

Anomeric and rotameric preferences of glucopyranose in vacuo, water and organic solvents

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Abstract Glucopyranose is the most stable form of glucose in solution. Identification of molecular structure of glucopyranose is very important because of its biological and synthetic significance; it is not an easy task because of the large number of possible configurations. Relative energies of exocyclic hydroxymethyl rotamers and α - β anomers of D-glucopyranose have been determined at the reference MP2/6-31G(d,p) level geometry by ab initio calculations at the infinite basis set limit of MP2 approach and with inclusion of CCSD(T) correction term evaluated with the aug-cc-pVDZ basis set in vacuum, water, dimethylsulfoxide, tetrahydrofuran and ethanol. The infinite basis set limit of MP2 level was determined by two point extrapolation using aug-cc-pVTZ and aug-cc-pVQZ basis sets. Solvent effects, relative energies and binding energies have been considered applying explicit calculations and implicit solvent models.

Keywords Anomer · Correlation consistent · Coupled cluster · Gaussian · Glucose · Rotamer

Introduction

The structural analysis of carbohydrates represents quite a complex task and requires consideration of several parameters. This could be facilitated by application of complementary experimental and theoretical methods [1, 2]. Although a number of studies have already been carried out on the title

species, carbohydrates are still far from being fully understood [3–6].

Great variety of isomers is one of the most important reasons that complicate the carbohydrate studies [7]. Three different structural isomers (pyranose, furanose and unchained), several rotational isomers (C-OH and C-CH₂OH), axial or equatorial preferences of hydroxyls groups, α or β configurations due to the position of hydroxyl group which is substituted to anomeric carbon (Fig. 1), and ring puckering of carbohydrates represent various types of isomerizations which make the structural analysis of carbohydrates a formidable task [3]. Consideration of glycosidic linkage preferences, solvent properties and other biochemical parameters implies complex studies and this means that understanding of carbohydrates included in biological systems should require a comprehensive cooperation of chemists and biologists. Owing to the complex structure-function relationship of carbohydrates, the primary step of experimental or theoretical characterization of these biopolymers involves detailed description of the conformations of their monomer units [8].

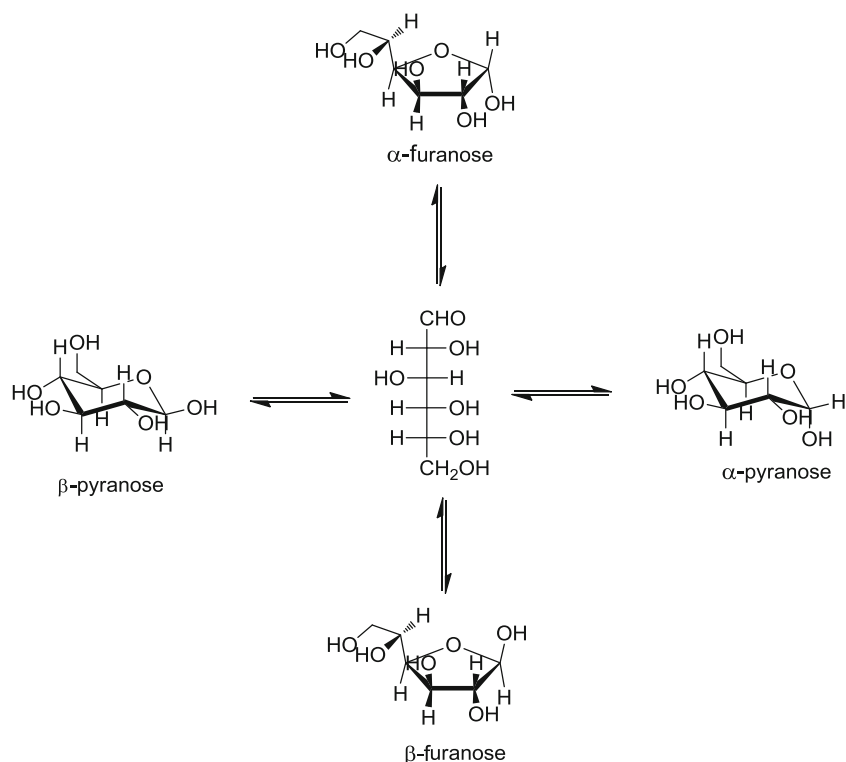
Though the carbohydrate studies are difficult, the variety and importance of applications of the investigated species continuously encourage scientists to undertake investigations of their structures and characteristics. This is evident from a comparison of the frequency of the use of selected terms in the last 10 years (ISI 2002–2012). When the term “glucose”, the most important carbohydrate [9], was searched in the topic section, approximately 177,500 results appear. For the same date span the corresponding number exceeds 40,000 for the title section, which represents high occurrence for a single molecule. This indicates that the scientific community has paid considerable attention to glucose.

