Ab Initio Molecular Orbital Calculation of Carbohydrate Model Compounds. 6. The Gauche Effect and Conformations of the Hydroxymethyl and Methoxymethyl Groups

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Received: November 12, 1996; In Final Form: January 27, 1997[⊗]

Conformational properties and the gauche effect of the two functional groups, hydroxymethyl and methoxymethyl, in hexopyranosides have been studied with *ab initio* methods using the methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**), methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**), methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**), and methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**) as models. The geometry of the conformers around the C5−C6 bond for the methyl 2,3,4-trideoxy-D-*glycero*-hexopyranosides was determined by gradient optimization at the SCF level using the 6-31G*, 6-31+G*, and 6-311++G** basis sets. The optimized geometries were used to calculate the energy of the gauche−trans (*gt*), trans−gauche (*tg*), and gauche−gauche (*gg*) conformers with the 6-31G*, 6-31+G* 6-31+G**, 6-31G**, 6-311G*, and 6-311++G** basis sets. Electron correlation effects were accounted for at the second-order Moller−Plesset perturbation (MP2) level using the 6-31G* basis set and using the adiabatic connection method (ACM) of density functional theory (DFT) using standard 6-31G*, dzvp, and cc-pvtz basis sets. Solvent effects on the stability of conformers were evaluated using a continuum model. At all levels of theory, **1** and **2** prefer the gauche over the trans conformers around the C5−C6 bond. This preference is due to internal hydrogen bonding which is possible in the *gg*(*sc*) and *gt*(−*sc*) conformers. Solvent effects decrease this preference by ∼0.9 kcal/mol. Methylation of the oxygen of the C6 hydroxyl completely reversed the relative energy of conformers, such that in **3** and **4**, the trans conformer is favored. The trans preference is decreased by solvent which stabilized the gauche conformers by 0.7−1.3 kcal/mol with respect to the trans. These results suggest that the gauche preference of the hydroxymethyl group in 1 and 2, is due to the presence of hydrogen bonding and not due to the gauche effect.

Introduction

The gauche effect was originally defined[1] as the tendency for a molecule to adopt that structure which has the maximum number of *synclinal* (*sc*, gauche, ±60°) interactions between adjacent electron pairs and/or polar bonds in a molecular fragment X−C−C−Y, where X and Y are two electronegative substituents. For compounds that contain the structural motif of O−C−C−O atoms this phenomenon means that the vicinal oxygen atoms prefer the synclinal, rather than the usual *antiperiplanar* (*ap*, trans, 180°) conformation. The exocyclic hydroxymethyl group in hexopyranosides represents such a segment (O5−C5−C6−O6), and it is of fundamental interest to determine the conformational behavior of this group. There are also significant practical concerns, given the importance of the conformation about the C5−C6 bond for determining the overall shape of oligosaccharides having (1→6) glycosidic linkages. Therefore, the conformational behavior of the C5−C6 linkage has been the subject of several investigations including both experimental and theoretical studies.[2]

The hydroxymethyl groups in carbohydrates usually exist in three staggered orientations (gauche−gauche, *gg*; trans−gauche, *tg*; and gauche−trans, *gt*) that correspond to local minima. In crystals,[3] the *gt* and *gg* rotamers are preferred for D-hexopyranoses having the hydroxyl group orientation at C4 as it is in D-glucopyranose (equatorial), while the *tg* and *gt* rotamers are preferred for those having the hydroxyl group orientation at C4 as it is in D-galactopyranose (axial). Solution conformations of the hydroxymethyl group are predominantly determined by NMR experiments using $^3J_{H5,H6}$ or $^3J_{C4,H6}$ coupling constants. Rotamer distributions based on the proton−proton couplings[4] are similar to those found in the solid state; however, very often a negative population for the *tg* conformer is reported. The calculated distributions of rotamers using the vicinal carbon−proton couplings[5] showed for both the gluco and galacto configurations the presence of all three rotamers with the population usually decreasing in the order *gt* > *gg* > *tg*. The gauche effect has often been used to rationalize the conformational behavior of the hydroxymethyl group in carbohydrates. However, it is important to realize that a gauche preference may result from intramolecular hydrogen bonding. Various computational methods have been used to predict the conformational preference of the hydroxymethyl group. In most studies the *tg* conformation is predicted to be the lowest energy conformation for the pyranoses of gluco configuration at C4. Results of calculations with the inclusion of solvent[6−8] showed a stabilization of the gauche conformation around the C5−C6 bond in solution and suggested that a preference for the *gt* and *gg* conformers over the *tg* might be due to interactions between the carbohydrate and its water environment. However, only a limited number of quantum chemical calculations for the O−C−C−O segment in carbohydrates or their cyclic models have been

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⊗ Abstract published in *Advance ACS Abstracts,* March 1, 1997.

S1089-5647(96)03766-2 CCC: $14.00

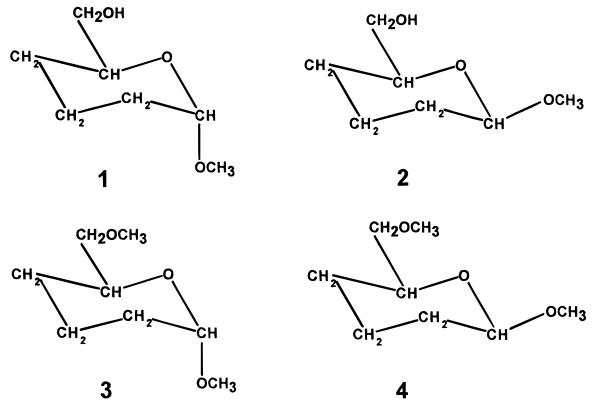

Figure 1. Schematic representation of methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**), methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**), methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**), and methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**).

