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Perspective

Sugar anomerism – a short and sweet digression
Perspective on "The application of ab initio molecular orbital theory to the anomeric effect"

Jeffrey GA, Pople JA, Radom L (1972) Carbohydr Res 25:117

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Abstract. The subject paper presented the first conformational analysis of the anomeric effect within the context of molecular orbital theory, discussed the utility of Fourier decomposition of a torsional coordinate as a method for analyzing disparate electronic influences on that coordinate, and helped settle debate on the nature of anomeric stabilization.

Key words: Carbohydrate – Conformational analysis – Stereoelectronic effects – Hyperconjugation

Sugars are the stepchildren of the biomonomer family. Unlike their more popular siblings peptides and nucleic acids, the study of which occupies a swarm of researchers, sugars appeal to a coterie of devotees.

Yet sugars are wonderfully appealing to those attracted to puzzles. Capable of exhibiting multiple tautomeric forms at equilibrium, festooned with functional groups generating potentially thousands of rotational isomers, and profoundly influenced by aqueous solvation, they are a theorists dream (or nightmare) vis-á-vis challenge!

I choose to focus here on the contributions of Jeffrey, Pople, and Radom (JP&R) [1] to fostering our early understanding of one particularly fascinating feature of sugar energetics, namely the anomeric effect [2–7]. This stereoelectronic effect was first noted in sugars, where the axial anomer of mannopyranose, for instance, is observed [8] to predominate over the equatorial anomer (this situation being contrary to expectations based on standard precepts of conformational analysis as applied to substituted cyclohexanes). However, the generality of the anomeric effect, or "negative hyperconjugation" as it is sometimes called, has come to be widely recognized, and it is a key component in the conformational analysis of a diverse array of organic and inorganic molecules [9, 10]. Its physical basis was poorly understood in 1972.

At the time two hypotheses (that were regarded for the most part as being mutually exclusive) had been put forward to account for the anomalous preference of electron-accepting substituents to orient themselves axially at the 2 positions in pyranose rings (i.e., the position next to the ring oxygen). In one analysis, the preference was ascribed to dipole–dipole and/or other Coulombic effects between the substituent group and the ring oxygen atom with its associated bonds [11, 12]. However, these models were of limited utility for predicting either experimental equilibria or geometrical differences between various pyranoside anomers; the latter were becoming increasingly available from X-ray crystallographic studies [13].

Indeed, crystal structure observations of lengthened axial bonds in 2-halopyranosides with concomitant shortening of the ring C(2)—O bonds led to an alternative proposal rationalizing the anomeric effect by invoking double bond–no bond resonance structures [14], i.e., negative hyperconjugation. This model, however, failed to account for another crystallographic observation, namely the shortening of axial $C(2)—O_{exo}$ bonds in 2-oxygenated pyranosides [15] – this phenomenon acquired the sobriquet "exo-anomeric effect".

It was at roughly this stage that theory first entered the game. In 1971, two papers appeared that were germane to this topic. The first, by Wolfe et al. [16], showed that the hydroxyl rotational coordinate of fluoromethanol (FCH_2OH) had a deep minimum for the gauche FCOH dihedral angle (60°), but no minimum for the trans dihedral angle (180°). That same year, similar results were obtained independently by Radom et al. [17] not only for fluoromethanol, but also for dihydroxymethane, which is the smallest molecule incorporating the acetal linkage that characterizes a pyranoside.

A limitation of these 1971 studies was that they did not attempt to optimize the molecular geometries (analytic derivatives not yet being available, such optimiza-

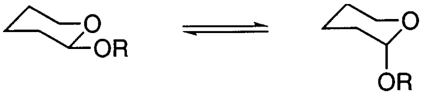

Fig. 1. Anomeric equilibrium in a model pyranose

tions were not routine) but rather employed ideal bond lengths and valence angles, adjusting only the torsion angles to specific, also nonoptimized values. As such, analysis hinted at explanations for the anomeric effect, but could not be regarded as definitive.

Key advances offered by the 1972 paper of JP&R included

1. Providing a complete 2D potential-energy surface for both C—O rotations in dihydroxymethane.
2. Optimization of the C—O bond lengths for various torsion angles so as to compare to analogous linkages in experimentally known crystal structures.
3. Decomposition of the C—O rotational coordinates in a Fourier sense to assess the relative contributions of dipole–dipole interactions, hyperconjugative stabilization, and steric interactions.

