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Ab initio conformational maps in the gas phase and aqueous solution for a prototype of the glycosidic linkage

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Abstract. Ab initio conformational maps for methoxyethoxymethane (MEM) in both the gas phase and aqueous solution have been constructed using two different approaches. The results obtained allow us to conclude that a rigid conformational map is able to predict the regions of the minima, in the potential energy surface of MEM, in full agreement with those found in the relaxed conformational map, in both phases studied. This is a good indication that ab initio rigid conformational maps may be reliably used to sort the stablest conformers of disaccharides in aqueous solution. Besides that, in the MEM case, the solvation effects do not give rise to any new local minimum in its potential energy surface, but just change the relative energies of the stablest conformers found in the gas phase. This may be an indication that even in aqueous solution the anomeric effect is still the determinant effect defining the conformation of the molecule.

Keywords: Methoxyethoxymethane – Conformational map – Ab initio conformational map

Introduction

Carbohydrates are undoubtedly the most abundant class of organic compounds present in nature. They play several different roles in living organisms, for example, in molecular recognition and energy storage [1, 2]. For many years, the study of this important class of molecules has been a challenge to theoreticians, particularly the calculation of their molecular structure. The difficulty of finding the stablest structure when dealing with saccharides is due to the fact that in most cases they present a variety of conformers very close in energy.

Depending on the number of glycosidic units, the saccharides can be divided into monosaccharides, disaccharides, oligosaccharides and polysaccharides. We are particularly interested in studying the disaccharides, mainly those presenting a 1,4 glycosidic linkage (the numbering is related to the carbon atom of each monosaccharide unit involved in the linkage). Our main interest is to establish a reliable methodology to properly describe the most abundant conformers of disaccharides in aqueous solution.

Many important papers devoted to this aim have been published, but since it is not our intention to present a review on the subject, just a few of them, those closely related to the main goal of this paper, will be cited. The majority of the previous works used classical methods, such as molecular mechanics, to investigate the structure of the conformers [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. Many specific force fields have been developed, in order to describe particular interactions present in saccharides [14, 15, 16, 17, 18, 19, 20]. More recently, a few papers reporting ab initio procedures to study the conformation of saccharides have also appeared [21, 22, 23, 24].

According to many authors, the most important geometrical parameters of disaccharides are the dihedral angles of the glycosidic linkage [25, 26] (Fig. 1), although the orientation of the secondary hydroxyl groups, as well as the hydroxymethyl groups, is also needed to completely define the whole structure of all conformers. The hydroxyl groups may be responsible for a large density of minima in the disaccharide potential energy surface; however they are not as decisive as the angles ϕ and ψ in defining the stablest conformers. Therefore, we will be mainly interested in developing a fully ab intio strategy for finding such dihedral angles for the stablest conformers, assuming that the dihedral angles ϕ and ψ are the parameters that define the mutual orientation of the monosaccharide units.

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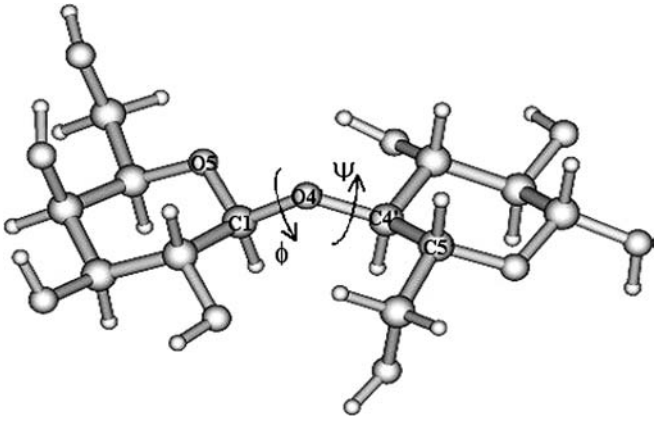

Fig. 1. β-Lactose, in the GGGG conformation of the methylene groups. The glycosidic linkage is defined by the values of the dihedral angles ϕ and ψ

