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Theoretical studies on the conformation of saccharides

VII. Structure and stereochemistry of α- and β-D-glucopyranose in solution

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The stereochemistry of D-glucopyranose has been studied theoretically in 11 solvents. The stability of the individual conformers in solution has been compared using a method in which the total energy is divided into the energy of an isolated molecule and the solvation energy. The structure and the energy of the isolated molecule have been estimated by geometry optimization using the PCILO quantum chemical method. The solvation energy consists of electrostatic, dispersion, and cavity terms which have been determined from calculated properties of the solute and physiochemical properties of the solvents. The influence of the solvent on rotation of the individual pendant groups and the stability of anomers have been investigated. The calculated composition of the anomeric mixture of D-glucopyranose in various solvents at 25°C (e.g., in pyridine 49% is α-anomer, in dimethyl sulfoxide 46%, and in water 32%) is in good agreement with the available experimental data and clearly demonstrates that the solvation properties of α- and β-D-glucopyranose differ. Based on the calculated abundances of anomers the magnitude of the anomeric effect has been estimated and compared with the results of corresponding calculations on other compounds.

Key words: Calculation of D-glucopyranose conformations — Solvent effect — Anomeric ratio — Magnitude of the anomeric effect

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1. Introduction

The problem of predicting the solid-state conformation and solution properties of saccharides and polysaccharides has attracted a good deal of attention in recent years. Although considerable progress has been made in the development of methods for calculation structure in the solid-state there is still little known about the prediction of the structure and behaviour of carbohydrates in solution [1–4]. It should be emphasized that calculations of saccharide or polysaccharide structures using either molecular mechanical or quantum chemical methods relate to an isolated molecule, i.e., to the situation *in vacuo*. In solutions, however, the molecular energy does not depend exclusively on the arrangement of atoms in an isolated molecule, i.e., on intramolecular interactions, but depends also on surrounding molecules, i.e., on intermolecular interactions and these may differ from one conformer to another. Comparison of properties calculated in this way with experimental data obtained from solutions (particularly from the aqueous ones) is therefore questionable and could well be misleading. In some cases of molecular mechanical calculations, the parameters of potential functions are obtained by fitting calculated molecular properties to experimental solution properties [1]. Such an approach involves (though not explicitly) certain solvation effects. The disadvantage here is that a set of potential functions obtained in this way cannot be applied to a situation in a different medium. In the case of aqueous solutions, the arbitrary selected increments, expressing the solvent influence, are added sometimes to the calculated energy of individual conformations [2, 4].

Recently we elaborated a method to explicitly involve the solvent effect in calculations of the molecular energy of carbohydrates. The method has been applied to a model compound for glycosides, 2-methoxytetrahydropyran (MTHP) [5], to the conformers of β-maltose [6] and β-cellobiose [7], and to acyclic model compounds for thiosugars [8, 9]. The results obtained have shown that solvation properties of individual conformers differ and their relative abundance in an equilibrium mixture strongly depends upon the solvent character. In the case of MTHP, the calculated anomeric ratios were in excellent agreement with the experimental data available for eleven solvents with various properties. We have continued in our efforts in this direction and now present studies on the D-glucopyranose structure and its stereochemical behaviour in various solvents. The calculations presented in this paper consist of two parts. In the first, we derive PCILO geometries for both D-glucopyranose anomers in their $^4C_1$ chair forms. In the second, we calculate the solvent effect on the rotational stability of the individual pendant groups and on the anomeric ratio, and we estimate the magnitude of the anomeric effect.

2. Methods

The quality and reliability of calculations of solution properties depend to a large extent on the quality of the method used for calculating the energy of the isolated molecule. Because of the great complexity of the problem under study, it is not possible to use quantum chemical methods at an *ab initio* level. Therefore, we

applied the semiempirical PCILO method [10] which has proved to be very efficient in studies of model saccharides. The initial geometrical data for D-glucopyranose in a $^4C_1$ form were selected as follows. For α-D-glucopyranose, we considered bond lengths, bond angles and torsional angles obtained by neutron diffraction [11]. Since analogous data for β-D-glucopyranose are not available in the literature, we used the average values of Arnott and Scott for this compound [12] derived from available crystal structures of saccharides. The structures of both anomers were determined in such a manner that we optimized the positions of all atoms. The minimization problem then had a dimensionality of sixty-six. If we consider there are three stable minima for each rotatable group, 729 conformers can be formed for each anomer. Fortunately, for sterical reasons most of these are energetically forbidden. Even then, however, optimization of the geometry of each conformer cannot be practically carried out. In our previous study of MTHP [13] we showed that conformational energy calculations with geometrical parameters corresponding to a particular conformer may lead to erroneous results. Therefore, in the study of pendant group stereochemistry, constant geometry was used which for α- and β-D-glucopyranose corresponded to the average ring geometries of Arnott and Scott [12]. Starting positions of pendant groups were those previously obtained from the PCILO optimization. We then used a cyclic search technique to select from the possible 729 conformers the thirteen most stable ones in a given solvent for each anomer. These results were used in calculations of the solvent effect on the $\alpha:\beta$ anomeric ratio.

