REVIEW

# Mechanisms of glycopyranosyl and 5-thioglycopyranosyl transfer reactions in solution

**Andrew J. Bennet * and Theresa E. Kitos**

*Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby British Columbia, V5A 1S6, Canada. E-mail: bennet@sfu.ca*

***Received (in Cambridge, UK) 22nd January 2002***
***First published as an Advance Article on the web 29th April 2002***

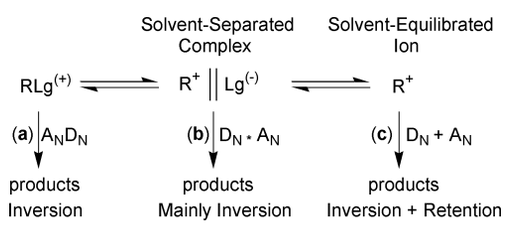
Covering: 1986–2001.

**1 Introduction**
**2 Glycopyranosides**
**2.1 Glycopyranosyl transfer from alkyl glycopyranosides**
**2.1.1 Acid-catalysed reactions in water**
**2.1.2 Acid-catalysed reactions in other solvents**
**2.1.3 Water-catalysed reactions**
**2.2 Glycopyranosyl transfer from glycopyranosyl pyridinium salts**
**2.2.1 Spontaneous reactions in water**
**2.2.2 Spontaneous reactions in alcoholic solvents**
**2.2.3 Base-promoted reactions**
**2.3 Glycopyranosyl transfer from glycopyranosyl fluorides and phosphates**
**2.3.1 Acid-catalysed reactions of glycopyranosyl fluorides**
**2.3.2 Base-catalysed reactions of glycopyranosyl fluorides**
**2.3.3 Spontaneous reactions of glycopyranosyl fluorides in water**
**2.3.4 Spontaneous reactions of glycopyranosyl fluorides in alcoholic solvents**
**2.3.5 Acid-catalysed and spontaneous reactions of glycopyranosyl phosphates**
**2.4 Glycopyranosyl transfer from aryl glycopyranosides**
**2.4.1 Acid-catalysed reactions of aryl glycopyranosides**
**2.4.2 Base-catalysed reactions of aryl glycopyranosides**
**2.4.3 Spontaneous reactions of aryl glycopyranosides**
**3 Thioglycopyranosides**
**3.1 Glycopyranosyl transfer from alkyl 5-thioglycopyranosides**
**3.1.1 Acid-catalysed reactions of alkyl 5-thioglycopyranosides**
**3.2 Glycopyranosyl transfer from 5-thioglycopyranosyl fluorides**
**3.2.1 Spontaneous reactions of 5-thioglycopyranosyl fluorides**
**4 Miscellaneous**
**5 Conclusions**
**6 Acknowledgements**
**7 References**

## 1 Introduction

The recent past has seen extensive documentation of the general chemical and biological aspects of carbohydrates and their furanose and pyranose ring structures.[1] Several older reviews outline the mechanistic aspects of glycosyl transfers and the tools necessary for the study of such reactions.[2] Although numerous contemporary articles on the mechanism of action of glycosidase enzymes have been published,[3] there are few recent treatises on the non-enzymatic processes. A forthcoming book chapter delineates the use of multiple kinetic isotope effects in combination with theoretical calculations to provide insight into transition state structure for both enzymatic and non-enzymatic glycopyranosyl and glycofuranosyl transfer reactions.[4] The present document deals with recent physical organic and kinetic studies that have led to elucidation of the mechanism for transfer of glycopyranosyl moieties from various substrates such as *O*-glycopyranosides, glycopyranosyl fluorides, and glycopyranosyl pyridinium salts to acceptors, the most notable of which is water. Glycofuranosyl transfer reactions are not within the scope of the present review.

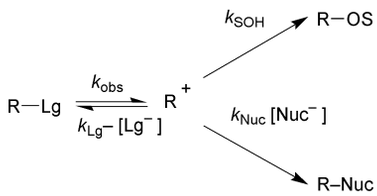
In the following report, a minor modification of the Winstein ion-pair mechanism[5] (Scheme 1) is used for the analysis of ion-pair intermediates. Specifically, the intimate ion-pair has been omitted in view of a paucity of information with respect to the occurrence, or lack thereof, of "internal return" at the stage of the intimate ion-pair, and as to whether the intimate ion-pair is in an energy well or is a transition state leading to the solvent-separated complex.




**Scheme 1**

For the purpose of this discussion, the lifetime of a cation ($\tau$) is defined as being equal to the reciprocal of the pseudo-first-order rate constant for reaction of the cation with solvent ($1/k_{SOH}$). This period of time ($\tau$) is equal to the average time that elapses before the intermediate reacts with solvent.[6] In the presence of other nucleophiles such as azide ion, the pseudo-first-order rate constant for capture of the cationic intermediate ($k_{cap}$) is equal to the sum of the two pseudo-first-order rate constants ($k_{SOH}$) and ($k_{Nuc}$[Nuc$^-$]) (Scheme 2).[7] This means that as the concentration of an added nucleophile is increased, there is a decrease in the average time that elapses before the cation reacts.

In the case of a carbenium ion with a lifetime that is sufficient ($\geq 10^{-10}$ s) to allow equilibration of the solvent around the cation prior to capture of the intermediate, the lifetime can be estimated using the "azide clock" methodology of Jencks and co-workers, where $f_{N_3^-}$ is the fraction of azide product formed [eqn. (1)].[8] This methodology relies on the assumption that azide ion reacts with a free, solvated carbenium ion at the diffusional rate ($k_{dif} = k_{N_3^-} \approx 5 \times 10^9$ M$^{-1}$ s$^{-1}$; Scheme 2, $k_{Nuc}$),[8,9] the validity of which has been confirmed by McClelland and co-workers *via* laser flash photolysis technique measurements




**Scheme 2**

of the diffusion-controlled second-order rate constants for the reactions of triarylmethyl,[10] diarylmethyl,[10,11] and *p*-methoxyphenylethyl[11] carbenium ion with azide ion.

$$f_{N_3^-} = 1 - \frac{k_{SOH}}{k_{N_3^-}} \times \frac{f_{N_3^-}}{[N_3^-]} \quad (1)$$

The term "nucleophilic solvent participation"[12] is used herein for cases in which the solvent acts as a nucleophile at the reaction transition state, *i.e.*, a concerted $A_ND_N$ ($S_N2$) reaction, whereas the term solvation (or dipolar solvation) is reserved for situations in which the interaction of the solvent with the carbenium ion is dipolar in nature. Solvent deuterium KIEs ($k_{H_2O}/k_{D_2O}$) for the hydrolyses of glycopyranosides are interpreted using the principles of isotopic fractionation factor analysis [eqn. (2)].[13] Eqn. (2) expresses the relationship between the rate constants observed in $D_2O$ and $H_2O$, and the fractionation factors $\phi_i^{TS}$ and $\phi_j^{R}$ refer to the exchangeable protons undergoing change in their bonding at the transition and reactant states, respectively.[13] The solvent deuterium KIE analysis can be simplified based on the following approximations: (1) hydrogen fractionation factors ($\phi$) refer to the tightness of bonding and are significantly less than unity for hydrogen atoms undergoing rate-limiting transfer "in flight" between two oxygen atoms. For hydrogen bonding situations in which the overall bonding is loose, the fractionation factors are less than unity, and this gives rise to normal solvent KIEs ($k_{H_2O}/k_{D_2O} > 1$);[13b] (2) $D_3O^+$ is a stronger acid in $D_2O$ than is $H_3O^+$ in $H_2O$ ($\phi = 0.69$); (3) $OD^-$ is a stronger nucleophile/base in $D_2O$ than is $OH^-$ in $H_2O$; either specific-base or nucleophilic catalysis would be expected to proceed faster in $D_2O$ unless there are other compensating factors such as protons "in flight" as a part of the rate-limiting step; and (4) fractionation factors for non-transferring protons are given by eqn. (3), where $\alpha$ is the fraction of progress towards product at the transition state.[13a]

$$k_{D_2O}/k_{H_2O} = \prod_i^n \phi_i^{TS} \Big/ \prod_j^n \phi_j^{R} \quad (2)$$

$$\phi_i^{TS} = (\phi_i^{R})^{\alpha} \times (\phi_i^{P})^{1-\alpha} \quad (3)$$

This review employs the IUPAC recommended nomenclature for reaction mechanism terminology as summarised by Guthrie and Jencks,[14] while the naming of carbohydrates and their simple derivatives adheres to the nomenclature recommended by IUPAC in 1996.[15] For example, the replacement of an oxygen atom by sulfur is designated as thio, *i.e.*, 5-thioxylopyranose (**1**), and the glucopyranosyl cation is referred to as the glucopyranosylium ion (**2**)[15] whereas generic cations such as **3**, **4**, and **5** are referred to as carbenium,[16] oxacarbenium, and thiacarbenium ions, respectively, because in standard IUPAC nomenclature replacement of a $CH_2$ group by either an oxygen or a sulfur atom is designated by the terms oxa or thia, respectively.[17] In addition, conformations of glycopyranosides are designated based on IUPAC recommended nomenclature rules.[18] As an example, Fig. 1 shows the conformations adopted by the

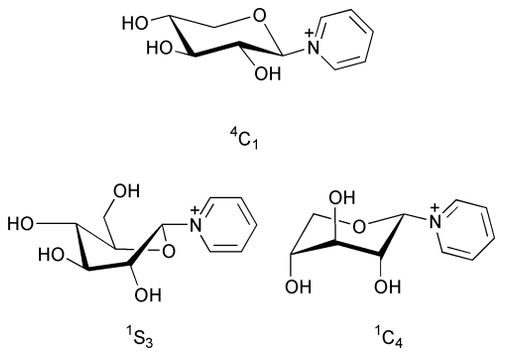
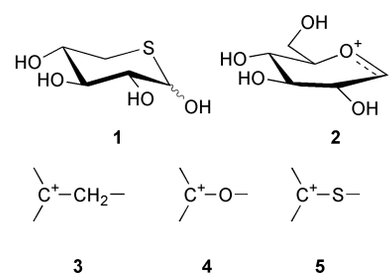



**Fig. 1** Conformations of gluco- and xylopyranosyl pyridinium salts in water.

pyridinium salts of β-xylopyranosyl, α-glucopyranosyl and α-xylopyranosyl: the $^4C_1$ chair, the $^1S_3$ skew-boat, and the $^1C_4$ chair, respectively.[19]




With respect to glycopyranosyl transfer reactions, the present report details the stoichiometry and, where applicable, characteristics such as lifetime ($\tau$) and partitioning to the various substitution products (R–OS and R–Nuc; Scheme 2) of the carbenium ion intermediate.

Three basic mechanisms (shown by pathways **a**, **b**, and **c** in Scheme 1) have been identified for the glycopyranosyl transfer process: (**a**) concerted ($A_ND_N$, $S_N2$); (**b**) dissociative *via* ion-pair intermediates ($D_N$ * $A_N$, $S_N1$); and (**c**) dissociative *via* a solvent-equilibrated intermediate ($D_N$ + $A_N$, $S_N1$). These three processes differ in the timing of the events involving C1–Nuc bond formation and C1–Lg bond cleavage. Within this mechanistic manifold, departure of the aglycon (Lg, Scheme 1) can occur with acid-, base-, or water-catalysis. Accordingly, this review has been organised into sections that are based on the aglycon of the glycopyranoside. In view of the fact that 5-thioglycopyranosides and related analogues are being investigated by several research groups as potential glycopyranosidase inhibitors,[20] we will conclude with a brief summary of the effects on the hydrolytic mechanism of substitution of the ring oxygen atom by a sulfur atom. Specifically, we will focus on the kinetic accessibility and reactivity of the thiacarbenium ion intermediate, relative to the analogous oxacarbenium ion.

Finally, mention should be made of a 1992 American Chemical Society publication that contains several articles in which the well-documented anomeric effect and the kinetic reactivity of glycopyranosides are analysed in support[21] of Deslongchamps' stereoelectronic theory,[22] or are presented as evidence that such stereoelectronic effects are very weak[23] or absent[24] during glycopyranosyl transfer reactions. Since publication of his book,[22] Deslongchamps and co-workers have proposed that synperiplanar lone pairs are as effective as antiperiplanar lone pairs in prompting acetal hydrolysis.[25] For the purpose of the current article, a detailed discussion of stereoelectronic effects is unwarranted: (1) it is apparent that stereoelectronic effects in other systems are absent;[26] (2) as their proponents suggest, both syn- and antiperiplanar lone pairs are effective in displacing a nucleofuge from an acetal centre; and (3) for all conformations of the flexible glycopyranosides either an aligned (within 30°) syn- or antiperiplanar lone pair is

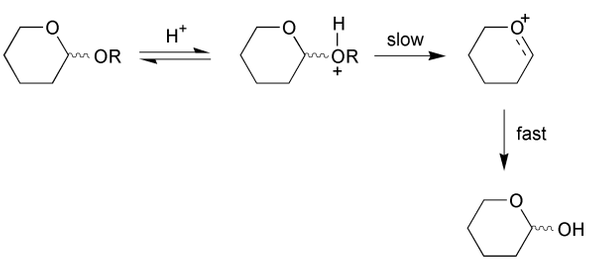
present. A final point with respect to this stereoelectronic theory is that the important interactions are envisioned using localised $sp^3$ orbitals rather than delocalised orbitals in which the HOMO is dominated by a p-type orbital on the heteroatom.[27]

## 2 Glycopyranosides

### 2.1 Glycopyranosyl transfer from alkyl glycopyranosides

#### 2.1.1 Acid-catalysed reactions in water

The more general elements of alkyl glycopyranoside hydrolysis in aqueous acid have been known for over thirty years:[2] (1) there is a linear dependence of the experimental rate constant on $[H_3O^+]$;[2] (2) fission of the glycopyranosyl–oxygen bond occurs, except in the case of aglycons such as *tert*-butyl,[28] where alkyl–oxygen bond cleavage yields kinetically more accessible carbenium ion intermediates; (3) the second-order rate constants for reaction in deuterium oxide are larger ($k_{D_3O^+}/k_{H_3O^+} \approx 1.8$–$2.5$)[28,29] than those for the analogous reaction in water; and (4) in general, entropies of activation are strongly positive ($\Delta S^{\ddagger} \approx +40$–$80$ J mol$^{-1}$ K$^{-1}$).[30] The ensuing reaction mechanism prototype, a specific acid-catalysed process in which there is formation of a cyclic oxacarbenium ion intermediate, is shown in Scheme 3.




**Scheme 3**

This mechanism was refined further when in 1986, Bennet and Sinnott reported a detailed kinetic isotope effect (KIE) study on the acid-catalysed hydrolyses of methyl α- and β-glucopyranosides.[31] The important positions of isotopic substitution are shown in Fig. 2 (R = $CH_2OH$).

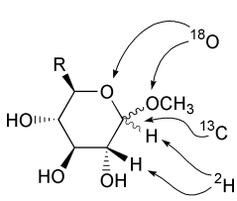
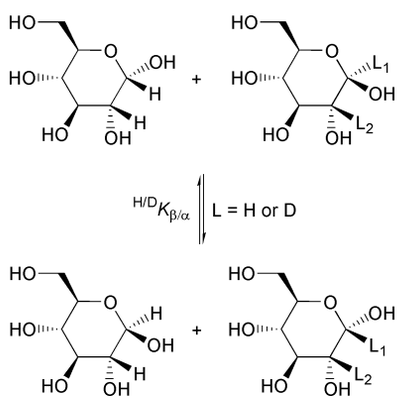



**Fig. 2** Positions of isotopic labelling used in the KIE studies on the hydrolysis of methyl xylo- and glucopyranosides.

