Theoretical studies on the conformation of saccharides XII.* The anomeric effect in glycosyl halides

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Dedicated to Academician V Kellö, in honour of his 70th birthday

Molecular orbital calculations have been carried out on 2-fluorotetrahydropyran and 2-chlorotetrahydropyran as models for examining the anomeric effect in glycosyl halides. The calculated population of chair conformers depends on the solvent and for the axial form of fluoro derivative decreases from 90.6 % in dioxan to 37.0 % in water. For chloro derivative the dependence is less pronounced; the population of the axial form decreases from 97.8 % in dioxan to 78.4 % in water. The calculations indicate that the magnitude of the anomeric effect decreases with increasing polarity of the solvent and that the anomeric energies for anomeric substitution decrease in the order of substituents Cl, OCH_3, F. The optimized bond lengths and bond angles reproduce successfully the differences in molecular geometry obtained by X-ray crystal structure analysis of the glycosyl halides.

Проведены расчеты методом молекулярных орбиталей 2-фтортетрагидропирана и 2-хлортетрагидропирана как моделей для изучения аномерного эффекта в галоидных гликозилах. Вычисленное содержание конформеров в форме кресла зависит от растворителя, и для аксиальной формы фторпроизводного падает с 90,6 % в диоксане до 37,0 % в воде. Для хлорпроизводного эта зависимость менее выражена; содержание аксиальной формы снижается с 97,8 % в диоксане до 78,4 % в воде. Расчеты показывают, что величина аномерного эффекта уменьшается с ростом полярности растворителя, а величина аномерных энергий для аномерного замещения возрастает в ряду F, OCH_3, Cl. Полученные оптимализированные значения длин связей и валентных углов хорошо отражают различия в молекулярной геометрии, наблюдаемые с помощью рентгеноструктурного анализа галоидных гликозилов.

The enhancement in population (relative to cyclohexane) of the axial configuration displayed by an electronegative substituent at the anomeric carbon of

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pyranose is called the anomeric effect. This effect, first identified in carbohydrate chemistry, is now recognized as being of a more general importance and has been subject to very extensive experimental and theoretical examination [1]. Glycosyl halides have found considerable utilization as synthetic intermediates in glycosidic bond-forming reactions [2]. In addition to their synthetic use, these compounds have been studied as substrate analogues for enzymes that affect reactions at the anomeric centre of carbohydrates [3]. A tendency toward the stabilization of the axial form of glycosyl halides is considerably pronounced, e.g. benzyl and acetyl derivatives of β-D-xylopyranosyl halides exist in solution predominantly in $^1C_4$ conformation with all substituents in the axial position [4—7]. In this case, the anomeric effect prevails over the unfavourable 1,3 diaxial interactions of bulky substituents. In view of this, reliable prediction of the axial : equatorial ratio and the magnitude of the anomeric effect in various solvents would be very useful for interpreting the overall behaviour of glycosyl halides. Determination of the relative abundance of the axial and equatorial form of glycosyl halides is a very difficult and demanding task. Therefore studies of the acyclic and cyclic models are of invaluable help in this field. Substituted dimethyl ethers CH_3OCH_2X with an electronegative group X are the simplest acyclics where the anomeric effect is operating. For chloro and fluoro substituents, the synclinal conformation (corresponding to the axial form) with O—C torsion angle about 69—71° was found as the most stable from the microwave spectra [8]. NMR measurements [9] of chloro derivative gave an energy difference 6.3—8.4 kJ mol^{-1} between antiperiplanar and synclinal forms. Similarly, in substituted tetrahydropyrans with a halogen in the position 2 axial forms are the sole detectable species [10—12]. The results of the conformational energy calculations by MO methods for acyclic models $ROCH_2X$, where R is H or CH_3 and X is halogen [13—15] are consistent with experimentally observed preference for synclinal conformation. The ab initio STO-3G calculations of 2-chlorotetrahydropyran [16] confirm the stabilization of the axial position of the Cl atom relative to the equatorial one. An energy difference of 5.0 kJ mol^{-1} was found if the C—Cl bond length 177 pm was assumed for both conformers, and 15.5 kJ mol^{-1} if the axial C—Cl bond was lengthened to 182 pm. It is important to realize that all the above-mentioned calculations refer to isolated molecules, whereas conformational equilibria are generally measured in liquid phase, where solvent effects can be substantial. Therefore, in the present paper, the conformational behaviour of 2-fluorotetrahydropyran (FTHP) and 2--chlorotetrahydropyran (CTHP) in 10 solvents is investigated with semiempirical MO methods. Based on the calculated abundances of conformers the magnitude of the anomeric effect has been estimated and compared with the results of corresponding calculations on other compounds.

