# Stereoelectronic Substituent Effects

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**ABSTRACT**

An investigation was carried out on the influence of the stereochemistry of substituents, particularly hydroxyl groups, on their electronic effects in piperidines, carbohydrates (pyranosides), and related compounds. Polar groups, such as OH, OR, and F, were found in the 3 and 4 position to be much more electron-withdrawing when positioned equatorially rather than axially. In contrast, little difference in electronic effects was observed from apolar groups as a result of epimerization. These observations were believed to be caused by differences in charge−dipole interactions and were used to explain why stereoisomeric glycosides hydrolyze with different rates. The conformational changes of hydroxylated piperidines and related compounds as a function of pH were likewise explained from the different substituent effects of axial and equatorial OH groups.

Carbohydrates are the most common organic molecules on Earth, and their chemistry and synthesis are of increasing fundamental interest. Carbohydrates are very important in foodstuffs and materials and as valuable chiral building blocks for organic synthesis. Though important carbohydrate commodities are too many to list here, cereals, potatoes, paper, and cotton are a few examples of products with essentially exclusive carbohydrate contents that clearly illustrate the reason for the importance of carbohydrate chemistry. Furthermore, complex carbohydrates are in the center of the rapidly expanding field of glycobiology as the many roles these biomolecules play in cell, viral, and antibody recognition are becoming exposed.[1] Therefore, the study of carbohydrate chemistry, which started with Fischer's elucidation of hexose stereochemistry,[2] is a field of long standing with many important contributions. Despite much progress in mono- and oligosaccharide chemistry, synthetic chemists are, nevertheless, often frustrated by the fact that carbohydrates behave differently than one expected, and are left with the feeling that something is missing in our understanding of these intriguing molecules. The present Account describes a line of research that reveals a new and fascinating aspect of carbohydrates by linking their reactivity and behavior to similar organic molecules.

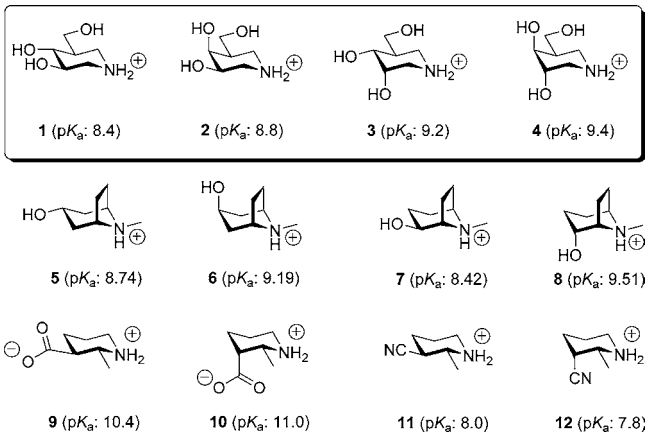


**FIGURE 1.** The variation of basicity in isofagomine (in parentheses) and other piperidine stereoisomers. Values are taken from refs 5 and 10 and references therein.

## The Base Strength of Hydroxylated Amines

Our research into the field of stereoelectronic effects originated in our interest in glycoside hydrolase inhibitors. After synthesis of members of a group of broad spectrum inhibitors known as the azafagomines, abnormalities in their basicity became apparent.[3] The same irregularity was quickly established also to be present in the more studied class of azasugar inhibitors known as the isofagomines. We observed that the p$K_a$ in the series of conjugate acids of isofagomine **1** and its stereoisomers **2**−**4** increased with an increasing number of OH groups being moved from equatorial to axial positions (Figure 1).[4,5] An axial 3-OH group appeared to increase[6] the base strength by 0.8 pH units compared to an equatorial OH group, while a 4-OH appeared to increase basicity by 0.4 pH units when placed axially rather than equatorially. An effect related to the axial or equatorial position of a substituent can be referred to as a *stereoelectronic* effect, since the substituent may be inverted from axial to equatorial position by epimerization of a stereocenter. It may also be considered a *conformational* effect because inverting from axial to equatorial position can occur by changing the conformation of the molecule from one chair conformation to the other. In this Account, we will use the former nomenclature.