Results from this study reveal that the acid-catalysed hydrolyses proceed *via* C–O exocyclic bond cleavage, that no nucleophilic solvent participation is present at the hydrolytic transition state, and that strengthening of the endocyclic C–O bond lags behind C–O bond cleavage. The reported leaving group $^{18}O$ KIEs for methyl α- and β-glucopyranoside (1.026 and 1.024, respectively)[31] are consistent with the occurrence of exocyclic C–O bond cleavage during methyl glucopyranoside hydrolysis (Scheme 3). The conclusion that there is no nucleophilic solvent participation at the transition state was derived from the results of measured anomeric $^{13}C$ KIE for these hydrolysis reactions ($k_{12}/k_{13}$) of approximately 1.01,[31] a value which is in the range typically associated with dissociative $D_N + A_N$ reactions ($S_N1$; $k_{12}/k_{13} = 1.00$–$1.01$),[32] rather than associative $A_ND_N$ reactions ($S_N2$; $k_{12}/k_{13} = 1.03$–$1.08$).[32] In support of the third key conclusion, the magnitudes of the KIEs associated with the ring oxygen, although inverse ($k_{16}/k_{18} < 1$), are close to 1 ($k_{16}/k_{18} \approx 0.991$–$0.996$),[31] and these results suggest that little strengthening of the endocyclic C–O is present at the hydrolytic transition states.

Based on the magnitude of the conformationally dependent β-secondary deuterium[33] and ring $^{18}O$ KIEs,[31] Bennet and Sinnott also proposed that the transition state conformations for the hydrolysis of methyl α- and β-glucopyranoside are a distorted $^1S_3$ skew-boat and a flattened $^1C_4$ chair, respectively. It was assumed that the hyperconjugative interaction σ(C2–H) ⟶ $n_p$(C1) at the transition state for hydrolysis of the α-anomer was greater than that for the corresponding β-anomeric transition state [the measured β-secondary KIEs ($k_H/k_D$) for the α- and β-anomers are 1.073, and 1.045, respectively].[31] Recent work by Lewis and Schramm has shown, however, that ground state force constant differences are likely to be present between the two anomeric glucopyranosides, as revealed by the existence of an equilibrium isotope effect (EIE; $^{H/D}K_{\beta/\alpha}$) of 1.027 ± 0.005 for the mutarotation of glucopyranose between its α- and β-anomers (Scheme 4; $L_2$ = D, $L_1$ = H).[34]




**Scheme 4**

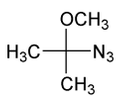
In their study Lewis and Schramm used various levels of theory up to RHF/6-31G**, including an Onsager dipole model correction ($e$ = 78.8), in calculations that showed the β-EIE originates from differences in $n_p$(O2) ⟶ σ*(C2–H) orbital overlap between the two anomers, differences that result from variations in the preferred H–C2–O2–H torsional angle. Clearly, the strength of the $n_p$(O2) ⟶ σ*(C2–H) orbital interaction will be mediated by solvent and, thus, the influence of this interaction on the magnitude of the measured β-SDKIEs (β-secondary deuterium KIEs) for the acid-catalysed hydrolysis reactions will be modulated by solvent reorganization along the reaction coordinate. As a result, derivation of transition state conformations will require explicit inclusion of solvent into the theoretical calculations. Another important result reported by Lewis and Schramm is the magnitude of the EIE on mutarotation of (1-$^2$H)-glucose, a value of 1.043 ± 0.004 (Scheme 4; $L_1$ = D, $L_2$ = H).[34] Thus, the ratio of measured α-SDKIEs ($k_H/k_D$) for the hydrolysis of methyl glucopyranosides ($KIE_\alpha$ = 1.137, $KIE_\beta$ = 1.089)[31] is roughly equal to the EIE for interconversion of the parent sugar [eqn. (4)].

$$^{H/D}K_{\beta/\alpha} \approx \frac{(k_H/k_D)_\alpha}{(k_H/k_D)_\beta} \quad (4)$$

Since the origin of an α-SDKIE is considered to arise mainly from the weakening of an out-of-plane $C_\alpha$–H(D) bond bending vibration as hybridisation at the reaction centre changes from $sp^3$ to $sp^2$, the larger observed α-SDKIEs associated with reaction of the α-anomer has been used as the basis for the proposal that reactions of α-glycopyranosides have later transition states than β-glycopyranosides. Not only are α-SDKIEs unreliable for distinguishing between unimolecular and bimolecular transition states in glycopyranosyl transfer reactions,[35] but also the use of such effects to analyse the "lateness" of glycopyranosyl

transition states is tenuous if the magnitude of ground-state EIEs are not considered.

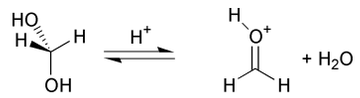
It is clear that the acid-catalysed hydrolysis reactions of methyl α- and β-glucopyranosides proceed *via* dissociative transition states, although at the time of Bennet and Sinnott's paper, there was uncertainty as to the type of cationic intermediate, either solvent-separated or solvent-equilibrated (Scheme 1), that is produced in these reactions. In regard to this problem, Amyes and Jencks estimated that the lifetime of the glucopyranosylium ion (**2**) in water is approximately $1 \times 10^{-12}$ s,[9] a value that was obtained by extrapolating the calculated lifetimes of acyclic oxacarbenium ions formed during the hydrolysis reactions of α-azido ethers such as **6**. In this particular reaction, trapping of the oxacarbenium ion intermediate by added azide ion re-forms the starting azido ether (Scheme 2, $Lg^- = N_3^-$).



**6**

In 1995, hydrolysis reaction data from a glucopyranosyl ring system lacking the 2-hydroxy group was used by Bennet and co-workers to estimate a lifetime for the glucopyranosylium ion (**2**) of at least $2.5 \times 10^{-12}$ s (section 2.2.1).[36] With estimated rate constants of $1.0 \times 10^{11}$ $s^{-1}$ for reorganisation within an ion-pair[37] and $1.6 \times 10^{10}$ $s^{-1}$ for diffusional separation of the ion-pair,[38] it is clear that insufficient time is available for the short-lived glucopyranosylium ion to become equilibrated with dilute solutes or solvent molecules prior to its capture. As a consequence, homologues of **2** that are generated in glycopyranosyl transfers will react with external nucleophiles, including solvent, at the stage of the solvent-separated complex (Scheme 1).

In an attempt to determine whether the conclusions that emerged from the mechanistic study on methyl glucopyranosides can be extended to other glycopyranosides, Induragalla and Bennet performed an in-depth KIE study on the acid-catalysed hydrolysis of methyl α- and β-xylopyranosides.[39] The results from this study reveal several similarities and, perhaps surprisingly, some significant differences between the hydrolytic transition states for methyl xylo- and glucopyranosides (Fig. 2, R = H, or $CH_2OH$, respectively). For instance, at the 95% confidence level, the following KIEs were indistinguishable for each of the corresponding anomers in the two systems: (1) anomeric $^{13}C$; (2) β-SDKIE (C2–H/D); (3) α-SDKIE (C1–H/D); and (4) leaving group $^{18}O$ KIE. On the other hand, the measured ring $^{18}O$ and solvent KIEs for the acid-catalysed hydrolyses of methyl gluco- and xylopyranosides are significantly different. Specifically, the ring $^{18}O$ KIE ($k_{16}/k_{18}$) for hydrolysis of methyl α- and β-xylopyranoside are 0.983 and 0.978,[39] but the respective values for the two glucopyranosides are 0.996 and 0.991.[31] Also, the measured solvent KIEs ($k_{D_3O^+}/k_{H_3O^+}$) for the hydrolyses of methyl α- and β-xylopyranosides are 2.31 ± 0.09 and 2.24 ± 0.01, respectively,[39] yet the reported value for the hydrolysis of methyl α-glucopyranoside is 1.8.[29] Based on the magnitude of the observed aglycon $^{18}O$ KIEs, it can be concluded that both anomers of methyl glucopyranoside and methyl xylopyranoside react *via* an acid-catalysed exocyclic C–O bond cleavage pathway. The differences observed between the ring $^{18}O$ KIEs for the anomeric pairs of xylo- and glucopyranosides are indicative of stronger $n_p(O5) \longrightarrow p(C1)$ interactions occurring at the xylopyranosyl transition states than at the corresponding transition states for glucopyranoside hydrolysis. Furthermore, the observed $^{18}O$ KIEs for both of the methyl xylopyranoside anomers are similar to EIEs calculated at the HF/4.31G level of theory for the acid-catalysed formation of an oxacarbenium ion from methanediol (Scheme 5, ring



**Scheme 5**

$^{18}O \approx 0.977$ and leaving group $^{18}O \approx 1.020$).[40] Although these calculations were performed on the smallest possible model compound, it is clear that significant exocyclic C–O bond cleavage and endocyclic C–O bond strengthening are critical attributes of the two anomeric xylopyranosyl hydrolytic transition states.

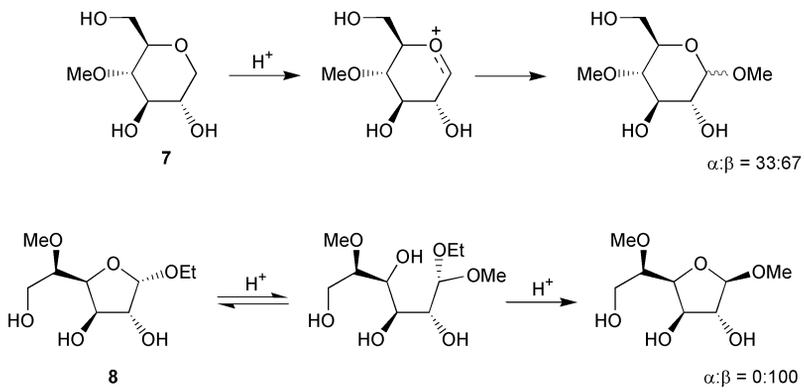
The differences in the magnitude of the solvent KIEs presumably result from unequal secondary KIE contributions that originate from dissimilar solvation requirements at the respective transition states rather than any involvement of a general-acid catalysed pathway.

As mentioned previously, the magnitudes of the ring-$^{18}O$ and the β-secondary deuterium KIEs were used as the basis for the proposal that methyl α- and β-glucopyranosides hydrolyse *via* flattened $^1S_3$ skew-boat and flattened $^4C_1$ chair transition state conformations, respectively.[31] With what is known at present, the use of measured β-SDKIEs on glycopyranoside hydrolysis reactions in order to derive conformational information is an approach that is more complicated than had been previously assumed. That being said, any ground-state β-EIE perturbation of the magnitude of the measured β-SDKIE for hydrolysis of methyl α-D-glucopyranoside would require that the H–C2–C1–Lg dihedral angle in the transition state be larger than the previously-estimated range of 31–43°. Therefore, the transition state structure would be further removed from that of the ground-state $^4C_1$ chair conformation than from that of the proposed flattened $^1S_3$ skew-boat. Of particular note, the likely transition state conformations for the acid-catalysed hydrolysis of methyl α- and β-xylopyranosides are close to the structure of the oxacarbenium ion itself, probably a $^4H_3$ half-chair conformation.

At this point, stop and consider why *tert*-butyl β-D-glucopyranoside undergoes alkyl–oxygen bond cleavage during acid-catalysed hydrolysis,[28] given that the *tert*-butyl carbenium ion $[(CH_3)_3C^+]$ has an estimated lifetime of $1 \times 10^{-12}$ s,[41] which is a value of less than or equal to that of **2** ($1–3 \times 10^{-12}$ s). Based simply on carbenium ion stability as defined by lifetime $\tau$ ($1/k_{HOH}$), a portion of the hydrolysis reaction would be expected to occur *via* cleavage of the glycosidic C–O bond. As a consequence, the dominance of alkyl C–O bond cleavage in the case of *tert*-butyl β-D-glucopyranoside can be regarded as further evidence for the occurrence of imperfect synchronisation during the hydrolysis of glucopyranosides. That is, because endocyclic C–O bond strengthening lags behind exocyclic C–O bond cleavage, the hydrolysis reactions of glucopyranosides exhibit higher-than-expected intrinsic barriers for exocyclic C–O bond cleavage.

### 2.1.2 Acid-catalysed reactions in other solvents

Capon and Thacker reported that the methanolysis ($CD_3OD$) of methyl β-glucopyranoside occurs with <2% retention of the original methyl group in the newly formed α-glucopyranoside and that greater than 80% of glucopyranosylium ion capture with $CD_3OD$ occurs from the opposite face to give the α-anomer.[42] In contrast, acid-catalysed anomerisation of methyl glucofuranosides has been proposed to occur *via* endocyclic cleavage of the furanose ring to give an acyclic acetal.[42,43] These mechanistic conclusions were further refined by two recent studies on the acid-catalysed alcoholysis of methyl and ethyl 4-*O*-methyl-α- and β-D-glucopyranosides,[44] and of methyl and ethyl 5-*O*-methyl-α- and β-D-glucofuranosides.[45] In these two reports, Konradsson and co-workers show that the isomeric glycosides solvolyse by different mechanisms: pyranosides react *via* a $D_N + A_N$ exocyclic C–O cleavage, while the




**Scheme 6**

furanosides react *via* an $A_ND_N$ endocyclic cleavage pathway. Scheme 6 illustrates the respective reactions and initial products for the methanolysis of ethyl 4-*O*-methyl-α-D-glucopyranoside (**7**) and ethyl 5-*O*-methyl-α-D-glucofuranoside (**8**), compounds that subsequently undergo acid-catalysed anomerisations.

At the moment, it appears that the 2-hydroxy group is an important determinant for the mechanism of anomerisation.[46] Specifically, the results from a recent study of the acid-catalysed methanolysis of methyl 2-deoxy-β-D-*arabino*-hexopyranoside[47] suggest that for 2-deoxyglycopyranosides both exo- and endocyclic C–O bond cleavage mechanisms occur simultaneously,[46] although at the present time it is not clear whether the ring-opening pathway occurs with or without nucleophilic solvent participation.

Other solvents that have been used for mechanistic studies of the acid-catalysed reactions of glycopyranosides include mixtures of acetic anhydride and acetic acid.[48] Results with these solvent systems are consistent with the formation of both cyclic and acyclic oxacarbenium ion intermediates. However, given the much lower polarity of such solvent mixtures as judged by permittivities (acetic acid $\varepsilon = 6.2$, acetic anhydride $\varepsilon = 20.7$) relative to water ($\varepsilon = 78.5$), it is likely that these reactions proceed *via* preassociation complexes or that they are concerted reactions.