Method of calculation

Energy of the axial and equatorial forms of FTHP and CTHP in the isolated state was calculated by semiempirical quantum-chemical methods MNDO [17] and PCILO [18]. In the calculation, all the bond lengths, bond angles, and dihedral angles were optimized. In calculating the solvent influence on axial : equatorial ratio (Fig. 1), a method in which the total Gibbs energy of a solute molecule in a given solvent is composed of the Gibbs energy of the isolated molecule and the Gibbs energy that characterizes solvent—solute interactions was used. The energy calculated by the PCILO or MNDO quantum-chemical method was used as Gibbs energy of the isolated solute molecule. Thereby we assumed that differences in rotational entropy between conformers were negligible. The Gibbs energy of solvent—solute interactions was partitioned into three contributions, namely cavity, electrostatic and dispersion terms. A more detailed description of the method and parameters for the calculations are given in our previous papers [19, 20].
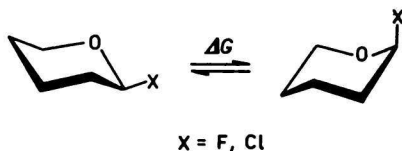

X = F, Cl

Fig. 1. Axial—equatorial equilibrium in 2-substituted halo derivatives of tetrahydropyran.

Results and discussion

The results of the energy calculations by the PCILO and MNDO methods corroborate the preference of axial form in both the studied compounds. For the fluoro derivative both methods predict an energy difference $6.7\,kJ\,mol^{-1}$. For the chloro derivative PCILO and MNDO methods give energies of $10.1\,kJ\,mol^{-1}$ and $13.2\,kJ\,mol^{-1}$, respectively. The Gibbs energy difference between axial and equatorial forms in 10 solvents based on the PCILO energy and mole fractions of axial form are given in Table 1. The PCILO energy difference for CTHP is in agreement with the energy difference $9\,kJ\,mol^{-1}$ observed in pure liquid [10, 11]. It follows from these results that the equilibrium composition in both compounds is solvent-dependent and the axial preference decreases with increasing polarity of solvent. Some differences exist between solvent-induced conformational changes for CTHP and those found for FTHP. In the case of CTHP, the abundance of the axial form decreases from 98.3 % in isolated molecule to 78.4 % in water. The values calculated for CTHP reproduce satisfactorily the observed axial preference of 93—96 % in acetonitrile and acetone [11]. For CTHP in chloroform the calculations predict the Gibbs energy difference of $8.5\,kJ\,mol^{-1}$. This agrees with the experimental value $8.8\,kJ\,mol^{-1}$

Calculated relative Gibbs energies ΔG (in kJ mol^{-1}) and mole fractions x_A (in %) for axial form of 2-fluoro- and 2-chlorotetrahydropyran

