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Note

The evidence for an anomeric effect of the proton

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Abstract—The significant excess in conformational free-energy at position 2 of an oxane ring and other chemical and physical properties are explained by an anomeric effect of the proton.

Keywords: Anomeric effect; Deuterium quadrupole resonance

In 1977, we reported that tetra-*O*-acetyl-1,5-anhydro-D-iditol carried three axial substituents and one equatorial (at C-5) in its stable conformation.[1] This anomaly found its explanation in a report by the Eliel group:[2] the conformational free energies (CFE) of methyl or hydroxymethyl substituents at position 1 of oxane[†] were measured with the help of variable-temperature NMR on such model compounds as *cis*-2,5-dimethyloxane. The figures reported in 1982, namely, 2.86 and 2.89 kcal mol^{-1} at −100 °C were higher than the value for the CFE of the methyl group at position 4, which is 1.95 kcal mol^{-1}. With these new values, we revised predictions for the conformations of hexopyranose sugars and came to the conclusion that chair conformations having axial side chains cannot be observed. Six configurations are locked in a very rigid chair form. For the α-*ido* configuration, an equilibrium mixture of flexible conformations was predicted and observed.[3] In such glycosaminoglycans as heparin, nature has taken care to introduce α-L-iduronic acid residues. These are sites of flexibility among the rigid hexopyranoses, which may be important for biological activity.

In contrast to the many papers about the classical anomeric effect, the 1982 report on this new effect received little attention. It was first explained by traditional considerations of conformational analysis: non-bonded interactions across the oxygen atom were assumed to be greater because the two C–O bonds are shorter. However, calculations from several groups showed that this explanation cannot be true. Jorgensen et al.[4] calculated the variations of the free energy of butane and methoxyethane as a function of the dihedral angles Φ, C–C–C–C and C–C–O–C. They found that the free energy of the ether in its eclipsed conformation, $\Phi = 0$, is smaller than that of butane by about 3.5 kcal mol^{-1}, although steric compression reaches its highest in this conformation. For $\Phi = 120°$, the free energy of the methyl ether is also smaller. Recently[5] calculations for the homologous ethoxypropyl ether by the Allinger group confirmed this decrease, the diminution being about 0.5 kcal mol^{-1}. The same authors found that the rotational barrier of the Me–O bond in methylpropyl ether was smaller than that of the Me–C bond in butane. As the outcome of extensive calculations, the authors of a third report[6] concluded that, if only non-bonded interactions are considered, the conformational energy of 2-methyloxane would be smaller than that of 2-methylcyclohexane. As the computed CFE of the methyl substituent in 2-methyloxane is 3.18 kcal mol^{-1} (not much above the experimental value), effects other than steric are involved.

Since non-bonded interactions are not greater, the CFE of the methyl substituent at position 2 should be at most equal to that at any other position of the ring, that is, 1.95 kcal mol^{-1}. Thus, the 0.91 kcal mol^{-1} excess

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[†] For oxane derivatives, the accepted nomenclature for heterocyclic compounds will be adopted, that is, number one on the oxygen atom.

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should be a measure of the stabilization of the molecule when the C-5–H bond is in axial orientation. Thus, we may speak of an anomeric effect of the proton.

We note first that the magnitude of the effect suggested here for the anomeric effect of the proton is of the expected order. For halogens, the effect is estimated as the free-energy difference between isomers havin axial and equatorial bonds at C-1 in a pyranose sugar. The figures in kcal mol^{-1} are F (near 1), Cl (2.7), Br (3.2), and I (3.1). The place of the fluorine atom shows definitely that the effect is not related to electronegativity, as is sometimes believed. On the other hand, the order corresponds roughly to that of the atomic polarizabilities, namely F (0.56), Cl (2.18), Br (3.05), and I (4.7). The accepted explanation of the effect is an overlap of the 2*p* lone-pair atomic orbital of the oxygen atom with σ*(C–H), and this is more efficient with atoms having more diffuse orbitals. We see that the value suggested for the anomeric effect of the proton (0.91 kcal mol^{-1}) is compatible with its atomic polarizability (0.67).

