Theoretical stereochemistry of molecules with heteroatoms linked to the tetrahedral centre and the anomeric effect

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The review documents the progress accomplished during the last ten years in the understanding of the anomeric effect (an anomalous stabilization of synclinal *sc* conformation). It is shown how the methods of theoretical chemistry assisted in the explanation of the anomeric effect in acetals, where it is of the primary importance, and in other acyclic molecules with heteroatoms of the type O or S linked to the tetrahedral centre. The paper summarizes for the model compounds the calculations of potential energies of individual conformers and their solvent dependence. The marked changes of valence geometry of molecules of this class at internal rotation are pointed out. The origin of the anomeric effect is explained as a consequence of electrostatic and delocalization interactions of lone electron pairs on heteroatoms. Finally, the attention is paid to the implication of results valid for small molecules to the prediction of conformational equilibrium in larger cyclic and polymeric analogues by means of the various semiempirical additive schemes.

Обзор отражает прогресс, происшедший в последние десять лет, в понимании аномерного эффекта (аномальной стабилизации синклинальной *sc* конформации). Показано, каким образом методы теоретической химии способствовали объяснению аномерного эффекта в ацеталях, где он имеет первостепенную важность, и в других ациклических молекулах с гетероатомами типа O или S, связанными с тетраэдрическим центром. В работе суммаризованы результаты расчетов потенциальных энергий индивидуальных конформеров и их зависимость от растворителя для модельных соединений. Отмечены существенные изменения валентной геометрии молекул этого класса при внутреннем вращении. Происхождение аномерного эффекта объясняется как следствие электростатических и делокализационных взаимодействий свободных электронных пар гетероатомов. Наконец, внимание обращается на применимость результатов, полученных для небольших молекул, для предсказания конформационного равновесия в больших циклических и полимерных аналогах с помощью различных полуэмпирических аддитивных схем.

I. Introduction

The fundamental conceptions of the molecular shape and the first quantitative predictions of stability of individual rotational isomers (conformers) have developed in the domain of cyclic and acyclic hydrocarbons. However, several anomalies (traditionally termed as "the effects") have arisen at the transfer of classic ideas to the more complex, and especially, more polar compounds. The reasons for formulation of the various conformational effects in physical organic stereochemistry have been clarified by *Zefirov* [1]. A behaviour representing the deviation from the usual (classical) norm is classified as a conformational effect. The saturated hydrocarbons are most often used as reference compounds for the comparison. The large part of stereochemical properties in the latter compounds can be qualitatively explained by the consideration of steric interaction (bulkiness) of atomic groups in the molecule. Evidently, this simplification is not sufficient for more polar molecules where for example also the dipole—dipole and electronic (delocalization) effects or formation of hydrogen bonds have to be taken into consideration.

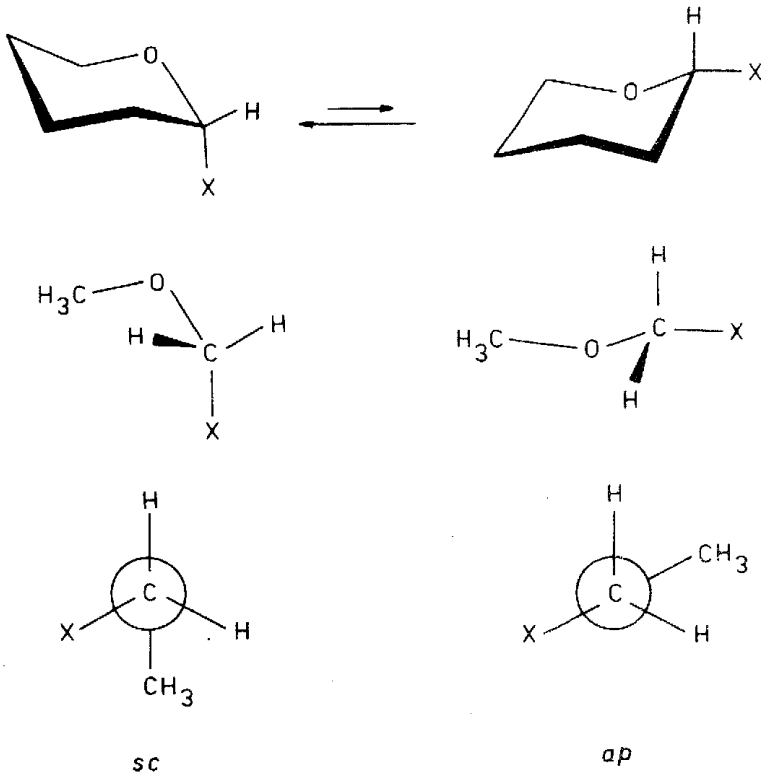
Of all conformational effects the anomeric effect originating in carbohydrate chemistry is paid the largest attention [2—6]. An additional stabilization of synclinal conformation with respect to antiperiplanar (unexpected from the classical point of view) is the most conspicuous manifestation of the anomeric effect. It turned out that this effect is rather frequent in polar molecules, especially in those involving segment of general formula —R—X—T—Y—. The group T represents a tetrahedral (anomeric) centre of the type —CH_2—, —PO_2^{2-}—, —$Si(CH_3)_2$—, —SO_2—, *etc.* X and Y are heteroatoms as O, S, N and also halogens in the case of terminal substituent Y. First of all, acetals and hemiacetals belong to this class of

compounds and corresponding bond segments C—O—C—O—C and C—O—C—O—H played a key role at the inception and development of the anomeric effect. Thioacetals, substituted sulfides, phosphates, siloxanes, and other molecules with heteroatoms in geminal 1,3 position in the backbone also belong to this group.

Concurrently with the gathering of experimental data, the attention was focused on the questions of prediction of the anomeric effect and understanding of its nature. Particularly the quantum chemical methods based on molecular orbitals (MO) brought a dramatic progress at generalization and classification of conformational properties of molecules with two (or more) heteroatoms linked to the tetrahedral centre. This paper reviews the advances achieved and has mainly issued from the authors' own work [7—17]. The interpretation of reasons, when and why the particular molecule exhibits the anomeric effect, is presented and the consequences of this effect on conformational equilibrium, internal geometry parameters, reactivity, and spectral properties are described. The attention is paid to the role of environment in determination of the magnitude of the anomeric effect. Starting from quantum chemical analysis of the anomeric effect in small molecules, the procedures are discussed for the inclusion of this effect into various simplified schemes used in stereochemistry of complex cyclic or polymer molecules.

II. Electronic effects in stereochemistry

The stable conformations of organic molecules are characterized by the torsional angles φ_i. The positions with $\varphi_i = 180°$ are denoted as *trans* or antiperiplanar (*ap*) and *gauche* or synclinal conformations lie near by $\varphi_i = 60°$ or 300° (sc^+ and sc^-). The anomeric effect in acyclic molecules is related to the Gibbs energy difference between *ap* and *sc* conformers (Scheme 1). Originally, the anomeric effect was observed in cyclic molecules; it was already known there that the axial (*ax*) position in monosubstituted cyclohexanes is less stable than the equatorial (*eq*) one due to 1,3 *syn* interaction in the ring [2]. It was found later for several pyranoses that the *ax* position of substituent on the anomeric centre was more stable than it had been expected. The tendency to an additional stabilization of axial substituent on the anomeric centre was denoted as the anomeric effect and it was observed after that for the great number of cyclic and acyclic molecules with 1,3 heteroatom moiety and termed the generalized anomeric effect [18]. An equivalent of *ax* position in cyclics is *sc* conformation in acyclics. From comparison of "calculated" and experimental values, the corrections on the anomeric effect have been assigned in simple calculations of the conformational equilibrium based on the interaction Gibbs energies of substituents in tetrahydropyran ring [2]. It turned out that the additional stabilization of *ax* position (or *sc* conformation in acyclics) due to the



Scheme 1

anomeric effect can be so large in some cases that it results in the preference of *ax* position over *eq* one or *sc* over *ap* conformation.

There exist several definitions of the energetic value of the anomeric effect. As mentioned above, the anomeric effect can be defined by ΔG_{AE}, the difference between the standard Gibbs energy ΔG°_{O} for *ax—eq* equilibrium in given molecule (tetrahydropyran derivative) and analogous value ΔG°_{CX} for similar derivative of cyclohexane [2]

$$\Delta G_{AE} = \Delta G^{\circ}_{O} - \Delta G^{\circ}_{CX} \qquad (1)$$

This definition is related to the values of Gibbs energy assigned from experiment and it is inconvenient for the theoretical prediction of the anomeric effect. According to this definition, the anomeric effect is present in all molecules in which the *ax—eq* equilibrium (or *sc—ap* one) is shifted closer to axial (*sc*) position than in a reference molecule. The ΔG_{AE} contributions for various substituents on heteroatom rings have been determined from the experiment using the group--additive scheme [19].

The second definition is based directly on the experimentally determined difference of Gibbs energy ΔG_{exp} of *sc* and *ap* conformation or *ax* and *eq* position. This value is compared with the difference of potential energy ΔE_{class} obtained by semiempirical calculations based on the classical mechanics. The calculation methods vary in their complexity from the simple estimation of steric energy by

atom—atom potentials [20, 21] on the one hand, to the highly elaborated molecular-mechanics calculations on the other hand [22]. In this concept, the anomeric effect E^*_{AE} is determined by that part of potential energy which is not accounted for by the calculation procedure and is "missing" in ΔE_{class}. Usually, the same entropy and volume of *sc* and *ap* conformation is assumed and the effect of solvent is neglected

$$\Delta G_{exp} \approx \Delta E_{exp} = \Delta E_{class} + E^*_{AE} \qquad (2)$$

The most convenient measure of the anomeric effect in the MO calculations is directly the positive difference of the potential energy of *ap* and *sc* conformation [23]

$$E_{AE} = E_{ap} - E_{sc} \qquad (3)$$

According to this definition which we will subsequently follow, a molecule exhibits the anomeric effect at rotation about the single bond if *sc* conformation is more stable than *ap* conformation. Evidently, this situation does not occur in hydrocarbons and other nonpolar molecules, nevertheless, it is surprisingly frequent in polar molecules with the geminal two (or more) heteroatoms with the lone electron pairs as are O, N, F, *etc.*

It has gradually appeared that an "anomalous" energetic contribution to the stabilization of *ax* position (*sc* conformation) is only one of the several manifestations of the anomeric effect. In addition, the specific changes of electron distribution occur at internal rotation in molecules with the anomeric effect. From this point of view, the anomeric effect is one of the several stereoelectronic effects [5], nevertheless, the most dramatic one. The anomeric effect influences the whole complex of molecular properties; for example the large variations in the internal geometry parameters of molecule at internal rotation or the difference in spectral properties and reactivity of conformers are some of its consequences. Abundant data on the multiface character of the anomeric effect have been accumulated for acetal segment, and therefore, the attention in the review is focused on that moiety. The simplest acetal, dimethoxymethane $CH_3—O—CH_2—O—CH_3$, is mainly used in the demonstration of the stereoelectronic behaviour typical for all the molecules with the segment —R—X—T—Y—.

The description and understanding of the origin of stereoelectronic effects is an appropriate field for the application of organic quantum chemistry. MO methods can describe the electron distribution in molecules and its changes at internal rotation. They give the total potential energy of individual conformers completely, without the necessity to correct it for the various "effects". Dipole moment, a property most frequently available from experiment (sometimes the only one), for molecules with the anomeric effect, is also correctly predicted by MO methods. Quantum chemical calculations make possible a deeper insight into the orbital

interactions in the molecule (of lone pairs particularly), and a profound analysis of the factors responsible for the stabilization of any conformation.

The best description of the stereochemical behaviour of isolated molecule is achieved by nonempirical *ab initio* calculations with the sufficiently extended basis of the atomic orbitals. However, one should bear in mind that investigation of conformational properties of molecule with only two torsional angles, resulting in the energy map $E(\varphi_1, \varphi_2)$ represents the multiple (even hundredfold) repetition of routine calculation of energy. Therefore, in practice one is mostly confined to the less time-consuming methods: either to the *ab initio* method with the restricted basis of orbitals or to the semiempirical MO methods. In both cases, a cautious approach is necessary, with the careful comparison of a computed property for the group of molecules with available experimental data, at first. We should like to point out that there exists an inclination to consider the *ab initio* results even with the restricted or minimal basis set as automatically superior to the results of any semiempirical MO method. Calculations of conformational energy for molecules with the anomeric effect (*e.g.* for acetals) give several examples on the deceptiveness of this claim (see below).

