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# Synthesis of Cyclic β-1,6-Oligosaccharides by Electrochemical Polyglycosylation of glucosamine monomers

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## Abstract

Synthesis of protected precursors of cyclic β-1,6-oligoglucosamines by electrochemical polyglycosylation of thioglycosides as a monomer is performed. The monomer with 2,3-oxazolidinone protecting group afforded the cyclic disaccharide exclusively. Cyclic oligosaccharides up to trisaccharide were obtained using the monomer with 2-deoxy-2-azido group.

## Keywords

cyclic oligosaccharide; electrochemical glycosylation; glucosamine; polyglycosylation

# Introduction

Electrochemical polymerization of organic molecules is an important process to prepare functional materials such as conducting polymers [1-5]. Electrochemical reactions can be controlled by electric potential or current, electrodes, and electrolytes, which are not available in conventional chemical reactions. Therefore, electrochemical polymerizations can be utilized selective synthesis. Cyclic oligosaccharides are important class of host molecules and some natural cyclic oligosaccharides are produced by enzymatic processes; however, their chemical syntheses are still primitive [6-10]. We have been interested in preparation of cyclic oligosaccharides under electrochemical conditions and electrochemical conversion of linear oligosaccharides of glucosamine into the corresponding cyclic oligosaccharides by intramolecular glycosylation (Figure 1a) [11]. One-pot two-step synthesis via electrochemical polyglycosylation and intramolecular glycosylation has also been achieved to synthesize unnatural cyclic oligosaccharides of glucosamine (Figure 1b) [12]. Here, we report direct synthesis of cyclic oligoglucosamines via electrochemical polymerization of thioglycoside monomers which are derived from glucosamine hydrochloride.