The method of free energy calculation of individual conformers in dilute solution has been described in detail in our previous papers [5, 6] and therefore, in the present work we shall repeat only the basic principles of the model. The process of dissolving a molecule in a solvent involves two steps. The first step is the creation of a cavity in the solvent of suitable size to accomodate the solute molecule in the given conformation. The radius of the cavity associated with the solute molecule was calculated from the van der Waals surface of the individual conformers. The cavity formation requires a Gibbs free energy G_{cav}. The second step is the introduction into this cavity of the solute molecule which interacts with the surrounding solvent molecules. In our model the interaction part of solvation free energy G_{solv} is composed of the free energy of dispersion G_{disp}, electrostatic G_{elst}, and specific G_{spec} interactions of the solute molecule with the solvent. We have not involved the last contribution in our calculations as we consider that this term is independent of the conformational changes studied. The total free energy G_T of the individual conformers with corresponding intramolecular energy G_u in the given solvent can be written as:

$$G_T = G_u + G_{\text{solv}} = G_u + G_{\text{cav}} + G_{\text{elst}} + G_{\text{disp}}.$$

The calculation of the cavity term is based on an expression taken from the Scaled Particle Theory which has been successfully used in studies of thermodynamical properties of aqueous and nonaqueous solutions [14]. The electrostatic term is calculated according to Onsager's theory of the reaction field as applied by Abraham [15]. The dispersion interactions take into account both attractive

Table 1. Values of dielectric constant ε, hard sphere radius a, reduced number density y, molar volume V, refractive index n, molecular polarizability α, and ionization potential I of dimethyl sulfoxide, water, and *N*-methylacetamide at various temperatures T used for calculations of G_{solv}

Solvent	T (K)	ε	a (pm)	y	V (10^6 m^3/mol)	n	α (10^{30} m^3/mol)	I (eV)
Dimethyl sulfoxide	302.2	45.82	246.5	0.5209	71.656	1.4752	7.99	9.01
	313.2	44.55	246.5	0.5161	72.326	1.4706	7.99	9.01
	323.2	43.25	246.5	0.5113	73.000	1.4654	7.99	9.01
	358.2	40.02	246.5	0.4994	74.741	1.4529	7.99	9.01
	373.2	36.86	246.5	0.4873	76.602	1.4404	7.99	9.01
Water	283.2	83.832	138.5	0.3719	18.02	1.3337	1.47	12.6
	293.2	80.103	138.5	0.3714	18.047	1.3330	1.47	12.6
	303.2	76.546	138.5	0.3704	18.094	1.3319	1.47	12.6
	313.2	73.151	138.5	0.3691	18.156	1.3306	1.47	12.6
	323.2	69.910	138.5	0.3676	18.233	1.3290	1.47	12.6
	333.2	66.815	138.5	0.3658	18.323	1.3272	1.47	12.6
	343.2	63.857	138.5	0.3638	18.424	1.3254	1.47	12.6
N-methylacetamide	298.2	198.3	247.5	0.4970	76.690	1.4286	7.84	8.9

and repulsive nonbonded interactions using a combination of the London dispersion equation and Born-type repulsion [5]. Although the eliptical cavity would be a more realistic model we have used the spherical cavity. This approach has shown to be useful in the case of 2-methoxytetrahydropyran which shape is very similar to the shape of the molecule under study. The individual terms of our procedure for studying solvent effects involve a number of simplifications [5]. However, for the purpose of studying conformational stability the energy difference is the important factor, rather than the absolute value of G_T and a cancellation of errors may contribute to the success of this method in estimating conformational energies of sugars [5–8]. Probably the ultimate approach for studying solvent effects is a computer simulation of the given solution. This can be based either on Monte Carlo or molecular dynamics calculations including explicitly the sugar and many solvent molecules. However such approaches are still far too expensive for accurate evaluation of solvation energies due to a high flexibility of sugars. Expressions for the individual terms of the solvation free energy function have been given, together with all necessary solvent parameters in our previous works [5, 6]. Exceptions are the parameters for *N*-methylacetamide, and for water and dimethyl sulfoxide at various temperatures, and these are given in Table 1. Both energy and parameters characterizing the individual D-glucopyranose conformers were calculated by the PCILO method with the exception of the refractive index, for which we used the value of 1.5600 [16]. The numbering scheme of atoms in D-glucopyranoses is given in Fig. 1. Figure 1 shows α-D-glucopyranose; in β-D-glucopyranose the substituents on

