On the Route of the Determination of Monosaccharides Conformations

Renato R. Andrade and Clarissa O. da Silva*

Departamento de Química, Universidade Federal Rural do Rio de Janeiro, BR 465, km 47 - Seropédica, Rio de Janeiro, Brazil, CEP 24949-900, Brazil

Abstract: Many theoretical studies on carbohydrates have been published in the last century. Building on these developments, a procedure is presented to select stable conformations of monosaccharides in aqueous solution from samplings on potential energy surfaces (PES) obtained from quantum mechanics. Considerations regarding the property chosen to validate conformational samplings are also presented. The conformations found for D-xylopyranose present an optical rotation value of +20.35°, which coincides with the experimental value (+18.8°).

Keywords: Monosaccharide conformations, monosaccharide potential energy surface, optical rotation calculations for carbohydrate, carbohydrate conformations.

1. INTRODUCTION

Carbohydrates are molecules that are responsible for many distinct biological functions, probably due to their structural and conformational versatility [1, 2]. In these molecules, small structural or conformational changes can lead to systems with drastically different physical-chemical properties, such as cellulose and starch, which are both made of glucose units linked to each other by different bond types, as can be seen from Fig. (**1**).

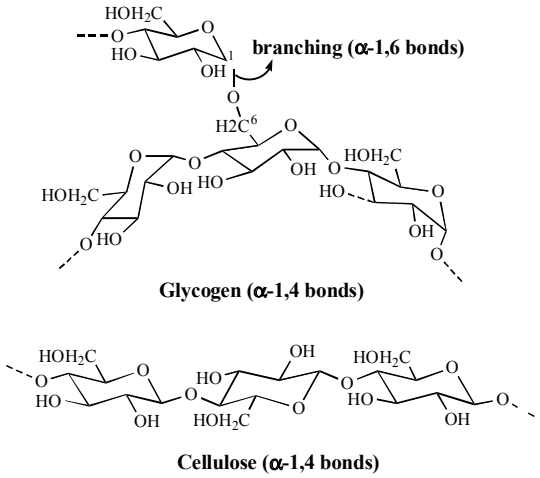

Fig. (1). The three-dimensional structures of cellulose and glycogen are defined by the type of the glycosidic bond between the monomeric units, which consequently responds also for their physical-chemical properties.

The presence of this class of molecules exerting several and distinct chemical and biochemical roles in all kingdoms imposes the necessity of obtaining reliable descriptions of them. But, ironically, the same conformational versatility that makes them special in nature makes it difficult to rationalize them from experimental data and, consequently, to describe them with theoretical models.

1.1. General Remarks on Experimental Information About Monosaccharides

In fact, experimental access to information about carbohydrates' structures, and in particular conformations, is not as straightforward as it is for rigid structures. The most common techniques employed are X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy. In the first instance, as discussed by Wormalm and coworkers [3], we first need perfect crystals, which are not easy to obtain for carbohydrates, even if they are more feasible for monosaccharides than for oligosaccharides. However, for monosaccharides, the major interest concerns their behavior in aqueous solution (due to the similarity with the biological medium), or in glycopeptides, and not in their crystalline state, and we cannot assume that the geometry of such a flexible system is independent of the environment [4]. In the second case, properties obtained from NMR (or any other experimental technique) spectra are average values for non-rigid structures [4], which saves no relation with a unique conformation. Then, in most cases, we are able to find many distinct combinations for the relative abundance values of conformers that resemble the experimental data. In addition, the use of experimental data in parameterizations should be avoided; otherwise, there is a high risk of obtaining a non-physical conformation. An additional complication arises when the measured property has similar values for similar conformations. For instance, the coupling constant (*J*) values obtained from nuclear magnetic resonance (NMR) spectra that are frequently used to validate carbohydrate conformations do not cover a large range. As discussed by Bock and Duus, in a detailed revision [5], the range spanned by the property is at most 10 Hz for the differences between the *gt* and *gg* or *tg* and *gg* hydroxymethyl group orientations. Although the empirical relationships between dihedral angles and heteronuclear or homonuclear *J* values for disaccharides—or direct measures for monosaccharides [6-9] —have been developed in many valuable works that helped us to achieve the level of conformational knowledge that we now have [10], they alone are not sufficient to solve the problem of identifying the most stable carbohydrates conformations.

More recently, the use of a combination of electronic and vibrational spectroscopy has shed more light on the conformational problem of monosaccharides and their hydrated complexes [11], but mainly treating carbohydrates as isolated systems.

Concerning the simplest members of the huge family of carbohydrates, the monosaccharides have been studied, both theoretically and experimentally, for a long time. A single monosaccharide can occur (as reported in Fig. (**2**)) as an open or closed structure or as a ring with various numbers of atoms (generally 5 or 6, which are called, respectively, furanoses and pyranoses). The latter in turn can occur in many different ring conformations (e.g., chair (C), boat (B), skew-boat (S)) or even the same ring conformation in different shapes (e.g., $^{1}C_{4}$ or $^{4}C_{1}$, $^{2,5}B$ or $B_{3,O}$, $^{1}S_{3}$ or $^{3}S_{5}$), where the super and subscripts indicate which atoms (e.g., C1, C2, C3, C4, C5 or O) are pointing above and below the plane defined by the four remaining atoms, which are always present in these conformations for pyranose rings. Finally, each conformation can occur with different orientations of the hydroxyl and hydroxymethyl groups. Such geometrical versatility is demonstrated in Fig. (**2**). It is not evidenced from the most common Fischer and Haworth projections,

*Address correspondence to this author at the Departamento de Química, Universidade Federal Rural do Rio de Janeiro, BR 465, km 47 - Seropédica, Rio de Janeiro, Brazil, CEP 24949-900, Brazil; Tel/Fax: +55-21-2682-2807; E-mail: clarissa-dq@ufrrj.br

1570-193X/11 $58.00+.00

which are used in many textbooks to represent a carbohydrate molecule, and which were proposed to emphasize the configuration of each chiral center and the cyclic prevalence against open forms, in carbohydrates with five or more carbon atoms, respectively. From the thermodynamic point of view, a carbohydrate present itself as an average of these different possibilities, weighted by their relative energy values referred to the global minimum.

The carbohydrates cyclization (a hemiacetal formation reaction), commonly called mutarotation [12-14], leads to the creation of an additional asymmetric carbon (C1 in aldoses and C2 in ketoses), called anomeric carbon. The anomers are called α or β if the hydroxyl group of the anomeric carbon assumes an axial or equatorial position, respectively, with respect to the ring plane.

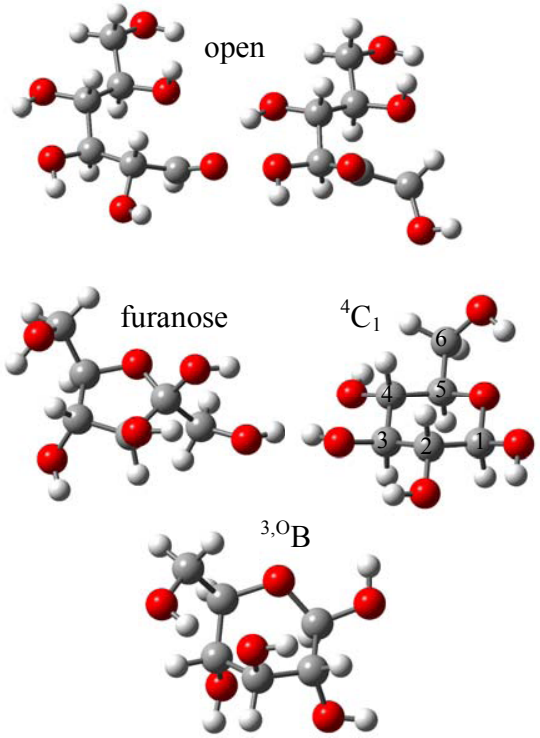

Fig. (2). Schematic 3D representation for some types of conformations possible for monosaccharides.

