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The (α-1,6) glycosidic bond of isomaltose: a tricky system for theoretical conformational studies

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ABSTRACT

Stable conformations of β-isomaltose (α-D-glucopyranosyl-(1→6)-β-D-glucose) in gas-phase and aqueous solution are investigated in this study using quantum mechanical calculations. Conformational maps are calculated at HF/6-31G(d,p) level and lower energy structures are sampled in the most stable regions. Entropic and thermal corrections are considered and the Boltzmann population is obtained for conformers that are representative of the 18 most stable regions found on the potential energy surface. B3LYP/6-31+G(d,p) and B3LYP/6-311+G(2d,2p) calculations are used in conformational samplings. Solvation effects are considered through the polarizable continuum model approach. Hydroxymethyl group orientations are investigated for the most stable conformers. The influence of electronic correlation and solvation on the glycosidic linkage preference (TG, GT, and GG) and hydroxymethyl group orientation (*tg*, *gt*, and *gg*) are discussed. Heteronuclear spin coupling constants ($^3J_{C,H}$) along the glycosidic linkage are calculated and comparison with other theoretical results and experiments is used to validate the obtained structures.

1. Introduction

In this study, the investigation of the most stable conformations of the disaccharide α-D-glucopyranosyl-(1→6)-β-D-glucose, hereinafter referred to as β-isomaltose, is performed through ab initio calculations. From a practical point of view, this disaccharide is generally used as a prototype of the starch and glycogen branching, once branching in these polymers occurs through an α-(1→6) bond between two glucose residues of the polymeric chain (Fig. 1).

Because conformational studies of carbohydrates are a keystone in the carbohydrate field,[1] there are many published papers devoted to similar purposes and other disaccharides. The large majority of them (just to cite those related to isomaltose) use classical[2–4] or semi-empirical[5] methods to obtain stable conformations. In fact, classical techniques are very powerful and particularly useful when the system is too large, very flexible, or the phenomenon studied does not involve stereo electronic effects. However, the latter is exactly the case: according to previous studies, in disaccharides the ϕ angle is defined by the exo-anomeric effect[6] and the ψ angle by non-bonded interactions.[7] An interesting comparison among the most used force fields dedicated to conformational studies of carbohydrates was performed by Engelsen and co-workers,[8] and Pérez et al.[9] The final conclusion is that we have not reached yet an acceptable level of parameterization of force fields able to describe either the exo-anomeric effects or the stabilization energy from an intermolecular hydrogen bond. Both effects are extremely important in determining conformation in carbohydrates and, therefore, from our point of view, preclude the use of non-specific force fields to investigate the conformational aspects of these systems in detail.

On the other hand, ab initio descriptions are very efficient in quantifying stereo electronic effects because no parameterizations are used to calculate electronic potentials. In fact, quantum mechanical descriptions can nowadays be extended to larger systems than those described 20 years ago due to two correlated facts: (a) we now have at our disposal very fast computers and, consequently, (b) very efficient computational codes were developed, which were able to deal with larger systems. Such a situation allows the adoption of a quantum approach to systems of a reasonable dimension (as a disaccharide), within an acceptable range of time.

In this context, the problem of accessing the quantum mechanical energy of a disaccharide is solved.[10,11] However, there remains the physical question related to its huge flexibility that is mathematically expressed as a potential energy surface with a high density of minima. By the adoption of ab initio models, we can determine very precisely the depth of each minimum but it is extremely important to assure that the most stable conformations are comprised in the potential energy surface. Clearly, it is an intrinsic characteristic of these systems and, therefore, a protocol must be established in order to avoid non-representative conformational sampling. In other words, it is important to look for any hierarchy with respect to the energy among the degrees of freedom of the disaccharides.

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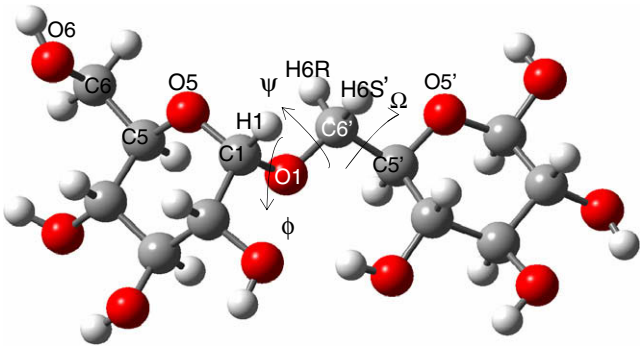

Figure 1. Definition of the dihedral angles ϕ (O5–C1–O1–C6′), ψ (C1–O1–C6′–C5′), and Ω (O1–C6′–C5′–O5′) in the β-isomaltose, a disaccharide with an α-(1→6) glycosidic linkage.

Moreover, a theoretical study on carbohydrates conformation can provide unique information because the available experimental data for carbohydrate in solution is always an average value. Therefore, it is impossible to recover the individual contributions from them because two sets of variables are ignored: each relevant conformation (at a certain temperature, pressure, and medium) and its individual contribution to the property.

