A test for the reverse anomeric effect

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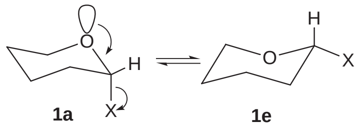
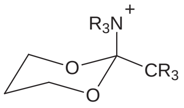
Conformational preferences and the geometry at the anomeric centre of a 1,3-dioxane with a trialkylammonium group in the 2-position (stable because part of a 1-azaadamantane) are consistent with a small, normal anomeric effect.

The anomeric effect—the preference for an electronegative substituent X in the 2-position of a tetrahydropyran for the axial conformation (**1a**)—is a well-characterised exception to the usual rules of conformational analysis.[1,2] The reverse anomeric effect (RAE)[3]—an apparent increased preference of a positively charged electronegative substituent for the *equatorial* conformation (**1e**)—is thus an exception to the exception, and presents something of a conceptual problem. The simplest solution to the problem would be that the effect does not exist.[3–6] We report the conformational preferences of a novel sterically balanced system (general structure **2**) consistent with this conclusion.



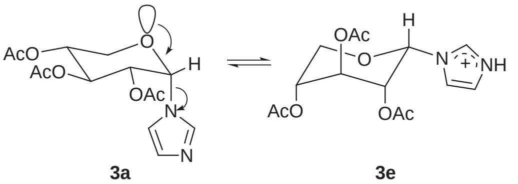
1a **1e**



2a

The normal anomeric effect can be understood in terms of a stereoelectronic effect involving the lone pair electrons of the ring oxygen: the stabilising n_O–σ^*_{C-X} interaction (arrows in **1a**, possible only for the axial geometry) outweighing the steric preference for the equatorial position.[1,2] Through-bond interactions of this sort play an important role in controlling reactivity as well as conformation[7,8] and thus in the way we think about both. They should not depend on the charge on the electronegative substituent X—hence the conceptual problem.

Experimental support for the RAE is neither extensive, nor generally clear-cut. The best experimental evidence,[9] recently reconfirmed,[10] is that N-protonation of *N*-triacetyl-α-D-xylopyranosylimidazole **3a** leads to an increase in the (already considerable) population of the $^1C_4$-conformation **3e**: corresponding to a RAE of 0.8–1.4 kcal mol^{-1}. On the other hand Perrin[5] concluded that the corresponding shift in the position of this equilibrium for a series of glucopyranosylamines could be accounted for on the basis of steric effects and a small, normal anomeric effect. (These results are not necessarily contradictory: the positions of such anomeric equilibria are known to depend on the structure of the sugar, with acetoxy groups in particular showing unusually small 1,3-diaxial interactions;[11] it has been suggested that the steric effect of an imidazole group may be increased on protonation.[5]) The most convincing evidence consistent with the operation of a small, normal anomeric effect comes from the NMR titration experiments of Fabian *et al.*,[6] which show that the axial imidazole is the more basic in an anomeric mixture of glucosylimidazoles.

