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Preparation and characterization of novel biodegradable tri- and tetraacrylate intermediates

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Abstract

Two biodegradable polymer intermediates, triacrylate **4** and tetraacrylate **7**, were prepared by polycondensation reaction of ethyl β-hydroxybutyrate using glycerol and pentaerythritol as initiators and dibutyltin oxide as a catalyst, followed by functionalization of the hydroxyl end groups with acryloyl chloride in the presence of triethyl amine. These polymer intermediates were characterized using ^{1}H-NMR and IR spectroscopic analysis and were employed as crosslinking agents during polymerization of partially neutralized acrylic acid to obtain the corresponding potentially biodegradable polyacrylates.

Introduction

Biodegradable polymers have found important applications because of their ability to degrade by biochemical reactions, particularly reactions catalyzed by enzymes which are produced by microorganisms under aerobic or anaerobic conditions.[1-6] Alternatively, biodegradable polymers can be produced from the reaction of conventional monomers with degradable crosslinking agents.

Particularly in the medical field, demand for biodegradable materials ranges from dissolving sutures and bone pins to drug delivery devices and wound dressing materials. Therefore, our research was directed towards the preparation and characterization of novel biodegradable polymer intermediates by a simple and efficient polycondensation method.[7] These chemical compounds can be used as key intermediates for the preparation of biodegradable polymer products or can be converted into other polymers useful in surgical applications or tissue regeneration scafolds.[8] More specifically we concentrated on making intermediates containing the basic unit of β–hydroxybutyrate, which is known to biodegrade.[9]

Experimental Section

Pentaerythritol, ethyl β-hydroxybutyrate, acryloyl chloride, dibutyltin oxide, and triethyl amine (Aldrich Chemical Co., Milwaukee, WI) and glycerol and α-chymotrypsin (Sigma Chemical Co., St. Louis, MO) were used as received. An 18% aqueous solution of ammonium persulphate was used as a free radical initiator. All polymerization reactions were conducted

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under a nitrogen atmosphere. ^{1}H-NMR spectra were recorded on a Varian Gemini 200 MHz spectrophotometer using deuteriated chloroform as a solvent. The chemical shifts are reported in δ values relative to that of the internal standard, TMS. Infrared spectra were recorded on a FT-IR spectrophotometer (Model 800, Nicolet Co., Madison, WI) using carbon tetrachloride as a solvent.

Polycondensation of ethyl β-hydroxybutyrate

i) Preparation of glyceryl poly(β-hydroxybutyrate) tri-ol (3): A dry 50 mL reaction flask equipped with a magnetic stirring bar and a reflux condenser was charged with 7.92 g (0.06 mol) ethyl β-hydroxybutyrate (**1**), 0.084 g (0.001 mol) glycerol (**2**) and 80 mg dibutyltin oxide. This mixture was then heated at 140-145 °C for 4 hours under N_2 atmosphere and then at 120 °C/10 mm Hg for 4 hours. The resulting viscous liquid was dissolved in 10 mL of CH_2Cl_2 and the desired polymer product, tri-ol **3**, was isolated by precipitation from a CH_2Cl_2 solution with *n*-hexane. Tri-ol **3** obtained in 4 g yield was purified by washing with *n*-hexane followed by drying under a reduced pressure of 10 mm of Hg.

^{1}H-NMR($CDCl_3$): δ 1.10-1.35 (m, -CH_3), 2.30-2.70 (m, -CH_2-), 2.90-3.30 (bs, -OH), 4.05-4.30 (m, -CH-O) and 5.30 (m, -CH_2-).

IR (CCl_4): 3450 cm^{-1} (hydroxyl) and 1745 cm^{-1} (ester), and average molecular weight[10]: 1898.

ii) Preparation of pentaerythrityl poly(β-hydroxybutyrate) tetra-ol (6): By making use of the above procedure, the preparation of 4.2 g tetra-ol **6** was achieved from the polycondensation of 7.92 g (0.06 mol) ethyl β-hydroxybutyrate (**1**) catalysed by 80 mg dibutyltin oxide and with 0.136 g (0.001 mol) pentaerythritol (**5**) as an initiator.

