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European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

Aldehyde-functional copolymers based on poly(2-oxazoline) for post-polymerization modification

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ARTICLE INFO

Article history:

Received 16 June 2014

Received in revised form 21 August 2014

Accepted 31 August 2014

Available online xxx

Keywords:

Aldehyde

Hydrogel

Poly(2-oxazoline)

Post-functionalization modification

Aldolization

ABSTRACT

Protected and non-protected homopolymers and related statistical copolymers based on poly(2-oxazoline) were synthesized by cationic ring-opening (co)polymerization, using a protected aldehyde 2-oxazoline monomer, namely, 2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazoline (DPOx). The (co)polymer precursors were subsequently used as reactive platforms enabling the synthesis of miscellaneous derivatives, including graft and cross-linked copoly(2-oxazoline)s. Aldehyde-functional (co)polymers were first reacted with mono- or bi-functional amino- and hydrazido-containing reagents, forming grafted copolymers or chemically cross-linked networks, respectively. The latter compound consisting of hydrazone-type linkages formed hydrogels that could be slowly degraded at physiological pH over 3 days, but be readily cleaved in a more acidic environment (pH = 3). Aldehyde-containing (co)polymers were also found to be subjected to an intermolecular self-aldolization reaction under acidic conditions, leading to branchings and ultimately to the formation of dense 3D-networks.

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1. Introduction

Post-polymerization modification (also called polymer-analogous modification) is a powerful synthetic tool in polymer chemistry. It consists in accessing new polymers by modification of a preformed polymer carrying functional handles that are chemically or physically transformed. Interestingly enough, diverse polymer derivatives with different structures and properties can be achieved from one single reactive polymer precursor [1–3]. For example,

post-polymerization modification allows for chemical transformation of commodity polyolefins into value-added materials [4], or to tailor poly(carbonate)s for specific biomedical applications [5–7]. A wide variety of chemoselective and/or orthogonal reactions, including thiol–ene addition [8], thiol exchange, Diels–Alder cycloaddition [9], Michael addition or reactions with active esters [10], epoxides, anhydrides, isocyanates, ketones and aldehydes, have been applied to modify functional polymer precursors [11,12].

Aldehyde functional groups are of special interest owing to the diversity of reactions that can be implemented with antagonist functional groups, such as alcohols, amines and hydrazines, forming reversible acetal, imine, and hydrazone linkages, respectively. Moreover, aldehydes can also be reduced into hydrocarbons via the so-called Wolff–Kishner

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reaction. They are also involved in key reactions in molecular chemistry, such as Grignard, Wittig and aldolization reactions [13,14]. Surprisingly, the number of reports describing polymers with pendant aldehydes is somewhat limited. Synthesis of polymers with aldehyde handles can be achieved by anionic [15] and cationic polymerization [16], ring opening metathesis polymerization [17], reversible addition-fragmentation chain transfer [18–21] or by modification of biopolymers [22]. Related (co)polymers have been further employed to engineer polymer materials for specific applications: injectable hydrogels [23–26], microgels via a microfluidic device [27], or shell cross-linked micelles [28] obtained with dihydrazide cross-linkers. Nanoparticles were also formed using a copolymer based on vinylbenzaldehyde units; further cross-linking or conjugation with chemotherapy compounds via Schiff base or imine formation was achieved [29]. Lastly, poly(4-vinyl benzaldehyde) has also been successfully functionalized with desired compounds using the Kabachnik–Fields post-polymerization reaction [30].

Here, we investigate the potential of poly(2-oxazoline)s (POx) possessing pendant aldehyde functions for polymer-analogous modification. POx represent a special class of polymers that have (re)gained an increasing interest in last decade. This is due, in particular, to their structural similarities with polypeptides [31], the biocompatible character and the stealth behavior of some POx [32–34]. In addition, the relatively easy access to POx by cationic ring opening polymerization [35,36] allows the tuning of their physico-chemical properties, such as hydrophilicity and thermo-responsiveness [37–39]. Synthesis of POx with functional handles can also be achieved by resorting to specific functional 2-oxazoline monomers, which most often requires a protection of the functional group prior to its (co)polymerization, in order to avoid side reactions. Synthetic strategies to functionalized POx have been recently reviewed [40,41]. Alkene- or alkyne-functionalized monomer can remain unprotected [42–44], but monomers containing amine [45], or alcohol [46] require protection in the form of *tert*-butyloxycarbonyl (BOC) or ester groups, respectively. To the best of our knowledge, there is only one report about the synthesis and post-polymerization modification of aldehyde-functional POx, as described by Taubmann et al. [16] who employed a protected aldehyde oxazoline monomer in the form of a ketal ring. POx with pendant aldehyde functions was readily obtained after deprotection, and subsequent modification by amino-oxy-containing reagents yielding the oxime was reported.