An optimal choice of quantum chemical method does not solve all the problems. The isolated molecule calculations can be performed by the full or partial optimization of molecular geometry at internal rotation, or assuming the rigid geometry, with torsional angles as the only degrees of freedom. Although the optimization considerably extends the computing time, it is often inavoidable due to the relatively large changes of geometrical parameters in —R—X—T—Y— bond segments at internal rotation. Finally, quantum chemical calculations for isolated molecule have to be supplemented by the procedure accounting for the influence of environment and thus employed, *e.g.* for estimation of conformational equilibria in solution.

III. Anomeric effect in substituted ethers and acetals

The most complete theoretical and experimental information on the anomeric effect with the —R—X—T—Y— segment exists for molecules in which the tetrahedral centre is methylene group, X is an oxygen atom and R is methyl, terminal alkyl or the hydrogen atom. The structural element R—O—C—Y is typical for substituted acyclic and cyclic ethers or hemiacetals or acetals (if Y is an oxygen atom). Conformations of these molecules are specified mainly by one or two torsional angles φ_1 and φ_2 for the rotation about C—O and C—Y bonds, respectively.

a) Torsional dependence of the potential energy

Torsional potential of C—O bond $E(\varphi_1)$, and the anomeric effect related to it depend on the number of factors, primarily, however, on the type of substituent Y on the anomeric centre and on the solvent. Fig. 1 illustrates the effect of substituents on the torsional potential of C—O bond in substituted dimethyl ethers CH_3OCH_2Y, where Y is F, Cl, OCH_3, SCH_3, NH_2, CH_3, and NH_3^+ [8, 16, 51].

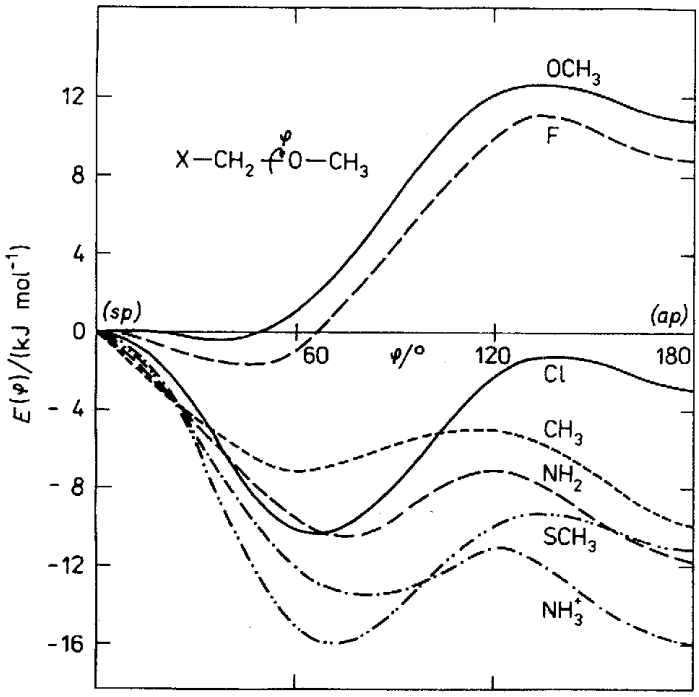


Fig. 1. Energy of rotation around C—O bond calculated by semiempirical quantum chemical methods for molecules X—CH_2—O—CH_3 where X = F, Cl, OCH_3, SCH_3, CH_3, NH_2, NH_3^+.

CNDO/2 method in standard parametrization was used in the calculation, except SCH_3 substituent which was treated by PCILO method (without inclusion of *d* orbitals). Geometrical parameters experimentally determined for dimethoxymethane (Y = OCH_3) [24] were assumed and for the bond lengths bond angles of the rest of substituents standard values were taken [25]. In four cases (OCH_3, F, Cl, SCH_3) the molecules prefer *sc* conformation to *ap* and exhibit the anomeric effect according to the adapted definition (eqn (*3*)). The preference of *sc* conformation expressed by E_{AE} (Table 1) diminishes in the order F, OCH_3, Cl, SCH_3. The calculated barriers of *sc*—*ap* transition through synperiplanar (*sp*) position increase in the opposite succession.

Torsional potential $E(\varphi_1)$ can approximately be decomposed by Fourier expansion [26]

$$E(\varphi) = (V_1/2)\,(1-\cos\varphi) + (V_2/2)\,(1-\cos 2\varphi) + \\ + (V_3/2)\,(1-\cos 3\varphi) \qquad (4)$$

Individual terms in the expansion represent one-, two-, and threefold contributions of the torsional potential. Although the decomposition is rather formal, the physical meaning is ascribed to the expansion coefficients. The terms V_3, V_2, and V_1 are identified with the inherent torsional barrier for single bond rotation, with the delocalization interaction of lone pairs and with the interaction of dipoles in the rotating segments, respectively.

The coefficients of Fourier expansion of potential $E(\varphi)$ are summarized in Table 1 for the collection of molecules from Fig. 1 with an oxygen and an additional heteroatom. For comparison, dimethyl ether where $Y = CH_3$ is also included. One can see that the term V_3 increases with the size of substituent, *e.g.* values for Cl and SCH_3 groups are double of those for OCH_3 and F derivatives. With the increase of the barrier of transition through *sp* (*cis*) position, a minimum in *sc* region is shifted to the larger torsional angle φ_1. While for OCH_3 the calculated minimum of φ_1 is at 35°, for F at 45°, for Cl at 65° and for SCH_3 at 70°. On the other hand, the barriers of transition from *ap* to *sc* are relatively small and almost the same for all derivatives. As seen from Fig. 1, *ap* conformation is predominant in three derivatives and the *sc*—*ap* energy difference increases in the succession NH_2, CH_3, NH_3^+. Accordingly, the anomeric effect is absent in the latter molecules and such a behaviour was referred to as the reverse anomeric effect [27].

Nearly identical picture of the influence of substituents on the anomeric effect

Table 1

Expansion coefficients of torsional potential of C—O bond and *ap*—*sc* conformational energy difference ΔE in CH_3—O—CH_2—Y molecules [8, 16, 51]

Y	V_1/(kJ mol^{-1})	V_2/(kJ mol^{-1})	V_3/(kJ mol^{-1})	ΔE/(kJ mol^{-1})
OCH_3[a]	14.65	1.45	−3.76	9.9
F	13.33	0.02	−4.37	10.0
Cl	3.60	−6.61	−6.43	7.7
SCH_3[a]	−3.96	−9.25	−7.12	3.7
NH_2	−9.08	−6.25	−2.73	−2.1
CH_3	−6.18	0.05	3.77	−3.1
NH_3^+	−9.96	−4.96	−6.17	−3.8

a) The second methyl group is in *ap* position.

results also from *ab initio* calculations. Prevailing majority of nonempirical calculations of stable conformations in molecules with 1,3 heteroatom moiety treats a simple segment H—O—CH_2—Y, where Y is F, Cl, NH_2, OCH_3, OH [28—38]. The most important results are collected in Table 2. Calculations predict as the most stable *sc* position of H with respect to C—Y bond at rotation about C—O bond. An exception is NH_2 derivative in which the lone pair on nitrogen atom is assumed to be in *ap* position to C—O bond. In this case, calculations with STO-3G and 4-31G basis yield *ap* conformation as the most stable while 4-21G calculation prefers *sc* conformer.

The most detailed investigation of the effect of basis on the energy difference between *sc* and *ap* conformation was performed by *Jeffrey et al.* for Y = F, Cl, OH (Table 2) [35, 36]. For F (Cl) substituent they have found that the energetical preference of *sc* conformer compared with *ap* increases from 13.1 (20.1) to 26.0 (22.6) kJ mol^{-1} by the transfer from STO-3G to 4-31G level. A further extension of basis to 6-31G level reduces this difference to 25.5 (21.3) kJ mol^{-1}. In methanediol, the same change from 4-31G to 6-31G level results in the reduction of the relative energy with respect to (*sc*, *sc*) conformation from 19.8 to 15.7 kJ mol^{-1} for (*sc*, *ap*) conformation and from 49.2 to 43.4 kJ mol^{-1} for (*ap*, *ap*) conformation. All computations have been performed with the rigid geometry, constant for all the conformations. Since the bonding parameters of molecules with 1,3 heterosegment depend considerably on conformation (see discussion later) it is questionable whether the calculated relative energies apply also for conformations with optimized geometry. It should also be noted that *ap* conformation represents a maximum on the energy hypersurface of these molecules.

It results from the decomposition of potential energy that preference of *sc* conformation in methanediol is caused by dipole—dipole interactions (V_1 term) and delocalization interactions (V_2 term). On the other hand, in aminomethanol, with the lone pair on N in *ap* position to C—O bond, dipole—dipole interactions are responsible for the preference of *ap* conformation. Scheme 2 illustrates dipole—dipole and delocalization interactions in the latter molecules for (*ap*, *sc*) and (*ap*, *ap*) conformations. The distinct conformational dependence of mentioned interactions is brought about by the different symmetry of rotating —OH and —NH_2 groups, and thus, by the different orientations of lone pairs on O and N atoms with respect to the rest of molecule. Oxygen lone pairs in methanediol are oriented in such a way that stabilizing delocalization of electron density into the vacant orbital on the central carbon atom is possible only in (*ap*, *sc*) conformation. Dipole moments of the two C—O—H segments are oriented in antiparallel way and their interaction is attractive. In (*ap*, *ap*) conformation, stabilizing delocalization does not occur owing to unfavourable orthogonal orientation of the appropriate orbitals and dipole—dipole interaction is repulsive due to the arrangement of dipoles of C—O—H groups. Just an opposite situation exists in aminomethanol.

Table 2

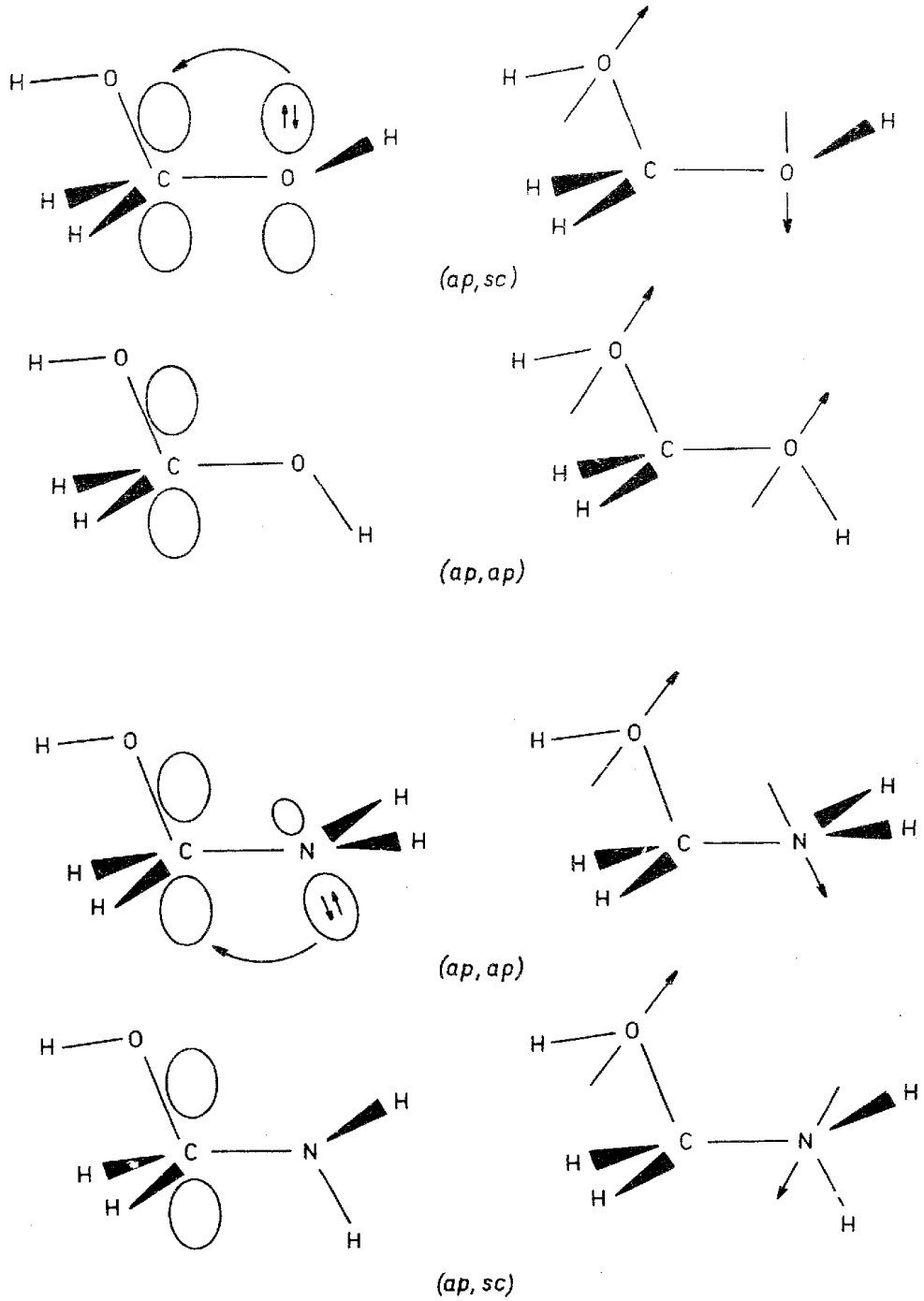
Influence of the basis size on the relative conformational energies ΔE in *ab initio* calculations of Y—CH_2—OH molecules

