

Synthesis and Characterization of Novel ABA Triblock Copolymers from L-Lactide, Glycolide, and PEG

J. MOHAMMADI-ROVSHANDEH,¹ S. M. F. FARNIA,¹ M. N. SARBOLOUKI²

¹ Chemistry Department, Faculty of Sciences, Tehran University, P.O. Box 14155-6455, Tehran, Iran

² Institute of Biochemistry and Biophysics, Tehran University, P.O. Box 13145-1384, Tehran, Iran

Received 5 November 1998; accepted 15 May 1999

ABSTRACT: A series of novel triblock copolymers, consisting of a poly(ethylene glycol) center block joined by two blocks of random L-lactide/glycolide copolymers, are synthesized and their characteristics (spectral, thermal, and mechanical) determined. Polymer compositions and structures are assessed via ¹H-NMR and ¹³C-NMR spectroscopies. DSC and stress-strain behavior studies demonstrate that these copolymers are generally more amorphous, more elastic, and tougher than are poly(L-lactides). © 1999 John Wiley & Sons, Inc. *J Appl Polym Sci* 74: 2004–2009, 1999

INTRODUCTION

Lactic acid (LA) and glycolic acid (GA) are Krebs cycle acids, where the acetyl moiety, in acetyl CoA, is oxidized completely to carbon dioxide and water. Polymers derived from these α -hydroxy acids are biocompatible and biodegradable, and their degradation products are nontoxic.¹ Presently, polylactide, polyglycolide, and poly(ϵ -caprolactone) homo- and copolymers constitute the most promising bioresorbable materials in the field of surgery and pharmaceuticals.^{2–5} Lately, however, a new family of triblock copolymers based on poly(ethylene glycol) (PEG) have attracted the attention of investigators.⁶ This is largely due to the unique properties that the PEG moiety can confer, namely, solubility in water and many organic solvents,⁷ lack of solubility in hexane and ethyl ether,⁷ lack of toxicity,⁸ rapid clearance from the body,⁹ lack of immunogenicity,¹⁰ high mobility and large exclusion volume in water, and FDA approval for internal consumption. When coupled

to another molecule, many of these properties are transferred to the conjugate product. Copolymerization of lactide or glycolide with PEG alters the flexibility and hydrophilicity of these materials, thus extending their applicability. A few block copolymers from DL-lactide and L-lactide with PEG have been synthesized and characterized.^{11–19} In these materials, the PEG and polylactide blocks constitute the center and two end blocks, respectively.

Because the PEG block is soluble in water while the end blocks are not, the resulting copolymers inevitably form micellar structures in water and are thus potential candidates for carriers in controlled drug-delivery systems. In this article, we describe the synthesis and characterization of some new ABA triblock copolymers where the B block is PEG and the two end (A) blocks are random copolymers of L-lactide and glycolide. The presence of glycolyl units in the two end blocks would conceivably lead to improved qualities compared to the well-known poly(ethylene oxide)–poly(lactic acid) (PEO–PLA) triblock copolymers, for example, superior biodegradation characteristics due to higher hydrophilicity and lower crystallinity of the resulting blocks.

Correspondence to: M. N. Sarbolouki

Journal of Applied Polymer Science, Vol. 74, 2004–2009 (1999)

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CCC 0021-8995/99/082004-06

EXPERIMENTAL

Materials

L-Lactide was prepared from a 90% L-lactic acid solution (Merck, Darmstadt, Germany) according to Gilding and Reed.²⁰ Glycolide was prepared likewise from glycolic acid (Merck). Both monomers were purified by multiple recrystallization from ethyl acetate. PEG, $\bar{M}_n = 35,000$ (Merck), was purified by dissolution in THF and precipitation in hexane. The catalyst, tin-2-ethyl hexanoate (Sigma, St. Louis, MO), was purified by vacuum distillation. All other chemicals or solvents were reagent grade (Merck) and, if necessary, were purified according to the established procedures.²¹

Polymerizations

Appropriate amounts of L-lactide, glycolide, and PEG—the macroinitiator—were charged into a polymerization tube and kept under a vacuum at 70°C for 2 h. Thereafter, a 0.1-mL catalyst solution [3% Sn(Oct)₂ in toluene] was added and kept under a vacuum until all volatiles were removed. The tubes were then sealed under a vacuum and polymerization carried out at 100–110°C for a period of 1 week. The tubes were subsequently

broken and the contents dissolved in chloroform, filtered, and finally precipitated by methanol.