^{1}H-NMR ($CDCl_3$): δ 1.15-1.35 (m, -CH_3), 2.30-2.80 (m, -CH_2-), 3.00-3.30 (bs, -OH), 4.05-4.30 (m, -CH-), and 5.20-5.40 (m, -OCH_2-).

IR (CCl_4): 3455 cm^{-1} (hydroxyl) and 1745 cm^{-1} (ester), and average molecular weight[10]: 2544.

Hydroxyl group functionalization

i) Preparation of glyceryl poly(β–hydroxybutyrate) triacrylate (4) from tri-ol 3: To a dry 50 mL reaction flask equipped with a rubber septum, a magnetic stirring bar and a reflux condenser there was placed 1.9 g tri-ol **3**, 0.4 g (4 mmol) triethyl amine and 10 mL dry CH_2Cl_2 at 0 °C under a N_2 atmosphere. To this mixture, 0.36 g (4 mmol) acryloyl chloride was added in 5 minutes at 0 °C. The resulting reaction mixture was stirred at room temperature for a period of 24 hours. Upon filtration of the reaction mixture, the CH_2Cl_2 filtrate was washed with dilute HCl and an aqueous $NaHCO_3$ solution in order to remove traces of triethyl amine and HCl, respectively. After drying the CH_2Cl_2 filtrate over an anhydrous $MgSO_4$, the solvent (CH_2Cl_2) was removed under a reduced pressure at room temperature to obtained the desired triacrylate **4** in 1.8 g yield.

^{1}H-NMR ($CDCl_3$): δ 1.10-1.40 (m, -CH_3), 2.30-2.70 (m,-CH_2-), 4.05-4.30 (m, -OCH-), 5.30 (m, -OCH- and -OCH_2-), 5.80-5.95 (m, olefinic H), 6.05-6.20 (m, olefinic H), and 6.35-6.55 (m, olefinic H).

IR (CCl_4): 1610 cm^{-1} (conjugated double bond), 1720 cm^{-1} (conjugated ester) and 1740 cm^{-1} (ester), and average molecular weight[10]: 2057.

ii) Preparation of pentaerytrityl poly(β-hydroxybutyrate) tetraacrylate (7) from tetra-ol 6: By making use of the above procedure, 2.1 g tetraacrylate **7** was prepared from the reaction of 2.3 g tetra-ol **6** with 0.4 g (4 mmol) acryloyl chloride in the presence of 0.5 g (5 mmol) triethyl amine in 10 mL dry CH_2Cl_2.

^{1}H-NMR ($CDCl_3$): δ 1.15-1.40 (m, -CH_3), 2.30-2.80 (m, -CH_2-), 4.05-4.30 (m, -OCH-), 5.30 (m, -OCH_2-), 5.80 (m, olefinic H), 6.10 (m, olefinic H), and 6.40 (m, olefinic H).
IR (CCl_4): 1610 cm^{-1} (conjugated double bond), 1725 cm^{-1} (conjugated ester), and 1735 cm^{-1} (ester), and average molecular weight[10]: 2760.

Polymerization of acrylic acid with triacrylate 4 and tetraacrylate 7 as crosslinking agents:

i) Polymerization of 40% neutralized AA with triacrylate **4**: In a typical reaction, to a solution of 0.78 g NaOH in 8 mL deionized H_20, 3.6 g AA was added at 0 °C under stirring. To this, 0.036 g (1 wt%) triacrylate **4** was added followed by addition of 0.15 g an 18% aqueous solution of ammonium persulphate as a free radical catalyst under agitation and N_2 atmosphere. The resulting polymerization mixture was kept in a polypropylene vial at 37 °C for a period of 24 hours. The desired crosslinked **polyacrylate-1** was isolated in 3.7 g yield after drying at 40 °C under vacuum for a period of several hours. Similar reactions were performed with other degrees of neutralization and crosslinking agents as shown below.
ii) Polymerization of 60% neutralized AA with triacrylate **4** yielded 3.75 g crosslinked **polyacrylate-2.**
iii) Polymerization of 40% neutralized AA with tetraacrylate **7** afforded 3.55 g crosslinked **polyacrylate-3.**
iv) Polymerization of 60% neutralized AA with tetraacrylate **7** gave 3.65 g crosslinked **polyacrylate-4.**