While simple substituent effects in achiral molecules are well described and were reviewed for their influence on amines by Clark and Perrin in 1964,[7] the influence of stereochemistry on substituent effects had, until the start of this project, received very little attention. Inouy studied

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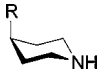
**Table 1. Axial and Equatorial Substituent Effects on Piperidine Base Strength in Water at 25 °C[a]**

| R group |  |  |  |  |
|---|---|---|---|---|
| OH | 1.3 | 0.5 | 0.6 | 0.2 |
| F | 2.3 | 1.5 | 1.0 | |
| COOMe | 1.2 | 0.2 | | |
| $CONH_2$ | 1.5 | 1.3 | | |
| $COO^-$ | 0.5 | −0.2 | 0.2 | |
| CN | 2.8 | 3.0 | | |
| $CH_2OH$ | 0.4 | 0.5 | | |

[a] The numbers are the $\sigma_s$ values and are in pH units. The p$K_a$ of the piperidine conjugate acid is decreased by the indicated substituent. Thus, base strength can be calculated as p$K_a$(substituted amine) = p$K_a$(unsubstituted amine) − $\sum\sigma_s$.

the basicity of various sugar amines and refined the p$K_a$ calculation method of Clark and Perrin to this particular subfield,[8] without, however, taking stereochemistry into account in his calculations. We, therefore, decided to study a larger number of compounds, and the p$K_a$ values of more than 60 different hydroxylated piperidines and hexahydropyridazines, which in the first examples appeared to be irregular, in fact turned out to fit a surprisingly systematic pattern.[5] These stereoelectronic effects are summed up in Table 1. The so-called $\sigma_s$ value of each substituent is the basicity decreasing effect in p$K$ units. As is seen, the axial OH decreases the base strength of the amine by 0.5 and 0.2 units when it is in the $\beta$ and $\gamma$ position, respectively, relative to the amine, while the equatorial OH decreases p$K_a$ by 1.3 and 0.6 in those instances. Thus, the equatorial OH is significantly more electron-withdrawing than the axial OH.

Other substituents were additionally studied,[5,9,10] and F, ester, and carboxylate functions were also found to result in considerable variation of p$K_a$ depending on whether they were axial, while epimerization of $CH_2OH$, $CONH_2$, and CN did not cause a great deal of change to base strength.

These substituent effects are so consistent within the framework of substituted piperidines and hexahydropyridazines that they can be used to calculate the p$K_a$ of a substituted piperidine or hexahydropyridazine, using the formulas $10.7 - \sum\sigma_s$ or $7.3 - \sum\sigma_s$, respectively, depending on whether the calculation is carried out for a piperidinium or hexahydropyridazinium ion. The accuracy falls within 0.1 p$K$ units.[5]

These differences are possibly caused by several effects but can, nevertheless, largely and satisfactorily be explained by differences in charge−dipole interactions. This is particularly evident by analyzing the effect of the 3-cyano substituent compared to the 3-hydroxyl group. As it is seen in Table 1, the electron-withdrawing power of the 3-OH increases almost 3-fold when it is placed equatorially. The same is not true for the cyano group, which actually has essentially an unchanged substituent effect. Charge−dipole interaction can be calculated using the equation $\Delta G = 69.13\mu \cos(\alpha/r^2)\ D_E$,[11] where $\mu$ is the dipole moment, $r$ is the distance between the center of the dipole and the charge, $\alpha$ is the angle between dipole and the line to the charge from the middle of the dipole, and $D_E$ is the effective dielectric constant. The geometric term in this equation $\cos\alpha/r^2$ is the variable portion for stereoisomers, and when this term is calculated, using the $\alpha$ and $r$ obtained from models, it is seen that it varies greatly for the 3-OH axial and equatorial isomers, while it does not for the nitriles (Figure 2). Thus, despite having a large dipole moment, which does result in a large substituent effect, no stereoelectronic effect is displayed by the cyano group, because the dipole is more distant than the C−O dipole. The angles involved are furthermore dissimilar.

Clark and Perrin[7] observed that the effect of the hydroxyl group on amine basicity was unreliable and suggested that hydrogen bonding in individual cases might stabilize either the amine or its conjugate acid. While the variations observed in Figure 1 might be caused by H-bonding as for the influence of the 3-OH, this seems much less plausible for the 4-position due to the large distance to the nitrogen.