Glucose is the most important carbohydrate in biochemical processes. Its epimers are involved in a variety of processes such as support of matrices, production of energy, molecular recognition processes, glycoconjugate antibiotics, cell attachment and bonding [8, 10].

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Fig. 1 Anomerization of glucose



The structure and reactivity of glucose have been the subject of many theoretical and experimental studies [11, 12]. Along with the biological importance, conformational preferences represent another interesting feature of glucose. When all isomeric factors are considered there are more than 700 possible conformers for glucose. However, only a few of them are stable in vacuo and solution [3]. In solution, glucose is found almost entirely in the pyranose form (Fig. 1) with the 4C_1 chair conformation [10]. There are two possible stereochemical isomers, based on the position of OH group on C₁: α and β glucopyranoses (Fig. 1), which are called specifically anomers. However, anomeric effect makes the α anomer energetically favorable in the gas phase [9, 13]. It has been found that the anomeric α : β ratio of glucopyranose is around 36:64 in aqueous solution. This is due to the strong solvation effects [10, 14, 15].

Owing to possible rotation of hydroxymethyl group (Fig. 2) there are two gauche (g^+ and g^-) and one trans (t) rotational isomers, which are more stable than the other rotational forms, both in vacuo and in solvents. Their stabilizations are due to the stereoelectronic effect, intramolecular hydrogen bonding, and solvent-solute interactions [3, 16]. “Gauche +” notation refers to a positive dihedral angle ($\sim +60^\circ$) between the ring oxygen and the oxygen of hydroxyl methyl group, “gauche -” refers to a negative one ($\sim -60^\circ$) and the term “trans” refers to 180° angle [3] (these three conformations are sometimes denoted gt , gg , and tg , respectively) (Fig. 2). The stabilities of these six conformations of glucopyranose (three α and three β) have been addressed in

several studies by experimental [3, 17–25], and theoretical [10, 26–30] approaches. The general conclusion of most of these studies is, that the trans conformer represents the most stable form in vacuo because of the enhanced anomeric effect and intramolecular hydrogen bonding stabilization. However, in aqueous solution this situation is completely changed due to the solvation effects and solvent-solute hydrogen bonding interactions. The g^+ and g^- conformations as likely to be present in equal concentrations along with a small amount of t rotamer were detected in aqueous solution [18, 19, 31, 32]. The increase in the stability of β anomer, relatively to the α anomer, is one of the most important results of the solvation effects that water imposes on glucopyranose structures. The strong interaction between the solvent molecules and the lone pairs of the anomeric oxygen atom in β -glucopyranose surpasses the combined contributions of the same interactions in α anomer (where the lone pairs of anomeric oxygen are hindered by the rest of the molecule) and also an anomeric effect which makes the α anomer more abundant in vacuo [3].

Another conformational parameter is represented by the clockwise and counter clockwise array of secondary hydroxyl groups, due to their hydrogen bond donor and acceptor abilities (Fig. 3) [33–35]. The results of previous studies indicate that the counter clockwise orientation of hydroxyl group has larger stabilizing effect than those of the clockwise orientation because of the more effective hydrogen bonding system formed, and also an anomeric effect that was revealed in both the vacuo and aqueous solutions [14, 32, 36–39].

