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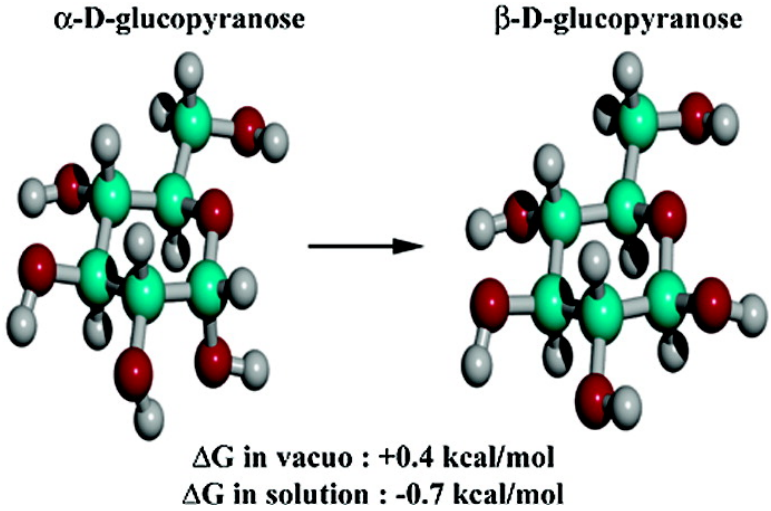

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Theoretical Study of the Relative Stability of Rotational Conformers of α and β-D-Glucopyranose in Gas Phase and Aqueous Solution

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Abstract: The α−β anomer energy difference and the stability of 10 rotamers of counterclockwise D-glucopyranose were studied in vacuo and in aqueous solution at the B3LYP/6-31+G(d,p) level. To obtain the solute charge distribution and the solvent structure around it, we used the averaged solvent electrostatic potential from molecular dynamics method, ASEP/MD, which alternates molecular dynamics and quantum mechanics calculations in an iterative procedure. The main characteristics of the anomeric equilibrium, both in vacuo and in solution, are well reproduced. The relative stability of the different anomers is related to the availability of the free pairs of electrons in the anomeric oxygen to interact with the water molecules. The influence of solvation in the conformer equilibrium is also analyzed.

Introduction

Monosaccharides are the major building blocks for many important carbohydrate systems. Polysaccharides, glycoproteins, and monosaccharides themselves play an essential role in many biochemical processes:[1] metabolic pathways, recognition processes, energy storage, or structural units are examples. It is therefore not surprising that the structure of the most important monosaccharide in biochemistry,[2] D-glucose, has been the focus of attention of many theoretical studies.[3−46] However, many questions about their conformational structure and behavior, both in gas phase and in solution, are still unanswered.[47]

In solution, D-glucose is found almost entirely in the pyranose form. Since the C_1 carbon atom of D-glucopyranose (the labeling for each atom is shown in Figure 1) is a chiral center, there are two stereochemical species according to the position of the OH group: the β anomer, with all the hydroxyl groups in the

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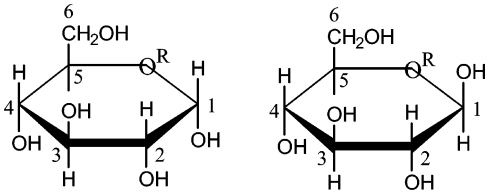

Figure 1. Atom numbering scheme for α-D-glucopyranose and β-D-glucopyranose.

equatorial orientation with respect to the ring, and the α anomer, which differs from the β anomer in the axial orientation of the hydroxyl group on C_1. Also, the hydroxymethyl group can adopt three orientations (rotamers) with different values of the torsion angle $O_R-C_5-C_6-O_6$. There are two gauche conformations, one with a positive (G+) and one with a negative torsion angle (G−), as well as an anti conformation between the two oxygens, O_R and O_6, which we shall denote as T (these three conformations are sometimes denoted *gt*, *gg*, and *tg*, respectively).

The conformational analysis is complicated by the rotational freedom of the hydroxyl and hydroxymethyl groups. Thus, if we consider all the possible rotations of these groups, we have more than 700 possible conformers,[34] which can be found in two chair forms, $^1C_4$ and $^4C_1$, and the two anomeric forms, α and β. Some conformers are high in energy and do not significantly contribute to the conformer distribution, but the existence of nearly isoenergetic conformers makes the analysis of the relative population of each conformer a difficult task. The situation becomes even more complicated in solution, where interactions with the solvent compete with intramolecular interactions, usually diminishing the differences between the conformers' stabilities.[4,17,18,34] Thus, the study of D-glucopyranose involves computing subtle energy differences so that highly accurate methods are required.

The differing stability of the conformers in vacuo is dominated by the network of interactions between adjacent and nonadjacent hydroxyl groups.[48] Therefore the proper description of these interactions is of the utmost importance in this kind of calculation. It is widely accepted that, for a correct computational description of the relative energies of glucose conformers, diffuse functions must be included. According to previous theoretical studies,[3,8,10] the inclusion of just one set of diffuse functions in a basis set accounts for most of the relative energy of the different structures of D-glucopyranose.

Solvent effects play an extremely important role in determining the stability and relative population of possible rotamers and anomers of monosaccharides. For instance, the anomeric effect,[1,43,49] which describes the axial preference for an electronegative substituent of the pyranose ring adjacent to the ring oxygen, makes the α anomer more stable than the β in vacuo. However, it has been observed experimentally[50,51] that, in aqueous solution, the stability order is reversed and the ratio between α and β is 36:64.

Despite the importance of the surroundings in the conformer stability of carbohydrates, the necessity of using diffuse functions and the large size of most of these systems have limited the use of rigorous quantum mechanical theoretical methods. The first ab initio study devoted to D-glucose in vacuo is due to Polavarapu and Ewig,[37] who found that a counterclockwise orientation of the exocyclic hydroxymethyl groups was energetically favored. They also found that the relative stability of the G+, G−, and T rotamers is different when calculated using Born−Oppenheimer electronic energies and Gibbs free energies. They also found that the α anomer was more stable than the β anomer by 0.4 kcal/mol. Barrows et al.[28] preformed an extensive study of the conformational space of β-D-glucopiranose using molecular mechanics, later refining their results using quantum mechanical methods. They found that in vacuo the $^4C_1$ chair is about 8 kcal/mol more stable than $^1C_4$. Probably the most sophisticated ab initio calculation performed to date[18] uses a composite energy including estimates of the effects of using very large basis sets and highly correlated methods. They conclude that at 298 K, the most stable rotamers in gas phase are G+ and G− (for both the α and β conformers), whose energies are very similar. On average, the α anomer is 0.4 kcal/mol more stable than β. In the most recent paper known to us, Appell et al.[5] reach the same conclusions after studying boat, skew, and chair structures of α- and β-D-glucopyranose using density functional methods.

