Theoretical studies on the conformation of saccharides XI. Stereochemistry of methyl α- and methyl β-D-glucopyranosides in solution

[a]I. TVAROŠKA and [b]T. KOŽÁR

[a] *Institute of Chemistry, Centre for Chemical Research, Slovak Academy of Sciences, CS-842 38 Bratislava*

[b] *Institute of Experimental Physics, Slovak Academy of Sciences, CS-040 01 Košice*

Received 20 May 1986

Stereochemistry of methyl α-D-glucopyranoside and methyl β-D-glucopyranoside in ten solvents has been studied theoretically. The energy of 14 basic forms of pyranose ring of methyl α- and methyl β-D-glucopyranosides was calculated by the PCILO quantum-chemical method. The calculated geometries of chair forms of both molecules were found to be in reasonable agreement with the available data obtained by X-ray diffraction of pyranosides. The stability of two axial and three equatorial chair conformers in solution was compared by using a method where the total Gibbs energy included the Gibbs energy of the isolated molecule and solvation Gibbs energy. Solvation Gibbs energy encompasses electrostatic, dispersion, and cavity terms. The calculated abundance of methyl α-D-glucopyranoside 63 % in methanol solution is in good agreement with the value 67 % found experimentally. The calculated values of *exo*-anomeric effect decrease with the increasing polarity of the solvent and are in the range of 3.7—4.0 kJ mol^{-1} for methyl α-D-glucopyranoside and 3.8—4.6 kJ mol^{-1} for methyl β-D-glucopyranoside.

Проведено теоретическое изучение стереохимии метил-α-D--глюкопиранозида и метил-β-D-глюкопиранозида в десяти растворителях. С помощью квантово-химического метода PCILO рассчитаны величины энергий 14 основных форм пиранового кольца метил-α- и метил-β-D-глюкопиранозидов. Рассчитанные геометрии обеих молекул в форме кресла оказались в достаточном согласии с имеющимися данными, полученными в результате изучения пиранозидов методом рентгеновской дифракции. Сравнивается устойчивость двух аксиальных и трех экваториальных конформеров в форме кресла в растворе с помощью метода, в котором общая свободная энергия Гиббса включала свободные энергии Гиббса изолированных молекул и Гиббсову энергию сольватации. Свободная энергия сольватации включает электростатическую, дисперсионную и кавитационную составляющие. Вычисленная доля метил-α-D-

-глюкопиранозида в метаноле 63 % хорошо согласуется с экспериментально найденной величиной 67 %. Рассчитанные величины *экзо*-аномерного эффекта уменьшаются при увеличении полярности растворителя и находятся в промежутке 3,7—4,0 кДж моль$^{-1}$ для метил-α-D-глюкопиранозида и 3,8—4,6 кДж моль$^{-1}$ для метил-β-D-глюкопиранозида.

It is well known that saccharides play an important role in biological systems [1]. For better understanding of biological functions of saccharides, it is necessary to recognize their conformational properties in solution. Experimental data obtained by chiroptical and NMR methods provide such information. These have been utilized to a great extent in studies of saccharides in solution [2, 3]. However, for complete interpretation of experimental data and for arriving at significant conclusions it is desirable to support these data by theoretical calculations which enable to determine the abundance of the individual conformers in the equilibrium mixture in the given solvent. Recently, we have elaborated a method which includes the solvent effect in calculation of the energy of saccharides [4, 5]. The method correctly described the behaviour of 2-methoxytetrahydropyran in various solvents [4]. Further, we estimated the effect of the solvent on abundance of the conformers of maltose and cellobiose [5, 6] and on the anomeric ratio of D-glucopyranose [7]. The predicted solvent effect on the abundance of conformers of maltose has lately been confirmed also experimentally [8]. Now we report on study of structure and conformational properties of methyl α-D-glucopyranoside (Me-α-D-Glcp) and methyl β-D-glucopyranoside (Me-β-D-Glcp) in various solvents. The calculations presented in this work consist of two parts. In the first one we determined the geometries for both anomers in their $^4C_1$ forms and calculated the energies of 14 forms of pyranose ring of Me-α-D-Glcp and Me-β-D-Glcp. In the second part we determined the influence of the solvent on the stability of conformers at rotation around the glycosidic linkage in $^4C_1$ chair form as well as on the magnitude of the *exo*-anomeric effect.

