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DFTMD studies of glucose and epimers: anomeric ratios, rotamer populations, and hydration energies ☆

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ABSTRACT

Results are presented from density functional molecular dynamics (DFTMD) simulations, based on constant energy dynamics, of glucose and its cyclic form of 6-carbon epimers. Both in vacuo and an implicit solvent method (COSMO) were examined, including simulations of low-energy conformations of each molecule. Analysis of the DFTMD results includes the following: energies averaged over the simulation time, calculated anomeric ratios, hydroxyl and hydroxymethyl rotamer populations, and hydration energies. Hydrogen-bonding networks persistence times were examined, and the effects of solvation on rotamer populations were described. Anomeric ratios calculated from energy optimization of an ensemble of low-energy conformers are compared to those obtained from ensemble averages from molecular dynamics, with dynamics simulations giving populations in best agreement with experimental anomeric ratios. Ensemble results in vacuo were not in agreement with experimental anomeric ratios or hydroxymethyl populations, producing in some cases reversal of the α:β ratios. The difficulty in obtaining correct α:β ratios increases with the number of axial groups; the mono-axial epimers being best represented, epimers with two axial groups being more difficult, and the epimers with three axial hydroxyl groups being most difficult to analyze, the result of a large number of very strong hydrogen-bonding networks that form the ensemble of low-energy conformations in the multi-axial structures.

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1. Introduction

1.1. Background

Glucose and its epimers are important biomolecules involved in a variety of processes such as supporting matrices, conversion to alcohol for energy, molecular recognition processes such as blood group incompatibility, glycoconjugate antibiotics, cell attachment and bonding, viral infections, antitumor agents, and control of many biological functions. In the bio-environment these molecules exist in a water environment, so the influence of solvent on flexibility and conformation must be of interest from a molecular point of view. In this work, structural and thermodynamic properties of the above-noted cyclic 6-carbon aldopyranoses are investigated by both optimization methods and density functional molecular dynamics (DFTMD). Figure 1 shows the conventional numbering system, and Figure 2 shows the different axial/equatorial positions of the hydroxyl groups for the eight epimers. The $^4C_1$ chair conformation of the ring shown in Figure 1 is the lowest energy ring conformation by these DFT calculations applied throughout the epimer series (see Table 1). All epimers have an anomeric site with two different anomeric forms, denoted α:β, which differ only by the orientation (axial or equatorial, respectively, with respect to the ring Fig. 1) of the C1–O1 bond. Hydroxymethyl groups can adopt three orientations associated with the C5–C6 internal rotation, characterized by the dihedral angles O5–C5–C6–O6 and C4–C5–C6–O6, that can be *gauche–gauche* (*gg*), *gauche–trans* (*gt*), or *trans–gauche* (*tg*). Hydroxyl groups are designated as clockwise, 'c', or counterclockwise, 'r', around the ring counting from the C1 atom. The O6–H group is observed to rotate fairly freely, and during dynamics it behaves much like a rotating top.

Experimental evidence[1–14] suggests that the glucose abundance ratio of the axial α anomer with respect to the equatorial β anomer in aqueous solution at room temperature is ~38:62%,[3] corresponding to a free-energy difference of ~0.4 kcal/mol favoring the β anomer. This number could be misleading by suggesting that one conformer of each anomer with this energy difference would be sufficient to give the anomeric ratio. However, there are in all the epimers many low-energy conformations, each with sufficiently low energy that it may contribute to the ensemble energy, and all low-energy conformers must be included in the analysis to obtain a correct anomeric ratio. Using cutting edge DFTMD calculations it is possible to answer important questions such as: What

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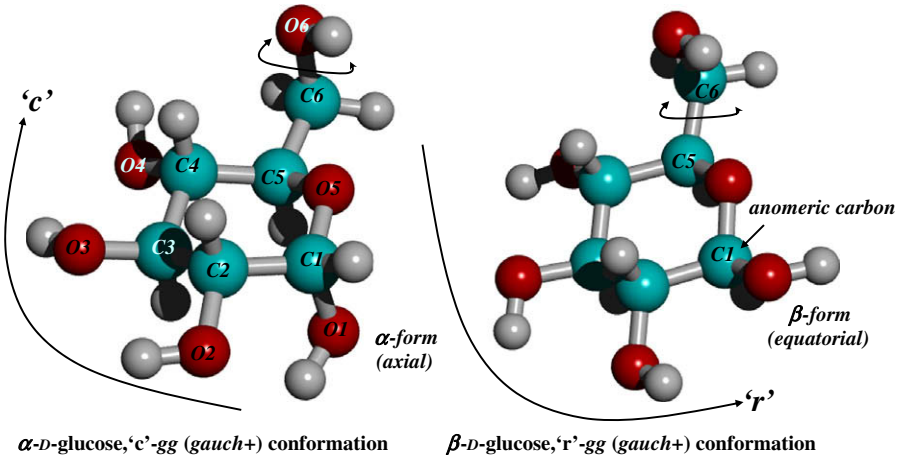

Figure 1. Shown are a ball and stick figures of D-glucose with conventional notions used. Rotation around the C6–O6 bond produces configurations labeled as *gauch+*, *gauch−*, and *trans* with C5–C6–O6–H ∼60°, ∼−60°, and ∼180°, respectively. Rotation around the C5–C5 bond produces configurations labeled as *gg*, *gt*, and *tg* with O5–C5–C6–O6 ∼−60°, ∼+60°, and ∼180°, respectively.

