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Concerning the Origin of the High β-Selectivity of Glycosidation Reactions of 2-Deoxy-2-iodo-glucopyranosyl Trichloroacetimidates

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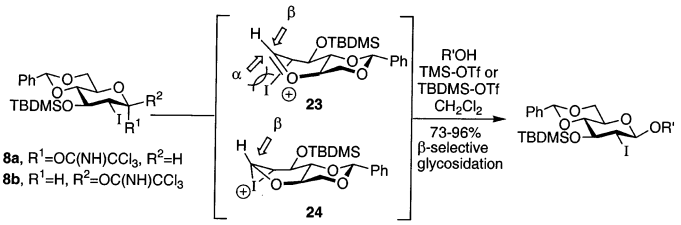
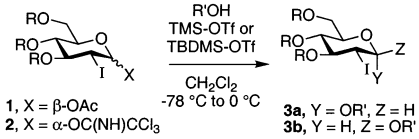
ABSTRACT



Studies on the glycosidation reactions of conformationally constrained glycosyl imidates 8a and 8b were performed to evaluate the possible involvement of "conformationally inverted" oxonium ion intermediates in glycosidation reactions with 2-deoxy-2-iodo-glucopyranosyl donors. The mechanistic implications of this study are discussed, and intermediates 23 and 24 are invoked to rationalize the observed β-selectivities.

We have previously reported several studies on the stereoselective synthesis of 2-deoxy-β-glycosides, which are important structural components of many natural products.[1−4] Readily accessible glycal precursors were elaborated to glycosyl donors with equatorial C(2) heteroatom substituents (−SePh, −SPh, −Br, and −I), which are removed reductively following glycosidation.[5] While initial work with 2-thiophenyl- and 2-selenophenyl-glucopyranosyl donors indicated that selectivity was highly substrate dependent,[1] the 2-iodo substituent was later found to be an excellent and considerably more general stereodirecting group. Thus, glycosidations employing 2-deoxy-2-iodo-β-D-glucopyranosyl acetates (**1**)[2] or 2-deoxy-2-iodo-α-D-glucopyranosyl trichloroacetimidates (**2**)[3] as the glycosyl donors proceeded with excellent β-stereoselectivities (in most cases, ≥19:1) in CH_2Cl_2 using either TMS−OTf or TBDMS−OTf as the promoter (Scheme 1). During the course of the studies with

Scheme 1



2-deoxy-2-iodo-glucopyranosyl acetates, it was noted that the reactivity was highly dependent on the conformational preference of the donor ground state and, thus, the combination of protecting groups of the glycosyl donor. In general, comparably substituted donors that exist in twist boat ground state conformations underwent glycosidations at lower temperatures than those in the normal chair conformation. This led us to consider the possibility that conformationally

(1) (a) Roush, W. R.; Sebesta, D.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825. (b) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837 and references therein.
(2) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541.
(3) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891.
(4) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124.
(5) Approaches to the synthesis of 2-deoxy-β-glycosides have been reviewed: (a) Castro-Palomino, J. C.; Schmidt, R. R. *Synlett* **1998**, 501. (b) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385.

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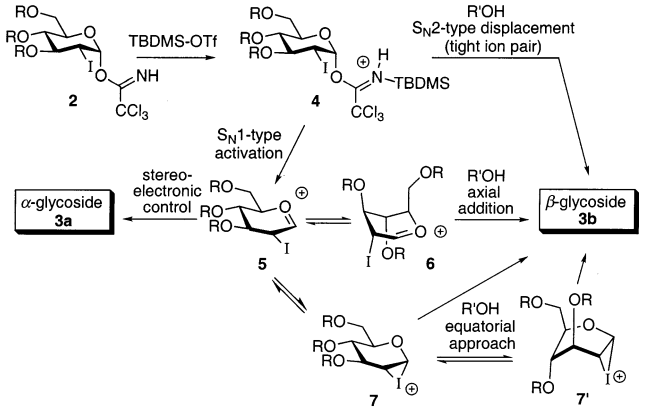
inverted intermediates represented by **6** might be kinetically significant reaction intermediates (Scheme 2).[1]

