Factors Controlling Relative Stability of Anomers and Hydroxymethyl Conformers of Glucopyranose

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ABSTRACT: The relative energies of 11 different conformers of D-glucose, including different exo-anomeric orientations and at least one of each hydroxymethyl conformer (G^-, G^+, and T) for each of the two anomeric forms (α and β), were calculated at much more complete levels of quantum mechanical (QM) electronic structure theory than previously available, and relative free energies in solution were calculated by adding rotational, vibrational, and aqueous solvation effects. The gas-phase results are based on very large basis sets (up to 624 contracted basis functions) and the coupled cluster method for electron correlation. Solvation Model 5.4/AM1 was used to calculate the effects of aqueous solvation. Factors contributing to the relative energies of these conformers have been analyzed. Relative energies varied considerably (up to 4.5 kcal/mol), depending on the theoretical level, and different levels of theory disagreed as to which anomer was lower in energy. The highest-level gas-phase calculations predicted the α-anomer to be lower in free energy by 0.4 kcal/mol (Boltzmann average). Gas-phase energies from several different classical force fields were compared to QM results. The QM structures optimized at the MP2/cc-pVDZ level of theory compared well with experiment for three different crystal structures. In water, the β-anomers were better solvated than the α-anomers by 0.6 kcal/mol (Boltzmann average). Contributions of individual hydrophilic groups to the solvation free energies were analyzed. J Comput Chem 19: 1111–1129, 1998

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Introduction

Portions of the conformational potential energy surface for D-glucose have been studied by many researchers.[1–23] The significant conformational issues addressed in these studies (for both gas and aqueous solution phases) revolve around one or more of the following questions: (1) What is the preferred ring form and what is the energetic separation between the two different chair forms ($^4C_1$ and $^1C_4$)? (2) What is the preferred configuration at the anomeric center C(1) (see Fig. 1) and how much higher in energy is the other anomer? (3) What are the preferred orientations of the exocyclic hydroxyl and hydroxymethyl substituents? (4) What are the energetic consequences that arise from the coupling of different conformational issues, that is, to what extent can one consider the anomeric equilibrium as separate from the hydroxymethyl conformation, etc? (5) How does a surrounding solvent change the intrinsic (gas-phase) conformational preferences? In particular, for hydrogen-bond donor and/or acceptor solvents, to what extent do intermolecular hydrogen bonds between glucose and the solvent compete with intramolecular hydrogen bonds between different glucose hydroxyl groups?

Because of the conformational complexity of glucopyranose, with six rotating groups, two possible anomers, and the possibility of alternative ring conformations, relative free (i.e., conformationally averaged) energies for anomers, rotamers, etc., can be difficult to model. Furthermore, the size of glucose (12 heavy atoms and 12 hydrogen atoms) has typically restricted computational studies to fairly modest levels of theory, raising questions with respect to the convergence of calculated relative energies.

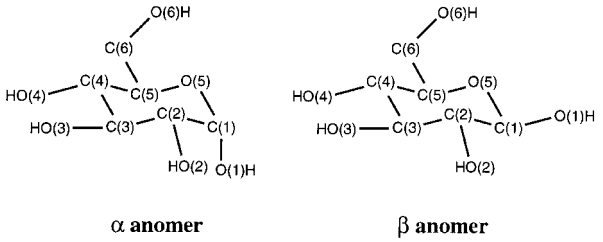

FIGURE 1. Configuration of α- and β-anomers.

We recently examined the question of the alternate chair-form equilibrium using four different conformers of β-glucose.[16] In that work, we identified a protocol that apparently converges the quantum mechanical relative energies, compared the relative utility of different molecular mechanics approaches[24–26] for structures and energetics, and examined the effects of aqueous and nonpolar solvation using the Austin Model 1–Solvation Model 4 (AM1-SM4) series of quantum statistical solvation models.[16,27–29]

Employing similar levels of theory as in that study, we here examine the anomeric equilibrium of glucose in the gas phase and aqueous solution using 11 different structures including at least one of each hydroxymethyl conformer for each of the two anomers (Fig. 2). We account for aqueous solvation effects using the recently developed SM5.4/AM1[30] solvation model. The present work represents a significant improvement over an earlier study by two of the present investigators,[10] both in terms of reliability of the theoretical treatment and in terms of scope. In the latter regard, we note that the previous study examined 6 of the 11 stereostructures discussed in what follows, but those structures had been optimized at an unconverged quantum mechanical level and the gas-phase free energies were similarly unconverged.[9] The earlier study focused solely upon the effects of aqueous solvation on the anomeric equilibrium; the present study, on the other hand, effectively converges the gas-phase quantum mechanical relative energies and also includes an examination of molecular mechanics levels of theory.

Furthermore, we use an improved solvation model. Our previous study[10] of the glucose anomeric equilibrium made use of the AM1-SM2[31] and PM3-SM3[32] solvation models to assess aqueous solvation effects. Those models are parameterized for general organic solutes and predict absolute free energies of solvation for such molecules with a reasonably high degree of accuracy (typically within about 1 kcal[33]—all energies in this article are molar), but they are not optimal for separating the relative importance of electrostatic effects from nonelectrostatic first-solvation-shell effects.[30] The present study employs a more so-

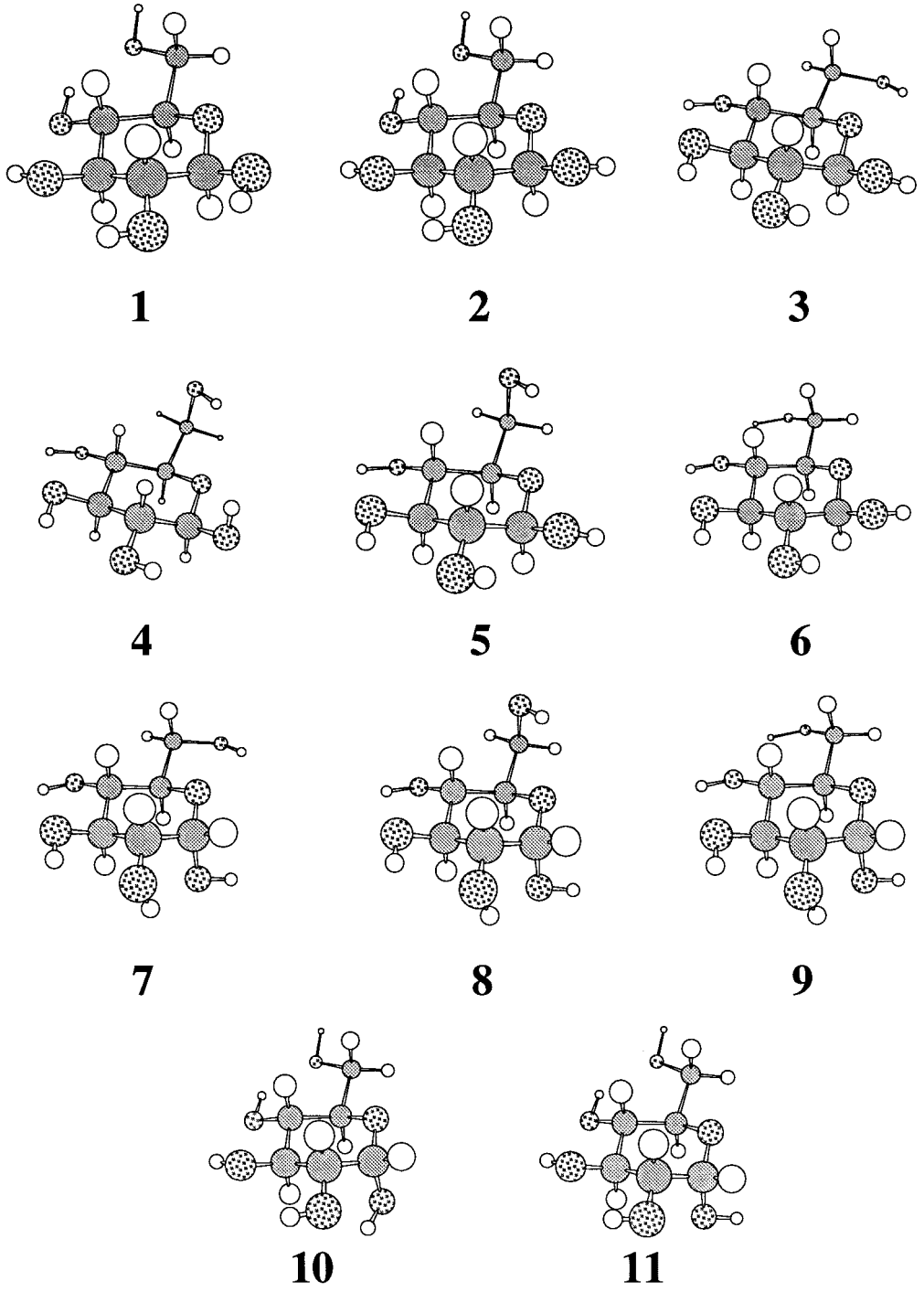

FIGURE 2. Eleven conformations of D-glucose optimized at the MP2/cc-pVDZ level.

phisticated aqueous solvation model, SM5.4/AM1, which has been designed to use a high-quality representation of the solute charge density[34] to give an optimal separation between electrostatic and first-solvation-shell effects. Our previous work on the $^4C_1/^1C_4$ equilibrium employed the AM1-SM4:sugar aqueous solvation model.[16,27] At the time of that study the aqueous SM5.4/AM1 model was not yet available. The AM1-SM4:sugar solvation model was specifically parameterized to reproduce aqueous solvation free energies for hydrocarbons, ethers, and alcohols with the goal of

providing a useful model for sugars. However, as will be described in further detail, the SM5.4/AM1 model offers a still more accurate description of solvation for the functional groups important in sugars, even though it was designed for completely general use.