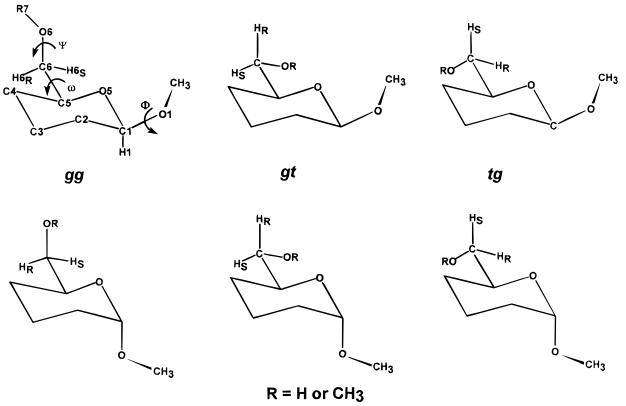

Figure 2. Schematic representation of the *gg*, *gt*, and *tg* conformers around the C5−C6 bond of methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**), methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**), methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**), and methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**) showing the labeling of atoms.

performed,[6,9−14] and a thorough study of the internal potential energy curves for rotation around the C5−C6 bond, using an extended basis set, has not been carried out.

Recently we have undertaken an *ab initio* analysis of the stereoelectronic effects on the geometry and the conformational behavior of the anomeric and aglycon part of the glycosidic linkage using cyclic model compounds.[15−18] In this paper we present results on the third type of exocyclic linkages that occur in carbohydrate derivatives, namely the C5−C6 linkage. The effects of basis set, electron correlation, and solvation on the energy of the conformers were calculated. The influence of intramolecular hydrogen bonding on the relative energy of the conformers was also evaluated.

Models and Computational Procedures

Methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**), methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**), methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**), and methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**) were chosen as models to study the gauche effect in hexapyranosides (Figure 1). The orientations about the C1−O1, C5−C6, and C6−O6 bonds (Figure 2) are described by torsion angles Φ [$\Phi = \Phi$(O5−C1−O1−C)], ω [$\omega = \omega$(O5−C5−C6−O6)], and Ψ [$\Psi = \Psi$(C5−C6−O6−R7)], where R is H (in **1**, **2**) or C (in **3**, **4**), respectively. An acronym of a conformer is based on the orientation about the C1−O1 bond (angle Φ) which is defined with respect to the O5 and C2 atoms as in our previous paper.[16] Thus, the three staggered conformers about the C1−O1 glycosidic bond are denoted as TG, GT, and GG. For the C5−C6 bond (angle ω) we used the standard nomenclature; the O5 and C4 are the reference atoms and staggered conformers are designated as the *gt* ($\omega \sim 60°$), *tg* ($\omega \sim 180°$), and *gg* ($\omega \sim -60°$).

The calculations were carried out using the GAUSSIAN 92 program[19] with standard basis sets. The optimizations of the geometry were performed at the SCF level with the 6-31G*, 6-31+G*, and 6-311++G** basis sets. The geometries were fully optimized using the gradient optimization routines in the program without any symmetry constraints, except for the dihedral angle ω, which was kept fixed. First, a 30° grid for ω was used, and the final refinement was carried out without freezing ω in order to locate the minimum on the rotational curve. Three different starting orientations of the hydrogen or methyl group (angle Ψ) linked to O6 were used, namely 180°, 60°, and −60°. Next, single-point calculations were performed for each minimum on the potential energy curve. For methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside and methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside calculations were carried out using the 6-31G*, 6-31+G*, 6-31G**, 6-31+G**, 6-311G*, and 6-311++G** basis sets, whereas for the methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside, and methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside only the 6-31G* and 6-311++G** basis sets were applied. Electron correlation effects were accounted for at the second-order Moller−Plesset perturbation (MP2) level[20] using the 6-31G* basis set. A hybrid Hartree−Fock density functional scheme, the adiabatic connection method[21] (ACM) of density functional theory,[22] was used with standard 6-31G* and valence double-ζ local DFT atom optimized plus single-polarization set per atom[23] (dzvp), and for some conformers also with correlation-consistent polarized valence triple-ζ[24] (cc-pvtz) basis sets. ACM calculations were carried out using the Turbomole 95.0 program.[25] Calculations of solvation energy were done using the Solvation 95.0 program.[26] The calculations were carried out at the University of Toronto on an HP 735 computer and at GlycoDesign Inc. on a Power Indigo 2 R8000 computer.

Results and Discussion

Hydroxymethyl Group. For **1** and **2**, in addition to the gauche effect, intramolecular hydrogen bonding between suitably located hydroxyl groups and the ring oxygen can also occur. As a result, conformational stability may be influenced. Therefore, in the first step of our calculations we attempted to eliminate the presence of hydrogen bonding in these compounds. Calculations were carried out by setting the C5−C6−O6−H7 dihedral angle Ψ at 180°. It appeared that for all optimized conformations the orientation of the H7 atom remained in the *ap* local minimum. For such an orientation of the H7, the intramolecular hydrogen bonding between H7 and O5 is not possible. The calculated conformational energy profiles for methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**) and methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**) are shown in Figure 3. The profiles calculated using the 6-31G* and 6-31+G* basis sets are almost identical for both compounds. The deepest minimum appears at $\omega = \sim 180°$ (*tg*), the second at $\omega = \sim 60°$ (*gt*), and the third at $\omega = \sim -60°$ (*gg*). The rotational barrier between the *tg* and *gt* conformers is approximately 4 kcal/mol and that between the *tg* and *gg* conformers is ∼6 kcal/mol. The synperiplanar barrier ($\omega = 0°$) between the *gt* and *gg* conformers is significantly larger, ∼9 kcal/mol. Besides the steric interactions, also electrostatic