Method

The complexity of the problem investigated made impossible to use the *ab initio* method even with minimal basis set. Therefore, we have chosen the PCILO semiempirical quantum-chemical method [9] which allows optimizations of geometrical parameters. Moreover, the PCILO method was successfully applied in conformational studies of model compounds of saccharides [10]. Calculations were performed with standard version of the PCILO method modified to optimization of geometry according to Powell—Zangwill algorithm [11, 12]. Polarities of all bonds were optimized during calculations. Optimization of geometry of $^4C_1$ chair conformers of Me-α-D-Glcp and Me-β-D-

-Glcp was accomplished in two steps. At first, we optimized all 75 internal coordinates. After several optimization steps, close to energetic minimum, we reduced the number of variables and optimized bond lengths, bond angles, and torsion angles of atoms of the pyranose ring and methoxy group, *i.e.* together 21 geometrical parameters. The accuracy required during optimization of geometry was 0.1 pm for bond lengths, 0.05° for bond angles, and 0.5° for torsion angles. The initial geometrical parameters were based on values calculated for D-glucopyranose [7] and 2-methoxytetrahydropyran [10].

The effect of solvent on stability of conformers was calculated by using the method where the total energy consisted of internal molecular PCILO energy and solvation Gibbs energy. Solvation Gibbs energy included cavity contribution and contributions of electrostatic and dispersion interactions of the solute with the solvent [4]. The expressions of the individual terms of solvation Gibbs energy together with the necessary parameters were reported in our previous works. The parameters characterizing the individual conformations of methyl D-glucoside were calculated by the PCILO method, except the refractive index for which we used the value 1.56. Numbering of the atoms is shown in Fig. 1.

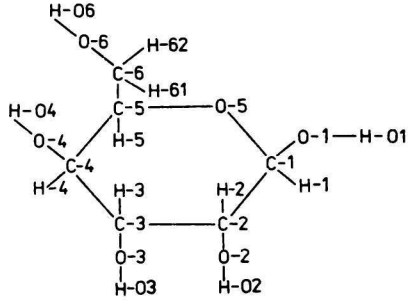

Fig. 1. Molecular structure and numbering of the atoms in the most stable methyl α- and methyl β-D-glucopyranoside conformers resulting from the rotation around the glycosidic linkage. The energy difference values for an isolated molecule were calculated by the PCILO method.

Results and discussion

Structures of $^4C_1$ *chair conformers*

Optimization of geometry of Me-α-D-Glcp and Me-β-D-Glcp with pyranose ring in $^4C_1$ chair form led to five minima (two for α and three for β anomer) differing in orientation of the methyl group. These are illustrated in Fig. 1. The selected geometrical parameters and atomic charges of these minima are presented in Tables 1 and 2. For Me-α-D-Glcp the lowest minimum at rotation around the C-1—O-1 bond occurred at $\Phi = 52.3°$ (denoted as A1) and the further one (A2), with energy higher by about 4 kJ mol^{-1}, at $\Phi = 152.5°$. Methyl β-D-glu-

copyranoside differs from the α anomer only in configuration around the anomeric centre at C-1, however, on the rotation curve around C-1—O-1 there are three minima corresponding to three different staggered arrangements. Energetically the most advantageous is the conformer E1 with $\Phi = -57.8°$. The conformations E2 ($\Phi = 42.7°$) and E3 ($\Phi = -156.6°$) are energetically higher by about 4.2 kJ mol^{-1} and 4.8 kJ mol^{-1}, respectively, than the conformer E1 which, in turn, has by 4.47 kJ mol^{-1} higher energy than the conformer A1.

