed an accelerated *in vivo* absorption with an excellent strength retention. For the copolymerization only small quantities of morpholinedione derivatives (up to 15%) were used.

Quite recently, Yonezawa et al.<sup>7</sup> reported the copolymerization of 6-isopropyl-2,5-morpholinedione and 6-isopropyl-4-methyl-2,5-morpholinedione with D,L-dilactide (2). The polymerization yields were rather low and an extensive characterization of the polymers was not described.

We now report on the synthesis, characterization and properties of copolymers of glycine and D,L-lactic acid. The copolymers were prepared by ring-opening polymerization of 6-methyl-2,5-morpholinedione (1) and D,L-dilactide [3,6-dimethyl-2,5-dioxanedione] (2).

## Experimental part

### Materials and methods

Glycine and D,L-2-bromopropionylbromide were purchased from Merck (Darmstadt, W-Germany). Tin bis(2-ethylhexanoate) was purchased from Polysciences (Warrington, USA). D,L-Dilactide was recrystallized twice from toluene and stored *i. vac.* until use. Organic solvents were of analytical grade and were used without further purification.

IR spectra were recorded on a Perkin Elmer 1310 IR spectrophotometer using KBr discs or thin films on NaCl crystals. A Nicolet NMR spectrometer running at 200 MHz was used to obtain <sup>1</sup>H NMR spectra. CDCl<sub>3</sub> or (C<sup>2</sup>H<sub>6</sub>)-DMSO were used as solvents and TMS as an internal reference. Glass transition temperature (*T<sub>g</sub>*) values were measured using a Du Pont 990 thermal analyzer and cell base. Prior to the measurements the samples (3–4 mg) were preheated at 130–150 °C, cooled and left at 25–30 °C for 15 min. A heating rate of 10 K/min and a sensitivity of 0,2 mcal/s were used. The *T<sub>g</sub>* values were taken as the intersection of the extrapolation of the baseline with the extrapolation of the inflexion.

Dynamic low-angle laser light scattering (LALLS) measurements were carried out in THF or DMF using a Chromatix KMX-6 light scattering photometer and a Waters Model GPC-200. The GPC was equipped with four series of styragel columns, 10<sup>5</sup>, 10<sup>4</sup>, 10<sup>3</sup> and 500 Å in pore size. Refractive index increments (*dn/dc*) were measured at 633 nm using a Brice-Phoenix differential refractometer.

**6-Methyl-2,5-morpholinedione (1):** This compound was synthesized as described previously<sup>5</sup>. Pure 1 (m. p. 98–100 °C) was obtained by repeated (5 ×) recrystallization from ethyl acetate.

### Copolymers of 6-methyl-2,5-morpholinedione (1) and D,L-dilactide (2)

Monomers 1 and 2 were copolymerized at mole ratios of 3 : 1, 1 : 1 and 1 : 3. Linear alternating poly(glycine-D,L-lactic acid) (3) and poly(D,L-lactic acid) (7) were synthesized as reference materials. Tin bis(2-ethylhexanoate) [stannous octoate] was used as initiator using a mole ratio of monomer(s) to initiator (M : I) of 2500.

Glass polymerization tubes were silanized using dichlorodimethylsilane (23 wt.-% in toluene), followed by thorough washing with toluene and methanol. The tubes were dried and kept in an oven until use.

The preparation of copolymer 5 is described as a typical example of the procedure used for the copolymerization. Monomer 1 (1,29 g; 10 mmol) was placed in the tube and melted *i. vac.* at 105 °C to remove traces of ethyl acetate. After cooling to room temperature, monomer 2

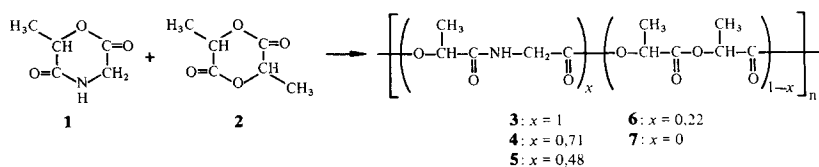
(1,44 g; 10 mmol) and 53  $\mu$ l of a solution of stannous octoate in toluene (0,15 mol/l) were added. The tube was again evacuated and purged twice with dry nitrogen. After complete evaporation of toluene i. vac. at room temperature, the tube was sealed. The tube was positioned in an oil bath of 135  $^{\circ}$ C. The polymerization mixture was stirred until the melt became too viscous. After 33 h, the tube was cooled in an ice bath. For purification, the crude yellow polymer was dissolved in chloroform (20 ml) and the polymer solution was added dropwise to 500 ml of ethanol in a silanized flask with vigorous stirring. The precipitated polymer was isolated, washed with diethyl ether and dried i. vac. at 90  $^{\circ}$ C for 4 h.

