Organic LETTERS

Letter

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An Update of the Rules for Pyranoside Sulfonate Displacement

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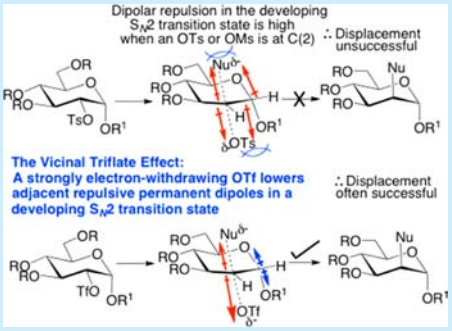
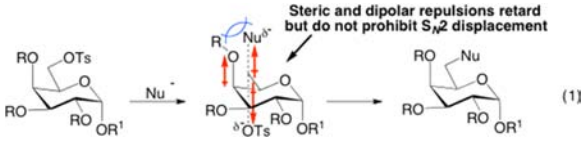
ABSTRACT: The original 1967 Richardson–Hough rules for predicting S_N2 displacement viability in carbohydrate sulfonate derivatives with external nucleophiles have now been updated. Not only do the original rules still hold, but the newly updated rules rationalize why O-triflates (trifluoromethanesulfonate esters) frequently allow many seemingly "disallowed" pyranosidic nucleophilic substitutions to proceed. The new guidelines, which are based on three decades of experimental evidence, allow the feasibility of many pyranosidic O-triflate S_N2 displacements to be gauged beforehand.



In 1967, Richardson and Hough put forward a new stereoelectronic theory for explaining why some carbohydrate alkyl- and aryl-sulfonates undergo S_N2 displacement with great ease and others with great difficulty.[1] The theory paid special attention to the strong *opposing* influence of adjacent *electronegative* C–X groups on the success of many S_N2 alkyl- and aryl-sulfonate displacements, in particular, the fixed permanent dipoles associated with those C–X groups. It was argued that when there is strong repulsive alignment between an adjacent fixed dipole and one of the dipoles of the partially bonded substituents in a developing S_N2 transition state (TS), that such a TS will be markedly disfavored. It was further proposed that this general reluctance to engage in S_N2 displacement will only be further magnified by added steric hindrance around the sulfonate undergoing replacement. These initial ideas were subsequently refined by Richardson into the now famous set of predictive rules[2a] that bear his name, which were further updated by him in 1973,[2b] and reiterated with Hough in a 1979 monograph.[2c]

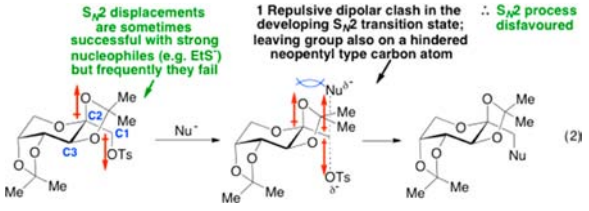
The 1979 Richardson–Hough rules for S_N2 displacement[2c] of carbohydrate OMs and OTs derivatives are summarized as follows:

(i) *Hexopyranose 6-sulfonates*: These will normally undergo nucleophilic displacement readily, except for systems where the O-4 substituent is large, electronegative, and axial, whereupon significant steric hindrance will hamper attainment of the S_N2 TS, as will dipolar repulsion of the partially bonded groups with the C(4)–O(4)-permanent dipole (eq 1). This, along with a significant *syn*-pentane interaction, will often translate into much longer reaction times to obtain a successful outcome.



(1)

(ii) *Hexulopyranose and hexulofuranose 1-sulfonates*: Generally, these will only undergo S_N2 replacement with great difficulty (eq 2), with many such displacements failing altogether unless



(2)

the anionic nucleophile is highly nucleophilic (e.g., EtS^-). The poor reactivity of these systems can be attributed to significant dipolar repulsions arising between the partially bonded substituents of the developing S_N2 TS and the C(2)–O(2)- and C(2)–O(6)-fixed dipoles, as well as significant steric hindrance provided by the C(2)-carbon, which is neopentyl in character.

