（様式２）

# 学 位 論 文 の 概 要 及 び 要 旨

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題　　目　Electrochemical Conversion of Glucosamine Monosaccharides into Variety of Linear and Cyclic Oligosaccharides（オリゴグルコサミン単糖の多様な鎖状・環状オリゴ糖への電気化学的変換）

学位論文の概要及び要旨

**General Introduction**

Chitin is the most abundant glucosamine polysaccharide in nature and the building material that gives strength to the exoskeletons of crustaceans, insects, and the cell walls of fungi (Fig. 1). Poly-*N*-acetylglucosamine (PANG) is also a polysaccharide of glucosamine which has β-1,6-glycosidic linkages. Although both polysaccharides are biologically important, it is difficult to obtain their oligosaccharides from natural sources. Thus, their chemical synthesis has been investigated by many researchers including our group and my project focused on the electrochemical method to access oligosaccharides efficiently.

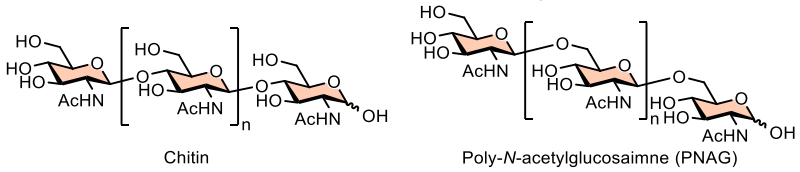


**Fig. 1. Structures of chitin and PNAG.**

**Chapter 1.**
**Synthesis of TMG-chitotriomycin analogues by automated electrochemical assembly**

TMG-chitotriomycin, which is a derivative of chitooligosaccharides, showed selective inhibition of GlcNAcases of insects and fungi, and our group reported the total synthesis of TMG-chitotriomycin using an automated electrochemical synthesizer (Fig. 2). Since then, we have been interested in biological activities of TMG-chitotriomycin and its analogues. Initially, we prepared two different disaccharide building blocks to synthesize three different analogues of TMG-chitotriomycin as shown in Fig. 2.

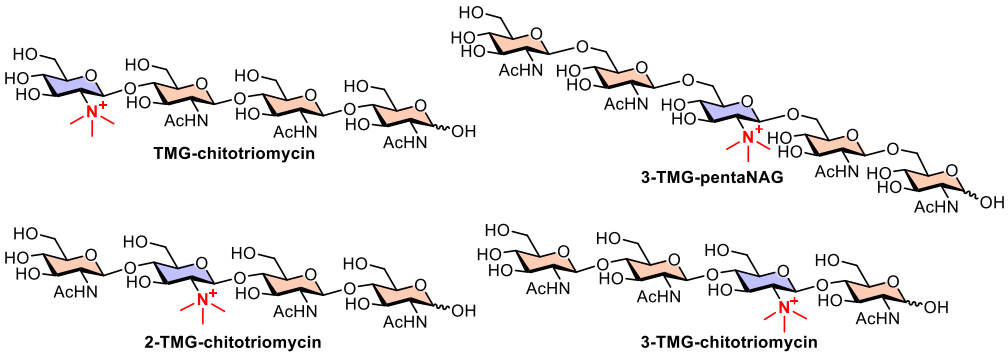


**Fig. 2. TMG-chitotriomycin and its analogues.**

For this purpose, we synthesized several monosaccharide buildings blocks from the same starting materials (Fig. 3). Through electrochemical assembly of these building blocks sequentially we obtained three different precursors using 1+1+2+1 assembly for 3-TMG-pentaNAG, 1+2+1 for 2-TMG-chitotriomycin and 1+1+2 for 3-TMG-chitotriomycin. The manipulation of azido group and global deprotection of other protecting groups produced targeted products 3-TMG-pentaNAG in 18% (8 steps) and 30% (8 steps) from -OBn and SAr group, respectively and 2- and 3-TMG-chitotriomycin with 22% (6 steps) and 13% (6 steps) yields, respectively.