Molecular orbitals were first introduced in carbohydrate chemistry in 1973 by calculations on 2-chlorooxane **1** as a model.[7,8] It was observed in a pictorial representation[8] that the 2*p* lone pair of the oxygen atom was delocalized not only, as anticipated, into the carbon–chlorine bond, but also, on the other side of the oxygen atom, into the C-5–H axial carbon–hydrogen bond. This is a property of the chair form of oxane, as seen from the HOMO picture in Figure 1, independent of the presence of an electronegative substituent at C-2. It is natural to associate this specific HOMO configuration to the anomeric effect of the proton, as in the case of electronegative substituents. The origin of the effect with halogen, as a consequence of a 2*p*–σ*(C–H) interaction, was proved by the determination of the ^{35}Cl nuclear resonance frequencies for a number of pyranosyl chlorides.[6] This suggests a similar approach for the C–H bond, that is, a discussion of the electric field gradient (EFG) at the hydrogen atom. I shall now review published evidence under this light.

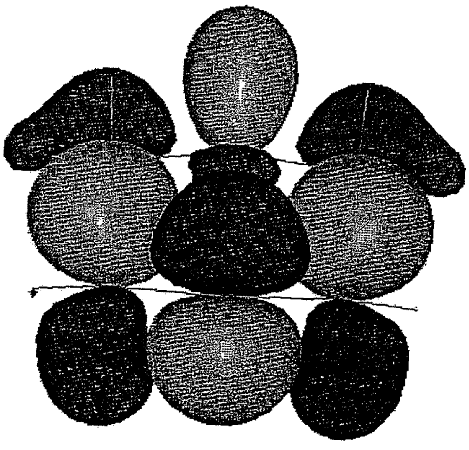
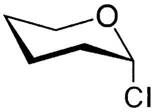
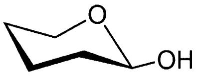


Figure 1. The HOMO of oxane in its stable conformation, as calculated with HYPERCHEM 5.1 and the program STO 6-31 G*. The orbital contour value is 0.045. This picture shows the interaction of the 2*p* lone-pair orbital of the oxygen atom in the front of the picture with the adjacent C–H orbital.



1

Deuterium quadrupole coupling constants have been calculated for all positions in deuterated derivatives of compounds **2** and **3** by Density Functional Theory.[9] The EFGs, (*eq*) calculated from these coupling constants were found to be smaller for the axial H-6 atoms than for the equatorial ones, by 0.16 and 0.27×10^5 dynes cm^{-1}. A similar decrease, 0.27×10^5 dynes cm^{-1}, is observed upon comparison of the H-2 atoms in **2** and **3**. However, the presence of two oxygen atoms on C-l makes the conclusion less certain, as the lone-pair orbital of the extracyclic oxygen may have an effect. To appreciate the meaning of these figures, we must recall the range of values for *eq* at the hydrogen atom in a C–H bonds is about $3.5–5 \times 10^5$ dynes cm^{-1}.



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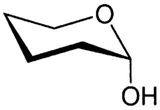


3

Experimental EFG's for C–H bonds, usually measured with deuterium as a probe, are not easily available. However, they are related to the stretching force-constant of the bonds, *k* which is generally more accessible. For diatomic molecules, Salem[10] predicted and observed a rough proportionality: $eq \approx 0.85\,k$ (range about $2–8 \times 10^5$ dynes cm^{-1}). Measurements[11] by deuterium NMR for a C–D bond in 17 aliphatic derivatives led to the following empirical relation, in which both *eq* and *k* are expressed in 10^5 dyne cm^{-1}:

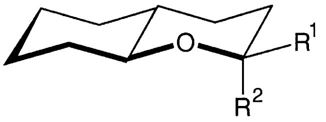
$$eq = 3.83k - 15.08, \quad 4.80 < k < 5.11$$

Unfortunately, extrapolation to lower values of *k* (some of interest to us) seems unrealistic. Nevertheless, we observed that the actual figures for *eq* and *k* are numbers of the same order and, we can be fairly confident that *eq* is a monotonic function of *k*, lower *k*'s corresponding to lower *eq*'s. I now review some IR data under this assumption.