The modeling approach we will use is similar to our earlier study of the chair equilibrium.[16] We have chosen our 11 conformers based on their coverage of interesting regions of conformational space and on prior molecular mechanical (MM) and quantum mechanical (QM) studies having identified them as being of low energy. We further use high-level QM calculations to refine the geometries and energies of these structures and to calculate rotational and vibrational contributions to the relative free energies. Solvation effects are modeled as described earlier (and discussed in further detail in what follows). By combining our best QM results with solvation effects, we arrive at our best estimates for free energies in aqueous solutions.

Having obtained our best estimates, we will also explore the reliability of less expensive theoretical methods, which are of considerable interest for modeling other sugars and more complicated problems like glycoproteins and sugar interactions. At the QM level, we test both semiempirical molecular orbital theory[35,36] and lower-level *ab initio* approaches[37]—the latter continue to find use in force-field development,[13,23,38] so it is critical to evaluate their quality. At the MM level, we test the predictive capabilities of the MM3[24,26] force field [as implemented in the MM3(96) program] and provide comparison to several other force fields as well.

Background

In aqueous solution, the anomeric equilibrium for D-glucopyranose has been established to be 40:60 α:β;[39] that is, the population of β-anomers is lower in free energy than α by 0.3 kcal. In contrast, for the simpler model system 2-methoxytetrahydropyran, the observed preference in most nonpolar solvents (in which glucose itself is insoluble) is for axial placement of the methoxy group by 0.9 kcal/mol.[40] Conformers with axially disposed hydroxyl or alkoxyl groups at the 2-position are stabilized by $n_O \rightarrow \sigma^*_{CO}$ hyperconjugative delocalization where the nonbonding lone pair is on the tetrahydropyran oxygen (the anomeric effect[41-47]); equatorial conformers are not geometrically able to take advantage of this stereoelectronic effect. Anomeric equilibria for both sugars and simplified sugar model systems can be quite sensitive to solvent effects—Graczyk and Mikolajczyk have provided a recent review,[47] and subsequent computational work in this area has also been summarized.[48,49]

Thus, the equilibrium preference for the β-anomer of glucose in aqueous solution inspires the question of whether this reflects a solvation effect upon a normal anomeric equilibrium, or whether it reflects an intrinsic preference associated with the greater complexity of glucose compared to tetrahydropyran model systems. A large number of computational studies have focused upon this issue—an exhaustive summary of the literature may be found in the 1994 review by Graczyk and Mikolajczyk,[47] in the 1993 volume edited by Thatcher,[46] and in the recent articles by Zuccarello and Buemi[15] and some of the present investigators.[10,14] In no quantum mechanical study to date, however, has any systematic attempt been made to identify the intrinsic (i.e., gas-phase) anomeric equilibrium. Instead, various solvation models that represent the surrounding solvent either explicitly or as a dielectric continuum (with or without correction for first-solvation shell effects) have been employed, and relative solvation free energies (or, in some cases, the electrostatic components thereof) have been compared for different anomers. However, in the absence of any value for the gas-phase equilibrium constant, it is difficult to assess critically the predicted magnitudes of the differential solvation effects derived from the modeling studies. One of the goals of the present study is to estimate a gas-phase free energy difference to resolve this issue.

One difficulty that arises in determining the free energy difference between anomers is that other kinds of conformational isomerism are also operative in the glucose system. Of special importance is the rotational isomerism associated with the hydroxymethyl group. The C(6)—O(6) bond can be oriented trans to the C(5)—O(5) bond (abbreviated T in the present nomenclature convention), or in one of two gauche positions (G^+ and G^-). Because rotation about the C(5)—C(6) bond causes a correspondingly large translocation of the O(6) hydroxyl group, the energetic consequences of this isomerism are expected to be large and potentially to influence the anomeric equilibrium by long-range interactions (including solvent-mediated ones) with the anomeric hydroxyl group. Experi-

mentally, there is some information available about the preferred orientation of the hydroxymethyl group in aqueous solution. In particular, the two gauche conformations are about equally populated, whereas the trans conformation appears to account for less than 2% of the equilibrium.[50] This observation is of special interest because most gas-phase modeling studies have predicted trans hydroxymethyl conformers to be lower in energy than gauche ones.[3,7,9] The dominant factor has been the intramolecular hydrogen bond to O(4), which is possible for the T conformer—similar hydrogen bonding arrangements are not available for either G^+ or G^- [although favorable electrostatic interactions can take place between the O(6) hydroxyl proton and O(5)]. It has thus been considered a good test of aqueous solvation models to determine whether they predict that gauche conformers are better solvated than trans conformers, so that the the experimental equilibrium can be reproduced. In our recent work, however, we showed that, when converged levels of quantum mechanics are used, the lowest energy G^+ conformer is in fact 0.6 kcal lower in energy than the lowest energy T conformer for the β-anomer[16] (the α-anomer was not addressed in that work). Thus, whereas differential solvation may well favor the gauche conformers, it is not necessarily *required*, and it should not be used as a criterion for measuring the quality of a solvation model. To more completely understand this conformational isomerism, the present article compares all 11 of the structures shown in Figure 2.

Additional conformational issues associated with glucose include its ring form and the rotameric populations of the various hydroxyl groups. With respect to the ring form, our previous work[16] predicts that the $^4C_1$ chair is the only 6-membered ring conformation that contributes to the room temperature equilibrium, either in the gas phase or in solution. Hydroxyl group rotations are less easily addressed. In the gas phase, glucose conformers characterized by multiple intramolecular hydrogen bonds are lower than those that do not have them.[14,16,21] Experimental studies of sugars in aqueous solution,[51–54] however, offer no evidence for long-lived intramolecular hydrogen bonds, suggesting that solvent competes effectively as donor and/or acceptor. By employing the intramolecularly hydrogen-bonded structures of Figure 2 in our modeling studies of the anomeric equilibrium, we are assuming that the energetic effects of hydroxyl rotation, both in the gas phase and in solution, are approximately similar for each anomer. The validity of this assumption is discussed further in what follows. We have discussed elsewhere the special issues associated with rotational isomerism of the anomeric hydroxyl group (the exo-anomeric effect) and aqueous solvation effects thereupon.[21]

Theoretical Methods

The methods employed were thoroughly described in our previous study of glucose chair forms.[16] The most important highlights are provided next. We also provide a description of the Solvation Model 5.4/AM1 water model.[30]

MOLECULAR MECHANICS

We used the MM3 force field,[24,26] which is a general model intended for the conformational analysis of organic molecules. For the parameters needed for glucose, with the exception of constants used to describe the torsional potential about HO—CO bonds, this is the same force field we used in our previous work,[16] there called MM3(94); for brevity, we simply use the nomenclature MM3 here. This force field includes an angle-dependent hydrogen-bonding potential and three-term Fourier series are parameterized to describe torsional potentials. Energetic and conformational consequences of the anomeric and exo-anomeric effects are incorporated into the Fourier potentials so as to yield gauche preferences for HOCO and COCO dihedral angles. The MM3 force field also contains stretch–torsion coupling terms that modify bond lengths at an anomeric center depending on the relevant torsion angle. The HOCO torsional parameters V1, V2, and V3 used here are −1.832, −2.208, and 0.547, respectively.[55]

Parameterization of MM3 has been carried out in part by assuming an artificial dielectric constant of $\varepsilon = 1.5$ and comparing to *ab initio* calculations. The present calculations assume the same dielectric constant. Several other studies have shown this to be suitable.[14,16,21,25,56–58]

