Ab Initio Computed Molecular Structures and Energies of the Conformers of Glucose

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Ab initio computations indicate the existence of several stable and some unstable conformers in isolated α and β glucose molecules. All of the lower-energy conformers exhibit a strikingly regular pattern of internal hydrogen bonding. Five such stable structures have been identified for each of the α and β anomers, differing primarily in the orientation of the CH_2OH group. In each conformer, the α anomer is predicted to be lower in energy than the corresponding conformers of β anomer. The difference is about 2 kcal/mol in the 4-31G basis but only 0.4 kcal/mol in the 6-31G* basis. It is found that the electronic contributions to the free energy difference stabilize the α anomer while the nuclear motion contributions stabilize the β anomer. The implications of these predictions and the future investigations required to understand the relative stabilities of the two anomers are pointed out.

INTRODUCTION

The molecular structures, energetically preferred conformers, and the energy differences between the anomeric α and β forms of glucose are central to understanding a variety of physical and chemical properties of carbohydrates and have been the subjects of several experimental studies employing a variety of techniques.[1] In aqueous solutions of D-glucose at ambient temperatures, the equilibrium distribution of anomers is known to be 36% α-D-glucopyranose and 64% β-D-glucopyranose, suggesting that the β form is more stable by about 0.3 kcal/mol. (The furanose and noncyclic forms are considered present in negligible amounts.) Stable conformations resulting from the orientations of the exocyclic hydroxymethyl group are also known to be possible for both α and β anomers, the relative amounts of these conformers depending upon the nature of the solvent.

The geometric nature of these various structures may be seen by referring to Figure 1, which depicts a $^4C_1$ conformer of α-D-glucose. (See Fig. 2 for the corresponding conformation of the β anomer.) The exocyclic C_6—O_6 bond may be oriented in three different positions: (1) *gauche* to both C_5—O_5 and C_5—C_4 bonds, which we will refer to as the GG conformer; (2) *gauche* to C_5—O_5 and *trans* to C_5—C_4 bonds, termed the GT conformer; and (3) *trans* to C_5—O_5 and *gauche* to C_5—C_4 bonds, termed the TG conformer. Of these three conformers, the experimental nuclear magnetic resonance (NMR) data for aqueous solutions[2] indicate that only two, namely, the GG and GT conformers, are prevalent. The population of the TG conformer in aqueous solutions is considered negligible. In crystalline glucose, the stable conformers[3,4] are apparently GT for α and GG for the β anomer. Although these exocyclic C_6—O_6 orientations are not known to influence the anomeric stabilization, it is useful to know the energetics of these orientations from a fundamental viewpoint. Such information is not available *ab initio*.

Additional conformers resulting from the orientations of individual hydroxyl groups at C_1 through C_4 and C_6 are also possible. The orientation of these hydroxyl groups are dictated by the intermolecular hydrogen bonding in the case of aqueous solutions and by the intramolecular hydrogen bonding for isolated molecules. Again, several stable conformers are possible, although experimental and theoretical data concerning the energetically preferred ones are meager.

A discussion of the structures of glucose would be incomplete without addressing the well-known anomeric effect.[5] This concept has, however, been developed almost entirely for derivatives of glucose and simple model compounds, rather than for glucose itself. For example, the experimental data for D-pyranosides such as methyl pyranoside indicates that the α anomer, with the anomeric OR group in the axial position, is more stable than the β anomer, which has the anomeric OR group in the equatorial position. This preference for the OR group in axial position is known as the anomeric effect. Differences

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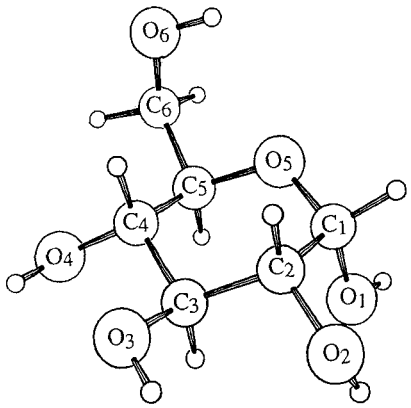

