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Quantifying the Electronic Effects of Carbohydrate Hydroxy Groups by Using Aminosugar Models

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Abstract: Methyl amino-deoxy-glycosides with α- and β-gluco, α-galacto, or α-manno stereochemistry with the amino functionality in each of the four possible non-anomeric positions have been synthesized and their pK_a values determined by titration. These model compounds were chosen because they are the amino derivatives of the most common glycosyl acceptors. From this study it was possible to evaluate the electron density at each of the given positions in the carbohydrate and compare them. Some general trends were observed: The basicity of the amino groups decreases in the order 6-NH_2 > 3-NH_2 > 2-NH_2 > 4-NH_2 (referring to the position). The basicity of a of an amino-deoxy-sugar generally increases when one or more substituents on the sugar ring are axial. The basicity decreases when the amine is antiperiplanar to an oxygen atom. These findings are in agreement with the observations obtained from glycosylation chemistry and the regioselective protection of sugars.

Keywords: acidity · amines · carbohydrates · reactivity · stereoelectronic effects

Introduction

With the increased knowledge of the interactions of carbohydrates in biological systems the need for complex oligosaccharides and glycoconjugates has increased. So far, the best way to obtain these desired molecules for biological evaluation and drug discovery has been by synthesis. This is, however, often very complicated due to the many functionalities present and expertise within the field is a must. Glycosylation[1,4] is often the most critical reaction type in which stereoselectivity (α vs. β), regioselectivity, moisture sensitivity, and poor nucleophilicity of the acceptor (often an OH nucleophile) complicate the outcome and purification of the reaction. To improve these reactions there has been increasing interest in studying the reactivity and selectivity of the glycosyl donor, and recently several methods to quantify the reactivity of donors containing different protective groups have appeared.[2] The reactivity of the glycosyl acceptor is, however, less studied and it is difficult to find a specific pattern in the different reactivities of the hydroxy groups,[3] although there are some rules of thumb, such as the greater reactivity of the 6-OH relative to the secondary hydroxy groups for steric reasons. Of the secondary hydroxy groups, the axial are normally less reactive than the equatorial, presumably due to unfavorable 1,3-diaxial steric interactions, and the 4-OH is often observed to be the least reactive. Most of these rules build on the knowledge gained from the glycosylation chemistry of partially protected acceptors and regioselective protective group manipulations.[4] Some of the conclusions on hydroxy group reactivity, obtained from studies on the acylation of methyl glycosides, are misleading because they do not take into account the effect of monoacylation of the remaining hydroxy groups[5] and the effect of different solvents[6] and reagent systems. In an early NMR study by Horton and Lauterback, the relative distribution of acetyl groups in the partial acetylation of methyl α-D-glucopyranoside using acetic anhydride–[D_5]pyridine was found to be 0.4 (O-6) to 0.2 (for each of the secondary hydroxy groups), that is, the secondary hydroxy groups have a similar reactivity.[7] Williams and Richardson came to the conclusion that the order of reactivity in acetylation is 2-OH > 3-OH > 4-OH for methyl α-D-glucoside and 3-OH > 2-OH > 4-OH for methyl α-D-mannoside, whereas for the galactoside the 3-OH and 2-OH have a similar reactivity and the 4-OH is still the least reactive.[8] From the ditosylation, acetylation, and benzoylation of pyranosides, 3,6-substitution has been observed to be dominant for α-mannosides and β-glucosides, whereas α-glucosides resulted in 2,6-substitution and α-galactosides in mixtures.[9] Studies of the differences in the reactivity of the different positions on the sugar ring have almost only been performed with hydroxy groups and only very few studies on the differences between amino-deoxy-sugars have appeared. Inouye compared the NMR shifts of different aminosugars and by looking at the shifts of the hydrochloride salts he estimated the order of decreasing basicity to be 6-amino > 3-amino > 2-amino in the glucopyranoside series.[10] We have earlier used aza-sugars as model compounds to investigate the effects of substituents on a given