		F		Cl						
Basis	φ_1	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.	Basis	φ_2^d	φ_1	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.
STO-3G	*sc*	0.0		0.0		STO-3G	*ap*	*ap*	0.0	[34]
	ap	12.7	[34]	18.6	[34]		*–sc*	*sc*	0.60	
STO-3G	*ap*	13.1	[36]	20.1	[36]		*ap*	*sc*	3.49	
4-31G	*ap*	26.0	[36]	22.6	[36]	STO-3G	*ap*	*sc*	4.9	[38]
6-31G	*ap*	25.5	[36]	21.3	[36]		*sc*	*sc*	6.0	
4-31G	*ap*	23.4	[30]				*sc*	*ap*	19.8	
4-31G	*ap*	26.8	[33][b]			4-21G	*ap*	*sc*	0.0	[37][a]
4-21G	*ap*	14.9	[37][a]				*ap*	*ap*	4.7	
GTF[c]	*ap*	52.6	[28]				*sc*	*sc*	5.7	
							sc	*ap*	32.3	
						4-31G	*ap*	*ap*	0.0	[29]
							ap	*sc*	6.2	
							sc	*sc*	8.8	
							sc	*ap*	30.4	
						4-31G	*ap*	*sc*	3.5	[38][b]
							sc	*sc*	9.1	

Table 2 (Continued)

OCH_3					OH				
Basis	φ_2	φ_1	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.	Basis	φ_2	φ_1	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.
4-31G	*sc*	*sc*	0.0	[32]	STO-3G	*sc*	*sc*	0.0	
	ap	*sc*	12.6			*sc*	*ap*	11.7	[34]
	sc	*ap*	18.0			*ap*	*ap*	28.3	
	ap	*ap*	39.4		STO-3G	*sc*	*ap*	9.4	[39]
4-31G	*ap*	*sc*	11.3	[32][b]		*ap*	*ap*	27.6	
	sc	*ap*	16.7			*sc*	*ap*	10.6	[39][b]
						ap	*ap*	26.9	
					4-31G	*sc*	*sc*	0.0	[29]
						sc	*ap*	19.7	
						ap	*ap*	46.9	
					4-31G	*sc*	*ap*	18.4	[31][b]
						ap	*ap*	46.1	
					4-31G	*ap*	*sc*	18.8	[33][b]
						ap	*ap*	44.8	
					4-31G	*sc*	*ap*	19.8	[35]
						ap	*ap*	49.2	
					6-31G	*sc*	*sc*	0.0	[35]
						ap	*sc*	15.7	
						ap	*ap*	43.4	

a) Full optimization of geometry; *b*) partial optimization of geometry (bond lengths or bond angles); *c*) Huzinaga's extended basis; *d*) φ_2 corresponds to torsional angle *lp*(N)—C- -O—H.



Scheme 2

Lone pair delocalization is possible in (*ap*, *ap*) conformation and dipole—dipole interaction is repulsive in (*ap*, *sc*) conformation.

CNDO/2 calculations of fluromethanol [40] give the same (positive) sign of *ap*—*sc* energy difference as *ab initio* calculations but its magnitude is reduced. The more complex molecules, substituted dimethyl ethers CH_3—OCH_2—Y with Y = F, Cl, OH, and OCH_3, have also been investigated by nonempirical calculations [32, 35, 36, 48, 49] and the most important results are presented in Tables 2 and 3.

STO-3G, 4-31G, and 4-21G calculations have been carried out for dimethoxymethane (Y = OCH_3), all other molecules have been studied at 4-31G level only.

Instability, a drawback of HO—CH_2—Y molecules, is responsible for the absence of experimental data suitable for comparison with computations. The predominance of *ax* conformer in their cyclic analogues, substituted tetrahydropyrans (THP), is considerably smaller than is predicted by the above discussed nonempirical calculations. For example, 47 % of 2-hydroxy-THP exists in *ax* form in CCl_4 at equilibrium [41], which corresponds to 0.17 kJ mol^{-1} in the energy difference. In 2-chloro-THP, the *ax* form is preferred to *eq* by about 8 kJ mol^{-1} [42].

There is a scarcity of experimental data on conformations of substituted dimethyl ethers CH_3OCH_2Y, too. For Cl- and F-methyl ethers, *sc* conformation with φ_1 around 69—71° has ensued as the most stable from microwave spectra [43]. From NMR measurement of Cl derivative [44] the values 6.3—8.4 kJ mol^{-1} and 17.6 kJ mol^{-1} have been estimated for the relative stabilization of *sc* conformation with respect to *ap* and for the barrier of rotation about C—O bond, respectively. In ethyl methyl ether, *ap* conformation has been determined as the most stable from microwave spectroscopy [45]. The *ap*—*sc* energy difference of halogen derivatives calculated by *ab initio* (at 4-31G level) is larger than the above quoted experimental results and partial optimization of geometry at calculations even enhances this discrepancy (Table 3).

From the point of view of the anomeric effect, the most important of all substituted methyl ethers and alcohols are the derivatives with OCH_3 or OH substituent, *viz.* dimethoxymethane (DMM), methanediol, and methoxymethanol. A possibility of internal rotation around two C—O bonds is responsible for the "double" presence of the anomeric effect, resulting in the stabilization of (*sc*, *sc*) conformation with methyl groups (or H atoms) on the opposite sides of —O—C—O— plane. In DMM and methanediol the latter conformation is doubly degenerated for symmetry reasons to (sc^+, sc^+) and (sc^-, sc^-) conformers. Similarly, the position with adjacent methyl groups on the same side of O—C—O plane corresponds to two conformers (sc^-, sc^+) and (sc^+, sc^-). However, due to the steric reasons these conformers are energetically unfavourable. Next, there are four minima on the conformational map of DMM and methanediol corresponding to (*ap*, *sc*) conformations and one minimum for DMM or one maximum in methanediol corresponding to (*ap*, *ap*) conformation. A structural intermediate between DMM and methanediol is methoxymethanol with the reduced symmetry due to the presence of two different rotors. For example, conformations (*ap*, *sc*) and (*sc*, *ap*) can be distinguished in this case and are doubly degenerated.

In gas-state DMM, (*sc*, *sc*) conformation only has been observed [24] with both torsional angles identical, $\varphi_1 = \varphi_2 = 66.3°$. The energy difference 7.1 kJ mol^{-1} between the most stable (*sc*, *sc*) conformer and (*ap*, *sc*) has been estimated from

Table 3

Ab initio relative conformational energies ΔE in Y—CH_2—O—CH_3 molecules and 1-methoxyethanol

F				Cl		OCH_3					1-Methoxyethanol				
Basis	φ_1	ΔE / kJ mol^{-1}	Ref.	ΔE / kJ mol^{-1}	Ref.	Basis	φ_1	φ_2	ΔE / kJ mol^{-1}	Ref.	Basis	φ_1	φ_2	ΔE / kJ mol^{-1}	Ref.
4-31G	*sc*	0.0	[36]	0.0	[36]	STO-3G	*sc*	*ap*	0.0	[48]	4-31G	*sc*	*sc*	0.0	[50]
	ap	18.0	[36]	5.9	[36]		*sc*	*sc*	1.0			*sc*	*ap*	20.2	
	ap	18.8	[36]^b	15.5	[36]^b		*ap*	*ap*	10.7			*sc*	*sc*	28.5	
	ap	21.4	[36]^b	12.1	[36]^b		*sc*	*sc*	0.0	[48]^b		*ap*	*sc*	10.2	
	ap	21.8	[36]^b	17.6	[36]^b		*sc*	*ap*	6.6			*ap*	*sc*	14.2	
							ap	*ap*	13.9			*ap*	*ap*	38.9	
						4-21G	*sc*	*sc*	0.0	[49]^a		*sc*	*sc*	0.0	[50]^b
							sc	*ap*	19.0			*ap*	*sc*	9.3	
							sp	*ap*	22.2						
							ap	*ap*	43.2						
						4-31G	*sc*	*sc*	0.0	[35]					
							sc	*ap*	10.8						
							ap	*ap*	32.2						
							sp	*ap*	37.5						
							sc	*−sc*	70.3						
							sc	*ap*	10.0	[35]^b					
							ap	*ap*	31.1						
							sc	*ap*	13.3	[35]^b					

a) Full optimization of geometry; *b*) partial optimization of geometry (bond lengths or bond angles).

dipole moment measurements and the latter conformation is preferred to (*ap*, *ap*) one by the same value [46]. Enthalpy difference 5.0 kJ mol^{-1} between (*sc*, *sc*) and (*sc*, *ap*) has been determined for DMM in liquid state by Raman spectroscopy [47]. For comparison, in analogous alkoxy-THP derivatives the *eq*—*ax* energy difference is in the range 2—12 kJ mol^{-1}.

The energy of DMM conformers calculated by 4-31G basis (Table 3) seems to be unrealistically high in comparison with experiment. This difference may diminish in calculation at 6-31G level if the similar effect of basis as observed in methanediol (Table 2) is assumed. Such crude estimation of this quantity gives about 7 kJ mol^{-1} and 26 kJ mol^{-1} for (*sc*, *ap*) and (*ap*, *ap*) conformers relative to (*sc*, *sc*), which is closer to experimental data. STO-3G calculations [48] in contrast to all other results predict (*sc*, *ap*) conformation as the most stable, although assumed (fixed) geometry might be responsible for this result. Computations by the same method with optimization of OCO angle support this notion and give the correct increasing ordering of stability (*sc*, *sc*)>(*sc*, *ap*)>(*ap*, *ap*). Energy differences calculated with the full optimization of DMM geometry at 4-21G level [49] are three times larger than experimental ones. The results in Table 3 indicate that the gradual extension of minimal basis in nonempirical calculations of DMM brings about at first the deterioration of predictability of the method and only sufficiently extended basis provides the energy difference close enough to experimental data.

Stability of DMM conformers as predicted by semiempirical MO approach also depends on the method (Table 4) [7, 13, 51]. CNDO/2, INDO, PCILO, and MNDO methods predict the correct order of conformer stability and the energy differences are in agreement with experimental data from dipole moment measurements [46]. Conformer population calculated from computed energy agrees well with the data for cyclic analogue 2-methoxy-THP (MTHP) obtained from NMR measurements in nonpolar solvents [18, 52]. For example, the population of *ax* form of MTHP is 81—83 % from experiment in CCl_4 and 78 % from CNDO/2 calculation. The calculated mean-average of dipole moment [7] exceeds the experimental value 2.2×10^{-30} Cm determined in gaseous state [46] but is close to 3.3×10^{-30} Cm measured in benzene [24]. EHT and MINDO/2 methods produce qualitatively incorrect relative energies of DMM conformers with the preference of *ap* positions.

