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Synthesis and characterization of copolyanhydrides of carbohydrate-based galactaric acid and adipic acid

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ABSTRACT

A series of copolyanhydrides, consisting of 2,3,4,5-tetra-*O*-acetylgalactaric acid (AGA) and adipic acid (AA) as monomer units, was polymerized. Synthesis of AGA monomer consisted of two steps. First, O-acetylation of galactaric acid secondary hydroxyl groups was performed using acetic anhydride as a reagent. Acetic anhydride was then further used as a reagent in the synthesis of diacetyl mixed anhydride of AGA. Polymerizations were conducted as bulk condensation polymerization at 150 °C. Thermal properties of the copolymers varied depending on monomer composition. Increase in the AGA content had a clear increasing effect on the T_g. A similar increasing effect was observed in T_m. The degree of crystallinity decreased as AGA content increased. There was a slightly lowering tendency in the molecular weights of the obtained polymers when the AGA content in the polymerization mixtures increased. The described synthesis route shows that bio-based aldaric acid monomers are potential candidates for the adjustment of thermal properties of polyanhydrides.

1. Introduction

The past decade has seen a dramatic increase in the research of bio-based materials. Diminishing fossil fuel resources and growing environmental concerns have increased the interest toward biorefinery concepts, where renewable resources offer a wide variety of molecules that can be further upgraded into useful compounds.[1,2] Development steps taken in the field of industrial biotechnology have provided access to new types of monomeric carbohydrate derivatives.[3–6] One particularly interesting class is aldaric acids, as they contain two terminal carboxylic acid functionalities, which make them suitable for use in condensation polymerization as rigid monomers.

Galactaric acid, often also called mucic acid, (Fig. 1) is an aldaric acid that can be produced from D-galacturonic acid by engineered filamentous fungi.[7] D-Galacturonic acid is abundant, for example, in pectin, which is common in primary cell wall and middle lamella of all higher plants. Pectin-rich residues are obtained as side streams, for example, from sugar beet processing as well as from apple and orange juice production. These residues are commonly utilized as animal feed and it would be beneficial to find higher-value products for these side streams.[8]

Many types of polymers have already been synthesized from aldaric acid based monomers. Production of polyamides from aldaric acids and alkylenediamines has been studied extensively by Ogata et al.[9–11] and more recently by Kiely et al.[12–14] In these studies the aldaric acid monomers were applied as such, without protection of the secondary hydroxyl groups. On the other hand, Muñoz-Guerra and Galbis et al. have extensively applied synthesis routes where the secondary hydroxyl groups were transformed to, for example, methyl ethers or acetals to ensure production of linear polymers. They have synthesized aldaric acid based polyesters,[15–18] polyamides,[19–21] polyurethanes,[22,23] and polyester amides.[24] The utilization of aldaric acids in synthesis of polydimethylsiloxanes[25] and polycarbonates[26] has also been reported. However, according to our knowledge, preparation of aldaric acid based polyanhydrides has not been previously reported.

Polyanhydrides are extensively studied materials for clinical applications. Due to their rapid hydrolytic degradation their main application is on controlled short-term delivery of bioactive agents.[27,28] The most common way to synthesize polyanhydrides from diacids is to first produce a diacetyl mixed anhydride of the diacid,[27,28] which is then further polymerized through polycondensation. Properties of polyanhydrides highly depend on the nature of the repeating units. Short aliphatic dicarboxylic acids, for example, adipic acid, provide polyanhydrides with low melting points and relatively rapid hydrolytic degradation rates.[29–31] On the other hand, incorporating rigid aromatic moieties into the polyanhydride

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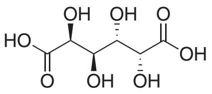


Figure 1. Galactaric acid.

structure provides increased melting points and decreased degradation rates.[32]

In this article we describe the synthesis of O-acetylated galactaric acid (AGA), and its utilization in the polymerization of a series of copolyanhydrides with adipic acid (AA). The O-acetylation step was performed through reaction of the galactaric acid secondary hydroxyl groups with acetic anhydride to give 2,3,4,5-tetra-*O*-acetylgalactaric acid. Through a synergistic fashion, acetic anhydride was then further used in the transformation of the AGA diacid to the diacetyl mixed anhydride monomer. Our target was to observe how the rigid AGA moiety affects the copolymerization reaction and the properties of the obtained copolymers. Based on the study, we regard bio-based aldaric acid monomers as potential candidates for the adjustment of polyanhydride properties.

