Synthesis of *O*-(2′-Bromopropionyl)glycolic Acid and Its Polymerization: Synthesis of an Alternating Lactic and Glycolic Acid Copolymer

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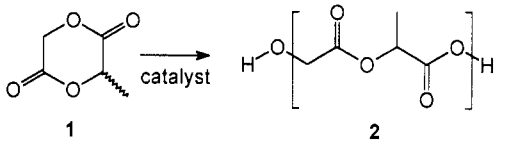
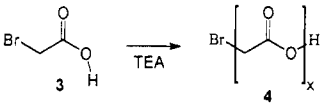
ABSTRACT: Poly(lactylglycolic acid) (**6**) polymer was synthesized by the condensation polymerization of *O*-(2′-bromopropionyl)glycolic acid (**5**). This is an alternating version of poly(lactic acid-*co*-glycolic acid) (50:50). Molecular weights as high as 66 000 were prepared. The triethylammonium salt of this acid (**5**) was formed, and the resulting anion displaced bromine to form the polyester, similar to the formation of poly(glycolic acid) by Pinkus and Subramanyam.[4] This is an unusual method of condensation polymerization, since a hydrobromic acid equivalent is lost instead of water. The method may be applicable to the formation of other polyesters. An improved method of synthesis of *O*-(2′-bromopropionyl)glycolic acid (**5**) is also described using a proton as a protecting group.

Introduction

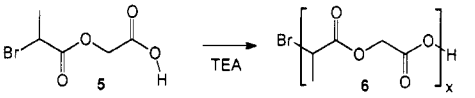
Copolymers of lactic and glycolic acid have long been of interest for biomedical applications.[1] Historically, the properties have widely varied from batch to batch.[2] This has been attributed to the random block nature of the polymer. This could also be attributed to poor control of experimental conditions. However, at the time this project was under taken, the bone regeneration researchers at our institute were finding variable properties in commercial material and attributed the variability to the random nature of the polymer. Therefore, one approach to increased uniformity is preparation of an alternating copolymer. The monomer 3-methyl-1,4-dioxan-2,5-dione (**1**) is reported to result in an alternating copolymer[3] (**2**) (Figure 1, eq 1). However, the traditional catalysts used in the synthesis are transesterfication catalysts, which tend to scramble the ester bonds and any sequence formed. In this paper a different approach using nucleophilic displacement was explored with some promising results. Bromoacetic acid (**3**) has been polymerized to poly(glycolic acid) (**4**) (Figure 1, eq 2).[4] Similarly, *O*-(2-bromopropionyl)glycolic acid (**5**) should be polymerizable to poly(lactylglycolic acid) (**6**) (Figure 1, eq 3). Ibay[5] prepared **5** by treatment of the sodium glycolate (**7**) with 2-bromopropionyl bromide (**8**) (Figure 2, eq 1). The first step became the synthesis of **5**.



Equation 1. Ring opening Polymerization to form alternating Poly(lactic-co-glycolic acid).

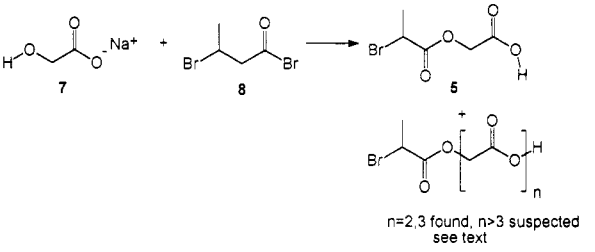


Equation 2. Nucelophilic Polymerization to form Poly(glycolic acid).

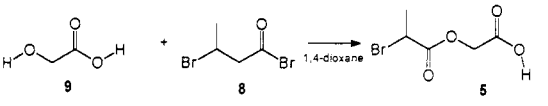


Equation 3. Nucelophilic Polymerization to form Poly(lactylglycolic acid).

Figure 1. Polymerization reactions.



Equation 1. Ibay's synthesis of O-(2'-bromopropionyl)glycolic acid



Equation 2. Present synthesis of O-(2'-bromopropionyl)glycolic acid.

Figure 2. Monomer synthesis.

Experimental Section

Materials. 1,4-Dioxane was distilled from sodium benzophenone under N_2. Triethylamine (Fisher or Aldrich) was dried over potassium hydroxide and fractionally distilled from calcium hydride and stored over 4-Å molecular sieves under N_2. The tetrahydrofuran and ethyl ether were obtained dry from Aldrich in sure-seal bottles and used as received. Benzene from Mallinckrodt was used as received. The chloroform was either used as received or filtered through alumina before use when dry solvent was required. The glycolic acid (Aldrich) was used as received. The 2-bromopropionyl bromide (Aldrich) was distilled under vacuum.

