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Carbohydrate Research 273 (1995) 129–145

CARBOHYDRATE RESEARCH

A theoretical study of D-glucose, D-galactose, and parent molecules: solvent effect on conformational stabilities and rotational motions of exocyclic groups

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Received 5 May 1994; accepted 14 February 1995

Abstract

D-Glucopyranose and D-galactopyranose, in their α and β forms, together with some of their mono- and di-substituted parent molecules, were investigated theoretically in order to evaluate the solvent effect on the differential stability of various regions of the potential surfaces. In particular, the aim of this study was to evaluate the solvent effect on the conformational stabilities and the possibility of wide oscillations and/or correlated motions of exocyclic groups in the presence of water. Energies of molecules in aqueous solution were calculated by the polarizable continuum model in conjunction with the semiempirical AM1 method. Water as solvent favours the *anti* conformation of the exocyclic hydroxyl groups (except the anomeric one), mostly reduces the oscillation amplitude, and lowers the barriers to the rotation of the hydroxymethyl group. Concerted motions of exocyclic groups imply barriers which are somewhat higher, especially in galactose.

Keywords: Monosaccharides; Tetrahydropyrans; Solvent effect; Hydrogen bond; Conformations

1. Introduction

Carbohydrates are of great importance in biological systems. In particular, D-glucopyranose and D-galactopyranose are components of oligosaccharides, glycolipids, and

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SSDI 0008-6215(95)00109-3

glycoprotein chains, and participate in all processes occurring in biological membranes as receptors. Moreover, their structure plays an important role in modifying the properties of such membranes [1,2]. Therefore, when studying the surface properties of glycolipid heads it is necessary to investigate possible correlated motions of the carbohydrate groups, especially in aqueous solution, since they can affect the interaction between oligosaccharide chains anchored at the membrane surfaces, so governing their main folding with consequent effects on the physico-chemical properties of biological membranes [3]. On that account an accurate knowledge is required of the relative weighting of the various energy contributions in the motions of such groups. In other words, we need to perform an energy balance, paying particular attention to hydrogen bond strengths and solvation energies.

Many experimental and theoretical studies concerning mainly the conformational flexibility of the ring and of the glycosidic bond (anomeric effect) of carbohydrates are available in the literature [4]. Calculations on the conformations of mono- and oligo-saccharides as isolated molecules have been performed at various levels of approximation, following improvements in the performance of computers and theoretical approaches, ranging from empirical [5–7] to molecular mechanics [8–12], semiempirical quantum mechanical [13–17], ab initio [18–22], Monte Carlo [23,24], and molecular dynamics [25–30] methods.

Estimations of the rotation barriers and the relative stability of α and β anomers of D-glucopyranose were performed by semiempirical quantum mechanical methods such as CNDO and PCILO [17]. Recent studies of the hydroxyl torsion potentials in some mono- and di-substituted tetrahydropyrans in vacuum [31] and of the relative stabilities of various possible isomers of α- and β-D-glucopyranose in vacuum [22] demonstrated that various conformations having similar energies, stabilized by weak intramolecular hydrogen bonds, are possible.

In the earlier studies, the solvent effect was evaluated by various continuum models, following the Onsager approximation [17]. Indeed, evaluation of solvent effects has been shown to be a crucial problem, especially for this class of compound, in which the conformational preferences are undoubtedly due to a delicate balance of different energetic contributions, among which the mutual interactions between highly polarized groups (exocyclic OH groups) and solvent molecules are particularly important. It has also been clear from free energy simulations [29] of D-glucopyranose that solvent could be a determinant factor in reversing the relative stabilities of α and β forms, although the choice of the function describing the solvent can produce differing results [21,22] in molecular dynamics simulations.

The aim of the present paper is to quantify the differential stability of various regions of the potential surfaces as a function of rotation of the exocyclic groups in order to evaluate whether wide group rotations and/or correlated motions characterized by low rotation barriers are possible in the presence of water. In particular, we carried out conformational calculations on the various conformations of some mono- and di-substituted tetrahydropyrans and of D-glucopyranose and D-galactopyranose as their α and β anomers, paying particular attention to the evaluation of the rotational barrier both in vacuum and aqueous solution.

2. Calculations

In Fig. 1, the $^4C_1$ conformation of β-D-glucose is schematically drawn together with the numbering system and the rotational symbolism adopted. For uniformity, the same numbering system is maintained in the substituted tetrahydropyrans.

The conformational energies of all conformers in the vacuum phase were evaluated by the semiempirical AM1 method available in the MOPAC computational package distributed by QCPE [31]. One could question the use of semiempirical methods in the conformational analysis of such molecules. It is well known that highly reliable results can be obtained only by ab initio calculations with extended basis sets and inclusion of polarization functions and evaluation of the correlation energy, but it is also evident that in the present case such analysis is nearly impracticable. Comparison between results from various semiempirical approaches and the most popular ab initio methods have been made on some glycosides [21,32]. In general, it can be inferred that the use of minimal basis sets leads to results whose reliability can be comparable with that of the most recent semiempirical methods, even if sometimes ab initio and AM1 results do not match well (e.g., it has been noted that AM1 tends to favor the *anti* conformations in some hydroxy derivatives of tetrahydropyran [21]). On the other hand, it has been found

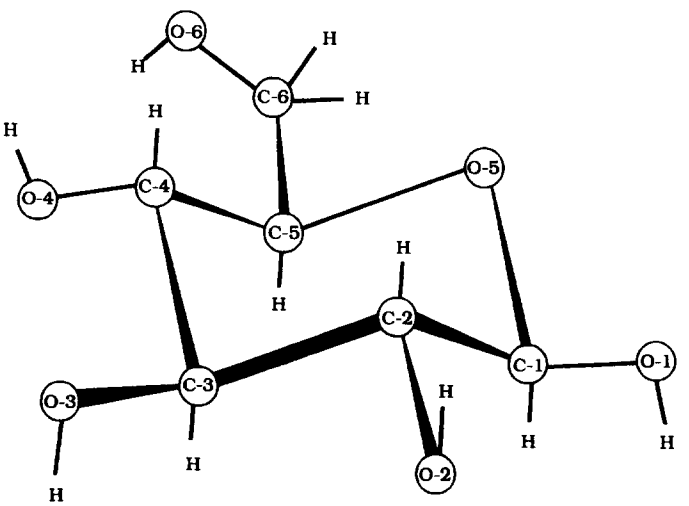

Fig. 1. β-D-glucopyranose and numbering system. All the other molecules discussed in the present paper can be obtained from this picture by suitable position changing or elimination of oxygen atoms. Symbols for the various rotamers are the following (counterclockwise rotation, starting from the eclipsed conformation, is assumed to be positive):