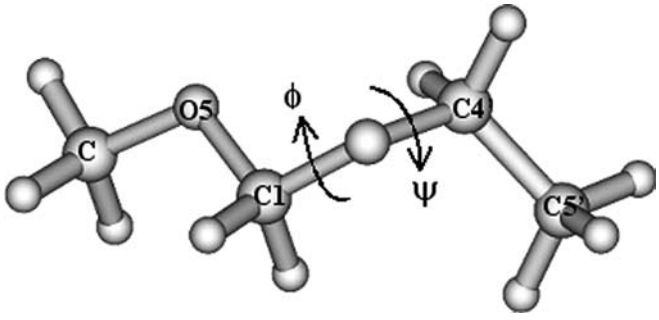

Fig. 2. Methoxyethoxymethane (*MEM*), used as a prototype for the glycosidic linkage. The glycosidic linkage is defined by the dihedral angles ϕ and ψ. The atom labeling is the same used for disaccharides

Our choice for ab initio procedures is justified by the nature of the interactions that define the dihedral angles of the glycosidic linkage. According to previous studies, it appears that while the ψ angle is determined by nonbonded interactions, the ϕ angle is defined by the exo-anomeric effect (Fig. 1) [26]. Both interactions are very difficult to take into account properly by classical procedures, since they are very specific and difficult to describe classically, as can be inferred from the detailed work by Woods [27, 28].

On the other hand, ab initio techniques are not so simple to use when dealing with compounds that present a variety of conformers. Conformational maps are difficult to access at this level since many local minima may exist, which can masquerade each other and also the global minimum. Thus, this possibility must be considered when making use of an ab initio procedure. Besides that, it is also important to remember that ab initio calculations are much more time-demanding than classical procedures such as molecular mechanics. Therefore, it would be desirable to establish an ab initio protocol, as simple as possible, to be used for systems as particular as disaccharides.

Since the angles (ϕ, ψ) are the most sensitive parameters in defining the stablest conformers of disaccharides, one could try to use a simpler molecule for establishing a protocol. For example, methoxyethoxymethane (MEM) in Fig. 2 can be viewed as a prototype of the glycosidic linkage. In Fig. 2 the dihedral angles are defined in the same sequence and using the same labeling for the disaccharide, in order to allow for future comparison. We believe that many exploratory tests can be quickly done using this prototype, and some important questions may be answered, before addressing a large system such as a disaccharide.

It is important to remember that this acyclic model cannot describe the asymmetry of conformational surfaces owing to steric interactions between the contiguous rings of a disaccharide. Therefore, one should not expect the minima in the conformational maps of MEM to occur for the same ϕ and ψ values found for a dissacharide [22].

2-Methoxytetrahydropyran (2-MTHP) is the molecule most frequently used in studies of conformational aspects of the anomeric effect [21, 29, 30, 31, 32, 33, 34]. Its cyclic structure can reproduce very well the intensity of the anomeric effect present in carbohydrates, and so their conformers obey the same energetic ordering generally found for conformers of monosaccharides. However, 2-MTHP was not considered by us the best prototype to be used in this preliminary step of methodological evaluation, since the main goal of this work is to investigate how the solvent affects the anomeric effect present on the solute, and if new structures, which are absent in the gas phase, are created owing to this new solute–solvent interaction. For this purpose, a smaller and much more flexible compound, such as MEM, but that still manifests the anomeric effect, would be more indicative.

In the next section we describe the procedure employed in the calculation of the ab initio conformational map of MEM, in both gas and solution phases. As previously mentioned, our intention is to investigate the possibility of adopting the rigid-residue approximation to generate reliable conformational maps at ab initio level, and also to check if this approximation can be used when solvation effects are taken into account. Since MEM is one of the simplest structures that presents the anomeric effect, it is our intention to verify in which way this effect is modified (and consequently the conformational map) by the presence of the solvent. Thus, relaxed and rigid conformational maps were calculated for MEM, in the gas phase and in aqueous solution.

Methodology

Conformational maps were calculated for MEM in both gas and solution phases, at the HF/6-31G(d,p) level of calculation. According to Lii et al. [35], this basis set, in a 5D form, at the B3LYP level of calculation, gives reasonably good structures but it overestimates the stabilization by hydrogen bonding. They also suggested that by using diffuse functions and a larger basis

(B3LYP/6-311 + + G**), most of the basis set superposition errors can be avoided. Before that, Csonka et al. [36] established the importance of considering diffuse functions to avoid errors in calculating the energy when electronic correlation effects are taken into account. Since the main purpose of the present work is to establish the simplest possible ab initio protocol to generate reliable conformational maps for disaccharides, and since this will necessarily involve the construction of many conformational maps, we adopted the HF/6-31G(d,p) level of calculation.

