An Experimental Reexamination of the Reverse Anomeric Effect in *N*-Glycosylimidazoles

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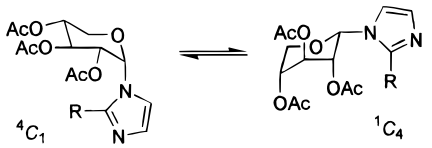
The anomeric effect describes the preference, in pyranoid rings, for an electronegative substituent at C1 to assume an axial orientation and has been rationalized by orbital mixing and electrostatic arguments.[1] The cause and influence of the anomeric effect and its extended version, the generalized anomeric effect (GAE), have provoked much debate.[1c] The reverse anomeric effect (RAE) describes the equatorial preference of a quaternary nitrogen substituent at C1, over and above any steric factors.[2,3] The failure of the GAE orbital mixing arguments to accommodate the RAE has been frequently noted.[4] However, the RAE is of significance in its own right, in its influence on nucleoside conformation. Furthermore, when generalized to cationic substituents at C1 in addition to quaternary nitrogen, the RAE is of significance in carbohydrate reactivity and synthesis. Recently, the evidence for the very existence of an RAE has been cast in doubt.[5]



1 R=H; **1H** *N*-protonated
2 R=Me; **2H** *N*-protonated

In discussions of the RAE, the most unambiguous experiment, that by Paulsen *et al.*,[3a] is quoted overwhelmingly.[6] The observed conformational shift from axial ($^4C_1$) to equatorial ($^1C_4$) in *N*-glycosylimidazoles on protonation is unlikely to be strongly influenced by changes in steric bulk of the aglycon.[7] In CCl_4, $CDCl_3$, or $(CD_3)_2CO$, the proportion of the $^1C_4$ conformer of *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)imidazole (**1**) was found to increase from 35% to 65% to 85%, respectively, and to increase further on protonation by trifluoroacetic acid (TFA). However, it has been shown that there is no RAE manifest in *N*-glucosylimidazoles, and it has been concluded that there is probably no RAE associated with any cationic substituent at C1.[5a,b] Thus, it seemed essential to us to reexamine the evidence for the RAE in **1**. Experimental error or the influence of solvent ionic strength on the GAE could be considered as the possible causes for the reported RAE. Anomeric effects are sensitive to solvent polarity. Since protonation of the imidazole ring by TFA will increase solution ionic strength, NMR titration of the glycoside with varying amounts of TFA and/or tetra-*n*-butylammonium bromide (TBAB) was planned to account for the effects of solvent ionic strength. A further novel imidazole **2** was chosen for comparison with our recent molecular orbital (MO) calculations on the RAE.[5c]

The synthesis of **1** was accomplished starting from 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide and imidazole using a standard procedure.[3] Imidazole **2** was prepared analogously, using 2-methylimidazole in place of imidazole. For **1**, the ^1H and ^{13}C NMR spectral data agreed with published values, while **2** gave spectra and combustion analysis consistent with the assigned structure. NMR spectra were obtained at 400 MHz for ^1H and 50 MHz for ^{13}C, at 25 °C. Conductivity measurements were performed with a YSI Model 31 conductivity bridge at 25 °C. All of the solvents and reagents were rigorously dried and purified by standard methods[8] prior to use. Conductivity measurements were performed to provide a means of comparing the polarities of TFA and TBAB in chloroform and the ionic strengths of the resulting solutions.[9] The molar conductivity in chloroform of TBAB was determined to be 20 times greater than that of TFA.[10]

In separate, duplicated experiments, **1** or **2** was dissolved in 0.5 mL of $CDCl_3$ (0.07 M), and successive portions of TFA (0.67 M) in $CDCl_3$, or TBAB (0.52 M) in $CDCl_3$, were added. Further experiments were performed in which protonation of **1** or **2** was accomplished by addition of TFA, followed by titration with TBAB. From comparison of the time-averaged coupling constants between H-5 and H-4 with values obtained for the limiting cases of the $^1C_4$ and $^4C_1$ conformations in the case of 1,2,3,4-tetra-*O*-acetyl-α-D-xylopyranose,[11] a measure of the percentage of $^1C_4$ conformer in solution could be obtained.[12] On protonation by TFA, both **1** and **2** exhibited shifts to the $^1C_4$ conformation, for **1H**, to an

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(2) (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1990**, *43*, 2205. (b) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *49*, 527.

