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B3LYP/6-311++G** study of α- and β-D-glucopyranose and 1,5-anhydro-D-glucitol: $^4C_1$ and $^1C_4$ chairs, $^{3,O}B$ and $B_{3,O}$ boats, and skew-boat conformations

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Abstract—Geometry optimization, at the B3LYP/6-311++G** level of theory, was carried out on $^4C_1$ and $^1C_4$ chairs, $^{3,O}B$ and $B_{3,O}$ boats, and skew-boat conformations of α- and β-D-glucopyranose. Similar calculations on 1,5-anhydro-D-glucitol allowed examination of the effect of removal of the 1-hydroxy group on the energy preference of the hydroxymethyl rotamers. Stable minimum energy boat conformers of glucose were found, as were stable skew boats, all having energies ranging from ~4–15 kcal/mol above the global energy $^4C_1$ chair conformation. The $^1C_4$ chair electronic energies were ~5–10 kcal/mol higher than the $^4C_1$ chair, with the $^1C_4$ α-anomers being lower in energy than the β-anomers. Zero-point energy, enthalpy, entropy, and relative Gibbs free energies are reported at the harmonic level of theory. The α-anomer $^4C_1$ chair conformations were found to be ~1 kcal/mol lower in electronic energy than the β-anomers. The hydroxymethyl *gt* conformation was of lowest electronic energy for both the α- and β-anomers. The glucose α/β anomer ratio calculated from the relative free energies is 63/37%. From a numerical Hessian calculation, the *tg* conformations were found to be ~0.4–0.7 kcal/mol higher in relative free energy than the *gg* or *gt* conformers. Transition-state barriers to rotation about the C-5–C-6 bond were calculated for each glucose anomer with resulting barriers to rotation of ~3.7–5.8 kcal/mol. No energy barrier was found for the path between the α-*gt* and α-*gg* $B_{3,O}$ boat forms and the equivalent $^4C_1$ chair conformations. The α-*tg* conformation has an energy minimum in the $^1S_3$ twist form. Other boat and skew-boat forms are described. The β -anomer boats retained their starting conformations, with the exception of the β-*tg*-$^{3,O}B$ boat that moved to a skew form upon optimization.
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Keywords: B3LYP/6-311++G**; Glucose; Boat; Skew; Transition state; Relative free energy

1. Introduction

The purpose of this study is to provide high level theoretical results that can reliably define conformationally dependent geometries and energies for the minimum-energy and transition-state conformations of glucose. Density functional methods were used to study the energetics and conformational preferences of the $^4C_1$ and $^1C_4$ chair conformations, as well as boat and skew-boat conformations of α- and β-D-glucopyranose. Further, 1,5-anhydro-D-glucitol was studied in order to observe the effect on the hydroxymethyl rotational states upon removal of the hydroxyl group at the one position. Two boat conformations ($^{3,O}B$ and $B_{3,O}$) and skew-boat forms of α- and β-D-glucopyranose were studied in order to obtain accurate energy and geometry values for these high-energy or energy-stressed conformations. Transition-state maxima associated with torsional rotation about the exocyclic hydroxymethyl group were also calculated for glucose $^4C_1$ chair conformations.

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† 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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Recent studies in this laboratory using the B3LYP/6-311++G** density functionals (DFT) on the disaccharides maltose[1] and cellobiose[2,3] have led us to believe that this level of theory will give consistently reliable conformationally dependent geometries and energies for carbohydrates, the interactions of which are very basis set dependent.

There is considerable ab initio and density functional literature on α- and β-D-glucopyranose[4–17]. Many of these studies are calculations in which small basis sets were applied to carbohydrates (i.e., semi-empirical, HF/4-31G, HF/6-31G*),[4–10,12,16,17] or the geometry results of smaller basis sets have been used to get energies at larger basis sets without further geometry optimization using the larger basis sets[12,14,15]. This latter methodology was found[1] to be misleading, suggesting in some cases incorrect and fundamentally flawed conclusions. Several previous studies did include correlation at the MP2/6-31G*,[11,13] and B3LYP/6-31G**[14] level of theory and some results of these studies will be compared with the work presented here.

The α- and β-D-glucopyranose anomers are of importance in the understanding of carbohydrates, and there are a number of important questions yet to be fully answered regarding this simple carbohydrate. One question of interest is the observed hydroxymethyl rotamer population found in solution and its relationship with the empirical vacuum conformational energies derived using our DFT methods. NMR studies[16] give relative *gg*/*gt*/*tg* solution populations of approximately 56/44/0% in favor of the *gg* form for the α-anomer, and a ratio of 53/45/2% for the β-anomer, relatively independently of the solvent. Recent DFT results,[1–3] as well as the results presented here, suggest that the relative electronic energy differences between the three hydroxymethyl conformations for a particular anomer are quite small. We found previously[1–3] that the *tg* conformation is entropically less favored than the *gg* and *gt* forms. Other authors[6–8,10,13] have suggested that solvent may favor *gg* and *gt* conformers nearly equally, and disfavor the *tg* conformation.

The MP2/6-31G* ab initio work of Brown and Wladkowski[11] and Wladkowski et al.[13] described a rotational barrier of ~6.8–6.9 kcal/mol between the *gg* and *gt* conformations of both the α- and β-D-glucopyranose, while the torsional barrier between the *gt* and *tg* conformations and between *gg* and *tg* was reported as ~4.7–5.5 kcal/mol, and ~3.6–3.8 kcal/mol, respectively. The electronic energy differences between gas-phase minima calculated at the MP2/6-31G*[11,13] level of theory gave preference to the hydroxymethyl conformations in the electronic energy sequence $gg < tg < gt$ for both anomers, although upon addition of solvation using continuum methods or corrections for relative free energy, the preferred series became $gg < gt < tg$, in agreement with experimental expectations.

Another attempt to bring light to this subject was the work of Cramer, Truhlar, and other authors[6–8] who examined aqueous solvation effects for glucose using the AM1-SM2, PM3-SM3, and AM1-SM1 solvation free-energy methods. These authors found[6–8] that there is little electronic energy difference between the three conformers for rotation around the C-5–C-6 bond, although with the addition of the solvation terms the energetic preference favors *gg* and *gt* over *tg*. These studies,[6–8] and those noted above,[10,12] strongly suggested that solvent plays a major role in dictating the conformational preference for *gg* and *gt*. None of the above studies included explicit water molecules.

Finally, several specific ab initio studies are noted. Melberg et al.,[4] Polavarapu and Ewig,[5] and Jebber et al.[16] carried out ab initio studies using small basis sets (e.g., 3-21G,[16] and 4-31G[4]) at the Hartree Fock level with some energies calculated at the 6-31G* level[5,16] on several conformations of glucose. From the 4-31G calculations,[5] the α-anomer energy was lower than the β-anomer by ~2 kcal/mol, and upon calculation of the free energy at the 6-31G* level, the α-anomer remained ~0.4 kcal/mol lower in energy. The *tg* conformation was again found to be most stable with the *gg* conformer next in energy. The energy of the *tg* conformation was also the lowest energy form found using B3LYP/6-31G* calculations[15] again possibly indicating a lack of diffuse functions, or a problem with the combination of the 6-31G* basis set and the density functional B3LYP. However, upon calculation of the free energy,[4] the order changed making the *gg* conformation the lowest free-energy state, *tg* second and *gt* highest in energy.

In 1995, Barrows et al.[7] calculated several hydroxymethyl conformations for the two chair forms of β-D-glucose at different levels of theory. The highest basis set level used was an MP2/cc-pVTZ calculation with resulting zero point vibrational energy (ZPVE), enthalpy, and entropy obtained from unscaled HF/6-31G* harmonic frequencies[7]. Their comparison of the two chair forms[7] concluded that the stability of the $^4C_1$ ring conformation over the $^1C_4$ form was ~8 kcal/mol in consensus free energy. Their calculations[7] at the MP2/cc–pVTZ//MP2/cc–pVDZ level of theory gave a value of ~3–4 kcal/mol for the electronic energy difference. Csonka et al.[12] also found similar energy differences with the two chair forms at various levels of theory. We have geometry optimized the $^1C_4$ and $^4C_1$ conformations at the B3LYP/6-311++G** level in order to have consistent electronic and free energy values for comparison with the other glucose results presented here.

More recently, Lii et al.[14] carried out B3LYP/6-31G** optimization studies on glucose and its epimers. They[14] calculated the energies of the *gg*/*gt*/*tg* conformers at a higher level (B3LYP/6-311++G**) but used the geometry obtained from a lower level of theory. Their results[14] showed significant energy differences between the two

levels of theory even though the geometry was the same. Hoffmann and Rychlewski[18] tested the effect of diffuse functions on the energetics of glucose and concluded, as did we, that diffuse functions were vital to achieve consistent energies. We have carried out the geometry optimization at the higher level of theory in order to have a consistent set of data for all the carbohydrate molecules being studied in this and future work.