Although MM3 is parameterized based on r_g values, that is, the bond lengths observed from gas-phase electron diffraction studies, the MM3(96) program[59] uses vibrational frequencies to also calculate r_e equilibrium bond lengths (for comparison to QM calculations), and r_α low temperature x-ray diffraction bond lengths.[25] These latter bond lengths are particularly important for validating

carbohydrate calculations, because essentially all structural data for these species come from crystallography (*vide infra*). Other important enhancements in the MM3(96) version of the MM3 program include improvement of the geometry optimization routines, one effect of which is to eliminate many structures spuriously identified as minima when batch procedures minimizing very large numbers of structures are undertaken (the torsion angles of hydroxyl groups started far from a local-minimum geometry would oscillate and not converge to the minimum-energy value). For this work, geometry optimizations were carried out by first using a block-diagonal routine to an intermediate level of convergence and then using a full matrix minimizer to achieve very precise final structures. These minimizations proceeded until the energy change per cycle was less than 1.92 cal and the rms forces were less than 0.1 cal/angstrom (Cartesian coordinates). This procedure gave reproducible energies for identical structures within 0.1 cal, irrespective of starting conformation. Minimizations were carried out for all 729 possible staggered orientations of the exocyclic substituents for both anomers, and final structures differing by 1 cal or more from all others were assumed to be different minima.

Conformational energies from other force fields were either taken from the literature or provided by other researchers as part of works in progress.

QUANTUM MECHANICS

Semiempirical molecular orbital theory was employed to optimize structures with the Austin Model 1[35] (AM1) and Parameterized Model 3[36] (PM3) Hamiltonians. *Ab initio* calculations were carried out at the restricted Hartree–Fock (HF) level[37] using a number of standard basis sets and also a hybrid basis set that combines the s and p functions of the cc-pVQZ[60] basis with the d and f polarization functions of the cc-pVTZ basis. We refer to this final basis as cc-p^{T}VQZ; it is our largest basis set, requiring 624 contracted Gaussian functions for glucose. Electron correlation effects were included using many-body perturbation theory truncated at second order (MP2),[37] and using the more complete coupled cluster formalism,[61] including single and double substitutions through infinite order (CCSD).[62]

Ab initio calculations were carried out using the GAUSSIAN-94 program suite.[63] AM1 and PM3 (and SM5.4/AM1, *vide infra*) calculations were carried out using a locally modified version of AMSOL version 6.1.1.[64]

SOLVATION EFFECTS

Aqueous solvation free energies were calculated using Solvation Model 5.4 parameterized for AM1 (SM5.4/AM1).[30] The SM5.4 model is an improvement over the AM1-SM4:sugar model used previously[16] insofar as it is more general, having been parameterized against more than 200 solute data points for free energies of aqueous solvation, and it employs a more physical functional form for determining the solvation free energies of different functional groups, to include, especially, hydroxyl groups and ethers.[30]

The SM5.4 model makes use of high-quality Charge Model 1 (CM1) class IV atomic partial charges,[34] derived from the SCF wave functions, to represent the continuous electronic probability density. The model uses a continuum approximation with a solute-shape-dependent (and hence conformation-dependent) treatment of the dielectric boundary to calculate the electrostatic free energy of solvation, and it includes corrections for local effects associated with the first solvation shell that are not accounted for in the electrostatic term (*vide infra*). The model is applied in the present paper in conjunction with the AM1 model for solute reorganization energies, the AM1-CM1 model for solute charge distributions, and MP2/cc-pVDZ geometries. Thus, the solvation free energies, ΔG_S^0, include the calculated effects of electronic relaxation (i.e., redistribution of electronic density), but do not include any effects of geometry relaxation; the latter would be dominated by the inaccurate gas-phase potential energy surface at the semiempirical level. Prior studies on smaller model systems have shown that solvent effects on anomeric equilibria are primarily manifested as effects on the electronic relaxation, not geometric relaxation.[48]

The free energy of solvation is given by:[65–68]

$$\Delta G_S^0 = \Delta E_{\text{internal}} + G_P + G_{CDS} \qquad (1)$$

where G_P accounts for the favorable effects of mutual electrostatic polarization of the solute and the solvent minus the associated cost of distorting the *solvent* structure and orientation of solvent molecules to achieve this; $\Delta E_{\text{internal}}$ accounts for the associated cost of internal distortion of the *solute*; and G_{CDS}, which depends on solvent-accessible surface area (SASA),[69,70] includes *inter alia*

the effects of cavitation, dispersion, solvent structural changes, and other interactions specific to (or dominated by) the first solvation shell. For SM5-water, the SASA is calculated with an effective solvent radius of 1.7 Å.

Calculations and Results

NOMENCLATURE

All structures are of the $^4C_1$ chair type. We use the conventional designations of α and β for specification of anomer stereochemistry and the following notation for description of the stereochemistry of the hydroxymethyl group:

- G^-: C(6)—O(6) bond gauche to both the C(5)—O(5) and C(5)—C(4) bonds.
- T: O(6) trans to the ring oxygen.
- G^+: C(6)—O(6) bond gauche to both the C(5)—O(5) and C(5)—H bonds.

These are sometimes called *gg*, *tg*, and *gt*, respectively.

We will use boldface designations for the conformers in Figure 2, which have been optimized at the MP2/cc-pVDZ level. Note that structures **1**–**6** are β-anomers and structures **7**–**11** are α-anomers. To simplify the discussion, we will use the same boldface number when the subject is a group of structures all having *qualitatively* similar anomer/hydroxymethyl/hydroxyl conformations, but over which small *quantitative* differences necessarily exist (e.g., the set of structures for **1** as calculated at many different levels of theory). The various hydroxyl group torsions, etc., do not differ significantly enough when comparing structures optimized at different levels of theory to warrant additional structural depictions. However, additional geometric details from certain levels of theory are presented in tabular form where appropriate.

STRUCTURES AND ENERGIES

In our previous work,[16] all 729 possible torsional stereoisomers for $^1C_4$ conformers of α-glucose and $^4C_1$ conformers of β-glucose were energy minimized at the MM3 level of theory and, based on analysis of the low-energy conformers from optimizations employing force-field dielectric constants of either 1.5 or 3.0, four structures were chosen for additional study at QM levels. In this work, we augment the two $^4C_1$ conformers of β-glucose with an additional nine $^4C_1$ conformers chosen to provide coverage of other anomers, exo-anomers,[21] and internal hydrogen-bonding patterns. Because of refinements in the geometry optimization routines in the MM3(96) program, however, we returned to the exhaustive minimization procedure to determine whether some of our earlier reported structures[16] represented incompletely optimized geometries. By reducing the maximum atomic movement during minimization with the full matrix minimizer to 0.05 Å, the number of unique energy values for β-glucose is substantially reduced. Only 107 unique $^4C_1$ conformers of α-glucose were found, and only 113 such conformers were found for β-glucose; our previous work had found 185 such β-glucose conformers. The MM3 energies for the α-and β-glucose conformers both range over about 15 kcal; Figure 3 provides histograms of these energies. Of these 220 minima, 23 are within 3.00 kcal of the global minimum. (The use of the nonzero HOCO torsional parameters[55] increased the number of stable minima for each anomer of glucose by 27 compared with the case where all zero values were used.)

All structures **1**–**11** are stationary at the MM3 level. The β-glucose structures (**1**–**6**) are within the 18 lowest-energy β-glucose structures found to be stationary by MM3. The other 12 structures in this set of 18 included four each of the three different hydroxymethyl torsions. With three exceptions, the nonselected structures had counterclockwise orientations of the O(2), O(3), and O(4) hydroxyl groups. Two were clockwise, and one had O(3) and O(4) clockwise and O(1) and O(2) counterclockwise. Several nonselected G^+ and G^- structures had the O(6) hydroxyl proton oriented away from the tetrahydropyran ring oxygen. The α-glucose structures (**7**–**11**) are within the 11 lowest-energy α-glucose structures found stationary by MM3. The 6 remaining structures in this set were identical except for having different torsional orientations of the O(6) hydroxyl.

