Guidelines for *O*-Glycoside Formation from First Principles

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The complexity and irreproducibility of glycosylation reactions retard progress in the glycosciences. Application of the steady-state hypothesis to transient oxocarbenium ion–counterion pair intermediates reveals the importance of concentration, temperature, and other factors in glycosylation stereoselectivity. Guidelines are then adduced for the practice of *O*-glycosylation reactions on the basis of which more reproducible, practical protocols can be established.

INTRODUCTION

Glycosidic bond formation is the central reaction of glycochemistry and is consequently critical to the glycosciences, as was recognized in the National Research Council's (NRC) 2012 report *Transforming Glycoscience: A Roadmap for the Future*.[1] The formation of glycosidic bonds is most frequently practiced by a nucleophilic substitution reaction in which a leaving group is displaced from an electrophilic glycosyl donor by a nucleophilic glycosyl acceptor typically with the aid of a promoter.[2−7] Unfortunately, while enormous progress has been made in glycosylation in recent decades, particularly since the advent of homogeneous glycosylation conditions and the thioglycoside and trichloroacetimidate classes of donors,[8−12] the field suffers from a long-standing reputation for unpredictability and irreproducibility that, according to the NRC report, hinders broader application by nonspecialists.[1] We have long maintained[13−17] that improved, more reproducible, and more broadly applicable glycosylation reactions will logically follow an enhanced understanding of glycosylation reaction mechanisms, and with that in mind, have recently reviewed the evidence supporting our current understanding of glycosylation reaction mechanisms both without and with participation by neighboring groups.[18,19] Building on this growing body[20−23] of physical organic studies directed at the mechanism(s) of glycosylation reactions, we derive here a set of simple guidelines to help practitioners think about the manner in which they conduct glycosylation reactions with the overall goal of rendering them more predictable and reproducible and so helping to open up the field to nonspecialists. Both Wang and co-workers and Seeberger and co-workers have made significant contributions, with additional input from Jensen and co-workers,[24] with similar goals in mind recently, but do not take into account the kinetic differences between reactions proceeding through associative as opposed to dissociative mechanisms in their, in some cases, necessarily empirical approaches.[25−29] We limit ourselves to the formation of *O*-glycosides, believing them to be more central

to glycobiology, and do not anticipate that the guidelines we offer will extrapolate directly to *C*-glycoside formation, which operate more closely to the S_N1 end of the mechanistic spectrum and appear to depend heavily on the conformational dynamics of the putative oxocarbenium ion.[30−32] The guidelines we present are general considerations for reactions conducted at the S_N1/S_N2 interface[18] without the assistance of neighboring group participation, which fall under a different kinetic regime.[19] Finally, we note that while the choice of nonparticipating groups for both glycosyl donors and acceptors can significantly influence the overall rate of a glycosylation reaction under a given set of conditions by shifting the S_N1/S_N2 interface,[25−27,29,33−35] the guidelines that we offer are general, and their application should improve reproducibility whatever the protecting group regime.