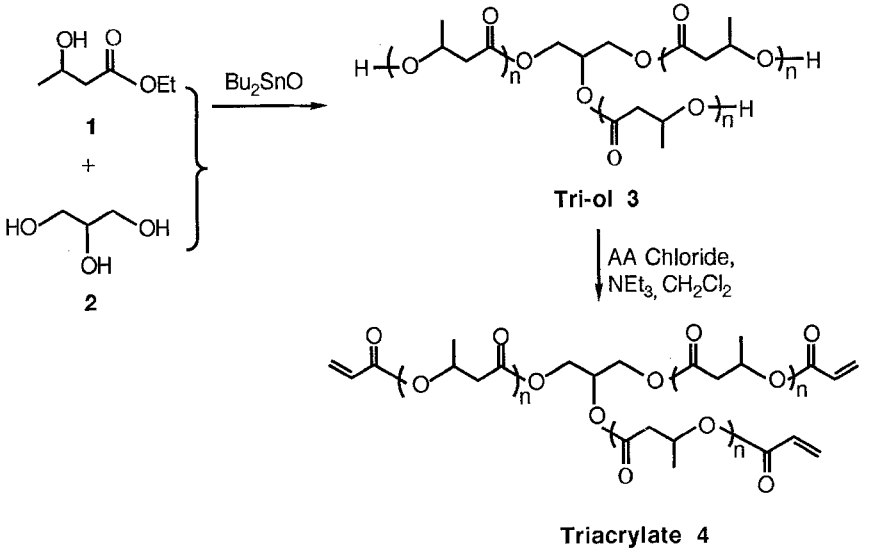
Degradation study

The enzymatic degradation of the previously prepared crosslinked polyacrylate samples was investigated by treating them with an α–chymotrypsin solution, in a process and determining their swelling behavior similar to that reported before.[11] The **polyacrylate 1-4** samples used for this study were in the form of thin disks of 0.3 mm thickness. After determining their dry weight, these samples were swollen in saline solution for 1 hour at room temperature and were subsequently placed in an aqueous solution of α–chymotrypsin of concentration 1mg/mL at 37 °C. The samples were weighed every 24 hours till they attained constant weight and under repeated change of the α-chymotrypsin solution.

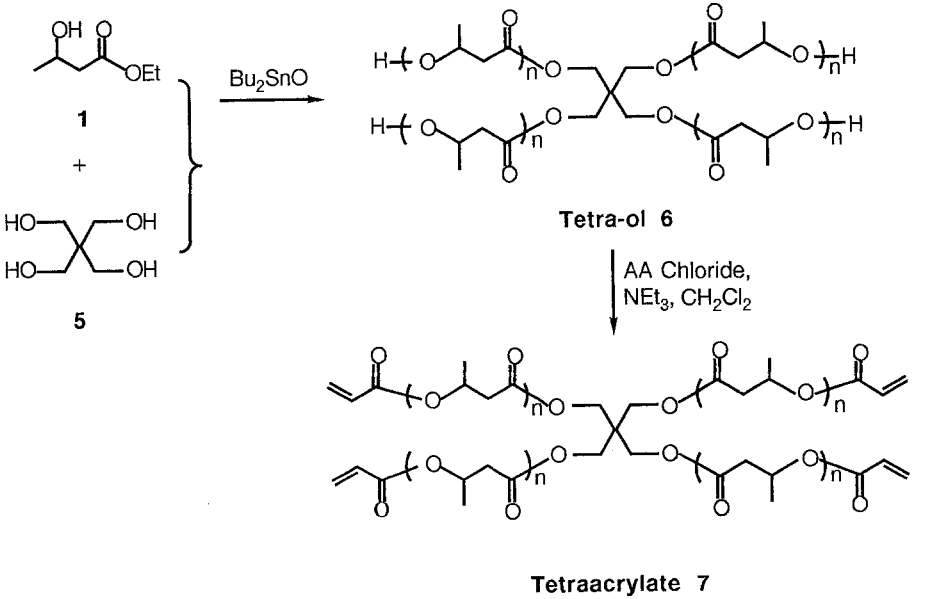
Results and Discussion

Novel biodegradable polymer intermediates were produced from ethyl β-hydroxybutyrate, glycerol and pentaerythritol. The polycondensation of ethyl β–hydroxybutyrate (**1**) with an initiator such as glycerol (**2**) or pentaerythritol (**5**) and catalyzed by dibutyltin oxide led to the corresponding tri-ol **3** and tetra-ol **6**, respectively (Scheme 1 and 2). The chemical structures of **3** and **6** were assigned on the basis of ^{1}H-NMR and IR spectroscopic analysis. The average