(3) (a) Paulsen, H.; Gyorgydeak, Z.; Friedmann, M. *Chem. Ber.* **1974,** *107*, 1590. (b) Finch, P.; Nagpurkar, A. G. *Carbohydr. Res.* **1976**, *25*, 275.

(4) (a) Sinnott M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, 1983.

(5) (a) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 6825. (b) Fabian, M. A.; Perrin, C. L.; Sinnott, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 8398. (c) Chan, S. S. C.; Szarek, W. A.; Thatcher, G. R. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 45.

(6) As Kirby states: "There is (just) one detailed collection of ^1H NMR data, on pentopyranoses, from Paulsen *et al* which supports the existence of the RAE", and furthermore, "There is....a growing body of evidence that the RAE.... cannot be generalized as can the anomeric effect". Kirby A. J.; Williams N. H. *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. Pinto and Leung suggest that "...the term RAE be reserved for those systems for which it was originally defined by Lemieux and Morgan, i.e. systems containing quaternary, nitrogen aromatic substituents". Pinto B. M.; Leung R. Y. N. *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. Thus the *N*-glycosylimidazole system represents the crux of the RAE. If there is no RAE in this system, there is no *raison d'etre* for any extended version of the RAE.

(7) Perrin, C. L.; Fabian, F. A.; Armstrong, K. B. *J. Org. Chem.* **1994**, *59*, 5246.

(8) Perrin, D. D; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Toronto, 1980.

(9) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods*; John Wiley & Sons: Toronto, 1980.

(10) Conductivity for both species was determined in the presence of 0.5 M *N*-methylimidazole to ensure dissociation of the TFA and to mimic the conditions of the experiment with the *N*-glycosylimidazoles.

(11) Durette, P. L.; Horton, D. *J. Chem. Soc., Chem. Commun.* **1969**, 516.

(12) The values used in these and previous calculations in ref. 3a for the limiting case of J_a and J_e were measured in acetone-d_6.[11] The coupling constants in $CDCl_3$ would not be expected to be identical; however, the use of these values is sufficient to demonstrate clear trends in conformational equilibria.

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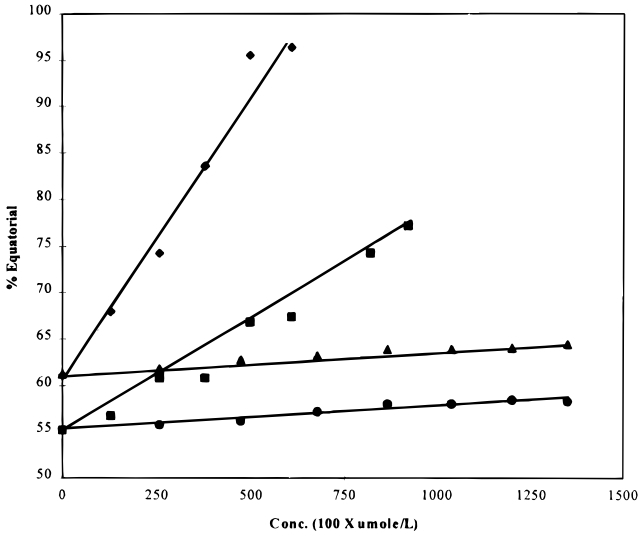

Figure 1. Percentage of equatorial form vs concentration of electrolyte: ◆, 1 + TFA; ■, 2 + TFA; ▲, 1 + TBAB; ●, 2 + TBAB.

Table 1. Percentage of Equatorial Form of 1H and 2H after TBAB Additions

TBAB (100 X μmol/L)	0	102	200	294	385	472	557
% eq **1H**	95	83	83	86	83	83	88
% eq **2H**	86	82	81.5	81	76	81	76

approximately fully $^1C_4$ equilibrium position. Unprotonated equilibria favored the $^1C_4$ conformer for **1** (61%) relative to **2** (55%), and the slope of the equatorial shift was greater for **1** than for **2** (Figure 1). Addition of TBAB had relatively little effect on the position of equilibrium; however, both an equatorial shift for **1** and **2** (unprotonated) and an axial shift for **1H** and **2H** (protonated) were discernable (Figure 1; Table 1).

