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The anomeric and *exo*-anomeric effects of a hydroxyl group and the stereochemistry of the hemiacetal linkage[1]

Igor Tvaroska[a,*], Jeremy P. Carver[b]

[a] *Institute of Chemistry, Slovak Academy of Sciences, SK-842 38 Bratislava, Slovakia*

[b] *University of Toronto, Faculty of Medicine, Department of Molecular and Medical Genetics, Toronto, Ontario, Canada, M5S 1A8*

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Abstract

The conformational properties and the anomeric and *exo*-anomeric effects of the hydroxyl group linked to the anomeric carbon in aldopyranoses have been studied with ab initio methods using 2-hydroxytetrahydropyran (**1**) as a model. The potential of rotation around the hemiacetal anomeric C–O bond has been calculated with the 6-31G* and 6-311++G**//6-31G* basis sets. The ab initio geometry and energy of the conformers have been determined by gradient optimization at various levels of the Hartree–Fock and density functional theory (DFT). Vibrational frequencies were calculated at the 6-31G* level and used to evaluate zero-point energies, thermal energies, and entropies for minima. Solvent effects on the stability of conformers were estimated using the continuum model. At all levels of theory, and contrary to the result on 2-methoxytetrahydropyran (**2**), three minima were found on the rotation curves around the C1–O1 bond for both anomers of **1**. Variations in calculated valence geometries for compounds display structural changes distinctive for the anomeric and *exo*-anomeric effects. The calculations predict the axial form of **1** as the preferred anomer in vacuum. Solvent effects change the equilibrium and the equatorial form is favored in aqueous solution. The calculated energy differences are in agreement with the experimental data on 2-hydroxytetrahydropyran. The magnitude of the anomeric effect for the hydroxyl group was estimated to be 2.0 kcal/mol. The hydroxyl group in the axial and equatorial position exhibits the *exo*-anomeric effect of 2.3 and 2.9 kcal/mol, respectively.

Keywords: Ab initio calculations; Hemiacetal linkage; Conformations; Anomeric and *exo*-anomeric effects

1. Introduction

The anomeric effect and related stereoelectronic effects have been extensively reviewed and discussed [2–19]. Recently we have undertaken an ab initio analysis of the anomeric, *exo*-anomeric,

* Corresponding author. Present address: GlycoDesign Inc., 480 University Avenue, Suite 900, Toronto, Ontario, Canada, M5G 1V2; Tel.: 001-5416-93-6027, ext. 230; fax: 001-5416-593-8988; e-mail: igor@gd.glycodesign.com

[1] Ab Initio Molecular Orbital Calculation of Carbohydrate Model Compounds. Part 7. For Part 6, see ref [1].

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reverse anomeric, and gauche effects on the geometry and the conformational behavior of cyclic model compounds of carbohydrates [1,20–24]. We have investigated the fluorine, chlorine, methoxyl, ethyl, methylamino, methylammonio, thiomethyl, hydroxymethyl, and methoxymethyl derivatives of oxane (tetrahydropyran). Calculated conformational equilibrium has been used to estimate the magnitudes of the anomeric and *exo*-anomeric effects. It has been predicted theoretically [23] that the anomeric effect decreases in the following order: chlorine > methoxyl ~ fluorine > thiomethyl > methylamino > ethyl > methylammonio, with the methylamino, ethyl and methylammonio groups exhibiting reverse anomeric effects. The *exo*-anomeric effect has been calculated to decrease in the order: methoxyl > methylamino > thiomethyl. The *sc* preference of the ethyl and methylammonio groups over the *ap* orientation around the C1–X1 bond was suggested [23] to result entirely from steric interactions. However, the 2-hydroxy derivatives of tetrahydropyran representing free sugar derivatives were not investigated. In this paper, as a continuation of this effort, we present the results of a conformational analysis of 2-hydroxytetrahydropyran (2-hydroxyoxane) in both the axial and equatorial forms.