At the empirical level, Dowd et al.[19] studied glucose chair and skew-boat forms using MM3. Their energy differences (~5 kcal/mol) between the two chair forms agrees with previous ab initio studies, although they did not find any stable boat forms, indicating that only skew-boat conformations are stable using MM3. This last result is not consistent with the DFT results presented here where stable boat forms are found, and indicates a possible flaw may exist in the MM3 potentials, or that the authors did not consider all the possible hydroxymethyl rotational states or include the β-anomers in their study.

2. Computational methodology

The B3LYP nonlocal exchange correlation functionals[20] and basis sets denoted 6-31+G* and 6-311++G** were used as described previously for maltose[1] and cellobiose[2,3]. In this work, the preliminary geometry optimization is at the B3LYP/6-31+G* level and optimization is continued from that result using the same DFT with the larger 6-311++G** basis set. Geometry optimization was considered satisfactory if energy differences between cycles of optimization were less than 1×10^{-6} Hartree and a gradient of less than 1×10^{-4} (or 1×10^{-5} a.u. in some cases) was achieved. The gradient was smaller than that used in our previous work on maltose[1] to get better convergence for calculation using the harmonic vibrational frequencies. The density functionals and basis set, B3LYP/6-31+G* and B3LYP/6-311++G**, were those included in the Parallel Quantum Solutions software (PQS V2.2 and V2.3)[21]. Parallel Quantum Solutions QS4-800S, QS4-1000S, QS4-1800, and QS4-2000 hardware was used for all DFT calculations. Vibrational contributions to the energy at the harmonic level of approximation were calculated after geometry optimization at the larger basis set to obtain the zero point vibrational energy (ZPVE), enthalpy, entropy, and relative free energy for each anomer and conformation. A numerical Hessian method (NUMHESS)[21] was used with semiempirical potentials to obtain a good preliminary Hessian, and after optimization at the higher level theory, it was found to improve the relative free energies. The application of NUMHESS with the higher basis set to give a refined Hessian gave results that included more anharmonic contributions. These results are included for three rotamers of the $^4C_1$ chair conformation.

In the studies reported here, the hydroxyl groups in the 1-, 2-, 3-, and 4-positions were taken in their lowest energy vacuum configurations. For example, in glucose the counter-clockwise (*r*) direction with the 2-position moving from the g^+ in the β-anomer to the g^- in the α-anomer was considered. Some clockwise (*c*) conformations were also calculated, but they are of higher energy than the counter clockwise conformers and are not reported here. Both *r* and *c* conformations are examined for the boat and twist forms because of unusual hydrogen-bonding networks. The energy barriers in glucose for rotation about the C-5–C-6 bond were examined by calculating the transition-state conformations and energies. Preliminary transition states were found using torsional constraints on the hydroxymethyl C-5–C-6 bond to bring the empirical conformation to a near transition state. The transition state search was carried out at the B3LYP/6-311++G** level using the PQS search algorithm[21,22]. This algorithm follows a negative eigenvalue to a maximum torsional energy. All initial boat conformations were created using in-house empirical potentials,[23,24] and for those structures in which the boat conformers were not stable using our empirical potentials, either limited soft energy minimization was carried out, or dihedral constraints were used to keep the boat geometry intact but acting to reduce any atom–atom contacts of high energy. The final structures were always energy optimized at the highest level of theory, and no intermediate or preliminary results are reported, with the exception of one boat-to-chair transition-path study in which the DFT/6-31+G* path is described.

3. Results

3.1. General considerations

The ideal definition of the sugar ring moiety of glucose and its epimers has been described previously in the literature,[25,26] and although ring-pucker parameters have been applied to sugar structures, we believe that the conformational assignments used here are best expressed as a set of three improper dihedral angles. The reason for this choice is our desire to convey a qualitative assessment of the effect of different hydrogen-bonding configurations on the ring conformations of the optimized structures. These are very confusing problems when described as ring-puckering parameters since that parameter is not a visual one. For this reason we adopt the following improper dihedral angles, $\tau1$, defined as C-4–O-5–C-2–C-1, $\tau2$ as O-5–C-2–C-4–C-3, and $\tau3$ as C-2–C-4–O-5–C-5. The calculated improper dihedral angles for all the conformations calculated here, and ideal ring

Table 1. Improper dihedral angles and relative electronic energies for geometry-optimized D-glucose

Geometry-optimized conformations	Starting conformations	C-4–O-5–C-2–C-1	O-5–C-2–C-4–C-3	C-2–C-4–O-5–C-5	ΔE
α-*gt*-$^4C_1$		−29.2	−31.8	−34.3	0.000
α-*gg*-$^4C_1$		−29.0	−33.7	−31.6	0.075
α-*tg*-$^4C_1$		−28.0	−33.2	−35.0	0.055
β-*gt*-$^4C_1$		−35.3	−30.5	−34.1	0.949
β-*gg*-$^4C_1$		−35.2	−31.5	−31.3	0.855
β-*tg*-$^4C_1$		−35.4	−30.6	−35.4	1.028
α-*gt*-$^{3,O}B$		−35.2	63.4	−31.6	12.535
α-*gt*-$^{3,O}B$#2		−44.1	54.0	−15.1	10.777
α-*gg*(O-5)-$^{3,O}B$		−43.6	54.8	−14.5	10.195
α-*gg*(C-4)-$^{3,O}B$		−42.9	56.6	−18.1	12.549
α-*tg*-$^{3,O}B$		−39.2	62.9	−25.9	13.538
α-*tg*-$^{3,O}B$#2		−45.7	52.8	−10.1	15.144
β-*gt*-$^{3,O}B$		−20.9	63.6	−48.1	8.811
β-*gg*(O-5)-$^{3,O}B$		−15.5	62.0	−50.6	9.211
β-*gg*(O-4)-$^{3,O}B$		−22.1	60.8	−22.1	11.520
β-*gt*-$B_{3,O}$		5.0	−62.3	38.3	7.344
β-*gg*-$B_{3,O}$		10.5	−64.0	33.8	4.747
β-*tg*-$B_{3,O}$		8.4	−62.9	38.9	8.588
α-*gt*-$^3S_5$-*c*	α-*gt*-$^{3,O}B$-*c*	−15.6	64.0	−48.9	6.813
α-*gt*-$^3S_5$-*r*	α-*gt*-$^{3,O}B$-*r*	−9.0	62.2	−51.8	5.318
α-*gg*-$^3S_5$-*c*	α-*gg*-$^{3,O}B$-*c*	−13.9	62.9	−51.2	7.142
α-*gg*-$^3S_5$-*r*	α-*gg*-$^{3,O}B$-*r*	−6.8	60.6	−52.4	5.544
α-*tg*-$^3S_5$-*c*	α-*tg*-$^{3,O}B$-*c*	−13.2	62.8	−53.6	5.816
α-*tg*-$^3S_5$-*r*	α-*tg*-$^{3,O}B$-*r*	−6.8	60.2	−56.1	6.935
α-*tg*-$^1S_3$	α-*tg*-$B_{3,O}$	59.9	−51.3	−10.6	9.041
α-*tg*-$^5S_1$	α-*tg*-$B_{1,4}$	−51.9	7.0	47.4	8.717
β-*tg*-$^1S_5$	β-*tg*-$^{3,O}B$	58.1	−4.0	−48.7	9.016
β-*tg*-$^1S_5$	α-*tg*-$B_{2,4}$	52.7	1.7	−55.6	8.716
α-*gt*-$^4C_1$	α-*gt*-$B_{3,O}$				
α-*gg*-$^4C_1$	α-*gg*-$B_{3,O}$				
α-*gt*-$^1C_4$		33.8	30.2	26.5	6.836
α-*gg*-$^1C_4$		33.6	27.4	27.7	5.348
α-*tg*-$^1C_4$		31.0	30.1	30.7	7.910
β-*gt*-$^1C_4$		30.1	33.4	19.3	9.063
β-*gg*-$^1C_4$		23.0	28.0	28.4	6.473
β-*tg*-$^1C_4$		29.5	32.9	22.1	10.124
gt-anhydro		−35.2	−30.8	−34.0	[a]
gg-anhydro		−35.4	−31.5	−31.4	
tg-anhydro		−34.5	−30.9	−35.0	

[a] These molecules are not glucose and relative energies are not given.

models proposed earlier,[25,26] are presented in Tables 1 and 2, respectively. There is clearly considerable variation between the DFT geometry-optimized conformers and the proposed ideal ring model,[25,26] and this difference is expected because of the inherent asymmetry of glucose and its intramolecular interactions. However, for the conformational assignments made here, we believe that a more accurate assessment does not exist amongst the chairs, boats, and *S*-type skew boats.

