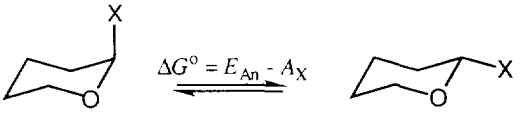
ought to be the steric preference for equatorial X in a tetrahydropyran, but it is customarily measured for a cyclohexane (eq 1) and then corrected for the different steric interactions associated with the shorter C-O bonds.[8] In some cases $E_{An}$ is larger than $A_X$, so that the axial conformer becomes dominant.

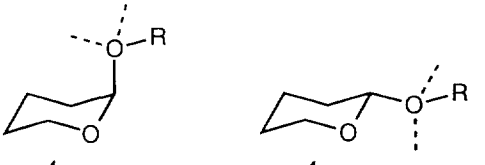



**2ax** **2eq**

The generalized anomeric effect is the extension of the anomeric phenomenon to acyclic systems and to rings other than six-membered. It corresponds to a tendency toward gauche conformers of C-O-C-X and related fragments (**3g**), even though steric repulsions between C and X would be avoided in the anti conformer (**3a**). It

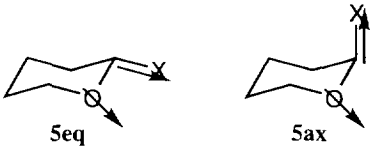

**3g** **3a**

also manifests itself in the exo-anomeric effect,[9] whereby an alkoxy group at C2 of an oxacycle prefers a conformation where the exocyclic O-R bond is gauche to the endocyclic C-O, regardless of whether the alkoxy is axial (**4ax**) or equatorial (**4eq**).




**4ax** **4eq**

The anomeric and generalized anomeric effects can be interpreted in terms of electrostatic interactions[10] or of negative hyperconjugation.[11] Electrostatic repulsion between the C-X dipole and the resultant dipole of the two C-O bonds and of the two oxygen lone pairs destabilizes the equatorial conformer (**5eq**), whereas there is little or no such destabilization of the axial conformer (**5ax**). Alternatively, negative hyperconjugation, or the delocalization of a lone pair of electrons in an n orbital on the oxygen into the antibonding σ* orbital of the C-X




**5eq** **5ax**

bond, is a stabilizing interaction. Figure 1a shows the stabilization due to mixing of these two orbitals and creation of a new, lower-energy orbital.

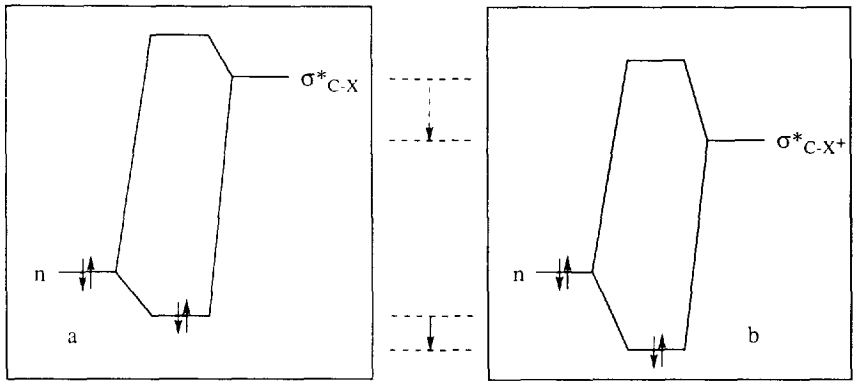
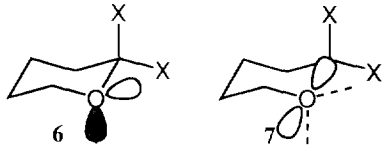
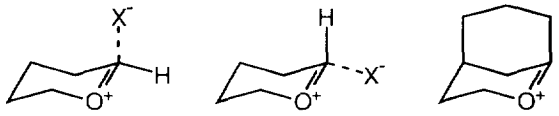



Fig. 1. (a) Filled-vacant stabilizing interaction of lone pair (n) and C-X antibonding (σ*) orbitals. (b) Greater stabilization (solid arrow) arising from lower energy (dashed arrow) of σ* orbital of C-X+.

For simplicity the lone pairs are often viewed as $sp^3$-hybridized (**6**). Delocalization of the (shaded) $sp^3$ lone pair antiperiplanar to the C-X bond in the axial conformer is considered to provide more stabilization than does delocalization of either lone pair that is synclinal in the equatorial conformer. A more proper view[3,12] is based on a different orbital model for an ether oxygen and focuses on the higher-energy, unhybridized, pure-p lone-pair orbital on the oxygen (**7**), which can delocalize into the σ* orbital of an axial C-X bond but is




orthogonal to an equatorial C-X bond. Either of these views corresponds to the contribution of an additional double-bond/no-bond resonance form (**8ax**), which can stabilize only the axial conformer. (The corresponding resonance form **8eq** of the equatorial conformer suffers poor pi overlap, similar to that in a Bredt-rule violation such as **8eq'**.)




**8ax** **8eq** **8eq'**

Likewise, for an acyclic C-O-C-X fragment only the gauche conformer (**9g**) has an $sp^3$ oxygen lone pair (shaded) antiperiplanar to the C-X bond, whereas in the anti conformer (**9a**) the lone pairs are synclinal to that

bond. Alternatively, in the preferred model for an ether oxygen the anti conformer (**9a'**) has the p orbital orthogonal to the σ* orbital of the C-X bond so that these orbitals cannot overlap, whereas in the gauche conformer (**9g'**) there is good but not perfect overlap between the p lone pair and the C-X bond. The relative importance of electrostatic interactions and negative hyperconjugation for anomeric and generalized anomeric effects is a matter of controversy[13] and probably depends on X, solvent, and other aspects.

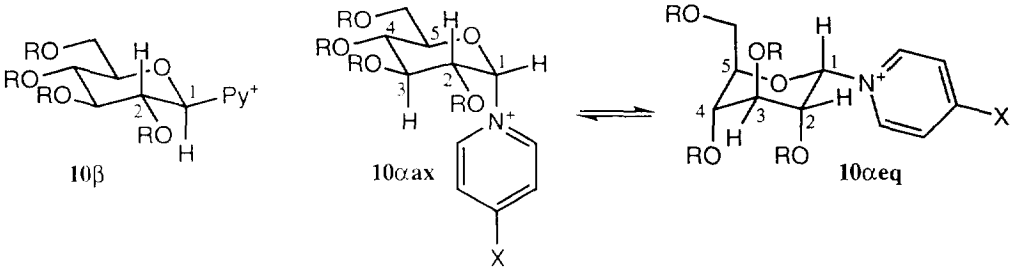
**9g'** **9g** **9a** **9a'**

*1.1.3. Reverse Anomeric Effect.* The reverse anomeric effect is a special case that arises with a cationic substituent $X^+$. It is claimed that the positive charge shifts the equilibrium back toward the equatorial (or anti) conformer and that this shift is due to an electronic interaction, not merely a steric one. In terms of eq 2, this shift corresponds to a negative value for $E_{An}$, which can amount to as much as 1-3 kcal/mol. It is the purpose of this review to explore the validity of this claim.

To avoid confusion, we should note that the term "reverse anomeric effect" has been used in several other senses. It might apply to electropositive (electron-donating) substituents, such as lithio, where the polarity of the C-X bond is reversed, but such substituents have not been investigated. It has also been applied to substituents such as COOR,[14] $CONH_2$,[15] $NHCH_3$,[16] $CH_3$ and $NH_2$,[17] and $CH_2NHAc$, $CH_2OAc$, and $CH(SO_2Et)_2$,[18] where the equilibrium has been thought to shift toward the equatorial conformer but where the comparison equilibrium may be uncertain. It has also been applied to CN,[19] based on some energetic considerations. Nevertheless, in this review we restrict the context of reverse anomeric effect to cationic substituents.

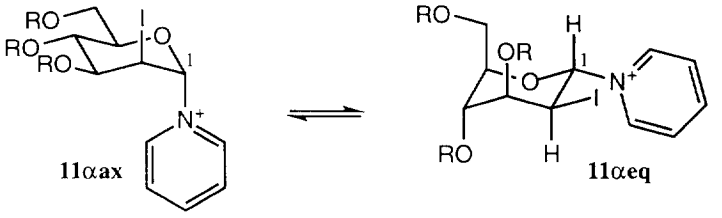
*1.2. Discovery of the Reverse Anomeric Effect*

*1.2.1. Glycosylpyridinium Ions.* Conformational analysis of glycosylpyridinium ions such as **10β** (in which all ring substituents can be equatorial) and **10α** (which may be **10αax** or **10αeq** or a mixture of these) is based on $^1H$ nuclear magnetic resonance (NMR) spectroscopy. The various vicinal coupling constants around the sugar ring are diagnostic, since they reveal the dihedral angles.[20] If vicinal hydrogens are both axial (as H1 and H2 of **10β** or H2 and H3 of **10αax**), then the coupling constant is 5-10 Hz, but it is 2-4 Hz if either or both hydrogens are equatorial (as H1 and H2 of **10αax** or **10αeq** or H2 and H3 of **10αeq**).



**10β** **10αax** **10αeq**

The first examples of a reverse anomeric effect were observed by Lemieux and Morgan, who proposed the terminology.[21] They studied the conformational equilibria of *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium ion (**10**α, R = Ac, X = $CH_3$) and *N*-(tri-*O*-acetyl-α-D-2-deoxy-2-iodomannopyranosyl)-4-methylpyridinium ion (**11**α, R = Ac). They recorded vicinal coupling constants, which are listed in Table 1. The uniformly small coupling constants observed in **10**α (R = Ac)—2.8, 3.1, 3.2, and 5.7 Hz—show that none of the vicinal hydrogens can be trans-diaxial as in **10αax** (R = Ac). This evidence shows that the pyridinium group is equatorial, as in **10αeq**. In contrast the large 9.0-Hz coupling constant in **11**α (R = Ac) shows that



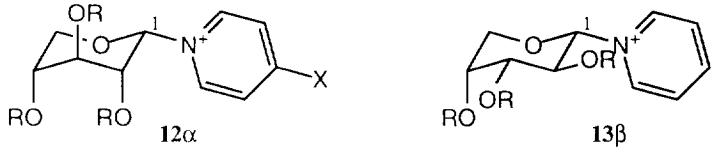

H1 and H2 must both be axial, as in **11αeq**. For both these cases the researchers concluded that the cationic heterocycle is equatorial even though other bulky substituents must then be axial.

Table 1. $^1$H NMR Coupling Constants of *N*-(α-Glycopyranosyl)pyridinium Ions.

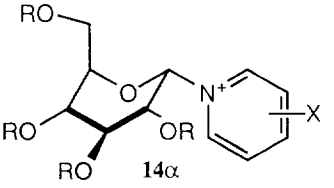
| Sugar | Pyridinium | Structure | Solvent | $J_{12}$, Hz | $J_{23}$, Hz | $J_{34}$, Hz | $J_{45}$, Hz | Ref. |
|---|---|---|---|---|---|---|---|---|
| $Ac_4$Gluco | 4-MePy$^+$ | **10**α,X=$CH_3$ | $D_2O$ | 2.8 | 3.1 | 3.2 | 5.7 | 21 |
| $Ac_3$Manno[a] | Py$^+$ | **11**α | $D_2O$ | 9.0 | — | (Sum | = 7) | 21 |
| $Ac_3$Xylo | Py$^+$ | **12**α | $CD_3NO_2$ | 1.4 | 2.7 | 2.5 | 1.8 | 22 |
| $Ac_3$Arabino | Py$^+$ | **13**β | DMSO-$d_6$ | 8.5 | 10.0 | 3.3 | — | 22 |
| Xylo | 4-MePy$^+$ | **12**α,X=$CH_3$ | $D_2O$ | 1.4 | 2.7 | 2.5 | 1.8,1.5 | 23 |
| Gluco | Py$^+$ | **10**α,X=H | $D_2O$ | 3.9 | 7.1 | 5.6 | — | 23 |
| Gluco | 4-BrIsoQ$^+$ | **10**α[b] | $D_2O$ | 3.7 | 6.8 | 6.2 | 8.3 | 23 |
| $Bn_4$Gluco | sColl$^+$ | **10**α[c] | $D_2O$ | 3.1 | 3.5 | 5.0 | 8.8 | 24 |

[a]2-Deoxy-2-iodo. [b]Heterocycle = 4-Bromoisoquinolinium. [c]Heterocycle = 2,4,6-Trimethylpyridinium.

