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Density Functional Study of the Optical Rotation of Glucose in Aqueous Solution

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Abstract: Optical rotation values were calculated for the eight most abundant structures of glucose in aqueous solution, following the TD-DFT/GIAO approach for the property and the PCM description for the solvent. The results show that all α structures give a large positive contribution to the OR property, while the *β* structures give both positive and negative contributions. The good agreement of the calculated OR, obtained as a Boltzmann average of the property of the eight conformers, with experimental data proves the validity of the quantum-mechanical approach and of the solvent modelization.

Historically, optical rotation (OR) has been the property associated with carbohydrates, due to the high number of chiral centers present in such compounds. Compared to other spectroscopic quantities, the experimental determination of OR values is relatively straightforward, and this has contributed to the extensive study of all saccharides by OR during the last century. Of course, OR has also been widely used to perform conformational analysis of flexible compounds other than saccharides. In the large majority of these studies, empirical relationships were used to relate the OR experimental values to the conformations of the compounds (for a recent review see ref 1), although semiempirical quantum-mechanical approaches have been developed as well.[2] Thanks to the enormous advances in computer power and algorithmic development, however, it is now routine to perform ab initio quantum-mechanical calculations for molecules as large as disaccharides,[3−5] and recently, these methods have been extended to the calculation of OR through the development of a variety of computational methods.[6−10]

Considering both the relevance of the OR property by itself and, in particular, in the conformational study of carbohydrates to validate structures theoretically obtained, in the present paper we investigate the possibility of obtaining the OR values for glucose in aqueous solution using accurate ab initio methods. This investigation has several intrinsic difficulties to be overcome, related to different aspects: the sensitiveness of the OR theoretical values to the computational method used, the suitable description of the solvent effects and finally the high flexibility of the system studied, that makes glucose occur in many different possible conformations. In the next paragraphs we will try to properly address each of these aspects.

Optical rotation calculations are very sensitive to the computational level and also depend strongly on the geometry of the compound. Stephens et al.[10] showed that the B3LYP-correlated hybrid functional combined with a suitable large basis set yields reliable results for rigid systems. For the OR property, the size of the basis set converges at aug-cc-pVTZ or 6-311++G(2d,2p). However, since these calculations would be very time demanding for systems as large as glucose, we decided to use two corresponding smaller basis sets (aug-cc-pVDZ and 6-31++G(d,p)) to compute the OR. As shown by Stephens et al., triple- and double-ζ "aug-cc" basis sets give very similar results, and we can expect the same behavior for the 6-311 and 6-31 basis sets because also here diffuse functions are kept in the smaller basis set.

To include solvent effects, we have used the integral equation formalism (IEF) version[11] of the polarizable continuum method (PCM).[12] The IEF-PCM scheme has recently been extended to compute OR of chiral systems in solution.[7] In the IEF-PCM the solute molecule, which is assumed to be hosted in a "cavity" inside a polarizable continuum dielectric, is treated quantum mechanically whereas the solvent polarization is described in terms of an induced surface charge on such a cavity. The shape of the cavity is obtained as the envelope of spheres centered on selected atoms of the solute and thus determined by the solute geometry. In the present case, we have placed spheres centered on each heavy atom (with radii equal to 2.40 Å for C and 1.80 Å for O) and on each hydroxyl hydrogen atom (1.44 Å). The presence of the solvent surface charge modifies the solute geometry and its wave function and thus, as a result, all its properties, including OR. Within the IEF-PCM scheme, the solvent effect is modeled in terms of proper operators to be added to the Hamiltonian of the isolated solute; as such operators are determined by the solvent surface charge which in turn is induced by the solute (and thus its depends on the solute geometry and wave function), the resulting problem to solve is nonlinear and the final

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solute and solvent states will be mutually polarized. All the calculations were performed with a development version of Gaussian01 computational code.[13]

Sampling the large conformational space of carbohydrates complicates the prediction of OR, especially when the energy differences of the most stable structures are of the same order as the accuracy of the theoretical models employed. Despite these difficulties, it has been determined that glucose occurs in aqueous solution with more than 99% as a six-membered pyranosic ring,[14] in a stable $^4C_1$ chair conformation.[15,16] Several ab initio studies have been reported on the orientation of the hydroxymethyl and hydroxyl groups. Barrows et al.[17] have selected the structures used in their work from a set of 729 different starting geometries obtained using the MM3(96) force field. They sampled the potential energy surface of glucose in the gas-phase, using a force field chemometrically tested.[18] This sampling resulted in a set of 13 final conformers, with the most stable ones being those that present the cooperative clockwise and anticlockwise orientation for the hydroxyl groups. Similar results were found by Ma and collaborators.[19] Polavarapu and Ewig[20] showed that conformations with this cooperative effect disrupted have higher energies and are therefore much less abundant.