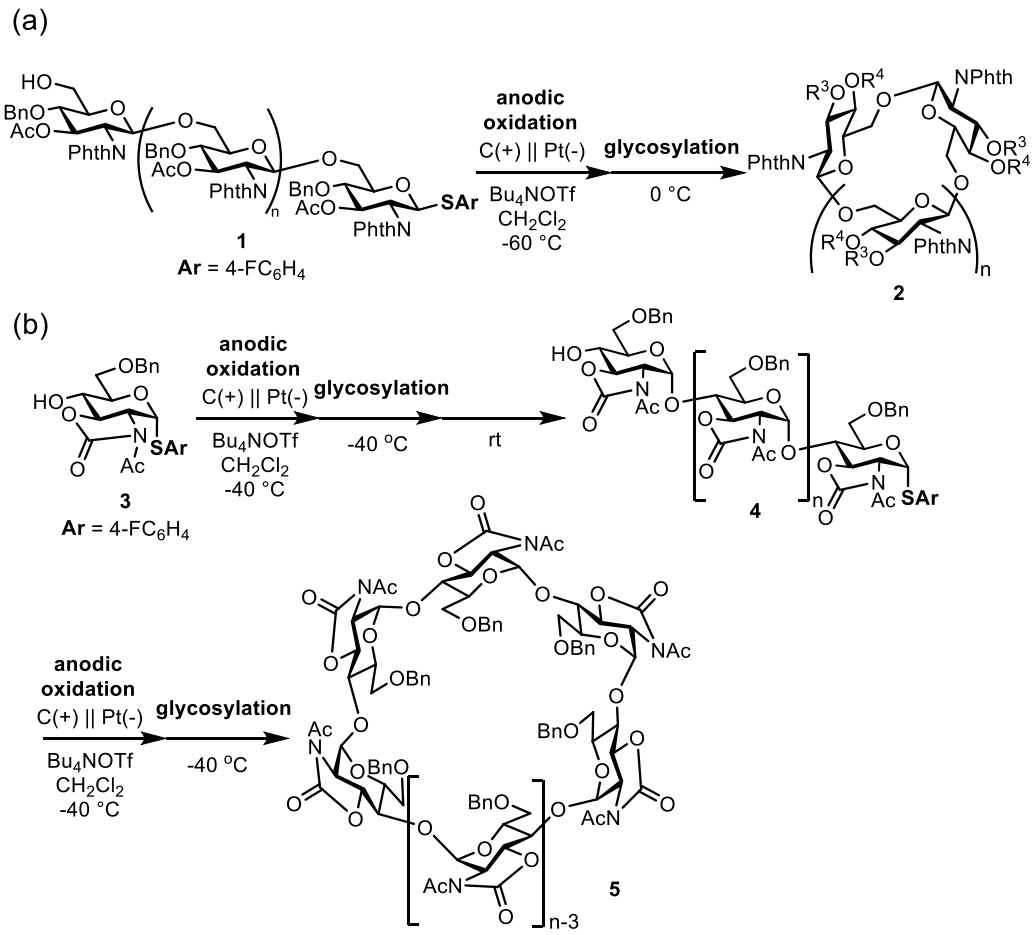


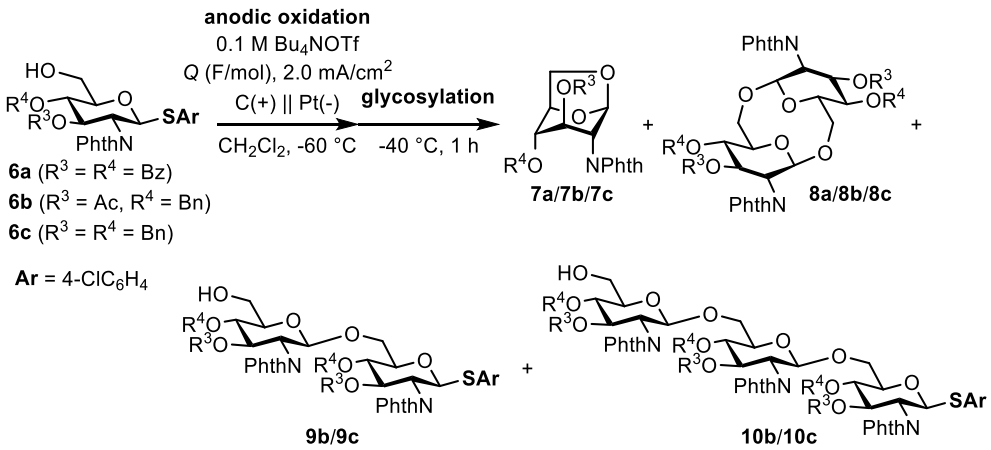

**Figure 1.** Preparation of cyclic oligoglucosamines. (a) via intramolecular glycosylation. (b) via polyglycosylation and intramolecular glycosylation.

# Results and Discussion

## Electrochemical Polyglycosylation of 2-deoxy-2-phtalimide thioglycoside monomer

We initiated our research from the electrochemical polyglycosylation of monomers **6** with 2-deoxy-2-phtalimide (2-PhthN) group (Table 1). The monomer **6a** ($R^3$ = $R^4$ = Bz) was completely consumed with the slight excess amount of total charge (*Q* = 1.05 F/mol); however, 1,6-anhydrosugar **7a** ($R^3$ = $R^4$ = Bz) was formed as a major product together with cyclic disaccharide **8a** ($R^3$ = $R^4$ = Bz) (entry 1). The monosaccharide **6b** ($R^3$ = Ac, $R^4$ = Bn) was also completely consumed under the same reaction conditions; however, the yield of 1,6-anhydrosugar **7b** ($R^3$ = Ac, $R^4$ = Bn) was lower than that of **7a** (entry 2). Because no linear oligosaccharides were obtained, we reduced the amount of total charge from 1.05 to 0.525 F/mol (entry 3). Linear disaccharides **9b** ($R^3$ = Ac, $R^4$ = Bn) and trisaccharide **10b** ($R^3$ = Ac, $R^4$ = Bn) were obtained in 13% and 6% yields, respectively. The protecting group $R^3$ of 3-OH was changed from acetyl (Ac) group to benzyl (Bn) group; however, conversion and yields of linear oligosaccharides **9c** and **10c** were decreased and the corresponding cyclic disaccharide **8c** was not obtained at all (entry 4). In all cases the major product was 1,6-anhydrosugar **7** which was the product of intramolecular glycosylation of monomer **6**. The proposed mechanism is shown in Figure 2. Anodic oxidation of thioglycoside **6** generated radical cation **11** which is converted to glycosyl triflate **12**. 1,6-Anhydrosugar **7** is produced via the $^4C_1$ to $^1C_4$ conformational change of the pyran ring to generate cation intermediate **13**. Therefore, prevention of the conformational change might be necessary to synthesize larger cyclic oligosaccharides.

