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B3LYP/6-311++G** study of monohydrates of α- and β-D-glucopyranose: hydrogen bonding, stress energies, and effect of hydration on internal coordinates

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Abstract—Twenty-six monohydrates of α- and β-D-glucopyranose were studied using gradient methods at the B3LYP/6-311++G** level of theory. Geometry optimization was carried out with the water molecules at different configurations around the glucose molecule. A new nomenclature for hydrated carbohydrates was developed to describe the water configurations. Zero-point vibrational energy, enthalpy, entropy, and relative free energy were obtained using the harmonic approximation. Hydrogen-bond energies for the monohydrates range from ∼−5 to −12 kcal/mol, and the average relative free energy is ∼5 kcal/mol. The 1-hydroxy position is the most energetically favored site for hydration, and the region between the two and three positions is the next-most favored site. A water molecule approaching α-D-glucose between the 1- and 2-hydroxy positions pulls the 2-hydroxyl hydrogen atom away from the 1-hydroxy oxygen atom, thus increasing the hydrogen-bond length and also increasing the α-D-glucose energy. The increase in energy that occurs with a similar interaction on the β-anomer is much less effective since the hydrogen bond is much longer. Using the calculated free energies of all 26 configurations, the anomer population (α/β) increases in the β-anomer population relative to the in vacuo case by ∼10% at the expense of the α-anomer, giving an (α/β) ratio of ∼50/50. This result arises from entropy contributions favoring the β-anomer more than the α-anomer. From analysis of donor and acceptor hydrogen-bond lengths, excellent correlation is found between the DFT calculated distances and those taken from carbohydrate structures in the Cambridge Crystallographic Data Bank.
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Keywords: B3LYP/6-311++G**; Glucose; Monohydrate; Entropy; Enthalpy; Hydrogen bonding; Relative free energy

1. Introduction

In carbohydrate chemical and structural literature, water has been shown to be a most important component, acting as a plasticizer in some cases and clearly dictating solubility and conformational behavior in many others. Many hydrolysis reactions show a kinetic medium effect with carbohydrate–solute interactions mediated by water molecules.[1] It is thought that these medium effects find their origin in hydration-shell overlap effects,[1] and that these effects in aldoses are determined by the relative stereochemistry of the 4-OH and 2-OH groups. Evidence from intrinsic viscosity measurements of aqueous solutions of α/β-D-glucopyranose showed that the van der Waals volume increased by a factor of two upon hydration.[2] This result is in agreement with experimentally measured hydration numbers of ∼8–10[3,4] and suggests that strong hydrogen bonding occurs between the hydroxyl groups of glucopyranose and water molecules. In a structural sense, most X-ray crystal structures of carbohydrates are found to have water molecules attached acting as a stabilization factor for the crystal formation. Solid state water–carbohydrate

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[†] Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may also be suitable.

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interactions have been analyzed in terms of the donor–acceptor hydrogen-bond lengths,[5] and this experimental data is compared with the hydrogen-bond lengths found here. α/β-D-glucopyranose chairs, boats, and twists were recently studied in vacuo at the DFT level of theory (i.e., B3LYP/6-311++G**) used here,[6] and numerous empirical computational studies of carbohydrate hydration have been carried out.[7–15]

Here we report on a series of density functional studies of water molecules interacting with carbohydrates at minimum energy sites around the substrate molecule. Although there are many different computational techniques for studying the hydration phenomenon, we believe that this DFT study, in which an explicit water molecule interacts with the carbohydrate, gives information unavailable from any other measurement or available calculation. For example, the reaction field continuum hydration model does not consider explicit water molecules and therefore lacks information about hydrogen bonding or conformational details dependent upon hydration effects. The explicit water molecule method using empirical force fields for molecular dynamics or Monte Carlo studies are useful for predicting solvation effects on moderately large molecular systems.[7–15] However, these empirical methods are notoriously poor at simulating solvation effects of carbohydrates, generally because they have not been parameterized for such calculations.

This paper deals with very specific interactions between water and α/β-D-glucopyranose, the water molecules being located at different energy optimized sites around the glucose molecule. Energies and geometries of each water molecule around glucose are reported, including the effects of these explicit water molecules on the internal coordinates and stress energies (i.e., that increase in energy associated with the reaction field as the molecules approach each other). Particular attention is paid to specific changes in the internal electronic energy of the glucose molecule, as well as the relative free energy, hydrogen-bond energy, and changes in exocyclic dihedral angles occurring upon binding to water molecules. To our knowledge, this information has never before been reported at this level of theory. Our results suggest that both the exocyclic hydroxy rotational states and the entropy contributions of the different configurations are crucial to the understanding the anomeric α/β ratio in solution.

Recent studies in this laboratory using the B3LYP density functional and the 6-311++G** basis set on glucose[6] and the disaccharides, maltose,[16] and cellobiose,[17,18] led us to believe that this level of theory will consistently give reliable conformationally dependent geometries and relative energies for carbohydrates, and more importantly for their hydrates, the interactions of which depend strongly on choice of basis set. One reason for this belief has to do with the small basis set superposition error (BSSE) for this level of theory.[19] The second reason has to do with the application of the density functionals (B3LYP), and the reduction in atom volume associated with addition of correlation. The addition of diffuse functions has also been clearly shown to add to the accuracy of the relative energies associated with carbohydrates.[6,16–18] Finally, we have found that this level of theory results in hydrogen-bond distances and energies in excellent agreement with experimental results, where they can be directly compared.[6,16–18]

It is possible to study many different water–glucose configurations because the glucose molecule is sufficiently small that one can add water molecules and still optimize the geometry of the complex at a high level of theory in a reasonable amount of computer time. The issue of computing time is an important consideration as we wish to examine many different conformations of the hydroxymethyl groups as well as the hydroxyl groups of glucose with water molecules located in different configurations around the molecule. In terms of the vacuum D-glucose case, our recent work[6] leads us to believe that the high level of theory used will be sufficient for useful relative energies, with the understanding that the errors in the absolute DFT energy (~1 kcal/mol) cancel out to some extent, as do the errors arising from the harmonic approximation in the calculation of the enthalpy and entropy terms. The lack of van der Waals interactions is recognized, but the complexes studied here are small, and thus any missing interactions should be few in number and contribute little to the overall energy differences. Clearly, one is able to correct for the lack of van der Waals interactions empirically if that were necessary.

2. Methodology

2.1. Computational methodology

The B3LYP non-local exchange correlation functionals,[19] and basis sets denoted 6-31+G* and 6-311++G**, were used as described previously for glucose,[6] maltose,[16] and cellobiose.[17,18] In this work, the preliminary geometry optimization is carried out at the B3LYP/6-31+G* level and then optimization is continued with the larger basis set. The use of 6-31+G* as a starting basis set has been found[17,18] to be more efficient and result in better carbohydrate geometry than the earlier[16] use of the 6-31G* basis set. In particular, the lone-pair orbitals are better described by the 6-31+G* than by the 6-31G* basis set.[16–18] Geometry optimization was considered satisfactory if energy differences between cycles of optimization were less than 1×10^{-6} Hartree and a gradient of less than 1×10^{-4} or 1×10^{-5} a.u., depending upon the case and analysis of the Hessian. The density functional and basis set software is included in the

Parallel Quantum Solutions package (PQS versions 2.2 and 2.3).[20] The computers used were the Parallel Quantum Solutions QS4-800S, QS4-1000S, QS4-1800S, and QS4-2000S.[20] Upgrades in machine speed and software took place during the 2–3 year time period for these calculations. Vibrational frequencies were calculated after geometry optimization at the larger basis set, as were the zero-point vibrational energies (ZPVE), enthalpy, entropy, and relative free energy for each anomer and conformation. A numerical Hessian method (NUMHESS)[20] was used with a semiempirical method to get an improved initial Hessian, which was then used as a starting point for further refinement at the higher levels of theory. It should be noted that we do not report here results of a Hessian calculated using NUMHESS at the higher level basis sets. However, results using this method have been carried out in specific cases, and errors in relative free energy arising from this question have been shown to be small.[6] The absolute values of the ZPVE, enthalpy, and entropy may be significantly different when NUMHESS is used with the large basis set to obtain the frequencies, and the results of the more exhaustive NUMHESS calculations will be presented elsewhere (manuscript in preparation).