In the five-membered ring, a difference in substituent effect between pseudoaxial and pseudoequatorial OH groups may also be anticipated (Figure 2). We explored this by preparing the azabicyclic tetrahydroxy compounds

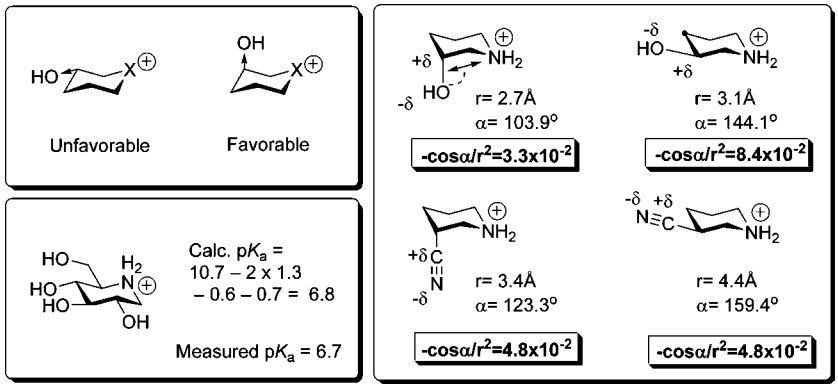



**FIGURE 2.** Charge dipole interactions are different in stereoisomeric hydroxylated piperidines (top left) and can explain why the axially substituted isomers are more basic. The geometric portion of the Kirkwood−Westheimer equation ($\cos\alpha/r^2$) is calculated from the distance $r$ and angle $\alpha$ between dipole and charge (right). The p$K_a$ of a hydroxylated piperidine can be calculated by using stereoelectronic effects as illustrated by the calculation of the p$K_a$ of 1-deoxynojirimycin (bottom left). The $\sigma$ values of each of the substituents are subtracted from the value of the amine (10.7) (0.7 is the value of $\alpha$-hydroxymethyl group).

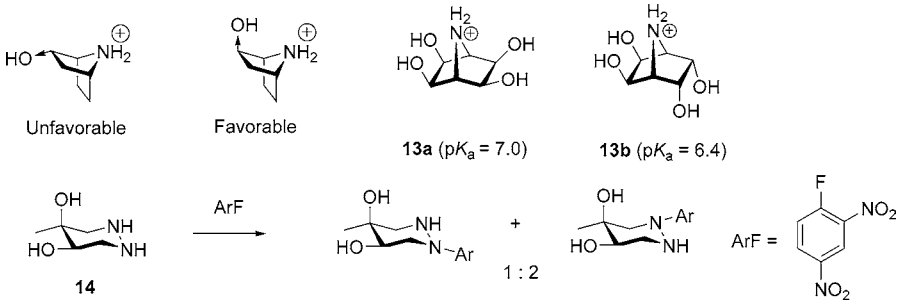



**FIGURE 3.** Charge dipole interactions in hydroxylated bicyclic amines (top) and preferential substitution at the nitrogen closest to the less-electron withdrawing OH (bottom).

**13a** and **13b**. The p$K_a$ difference between these compounds was found to be comparatively small but largely consistent with the expectations based on charge−dipole interactions as predicted by models and calculations.[12]

The different influence of axial and equatorial OH on amines can also be observed in their reactivity. The cyclic hydrazine **14** reacts preferentially at the nitrogen closer to the less electron-withdrawing axial OH (Figure 3), possibly due to a greater electron density residing on this N-atom.[13]

## Conformational Changes in Substituted Piperidines

A consequence of the above is that piperidines with hydroxyl, fluoro, carboxylate, or ester substituents will have different p$K_a$ values in the two alternative chair conformations (Figure 4). Thus, the isofagomine isomer **4** can be predicted to have a widely different base strength in the $^4C_1$ conformation **4a** and $^1C_4$ conformation **4b**.[14] Therefore, according to Le Chatelier's principle, the conformational equilibrium between **4a** and **4b** must be influenced by a change in pH (Figure 4). The observed p$K_a$ of 9.4 as determined by titration reflects that the compound is predominantly in conformation **4a**, but that the equilibrium is significantly perturbed during the process.[5] This is clearly demonstrated by glucuronic acid analogue **15**, which in its basic form, **15a**, is predominantly in the $^4C_1$ conformation, while the acidic form **15b** is predominantly in the $^1C_4$ conformation.[15] The p$K_a$ values of **15a** and **15b** are, in this case, as determined from calculations 4.9 and 6.4, respectively, and thus widely