***O*-(2′-Bromopropionyl)glycolic Acid (5).** An oven-dried 1-L round-bottom flask equipped with a magnetic stirrer, thermometer, N_2 inlet, and two dropping funnels (250 and 125 mL) was attached to an oven-dried fractional distillation apparatus connected to the 125-L dropping funnel and assembled under N_2. 2-Bromopropionyl bromide (**8**) was placed in the distillation flask, and approximately 68 mL (650 mmol) was distilled into the dropping funnel under vacuum and allowed to flow into the 1-L round-bottom flask. The distillation apparatus was removed. The bromide was dissolved in 225 mL of 1,4-dioxane and the N_2 inlet replaced with a gas dispersion tube. This solution was cooled to 15 °C using an ice bath. The N_2 leaving the flask was routed through water to absorb the HBr produced. Glycolic acid (42.0 g, 561 mmol) (**9**) was placed in an

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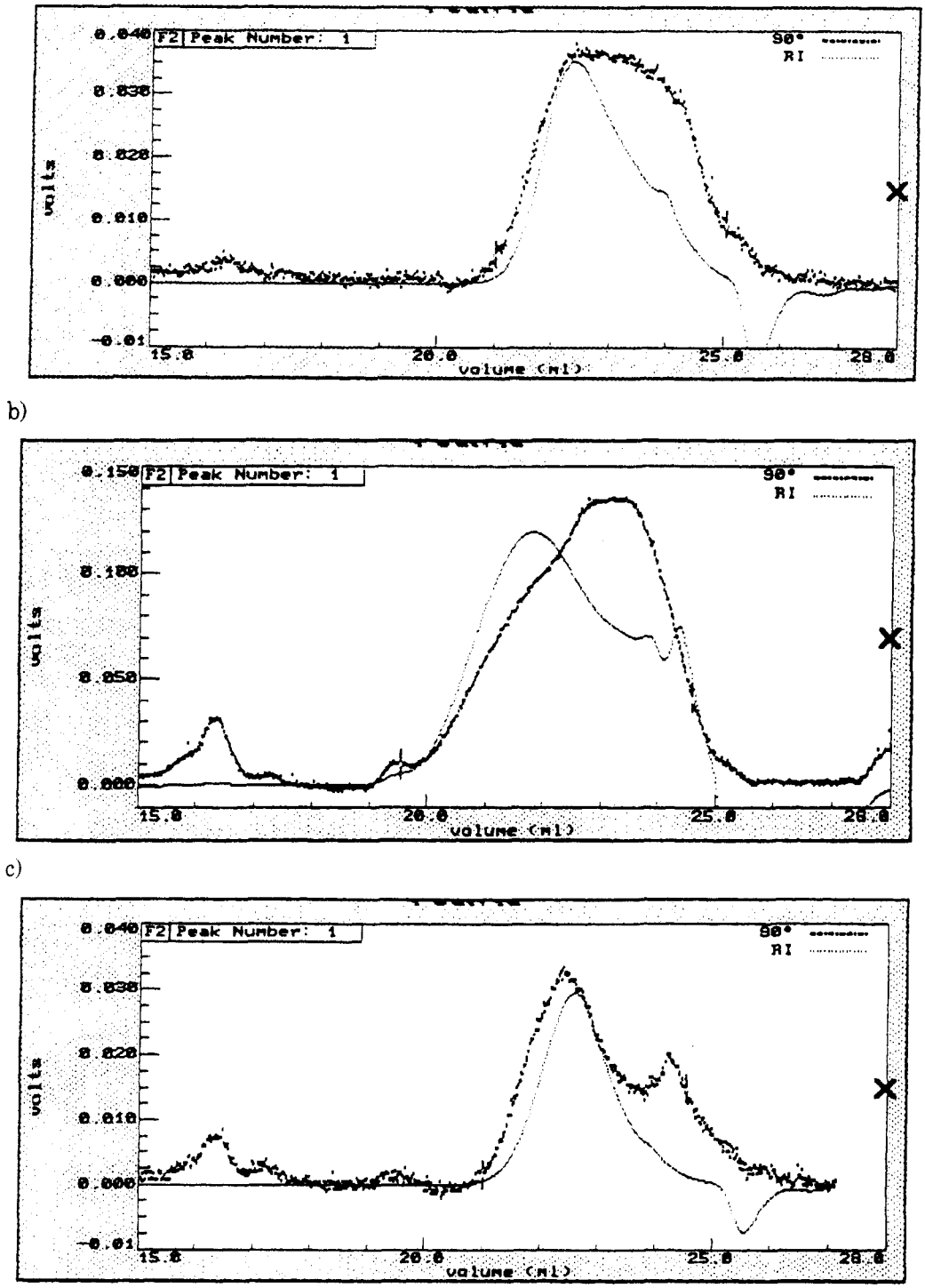

