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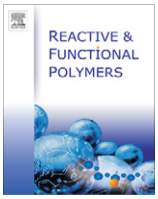

Functionalized oligoesters from poly(3-hydroxyalkanoate)s containing reactive end group for click chemistry: Application to novel copolymer synthesis with poly(2-methyl-2-oxazoline)

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ABSTRACT

Well defined poly(3-hydroxyalkanoates) PHAs containing an alkyne end group were prepared in a one step reaction by direct alcoholysis from natural polyesters using propargyl alcohol. The reactions were allowed to proceed with dibutyltin dilaurate as catalyst at different concentrations from 0.5 up to 24% mol/mol of the alcohol. Oligoesters were obtained with molar masses ranging from 44,500 to 2700 g mol^{-1}. Analysis of the MALDI-TOF mass spectra of the obtained oligomers has revealed the presence of alkyne group on one side and hydroxyl end group on the other side when the reaction was conducted in dried chloroform. The reaction rate of oligomer formation was depending on the nature of the PHAs and decreased with the length of the side chains. The Huisgen 1,3-dipolar cycloaddition has been investigated between the alkyne group of PHAs and 2-azido-2-deoxy-D-glucose or azido-poly(2-methyl-2-oxazoline) (N$_3$-POXZ). The click reaction allowed the preparation of novel diblock copolymer PHA-*b*-POXZ soluble in water.

1. Introduction

Poly(3-hydroxyalkanoate)s PHAs are bacterial polyesters that can be considered as promising biopolymers due to their renewability, biodegradability and biocompatibility [1]. Two types are distinguished, one with short-chain length, or *scl*-PHAs, possessing alkyl side chains having up to two carbons and medium-chain-length PHAs, or *mcl*-PHAs, having at least three carbon atoms on their side chains. Their properties make them good candidates for medical temporary applications [2,3]. Unsaturated PHAs as poly((3-hydroxyoctanoate)-co-(3-hydroxyundecenoate)) PHOU has the major advantage to be functionalized on its side chains, allowing chemical modifications. A range of functional groups have been introduced such as epoxide [4], carboxylic groups [5,6], chlorine [7], amine groups [8], hydroxyl groups [9–11], and more recently alkyne group [12]. Ritter and co-workers [13] recently prepared by bacterial fermentation an unsaturated PHAs with pendent alkyne end groups. Various methods have also been developed for preparing functionalized PHAs oligomers like acid-catalyzed methanolysis [14,15], thermal treatment [16], and transesterification reaction [17,18]. Telechelic dihydroxylated poly(3-hydroxybutyrate)s were prepared by a transesterification procedure with ethylene glycol and were used as segments in the synthesis of copoly(ester-urethane)s [19]. They were also used to prepare thermoplastic block copolymer by enzymatic catalyzed polycondensation [20]. A hydroxyl-terminated poly(3-hydroxyoctanoate) oligomer obtained by methanolysis in presence of sulfuric acid [21] was required to prepare diblock copolymers by ring-opening polymerization of cyclic monomer as ε-caprolactone or lactide. PHAs oligomers with alkyne end group were recently prepared in a two steps procedure [22]. First, oligomers were prepared by thermal treatment and then carboxylic acid end groups were quantitatively coupled with propargylamine. From this starting oligomers, amphiphilic copolymers could be designed. Among amphiphilic and water soluble polymers, polyoxazolines are very attractive for their low toxicity which makes them interesting as biomaterials [23–26] and non ionic surfactants. Recently, novel polyoxazoline copolymers based on vegetable oil were described [27].