2.2. Nomenclature

In order to study explicit water molecules interacting with a carbohydrate molecule, we require a nomenclature to describe the specific configurational states. An original nomenclature is described here for that purpose. The necessary parameters in this new descriptive method include the anomer type, (α/β), the conformational state of the hydroxymethyl group (*gg*/*gt*/*tg*), and the position of the water molecule in terms of the glucose (or other carbohydrate) groups as acceptor or donor (a/d), atoms. For example, if the water molecule's (molecule I) oxygen atom hydrogen bonds to the 3-position hydroxyl hydrogen, it would be defined as a 3d interaction. Then if the same water hydrogen bonds with one of its hydrogen atoms to the 2-position oxygen on the glucose ring, this interaction would be defined as a 2a type interaction. For the hydroxyl groups on glucose, we include the clockwise (*c*) or retro-clockwise (*r*) notations to the sequence of symbols, as well as a specific conformational definition of $g^+/g^-/t$ when required to resolve ambiguity. The total nomenclature for an β-anomer in the *gt* hydroxymethyl conformation and *r* conformation for the exocyclic hydroxyl groups, with one water as described above, is shown in Figure 1 and described in Eq. 1.

$$\text{Configuration} = \mathbf{1}\beta rgt\mathbf{1}[\text{2a3d}]. \tag{1}$$

The generalized formula for this nomenclature can be written as shown in Eq. 2.

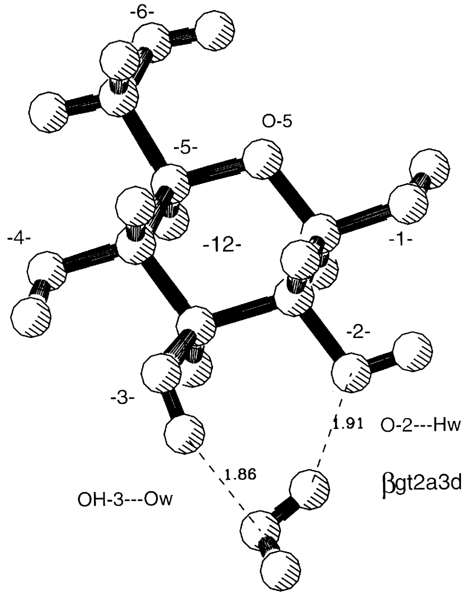

Figure 1. Atom numbering, # of configuration, and example of nomenclature on a water–glucose configuration.

$$\begin{aligned}\text{Configuration} = {} & \textbf{Residue\#}[(\alpha/\beta)(c/r)(gg/gt/tg)(g^+/g^-/t) \\ & \times \textbf{water\#}[n\{\text{\#ring position(a/d)}\}] \\ & \times \textbf{water\#}[\ldots\ldots]].. \end{aligned} \tag{2}$$

The equation continues for as many residues and water molecules as are to be described. This equation is valid for as many water molecules as are interacting with the sugar and may include three or four hydrogen bonds to a single water molecule by extension. In the example above, only one carbohydrate residue and one water molecule are defined, and so neither the residue # nor the water # needed to be included, although we have included both in bold print. If one has water–water interactions as well as water–carbohydrate interactions, the second water number is taken in bold print with (a/d) as shown above in the curly brackets, { }. In this case one of the bracketed units would not be #ring but would be # of water molecules interacting with the primary water molecule. The water molecules are numbered so that by working through the water numbers, smallest number first, one does not repeat the same water–water interaction for any higher numbered water molecule. These complexities with water interactions only appear when many water molecules are considered (manuscript in preparation).

In the cases studied here, the hydroxyl groups in the 1, 2, 3, and 4-positions were taken in their lowest energy vacuum configurations, that is, the counter clockwise (*r*) direction with the 2-position moving from the g^+ in the β-anomer to the g^- in the α-anomer. Several studies were made with the hydroxyl groups pointing toward a water oxygen atom in a crab-like configuration, that is, both *c* and *r* configurations.

Starting configurations of the complex of water plus glucose were obtained from energy minimization of the complex with in-house empirical potentials modified from a previously published version (AMB01C).[21,22] The hydroxymethyl rotamers of both anomers were included, and favorable solvent configurations around the hydroxyl positions were obtained from energy minimization using the empirical potentials. Each optimized configuration found from the empirical search was then geometry optimized at the B3LYP/6-311++G** level using the PQS software.[20]

3. Results

3.1. Glucose + water configurations

The following glucose + water molecule configurations, described in the above nomenclature (Table 1) were geometry optimized using the DFT and basis sets noted previously and the results are presented in Table 2. The relative energy listed with the descriptions is the difference in total electronic energy relative to configuration #2.

The number of water molecules in each configuration is always one in this case, and so this number is not included in the above list. The average relative electronic energy difference is 3.9 kcal/mol, with the largest value being 7.8 kcal/mol The 26 hydrogen-bonded water configurations described next were chosen to cover much of the three-dimensional space around the glucose molecule with nearly equivalent populations between the two anomers and the three different hydroxymethyl conformations. Fourteen α- and twelve β-anomers are included. The *gt* conformation is studied most often with a total of 11 configurations. The *gg* conformation is next with nine, and the *tg* is least studied with six configurations.

Table 1. Glucose + water molecules, and relative electronic energy values

Configuration #	Description	Relative electronic energy (kcal/mol)[a]
1	α*ggr*5a1d	2.4
2	α*gtr*6a1d	0.0
3	α*tgr*5a1d	1.9
4	β*ggr*5a1d	3.2
5	β*gtr*1d(g^-)	4.9
6	β*tgr*5a1d	2.9
7	α*gtr*3a4d	5.6
8	β*gtr*4a3d	7.6
9	β*gtr*1d(g^+)	3.8
10	β*gtr*4a	5.6
11	β*tgr*4a6d	4.2
12	β*gtr*2a3d	1.9
13	α*ggr*4a6a	4.1
14	α*tgr*4a6d	3.9
15	α*gtr*1a2d	3.4
16	β*gtr*1a2d	2.4
17	α*ggr*1d	2.4
18	α*tgr*1a2d	3.1
19	β*ggr*1a(g^+)	5.4
20	α*gtr*2a3d	0.9
21	α*gtr*4a3d	7.5
22	α*ggc*4a3d	5.6
23	α*ggr*3a4d	1.3
24	α*tgc*4a3d	5.0
25	β*ggr*1a2d	3.6
26	β*ggr*1d2d	$\underline{7.8}$

[a] Average relative electronic energy, $\Delta E = 3.9$ $(14, \alpha = 3.3; 12, \beta = 4.4)$.

Electronic energies, relative electronic energies, zero-point vibrational energy (ZPVE), enthalpy, relative free energy, and entropy values are listed in Table 2. Atom numbering around glucose is shown in Figure 1, as is the configuration number located inside the ring.

