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Synthesis and characterization of allyl functionalized poly(α-hydroxy)acids and their further dihydroxylation and epoxidation

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Abstract

In this study, the synthesis of an allyl functionalized aliphatic polyester and the subsequent oxidation of the double bonds was investigated. Allylglycolide (3-allyl-1,4-dioxane-2,5-dione) was synthesized and its homopolymer and copolymers with L-lactide were prepared by ring opening polymerization in the melt using benzyl alcohol and $SnOct_2$ as initiator and catalyst, respectively. The polymerizations proceeded with high yields and conversions and good control over molecular weights and copolymer composition. The obtained polymers were amorphous materials and their T_g increased with increasing lactide content. Dihydroxylation of the double bonds in poly(allylglycolide) and copolymers with lactide was attempted with osmiumtetroxide/4-methylmorpholine-4-oxide (OsO_4/NMO). However, particularly the polymers rich in allylglycolide could not be isolated after dihydroxylation because they likely underwent degradation during workup. Optimizing the reaction conditions gave partially dihydroxylated copolymers only for copolymers with high lactide content (50 and 75 mol%) with a conversion of the double bonds of only ~60%. GPC analysis showed that chain scission had occurred during the dihydroxylation reaction and/or workup.

The allyl groups of poly(allylglycolide) homopolymers and copolymers with lactide were oxidized using *m*-chloroperoxy benzoic acid (mCPBA) to yield the corresponding epoxidated polymers in high yield. NMR analysis showed that conversion of the double bonds to epoxides was quantitative, whereas GPC analysis showed that the epoxidation was not associated with chain scission. All epoxidated polymers were amorphous materials with a T_g depending on the composition.

Keywords: Functionalized poly(α-hydroxy)acids; Dihydroxylation; Epoxidation; Biodegradable

1. Introduction

The use of biodegradable polyesters in pharmacy and medicine is growing rapidly. In particular,

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polyesters based on endogenous compounds like lactic and glycolic acid are often used as biomaterials in medical devices, drug delivery systems and tissue engineering scaffolds [1–7]. For this purpose homopolymers and copolymers of lactic and glycolic acid as well as their copolymers with other monomers like ε-caprolactone and trimethylene carbonate (TMC) have been synthesized and characterized [4]. Poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers (poly(lactic acid-co-glycolic acid), PLGA) have advantageous properties for e.g. use as surgical sutures because of their good mechanical strength, processability and degradability. The hydrophobicity of PLA type polymers causes them to degrade slowly under physiological conditions (degradation times ranging from 2 months to 2 years). For drug delivery purposes there is a need for polymers that degrade more rapidly, and that thereby release the loaded drug over a short period of time. Substantial efforts have been made over the past years to tailor the degradation rates of PLGA copolymers, e.g. by copolymerization with less hydrophobic comonomers such as sugars [8], amino acids [9] and substituted (di)lactones [10], or by the introduction of functional groups [11–16]. By the introduction of functional groups in the polymer main chain the range of applications of these polymers can be enlarged. Their degradation behavior in aqueous media can be modulated because of a higher water-absorbing capacity of the polymer matrix. Also, these functional groups can be used for the conjugation of e.g. RGD peptides to promote cell adhesion [17].

PLGA, PCl and PTMC are generally synthesized via a ring opening polymerization (ROP). ROP needs a cyclic monomer such as a lactone or a dilactone; for instance lactide is used in the case of poly(lactic acid) [13]. A great number of different cyclic compounds have been employed to obtain functionalized polyesters with higher hydrophilicity than PL(G)A [14–16]. Previously, we reported the synthesis and degradation of hydroxyl functionalized poly(α–hydroxy) acids synthesized by the ring opening polymerization of benzyl protected, hydroxyl functionalized dilactone [18,19]. To investigate possible routes to other functionalized aliphatic polyesters we synthesized allylglycolide (3-allyl-1,4-dioxane-2,5-dione).

In this study, allyl functionalized aliphatic polyesters were synthesized and characterized. First the synthesis of the monomer allylglycolide is described followed by its homopolymerization and copolymerization with L-lactide. These allyl fuctionalized polymers were dihydroxylated (partly successful) and epoxidated (fully successful) which demonstrates the versatility of these polyesters.

2. Experimental section

2.1. Chemicals and analytical equipment

Glyoxylic acid monohydrate (97+%), hyflo, bismuth trichloride (97+%), bromoacetyl bromide (98+%), 4-dimethylaminopyridine (DMAP) (99+%) and 50% 4-methylmorpholine-4-oxide solution (NMO) in water were obtained from Fluka (Buchs, Switzerland). Zinc powder (99+%) and osmium tetraoxide (very toxic) were obtained from Riedel de Haën (Seelze, Germany). Allyl bromide (99+%), *m*-Chloroperoxy benzoic acid (70% aqueous dispersion) and stannous octoate (>96%), were obtained from Aldrich (Steinheim, Germany). Silicagel, sodium sulfate (anhydrous) and isopropanol (p.a.) were obtained from Acros (Geel, Belgium). Sodium carbonate (p.a. (>99.9%)), acetone (p.a. (99.6%)), pentane (p.a.), ammonium acetate (p.a.) and benzyl alcohol (BnOH, (p.a.)) were obtained from Merck (Darmstadt, Germany). Benzyl alcohol was distilled from CaH_2 prior to use. THF (HPLC), diethyl ether (AR), dichloromethane (peptide synthesis grade), methyl tertiary butyl ether (MTBE) (AR-S glass distilled) and *N,N'*-dimethylformamide (DMF) (peptide synthesis grade), were obtained from Biosolve (Valkenswaard, the Netherlands). All mentioned chemicals were used without further purification, unless stated other wise.

NMR measurements were preformed at 298 K on a Varian Gemini-300 NMR machine, at 300 MHz (^1H) or 75 MHz (^{13}C). Chemical shifts (δ) are reported in ppm relative to TMS (^1H) or with the solvent peak as internal reference (^{13}C). Thermographic analyses were done on a TA Instru ments DSC Q1000 machine. Scans were taken from −50 to 190 °C at a heating rate of 10 °C/min. Inflection points of glass transition temperatures of the second run are reported. Gel permeation chromatography (GPC) was carried out on a Waters Aliance system, with a Waters 2695 separating module and a Waters 2414 Refractive Index Detector. Two PL-gel 5 μm mixed-D columns fitted with a guard column (Polymer Labs, M_w range 0.2–400 kDa) were used. The columns (thermostatted at 40 °C) were calibrated with polystyrene standards using THF (Biosolve, Valkenswaard, the Netherlands) as the mobile phase