Solvent	FTHP		CTHP	
	ΔG	x_A	ΔG	x_A
PCILO	6.7	93.6	10.1	98.3
Dioxan	5.6	90.6	9.4	97.8
Carbon tetrachloride	6.0	91.7	9.7	98.0
Carbon disulfide	5.6	90.6	9.4	97.8
Chloroform	4.8	87.5	8.5	96.9
Pyridine	4.4	85.6	8.1	96.3
Acetone	4.5	86.1	8.2	96.5
Methanol	3.1	77.6	6.9	94.1
Acetonitrile	3.6	81.0	7.4	95.1
Dimethyl sulfoxide	4.1	84.1	7.8	95.9
Water	− 1.3	37.0	3.2	78.4

from a recent NMR study in the mixture of CFCl$_3$ and CDCl$_3$ [12]. A similar trend, although more pronounced, is observed for FTHP. The abundance of the axial form decreases from 93.6 % in isolated molecule to 37.0 % in water. Thus, the equatorial form is preponderant form of FTHP in aqueous solution. The influence of water on the conformational equilibrium of both CTHP and FTHP differs from the influence of other solvents.

The results of this study make it possible to estimate the solvent effect on the anomeric effect quantitatively. The Gibbs energy of the anomeric effect [1] was calculated as the difference ΔG of conformational Gibbs energies for 2-substituted tetrahydropyran and for the same substituent on cyclohexane A parameter. The magnitude of the anomeric effect estimated by this procedure for CTHP and FTHP compared with values for 2-methoxytetrahydropyran [19] is given in Table 2. The constant values of the A parameter, 3.2, 1.6, and 6.5 kJ mol^{-1} corrected for tetrahydropyran ring [21] were used for Cl, F, and OCH$_3$ groups, respectively. The dependence of the anomeric effect upon the solvent follows the trends in equilibrium composition discussed in the previous paragraph. The anomeric effect exhibits a maximum in the isolated molecules and gradually decreases in more polar solvents. The major difference appears between the effect in organic solvents and in water. The magnitude of the anomeric effect as a function of the substituent decreases in the order: Cl, OCH$_3$, F. In the case of fluoro group, the equatorial position is preferred in aqueous solution. However, a correction of the A parameter for this group results in a

Table 2

Solvent dependence of the calculated anomeric effect (in kJ mol^{-1}) of the chloro, fluoro, and methoxy groups

Solvent	Cl	F	OCH$_3$
PCILO	13.3	8.3	9.5
Dioxan	12.6	7.2	9.1
Carbon tetrachloride	12.9	7.6	9.4
Carbon disulfide	12.6	7.2	9.3
Chloroform	11.7	6.4	8.7
Pyridine	11.3	6.0	8.5
Acetone	11.4	6.1	8.6
Acetonitrile	10.6	5.2	8.3
Dimethyl sulfoxide	11.0	5.7	8.4
Water	6.4	0.3	6.3

Table 3

Calculated bond lengths (pm) and bond angles (°) for 2-chlorotetrahydropyran and 2-fluorotetrahydropyran compared with the observed data on carbohydrates [22, 23]

X	Position	Method	r(C—O)	r(O—C)	r(C—X)	α(C—O—C)	α(O—C—X)
F	Axial	PCILO	139.7	138.9	136.6	110.9	106.8
		MNDO	141.1	140.6	135.7	120.2	107.4
		Exp.	145.0	136.2	138.9	112.6	110.7
	Equatorial	PCILO	139.6	139.2	136.3	110.1	103.2
		MNDO	140.6	140.9	135.2	117.7	104.4
		Exp.	142.8	140.6	136.7	109.9	105.7
Cl	Axial	PCILO	139.8	137.5	183.5	112.9	107.8
		MNDO	141.3	138.1	184.3	120.1	109.9
		Exp.	145.1	138.3	185.9	113.0	107.9
	Equatorial	PCILO	139.8	138.4	182.3	108.2	103.4
		MNDO	140.9	139.1	182.4	119.4	105.7
		Exp.	142.7	141.5	175.4	111.1	107.1

larger preference of the axial form than could be expected on the basis of steric considerations. Therefore, the fluoro group exhibits the anomeric effect. From these results it is evident that polar medium acts in an opposite direction to the anomeric effect thus weakening its influence on the anomeric equilibrium.