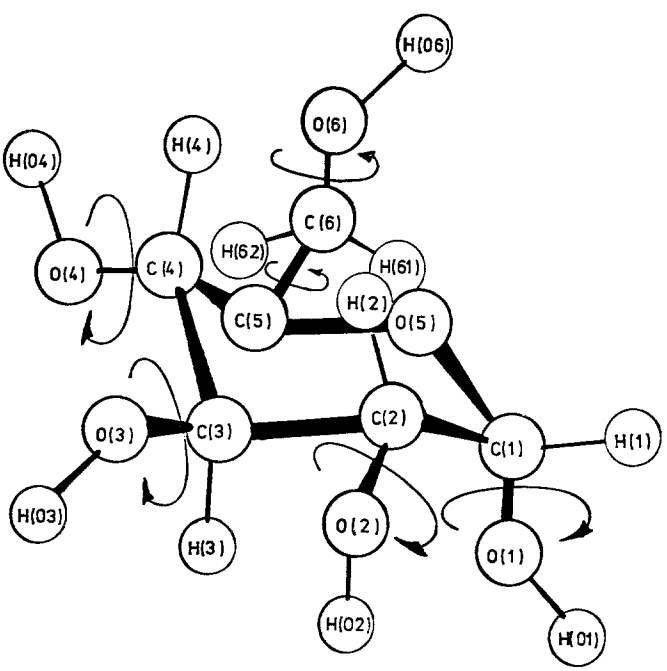

Fig. 1. Numbering scheme of atoms in the α-D-glucopyranose

the anomeric carbon atom, C(1), are inversed. The rotation of the individual pendant groups are described by the angles χ_i which are defined as follows: $\chi_1 = \chi$[H(O1)-O(1)-C(1)-O(5)], $\chi_2 = \chi$[H(O2)-O(2)-C(2)-C(3)], $\chi_3 = \chi$[H(O3)-O(3)-C(3)-C(4)], $\chi_4 = \chi$[H(O4)-O(4)-C(4)-C(5)], $\chi_5 = \chi$[O(6)-C(6)-C(5)-O(5)], $\chi_6 = \chi$[H(O6)-O(6)-C(6)-C(5)]. The notation of the individual conformers is based on the values of the dihedral angles χ_i. In this way G means that angle χ_i is close to that in a synclinal (*sc*) or gauche (G) conformation (+60°), G^- corresponds to a $-sc$ (−60°) and T to an antiperiplanar (*ap*) or trans (T) conformation (180°).

3. Results and discussion

3.1. Structure of α- and β-anomers of D-*glucopyranose*

The final coordinates for α-D-glucopyranose calculated by complete geometry optimization using the PCILO method, together with the net atomic charges, are given in the Table 2 and those for 3-D-glucopyranose are given in Table 3, for comparison. The bond lengths derived in this manner vary in the interval 149.0–150.6 pm in the case of C–C bonds, 138.5–139.6 pm for C–O, 113.8–115.1 pm for C–H, and 104.8–105.0 pm for O–H bonds. The greatest deviation from experimental values is 3 pm, i.e., approximately 2%, but it is usually smaller. Since the

Table 2. Optimized coordinates (in pm) and net atomic charges (in e) for α-D-glucopyranose calculated by PCILO method

Atom	*x*	*y*	*z*	Net charge
C(1)	0.0	0.0	0.0	0.2184
O(5)	141.4	0.0	0.0	−0.1742
C(5)	199.6	61.7	−115.9	0.1237
C(4)	157.7	208.1	−123.1	0.0743
C(3)	5.9	219.7	−119.3	0.0765
C(2)	−50.1	143.8	0.0	0.0670
C(6)	349.5	44.2	−104.4	0.1175
O(6)	401.2	105.6	13.6	−0.1386
O(1)	−52.1	−65.4	−114.1	−0.1805
O(4)	208.9	264.1	−243.9	−0.1627
O(3)	−31.7	357.3	−110.6	−0.1685
O(2)	−192.4	144.1	−2.3	−0.1601
H(1)	−36.7	−51.7	89.9	−0.0302
H(O1)	−11.6	−162.1	−112.5	0.0949
H(5)	165.5	9.2	−206.4	−0.0121
H(61)	377.8	−66.0	−102.5	−0.0310
H(62)	401.2	86.0	−197.1	−0.0274
H(O6)	505.4	94.9	7.0	0.0788
H(4)	195.2	261.4	−34.5	−0.0067
H(O4)	174.0	363.0	−247.3	0.0848
H(3)	−36.4	178.6	−212.1	−0.0063
H(O3)	7.6	403.7	−196.1	0.0838
H(2)	−19.0	193.6	93.1	−0.0181
H(O2)	−218.6	245.6	2.4	0.0968

deviations proceed in the same direction in the majority of cases, they can be considered as characteristic of the PCILO method with the CNDO Hamiltonian. The bond angles deviate from the experimental values by less than 3°. An exception is the angle O(5)-C(1)-C(2) in the α-anomer, which differs by 5°. The ring torsional angles in the β-anomer are close to experimental values, whilst in the α-anomer the calculated ring shape is more flattened. The ring flattening is most probably due to the intramolecular hydrogen bond of the hydroxyl group hydrogen at C(2) with the glycosidic oxygen. This is indicated by the distances H(O2)-O(1) (191.9 pm) and O(2)-O(1) (256.8 pm). Recently, the shift of the hydroxyl-stretching vibration bands in *p*-substituted phenyl 3,4,6-tri-O-methyl-β-D-glucopyranosides was attributed to this intramolecular hydrogen bond [17]. It is also worth noting in this context that the *ab initio* (4–31 G) calculations [18] with methoxy ethanediol also predict the same hydrogen bond for the conformation which corresponds to α-D-glucopyranose configuration.