Different approaches have been proposed to treat solvent effects. Most calculations have been based on continuum models. Thus, in the first paper to study solvated glucose using ab initio methods, Cramer and Truhlar[34] explored the relative stability of the three conformers described above using the AM1-SM2 and PM3-SM3 semiempirical solvation models. In subsequent work, they improved both the description of the solute and the solvent using a more sophisticated electronic structure and better continuum solvation methods.[18,19,28] At the higher level of theory,[18] they reproduced the experimental preference for β anomers in solution, obtaining a Boltzmann-averaged difference of 0.2 kcal/mol between α and β anomers (the later being more stable). They found that the most populated rotamers for both the α and β anomers were G+, in disagreement with experimental NMR studies[52−54] which indicate than G− is the most populated conformer, although the differences between the G+ and G− populations are very small. Wladkowski et al.[17] studied the solvation effects on the exocyclic hydroxymethyl rotational surface for β-D-glucopyranose using the self-consistent isodensity polarized continuum model (SCIPCM). Although their results point in the right direction, they find that discrete solvent molecules must be included for a proper description of the different stabilization of the conformers.

A much better representation of the solvent structure can be obtained from simulations where water molecules or other surrounding molecules are considered explicitly. In classical simulations, the calculations have been mainly addressed at determining the solvation free energy differences between the different conformers.[14,23,26,33,35,38,41,42,44] In this type of calculation, both the solute and solvent molecules are represented

(48) Although adjacent hydroxyl groups are usually said to be hydrogen-bonded, strictly speaking only hydroxyl groups separated by three, rather than two, carbon atoms are capable of forming internal hydrogen bonds, according to ref 7. Therefore we prefer to talk about hydroxyl interactions rather than hydrogen bonds.

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classically, and in general, the mutual polarization between the solute and the solvent is neglected. Moreover, they usually rely on an adequate molecular mechanics force field for the description of the solute, but this is not always accurate enough to properly describe the small differences between glucose conformers. A second type of simulation[16] based on the Car−Parrinello method[55−57] permits the polarization of the solute in response to the perturbation of the solvent, as well as a much more accurate description of the system (by using density functional theory methods), but due to the computational cost, it does not calculate the relative free energies of the different conformers.

A different approach to treating the effects of solvation on glucose is microsolvation. Although it cannot provide information on the thermodynamic properties of the molecules in solution, it allows one to examine in detail the changes in the solute when it interacts with the solvent molecules. Thus, Klein[7] studied electron density and vibrational frequencies of glucose surrounded by six water molecules and concluded that there is no hydrogen bonding between adjacent hydroxyl groups but that they can form hydrogen bonds with surrounding water molecules. Momany et al.[4] find that including a water molecule reduces the differences in stability between the α and β anomers and predict that further addition of water molecules can explain the preference for the β anomer in aqueous solution.

The present paper explores the role of solvation effects in determining the stability and relative population of the possible rotamers and anomers of D-glucopyranose. Since mapping the whole conformational space using accurate computational methods is a formidable task, we selected only a subset of conformers which, as discussed above, seem to be the most stable. We only considered the $^4C_1$ chair with the hydroxyl groups forming a counterclockwise array of intramolecular links. Thus, six conformers were included in our calculations, namely the α and β anomers of the G+, G−, and T conformers. Additionally, we analyzed the effect of the rotation of the hydroxyl group in the hydroxymethyl group by computing four more rotamers. In the most stable G+ and G− conformers, the O−H bond of the hydroxyl group on carbon number six is gauche to the C_5-C_6 bond in order to gain additional stabilization from the interaction between the hydrogen atom and the ring oxygen atom. However, if this O_6-H bond is anti to the C_5-C_6 bond, from geometrical considerations it seems that solvation of the hydroxyl group will be favored. To study the competition between these two effects, we calculated for each G+ and G− rotamer of the α and β anomers two conformers, one with a gauche O_6-H bond (with respect to the C_5-C_6 bond) and another with an anti O_6-H bond. They will be denoted as G+*g* (or G−*g*) and G+*t* (or G−*t*), respectively, where the lowercase *g* or *t* indicates the orientation of the O_6-H group with respect to the C_5-C_6 bond. In total, 10 different conformers were computed.

To include solvation effects, we used a nontraditional quantum mechanics/molecular mechanics (QM/MM) method[58−70] known as ASEP/MD[71−75] (averaged solvent electrostatic potential from molecular dynamics calculations), which alternates molecular dynamics and quantum mechanics calculations in an iterative procedure and permits solute polarization, as well as the calculation of free energy differences. By its combination of a quantum description of the solute molecule and explicit consideration of solvent molecules, the method seems especially suitable for the study of the subtle interplay between anomeric and solvent effects. We used it to compare the free energy of the different conformers and rotamers, and we shall discuss the different factors that affect their relative order of stability.

Method

The main characteristics of the ASEP/MD have been discussed elsewhere,[71−75] so that they will only be outlined here. The ASEP/MD method is a QM/MM method that employs a mean field approximation to represent the solute−solvent interaction.

As in traditional QM/MM methods,[58−70] in ASEP/MD the energy and state function of the solvated solute molecule are obtained by solving the effective Schrödinger equation:

$$(H_{QM} + H_{QM/MM})|\Psi> = E|\Psi> \quad (1)$$

The interaction term, $H_{QM/MM}$ takes the form:

$$\hat{H}_{QM/MM} = H^{elect}_{QM/MM} + H^{vdw}_{QM/MM} \quad (2)$$

$$\hat{H}^{elect}_{QM/MM} = \int dr \cdot \hat{\rho} \cdot \langle \hat{V}_S(r;\rho) \rangle \quad (3)$$

where $\hat{\rho}$ is the solute charge density and the brackets denote a statistical average. The term $\langle \hat{V}_S(r;\rho) \rangle$ is the averaged electrostatic potential generated by the solvent at the position *r* and is obtained from MD calculations, where the solute molecule is represented by the charge distribution ρ and a geometry that is fixed during the simulation. The term $H^{vdw}_{QM/MM}$ is the Hamiltonian for the van der Waals interaction, in general represented by a Lennard−Jones potential. Given that the solvent structure, and hence the ASEP, is a function of the solute charge density, eqs 1 and 3 have to be solved iteratively. In general, only a few cycles of quantum calculation/molecular dynamics simulations are needed for convergence.

