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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

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 $^4C_1$ 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 $^OS_2$ 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 $^4C_1$ and $^1C_4$ 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 $^4C_1$ 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 $^1C_4$ 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 $^4C_1$ conformer. Many boat and skew-boat forms result from transitions without barrier from unstable boat forms. The $^4C_1$ 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 $^4C_1$ structures.

3.2. $^4C_1$ conformations

Anomeric effects, rotamer conformations, and the orientation of the hydroxyls (with an emphasis on the C-4 hydroxyl orientation) are the focus of the $^4C_1$ investigations (see Tables 1 and 2, and Figs. 1 and 2). In the case of glucopyranose, the α-*gt*-$^4C_1$-r conformation was of lowest energy, while in the galactopyranose structures studied here, the α-*gg*-$^4C_1$-c conformation is the lowest energy conformer. Interestingly, the galactose electronic energy of α-*gg*-$^4C_1$-c is lower than that found for glucose or mannose using the same DFT methods and basis set (−431,354.02 (Gal) vs −431,352.64 (mannose recalculated for β-*gg*-$^4C_1$-c)[30] vs −431,353.43 (Glc)[10] kcal/mol, respectively). The resulting ~0.59 kcal/mol difference in energy favoring galactose over glucose is within the error limits expected from these calculations. When the energy is corrected for $ZPVE$, the energy difference becomes ~0.42 kcal/mol, with galactose remaining favored over glucose. Thus, the C-4 hydroxyl epimer results in a decrease in overall electronic and free energy relative to the lowest energy glucose structure, α-*gt*-$^4C_1$-r. This extra stabilization energy was not observed in the mannose study[11] in which the 2-position hydroxyl group is axial. It is also of interest to examine the energy difference between the lowest energy α anomer and the lowest energy β anomer. The 'c' orientation of exocyclic hydroxyl groups is favored in the α anomer *gg* case and the 'r' orientation is favored in the β anomer *gt* conformer with a free-energy difference of ~1.04 kcal/mol favoring the α anomer.

3.3. $^4C_1$ conformation: orientation of hydroxyl groups and the hydroxymethyl group

The orientation of the hydroxyl groups and their synergistic, non-covalent interactions are the significant factors in relating geometry to energy for the $^4C_1$ conformations. All $^4C_1$ chair structures of galactose, both 'r' and 'c' conformations, contain a chain of HO-4···HO-3···HO-2···HO-1 intramolecular interactions (see Tables 1 and 2 and Figs. 1 and 2) with the *gg* and *tg* forms having further HO-6···O-4 and HO-4···O-6 interactions, respectively. For example in the 'r' form, the lowest energy *gg* rotamers exhibit a ~2 Å hydrogen bond between the HO-6 hydroxymethyl and O-4 resulting in an HO-6···O-4···HO-4···O-3···HO-3···O-2···HO-2···O-1 network of hydrogen bonds. The *tg* rotamers have a longer HO-6···O-4 interaction, ~2.4 Å. The lowest energy conformation of galactopyranose in this investigation, the α-*gg*-$^4C_1$-c conformation, possesses an extensive network of hydrogen

Table 1. B3LYP/6-311++G** energies and geometries for α- and β-$^4C_1$-r chair conformations of D-galactopyranose[a]

	α-*gg*-$^4C_1$-r	α-*gt*-$^4C_1$-r	α-*tg*-$^4C_1$-r	β-*gg*-$^4C_1$-r	β-*gt*-$^4C_1$-r	β-*tg*-$^4C_1$-r
Energy	−431,352.573	−431,353.182	−431,352.458	−431,351.024	−431,151.830	−431,351.202
ΔE	1.450	0.841	1.565	2.999	2.193	2.821
$ZPVE$	124.149	123.992	124.202	123.654	123.561	123.720
ΔE (Corr)	1.319	0.553	1.487	2.373	1.474	2.261
Enthalpy (H)	132.225	132.217	132.386	131.887	131.917	132.042
$H - ZPVE$	8.076	8.225	8.184	8.233	8.356	8.322
Entropy (cal/mol K)	104.847	106.077	106.163	106.013	107.014	107.135
$H - TS$ (298 K)	100.981	100.606	100.749	100.295	100.027	100.116
ΔG^0_{298}	1.247	0.263	1.130	2.110	1.036	1.7528
Hydrogen bonds						
HO-4···O-3	2.224	2.249	2.216	2.195	2.220	2.191
HO-3···O-2	2.433	2.428	2.427	2.401	2.394	2.394
HO-2···O-1	2.263	2.267	2.274	2.526	2.527	2.521
HO-1···O-5	2.619	2.614	2.617	2.439	2.518	2.475
HO-6···O-4	1.980		2.494	1.981		2.450
HO-6···O-5		2.424			2.437	
Bond lengths						
O-1–C-1	1.426	1.423	1.424	1.397	1.397	1.397
C-5–O-5	1.437	1.446	1.442	1.429	1.437	1.433
C-1–O-5	1.401	1.404	1.402	1.415	1.417	1.415
Bond angles						
C-5–O-5–C-1	116.4	116.1	116.8	113.6	113.4	114.0
O-1–C-1–O-5	112.9	112.9	113.1	108.8	109.1	108.9
C-1–C-2–C-3	110.5	110.7	110.3	109.4	109.6	109.2
Improper dihedral angles						
C-4–O-5–C-2–C-1	−30.8	−30.2	−31.6	−37.4	−36.9	−38.4
O-5–C-2–C-4–C-3	−33.3	−33.5	−33.1	−30.2	−30.6	−30.0
C-2–C-4–O-5–C-5	−28.7	−30.4	−26.8	−29.8	−31.1	−27.9

[a] All energies are in kcal/mol unless noted otherwise. All bond lengths are in Å, bond angles in degrees.