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position, normally the anomeric, and piperidines have turned out to be very good model compounds.[21]

Hydrogen bonding within the glycosyl acceptor is another important factor to consider when looking at the reactivity and selectivity of unprotected carbohydrates. The influence and pattern of the hydrogen bonding are a matter of debate,[11] but they are generally accepted to play a role in the reactivity of hydroxy groups. This also explains to some extent the observed solvent effects in regioselective protection, apolar solvents such as CH_2Cl_2 and $CHCl_3$ tending to give higher selectivity than more polar solvents.[12,15] The hydrogen-bonding network in carbohydrates has ingeniously been used to increase or change the regioselectivity in reactions. Hence, the intrinsically less reactive 4-OH in glucose can selectively be functionalized[13] or shielded[14] depending on the approach. As an example, selective functionalization at the 3-position was achieved by having a directing pyridyl residue at the 6-position shielding the 4-OH by hydrogen bonding. Internal hydrogen bonds have been shown to reduce the reactivity of the hydroxy groups in partially protected *N*-acetylglucosamine derivatives towards glycosylation, which is a significant problem in the synthesis of biologically important oligosaccharides.[15]

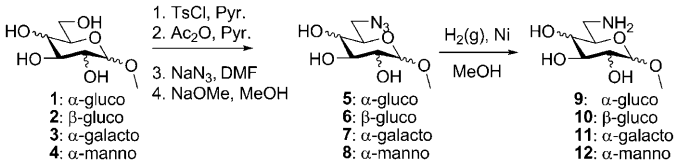
Another point to consider when looking at the reactivity of the acceptor towards the donor is the fact that the glycosylation often involves two chiral reactants. Therefore the reaction is subject to double diastereodifferentiation,[16] also referred to as the "match–mismatch concept"[17] or "reciprocal donor–acceptor selectivity"[18] in carbohydrate chemistry. The outcome of a glycosylation reaction clearly also depends on this and not only the nucleophilicity of the acceptor.

In previous work we were very interested in quantifying the reactivity of glycosyl donors and finding ways to control and, in particular, to increase their reactivity. By studying various model systems we found a good correlation between the reactivity of carbohydrates, that is, hydrolysis[19] and glycosylation,[2e] and the pK_a of piperidine analogues (azasugars).[21] From this work it is clear that all substituents on the sugar ring play a role and that the stereochemistry is crucial. By using less electron-withdrawing protective groups (silyl or alkyl) in combination with conformational changes to the axial-rich conformation, highly reactive glycosyl donors (super-armed) were prepared and used in glycosylation reactions.[20] The use of highly reactive donors solves many problems relating to the "difficult glycosylation" of acceptors with low nucleophilicity; ex. rhamonosylation of the poor nucleophile benzyl 3-*O*-acetyl-6-*O*-benzyl-*N*-acetyl-β-D-glucosamine was performed at −78 °C to give a quantitative yield of the α-disaccharide.[22] From the work carried out to gain an understanding of glycosyl donors we became interested in glycosyl acceptors: Is it possible to quantify the reactivity of hydroxy groups by using an amine model system and does it correlate with observations reported in the literature? In this study, model compounds with a single amino group in one of the four available non-anomeric positions were prepared and their pK_a values obtained by titration. From these data the relative electron density at each position was obtained and used to create a picture of the reactivities in each position.

Results and Discussion

Preparation of model compounds: We began our study by preparing model compounds. From the work on glycosyl donors, amines had proved to be an excellent functional group for investigating the charge distribution within the ring system. We applied this approach to acceptors and decided to prepare the four possible amino derivatives of each sugar in the study. To limit the number of compounds we decided to study the most common carbohydrate acceptors, that is, α- and β-glucosides, α-galactosides, and α-mannosides. With both glucoside anomers we can obtain information on the influence of the anomeric configuration on the charge distribution in the sugar ring.