The mean field approximation was used in the calculation of the gradient and Hessian needed for the determination of stationary points on the free energy surfaces (FES). The force on the FES is approximated by[76−78]

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$$F(r) = -\frac{\partial G(r)}{\partial r} = -\left\langle \frac{\partial V(r)}{\partial r} \right\rangle \approx -\frac{\partial \langle V \rangle}{\partial r} \quad (4)$$

where $G(r)$ is the free energy, V is the sum of the contributions associated with the interaction with the other atoms of the solute molecule, V_i, and with the solute−solvent interaction energy, V_s, and the brackets denote a statistical average.

The Hessian is approximated by

$$H = \left\langle \frac{\partial^2 V}{\partial r \partial r} \right\rangle - \beta[\langle F^2 \rangle - \langle F \rangle^2] \approx \frac{\partial^2 \langle V \rangle}{\partial r \partial r} \quad (5)$$

where $\beta = 1/RT$. The term in square brackets is related to the thermal fluctuations of the force.

At each step of the self-consistent process, the solute charges used in the MD calculation were obtained by fitting the molecular electrostatic potential of the solute molecule in the presence of the solvent perturbation in the standard way. The GCHELP method was used.[79,80]

As was noted above, Hoffmann et al.[10] analyzed the performance of different quantum mechanical methods in studying gas-phase glucose, and concluded that it is sufficient to calculate single point energies calculated at the 6-31+G(d,p) basis set[81] level with the Becke three-parameter Lee−Yang−Parr (B3LYP) density functional method[82] to compare the energies of different conformers in the gas phase. In view of their work, all our quantum calculations were done with the 6-31+G(d,p) basis set and B3LYP functional method. The computer program used was Gaussian 98.[83] The geometries of the conformers were optimized both in vacuo and in solution.[75]

The molecular dynamics calculations were carried out with the program MOLDY.[84] The glucose molecule in its pyranoid conformation surrounded by 214 TIP3P[85] water molecules was simulated at a fixed intramolecular geometry by combining Lennard−Jones interatomic interactions with electrostatic interactions in a cubic simulation box of 18.85 Å side. The glucose-water Lennard−Jones potential parameters were taken from ref 44. Periodic boundary conditions were applied, and spherical cutoffs were used to truncate the molecular interactions at 9.0 Å. A time step of 0.5 fs was used, and the electrostatic interaction was calculated with the Ewald method. The temperature was fixed at 298 K by using a Nosé−Hoover[86] thermostat. Finally, each MD calculation simulation was run for 250 000 time steps (50 000 to equilibration, 200 000 to production).

The ASEP/MD calculations were performed using the ASEP/MD code,[87] interfacing both the Gaussian 98 and Moldy programs. The in solution energy values are given as the average value of the last five ASEP/MD cycles.[88]

The solution free-energy simulations were obtained using the free-energy perturbation (FEP) method[89,90] with single topology. The coupling parameter λ was divided into 20 equally distributed intervals of 0.05 units. Having obtained the final geometry and charges for the different rotamers with the ASEP/MD method, free energy simulations in a canonical ensemble (N,V,T) were performed to transform one of the conformers into the other. The free energy thus obtained is completely classical, so one must add the difference in the distortion energies of the two solutes calculated with ab initio methods.[91]

In addition, although the solute geometry is fixed during molecular dynamics simulations, the contributions to the free energy due to internal motion of the solute (vibrations) were estimated both in vacuo and in solution by using harmonic quantum mechanical vibrational partition functions. Rotational and translational contributions were estimated by using classical partition functions.[92] Although the harmonic oscillator is not an accurate model for treating large amplitude vibrations, such as the hydroxyl rotations around the C−O bond, we can expect the errors introduced by this approximation to be similar in vacuo and in solution and that they will approximately cancel out when calculating energy differences.

Results

Solute Geometry. Tables 1 and 2 show some selected geometrical parameters of 10 conformers of counterclockwise D-glucose, optimized both in vacuo and in aqueous solution. Five are α anomers, and five are β anomers. The G+, G−, and T conformers are characterized by the different torsion angles between the ring oxygen, O_R, the carbons C_5 and C_6, and the oxygen bonded to C_6, O_6. There are two possible gauche conformations, one with a positive torsion angle (G+) and one with a negative torsion angle (G−), as well as an anti conformation between the two oxygens, O_R and O_6, which we denote as T. The *g* and *t* conformers are characterized by the different torsion angles between the carbons C_5 and C_6, the oxygen O_6, and the hydrogen bonded to the latter, $H(O_6)$. In the *t* conformers the O_6-H bond is anti to the C_5-C_6 bond, while in the *g* conformers it is gauche. The geometrical parameters listed in Tables 1 and 2 are some selected distances between different atoms and the torsion angles $O_R-C_5-C_6-O_6$ and $C_5-C_6-O_6-H(O_6)$. A complete set of Cartesian coordinates for each conformer optimized both in vacuo and in solution is given as Supporting Information (Tables S1−S10).

