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THE PROBLEM OF CONFORMATIONAL EFFECTS

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INTRODUCTION

After the pioneering work of Barton[1] conformational analysis became one of the most developed branches of theoretical chemistry. The notions, concepts, and ideas of conformational analysis are deeply rooted in organic chemistry and are widely used in the interpretation of various phenomena, reaction mechanisms, chemical transformations, etc. General adoption of conformational analysis has been to a considerable degree conditioned by the relative simplicity and universality of its basic postulates, especially on the qualitative level. The main tool is generally the conception of steric bulk or size. A simple accounting of steric repulsion permits us to predict correctly a large body of facts concerning the relative stabilities of conformers, their reactivities, the stereochemistry of products, etc. However, quite a large number of cases have now accumulated in the literature in which the stability of the conformations actually observed cannot be explained solely by steric factors. In most cases this is especially true for systems containing heteroatoms, electron pairs, or polar bonds. These cases are sometimes treated as special "conformational effects". To date many conformational effects have been proposed, all of which have had some kind of experimental "verification". Many of them have special names, e.g. "*gauche*"[2-5] "*rabbit-ears*",[6,7] "*hockey-sticks*",[8-12] "*anomeric*"[5,11,13-20] effects. Also some electronic effects, e.g. "*through bond* and *through space*,"[21-24] "*superjacent*",[14,25] "*bicycle*"[26] effects, have sometimes been involved in the explanation of some conformational phenomena.

Such development of conformational analysis has led to a paradoxical situation: the abundance of "effects" permits us to explain everything but to predict close to nothing! Thus, it is of interest and importance to pose fundamental questions: (1) What is the "conformational effect"? (2) When do we need to resort to the help of "conformational effect" for the explanation?, (3) What is the origin(s) of the "conformational effects"? The goal of this paper is to discuss the answers.

1. WHAT IS THE "CONFORMATIONAL EFFECT"?

For this discussion we must define precisely what we understand by the notion "conformational effect". First of all what does the word "effect" mean? We do not intend to go into an etymological discussion and for our purposes shall restrict ourselves to two senses of this word.

Firstly, one labels as "an effect" a certain phenomenon, which is perfectly explainable by one theory but is not by other theories. For example, the term "quantum mechanical effect" is often used in that sense. In this case, the notion "conformational effect" has to reflect the origin of the phenomenon and, therefore, it has to be used in an *etiological sense* (*vide infra*).

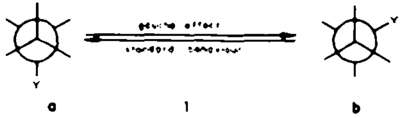
Secondly, one labels as "an effect" the deviation of a certain phenomenon from usually observed behaviour or from usually expected dependence. Roughly speaking, if one point falls out from a linear plot one may designate its behaviour as "an effect". In this case the notion "conformational effect" has a comparative sense, because one needs to have the "standard" or "reference" compounds whose conformational behaviour is assumed as a "normal" one. Thus the notion "conformational effect" has in this case a purely *phenomenological sense*. The following could serve as examples of typical "reference" behaviour (a) the relative stability of *anti* vs *gauche*-conformations in 1,2-disubstituted ethane framework (classical example is n-butane), (b) the relative stability of equatorial vs axial conformations in monosubstituted cyclohexanes (methylcyclohexane), (c) the relative stability of chair vs boat conformations in 6-membered rings and (d) low inversion barriers in R_3N and high ones in R_3P. Effects of this type are often regarded as specific for a certain structural unit, as "built-in", as inherent in some structural framework.

2. PHENOMENOLOGICAL CONFORMATIONAL EFFECTS

At this stage of discussion it is well to list briefly some of the well-known and most important phenomenological conformational effects.

2.1 *Effects of preference of* gauche-*conformations*

(a) Gauche-*effect*.[2,5,9,27] This effect has been postulated to explain a tendency of the ethane fragment to adopt the conformation which has a maximum number of *gauche*-interactions between the adjacent electron pairs and/or polar bonds. This effect has been usually observed in the case of highly electronegative substituents such as F or OR (1). The preference of a *gauche*-form



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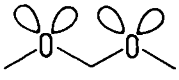

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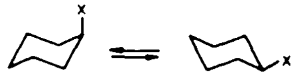
has also been observed for 1-halogenopropanes (e.g. **1b**, X = CH$_3$, Y = Cl).[27,28]

(b) "*Rabbit-ears*" *effect*.[6,7] At first this effect declared the instability of planar zigzag conformations, **2**, of the acetal framework. Later it has been generalized to include nitrogen containing heterocycles[29] and applied to the rationalization of the conformational behaviour and reactivity of cyclic acetales.[30]