The influence of the anomeric effect on the geometry of the hemicetal segment is clearly demonstrated by the increase of the bond angle O(5)-C(1)-O(1) in the α-anomer to 110.8° in comparison with a corresponding value of 106.0° for β-anomer (the experimental values are 111.6° and 107.0°), and by the decrease of the C(5)-O(5)-C(1) bond angle from 112.5° to 110.8° (113.8°, 112.7°). Differences in the bond lengths C(1)-O(1) and O(5)-C(1) in the α-anomer 139.2 pm and 139.4 pm (experimental values are 138.9 pm and 142.5 pm) in relation to corresponding values for the β-anomer of 138.9 pm and 139.7 pm (138.4 pm, 143.3 pm), are also correctly described.

In connection with the influence of the anomeric effect on the structure, the charge distribution (Tables 2, 3) is also interesting. The greatest differences between the α- and β-anomers are at atoms C(1), O(1), and H(1). These are due to the different delocalization of the lone-pairs electrons in the various conformations of the hemiacetal segment. The PCILO calculated dipole moment of the α-anomer is 3.52 D and that of the β-anomer 4.47 D ($1\,D = 3.33564 \times 10^{-30}$ Cm). These values are higher than in the case of MTHP. It is also worth mentioning in this context that while in MTHP the magnitude of the dipole moment is determined by the mutual orientation of both the ring C-O and glycosidic C-O bonds, in D-glucopyranose, all the major contributions to the dipole moment, apart from the ring C-O bond, are from the pendant groups (four hydroxyls and one hydroxymethyl). The dipole moments of the most stable conformations of the α- and β-D-glucopyranose calculated using the minimal basis set *ab initio* method are 2.74 and 4.64 D [19]. The combination of experimental data and Buckingham theory lead to $\mu = 4.5$ D for D-glucose (an equilibrium mixture of the α- and β-anomer) in aqueous solution [20].

The calculated orientations of H(O1), H(O2), H(O3), H(O4), O(6), and H(O6) atoms in the case of the α-anomer are *G*, *G*, *G*, *T*, G^-, *T* in comparison with the neutron diffraction results *G*, *G*, *G*, *G*, *G*, *T*. In the case of the β-anomer the orientations calculated are as follows G^-, *T*, *G*, *T*, G^-, *T*. In both cases, in

Table 3. Optimized coordinates (in pm) and net atomic charges (in e) for β-D-glucopyranose calculated by PCILO method

Atom	*x*	*y*	*z*	Net charge
C(1)	0.0	0.0	0.0	0.2262
O(5)	142.9	0.0	0.0	−0.1802
C(5)	197.3	60.8	−118.1	0.1185
C(4)	155.8	207.4	−125.7	0.0750
C(3)	4.1	219.4	−120.1	0.0699
C(2)	−50.4	143.7	0.0	0.0964
C(6)	347.5	42.9	−111.7	0.1190
O(6)	403.4	104.7	4.2	−0.1363
O(1)	−41.3	−61.0	117.8	−0.1574
O(4)	205.7	262.6	−274.4	−0.1650
O(3)	−33.0	357.1	−110.9	−0.1637
O(2)	−192.7	143.6	−0.7	−0.1573
H(1)	−36.7	−51.8	−89.8	−0.0545
H(O1)	9.2	−152.8	120.4	0.0984
H(5)	160.5	7.6	−207.1	−0.0278
H(61)	375.3	−67.4	−108.4	−0.0314
H(62)	396.1	83.2	−206.6	−0.0263
H(O6)	507.4	96.9	−7.7	0.0799
H(4)	200.1	262.5	−41.4	−0.0024
H(O4)	171.6	361.7	−250.6	0.0857
H(3)	−39.4	178.1	−212.4	−0.0170
H(O3)	7.5	403.8	−195.7	0.0845
H(2)	−18.5	193.8	92.6	−0.0038
H(O2)	−221.0	244.6	−0.9	0.0966

agreement with the exo-anomeric effect, H(O1) prefers the synclinal position. In comparison with experimental data the α-anomer differs in the positions of the O(6) and H(O4) atoms. The most stable positions of the other atoms are in the same region but the values of dihedral angles are different. Since values of the exocyclic angles in the crystalline state are highly influenced by packing interactions and as our calculation does not consider these, the differences obtained are quite understandable.

3.2. The stereochemistry of pendant groups

3.2.1. Conformations of the secondary hydroxyl groups. It is very often considered in discussions of properties of saccharides that the rotation of hydroxyl groups is not hindered and is very rapid. In the following part of our work we investigate the extent to which this assumption is correct and the way in which the solvent influences the orientation of rotatable side groups. The variation in the relative energy of rotation around the individual C(i)-O(i) bonds for both the isolated molecule and for the molecule in water are shown in Figs. 2 and 3. The course of rotation around the i-th bond was calculated with the other groups fixed in the most stable conformations. Three staggered minima are evident for each