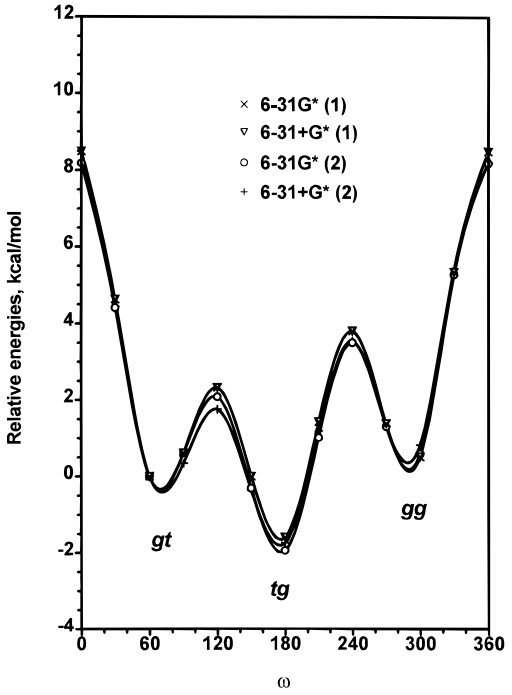

Figure 3. *Ab initio* potential energy of rotation about the C5−O6 linkage for methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**) and methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**) calculated at 6-31G* (×, ▽) and 6-31+G*//6-31G (○, +) levels with the *ap* starting orientation of Ψ.

TABLE 1: Comparison of the *ab Initio* Energies (hartrees) and Relative Energies (kcal/mol) of the Hydroxymethyl Group Conformers for Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (1) and Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (2) Calculated by Different Methods[a]

geometry	energy	*tg*	*gt*	*tg*	*gg*
Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (**1**)					
6-31G*	6-31G*	−497.796 517 7	1.24	0.00	1.78
	6-31+G*	−497.808 652 6	1.12	0.00	1.77
	6-31G**	−497.822 988 2	1.18	0.00	1.74
	6-31+G**	−497.834 758 8	1.08	0.00	1.73
	6-311G*	−497.904 399 9	1.17	0.00	1.82
	6-311++G**	−497.938 962 2	0.98	0.00	1.58
6-31+G*	6-31+G*	−497.808 737 6	1.11	0.00	1.75
	6-311++G**	−497.938 995 6	0.95	0.00	1.55
6-311++G**	6-311++G**	−497.939 079 2	0.95	0.00	1.56
Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (**2**)					
6-31G*	6-31G*	−497.794 440 3	1.62	0.00	2.17
	6-31+G*	−497.807 186 4	1.36	0.00	2.14
	6-31G**	−497.820 994 1	1.59	0.00	2.12
	6-31+G**	−497.833 332 5	1.33	0.00	2.12
	6-311G*	−497.902 829 1	1.53	0.00	2.2
	6-311++G**	−497.937 683 1	1.19	0.00	1.96
6-31+G*	6-31+G*	−497.807 263 8	1.36	0.00	2.14
	6-311++G**	−497.937 700 0	1.17	0.00	1.94
6-311++G**	6-311++G**	−497.937 779 5	1.17	0.00	1.94

[a] Torsional angle Ψ is in the *ap* local minimum.

repulsion between the dipole moments of the C1−O5−C5 and C6−O6−H7 segments contributes to these barrier heights. In fact, a larger resultant dipole moment is found for the conformer at $\omega = 0°$ than for the other orientations.

The energies of the *ap* local minima, calculated at different *ab initio* levels, are listed in Table 1. Considering the data in Table 1, it is clear that for the *ap* orientation of H7, regardless of the method, the *tg* orientation of the hydroxyl group is the most stable. The next most stable conformer is the *gt* orientation. The energy of the *gg* conformer is ∼0.5 kcal/mol higher than that of *gt*. A comparison of the relative energies (Table 1) reveals that the inclusion of diffuse functions into the basis set, i.e., the 6-31G* basis set versus the 6-31+G* basis set, decreases only slightly the energy difference between the *tg* and gt conformers from 1.24 to 1.12 kcal/mol for **1**, and from 1.62 to 1.36 kcal/mol for **2**. Further increase of basis set to 6-311++G** has only a small effect on this energy difference (decreased to 0.95 kcal/mol for **1**, and 1.19 kcal/mol for **2**).

TABLE 2: *Ab Initio* Calculated Relative Energies (Δ*E*, kcal/mol) at the 6-31G* Level and the Position of the *gt*, *tg*, and *gg* Minima[a] of the Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (1) and Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (2) in GT, TG, and GG Conformations around the Anomeric Bond

	GT		TG		GG	
C5−C6	*ω*	Δ*E*	*ω*	Δ*E*	*ω*	Δ*E*
Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (**1**)						
gt	70.7	1.23	71.5	6.18	72.6	12.59
tg	175.8	0.00[b]	176.9	3.88	176.1	10.00
gg	−69.8	1.78	−69.9	5.50	−70.7	12.05
Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (**2**)						
gt	70.4	1.62	71.1	5.05	70.0	6.68
tg	176.0	0.00[c]	176.3	2.89	176.1	4.36
gg	−70.5	2.16	−69.7	4.57	−71.7	6.63

[a] Torsional angle Ψ is in the *ap* local minimum. [b] $E = -497.796\,517\,7$ hartrees. [c] $E = -497.794\,440\,3$ hartrees.

The geometry of the above conformers was also optimized at the 6-31+G* and 6-311++G** levels to investigate the effect of further improvement of the basis set on the optimized geometry. The differences in geometrical parameters calculated at these three theoretical levels are not significant. This is also illustrated by data in Table 1. The calculated energies of conformers at 6-31+G* and 6-311++G** levels for the 6-31G* geometries are very close to those for the 6-31+G* and 6-311++G** geometries. The maximum deviation is less than 0.1 kcal/mol. Similar results were obtained in the case of 2-substituted tetrahydropyrans.[15,16] This suggests that the 6-31G* basis set is adequate to represent the geometrical features of C5−C6 conformers. Table 1 also indicates an influence of the configuration at the anomeric center on the stability of conformers.