2.2 *Effects of preference of axial conformations in 6-membered rings*

2.2.1. *Monosubstituted compounds*. The preference for the equatorial (**3b**) vs axial (**3a**) substituents is one of the basic conceptions of conformational analysis. However, there is one exception even in a monosubstituted cyclohexane: the axial conformation is preferred in cyclohexylmercuric chloride, **3** (X = HgCl, ΔG_{eq} = 0.3 kcal/mol).[31] For heterocyclic derivatives such "exceptional" behaviour has been observed quite often. For example it is true for sulfoxides **4** (X = CH$_2$, ΔG_{eq} at −90° equal 0.175 kcal/mol),[32,33] heterosulfoxides **4** (X = O, $\Delta G_{-80°}$ = 0.68 kcal/mol)[34] and **5a**,[35-37] sulfite **6**,[35,38] and for a variety of P^{IV} derivatives **7** (X = OCH$_3$, Cl).[39]



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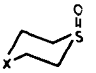

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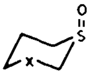
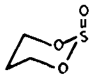


5 a X = O
b X = S



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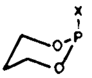

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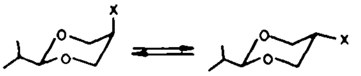
8 a Y = CH$_2$
b Y = O
c Y = S

This type of effect often appears in a 6-membered ring after the insertion of heteroatom(s) which is not bonded directly to a substituents. The most well known of them is the "*anomeric effect*" which manifests the preference of axial over equatorial C-1 electronegative substituent in the tetrahydropyran ring system **8a**, including the pyranose sugars (from which it received its name). This effect has been extensively studied and reviewed.[5-11,13-20] It should be noted that conformations of cyclic acetals—2-alkoxytetrahydropyrans **8a**—can be generalized to the acyclic compounds ("generalized anomeric effects",[40] cf Section 2.1).



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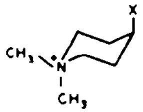

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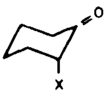
The predominance of axial conformations has been observed for the equilibrium of a number of 5-substituted 1,3-dioxanes, **9** (e.g. X = F, NO$_2$, SOCH$_3$, SO$_2$CH$_3$),[41] and 4-substituted pyridinium compounds **10** (X = Cl, OAc, OBz).[42]

2.2.2. *Disubstituted compounds*. (a) *Conformational effects in cyclohexanones*. For a number of 2-halocyclohexanones and related structures the predominance of axial conformations **11** has been observed.[43] The magnitude of this effect rises with the increasing of the atomic number of halogen atoms (F < Cl < Br). A formally analogous effect has been postulated for exo-olefin **12**.[44] Certain substituents in the 3 position also show a greater preference for the axial form, **13**, than in the parent cyclohexanes. When the substituent is alkyl this phenomenon has been called the "3-alkylketone effect".[45,46] An analogous effect has been observed for the exo-methylenecyclohexane system **14**.[46]



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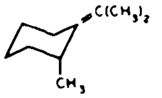

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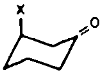

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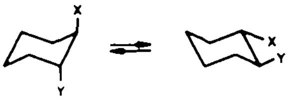
(b) *Axial conformations of* trans-1,2-*disubstituted cyclohexanes*. These compounds often show a relatively increased content of diaxial conformation **15a** for a variety of substituents in non-polar solvents.[9,47] This effect is especially remarkable for the elements of low periods (Br, SR).[9] Another interesting effect is the increased content of diaxial form **15a** for the compounds containing the bulky CCl$_3$ group (X = CCl$_3$). In the cyclohexane system this effect has been studied only for **15** (X = CCl$_3$, Y = Hal)[48] but in cyclohexene system **15A** it has been observed for a large number of second substituents (X = NO$_2$, CN, COOH, COCl).[49]



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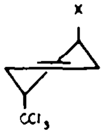
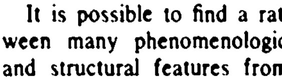


15A

(c) *Axial conformations of* trans-1,4-*disubstituted* 6-*membered rings*. This effect has been observed in *trans*-1,4-dichloro, dibromo, and ditrifluoroacetoxy cyclohexanes, **16**, and has not been studied in detail.[50,51]



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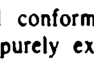

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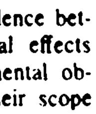

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However, there are some examples of this effect in heterocyclic systems, for example **17**[38b] and **18**.[34]

2.3 *Effects of the disappearance of effect*

It is possible to find a rather strict dependence between many phenomenological conformational effects and structural features from purely experimental observations and consequently to determine their scope and limitations. Hence one can meet another paradoxical situation: *the disappearance of a certain conformational effect has to be accounted for in terms of the operation of other new conformational effect(s)*.

Consider some examples. The *axial* conformation has been observed in a variety of structures of type **8a**[13] and **8b**[52] due to the anomeric effect. Thus, one may consider this axial form as a "normal anomaly". However, the axial preference does not survive the introduction of a S atom at 4 position; the equatorial conformation **19** became more stable than axial, **8c**, one,[8b] and these compounds show the "reference normal" behaviour. Generalization of these facts permitted us to suggest that *the new effect of additional destabilization of* gauche-

conformations is sometimes included in 1,2-disubstituted ethane moiety.[8,9] This effect is the opposite of the *gauche*-effect and operates for elements of low periods having lone pairs like Br, I, SR.