Scheme 2. Mechanistic Pathways for Glycosidation Reactions with 2-Deoxy-2-iodo-glucopyranosyl Trichloroacetimidates (**2**)

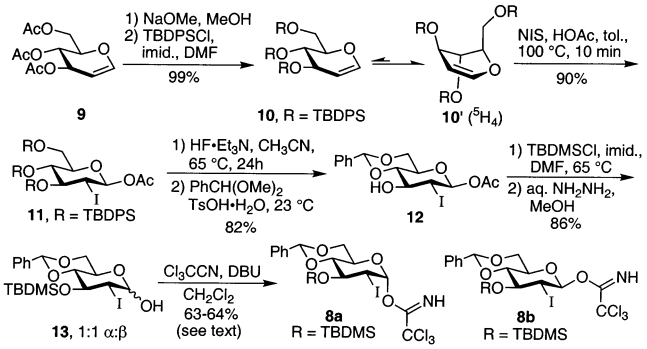


Considering the likely pathways outlined in Scheme 2, oxonium ion **5** can arise from the decomposition of intermediate **4**, upon activation of imidate **2** with TMS−OTf or TBDMS−OTf. If **5** were an important reaction intermediate, one would expect a significant amount of α-glycoside products to be formed by stereoelectronically favored axial addition. However, this outcome is not consistent with our findings. To rationalize the observed highly favored *β*-face approach of the acceptor, we speculated that the reaction might operate by way of a conformationally inverted oxonium ion **6**.[1] Axial approach of an acceptor to **6** should then be stereoelectronically favored, due to a resultant anomeric effect as well as a Felkin−Anh-type stabilization of the developing C−O bond (overlap with the *σ** orbital of the adjacent C−I bond in the transition state). A subsequent report by Woerpel's group on the involvement of pseudoaxial conformers in the nucleophilic substitution of heteroatom-substituted pyranyl oxonium ions lends support to the possible involvement of intermediate **6**.[6] In addition, Bowen's group has reported molecular mechanics calculations that suggest that six-membered ring oxonium ions prefer to adopt conformations in which hydroxyl groups at C3 and C4 occupy pseudoaxial positions in the half-chair conformation.[7]

To investigate the possible involvement of oxonium ion **6** as a stereodetermining intermediate in the glycosidation reactions of 2-iodoglycosyl donors of general structures **1** and **2**, we targeted constrained glycosyl imidate **8**, in which the 4,6-*O*-benzylidene acetal renders conformationally inverted oxonium ion **6** inaccessible. We also considered that the *β*-glucosides might arise from displacement of **4** by an acceptor in an S$_N$2-like manner or via substitution of a tightly solvated ion pair, as well as a pathway that involves iodonium ion **7**, where participation of the C-2 iodo substituent would direct *β*-face approach of the alcohol.[8] We herein report the stereochemical outcome of glycosidation reactions of imidate **8** and the mechanistic implications of these results.

Imidate **8** was prepared from tri-*O*-acetyl-D-glucal **9** as summarized in Scheme 3. Deacetylation of **9** and reprotection

Scheme 3. Synthesis of Imidates **8a**,**b**



of the triol with the sterically bulky *tert*-butyldiphenylsilyl groups afforded glycal **10**,[9] in which the $^5H_4$ ground state conformation (**10′**) is predominant.[10] We were aware that the iodoacetoxylation of glycals in the $^5H_4$ conformation proceeds with high stereoselectivity in favor of the gluco isomer.[11] Accordingly, treatment of glycal **10** with NIS in HOAc provided iodoacetate **11** in a ca. 14:1 ratio of *β*-gluco: α-manno isomers. The *β*-gluco anomer was isolated in 90% yield and desilylated using HF•Et$_3$N to provide the triol, which was subsequently treated with benzaldehyde dimethyl acetal in the presence of catalytic TsOH•H$_2$O to afford the 4,6-*O*-benzylidene acetal **12** in 82% yield over two steps. Silylation of **12** using TBDMS−Cl followed by deacetylation of the anomeric acetate using aqueous hydrazine in methanol led to hemiacetal **13**, which exists as a 1:1 ratio of α:*β* anomers.