To introduce the solvent effects we used the polarizable continuum model [37, 38], in its integral equation formalism formulation [39, 40]. In this approach, the solvent is described as a dielectric continuum medium, polarized by the presence of the solute. A term representing the electrostatic interaction between the solute and the solvent is added to the solute Hamiltonian. The resulting equation, solved self-consistently, furnishes the electrostatic contribution to the solvation energy and the solute wave function modified by the solvent due to the mutual polarization. In this model the solute molecule is placed inside a cavity, opened in this dielectric, whose shape takes into account the geometry of the molecule. The polarization charges that mimic the solvent polarization due to the presence of the solute are located on the surface of such a cavity. In the present case, the molecular cavities were built from interlocking spheres centered on selected atoms or groups of atoms. The radii of the spheres were 2.28 Å for CH or a CH_2 group, 1.80 Å for an oxygen atom and 1.44 Å for hydrogen bonded to the oxygen atom of the hydroxyl groups.

All the gas-phase calculations were performed using the Jaguar program [41], and for the calculations in solution we used the Gaussian98 code [42]. The conformational maps were generated from the interpolation of the respective energy data set, using the radial basis function method [22], unless otherwise specified.

Results and discussion

Relaxed conformational map in the gas phase

According to the methodology previously described, a conformational map, in the gas phase, was built by scanning the angles ϕ (O5–C1–O4′–C4′) and ψ (C1–O4′–C4′–C5′) over an entire cycle, in intervals of 30° for each angle. The starting geometry was obtained from a fully optimized structure calculated at the HF/6-31G(d,p)/ level, whose geometrical parameters are reported in Table 1.

For each pair of (ϕ,ψ) values kept fixed, all the other geometric parameters were reoptimized. The starting geometry used in each step was the optimized structure obtained from the preceding one. The potential energy surface generated according to this procedure will be called from now on a ''relaxed conformational map''. The conformational map obtained from interpolation of the aforementioned data, using the radial basis function method [22], is shown in Fig. 3.

From Table 1, the geometrical parameters indicate that the starting structure is very close to that of the (ap,−sc) [43] conformer of 2-MTHP, which is the second or the third stablest structure (depending on the level of calculation) [44], among the six possible conformers. The stablest conformer of 2-MTHP is (+sc,+sc), in which the methoxy group is in the axial position. However, we decided to use the MEM structure with the methoxy group in the equatorial arrangement because having a higher dipole moment than the one with the methoxy group in the axial arrangement it would interact more effectively with the solvent (water). Therefore, any modifications of the conformational map of MEM due to solvent interactions would be surely magnified in the ''equatorial conformer''.

From the data in Table 1, it can be observed that among all bond distances reported for the MEM structure, the C1–O4′ is the shortest one. This same pattern is observed in 2-MTHP, as can be seen from the data reported. Therefore, we believe that the shortening of the C1–O4′ bond can be a reliable indication of the presence of the anomeric effect [37] in this small prototype.

From Fig. 3 one can clearly identify two minima, in a very symmetrical map, both inside a region containing conformers which differ by at most 1.0 kcal/mol from the global minimum, defined by $\phi = 300°$ and $\psi = 180°$. The ϕ angles that define such local minima are around 60° and 300° (or −60°). These values are in full agreement with the manifestation of the exo-anomeric effect, that stabilizes preferentially the gauche conformations,