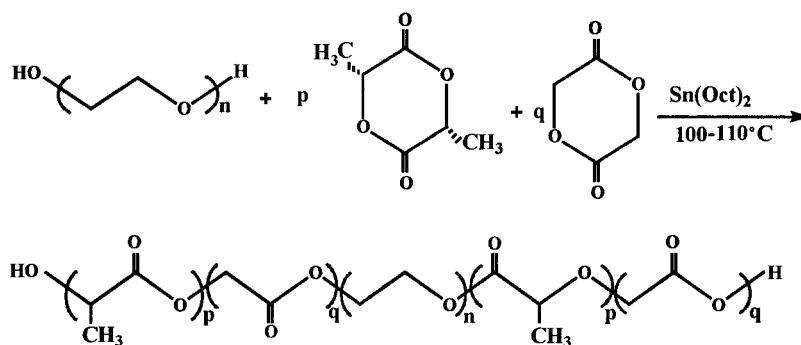
Measurements

¹H- and ¹³C-NMR spectra of the copolymers were recorded on a Varian VXR-300 spectrometer at 300 and 75 MHz, respectively. Chloroform-*d*₁ and TMS were used as the solvent and internal standard, respectively. Film specimens (70 × 20 × 0.1 mm) of the soluble copolymers were prepared by solvent casting, and their stress-strain behavior was studied via an Instron universal testing machine, Model 4204, at a 100 mm/min crosshead speed. Differential scanning calorimetry (DSC) thermograms were obtained using a Mettler Instrument DSC series PC11. Water absorption (water content) of the copolymers was estimated by measuring the relative weight increase of the samples after their equilibrium swelling in distilled water at 20°C for 1 week.

RESULTS AND DISCUSSION

Spectral Characterization

The following equation shows the general reaction formula:



Since the two terminal hydroxyl groups of the PEG essentially have equal reactivities toward monomers, it acts as a macroinitiator for the ring-opening polymerization of lactones in the side blocks. The mechanism of this polymerization has been studied and it has been clearly demonstrated that a hydroxyl-bearing species initiates the lactone polymerization.²² Because the ¹H-NMR signals of each monomer residue are distinguished and well separated, the molar ratio of each in the polymer can readily be determined. For this purpose, the peaks at $\delta = 5.2$ ppm (lac-

tide CH), $\delta = 4.8$ ppm (glycolide CH₂), and $\delta = 3.6$ ppm (CH₂ of PEG) were used. If x is the peak area at $\delta = 5.2$ ppm; y , one-half of the peak area at $\delta = 4.8$ ppm; and z , one-fourth of the peak area at $\delta = 3.6$ ppm, the molar ratios of the monomers in the copolymer can be calculated through the following relations:

$$\text{Molar fraction of LA} = \frac{x}{x + y + z}$$

$$\text{Molar fraction of GA} = \frac{y}{x + y + z}$$

Table I Composition of the Copolymers as Assessed by $^1\text{H-NMR}$ Analysis

Sample	LA/GA/EO (Molar Ratio)	Yield ^b (%)	Water Absorption (%)
1 PLA100 ^a	100 : 0 : 0	95	—
2 P(LA75EO25) ^a	75 : 0 : 25	91	6.5
3 P(LA58GA18EO25)	58 : 18 : 25	85	7.0
4 P(LA60GA22EO18)	60 : 22 : 18	89	5.2
5 P(LA45GA28EO27)	45 : 28 : 27	86	8.5
6 P(LA52GA43EO5)	52 : 43 : 5	85	3.2

^a Prepared similarly as other copolymers except that PEG and glycolide are absent in PLA100 and glycolide in P(LA75EO25).

^b After purification.