From Table 2 and Figure 2 it can be seen that the enhanced stabilization of α-anomer complexes over the β-anomer complexes is partially a result of a short (~2.25 Å vs ~2.55 Å, respectively) hydrogen bond between the polar hydrogen on the 2-hydroxy to the oxygen of the 1-hydroxy group. This interaction was discussed in our previous glucose in vacuo study,[6] but it is important to point out that this is a very favorable stabilizing interaction for the α-anomer. Angyal[23] pointed out that when no hydroxyl group was on the C-2 position (i.e., 2-deoxyglucose) the α- and β-anomers were found in nearly equal concentration in solution. In the in vacuo case, rotating only the 2-OH group in the α-anomer from the favored g^- to the g^+ conformation results in a loss in minimized energy (B3LYP/6-311++G**) of ~3.5 kcal/mol, irrespective of the hydroxymethyl rotamer.[6] Since the g^+ form is the favored one for the β-anomer, one must conclude that the enhanced stability of the α-anomer over the β-anomer is somewhat dependent upon the conformation of the hydroxyl group at the 2-position. However, because of the hydrogen-bond energy advantage noted above, even when the total harmonic Gibbs free energy, $[G^0_{298} = E_{\text{elec}} + (H - TS) + RT]$, is calculated, the in vacuo glucose α-anomer *gg* conformation remains ~0.3 kcal/mol lower in free energy than the lowest energy *gg* conformation of the β-anomer.[6]

It is only necessary to argue that a slight solvent preference exists for the *gg* form over the *gt* form in solution since the observed ratio of 55/45[17] for the *gg*/*gt* ratio is not totally achieved with the vacuum free-energy calculations (38/41).[6] The effect of solvent on the rotational population of the hydroxymethyl group has been studied previously.[13] In this work we will be interested in observing how the hydroxymethyl group influences the water binding energy and position, but will not consider in detail at this time the hydroxymethyl rotational population.

3.2. Hydrates

Although it is clear that a single water molecule is unable to fully hydrate glucose, we obtained structures with reasonable hydrogen-bond energies and excellent

Table 2. B3LYP/6-311++G** geometry optimized energies (kcal/mol) and configurations of α- and β-D-glucopyranose monohydrates

#	1	2	3	4	5	6
Configuration	α*ggr*5a1d	α*gtr*5a1d	α*tgr*5a1d	β*ggr*5a1d	β*gtr*1d(g^-)	β*tgr*5a1d
Energy	−479,339.841	−479,342.203	−479,340.264	−479,339.019	−479,338.335	−479,339.309
ZPVE	145.483	145.729	146.080	146.148	146.026	146.049
Δ*E*(Corr)[a]	2.11	0.00	2.29	3.60	4.16	3.21
E, glucose (Stressed)[b]	−431,353.034	−431,351.424	−431,353.053	−431,352.139	−431,352.219	−431,352.046
E, glucose (Optim)[c]	−431,353.351	−431,353.426	−431,353.371	−431,352.477	−431,352.541	−431,352.343
Δ*E*(Optim − Stressed)	−0.32	−2.00	−0.32	−0.34	−0.32	−0.30
E, water (Stressed)	−47,978.344	−47,978.323	−47,978.363	−47,978.361	−47,978.440	−47,978.362
E, water (Optim)	−47,978.459	−47,978.459	−47,978.459	−47,978.459	−47,978.459	−47,978.459
Δ*E*(Optim − Stressed)	−0.12	−0.14	−0.10	−0.01	−0.02	−0.10
Hydrogen-bond energy[d]	−8.163	−12.456	−8.898	−8.519	−7.354	−8.901
Enthalpy (*H*)	155.372	155.447	155.842	155.899	156.250	155.685
H − ZPVE	9.889	9.718	9.762	9.751	10.224	9.636
Entropy (*S*) (cal/mol K)	119.483	117.619	118.477	118.430	124.804	117.294
H − *TS* (298 K)	119.766	120.397	120.536	120.607	119.058	120.731
Δ(*H* − *TS*)	1.06	1.69	1.83	1.90	0.36	2.03
ΔG^0_{298}	2.73	0.00	2.08	3.39	2.53	3.22
Hydrogen-bond length (Å)						
Ow···H-1	1.95	1.90	1.95	1.94	1.86	1.92
Hw···O-5	2.10	2.89	2.13	2.08		2.06
Hw···O-6		1.99				

	7	8	9	10	11
	α*gtr*3a4d	β*gtr*3d4a	β*gtr*1d(g^+)	β*gtr*4a	β*btg*r6a4d
Energy	−479,336.629	−479,334.607	−479,338.422	−479,336.663	−479,337.971
ZPVE	145.380	146.795	145.921	145.334	146.193
Δ*E*(Corr)[a]	5.22	8.56	3.97	5.14	4.69
E, glucose (Stressed)[b]	−431,353.217	−431,347.755	−431,351.468	−431,352.392	−431,349.200
E, glucose (Optim)[c]	−431,353.426	−431,353.426	−431,352.541	−431,352.541	−431,352.343
Δ*E*(Optim − Stressed)	−0.21	−5.66	−1.07	−0.15	−3.14
E, water (Stressed)	−47,978.388	−47,978.345	−47,978.366	−47,978.393	−47,978.294
E, water (Optim)	−47,978.459	−47,978.459	−47,978.459	−47,978.459	−47,978.459
Δ*E*(Optim − Stressed)	−0.07	−0.11	−0.09	−0.07	−0.26
Hydrogen-bond energy[d]	−5.024	−8.497	−8.588	−5.663	−10.477
Enthalpy (*H*)	155.460	156.306	155.694	155.407	155.878
H − ZPVE	10.080	9.511	9.773	10.073	9.685
Entropy (*S*) (cal/mol K)	123.347	116.657	118.111	122.697	117.380
H − *TS* (298 K)	118.703	121.452	120.497	118.843	120.898
Δ(*H* − *TS*)	0.00	2.75	1.79	0.14	2.19
ΔG^0_{298}	3.88	7.42	3.88	3.99	4.73

Table 2 (*continued*)

	7	8	9	10	11
	α*gtr*3a4d	β*gtr*3d4a	β*gtr*1d(g^+)	β*gtr*4a	β*btg*r6a4d
Hydrogen-bond length (Å)[e]					
Ow···HO-1			1.91	1.94	
Ow···HO-6					1.91
Ow···HO-3	2.01	2.00			
Hw···O-4		2.03			1.88
Hw···O-5			2.08		

*α- and β-*D*-Glucopyranose monohydrates with water located at different positions*

	12	13	14	15	16
	β*gtr*2a3d	α*ggr*4a6a	α*tgr*4a6d	α*gtr*1a2d	β*gtr*1a2d
Energy	−479,340.337	−479,338.075	−479,338.281	−479,338.845	−479,339.828
ZPVE	146.938	145.635	147.166	145.324	146.365
Δ*E*(Corr)[a]	3.08	4.03	5.36	2.95	3.01
E, glucose (Stressed)[b]	−431,351.531	−431,352.931	−431,349.680	−431,351.791	−431,351.688
E, glucose (Optim)[c]	−431,353.426	−431,353.351	−431,353.371	−431,353.426	−431,353.426
Δ*E*(Optim − Stressed)	−1.89	−0.42	−2.96	−1.64	−1.74
E, water (Stressed)	−47,978.333	−47,978.406	−47,978.310	−47,978.352	−47,978.357
E, water (Optim)	−47,978.459	−47,978.459	−47,978.459	−47,978.459	−47,978.459
Δ*E*(Optim − Stressed)	−0.13	−0.05	−0.15	−0.11	−0.10
Hydrogen-bond energy[d]	−9.473	−6.738	−10.291	−8.702	−9.882
Enthalpy (*H*)	156.938	155.130	156.645	155.051	156.116
$H-\mathrm{ZPVE}$	9.448	9.495	9.479	9.727	9.751
Entropy (*S*) (cal/mol K)	115.582	115.848	115.992	118.140	117.930
$H-TS$ (298 K)	121.943	120.607	122.079	119.845	120.973
$\Delta(H-TS)$	3.24	1.90	3.38	1.14	2.27
ΔG^0_{298}	4.42	5.34	6.61	3.81	3.96
Hydrogen-bond length (Å)[e]					
Ow···HO-2				1.86	1.86
Ow···HO-3	1.86				
Ow···HO-6			1.86		
Hw···O-1				1.94	1.96
Hw···O-2	1.91				
Hw···O-4		2.14	1.84		
Hw···O-6		2.10			

