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α- and β-Glycosyl Sulfonium Ions: Generation and Reactivity

Toshiki Nokami,[a] Akito Shibuya,[a] Shino Manabe,*[b] Yukishige Ito,[b] and Jun-ichi Yoshida*[a]

Long-standing interest in glycosyl onium ions such as ammonium, imidazoylium, phosphorium, and sulfonium ions in carbohydrate chemistry[1] has recently been stimulated by their utilitiy in the control of the stereoselectivity of glycosylation reactions.[2] Schuerch reported the first example of stereoselective glycosylation reactions using a glucosyl sulfonium ion. A glucopyranosyl dimethylsulfonium bromide was supposed to be generated by the reaction of the corresponding glucosyl bromide with Me_2S, although its characterization was not reported.[2a] Boons and co-workers reported the generation of β-glycosyl sulfonium ion intermediates by inter- and intramolecular reactions of glycosyl donors with sulfides.[3] The NMR analyses revealed that only the β-glycosyl sulfonium ion was generated, which gave α-glycosides by the action of glycosyl acceptors. These fascinating findings prompted us to investigate the generation, structures, and reactivity of glycosyl sulfonium ions in further detail. We report herein the results of our studies on α- and β-glycosyl sulfonium ions.

The present work stems from our earlier finding[4] that glycosyl triflates[5] were effectively generated by low-temperature electrochemical oxidation[6,7] of thioglycosides (the glycosyl triflate pool methodology). Because only intact Bu_4NOTf and disulfide are present in the solution besides glycosyl triflates, we envisioned that the electrochemically generated glycosyl triflates serve as excellent precursors of glycosyl sulfonium ions for mechanistic studies by using spectroscopic methods.

[a] Dr. T. Nokami, A. Shibuya, Prof. Dr. J. Yoshida
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering Kyoto University
Nishikyo-ku, Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2727
E-mail: yoshida@sbchem.kyoto-u.ac.jp

[b] Dr. S. Manabe, Dr. Y. Ito
RIKEN (The Institute of Physical and Chemical Research)
Hirosawa, Wako, Saitama 351-0198 (Japan)
E-mail: smanabe@riken.jp

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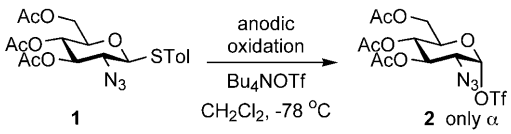
We began with the preparation of a glycosyl triflate of 2-deoxy-2-amino sugar from a thioglycoside using our glycosyl triflate pool method. We chose thioglycoside **1** as a starting material, because the 2-azido group has already been shown to function as a protecting group without neighboring group participation. This is an important property of the 2-azido group in terms of the ability to examine the stereochemistry of glycosylations. Electrochemical oxidation of thioglycoside **1** in the presence of Bu_4NOTf (0.1 M) in CD_2Cl_2 at −78 °C gave a solution of the corresponding glycosyl triflate **2** (Scheme 1).[8] As shown in Figure 1, the anomeric proton signal, which was observed at $\delta = 6.13$ ppm (d, $J = 3.4$ Hz), indicates an α-configuration at the anomeric center.[5a] The ^{13}C NMR signal observed at $\delta = 103.6$ ppm was assigned to the anomeric carbon based on HMQC (heteronuclear multiple quantum coherence) analysis. The chemical shift of the anomeric carbon indicated that the triflate oxygen was bound covalently to the anomeric carbon.



Scheme 1. Electrochemical generation of glycosyl triflate.

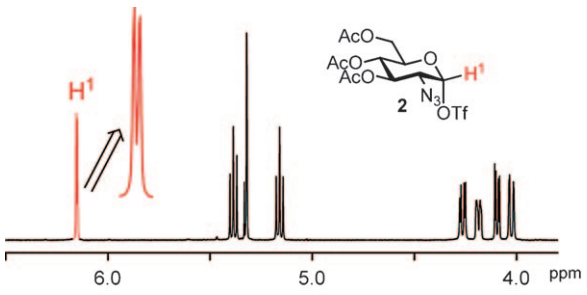
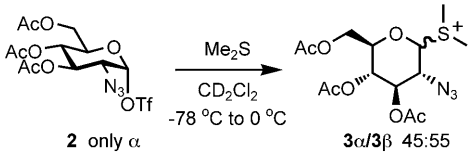


Figure 1. ^1H NMR spectrum of the glycosyl triflate **2** (600 MHz, CD_2Cl_2, −80 °C).