The purpose of the present study is to develop a simple and efficient method to prepare functionalized PHAs oligoesters containing alkyne end group in a one step reaction by direct alcoholysis. The

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preparation of oligomers from polyesters was achieved by direct reaction with propargyl alcohol using dibutyltin dilaurate as catalyst. This reaction was applied to poly(3-hydroxyoctanoate-co-3-hydroxyhexanoate) PHOHHx, poly(3-hydroxyoctanote-co-3-hydroxynonenoate) PHOHNe and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) PHBHV. The reactions are made in different solvents, diglyme or chloroform, in presence of dibutyltin dilaurate as catalyst at different concentrations. The alkyne terminal end group of PHBHV was used to react with 2-azido-2-deoxy-D-glucose or with azido-poly(2-methyl-2-oxazoline) (N_3-POXZ) using the copper (*I*) catalyzed azide-alkyne cycloaddition. The identification of the structure was realized by ^{1}H NMR, ^{13}C NMRand MALDI-TOF mass spectrometry to investigate the nature of the functional end groups formed.

2. Experimental section

2.1. Materials

Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBHV) with 6 mol% of hydroxyvalerate was obtained from ICI. Poly(3-hydroxyoctanoate-co-3-hydroxyhexanoate) (PHOHHx) was obtained from EMPA (Swiss Federal Laboratories for Materials Testing and Research, Laboratory for Biomaterials, St Gallen, Switzerland). Poly (3-hydroxyoctanoate-co-hydroxynonenoate) (PHOHNe) was obtained from Ifremer, France. The monomer 2-methyl-2-oxazoline (Aldrich, purity 99%) was dried overnight over calcium hydride and purified by distillation under a nitrogen atmosphere. Acetonitrile (SDS, Peypin, France) was distilled over calcium hydride before use, the chloroform used as the reaction solvent was dried over calcium chloride. Diglyme (Acros Organics, 99%), chloroform (SDS, analytical grade), petroleum ether (SDS, analytical grade), diethyl ether (SDS, analytical grade), propargyl alcohol (Aldrich, 99.5%), dibutyltin dilaurate (Aldrich, 95%), 1-iodopropane (Aldrich, 99%) and sodium azide (Aldrich, 99.5%), 2-azido-2deoxy-D-glucose (Aldrich), copper (*I*) iodide (Aldrich,99.5%), N,N,N′,N″,N″-pentamethyldiethylenetriamine (Aldrich, 99.5%), were used without further purification. Silica gel 60 Å was used for column chromatography. The dialysis membranes were purchased from Spectrum Laboratories (regenerated cellulose).

2.2. Preparation of alkyne terminated scl-PHA

The amount of propargyl alcohol was set, for the PHBHV, to 0.4 equivalent of the quantity of monomeric units which is tenfold excess of the required amount for a final length of about 25 monomers (*i.e.* a molar mass of 2200 g mol^{-1}). In a typical synthesis of alkyne terminated PHBHV, 250 mg of PHBHV (2.8×10^{-6} mol) were dissolved in 2.5 mL of diglyme in a 3-neck round-bottom flask with a magnetic bar under argon at 120 °C in an oil bath. After cooling at 110 °C, to avoid further evaporation of propargyl alcohol (*bp* = 114–115 °C), 67 μL of propargyl alcohol (1.15×10^{-3} mol) and 40.8 μL of dibutyltin dilaurate (6.9×10^{-5} mol, 6 mol% of propargyl alcohol) were introduced and the mixture was stirred at 110 °C for 6 h. At the end of the reaction it was quickly cooled at room temperature, 10 mL of chloroform were added and the solution was precipitated in petroleum ether. The solid obtained was dried under vacuum at 80 °C overnight.

2.3. Preparation of alkyne terminated mcl-PHA oligomers

In a typical synthesis of alkyne terminated PHOHHx, 122 mg of PHO (9.1×10^{-7} mol of PHA) were dissolved in 1.2 mL of chloroform in a seal-capped tube with a magnetic bar at 100 °C in an oil bath. 20 μL of propargyl alcohol (3.4×10^{-4} mol) and 40 μL of dibutyltin dilaurate (0.68×10^{-4} mol, 20 mol% of propargyl alcohol) were introduced and the mixture was stirred at 100 °C for 20 h. The reaction was stopped by quickly cooling it at room temperature and the mixture was transferred in a dropping-funnel for work-up: the solution was washed twice with distilled water, the product was extracted with chloroform, the organic phase was dried with $MgSO_4$, filtered and then the solvent was removed by evaporation. The crude product was dissolved in chloroform, filtered through a column (12 cm of silica gel and a 2 cm upper layer of Celite) with $CHCl_3$/Acetone 98/2 as eluent.