Synthesis of the trichloroacetimidates **8a**,**b** was achieved by treatment of hemiacetal **13** with CCl$_3$CN in CH$_2$Cl$_2$ at 0 °C in the presence of catalytic DBU.[12] Under these conditions, α-imidate **8a** was the major product, isolated in 54% yield, while *β*-imidate **8b** was formed in 10% yield. On the other hand, when trichloroacetonitrile was used as the reaction solvent, *β*-imidate **8b** was isolated as the major product in 50% yield, while α-imidate **8a** was obtained in 13% yield.[13]

Glycosidation reactions were performed by addition of catalytic TBDMS−OTf (0.2−0.4 equiv) to a precooled

(6) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168.

(7) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859. This has been attributed to an electrostatic stabilization.

(8) In the latter scenario, the transition state for substitution of **7** should likely resemble the kinetically disfavored boatlike conformation (**7′**), as this represents a formal diequatorial opening of the iodonium ion.

(9) Friesen, R. W.; Sturino, C. F.; Dalijeet, A. K.; Kolaczewska, A. *J. Org. Chem.* **1991**, *56*, 1944.

(10) The $^5H_4$ conformation minimizes gauche interactions. This is evident from ^{1}H NMR analyses of **10**, consistent with our previous work as well as that of McDonald's group. See refs 1, 2, and 11.

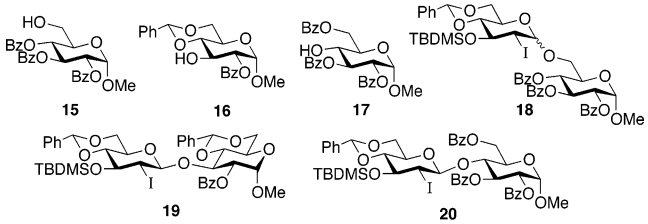
(11) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4303.

(12) Use of NaH as a base led to lower isolated yields.

(13) In both cases, a small amount of α-manno imidate **14** was also formed, presumably due to the base-catalyzed epimerization at C(2) via the ring-opened aldehyde. See ref 5.

solution of imidate **8a** or **8b** and acceptor in CH_2Cl_2 in the presence of 4 Å molecular sieves. Glycosidations of acceptors **15**−**17** with 4,6-*O*-benzylidene glucopyranosyl α-imidate **8a** afforded disaccharides **18**, **19** and **20** in 89, 76, and 86% yields, respectively, and with high *β*-selectivities (Table 1,

Table 1. Glycosidations of Acceptors with Imidates **8a**,**b**



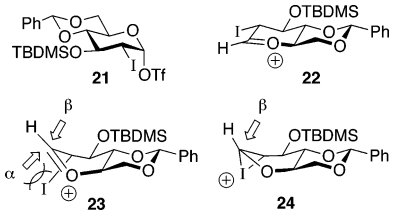
entry	acceptor	donor	conditions[a]	product	yield (%)	*β*:α ratio[b]
1	**15**	**8a**	−78 °C, 1 h	**18**	89	87:13
2	**16**	**8a**	−78 °C, 2 h	**19**	76	*β* only
3	**17**	**8a**	−40 °C, 2 h	**20**	86	*β* only
4	**15**	**8b**	−78 °C, 1 h	**18**	92	86:14
5	**17**	**8b**	−40 °C, 2 h	**20**	85	*β* only
6[c]	**15**	**8b**	−78 °C, 1 h[c]	**18**	85	86:14
7[d]	**15**	**8b**	−78 °C, 1 h[d]	**18**	73	86:14
8	**15**	**8a**	rt, 30 min	**18**	96	93:7
9[e]	**15**	**8b**	−78 °C, 1 h[e]	**18**	79	84:16
10[e]	**15**	**8a**	rt, 30 min[e]	**18**	91	97:3
11[e]	**15**	**8b**	rt, 30 min[e]	**18**	89	96:4

[a] All reactions were performed in CH_2Cl_2 using 0.2−0.4 equiv of TBDMS−OTf in the presence of 4 Å molecular sieves unless indicated otherwise. [b] *β*:α product ratios were determined by ^{1}H NMR analysis of the crude product. [c] Donor was preequilibrated with promoter for 10 min prior to slow introduction of the acceptor. [d] Donor was introduced by slow addition to a preequilibrated solution of acceptor and TBDMS−OTf. [e] Reactions were performed in diethyl ether.