It is known that the orientation of the hydroxymethyl group influences the conformational properties around the glycosidic linkage.[27] To evaluate how the conformation about the anomeric C1−O1 bond influences the stability of conformers about the C5−C6 bond, we have optimized the structure of the *tg*, *gt*, and *gg* conformers for three different orientations around the C1−O1 bond at the 6-31G* level. Table 2 shows the results for the minima we considered. As expected, small effects on the dihedral angle *ω* and the relative energy of the *tg*, *gt*, and *gg* conformers were observed. However, the relative energies of conformers with the TG and GG orientations around C1−O1 bond are too high for these conformers to be present in an equilibrium. For both compounds, conformers with the GT orientation are the dominant species in vacuum. It is noteworthy that the TG conformation is not a minimum on the conformational surface for methoxytetrahydropyran.[16] Therefore, in the remainder of this paper we have used the GT conformation as the only starting orientation around the C1−O1 bond.

The *tg* minimum corresponds to placing the O6 atom antiperiplanar (trans) to the ring oxygen. Apparently, the predicted preference of this conformer (Table 1) suggests that the O−C−C−O segment in carbohydrates does not exhibit a preference for the gauche orientation. These results are contradictory to experimental data on the conformational preference of the primary hydroxyl group in carbohydrates.[2]

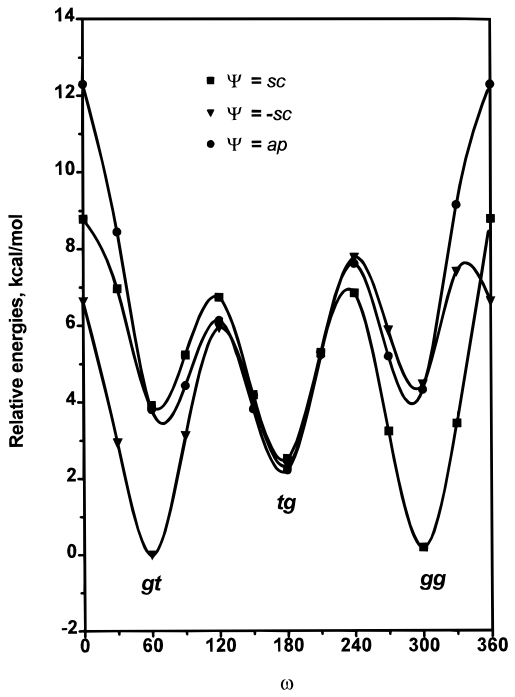

Figure 4. *Ab initio* 6-31G* potential energy of rotation about the C5−O6 linkage for methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**) calculated with a starting orientation of Ψ in the (a) *sc* (□) (b) −*sc* (▽), and (c) *ap* (○) orientation.

However, the above calculations with the *ap* orientation for the C5−C6−O6−H7 torsion angle eliminated the possibility of internal hydrogen bonding. To explore the influence of such an interaction on the stability of the C5−C6 conformers and to determine the energy difference between the conformers that are able to form intramolecular hydrogen bonds and those where this bond is not possible, we have repeated the calculation of the rotational profiles with the torsional angle Ψ in the *sc* and −*sc* starting positions using the 6-31G* basis set. The results are given in Figure 4. The structures of the nine minima were optimized without any geometrial constraints at the 6-31G* level. The location and dipole moments of the final minima for **1** and **2** are presented in Table 3.

It is evident, from a comparison of the two sets of calculations for **1** and **2**, that allowing the H7 hydrogen to adopt the *sc* or −*sc* orientations, changed the relative energy of conformers. Clear stabilization of *gt* ($\omega \sim -60°$) and *gg* ($\omega \sim 60°$) regions is seen on the conformational energy profiles (Figure 4). Two conformers, the *gt* with $\Psi = -sc$ and *gg* with $\Psi = sc$, are stabilized by a hydrogen bond between the H7 and O5 atoms (Figure 5). For 1, in *gt* (−*sc*), the nonbonded distances H7···O5 and O5···O6 are 2.32 and 3.73 Å, respectively, and the bond angle O5−H7−O6 is 105.8°; in *gg*(*sc*), these structural parameters are not significantly different, namely, 2.34 Å, 3.75 Å, and 105.7°, respectively. For **2**, in both corresponding conformers, nonbonded distances H7···O5 and O5···O6 are 2.34 and 3.76 Å, respectively and the bond angle O5−H7−O6 is 105.8°. As expected, in both compounds these conformers are lower in energy than any of the conformers which cannot form intramolecular hydrogen bonds. In **1**, the *gt* and *gg* conformers are 2.2 and 2.0 kcal/mol lower than the *tg* conformer. Similarly, in **2**, the *gt* and *gg* confromers are 1.6 and 2.2 kcal/mol lower than the *tg* conformer. Comparison of relative energy values in Table 3 with those in Table 1, shows that the stabilization of the *tg* and *gg* conformers due to intramolecular hydrogen bonding is 3.4 kcal/mol in **1** and 3.8 kcal/mol in **2**, respectively. These values can be assumed to be crude estimates of the hydrogen bond energy in **1** and **2** at the 6-31G* level. These

TABLE 3: Relative Energies (Δ*E*, kcal/mol), Location, and Dipole Moments (*D*) for Conformers of Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (1) and Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (2) Calculated Using the 6-31G* Basis Set

C5−C6	C6−O6	ω	Ψ	μ	Δ*E*
Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (**1**)					
gt	*sc*	65.8	66.4	1.94	3.82
	ap	70.7	−168.5	1.65	3.41
	−*sc*	58.2	−55.8	1.87	0.00[a]
tg	*sc*	176.0	79.5	1.62	2.49
	ap	175.7	178.9	1.44	2.18
	−*sc*	176.5	−72.2	1.76	2.33
gg	*sc*	−59.1	54.5	1.95	0.20
	ap	−67.0	170.3	1.72	3.96
	−*sc*	−67.0	−74.4	1.92	4.35
Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (**2**)					
gt	*sc*	63.6	63.6	3.21	3.86
	ap	70.3	178.7	2.06	3.50
	−*sc*	59.3	−54.8	1.87	0.07
tg	*sc*	176.5	81.1	1.29	2.27
	ap	176.0	178.5	1.36	1.88
	−*sc*	176.7	−74.2	2.48	2.21
gg	*sc*	−59.2	53.8	2.62	0.00[b]
	ap	−70.5	169.7	2.91	4.05
	−*sc*	−66.8	−73.9	3.23	4.44

[a] $E = -497.796\,517\,7$ hartrees. [b] $E = -497.794\,440\,3$ hartrees.