The 6-amino sugars **9–12** with gluco,[23] galacto,[24] and manno[25] stereochemistry were synthesized from the corresponding methyl glycosides **1–4** by selective monotosylation of the 6-OH followed by acetylation of the remaining hydroxy groups and substitution of the tosyl with azide in DMF. Deacetylation using sodium methoxide in methanol and nickel-catalyzed azide reduction gave the desired 6-aminosugars **9–12** in excellent yields (96–99 %; Scheme 1).

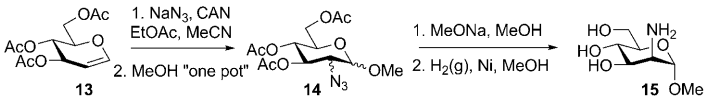


Scheme 1. Synthesis of the 6-amino model compounds (Pyr. = pyridine).

Methyl 2-amino-2-deoxy-α-D-glucopyranoside and methyl 2-amino-2-deoxy-α-D-galactoside were synthesized from D-glucosamine and D-galactosamine, respectively, following known procedures.[26] When applying the procedure to D-mannosamine, purification became a problem and another approach was necessary. Azidonitration of peracetylated glucal following Paulsen and co-worker's modification[27] of the original Lemieux and Ratcliffe procedure[28] followed by methanolysis gave a mixture of four possible compounds, anomeric mixtures of methyl 2-azido-2-deoxy-gluco- and -mannosides. The methyl 2-azido-3,4,6-tri-*O*-acetyl-β-D-mannoside was removed by chromatography and after deacetylation using sodium methoxide the desired α anomer was isolated in an overall yield of 17 %.[28] Nickel-catalyzed reduction afforded the known[29] amine **15** in quantitative yield (Scheme 2).

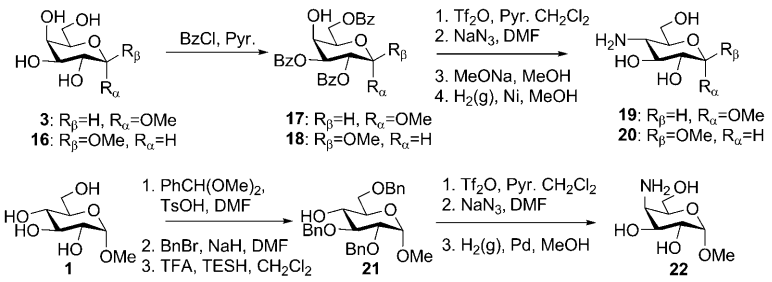
The 3-aminosugars[30] were prepared from the corresponding 3-nitro compounds following a known procedure.[31] The

pK_a values of methyl 3-amino-3-deoxy-α-D-glucoside, methyl 3-amino-3-deoxy-β-L-glucoside, and methyl 3-amino-3-deoxy-α-D-mannoside were already known.[32]



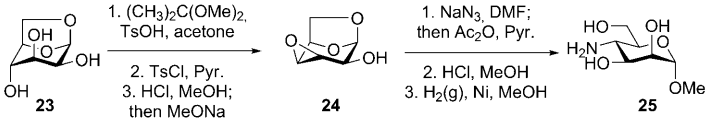
Scheme 2. Synthesis of methyl α-D-mannosamine from glucal following the procedure of Lemieux and Ratcliffe.[28]

The 4-aminosugars **19**, **20**, and **22** with gluco and galacto stereochemistry were prepared by azide substitution of the corresponding triflated hydroxy group. Methyl α- and β-D-galactosides **3** and **16** were regioselectively benzoylated at the 2-, 3-, and 6-positions[9] and then a triflate was introduced on the free 4-OH. Treatment of this triflate with NaN_3 in DMF gave the 4-azido-D-glucosides, which were debenzoylated[33] and reduced to give the two target compounds **19** and **20**, respectively (Scheme 3).[34] The methyl 4-amino-4-deoxy-α-D-galactoside **22** was prepared from the known methyl 2,3,6-tri-*O*-benzyl-α-D-glucoside **21**,[35] which was triflated and treated with NaN_3 in DMF to give the 4-azide with galacto stereochemistry. Palladium-mediated hydrogenolysis afforded the 4-amino product **22** (Scheme 3).[36]



Scheme 3. Synthesis of the methyl 4-amino-4-deoxygalacto- and -glucopyranosides from the 4-OH epimers.