2. Methods

Structures of 2-hydroxytetrahydropyran with the axially (**1a**) and equatorially (**1e**) oriented hydroxyl group are illustrated in Fig. 1. For a description of atoms we use the numbering of atoms as in the carbohydrate nomenclature, where the anomeric atom is denoted as C1 (Fig. 1), etc. The rotation about the anomeric C1–O1 linkage is described by the dihedral angle, Φ, where Φ = Φ[O5–C1–O1–H]. The three staggered orientations for rotation about the C1–O1 bond in both the axial and equatorial forms of (**1**) are referred as GT, TG, and GG (Fig. 2). In this notation [21], the description of the torsion angle Φ = Φ [O5–C1–O1–H] is stated first, then the torsion angle Θ = Θ [C2–C1–O1–H]. In this way, e.g., GT means that the angles Φ and Θ are approximately in *synclinal* or gauche (G) and *antiperiplanar* or trans (T) conformations, respectively (Fig. 2).

The ab initio calculations were carried out using GAUSSIAN 92 [25] and the standard basis sets [26]. The optimization of the geometry was performed at the SCF level with the 6-31G* basis set. The geometries were fully optimized using the gradient optimization routines of the program without any symmetry constraints, except for the dihedral angle Φ, which was kept fixed. First, a 30° grid for the dihedral angle Φ was used, and then the final refinement was performed without freezing the dihedral angle Φ in order to locate the minimum on the rotational curve. Next, single-point calculations were performed for each point on the potential energy curve and for each minimum using the 6-311++G** basis set. It has been shown [20,21,27] that inclusion of electron correlation at the MP2/6-31G* level does not improve the results.

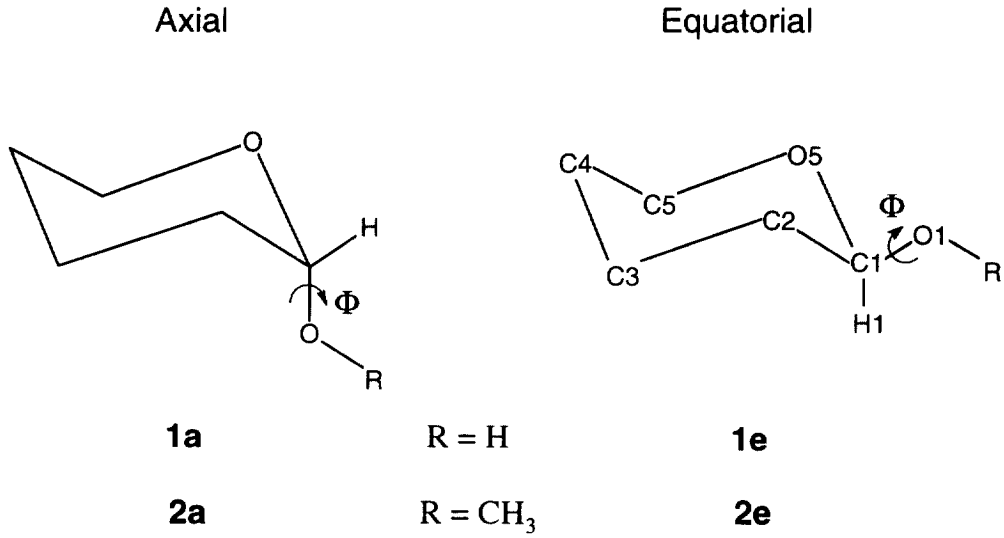

Fig. 1. Schematic representations of 2-hydroxy (**1**) and 2-methoxytetrahydropyran (**2**) with an axial (**a**) and equatorial (**e**) substituent, and the labeling of the atoms.

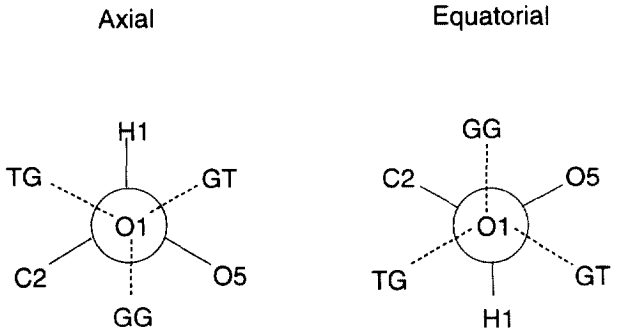

Fig. 2. Schematic representation of the GT, TG, and GG conformers around the C1–O1 bond for the axial (**1a**) and equatorial (**1e**) 2-hydroxytetrahydropyran..

