Angular Dependence of the C-6 Chemical Shift and the Conformation of the Hydroxymethyl Group in Carbohydrates*

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Semiempirical quantum-mechanical nuclear shielding calculations (FTP INDO method) have been performed on a series of 16 hexopyranoses for conformational studies of hydroxymethyl groups in carbohydrates. The calculated shielding for the C-6 and C-5 atoms shows an angular dependence of up to $\delta = 8$ which is in agreement with that found experimentally. The dependence of the C-6 chemical shift on the dihedral angle ω is presented by a trigonometric function of the form $\delta(C) = A \sin\omega + B \sin 2\omega + C \sin 3\omega + D \cos\omega + E \cos 2\omega + F \cos 3\omega + G$ with different A—G constants for both series of hexopyranoses with different configuration at their C-4 atoms. This angular dependence may be applied for prediction of conformations about the C-5—C-6 bond in noncrystalline materials. It is also demonstrated that this dependence together with the angular dependence for C-5 atom, can be useful in estimating the conformational preferences of the hydroxymethyl group in carbohydrates in solution having the configurations at C-4 as in D-glucose and D-galactose.

Carbohydrates are the most abundant biomolecules occurring in all living organisms. Recently, parallel to the effort to understand and explain their function and specificity [1], there has been a considerable interest in the elucidation of three-dimensional structures of carbohydrates [2]. The major experimental tools for determining three-dimensional structures are X-ray diffraction and nuclear magnetic resonance (NMR) spectroscopy. Unfortunately, the amount of available crystallographic data on complex carbohydrates is very limited due to their poor crystallinity. In solution, a carbohydrate conformation can be elucidated using chemical shifts, coupling constants, and nuclear Overhauser effects. However, due to the flexibility of carbohydrates, NMR experimental data represent a weighted average on the NMR time-scale of all conformers accessible by the molecule. Therefore, NMR studies must be generally performed in conjunction with molecular modelling [3]. Furthermore, to use the structural information contained in NMR spectra, it is necessary to relate them with geometrical parameters. In the case of coupling constants a number of correlations between their magnitude and stereochemical structure have been published [4, 5].

The carbon chemical shift, $\delta(C)$, is one of the most important NMR parameters for providing information concerning a molecular structure. Recent ^{13}C NMR studies on saccharides in the solid state [6—13], as measured by the cross-polarization magic angle spinning (CP/MAS) technique, demonstrated that ^{13}C chemical shifts of C-1, C-4, and C-6 atoms of hexoses are displaced up to $\delta = 8$, depending on the particular conformations adopted. The anomeric and *exo*-anomeric effects have been suggested as an explanation [14] for the relationships between chemical shift and glycosidic conformation. Recently, *ab initio* quantum-mechanical shielding calculations have been performed on the acyclic model of α-(1→4) glycosidic linkage [15]. Empirical correlations between chemical shift and conformation have been established for groups of related saccharides [7, 12, 16, 17]. It is clear, however, that these correlations should be continuous functions of torsion angles and a development of such a dependence is of interest from many aspects.

Besides rotations about the glycosidic torsion angles, the conformation of hydroxymethyl groups is one of the main degrees of conformational freedom in carbohydrates. Furthermore, for oligosaccharides with (1→6) glycosidic linkages, the orientation around the C-5—C-6 bond constitutes an important factor describing the overall shape of molecules. In this paper we report on the angular dependence of C-6 and C-5

