Exocyclic Hydroxymethyl Rotational Conformers of β- and α-D-Glucopyranose in the Gas Phase and Aqueous Solution

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The intrinsic exocyclic hydroxymethyl rotational surface for β-D-glucopyranose as well as the β−α anomer energy difference for D-glucopyranose has been studied using ab initio quantum mechanical methods including continuum solvation. Relevant stationary points, including rotational transition states, have been characterized by full geometry optimization using the 6-31G(d) basis set for the most stable counterclockwise (cc) overall conformation. Effects of dynamic electron correlation on both the geometric structures and the relative energetics of this system are also explored using Møller−Plesset perturbation theory (MP2 through MP4-(SDTQ)) and density functional methods (BLYP). A total of six stationary points, including three minima and three transition states, were identified along the exocyclic rotational surface. All three minima were found to be very close in energy with a final order of GG (0.0) < GT (2.84) < TG (3.05) based on the relative free energy, ΔG°_{298}, determined at the MP4(SDTQ)/6-31G(d)//MP2/6-31G(d) level of theory. The rotational transition state free energy differences varied from 18.8 to 28.9 kJ mol^{-1} at the same level of theory with the transition state connecting the TG and GG minima being the lowest. The intrinsic gas-phase β−α anomer free energy difference for the cc-TG conformer of D-glucopyranose was also determined at various levels of theory. On the basis of the convergence of the MP series, this energetic quantity has been estimated at 8 ± 2 kJ mol^{-1} favoring the α-anomer, and is insensitive to exocyclic hydroxymethyl rotation. Two different solvation models were used to explore the effects of aqueous solvation on the energetic parameters mentioned above. The Onsager continuum solvation model and the self-consistent isodensity polarized continuum model (SCIPCM) showed significant, yet predictable, effects on the exocyclic hydroxymethyl rotational surface for β-D-glucopyranose. Shifts in the relative energetics compared to those for the gas phase ranged from −0.8 to +2.8 kJ mol^{-1} for Onsager dipole model and −1.6 to as much as +4.7 kJ mol^{-1} for the SCIPCM model at the MP2 6-31G(d) level, resulting in a qualitative change in the ordering of the relative stability of the three stable minima. The effects of the solvation models on the β−α anomer energy difference were also significant, showing a relative decrease in the β−α anomer energy difference from the intrinsic gas-phase result. However, it is clear that these specific continuum solvation models alone cannot account for the experimentally observed preference of the β-anomer in aqueous solution.

Introduction

Carbohydrates and the individual monosaccharide subunits comprising them play an essential role in many fundamental biochemical processes ranging from energy metabolism to recognition processes involving glycolipids and glycoproteins. Not surprisingly, the structure and relative stability of conformers as well as the interaction of monosaccharides with various biochemical environments continue to be areas of intense research activity for computational and experimental biochemists alike. Despite this intensity, a number of fundamental questions surrounding the electronic structure of even the simplest monosaccharides remain unanswered. In particular, neither the fraction of α- and β-anomers nor the populations of the exocyclic hydroxymethyl rotational conformers observed experimentally in aqueous solution for simple monosaccharides, including the quintessential monosaccharide D-glucopyranose (D-glucose), has yet to be completely rationalized using any computational model.

Much of the difficulty in resolving these basic electronic structure issues stems from two important characteristics of all monosaccharides: their nearly isoenergetic, conformational states and their ability to form a strong intramolecular hydrogen bonding network or a strong intermolecular hydrogen bonding network with a polar environment. Consequently, the structure and relative stability of the isolated monosaccharides tend to be very different from their counterparts existing in an aqueous or a biochemical environment, making it difficult to separate intrinsic electronic effects from those due to the surroundings.

Despite the complexity of the problems surrounding carbohydrates, theoretical chemists continue to pursue them using an array of computational techniques. Much of the computational work to date has focused on carbohydrates in aqueous solution[1−23] or on carbohydrate−protein interactions,[24,25] by using classical mechanics including molecular mechanics, molecular dynamics, and free energy perturbation theory. Considerable work has gone into the development of appropriate

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force fields to accurately characterize these molecules, and the theoretical modeling of the basic monosaccharide subunits using classical-based methods continues to yield interesting results about the interaction of carbohydrates with various environments. Recent studies by Ha et al.[17] and Brady[20] using classical-based methods have revealed interesting information regarding the relative population of various D-glucopyranose conformers. Through molecular dynamics simulations, Ha et al. found an average free energy difference between the α- and β-anomers of -1.3 kJ mol^{-1}, in close agreement with that found experimentally in aqueous solution ($+1.3$ kJ mol^{-1}). Unfortunately, although such methods can provide valuable insight regarding qualitative issues, they are not sensitive enough to definitively resolve the basic electronic structure questions raised above, especially in cases where the energy differences are on the order of a few kJ mol^{-1}.