Therefore, the electron correlation at MP2 level was not included in the present study. Instead, a hybrid Hartree–Fock-density functional scheme, the adiabatic connection method [28] (ACM) of density functional theory (DFT) [29] was used for all minima with valence double-zeta plus single polarization set per atom (dzvp) and valence triple-zeta plus single polarization set per atom (tzvp) basis sets using the TURBOMOLE 95.0 program [30]. For all minima, the vibrational frequencies were calculated at the 6-31G* level, and the zero-point energy, thermal and entropy corrections were evaluated. Calculations of solvation energy were performed using the Solvation 95.0 program [31]. The calculations were carried out at the University of Toronto on an HP 735 computer and at Glyco-Design Inc. on a Power Indigo 2 R8000 computer.

3. Results and discussion

Conformational energies.—The calculated conformational energy profiles for 2-hydroxytetrahydropyran (**1**) at the 6-31G* and 6-311++G**//6-31G* levels are shown in Fig. 3. To compare effects of changing the C1 substituent from methoxyl to hydroxyl, previously calculated profiles for 2-methoxytetrahydropyran (**2**) [21] are also included. The location, dipole moments and energies of the minima are listed in Tables 1 and 2. The relevant geometrical parameters at the 6-31G* level are found in Table 3.

It can be seen that both the 6-31G* and 6-311++G**//6-31G* calculations predicted very