### 2.1.3 Water-catalysed reactions

In the absence of $H_3O^+$ catalysis, the water-promoted hydrolysis of unactivated glycopyranosides such as methyl β-glucopyranoside is exceedingly slow, with estimated rate constants of the order of $5 \times 10^{-15}$ s$^{-1}$ at 25 °C, or half-life values of approximately 20 million years.[49] It is of note that these reactions, which were monitored at temperatures of 180–260 °C, do not involve alkyl–O cleavage; instead, reaction occurs at the anomeric centre.[49] The large negative entropies of activation associated with the water-catalysed hydrolysis of methyl α- and β-glucopyranosides ($\sim\Delta S^{\ddagger} = -100$ J mol$^{-1}$ K$^{-1}$)[49] are presumably a consequence of the reaction circumventing the formation of highly charge-localized species that would arise from the attack of neutral water. It is likely that these reactions involve highly-ordered transition states that incorporate several water molecules acting simultaneously to solvate both the departing aglycon and the attacking nucleophilic water (Fig. 3).[50] Highly-ordered transition states (such as that shown in Fig. 3) which include protons "in flight" should generate sizable solvent KIEs ($k_{H_2O}/k_{D_2O}$). No such study has been reported.

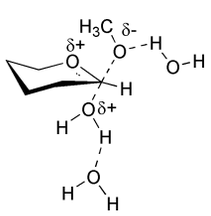
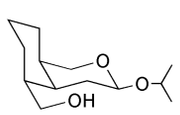



**Fig. 3** Possible transition state structure for the spontaneous hydrolysis of methyl β-D-glucopyranoside.

The measurement of hydrolysis reactions at such high temperatures introduces an unavoidable bias in favour of mechanisms that possess large $\Delta H^{\ddagger}$ values ($\Delta H^{\ddagger} \approx 125$ kJ mol$^{-1}$ in this case). Thus, it is possible that at ambient temperatures, a concerted mechanism for the spontaneous hydrolysis of alkyl glycopyranosides that involve a cyclic array of water molecules may be preferred. Such a mechanism avoids the formation of charged species.

As a final point, it has yet to be established whether these uncatalysed processes involve exo- or endocyclic cleavage and whether the mode of cleavage depends on the reaction temperature. Indeed, Liras *et al.* described a glycopyranoside model (**9**) in which as the temperature is lowered, acid-catalysed hydrolysis gives rise to a greater fraction of reaction *via* endocyclic C–O bond cleavage.[51]

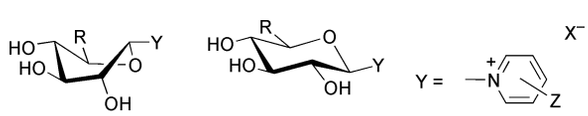



**9**

## 2.2 Glycopyranosyl transfer from glycopyranosyl pyridinium salts

### 2.2.1 Spontaneous reactions in water

Glycopyranosyl transfer reactions that utilize pyridinium derivatives such as **10** and **11** (R = $CH_2OH$) as substrates are more amenable to mechanistic studies involving modification of the reaction nucleophile simply because the nucleofuge (aglycon) does not require catalysis for departure. As a consequence, rate constants for hydrolyses of α- and β-D-glycopyranosyl pyridinium salts are typically independent of pH between pH 4 and 9.[52] Linear free energy relationships (LFER) such as the Swain–Scott correlation can therefore be probed with anionic nucleophiles that would otherwise be protonated at the acid concentrations necessary to hydrolyse alkyl glycopyranosides.

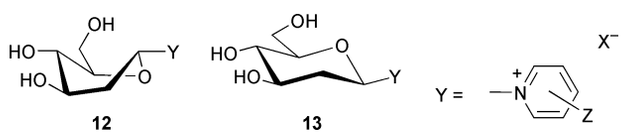



In contrast to most glycopyranosyl derivatives, the ground-state conformations for the α-pyridinium salts are not $^4C_1$ chairs, but instead are $^1S_3$ skew-boat and $^1C_4$ chair conformations for glucopyranosyl (**10**, R = $CH_2OH$) and xylopyranosyl (**10**, R = H) compounds, respectively (Fig. 1).[52]

The measured Brønsted $\beta_{Lg}$ values for glycopyranosyl transfer reactions in water provide confirmation that the spontaneous cleavage of the C–N bond is a component of the

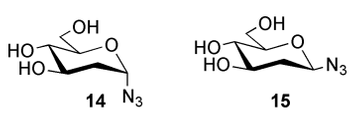
rate-determining step. Specifically, the $\beta_{Lg}$ values for **10** (R = $CH_2OH$), **10** (R = H), and **11** (R = H) are $-1.06 \pm 0.12$, $-1.28 \pm 0.08$, and $-1.2 \pm 0.2$, respectively.[52] Spontaneous reaction in water of the two xylose anomers **10** and **11** (R = H, Y = 4-bromoisoquinolin-2-iumyl) also display only small salt effects on the hydrolytic rate constants, and the neutral nucleophile thiourea has no effect on the observed rate constants.[31] Taken together, these results lead to the conclusion that the reactions of aldopyranosyl derivatives in water are unimolecular reactions.[31] Amyes and Jencks re-analysed this data in 1989[53] in light of the well known steric hindrance to $A_ND_N$ ($S_N2$) reactions on six-membered rings.[54] Just as the reaction of iodide with cyclohexyl bromide is approximately 100-fold slower than the corresponding reaction with 2-bromopropane,[55] Amyes and Jencks concluded that the reported rate constant data for reaction of **10** (R = H, Y = 4-bromoisoquinolin-2-iumyl, X = bromide)[31] in the presence and absence of azide ion was consistent with nucleophilic participation at the reaction transition state.[53]

Recently, Bennet and co-workers ruled out this possibility based on the results from a comprehensive series of experiments on the hydrolysis reactions of 2-deoxy-α-[56] and β-[36] D-*arabino*-hexopyranosyl pyridinium salts (**12** and **13**) in the presence of various anionic nucleophiles. A solvolytic study was also performed on **12** and **13** (Y = 4-bromoisoquinolin-2-iumyl, X = tetrafluoroborate) in aqueous methanol, ethanol and trifluoroethanol, and binary mixtures of ethanol and trifluoroethanol (TFE).[57]




**12** **13**

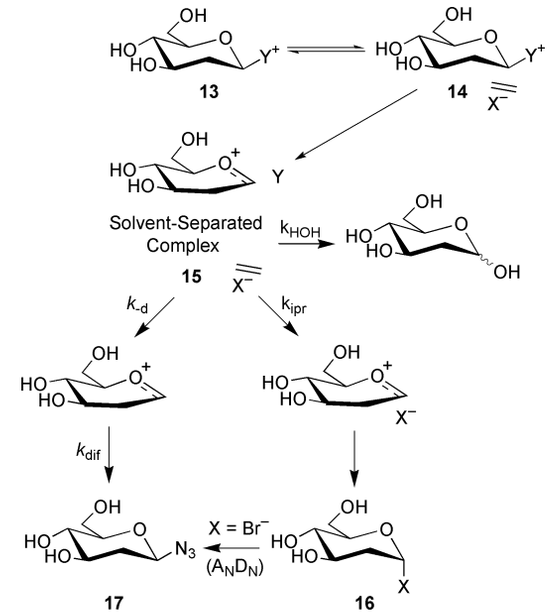
Critical observations made from the experiments involving the β-anomeric substrates (**13**) are as follows: (1) the calculated Brønsted $\beta_{Lg}$ value is $-1.0 \pm 0.1_6$; (2) the calculated Swain–Scott sensitivity parameter is $0.03 \pm 0.05$; (3) the reaction in the presence of azide ion (1.98 M) gives a substantial quantity of substitution product (~50%), and this material is predominantly the α-anomer **14** (~96%); (4) reaction in the presence of azide ion (0.99 M) and another anion (0.99 M) gives a quantity of retained azide substitution product (**15**) that is related to the second anion's nucleophilicity; and (5) the small variance in the hydrolytic rate constants for **13** (Y = 4-bromoisoquinolin-2-iumyl) follow the order $k_{obs}(F^-) > k_{obs}(Cl^-) > k_{obs}(Br^-)$.[36]




**14** **15**

Based on the observed large negative Brønsted $\beta_{Lg}$ value and reaction rate insensitivity to the nature of the added nucleophile, it was concluded that the rate-determining step for reaction of **13** involves a unimolecular cleavage of the anomeric-pyridinium C–N bond.[36] Given that the rate of reaction is independent of nucleophile concentration and yet the majority of the azide substitution product is the α-anomer (*i.e.*, reaction has occurred with inversion of configuration), capture of the cationic intermediate must occur prior to solvent equilibration of the oxacarbenium ion.

In keeping with these observations, a proposed mechanistic outline for the nucleophilic substitution reactions of 2-deoxy-β-D-*arabino*-hexopyranosyl pyridinium salts is shown in Scheme 7. In this scheme, a solvent-separated preassociation complex (**14**) generates the first-formed cationic intermediate, a solvent-separated complex in which the anionic nucleophile is associated with the newly-formed oxacarbenium ion (**15**). Collapse of this complex to give inverted azide product (**16**, X = $N_3$; Scheme



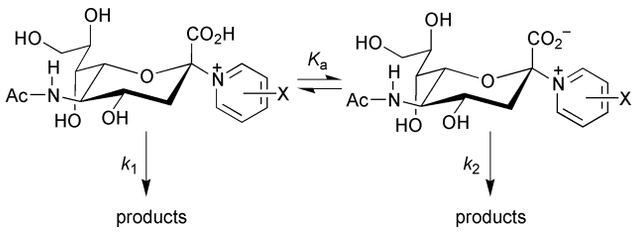

**Scheme 7**

7) occurs *via* ion pair reorganisation ($k_{ipr}$), a process that is expected to occur with a rate constant of $1 \times 10^{11}$ $s^{-1}$.[37] Given that approximately equal quantities of substitution products are formed from azide ion or water attack on this intermediate, the lifetime for the 2-deoxy-D-*arabino*-hexopyranosylium ion is estimated to be $1 \times 10^{-11}$ s (*i.e.*, $k_{HOH} = k_{ipr}$). Another strong piece of evidence in support of this scheme is the observation that in the presence of an additional anion (*i.e.*, both azide and a second anion are present simultaneously), the quantity of retained azide product (**17**) follows the order $Br^- > Cl^- > F^-$, whereas the reverse trend is observed for the rate constants, *i.e.*, $k_{obs}(F^-) > k_{obs}(Cl^-) > k_{obs}(Br^-)$. These results argue for the formation of a greater quantity of a second transient intermediate in the presence of bromide ion (**16**, X = Br), and this species can then react with azide ion *via* an $A_ND_N$ ($S_N2$) mechanism to give **17** (see Section 2.3).

The notion of solvent-separated complexes can explain the trend in rate constants seen for the halide ions. That is, the greater the dipolar solvation of the developing carbenium ion the lower the energy of the transition state. The smaller, more basic fluoride ion forms stronger hydrogen bonds to the surrounding water molecules and as a result, effects a lowering of the transition state energy for formation of the solvent-separated complex *via* polarization of the solvating water molecules.

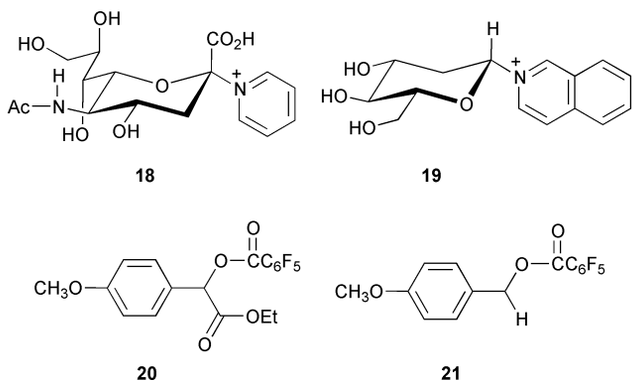
Similarly, the solvolysis reactions of α-anomeric pyridinium salts (**12**) display a Brønsted $\beta_{Lg}$ value of $-0.84 \pm 0.08$ and a Swain–Scott sensitivity parameter of $0.03 \pm 0.10$.[56] The substitution reactions in the presence of azide ion for the two anomeric 2-deoxy-D-*arabino*-hexopyranosyl 4-bromoisoquinolin-2-ium salts give different product ratios: in the presence of 2 M sodium azide the α-anomer gives more inverted and retained azide product (70 and 6%, respectively)[56] than does the β-anomer (50% inverted; 2% retained).[36] These observations suggest that in the absence of a second nucleophilic anion, the retained azide product is the result of diffusional reaction of a cationic intermediate with free azide ion ($k_{dif}$, Scheme 7).[56] Clearly, these dissociative glycopyranosyl transfer reactions do not proceed through a common intermediate; the 2-deoxy-D-*arabino*-hexopyranosylium ion is not solvent-equilibrated in water.

In a recent study on the spontaneous reactions of pyridinium α-D-*N*-acetylneuraminides,[58] Chou *et al.* found that the rate of C–N bond cleavage for these substrates displays two first-order rate constants $k_1$ and $k_2$ and an ionisation constant ($K_a$) for their ionisable carboxylic acid group (Scheme 8).




**Scheme 8**

During the C–N bond cleavage reactions, the carboxylate group does not act as a nucleophile to effect transient formation of an α-lactone. In comparison to an expected rate increase of at least $10^4$-fold for nucleophilic attack by an acetate–acetic acid pair,[59,60] the zwitterionic form of pyridinium α-D-*N*-acetylneuraminides only reacts about three times more rapidly than the cationic form. Also consistent with these reactions proceeding *via* dissociative transition states are the observations that $\beta_{Lg}$ values for the two first-order processes are identical for the cationic ($k_1$) and the zwitterionic ($k_2$) forms ($-1.22 \pm 0.16$ and $-1.22 \pm 0.07$, respectively), and that the $\Delta S^{\ddagger}$ value is $28 \pm 4$ J mol$^{-1}$ K$^{-1}$ for reaction of the zwitterionic form of **18**.




Despite the presence of the electron withdrawing carboxylic acid group, **18** reacts approximately 60-fold more rapidly than **19**. This is in contrast to the two 4-methoxybenzyl derivatives where the carboxylic ester **20** reacts $\frac{1}{40}$ times as rapidly as the unsubstituted compound **21**.[61] Thus, on approach to the oxacarbenium ion-like transition state, relief of ground state 1,3-diaxial (gauche) interactions in **18** must be more dominant than the unfavourable electronic interactions introduced by the electron-withdrawing $CO_2H$ group.

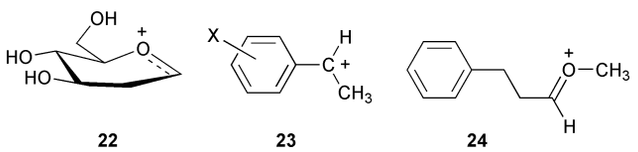
### 2.2.2 Spontaneous reactions in alcoholic solvents

In aqueous alcoholic solvent mixtures, the anomeric 2-deoxy-D-*arabino*-hexopyranosyl 4-bromoisoquinolin-2-ium salts **12** and **13** give *m* values of $-3.64 \pm 0.34$ and $-4.78 \pm 0.33$ respectively,[57] for solvolytic rate constant data that is fitted to the standard Grunwald–Winstein eqn. (5),[62] where the $Y^+$ parameter is calculated from the solvolysis of 1-adamantyldimethylsulfonium triflate.[63]

$$\log (k_{obs}/k_0) = m Y^+ \qquad (5)$$

Small increases in the rate constants for solvolysis of compounds **12** and **13** are associated with a decrease in solvent polarity.[64] Negative derived *m* values indicate that a change in the ionising power of the solvent has a more pronounced effect on the charge-localised ground state than on the delocalised oxacarbenium ion-like transition states, a situation which is in contrast to that seen with 1-adamantyldimethylsulfonium triflate.[57] The larger *m* value obtained from the β-anomer (**13**) reaction data is consistent with greater charge delocalisation occurring at the transition state for solvolysis of the β-anomer. This conclusion is in agreement with the reported ring oxygen kinetic isotope effects ($^{18}$O-KIEs) for the specific acid-catalysed hydrolyses of methyl glycopyranosides (see section 2.1.1).