The size of most biologically relevant carbohydrate systems has severely limited the use of rigorous quantum mechanical theoretical methods. In order to reduce the computational expense, the early ab initio studies of carbohydrates and monosaccharides focused on simple model systems. In a series of papers by Jeffrey et al. in the 1970s,[26−28] the structure and relative stability of various rotational conformers of model compounds including methanediol, methoxymethanol, and dimethoxymethane were studied at the RHF level to gain insight into the behavior of related pyranoses. Several years later, Garrett and Serianni[29] and Bosch et al.[30] considered the conformational flexibility and internal hydrogen bonding of furanose rings at the RHF level using a 6-31G* basis set. By far, however, most of the computational work on these systems has been done to probe the anomeric stability of monosaccharides in both the gas phase and in solution. The more recent studies in this area use tetrahydropyrans or substituted analogues as model compounds. Zheng et al.[15] mapped the exocyclic hydroxymethyl rotational surface for a related molecule, 2-hydroxymethyltetrahydropyran (2-HMTHP), through a series of single-point calculations at the 6-31G(d)//3-21G(d) level but did not explicitly identify rotational transition states.

Since D-glucopyranose represents the major building block for so many important carbohydrate systems, it has become the primary focus of the most recent computational studies. Due to its relatively large size, however, ab initio theoretical studies on glucopyranose are fairly limited. Polavarapu and Ewig[31] were the first to report ab initio results on glucopyranose in 1992. Several stable conformers of both α- and β-glucopyranose were explored, and in all cases the α-anomer was found to be more stable than the β-anomer by 0.4−2 kcal mol^{-1} at the RHF level. Salzner and Schleyer[32] later considered various glucopyranose conformations as part of a study probing the anomeric effects in monosaccharides.

Glennon et al.[7] has performed the most extensive computational study of mono- and disaccharides to date, focusing on conformers of α-D-glucopyranose, and the exocyclic hydroxymethyl rotational surface in particular. Three minimum conformations were found along the exocyclic hydroxymethyl rotational surface (rotation about the C5−C6 bond, Figure 1) designated GG, GT, and TG, each separated by an approximately 120° dihedral rotation. The relative energy differences between conformers were found to be small (<4 kJ mol^{-1}) and somewhat basis-set dependent. In a very recent article, Barrows et al.[33] studied the relative stability of various conformers associated with both the axial ($^1C_4$) and equatorial ($^4C_1$) chair forms of β-D glucopyranose using both classical molecular mechanics and quantum mechanics at an exceedingly

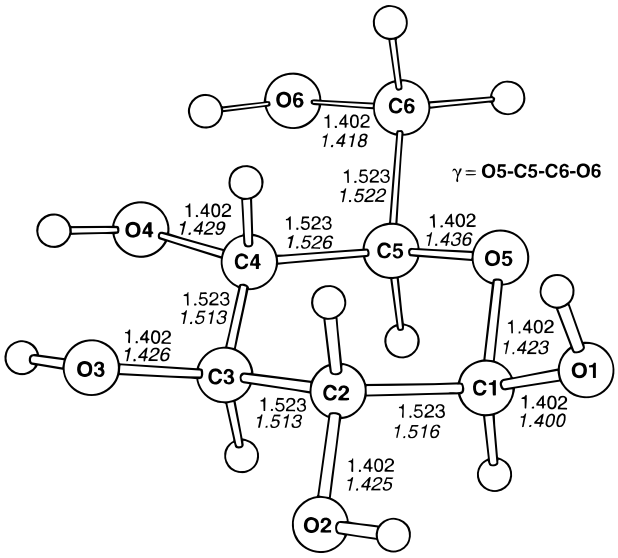

Figure 1. Counterclockwise-TG conformation of β-D-glucopyranose. Bond distances (Å) are those obtained at the RHF 6-31G(d) and MP2 6-31G(d) (in italics) levels of theory.

high level of theory. The relative energetic results were found to be somewhat dependent on both basis set and extent of electron correlation. At the highest level, the $^4C_1$ chair form was found to be the lowest in energy by 8 kcal mol^{-1}, and the GT conformer of the $^4C_1$ chair was found to be lower than TG. The $^4C_1$ chair forms were also found to be better solvated than the $^1C_4$ chairs by approximately 5−9 kcal mol^{-1} based on the SM4 solvation model. The predominant solvation effects appeared to be related to both polarization and improved hydrogen bonding with first-shell water molecules. The recent work of Barrows et al.[33] highlights the complexity of the problem and the importance of extending the level of electronic structure theory in evaluating the relative stability of rotamers in simple monosaccharides. The effects of solvation also play an extremely important role in determining the stability and relative population of possible rotamers and anomers of monosaccharides. Cramer and Truhlar[34] are the only researchers to consider the effects of aqueous solvation on the anomeric and conformational stability of D-glucopyranose using a quantum-based solvation model. Utilizing the AM1-SM2 and PM3-SM3 solvation models, Cramer and Truhlar explored the three important conformers associated with rotation of the exocyclic hydroxymethyl group and found that the relative stability of these rotational conformers followed the order GG > GT > TG. Moreover, they found little difference in the free energies of aqueous solvation between the α- and β-anomers of D-glucopyranose.

