

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 синклиальной *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.

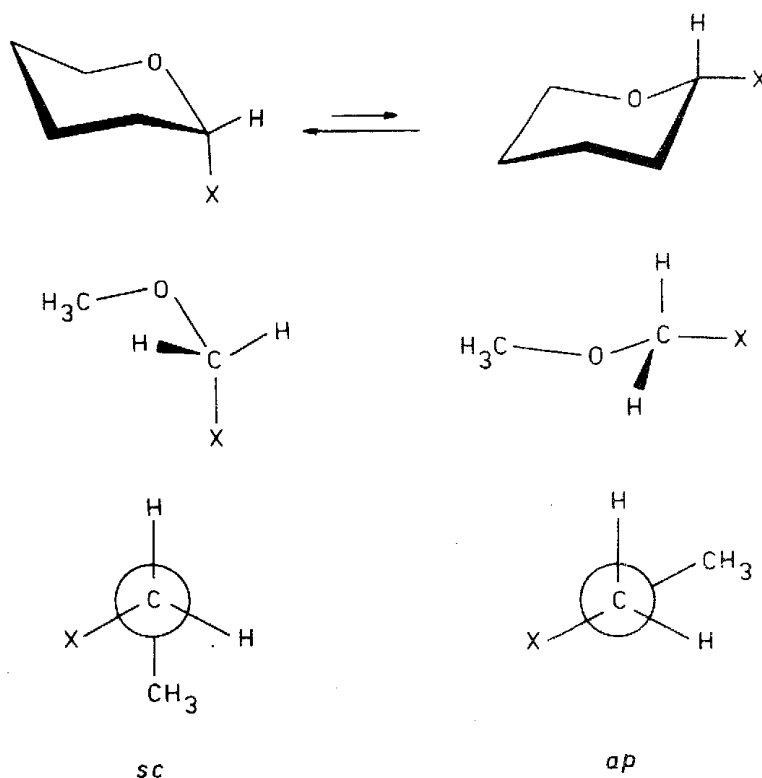
Of all conformational effects the anomeric effect originating in carbohydrate chemistry is paid the largest attention [2—6]. An additional stabilization of synclinal conformation with respect to antiperiplanar (unexpected from the classical point of view) is the most conspicuous manifestation of the 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 $\text{—CH}_2\text{—}$, $\text{—PO}_2^{2-}\text{—}$, $\text{—Si(CH}_3)_2\text{—}$, $\text{—SO}_2\text{—}$, 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 $\varphi_i = 180^\circ$ are denoted as *trans* or antiperiplanar (*ap*) and *gauche* or synclinal conformations lie near by $\varphi_i = 60^\circ$ 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° for *ax*—*eq* equilibrium in given molecule (tetrahydropyran derivative) and analogous value ΔG_{CX}° for similar derivative of cyclohexane [2]

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

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

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

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]

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

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 multifaceted 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 $\text{CH}_3\text{—O—CH}_2\text{—O—CH}_3$, 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 unavoidable 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 $\text{CH}_3\text{OCH}_2\text{Y}$, where Y is F, Cl, OCH_3 , SCH_3 , NH_2 , CH_3 , and NH_3^+ [8, 16, 51].

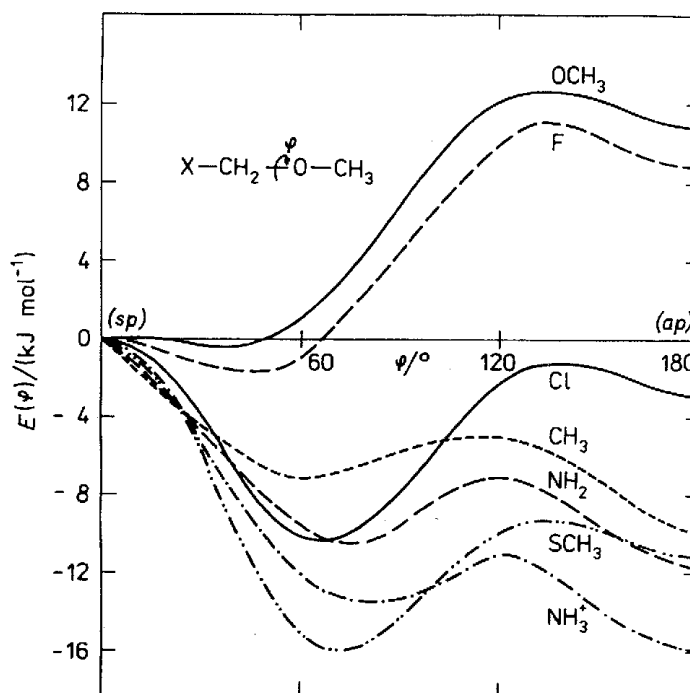


Fig. 1. Energy of rotation around C—O bond calculated by semiempirical quantum chemical methods for molecules $\text{X—CH}_2\text{—O—CH}_3$ where $\text{X} = \text{F, Cl, OCH}_3, \text{SCH}_3, \text{CH}_3, \text{NH}_2, \text{NH}_3^+$.