Undoubtedly, the most commonly studied monosaccharide is glucose, but some questions are still open with regard to its behavior in aqueous solution, as we will see. As the number of works dedicated to this subject is very large, some references may not be cited, because this paper is not intended to provide a full review of carbohydrate chemistry. Instead, we restrict ourselves to mentioning those that shed some light on our understanding of carbohydrate behavior. A very recent study performed by Schnupf and coworkers [15] provides an extensive bibliographical review of conformational studies of glucose and its epimers.

The experimental α:β anomeric ratio for glucose in the pyranosydic form in aqueous solution is reported as 34:66. Other forms, such as furanoses or open aldehyde, have a negligible occurrence (0.4% and 0.0040%, respectively) [16-19]. This ratio is reversed for the isolated system, which is attributed to the anomeric effect and causes the α anomer to be energetically favored over the β one. The origin of the anomeric effect is controversial, being attributed to electrostatic repulsions between the O1 and O5 lone pairs, in some works, and to the electron delocalization (hyperconjugation) from the O5 lone pairs to the vacant antibonding orbital σ^*_{C1O1}, in others [20-23].

1.2. Theoretical Information About Glucose Conformations

Many theoretical studies in aqueous solution using classical dynamics and continuum solvation models reproduce the α:β glucose anomeric ratio, but there is one, in particular, performed by Molteni and Parrinello [24], that goes further. These authors reported remarkable differences in the solvation scheme of both anomers. In the simulations performed, water molecules that solvate the crucial anomeric site were less tightly bound and had a shorter residence time in β than in α. The β anomer, which is the most abundant in water, allows water molecules to flow freely around its anomeric site, while the α anomer tends to bind them more tightly and in a more orderly manner. According to these authors, the difference in the solvation of the two anomers is therefore more qualitative than quantitative.

The theoretical works that are in agreement with these anomeric ratios refer primarily to the pyranosidic form of the $^4C_1$ chair conformation, which has been reported as more prevalent than other shapes by many authors [25-27]. With regard to the hydroxymethyl orientations, many works can be found dedicated to this study [28-35]. The large majority of them show that the *gg* and *gt* conformations are preferred in aqueous solution over the *tg* one, due to the competition between the intermolecular (O(water)---HO6) and intramolecular (O4---HO6) interactions, this latter possible only in the *tg* rotamer. Of course, these hydroxymethyl orientations are influenced by the secondary hydroxyl groups' positions, and the determination of these secondary hydroxyl positions is the most difficult task, because rigorously it would be necessary to consider all 1458 conformations generated (being 729 for each anomer), if it is assumed that the staggered positions of the hydroxyl hydrogen atoms along the C-OH bond are energetically favored (3(C1) x 3(C2) x 3(C3) x 3(C4) x 3(C5) x 3(C6) = 729). The main challenge here (and in any other conformational study on carbohydrates) is to identify the most stable conformers among the 1458 possible in this case, obtained from the rotations around the ~C-OH~ (secondary hydroxyls) and ~C-CH_2OH bonds. The crucial issue is thus determining which conformers are abundant in aqueous solution at room conditions.

1.3. Sampling Criteria and Conformational Validation—the Key Points

If the theoretical route is chosen to study a carbohydrate, the description chosen has to encompass the main stabilizing effects of these molecules, such as the anomeric (and exo-anomeric) effect and hydrogen bonding [36]. The theoretical approaches historically used to study carbohydrates are based on classical descriptions (molecular mechanics or dynamics), which are particularly useful when the system is large (oligo and polysaccharides) or very flexible. Due to the possibility of scanning a variety of different conformations in a molecular simulation, these methods have dominated the study of carbohydrates. In these methods, the force field is the key expression. Many different parameterizations have been found in the literature to account for specific interactions among carbohydrates [37, 38], principally because the transferability of the force field parameters into the carbohydrate family cannot be assured in most cases, even when accurately obtained [39, 40]. Complementing this scenario, there are the quantum mechanical methods, which are very efficient in quantifying stereo electronic effects because no parameterizations are needed. Nevertheless, they consist of calculations performed on selected geometries, and there still remains the physical question related to the vast carbohydrate flexibility, which is mathematically expressed as a potential energy surface (PES) with a high density of minima. By adopting quantum mechanical methods, the depth of each region that is a minimum on the PES can be determined precisely (and consequently, the relative energies among conformers can be calculated). However, it is necessary to assure that the most stable conformations are included in the PES. Clearly, if an *ab initio* study is to be performed, a protocol

should be established to "walk" on the potential energy surface, in order to avoid non-representative conformational samplings.

In the large majority of the theoretical works found in the literature that make use of quantum mechanical methods, a set of conformations is generally chosen based on some initial criteria and tested in their ability to reproduce a property, which is very often the anomeric ratio.

If all conformations possible (1458 for glucose, for instance) are not considered, the criteria used will be at some extent qualitative, based mainly on the consideration of conformations where the cooperativity effects are magnified (clockwise and counterclockwise hydroxyl orientations) [41]. However, two main problems can be identified in these procedures: the first is related to the criteria for sampling conformations themselves, and the other is related to the validation process of the conformations found.

In the former case, the procedure obviously favors conformations that present the cooperativity effect, which is discussed by Klein [41], either as the starting geometry or even as the final conformations obtained after a partial conformational search. This is a very frequent result found in many theoretical studies not only for glucose [42] but also for other monosaccharides [43-46].

The second problem concerns the validation step. The problem now is the accuracy of the calculation of the selected property. In almost all cases (even when the theoretical level is very sophisticated), it has the same magnitude of the difference of the property values for distinct conformers. A quick illustration of this problem can be given as follows: the eleven individual glucose conformers that seems to respond for its tautomeric equilibrium in aqueous solution were recently identified, by Barrows and coworkers [47], after a full exploration of glucose PES using molecular mechanics (all 1458 conformations were computed by molecular mechanics). The rotameric hydroxymethyl relative abundance found (after improvements in the description level were introduced on the most stable conformations) was 27:66:5 to the sequence *gg:gt:tg*. If only the β anomers are considered, the corresponding proportion remains, coincidentally, the same. The most recent proportion of 31:59:10 was found by Suzuki *et al.* [48] to *β-glycopyranse*. They are in good agreement with the most recent experimental proportion of 32:59:9 found to *β-glycopyranse* by Serianni *et al.* [49]. These latter authors have found for the relative hydroxymethyl groups population, in both sets of anomers, the values of 37:55:8 (although the rms errors have the same magnitude of the tg population), revising the values used as benchmark for years, from Nishida *et al.* [50]) which are 53:45:2 to *β-glycopyranse* and 55:44:1 for both sets of anomers. A very small change in the former theoretical set of conformers, which includes a new conformation present in previous studies [51, 52], changes the proportion to 34:57:8 [53]. Considering that the energy difference that responds for these relative populations is smaller than the accuracy of the calculation levels used, are they equivalent sets? This question cannot be answered if the anomeric ratio, hydration energies or coupling constants are the only properties used in the validation procedure.

Taking into account the previous considerations, this study has a dual goal: (1) to show that a quantitative sampling procedure based on quantum mechanical methods is now feasible and is able to select the most stable conformations for monosaccharides in aqueous solution and (2) to validate these conformations, and consequently the procedure itself, by calculating a property that is extremely sensible to small conformational changes, which values change very much from one conformer to another [53, 54], and which is easily available to solutions of carbohydrates—the optical rotation (OR). It is important to mention that almost all considerations here are based on theoretical and experimental data available in the literature, that when combined, enable us to perform an analysis from a new perspective.

2. COMPUTATIONAL ASPECTS

To start with a system simpler than glucose, xylopyranose was the carbohydrate chosen as a test case in this study. Compared to glucose, the conformational problem is reduced by a factor of 3x3, because the hydroxymethyl group is missing on the C5 atom of this molecule (see Fig. (**3**)).

A continuum model was used to describe the aqueous solution environment; thus, we are describing the molecules in an aqueous solution after thermodynamic equilibrium is reached. It is equivalent to assume that the conformations considered resemble those of a larger residence time in a molecular dynamics simulation. This correspondence is possible [55] because the electrostatic effects are those that mostly govern the interaction of carbohydrates and water, due to the high dielectric constant of water and due to the high dipole moments of the hydroxyl groups present in large numbers in the carbohydrate structure, which are not geometrically compensated. The hydrogen bond interactions, although they have well-defined orientations, can also be included among the electrostatic interactions because their largest component has an electrostatic nature [56-58].