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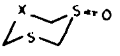

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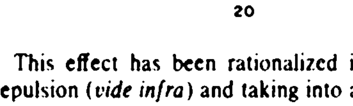
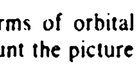
This effect has been rationalized in terms of orbital repulsion (*vide infra*) and taking into account the picture of orbital overlap, **20**, it was referred to as the "hockey-sticks" effect.[8-12] Consider other examples of the action of the effect of additional *gauche*-repulsion. As it has been shown above the sulfoxides **4** (X = O) and **5a** have the *axial* conformation which is the "normal" for 6-membered sulfoxides (e.g. **4** (X = CH_2)).[32-37] However, the axial preference of the sulfinyl oxygen is reversed in 1,3-dithiane-1-oxides and equatorial conformation **21** (X = CH_2) became more stable than axial conformation **5b**. For the 1,3,5-trithiane-1-oxide has been found that only a single conformation **21** (X = S) is present.[37] Analogously, for compounds **9** and **14** the magnitude of $-\Delta G_X$ is *smaller* than this value in cyclohexane in the case of X = OCH_3 but *larger* if X = SCH_3.[41,46]

Consider another example. Compound **22** should adopt the diaxial conformation **22a** due both to the anomeric effect of the OMe group and the axial preference of the HgCl group (see Section 2.2.1). However, the experimental data showed an appreciable content of the diequatorial conformation **22b** and hence indicated the specific interaction of the substituents (**23**, see Section 4.3).[53]



a **22** b



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In conclusion we would like to emphasize that the authors of some of the above-mentioned conformational effects treated them not as purely phenomenological ones, but they tried to ascribe to them some physical sense, to include some sort of rationalization. For example, the "rabbit-ears" effect (**2**) was connected with electrostatic interaction of "ears"[6] and the "hockey-sticks" effect was discussed in terms of orbital repulsion.[8,9]

There are also many other conformational "effects" and "anomalies"; however, the discussion of them is beyond the scope of this paper.

3. GENERAL METHODOLOGICAL REMARKS

The basic theoretical problem of the matter discussed could be formulated as a question: What are the origins of the conformational effects? However, before answering this question one first has to recognize that the answer depends upon the terminology and the conceptual content of the theory one has chosen to apply in answering the question. One may receive a number of answers, each of which is correct from the point of view of one theory yet which has no sense from the point of view of the other theories. As always, the depth of ones penetration into any problem will never exceed the limits of the theory used.

Organic chemistry is now using the ideas, conceptions, and principles which have resulted from two basic theories which have dealt with molecular structure: (1) classical structural theory supplemented with electronic effects and conceptions and (2) quantum chemistry. These theories operate with different logics and conceptual apparatuses. To avoid useless "theoretical" discussions (which are, in fact, all too frequent) one must precisely relate every particular conception to one of the two basic theories. Conformational analysis, which is a part of theoretical organic chemistry, likewise, did not escape this dualism and uses the notions of both theories. Therefore, it is expedient to summarize briefly the theoretical principles of conformational analysis and to discuss the problem of conformational effects from the standpoints of these fundamental theories.

4. CLASSICAL APPROACH

4.1. *Steric interactions*

The fundamental notion of the classical theory is the bond between a pair of atoms which is marked by a valent line. Thus all interactions in a molecule are divided into (i) interactions of bonded atoms and (ii) interactions of non-bonded atoms ("mutual influence"). Following this logic conformational analysis must take into account additively the both properties inherent in some particular type of bond (magnitude and order of a barrier) and the ones depending on non-bonded interactions. Hence there results the familiar scheme of accounting for steric interactions (actually repulsions) which permits us to make explanations on a qualitative level. The classical examples are the consideration of *gauche*-repulsions in 1,2-substituted ethane framework and 1,3 H...R or R...R repulsive interactions in axial conformations of substituted cyclohexanes.

This approach can be developed to a quantitative level. In this case conformational analysis is based on examination of the energy contributions made by changes in bond lengths, E_l, and angles, E_θ, torsional strain, E_τ, and by interaction between non-bonded atoms, $E_{n.b.}$ (eqn 1). One may designate this sum as an energy of "steric interactions", E_{ster}.

$$E_{ster} = E_l + E_\theta + E_\tau + E_{n.b.} \qquad (1)$$

The determination of stable conformation(s) is achieved by *minimizing* E_{ster} *as a function of the coordinates of atoms*. Since the classical works of Hill and Westheimer, this logic has been the basis of a great number of conformational calculations. To date these computational schemes have been developed to near perfection and in many cases yield reasonable correlation with experimental data.[54-57]

Now we can define the group of conformational effects which are steric in their nature. Indeed, if a certain phenomenological conformational effect can be reasonably rationalized in terms of eqn (1), one may refer this effect to the category of *steric conformational effects*. For example, bicyclo[3,3,1]nonane exists in double-chair conformation **24**;[58,59] the difference between the energies of conformations **24** and **25b** (X = H) was