	17	18	19	20	21
	α*ggr*1d	α*tgr*1a2d	β*ggr*1a(g^+)	α*gtr*2a3d	α*gtr*3a
Energy	−479,339.807	−479,339.092	−479,336.765	−479,341.279	−479,335.737
ZPVE	146.661	145.091	145.369	144.904	145.061
Δ*E*(Corr)[a]	3.33	2.47	5.08	0.10	5.80
E, glucose (Stressed)[b]	−431,353.023	−431,351.519	−431,351.085	−431,352.561	−431,348.768
E, glucose (Optim)[c]	−431,353.426	−431,353.351	−431,353.371	−431,353.426	−431,353.426
Δ*E*(Optim – Stressed)	−0.40	−1.83	−2.29	−0.87	−4.66
E, water (Stressed)	−47,978.356	−47,978.348	−47,978.447	−47,978.308	−47,978.343
E, water (Optim)	−47978.459	−47978.459	−47978.459	−47978.459	−47,978.459
Δ*E*(Optim – Stressed)	−0.10	−0.11	−0.01	−0.15	−0.12
Hydrogen-bond energy[d]	−8.428	−9.225	−7.233	−10.410	−8.626
Enthalpy (*H*)	156.386	154.374	155.225	154.165	154.412
H − ZPVE	9.725	9.283	9.856	9.261	9.351
Entropy (*S*) (cal/mol K)	118.303	114.012	119.871	113.680	113.965
H − *TS* (298 K)	121.132	120.398	119.503	120.288	120.450
Δ(*H* − *TS*)	2.43	1.70	0.80	1.59	1.75
ΔG^0_{298}	0.85	4.42	5.55	1.82	7.52
Hydrogen-bond length (Å)[e]					
Ow· · ·HO-1	1.85				
Ow· · ·HO-2		1.86			
Ow· · ·HO-3				1.87	
Ow· · ·HO-6					
Hw· · ·O-1		1.95	1.90		
Hw· · ·O-2				1.89	
Hw· · ·O-3					1.94

	22	23	24	25	26
	α*ggr*4a3d	α*ggr*3a4d	α*tgr*4a3d	β*ggr*1a2d	β*ggr*1d2d
Energy	−479,336.619	−479,340.938	−479,337.188	−479,339.814	−479,334.940
ZPVE	146.006	154.810	150.500	144.772	146.220
Δ*E*(Corr)[a]	5.86	10.35	9.79	1.43	7.75
E, glucose (Stressed)[b]	−431,349.196	−431,352.441	−431,348.807	−431,351.773	−431,346.096
E, glucose (Optim)[c]	−431,353.426	−431,353.351	−431,353.371	−431,353.426	−431,353.426
Δ*E*(Optim – Stressed)	−5.33	−0.91	−4.56	−1.65	−7.33
E, water (Stressed)	−47,978.331	−47,978.334	−47,978.315	−47,978.354	−47,978.434
E, water (Optim)	−47,978.459	−47,978.459	−47,978.459	−47,978.459	−47,978.459
Δ*E*(Optim – Stressed)	−0.12	−0.13	−0.14	−0.10	−0.03
Hydrogen-bond energy[d]	−9.092	−10.163	−10.066	−9.687	−10.410
Enthalpy (*H*)	155.715	163.945	159.831	159.117	155.996
H − ZPVE	9.709	9.135	9.331	14.345	9.776
Entropy (*S*) (cal/mol K)	118.329	114.219	115.727	115.074	119.070
H − *TS* (298 K)	127.386	129.908	125.344	124.825	120.513
Δ(*H* − *TS*)	8.683	9.821	6.641	6.122	1.810
ΔG^0_{298}	12.58	9.49	9.97	6.82	7.40

Table 2 (*continued*)

	22	23	24	25	26
	α*ggr*4a3d	α*ggr*3a4d	α*tgr*4a3d	β*ggr*1a2d	β*ggr*1d2d
Hydrogen-bond length (Å)[e]					
Ow···HO-1					2.05
Ow···HO-2				1.86	2.01
Ow···HO-3	1.94		1.91		
Ow···HO-4		1.87			
Hw···O-1				1.94	
Hw···O-3		1.88			
Hw···O-4	1.92		1.87		

[a] *E*(Corr) has been corrected for ZPVE differences. For example, the stressed states of glucose and water are corrected for the ZPVE that was calculated from the optimized structures. ZPVE (water optim) = 14.214 kcal/mol.

[b] Stressed implies the minimized energy of the molecule relative to the vacuum state energy calculated at the geometry found.

[c] Optim implies an energy after full optimization of the molecule.

[d] Hydrogen-bond energy is the stressed glucose plus stressed water energies, subtracted from the total energy. It is not energy per H···O interaction.

[e] Ow denotes the water oxygen atom, Hw the water hydrogen atom closest to the specified glucose oxygen.

geometries, and from that it was possible to observe conformational and energetic changes (stress energy) associated with these monohydrate interactions. As water molecules approach D-glucose, the conformations of the hydroxyl groups (and to some extent the ring structure) deviate from the optimized glucose conformations in vacuo. Coordinate deviations from the global energy minimum structure increase the electronic energy of the D-glucose molecule as well as increase the energy of the water molecule from its in vacuo energy. These changes in energy state are referred to as the ‘stressed’ forms of the molecules and they are reported in Table 2 and range from a low value (configuration #10) of −0.15 kcal/mol to a high stress value (configuration #8) of −5.66 kcal/mol. The energy stress changes found for the water molecule are very small, as expected. The stress energies will be of interest to those working with solvation continuum methods as these energies must be taken into account for solvation methods to have a greater degree of validity. Further, we believe that this and other data reported here is very useful in the parameterization of empirical potentials, in particular those potentials which are to be used with explicit water molecules.

3.3. 1-Position configurations

Some 1-position results are found as configurations 1–6 in Table 2. The structures of the three α- and three β-rotamers (*gg*/*gt*/*tg*) are shown in Figure 2. Other configurations (see Fig. 3) such as #9, #15–19, and #25–26 also have a water molecule interacting with the 1-hydroxy group in different orientations. The observed variability in energy difference [Δ*E*(Corr), corrected for ZPVE] depends upon the number of different polar interactions that can contribute for the particular configuration of the water molecule. For example, from Figure 2 it is clear that the α-anomer *gt* conformer binds water much differently than the β-anomer *gt* conformer. This is not an unexpected result since the position of the 1-hydroxyl group relative to the O-5 ring oxygen is important as is the position of the O-6–H-6 hydroxyl group. Also of interest is the different orientation of the binding of water to the α-anomer *gt* conformation relative to the *gg* and *tg* conformations. In this case, the water molecule tilts one hydrogen atom toward the ring ether O-5 atom while keeping the hydrogen bond to the 1-position hydroxyl group. In the β-anomer *gt* conformation, the water tilt is not found because the hydroxymethyl O-6–H-6 group is in a blocking position, and a short (1.86 Å) linear hydrogen bond (H-1···Ow) results. The α-anomer *gt* conformation does not have the hydroxymethyl group blocking the interaction at the O-5 position and takes up a configuration similar to the other complexes. This result is interesting in that it is one case where the conformation of the hydroxymethyl