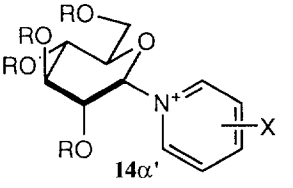
Similar equatorial preferences are shown by pyridinium groups in other such ions. Coupling constants in *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)pyridinium ion (**12**α, R = Ac, X = H), *N*-(tri-*O*-acetyl-β-D-arabinopyranosyl)pyridinium ion (**13**β, R = Ac),[22] *N*-(α-D-xylopyranosyl)-4-methylpyridinium ion (**12**α, R = H, X = $CH_3$), and *N*-(α-D-glucopyranosyl)-pyridinium (**10**α, R = X = H) and -4-bromoisoquinolinium ions[23] are



included in Table 1. Uniformly small coupling constants of 1.4, 2.7, 2.5, and 1.8 Hz in **12**α (R = Ac, X = H) and of 1.4, 2.7, 2.5, 1.8, and 1.5 Hz in **12**α (R = H, X = $CH_3$) have been interpreted as indicating a preponderance of the chair conformation with the pyridinium group equatorial even though the three acetoxy or hydroxy substituents must be axial. Similarly, the large coupling constants of 8.5 and 10.0 Hz in **13**β (R = Ac) indicate that these hydrogens are trans-diaxial, so that the pyridinium ring must be equatorial. However, intermediate coupling constants of 3.9, 7.1, and 5.6 Hz in **10**α (R = X = H) and of 3.7, 6.8, 6.2, and 8.3 Hz in *N*-(α-D-glucopyranosyl)-4-bromoisoquinolinium ions are larger those above but smaller than those expected for **10**β. Therefore these coupling constants were interpreted as indicating the presence of a boat form (**14**α or **14**α'), which again permits the aromatic heterocycle to be pseudoequatorial. The intermediate coupling constants in *N*-(tetra-*O*-benzyl-α-D-glucopyranosyl)collidinium ion (**10**α, R = $PhCH_2$), included in Table 1, also indicate a distorted conformation.[24]




**14**α

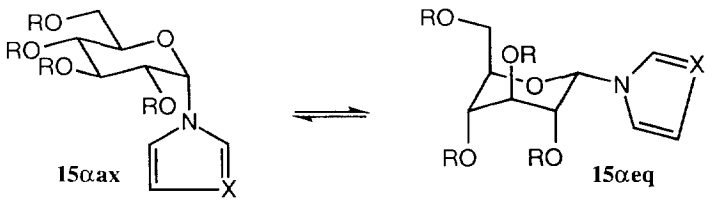



**14**α'

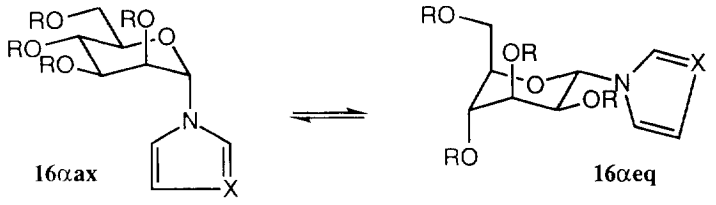
It must be recognized that NMR coupling constants may not provide exact conformational descriptions of these derivatives. More definitive evidence comes from the X-ray structure of crystalline *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium ion (**10**α, R = Ac, X = $CH_3$), which shows a boat conformation (**14**α'),[25] in mild contradiction to the NMR spectrum (Table 1), which was interpreted[21] as indicating the chair form **10**α**eq**. Of course, a glucose derivative is the least likely to take this chair conformation, which requires the other four substituents to be axial. The easy conclusion from all the data is that none of these glycosylpyridinium ions adopts an undistorted chair conformation in which the pyridinium ion is axial.

A pyridinium ion is quite bulky. It is at least as large as a phenyl group, since it has a shorter C-N bond and also, more importantly, a positive charge that must be solvated. Consequently all the observed conformational preferences could be due simply to avoidance of severe steric repulsions associated with placing that group in the axial position. The data show only that the form with the pyridinium group axial is strongly disfavored, but they do not reveal whether this disfavor is due to a reverse anomeric effect or simply to steric repulsion.

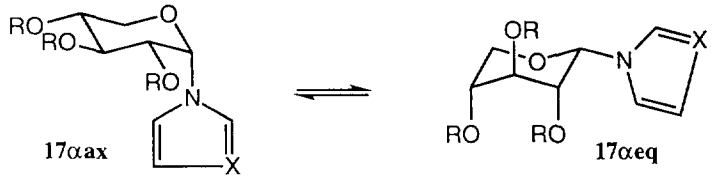
*1.2.2. Glycosylimidazolium Ions.* An imidazolyl group provides an opportunity to distinguish between steric repulsions and a reverse anomeric effect. Protonation or methylation occurs at the $sp^2$ nitrogen, which is so distant that the added proton or methyl is unlikely to change the size of the group. Thus an imidazolyl serves as its own control for steric factors. Any shift of equilibrium toward the conformer with the imidazolyl equatorial should then be attributable to the positive charge and not to any steric effect. The $^1H$ NMR coupling constants in *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)imidazole (**15**α, R = Ac, X = N) and *N*-(tetra-*O*-acetyl-α-D-manno-pyranosyl)imidazole (**16**α, R = Ac, X = N) and in their *N*-protonated or *N*-methylated derivatives (X = $NH^+$ or $NCH_3^+$) were reported by Lemieux[26] and are listed in Table 2. The vicinal coupling constants generally




decrease on protonation or methylation, except for $J_{12}$ of the mannose derivative. These are the same features that were seen in the glycosylpyridinium ions and that led to the conclusion that the pyridinium ion cannot be axial. Here such data are again consistent with a protonation- or methylation-induced shift of the equilibrium toward the conformer (**15αeq** or **16αeq**) with the imidazolyl group equatorial.




Paulsen, Györgydeák, and Friedmann[22] obtained quantitative data regarding conformational equilibria in glycosylimidazoles. Their observed vicinal coupling constants for *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)imidazole (**17**α, X = N, R = Ac) and for its *N*-protonated form (**17**α, X = $NH^+$, R = Ac) are included in Table 2. By comparing $J_{45}$ (and $J_{45'}$, observable in pentopyranosides) with the coupling constants seen in model compounds, they could estimate the proportions of each conformer, and these are also indicated in Table 2. They concluded that there is 65% equatorial conformer (**17αeq**, X = N) in $CDCl_3$, whereas in the presence of trifluoroacetic acid the proportion of **17αeq** (X = $NH^+$) increases to >95%. This difference corresponds to a free-energy change of >1.4 kcal/mol, which is substantial. If *N*-protonation does not change the size of the imidazolyl group, the shift of the equilibrium cannot be due to steric effects but must be attributed to the positive charge. Such results have been widely accepted[3,5] as the best evidence for a reverse anomeric effect.

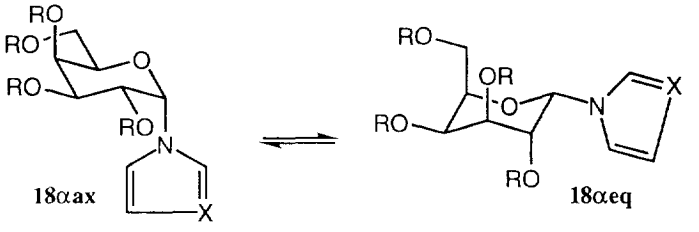



A more extensive study by Finch and Nagpurkar[27] provided similar results, also listed in Table 2, but their conclusions are more equivocal. By comparison of all four vicinal coupling constants with those of model sugars, they could obtain estimates of the population of equatorial conformer more reliable than those obtained from $J_{45}$ alone. They concluded that neither α-glucopyranosylimidazole (**15**α, X = N, R = H) nor α-

Table 2. $^1$H NMR Coupling Constants of *N*-(α-Glycopyranosyl)imidazoles.

| Sugar | Structure | X | Solvent | $J_{12}$, Hz | $J_{23}$, Hz | $J_{34}$, Hz | $J_{45}$, Hz | %eq | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| $Ac_4$Gluco | **15α** | N | $CDCl_3$ | 5.3 | 10.4 | 9.2 | 9.6 | — | 26 |
| $Ac_4$Gluco | **15α** | $NH^+$ | $CDCl_3$ | ~3.4 | — | ~5.6 | 7.7 | — | 26 |
| $Ac_4$Gluco | **15α** | $NMe^+$ | $CDCl_3$ | 3.8 | 6.5 | ~5.5 | ~6.5 | — | 26 |
| $Ac_4$Manno | **16α** | N | $(CD_3)_2CO$ | 5.1 | 2.9 | 7.0 | ~6.0 | — | 26 |
| $Ac_4$Manno | **16α** | $NH^+$ | $CDCl_3$ | 6.8 | 3.2 | 5.3 | 4.7 | — | 26 |
| $Ac_4$Manno | **16α** | $NMe^+$ | $CDCl_3$ | 6.8 | 3.0 | 5.5 | 4.1 | — | 26 |
| $Ac_3$Xylo | **17α** | N | $CCl_4$ | 4.3 | 8.0 | 8.0 | 4.6,7.7 | 35 | 22 |
| $Ac_3$Xylo | **17α** | N | $(CD_3)_2CO$ | 2.4 | 4.3 | 4.3 | 3.0,2.8 | 85 | 22 |
| $Ac_3$Xylo | **17α** | N | $CDCl_3$ | 3.0 | 5.8 | 5.0 | 3.3,4.6 | 65 | 22 |
| $Ac_3$Xylo | **17α** | $NH^+$ | $CDCl_3$ | 1.6 | 3.0 | 2.8 | — | >95 | 22 |
| $Ac_4$Gluco | **15α** | N | $CDCl_3$ | 5.5 | 10.25 | 8.5 | 10.0 | low | 27 |
| $Ac_4$Gluco | **15α** | $NH^+$ | $CDCl_3$ | 3.1 | 8.0 | 7.4 | 7.4 | 27±5 | 27 |
| $Ac_4$Manno | **16α** | N | $CDCl_3$ | 5.1 | 2.2 | 7.75 | 7.1 | low | 27 |
| $Ac_4$Manno | **16α** | $NH^+$ | $CDCl_3$ | 6.5 | 3.1 | 5.9 | 4.4 | 67 | 27 |
| $Ac_4$Manno | **16α** | N | $(CD_3)_2CO$ | 5.2 | 3.1 | 6.9 | 5.8 | 51±1 | 27 |
| $Ac_4$Manno | **16α** | $NH^+$ | $(CD_3)_2CO$ | 7.0 | 3.0 | 5.5 | 4.2 | 72±1 | 27 |
| Gluco | **15α** | N | $D_2O$ | 5.5 | 10.0 | 8.8 | 10.0 | low | 27 |
| Gluco | **15α** | $NH^+$ | $D_2O$ | 5.1 | 10.1 | 8.9 | 10.1 | low | 27 |
| Manno | **16α** | N | $D_2O$ | 3.7 | 3.55 | 7.0 | 7.4 | 30±2 | 27 |
| Manno | **16α** | $NH^+$ | $D_2O$ | 4.1 | 3.05 | 7.0 | 7.7 | 31±5 | 27 |
| Galacto | **18α** | N | $D_2O$ | 5.5 | 10.3 | 3.15 | 0.9 | low | 27 |
| Galacto | **18α** | $NH^+$ | $D_2O$ | 4.7 | 9.35 | 3.1 | 0.4 | low | 27 |

galactopyranosylimidazole (**18α**, X = N, R = H) nor their protonated forms (**15α**, **18α**, X = $NH^+$, R = H) exist appreciably in an equatorial conformation (**15αeq**, **18αeq**). In contrast they found 27±5% **15αeq** (X =

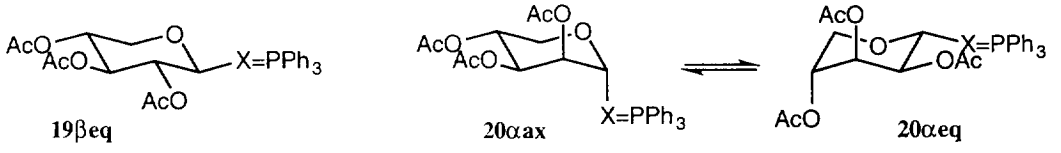



$NH^+$, R = Ac) for *N*-(α-tetra-*O*-acetyl-D-glucopyranosyl)imidazolium ion. The increase of equatorial proportion on protonation is evidence for a reverse anomeric effect, even though a glucose derivative is again the least likely to show this. (That the increase appears here but not with **15αeq** (X = $NH^+$, R = H) was attributed to the reduced steric bulk of acetoxy compared to aquated hydroxy.) Yet the effects on protonating the

mannosylimidazoles are also small. Protonation of *N*-(α-D-mannopyranosyl)imidazole (**16α**, R = H) "increases" the proportion of **16αeq** from 30±2% to 31±5%, and protonation of *N*-(tetra-*O*-acetyl-α-D-mannopyranosyl)imidazole (**16α**, R = Ac) increases the proportion of **16αeq** from 51±1% to 72±1%. These margins of error were evaluated from the experimental variations in coupling constants and do not reflect any systematic errors from an inappropriateness of model compound. Therefore the increased percentages do not represent strong support for a reverse anomeric effect.

Again a more definitive result comes from an X-ray diffraction study. Crystalline *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)imidazolium ion (**17α**, X = $NH^+$, R = Ac) does exist in conformation **17αeq**,[28] as inferred from the NMR solution data.

*1.2.3. Other Examples.* Another comparison of cationic and neutral substituents is possible with phosphineimines, glycosyl-N=$PPh_3$, which can be protonated to glycosyl-$NHPPh_3^+$. NMR data are listed in Table 3.[22] According to the coupling constants $J_{45}$ and $J_{45'}$, the β-xylopyranose derivative is >95% all-equatorial (**19βeq**), whether protonated (X = $NH^+$) or not (X = N), just as expected. In contrast, the



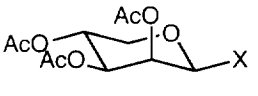

estimated proportion of the α-lyxopyranose conformer with the $NPPh_3$ group equatorial (**20αeq**) increases from 17% in the neutral form (X = N) to 92% on protonation (X = $NH^+$).