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 ($\text{Y} = \text{OCH}_3$) [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]

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

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 $Y = \text{CH}_3$ 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 $\text{CH}_3\text{—O—CH}_2\text{—Y}$ molecules [8, 16, 51]

Y	$V_1/(\text{kJ mol}^{-1})$	$V_2/(\text{kJ mol}^{-1})$	$V_3/(\text{kJ mol}^{-1})$	$\Delta E/(\text{kJ mol}^{-1})$
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—CH₂—Y, where Y is F, Cl, NH₂, OCH₃, 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 NH₂ 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 —NH₂ 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

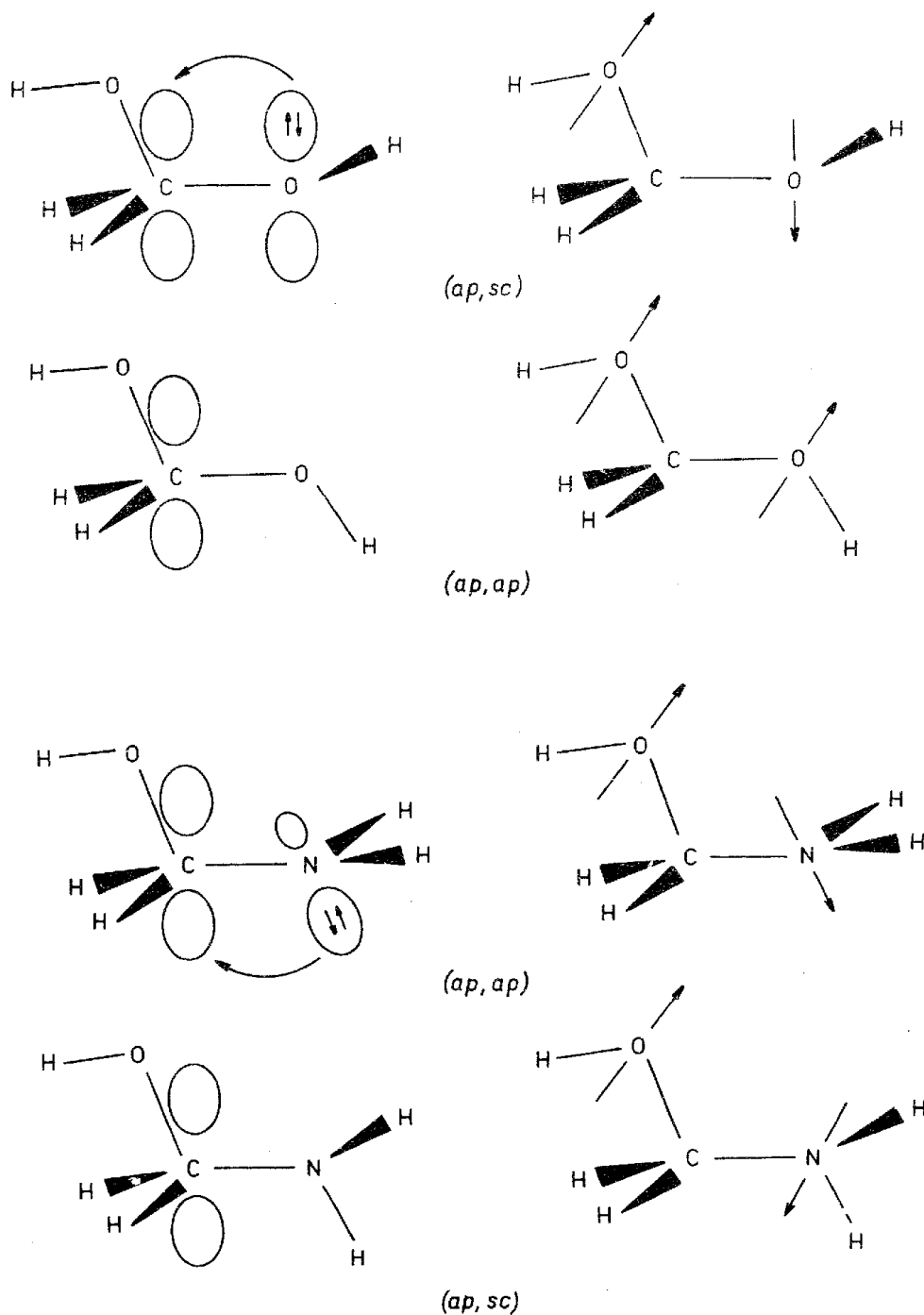
Influence of the basis size on the relative conformational energies ΔE in *ab initio* calculations of Y—CH₂—OH molecules

