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Glycosyl Sulfonium Ions as Storable Intermediates for Glycosylations

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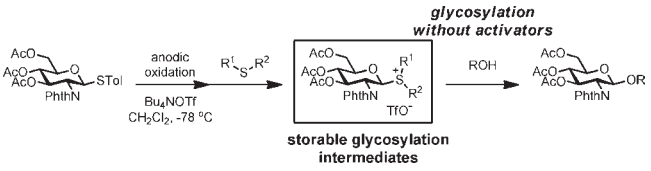
ABSTRACT



Glycosyl sulfonium ions, which serve as persistent glycosyl cation equivalents, were prepared by the addition of diorganosulfides to an electrochemically generated glycosyl triflate. Low-temperature and variable-temperature NMR studies were performed to reveal the structure, stability, and reactivity of glycosyl sulfonium ions. The glycosyl sulfonium ions could be used as storable intermediates for reactions with various glycosyl acceptors including thioglycosides to give the corresponding disaccharides.

Recent progress in the development of methodologies for oligosaccharide synthesis enables us to access complex oligosaccharides and glycoconjugates readily.[1] Glycosyl triflates,[2,3] which have been used for stereoselective glycosylation and iterative glycosylation for many years, are one of the most reactive glycosylation intermediates among the spectroscopically observable intermediates.[4] Although various methods including the electrochemical method[5] have been developed to generate glycosyl triflates from stable glycosyl donors, glycosyl triflates are so reactive that it is necessary to use them immediately after their preparation or generate them in the presence of glycosyl acceptors. If it were possible to store such highly reactive glycosylation intermediates for prolonged periods of time, this might open many new possibilities in chemical glycosylation. Therefore, it is highly desired to develop novel glycosylation intermediates that have enough stability for storage and sufficient reactivity to couple with glycosyl acceptors under mild reaction conditions without any activation steps.

Various glycosyl cation equivalents such as glycosyl sulfonates[2,3,6] and glycosyl onium ions already existed.[3,7] Schuerch performed pioneering work on glycosyl sulfonium ions in the development of α-selective glycosylation.[8] Boons and co-workers prepared β-glycosyl sulfonium ions in inter- and intramolecular manners and elegantly applied

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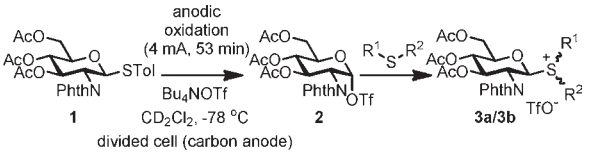
Scheme 1. Preparation of Glycosyl Sulfonium Ions **3** via Electrochemically Generated Glycosyl Triflate **2**



them to α-selective glycosylations.[9] These findings prompted us and other groups to investigate the stability and reactivity of glycosyl sulfonium ions.[10,11] We developed a novel method for preparing glycosyl sulfonium ions using the reaction of electrochemically generated glycosyl triflates with diorganosulfides. On the basis of these results, it is reasonable to assume that stability and reactivity of glycosyl sulfonium ions can be tuned by changing substituents on the sulfur atom. In this study, we demonstrate that glycosyl sulfonium ions bearing appropriate substituents on the sulfur atom can serve as storable intermediates for glycosylation.

Thioglycoside **1**, which has a *N*-phthalimide (*N*-Phth) group, was chosen as a glycosyl donor because this group could be expected to suppress formation of the orthoester and control the stereochemistry of generating glycosides in a β-form (Scheme 1).[12] The corresponding glycosyl sulfonium ions **3** were prepared by the reaction of diorganosulfide (R^1SR^2) and the highly reactive glycosyl triflate **2** that was electrochemically generated from thioglycoside **1** at −78 °C.