Table 3. $^1H$ NMR Coupling Constants of *N*-(Tri-*O*-acetylglycopyranosyl)amine Derivatives.[22]

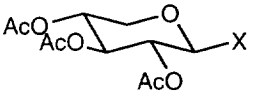
| Sugar | Structure | X | Solvent | $J_{12}$, Hz | $J_{23}$, Hz | $J_{34}$, Hz | $J_{45}$, Hz | $J_{45'}$, Hz | %eq |
|---|---|---|---|---|---|---|---|---|---|
| Ac3βXylo | **19β** | N | DMSO-$d_6$ | 7.0 | — | — | 5.0 | 10.0 | >95 |
| Ac3βXylo | **19β** | $NH^+$ | DMSO-$d_6$ | — | — | — | 5.2 | 10.4 | >95 |
| Ac3αLyxo | **20α** | N | $CDCl_3$ | 2.7 | 3.2 | 9.0 | 5.4 | 9.3 | 17 |
| Ac3αLyxo | **20α** | $NH^+$ | DMSO-$d_6$ | 9.0 | 3.0 | 3.8 | 2.0 | 2.0 | 92 |
| Ac3βLyxo | **21β** | $NH_2$ | $CDCl_3$ | 1.3 | 3.0 | — | 4.8 | 10.0 | 90 |
| Ac3βLyxo | **21β** | $NH_3^+$ | DMSO-$d_6$ | — | — | — | 5.0 | 10.8 | 98 |
| Ac3βXylo | **22β** | $NH_2$ | $CDCl_3$ | 8.8 | 9.3 | 9.3 | 5.3 | 10.2 | >95 |
| Ac3βXylo | **22β** | $NH_3^+$ | DMSO-$d_6$ | — | — | — | 5.2 | 10.4 | >95 |

Another comparison is of cationic $NH_3^+$ and neutral $NH_2$ substituents, for which NMR data are also listed in Table 3.[22] The small variations of $J_{45}$ and $J_{45'}$ observed in *N*-(tri-*O*-acetyl-β-lyxopyranosyl)amine (**21β**, X = $NH_2$) may signify an increase of the proportion of equatorial conformer (**21βeq**) from 90% to 98% on *N*-protonation (X = $NH_3^+$), but the conclusion is uncertain. No significant change could be seen on protonating *N*-(tri-*O*-acetyl-β-xylopyranosyl)amine, which is >95% equatorial (**22βeq**, X = $NH_2$ or $NH_3^+$). No change should be expected for either of these glycosylamines, since three or four substituents will be equatorial

regardless of the state of protonation of the amino group, and any reverse anomeric effect will be difficult to detect.

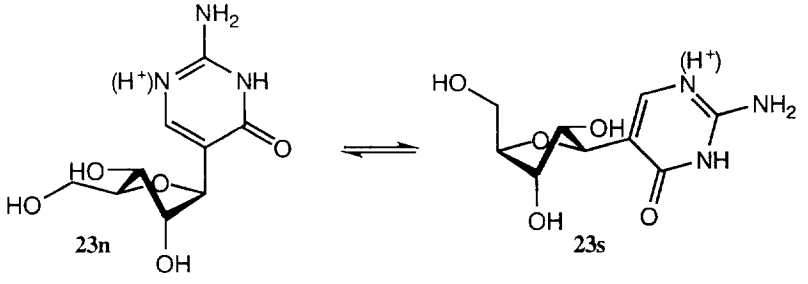



**21βeq**




**22βeq**

Yet another case that may represent a reverse anomeric effect involves the conformational behavior of the five-membered ring in ψ-isocytidine (**23n**,**23s**).[29] At 298K the proportion of **23n** increases from 38% to 52% on *N*-protonation. The temperature dependence of the **23n**-**23s** equilibrium corresponds to $\Delta H^{o}$ = -0.5±0.1 kcal/mol and $\Delta S^{o}$ = -0.7±0.5 cal/mol-deg for the unprotonated species and $\Delta H^{o}$ = +0.9±0.05 kcal/mol and $\Delta S^{o}$ = +3.0±0.15 cal/mol-deg for the protonated species. Still another possible example of a reverse anomeric effect is that of glycosylaminoguanidinium ions, where the sole observable anomer is the one with the $NHNHC(NH_2)_2^+$ group equatorial.[30] Unfortunately no comparison was made with the corresponding neutral analog. In both these cases the positive charge is more distant from the anomeric center, so any reverse anomeric effect could be small.




**23n** **23s**

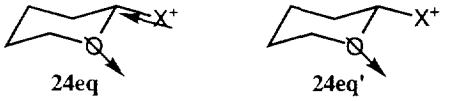
In summary, there are many examples where NMR data indicate that cationic substituents at an anomeric carbon substantially prefer the equatorial position, often more so than do the corresponding neutrals. These examples have long been accepted as evidence for a reverse anomeric effect. The dilemma is that the theoretical basis for such a reverse is weak. We next turn to theories that have been proposed to account for the reverse anomeric effect.

## 2. THEORIES OF THE REVERSE ANOMERIC EFFECT

### *2.1. Qualitative Explanations*

*2.1.1. Electrostatic Explanation.* The first explanation for the reverse anomeric effect[21] was based on the electrostatic interpretation of the anomeric effect itself. Dipole-dipole repulsion destabilizes the equatorial conformer (**5eq**) of a neutral molecule, whereas there is little or no destabilization of the axial conformer (**5ax**). With a cationic X group the C-X dipole was considered to reverse its direction (**24eq**), as compared to **5**, thereby stabilizing the equatorial conformer. This explanation cannot be valid, since dipole moment has no intrinsic meaning when there is net charge. (The dipole moment of an ion is not invariant to changing the origin

of the coordinate system,[31] so that any value whatsoever can be calculated merely by changing the origin appropriately. A common computer algorithm for calculating the molecular dipole moment chooses the center of mass as origin, but this is arbitrary. The most pertinent choice of origin is the centroid of charge, whereby the dipole moment would be calculated to be zero.) Instead, one must focus on the monopole-dipole interaction. In the equatorial conformation (**24eq'**) the positive charge is closer to the negative end of the dipole. Therefore electrostatic interactions are attractive, not repulsive, and can stabilize this conformation. On the other hand, this electrostatic interpretation is not entirely satisfactory because it cannot account for the presence of boat form **14α'**,[25] which is apparently stabilized even though the positive charge has moved away from the negative end of the dipole.




**24eq** **24eq'**

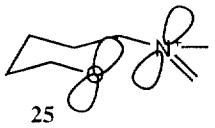
*2.1.2. Delocalization Explanation.* An alternative theory for the anomeric effect itself involves negative hyperconjugation.[11] Delocalization of a $sp^3$ (**6**) or p (**7**) oxygen lone pair into the $\sigma^*_{C\text{-}X}$ orbital can stabilize the axial conformer. In equivalent parlance the axial conformer is said to be stabilized by an additional double-bond/no-bond resonance form (**8ax**). Introduction of a positive charge makes substituent X even more electronegative. Consequently, the energy of the $\sigma^*_{C\text{-}X}$ orbital is lowered, as shown in Figure 1b. This lowering permits a stronger interaction with the lone-pair orbital and produces a greater stabilization from the mixing of the two orbitals. In resonance terminology, with a cationic $X^+$ the resonance form **8ax** is no longer destabilized by the necessity for charge separation, and it can contribute more. Thus negative hyperconjugation, which preferentially stabilizes the axial conformer, becomes stronger. Consequently the proportion of that axial conformer ought to increase, contrary to what is seen experimentally. In summary, according to this view the anomeric effect ought to increase and not to reverse when substituent X carries a positive charge.

*2.1.3. Other Explanations.* The inability of electron delocalization to account for a reverse anomeric effect has often been pointed out. This inability is troubling, inasmuch as a delocalization explanation is currently favored to account for anomeric effects in general, even by Lemieux,[32] the original proponent of electrostatic attraction.[21] Therefore various attempts have been made to find other explanations for a reverse anomeric effect.

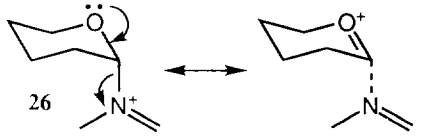
Confusion has arisen from the erroneous view of cationic substituents such as $NR_3^+$ as being electropositive or less electronegative than H.[33,34] An X substituent less electronegative than H or C would indeed reverse the direction of the C-X dipole (**24eq**). Such a substituent would also raise the energy of the $\sigma^*_{C\text{-}X}$ orbital (Figure 1) and reduce the delocalization of the oxygen lone pair into the C-X bond. Either of these consequences of a lower electronegativity could eliminate or reverse the usual anomeric effect. Nevertheless it is indisputable that the positive charge cannot make the substituent less electronegative but must make it even more electronegative,[27] so that the anomeric effect would be augmented.

Several proposals have invoked other types of orbital overlap. One proposal contends that a reverse anomeric effect arises from a stabilizing homoallylic-type overlap between the pure-p oxygen lone pair and a $\pi^*$ orbital of the aromatic heterocycle, an overlap that is favored geometrically in the equatorial conformer (**25**).[27] Examples of crystal structures where the observed O-C-$N^+$-C dihedral angle is small were cited in support. (A similar homoconjugative overlap, but focusing on $sp^3$ lone pairs, has also been proposed.[35]) However, there is

one crystal structure that shows an O-C-N$^+$-C dihedral angle of 40°.[36] Moreover, 6-31G* calculations on *N*-(hydroxymethyl)pyridinium ion suggest that the barrier to C-N$^+$ rotation is only 0.3 kcal/mol, with maximum energy, not minimum, when the p and π* orbitals are parallel.[37] Besides, there is no evidence in UV spectra of 2-, 3-, or 4-(hydroxymethyl)pyridinium ions[38] for such a p-π* interaction.



25



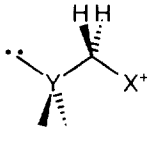
26

Another suggestion[39] is that a cationic nitrogen that is axial precludes exo-anomeric stabilization, which arises from delocalization of a nitrogen lone pair into the $\sigma^*_{C\text{-}O}$ orbital.[9,32] This loss of anomeric stabilization is not simply due to the absence of a lone pair with cationic nitrogen, since that would be comparable when the N$^+$ is equatorial. Instead, it arises because in the axial case delocalization of the oxygen lone pair into the $\sigma^*_{C\text{-}N^+}$ orbital is so strong that the C-N$^+$ bond is weakened and lengthened (**26**). However, since the exo-anomeric effect usually favors equatorial conformers, its elimination would leave only the n-σ* delocalization operative, which ought to favor the axial conformer even more.

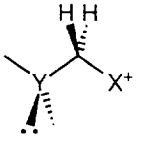
*2.2. Quantitative Molecular-Orbital Calculations*

Molecular-orbital calculations at various levels of approximation, both ab initio and semiempirical, can provide several kinds of information bearing on the reverse anomeric effect. Among these are the relative energies of the various conformations, "electronic" parameters, and structural data. Various types of structures can be calculated, from the full sugar derivative to a substituted tetrahydropyran to a $CH_3$-O-$CH_2$-X or HO-$CH_2$-X fragment. The energies can distinguish whether the equatorial (or anti) conformer is indeed the most stable, as predicted by the reverse anomeric effect. Unfortunately, relative energies depend strongly on hydrogen bonding and on solvation, which ordinarily is not taken into account, even though all the experimental evidence is from studies in solution and the question can be raised whether there would be a reverse anomeric effect in the gas phase. Calculated electronic parameters include dipole moments and electron densities, which may help to distinguish electrostatic, delocalization, and steric effects, but these distinctions are not unambiguous. The most useful structural data are O-C and C-X bond lengths, which indicate the extent to which a resonance form equivalent to **8ax** contributes.

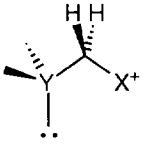
*2.2.1. Model Structures.* Results of calculations on $HOCH_2OH_2^+$[40-42] and $HOCH_2NH_3^+$,[43] on $H_2NCH_2NH_3^+$,[44] on all of these plus $H_2NCH_2OH_2^+$,[45] on all plus $HOCH_2FH^+$ and $H_2NCH_2FH^+$,[46] on $CH_3OCH_2NH_3^+$,[47,48] and on $CH_3OCH_2O(H)CH_3^+$[49] are listed in Table 4. Relative energies of Y-$CH_2X^+$ conformers **27a** and **27g** (or **27s**) (Y = $H_2N$ or HO, X = $NH_3$ or $OH_2$ or FH, as well as methylated analogs)



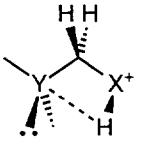
**27a**



**27g**



**27s**



**27H**

are presented as $\Delta E = E_{anti} - E_{syn}$, which is a positive number if a reverse anomeric effect makes antiperiplanar less stable than synclinal (gauche) or synperiplanar. Notice that here the designation as anti or syn reflects the relation between a lone pair on Y and the C-$X^+$ bond, not the relation between bonds, as in **3**. For $YCH_2OH_2^+$ there are three conformers differing by rotation about the C-$O^+$ bond, but the most stable one was used. Calculations on $(HO)_2CHOH_2^+$[45] and $(HO)_2CHNH_3^+$[50] are also included in Table 4, although the energies are complicated by an anomeric effect in the $(HO)_2C$ fragment, such that the globally most stable conformer has one H-O-C-O anti and the other gauche.[51] Table 4 also includes Y-C and C-X bond lengths in anti and syn conformers.