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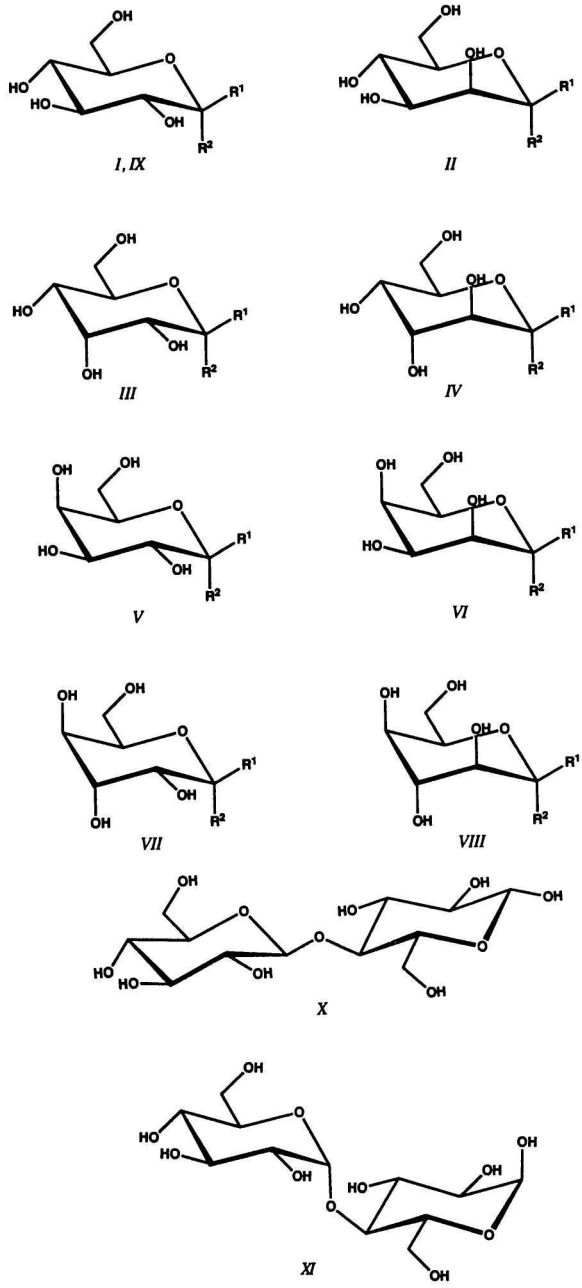

Scheme 1

Schematic representation of D-glucopyranose (*I*), D-mannopyranose (*II*), D-allopyranose (*III*), D-altropyranose (*IV*),D-galactopyranose (*V*), D-talopyranose (*VI*), D-gulopyranose (*VII*), D-idopyranose (*VIII*), methyl D-glucopyranoside (*IX*), cellobiose (*X*), and maltose (*XI*). For compounds *I*—*VIII* R^1 = H and R^2 = OH (α-anomer), R^1 = OH and R^2 = H (β-anomer). For compound *IX*, R^1 = H and R^2 = OMe (α-anomer), R^1 = OMe and R^2 = H (β-anomer). Only the β-form of cellobiose and α-form of maltose have been represented.

chemical shifts on the torsion angle ω (C-4—C-5—C-6—O-6) which describes the orientation about the C-5—C-6 bond. The angular dependences of carbon shielding on hydroxymethyl conformations were investigated in a series of 16 hexopyranoses using quantum-chemical methods. The calculated dependences were expressed in the form of trigonometric equations and then adjusted to chemical shift values obtained in the solid state.

METHODS

Structures of the α- (*a*) and β-anomers (*b*) of D-glucopyranose (*I*), D-mannopyranose (*II*), D-allopyranose (*III*), D-altropyranose (*IV*), D-galactopyranose (*V*), D-talopyranose (*VI*), D-gulopyranose (*VII*), and D-idopyranose (*VIII*) were obtained using the molecular mechanics program CHARMm [18]. These compounds are represented in Scheme 1. Optimization of the conformer geometry about the C-5—C-6 bond, described by the torsion angle ω (C-4—C-5—C-6—O-6), was performed using the original CHARMm force field [18]. These gas-phase structures of individual hexopyranose conformers were used in further calculations.