A second problem that we have is making decisions as to the type of conformation found, there being large ambiguities between some skew boats and those called boat structures. As shown in Table 1 we found structures that lie between the boat and skew-boat definitions, and

Table 2. Approximate improper dihedral angles for ideal D-glucose ring conformations[26]

Conformations	C-4–O-5–C-2–C-1	O-5–C-2–C-4–C-3	C-2–C-4–O-5–C-5
$^4C_1$	−35	−35	−35
$^1C_4$	35	35	35
$^{3,O}B$	−30	60	−30
$B_{3,O}$	30	−60	30
$^1S_3$	60	−60	30
$^1S_5$	60	0	−60
$^3S_5$	0	−60	60

a decision must be made as to which to choose. Our choice has been to define the structure as that closest to the 'standard' improper dihedral angles found in Table 2, deciding upon either boat or skew boat.

3.2. $^4C_1$ Chair conformations

Energy results of the vacuum B3LYP/6-311++G** calculations on the $^4C_1$ chair conformation of α- and β-D-glucopyranose rotamers are presented in Table 3, selected molecular geometries of the $^4C_1$ chair forms in Table 4, and transition-state energies in Table 5. Free-energy differences and population analysis are included in Table 3 for each hydroxymethyl conformer of the two anomers, and the relative free energy anomeric ratios are calculated. Selected calculations of the clockwise-rotated hydroxyl groups were carried out (not listed) and were between 1.65 (α-anomer) and 3.97 (β-anomer) higher in energy than the counter-clockwise conformers.

The electronic energies of the α-anomers for the $^4C_1$ conformations are ~0.9 kcal/mol lower than the β-anomers and remain between ~0.3 and 1.7 kcal/mol lower in energy than the β-anomers when corrected for the harmonic zero point vibrational energy (ZPVE). From Figure 1 it can be seen that the enhanced stabilization of the α-anomer over the β-anomer is partially a result of a short (2.25 Å vs 2.55 Å, respectively) hydrogen bond between the polar hydrogen on the 2-hydroxy to the oxygen of the 1-hydroxy group. This interaction was discussed previously,[4] but it is important to point out that this is a very favorable stabilizing interaction. Rotating only the OH-2 group in the α-anomer from the favored g^- to the g^+ conformation results in a loss in minimized energy (B3LYP/6-311++G**) of ~3.5 kcal/mol for all three rotamers.

The g^+ form at the OH-2 group is the favored one for the β-anomer. Thus one must conclude that the enhanced stability of the α-anomer over the β-anomer is largely but not totally dependent upon the conformation of the hydroxyl group at the 2-position. An attempt to minimize the β-anomer with the OH-2 group in the g^- conformation was unsuccessful, the OH-2 group moving back to the favored g^+ form upon minimization.

Other authors[27–30] have commented at length on the α-anomer stabilization resulting from the anomeric and exo-anomeric effects, and that debate will not be continued here. However, because of the hydrogen-bond energy advantage noted above, when the total harmonic

Table 3. B3LYP/6-311++G** electronic energy, harmonic zero point vibrational energy (ZPVE), enthalpy (*H*), entropy (*S*), free energy (*G*), and numerical Hessian (NUMH) results for α- and β-D-glucopyranose $^4C_1$ conformers

	α-Anomer			β-Anomer		
	gg	*gt*	*tg*	*gg*	*gt*	*tg*
Energy (a.u.)	−687.405236	−687.405355	−687.405267	−687.403843	−687.403944	−687.403629
Energy[a]	−431,353.351	−431,353.426	−431,353.371	−431,352.477	−431,352.541	−431,352.343
ΔE_0	0.075	0.000	0.055	0.949	0.885	1.028
ZPVE	129.135	129.309	129.243	128.639	129.659	129.791
Energy (Corr)	−431,224.22	−431,224.12	−431,224.13	−431,223.84	−431,222.88	−431,223.55
ΔE_0 (Corr)	0.00	0.10	0.09	0.38	1.34	1.67
Enthalpy (*H*)	137.054	137.223	137.098	136.786	137.592	137.674
H-ZPVE	7.919	7.914	7.855	8.147	7.933	7.883
Entropy (*S*) (cal/mol K)	104.255	104.140	103.514	105.215	104.226	103.785
$H - TS$ (298 K)	105.987	106.189	106.251	105.432	106.533	106.538
$\Delta(H - TS)$	0.554	0.757	0.819	0.000	1.101	1.314
ΔG^0_{298}	0.00	0.13	0.24	0.32	1.36	1.77
ZPVE, NUMH	124.109	124.109	124.324	123.709	123.713	123.902
Energy, NUMH	−431,229.24	−431,229.32	−431,229.05	−431,228.77	−431,228.83	−431,228.44
ΔE, NUMH Corr	0.12	0.00	0.27	0.55	0.49	0.88
Enthalpy (*H*), NUMH	132.374	132.380	132.481	132.088	132.108	132.184
H-ZPVE	8.265	8.271	8.157	8.379	8.395	8.282
Entropy (*S*), NUMH	106.521	106.561	105.631	107.441	107.520	106.523
$H - TS$ (298 K)	100.631	100.625	101.003	100.071	100.067	100.440
$\Delta(H - TS)$ NUMH	0.564	0.558	0.936	0.004	0.000	0.373
ΔG^0_{298}	0.07	0.00	0.43	0.39	0.32	0.69
$e^{-\Delta G/RT}$	0.89	1.00	0.49	0.52	0.58	0.31
Population (%)	24	26	13	14	15	8
Total population ratio, α/β 63/37						
Experimental population ratio, α/β 36/64						
Experimental rotamer populations[b] 54% *gg*; 44% *gt*; 2% *tg*						

[a] Energy values are in kcal/mol unless otherwise noted. NUMH implies NUMHESS, the numerical Hessian.
[b] Ref. 17.

Table 4. Selected bond lengths, bond angles, hydrogen bond lengths, and dihedral angles for α- and β-D-glucopyranose from vacuum B3LYP/6-311++G** geometry optimization and other theoretical and experimental results

	α-Anomer				β-Anomer			
	gg	*gt*	*tg*	Standard Exptl.[a]	*gg*	*gt*	*tg*	Standard Exptl.[a]
Bond lengths (D)								
O-5–C-5	1.447 (1.451)[b]	1.448 (1.428)[c]	1.442	1.434	1.438 (1.439)[d]	1.439	1.433	1.426
C-1–O-5	1.408 (1.427)[b]	1.408 (1.427)[c]	1.408	1.419	1.420 (1.431)[d]	1.421	1.421	1.428
O-1–C-1	1.420 (1.412)[b]	1.419 (1.391)[c]	1.420	1.398	1.397 (1.394)[d]	1.396	1.396	1.385
C-6–C-5	1.524 (1.510)[b]	1.521 (1.511)[c]	1.530		1.525 (1.513)[d]	1.522	1.530	
C-3–C-4	1.524 (1.521)[b]	1.524 (1.520)[c]	1.521		1.526 (1.531)[d]	1.527	1.524	
Bond angle (deg)								
C-1–O-5–C-5	116.6 (113.1)[b]	116.1 (113.8)[c]	115.8	114.0	114.3 (111.9)[d]	113.4	113.1	112.0
O-1–C-1–O-5	112.6 (110.2)[b]	112.9 (111.5)[c]	112.7	112.1	108.7 (106.8)[d]	109.0	108.8	108.0
C-2–C-1–O-5	111.8	111.5	112.0		110.2	109.9	110.4	
O-5–C-5–C-4	110.3	109.5	108.7		110.2	109.3	108.4	
O-5–C-5–C-6	105.6	105.9	106.8		106.0	106.5	107.5	
C-5–C-4–O-4	107.2	108.1	108.5		107.2	108.1	108.6	
HO-6–O-6–C-6	107.3	107.2	107.7		107.4	107.2	107.7	
C-1–C-2–C-3	110.5	110.6	110.7		109.3	109.5	109.7	
Dihedral angle (deg)								
HO-1–O-1–C-1–O-5	68.8	67.6	67.5		−65.2	−66.9	−62.2	
C-1–O-5–C-5–C-4	56.1 (61.4)[b]	58.7 (62.2)[c]	59.3 (60.0)		68.8 (66.5)[d]	62.0	62.7	64.0
O-5–C-5–C-4–C-3	−54.6 (−58.5)	−56.6 (−57.5)[c]	−58.5 (−56.0)		−53.1 (−60.4)[d]	−55.6	−57.5	−57.0
C-5–O-4–C-3–C-2	55.3 (53.4)[b]	55.9 (53.3)[c]	57.0 (53.0)		52.7 (52.6)[d]	53.2	54.3	53.0
C-1–O-5–C-5–C-6	179.2	−178.7	−178.1		−178.2	−175.3	−174.6	
O-5–C-5–C-6–O-6	−57.8 (−57.8)[e]	60.8 (58.7)[e]	165.7 (167.7)[e]		−57.7 (−83.0)[e]	60.7 (58.7)[e]	166.1 (168.5)[e]	
HO-6–O-6–C-6–C-5	57.9	−58.0	51.0		56.6	−57.6	51.9	

[a] Ref. 26.
[b] Ref. 33 in brackets.
[c] Ref. 34 in brackets.
[d] Ref. 32 in brackets.
[e] MP2 optimized geometry, Refs. 10 and 12 in brackets.