The conversion of glycosyl triflate **2** to the glycosyl sulfonium ion was performed by addition of Me_2S (5 equiv) to a solution of **2** at −78 °C followed by raising the temperature to 0 °C (Scheme 2). Signals from two novel species appeared at the expense of signals of **2** at −60 °C (Figure 2). The spe-



Scheme 2. Generation of glycosyl sulfonium ions by the action of glycosyl triflate with dimethyl disulfide.

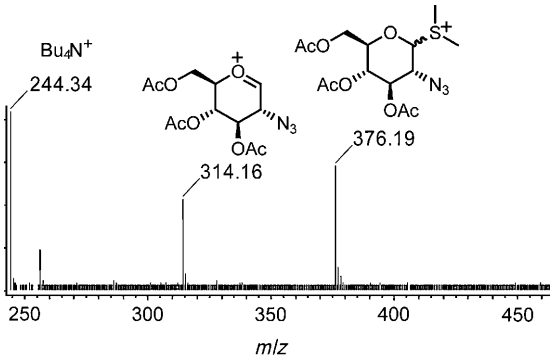


Figure 3. Cold-spray mass spectra of glycosyl sulfonium ions **3α/3β**. (spray temperature 0 °C).

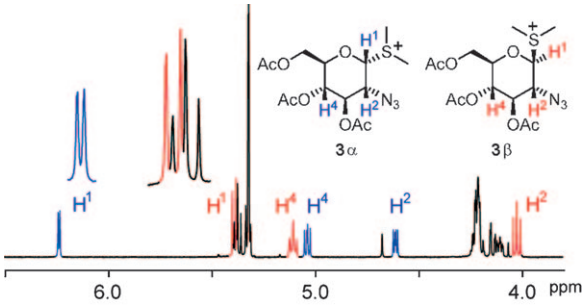
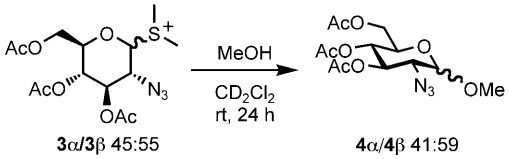


Figure 2. ^{1}H NMR spectra of the glycosyl sulfonium ions **3α/3β** (600 MHz, CD_2Cl_2, 0 °C). The blue peaks indicate H-1, H-2, and H-4 of the α-glycosyl sulfonium ion **3α**. The red peaks indicate H-1, H-2, and H-4 of the β-glycosyl sulfonium ion **3β**.

cies that exhibited a signal from the anomeric proton at $\delta =$ 6.27 ppm (d, $J = 4.8$ Hz) was assigned to the α-glycosyl sulfonium ion **3α** based on the NOE (nuclear Overhauser effect) correlation between H-1 and H-2 (3.3 %). HMBC (heteronuclear multiple-bond connectivity) analysis and the NOE correlation between H-1 and the methyl protons of Me_2S indicate the presence of a covalent bond between the anomeric carbon and sulfur. The larger coupling constant of the anomeric proton ($J = 4.8$ Hz) and the relatively small coupling constant between H-3 and H-4 ($J = 6.9$ Hz) suggested that the pyranose ring conformation was distorted. To the best of our knowledge, this is the first observation of an α-glycosyl sulfonium ion. The species that exhibited a signal from the anomeric proton at $\delta = 5.43$ ppm (d, $J = 10.3$ Hz) was assigned to the β-glycosyl sulfonium ion **3β**.[3a] A cold-spray mass spectrum of the mixture showed two major peaks (Figure 3). The first peak was assigned to the glycosyl cation (*m*/*z* calcd for $C_{12}H_{16}N_3O_3$: 314.10; found: 314.16), and the second peak was assigned to the glycosyl sulfonium ion (*m*/*z* calcd for $C_{14}H_{22}N_3O_7S$: 376.12; found: 376.19). The glycosyl cation seemed to be produced by fragmentation of the glycosyl sulfonium ion in the mass spectrometer, because it was not observed by NMR spectroscopy.