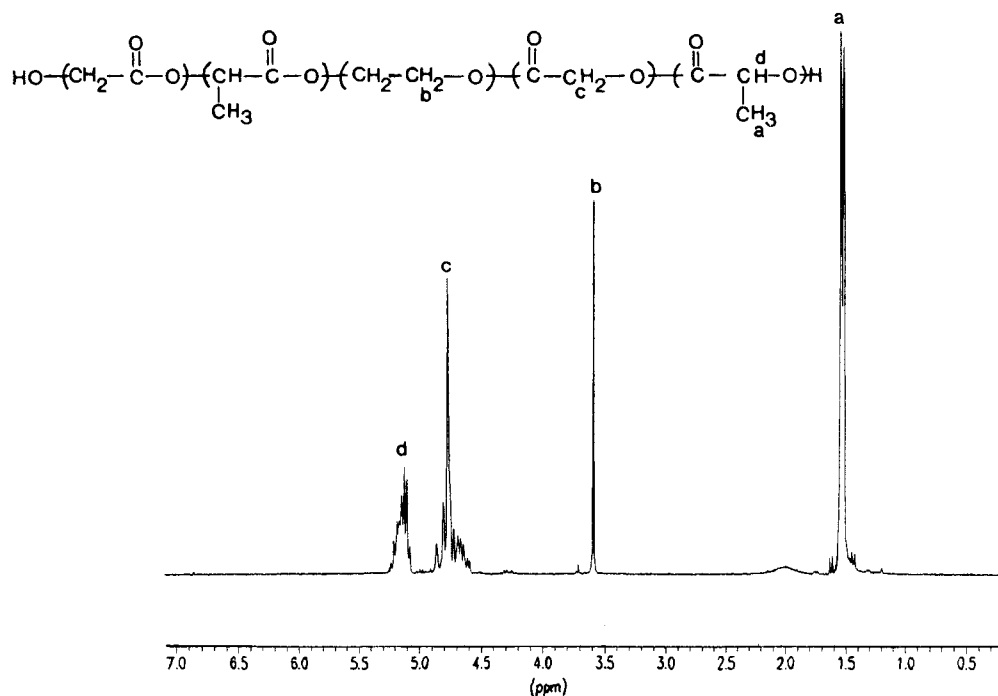
$$\text{Molar fraction of ethylene oxide (EO)} = \frac{z}{x + y + z}$$

Table I shows the composition, yield, and the percent of water absorption of the copolymers thus far obtained. Typical $^1\text{H-NMR}$ spectra of the copolymers together with specified resonances are shown in Figure 1.

The $^{13}\text{C-NMR}$ spectrum (Fig. 2) shows all the carbon resonances together with resonances sensitive to microstructure sequences. The assign-

ment of lines in Figure 2 are as follows: $\delta = 16.66$, 69.05, and 169.59 ppm, respectively, correspond to the carbon atoms of methyl, methine, and carbonyl groups of the lactyl unit; $\delta = 60.8$ and 166.48 ppm, respectively, correspond to the carbon atoms of methylene and carbonyl groups of the glycolyl unit and $\delta = 70.6$ ppm corresponds to the methylene carbon of the ethylene oxide unit. Figure 3(a) shows part of the expanded 300-MHz $^1\text{H-NMR}$ spectra of methylene and methine protons belonging to glycolyl and lactyl units of sample no. 6 (Table I). Due to spin-spin coupling, the signals in the lactyl methine region do not lend themselves to an easy analysis.

According to the analysis procedure by Kasperczyk,²³ the nine lines in methylene protons of the glycolyl unit relate to various pentads. Lines 1, 2, 8, and especially, 7 correspond to the pentads containing GLG or LGL sequences, reflecting the extent of trans-esterification during polymerization. Figure 3(a) clearly demonstrates that the intensities of these lines are low, that is, the mild polymerization conditions used led to a lower extent of transesterification. A comparison between Figure 3(a) and exactly similar spectra reported by others²³ regarding their quantitative analysis confirms that the tendency for formation of long blocks in the lactide-glycolide copolymer is cer-

