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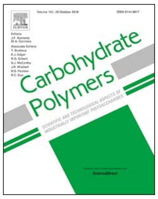

Thermo-reversible supramolecular hydrogels of trehalose-type diblock methylcellulose analogues

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ABSTRACT

This paper describes the design and synthesis of new trehalose-type diblock methylcellulose analogues with nonionic, cationic, and anionic cellobiosyl segments, namely 1-(tri-*O*-methyl-cellulosyl)-4-[β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazole (**1**), 1-(tri-*O*-methyl-cellulosyl)-4-[(6-amino-6-deoxy-β-D-glucopyranosyl)-(1 → 4)- 6-amino-6-deoxy-β-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazole (**2**), and 4-(tri-*O*-methyl-cellulosyloxymethyl)-1-[β-D-glucopyranuronosyl-(1 → 4)-β-D-glucopyranuronosyl]-1*H*-1,2,3-triazole (**3**), respectively. Aqueous solutions of all of the 1,2,3-triazole-linked diblock methylcellulose analogues possessed higher surface activities than that of industrially produced methylcellulose and exhibited lower critical solution temperatures, that allowed the formation of thermoresponsive supramolecular hydrogels at close to human body temperature. Supramolecular structures of thermo-reversible hydrogels based on compounds **1**, **2**, and **3** were investigated by means of scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Detailed structure-property-function relationships of compounds **1**, **2**, and **3** were discussed. Not only nonionic hydrophilic segment but also ionic hydrophilic segments of diblock methylcellulose analogues were valid for the formation of thermo-reversible supramolecular hydrogels based on end-functionalized methylcellulose.

1. Introduction

Methylcellulose (MC) is one of the more common cellulose ethers and has been of particular interest for the investigation of its structure–property relationships, such as the surface activity of its aqueous solution and its thermo-reversible gelation properties at elevated temperature. These properties of industrial and academic interest are attributed to the chemical structure of the methylcellulose skeleton. Therefore, many researchers have previously investigated MC. 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 highly methylated region – a sequence of 2,3,6-tri-*O*-methyl-glucosyl residues – of the cellulose skeleton is said to cause micelles, that is, liquid–liquid phase separations in aqueous solution (Rees, 1972). These micelles are known as “crosslinking loci” (Kato, Yokoyama, & Takahashi, 1978). In addition, it is well known that reversible crosslinks must exist in any reversible gel (Kato et al., 1978).

We have reported diblock methylcellulose derivatives with regioselective functionalization patterns (Nakagawa, Fenn, Koschella, Heinze, & Kamitakahara, 2011b). We found direct evidence that a sequence of 2,3,6-tri-*O*-methyl-glucopyranosyl units causes thermo-reversible gelation of aqueous MC solution and that an idealized diblock structure consisting of 2,3,6-tri-*O*-methyl-glucopyranosyl and unmodified cello-oligosaccharides caused gelation (Nakagawa, Fenn, Koschella, Heinze, & Kamitakahara, 2011a). However, we had to simplify a synthetic route for new methylcellulose derivatives possessing lower critical solution temperature (LCST) behaviors in aqueous solution. Glycosylation of a cellobiose derivative with a polymeric methyl tri-*O*-methylcelluloside having one hydroxy group at the C-4 position of the glucosyl residue at the non-reducing end consumed a large amount of cellobiosyl trichloroacetimidate derivative to afford only the diblock methylcellulose. To improve the efficiency of the coupling reaction between the hydrophobic and hydrophilic segments, we synthesized a diblock methylcellulose analogue via Huisgen 1,3-dipolar cycloaddition (Nakagawa, Kamitakahara, & Takano, 2012). A 2-propynyl group was introduced to the C-4 hydroxy group at the non-reducing end of the methyl tri-*O*-methylcelluloside. Huisgen 1,3-dipolar cycloaddition was more efficient than glycosylation for connecting the hydrophobic and hydrophilic segments.