Table 4. Calculated Relative Energies, $\Delta E = E_{anti} - E_{syn}$ (kcal/mol), and Bond Lengths, $d$ (Å), in Conformers of Y-$CH_2X^+$ with Anti (**27a**) and Syn (**27g** or **27s**) Lone Pairs.

| Entry | Y | X | Level | $\Delta E$ | $d_{Y\text{-}C}^a$ | $d_{C\text{-}X}^a$ | $d_{Y\text{-}C}^s$ | $d_{C\text{-}X}^s$ | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $H_2N$ | $NH_3$ | 4-31G | 10.0[a] | 1.424 | 1.571 | 1.423 | 1.501 | 44 |
| 2 | $H_2N$ | $NH_3$ | 6-31G** | 5.62[a] | 1.401 | 1.561 | 1.427 | 1.513 | 45 |
| 3 | $H_2N$ | $OH_2$ | 6-31G** | -13.45 | 1.289 | 2.381 | 1.401 | 1.546 | 45 |
| 4 | $H_2N$ | FH | 6-31+G* | -1.89[b] | 1.282 | 2.633 | 1.283 | 2.696 | 46 |
| 5 | HO | $NH_3$ | AM1 | -2.38[c] | 1.389 | 1.521 | 1.409 | 1.502 | 43 |
| 6 | HO | $NH_3$ | AM1-SM2 | -1.23[c] | 1.408 | 1.486 | 1.417 | 1.480 | 43 |
| 7 | HO | $NH_3$ | 6-31G** | 3.80 | 1.350 | 1.534 | 1.365 | 1.501 | 45 |
| 8 | HO | $NH_3$ | 6-31G** | -0.17[c] | 1.356 | 1.523 | 1.366 | 1.501 | 43 |
| 9 | HO | $OH_2$ | MNDO | 1.56 | 1.353 | 1.515 | 1.378 | 1.491 | 42 |
| 10 | HO | $OH_2$ | AM1 | 2.12 | 1.357 | 1.508 | 1.381 | 1.501 | 42 |
| 11 | HO | $OH_2$ | AM1 | -3.84[c] | 1.353 | 1.564 | 1.384 | 1.505 | 43 |
| 12 | HO | $OH_2$ | AM1-SM2 | -2.18[c] | 1.378 | 1.479 | 1.403 | 1.437 | 43 |
| 13 | HO | $OH_2$ | PM3 | 2.02 | 1.335 | 1.544 | 1.367 | 1.492 | 42 |
| 14 | HO | $OH_2$ | 4-31G | 1.4 | — | 1.512 | — | 1.475 | 40 |
| 15 | HO | $OH_2$ | 4-31G | 4.6 | 1.321 | 1.669 | 1.367 | 1.527 | 41 |
| 16 | HO | $OH_2$ | 6-31G* | 1.69 | 1.323 | 1.542 | 1.352 | 1.505 | 42 |
| 17 | HO | $OH_2$ | 6-31G** | -1.18 | 1.303 | 1.656 | 1.348 | 1.503 | 45 |
| 18 | HO | $OH_2$ | 6-31G** | -4.12[c] | 1.301 | 1.659 | 1.347 | 1.500 | 43 |
| 19 | HO | $OH_2$ | MP2[d] | 0.44 | 1.334 | 1.559 | 1.369 | 1.504 | 42 |
| 20 | HO | FH | 6-31G** | 22.4 | 1.232 | 2.574 | 1.237 | 2.320 | 46 |
| 21 | $CH_3O$ | $NH_3$ | CNDO/2 | 0.9 | — | — | — | — | 47 |
| 22 | $CH_3O$ | $NH_3$ | 6-31G* | 1.34 | 1.375 | 1.587 | 1.396 | 1.544 | 48 |
| 23 | $CH_3O$ | $O(H)CH_3$ | 6-31G* | -1.9 | 1.312 | 1.563 | 1.346 | 1.475 | 49 |
| 24 | $(HO)_2$[e] | $OH_2$ | 4-31G | 6.05[f] | — | — | — | — | 45 |
| 25 | $(HO)_2$[e] | $NH_3$ | 4-31G | 8.0 | 1.397[g] | 1.600[g] | 1.421[g] | 1.509[g] | 50 |

[a]Synperiplanar most stable. [b]Relative to synperiplanar. [c]Most stable with H-O-C-$X^+$ dihedral angle ~90°. [d]MP2/6-311++G**. [e]$(HO)_2CHX^+$. [f]$E_{a,a} - E_{g,g}$. [g]STO-3G.

The only consistent result in Table 4 is a universal shortening of the Y-C distance ($d_{Y\text{-}C^a} < d_{Y\text{-}C^s}$) and a lengthening of the C-X distance ($d_{C\text{-}X^a} > d_{C\text{-}X^s}$) when a lone pair is antiperiplanar to the C-X bond. This is the expected consequence of a normal anomeric effect arising from negative hyperconjugation (**6**, **7**, or **8ax**), but it does not support a reverse anomeric effect.

The relative energies in Table 4 do not conclusively support a reverse anomeric effect. Whether the conformation with a lone pair syn to the C-$X^+$ bond is most stable ($\Delta E > 0$ in Table 4) depends on X, Y, and the level of calculation. Entries 1, 2, 7, 9, 10, 13, 14, 15, 16, 19, 20, 21, 22, 24, and 25 are consistent with a reverse anomeric effect, but the other 40% are not. Differences occur even within the same level of calculation, according to how thoroughly the possible geometries were explored. A significant example of this involves the 6-31G** results on $HOCH_2NH_3^+$ (Entries 7 and 8), where the most stable conformation has an H-O-C-N dihedral angle near 90°,[43] not the idealized 60° of **27g**. A similar preference for torsional angles near 90° was obtained in a survey of the X-ray structures of pyranoses and furanoses.[52] This torsional preference is strong evidence for delocalization of the pure-p orbital of the oxygen, rather than of an $sp^3$ hybrid. However, like the bond-length changes, this delocalization does not support a reverse anomeric effect.

Even those energy differences in Table 4 (Entries 1-2, 7, 9-10, 13-16, 19, 20-22, 24-25) that seem to support a reverse anomeric effect may reflect only hydrogen bonding. The preference for a lone pair on Y syn to the $OH_2^+$ or $NH_3^+$ may arise from a (badly bent) hydrogen bond to that lone pair (**27H**). Evidence for such a hydrogen bond can be seen in a greater stability of those $HOCH_2\text{-}OH_2^+$ conformers that have H toward the lone pair(s) on HO (omitted from Table 4).[40,42] Depending on the level of approximation, this preference amounts to between 4.6 and 10.0 kcal/mol,[42] which seems too large to be due to an anomeric effect of the weakly delocalizable $OH_2^+$ lone pair anti to the C-OH bond, as has been suggested.[7] Instead, it seems likely that this preference is due to an electrostatic attraction between the lone-pair electrons on OH and the $H^{\delta+}$. This attraction is unusually strong because the small size of hydrogen permits close approach, and such an attractive interaction is commonly called a hydrogen bond. Thus we suggest that hydrogen bonding may account for those $\Delta E$s in Table 4 that are positive and support the reverse anomeric effect. Yet in contrast to the $YCH_2NH_3^+$ or $YCH_2OH_2^+$ that were calculated, all the experimental examples of the reverse anomeric effect involve quaternary nitrogens with no capability for hydrogen bonding. Therefore the calculations may not be relevant.

Most calculations do not take account of solvation, which may modify the conformational behavior of $Y\text{-}CH_2X^+$. One way to model the solvent is as a continuum dielectric, as in the AM1-SM2 method.[44] For example, for $HOCH_2NH_3^+$ and $HOCH_2OH_2^+$ the AM1 results (Entries 5 and 11) do not support a reverse anomeric effect but suggest operation of a normal anomeric effect. The consequence of aqueous solvation is to reduce the anomeric effect (Entries 6 and 12). This reduction is viewed as arising because negative hyperconjugation, which stabilizes anti conformations, disperses the positive charge onto the HO group, but a polar solvent stabilizes a concentrated charge and makes that charge dispersal less important. Even these calculations may not be relevant for comparison with the experimental examples involving quaternary nitrogens with no capability for hydrogen bonding (Tables 1 and 2). Nor may a continuum dielectric be adequate for comparison with experimental studies on $YCH_2NH_3^+$ (Table 3), where hydrogen bonding to the lone pair on Y may not be so important if the $NH_3^+$ can hydrogen bond to solvent.

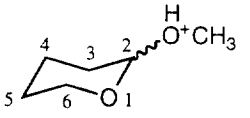
Methods exist for dissecting energy differences to gain more insight into how they arise. One approach is through Fourier analysis,[51] which attributes the onefold, twofold, and threefold components of the rotational barrier as arising from polar, delocalization, and torsional effects, respectively. For example, in

$CH_3OCH_2NH_3^+$ the polar interaction is thereby seen to be the dominant contribution to the greater stability of the conformer with the oxygen lone pairs syn to $NH_3^+$ (Entry 21).[47] This polar contribution does not distinguish between hydrogen bonding and electrostatic attraction, but it does show that anomeric delocalization is insufficient to produce a normal anomeric effect. In contrast Fourier analyses of $H_2NCH_2OH_2^+$, $H_2NCH_2FH^+$, and $HOCH_2FH^+$ (Entries 3-4, 20) indicate very strong delocalization contributions, probably because the geometries optimize to structures where the bond to $X^+$, a potential leaving group, is very long.[46]

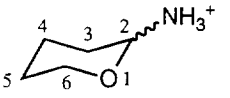
Grein and Deslongchamps[45] proposed an alternative method for dissecting energy differences into components. They concluded that each 1,3 H/H repulsion or 1,3 lone-pair/lone-pair repulsion raises the 6-31G** energy by ca. 1 kcal/mol, whereas a 1,3 H/lone-pair attraction lowers the energy by ca. 1 kcal/mol. They could then estimate that an oxygen lone pair antiperiplanar to a C-$O^+$ or C-$N^+$ bond provides 2 kcal/mol of anomeric stabilization, whereas a nitrogen lone pair antiperiplanar to C-$O^+$ provides 15 kcal/mol of stabilization. Moreover, a nitrogen or oxygen lone pair synperiplanar to C-$N^+$ provides 5 or 4 kcal/mol, respectively. This analysis then accounts for the reverse anomeric effect calculated for $H_2NCH_2NH_3^+$ (Entry 2) and $HOCH_2NH_3^+$ (Entry 7). However, the energy dissection is somewhat arbitrary, since it assumes that hydrogen bonding (i.e., H/lone-pair attraction) is independent of whether the H is on a positively charged atom. Furthermore, it does not clarify why there is no reverse anomeric effect with $H_2NCH_2OH_2^+$ (Entry 3) and $HOCH_2OH_2^+$ (Entry 17). Similar objections have been raised by Graczyk and Mikołajczyk.[7]

One way to avoid the complication due to the potential for hydrogen bonding in $H_mYCH_2XH_n^+$ would be to carry out calculations on $(CH_3)_mYCH_2X(CH_3)_n^+$, even though the methyl groups may introduce steric repulsions. It is surprising that no such calculations have been reported. Fortunately, calculations on tetrahydropyran derivatives have become feasible recently, and these are more realistic.

*2.2.2. Tetrahydropyrans.* Calculations at the 6-31G* level on protonated equatorial and axial 2-methoxytetrahydropyrans (**28**) indicate that the ring distorts to a half-chair-like conformation where the C6-O1-C2-C3 dihedral angle is near 0°.[53] The stabilizations due to this distortion amount to 6 and 9 kcal/mol, respectively. These results are consistent with delocalization of the pure-p orbital of the oxygen, as in the above results on $HOCH_2NH_3^+$ (Entry 8 compared to 7), but it is not consistent with a reverse anomeric effect.




**28**




**29**

The results of calculations on 2-tetrahydropyranosylammonium ion (**29**)[43,54] are listed in Table 5. Relative energies are presented as $\Delta E = E_{axial} - E_{equatorial}$, along with $\Delta E_C$, the corresponding energy difference for cyclohexylammonium ion. As in Table 4, if there is a reverse anomeric effect, $\Delta E$ is positive and larger than $\Delta E_C$, which ought to be a positive number that reflects the steric effect of an axial $NH_3^+$. Table 5 also includes O-C and C-N bond lengths in axial and equatorial conformers. Again the AM1 results (Entry 1) do not support a reverse anomeric effect but suggest the operation of a normal anomeric effect. However, these results are unreliable because even cyclohexylammonium ion is calculated to be more stable with the $NH_3^+$ axial (Entry 1, $\Delta E_C$). Both sets of ab initio calculations (Entries 3 and 4) support a reverse anomeric effect, since the equatorial conformer is more stable ($\Delta E > 0$). Even if $\Delta E_C$ is multiplied by 1.53, to correct for the greater steric repulsions

associated with the shorter C-O bonds in a tetrahydropyran,[8] $\Delta E$ is still significantly larger than $\Delta E_C$. Nevertheless, the bond-length variations ($d_{O\text{-}C}^{ax} < d_{O\text{-}C}^{eq}$, $d_{C\text{-}N}^{ax} > d_{C\text{-}N}^{eq}$) are consistent with negative hyperconjugation, rather than with a reverse anomeric effect.

Table 5. Calculated Relative Energies, $\Delta E = E_{axial} - E_{equatorial}$ (kcal/mol), and Bond Lengths, $d$ (Å), of Axial and Equatorial 2-Tetrahydropyranosylammonium Ions (**29**) and Cyclohexylammonium Ions.