Figure 3. Light scatter gel permeation chromatography by Wyatt Technology: (a) polymer formed in benzene, (b) polymer formed in dried chloroform, (c) polymer formed in "wet" chloroform. The voltage scale only applies to the DAWN plot. Molecular weights are given in Table 1.

oven-dried 250-mL round-bottom flask under N_2 and dissolved in 200 mL of 1,4-dioxane. This solution was transferred to the 250-mL dropping funnel, slowly added to the bromide solution over approximately 2 h, and stirred for another 0.5 h. The reaction mixture was then transferred to a single-neck 1-L round-bottom flask and the dioxane removed under aspirator vacuum on the rotary evaporator. The resulting oil was distilled under vacuum. The fraction boiling below 60 °C was discarded. The fraction boiling from 64–132 °C (0.6 Torr) was collected as a colorless oil, that crystallized upon standing to yield 98.23 g (465 mmol, 82.9% yield). Typical yields were in the 70–80% range on scales up to 1 mol. The colorless oil boiling between 60 and 130 °C could be further purified by recrystallization from toluene. ^{1}H NMR ($CDCl_3$): δ 11.34 (br, 1 H, OH), 4.79, 4.71 (d, 2 H, C_2H, $J_{a,b}$ = 16.4 Hz), 4.48 (q, 1 H, C_5H, $J_{5,6}$ = 6.9 Hz), 1.88 (d, 3 H, C_6H, $J_{6,5}$ = 6.9 Hz), ^{13}C NMR δ 173.156 (C=O, C_1), 169.645 (C=O, C_4), 61.002 (C_2), 38.817 (C_5), 21.556 (C_6). IR(CCl_4): 3054.4 (OH), 3001.7 and 2938.4 (C–H), 1768.0 and 1746.9 (C=O) cm^{-1}. GC: methyl ester (BF_3–methanol) DB-17 (OV-17) column; isothermal 125 °C, inj.; 250 °C, det. (FID); 300 °C, retention time = 3.140 × 100%. High-resolution MS for ^{79}Br. Found: 209.9528. Calcd: 209.9528.

Poly(lactylglycolic acid) (6). To a flame-dried 100-mL round-bottom flask, with a reflux condenser and magnetic stirrer under N_2 were added 16.65 g of *O*-(2′-bromopropionyl)glycolic acid (5) and 1.6 g of 4-Å molecular sieves followed by 50 mL of the appropriate solvent.[6] The mixture was brought to reflux and 11 mL of previously distilled triethylamine was added by syringe over approximately 10 min. Triethylamine hydrogen bromide usually started to precipitate after about half of the triethylamine was added. The reaction mixture was allowed to

Table 1. Polymer Yield and Characteristics for Various Solvents

reaction no.	solvent (bp, °C)	yield (%)	mol wt × 10^{-3}	intrinsic viscosity (dL/g)
1	1,4-dioxane (101)	82.0	14.4	0.20
2	benzene (80)	86.2	66.0	0.42
3	THF (67)	79.3	10.2	0.18
4	chloroform (61)	82.0	8.10	0.33
5	chloroform[a] (61)	67.1	3.96	0.70

[a] This reaction was run without any special precautions to exclude water.

reflux for 24 h. The mixture was allowed to cool, and the contents was dissolved in 100 mL of dichloromethane and filtered through sodium sulfate (anhydrous) to remove the sieves. The resulting solution was washed with 50 mL each of 20% aqueous hydrochloric acid (once), water (twice), and brine (once), dried over sodium sulfate (anhydrous), and filtered, and the solvent was removed under vacuum. ^{1}H NMR ($CDCl_3$): δ 5.3 (d, 1H, C_5H, $J_{5,6}$ = 6.0 Hz), 5.0–4.5 (m, 2 H, C_2H), 1.6 (d, 3 H, C_6H, $J_{6,5}$ = 6.0 Hz), ^{13}C NMR δ 169.684 (C=O, C_1), 166.808 (C=O, C_4), 69.600 (C_2), 61.447 (C_5), 17.141 (C_6). IR (film): 3504 (OH), 2996 and 2950 (CH), 1756 (C=O) cm^{-1}.