Figure 1. Atomic numbering scheme for α-D-glucose ($^4C_1$ GG,G1 conformation).

in molecular structure, such as lengthening of the C_1—O_1 bond in the α anomer, are also associated with this effect. As noted above, for simple unsubstituted sugars like glucose the experimental data for aqueous solutions point to the predominance of β anomer, contrary to the situation in pyranosides. Therefore, it has been postulated[6] that for simple sugars such as glucose the anomeric effect is either absent or dominated by the intermolecular hydrogen bonding to the solvent. Here again, *ab initio* theoretical investigations are important to understand the reasons for relative energetics of the anomers of glucose.

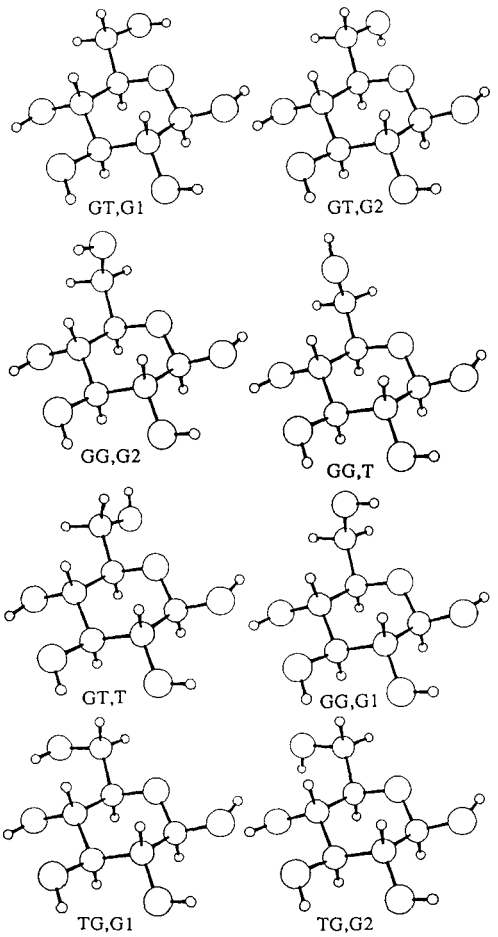

Figure 2. Structures of hydroxymethyl conformers of β-D-glucose examined in this study. The corresponding conformers of α-D-glucose are obtained by interchanging the C_1—H and C_1—O_1H bond positions and orienting O_1—H and O_2—H as in Figure 1.

The above mentioned issues have been subjected to several theoretical investigations,[7-14] primarily employing approximated potential functions. Of these, perhaps the most germane to the present study is the recent work of Ha et al.[12] This reported a molecular dynamics representation of glucose in a simulated aqueous solution to obtain the equilibrium conformers and estimate the anomeric energy difference. They predicted the TG conformer to be energetically favored over the GG and GT conformers for an isolated molecule and the opposite for aqueous solutions. They also obtained the α anomer as being the more stable, in accord with the anomeric effect but contrary to experiment, and concluded that a more sophisticated treatment of the solvation energy was needed to reproduce this (relatively small) observed difference. Interestingly, using the empirical force field parameters Rasmussen and coworkers[7] predicted the β anomer to be lower in energy and the relative energy difference between the anomers of free glucose molecules to be comparable to that known in aqueous glucose solutions.

Ab initio studies at the respective optimum structures have not been undertaken, to our knowledge, on glucose or any other pyranose sugar. Model systems such as methanediol, methoxymethanol, and dimethoxy methane have been used for detailed *ab initio* investigations,[8,11] in general substantiating the anomeric preference for α form. A minimal STO-3G basis set calculation of the energies for the α and β anomers of glucose, obtained for the geometries optimized with an empirical force field, was reported.[15]

The interpretation of vibrational spectra of glucose requires the knowledge of the different conformers mentioned above. In particular, vibrational circular dichroism (VCD) spectral interpretations for sugars, which has been the focus of investigations[16] in our laboratory, are quite sensitive to the conformational details. To understand the origins of VCD in glucose, as well as many other carbohydrates, it became necessary for us to undertake a detailed investigation of the conformers of glucopyranose.