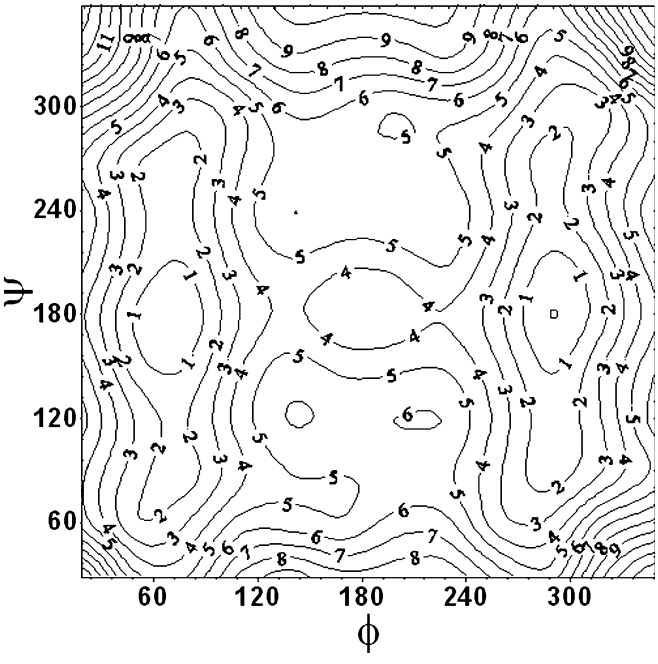

Fig. 3. Relaxed conformational map calculated for MEM at the HF/6-31G(d,p) level (144 points) in the gas phase. Energy in kilocalories per mole

Table 1. Geometrical parameters of the starting methoxyethoxymethane (*MEM*) structure, optimized in the gas phase. The distances are in angstroms and the angles in degrees. *2-MTHP* is 2-methoxytetrahydropyran

Parameter	MEM	2-MTHP		
	HF/6-31G(d,p)	HF/6-31G(d,p) [45]	MP2/6-31(d) [32]	B3LYP/6-31G(d,p) [34]
C–O5	1.393	1.403	1.430	1.428
O5–C1	1.390	1.398	1.426	1.414
C1–O4′	1.368	1.372	1.392	1.373
O4′–C4′	1.411	1.401	1.428	–
C4′–C5′	1.521	–	–	–
C–O5–C1–O4′	178.76	179.30	178.00	177.70
O5-C1-O4′-C4′	288.65	296.90	297.50	–
C1-O4′-C4′-C5′	267.79	–	–	–

which are also labeled as (ap, + sc = 60°) and (ap,−sc = 300°) [25, 43, 44]. The ψ angle is practically the same for both minima, and has a value of approximately 180°; however, the ϕ angle can be more precisely defined than the ψ angle because, on the potential surface energy shown in Fig. 3, the energy gradient along the ϕ direction is much more pronounced than in the ψ direction. This is due perhaps to the difference in the magnitude of the effects that define each of these two angles. It is important to emphasize that one cannot know precisely which structure is the global minimum, not only because their energy differences are below the limit of the accuracy of a Hartree–Fock calculation but also because we are dealing with energy differences of structures that have not been fully optimized (the dihedral angles are kept frozen).

Rigid conformational maps in the gas phase

The results obtained from the map of Fig. 3 are in conformity to what would be expected for MEM just based on our knowledge about the preferred conformers of saccharides. However, since the calculation of a relaxed conformational map is very time demanding for disaccharides, it would be convenient to examine the possibility of constructing approximate maps that are qualitatively as good as the relaxed ones. For this purpose a conformational map was constructed, considering just variations of the two dihedral angles (ϕ,ψ) that define the glycosodic bond, within the rigid-residue approximation. This approximation is based on the assumption that the effects which define the optimum dihedral angles are strong enough to manifest themselves even when a geometry relaxation is not allowed. The starting geometry was the same used in the previous case. Again intervals of 30° were considered for each angle, and the structures obtained were not optimized. A set of 144 single-point calculations, performed at the HF/6-31G(d,p) level, generated the grid values used to construct the map, using the same interpolation scheme previously described. The respective rigid conformational map that arises from this rigid-residue approximation is shown in Fig. 4.

The first point to be noted when comparing Figs. 3 and 4 is that the positions of the two most pronounced minima in the relaxed map are reproduced in the rigid approximation. In this rigid approximation, one of the minima ($\phi = 300°$, $\psi = 175°$) occurs in a region of lower energy than the other ($\phi = 60°$, $\psi = 175°$). Additionally, in the rigid map the contour lines correspond to higher values of energy. This was expected since geometry relaxation was not allowed. The conformers with the highest energies are found for ϕ and ψ values close to 0° (or 360°), owing to the strong steric repulsion between the hydrogen atoms bound to the C1 and to the C4 atoms.