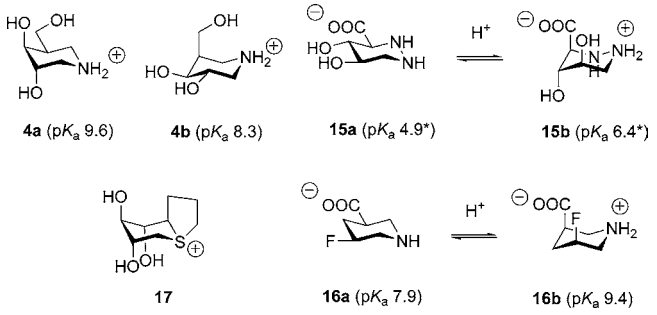



**FIGURE 4.** Expected p$K_a$ values of piperidine and hexahydropyridazine conformers as calculated from the equations p$K_a$ = 10.7 − $\sum\sigma_s$ or p$K_a$ = 7.3 − $\sum\sigma_s$. The ∗ indicates that the p$K_a$ of the most basic nitrogen is given.

different. Interesting examples of this phenomena involving fluorine in place of hydroxyl have been reported by Lankin, Snyder, and co-workers.[16,17] The fluoropiperidine **16**, which completely flips from one chair conformation to the other on protonation (Figure 4), is a remarkable case.[16]

Alternatively these conformational changes can be observed as a result of introducing positive charge by other means than protonation. Pinto's group has reported that the sulfonium salt **17** adopts the unexpected conformation where all hydroxyl groups are axial and not the conventional all-equatorial conformation (Figure 4).[18] This is explained by the molecule preferring the OH groups to be in their less electron-withdrawing axial position due to the positive charge.

## Glycoside Hydrolysis

Glycopyranoside hydrolysis and other glycoside cleavage reactions are known to involve oxacarbenium ion intermediates and oxacarbenium ion like transition states, containing a high degree of positive charge in the six-membered ring. The generally accepted mechanism for acid-catalyzed cleavage (or formation) of an α-galactoside is shown in Figure 5: Protonation of the exocyclic oxygen in a fast preequilibrium step is followed by rate-determining cleavage of the C−O bond to give an oxacarbenium ion that subsequently is hydrated. The transition state of the C−O cleavage reaction is late thus resembling the oxacarbenium ion[19] with much of the charge located on the ring oxygen and anomeric carbon. We, therefore, at an early stage realized that a difference in electron-withdrawing effect from axial and equatorial OH groups should be reflected in different reactivity of monosaccharide derivatives with axial and equatorial OH groups in these reactions. Indeed, the variation in rate of various hydrolytic reactions of glycosides was found to closely parallel the variations in base strength of isofagomines. Thus, the acidic hydrolysis of methyl α-galactoside is 5 times faster than the hydrolysis of methyl α-glucoside,[19] indicating that formation of positive charge at the anomeric center is easier in the *galacto* case, which, indeed, coincides with **2** (p$K_a$ = 8.8, Figure 1) being more basic than **1** (p$K_a$ = 8.4). Likewise, the methyl α-D-idoside undergoes acidic hydrolysis 25 times more readily than the altroside, reflected in the 1 p$K$ unit higher base strength of **4** (p$K_a$ = 9.4) than **1** (p$K_a$ = 8.4).

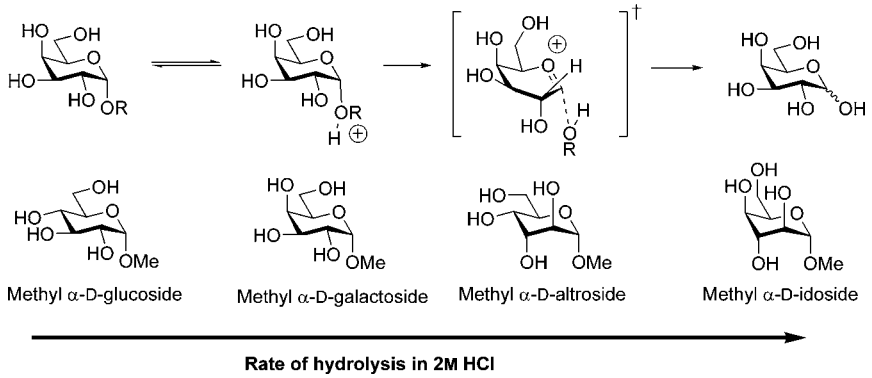



**FIGURE 5.** Mechanism of acid-catalyzed glycoside hydrolysis (top) and the structure of several stereoisomeric glycosides ordered according to their relative rate of acidic hydrolysis (below).

