

A Simple One-Step Synthesis of Unsaturated Copolyesters

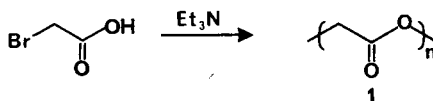
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Synopsis

Copolyesters containing pendent vinylidene groups were prepared in a one-step synthesis by reacting either chloro- or bromoacetic acid with 2-(bromomethyl)acrylic acid and triethylamine in diethyl ether. Polymers were characterized by IR, ^1H - and ^{13}C -NMR, DSC, and TGA. Copolymer formation supports a mechanism involving a triethylammonium carboxylate salt acting as an active nucleophilic species in a manner analogous to that seen in phase transfer catalysis involving carboxylate anions. Comparison of ^{13}C -NMR spectra intensities indicates that 2-(bromomethyl)acrylic acid is much more reactive than the haloacetic acids leading to higher copolymer incorporation than in the monomer feed. Unsaturation in the copolymers provides a site for crosslinking during radical polymerization with an added vinyl monomer, similar to the way unsaturated polyesters function in commercial fiberglass formulations. This was confirmed by polymerization of both styrene and methyl methacrylate in the presence of an unsaturated copolymer giving insoluble semi-interpenetrating networks. These unsaturated copolymers are the first examples of soluble biodegradable glycolic acid polyesters containing such reactive functionality.

INTRODUCTION

Polyglycolide (1) is the simplest polyester.¹ It is an important synthetic suture component and is used in controlled drug delivery devices either as the homopolymer or in copolymers with lactic acid.²



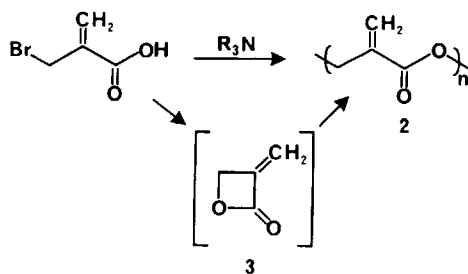
Scheme 1a

The enzymatic and hydrolytic degradation of these polymers leads to non-toxic products. The properties and applications of the polyesters have been described in numerous patents and publications.¹⁻³ While currently available materials possess a good combination of physical properties and chemical innocuousness, it would be desirable in some applications to extend the *in vivo* lifetime of the materials, and in some situations to also improve the strength and toughness of the polymers before they undergo biodegradation.

Polyglycolides, polylactides, and their copolymers are generally made by the high-temperature cationic ring-opening polymerization of the cyclic dimers of glycolic acid and lactic acid; hence the common names that are in general use for these materials. However, a recently described synthesis of polyglycolide involves very mild reaction conditions.⁴ Bromo- or chloroacetic acid was

found to polymerize in good yield on treatment with triethylamine in nitromethane at relatively low temperatures. Surprisingly, cyclodimerization to the six-membered ring glycolide was not a significant side reaction.

A similar reaction was reported by others in which 2-(bromomethyl)acrylic acid gave the unsaturated polyester (2) on treatment with tertiary amines in toluene.^{5,6} β -Propiolactone (3) was proposed as the active monomer or intermediate in this polymerization.



Scheme 1b

We were intrigued by the possibility of generating copolymers of these two monomers. Such an approach to new materials would require, however, similarity in the polymerization mechanism and relative reactivity of the two monomers. We describe here our success in obtaining such copolymers, and postulate a simple polyaddition reaction of the two monomers to account for comparable incorporation.

EXPERIMENTAL

Infrared spectra were obtained on a Nicolet 5DX spectrometer, ¹H and ¹³C spectra on a Bruker MSL-200, and differential scanning calorimetry (DSC) and thermal gravimetric analytical (TGA) data on a DuPont 9900 thermal analysis system. Gas chromatography was run on a Hewlett-Packard 5880 with a 5% polyphenylmethylsiloxane fused silica open tubular capillary column. Intrinsic viscosities (given in dL/g) were determined with a Cannon-Ubbelohde microviscometer at 25 ± 0.2°C using hexafluoroisopropanol (HFIP) as solvent.

Azobisisobutyronitrile (AIBN) was recrystallized from methanol. Triethylamine was distilled and stored over 4A molecular sieves. Haloacetic acids and 2-(bromomethyl)-acrylic acid were purchased from Aldrich and, along with other solvents and reagents, were used as obtained.

Polyglycolide

Bromoacetic acid (3.67 g, 26.6 mmol) in anhydrous diethyl ether (30 mL) was treated with 1 eq of triethylamine at room temperature. Refluxing for 12 days gave a white precipitate. After cooling, the precipitate was removed by filtration and purified by reprecipitation from HFIP into methanol. The white solid was then air dried to give 2.1 g; 67.1% of the theoretical amount; mp 214–219°C, lit.⁴ 216–218°C. IR (KBr): 1765, 1749, 1439, 1421, 1236, 1217, 1198, 1178, and 1095 cm⁻¹; ¹H-NMR (HFIP): 4.91 ppm; ¹³C-NMR (HFIP):

170.6, 63.0 ppm; (DMSO- d_6): 166.7, 60.7 ppm. TGA analysis showed maximum catastrophic decomposition at about 390°C.

Polyglycolide, purified as above, was also prepared in only 7% yield using triisooctylamine; mp 196°C.

Poly(α -Oxymethylacrylate)^{5,6}

2-(Bromomethyl)acrylic acid was stirred with an equimolar amount of triethylamine in chloroform or diethyl ether for several days at room temperature. A precipitate formed which was filtered, washed repeatedly with ethanol to remove the triethylammonium salts, and reprecipitated several times from HFIP into absolute methanol. The white product was dried for 12 h under vacuum giving poly(α -oxymethylacrylate) in yields of approximately 55%; mp 189–203°C, lit.⁵ 195–213°C. IR (KBr): 3117, 3010, 2951, 1723, 1643, 1457, 1423, 1331, 1271, 1138, 1039, 979, 826, and 653 cm^{-1} ; ¹H-NMR (HFIP): 6.57, 6.09, and 4.99 ppm; ¹³C-NMR (HFIP): 168.7, 135.6, 132.5 and 65.3 ppm. TGA analysis showed maximum catastrophic decomposition at about 470°C.