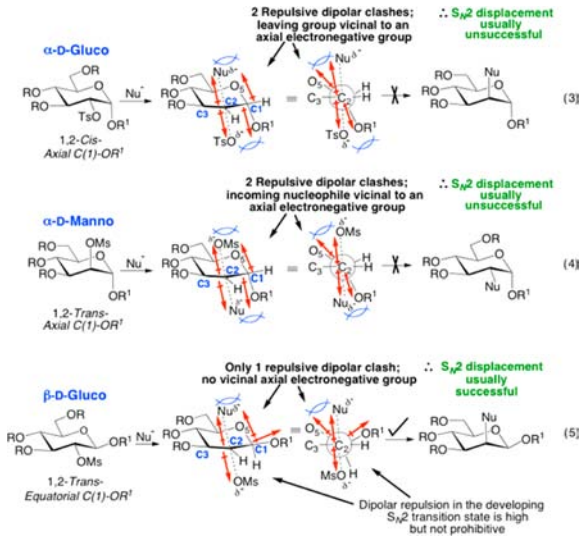
(iii) *Pyranoside 2-sulfonates*: These are normally highly resistant to S_N2 replacement when the C(2)-OTs or -OMs has either a 1,2-*cis*- or 1,2-*trans*-relationship with a ***vicinal axially oriented*** α-glycoside at C(1). Indeed, most such systems either do ***not*** undergo S_N2 displacement (eqs 3 and 4) or only react marginally, giving very low yields of product.

In contrast, pyranoside C(2)-OMs and -OTs derivatives with an equatorial β-glycoside at C(1) often undergo S_N2 displacement with reasonable facility when heated in solvents such as DMF (eq 5).

The generalized examples shown in eqs 3 and 4 are actually illustrative of a more general phenomenon in pyranosidic sulfonate displacement, namely: **the Pyranosidic Vicinal Axial Effect**,[2a] where axial pyranosidic C–X substituents adjacent to the sulfonate usually set up repulsive dipolar alignments as the S_N2 TS

Received: July 24, 2014
Published: September 12, 2014

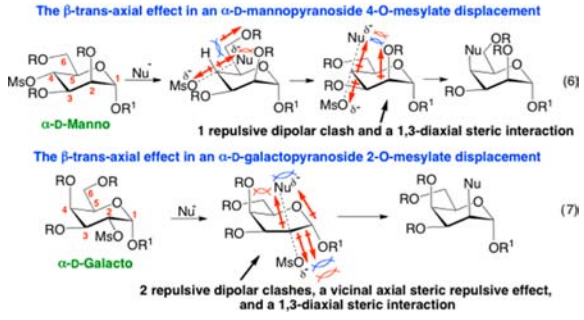
dx.doi.org/10.1021/ol502193j | *Org. Lett.* 2014, 16, 4838–4841



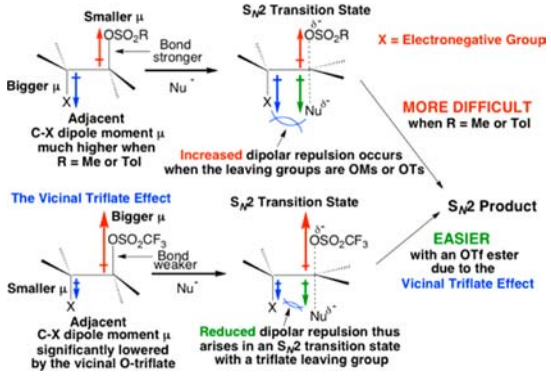
advances, repulsions that often prevent the desired S_N2 reaction from ever occurring. Incoming and outgoing groups also usually experience a much greater degree of steric repulsion when they are stationed next to an axial group.