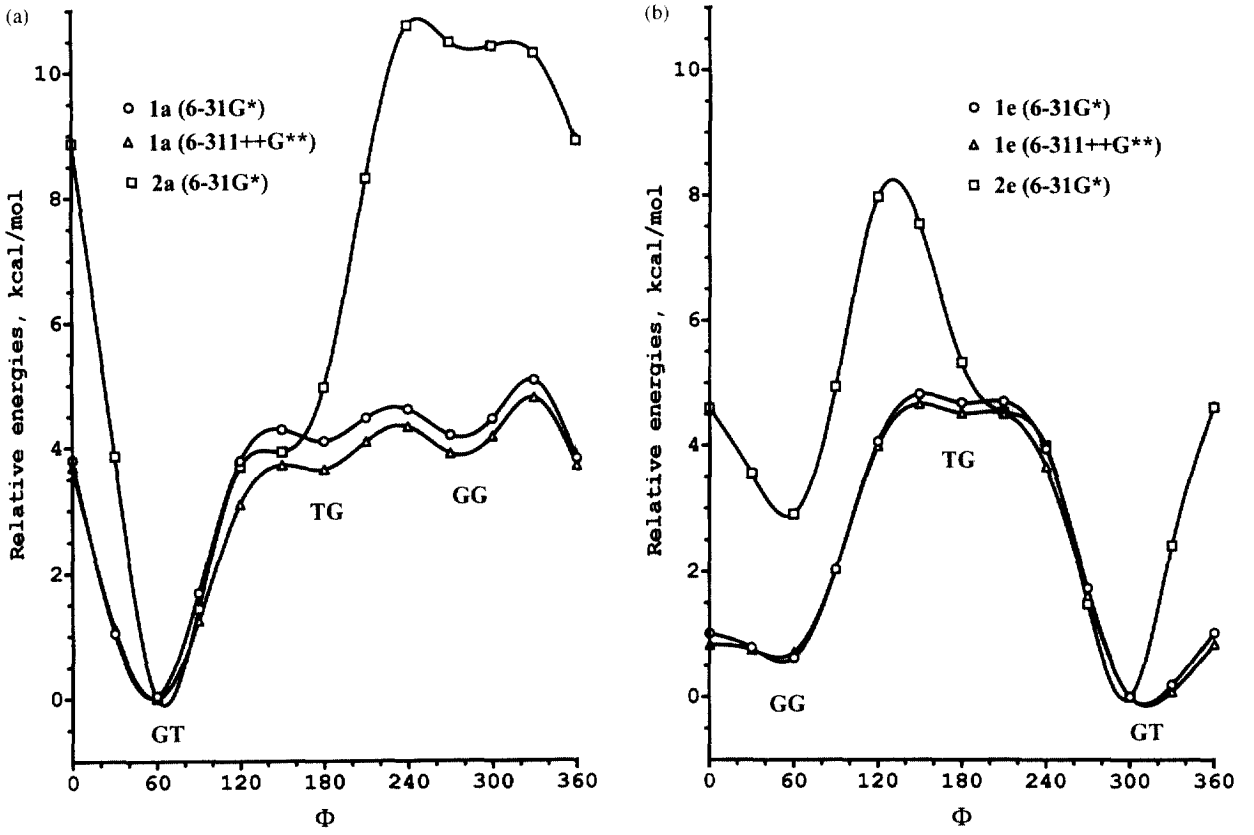

Fig. 3. Ab initio potential energy of rotation about the C1–O1 linkage for the (a) axial and (b) equatorial 2-hydroxytetrahydropyran calculated at the 6-31G* (○) and 6-311++G**//6-31G* (Δ) levels compared with the 6-31G* data for 2-methoxytetrahydropyran (□) [21].

Table 1
Ab initio relative energies (ΔE, kcal/mol), dipole moments (μ, D) and the position (Φ, deg) of the conformational minima of 2-hydroxytetrahydropyrans calculated at the 6-31G*, 6-311++G**//6-31G*, ACM/dzvp, and ACM/tzvp levels

Conformers	6-31G*			6-311++G**		ACM/dzvp			ACM/tzvp		
	Φ	μ	ΔE	μ	ΔE	Φ	μ	ΔE	Φ	μ	ΔE
Axial 2-hydroxytetrahydropyran (**1a**)											
GT	55.0	0.39	0.00[a]	0.48	0.00[b]	56.1	0.41	0.00[c]	56.1	0.45	0.00[d]
TG	177.8	2.40	4.09	2.51	3.04	−166.3	2.68	3.72	−162.7	2.73	3.64
GG	−81.8	2.97	4.14	3.10	3.85	−87.8	3.00	3.04	−86.8	3.01	2.90
Equatorial 2-hydroxytetrahydropyran (**1e**)											
GT	−49.1	2.11	1.33	2.29	0.69	−51.2	2.06	0.77	−51.2	2.11	0.79
TG	−174.2	3.20	6.13	3.40	5.36	−174.3	3.18	5.32	−174.5	3.21	5.19
GG	50.1	2.49	2.00	2.69	1.47	57.4	2.54	1.43	57.8	2.58	1.39

[a] $E = -344.8833633$ hartrees.
[b] $E = -344.9828390$ hartrees.
[c] $E = -346.9461421$ hartrees.
[d] $E = -346.99498815$ hartrees.

Table 2
Summary of corrections to the calculated energy differences (kcal/mol) for the GT, TG, and GG conformers of the axial (**1a**) and equatorial (**1e**) 2-hydroxytetrahydropyran using the 6-31G* basis set at 298 K

	Axial (**1a**)			Equatorial (**1e**)		
	GT	TG	GG	GT	TG	GG
Zero-point energy	102.5	102.1	102.2	102.1	101.8	102.1
Thermal energy	106.3	106.1	106.1	106.0	105.8	106.0
Entropy contribution	−23.0	−23.3	−23.2	−23.2	−23.6	−23.3
Total correction	185.8	184.9	185.1	184.9	184.0	184.7
Relative total correction	1.8	0.9	1.2	1.0	0.0	0.8
ab initio relative value	0.0	4.1	4.1	1.3	6.1	2.0
Corrected value ΔG_{298}	0.0	3.2	3.5	0.5	4.3	1.0
Solvation correction	−4.3	−5.7	−4.7	−4.8	−7.2	−4.5
Relative solvation	2.8	1.5	2.4	2.3	0.0	2.9
ΔG_{solv}	0.04	1.83	3.14	0.0	1.53	0.85

