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A TWIST IN THE ANOMERIC EFFECT

RADU SILAGHI-DUMITRESCU[a],
JUAN FRANCISCO CARRASCOZA MAYEN[a,*]

ABSTRACT. Several explanations have been proposed for the anomeric effect – based mainly on sterical interactions, charge separation, and hyperconjugation. Revisiting this topic with computational methods, we find that the pyranoid oxygen is not sp^3-hybridized, and as a result of this situation one of the oxygen lone pairs is found in an *eclipsed* conformation with respect to an equatorial substituent at a neighboring carbon atom. This sterical conflict by itself appears as an important cause of the anomeric effect. The non-sp^3-hybridized nature of the oxygen atom is in fact found not to be limited to carbohydrates, but rather be encountered in basic structural motifs (e.g., water, methanol, formaldehyde). Differences between this situation and those encountered with other heteroatoms (nitrogen, sulfur) are also discussed.

Keywords: *Anomeric effect; sugar, pyranoid oxygen.*

INTRODUCTION

In the typical ‘chair’ conformation of saturated cyclohexane-type six-membered rings, substituents prefer equatorial positions over axial ones (Figure 1). However, when one of the six carbon atoms is substituted by a heteroatom (such as in the pyranose form of certain carbohydrates), substitution at the vicinal carbon atom is found experimentally to entail much smaller differences between the axial and equatorial isomers, compared to what is seen in simple hexane-type structures. Several explanations have been proposed based on solid experimental and theoretical data for this so-called anomeric effect; among these were sterical repulsion between the axial/equatorial substituents and the lone pair of the pyranoid oxygen atom, different degrees of charge separation (manifested in different dipole moments), hyperconjugation involving the lone pairs of the pyranoid oxygen atom, and CH---O hydrogen bonding.[1-6]

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[a] *Babeş-Bolyai University, Faculty of Chemistry and Chemical Engineering, 11 Arany Janos str., RO-400028, Cluj-Napoca, Romania*
** Corresponding author: carrascoza@chem.ubbcluj.ro*

Here, we report data highlighting the important role of the pyranoid oxygen atom, via its previously undiscussed tendency to maintain its lone pairs in a *non-sp^3-hybridized* orientation, and thus force an *eclipsed* conformer involving the equatorial substituents at the neighboring carbon atom, as opposed to the commonly invoked situation where this oxygen is *sp^3-hybridized* and the respective conformer is *staggered*. We further show how the same 'non-sp^3-hybridized'-like description of the oxygen in terms of the spatial location of its two lone pairs of electrons, is seen even in some of the most basic organic and inorganic systems.

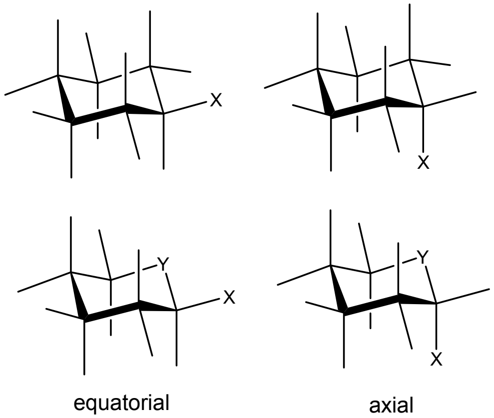

Figure 1. Structures of interest for the present study. X and Y are typically oxygen atoms, in which case the structural motif is relevant for carbohydrate chemistry.

RESULTS AND DISCUSION

Figure 2 illustrates frontier molecular orbitals computed at DFT level for the axial and equatorial isomers of tetrahydropyran-2-ol, one of the simplest compounds expected to present an anomeric effect. It may be seen that one of the pyranoid oxygen lone pairs is perpendicular to the ring's C-O-C plane (in the HOMO), while the other lone pair of the same oxygen atom is contained in this plane (HOMO-2 in the equatorial isomer, HOMO-1 in the axial one). Thus, the pyranoid oxygen atom has two p orbitals essentially perpendicular to each other