In this contribution, we wish to further exploit the reactivity of such POx-based (co)polymers bearing pendant protected and non-protected aldehyde functions. We demonstrate that aldehyde-containing POx can readily react towards mono- and bi-functional amines and hydrazines, enabling the synthesis of both grafted POx and POx-based hydrogels that can be chemically cleaved off under acidic conditions. We also evidence that aldehyde-containing POx chains can undergo intermolecular aldolization reaction under acidic conditions.

2. Experimental section

2.1. Materials

2-Methyl-2-oxazoline (99%), methyl trifluoromethanesulfonate (96%) (MeOTf), and acetonitrile (99%) were purchased from Sigma–Aldrich, stored over calcium hydride and purified by vacuum distillation prior to use. Methanol (Sigma–Aldrich) was refluxed with sodium and distilled prior to use. Dimethylsulfoxide (DMSO, from Sigma–Aldrich) was cryo-distilled prior to use. Piperidine (99%, from Acros) was distilled prior to use. Trifluoroacetic acid (99%) (TFA), diethyl ether, ethanol, potassium hydroxide (KOH), sodium hydroxide (NaOH), hydrochloric acid solution (37%) (HCl), cyclohexane (99%), *p*-toluene sulfonic acid (APTS), sodium acetate and Jeffamine D400 were used as received from Sigma–Aldrich. Benzylamine (98%), adipic acid dihydrazide (98%), molecular sieves 3 Å (0.4–0.8 mm) and sodium cyanohydroborate (NaBH₃CN) were used as received from Alfa Aesar.

2-[3-(1,3)-Dioxolan-2-ylpropyl]-2-oxazoline (DPOx) was synthesized following a procedure reported in the literature [16]. Analysis by ¹H and ¹³C NMR showed all expected peaks (ESI⁺). *N*-methyl-2-methyl-2-oxazolinium triflate (MeOxOTf) was synthesized following the procedure described by Kobayashi et al. (ESI⁺) [47].

2.2. Instrumentation and measurements

¹H NMR, ¹³C NMR and HSQC measurements were carried out at 298 K on a Bruker Avance spectrometer operating at 400 MHz. CDCl₃ was used as an internal reference ($\delta = 7.26$ ppm), and the relaxation time was fixed to 2 s for all measurements.

¹³C CPMAS (cross polarization magic angle spinning) NMR measurements were carried out on a 9,4T spectrometer operating at 100.6 MHz and equipped with a CPMAS probe (impulsion at 90°: 3.4 μ s at 59.6 W, 2 ms contact time, 3 s relaxation time, 35 ms acquisition time).

Size-exclusion chromatography (SEC) using dimethylformamide (DMF) with LiBr (1 g/L) as the eluent was performed at 80 °C at a flow rate of 0.8 mL/min. The column set consisted of two 7.5 mm \times 300 mm PLgel, 5 μ m Mixed-D columns (Polymer laboratories) coupled to a 7.5 mm \times 50 mm, PLgel, 5 μ m guard column (Polymer laboratories). Injections were realized in a 20 μ L loop and calibration was performed with polystyrene standard. Differential refractive index (RI) and UV detectors were used.

SEC was performed at 40 °C at a flow rate of 0.6 mL/min, using Tris buffer as the eluent. The column set consisted of two 8.0 mm \times 300 mm columns, OHPak, 10 μ m and 6 μ m respectively (Shodex) coupled to a guard column, 6.0 mm \times 500 mm, OHPak (Shodex). Injections were realized in a 20 μ L loop and calibration was performed with PEG standards from Polymer Laboratories. Differential refractive index (RI) and UV detectors were used. Ethylene glycol was used as a flow marker.

Infrared spectra were obtained from a Thermoscientific Nicolet IS10 spectrometer using the attenuated total

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