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A versatile pathway to end-functionalized cellulose ethers for click chemistry applications

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ABSTRACT

This paper describes a versatile pathway to heterobifunctional/telechelic cellulose ethers, such as tri-*O*-methyl cellulosyl azide and propargyl tri-*O*-methyl celluloside, having one free C-4 hydroxyl group attached to the glucosyl residue at the non-reducing end for the use in Huisgen 1,3-dipolar cycloaddition and copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). The one-step end-functionalization of cellulose ethers for molecular rod synthesis involves the introduction of two reactive groups at both ends of the cellulose molecule, and can afford linear triblock copolymers via CuAAC and further reactions. We were able to tailor the degree of polymerization of end-functionalized cellulose ethers with controlled amounts of a Lewis acid, namely $SnCl_4$. Chemical structures of the above cellulose ethers and the reaction conditions for controlling molecular length are discussed.

1. Introduction

Methylcellulose (MC), being one of the more common cellulose ethers, has been of interest in the investigation of structure-property relationships, such as thermoreversible gelation properties at elevated temperature. Our research focuses on the design and synthesis of regioselectively methylated cellulose derivatives via ring-opening polymerization of glucose orthopivalate derivatives (Kamitakahara, Hori, & Nakatsubo, 1996; Karakawa, Mikawa, Kamitakahara, & Nakatsubo, 2002; Nakatsubo, Kamitakahara, & Hori, 1996) or from natural cellulose (Kamitakahara et al., 2008; Nakagawa, Ishizu et al., 2012) and diblock methylcellulose with regioselective functionalization patterns (Nakagawa, Fenn, Koschella, Heinze, & Kamitakahara, 2011a; Nakagawa, Fenn, Koschella, Heinze, & Kamitakahara, 2011b; Nakagawa, Steiniger et al., 2012). As a result, we found that a diblock structure composed of hydrophilic cellobiosyl and hydrophobic 2,3,6-tri-*O*-methylcellulosyl segments is crucial for the thermoreversible gelation of aqueous MC solutions (Nakagawa et al., 2011a). Commercial MC prepared under heterogeneous conditions is an alternating block copolymer composed of densely substituted hydrophobic and less densely substituted hydrophilic block sequences (Savage, 1957). The synthetic route to multiblock MC derivatives composed of hydrophobic 2,3,6-tri-*O*-methylcellulosyl and hydrophilic cellulosyl segments remains open.

Precise control of the monosaccharide sequence to prepare multiblock derivatives is, however, extremely difficult and time-consuming. We synthesized 1,2,3-triazole-linked diblock MC composed of low molecular weight cellulose and 2,3,6-tri-*O*-methyl cellulose (Nakagawa, Kamitakahara, & Takano, 2012) and found that a 2 wt.% aqueous solution of this MC analogue exhibited thermoreversible gelation behavior, meaning that linkages between hydrophilic and hydrophobic segments do not affect gelation properties. Thus, we considered utilizing linkages other than the glycosidic bond to prepare multiblock MC copolymers.

To be suitable building blocks for the multiblock MC copolymers, the cellulose derivatives must have functional groups at both ends of the linear molecule. Heterobifunctional/telechelic derivatives are more desirable than homobifunctional/telechelic ones (Kim, Stannett, & Gilbert, 1973, Kim, Stannett, & Gilbert, 1976; Pohjola & Eklund, 1977; Steinmann, 1968, 1970) for the preparation of multiblock copolymers.

Abbreviation: CuAAC, copper(I)-catalyzed azide-alkyne cycloaddition; MC, methylcellulose; CTA, cellulose triacetate; GPC, gel permeation chromatography; DHB, 2,5-dihydroxybenzoic acid; DP, degree of polymerization.

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Derivatives having two different functional groups at both ends of the linear polymer are therefore attractive and promising for the exploration of a new research field in cellulose chemistry.

On the other hand, cellulose derivatives are known to be semi-rigid polymers (De Oliveira & Glasser, 1994), which controls their physical properties. The concept of a 'molecular rod' is therefore applicable to heterobifunctional/telechelic cellulose derivatives, which can be viewed as bricks of a molecular Lego (Lepage, Schneider, Bodlenner, & Compain, 2015; Meldal, 2008). To connect several bricks of the cellulosic Lego, two ends of the molecular rod must be separately functionalized under independent activation conditions. It is then possible to covalently bind several molecular bricks, adding other brick units under different reaction conditions.

We have previously reported the synthesis of tri-*O*-acetyl cellulosyl azide (Kamitakahara, Enomoto, Hasegawa, & Nakatsubo, 2005). This molecule is a key compound for the end-functionalization of cellulose derivatives. The azide group can be easily converted into an amino group, which can be used in a subsequent amidation reaction. For instance, we successfully synthesized cellulose triacetate (CTA)-*block*-oligoamide-15 (Kamitakahara et al., 2005; Kamitakahara & Nakatsubo, 2005), a CTA derivative carrying a single pyrene group at the reducing end (Enomoto, Kamitakahara, Takano, & Nakatsubo, 2006), and a CTA derivative having a single lipoic acid moiety at the reducing end (Enomoto-Rogers, Kamitakahara, Yoshinaga, & Takano, 2010). The high reactivity of the azide group towards alkynes is known as the click chemistry approach, and is based on Huisgen 1,3-dipolar cycloaddition and copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) (Kolb, Finn, & Sharpless, 2001). We have prepared comb-shaped graft copolymers with CTA side chains (Enomoto-Rogers, Kamitakahara, Yoshinaga, & Takano, 2012) and CTA-block-poly(γ-benzyl-L-glutamate) (Kamitakahara, Baba, Yoshinaga, Suhara, & Takano, 2014), knowing that the CuAAC reaction is a more powerful tool for bonding two polymeric segments than amidation.