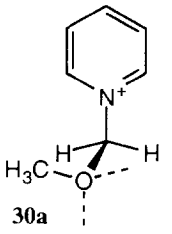
| Entry | Level | $\Delta E$ | $\Delta E_C$ | $d_{O\text{-}C}^{ax}$ | $d_{C\text{-}N}^{ax}$ | $d_{O\text{-}C}^{eq}$ | $d_{C\text{-}N}^{eq}$ | Ref. |
|---|---|---|---|---|---|---|---|---|
| 1 | AM1 | -3.30 | -0.87 | — | — | — | — | 43 |
| 2 | AM1-SM2 | -1.17 | 1.19 | — | — | — | — | 43 |
| 3 | 6-31G* | 3.0 | 1.4 | 1.351 | 1.560 | 1.367 | 1.513 | 54 |
| 4 | MP2/6-31G** | 2.24 | 1.01 | — | 1.561 | — | 1.513 | 43 |
| 5 | MP2-SM2 | 4.37 | 3.07 | — | — | — | — | 43 |

Although AM1 energies of 2-tetrahydropyranosylammonium ion (Entry 1) are unreliable, the AM1-SM2 results (Entry 2)[43] are a measure of the effect of solvation on conformational preferences. If this measure of solvation is then grafted onto the MP2/6-31G** result ("MP2-SM2", Entry 5), the equatorial preference is calculated to be enhanced in a polar solvent. The enhancement is nearly the same for 2-tetrahydropyranosylammonium ion (**29**) as for cyclohexylammonium ion, and it arises primarily because the equatorial $NH_3^+$ is more accessible to solvent. However, the preference for equatorial **29** is not evidence for a reverse anomeric effect because $\Delta E$ is not larger than $\Delta E_C$ if the latter be corrected for the greater steric repulsions in a tetrahydropyran.[8]

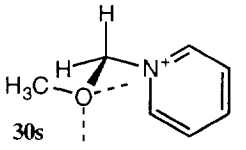
Natural Bond Orbital (NBO) analysis[55] permits a separation of the energy differences in Table 5 into delocalization contributions and "localized" ones that include steric and dipolar repulsions. The 3.0-kcal/mol greater stability of equatorial 2-tetrahydropyranosylammonium ion (Entry 3) is the net result of negative hyperconjugation, which stabilizes the axial stereoisomer by 12.0 kcal/mol, and the localized interactions, which destabilize the axial or else stabilize the equatorial, by 15.0 kcal/mol.[54] The localized interactions were viewed as not due primarily to steric repulsions, since steric repulsions are much smaller in axial cyclohexylammonium ion. Nor could they be due to dipole repulsions, since the positive charge is distributed over the hydrogens, leaving the nitrogen negatively charged, so that the (meaningless)[31] dipole moment of the C-$NH_3^+$ bond is not reversed. An electrostatic origin was therefore proposed, but not further explained.[54]

In summary, these calculations do generally support a reverse anomeric effect, with equatorial 2-tetrahydropyranosylammonium ion more stable than axial. It is again difficult to distinguish whether this preference is due to a reverse anomeric effect, to an enhanced steric effect, or to hydrogen bonding of the $NH_3^+$ hydrogens to the oxygen lone pair, as in **27H**.

*2.2.3. Pyridinium and Imidazolium Ions.* In *N*-(methoxymethyl)pyridinium ion (**30a**,**30s**) hydrogen bonding does not exist and therefore cannot affect the conformational equilibrium. This is a good model for the original examples of the reverse anomeric effect (Sections 1.2.1 and 1.2.2), since it is also free of most of the steric repulsions. Results of MNDO calculations are included in Table 6,[56] where anti and syn refer to the




**30a**




**30s**

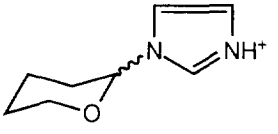
relation between an oxygen lone pair and the C-$N^+$ bond. The calculations include minimization with respect to rotation about this bond, to avoid steric repulsions between the pyridine ring and the methoxy group. Relative energies for **30** are presented as $\Delta E_+ = E_{anti} - E_{syn}$, so that, as in Tables 4 and 5, a reverse anomeric effect would correspond to positive $\Delta E_+$. Also included are O-C and C-N bond lengths in the two conformers **30a** and **30s**. The bond-length variations ($d_{O\text{-}C}{}^a < d_{O\text{-}C}{}^s$, $d_{C\text{-}N}{}^a > d_{C\text{-}N}{}^s$) and the $\Delta E_+ < 0$, as well as a calculated C-O-C-N dihedral angle of 106° (near 90°), are consistent with an anomeric effect favoring a p lone pair anti to the C-$N^+$ bond, but not with a reverse anomeric effect.

Table 6. Calculated Relative Energies, $\Delta E = E_{anti} - E_{syn}$ (kcal/mol), and Bond Lengths, $d$ (Å), of Conformers of *N*-(Methoxymethyl)-pyridinium (**30**) and -imidazolium Ions (**32**) with Anti and Syn Lone Pairs.

| Structure | Level | $\Delta E_+$ | $\Delta E_0$ | $d_{O\text{-}C}{}^a$ | $d_{C\text{-}N}{}^a$ | $d_{O\text{-}C}{}^s$ | $d_{C\text{-}N}{}^s$ | Ref. |
|---|---|---|---|---|---|---|---|---|
| **30** | MNDO | -0.8 | — | 1.370 | 1.540 | 1.382 | 1.520 | 56 |
| **32**, R=H | MP2/6-31G* | -0.44 | -2.87 | 1.356[a] | 1.490[a] | 1.366[a] | 1.471[a] | 57 |
| **32**, R=F | MP2/6-31G* | -1.39 | -2.53 | 1.351[a] | 1.497[a] | 1.366[a] | 1.468[a] | 57 |
| **32**, R=$CH_3$ | MP2/6-31G* | -1.19 | -0.89 | 1.360[a] | 1.482[a] | 1.371[a] | 1.460[a] | 57 |

[a] 6-31G*.

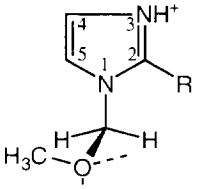
Nor can hydrogen bonding affect the conformational equilibrium in *N*-(2-tetrahydropyranosyl)imidazolium ion (**31**). Any steric effects can be assessed by comparison with the corresponding unprotonated imidazole.



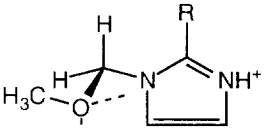

**31**

Unfortunately this molecule is too large and too flexible for high-level molecular-orbital calculations. Therefore the axial and equatorial conformers were modeled with conformationally restricted anti and syn *N*-(methoxymethyl)imidazolium ions (**32a**, **32s**, R = H, F, $CH_3$).[57] Results of MP2/6-31G* energy calculations at 6-31G*-optimized geometries, minimized with respect to rotation about the C-N bond, are also listed in Table 6. Relative energies are presented as $\Delta E_+ = E_{anti} - E_{syn}$, along with $\Delta E_0$, the energy difference for the corresponding unprotonated imidazole. The bond-length variations ($d_{O\text{-}C}{}^a < d_{O\text{-}C}{}^s$, $d_{C\text{-}N}{}^a > d_{C\text{-}N}{}^s$) are again consistent with a normal anomeric effect arising from negative hyperconjugation (**6**, **7**, or **8ax**). The values of

$\Delta E_+$ in Table 6 are negative and by themselves do not support a reverse anomeric effect. A more reliable measure is the comparison of $\Delta E_+$ with $\Delta E_0$, which indicates that, except for R = $CH_3$, the anomeric effect is reduced by *N*-protonation, consistent with a reverse anomeric effect.




**32a**




**32s**

NBO analysis[55] provides insight into the reasons for this reduction.[57] Cations **32a** (R = H) and **32s** (R = H) have 24 and 6 kcal/mol, respectively, of hyperconjugative stabilization, and these stabilizations are reduced by ca. 30% in the corresponding unprotonated imidazoles. This difference between conformers is counteracted by steric repulsions, which are stronger in **32a**, and by a 4.5-kcal/mol greater electrostatic stabilization in **32s** (R = H) than in **32a** (R = H), an amount that can be traced to a hydrogen bond between the C2H of the imidazole and the oxygen.

The effect of solvent on the conformational equilibria could be modeled by a continuum dielectric.[57] Although aqueous solvation shifts the equilibrium in the unprotonated imidazoles by 0.7 kcal/mol toward the syn conformer, the equilibrium between **32a** and **32s** (R = H) is shifted by 1.3 kcal/mol toward the anti conformer. These calculated shifts correlate with the calculated dipole moments of the various species, although it must be remembered that the dipole moment of an ion is meaningless.[31] Regardless of the origin of those shifts, the reverse anomeric effect was predicted to be reduced in polar solvents, and perhaps to disappear or even revert to a normal anomeric effect.[57]

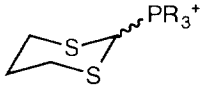
## 3. QUESTIONS

### *3.1. Counterexamples*

*3.1.1. Theory.* Although electrostatic attraction can account for a reverse anomeric effect, at least qualitatively,[21] a delocalization explanation is currently favored to account for anomeric effects in general. Yet n-$\sigma^*$ delocalization is totally unable to explain a reverse anomeric effect, as has often been recognized. The calculated lengthenings of C-$X^+$ bonds that are antiperiplanar to a lone pair are consistent with such delocalization, rather than with a reverse anomeric effect. The conflicting energy results given above are evidence that theory does not always support a reverse anomeric effect, and even those calculations that do seem to support it could be a manifestation of hydrogen bonding.

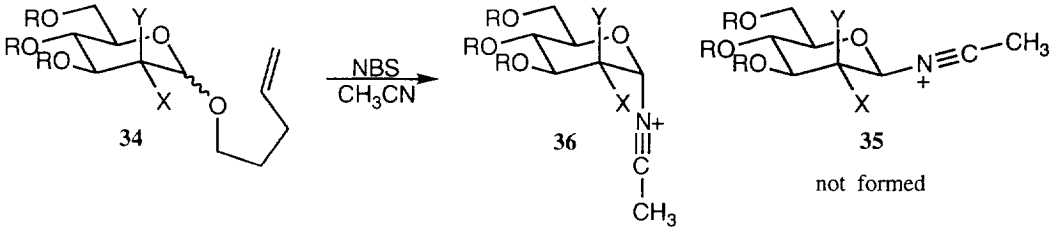
*3.1.2. Experimental Counterexamples.* Various experimental observations have raised doubts about the reverse anomeric effect. No such effect is seen in the crystal structures of an oxybis(*N*-methylenepyridinium ion),[36] of a furanosylammonium ion,[58] or of $HC^-[SO_2N(CH_3)_3^+]_2$, which shows a conformation characteristic of a normal anomeric effect due to delocalization of a carbon lone pair.[59] Nor is a reverse anomeric effect seen in the conformational equilibria of 2-(triphenylphosphonio)-1,3-dithiane (**33**, R = Ph),[60] where the net

equatorial preference for bulky $PPh_3^+$ is only 0.92 kcal/mol. This is also the case for 2-(trimethylphosphonio)-1,3-dithiane (**33**, R = $CH_3$),[61] where there is a 2:1 preference for axial $P(CH_3)_3^+$ despite a steric repulsion estimated as 1.8 kcal/mol. Likewise 2-$PPh_2CH_3^+$ and 2-$PPh(CH_3)_2^+$ groups on a 1,3-dithiane show only small equatorial and axial preferences, respectively.[62]




**33**

One of the more instructive examples is the reaction of *N*-bromosuccinimide with 1-pent-4-enyl tetra-*O*-benzyl-D-glucopyranoside (**34**, R = $PhCH_2$, X = $OCH_2Ph$, Y = H) or -mannopyranoside (**34**, R = $PhCH_2$, X = H, Y = $OCH_2Ph$). In acetonitrile with a suitable trapping agent these lead exclusively to derivatives of the *N*-(α-D-glycopyranosyl)acetamide.[63] This reaction had been thought[64] to proceed via the β-acetonitrilium ion (**35**), stabilized by a reverse anomeric effect. Nevertheless, reinterpretation[63] of the product assignments showed that the reaction proceeds via the α-acetonitrilium ion (**36**). Indeed, independent generation of this ion, as well as the *N*-(tetra-*O*-benzyl-D-galactopyranosyl)acetonitrilium ion, gives $^1H$ NMR coupling constants consistent only with the α ion, perhaps in a boat conformation, even though molecular modeling, with the CHARMm force field, gives the β ions (**35**) as more stable than the α.[65] This story shows the dangers of relying on a reverse anomeric effect or on molecular modeling to assign configurations.




*3.1.3. Neutral Examples.* Cases exist where bulky neutral heterocyclic substituents force distortions from the chair conformation with that substituent axial. The large $J_{12}$s of *N*-(α-D-mannopyranosyl)theophylline and of its tetraacetate indicate that the mannose takes a chair conformation in which the heterocycle is equatorial, as in **16αeq**.[66] Similarly, in solution *N*-(α-D-mannopyranosyl)isocyanuric acid derivatives adopt a twist-boat form, with the heterocycle pseudoequatorial, although in the crystal the ring is a distorted chair, with that group pseudoaxial.[67] These exemplify a reverse anomeric effect only insofar as resonance within the heterocycle places a partial positive charge adjacent to the anomeric carbon, but the observation of distorted conformers even with neutral substituents is a warning that observations attributed to reverse anomeric effects might be due to steric repulsions of a bulky heterocyclic ring.

*3.1.4. Proposal.* In view of all these questions and counterexamples, the reverse anomeric effect calls for reinvestigation. Theory does not support it, and the original examples suffer from uncertainties about steric effects. A careful study is needed, and such a study was proposed by Perrin.[68]

## 4. SIGNIFICANCE

### *4.1. Structural Questions*

Anomeric effects have long been of importance for understanding molecular structure, especially of carbohydrates. They have provided tests of our ability to calculate, measure, model, and predict energies and structural parameters. The reverse anomeric effect represents a conspicuous puzzle regarding the structure and energetics of carbohydrate derivatives with cationic substituents. Many bioactive molecules have cationic or protonatable heterocyclic bases attached to a sugar, the most familiar examples being $NAD^+$ and the conjugate acids of nucleosides. To what extent does the positive charge alter conformational behavior? The reverse anomeric effect severely tests our understanding, since it represents a contradiction between that understanding and the experimental evidence.