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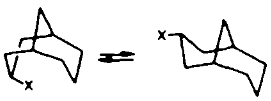
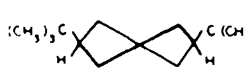


a **25** b

estimated to be 2.7–3.7 kcal/mol.[58,60,61] This is significantly lower than the ΔH value, 5–6 kcal/mol, associated with the chairboat conversion in cyclohexane. The difference results from a strong destabilization of **24** due to a repulsion of 3- and 7-carbons and *endo*-hydrogens. An introduction of 3-*endo*-substituent X (**25**), which is bulkier than hydrogen has to lead to the increasing of repulsion in double-chair conformation **25a**. These repulsion interactions can be severe enough to change the relative stability of the conformations **25a** and **25b**. Indeed, the preference for boat-chair conformation has been observed in a variety of compounds of type **25** (X = OH, Br, COOR).[58,62] Other examples of steric conformational effect are the preference for twist-boat conformations in t-butyl substituted cyclohexanes (e.g. **26**)[63a] or the operation of attractive steric effect in 1,3,5-trineopentylbenzene, which leads to the predominance of a rotamer with all three neopentyls on the same side of the benzene ring.[63b]

It is worthy to note here that an order or a magnitude of a "size" of substituents depends on their position with respect to the rest of the molecular framework. For example, the OH, Br and COOMe groups have effectively small steric requirements in ordinary cyclohexane systems, but one has to regard them as "large" groups in the 3-*endo* position of bicyclo[3,3,1]nonanes.[58]



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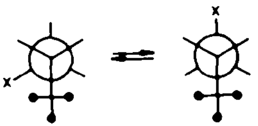

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Analogously, the low correlation has been observed between the values ΔE_{eq} for the equilibrium 27 and corresponding A-values in monosubstituted cyclohexanes[64] (Discussion of "anisotropy of the van der Waals radius" see Ref. 65).

The concept of steric conformational effects can be applied to the other types of conformational interconversions, for example to pyramidal inversion processes. Indeed, the dramatical increasing of the inversion barriers in N-substituted aziridines as compare with R_3N and ammonia[66] has been reasonably rationalised by using the simple steric arguments: a destabilisation of a planar transition state due to insertion of a pyramidal atom in a 3-membered ring is much greater than that of a pyramidal ground state (MO theory of pyramidal inversion see Ref. 66*a*).

4.2. *Electrostatic interactions*

Following the logic of the classical approach, every additional interaction of non-bonded atoms in the molecule has to lead to a "non-steric conformational effect", which is regarded as the additional term in eqn (1). The origins of these effects can be essentially different. It is expedient to discuss separately *non-specific* interactions (electrostatic ones) and *additional specific* interactions (the conformational effect proper which is specific for a certain structural unit) of non-bonded atoms and groups.

It is evident that interactions of dipoles or charges are an important factor in conformational control of the compounds containing polar bonds and/or charged atoms and groups. This electrostatic interaction must be accounted for as a new additive term, E_μ, in eqn (2).

$$E = E_{ster} + E_\mu \qquad (2)$$

$$E = E_{ster} + E_\mu + E_{effect}. \qquad (3)$$

We have to stress that up to date *the* eqn (2) *serves as a methodological basis of a consideration of conformational problems on a qualitative level.*

There exists a number of quantitative schemes for the calculation of electrostatic interactions in terms of either dipole-dipole or charge-charge approximations. Therefore, we can clear-cut define the notion "*electrostatic conformational effect*" if the conformational behaviour can be reasonably rationalized in terms of eqn (2). Many workers have applied this conception in explaining some of the effects already discussed, e.g. anomeric effect,[6,7,13,18] preference for axial conformations in 1,2-[67] and 1,4-disubstituted cyclohexanes[42,50,51] 5-substituted 1,3-dioxanes **9** (X = SO_2R, NH_3^+),[41] quaternary ammonium ions of type **10**,[42,68] etc.

However the calculations of electrostatic interactions are far from perfect, and what is more, they include crude simplifications, uncertain (and strictly speaking indeterminable) parameters and arbitrary assumptions. Hence the predictive power of these calculations is sometimes negligible, and this is the greatest and essential difficulty in the classical approach to conformational problems.

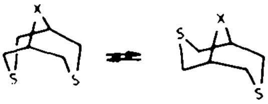
4.3. *Specific interactions of non-bonded substituents*

If a pair of substituents is characterized by some additional specific interaction, the calculation of the relative stability of the conformations must include it as an additional corrective term in eqn (2) which gives eqn (3). These new terms can be referred to as conformational effects specific to certain structural fragments. This is a purely phenomenological treatment which does not depend on the knowledge of the origin of a "specific conformational effect". In this section we restrict ourselves to a discussion of two types of such effects and the methodological problem of correct introducing of new conformational effects.