Calculations of the ^{13}C shielding constants, σ(C), were carried out by the finite perturbation theory (FTP) formulation with the intermediate neglect of differential overlap (INDO) approximation of unrestricted self-consistent-field (SCF) semiempirical molecular orbitals (MO) theory [19, 20] using a parameter set of $\beta_H^* = -13$ eV, $\beta_H^* = -15$ eV, and $\beta_O^* = -27$ eV. It has been demonstrated [19—21] that FTP INDO method adequately represents important chemical trends at a computational cost low enough to allow investigations of relatively large molecules. However, as a result of lower magnitudes, we must resort to a linear scaling of the calculated shielding constants. For this purpose, the available *ab initio* values on angular dependence of ^{13}C shieldings in ethane [22] are used. Linear regression analysis led to a fit of $\delta(C)_{ab\ initio} = 5.22\ \delta(C)_{INDO} - 0.01$ (with a correlation coefficient $r = 0.99997$). This linear fit has been used throughout the study for a conversion of FTP INDO shieldings values to *ab initio* values. In order to evaluate the influence of the medium on the calculated shieldings, FTP INDO calculations of σ(C) were performed for two different relative permittivities ($\varepsilon_r = 1$ for crystalline structures and $\varepsilon_r = 78$ for aqueous solutions).

All samples of α- and β-D-glucopyranose (*I*), α- and β-D-galactopyranose (*V*), methyl α- and β-D-glucopyranoside (*IX*), cellobiose (*X*), and maltose (*XI*) (see Scheme 1) used for NMR measurements were commercial compounds from Sigma. They were dissolved in 99.8 % D_2O as 30 mg cm^{-3} solutions. The spectra were recorded at 75 MHz for ^{13}C with a Bruker spectrometer (AC 300) equipped with a process controller, an Aspect 3000 computer, and varying temperature system. They were obtained in the FT mode at 298 K with a spectral width of 15000 Hz and a resolution of 1.85 Hz per point. Chemical shifts are given with respect to internal acetone ($\delta = 31.1$ from TMS).

Table 1. Calculated *A*—*G* (Hz) Constants of Eqn (*1*) for σ(C-6) Shielding Values in D-Hexopyranoses (*I*—*VIII*)

$\varepsilon_r = 1$

Compound	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Ia	−1.79	1.66	0.88	0.35	0.14	−0.03	−0.01
Ib	−1.75	1.65	0.85	0.33	0.31	0.05	0.10
IIa	−1.78	1.64	0.88	0.39	0.16	−0.04	−0.04
IIb	−1.75	1.59	0.86	0.34	0.31	0.00	0.10
IIIa	−1.77	1.66	0.89	0.47	0.30	−0.06	−0.04
IIIb	−1.75	1.65	0.86	0.43	0.44	0.00	0.07
IVa	−1.75	1.64	0.90	0.52	0.31	−0.07	−0.09
IVb	−1.74	1.59	0.86	0.44	0.46	−0.04	0.08
Va	−1.36	2.24	0.09	1.03	0.01	−0.34	−1.60
Vb	−1.35	2.19	0.22	0.93	0.04	−0.41	−1.63
VIa	−1.44	2.15	0.10	1.06	0.05	−0.34	−1.50
VIb	−1.44	2.13	0.23	0.94	0.08	−0.42	−1.52
VIIa	−1.31	2.31	0.03	1.07	0.09	−0.39	−1.73
VIIb	−1.27	2.26	0.15	0.95	0.13	−0.44	−1.74
VIIIa	−1.44	2.14	0.10	1.05	0.05	−0.34	−1.50
VIIIb	−1.41	2.17	0.09	1.01	0.16	−0.37	−1.48
I—*IV*	−1.76	1.64	0.87	0.41	0.30	−0.02	0.02
V—*VIII*	−1.38	2.20	0.12	1.00	0.08	−0.38	−1.59

$\varepsilon_r = 78$

Compound	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Ia	−2.21	2.15	0.75	−0.04	−0.27	−0.16	−0.04
Ib	−2.32	2.20	0.69	−0.09	−0.08	−0.11	0.18
Va	−2.24	2.23	−0.32	0.52	−0.10	−0.12	0.03
Vb	−2.40	2.14	−0.31	0.35	−0.05	−0.07	0.37
gluco	−2.26	2.18	0.72	−0.07	−0.18	−0.13	0.07
galacto	−2.32	2.18	−0.31	0.43	−0.07	−0.10	0.20