The anomeric effect is a complex phenomenon characterized besides the conformational preferences also by the specific variations of the valence geometry. The calculated bond angles and bond lengths for CTHP and FTHP are summarized in Table 3 and compared with experimental data on xylopyranosyl

halides [22, 23]. The calculated bond angles and lengths agree rather well with experiment, though some differences are apparent. For 2-fluorotetrahydropyran, the calculations predict that the axial form has the larger O—C—F bond angle than the equatorial form. This agrees with experimental data, although the PCILO calculated difference of 3.6° is less than that observed 5.0° The theory also predicts that the axial C—F bond is longer than equatorial bond. The calculated differences for C—O bonds are also in the direction of those observed but considerably smaller. The calculated data for CTHP parallel those of FTHP. Here, calculated molecular dimensions from an isolated molecule of substituted tetrahydropyran are compared with experimental data collected for more complex carbohydrate derivatives in a crystal lattice. Therefore for testing validity of geometrical variations in glycosyl halides further experimental data are required. However, the calculated data indicate that there are small but significant differences in the bond lengths and bond angles depending on the conformation of glycosyl halides. The characteristic patterns of the molecular geometry variations represent a convincing manifestation of the anomeric effect.

References

1. Tvaroška, I. and Bleha, T., *Adv. Carbohydr. Chem. Biochem.*, in press.
2. Igarashi, K., *Adv. Carbohydr. Chem. Biochem. 34*, 243 (1977).
3. Walsh, C., in *Advances in Enzymology*, Vol. *V*, p. 197. (Meisler, A., Editor.) J. Wiley, New York, 1983.
4. Paulsen, H., Luger, P., and Heiker, F. R., in *Anomeric Effect, Origin and Consequences*, ACS Symposium Series, Vol. *87*, p. 63. (Szarek, W. A. and Horton, D., Editors.) American Chemical Society, Washington, 1979.
5. Durrette, P. L. and Horton, D., *Carbohydr. Res. 18*, 57 (1971).
6. Durrette, P. L. and Horton, D., *Carbohydr. Res. 18*, 289 (1971).
7. Durrette, P. L. and Horton, D., *Adv. Carbohydr. Chem. Biochem. 26*, 49 (1971).
8. Hyashi, M. and Kato, H., *Bull. Chem. Soc. Jpn. 53*, 2701 (1980).
9. Anet, F. A. L. and Yavari, J., *J. Am. Chem. Soc. 99*, 6752 (1977).
10. Booth, G. E. and Ouellette, R. J., *J. Org. Chem. 31*, 544 (1966).
11. Anderson, C. B. and Sepp, D. T., *J. Org. Chem. 32*, 607 (1967).
12. Both, H., Khedair, K. A., and Readshaw, S. A., *Tetrahedron 43*, 4699 (1987).
13. Jeffrey, G. A. and Yates, J. M., *J. Am. Chem. Soc. 101*, 820 (1979).
14. Tvaroška, I. and Bleha, T., *Tetrahedron Lett. 1975*, 249.
15. Tvaroška, I. and Bleha, T., *Chem. Papers 39*, 805 (1985).
16. Quibe, L., Auge, J., David, S., and Eisenstein, O., *J. Chem. Phys. 58*, 5579 (1973).
17. Dewar, M. J. S. and Thiel, W., *J. Am. Chem. Soc. 99*, 4899 (1977).
18. Diner, S., Malrieu, J. P., Jordan, F., and Gilbert, M., *Theor. Chim. Acta 15*, 100 (1969).
19. Tvaroška, I. and Kožár, T., *J. Am. Chem. Soc. 102*, 6929 (1980).
20. Tvaroška, I., *Biopolymers 21*, 1887 (1982).
21. Franck, R. W., *Tetrahedron 39*, 3251 (1983).
22. Kothe, G., Luger, P., and Paulsen, H., *Acta Crystallogr., B 32*, 2710 (1976).
23. Kothe, G., Luger, P., and Paulsen, H., *Acta Crystallogr., B 35*, 2079 (1979).