The preparation of the 4-amino-mannoside was more demanding because methyl α-D-talose (the 4-epimer of mannose) is not readily available and not straightforward to regioselectively protect. Therefore another synthesis was planned starting from D-mannose, which was transformed into the 1,6-anhydro-mannoside **23**[37] and protected with an isopropylidene,[38] leaving the 4-OH free for tosylation. Removal of the isopropylidene under acidic conditions and base treatment gave the 3,4-epoxide **24**,[39] which was opened with the azide to give the 1,6-anhydro-4-azido-4-deoxy-mannoside[40] with overall retention of stereochemistry. Acidic hydrolysis gave an anomeric mixture of methyl mannosides, which could be separated by flash chromatography. Nickel-catalyzed reduction of the azide in the α anomer gave the desired methyl 4-deoxy-4-amino-α-D-mannoside **25**[50] (Scheme 4).



Scheme 4. Synthesis of the methyl 4-amino-4-deoxy-α-D-mannoside from 1,6-anhydro-β-D-mannoside.

pK_a measurements: With the aminosugars in hand their pK_a values were determined by titration. The results are presented in Table 1 along with previously published data. Entries 1–4 show the four possible methyl aminosugars with α-gluco stereochemistry, entries 5–8 the four aminosugars with β-gluco stereochemistry, entries 9–12 the four aminosugars with α-galacto stereochemistry, and entries 13–16 the four aminosugars with α-manno stereochemistry. From this complete data set for the model compounds representing the most common carbohydrate acceptors, some general trends can be observed. Because the pK_a value is a measurement of the electron density at a given position, in this study a methyl amino-deoxy-glycoside, it can be correlated with the nucleophilicity of the corresponding hydroxy group, that is, the equivalent hydroxy acceptor in glycosylation chemistry. By measuring the pK_a value of the sugar with an ammonium group at a given position, quantification of the nucleophilicity is achieved.

In general, the 6-amino groups have a higher pK_a value (ranging from 8.6 to 9.0). This is in accordance with the 6-OH acceptor being the most reactive/nucleophilic. This observation is not surprising and can be explained by the fact that the 6-position is more remote from the remaining electron-withdrawing substituents on the sugar ring and only has one β-hydroxy group (the ring oxygen), whereas the secondary hydroxy groups have two. As mentioned in the Introduction the electron density will both influence the nucleophilicity of a given hydroxy or amino group and be influenced by the electron-withdrawing capacity of nearby substituents.

Second to the 6-position, the 3-amino group is the most basic and hence the 3-hydroxy group should be the most nucleophilic. This is more surprising because the 2-OH is sometimes found to be more reactive than the 3-OH in protective chemistry. These observations are probably due to effects other than stereoelectronics and in most cases the hydrogen-bonding pattern, other protective groups, and steric effects can explain the outcome of these reactions. The lower basicity of the 2-amino group can be explained by being closer to the ring oxygen, which to a greater extent pulls electron density away from the 2-position in comparison with the 3-position (inductive effect). The same trend

Table 1. pK_a values of the aminosugars.[a]

