



Degradable “click” polyesters from erythritol having free hydroxyl groups

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ABSTRACT

Click Cu(I)-catalysed polymerization and thermal polyaddition of diynes having ester linkages and 1,4-diazido-1,4-dideoxyerythritol were performed to obtain polyesters containing 1,2,3-triazole rings along the polymer chain. The resulting polyesters had weight-average molecular weights in the 13,000–37,000 range. Thermal studies revealed them to be mainly amorphous and stable up to 250 °C under nitrogen. The polymers are hydrophilic, several of them being water-soluble. Degradation studies of a water-soluble prototype polymer showed they are hydrolytically degradable. These studies were carried out at 37 °C in doubly distilled water and buffered salt solution at pH 7.4, and were monitored by GPC, and IR and NMR spectroscopies.

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1. Introduction

The synthesis of polymers based on sustainable chemistry makes carbohydrates and polysaccharides very attractive materials. They are produced in large amounts by plants and microorganisms every year, and in some cases they even come from agricultural wastes. In addition, they are found in a very rich structural and stereochemical diversity. Unfortunately, the use of sugars as monomers is not straightforward [1,2]. In most cases, due to their multifunctionality, protecting groups have to be introduced in order to obtain a convenient monomer. Furthermore, if the final requirement is the deprotected polymer, the protecting groups must be eliminated, with the obvious risk of degradation of the polymer backbone [3].

The 1,3-dipolar cycloaddition of an azide moiety and a triple bond [4] (Huisgen reaction) or the highly efficient, orthogonal and regioselective copper (I)-catalysed azide-alkyne cycloaddition [5,6] (CuAAC) could help to overcome these drawbacks. These reactions, apart from requiring stoichiometric amounts of starting materials, could be performed without the need to protect the remaining alcohol functions in the carbohydrate monomer and without producing by-products.

These cycloaddition reactions have been successfully applied to synthesize a large variety of materials [7–11]. In particular, the

preparations of linear triazole-linked polymers have been limited. In this respect, polyaddition of small bis-azide and bis-alkyne monomers have been used for the preparation of different poly-triazoles [13–15,18], polyester [12], multifunctional PEGs [16], poly(aroyltriazole)s [17], poly(alkyl aryl ether)s [19], or poly(glycoamidoamine)s [20]. To the best of our knowledge, this is the first time that click chemistry has been used to synthesize a series of polyesters from an open-chain carbohydrate derivative with its alcohol functions free.

In this paper, we present the synthesis of new sugar-derived polyesters containing 1,2,3-triazole units along the polymer backbone. These polymers were prepared by catalyst- and solvent-free 1,3-dipolar Huisgen cycloaddition and by CuAAC by combining a diazide derived from erythritol and diverse diynes derived from polyethylene glycol, aliphatic diols, or isosorbide. Poly(ethylene glycol) (PEG) is a very well-known material that has been extensively used in drug delivery systems because of its biocompatibility and its good solubility in both organic solvents and water [21–23]. The use of aliphatic diols rather than PEG as starting materials will provide greater hydrophobicity to the resulting polymers, while isosorbide, a bicyclic diol that contains four asymmetric carbons and is produced industrially from starch [24], will increase the rigidity of the polymer chain. The good accessibility of isosorbide has encouraged its use for the synthesis of a variety of linear polymers [24,25].

The preparation and study of new triazole-based polymers is a subject of considerable interest in polymer and material science [26]. They have been studied as binders for explosives and high-

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energy propellants [27–30]. It has long been known that triazoles have a strong affinity for metal ions and surfaces, and both small molecules and polymers containing these units are used as anti-corrosive agents [31–33] and metal adhesive materials [34]. In addition, the presence of the triazole rings in these new poly-triazoles and/or in their degradation products, as well as the free hydroxyl groups present in the sugar-based units, could induce the development of biological activity by association with biological targets through hydrogen bonding and dipole interactions [35].