It is seen from the survey of calculated and experimental data in Tables 2 and 3 for DMM and related molecules that the anomeric effect at rotation about the first C—O bond depends on the conformation of the second C—O bond and consequently, it is not additive. Internal rotation from (*ap*, *ap*) to (*ap*, *sc*) usually leads to greater energy stabilization (E^1_{AE}) than the second rotation from (*ap*, *sc*) to (*sc*, *sc*) (E^{12}_{AE}, shown in Table 4). The total anomeric effect in DMM, E_{AE}, is given by the sum of E^1_{AE} and E^{12}_{AE}.

Generally, it seems that MO methods successfully predict the energy value of the

Table 4

Comparison of relative energy ΔE and of the anomeric effect energy E_{AE}^{12} of DMM conformers calculated by various semiempirical methods and observed by experiment

Method	ΔE/(kJ mol^{-1})			E_{AE}^{12}/(kJ mol^{-1})	Ref.
	(*sc*, *sc*)	(*sc*, *ap*)	(*ap*, *ap*)		
EHT	7.1	2.4	0.0	−4.7	[7]
CNDO/2	0.0	4.6	15.8	4.6	[7]
CNDO/2	0.0	4.9	14.9	4.9	[48]
CNDO/2	0.0	3.8	10.9	3.8	[53]
INDO	0.0	5.1	14.2	5.1	[7]
MINDO/2	46.9	32.8	0.0	−14.1	[7]
PCILO	0.0	5.0	10.9	4.2	[13]
MNDO	0.0	5.2	17.2	5.2	[51]
Exp	0.0	7.1	14.2	7.1	[46]
Exp	0.0[a]	8.1	18.8	8.1	[53]
	0.0[b]	6.2	12.4	6.2	
	0.0[c]	6.3	13.0	6.3	
Exp	0.0	5.0		5.0	[47]

a) Gaseous phase; *b*) neat liquid; *c*) DMM—heptane mixture (volume ratio = 1 : 1).

anomeric effect in substituted ethers and acetals. At the same time, it is interesting to note that the agreement of calculated results with the available experimental data seems to be better at some semiempirical MO methods than at some nonempirical calculations, apparently due to the fortuitous circumstances.

b) Molecular geometry and the anomeric effect

Significant changes of internal geometry are another manifestation of the anomeric effect in molecules with 1,3 heterosegments. It is well known that the carbon—substituent bond length shortens with the increase of the number of electronegative substituents on carbon centre. An example provides the shortening of carbon—halogen bonds in polyhalomethanes or contraction of internal C—O bonds in DMM in comparison with the terminal ones [24]. Recent experimental studies have elucidated the connection of valence geometry in the vicinity of the anomeric centre and conformation. Above all, X-ray and neutron diffraction analyses of a large number of saccharides have confirmed the differences in geometry of acetal and hemiacetal segments in various conformational (configurational) isomers.

Quantum chemical calculations correctly reproduce the experimentally determined variation of geometry with conformation. It is clearly seen from Table 5 in which we present selected geometry parameters for *sc* and *ap* conformations of some molecules except DMM. Optimized geometry of DMM calculated by semiempirical and *ab initio* methods and that derived from experiment are compared in Table 6 with the average crystallographic parameters of saccharides with various conformations of acetal segment.

One important characteristic which can be noticed from the data in Table 6 is the shortening of one internal C—O bond on going from *ap* to *sc* conformation and, on the contrary, the elongation of the second internal C—O bond. In bond angles, the most striking changes occur in OCO angle. In 4-21G basis calculation this angle reduces from 112.4° to 109.5° and 105.9° on going from (*sc*, *sc*) to (*sc*, *ap*) and (*ap*, *ap*) conformations. PCILO calculations furnish the similar values: 113.2°, 110.9° and 105.8°, respectively. The calculated trends are in accord with experimentally determined changes in saccharides and their derivatives. Variation in OCY bond angle is the most important in the other substituted dimethyl ethers (Table 5) and this angle increases by 1.1—4.7° at *ap* to *sc* conformational transition. The largest increase is observed in derivatives in which also energetic value of the anomeric effect is most pronounced. The conformational variation of bond lengths is less unambiguous than in DMM; it depends on the type of substituent and the method used. CNDO/2 provides elongation of O—C and C—Y bonds at the anomeric centre during *sc* to *ap* conversion in all derivatives except that with NH_2. 4-31G and MNDO predict mostly elongation of O—C bond but shortening of C—Y bond.

Conformational changes of valence geometry in —X—O—C—Y molecules pose a question what, reversely, is the influence of input geometry on conformational energy differences. Apparently, this influence may be important since, as already mentioned, CNDO/2 and STO-3G calculations [48] predict as the most stable conformer either (*sc*, *sc*) or (*sc*, *ap*) depending on the choice of OCO angle. Therefore, if the optimization of geometry in each conformation is not feasible, the use of conformationally averaged geometry parameters is more appropriate than of those corresponding to one individual conformer. Such an approach in conformational calculations of molecules with 1,3 heterosegment is supported also by computation of C—O bond torsional potential in MTHP [57].

We have already noted that MO methods in general provide a qualitatively correct picture of internal geometry changes with conformation. A closer inspection of data in Table 6 indicates that neither method can be preferred in prediction of absolute values of bond lengths and bond angles. Bond lengths calculated by MNDO method most closely reproduce experimental data of DMM. Nonempirical calculations at 4-31G and 4-21G level predict C—O bond lengths by about 2—4 pm larger and semiempirical PCILO and CNDO/2 methods by 2 pm shorter than

Table 5 (Continued)

Y	φ_1	φ_2	Method	*a*/pm			φ/°		Ref.
				C—O	O—C	C—Y	C—O—C	O—C—Y	
CH_3	*ap*	*sc*	CNDO	138.2	137.0	146.6	106.0	116.7	[51]
			MNDO	140.3	140.2	154.8	120.7	111.9	[51]
	ap	*ap*	CNDO	138.1	137.1	146.7	107.7	110.4	[51]
			MNDO	140.3	140.1	154.5	119.6	109.7	[51]
SCH_3	*ap*	*sc*	MNDO	139.2	140.5	175.0	120.1	110.4	[16]
	ap	*ap*	MNDO	138.9	140.6	176.1	119.6	105.9	[16]
	sc	*sc*	MNDO	138.5	140.7	176.2	121.4	114.5	[16]

a) *d* Functions added to the chlorine atom.

Table 6

Selected bond lengths a and bond angles φ in DMM optimized by quantum chemical methods

φ_1	φ_2	Method	a/pm				φ/°			Ref.
			C_1—O_2	O_2—C_3	C_3—O_4	O_4—C_5	C_1—O_2—C_3	O_2—C_3—O_4	C_3—O_4—C_5	
sc	*sc*	Exp	140.3	140.3	140.3	140.3	114.2	112.6	114.2	[24]
		Exp[a]	143.5	141.6	140.4	143.1	113.4	112.3	113.1	[35]
		4-31G	144.4	142.3	142.3	144.4	115.9	113.9	115.9	[35]
		4-21G	144.9	142.2	142.2	144.9	114.5	112.4	114.5	[37]
		CNDO/2	137.9	137.6	137.6	137.9		114.9		[9]
		PCILO	138.5	138.4	138.4	138.5	106.3	113.2	106.3	[51]
		MNDO	140.5	139.9	139.9	140.5	123.5	113.6	123.5	[51]
ap	*sc*	Exp[a]	143.3	142.8	138.3	142.7	111.4	107.9	113.4	[35]
		4-31G	143.4	142.5	140.0	144.3	115.8	110.9	116.1	[35]
		4-21G	144 2	143.2	140.9	144.8	114.3	109.5	114.9	[37]
		CNDO/2		137.9	137.7			110.0		[9]
		PCILO	138.4	138.5	138.4	138.5	105.5	110.9	107.5	[51]
		MNDO	140.2	140.5	139.3	140.6	120.0	108.2	123.4	[51]
ap	*sc*	4-31G	143.5	140.6	140.6	143.5				[35]
		4-21G	144.4	142.0	142.0	144.4	114.0	105.9	114.0	[37]
		CNDO/2		137.8	137.8			104.6		[9]
		PCILO	138.4	138.4	138.4	138.4	105.8	105.8	105.8	[51]
		MNDO	140.3	140.0	140.0	140.3	119.3	103.1	119.3	[51]

a) Average values from X-ray structures of methylpyranosides.

the experiment. On the other hand, bond angles are better described by *ab initio* methods. The results of semiempirical methods considerably deviate from experiment in the case of COC angle. MNDO method provides for this angle about 10° larger and PCILO method about 8° smaller value in comparison with experiment. Similar trends as described in DMM are visible in Table 5 also for the remaining substituted dimethyl ethers.

The presence of two electronegative atoms with lone electron pairs on one centre is reflected also in the electron distribution in molecule. The change of lone pairs orientation with conformation affects the electron delocalization and thus, the conformer electron distribution will differ. It follows from MNDO and CNDO/2 calculations of substituted dimethyl ethers that the largest net charge difference occurs at the central carbon atom and its substituents, *i.e.* on the atoms where delocalization interactions take place. One can clearly see the enhancement of negative charge on the Y and O atoms at conversion of *ap* to *sc* conformation. Even striking net charges variation can be found in hydrogen atoms of central methylene group since their orientation to lone pairs substantially changes with conformation.

Bond-length shortening or elongation in dependence on torsional angle, *i.e.* strengthening or weakening of bond is reflected, except of charge distribution, also in different reactivity of conformers. From experiment, such differences are well known for example in the cleavage of the C—O bond in acetals or related tetrahedral intermediates formed by addition on carbonyl group. *Lehn et al.* [58] have concluded from *ab initio* calculations for methanediol and related hydroxymethanes that lone pairs on the oxygen atom O_4 with *ap* position to the another oxygen atom O_2 shorten (strengthen) C_3—O_4 bond and at the same time elongate C_3—O_2 bond. Similarly, the position of lone pairs is related to the C—H bond lengths of the central methylene group. They assumed sp^3 hybridization on the oxygen atoms with two equivalent lone pairs. This type of stereoelectronic behaviour has been explored in detail by *Deslongschamps* [59] who formulated simple rules from a large number of experimental data on reactivity of molecules with heteroatoms bonded to tetrahedral centre. In some cases bond length variation with conformation can be directly correlated with the kinetic parameters. Thus, elongation of exocyclic C—O bonds by 1 pm at spontaneous hydrolysis of cyclic aryl acetals is equivalent to about 12 kJ mol^{-1} decrease of activation energy of hydrolysis [60]. It should be stressed, however, that such structure—activity correlations rely on reactivity data from the experiment. Although quantum chemical methods provide generally reliable picture of stereoelectronic properties of molecules in ground state, a similarly complete theoretical description of reaction path (*e.g.* for C—O bond hydrolysis) will require yet much effort.

c) The effect of solvent

In the foregoing section we have shown that the change of conformation in —R—X—T—Y— molecules is accompanied by the variation of geometry and electron distribution. These factors are evidenced as the changes of molecular volume (surface), dipole moment and other quantities relevant in the effect of solvent on the stereochemical properties. One can expect that the change of environment will be reflected in the relative abundance of conformers and in this way, in experimentally observable quantities representing the mean values for conformational equilibrium. However, the experimental data on stereochemical medium effect are rather scarce for simple acyclic —R—X—T—Y— molecules. Significant differences in conformer population have been observed for more complex molecules by NMR in various solvents. As already mentioned, more than 80 % of MTHP exists in *ax* form (*sc* conformation) in nonpolar solvent CCl_4 [18, 52]. The population of *ax* form in MTHP diminishes with the raising solvent polarity and attains in water 52 % only. Hence, the anomeric effect is reduced in polar medium.

One can proceed along several paths in the theoretical prediction of the solvent effect on conformation [61]. In the first way, a limited number of solvent molecules is included in the quantum chemical calculation and solute plus few solvent molecules are treated as a supermolecule. This approach is useful for the determination of specific solvation sites but in order to get overall solvation energy large number (hundreds) of solvent molecules should be present and their position varied. Such computations are extremely time-consuming and not feasible for the large molecules. In theories of solvent effect it is assumed mostly that the energy of solute in solvent E_{soln} is given as a sum of isolated molecule energy E_{is} and solvent term E_{solv}. The latter term encompasses the energy of cavity formation in solvent to accomodate the solute, E_{cav} and the energy of subsequent solute—solvent interactions, E_{int}. The *Sinanoglu*'s solvophobic theory [62] and scaled particle theory [63], based on the above assumptions proved to be the most successful procedures for estimation of solvent effect [12, 13, 66], mainly due to the elaborated parametrization.