First, we will analyze the geometry of the anomeric center in vacuo. As noted elsewhere,[37] the C_1-O_R bonds are shorter in the α anomers than in their β counterparts, while the C_1-O_1 bonds are longer as a consequence of the anomeric effect. These trends are also observed in the crystal structures of glucose.[30,93−95] When moving from vacuum to solution, the C_1-O_R bonds in the α conformers stretch more than in the β conformers, while the C_1-O_1 bonds in the α conformers shorten in solution more than in β conformers. If one accepts that the anomeric effect is caused by a back-donation of electron density from the lone pairs of the O_R into an antibonding σ^* C_1-O_1 orbital, then the

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Table 1. Selected Geometrical Parameters of the α Conformers of D-Glucose (Distances Are in angstroms, and Angles Are in Degrees)

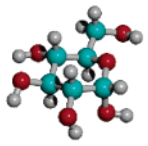
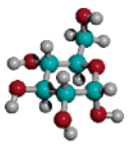
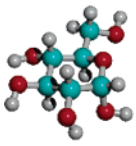
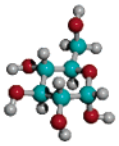
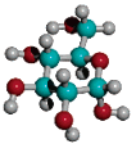
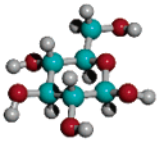
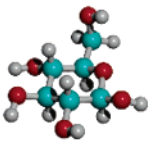
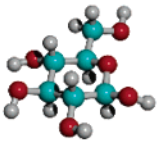
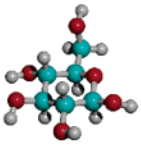
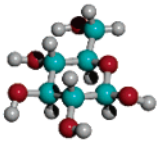
	αG+*g*		αG-*g*		αG+*t*		αG-*t*		αT	
										
	Vacuum	**Solution**	**Vacuum**	**Solution**	**Vacuum**	**Solution**	**Vacuum**	**Solution**	**Vacuum**	**Solution**
C_1-O_R	1.411	1.412	1.410	1.410	1.406	1.418	1.405	1.417	1.410	1.421
C_1-O_1	1.419	1.414	1.420	1.416	1.421	1.411	1.425	1.414	1.421	1.409
O_1-H(O_1)	0.967	0.969	0.967	0.969	0.967	0.969	0.966	0.968	0.967	0.969
O_6-H(O_6)	0.967	0.970	0.967	0.969	0.965	0.967	0.964	0.968	0.970	0.973
O_R-H(O_6)	2.406	2.399	2.390	2.443	---	---	---	---	---	---
O_4-H(O_6)	---	---	---	---	---	---	---	---	2.081	2.030
C_5-C_6-O_6-H(O_6)	58.0	59.8	57.7	59.6	177.4	178.7	171.6	176.4	52.0	55.0
O_R-C_5-C_6-O_6	60.7	60.7	58.0	60.9	71.6	67.9	66.1	64.2	165.8	169.0

Table 2. Selected Geometrical Parameters of the β Conformers of D-Glucose (Distances Are in angstroms, and Angles Are in Degrees)

	βG+*g*		βG-*g*		βG+*t*		βG-*t*		βT	
										
	Vacuum	**Solution**	**Vacuum**	**Solution**	**Vacuum**	**Solution**	**Vacuum**	**Solution**	**Vacuum**	**Solution**
C_1-O_R	1.423	1.422	1.422	1.423	1.418	1.427	1.419	1.422	1.423	1.432
C_1-O_1	1.397	1.394	1.398	1.396	1.398	1.393	1.398	1.396	1.397	1.390
O_1-H(O_1)	0.967	0.969	0.967	0.969	0.968	0.969	0.967	0.970	0.967	0.970
O_6-H(O_6)	0.967	0.969	0.968	0.969	0.965	0.967	0.964	0.968	0.970	0.973
O_R-H(O_6)	2.411	2.436	2.382	2.527	---	---	---	---	---	---
O_4-H(O_6)	---	---	---	---	---	---	---	---	2.079	2.009
C_5-C_6-O_6-H(O_6)	57.6	61.3	56.3	63.9	179.7	178.7	172.0	176.3	52.0	50.1
O_R-C_5-C_6-O_6	60.6	60.7	57.8	62.5	72.3	67.2	66.3	66.6	166.3	171.0

stretching of the C_1-O_R bond will reduce this effect. Maybe to compensate this, the C_1-O_1 shortens significantly more in α than in β, where this back-donation will be less important. In any case, it seems that part of the anomeric effect is lost when moving from vacuum to solution.

With respect to the hydroxymethyl group rotation, the T, G+*g*, and G−*g* conformers gain additional stability with respect to the G+*t* and G−*t* conformers from an intramolecular attractive interaction between the hydrogen bonded to O_6, H(O_6), and the oxygen O_4 (T conformers) or O_R (G conformers). The distances between the oxygen and the hydrogen participating in this interaction increase with solvation for the G conformers (with the exception of the αG+*g* conformer), while for the T conformers they diminish. Thus, we can expect that solvation of the O−H in the hydroxymethyl group will be more effective for G conformers, while for T conformers this group will be prone to keep its interaction with the O_4 oxygen rather than to interact with solvent molecules. Notice that the effects of solvation on the $O_6-H(O_6)$ bond distances are similar to those observed for the $O_1-H(O_1)$ bond.

Relative Anomeric Stability. Figure 2 shows the relative free energies of the 10 studied conformers of D-glucose in vacuo and in aqueous solution. The energy of the αT conformer is arbitrarily taken as the reference value. The most significant effect of the solvation of D-glucose is the larger stabilization of the β relative to the α conformers. As a result, we found that in vacuo the α conformers are more stable than their β counterparts and in aqueous solution the most stable conformers are β conformers. The difference in energy in solution between the most stable β conformer, βG+*g*, and the most stable α conformer, αG+*g*, is 0.7 kcal/mol. Our explanation is that the anomeric effect, which makes α conformers more stable in the gas phase, is not powerful enough to compete with the effect of a larger interaction between the solvent and the free pairs in oxygen in the β conformers than in the α conformers, where this interaction is hindered by the rest of the pyranose ring.

Also noteworthy is the major stabilization of the *t* conformers. They have the hydroxyl group $O_6-H(O_6)$ oriented more favorably for interaction with the solvent molecules than the *g* conformers, and they leave the O_R oxygen unprotected and more available for interaction with the solvent. Thus, the βG+*t* conformer, which in vacuo is 1.8 kcal/mol higher in free energy than the βG+*g* conformer, in solution is only 0.5 kcal/mol higher than βG+*g*, becoming the second most stable conformer.

Experimental evidence[50,51] suggests that the difference in free energy between β and α conformers of glucose in aqueous solution is around 0.4 kcal/mol (a ratio between α and β of 36:64). Our results slightly overestimate these differences in energy (we obtain a ratio between α and β of 25:75), but given the approximations made in our study, this result is very encouraging. The ASEP/MD method shows itself to be a powerful as well as an efficient technique for the study of solvent effects.