Previously, our group studied the intrinsic gas-phase exocyclic hydroxymethyl rotational surface of α-D-glucopyranose using ab initio quantum mechanical methods.[35] The relative energy of the three important rotational conformers (GT, GG, and TG) as well as the rotational transition states connecting them were explored at the RHF and MP2 levels with basis sets ranging in complexity from 6-31G(d) to 6-311G(2d,1p). The three conformers were found to be very similar in energy with a relative free energy difference of ~1 kJ mol^{-1}, following the order GG < TG < GT. These results were also compared to molecular mechanics results obtained using the modified AMBER force fields of Homans[18] and Glennon et al.[7] When the quantum and classical results were compared, a number of inconsistencies were found between the relative energy of the three minima as well as between the three rotational transition

states connecting them, which may have important implications for the use of such force fields in modeling conformer distributions. In the present investigation, the computational model has been extended to include results on the exocyclic hydroxymethyl rotational surface of the corresponding β-D-glucopyranose anomer. The structure and relative energetics of the three conformational minima and their connecting transition states have been characterized in the gas phase at the RHF and MP correlated levels as well as in aqueous solution using both a simple continuum dipole model and a polarized continuum solvation model. With these results, and through the use of the two different continuum solvation models, a number of important questions regarding the relative energies of glucopyranose conformers can be further addressed, including what effect, if any, the anomeric difference at C_1 has on the intrinsic exocyclic hydroxymethyl rotational surface, whether or not the $\beta-\alpha$ anomer energy difference observed in solution can be accounted for by intrinsic electronic effects, and finally, what effect aqueous solvent has on mediating these relative energetics.

Computational Model[45]

The structures, relative energies, and vibrational frequencies of the salient stationary points associated with rotation about the exocyclic C5−C6 bond of β-D-glucopyranose have been determined at both the RHF and MP correlated levels. A total of six critical structures were identified, including three stable minima and three connecting transition states. On the basis of our previous study,[35] the 6-31G(d) basis set was found to be adequate in characterizing both the structure and relative energetics of these molecules and, subsequently, was used exclusively in this study. Effects of dynamic electron correlation on the structure and the relative energies were estimated using second order Møller−Plesset perturbation theory[36] (MP2 through MP4(SDTQ)) as well as density functional theory[37−39] (Becke exchange functionals and Lee−Yang−Par correlation functionals, BLYP). As was pointed out by Cramer and Truhlar,[34] D-glucopyranose could potentially exhibit nearly 3000 stable conformers if both α- and β-anomers, both axial and equatorial chair forms, and rotation of the five hydroxyl groups and one exocyclic hydroxymethyl group are considered. Although many of these conformers are unimportant energetically, exploration of even a small fraction of these structures quantum mechanically would be a daunting task. Consistent with our previous study, the focus here centers only around the exocyclic hydroxymethyl rotational surface; therefore, only the most stable overall rotational conformation for the hydroxyl groups at C1 through C4, the cc arrangement, is considered and is taken as the reference state.

The various stationary points associated with exocyclic hydroxymethyl rotation were located by displacement of the O5−C5−C6−O6 dihedral angle in 60° increments, followed by complete optimization. Each stationary point was verified as a minimum or a transition state via analytic second derivative calculations. To ensure that each stationary point on the C5−C6 rotational surface represents the most stable structure within the cc arrangement, the exocyclic hydroxyl rotational surface was also explored by rotation about the C6−O6 bond. Completely optimized structures were obtained for each stationary point at the RHF and MP2 levels using the 6-31G(d) basis set. Vibrational frequencies were then obtained at the RHF 6-31G(d) level and used to determine the absolute entropy and relative free energy of each stationary point through a standard statistical thermodynamics analysis. Finally, the effects of aqueous solvation on the relative energetics were determined using both the simple Onsager dipole continuum model and the more sophisticated self-consistent isodensity polarized continuum model (SCIPCM) developed by Tomasi et al.[40] and Frisch et al.[41,42] All 12 α- and β-D-glucopyranose stationary points were reoptimized at both RHF and MP2 levels of theory, with the consistent application of the 6-31G(d) basis set. In both cases, a dielectric constant of 80 was used throughout.

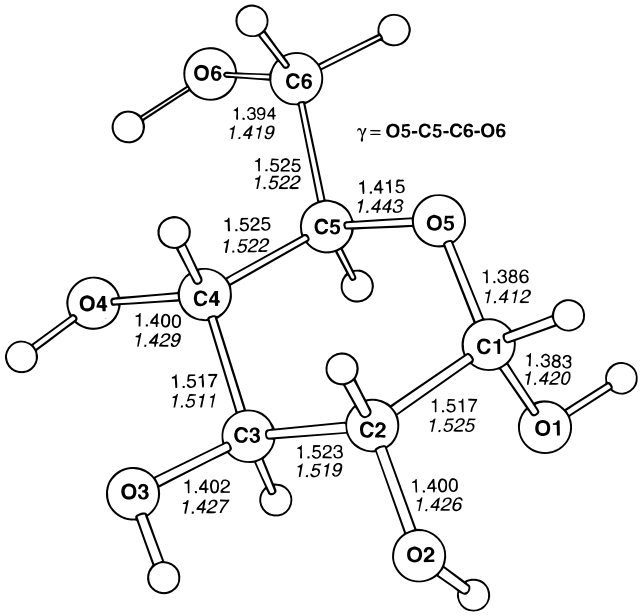

Figure 2. Counterclockwise-TG conformation of α-D-glucopyranose. Bond distances (Å) are those obtained at the RHF 6-31G(d) and MP2 6-31G(d) (in italics) levels of theory.