It is known that a cationic substituent such as Me_2S^+ at an anomeric center prefers to occupy the equatorial position.[1,9] Therefore, **3α** seems to be less stable than **3β**. In fact, molecular orbital calculations (HF/6-31G*) indicated that **3α** is distorted from the chair conformation and 3.2 kcal mol^{-1} less stable than **3β** (see the Supporting Information). However, in the present case, **3α** was produced in a significant amount (**3α/3β** 45:55). The α/β ratio did not change on varying the temperature (−80 °C to 0 °C). Based on these arguments, it seems to be reasonable to consider that the observed stereoselectivity is based on kinetics in the present case.

Next, the reactivities of glycosyl sulfonium ions **3α** and **3β** were investigated (Scheme 3). When MeOH (5 equiv)



Scheme 3. Glycosylation of the glycosyl sulfonium ion **3α/3β** with MeOH.

was added to a solution of **3α** and **3β** at room temperature, only **3α** was consumed after 1 h (Figure 4). At this stage, methyl glycosides **4α** and **4β** were produced in the ratio of 40:60.[10] After consumption of **3α**, **3β** began to react with MeOH. Eventually, both **3α** and **3β** were consumed, and methyl glycosides **4α** and **4β** were produced in the ratio of 41:59 after 24 h. The present time-course NMR study clearly shows higher reactivity of **3α** than **3β**. The stereochemical outcome cannot be explained by a simple S_N2 displacement at the anomeric carbon atom. Rather, the reaction may proceed by intermediacy of a glycosyl cation.[11] If we assume such a mechanism, the higher reactivity of **3α** can be explained by the relative stability of **3α** and **3β**, because the energy required for ionization of less stable **3α** should be smaller than that for more stable **3β**.

It is also noteworthy that the **4α/4β** ratio observed for the glycosylation of glycosyl sulfonium ions **3α** and **3β** with MeOH is different from that observed for the glycosylation

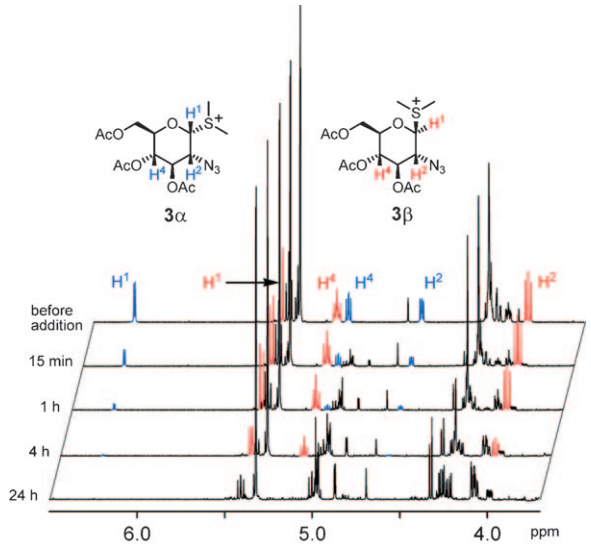


Figure 4. The time-course ^{1}H NMR spectra of the reaction between the glycosyl sulfonium ions **3α/3β** and MeOH (600 MHz, CD_2Cl_2, room temperature). The blue peaks indicate H-1, H-2, and H-4 of the α-glycosyl sulfonium ion **3α**. The red peaks indicate H-1, H-2, and H-4 of the β-glycosyl sulfonium ion **3β**.

of glycosyl triflate **2** (**4α/4β** 13:87).[8] On the other hand, the reaction may proceed by a contact ion pair (CIP) mechanism[11a] or an S_N2 like mechanism in the case of the glycosylation of glycosyl triflate **2**, although more data should be accumulated before the elucidation of a detailed mechanism.