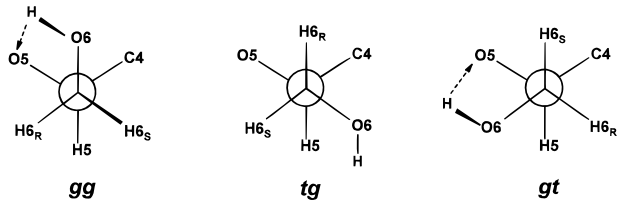

Figure 5. Schematic representation of the possibility for hydrogen bonding between H7 and O5 atoms in the *gg*, *gt*, and *tg* conformers of methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**) and methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**).

results are in agreement with the IR studies of 2-(hydroxymethyl)tetrahydropyran in carbon tetrachloride solution,[28] which showed that the hydroxyl group is completely hydrogen bonded. The relative energies of some *gt* and *gg* conformers are slightly higher (0.3−0.4 kcal/mol) for **2** than they are for **1**. This implies that the conformational equilibrium around the C5−C6 bond also depends on the configuration at the anomeric center.

Calculated structural parameters for the hydroxymethyl group showed several interesting trends. A comparison of the C5−C6 bond length for different rotamers around C5−C6 bond revealed a variation between 1.52 and 1.56 Å. This bond length enlarges as the energy of the conformer increases. Larger bond lengths were found for barriers, whereas smaller values occurred for minima on the rotational energy profiles. Such a dependence indicates that steric interactions play a major role in determining the stability of the C5−C6 conformations. On the other hand, insignificant differences in the C5−C6 bond length between the *gt*, *gg*, and *tg* conformers are not consistent with an explanation for the gauche preference based on $\sigma \rightarrow \sigma^*$ orbital interactions.[29,30] The calculated dihedral angles given in Table 3 show that the ω dihedral angle for a given rotamer varied up to 12°, depending on the orientation around the C6−O6 bond. The ω angle tends to move further away from its "ideal" staggered value, presumably to maximize or minimize steric and electrostatic interactions. The smallest deviations from these "ideal" values were found for conformers with hydrogen bonding, i.e., *gt*(−*sc*) and *gg*(*sc*). Since estimation of conformational equilibrium populations around the C5−C6 bond using measured vicinal coupling constants[2] is very sensitive to the

TABLE 4: Comparison of the *ab Initio* Relative Energies (kcal/mol) for Nine Conformers of Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (1) and Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (2) Calculated by Different Methods Using the 6-31G* Geometry

C5−C6	C6−O6	6-31G*	MP2/6-31G*	ACM/6-31G*	ACM/dzvp
Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (**1**)					
gt	*sc*	3.82	4.21	3.73	3.36
	ap	3.41	3.98	3.87	3.38
	−*sc*	0.00[a]	0.00[b]	0.00[c]	0.00[d]
tg	*sc*	2.49	3.31	2.93	2.75
	ap	2.18	3.31	3.20	2.83
	−*sc*	2.33	3.15	2.76	2.62
gg	*sc*	0.20	0.03	0.16	0.23
	ap	3.96	4.48	4.35	3.93
	−*sc*	4.35	4.45	4.08	3.84
Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (**2**)					
gt	*sc*	3.86	4.53	3.77	3.31
	ap	3.50	4.49	4.00	3.33
	−*sc*	0.07	0.43	0.15	0.00[h]
tg	*sc*	2.27	3.27	2.75	2.59
	ap	1.88	3.20	2.95	2.61
	−*sc*	2.21	3.19	2.68	2.60
gg	*sc*	0.00[e]	0.00[f]	0.00[g]	0.13
	ap	4.05	4.69	4.43	4.06
	−*sc*	4.44	4.69	4.18	4.01

Absolute energies: [a]$E = -497.796\,517\,7$; [b]$E = -499.282\,423\,6$; [c]$E = -500.661\,141\,3$; [d]$E = -500.751\,266\,6$; [e]$E = -497.794\,440\,3$; [f]$E = -499.278\,987\,6$; [g]$E = -500.659\,095\,4$; and [h]$E = -500.749\,541\,4$ hartrees.

values assumed for the dihedral angles for these conformers, the use of "ideal" values for the ω angle may considerably influence the predicted equilibrium populations. Especially, since a variation of 12° in the ω angle can lead to ±0.5 Hz change in vicinal coupling constants.[2,31]

Single-point calculations were carried out to estimate the electron correlation effects on the stability of conformers. These results are listed in Table 4. Compared with the relative energies determined with HF/6-31G* calculations, the MP2 energies of the conformers without hydrogen bonds rise relative to conformers with hydrogen bonds by 0.2−0.4 kcal/mol for *gt* and *gg* conformers and by 0.7−1.4 kcal/mol for *tg* conformers. Thus, the energy difference between the lowest energy conformers of the gauche and trans rotamers around the C5−C6 bond, the *gt*(−*sc*) versus *tg*(*ap*) conformer, increases by 1.13 kcal/mol to give 3.31 kcal/mol for **1**, and by 1.32 kcal/mol to give 3.20 kcal/mol for **2**. For **1**, the *tg*(−*sc*) and *gg*(*sc*) conformers, which both possess a hydrogen bond, become essentially equal in energy. In contrast, the corresponding energy difference for 2 increases to 0.4 kcal/mol. Note that inclusion of electron correlation changes the relative stability of conformers around the C6−O6 bond (angle Ψ) in the *tg* rotamer. The stability of conformers around C6−O6 for *tg* species decreases in the order $-sc > sc \sim ap$, whereas without electron correlation the order is $ap > -sc > sc$.