Copolyesters⁷

One equivalent of triethylamine in anhydrous diethyl ether was added dropwise to stirred refluxing diethyl ether containing 2-(bromomethyl)acrylic acid and a haloacetic acid. Reflux was continued for several days giving a precipitate. This material was filtered, washed three times with ethanol, and reprecipitated from HFIP into absolute methanol. The white copolymers were filtered and dried at 80°C for 12 h.

Crosslinked Systems

A 9 : 1 by weight mixture of styrene or methyl methacrylate and one of the unsaturated copolyesters containing approximately 10% pendent vinyl groups was dissolved in 4 wt eq of DMSO along with 5 wt % AIBN in a glass vial. This was sealed with a rubber septum, degassed with three freeze-thaw cycles, and heated at 80°C for 3 days. The gelled material was stirred with diethyl ether to remove residual monomer and solvent, filtered, and dried under vacuum, giving 20–30% yield of the insoluble product. IR and CP/MAS spectra of these materials are similar to the homopolymers of styrene and methyl methacrylate, respectively.

RESULTS AND DISCUSSION

Polymer Synthesis

The effect of solvent on polymer formation was surprising in its specificity. Whereas polyglycolide was originally reported to form most readily in highly polar nitromethane,⁴ we found that diethyl ether also worked well. Polymerization of 2-(bromomethyl)acrylic acid proceeded well in both diethyl ether and chloroform, although precipitation during polymerization occurred here as for the polyglycolide. It is not yet clear what effect this precipitation has on the molecular weight of the two homopolymers, since none were reported for the polyglycolide⁴ and the solubility of the unsaturated polyester only in

TABLE I
 Homopolymer Synthesis Results and Properties

Charge	Poly-1a	Poly-1b	Poly-2a	Poly-2b	Poly-2c
Reaction time (days)	2	12 ^a	1.5	7	2
Feed composition (mmoles)					
Haloacetic acid	54.0	26.6			
Acrylic acid			10.0	25.5	12.5
Triethylamine	56.4	26.3	13.7	32.3	14.6
Yield (%)	67.1	6.9	52.7	51.9	56.9
T_m , (°C)	193	196	189	191	203
T_g , (°C)	140	123	85 ^b	78 ^b	81 ^b
Viscosity (dL/g)	0.08	0.09	0.17	0.17	^c
DP (estimated)	80	90	50	90	230

^a Diethyl ether (solvent) and triisooctylamine (base).

^b Glass transition evident only on first heating cycle does not reappear on subsequent heating/cooling cycles.

^c Polymeric material is no longer soluble.

HFIP has limited its MW characterization to intrinsic viscosities (Table I). The relatively low viscosities indicate that precipitation during polymerization does limit the molecular weight obtainable under these conditions.

Attempted copolymerization of the two monomers in chloroform (ambient and refluxing), nitromethane and 2-nitropropane gave either no polymer and/or very low molecular weight material. In addition, nitromethane reacted to give charcoal-like by-products. Diethyl ether was the only solvent examined which cleanly gave polymer, although precipitation occurred again which inherently limits copolymer molecular weight.

Table II lists the conditions and results for copolymerization of 2-(bromomethyl)acrylic acid in diethyl ether with chloro- or bromoacetic acid comonomers. Yields of the copolymers were comparable to those of the homopolymers, consistent with essentially random monomer incorporation and comparable reactivity of the comonomers. Viscosity values indicate rela-

 TABLE II
 Copolymer synthesis results and properties

Charge	Poly-8a	Poly-8b	Poly-8c	Poly-8d	Poly-8e
Reaction time (days)	1.5	2	3	3	2
Feed composition ^a					
Haloacetic acid	0.87 ^b	0.87 ^c	0.51 ^b	0.50 ^c	0.74 ^b
Acrylic acid	0.13	0.13	0.49	0.50	0.26
Yield (%)	62.3	44.2	58.1	46.4	60.5
T_m , (°C)	139–152	184	187		
T_g , (°C)	135	109	125	120	136
Viscosity (dL/g)	< 0.2	< 0.2	0.19	^d	0.13
DP (estimated)	360	100	50	440	50

^a Mole fraction.

^b Chloroacetic acid.

^c Bromoacetic acid.

^d Polymeric material is no longer soluble.