RESULTS AND DISCUSSION

The σ(C) shielding values of the C-6 carbon atom were calculated using a 20° increment step for the ω range, and for the α- and β-anomers of all hexopyranoses (*I*—*VIII*). The range of the values of carbon shieldings in *I*—*VIII* is $\sigma = 8$ with a minimum at $\omega \approx 120°$. The calculated results are fitted to eqn (*1*) and coefficients *A*—*G* are listed in Table 1.

$$\sigma(\mathrm{C}) = A\sin\omega + B\sin 2\omega + C\sin 3\omega + D\cos\omega + E\cos 2\omega + F\cos 3\omega + G \qquad (1)$$

Inspection of the data in Table 1 indicates that configuration at the anomeric carbon atom has a very little effect on the calculated σ(C-6) values. On the contrary, a difference between the calculated angular dependence for hexopyranoses having the configurations at C-4 as in D-glucose and D-galactose is noticeable. Based on this difference, it seems reasonable to establish a different angular dependence of σ(C-6) values for these hexopyranoses. The dependences of σ(C-6) on the dihedral angle ω were derived by fitting the *A*—*F* constants to calculated σ(C-6) values for compounds *I*—*IV* having the same configuration at C-4 as it is in D-glucose and compounds *V*—*VIII* with the configuration at C-4 as in D-galactose.

Though angular dependences of σ(C-6) are assumed to be described adequately [19—21], their absolute values still have to be adjusted. Since a difference in absolute values is associated with the constant *G*, a shift of all the values by a constant amount based on experimental data is a common procedure [5]. Thus, the constants *G* were adjusted using δ(C-6) values from solid state NMR [7, 23] and known crystal structures for β- and α-D-glucopyranose [24] $\omega = 59.1°$, δ(C-6) = 61.15, β-D-galactopyranose [25] $\omega = 178.7°$, δ(C-6) = 62.50. As a result, the *G* values of 61.08 and 63.17 were obtained for both types of configurations, respectively. Furthermore, in this way the C-13 shieldings were converted to the carbon chemical shifts δ(C) usually observed by experiment. The resultant angular dependence of δ(C-6) has the following form for the same configuration at C-4 as it is in D-glucose

$$\delta(\mathrm{C\text{-}6}) = -1.76\sin\omega + 1.64\sin 2\omega + 0.87\sin 3\omega + 0.41\cos\omega + 0.30\cos 2\omega - 0.02\cos 3\omega + 61.08 \qquad (2)$$

and for the configuration as in D-galactose

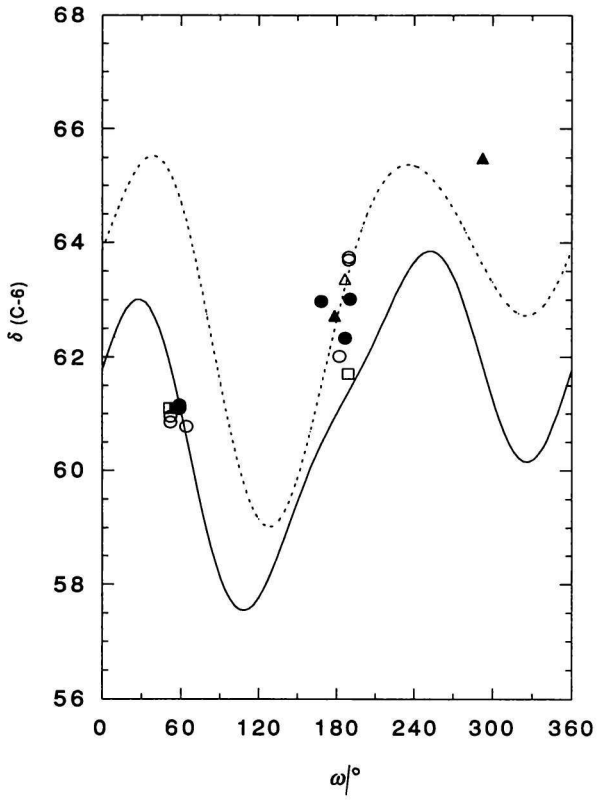

Fig. 1. A plot of the final angular dependence of δ(C-6) values (δ relative to TMS) on ω torsion angle for hexopyranoses with the configuration at C-4 as in D-glucose (—) and D-galactose (– – –). For a comparison, solid state experimental data on β-D-glucopyranose (●), α-D-glucopyranose (○), β-D-galactopyranose (△), α-D-galactopyranose (▲), α-cyclodextrin (□), and β-cyclodextrin (■) [7, 9, 13, 22] using known crystal structures [23—32] are included.