(iv) *Pyranoside 3- and 4-sulfonates*: While these are often displaced readily, there are two scenarios where marked opposition to attainment of the requisite S_N2 TS occurs: ***(a) when there is a vicinal axial electronegative substituent next to the sulfonate undergoing replacement and (b) when there is a β-trans-axial group relative to the C−OSO$_2$R grouping.***

The Pyranosidic *β*-Trans Axial Effect:[2a] This is observed for pyranosidic 2-, 3-, and 4-O-sulfonates, when a substantially sized electronegative substituent has a *β*-trans-axial relationship with the departing group, and the incoming nucleophile must trace a hindered *endo* path ***over the pyranoside ring*** to displace the sulfonate group. Such displacements are often strongly retarded by the *β*-trans axial group. S_N2 TSs of this sort also often encounter a severe 1,3-diaxial interaction and dipolar repulsion en route to the product, which can further impede S_N2 displacement.



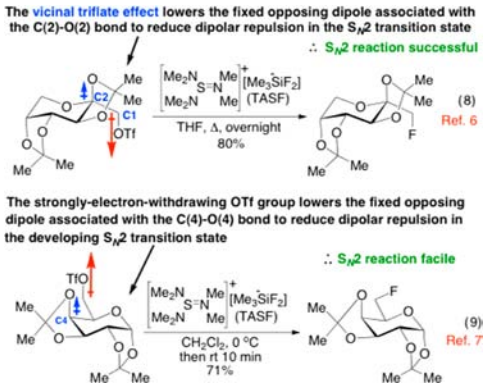
While the 1970s saw no violations to the aforementioned nucleophilic substitution rules, the success of many pyranosidic O-triflate ester displacements[3] has recently led some[4] to question whether the Richardson−Hough displacement rules[1,2] still apply. We contend that they do, and here we update the original rules[1,2] to account for recent observations that have been made with pyranoside O-triflates. *Specifically, we argue that a strongly electron-withdrawing O-triflate will have a massively enhanced ability (~460-fold)[5] to significantly diminish the magnitude of an adjacent, aligned, fixed repulsive C−X dipole in a developing S_N2 TS, most especially when the adjacent X group is a much less electronegative acetal or ether group* (we now term this effect: **the Vicinal Triflate Effect**). This, along with the much weaker C−O bond of a triflate, and the enhanced δ^+ character of the carbon undergoing attack (which makes it more attractive to a nucleophile), will often help to promote triflate S_N2 displacements from pyranosides by external nucleophiles.



We also argue that certain additional strongly electron-withdrawing ester groups vicinal to a C−X bond (e.g., OAc) will, in some instances, enhance this O-triflate C-X dipole-lowering effect, to further counteract some of the opposing dipolar repulsive barriers to attainment of appropriate S_N2 TSs.

The updated rules for predicting anionic S_N2 displacement viability in carbohydrate pyranoid O-triflates are as follows:

(i) Displacements at primary positions are normally successful, even when the −CH$_2$OTf group is neopentylic (e.g., C(1)-triflates of ketoses) (eq 8),[6] or when an axial electronegative C(4)-substituent is also present (e.g., galactopyranosides, gulopyranosides, talopyranosides, idopyranosides, etc.) (e.g., eq 9).[7]