## RESULTS AND DISCUSSION

Glycosylation reactions are best understood in terms of a mechanistic continuum of nucleophilic substitution reactions spanning the full range of S_N1 to S_N2 mechanisms (Scheme 1); as such, they are a microcosm of Winstein's ion pair theory[22,36−38] as recognized as early as the 1960s.[39] Glycosylation reactions, however, have long been depicted mostly as S_N1 reactions proceeding through intermediate oxocarbenium ions with the obligatory counterions considered as mere spectators and so typically omitted from reaction schemes. As we have discussed elsewhere,[16] this viewpoint is no longer sustainable in the light of the current physical organic record.[18−21,23] In brief, glycosyl oxocarbenium
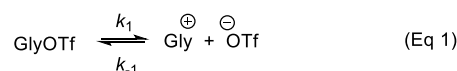
Scheme 1. General Glycosylation Mechanism
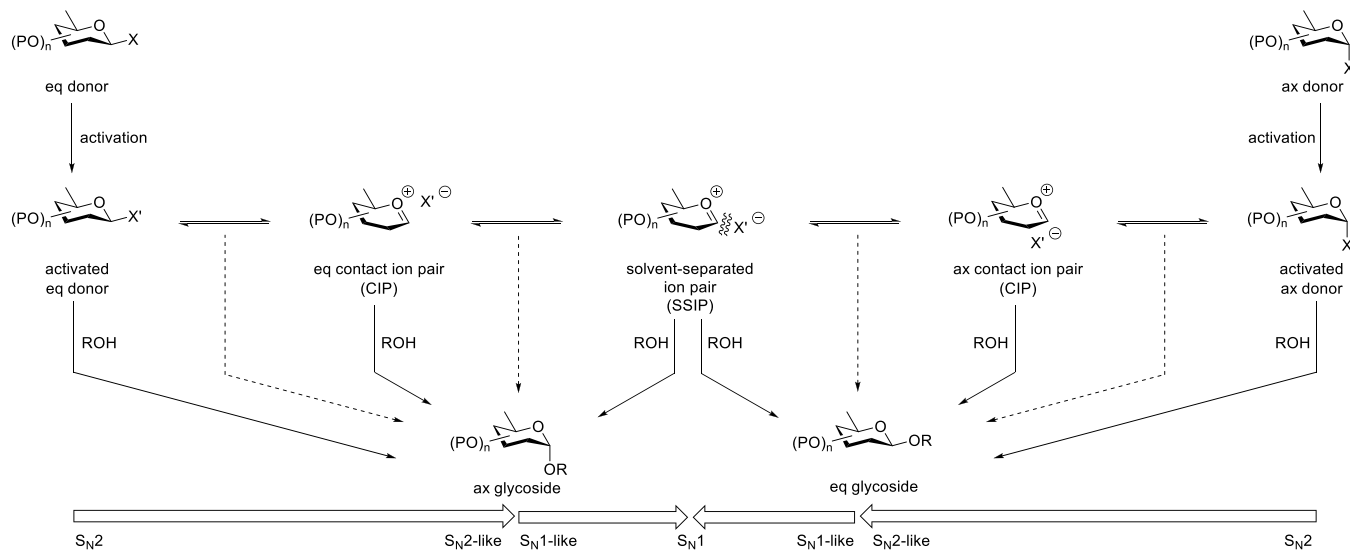
ions are highly destabilized by the presence of multiple electron-withdrawing C−O bonds to the extent that they might be considered borderline "superelectrophiles"[14,15,40,41] and have yet to be observed spectroscopically, with the exception of the 2-deoxy and 2-deoxy-2-bromo pyranose series lacking the C−O bond at the 2-position even in superacid media.[42−45] On the other hand, the NMR spectra of many activated covalent glycosyl donors in solvents typically employed for glycosyl reactions have been reported in the literature,[18,46−49] with the continual addition of new examples.[20,21] Modern kinetic analyses of glycosylation reactions, including computational studies when conducted in the presence of the counterion, come down on the side of associative mechanisms.[16,18] The preponderance of evidence therefore suggests that typical homogeneous glycosylation reactions conducted in organic solution with rare exceptions[50−52] will hew to the S_N2 end of the mechanistic spectrum.[16] On the basis of this understanding, we offer here a series of guidelines derived from first principles that are intended to help practitioners and nonpractitioners alike derive and execute *O*-glycosylation reactions with increased reproducibility. These guidelines are not intended to be specific to any specific class of glycosidic bond, nor to any particular set of nonparticipating groups; rather, they provide what we consider to be solid foundations onto which selectivity for many classes of glycosidic bonds can be built through the informed choice of protecting groups. Tried and tested recipes for an increasing number of specific types of glycosidic bonds can be found in the *Carbohydrate Chemistry: Proven Synthetic Methods* series edited by Kováč. In view of the generality of the guidelines, we describe glycosidic bonds and glycosyl donors as

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having either the axial or the equatorial configuration (abbreviated as ax and eq in schemes and figures).

We begin with an analysis of the kinetics of glycosylation, which leads directly into the first group of guidelines that focus on the role of concentration in glycosylation reactions, which we consider to be of primordial importance and the root cause of many supposedly irreproducible reactions. We continue with guidelines on the choice of reaction temperature, the importance of counterions and additives, the selection of the acceptor, and finally solvent.