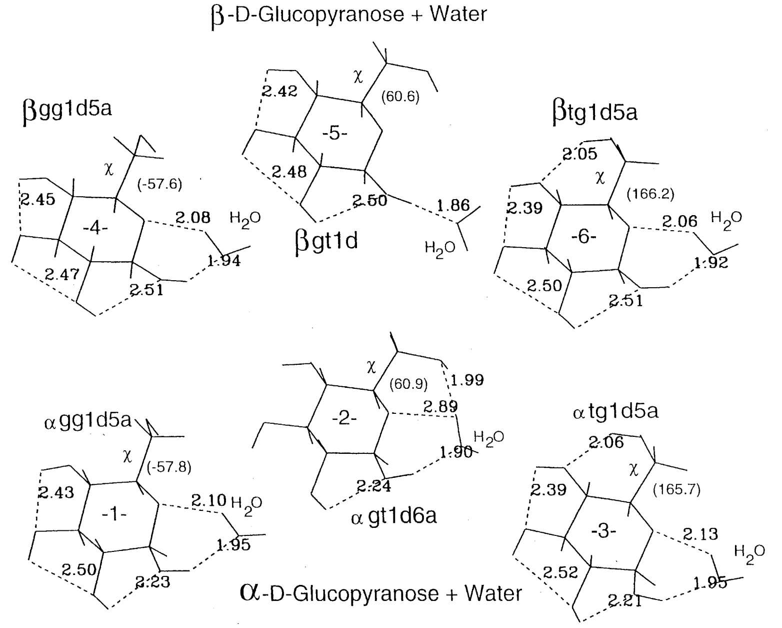

Figure 2. α- and β-anomers of six 1-position glucose monohydrates with three hydroxymethyl orientations. Specific hydrogen bonding distances are shown. Values in parentheses are dihedral angles for each particular conformation of glucose without water.

group is directly responsible for the particular water molecule interaction.

Adding a water molecule to D-glucose at the 1-position and optimizing the complex can impart significant molecular stress (~#2 configuration is stressed by ~−2.0 kcal/mol) upon the D-glucose molecule, but little stress on the water molecule (~−0.14 kcal/mol). The interaction or hydrogen-bond energy, however, depends strongly upon the particular complex formed. For example, in configuration #5 (β-*gt*), the hydrogen-bond energy is ~−7.3 kcal/mol (uncorrected for ZPVE), while configuration #2 (the α-*gt* form) has a hydrogen-bond energy of ~−12.5 kcal/mol. This particular difference is a result of the α-anomer forming more hydrogen bonds, including the hydroxymethyl O-6 as well as the interactions at the 1- and 5-positions, than are formed in the β-anomer. This effect is reduced in both the α-*gg* and α-*tg* conformations, resulting in hydrogen bond strengths equivalent to those found in the β-anomers.

The (H-ZPVE) thermal energy terms are nearly the same for all the 1-position configurations for both anomers. Further, $\Delta(H - TS)$ terms favor the *gt* conformation of the β-anomer but this energy difference is not sufficient to overcome the very favorable hydrogen bonds formed for the α-anomer *gt* conformation, which is reflected in the calculated ΔG^0_{298} values. Anharmonic contributions may change the resulting energies somewhat; however, some entropic and enthalpic tendencies toward the gt β-anomer preference are preserved in the 1-position monohydrate study, even at the harmonic level. The main reason appears to be a tendency for the linear (i.e., weaker) hydrogen bond in configuration #5 (β-*gt*) to contribute low-frequency modes to the calculation of the thermal parameters. The lowest frequencies (not shown) for all the 1-position configurations are associated with configuration #5 (manuscript in preparation). The other 1-position complexes do not have as many low frequencies and thus have smaller contributions from these terms to the entropy.

Figure 3 shows all 26 configurations studied. Continuing discussion of the 1-position, configuration #9 has the 1-OH group in the g^+ orientation and the water located above the glucose ring. A strong hydrogen bond (~−8.6 kcal/mol) from the water molecule to the H-1 atom is found; interestingly, this is a stronger hydrogen bond than that of configuration #5 (~−7.4 kcal/mol), where the g^- orientation is found and the water molecule is nearly in the plane of the glucose molecule.

Configurations #15, #16, #18, and #25 all have a 1-position acceptor configuration, while #26 is a 1- and 2-position donor. Configuration #17 (α*ggr*1d), with a corrected ΔE of ~3.3 kcal/mol, is the second lowest relative free energy structure ($\Delta G^0 = 0.85$ kcal/mol) and has a single hydrogen bond between H-1 and Ow.

3.4. 2-Position configurations

Configurations #15 and #25, shown in Figures 3 and 4, are of special interest. The point of interest is the variation in H-2 to O-1 distance relative to the vacuum case. In vacuo this non-bonded distance is found to be ~2.25 Å, while in #15, after interacting with water located between the 1- and 2-positions, the H-2 to O-1 distance has increased to ~2.63 Å, a significant increase in distance and a loss of internal energy of ~1.6 kcal/mol

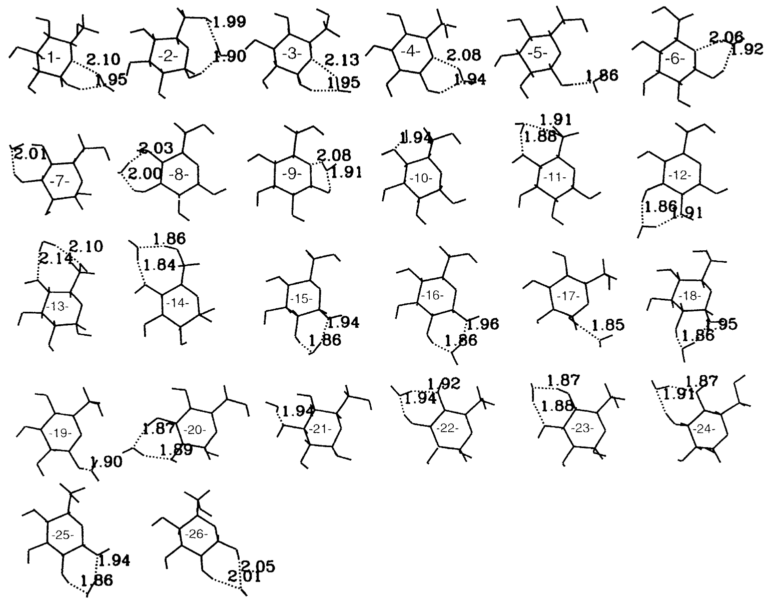

Figure 3. Twenty-six monohydrate configurations with water-to-glucose hydrogen-bond distances. Glucose-to-glucose hydrogen bonding is not shown.

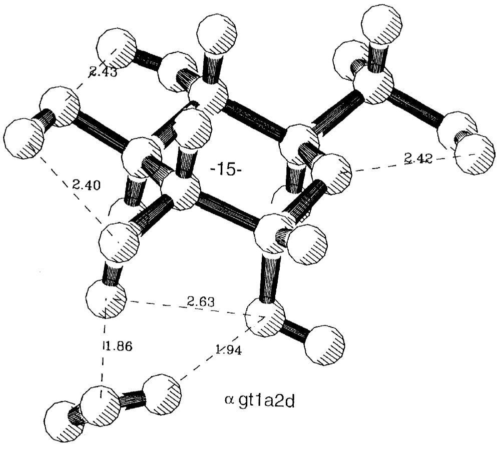

Figure 4. Configuration #15, showing an increase in the H-2···O-1 hydrogen-bond distance upon interacting with water.