Of considerable interest are the results obtained with the emerging density functional methods[22] (DFT). These methods include electron correlation effects while being significantly less demanding than conventional approaches such as perturbation or coupled cluster methods. It has been recently shown[32,33] that among the several density functionals, the adiabatic connection method[21] (ACM) provides the best choice for the prediction of both energies of reactions and molecular geometries. The relative energies of nine conformers of **1** and **2** calculated by the ACM with 6-31G* and valence double-ζ local DFT atom optimized plus single-polarization set per atom[23] (dzvp) basis sets are compared with MP2/6-31G* results in Table 4. It can be seen that the extent of correlation effects at the 6-31G* level on relative energies is smaller using the ACM method compared to the MP2 method. The energy split between the conformers with and without hydrogen bonds decreased to 2.8 kcal/mol compared to 3.3 kcal/mol calculated with the MP2/6-31G* method. This value is ∼0.6 kcal/mol larger than that calculated by the HF/6-31G* method. The relative energies of other conformers calculated by the ACM/6-31G* method appeared also to be between the corresponding values calculated by the 6-31G* and MP2/6-31G* methods. ACM relative energies are basis set dependent. Examination of the energies in Table 4 shows a gradual decrease in ΔE as the basis set is enlarged. For the dzvp basis set, the ACM relative energies are 0.2−0.4 kcal/mol smaller compared to those at the 6-31G* level. For instance, at the ACM/6-31G* level, the relative energy of the *tg*(*ap*) conformer is 3.20 kcal/mol, but at the ACM/dzvp level the difference drops to 2.83 kcal/mol. To evaluate further the effect of basis set, we have calculated the relative energies of six relevant conformers of **2** using the correlation-consistent polarized valence triple-ζ (cc-pvtz) basis set[24] with the ACM method. The ACM/cc-pvtz relative energies of the *gg*(*sc*), *gg*(*ap*), *gt*(−*sc*), *gt*(*ap*), *tg*(−*sc*), and *tg*(*ap*) are 0.0, 3.57, 0.0, 2.90, 2.21, and 2.29 kcal/mol, respectively. It can be seen that a preference of conformers with hydrogen bonds, compared to those without such stabilizing interactions, has been decreased to 2.2 kcal/mol. This value is similar to that predicted by the 6-31G* basis set without taking into account electron correlation. The largest differences (∼0.6 kcal/mol) between the HF/6-31G* and ACM/cc-pvtz methods have been found for high-energy confomers. These results suggest that the MP2/6-31G* method overestimates both the hydrogen-bonding interactions and gauche−trans energy differences. These results are not unexpected. It has been shown[12,14−16] that the correlation effects at MP2/6-31G* are overestimated and may be decreased by using larger basis sets and by inclusion of the correlation energy at a higher level. On the other hand, these results also suggest that calculations with the 6-31G* basis set give reasonable prediction, of the relative energies of the low-energy conformers around the C5−C6 bond.

To provide some insight into the importance of solvent effects on the stability of conformers, we carried out calculations of solvation energy for all conformers using the solvation model of BIOSYM.[26] Within this continuum model, the total solvation free energy ΔG_{solv} is assumed to be the sum of an electrostatic contribution ΔG_{elst} with nonpolar contribution ΔG_n from van der Waals interactions with solvent and from the hydrophobic effect. The nonpolar component of the solvation energy appeared to be insensitive to the hydroxymethyl group conformational changes, the variation in ΔG_n being less than 0.1 kcal/mol. In contrast, the results with the electrostatic component of the solvation energy varied by 3 kcal/mol; $\Delta G_{elst} = -7.3$ to -9.6 kcal/mol for **1**; and $\Delta G_{elst} = -7.5$ to -10.3 kcal/mol for **2**. The total solvated relative free energies of all conformers, computed as the sum of the 6-31G* energy and the solvation free energy, are given in Table 5. These values show that in water, similarly as in vacuum, the *gt* and *gg* rotamer remained preferred relative to the *tg* rotamer. The relative energies of these rotamers, however, differ. Solvent effects considerably decrease the relative energy of all confomers that lack a hydrogen bond. For example, the energy difference between *gt*(−*sc*) and *tg*(*ap*) fell from 2.2 to 1.2 kcal/mol for **1** and from 1.9 to 0.8 kcal/mol for **2**. In other words, water decreases the relative energy difference between the trans (*tg* conformers) and gauche rotamers (*gt* and *gg* conformers) around the C5−C6 bond by ∼1 kcal/mol. However, when comparing only conformers that lack an intramolecular hydrogen bond, the

TABLE 5: Solvent Effect Contributions[a] to the Calculated 6-31G* Energy Differences (kcal/mol), for Nine Conformers of Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (1) and Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (2)

C5−C6	C6−O6	ΔE	ΔG_{solv}	ΔG_{tot}
Methyl 2,3,4-Trideoxy-α-D-*glycero*-hexopyranoside (**1**)				
gt	*sc*	3.82	−6.53	1.69
	ap	3.41	−5.98	1.83
	−*sc*	0.00	−4.40	0.00
tg	*sc*	2.49	−5.48	1.41
	ap	2.18	−5.42	1.16
	−*sc*	2.33	−5.60	1.13
gg	*sc*	0.20	−4.28	0.32
	ap	3.96	−6.21	2.15
	−*sc*	4.35	−6.45	2.29
Methyl 2,3,4-Trideoxy-*β*-D-*glycero*-hexopyranoside (**2**)				
gt	*sc*	3.86	−7.11	1.24
	ap	3.50	−6.37	1.62
	−*sc*	0.07	−4.56	0.00
tg	*sc*	2.27	−5.73	1.03
	ap	1.88	−5.56	0.81
	−*sc*	2.21	−6.19	0.51
gg	*sc*	0.00	−4.49	0.00
	ap	4.05	−6.92	1.63
	−*sc*	4.44	−7.28	1.65

[a] $\Delta G_{tot} = \Delta E + \Delta G_{solv}$.

influence of solvent is reversed. The gauche rotamers are more stabilized by water than the trans rotamers by 0.4−1.0 kcal/mol.