All calculations were performed using the Gaussian94 electronic structure package[43] running on a variety of platforms.[44]

Results and Discussion

Exocyclic Hydroxymethyl Rotational Surface. Shown in Figure 1 is a three-dimensional representation of the most stable conformer of β-D-glucopyranose, TG, along with bond distances determined at the RHF 6-3lG(d) and MP2 6-31G(d) levels. As seen from the data, electron correlation at the MP2 level has only a moderate effect on these structural parameters. The C−O bonds are slightly longer at the MP2 level (ca. 0.025 Å), whereas interestingly, there is a slight contraction of the C−C bonds (ca. 0.004 Å) relative to the RHF structures. While the specific reason for this trend is still unclear, it may be due either to incorporation of charge transfer type configurations into the wavefunction, which gives rise to an electron-deficient ring at the MP2 level, or to the limited flexibility of the 6-31G(d) basis set. Such findings are consistent with a previous analysis of α-D-glucopyranose performed by our group[35] as can be seen from the equivalent TG stationary point representation for this anomer provided in Figure 2. The corresponding bond distances determined at the RHF 6-31G(d) and MP2 6-31G(d) levels for α-D-glucopyranose also indicate a C−O bond elongation of ca. 0.025 Å, and slight C−C bond contraction of ca. 0.003 Å.

Table 1 shows the relative energetic data for the exocyclic hydroxymethyl surface including the intrinsic relative electronic energy, ΔE_e° and the relative free energy at 298 K, ΔG_{298}°, at the RHF, RB-LYP, MP2, and MP4(SDTQ) levels of theory. Similar to the α-anomer, β-D-glucopyranose also exhibits three stable minima and three connecting transition states along the

TABLE 1: Relative Electronic Energies, ΔE_e° (kJ mol^{-1}), and Free Energies, ΔG_{298}° (kJ mol^{-1}), for Exocyclic Hydroxymethyl Rotational Conformations of β-D-Glucopyranose[a,b]

	6-31G(d) RHF		6-31G(d) RB-LYP		6-31G(d) MP2(fc)		6-31G(d) MP4(SDTQ)[d]	
conformer	ΔE_e°	ΔG_{298}°	ΔE_e°	ΔG_{298}°	ΔE_e°	ΔG_{298}°	ΔE_e°	ΔG_{298}°
TG	0.22	2.72	−1.38	1.12	0.68	3.18	0.55	3.05
TS1	17.74	21.32	11.47	15.05	15.71	19.29	15.24	18.82
GG	0.00[c]	0.00	0.00[c]	0.00	0.00[c]	0.00	0.00[c]	0.00
TS2	27.39	27.99	24.42	25.02	28.93	29.52	28.34	28.94
GT	0.84	1.31	1.24	1.71	2.55	3.02	2.38	2.84
TS3	19.90	22.40	18.59	21.09	22.83	25.33	22.06	24.56

[a] ΔG_{298}° were obtained directly from the electronic energies, and corrections including zero-point vibrational energy, thermal, and entropic terms, were determined from a standard thermodynamic analysis using harmonic frequencies obtained at the RHF 6-31G(d) level. [b] 1 kcal mol^{-1} = 4.184 kJ mol^{-1}. [c] Absolute energies for the GG conformation, in hartrees, are −683.3322 2732 9, −686.9402 2542 5, −685.1772 0062 2, and −685.3062 06 for RHF 6-31G(d), RB-LYP 6-31G(d), and MP4 6-31G(d) calculations, respectively. The GG conformer was defined as zero by convention. [d] Based on the MP2 6-31G(d) structures.