The highest level at which we optimized the geometries of **1**–**11** is MP2/cc-pVDZ. Our best composite (C) electronic energies are obtained as:

$$\begin{aligned} E(\mathrm{C}) = {} & E(\mathrm{MP2/cc\text{-}pVTZ/MP2/cc\text{-}pVDZ}) \\ & + \{E(\mathrm{CCSD/6\text{-}31G^*//MP2/6\text{-}31G^*}) \\ & - E(\mathrm{MP2/6\text{-}31G^*})\} \\ & + \{E(\mathrm{HF/cc\text{-}p^TVQZ//MP2/cc\text{-}pVDZ}) \\ & - E(\mathrm{HF/cc\text{-}pVTZ//MP2/cc\text{-}pVDZ})\} \quad (2) \end{aligned}$$

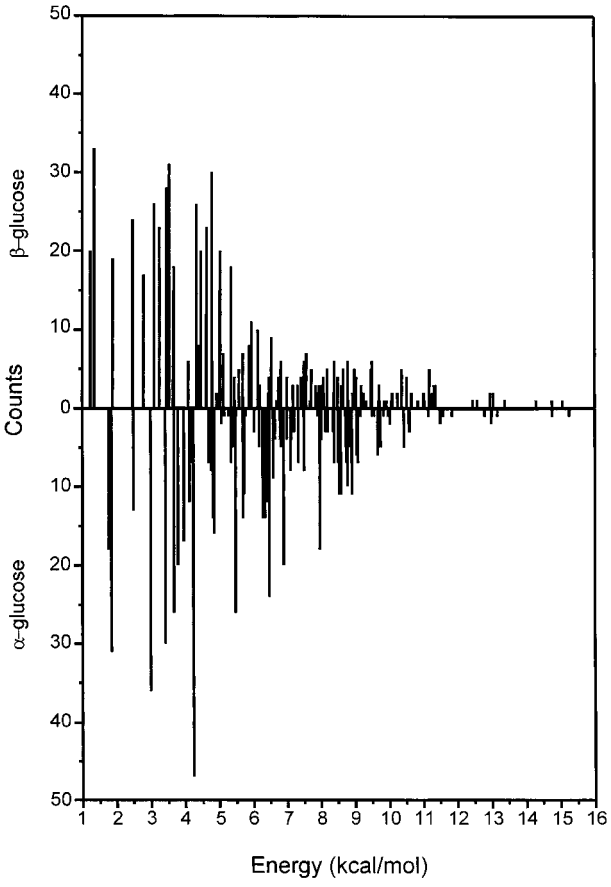

FIGURE 3. Histogram illustrating the energies of the stationary $^4C_1$ conformers of glucose anomers as optimized at the MM3 level. The ordinate measures how many of the 729 unique starting structures converged to a given energy.

The notation $w/x//y/z$ implies that the energy is evaluated with level of theory w using basis set x at the geometry calculated with level of theory y and basis set z. The required calculations and final relative composite energies for the structures in Figure 2 are summarized in Table I. Rovibrational contributions to the free energies at 298 K were calculated at the HF/cc-pVDZ level, and are also presented in Table I. Adding the rovibrational contributions to the composite electronic energies tends to stabilize β-anomers over corresponding α-anomers by 0.4–0.6 kcal.

Aqueous solvation free energies without geometry relaxation were calculated for all of the 11 conformers using the SM5.4/AM1 solvation model. Also, provided in Table II are the net relative free energies in aqueous solution for all 11 conformers (i.e., the sum of the relative free energies in the gas phase and the relative free energies of aqueous solvation). Aqueous solvation effects also stabilize β-anomers over corresponding α-anomers, although the magnitude of that stabilization is not uniform.

Table III lists the relative free energies for all 11 conformers in both the gas phase and aqueous solution and provides the corresponding populations for an equilibrium mixture at 298 K. By summing the total population of α- and β-anomers, the free energy of $\alpha \longrightarrow \beta$ anomerization at 298 K is calculated to be 0.4 kcal in the gas phase and -0.2 kcal in aqueous solution; that is, the aqueous solvation effect on the anomeric equilibrium favors the β-anomer by 0.6 kcal. Note that

TABLE I.
Calculated Relative Energies (Kilocalories) of D-Glucose Conformers in Gas Phase.[a]

Level of theory	1	2	3	4	5	6	7	8[b]	9	10	11
MP2/cc-pVTZ//MP2/cc-pVDZ	4.3	4.7	1.7	2.4	1.4	1.8	0.3	0.0	0.3	1.4	3.3
HF/cc-pVTZ//MP2/cc-pVDZ	2.9	3.1	−0.2	1.2	−0.1	0.2	−0.3	0.0	0.1	1.2	2.7
HF/cc-p^{T}VQZ//MP2/cc-pVDZ	2.6	2.8	−0.6	0.9	−0.4	−0.1	−0.4	0.0	0.1	1.1	2.6
MP2/6-31G*	5.3	5.9	3.0	3.5	2.4	2.5	0.5	0.0	−0.0	1.3	3.6
CCSD/6-31G*//MP2/6-31G*	5.2	5.6	2.7	3.2	2.1	2.3	0.5	0.0	0.0	1.3	3.5
Composite E[c]	3.8	4.1	1.1	1.9	0.9	1.3	0.1	0.0	0.25	1.3	3.1
ZPVE[d]	−0.5	−0.5	−0.4	−0.5	−0.4	−0.3	−0.1	0.0	0.1	−0.0	−0.2
ΔH_{298}(rot.-vib.)[d]	−0.4	−0.4	−0.3	−0.3	−0.3	−0.2	−0.0	0.0	0.1	−0.1	−0.2
$-T\Delta S_{298}$(rot.-vib.)[d]	−0.3	−0.4	−0.3	−0.3	−0.3	−0.1	−0.1	0.0	0.2	0.0	−0.1
ΔG_{298}(rot.-vib.)[d]	−0.7	−0.8	−0.6	−0.7	−0.5	−0.3	−0.1	0.0	0.2	−0.1	−0.3
Composite G^e_{298}	3.1	3.3	0.4	1.3	0.4	1.0	0.0	0.0	0.5	1.2	2.8

[a] See text after eq. (2) for $w/x//y/z$ notation. [b] Absolute energies (E_h) for this column are −686.053 24, −683.605 83, −683.649 39, −685.180 81, −685.252 13, −686.168 11, 0.214 17, 0.226 52, −0.048 85, 0.177 67, −685.990 45. [c] From eq. (2). [d] Zero-point vibrational energy (ZPVE) and thermal rotational–vibrational enthalpy and entropy terms calculated from unscaled HF/cc-pVDZ frequencies. [e] Composite $E + \Delta G_{298}$(rot.-vib.).

TABLE II.
Individual Components and Total Free Energies of Aqueous Solvation (Kilocalories) for Glucose Conformers 1–11.[a]

SM5.4/AM1	1	2	3	4	5	6	7	8	9	10	11
G_P	−13.0	−14.8	−12.5	−12.1	−12.2	−11.8	−11.8	−12.0	−10.7	−11.4	−13.8
$\Delta E_{internal}$	1.5	1.8	1.2	1.2	1.3	1.1	1.4	1.5	1.2	1.4	1.6
ΔG_{ENP}	11.5	−13.0	−11.3	−10.9	−10.9	−10.6	−10.5	−10.5	−9.5	−10.0	−12.1
G^0_{CDS}	−2.9	−2.1	−3.7	−4.0	−3.0	−3.2	−3.9	−3.3	−3.8	−2.9	−2.1
ΔG^0_S	−14.4	−15.1	−14.9	−14.9	−13.9	−13.9	−14.4	−13.8	−13.3	−12.9	−14.2
Relative ΔG^{0b}_S	−0.6	−1.3	−1.1	−1.1	−0.1	−0.1	−0.6	0.0	0.5	0.9	−0.4

[a] SM5.4/AM1//MP2/cc-pVDZ. [b] Relative to **8**.

the predicted aqueous free energy of anomerization is in close agreement with the experimentally observed value of −0.3 kcal.[39] In addition, the predicted ratio of G^+/G^- hydroxymethyl rotamers (**3** + **7** vs. **4** + **5** + **8**) in aqueous solution is 71/29, which is in reasonable agreement with the experimentally determined ratio of nearly 50/50.[50] The remaining T hydroxymethyl rotamers are predicted to comprise only 5% of the total aqueous equilibrium population, which is consistent with the failure to observe this rotamer in the NMR experiments.[50]

Discussion of Energetics

GAS PHASE

At our best level of theory (C) in the gas phase, the calculated relative electronic energies show several trends. First, in conformers having a complete counterclockwise array of intramolecular hydrogen bonds, the α-anomers (**7**, **8**, and **9**) are favored over their corresponding β-anomers (**3**, **5**, and **6**, respectively) by about 1 kcal. Each of these sets of three anomers includes all three possible hydroxymethyl rotamers, G^+, G^-, and T and, in each case, the G^- conformer is the lowest in energy, being about 0.2 kcal below G^+, whereas G^+ itself is 0.2–0.3 kcal below T.