C-4–C-5–C-6–O-6	0–120	*GG*	C-5–C-6–O-6–H	0–120	g^+
	120–240	*GT*		120–240	*t*
	240–360	*TG*		240–360	g^-

For the H–C–O–H torsion angles the same symbolism as for C-5–C–O–H is adopted. The C-4–C-5–C-6–O-6 torsion angle is zero when the C-6–O-6 bond eclipses the C-4–C-5 bond. The C-5–C-6–O-6–H torsion angle is zero when the HO-6 bond eclipses the HC-5 bond.

that AM1 is able to describe weak hydrogen bonds [33,34] sufficiently well; it works less well in describing very strong hydrogen bridges [35] (i.e., characterized by O · · · O distances shorter than 2.5 Å). On these grounds, we adopted the AM1 method because, on the whole, it is sufficiently reliable for the main aim of the present investigation, which is to evaluate the possibility of free rotation or in-phase motion of OH groups in monosaccharides, especially in the presence of aqueous solvent.

Energies of molecules in solution were calculated following the dielectric continuum model; i.e., the total Gibbs energy was put equal to the total energy of the isolated molecule plus a contribution due to solvation. The latter includes the electrostatic solute–solvent interaction, the cavitation energy, and a contribution deriving from dispersion forces. The electrostatic interaction energy was evaluated following the polarizable continuum model [36,37] with a realistic description of the solvent cavity which modifies its shape to accommodate best the different conformers of solute [38].

The choice of a structureless continuum model of solvation could appear inadequate when applied to H-bonding systems. However, a comparison between continuum dielectric models and calculations of molecular aggregates showed that structureless models give a satisfactory description of these interactions [39] giving good results in a fairly wide variety of problems (for a concise overview of the theoretical model based on the continuum distribution of solvent molecules see ref. [40]).

Cavitation and dispersion contributions to solvation energy were calculated in the usual approximate way [41]. Interestingly, the cavitation and dispersion energies compensate each other and their values remain nearly unchanged for all conformers. In the present case, the major contributor to the solvation energy is the electrostatic term.

Bond distances and bond angles were fully optimized and the chair form was imposed on the ring skeleton throughout all calculations. In drawing energy curves and maps, the torsional angles were varied with steps of 30°, giving 144 calculated grid points for each map.

3. Results and discussion

To rationalize the effects of the various interactions, which involve the functional groups with themselves and with the solvent, on the relative stabilities of the conformers and on the motions of the pendant groups, the present study is divided into two sections.

In the former we examine the rotation of the anomeric OH group in axial as well as in equatorial position, in vacuum and in aqueous solution. Thereafter, we analyze how much the rotational motion of each hydroxyl group is affected by a vicinal OH group. Moreover, the minimum energy conformations and the possibility of internal motions of the CH_2OH framework are examined on the grounds of the isoenergetic maps. Successively, such maps were drawn for conformations having suitable orientations of the OH group bound to C-4 (see Fig. 1), both in the axial and equatorial positions (in gas as well as in solution phases).

In the latter section the energies of the most stable conformations and some possible interconversion pathways were analyzed for α- and β-D-glucose and α- and β-D-galactose, taking into account the solvent effect.

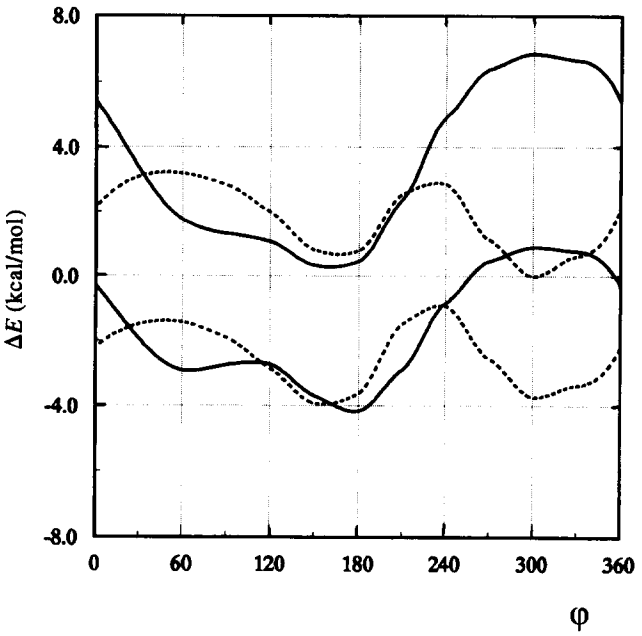

Fig. 2. Potential energy curves (relative energy values) for the HO-1 rotation (φ) in "1-hydroxy-tetrahydropyran" ($\cdots$, axial isomer; ———, equatorial isomer). Upper curves refer to vacuum, the lower curves to solution. The torsion angle is zero when the O–H bond eclipses the C–H bond.

Tetrahydropyran-2-ol ("1-hydroxy-tetrahydropyran") [1].—In vacuum, rotation of the anomeric hydroxyl group (HO-1 in our numbering system) gives (when it is in axial position) two minimum energy points (Fig. 2, dashed line): $\varphi = -60°$ (g^-) and 165° (t). The former is ca. 0.5 kcal/mol lower in energy, and located in a rather wide valley; it is characterized by the OH bond pointing toward the ring oxygen. The related barriers are ca. 3.1 and 3.4 kcal/mol, respectively. The presence of the solvent causes the inversion of the previous stability order so that the t form becomes 0.3 kcal/mol more stable than the g^- one, with barriers of 3.3 and 2.7 kcal/mol, respectively.