In Tables 1 and 2 some calculated geometrical parameters are compared with experimental values [13, 14] in crystalline structure. The calculated values agree relatively well with the X-ray data. The observed differences between the experimental and PCILO values reflect the properties of the PCILO method with CNDO Hamiltonian in prediction of geometry of this type of molecules [7]. The calculated bond lengths C—C are by about 2 pm shorter than the experimental values. Similarly, the external C-O bonds of the acetal segment C-5—O-5 and O-1—C are shorter by 3—5 pm. However, the differences do not exceed 4%. The calculated bond angles, except the glycosidic angle C-1—O-1—C, do not differ by more than 2°. Anomeric and *exo*-anomeric effects manifest themselves in dependence of magnitude of the bond angle O-5—C-1—O-1 on conformation of the acetal segment. Depending on conformation of the acetal segment (angle Φ), the O-5—C-1—O-1 varies in the interval of 103—111°. The lowest value 103° corresponds to all *trans* arrangement of the acetal segment in E2 conformer of Me-β-D-Glcp and the highest one 111° to all *gauche* arrangement in A1 conformer of Me-α-D-Glcp.

Relatively great differences were observed in the form of the pyranose ring in crystalline state [13, 14]. The ring of β anomer is a less regular chair and more puckered than that of α anomer with ring torsion angles changing from 52° to 70°. The calculated values suggest that this difference is observable in all conformers, though the differences are smaller. In the case of α anomer the values calculated are in very good agreement with the X-ray data. With β anomer this agreement is worse when the difference is in two cases 8°. Since the amount of hydrogen bonds in β anomer is far more higher than in α anomer, it can be assumed that these, together with the present water molecules in the crystal of methyl β-D-glucopyranoside hemihydrate [13], are the main reason of greater distortion of the pyranose ring in Me-β-D-Glcp.

Flexibility of pyranose ring

It is well known that chair conformers are the most stable forms of the pyranose ring. With most saccharides the more stable of the two chair conformers is the one which has more substituents in equatorial position, except the

Table 1

Comparison of puckering parameters, bond lengths, and bond angles of optimized $^4C_1$ chair conformers of methyl α- and methyl β-D-glucopyranosides with the values in crystal [13, 14]

	A1	Exp [14]	A2	E1	Exp [13]	E2	E3
Q/°	55.2	56.9	55.3	54.9	59.8	54.7	55.3
Φ_p/°	2.79	2.26	2.86	4.05	7.0	4.17	3.76
d(C-1—C-2)/pm	150.1	152.4	150.2	149.9	152.4	150.3	150.1
d(C-2—C-3)/pm	150.1	152.9	150.1	150.2	151.5	150.2	150.2
d(C-3—C-4)/pm	150.3	152.0	150.3	150.5	152.8	150.5	150.5
d(C-4—C-5)/pm	150.6	152.9	150.6	150.7	152.7	150.7	150.7
d(C-5—O-5)/pm	140.4	143.4	140.4	140.3	144.0	140.3	140.3
d(O-5—C-1)/pm	139.8	141.4	139.8	139.7	143.3	139.7	139.7
d(C-1—O-1)/pm	139.5	141.1	139.8	139.8	138.0	139.3	139.3
d(O-1—C-m)/pm	138.1	143.0	138.1	138.0	143.0	138.0	138.0
α(O-5—C-1—C-2)/°	111.7	110.6	111.7	111.9	108.4	112.0	112.1
α(C-1—C-2—C-3)/°	110.8	110.3	110.7	111.4	108.2	111.3	111.1
α(C-2—C-3—C-4)/°	109.4	110.6	109.5	109.5	110.9	109.7	109.6
α(C-3—C-4—C-5)/°	111.4	110.1	111.4	111.1	111.1	111.1	111.0
α(C-4—C-5—O-5)/°	110.0	110.8	110.1	110.2	108.6	110.2	110.3
α(C-5—O-5—C-1)/°	112.4	114.3	112.2	112.1	111.5	112.2	112.2
α(O-5—C-1—O-1)/°	110.9	112.4	106.9	107.1	108.1	103.3	107.8
α(C-1—O-1—C-m)/°	107.5	113.9	107.2	107.5	113.1	107.6	108.7