As is the case for alkyl glycopyranoside hydrolysis reactions (section 2.1.1), nucleophilic solvent participation is unimportant in these solvolysis reactions since short-lived, cationic intermediates such as the 2-deoxy-β-D-*arabino*-hexopyranosylium ion **22** are expected to display an increased nucleophilic selectivity [$k_{ROH}/k_{HOH}$, eqn. (6)][65] upon reduction of the solvent polarity. In reality, the selectivity is lower in less polar, more nucleophilic, alcoholic solvents such as EtOH and MeOH.

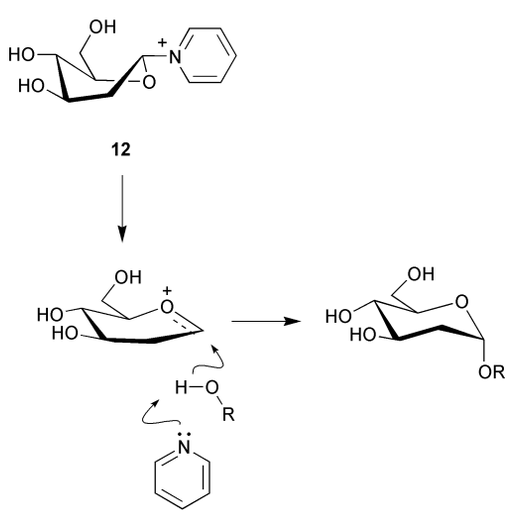



$$\frac{k_{ROH}}{k_{R'OH}} = \frac{[Gly-OR][R'OH]}{[Gly-OR'][ROH]} \qquad (6)$$

The observed nucleophilic selectivities obtained from reactions run in alcoholic solvent mixtures can also be used to estimate the lifetime of cationic intermediates. In mixtures of 5 : 45 : 50 (v/v) EtOH–TFE–$H_2O$, the nucleophilic selectivity values ($k_{EtOH}/k_{TFE}$) for the capture of substituted 1-phenylethyl carbenium ions (**23**)[38] and 2-deoxy-β-D-*arabino*-hexopyranosylium ion (**22**)[57] in conjunction with the lifetime estimates for the 1-arylethyl cations in 50 : 50 (v/v) TFE–$H_2O$[8b] generate a computed lifetime for the 2-deoxy-β-D-*arabino*-hexopyranosylium ion (**22**) that falls between $1.0 \times 10^{-12}$ and $3.3 \times 10^{-10}$ s. This range of extrapolated values agrees remarkably well with a value estimated by azide trapping experiments of approximately $1.0 \times 10^{-11}$ s for the lifetime of the 2-deoxy-β-D-*arabino*-hexopyranosylium ion in water.[36]

Capture of the cationic intermediates formed from **12** and **13** occurs prior to solvent equilibration and thus, stereoselectivity values as defined by eqn. (7) give information concerning the mechanism of trapping of these short-lived intermediates. The lower stereoselectivity of the α-anomer (**12**) in the solvolysis reactions probably results from a greater degree of general-base catalysed solvent capture by the departing aglycon at the transition state for formation of the retained product (Scheme 9).

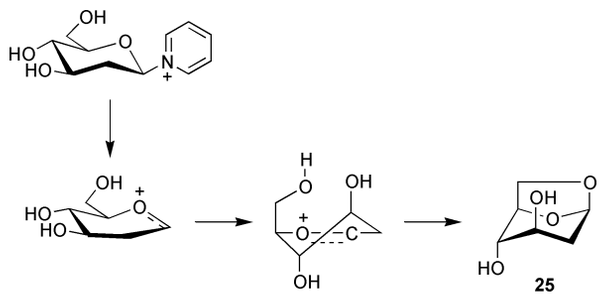
$$\text{Stereoselectivity} = \frac{[Gly-OR]_{inv}}{[Gly-OR]_{ret}} \qquad (7)$$




**Scheme 9**

Moreover, a significant fraction of the solvolysis products formed during the reactions of **12** and **13** in the poorly nucleophilic yet polar solvent TFE results from intramolecular

capture of the cationic intermediate by the 6-hydroxy group to give 1,6-anhydro-2-deoxy-β-D-*arabino*-hexopyranose (**25**). Formation of **25** in solvents containing a high proportion of TFE suggests that the cationic intermediate possesses a longer lifetime ($1/k_{SOH}$) in these solvents, thereby allowing enough time for the intermediate to attain the necessary conformation for ring closure (Scheme 10).




**Scheme 10**

### 2.2.3 Base-promoted reactions

At pH values of ⩾10, a base-promoted process is evident in the reactions of glycopyranosyl pyridinium salts (**10** and **11**).[52] Products from the base-promoted reaction of **10** (R = $CH_2OH$, Y = 3-bromopyridiniumyl) are obtained *via* two distinct pathways: 90% of the reaction occurs by attack on the anomeric centre, a process that generates both glucose and 1,6-anhydroglucose as products, while the remaining 10% of the reaction proceeds *via* attack on the pyridine ring, a pathway that probably involves intramolecular attack by an ionised sugar hydroxy group.[52] Why does hydroxide ion react in a bimolecular fashion with glycopyranosyl pyridinium derivatives while azide ion does not? At the present time this question is unanswered. It is possible that proper alignment of the hydroxide ion for nucleophilic displacement occurs through its hydrogen bonding with the sugar hydroxy groups. Relative to other nucleophiles, $OH^-$ displays greatly enhanced reactivity with α-D-glucopyranosyl fluoride (section 2.3.2).

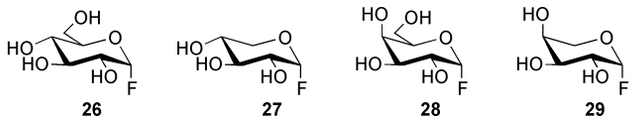
At this point, stop and consider why the two oxacarbenium ions **22**[36] and **24**[66] have similar estimated lifetimes in water ($\tau \approx 10^{-11}$ s) and yet exhibit different azide ion capture characteristics. In the case of **22**, significant quantities of azide substitution products are generated,[36,56] but with **24** there is little or no trapping with azide ion.[66] The oxacarbenium ions **22** and **24** are generated from cationic and neutral substrates, respectively. By virtue of electrostatic interactions, the cationic substrate will form a greater concentration of azide ion-containing pre-association complexes than will the corresponding neutral substrate. Thus, the cationic substrate should give more solvent-separated complexes (Scheme 7) and this will result in greater trapping by the associated azide ion.

## 2.3 Glycopyranosyl transfer from glycopyranosyl fluorides and phosphates

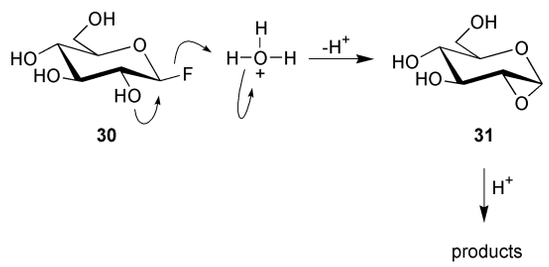
The synthesis[67] of glycopyranosyl fluorides and their use in both the enzymatic[68] and the non-enzymatic[67a,69] formation of glycopyranosides have been reviewed recently. Despite the fact that glycopyranosyl fluorides have been known for many years, few thorough non-enzymatic mechanistic studies of them have been performed.

### 2.3.1 Acid-catalysed reactions of glycopyranosyl fluorides

Barnett reported that the acid-catalysed hydrolyses (0.5–3.0 M $HClO_4$) of α-D-gluco-, α-D-xylo-, α-D-galacto-, and β-L-arabino-pyranosyl fluorides (**26**, **27**, **28**, and **29** respectively) proceed *via* a specific-acid-catalysed dissociative mechanism, a conclusion that was based on measured activation entropies ($\Delta S^{\ddagger}$) in the range of +22 to +50 J $mol^{-1}$ $K^{-1}$ for these four fluoroacetals.[70]

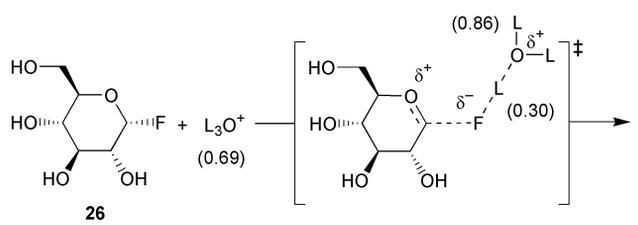



In contrast, β-D-glucopyranosyl fluoride (**30**) displays an enhanced reactivity relative to its α-anomer and has an associated $\Delta S^{\ddagger}$ of −26 J $mol^{-1}$ $K^{-1}$.[70] From this study it was concluded that β-D-glucopyranosyl fluoride undergoes acid-catalysed hydrolysis *via* an intramolecular $A_ND_N$ reaction that generates the 1,2-epoxide (**31**) as an intermediate (Scheme 11).[70]




**Scheme 11**

In 1991 Banait and Jencks reported a thorough study of the nucleophilic substitution reactions of α-D-glucopyranosyl fluoride (**26**).[71,72] Their work revealed that hydrolysis of **26** occurs *via* a general-acid-catalysed mechanism in which the rate-limiting step involves a proton "in flight". This reaction is characterised by a shallow Brønsted slope ($\alpha = 0.15$), although the value for $\alpha$ increases to 0.4 if the catalytic constant for $H_3O^+$ is included in the correlation.[72] The solvent KIE effect for the hydronium ion-catalysed reaction of **26** ($k_{H_3O^+}/k_{D_3O^+} = 1.4$) is consistent with rate-limiting proton transfer. Specifically, substitution of the derived Brønsted $\alpha$ value of 0.4 into eqn. (3) generates a fractionation factor ($\phi^{TS}$) of 0.86 for the two non-transferring protons. When this value and the measured solvent KIE are entered into eqn. (2), a transition state fractionation factor ($\phi^{TS}$) of 0.3 can be calculated for the "in flight" proton (Scheme 12).




**Scheme 12**

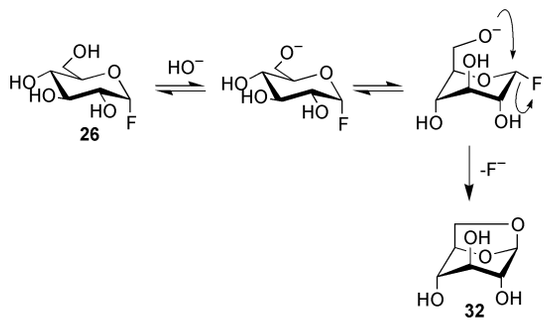
Presumably this reaction occurs without nucleophilic solvent participation because the electrophilic catalysis provided by the general-acid should obviate the need for nucleophilic catalysis to assist the fluoride anion departure.

In summary, Barnett's conclusion that these reactions involve specific-acid catalysis is invalid. Clearly, departure of the fluoride ion commences prior to installation of the proton. The conjugate acid of **26** is not an intermediate in these reactions.

### 2.3.2 Base-catalysed reactions of glycopyranosyl fluorides

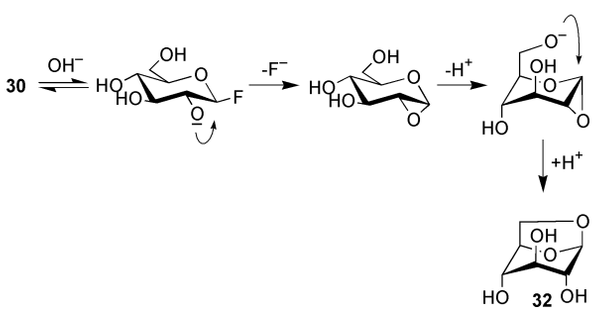
Hydrolysis reactions of **27** and **29** at high base concentrations (0.2–5.0 M NaOH) give the corresponding aldose as the sole reaction product. These base-catalysed reactions presumably occur by direct nucleophilic attack of hydroxide ion on the pentopyranosyl fluoride.[70] In contrast, when treated under identical conditions, both **26** and **28** produce a substantial quantity of a cyclic anhydro sugar; their respective bicyclic

products are the result of intramolecular $A_ND_N$ reactions as is illustrated for α-D-glucopyranosyl fluoride in Scheme 13.[70]



**Scheme 13**

In basic solutions β-D-glucopyranosyl fluoride (**30**) also reacts to generate the anhydrosugar **32** as the main reaction product. However this chemical conversion presumably involves two sequential intramolecular $A_ND_N$ reactions (Scheme 14).[70]



**Scheme 14**

As proposed by Barnett,[70] the measured solvent KIE ($k_{OH^-}/k_{OD^-} = 0.67$)[72] for the reactions of **26** is in accord with the occurrence of two specific-base pathways: (1) rate-limiting attack of an ionised 6-OH group on the anomeric centre (Scheme 13); and (2) concerted nucleophilic displacement ($A_ND_N$) of the fluoride ion by hydroxide ion (not depicted).[71] Hydrolysis of α-D-glucopyranosyl fluoride also occurs *via* a general-base catalysed reaction, and this process is characterised by a Brønsted $\beta$ coefficient of 0.06 to give glucose and methyl β-D-glucopyranoside as the two products when the reaction is run in aqueous methanol solutions.[72] Fig. 4 illustrates the

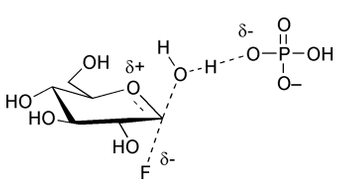


**Fig. 4** Transition state structure for the general-base catalysed hydrolysis of α-D-glucopyranosyl fluoride.

likely transition state for hydrolysis of **26** in a reaction catalysed by phosphate dianion in which the solvent KIE ($k_{H_2O}/k_{D_2O}$) is 1.9.[72]

β-Glucopyranosyl fluoride (**30**), which also undergoes general-base catalysed hydrolysis,[73] is catalysed more efficiently by the monoanion than the dianion of succinic acid. Thus, this particular reaction probably occurs *via* a pre-equilibrium deprotonation (specific-base) followed by a general-acid catalysed reaction (*i.e.*, the kinetic equivalent of general-base catalysis).[73] Furthermore, this catalysed reaction displays an anomeric $^{13}C$ KIE of 1.06, thereby supporting a transition state structure such as that shown in Fig. 5 in which a C2 oxyanion displaces the anomeric fluoride with general-acid assistance from the neutral form of succinic acid.[73]

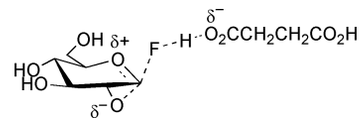


**Fig. 5** Possible transition state structure for the reaction of β-D-glucopyranosyl fluoride with the monoanion of succinic acid.