Table 2. B3LYP/6-311++G** energies and X-ray and calculated geometries for α- and β-$^4C_1$-c chair conformations of D-galactopyranose[a]

	α-*gg*-$^4C_1$-c	α-*gt*-$^4C_1$-c[b]	α-*tg*-$^4C_1$-c		β-*gg*-$^4C_1$-c	β-*gt*-$^4C_1$-c	β-*tg*-$^4C_1$-c
Energy	−431,354.023	−431,350.214	−431,350.498		−431,351.210	−431,347.624	−431,347.702
Δ*E*	0	3.809	3.525		2.813	6.399	6.321
ZPVE	124.280	123.767	123.948		123.919	123.385	123.567
Δ*E* (Corr)	0	3.296	3.193		2.452	5.504	5.608
Enthalpy (*H*)	132.276	132.060	132.201		132.045	131.807	131.941
$H - ZPVE$	7.996	8.293	8.253		8.126	8.422	8.374
Entropy (cal/mol K)	104.337	106.618	106.539		105.386	107.601	107.359
$H - TS$ (298 K)	101.184	100.288	100.452		100.640	99.742	99.948
ΔG^0_{298}	0	2.913	2.793		2.269	4.957	5.085
Hydrogen bonds							
HO-3···O-4	2.211	2.230	2.198		2.172	2.191	2.160
HO-2···O-3	2.454	2.446	2.435		2.485	2.485	2.475
HO-1···O-2	2.205	2.216	2.236		2.344	2.359	2.328
HO-4···O-6	1.949		2.414		1.931		2.378
HO-6···O-5	2.469	2.363			2.434	2.361	
				X-ray diffraction[c]			
Bond lengths							
O-1–C-1	1.415	1.414	1.417	1.384	1.397	1.397	1.397
O-2–C-2	1.427	1.426	1.427	1.427			
O-3–C-3	1.425	1.424	1.425	1.430			
O-4–C-4	1.426	1.434	1.432	1.429			
O-5–C-1	1.405	1.403	1.401	1.431	1.415	1.412	1.411
O-5–C-5	1.436	1.437	1.432	1.436	1.427	1.427	1.423
O-6–C-6	1.433	1.417	1.434	1.424			
C-1–C-2	1.536	1.537	1.535	1.527			
C-2–C-3	1.532	1.533	1.530	1.519			
C-3–C-4	1.530	1.530	1.529	1.540			
C-4–C-5	1.538	1.536	1.538	1.531			
C-5–C-6	1.524	1.522	1.528	1.520			
Bond angles							
C-1–O-5–C-5	115.3	115.6	116.1	112.6	113.2	113.0	113.3
O-1–C-1–O-5	109.1	109.4	109.6	113.4	105.8	106.0	106.0
O-1–C-1–C-2	111.0	111.0	111.0	108.2			
O-5–C-1–C-2	110.8	110.5	110.4	108.7			
O-2–C-2–C-3	110.9	110.7	110.7	112.4			
O-3–C-3–C-4	112.1	112.3	112.0	109.9			
O-4–C-4–C-5	114.5	114.2	113.3	112.9			
O-5–C-5–C-6	105.6	105.4	104.2	104.3			
O-6–C-6–C-5	112.2	111.9	108.2	107.6			
C-1–C-2–C-3	111.5	111.2	110.8	108.9	110.3	110.0	109.4
C-2–C-3–C-4	110.5	110.7	111.2	109.5			
C-3–C-4–C-5	109.4	109.2	110.1	108.0			
C-4–C-5–O-5	111.9	111.7	113.0	111.0			
Dihedral angles							
C-5–O-5–C-1–C-2	−56.6	−56.9	−56.9				
O-5–C-1–C-2–C-3	53.3	53.5	55.3				
C-1–C-2–C-3–C-4	−52.6	−53.1	−53.5				
Improper dihedral angles							
C-4–O-5–C-2–C-1	−30.9	−31.1	−33.2		−36.9	−37.7	−40.0
O-5–C-2–C-4–C-3	−31.5	−31.9	−31.4		−30.4	−29.8	−29.3
C-2–C-4–O-5–C-5	−32.5	−32.2	−28.3		−30.9	−31.7	−27.9

[a] All energies are in kcal/mol unless noted otherwise. All bond lengths are in Å, bond angles in degrees.

[b] Moving HO-4 to point toward O-5 resulted in an energy for α-*gt*-$^4C_1$(HO-4···O-5)-c of −431,351.115 kcal/mol and for β-*gt*-$^4C_1$(HO-4···O-5)-c an energy of −431,349.163 kcal/mol (not shown in figures).

[c] Ref. 4.

bonding going in the clockwise direction. The axial configuration at the C-4 position in $^4C_1$ clockwise conformations of galactopyranose presents a special case in which the interaction of the HO-4 to O-6 forms a very stable interaction when the hydroxymethyl is in both the *gg* and *tg* conformations. The relative entropies of each ‘r’ and ‘c’ form are also lowest for the *gg* conformers. In the ‘r’ form, the *gt* conformers have a ~0.6 kcal/

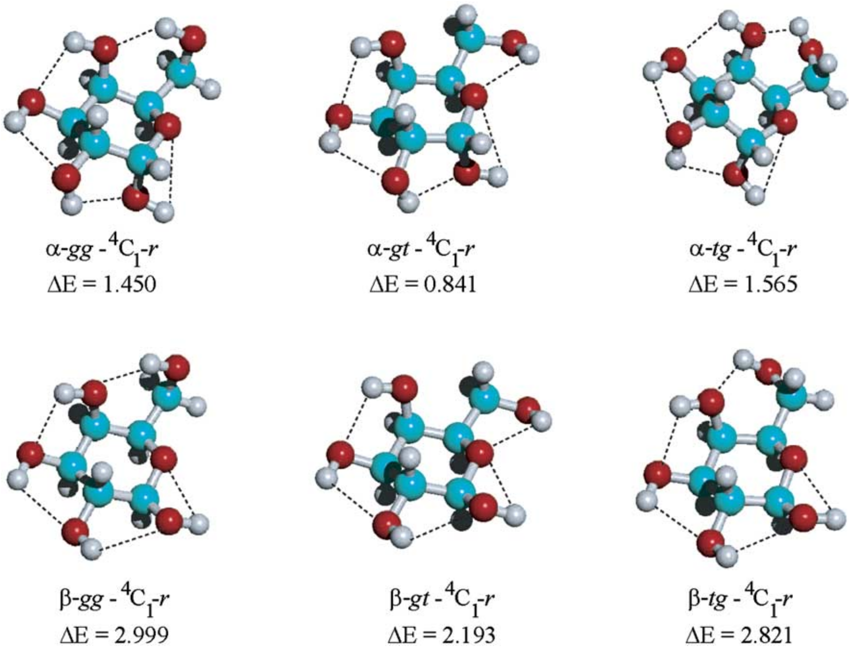


Figure 1. Geometry-optimized α- and β-D-galactopyranose structures in the $^4C_1$-r conformation. All energies are in kcal/mol. Dotted lines represent hydrogen bonds.