A free linear energy relationship can be made by comparing the change in basicity of an isofagomine analogue by epimerization of one or two hydroxyl groups with the change in rate of acidic hydrolysis of a methyl glycoside when the same epimerization is made.[4] This analysis results in a plot, $\Delta\Delta G^{\ddagger}$(rate) vs $\Delta\Delta G^{\theta}$(acidity), which is shown in Figure 6a and which displays a good correlation ($\rho = 0.82$, $r^2 = 0.88$). This free energy plot reflects how much positive charge development is occurring at the anomeric center, because protonation of the isofagomines mimics charge in this position. However, positive charge at the ring oxygen is equally, if not in some cases more, important. When the free energy relationship plots are made using substituent constants ($\sigma_s$) instead of a direct comparison of amines and glycosides, charge development at both atoms can be investigated.[9] The rate of hydrolysis of a glycoside, in the form of the negative logarithm of the rate constant (p$k$), is compared with the sum of the $\sigma_s$ constants for its ring substituents ($\Sigma\sigma_s$) calculated in relation to either anomeric carbon or ring oxygen. By this method, plots for the hydrolysis of methyl glycosides under acidic conditions and dinitrophenyl glycosides under neutral conditions were made for charge development in both positions.[9] An excellent correlation for hydrolysis of 2,4-nitrophenyl $\beta$-glycosides was found under the assumption that the positive center is the ring oxygen atom (Figure 6b). For acidic hydrolysis of methyl glycosides, the best correlations were found when charge at oxygen was assumed.

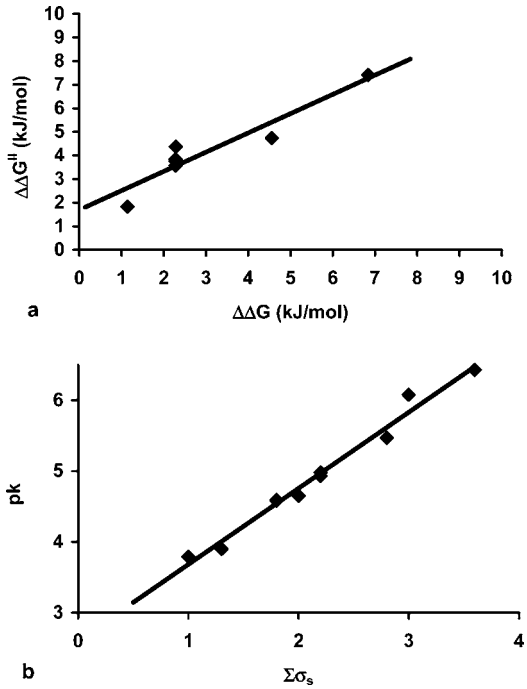



**FIGURE 6.** Free energy relationship plots. Panel a is a correlation of $\Delta\Delta G^{\ddagger}$(rate) for hydrolysis of methyl glycopyranosides in 2 M HCl versus $\Delta\Delta G^{\theta}$(acidity) for isofagomines ($\rho = 0.82$, $r^2 = 0.88$). Each point is a comparison of the effect of an epimerization of rate and base strength. In panel b is shown the correlation of p$k$ of the rate of spontaneous hydrolysis of 2,4-dinitrophenyl glycosides versus the sum of stereoelectronic constants for that substrate in relation to charge build-up on O5 ($\rho = 1.07$, $r^2 = 0.98$).

The above work clearly shows that electronic effects are the major reason stereoisomeric glycosides hydrolyze with different rates. It is also in agreement with work by Namchuk et al.[20] who found that the rate of hydrolysis of dinitrophenyl glycosides depends mainly on electronic effects. In this work, it was also shown that the variations in rate differences observed by different stereoisomers could be satisfactorily explained using Kirkwood−Westheimer analysis, that is, the rate differences as a result of stereoisomerism could be explained by charge−dipole interactions. Also in agreement with this is the work by Woods et al. who by using a molecular mechanics approach showed that a saccharide containing an axial OH group is more reactive than one with an equatorial group for electronic reasons.[21] A study by Milkovic et al. also confirms our results in a system where hydrogen bonds cannot be playing a role. They showed that in glycoside acetolysis, with a similar mechanism although not conducted in an aqueous medium, saccharides containing various axial polar 4-substituents were more reactive than their equatorial 4-epimers, and they concluded that this was due to a stabilizing electronic effect of the substituent on the oxacarbenium ion.[22] They also observed that the stereoelectronic effect depends much on the C4 substituent with OMe giving a higher variation than acetoxy, which again was higher than acetamido; this also agrees with our observations on piperidines (Table 1).