Table 5. B3LYP/6-311++G** electronic energy for vacuum α- and β-D-glucopyranose transition states (TS)

	α-Anomer			β-Anomer		
	TS1	TS2	TS3	TS1	TS2	TS3
Φ (deg) (O-5–C-5–C-6–O-6)	−137.13	0.30	140.57	−136.19	−0.60	−141.85
Energy[a]	−431,349.600	−431,347.619	−431,347.589	−431,348.708	−431,346.908	−431,346.580
Δ*E*	3.751	5.807	5.782	3.769	5.633	5.753
Δ*E* (MP2/6-31G*)[b,c]	3.647	6.764	4.656	3.755	6.914	5.457

[a] Energy values are in kcal/mol unless otherwise noted.
[b] Refs. 11 and 13.
[c] ZPVE for a transition state does not contain vibrational contributions from the torsional modes around the C-5–C-6 bond and therefore cannot be compared to the other minimum energy glucose values.

Gibbs free energy $(G^{o}_{298} = E_{\text{elec}} + (H - \text{TS}) + RT)$ is calculated, the α-anomer *gg* conformation remains ~0.3 kcal/mol lower in free energy than the lowest energy *gg* conformer of the β-anomer. Of interest is the observation in Table 1 that after the NUMHESS frequency results are included, the α-anomer *gg* and *gt* free energies remain slightly lower than the β-anomer conformers, and are ~0.4–0.7 kcal/mol lower in energy than the α- and β-anomer *tg* conformers, respectively. Thus, previous calculations that gave the α-anomer in the vacuum state to be slightly free-energy preferred are confirmed, but the *gg* and *gt* conformations are found to be in high population in the vacuum state at this high level of theory. This free-energy advantage for the *gg* and *gt* conformers is a result of a significant entropy disadvantage for the *tg* rotamer. The calculated α/β free energy anomer population ratio of 63/37 is virtually reversed from the experimentally observed[31] ratio of 36/64. The calculated hydroxymethyl rotamer populations agree with experimental values although the calculated population of the *tg* rotamer (~13% α- and ~8% for the β-anomer) is higher than that found in solution (~2%),[17] indicating a modest role for solvent in the hydroxymethyl rotamer population.

Examination of the experimental hydroxymethyl rotamer population for just the α- or just the β-anomer (e.g., by specific analog preparation) also confirmed the conformational preference as *gg*/*gt* preferred with the *tg*

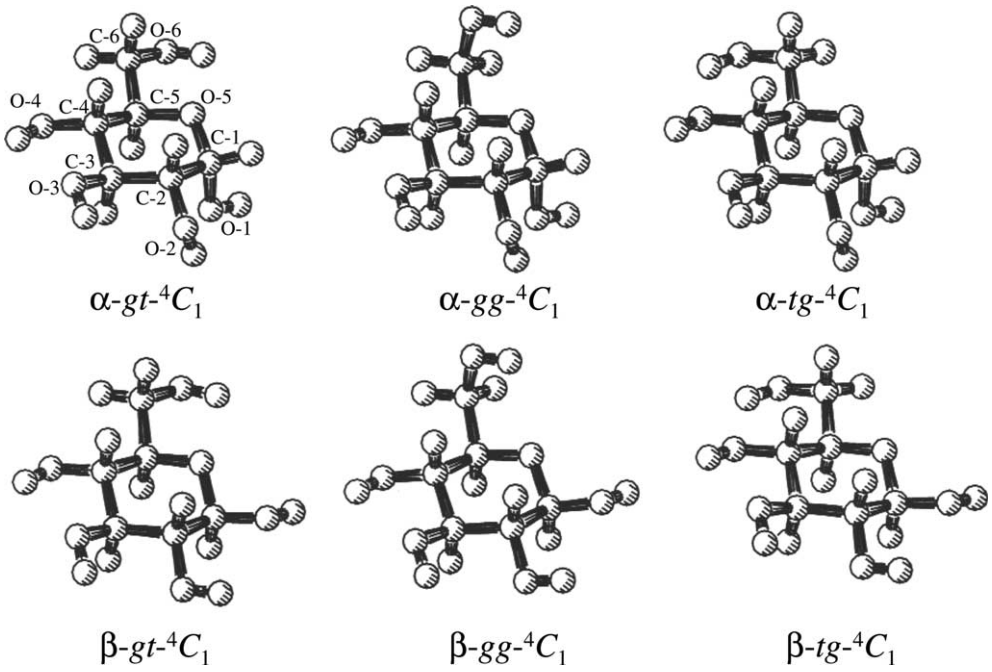

Figure 1. Geometry optimized glucopyranose structures in the $^4C_1$ chair conformation. Atom numbering is shown on the α-*gt*-$^4C_1$ conformer.

conformer being of low population for both anomers. Thus the calculations are consistent with experimental observations,[17] regardless of the effect of solvent on the anomer ratio. It is only necessary to argue that a slight solvent preference exists for the *gg* form over the *gt* form in solution since the observed ratio of 55/45[17] for the *gg*/*gt* ratio is not totally achieved with our vacuum free-energy calculations (38/41).

From the molecular geometry of Table 4, it is clear that changing from the α- to the β-anomer does not measurably change the global minimum energy hydroxymethyl dihedral angle. These values are nearly identical, even though one might believe that the anomeric geometry could play a role in the position of the hydroxymethyl group. There are some interesting differences between the B3LYP/6-311++G** geometries and standard dimensions for pyranosides.[32] For example, the magnitude of the experimentally observed shortening of the C-5–C-6 (*exo*) bond (1.516 Å average) is not found from our calculations (∼1.525 Å), nor for that matter is the shorter bond found from the MP2/6-31G* studies of β-D-glucopyranose described previously[10,12]. We observed the same internal geometry for the C-5–C-6 bond from similar calculations at the same level of theory for maltose[1] and cellobiose[2,3]. The *trans* effect is responsible for ∼0.01 Å lengthening of the C-5–C-6 bond when the O-5–C-5–C-6–O-6 dihedral angle is ∼180°.

Both the experimental and calculated studies give the same trends in ring bond lengths with the α-anomer shorter in C-1–O-5 than the β-anomer, and the C-5–O-5 being on average longest in the α-anomer. The C-1–O-1 bond lengths are longer than C-1–O-5 bonds in the α-anomer and shorter in the β-anomer, as anticipated from previous studies on anomeric effects[4,6,8]. The calculated C-1–O-1 bond lengths are somewhat longer than the experimental values, probably as a result of crystal packing and hydrogen bonding associated with this position in the crystals. Results from MP2/6-31G*[10,12] calculations for C-1–O-1 also were longer than the experimental values (∼0.01 Å), depending upon the hydroxymethyl conformation compared. The ring bond angles follow the experimental trends, with the C-1–O-5–C-5 angle larger for the α-anomer, and the calculated values larger than the experimental values. Similarly, the O-1–C-1–O-5 angle shows the larger variance between the anomers, being ∼4° larger for the α-anomer, in agreement with the observed experimental difference. The calculated values are somewhat larger than the experimental values for both anomers. No attempt was made to convert the experimental geometries to the vibrationless state for comparison purposes, and slight differences between the experimental and calculated internal geometries are to be expected.