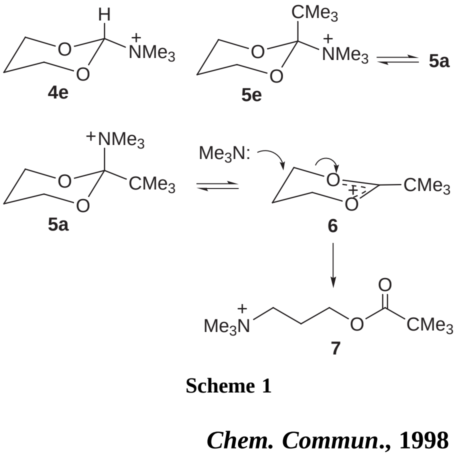


3a **3e**

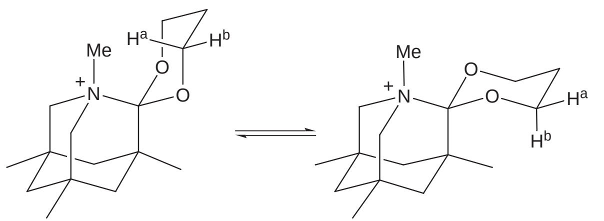
We sought a direct experimental test for the existence of the RAE in a simple sterically balanced system, uncomplicated as far as possible by solvation effects. In order to maximise stereoelectronic effects we chose to work with the dioxane ring, and to set trialkylammonium, with a full positive charge on N, against an isosteric tertiary alkyl group. The problems involved are illustrated by the following sequence of results. Simple systems with X = R_3N^+ already have a strong steric preference for the equatorial conformation:[12] thus 2-trialkylammonium systems **4e**, although stable, are exclusively equatorial. But the sterically balanced system **5e** is not isolable: addition of Me_3N to the dioxocarbenium ion **6** probably gives **5a** as a kinetic product, but what we isolate is the pivalate ester **7**, formed by the alternative (S_N2) reaction shown (Scheme 1).

To encourage the three heteroatoms to stay together on the quaternary center of interest we embedded it in the azaadamantane structure **8**. The critical test for RAE *vs.* normal anomeric effect now becomes simply the conformational preference of the dioxane ring. The conformational equilibrium **8a**$\rightleftharpoons$**8e** is as far as possible sterically neutral: because the CH_3–N^+ bond is shorter than CH_3–C it will have a slight preference for the conformation (**8e**) favored by RAE. In solution we find a clear preference for a conformation closer to **8a**, and in the crystal the pattern of bond lengths at the 'anomeric' centre expected if a normal anomeric effect is operating. However, the evidence from two crystal structures shows that the conformational picture is not as simple as depicted by **8a**$\rightleftharpoons$**8e**.

In the ^{1}H NMR spectrum protons H^a and H^b of **8** show nuclear Overhauser effects[13] of 12.3% to the $^+NCH_3$ and 2.0% to the CCH_3 groups, respectively, and vicinal couplings (*J* 11.4, 5.6 Hz for H^a, *J* 2.4, 2.4 Hz for H^b) not far from the expected magnitudes for conformation **8a**. However, X-ray structure determinations[14] of two different salts show pronounced flattening of the dioxane ring at the two oxygen centres. This is the not unexpected result of steric interactions—almost equally severe in either chair conformation—between the two O–CH_2 bonds and the ^+N–CH_3 and C–CH_3 groups (in **8a** and **8e**, respectively: indicated by the open arrows in Fig. 1). What *is* unexpected is that the conformations of the iodide and hydrogenfluoride salts in the crystalline state differ sig-



Scheme 1



8a **8e**

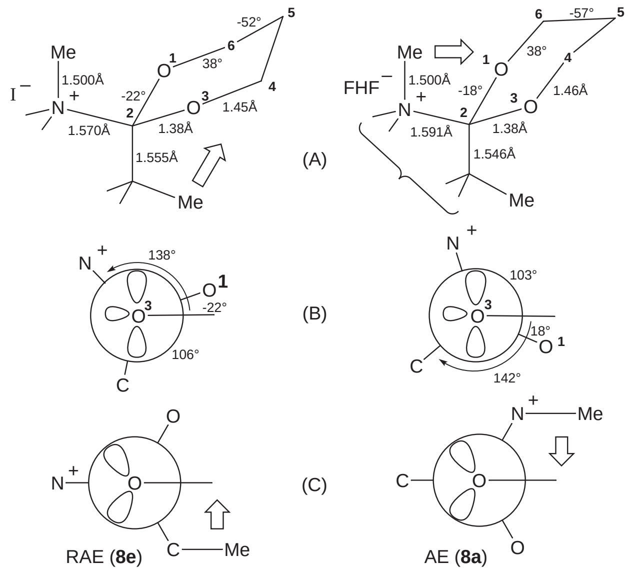


Fig. 1 Selected structural features at the anomeric centre of the iodide (left) and hydrogenfluoride (right) salts of **8**. The cation is formally (although not crystallographically) symmetrical about the mirror plane through C(2) and C(5) of the dioxane ring: mean values of bond lengths and angles are given. Individual bond lengths and angles have esd values of ±0.003 Å and 0.2°, respectively. (A) Observed conformations of the dioxane ring (in-ring torsion angles are given) and bond lengths at the anomeric centre. (B) Torsion angles at the anomeric centre, compared with (C) the geometry expected for a (hypothetical) system with normal bond angles showing the reverse (RAE) or normal (AE) anomeric effect. The open arrows represent major steric interactions responsible for flattening the dioxane chair of **8** (see the text).

nificantly, being closer in the former case to **8e** and in the latter to **8a**.