The samples for homopolymerization were treated in a similar manner, except for polymer 3, which was dissolved in 5 ml of DMF in the purification step.

## Results and discussion

Copolymers of glycine and D,L-lactic acid were obtained by ring-opening copolymerization of monomers 1 and 2 using tin bis(2-ethylhexanoate) as initiator. Molar feed ratios of monomers 1 and 2 of 3:1, 1:1 and 1:3 were used.

The results of the (co)polymerizations are summarized in Tab. 1 and Tab. 2. Homopolymers 3 and 7 were synthesized as reference materials.



Tab. 1. Melt (co)polymerization of 6-methyl-2,5-morpholinedione (1) and D,L-dilactide (2) using tin bis(2-ethylhexanoate) as initiator

No.	Mole fraction of 1 in feed	Conversion <sup>a)</sup> in %	Polym. yield in %	$10^{-4} \cdot \bar{M}_w$ <sup>b)</sup>	$10^{-4} \cdot \bar{M}_n$ <sup>b)</sup>	$\frac{dn/dc}$ <sup>c)</sup> ml $\cdot$ g <sup>-1</sup>
3	1	65	50	1,0 <sup>d)</sup>	0,6 <sup>d)</sup>	0,067
4	0,75	80	60	2,4 <sup>d)</sup>	1,9 <sup>d)</sup>	0,056
5	0,50	85	70	2,8	1,6	0,066
6	0,25	90	80	2,8	2,2	0,058
7	0	95	95	23,5	15,4	0,047

<sup>a)</sup> The conversion was estimated from the methyl proton integrations of the monomer(s) and (co)polymer in the NMR spectrum of the crude (co)polymers.

<sup>b)</sup>  $\bar{M}_w$  and  $\bar{M}_n$  were determined by LALLS measurements in DMF (3 and 4) or THF (5, 6 and 7).

<sup>c)</sup> Refractive index increments were determined in the same solvents as used for the LALLS measurements.

<sup>d)</sup>  $\bar{M}_w$  and  $\bar{M}_n$  values are not very accurate ( $\pm 20\%$ ) due to low LALLS signals.

Tab. 2. Glass transition temperature  $T_g$  and composition of the (co)polymers

No.	Mole fraction of 1 in feed	Mole fraction of 1 in copolymer <sup>a)</sup>	Mole fraction of lactic acid in copolymer <sup>a)</sup>	$T_g / ^\circ\text{C}^{\text{b)}$
3	1	1	0,50	109
4	0,75	0,71	0,66	86
5	0,50	0,48	0,76	71
6	0,25	0,22	0,89	62
7	0	0	1	53

a) The values were determined using the methylene proton integrations of glycine and the methine proton integration of D,L-lactic acid in the NMR spectra of the purified copolymers. The accuracy is  $\pm 0,03$ .

b) The  $T_g$  values were taken as the intersection of the extrapolation of the base line with the extrapolation of the inflexion. A heating rate of 10 K/min was used.

The composition of the copolymers could be estimated from  $^1\text{H}$  NMR spectra. Fig. 1 shows the NMR spectrum of the purified copolymer 5. The methylene proton signal at 4,0 ppm is characteristic of the glycine moiety from monomer 1. The methine proton signal at 5,1 ppm results from both monomers. The composition of the copolymers was calculated by comparing the methylene and methine proton integrations. As shown in Tab. 2 the composition of the copolymers at conversions of 80–90% was not very different from the composition of the monomer feed.