^{1}H NMR spectra of glycosyl triflate **2** and that of glycosyl sulfonium ion **3a** are shown in Figure 1. Although it was not possible to determine the structure of the minor product due to their instability,[13] α-triflate was obtained exclusively (Figure 1a). The addition of dimethyl sulfide (Me_2S) to a solution of glycosyl triflate **2** gave a single set of peaks of the β-isomer (Figure 1b). On the other hand, glycosyl sulfonium ion **3b**, which was obtained by the reaction with unsymmetrical methyl phenyl sulfide (MeSPh), exhibited two sets of peaks. These two species are attributed to the two diastereomers of glycosyl sulfonium ion **3b**, because the sulfur atom is a stereogenic center (Figure 1c).

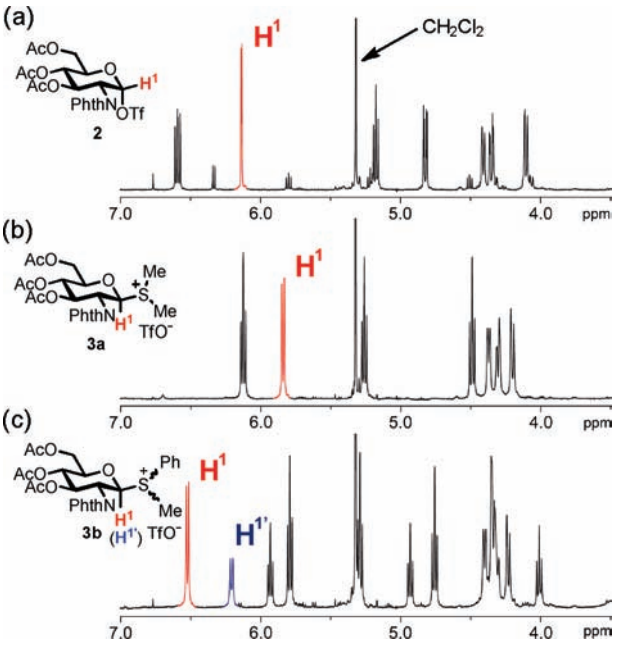


Figure 1. ^{1}H NMR spectra at −80 °C: (a) glycosyl triflate **2**, (b) glycosyl sulfonium ion **3a**, and (c) glycosyl sulfonium ion **3b**.

Electrospray ionization (ESI) and cold-spray (CS) TOF MS analyses were also performed to confirm the generation of the glycosyl sulfonium ions. Although the parent peak was observed in addition to several fragments in the case of glycosyl sulfonium ion **3a**, only fragment peaks were observed for **3b** in both ESI and CS-TOF MS spectra. These results indicate that glycosyl sulfonium ion **3b** is less stable than **3a**. (For ^{13}C NMR, H−H-COSY, HMQC, and ESI/CS-TOF MS spectra, see the Supporting Information).

The thermal stability of glycosyl sulfonium ions **3** was particularly important in helping us to optimize the reaction conditions in an efficient manner. We performed

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(13) α-Glycosyl triflate **2** is also unstable and gradually decomposes in a freezer at −80 °C.

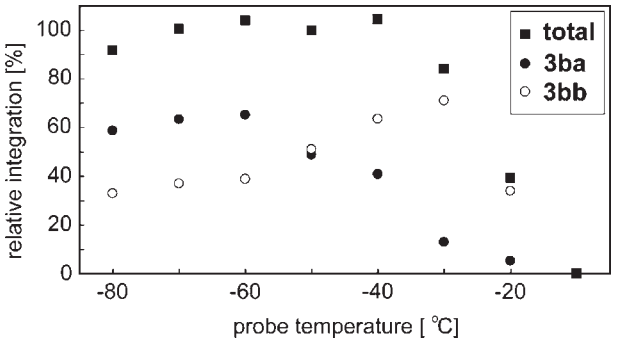
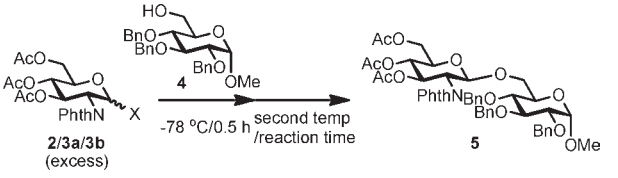