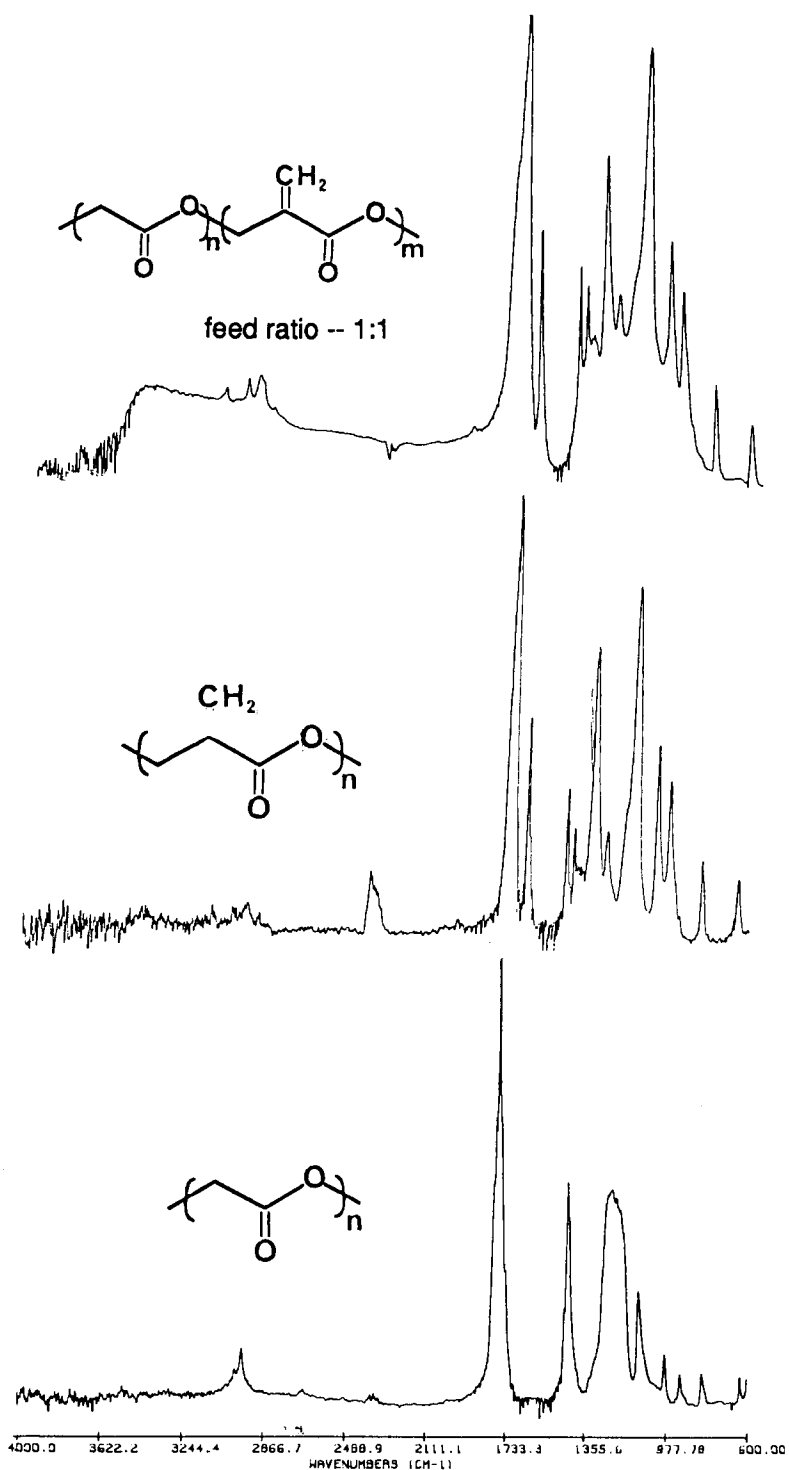


Fig. 1. Infrared spectra of a copolyester (1:1 feed ratio), polyglycolide, and poly(α -oxymethylacrylate).

tively low molecular weight copolymers. NMR estimation of the polymer DP's is described in the following section.

Polymer Characterization

Figure 1 shows the infrared spectra of polyglycolide, poly(α -oxymethylacrylate), and a copolymer from a 1:1 monomer feed ratio. Copolymers show ester absorbances at about 1720 and 1180 cm^{-1} and a vinyl stretch at approximately 1640 cm^{-1} . At low acrylate concentrations the vinyl stretch is of low intensity or is not seen.

Figure 2 shows the ^{13}C -NMR spectra of polyglycolide, poly(α -oxymethylacrylate), and a typical copolymer. Prominent peaks due to both carbonyls, the vinyl carbons, and both methylenes are readily evident. Despite a 1:1 monomer feed ratio, significantly greater incorporation of unsaturated units in the copolymer is evident from relative peak heights. Triethylammonium end groups, evident as carboxylate carbonyls and alkyltriethylammonium salts,

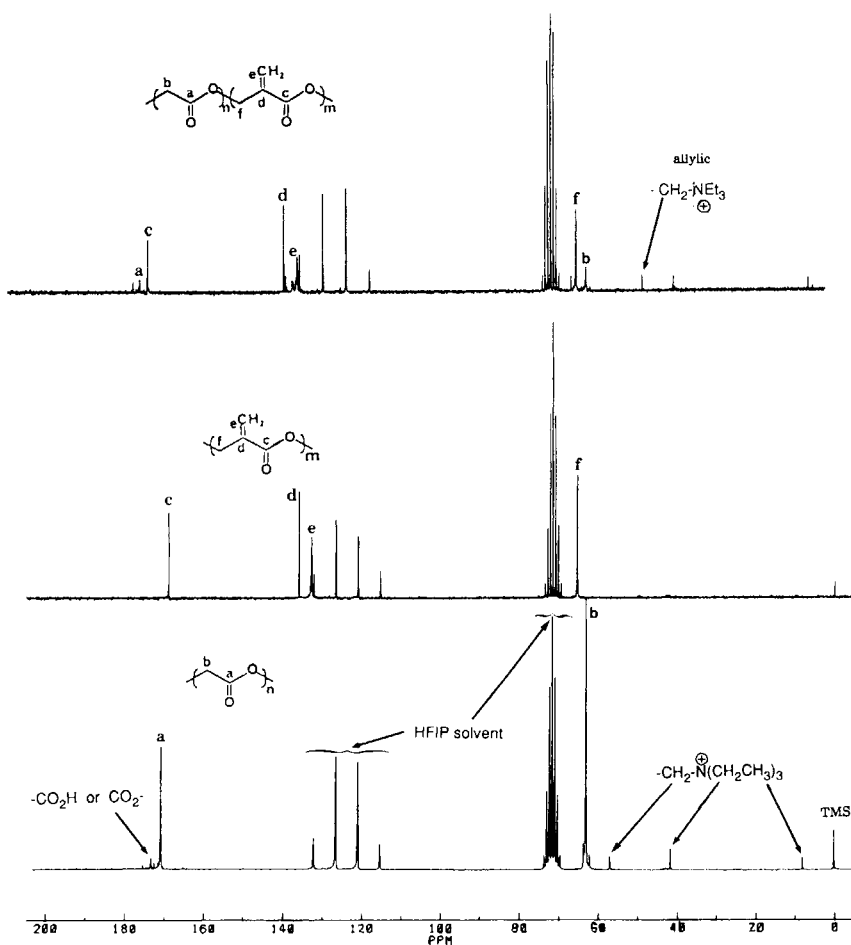


Fig. 2. ^{13}C -NMR spectra of a 1:1 feed copolyester, polyglycolide and poly(α -oxymethylacrylate) in HFIP.