In this article, we present the first *ab initio* theoretical study of the equilibrium molecular structures and free energies of the various conformers in isolated molecules of glucopyranose. The objectives were not only to identify the stable structures but also to determine the extent to which these conformational factors affect the α–β energy differences. In the course of this work, it was also necessary to compute all the vibrational frequencies for each structure. A detailed discussion of the observed and computed vibrational spectra will be presented in a

future publication. The present results provide the current status of *ab initio* predictions for glucose and offer directions for future investigations.

COMPUTATIONAL DETAILS

All calculations were done on an SCS-40 computer (4 Mword main memory and 3 Gb disk space) using the CADPAC program (Issue 4.0).[17] Several factors, namely, the reliability, feasibility, and computational time, were considered in choosing the basis set. The 4-31G basis set was preferred over the smaller 3-21G basis set due to the emphasis on vibrational properties. Larger basis sets such as 6-31G* were found to be practically impossible for geometry optimization and vibrational properties with the computational facilities available to us. Both structure optimizations and frequency computations were performed in Cartesian coordinates and employed the 4-31G basis set.[18] For each conformer, initial optimizations were done with a default Hessian matrix, followed by another Hessian calculation. This second Hessian matrix was used for further optimization, and the process repeated. The vibrational frequencies were evaluated at the fully optimized geometries to verify that this geometry represented a true minimum on the energy surface. For some conformers, an imaginary vibrational frequency was noted in the Hessian calculation at the partially optimized geometries. When the energies were relatively high, such conformers are not considered to have stable minima on the energy surface and were therefore not optimized further. For each stable conformer, the CPU time needed for full optimization and the vibrational frequency calculation was in excess of 100 h (equivalent to ~30 h on a Cray XMP-48 computer). For selected conformers, the energies were also calculated with the 6-31G* basis set[19] at the 4-31G geometry.

RESULTS AND DISCUSSION

As noted above, the exocyclic C_6—O_6 bond may be oriented in three different positions relative to C_4—C_5 and C_5—O_5, corresponding to three possible structures that we will call GG, GT, and TG. For our present purposes, it is also useful to specify the orientation of the exocyclic hydroxymethyl group. For a given orientation of the C_6—O_6 bond, the O_6—H bond can be placed in any one of the three different plausible positions. For example, when C_6—O_6 is in the GG orientation (*gauche* to both C_5—O_5 and C_5—C_4), the O_6—H can be in the position *trans* to either of the C_6—H bonds (conformers labeled GG,G1 and GG,G2) or in a position *trans* to the C_6—C_5 bond (labeled GG,T). Thus, there would be as many as nine different plausible conformers involving the hydroxymethyl group. Eight of these possibilities that we studied are depicted in Figure 2 for β-D-glucose.

Of course, complete identification of the conformers also requires specifying the orientations of the remaining four OH groups. However, we found that their most stable arrangement always consisted of the same rather striking pattern of concerted counterclockwise orientations as shown in Figures 1 and 2. Other possibilities in which this internal ordering was disrupted correspond to conformers with energies several kcal/mol higher. In the molecular modeling of α-D-glucopyranose by French et al.,[13] a *clockwise* pattern of internal hydrogen bonding was employed that we predict to be higher in energy than the one shown in Figures 1 and 2 (*vide infra*).

The energies and molecular structures of each of the structures shown in Figure 2 were computed for both the α and β anomers. Of these, the GG,G2, GT,G2, and TG,G2 structures exhibited imaginary vibrational frequencies and relatively high energies and thus were not investigated further. The TG,T conformation was not investigated due to the higher energy associated with this conformer, as with GG,T and GT,T. The computed energies (not including nuclear motion) and also the dipole moments of the five remaining stable conformers studied are summarized in Table I. These will be the focus of the following discussion.