2. Experimental section

2.1. Materials

Chemicals were all used as purchased from Sigma-Aldrich Chemical Co. Solvents were dried and purified when necessary, by appropriate standard procedures. 1,4-Diazido-1,4-dideoxyerythritol was obtained according to the procedure described by Glacon et al. [36]. This compound was also prepared in two steps, starting from erythritol, by first obtaining its ditosylate and then, nucleophilic displacement with sodium azide in *N,N*-dimethylformamide. Propiolates **1–3** [37], **4** [27], and **5** [38] were prepared according to the procedures reported in the bibliography.

2.2. Measurements

Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 (E. Merck) with detection by UV light or charring with H₂SO₄ or phosphomolybdic acid. Flash column chromatography was performed using E. Merck Silica Gel 60 (230–400 mesh). IR spectra were recorded with a JASCO FT/IR-4200 spectrometer equipped with ATR. ¹H and ¹³C NMR spectra were recorded with a Bruker AMX-500 or Bruker AV-300 spectrometer. Chemical shifts are reported as parts per million downfield from tetramethylsilane. Two-dimensional ¹H–¹H homonuclear and ¹³C–¹H heteronuclear shift correlation spectra were recorded with the COSY and HETCOR pulse sequences, respectively. Elemental analyses were determined in the Microanalysis Laboratories of the CITIUS Service at the University of Seville and in the Instituto de Investigaciones Químicas (CSIC) of Seville. Chemical ionization (CI) was performed on a micromass Autospec spectrometer. The thermal properties of the polymers were determined by differential scanning calorimetry (DSC) using a TA Instruments DSC Q200, calibrated with indium. Samples of about 2–3 mg were heated at a rate of 10 °C/min under a nitrogen atmosphere (flow rate of 20 mL/min) and cooled to room temperature. The peak temperatures were taken as melting points. Thermogravimetric analyses (TGA) were performed with a SDTQ600 TA instrument at a heating rate of 10 °C/min under a nitrogen flow of 100 mL/min. Gel permeation chromatography (GPC) analyses were performed using a Waters apparatus equipped with a Waters 2414 refractive-index detector and two Styragel HR columns (7.8 × 300 mm) linked in series, maintained at 60 °C, using *N*-methylpyrrolidone (NMP) as the mobile phase, at a flow rate of 0.5 mL/min. Calibration was performed using 12 polystyrene samples of narrow molecular-weight distribution. HPLC analyses were carried out in an Agilent 1200 series apparatus fitted with an ultraviolet detector. The analysis was performed at a flow rate of 0.7 mL/min using an AD column and hexane–isopropanol (3:1) as the mobile phase.

2.3. Synthesis

2.3.1. 1,4:3,6-Dianhydro-2,5-di-*O*-propioloyl-*D*-glucitol (**6**)

A mixture of 1,4:3,6-dianhydro-*D*-glucitol (2.34 g, 40.4 mmol), propiolic acid (2.5 mL, 40.4 mmol), and *p*-toluenesulphonic acid

(0.15 g) in toluene (100 mL) was heated to reflux through a Dean-Stark apparatus for 24 h. Toluene was evaporated under reduced pressure, and the residue was diluted with dichloromethane (200 mL), washed with saturated NaHCO₃ (30 mL), and dried over anhydrous MgSO₄. Filtration and evaporation of the solvent gave a residue that was purified by column chromatography (6:1:4.1 hexane–ethyl acetate), giving after evaporation of the solvents **6** as a solid (2.0 g, 50%), mp 105–106 °C. IR: ν_{\max} 2116 (C≡C), 1723, 1708 cm⁻¹ (CO); NMR data (CDCl₃): ¹H, δ 5.28 (m, 1H, H-2), 5.24 (m, 1H, H-5), 4.91 (t, 1H, H-4), 4.54 (d, 1H, H-3), 4.12–3.84 (m, 4H, H-1, H-6), 2.97 (s, 2H, HC≡C); ¹³C, δ 151.79, 151.60 (CO), 86.69 (C-3), 80.71 (C-4), 79.47 (C-2), 70.06, 75.96 (HC≡C), 75.44 (C-5), 74.06, 74.01 (HC≡C), 73.01 (C-1), 70.41 (C-6). Anal. Calcd for C₁₂H₁₀O₆: C, 57.60; H, 4.03. Found: C, 57.68; H, 4.11.