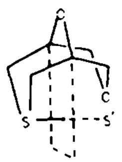
Hydrogen bond. An intramolecular H-bond can have energy significantly in excess of the usually observed energy differences between the conformations. Therefore a H-bond often operates as a dominant factor, controlling conformational equilibrium. These examples are numerous and well studied.

Coordinational stabilization effect of unstable conformations. An intramolecular coordination (donor-acceptor) bond is well known in organometallic chemistry.[69] The conformational effect discussed is the stereochemical consequence of the existence of this bond. For example, diequatorial conformation **22b** can be explained in terms of coordinational interaction between *gauche* MeO and HgCl groups, **23**.[51a] The conformational approach permits us to evaluate the magnitude of this effect (0.7–0.9 kcal/mol[51]).

Now let us return to the problem of introducing specific conformational effects. As has been stated above, they are introduced as effects additional to the steric and electrostatic ones. In other words, if the molecular mechanics calculations using eqn (2) explain the conformational equilibria observed, there is no need to postulate a more complicated explanation via the introduction of new effects (the principle of "Ockham's razor"[70]). We shall illustrate this statement with two examples. The molecular mechanics calculation of 3,7-dithiabicyclo[3,3,1]nonane, **28** (X = CH_2), predicts that a double-chair conformation, **28a** (X = CH_2), has to be more stable than **28b**.[14] However the X-ray[71] and PMR-



a **28** **b**



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data[72] for a related compound **28** (X = O) evidence a preference for a *boat-chair conformation* **28b** (X = O). The double-chair geometry of compound **29**[73] also permits us clearly to eliminate the explanation based on the steric arguments: the $S_1...S_7$ distance for **28a** (X = O) could be evaluated as 4.05 A (Scheme **29**), which is larger than the sum of van der Waals radii of two sulfur atoms (3.64 Å[14,74]). Hence *we need to postulate a new conformational effect but we have to find the origin of this effect outside the limits of the classical approach.*†

The second example concerns the equilibrium of trans-1,2-disubstituted cyclohexanes **15**.[9] The experimental ΔG_{eq} values have been divided in accordance with additive scheme:

$$\Delta G_{eq} = \Delta G_{X/Y} + \Delta G_X + \Delta G_Y$$

where ΔG_X and ΔG_Y are the free energies of conformational equilibria of corresponding monosubstituted cyclohexanes, and term $\Delta G_{X/Y}$ reflects the *gauche*-interaction of the substituents in the diequatorial conformation **15b**. The values $\Delta G_{X/Y}$ have been correlated with E_{ster} and E_μ (eqn 2) as the plot in coordinates $\Delta G_{X/Y} - E_{ster}$ vs E_μ. If the value $\Delta G_{X/Y}$ fall on the "borderline" $\Delta G_{X/Y} - E_{ster} = E_\mu$ that means that conformational behaviour of this particular compound can be adequately interpreted in terms of steric and electrostatic interactions of substituents. This was precisely observed for the O/Cl, O/Br and O/I fragments. However, the points of O/O and F/I fragments were distinctly in the field of additional attraction and points belonging to S/Cl, S/S, S/Br and Br/Br fragments were distinctly in the field of additional repulsion. In summary, it has been concluded that *conformational behaviour of some compounds* **15** *investigated can be rationalized only by involving the additional effects*, namely (a) additional *gauche*-attraction for the strong electronegative fragments (O/O, F/I) and (b) additional *gauche*-repulsion for the elements of low periods.[9]

Now two concluding remarks are in order. First although the logic of the classical approach is satisfactory in general, the concrete practical calculation of steric and especially electrostatic terms is accomplished with considerable difficulties. Hence it is often impossible to give indubitable answers; does one or does one not need to introduce the new specific conformational effect (see for example the discussion concerning 1,2-difluoroethane[75,76] or anomeric effect[14-18]). Secondly, the identification of the specific effect is only one aspect. A chemist needs to explain the nature of the specific effects. However, the classical theory cannot answer this question because the notion "specific conformational effect" is treated as a phenomenological one. Hence, we need to apply quantum mechanical theory in analyzing this problem.

5. QUANTUM CHEMICAL APPROACH

The logic of quantum chemistry is absolutely different. First every molecule is considered as a whole, namely as a set of a certain number of nuclei and electrons. Hence there emerges no notion of a bond between pairs of atoms in quantum chemistry‡ and roughly speaking, every atom is bonded with every other. Secondly there emerges no set of transferable properties associated with the notion of a functional group.[77] Therefore, quantum chemistry is not well suited by its nature to operate with additive schemes.