### 2.3.3 Spontaneous reactions of glycopyranosyl fluorides in water

The pH–rate profile for hydrolysis of **26** is flat for reactions conducted between the pH values of 4 and 10,[72] indicating that in this pH region neither $H_3O^+$ nor $HO^-$ catalyses the reaction. Banait and Jencks noted that within this pH regime, anionic nucleophiles react with **26** *via* an $A_ND_N$ ($S_N2$) reaction that is characterised by a Swain–Scott nucleophilic sensitivity parameter ($s$) of 0.18, to give a stable inverted substitution product when azide ion is the nucleophile.[71] It is of particular interest that the neutral nucleophile pyridine produces no β-D-glucopyranosyl pyridinium salt when reacted with α-D-glucopyranosyl fluoride.[72] Based on the principle of microscopic reversibility, it must be concluded that anionic nucleophiles cannot react with β-D-glucopyranosyl pyridinium salts *via* $A_ND_N$ mechanisms (Section 2.2.1) and, therefore, only anionic nucleophiles and solvent (*vide infra*) are capable of displacing the fluoride ion from α-D-glucopyranosyl fluoride *via* a concerted $A_ND_N$ mechanism.[71] Microscopic reversibility dictates that the reaction of β-D-glycopyranosyl fluoride with fluoride ion and, presumably, other anions also proceeds *via* an $A_ND_N$ mechanism, although to date, detailed kinetic and product studies on this topic have not been reported.

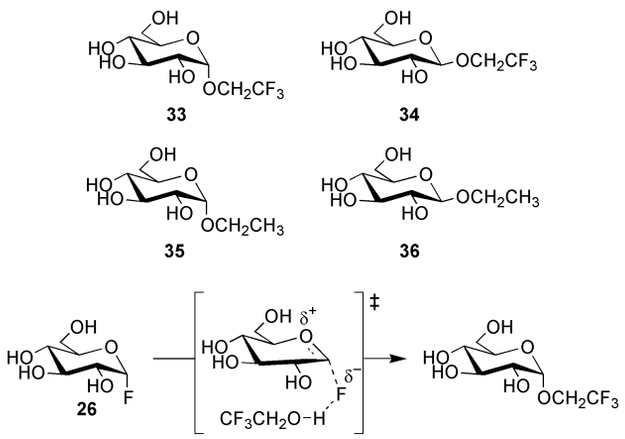
In 1994, Zhang *et al.* reported a detailed KIE study on the spontaneous hydrolyses of α- and β-glucopyranosyl fluorides (**26** and **30**, respectively) and on the nucleophilic substitution of **26** with azide ion.[73] Key conclusions that emerged from this study are: (1) measured anomeric $^{13}C$ KIEs for the nucleophilic substitution reactions of α-glucopyranosyl fluoride (**26**) with either azide ion (1.085) or water (1.032) are consistent with these reactions occurring *via* concerted $A_ND_N$ mechanisms;[32] (2) the hydrolysis of β-glucopyranosyl fluoride (**30**) occurs *via* a transition state that features little or no nucleophilic solvent participation ($k_{12}/k_{13}$ = 1.017); and (3) the spontaneous hydrolyses of both anomeric glucopyranosyl fluorides proceed *via* transition states in which significant charge build-up on the ring oxygen atom has occurred (ring $^{18}O$-KIEs for the reactions of **26** and **30** are 0.984 and 0.985, respectively).[73]

### 2.3.4 Spontaneous reactions of glycopyranosyl fluorides in alcoholic solvents

The solvolysis reactions of α-D-glucopyranosyl fluoride in aqueous solutions of methanol and ethanol–trifluoroethanol (1 : 1 v/v) unexpectedly gave glucose as the only observed product, even when the organic solvent component was present in large excess (up to 90% v/v methanol and 95% 1 : 1 ethanol–trifluoroethanol).[71] These observations led the authors to postulate that during solvolysis of α-D-glucopyranosyl fluoride, development of high charge density at the transition state is facilitated by a localised solvent effect in which the presence of water is favoured in the restrictive environment at the anomeric carbon.[71] This remarkable nucleophilic selectivity for attack by water vanishes when either the fluoride ion leaving group is associated with a general-acid[72] or the leaving group is changed to a neutral molecule such as a pyridine.[57]

A 1980 study by Sinnott and Jencks[74] presents glucopyranosyl fluoride solvolysis results from reactions run in an equimolar mixture of EtOH and TFE that give the four substitution products **33**–**36**. Their data agrees with the conclusion that α-glucopyranosyl fluoride requires greater assistance for departure of the fluoride ion than does the β-fluoride.[73] For

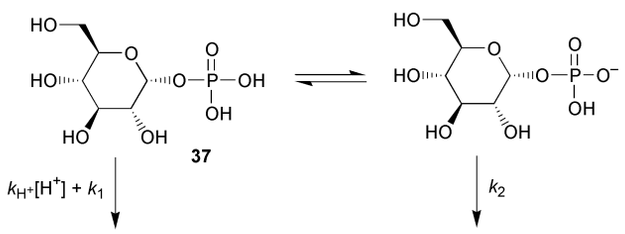
these reactions of α-D-glucopyranosyl fluoride, electrophilic catalysis of fluoride departure by trifluoroethanol results in the formation of more retained than inverted trifluoroethyl glucopyranoside in the product mixture (Scheme 15).




**Scheme 15**

### 2.3.5 Acid-catalysed and spontaneous reactions of glycopyranosyl phosphates

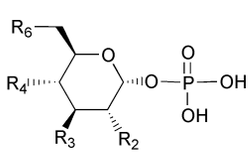
The hydrolysis of α-D-glucopyranosyl phosphate (**37**) to give glucose has been shown to proceed *via* the kinetic pathways illustrated in Scheme 16.[75] Reaction of the monoanionic form of




**Scheme 16**

α-D-glucopyranosyl phosphate ($k_2$) occurs with P–O bond cleavage, while both the spontaneous ($k_1$) and the acid-catalysed ($k_{H^+}$) reactions of the neutral compound proceed exclusively with C–O bond cleavage, giving $H_2PO_4^-$ and $H_3PO_4$ as the respective leaving groups.[75a]

In 1986, Withers and co-workers monitored hydrolysis in 1.0 M $HClO_4$ of the four deoxyfluoro derivatives of α-D-glucopyranosyl phosphate (**38**–**41**, R = F).[76] In addition, the hydrolysis of 2-deoxy-2-fluoro-α-D-*arabino*-hexopyranosyl phosphate (**38**, $R_2$ = F) was followed over a pH range of 1.0–6.2.



**38**: $R_3 = R_4 = R_6$ = OH: $R_2$ = F, H

**39**: $R_2 = R_4 = R_6$ = OH: $R_3$ = F, H

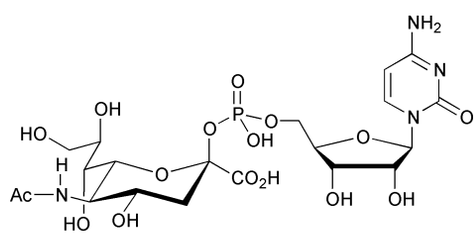
**40**: $R_2 = R_3 = R_6$ = OH: $R_4$ = F, H

**41**: $R_2 = R_3 = R_4$ = OH: $R_6$ = F, H

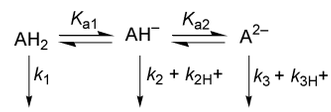
At low pH, the order of hydrolytic reactivity for these glycopyranosyl phosphate compounds is glucopyranosyl (**37**) > 6-fluoro (**41**, $R_6$ = F) > 3-fluoro (**39**, $R_3$ = F) > 4-fluoro (**40**, $R_4$ = F) > 2-fluoro (**38**, $R_2$ = F), an order that is consistent with the neutral phosphate reacting with C–O bond cleavage *via* oxacarbenium ion-like transition states in which the positive charge is delocalised over C1 and O5.[76] The observed pH–rate profile for hydrolysis of the 2-deoxyfluoro compound **38** ($R_2$ = F)[76] is similar in appearance to that reported for the parent α-D-glucopyranosyl phosphate (**37**).[75a] Introduction of a 2-fluoro group onto the parent structure affects the kinetic term $k_1$, causing a 64-fold rate reduction, while $k_2$ is hardly affected. This result is expected, given that hydrolysis of the neutral species involves reaction *via* an oxacarbenium ion-like transition state and that the energy of this species will be raised by the presence of the electron-withdrawing fluorine atom. In contrast, the mechanistic pathway that involves P–O bond cleavage ($k_2$) is accelerated slightly by the introduction of the 2-fluoro group and this enables the oxyanion of 2-deoxy-2-fluoro-*arabino*-hexopyranoside to function as a better leaving group than does the corresponding anion of glucose.

In an extension of their previous work, Withers and co-workers reported the hydrolytic rate constants for the reaction in 1.0 M $HClO_4$ with a series of deoxyglycopyranosyl phosphates (**38**–**41**, R = H).[77] The reactivity order for these deoxy compounds of 6-deoxy (**41**, $R_6$ = H) < 3-deoxy (**39**, $R_3$ = H) < 4-deoxy (**40**, $R_4$ = H) < 2-deoxy (**38**, $R_2$ = H) is the reverse of that for the deoxyfluoro derivatives. These reactivity orders suggest that the dominant effect of a substituent in the hydrolytic rate constant is its field effect (see also section 2.4.3).[77]

In 1996, Horenstein and Bruner reported a kinetic study of the hydrolysis of the sugar-containing cytidine monophosphate derivative of *N*-acetylneuraminic acid CMP-β-D-*N*-acetylneuraminide **42**.[78] Because this biologically important carbohydrate contains two ionisable groups, a mechanistic scheme for both the acid-catalysed and spontaneous reactions, shown in Scheme 17, is relevant (compound **42** is represented by $AH_2$ in the scheme).



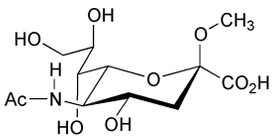
**42**



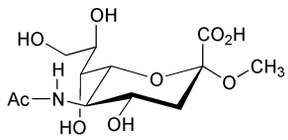

**Scheme 17**

Horenstein and Bruner analysed a pH–rate profile that was measured between 3.23 and 7.16 and found it to be in accordance with three distinct reaction pathways: (1) acid-catalysed hydrolysis of the monoanion ($k_{2H^+}$); (2) acid-catalysed hydrolysis of the dianion ($k_{3H^+}$) or the kinetically-equivalent spontaneous hydrolysis of the monoanion; and (3) spontaneous hydrolysis of the dianion ($k_3$).[78] At a pH of 5, the majority of the reaction (91%) proceeds *via* pathway 2, and the rate of reaction is independent of buffer concentration. Given that this pathway is associated with a large β-secondary deuterium KIE ($k_{H_2}/k_{D_2}$ = 1.25), it is apparent that the reaction proceeds with C–O bond cleavage. The reaction is analogous to the α-D-glycopyranosyl phosphate reaction in that it involves departure of a phosphate anion which is, in this case, the oxyanion of CMP. The measured $^{14}C$ KIE of 1.030 at the anomeric carbon corresponds to a $^{13}C$ KIE of about 1.016[79] which is indicative of a dissociative ($D_N$ * $A_N$ or $D_N$ + $A_N$) reaction.[32] The conclusion that this is a dissociative reaction agrees with the

solvolysis products formed in aqueous methanol, products that include both anomers of methyl *N*-acetylneuraminide (**43** and **44**).[78]

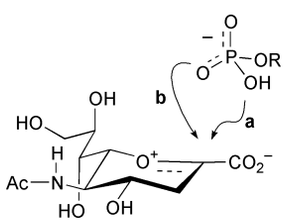


**43**



**44**

In a subsequent manuscript, Horenstein and Bruner refined their proposed mechanism for the hydrolysis of CMP-β-D-*N*-acetylneuraminide (**42**).[80] Based on an observed solvent KIE ($k_{H_2O}/k_{D_2O}$) of 0.45 at pH 5, they suggested that the reaction involves protonation on the glycosidic oxygen atom.[80] However, this measured isotope effect is also consistent with equilibrium protonation on a non-bridging phosphorus-oxygen atom.[13] Indeed, it seems unlikely that the productive reaction channel for hydrolysis involves protonation on the glycosidic oxygen atom because the principal of microscopic reversibility requires that the *N*-acetylneuraminyl oxacarbenium ion be captured by the P–OH oxygen atom of the monoanion of CMP (pathway **a**, Scheme 18) rather than by one of the two oxygen atoms which formally share the negative charge (pathway **b**, Scheme 18).



**Scheme 18**

The reaction of **42** in the presence of azide ion shows a small dependence on the concentration of azide ion and, importantly, both of the anomeric *N*-acetylneuraminyl azides **45** and **46** are formed.[80] Horenstein and Bruner analysed the nucleophilic substitution reactions of **42** in terms of three separate reaction channels: (**a**) capture of a tight ion-pair; (**b**) capture of a solvent-separated ion-pair; and (**c**) capture of a free oxacarbenium intermediate (Scheme 19; pathway **b** is not shown in order to simplify the diagram).[80] From their data, Horenstein and Bruner estimated the lifetime of the *N*-acetylneuraminyl cation in water to be $\geq 3 \times 10^{-11}$ s,[80] a value which is slightly larger than that estimated by Bennet and co-workers for the 2-deoxyglucopyranosylium ion (section 2.2.1).[36]

Given that the leaving group for CMP-β-D-*N*-acetylneuraminide hydrolysis at pH 5 is anionic (or dianionic if the catalytic proton is on the carboxylate group), similarities can be seen between this azide ion-promoted reaction and the substitution reactions of α-D-glucopyranosyl fluoride. That is, if the azide ion is properly aligned to attack the nascent oxacarbenium ion, then the tight ion-pair (**47**, Scheme 19) cannot be a discrete intermediate[71] and the observed second-order reaction will occur *via* a direct displacement $A_ND_N$ mechanism. This type of mechanism should produce a large anomeric $^{13}C$ KIE.[73] On the other hand, if reorganisation within the triple ion pair is rate limiting, then the anomeric $^{13}C$ KIE should be similar in magnitude to that for formation of an oxacarbenium ion intermediate (*i.e.*, $k_{12}/k_{13} \approx 1.01$). No such study has yet been reported.

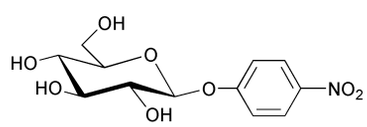
### 2.4 Glycopyranosyl transfer from aryl glycopyranosides

Reminiscent of the α-D-glucopyranosyl fluoride reactions discussed previously, hydrolysis of aryl glycopyranosides can occur *via* acid- and base-catalysed, as well as by spontaneous reaction pathways.