To introduce the solvent effects, we used the Polarizable Continuum Model [59, 60] in its Integral Equation Formalism (PCM) formulation [61, 62]. This solvation model has been successfully used in the study of many important physical chemical properties [63], and it was proven to be a robust model to describe the solvation energy of many different systems. The radii of the spheres that define the cavity are the following: 2.40Å for CH or CH_2 group, 1.80Å for O atom and 1.44Å for H bonded to the oxygen atom of the hydroxyl groups [64]. In this PCM version, we computed the solvation energy (G_{solv}) as the sum of the electrostatic (G_{elect}) and non-electrostatic ($G_{non\text{-}elect}$) components. The latter is obtained from the computation of the dispersion, repulsion and cavitation terms [65]. The calculations were all performed with the Gaussian03 [66] computational code and the GaussView2.1 molecular editor [67] in a cluster of five computers with AMD Opteron processors such as QuadCore 2.3GHz or DualCore 3.0GHz—and 6Gby of RAM.

All calculations related to the conformational sampling on xylopyranose potential energy surface were performed at the HF/6-31G (d) and B3LYP/6-31+(d,p) levels because they have been identified in the literature as the simplest calculation levels that are still reliable to describe geometrical aspects of carbohydrate conformations [68, 69]. The diffuse functions must attend density functional descriptions to assure reliable conformations [68].

Single point (SP) and geometry optimization (GO) calculations were performed at the HF/6-31G(d) level for all conformers in the gas phase, and B3LYP/6-31+G(d,p) geometry optimization calculations were performed only for the fifteen most stable conformations. The final population values were obtained from geometry optimization calculations in PCM using a B3LYP/6-31+G (d,p) description for the fifteen most stable conformers found in the previous step. The corresponding frequency calculations characterized the structures as stationary points with minimum energy on the xylopyranose potential energy surface and allowed the introduction of thermal and entropic corrections into the fifteen most stable conformations.

Two starting structures were obtained for both xylopyranose anomers (alpha(α) and beta(β)) from geometry optimization calculations at the HF/6-31G(d) level in the gas phase, using the initial geometrical coordinates generated by the GaussView. These starting structures are reported in Fig. (**3**) and have all the hydroxyl groups in staggered orientations regarding the ring. The β conformation seems to have the maximal possible cooperativity effect, but this phenomenon is not observed for the α conformation, where the O1---HO2 interaction is not allowed.

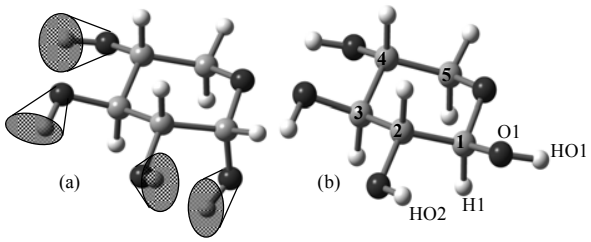

Fig. (3). Alpha (α) and beta (β) anomers of xylopyranose. In (**a**), the free rotations of the hydroxyl groups are represented and in (**b**), the labels of the atoms are presented.

Systematic rotations of 120° for the dihedral angles ϕ1 (HO1-O1-C1-O5), ϕ2 (HO2-O2-C2-C1), ϕ3 (HO3-O3-C3-C2) and ϕ4 (HO4-O4-C4-C3) were imposed after the geometry optimization step was performed for each anomer. This gave rise to 162 conformers (81 for each anomer), because only the $^4C_1$ chair conformation for the ring was considered. Other xylopyranose ring conformations ($^1C_4$ chair, boat, half-chair, skew boat) have negligible occurrence in aqueous solution at room conditions [27, 70, 71]. All these 162 conformations were subjected to single point energy and geometry optimization calculations in the gas phase.

The optical rotation (OR) values were calculated at B3LYP/6-311++G (2d,2p), as suggested in the literature for rigid systems [72, 73], to validate the final set of conformers found. Each conformer contributed to the final property in a weighted average. The weights were obtained from the Boltzmann distribution, once the system (a xylopyranose aqueous solution in an infinite dilution) is assumed to follow this type of distribution (it can be described as a system with extensive entropy [74]) when it reaches thermodynamical equilibrium at room conditions. OR values were calculated for the conformers in PCM following the TD-DFT/GIAO approach described previously [75]. The results obtained are reported as the specific rotation $[\alpha]_D$ calculated at the sodium D line frequency (the specific rotation $[\alpha]_D$ is the observed rotation corrected for concentration (g/mL) and a defined path length (dm), namely $[\alpha]_D = \alpha_{obs}/(c \times l)$).

3. RESULTS AND DISCUSSION

3.1 Conformational Sampling

In Fig. (**4**), all 162 single point energy and geometry optimization calculations are reported in the same graph for the alpha and beta anomers. As can be seen in the figure, the geometry optimization procedure generated conformations that cover a range of electronic energy of approximately 10 kcal/mol in the alpha set and 12 kcal/mol in the beta set, while for the single point calculations, the range span is larger (as could be expected): 24 kcal/mol and 20 kcal/mol, respectively.

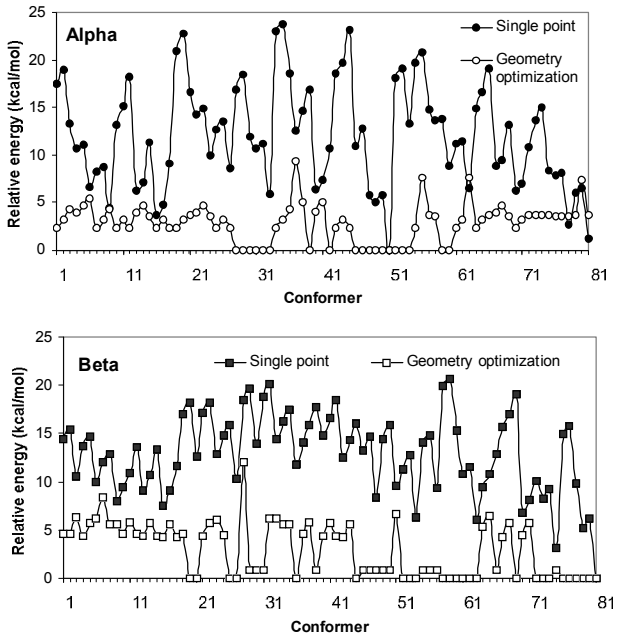

Fig. (4). Relative electronic energy values in the gas-phase for single point (SP) and geometry optimization (GO) calculations for all 162 xylopyranose conformers investigated at HF/6-31G (d) level, in kcal/mol. Each curve has its own energy reference value, as reported in the text.

The lowest absolute values in the SP calculations are α(conf. 51)= –569.441049 a.u. and β(conf. 81)= –569.443170 a.u., while in the GO calculations, the lowest absolute values are α=–569.444991 a.u. and β=–569.443170 a.u. (in this case, the starting structure was the global minimum among the β anomers). Because many conformers converged to the same geometry in the geometry optimization calculations, the reference absolute values for the α and β anomers correspond to several conformations, which are reported in Table **1**.

Table 1. Conformations Described by Single Point Energy Calculations (SP) that Converged to the Same Geometry, During the Geometry Optimization Calculations (GO)

Alpha anomers		
GO	**SP**	**ΔE (kcal/mol)**
1	28,29,30,31,32,33,39,42,46,47,48,49,50,51,52,53,54,59,60	0.00
2	1,7,10,12,16,18,19,25,27,34,43,45,55,61,64,70	2.34
3	2,8,11,17,20,26,35,44,62,65,71	3.23
4	15,24,58,69,76,77,78	3.54
5	21,57,66,72,73,74,75,79,81	3.65
6	4,13,22,67	3.94
7	40	4.10
8	3,9,36	4.36
9	5,14,23,68	4.64
10	38,41	5.00
11	6	5.46
12	80	7.43
13	56,63	7.65
14	37	9.38

Table 1. contd…..