This situation is at odds with the sp^3 hybridization generally invoked when discussing the anomeric effect and in fact generally expected of oxygen atoms in organic chemistry. Two p orbitals perpendicular with each other, in an atom not involved in multiple bonding would appear to best be explained as a non-hybridized atom. An alternative explanation, involving sp^2 hybridization, would be at odds with the formal lack of π bonding in the models of Figure 2, as well as in the models further explored in Figure 3. This situation, with a non-hybridized oxygen atom, then poses a simple conformational problem – substituents found in equatorial positions at the carbon atoms directly bound to the pyranoid oxygen will be found in an eclipsed conformation with one of the lone pairs of the oxygen atom, thus being energetically-disfavored, cf. Figure 2. This finding by itself offers a strong explanation for the anomeric effect. Additionally, the particular conformation of the pyranoid oxygen lone pairs also predicts that in the equatorial conformer of the tetrahydropyran-2-ol the oxygen atoms together with the two carbon atoms vicinal to the pyranoid oxygen will, all four, be found almost in the same plane. Upon our theoretical results, perpendicular to this plane within the equatorial conformer will be the lone pairs from both oxygen atoms and the C-H bonds from the two carbon atoms. All of this makes for an ideal conformation for hyperconjugation in the equatorial isomer – a configuration which would be lost in the axial conformer. Thus, the non-hybridized character of the pyranoid oxygen atom has two effects: creating eclipsed conformers (as opposed to staggered ones) and thus partially destabilizing the equatorial isomer relative to the axial one, and on the other hand favoring hyperconjugation in the equatorial isomer.

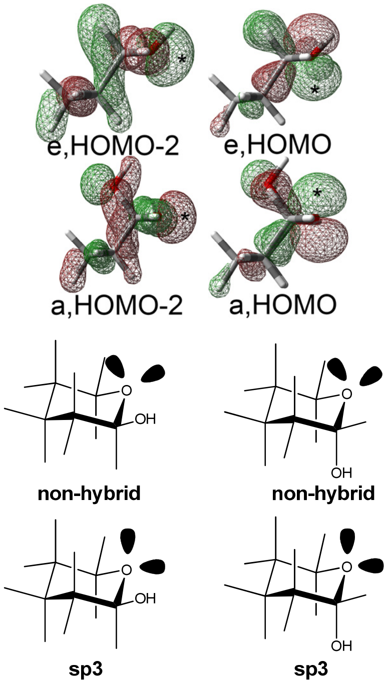

Figure 2. Up: computed frontier orbitals for tetrahydropyran-2-ol, showing the two lone pairs of the pyranoid oxygen atom (each lobe marked with a * symbol), at an angle of 90º to each other. **Down:** comparison of the sterics of a sp^3-hybridized vs a non-hybridized pyranoid oxygen atom in the models examined here; lone pairs are shown as hollow wedges at the oxygen.

Figure 3 illustrates molecular orbitals computed with DFT for a series of simpler molecules, as reference models for the anomeric structures of Figure 1; identical pictures were obtained at the MP2/6-311+G** level (not shown). Water is the simplest molecule where the oxygen is involved in two single bonds, similarly to the anomeric oxygen atom in the tetrahydropyran-2-ol already examined in Figure 2. It can be seen that even in the water molecule there are two perpendicular p orbitals – HOMO and HOMO-1; these two orbitals are the equivalents of those shown in Figure 2 for the anomeric oxygen atom. The water HOMO-2 is also perpendicular to the HOMO, and, although its lobes are elongated towards the hydrogen atoms, they may also be interpreted to be perpendicular to HOMO-1. One may then ask, if the oxygen is non-hybridized, why would the two O-H bonds form a 105° angle, instead of 90°? The answer to this question is in the distance between the two hydrogens in the water molecule – 1.45 Å, which is distinctly shorter that the 2.40 Å representing their sum of van der Waals radii; one may then propose that a distinct repulsion between these two hydrogen atoms is the main reason why the H-O-H angle is not 90° in water.