The significant ring dihedral angle changes that occur upon change in hydroxymethyl torsion occur at the C-1–O-5–C-5–C-4 dihedral angle, where the α-anomer increases by ∼3° upon moving from the *gg* to the *gt* conformer, while in the β-anomer case the decrease is by a larger amount, ∼7° upon going from the *gg* to the *gt* conformer. The difference between the α- and β-anomers reflects the same pattern observed experimentally with the β-anomer having somewhat larger values for this

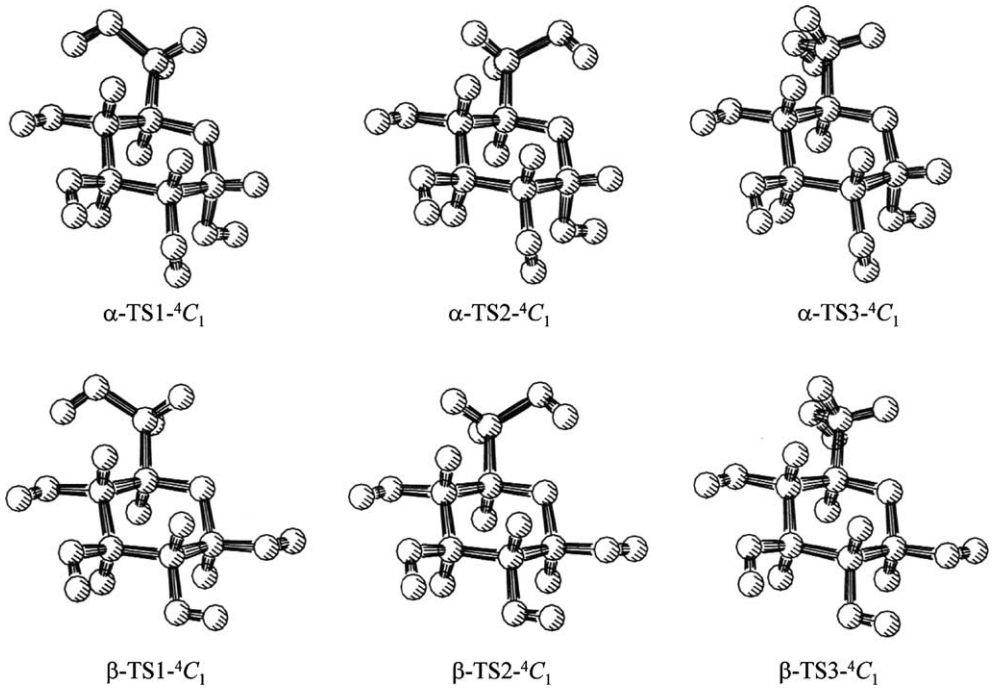

Figure 2. Transition state conformations (TS1, TS2, TS3) for α- and β-anomers of D-glucose.

dihedral angle than the α-anomer. The calculated C-1–O-5–C-5–C-4 dihedral angle in the β-anomer *gg* conformation was 68.8°. This value compares favorably with experimental values of 64.0°[31] and 66.5°.[33]

3.3. Transition states

From Table 5 it is seen that the transition-state barriers for rotation about the C-5–C-6 bond are in the range of 3.7–5.8 kcal/mol for both anomers. Historically, the calculation of transition-state energies as one rotates about the C-5–C-6 bond has resulted in rather different barriers depending upon the method used.[10,12] On the one hand, MP2/6-31G* studies resulted in the highest barriers to rotation being between the *gg* and *gt* conformational states[10,12] (see Table 2). Empirical AMBER calculations gave the highest energy barriers between the *gg* and *tg*, as well as the *gt* and *tg* conformations.[10,12] The values of the barriers obtained here for rotation about the C-5–C-6 bond are smaller than those calculated previously by ab initio methods[10,12] and are much smaller than the AMBER values.

The six TS structures are shown in Figure 2. Of particular interest is the observation that the C-5–C-6 bond length is lengthened in the TS structures relative to the minimum-energy structures. This was expected because of the stress on the bond resulting from the *cis* conformations. The C-1–O-5–C-5 angle is ~3° larger in the β-anomer, relative to that of the α-anomer. This is consistent with the unstrained glucose ring.

3.4. 1,5-Anhydro-D-glucitol

The conformational energies for the three hydroxymethyl rotations are presented in Table 6. Geometry-optimized structures are shown in Figure 3. Removing the HO-1 from the hydrogen bond network has little effect on the HO-4···HO-3···HO-2 hydrogen-bond lengths. However, there is a clear difference between glucose and 1,5-anhydro-D-glucitol, in that the rotamer preference becomes predominately *gt* after the 1-hydroxy group has been removed. This difference is found for the electronic as well as relative free energy, where it is magnified. The *gg* free energy is not close to that of

Table 6. B3LYP/6-311++G** electronic energy, harmonic zero point vibrational energy (ZPVE), enthalpy (*H*), entropy (*S*), and relative free energy (*G*) results for 1,5-anhydro-D-glucitol conformers

	gg	*gt*	*tg*
Energy[a]	−384,130.052	−384,130.303	−384,129.842
Δ*E*	0.251	0.000	0.461
ZPVE	120.216	119.835	121.128
Energy (Corr)	−384,009.836	−384,010.468	−384,008.714
Δ*E* (Corr)	0.63	0.00	1.75
Enthalpy	127.533	127.216	128.459
H-ZPVE	7.317	7.381	7.331
Entropy (cal/mol K)	99.541	100.088	99.513
$H - TS$ (298 K)	97.870	97.390	98.804
$\Delta(H - TS)$	0.480	0.000	1.414
ΔG^0_{298}	0.731	0.000	1.875

[a] Energy values are in kcal/mol unless noted otherwise.

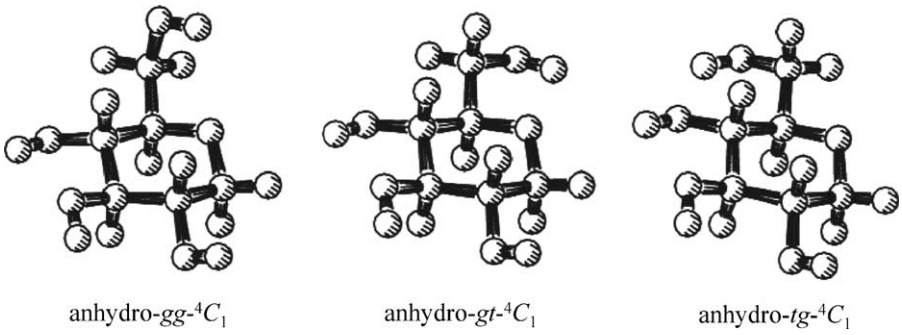

Figure 3. Conformations of 1,5-anhydro-D-glucitol.

the *gt* form because there is no polarization effect on O-5 from the 1-hydroxy group, and further there is no polar HO-1 group acting to hydrogen bond to the HO-6 group and stabilize the *gg* conformation relative to the *gt* conformation. The *tg* conformation is of high relative free energy in 1,5-anhydro-D-glucitol (~1.9 kcal/mol) and would not be a factor in solution even if it were favored by the solvent.

The dihedral angles about the sugar ring change with different hydroxymethyl group conformations by a little over one degree, in comparison to a variance of several degrees in glucose. This difference is reflected in small changes in the hydrogen bond lengths (see Fig. 3) between hydroxyl groups, even across the ring from the hydroxymethyl group to the 1-hydroxyl position. In the *tg* conformation where the dihedral angle O-5–C-5–C-6–O-6 is ~180°, a significant *trans* effect is observed, that is the C-5–C-6 bond length increases, relative to the same bond length in both the *gt* and *gg* conformations (see Fig. 3). The C-1–O-5–C-5 bond angle in the three hydroxymethyl group positions in 1,5-anhydro-D-glucitol is nearly identical to each equivalent rotamer in the β-anomer in glucose. The α-anomer values for this angle in glucose are generally 2° larger (see Fig. 3 and Table 4) suggesting that 1,5-anhydro-D-glucitol structure is structurally closer to the β-anomer of glucose than the α-anomer. However, this is not always the case as some molecular parameters change considerably between the 1,5-anhydro-D-glucitol and glucose, in particular in the *gg* comparisons where the hydroxymethyl group can interact closely with the 1-hydroxy group in glucose.