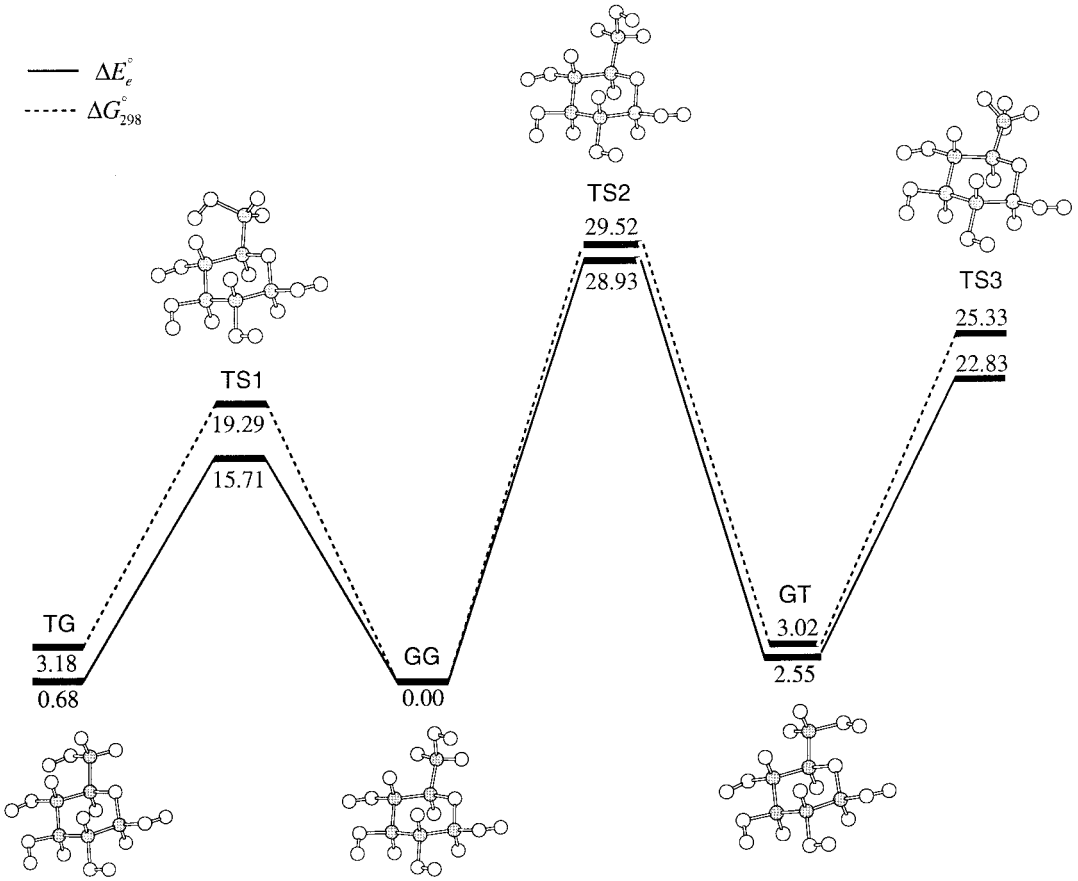

Figure 3. Relative electronic energy, ΔE_e° (solid line), and free energy, ΔG_{298}° (dashed line), diagram (kJ mol^{-1}) for the stationary points along the exocyclic hydroxymethyl rotational surface of β-D-glucopyranose at the MP2 6-31G level of theory.

exocyclic hydroxymethyl rotational coordinate, γ. Starting arbitrarily from the TG minimum structure, where the hydroxymethyl group is roughly parallel to the plane of the glucopyranose ring with an O5−C5−C6−O6 dihedral angle (γ) of 168.5° at the RHF level, rotation about γ passes through an initial transition state structure, TS1 (γ = −137.8°), and then through a second minimum conformer GG (γ = −83.0°) in which the exocyclic hydroxymethyl group is nearly perpendicular to the pyranose ring. The electronic energy of the GG conformer proves to be the lowest for all levels of theory except for that of the RB-LYP where TG is the lowest; however, the differences are less than 2 kJ mol^{-1}. As the hydroxymethyl group is further rotated, a second transition state, TS2 (γ = −57.8°), is reached, followed by a third minimum, GT (γ = 58.7°), and a third transition state, TS3 (γ = 108.4°), before leading back to the initial TG structure. Apart from minor variations in the C5−C6 bond length for each rotational minima compared to its associated transition states due to electron−electron repulsion as well as slight changes in the orientation of the primary hydroxyl group, the overall structure of each conformer is very similar.

The incorporation of zero-point vibrational energy, constant volume heat capacity, and entropic ($T\Delta S$) corrections based on RHF 6-31G(d) vibrational frequencies yields values of ΔG_{298}° for each conformer which are also given in Table 1 and graphically depicted in Figure 3. While the energetic effect of this analysis proves minor for the majority of the structures, with a relative energetic difference on the order of 0.35 kJ mol^{-1}, the TG minimum and its associated transition states, TS1 and TS3, exhibit the largest relative shifts (2.51, 3.60, and 2.50 kJ mol^{-1}, respectively). This increased effect is primarily the result of intramolecular interactions due to the parallel orientation of the exocyclic hydroxymethyl group with respect to the plane of the glucopyranose ring and is consistent with a thermody-

namic analysis performed on α-D-glucopyranose.[35] In our previous study, the relative energetic difference of 0.20 kJ mol^{-1} for the α-anomer was also found to be surpassed by the shifts of the TG minimum (1.10 kJ mol^{-1}) and its associated transition states TS1 (2.81 kJ mol^{-1}) and TS3 (3.31 kJ mol^{-1}).