To give a more detailed view of the solvation process, Table 3 lists the energy for each conformer decomposed into several

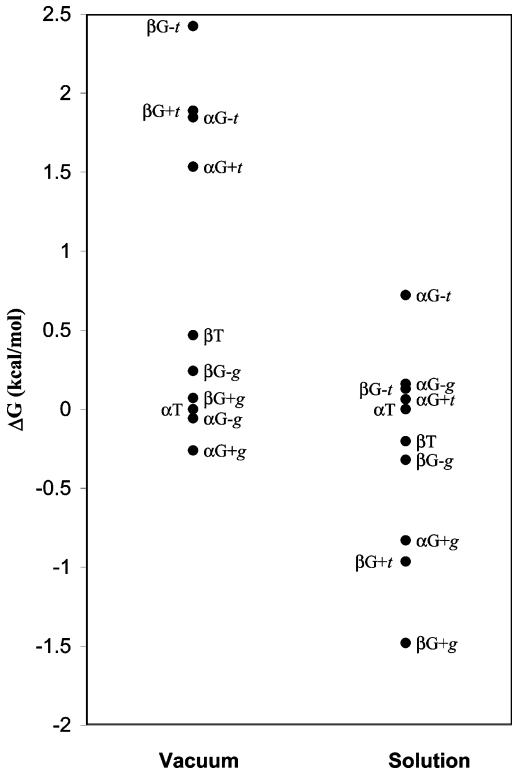


Figure 2. Relative energies of the conformers of D-glucose in vacuo and in aqueous solution. The energy of αT is arbitrarily taken as the reference value.

Table 3. Decomposition of the Relative Free Energies in Vacuo and in Solution[a]

	vacuo			solution			
	E_e[b]	ΔG[c]	pop.[d]	ΔG_i[e]	ΔG_s[f]	ΔG[g]	pop.[h]
α G+*g*	0.0	−0.3	27%	−0.3	−0.5	−0.8	14%
α G−*g*	0.2	−0.1	19%	−0.8	1.0	0.2	3%
β G+*g*	1.0	0.1	15%	0.1	−1.6	−1.5	43%
β G−*g*	1.1	0.2	11%	−0.5	0.2	−0.3	6%
β T	1.0	0.5	8%	1.9	−2.1	−0.2	5%
α T	0.0	0.0	17%	0.0	0.0	0.0	4%
α G+*t*	2.3	1.5	1%	2.0	−2.0	0.1	3%
α G−*t*	2.7	1.8	1%	2.5	−1.8	0.7	1%
β G+*t*	3.3	1.9	1%	3.4	−4.4	−1.0	18%
β G−*t*	4.0	2.4	0%	4.3	−4.2	0.1	3%
total α population			65%				25%
total β population			35%				75%

[a] The αT conformer is taken as reference. All the energies are in kcal/mol. [b] Electronic energy for each conformer in vacuo. [c] Free energy for each conformer in vacuo. [d] Relative population of each conformer in vacuo. [e] Internal free energy for each conformer in the electric field created by the solvent with contributions to the free energy from internal (rotational and vibrational) motions of the solute. [f] Contribution to the free energy from the polarization and motions of the solvent. [g] Free energy of each conformer in solution. [h] Relative population of each conformer in solution.

terms. For the in vacuo calculations we list the electronic (Born−Oppenheimer) energy and the Gibbs free energy. For the in solution calculations we list the internal free energy of the solute (which is the Born−Oppenheimer electronic energy calculated in the electric field created by the solvent, plus the enthalpy and entropy contributions to the Gibbs free energy from the internal motion of the solute) and the contribution to the free energy due to the solvent. If we add these two contributions, we obtain the Gibbs free energy in solution for a given conformer, also listed in the table. We also give the relative population for each conformer (Boltzmann averaged) and the relative population of α and β conformers.

In general, we note that in vacuo the free energy behaves differently from the purely electronic energy. Thus, T conformers are equally stable as G+ and more stable than G− energetically. However, according to their free energy values, they are less stable than G+*g* and G−*g*. Moreover, the differences between the α and β conformers diminish, although the prediction in vacuo is that α conformers are more populated, in agreement with earlier results.[17,18]

In solution, we note that the internal free energy of the solute and the free energy of the solvent follow different trends. The former indicates how much the solute deviates from its more stable conformation in order to facilitate its interaction with the solvent, while the latter is a measure of the stability gained by the solute−solvent interaction. Thus, high (more positive) values of ΔG_i indicate that the solute is strongly polarized by the solvent, while low (more negative) values of ΔG_s indicate that the solute−solvent interaction is stronger. The two contributions go in different directions: the more polarized the solute (larger ΔG_i), the better is its interaction with the solvent (lower ΔG_s). Thus, α G−*g*, which is the least polarized conformer, has the least stabilizing interaction with the solvent, while the β G−*t* conformer, which is the most polarized, is greatly stabilized upon solution. When we add the two effects (polarization of the solute and interaction with the solvent), we obtain the free energy for each conformer in solution. It is this subtle interplay between the solute polarization and solute−solvent interaction that is at the origin of the differences between the α and β populations. Thus, if we analyze the most populated conformer in the two anomeric forms, α G+*g* and β G+*g*, we can see that according to its internal free energy α G+*g* is 0.4 kcal/mol more stable. However, β G+*g* interacts better with its environment, obtaining a stabilization 1.1 kcal/mol greater than that of the α G+*g* conformer from its interaction with the solvent. As a result, β G+*g* is 0.7 kcal/mol more stable than α G+*g* in solution. Comparing the two anomers for each pair of conformers, one reaches the same conclusions. Therefore we can say that solvation of the β conformers is more efficient because they interact better with the solvent environment.

The doubly occupied oxygen orbitals of O_1 are more available for interaction in the β conformers. In the α conformers they are screened by the rest of the pyranose ring, making the β conformers more stable than α in solution. In addition, the hydroxymethyl group orientation seems to influence the difference between the α and β anomers in solution. Thus, while the difference between the αT and βT conformers is only 0.2 kcal/mol, this difference is larger for the G− conformers (0.5 and 0.6 kcal/mol for the G−*g* and G−*t* pairs of conformers, respectively) and even more so for the G+ (0.7 and 1.1 kcal/mol for G+*g* and G+*t*, respectively). On the other hand, the G+ conformers seem to become the most stable conformers on solvation, being the orientation shown by the three most stable conformers.