(see Table 2 stress energy for glucose). The stress energy in #25 is very similar to that of #15, since the water takes up a slightly different configuration. However, in configuration #26, the 1-OH has been rotated away from the O-5 atom and is pointing toward the 2-OH group, forming a complex with the water molecule in a crab-like configuration. In this configuration, the internal stress energy on glucose has increased to ~7.3 kcal/mol. This is the largest change in internal energy of all the configurations studied, and it was the only crab-like conformation found that did not convert to another non-crab-like conformation during energy minimization. Configurations #16, #18, #25, and #26 all have rather large hydrogen-bond energies, again indicating that the 1- and 2-positions form very stable monohydrate complexes with different configurations.

3.5. 3-Position configurations

Water molecules were also moved into positions below the 3-position hydroxyl group resulting in configuration #10. A variety of configurations were found in which both the 3- and 4-OH groups were taking part in the interaction with water. The configurations that complex water through the 3- and 4-positions include #7, #8, #21, #22, #23, and #24, and are depicted in Figure 3. It was interesting that in the case of the water started from a position below the 3-OH, the water moved upon geometry optimization to a preferential position slightly below the 4-OH. One complex with the water above the 3-OH (#21) remained close to the starting configuration. The ΔE(Corr) values show that the 3- and 4-position configurations are several kcal/mol higher in energy than the lowest energy 1-position configuration (α-*gt*). Part of the energy disadvantage of the 3- and 4-position complexes may be a result of disturbance of the optimal network of hydroxyl groups interacting through hydrogen bonding around the ring in the vacuum state. That is, when one particular hydroxyl groups hydrogen atom moves toward a water molecule above or below the ring, the favored network of hydrogen bonds is disturbed (i.e., the lone-pair electrons are also rotated), and the other hydroxy groups must readjust by rotating about their O–C bonds to positions removed from their optimum positions. For this reason, the energy of these configurations is not as low as that when the water is near the 1-position where reorientation of the complete ring network of hydrogen bonds is not necessary to obtain very favorable energies. However, the entropy contribution for the broken ring hydrogen-bonding configuration is larger than the unbroken ones, and for this reason the net free energy remains close among all the monohydrates studied.

Configurations #12 and #20, all have water molecules close to the 3-position while also interacting with the 2-position.

3.6. 4-Position configurations

Configurations' #7, #8, #10, #11, #13, #14, and #22–24 have water molecules near the 4-position and also, as in the case of #11, #13, and #14, near the hydroxymethyl group. The other configurations are described above in the 3-position section. In general, the hydrogen-bond energies are strong, but the disruption in the glucose network of hydroxyl group hydrogen bonds leaves its mark as fairly high relative free energies for these configurations. From this one could suggest that when the 4-position is coupled to form maltose or longer chain amylose fragments, little favorable energy contribution is lost as a result of removing this position from solution.

3.7. Hydroxymethyl configurations

Configurations #2, #11, #13, and #14, are those in which water interacts with the hydroxymethyl groups in some manner. Configuration #2 has been described in the 1-position description, and the other three have been described as interacting with the 4-position.

3.8. Hydrogen-bond lengths

Comparisons between donor and acceptor oxygen (carbohydrate) to oxygen (water) hydrogen-bond distances measured in the crystal structures of carbohydrates[5] and the calculated results presented here, are found in Table 3. Inspection shows these to contain some interesting correlations. In general it can be observed that the calculated donor distances are slightly longer than the X-ray results, while the calculated acceptor distances are slightly shorter than the crystal results. Of importance is that the calculated average distances are very close (~0.05 Å for donors and ~0.01 Å for acceptors) to the experimentally measured hydrogen-bond distances. These results are particularly important since the distances are close in spite of the fact that there are very few of some interaction types, both from the crystal side, where experimentally the O-4 and O-5 acceptor terms are very few or not found at all, and also from the DFT calculations, where only one donor at O-4 was examined, and only two O-6 terms were included. Further, when comparing the two structure methods, note that the measurements are from completely different physical descriptions, X-ray geometry being defined by the center of the electron cloud and the DFT geometry being defined from nuclear centers. It is therefore remarkable that the trends found from the crystallographic data between donor and acceptor interaction distances are well reproduced in the DFT results.

3.9. Geometry changes upon hydration

There are several bond lengths that change upon formation of a hydrogen bond with a water molecule. The most important changes are found for the H–O and C–O(hydroxyl) bonds. In general, the hydroxyl H–O bond in an O–H···Ow type interaction, is lengthened by ~0.01 Å relative to the H–O bond lengths at sites located around the glucose ring involved in hydrogen bonding to other hydroxyl groups. The H–O distances of the 2- through 4-positions are ~0.964 Å in length, when in the *r* configuration around the ring, but lengthen when the water molecule comes close in a donor-type interaction. Acceptor-type interactions appear not to be strongly influenced by the water, changing by only ~0.003 Å or less. The crab-like interaction in which

Table 3. Hydrogen-bond lengths (Å) between carbohydrate and water from the Cambridge Crystallographic Database (CCD) and DFT results

Atom #	Donor			Acceptor		
	Mean		Δ*r*	Mean		Δ*r*
	This work	CCD[5]		This work	CCD[5]	
O-1[a]	2.82	2.81(43)[b]	0.01	2.84	2.84(39)[b]	0.00
O-2	2.83	2.77(46)	0.05	2.79	2.88(82)	−0.09
O-3	2.91	2.77(59)	0.14	2.83	2.90(110)	−0.07
O-4	2.81	2.78(8)	0.03	2.86	3.07(1)	−0.21
O-5	—	—	—	2.86	—[c]	—
O-6	2.82	2.79(47)	0.03	2.95	2.84(64)	0.11
Average	2.83	2.78[d]	0.05	2.86	2.87[d]	−0.01

[a] Atom numbers are those shown in Figure 1.

[b] Values in parenthesis are number of times that particular interaction appears in the Cambridge Crystallographic Database (CCD)[5].

[c] The crystallographic analysis did not find O-5 position acceptor hydrogen bonding.

[d] Number weighted average.

two hydroxyl groups point toward the Ow of a water molecule increases in H–O length by only ~0.003 Å over the normal ring value. The water bonds, Ow–Hw also change slightly when in contact with the glucose oxygen atoms. For example, the Hw–Ow bond length of an Ow–Hw···O-5 (ring ether) interaction is ~0.970 Å, while in the Ow–Hw–O (hydroxyl) interaction the Hw–Ow bond length is ~0.973 Å. For the water acting as a donor, the Hw–Ow bond length of an H (hydroxyl)–Ow–Hw is ~0.963 Å on average. These are very small changes but play a role in determining the stress energy of the water molecule.

The C–O bonds also reflect the interaction of water molecules and also depend upon the anomer being studied. For example, in the case of conformers #1, 2, and 3, which are α-anomers with a water molecule near the 1-position, the C-1–O-1 bond length average is ~1.404 Å, relative to the no-water case of 1.420 Å, a difference of ~0.016 Å. This is a significant shortening of the bond upon interaction with water. In β-anomers conformers #4, 5, and 6, with a water molecule near the 1-position, the C-1–O-1 bond length average is 1.385 Å, relative to the no water case of 1.397 Å, for a difference of 0.012 Å. The larger difference for the α-anomer is consistent with a stronger hydrogen bond than with the β-anomer, in agreement with the hydrogen-bond energies in Table 2. Other hydroxy positions for bond-length variations with water molecules can also be examined. For example, in the case of the C-3–O-3(H-3)···Ow interactions, the C-3–O-3 bond length average is 1.413 Å, while in the no-water case the bond length is 1.426 Å, a difference of ~0.013 Å, which is in general agreement with the results from the 1-position. The C-4–O-4(H-4)···Ow interactions are complicated by the fact that hydrogen bonding with the O-6–H-6 hydroxyl changes this bond length with or without water around. However, in configuration #23 the C-4–O-4(H-4)···Ow interaction has a C-4–O-4 bond length of 1.415 Å, which can be compared to a no-water bond length of 1.424 Å, a difference of ~0.009 Å. This configuration has the *gg* hydroxymethyl group conformation and does not complicate the hydrogen-bond interaction.