Conformers **1** and **10**, on the other hand, are β- and α-anomers, respectively, characterized by complete *clockwise* arrays of intramolecular hydrogen bonds. Conformer **1** is 2.5–3 kcal higher in energy than the counterclockwise β-anomers **3**, **5**, and **6**, whereas **10** is only a bit more than 1 kcal higher in energy than the counterclockwise α-anomers—anomeric stabilization of α-anomers over β-anomers is evidently more important for **1** vs. **10** than for all of the other α/β pairs, presumably because all of the other pairs oriented the C(1) hydroxyl to take advantage of the exo-anomeric effect. Clockwise conformers **2** and **11** support this interpretation; each has a C(1) hydroxyl oriented to take advantage of the exanomeric effect, and the energy separation between them is about the same order of magnitude (1 kcal) as that seen for other α/β comparisons.

Table I additionally shows, by comparing rows 1 and 2, that electron correlation effects always stabilize the α-anomers over their corresponding β-anomers by 1–2 kcal. By comparing rows 4 and 5, it appears that this effect is slightly overestimated at the MP2 level compared to the CCSD,

TABLE III.
Relative Free Energies (Kilocalories) and Boltzmann-Averaged Populations (298 K) and Anomerization Free Energies at Equilibrium for Glucose Conformers 1–11 in Gas Phase and Aqueous Solution.

Group	1	2	3	4	5	6	7	8	9	10	11	Anomer[a]
Gas-phase *G*	3.1	3.3	0.4	1.3	0.4	1.0	0.0	0.0	0.5	1.2	2.8	
Aqueous *G*	2.5	2.0	−0.7	0.1	0.3	0.9	−0.6	0.0	0.9	2.1	2.4	
Gas-phase populations (%)	0	0	13	3	14	5	25	25	12	3	0	0.4
Aqueous populations (%)	0	0	37	9	7	3	29	11	2	0	0	−0.2

[a] Anomerization free energy for the given equilibrium populations.

but only by about 0.2 kcal. An effect of this magnitude is typical when one conformer experiences the anomeric effect and the other does not.[47,71–74]

AQUEOUS SOLUTION

The aqueous solvation free energies listed in Table II span a range of 2.2 kcal. Because ΔG_S^0 is a sum of contributions from multiple groups and, moreover, a sum of ENP and CDS contributions from those groups, it is difficult to interpret differences in conformer solvation free energies as a whole. One trend that does emerge, however, is that β-anomers are always better solvated than α-anomers. For the five corresponding pairs that differ only as anomers, the average difference in solvation free energies is 0.7 kcal. When averaged over major equilibrium contributors (i.e., in a Boltzmann sense) the effect is reduced to 0.6 kcal, as indicated in Table III.

To provide more chemical insight into the differences in solvation free energies, we separately consider the sum of G_P and G_{CDS} for the six hydrophilic groups, namely the tetrahydropyran ring oxygen, the four hydroxyl groups, and the hydroxymethyl group, for each conformer (see Table IV). This analysis causes certain trends to become apparent. For instance, the favorable solvation of the ring oxygen is maximized in conformers **1** and **10**; these conformers are unique in that the proton of the C(1) hydroxyl group is directed *away* from the ring oxygen. Thus, water molecules in the region between the ring oxygen and the C(1) hydroxyl can solvate the lone pairs of each simultaneously; that is, the solvation effects for these two groups reinforce. The remaining conformers, having negative solvation free energies for the ring oxygen, all have the hydroxymethyl group in the *T* conformation. This exposes the ring oxygen to the surrounding solvent and avoids having to place the C(6) hydroxyl proton in the vicinity of the ring oxygen, which would frustrate the local solvation.

As already noted, directing the oxygen lone pairs of both the ring oxygen and the C(1) hydroxyl into the same region of space maximizes the solvation free energy of the ring oxygen—it also leads to a very favorable solvation of the C(1) hydroxyl group for the same reasons discussed earlier. However, the best solvated C(1) hydroxyl groups occur for conformers **2** and **11**. In those instances, the lone pairs of the C(1) hydroxyl group are directed into the same region of space as the lone pairs of the C(2) hydroxyl group. This again leads to a synergy in the solvation of these two groups, and indeed, it is for conformers **2** and **11** that the solvation free energy of the *latter* hydroxyl group is most favorable. For all other conformers, the C(2) hydroxyl both donates and accepts one intramolecular hydrogen bond, and its solvation free energy ranges over only 0.4 kcal. The C(3) hydroxyl both donates and accepts one intramolecular hydrogen bond in *all* conformers, and its solvation free energy also spans a fairly narrow range compared with the other hydrophilic groups, in this case 0.8 kcal.

Returning to the C(1) hydroxyl group, it is also apparent that this group is always better solvated for β-anomers than for α-anomers by about 1.5 kcal. This improved solvation presumably derives simply from the greater accessibility of solvent to an equatorial substituent on a six-membered ring compared with an axial substituent; the average solvent-accessible surface area for this group in conformers **1**–**6** compared with **7**–**11** is 56.6 Å^2 and 45.0 Å^2, respectively. Whereas this observation has often been made in rationalizing an aqueous solvent effect on the glucose anomeric equilibrium,

TABLE IV.
Sum of G_P and G_{CDS} (Kilocalories) for Different Heteroatom-Containing Groups of Glucose Conformers 1–11.[a]

Group	1	2	3	4	5	6	7	8	9	10	11
Ring oxygen	−2.4	−1.1	0.3	0.7	0.5	−0.8	0.9	1.0	−0.4	−2.1	−1.0
C(1) hydroxyl group	−4.6	−4.8	−3.0	−3.5	−2.9	−3.0	−1.6	−1.6	−1.6	−3.6	−3.9
C(2) hydroxyl group	−2.5	−4.0	−2.4	−2.7	−2.4	−2.4	−2.5	−2.7	−2.5	−2.3	−3.6
C(3) hydroxyl group	−2.4	−2.8	−2.4	−2.4	−2.6	−2.2	−2.6	−2.9	−2.3	−2.0	−2.7
C(4) hydroxyl group	−2.1	−2.2	−3.1	−3.1	−3.0	−1.9	−3.2	−3.1	−1.9	−2.2	−2.6
Hydroxymethyl group	−3.6	−3.8	−4.7	−3.8	−3.6	−3.8	−5.0	−3.9	−3.8	−3.8	−4.0

[a] SM5.4/AM1//MP2/cc-pVDZ.

this study is the first to quantify the effect specifically for the C(1) hydroxyl group as opposed to the entire molecule.

It is also noteworthy that when the C(4) hydroxyl both accepts and donates one intramolecular hydrogen bond, it is solvated about as well as the C(2) or C(3) hydroxyl groups when they similarly act as donors and acceptors. However, in those cases where the C(4) hydroxyl group oxygen lone pairs are not used for a hydrogen bond with the C(6) hydroxyl (**3**, **4**, **5**, **7**, and **8**), its solvation free energy increases by about 1 kcal.

Last, the hydroxymethyl group enjoys its most favorable solvation when it adopts a G^+ orientation, which maximizes the exposure of the C(6) hydroxyl group to the surrounding solvent. As already noted, however, this places the C(6) hydroxyl proton in a region that interferes with solvation of the ring oxygen, and these two effects offset each other. This last point is an example of how complicated it can be to interpret the total solvation free energies presented in Table II without carrying out a groupwise decomposition. [We note that we have *not* examined solvation effects for O(6) hydroxyl orientations that would rotate the hydroxyl group proton *away* from the tetrahydropyran ring oxygen. Solvation effects might be expected to balance loss of the favorable gas-phase interaction in this case.]

In concluding this section, we note that all of the aqueous solvation free energies were carried out for frozen gas-phase structures. A prior study on many different conformers of D-glucose allows us to estimate that the energetic effect of geometric relaxation in water will be about -0.2 kcal for every conformer.[10] Such corrections would, of course, have no effect on the *relative* free energies in solution.

Structural Aspects and Comparison of Theoretical Models

STRUCTURAL COMPARISONS

There are three different crystal structures available for glucose, two conformers, **5**[75] and **8**,[76] solved by x-ray diffraction, and one conformer, **7**,[77] solved by neutron diffraction. Table V compares the gas-phase MM3 and MP2/cc-pVDZ structures to the crystal data for selected geometrical parameters. In general, the agreement is quite good for both methods, with the mean absolute errors in bond lengths being less than 0.01 Å for all three cases and the mean absolute errors in valence and dihedral angles ranging from 1.7–3.2°. Puckering parameters are predicted very accurately for conformers **7** and **8**. Both theoretical models show a 5.5° error in predicting θ for conformer **5**. Experimentally determined puckering parameters for β-glucose range as high as 18.9°;[78] such a distortion for an isolated molecule was estimated to cost 2.0 kcal by Dowd et al. using an MM3(92) potential energy surface.[14] This suggests that the observed puckering angle of 7.9° is well within the expected range for distortions that might be caused by the crystal field.