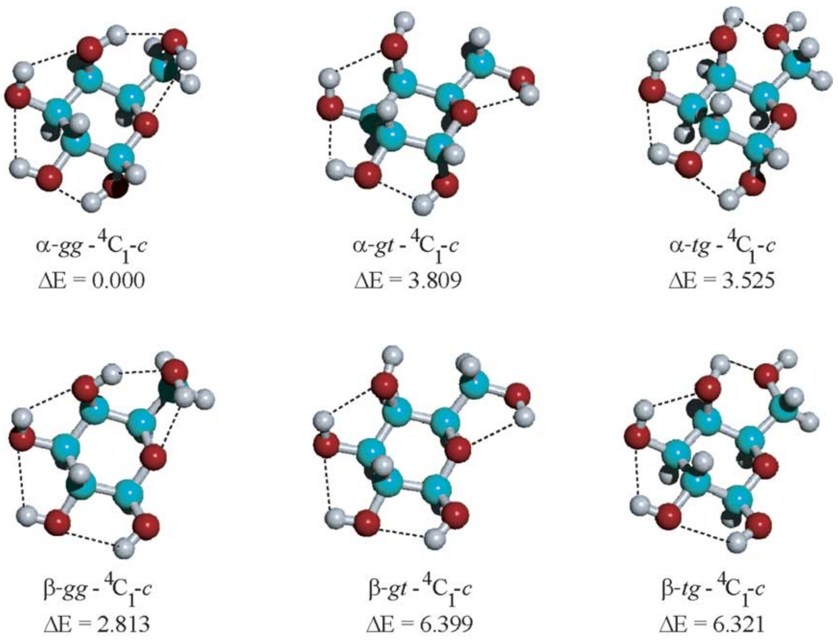


Figure 2. Geometry-optimized α- and β-D-galactopyranose structures in the $^4C_1$-c conformation. All energies are in kcal/mol. Dotted lines represent hydrogen bonds.

mol energy advantage in making the HO-6···O-5 interaction rather than an HO-6···O-4 interaction. This energy advantage is not found in the 'c' form. However, the *gt* conformer does form a stable HO-4···O-5 with the 'c' conformer (see Table 2).

The effect of rotamer conformation on energy also depends on how the HO-6 hydroxymethyl interacts with the $^4C_1$ galactopyranose ring ether. Both rotamers of α-*gt*-$^4C_1$-r and β-*gt*-$^4C_1$-r exhibit a ~2.4 Å hydrogen bond between the HO-6 hydroxymethyl and the O-5 ring ether as do both α- and β-*gg* and *gt* rotamers with 'c' orientation of the hydroxyls. The *gt* rotamers also hydrogen bond between the HO-4···O-5 at ~2.5 Å.

3.4. $^4C_1$ conformation: anomeric influence

Most $^4C_1$ conformations of galactopyranose studied are within ~6 kcal/mol of each other, with the lowest energy α and β anomers of the 'r' form differing by ~2 kcal/mol while the 'c' forms differ by more than ~6 kcal/mol. The position of the H atom on the 1-hydroxyl is of interest in the β anomer 'c' form since it can take on a stable gauche conformation (relative to O-5) rather than the trans form shown in Figure 2. This change in hydroxyl conformation cost ~2 kcal/mol in energy relative to the trans form, a result of clashing lone-pairs between O-2 and O-1. The α anomer is not stable in another 1-hydroxyl conformation reverting to that shown in Figures 1 and 2. The anomeric ratio as calculated from the free energy is predominantly α favored since the two α-*gg*-c and α-*gt*-r conformers are of relatively low energy and β conformers of both 'r' and 'c' have ΔE's of ~2 kcal/mol relative energy. There is an anomeric influence on the C-5–O-5–C-1 bond angle. Most β anomers have a C-5–O-5–C-1 bond angle of ~113°, while most α anomers have a C-5–O-5–C-1 bond angle of ~116°, suggesting that the trans effect is the dominant determinate for this internal coordinate. The O-1–C-1–O-5 bond angle is dependent on the 'r' or 'c' conformation: as the α anomers in the 'r' form have ~113° bond angles while in the 'c' form they are ~109°. Similarly, the β anomers have O-1–C-1–O-5 bond angles of ~109° in the 'r' form compared to ~106° in the 'c' form. This is in agreement with previous calculations.[37]