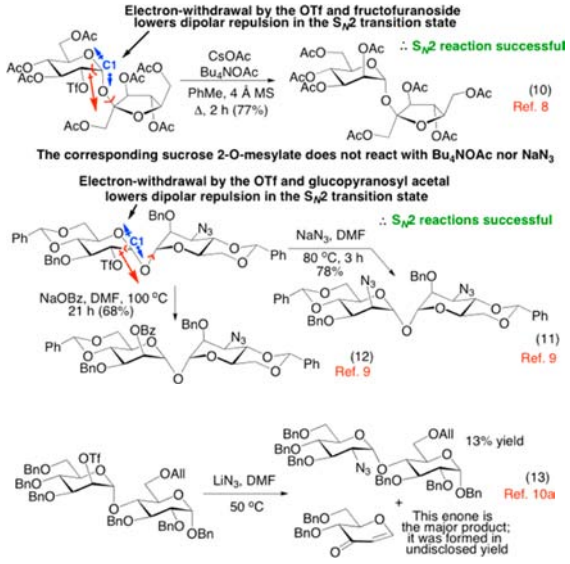
(ii) S_N2 displacements of ***nonreducing*** disaccharide *α*-D-pyranoside O(2)-triflates (e.g., derived from sucrose,[8] *α*,*α*-trehalose,[9] *α*,*β*-trehalose) are normally facile (see eqs 10−12),[8,9] even for basic anions of modest nucleophilicity (e.g., AcO$^-$).

Of the limited data available for *α*-D-pyranoside 2-O-triflates of ***reducing*** disaccharides,[10] the indications are that they perform poorly in S_N2 displacements (eq 13), due to them lacking the *additional* key dipole-lowering C(1)−O(1) acetal feature.

(iii) C(2)−O-Triflate displacements from simple *α*-D-gluco- and manno-pyranose derivatives are most successful when an electron-withdrawing ester (e.g., OAc) is the anomeric group;[11a] the corresponding *β*-D-systems also react successfully,[11b] as do the analogous *β*-D-O(1)-carbonates.[11c]

(iv) Anionic displacements of O(2)-triflates from simple alkyl *α*-D-gluco-,[12a−c] *β*-L-arabino-,[12d] *α*-D-galacto-,[12e] and *α*-D-manno-pyranosides[10b,12f] are frequently difficult, but sometimes succeed with