are easily observed in many of the purified polymers. Peak assignments for end groups are given in Figure 2. The terminal $-\underline{\text{C}}\text{H}_2-\text{NEt}_3^+$ for the polyglycolide appears at 56.9 ppm, while in the copolymer the terminal allylic $-\underline{\text{C}}\text{H}_2-\text{NEt}_3^+$ is seen at 49.3 ppm. End groups are hardly visible for the acrylic homopolymer, however. Thus, 2-(bromomethyl)acrylic acid is more

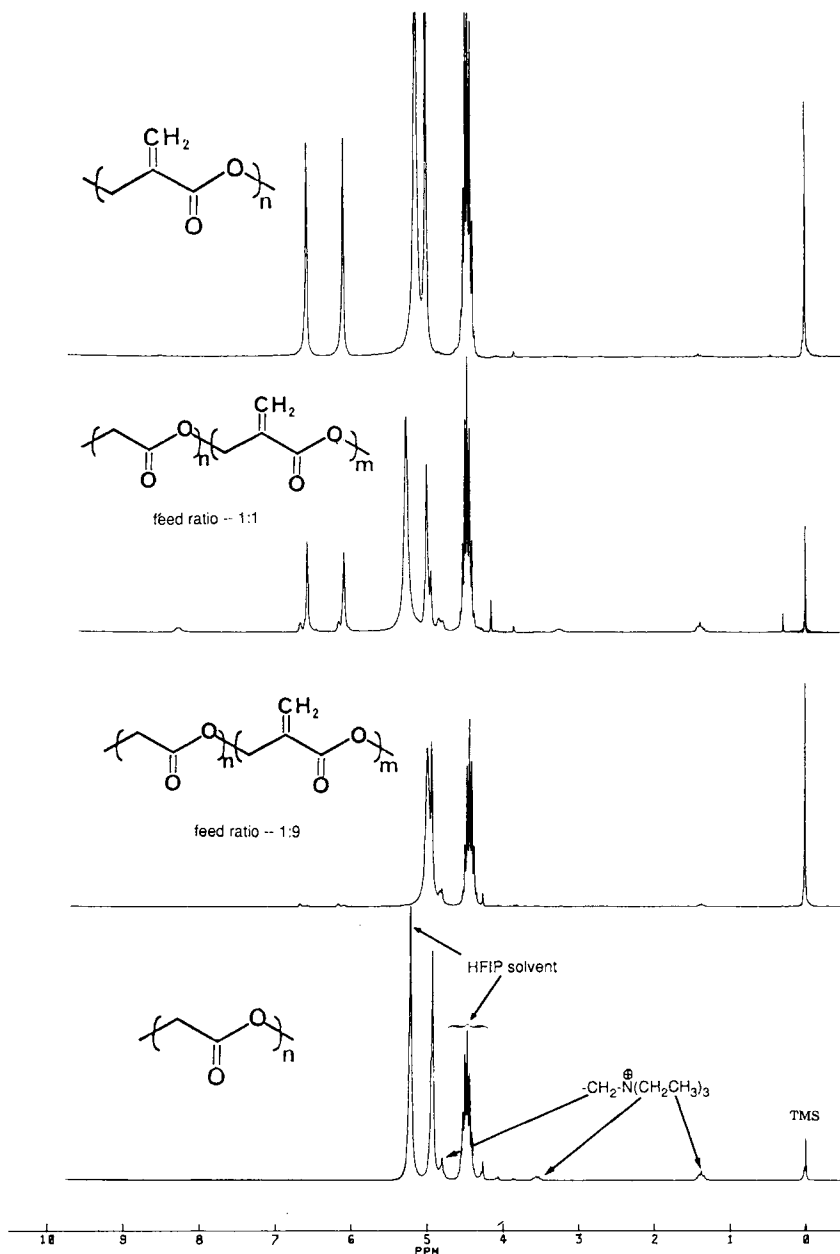


Fig. 3. $^1\text{H-NMR}$ spectra of polyglycolide, a 1:1 feed copolyester, a 1:9 feed copolyester, and poly(α -oxymethacrylate) in HFIP.

reactive than the haloacetic acids in terms of copolymer incorporation and in forming higher molecular weight homopolymer before precipitation.

Sodium fusion tests for halogen⁸ were negative for homo- and copolymers, although the more sensitive Beilstein test⁹ indicated the presence of halogen in some samples. It appears, then, that very small amounts of halogen terminal groups are still present in some cases, although ¹³C-NMR indicates that termination of the active halocarbon end groups usually involves formation of alkyltriethylammonium moieties which do not undergo chain extension or have reduced reactivity.