entries 1−3). In the latter two cases, no α-disaccharide was detected. For the less reactive acceptors, longer reaction times (−78 °C, 2 h for **16**) and/or elevated reaction temperatures (−40 °C, 2 h for **17**) were required. The high *β*-selectivity observed in these reactions is comparable to that previously observed for analogous glycosidation reactions of glycosyl imidates lacking the benzylidene acetal.[3] As intermediate **6** is inaccessible for donor **8a**, we looked for an alternative mechanistic rationale for the observed *β*-selectivity.

In light of the documented torsional disarming effect of a 4,6-*O*-benzylidene acetal,[14,15] we considered a scenario in which slow collapse of activated imidate **4** to oxonium **5** might allow S_N2-like displacement by an incoming alcohol to be operative for imidate **8a** but not necessarily for our previously reported conformationally unconstrained 2-deoxy-2-iodo-glucopyranosyl donors. In support of this possibility,

Scheme 4



we noted that in the absence of acceptor, both imidates **8a** and **8b** are recovered stereochemically intact when treated with TMS−OTf or TBDMS−OTf in CH_2Cl_2 at −78 °C, with only trace amounts of the other anomer. Clearly, under these conditions, the anomeric C−O bond of the glycosyl imidate remains either intact or as a tightly associated ion pair that recombines upon workup without significant loss of stereochemistry.

We performed the glycosidations of acceptors **15** and **17** with *β*-imidate **8b** (entries 4 and 5) and observed the same α:*β* product ratios as those found in the reactions with α-imidate **8a** (entries 1 and 3), indicating that both reactions must proceed via a common intermediate that lacks the stereochemical information of the starting imidate. Thus, we ruled out an S_N2-like pathway.[16]

Crich has shown that glycosyl triflates are intermediates in glycosidation reactions that proceed by activation of anomeric sulfoxides and thioglycosides with Tf_2O and PhSOTf, respectively, suggesting that they may also be intermediates in other glycosidation reactions employing triflates as activating reagents.[15] We found that despite the disarming effect of the benzylidene acetal, the order of addition (entries 6 and 7) had no effect on α:*β* product ratios, which suggests that a time-dependent intermediate is not involved.[17] Additionally, although glycosyl triflate **21** may be an intermediate, we discounted it as being stereodetermining on the basis of Crich's reports that the glycosyl triflates derived from 4,6-*O*-benzylidene-protected glucosides gave rise to α-glycosides in the absence of protecting group participation.[18]

Given the conformational constraint of the benzylidene acetal, we rationalized the *β*-selectivity of the glycosidation reactions of **8a** and **8b** by invoking twist boat conformation **23**, in which the pseudoaxial orientation of the iodine substituent sterically disfavors approach of the nucleophile from the α-face (Scheme 4). Note that in this conformation, axial approach to produce the *β*-product should be favored for the same reasons as previously stated for the inverted oxonium **6**. Intermediate **23** approaches the geometry required for the participation of the iodine group, which gives

(14) (a) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434. (b) Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280.

(15) Crich has demonstrated that this torsional effect can strongly influence anomeric selectivities of reactions of 4,6-*O*-benzylidene mannosyl donors: (a) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321. (b) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

(16) At first, this seems to be inconsistent with the observation that the imidates are stereochemically preserved in the presence of just activator. To reconcile this, we speculate that the decomposition of **4** to oxonium **5** occurs rapidly in the presence of an acceptor (possibly due to the presence of TfOH, generated from the promoter after activation of imidate in the presence of acceptor).

(17) The existence of a time-dependent stereodetermining intermediate would most likely change the α:*β* product ratio.

(18) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926.

rise to iodonium ion intermediate **24**.[19] Existing literature examples of β-selective glycosidations using 4,6-*O*-benzylidene donors typically utilize C(2) ester and carbamate participating groups that benefit from facile five-membered ring formation to exert high diastereocontrol on the glycosidations.[20] However, participation of the C(2)-iodo group to give iodonium ion **24** is likely to be more torsionally strained. It is worth noting that it is experimentally difficult to distinguish between intermediates **23** and **24**; however, they are structurally similar, and the reaction pathway could involve either or both of them as stereodetermining intermediates.