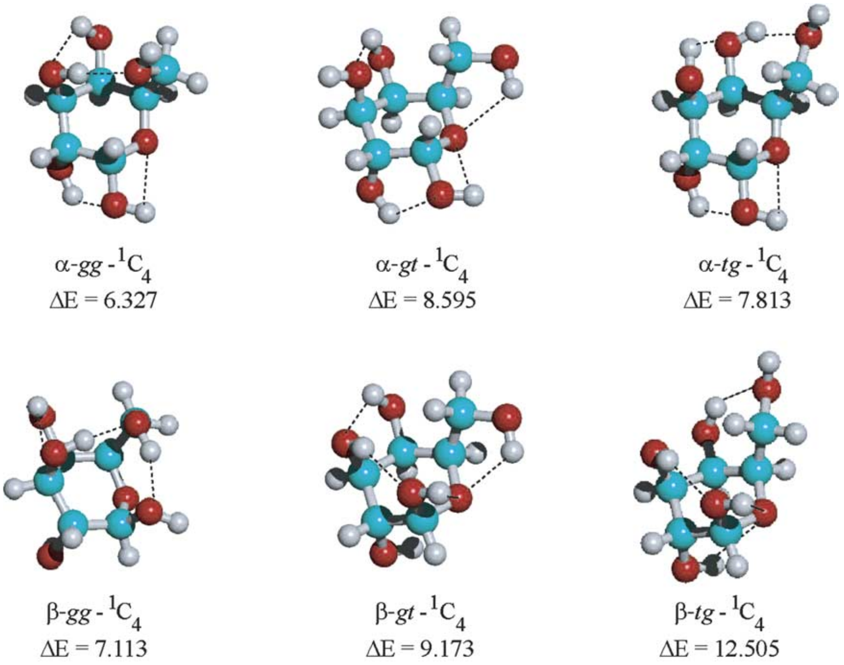
3.5. $^1C_4$ conformation

Transition from the $^4C_1$ conformation to the $^1C_4$ conformation exchanges the positions of the axial and equatorial substituents; the effects of this inversion on galactose can be seen in the more disordered hydroxyl interactions (see Fig. 3 and Table 3). The $^1C_4$ α- and β-*gg* rotamers exhibit short (~1.8 Å) HO-3···O-6 hydrogen bonds. The α-forms of the $^1C_4$ conformations possess ~2.1 Å HO-2···O-1 interactions (see Fig. 3), but this is not found in the β anomers. Ring inversion to the $^1C_4$ form places the hydroxymethyl group in the unfavored axial position, and the resulting energies are larger by ~6 kcal/mol than the lowest energy $^4C_1$ conformation. The shortest hydrogen bond in the β anomer group is the HO-6···O-1 (~1.8 Å) interaction found in the β-*gg*-$^1C_4$ conformation. The electronic and relative free energies of the $^1C_4$ conformations are ~6–12 kcal/mol higher than the lowest electronic and relative free energy $^4C_1$ conformations of galactopyranose.

The $^1C_4$ conformations exhibit an anomeric influence on bond angle with the C-5–O-5–C-1 bond angle of ~116° for the α anomers and ~119° for the β anomers.

3.6. Boat and skew forms

Numerous boat conformers, $^{3,O}B$, $B_{3,O}$, $^{1,4}B$, $B_{1,4}$, $^{2,5}B$, and $B_{2,5}$ were geometry optimized and the energies and geometries of the structures are shown in Tables 4–6 (see Figs. 4–6). Some boat forms were not stable



α-*gg* - $^1C_4$
$\Delta E = 6.327$

α-*gt* - $^1C_4$
$\Delta E = 8.595$

α-*tg* - $^1C_4$
$\Delta E = 7.813$

β-*gg* - $^1C_4$
$\Delta E = 7.113$

β-*gt* - $^1C_4$
$\Delta E = 9.173$

β-*tg* - $^1C_4$
$\Delta E = 12.505$

Figure 3. Geometry-optimized structures of α- and β-D-galactopyranose in the $^1C_4$ conformations listed in Table 3. All energies are in kcal/mol. Dotted lines represent hydrogen bonds.

Table 3. B3LYP/6-311++G** energies and geometries for α- and β-$^1C_4$ chair conformations of D-galactopyranose[a]

	α-*gg*-$^1C_4$	α-*gt*-$^1C_4$	α-*tg*-$^1C_4$	β-*gg*-$^1C_4$	β-*gt*-$^1C_4$	β-*tg*-$^1C_4$
Energy	−431,347.696	−431,345.428	−431,341.518	−431,346.910	−431,344.850	−431,341.518
ΔE	6.327	8.595	12.505	7.113	9.173	12.505
ZPVE	124.213	123.736	123.750	124.859	124.324	123.750
ΔE (Corr)	6.260	8.051	11.975	7.692	9.217	11.975
Enthalpy (H)	132.311	132.120	132.108	132.613	132.434	132.108
$H - ZPVE$	8.098	8.384	8.358	7.754	8.110	8.358
Entropy (cal/mol K)	104.449	107.008	106.285	102.042	105.045	106.286
$H - TS$ (298 K)	101.185	100.232	100.435	102.205	101.131	100.435
ΔG^0_{298}	6.238	7.643	11.756	8.133	9.120	11.756
Hydrogen bonds						
HO-4···O-3	2.201	2.250		2.193	2.180	
HO-2···O-1	2.161	2.186				
HO-1···O-5	2.326	2.317	2.571		2.606	2.571
HO-3···O-6	1.831			1.779		
HO-3···O-1			2.625		1.993	2.039
HO-4···O-6			2.039			1.986
HO-2···O-5			1.986			2.625
HO-6···O-5		2.391		2.773	2.273	
HO-6···O-1				1.835		
Bond lengths						
O-1–C-1	1.405	1.405	1.424	1.433	1.421	1.424
C-5–O-5	1.434	1.449	1.450	1.421	1.464	1.450
C-1–O-5	1.427	1.420	1.415	1.410	1.415	1.415
Bond angles						
C-5–O-5–C-1	116.8	115.9	118.5	119.0	118.7	118.5
O-1–C-1–O-5	106.4	106.9	112.6	112.4	113.4	112.6
C-1–C-2–C-3	111.5	110.5	110.7	115.0	110.5	110.7
Improper dihedral angles						
C-4–O-5–C-2–C-1	27.5	32.9	28.9	22.9	34.3	28.9
O-5–C-2–C-4–C-3	27.7	28.5	33.0	25.5	30.8	34.0
C-2–C-4–O-5–C-5	27.5	29.1	26.1	32.5	20.5	26.3

[a] All energies are in kcal/mol unless noted otherwise. All bond lengths are in Å, bond angles in degrees.

and went through transitions without barrier to skew-boat forms such as $^3S_5$ and $^5S_1$. Further, other skew-boat forms were energy optimized, such as the $^OS_2$ conformers that were described in experimental[24] studies of constrained systems.