Another critical strength of this paper was that it used the electronic calculations in conjunction with a simple steric model to successfully rationalize 18 different pyranose crystal structures. While this latter aspect cannot be discussed here in any detail owing to space limitations, this careful comparison of the model to experiment had a tremendous impact on experimental carbohydrate chemists, who were impressed to see theory being used to make predictions about exactly the same crystal structures they were concerned with from their own perspectives. Indeed, JP&R set a remarkably high standard to be emulated in future theoretical papers, and contributed to the generally good reputation theory has enjoyed within the carbohydrate community. The calculations of JP&R, described below, were carried out at the HF/4-31G level [18].

With respect to the 2D analysis, JP&R clearly described for the first time the simultaneous hyperconjugative effects deriving from delocalization of lone-pair density on each oxygen atom into the σ^*_{CO} antibonding orbitals associated with their counterpart oxygens. While they did not refer to this by name, in essence this was the first demonstration of simultaneous anomeric and exo-anomeric effects.

The various changes in C—O bond lengths associated with the torsional coordinate were substantial. Thus, JP&R predicted variations in the C—O bond length of up to 0.032 Å depending on whether the oxygen atoms were acting as lone-pair donors or as part of acceptor antibonding orbitals. Results of this magnitude were in good agreement with the range observed in crystal structure data, and provided a critical validation of the theoretical approach.

JP&R properly associated these bond length deviations with hyperconjugation (which had been suggested before based on intuition and analogy [13]) but did so by a more convincing analysis than had hitherto been advanced. That analysis involved the decomposition of individual oxygen rotational coordinates in a Fourier sense. As described by Radom et al. [19] that same year, such an analysis can be applied in simple instances to qualitatively assess the relative dependence of the torsional coordinate on dipole–dipole interactions (which should show a onefold symmetry over the full rotation angle of 2π rad), hyperconjugation (which should show a twofold periodicity since it is locally maximized for eclipsed and antiplanar arrangements by virtue of most favorable overlap between donor and acceptor orbitals), and sp^3-sp^3 steric interactions (which are threefold periodic by the tetrahedral nature of the atoms involved). JP&R showed for dihydroxymethane that the twofold periodic term was nontrivial, and discussed its general importance for sugar conformational analysis. (To be fair, their analysis did underestimate the magnitude of the importance of hyperconjugation because, inter alia, they used ideal bond angles – the anomeric effect causes an increase in the valence angle at the central carbon, and without accounting for this the gauche structures were somewhat higher in energy than they should have been – such approximations are difficult to criticize given the computational resources available at the time.)

It is important to note that the results of JP&R significantly influenced the thinking of subsequent researchers. In the interests of brevity I note here only the key papers of Tvaroska and Bleha [20, 21], which further demonstrated the utility of Fourier analysis, the particularly elegant paper in 1979 by Wolfe et al. [22], which refined many of the ideas laid out in JP&R's prior work and extended its range of applicability, and the efforts of Thøgersen et al. [23], who built upon the work of JP&R in the construction of an empirical potential function for oligosaccharide conformational analysis.

To conclude on a personal note, I first encountered the JP&R paper several years ago when I became interested in the characterization of solvation effects on various anomeric equilibria in pyranosides [24, 25]. It goes without saying that phenomenal advances in computational power now permit us to address considerably larger model systems than those accessible to JP&R and moreover to do so at much more refined levels of electronic structure theory [26–28]. Nevertheless, subsequent work has been guided by JP&R's seminal 1972 contribution, which convincingly elucidated the key physical underpinnings of the anomeric effect, successfully predicted the most important qualitative consequences, and set the foundation stone for future quantum chemical conformational analysis of sugars.

(In the spirit of the paper's title, I feel I must digress at the end point out one other important contribution of John Pople to the general area of sugar conformational analysis. He, together with Dieter Cremer, developed the systematic classification of ring geometries that continues to be used today to describe the variety of shapes furanose and pyranose rings can adopt [29]. This scheme, which expresses these shapes in terms of the Cremer–Pople ring puckering coordinates, is in my opinion an extraordinary example of the kind of impact a theoretician can have on a particular field when he or she focuses upon it as a new challenge.)

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