

QM/MM study of D-fructose in aqueous solution

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Abstract—The QM/MM molecular dynamics methodology was applied to the study of the two main D-fructose tautomers present in aqueous solution, β -D-fructofuranose and β -D-fructopyranose. The solute was treated at the AM1 semi-empirical level, and for the solvent water molecules we used the TIP3P potential. We analyzed the structure of the water molecules around the hydroxyl groups to explain the differences in sweet taste between the two tautomers.

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1. Introduction

The only crystalline form of D-fructose, β -D-fructopyranose,^{1,2} is known to be about twice as sweet as sucrose. However, in aqueous solution, where the two main tautomers present are β -D-fructofuranose and β -D-fructopyranose,^{3–6} sweetness is considerably diminished.⁷ From this observation, one can predict that the furanoid form is substantially less sweet than the pyranoid form, or not sweet at all.⁸

Consequently, interpretation of fructose sweetness is based on the β -pyranoid form. Shallenberger, Acree⁹ and Kier¹⁰ tried to explain the sweet taste via the existence of an AH–B– γ glucophore unit, and several possible glucophores have been proposed in the case of D-fructose. Shallenberger and Lindley¹¹ identified the OH-2–O-1–C-6 glucophore unit. Mathlouthi and Portmann¹² made the inverse assignment: OH-1–O-2–C-6. Birch et al.¹³ concluded at the OH-3–O-4–C-6 or OH-4–O-3–C-6 assignment. Lichtenthaler and Immel¹⁴ arrived at the same conclusion regarding the hydrophilic AH–B part, but the hydrophobic γ part would be an entire region rather than a specific corner, located oppo-

site to the hydrophilic region and reaching from CH₂-1 to CH₂-6 (see Fig. 1). All these assignments are particular cases of the more general multipoint attachment theory proposed by Nofre and Tinti,¹⁵ that assumes the presence of four hydrogen bond acceptor sites.

Fructose theoretical calculations available in the literature concern mainly conformational studies in gas phase, using various levels of approximation.^{16–23} The major role of water–sugar interactions on the sweetness of the most common nutritive sugars has been emphasized by various studies.^{24–29} It is therefore particularly important to consider the solvent explicitly in the calculations. Molecular dynamics simulations using classical force fields have been widely applied to aqueous solutions of different carbohydrates,³⁰ but are scarce for fructose.^{31,32} While classical force fields may be sufficient to represent the solvent, the carbohydrate molecules, which contain highly polarized groups, are not accurately described.³³ This shortcoming is overcome with the use of hybrid quantum mechanics/molecular mechanics (QM/MM) potentials,^{34–38} in which the solute molecule is treated with a quantum mechanical method and the solvent with an empirical potential.

In this study, we applied the QM/MM molecular dynamics methodology in order to get a deeper insight on the behaviour of carbohydrates in aqueous solution.

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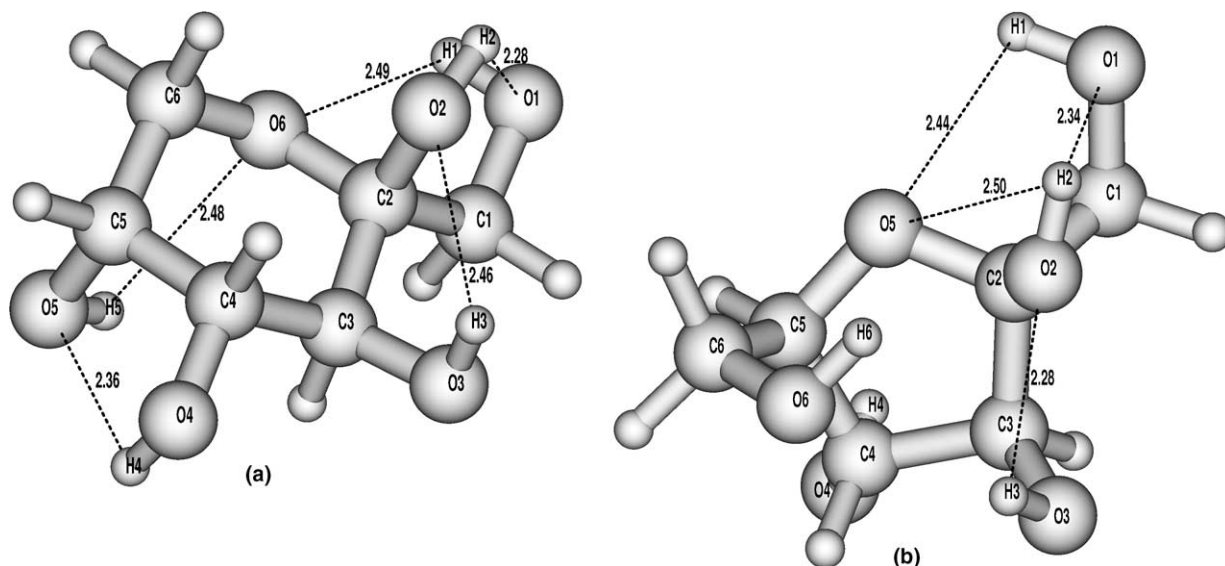