When OH is in equatorial position, its rotation produces (in vacuum) a very wide well ranging from 60° to 200°, with a minimum at 165° (t) and an inflection at 75° (Fig. 2, full line). This means that the anomeric OH group can undergo wide oscillations. The barrier was evaluated to be 6.7 kcal/mol. In the presence of solvent the t conformation is stabilized and the inflection becomes a local minimum (g^+, $\varphi = 75°$ and $\Delta E = 1.2$ kcal/mol) which can be reached by overcoming a barrier of 1.6 kcal/mol ($\varphi = 110°$).

It should be pointed out that the orientation of the OH group in the minima indicates that the H-bridge with the ring oxygen is so weak that it is not able to counterbalance the torsion barrier.

[1] The hydroxyl group corresponds to the anomeric hydroxyl group in glucose and galactose.

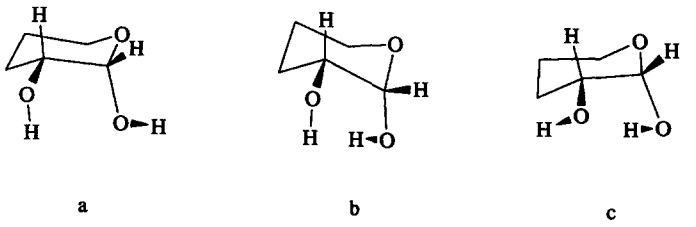

Fig. 3. Pattern of proton orientation of hydroxyl groups for "1,2-dihydroxy-tetrahydropyran" minimum energy isomers (a) g_1^-,t_2; (b) t_1,t_2; (c) g_1^+,g_2^+.

The most interesting effect of solvent is observed in the relative stability of the axial and equatorial isomers. In fact, whilst in the gas phase the former is 0.45 kcal/mol more stable than the equatorial one, in solution the equatorial becomes 0.15 kcal/mol more stable than the axial isomer, confirming the importance of solvent on the anomeric equilibrium, as found experimentally [42–44] and in other theoretical works [25–30]. Indeed, it has been found that the free energy difference between axial and equatorial alkoxytetrahydropyrans is close to 0.9 kcal/mol in solvents with low dielectric constants, the former being more stable [42,43], while there is evidence that the stability of the two conformers is equal, or indeed reversed, in water [44].

Tetrahydropyran-2,3-diols ("1,2-dihydroxy-tetrahydropyran").—The OH group attached to C-3 (corresponding to C-2 in the numbering used in this paper) was considered only in the equatorial position, as occurs in glucopyranose and galactopyranose. The axial anomeric isomer in vacuum shows a minimum for the g_1^-,t_2 ($\varphi = -53°$, $\psi = 179°$, see Figs 3a and 4a) conformation, and two other minima for the t_1,t_2 and

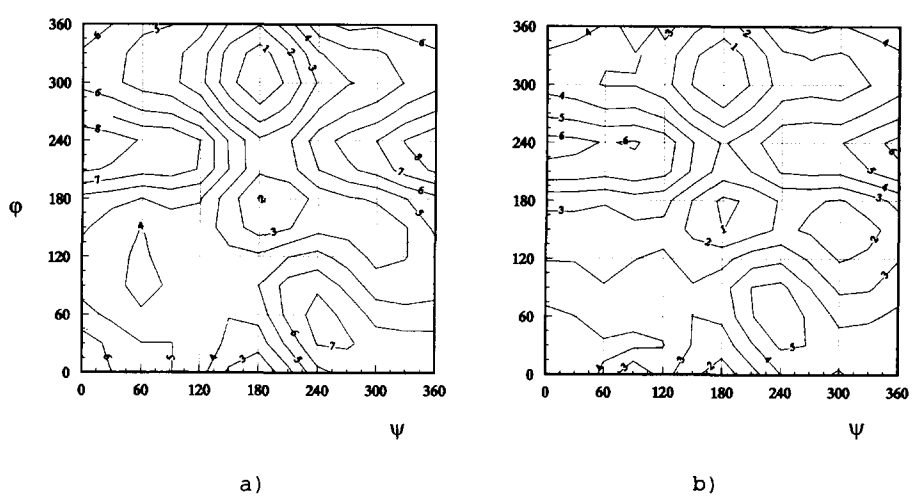

Fig. 4. Contour map for HO-1 (φ) and HO-2 (ψ) rotations in the α isomer of 1,2-disubstituted tetrahydropyran: (a) vacuum; (b) solution. Quoted figures are relative energies (in kcal/mol). Zero is the energy of the most stable conformation. The zero of the torsion angle is defined with respect to the C–H bond(s).

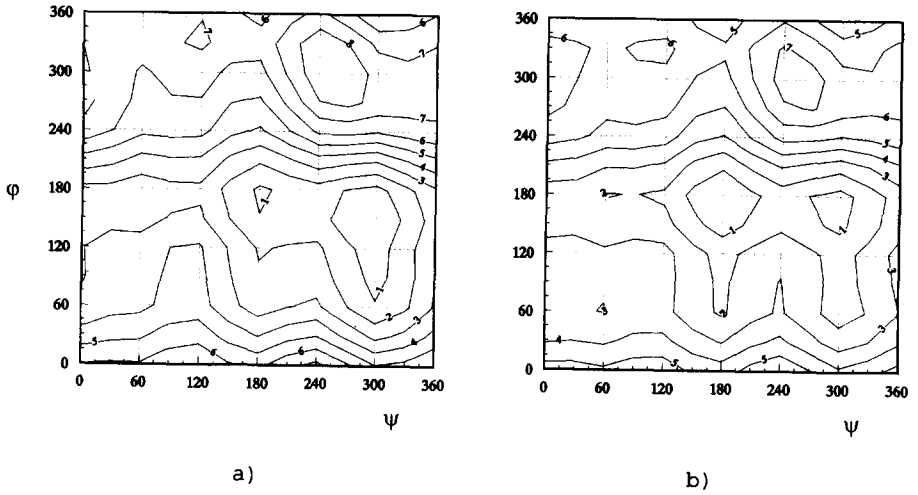

Fig. 5. Contour maps for HO-1 (φ) and HO-2 (ψ) rotations in the β-anomeric isomer of 1,2-disubstituted tetrahydropyran: (a) vacuum; (b) solution. Quoted figures are relative energies (in kcal/mol). Zero is the energy of the most stable conformation.