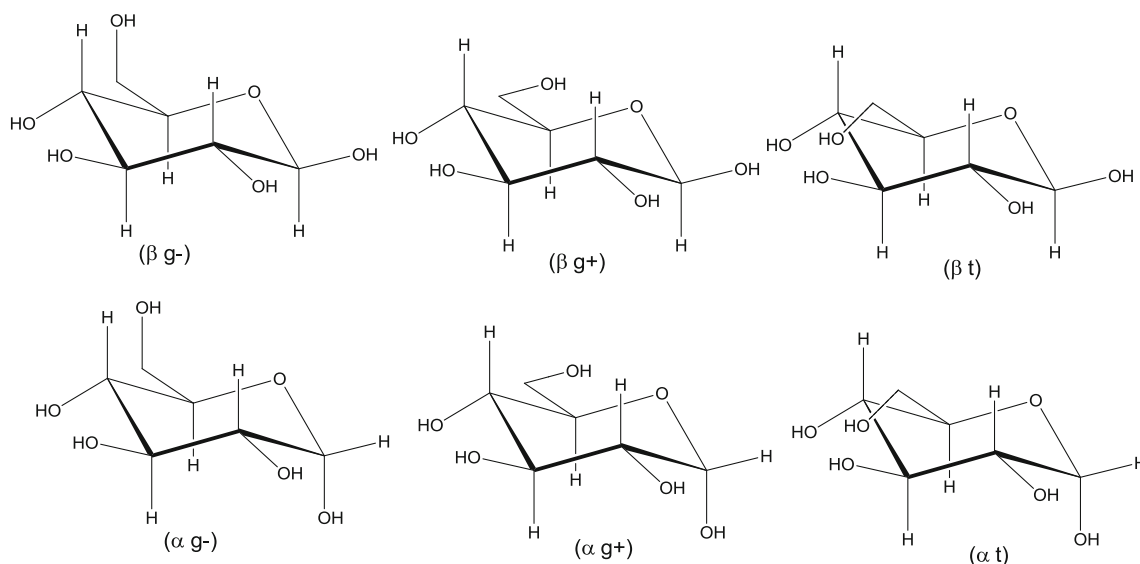


Fig. 2 Rotational isomerism of glucopyranose structure

A formation of an extensive hydrogen bonding system between glucose chains facilitates the formation of cellulose sheets. This feature also limits the dissolution of cellulose in many solvents [40]. On the other hand, glucose can dissolve in water very easily and there are several biochemical applications of this species in water. Therefore, the majority of structural studies related to glucose have been performed in aqueous solutions [13, 14, 34, 41–44]. This focus on aqueous solutions limits detailed studies of glucose structure in other solvents.

The purpose of this study is characterization of the major forms of glucopyranose isomers both in vacuo and in various solvents. This has been achieved by comprehensive computational approach that involves applications of high level methods, including CCSD(T) methodology, and basis set extrapolation. This study also investigates the solvation effects on the relative stability order of rotamers of α and β D-glucopyranose in water, DMSO, THF, and ethanol. Since predictions of the all possible conformations of glucose with accurate methods are too expensive we selected α -g+, α -g-, α -t, β -g+, β -g- and β -t conformers, which as discussed above, represent the most stable forms.

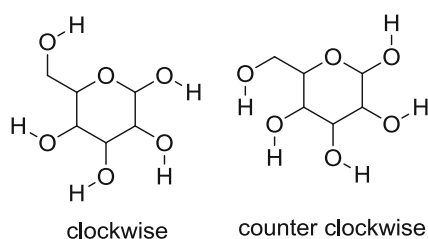


Fig. 3 Clockwise and counter clockwise positions of hydroxyl groups of glucopyranose

Methods

Full geometry optimizations have been performed on the six glucopyranose isomers at the MP2/6-31G(d,p) level. In addition, single point calculations have been carried out at the MP2 (aug-cc-pVDZ, aug-cc-pVTZ and aug-cc-pVQZ basis sets [45]) and CCSD(T) (6-31G(d,p) and aug-cc-pVDZ basis sets) levels applying GAUSSIAN09 suite of programs [46]. Single point energies have been extrapolated to the infinite basis set by using two largest basis sets (aug-cc-pVTZ and aug-cc-pVQZ) for MP2 method based on the Eq. 1 [47].

$$Y(x) = Y_{\text{CBS}} + Ax^{-3} \quad (1)$$

In this equation $Y(x)$ is the calculated energy value at related basis set level, Y_{CBS} is the complete basis set limit, A is fitted parameter, x is 3 for cc-pVTZ and 4 for cc-pVQZ.