Figure 1. Minimum-energy gas phase AM1 structures of (a) β -D-fructopyranose and (b) β -D-fructofuranose.

We treated β -D-fructofuranose and β -D-fructopyranose quantum mechanically at the AM1 semi-empirical level,^{39,40} which is well adapted to the study of monosaccharides.^{20,21,41} The solvent is composed of TIP3P classical water molecules.⁴² We tried to interpret the differences in sweetness in terms of different behaviours of the two tautomers towards water.

2. Computational methodology

The system is composed of the solute molecule treated quantum mechanically (QM region) at the AM1 semi-empirical level,^{39,40} and 512 water molecules described by molecular mechanics (MM region) using the TIP3P potential.⁴² The whole system is placed inside a cubic box of 25 Å with periodic boundary conditions.

The QM/MM interaction involves an electrostatic term that depends on the QM electrons, and therefore must be included in the HF-SCF iterative procedure. For the electrostatic interaction between the MM atoms and the QM nuclei, we used the AM1 repulsive function for consistency. We used a Lennard–Jones potential for the QM/MM van der Waals contribution with, for the QM atoms, the optimized Lennard–Jones parameters proposed by Gao.⁴³

MD simulations were made in the NVE ensemble. The equations of motion were numerically integrated using the Verlet algorithm for the solute and the quaternion based algorithm of Fincham for the rigid solvent molecules.⁴⁴ The target temperature was 298 K, and velocities were scaled every 200 time steps to avoid small systematic drifts. A smooth truncation function was applied to the solvent–solvent and solute–solvent interactions.⁴⁵

After an equilibration period of 100 ps, the average collection was performed for a period of 500 ps. The

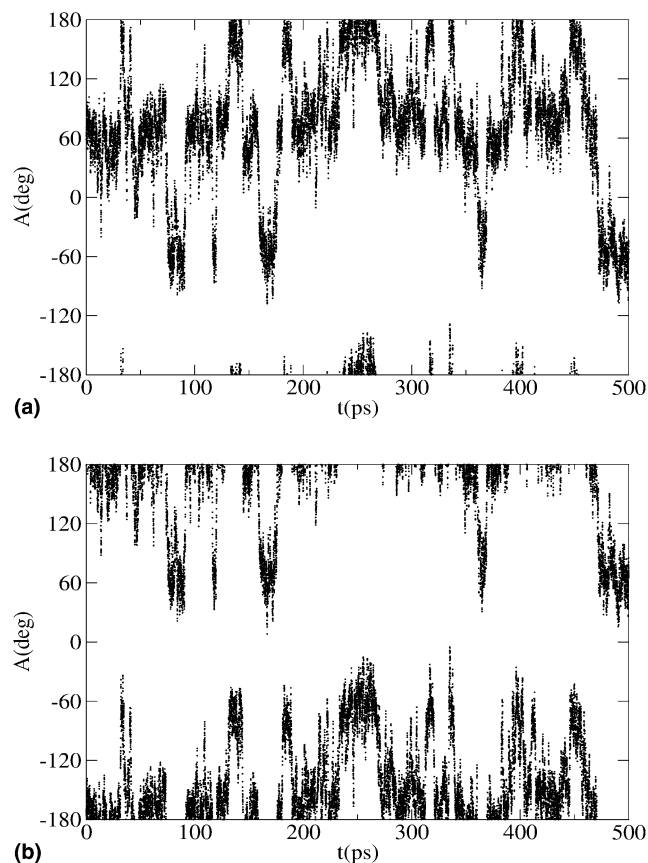


Figure 2. History of the β -D-fructopyranose primary alcohol group orientation in aqueous solution: (a) O-1-C-1-C-2-O-5 and (b) O-1-C-1-C-2-C-3.

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