The three hydroxymethyl rotational minima (TG, GG, and GT) are found to be very similar in energy. Relative free energy differences were found to be within ~3 kJ mol^{-1} at all levels of theory. Improved electron correlation from RHF 6-3lG(d) to MP2 6-3lG(d) results in a minor increase in energy, with the greatest difference of 1.71 kJ mol^{-1} for the GT conformer. The relative free energies vary slightly at the BLYP level, primarily as a result of TG conformer stabilization. The final ordering of the relative free energies at the MP2 level is GG (0.00 kJ mol^{-1}) > GT (3.02 kJ mol^{-1}) > TG (3.18 kJ mol^{-1}). Probing the effects of electron correlation further through MP4(SDTQ) shows little difference between MP4 and MP2 and no qualitative change in the ordering of the relative energies for the various conformers and associated transition states. In fact, the relative energy differences for each stationary point along the hydroxymethyl rotational surface are all within 1 kJ mol^{-1} when comparing the MP2 and MP4 results. The intrinsic exocyclic hydroxymethyl rotational barriers connecting these minima, however, are substantial. The relative free energies range from 18.8 kJ mol^{-1} for TS1 to 29 kJ mol^{-1} for TS2 at the MP4-(SDTQ) level. With improved electron correlation from RHF to MP2, an average increase of 0.77 kJ mol^{-1} is found, and similar to that of the minima, the relative order of stability is independent of computational level with TS1 < TS3 < TS2. While these barriers preclude rapid conformer interconversion in the gas phase at room temperature, the most favorable conversion, as for the α-D-glucopyranose,[35] remains that between TG and GG.

The close proximity of the C6 hydroxyl group to nearby oxygen atoms influences each of the stationary points identified on the rotational surface. While the precise spatial requirements for a "hydrogen bond" remain an issue of much debate, a comparison of the optimized β-D-glucopyranose structures can nevertheless provide pertinent information regarding the relative strengths of hydrogen bond interactions between the C6 hydroxyl and nearby oxygens. The TG conformer C6 hydroxyl forms an intramolecular hydrogen bond with O4 (O6H−O4 distance 2.00 Å, O6-O6H−O4 angle 136.5°), which is maintained through rotation to the TS1 transition state (O6H−O4 distance 1.96 Å, O6-O6H−O4 angle 133.4°) and in the GG minimum conformer (O6H−O4 distance 2.41 Å, O6−O6H−O4 angle 121.2°). In the TS2 conformer, however, the O6 hydroxyl orients itself away from O4 and toward O5, resulting in a less extensive hydrogen bond interaction (O6H−O5 distance 2.27 Å, O6−O6H−O5 angle 108.9°). This trend continues through rotation to the GT conformer (O6H−O5 distance 2.27 Å, O6−O6H−O5 angle 109.2°). In the TS3 structure, interaction is again predominant between the C6 hydroxyl and O4, yet the possibility of hydrogen bond interaction is very low (O6H−O4 distance 3.31 Å, O6−O6H−O4 angle 104.7°). Although the potential for intramolecular hydrogen bonding may stabilize the TS1 conformer over the remaining transition states, consequently resulting in the lowest interconversion barrier, the lack of a clear relationship corresponding to minima stability would indicate that the current definition of hydrogen bonding, which remains somewhat arbitrary, fails to fully describe intramolecular carbohydrate interactions. Such findings are consistent with previous ab initio studies performed by our group[35] and with dynamics simulations performed by Glennon et al.[7] on α-D-glucopyranose. The latter analysis found " 'nonstandard' (in the sense of the preferred angle between the hydrogen bond donor and acceptor)" intramolecular hydrogen bonds, and a distance-only hydrogen bond showed a better correlation with the relative C−C−O−O dihedral angle flexibility.

TABLE 2: Intrinsic Electronic Energy Difference ΔE_e° (kJ mol^{-1}) between β- and α-D-Glucopyranose for Each Stationary Point along the Exocyclic Hydroxymethyl Rotational Surface

stationary point	6-31G(d) RHF	6-31G(d) BLYP	6-31G(d) MP2(fc)	6-31G(d) MP4(SDTQ)
TG	4.88	9.45	10.75	10.96[a]
TS1	4.12	8.97	10.14	
GG	4.18	8.80	9.99	
TS2	3.75	8.16	9.20	
GT	4.68	8.68	10.27	
TS3	5.08	9.79	1.14	

[a] Taking into account zero-point vibrational energy, heat capacity, and entropic corrections determined from frequencies at the RHF 6-31G(d) level, this corresponds to ΔG_{298}° (β−α) = 8.65 kJ mol^{-1}.

β−α Anomer Energy Difference. The energetic results for β-D-glucopyranose given in Table 1 combined with the energetic results on α-D-glucopyranose from our previous work[35] provide the necessary data to analyze the intrinsic β−α anomer energy difference for each hydroxymethyl rotational conformer, including the rotational transition states. These relative energetic results at various levels of theory are given in Table 2 and graphically presented in Figure 4. As can be seen from the data, at all theoretical levels the α-anomer proves to be more stable than the β-anomer in the gas phase. The average β−α electronic energy difference over all six stationary points is found to be 4.4 kJ mol^{-1} at the RHF level and 10.2 kJ mol^{-1} at the MP2 level.