Methoxymethyl Group. Conformational preferences around the C5−C6 bond in the methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**) and methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**) are of particular relevance to (1→6)-linked oligosaccharides. As intramolecular hydrogen bonding is not possible in these compounds, the values obtained also provide more direct information on the gauche effect in carbohydrates than those from **1** and **2**. On the other hand, steric interactions between the O6 methyl group and ring substituents may be more severe for some conformations than in 1 and 2. This is also reflected in the conformational energy profiles calculated using the 6-31G* basis set which are shown for **3** in Figure 6. For the *ap* starting orientation of the methyl group, the calculation predicted an approximate 3-fold symmetry for the torsional potential (Figure 6). The optimized orientation of the methyl group in this case remained the *ap* orientation for all conformers. The *ap* profile resembles those calculated for **1** and **2** with $\Psi = ap$. For the *sc* and −*sc* starting orientations, however, due to the steric interactions mentioned above, these orientations changed for some values of the ω angle during minimization. For the *sc* starting orientation we have not found the *sc* local minimum for values of the dihedral angle ω between 150° and 240°. During the optimization of geometry, the orientation of the methyl group always shifted to the *ap* orientation. Therefore, for this region we have fixed the Ψ angle at 60°. A barrier of ∼11 kcal/mol then occured at $\omega = 150°$. Similarly, we observed a shift of Ψ from the −*sc* starting orientation to the *ap* orientation for $\omega = 270°$ and 300°. For this case, we have the Ψ diheral angle at a value of −60°. As a result, the energy of the local minimum in the *gg* region increased to ∼8 kcal/mol. The final refinement without constraints led to seven minima for each of the compounds. As expected from the rotational profile calculations, two minima *tg*(*sc*) and *gg*(−*sc*) were not found. The location, dipole moments and relative energies of the seven final minima at 6-31G* level are given in Table 6.

The effect of methylation of O6, going from **1** (**2**) to **3** (**4**), results in a large stabilization of the *tg* relative to the *gt* and *gg* rotamers. On the basis of the results for **1** and **2**, we assume that the increase in the relative energies of the *gt* and *gg* rotamers arises from a loss of the stabilization from the internal hydrogen bonding. At all levels of theory (Table 6), the *tg*(*ap*) conformer has the lowest energy. The relative energy of the second lowest energy confromer, *gt*(*ap*), slightly decreases with increasing basis set from 6-31G* to 6-311++G**. An interesting feature is that this decrease is larger for **4** than for **3**, 0.43 versus 0.21 kcal/mol. A similar pattern of relative energies was obtained at the ACM/dzvp//6-31G* level. Again, as in the case of **1** and **2**, larger differences between the relative energies calculated

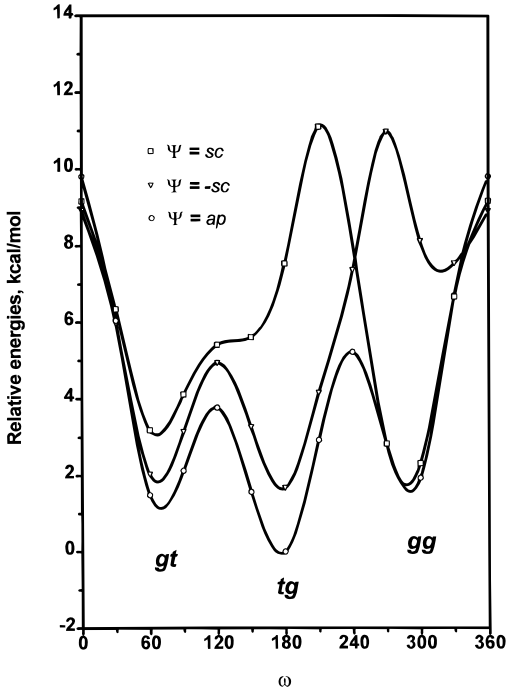

Figure 6. *Ab initio* 6-31G* potential energy of rotation about the C5−O6 linkage for methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**), calculated with a starting orientation of Ψ in the (a) *sc* (□) (b) −*sc* (▽), and (c) *ap* (○) orientation.

TABLE 6: Location and Dipole Moments (*D*) for Conformers of Methyl 6-*O*-Methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (3) and Methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (4) Calculated Using the 6-31G* Basis Set and Relative Energies (ΔE, kcal/mol) Calculated by Different Methods Using the 6-31G* Geometry

C5−C6	C6−O6	ω	Ψ	μ	6-31G*	6-311++G**	ACM/dzvp
Methyl 6-*O*-Methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**)							
gt	*sc*	67.6	85.3	1.57	3.07	3.02	1.93
	ap	70.3	184.5	1.31	1.17	0.96	1.14
	−*sc*	67.4	−99.0	1.21	1.89	1.83	2.10
tg	*ap*	175.8	179.9	1.11	0.00[a]	0.00[b]	0.00[c]
	−*sc*	177.7	−86.4	1.41	1.72	1.91	1.34
gg	*sc*	−72.3	87.6	1.40	1.95	2.16	1.13
	ap	−69.5	176.8	1.37	1.65	1.51	0.95
Methyl 6-*O*-Methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**)							
gt	*sc*	65.0	82.8	2.99	3.37	3.22	2.03
	ap	70.0	184.4	2.00	1.54	1.14	0.66
	−*sc*	67.9	−100.6	0.77	2.37	2.10	1.45
tg	*ap*	176.1	179.8	1.37	0.00[d]	0.00[e]	0.00[f]
	−*sc*	177.9	−87.8	2.32	1.85	2.08	1.47
gg	*sc*	−72.9	85.3	1.85	1.95	2.19	1.16
	ap	−69.9	176.3	2.65	2.00	1.86	1.28

[a] $E = -536.825\,448\,4$ hartrees. [b] $E = -536.970\,521\,1$ hartrees. [c] $E = -540.039\,623\,2$ hartrees. [d] $E = -536.823\,340\,2$ hartrees. [e] $E = -536.969\,221\,2$ hartrees. [f] $E = -540.039\,012\,9$ hartrees.