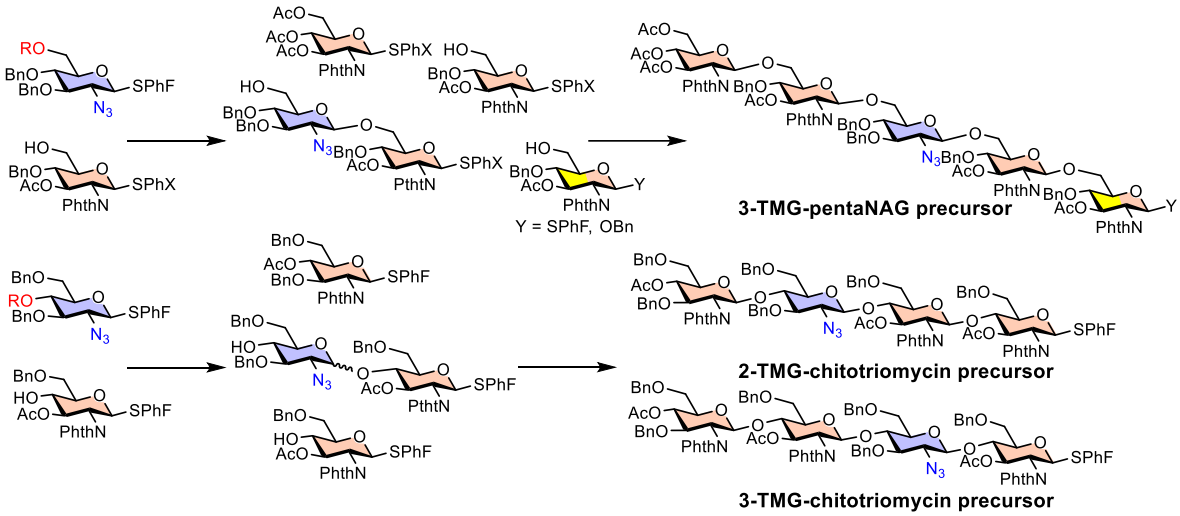


**Fig. 3. Synthetic plan of precursors of TMG-chitotriomycin analogues.**

## Chapter 2.
## Synthesis of Protected Precursors of Chitooligosaccharides by Electrochemical Polyglycosylation

Although we have achieved total synthesis of TMG-chitotriomycin analogues, synthesis of their precursors was time consuming. Thus, we initiated developing electrochemical polyglycosylation as a new synthetic route to synthesis longer oligosaccharides in short time (Fig. 4)

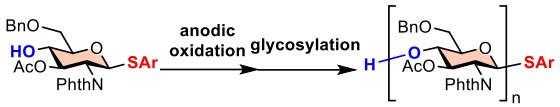


**Fig. 4. Electrochemical polyglycosylation of glucosamine.**

We have optimized several parameters including the leaving group ArS and temperatures of anodic oxidation and glycosylation as following (Fig. 5-7) Formation of oligosaccharides up to heptasaccharide was observed and conversion of monosaccharide was higher at elevated temperatures; however, by-products were formed at higher temperature as confirmed by MALDI-TOF MS analysis (Fig. 8).

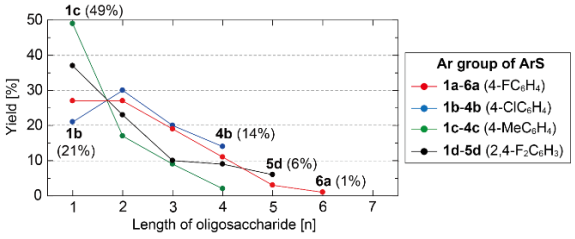


**Fig. 5. Optimization of anomeric leaving group.**

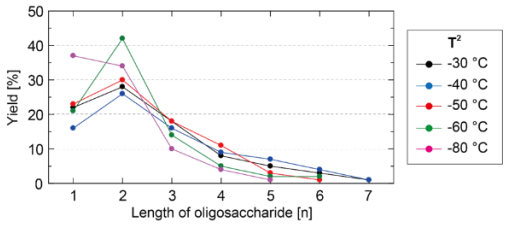


**Fig. 6. Optimization of glycosylation temperature $T_2$.**

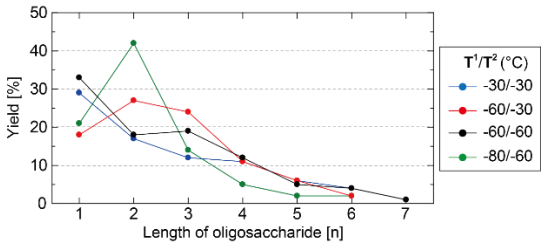


**Fig. 7. Optimization of anodic oxidation and glycosylation temperature $T_1$ and $T_2$.**

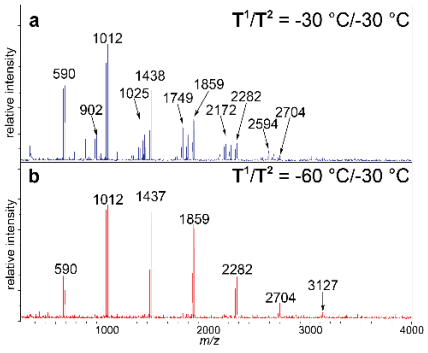


**Fig. 8. Comparison of MALDI-TOF MS.**

It might be difficult to synthesize heptasaccharide and octasaccharide by further optimization of the process. Thus, we investigated the modified process which repeats electrochemical polyglycosylation with addition of monosaccharide. (Fig. 9). Based on the mechanistic analysis of the electrochemical polyglycosylation, monosaccharide must be selectively activated and react with oligosaccharides. Indeed, yields of longer oligosaccharides were increased during cycles and octasaccharide was obtained after the 3rd cycle (Fig. 10).