In view of the transient nature of glycosyl oxocarbenium ions, the kinetics of glycosylation reactions is best understood in terms of the steady-state approximation with a very low but essentially constant concentration of contact ion pairs. Using glycosyl triflates as an example and without regard to the stereochemical outcome of the process, for a single anomer of a covalent donor (Gly-OTf), the glycosylation reaction proceeding via an ion pair can be expressed as a combination of eqs 1 and 2

$$\text{GlyOTf} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{\oplus}{\text{Gly}} + \overset{\ominus}{\text{OTf}} \qquad \text{(Eq 1)}$$

$$\overset{\oplus}{\text{Gly}} \xrightarrow{k_2\text{ROH}} \text{GlyOR} \qquad \text{(Eq 2)}$$

in which an initial reversible cleavage into an oxocarbenium intermediate Gly$^+$ and a stable anion TfO$^-$, governed by the forward and reverse rate constants k_1 and k_{-1}, is followed by the irreversible reaction of the oxocarbenium ion with the alcohol ROH described by the rate constant k_2. For the sake of simplicity, we limit ourselves in this discussion to the consideration of a single ion pair, as opposed to the more fundamentally correct series of contact or intimate and then solvent-separated ion pairs. We stress, however, that the overall conclusions from this simplified analysis regarding the overall importance of concentration and temperature in the reproducibility of glycosylation reaction are valid, as is clear from a previous analysis that takes into account multiple ion pairs.[47]

The rate of glycoside formation can therefore be expressed as in eq 3

Applying the steady-state approximation gives eq 4.

$$\frac{d[GlyOR]}{dt} = k_2[\overset{\oplus}{Gly}][ROH] \qquad \text{(Eq 3)}$$

$$\frac{d[\overset{\oplus}{Gly}]}{dt} = k_1[GlyOTf] - k_{-1}[\overset{\oplus}{Gly}][\overset{\ominus}{OTf}] - k_2[\overset{\oplus}{Gly}][ROH] = 0 \qquad \text{(Eq 4)}$$

such that the concentration of the oxocarbenium ion is given by eq 5, which, when substituted in eq 3, gives eq 6

$$[\overset{\oplus}{Gly}] = \left(\frac{k_1[GlyOTf]}{k_{-1}[\overset{\ominus}{OTf}] + k_2[ROH]} \right) \qquad \text{(Eq 5)}$$

$$\frac{d[GlyOR]}{dt} = \frac{k_1 k_2[GlyOTf][ROH]}{k_{-1}[\overset{\ominus}{OTf}] + k_2[ROH]} \qquad \text{(Eq 6)}$$

The rate of the glycosylation reaction therefore shows first-order dependence on the concentration of the glycosyl triflate and more complex dependence on the concentration of the alcohol, which is found in both the numerator and the denominator. The rate of the reaction will also show inverse dependence on the concentration of the triflate counterion, such that added triflate will retard the progress of the reaction—a manifestation of the common ion effect. When $k_{-1}[TfO^-] \ll k_2[ROH]$, the $k_{-1}[TfO^-]$ term can be effectively set to zero, and eq 6 simplifies to eq 7, the familiar rate law for an S_N1 reaction.

$$\frac{d[GlyOR]}{dt} = k_1[GlyOTf] \qquad \text{(Eq 7)}$$

On the other hand, when $k_{-1}[TfO^-] \gg k_2[ROH]$ eq 6 effectively simplifies to eq 8, the rate law of a bimolecular

$$\frac{d[GlyOR]}{dt} = \frac{k_1 k_2[GlyOTf][ROH]}{k_{-1}[\overset{\ominus}{OTf}]} \qquad \text{(Eq 8)}$$

reaction taking place via an intermediate in equilibrium with the substrate.

It follows that if the mechanism of the glycosylation reaction can indeed be considered on a sliding scale somewhere between the extreme ends represented by S_N1 and S_N2 reactions, the position of a particular reaction on that scale depends on and can be influenced by the relative importance of the two terms in the denominator of eq 6, namely, $k_{-1}[OTf^-]$ and $k_2[ROH]$, with the reactivity of the putative oxocarbenium ion represented in the magnitude of the rate constants k_{-1} and k_2. It is clear then that for preparative reactions conducted in the condensed phase, as opposed to reactions conducted in the gas phase in a mass spectrometer or in silico, the nature and concentration of the inescapable counterion and the concentration of the acceptor alcohol play significant roles in the positioning of a given reaction on the mechanistic continuum.