The solution of conformational problems by quantum chemical methods in principle comes to following: one has to solve the Schrödinger equation for a certain system of nuclei and electrons in order to obtain the dependence of energy on geometry in the system under consideration. In other words the problem consists in calculating the energy surface as a function of the nuclei coordinates; the minima on this surface will correspond to stable conformations and the "saddle" points to conformational barriers. At this stage of the discussion one important point has to be emphasized: in this fundamental approach the notion "conformational effect" does not emerge at all! A calculation of every particular molecule can be performed, and if it is correct, one has to get the description of the conformational behaviour which automatically conforms to the experimental data. Hence it has to be clearly understood that a particular calculation describes a particular conformational event but contributes little to the solving of conformational problems in general.§ The most important question here is to extract the chemically useful picture, to make the conceptual generalization. Such "conceptualization" extracted from quantum chemical description and expressed in terms of theoretical organic chemistry has to represent the theoretical content of conformational analysis.¶ A chemist needs chemically sound models, needs an "*understanding*" of the calculation which means that he may predict on a qualitative level on the basis of chemical conceptions the computation data.[77] The emphasis, therefore, of this section will not be on particular calculations but on their conceptual content.

Two approaches could be outlined here. The first one is connected with the problem of the partitioning of total energy into its component parts. This energy-component description can permit us to analyze their relative importance for conformational barriers and stability of conformations etc. This approach is especially useful if it is possible to ascribe to these energy components some really sound sense in terms of theoretical organic chemistry.

Secondly the compromise, "semilocalized" approach is widely used.[21] The MO-equivalent of the classical notion of the bond is the notion of localized orbital. The compromise consists in using a set of localized orbitals

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†Professor R. Gleiter and this writer are currently investigating this problem by photoelectron spectroscopy.

‡Of course it is possible to introduce some criteria of bonding between a chosen pair of atoms; however, strictly speaking, this operation is necessary only to relate the quantum chemical conclusions to conclusions obtained from the classical theory.

§Dewar has written:* "... *any attempts to draw general conclusions from the results of such calculations fall in the same category as attempts to draw empirical conclusions from experimental data*"

¶Roughly speaking, the theory of organic chemistry in general (at least which concerns an unreacting molecule) is the qualitative verification of the quantitative quantum mechanical data using the chemical language.

and accounting for the delocalization of only a part of them. Thus one considers only "lakes" of delocalization on "a continent" of localization.† The basis of this approach is usually the perturbation method which has gradually become the general language of modern theoretical organic chemistry.[21,25,26,77-79] Hence one can evaluate the quantum mechanical interaction for a certain fragment and account for it as an additional term in a classical picture (e.g. using eqn 3).

5.1. *Energy component* (E_{att} *and* E_{rep}) *analysis*

The total energy, E, of a system can be partitioned into four components: the nuclear repulsion potential, V_{nn}; the electron-electron repulsion, V_{ee}; the kinetic energy of electrons, T, and the attraction of electrons for the nuclei, V_{ne}.[80-82] The first three terms represent the repulsive term, E_{rep}; the last one is the attractive term, E_{att} (eqn 4). In conformational transition between two conformations, the energy change, ΔE, can be expressed by eqn (5). If we accept the approximation that the virial

$$E = (V_{nn} + V_{ee} + T) + V_{ne} = E_{rep} + E_{att} \tag{4}$$

$$\Delta E = \Delta E_{rep} + \Delta E_{att} \tag{5}$$

$$\Delta E = (\Delta V_{ne} + \Delta V_{nn} + \Delta V_{ee})/2 \tag{6}$$

theorem, $\Delta E = -\Delta T$, holds, eqn (5) is transformed into a three component eqn (6).[80] Therefore, the energy difference between the two conformations (between two minima or between minimum and maximum = barrier) depends on a delicate balance between the attractive and repulsive forces. If $\Delta V_{ee} + \Delta V_{nn} > |\Delta V_{ne}|$ the steric bulk approach is satisfied and gives the correct predictions of the stability of conformations. If $|\Delta V_{ne}| > \Delta V_{nn} + \Delta V_{ee}$, the steric approach fails.

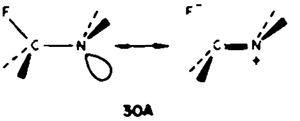
This energy-component approach has been applied to the problems of *gauche*-effect,[2,3] rotation in n-butane and ring reversal in cyclohexane,[80] pyramidal inversion,[66a,81] It gives the physical picture of conformational processes (see, e.g. the conception of "attractive and repulsive barriers"[81]). Most importantly, it offers an explanation for the occurrence of an attractive steric interaction which cannot be satisfactorily handled in other ways. However, it is sometimes difficult (i) "to translate" this approach into usual chemical language and (ii) to predict the energy-component balance based on chemical conceptions, and this approach has still to "be considered as interpretive rather than a predictive tool".[80]

5.2. *Fourier-type expansion of the potential function*

The total potential curve of internal rotation around X–Y bond can be written, in general, as the Fourier expansion (eqn 7):[15,17,81]

$$V(\varphi) = \sum_{n=1}^{n} \frac{V_n}{2}(1 - \cos n\varphi). \tag{7}$$

Usually only the first three terms of the expansion are considered. This separation of $V(\varphi)$ into three components permits us to analyse the conformational problems because it is possible to ascribe to these terms a definite chemical sense. Usually the one-fold potential is related to dipole-dipole interaction and the three-fold potential is considered as the intrinsic one.[17,81a] The two fold potential is attributed to electron delocalization involving σ-electron withdrawal and n-electron donation (hyperconjugation). Formulas **30A** represent this effect in terms of "no-bond" resonance (MO-description see Section 5.3):