Table 2

Comparison of some significant torsion angles of optimized $^4C_1$ chair conformers of methyl α- and methyl β-D-glucopyranosides with the values in crystal [13, 14]

Torsion angle	A1	Exp [14]	A2	E1	Exp [13]	E2	E3
v(O-5—C-1—C-2—C-3)/°	55.4	58.0	55.7	54.4	62.0	54.0	54.3
v(C-1—C-2—C-3—C-4)/°	−51.1	−55.0	−51.0	−49.8	−54.0	−49.5	−50.0
v(C-2—C-3—C-4—C-5)/°	52.3	54.0	52.0	51.6	52.0	51.5	51.9
v(C-3—C-4—C-5—O-5)/°	−56.6	−55.0	−56.5	−57.2	−54.0	−57.1	−57.1
v(C-4—C-5—O-5—C-1)/°	60.7	58.0	60.8	61.4	63.0	61.3	61.0
v(C-5—O-5—C-1—C-2)/°	−60.7	−60.0	−61.0	−60.4	−68.0	−60.2	−60.0
v(C-5—O-5—C-1—O-1)/°	61.8	59.3	63.0	178.5	178.7	176.6	172.9
v(O-5—C-1—O-1—O-m)/°	65.8	63.0	152.5	−57.8	−73.2	−156.6	42.7

anomeric carbon. However, pyranose ring may occur also in less advantageous conformations and on its pseudorotational way six different skew conformers separated by six distinct boat conformers can be identified [15]. The structures of these forms of pyranose ring were studied in detail with 2-methoxytetrahydropyran (MTHP) [16, 17]. It was, therefore, of interest to compare the influence of hydroxyl groups on stability of the individual flexible forms of the pyranose ring. In this study we made use of great similarity in geometry of the chair forms of MTHP and methyl α- and methyl β-D-glucopyranoside. The geometry of flexible conformers of Me-α-D-Glcp and Me-β-D-Glcp was constructed by using the geometrical parameters of the corresponding forms of MTHP. The positions of the rotating side groups were fixed in minima without repulsion sterical interactions. The relative energies calculated in this way, together with dipole moments of the individual forms, are presented in Table 3. Energetical differences between the $^4C_1$ conformer and the flexible conformers are higher than in the case of MTHP. Comparison with the values calculated for D-glucopyranose [18] by using a simple force-field method shows that in both cases the most stable of the flexible forms are $^3S_1$, $^1S_3$, and $^0S_2$. From comparison of relative energies of MTHP and Me-α-D-Glcp and Me-β-D-Glcp it follows that the occurrence of flexible forms of pyranose ring is less probable with methyl glucopyranosides than with 2-methoxytetrahydropyran. Though optimization

Table 3

Energy differences and dipole moments of rigid chair and flexible conformers of methyl α- and methyl β-D-glucopyranosides, calculated in optimized geometry of 2-methoxytetrahydropyran

Conformer	$\Delta E/(\mathrm{kJ\,mol^{-1}})$		$\mu/(\mathrm{C\,m})$	
	α	β	α	β
$^4C_1$	0.0	3.2	30.3	45.9
$^1C_4$	52.3	73.7	37.3	38.9
$^{3,0}B$	19.1	23.6	41.6	48.6
$^3S_1$	14.5	18.1	48.3	60.3
$B_{1,4}$	51.7	57.6	51.2	65.6
$^5S_1$	48.4	49.9	35.6	41.3
$^{2,5}B$	35.6	35.7	44.9	38.3
$^2S_0$	41.7	43.7	32.0	20.6
$B_{3,0}$	40.9	56.7	53.6	35.3
$^1S_3$	15.2	26.1	51.3	32.6
$^{1,4}B$	26.6	26.6	46.9	26.6
$^1S_5$	18.4	18.9	47.9	32.6
$B_{2,5}$	114.1	115.6	56.6	58.6
$^0S_2$	15.3	17.8	44.6	41.6