dx.doi.org/10.1021/ol502193j | Org. Lett. 2014, 16, 4838−4841

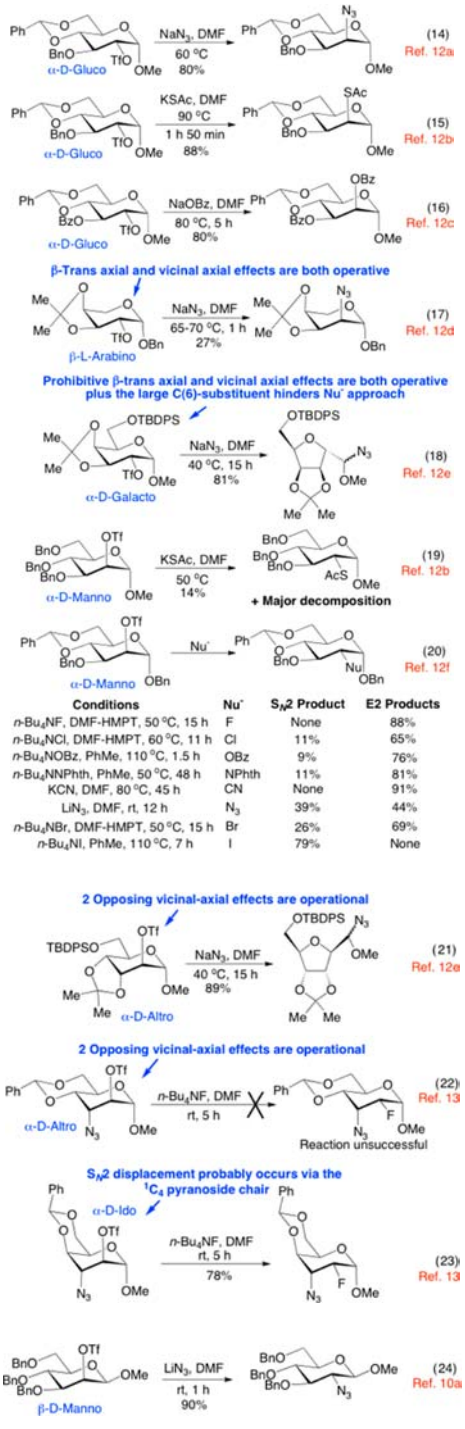


anionic nucleophiles that are "soft", nonbasic, and highly nucleophilic (e.g., I^-, AcS^-, $^-BH_4$, etc.). Less nucleophilic anions of significant basicity (e.g., F^-, Cl^-, Br^-, AcO^-) and higher electronegativity often give rise to poor results in such systems, due to the operation of an opposing C(1)−OR vicinal axial dipolar effect. N_3^- anions sit at the borderline, with a strong tendency to cause competing elimination, most especially in α-D-mannopyranoside systems. When the aforementioned triflates do engage in S_N2 displacement with less nucleophilic anions, they usually do so only in low yield, with accompanying side reactions or even full skeletal rearrangement (see eq 18[12e]). Of the above 2-OTf pyranoside classes, the α-D-glucopyranosides typically give rise to the best results (eqs 14−16), and the β-L-arabino-,[12d] α-D-galacto-,[12e] and α-D-mannopyranosides,[10b,12f] the worst (eqs 17−20), particularly when the O(1)-group is bulky. α- and β-L-fuco-pyranoside 2-O-triflates generally rearrange to 2,5-anhydro sugars when they are subjected to attempted S_N2 displacement.[12g]

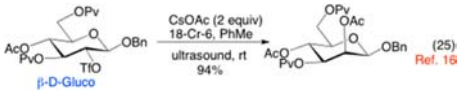
(v) O(2)-Triflates of simple alkyl α-D-altropyranosides are particularly problematical substrates for S_N2 displacement,[12e,13] it being quite common to find that such reactions do not proceed at all (eqs 21 and 22). O(2)-Triflates of alkyl α-D-allopyranosides can likewise be predicted to be disfavorable for S_N2 displacement, particularly when constrained in the $^4C_1$ chair conformation; this will be due to the two opposing vicinal axial effects of the −I groups at C(1) and C(3) (cf. α-D-altropyranosides). However, this prediction has yet to be experimentally confirmed.

Alkyl α-D-idopyranoside 2-O-triflates will undergo displacement,[13] even with poor nucleophiles such as the fluoride ion in DMF (eq 23), provided the C(1)- and C(3)-groups are nonbulky and one of them is strongly electron-withdrawing (e.g., $-N_3$). For such pyranosides, reaction via the alternate $^1C_4$ chair seems most likely.

(vi) Unlike their α-anomers, β-D-mannopyranoside O(2)-triflates are frequently displaced cleanly by nucleophiles that are reasonably nonbasic (eq 24).[10b] Yet, the degree of success often depends upon the correct choice of protecting group at O(3), with bulkier R groups (e.g., Bn) sometimes diminishing S_N2 product yields (cf. β-D-talopyranoside O(2)-triflates, eq 27). If problems are encountered, the use of β-D-1,6-anhydro-manno-2-O-triflates is recommended.[14] Not surprisingly, thiophenyl β-D-mannopyranoside O(2)-triflates are exceptionally good substrates for nucleophilic substitution by most nucleophiles,[15]

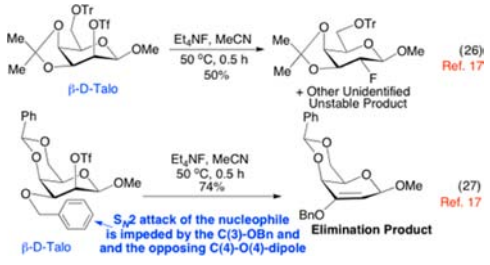


due to their lower C(1)−S(1) dipole moments, and the reduced dipolar repulsions that are encountered in their S_N2 TSs. Indeed, the corresponding thiophenyl β-D-mannopyranoside 2,4-di-O-triflates can even be *selectively* displaced at C(2), due to the prohibitive β-trans-axial effect from the axial O(2)-triflyl group.[15] While the 2-O-triflates of β-D-glucopyranosides are usually displaced readily[16] by anionic nucleophiles (eq 25), their β-D-galactopyranoside 2-O-triflate cousins can be problematical,[12e] due to the contrary workings of the β-trans-axial group at O(4).[2a]