Scaling factors that account for relative energies differences between cc-pVDZ basis set calculations using CCSD(T) and MP2 methods for each considered species have been calculated. The difference between the calculated energy values is then used as a scaling factor that has been applied to the MP2 extrapolation results in order to calculate a more accurate energy value for each isomer in vacuum and solvents.

Vibrational frequencies of all implicit and explicit models have been calculated in vacuo and related solvent at MP2 6-31G(d,p) level. All structures are characterized as minima on the respective potential energy surfaces.

The interaction between a solvent and glucopyranose has been considered by applying two different methodologies, in vacuo and in solvent (with scrf option). The optimizations have been carried out with explicitly defined two solvent molecules at MP2/6-31G(d,p) level. Binding energies and

relative energies are obtained for vacuo and solvent media calculations.

Results and discussion

Calculated relative energies are listed in Tables 1 and 2. The largest basis set (aug-cc-pVQZ) results with MP2 method (MP2/aug-cc-pVQZ), extrapolation to the infinite basis set results (Ext. MP2), and CCSD(T) correction to the extrapolated values (CCSD(T) Corr.) are given for all isomers in vacuo and in all solvents. Comparison of these results has been provided to understand how relative energies vary when applying the basis set extrapolation and CCSD(T) scaling.

According to experimental results β isomer of glucopyranose is more stable than α isomer in water [10, 14, 15]. However, the obtained results favor α anomers. One notices that the inclusion of the CCSD(T) level electronic correlation provides a closer agreement with the experimental results by decreasing the energy difference between the α and β anomers in water and selected solvents (see Tables 1 and 2). We conclude that since the models considered in the present study do include only two explicit solvent molecules in the first solvation shell and obviously, such models do not contain all molecules that form such a shell, therefore the current calculations could be considered as the first approximation. They are too small to entirely describe complex solute – solvent interactions in the considered species. The prediction of static property of investigated species using explicit solvent molecules may be another reason for observed differences between calculations and experimental results. The dynamic studies with more solvent molecules should be considered as the next step that could provide an additional insight in the studied phenomena. The comparison of calculated results (Tables 1 and 2) and previous molecular dynamic studies [10] also supports this conclusion. Calculation results (Table 1) and data from reference [10] both favor the α anomer in vacuo but the situation is

completely different in solvent. While the current results (Table 2) still suggest a more stable α -anomer, the molecular dynamic studies predict the β -anomer to be more stable, in agreement with experimental results.

The relative energy of “g- and g+” rotamers is predicted to be almost the same in all solvents and vacuo after CCSD(T) correction and “t” rotamer is less stable than the other rotamers (Tables 1 and 2). This result is compatible with the published data [3, 20]. Since the calculated relative energies of the glucopyranose rotamers agree with experiments, it can be concluded that the factors that determine the exocyclic hydroxyl methyl rotamers are defined by the intramolecular, rather than intermolecular forces, because the models considered in calculations are all implicitly designated.

In the considered species the CCSD(T) corrections generally cause a decrease in relative energies among the glucopyranose isomers in vacuo, except α -t isomer. Energy difference between the most stable rotamer (α -g-) and α -t rotamers increases by approximately 1 kcal mol⁻¹ after CCSD(T) correction. Compared to the MP2 level results the CCSD(T) corrections do not change relative energies of five isomers (α -g-, α -g+, β -g-, β -g+, β -t) but destabilize by approximately 1 kcal mol⁻¹ the α -t isomer. Therefore, it can be concluded that the α -g- and α -g+ rotamers are more stable than α -t rotamer both in vacuo and in solvents. While the protic hydrogen of primer alcohol group (H-OCH₂-) forms hydrogen bond with the oxygen of the hydroxyl group, which connects to C₄ carbon in α t rotamer, the hydrogen bond between the etheric oxygen and primer alcohol replaces this type of interaction in α -g- and α -g+ rotamers (Fig. 4). It appears that in the gas phase the formation of a hydrogen bond with etheric oxygen is more favorable than establishment of a hydrogen bond with hydroxyl oxygen. Based on the obtained results negative isosurfaces were visualized for g- and g+ rotamers (Fig. 5b and c) and for trans configuration (Fig. 5a).

