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Theoretical Conformational Analysis of Organic Molecules

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I. Introduction

The conformational analysis of molecules is a subject of extended research both of a theoretical and an experimental nature. In this article we review the theoretical methods which are used nowadays. It is not our intention to cover all papers which lie within the scope of this review, which would require over a thousand references. Our aim is rather to analyze the present day state of theoretical conformational analysis, supporting the analysis by a large although still limited number of selected references up to the first months of 1973.

Methods of the theoretical conformational analysis can be classified in several ways. We have classified them as follows:

1. Direct methods
   a. Non-uniform methods
      i. Classical methods
      ii. Quantum-mechanical methods
   b. Uniform methods
      i. Semiempirical quantum-mechanical methods
      ii. Nonempirical quantum-mechanical methods
2. Indirect methods

In direct methods the total energy of the molecule E is minimized with respect to all or certain structural parameters. In indirect methods, on the other hand, conclusions are drawn from the analysis of dipole moments, spin densities, absorption spectra, etc. This review is restricted to direct methods only.

Typical for a non-uniform method is the use of two or more theoretical schemes in estimating the total energy, E. Usually E is split into the energy of nonbonded interactions, W, and the remaining energy contributions, V, such that $V = E - W$, the contributions W and V being estimated on a completely different basis. If only one theoretical scheme is used for estimation of E, the method is said to be uniform. Uniform methods are either all-electron treatments or all-valence-electron ones.

II. Non-uniform Methods

There are two nontrivial problems in any direct method of theoretical conformational analysis: how to find the dependence of E on structural parameters and how to minimize E. Concerning the first problem, one assumes usually in non-uniform methods that

$$E = V + W \tag{1}$$

where the interaction energy between nonbonded atoms, W, is estimated in accordance with the central field model

$$W = \sum W_j(R_j) \tag{2}$$

The index j refers to various pairs of nonbonded atoms and R_j is the distance between these atoms.

A typical expression for the interaction energy $W_j(R_j)$ consists of two parts. One part gives the repulsion energy of two atoms at small distances; the other leads to a weak attraction at large distances. The second term is often called the *van der Waals energy*.

The attraction at large distances is believed to be caused mostly by various types of dipole–dipole interactions. If neither of the interacting atoms has a permanent dipole moment, the dipole–dipole interaction leads to what is called *London forces* or *dispersion forces*. The appropriate energy depends on R_j as R_j^{-6}. A detailed discussion of all these interactions can be found in Pitzer's paper[1] and in other works.[2-5]

Repulsive interactions at small distances are caused mainly by the mutual interpenetration of closed-shell electrons. One assumes either an exponential dependence of R_j or a dependence $1/R_j^n$, where $n > 10$.

Thus one of the following two formulas is usually used: the Lennard-Jones formula

$$W_j(R_j) = -A_j/R_j^6 + B_j/R_j^{12} \qquad (3)$$

or the Buckingham one

$$W_j(R_j) = -A_j/R_j^6 + B_j \exp(-C_jR_j) \qquad (4)$$

where A_j, B_j, and C_j are positive constants.[5-8]

Sometimes a hard-sphere model is used, however,

$$\begin{aligned} W_j(R_j) &= 0 \text{ for } R_j \geq R_j^0 \\ &= \infty \text{ for } R_j < R_j^0 \end{aligned} \qquad (5)$$

where R_j^0 is the sum of van der Waals radii of interacting atoms.

Helpful in estimating the constants in eq 3 and 4 are the investigations of real gases and liquids. In this way, for example, the constants have been estimated for the pairs He···He, Ar···Ar, and Ne···Ne.[9] In principle, the constants can be estimated theoretically.[1,2,4] In practice, however, they are treated usually as empirical parameters of the appropriate method in question.[8,10-14]

The estimation of W with the central field model is certainly an oversimplification. This is particularly true in the case of heteroatomic systems. Nevertheless, more elaborate estimates of W are hardly used in conformational analysis.

Various non-uniform methods differ mainly in the way of estimating V and in the way they minimize the total energy.