Examination of the frontier orbitals in methanol (Figure 3) again reveals that the two oxygen lone pairs, as major contributors to the respective HOMO and HOMO-1, are perpendicular to each other and thus irreconcilable with an sp^3 description, all in line with the data shown in Figure 2 for the anomeric oxygen. The relative orientations of the methanol HOMO-2 and HOMO-4, at an apparent 120°, may tempt one to invoke an sp^2 situation, as could have been done for the anomeric oxygen of Figure 2. Such an sp2 description would be somewhat in line with the fact that the C-O-H angle at the oxygen atom is computed to be 109°, as opposed to the 90° expected of an non-hybridized oxygen. However, as in the case of the water molecule, one may identify a sterical reason for this deviation from 90°: the distances between the water-bound proton and the two closest methyl protons are 2.39 Å each, 0.01 Å shorter than the sum of van der Waals radii and suggesting again sterical repulsion as the main factor dictating the bond angles around the oxygen atom. Strongly arguing against a hybridized description is also the HOMO-2 orbital in methanol: in an sp^2 situation this orbital should have been directed along the carbon-oxygen axis – which is not the case.

The frontier molecular orbitals of CH3SH are also instructive to follow (cf. Figure 3): they are almost identical to the ones in CH3OH, even though the bond angle around the sulfur is now only 97° - much closer to 90° and clearly symptomatic of a non-hybridized atom. We then propose that the deviations of orbitals HOMO-1 and HOMO-4 in CH_3SH and CH_3OH from the expected 90° are caused by the need to optimize interaction with the carbon and hydrogen atoms respectively, but that the sulfur and oxygen should equally be described as non-hybridized, rather than sp^2 or sp^3.

Figure 3 also shows that an oxygen atom involved in a double bond (as in formaldehyde) is even more clearly describable as non-hybridized, with all its three p orbitals clearly perpendicular to each other. One may then advocate, starting with the example of the anomeric effect, that oxygen atoms in organic chemistry should always be regarded as non-hybridized, and that their lone pairs are always perpendicular to each other.

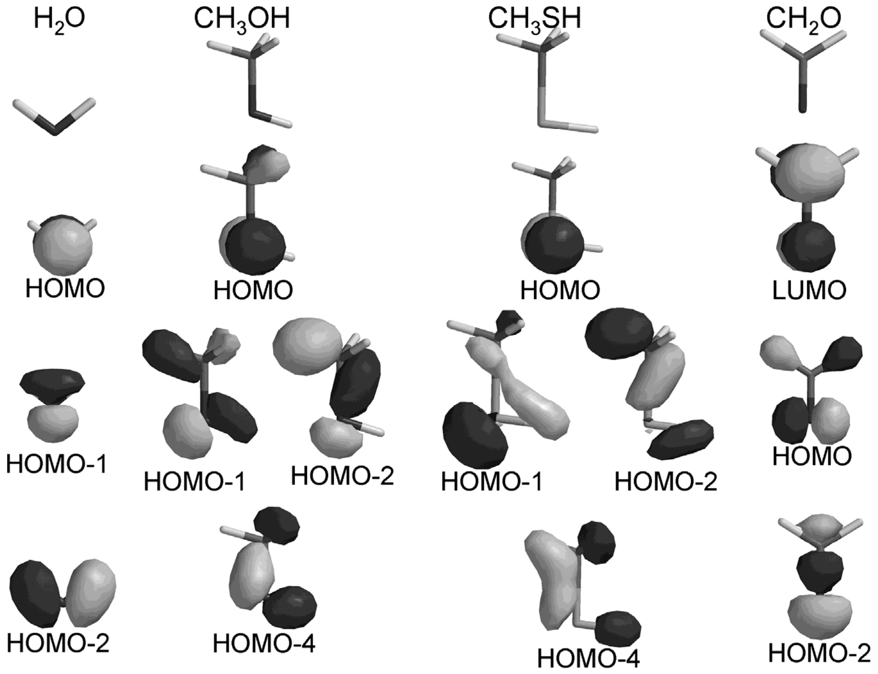

Figure 3. Frontier molecular orbitals for H_2O, CH_3OH, CH_3SH and CH_2O.