**Table 1.** Electrochemical polyglycosylation of monomers **6** with 2-PhthN group.




| entry | $R^3$ | $R^4$ | total charge *Q* (F/mol) | conv. | yield of **7** | yields of oligosaccharides **8** | **9** | **10** |
|---|---|---|---|---|---|---|---|---|
| 1 | Bz | Bz | 1.05 | >99% | 73% **7a** | 3% **8a** | - | - |
| 2 | Ac | Bn | 1.05 | >99% | 28% **7b** | 6% **8b** | - | - |
| 3 | Ac | Bn | 0.525 | 67% | 25% **7b** | 7% **8b** | 13% **9b** | 6% **10b** |
| 4 | Bn | Bn | 0.525 | 59% | 25% **7c** | - | 4% **9c** | 2% **10c** |

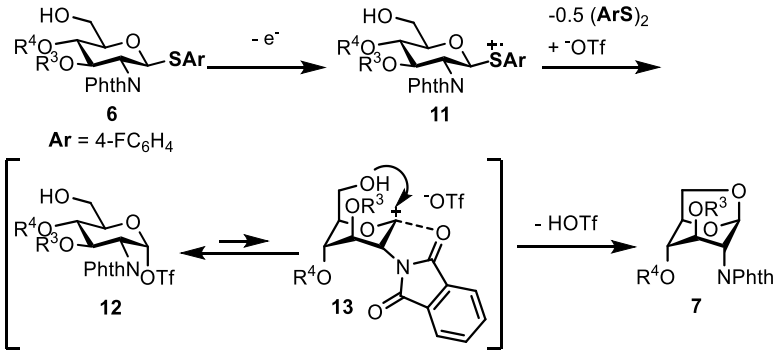



**Figure 2.** Proposed reaction mechanism of formation of 1,6-anhydrosugar **7**.

## Electrochemical Polyglycosylation of 2,3-oxazolidione thioglycoside monomer

To avoid formation of 1,6-anhydrosugar we introduced *N*-acetyl-2,3-oxazolidione protecting group into the thioglycoside monomer **14** (Figure 3) [13,14]. The electrochemical polyglycosylation of **14** was carried out in the presence of 2,6-di-*tert*-

butyl-4-methylpyridine (DTBMP) to ensure the formation of β-glycosidic bonds [15]. Although we could suppress formation of 1,6-anhydrosugar **15**, cyclic disaccharide **16** was obtained as an exclusive product. The optimized structure of **15** calculated by DFT (B3LYP/6-31G(d)) suggested that the pyran ring preferred the boat conformation because the chair conformation of the pyran ring was controlled by the introduction of the 2,3-oxazolidinone protecting group (See Supporting Information for DFT calculation). Therefore, it was proved that the 2,3-oxazolidinone protecting group was powerful enough to prevent intramolecular glycosylation of monomer **14**; however, it was not useful to prevent intramolecular glycosylation of the linear disaccharide and promote the formation of larger cyclic oligosaccharides.