similar conformational energy profiles for each of the two anomeric forms of **1**. Energy differences of 0.5–0.8 kcal/mol were found only for the region 120–240° in the axial form (**1a**). For others conformers these differences are less than 0.5 kcal/mol. Surprisingly, the calculated profiles for **1** differ considerably from profiles calculated for 2-methoxytetrahydropyran. The only similarity between the conformational properties around the C1–O1 bond of the 2-hydroxy and 2-methoxy derivatives of tetrahydropyran is the preference of the GT conformer for each anomer due to the *exo*-anomeric effect. For the methoxyl group, one minimum (GT) for the axial form and two minima (GT and GG) for the equatorial form were found [21]. Rotational profiles for **2** display a large barrier in the GG region, which significantly hinders rotation around the anomeric C1–O1 bond. In contrast, three minima are clearly seen on the rotational profiles obtained for the hydroxyl group. Inspection of Fig. 3 reveals that the barriers for transitions between conformers are considerably lower and minima wells are broader in **1** compared to those for **2**. The potential of rotation and relative energies of conformers around the C1–O1 anomeric bond are influenced by the *exo*-anomeric effect, electrostatic, and steric interactions. The *exo*-anomeric effect is assumed to be responsible for a relative destabilization of *trans* region (TG) around the anomeric C1–O1 bond. On the other hand, a significant decrease of steric interactions in **1** can account for the above mentioned differences in energy profiles between **1** and **2**, since steric interactions are significantly decreased going from the methoxyl to hydroxyl group.

The final optimizations without constraining the dihedral angle Φ gave three minima for each of the anomeric forms of **1**, at all levels of theory. Data in

Table 1 show that for the axial hydroxyl group (**1a**) the most stable orientation is the *sc* orientation with respect to the ring oxygen ($\Phi = 55.0°$, GT). The next stable conformers are the *ap* (177.8°, TG) and *-sc* (−81.8°, GG) conformers. The lowest energy conformer of the equatorial form (**1e**) is the *-sc* orientation (49.1°, GT). The energy of this conformer, calculated at the 6-31G* level, is ~1.3 kcal/mol higher than that for the axial GT. This feature is attributed to the presence of the anomeric effect. An increase of the basis set from 6-31G* to 6-311++G** decreased the energy difference between the lowest energy conformer GT of the equatorial (**1e**) and axial anomer (**1a**) by ~0.6 kcal/mol, and this energy difference is ~0.7 kcal/mol at the 6-311++G**//6-31G* level. This result is consistent with our investigation of the effect of basis set on calculated axial-equatorial energy difference in 2-substituted tetrahydropyrans [20–23]. The *-sc* (50.1°, GG) and *ap* (−174.2°, TG) orientations are the other minima observed for the equatorial form. These minima are in agreement with results reported recently [32]. The common preference for the GT conformer in both anomers of **1** and **2** is consistent with the preference due to the *exo*-anomeric effect. In the GT conformer of **1**, the proton of the hydroxyl group is oriented gauche (*sc*) with respect to the ring oxygen atom. This leads to a stabilization of the GT conformer by delocalization interactions of glycosidic oxygen O1 lone pairs into adjacent antibonding C1–O5 orbital [32,33]. Such delocalizations are not present in the TG conformer, where the proton is in the trans (*ap*) orientation with respect to the ring atom. It is noteworthy that these delocalization interactions were found [32] to be even stronger in the GG conformers, where the proton is *sc* to the ring oxygen and lies above (**1e**) or below (**1a**) the ring. Nevertheless, due to steric interactions, the GG conformer, especially that in the axial form, is less favored than the GT conformer.

To provide some insight into the importance of electron correlation effects on the stability of conformers, we carried out calculations of structure and energy for minima using the emerging ACM DFT method [28,30]. The ACM DFT method uses a 'hybrid' functional by mixing a portion of the exact Hartree-Fock exchange with the DFT exchange-correlation [28]. The extent of correlation effects at the ACM/6-31G* level on relative energies has been found to be smaller using the ACM method than that found with the MP2 method [1]. The relative energies of the six conformers of **1** calculated by the ACM with the dzvp and tzvp basis sets are compared with the 6-31G* and 6-311++G*//6-31G* results in Table 1. The relevant geometrical parameters calculated at the ACM/tzvp level are listed in Table 4. It can be seen that all methods predict the same order of stability for conformers of **1**. The energy split between the conformers slightly decreases when electron correlation effects are included. The larger difference has been observed only for the highest energy conformer. The geometries optimized at the HF/6-31G* and ACM/tzvp levels of theory differ primarily in the hydroxyl group orientation in some conformers and in the C–O and C1–H1 bond lengths. The largest difference observed for the Φ dihedral angle is 20° in TG conformer of **1a**. On the other hand, the predicted difference in the Φ dihedral angle for the lowest energy conformers TG is less than 2°. Systematic deviations are associated with the C–O bonds. The HF/6-31G* theory predicts C–O bonds to be 0.02 Å shorter compared to those calculated at ACM/tzvp theory. In contrast, the C1–H1 bond is longer by 0.12 Å at the HF/6-31G* level. Other bond lengths, bond angles and dihedral angles show far less deviations.