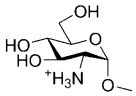
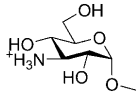
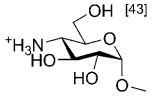
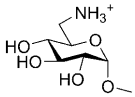
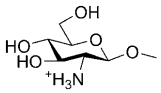
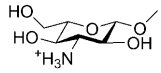
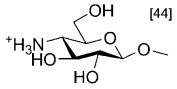
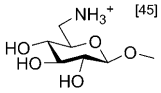
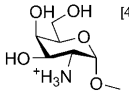
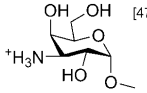
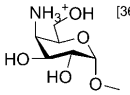
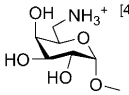
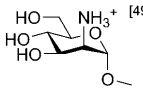
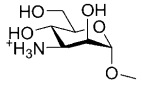
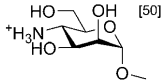
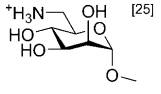
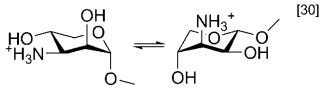
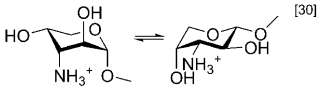
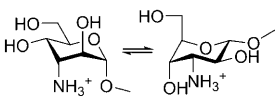
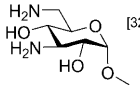
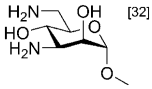
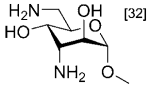
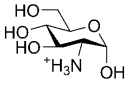
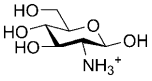
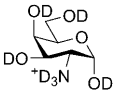
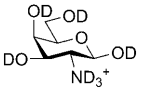
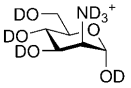
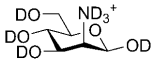
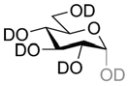
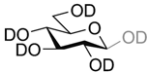
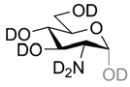
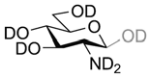
Entry	Aminosugar	pK_a
1		7.5[32]
2		7.8[32]
3		6.8
4		8.9[32]
5		7.2[32]
6		7.6[32]
7		6.7
8		8.6
9		7.9
10		8.0
11		7.3
12		8.9
13		7.2
14		8.1[32]
15		7.2
16		9.0
17		7.8
18		7.8

Table 1. (Continued)

Entry	Aminosugar	pK_a
19		7.7
20		7.3 9.0
21		7.4 9.0
22		7.4 8.8
23		7.7[51][b] 8.1[52][c]
24		7.3[51][b] 7.9[52][c]
25		8.5[52][c]
26		8.1[52][c]
27		7.8[52][c]
28		8.4[52][c]
29		13.7[52][d]
30		13.2[52][d]
31		11.8[52][d]
32		11.6[52][d]

[a] References to the structures refer to the literature synthesis/data, references to the pK_a values refer to literature values. [b] Estimated values. [c] Obtained from NMR studies; deuterium effects apply. [d] Estimated from NMR studies in D_2O.

has been previously studied in α-mannosides, in which it was found by calculation that the 3-OH is more nucleophilic than the 2-OH, which was also confirmed by experimental data.[41] As expected from knowledge of carbohydrate chemistry, the 4-position is the least basic and therefore the least nucleophilic in electronic terms. The lower electron density at the 4-position results from the fixed antiperiplanar relationship between the C4–OH (here C4–NH_2) and C5–O5 bonds, which maximize the electron-withdrawing capacity of the O1 atom.[20a,21a] The electron-withdrawing ca-

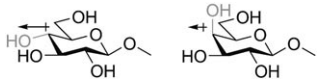
pacity of the C5–O1 bond has been noted to play a role in protective group manipulations; Crich and Vinogradova observed that 4-*O*-benzyl groups were more easily oxidatively removed with DDQ under wet conditions than other benzyl groups in perbenzylated mannosides. This was explained by accelerated decomposition of the radical cation caused by the above-mentioned effect.[42]