Figure 2. The decomposition profile of two diastereomers of glycosyl sulfonium ion **3b** (**3ba**/**3bb**) between −80 and −10 °C.

variable-temperature (VT) NMR measurements from −80 to −10 °C to obtain the decomposition profile of the two diastereomers of glycosyl sulfonium ion **3b** (**3ba**/**3bb**) (Figure 2). The probe temperature was raised in 20 min intervals and an NMR spectrum was recorded every 10 °C. Although more than 60% of glycosyl sulfonium ion **3a**, which was prepared from Me_2S, remained unchanged after remaining at 0 °C for 17 h, glycosyl sulfonium ion **3b**, prepared from MeSPh, immediately decomposed at 0 °C. Signals derived from one of the two diastereomers **3ba**, which is the major isomer at −80 °C (Figure 1c), gradually decreased above −60 °C. There was a clear difference of stability in the two diastereomers, with the minor diastereomer **3bb** starting to decompose above −30 °C, then completely disappearing at around −10 °C. The major decomposition product was found to be the corresponding β,β-trehalose[14] of glucosamine.[15] Although the change in the ratio of two diastereomers suggests an isomerization between two diastereomers of glycosyl sulfonium ion **3b**, the decomposition profile revealed that **3b** was stable below −40 °C.

Table 1. Glycosylation of Glycosyl Triflate and Glycosyl Sulfonium Ions with a Glycosyl Acceptor

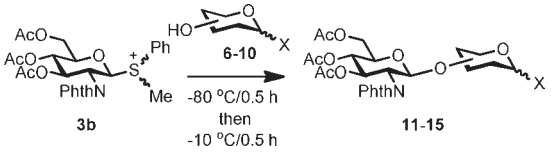


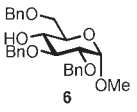
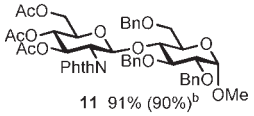
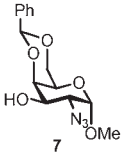
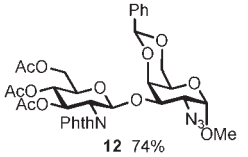
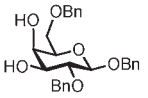
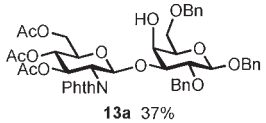
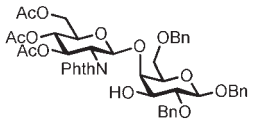
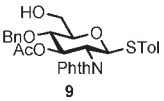
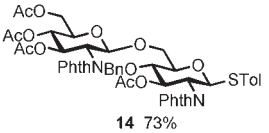
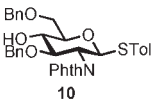
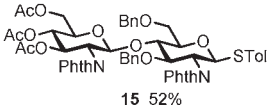
entry	donor (X)	second temp/reaction time	yield, [a] %
1	**2** (OTf)	−/−	56
2	**2** (OTf)	−60 °C/0.5 h	90
3	**3a** (Me_2S)	23 °C/0.5 h	52
4	**3a** (Me_2S)	23 °C/3.0 h	69
5	**3b** (MeSPh)	−30 °C/0.5 h	62
6	**3b** (MeSPh)	−10 °C/0.5 h	93

[a] NMR yield based on 1,1,2,2-tetrachloroethane as an internal standard.

Next, the reactions of glycosyl sulfonium ions **3a** and **3b** with the glycosyl acceptor **4** were compared with those of glycosyl triflate **2** (Table 1). The most reactive glycosyl triflate **2** afforded the corresponding disaccharide **5** in 56% yield at −78 °C (entry 1). As we expected, the yield of **5** was improved from 56% to 90% by raising the reaction temperature from −78 to −60 °C (entry 2). Taking the thermal stability of the glycosyl sulfonium ion **3a** into consideration, glycosylation of **3a** with **4** was performed at 23 °C (entries 3 and 4). The yield of disaccharide **5** was moderate even at ambient temperature (23 °C) with 30