In the case of 2-methoxytetrahydropyran (**2**) we have found [21] that the zero-point energy, thermal energy and entropy contributions decreased the free energy difference between the axial and equatorial conformers of **2**. The zero-point vibrational energies, thermal energies and entropies for six conformers of **1** were estimated using calculated vibrational frequencies at the 6-31G* level. The results are summarized in Table 2. The zero-point vibrational energies and thermal energies are found to be slightly higher for the axial conformers of **1**. The entropy of the axial GT conformer is lower than in the other conformers. Thus, all above-mentioned contributions decrease the free energy difference between axial and equatorial conformers of **1**. Combining the above corrections with the 6-31G* ΔE value of 1.33 kcal/mol leads to a prediction of ΔG_{298} of 0.48 kcal/mol for the difference between the GT conformer of the axial and equatorial 2-hydroxytetrahydropyran, which is in good agreement with the experimental data in non-polar solution. The experimental ΔG_{308} value, obtained by ^{13}C NMR measurements in CCl_4-C_6D_6, is 0.47 kcal/mol [34]. The thermodynamics corrections also decrease the energy difference between

the GT and TG conformers about the C1–O1 bond by 0.8 kcal/mol approximately.

A stabilization of the equatorial form of **2** by polar solvents is well documented experimentally and theoretically [14,21]. To provide insight into the importance of solvent effects on the stability of the hemiacetal linkage conformers, we calculated solvation energies for all six conformers of **1** using Solvation 95.0 program [31] that allows an estimate of the free energy of a molecular solute in aqueous solution. Within this continuum model, the free solvation energy, ΔG_{solv}, is assumed to be sum of an electrostatic contribution, ΔG_e, with nonpolar contributions, ΔG_n, from van der Waals interactions with solvent and from the hydrophobic effect. The solvation energies of minima vary by 2.8 kcal/mol (Table 2). The nonpolar component of the solvation energy appeared to be insensitive to the hydroxyl group conformational changes, the variation in ΔG_n being less than 0.1 kcal/mol. In contrast, the electrostatic term, ΔG_e, of the solvation energy varied by 2.9 kcal/mol from (−6.8 to −9.7 kcal/mol).

The total solvated free energies of all conformers, computed as the sum of the 6-31G* free energy and the solvation free energy, are given in Table 2. These values show that in water, contrary to vacuum, the GT conformer of the equatorial form of **1** is preferred over the GT conformer of the axial form by 0.04 kcal/mol. This preference is 0.67 kcal/mol using the 6-311G**/6-31G* vacuum energy differences. The calculated differences are in qualitative agreement with the observed free energy differences of 0.1–0.6 kcal/mol in polar solvents [34–36]. The stabilization of the equatorial form in aqueous solution seems to be slightly underestimated. This may be attributed to the difference in hydrogen bond interactions with water in the equatorial and axial conformers, which are indicated by experimental data [34]. These specific interactions were not taken into account in the present estimate of solvent effects. The calculated energy difference between the axial and equatorial anomer of 2-hydroxytetrahydropyran is also in accordance with the observed presence of the α anomer (47.5%) for 2-deoxy-D-*arabino*-hexopyranose [37].