Not only cellulose esters, such as cellulose acetate, but also a representative cellulose ether, methylcellulose, were also important molecular Lego bricks. Methyl tri-*O*-methyl celluloside, with a single hydroxyl group at the C-4 position of the glucosyl residue at the non-reducing end was prepared by methanolysis of 2,3,6-tri-*O*-methyl cellulose (Nakagawa et al., 2011b; Nakagawa, Kamitakahara, & Takano, 2011). Propargylation of one end of the cellulose ether derivative afforded a cellulose ether carrying a single alkyne group at the end of the cellulosic molecular rod, methyl tri-*O*-methyl celluloside (Nakagawa, Kamitakahara et al., 2012). Cellulose ethers are more stable than the corresponding esters in both acidic and alkaline reaction conditions used to construct the cellulosic molecular architecture. Thus, we focused on the synthesis of cellulosic molecular rods carrying two independent end-functional groups.

Propargylated methyl tri-*O*-methyl celluloside was synthesized from commercial methylcellulose in three reaction steps: complete methylation, methanolysis, and propargylation. This molecular rod has a functional group at one end (Nakagawa et al., 2011b), which is a disadvantage. Therefore, we were motivated to synthesize cellulosic molecular rods carrying two independent end-functional groups, in other words, cellulosic heterobifunctional/telechelic polymers.

To introduce an azide group at the C-1 position of the glucosyl residue at the reducing end of CTA, it was treated with hydrogen bromide in acetic acid to afford the α-anomer of tri-*O*-acetyl cellulosyl bromide. The bromide was then treated with acetic acid and silver oxide to yield the β-anomer of acetyl tri-*O*-acetyl cellulose, which was finally converted into the β-anomer of tri-*O*-acetyl cellulosyl azide using trimethylsilyl azide and $SnCl_4$ (Kamitakahara et al., 2005). We tried to produce tri-*O*-methyl cellulosyl azide (**2**) with a controlled molecular weight from tri-*O*-methyl cellulose (**1**) in a one-step reaction. Azide and alkyne groups form a pair for the 1,3-dipolar cycloaddition, and preparing propargyl tri-*O*-methyl celluloside (**3**) is, therefore, of critical importance. Thus, we attempted to produce propargyl tri-*O*-methyl celluloside (**3**) with a controlled molecular weight from tri-*O*-methyl cellulose (**1**) in a one-step reaction.

Moreover, the free C-4 hydroxyl of the glucosyl residue at the non-reducing end could connect with other molecular bricks having epoxide, acyl, isocyanate, and other functionalities, thereby extending the variety of molecular architecture motifs. Heterobifunctional/telechelic cellulose derivatives, at least, provide molecules with triblock structures. The production of cellulosic triblock copolymers from homobifunctional/telechelic cellulose derivatives has already been reported (Kim et al., 1973, 1976; Pohjola & Eklund, 1977; Steinmann, 1968, 1970), however, heterobifunctional/telechelic cellulose derivatives are still unknown, to the best of our knowledge.

Consequently, the aim of this research was to find the appropriate reaction conditions affording end-functionalized cellulose ethers, such as tri-*O*-methyl cellulosyl azide (**2**) and propargyl tri-*O*-methyl celluloside (**3**), for click chemistry and further conversion using the remaining functionalized end of the ethers. This paper describes well-controlled synthetic methods for preparing cellulosic precursors for CuAAC, namely tri-*O*-methyl cellulosyl azide (**2**) and propargyl tri-*O*-methyl celluloside (**3**). The reaction conditions used to introduce azide and propargyl groups onto the tri-*O*-methyl cellulose (**1**) scaffold and the structures of reaction products are also discussed.

2. Materials and methods

2.1. Materials

All reagents and solvents were obtained from Nacalai Tesque, Wako Chemical, and Sasaki Chemical, Japan, and were used as received.

2.2. Analytical measurements

^1H and ^{13}C NMR spectra were acquired in $CDCl_3$ on a Varian 500 NMR spectrometer at room temperature. The molecular weights of the products were measured by gel permeation chromatography (GPC) in chloroform on a Shimadzu SEC system (CBM-20A, SPD-10A$_{VP}$, SIL-10A, LC-10AT$_{VP}$, FCV-10AL$_{VP}$, CTO-10A$_{VP}$, RID-10A, and FRC-10A, Shimadzu, Japan). Sample solutions were passed through a syringe filter (Sartorius Stedim, Minisart RC 4 or RC 15; pore size 0.45 μm) before GPC analysis. Shodex columns (K802, K802.5, and K805) with a guard column (Shodex, K-G) were used. Number- and weight-averaged molecular weights (M_n and M_w) and polydispersity indices (M_w/M_n) were estimated using polystyrene standards (Shodex). Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF MS) were recorded on a Bruker Autoflex III machine in the positive ion linear mode. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix for these measurements.