3.7. Boat and skew forms: $^{3,O}B$ and $B_{3,O}$ boats

The $^{3,O}B$ conformer is a stable 'hard-boat'-like form relatively high in energy. The $B_{3,O}$ conformers are somewhat lower in energy and are denoted the 'soft-boat' forms. Many galactopyranose boat forms were found to be stable as seen in Tables 4–6 and shown in Figures 4–6. Internal coordinates such as C-5–O-5–C-1 are not easily classified relative to the α and β anomers because of complications resulting from different hydrogen-bonding networks. For example, the α-*gg*-$^{3,O}B$ conformer, the C-5–O-5–C-1 bond angle is 116.0°, while in the *gt* form it is 113.8°; this is a rather large spread in angle when compared to the β anomer in which the values range from 112.0° to 112.5°. In the case of the $B_{3,O}$ conformers (Table 5 and Fig. 5), we find just the reverse with the α anomers fairly constant (±0.7°) and of smaller magnitude than the β-anomers, which vary from 117.7° to 119.7°. The lowest energy boat form is the β-*gg*-$B_{3,O}$ conformer (Fig. 5), which is only ~4 kcal/mol higher in energy than the lowest energy galactopyranose conformation.

Two $^3S_5$ skew-boat conformers are shown with the $^{3,O}B$ structures in Table 4 and Figure 4. In both cases, these skew-boat forms were the result of optimization of a $^{3,O}B$ conformer, with β-*gt*-$^{3,O}B$ going to β-*gt*-$^3S_5$, and β-*tg*-$^{3,O}B$ going to β-*tg*-$^3S_5$ upon minimization.

3.8. Boat and skew forms: $^{1,4}B$ and $B_{1,4}$ boats

In one case, the starting α-*gg*-$^{1,4}B$ boat moved upon optimization to an α-*gg*-$B_{3,O}$ form, as shown in Table 5. One $B_{1,4}$ boat conformer was stable, and this conformer is noted in Table 6 and is described particularly by the improper dihedral angles. In general, these are high-energy conformations stabilized by specific hydrogen bonds as shown in Figure 6.

Table 4. B3LYP/6-311++G** energies and geometries for α- and β-$^{3,O}B$ boat and $^{3}S_5$ skew-boat conformations of D-galactopyranose[a]

	α-*gg*-$^{3,O}B$ (α-*gg*-$^{O}S_2$)[b]	α-*gg*-$^{3,O}B$ (α-*gg*-$^{O}S_2$) (α-*gg*-$B_{2,5}$)	α-*gt*-$^{3,O}B$	α-*tg*-$^{3,O}B$	β-*gg*-$^{3,O}B$	β-*gg*-$^{3,O}B$[c] (β-*gg*-$^{O}S_2$)	β-*gt*-$^{3}S_5$ (β-*gt*-$^{3,O}B$)	β-*tg*-$^{3}S_5$ (β-*tg*-$^{3,O}B$)
Energy	−431,344.933	−431,346.505	−431,346.247	−431,347.204	−431,343.374	−431,344.316	−431,344.098	−431,345.120
ΔE	9.090	7.518	7.776	6.819	10.649	9.707	9.925	8.903
ZPVE	123.982	124.498	124.155	124.564	123.735	124.156	123.682	124.172
ΔE (Corr)	8.792	7.736	7.651	7.103	10.104	9.583	9.327	8.795
Enthalpy (H)	132.238	132.440	132.311	132.537	131.982	132.223	132.055	132.307
$H - ZPVE$	8.256	7.942	8.156	7.973	8.247	8.067	8.373	8.135
Entropy (cal/mol K)	106.615	104.186	105.827	104.376	106.333	105.815	109.106	106.836
$H - TS$ (298 K)	100.467	101.288	100.775	101.433	100.295	100.584	99.541	100.469
ΔG^{0}_{298}	8.373	7.622	7.367	7.068	9.760	9.107	8.282	8.189
Hydrogen bonds								
HO-4···O-3		2.046	2.093	2.107	3.046	1.919	2.058	2.098
HO-2···O-1	2.062	2.060	2.056	2.048	2.929			
HO-1···O-5	2.570	2.550	2.556	2.551	2.456	2.324	2.414	2.410
HO-3···O-5	2.223	2.260	2.239	2.218	2.583		2.307	2.197
HO-3···O-1						2.002	2.538	2.793
HO-4···O-6	2.339							
HO-6···O-4		2.003		2.464	2.125	1.971		2.109
HO-6···O-5	2.452		1.971				2.459	
Bond lengths								
O-1–C-1	1.413	1.414	1.411	1.412	1.395	1.421	1.401	1.397
C-5–O-5	1.454	1.450	1.460	1.453	1.435	1.442	1.453	1.445
C-1–O-5	1.415	1.412	1.415	1.413	1.421	1.407	1.423	1.425
Bond angles								
C-5–O-5–C-1	116.0	113.6	113.8	114.3	112.3	116.5	112.5	112.0
O-1–C-1–O-5	112.3	112.6	112.7	112.6	109.0	107.2	107.4	107.6
C-1–C-2–C-3	109.0	109.0	109.1	109.0	110.9	109.8	110.2	110.3
Improper dihedral angles								
C-4–O-5–C-2–C-1	−13.1	−9.5	−10.2	−11.7	−56.5	8.1	−14.2	−23.5
O-5–C-2–C-4–C-3	64.8	61.1	62.0	62.8	57.5	48.7	60.8	53.2
C-2–C-4–O-5–C-5	−43.7	−53.6	−52.4	−50.0	−11.4	−56.8	−52.7	56.2

[a] All energies are in kcal/mol unless noted otherwise. All bond lengths are in Å, bond angles in degrees.

[b] Conformation in parenthesis is the starting conformation, which upon energy optimization moved to the top form shown.

[c] Conformation similar to previous conformer but with HO-3 pointing toward O-1.