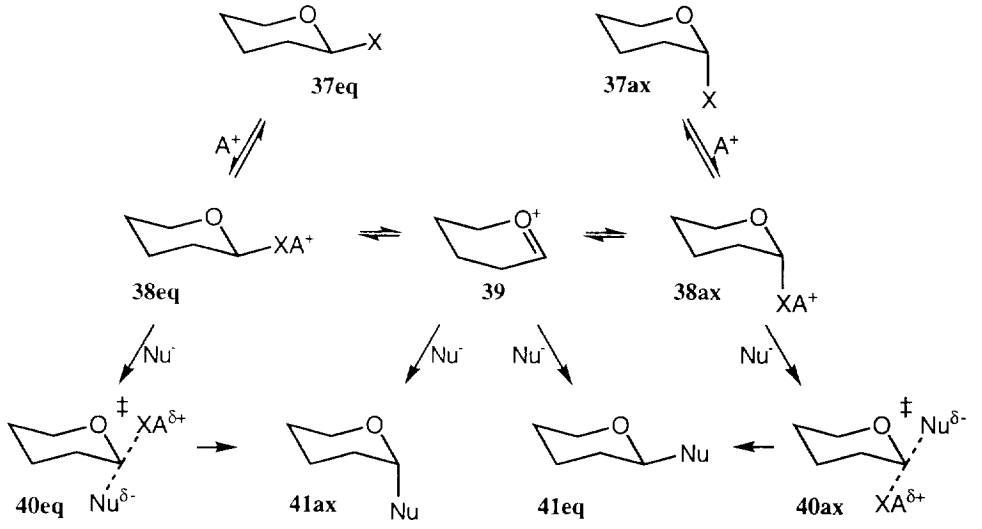
Quite generally the influence of charged substituents is a poorly understood aspect of conformational analysis, and a new method for precise assessment of the effect of the charge is providing insight into the old problem of steric hindrance to solvation.[69] In order to have adequate force fields for molecular modeling, it is necessary to know the conformational behavior of anomeric systems, including those that may show a reverse anomeric effect.[70] The reported discrepancy between experimental and calculated conformations of glycopyranosylacetonitrilium ions[65] is but one caution regarding the current state of molecular modeling.

### *4.2. Reactivity*

Understanding the reverse anomeric effect is key to interpreting and predicting the reactivity of carbohydrates, which often react via their protonated forms as intermediates. The most familiar such enzymic reaction is glycoside hydrolysis, where an acid protonates the glycosidic oxygen and activates it for cleavage. A reverse anomeric effect is sometimes invoked to account for relative reactivities or stereoselectivities involving cationic leaving groups.[71]

Scheme 1 illustrates the general principle. Reactant **37eq** or **37ax** is activated by Brønsted or Lewis acid $A^+$, to form **38eq** or **38ax**, with a cationic leaving group. If these do not equilibrate, either may react stereospecifically with nucleophile by $S_N2$ displacement with inversion of configuration, via transition state **40eq** or **40ax**, to produce **41ax** or **41eq**, respectively. Alternatively they may react by rate-limiting $S_N1$ cleavage to oxocation **39**. This cation is then captured by nucleophile to produce a mixture of **41ax** and **41eq**, usually with **41ax** predominating because of a preference for nucleophile to attack antiperiplanar to an oxygen lone pair. This preference is often referred to as stereoelectronic control,[72] or as a kinetic anomeric effect.[3] The reactivities of **38eq** or **38ax** may also be under stereoelectronic control, but not necessarily.[73]

The more interesting case is when **38eq** and **38ax** equilibrate rapidly under the reaction conditions, possibly via **39**. If product formation occurs by nucleophilic capture of **39**, the product mixture may be governed by stereoelectronic control, as above. If reaction occurs by nucleophilic substitution on **38eq** and **38ax**, the product mixture depends on their relative stabilities and reactivities. If a reverse anomeric effect is operative, **38eq** is more stable than **38ax**. Since **38eq** would then be present in higher equilibrium concentration, it might be expected that more product would be derived from it. Or, since **38ax** is less stable, it might be more reactive, so that more product would be derived from it. Actually, if equilibration of **38eq** with **38ax** is rapid, then the Curtin-Hammett Principle[74] applies, and the product ratio is determined only by the relative




Scheme 1. Stereoselectivity in Reactions of Tetrahydropyranyl and Glycosyl Derivatives.

stabilities of the two transition states, **40eq** and **40ax**. It is likely that a linear-free-energy relationship holds,[75] such that these transition states resemble **38eq** and **38ax**, but with longer, partially broken C-X bonds. However, the relative energies of these transition states depend on whether there really is a reverse anomeric effect. If there is, then **38eq** and **41ax** will predominate, but if not, then transition state **40ax**, with a lone pair antiperiplanar to the leaving group, may be stabilized stereoelectronically,[72] favoring production of **41eq**.

*4.3. Application to Organic Synthesis*

An understanding of reactivity is essential for predictability in organic synthesis. Scheme 1 shows that either **41ax** or **41eq** can be produced, depending on mechanism and energetics, including the possible role of a reverse anomeric effect. These aspects should be understood in order to plan a stereoselective synthesis, and a misunderstanding might lead to a wrong prediction. For example, a reverse anomeric effect was invoked to assign a product as equatorial,[64] but this was subsequently shown[63] to be in error.

A current challenge is the synthesis of carbohydrate derivatives with a particular stereochemistry at the anomeric center.[76] Scheme 1 again applies, with a nucleophile usually derived from an alcohol, to produce a glycoside (although there are additional possibilities if the substituent at the adjacent C2 is nucleophilic). If **41ax** is desired, reaction should be conducted under conditions that create cation **39**, which can then be captured with stereoelectronic control.[72] Alternatively, **41ax** can be produced by $S_N2$ displacement on **38eq**, which will be more stable if $XA^+$ is bulky or subject to a reverse anomeric effect. If instead **41eq** is desired, researchers should utilize a substituent where **38ax** is the more stable anomer. A wide variety of possibilities are in current use,[77] with much of the control over stereochemistry coming from the choice of the leaving group X and the activating reagent $A^+$. Of particular relevance to the reverse anomeric effect are the classic $S_N2$ syntheses of α glycosides (**41ax**),[33] which rely on the preference of glycosyl onium ions (AX = $NEt_3$, $SMe_2$, $PPh_3$) for the β anomer (**38eq**), even if it is not clear whether that preference is really due to a reverse anomeric effect or might be due to steric repulsion.

## 5. REINVESTIGATION OF THE REVERSE ANOMERIC EFFECT

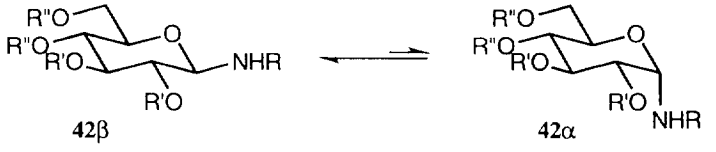
### *5.1. Amino Groups for Control of Steric Effects*

In view of the questions raised above (Section 3) the reverse anomeric effect is suspect. Since both a reverse anomeric effect and any steric repulsions favor the equatorial conformer, it is essential to assess steric factors quantitatively. In particular, the preference of pyridinium and imidazolium systems for the equatorial conformer could be due merely to the steric effects of these heterocyclic rings. Unfortunately these substituents are too bulky to be assessed reliably.

It would be preferable to probe the reverse anomeric effect with a protonatable cyclohexyl substituent whose steric size is known in both protonated and unprotonated forms. Such a substituent is $NH_2$, whose *A* value ($A_{NH_2}$, eq 1) is 1.6 kcal/mol in $D_2O$ or 1.4 kcal/mol in aprotic solvents.[78] The value for $NH_3^+$, $A_{NH_3^+}$, is slightly larger, 1.9 in $D_2O$ or 1.6 kcal/mol in aprotic solvents. The increase of *A* on *N*-protonation is a measure of the extra steric bulk of the protonated substituent, relative to the unprotonated. This extra bulk is due to the additional proton itself and also to the additional solvent needed around the cationic group. (The increase in protic solvents is due to hydrogen bonding, which accumulates solvent around the polar group.[79]) Actually, $A_{NH_2}$ and $A_{NH_3^+}$ from cyclohexane rings are underestimates for steric repulsions to be expected in an anomeric tetrahydropyran system, since a C-O bond is shorter than a C-C bond. By comparison of 2-alkyltetrahydropyrans with the corresponding alkylcyclohexanes[8] $A_{NH_2}$ and $A_{NH_3^+}$ on a tetrahydropyran ring can be corrected to 2-2.5 kcal/mol and 2.4-2.9 kcal/mol, respectively, with the lower limits applicable to aprotic solvents. The difference between these corrected $A_{NH_2}$ and $A_{NH_3^+}$ values provides an estimate of the steric contribution to the shift of a conformational equilibrium of an aminotetrahydropyran upon *N*-protonation. Any increased preference for the equatorial conformer beyond these values may then be attributed to a reverse anomeric effect.

### *5.2. Glucopyranosylamines*

Perrin and Armstrong accordingly carried out a $^1H$ NMR study of the anomeric equilibrium of a wide variety of glucopyranosylamine derivatives (**42**, R = H, Me, Et, Bu; R' = R" = H or Ac, or R' = H and $(R")_2$ = PhCH), along with their conjugate acids.[80] In contrast to previous experimental investigations into the reverse anomeric effect, the equilibration of these aminals involves simply the epimerization of the amino group from equatorial to axial, or anomerization between **42β** and **42α**, without ring inversion. This interconversion is known to proceed by protonation of the ring oxygen, ring opening to an iminium ion, rotation about the C1-C2 bond, and reclosure.[81] It is surprising that so simple a study had never been done before. (The closest studies were on 2-aminotetrahydropyrans,[82] but did not include their conjugate acids, and on a β-lyxopyranosylamine (**21β**),[22] but where the shift of the conformational equilibrium on *N*-protonation was based on coupling constants, not on an anomeric equilibrium.) Experimental difficulties are the sensitivity of an aminal to hydrolysis and the problem of assigning the NMR signals of the axial stereoisomer, present only in low concentration.




**42β** **42α**

Signals were assigned to the α anomer on the basis of a characteristic 5.1±0.4-Hz doublet 0.65±0.2 ppm downfield of H1 of the β anomer, along with the observation of magnetization transfer between these two signals, corresponding to rate constants for chemical interconversion of ca. 1 $s^{-1}$.[80] Moreover, coupling constants $J_{23}$ and comparisons with the benzylidene acetal (**42**, R"$_2$ = PhCH), whose trans-fused six-membered rings prevent ring inversion, verify that none of these systems distort significantly from the chair conformation, even when the moderately bulky amino substituent must be axial, as in **42α**.

By integration of representative $^1$H NMR signals each **42α**:**42β** ratio was measured across a range of solvents, for both the glucosylamine and its protonated form.[80] For the amines the proportion of α anomer varies from 3 to 21%. In general, the lower proportions pertain to aqueous media, where the amino group is slightly bulkier, and the higher proportions pertain to the *N*-alkyl derivatives, probably because their axial conformers can have two populated conformers about the C-N bond, leading to a greater entropy. The average percentages of α anomer, $\overline{\%\alpha}_{obs}$, are listed in Table 7. These observed percentages can be converted to $\Delta G^{o}_{\beta\rightarrow\alpha}$, the free-energy change for conversion of equatorial **42β** to axial **42α**. The averages of these values, averaged over all the glucosylamines, are included in Table 7, with a separate entry (Entry 2) for the *N*-alkylglucosylamines (**42**, R = alkyl), which have been corrected for the additional conformational entropy. For comparison Table 7 also includes $A_{NH_2}$ in cyclohexanes, $A^{cHx}$, the first of the two values applying to $D_2O$ and the second to aprotic solvents. The close agreement between $\Delta G^{o}_{\beta\rightarrow\alpha}$ and $A_{NH_2}$ indicates that the preference for equatorial $NH_2$ or NHR in glucosylamines is largely due to steric bulk.

Table 7. Anomeric Equilibria (average percentage α anomer, $\overline{\%\alpha}_{obs}$, and free-energy change, $\Delta G^{o}_{\beta\rightarrow\alpha}$, kcal/mol) and $A_{NH_2}$ or $A_{NH_3^+}$ (kcal/mol) in Glucopyranosylamines (**42**) and -ammonium Ions (**42·H$^+$**).[80]

| Entry | Amines | $\overline{\%\alpha}_{obs}$ | $\Delta G^{o}_{\beta\rightarrow\alpha}$ | $A^{cHx}$ | $A^{THP}$ | $\overline{\%\alpha}_{est}$ |
|---|---|---|---|---|---|---|
| 1 | Primary | 10 | 1.6±0.4 | 1.6 or 1.3 | 2.5 or 2 | — |
| 2 | *N*-Alkyl | 13 | 1.5±0.3[a] | 1.6 or 1.3 | 2.5 or 2 | — |
| 3 | ·H$^+$, aq. | 3.5 | 2.0±0.1 | 1.9 | 2.9 | 0.8 |
| 4 | ·H$^+$, nonaq. | 7.5 | 1.5±0.1 | ca. 1.6 | ca. 2.4 | 1.7 |

[a]Corrected for conformational entropy.

