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Origins of Selectivity in Glycosylation Reactions with Saccharosamine Donors

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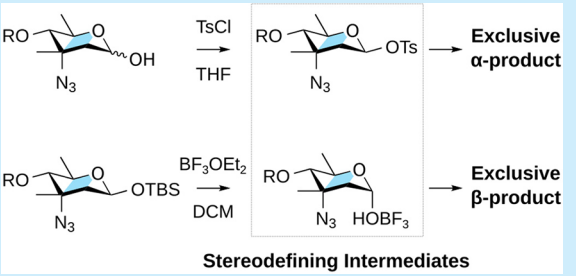
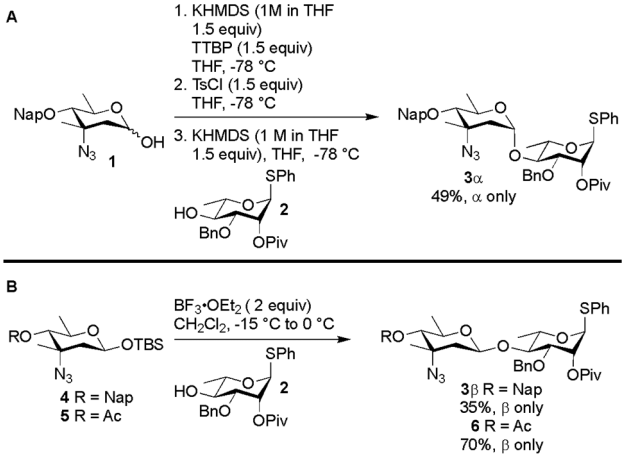
ABSTRACT: A combination of DFT calculations and experiments is used to describe how the selection of a promoter can control the stereochemical outcome of glycosylation reactions with the deoxy sugar saccharosamine. Depending on the promoter, either α- or β-linked reactive intermediates are formed. These studies show that differential modes of activation lead to the formation of distinct intermediates that undergo highly selective reactions through an S_N2-like mechanism.



Many natural products possess glycans composed of deoxy sugars, which are critical for their biological activity.[1] Importantly, the introduction on non-native sugars into natural products can modulate their activity through increasing potency or mitigating toxicity.[2] Thus, glycodiversification, where a natural product is obtained through fermentation and its sugar components are modified, represents an attractive prospect for the discovery of new therapeutics. A significant hurdle to the wider adoption of glycodiversification using deoxy sugars lies in the fact that controlling the diastereoselectivity in glycosylation reactions with these substrates is extremely challenging.[3] This is especially true in the context of substrates possessing multiple sites of deoxygenation, unusual configurations, or the addition of heteroatoms other than oxygen. While this situation has spurred a number of elegant methods for selective direct synthesis of both α- and β-linked deoxy sugars, general solutions for controlling selectivity in reactions with these compounds have yet to arise.[4] Such a situation could be remediated through a better understanding of the factors controlling the selectivity in these reactions. Here we describe studies directed at elucidating the mechanisms of selectivity in glycosylation reactions using 2,3,6-trideoxy-3-methyl-3-amino sugar saccharosamine (Sac). This sugar undergoes both highly α- and β-selective glycosylation reactions, where the selectivity is controlled entirely by the mode of activation.

Recently, one of our laboratories had the need to synthesize β-linked saccharosamine as part of a larger campaign directed at the total synthesis of the heptadecasaccharide antibiotic saccharomicin B.[5] Our initial approach to controlling selectivity in this glycosylation reaction was to use our sulfonate-mediated dehydrative glycosylation reaction.[6] We chose this reaction because this chemistry had produced products with very high to exclusive levels of β-selectivity through S_N2-like displacement of an α-linked sulfonate, with other substrates studied in our lab. Surprisingly, when saccharosamine **1** was activated with tosyl chloride and KHMDS at low temperature, followed by treatment with acceptor **2**, compound **3α** was formed exclusively as the α-anomer (Scheme 1). Despite several attempts at optimization, we were unable to reverse the selectivity of the reaction. In an

Scheme 1. Effects of Sulfonate-Mediated Glycosylation (A) and OTBS Glycoside Activation (B) on the Stereochemical Outcome of Glycosylation Reactions with Saccharosamine



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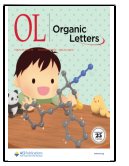