Molecular Structures

The equilibrium structural parameters for these five low-energy conformers of glucose are not listed due

Table I. Computed total energies[a] and dipole moments[b] for differing conformers of glucose.

	α		β	
Conformer	Energy	Dipole moment	Energy	Dipole moment
GG,G1[c]	−682.35391954	4.21	−682.35046325	3.76
TG,G1	−682.35446068	3.46	−682.35049720	3.53
GT,G1	−682.35338552	3.10	−682.34943942	3.28
GT,T	−682.34844957	1.21	−682.34440942	1.13
GG,T	−682.34829891	3.18	−682.34423974	2.36

[a]In Hartrees, not including rotation, translation, or vibration.
[b]In Debyes.
[c]At the 4-31G optimized geometry with the 6-31G* basis set the energies are −683.3272997 and −683.3257607 Hartrees for α and β, respectively.

to space considerations, but can be obtained from the authors.

Theoretical bond lengths and angles can be compared with the corresponding experimental values[3,4] obtained from neutron diffraction study on α-glucose (GT,T conformer) and X-ray diffraction study on β-glucose (GG,T conformer). However, because the experimental data were obtained for solid-state samples, while the theoretical calculations correspond to isolated molecules, one can anticipate significant differences. Comparing the ring bond lengths for α-glucose (GT,T conformer), the differences for C_3—C_4 and C_2—C_3 from the experimental values are small (0.004 and 0.007 Å, respectively) while the differences for other ring bond lengths range from 0.01–0.02 Å. Similar observations are noted for β-glucose. For exocyclic C_1—O_1 bond length, the difference from the experimental value is 0.03 Å for α and 0.017 Å for β. The calculated C_1—O_1 bond length is longer than the corresponding value in the experimental structures for both anomers. Bond angles also exhibit similar differences. It is difficult to draw definite conclusions on the relative merits of theoretical predictions because the solid-state environment is certain to influence the structural parameters in the experimental data. For this reason, the discussion below will summarize the structural differences between the anomers as obtained in the theoretical predictions.

1. The computed C_1—O_1 bond length in each of the conformers of the α anomer is found to be ~0.02 Å longer than that in the corresponding conformer of the β anomer. Also, the C_1—O_5 bond length is computed to be ~0.01 Å shorter in α than in β. Both these trends are expected for carbohydrates exhibiting the anomeric effect, although they are much less pronounced in the experimental crystal structures of glucose.[3,4] The C_1—O_5 bond length in the β anomer is approximately the same as the C—O bond lengths at C_2, C_3, and C_4. The averages of calculated C_1—C_2 and C_2—C_3 and C_5—O_5 bond lengths in the α anomer are longer than those in β, which combined with the above observations indicates that the ring sizes of the α and β anomers are different.
2. Our calculations also indicate that the C_1—H bond length is shorter in the α anomer than in β by 0.008 Å. This prediction is, however, difficult to verify experimentally because the positions of hydrogen atoms in glucopyranoses are not accurately determined for the β anomer from the X-ray data. Support for this trend can, however, be seen in the crystal structures of α and β pyranosides,[5] where C_1—H bond length in the α anomer was found to be shorter than that in β anomer.
3. Differences in bond lengths between conformers of a particular anomer are slight except for the C_5—O_5 and C_5—C_6 bonds. Differences in bond angles and dihedral angles are even less except for the O_6-C_6-C_5-C_4 angle and, surprisingly, for the H-O_1-C_1-C_2 dihedral angle of the β anomer. In particular, for the GG,G1 and GG,T conformers of the β anomer this dihedral angle differs by ~15°.