If we now turn to the question of stereoselectivity, we posit that eq 8 can be rewritten as eqs 9 and 10 to describe the rates of formation of the α- and β-anomers from a given donor,

$$\frac{d[\alpha\text{-}GlyOR]}{dt} = \frac{k_1 k_{2\alpha}[GlyOTf][ROH]}{k_{-1}[\overset{\ominus}{OTf}] + k_{2\alpha}[ROH]} \qquad \text{(Eq 9)}$$

$$\frac{d[\beta\text{-}GlyOR]}{dt} = \frac{k_1 k_{2\beta}[GlyOTf][ROH]}{k_{-1}[\overset{\ominus}{OTf}] + k_{2\beta}[ROH]} \qquad \text{(Eq 10)}$$

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Dividing eq 9 by eq 10 gives the relative rate of α- vs β-glycoside formation as in eq 11, which simplifies to eq 12.

$$\frac{d[\alpha\text{-}GlyOR]}{dt} \cdot \frac{dt}{d[\beta\text{-}GlyOR]} = \frac{k_1 k_{2\alpha}[GlyOTf][ROH]}{k_{-1}[\overset{\ominus}{OTf}] + k_{2\alpha}[ROH]} \cdot \frac{k_{-1}[\overset{\ominus}{OTf}] + k_{2\beta}[ROH]}{k_1 k_{2\beta}[GlyOTf][ROH]} \qquad \text{(Eq 11)}$$

$$\frac{d[\alpha\text{-}GlyOR]}{d[\beta\text{-}GlyOR]} = \frac{k_{2\alpha}\{k_{-1}[\overset{\ominus}{OTf}] + k_{2\beta}[ROH]\}}{k_{2\beta}\{k_{-1}[\overset{\ominus}{OTf}] + k_{2\alpha}[ROH]\}} \qquad \text{(Eq 12)}$$

In an alternative approach, glycosylation reactions can be considered as taking place via two concurrent competing pathways, namely, the S_N1 and S_N2 pathways, with the operative mix being dependent on a number of factors. Such a scenario has been considered by multiple authors for various types of nucleophilic substitution reaction under nonsolvolytic conditions,[53−68] as exemplified by Mayr and co-worker's study of the substitution reactions of benzhydryl halides,[69] and their kinetics are typically described by equations of the form of eq 13, which has been written here for the glycosylation reaction.

$$\frac{d[GlyOR]}{dt} = (k_1 + k_2[ROH])[GlyOTf] \qquad \text{(Eq 13)}$$

Processing eq 13 for the formation of the two separate anomers then leads to eq 14, which describes the relative rates of formation of the α- and β-anomers if concurrent S_N1 and S_N2 mechanisms are operative.

$$\frac{d[\alpha\text{-}GlyOR]}{d[\beta\text{-}GlyOR]} = \frac{(k_{1\alpha} + k_{2\alpha}[ROH])}{(k_{1\beta} + k_{2\beta}[ROH])} \qquad \text{(Eq 14)}$$

The most important difference between eqs 12 and 14 is the inclusion of terms for the concentration of the counterion and the rate constant for its recombination with the oxocarbenium ion in the former as is fitting for a mechanism based on the ion pair hypothesis. Clearly, such terms have no place in the alternative mechanistic scenario of concurrent competing S_N1 and S_N2 reactions. Irrespective of whichever of the two mechanistic scenarios is ultimately correct, it is clear that the selectivity of the reaction is a complex function of the concentration of the acceptor alcohol, which appears in both the nominator and denominator of eqs 12 and 14. It is also clear that as the concentration of the acceptor drops over the course of a glycosylation reaction, the selectivity will change.

We believe that together these two factors, influence of concentration on selectivity and change of selectivity with reaction progress, are major underlying reasons for the lack of

reproducibility of glycosylation reactions. That is, unless a given glycosylation reaction is conducted at the initial concentration reported in the literature and stopped at the same conversion, it will not give the same selectivity. It is not the glycosylation reaction that is not reproducible, but rather the irreproducibility arises from inadequate specification of concentration in reported experimental parts and insufficient attention to reproducing reported conditions. This leads us to our first set of guidelines:

Guidelines 1−4. Concentration.