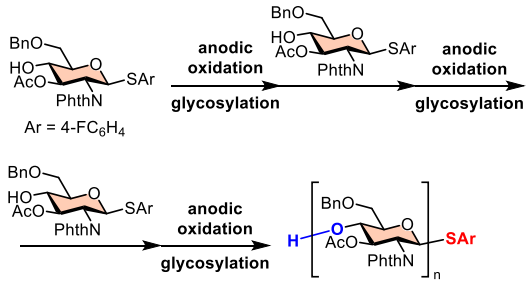


**Fig. 9. Synthetic scheme of the modified process.**

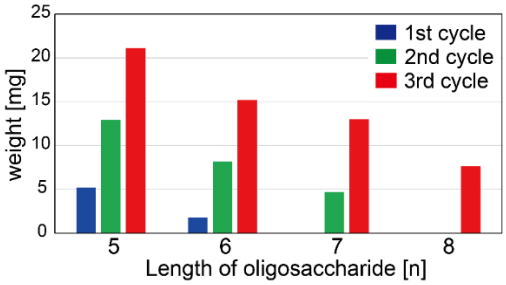


**Fig. 10. Yields of oligosaccharides after cycles.**

## Chapter 3.
## Synthesis of Cyclic Oligosaccharides of PNAG by Electrochemical Polyglycosylation

Successful synthesis of protected precursors of chitooligosaccharides by electrochemical polyglycosylation encouraged us to synthesize PNAG oligosaccharides under the same reaction conditions. Initially, the monosaccharide of PNAG was used for electrochemical polyglycosylation; however, we obtained the corresponding 1,6-anhydrosugar as a major product (Fig. 11).

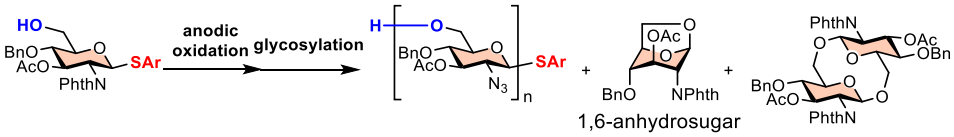


**Fig. 11. Electrochemical polyglycosylation of the PANG monosaccharide.**

We assumed that the protecting group at 2-$NH_2$ might influence products of electrochemical polyglycosylation. Therefore, the 2-phthalimide (Phth) group was changed to azido ($N_3$) group, and linear oligosaccharides were obtained together with cyclic oligosaccharides up to the tetrasaccharide which was never produced from the monosaccharide with 2-Phth group (Fig. 12).

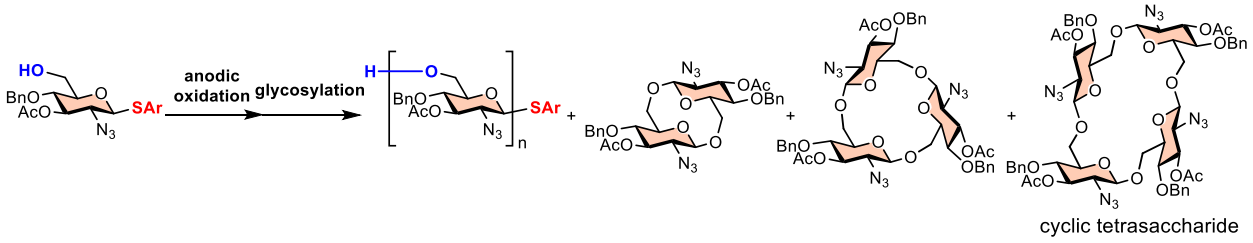


**Fig. 12. Electrochemical polyglycosylation of glucosamine.**

Now we are optimizing reaction conditions of electrochemical polyglycosylation of the monosaccharide with the $N_3$ group at 2-position to produce linear oligosaccharides and cyclic oligosaccharide selectively. We believe that both linear and cyclic oligosaccharides are important oligosaccharides which can be used as precursors of biologically active oligosaccharides and functional carbohydrate materials because the $N_3$ group is a typical functional group of "click chemistry".