g_1^+, g_2^+, conformations (Figs 3b,c and 4b), with energies ca. 1.9 and 3.7 kcal/mol higher than the previous one (Fig. 4a). In other words, the interaction between the H atom of the OH-2 group and the OH-1 group stabilizes the g^- conformation of the anomeric OH group more than the t conformation. The interconversion barrier between these two isomers is ca. 3.2 kcal/mol.

The solvent effect (Fig. 4b) reduces the energy difference between the first two minima to 0.56 kcal/mol and lowers by ca. 0.7 kcal/mol the related interconversion barrier. Moreover, it can be observed that the potential well of the g_1^-, t_2 conformation becomes slightly more shallow, so allowing a wider oscillation of both OH groups. The third local minimum assumes the t_1, g_2^- conformation, with an energy ca. 2 kcal/mol higher than the most stable one.

The equatorial anomeric isomer, in vacuum, shows a minimum characterized by $\varphi = 156°$ and $\psi = -67°$ (t_1, g_2^-,) with a very wide well (Fig. 5a) as occurs in the parent tetrahydropyran. Therefore, the equatorial-anomeric OH group can oscillate around the C-1–O-1 bond (in the range of eclipsing between OH and the C-1–C-5 bond) more widely than the axial one, as in the monosubstituted parent molecule. A second minimum (t_1, t_2; 0.71 kcal/mol less stable) is also present; it shows an interconversion barrier amounting to ca. 1.3 kcal/mol. Another possible interconversion pathway (crossing through 150°, 60°) implies a barrier of ca. 2.8 kcal/mol. The solvent reverses the stability order ($\Delta E = 0.49$ kcal/mol), favouring the conformation without intramolecular hydrogen bonding (Fig. 5b). Moreover, it increases the oscillation range in the t_1, t_2 minimum. The barrier in going to the t_1, g_2^- conformer is ca. 1.20 kcal/mol.

Looking at the anomeric effect, it can be noted that, in contrast to the corresponding monosubstituted compound, the axial isomer is more stable than the equatorial one both

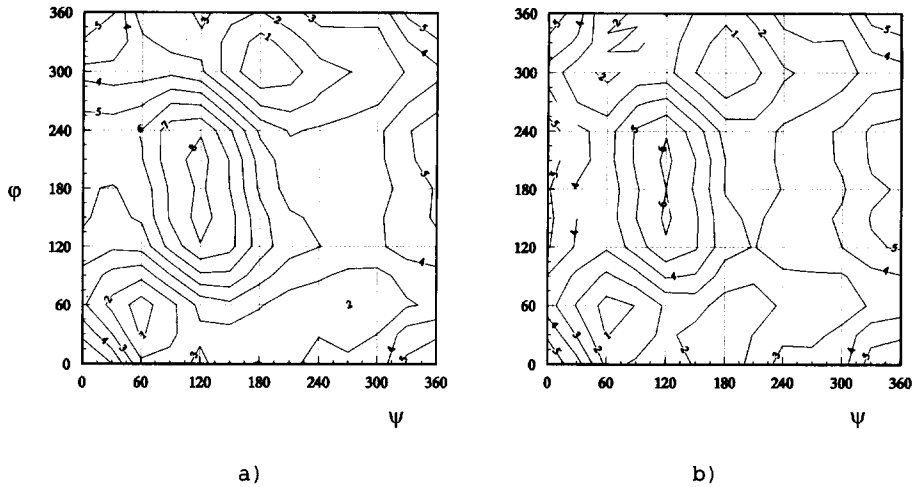

Fig. 6. Contour maps for C-5–C-6 (ψ) and C-6–O-6 (φ) rotations in "5-hydroxymethyl-tetrahydropyran": (a) vacuum; (b) solution.

in vacuum and in aqueous solution; however, in solution the energy difference between equatorial (*eq*) and axial (*ax*) conformers becomes very low (ΔE in kcal/mol):

1-hydroxy-tetrahydropyran	1,2-dihydroxy-tetrahydropyran
$\Delta E(eq\text{-}ax) = 0.45$ (vacuum)	$\Delta E(eq\text{-}ax) = 1.90$ (vacuum)
$\Delta E(eq\text{-}ax) = -0.15$ (solution)	$\Delta E(eq\text{-}ax) = 0.43$ (solution)

It is evident that the proximity of an OH group stabilizes further the axial anomeric isomer, while the solvent stabilizes the equatorial one. Anyway, it seems that in both cases, the strengths of the H-bonds are not relevant, given the stabilization of the *t* conformer in water (and the values of interatomic distances, too).

Tetrahydropyran-2-methanol ("5-hydroxymethyl-tetrahydropyran") (HMTHP).— Isoenergetic curves of HMTHP as a function of the torsion angles ψ (O-6–C-6–C-5–C-4 torsion) and ψ (H–O-6–C-6–C-5 torsion) in vacuum and in solution are shown in Fig. 6a and b, respectively. The Newman projections of the possible rotamers around the

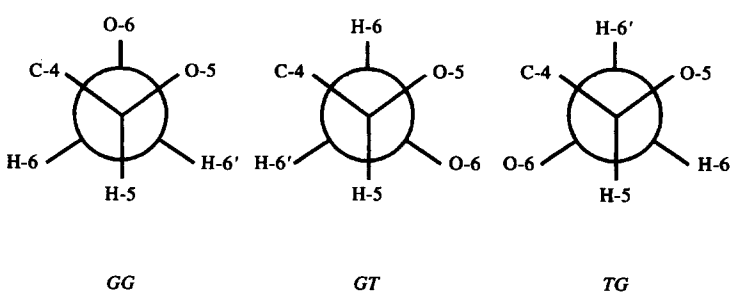

Fig. 7. The possible rotamers about the C-5–C-6 bond: *GG*, *GT*, and *TG*.

