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

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Abstract—Forty-one conformations of α- and β-D-galactopyranose were geometry optimized using the B3LYP density functional and 6-311++G** basis set. Full geometry optimization was performed on different ring geometries and different hydroxymethyl rotamers (*gg*/*gt*/*tg*). Analytically derived Hessians were used to calculate zero point energy, enthalpy, and entropy. The lowest energy and free-energy conformation found is the α-*gg*-$^4C_1$-c chair conformation, which is of lower electronic and free energy than the lowest energy α-D-glucopyranose conformer because of favorable hydrogen-bonding interactions. The in vacuo calculations showed considerable (~2.2 kcal/mol) energetic preference for the α over the β anomer for galactopyranose in both the $^4C_1$ and $^1C_4$ chair conformations. Results are compared to glucopyranose and mannopyranose calculations in vacuo. Boat and skew-boat forms were found that remained stable upon gradient optimization, although many starting conformations moved to other boat forms upon optimization. As with glucopyranose and mannopyranose, the orientation and interaction of the hydroxyl groups make the most significant contributions to the conformation–energy relationship in vacuo.

Keywords: B3LYP/6-311++G**; Galactose; Chair; Skew-boat; Conformation; Hessian; Relative free energy

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1. Introduction

This work is a continuation of the structural and energetic study of epimers of glucose from this laboratory. High-level density functional (DFT) methods are applied to the structural study of the $^4C_1$ and $^1C_4$ chair conformations as well as boat and skew-boat conformations of α- and β-D-galactopyranose (galactose). The purpose of this study is to investigate the effects of epimerization at the C-4 position on the energy–property relationships of the pyranose carbohydrates and apply these relationships in the design of new carbohydrate polymers with desired properties. Further, galactose is an important component in many biological systems.

A computational study of galactose of this scope and at this level of theory has not been reported although specific $^4C_1$ conformations have been studied at a level of theory similar to that used here.[1–3] Many empirical[1,4–8] and semiempirical[9] computational studies on galactose have appeared in the literature but will not be reviewed in detail as they bear no relationship to the high-level DFT calculations carried out here. Previous DFT calculations from this laboratory on glucose[10] and mannose[11] are briefly compared with the galactose results as are specific experimental studies in which structural or energetic material is presented.

[†] Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may also be suitable.

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The internal coordinates and relative energies among conformers of carbohydrates have been shown to be very dependent on both the basis set (6-311++G**) and the density functional (B3LYP) employed in these calculations.[12–19] Experience with many carbohydrate molecules has shown that energies and conformations obtained from a large basis set do not necessarily correspond closely to geometries optimized with a smaller basis set, even if the large basis set calculations use the smaller basis set geometry as a starting structure. This inherent discrepancy was shown to lead in some cases to significant errors in optimized geometries and energies.[13] Further, differences in relative energies obtained from different basis sets on the same geometry of glucose and its epimers have been reported,[14] and the inclusions of diffuse functions have been found to be very important.[15] Basis set dependence has also been reported for molecular structures related to carbohydrates.[18]

DFT in vacuo studies from this laboratory on glucose,[10] mannose,[11] maltose,[13] cellobiose,[16,17] and mono-[12] and penta-hydrates of glucose,[20] have shown that the B3LYP/6-311++G** level of theory will give consistently reliable geometries, conformations, and energies for carbohydrates. Further, this basis set allows us to study explicit solvation using water molecules, and the smaller basis sets fail in some cases on complexes with water. For this reason, all structures reported here were geometry optimized at the level of theory (B3LYP/6-311++G**) utilized previously.

The conformational preferences of galactose and its derivatives have been explored experimentally by ^{1}H NMR studies[2,21–24] and X-ray crystal structures.[4,6,24–28] The molecule exists in crystals in the $^{4}C_{1}$ chair conformation except in the case of an unusually constrained analog.[24] This analog is of particular structural interest as the experimental observation[24] confirms a $^{\mathrm{O}}S_{2}$ skew-boat conformation. Recently, the gas phase conformations of phenyl-substituted monosaccharides were investigated by means of a combination of mass-selected, ultraviolet and infrared double-resonance hole-burning spectroscopy.[29,30] Galactose was examined both experimentally and with limited ab initio methods.[30]

The α/β anomeric ratio of galactose in solution is reported to be ~32/64%.[28] This ratio is nearly identical to the anomeric ratio of glucose in water where the β anomer is also strongly preferred even though the in vacuo DFT results favored the α anomer.[10] On the other hand, the hydroxymethyl rotamer population[21] (*gg*/*gt*/*tg* = 14/47/39%) of methyl α-D-galactopyranose is not similar to that found for glucose, galactose having a much higher *tg* population than that found in glucose, apparently increasing at the expense of the *gg* state. Other analogs of galactose also show a high *tg* population at the expense of the *gg* conformation and a new vacuum-ultraviolet circular dichroism (VUVCD)[31] study puts the *gg*/*gt*/*tg* hydroxymethyl rotamer population at the ratio of 1:2:1, differing significantly from the NMR results.

2. Computational methodology

Calculations were carried out using the B3LYP nonlocal exchange functionals with optimization using the 6-31+G* and subsequently 6-311++G** basis sets as described previously.[10,11,13,16,17] Calculations were carried out on Parallel Quantum Solutions software and hardware.[32] All results reported here are at the B3LYP/6-311++G** level of theory. Convergence criteria were set at an energy change of less than 1×10^{-6} Hartree and a gradient of less than 3×10^{-4} a.u. Vibrational frequencies (not presented here) were calculated on geometry-optimized structures using an analytical Hessian program with the threshold set at 1×10^{-3}, which provided consistent zero point vibrational energies, enthalpies, and entropies. Results have been displayed using HyperChem v7.5.[33]

Several $^{4}C_{1}$ and $^{1}C_{4}$ conformations of galactose have been considered in this study. The hydroxyl group orientations (clockwise 'c' and counterclockwise 'r') in these studies were taken from lower energy vacuum calculations using the AMB02C force field, an in-house AMBER-based empirical force field developed using results from our previous DFT calculations on carbohydrates.[34,35] In several cases, 'soft minimization' (i.e., minimization with modest convergence criterion) was used to maintain desired geometries and minimize the empirical bias prior to the DFT calculations. Geometric assignments of the boat and skew forms were made using improper dihedral angles and adding dihedral constraints if needed, as described previously.[10,36,37]

3. Results

3.1. Conformations

The $^{4}C_{1}$ conformations have relative electronic energies in the range of 0→6 kcal/mol and a relative free-energy range of 0→5 kcal/mol. In contrast, the $^{1}C_{4}$ conformations are generally higher in relative energy (~6–12 kcal/mol) and similarly higher in relative free energy. The stable boat and skew-boat forms evaluated are ~6–11 kcal/mol higher in energy than the lowest energy $^{4}C_{1}$ conformer. Many boat and skew-boat forms result from transitions without barrier from unstable boat forms. The $^{4}C_{1}$ conformations are the energetically preferred conformations, as found in the glucose[10] and mannose[11] studies. A relatively extensive conformational analysis was performed on these $^{4}C_{1}$ structures.