Beta anomers		
GO	**SP**	**ΔE (kcal/mol)**
1	20,21,26,27,36,45,52,53,54,58,59,60,61,62,63,69,72,73,74,76,77,78,79,80,81	0.00
2	29,30,31,39,46,47,48,49,50,55,56,57,66,75	0.89
3	16,18,43,67	4.23
4	4,13,15,22,40,42	4.36
5	25,70	4.50
6	1,2,10,12,19,37	4.58
7	64	5.36
8	8,9,34,35	5.53
9	17,44	5.61
10	71	5.66
11	5,14,23,41,68	5.72
12	11,38	5.86
13	24	6.04
14	6,32,33	6.20
15	3	6.30
16	65	6.45
17	51	6.64
18	7	8.36
19	28	11.99

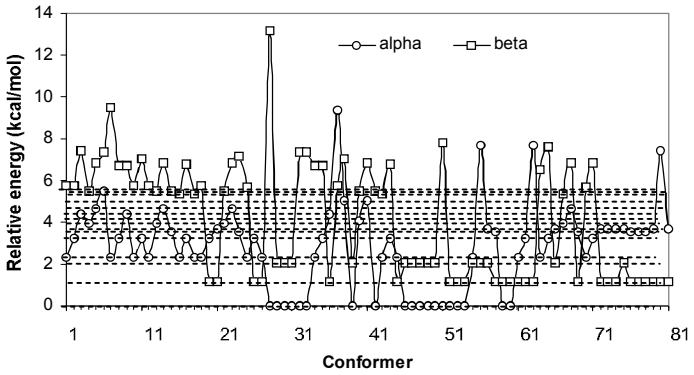

Fig. (5). Relative electronic energy values for geometry optimization (GO) calculations for xylopyranose conformers, at HF/6-31G(d) level, assuming the global minimum (α =–569.444991 a.u.) as the reference value for both sets of anomers.

As can be seen from Table **1**, after the geometry optimization step, the number of distinct conformations decreased to 33, if compared to the 162 initial ones. The initial 81 conformers of the alpha set converged to only 14 distinct conformations, while those 81 of the beta set converged to 19 final different conformations. It is important to recall that most likely only a small part of this set will be abundant in aqueous solution at room conditions.

Another way to visualize these identical conformations is exhibited in Fig. (**5**).

When the lowering in the electronic energy is computed in the geometry optimization procedure and quantified for each conformer, maximum values of approximately 20.8 kcal/mol (conformer 45 of alpha set and 59 of beta set) are found for both sets of anomers.

In Fig. (**5**), where the same absolute energy value was taken as the reference value for both sets of α and β anomers, the fifteen most stable conformations are highlighted by the horizontal dashed lines. As can be seen, among these fifteen conformations, eleven are α and four are β. These fifteen conformations span an energy range of 5.5 kcal/mol. The global minimum is an α anomer, as expected due to the anomeric effect [20,21], which is not compensated by intermolecular electrostatic interactions with the environment (solvent) because the system is isolated in this model.

If all conformational space is scanned, the energetic ordering is automatically obtained. Because the theoretical level used does not furnish reliable relative energies, some changes in this energetic ordering could be expected if a more complete description were used. However, the geometries are reliable at this computational level.

When samplings are performed on a potential energy surface of a carbohydrate molecule, it is desirable to follow a protocol that is able to select the most stable conformations, without having to consider all possibilities, as we have just demonstrated. It should be noted that, while a HF/6-31G(d) geometry optimization calculation takes, on average, 1 hour and 13 minutes in our cluster, a single point calculation at the same theoretical level on the same machine takes, on average, 40 seconds. This is a difference that cannot be neglected and that prompted us to consider more carefully the set of single point energy calculations as a possible source of information to drive conformational samplings, as described in the following.

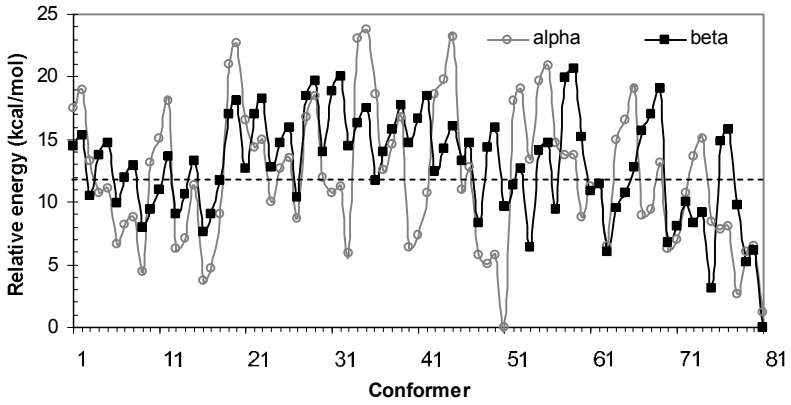

Fig. (6). Relative electronic energy values for single point (SP) calculations for xylopyranose conformers, at HF/6-31G(d) level. Each anomer set has its own reference value.

Table 2. Relative Electronic Energy ($\Delta U_{T=0K}$), Standard Gibbs Free Energy ($\Delta G°_{T=295.15K}$) in kcal/mol and Boltzmann Population (%) Values for Xylopyranose, at HF/6-31G(d) and B3LYP/6-31+G(d,p) Levels, in the Gas-Phase

	HF			B3LYP		
Conf.	$\Delta U_{T=0K}$[1]	$\Delta G°_{T=295.15K}$[2]	p_i	$\Delta U_{T=0K}$[1]	$\Delta G°_{T=295.15K}$[2]	p_i
28α	0.0	0.00	0	0.00	0.00	56.24
20β	1.15	0.55	0	0.95	0.38	29.61
29β	2.04	1.30	0	1.69	1.05	9.51
1α	2.34	-6.07	100.0	2.26	1.96	2.06
2α	3.23	3.04	0	2.87	2.62	0.67
15α	3.53	2.99	0	3.59	2.99	0.36
21α	3.65	3.38	0	3.34	2.96	0.38
4α	3.94	3.52	0	3.80	3.26	0.23
40α	4.10	3.74	0	3.90	3.48	0.16
3α	4.16	4.21	0	3.94	3.73	0.10
5α	4.30	4.25	0	4.21	3.80	0.09
38α	4.52	4.32	0	4.47	4.20	0.05
16β	4.85	4.76	0	4.72	3.76	0.10
6α	5.10	5.02	0	5.04	3.76	0.10
4β	4.95	4.40	0	4.84	3.97	0.07

1. The absolute values for electronic energy ($U_{T=0K}$) at HF and B3LYP levels are –569.444991 a.u. and –572.693014 a. u. for conformer 28α, respectively. ΔU= U(conformer X) – U(conformer 28α).
2. The absolute values for Gibbs standard free energy ($\Delta G°_{T=295.15K}$) at HF and B3LYP levels are –569.299142 a.u. and –572.562539 a. u. for conformer 28α, respectively. $\Delta G°_{T=295.15K} = G°_{T=295.15K}$ (conformer X) – $G°_{T=295.15K}$ (conformer 28α).

If the relative energy values for the geometry single point calculations of all 162 conformers are reported assuming the corresponding "global minimum" value (**in SP calculations**) as the reference for each alpha and beta series (conf. 51 and conf. 81, respectively), we obtain the graph in Fig. (**6**).

From Fig. (**6**), the whole set of conformers spans an energy range of ≈24kcal/mol. If an energy cutoff of 12 kcal/mol (dashed line) is assumed, and only the conformers under this energy limit are considered in the geometry optimization step, 75 calculations must be performed instead of the 162 geometry optimization calculations for xylopyranose. The energy cutoff value was estimated from the geometry optimization step, as the largest observed energy range covered, even though during the geometry optimization procedure for all the xylopyranose conformers, changes of up to 20.8 kcal/mol were observed. Due to this reason, the energy cutoff value proposed here is only a tentative limit. Nevertheless, if the set of conformers it provides is not able to reproduce the experimental property chosen in the validation step, the graph of Fig. (**6**) (or an equivalent to any other monosaccharide) is still able to suggest an ordering for including missing conformations, thus furnishing a mathematical criterion to introduce them in the previous set of conformers that is already considered below the energy cutoff value. Moreover, with such a large energy cutoff to select conformations from single point calculations, the HF/6-31(d) deficiencies in describing reliable energetic ordering for the conformations are completely overcome.