The stretching force-constants of the C–H bonds have been derived from the IR spectra for three inositols.[12] From these, the authors derived a formula, which relates

k for the C–H bond in one H–C–OH unit to the angle between the bond and the lone-pair orbital on the oxygen atom. The extreme values are 4.24 and 4.77×10^5 dyne cm^{-1} for the parallel and gauche bonds. These conformations correspond, respectively, to those of the axial and equatorial C–H bonds at position 2 of an oxane.

In units of 10^5 dyne cm^{-1}, the decrease in k from the vibration of the bond gauche to the lone pair on the oxygen atom to the vibration of the parallel one is 0.53 in the foregoing example, 0.19 for methanol, 0.19 for ethanol, 0.33 for dimethyl ether, and 0.26 for 1,4-dioxane.[13] The observed[14] wave numbers for the C–D stretching vibration in **4** and **5** are 2185 and 2103 cm^{-1}. Assuming pure vibrations, these figures correspond to a decrease of 0.36 in k. All of these figures are comparable and we may assume a decrease of the same order of the corresponding eq.



4 $R^1 = D$, $R^2 = H$

5 $R^1 = H$, $R^2 = D$

A simplified theoretical expression for the EFG of a hydrogen atom at the site A is

$$(eq)_A = \sum_{A \neq B}[(3\cos^2\theta_{AB} - 1)/R^3_{AB}] \times Z_B - eI_{2C}$$

In this formula, Z_B is the charge on any nucleus different from A, θ_{AB} is the angle between the direction of the chemical bond and the radius vector R from B to A, and I_{2C} is the so-called two-center integral, which involves the molecular orbitals of atoms near to A. Both terms are positive.[11] This formula indicates that a decrease in eq may be the consequence of a decrease of the first term, or an increase of the second, or both.

If it is a diminution of the first term that is responsible, at least partly, for the decrease in eq, this means that R, the length of the bond, is greater for the axial than for the equatorial bond. Now such an effect is well known in the case of anomeric carbon–halogen bonds, and has been indeed considered as a proof of the $2p$–σ*(C–X) interaction. Calculations[9] indicate that the axial C-6–H bonds in **2** and **3** are longer (by 0.5 and 1.1 pm, respectively) than the equatorial ones. But so far, neutron-diffraction spectroscopy does not support this calculation.[15] No such differences of lengths were found in the constitution of the methyl α-glycopyranosides of mannose and glucose (respective standard deviation 0.2 and 0.5 pm). In β-D-fructopyranose, the lengths of the C-6–H bonds are 109.3 and 109.5 nm, respectively, for the equatorial and the axial bonds, but the authors warn us that these (very small) differences are probably not significant, owing to the uncertainty on the estimation of the thermal riding rotor effect. Thus, for the time being, we may consider the variations of the first term as not significant.

Now coming to the two-center integral, we have to discuss a term whose complete expression is fairly complicated, but all we need to know is that it is the product of the populations of atomic orbitals involved in the bonding by a geometry-dependent factor. The geometry should not change appreciably between the pairs considered. Thus, an augmentation of the I_{2C} term, which is responsible for the decrease of eq, means that the electronic-density probability at the site of the hydrogen atom is higher when the C–H bond is axial. This is in conformity with the drawing of the HOMO in Figure 1. Thus, the behavior of a C–H bond geminal to an oxygen atom is similar to that of a carbon–halogen bond. We may speak of an anomeric effect of the proton, which, like its classical counterpart, has stereochemical consequences. This achieves a unified picture of interactions in pyranoses other than the traditional nonbonding ones.

The 'generalized Bohlmann effect' is the diminution of the frequency of the stretching vibration of a C–H bond when it is antiparallel to the lone pair of an adjacent oxygen atom. This has been related in a qualitative manner to a weakening of this bond due to antibonding electrons. We see here that the effect can be related to a precise observable physical quantity, the electric field gradient at the nucleus of the hydrogen atom.

However, we have only evidenced here for orbital delocalization. It has been accepted for a long time that this was a source of stabilization. This view has been challenged recently for such archetypes of resonance as benzene and the allyl radical.[16]

Acknowledgements

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