In solvophobic theory the solute—solvent interaction energy is expressed by electrostatic and dispersion contributions and the final expression for E_{soln} is

$$E_{soln} = E_{is} + E_{cav} + E_{disp} + E_{elst} \qquad (5)$$

This relation was used in calculation of conformational medium effect in acetals [13]. Energy of isolated DMM was calculated by PCILO method. Electrostatic interaction of solute with the polarizable solvent E_{elst} was calculated by the reaction field theory according to *Abraham* [64] with the dipole and quadrupole contributions. The energy E_{elst} depended on the radius of spherical solute cavity, dipole and

quadrupole moments, and refraction index of solute and on relative permittivity (ε_r) of solvent. Dispersion term was estimated by *Sinanoglu* procedure [62] based on the determination of effective interaction potential of solute with solvent in the first solvation shell.

The calculation for DMM in CCl_4 has shown that the conformational hypersurface is very similar to that for the isolated molecule. Some small differences are noticeable; the energy difference between (*sc*, *sc*) and (*ap*, *sc*) conformations decreased from 4.96 to 2.75 kJ mol^{-1} and (*ap*, *ap*) conformation is degenerated to four symmetrical minima of the type (160°, 170°) in CCl_4. The conformational map of DMM is significantly amended in water as a solvent. The absolute minimum corresponds to the (*ap*, *ap*) conformation, slightly less stable are (*sc*, *sc*) conformations and the third in stability order are (*sc*, *ap*) conformations.

The analysis of individual terms of solvation energy reveals that their absolute values decrease in the order: E_{disp}, E_{cav}, E_{elst}. The conformational variation of these terms is of larger importance and it should be pointed out that the relatively reliable computation of E_{elst} term is combined in this procedure with the less satisfactory treatment of the remaining terms. Torsional dependences of E_{disp} and E_{cav} have an opposite character in DMM and they partially compensate. It is not clear, however, whether the latter terms can be neglected also in related molecules and solvent effect expressed by electrostatic contribution only. The reliability of estimation of all terms in E_{solv} critically depends on the evaluation of molecular volume of solute (cavity) and its change with conformation. The precise calculation of this quantity is one of the limiting factors of successful prediction of medium effect on conformational equilibrium.

The representation of molecule as a geometrical body formed by mutually interlocking spheres with the centres on atoms and van der Waals radii seems to be at present the most promising approach for calculation of conformational dependence of molecular volume and surface. Van der Waals surface S_w and volume V_w of conformers calculated in this way may differ by several percent as was demonstrated for n-alkanes and their chloro derivatives [65]. On the other hand, the same approach applied to DMM and related molecules with O—T—O segment [15] resulted only in small differences in van der Waals surface of conformers on the map $S_w(\varphi_1, \varphi_2)$. Unimportant differences in surface of conformers have been obtained also in calculations where the contribution of lone pairs on oxygens to S_w has been taken into account. This finding supports the presumption of insignificant role of the terms E_{disp} and E_{cav} in conformational solvation energy of acyclic acetals and related molecules.

The reduction of the anomeric effect with the raising polarity of environment and the dominance of electrostatic term in conformational solvation energy of acetals are confirmed by the dielectric measurements of DMM in gaseous and liquid phase combined with CNDO/2 calculation [53]. It was found that the Gibbs energy

difference of (*ap*, *ap*) and (*ap*, *sc*) conformations with respect to (*sc*, *sc*) gradually diminished for DMM in the succession: gaseous phase, solution of DMM and heptane (volume ratio = 1 : 1), neat liquid DMM (Table 4). Experimental ΔG values have been in very good agreement with the solvation energies estimated from the dipole (Onsager) contribution to E_{elst}.

Among the methods considering the electrostatic solute—solvent interactions only, one can place also two simple quantum chemical approaches [67, 68]. In the first one [67], the solvation energy is calculated from net charges of the isolated molecule using the Coulomb law. In *Germer* method [68], the interaction of point charges of solute with the induced charges in solvent is included into Hamiltonian. Solvent properties are described in both methods by means of the function of ε_r and solvent incorporation leads to the solute stabilization. In contrast to the empirical rule on the enhanced stabilization of conformers with larger dipole moment, the influence of solvation calculated for DMM [56] by both methods is just opposite. Hence, the latter methods fail even at the qualitative prediction of the conformational solvent effect in acetals. The deeper analysis has shown that both methods lead to the formally identical expression for solvation electrostatic energy in CNDO/2 approximation in which they are usually employed. The neglection of lone pairs contribution in calculation of E_{elst} can be identified as the reason of their failure in prediction of conformational solvation trends in acetals. The total dipole moment is in MO methods given as a sum of the net charges contribution μ_q and summation of hybridization dipole moments

$$\mu = \mu_q + \Sigma\, \mu_h \tag{6}$$

Dipole moments μ_h account for the anisotropy of electron distribution on atoms and are particularly large for heteroatoms with lone pairs. Both mentioned methods take into account only the net charge distribution and μ_q contribution in calculation of the E_{elst} term. Yet for example in DMM, sum of μ_h moments of two oxygen lone pairs is about 9.3×10^{-30} Cm, *i.e.* lone pairs in principle determine the total moment μ of DMM which is about 10.9×10^{-30} Cm for (*ap*, *ap*) conformation in CNDO/2 approximation. The hybridization terms determine the torsional function of total moment μ also in other substituted ethers [10]. One can conclude that the application of above methods [67, 68] for the treatment of conformational solvent effect is not appropriate for molecules where distinct changes in orientation of lone pairs occur.

Summing up, our studies of solvent effect on conformational stability of acetals have proved that the preference of *sc* conformation over *ap* depends not only on intramolecular force field but also on environment. The magnitude of the anomeric effect is a result of the mutual interplay of intra- and intermolecular interactions. Similar conclusion should be valid quite generally for all the substituted ethers although the solvent effect calculations have not yet been performed, apart from

the treatment of substituted 1,3 dioxan [69] with *Abraham* theory [64]. The conformational variation of solvation energy in $CH_3—O—CH_2—Y$ can be approximately estimated from the dipole part of E_{elst} term. The total dipole moment is determined in this type of molecules by mutual orientation of dipoles of substituents linked to the central methylene group. At rotation about $O—CH_2$ bond in halogen derivatives, the total dipole moment is largest in *ap* conformation with almost parallel orientation of dipoles of both substituents. It is of interest that in isolated molecules the order of stability of conformers of derivatives with Y = Cl, F, OH, OCH_3, and SCH_3 is opposite to the ordering of conformations according to their dipole moments. Evidently, it brings about the change of conformer population in solution since in polar medium the most stabilized positions are those with maximum dipole moment, *i.e.* those ones with the lowest stability in isolated state.

IV. The anomeric effect in related molecules with 1,3 heterosegment

By substitution of oxygen atom in segment $ROCH_2Y$ one obtains sulfur or nitrogen analogues of dimethyl ether and methanol derivatives, *i.e.* substituted methylthiols, dimethyl sulfides, and methylamines. Similarly, the replacement of central methylene group by another tetrahedral group as PO_2^-, SO_2, $Si(CH_3)_2$, *etc.* provides the additional types of molecules with 1,3 heterosegment. In contrast to $ROCH_2Y$ segment, stereochemistry of the above type of molecules (apart from phosphates) has been far less theoretically investigated. Hitherto accumulated information, although far from completeness, indicates the conformational behaviour characteristic of the anomeric effect also in the above-mentioned groups of molecules. Molecular conformations are also in this case determined mainly by the angles φ_1 and φ_2 for the rotation around single bonds on the anomeric centre.

It should be noted that situation is much more difficult in quantum chemical calculations of these molecules than that with acetals, from methodological point of view. A presence of multielectron "heavy" atoms of the type S, P, Si opens the question of incorporation of *d* orbitals into the basis set, the convergence of SCF procedure is not always secured, computational time considerably increases, *etc.* These and other factors cause that, in general, much worse agreement of the anomeric effect characteristics is obtained when comparing the results of two different methods or calculated and experimental data.

a) Monosubstituted methylthiols and dimethyl sulfides

The replacement of the atoms of oxygen by sulfur in hemiacetals or acetals brings about the significant changes in chemical and biochemical properties of these molecules. The difference in behaviour of oxygen and sulfur analogues is often

ascribed to the change of conformational properties ensuing from the alternation of electron distribution, bond angles and bond lengths, accompanying oxygen—sulfur replacement. It is assumed at the same time that the anomeric effect for —SR group is smaller than that for —OR group, judging from NMR measurement of the *ax—eq* equilibrium in series of 2-substituted thians [70, 71] and 1-thio-D-aldopentapyranose tetraacetals [72]. Monosubstituted methylthiols and dimethyl sulfides are used in theoretical studies as model compounds.

The first nonempirical calculations treated $HSCH_2Cl$ and $HSCH_2F$ [34]. STO-3G energy differences *sc—ap*, 11.1 and 11.0 kJ mol^{-1} for the above molecules, respectively, are smaller than in oxygen analogues (Table 2). Geometrical changes accompanying the transition from *sc* to *ap* display the same trend as in oxygen molecules, for example, optimized C—S bonds are longer and C—F and C—Cl bonds shorter in *sc* conformation in comparison with *ap* conformation.

The largest attention in computations was paid to the sulfur analogues of methanediol, methoxymethanol, and DMM formed by the replacement of one or two oxygen atoms, *i.e.* $HOCH_2SH$, $CH_3OCH_2SCH_3$, $CH_2(SH)_2$, $CH_2(SCH_3)_2$ and CH_3SCH_2SH. Again, a presence of two rotors on methylene group results in "double" manifestation of the anomeric effect. Experimental studies for these molecules [73—76] give the (*sc*, *sc*) conformation as the most stable in solid state. The latter conformation dominates also in liquid state, where the additional conformations (*sc*, *ap*), (*ap*, *sc*), and (*ap*, *ap*) are present, too. These findings suggest that stabilization of *sc* position with respect to *ap* is reduced at rotation around C—S bond in comparison with C—O bond. This view is supported by the dipole moment and Kerr constant measurements of dithioacetals by *Exner et al.* [77, 78] who have observed the (*sc*, *ap*) conformation as the most stable one for some derivatives in CCl_4 solution. No data on the conformational energy differences in the above molecules are available from experiment and theoretical calculations provide the first estimation of relative stability of conformers.