Table 2. Glycosylation of Glycosyl Triflate and Glycosyl Sulfonium Ions with Carbohydrate Acceptors



entry	glycosyl acceptor	product (yield)
1[a]		
	6	**11** 91% (90%)[b]
2[c]		
	7	**12** 74%
3[c]		
	8	**13a** 37%
		
		13b 32%
4[c]		
	9	**14** 73%
5[c]		
	10	**15** 52%

[a] Excess amount of glycosyl donor (1.5 equiv) was used. [b] Glycosyl sulfonium ion was stored at −80 °C for 24 h before use. [c] Excess amount of glycosyl acceptor (2.0 equiv) was used.

min reaction time (entry 3). Due to the stability of glycosyl sulfonium ion **3a**, the yield was improved from 52% to 69% with extended reaction time (entry 4) at 23 °C. The decomposition profile (Figure 2) suggested that glycosylation with glycosyl sulfonium ion **3b** should be carried out below 0 °C. Indeed, **3b** reacted with **4** to give **5** in 62% yield at −30 °C but the yield improved to 93% at −10 °C (entries 5 and 6). It is important to note that glycosyl sulfonium ion **3b** afforded disaccharide **5** in comparable yield with that of glycosyl triflate **2**. Although the optimum reaction temperature was different, glycosyl sulfonium ion **3b** also serves as a reactive glycosylation intermediate.

Glycosylation of other glycosyl acceptors **6**−**10** were also examined under the optimized conditions (Table 2). The secondary hydroxyl group of glycosyl acceptor **6** is effective to give the corresponding disaccharide **11** in 91% yield (entry 1). It is important to note that the yield of disaccharide **11** was 90% when glycosyl sulfonium ion **3b** was stored for 24 h before use.[16] This result clearly shows the storability of the glycosyl sulfonium ion **3b**. The disaccharide **12**, which has 2-azido and 4,6-benzylidene protecting groups, was obtained in 74% yield (entry 2). The diol glycosyl acceptor **8** affords both (1→3) and (1→4) β-linked disaccharides **13a** and **13b** in 37% and 32% yields, respectively (entry 3).[17] Another benefit of this method is that thioglycosides could be used as glycosyl acceptors (entries 4 and 5). Although there was a possibility that glycosyl sulfonium ion **3b** works as an activator of thioglycosides, thioglycosides **9** and **10** afforded the corresponding disaccharides **14** (73%) and **15** (52%), respectively, without affecting anomeric *S*-tolyl groups. The yield of **15** was moderate, however, presumably because of low reactivity of glycosyl acceptor **10** due to the steric hindrance of the *N*-Phth group.[2g,18] The resulting thioglycosides **14** and **15** could be directly used as glycosyl donors for the subsequent glycosylations. The disaccharide **14** is a part of lipid A[19] and disaccharide **15** is also a part of the core unit of *N*-linked oligosaccharide[20] and Nod factor.[12a,b]

In summary, we have found that glycosyl sulfonium ions prepared by the reaction of electrochemically generated glycosyl triflates and diorganosulfides have both reasonable stability and reactivity for glycosylation reactions. The reactivity of glycosyl sulfonium ions can be tuned by placing appropriate substituents on the sulfur atom. Furthermore, it has been clearly shown that the glycosyl sulfonium ions serve as glycosyl donors in the presence of a thioglycoside acceptor. This methodology can be achieved by accumulation of glycosyl sulfonium ions in a pure form by the assistance of electrochemistry. Scope and limitations, mechanistic studies,[21] and further applications including space integration[22] of glycosylation using flow microreactors by taking advantage of the stability and reactivity of glycosyl sulfonium ions are currently in progress in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Although we observed β,β-trehalose as a major product in the reaction mixture after the disappearance of glycosyl sulfonium ion **3b**, β,β-trehalose might be obtained by the reaction with adventitious water during variable-temperature NMR measurement.

(16) We transferred glycosyl sulfonium ion **3b** from the electrolysis cell to the Schlenk tube and stored it in a freezer at −80 °C for 24 h before use.

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