Recently, we have reported a versatile pathway to heterobifunctional/telechelic cellulose ethers, such as tri-*O*-methylcellulosyl azide

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and propargyl tri-*O*-methylcelluloside, with one free C-4 hydroxy group attached to the glucosyl residue at the non-reducing end for the use in the Huisgen 1,3-dipolar cycloaddition (Kamitakahara et al., 2016). This new method enables us to prepare a hydrophobic segment for the Huisgen 1,3-dipolar cycloaddition from tri-*O*-methylcellulose in a one-step reaction.

If the chemical structure of trehalose-type diblock polysaccharide analogues exhibited the same physical properties as those of the original diblock polysaccharides, the Huisgen 1,3-dipolar cycloaddition of azido and alkyne derivatives could produce a variety of diblock polysaccharide analogues more easily than a glycosylation method, to afford, for instance, cellobiosyl-(1 → 4)-methylcelluloses. As an example, cellobiosyl-(1 ↔ 1)-methylcelluloside, a trehalose-type diblock copolymer, possesses an analogous structure to cellobiosyl-(1 → 4)-methylcellulose. Moreover, 1-methylcellulosyl-4-cellobiosyloxymethyl-1*H*-1,2,3-triazole and 4-methylcellulosyloxymethyl-1-cellobiosyl-1*H*-1,2,3-triazole have analogous structures to cellobiosyl-(1 ↔ 1)-methylcelluloside. Therefore, 1-methylcellulosyl-4-cellobiosyloxymethyl-1*H*-1,2,3-triazole and 4-methylcellulosyloxymethyl-1-cellobiosyl-1*H*-1,2,3-triazole exhibit analogous structures to cellobiosyl-(1 → 4)-methylcellulose, a diblock methylcellulose. These triazole-linked diblock methylcellulose analogues would allow us to gain deep insights into not only fundamental but also potential properties of methylcelluloses.

A hydrophilic segment would be chosen to tune the properties of the methylcellulose, thereby producing new functional methylcellulose derivatives. Methylcellulose is nonionic. Cationic and anionic cellulose ethers are also of industrial importance. Commercial cationic hydroxyethyl cellulose (QC-10), *O*-[2-hydroxy-3-(trimethylammonio)]propyl hydroxyethyl cellulose chloride, is well known as a conditioning polymer for hair-care products (Hossel, Dieing, Norenberg, Pfau, & Sander, 2000). Chitosan, poly(2-amino-2-deoxy-glucopyranose), an analogous structure to cellulose, is the second most abundant natural polymer (Rinaudo, 2006). 6-Amino-6-deoxycellulose (Teshirogi, Yamamoto, Sakamoto, & Tonami, 1979) is an analogous polymer to chitosan. Carboxymethyl cellulose (Heinze, Erler, Nehls, & Klemm, 1994) is an anionic cellulose ether, and its application fields are widely spread. Recently, cellouronic acid (Isogai & Kato, 1998) and cellulose nanofibers prepared by TEMPO (2,2,6,6-tetramethylpiperidinyloxy) oxidation (Saito, Kimura, Nishiyama, & Isogai, 2007; Saito, Nishiyama, Putaux, Vignon, & Isogai, 2006) have gained increasing attention as anionic cellulosic materials.

To gain deep insights into the influence of the hydrophilic segments of the diblock methylcellulose analogues on the general properties of the original methylcellulose, we chose three hydrophilic segments: β-ᴅ-glucopyranosyl-(1 → 4)-β-ᴅ-glucopyranose, (6-amino-6-deoxy-β-ᴅ-glucopyranosyl)-(1 → 4)-6-amino-6-deoxy-β-ᴅ-glucopyranose, and (β-ᴅ-glucopyranuronosyl)-(1 → 4)-β-ᴅ-glucopyranuronic acid.