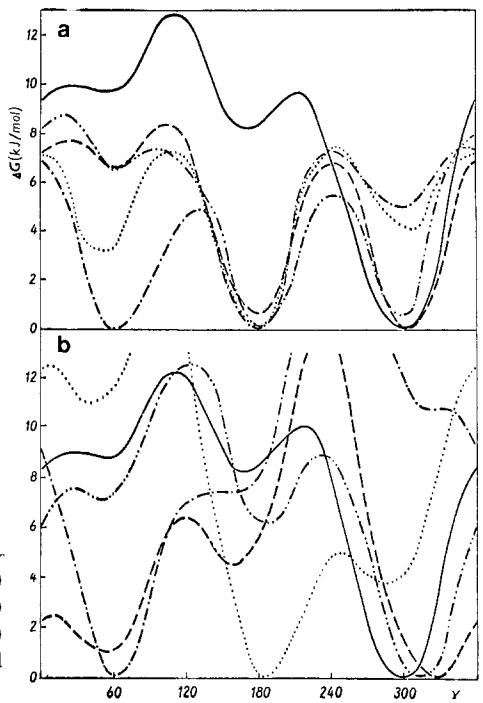

Fig. 2ab. Variation of the total free energy G_T (in kJ/mol) of the rotation around the C(1)-O(1) bond (——), C(2)-O(2) bond (– – –), C(3)-O(3) (– · –), C(4)-O(4) bond (– · · –), and C(6)-O(6) bond (· · · ·) for the β-D-glucopyranose in isolated molecule (**a**) and in aqueous solution (**b**)

hydroxyl group from the energy curve. These minima can be identified as G, T, and G^- positions of the rotating atom. The solvation energy influences both the stability of conformers and the shape of energy curves. The magnitude of the barrier in the isolated molecule does not usually exceed 12 kJ/mol. The barriers calculated are great enough, however, that the hydroxyl group rotations cannot be considered as free. Of the solvents considered, the most noticeable influence can be observed with water. In the case of H(O1) the G and G^- remain the most stable positions regardless of the solvent character. The abundance of G in the α-anomer decreases in water and the abundance of the G^- conformer increases. In the β-anomer, the relative abundance of conformers does not change. The abundance of the T position of the hydroxyl group at carbon C(2) decreases with increase of solvent polarity (represented by the dielectric constant) and the abundance of the G position increases. The solvent effect on the mutual stability of conformers formed by rotation around C(3)-O(3) and C(4)-O(4) bonds is very interesting. In the isolated molecule, positions G and T are almost similarly abundant for both hydroxyl groups. An increase of solvent polarity leads to a remarkable stability of the G conformer on account of the abundance of the T conformer in both anomers. The hydrogen of the primary hydroxyl group H(O6) prefers the same T conformation in all media considered and its abundance increases moderately with solvent polarity. Comparison of the energy profiles in Fig. 2 and Fig. 3 also shows that the barriers to hydroxyl group rotations are higher in aqueous solution than in the isolated molecule and therefore their rotational motion in water is more restricted. From our results, a similar influence

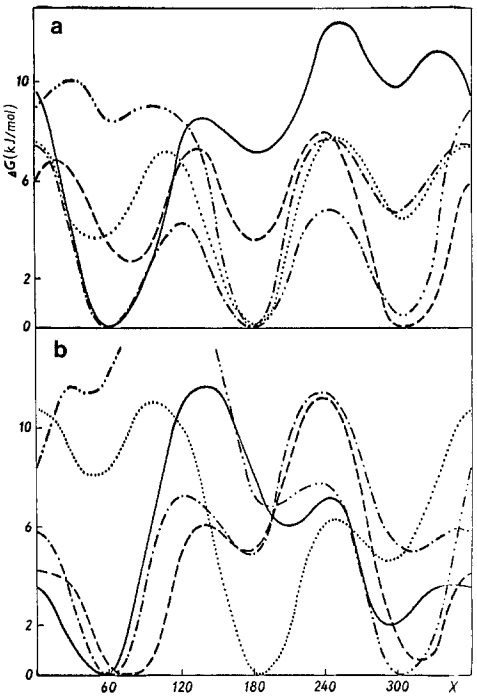

Fig. 3ab. Variation of the total free energy G_T (in kJ/mol) of the rotation around the C(1)-O(1) bond (——), C(2)-O(2) bond (- - -), C(3)-O(3) bond (- · - ·), C(4)-O(4) bond (- · · -), and C(6)-O(6) bond (· · · ·) for the α-D-glucopyranose in isolated molecule (**a**) and in aqueous solution (**b**)

of the medium is evident on the relative abundance of hydroxyl group conformers in each anomer.

3.2.2. Conformations of the hydroxymethyl group. As the hydroxymethyl group conformation is an important variable in hexopyranoid structures, the calculated results will be compared with those from experimental data in more detail. The course of rotation around the C(5)-C(6) bond for both anomers in the isolated molecule and in water are illustrated in Fig. 4. In the isolated molecule, the energy curve is the same for both anomers. The relative energies of G^-, T, and G conformers are 0.0, 2.6, and 4.3 kJ/mol respectively, and conformers are in the ratio 66:11:23. In the literature, these conformers are usually designated as *gauche-gauche*, *trans-gauche*, and *gauche-trans*. In this terminology the torsional angle χ_5 is stated first, then the torsional angle $\chi'_5 = [O(6)\text{-}C(6)\text{-}C(5)\text{-}C(4)]$. An increase in polarity of the solvent decreases the abundance of *gauche-gauche* ($\mu = 2.7$ D) and *trans-gauche* ($\mu = 2.3$ D) conformers for the α-anomer, whilst the abundance of the *gauche-trans* ($\mu = 3.5$ D) increases. In CCl_4, for example, their ratio is 65:10:25, whilst in acetone and DMSO it is 61:8:31 and 59:8:33 respectively, and in water it is 44:4:52. For the β-anomer, the *gauche-gauche* conformer ($\mu = 4.3$ D) is stabilized in a more polar medium, the abundance of the *trans-gauche* ($\mu = 2.5$ D) conformer decreases and the abundance of the *gauche-trans* ($\mu = 4.2$ D) conformer remains almost constant. The conformer ratio is 69:8:23 in CCl_4, 73:4:23 in acetone, 74:4:22 in DMSO, and 79:1:20 in water. The solvent effect also influences the shape of the rotational energy