Scheme-1



Scheme-2



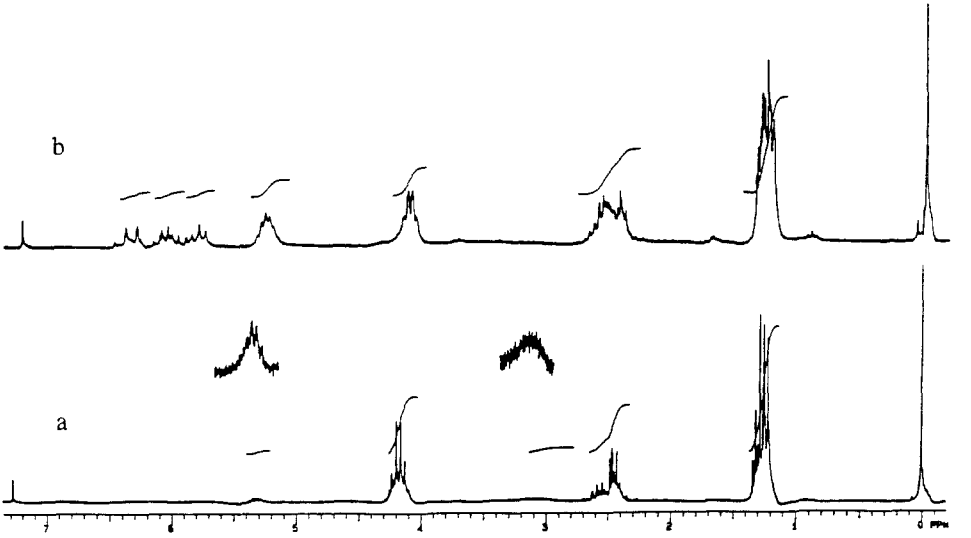


Figure 1: ^{1}H-NMR spectra of tri-ol **3** (a) and triacrylate **4** (b)

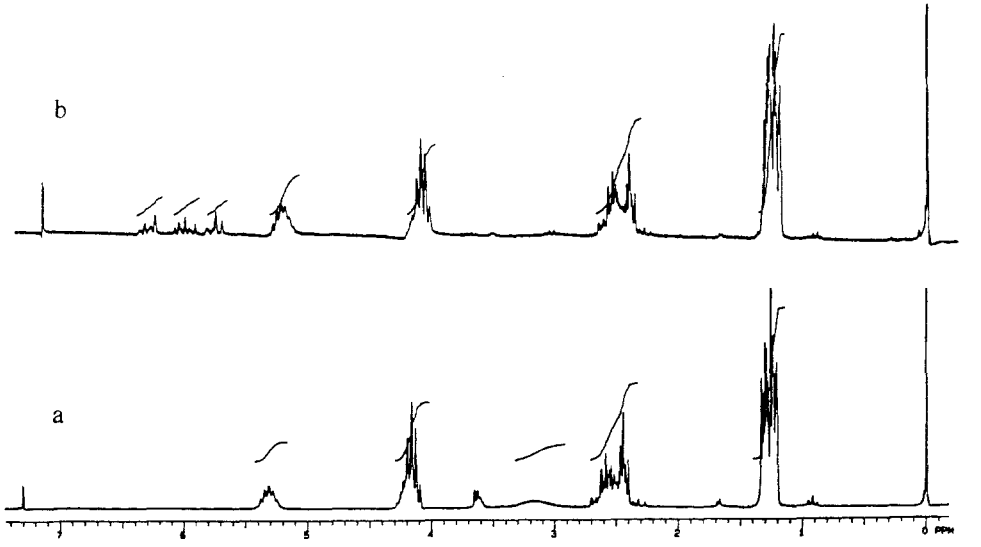


Figure 2: ^{1}H-NMR spectra of tetra-ol **6** (a) and tetraacrylate **7** (b)

value of n =7 for intermediates **3** and **6** was determined from the integration ratio of -OCH_2- protons with that of -CH_3 protons in the ^{1}H-NMR spectra (Figures 1a and 2a). In the IR spectra a broad signal at 3450 cm^{-1} and a sharp signal at 1735 cm^{-1} were indicative of the presence of hydroxyl groups and ester linkages, respectively, for intermediates **3** and **6.**