Conformer Stability. The calculations described up to now explain the experimentally observed trends of the behavior of the α and β anomers of glucose in solution. However, Nishida et al.[53,54] found β G+ and β G− to be almost equally populated, with β G− being slightly more abundant in solution, while our results predict β G+*g* and β G+*t* to be more stable than β G−*g*

Table 4. Dipole Moments and Charges in Vacuo (q^0, μ^0) and in Solution (q, μ) for the Oxygen and Carbon Atoms of the Different α Conformers[a]

	αG+*g*		αG+*t*		αG−*g*		αG−*t*		αT	
	q^0	q	q^0	q	q^0	q	q^0	q	q^0	q
C_1	0.389	0.444	0.263	0.443	0.140	0.223	0.258	0.324	0.417	0.580
C_2	0.236	0.178	0.272	0.149	0.374	0.350	0.331	0.288	0.208	0.118
C_3	0.328	0.430	0.232	0.418	0.067	0.171	0.147	0.241	0.216	0.394
C_4	0.176	0.098	0.060	0.011	0.479	0.448	0.370	0.266	0.236	0.185
C_5	0.201	0.171	0.347	0.326	0.077	0.146	0.340	0.289	0.138	0.203
C_6	0.351	0.468	0.319	0.384	0.307	0.375	0.209	0.355	0.418	0.510
O_1	−0.700	−0.747	−0.696	−0.727	−0.660	−0.710	−0.685	−0.704	−0.708	−0.760
O_2	−0.665	−0.747	−0.659	−0.714	−0.674	−0.757	−0.677	−0.742	−0.652	−0.723
O_3	−0.724	−0.791	−0.676	−0.774	−0.703	−0.788	−0.720	−0.778	−0.712	−0.816
O_4	−0.741	−0.816	−0.685	−0.783	−0.747	−0.841	−0.741	−0.793	−0.735	−0.842
O_6	−0.714	−0.859	−0.706	−0.830	−0.641	−0.758	−0.708	−0.839	−0.734	−0.892
O_R	−0.564	−0.579	−0.494	−0.594	−0.417	−0.454	−0.476	−0.559	−0.583	−0.703
	μ^0	μ	μ^0	μ	μ^0	μ	μ^0	μ	μ^0	μ
	2.83	3.60	0.90	1.12	3.72	5.22	2.62	3.74	2.88	3.84

[a] Charges are in atomic units and dipole moments in debyes.

by 1.2 and 0.7 kcal/mol, respectively (note the experimental NMR studies by Nishida et al. could not differentiate the β-G+*g* and β-G+*t* conformers, so that they both form part of the β-G+ conformer population). In particular, we obtained populations of 81% for β-G+, 12% for β-G−, and 7% for β-T. To shed some light on the reasons for this discrepancy, we performed some additional calculations using larger basis sets and a different electronic structure method. The most time-consuming processes in our calculations are the geometry optimization of the solute and the molecular dynamics calculations required to obtain the averaged electrostatic potential. We hence chose to use the solution geometries and average electrostatic potential from our B3LYP/6-31+G(d,p) calculations and perform electronic energy calculations using the MP2/6-31+G(d,p) level (where MP2 indicates second-order Møller−Plesset perturbation theory[96] for the calculation of electron correlation energies) and the MP2/6-311++G(d,p) level.[97] The results of these calculations, however, have to be taken with caution, since we are analyzing very small effects, and errors associated with energies based on geometries or electrostatic potentials taken from a different method that creates a different charge distribution may mask the differences in energy that we are trying to calculate. These results (a complete listing of the results is provided in Table S-12 in the Supporting Information) show that increasing the level of calculation reduces the differences in energy between β-G+*g* and β-G−*g* slightly, from 1.2 kcal/mol at the B3LYP/6-31+G(d,p) level, to 1.0 at the MP2/6-31+G(d,p) level, to 0.8 kcal/mol at the MP2/6-311+G(d,p) level. The difference between the energies of the β-G+*t* and β-G−*g* conformers is also reduced, from 0.7 to 0.3 down to 0.1 kcal/mol using the aforementioned levels. The same effect is observed for the α anomer. While at the B3LYP/6-31+G(d,p) level the αG+*g* conformer is 1.0 kcal/mol more stable than αG−*g*, at the higher level it is only 0.5 kcal/mol more stable, bringing our results closer to the experimental values which indicated a similar population of the two α conformers. It thus seems that increasing the quantum mechanical level of calculation slightly reduces the discrepancy between our results and the experimental observations (note that the differences between αG+*g* and β-G+*g* also diminish, from 0.7 to only 0.1 kcal/mol at the highest level of calculation, bringing the ratio α:β closer to equality from 25:75 to 46:54.)

It is difficult, however, to determine the main reason for the low population of the β-G− conformers obtained in our calculations. It is possible that a more detailed study of the conformational space of β-D-glucose in solution would find that other G− conformers are more stable than β-G−*g* or at least have a similar energy, thereby increasing the total G− population.

We have seen that, unfortunately, the relative stability of the conformers is very different in vacuo and in solution (the difference between αG+*g* and β-G+*t* is especially noticeable, being 2.2 kcal/mol in vacuo and −0.2 kcal/mol in solution). A preliminary exploration of the conformational space of β-D-glucose in vacuo in order to select the most stable conformers, assuming that they will be the most stable conformers in solution, hence does not guarantee successful results. This is particularly noticeable if only electronic energies are taken into account (as an example, the difference in electronic energy between the aforementioned αG+*g* and β-G+*t* conformers is 3.3 kcal/mol). It is therefore necessary to perform the exploration of the conformational space in solution using high levels of calculation. This is a complicated task. At a rough estimate, using the same methods and computational facilities we used in the present work, we would require about 10 years to analyze all the possible conformations of β-D-glucose in solution.