The solvation effects represent one of the most important factors in the stability of glucopyranose anomers. Since it is not possible to consider all aspects of solvent-solute interactions with implicitly defined solvents, the results obtained here are not in a good agreement for the α : β ratio with experimental data. Such phenomena could be revealed by considering solvent molecules explicitly and also after the dynamic effects are taken into consideration. However, calculations with inclusion of an appropriate amount of solvent molecules that are necessary to create a few solvation shells around the solute are very expensive and not practical. Usually, one forms model complexes with only a small number of solvent molecules, though this might not be sufficient to accurately account for the solvent effects.

The explicitly defined solvent calculations have been performed at the MP2/6-31G(d,p) level because higher level

Table 1 Relative energies (kcal mol⁻¹) of glucopyranose isomers, in vacuo

	Vacuo		
	MP2 aug-cc-pVDZ	Ext. MP2	CCSD(T) Corr.
α - g-	0.0	0.0	0.0
α - g+	0.1	0.1	0.0
α - t	0.2	0.2	1.3
β - g-	2.1	2.0	1.9
β - g+	1.8	1.7	1.6
β - t	2.3	2.2	2.0

Table 2 Relative energies (kcal mol⁻¹) of glucopyranose isomers, in solvents

	THF			DMSO			Water			EtOH		
	MP2 aug-cc-pVDZ	Ext. MP2	CCSD(T) Corr.	MP2 aug-cc-pVDZ	Ext. MP2	CCSD(T) Corr.	MP2 aug-cc-pVDZ	Ext. MP2	CCSD(T) Corr.	MP2 aug-cc-pVDZ	Ext. MP2	CCSD(T) Corr.
α -g-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
α -g+	0.1	0.1	0.1	0.2	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1
α -t	0.5	0.5	0.3	0.5	0.5	0.4	0.5	0.5	0.5	0.5	0.5	0.4
β -g-	1.6	1.6	1.5	1.5	1.5	1.4	1.5	1.5	1.4	1.5	1.5	1.4
β -g+	1.5	1.5	1.4	1.5	1.4	1.3	1.5	1.4	1.3	1.5	1.4	1.3
β -t	2.1	2.0	1.8	2.0	2.0	1.8	2.0	2.0	1.8	2.0	2.0	1.8

calculations would be very expensive, even for implicit calculations, especially for protic solvents. The binding energies (BE) between solute and two explicit solvent molecules and relative energies (RE) of such obtained complexes are closely interconnected both for the in vacuo and solvent species (Tables 3 and 4). Higher binding energy causes a decrease in relative energy of the complex. The position of primary alcohol group and the anomeric hydroxyl group determine the strength of interaction between solvent molecule and the glucopyranose, because the other parts of isomers adopt almost the same configuration. In the models considered here the first solvent molecule was placed around etheric oxygen (close to the primer alcohol group and anomeric alcohol). The second solvent molecule was placed at the largest possible distance from the first molecule to minimize the solvent-solvent interactions and focus on solvent-solute interaction (Fig. 6). Such complexes were fully optimized, without any symmetry restrictions, and harmonic vibrational frequencies were calculated, to assure that the optimized structure is a minimum on the respective potential energy surface.

The binding energies of water-glucopyranose systems are closer to ethanol-glucopyranose than to dimethylsulfoxide-glucopyranose system in vacuo and in solution (Tables 3 and 4). This means that binding energy is closer linked with protic properties of solvent molecules than with polarities since the polarity of water is closer to DMSO than EtOH.

The calculated binding energies (BE) between the considered isomers and solvent molecules in vacuo are higher than in solvent. The increase in binding energy from solvent to vacuo (Tables 3 and 4) varies by the solvent (Water: ~% 50, EtOH: ~% 36, DMSO: ~% 23, THF: ~% 11). Glucopyranose is a polar molecule and has six hydrogen bond acceptors and five donors. Because of this, glucopyranose is more stabilized in polar and protic solvents than nonpolar and aprotic solvents. Thus the amount of energy decrease of glucopyranose complexes from vacuo to solvent is related to the polar and protic properties of solvent and this phenomenon explains variation in binding energy differences between the vacuo and different solvents. Water is the best polar and protic solvent and the binding energy difference is in this case the highest on going from vacuo to water. Ethanol is the second most polar solvent so this difference is smaller than for water. Because of its nonpolar and aprotic properties, THF displays almost the same binding energy for its complexes in vacuo and in solvent.