Table 5. B3LYP/6-311++G** energies and geometries for α- and β-$B_{3,O}$ boat conformations of D-galactopyranose[a]

	α-*gg*-$B_{3,O}$	α-*gg*-$B_{3,O}$ (α-*gg*-$^{1,4}B$)[b]	α-*gt*-$B_{3,O}$	α-*tg*-$B_{3,O}$	β-*gg*-$B_{3,O}$	β-*gt*-$B_{3,O}$	β-*tg*-$B_{3,O}$
Energy	−431,346.537	−431,343.496	−431,345.416	−431,345.873	−431,350.034	−431,345.074	−431,347.013
ΔE	7.486	10.527	8.607	8.150	3.989	8.949	7.010
ZPVE	123.794	123.974	123.380	123.789	125.012	124.074	124.266
ΔE (Corr)	7.000	10.221	7.707	7.659	4.731	8.746	6.996
Enthalpy (*H*)	132.072	132.132	131.896	132.145	132.732	132.197	132.399
$H - ZPVE$	8.278	8.158	8.516	8.356	7.720	8.123	8.133
Entropy (cal/mol K)	107.015	106.243	109.167	107.658	101.904	105.450	106.176
$H - TS$ (298 K)	100.182	100.365	99.634	100.063	102.263	101.926	100.759
ΔG^0_{298}	6.484	9.708	6.787	7.029	5.079	8.126	6.585
Hydrogen bonds							
HO-4···O-3	2.331	2.321	2.367	2.335	2.144	2.051	2.101
HO-3···O-2	2.846	2.995	2.896	2.852	2.293	2.265	2.265
HO-2···O-1	2.047		2.074	2.060	3.036	2.895	2.947
HO-2···O-5		2.863					
HO-1···O-2		2.109					
HO-1···O-5	2.402		2.399	2.341	2.558	2.365	2.555
HO-1···O-6					1.911	1.941	
HO-6···O-4	2.000	2.002		2.243	2.011		2.057
HO-6···O-5			2.411			2.745	
Bond lengths							
O-1–C-1	1.399	1.381	1.400	1.401	1.399	1.406	1.415
C-5–O-5	1.437	1.435	1.450	1.442	1.435	1.436	1.444
C-1–O-5	1.421	1.437	1.422	1.419	1.425	1.422	1.412
Bond angles							
C-5–O-5–C-1	114.7	113.9	114.6	114.1	119.7	117.7	119.0
O-1–C-1–O-5	107.8	109.3	108.0	107.9	113.7	112.6	113.1
C-1–C-2–C-3	110.1	111.2	110.4	109.9	110.4	108.7	108.8
Improper dihedral angles							
C-4–O-5–C-2–C-1	56.7	61.5	58.4	57.2	13.3	0.0	6.2
O-5–C-2–C-4–C-3	−54.0	−51.3	−51.9	−53.8	−64.0	−60.2	−63.2
C-2–C-4–O-5–C-5	0.0	−1.6	−5.4	0.7	37.3	52.1	42.2

[a] All energies are in kcal/mol unless noted otherwise. All bond lengths are in Å, bond angles in degrees.

[b] Conformation in parenthesis is the starting conformation, which upon energy optimization moved to the top form show.

3.9. Boat and skew forms: $^{2,5}B$ and $B_{2,5}$ boats

These boat forms are of high energy but are stable in the β-*gg* conformation, undergoing transitions to other conformations when started in the *gt* and *tg* forms or in α configurations. Two stable conformers that did not undergo transitions to other conformations are presented in Table 6 and Figure 6.

3.10. Boat and skew forms: $^{O}S_2$ skew form

Three α-*gg*-$^{O}S_2$ skew forms all moved during optimization without barrier to the α-$^{3,O}B$ boat forms. We found no stable $^{O}S_2$ forms for vacuum galactose at our level of theory, although under some severe analog conditions these conformers appear experimentally. Roslund et al.[24] reported that using the DFT B3LYP/6-31G*, a stable $^{O}S_2$ conformation was obtained for a chemically constrained cyclic analog of galactose. In that case the molecule was designed such that there was no possibility of a conformational change upon geometry optimization.

4. Conclusions

Results from this study of galactose conformers can be compared with similar calculations on energetically stable forms of glucose and mannose studied at the same level of theory. It is of interest that the electronic energy of the galactose conformation, α-*gg*-$^4C_1$-c, is lower than that of the lowest energy glucose conformation. This is of course a result of a selective network of hydrogen-bonding interactions, which are not in competition with water during these calculations, and thus would not be experimentally functional in solution. The classical argument that suggests that substituting an axial substituent for an equatorial substituent will make the molecular enthalpy higher in cyclic molecules is only true when one cannot compensate for this increase in energy through extra hydrogen bonding, as found in this case.

The relative free-energy profiles of the α-$^4C_1$ conformations suggest that the α-*gg*-c conformation is lowest in energy, with α-*gt*-r next at ~0.3 kcal/mol, and the α-*tg*-r hydroxymethyl conformation third at ~1.1 kcal/

Table 6. B3LYP/6-311++G** energies and geometries for α- and β-$^{1,4}B$, $B^{1,4}$, $^{2,5}B$, $B^{2,5}$ and $^5S_1$ boat conformations of D-galactopyranose[a]