Basis	F		Cl		NH ₂		Ref.
	φ_1	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	φ_1	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	φ_1^d	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	
STO-3G	sc	0.0		0.0	ap	0.0	[34]
	ap	12.7		18.6	sc	0.60	
STO-3G	ap	13.1	[34]	20.1	ap	3.49	[38]
4-31G	ap	26.0	[36]	22.6	ap	4.9	
6-31G	ap	25.5	[36]	21.3	sc	6.0	
4-31G	ap	23.4	[30]		sc	19.8	
4-31G	ap	26.8	[33] ^b		ap	0.0	[37] ^a
4-21G	ap	14.9	[37] ^a		ap	4.7	
GTF ^c	ap	52.6	[28]		sc	5.7	
					sc	32.3	
					ap	0.0	[29]
					ap	6.2	
					sc	8.8	
					sc	30.4	
					ap	3.5	[38] ^b
					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	
4-31G	ap	ap	39.4	[32] ^b	STO-3G	sc	ap	9.4	[39]
	ap	sc	11.3			ap	ap	27.6	
	sc	ap	16.7			sc	ap	10.6	[39] ^b
					4-31G	ap	ap	26.9	
						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 $\varphi_p(\text{N})-\text{C}-\text{O}-\text{H}$.



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 fluoromethanol [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 $\text{CH}_3\text{—OCH}_2\text{—Y}$ with $\text{Y} = \text{F}$, 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 ($Y = \text{OCH}_3$), all other molecules have been studied at 4-31G level only.

Instability, a drawback of $\text{HO}-\text{CH}_2-\text{Y}$ 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 $\text{CH}_3\text{OCH}_2\text{Y}$, too. For Cl- and F-methyl ethers, *sc* conformation with φ_1 around $69-71^\circ$ has ensued as the most stable from microwave spectra [43]. From NMR measurement of Cl derivative [44] the values $6.3-8.4 \text{ kJ mol}^{-1}$ 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, $\varphi_1 = \varphi_2 = 66.3^\circ$. 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						OCH ₃			1-Methoxyethanol					
Basis	φ_1	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Cl	φ_1	φ_2	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.	Basis	φ_1	φ_2	$\frac{\Delta E}{\text{kJ mol}^{-1}}$	Ref.
4-31G	sc	0.0	[36]	0.0		sc	ap	0.0	[48]	4-31G	sc	sc	0.0	[50]
	ap	18.0	[36]	5.9		sc	sc	1.0			sc	ap	20.2	
	ap	18.8	[36] ^b	15.5		ap	ap	10.7			sc	sc	28.5	
	ap	21.4	[36] ^b	12.1		sc	sc	0.0	[48] ^b		ap	sc	10.2	
	ap	21.8	[36] ^b	17.6		sc	ap	6.6			ap	sc	14.2	
						ap	ap	13.9			ap	ap	38.9	
						sc	sc	0.0	[49] ^a	4-21G	sc	sc	0.0	[50] ^b
						sc	ap	19.0			sc	sc	0.0	
						sp	ap	22.2			ap	ap	9.3	
						ap	ap	43.2			ap	ap		
						sc	sc	0.0	[35]	4-31G	sc	sc		
						sc	ap	10.8			sc	ap		
						ap	ap	32.2			ap	ap		
						sp	ap	37.5			sp	ap		
						sc	-sc	70.3			sc	-sc		
						sc	ap	10.0	[35] ^b		sc	ap		
						ap	ap	31.1			ap	ap		
						sc	ap	13.3	[35] ^b		sc	ap		

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 $2\text{--}12 \text{ kJ mol}^{-1}$.

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 $2.2 \times 10^{-30} \text{ Cm}$ determined in gaseous state [46] but is close to $3.3 \times 10^{-30} \text{ Cm}$ 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_{AE}^1) than the second rotation from (*ap*, *sc*) to (*sc*, *sc*) (E_{AE}^{12} , shown in Table 4). The total anomeric effect in DMM, E_{AE} , is given by the sum of E_{AE}^1 and E_{AE}^{12} .

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 $E_{AE}^{1,2}$ of DMM conformers calculated by various semiempirical methods and observed by experiment

Method	$\Delta E / (\text{kJ mol}^{-1})$			$E_{AE}^{1,2} / (\text{kJ mol}^{-1})$	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 NH₂. 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	α /pm				φ /°			Ref.
				C—O	O—C	C—Y	C—O—C	O—C—Y	O—C—Y		
CH ₃	<i>ap</i>	<i>sc</i>	CNDO	138.2	137.0	146.6	106.0	116.7	[51]		
			MNDO	140.3	140.2	154.8	120.7	111.9	[51]		
	<i>ap</i>	<i>ap</i>	CNDO	138.1	137.1	146.7	107.7	110.4	[51]		
SCH ₃	<i>ap</i>	<i>sc</i>	MNDO	140.3	140.1	154.5	119.6	109.7	[51]		
	<i>ap</i>	<i>ap</i>	MNDO	139.2	140.5	175.0	120.1	110.4	[16]		
	<i>ap</i>	<i>ap</i>	MNDO	138.9	140.6	176.1	119.6	105.9	[16]		
	<i>sc</i>	<i>sc</i>	MNDO	138.5	140.7	176.2	121.4	114.5	[16]		

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