#### 2.4.1 Acid-catalysed reactions of aryl glycopyranosides

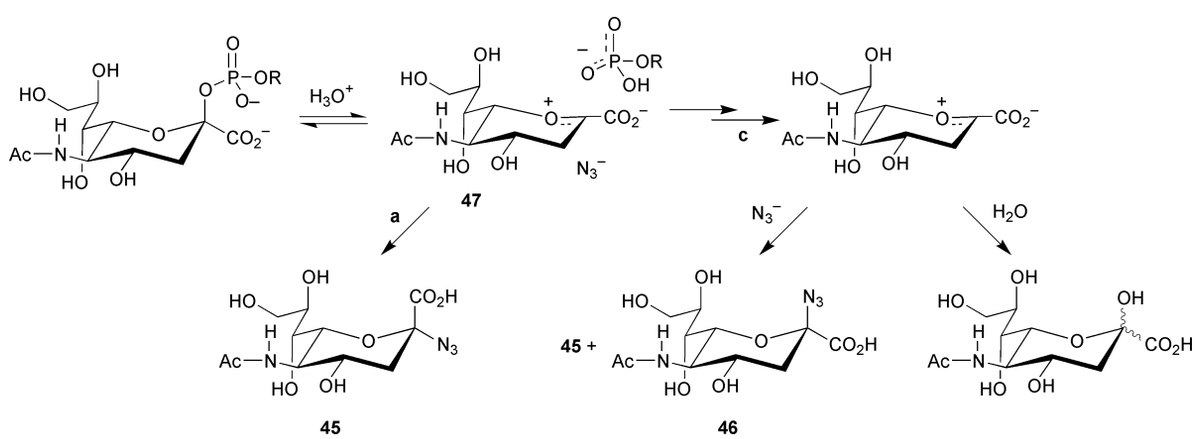
Acid-catalysed hydrolyses of aryl glycopyranosides are associated with Brønsted $\beta_{Lg}$ values that are either close to zero[81] or slightly positive,[82] values which are consistent with rate-limiting exocyclic C–O cleavage of the substrate's conjugate acid. The hydrolytic mechanism is expected to change from specific- to general-catalysis as the p$K_a$ of the leaving group's conjugate acid decreases. In particular, as the aryl-oxygen atom becomes less basic, the lifetime of the conjugate acid of the aryl glycopyranoside becomes shorter and the overall result is a change in hydrolytic mechanism from specific- to general-catalysis.

For aryl β-glucopyranosides the mechanistic change occurs when the leaving group is 4-nitrophenol.[83] It is remarkable that the reactions of 4-nitrophenyl β-glucopyranoside (**48**) appear to be balanced finely between the two types of acid-catalysis as demonstrated by both 1-$^{18}O$ and solvent KIEs. At a temperature of 50 °C, the two KIEs are consistent with the occurrence of general-acid catalysis ($k_{16}/k_{18}$ = 1.035[84] and $k_{H_3O^+}/k_{D_3O^+}$ = 1.01[83]) yet at 80 °C, the $^{18}O$-KIE value is in the range normally associated with specific-acid catalysis (1.025),[83] and the solvent effect is significantly smaller at this higher temperature (0.71).[83]

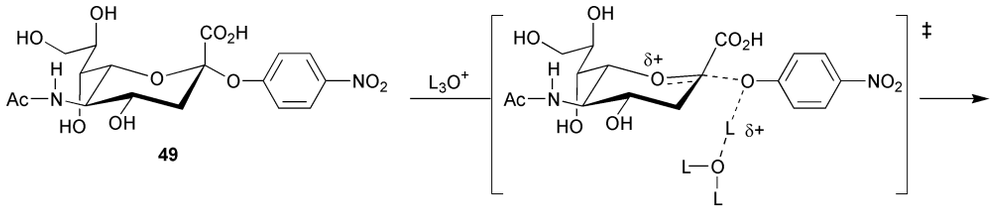


**48**

The acid-catalysed reaction of neutral aryl α-D-*N*-acetylneuraminides exhibits a $\beta_{Lg}$ value of 0 and, when taken together with the observed solvent KIE ($k_{H_3O^+}/k_{D_3O^+}$) value for the 4-nitrophenyl compound (**49**) at a pH of 1.36, is consistent with a general-acid catalysed $D_N + A_N$ mechanism as depicted in Scheme 20.[85]



**Scheme 19**



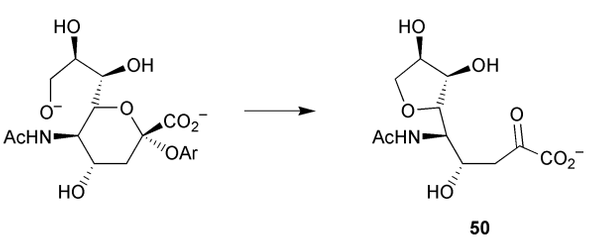
**49**

**Scheme 20**

Ashwell *et al.* also proposed that the hydrolysis of aryl α-D-*N*-acetylneuraminides at pH values around 3 is dominated by a general-acid-catalysed mechanism that is similar to that depicted in Scheme 20 except that the carboxylic acid group is deprotonated.[85]

### 2.4.2 Base-catalysed reactions of aryl glycopyranosides

Base-catalysed hydrolysis of aryl glycopyranosides generally occurs *via* a mechanism that involves an intramolecular nucleophilic attack by an ionised sugar hydroxy group on either the anomeric centre ($A_ND_N$)[82,86] or the *ipso*-carbon of the aromatic ring ($A_N + D_N$; $S_N2Ar$).[87] The base-catalysed reactions of aryl glycopyranosides are much slower than those of the corresponding glycopyranosyl fluorides because fluoride ion is a better leaving group than a phenoxide ion of similar basicity.[88] As a consequence, the more severe reaction conditions required for the base-catalysed hydrolysis of aryl glycopyranosides can give rise to extensive product decomposition during the reaction. As an example, Scheme 21 illustrates the postulated



**50**

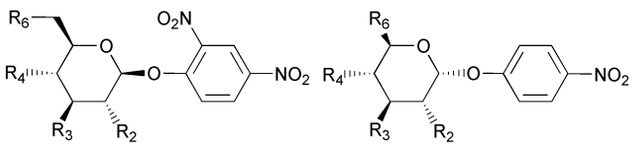
**Scheme 21**

reaction pathway for base-catalysed hydrolysis of aryl α-D-*N*-acetylneuraminides in which the intramolecular nucleophilic attack of the ionised C9-hydroxy group on the C6 atom gives a highly substituted furan derivative (**50**) that is unstable under the 0.1 M NaOH, 50 °C reaction conditions.[85]

### 2.4.3 Spontaneous reactions of aryl glycopyranosides

In contrast to the situation with alkyl glycopyranosides, the spontaneous hydrolysis of aryl glycopyranosides containing weakly basic aryl oxide ion leaving groups has been known for many years.[89] Spontaneous reactions of aryl glycopyranosides are greatly accelerated by the addition of electron-withdrawing groups on the aromatic ring, as can be seen by the Brønsted parameter $\beta_{Lg}$ estimate of −1.08 for the reactions of aryl galactopyranosides.[88] In a recent mechanistic study, Namchuk *et al.* monitored the hydrolyses of a series of 2,4-dinitrophenyl β-D-glycopyranosides in which the various carbohydrate hydroxy groups were substituted by either a fluorine or a hydrogen atom.[90] Two of the series of compounds studied employed the glucopyranoside skeleton modifications and are illustrated below (**51**, **52**).

The observed relative rates for hydrolysis of these glycopyranoside derivatives followed the order 2-deoxy > 4-deoxy > 6-deoxy ≈ 3-deoxy > glycopyranoside > 6-fluoro > 3-fluoro > 4-fluoro > 2-fluoro.[90] In addition, when the observed rate constants for reaction of each series were plotted according to the Hammett equation, eqn. (8), derived for systems in which only inductive or field effects are possible, the analysis indicated



**51**: $R_3 = R_4 = R_6 = OH$: $R_2$ = H, OH, F

**52**: $R_2 = R_4 = R_6 = OH$: $R_3$ = H, OH, F

**53**: $R_2 = R_3 = R_4 = R_6$ = H

**54**: $R_2 = R_3 = R_4 = R_6 = CH_3$

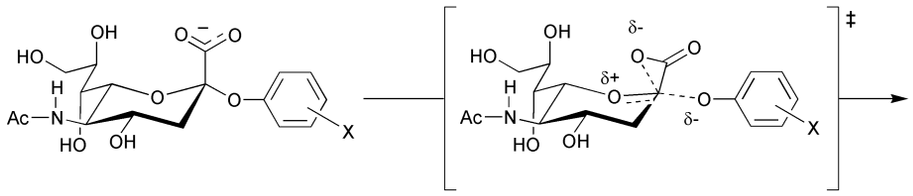
a general order for the calculated $\rho_I$ values of 6-substitutents ($\rho_I \approx -2$) > 3-substitutents ($\rho_I \approx -3$) > 4-substitutents ($\rho_I \approx -4$) > 2-substitutents ($\rho_I \approx -9$).[90]

$$\log (k) = \rho_I\sigma_I + \log (k_0) \quad (8)$$

The expected relative rate constants for substituted 2,4-dinitrophenyl glucopyranosides were calculated using eqn. (9), where $\theta$ is the angle between a line of length $R$ joining the centre of the substituent's dipole and the centre of charge development, and $e_{C1}$ and $e_{O5}$ are the fractional transition state charges on C1 and O5, respectively.

$$\log (k_{rel}^{calc}) = \sum_{i=C2}^{C6} e_{C1}[\sigma_{Ii} \cos\theta_i /(R_{C1i})^2] + e_{O5}[\sigma_{Ii} \cos\theta_i /(R_{O5i})^2] \quad (9)$$

From these results, Namchuk *et al.* concluded that for the glucopyranoside series the major determinant of their relative hydrolytic rates is the field effect of the substituent on the oxacarbenium ion-like transition state in which substantial positive charge is present on the ring oxygen atom. A possible concern with the above analysis is the basic assumption that all of the aryl glycopyranosides in the study react by the same mechanism, in this case a dissociative mechanism. It seems eminently reasonable that the hydrolysis of 2,4-dinitrophenyl β-D-glucopyranoside does occur *via* a $D_N$ * $A_N$ dissociative mechanism since this compound[31] and several glycopyranosyl pyridinium salts,[31,36,56] compounds that react *via* such a mechanism (section 2.2.1), display very similar salt effects. However, the hydrolytic mechanism for substituted glycopyranosides must change at the point where the oxacarbenium ion intermediate becomes so reactive that it cannot become a discrete entity. That is, a dissociative reaction ($D_N$ * $A_N$) that generates a non-equilibrated cationic intermediate will become a weakly associative reaction ($A_ND_N$) when the solvent's role changes from that of dipolar solvation to one of nucleophilic solvent participation. Amyes and Jencks reported[9] that for acyclic acetal derivatives a 600-fold change in rate of oxacarbenium ion formation is associated with a 4-fold change in the cation's lifetime ($\tau = 1/k_{HOH}$). If a similar relationship holds for aryl glycopyranosides, then the 40-fold faster reaction of **51** ($R_2$ = OH) compared to **51** ($R_2$ = F) suggests that the lifetime of the 2-deoxy-2-fluoroglucopyranosylium cation would be about one half that of the parent cation (**2**).[91] There is evidence to suggest that 2-deoxy-2-fluoroglycopyranosyl systems have crossed, or are close to, the boundary between $D_N$ * $A_N$ and $A_ND_N$ mechanisms. In Hammett plots of reaction rate data for 2-substituted glucopyranosides (**51**, $R_2$ = H, OH and F) and



**Scheme 22**

mannopyranosides (structures not shown), the 2-deoxy-2-fluoro data points display positive deviations from correlations that are based solely on the 2-deoxy and 2-hydroxy compounds.[90] As a consequence, the application of other mechanistic probes such as anomeric $^{13}C$ KIE, salt effects, and solvolysis product analysis would be useful for exploring the possibility that spontaneous hydrolyses of aryl 2-deoxy-2-fluoroglycopyranosides occur *via* weakly associative mechanisms ($A_ND_N$).

In a recent study, Dean *et al.* noted that 2-(4-nitrophenyl)-tetrahydropyran (**53**) undergoes spontaneous hydrolysis 4 times faster than the tetramethyl analogue **54**.[92] In light of the expected 30-fold increase in hydrolytic rate upon incorporation of methyl substituents, this reactivity difference provides evidence in support of torsional effects slowing glycopyranosyl transfer reactions.[92] Such torsional effects, however, clearly perturb the process of charge delocalisation onto the ring oxygen atom, and this results in imperfect synchronisation between endocyclic C=O bond formation and exocyclic C–O bond cleavage at the hydrolytic transition state (see ring $^{18}O$-KIE discussion in section 2.1.1). It is not clear how such torsional effects alter the lifetime of the oxacarbenium ion intermediate: based on microscopic reversibility, if the transition state for oxacarbenium ion formation is unbalanced, then a similar imbalance will be evident at the transition state for capture of the cationic intermediate.

The spontaneous hydrolyses of aryl α-D-*N*-acetylneuraminides are more facile than those for the corresponding aryl glycopyranosides. For instance, spontaneous hydrolysis of 2,4-dinitrophenyl β-D-glucopyranoside (**51**, $R_2$ = OH) at 50 °C is estimated to occur with a rate constant of $1.72 \times 10^{-5}$ $s^{-1}$,[90] while an extrapolation using the published $\beta_{Lg}$ value for aryl α-D-*N*-acetylneuraminides yields an estimated rate constant of 2 $s^{-1}$ for hydrolysis of 2,4-dinitrophenyl α-D-*N*-acetylneuraminide at 50 °C.[85] Scheme 22 illustrates the proposal of Ashwell *et al.* that spontaneous hydrolysis of aryl α-D-*N*-acetylneuraminide occurs with some participation of the C1 carboxylate at the reaction transition state, although such an effect would not necessarily generate a transient α-lactone.[85]

Indeed, the Brønsted plot for hydrolysis of aryl α-D-*N*-acetylneuraminides shows an upward curvature that is consistent with greater participation occurring with the poorer phenoxide leaving groups. Again, it would be instructive to utilise other mechanistic probes such as anomeric $^{13}C$ KIEs to help identify possible intramolecular participation of the ionised carboxylate group during hydrolysis of aryl α-D-*N*-acetylneuraminides. However, such participation during the hydrolysis of CMP β-D-*N*-acetylneuraminides[80] and pyridinium α-D-*N*-acetylneuraminides has been ruled out.[58]

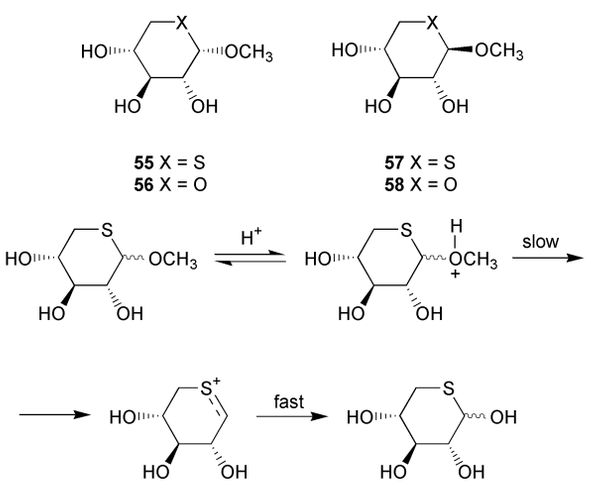
## 3 Thioglycopyranosides

### 3.1 Glycopyranosyl transfer from alkyl 5-thioglycopyranosides

Compared to glycopyranosides, 5-thiopyranosides adopt a more puckered ring conformation due to the longer C–S bond and the smaller C–S–C angle.[93] Other ground state effects in alkyl 5-thiopyranosides include a larger anomeric effect than their oxygen containing counterparts[94,95] and this enhanced tendency for an electronegative group to adopt an axial orientation is caused mainly by electronic factors.[96] Furthermore, both experimental results[97] and theory[98] suggest that an adjacent sulfur atom stabilizes a carbenium ion to a greater extent than does an adjacent oxygen atom.

