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DFT study of α- and β-D-mannopyranose at the B3LYP/6-311++G** level

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Abstract—Thirty-five conformations of α- and β-D-mannopyranose, the C-2 substituted epimer of glucopyranose, were geometry optimized using the density functional (B3LYP), and basis set (6-311++G**). Full geometry optimization was performed on the hydroxymethyl rotamers (*gg*/*gt*/*tg*) and an analytical hessian program was used to calculate the harmonic vibrational frequencies, zero point energy, enthalpy, and entropy. The lowest energy conformation investigated is the β-*tg* in the $^4C_1$ chair conformation. The in vacuo calculations showed little energetic preference for either the α or β anomer for mannopyranose in the $^4C_1$ chair conformation. Results are compared to similar glucopyranose calculations in vacuo where the α anomer is ~1 kcal/mol lower in electronic energy than the β anomer. In the case of the generally higher energy $^1C_4$ chair conformations, one low-energy, low-entropy β-*gg*-$^1C_4$ chair conformation was identified that is within ~1.4 kcal/mol of the lowest energy $^4C_1$ conformation of mannopyranose. Other $^1C_4$ chair conformations in our investigation are ~2.9–7.9 kcal/mol higher in overall energy. Many of the $^{3,O}B$, $B_{3,O}$, $^{1,4}B$, and $B_{1,4}$ boat forms passed through transitions without barriers to $^1S_3$, $^5S_1$, $^1S_5$ skew forms with energies between ~3.6 and 8.9 kcal/mol higher in energy than the lowest energy conformation of mannopyranose. Boat forms were found that remained stable upon gradient optimization. As with glucopyranose, the orientation and interaction of the hydroxy groups make a significant contribution to the conformation/energy relationship in vacuo.
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Keywords: B3LYP/6-311++G**; Mannose; Glucose; Chair; Hessian; Relative free energy

1. Introduction

1.1. Background

In this work high-level density functional methods were used to study the conformational preferences of the $^4C_1$ and $^1C_4$ chair conformations as well as boat and skew–boat conformations of α- and β-D-mannopyranose. The purpose of this study is to investigate the effects of epimerization at the C-2 position on the energy/property relationships of carbohydrates, and apply these relationships in the design of new polymers with desired properties. Mannose is also of general interest as a component in biological systems.

To our knowledge, a study of mannopyranose of this scope and at this level has not been reported. Many computational studies on carbohydrates, including glucose and its epimers, or related substructures have appeared in the literature and will not be reviewed in detail in this paper.[1–24] However, work related to our calculations of mannopyranose will be compared with the results presented here.

The interactions and thus the geometries and relative energies among conformers of carbohydrates are known to be very dependent on selection of both the basis set and density functional with DFT calculations.[1–7] Energies obtained from a larger basis set using structures optimized with a smaller basis set do not necessarily correspond with energies and resulting geometries

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optimized with a larger basis set. This inherent discrepancy was shown to lead to significant errors in optimized geometries and energies.[1] Also, differences in relative energies obtained from different basis sets on the same geometry of structures of glucose and its epimers have been reported,[2] and the inclusions of diffuse functions have been found to be important.[3] This dependence has also been reported for structures related to carbohydrates.[8]

DFT studies in this laboratory on glucose[4] in vacuo and monohydrates of glucose,[5] as well as maltose[1] and cellobiose in vacuo[6,7] have shown that the B3LYP/6-311++G** level of theory will give consistently reliable geometries and conformationally dependent energies for carbohydrates. To ensure that this is the case in the work presented here, all structures were geometry optimized at this level of theory (B3LYP/6-311++G**).

