



Amphiphilic polymers bearing gluconolactone moieties: Synthesis and long side-chain crystalline behavior

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ABSTRACT

The synthesis and characterization of amphiphilic polymers bearing gluconolactone moieties has been described. In a first step, an unprotected glycomonomer 2-([4-(D-gluconamid-N-yl)butyl]amino)carbonyloxy]ethyl acrylate, HEAG, has been synthesized. Posterior, this glycomonomer has been copolymerized with methyl methacrylate at different compositions and the kinetic behavior has been also studied calculating the monomer reactivity ratios by Kelen–Tüdös extended equation. In addition, the long side-chain crystalline behavior of these carbohydrate-based copolymers with high composition of glycomonomer has been examined by using conventional and modulated differential scanning calorimetry and X-ray diffraction measurements. At the same time, the phase separation behavior of carbohydrate-based copolymers with lower HEAG content has been determined by their glass transition temperature measurements. Finally, the thermal stability of all these amphiphilic copolymers has been evaluated by thermogravimetric analysis.

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1. Introduction

Synthetic polymers bearing carbohydrate groups in the side chain or at the end of the macromolecular chain (also known as glycopolymers) have become a hot topic for investigation within the scientific community and attracted great interest because of their potential applications in biomedicine and biomaterials (Okada, 2001; Varma, Kennedy, & Galgali, 2004). In particular, carbohydrate-based polymers containing cyclic saccharides potentiate multivalent protein–carbohydrate interactions in living organisms, which lead to biomolecular recognition events that are dramatically different from those elicited by monovalent interactions (Bertozzi & Kiessling, 2001; Kiessling, Gestwicki, & Strong, 2006; Mammen, Choi, & Whitesides, 1998) Much research has been focused on hydrogels (Chen, Dordick, & Rethwisch, 1995; Zhou, Kurth, Hsieh, & Krochta, 1999) cell culture substrates (Bahulekar et al., 1998) artificial organs (Karamuk, Mayer, Wintermantel, & Akaike, 1999) lectin recognition materials (Bertozzi & Kiessling, 2001; García-Oteiza, Sánchez-Chaves, & Arranz, 1997; Kobayashi, Tsuchida, Usui, & Akaike, 1997; Ting, Chen, & Stenzel, 2010) and drug delivery systems (Polikarpov, Kaufmann, Kluge, Appelhans, &

Voit, 2010; Top & Kiick, 2010). Also, these carbohydrate polymers are potential surface modifiers for the development of interfacial properties to meet the requirements of biomedical uses. In contrast, saccharides with open-chain structures are more efficient than those with cyclic ones (Okada, 2001) in improving the hydrophilicity of the polymeric material surface. This increase in hydrophilicity at surface favors undesirable adhesion of proteins, cells, or other molecules (Bordegé et al., 2011; Ting et al., 2010; Xu, Wan, & Huang, 2009; Yang, Xu, Dai, Wang, & Ulbricht, 2005) and promotes a characteristic as important as hemocompatibility.

In some cases carbohydrate polymers can be then considered as grafted amphiphilic chemical architectures because of their pendant carbohydrate moieties linked to the backbone. Graft copolymers, as well as the block ones, have been recognized as advanced nanomaterials because they can self-assemble into various ordered patterns (spheres, cylinders, lamellae, or bicontinuous double diamonds) in the condensed state and in solution depending, basically, on the volume fraction of each component, the difference in their solubility parameters, sample preparation, and thermal history (de la Fuente, Fernandez-Garcia, Cerrada, Spiess, & Wilhelm, 2006; Hadjichristidis, Pispas, & Floudas, 2003; Lee et al., 1997; Matsushita & Noda, 1996; Muñoz-Bonilla, Cerrada, & Fernandez-Garcia, 2007a, 2007b; Muñoz-Bonilla, Fernandez-Garcia, Cerrada, Mantovani, & Haddleton, 2007; Muñoz-Bonilla, Fernandez-Garcia, & Haddleton, 2007; Muñoz-Bonilla et al., 2012)

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This self-assembly capability, sometimes called nanophase separation (Chen & Wunderlich, 1999) is observed in X-ray scattering measurements by characteristic “peaks” at scattering vector scale in the range $0.2 \leq q \leq 0.6 \text{ \AA}^{-1}$. Moreover, carbohydrate copolymers, mainly those with open-chain structure, could be able of exhibiting side-chain crystallization if their pendant chains are long enough. Nevertheless, to the best of our knowledge, no examples of extensive studies about synthetic semi-crystalline carbohydrate polymers have been reported. Crystallization behavior of polymers containing long *n*-alkyl groups in the side chain has been analyzed in the past decades by various groups focusing on different aspects (Beiner, 2001; Cowie, Haq, McEwen, & Veličkovič, 1981; Jones, 1964; Jordan, 1971; Jordan, Artymyshyn, Specca, & Wrigley, 1971; Karaky, Clisson, Reiter, & Billon, 2008; López-Velázquez, Bello, & Pérez, 2004; McKenzie, Nudelman, Bomans, Holder, & Sommerdijk, 2010; Mogri & Paul, 2001a, 2001b; Neugebauer, Theis, Pakula, Wegner, & Matyjaszewski, 2005; O’Leary & Paul, 2006; Pankaj, Hempel, & Beiner, 2009). This capability of organizing at short range into three-dimensional crystallites confers a very interesting feature since the whole properties array will depend on the crystalline morphology. Accordingly, variations on crystallization conditions, which might lead primarily to changes in degree of crystallinity and crystallite size, would allow tuning specific requirements and, thus, designing “smart” materials exhibiting desirable complex responses.