At each level of theory, the β−α anomer energy difference is consistent for the various minima and transition states along the exocyclic hydroxymethyl rotational surface within 1−2 kJ mol^{-1}. Moreover, the intrinsic electronic energy difference between the α- and β-anomers does become more pronounced with improved electron correlation. Figure 4 depicts the relative free energy differences at the MP2 level, with the most stable α-D-glucopyranose GG conformer defined as zero. Clearly, the α-anomer is more stable than the β-anomer regardless of exocyclic hydroxymethyl rotation, with very little variation. To assess the convergence of the MP2 results, the β−α anomer energy difference for the most stable TG conformer was also determined at the MP4(SDTQ) 6-31G(d) level. As seen in Table 2, the MP2 and MP4 results differ by less than 0.25 kJ mol^{-1}, suggesting that the MP2 results are accurate to at least 2 kJ mol^{-1} and well within chemical accuracy. It is clear from the intrinsic gas-phase electronic structure results presented here that α-D-glucopyranose is more stable than the corresponding β-anomer in the gas phase, and given the convergence in the MP series seen for the rotational conformers of β-D-glucopyranose, the β−α anomer energy difference presented here at the MP4(SDTQ) 6-31G(d) level is unlikely to change significantly at higher levels. A conservative estimate of the intrinsic gas-phase β−α anomer energy difference could be placed at 11 ± 2 kJ mol^{-1}. Incorporating thermal and entropic corrections, the gas-phase free energy difference is estimated to be 8 ± 2 kJ mol^{-1} favoring the α-anomer. These results, although consistent with previous theoretical studies on glucopyranose, are at variance with the experimentally determined distribution favoring β-D-glucopyranose in aqueous solution.

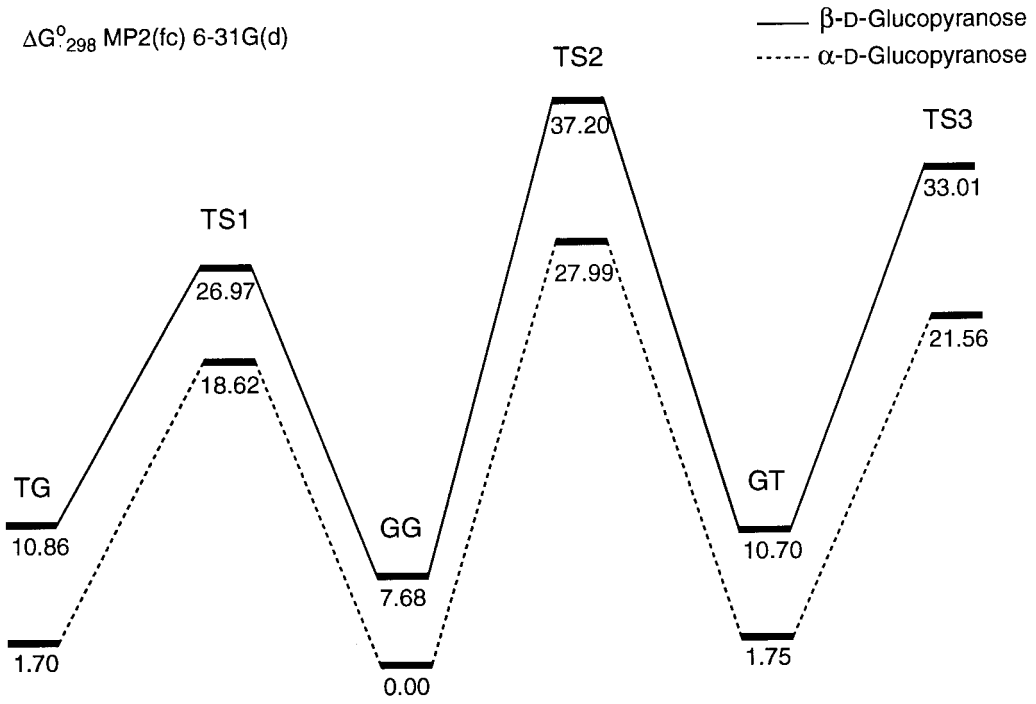

Figure 4. The $\beta-\alpha$ anomer free energy diagram (k*J* mol^{-1}) for the stationary points along the exocyclic hydroxymethyl rotational surface of D-glucopyranose at the MP2 6-31G level of theory. All values are referenced to the counterclockwise-GG conformer of α-anomer which represents the lowest energy conformer found.