The differences are limited to the $(CH_2)_3$ chain of the dioxane ring: the structures are otherwise identical—and remarkable. The COC bond angles (120 ± 1.4°) show that the two dioxane oxygens are effectively sp^2-hybridised. This, together with the large OCO bond angle (118.0 ± 0.5°) and very long C(2)–N^+ and short O–C(2) bonds at the anomeric centre [Fig. 1(A)] is consistent with a well-developed n_O–σ^{*+}_{C-N} interaction, and thus a normal anomeric effect, with C–N^+ bond breaking being well advanced in the ground state. (The extent of the effect shows very clearly why simpler systems like **5** are not viable synthetic targets.) The C(2)–N^+ bonds are in both cases close to parallel to p-type non-bonding electron pairs on oxygen, which allows relatively efficient p_O–σ^{*+}_{C-N} overlap: closer in the case of the hydrogenfluoride [Fig. 1(B)], which—presumably consequently—has the longer C(2)–N^+ bond. This lengthening of the bond to N^+ can be interpreted as the stereoelectronically most efficient means of relieving strain at the crowded anomeric centre: there is very little lengthening of the equally crowded C(2)–C bond.

The observed conformations of the dioxane ring of the cation **8** represent two different compromises between stereoelectronic effects and powerful steric forces. It is reasonable to expect a unique minimum energy conformation, so the difference in the crystalline state may be presumed to derive from anion-related packing forces.§ (Iodide and hydrogenfluoride differ markedly in size, shape and charge-density.) Since the conformation in solution is clearly closer to **8a** we conclude that there is no conclusive evidence for a reverse anomeric effect in this test system. As found by Perrin,[5] in a very different system, the observed conformations can be explained on the basis of steric effects and a small, normal anomeric effect.[15]

Notes and References

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§ The inference is clear that this difference in conformation is driven by a packing-induced ring-flip at C(5), the most flexible part of the system. The conformation of the rest of the dioxane ring must adjust to accommodate this change: ending up much the way it started, except that N^+ and C have changed places [Fig. 1(B)].

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13 NMR spectra were measured in $CDCl_3$ on a Bruker 500 MHscz instrument. NOEs were obtained from NOE build-up curves according to K. Stott, J.H. Keeler, Q. N. Van and A. J. Shaka, *J. Magn. Reson.*, 1997, **125**, 302.
14 *Crystal data* for **8** (iodide salt): $C_{16}H_{28}INO_2$, colourless tablet, 0.4 × 0.3 × 0.15 mm, monoclinic, *Cc*, a = 7.8145(6), b = 14.9324(12), c = 14.5044(14) Å, β = 96.171(8)° (at −100 °C), μ = 1.906 mm^{-1}, Z = 4. Final $wR2$ = 0.040, $R1$ = 0.018, S = 1.00 for 3349 reflections and 186 parameters. For **8** (hydrogenfluoride salt): $C_{16}H_{29}F_2NO_2$, colourless tablet, 0.6 × 0.6 × 0.3 mm, monoclinic, $P2_1/c$, a = 10.206(2), b = 11.797(3), c = 26.344(7) Å, β = 92.09(3)° (at −130 °C), μ = 0.098 mm^{-1}, Z = 8 (two independent molecules). Final $wR2$ = 0.129, $R1$ = 0.049, S = 1.02 for 5584 reflections and 395 parameters. The nitrogen atoms were clearly distinguished from their carbon counterparts at C2 (Fig. 1) by comparison with the R values and displacement parameters for a refinement with C and N transposed. For the iodide salt, which represents an extreme case (heavy-atom structure, non-centrosymmetric), refinement of a C/N disorder model gave the occupation factor 0.89(2) for the structure as reported, *i.e.* there is no significant component with C and N exchanged. CCDC 182/929.
15 We find further support for this conclusion in the crystal structures of two *gem*-diols, hydrates corresponding to the acetal **8** (N. Feeder, A. J. Kirby and I. V. Komarov, *J. Am. Chem. Soc.*, in the press, and unpublished work). For both NH^+ and NMe^+ compounds the two O–H bonds adopt conformations corresponding to **8a**. Steric effects are reduced in these systems, and C–O–H angles are closer to tetrahedral values.

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