It was possible to perform this check because the geometry calculations had already been done for all possible conformers. The set of the fifteen most stable conformations was reproduced. This information can be confirmed by the analysis of data presented in Table **1** and Fig. (**6**). Additionally, it is worth mentioning that the recovery of the most stable conformations from single point energy calculations (performed on geometries selected from an energy cutoff value) is possible, even when the starting conformation used is not the most stable one (α anomer in Fig. (**3**)), probably because the cutoff value adopted was not too small.

3.2. Relative Abundance and Validation of Conformers

Once the fifteen most stable conformations were selected in the previous step, their relative abundance was calculated and reported in Table **2**, for the systems in the gas phase.

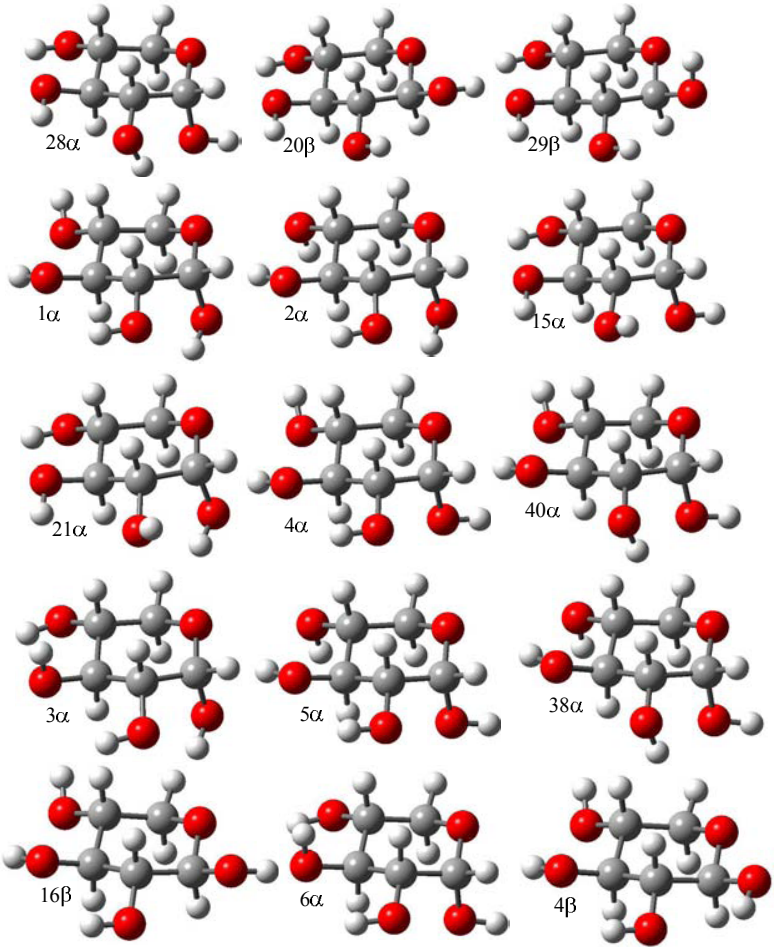

Fig. (7). Fifteen most stable xylopyranose conformers found following a B3LYP/6-31+G(d,p) description for the isolated system. The distance values between atoms are in Å, and refer to the isolated and in PCM (italic) systems.

The relative electronic energy values reported in Table **2** for xylopyranose conformers are very similar in both theoretical levels, and this can be an indication that the geometries found are similar in both descriptions. However, when thermochemical corrections are introduced, the descriptions diverge from each other. This happens because the entropy value calculated for 1α conformer is 121.30 cal/mol.K, whereas all other values for the remaining conformations are approximately 90cal/mol.K. This unexpected behavior seems to be a calculation artifact that leads to HF population values that are still less reliable than usual, contrary to those obtained from the B3LYP description. The α:β anomeric ratio found is 61:39 for xylopyranose as an isolated system at room conditions, following this latter description. Previous theoretical studies of xylopyranose decomposition [76] have used conformations for the most stable alpha and beta anomers very similar to those found in this study (28α and 20β) for the isolated system. The optimized conformers are reported in Fig. (**7**).

These fifteen conformers were solvated in PCM and geometry optimization calculations were performed at the B3LYP/6-31+G (d,p) level. During the geometrical optimization process, very small geometrical changes were observed in fourteen conformers. As a general remark, we can say that, in all the conformations, the values of the plane angle HO-O-C~ and the intramolecular OH---O interactions were enlarged in PCM, compared to the corresponding value in the gas-phase (see Fig. (**7**)). In some α anomers, however, this interaction involving the O1 atom, was shortened, reinforcing perhaps the idea that the α and β anomers have a distinct solvation pattern [24]. Surprisingly, it was not possible to obtain the first conformer (28α) as a stationary point in PCM calculations. From Fig. (**7**), it can be seen that there is an electrostatic interaction between OH2 and O1 (the OH2---O1 distance is 2.23Å, shorter than the others in the same conformer ─ but not the shortest among all conformers ─ which are 2.50 Å and 2.44 Å, for OH3---O2 and OH4---O3, respectively) for the isolated system, which seems to be strongly disturbed by the solvent presence. In fact, this conformation becomes stable in PCM only if smaller atomic radii are assumed in the cavity definition (this procedure artificially magnifies the solvent effects and was used to check the reason for the instability of this conformation).

The main energetic parameters for the fourteen stable conformations are reported in Table 3, and all the conformers with a relative abundance higher than 3% are highlighted. A more detailed analysis to evaluate the effects of different descriptions on the geometries, energies and optical rotation values can be found elsewhere [77].

When solvation effects are considered, the β anomers become more abundant than the α anomers. The environmental effects (solute–solvent interactions) overcome the anomeric effect for glucose [24]. The α:β ratio found changes from 61:39 in the gas-phase to 35:65 in PCM (at the description level employed). This ratio is kept the same, even if the description level is improved [77], and it is in close agreement with the experimental reference value of 34:66 [78], and with other theoretical studies [70, 80].

The most abundant conformations found (20β and 29β) present the hydroxyl groups pattern as being counterclockwise oriented, as

Table 3. Relative Solvation Free Energy (ΔG_{solv}), Standard Solvation Free Energy (in kcal/mol) and Boltzmann Population at the B3LYP/6-31+G (d,p) level in PCM, for the Fourteen Conformations Obtained. Specific Rotation Values $[\alpha]_D$ (in deg/(dm(g/cm^3))) are at the B3LYP/6-311++G (2d,2p) Level in PCM

Conf.	ΔG_{solv} [1]	$\Delta G°_{solv,298.15K}$ [2]	p_i (%)	$[\alpha]_D$
20β	0.00	0.00	37.28	-21.28
29β	0.67	0.64	12.65	43.19
1α	1.40	1.52	2.85	71.76
2α	1.89	2.24	0.84	83.56
15α	1.13	0.68	11.81	150.29
21α	1.45	1.85	1.62	120.28
4α	1.10	1.18	5.10	94.02
40α	0.35	0.93	7.73	127.83
3α	2.00	2.79	0.34	92.27
5α	1.45	1.84	1.67	108.32
38α	0.75	1.62	2.41	143.81
16β	0.90	0.69	11.60	-73.58
6α	1.71	2.33	0.73	115.58
4β	2.32	1.42	3.37	-31.51
Weighted average				+20.36
Exp.[a]				+18.8

a. Reference [84]

1. The absolute values for solvation energy (G_{solv}) are –572.705691 a.u. for conformer 20β and $\Delta G_{solv} = G_{solv}$ (conformer X) – G_{solv} (conformer 20β).$G_{solv}= G_{elect}+ G_{cav} + G_{disp-rep}$.

2. The absolute value for the standard solvation free energy ($G°_{solv,298.15K}$) is –572.578622 a.u. for conformer 20β and $\Delta G°_{solv,298.15K} = G°_{solv,298.15K}$ (conformer X) – $G°_{solv,298.15K}$ (conformer 20β). $G°_{solv,298.15K}$ takes into account the thermal and entropic corrections to G_{solv}.

already observed in molecular dynamics simulation studies [81]. In particular, the dihedral angle defined by the sequence OH4-O4-C4-H4 was studied [82, 83], and the most common values found were 300° and 60°, which is in full agreement with the conformations obtained in this study.