By comparing the α-glucosides (Table 1, entries 1–4) with the β-glucosides (entries 5–8), the influence of the anomeric configuration on the electron density at different positions can be observed. The differences in pK_a values show that an axial *O*-methyl group gives more basic amines at the 2- and 3-positions (0.2 to 0.3 pK_a units; entries 1–8); the effect at the 4-position is somewhat lower (ca. 0.1 pK_a). The pK_a of the 6-OH group is surprisingly 0.3 units lower for the β anomer. From these results it seems that α-glucosides should be slightly more reactive at the 2- and 3-positions compared with the β-glucosides. Looking at the α-mannosides (Table 1, entries 13–16) and α-galactosides (entries 9–12) and comparing them with the α-glucosides (entries 1–4) a general trend can be seen: When the amine has a neighboring axial hydroxy group (see entries 2 and 10) the pK_a increases by about 0.2 pK_a units. This effect is further increased when comparing the 3-amino-mannosides and glucosides (entries 2 and 14) for which the difference in pK_a is almost 0.3 units. Regarding the differences in the basicity of the epimeric amines (entries 3 and 11, 1 and 13, 21 and 22, 17 and 18) it is difficult to find a trend. At the 2-position the difference is about 0.3 pK_a units (entries 1 and 13), with the equatorial being the most basic. This can again be explained by the antiperiplanar relation between the axial amino group and the axial OMe, which is more electron-withdrawing than the ring oxygen because it is antiperiplanar to the equatorial amino group. At the 4-position (entries 3 and 11) the difference is about 0.5 pK_a units with the axial amine being the most basic. This can again be explained by the O5 antiperiplanar to the equatorial amine (entry 3) drawing electron density away from the 4-position; this can only happen to a much smaller extent with the axial epimer (entry 11) due to the geometry. The lower reactivity of the axial 4-OH in acylation and glycosylation reactions seems to be mainly influenced by steric effects and not to an intrinsically higher reactivity of the equatorial counterpart. At the 3-position (entries 14 and 19) there is a difference of about 0.5 pK_a units when looking at the manno and altro epimer pair. The effect is amplified by having the neighboring group axial, which lowers the pK_a of the axial epimer significantly. This is in contrast to the 3,6-diamino derivatives (entries 21 and 22) for which the pK_a values are essentially the same for the manno and altro derivatives.

Conformational change is probably also the explanation for the similar pK_a values obtained for the 3-amino-pentoses (entries 17 and 18). Internal hydrogen bonding might be possible in the methyl 3-amino-α-glycosides, but because this would stabilize an ammonium ion further and therefore increase the pK_a of the axial amines, this is probably not a significant contribution. Because a linear relationship between the hydrogen-bond donor and acceptor is geometrically impossible, the effect would be minimal. When dissolved in water it would be expected that all the amino and hydroxy groups in the compounds are mainly hydrogen-bonded to water molecules thereby further diminishing the effects of internal hydrogen bonds.

Analysis of the three diaminosugars (entries 20–22) and comparison with the corresponding monoaminosugars, with an amino group at the 3- or 6-position, shows there is no change in the pK_a of the 6-amino group. The 3-amino group is more affected by the presence of a 6-ammonium group (more EWD) and it is more difficult to protonate the second amine, hence a lower pK_a. The pK_a is lowered by 0.3 pK_a units for the altro and 0.7 pK_a units for the manno. The gluco isomer is in between with a difference of 0.5 pK_a units. This lowering can be explained by the field effect (+I) of the 6-ammonium group and the fact that it is more electron-withdrawing than the amine, which makes the 3-amino groups more acidic. Hence, there is a smaller effect on the altro because the amino is more distant from the ammonium group.

In general, when there are axial hydroxy groups on the sugar ring an increase in the pK_a of the given ammonium ion is observed. This can be explained by the dipole–dipole interactions between a substituent and the sugar ring. When the substituent, in this case a hydroxy group, is axial it is perpendicular to the ring and the vector of the dipole moment is relatively small and its electron-withdrawing capacity is minimized as well as the ring effects on the substituent (Scheme 5). When there is an equatorial substituent the dipole moment is in almost the same plane as the ring giving a relatively large dipole vector and hence a larger effect on the other substituents as well as the other way around.



Scheme 5. Difference in the dipole moment vector between an equatorial (galacto) and an axial (gluco) hydroxy group.