C-5–C-6 bond (*GG*, *GT*, and *TG*) are drawn in Fig. 7. The minimum energy conformations and corresponding relative energies (kcal/mol) are the following:

Conformation	ψ	φ	ΔE (Vacuum)	ΔE (solution)
GT, g^-	183	−54	0	0
GG, g^+	61	50	0.54	0.58
TG, g^+	281	59	1.9	2.17

Starting from the most stable conformations, two interconversion pathways are possible:

(1) OH rotation from g^- to g^+, crossing through t (with small change in ψ) allows the GT,g^- conformation to reach the TG,g^+ one by overcoming a barrier of ca. 3.3 kcal/mol in the gas phase and 2.4 kcal/mol in solution.

(2) OH rotation crossing through $\psi = 0°$ allows conversion into either the GG,g^+ or the TG,g^+ conformation, with barriers slightly lower than the previous ones. Conformational changes passing through $\psi = 0°$ are very unlikely.

The difference in energies between the GT,g^- and TG,g^+ conformations gives a measure of the strength of the hydrogen bridge between HO-6 and the ring oxygen. The weak H-bond between CH_2OH and the ring oxygen is evidenced also by the H · · · O-5 and O-5 · · · O-6 distances, which are ca. 2.3 and 2.8 Å, respectively, and by the small charge displacement from H to O-5 (0.02 a.u.) with respect to situations without the H bridge. Practically, it can be argued that the prevailing contribution is the electrostatic interaction.

3-Hydroxytetrahydropyran-2-methanol ("4-hydroxy-5-hydroxymethyl-tetrahydropyran").—The presence of an OH group at C-4 produces a wide variety of conformers, including those characterized by a hydrogen bridge between the H of HO-4 and the oxygen atom of CH_2OH as well as the opposite situation with H-bonding between CH_2OH and the O-4 atom.

The energy curves for the HO-4 rotation were examined both in the axial (galactopyranose-like) and in the equatorial (glucose-like) positions for the three minimum energy conformations found in HMTHP, and the isoenergetic maps related to the CH_2OH motions for some specific fixed orientations of the HO-4 group were also drawn. We were obliged to adopt the latter procedure because, during minimization with full geometry optimization, the conformational characteristics of the starting geometries were often lost. For conciseness we report here only the results for some particularly stable conformations (Table 1) and the most meaningful maps, summarizing what was found about the rotation barriers.

Table 1 shows that the proximity of an equatorial HO-4 group makes the energy of the *TG* conformation nearly comparable with that of the *GT* one, both in vacuum and in water solution. This does not happen with the axial HO-4 group.

When the energy curves for the rotation of the OH group equatorially bound to the C-4 atom are examined, the trend is almost independent of the orientation of the CH_2OH group, apart from a destabilization of at most 1 kcal/mol for the *GG* conformation with HO-4 at 180°. So it is not surprising that the maps of the CH_2OH

Table 1
Minimum energy conformations for various HO-4 rotation angles and relative energies (kcal/mol)

Equatorial HO-4					
Rotation	*GT,g*$^-$	*GG,g*$^+$		*TG,g*$^+$	*TG,g*$^-$
		Vacuum			
180°	0	0.91		0.12	
60°	1.77	1.42			1.48
−60°	1.70	2.25		1.90	
		Solution			
180°	0	0.57		0.38	
60°	1.13	1.35			1.50
−60°	1.81	2.16		2.18	
Axial HO-4					
	GT,g$^-$	*GG,g*$^+$	*GG,g*$^-$	*TG,g*$^+$	*TG,g*$^-$
		Vacuum			
180°	0	2.34	1.91	2.03	
60°	4.65	6.19	6.08	6.13	
−60°	4.46	3.01			5.63
		Solution			
180°	0	1.26	0.35	2.64	
60°	3.29	4.68	4.33	5.00	
−60°	2.72	1.98			4.78
HMTHP					
	GT,g$^-$		*GG,g*$^+$		*TG,g*$^+$
Vacuum	0		0.54		1.90
Solution	0		0.58		2.17

group at various orientations of HO-4 are very similar to those of the parent molecule HMTHP (see Fig. 6), both in vacuum and in solution, except the remarkable stabilization of the *TG,g*$^+$ conformation when HO-4 is at 180° (data not shown). No conformation characterized by significant H-bonding between HO-4 and CH_2OH was found for this isomer, so that the stabilization of the *TG* conformation is explainable only in terms of favorable electrostatic interactions. In water solution the *GG* and *TG* forms become nearly isoenergetic. From these results it is evident that the energies of various conformers are so close to each other that the predicted equilibrium is to be taken with caution, since small geometry changes or improvement in the adopted methods of calculation can modify the calculated stability order. Anyway, it appears that in these systems the solvent plays a very important role. In the gas phase the interconversion barriers are similar to those found for HMTHP; in solution they are slightly lowered.