#### 3.1.1 Acid-catalysed reactions of alkyl 5-thioglycopyranosides

In 1963, Whistler and Van Es noted that methyl 5-thio-α-D-xylopyranoside (**55**) hydrolyses approximately ten times faster than does methyl α-D-xylopyranoside (**56**) and that the corresponding rate difference for the β-homologues is about fourteen times faster for the thio- than the non-thio compound (**57** and **58**, respectively).[99] Recently, Induragalla and Bennet reported a detailed KIE study for the acid-catalysed hydrolyses of **56** and **58**, reactions that yield 5-thioxylose as the sole carbohydrate reaction product.[39] These hydrolysis reactions are specific-acid-catalysed as determined by the magnitude of the solvent deuterium KIEs ($k_{D_3O^+}/k_{H_3O^+}$) for **56** and **58** of 2.37 and 2.63, respectively. In addition, the respective measured leaving group $^{18}O$-KIEs for **56** and **58** are 1.027 and 1.035. Thus, pre-equilibrium protonation occurs on the exocyclic oxygen atom followed by rate-limiting exocyclic C–O cleavage to generate a 5-thioxylopyranosylium ion (**59**) as the first-formed intermediate (Scheme 23).[39]



**55** X = S
**56** X = O
**57** X = S
**58** X = O
**59**

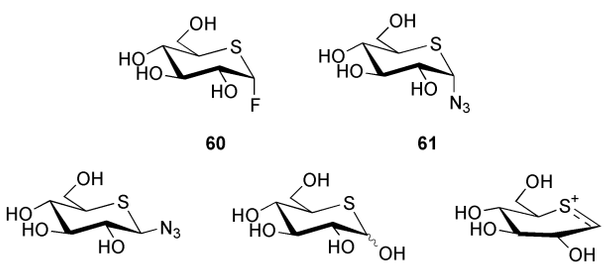
**Scheme 23**

The larger leaving group and solvent ($k_{D_3O^+}/k_{H_3O^+}$) KIEs for methyl 5-thio-β-D-xylopyranoside relative to those of their α-diastereomer are consistent with a later transition state for C–O bond cleavage in the acid-catalysed reactions of this anomer. Hydrolysis of **56** and **58** gives observed anomeric $^{13}C$ KIEs of 1.031 and 1.028, respectively, values that are larger than those expected for a dissociative $D_N + A_N$ reaction (1.00–1.01).[32] The larger anomeric $^{13}C$-KIEs for the thio- *versus* oxygen-containing glycopyranosides probably originate from a lower degree of synchronisation between C–S bond strengthening and C–O bond breaking at the transition state for hydrolysis of 5-thioxylopyranosides compared to that associated with the corresponding endo- and exocyclic bonds in xylopyranosides. This conclusion is in accord with a higher intrinsic barrier for formation of a thiacarbenium ion than for formation of the analogous oxacarbenium ion.[97]

### 3.2 Glycopyranosyl transfer from 5-thioglycopyranosyl fluorides

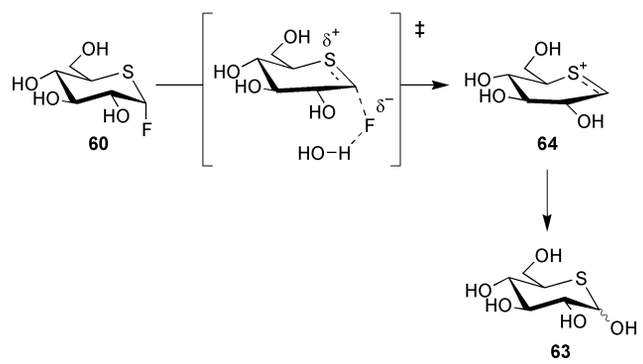
#### 3.2.1 Spontaneous reactions of 5-thioglycopyranosyl fluorides

A recent publication by Johnston *et al.* presents an in-depth study of the mechanism of hydrolysis for a 5-thioglycopyranosyl fluoride.[100] Prior to this report, mention had been made in a footnote that 5-thio-α-D-glucopyranosyl fluoride hydrolyses rapidly in the absence of enzyme catalysis.[101] Notably, the hydrolytic rate constant for **60** is independent of pH in a range of at least 7.5–10.0 and thus the reaction is neither acid- nor base-catalysed.[100] When tested at 30 °C with $I$ = 2.0 M $NaClO_4$, compound **60** hydrolyses about 800-fold more rapidly than α-D-glucopyranosyl fluoride (**26**). Presumably, this enhanced reactivity is due, in part, to ground state destabilisation of compound **60**, the result of a smaller ground-state stabilisation in the S–C–F system than in the O–C–F system.[102]




As mentioned previously (section 2.3.3), α-D-glucopyranosyl fluoride (**26**) reacts with azide ion *via* a weakly associative $A_ND_N$ mechanism to give β-D-glucopyranosyl azide,[71] although the observed first-order rate constants ($k_{obs}$) for reaction of **60** as a function of various anion concentrations are essentially invariant.[100] In $D_2O$ solutions, the observed pseudo-first-order rate constant for reaction of **60** at an azide ion concentration of 1.0 M is only about 1.19-fold faster than that for the corresponding reaction run in the absence of azide ion.[100] Given the above observation, a substitution mechanism involving an $A_ND_N$ reaction would be expected to generate reaction products that consist of about 16% **62** and 84% **63**. The actual product percentages formed under these conditions are 24, 52, and 24% of **61**, **62**, and **63**, respectively.[100] From these results, it is clear that the reactions of **60** occur *via* a dissociative mechanism.

Using the "azide clock" methodology of Jencks and co-workers,[8] Johnston *et al.* estimated a lifetime for the 5-thioglucopyranosylium ion (**64**) of $1.1 \times 10^{-9}$ s,[100] sufficient time for the intermediate to become solvent-equilibrated.[103] In contrast, the estimated lifetime for the glucopyranosylium ion is around $(1–3) \times 10^{-12}$ s.[9,36] Clearly, substitution of the ring oxygen by a sulfur atom increases the lifetime of the cyclic carbenium ion at least 360-fold. The solvent KIE of 1.24 ± 0.11 measured for the hydrolysis of **60** suggests that the rate-limiting departure of fluoride ion occurs with some electrophilic assistance originating from H-bonding to water (Scheme 24).

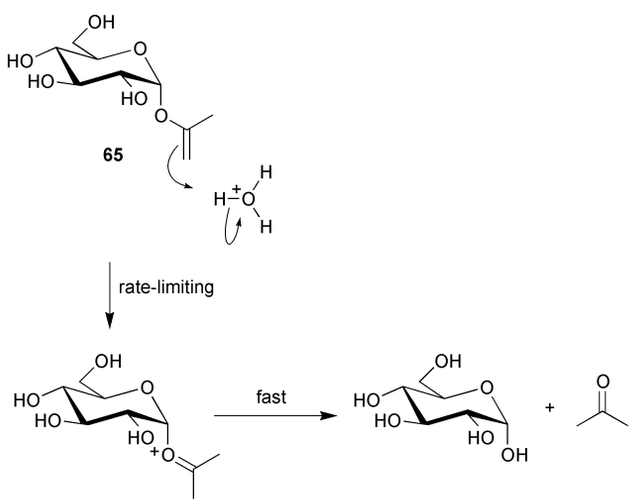



**Scheme 24**

Bennet and co-workers also noted that the ratio of the two azide substitution products **61** and **62** increases concordantly with the azide ion concentration.[100] Such a change in product ratios is consistent with either the occurrence of concurrent $A_ND_N$ and $D_N + A_N$ reactions or non-equilibrated carbenium ion intermediates. Simultaneous $A_ND_N$ and $D_N + A_N$ reactions have been postulated for sterically unencumbered secondary alkyl systems in which the carbenium ion has a short lifetime ($\leq 2.5 \times 10^{-10}$ s).[8b] Therefore, the pseudo-first-order rate constant for capture of the 5-thioxylopyranosylium ion ($k_{SOH} + k_{Nuc}[Nuc^-]$, Scheme 2) is probably similar to that for conformational interconversion of the various half-chair and boat conformations. In other words, the observed changes in product ratio reflect reactions from different conformational ensembles of the cation.[100]

## 4 Miscellaneous

Recently, Chenault and Chafin studied the mechanism for acid-catalysed hydrolysis of the two anomeric isopropenyl glucopyranosides.[104] Key observations reported in this study are: (1) the initial products of hydrolysis are α-D-glucopyranose and β-D-glucopyranose for the reactions of the α-anomer (**65**) and the β-anomer (not shown), respectively; (2) no $^{18}O$ is incorporated into the carbohydrate product when the reaction is run in $^{18}O$-water; (3) the reactions are general-acid catalysed; and (4) the solvent KIEs ($k_{H_3O^+}/k_{D_3O^+}$) are approximately 3 for both anomers.[104] These vinyl acetals hydrolyse *via* rate-limiting protonation on the terminal carbon of the alkene to generate an oxacarbenium ion intermediate that, following attack by water, ultimately generates glucopyranose and acetone as the two reaction products. Scheme 25 illustrates the proposed mechanism for acid-catalysed hydrolysis of **65**.[104]




**Scheme 25**

In summary, isopropenyl glycopyranosides are a third class of glycopyranosides that, in addition to aryl glycopyranosides containing electron-withdrawing groups on the aromatic ring and alkyl glycopyranosides generating stabilised carbenium ions, react with cleavage of the aglycon C–O bond.

## 5 Conclusions

This review summarises the general pathways by which glycopyranosyl groups are transferred non-enzymatically between various acceptor molecules. An underlying theme common to these glycopyranosyl transfer reactions is the intrinsic attribute of these systems to span the mechanistic borderline between dissociative ($S_N1$) and associative ($S_N2$) reactions. For instance, a reaction parameter alteration such as changing from one particular nucleophile or leaving group to another can modify the mechanism from $A_ND_N$ to $D_N$ * $A_N$. Acid-, and to a lesser

extent base-catalysis operates in these systems. Catalysis of these types are most effective when employed on reaction steps that have high energetic barriers. In the case of methyl glucopyranoside, when acid-catalysis is absent, the water-promoted reaction is exceedingly slow because methoxide is a very poor leaving group. However, for aglycons such as fluoride, 2,4-dinitrophenyl, and pyridinium which can react without electrophilic catalysis, spontaneous cleavage of the glycopyranosyl-aglycon bond occurs readily.

Yet another characteristic of these glycopyranosyl transfer reactions is that the glucopyranosylium ion has a very short lifetime in aqueous solutions when anionic nucleophiles are absent. Consequently, when both the leaving group and the nucleophile are anionic, the nucleophilic substitution reactions of glycopyranosyl derivatives occur *via* associative transition states. On the other hand, except for reactions with hydroxide ion or an ionised sugar hydroxy group as the nucleophile, neutral leaving groups such as pyridine engender a dissociative mechanism for glycopyranosyl transfer.

In summary, with respect to the reaction mechanism, glycopyranosyl transfer appears to be a true "borderline" reaction in which the mechanism in aqueous solution depends on: (1) charge on the nucleophile; (2) leaving group charge; (3) anomeric configuration; (4) presence of acid- or base-catalysis; and (5) type of catalysis (*i.e.*, general or specific).

## 6 Acknowledgements

The authors thank Drs Paul Berti and Kelly Tanaka, and Professor Konradsson for preprints of their respective manuscripts prior to publication, and Dr. Paul Kitos for reading a preliminary draft of this review. Grants from the Natural Sciences and Engineering Research Council of Canada (NSERC) provided support for research conducted by AJB at Simon Fraser University.

## 7 References

1 Recent reports include: E. Juaristi and G. Cuevas, *The Anomeric Effect*, CRC Press, Boca Raton, 1995; J. F. Robyt, *Essentials of Carbohydrate Chemistry*, Springer, New York, 1998; J. F. Robyt, *Carbohydrate Chemistry*, ed. G.-J. Boons, Blackie Academic & Professional, London, 1998; J. F. Robyt, *Carbohydrate: Structures, Synthesis and Dynamics*, ed. P. Finch, Kluwer Academic Publishers, Dordrecht, 1999; J. F. Robyt, *Bioorganic Chemistry: Carbohydrates*, ed. S. M. Hecht, Oxford University Press, New York, 1999; G.-J. Boons and K. J. Hale, *Organic Synthesis with Carbohydrates*, Sheffield Academic Press, Sheffield, 2000; R. V. Stick, *Carbohydrates: The Sweet Molecules of Life*, Academic Press, San Diego, 2001.

2 B. Capon, *Chem. Rev.*, 1969, **69**, 407; E. H. Cordes, *Prog. Phys. Org. Chem.*, 1967, **4**, 1; J. N. BeMiller, *Adv. Carbohydr. Chem.*, 1967, **22**, 25; C. A. Vernon, *Proc. R. Soc. London, Ser. B*, 1967, **167**, 389; T. H. Fife, *Acc. Chem. Res.*, 1974, **74**, 581; E. H. Cordes and H. G. Bull, *Chem. Rev.*, 1974, **74**, 581; M. L. Sinnott, in *New Comprehensive Biochemistry: The Chemistry of Enzyme Action*, ed. M. I. Page, Elsevier, Amsterdam, 1984, vol. 6, p. 389.

3 For example: M. L. Sinnott, *Chem. Rev.*, 1990, **90**, 1171; J. D. McCarter and S. G. Withers, *Curr. Opin. Struct. Biol.*, 1994, **4**, 885; A. White and D. R. Rose, *Curr. Opin. Struct. Biol.*, 1997, **7**, 645; G. Davies, M. L. Sinnott and S. G. Withers, in *Comprehensive Biological Catalysis*, ed. M. L. Sinnott, Academic Press, 1998, vol. 1, p. 119; D. L. Zechel and S. G. Withers, *Acc. Chem. Res.*, 2000, **33**, 11; S. G. Withers, *Carbohydr. Polym.*, 2001, **44**, 325.

4 P. J. Berti and K. S. E. Tanaka, *Adv. Phys. Org. Chem.*, 2002, **37**, in press.

5 S. Winstein, B. Appel, R. Baker and A. Diaz, *Spec. Publ. Chem. Soc.*, 1965, **19**, 109; J. M. Harris, *Prog. Phys. Org. Chem.*, 1974, **11**, 89; D. J. Raber, J. M. Harris and P. v. R. Schleyer, in *Ions and Ion Pairs in Organic Reactions, Vol. 2: Role of Ions and Ion Pairs in Chemical Reactions*; ed. M. Swarc, Wiley, New York, 1974, p. 247.

6 F. Wilkinson, *Chemical Kinetics and Reaction Mechanisms*, Van Nostrand Reinhold, New York, 1980, p. 17.

7 H. Maskill, *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford, 1985, p. 270.

8 (*a*) J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, 1982, **104**, 4689; (*b*) J. P. Richard, M. E. Rothenberg and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 1361; (*c*) J. P. Richard, *J. Am. Chem. Soc.*, 1989, **111**, 1455; (*d*) J. P. Richard, T. L. Amyes and M. M. Toteva, *Acc. Chem. Res.*, 2001, **34**, 981.