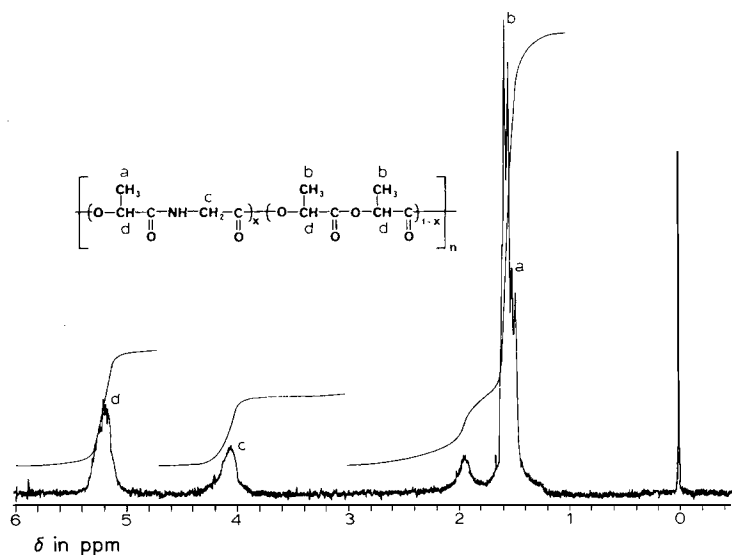


Fig. 1. 200 MHz  $^1\text{H}$  NMR spectrum of the purified copolymer 5, synthesized using a feed ratio of 6-methyl-2,5-morpholinedione (1) to D,L-dilactide (2) of 1 : 1

The IR spectra of the copolymers provided results consistent with the NMR data. The relative peak intensity of the amide I ( $1680\text{ cm}^{-1}$ ) to carbonyl ester ( $1755\text{ cm}^{-1}$ ) reduced as the mole fraction of monomer **1** decreased.

Attempted copolymerization may result in physical mixtures of the homopolymers instead of the formation of copolymers. The difference between the solubility properties of the copolymers and "homopolymer" **3** suggested the formation of copolymers. Copolymers **5** and **6** are soluble in THF and chloroform, copolymer **4** in chloroform, while polymer **3** is not soluble in these solvents.

Glass transition temperatures ( $T_g$ ) of the homo- and copolymers, which were determined by using DSC, are presented in Tab. 2. The glass transition temperature decreased with increasing mole fraction of D,L-lactic acid in the copolymers (Fig. 2). The copolymers revealed an increasing toughness with an increasing mole fraction of D,L-lactic acid.

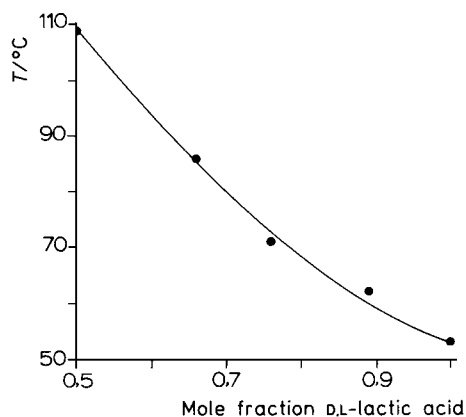


Fig. 2. Glass transition temperatures of the (co)polymers as a function of the mole fraction of D,L-lactic acid

Molecular weights of the copolymers, ranging from  $2,4 \cdot 10^4$  to  $2,8 \cdot 10^4$ , are somewhat higher than the molecular weight of "homopolymer" **3** (Tab. 1). However, the values are still markedly lower than that of homopolymer **7**. Both conversion and polymer yield increase with increasing mole fraction of monomer **2** in the copolymers.

The mechanism of the polymerization is not exactly known. A study of the interaction between monomers **1** and **2** and tin bis(2-ethylhexanoate) is currently being performed in our laboratory. This study may elucidate the reasons for the low molecular weight and polymerization yield of the copolymers as compared to those of polymer **7**.

In conclusion, copolymers of glycine and D,L-lactic acid of various compositions were obtained by ring-opening copolymerization of 6-methyl-2,5-morpholinedione (**1**) and D,L-dilactide (**2**). These polymers are currently evaluated for their application as biodegradable polymers.

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- <sup>1)</sup> J. Kopecek, K. Ulbrich, *Prog. Polym. Sci.* **9**, 1 (1983)
- <sup>2)</sup> R. Langer, N. Peppas, *J. Macromol. Sci., Rev. Macromol. Chem.* **23**, 61 (1983)
- <sup>3)</sup> D. K. Gilding, A. M. Reed, *Polymer* **20**, 1459 (1979)
- <sup>4)</sup> D. K. Gilding, "Biodegradable polymers" in "Biocompatibility of clinical implant materials", ed. by D. F. Williams, CRC Press, Boca Raton, Florida, 1981, vol. II, p. 209
- <sup>5)</sup> J. Helder, F. E. Kohn, S. Sato, J. W. van den Berg, J. Feijen, *Makromol. Chem., Rapid Commun.* **6**, 9 (1985)
- <sup>6)</sup> Eur. Pat. Appl. EP 86 613 (1983), Ethicon Inc., invs.: S. W. Shakaby, D. F. Koelmel; *Chem. Abstr.* **99**, 200560p (1983)
- <sup>7)</sup> N. Yonezawa, F. Toda, M. Hasegawa, *Makromol. Chem., Rapid Commun.* **6**, 607 (1985)