The results of conformational calculations of sulfur derivatives with two rotors are summarized in Table 7. The relative energy of conformers appreciably depends on the calculation method. Relatively univocal trends are observed in thioacetals (O—C—S segment) where all methods predict the preference of (*sc*, *sc*) position with the smaller energy differences between conformers than in oxygen analogues. Apparently, incorporation of *d* orbitals into the basis set is not important in this case. A more contradictory picture is provided by calculations for molecules with dithioacetal segment —S—C—S—. Judging from one computation [79] STO-3G basis might appear to be inappropriate in this case. However, the conformational energy differences are abnormally large in that paper which makes the results questionable possibly due to the unsufficient convergence of SCF procedure. The methods with extended bases, as 4-31G and general basis with *d* orbitals, when applied to this segment failed to converge [79]. On the other hand, more

elaborated study of $CH_2(SH)_2$ has shown [39] that STO-3G basis does correctly predict the preference of (*sc*, *sc*) conformation even without inclusion of *d* orbitals. From semiempirical methods, MNDO and PCILO without *d* orbitals seem to be the most appropriate in this case (Table 7). Modified CNDO/2 method describes

Table 7

Relative conformational energies ΔE of simple thio- and dithioacetals calculated by quantum chemical methods

Molecule	Method	ΔE/(kJ mol^{-1})				Ref.
		(*sc*, *sc*)	(*sc*, *ap*)	(*ap*, *sc*)	(*ap*, *ap*)	
$HSCH_2SH$	STO-3G	325.6	104.8		0.0	[79]
	4-31G	0.0	2.4		10.5	[79]
	D[a]	2.1	0.0		5.8	[79]
	CNDO(*d*)	1.3	0.0		6.3	[79]
	STO-3G	0.0	0.8		4.1	[39]
	STO-3G[b]	0.0	4.3		9.2	[39]
	STO-3G[c]	0.0	0.5		3.5	[39]
	4-31G	0.0	9.0		19.0	[39]
CH_3SCH_2SH	STO-3G	632.7	434.0	102.7	0.0	[79]
	4-31G	*n*	*n*	*n*	*n*	[79]
	D[a]	20.2	0.0	*n*	*n*	[79]
	MCNDO(*d*)	0.8	0.0	83.5	4.8	[80]
	MCNDO	12.8	4.1	6.0	0.0	[80]
	CNDO(*d*)	3.7	0.0	9.2	15.0	[79]
$CH_3SCH_2SCH_3$	STO-3G	0.0	4.2		7.4	[39]
	MCNDO(*d*)	0.0	78.3		147.4	[80]
	MCNDO	11.7	4.4		0.0	[80]
	PCILO	3.41	0.0		0.41	[17]
	MNDO[b]	0.0	5.0		11.1	[17, 81]
	MNDO($CHCl_3$)[d]	0.0	3.8		9.2	[17]
	MNDO(DMSO)	0.0	3.2		8.1	[17]
	MNDO(H_2O)	0.0	0.1		2.8	[17]
$HOCH_2SH$	STO-3G	0.0	2.8	9.8	14.1	[39]
	STO-3G[b]	0.0	4.9	11.8	16.6	[39]
	STO-3G[c]	0.0	2.0	9.8	13.9	[39]
$CH_3OCH_2SCH_3$	PCILO	0.0	1.7	1.1	5.5	[16]
	MNDO[b]	0.0	9.6	7.2	17.5	[16]
	MNDO($CHCl_3$)[d]	0.0	9.0	6.7	16.5	[16]
	MNDO(DMSO)	0.0	8.3	6.1	15.5	[16]
	MNDO(H_2O)	0.0	5.4	3.7	11.1	[16]

a) General basis with *d* orbitals; *b*) full optimization of geometry; *c*) optimization of bond lengths; *d*) calculations including the effect of solvent; *n* — calculations did not converge.

qualitatively correctly the conformer stability [80], but the energetical differences seem to be unrealistically large.

Detailed conformational energy maps are available for two methanediol analogues from STO-3G calculations [39] and for two DMM analogues from PCILO and MNDO calculations [16, 17]. The results resemble those for the parent oxygen molecules with reduced dependence on the choice of input geometry and diminished conformational energy differences. SCS and OCS bond angles are the conformationally most sensitive geometry parameters. In $CH_2(SCH_3)_2$ the former angle is 105.5° and 115.9° in (*ap*, *ap*) and (*sc*, *sc*) conformations and in similar conformations of $CH_3OCH_2SCH_3$ the latter angle is 105.9° and 114.5°. In contrast to DMM the minimum of C—S bond torsional angle is shifted to about 70° [16, 17].

We have investigated the effect of environment for both thio analogues of DMM according to eqn (*5*) by means of procedure described in [66] in combination with MNDO energy of isolated molecule. Similarly as in DMM, the effect of solvent manifests itself by the stabilization of *ap* positions. Relative conformational energies in $CHCl_3$, DMSO and water are given in Table 7. The largest influence was found for $CH_2(SCH_3)_2$ where 78 % representation of (*sc*, *sc*) conformation in isolated state is reduced to 31 % in water. At the same time, the abundance of (*ap*, *sc*) conformation increases from 21 % to 59 %. Analysis of the solvation terms in eqn (*5*) has revealed that the electrostatic solute—solvent interaction term is mostly affected by the change of conformation, again, mainly due to the torsional dependence of the dipole moment.

All results confirm the presumption of lower preference of *sc* position to *ap* at rotation around C—S bond in comparison with C—O bond. It is documented by the estimation of the anomeric energy effect of C—S bond which is about 3.7—7.2 kJ mol^{-1} for O—C—S segment and 0.1—5.0 kJ mol^{-1} for S—C—S segment in dependence on solvent [16, 17].

b) Phosphates

Numbers of data exist on the energy and geometry manifestation of the anomeric effect in phosphates. It is connected with exceptional importance of biological phosphates, mainly as an interconnecting unit in nucleic acid macromolecule and as a polar head in phospholipides. Dimethyl phosphate anion $CH_3OPO_2OCH_3^-$ (DMP^-) with two "anomeric" torsional angles is mostly used in theoretical studies as a model of phosphate group. Tens of theoretical papers have been devoted to conformational equilibrium in isolated DMP^- and related simple phosphates, to their interaction with water molecules and cations and to the estimation of the full solvation energy. The results are in many respects similar to those for DMM and some representative example are summarized in Table 8. Computations show the

Table 8

Comparison of relative conformational energy ΔE in DMP^- calculated by various quantum chemical methods

Method	ΔE/(kJ mol^{-1})			Ref.
	(*sc*, *sc*)	(*sc*, *ap*)	(*ap*, *ap*)	
STO-3G	0.0	13.8	30.1	[83]
STO-3G	0.0	14.2	33.5	[84]
STO-3G	0.0	10.2	27.5	[88]
STO-3G[a]	0.0	0.6	3.7	[88]
STO-3G	0.0	7.5	23.3	[87]
STO-3G[b]	0.0	11.4	37.9	[87]
CNDO/2	0.0	11.3	14.2	[82]

a) Gradual optimization of geometry parameters; *b*) including *d* orbitals on phosphorus atom.

dominance of (*sc*, *sc*) conformation with (*ap*, *ap*) conformation being an unfavourable minimum or even maximum on hypersurface. In contrast to DMM, the most of computations confirm the presence of (sc^+, sc^-) conformations with the same orientation of methyl groups with respect to O_e—P—O_e plane (O_e — ester oxygen). Their relative energy depends considerably on the assumed geometry.

It is seen from Table 8 that CNDO/2, PCILO [85] and nonempirical calculations with the minimal basis give comparable picture of the conformational energetics in DMP^-. As already mentioned, some disharmony in the results is associated with the question of neglect of *d* orbitals on the phosphorus atom, although it is claimed that inclusion of *d* orbitals modifies the DMP^- conformational energies only little [86]. For example, the CNDO/2 energy decrease on going from (*ap*, *ap*) conformation to (*ap*, *sc*) is 13.5 and 11.8 kJ mol^{-1} with and without *d* orbitals [14], respectively. In nonempirical calculations it seems [87] that the relative energy results deteriorate by the extension of minimal basis at first, accompanied by the unrealistically large net charges on the phosphorus and oxygen atoms. In rather extended bases the results have improved but the problems with energy convergence occurred. Therefore, STO-3G basis with *d* orbitals on P has been recommended [87] as the most appropriate basis for DMP^-.

The choice of geometry parameters has the most pronounced influence on the magnitude of the anomeric effect. Phosphate segment has proved to be much more flexible than the acetal segment, displaying considerable changes of internal geometry (mainly O—P—O angles) at internal rotation. Accordingly, the optimization of almost all geometry parameters is apparently inavoidable in calculations of DMP^- and other phosphates. The pronounced reduction of the anomeric effect

in calculations with the optimized geometry is evident from the papers of *Gorenstein et al.* [48, 82, 88]. The striking conformational changes of bond lengths and bond angles obviously project into phosphate reactivity and form the basis for the rationalization of stereoelectronic effects in phosphate hydrolysis [82, 89].

Crystallographic data for phosphates fully confirm the characteristics of the anomeric effect derived from calculations, *i.e.* preference of (*sc*, *sc*) conformation and mutual coupling of bond lengths and bond angles with torsional angles [82, 83, 85]. For example, from 51 phosphate structures in Cambridge Crystallographic Data Bank, 45 correspond to (*sc*, *sc*) conformations, 6 to (*sc*, *ap*) and neither of them to (*ap*, *ap*) conformation [90].

The inherent anomeric effect in phosphates can be considerably influenced by counterions and intermolecular (solvent) interactions. Theoretical estimation of the role of these factors in the anomeric effect is still far less reliable than isolated molecule calculations. The computations for some cations indicate [91] that their presence perturbs only slightly DMP^- relative energies. Much effort was oriented to the description of solvation (hydration) of phosphates but the results depend to large extent on the method used. The "supermolecular" approach resulted in specification of hydration sites of DMP^- by few (maximum six) water molecules. Full hydration of DMP^- by the first solvation shell leads to the partial suppression of the preference of (*sc*, *sc*) conformation in comparison with isolated molecule [92]. On the other hand, continuum model of solution predicts an additional stability energy increase of (*sc*, *sc*) conformation, by about 4 kJ mol^{-1} [92].

The effect of dissociation on hydration energy of phosphates has been investigated in paper [12]. We have there compared the solvation energy calculated by eqn (*5*) for DMP^-, its neutral form DMPH and tight ion pair DMP^-H^+. A pronounced dependence of solvation energy on conformation has been found with contradictory trends in individual terms of eqn (*5*), different for each of the three molecules. Later, the more reliable calculations by the model of interlocking spheres have shown [15] that conformational variation of the intrinsic volume of DMP^- is considerably less pronounced than assumed in [12] and thus, the terms E_{cav} and E_{disp} should be of small importance only. Apparently, in phosphates, similarly as in acetals, the crucial contribution to the solvation energy is electrostatic interaction of solute with environment. The latter interaction stabilizes (*sc*, *sc*) and (*sc*, *ap*) conformations in DMP^- and DMPH and (*ap*, *ap*) conformation in DMP^-H^+.

Besides DMP^-, the anomeric effect was theoretically investigated also in some other simple molecules as trimethyl phosphate [82], ethyl methyl phosphate anion [93], $H_2PO_4^-$, HPO_4^{2-} [94] with the similar conclusions as in DMP^-. Extensive quantum chemical calculations have been performed also for the more complex phosphates, especially nucleic acid oligomers, for example in Ref. [95, 96]. However, it is very difficult to separate the energy value of the anomeric effect from these calculations since the resulting conformational equilibrium in phosphate

segment is determined there also by the additional factors as furanose ring interactions, stacking interactions of vicinal purine and pyrimidine bases, *etc.*

c) Miscellaneous molecules

Apart from thioacetals and phosphates, for the remaining molecules with 1,3 heterosegment exists just fragmentary information on the anomeric effect from MO calculations. Rather unexpected behaviour was found for the analogues of methanediol and DMM with fluoromethylene group, $CF_2(OH)_2$ and $CF_2(OCH_3)_2$ [97]. In the first molecule nonempirical calculations give (*ap*, *sp*) conformation of the type (180°, 0°) as the most stable followed by (*sc*, *sc*) and (*ap*, *ap*) conformations. In the second molecule the stability increases in the order (*ap*, *sc*), (*ap*, *ap*), (*sc*, *sc*) from nonoptimized geometry calculations and (*ap*, *ap*), (*ap*, *sc*), (*sc*, *sc*) by optimization of bond angles.

The anomeric effect is present also in molecules where silicon atom is introduced into the anomeric centre. This has been confirmed by the nonempirical calculations of the simplest hydroxysilanes [98]. In silanediol $SiH_2(OH)_2$, similarly as in methanediol, (*sc*, *sc*) conformation was found as the most stable, by relative energy difference of 2.8 kJ mol^{-1} over (*sc*, *ap*) conformation. We have investigated [56] the conformational properties of dimethyldimethoxysilane (DDMS) $Si(CH_3)_2(OCH_3)_2$ by CNDO/2 and PCILO methods without inclusion of *d* orbitals and assuming the fixed bond lengths and bond angles. Again, (*sc*, *sc*) conformation proved to be the most stable, by relative energy difference of 2.2 kJ mol^{-1} over (sc^+, sc^-) and in contrast to DMM, (*ap*, *ap*) conformation represents a local maximum with the relative energy 15.9 kJ mol^{-1}. Calculated dipole moment of (*sc*, *sc*) conformation is in a very good agreement with the experimental value for DDMS in solution [99, 100]. Furthermore, the effect of solvent has been calculated according to eqn (*5*) with the parameters summarized in Ref. [66]. It has turned out that (*sc*, *sc*) and (sc^+, sc^-) conformations are almost equienergetical in nonpolar solvents. The preference of the latter conformation, with larger dipole moment, rapidly increases with the raising solvent polarity. The term E_{elst} again dominates in the overall solvent effect whereas the remaining two terms are negligible due to minimum conformational dependence of the inherent volume of DDMS [15]. The same method has been used also for dimethyldisiloxane $Si(CH_3)_2(OSiH_3)_2$ [56]. The calculations have shown the existence of deep minimum at the energy surface nearby (*sp*, *sp*) conformation within the range of torsional angles ±30°. The preference of eclipsed *sp* position is apparently facilitated by the large SiOSi bond angle and practically does not change with solvent.