9 T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, 1989, **111**, 7888.

10 R. A. McClelland, V. M. Kanagasabapathy, N. S. Banait and S. Steenken, *J. Am. Chem. Soc.*, 1991, **113**, 1009.

11 R. A. McClelland, V. M. Kanagasabapathy and S. Steenken, *J. Am. Chem. Soc.*, 1988, **110**, 6913.

12 J. P. Richard, M. M. Toteva and T. L. Amyes, *Org. Lett.*, 2001, **3**, 2225.

13 (*a*) F. J. Alvarez and R. L. Schowen, in *Isotopes in Organic Chemistry*, ed. E. Buncel and C. C. Lee, Elsevier, Amsterdam, 1987, vol. 7, pp. 1–60; (*b*) A. J. Kresge, R. A. More O'Ferrall and M. F. Powell, in *Isotopes in Organic Chemistry*, ed. E. Buncel and C. C. Lee, Elsevier, Amsterdam, 1987, vol. 7, pp. 177–273.

14 Commission on Physical Organic Chemistry, IUPAC, *J. Pure Appl. Chem.*, 1989, **61**, 23; R. Guthrie and W. P. Jencks, *Acc. Chem. Res.*, 1989, **22**, 343.

15 A. D. McNaught, *Pure Appl. Chem.*, 1996, **68**, 1919.

16 G. A. Olah, *J. Org. Chem.*, 2001, **66**, 5943 and references therein.

17 J. Rigaudy and S. P. Klesney, *Nomenclature of Organic Chemistry: Sections A, B, C, D, E, F and H*, Pergamon Press, Oxford, 1979, p. 53.

18 J. C. P. Schwarz, *J. Chem. Soc., Chem. Commun.*, 1973, 505.

19 L. Hosie, P. J. Marshall and M. L. Sinnott, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1121.

20 For example: H. Yuasa, O. Hindsgaul and M. M. Palcic, *J. Am. Chem. Soc.*, 1992, **114**, 5891; S. Mehta, J. S. Andrews, B. D. Johnston, B. Svensson and B. M. Pinto, *J. Am. Chem. Soc.*, 1995, **117**, 9783; J. S. Andrews, T. Weimar, T. P. Frandsen, B. Svensson and B. M. Pinto, *J. Am. Chem. Soc.*, 1995, **117**, 10799; B. D. Johnston and B. M. Pinto, *J. Org. Chem.*, 1998, **63**, 5797; B. D. Johnston and B. M. Pinto, *Carbohydr. Res.*, 1998, **310**, 17; O. Tsuruta, H. Yuasa, H. Hashimoto, S. Kurono and S. Yazawa, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1019; T. Weimar, B. Stoffer, B. Svensson and B. M. Pinto, *Biochemistry*, 2000, **39**, 300; H. Yuasa and H. Hashimoto, *Trends Glycosci. Glycotechnol.*, 2001, **13**, 31.

21 P. Deslongchamps, in *The Anomeric Effect and Associated Stereoelectronic Effects*, ed. G. R. J. Thatcher, American Chemical Society, Washington D.C., 1992, ACS Symposium Series vol. 539, p. 26.

22 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, New York, 1983.

23 C. L. Perrin, in *The Anomeric Effect and Associated Stereoelectronic Effects*, ed. G. R. J. Thatcher, American Chemical Society, Washington D.C., 1992, ACS Symposium Series vol. 539, p. 70; C. L. Perrin, *Acc. Chem. Res.*, 2002, **35**, 28.

24 M. L. Sinnott, in *The Anomeric Effect and Associated Stereoelectronic Effects*, ed. G. R. J. Thatcher, American Chemical Society, Washington D.C., 1992, ACS Symposium Series vol. 539, p. 97.

25 S. Li, A. J. Kirby and P. Deslongchamps, *Tetrahedron Lett.*, 1993, **34**, 7757; P. Deslongchamps, P. G. Jones, A. J. Kirby, S. Kuusela and Y. Ma, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2621.

26 R. S. Brown, A. J. Bennet and H. Slebocka-Tilk, *Acc. Chem. Res.*, 1992, **25**, 481; C. L. Perrin and J. D. Thoburn, *J. Am. Chem. Soc.*, 1993, **115**, 3140.

27 S. Wolfe and Z. Shi, *Isr. J. Chem.*, 2000, **40**, 343 and references therein.

28 C. Armour, C. A. Bunton, S. Patai, L. H. Selman and C. A. Vernon, *J. Chem. Soc.*, 1961, 412.

29 W. G. Overand, C. W. Rees and J. S. Sequeira, *J. Chem. Soc.*, 1962, 3429.

30 R. J. Withey and E. Whalley, *Can. J. Chem.*, 1964, **42**, 1456; T. E. Timell, W. Enterman, F. Spencer and E. J. Soltes, *Can. J. Chem.*, 1965, **43**, 2296.

31 A. J. Bennet and M. L. Sinnott, *J. Am. Chem. Soc.*, 1986, **108**, 7287.

32 L. Melander and W. H. Saunders, *Reaction Rates of Isotopic Molecules*, Wiley Interscience, New York–Chichester–Brisbane–Toronto, 1980, p. 242.

33 L. Melander and W. H. Saunders, *Reaction Rates of Isotopic Molecules*, Wiley Interscience, New York–Chichester–Brisbane–Toronto, 1980, pp. 174–180.

34 B. E. Lewis and V. L. Schramm, *J. Am. Chem. Soc.*, 2001, **123**, 1327.

35 X. Huang, K. S. E. Tanaka and A. J. Bennet, *J. Am. Chem. Soc.*, 1997, **119**, 11147.

36 X. Huang, C. Surry, T. Hiebert and A. J. Bennet, *J. Am. Chem. Soc.*, 1995, **117**, 10614.

37 M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 1; J. P. Richard and Y. Tsuji, *J. Am. Chem. Soc.*, 2000, **122**, 3963.

38 J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 1373.
39 D. Indurugalla and A. J. Bennet, *J. Am. Chem. Soc.*, 2001, **123**, 10889.
40 J. A. Barnes and I. H. Williams, in *Organic Reactivity: Physical and Biological Aspects*, ed. B. T. Golding, R. J. Griffin and H. Maskill, Royal Society of Chemistry, Cambridge, 1995, pp. 437–443.
41 M. M. Toteva and J. P. Richard, *J. Am. Chem. Soc.*, 1996, **118**, 11434.
42 B. Capon and D. Thacker, *J. Chem. Soc. B*, 1967, 1010.
43 B. Capon and D. Thacker, *J. Chem. Soc. B*, 1967, 1322.
44 P. J. Garegg, K.-J. Johansson, P. Konradsson, B. Lindberg and Z. Trumpakaj, *Carbohydr. Res.*, 2002, **337**, 517.
45 K. J. Johansson, P. Konradsson and Z. Trumpakaj, *Carbohydr. Res.*, 2001, **332**, 33.
46 A. Nowacki, K. Smiataczowa, R. Kasprzykowska, B. Dmochowska and A. Wiśniewski, *Carbohydr. Res.*, 2002, **337**, 265.
47 The recommended IUPAC name for 2-deoxy-D-glucopyranose is 2-deoxy-D-*arabino*-hexopyranose (ref. 2).
48 (*a*) J. Kaczmarek, M. Preyss, H. Lönnberg and J. Szafranek, *Carbohydr. Res.*, 1995, **279**, 107; (*b*) J. Kaczmarek, Z. Kaczynski, Z. Trumpakaj, J. Szafranek, M. Bogalecka and H. Lönnberg, *Carbohydr. Res.*, 2000, **325**, 16.
49 R. Wolfenden, X. Lu and G. Young, *J. Am. Chem. Soc.*, 1998, **120**, 6814.
50 As the rate for this reaction does not vary significantly with changing the buffer concentrations, it is apparent that a single type of general catalysis is ineffective at promoting the water reaction.
51 J. L. Liras and E. V. Anslyn, *J. Am. Chem. Soc.*, 1994, **116**, 2645; J. L. Liras, V. M. Lynch and E. V. Anslyn, *J. Am. Chem. Soc.*, 1997, **119**, 8191.
52 L. Hosie, P. J. Marshall and M. L. Sinnott, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1121.
53 T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, 1989, **111**, 7900.
54 E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, 1957, **79**, 5995.
55 P. J. C. Fierens and P. Verschelden, *Bull. Soc. Chim. Belg.*, 1952, **61**, 427.
56 J. Zhu and A. J. Bennet, *J. Am. Chem. Soc.*, 1998, **120**, 3887.
57 J. Zhu and A. J. Bennet, *J. Org. Chem.*, 2000, **65**, 4423.
58 D. T. H. Chou, J. N. Watson, A. A. Scholte, T. J. Borgford and A. J. Bennet, *J. Am. Chem. Soc.*, 2000, **122**, 8357.
59 Acetic acid is about 100-fold less nucleophilic than water based on $N_{OTs}$ values, while water is about 500-fold less nucleophilic than acetate based on Swain–Scott *n* values (ref. 60).
60 K. A. Connors, *Chemical Kinetics: The Study of Reaction Rates in Solution*, VCH Publishers Inc., New York, 1990.
61 T. L. Amyes, I. W. Stevens and J. P. Richard, *J. Org. Chem.*, 1993, **58**, 6057.
62 E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, 1948, **70**, 846; A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, 1956, **78**, 2770; F. L. Schadt and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1973, **95**, 7860; T. W. Bentley, F. L. Schadt and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1972, **94**, 992; W. Schadt, T. W. Bentley and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1976, **98**, 7667; T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, 1977, **14**, 32; T. W. Bentley and G. Llewellyn, *Prog. Phys. Org. Chem.*, 1990, **17**, 121.
63 D. N. Kevill and S. W. Anderson, *J. Am. Chem. Soc.*, 1986, **108**, 1579.
64 J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Wiley Interscience, New York, 1991, 4th edn., pp. 357–362.
65 R. Ta-Shma and Z. Rappoport, *Adv. Phys. Org. Chem.*, 1992, **27**, 239–291.
66 T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, 1988, **110**, 3677.
67 (*a*) M. Shimizu, H. Togo and M. Yokoyama, *Synthesis*, 1998, 799; (*b*) M. Yokoyama, *Carbohydr. Res.*, 2000, **327**, 5.
68 S. J. Williams and S. G. Withers, *Carbohydr. Res.*, 2000, **327**, 27.
69 K. Toshirna, *Carbohydr. Res.*, 2000, **327**, 15.
70 J. E. G. Barnett, *Carbohydr. Res.*, 1969, **9**, 21.
71 N. S. Banait and W. P. Jencks, *J. Am. Chem. Soc.*, 1991, **113**, 7951.
72 N. S. Banait and W. P. Jencks, *J. Am. Chem. Soc.*, 1991, **113**, 7958.
73 Y. Zhang, J. Bommuswamy and M. L. Sinnott, *J. Am. Chem. Soc.*, 1994, **116**, 7557.
74 M. L. Sinnott and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 2026.
75 (*a*) C. A. Bunton, D. R. Llewellyn, K. G. Oldham and C. A. Vernon, *J. Chem. Soc., C*, 1958, 3588; (*b*) C. A. Bunton and E. Humeras, *J. Org. Chem.*, 1969, **34**, 572.
76 S. G. Withers, D. J. MacLennan and I. P. Street, *Carbohydr. Res.*, 1986, **154**, 127.
77 S. G. Withers, M. D. Percival and I. P. Street, *Carbohydr. Res.*, 1989, **187**, 43.
78 B. A. Horenstein and M. Bruner, *J. Am. Chem. Soc.*, 1996, **118**, 10371.
79 Calculated according to the equation $\ln (k_{^{12}C}/k_{^{14}C})/1.9 = \ln (k_{^{12}C}/k_{^{13}C})$, ref. 32, pp. 74–75.
80 B. A. Horenstein and M. Bruner, *J. Am. Chem. Soc.*, 1998, **120**, 1357.
81 A. N. Hall, S. Hollingshead and H. N. Rydon, *J. Chem. Soc.*, 1961, 4290; F. Van Wijnendaele and C. K. De Bruyne, *Carbohydr. Res.*, 1969, **9**, 277; C. K. De Bruyne and A. De Bock, *Carbohydr. Res.*, 1979, **68**, 71.
82 R. L. Nath and H. N. Rydon, *Biochem. J.*, 1954, **57**, 1.
83 A. J. Bennet, A. J. Davis, L. Hosie and M. L. Sinnott, *J. Chem. Soc., Perkin Trans. 2*, 1987, 581.
84 S. Rosenberg and J. F. Kirsch, *Biochemistry*, 1981, **20**, 3196.
85 M. Ashwell, X. Guo and M. L. Sinnott, *J. Am. Chem. Soc.*, 1992, **114**, 10158.
86 Y.-Z. Lai and D. E. Ontto, *Carbohydr. Res.*, 1979, **75**, 51.
87 D. Horton and A. E. Luetzow, *J. Chem. Soc., Chem. Commun.*, 1971, 79.
88 C. C. Jones and M. L. Sinnott, *J. Chem. Soc., Chem. Commun.*, 1977, 767.
89 D. Cocker and M. L. Sinnott, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1391.
90 M. N. Namchuk, J. D. McCarter, A. Becalski, T. Andrews and S. G. Withers, *J. Am. Chem. Soc.*, 2000, **122**, 1270.
91 Thus, the assumption is that a change in $\Delta G^{\ddagger}$ for formation of the cation ($\Delta\Delta G^{\ddagger}$) is related to a change in the free energy for reaction of the cation, and $\ln (k_1/k_2) = \text{constant} \times \ln (\tau_2/\tau_1)$.
92 K. E. S. Dean, A. J. Kirby and I. V. Komarov, *J. Chem. Soc., Perkin Trans. 2*, 2002, 337.
93 J. B. Lambert and S. M. Wharry, *Carbohydr. Res.*, 1983, **115**, 33; R. L. Girling and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, 1973, **29**, 1102.
94 J. B. Lambert and S. M. Wharry, *J. Org. Chem.*, 1981, **46**, 3193.
95 N. A. Hughes and N. M. Munkombwe, *Carbohydr. Res.*, 1985, **136**, 397.
96 B. M. Pinto and R. Y. N. Leung, in *The Anomeric Effect and Associated Stereoelectronic Effects*, ed. G. R. J. Thatcher, American Chemical Society, Washington, 1993, p. 126.
97 V. Jagannadham, T. L. Amyes and J. P. Richard, *J. Am. Chem. Soc.*, 1993, **115**, 8465.
98 F. Bernardi, C. I. G. Csizmadia, H. B. Schlegel and S. Wolfe, *Can. J. Chem.*, 1975, **53**, 1144; J. R. Larson and N. D. Epiotis, *J. Am. Chem. Soc.*, 1981, **103**, 410; Y. Apeloig and M. Karni, *J. Chem. Soc., Perkin Trans. 2*, 1988, 625; N. Buckley and N. J. Oppenheimer, *J. Org. Chem.*, 1996, **61**, 8048.
99 R. L. Whistler and T. Van Es, *J. Org. Chem.*, 1963, **28**, 2303.
100 B. D. Johnston, D. Indurugalla, B. M. Pinto and A. J. Bennet, *J. Am. Chem. Soc.*, 2001, **123, in press.**
101 S. Cottaz, C. Apparu and H. Driguez, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2235.
102 S. Wolfe, B. M. Pinto, V. Varma and R. Y. N. Leung, *Can. J. Chem.*, 1990, **68**, 1051; C. Scott and F. Grein, *Can. J. Chem.*, 1996, **74**, 1221.
103 J. P. Richard, *Tetrahedron*, 1995, **51**, 1535.
104 H. K. Chenault and L. F. Chafin, *J. Org. Chem.*, 1998, **63**, 833.