Relative Energies

From the optimized molecular structures and vibrational frequencies, we computed the zero-point energy E_0°, as well as the total energy, entropy, Gibbs free energy, and heat capacity at 298 K and 1 atmosphere pressure for the α and β glucose and for each of the five lower-energy conformers. The results are listed in Table II. Although the results for the various conformers are similar, the values of G_{298}° differ by more than 1 kcal/mol between conformers and by nearly 1 kcal/mol between anomers. Combining these values with the electronic energies in Table I, we obtain the relative free energies listed in Table III. From these values we concluded that:

1. For any given orientation of the exocyclic hydroxymethyl group, the α anomer is predicted to be lower in energy than the corresponding β anomer by ~2 kcal/mol at the 4-31G level.
2. From the electronic energies alone, the conformer with the C_6—O_6 bond *trans* to C_5—O_5 and *gauche* to C_5—C_4 and with the O_6—H is a favorable position for hydrogen bonding to O_4 (the TG,G1 conformer) is the most stable. The next most stable conformer is GG,G1. However, this order is *reversed* when the Gibbs energies are considered. Therefore, even for a free molecule, the GG,G1 conformer is more stable than TG,G1. These predictions contradict the predictions[7] obtained with

Table II. Computed nuclear motion energies[a] E_0°, E_{298}°, and G_{298}°, entropies[b] S_{298}°, and heat capacities[b] C_v of differing conformers of α-glucose (β in parentheses).

Conformer	E_0°	E_{298}°	S_{298}°	G_{298}°	C_v
GG,G1	133.48 (133.09)	140.60 (140.35)	102.74 (103.81)	110.56 (109.99)	43.90 (44.37)
TG,G1	133.73 (133.25)	140.74 (140.44)	102.01 (103.28)	110.92 (110.24)	43.56 (44.16)
GT,G1	133.43 (133.00)	140.57 (140.30)	103.00 (104.23)	110.46 (109.82)	43.99 (44.54)
GT,T	133.07 (132.59)	140.37 (140.07)	104.29 (105.55)	109.87 (109.19)	44.40 (44.99)
GG,T	133.06 (132.46)	140.40 (140.04)	104.45 (106.38)	109.85 (108.92)	44.43 (45.16)

[a]In kcal/mol.
[b]In cal/mol/K.

Table III. Computed relative free energies[a] G°_{298} of differing conformers of glucose.

Conformer	α (relative to GG,G1)	β (relative to GG,G1)	$\beta - \alpha$
GG,G1	0	0	1.60
TG,G1	0.02	0.23	1.82
GT,G1	0.23	0.47	1.84
GT,T	2.74	3.00	1.86
GG,T	2.82	2.83	1.61

[a]In kcal/mol.

empirical parameters where GT,G2 conformation was found to have the lowest energy. Also in contradiction are the results of Ha et al.,[12] who obtained only the TG,G1 conformer for isolated molecule employing the molecular dynamics approach.

3. The difference in energy between a conformer with O_6—H in a favorable position for internal hydrogen bonding to the ring oxygen atom, and that of the conformer where O_6—H is *trans* to C_6—C_5 and hence free from hydrogen bonding, can be considered the stabilization energy resulting from hydrogen bonding to the ring oxygen atom. This stabilization energy is 2.8 kcal/mol for the GG conformer and 2.5 kcal/mol for the GT conformer. In the TG conformer, hydrogen bonding to the ring oxygen is not possible.
4. The energy of the GG,G1 conformer was also calculated with the 6-31G* basis set[18] at the 4-31G optimized geometry (see Table I) to assess the role of basis set size on the relative stabilities of the α and β anomers. At this level, the α anomer is again predicted to be more stable than β. However, the free energy difference between the anomers in the 6-31G* basis (employing the 4-31G geometry and vibrational frequencies) is now only 0.40 kcal/mol. This value results from a smaller electronic energy difference stabilizing α (0.97 kcal/mol) and a roughly comparable free energy difference due to nuclear motion stabilizing β (0.57 kcal/mol). It should be noted that the nuclear motion energy difference of the anomers is mostly the zero point energy difference because translational and rotational energies are the same for α and β and thermal contribution to the vibrational energy difference is relatively small.

