



Synthesis, characterization, and antibacterial property of novel starch derivatives with 1,2,3-triazole



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ABSTRACT

Four novel starch-linked-1,2,3-triazole derivatives were synthesized including 6-hydroxymethyltriazole-6-deoxy starch (**HMTST**), 6-bromomethyltriazole-6-deoxy starch (**BMTST**), 6-chloromethyltriazole-6-deoxy starch (**CMTST**), and 6-carboxyltriazole-6-deoxy starch (**CBTST**). Their antibacterial properties against *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) were evaluated *in vitro*, respectively. The inhibitory property of the obtained amphiprotic starch derivatives exhibited a remarkable improvement over starch. And the antibacterial indices of most of the products were higher than 60% and 40% at 1.0 mg/mL when the culture time was 8 h and 16 h, respectively. Moreover, the inhibitory index of **CBTST** attained 97% above at 1.0 mg/mL. Generally, the inhibitory activity decreased in the order: **CBTST** > **CMTST** > **BMTST** > **HMTST** > starch. Furthermore, the order of their antibacterial activity was consistent with the electron-withdrawing property of different substituted groups of the 1,2,3-triazole groups. The substituted groups with stronger electron withdrawing ability relatively possessed greater antibacterial activity.

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Chemical compounds studied in this article: Potato starch (PubChem CID: 135306210); *N*-bromosuccinimide (PubChem CID: 67184); Triphenylphosphine (PubChem CID: 11776); Sodium azide (PubChem CID: 33557); Cuprous iodide (PubChem CID: 24350); Triethylamine (PubChem CID: 8471); Propargyl alcohol (PubChem CID: 7859); Propargyl bromide (PubChem CID: 7842); Propargyl chloride (PubChem CID: 12221); Propiolic acid (PubChem CID: 10110).

1. Introduction

As a biopolymer of considerable significance for humans, starch is the principal carbohydrate reserve in a large variety of higher green plants, such as corn, wheat, rice, potato, and tapioca. Starch is mainly composed of α -D-glucopyranosyl unit (Klaohanpong, Puttanlek, Rungsardthong, Pancha-arnon, & Uttapap, 2015; Miao, Li, Huang, Jiang, & Zhang, 2015; Moore, Ai, Chang, & Jane, 2015; Warren, Zhang, Waltzer, Gidley, & Dhital, 2015). As an abundant,

cheap, environmentally benign, biodegradable, and biocompatibility polysaccharide, starch can be utilized in some level of industrial applications involving food, pharmaceutical, beverages, papermaking, packaging, and textiles (Cieřla, Sartowska, & Królak, 2015; Li et al., 2015). However, compared with hyaluronic acid, heparin, and chitosan, native starch is inherently unsuitable for further industrial applications, because of the absence of active groups such as carboxyl, sulfate ester, and amino. One valid solution is often tailored through chemical modification to develop desirable functional properties, such as solubility, pasting properties, dispersion, and digestibility (Miao et al., 2015). Moreover, as biological activities of polysaccharide are related with its molecular structure, increasing attention has been attracted to the structure-activity relationship of polysaccharides (Hu et al., 2014).

The Cu(I) catalyzed azide-alkyne [3 + 2] cycloaddition (CuAAC) has emerged as a powerful strategy for the design of sophisticated biomaterials requiring high levels of precision and control, initiated by Sharpless and co-workers (Baraniak, Kacprzak, & Celewicz, 2011; Singh et al., 2015; Singh, Mangat, Singh, Arora, & Garg, 2014). As reaction products of CuAAC, 1,2,3-triazoles are attractive constructs of target molecules due to their wide range of biological properties, such as antimicrobial (Garudachari,

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Isloor, Satyanarayana, Fun, & Hegde, 2014), antitubercular (Pyta, Klich, Domagalska, & Przybylski, 2014), antimalarial (Pereira et al., 2014), antibiotic (Aufort, Herscovici, Bouhours, Moreau, & Girard, 2008), anticancer (Kamal et al., 2008; Kumar et al., 2011), cytotoxic agents (Baraniak et al., 2011; Farooq et al., 2014; Singh et al., 2011), and antioxidant (Singh, Sindhu, Khurana, Sharma, & Aneja, 2014; Tan, Li, Li, Dong, & Guo, 2016). Meanwhile, some evidences had proved that triazole-functionalized derivatives of polysaccharide showed obviously enhanced biological activities in comparison to raw polysaccharide. Amphiphilic aminated inulin synthesized via 'click chemistry' exhibited improved antibacterial property against *Staphylococcus aureus* (Dong et al., 2014). (1,2,3-Triazol-4-yl)methyl nicotinate chitosan had obviously enhanced antifungal activity after chemical modification compared with original chitosan (Qin et al., 2013). Therefore, to improve their certain biological properties, the modification of carbohydrate polymers by 'click chemistry' will be a powerful tool. However, there was very few research on synthesis and bioactivity of starch derivatives with 1,2,3-triazole, which were very indispensable contents of starch researches.