Guideline 1: Experimental parts and reaction schemes for glycosylation reactions should report molar concentrations of all reactants and reagents and not simply stoichiometry in terms of equivalents. So-called empirical optimization schemes for glycosylation reactions[25−28] must specify concentration and conversion, and ideally include optimization of concentration.

Guideline 2: A standard conversion (or product yield) should be adopted (we suggest an 80% yield of product) to remove concerns of reproducibility and to enable true comparison between methods.

Guideline 3: Whenever possible glycosylation reactions should be conducted under pseudo-first-order conditions in acceptor, that is, with sufficient acceptor to minimize the change in its concentration over the course of the reaction, so as to overcome the dependence on conversion.

Guideline 4: Big data approaches to predicting glycosylation[28] should not include glycosylations for which concentration is not specified in the training data set.

Guidelines 5 and 6. Temperature.
Temperature influences the reaction rate through its relationship to the activation energy (E_A) and rate constant (k) as specified in the Arrhenius equation (eq 15), where A is the pre-exponential factor and R the universal gas constant.

$$k = Ae^{(-E_A/RT)} \qquad \text{(eq 15)}$$

In eq 12, describing the selectivity of a glycosylation reaction, temperature will therefore manifest itself in changes to the rate constants $k_{2\alpha}$, $k_{2\beta}$, and k_{-1}, and in eq 14 through changes in rate constants $k_{1\alpha}$, $k_{1\beta}$, $k_{2\alpha}$, and $k_{2\beta}$. The pre-exponential factor A is related to the entropy of activation $\Delta S^{\ddagger}$, which differs for dissociative (S_N1) and associative (S_N2) substitution reactions or as a mechanism shifts from S_N1-like to S_N2-like across the ion pair continuum of Scheme 1. Reaction temperature will therefore influence each of the rate constants $k_{1\alpha}$, $k_{1\beta}$, $k_{2\alpha}$, $k_{2\beta}$, and k_{-1} in eqs 12 and 14 differently, leading to the conclusion that, whichever of the two mechanistic scenarios is adopted, selectivity will vary with temperature.

The influence of activation entropy on the reaction rate as a function of temperature is most easily appreciated from the Gibbs equation for the free energy of activation (eq 16).

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad \text{(eq 16)}$$

The dependence of glycosylation selectivity on temperature is evident in the empirical studies published by the Seeberger laboratory,[27,28] and is described in recent work by the Jensen and Zhang laboratories.[23,24] It follows that if a glycosylation reaction is to be reproducible, the temperature at which it is conducted must be recorded and adhered to. Reactions initiated by warming from low temperature to zero or room temperature are unlikely to give reproducible selectivities from

laboratory to laboratory simply because the rate of warming is difficult to reproduce, especially as reaction scale and cooling bath sizes are varied. Again, it is not the chemistry that is irreproducible but the manner of conducting it.

The differences in activation entropies between S_N1 and S_N2 reactions are not easy to predict once solvation is accounted for. Nevertheless, it is commonly considered that S_N1 reactions typically possess greater positive or smaller negative entropies of activation than closely analogous S_N2 reactions,[70,71] such that the rate of S_N1 reactions increases with temperature to a greater extent than that of corresponding S_N2 reactions. The gradual erosion of stereoselectivity with increasing temperature catalogued by Seeberger and others[23,24,27,28] can therefore be understood in terms of a shift in mechanism toward the S_N1-like end of the continuum as reaction temperature is increased.

Overall, two guidelines are suggested with respect to temperature:

Guideline 5: Glycosylation reactions should be conducted at a single controlled reaction temperature and not with a gradual increase in temperature over the course of the reaction.

Guideline 6: If a more S_N2-like mechanism is required to enhance stereoselectivity, glycosylation reactions should be conducted at the lowest temperature consistent with a practical overall reaction time.