The relative stability of different configuration varies by the solvent but generally, α isomers are more stable than β and the relative energies are small, especially in solvents, except β -g- (Table 4). One water molecule donates hydrogen to etheric oxygen and accepts hydrogen from anomeric hydroxyl; the primary alcoholic hydroxyl group forms hydrogen bond with the hydroxyl which links to C₄ position in β -t isomer. Both of these interactions result in formation of a six membered ring structure, which is favorable (Fig. 6a).

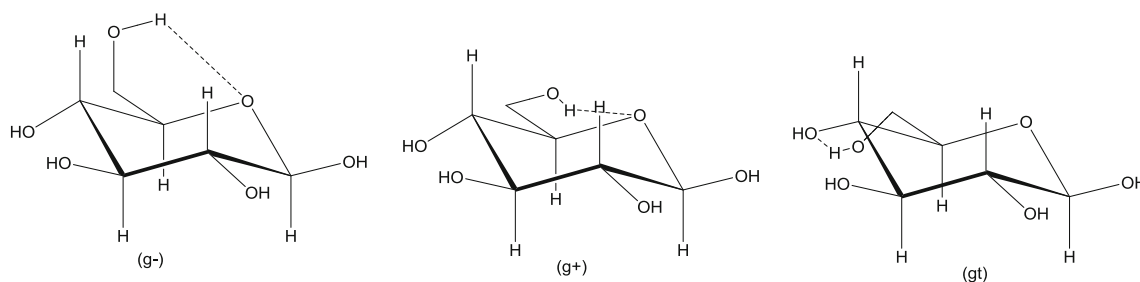
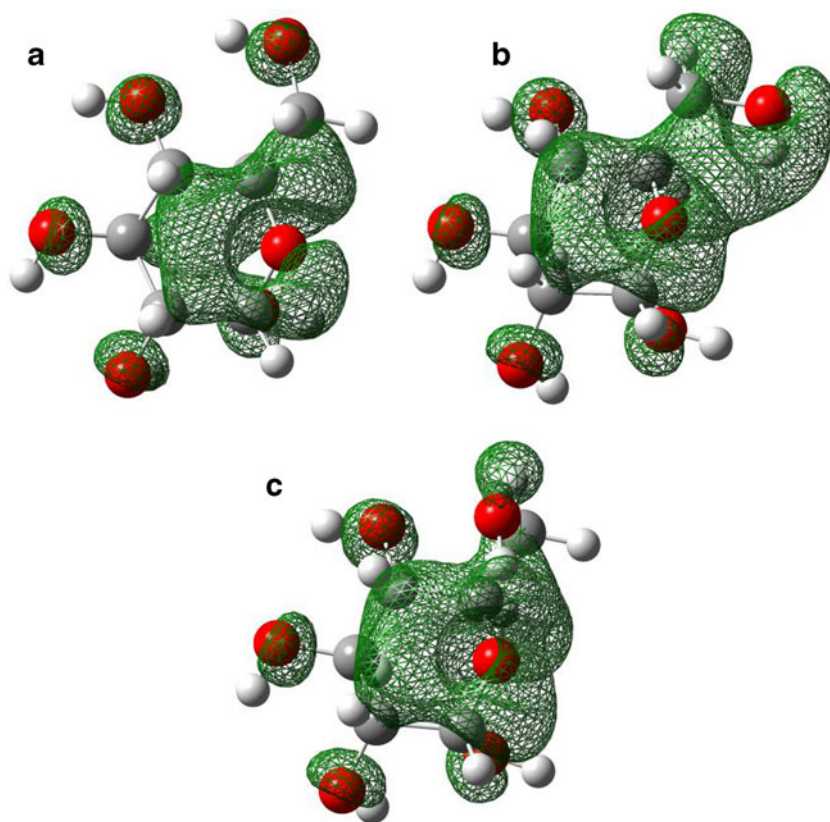
**Fig. 4** Hydrogen bonding preferences of glucopyranose rotamers