$$\delta(\text{C-6}) = -1.38\sin\omega + 2.20\sin 2\omega + 0.12\sin 3\omega + 1.00\cos\omega + 0.08\cos 2\omega - 0.38\cos 3\omega + 63.17 \quad (3)$$

These final angular dependences are plotted as a function of ω in Fig. 1. For a qualitative comparison, experimental δ(C-6) values, from solid state NMR for several saccharides [7, 9, 13, 23] having known crystal structures [24—33], are also included in Fig. 1. Since hydroxymethyl groups in crystal structures of carbohydrates assume one of the favoured conformations, the experimental results are not distributed over all ω angles. In spite of this, the agreement (within δ = 1—2) between observed and calculated chemical shifts is reasonable (especially, when solid state NMR studies of carbohydrates [9] showed that chemical shifts of C-6 are very sensitive to molecular conformation and lattice structure). Also the interval of accuracy of dihedral angles is often found between 2 and 7°. Moreover, in complex carbohydrates as cyclodextrins, the ω angle for the different residues may show a very large range of dihedral angles. Then it should be noted that chemical shift differences may be a result of such distortion, or inadequacies of the X-ray-determined model. Based on these results, it is assumed that the angular dependence of δ(C-6) values on ω torsion angle presented here might be particularly useful for evaluating the C-5—C-6 conformation in carbohydrates with poor crystallinity, such as polycrystalline or powder samples and gels, for which the use of X-ray is limited.

Next, we have attempted to estimate the rotamer populations about the C-5—C-6 bond for some saccharides in solution using the calculated angular dependences of δ(C-6) values. For this purpose, the angular dependences of δ(C-6) values were calculated using the solvent relative permittivity ε_r = 78. The corresponding *A*—*G* constants are given in Table 1. Application of the angular dependence of C-6 chemical shift to elucidate the hydroxymethyl group conformation in solution is not so straightforward as in solid state due to the motionally averaged character of chemical shifts.

The exocyclic hydroxymethyl groups in carbohydrates in solution usually exist in three staggered orientations (*gauche-gauche*, *gg*; *trans-gauche*, *tg*; and *gauche-trans*, *gt*) that correspond to local minima. The solution conformation of the hydroxymethyl groups can be determined by NMR studies using three-bond proton—proton coupling constants [4]. However, interpretation of the coupling constants is sometimes complicated by estimation of a negative population for the *tg* conformer, which has, of course, no physical meaning. Therefore, carbon—proton coupling constants [5, 34] have been also used for this purpose. However, as when dealing with energy calculations, the problems of conformational analysis of carbohydrates are numerous and depend on several parameters: flexibility, extensive hydrogen bonding, and stereoelectronic effects, such as the anomeric, *exo*-anomeric, and *gauche* effects [35]. Thus, a theoretical prediction of the hydroxymethyl group conformation in solution is a very difficult task [36] and an exhaustive discussion of these questions is out of the scope of this paper.

The schematic representation of the preferred rotamers about the C-5—C-6 bond in D-hexopyranoses and the numbering of the relevant atoms is shown in Fig. 2. Their populations can be calculated on the basis of eqns (*4*—*6*)

$$x_{gg} + x_{gt} + x_{tg} = 1 \quad (4)$$

$$\delta(\text{C-6})_{gg}x_{gg} + \delta(\text{C-6})_{gt}x_{gt} + \delta(\text{C-6})_{tg}x_{tg} = \delta(\text{C-6})_{\text{exp}} \quad (5)$$

$$\delta(\text{C-5})_{gg}x_{gg} + \delta(\text{C-5})_{gt}x_{gt} + \delta(\text{C-5})_{tg}x_{tg} = \delta(\text{C-5})_{\text{exp}} \quad (6)$$