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Guidelines 7−9. Counterions and Additives.
Counterions are critical components in all glycosylation reactions and play fundamental roles in the determination of reaction rate and selectivity. Depending on the mechanistic scenario adopted, they are either directly represented in the determination of selectivity (eq 12) and/or are indirectly represented (eqs 12 and 14) through their influence on the rate constants ($k_{1\alpha}$ and $k_{1\beta}$) that are critical components of selectivity determination. Comparative studies are rare but never fail to underline the influence of counterions on selectivity.[18,72−77] Clearly, the choice of counterion is critical and is made all the more so by recent determinations[15,21,78] that the most common counterion, triflate, functions as a competing nucleophile for the acceptor alcohol. Even more pertinent is the observation[21] that, at least for triflate, Curtin−Hammett kinetics,[79] such as required for the operation of Lemieux's bromide ion catalyzed α-glucopyranoside synthesis,[80] are not always operative. When Curtin−Hammett kinetics are not operative, the rate of glycosylation is more rapid than that of equilibration of the two anomeric donors and, assuming S_N2-like mechanisms, the stereoselectivity of the glycosylation reaction will be an inverse function of the initial ratio of the two anomeric donors. It is therefore imperative to maximize the ratio of the two anomeric donors. For an intended equatorially selective reaction, this means that the percentage of the axial donor should be maximized, which can be achieved through consideration of the anomeric effect.[81] Simply stated, the more electronegative the counterion, the greater the extent to which the axial donor will be favored, and
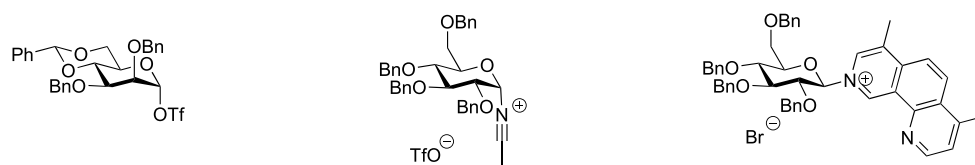
Figure 1. A glycosyl triflate, glycosyl nitrilium ion, and a glycosyl phenanthrolidinium ion.

the greater the equatorial selectivity will be, leading to Guideline 7.

Guideline 7: Equatorial selectivity in a given system will be maximized by employing the most electronegative counterion capable of forming a covalent adduct with the putative oxocarbenium ion at the optimal temperature.

Fortuitously, the most common counterion in modern glycosylation reactions, the triflate anion, is among the most electronegative, and it is not surprising therefore that it figures prominently in well-known equatorially stereoselective glycosylation reactions (Figure 1).

Additives have long been recognized as having significant influences on the stereochemical outcomes of glycosylation reactions. By far the most common of these has been acetonitrile,[82−84] which is frequently employed as a solvent or cosolvent when it enhances equatorial selectivity. The acetonitrile effect is widely considered to arise from the formation of axial glycosyl nitrilium ions (Figure 1) in which the acetonitrile serves as a leaving group in S_N2-like processes. This long-standing hypothesis is supported by a series of trapping studies,[85−96] and by NMR spectroscopic characterization in a limited number of cases.[97,98] The preferential axial location of the slender positively charged nitrilium moiety is consistent with its strongly electronegative nature and so with the dictates of the anomeric effect. The additive acetonitrile therefore functions analogously to that of a strongly electronegative counterion, leading to Guideline 8.

Guideline 8: When equatorial selectivity is desired and the use of a strongly electronegative coordinating counterion is not possible, acetonitrile or its lower freezing homologue propionitrile should be employed as an additive or solvent.

Other more voluminous additives that form positively charged covalent adducts with glycosyl oxocarbenium ions can be expected to occupy equatorial sites to avoid 1,3-diaxial interactions that destabilize their axial counterparts and so to promote axial glycoside formation through S_N2-like mechanisms. The classic examples of this phenomenon are the glycosylpyridinium (and related N-heterocyclic), ammonium, sulfonium, and phosphonium ions,[99] although these are typically insufficiently reactive to take part in practically useful glycosylation reactions, and the "reverse-anomeric effect" is no longer a satisfactory explanation for the pseudoequatorial preference of such ions.[100] Recent advances with the use of 1,10-phenanthroline derivatives as an additive (Figure 1), however, show promise in terms of excellent axial selectivity for glycosylation in reasonable reactions times.[101,102] The use of ethers as a solvent is widely reputed to involve the use of equatorial glycosyl oxonium ion adducts,[83] for which the best evidence is found in the form of equatorial ω-haloalkyl glycosides arising from the nucleophilic opening of the adduct by the halide counterion,[103−105] and typically leads to axially selective reactions.