In addition, to ascertain that the orientations of exocyclic hydroxyl groups, as shown in Figure 1, are in energetically preferred positions, selected calculations are performed for the GG conformer of the β anomer and the GT conformer of the α anomer by rotating one or more of the hydroxyl groups at C_2, C_3, and C_4. In these new orientations (Fig. 3) of exocyclic hydroxyl groups, the potential energy surface has minima as revealed by all real vibrational frequencies at the optimized structures shown in Figure 3. But, these energy minima are 6–8 kcal/mol higher than the minima for the corresponding structures with counterclockwise hydrogen bonding shown in Figure 2. The relative energies obtained with the 6-31G* basis set, at 4-31G optimized geometries, are also similar (see caption to Fig. 3). The main difference between the GG,G1 conformation of β-D-glucose shown in Figure 3b and that in Figure 2 is in the orientation of exocyclic hydroxyl hydrogens at C_2, C_3, and C_4. The higher energy orientations of the OH groups at C_2, C_3, and C_4 shown in Figure 3b correspond to the ones predicted to have the lowest energy in the empirical calculations.[7]

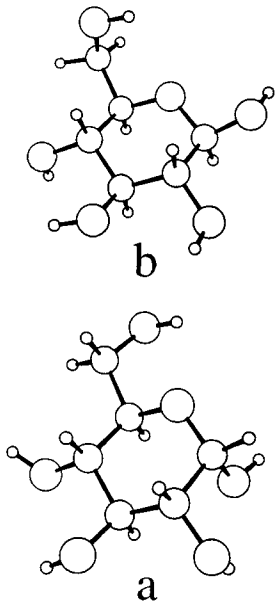

Figure 3. Optimized structures of two selected higher-energy conformers of glucose with disrupted internal hydrogen bonding obtained with 4-31G basis set. (a) GT,G1 conformer of α-D-glucose (computed energy, −682.343236 Hartrees); (b) GG,G1 conformer of β-D-glucose (computed energy, −682.337216 Hartrees). Energies obtained with 6-31G* basis set at 4-31G optimized geometries are −683.319714 and −683.316395 Hartrees for (a) and (b), respectively.

Origins of Energy Differences

The basis of the anomeric effect in small model compounds has been extensively investigated. Early explanations of the anomeric energy preference invoked an energetically unfavorable addition of dipole moments resulting from the O_5 electron lone pair and the C_1—(OH) group in the β anomer. However, this explanation was not supported in the literature, as well as by the present data, because in Table I little correlation between the dipole moments and relative stabilities is seen. A second mechanism postulates that the lone pair on O_5 donates electrons to the localized antibonding orbital associated with the C_1—O_1 bond in the α anomer, leading to antibonding behavior that is, overall, stabilizing.[14,20,21]

A detailed discussion of this specific electronic interaction and the magnitude of its contribution to the anomeric effect are beyond the scope of this article. However, some additional insight may be gained by partitioning the total electronic energies of the α and β structures into their constituent one- through four-center terms[22] for the TG,G1 conformer (which exhibits the lowest electronic energy). The differences between anomers in the one-center energies of each atom are quite small. Ten two-center energies, in order of decreasing difference between α and β, are listed in Table IV. As anticipated, the C_1—O_1 bond is weaker (less negative) and the C_1—O_5 bond is stronger in the α anomer. However, the $O_1\cdots H(O_2)$ energy, which contains the internal hydrogen bond, is much more stabilizing in the α form, and suggests that this may be an important interaction in stabilizing free glucose. There are smaller electrostatic energies between O_1 and the axial hydrogens at C_3 and C_5, which stabilizes the α form (O_1 axial), and also with the hydrogen at C_4, which stabilizes β (O_1 equatorial). Other appreciable shifts are also seen around the ring, such as for the C_3—C_4 bond. Enumeration of these terms in the molecular energies supports the conclusion drawn above from comparison of the optimized structures that the differences between anomers are not completely localized about the anomeric carbon and, in fact, the entire ring is altered on going from one anomer to the other.