To our knowledge when the pyranoid oxygen in the tetrahydropyran-2-ol is replaced with an NH group the anomeric effect is essentially lost.[4] In fact, unlike the pyranoid oxygen in the tetrahydropyran-2-ol, the NH atom has largely a tetrahedral sp^3-like geometry, inevitably since it has three substituents in addition to the lone pair. In such a true-sp^3 situation, the sterical argument, in its form traditionally invoked when explaining the anomeric effect, does not seem to provide enough repulsive energy to generate an anomeric effect – further strengthening our argument that the *eclipsed* conformation induced by the lack of hybridization at the anomeric oxygen atom is the main reason for the anomeric effect. It is important to note that the same computational methods that predict a 'non-hybrid' nature in the oxygen atom, do in fact predict an sp^3-like orientation of the nitrogen-based molecular orbitals in systems as simple as ammonia. A final comment is that we are merely concerned with the spatial location of the lone pairs of the respective heteroatoms, and labels such as ‘sp^3’ should be viewed merely as such, and not as attempts to endorse an otherwise debated bonding theory.

Information extracted from Natural Bonding Orbital (NBO) analysis (cf. Table 1) for the models shown in Figure 1 indicates that in the equatorial conformer one of the oxygen’s lone pairs is 56.4% s and 43.6% p character, while the other lone pair orbital is 0.3% s and 99.7% p, meaning that only one of the lone pairs is not hybrid. Likewise, in the axial conformer the percentages are 54% s and 46% p while the other lone pair is 1.4% s and 98.6% p. These data then may be taken to support an sp^2 description of the pyranoid oxygen. Such a description is in line with observations made on the spatial orientation of the oxygen models in most of the models in Figure 3 – and the spatial orientation of the pyranoid oxygen orbitals as well – in that they are not *all* perpendicular to each other. It remains to be debated whether the argument discussed above for the Figure 3 models, of repulsion between the atoms bound to the oxygen, is acceptable here as well, and whether the NBO data is a manifestation of that effect, or a cause.

Table 1. NBO Analysis for pyranoid oxygen in the equatorial conformer. Only lone pair and Rydberg orbitals are shown.

Equatorial Conformer			Axial Conformer	
OT	**Occ**	**% Hybridation**	**Occ**	**Coefficients/ Hybrids**
LP(1)	-1.97	s 56.42% p 43.58%	-1.96	s 49.61% p 50.39%
LP(2)	-1.93	s 0.36% p 99.64%	-1.90	s 0.87% p 99.13%
RY*1	-5.97e-3	s 16.75% p 83.25%	$-5.12e^{-3}$	s 1.26% p 98.74%
RY*2	-2.40e-3	s 22.45% p 77.55%	$-2.23e^{-3}$	s 6.57% p 93.43%
RY*3	-6.80e-3	s 11.55% p 88.45%	-16.0e-3	s 44.75% p 55.25%
RY*4	- 4.70e-3	s 12.73% p 87.27%	- 1.0e-3	s 10.76% p 89.24%

Abbreviations. OT: Orbital type; Occ: Occupancy. LP: Lonely pair orbital; RY*: Rydberg orbital.

CONCLUSIONS

In conclusion, the results shown here support the concept that the ability of the pyranoid oxygen to remain in a ‘non-sp^3-hybridized’-like conformation, i.e. at 90º from each other, leads to an eclipsed position of an equatorial substituent at the carbon atom bound directly to this oxygen in a tetrahydropyranoid structure, and this factor has an important role in the anomeric effect. This 'non-sp^3-hybrid'-like (or even 'non-hybrid-like) situation of the oxygen atom is proposed to be relatively common in (bio)organic molecules.

METHODS

Geometries for all models were optimized using the BP86 functional, which uses the gradient-corrected exchange functional proposed by Becke,[7] the correlation functional by Perdew,[8] 6-31G** were used as implemented in Spartan.[9] For the SCF calculations, a fine grid was used, and the convergence criteria were set to 10^{-6} (for the root mean square of electron density) and 10^{-8} (energy), respectively. For geometry optimization, convergence criteria were set to 0.001 a.u. (maximum gradient criterion) and 0.0003 (maximum displacement criterion).

NBO analysis were obtained optimizing using density functional theory also with BVP86 functional and 6-31(d,p) basis set, at vacuum as implemented in Gaussian 09[10] using default SCF convergence criteria for geometry optimization.

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