Figure 3 shows the ¹H-NMR spectra of polyglycolide, poly(α -oxymethylacrylate), plus 1:1 and 1:9 monomer feed copolymers. Characteristic peaks of the vinyl protons are cleanly observed. Peaks for both isolated and allylic methylenes are readily visible in the homo- and copolymers but are somewhat obscured by HFIP solvent. The random character of the copolymer is illustrated in the vinyl region which exhibits multiple peaks presumably due to acrylate units in blocks or adjacent to glycolide groups. Figure 4 shows expanded views demonstrating a consistent change in the ratio of the two sets of peaks on going from homopolymer to copolymer high in acrylate and low in

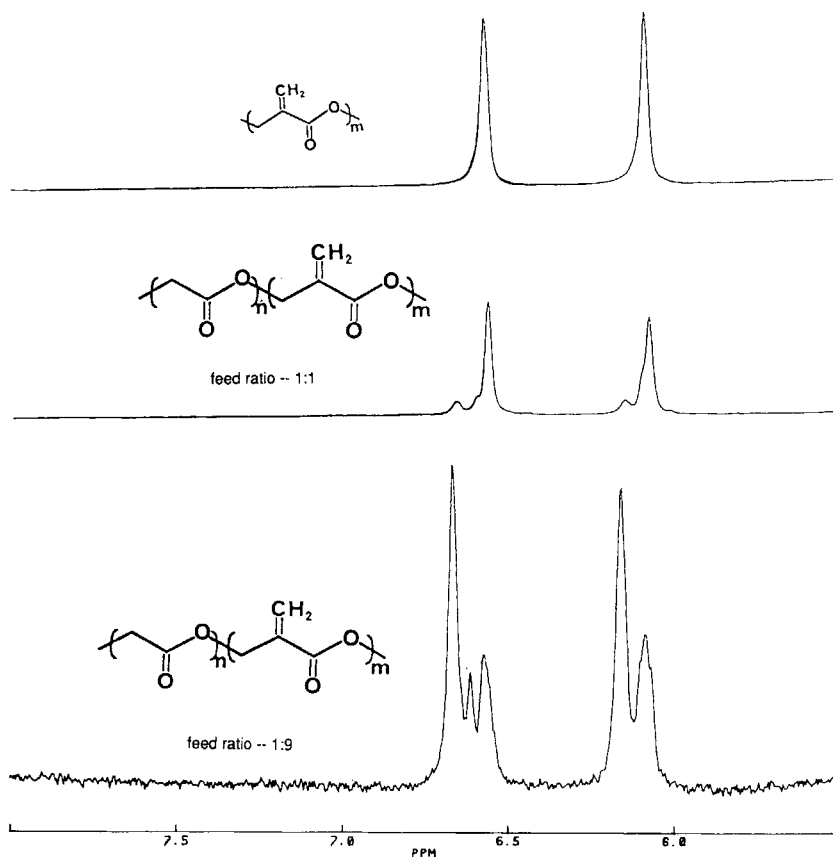


Fig. 4. Expanded ¹H spectra of the vinyl peaks of Figure 3 qualitatively showing the copolymer microstructures.

acrylate content. The downfield set of peaks is assigned to acrylate groups adjacent to glycolide units. More detailed analysis of the relative monomer reactivities and copolymer run lengths was not deemed justified due to restraints on the polymerization process caused by precipitation during formation.

Triethylammonium end groups are also observable in the proton NMR of purified copolymers, thus providing a basis for determining the DP of the copolymers. DP's of about 50–450 were determined by integrating the end-

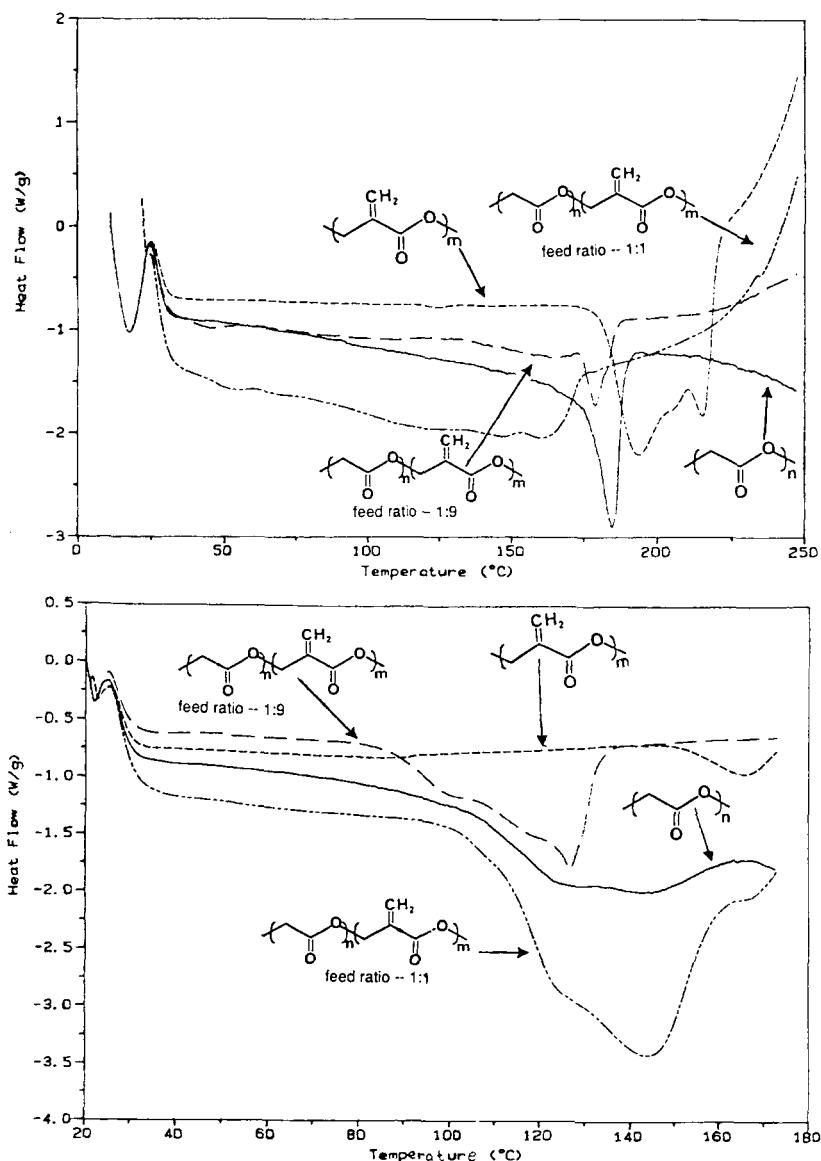


Fig. 5. DSC thermograms of polyglycolide, a 1:1 copolyester, a 1:9 copolyester, and poly(α -oxymethylacrylate); lower scans are for samples heated to 170°C and cooled, upper scans are for the same samples then heated to 250°C.