**Figure 1** $^1\text{H-NMR}$ spectrum of P(LA52GA43EO5).

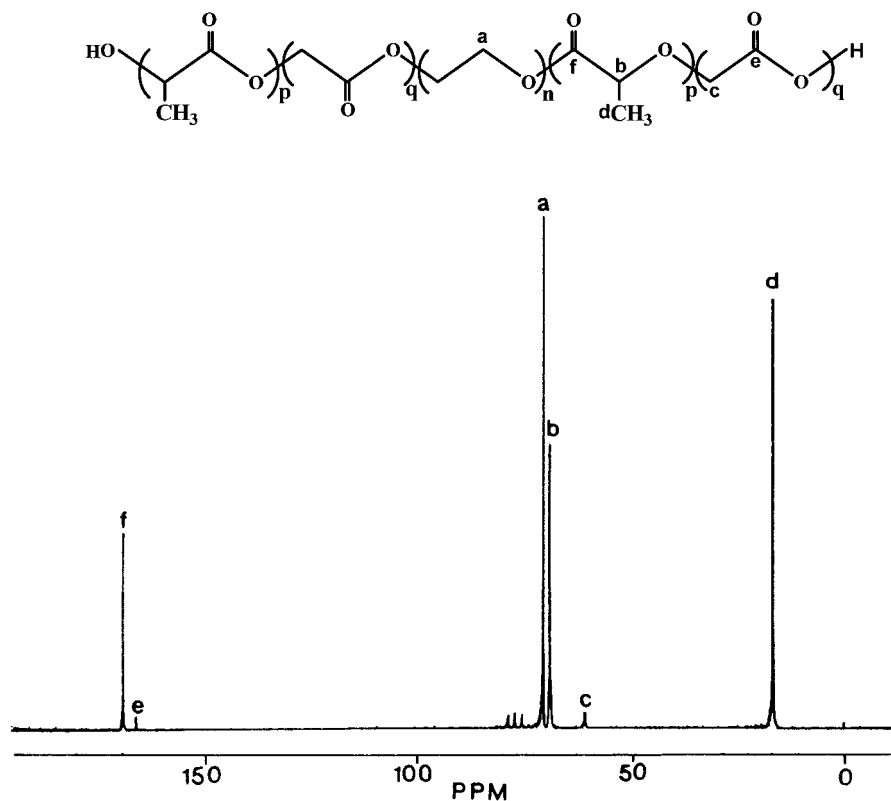


Figure 2 ^{13}C -NMR spectrum of P(LA58GA18EO25).

tainly high. Figure 3(b) also shows part of the expanded 75-MHz ^{13}C -NMR spectra of methylene and methine carbons. Being sensitive to the monomer sequence, the methylene carbon also shows a multiplet. The methine carbon of the lactyl unit also shows a multiplet owing to its

sensitivity toward the monomer sequence and racemization.

Solubility, Thermal, and Mechanical Characteristics

The solubility of copolymers in organic solvents decreased as their lactide content decreased. In

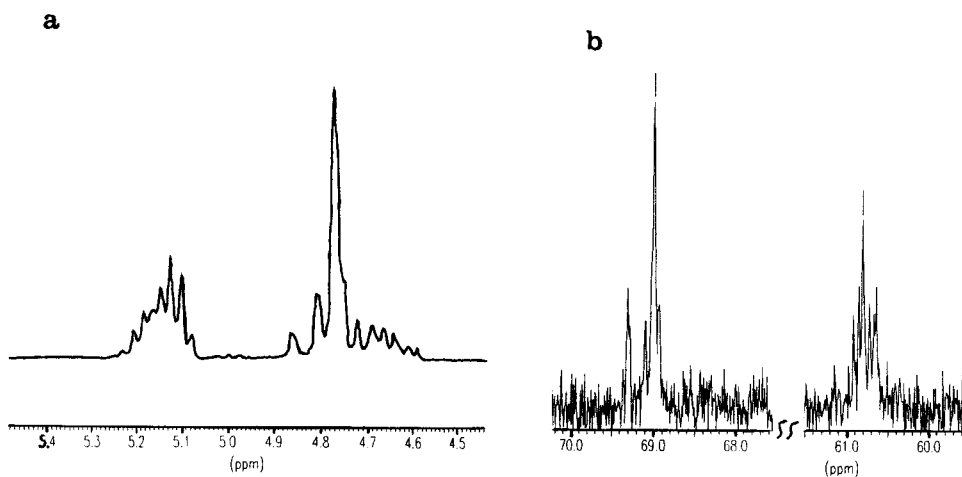


Figure 3 Part of expanded (a) ^1H -NMR spectrum and (b) ^{13}C -NMR spectrum of sample no. 6 (Table I).

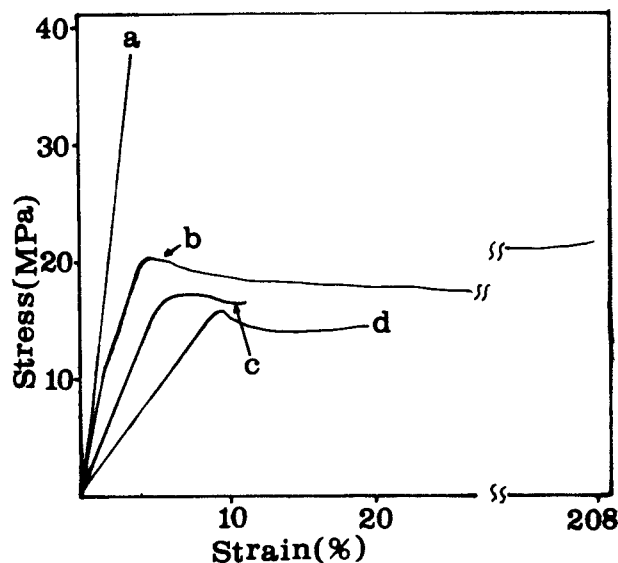


Figure 4 Stress-strain diagrams of (a) PLA100, (b) P(LA75EO25), (c) P(LA60GA22EO18), and (d) P(LA58GA18EO25).