In this paper, we reported the synthesis and antibacterial property of a group of starch derivatives with 1,2,3-triazole including **HMTST**, **BMTST**, **CMTST**, and **CBTST**. To begin with, *N,N*-dimethylformamide (DMF)/LiBr was been used as the reaction medium to dissolve starch because it could save both time and labor. It was reported that *N*-bromosuccinimide (NBS), triphenyl phosphine (Ph_3P) could selectively replace primary hydroxyl groups of polysaccharide with bromine (Fox & Edgar, 2012; Fox, Li, Xu, & Edgar, 2011; Ifuku, Matsumoto, Wada, Morimoto, & Saimoto, 2013). Therefore, the 6-bromo-6-deoxy-starch selected as intermediate was first synthesized by reaction between the primary hydroxyl of starch and NBS, Ph_3P . Then, the 6-azido-6-deoxy-starch was obtained by reaction between the 6-bromo-6-deoxy-starch and NaN_3 . Subsequently the alkyne components were introduced into 6-azido-6-deoxy-starch through 'click reaction'. The chemical structures, the degrees of substitution, and thermal characteristics of the derivatives were investigated. *Escherichia coli* and *S. aureus* were selected as the model Gram-negative and Gram-positive bacteria to evaluate the antibacterial property of starch and starch derivatives synthesized *in vitro*. The relationship between the structure and antibacterial activity of starch derivatives was discussed, simultaneously.

2. Experimental

2.1. Materials

Soluble starch from potato was purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Propargyl alcohol, propargyl bromide, propargyl chloride, and propiolic acid were obtained from Aladin Chemical Corp (Shanghai, China). The other reagents were all of analytical grade and used without further purification.

2.2. Analytical methods

Fourier transform infrared (FTIR) spectra were performed ranging from 4000 cm^{-1} to 400 cm^{-1} using a Jasco-4100 FT-IR spectrometer (Japan, provided by JASCO Co., Ltd., Shanghai, China) with KBr disks. ^1H nuclear magnetic resonance (^1H NMR) spectra were all measured with a Bruker AVIII-500 Spectrometer (500 MHz, Switzerland, provided by Bruker Tech. and Serv. Co., Ltd., Beijing, China), using $(\text{CD}_3)_2\text{SO}$ ($\text{DMSO}-d_6$) as solvents with tetramethylsilane (TMS) as internal standard. Chemical shift values were given in δ (ppm). The UV-Vis absorbance of the tested mixture was

measured with a T6 New Century UV spectrometer (China, provided by P General Co., Ltd., Beijing, China). The elemental analyses (C, H, and N) were performed on a Vario EL III (Elementar, Germany). The degrees of substitution (DS) of starch derivatives were calculated on the basis of the percentages of carbon and nitrogen. The thermogravimetric analysis (TGA) was performed using the TGA/DSC 1/1100 (Mettler-Toledo). The samples were heated from 25°C to 800°C under $10^\circ\text{C}/\text{min}$. Nitrogen gas was used in the experiment to confirm thermal behavior.

2.3. Synthesis

2.3.1. The dissolution of starch

Soluble starch (3.24 g, 20 mmol) was stirred in 80 mL anhydrous *N,N*-dimethylformamide (DMF), while the mixture was heated to 120°C for 1 h. The slurry was then allowed to cool to 90°C , at which point LiBr (3.47 g, 40 mmol) was added. The starch dissolved within 5 min to form a transparent solution. The contents of the flask were allowed to cool further to room temperature while stirring.

2.3.2. Synthesis of 6-bromo-6-deoxy starch

As shown in Scheme 1, when transparent solution above-mentioned was cooled to 0°C , *N*-bromosuccinimide (NBS) (14.24 g, 80 mmol) and triphenylphosphine (Ph_3P) (20.99 g, 80 mmol) were added. The reaction solution was heated to 80°C for 3 h under an argon atmosphere. The product was isolated by adding the reaction mixture slowly to 400 mL of 95:5 (v/v) mixture of absolute ethanol and deionized water, followed by filtration. The unreacted NBS, Ph_3P , and other outgrowth were extracted in a Soxhlet apparatus with ethanol and acetone for 48 h, respectively. The product was freeze dried overnight in vacuum, yield: 89.3%.

2.3.3. Synthesis of 6-azido-6-deoxy starch

In a 100 mL three-necked round-bottom flask, 6-bromo-6-deoxy-starch (2.25 g, 10 mmol) was weighed and dissolved in 40 mL of anhydrous DMSO. Then, NaN_3 (1.3 g, 20 mmol) was added to the flask and dissolved. The solution was heated to 80°C and stirred for 24 h under an argon atmosphere. The product was isolated by pouring the reaction solution into 200 mL of absolute ethanol. The precipitate was collected by filtration, washed with acetone. After using Soxhlet extraction with ethanol for 48 h and dialyzed against deionized water for 2 days to remove the probable remained sodium azide, the product was obtained by freeze drying, yield: 71.1%.

2.3.4. Synthesis of amphiprotic starch derivatives (HMTST)

6-Azido-6-deoxy starch (187 mg, 1 mmol) was dissolved in 20 mL DMSO, cuprous iodide (19 mg, 0.1 mmol), triethylamine (0.14 mL, 1 mmol), propargyl alcohol (0.173 mL, 3 mmol) were added, and the solution was stirred at 75°C for 24 h under an argon atmosphere. The mixture was precipitated in acetone, collected by filtration. The probable remained reagents were extracted in a Soxhlet apparatus with acetone for 2 days. After dialyzed against deionized water for 2 days, the products were obtained by lyophilization of their aqueous solutions, yield: 93.8%.

2.3.5. Synthesis of amphiprotic starch derivatives (BMTST, CMTST)

6-Azido-6-deoxy starch (187 mg, 1 mmol) was dissolved in 20 mL DMSO, cuprous iodide (19 mg, 0.1 mmol), triethylamine (0.14 mL, 1 mmol), propargyl bromide (0.235 mL, 3 mmol) or propargyl chloride (0.217 mL, 3 mmol) were added, and the solution was stirred at 75°C for 72 h under an argon atmosphere. Then, equivalent above-mentioned reagents were added once again, and the reaction solution was stirred at 75°C for 72 h under an argon atmosphere. The mixture was precipitated in

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