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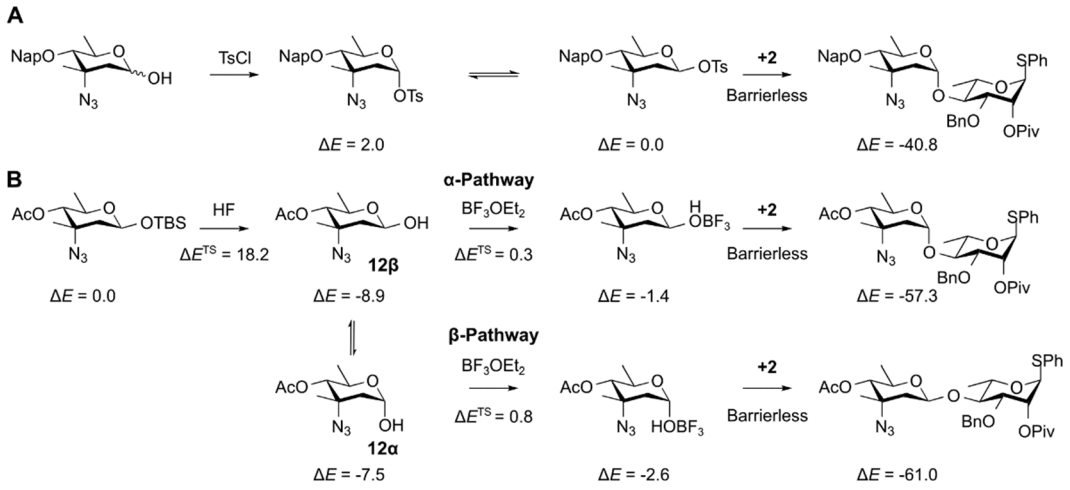

Figure 1. Proposed mechanisms for the reactions depicted in Scheme 1 with relative energies, ΔE, in kcal mol^{-1} obtained through DFT and the PCM solvation model.

attempt to obtain the desired β-linked product we screened several other glycosylation reactions.[7] Just as surprising we found that the selectivity in the reaction could be reversed through conversion of **1** to the anomeric *O*-TBS ether **4** followed by activation with $BF_3{\cdot}OEt_3$ to afford the β-linked product **3*β*** exclusively.[8] This selectivity was independent of the protecting group on the sole alcohol of the molecule, and changing the Nap protecting group to an acetate resulted in an increase in yield with no change in selectivity.

While we were satisfied with the outcome with these conditions, it was confusing how such simple changes could lead to a complete reversal in selectivity of this reaction. In the case of the sulfonate chemistry, previous work from our lab and others had shown that the glycosyl sulfonates preferentially adopt an α-configuration at the anomeric center. While we could not rule out the intermediacy of a glycosyl cation, such a situation was deemed unlikely as the observed high level of selectivity would not be expected based off models for addition oxocarbenium ions.[9] Furthermore, the β-specificity we observed with the *O*-TBS glycoside also did not fit with the established stereoelectronic models of addition to oxocarbenium cations. These observations led us to consider that the selectivities could be the result of two different modes of S_N2 displacement.[10]

In order to obtain a better picture of what was going on in our reaction, we turned to DFT calculations. We performed geometry optimization and transition state searches using Gaussian16[11] at the PBE1PBE+D3/6-311+G(d,p) level of theory and with the PCM solvation model.[12−14] The presented energies represent the relative changes in energetics of the reaction species along the reaction profile but do not include factors such as availability and concentration of the reagents. The functional had been performing reliably in conformational and reactivity studies of glycans.[15] Due to convergence problems of this transition state using the PCM solvent model, the energy of this step was obtained by optimizing the gas phase structure and adding single-point solvent corrections. Because the energy of this transition state is lower than that of the individual reactants, we defined this reaction step as barrierless.

For the glycosyl tosylate chemistry, calculations showed that the β-linked tosylate was favored over the α-tosylate by a ΔE value of 2.0 kcal mol^{-1} (Figure 1A). Both tosylates then react with deprotonated acceptor **2** in a barrierless step. Therefore, the DFT calculations confirm that **1** yields the α-linked product through the S_N2-displacement of the β-linked sulfonate intermediate, which is significantly more stable among two anomers of the tosylate intermediate.

Ascertaining the cause of selectivity in OTBS glycoside activation was less straightforward. As noted above, we ruled out a glycosyl cation because the selectivity did not fit into established stereoelectronic models for addition (Figure 2).