the case of lactide and glycolide copolymers, it is known that an increase in the glycolide molar ratio leads to further insolubility of the copolymer in organic solvents,²⁴ for example, when the glycolide molar ratio in the random copolymer exceeds 40%, it becomes insoluble.²⁴ In the case of the triblock copolymers involved, however, we are dealing with materials that contain a water-soluble center block and two insoluble side blocks. As reported by others, such materials can produce micellar structures and physical networks that have limited solubilities in organic media. Due to the limited solubility of the two end blocks in water and most organic solvents, on the one hand, and the solubility of the center block in water, on the other, these products are believed to form micellar-type structures. This offers them the unique potential of being capable of use in a variety of applications ranging from controlled release to rheological modifications.²⁵ Similar behavior was observed as well for the equivalent system of BAB triblock copolymers where the center block is water-insoluble.²⁶ In our case, samples P(LA52GA43EO5) and P(LA45GA28EO27) swell extensively and form gels (in chloroform), wherein the PEG blocks presumably align and constitute intermolecular bundles that function as crosslinking nodes throughout the system. When sample no. 5, P(LA45GA28EO27), was placed in chloroform for 1 week, it formed a swollen gel. The gel and the supernatant liquid con-

taining the soluble fractions were analyzed via ¹H-NMR. Their respective molar ratios, that is, LA38GA38EO24 and LA67GA18EO15, confirmed the high glycolyl content of this insoluble polymer. The glycolyl units, as a result, play a significant role in the solubility of the entire copolymer.

Although polylactides and their glycolide copolymers are all brittle, the introduction of a PEG block with its flexible bonds increases their flexibility and toughness. Figure 4 compares the typical stress-strain diagrams of poly(L-lactide) with the new triblock copolymers. As expected, there is an increasing change in elasticity (decrease in the Young's modulus and increase in elongation) as one goes from pure lactide to lactide-glycolide copolymers, incorporating a PEG center block where the overall behavior is controlled both by the PEG center block and the two end-block copolymers. Such alterations are highly desirable in tailoring products suitable for a wide range of new applications, where currently available biodegradable materials cannot be utilized. Figure 5 shows DSC results of the triblock copolymers: (a) and (c) refer to the first heating and (b) and (d) are the first cooling. As can be seen, no transition is observed upon cooling for (a) (glycolide-lactide random blocks). For (c) (no. 3, Table I), the endotherm of the PEG block occurs at 50°C, whereas the exotherm and endotherm of the two end blocks occur at 90 and 144°C, respectively, which indicates the presence of some regularity in the

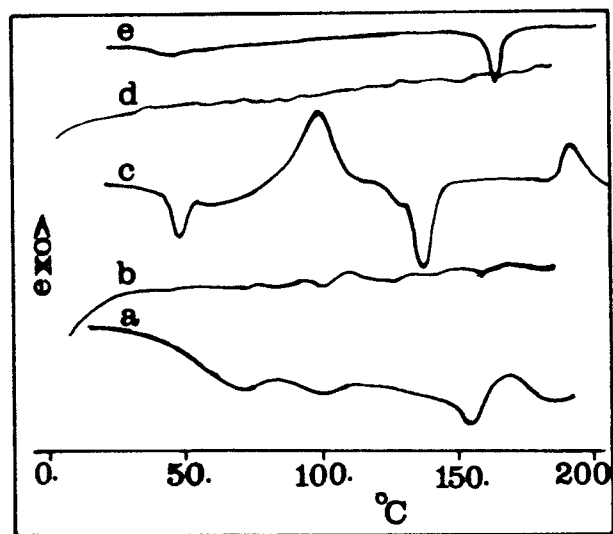


Figure 5 DSC plots (rate: 10°C/min): (a,b) first heating and then cooling of P(LA45GA28EO27); (c,d) first heating and then cooling of P(LA58GA18EO25) and (e) first heating of P(LA75EO25).

monomer sequences in the end-block copolymers. The exotherm related to degradation of the PEG block occurs at 195°C. The DSC thermograms of the remaining copolymers show no transitions related to the glycolide–lactide end blocks. The evidence from the NMR, mechanical, and DSC studies convincingly demonstrate that a variety of copolymers with distinct properties suitable for different applications can easily be formulated.

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