To validate the conformational sampling performed, the individual OR values were calculated as previously described and reported in Table **3**. Because the α anomers in general have very high individual OR values, conformers with Boltzmann population values lower than 3% were not considered in the final OR weighted average. These relative abundance values can be considered to be below the accuracy of the method for the energy values (in other words, a relative abundance of 3% cannot be distinguished from that of 0%). Because the sensitiveness of this property is very high, non-abundant α conformers can cause unrealistic distortions to the final OR value. The individual OR values and the corresponding relative abundance values considered are gray-highlighted in Table 3. When 89.54% of the xylopyranose conformers are considered in a weighted average, the final specific rotation value obtained is +20.36 °/(dm(g/cm^3)), which is in agreement with the experimental benchmark value of +18,8°/(dm(g/cm^3)) [84].

4. CONCLUSIONS

In this study, we have used D-xylopyranose as a test case to illustrate the possibility of using quantum mechanical single point energy calculations to sample the most stable conformations of a monosaccharide. The sampling procedure consists of selecting those conformations from the previous step that have relative energy values below an assumed energy cutoff value. Geometry optimization calculations were performed only on these selected conformations.

This suggestion is subject to criticism because there is no guarantee that all relevant conformations at room conditions will be recovered from those that are below the chosen energy cutoff value. Nevertheless, it is at least a quantitative, unbiased criterion to sample on potential energy surfaces of hexoses, which have at least 1458 conformers each (if we consider as abundant in the group of glucose epimers only the $^4C_1$ chair conformation for the pyranose ring).

The generalization of the energy cutoff value to other monosaccharides is a work in progress. If a smaller energy cutoff is assumed, to diminish the number of geometry optimization calculations needed, it may be convenient to change the description from HF to B3LYP/6-31+G(d,p) because, in the latter, the relative energy values are more reliable, which demonstrates a very good correlation (r^2= 0.99354) value [85], with those obtained from the B3LYP/6-311++G(d,p) calculations. The B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p) description gives converged relative energies with a mean absolute deviation of about 0.3 kcal/mol compared to MP2 reference results [69].

The fifteen most stable xylopyranose conformers selected by the procedure proposed here were solvated in PCM, and the solvent effects on the geometry were also considered. Although very small geometrical differences were found, the most stable conformer found in the gas phase was not found in PCM as a stable conformation. The intramolecular interactions present in this conformation are significantly disturbed by the electrostatic interactions with the continuum, which seems to be unable to replace them.

The optical rotation property is much more sensitive to individual conformational variations than the anomeric or hydration energies. In fact, the differences found among the individual OR values for the set of conformers considered is higher than the accuracy of the calculated property. We believe that this property should be used in any validation process, in addition to other properties, to help in the selection of monosaccharides conformations as reliable as possible.

ACKNOWLEDGMENTS

The authors would like to thank the Brazilian agencies FAPERJ, CAPES and CNPq for the financial support given to this study.

SUPPORTIVE/SUPPLEMENTARY MATERIAL

The optimized geometries in the Cartesian coordinates and the energy values in PCM ($G_{electrostatic}$) for the fourteen conformers at B3LYP/6-31+G(d,p) level can be found in the supplementary material.

Supportive/Supplementary material as available on the publisher web site along with the published article.

REFERENCES

[1] Sears, P.; Wong, C.-H. Toward automated systhesis of oligosaccharides and glycoproteins. *Science* **2001,** *291*, 2344-2350.

[2] Bertozzi, C. R.; Kiessling, L. L. Chemical glycobiology. *Science* **2001**, *291*, 2357-2364.

[3] Wormald, M. R.; Petrescu, A. J.; Pao, Y-L; Glithero, A.; Elliott, T.; Dwek, R. A. Conformational studies of oligosaccharides and glycopeptides: complementarity of NMR, X-ray crystallography and molecular modelling. *Chem. Rev*. **2002**, *102*, 371-386.

[4] Molteni, C.; Parrinello, M. Condensed matter effects on the structure of crystalline glucose. *Chem. Phys. Lett.* **1997**, *275*, 409-413.

[5] Bock, K.; Duus, J. Ø. A conformational study of hydroxymethyl groups in carbohydrates investigated by ^{1}H NMR spectroscopy. *J. Carbohydr. Chem.* **1994**, *13*, 513-543.

[6] Tvaroška, I,; Gajdoš, J. Angular dependence of vicinal carbon-proton coupling constants for conformational studies of the hydroxymethyl group in carbohydrates. *Carbohydr. Res.* **1995**, *271*, 151-162.

[7] Tvaroška, I,; Taravel, F. R.; Utille, J. P.; Carver, J. P. Quantum mechanical and NMR spectroscopy studies on the conformations of the hydroxymethyl and methoxymethyl groups in aldohexosides. *Carbohydr. Res*. **2002**, *337*, 353-367.

[8] Zhao, H.; Pan, Q.; Zhang, W.; Carmichael, I.; Serianni, A. S. DFT and NMR studies of $^2J_{COH}$, $^3J_{HCOH}$, and $^3J_{CCOH}$ spin-couplings in saccharides: C-O torsional bias and H-bonding in aqueous solution. *J. Org. Chem.* **2007**, *72*, 7071-7082.

[9] Tvaroška, I,; Hricovíni, M.; Petráková, E. An attempt to derive a new Karplus-type equation of vicinal proton-carbon coupling constants for C-O-C-H segments of bonded atoms. *Carbohydr. Res*. **1989**, *189*, 359-362.

[10] Duus, J. Ø.; Gotfredsen, C. H.; Bock, K. Carbohydrate structural determination by NMR spectroscopy: modern methods and limitations. *Chem. Rev.* **2000**, *100*, 4589-4614.

[11] Simons, J. P.; Jockusch, R. A.; Çarçabal, P.; Hünig, I.; Kroemer, R. T.; Macleod, N. A.; Snoek, L. C. Sugars in the gas-phase. Spectroscopy, conformation, hydration, co-operativity and selectivity. *Int. Rev. Phys. Chem.* **2005**, *24*, 489-531.

[12] Lewis, B. E.; Choytun, N.; Schramm, V. L.; Bennet, A. J. Transition states for glucopyranose interconversion. *J. Am. Chem. Soc.* **2006**, *128*, 5049-5058.

[13] Lin, C.-E.; Yu, C.-J.; Chen, C.-L.; Chou, L.-D.; Chou, C. Kinetics of glucose mutarotation assessed by an equal-amplitude paired polarized heterodyne polarimeter. *J. Phys. Chem. A* **2010**, *114*, 1665-1669.

[14] Silva, A. M.; Silva, E. C.; Silva, C. O. A theoretical study of glucose mutarotation in aqueous solution. *Carbohydr. Res.* **2006**, *341*, 1029-1040.

[15] Schnupf, U.; Willett, J. l.; Momany, F. DFTMD studies of glucose and epimers: anomeric ratios, rotamer populations and hydration energies. *Carbohydr. Res.* **2010**, *345*, 503-511.

[16] Roslund, M. U.; Tähtinen,P.; Niemitzc, M. ; Sjöholm, R. Complete assignments of the ^{1}H and ^{13}C chemical shifts and $J_{H,H}$ coupling constants in NMR spectra of D-glucopyranose and all D-glucopyranosyl-D-glucopyranosides. *Carbohydr. Res.* **2008**, *343*, 101-112.

[17] Zhu, Y.; Zajicek, J.; Serianni, A. S. Acyclic forms of [1-^{13}C]aldohexoses in aqueous solution: quantification by ^{13}C NMR and deuterium isotope effects on tautomeric equilibria. *J.Org. Chem*. **2001**, *66*, 6244-6251.

[18] Angyal, S. J. Conformational analysis in carbohydrate chemistry. I. Conformational free energies. The conformations and α:β ratios of aldopyranoses in aqueous solution. *Aust. J. Chem*., **1968**, *21*, 2737-2746.

[19] Eijck, B. P.; Hooft, R. W. W.; Kroon, J. Molecular dynamics study of conformational and anomeric equilibria in aqueous D-glucose. *J. Phys. Chem.* **1993**, *97*, 12093-12099.