A. Classical Conformational Analysis

1. Nonconjugated Systems

a. General Principles

Let Q be the vector of actual values of all bond lengths and all valence angles of a molecule in question. Let Q_0 be a particular case of vector Q for which the total energy is a minimum provided the interactions between nonbonded atoms have been neglected. Interactions between nonbonded atoms will distort the shape of the molecule. Thus

$$\Delta Q = Q - Q_0 \neq 0 \qquad (6)$$

where Q refers to the real equilibrium conformation.

For the energy of the system we can write

$$E(Q) = V(Q) + \sum_j W_j[R_j(Q)] \qquad (7)$$

It is often convenient to consider what is called the strain energy

$$D(Q) = V(Q) - V(Q_0) + \sum_j W_j[R_j(Q)] \qquad (8)$$

The equilibrium conformation follows then from minimization either of the total energy E or the strain energy D.

The last term of eq 8 was described earlier. The difference $V(Q) - V(Q_0)$ is called a deformation energy, ΔV. In the case of a small steric hindrance and nonconjugated systems, it is possible to estimate ΔV with a harmonic model. Then

$$\Delta V = \frac{1}{2}\Delta Q K \Delta Q^T \qquad (9)$$

where K is a square symmetrical matrix of force constants and T means transposition of the row vector. Usually, with an accuracy believed to be sufficient for the purpose of conformational analysis, one neglects off-diagonal terms. Then

$$\Delta V = \frac{1}{2}\sum_i K_{ii}\Delta Q_i^2 \qquad (10)$$

Changes of energy due to the barrier of rotation about single bonds are estimated in the following way

$$\Delta V_{\text{rot}} = U_0(1 + \cos n\varphi) \qquad (11)$$

where n is the multiplicity of the rotation axis and φ is the angle of rotation. The barrier of rotation is $2U_0$.

In general, the deformations ΔQ_i are not independent of each other. Let q be the row vector of all independent deformations ΔQ_i, sufficient to describe the conformation. The strain energy can be minimized either in respect to all ΔQ_i's with the use of Lagrangian multipliers or with respect to all independent coordinates, q_i.

b. Review of Methods

Principles of the classical conformational analysis of organic molecules have been given by Hill[15] and Westheimer.[6,16-18] Other methods are basically extensions of these ones. They take into account the new possibilities given by computers. Hendrickson[19] was the first to adapt the method for computers. His computational scheme was rather limited, however. Full computations were carried out only for cyclopentane. In less complete calculations he considered also higher cycloalkanes.

A more general scheme was derived by Wiberg.[20] He defines the energy in terms of small changes of bond lengths and valence angles and includes the rotational energy of alkyl groups. These valence coordinates are then transformed to Cartesian coordinates, and E is minimized with the help of the steepest descent method. Because of computer limitations, only isomers of cyclohexane and cyclooctane were investigated. Less complete calculations were carried out for cyclodecane and cyclododecane. Extended calculations with Wiberg's method were carried out by Allinger, *et al.*[21-25] They investigated the various conformations of cyclohexane and its alkyl derivatives, of decahydronaphthalene, and of some simple unsaturated systems. Their later work[23] was concerned with isomers of molecules containing oxygen, sulfur, nitrogen, and chlorine.

A modification of Wiberg's method was suggested by Jacob, Thompson, and Bartell.[24] These authors express the strain energy in terms of independent coordinates q_i, $i = 1, 2, \ldots, f$, and optimize the conformation iteratively, in accordance with the Gauss-Newton scheme. At a given iteration they solve the set of linear algebraic equations

$$\left(\frac{\partial D}{\partial q_j}\right)_0 + \sum_i \left(\frac{\partial^2 D}{\partial q_i \partial q_j}\right)_0 (q_i - q_i^0) = 0 \qquad (12)$$

where all quantities provided with the index 0 are taken from the preceding iteration. Obviously eq 12 follows from the Taylor expansion of the strain energy D and from the condition of its minimum. With this method several unsaturated hydrocarbons have been also considered, including olefins. Theoretical values of bond lengths and valence angles agreed well with experiment. The strain energy was also discussed, together with the isomerization energies and intramolecular barriers to rotation.[24,25]

A somewhat similar approach was given by Boyd.[26] He also started with a Taylor expansion of the strain energy in terms of valence coordinates, Q_i. Then, however, he transformed the expression to Cartesian coordinates. From the condition of minimum he obtained a set identical with eq 12 after replacing q_i's by Cartesian coordinates. This method was applied to [2.2]paracyclophane, [2.2]metacyclophane, [2.2]metaparacyclophane, and [3.3]paracyclophane.