Certain noteworthy trends are observed across the three conformers. In particular, the predicted gas-phase C(1)—O(5) bond lengths are all shorter than those measured in the crystal by 0.010–0.015 Å, and the calculated C(5)—C(6) bond lengths are all 0.008–0.015 longer than those observed. Other comparisons are also of interest. For instance, the MP2-calculated C(1)—O(1) bond lengths in conformers **5** and **8** agree with experiment to within 0.002 Å, but the error for conformer **7** is 0.023 Å. However, the difference in the experimental bond lengths comparing conformers **7** and **8** is 0.021 Å—a remarkably large change given that these conformers differ only in the hydroxymethyl orientation. Both MM3 and MP2 predict no change in this bond length for **7** and **8**, suggesting that there is either some difficulty in interpreting the neutron diffraction data or that there is a crystal packing effect in **7** not accounted for in the gas-phase calculations.

The remarkably good agreement between MM3 and MP2 for many bond lengths is possibly fortuitous. The MM3 bond lengths are (corrected) r_α values, but the MP2 bond lengths are r_e values. The average correction factor for C—C bond lengths is 0.0065 Å and for C—O bonds is 0.0053 Å (the correction is always such that r_α is shorter than r_e). Were these corrections to be applied to the MP2 data, the mean errors in bond lengths would shift from near zero to being consistently too short by about 0.005 Å. Moreover, the predicted C(1)—O(1) bond lengths would no longer be in such good agreement with experiment, and the predicted C(1)—O(5) bond lengths would be moved further from agreement than they already are. These bond lengths reflect the geometrical consequences of the anomeric and exo-anomeric effects and are either a particularly sensitive test of the quality of a theoretical model or are themselves particularly sensitive to crystal packing ef-

TABLE V.
Comparison of MM3 and MP2/cc-pVDZ Structures to Crystal Data.[a]

Geometrical data	5			7			8		
	Expt.[b]	MM3	MP2	Expt.[c]	MM3	MP2	Expt.[d]	MM3	MP2
Bond lengths (Ångstroms)									
C-1—C-2	1.512	1.520	1.522	1.534	1.523	1.529	1.510	1.522	1.528
C-2—C-3	1.513	1.517	1.516	1.525	1.518	1.524	1.522	1.518	1.523
C-3—C-4	1.531	1.521	1.519	1.520	1.519	1.518	1.521	1.519	1.517
C-4—C-5	1.519	1.527	1.529	1.529	1.523	1.523	1.513	1.524	1.526
C-5—C-6	1.513	1.525	1.523	1.511	1.524	1.519	1.510	1.525	1.523
C-1—O-5	1.431	1.423	1.421	1.427	1.417	1.412	1.427	1.417	1.412
C-1—O-1	1.394	1.418	1.394	1.391	1.426	1.414	1.412	1.427	1.414
C-2—O-2	1.429	1.431	1.420	1.417	1.433	1.422	1.422	1.434	1.422
C-3—O-3	1.427	1.432	1.421	1.416	1.432	1.422	1.422	1.432	1.422
C-4—O-4	1.422	1.431	1.419	1.426	1.431	1.418	1.435	1.431	1.420
C-5—O-5	1.439	1.438	1.437	1.428	1.441	1.446	1.451	1.441	1.445
C-6—O-6	1.424	1.431	1.416	1.414	1.430	1.416	1.437	1.430	1.417
Mean error		0.005	−0.001		0.007	0.002		0.003	−0.001
Mean absolute error		0.008	0.007		0.012	0.008		0.009	0.009
Valence angles (Degrees)									
C-5—O-5—C-1	111.9	112.3	112.3	113.8	115.1	113.9	113.1	115.2	114.5
O-5—C-1—O-1	106.8	105.4	109.0	111.5	108.4	113.2	110.2	108.4	112.8
Dihedral angles (Degrees)									
O-5—C-1—C-2—C3	53.3	61.0	58.6	54.1	54.0	53.8	53.0	54.4	54.2
C-1—C-2—C-3—C-4	−49.7	−57.5	−54.8	−51.3	−55.5	−54.0	−50.5	−56.0	−54.6
C-2—C-3—C-4—C-5	52.6	55.8	53.6	53.3	57.9	56.5	53.5	57.3	56.1
C-3—C-4—C-5—O-5	−60.4	−57.0	−55.2	−57.5	−59.1	−57.9	−58.5	−57.9	−56.0
C-4—C-5—O-5—C-1	66.5	62.2	60.4	62.2	60.0	60.1	61.4	58.7	57.5
C-5—O-5—C-1—C-2	−61.9	−64.3	−62.4	−60.9	−57.0	−57.9	−58.7	−56.2	−56.8
Mean error in tabulated angles		−0.1	0.3		−0.2	0.3		0.0	0.5
Mean absolute error in tabulated angles		3.8	3.2		2.6	1.7		2.6	2.5
Cremer–Pople puckering parameters									
Q (Ångstroms)	0.580	0.604	0.577	0.567	0.578	0.570	0.560	0.571	0.560
θ (Degrees)	7.9	2.4	2.4	3.5	4.6	3.4	4.9	4.3	3.1

[a] MM3 bond lengths and puckering parameters are derived from (corrected) r_α values, MP2 data are from r_e values. [b] Ref. 75. [c] Ref. 77. [d] Ref. 76.

fects. In this regard we note that the worst performance of MM3 is associated with the C(1)—O(1) bond length, which is consistently overestimated by about 0.02 Å.

OTHER QUANTUM MECHANICAL METHODS

Relative electronic energies and anomerization energies as calculated at a variety of less complete levels of electronic structure theory are provided in Table VI (as are the best composite energies for comparison). Analysis of these data is of interest because it permits an identification of particular physical effects operative in some conformers but not others. In addition, while it is always desirable (and almost always impossible) to converge quantum mechanical calculations with respect to basis set and treatment of electron correlation, it may sometimes be acceptable to employ an unconverged level of theory that has been demonstrated to have a fortuitous cancellation of errors in related systems, particularly for carbohydrate force-

TABLE VI.
Calculated Relative Energies (Kilocalories) of D-Glucose Conformers in Gas Phase.[a]

Level of theory	1	2	3	4	5	6	7	8[b]	9	10	11	Anomer[c]
AM1	*d*	6.8	2.3	2.1	2.7	2.2	−0.4	0.0	−0.5	4.5	5.3	2.5
PM3	2.2	2.9	0.5	−0.1	0.9	0.7	−0.4	0.0	−0.3	1.8	3.9	0.5
HF/STO-3G	1.9	1.9	1.1	1.8	1.1	−0.2	−0.1	0.0	−1.4	0.0	0.6	1.2
HF/3-21G	5.7	6.4	5.3	5.2	3.9	3.2	1.0	0.0	−1.1	−1.0	2.4	4.5
HF/6-31G*	3.9	4.2	1.2	2.3	1.0	1.1	0.1	0.0	−0.1	0.8	2.8	1.1
HF/cc-pVDZ	4.0	4.2	1.4	2.2	1.0	1.3	0.3	0.0	0.1	1.0	3.0	1.1
HF/cc-pVTZ//HF/cc-pVDZ	3.1	3.3	0.2	1.3	0.2	0.5	0.0	0.0	0.2	1.0	2.7	0.2
HF/cc-pVDZ//MP2/cc-pVDZ	4.0	4.2	1.2	2.1	0.8	1.2	0.2	0.0	0.2	1.2	3.0	0.9
HF/cc-pVTZ//MP2/cc-pVDZ	2.9	3.1	−0.2	1.2	−0.1	0.2	−0.3	0.0	0.2	1.2	2.7	0.0
HF/cc-p^{T}VQZ//MP2/cc-pVDZ	2.6	2.8	−0.6	0.9	−0.4	−0.1	−0.4	0.0	0.1	1.1	2.6	−0.2
MP2/6-31G*	5.3	5.9	3.0	3.5	2.4	2.5	0.5	0.0	0.0	1.3	3.6	2.5
MP2/cc-pVDZ	5.2	5.7	3.1	3.2	2.3	2.6	0.7	0.0	0.1	1.6	3.7	2.3
MP2/cc-pVTZ//MP2/cc-pVDZ	4.3	4.7	1.7	2.4	1.4	1.8	0.3	0.0	0.3	1.4	3.3	1.4
CCSD/6-31G*//MP2/6-31G*	5.2	5.6	2.7	3.2	2.1	2.3	0.5	0.0	0.0	1.3	3.5	2.2
Composite *E*[e]	3.8	4.1	1.1	1.9	0.9	1.3	0.1	0.0	0.2	1.3	3.1	0.9

[a] See text after eq. (2) for w/x//y/z notation. [b] Absolute energies (E_h) for this column are −0.483 787, −0.428 91, −674.482 34, −679.560 92, −683.333 87, −683.409 20, −683.617 94, −683.400 96, −683.605 83, −683.649 39, −685.180 81, −685.345 96, −686.053 24, −685.252 13, −686.168 11. [c] Anomerization free energy for the derived equilibrium populations at given level of theory. [d] Not stationary. [e] See Table I.

field development—for instance, in cases where the relative energies of a large number of conformers might be required.