The synthesis of carbohydrate-containing polymers with well-defined structure is usually performed by two methods (Cameron et al., 2008; Gauthier, Gibson, & Klok, 2009; Ladmiraal, Melia, & Haddleton, 2004; Okada, 2001; Spain & Cameron, 2011; Spain, Gibson, & Cameron, 2007; Ting et al., 2010; Varma et al., 2004): (a) the polymerization or copolymerization of carbohydrate-bearing monomers by conventional or controlled polymerization techniques; and (b) the chemical modification of a reactive polymer scaffold with carbohydrates. In these two methodologies, the saccharide is attached to the polymer by ester, amide, carbamate, ether linkages among others. It is important to avoid, if possible, undesirable sugar protecting/deprotecting processes because these multi-step reactions make tedious the synthetic protocol in addition to reduce their overall yield.

This investigation is focused on the synthesis of several glycopolymers based on methyl methacrylate, MMA, and 2-[(4-(D-gluconamid-N-yl)butyl)amino]carbonyloxyethyl acrylate, HEAG, an unprotected glycomonomer. Classical free radical polymerization has been chosen as synthetic methodology in this investigation since, on one hand, it is a versatile, robust and the most industrially used protocol and, on the other hand, because the preparation of these proposed novel and very interesting amphiphilic carbohydrate copolymers is feasible in rather mild conditions without further requirements of protecting/deprotecting processes. In addition, copolymerization reactions have been thoroughly studied and their kinetic, copolymer composition variation and monomer reactivity ratios have been determined.

A major field of applicability for carbohydrate based copolymers is related to their potential capability for protein binding in water solutions. Other properties, different than those evaluated in solution, should be, however, explored in order to seek other high-added-value applications, replacing the existing materials and allowing also new markets to be created. A very important aspect is, then, to learn how these carbohydrate polymeric chains are organized at molecular level in the solid state which allow us to interpret changes in their physical properties. Accordingly, determination of the phase transitions and thermal stability become an important issue in these copolymers that are used, for instance, in pharmaceutical products in order to perform a proper handling, manufacturing and storage conditions of these materials. To assess this additional target, phase transitions have been analyzed by

X-ray diffraction measurements at small and wide angles using synchrotron and conventional radiation, respectively, as well as by conventional and modulated differential scanning calorimetry, DSC and MDSC, experiments; and, the thermal stability of the resultant carbohydrate copolymers has been checked by thermogravimetry, TGA.

2. Experimental

2.1. Materials

2-Hydroxyethyl acrylate, HEA (Fluka, 99%) and methyl methacrylate, MMA (Merck), were purified by a conventional method (Stickler, 1987) 2,2'-Azobisisobutyronitrile, AIBN (Fluka), was purified by successive crystallizations from methanol. *p*-Nitrophenyl chloroformate (Fluka, 97%), glucono-1,5 lactone (99%, Fluka) and 1,4-diaminobutane (Fluka) were used without further purification. Dimethyl sulfoxide, DMSO (Scharlau), and triethylamine (Scharlau) were previously distilled; methanol (Fluka), ether dioxides (SDS), and ethanol (Normapur) were used as received.

2.2. Synthesis of glycomonomer, HEAG

The aminosaccharide, N-(4-aminobutyl)-D-gluconamide, NABG (Cerrada, Sanchez-Chaves, Ruiz, & Fernandez-Garcia, 2009) and activated HEA with *p*-nitrophenyl chloroformate, HEAN (Bordegé et al., 2011) were prepared as described in literature. Then, the glycomonomer, 2-[(4-(D-gluconamid-N-yl)butyl)amino]carbonyloxyethyl acrylate, HEAG, was synthesized as follows (see Scheme 1):

N-(4-aminobutyl)-D-gluconamide (4.75 g, 17.8 mmoles) with hydroquinone (0.01 g) solved in DMSO (20 mL) was slowly added at 30 °C to a DMSO solution (20 mL) of HEAN (5.02 g, 17.8 mmoles). The mixture was stirred for 2 h and afterwards, it was precipitated into a large excess of dichloromethane. The product was filtered and washed with acetone giving a white solid, HEAG glycomonomer (6.59 g, 91%). The ¹H and ¹³C NMR spectra are shown in Fig. S1 of Supporting Information.

2.3. Polymerization reaction

The monomers were polymerized with AIBN as initiator (3×10^{-2} mol/L) and with DMSO as solvent (1 mol/L) at 70 ± 0.5 °C. The copolymerization was monitored by in situ ¹H NMR measurements using a tube sealed under argon atmosphere. These copolymers were also obtained at high conversions using Pyrex glass ampoules sealed under argon atmosphere in a thermostatic bath at 70 ± 0.1 °C. The carbohydrate copolymers purification was performed by dialysis using a membrane of 3500 Daltons (Cellu Sep T1) and posterior lyophilization in a Telstar Lioalfa-6.

The carbohydrate based statistical copolymers performed at total conversion have been labeled as P(MxGy), *x* and *y* referring the MMA and HEAG molar fraction in the copolymer, respectively.

2.4. Nuclear magnetic resonance spectroscopy (NMR)

Proton spectra, ¹H NMR, were recorded using a Varian Inova-400 spectrometer operating at 400 MHz in DMSO-*d*₆ solutions (25%, w/v) at 70 °C. The spectra parameters were: acquisition time 3.7 s, pulse of 7.0 μs, 128 runs and without delayed time. The delayed time variation (2, 5, 10 s) and/or pulse width do not imply a significant change in the signals.

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