In the axial HO-4 conformers, two opposite orientations of OH groups, both able to give H-bonding, are possible, so that the number of stable conformations increases with respect to HMTHP (Table 1). The *GT,g*$^-$ with OH at 180° is the most stable conformation both in vacuum and in solution. However, in solution *GG,g*$^-$ becomes nearly isoenergetic with *GT,g*$^-$. Moreover, as can be seen from the maps reported in Fig. 8 (when HO-4 is at 180°), the solvent effect causes barrier lowering so that it is

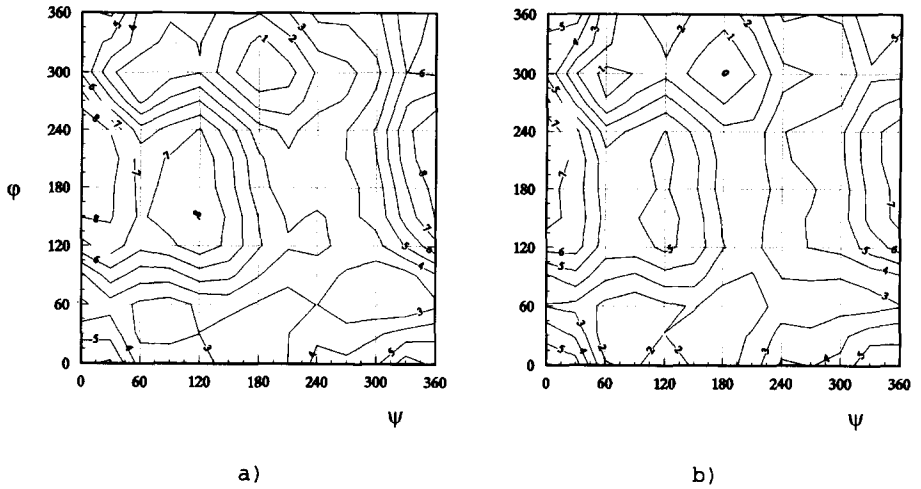

Fig. 8. Contour maps for C-5–C-6 (ψ) and C-6–O-6 (φ) rotations in "4-hydroxy-5-hydroxymethyl-tetrahydropyran"; the HO-4 group is axial and *t*-oriented: (a) vacuum; (b) solution.

possible for the GT,g^- to convert to the GG,g^- or GG,g^+ conformation by overcoming barriers lower than 2 kcal/mol. The maps obtained for HO-4 at $+60°$ or $-60°$ (here unreported) show, on the whole, energies higher than in the case of 180°; some high barriers, due to torsional and steric effects, are also evident.

Monosaccharides.—On the basis of the results previously described, calculations with full geometry optimization were performed on the most energetically meaningful conformations of glucopyranose and galactopyranose, considered both in their axial (α) and equatorial (β) isomeric structures. Moreover, some peculiar interconversion pathways between the three minimum energy conformations of CH_2OH, other than the in-phase rotation of OH groups bound to the pyran ring, were examined, both in vacuum and in aqueous solution.

The calculated minimum energy conformations of glucopyranose are shown in Table 2. The most stable conformations are characterized by the *GT* orientation of the hydroxymethyl group, both for the α and β isomers. The energies of the *GT*, *GG*, and *TG* conformers are closer to each other in the β anomer of glucopyranose than in the α anomer. Experimental data indicate comparable percentages for the *GT* and *GG* conformations, with *TG* present only in traces, both in the solid phase [5] and in solution [45,46]. The agreement between our results and experimental data is fair for the α anomer, but poor in the β case; however, it is evident that the stability of the *GG* conformer is slightly underestimated. On the other hand, the poor agreement may be explicable when we recall that, having three conformations with comparable energies, small errors in the calculated relative conformational energies can reverse the equilibrium percentages.

In both α and β anomers, the ring OH groups are oriented essentially counterclockwise in vacuum; solvent breaks the weak intramolecular hydrogen bridges so that they

Table 2
Energies of some fully optimized isomeric conformations of glucose (energies in kcal/mol)

	Conformations					Energy	
	CH_2OH	HO-4	HO-3	HO-2	HO-1	Vacuum	Solution
α-Glucose	GT,g^-	t	t	t	t	−300.3673	−308.6660
		t	t	t	g^-	−302.5764	−309.1112
		t	g^-	t	g^-	−302.2729	−308.3357
		g^-	t	t	t	−302.3165	−307.6206
		g^-	t	t	g^-	−302.9230	−308.1933
		g^-	g^+	t	g^-	−303.7549	−307.9274
	GG,g^+	t	t	t	g^-	−301.9695	−308.5708
		t	g^-	t	g^-	−301.5427	−307.7013
		g^-	t	t	t	−300.8565	−307.4488
		g^-	g^+	t	t	−301.9443	−307.1183
		g^-	t	t	g^-	−302.6161	−308.0110
	GG,g^-	t	t	t	g^-	−301.0233	−307.6031
		g^-	g^+	t	t	−300.7111	−305.7268
		g^-	g^+	t	g^-	−302.3864	−306.8397
		g^-	t	t	g^-	−301.4480	−307.2680
	TG,g^+	g^-	g^+	t	t	−302.0792	−307.1883
β-Glucose	GT,g^-	t	t	t	t	−299.2156	−308.4410
		g^-	g^+	g^-	g^+	−300.9756	−305.1265
		g^-	g^+	g^-	t	−301.7404	−306.3469
		g^-	t	t	t	−298.9876	−307.5013
	GG,g^+	t	t	t	g^-	−298.5073	−307.8481
		g^-	g^+	g^-	g^+	−300.5936	−304.8872
		g^-	g^+	g^-	t	−301.2153	−306.0619
	GG,g^-	t	t	t	t	−297.4808	−306.3859
		g^-	g^+	g^-	t	−300.3436	−305.1629
	TG,g^+	t	t	t	t	−298.9960	−307.9460
		g^-	g^+	g^-	g^+	−300.9884	−304.9831
		g^-	g^+	g^-	t	−301.5069	−305.9638

[a] Symbols referring to the torsion angles are given in Fig. 1.

assume the t orientation, in agreement with data obtained in the solid state [47] and molecular dynamic calculations [25–28].

The minimum energy conformations of galactose obtained are shown in Table 3. The same conclusions as for glucose can be drawn by comparing data in this table with the available experimental data for galactopyranosides [5,45,46], but the agreement for this isomer is worse since we find very small percentages of the *TG* form. In all cases the ring OH groups tend to a t orientation, independently of the phase, except for the anomeric OH group which prefers the g^- orientation.