3.5. Boat and skew forms

Low-energy rotamers of α- and β-D-glucose in the $^{3,O}B$ and $B_{3,O}$ boat conformations were investigated, as well as selected rotamers of $B_{1,4}$ and $B_{2,5}$ boat conformations (see Figs. 4 and 5). Skew-boat conformations of the *S*-type were also studied, some obtained when they moved to the skew form from specific higher energy boat forms. Results of energy minimization of the boat and skew conformations are presented in Tables 7 and 8. When comparing the electronic and free-energy differences of the boat and skew forms, we use the lowest energy chair conformation as the zero base. Thus, for example, the α-*gt*-$^{3,O}B$ conformation is ~11 kcal/mol in electronic energy higher in energy than the α-*gt*-$^4C_1$ conformation, the electronic energy difference being ~9 kcal/mol for the β-*gt*-$^{3,O}B$. When the free energy is considered

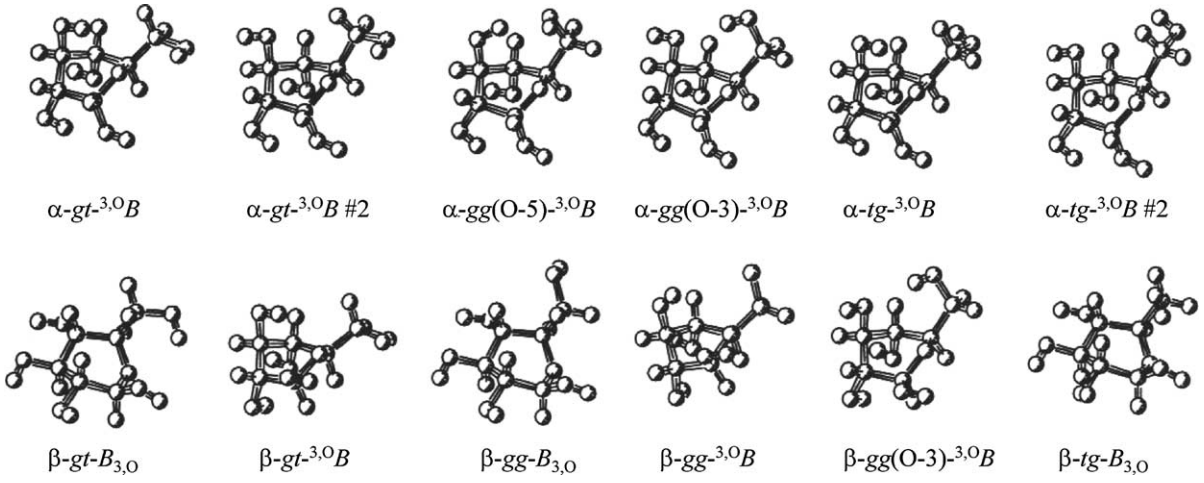

Figure 4. Conformations for boat structures listed in Table 7.

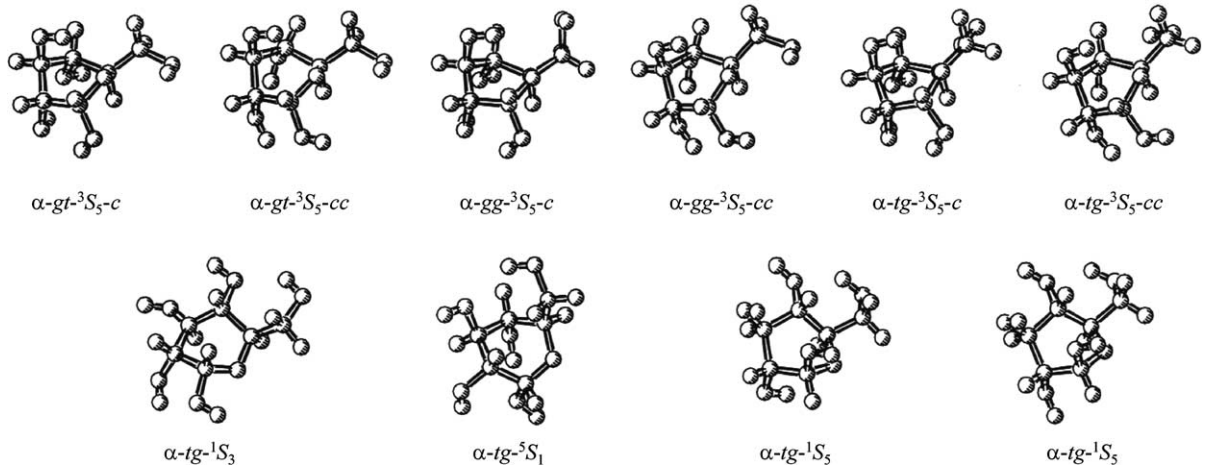

Figure 5. Conformations for skew structures listed in Table 8.

β-*gt*-$^{3,O}B$ remains ~2 kcal/mol lower in relative free energy than α-*gt*-$^{3,O}B$. When starting conformations were of the type, α-$B_{3,O}$, gradient energy minimization did not find stable boat conformations. That is, the α-*gt*-$B_{3,O}$ and α-*gg*-$B_{3,O}$ boats moved down in energy during minimization to fall into the $^4C_1$ chair conformation without encountering an energy barrier (see Fig. 6), while the initial α-*tg*-$B_{3,O}$ structure converged into an α-*tg*-$^1S_3$ skew boat. This result was not fully anticipated since our empirical potentials maintained skew boat, not boat forms, for these starting structures, but did not progress to the α-*gt*-$^4C_1$ chair during minimization. To test that this was not a result peculiar to the B3LYP/6-31+G* level of theory during preliminary gradient optimization, the α-*gt*-$B_{3,O}$ boat was restarted and optimized completely at the B3LYP/6-311++G** level of theory. The same result as described above was obtained using the larger basis set throughout the optimization. There exists a nearly flat plateau in energy about 2 kcal/mol above the chair form, but there is no energy barrier to maintain the boat conformer during minimization. Investigation of the geometry showed that the OH-2···O-1 distance is ~2.34 Å for the α-*gt*-$B_{3,O}$ boat form, and this distance is ~2.24 Å when the conformation is in the $^4C_1$ chair, favoring the chair with a stronger hydrogen-bond energy for this interaction. The OH-6···O-5 distance is approximately the same for both conformations, and probably does not play a significant role in energetic preference. However, the α-*tg*-$B_{3,O}$ conformation goes through a transition, not to the α-*gt*-$^4C_1$ chair, but to an α-*tg*-$^1S_3$ twist-boat containing a cooperative, counterclockwise hydrogen bond network. In contrast, all of the β-$B_{3,O}$ rotamers that were investigated were stable upon energy minimization and remained ~5 kcal/mol or higher in energy than the equivalent chair forms.

Particular orientation of the hydroxyl groups around the ring plays a significant role in determining the energy and stable conformation of the boat and skew conformations. For example, in Tables 1 and 7 we find that rotating the HO-3 hydroxyl hydrogen toward the ring ether O-5 atom in the two different α-*gt*-$^{3,O}B$ and α-*tg*-$^{3,O}B$ boat conformers results in ~2 kcal/mol decrease in electronic energy. Even more interesting, rotating the HO-4 hydroxyl to form a hydrogen-bond network in the clockwise or counterclockwise orientation results in a transition to the $^3S_5$ conformation during geometry optimization (see Tables 1 and 8).

Some general trends can be seen in Table 1. Orientation of the *gg*/*gt*/*tg* rotamers of the α-$^{3,O}B$ and β-$B_{3,O}$ conformers has little effect on ring geometries, while, the conformation of the cyclohexose moiety of the β-$^{3,O}B$ and α-$B_{3,O}$ conformers is sensitive to the orientation of the hydroxymethyl substituent.

Some structural details of the different boat forms are shown in Figure 4, where it is apparent that the α- and β-$^{3,O}B$ forms are not equivalent, the α-anomer being a distorted or twisted boat with the O-5 atom pointed down and away from the C-6 atom, and the β-anomer being a more standard boat form (with the exception of β-*tg*-$^{3,O}B$ that is a twisted or skewed form) with the O-5 atom pointing up and toward the C-6 atom. The near symmetry of the β-anomer is observed in the dihedral angles of the structure shown in Figure 4. For β-*gt*-$^{3,O}B$, the O-5–C-1–C-2–C-3 dihedral angle is −4.7° and the O-5–C-5–C-4–C-3 dihedral angle is −10.9°. The equivalent dihedral angles for the β-*gt*-$B_{3,O}$ boat are 27.9° and 7.0°, respectively. The small distortion from a purely symmetric form is from the C-5–C-6 versus C-1–O-1 bond differences and the electronic effect the C-1–O-1 bond has on the C-1–O-5 bond length. A significant difference in the O-5–C-5–C-6 bond angle is found between the α/β-$^{3,O}B$ and the α/β-$B_{3,O}$ boats, with the $^{3,O}B$ O-5–C-5–C-6 angle being smaller and in the same range as glucose values (~105°), while the $B_{3,O}$ values are generally closer to tetrahedral values (~109°–112°). This difference is a

Table 7. B3LYP/6-311++G** electronic energy, harmonic zero point vibrational energy (ZPVE), enthalpy (*H*), entropy (*S*), and free energy (*G*) results for α- and β-boat conformers