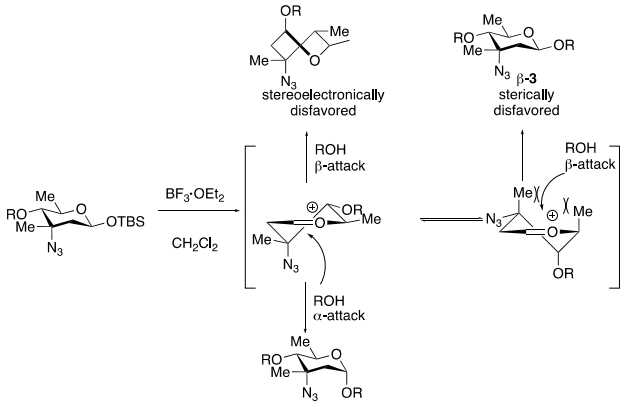

Figure 2. Established modes of addition to oxocarbenium cations do not account for the observed β-specific glycosylation upon activation of *O*-TBS glycosides with $BF_3{\cdot}OEt_2$.

Moreover, non-half-chair intermediates were found to be unstable during DFT optimizations and always converged to the models shown in the figure. In order to gain a better picture of what was happening, we first ran a series of experiments to help identify potential intermediates (Scheme 2). We initially varied the protecting groups on both the donor and acceptor to examine armed/disarmed effects on the reaction.[16] As a baseline we examined the reaction between **5** and **7**, which had been previously described in our efforts toward saccharomicin A.[5a] This reaction consistently afforded the desired β-linked **8** as the only product, regardless of the amount of promoter used in the reaction. When **5** was replaced with armed donor **4** we again only observed the β-linked product **9**, albeit in a greatly reduced yield consistent with our previous observations. Finally using acceptor **10** possessing

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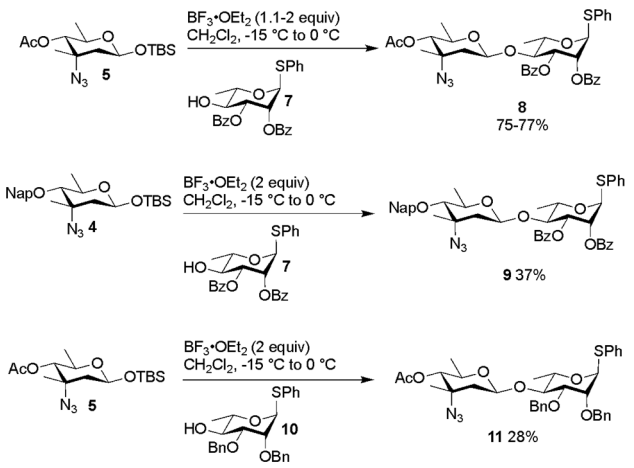
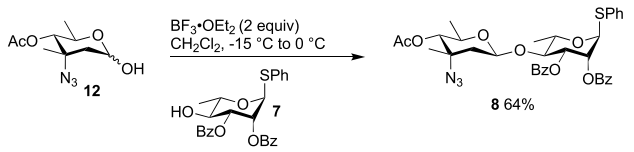
Scheme 2. Effect of Protecting Groups on Glycosylation



arming protecting groups in place of **7** again led to formation of the β-linked product **11** along with a number of decomposition products arising from intramolecular aglycone transfer.[17] Importantly we were unable to detect any α-linked product.

Having established that the protecting groups on the coupling partners were not affecting the outcome of the reaction, we next turned our attention to examining how putative intermediates performed under the reaction conditions (Scheme 3). Noting that $BF_3{\cdot}OEt_2$ can deprotect *O*-

Scheme 3. Activation of Hemiacetal with $BF_3{\cdot}OEt_2$



TBS ethers,[18] we chose to examine hemiacetal **12** in the reaction. Pleasingly, we were able to obtain the product as a single β-linked isomer, albeit in a slightly attenuated yield. With this information in hand, we again turned to DFT to further inform on the reaction. Herein, the calculations have been carried out using the same level of theory as the previous reaction. The optimization of the transition state of the attack by the deprotonated nucleophile **2** in PCM required adding one explicit DCM molecule, which was then included in the overall reaction balance.[19] Because the energy of this transition state is again lower than that of the individual reactants, we marked this reaction as barrierless.