Semiempirical methods have been previously noted to perform marginally with respect to carbohydrate conformational analysis.[10, 16, 46, 47] In particular, spurious low-energy minima arising from artifacts in H—H core repulsion functions have been identified with the PM3 Hamiltonian.[16] Nevertheless, within the range of conformers examined here, PM3 performs better than AM1, primarily because the latter level significantly destabilizes clockwise arrangements on intramolecular hydrogen bonding—indeed, conformer **1** is not stationary at the AM1 level (it rearranges to **2**). Although it is apparent that semiempirical models are not ideal choices for carbohydrate conformational analysis, we emphasize that the semiempirical *solvation* models employed in this and earlier[10, 16] studies do *not* depend on the ability of the gas-phase Hamiltonians to accurately predict solute energies. Rather these studies depend on the quality of the predicted electronic charge distribution, and for that purpose the semiempirical models have been shown to be in good agreement with higher level calculations.[79–83] The present SM5.4/AM1 solvation calculations rely even less on the semiempirical methods, using them only for the solute reorganization energy and as the operand for a CM1[34]-type mapping.

Table VI shows that the minimum-basis-set HF/STO-3G level predicts a somewhat smaller range in relative energies spanned by the eleven conformers than predicted at the best composite level of theory. The HF/STO-3G level predicts a large stabilization of *T* hydroxymethyl rotamers and of clockwise intramolecular hydrogen bonding motifs. Among these structures, conformers **1**, **6**, **9**, and **10** all have four intramolecular hydrogen bonds, compared with the three found in all other structures. We have noted previously the tendency of this level to overemphasize the strength of these intramolecular hydrogen bonds in other glucose conformers.[16] It is not as obvious what contributes to the anomalous stabilization of **2** and **11** at this level of theory.

At the unpolarized-valence double-ζ HF/3-21G level, the energetic separation between the two anomers is predicted to increase significantly, in particular to a far greater extent than found at the best composite level of theory (Boltzmann-averaged anomerization energy of 4.5 compared with 0.9 at the composite level). However, as we noted previously when comparing $^4C_1$ and $^1C_4$ glucose chairs,[16] HF calculations using the *polarized*-valence double-ζ 6-31G* and cc-pVDZ basis sets rectify anomalies associated with the smaller bases. At the HF level, the effect of placing p functions on hydrogen seems fairly small (cc-pVDZ has them, whereas 6-31G* does not). However, ex-

panding the valence space to doubly polarized, triple-ζ (cc-pVTZ) decreases the relative energies of the β-anomers by about 1 kcal. Further improvement of the valence space, using the cc-pT VQZ basis set, provides only another 0.3 kcal or so, suggesting that these energies are reasonably well converged with respect to basis set size.

As noted in the last section, electron correlation effects stabilize the α-anomers in comparison to the β-anomers, and it is noteworthy that this effect is opposite to the trend observed with increasing basis set size (where β-anomers are stabilized over α-anomers). This suggests that, by ignoring correlation and working with an incomplete basis set, one may potentially be able to take advantage of canceling errors and, indeed, the HF/cc-pVDZ level provides results that are in (obscenely) good agreement with the best composite level for the relative energies of all 11 conformers—the mean absolute error in relative energies is only 0.1 kcal. The HF/6-31G* level is nearly as good, with a mean absolute error in relative energies of 0.2 kcal, but it does erroneously predict conformer **9** to be lower in energy than **8**. This analysis is consistent with previous work on carbohydrate conformational analysis at these levels of theory.[16,74,84]

MOLECULAR MECHANICAL METHODS

Table VII presents the relative energies for different glucose conformers as calculated by several different force fields, including all-atom OPLS-AA,[23] the Weiner et al. force field[85] as extended by Glennon et al. and implemented in AMBER (WGA),[13] the force field of Ha et al.[7] and further employed by Glennon et al. implemented in CHARMM (HGC),[13] GROMOS,[11] the united-atom[19] and all-atom[22] versions of the AMBER* force field of Still and coworkers, MMFF,[86] the Cornell et al.[87] force field as modified by Simmerling and Kollman[88] and implemented in AMBER (CSK), CHEM-X[89] (this work), and MM3[24,26] (this work). Energies for structures **3**, **5**, **6**, **7**, **8**, and **9** have been reported for all of these force fields, energies for structures **1** and **10** have been reported for the OPLS-AA force field, and energies for all 11 structures are available for the AMBER* and MMFF force fields. Table VII also includes the rotational and vibrational thermal corrections to the free energy as calculated at the MM3 and HF/cc-pVDZ levels of theory.

The CSK force field provides the best overall agreement with the composite QM level although there is a systematic destabilization of about 1 kcal for the clockwise hydrogen-bonded conformers. Conformer **7** is also found to be too stable, as it is by all of the force fields except for WGA and CHEM-X. The modifications by Simmerling and Kollman[88] to the Cornell et al.[87] force field involved adding specific anomeric torsional parameters based on fitting to dimethoxymethane and dihydroxymethane. The good performance of the CSK force field suggests that these parameters are indeed transferable.

The OPLS-AA force field provides agreement of essentially the same quality as CSK, although comparison can be made for only eight conformers. In this case, there is a systematic destabilization of

TABLE VII.
Additional Calculated Relative Energies (Kilocalories) of Glucose Conformers in Gas Phase.

Level of Theory	1	2	3	4	5	6	7	8	9	10	11
OPLS-AA[a]	2.2		0.7		1.3	1.0	−0.2	0.0	−0.3	−0.2	
WGA[b]			3.0		8.9	0.7	0.6	0.0	−0.4		
HGC[c]			2.4		−0.1	4.5	−0.3	0.0	−0.8		
GROMOS[d]			−0.8		−0.8	−4.2	−0.1	0.0	−3.3		
UA-AMBER*[e]	3.1	5.7	0.2	2.0	0.7	0.4	−0.6	0.0	−0.6	1.6	4.7
AA-AMBER*[e]	3.6	5.8	−0.1	2.5	1.2	0.6	−1.3	0.0	−0.8	1.7	4.5
MMFF[e]	2.1	3.8	−1.0	2.1	0.3	0.2	−1.2	0.0	−0.1	0.4	1.6
CSK[f]	4.7	5.4	0.3	2.2	0.8	1.0	−0.7	0.0	0.1	2.4	3.8
CHEM-X	2.8	2.1	1.3	1.6	1.3	1.4	0.2	0.0	0.3	0.4	0.4
MM3	2.3	1.0	−1.3	1.1	−0.6	−1.4	−0.7	0.0	−0.6	1.7	0.9
Composite E[g]	3.8	4.1	1.1	1.9	0.9	1.3	0.1	0.0	0.2	1.3	3.1
MM3 ΔG_{298}(rot.-vib.)[h]	−1.0	−0.9	−0.8	−0.7	−0.6	−0.2	−0.1	0.0	0.4	−0.4	−0.4
HF/cc-pVDZ ΔG_{298}(rot.-vib.)[h]	−0.7	−0.8	−0.6	−0.7	−0.5	−0.3	−0.1	0.0	0.2	−0.1	−0.3

[a] Ref. 23. [b] Ref. 13. [c] Refs. 7, 13. [d] Ref. 11. [e] W. C. Still, personal communication. [f] C. Simmerling and P. A. Kollman, personal communication. [g] Eq. (2). [h] Zero-point vibrational energy (ZPVE) and thermal rotational–vibrational enthalpy and entropy.

the G^- conformers **5** and **8** relative to the other conformers having counterclockwise hydrogen bonding, but this amounts to only about 0.4 kcal. Conformers **1** and **10** are both predicted to be 1.6 kcal more stable at the OPLS-AA level than at the composite QM level (this is the largest disagreement between the two levels), suggesting that the balance between O(1) hydrogen bonding and the exo-anomeric effect is not well modeled by this force field. A similar anomaly is particularly evident in the AMBER* force fields, namely that conformers **2** and **11** are destabilized relative to conformers **1** and **10**, respectively, by a significantly larger margin than found at the QM level. This appears to reflect a similar imbalance in the treatments of hydrogen bonding and the exo-anomeric effect (the former is maximized for **1** and **10**, whereas the latter is present in **2** and **11**); OPLS-AA results have not been reported for **2** and **11**.