Many other additives have been investigated,[106−108] and an increasing number have been spectroscopically[46] and in rare cases even crystallographically[109] characterized. The most promising in recent years appears to be a series of tertiary formamides, with

DMF as the prototypical example and varying in size and electronic character of the N-substituents.[110,111] The use of amides in this manner results in the formation of a pair of glycosyl imidates, with the axial isomer being the more stable and the equatorial one the more reactive, leading overall to preferential formation of the axial glycoside provided the conditions are such as to promote rapid equilibration of the two imidates.[110] The use of additives to promote stereoselective axial glycosylation reactions is clearly a rapidly evolving field, but on the basis of the current state of the art the following guideline is reasonable.

Guideline 9: Highly axially selective glycosylation reactions by displacement of equatorial glycosyl onium salts can be promoted through the use of 1,10-phenanthroline derivatives or tertiary amides (with some optimization of substituents in both cases) provided that anomeric equilibration of the anomeric salts is rapid in comparison to the rate of glycosylation.

Guidelines 10 and 11. The Acceptor. The steric environment and nucleophilicity of acceptor alcohols are major factors influencing the stereoselectivity of glycosylation reactions, with the more nucleophilic and less sterically hindered alcohols hewing closer to the S_N2 end of the mechanistic spectrum. The influence of acceptor protecting groups and steric hindrance on glycosylation selectivity, while long recognized, have been most clearly illustrated by the systematic studies of van der Marel, Codeé, and their co-workers,[112] and by the more recent and more extensive predictive nucleophilicity scales of Wong and Wang and their co-workers.[29] As the area has recently been thoroughly reviewed,[35] we simply offer the following guideline.

Guideline 10: For a given acceptor alcohol, nucleophilicity should be maximized by minimizing the electronic and steric influences of adjacent functionality by the choice of the least electron-withdrawing and sterically demanding protecting groups.

Some protecting groups have the potential to interfere directly in glycosylation reactions, as demonstrated by Auzanneau and co-workers for acetamides, which function as competing nucleophiles[113,114] or indirectly by serving as Lewis or Brønsted bases that buffer the promoter, leading to Guideline 11.

Guideline 11: Whenever possible, the presence of amides and other nucleophilic or basic protecting groups should be avoided.

Guideline 12. The Solvent. The choice of solvent is critical for the outcome of most glycosylation reactions. Some solvents, most notably nitriles, ethers, and amides, participate directly as discussed in the context of additives above and should be avoided unless such effects are desired. Otherwise, in a class of reactions that operates on the borderline between S_N1 and S_N2 mechanism, solvent polarity is a critical factor with more polar solvents supporting greater dissociation of the critical covalent donors into longer-lived and looser ion pairs and consequently resulting in an erosion of stereoselectivity. Slow reactions on the other hand can in principle be accelerated by the use of a more polar solvent albeit with the risk of a potential reduction in selectivity. In general, the choice of

solvent for an S_N2-like glycosylation reaction should be made according to Guideline 12.

Guideline 12: The least polar solvent consistent with achieving homogeneous solution at the desired reaction temperature should be selected; most frequently, this will be dichloromethane when seeking to conduct stereoselective S_N2-like glycosylation reactions.

> It is hoped that application of these guidelines in the conduct of O-glycosylation reactions, in the absence of neighboring group participation, will provide a solid foundation on which to build and describe a more reliable, reproducible set of glycosylation reactions suitable for many classes of glycosidic bonds that will amenable to use by specialist and nonspecialist practitioners alike.

◼ CONCLUSIONS

An appreciation of the kinetics of modern homogeneous O-glycosylation reactions as functioning at the S_N1/S_N2 interface through transient intermediate ion pairs reveals the importance of concentration in the reproducible conduct of such reactions and results in an initial set of four guidelines. Similar considerations reveal changes in activation entropy as the mechanistic spectrum is traversed from pure S_N2 to pure S_N1 reactions, which lead to a second set of two guidelines about the choice and control of reaction temperature. Yet further consideration of the reaction mechanism leads to three guidelines on the choice of counterion and of additives, two on the selection of the acceptor alcohol, and a final one on the choice of solvent. It is hoped that application of these guidelines in the conduct of O-glycosylation reactions, in the absence of neighboring group participation, will provide a solid foundation on which to build and describe a more reliable, reproducible set of glycosylation reactions suitable for many classes of glycosidic bonds that will be amenable to use by specialist and nonspecialist practitioners alike.

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