Fig. 5 Negative isosurfaces of LUMO of trans (a), gauche + (b) and gauche – (c) rotamers of α -glucopyranose. (Isovalue: 0.02)



This situation is similar in β -g+ isomer. However, in this case the primary hydroxyl group forms hydrogen bond with etheric ring oxygen, and as a result of these interactions one six and one five membered ring is formed (Fig. 6b). Interestingly, in β -g– isomer both of the anomeric hydroxyl and primary alcoholic hydroxyl are at the same side of ring plane and one water molecule accepts hydrogen both from the anomeric and primary alcoholic hydroxyls. Both interactions result in creation of five membered ring configuration, which is however

less favorable than the six membered structure (Fig. 6c). Double interaction of hydroxyls with the same water molecule causes an increase in energy in β -g– isomer with respect to other isomers, because of a transition state like position of water (Fig. 6c). The relative energy of β -g– amounts to $7.1 \text{ kcal mol}^{-1}$ in water, which is significantly higher than analogous energy of other isomers. Accordingly, it can be concluded that the interaction geometry of hydroxyl groups with solvent molecules is one of the important factors governing relative energies.

Table 3 Binding energies (BE) and relative energies (RE) (kcal mol^{-1}) of glucopyranose isomers with explicitly defined two solvent molecules in vacuo at MP2/6-31G(d,p) level

	Vacuum							
	Water		THF		DMSO		EtOH	
	BE	RE	BE	RE	BE	RE	BE	RE
α -g–	26.2	3.5	35.2	2.2	32.8	1.7	28.3	3.6
α -g+	30.2	0.0	36.2	1.6	31.8	3.3	32.4	0.0
α -t	27.1	2.8	37.5	0.0	34.6	0.0	29.6	2.4
β -g–	23.2	9.8	36.5	4.2	31.7	6.2	28.6	6.7
β -g+	26.7	6.5	36.1	4.8	36.6	1.4	27.6	7.8
β -t	27.4	5.8	36.0	4.8	33.2	4.7	29.7	5.6

Table 4 Binding energies and relative energies (kcal mol^{-1}) of glucopyranose isomers with explicitly defined two solvent molecules in related solvent at MP2/6-31G(d,p) level

	Solvent							
	Water		THF		DMSO		EtOH	
	BE	RE	BE	RE	BE	RE	BE	RE
α -g–	13.1	1.6	30.0	1.1	25.3	2.0	17.1	1.8
α -g+	15.4	0.0	31.0	0.8	25.1	2.8	19.5	0.0
α -t	13.9	1.4	31.6	0.0	27.9	0.0	18.0	1.4
β -g–	10.5	7.1	31.1	3.0	24.0	6.2	17.9	3.9
β -g+	14.0	4.1	30.9	3.7	28.1	2.6	18.6	3.6
β -t	14.1	4.1	31.1	3.6	26.9	3.9	18.2	4.1