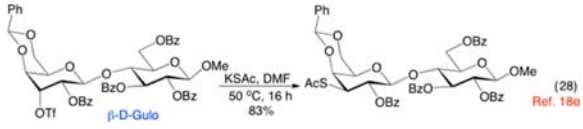
dx.doi.org/10.1021/ol502193j | Org. Lett. 2014, 16, 4838−4841

(vii) Alkyl β-D-talopyranoside O(2)-triflates can be invertively displaced with nucleophiles that include F^-, as long as the O(3) and O(4) atoms are bridged by an O-isopropylidene acetal (eq 26).[17] Yet, as with α- and β-D-mannopyranoside O(2)-triflates, when a



more bulky protecting group is attached to O(3), this can sterically impede the S_N2 approach of nucleophiles to C(2), often making such S_N2 displacements fail (eq 27) or proceed in very low yield. O-Isopropylidenation allows the C(4)−O(4)-bond (and its dipole) to twist away from the pyranoside ring to help lower dipolar repulsions in the developing S_N2 TS.

(viii) 3-O-Triflates of α-D-allo-,[18a] α-D-altro-,[18b] β-D-gluco-,[18a] and β-D-galacto-pyranosides[18c,d] are often readily substituted with inversion by the majority of good nucleophiles (e.g., N_3^-, BH_4^-).[18] For NO_2^- displacements, however, one *equatorial* ester (e.g., OAc) or amide must be adjacent to the 3-OTf.[18c,d] α- and β-D-gulopyranosyl-3-O-triflates will also undergo S_N2 displacements.[18e] The strong vicinal triflate effect of the O(3)-triflate is sufficient to overcome the vicinal axial dipolar repulsion set up by the C(4)-electronegative substituent (eq 28). Yet, when an OBn

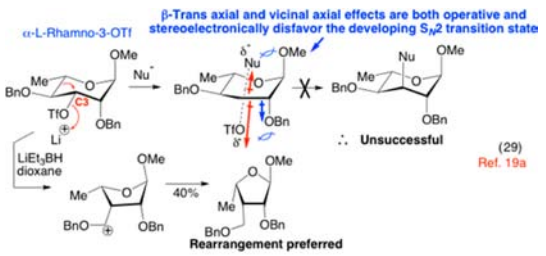


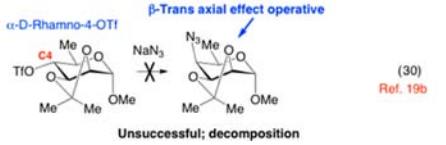
is located at C(2),[18e] or bulky groups sit at O(4) (e.g., Pv), these can often shield C(3) sufficiently to prevent displacement.[18c] In some instances, OAc groups at C(4) can also anchimerically assist to cause retention alongside desired S_N2 inversion.[18c]

(ix) 4-O-Triflates of α- and β-D-galacto-[16] and D-gluco-pyranosides[18c] usually engage in S_N2 displacements readily.

(x) α-L- and α-D-rhamnopyranoside 3- and 4-O-triflates are particularly difficult to displace with external nucleophiles, often rearranging with nucleophile trapping (eqs 29 and 30).[19a,b]

It is hoped that with this update of the original guidelines,[1,2] the community will now be able to more effectively plan future routes to desired sugar derivatives and avoid possible snares.





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Notes

The authors declare no competing financial interest.

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dx.doi.org/10.1021/ol502193j | *Org. Lett.* 2014, 16, 4838−4841