Variations in bond angles also occur near the site of binding of the water molecule. In general, there is very little change in the H–O–C bond angles when they act as acceptors. However, when the H–O–C is a donor to water, the angle opens by ~1–2°. In the case of the water molecule, the H–O–H angle also changes depending upon the hydrogen bonding configuration. In the case of configuration #13, where the water molecule acts as a double donor, the angle is reduced to 103.5° from a normal angle of ~106–107° depending upon the configuration. In configuration #25, the water acts as both donor and acceptor, and the H–O–H angle is found to be 106.9°, while in #26 the water is a double acceptor, and the angle is 106.2°. These are small deviations but do contribute to the overall energy of the water complex.

It was expected that there would be major changes in the dihedral angles upon binding of a water molecule, and that was confirmed from these calculations, as shown in Figure 5. There are no particular trends in the dihedral angle changes because it depends upon the direction from which the water is forming the hydrogen bond and the torque placed on the H–O–C–C dihedral from the interaction energy. For example, there is a 20° variation in the H-1–O-1–C-1–O-5 dihedral angle in going from configuration #2 to configuration #3. Both are α-anomers with water hydrogen bonding to the 1-position, but the hydroxymethyl group has interfered in such a way that the water is in a different position in the two cases. There is a ~15° difference in the same dihedral angle in the β-anomer cases as shown in configurations #5 and #6. A 43° variation in the H-6–O-6–C-6–C-5 dihedral angle was found between configurations #6 and #14, when the water was moved to a position near the 4-hydroxy group. In configuration #26 the 1-position hydroxyl group has flipped into the *trans* conformation to bind a water molecule in a double-donor configuration. In this case one could say that a change of ~100° has taken place relative to the normal 1-position conformation. To summarize this section, it is apparent that dihedral angles are very soft variables and will be strongly affected by the approach of water molecules. In our studies on penta- and deca-hydrates these variations in a dihedral angle become even more important to understanding the stress put on the glucose molecule by the solvent (manuscript in preparation).

3.10. O–H···O geometry

The geometry around the hydrogen bonds made when water binds to glucose is of interest as it has been suggested from neutron diffraction studies of carbohydrates[24] that the shorter the O–H bond, the more linear the O–H···O angle. A plot of O–H bond lengths versus O–H···O angle is shown in Figure 6. Clearly, there is a correlation between these two parameters, although there are points outside the standard deviation that belong to specific types of interactions.The average values of the H···O hydrogen bond length (1.904 Å) and O–H–O angle (154.2°) found from the DFT calculations are closer to the bifurcated bonds (~2.03 Å and 151.1°) than to the linear hydrogen bonds (~1.82 Å and 167.1°). In fact most of the hydrogen-bonding configurations of water molecules to glucose make multiple or bifurcated interactions and are not linear, and should be longer than the linear forms. For example, two linear configurations at the 1-position (1.86 Å, 175.9°; 1.85 Å, 172.9°) are very close to the observed linear hydrogen bonds found crystallographically.[24] However for a linear hydrogen bond at the 4-position, the bond lengths are

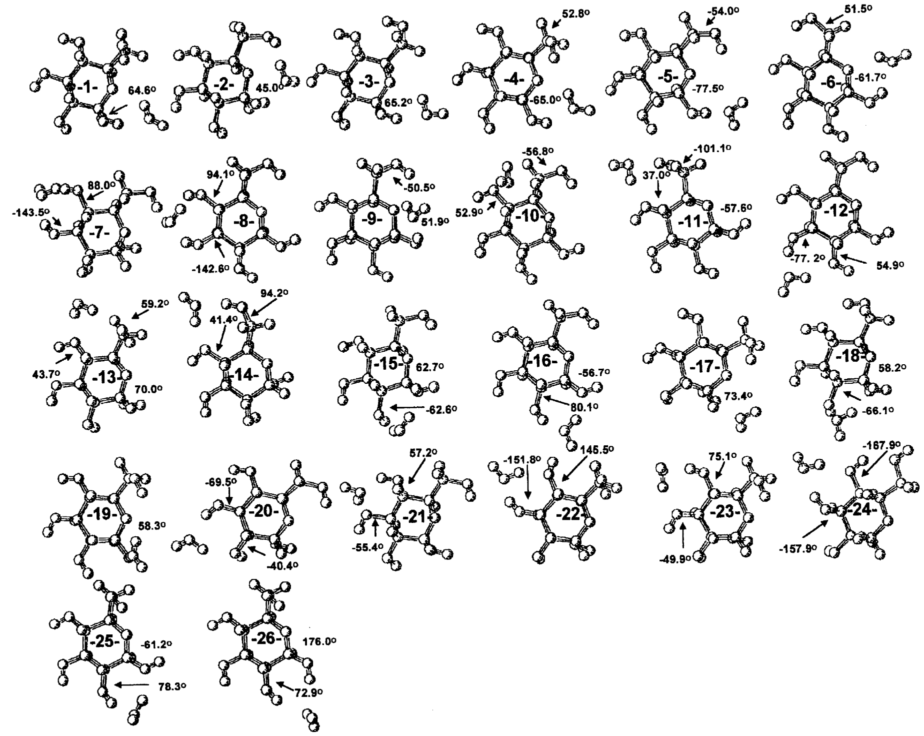

Figure 5. Twenty-six monohydrate configurations of glucose with selected exocyclic dihedral angles. An example is the H-1–O-1–C-1–O-5 dihedral angle of 64.6° in configuration #1.

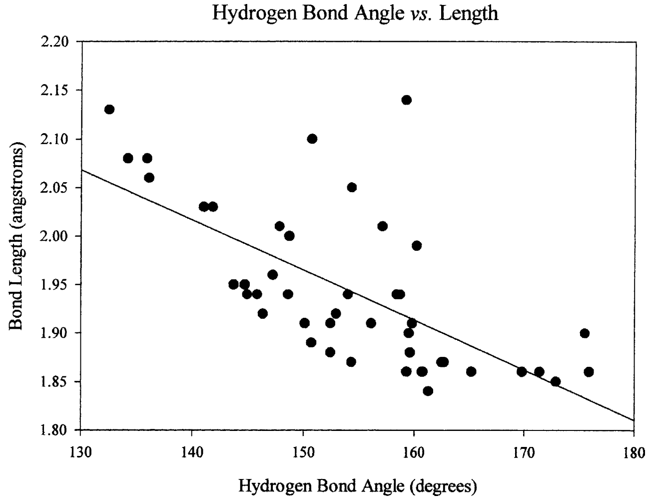

Figure 6. O–H bond lengths versus O–H···O angle for glucose monohydrate hydrogen bonding interactions. Glucose–glucose hydrogen bonds are not included.

longer (1.94 Å for both) and the O–H···O angle is ~158° for both configurations, which suggests that the hydrogen bond at this site is weaker than the 1-position hydrogen bond. This is consistent with other results presented here.