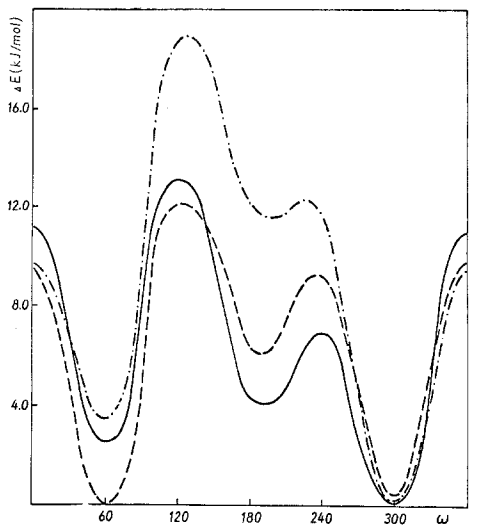

Fig. 4. Variation of the total free energy G_T (in kJ/mol) of the rotation around the C(5)-C(6) bond in isolated α- and β-glucopyranose (——) and in aqueous solution; α-anomer (- - -), β-anomer (- · - · -)

curve. The calculated ratio of conformers can be compared with experimental values. According to X-ray analysis [11, 21, 22], the conformations about the C(5)-C(6) bond are *gauche-trans*, *gauche-gauche*, and *gauche-gauche* for α-D-glucopyranose, α-D-glucopyranose·H_2O, and β-D-glucopyranose crystals, respectively. Perez and Marchessault [23] have analyzed the solid state orientation of the hydroxymethyl group in aldohexopyranosides. For the gluco-configuration, in 101 known structures they found only the *gauche-gauche* and *gauche-trans* conformers with a 60% preference for the *gauche-gauche* conformer. Mean values of angles in the *gauche-gauche* conformer are −66.5° and 65.0° for the angles χ_5 and χ'_5, whilst in the *gauche-trans* conformer, these have the values 54.8° and 183.0°. These authors did not separately analyze the situation in the α- and β-anomers. On the other hand, the conformation of the hydroxymethyl group in native cellulose is found to be *trans-gauche* [24]. From NMR studies of per-O-trimethylsilyl derivative of α- and β-D-glucopyranose in acetone the ratio of 77:0:23 for α-anomer and the ratio of 63:3:34 for β-anomer was found [25]. It should be noted that *trans-gauche* conformer is strongly disfavored because of the parallel 1,3 interactions between the bulky trimethylsilyl groups at O(4) and O(6). De Bruyn and Anteunis [26] concluded, on the basis of analysis of data in aqueous solutions of D-glucose and D-mannose, that conformer *trans-gauche* is also present in D_2O, though the main conformers are *gauche-gauche* and *gauche-trans*. However, they have not reported populations of individual conformers.

3.3. The equilibrium ratio of α- and β-anomers

3.3.1. The anomeric ratio in the isolated molecule. The energy calculation with individual conformers formed by rotation of pendant groups has shown that of 729 conformers, the majority have a high energy. Therefore, we have selected for α- and β-anomer the 13 most stable conformers for each solvent and have

calculated their abundance in an equilibrium mixture. The $\alpha:\beta$ ratios and dipole moments calculated on this basis, the values of the determined anomeric effect and the available experimental data for the anomeric ratio [2, 27–29], are given in Table 4. On the basis of PCILO energies, the $\alpha:\beta$ ratio is 76:24 in the isolated molecule at 25°C. The α-anomer preference can be assumed as a manifestation of the well known anomeric effect. This ratio is close to the value calculated for the ratio of axial (A-MTHP) to equatorial forms (E-MTHP) of 2-methoxytetrahydropyran [5] (77:23). The similarity of results indicates correctness of the conclusion reached from studies of model compounds that, in the isolated molecule the equilibrium of conformers at the anomeric centre is mainly influenced by interactions in the acetal segment. Other intramolecular interactions, like those among the ring substituents, influence this equilibrium only slightly. The substituent effect is mainly reflected in a different solvent effect. The $\alpha:\beta$ ratio calculated for an isolated molecule differs significantly from values obtained by other authors which predict the β-anomer as the preferred one. Thus, Dunfield and Whittington [30] determined 47% of D-glucose in α-anomer and Rasmussen [31] obtained, according to the type of potential energy function, 25%–44% of α-anomer. In 1969, Neely employed the Extended Hückel Theory to study the relative conformational stabilities of D-glucopyranose [33]. The β-anomer comes

Table 4. Calculated dipole moments μ (in D) of α- and β-anomers of D-glucopyranose, the anomeric effect (in kJ/mol) and the comparison of calculated and experimental molar fractions of the α-anomer in the isolated state and in solution