Actually, $A_{NH_2}$ should be corrected for the larger steric effects in a tetrahydropyran, and those values, $A^{THP}$, for both aqueous and aprotic solvents, are also included in Table 7 (Entries 1 and 2). Since $\Delta G^{o}_{\beta\rightarrow\alpha}$ is less than $A_{NH_2}{}^{THP}$, the observed equatorial preference in glucosylamines is actually lower than expected simply on the basis of steric effects. This lowering means there is a small normal anomeric effect, as previously noted for aminotetrahydropyrans.[8] It may be surprising that the exo-anomeric effect[9] does not lead to a greater equatorial preference, but it should be noted that anomeric effects can be smaller for nitrogen than for oxygen.[13]

*5.3. Effect of Protonation on Anomeric Equilibrium in Glucopyranosylamines*

Our concern is the anomeric equilibrium in glucopyranosylammonium ions. How does this equilibrium shift upon protonation? To what extent does the proportion of **42β** increase? If a reverse anomeric effect is operative, then *N*-protonation should increase the proportion of equatorial **42β** by more than the difference between $A_{NH_3^+}$ and $A_{NH_2}$ would predict.

The key result[80] is that even in acid the proportion of axial **42α** is appreciable, although it decreases in aqueous media, where the $NH_3^+$ or $NH_2R^+$ group is slightly bulkier. The average percentages of α-glucopyranosylammonium ions are shown in Table 7 (Entries 3 and 4), along with the average $\Delta G^o_{\beta\rightarrow\alpha}$ values, which are only slightly larger than those of the neutral glucopyranosylamines. These $\Delta G^o_{\beta\rightarrow\alpha}$s are also close to the values of $A_{NH_3^+}{}^{cHx}$, which are included in Table 7. Therefore the anomeric equilibrium of the glucopyranosylammonium ions too can be accounted for largely by steric effects. Even the slight increase of $\Delta G^o_{\beta\rightarrow\alpha}$ in water (Entry 3) may be due only to the increased effective size of aquated $NH_3^+$ or $NH_2R^+$.

Again it is necessary to correct for the inherently larger steric effects in a tetrahydropyran. The $\Delta G^o_{\beta\rightarrow\alpha}$ values are considerably lower than the $A_{NH_3^+}{}^{THP}$ values included in Table 7. Therefore the preference of the $NH_3^+$ or $NH_2R^+$ group for the equatorial position is actually lower than would be expected on the basis of steric bulk. According to eq 2, $E_{An}$ is thus a small but significant 1 kcal/mol. This quantity is the extra preference for axial position, and it represents an anomeric effect, albeit weak, but not a reverse anomeric effect!

This reasoning may be clearer in terms of concentrations. If steric repulsions alone were operative, the average percentage of α anomer of an *N*-protonated glucosylamine can be estimated from $A_{NH_3^+}{}^{THP}$. Those estimates, $\overline{\%\alpha}_{est}$, are included in the last column of Table 7. If there were any reverse anomeric effect favoring the β anomer, the observed percentage of α anomer would be even lower than those estimates. Yet the average proportions observed are found to be substantially greater than $\overline{\%\alpha}_{est}$, according to Entries 3 and 4 of Table 7. There is definitely no increased tendency for a positively charged substituent to prefer the equatorial position. The increased proportion of axial **42α** is evidence against the reverse anomeric effect and consistent with a small normal anomeric effect.

Yet another measure of any reverse anomeric effect is $\Delta\Delta G^o_{N\rightarrow N^+} = \Delta G^o_{\beta\rightarrow\alpha}(NH^+) - \Delta G^o_{\beta\rightarrow\alpha}(N)$, the difference in anomerization free-energy changes between protonated and unprotonated glucosylamines. This $\Delta\Delta G^o$ is the extent to which *N*-protonation increases the preference of the amino substituent for the equatorial position. Across all the glucosylamines the average $\Delta\Delta G^o_{N\rightarrow N^+}$ is found to be 0.1 ± 0.1 kcal/mol,[80] which is not significantly different from zero. Furthermore this value is definitely less than $A_{NH_3^+} - A_{NH_2}$, which is what would be expected from the increase in steric bulk. Even though $NH_3^+$ is certainly bulkier than $NH_2$, the proportion of axial isomer **42α** does not decrease on *N*-protonation. In opposition to the increased bulk there appears to be a slight extra tendency for cationic nitrogen to be axial, not equatorial. This tendency corresponds to a small normal anomeric effect, and there is certainly no need to invoke a reverse anomeric effect.

How general is this conclusion that a reverse anomeric effect does not exist? *N*-Protonated glucosylamines are not the same as the original examples with quaternary nitrogens in aromatic heterocycles. Although it had been suggested[27] that a reverse anomeric effect can arise from a homoallylic-type overlap between an oxygen lone pair and the π* orbital of the aromatic, this possibility was rejected above. The principal difference between the two kinds of nitrogens is the opportunity for hydrogen bonding between the $NH_3^+$ on C1 and the ring oxygen or the OH or OAc substituent on C2. According to the theoretical calculations discussed above, such hydrogen bonding may be one basis for a reverse anomeric effect. Therefore a reverse anomeric effect is more likely with glucosylamines, which can hydrogen bond, than with the aromatic heterocycles that were claimed to show a reverse anomeric effect, and yet the former do not show such an effect. Besides, the anomeric equilibrium is unchanged in the tetraacetates, which might have different hydrogen-bonding properties from those of their hydroxy parents. Therefore Perrin and Armstrong[80] concluded that there is probably no reverse anomeric effect with any cationic nitrogen substituent.

The absence of any reverse anomeric effect is reassuring. A cationic substituent is more electronegative than the neutral and lowers the energy of the C-N σ* orbital (Figure 1b) or, in alternative parlance, increases the contribution of the double-bond/no-bond resonance form **8ax**. Therefore, according to this simple view, the anomeric effect is expected to be augmented, as observed experimentally ($\Delta G^{o}_{\beta\rightarrow\alpha} < A_{NH_3^+}^{THP}$ in Table 7).[80] Nevertheless, the ab initio results included in Table 5, with $\Delta E$ larger than $\Delta E_C$,[43,54] even as corrected for the greater steric repulsions in a tetrahydropyran,[8] would support a reverse anomeric effect, at variance with these experimental observations (even though the calculational results were viewed as being in perfect agreement with the observations).

## 6. ARE STERIC EFFECTS RESPONSIBLE FOR AN APPARENT REVERSE ANOMERIC EFFECT?

### *6.1. Comparison of Effective Steric Sizes of Imidazolium and Imidazole*

Since these observations on glucosylamines (Table 7) repudiate the reverse anomeric effect, a closer look at the earlier evidence is warranted. In many of those cases the preference for the equatorial conformer could be due simply to the steric bulk of a heterocyclic substituent. Even the best evidence, from the protonation-induced shift of the conformational equilibrium of *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)imidazole (**17**α, R = Ac),[22] is now suspect. It was assumed that the steric requirements of the imidazolyl substituent do not change on protonation. Yet even though the distant proton itself does not add much bulk, introduction of a positive charge is likely to change the solvation shell about the substituent, and the associated counterion may also influence the equilibrium.[27] The positive charge on an imidazolium group is delocalized, with a portion of it on the nitrogen attached to the pyranose ring. Besides, the C1-N bond may shorten. All these effects ought to increase the effective size of the imidazolyl substituent. The increase would need to be large, to account for the >1.4-kcal/mol shift of the equilibrium, but this might be a characteristic of the additional solvation requirements of an ionic substituent whose neutral is already quite bulky. Therefore the assumption that there is no change in effective size[22,26] must be tested.[7,68]

The appropriate measures of the effective sizes of imidazolyl and *N*-protonated imidazolyl are $A_{Im}$ and $A_{ImH^+}$ (eq 1), respectively. These *A* values are obtainable in principle by measurement of the proportions of axial conformer in *N*-cyclohexylimidazole and in its conjugate acid at low temperature. For greater experimental accuracy a more balanced conformational equilibrium is advantageous, so *cis*-*N*-(4-methylcyclohexyl)imidazole (**43c**, R = $CH_3$) and *cis*-*N*-(4-phenylcyclohexyl)imidazole (**43c**, R = Ph) are more suitable substrates. From

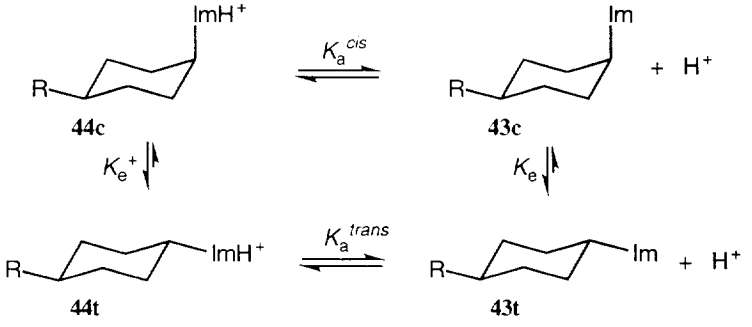

**43c**

either of these $A_{Im}$ was found to be 2.2 kcal/mol.[83] An *N*-imidazolyl group is indeed bulky. It is larger than methyl but smaller than phenyl. From measurements in acidic media $A_{ImH^+}$ was also found to be 2.2 kcal/mol, but the error is unfortunately so high as to preclude an accurate comparison of $A_{ImH^+}$ with $A_{Im}$. It is desirable

to reduce experimental error and obtain a better estimate of the difference in size between neutral and protonated imidazole rings.

*6.2. NMR Titration for Measuring Steric Difference between Imidazolium and Imidazole*

To measure more precisely the change in $A_{Im}$ upon *N*-protonation, we developed a new NMR titration method.[83] A convenient feature of this method is that it is applicable to a mixture of *cis*- and *trans*-(4-alkylcyclohexyl)imidazoles (**43c**, **43t**), without any necessity for separation. In practice, successive microliter portions of DCl were added to this mixture (R = Ph), and the 500-MHz $^1$H NMR chemical shifts of H1 in both isomers were recorded after each addition. What makes this method feasible is that the chemical shift of H1, which is well resolved, undergoes sufficient change on *N*-protonation. That chemical shift is thus a reporter of the state of protonation of its imidazole. If one diastereomer is more basic than the other, then during a titration its chemical shift will change earlier than that of the other. Comparison of those changes then provides a measure of the difference in basicity between the two stereoisomers.




Scheme 2. Acid Dissociations of *cis*- and *trans*- (4-Alkylcyclohexyl)imidazolium Ions (**44**).

What is readily measurable is $K$, the ratio ($K_a^{cis}/K_a^{trans}$) of the acidity constants of the two stereoisomers **44c** and **44t**, as defined in Scheme 2. It can readily be shown that the observed chemical shifts $\delta_{cis}$ and $\delta_{trans}$ are related to $K$ by the linear eq 3, where $\delta_{CH^+}$, $\delta_C$, $\delta_{TH^+}$, and $\delta_T$ are limiting chemical shifts of protonated and

$$(\delta_{trans} - \delta_T)(\delta_{CH^+} - \delta_{cis}) = K(\delta_{cis} - \delta_C)(\delta_{TH^+} - \delta_{trans}) \quad (3)$$

unprotonated *cis* and *trans* forms, respectively, which can be measured at the beginning of the titration and at its endpoint. This equation means that a plot of $(\delta_{trans} - \delta_T)(\delta_{CH^+} - \delta_{cis})$ vs. $(\delta_{cis} - \delta_C)(\delta_{TH^+} - \delta_{trans})$ ought to be a straight line, with slope $K$ and zero intercept.

Figure 2 shows such a plot from the titration of a mixture of *cis* and *trans N*-(4-phenylcyclohexyl)-imidazoles (**43**) with DCl. The excellent linearity is confirmed by a correlation coefficient of 0.9996. From two such plots the average slope is 1.118 ± 0.005, corresponding to a $\Delta pK_a = -\log(K_a^{cis}/K_a^{trans})$ of -0.048 ± 0.002.[83] It is remarkable that this ratio of acidity constants and the $\Delta pK_a$ can be measured with such precision, higher than for the acidity constants or the $pK_a$s themselves. Note that this method is quite general, applicable to the determination of the difference in basicities or acidities of any pair of similar substituents.

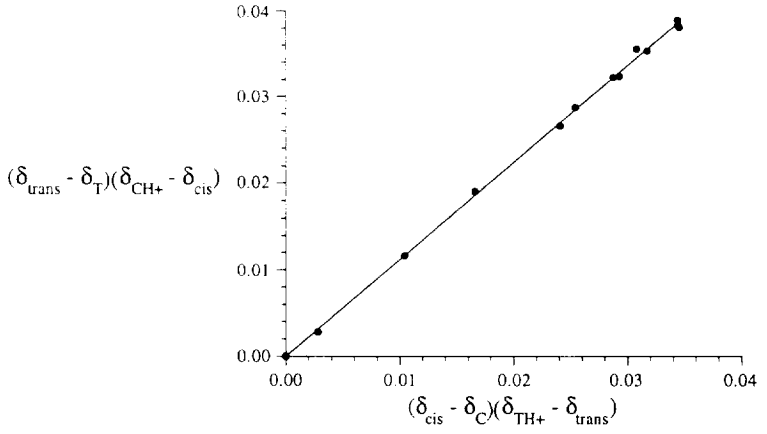



Fig. 2. Linearized Plot of Chemical Shifts During Titration of 1:1 Mixture of *cis* and *trans N*-(4-Phenylcyclohexyl)imidazoles (**43**) with DCl in 1:1 Acetone-$d_6$/$D_2O$.[84]

Scheme 2 establishes a thermodynamic cycle that relates the acidity constants to the equilibrium constants for epimerization of *trans*-*N*-(4-alkylcyclohexyl)imidazole (**43t**) to *cis* (**43c**) and for epimerization of their conjugate acids (**44t** to **44c**), designated as $K_e$ and $K_e^+$, respectively. Comparison with eq 1 shows that these epimerization equilibrium constants are related to the *A* values of imidazolyl and protonated imidazolyl and that $\Delta A$, the difference between these, is given by eq 4.

$$\Delta A = A_{ImH^+} - A_{Im} = RT\ln(K_e/K_e^+) \tag{4}$$

It follows from the thermodynamic cycle of Scheme 2 that the desired ratio $K_e/K_e^+$ must equal $K_a^{cis}/K_a^{trans}$, which was obtained as the slope in Figure 2. (Actually, there is a small correction, evaluated independently,[83] to account for ring inversion of **43c** and of its conjugate acid **44c**. No correction is needed for **43t** or **44t** because these have such a low population of ring-inverted diaxial conformer.) With this correction $K_e^+/K_e$ becomes 1.161 ± 0.008, corresponding to a $\Delta A$ of 0.089 ± 0.004 kcal/mol. It is remarkable that $\Delta A$ can be measured with such high accuracy! Moreover, this method is quite general, applicable to the determination of the difference in size between any ionic substituent and its corresponding neutral.