First proposed by Lemieux and Koto,[12] and afterwards recognized by important studies,[13] the most relevant geometrical parameters to define the three-dimensional structure of disaccharides are the dihedral angles (ϕ and ψ) of the glycosidic linkage. French et al.[14] mention the necessity of a reliable technique for scanning such angles in a study dedicated to describe crystalline structures. In the case of the 1→6 bond, a third dihedral angle called Ω needs to be specified, in order to univocally define the relative monosaccharidic orientations (Fig. 1). Such degrees of freedom must be properly investigated by the adopted description; otherwise, as already mentioned, the final obtained structures will not be a representative ensemble of the β-isomaltose compound. Previous studies using ab initio calculations to obtain potential energy surfaces[15,16] to sample conformers on them and also to calculate kinetic[17] and optical properties[18] of carbohydrates encouraged us. This is because they furnished theoretical values for them which are in better agreement with the experimental data than those obtained when classical methods were employed in the sampling of stable structures. However, such studies were performed for monosaccharides or disaccharides with 1→1 and 1→4 glycosidic linkages, and the protocol adopted in these cases needs to be tested for the more flexible 1→6 bond.

Surprisingly, despite the importance of the isomaltose, few published studies can be found that really provide insights into its most abundant conformations. Among the most important contributions, we can detail two studies. In the first, Pérez and co-workers[5] have performed semi-empirical calculations for the isolated molecule in four different solvents. The results obtained identified 15 stable conformers on the potential energy surface of this carbohydrate and relative population in vacuum for the structures with orientation gauche–gauche (GG), gauche–trans (GT), and trans–gauche (TG) of 71%, 17%, and 12%, respectively, corresponding to values of 300°, 60°, and 180° for the dihedral Ω angle of the glycosidic bond. For the same parameters in an aqueous solution, the relative distribution found was 52%, 31%, and 12%. In the second study, Dowd et al.[3] used molecular mechanics (MM3) calculations to finally identify 13 structures (7 for alpha and 6 for beta anomers) with the GT orientation for the glycosidic bond preferred over the GG orientation in the set of obtained conformations.

A central question always present in conformational studies of carbohydrates in general regards the proper consideration of solvation effects. Our first choice is to describe the β-isomaltose (which has a higher dipole moment than the α-anomer and, therefore, could be more sensitive to solvation effects than the latter) in an aqueous solution through a polarizable continuum model. We recognize that sometimes this kind of approach may not be suitable to reproduce solvent effects and explicit solvent molecules must be added to the solute, principally when dynamical aspects play a central role.[19] Here it is not the case and by adopting this model we are tacitly assuming that we are describing the molecule in an aqueous solution, after the thermodynamic equilibrium is reached. It is the same to assume that the conformations considered resemble those of larger residence time in a molecular dynamic simulation. Such correspondence is possible because the electrostatic effects mostly govern the interaction of carbohydrates and water due to the high dielectric constant of water and to the high dipole moments of the hydroxymethyl groups present in a large number in the carbohydrate structure. Therefore, hydrogen bond interactions, although with well-defined orientations, can also be included among the electrostatic interactions because, as suggested,[20] its largest component is of an electrostatic nature.

In fact, solvation is a delicate task for carbohydrates in general, as highlighted by the renowned study of Kirschner and Woods.[21] In that study, the authors concluded that molecular mechanics simulations are better than quantum mechanical calculations to reproduce the experimental[22] relative abundance of GT, TG, and GG rotamers in the aqueous solution of methyl α-D-glucopyranoside and methyl α-D-galactopyranoside. Because the simulations are based on force-field parameters derived from gas-phase data,[23] interactions with explicitly included water must be responsible for the resultant gauche population preference. The primary role of water, according to the authors, appears to be to weaken the internal hydrogen bonds of the carbohydrates. Due to these important observations, it is mandatory to properly take into account solvation effects to describe isomaltose conformers. Additionally, once the vapor pressure of carbohydrates can be neglected at room temperature, the large majority of experimental results for carbohydrate properties are obtained in aqueous solution. Therefore, to validate the set of conformers obtained through the comparison of any property calculated from the selected set and its corresponding experimental value, a more realistic description of these systems has to consider the solution phase. Instead of comparing geometries of the most stable conformers obtained in this study with those already published,[3,5] we believe that a comparison with an experimental property is much more useful. Accordingly, the properties used to validate the conformational sampling proposed here are the heteronuclear spin coupling constants ($^3J_{C,H}$) across the glycosidic linkage.

2. Methodology

2.1. Calculations

Conformational maps were calculated for β-isomaltose in gas-phase at HF/6-31G(d,p) level.[24] The extensive studies of Lii et al.[25] on potential energy surfaces of more than 80 conformers (D-aldo and D-ketohexoses) show the importance of considering diffuse functions for heavy atoms into the basis set, if density functional theory is used. Csonka[24] also confirmed these findings and showed, however, that HF/6-31G(d) is already an acceptable description, once intramolecular hydrogen bonds energies are well described at this level of calculation. These studies were performed on monosaccharides but it is our goal to establish the simplest possible ab initio protocol to generate reliable conformational maps for disaccharides. As for disaccharides, the location of the stability regions in conformational maps was proved to be the same in both descriptions[15] and conformational maps were calculated at the HF/