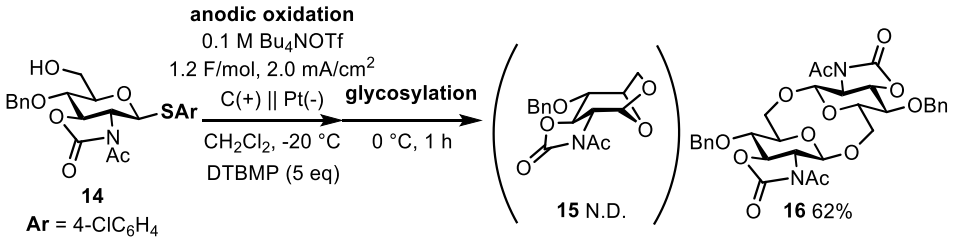


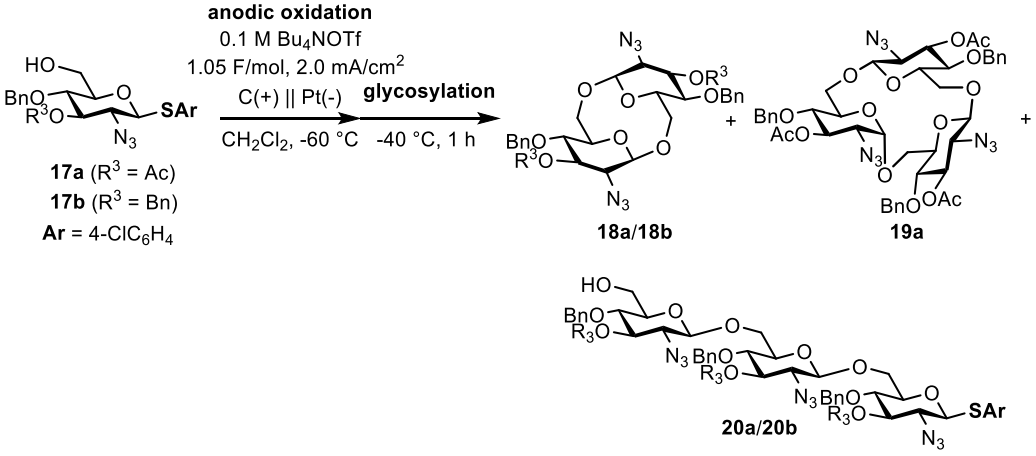

**Figure 3.** Electrochemical polyglycosylation of monomer **14** with 2,3-oxazolidione protecting group.

## Electrochemical Polyglycosylation of 2-deoxy-2-azido thioglycoside monomer

Based on the results of table 1 and figure 3, we changed the substituent of C-2 position of the thioglycoside monomer from phthalimide (PhthN) group to azido ($N_3$) group which has no neighboring group effect. Although glycosyl donors with $N_3$ group at C-2 position have been used for α-selective glycosylation [16,17], we have already found that β-selective glycosylation proceeded using a glycosyl donor with $N_3$ group under the electrochemical conditions [18]. The results of electrochemical

polyglycosylation using the thioglycoside monomer **17** with $N_3$ group are summarized in Table 2. Cyclic trisaccharide **19a** was obtained together with cyclic disaccharide **18a** and the trace amount of linear and cyclic tetrasaccharides by the introduction of $N_3$ group (entry 1). Cyclic disaccharide **18b** and linear trisaccharide **20b** were produced with monomer **17b** with 3,4-di-*O*-benzyl group (entry 2). Although the protecting group ($R^3$) at 3-OH also affected the product distribution, formation of the corresponding 1,6-anhydrosugars were not observed in both cases. NMR data suggested that cyclic trisaccharide **19a** contains one α-glycosidic bond and two β-glycosidic bonds. Based on these results we assume that the formation of α-glycosidic bond is crucial to produce cyclic trisaccharide **19a** (Figure 4). Moreover, the α-glycosidic bond might be formed in the first step and linear disaccharide **21α** which did not afford cyclic disaccharide should be produced as an intermediate of **19a**.