Solvent		% α-Anomer calculated	experimental	Dipole moment μ_α	μ_β	$\langle\mu\rangle$	Anomeric effect without A value	with
Isolated molecule		76.0		2.9	4.1	3.2	2.86	5.76
Dioxan		68.5		3.2	4.3	3.6	1.93	4.83
Carbon tetrachloride		71.4		3.1	4.3	3.5	2.27	5.17
Carbon disulfide		69.4		3.2	4.4	3.6	2.03	4.93
Chloroform		62.5		3.5	4.6	3.9	1.26	4.16
Pyridine		48.9	45	3.6	4.9	4.3	−0.11	2.79
Acetone		49.9		3.6	4.9	4.3	−0.01	2.89
Methanol		37.3		3.9	5.2	4.7	−1.29	1.61
Acetonitrile		41.9		3.8	5.1	4.6	−0.81	2.09
Dimethyl sulfoxide	25°C	45.7	44	3.7	5.0	4.4	−0.43	2.47
	40°C	46.4		3.6	4.9	4.4	−0.37	2.53
	50°C	47.2		3.6	4.9	4.3	−0.30	2.60
	75°C	48.5		3.5	4.8	4.3	−0.17	2.73
	100°C	49.7		3.5	4.8	4.2	−0.04	2.86
Water	10°C	29.7	32 (5°C)	4.3	5.4	5.1	−2.03	0.87
	25°C	32.2	34–37	4.3	5.4	5.1	−1.85	1.05
	40°C	34.1		4.3	5.4	5.0	−1.72	1.18
	50°C	35.5		4.2	5.3	5.0	−1.60	1.30
	60°C	37.0		4.2	5.3	4.9	−1.48	1.42
	70°C	37.9		4.2	5.3	4.9	−1.41	1.49
N-methylacetamide		40.3		4.0	5.0	4.6	−0.97	1.93

out as 38 kJ/mol more stable than the α form. The energy difference between both anomers as determined by Melberg et al. [18] using *ab initio* calculations with minimal basis set is 6.72 kJ/mol and leads to 94% of β-D-glucopyranose.

3.2.2. The solvent effect on the anomeric ratio. Although the results given in Table 4 indicate an increased abundance of the β-anomer with increasing solvent dielectric constant, the dependence is not a simple one. The proposed method of incorporating the solvent effect takes into account also fine effects such as a relatively weak effect of dimethyl sulfoxide and *N*-methylacetamide on the increase of the β-anomer abundance compared with less polar solvents and, conversely, the much more pronounced effect of water on the decrease of the α-anomer abundance. These results also show that the solvent effect on the conformation of saccharides is not purely a function of solvent polarity as represented by dielectric constant. Previously we have observed similar, marked differences in the solvent effect of aqueous and nonaqueous solutions on the conformational equilibrium around the glycosidic linkage [5–9]. Such solution behaviour is likely to be a feature inherent to all saccharides. We explained the special behaviour of these solvents by their improved or diminished ability to approach a solute molecule forming in this way a reaction field which in the first case better stabilizes more polar conformer [5]. The change of $\alpha:\beta$ ratio as the result of medium effects can be compared with the abundance calculated for both axial and equatorial forms of 2-methoxytetrahydropyran. In non-polar solvents and in the isolated state, the anomeric ratio is very close for both molecules. In polar solvents, however, the pendant groups of D-glucopyranose cause its β-anomer to be preferred more than is the corresponding equatorial form of MTHP. For example, in methanol 69% and in water 48% of MTHP molecules are in the axial form, while for D-glucopyranose in those same solvents the corresponding abundances of the α-anomer are 37% and 32%.

The calculated values of the $\alpha:\beta$ ratio agree to within 4% with the experimental data obtained for pyridine, dimethyl sulfoxide, and water. It would seem that such good fits of the $\alpha:\beta$ ratio in three different solvents for D-glucopyranose and in eleven various solvents for MTHP [8] could not be entirely fortuitous. This correct prediction of the anomeric ratio for D-glucopyranose adds extra credence to the validity of our model and also reflects the power of the method used to estimate solvent effects on conformational equilibria of carbohydrates.

As further test of our approach we have estimated the temperature dependence of anomeric equilibrium in DMSO and in water. It is evident from the experimental values for aqueous solutions of D-glucose that the $\alpha:\beta$ ratio increases monotonically with temperature [2]. The calculated temperature dependence of this ratio has the same trend, as is shown in Table 4. The increase of the α-anomer abundance is, however, higher than expected from the tendency of temperature to produce a statistical anomeric ratio. It is evident from the analysis of individual contributions to the solvation free energy that the electrostatic term has a decisive influence on the increase of α-anomer abundance with the rise of temperature. This influence can be explained as follows. The dielectric constant of water decreases with increasing temperature. The reaction field formed by water which

preferentially stabilizes the more polar conformers, thus decreases. The result is reduced stabilization of conformers contributing to the β-anomer at the higher temperature. For dimethyl sulfoxide solution, Franks mentioned [2] that the experimentally observed proportion of β-D-glucose in an equilibrium mixture exhibits a minimum at 50°C, but he did not list any values. On the other hand, our results show that the $\alpha:\beta$ ratio increases with temperature. However, this dependence is less pronounced than in water. We assume that this discrepancy may be due to approximations in the calculation of conformational energies for the isolated molecule, or in the estimation of the most stable conformers in dimethyl sulfoxide, or in both.