Methylcellulose-based diblock copolymers bearing cationic or anionic hydrophilic segments would enhance the physical performance of commercially available methylcellulose. Thus, we describe, in this paper, the synthesis and structure–property relationships of 1-(tri-*O*-methyl-cellulosyl)-4-(β-ᴅ-glucopyranosyl-(1 → 4)-β-ᴅ-glucopyranosyloxymethyl)-1*H*-1,2,3-triazole (**1**), 1-(tri-*O*-methyl-cellulosyl)-4-((6-amino-6-deoxy-β-ᴅ-glucopyranosyl)-(1 → 4)-6-amino-6-deoxy-β-ᴅ-glucopyranosyloxymethyl)-1*H*-1,2,3-triazole (**2**), and 4-(tri-*O*-methyl-cellulosyloxymethyl)-1-((β-ᴅ-glucopyranuronosyl)-(1 → 4)-β-ᴅ-glucopyranuronosyl)-1*H*-1,2,3-triazole (**3**). In particular, their surface activities, thermal properties, and thermoresponsive gelation properties will be discussed.

2. Experimental

2.1. General measurements

^{1}H and ^{13}C NMR spectra were recorded with Varian 500 NMR (500 MHz) or Varian INOVA300 (300 MHz) spectrometer in chloroform-*d* with tetramethylsilane as an internal standard or in deuterium oxide with 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an external standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis was performed with a Bruker MALDI-TOF MS Autoflex III in the positive ion and linear modes. For ionization, a smartbeam laser was used. All spectra were measured in the linear mode by using external calibration. MALDI-TOF MS used 2,5-dihydroxybenzoic acid as a matrix. A Shimadzu liquid chromatography injector (LC-10ATvp), Shimadzu column oven (CTO-10Avp), Shimadzu ultraviolet visible detector (SPD-10Avp), Shimadzu refractive index detector (RID-10A), Shimadzu communication bus module (CBM-10A), Shimadzu LC workstation (CLASS-LC10), and Shodex columns (KF802, KF802.5, and KF805) were used. Number- and weight-averaged molecular weights (M_n, M_w) and polydispersity indices (M_w/M_n) were estimated by using polystyrene standards (Shodex). A flow rate of 1 mL/min at 40 °C was chosen. Chloroform was used as the eluent.

2.2. Differential scanning calorimetry (DSC) measurements

DSC thermograms were recorded on a DSC823^e instrument (Mettler Toledo, Zurich, Switzerland) with an HSS7 sensor under a nitrogen atmosphere during a heating/cooling cycle (0 → 90 → 0 °C) with a heating and cooling rate of 3.5 °C/min. Each temperature cycle was sequentially repeated three times in order to ensure and check the reproducible response of the instrument. The sample concentration for DSC measurements was 2.0 wt.%.

2.3. Dynamic light scattering (DLS) measurements

DLS measurements were performed with an ELS-Z zeta-potential and particle-size analyzer (Otsuka Electronics Co., Ltd, Osaka, Japan) and observed in the temperature range from 10 to 90 °C. The sample solutions were kept for 5 min at the required temperature before each measurement. The sample concentration for DLS measurements was 0.2 or 2.0 wt.%. The hydrodynamic diameters were obtained by Cumulant method. Intensity and number size distributions were obtained by Marquardt method.

2.4. Surface tension measurements

Surface tension was measured by the Wilhelmy method by using a CBVP-A3 surface tensiometer (Kyowa Interface Science, Co. Ltd., Tokyo, Japan) at 25 °C. A Teflon cell containing 700 μL of solution was used for the measurement. The surface tension gradually decreased during the measurements. The values were stable after 30 min and were recorded.

2.5. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)

The three kinds of hydrogels from aqueous solutions of compounds **1**, **2** and **3** were frozen with liquid nitrogen, lyophilized, and cut with a razor blade. The cut surfaces of the hydrogels were sputter-coated with gold with an ion-coater (JFC-1100E, JEOL, Tokyo, Japan) and observed under a scanning electron microscope (JSM-6060, JEOL) at an accelerating voltage of 5 kV.

A drop of aqueous dispersion of compound **1** was mounted on a copper grid with an elastic carbon supporting film (Oken Shoji, Tokyo, Japan) and observed under a transmission electron microscope (JEM1400, JEOL) at an accelerating voltage of 100 kV after negative staining with uranyl acetate.