The conformational preferences of mannopyranose and its derivatives have been explored experimentally by ^{1}H NMR studies[18,24–26] and X-ray crystal structures.[27–30] The X-ray structure for α-D-mannopyranose showed that the molecule exists in the crystal environment in the $^4C_1$ chair conformation.[29] Hydrogen bonding has been shown to be prevalent in carbohydrate crystal structures with the hydroxy groups acting as both hydrogen bond donors and acceptors.[27–30] It has also been experimentally observed that the hydrogen bond network can form long, cooperative chains, linking the sugar molecules to water molecules when crystal hydrates are studied.[28]

The preference of mannopyranose for the $^4C_1$ chair conformation has also been observed in solution by NMR spectroscopy.[26] The anomeric ratio in solution was found to be 68:32 (α/β) by NMR spectroscopy.[26] This is opposite to the anomeric ratio of glucose in solution, where the β anomer is preferred. An investigation into the rotamer population of pseudo-D-mannose by ^{1}H NMR studies reveal a 50:43:7 *gg*/*gt*/*tg* ratio for the α anomer and a 56:43:2 ratio for the β anomer.[25] The rotamer population of mannopyranose is similar to that of glucopyranose. However, as will be described later, the results reported here suggest stability of the *tg* form in vacuo. Discrepancies like this are not unique to the work presented here; differences between DFT/molecular mechanics and experimental results have been previously observed.[2]

Recent gas-phase studies using UV and IR ion-dip spectroscopy have experimentally supported previous in vacuo DFT and ab initio calculations.[31–33] From a previous study of cellobiose[6,7] at the B3LYP/6-311++G** level of theory, it has been found that the 'flipped' form is preferred in vacuo over the experimentally observed (solvated) 'normal' form. This 'flipped' form has recently been reported to be observed for another disaccharide in the gas phase (a lactoside derivative).[31]

1.2. Computational methodology

Calculations were carried out using the B3LYP nonlocal exchange functionals and the 6-31+G* and 6-311++G** basis sets as previously described.[1,4–7] Calculations were carried out on Parallel Quantum Solutions software and hardware.[34] Preliminary geometry optimizations were carried out at the B3LYP/6-31+G* level, followed by further optimization at the higher level. All results reported here are at the B3LYP/6-311++G** level of theory. Convergence criteria were set at 1×10^{-6} Hartree and a gradient of less than 3×10^{-4} a.u. Vibrational frequencies were calculated on geometry-optimized structures using an analytical hessian program with the threshold set at 1×10^{-3}, which provided consistent zero vibrational energies, enthalpies and entropies. Results have been displayed using HYPERCHEM v7.5.[35]

Several $^4C_1$ chair conformations of mannopyranose have been considered in this study. The hydroxy group orientation in these studies were taken from lower energy vacuum calculations using the AMB02C force field, an in-house AMBER-based empirical energy force field developed using results from our previous DFT calculations on carbohydrates.[20,21] In several cases, soft minimization was used to maintain desired geometries and minimize the empirical bias prior to the DFT calculations. Geometric assignments were made using improper dihedral angles as described previously.[4,22,23]

2. Results

2.1. Conformations

The $^4C_1$ chair conformations have energies within ~2 kcal/mol of each other and a relative free energy of up to ~2 kcal/mol. In contrast, the $^1C_4$ chair conformations are generally higher in energy (~1.4–7.9 kcal/mol) and higher in relative free energy (4.1–8.3 kcal/mol). The stable boat and skew forms evaluated are ~3.6–8.9 kcal/mol higher in energy. The skew forms are the results of transitions without barrier from modeled, unstable boat forms. The $^4C_1$ chair conformations are the preferred conformations, and a relatively extensive conformational analysis was performed on these structures.

2.2. $^4C_1$ Chair

The effects of anomers, rotamer conformations, and the orientation of the hydroxyls (with an emphasis on the C-2 hydroxyl orientation) were the focus in our $^4C_1$ chair investigation (see Tables 1 and 2, and Figs. 1 and 2). As found in the case of glucopyranose, the $^4C_1$ chair conformation is the lowest energy ring conformation for mannopyranose at this level of theory. Epimerization