	α-*gt*-$^{3,O}B$	α-*gt*-$^{3,O}B$#2	α-*gg*-(O-5)-$^{3,O}B$	α-*gg*-(O-3)-$^{3,O}B$	α-*tg*-$^{3,O}B$	α-*tg*-$^{3,O}B$	β-*gt*-$B_{3,O}$	β-*gt*-$^{3,O}B$	β-*tg*-$B_{3,O}$	β-*gg*-$^{3,O}B$	β-*gg*(O-3)-$^{3,O}B$	β-*gg*-$B_{3,O}$
Energy[a]	−431,342.649	−431,340.891	−431,343.231	−431,340.877	−431,339.888	−431,338.282	−431,346.082	−431,344.615	−431,344.838	−431,344.215	−431,341.906	−431,348.679
Δ*E*	10.777	12.535	10.195	12.549	13.538	15.144	7.334	8.811	7.344	9.211	11.520	4.747
ZPVE	127.116	127.475	129.378	128.618	128.161	129.503	129.070	127.172	127.481	127.503	128.622	127.693
E-ZPVE	−431,215.533	−431,213.416	−431,213.843	−431,212.259	−431,211.727	−431,208.779	−431,217.012	−431,217.443	−431,217.357	−431,216.712	−431,213.284	−431,220.986
Δ*E* (Corr)	8.683	10.800	10.363	11.957	12.489	15.437	7.204	6.773	6.859	7.504	10.932	3.230
Enthalpy	135.230	135.703	137.306	136.768	136.125	137.428	137.053	135.142	135.542	135.485	136.770	135.528
H-ZPVE	8.114	8.228	7.928	8.150	7.964	7.925	7.983	8.000	8.061	7.982	8.148	7.835
Entropy (cal/mol K)	106.989	107.019	104.343	105.753	105.893	104.778	106.098	105.271	106.042	105.904	105.755	103.366
$H - TS$ (298 K)	103.347	103.811	106.212	105.254	104.569	106.204	105.436	100.057	103.940	103.926	105.255	104.725
$\Delta(H - TS)$	3.754	6.155	5.187	3.612	1.222	6.147	2.089	0.415	0.594	0.579	1.908	1.378
ΔG^0_{298}	8.062	10.187	10.345	11.741	12.045	15.286	6.718	6.511	6.467	7.075	10.713	3.410

α-gt glucose chair energy = −431,353.426 kcal/mol.
(O-5) and (C-4) indicate the atoms toward which the 6-OH hydrogen atom is pointing.
[a] Energy values are in kcal/mol unless noted otherwise.

Table 8. B3LYP/6-311++G** electronic energy, harmonic zero point vibrational energy (ZPVE), enthalpy (*H*), entropy (*S*), and free energy (*G*) results for α- and β-skew conformers

	α-*gg*-$^3S_5$-*c*	α-*gg*-$^3S_5$-*r*	α-*gt*-$^3S_5$-*c*	α-*gt*-$^3S_5$-*r*	α-*tg*-$^3S_5$-*c*	α-*tg*-$^3S_5$-*r*	α-*tg*-$^1S_3$	α-*tg*-$^5S_1$	α-*tg*-$^1S_5$	α-*tg*-$^1S_5$
Energy[a]	−411,346.284	−431,347.882	−431,346.613	−431,348.108	−431,347.610	−431,346.491	−431,344.385	−431,344.709	−431,344.710	−431,344.410
Δ*E*	7.142	5.544	6.813	5.318	5.816	6.935	9.041	8.717	8.716	9.016
ZPVE	128.152	128.246	127.911	128.652	128.280	128.521	127.141	129.210	128.299	128.422
E-ZPVE	−431,218.132	−431,219.636	−431,218.702	−431,219.456	−431,219.330	−431,217.970	−431,217.244	−431,215.499	−431,216.411	−431,215.988
Δ*E* (Corr)	6.084	4.580	5.514	4.760	4.886	6.248	6.972	8.717	7.805	8.228
Enthalpy	135.759	135.970	135.519	136.256	135.881	136.171	135.185	136.806	136.168	136.446
H-ZPVE	7.607	7.724	7.608	7.604	7.601	7.650	8.044	7.596	7.869	8.024
Entropy (cal/mol K)	102.397	103.012	102.475	102.271	102.098	102.460	105.759	101.691	103.949	104.945
$H - TS$ (298 K)	105.229	105.257	104.966	105.764	105.440	105.622	103.653	106.487	105.176	105.157
$\Delta(H - TS)$	1.882	1.901	1.619	2.417	2.093	2.276	0.306	3.140	1.829	1.810
ΔG^0_{298}	6.309	4.739	5.717	5.020	5.194	6.496	6.632	9.142	7.830	8.111

α-gt glucose chair energy = −431,353.426 kcal/mol.
(O-5) and (O-4) indicate the atoms toward which the 6-OH hydrogen atom is pointing.
[a] Energy values are in kcal/mol unless noted otherwise.

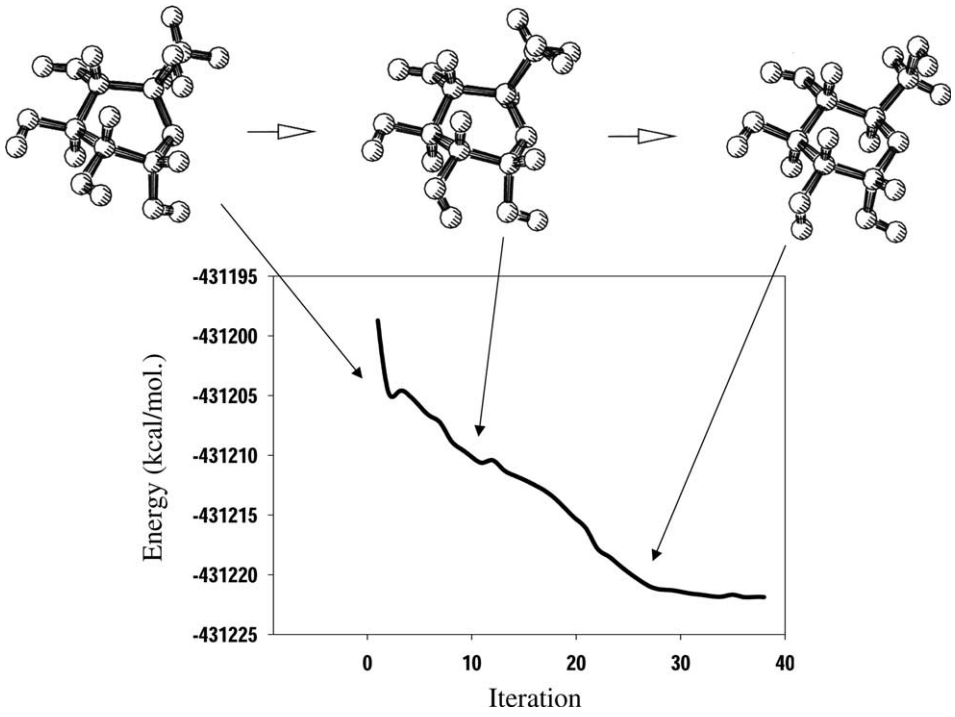

Figure 6. Conformation and energy (B3LYP/6-31+G*) versus optimization cycle pathway for the transition from the α-*gg*-$B_{3,O}$ boat form of D-glucose to the $^4C_1$ chair.

result of the different orientation of the O-5 oxygen relative to the C-5–C-6 bond. For the most part the remaining bond angles for the two boat forms closely match the glucose chair values.

Recent atomic force microscopy (AFM) studies[35] stretched the glucose residue into a conformation with an O-1···O-4 distance ~0.875 Å greater than that found (4.533 Å) in the $^4C_1$ chair conformation, and proposed a ΔG of 4.6 kcal/mol. From the work reported here, it would appear that this process may proceed from the $^4C_1$ chair through two different skew conformations, the first being the α-*tg*-$^3S_5$-*r* with a ΔG of 5.2 kcal/mol and O-1···O-4 distance of 4.63 Å, a distance only slightly larger than the 4.58 Å in the $^4C_1$ chair. Upon further stretching, the α-*tg*-$^1S_3$-*r* at 6.6 kcal/mol with a O-1···O-4 distance of 5.44 Å may be reached. It may be that the first conformation, (i.e., α-*tg*-$^3S_5$-*r*) would not appear in the AFM stretching, since the AFM work suggested that only one boat conformation was found. From our calculations, it would be the skew form noted above that would be observed in the AFM experiment, not a boat form. Although our free-energy difference is larger than that found experimentally,[35] one must consider that in the polymer matrix the hydrogen bonding is more complicated than we find in the in vacuo case examined here, and for that reason the energy differences during the stress experiment may be lower than the vacuum free energies noted in this work. However, from the O-1···O-4 distance data, it is quite reasonable to suggest that the AFM stress transitions may follow the calculated path described here fairly closely.