The present results generally confirm previous experimental observations on **1**, with minor modification.[13] It was concluded from our MO calculations that the dominant contributions to the conformational equilibrium of *N*-pyranosylimidazoles were stabilizing anomeric hyperconjugation and destabilizing steric interactions in the axial conformer.[5c] Both effects are expected to increase on *N*-protonation. It was predicted that the fine balance between these opposing contributions would allow small intramolecular electrostatic effects to control the position of equilibrium. Stabilizing electrostatic interactions in the *N*-protonated equatorial conformers were identified associated with ImH2---O2 hydrogen bonding (type 1) and dipole−monopole electrostatic stabilization between the nonbonding electrons on O2 and the cationic imidazolium monopole (type 2). An equatorial shift on *N*-protonation of 0.4−2.4 kcal/mol was predicted using models for **1**. The observed equatorial shifts for **1** (61−96%) and **2** (55−86%) represent stabilization of the equatorial conformers on protonation by approximately 1.5 and 0.9 kcal/mol, respectively. The elegant work of Perrin *et al.*[5a] suggests that only 0.024−0.089 kcal/mol should result from the steric effect of imidazole *N*-protonation. Thus, a reverse anomeric effect of approximately 0.8−1.4 kcal/mol is manifest for the *N*-(xylopyranosyl)imidazoles.

(13) Paulsen *et al.*[3a] claim that in the less-polar CCl_4 the amount of the $^1C_4$ conformation was 35% for **1**. In our hands, the compound was insufficiently soluble in CCl_4 to obtain an ^1H NMR spectrum.

It is accepted that the GAE diminishes on increasing solvent polarity.[14] A small equatorial shift is observed for **1** and **2** on increasing solution ionic strength with TBAB, a result consistent with the influence of the GAE. Addition of TFA to *N*-methylimidazole increases solvent ionic strength and is a model for addition of TFA to **1**. However, the influence of TFA on ionic strength as measured by conductivity is minimal compared to addition of TBAB. Clearly, the large equatorial shifts observed for **1** and **2** on *N*-protonation are not the result of solvent and ionic strength effects. Interestingly and conversely, the effect of increasing solution ionic strength with TBAB is a small axial shift for **1H**.

The simplest explanation for the experimental observations in light of theoretical data is as follows. The balance of destabilizing steric and stabilizing GAE contributions controls the conformational equilibria observed for **1** and **2**. On increasing ionic strength, the GAE is diminished, yielding a small shift to the equatorial $^1C_4$ conformation for both **1** and **2**. On *N*-protonation, stabilizing electrostatic interactions of types 1 and 2 (see above) in the $^1C_4$ conformer of **1H** yield a substantial equatorial shift. The lack of type-1 interactions in the $^1C_4$ conformer of **2H** results in a lessened equatorial shift on *N*-protonation. On increasing solution ionic strength, the stabilizing intramolecular electrostatic contributions in the $^1C_4$ conformer of **1H** are diminished, yielding a further small ionic strength-dependent equilibrium shift, in this case in the axial direction.

In summary, we have demonstrated that the stabilization of the $^1C_4$ conformation of *N*-glycosylimidazoles may be strongly dependent on *N*-protonation and weakly dependent on solution ionic strength and, in the case of xylopyranosyl derivatives, leads to an RAE. We suggest that the RAE is the result of stabilizing intramolecular electrostatic contributions to the $^1C_4$ conformer on *N*-protonation.[5c,15] The size of the effect in the two xylopyranosyl systems studied is quantified as 0.8−1.4 kcal/mol. Since contributions from this electrostatic RAE may be small, they may be overwhelmed by other contributions to conformational energy and will be diminished on transferring to solvents more polar than chloroform.[16]

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Supporting Information Available: Complete experimental details for the synthesis of **2**; complete tables of points from plots (3 pages).

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(16) The lack of evidence for a RAE manifest in the *N*-(glucopyranosyl)imidazole systems studied by Fabian *et al.*[5b] is not incompatible with the present data on the *N*-(xylopyranosyl)imidazoles. Previous studies on *N*-hexosylimidazoles have shown that the position of conformational equilibria is dependent on the identity of the hexosyl moiety.[2b,3b] Indeed, Perrin has recently concluded that some experimental evidence is compatible with an RAE of electrostatic origin: Perrin, C. L. *Tetrahedron* **1995**, *51*, 11901. The influence of the stereochemistry and identity of glycosyl-ring substituents on the conformational equilibrium is not well understood, and the size of such systems has precluded high-level MO calculations. It is not unreasonable that contributions to conformational energy may differ in type and magnitude in the *N*-(glucopyranosyl)- and *N*-(xylopyranosyl)-imidazoles such that an RAE, the result of a small electrostatic contribution, is manifest in the latter only.