Theoretical calculations of the anomeric effect in sulfates are restricted so far to the simplest model, sulfuric acid $SO_2(OH)_2$. Nonempirical 4-31G calculation

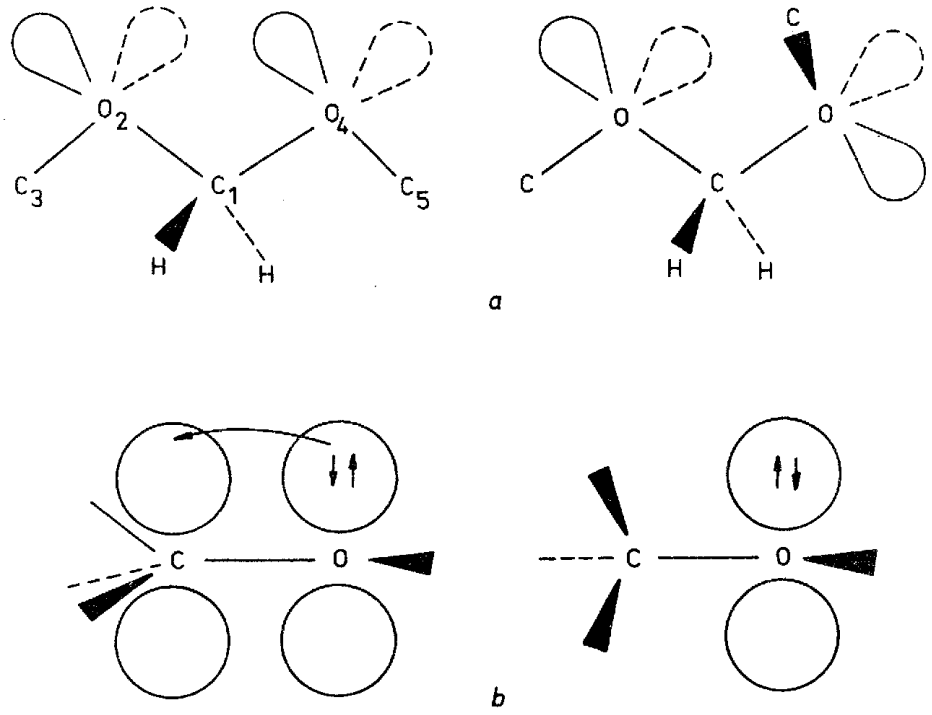
favours (*sc*, *sc*) conformation, in agreement with experiment, by relative energy difference of 11.5 kJ mol^{-1} over (sc^+, sc^-) position [101]. Situation can be slightly different in more complex sulfate $SO_2(OCH_3)_2$ since experiment [102] indicates population of (*sc*, *sc*) and (*ap*, *ap*) conformations in the ratio 2:1. Distorted conformation (*sc*, *sc*) with $\varphi_1 = \varphi_2 = 90°$ should be the most stable structure of aminosulfonic acid NH_2SO_2OH [38]. STO-3G and 4-31G calculations predict also an additional minimum (*sc*, *ap*) with relative energy being dependent on the input geometry.

One can reasonably expect the appearance of the anomeric effect also in other molecules, with the more "exotic" atoms either in tetrahedral centre (Ge, Sn) or as heteroatoms (for example, in selenoacetals, —$SeCH_2Se$—). Furthermore, in analogy with siloxanes and sulfates one can place here also silicates $Si(OR)_4$, borates $B(OR)_4^-$ and many other compounds with tetrahedral centre containing at least two heteroatoms. There are already some experimental indications of the anomeric effect in the above compounds, but its theoretical description here is still a matter of future.

V. Interpretation of the anomeric effect

After arising and formulation of the anomeric effect, two concepts have evolved for its rationalization, namely the "rabbit ears" effect and the "delocalization" interpretation. Both the concepts have developed first of all for O—C—Y segment, therefore the following discussion concentrates mainly on molecules of this type. Conclusion should be valid for all R—X—T—Y segments though situation can be there sometimes more complicated especially when *d* orbitals on T, or X, Y groups should be taken into account. Both the concepts provide a simple qualitative picture of the changes of intramolecular electron interactions at internal rotation. Scheme 3 shows these two interpretations for the acetal segment which played a dominant role at elucidation of the nature of anomeric effect.

In "rabbit ears" effect [103—105], classical electrostatic interaction is assumed between lone electron pair dipoles on the oxygen atoms in sp^3 hybridization. The relative energy value about 4 kJ mol^{-1} is assigned to each eclipsed interaction of lone pairs. The less of "parallel" positions of lone pairs is in conformation the more stable it is. Two repulsive interactions are present in (*ap*, *ap*) conformation of DMM, one in (*ap*, *sc*) and none in (*sc*, *sc*) position (Scheme 3*a*). The dipole of lone pair effectively involves also the dipole of C—O bond or of similar polar bond in related molecules. The largest support for this interpretation comes from frequently observed reduction of the anomeric effect by the raise of solvent polarity. However, this concept is unable to rationalize the conformational variation of bonding parameters on the anomeric centre.



Scheme 3

According to the second, perhaps more popular concept [106—108] stabilization of the *sc* conformation is associated with the delocalization of dominant lone pair of the oxygen atom to suitably oriented σ^* antibonding orbital of the adjacent C—O bond (Scheme 3*b*). The delocalization is minimal at the orthogonal position of both orbitals. In this reasoning, the different character of two lone pairs on the oxygen atom is assumed in accordance with MO results. The first, unhybridized *lp*(*p*) lone pair is of the π type and is oriented perpendicularly to COC plane. The second, *lp*(*sp*) pair, with lower energy, is oriented in harmony with sp^2 hybridization in COC plane.

Both the above concepts based on the directionally oriented lone pairs have been criticized from various standpoints [28, 109] and some other explanations have been suggested. The anomeric effect was regarded as a consequence of fine equilibrium between electron—electron repulsion and nucleus—electron attraction [28], of barrier of internal rotation around the C—X bond [109] or of the Jahn—Teller effect [110]. Neither of these proposals elucidated all the complexities of the anomeric effect and they did not gain wider support. The two leading concepts, rabbit ears effect and delocalization interaction have been gradually advanced by means of quantum chemical calculations. Only simple molecules have been treated due to practical limitations on the size of molecules in MO calculations and the results have been generalized for more complex molecules. "Explanations" of MO results by the terms usual in physical organic chemistry is the prevailing trend in this area of applied quantum chemistry.

Various overlap populations serve as indicators of electron density shift in MO methods. Their variation at internal rotation provides quantitative data for delocalization concept of the anomeric effect. *Pople* [111] has proceeded in this way at the interpretation of 4-31G calculations for methanol, fluoromethanol, and methanediol. Stabilization by back donation of electron density between $lp(p)$ lone pair on oxygen atom perpendicular to COH plane and polar C—X bond is maximal in orthogonal position with $\varphi = 90°$ (Scheme 3). Extent of back donation is illustrated by π-orbital population of lone pair on the oxygen atom. Even in CH_3OH, lone pair of the π type is subjected to back donation to antibonding orbital of proper symmetry at the methyl group resulting in the decrease of population from 2.00 *e* (in water) to 1.97 *e*. A comparable electron displacement occurs in fluoromethanol when the C—F bond is in nodal plane of oxygen π lone pair. However, if FCO and COH planes were perpendicular, the displacement of π-electrons to fluor caused a higher vacancy on the carbon atom. That increases the back donation, reduces the π-orbital population to 1.94 *e* and brings about the additional stabilization. The back donation of 0.05 *e* was calculated [111] for methanediol in (*sc*, *sc*) conformation. Besides the decrease of total energy ensuing from the stabilizing σ^*—$lp(p)$ orbital interaction, the shortening of T—O bond (increase of double bond character), the elongation of Y—T bond (increase of σ^*-antibonding orbital population), and opening of Y—T—O angle should occur according to the delocalization concept. These conclusions based on the simple perturbation theory enable to rationalize the conformational changes of bonding parameters as given by the X-ray data [31, 48, 112] and differences in NQR frequency in chloro derivatives with ROCHClR′ moiety [106, 113].

Delocalization concept has been further advanced by stressing the necessity to analyze the orbital interactions of both lone pairs on oxygen atom [114]. Even though the second lone pair has much larger *s* character and is more strongly bonded its interactions cannot be neglected. Hence, the anomeric effect is determined by the final equilibrium between the interactions of two lone pairs on the one hand and a couple of vacant antibonding orbitals of proper symmetry on the anomeric centre, e.g. σ^*_{CX} and $\sigma^*_{CH_2}$, on the other hand. The incorporation of two lone pairs differing in energy, into analysis of the nature of the anomeric effect was a step of considerable importance, nevertheless, the qualitative reasoning still prevailed without actual calculation of orbital interactions.

Fourier expansion of torsional potential $E(\varphi)$, eqn (4), can be used to get an approximate idea about the delocalization contribution to the stabilization of some conformations. As mentioned earlier, anyhow is the expansion formal it helps in interpretation of stereochemical properties since distinct electronic effects determine individual expansion coefficients. Fourier decomposition of torsional potential enables to get a new insight into the nature of the anomeric effect [8].

Eqn (4) yields for the energy difference between ideal *ap* and *sc* conformations (180° and 60°)

$$E_{AE} = 0.75(V_1 - V_2) \tag{7}$$

Hence, the anomeric effect (positive value of E_{AE}) can appear at a suitable combination of V_1 and V_2 terms. Since the V_1 term is associated with the dipole—dipole interactions of polar groups and V_2 term with the electron back donation of lone pairs on heteroatoms one can conclude that the latter equation effectively describes also a balance of two sources of the anomeric effect: rabbit ears effect and delocalization interaction. Depending on the character of the anomeric centre T and especially of heteroatoms X, Y, one or another factor may prevail. The definitive appraisal can be obtained only by the independent calculation of V_1 and V_2 term for a given molecule.

A detailed perturbation calculation of delocalization interactions has been performed so far only for DMM [9]. Our starting point there has been a procedure developed by *Hoffmann* [115] distinguishing the orbital interactions through-space and through-bond. In DMM two lone pairs $lp(p)$ and $lp(sp)$ belong to each of two equivalent oxygen atoms, and would be degenerated in the absence of interactions. However, their energy differs due to mutual interaction and interaction with properly oriented π_z^* and π_x^* orbitals of the methylene group. Variation of the mentioned interactions with conformation has been calculated by perturbation theory using CNDO/2 results for dimethyl ether as unperturbed electronic characteristics at oxygen and CH_2 group. It has turned out that the delocalization stabilization energy is rather large, about 37 kJ mol^{-1}, but its conformational dependence is not pronounced. The shape of the latter function resembles the V_2 term of Fourier expansion (with the positive sign) with orthogonal position ($\varphi = 90°$) being about 2 kJ mol^{-1} less stable than synperiplanar *sp* position ($\varphi = 0°$). This situation arises as a consequence of opposite conformational functions of $lp(p)$ and $lp(sp)$ lone pairs interactions. This fact underlines the importance of simultaneous treatment of both lone pairs and documents the limitations of the simple analysis based on $lp(p)$ interactions only

Similarly, a minor conformational change has resulted for the interaction of lone pairs on oxygen with the σ^*-antibonding orbital on C—O bond [9]. This interaction leads to the slight stabilization of *sc* conformation with respect to *ap* yet by 1 kJ mol^{-1} only. Summing up, our analysis of orbital interactions in DMM has not confirmed the delocalization concept as a reason of the energetic manifestation of the anomeric effect. On the other hand, the results have shown that the electron transfer accompanying orbital interactions is actually in qualitative accord with the trends observed for geometry parameters close to the anomeric centre.