Table 4

Equilibrium distribution of chair conformers of methyl α- and methyl β-D-glucopyranosides in isolated state and in various solvents at $T = 298.2$ K

Solvent	x(A1)/%	x(A2)/%	x(E1)/%	x(E2)/%	x(E3)/%
Isolated molecule	70.54	14.05	11.63	2.09	1.69
p-Dioxan	66.36	13.43	15.04	2.85	2.31
CCl_4	67.48	14.05	13.66	2.67	2.14
Chloroform	61.91	12.24	19.14	3.66	3.04
Pyridine	59.16	11.74	21.41	4.20	3.50
Acetone	59.39	12.57	20.31	4.26	3.46
Ethanol	57.08	12.13	22.21	4.74	3.84
Methanol	51.86	11.11	26.44	5.83	4.76
Acetonitrile	54.72	11.72	24.03	5.25	4.28
Dimethyl sulfoxide	57.36	12.49	21.61	4.74	3.80
Water	32.21	7.30	41.03	10.67	8.79

Table 5

Magnitude of anomeric and *exo*-anomeric effects in methyl D-glucopyranoside in various solvents

Solvent	Anomeric effect	*Exo*-anomeric effect	
	kJ mol^{-1}	kJ mol^{-1}	
		α	β
Isolated molecule	4.22	4.00	4.59
p-Dioxan	3.40	3.96	4.47
CCl_4	3.68	3.89	4.41
Chloroform	2.61	4.02	4.47
Pyridine	2.21	4.01	4.42
Acetone	2.34	3.85	4.26
Ethanol	2.01	3.84	4.23
Methanol	1.32	3.82	4.16
Acetonitrile	1.69	3.82	4.18
Dimethyl sulfoxide	2.08	3.78	4.16
Water	−1.06	3.68	3.82

of geometry of flexible forms can alter the relative energies of these conformers, from the results it follows that the presence of hydroxyl groups and hydroxymethyl group in axial and quasi-axial positions on pyranose ring is a significant factor contributing to instability of these forms.

Effect of solvent on stability of conformers

Table 4 presents the abundance of five chair conformers of methyl α- and β-D-glucopyranosides in various solvents calculated on the basis of Gibbs energies of the individual conformers in solution. Though equilibrium between the conformers of α and β anomers of methyl glucopyranoside does not develop, except in methanol solution, such hypothetical equilibrium composition makes possible to express the influence of the medium on relative stability of the individual conformers and to determine the magnitude of anomeric and *exo*--anomeric effects. It is evident from the results in Table 4 that the effect of the medium on the abundance of the α anomer is lower than in the case of MTHP and glucopyranose [4, 7]. The calculated $x_\alpha : x_\beta$ ratio in methanol 63 : 37 is close to the experimental value 67 : 33 [15]. Analysis of individual contributions to solvation Gibbs energy revealed that dispersion interactions and cavity contribution are conformationally almost independent. It is connected with small changes of the cavity radii which are for A1, A2, E1, E2, and E3 conformers 380.5 pm, 379.5 pm, 385.5 pm, 379.8 pm, and 380.5 pm, respectively. Dominant is the contribution of electrostatic interactions, the magnitude of which determines the magnitude of dipole moment of the respective conformer. The calculated abundance of the individual conformers corresponds to the most stable position of side groups. It is obvious that in more detailed study it would be necessary to take into account the distribution of conformers, formed by rotation of hydroxyl and hydroxymethyl groups around the C-1—O-1 bond for each conformer similarly as in the case of D-glucopyranose [7].