An important point, however, emerges when the differences in electronic and nuclear motion contributions to free energies of the anomers are compared. As stated earlier, the nuclear motion contribution to the free energy difference stabilizes the β anomer by 0.57 kcal/mol. This value was obtained with the unscaled *ab initio* vibrational frequencies (at 4-31G level), known to be 10–15% higher in magnitude than the experimental frequencies. Thus, a scaled value for the nuclear motion contribution to free energy difference would be ~0.5 kcal/mol. Because the experimental data (in aqueous solutions at room temperature) indicate a free energy difference of ~0.3 kcal/mol, it becomes apparent that to support the experimental preference for the β anomer the electronic energy difference should stabilize the α anomer only by ~0.2 kcal/mol. The trend seen in the electronic energy differences obtained with 4-31G and 6-31G* basis sets (which are 2.17 and 0.97 kcal/mol, respectively) confirm in a qualitative sense that the electronic energy difference between the anomers is becoming smaller in higher-level calculations. This argument will have validity if the vibrational energy difference in higher-level calculations remains approximately the same as it is in the 4-31G calculation, but that remains to be verified and it is unwise to speculate.

Table IV. Dominant two-center energies[a] of α and β glucose in the TG,G1 conformer.

Centers	α	β
C_2—O_2	−0.930	−0.871
C_1—O_1	−1.034	−1.093
$O_1\cdots H(O_2)$	−0.131	−0.087
C_3—C_4	−1.271	−1.313
$O_1\cdots H(C_5)$	−0.067	−0.027
C_1—H	−1.161	−1.201
$O_1\cdots H(C_3)$	−0.068	−0.029
$(C_2)H\cdots H(C_1)$	0.062	0.026
C_1—O_5	−1.102	−1.074
C_2—H	−1.055	−1.027

[a]At the computed equilibrium geometry in Hartrees/molecule.

CONCLUSIONS

Ab initio calculations indicate the presence of a large number of stable conformers of α and β glucose. GG,G1, TG,G1, and GT,G1 are the low-energy conformers. GT,T and GG,T are ~2.5 kcal/mol higher in energy than the other three. TG,T is expected to be similar in energy to GT,T and GG,T and was not investigated in this study. We compute the GG,G1 conformer to be more stable than the other conformers. Our calculations also identify the preferred orientations of hydroxyl hydrogen atoms for isolated glucose molecules (Figs. 1 and 2). These results do not support the conformations used with empirical force field parameters.[7,12,13] For all conformers, the total free energy predicts that the α anomer is more stable than β at the 4-31G level. This conclusion may not be supported by higher-level basis sets because single point calculation with the 6-31G* basis set indicates that the energy difference is sensitive to the choice of basis set. The differences between α and β in the computed equilibrium molecular structures are consistent with generally accepted predictions of the anomeric effect.

The computed nuclear motion or equivalently the vibrational energy contributions to the free energy differences between the α and β anomers are found to be significant compared to the total anomeric energy differences for each conformer. (Nuclear motion contributions to the free energy differences between conformers due to various patterns of internal hydrogen bonding are larger yet.) In fact, the contributions of these differences in free energy due to nuclear motion are found to be comparable in magnitude to the corresponding electronic energy differences as computed in the 6-31G* basis. The former favors the β anomer, while the latter stabilizes α. Our best value of this energy difference, 0.40 kcal/mol [electronic (6-31G* basis set) + nuclear (4-31G basis set) = (0.97 − 0.57) kcal/mol] for the GG,G1 conformer, is in the same range as that obtained with the molecular dynamics approach[12] for the simulated aqueous solution (0.31 ± 0.43 kcal/mol).

Finally, the present calculations reflect the properties of isolated molecules. The experimental data on the relative stabilities of anomers in aqueous solutions, on the other hand, may or may not have been influenced by the intermolecular interactions. As a consequence, caution is warranted in making any speculative claims. Nevertheless, a trace of evidence emerges from the present results for the possibility that the vibrational energy difference between the anomers might be the ultimate reason for the relative stability of the anomers of **free** glucose molecule. Verification of this possibility through higher-level calculations is both important and necessary.

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