Another similar method of classical conformational analysis was worked out by Kitaygorodsky.[12] Originally the method was applicable to saturated systems only, like alkanes and simple cyclic systems. An extended version was applicable also to unsaturated molecules.[13,14]

c. Further Applications

Based on these methods, many conformational calculations have been performed. Some typical examples follow.

Abe, Jernigan, and Flory[27] and Scott and Scheraga[28] discussed the dependence of E on the twist angle of methyl groups in alkanes. A similar discussion of halogen derivatives of alkanes[29] and dihalogen derivatives of butadiene and hexane[30] was given by Heublein, Kühmstedt, Dawczynski, and Kadura.[30] Altona and Sundaralingam performed conformational calculations for several derivatives of cyclohexane, optimizing all structural parameters.[31] Agreement of their results with experiment was rather good. Their program for the Univac 1108 computer is able to deal with a system up to 60 atoms and up to 1200 nonbonded interactions. Still continuing are the works of Dashevsky and his group.[32-36]

Wiberg's method was used most recently by Dodziuk with the purpose of estimating the optimal conformation and barriers of rotation of monosubstituted methylbutadienes,[37] 2,3-dimethylbutadiene,[38] 2,4-dimethylpentadiene-1,3,[39] methyl vinyl ketone, *cis*-penten-2-one-4, 2-methylpenten-2-one-4, monomethylacrolein, and methyl derivatives of propane.[40]

The role of nonchemical interactions in the strain energy of adamantane was discussed by Schleyer, Williams, and Blanchard.[41]

Wiberg and Boyd investigated the path of interconversion of the two forms of cyclohexane.[42]

Lugovsky and Dashevsky have improved the classical scheme by including electrostatic interaction of charges localized on atoms and by additional consideration of hydrogen bonds.[43] They have applied this method to a conformational analysis of eight heterocyclics containing oxygen.[43]

Kitaygorodsky's method was applied by Levin and Shlyapochnikov to several aliphatic nitro compounds, like $ClCH_2NO_2$, CX_3NO_2, and $XC(NO_2)_3$, where X is a halogen.[44]

The classical Lennard-Jones potential including an electrostatic term and a torsional energy correction was used by Kang, Johnson, and Green in order to find the conformation of 5-hydroxytryptamine.[45] Both this classical and an EHT calculation did not allow the establishment of the conformation unambiguously.

Rather atypical is the analysis carried out by Lipkind, Arkhipova and Popov, who investigated the influence of solvent on the structure of molecules. Their classical analysis included electrostatic interactions.[46]

d. Pauncz and Ginsburg's Method

According to Pauncz and Ginsburg, the conformation of a molecule with a large steric hindrance depends mainly on interactions between nonbonded atoms.[47] For this reason they minimize simply $W(Q)$. With this rather oversimplified model they determined the relative stability of various conformations of cyclohexane, cyclooctane, cyclodecane, cycloheptene, cyclooctene, and 1,5-cyclooctadiene.

2. Conjugated Systems

a. Standard Methods

Methods of section 1 are applicable, at least in principle, to systems which contain no conjugated double bonds and which exhibit no large steric hindrance. Otherwise, a delocalization of any local distortion has to be considered. However, Kitaygorodsky and Dashevsky were able to show that in the case of small distortions the classical method works just as well as in the case of nonconjugated systems.[13,14] They have successfully discussed the conformation of octachloronaphthalene, 1,4,5,8-tetrabromonaphthalene, 3,5-dichloroacenaphthene, hexahalogenobenzene, tetrachloro- and tetrabromobenzene, [2.2′]paracyclophane, biphenyl, binaphthyl, and dichlorodiphenylnaphthacene. Agreement with X-ray data was excellent.[14]

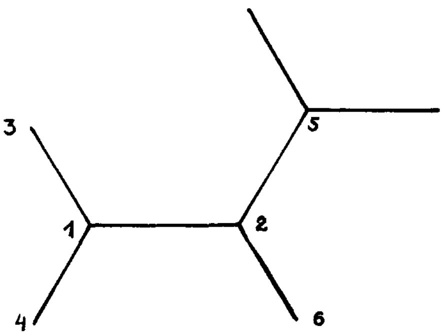

Figure 1. Fragment of a conjugated system.