When we pass to aqueous solution, experiments seem to indicate that this concerted structure of intramolecular H-bonds is perturbed by the presence of donor and acceptor H-bonding waters.[21] From a theoretical point of view, Cramer and Truhlar[22] investigated the hydroxyl rotamers of glucose in solution and found that despite the arrays of conjugated hydrogen bonds being "somewhat less well solvated than rotamers with disrupted hydrogen bonded patterns, still they are stable enough to be well populated in solution". In addition, previous studies on smaller systems have shown that solvent effects on anomeric equilibrium are primarily manifested as effects on the electronic relaxation, not on the geometrical relaxation.[23] More recently, Klein[24,25] showed that the hydroxyl groups can remain anticlockwise oriented in water even if intermolecular H-bond between some waters and the glucose hydroxyl groups are formed. Thus, the concerted clockwise and anticlockwise orientation of the hydroxyl groups does not necessarily exclude intermolecular hydrogen bonds with solvent; on the contrary, it confirms the importance of cooperativity effects also in aqueous solution.

On the basis of these analyses and also following the strategy defined by Barrows et al.,[17] we have here neglected the effects of the solvent on the geometry of each conformer, and used for both the gas phase and solution phase the structures obtained in gas phase. In particular, we have defined our final set of eight conformers by combining the six structures (αGG, αGT, αTG, *β*GG, *β*GT, and *β*TG) found by Allinger and co-workers as the most stable conformers in gas phase[19,26] and the two additional conformations found to be also important in the quoted study of Barrows et al.[17] and here named *β*GG′ and *β*GT′. We recall that the GG, GT, and TG labels refer to the orientation of the hydroxymethyl group. Considering the quoted conformational studies about glucose in the gas phase and aqueous solution, it seems that the set of gas-phase conformations is probably highly populated in solution, although the existence of other structures, in a solvated medium, different from those stable in the gas-phase cannot be excluded. At this point it would be important to stress that the procedure adopted in this work brings as tacit assumption that such missing conformations are less stable than those sampled in the gas-phase.

The geometries of all conformers were obtained in the gas phase at the B3LYP/6-31G(d,p)(5D) level. This same level was used to compute frequencies and thermal and entropic corrections to the free energy in the gas phase, while the B3LYP/6-311G++(2d,2p) level was used to obtain the energy ordering in the gas phase and in aqueous solution. The structures of the eight conformers used in this work are shown in Figure 1.

Aqueous solvation free energies and populations, using the gas-phase geometries, were then calculated for all the eight conformers; the corresponding quantities are reported in Table 1, together with the populations found by Barrows et al.[17] We recall that also in that work, the populations in solution were obtained by computing solvation energies on gas-phase geometries, but using a different solvation model (in our work we use the IEF-PCM method, while Barrows used SM/5.4[27]).

The results show that in aqueous solution four conformers (α-GT, α-GG, *β*-GT′, and *β*-GG) represent more than 75% of the glucose occurrence, of which about 55% is due to the two *β* anomers. We note that a similar result is obtained in gas-phase, but in this case the *β* conformers represent only 38%. This inversion may be attributed,