The region around 180°, for both dihedral angles, also presents some differences when compared with the respective region in the map of Fig. 3. The barrier between the two stablest structures seems to be not so well described in the rigid approach.

It would also be interesting to evaluate the effect of improving the interpolation grid by using a larger amount of data to be interpolated. For this purpose, a new enriched map was obtained, using a step of 8° for the angles ϕ and ψ. A set of 2,025 points was obtained, and the conformational map generated from the inter-

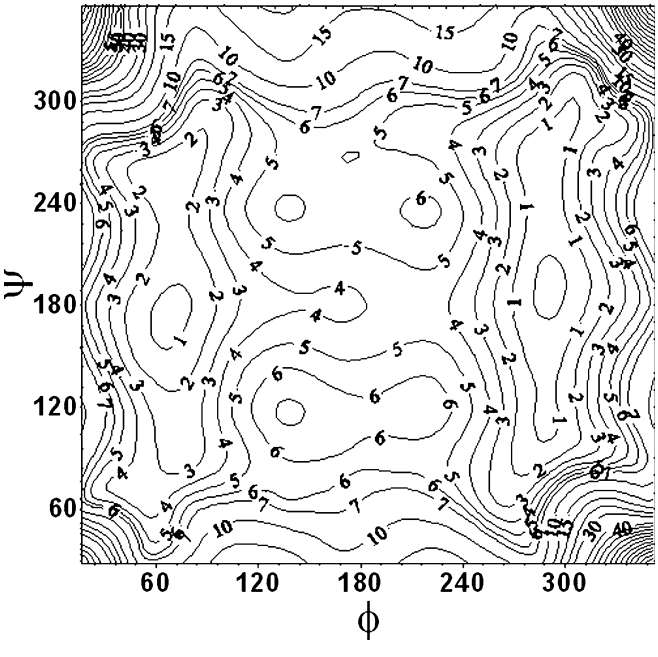

Fig. 4. Rigid conformational map calculated for MEM at the HF/6-31G(d,p) level (144 points) in the gas phase. Energy in kilocalories per mole

polation of these data is exhibited in Fig. 5. It is important to mention that the interpolation procedure adopted had to be modified owing to this new enriched set of data. For this case, since the energy values are very close together, a triangulation with linear interpolation procedure was adopted.

Again, as in the two previous maps, the position of the minima remained unchanged, although this rigid approximation map still presents contour lines higher in energy than those of the relaxed map (Fig. 3). The depths of the resulting minima are practically the same as the ones observed in the map of Fig. 4, where 144 points were used in the interpolation. Thus, it can be concluded that the map of Fig. 4 is accurate enough for our purposes of locating the minima in the conformational map. Thus, by comparing Figs. 3, 4 and 5, it can be said that the rigid-residue approximation can be used, instead of the relaxed conformation approach, to properly locate the most stablest structures on the conformational map of MEM in the gas phase.

On the other hand, disaccharides are larger systems than MEM, and care must be exercised before making any generalization. However, the results obtained for MEM certainly encouraged us to perform similar studies for a disaccharide [46].

Relaxed conformational map in aqueous solution

The procedure used to calculate the conformational maps for MEM in the gas phase was rigorously repeated in aqueous solution. The starting structure obtained in a vacuum (Fig. 2, Table 1) was solvated and the scans of the dihedral angles ϕ and ψ were performed, with increments of 30° for each angle. All the geometrical parameters were relaxed for each of the 144 calculations, except the dihedral angles.

To introduce the solvent effects we used the polarizable continuum model [31, 32, 33, 34], as discussed in Sect. 2. The map obtained is shown in Fig. 6, from which we can see that the locations of the stablest structures appear approximately in the same regions where they occur in the gas phase (Fig. 3). It seems that, for MEM, the interaction with the solvent does not generate a structure different from the structures found in the gas phase, which are believed to be stabilized owing to the anomeric effect. On the other hand, some changes are noticeable in the region between the conformers: in the map of Fig. 6, this region is much shallower than that in Fig. 3. This result suggests that the interaction with the solvent facilitates the interconversion of the stabilized forms, probably leading to a concentration ratio between the two stable structures in aqueous solution somehow different from that observed in the gas phase.