The pK_a (H and D) values of the reducing sugars glucosamine, galactosamine, and mannosamine have previously been measured by various methods in which the mutarotation has been taken into account. When comparing the differences in the pK_a values between the α- and β-2-amino-2-deoxyglucopyranosides the same trend as with the methyl glucosides is observed; the axial epimer is 0.2–0.4 units (depending on the method) more basic than the equatorial counterpart (entries 23 and 24). The same was observed with the methyl glucosides and therefore it is appropriate to compare the reducing sugars with the methyl glycosides in this study. There is a difference of 0.5 pK_a units between the epimers of 2-amino-2-deoxy-galactosamine, again with the α epimer being the most basic (8.1 vs. 8.5). The higher values for the galactosamines are in line with more axial hydroxy

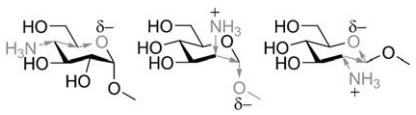
groups on the sugar ring, as seen with previous model compounds. A comparison with the anomers of mannosamine shows that the α anomer is less basic than the β anomer, with a difference of 0.6 units. This is in contrast to the glucosamine and galactosamine described above, for which the β anomers are the most acidic. This again illustrates the strong effect of an anti-periplanar hydroxy group, which in all cases have been shown to significantly lower the pK_a value and in this case over-rule the effect of an additional equatorial substituent.

In entries 29–32 of Table 1 the pK_a (D)[52] values of the anomeric hydroxy group are listed. The values are estimates from NMR studies, but the tendency for equatorial hydroxy groups to be more acidic than the axial counterpart is confirmed. When in an equatorial position the EWD capacity of the sugar ring with its electronegative substituents is maximized. The dipole of the equatorial hydroxy group lies in the same plane as the ring and the effect is therefore maximized. An axial hydroxy group is almost perpendicular to the plane of the sugar ring and only experiences a dampened effect of the EWD capacity of the remaining hydroxy groups on the ring. This is just one more example, but it has to be underlined that the anomeric hydroxy group is special compared with the amino-deoxy-sugars in this study and a direct comparison is not appropriate. The difference between the pK_a (D) values obtained for glucose and glucosamine might arise from hydration[53]/solvation effects or different interactions with the counterion, respectively.

Conclusion

pK_a values have been obtained for 32 sugars representing the most common sugar configurations. The pK_a values give information about the charge density at substituted positions and hence provide a measure of the stereoelectronic influence of the sugar ring at the given positions. Some general trends have been observed that enable the nucleophilicity to be predicted.

1) The pKa of the amine generally increases at all positions when an axial substituent is present. However, the pK_a decreases when the amine is antiperiplanar to the neighboring hydroxy group, as in 1,2-diaxial sugars.
2) This also explains the low pK_a of the equatorial 4-amino group and hence the low nucleophilicity of the 4-OH, which is fixed antiperiplanar to the ring oxygen O5 (Scheme 6). The antiperiplanar relationship is optimal for the electron-withdrawing nature of the C5−O5 bond. The 4-amino group is always the least basic and therefore the 4-OH sugar analogue the least nucleophilic. This is even more pronounced in the gluco configuration, which is known to be less reactive.
3) The 6-amino group is always the most basic and hence the 6-OH sugar is the most nucleophilic. Therefore the 6-OH is the most reactive from the viewpoints of both stereoelectronic effects and steric accessibility.
4) The 3-position is always more basic than the 2-position, and so from a stereoelectronic point of view the 3-position is more reactive than the 2-position. This can again be explained by the antiperiplanar relationship between the 2-OH and either the ring oxygen (galacto and gluco) or the α-*O*-methyl (manno), and the effect is more significant for manno stereochemistry. In carbohydrate chemistry the 2-position is sometimes found to be more reactive than the 3-position, but this is due to steric effects.



Scheme 6. Anti-periplanar relationship between the ammonium groups and the ring oxygen (O5) causes a decrease in the pK_a value and hence a lower nucleophilicity of the corresponding OH acceptor.

Experimental Section

For details regarding the synthetic and analytical procedures see the Supporting Information.

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