groups relative to polymer methylenes as given by the formula below.

$$DP = (\text{area methylenes}/2)(\text{area end group CH}_3/9)$$

Unfortunately, there is some inaccuracy in this determination due to the proximity of methylene absorbances with solvent absorbances, and the values given in Tables I and II should only be taken as estimates.

Figure 5 shows the DSC thermogram of polyglycolide, poly(α -oxymethylacrylate), and 1:9 and 1:1 monomer feed copolymers. Copolymers show weak glass transitions at about 110–130°C and in some cases a melting transition at about 185°C.

Figure 6 shows the TGA thermograms of polyglycolide, poly(α -oxymethylacrylate), and the 1:9 and 1:1 monomer feed copolymers. Poly(α -oxymethylacrylate), which is thermally more stable than polyglycolide, adds some thermal stability to the copolymers, especially at the higher compositions.

The *in vivo* dissolvability of copolymers is of prime consideration to the synthesis of polymers having known levels of biodegradability and/or stability. The hydrolysis of copolymers in dilute sodium bicarbonate (Fig. 7) indicates that the extent of hydrolysis is directly related to the acrylate composition in the copolymers. In strong alkali, the copolymers hydrolyzed to glycolic acid and another component presumed to a α -hydroxymethylacrylic acid.

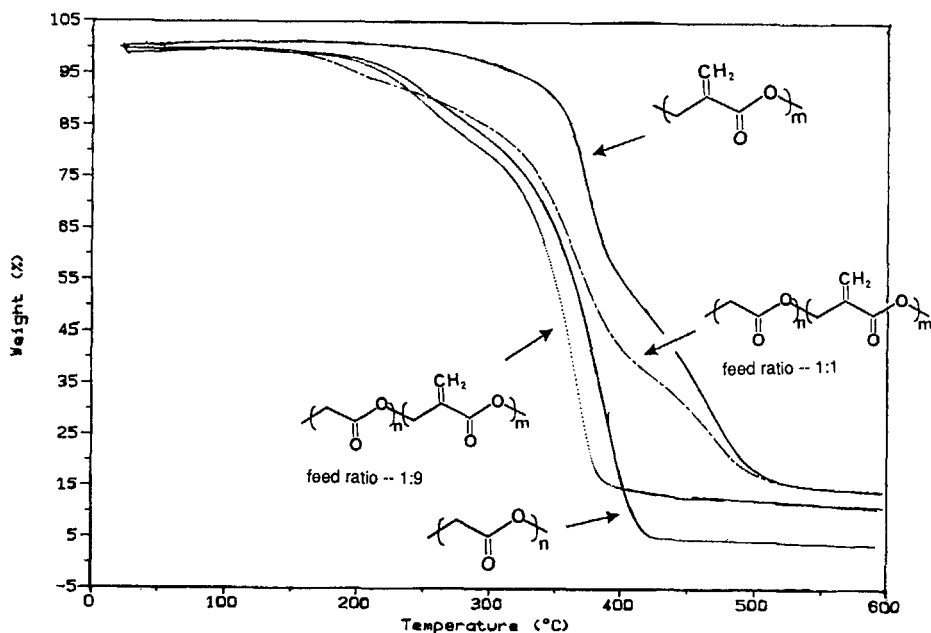


Fig. 6. TGA thermograms of polyglycolide, a 1:1 copolyester, a 1:9 copolyester, and poly(α -oxymethylacrylate).

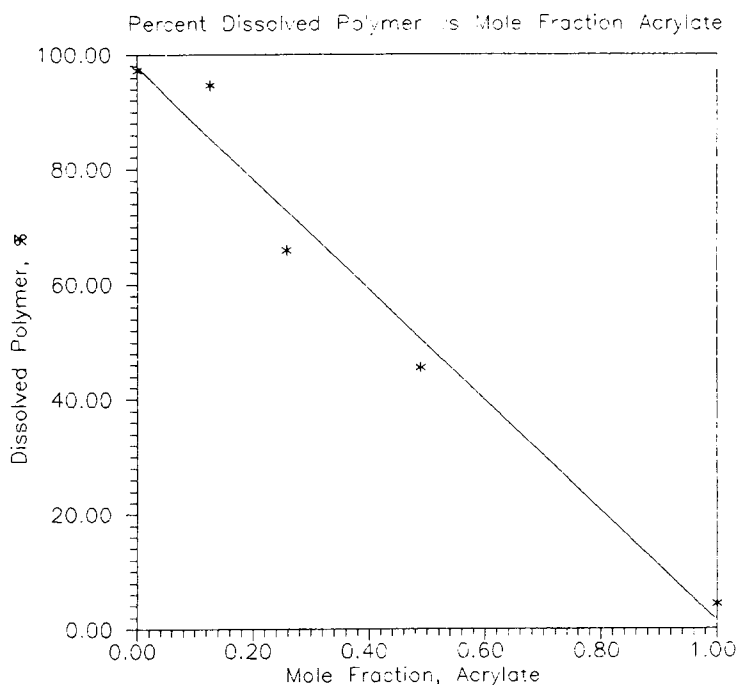


Fig. 7. Dissolved polymer (%) vs. acrylate copolymer composition.