Tvaroška and Pérez [45] have showed that the use of a starting geometry that corresponds to a local minimum can influence the shape of the potential energy surface of the compound by overstabilizing conformers in regions closer to that minimum. In order to avoid such a possibility, which could compromise the comparison between the maps in the gas phase and in aqueous solution, when constructing the map of Fig. 6 we avoided starting the scanning of the dihedral angles from the fully optimized structure in solution. However, in order to check how different

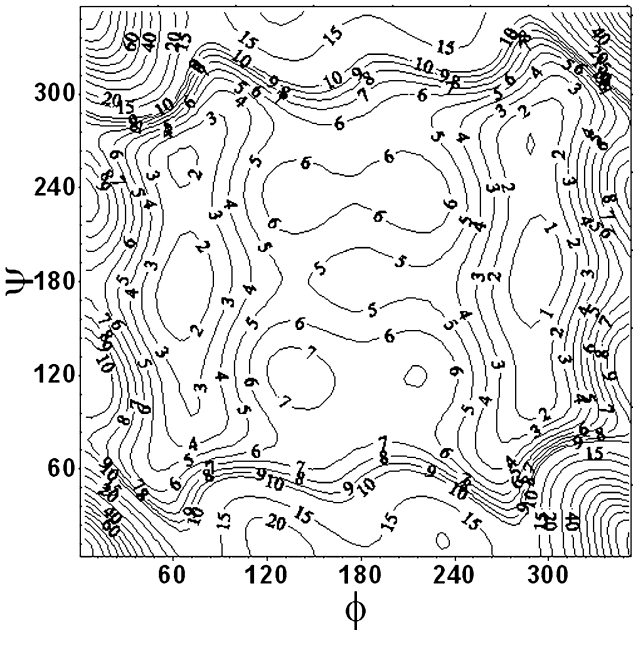

Fig. 5. Rigid conformational map calculated for MEM the at HF/6-31G(d,p) level (2,025 points) in the gas phase. Energy in kilocalories per mole

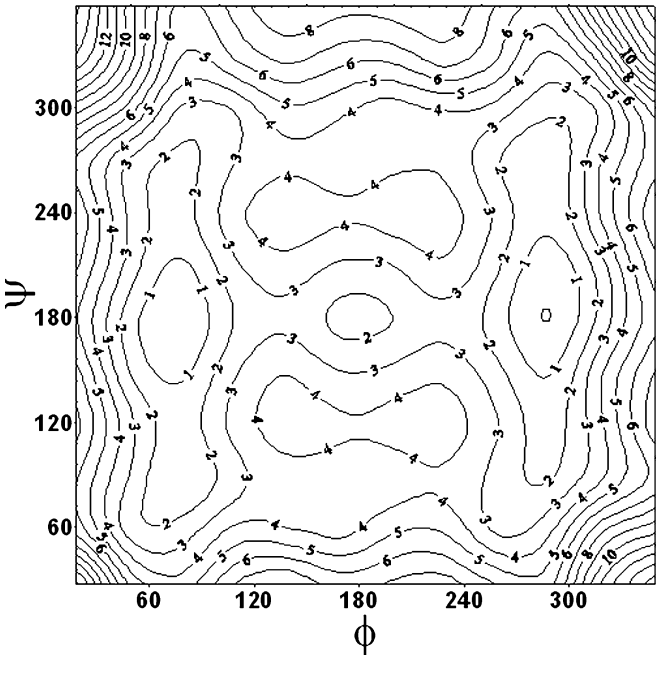

Fig. 6. Relaxed conformational map calculated for MEM at the HF/6-31G(d,p) level (144 points) in aqueous solution. Energy in kilocalories per mole

Table 2. Geometrical parameters of the starting MEM structure, optimized in aqueous solution in two different ways. The distances are in angstroms and the angles in degrees

Parameter	MEM[a]	MEM[b]
C–O5	1.402	1.402
O5–C1	1.393	1.394
C1–O4′	1.375	1.375
O4′–C4′	1.417	1.417
C4′–C5′	1.520	1.519
C–O5–C1–O4′	176.46	177.26
O5–C1–O4′–C4′	288.65	282.91
C1-O4′-C4′-C5′	267.79	267.91

[a]HF/6-31G(d,p) calculation, keeping the ϕ and ψ angles frozen. This is the starting structure used to generate the set of 144 points calculated in solution
[b]HF/6-31G(d,p) calculation, relaxing all geometrical parameters including the ϕ and ψ angles

this structure would be from the one used to construct the map, we considered a full optimization in aqueous solution of the structure obtained in a vacuum. Some geometrical parameters of both structures are given in Table 2.