First, we discarded the mechanism where $BF_3{\cdot}OEt_2$ directly attaches to the *O*-TBS of donor **5** (Figure S1). Here, the reaction leads to the formation of F-TBS and a glycosyl donor with an $-OBF_2$ moiety attached to the anomeric carbon. Although the predicted transition state energy, ΔE^{TS}, of 19.9 kcal mol^{-1} is comparable with the mechanisms discussed later, we found that the $-OBF_2$ moiety is a very poor leaving group, and even activation with another BF_3 yields a highly unstable intermediate (ΔE > 30 kcal mol^{-1}). Thus, we explored alternative reaction paths.

Next, we considered the deprotection of *O*-TBS by a HF molecule, putatively generated by decomposition of BF_3, to form a hemiacetal **12*β*** and a stable F-TBS.[20] These products are favored by 8.9 kcal mol^{-1} over the reagents (Figure 1B). The deprotection of **5** to form a β-hemiacetal requires crossing a ΔE^{TS} of 18.2 kcal mol^{-1}. The hemiacetal **12*β*** can then undergo anomerization, although DFT calculations predict that the β-anomer is more stable than the α-anomer by a ΔE value of 1.4 kcal mol^{-1}. The hydroxyl group can then be activated by a transfer of BF_3 from $BF_3{\cdot}OEt_2$.[21] Importantly, the attachment of the BF_3 to the less stable α-anomer has an activation energy E_a (defined as $E_a = \Delta E^{TS} - \Delta E$) of 8.3 kcal mol^{-1}, which is lower that the E_a value of 9.2 kcal mol^{-1} for the reaction with the β-anomer. This suggests that the reaction follows the Curtin–Hammet principle where a less stable intermediate gives better access to the transition state (Figure 3).[22] The BF_3-adduct of the α-anomer is also more stable by

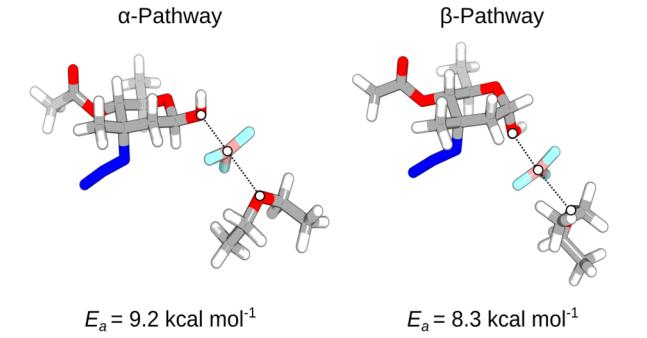


Figure 3. Activation energy, E_a, is defined as the energy difference between the transition state and the preceding intermediate, $\Delta E^{TS} - \Delta E$, for the two competing pathways. Despite being more stable by 1.4 kcal mol^{-1}, the β-intermediate (left) must overcome a larger E_a of 9.2 kcal mol^{-1} than the 8.3 kcal mol^{-1} needed for the α-intermediate (right). Hence the β-pathway is preferred.

1.2 kcal mol^{-1} in comparison to the β-anomer. Next, the activated α-anomer **12*α*** will then undergo an S_N2 reaction with deprotonated acceptor **2** to form product **3*β*** in a barrierless process. Therefore, the DFT suggests that the β-selectivity of the *O*-TBS ethers is afforded by the anomerization of the deprotected hemiacetal **12*β***, which opens the pathway leading to the β-product.

In conclusion, using DFT calculations, we have shed insight into the apparent aberrant behavior of saccharosamine donors under different activation conditions. Using *O*-alkylation to activate the saccharosamine hemiacetal under basic conditions leads to the formation of a β-linked sulfonate, which undergoes displacement to afford α-linked products. Conversely, activating either the same hemiacetal or the corresponding β-linked anomeric TBS ether using Lewis acidic conditions leads to the formation of β-linked products through the intermediacy of an α-linked OBF_3 leaving group. In both cases, DFT predicts that the stereochemical outcome of the reaction is the result of the formation of different reactive intermediates as a result of different modes of activation. These studies lend support to the growing notion that it is important to consider the nature of the active intermediate, and hence the selection of the promoter, in chemical glycosylation reactions. In light of growing evidence that glycosylation reactions proceed through S_N2-like manifolds,[23] we anticipate that such information will be useful in future efforts to develop stereoselective glycosylation reactions.

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■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03607.

Experimental details, characterization data (^{1}H NMR, ^{13}C NMR, 2-D NMR spectral data), and *xyz* structures of intermediates and transition states (PDF)

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Notes

The authors declare no competing financial interest.

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