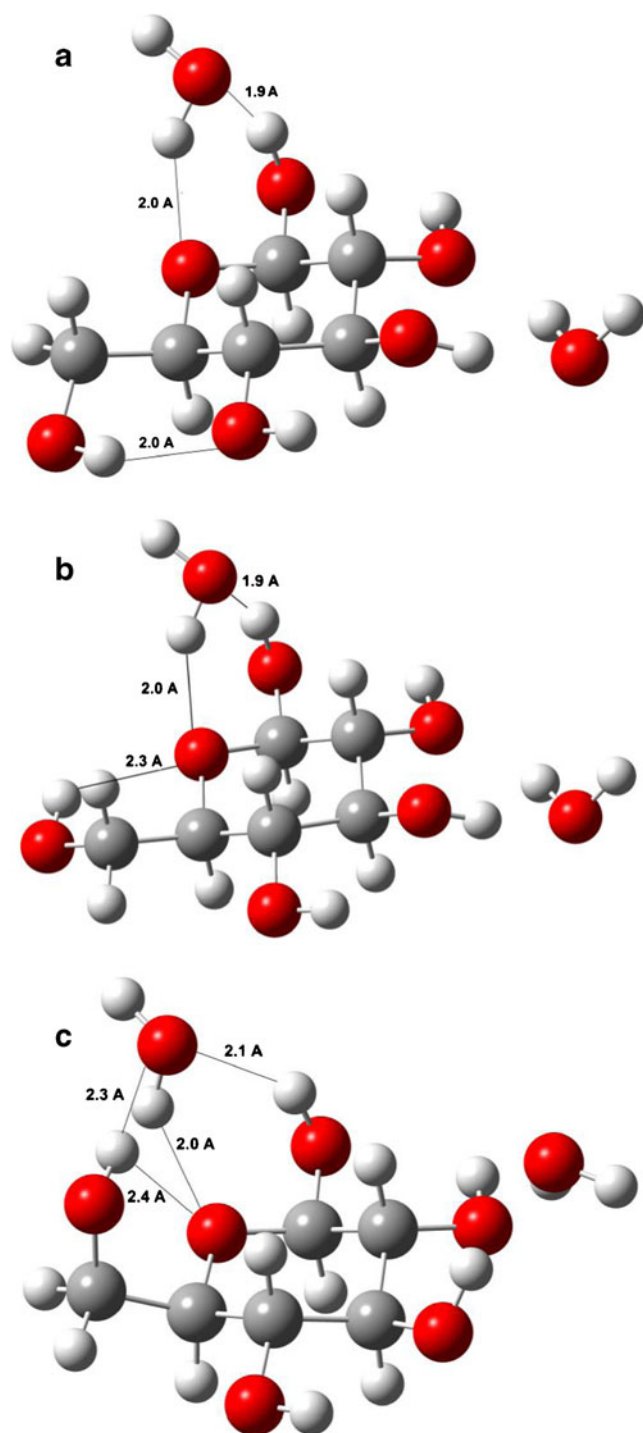


Fig. 6 Considered complexes with explicit two water molecules, six and five membered hydrogen bond cyclic systems of t (a), g⁺ (b) and g⁻ (c) rotamers of β -glucopyranose with water

Conclusions

Two types of isomerization, anomerization (α and β) and rotamerization (g⁻, g⁺ and t) have been studied. Relative energies of exocyclic hydroxy methyl rotamers and anomers

of glucopyranose were determined in the gas phase as well as in various solvents (H₂O, DMSO, THF and EtOH) by the results of ab initio calculations that include basis set extrapolation (MP2 aug-cc-pVTZ and aug-cc-pVQZ) and CCSD(T) scaling. Relative energies of glucopyranose isomers are generally similar and are highly sensitive to environment.

The relative energy differences between α and β anomers are almost 1.5 kcal mol⁻¹ in implicit calculations and almost 5 kcal mol⁻¹ when explicit water molecules are considered. Both approaches favor α anomer. Despite the inclusion of two water molecules the difference between calculated data and experimental results increased. Interestingly, as illustrated by data in Table 2, the inclusion of the two water molecules for the in vacuo models for the α and β anomers revealed a clear preference for the α species. This is in contrast to the experimentally observed trend. Whilst the implicit model is considered (no discrete solvent molecules) the difference between α and β forms at the same level of theory is small (and closer to the experiment), however, once the discrete molecules are included the α anomer is much more favored. The BE values (Tables 2 and 3) indicate that the interaction with the discrete molecules is either similar or more stabilizing for all the α - anomers (13.1, 15.4 and 13.9) compared to the β - structures (10.5, 14.0, 14.1 kcal mol⁻¹ respectively). One might conclude that the model calculations reported here are only the first approximations of the complicated equilibrium in the solution where collective interactions among anomers and water molecules that form complex hydrogen bonding networks are responsible for experimentally observed stabilization of the β - forms.

Extrapolation of the energy at the MP2 level and CCSD(T) corrections decreased the energy difference between α - and β - anomers for vacuo, aprotic solvents and protic solvents. However, the results obtained for protic solvents should be considered with a caution since the complexity of interactions in such solutions could not be simply overcome even with the highest level static calculations. According to the experimental results the α : β forms ratio is 36:64 in water, this means that β anomer is by 0.34 kcal mol⁻¹ more stable. Though the experimental result is still different from calculation, it is clear that the CCSD(T) correction shifted the calculated relative energy approximately 1-kcal mol⁻¹ closer to experiment.

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