Analytical Methods. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker ACF-300 FT-NMR system with a 5-mm ^{13}C/^{1}H dual probe. IR spectra were recorded on a Perkin-Elmer 16 FT-IR spectrometer. The O-(2'-bromopropionyl)glycolic acid (5) was obtained as a CCl_4 solution. The polymer spectra were obtained as thin films deposited by solvent evaporation on potassium chloride plates. The GC results were obtained on a Perkin-Elmer Autosystem. The mass spectroscopy was performed on a Finigan BEQ system. GPC results were obtained by Wyatt Technology Corp. (Santa Barbara, CA). The intrinsic viscosity results were obtained on a PenKem microviscometer. Differential scanning calorimetry (DSC) gave no detectable melting point or glass transition temperature.

Results and Discussion

Monomer Synthesis. Ibay's procedure was first repeated. This yielded a viscous oil that contained not only 5 but 5 plus up to two glycolic residues attached. From the large-pot residue, it is likely that much higher homologues were formed. According to Davies,[7] the proton on the carboxylate could function as a protecting group in 1,4-dioxane. The reaction was attempted in dioxane with glycolic acid (9), and a low yield of 5 as a pure white crystalline material was obtained. The yield was eventually increased to a routine yield of about 70–80% on a 1 mol scale (Figure 2).

Polymer Synthesis. Initial attempts at polymerization in ethyl ether were plagued by a low yield. This was found to be due to the low molecular weight of the product. In order to increase the yield, higher boiling solvents were tried. The yield increased to about 80% for all solvents tried (Table 1). The product tends to be a pale yellow to orange material. A comparison experiment was performed in chloroform without any attempt to exclude water that gave a 67% yield, about 15% less than without water. However, the material was a white crystalline powder. The gel permeation chromatography (GPC) results gave weight-average molecular weights ranging from 66 000 with benzene as the solvent to a low of 3960 with wet chloroform. Higher reaction temperatures resulted in higher molecular weights. It was also found that the drier the solvent, the higher the polymer molecular weight became. This is consistent with a competing degradation process that consumes water. The presence of water, however, did reduce the amount of impurities. The presence of impurities was evident from the chromatograms from Wyatt Technology Corp. (Santa Barbara, CA) (Figure 3).

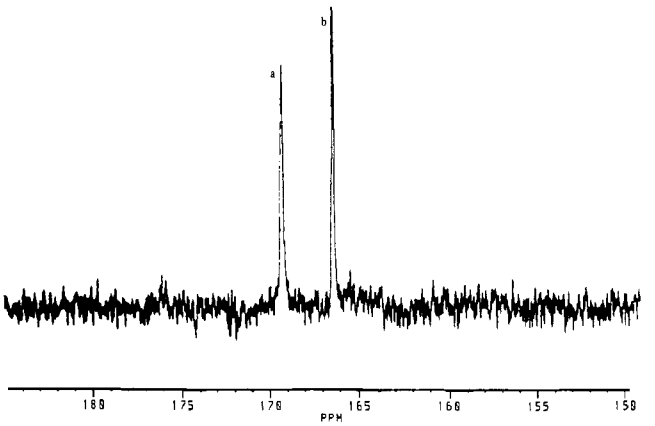

Figure 4. ^{13}C NMR spectra of the poly(lactylglycolic acid) carbonyl region: (a) glycolic acid carbonyl; (b) lactic acid carbonyl.

Another possible interference is displacement of the bromide by triethylamine to form the ammonium salt. This should not change anything, since carboxylate can displace triethylamine to form polymer. The other possibility is that carboxylate could react so as to form the ethyl ester and the diethylamino-terminated polymer. This could also be a possible cause of low molecular weight. It is unlikely that this occurred to any great extent since there was no indication of either ethyl ester or diethylamino groups in the NMRs taken of the material.

The ^{13}C NMR spectra of the polymers are indicative of the alternating nature of the polymer. There is only one peak for each of the carbonyls (δ 169.68 lactic; δ 166.80 glycolic) (Figure 4). According to Kricheldorf,[8] the single peak for lactic acid would imply only triplets of gly–*lac*–gly are present to the limits of our ability to detect. While the existence of other triplets in quantities not detectable by NMR cannot be ruled out, for all practical purposes this material can be considered an alternating copolymer. Similar arguments apply to the glycolic residues. There were no other impurities detectable by NMR.

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References and Notes

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