	β-*gg*-$^{1,4}B$	β-*tg*-$^{1,4}B$ (β-*gg*-$^{2,5}B$)[b]	β-*gg*-$B_{1,4}$	β-*gg*-$^{2,5}B$ (β-*gg*-$^{1,4}B$)	β-*gg*$^{2,5}B$	α-*gg*-$^5S_1$ (α-*gg*-$^{2,5}B$)
Energy	−431,341.017	−431,347.010	−431,346.241	−431,345.105	−431,345.110	−431,345.377
ΔE	13.006	6.923	7.782	8.918	8.909	8.646
$ZPVE$	123.939	124.264	124.252	124.995	125.032	124.275
ΔE (Corr)	12.665	6.997	7.754	9.633	9.665	8.641
Enthalpy (H)	132.150	132.395	132.308	132.613	132.640	132.384
$H - ZPVE$	8.211	8.131	8.056	7.618	7.608	8.109
Entropy (cal/mol K)	105.755	106.103	106.320	102.077	101.963	104.619
$H - TS$ (298 K)	100.635	100.695	100.625	102.194	102.255	101.208
ΔG^0_{298}	12.458	6.524	7.224	9.929	9.984	8.670
Hydrogen bonds						
HO-4···O-3	2.089	2.104	2.141	1.894	1.895	2.293
HO-2···O-1		2.955	2.514			
HO-2···O-3	2.468					
HO-2···O-5				2.234	2.236	
HO-1···O-2	2.749					
HO-1···O-5		2.558	2.493			2.580
HO-3···O-1				1.940	1.940	
HO-3···O-2		2.267				3.090
HO-1···O-6				1.913	1.913	
HO-6···O-3						1.985
HO-6···O-4		2.059		2.110	2.112	
HO-6···O-1	1.950					
HO-6···O-5			2.408			
Bond lengths						
O-1–C-1	1.432	1.415	1.399	1.418	1.418	1.430
C-5–O-5	1.447	1.444	1.445	1.454	1.454	1.449
C-1–O-5	1.395	1.412	1.424	1.408	1.408	1.401
Bond angles						
C-5–O-5–C-1	119.5	113.1	116.7	118.9	118.9	119.6
O-1–C-1–O-5	108.7	119.0	107.7	113.2	113.2	112.7
C-1–C-2–C-3	108.3	108.8	112.4	109.2	109.2	111.7
Improper dihedral angles						
C-4–O-5–C-2–C-1	−0.4	6.4	−63.5	−52.6	−52.5	−54.6
O-5–C-2–C-4–C-3	−59.6	−63.2	29.2	16.1	17.1	7.2
C-2–C-4–O-5–C-5	47.3	42.1	22.0	−6.9	−6.7	44.0

[a] All energies are in kcal/mol unless noted otherwise. All bond lengths are in Å, bond angles in degrees.

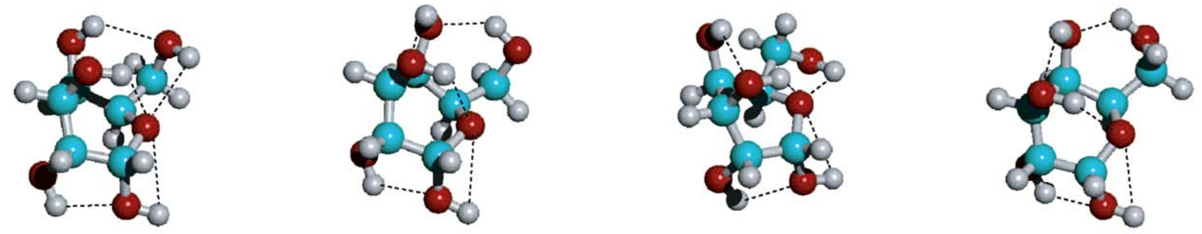
[b] Conformation in parenthesis is the starting conformation, which upon energy optimization moved to the top form shown.

mol. Of the β anomers, only the β-*gt*-r form is of low relative energy, and it is ~1 kcal/mol higher than the best α anomer. This favored β anomer appears to be in agreement with experimental infrared data.[29,30] From this one could assume that the α anomers will be preferred in solution, which is just the opposite of the observed solution populations (α/β = 32/64%). This is very similar to the glucose case where we also found that the DFT energy strongly favored the α-anomeric form over the β-form, and the opposite was found in solution experimentally. The clockwise orientation of the exocyclic hydroxyl groups is favored for some hydroxymethyl orientations but again depends upon the hydrogen-bonding network available.

The $^1C_4$ conformations are all of high energy with the *tg* forms being higher in energy than the *gg* and *gt* conformations for both α- and β-anomers.

The $^{3,\mathrm{O}}B$ boats are all of relatively high energy, as are the $^3S_5$ skew-boat conformers (see Table 4). The relative free-energy values span from 7 to 9 kcal/mol with little differences between the entropy or H-TS values for the different stable $^{3,\mathrm{O}}B$ boat forms. Similar energy values were found for $^3S_5$ conformations. Somewhat surprising was the observation that the β-*gg*-$B_{3,\mathrm{O}}$ conformation was only ~4 kcal/mol higher in energy than the lowest energy chair form. This was the only medium-energy conformation of a boat form found, with none of the other stable $B_{3,\mathrm{O}}$ conformers even close to this value. Of interest is the relative free energy of this conformer, which increases to ~5 kcal/mol, suggesting an unfavorable entropy contribution, as is observed in Table 5.

In this high-level DFT study, intramolecular interactions, including hydrogen bonding and cooperative hydrogen bonding, are significant factors in determining relative energies and ring geometries in vacuo. These strong interactions make finding all possible low-energy rotamers very difficult since there are many possible ways to orientate the hydroxyl groups. We have previ-

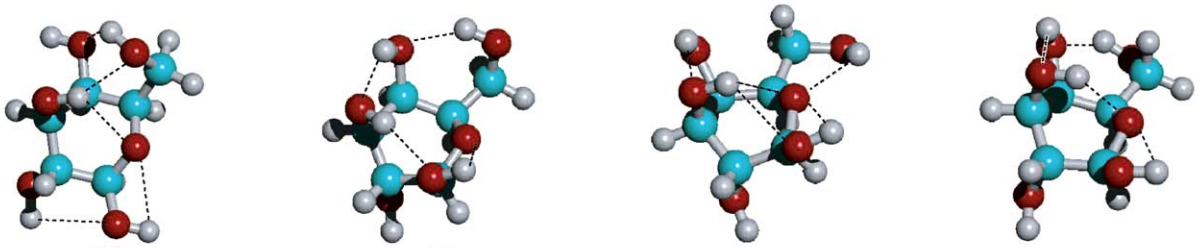


α-*gg* -$^{3,\mathrm{O}}$B
$\Delta E = 9.090$

α-*gg* -$^{3,\mathrm{O}}$B
$\Delta E = 7.518$

α-*gt* -$^{3,\mathrm{O}}$B
$\Delta E = 7.776$

α-*tg* -$^{3,\mathrm{O}}$B
$\Delta E = 6.819$



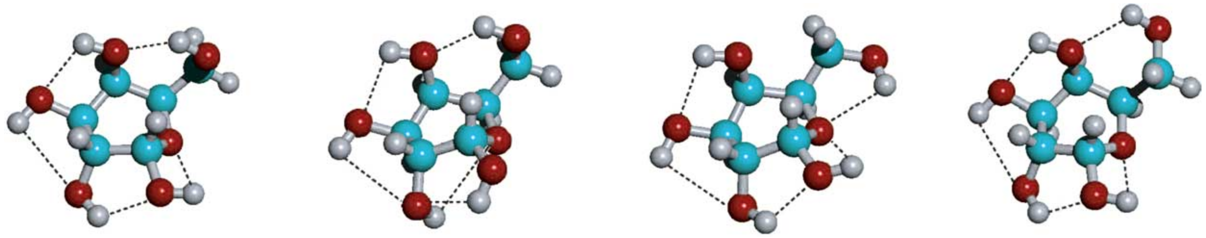
β-*gg* -$^{3,\mathrm{O}}$B
$\Delta E = 10.649$