Anomeric and exo-anomeric effects

The calculated energies for the individual conformers made possible to calculate the magnitude of the anomeric effect of OCH_3 group and of the *exo*--anomeric effect in both anomers of methyl D-glucopyranoside as the difference in energies of the corresponding conformers (Table 5). The anomeric effect of OCH_3 group, *i.e.* the preference of the α anomer over the β anomer is higher than in the case of MTHP. The influence of solvent manifests itself in decrease of magnitude of the anomeric effect with the increasing polarity (characterized by relative permittivity) of the solvent. In water the β anomer is more stable and, therefore, methyl D-glucoside does not exhibit anomeric effect defined in such a way. However, if to this energetic difference we add the value of $A = 5$ kJ · $\cdot$ mol^{-1} for OCH_3 group [19], characterizing the corresponding equilibrium in methoxycyclohexane, the anomeric effect in water will be 0.1 kJ mol^{-1}. The respective values of anomeric effects calculated for hydroxyl group, substituents

fluorine and chlorine are 2.9 kJ mol^{-1}, 6.7 kJ mol^{-1}, 10.1 kJ mol^{-1} [18]. Thus, the magnitude of anomeric effect as a function of the substituent increases in the order: OH, OCH_3, F, Cl in agreement with the trend observed experimentally [19]. The magnitude of *exo*-anomeric effect, defined as the difference in energies of *sc* and *ap* conformations, is smaller than in the case of 2-methoxytetrahydropyran. Lower is also the solvent effect on its magnitude. The decrease of magnitude of *exo*-anomeric effect in water is smaller than with MTHP, where the *exo*-anomeric effect decreases to about one third of its value in the isolated molecule.

References

1. Sharon, N. and Lis, H., *Chem. Eng. News 59*, 21 (1981).
2. Rees, A. A., *Pure Appl. Chem. 53*, 1 (1981).
3. Bock, K., *Pure Appl. Chem. 55*, 605 (1983).
4. Tvaroška, I. and Kožár, T., *J. Amer. Chem. Soc. 102*, 6929 (1980).
5. Tvaroška, I., *Biopolymers 21*, 1887 (1982).
6. Tvaroška, I., *Biopolymers 23*, 1951 (1984).
7. Tvaroška, I. and Kožár, T., *Theor. Chim. Acta* (Berlin) *70*, 99 (1986).
8. Perez, S., Taravel, F., and Vergelati, C., *Nouv. J. Chim. 9*, 561 (1985).
9. Diner, S., Malrieu, J. P., and Claverie, P., *Theor. Chim. Acta* (Berlin) *13*, 1 (1969).
10. Tvaroška, I. and Kožár, T., *Theor. Chim. Acta* (Berlin) *53*, 9 (1979).
11. Powell, M. J. D., *Comput. J. 7*, 155 (1964).
12. Zanqwill, V. I., *Comput. J. 8*, 293 (1965).
13. Jeffrey, G. A. and Takagi, S., *Acta Crystallogr. B33*, 738 (1977).
14. Jeffrey, G. A., McMullan, R. K., and Takagi, S., *Acta Crystallogr. B33*, 728 (1977).
15. Stoddart, J. F., *Stereochemistry of Carbohydrates*. Wiley—Interscience, New York, 1971.
16. Tvaroška, I. and Kožár, T., *J. Mol. Struct. (Theochem) 123*, 141 (1985).
17. Kildeby, K., Melberg, S., and Rasmussen, K., *Acta Chem. Scand. A31*, 1 (1977).
18. Tvaroška, I., in *Theoretical Chemistry of Biological Systems*. (Náray-Szabó, G., Editor.) Pp. 283—348. Elsevier, Amsterdam, 1986.
19. Eliel, E. L., Allinger, N. L., Angyal, S. J., and Morrison, G. A., *Conformational Analysis*. Wiley—Interscience, New York, 1965.

Translated by A. Kardošová