30A

CH_3O-CH_2X

30 a X=OCH$_3$

b X=Cl

Therefore such decomposition permits us to discuss conformational phenomena in terms of theoretical organic chemistry. As an example consider the CNDO/2 calculations of dimethoxymethane (DMM, **30a**) and chlorine methoxymethane (CMM, **30b**) chosen as model compounds for the investigation of "generalized anomeric effect".[17] The values of V_3 coefficients are negative for both molecules. The term of dipole-dipole interaction, V_1, has the substantially lower value in CMM. The term V_2 which characterized the electron delocalization, has a small positive value in the case of DMM and negative value in the case of CMM. Hence, the anomeric effect can be interpreted in terms of a balance of dipole-dipole and hyperconjugation interactions: the former prevails in DMM and the latter in CMM. Thus, these results suggest the different nature of anomeric effect for oxygen and chlorine substituents.

5.3. *The compromise "semilocalized" approach*[21]

In this case a molecule is considered as a classical system with localized bonds using eqn (2). However, for a certain group or fragment the orbital interaction ("delocalization") has to be accounted for. This interaction is treated as a "quantum chemical conformational effect" and is considered as an additional term in eqn (3). Therefore, this effect is not treated as a purely corrective term in eqn (3), but as one having some physical reason, some quantum chemical nature.

Let us begin with the simplest case of interaction of two orbitals (Fig. 1), which results in bonding and antibonding combinations. In this case the upper level is destabilized more than the lower one is stabilized and $|E_r| > |E_a|$.[77,84] If these orbitals are occupied by four electrons, the interaction results in destabilization. This repulsive interaction **20** was picturesquely referred to as

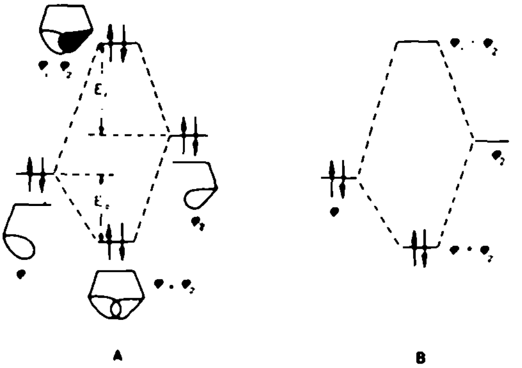


Fig. 1. First-order interaction of two orbitals with overlap included. A—four electrons case; B—two electrons case.

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† In fact this approach is very familiar to organic-chemists. For example the typical model of unsaturated compounds includes the localized σ-framework and the delocalization of p-orbitals.

the "hockey-sticks" effect[8,9] and considered as the origin of an additional repulsion of *gauche*-substituents (see Section 2.3).[9] An analogous concept has been stated by Hoffmann[21] ("through space" effect) and by Müller.[85]

R. Hoffmann has developed a more general approach concerning the *two types* of electronic interactions, "through space" and "through bond" effects.[21-24]. Consider briefly this approach. The four electrons "through space" interaction results in destabilization, as it is illustrated in Fig. 1. However, the interaction of two orbitals with a total occupancy by *two electrons* results in stabilization. Thus, the interaction of antibonding, $\varphi_1 - \varphi_2$, combination (Fig. 1) with some other empty orbital would be stabilizing. In the case of fragment **20** the bonding, $\varphi_1 + \varphi_2$, and antibonding, $\varphi_1 - \varphi_2$, combinations (Fig. 1) can then interact with orbitals of σ-bond (Fig. 2). There are two types of this "through bond" interactions: destabilizing interaction **A** (Fig. 2) of doubly occupied orbitals and stabilizing interaction, **B**. The latter interaction can be stronger than the former and *the net result of the two interactions can be that the lone pair interaction is attractive*. Hence, the fact of interaction of orbitals as in **20** does not permit *a priori* conclusion concerning the relative stability of conformers, because "through space" and "through bond" effects can change a relative stability of the conformers in opposite directions. The concept of non-bonded attraction has been developed by Hoffmann,[21,22] Epiotis[26,86] and Salem[14,25] who showed its important stereochemical implications. In particular, the "through-bond" interaction in the fragment **20** (Fig. 2) has been suggested as the origin of the general phenomenological *gauche*-effect.[86]

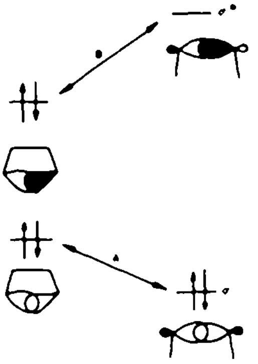
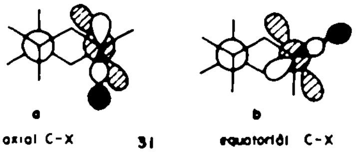


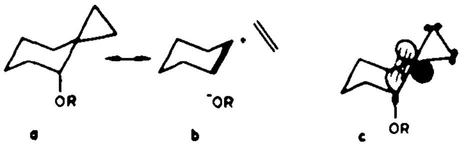
Fig. 2. "Through-bond" interaction.