Data in Table 2 show that solvation affects different conformers around the C1–O1 bond differently. For both anomers of **1** we found that the largest change in relative energy upon solvation is calculated for the TG conformer. For example, for **1e**, the TG conformer is better solvated than the GT conformer by 2.3 kcal/mol. For **1a**, the energy difference between GT and TG fell from 3.2 to 1.8 kcal/mol. This result may be compared to results recently obtained [33] for the TG and GT conformers of **1a** using the aqueous Solvation Model 5.4/AM1 [38]. Calculations using this model predicted the TG conformer to be better solvated than the GT conformer by 1.7 kcal/mol. The agreement between solvent effects calculated by the two different approaches indicates the reliability of the results. Thus, solvent effects considerably

Table 3
Selected ab initio calculated geometrical parameters of the axial (**1a**) and equatorial (**1e**) 2-hydroxytetrahydropyran conformers calculated at the HF/6-31G* level[a]

Parameter	(1a)			(1e)		
	GT	TG	GG	GT	TG	GG
			Bond lengths			
C1–O1	1.393	1.402	1.392	1.378	1.387	1.379
C1–O5	1.392	1.379	1.394	1.398	1.385	1.397
C1–C2	1.521	1.528	1.528	1.517	1.524	1.524
C1–H1	1.084	1.084	1.078	1.093	1.094	1.087
C5–O5	1.411	1.412	1.404	1.404	1.403	1.405
			Bond angles			
C1–O1–H	108.6	109.8	111.2	108.6	109.4	108.5
O1–C1–O5	111.3	108.0	112.4	108.0	104.9	108.0
C1–O5–C5	115.7	115.7	116.1	114.0	114.1	114.6
H1–C1–O5	104.6	105.4	105.0	108.1	109.0	109.6
			Torsional angles			
Φ	55.1	177.8	−81.8	−49.1	−174.2	50.1
C5–O5–C1–O1	65.3	65.0	69.4	179.5	177.6	176.0
C5–O5–C1–H1	−175.8	−177.7	−176.8	60.6	61.0	61.0

[a] Lengths in angstroms, angles in degrees.

decrease the relative energy between conformers. However, in water and in vacuum, the GT conformer remained preferred relative to the TG conformer.

Geometrical characteristics for **1** listed in Tables 3 and 4 are consistent with the above-noted oxygen lone pair delocalization and are similar to those found in other compounds exhibiting anomeric and *exo*-anomeric effects [23]. Comparison of the 6-31G* geometries for the axial and equatorial hydroxyl group revealed an increase of the C1–O1 and C1–H1 bond lengths, a decrease of the C1–O5 bond length and a widening of the O1–C1–O5 bond angle in the axial form. Similarly in conformers of both anomeric forms, there are several geometrical features characteristic of delocalizations of the anomeric oxygen lone pairs into the C1–O5, C1–C2, and C1–H1 bonds. Geometrical consequences of this *exo*-anomeric delocalization in the GT and TG conformer of **1a** were thoroughly discussed recently [33]. Results in Table 3 show that delocalization lengthens the C1–O5 bond length and shortens the C1–O1 bond length in the GT and GG conformers. As previously observed for **2** [23], the O1–C1–O5 bond angle is smaller in the TG conformer. The delocalization of glycosidic oxygen lone pairs also affects other bonds linked to the anomeric carbon. This is documented in changes of the C1–H1 and C1–C2 bond lengths. The C1–H1 bond length is elongated in the GT and TG conformers compared to GG. The relative orientation of the C1–C2 bond with respect to the glycosidic oxygen lone pairs differs from that of the C1–H1 bond. As a result, the C1–C2 bond length exhibits a different conformational variation than the C1–H1 bond length. Indeed, the C1–C2 bond is longer in the TG and GG conformers compared to GT. The observed variation in the C1–O1–H bond angle of **1** is smaller relative to that for the C1–O1–C bond angle of the methoxyl group in **2**. This observation is consistent with the lesser steric interactions of the hydroxyl group. Similar variations, except for the C1–H1 bond, are predicted by the ACM/tzvp method (Table 4).