Solvation Effects. Given the intrinsic gas-phase energetic results presented above and the fact that D-glucopyranose in aqueous solution favors the β- anomer over the α-anomer by a ratio of 2:1, corresponding to a $\beta-\alpha$ free energy difference of approximately -1.3 kJ mol^{-1}, the effects of solvation are clearly qualitatively essential for the accurate modeling of this simple carbohydrate system. To qualitatively account for these solvation effects in both the exocyclic hydroxymethyl rotational surface of β-D-glucopyranose and the $\beta-\alpha$ anomer energy difference, two different continuum solvation models were tested, including an Onsager dipole model and an SCIPCM model using both RHF 6-3lG(d) and MP2 6-31G(d) wave functions.

The effects of these continuum solvation models on the absolute energetics of the different β-D-glucopyranose conformers were found to vary considerably. While application of the dipole model stabilized the β-D-glucopyranose conformers at the RHF level by an average of 3.5 kJ mol^{-1}, an average destabilization of 16.9 kJ mol^{-1} was exhibited at the MP2 level. An average stabilization of -84.6 and -54.3 kJ mol^{-1} at the RHF and MP2 levels, respectively, resulted from the SCIPCM model. Such large increases in stabilization over the simple dipole model are most likely due to the effect of electron density polarization and to the contribution of additional multipole terms included in the continuum model.

The effects of the solvation models on the relative energetics for the rotational surface are presented in Table 3. As seen in the table, both the TG and TS1 conformers were destabilized relative to the GG minimum at the MP2 level using the SCIPCM model. Rotation of the exocyclic hydroxymethyl toward O4, however, diminishes the effects of solvation, as in the case of the TS2 and GT conformers which are unchanged, or slightly improved, as is the TS3 conformer. The relative stability ordering of the minima remains the same as for gas-phase MP2 calculations incorporating free energy corrections with GG (0.00 kJ mol^{-1}) > GT (2.39 kJ mol^{-1}) > TG (5.29 kJ mol^{-1}). However, the transition states exhibit some variation as TS3 (21.21 kJ mol^{-1}) < TS1 (21.71 kJ mol^{-1}) < TS2 (28.57 kJ mol^{-1}). Primarily as a result of the increased TS1 rotational barrier, interconversion in the solvated model between the GT and TG minima proves to be roughly equivalent to that between TG and GG.

TABLE 3: Relative Electronic Energies Including Solvation ΔE_e° (kJ mol^{-1}), for Each Conformer along the Exocyclic Hydroxymethyl Rotational Surface of β-D-Glucopyranose

	6-31G(d) RHF			6-31G(d) MP2(fc)		
conformer	gas phase	dipole	SCIPCM	gas phase	dipole	SCIPCM
TG	0.22	1.51	6.70	0.68	2.02	5.29
TS1	17.74	18.72	23.67	15.71	17.00	21.71
GG	0.00[a]	0.00[a]	0.00[a]	0.00[a]	0.00[a]	0.00[a]
TS2	27.39	27.13	27.59	28.93	28.20	28.57
GT	0.84	2.05	2.18	2.55	3.35	2.39
TS3	19.90	23.35	19.34	22.83	25.65	21.21

[a] Absolute energies for the GG conformation, in hartrees, are $-683.332\,273\,9$, $-683.334\,030\,9$, and $-683.365\,345\,4$ for RHF 6-31G(d) gas phase, dipole, and SCIPCM calculations, and $-685.177\,006\,2$, $-685.170\,889\,3$, and $-685.198\,224\,2$ for MP2 6-31G(d) gas phase, dipole, and SCIPCM calculations, respectively. The GG conformer was defined as zero by convention.

TABLE 4: Electronic Energy Differences Including Solvation Effects, ΔE°_{solv} ($\beta-\alpha$) (kJ mol^{-1}) between β- and α-D-Glucopyranose for the Counterclockwise-TG Conformation

stationary point	gas phase	dipole	SCIPCM
RHF 6-31+G(d)	4.88	4.40	1.81
MP2(fc) 6-31+G(d)	10.75	9.72	7.41

Data from the analysis of the effect of solvation on the anomeric electronic energy difference is provided in Table 4. As can be seen from the data in the table, β-D-glucopyranose is preferentially stabilized over the α-anomer with incorporation of the dipole model, resulting in a 0.5 kJ mol^{-1} and 1.0 kJ mol^{-1} decrease in the electronic energy difference of the TG minimum at the RHF and MP2 levels, respectively. Improvement to SCIPCM leads to a further dramatic decrease in the $\beta-\alpha$ energy

difference; shifts of more than 3 kJ mol^{-1} occur at each computational level. While the α-D-glucopyranose anomer remains the more stable, the gap is reduced to 1.81 kJ mol^{-1} at the RHF level, and to 7.41 kJ mol^{-1} with the improved electron correlation of MP2. Although their effects are significant and the shifts are in the right direction, these specific continuum-based solvation models are obviously insufficient to account for the overall β-anomer preference observed in aqueous solution for D-glucopyranose. Clearly, discrete solvent molecules must be involved in the preferential stabilization of the β-anomer. Studies aimed at exploring the relative stability of the α- and β-anomers of D-glucopyranose with discrete water molecules, and in particular the number of discrete water molecules necessary to account for the observed $\beta-\alpha$ anomer energy difference, are currently underway.

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