As can be seen from the results in Table 2, there are no appreciable differences between the two structures considered. The angle ϕ is the parameter most affected by the optimization of the dihedral angles, and even so the difference observed is just approximately 6°. In both solvated structures, the shortest bond is still between the C1 and O4′ atoms, a clear manifestation of the anomeric effect.

Rigid conformational map in aqueous solution

The rigid conformational map in solution was obtained following the same procedure used in the gas phase as described in Sect. 3.2, and including the solvent effects in exactly the same way as described in Sect. 3.3. The resulting map is shown in Fig. 7.

Again, no appreciable differences can be observed in this conformational map when compared with those obtained in the gas phase or even with the relaxed map in solution with regard to the location of the minima. However, as expected, in general the contour lines of Fig. 7 have higher energy values than those found for the map of Fig. 6, particularly in the region between both minima. Thus, one should not expect the barrier for interconversion to be well reproduced with the rigid model.

Conclusions

Ab initio conformational maps for MEM, in gas and solution phases, have been constructed at the HF/6-31G(d,p) level of calculation.

The results of the gas-phase ab initio calculations allow us to conclude that a rigid conformational map is able to predict the regions of the minima in the potential

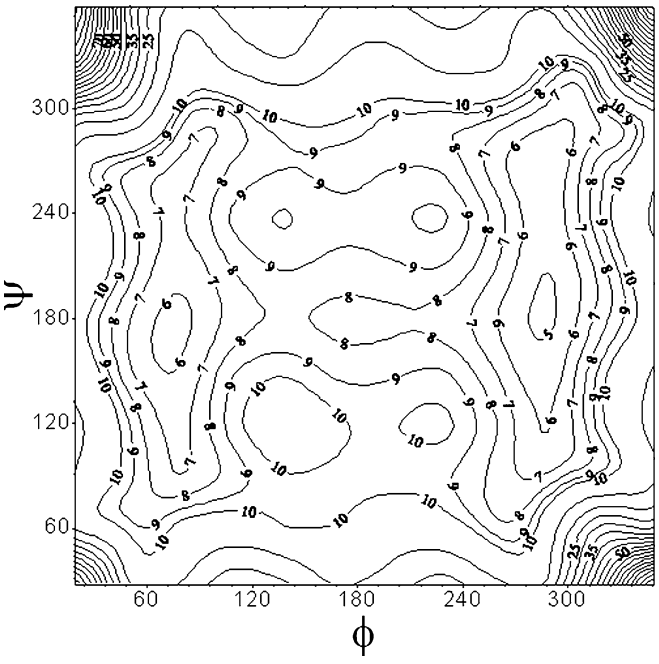

Fig. 7. Rigid conformational map calculated for MEM at the HF/6-31G(d,p) level (144 points) in aqueous solution. Energy in kilocalories per mole

energy surface in full agreement with those found in the relaxed conformational map.

Inclusion of the solvent effects does not change the location of the minima in the conformational maps regardless of the approach used to construct them: the rigid-residue approach or the relaxed approach. Also, the fact that including the solvent effects does not give rise to a new local minimum in the potential map may be an indication that these effects are not able to overcome the anomeric effect that ultimately defines the glycosidic orientation. Similar results were obtained by Cramer and Truhlar [47] for glucose, a cyclic compound that is more rigid than MEM. These findings strongly suggest that the procedure adopted may be very useful for determining the stablest conformers of disaccharides using rigid conformational maps, whose construction is much less time-demanding than for the relaxed maps. On the other hand, barriers for interconversion among conformers may not be well reproduced by the rigid maps.

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