Does intramolecular hydrogen bond play a key role in the stereochemistry of α- and β-D-glucose?

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**A B S T R A C T**

Four α- and three β-isomers of the D-glucose were optimized in gas phase using ab initio (MP2) and DFT (B97X-D) methods, both using the aug-cc-pVDZ basis set. While earlier works suggest that the orientation of the hydroxyl groups is due to intramolecular hydrogen bonds (H-bonds), the present study reveals that most H-bonds forming five-membered rings are either weak or even do not exist. The quantum theory of atoms in molecules (QTAIM) analysis showed only a few cases of H-bond in α-glucose, particularly for those H-bonds forming six-membered rings, while the non-covalent interactions (NCI) analysis indicated that most intramolecular H-bonds are not strong enough to justify the counter-clockwise arrangement of the OH−O chains. Natural bond orbital analysis supported the findings obtained from QTAIM and NCI analyses and indicated that the anemic effect for α-glucose in the gas phase is governed by a balance of steric, electrostatic, and hyperconjugative interactions.

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1. Introduction

Carbohydrates are biomolecules widely studied due to numerous applications, that range from pharmacological action, for example, the anticoagulant activity of heparin, to technological interest in developing cellulose nanofibers that can exhibit mechanical properties comparable to carbon nanotubes. Such properties are related to the molecular architecture, which is governed by intra- and intermolecular interactions, such as hydrogen bond. In addition to carbohydrates, many other compounds and biological molecules exhibit hydrogen bonding as generally one of the main stabilizing interactions, generating great interest of the scientific community for new studies with emphasis on this type of interaction, for example, in supramolecular chemistry.

Phenyl-substituted monosaccharides (mannose, galactose, and glucose) and their single hydrated complexes have been studied in gas-phase by UV and IR double resonance hole burning spectroscopy techniques, revealing that the most stable conformations are those having a sequence of H-bonds (OH…O) surrounding the carbohydrate. Microwave studies in isolated phase (LA-MB-FTMW experimental technique) and ab initio calculations suggest that the most stable conformers of α- and β-2-deoxy-α-ribose are controlled by the anomic effect and H-bond cooperativity. Alonso et al. identified four conformers for α-β-glucopyranose, indicating the importance of hyperconjugative factors, like those associated with anemic or gauche effects, as well as the cooperative OH…O chains extended along the entire molecule, as the main factors driving the conformational behavior. However, H-bond forming five-membered rings has not shown to be stable in a variety of 2-substituted alcohols.

The presence or not of these OH…O interactions, which are assumed to give rise to the counter-clockwise arrangement of the network of intramolecular H-bonds in α-glucose, were theoretically investigated using natural bond orbital analysis (NBO), noncovalent interactions (NCI) method, and the quantum theory of atom in molecules (QTAIM), in order to check the importance of these and other interactions on the conformational equilibrium of the seven energy minima experimentally found for α- and β-α-glucose (Fig. 1).

2. Theoretical calculations

Optimization calculations in the gas phase at the MP2 and DFT/B97X-D basis set were performed for the most stable rotamers of α- and β-α-glucose (Cartesian coordinates are given in Supplementary material), experimentally determined elsewhere, using the Gaussian 09 program. Natural bond orbital (NBO) analysis at the B97X-D/aug-cc-pVDZ level was carried out over the optimized geometries, using the NOSTAR and STERIC keywords as inputs to determine the energy of the hypothetical Lewis structure and the steric
exchange energy, respectively (minimum energy cut-off of 0.5 kcal mol\(^{-1}\)). Non-covalent interactions (NCL using the NCIPLoT program\(^{18}\)) and quantum theory of atoms in molecules (QTAIM, using the AIMAll program\(^{13}\)) calculations were used to analyze the formation of five- and six-membered rings due to intramolecular OH···O H-bonds.

### 3. Results and discussion

Four out 7 stable rotamers of isolated d-glucose found in the gas phase are \(\alpha\) anomers (\(G-g+/cc/t, G+g-/cc/t, Tg+/cc/t\) and \(G-g+/cl/g-\)), while 3 are \(\beta\) anomers (\(G-g+/cc/t, G+g-/cc/t\) and \(Tg+/cc/t\)). The rotamers were optimized using both MP2 and DFT (\(\text{B97X-D}\)) methods and the aug-cc-pVDZ basis set. The relative energies (\(E_{\text{rel}}\)) are similar for both theoretical levels (Table 1) and, therefore, the remaining calculations were carried out using the \(\text{B97X-D}/\text{aug-cc-pVDZ}\) level only. In agreement with the anomic effect, the 4\(\alpha\)-d-glucose rotamers are more stable than the \(\beta\). The hyperconjugative and electrostatic contributions for this effect have been widely discussed elsewhere for 2-substituted tetrahydropyrans.\(^{19,20}\) The origin of such effect for 2-deoxy-D-glucose (positive values are destabilizing and negative ones are stabilizing interactions).

![Figure 1. Hydrogen bonds (dashed lines) and their respective \(n_0\) and \(\sigma^{\text{rel}}\) interactions (kcal mol\(^{-1}\)), according to NBO analysis.](image)

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(G-g+/cc/t)</th>
<th>(G+g-/cc/t)</th>
<th>(Tg+/cc/t)</th>
<th>(G-g+/cl/g-)</th>
<th>(G-g+/cc/t)</th>
<th>(G+g-/cc/t)</th>
<th>(Tg+/cc/t)</th>
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<tr>
<td>(E_{\text{MP2}})</td>
<td>0.0</td>
<td>0.2</td>
<td>0.5</td>
<td>0.9</td>
<td>1.3</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>(E_{\text{DFT}})</td>
<td>0.0/0.0(w)</td>
<td>0.1/0.1(w)</td>
<td>0.1/0.4(w)</td>
<td>0.6/1.5(w)</td>
<td>0.9/0.7(w)</td>
<td>1.1/0.8(w)</td>
<td>1.2/1.1(w)</td>
</tr>
<tr>
<td>(E_{\text{steric}})</td>
<td>8.2/9.7(w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.0/0.0(w)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(E_{\text{electrostatic}})</td>
<td>0.0/0.0(w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11.7/17.9(w)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(E_{\text{hyperconjugation}})</td>
<td>0.0/0.0(w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-2.6/-7.5(w)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) For all rotamers.