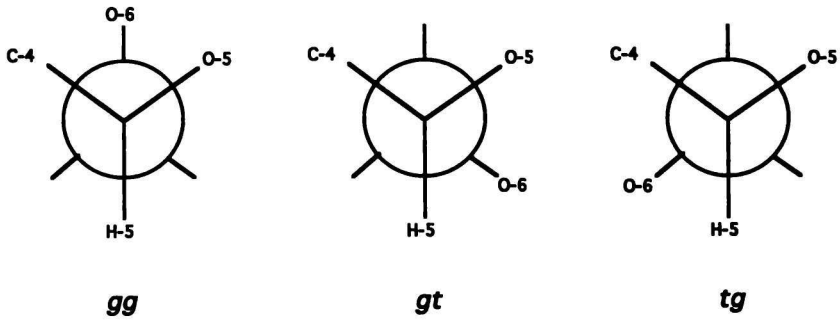

Fig. 2. Schematic representation of the three staggered conformations for the hydroxymethyl group of D-hexopyranoses and the numbering of relevant atoms.

where x_{gg}, x_{gt}, and x_{tg} are the rotamer populations, $\delta(\text{C-6})_i$ ($i = gg, gt$, and tg) are the calculated values of carbon chemical shifts in the individual gg, gt, and tg rotamers using eqns (*7*—*10*), and $\delta(\text{C})_{\text{exp}}$ are the corresponding experimental values.

The solution of these equations necessitates to know the corresponding $\delta(\text{C-5})_i$ values. Therefore, the angular dependences of δ(C-5) for D-glucopyranose and D-galactopyranose have been calculated using the same approach as for δ(C-6) values. For δ(C-5), besides the change of the torsion angle ω, there are other factors which influence the magnitude of δ(C-5). For example, the influence of structural features in terms of spatial proton—proton interactions which results in upfield or downfield shift of the signal has been thoroughly studied [16, 37]. This suggests that a universal equation for the angular dependence for δ(C-5) is certainly difficult to establish. Though the angular dependences of δ(C-5) for different compounds might be similar, the absolute values of δ(C-5) may differ by $\delta = 1$—7. Therefore, the angular dependences of δ(C-5) for D-glucopyranose and D-galactopyranose were calculated assuming also different absolute values for α- and β-anomers. This led to the following dependences for D-glucopyranose

$$\delta(\text{C-5}) = -2.18\sin\omega + 2.32\sin 2\omega + 0.86\sin 3\omega + 0.13\cos\omega - 0.70\cos 2\omega - 0.24\cos 3\omega + G \quad (7)$$

with $G = 71.50$ (α-anomer) or 76.10 (β-anomer),

$$\delta(\text{C-6}) = -2.26\sin\omega + 2.18\sin 2\omega + 0.72\sin 3\omega - 0.07\cos\omega - 0.18\cos 2\omega - 0.13\cos 3\omega + G \quad (8)$$

with $G = 61.0$ (α- and β-anomers), and for D-galactopyranose

$$\delta(\text{C-5}) = -1.61\sin\omega + 2.51\sin 2\omega + 0.24\sin 3\omega + 0.61\cos\omega - 0.97\cos 2\omega - 0.60\cos 3\omega + G \quad (9)$$

Table 2. Carbon Chemical Shifts δ(C) for Staggered Rotamer s[a] about the C-5—C-6 Bond in D-Hexopyranoses having the Configurations as in D-Glucose and D-Galactose Calculated Using Eqns (*7*—*10*)

Rotamer	ω	δ(C-5)	δ(C-6)
	α-gluco		
gg	57.3	72.50	61.35
gt	−167.4	71.87	61.99
tg	−59.1	71.92	61.16
	β-gluco		
gg	56.8	77.14	61.39
gt	−168.1	76.42	61.94
tg	−58.4	76.43	61.09
	α-galacto		
gg	55.8	72.84	61.41
gt	−163.8	71.11	62.65
tg	−47.2	69.99	61.10
	β-galacto		
gg	55.8	77.54	61.41
gt	−164.0	75.80	62.63
tg	−46.9	74.66	61.09

a) The magnitudes of torsion angles are based on structures of methyl D-glycoside models calculated by the *ab initio* method using the 6-31G* basis set [34].

with $G = 70.50$ (α-anomer) or 75.20 (β-anomer),

$$\delta(\text{C-6}) = -2.32\sin\omega + 2.18\sin 2\omega - 0.31\sin 3\omega + 0.43\cos\omega - 0.07\cos 2\omega - 0.10\cos 3\omega + G \quad (10)$$

with $G = 61.0$ (α- and β-anomers).