[20] Tvaroška, I.; Bleha, T. Anomeric and exo-anomeric effects in carbohydrate chemistry. *Adv. Carbohydr. Chem. Biochem.*, **1989**, *47*, 45-123.

[21] Bitzer, R. S.; Barbosa, A. G. H.; Silva, C. O.; Nascimento, M. A. C. On the generalized valence bond description of the anomeric and exo-anomeric effects: an *ab initio* conformational study of 2-methoxytetrahydropyran. *Carbohydr. Res*., **2005**, *340*, 2172-2184.

[22] Mo, Y. Computational evidence that hyperconjugative interactions are not responsible for the anomeric effect. *Nat. Chem.* **2010**, DOI: 10.1038/NCHEM.721

[23] Salzner, U.; Schleyer, P. R. Ab initio examination of anomeric effects in tetrahydropyrans, 1,3-dioxanes, and glucose. *J. Org. Chem.* **1994**, *59*, 2138-2155.

[24] Molteni, C.; Parrinello, M. Glucose in aqueous solution by first principles molecular dynamics. *J. Am. Chem. Soc.* **1998**, *120*, 2168-2171.

[25] Barrows, S. E., Dulles, F. J., Cramer, C. J., French, A. F., Truhlar, D. G. Relative stability of alternative chair forms and hydroxymethyl conformations of β-D- glucopyranose. *Carbohydr. Res.* **1995**, *276*, 219-251.

[26] Appell, M.; Strati, G.; Willett, J. L.; Momany, F. A. B3LYP/6-311++G** study of α- and β-D-glucopyranose and 1,5-anhydro-D-glucitol: $^4C_1$ and $^1C_4$ chairs, ^{3,O}B and $B_{3,O}$ boats, and skew-boat conformations. *Carbohydr. Res.* **2004**, *339*, 537-551.

[27] Rao, V. S. R., Qasba, P. K., Baslaji, P. V., Chandrasekaran, R. *Conformation of Carbohydrates*, Hardwood Academics: Amsterdam, **1998**.

[28] Corchado, J. C.; Sanchez, M. L.; Aguilar, M. A. Theoretical study of the relative stability of rotational conformers of α and β-D-glucopyranose in gas phase and aqueous solution. *J. Am. Chem. Soc.* **2004**, *126*, 7311-7319.

[29] Brown, J. W.; Wladkowski, B. D. *Ab initio* studies of the exocyclic hydroxymethyl rotational surface in α-D-glucopyranose. *J. Am. Chem. Soc.* **1996**, *118*, 1190-1193.

[30] Cramer, C. J.; Truhlar, D. G. Quantum chemical conformational analysis of glucose in aqueous solution. *J. Am. Chem. Soc.* **1993**, *115*, 5745-5753.

[31] Momany, F. A.; Appell, M.; Strati, G.; Willett, J. L. B3LYP/6-311++G** study of monohydrates of α- and β-D-glucopyranose: hydrogen bonding, stress energies, and effect of hydration on internal coordinates. *Carbohydr. Res.* **2004**, *339*, 553-567.

[32] Momany, F. A.; Appell, M.; Willett, J. L.;Bosma, W. B. B3LYP/6-311++G** geometry-optimization study of pentahydrates of α- and β-D-glucopyranose. *Carbohydr. Res*. **2005**, *340*, 1638-1655.

[33] Tvaroška, I.; Taravel, F. R.; Utille, J. P.; Carver, J. P. Quantum mechanical and NMR spectroscopy studies on the conformations of the hydroxymethyl and methoxymethyl groups in aldohexosides. *Carbohydr. Res.* **2002**, *337*, 353-367.

[34] Barnett, C. B.; Naidoo, K. J. Stereoelectronic and solvation effects determine hydroxymethyl conformational preferences in monosaccharides. *J. Phys. Chem. B* **2008**, *112,* 15450-15459.

[35] Spiwok, V.; Tvaroška, I. Metadynamics modeling of the solvent effect on primary hydroxyl rotamer equilibria in hexopyranosides. *Carbohydr. Res.* **2009**, *344*, 1575-1581.

[36] Woods, R. J. The Application of Molecular Modelling Techniques to the Determination of Oligosaccharide Solution Conformations. In *Reviews in Computational Chemistry*; Lipkowitz, K.B.; Boyd, D.B. Eds.; VCH: New York, **1996**, vol. *9*, pp.129-165.

[37] Hemmingsen, L., Madsen, D. E., Esbensen, A. L., Olsen, L., Engelsen, S. B. Evaluation of carbohydrate molecular mechanical force fields by quantum mechanical calculations. *Carbohydr. Res.*, **2004**, *339*, 937-948.

[38] Pérez, S., Imberty, A., Elgensen, S. B., Gruza, J., Mazeau, K., Jiménez-Barbero, J., Poveda, A., Espinosa, J-F., van Eyck, B. P., Johnson, G., French, A. D., Kouwijzer, M. L. C. E., Grootenius, P. D. J., Bernardi, A., Raimondi, L., Senderowitz, H., Durier, V., Vergoten, G., Rasmussen, K. A comparison and chemometric analysis of several molecular mechanics force fields andparameter sets applied to carbohydrates. *Carbohydr. Res*., **1998**, *314*, 141-155.

[39] Silva, C.O.; Menezes, A. O.; Coelho, A. V.; Paralovo, V. O.; Soares, C. S. Quantum Mechanical Calculations on Carbohydrates: what they Can Tell us? In *Strategies for the Determination of Carbohydrates Structure and Conformation*, Hugo Verli Ed.; Transworld Research Network : Kerala, **2010**; Chapter 1, pp. 1-37 (in press)

[40] Guvench, O.; Hatcher, E.; Venable, R. M.; Pastor, R. W.; MacKerell Jr., A. D. CHARMM additive all-atom force field for glycosidic linkages between hexopyranoses. *J. Chem. Theory Comput.,* **2009**, *5*, 2353-2370.

[41] Klein, R. A. Electron density topological analysis of hydrogen bonding in glucopyranose and hydrated glucopyranose. *J. Am. Chem. Soc.*, **2002**, *124*, 13931-13937.

[42] Polavarapu, P.L.; Ewig, C.S. *Ab initio* computed molecular-structures and energies of the conformers of glucose. *J. Comput. Chem*. **1992**, *13*,1255–1261.

[43] Appell, M.; Willet, J. L.; Momany, F. A. DFT study of α- and β-D-mannopyranose at the B3LYP/6-311++G** level. *Carbohydr. Res.* **2005**, 340, 459-468.

[44] Momany, F. A.; Appell, M.; Willett, J. L.; Schnupf, U.; Bosma, W. B. DFT study of α- and β-D-galactopyranose at the B3LYP/6-311++G** level of theory. *Carbohydr. Res.* **2006**, *341*, 525-537.

[45] Schnupf, U.; Willett, J. L.; Bosma, W. B.; Momany, F. A. DFT study of α- and β-D-allopyranose at the B3LYP/6-311++G** level of theory. *Carbohydr. Res.* **2007**, *342*, 196-216.

[46] Kurihara, Y.; Ueda, K. An investigation of the pyranose ring interconversion path of α-L-idose calculated using density functional theory. *Carbohydr. Res.* **2006**, *341*, 2565-2574.

[47] Barrows, S. E., Storer, J. W., Cramer, C. J., French, A. F., Truhlar, D. G. Factors controlling relative stability of anomers and hydroxymethyl conformers of glucopyranose. *J. Comp. Chem.* **1998**, *19*, 1111-1129.

[48] Suzuki, T.; Kawashima, H.; Sota, T. Conformational properties of and a reorientation triggered by sugar-water vibrational resonance in the hydroxymethyl group in hydrated β-glucopyranose. *J. Phys. Chem. B*, **2006**, *110*, 2405-2418.

[49] Nishida, Y.; Ohrui, H.; Meguro, H. 1H-NMR studies of (6R)- and (6S)-deuterated D-hexoses: assignment of the preferred rotamers about C5-C6

bond of D-glucose and D-galactose derivatives in solutions. *Tetrahedron Lett.*, **1984**, *25*, 1575-1578.