Nevertheless, these new papers contrast the classical explanation as to why galactosides are more reactive than

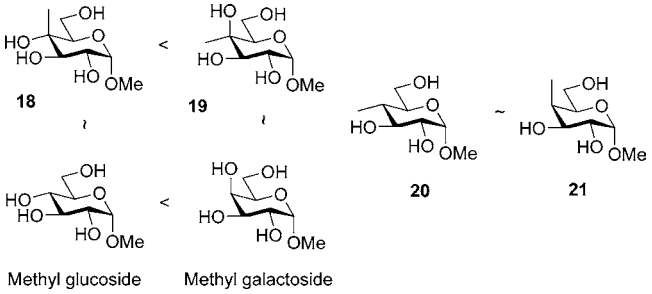



**FIGURE 7.** Structure of 4-C-methylated glycosides **18**−**21** used to test Edward's hypothesis. Compound **19** has roughly the same reactivity as the unmodified galactoside and is thus more reactive than **18**, which is as reactive as the unmodified glucoside. Compounds **20** and **21** have approximately the same reactivity.

glucosides as forwarded by Edward.[23] In his rationale, he argued that these variations in reactivity were caused by differences in sterical hindrance in the reactant state of glycosides containing axial or equatorial substituents. Glycosides with the former types would more readily go to the transition state, because of steric crowding occurring between the substituent and axial hydrogens such as H-2, which would be relieved when the compound changes conformation and the reaction coordinate approaches the transition state (Figure 5). To investigate whether such sterical activation might play a role, we made a series of molecules designed to probe whether sterical hindrance from axial substituents would seriously affect the rate of hydrolysis.[24] Thus, the 4-*C*-methyl glycosides **18**−**21** were prepared (Figure 7), and their rate of acidic hydrolysis was determined. Compounds **18** and **19**, which are C-4 epimers, both have sterical hindrance in the reactant state between an axial substituent in C-4 and the axial H-2. In **18**, this 2−4 diaxial sterical interaction would occur between a methyl group and hydrogen, while in the case of **19**, the interaction is between OH and hydrogen and should be smaller.[25] Therefore, the Edward hypothesis dictates that **18** should be the more reactive, but hydrolysis experiments show that **19** hydrolyzes 5 times faster than **18**.[24] In the other epimeric pair, **20** and **21**, the 4-OH group has been removed. Now **21** has an unfavorable sterical interaction in the reactant state, between methyl and H-2, while **20** has not. The Edward hypothesis therefore predicts that **21** will be the more reactive. However, **20** and **21** are observed to hydrolyze at essentially the same rate, or in fact, **20** is slightly more reactive.

There was, therefore, found to be no support for the Edward hypothesis, and the data fully support our claim that the increased reactivity of galactosides over glucosides is caused by the axial OH group being less electron-withdrawing than the equatorial one. Compound **19**, which has an axial OH, is more reactive than the epimer **18**, and when the 4-OH has been removed, in **20** and **21**, essentially no, or at least much lower, variation in reactivity is seen as a result of epimerization.

When axial and equatorial OH groups have different electron-withdrawing power, it follows that different glycoside conformers have different hydrolytic lability. Therefore, a glycoside may become *more (or less) reactive by simply changing its conformation* from one chair conformation to the other. From $\sigma_s$ values it is estimated that a glycoside containing equatorial OH groups at 2, 3, and 4 will become 100 times more reactive when it is flipped into the conformation where the OH groups become axial ($\Delta\Sigma\sigma_s = 2.0$ assuming charge mainly at ring oxygen[26]). To verify this theoretical finding, we investigated 3,6-anhydroglycoside derivatives, because the 3,6-anhydro bridge can force glucose into a $^1C_4$ chair conformation rather than the normal and much more stable $^4C_1$ conformation. The hydrolysis of methyl 3,6-anhydroglucoside **22** in 2 M HCl was found to be *446 times faster* than the hydrolysis of methyl α-D-glucoside confirming that changing the conformation has a remarkable effect (Figure 8).[27] In contrast, 3,6-anhydrogalactose derivative **23**, which is in a boat conformation and therefore does not have more hydroxyl groups axially than the methyl α-D-galactoside, does not hydrolyze faster than methyl α-D-galactoside; in fact, it hydrolyzes slightly slower.