Solute Charge Distribution. The dipole moments and CHELPG charges in vacuo and in solution for the different anomers are given in Tables 4 and 5. The first conclusion is that all the molecules are strongly polarized by the solvent, the polarization being greater in the β anomers, except for the most stable conformers, G+*g*. The second conclusion is that the interaction energies do not correlate with the dipole moment. In fact, the largest interaction energy corresponds to the β-G+*t* anomer, which has the smallest dipole moment of the 10 conformers both in vacuo and in solution. However, those conformers whose dipole moment changes the most after solvation (β-G+*t*, β-G−*t*, and β-T, with dipole moments that increase by more than 50%) are those that get more stabilization from the solvent (column ΔG_s in Table 3). Given the complex nature of the charge distribution of the molecule, with several polar groups

(96) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618−622.
(97) Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1992**, *197*, 499−505.

Table 5. Dipole Moments and Charges in Vacuo (q^0, μ^0) and in Solution (q, μ) for the Oxygen and Carbon Atoms of the Different β Conformers[a]

	βG+*g*		βG+*t*		βG−*g*		βG−*t*		βT	
	q^0	q	q^0	q	q^0	q	q^0	q	q^0	q
C_1	0.493	0.554	0.487	0.529	0.373	0.402	0.394	0.435	0.603	0.688
C_2	0.204	0.193	0.162	0.185	0.231	0.284	0.280	0.289	0.148	0.100
C_3	0.307	0.423	0.323	0.367	0.128	0.200	0.165	0.228	0.274	0.392
C_4	0.168	0.112	−0.001	0.023	0.436	0.500	0.346	0.413	0.225	0.186
C_5	0.161	0.141	0.412	0.285	0.074	0.078	0.287	0.217	0.154	0.166
C_6	0.400	0.483	0.308	0.430	0.313	0.376	0.271	0.371	0.458	0.499
O_1	−0.689	−0.782	−0.699	−0.766	−0.672	−0.772	−0.682	−0.781	−0.713	−0.768
O_2	−0.725	−0.828	−0.713	−0.811	−0.709	−0.822	−0.729	−0.840	−0.717	−0.798
O_3	−0.736	−0.822	−0.706	−0.785	−0.728	−0.827	−0.733	−0.819	−0.744	−0.835
O_4	−0.737	−0.799	−0.690	−0.778	−0.749	−0.842	−0.740	−0.826	−0.750	−0.818
O_6	−0.716	−0.844	−0.713	−0.832	−0.652	−0.762	−0.693	−0.836	−0.740	−0.884
O_R	−0.542	−0.591	−0.539	−0.585	−0.453	−0.487	−0.480	−0.540	−0.611	−0.701
	μ^0	μ	μ^0	μ	μ^0	μ	μ^0	μ	μ^0	μ
	2.95	3.27	0.68	1.04	3.50	4.53	2.14	3.51	3.01	4.51

[a] Charges are in atomic units and dipole moments in debyes.

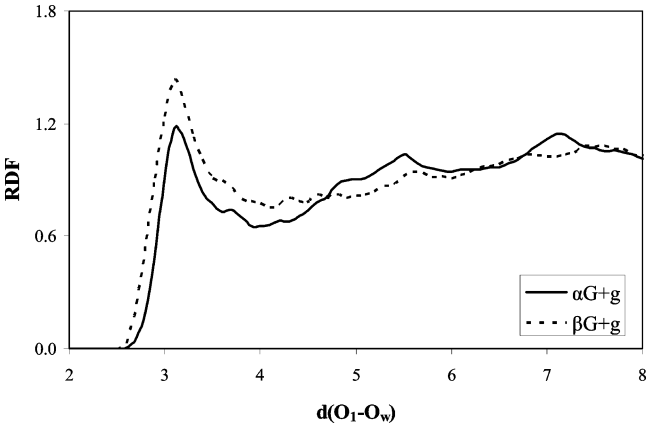


Figure 3. Anomeric oxygen-water oxygen radial distribution functions for the most stable conformers, α G+*g* (solid line) and βG+*g* (dotted line).

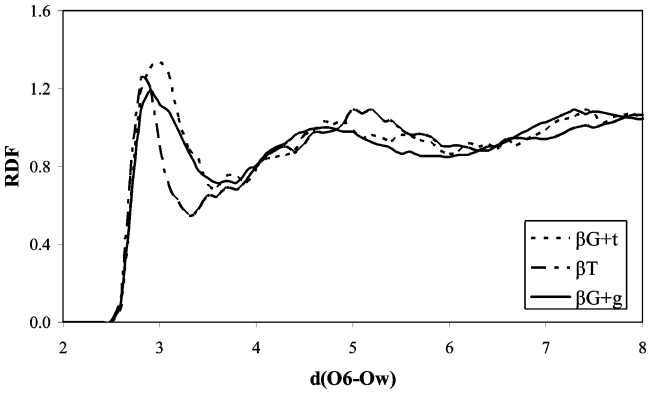


Figure 4. O_6-water oxygen radial distribution function for selected conformers.

pointing in different directions, the study of the dipole moment does not provide as much information as in simpler systems. In this case, it seems preferable to analyze the atomic charges. In this regard, the α anomers have similar charges to their β counterparts except on the C_1 atom where, in vacuo, the charges on the β anomers are on average 75% greater than on the α anomers. This difference is reduced in solution (average value: 35%.) The same trend was found in a previous study of the anomeric equilibrium of D-xylose.[90] The hydroxyl group that is most polarized is that on C_6, especially in the *t* conformers, this being the group that is most accessible to the solvent.

Solvent Structure. To gain a deeper insight into the solvation effects, in Figure 3 we plot the radial distribution function (rdf) for the anomeric oxygen, O_1, and the water solvent oxygen, O_w, for the α G+*g* and βG+*g* conformers. From this plot we can again conclude that solvation is more effective for the β conformers, which have a peak (at around 3.1 Å) that is higher than that of the α conformers. One can therefore expect that the β conformers are more stabilized by solvation than the α conformers, the solvent molecules being more tightly bonded to the anomeric oxygen in the β conformers. It has to be remarked that we have selected the α G+*g* and βG+*g* conformers because they are the most stable conformers in solution, but all of the α and β conformers show very similar trends.