In conclusion, both α- and β-glycosyl sulfonium ions were successfully produced from an electrochemically generated glycosyl triflate and were characterized by NMR spectroscopy and mass spectrometry. The time-course NMR study for the reaction with MeOH clearly revealed that the α-glycosyl sulfonium ion is more reactive than the β-glycosyl sulfonium ion. The stereochemical outcome indicates that the reaction does not proceed by a simple S_N2 mechanism. Rather, the reaction seems to proceed via an glycosyl cation intermediate. We believe that the present observations will make a significant contribution to mechanistic studies on glycosylation reactions. Further work aimed at the elucidation of the stereochemistry and reactivity of various glycosyl sulfonium ions is currently in progress.

Experimental Section

The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode and a platinum plate cathode. In the anodic chamber were placed the thioglycoside **1** (43.4 mg, 0.0992 mmol) and 0.1 M Bu_4NOTf in CD_2Cl_2 (5.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (22 μL, 0.25 mmol) and 0.1 M Bu_4NOTf in CD_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at −78 °C with magnetic stirring. After 1.5 F mol^{-1} of electricity was consumed, the reaction mixture in the anodic chamber was transferred to a 5 mm NMR tube with a septum cap under an argon atmosphere at −78 °C. After the NMR measurement of triflate **2**, dimethyl sulfide (5 μL, 0.05 mmol) was added under an argon atmosphere at −78 °C. The NMR measurement, which was carried out at various temperatures (from −80 °C to 0 °C), indicated that **2** was converted to glycosyl sulfonium ions as a mixture of α- and β-isomers (**3α/3β** 45:55). The reaction mixture was warmed to room temperature and then MeOH (2 μL, 0.05 mmol) was added under an argon atmosphere. During the NMR measurement, which was carried out at room temperature for 1 day, the glycosyl sulfonium ion **3α** and **3β** was converted to a mixture of α- and β-isomers of the methyl glycoside (**4α/4β** 41:59).

(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl)dimethylsulfonium ion (3α): Selected data for **3α** (6.5–2.9 ppm for ^{1}H NMR at 0 °C, 100–55 ppm for ^{13}C NMR at −40 °C). ^{1}H NMR (CD_2Cl_2, 600 MHz): δ = 6.26 (d, J = 4.8 Hz, 1H, H-1), 5.33 (dd, J = 8.3, 6.9 Hz, 1H, H-3), 5.04 (dd, J = 7.6, 6.9 Hz, 1H, H-4), 4.62 (dd, J = 7.6, 4.8 Hz, 1H, H-2), 4.24–4.21 (m, 1H, H-6), 4.16 (dd, J = 12.4, 2.0 Hz, 1H, H-6′), 4.13–4.11 (m, 1H, H-5), 3.16 (s, 3H, SCH_3), 2.94 ppm (s, 3H, SCH_3); ^{13}C NMR (CD_2Cl_2, 150 MHz): δ = 90.0 (C-1), 73.9 (C-5), 70.5 (C-3), 66.3 (C-4), 61.6 (C-6), 58.5 ppm (C-2).

(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranosyl) dimethylsulfonium ion (3β): Selected data for **3β** (6.5–2.9 ppm for ^{1}H NMR at 0 °C, 100–55 ppm for ^{13}C NMR at −40 °C). ^{1}H NMR (CD_2Cl_2, 600 MHz): δ = 5.42 (d, J = 10.3 Hz, 1H, H-1), 5.38 (pseudo t, J = 9.6 Hz, 1H, H-3), 5.12–5.09 (m, 1H, H-4), 4.24–4.21 (m, 3H), 4.02 (dd, J = 10.3, 9.6 Hz, 1H, H-2), 3.10 (s, 3H, SCH_3), 2.96 ppm (s, 3H, SCH_3); ^{13}C NMR (CD_2Cl_2, 150 MHz): δ = 81.4 (C-1), 76.7 (C-5), 73.9 (C-3), 66.5 (C-4), 60.7 (C-6), 58.6 ppm (C-2); LRMS (CS): m/z: calcd for $C_{14}H_{22}N_3O_7S$ $[M]^+$, 376.12; found, 376.19. Further details are given in the Supporting Information.

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Keywords: carbohydrates · glycosylation · NMR spectroscopy · oxidation · stereochemistry

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[8] After addition of MeOH (5 equiv) to a solution of glycosyl triflate **2**, the corresponding methyl glycoside **4** was obtained in 88% yield (**4α**/**4β** 13:87).

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