Crosslinking

The unsaturated copolyesters crosslink styrene and methyl methacrylate in DMSO with AIBN. Figure 8 shows the IR spectrum of a 1 : 9 feed copolyester and the same polymer crosslinked with styrene or crosslinked with methyl methacrylate. Figure 9 gives the CP-MAS spectra of the same polymers.

In these spectra, the styrene-crosslinked copolymer shows distinct aromatic carbons at 145.5 and 128.0 ppm, a carbonyl at 167.3 ppm, aromatic CH stretches at about 3100–3000 cm^{-1} , a carbonyl stretch at 1761.7 cm^{-1} , and a monosubstituted aromatic pattern at 760.9 and 695.3 cm^{-1} .

The copolymer crosslinked with methyl methacrylate shows two carbonyls at 178.1 and 167.8 ppm and two large absorbances at 52.2 and 45.1 ppm due to methylenes. The infrared spectrum is similar to poly(methyl methacrylate).

Mechanism

Copolymer formation supports a mechanism involving a triethylammonium carboxylate salt as the active nucleophilic species functioning in a manner analogous to that seen in phase transfer catalysis involving carboxylic acid anions. The mechanism discussed here is similar to that reported by Pinkus and Subramanyan.⁴

Triethylamine and a carboxylic acid react reversibly to give a salt or hydrogen-bonded complex (4) in a manner similar to the equilibrating system

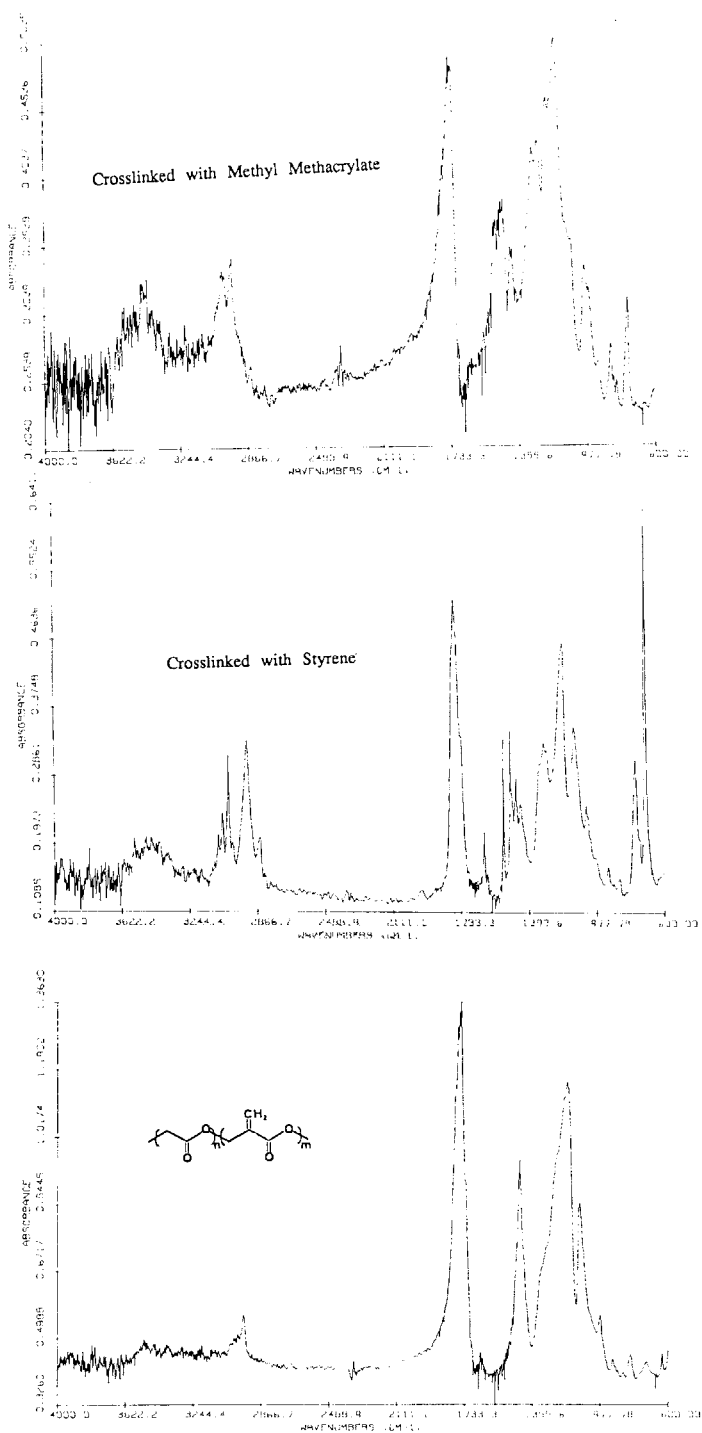


Fig. 8. Infrared spectra of a 1:9 copolyester crosslinked with methyl methacrylate, a 1:9 copolyester crosslinked with styrene and a 1:9 copolyester.