2.3.2. 2-(2-Methoxyethoxy)ethyl propiolate (**7**)

Treatment of a solution of diethylene glycol methyl ether (1.92 g, 16.0 mol) with propiolic acid and *p*-toluenesulphonic acid as described above gave, after column chromatography, **7** as a liquid (2.0 g, 72%). NMR data (DMSO-*d*₆): ¹H, δ 4.53 (s, 1H, HC≡), 4.26 (m, 2H, H-1), 3.63 (m, 2H, H-2), 3.54 (m, 2H, H-3), 3.44 (m, 2H, H-4), 3.25 (s, 3H, H-5); ¹³C, δ 152.24 (CO), 79.12 (HC≡), 74.67 (HC≡C), 71.22 (C-4), 69.57 (C-3), 67.79 (C-2), 65.15 (C-1), 58.07 (C-5).

2.3.3. General procedure for the synthesis of polytriazoles

2.3.3.1. Procedure A: thermal polymerization. Bis-propiolate **1–6** (0.37 mmol) and 1,4-diazido-1,4-dideoxyerythritol (0.37 mmol) were mixed together and stirred at 56 °C for 24 h to obtain the triazole polymers.

2.3.3.2. Procedure B: copper-catalysed reaction. The above bifunctional monomers were condensed in (1:1) *tert*-butanol–H₂O at room temperature for 24 h in the presence of 5% CuSO₄ and 10% sodium ascorbate. Polytriazole **11** was isolated by evaporation of the solvents, dissolution of the residue in DMSO, and precipitation by the addition of methanol. Polytriazoles **12–14** were isolated and purified as follows: after the polymerization period, the suspended polymer was recovered by filtration on a glass filter and washing with (1:1) *tert*-butanol–H₂O. The isolated yields and some characteristics of the polymers are given in Tables 1 and 2. Their spectroscopic properties (IR and NMR spectra) are described below.

2.3.4. Polytriazole **8**

IR: ν_{\max} 3400 (OH), 3122 (aromatic), 1718 cm⁻¹ (CO); NMR data (DMSO-*d*₆): ¹H, δ 8.62, 8.26 (s, H_a-triazole), 5.70–5.35 (d, OH), 5.00–4.30 (m, H-1', H-4'), 4.50–4.30 (m, H-1, H-4), 3.85–3.65 (m, H-2, H-3), 3.85–3.65 (m, H-2', H-3'), 3.65–3.40 (m, PEG); ¹³C, δ 160.37, 158.22 (CO), 138.32 (C_b, triazole), 137.31, 130.18 (C_a, triazole), 70.78 (C-2', C-3'), 69.77 (PEG), 68.31 (C-2, C-3), 63.75 (C-1, C-4), 53.09 (C-1', C-4').

2.3.5. Polytriazole **9**

IR: ν_{\max} 3390 (OH), 3130 (aromatic), 1720 cm⁻¹ (CO); NMR data (DMSO-*d*₆): ¹H, δ 8.61, 8.25 (s, H_a-triazole), 5.70–5.35 (d, OH), 5.00–4.30 (m, H-1', H-4'), 4.50–4.30 (m, H-1, H-4), 3.85–3.65 (m, H-2, H-3), 3.85–3.65 (m, H-2', H-3'), 3.65–3.40 (m, PEG); ¹³C, δ 160.32, 158.18 (CO), 138.28 (C_b, triazole), 137.31, 130.12 (C_a, triazole), 70.74 (C-2', C-3'), 69.73 (PEG), 68.26 (C-2, C-3), 63.70 (C-1, C-4), 53.04 (C-1', C-4').

2.3.6. Polytriazole **10**

IR: ν_{\max} 3420 (OH), 3132 (aromatic), 1731 cm⁻¹ (CO); NMR data (DMSO-*d*₆): ¹H, δ 8.61, 8.25 (s, H_a-triazole), 5.70–5.35 (d, OH), 4.80–4.30 (m, H-1', H-4'), 4.50–4.30 (m, H-1, H-4), 3.85–3.65 (m, H-2, H-3), 3.85–3.65 (m, H-2', H-3'), 3.65–3.40 (m, PEG); ¹³C,

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