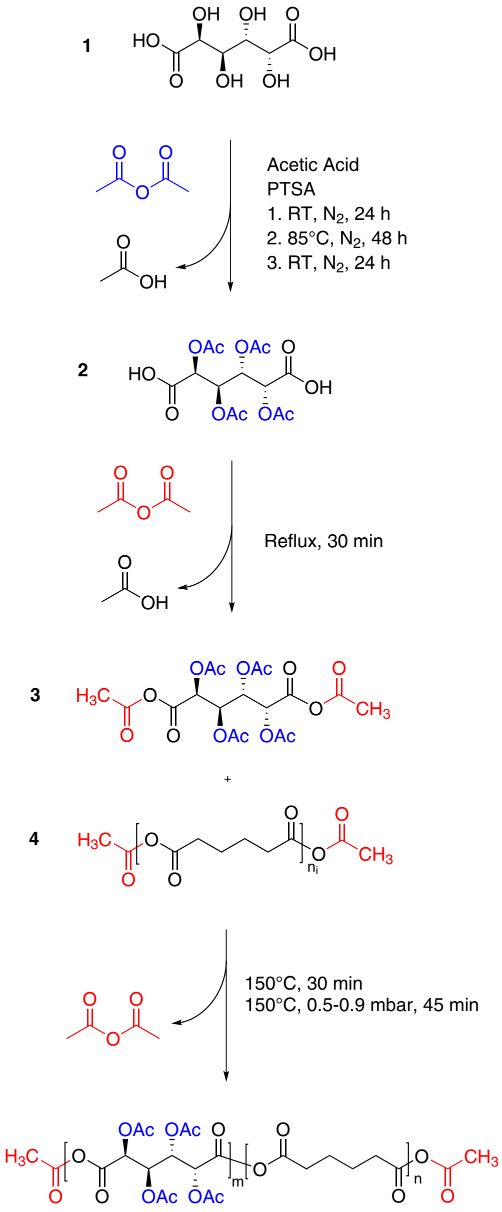
2. Results and discussion

A series of copolyanhydrides, consisting of 2,3,4,5-tetra-*O*-acetylgalactaric acid (AGA) and adipic acid (AA) as monomer units, was synthesized according to Scheme 1. The monomer unit composition was varied throughout the series in order to observe how the rigid AGA moiety affects the polymerization reaction and the properties of the obtained copolymers. As presented in Scheme 1, the acetylation of secondary hydroxyl groups of galactaric acid (**1**) was performed using acetic anhydride as a reagent. Acetic anhydride was further used as a reagent in the synthesis of diacetyl mixed anhydride (**3**). Utilization of acetic anhydride in both of the monomer synthesis steps offers synergistic advantages to the synthesis route, and these reaction steps could be even considered to be combined into a more continuous process in future.

2.1. Monomer synthesis

2,3,4,5-Tetra-*O*-acetylgalactaric acid (AGA) (**2**) was synthesized from commercially available galactaric acid (**1**) in acidic conditions through reaction with acetic anhydride.[33,34] The reaction was performed under relatively mild conditions using acetic acid as a reaction medium. As both galactaric acid and AGA were poorly soluble in the reaction medium, the reaction proceeded as a two phase system. After recrystallization from water the desired product was obtained as needle-like white crystals. ^{1}H and ^{13}C NMR characterizations were conducted in DMSO-d_6 at 70 °C and the obtained spectra are presented in Figure 2. Peaks shown at 2.14 ppm and 2.26 ppm in the ^{1}H NMR spectrum as well as two peaks at 20.6 ppm in the ^{13}C NMR spectrum are distinctive to *O*-acetyl CH_3 groups, indicating successful acetylation. The ^{13}C NMR spectrum also shows peaks at 169.0 ppm and 169.9 ppm distinctive *O*-acetyl carbonyls. As neither spectra show signals from OH-bound backbone CHs it can be stated that pure and fully O-acetylated product was obtained. Partial O-acetylation would lead into peak splitting which is not observed in the obtained spectra.

Diacetyl mixed anhydride of AGA (**3**) was synthesized from **2** by refluxing in excess of acetic anhydride. As the reaction proceeded, the insoluble starting material **2** dissolved into the reaction mixture. After purification the product was obtained as white powder. Solubility of the compound organic solvents such as chloroform, THF and acetone was significantly improved when compared to starting material (**2**). The ^{1}H NMR and ^{13}C NMR spectra of **3** with assigned peaks are presented in Figure 3. The acetyl anhydride end-group signals are observed at 2.22 ppm in the ^{1}H NMR spectrum and at 22.2 ppm in the ^{13}C NMR spectrum. It is known from the literature that preparation of diacetyl mixed anhydrides often yields oligomeric products, consisting of acetyl end-capped short polyanhydrides.[31] The ^{1}H NMR integral areas of AGA backbone CH signals at 5.22 ppm and 5.76 ppm were compared to the anhydride acetyl end-group signal at 2.22 ppm. As the ratio was corresponding to monomeric structure (**3**), no oligomerization was found to have occurred during the synthesis.



Scheme 1. Reaction scheme from galactaric acid to poly(2,3,4,5-tetra-*O*-acetylgalactaric-*co*-adipic anhydride).

Diacetyl mixed anhydride of adipic acid (AA) (**4**) was prepared as previously reported by Domb et al.[31] The ^{1}H NMR and ^{13}C NMR spectra of **4** with assigned peaks are presented in Figure 4. The acetyl anhydride end-group signals are observed at 2.23 ppm in the ^{1}H NMR and 22.3 ppm in the ^{13}C NMR spectrum. Through comparison of backbone methylene signals in ^{1}H NMR at 1.74 ppm and 2.51 ppm, and acetyl anhydride end-group signal at 2.23 ppm, the mixed anhydride was found to have 1.8 adipoyl