The points on Figure 6 that lie above the best fit line and appear to be outliers, all have very unusual hydrogen-bonding networks. The two points at 2.14 and 2.10 Å with angles of 159.2° and 150.7° are from a situation in which the water is donating hydrogen atoms to two oxygen atoms on glucose. This configuration is a very stressed condition. Two other points at 2.01 and 2.05 Å with angles of 157.1° and 154.3° are from a crab-like configuration with two hydroxyl hydrogens being donated to the same water oxygen atom. Removing these points from consideration brings about a change in the overall r^2 fit from 0.44 to 0.67. The different configurations noted have hydrogen bond lengths very much in agreement with the neutron diffraction work reported[25] even though the experimental values have not been scaled to the vibrationless state.

4. Discussion

The solution preference of the β-anomer over the α-anomer is due in part to reorientation of the glucose hydroxyl groups upon interaction with the water molecules. That is, as water approaches glucose the hydroxy hydrogen atoms move toward the water, and the counterclockwise cyclic hydrogen-bonding pattern around the glucose molecule is disrupted. In vacuo, considerable increase in electronic energy was found when the α-*gt* 2-OH hydroxyl group was rotated away from the optimal position and into the second *gauche* position. This rotation breaks the very short hydrogen bond between the 2-OH and the 1-OH while maintaining a favorable lone-pair interaction of the 2-OH oxygen

Table 4. Selected internal coordinates of β-*gt* form of D-glucose in vacuo, #5 monohydrate, #10 monohydrate, and a β-*gt* pentahydrate[22]

	Vacuum[6]	#5[a]	#10[a]	Pentahydrate[22]	Δ(Vac − penta)
	β*gtr*	β*gtr*1d(g^-)	β*gtr*4a	β*gt*	
Bond lengths (Å)					
C-1–O-5	1.421	1.430	1.423	1.422	−0.001
C-1–O-1	1.396	1.386	1.396	1.405	−0.009
O-1–HO-1	0.964	0.973	0.963	0.964	0.000
C-2–O-2	1.423	1.424	1.422	1.412	+0.011
O-2–HO-2	0.964	0.964	0.964	0.980	−0.016
C-3–O-3	1.424	1.426	1.426	1.434	−0.010
O-3–HO-3	0.964	0.964	0.964	0.968	−0.004
C-4–O-4	1.421	1.422	1.433	1.425	−0.004
O-4–HO-4	0.965	0.965	0.966	0.979	−0.014
C-6–O-6	1.420	1.421	1.419	1.428	−0.008
O-6–HO-6	0.964	0.964	0.964	0.965	−0.001
C-5–C-6	1.522	1.522	1.522	1.520	+0.002
Bond angles (°)					
C-1–O-5–C-5	113.4	113.3	113.3	113.7	−0.3
O-1–C-1–O-5	109.0	109.5	108.9	107.5	+1.5
C-1–O-1–HO-1	109.3	109.5	109.3	109.2	+0.1
C-2–O-2–HO-2	108.2	107.5	109.2	109.7	−1.5
C-3–O-3–HO-3	108.0	107.8	108.0	105.9	+2.1
C-4–O-4–HO-4	107.4	107.3	106.8	109.5	−2.1
C-6–O-6–HO-6	107.2	106.5	107.2	107.2	0.0
Dihedral angles (°)					
C-1–O-5–C-5–C-4	62.0	62.2 (−0.2)	62.1 (−0.1)	61.7	+0.3
C-2–C-1–O-5–C-5	−62.8	−63.2 (0.4)	−63.9 (1.1)	−64.0	+1.2
HO-1–O-1–C-1–O-5	−66.9	−77.5 (10.6)	−69.0 (2.1)	−75.5	+8.6
HO-2–O-2–C-2–C-1	62.4	58.0 (4.4)	61.6 (0.8)	94.6	+32.2
HO-3–O-3–C-3–C-2	−56.7	−55.4 (−1.3)	−59.6 (2.9)	−49.2	−7.5
HO-4–O-4–C-4–C-3	50.9	50.7 (0.2)	52.9 (−2.0)	71.8	−19.1
O-6–C-6–C-5–O-5	60.7	58.1 (2.6)	61.2 (−0.5)	58.7	+2.0
HO-6–O-6–C-6–C-5	−57.6	−54.0 (−3.6)	−56.8 (−0.8)	−52.6	−5.0

[a] Values in parenthesis are (vacuum hydrated).

with the 3-OH hydrogen atom resulting in a higher relative energy (~3.5 kcal/mol) overall. When a similar calculation was carried out for the β-*gt* anomer, moving the 2-OH to the g^- gauche position (the favored position for the α-anomer), the results were interesting in that upon minimization the conformation returned to the original low-energy position. This result makes it difficult to say with certainty that the 2-position hydroxyl rotation plays a significant role in the preference for the β-anomer in water, but the suggestion is strong.

Using the hydrated configurations in Table 2 to calculate populations of anomers, the ratio from the electronic energy difference values is 58/42 (α/β), while using the calculated free-energy differences the ratio becomes 52/48 (α/β). This is quite a significant improvement from the previous in vacuo studies on glucose[6] where a ratio of 63/37 (α/β) was found from the free-energy differences, and the hydrate results are considerably closer to the experimental ratio, 36/64 (α/β), where the β-anomer is strongly preferred. Of further interest is the observation[25] that the mole fraction of the β-anomer of the molecule 2,3,4,6-tetra-*O*-methyl-D-glucopyranose is 0.39 in water. In this case the 2-hydroxy group is no longer available to influence the anomeric ratio, and a population shift favoring the α-anomer is found. Of course, the *exo*- and *endo*-anomeric effects described[25] also play a role in the anomeric populations in different solvents.

It is quite remarkable that from the calculations we report here, the addition of one water molecule interacting with glucose has significantly reduced the theoretical discrepancy in the anomeric population in solution. From examination of the values in Table 2, it is clear that the improvement in the anomeric population ratio is a result of larger entropy terms for the β-anomer hydrated structures. The enthalpy terms are quite constant, varying between ~154 and ~158 kcal/mol. However, the entropy contribution to the relative free energy is large. Considering configuration #5 as an example, the ΔE(Corr) value is 4.16 kcal/mol, while the ΔG^0_{298} value is reduced to 2.53 kcal/mol, a result of the rather large entropy contribution to the free energy for this configuration. In general, entropy contributions lowered the β-anomer configurational free energies more than it lowered the α-anomer configurational free energies.

Hydration studies at the B3LYP/6-311++G** level are now in progress using five and ten water molecules located around the glucose molecule. New insights into the interaction of water with carbohydrates are being discovered from these more complex explicit solvation studies. One result of interest is the observed decrease in the average hydrogen bond energy as more water molecules are included. Clearly, the hydrogen bond energy described here for monohydrates appears at first sight to be very large, of the order of 5–10 kcal/mol of attractive energy. However, when we add more water, the average hydrogen-bond energy is reduced to 3–5 kcal/mol. This result is more in line with current thinking as to the energy of a hydroxyl–water hydrogen bond in solution. The above points will be addressed elsewhere (manuscript in preparation).

The hydrogen-bond energy of a water molecule interacting with glucose appears to be strongest when near the 1-position relative to the other ring hydroxyl positions examined. This result is further enhanced with the larger water clusters around glucose (manuscript in preparation).

Finally, we have included in Table 4 results from one pentahydrate study that clearly shows significant variance in hydroxyl dihedral angles when compared to the vacuum state. Deviations of up to 32° from the vacuum state were found between the vacuum and pentahydrate studies, while variances of 10–12° were routinely found in the monohydrate studies relative to vacuum. These large differences in dihedral angles upon adding water molecules are important in understanding solvation effects in carbohydrates and are the source of the stress energy noted in Table 2.

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