[50] Thibaudeau, C.; Stenutz, R.; Hertz, B; Klepach, T.; Zhao, S.; Wu, Q.; Carmichael, I.; Serianni, A. S. Correlated C-C and C-O bond conformations in saccharide hydroxymethyl groups: parametrization and application of redundant ^{1}H-^{1}H, ^{13}C-^{1}H, and ^{13}C-^{13}C NMR *J*-couplings. *J. Am. Chem. Soc.*, **2004**, *126*, 15668-15685.

[51] Ma, B., Schaefer III, H. F., Allinger, N. L. Theoretical studies of the potential energy surfaces and compositions of the D-aldo- and D-ketohexoses. *J. Am. Chem. Soc.*, **1998**, *120*, 3411-3422.

[52] Lii, J-H., Ma, B., Allinger, N. L. Importance of selecting proper basis set in quantum mechanical studies of potential energy surfaces of carbohydrates. *J. Comp. Chem.*, **1999**, *15*, 1593-1603.

[53] Silva, C. O., Vreven, T., Mennucci, B. Density functional study of the optical rotation of glucose in aqueous solution. *J. Org. Chem.*, **2004**, *69*, 8161-8164.

[54] Silva, C. O.; Mennucci, B. The optical rotation of glucose prototypes: a local or a global property? *J. Chem. Theory Comp*. **2007**, *3*, 62-70.

[55] Kongsted, J.; Mennucci, B.; Coutinho, K.; Canuto, S. Solvent effects on the electronic absorption spectrum of camphor using continuum, discrete or explicit approaches. *Chem. Phys. Lett.* **2010**, *484*, 185-191.

[56] Umeyama, H., Morokuma, K. The origin of hydrogen bonding. An energy decomposition study. *J. Am. Chem. Soc.*, **1977**, *99*, 1316-1332.

[57] Singh, U. C.; Kollman, P. A. A water dimer potential based on *ab initio* calculations using Morokuma component analyses. *J. Chem. Phys.*, **1985**, *83*, 4033-4040.

[58] Mo, Y.; Gao, J.; Peyerimhoff, S. D. Energy decomposition analysis of intermolecular interactions using a block-localized wave function approach. *J. Chem. Phys.* **2000**, *112*, 5530-5538.

[59] Miertus, S., Scrocco, E., Tomasi, J. Eletrostatic interaction of a solute with a continuum. A direct utilization of ab initio molecular potentials for the prevision of solvent effects. *Chem. Phys*., **1981**, *55*, 117-129.

[60] Cammi, R., Tomasi, J. Remarks on the use of the apparent surface charges (ASC) methods in solvation problems: iterative *versus* matrix-inversion procedures and the renormalization of the apparent charges. *J. Comp. Chem.*, **1995**, *16*, 1449-1458.

[61] Mennucci, B., Cancès, E., Tomasi, J. A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics. *J. Chem. Phys.*, **1997**, *107*, 3032-3041.

[62] Mennucci, B., Cancès, E., Tomasi, J. Evaluation of solvent effects in isotropic and anisotropic dielectrics and in ionic solutions with a unified integral equation method: theoretical bases, computational implementation, and numerical applications. *J. Phys. Chem. B*, **1997**, *101*, 10506-10517.

[63] (a) da Silva, C. O., Mennucci, B., Vreven, T. Combining microsolvation and Polarizable Continuum Studies: new insights in the rotation mechanism of amides in water. *J. Phys. Chem. A*, **2003**, *107*, 6630-6637; (b) Mennucci, B., Martinez, J. M., Tomasi, J. Solvent effects on nuclear shieldings: continuum or discrete solvation models to treat hydrogen bond and polarity effects? *J. Phys. Chem. A,* **2001**, *105*, 7287-7296; (c) Mennucci, B. Hydrogen bond versus polar effects: an *ab initio* analysis on n-pi* absorption spectra and N nuclear shieldings of diazines in solution. *J. Am. Chem. Soc*., **2002**, *124*, 1506-1515.

[64] Bondi, A. van der Waals volumes and radii. *J. Phys. Chem.*, **1964**, *68*, 441-451.

[65] Mennucci, B., Cammi, R. Eds. *Continuum Solvation Models in Chemical Physics: from Theory to Applications.* Wiley & Sons: USA, **2007**.

[66] Gaussian 03, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Wallingford CT, **2004**.

[67] GaussView 2.1, Gaussian, Inc. **2000**.

[68] Csonka, G.I. Proper basis set for quantum mechanical studies of potential energy surfaces of carbohydrates. *J. Mol. Struct. (THEOCHEM)*, **2002,** *584*, 1-4.

[69] Csonka, G.I., French, A. D., Johnson, G. P., Stortz, C. A. *J. Chem. Theory Comp.*, **2009**, *5*, 679-692.

[70] Angyal, S. J. The composition and conformation of sugars in solution. *Angew. Chem.*, **1969**, *8*, 157-166.

[71] Guler, L. P.; Ying-Qing, Y.; Kenttämaa, H. I. An experimental and computational study of the gas-phase structures of five-carbon monosaccharides. *J. Phys. Chem. A*, **2002**, *106*, 6754-6764.

[72] Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. Calculation of optical rotation using density functional theory. *J. Phys. Chem. A*, **2001**, *105*, 5356-5371.

[73] Campos, C. T.; Jorge, F. E.; Silva, T. P.; Coppo, M. R. Basis set convergence on optical rotation DFT calculations. *Chem. Phys. Lett.* **2010**, *494*, 170-173.

[74] Tsallis, C. *Introduction To Nonextensive Statistical Mechanics: Approaching A Complex World*. Srpinger-Verlag: USA **2009**.

[75] Mennucci, B.; Tomasi, J.; Cammi, R.; Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Gabriel, S.; Stephens, P. J. Polarizable continuum model (PCM) calculations of solvent effects on optical rotations of chiral molecules *J. Phys. Chem. A* **2002,** *106*, 6102-6113.

[76] Nimlos, M. R.; Qian, X.; Davis, M.; Himmel, M. E.; Johnson, D. K. Energetics of xylose decomposition as determined using quantum mechanics modelling. *J. Phys. Chem. A*, **2006**, *110*, 11824-11838.

[77] Andrade, R. R.; Silva, C. O. Manuscript in preparation.

[78] Kabayama, M. A.; Patterson, D.; Piche, L. The thermodynamics of mutarotation of some sugars.I. Measurement of the heat of mutarotation by microcalorimrtry. *Can. J. Chem.*, **1958**, *36*, 557-562.

[79] Höög, C.; Widmalm, G. Free energy simulations of D-xylose in water and methyl D-xylopyranoside in methanol. *J. Phys. Chem. B*, **2001**, *105*, 6375-6379.

[80] Angyal, S. J. Conformational analysis in carbohydrate chemistry. I. Conformational free energies. The conformations and α:β ratios of aldopyranoses in aqueous solution. *Aust. J. Chem.*, **1968**, *21*, 2737-2746.

[81] Schmidt, R. K.; Karplus, M.; Brady, J. M. The anomeric equilibrium in D-xylose: free energy and the role of solvent structuring. *J. Am. Chem. Soc.*, **1996**, *118*, 541-546.

[82] Mason, P. E.; Neilson, G. W.; Enderby, J. E.; Saboungi, M-L.; Brady, J. W. Neutron diffraction and computer simulation studies of D-xylose. *J. Am. Chem. Soc*., **2005**, *127,* 10991-10998.

[83] Mason, P. E.; Neilson, G., W.; Enderby, J. E.; Saboungi, M-L.; Brady, J. W. *J. Phys. Chem. B*, **2006**, *110*, 2981-2983.

[84] Bates, F. J. Polarimetry, Saccharimetry and the Sugars, NBS Circular C440**,** U.S. Government Printing Office, Washington D.C., **1942**, p. 762.

[85] Schnupf, U.; Willet, J. L.; Bosma, W. B.; Momany, F. A. DFT studies of the disaccharide α-maltose: relaxed isopotential maps. *Carbohydr. Res.*, **2007**, *342*, 2270-2285.

Received: March 29, 2010 Revised: August 13, 2010 Accepted: August 24, 2010