Considering the anomeric effect, Tables 2 and 3 show that in vacuum, for both molecules, the α anomers are more stable than the corresponding β anomers (2.01 and 3.21 kcal/mol in glucose and galactose, respectively). In solution, although the stability order does not change, the energy difference practically vanishes (0.67 and 0.22 kcal/mol in glucose and galactose, respectively). Even if the experimental value of 0.33 kcal/mol, in favor of the β anomer, found from NMR measurements in water solution

Table 3
Energies of some fully optimized isomeric conformations of galactose (energies in kcal/mol)

	Conformations [a]					Energy	
	CH_2OH	HO-4	HO-3	HO-2	HO-1	Vacuum	Solution
α-Galactose	GT,g^-	t	t	t	t	−301.6667	−309.9891
		t	t	t	g^-	−303.8677	−310.2254
		t	t	g^-	t	−300.6067	−309.1421
		t	g^+	t	g^-	−301.8082	−308.2258
		g^+	g^+	t	g^-	−302.6816	−307.8690
		g^+	g^+	t	t	−300.8857	−307.1203
		g^-	t	t	t	−299.6817	−308.0034
		g^-	t	t	g^-	−301.7276	−308.3270
	GG,g^+	t	t	t	t	−301.1602	−309.5313
		g^-	t	t	t	−301.4336	−309.1466
		g^-	t	t	g^-	−303.6219	−309.5911
	GG,g^-	t	t	t	g^-	−302.8339	−310.2162
		t	g^+	t	g^-	−300.6724	−308.3664
	TG,g^+	t	t	t	t	−300.5409	−308.0341
	TG,g^-	g^-	t	t	g^-	−300.9399	−306.7639
β-Galactose	GT,g^-	t	t	t	t	−300.6434	−310.0027
		t	t	t	g^+	−299.4815	−308.2210
		t	t	g^-	t	−300.6606	−308.7598
		t	t	g^-	g^+	−300.3691	−307.7498
		g^-	t	t	t	−298.6466	−308.3039
		g^-	t	g^-	t	−298.6318	−305.2819
	GG,g^+	t	t	t	g^+	−298.5348	−307.6245
		t	t	g^-	t	−299.6303	−308.3004
		t	t	g^-	g^+	−299.3821	−307.4328
		g^-	t	t	t	−300.3155	−309.4746
		g^-	t	g^-	t	−300.3360	−308.6050
	GG,g^-	t	t	t	t	−300.1505	−309.6399
		g^+	g^+	g^-	t	−299.2767	−306.5774
	TG,g^+	t	t	t	t	−299.5039	−308.1802
		t	t	t	g^+	−298.4775	−306.4461
		t	t	g^-	t	−299.6138	−306.9159
		t	t	g^-	g^+	−299.4217	−305.9484

[a] Symbols referring to the torsion angles are given in Fig. 1.

for the α,β equilibrium is not exactly reproduced, from calculations it is evident that solvent induces an appreciable stabilization of the β conformer, so confirming the view that, in large part, the anomeric preferences of monosaccharides are conditioned by solvation effect [5,25–30,48]. Consequently, we think that a better evaluation of the conformational energies in vacuum would improve the agreement with the experimental trend.

The energy curves for the CH_2OH group rotation in glucopyranose and galactopyranose were drawn. In particular, the β-glucose and β-galactose molecules with all OH groups t oriented were considered. All parameters were optimized, including the torsion of the OH group bound to methylene. The curves obtained are shown in Fig. 9. From

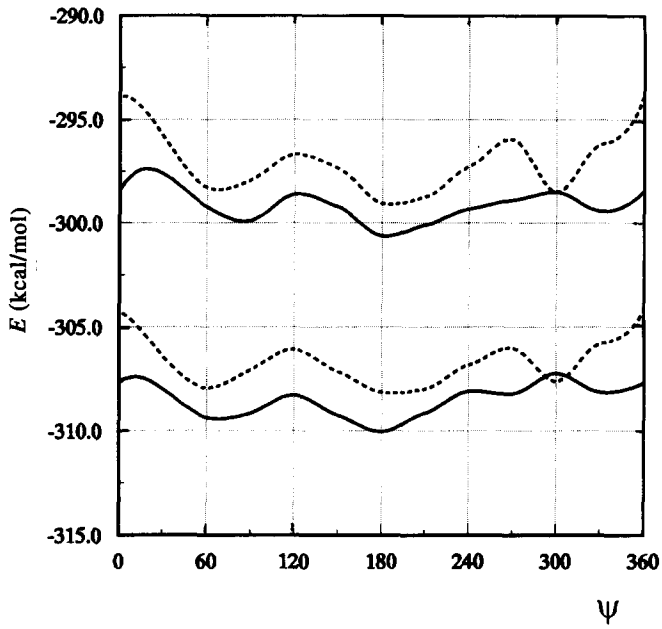

Fig. 9. Potential energy curves for the CH_2OH rotation (ψ) in β-glucose (dotted line) and β-galactose (full line). All OH groups are *t*-oriented. Upper curves refer to vacuum, the lower to solution.

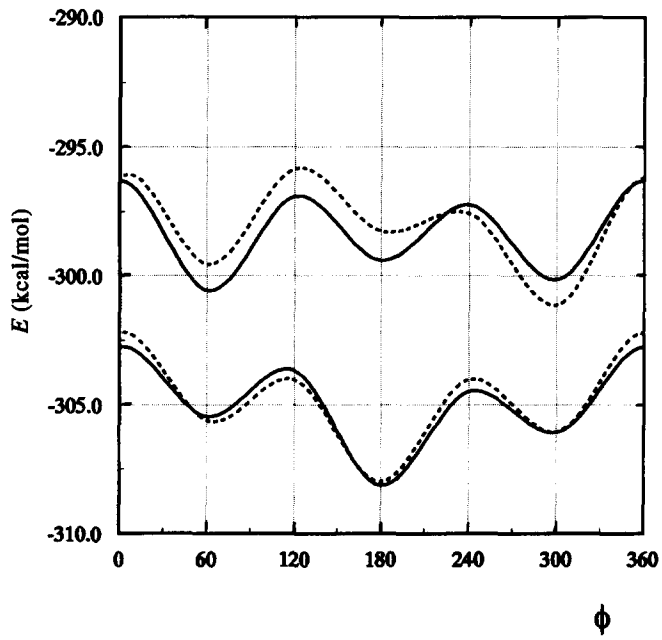

Fig. 10. Potential energy curves for the in-phase rotation (ϕ) of HO-2, HO-3, and HO-4 groups in α-glucose (full line) and β-glucose (dotted line). Upper curves refer to vacuum, the lower to solution. The CH_2OH group was maintained in the *GG* orientation.