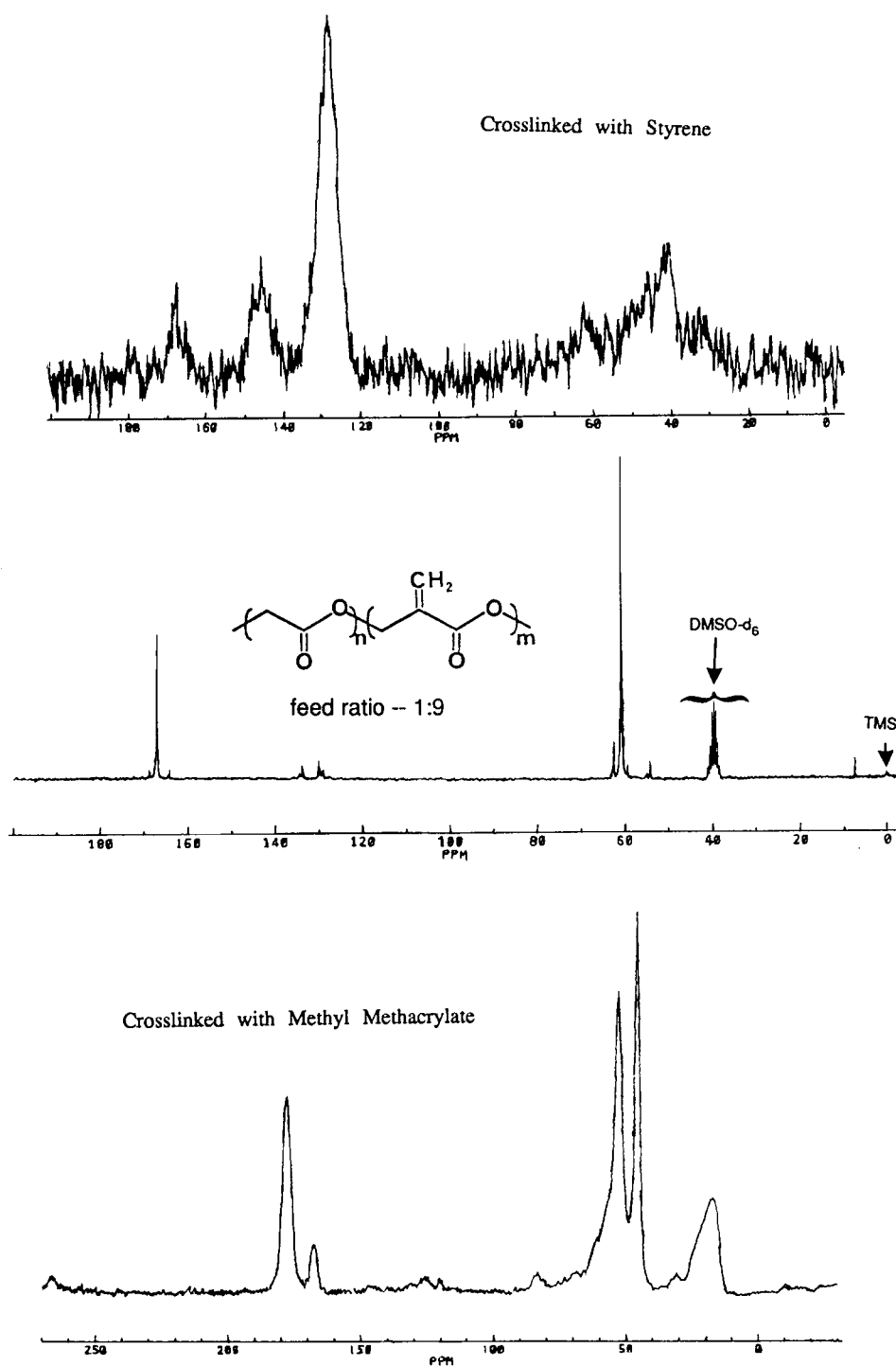
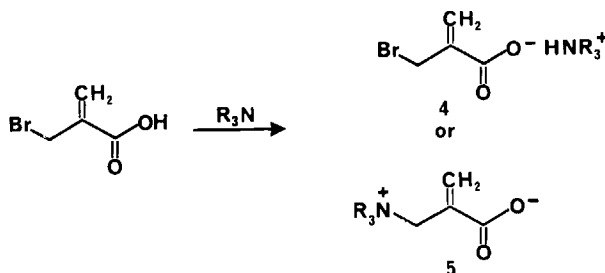


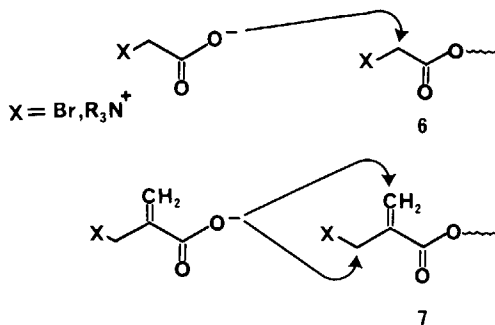
Fig. 9. CP-MAS spectra of a 1:9 copolyester crosslinked with styrene, a solution ^{13}C -NMR of a 1:9 copolyester and a CP-MAS of a 1:9 copolyester crosslinked with methyl methacrylate.

of Golubev et al.¹⁰ Formation of the zwitterion **5** is also possible, consistent with the presence of triethylammonium end groups in the isolated polymers:



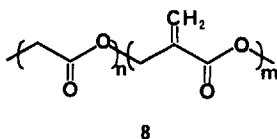
Scheme 2a

An intermolecular nucleophilic substitution reaction produces a dimeric intermediate (**6**) and triethylammonium halide:



Scheme 2b

Repeating this in the propagation step leads to polymeric product. Similar reaction of **7** is facilitated by two sites of attack plus the inherently greater reactivity of the allylic position to substitution reactions. This mechanism does not require β -propiolactone intermediate **3** (to give copolymer **8**) as was earlier described in the synthesis of poly(α -oxymethylacrylate)⁵:



Scheme 3

CONCLUSIONS

We have demonstrated a simple one pot synthesis of unsaturated copolyesters giving low molecular weight products. These copolymers have been shown to crosslink vinyl monomers such as styrene and methyl methacrylate and display properties (T_g , T_m , and solubility) dependent on composition. These copolyesters may have some use in biodegradable sutures

and other applications demanding improved physical properties and extended *in vivo* lifetimes compared to currently available materials.

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