This result means that the effective size of an axial *N*-protonated imidazolyl group is detectably greater than that of the unprotonated. This increase is due solely to the positive charge, since the site of protonation of an *N*-cyclohexylimidazole is remote from the cyclohexane hydrogens. The size of the imidazolyl substituent does not change, but its effective size does. This change is genuinely a solvation phenomenon, since in $CD_2Cl_2$ and DMSO-$d_6$ $\Delta A$ is 0.024 ± 0.013 and -0.09 ± 0.01 kcal/mol, respectively. In $CD_2Cl_2$ the effect diminishes, and in DMSO-$d_6$ it reverses, with the protonated imidazolyl having a higher axial population than the unprotonated has.

The changes in effective size on *N*-protonation of the imidazolyl substituent are quite small, producing a maximum of 0.089 kcal/mol of additional steric repulsions. There are indeed no large steric differences between imidazolyl and protonated imidazolyl substituents, just as expected by Lemieux[26] and by Paulsen.[22] Therefore

the large protonation-induced shift of the conformational equilibrium of *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)-imidazole (**17**α, R = Ac)[22] cannot be due to an increase of steric requirements of the imidazolyl substituent on protonation. It would appear that this shift of equilibrium for **17**α must therefore be due to a reverse anomeric effect, arising from the positive charge. Yet this xylopyranosylimidazole result is in contradiction to the absence of a reverse anomeric effect in glucopyranosylamines.[80]

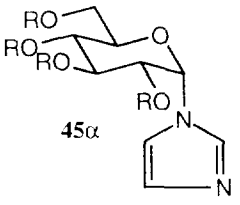
## 7. REAPPRAISAL OF PREVIOUS INVESTIGATIONS

### *7.1. Contradiction*

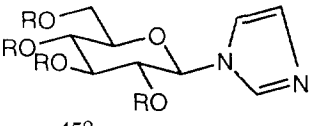
There is an apparent contradiction between an enhanced anomeric effect in the anomerization of glucopyranosylamines (**42**)[80] and a reverse anomeric effect in the conformational equilibrium of *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)imidazole (**17**α).[22] Yet it must be recognized that the populations of the individual conformers of **17**α were never determined from direct observation at low temperature. Finch and Nagpurkar[27] did attempt to freeze out the separate conformers of (tetra-*O*-acetyl-α-glucosyl)- and (tetra-*O*-acetyl-α-mannosyl)-imidazolium ions, but they saw only progressive broadening of the signals, down to -60°C, when the samples solidified. Instead, those populations, and the shifts of equilibrium on protonation, were evaluated from small changes in observed coupling constants.[22] Since coupling constants are sensitive to substituent electronegativity and to slight geometric distortions from the ideal chair conformation,[85] they are difficult to interpret and may not provide reliable equilibrium constants.

### *7.2. Reinvestigation of Glycosylimidazole*

*7.2.1. NMR Titration of Glycosylimidazoles.* Fabian, Perrin, and Sinnott[86] reinvestigated the effect of *N*-protonation on an anomeric equilibrium, not of *N*-(tri-*O*-acetyl-α-D-xylopyranosyl)imidazole (**17**α) but of *N*-(D-glucopyranosyl)imidazole (**45**, R = H) and its 2,3,4,6-tetraacetate (**45**, R = Ac). Glucose derivatives, with bulky groups that remain equatorial, were chosen so as to avoid complications due to ring inversion. In principle the magnitude of any reverse anomeric effect could be measured as the increase in the proportion of the β anomer on protonation of an equilibrating mixture of anomers. However, in contrast to glycosylamines, glycosylimidazoles happen to be configurationally stable and do not equilibrate.[87] Fortunately the reverse anomeric effect can be measured instead from the difference in $pK_a$ of the two anomers, according to the NMR titration method described above.[86]




**45**α




**45**β

A mixture of α and β *N*-(D-glucosyl)imidazoles (**45**) was thus titrated with successive portions of HCl or trifluoroacetic acid, and the $^1H$ chemical shifts were recorded. In this context eq 3 becomes eq 5, relating

$$(\delta\beta - \delta\beta^{o})(\delta\alpha^{+} - \delta\alpha) = (K_a^{\alpha}/K_a^{\beta})(\delta\alpha - \delta\alpha^{o})(\delta\beta^{+} - \delta\beta) \quad (5)$$

observed chemical shifts $\delta\alpha$ and $\delta\beta$ of $\alpha$ and $\beta$ anomers to $K_a^{\alpha}/K_a^{\beta}$, the ratio of their acidity constants, and to $\delta\alpha^{+}$, $\delta\alpha^{o}$, $\delta\beta^{+}$, and $\delta\beta^{o}$, the limiting chemical shifts of protonated and unprotonated $\alpha$ and $\beta$ forms, respectively. Thus a plot of $(\delta\beta - \delta\beta^{o})(\delta\alpha^{+} - \delta\alpha)$ vs. $(\delta\alpha - \delta\alpha^{o})(\delta\beta^{+} - \delta\beta)$ ought to be linear with zero intercept and with slope equal to $K_a^{\alpha}/K_a^{\beta}$. Table 8 lists the slopes of such plots, from observation of the H1 signal of the glucose or the H2' signal of the imidazole, in a range of solvents.

Table 8. $K_a^{\alpha}/K_a^{\beta}$ (eq 5) and $\Delta\Delta G^{\circ}$ (eq 6), from Titrations of Mixed $\alpha$ and $\beta$ Anomers of *N*-(Glucopyranosyl)imidazoles (**45**).[86]

| Entry | R | Solvent | $K_a^{\alpha}/K_a^{\beta}$[a] | $\Delta\Delta G^{\circ}$, kcal/mol[a] | $\Delta\Delta G^{\circ}$, kcal/mol[b] |
|---|---|---|---|---|---|
| 1 | H | $D_2O$ | 0.520±.006 | -0.386±0.007 | -0.375±0.003 |
| 2 | H | $CD_3OD$ | 0.798±.002 | -0.134±0.002 | -0.133±0.003 |
| 3 | H | DMSO-$d_6$ | 0.970±.012 | -0.018±0.007 | -0.021±0.004 |
| 4 | Ac | $CD_3OD$ | 0.882±.004 | -0.074±0.002 | -0.068±0.001 |
| 5 | Ac | DMSO-$d_6$ | 0.803±.006 | -0.130±0.004 | -0.131±0.006 |
| 6 | Ac | $CD_2Cl_2$ | 0.889±.008[b] | — | -0.069±0.005 |

[a]From H1 signal. [b]From H2' signal.

Again it follows from a thermodynamic cycle that $\Delta\Delta G^{\circ}_{\beta\rightarrow\alpha}$, the difference in $\Delta G^{\circ}_{\beta\rightarrow\alpha}$ between protonated and unprotonated imidazolyl groups, is given by eq 6.[83] The $\Delta\Delta G^{\circ}_{\beta\rightarrow\alpha}$ are also listed in Table 8.[86]

$$\Delta\Delta G^{o}_{\beta\rightarrow\alpha} = \Delta G^{o}_{ImH^{+}} - \Delta G^{o}_{Im} = RT\ln(K_a^{\alpha}/K_a^{\beta}) \quad (6)$$

The values are the same from either H1 of the glucose or H2' of the imidazole. Notice that these values are obtained without equilibration of the anomers and also without interchange of axial and equatorial imidazolyls through ring inversion. That these $\Delta\Delta G^{o}$s can be measured with such precision—higher than for the $\Delta G^{o}$s themselves—is striking.

*7.2.2. Anomeric Effect in Glucosylimidazolium Ions.* The $\Delta\Delta G^{o}$s in Table 8 represent the extra energy cost to place a protonated imidazolyl in the axial position of the $\alpha$ anomer, relative to the energy cost of an unprotonated imidazolyl. All the values are small but significantly less than zero. This means that there is a greater preference of the protonated imidazolyl group for the axial position than of the unprotonated. In other words, *N*-protonation does not shift the equilibrium toward an equatorial imidazolyl but instead shifts the equilibrium toward axial. This is exactly opposite to what is expected from a reverse anomeric effect!

Steric effects cannot account for these results. In most solvents *N*-protonation of an imidazolyl group increases its effective steric bulk[83] because of the need for solvation of the ion, but the extent is small. Any such increase would reduce the proportion of $\alpha$ anomer, contrary to what is seen. Therefore the protonated imidazolyl is subject to an enhanced anomeric effect, not a reverse anomeric effect.[86]

These results do not agree with the claim of a significant proportion of equatorial *N*-(tetra-*O*-acetyl-α-D-glucosyl)imidazolium ion (**15αeq**, X = $H^{+}$, R = Ac), compared to none in *N*-(α-D-glucosyl)imidazolium ion

(**15**α, X = $NH^+$, R = H).[27] The data in Table 8 show that in methanol or DMSO there is no significant trend associated with *N*-protonation of the acetylated glucose derivative.

*7.2.3. Solvent Dependence, Electrostatics, and Reverse Anomeric Effect.* The data in Table 8 show small variations with solvent, but such small effects are more readily measured than interpreted.[88] The only unusual value is in water (Entry 1), where the protonation-induced enhancement of the anomeric effect is larger. This is opposite to the SM2-model results in Table 5, where the reverse anomeric effect in 2-tetrahydropyranosylammonium ion (**29**) was calculated to be enhanced in polar solvent.[43] This discrepancy may be a feature of the solvation of an $NH_3^+$ group. Indeed, the experimental results are consistent with the prediction that increased solvent polarity reduces the reverse anomeric effect in *N*-(methoxymethyl)imidazolium ions (**32**).[57]

It was originally suggested that the unusually large negative value of $\Delta\Delta G^o$ in water is due to an enhanced anomeric effect.[86] Although such an enhancement has been seen for neutral molecules,[32,89] where it is attributed to a greater contribution of the charge-separated resonance form **8ax**, a polar solvent is less likely to enhance the anomeric effect in a cation, where **8ax** does not involve charge separation.

We now suggest that this reduction in water may be evidence for a reverse anomeric effect and for its electrostatic origin, as originally proposed by Lemieux.[21] It cannot be due to the higher dipole moment calculated for **32a**,[57] since the dipole moment of an ion is meaningless.[31] Instead, we propose that the monopole-dipole attraction stabilizes the equatorial form (**24eq'**) and opposes the negative hyperconjugation that stabilizes the equatorial. In most solvents the net effect of these, along with the slight change in steric bulk associated with *N*-protonation,[83] leads to the very small $\Delta\Delta G^\circ_{\beta\rightarrow\alpha}$s in Table 8. However, in water (Entry 1) the electrostatic interaction and the reverse anomeric effect are reduced, so that $\Delta\Delta G^\circ_{\beta\rightarrow\alpha}$ is more negative.

## 8. SUMMARY AND CONCLUSIONS

The reverse anomeric effect is the tendency for cationic substituents on a tetrahydropyran ring to take the equatorial position. The original examples involved bulky substituents, such as pyridinium ions, but the tendency was also exhibited by a protonated imidazolyl group, relative to the unprotonated, which was viewed as having the same bulk. Nevertheless, current understanding of the anomeric effect does not encompass a reverse anomeric effect, and theoretical calculations often do not support such an effect. Therefore it was reinvestigated.

The proportions of axial anomers of various glucosylamines (**42**) and their conjugate acids were determined by $^1H$ NMR. The change upon *N*-protonation is small and can be accounted for by steric effects and an enhanced anomeric effect, without any "reverse anomeric effect." To test whether *N*-protonation changes the effective steric bulk of an imidazolyl group, an NMR titration method was developed and applied to a mixture of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazoles (**43**, R = Ph). In $D_2O$ the *cis* isomer is found to be 0.048 p*K* unit less basic, corresponding to a $\Delta A$ ($= A_{ImH^+} - A_{Im}$) of 0.089 ± 0.004 kcal/mol, with protonated imidazolyl detectably larger. To reinvestigate the effect of *N*-protonation on conformational equilibria in sugar derivatives, this NMR titration method was applied to a mixture of α- and β-*N*-(glucosyl)imidazoles (**45**). The $\Delta A$ is -0.018 to -0.368 kcal/mol, and the negative values are exactly opposite to what is expected from the reverse anomeric effect! However, the variation with solvent is consistent with a contribution of a reverse anomeric effect arising from monopole-dipole interactions.

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