\(^b\) For most stable rotamers of \(\alpha\) and \(\beta\)-d-glucose (positive values are destabilizing and negative ones are stabilizing interactions).
computational tools to identify H-bonds were applied to study the seven main conformations of D-glucose in the gas phase.

The non-covalent interactions (NCI) method introduced by Johnson et al.\textsuperscript{10} can serve as a complement to the Bader’s theory (QTAIM)\textsuperscript{21,22} to characterize, for example, weak H-bonds in 3D space of five-membered rings, since there has been controversial cases in the literature in which a bond critical point (BCP) cannot be found for compounds where a H-bond is expected to be formed, such as in the QTAIM analysis of 2-fluorophenol\textsuperscript{23} and 3-fluoro-1,2-propanediol.\textsuperscript{9} The NCI method is based on the analysis of the electron densities $\rho(r)$ and their reduced gradients, $s(r)$. In this sense, the non-covalent interactions will be predicted in regions where the $\rho(r)$ and $s(r)$ are low. Attractive interactions (blue), such as H-bonds, Van der Waals contact (green) and repulsive interactions/electron density depletion regions (red) can be visualized on isosurfaces of $s(r)$, as shown for the energy minima of D-glucose in Figure 2. Here, the attractive and repulsive interactions are mixed in the region between the (H)O/C1/C1/C1 contacts. However, the blue volume corresponding to H-bonding appears when forming six-membered rings, but the corresponding region in five-membered rings is modest. The red volume appears as a consequence of ring formation on the five- and six-membered rings, being related to the QTAIM ring critical points (RCPs). The NCI isosurfaces for five-membered rings in Figure 2 suggest very weak intramolecular H-bonds, since such isosurfaces are single volumes encompassing both the H-bond isosurface (blue color) and its corresponding RCP isosurface (red color), that cannot be detected by other theoretical methods (vide infra). Indeed, such five-membered rings are similar fragments of the 1,2-butanediol molecule, which was previously studied by Lane et al.,\textsuperscript{24} by the NCI method and despite not detected by the QTAIM, they were characterized as weak H-bonds having the same nature as H-bonds in 1,3-butanediol and 1,4-butanediol. Accordingly, the six-membered H-bonds are similar to a 1,3-propanediol fragment, which forms a stronger H-bond in the NCI point of view, since the H-bond blue isosurfaces and RCP red isosurfaces are not completely mixed up as for the five-membered rings and suggest stronger and more stable H-bonds.

The NCI results are consistent with the NBO findings, which describe H-bonds as $n_O \rightarrow \sigma^{\#}$ interactions. Indeed, important electron delocalizations from oxygen lone pairs to antibonding OH orbitals are found mostly for H-bonds forming six-membered rings (involving CH$_2$OH as proton donor and O$_4$ as proton acceptor, e.g., the Tg+/cc/t conformations in Figs. 1 and 3). H-bonds forming five-membered rings are weaker or even not detected by the NBO analysis. The QTAIM analysis shows that a BCP is found only between CH$_2$O-H...O$_4$ in the Tg+/cc/t conformation of both $\alpha$ and $\beta$ anomers (Fig. 4), while H-bonds forming five-membered rings are not observed at all, in agreement with the study of Lane et al.\textsuperscript{24}

In water solution, where the stereochemistry of carbohydrates proves to be more interesting, intramolecular H-bonds are expected to play a still weaker role. The seven main conformers of D-glucose were further optimized using implicit water according to the Polarizable Continuum Model.\textsuperscript{25} Even not considering specific solute–solvent interactions (which would compete with intramolecular interactions), the calculations indicate that the

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**Figure 2.** NCI isosurfaces indicating some intramolecular non-covalent interactions in $\alpha$- and $\beta$-D-glucose. The isosurfaces were constructed with RGD = 0.5 au and blue–red colors scaling from $-0.02$ au to $+0.02$ au. Peaks at negative sign($\pm$) values indicate attractive non-covalent interactions corresponding to five- and six-membered H-bonds and peaks at positive sign($\pm$) values indicate ring critical point regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
conformational preferences are not substantially different from those obtained for the gas phase (Table 1), while NBO, QTAIM, and NCI exploration (Supplementary material) indicates that no additional intramolecular H-bond appears in implicit water. 2-Hydroxytetrahydropyran forms intermolecular H-bond with explicit water molecule; the same is expected for D-glucose, which would compete with the six-membered ring-forming intramolecular H-bond to make it weaker or even absent.

4. Conclusions

Intramolecular hydrogen bonds are not responsible for the counter-clockwise arrangement of hydroxyl groups in D-glucose. The repulsion between the lone pairs of electrons in the endocyclic oxygen with oxygen bonded to the anomeric carbon dictates the preferred conformations of this compound, since this interaction induces the orientation of the remaining hydroxyl groups. These findings are instructive because they suggest that derivatization of D-glucose through replacement of hydroxyl by OR groups, which should not exhibit H-bond, can lead to counterclockwise arrangement, such as the prevalent rotamers of D-glucose.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2014.06.013.

References