The calculated δ(C) values for rotamers of D-hexopyranoses having the configurations as in D-glucose and D-galactose using eqns (*7*—*10*) are given in Table 2. Values of the torsion angles ω are based on rotamer structures of methyl D-glycoside models calculated by *ab initio* molecular orbital method using the 6-31G* basis set [38]. Unfortunately, as can be seen from Table 2, the δ(C-5) values for the three rotamers about the C-5—C-6 bond differ only slightly. As a consequence, the calculated values of rotamer populations are very sensitive to the absolute values of δ(C-5). Since the values of chemical shifts are influenced by many factors and might

Table 3. Measured Carbon Chemical Shifts δ(C) for the C-5 and C-6 Atoms and Calculated Populations of the Rotamers for the Hydroxymethyl Group

Compound	δ(C-5)	δ(C-6)	Rotamer populations[a]		
			gg	*gt*	*tg*
β-D-Glucopyranose	76.8	61.6	52.7	41.4	5.9
α-D-Glucopyranose	72.3	61.5	67.7	25.5	6.8
β-D-Galactopyranose	76.0	61.8	30.8	39.7	29.5
α-D-Galactopyranose	71.3	62.0	25.1	53.0	21.8
Methyl β-D-glucopyranoside	76.8	61.6	52.7	41.4	5.9
Methyl α-D-glucopyranoside	72.3	61.4	66.7	13.7	19.7
Cellobiose[b]	76.9	61.4	66.4	13.0	20.6
Maltose[b]	73.5	61.3	–	–	–

a) Based on values of torsion angles shown in Table 2. *b*) Nonreducing residue.

change relatively by $\delta = 0.1$—1.0 depending on the concentration, temperature effects, pH, and the reference standard used, then the calculated rotamer populations are only qualitative. Experimental values of δ(C) for β-D-glucopyranose, α-D-glucopyranose, β-D-galactopyranose, α-D-galactopyranose, methyl β-D-glucopyranoside, methyl α-D-glucopyranoside, cellobiose, and maltose are given together with calculated rotamer distributions in Table 3. These values can be compared, and are in qualitative agreement, with the populations reported for *gluco* and *galacto* monosaccharides on the basis of vicinal proton—proton coupling constants [4]: approximately $gg : gt : tg \simeq 60 : 40 : 0$ for *gluco* (*trans*) and $\simeq 20 : 60 : 20$ for *galacto* (*cis*). However, they are at variance with the populations obtained on the basis of vicinal carbon—proton coupling constants [34]. The case of maltose represents an exception. For this compound, δ(C-5) is shifted upfield ($\Delta\delta = 1.2$) in comparison with that of α-D-glucopyranose. The magnitude of δ(C-5) is higher than δ(C-5) values calculated for the C-5—C-6 rotamers (Table 2). As a consequence, their populations cannot be estimated by the present method. It seems likely that the equations (*7*—*10*) that were calculated for D-glucopyranose and D-galactopyranose cannot be used directly for the calculations of δ(C-5) in other saccharides and the absolute values of δ(C-5) must be adjusted for constant G in eqn (*1*) using experimental data.

In conclusion, based on the reasonable agreement with solid state data, the proposed angular dependences might be useful in estimating hydroxymethyl group conformation in noncrystalline compounds. Extrapolation of these dependences to solution could represent complementary probes to the other NMR parameters, as vicinal proton—proton and carbon—proton coupling constants [4, 5, 34]. It is clear, however, that the validity of these dependences should be further tested and refined as a larger number of accurately determined δ(C) values for rigid molecules becomes available.

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