The differential solvation of the hydroxymethyl rotamers can be better analyzed with reference to Figure 4, which shows the rdf for the interaction between O_6 and O_w. For the sake of clarity, we only plot β anomers, since the behavior of these rdf's shows little dependency on the orientation of the anomeric oxygen. One sees that, while the G+*g* and G+*t* conformers have a broad peak, the T conformer has a much narrower peak, which occurs at shorter distances (at around 2.8 Å), and hence the smallest area beneath this peak. Also, the peak of the G+*t* conformer is higher and broader than that of G+*g*. Plotting the G− conformers, we find the same behavior as G+, although the peaks are slightly lower. Hence, the T conformers show a lower degree of solvation than the G+*g* and G−*g* conformers, with the G+*t* and G−*t* being the best solvated conformers. This was also to be expected, since, besides geometrical considerations, the intramolecular interaction observed for the T and *g* conformers reduces the ability of the O_6−H group to interact with solvent molecules.

Further inspection of Figure 4 shows the O_6−O_w rdf of the G+*g* and G+*t* conformers to have a broad double peak rather than a single peak as occurs in βT. This might be an indication of the two possible interactions between the hydroxyl group and the water solvent molecules that can take place for the G+*g* and G+*t* conformers, namely the O_6−H acting as proton donor and the O_6−H acting as proton acceptor. The T conformer only shows the first peak, indicating that it acts only as proton acceptor. This is consistent with the fact that the hydrogen in O_6−H is more available for interaction in the *t* conformers, while T conformers in solution, which show a shorter H(O_6)−O_4

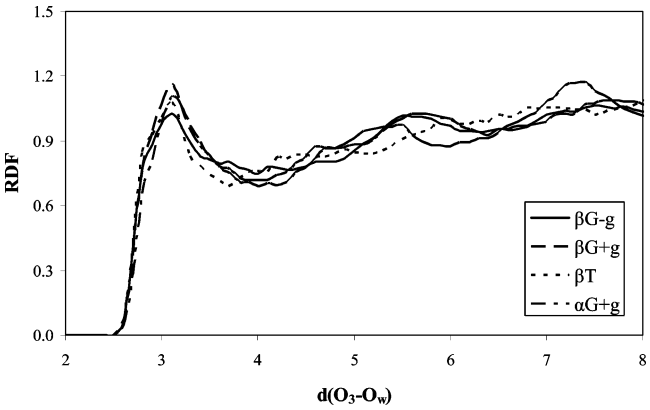


Figure 5. O_3-water oxygen radial distribution function for selected conformers.

Table 6. Coordination Numbers (N_c) of the O_1, O_3, and O_6 Atoms

conformer	$N_c(O_1–O_w)$	$N_c(O_3–O_w)$	$N_c(O_6–O_w)$
α G+*g*	4.0	4.0	3.6
α G−*g*	3.9	3.9	3.4
α G+*t*	4.0	3.9	4.3
α G−*t*	4.2	3.8	4.4
α T	4.1	3.7	2.1
β G+*g*	5.5	4.1	3.3
β G−*g*	5.2	4.0	3.5
β G+*t*	5.4	3.8	4.3
β G−*t*	5.6	3.9	4.0
β T	5.6	3.8	2.1

distance than that in vacuo, have little interaction between $H(O_6)$ and solvent.

The fact that the O_6-O_w rdf's for the α and β anomers are similar indicates that solvation of the nonanomeric OH groups of the pyranose ring has little dependence on the anomeric oxygen. To look further into this aspect, we analyzed the O_3-O_w rdf for the 10 conformers. As a summary and for the sake of clarity, Figure 5 shows this rdf for only four conformers. Although some differences arise due to statistical uncertainties and averaging, the functions are too similar to allow any conclusion to be drawn about differences in solvation for nonanomeric OH groups other than $O_6-H(O_6)$.

To give a simpler presentation of the trends discussed above, Table 6 gives the values of the coordination numbers for the atoms O_1, O_3, and O_6. As concluded above from the rdf plots, the anomeric oxygen in β conformers is surrounded by more solvent molecules than that in α conformers, the solvation of O_3 shows little dependence on the anomeric oxygen, the T conformers are less stabilized than G+ and G−, and *t* conformers are better solvated than *g* conformers.

It is interesting to note that all the calculated coordination numbers are around four, except for the anomeric oxygen in β conformers which are better solvated than the remaining OH groups and the O_6-H group in T conformers which seems to be less solvated than the remaining OH groups. Therefore, the analysis of the rdf's and coordination numbers explains the experimental observations that the β anomer is more abundant in solution and the T populations are low.

Conclusions

The role of solvation effects in determining the stability and relative populations of possible rotamers and anomers of D-glucopyranose was analyzed. The most significant effect of the solvation of D-glucose is the greater stabilization of the β conformers relative to the α conformers. In aqueous solution, β conformers are more abundant than α conformers. The explanation is that the anomeric effect, which makes α conformers more stable in the gas phase, is not powerful enough to compete with the effect of a larger interaction between the solvent and the free electron pair of the anomeric oxygen in the β conformers than in the α conformers, where this interaction is hindered by the rest of the pyranose ring. This is confirmed by the analysis of the O_1(anomeric)$-O_w$ rdf's and by the greater number of water molecules that surround the β conformers. The solvation of the rest of the OH groups of the pyranose ring depends hardly at all on the anomeric oxygen and, hence, has no influence on the relative stability of the α and β forms.

Another interesting point is that the solvent stabilizes more the G than the T conformers. This is related to the availability of the hydrogen bonded to O_6 to interact with the water molecules. In the T conformer, the O_6-H group is involved in an intramolecular hydrogen bond with the O_4 oxygen, which is not weakened by the solvent, while G conformers distort in solution in order to facilitate the interaction of the O_6-H group with the surrounding water. Consequentely, solvation is more effective for G conformers than for T conformers. The analysis of the coordination numbers points in the same direction.

As a final point to guide further studies, the gas phase relative stabilities of the different conformers change markedly when solvation is included. Therefore, assuming that the most stable conformers in vacuo are the most stable conformers in solution is a mistake that leads to neglecting conformers that could exist in significant amounts in solution. Since the differences in energy between conformers are very small, high-level computational methods are required. Thus, the only way to successfully explain the observed populations of the different conformers is by performing accurate studies of the conformational space in solution. Since this is a computationally very demanding task, we believe that glucose in water is an open problem that will only be solved by further developments of computational chemistry in solution.

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Supporting Information Available: Cartesian coordinates optimized at B3LYP/6-31+G(d,p) both in vacuo and in solution for the structures of the conformers described in the present work, as well as electronic and free energies in vacuo and in solution. This material is available free of charge via the Internet at http://pubs.acs.org.

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