3.6. $^1C_4$ conformations

Although the $^4C_1$ chair is the established form found for glucose, it is of interest to study the higher energy $^1C_4$ forms in order to establish the energy required to achieve this conformation. The results of calculations on the $^1C_4$ conformations are presented in Table 9 and the structures shown in Figure 7. Similarly to the glucose case, the α-anomers are of lower energy overall than the β-anomers. The lowest energy $^1C_4$ conformation is the α-*gg* conformer, with an energy ~5 kcal/mol higher than the α-*gg* $^4C_1$ conformation. The *gt* and *tg* $^1C_4$ conformers for both α- and β-glucopyranose are higher ;in energy than the *gg* conformer by ~1–5 kcal/mol, and the difference between the α- and β-anomers becomes larger when the relative free energy is included, the α-anomer being 7–9 kcal/mol lower in relative free energy.

There exist significant geometry differences in the bond angles between the chair $^4C_1$ form and the $^1C_4$ form. For example, the C-1–O-5–C-5 bond angle in the β-anomer $^1C_4$ form is ~5° larger than in the $^4C_1$ form, while this angle in the α-anomer is not changed from the $^4C_1$ conformation. The same is true of the O-5–C-5–C-6 bond angle in both the α- and β-anomers, where the $^1C_4$ form is ~5° larger than found in the $^4C_1$ form. Other angles are not significantly different in the two confor-

Table 9. B3LYP/6-311++G** electronic energy, harmonic zero point vibrational energy (ZPVE), enthalpy (*H*), entropy (*S*), and free energy (*G*) results for α- and β-D-glucopyranose $^1C_4$ conformers

	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[a]	−431,348.078	−431,346.590	−431,345.516	−431,346.953	−431,344.363	−431,343.302
Δ*E*	5.348	6.836	7.910	6.473	9.063	10.124
Δ*E* (rel to $^4C_1$)[b]	5.283	6.836	7.855	5.524	8.118	9.005
ZPVE	128.176	127.531	128.137	128.751	129.452	127.981
Energy (Corr)	−431,225.268	−431,219.059	−431,217.379	−431,218.202	−431,214.911	−431,215.321
Δ*E* (Corr)	4.314	5.157	6.837	6.014	9.305	8.895
Enthalpy	135.858	135.502	135.502	136.113	137.348	135.805
H-ZPVE	7.682	7.971	7.365	7.362	7.896	7.824
Entropy (cal/mol K)	101.573	104.417	104.417	99.157	103.881	102.778
$H - TS$ (298 K)	105.589	104.386	104.386	106.564	106.391	105.177
$\Delta(H - TS)$	2.242	1.039	1.039	3.217	3.044	1.830
ΔG^0_{298}	4.875	5.160	5.160	6.975	9.392	9.239

[a] Energy values are in kcal/mol unless noted otherwise.

[b] α-*gt* chair energy = −431,353.426, α-*gg* chair energy = −431,353.351, α-*tg* chair energy = −431,353.371 kcal/mol, β-*gt* chair energy = −431,352.541, β-*gg* chair energy = −431,352.477, and β-*tg* chair energy = −431,352.343 kcal/mol.

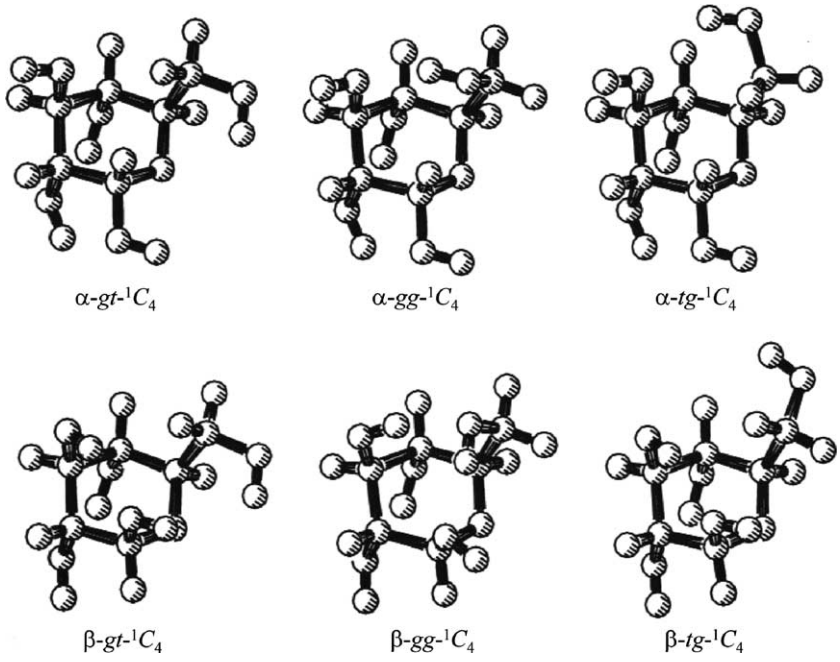

Figure 7. Structures of the α- and β-anomers of $^1C_4$ conformations of D-glucose.

mations. There are significant differences in the ring dihedral angles between the α- and β-anomers in the $^1C_4$ form, with the C-1–O-5–C-5–C-4 dihedral angle being more than 5° more negative in the α-anomer. This is the opposite of the glucose case where this dihedral angle in the β-anomer was ∼5° larger on average than the α-anomer. In the $^1C_4$ form, a large difference also appears in the C-2–C-1–O-5–C-5 dihedral angle, where the α-anomer is ∼7–8° larger than found in the β-anomer.

All of the $^1C_4$ forms exist with an OH-4···OH-2 hydrogen bond. The short hydrogen bonds (2.30–2.34 Å) between OH-1 and O-5 in the α-anomers are not available in the β-anomers where the hydroxyl is now in the axial position. The HO-2···O-1 hydrogen bond is also very short (∼2.15 Å) in the α-anomer. These structural differences are consistent with the energies presented in Table 9.

4. Conclusions

Of the many results presented here, several stand out and require more discussion. For example, it is apparent that in both glucose and 1,5-anhydro-D-glucitol, the *tg* conformation at the hydroxymethyl group is higher in free energy than the *gg* or *gt* conformations, and this is most probably the primary reason this conformer is not found in solution in significant amounts. Solvent

interactions must play a small role in the preference of the *gg* over the *gt* conformations since their free energies are so close, but as is well known, the methods by which water molecules interact with carbohydrates are complex, and one may not easily explain how this interaction favors one rotamer over the other. The preference of the β-anomer over the α-anomer in water is yet to be fully explained.

The study of the boat forms of glucose also took some surprising directions. The stable boat forms, and those that converged to *S*-type skew boats, maintain their cooperative hydrogen-bond network. That is, boat conformations that moved upon optimization to skew boats were those that maintained a synergistic hydrogen-bond network involving the hydroxymethyl group. During geometry optimization of the α-*gt*-$B_{3,O}$ and α-*gg*-$B_{3,O}$ soft boat forms, convergence was to the $^4C_1$ chair form. The transition from an α-$B_{3,O}$ boat conformation to a chair conformation was somewhat surprising, and to our knowledge, unreported in previous DFT calculations. MM3 studies[19] did not find stable boat forms, only skew-boat forms. This boat-to-chair transition was not observed for those *gt* and *gg* rotamers of the β-boat conformations that have the hydroxymethyl HO-6 group forming a hydrogen-bond with the hydroxyl at the 1-position. It is intriguing that there exist transitions without barrier for the α-$^{3,O}B$ boat forms to the $^3S_5$ forms when the hydroxyls were oriented in a HO-4×HO-2×HO-1 hydrogen-bond network in the clockwise or counterclockwise orientation. However, the α-$^{3,O}B$ conformers with the HO-4 hydroxyl rotated out of the network retain the α-$^{3,O}B$ form during geometry optimization. This infers that hydrogen bonding makes a significant contribution to the ring conformation of glucose boats or skew boats in vacuo.

The observations that high energy boat, skew, and $^1C_4$ chair conformations of analogs of glucose exist in both crystal structures[36] and solution,[37] are evidence that the strain or distortion energies for these complex carbohydrates are relatively small, as found in this study. 2,3,6-Tri-*O*-methyl-D-glucose has been found to take up both skew and $^1C_4$ chair conformations in different β-cyclodextrins, and in selected acylated α- and β-CD macrocycles.[36,38]

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