b. Coulson and Senent's Method

An alternative approach comes from Coulson and Senent.[48,49] According to these authors the steric hindrance is counterbalanced by out-of-plane deformations of a conjugated π-electron system. Let us consider a fragment of a molecule shown in Figure 1. the authors introduce two kinds of coordinates, a_i and b_{ij}. For example, the coordinate a_1 is equal to the distance of atom 1 from the plane defined by its three neighbors. The coordinate b_{12} is proportional to the angle between the projection of two vectors perpendicular to the planes defined by atoms 1, 3, 4 and 2, 5, 6, accordingly, on the plane perpendicular to the bond 1–2. In the case of small out-of-plane deformations and the sp^2 hybridization, one finds that

$$a_1 = 1.40\{(z_4 - z_1)/R_{14} + (z_3 - z_1)/R_{13} + (z_2 - z_1)/R_{12}\} \quad (13)$$

$$b_{12} = 1.40\{(z_3 - z_1)/R_{13} + (z_6 - z_2)/R_{26} - (z_4 - z_1)/R_{14} - (z_5 - z_2)/R_{25}\} \quad (14)$$

where z_i is the out-of-plane displacement of atom i from the average plane of the molecule or its major fragment and R_{ij} is the distance between atoms i and j. It was shown by Coulson and Golebiewski that off-diagonal force constants can well be neglected in this case, whereas the same is not true in the case of the commonly used coordinates of Crawford and Miller.[50,51]

Coulson and Senent's method did not consider changes of bond lengths and valence angles. For nonbonded interactions the hard-sphere model was used (eq 5). Thus the strain energy was a function of z coordinates only, some of the coordinates being fixed by using the hard-sphere model.

Despite evident limitations, the method was applied with some success to 3,4:5,6-dibenzophenanthrene,[52] phenanthrene, 3,4-benzophenanthrene, tetrabenzonaphthalene,[53] perylene, triphenylene,[54] 5,6:7,8-dibenzoperylene, 1,12:5,6:7,8-tribenzoperylene, tetrabenzoperopyrene,[55] and [18]annulene.[56]

c. Coulson and Haigh's Method

Coulson and Senent's method was improved by Coulson and Haigh by variation of bond lengths and valence angles and by replacing the hard-sphere model (eq 5) by a more sophisticated one (eq 3 and 4).[57]

Let x be a row vector of all considered planar deformations and z the row vector of out-of-plane deformations just described. Provided there is one type of nonbonding interactions, we find that

$$D = \frac{1}{2}xK_xx^T + \frac{1}{2}zK_zz^T + tW(R) \quad (15)$$

where

$$tW(R) = \sum_{i} W_j(R_j) \tag{16}$$

t being the multiplicity of the interaction and R the common distance between interacting atoms. R is obviously a function of x and z. For small deformations

$$H(R,x,z) = Mx^T + \frac{1}{2}zGz^T + R_0 - R = 0 \tag{17}$$

The row vector M, the square matrix G, and the starting distance between interacting nonbonded atoms, R_0, follow from the trigonometric analysis of the original shape of the molecule. In-plane coordinates are, in general, not independent of one another. From a trigonometric analysis one obtains the constraints

$$g(x) = xC + d = 0 \tag{18}$$

where g, x, d, and 0 are row vectors and C is a rectangular matrix.

Thus the optimal structure follows from the minimum condition of f with respect to R, all x_i's, and all z_i's, where

$$f = D + lH + Lg^T \tag{19}$$

In this equation l and the elements of the row vector L are the undetermined Lagrangian multipliers.

Coulson and Haigh's method is applicable to systems in which the steric hindrance is not large. The authors investigated with this method the structures of phenanthrene, chrysene, and triphenylene.[57] Also crystalline biphenyl was discussed in this way.[58]

Classical conformational analysis is easily applicable even to relatively large molecules. However, owing to many oversimplifications the results are often uncertain. There are internal difficulties in the case of heteroatomic systems. The classical analysis is certainly not justified in the case of large distortions, particularly in the case of π-electron systems with conjugated double bonds. In such a case one should turn to a more sophisticated method.