β-*gg* -$^{3,\mathrm{O}}$B
$\Delta E = 9.707$

β-*gt* -$^{3}S_{5}$
$\Delta E = 9.925$

β-*tg* -$^{3}S_{5}$
$\Delta E = 8.903$

Figure 4. Geometry-optimized structures of α- and β-D-galactopyranose listed in Table 4. All energies are in kcal/mol. Dotted lines represent hydrogen bonds.

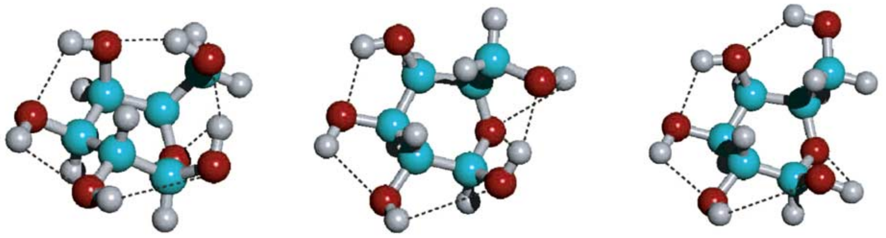


α-*gg* - $B_{3,\mathrm{O}}$
$\Delta E = 7.486$

α-*gg* - $B_{3,\mathrm{O}}$
$\Delta E = 10.527$

α-*gt* - $B_{3,\mathrm{O}}$
$\Delta E = 8.607$

α-tg - $B_{3,\mathrm{O}}$
$\Delta E = 8.150$



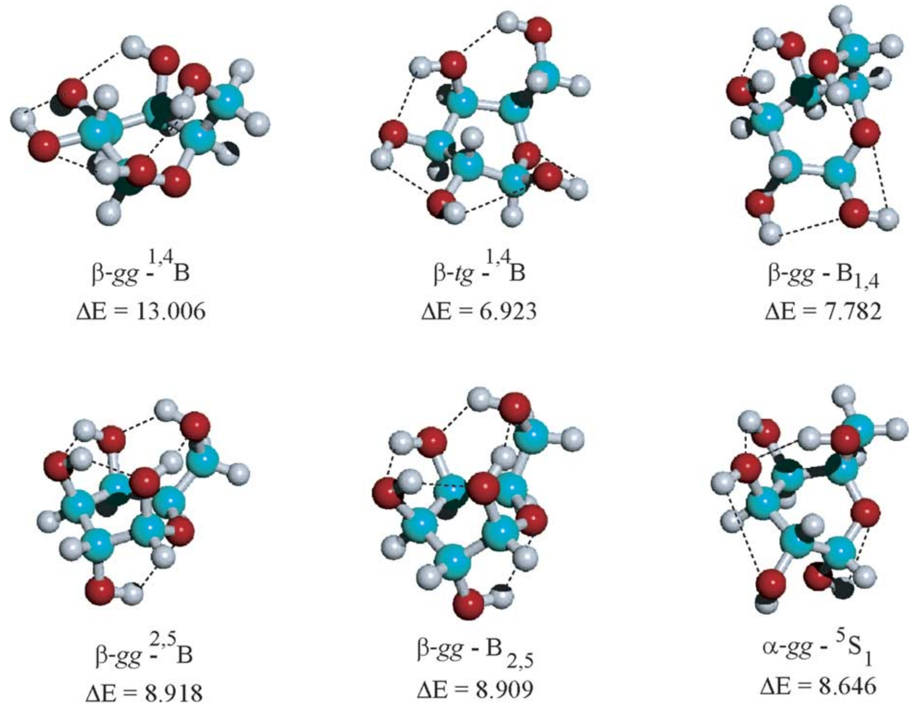
β-*gg* - $B_{3,\mathrm{O}}$
$\Delta E = 3.989$

β-*gt* - $B_{3,\mathrm{O}}$
$\Delta E = 8.949$

β-*tg* - $B_{3,\mathrm{O}}$
$\Delta E = 7.010$

Figure 5. Geometry-optimized structures of α- and β-D-galactopyranose listed in Table 5. All energies are in kcal/mol. Dotted lines represent hydrogen bonds.

ously noted that discrepancies between anomeric ratio and rotamer preferences between these calculations and experimental results may be explained by hydration effects, where water may act as an explicit hydrogen-bond donor or acceptor in many positions. Water acting as both a hydrogen-bond donor and acceptor has been observed in X-ray crystal structures of carbohydrates.[28] Explicit monohydrate calculations have also been



β-*gg* - ^{1,4}B ΔE = 13.006

β-*tg* - ^{1,4}B ΔE = 6.923

β-*gg* - $B_{1,4}$ ΔE = 7.782

β-*gg* - ^{2,5}B ΔE = 8.918

β-*gg* - $B_{2,5}$ ΔE = 8.909

α-*gg* - $^5S_1$ ΔE = 8.646

Figure 6. Additional geometry-optimized boat and twist-boat structures from Table 6. All energies are in kcal/mol. Dotted lines represent hydrogen bonds.

reported to account for similar discrepancies in the anomeric ratio for glucopyranose,[12] and more importantly, when five explicit water molecules were placed around glucose and optimized as described here, the anomeric ratio calculated, using the energy differences, became β-anomer favored.[20]

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