Although we believe that conformation **22** is not a major stereodetermining intermediate, on the basis of the observed β-selectivity, we wondered if the α:β ratio might be influenced if **22** were stabilized by performing the glycosidation reaction in diethyl ether. Schmidt has shown that glycosidations performed in diethyl ether as a solvent, using imidate donors containing C(2)-nonparticipating groups, lead to selective α-glycosidation.[21,22] Participation of the solvent from the β-face (due to a reverse anomeric effect) has been proposed as an explanation for the observed α-selectivity.[23] We found no improvement in the α:β ratio (Table 1, entries 9−11) under these conditions, even in reactions performed at room temperature. In fact, the β-selectivity was significantly enhanced when the glycosidations were performed in diethyl ether at room temperature (entries 10 and 11). The equivalent reaction in methylene chloride (entry 8) led us to conclude that this enhancement is predominantly a temperature effect indicating that conformation **23** and/or **24** is thermodynamically preferred relative to **22**. The slight improvement in β-selectivity that is solvent derived (entry 8 vs 10) may be due to coordination of ether at the α-face of **23**.

Interestingly, in this and our previously reported studies of glycosidation reactions with 2-deoxy-2-iodo-glucopyranosyl donors, the less reactive or sterically more hindered acceptors undergo glycosidations with higher β-selectivities than do primary alcohols. In the present system, this can be rationalized using intermediate **23** where the steric requirements of the acceptor should come into play, leading to greater facial discrimination for the more sterically hindered alcohols.

In summary, the use of 4,6-*O*-benzylidene glycosyl imidates gave us some insight into the likely pathway of glycosidation reactions using 2-deoxy-2-iodo-glucopyranosyl donors. Using these conformationally constrained donors, we found that the glycosidations were still highly β-selective. An S_N2-like displacement pathway was discounted because the stereoselectivity of glycosidation was independent of the starting donor configuration. Although this study cannot rule out the possibility of conformationally inverted oxonium ions **6** in the unconstrained donors, it is clear that it is not necessary to invoke them in order to explain the observed β-selectivities. Twist boat conformation **23** and iodonium ion **24** may be invoked to rationalize the β-selectivity of imidates **8a**,**b** and may also apply to the unconstrained 2-deoxy-2-iodo-glucopyranosyl donors.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM 38907) for financial support and the Susan G. Komen Breast Cancer Foundation for a postdoctoral fellowship to P.Y.C. We also thank D. J. Mergott for providing **15**−**17**.

Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) This would be mechanistically similar to the iodoglycosidation reaction of glycals: Seeberger, P. H.; Bilodeau, M. T.; Danishefsky, S. J. *Aldrichimica Acta* **1997**, *30*, 75.

(20) Selected references: (a) Chiesa, M. V.; Schmidt, R. R. *Eur. J. Org. Chem.* **2000**, 3541. (b) Duynstee, H. I.; de Koning, M. C.; Ovaa, H.; van der Marel, G. A.; van Boom, J. H. *Eur. J. Org. Chem.* **1999**, 2623. (c) Aly, M. R. E.; Ibrahim, E. I.; El Ashry, E. H. Schmidt, R. R. *Carbohydr. Res.* **1999**, *316*, 121. (d) Qui, D.; Koganty, R. R. *Tetrahedron Lett.* **1997**, *38*, 45.

(21) Wegmann, B.; Schmidt, R. R. *J. Carbohydr. Chem.* **1987**, *6*, 357.

(22) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

(23) Glycosidations using 2-deoxy-2-azido-4,6-*O*-benzylidene glucopyranosyl trichloroacetimidates in diethyl ether have been shown to proceed with good α-selectivities: (a) Martín-Lomas, M.; Khiar, N.; García, S.; Koessler, J.-L.; Nieto, P. M.; Rademacher, T. W. *Chem. Eur. J.* **2000**, *6*, 3608. (b) Martín-Lomas, M.; Flores-Mosquera, M.; Chiara, J. L. *Eur. J. Org. Chem.* **2000**, 1547.