As another example we shall discuss the application of this concept to the anomeric effect (see Section 2.2.1). On the basis of this approach, the conformational preference is due to the stabilizing interaction of oxygen p-orbital and σ^*-orbital of C–X bond. A magnitude of such attractive interaction depends on the overlap of orbitals interacting which in turn depends on the conformation. Scheme **31** evidences that the overlap in an axial conformation **31a** is better than in an equatorial **31b** one.



axial C–X **31** equatorial C–X

This conclusion concerning the origin of anomeric effect leads to some consequences which can be experimentally proved. In particular, this charge-transfer from p to σ^*-orbital has to result in the lengthening of the C–X bond and the shortening of the C_2-heteroatom bond, which has been actually found for some cases.[16] This simple MO representation can be used as a guiding force for the search of new model compounds having the same conformational behaviour. For example, the compound **32a** exists preferentially in axial confor-



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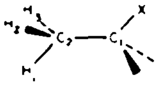
mation, which can be explained analogously (in terms of resonance theory as **32b**, MO representation **32c**).[87a]

On the basis of the "semilocalized" approach another explanation for the *gauche*-effect can be suggested. In general, if the *gauche*-conformer is more stabilized than the anti-conformer, the first may be stabilized, as it has been assumed above, *or the second may be destabilized*. This latter conclusion has been derived from the simple perturbation treatment taking into account the charge densities in an ethane fragment **33**.[87b,88] Two frontier orbitals of ethane are shown in Scheme **34**.[89,90] If we begin to increase the electronegativity of X this perturbation will lead to the mixing of the orbitals accounted and will result in a lowering of the electron density at H_1 (**34**).



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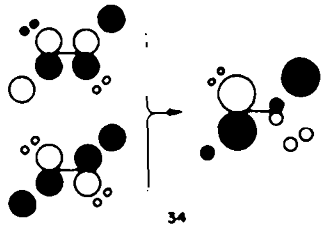

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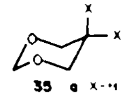
Hence, the most electronegative ligand of C_2 will tend to escape the anti-position and to be *gauche* to the ligand X. Generalization of this simple "rule of *anti*-destabilization" permits us to rationalize many conformational phenomena.[87b,88] Analogous argument has been applied to the problem of electronic "long-range" and conformational effects in 6-membered rings.[91] The concept of anti-destabilization has been also achieved from the point of view of electron delocalization in an ethane fragment which is greater for elongated, *anti*-conformation than for bent, *gauche*-conformation.[92]

As an example consider the preference for axial fluorine in 5-fluoro-2-isopropyl-1,3-dioxanes, **9** (X = F).[41] This fact can be explained either by attractive interactions O...F in conformation **9a** due to the "through bond" effect or by "*anti*-destabilization" O–C–C–F in equatorial conformation **9b**. Now let us compare the ring inversion barrier in 1,3-dioxane, **35a**, with the one in 5,5-difluoro-1,3-dioxane, **35b**. Because the both alternative types of interactions discussed have to be diminished in the transition state, the difference between these barriers must depend only on the difference between the energy of the ground states. In the former case



35 a X=H
b X=F

the attractive interactions have to stabilize the ground state of **9a** as compared with **9b** and the ground state of **35b** as compared with **35a** which has to lead to the *increasing* of the barrier for **35b**. In the second case the energy of the ground state of **9b** has to be raised and analogously the inversion barrier in **35b** has to be *lower* than in **35a** which is consisted with the experimental observation.[93]

Two concluding remarks are in order. Firstly, this approach is flexible enough to cover many conformational problems even for complex structures. Secondly, and the most important, it permits us *to discuss the origin of reference conformational relationships*, f.e. staggered vs eclipsed in ethane[89,90] or rotameric conformations about C_{sp^3}–C_{sp^2} and C_{sp^2}–C_{sp^2} bonds,[94,95] which are considered purely phenomenologically as inherent in torsional potentials in the classical approach. A simple orbital approach is now widely and successfully used for the interpretation of conformational (and electronic) effects.

CONCLUSION

In this Report we have discussed the problem of conformational effects including the methodological aspect. We have attempted to show that this problem is treated in different ways by using different theories. The conformational behaviour of many compounds can be explained or rationalized by the classical approach. However some quantum mechanical conformational effects may be useful in discussing this problem and quantum chemical approach permits us to rationalize the basic conformational relationships. Of course we are still far from the quantitative and even qualitative prediction of conformational equilibria, but our theoretical knowledge permits us to formulate *the search for new conformational effects as synthetical goal*. It seems clear that this is a promising field of activity for both synthetic chemists and quantum chemists. More work is required to approach the solution of one of the fundamental problems of conformational analysis, namely prediction and explanation of the relative stabilities of conformations.

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