The resulting tri-ol **3** and tetra-ol **6** with hydroxyl groups at the end of each chain were then reacted with acryloyl chloride in the presence of triethyl amine to obtain the corresponding triacrylate **4** and tetraacrylate **7**, respectively (Scheme 1 and 2). ^{1}H-NMR and IR spectroscopic analysis provided evidence for their chemical structures. In the ^{1}H-NMR spectra (Figures 1b and 2b) the presence of three multiplets for three olefinic protons confirms the presence of acrylate functionilty in polymers **4** and **7**, respectively. Additionally, the absence of the hydroxyl group frequency at 3450 cm^{-1} and the presence of a conjugated double bond frequency (C=C-CO-) at 1610 cm^{-1} and a conjugated ester at 1720 cm^{-1} proves the absence of hydroxyl groups and the existence of acrylate groups in the structure of polymer intermediates **4** and **7.**

In order to examine their biodegradability, the acrylates produced were used as crosslinking agents during the free radical polymerization of 40 and 60% neutralized acrylic acid catalyzed by ammonium persulphate to obtain the corresponding crosslinked **polyacrylates 1-4.** The degradation of **polyacrylate 1-4** samples was investigated by determining their swelling behavior in an α-chymotrypsin (1mg/mL of H_2O) solution at 37 °C. For the degradation experiments the swelling ratio, q = (g of swollen PAA/g of dry PAA), was plotted as a function of time as shown in Figure 3. As seen from the results, the weight swelling ratio attains values as high as 300 for polyacrylates crosslinked with these biodegradable crosslinking agents. However, in the presence of α-chymotrypsin a rapid degradation occurs and the network starts dissolving, leading to significantly decreased swelling of the remaining network.

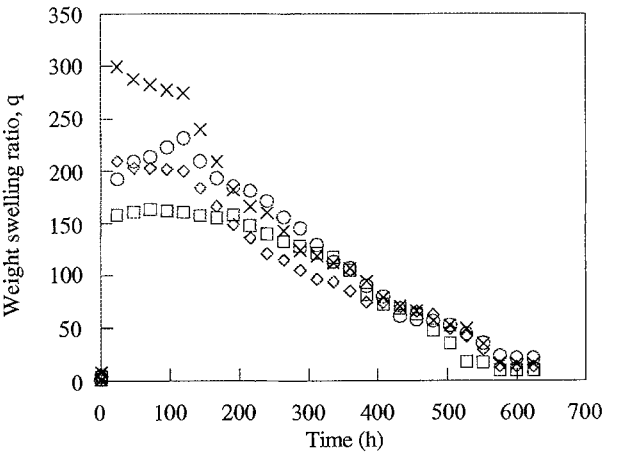


Figure 3: Weight swelling ratio, q, of polyacrylate networks in an α-chymotrypsin solution at 37 °C, for samples prepared from a free radical copolymerization of 40 and 60% neutralized AA with triacrylate **4** and tetraacrylate **7** as crosslinking agents (1 wt%). Polyacrylate 1 (O), Polyacrylate 2 (❑), Polyacrylate 3 (◊) and Polyacrylate 4 (X).

Conclusions

Two types of biodegradable polymer intermediates were synthesized and characterized. In order to examine their biodegradable behavior, they were utilized as crosslinking agents for the free radical polymerization of the partially neutralized acrylic acid to obtain the corresponding crosslinked polyacrylates. The ensuing crosslinked polymers were examined for biodegradation using α-chymotrypsin solution and found to be biodegradable.

Acknowledgment

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10. The average molecular weights were determined from the integration ratios of -OCH_2- protons from initiator units with that of -CH_3 protons from butyrate repeated units.

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