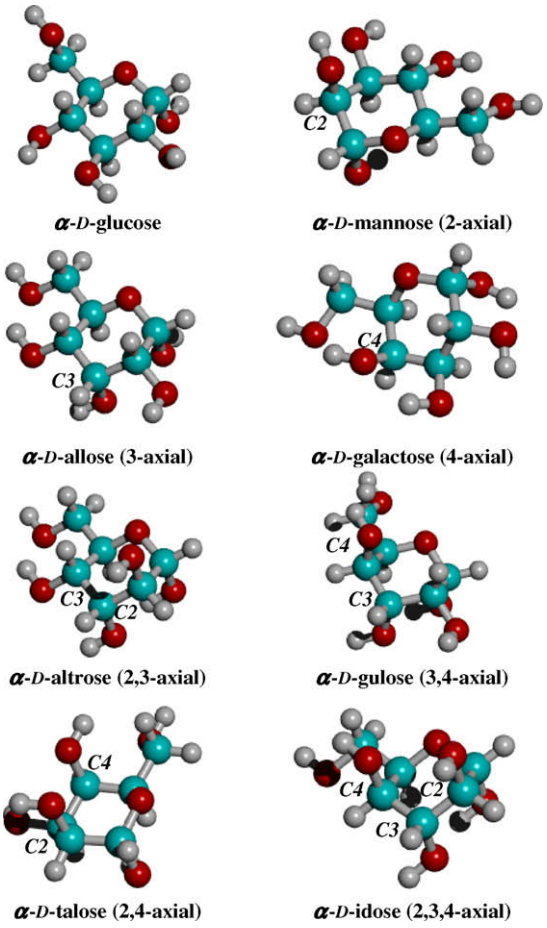

Figure 2. Shown are a ball and stick figures of D-glucose epimers.

is the source of the anomeric ratio in water, is it from the solvent, an entropic contribution, or both? Of further interest is the flexibility of these molecules, and DFTMD gives explicit information on the flexibility and stability of specific conformations in water. Comparing results from vibrational analysis of DFT optimized in vacuo and implicitly solvated structures with the results from the DFTMD, one can find answers to questions concerning the source of the anomeric ratios, rotamer populations, conformational flexibility, and solvent-directed conformational effects.

There have been many experimental NMR and circular dichroism (CD) studies[1–13] and a host of computational studies of glucose and its epimers at various levels of theory.[14–18,11,19–96] Several individual studies will be noted here for background information. Isolated glucose and epimers have been examined computationally starting in the late 1960s and 1970s,[13–18,11,19,20] and computational studies continue to be published today. In most cases, but not all, empirical force-field calculations have been carried out. Quantum mechanical (QM) studies at various levels of theory are also found throughout the literature.[20,24,29,33–35,40,42,43,45,47,48,52,53,56,58–60,63,66,70,72–80,85,86,91–94] Early work generally used energy optimization of several conformers, expanding to a few empirical dynamics simulations of glucose in a box with explicit water molecules, and in later years to quantum optimization of a few conformations. The 'first principle' molecular dynamics study of glucose by the Car–Parrinello method[53,58] was the first to try treating both solute and solvent by quantum methods. In those works the BLYP gradient corrected functional and Troullier–Martins norm-conserving pseudopotentials were utilized. The electronic wave function was expanded in a plane-wave basis set with cutoff criteria. Constant energy dynamics were performed at room temperature for ∼6 ps. The hydroxymethyl group in all studies remained at the starting orientation for ∼3 ps of the simulation, after which it moved to the *tg* conformation and remained there throughout the remaining simulation. As will be seen, this result is not in agreement with the DFTMD studies reported here, nor for that matter, is it agreement with experimental NMR studies.[3]

An earlier QM optimization approach by Polavarapu and Ewing[29] examined only the 'r' glucose conformations, and then only a small subset of low-energy in vacuo structures. This study[29] did not use DFT or solvation methods, and carried out calculations using the 4-31G and 6-31G* basis sets.

Many different empirical molecular dynamics simulations have been carried out, with Brady's work[23] in 1986 being the first in which solvation was included in the dynamics. At that time the force field used was that of Rasmussen and his co-workers.[22] Although this work[23] included both the $^4C_1$ and $^1C_4$ ring structures, today we understand that the $^1C_4$ relative energy is, for the most part, too high to be of interest at room temperature (see Table 1). The favored hydroxymethyl form found in that work was *tg*, and the hydroxyl orientations favored the 'r' form with some rotations to the 'c' form taking place during the ∼20 ps simulation.[23] Some studies found that once the ring transitioned into a boat or skew form, it never returned to the $^4C_1$ form, a result of empirical potentials that were unable to drive the boat structure back to the chair