The results of this work make it possible to calculate the mean dipole moments of both anomers as well as the mean dipole moment of D-glucopyranose in different solvents. The comparison of $\mu_{app} = 4.5$ D as given by computation from static permittivity measurements on aqueous solution [2] with $\mu = 5.0$ D (Table 4), shows good agreement and lends further credibility to the method used in the calculation of the solvent effect.

3.3.3. The influence of the hydration on the anomeric ratio. The above results clearly demonstrate that the solvation properties of both anomers of D-glucopyranose differ. In a non-polar environment the α-anomer is preferred due to the anomeric effect. In more polar solvents, however, the influence of the anomeric effect is overcome by solute-solvent interactions and the β anomer is preferred one. The above results together with the previous ones on MTHP [5, 33] also indicate that specific solute-solvent interactions, e.g., hydrogen bonds do not influence the anomeric equilibrium in D-glucopyranose. In the literature, the term "specific hydration" has been used mainly to describe interactions between water molecules and polar sites of the solute by hydrogen bonds. It is often assumed that the latter are determined by a so-called solvent structural compatibility and depend upon the spatial orientations of the interacting groups. In the case of aqueous saccharide solutions, such compatibility is connected with the number of equatorial hydroxyl groups [20, 34]. Thus, saccharides, with a relatively high proportion of equatorial hydroxyl should be relatively more extensively hydrated. Probably the most detailed analysis of carbohydrate-water interactions is that of Suggett et al. [35-37]. They have been able to estimate the extents of the interactions between water and sugars by using dielectric and nuclear magnetic relaxation methods. Hydration numbers estimated by them however, do not show such large differences from sugar to sugar as indicated in previous studies [20, 34]. They observed similar degrees of hydration for D-glucose and D-mannose, as demonstrated by hydration numbers of 3.7 and 3.9, respectively, whereas purely on the basis of equatorial hydroxyl groups one would have expected a significant difference.

Dunfield and Whittington [30] used a specific hydration model when they proposed a "solvation" correction of -1.13 kJ/mol for each equatorial hydroxyl group to improve the correspondence between the calculated (47% of α-form) and experimental (36% of α-form) anomeric ratio in water. Using such a correc-

tion, they obtained 33% abundance of the α-anomer in water. Besides methodological objections this approach has many other shortcomings. For example, it implicitly invokes the assumption that apart from specific hydration, all solvation effects are conformationally independent, or they do not exist at all. However, it can be assumed that hydrogen bonds between glucose and the solvent exist in other polar solvents as well. For example, experimental data [38, 39] point to the formation of different hydrogen bonds by the individual glucose hydroxyl groups in dimethyl sulfoxide and in water. Recently, Jasra and Ahluwalia [40] also concluded, on the basis of studies of enthalpies of solution, partial molal heat capacities, and apparent molal volumes of aqueous sugar solutions, that the change of OH or OCH_3 group from α to β position does not influence the mode or the size of hydration. Our results are in agreement with this finding.

3.4. Magnitude of the anomeric effect

The results of this study make it possible to estimate the solvent effect on the magnitude of the anomeric effect quantitatively. We have calculated the magnitude of the anomeric effect for D-glucose in dilute solution in two ways and the results are given in Table 4. In the first, the anomeric effect was determined as the difference of free energies between α- and β-anomers. In the second, we added to this difference the A value [41] 2.9 kJ/mol, which expresses the free energy difference for the same substituent in cyclohexane. According to the first definition, the anomeric effect has its greatest value in the isolated state, i.e., 2.9 kJ/mol. The corresponding values of the anomeric effect calculated by PCILO method for methoxyl group, fluorine, and chlorine substituents are 3.0 [5], 6.7 [42], and 10.1 kJ/mol [42], respectively. Thus, the magnitude of the anomeric effect as a function of the substituent decreases in the order of $OH < OCH_3 < F < Cl$ in agreement with the experimentally observed trend [41]. The magnitude of the anomeric effect gradually decreases with the increase of solvent polarity and in more polar solvents, starting from pyridine, D-glucose does not exhibit an anomeric effect. According to the second definition, the highest effect (5.8 kJ/mol) is again in the isolated state. However, it also predicts a value of approximately 1 kJ/mol in water. The shortcoming of this definition lies in the fact that it depends upon a correct magnitude for the A value, and this is both solvent and temperature dependent. For example, an experimental range of A values for the hydroxyl group is 1–6 kJ/mol [41]. However, it is evident, regardless of the definition used for the anomeric effect, that the polar medium acts in a direction opposite to the anomeric effect and thus weakens its influence on the anomeric equilibrium of sugars.

4. Conclusions

In summary, our results show that the PCILO semiempirical quantum chemical method is able to successfully describe the structure and the conformational behaviour of saccharides, that solvation effects contribute significantly to the conformational energies of D-glucopyranose in solution, that the rotation of the pendant groups and their most stable orientations depend on the solvent, and

that preference for the β-anomer of D-glucopyranose in polar solvents is due to solvent-solute electrostatic interactions whereas in a nonpolar environment the α-anomer is more populated because of the anomeric effect.

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