The performance of the UA- and AA-AMBER* force fields is otherwise fairly good, although conformers **4**, **5**, and **8** (i.e., G^+ conformers with counterclockwise hydrogen bonding) appear destabilized relative to counterclockwise T and G^- conformers (i.e., **3**, **6**, **7**, and **9**; because **8** is the relative zero this trend manifests itself in Table VII by low energies for the T and G^- conformers relative to Composite QM).

Interestingly, the CHEM-X force field does extremely well in predicting the relative energies of the counterclockwise hydrogen-bonded conformers; however, it fails to predict accurately the higher energies of the clockwise hydrogen-bonded conformers. The MMFF force field uniformly overstabilizes clockwise intramolecular hydrogen-bonding arrangements and also, like the AMBER* force fields, has a bias toward predicting the G^+ conformers to be more stable than is found at the QM level relative to the alternative hydroxymethyl rotamers.

The WGA force field provides a reasonable range of relative energies for conformers **6**–**9**, but overestimates the relative energy of **3** by 1.9 kcal and of **5** by a surprisingly large 8.0 kcal; Glennon et al. did not offer any explanation for this unusual behavior.[13] The relative energies predicted by the HGC force field do not show any disagreements as large as the WGA value for **5**, but the overall agreement is not particularly good, with conformers **3** and **6** being considerably too high in energy, and **5** and **9** too low. The performance of the GROMOS force field is also quite poor, with all three β-anomers and also **9** being overstabilized relative to **8** by as much as 4.5 kcal. Ott and Meyer[38] recently modified the GROMOS force field to improve carbohydrate simulations, but gas-phase conformer energies were not reported. It should be noted that these last three force fields permit comparisons against QM for only six conformers, and the remaining conformers were often more challenging for other force fields, so performance might be further degraded if these data were available.

Finally, while MM3 conformer energies span a range similar to that predicted by the composite QM level of theory, conformer **8** appears anomalously destabilized at the MM3 level (again, because **8** is relative zero, this makes all other energies in Table VII less positive than the corresponding QM energies). There is also a curious overstabilization of conformer **1** relative to **10**, with both differing as anomers and each having a C(1) hydroxyl orientation that does not permit the exo-anomeric effect. This performance of MM3 for carbohydrate conformational energies is not as good as our earlier observations on a set of four glucose conformers,[16] but is in keeping with other unpublished results.[90] Changing the artificial dielectric constant does not improve the quality of the MM3 results, nor did using the 1992 parameters for hydrogen bonding, nor did changing the OCCO torsional parameters as suggested by Rockwell and Grindley.[91]

Interestingly, however, the thermal rovibrational contributions to the free energy calculated at the MM3 level agree quite well with those at the composite QM level. So, although MM3 does not successfully predict the relative depths of the wells on the conformational potential energy surface, it seems to do much better with the shapes of those wells. This lends credibility to the bond length conversions (r_e to r_α) discussed earlier, because these conversions depend on the molecular normal modes.

OVERALL RELIABILITY OF DIFFERENT MODELS

Table VIII provides a breakdown of model reliability ranked by mean unsigned error in predicted energies relative to global minimum conformer **8** compared with the composite QM level of theory. Other error analyses may certainly be envisioned and, in particular, an analysis that overlaps means in the conformer energy distributions might be considered. However, insofar as the global minimum dominates the equilibrium population, and

TABLE VIII.
Mean Unsigned Error (Kilocalories per Mole) of Various Methods Compared to Composite QM Energies in Rank Order.[a]

Level	Data points	Mean unsigned error	Level	Data points	Mean unsigned error
GROMOS	6	2.1	PM3	11	0.8
HF/3-21G	11	2.0	UA-AMBER*	11	0.7
WGA	6	1.9	CHEM-X	11	0.7
MM3	11	1.5	HF/cc-pVTZ //MP2/cc-pVDZ	11	0.6
AM1	10	1.4	OPLS-AA	8	0.6
HGC	6	1.2	CSK	11	0.6
HF/STO-3G	11	1.1	HF/cc-pVTZ //HF/cc-pVDZ	11	0.5
MP2/6-31G*	11	1.0	MP2/cc-pVTZ //MP2/cc-pVDZ	11	0.4
MP2/cc-pVDZ	11	1.0	Eq. (2) with no line 2[b]	11	0.3
MMFF	11	0.9	Eq. (2) with no line 3[c]	11	0.2
HF/cc-pVqZ //MP2/cc-pVDZ	11	0.8	HF/6-31G*	11	0.2
CCSD/6-31G* //MP216-31G*	11	0.8	HF/cc-pVDZ	11	0.1
AA-AMBER*	11	0.8	HF/cc-pVDZ //MP2/cc-pVDZ	11	0.1
			Composite QM energy[d]	11	0.0

[a] Ranked from highest to lowest mean unsigned error. [b] Eq. (2) without correcting for higher order correlation effects. [c] Eq. (2) without correcting for incomplete basis set effects. [d] Eq. 2.

composite QM predicts structure **8** to be that global minimum, we have chosen to assign the zero of each model to that structure and we evaluate mean unsigned errors in relative energies accordingly. The model that this choice most affects is MM3, where **8** alone seems anomalously destabilized and hence the error is magnified across the 11 conformers—overlapping the mean of the energy distributions would reduce the mean unsigned error for MM3 compared to composite QM from 1.5 to 0.9 kcal.

Molecular mechanics methods account for four of the six least successful models, but also account for two models with mean unsigned errors within 0.6 kcal (for OPLS-AA that comparison involves only eight conformers) and another two within 0.7 kcal. Correlated quantum mechanical methods with basis sets of moderate size are only about as good as the semiempirical models or the minimum basis set HF/STO-3G model; Hartree–Fock calculations with very large basis sets offer no improvement. However, the directions of these errors (electron correlation vs. basis set size) are opposite and, by coincidentally offsetting them, HF/cc-pVDZ and HF/6-31G* offer the best quantitative accuracy of the noncomposite quantum mechanical methods. The remarkably delicate nature of this cancellation of errors is made apparent by considering the effect of removing either the higher-order electron correlation effects or the final basis-set size correction from the composite QM energy [lines 2 and 3 of eq. (2), respectively]—HF/cc-pVDZ and HF/6-31G* are more quantitatively accurate than eq. (2) with either deletion.

Conclusions

Eleven different conformers of D-glucose, including different exo-anomeric orientations and at least one of each hydroxymethyl conformer (G^-, G^+, and T) for each of the two anomeric forms (α and β), were calculated at levels of quantum mechanical (QM) electronic structure theory that give relative energies that converged to within about 0.2 kcal/mol. Electronic energies were converted into relative free energies in solution by adding rotational, vibrational, and aqueous solvation effects, the latter using the SM5.4/AM1 solvation model. The converged gas-phase calculations, av-

eraged over all conformations in a Boltzmann sense, predict the α-anomer to be lower in free energy by 0.4 kcal/mol, consistent with a normal anomeric effect, albeit of small magnitude. For the three QM structures (optimized at the MP2/cc-pVDZ level of theory) that could be compared directly with experimental crystal structure data, the average error in bond lengths and valence and dihedral angles was 0.008 Å and 2.5°, respectively. In aqueous solution, the SM5.4/AM1 solvation model predicts the β-anomers to be better solvated than the α-anomers by 0.6 kcal/mol (again, Boltzmann averaged). Combining the gas-phase equilibrium results with the solvation free energy leads to an aqueous anomerization free energy of −0.2 kcal/mol, which compares very well with the experimentally observed value of −0.3 kcal/mol.[39]

Analysis of the contributions of individual hydrophilic groups to the total solvation free energies reveals, as one would expect, that increased solvent exposure of hydrophilic groups (e.g., by breaking up intramolecular hydrogen bonding) leads to improved solvation of those groups. However, interactions between different groups in a nonlinear fashion can also be important, and those conformers that place similar charges (e.g., lone pairs or hydroxyl protons) into nearby regions of space enjoy improved solvation from solvent cooperativity.

Such separate analyses of converged gas-phase and high-quality liquid-phase solution relative energies should prove useful for the further development of force fields for carbobydrate conformational analysis. Many current force fields continue to have systematic deficiencies in their potential functions, but the energetic consequences of such deficiencies have been reduced to an acceptable level in certain instances. An interesting topic for future studies will be characterizing the torsional transition states connecting various minima and evaluating force field performance for such structures.

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