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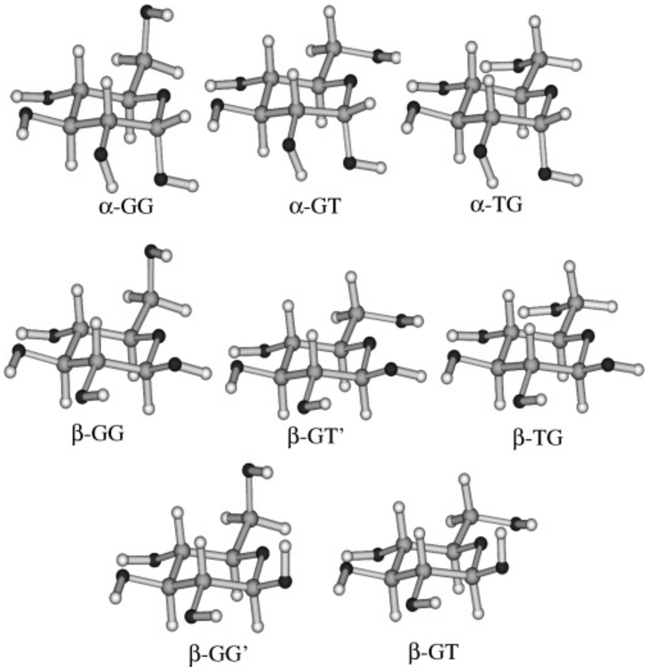
α-GG α-GT α-TG
β-GG β-GT' β-TG
β-GG' β-GT

FIGURE 1. Eight most stable conformers used to calculate OR of glucose in water.

TABLE 1. Relative Energies of the Glucose Conformers in Aqueous Solution at 298 K: *E* (Internal Energy in the Gas Phase), G^{corr} (Thermal and Entropic Corrections in the Gas Phase), G^{vac}(Gibbs Free Energy in the Gas Phase), δG_{solv} (Solvation Energy), G^{sol} (Gibbs Free Energy in Solution), in kcal/mol, and p_i, the Populations in the Gas Phase and in Aqueous Solution (%)

	ΔE	ΔG^{corr}	ΔG^{vac}	$\Delta\delta G_{solv}$	ΔG^{sol}	p_i^{gas}	$p_i^{gas\ 17}$	p_i^{sol}	$p_i^{sol\ 17}$
αGG	−0.09	−0.30	−0.39	−0.39	−0.78	21	25	15	11
αGT	−0.13	−0.35	−0.48	−0.48	−0.96	25	25	20	29
αTG[a]	0.0	0.0	0.0	0.0	0.0	11	12	4	2
βGG	0.67	−0.85	−0.18	−0.62	−0.80	15	14	15	7
βGT′	0.71	−0.84	−0.13	−1.00	−1.13	13	13	26	37
βTG	0.90	−0.60	0.30	−0.42	−0.12	7	5	5	3
βGG′	1.65	−0.90	0.75	−1.03	−0.28	3	3	6	9
βGT	1.18	−0.76	0.42	−0.90	−0.48	5	-	9	

[a] For the αTG conformer the absolute values are $E = -687.42621$ au, $G^{corr} = 101.45$ kcal/mol, and $G_{solv} = -687.44362$ au.

TABLE 2. Dipole Moments (in debye) of the Glucose Conformers in Aqueous Solution and in the Gas Phase[a]

	αGG	**αGT**	αTG	**βGG**	**βGT′**	βTG	βGG′	βGT
μ_i^{gas}	**3.575**	**2.727**	2.823	**3.482**	**2.907**	2.960	2.302	3.217
μ_i^{sol}	**4.610**	**3.460**	3.469	**4.506**	**3.606**	3.580	3.004	4.063

[a] The boldface columns identify the four most abundant conformers.

TABLE 3. Specific Rotations $[\alpha]_D$ Calculated in Aqueous Solution (in deg/(dm(g/cm^3)))

	aug-cc-pVDZ	6-31++G(d.p)
αGG	160.72	149.98
αGT	137.94	129.41
αTG	119.77	109.57
βGG	−10.16	−9.79
βGT′	−2.38	−4.03
βTG	−46.72	−46.76
βGG′	68.70	72.28
βGT	78.51	79.40
	62.56[a]	58.75[a]
Exp[29]	52.7	

[a] Boltzman weighted average.