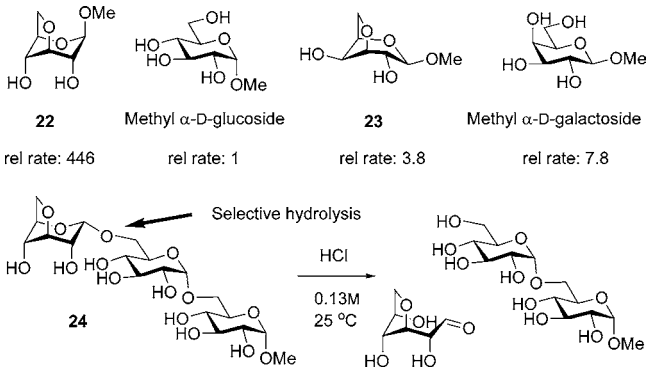



**FIGURE 8.** 3,6-Anhydrosugars that have all oxygen substituents axial are much more reactive toward hydrolysis. This is illustrated by the observation that **22**, but not **23**, hydrolyzes much faster than its nonlocked counterpart with relative rates toward 2 M HCl shown (top) and by the observation that compound **24** can be hydrolyzed selectively at only one of its three glycosidic linkages (below).

The high reactivity toward hydrolysis of sugar residues with axial groups is powerfully illustrated by the observation that oligosaccharides containing a 3,6-anhydrosaccharide, such as **24**, are selectively hydrolyzed at the anhydro residue under mild conditions (Figure 8).[27]

It is known that a 4,6-benzylidine protection group in a saccharide reduces its reactivity (i.e., "disarms" it) in glycosylation reactions.[28] Thus, a thiosaccharide glycosyl donor with a 4,6-benzylidene is less reactive toward reaction with MeOH than its fully benzylated analogue (Figure 9).[32] This phenomenon, which has been attributed to torsional effects or more specifically the locking together of the hydroxymethyl group and 4-OH, is believed to make the molecules transition to a half chair transition state conformation more difficult.[29,30] However, given the very directional electronic effects from the ring hydroxyl groups of carbohydrates observed in this line of work, one realizes that the conformation of the exocyclic hydroxymethyl group of a hexopyranoside may be of importance for its reactivity. Looking at the possible conformers of

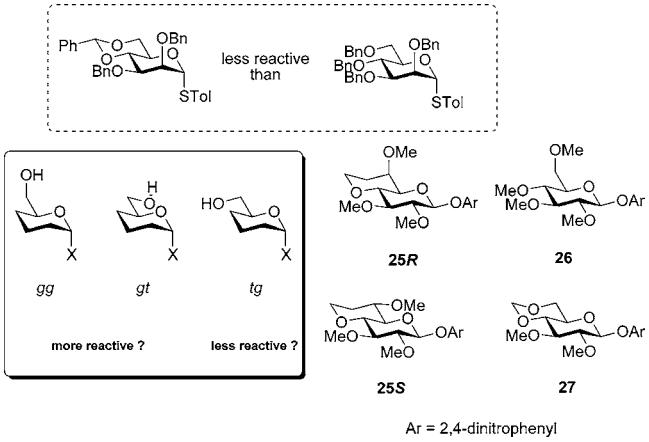



**FIGURE 9.** Different reactivities associated with the different hydroxymethyl rotamers based on the anticipated electronic effect (below left) and probe glycosides synthesized used to study torsional versus electronic effects (below right).

the exocyclic hydroxymethyl group, it is clear that in the *tg* conformer the 6-OH C−O bond is a dipole directed away from the ring oxygen and anomeric carbon, while in the *gg* and *gt* conformers, this dipole is much closer to being perpendicular (Figure 9). Therefore, we expected a glycoside with its 6-OH in the *tg* conformer to be less reactive, and the low reactivity of 4,6-benzylidene-protected saccharides could be a result of this electronic deactivation rather than a torsional effect. We, hence, tried to investigate a phenomenon in synthetic chemistry typically carried out in organic solvents by studying the hydrolytic reactivity of probe molecules. To determine which of these effects were responsible for the low reactivity of the 4,6-benzylidene-protected saccharides, the two probe molecules **25***R* and **25***S* were prepared.[31] These two molecules contain a ring fused to the pyranoside similar to a benzylidene and should be just as torsionally disarmed, but they do not have the methoxymethyl group in the potentially deactivating *tg* conformation. The rates of uncatalyzed hydrolysis of **25*R*** and **25*S*** were compared with those of **26** and **27**, the unrestrained and 4,6-acetal-protected analogues, respectively (Figure 9). The relative hydrolysis order was found to be **26** > **25*R*** > **25*S*** > **27** with the relative hydrolysis rates being 1:0.24:0.16:0.07, respectively. The same order and relative rates were found for acid-catalyzed hydrolysis of the corresponding methyl α-glycosides.[31] In other words, the most reactive glycoside is the unrestrained glucoside, the 4,6-acetal protected saccharide is the least reactive, and the probe molecules **25*R*** and **25*S*** are in between. This means that there are both a torsional "disarming" effect, which caused **25*R*** and **25*S*** to be less reactive than **26**, and an electronic "disarming" effect, which causes **27** to be less reactive than **25*R*** and **25*S***.[31]