B. Quantum-Mechanical Conformational Analysis

Among known semiempirical treatments of π-electron systems, two of them have gained enormous popularity: the familiar Hückel method (HMO) and the Pariser, Parr, and Pople method (PPP).[59] In both methods π-electron orbitals are linear combinations of atomic $2p_\pi$ orbitals. In the Hückel method the MO's are eigenfunctions of an effective one-electron Hamiltonian. In the PPP method the π-electron interactions are considered explicitly. However, large simplifications are introduced, like the π-electron approximation and the assumption of zero differential overlap (ZDO).[59]

In theoretical conformational analyses both methods have been used.

1. HMO Based Analysis

a. General Principles

In the HMO-based analysis any change of the total energy is split into three components

$$\Delta E = \Delta E_\pi + \Delta E_\sigma + \Delta W \tag{20}$$

The Hückel method is used in order to estimate ΔE_π. The total π-electron energy is here a sum of orbital energies of all π electrons. This is certainly a crude approximation, as the interelectronic repulsion energy is calculated twice.[59] Essential in the HMO theory is the approximation of the resonance integral β_{ij}. In the original HMO theory the resonance integrals were independent of structural parameters. In conformational analysis most authors consider only the dependence on the twisting angle of the bond, ϑ_{ij}[60-63]

$$\beta_{ij} = \beta_{ij}^0 \cos\vartheta_{ij} \tag{21}$$

Other authors assume additionally a dependence on the bond length, for example[64-71]

$$\beta_{ij} = B_{ij}\exp(-gR_{ij})\cos\vartheta_{ij} \tag{22}$$

$$\beta_{ij} = \beta_{ij}^0 S_{ij}/S_{ij}^0 \tag{23}$$

where B_{ij}, g, and β_{ij}^0 are constants, S_{ij} is the overlap integral for the assumed bond length and the assumed twisting angle, and S_{ij}^0 is the overlap integral for a standard bond length and no twist.

This method has been applied mostly to a twisting of an almost single bond. For this reason one notices three basically different approaches to the change ΔE_σ. In the simplest calculations, the change was neglected completely.[60-62,69] In more accurate treatments, ΔE_σ was estimated for the twisted bond only, usually with the Hooke model[70,71]

$$\Delta E_\sigma = \frac{1}{2}K_{ij}(R_{ij} - R_{ij}^0)^2 \tag{24}$$

where R_{ij}^0 is the standard bond length of a pure single bond and K_{ij} is the appropriate force constant. In more advanced treatments, like self-consistent conformational analysis,[64-68] the simultaneous changes of all or most of the σ-bond energies were considered.

For nonbonded interactions, the hard-sphere model was sometimes used.[71] More often, however, ΔW is calculated with the Buckingham potential.[61,62,64-69]

b. Applications

Let us show some typical applications of the HMO based conformational analysis.

Neglecting ΔE_σ, Adrian[60] estimated the twisting of the central bond in biphenyl (20–30°), *cis*-stilbene (30–40°), and *cis*-azobenzene (40°). Stegemeyer and Rapp[69] searched for a stable conformation of aryl ethylenes like stilbene. Wettermark and Schor[61] determined the optimal conformation of 1,4-diphenylbutadiene-1,3. Goodwin and Morton-Blake[62] evaluated the parameters of nonbonded interactions between two hydrogen atoms from the known angle of twist of the central bond in biphenyl (42°). Allowing for a variation of the bond length of the twisted bond and evaluating corresponding corrections ΔE_σ and ΔE_π, Gamba, Rusconi, and Simonetta[70] estimated the stable conformation of 1-phenylnaphthalene, 2-phenylnaphthalene, 1-(1′-naphthyl)naphthalene, 1-(2′-naphthyl)naphthalene, and 2-(2′-naphthyl)naphthalene. The hard-sphere model was used by Chapman and Schaad[71] in their discussion of ortho derivatives of biphenyl. Their purpose was to find a relationship between the bond length of the central bond and the appropriate angle of twist. The dependence they found is not in agreement with experiment.