**Table 2.** Electrochemical polyglycosylation of monomer **17** with 2-azido group.




| entry | $R^3$ | conv. | yields of oligosaccharides | | |
|---|---|---|---|---|---|
| | | | **18** | **19** | **20** |
| 1 | Ac | >99% | 49% **18a** | 16% **19a** | - |
| 2 | Bn | 73% | 14% **18b** | - | 13% **20b** |

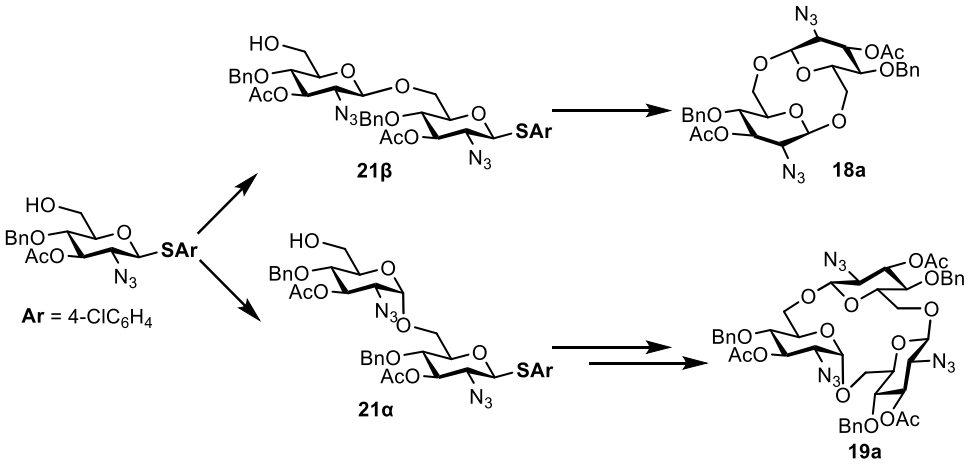



**Figure 4.** Proposed reaction mechanism of formation of cyclic trisaccharide **19a**.

# Conclusion

In conclusion, we have investigated synthesis of cyclic β-1,6-oligoglucosamines under the electrochemical polyglycosylation condition. The choice of protecting group of monomers is important to prevent intramolecular glycosylation which forms 1,6-anhydrosugar as a side product. It was revealed that the formation of cyclic disaccharide must be controlled to produce cyclic β-1,6-trisaccharide. Further optimization of monomers and another synthetic approach using dimers for production of larger cyclic oligosaccharides are in progress in our laboratory.

# Experimental

Electrochemical polyglycosylation (Figure 3) has been performed using our second-generation automated electrochemical synthesizer equipped with the H-type divided electrolysis cell. Thioglycoside **14** (0.40 mmol, 186 mg), $Bu_4NOTf$ (1.0 mmol, 393 mg), DTBMP (2.0 mmol, 411 mg), and dry $CH_2Cl_2$ (10 mL) were added to the anodic chamber. Triflic acid (0.4 mmol, 35 μL) and $CH_2Cl_2$ (10 mL) were added to the cathodic chamber. Electrolysis was performed at -20 °C under the constant current condition

until 1.2 F/mol of total charge was consumed. Then the reaction temperature was elevated to 0 °C and the temperature was kept for 1 h. The reaction was quenched with $Et_3N$ (0.5 mL), and the reaction mixture was dissolved in EtOAc and washed with water to remove electrolyte. It was further washed with aqueous 1 M HCl solution and dried over $Na_2SO_4$. Then the solvent was removed under reduced pressure and the crude product (220 mg) was purified with preparative GPC to obtain pure cyclic oligosaccharides **16** (0.125 mmol, 79.7 mg, 62%).

# Supporting Information

Supporting Information File 1:

File Name: SI-Cyclic oligoglucosamine

File Format: PDF

Title: Supporting Information of Synthesis of Cyclic β-1,6-Oligosaccharides by Electrochemical Polyglycosylation of glucosamine monomers

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