## Glycosylation Reactions

Even though glycosyl coupling reactions are performed in organic solvents and under very different conditions than those of the hydrolytic reactions described above, it is nevertheless found that the reactivity of glycosyl donors containing axial O-substituents are more reactive than their equatorial epimers. This is clearly seen from the large collection of relative rate data for reaction of thioglycosides with methanol upon activation with NIS, which has been reported by Zhang et al.[32] For example, a benzylated tolylthiogalactoside has been found to react 6.4 times faster than the corresponding thioglucoside, which is a surprisingly similar value to the ratio of relative hydrolysis rates between dinitrophenyl galacto- and glucosides (4.7 times)[20] and methyl galacto- and glucoside toward acidic hydrolysis (5.0 times).[19] To investigate the generality of the ratio, we have looked at the difference in reactivity between other galactosyl and glucosyl donors and found a Gal/Glu ratio of 5 times for benzyl-protected trichloracetimidates and 4.1 times for the benzylated glycosyl chlorides.[33] Notably this ratio is only 1.3 times between the benzyl-protected galacto and glucosyl 4-pentenyl glycosides toward NIS activation. Probably this latter case differs in that the rate-determining step is not $C_1-O_1$ bond cleavage but a step involved in the pentenyl activation.

The higher reactivity observed in glycosylations of donors with axial OR groups should make it possible to *conformationally* "arm" glycosyl donors by forcing their oxygen substituents into an axial position. This was achieved for a glucosyl donor by using bulky silyl protection groups, such as TBDMS or TBDPS, which cannot be accommodated in the $^4C_1$ conformation and force the molecule into a $^1C_4$ conformation. The donor **28** is an example of such a "conformationally armed" glycosyl donor. The armament in this case exceeds the armament of having equatorially placed benzyl ethers, which makes it possible to selectively couple it with an armed glycosyl donor **29** to give adduct **30** without any self-coupling of **29** occurring (Figure 10).[34] This example very clearly shows the very considerable difference in electronic effect of the axial and equatorial OR groups.

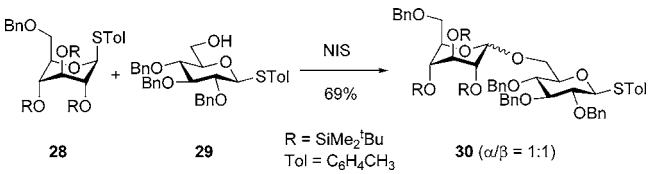



**FIGURE 10.** Glycosylation with conformationally armed donor.

## Conclusion

The line of research described in this Account has shown that carbohydrates and carbohydrate-like molecules are "creatures" of electronic effects. Furthermore, it has been shown that not only the identity and regiochemical position but also the stereochemical placement of substituents is of critical importance for the properties and reactivity of these molecules. The main findings can be summed up as follows: First, in a six-membered ring in chair conformation, the axial OH group is less electron-withdrawing than the equatorial OH group in relation to another ring atom 2−3 positions away. This is also true for other electronegative substituents. Second, the two chair forms of a six-membered ring with electronegative

substituents will have different properties such as different acidity or different reactivity.

The implications of these findings are quite far reaching with respect to carbohydrate chemistry. The large boost in reactivity found caused by ring inversion of some saccharides suggests that glycosides may spontaneously undergo conformational changes during hydrolysis or glycosylation reactions, which of course may affect the stereochemical outcome of the latter reactions. These findings, furthermore, offer new explanations not relying on the questioned stereoelectronic effect as to why enzymes may change the conformation of a monosaccharide unit or possibly preferentially stabilize the 6-OH in the *gg* orientation to make the substrate more reactive.

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