TABLE 7: Solvent Effect Corrections[a] to the Calculated 6-31G* Energy Differences (kcal/mol) for Seven Conformers of Methyl 6-*O*-Methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (3) Methyl 6-*O*-Methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (4)

C5−C6	C6−O6	ΔE	ΔG_{solv}	ΔG_{tot}
Methyl 6-*O*-Methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**)				
gt	*sc*	3.07	−0.39	2.39
	ap	1.17	−0.40	0.48
	−*sc*	1.89	−0.19	1.79
tg	*ap*	0.00	0.29	0.00
	−*sc*	1.72	0.26	1.68
gg	*sc*	1.95	0.27	1.93
	ap	1.65	−0.41	0.94
Methyl 6-*O*-Methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**)				
gt	*sc*	3.37	−1.07	2.31
	ap	1.54	−0.78	0.77
	−*sc*	2.37	−0.44	1.94
tg	*ap*	0.00	−0.02	0.00
	−*sc*	1.85	−0.24	1.63
gg	*sc*	1.95	−0.14	1.83
	ap	2.00	−1.36	0.65

[a] $\Delta G_{tot} = \Delta E + \Delta G_{solv}$.

by the 6-31G* and ACM/dzvp methods were observed for the higher energy conformers.

The solvation free energies and total solvated relative free energies of all conformers of **3** and **4** are given in Table 7. As for **1** and **2**, we observed that the electrostatic component of the solvation energy is responsible for the conformational dependence of the solvation free energy. The variation in ΔG_{solv} is 0.7 kcal/mol for **3** and 1.34 kcal/mol for **4**. Thus, the relative energies of conformers are considerably changed by including solvent effects. Since the stabilization of *tg* rotamers by solvent effects is less favorable than that for *gt* and *gg* rotamers, solvent effects decrease the energy difference between the *tg* rotamers and the *gt* and *gg* rotamers by 0.7−1.3 kcal/mol.

Gauche Effect and the Conformation around the C5−C6 Bond. There are four major effects assumed to influence the conformational preferences around the C5−C6 bond, the gauche effect, hydrogen bonding, steric interactions, and solvent effects. Their relative importance can be estimated by a comparison of the results for **1**−**4**. The calculations clearly showed that the *tg* conformation of the C5−C6 dihedral angle is most favored in methylated compounds (**3**, **4**) and in nonmethylated compounds (**1**, **2**) with the *ap* orientation of H7. On the other hand, hydrogen bonding in the *gt*(−*sc*) and *gg*(*sc*) conformers favor the *gt* and *gg* conformations over the *tg* conformation around the C5−C6 bond in **1** and **2**. The effect of solvent on the stability of conformers depends on the character of the atoms linked to the oxygen atom. For **1** and **2**, the solvent effect stabilized the *tg* conformation. This stabilization decreases the calculated preferences of *gg* and *gt* conformers by ∼1 kcal/mol. The gauche preference in **1** and **2** is in accordance with the gauche preference observed for saccharides.[2] However, the stability of conformers around the C5−C6 bond in saccharides is influenced by the presence of ring substituents, such as hydroxyl groups. Interactions between these groups were not accounted for in this study. Therefore, quantitative comparison were not performed here. We have carried out an investigation of the C5−C6 equilibrium for D-glucopyranose and D-galactopyranose derivatives at a similar level of theory as used in this work and will report these results shortly. In contrast, for **3** and **4**, solvent effects stabilize the gauche conformer around the C5−C6 bond (*gt* and *gg* conformers) by 0.7−1.3 kcal/mol with respect to the trans conformation (*tg* conformers). This amount is, however, not quite enough to reverse the conformational preference in favor of the *gg* or *gt* conformers. It should be noted that ∼0.9 kcal/mol stabilization of the gauche conformer with respect to the trans conformer by solvent effects was estimated recently for *β*-D-glucopyranose[14] and 1,2-dimethoxyethane.[34] The results presented here suggest that the gauche preference of the hydroxymethyl group is mainly due to the presence of hydrogen bonding and not to some intrinsic conformational preference (gauche effect).

Conclusion

Geometries and energies of conformers around the exo-cyclic C5−C6 bond in the methyl 2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**1**), methyl 2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**2**), methyl 6-*O*-methyl-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside (**3**), and methyl 6-*O*-methyl-2,3,4-trideoxy-*β*-D-*glycero*-hexopyranoside (**4**) have been obtained at various levels of *ab initio* quantum chemical calculations involving Hartree−Fock, perturbation (MP2), and the adiabatic connection method (ACM) of density functional theory (DFT).

At all levels of theory, the *gg*(*sc*) and *gt*(−*sc*) conformers are favored over the *tg* conformers for **1** and **2**. This preference is due to internal hydrogen bonding which is possible only in these conformers. Solvent effects decrease this preference by ∼0.9 kcal/mol.

Methylation of the hydroxymethyl group oxygen completely reverses the relative energy of conformers. As a result, in **3** and **4**, the *tg* conformer is favored. Solvent stabilizes the *gt* conformer by 0.7 kcal/mol with respect to the *tg*.

These results suggest that in the gas phase the gauche effect does not play a dominant role in determining the conformational properties of the hydroxymethyl and methoxymethyl groups. These results also contribute to a better understanding of the effects which determine the conformational properties of the (1→6) glycosidic linkage in complex carbohydrate molecules.

Acknowledgment. This investigation was supported by grants from the Canadian Protein Engineering Network of Centres of Excellence and from the Slovak Grant Agency of Sciences.

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