in general terms, to the larger dipole moments of the β anomers compared to the corresponding α structures (see Table 2), what confers a higher stabilization of the β structures in polar solvents.[28] This effect is well-known experimentally, and confirms that the PCM solvation model can correctly describe the different solvation of β and α anomers qualitatively. However, it is important to notice that the electrostatic effects are not the only factor in determining the sensitive energetic balance among such structures, since the β-GT conformer has a higher dipole moment than the β-GT′, but is not more abundant than the latter one (see Tables 1 and 2); entropic and thermal corrections also play their role. Considering solvation and entropic and thermal corrections, from the population values reported in Table 1, all α anomers become less abundant in solution than they are in gas phase, while the β conformers present exactly an opposite trend. The only β conformer that does not follow this pattern is the TG one. Such hydroxymethyl orientation is not favored in solution, regardless the anomeric conformation. This may be an indication that the intramolecular hydrogen bond between the hydroxymethyl group and the oxygen atom of the pyranosidic ring is an important stabilizing effect of these structures, even in aqueous solution.

Furthermore, comparison of our gas-phase populations with those obtained with Barrow's composite level shows that the agreement is very satisfactory (the population of the conformer missing in Barrow's work is so small that it does not significantly affect the other populations). However, when we compare the populations of the solvated systems, the differences are larger, which is most likely the result of the different solvation models adopted in both works. Still, both approaches give the same qualitative description.

OR values were calculated for the eight structures in water following the TD-DFT/GIAO approach described previously.[7] The results obtained with two different basis sets are reported in Table 3 as specific rotation $[\alpha]_D$ calculated at the sodium D line frequency (we recall that the specific rotation $[\alpha]_D$ is the observed rotation that is corrected for concentration (g/mL) and a defined path length (dm), namely $[\alpha]_D = \alpha_{obs}/(c \times l)$).

The results show that all α structures give a large positive contribution to the global $[\alpha]_D$, while the β structures give both positive and negative contributions. However, the most abundant β anomers (βGT′ and βGG) always give a negative contribution to the $[\alpha]_D$ net value. From data in Table 3, it is also interesting to note that the sign of the $[\alpha]_D$ is closely related to the anomeric hydroxyl position: both β anomers with the hydroxyl group upward oriented (βGG′ and βGT) present a positive $[\alpha]_D$ value. A detailed analysis of the importance of the various conformers and their different chiral centers on the $[\alpha]_D$ of glucose will be presented elsewhere.[30]

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Comparison of the calculated Boltzmann weighted $[\alpha]_D$ values to the experiment is indeed quite good. We obtained 62.56 with the aug-cc-pVDZ basis set and 58.75 with the 6-31++G(d,p) basis set, which is fairly close to the experimental value of 52.7.[31] We note that the weighted values using gas-phase populations are 82.31 and 76.82, respectively. The shift is the result of the α population dominating in the gas phase, while the β population dominates in solution. Since both anomers have very different $[\alpha]_D$ values (including the sign, with the α anomers always large and positive), the inclusion of the solvent effects in the calculation of the relative energies of the various conformers is crucial. On the other hand, the solvation effect on the $[\alpha]_D$ of an individual conformer is less significant and, in fact, always less than 5%.

To complete the analysis, we have to note that a further solvent effect has been neglected here, namely that on the geometry of each conformer. However, this limit of our calculations can be considered of minor importance: the OR of glucose is in fact not a single-molecule property, but the result of a combination of contributions from different conformers. Therefore, the possible changes induced by the solvent on the geometry of each single conformer, and thus indirectly on its respective OR value, can be regarded as a second-order effect. Clearly this approach is valid only if no additional conformers appear in solution, i.e., if the set of gas-phase conformers still represents the most abundant structures in solution, which, in fact, seems to be exactly the case for glucose.[22,32]

Additionally, the validity of our approach is supported by the good agreement between the experimental and the theoretical OR values. From such an agreement, it can be inferred that the geometries of the most stable conformers seem to be determined by intramolecular stereoelectronic effects, which are already present in gas-phase structures, and that are not overwhelmed by environmental effects such as the solute–solvent interactions that takes place in aqueous solution.

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Supporting Information Available: Cartesian coordinates (in Å) and Electronic Energies (in au) for the eight conformers of glucose in the gas phase at the (B3LYP/6-311G++(2d,2p)//B3LYP/6-31G(d,p)(5D)) level. This material is available free of charge via the Internet at http://pubs.acs.org.

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