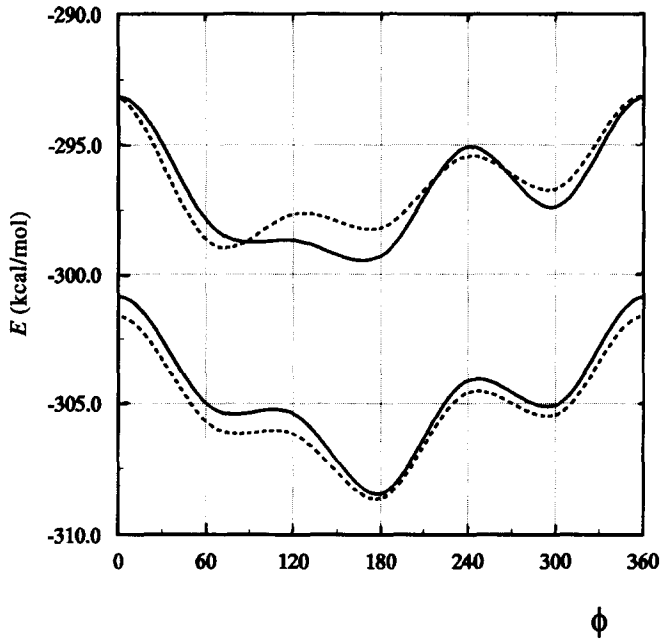

Fig. 11. Potential energy curves for the in-phase rotation (ø) of HO-2, HO-3, and HO-4 groups in α-galactose (full line) and β-galactose (dotted line). Upper curves refer to vacuum, the lower to solution. The CH_2OH group was maintained in the *GG* orientation.

comparison with the maps of the parent "4-hydroxy-5-hydroxymethyl-tetrahydropyrans" previously described, it is clear that no appreciable effects are produced by the presence of other OH groups; small differences are attributed to the fact that all the OH groups are free to assume the best orientation for each point of the O-6–C-6–C-5–C-4 torsion pathway.

The curves show once again that in galactopyranose the barriers for conversion between one CH_2OH conformation and another are lower than in glucopyranose; moreover, in both molecules the solvent induces a lowering of the barrier and a smoothing of the minima centered at 180°, allowing a greater mobility of the hydroxymethyl group.

Finally, the potential curves for the in-phase rotation of HO-2, HO-3, and HO-4 groups in glucopyranose and galactopyranose in their α and β anomers were examined. The CH_2OH group was oriented in the *GG* conformation. For each single point calculation, the molecular geometry was fully optimized, including the HO-1 rotation, since test calculations confirmed high barriers to free rotation but wide oscillations.

Figs 10 and 11 show the curves obtained, both in vacuum and in water solution. These curves show once again the remarkable action of the solvent in stabilizing the *t* orientation of the OH groups, as previously noted. Interestingly, both in α- and β-galactopyranose, the solvent strongly reduces the wide in-phase oscillation, which is possible in the gas phase. It is to be pointed out that in solution the complete in-phase

rotation of the OH groups, starting from the *t* conformation, requires that barriers of over 3.5 kcal/mol are overcome. These results are in substantial agreement with the interpretation of molecular dynamics results [5], in which the solvent renders easy noncorrelated motions of OH groups, while in-phase motions require higher barriers to be overcome.

4. Conclusion

Two main aspects were taken into account in the present investigation of the aqueous solvent effect in two monosaccharides and model compounds. The first concerns the relative stability of the various possible isomers, the second the evaluation of rotation barriers in order to establish if wide oscillations or free rotation are possible as a result of cooperative effects between the pendant groups of the monosaccharide molecule.

As far as the first aspect is concerned, it was found that in vacuum the cooperative OH-groups effect mostly favors the counterclockwise orientation of such groups; solvent tends to break the weak hydrogen bonds so that the *all-anti* orientation preponderates in water solution.

Looking at the CH_2OH group, three main rotamers are found, two of which (*GT* and *GG*) differ very little in energy, and their relative stability depends on the position and orientation of the vicinal OH group.

An indication of the stability of the anomeric isomers was obtained in this study. In the gas phase, especially in presence of cooperative effects between the vicinal OH groups, the α anomer is preferred; the β anomer is stabilized mainly from the solvent action.

As far as the degree of rotational freedom of the pendant groups is concerned, different behavior is noted between the CH_2OH and the lateral OH groups. In fact, the former can oscillate widely about the minimum energy points and it is possible to pass from one conformation to another by overcoming rather low barriers (see Fig. 9); these are further decreased in solution. From the energy balance for the in-phase rotation of the ring OH groups in the various isomers of glucopyranose and galactopyranose, it can be observed that the in-phase rotation requires slightly higher energies than found for the singly hydroxy-substituted tetrahydropyrans [2], as well as for the homologous disubstituted derivatives; i.e., there is no barrier decrease resulting from cooperative interactions. Besides, the solvent causes a noticeable stabilization of the *anti* (*t*) conformation and reduces the allowed oscillation of the nonanomeric OH groups, which appears to be wide in the gas phase.

Acknowledgement

Financial support from the Italian Consiglio Nazionale delle Ricerche (Roma) is gratefully acknowledged.

[2] Preliminary calculations on equatorial cyclohexanol gave minima at 180° and ±60° (ΔE ca. 2 kcal/mol) and maxima at ±120° and 0° with energy ca. 2.6 and 3.1 kcal/mol over the minimum.

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