2.4. Preparation of azido-poly(2-methyl-2-oxazoline) (N_3-POXZ)

The azido-poly(2-methyl-2-oxazoline) (N_3-POXZ) has been prepared following the typical procedure: 2 mL of 2-methyl-2-oxazoline (24×10^{-3} mol) was added in 6 mL of dry acetonitrile, under dry nitrogen. 70 μL (0.72×10^{-3} mol) of 1-iodopropane were added. The reaction mixture was stirred during 18 h at 80 °C. The polymerization was stopped by adding an excess of sodium azide and kept at 80 °C during 24 h. The polymer was purified by precipitation in diethyl ether, and then dried under vacuum. The azido-POXZ has a Mn (determined by SEC) of 2800 g mol^{-1} and a polydispersity of 1.18.

2.5. Click reaction of alkyne terminated $_{scl}$PHA with 2-azido-2-deoxy-D-glucose

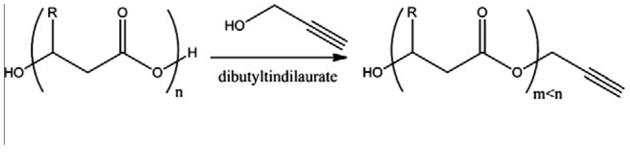
100 mg of an alkyne terminated PHBHV oligomer (Mn = 2200 g.mol^{-1}, $4.6 \times 10^{-2} \times 10^{-3}$ mol) were dissolved in 5 mL of DMSO. 29 mg of 2-azido-2-deoxyglucose (0.14 mmol), 9 mg of CuI (4.7×10^{-2} mmol) and 10 μL of PMDETA ($4.8 \times 10^{-2} \times 10^{-3}$ mol) were added. The solution is stirred for 72 h at 100 °C and then dialyzed against distilled water for 5 days with a 1000 Da membrane. 64 mg of final product are obtained.

2.6. Click reaction of alkyne terminated ^{scl}PHA with poly(2-methyl-2-oxazoline)

100 mg of an alkyne terminated PHBHV oligomer (Mn = 1500 g mol^{-1}, $6.7.10^{-2} \times 10^{-3}$ mol) are dissolved in 5 mL of CH_2Cl_2. 570 mg of azido-poly(2-methyl-2-oxazoline) (Mn = 2800 g mol^{-1}, 0.2 mmol), 5 mg of CuI (2.7×10^{-2} mmol) and 14 μL of PMDETA (6.7×10^{-2} mmol) are added. The solution is stirred for 3 days in an oil bath at 50 °C. The solvent is then evaporated, the product obtained solubilized in DMSO, dialyzed against distilled water with a MWCO of 12000–14000 Da and then lyophilized.

2.7. Polymer characterization

Average molar masses of PHAs were determined by SEC using a Shimadzu LC-10AD pump with two styragel columns connected in



Polymer	R=
PHBHV	0.94 CH_3, 0.06 CH_2CH_3
PHOHHx	0.15 $(CH_2)_2CH_3$, 0.85 $(CH_2)_4CH_3$
PHOHNe	0.69 $(CH_2)_4CH_3$, 0.19 $(CH_2)_4CH{=}CH_2$, 0.03 $(CH_2)_4CH_3$, 0.08 $(CH_2)_4CH{=}H_2$

Fig. 1. Transesterification reaction of poly(3-hydroxyalkanoate)s with propargyl alcohol.