Besides geometry parameters, the role of orbital interactions in frontier molecular orbitals has been elucidated in Ref. [9], pertinent for the difference in reactivity

on the anomeric centre in monosaccharides [116]. Frontier MO's, *i.e.* the highest occupied MO (HOMO), the next highest occupied (NHOMO) and lowest unoccupied MO (LUMO) are formed in DMM primarily as a combination of lone pair orbitals. Accordingly, HOMO energy depends on the magnitude of lone pairs interaction. The calculation [9] has revealed that HOMO has considerably lower energy close to *sc* conformation, at $\varphi = 80°$, than in *ap* conformation where the interaction of lone pairs is maximal. Energy of the second highest MO, NHOMO exhibits only a small conformational dependence. Consequently, energy difference between HOMO and NHOMO should decrease in the order (*ap*, *ap*), (*ap*, *sc*), (*sc*, *sc*). Recent study of *trans*-1,8-dioxadecaline by photoelectron spectroscopy [81] has confirmed the correctness of DMM theoretical analysis. Acetal segment which is in (*ap*, *ap*) conformation in the above compound has two well resolved low ionization energies at 9.08 eV and 9.93 eV in the spectrum, corresponding to two combinations of lone pairs. The difference between the above potentials, 0.85 eV, is maximal hitherto observed in acetals and indicates a very strong interaction of lone pairs in (*ap*, *ap*) conformation of acetal segment.

Since the V_2 term appears to be small in DMM, the V_1 term has to be responsible according to eqn (7) for the energetic aspects of the anomeric effect. In fact, classical electrostatic calculations of the interactions between bond and lone pair dipoles, if correctly estimated [11] give about 12 kJ mol^{-1} for the conformational difference *ap*—*sp*, *i.e.* they bring about the significant destabilization of *ap* position with respect to *sc*. The electrostatic origin of the anomeric effect in DMM is supported also by V_1 and V_2 terms calculated from the decomposition of CNDO/2 torsional potential (Table 1). Electrostatic stabilization of *sc* conformation should be operative also in acetal segment in more complex cyclic or polymeric acetals.

Different conditions may exist in other, nonacetal segments. For example, it is very probable that in RCH_2—OCHR′—Cl moiety the delocalization effects cause not only a conformational variation of valence geometry but they are also the principal source of *gauche* stabilization. That is supported by Fourier expansion coefficients for chloromethyl ether with the dominance of V_2 term over V_1 (Table 1). Therefore, it is not surprising that this segment was in the focus of attention in those papers where the delocalization origin of the anomeric effect was advanced. On the other hand, a pronounced dependence of V_1 term on nitrogen lone pair orientation in NH_2CH_2OH [38] indicates a significant role of dipole interactions favouring in this case *ap* position. A comparison of V_i terms of remaining substituted ethers in Table 1 shows that the type of substituent chiefly determines which of fundamental sources, delocalization or electrostatic, is of primary importance in energetic aspects of the anomeric effect.

The simple interpretation of Fourier terms is often no more appropriate in R—X—T—Y heterosegments where the methylene group T is replaced by a group

of electronegative atoms. Electrostatic, delocalization and steric interactions cannot be easily separated since they contribude to each term of the Fourier expansion. Aminosulfonic acid NH_2SO_2OH is an example where despite of central group complexity the analysis enables to presume the preponderance of dipole interactions at rotation around S—OH bond, similarly as in aminomethanol. It ensues from the variation of V_1 term with the position of nitrogen lone pair, which is -1.4 kJ mol^{-1}, -42.1 kJ mol^{-1}, and -1.7 kJ mol^{-1} for *sp*, *ap*, and *sc* orientation of *lp*(N) with respect to S—OH bond [38]. Different conditions occur in phosphates where Fourier coefficients for P—O bond torsion in DMP^- [14] point to the more important role of delocalization V_2 term in stabilization of *sc* position than in acetals [14]. Delocalization character of the anomeric effect in phosphates is corroborated also by the mentioned large flexibility of phosphate segment observed by experiment [90] and by a considerable influence of input geometry on the calculated stability of DMP^- conformers. The Fourier series of torsional energy, eqn (*2*), in less symmetrical structures, for example even in XCH_2OCH_3 molecules with substituents $X = OCH_3$, OH, NH_2 oriented otherwise than in *sp* or *ap* conformations, have to be expanded by the additional terms. However, physical interpretation of the latter terms is much less obvious. In summary, although the energy decomposition is influenced by several factors, as the method used, character of X, Y, T atoms and groups, their orientation, and the geometry used, still the decomposition contributes to the qualitative discrimination of those interactions which are the principal reason of unusual torsional behaviour of the R—X—T—Y segment.

VI. The anomeric effect in complex molecules

Theoretical treatment of stereochemical properties of R—X—T—Y segment in small molecules provides a basis for understanding and prediction of the behaviour of more complex molecules with the above moiety. We have in mind above all cyclic derivatives with heteroatoms in ring and also in substituents, and polymeric derivatives formed by an alternation of T groups and heteroatoms. Nevertheless, one has to be aware of some structural differences in complex molecules when transferring the results from model compounds. For example, the substituents on the anomeric centre need not be identical, as in tetrahydropyran derivatives with $—CH(CH_2R)—$ as T group. Moreover, the conformational equilibrium in cyclic derivatives can deviate from those in acyclics due to the valence restrictions in ring. That makes necessary to distinguish between the conformational preference at rotation about the same bond (*e.g.* C—O bond) in ring or in substituent. One can speak about the (endo)anomeric and exoanomeric effect, respectively and their energy can be different. These specific factors of the anomeric effect in tetrahydro-

pyrans as compared to DMM are successfully reproduced by PCILO calculations, alone, or in combination with the effect of solvent [66, 117, 118].

A specific feature of polymeric analogues is the formation of helical structures due to the cooperative action of the anomeric effect in each monomer unit. For example, polymeric acetal poly(methylene oxide) $-(OCH_2)_n-$ crystallizes in helix formed by concerted rotation of all bonds in chain into *sc* position. Similar helices are observed in poly(methylene sulfide) $-(CH_2S)_n-$ and poly(methylene selenide) $-(CH_2Se)_n-$. Anomeric effect should be thus regarded as a new helix-making factor. Traditionally in this sense only two elements are emphasized in polymer chemistry, *viz.* bulkiness of substituents, for example in vinyl polymers, and hydrogen bond formation between neighbour groups in chain, as in α-helix in proteins. Stereoelectronic intramolecular factors responsible for the anomeric effect contribute undoubtedly also to the stabilization of double-helices in nucleic acids having *sc* conformations in phosphate internucleoside unit. In seemingly distant but structurally related area of inorganic chemistry the anomeric effect co-decides in the selection of preferred conformations of linear chain silicates and phosphates in crystalline state, in dependence on electronegativity and size of cation [119]. Quantum chemical calculations of the anomeric effect in polymers have been performed for poly(methylene oxide) only [120, 121]. Energetical and geometrical parameters calculated for chains with the perfect conformational order are in accord with the findings for low molecular acetals as DMM.

In theoretical calculations of preferred spatial structure of very complex molecules one is usually confined to the simpler empirical methods related to classical-mechanical concepts which can be termed as potential function methods (PFM). In the application of the latter methods definition of the anomeric effect according to eqn (2) is relevant, as a difference between the calculated and experimental values, without the possibility of its prediction for molecules where experimental data are not available. In principle, MO methods can provide the actual *ap*—*sc* energy difference, corresponding to the experimental value and identify the "missing" part of energy in empirical calculations. Due to the considerable computational simplicity in comparison with MO methods and transparency of underlying physical principles it is an ultimate goal to improve the PFM calculations in such a way they would be able to describe conformational energy completely, "without rest", and the anomeric effect based on eqn (2) would be zero.

There are several reasons why PFM calculations for molecules with several heteroatoms do not supply the results in agreement with experiment. Firstly, because experimental data usually correspond to solution and calculations do not include the effect of solvent at all or in oversimplified way only, for example by the choice of non-unit relative permittivity in the Coulomb law expression for intramolecular electrostatic interactions. We have shown [12, 13, 66] what a significant role can be played by the medium effect in conformational equilibrium

of polar molecules. Secondly, PFM calculations start usually from standard fixed values of bond lengths and bond angles. The deviation of the selected geometry parameters from the actual ones can be considerable in some molecules. Thirdly, potential function parameters in empirical calculations are not always of sufficient quality.

MO methods are indispensable in the removal of the latter two shortcomings of PFM calculations. Quantum chemical results for small molecules provide correct valence geometry and various input parameters, as inherent torsional barrier or atom net charges used in calculation of intramolecular electrostatic interactions. This function of MO methods is especially important for molecules with several heteroatoms because of lack of suitable experimental data to derive parameters to PFM schemes for the above molecules.

An additional problem typical for heteroatoms is, how to incorporate the lone pairs into calculation of intramolecular energy by PFM. For example, the anomeric effect E_{AE} defined in the sense of eqn (*2*) is about 2.5—4.6 kJ mol^{-1} in cyclic and polymeric acetals [21, 122]. In this case the deficiency of PFM calculations can be completely eliminated by the explicit inclusion of lone pair interactions [11, 123]. The magnitude and orientation of lone pair dipoles can be obtained from MO calculations for model compounds or from a simple expression [10] which relates orientation and magnitude of lone pair dipole moment to valence geometry (hybridization) on heteroatom. Proper localization of lone pairs and their interactions should be considered also in calculations of the mean square of end-to-end distances and dipole moment of the chain $\bar{r}_\circ^2$ and $\bar{\mu}_\circ^2$ in macromolecules with the anomeric effect [124, 125]. In opposite case, neglecting the lone pairs and following the customary approach with intrachain conformational energies as adjustable parameters, one can reach an agreement between experimental and computed data of $\bar{r}_\circ^2$ and $\bar{\mu}_\circ^2$ at such energy values which do not represent a real situation in the chain.

A successful description of conformational behaviour of 1,3 heteroatom moiety by MO methods is recently used in improvement of PFM calculations. One starts usually from the definition of the anomeric effect by eqn (*2*) with energies from quantum chemical calculations instead of experimental data. Conformational energy differences resulting from MO methods are then fitted by means of "standard" PFM supplemented with the additional simple potential functions. The latter functions are then regarded as an arbitrary representation of the anomeric effect. For example, the correct description of conformational energy in phosphate segment by PFM necessitates [126, 127] the inclusion of twofold potential analogous to V_2 term in eqn (*4*). A potential function expressed by three terms of Fourier expansion has been proposed for conformation of acetal segments in oligosaccharides [128]. It represents the difference between *ab initio* torsional

energy of C—O bond in DMM [35] and torsional dependence of nonbonded interactions. An application of the above approach of inclusion of the anomeric effect in PFM, although simple and sometimes successful, is hindered by several obstacles. The additional potential functions depend on the PFM variant and include mostly also the interactions which are not connected with the anomeric effect. Their transferability to another PFM scheme is thus questionable. The choice of reference acyclics for MO calculations is of no less significance since their conformational properties can be slightly different from those in complex compound treated by PFM. Some of the above problems we tried to avoid in derivation of potential function for the exoanomeric effect in glycosides [129]. We started from the definition of the exoanomeric effect in analogy with eqn (*1*). 2-Methoxytetrahydropyran has been compared with the reference molecule 2-ethyltetrahydropyran. The difference in torsional variation of PCILO energy of the above molecules represents the exoanomeric effect dependence. Potential functions derived in analogous way should be independent of PFM type and applicable as an additional term in various PFM schemes.

Very recently, the interactions of lone pairs have begun to be regarded in molecular mechanics, the most sophisticated empirical scheme [22, 130, 131]. In this way it became possible to describe correctly for example conformational equilibria in substituted tetrahydropyrans, 1,3 dioxans, and other complex acetals with E_{AE} term in eqn (*2*) being zero. Improving the PFM parametrization, the energetics of conformational equilibrium could be predicted perhaps also for the other 1,3 heterosegments. Characterization of the additional specific features of the anomeric effect, besides the energy, by PFM calculations is much less satisfactory and more difficult. Empirical schemes, including molecular mechanics, are based on the concept of an atom or group additivity of interactions which functions excellently only in hydrocarbons. The striking changes of electron distribution on the anomeric centre are difficult to incorporate into the additive schemes with reasonable number of input parameters. Apparently, the full description of stereoelectronic effects and of associated variation of valence geometry and reactivity of conformers will be a domain of MO methods also in the next future.

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