Anomeric and exo-*anomeric effects.*—The results reported above show that the axially oriented hydroxyl group is the preferred form of **1** in vacuum. In fact, the calculated axial-equatorial energy difference is 1.33 kcal/mol at the 6-31G* level. After thermodynamics corrections, the free energy difference ΔG_{298} is 0.48 kcal/mol. This gives a 2.0 kcal/mol magnitude of the anomeric effect for the hydroxyl group [14]. The calculations on 2-tetrahydropyranosylammonium at MP2/6-31G*//6-31G* level [39] predicted the preference of 2.24 kcal/mol for the equatorial conformer. Using this value [39] together with previously published values calculated at the 6-31G* level [20,21,23] the magnitude of the anomeric effect decreases in the order: chlorine > fluorine ~ methoxyl > thiomethyl > hydroxyl > methylamino > ammonio > ethyl > methylammonio (2.8, 2.4, 2.4, 2.3, 2.0, −0.4, −0.7, −1.5, and −1.9 kcal/mol). It appears from these results that the anomeric effect decreases

Table 4
Selected ab initio calculated geometrical parameters of the axial (**1a**) and equatorial (**1e**) 2-hydroxytetrahydropyran conformers calculated at the ACM/tzvp level[a]

Parameter	(1a)			(1e)		
	GT	TG	GG	GT	TG	GG
			Bond lengths			
C1–O1	1.416	1.426	1.414	1.395	1.407	1.395
C1–O5	1.414	1.398	1.415	1.422	1.405	1.421
C1–C2	1.521	1.528	1.527	1.516	1.524	1.523
C1–H1	0.965	0.963	0.964	0.965	0.963	0.966
C5–O5	1.433	1.432	1.425	1.424	1.423	1.424
			Bond angles			
C1–O1–H	107.3	108.6	109.3	107.5	108.0	107.5
O1–C1–O5	111.7	108.0	112.5	107.8	104.1	107.9
C1–O5–C5	114.0	114.1	114.2	111.9	112.0	112.6
H1–C1–O5	103.8	104.5	104.2	107.6	108.7	109.2
			Torsional angles			
Φ	56.1	−162.7	−86.8	−51.2	−174.5	57.8
C5–O5–C1–O1	66.7	67.0	70.1	178.8	177.1	175.5
C5–O5–C1–H1	−174.6	−176.1	−176.6	59.3	59.7	61.3

[a] Lengths in angstroms, angles in degrees.

in the order: chlorine > fluorine ~ methoxyl > thiomethyl > hydroxyl whereas the reverse anomeric effect increases in the order: methylamino < ammonio < ethyl < methylammonio.

The *exo*-anomeric effect has been defined by analogy to the anomeric effect [23]. In this case, the *sc-ap* energy difference in the 2-ethyltetrahydropyran anomers of 0.9 kcal/mol, which is assumed to be entirely steric, represents a reference value. The energy difference of 3.2 kcal/mol and 3.8 kcal/mol between the *sc* and *ap* conformers around the C1–O1 bond has been calculated for the axial and equatorial form of **1**, respectively. These differences are larger that the energy difference in 2-ethyltetrahydropyran. The magnitude of the *exo*-anomeric effect in 2-hydroxytetrahydropyrans can be estimated as 2.3 and 2.9 kcal/mol, respectively. Thus, the exo-anomeric effect decreases in the order: methoxyl > methylamino > hydroxyl > thiomethyl.

4. Conclusion

In this paper we have examined the conformational properties of the hemiacetal linkage using 2-hydroxytetrahydropyran as a model. The geometries and energies of the conformers around the exocyclic C1–O1 bond in the axial and equatorial form have been obtained at different levels of ab initio molecular orbital calculations. In vacuum, the axial anomer is the preferred form of **1**. Solvent effects stabilize the equatorial orientation, which becomes the favored anomer in aqueous solution, in agreement with experimental data.

Calculated differences between bond lengths and bond angles for different conformers of the compounds studied display structural differences that reflect a delocalization interaction of the oxygen lone pairs into antibonding orbitals of the C1–O1 or C1–O5 linkages.

Calculated energy differences have been used to estimate the magnitude of the anomeric and *exo*-anomeric effects. The anomeric effect decreases in the following order: chlorine > fluorine ~ methoxyl > thiomethyl > hydroxyl. The *exo*-anomeric effect in the axial anomer has been found to be larger than in the equatorial anomer, nevertheless its magnitude is smaller for the hydroxyl group than for the methoxyl group.

From these calculations it appears obvious that the hemiacetal linkage exhibits a larger extent of flexibility and different conformational preferences compared to the acetal linkage.

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