c. Polansky's Method

An atypical application of the Hückel method was suggested by Polansky.[63] He estimated the change in the π-electron energy with the aid of the Hückel method in a standard way. However, the change in the remaining energy was evaluated with the point charge model

$$V = c\sum_{i<j}\sum 1/R_{ij} \tag{25}$$

If the distances are measured in ångströms, the optimal value of C is 0.89. The method was applied to biphenyl, o- and p-terphenyl, butadiene, tetraphenylmethane, and triphenylmethyl. The author obtained a satisfactory estimate of angles of twist and barriers.

d. Self-Consistent HMO Based Conformational Analysis

According to Longuet-Higgins and Salem's theory,[72] the resonance integral should depend exponentially on R_{ij}, the bond length R_{ij} being related to the mobile bond order p_{ij} by

$$R_{ij} = a - bp_{ij} \qquad (26)$$

R_{ij}'s are always estimated from p_{ij}'s of the preceding iteration. If nothing is changed in two subsequent iterations, the results are self-consistent.

In the self-consistent HMO based conformational analysis,[64–68] resonance integrals depend both on R_{ij} and ϑ_{ij} (eq 22) and the linear relation (eq 26) is replaced by a generalized one

$$R_{ij} = a - bp_{ij} \cos \vartheta_{ij} + \frac{b}{2g\beta_{ij}(R_{ij},0)} \sum_{k} \frac{dW_k(R_k)}{dR_k} \frac{\partial R_k}{\partial R_{ij}} \qquad (27)$$

where k runs over all pairs of nonbonded atoms. Corrections of valence angles and small out-of-plane coordinates are carried out with the aid of harmonic field approximation. Large twisting angles follow from the condition of minimum of $E_\pi + W$. The results are made self-consistent with respect to all varied parameters.

The self-consistent HMO based conformational analysis was applied to *cis*- and *trans*-butadiene,[65] to neutral and ionic biphenyl,[66,67] and to *cis*- and *trans*-stilbene.[68] In the case of *trans*-butadiene, where the structure is known from the electron diffraction analysis, the agreement with experiment is surprisingly high. A good agreement with experiment was also obtained for barriers and isomerization energies.

2. PPP Based Analysis

a. General Principles

Classification of methods based on the Pariser, Parr, and Pople π-electronic theory[59] can be put on the same line as in the case of the Hückel method. Again the validity of eq 20 is assumed. The change ΔE_σ is either neglected[73–76] or approximated with the harmonic field model.[77] The change ΔW is either neglected or approximated with the central-field model.[74–77] Sometimes $E_\sigma + W$ is replaced by an "effective nuclear interaction"

$$\sum_{r<s}\sum Z_r Z_s / R_{rs}$$

Z_r and Z_s being equal to 1 in the case of carbon atoms.[73]

Molecular orbitals are derived in an iterative way in what is called the SCF LCAO MO scheme.

In the PPP theory of closed-shell systems, the π-electron energy follows from the formula

$$E_\pi = 2 \sum_{i}^{\text{occ MO}} e_i - \frac{1}{2} \sum_{i}^{\text{at.}} \sum_{j}^{\text{al.}} (q_i q_j - \frac{1}{2} p_{ij}{}^2) \gamma_{ij} \qquad (28)$$

where the first sum is a sum of orbital energies of all π-electrons and the second sum represents a correction due to π-electron interaction energy. The quantity q_i is the average number of π electrons at atom i, p_{ij} is the mobile bond order between atoms i, j, and γ_{ij} is the Coulomb interaction energy of two $2p_\pi$ electrons, one being at atom i and the other one at atom j. By definition $p_{ii} = q_i$.

The PPP method contains more empirical parameters than the Hückel method. There are also several different ways of estimating the Coulomb integrals γ_{ij}: the Mataga–Nishimoto formula,[78] the Ohno formula,[79] a combination of them,[80] the uniformly charged spheres model,[59] and the point charge model.[73] In a most recent method of conformational analysis,[81] a variable electronegativity version of the PPP method is used, due to Brown and Heffernan.[82] Almost all authors use a small variant of the original method. A good review of all of these variants can be found in review articles[83,84] and books.[59]

b. Applications

Borrell and Greenwood[73] analyzed the dependence of ΔE on the twist angle of the central bond in stilbene. In an interesting analysis, they considered both the ground state and some excited states. Concerning the relative stability of isomers, the model is crude, however. It predicts that *cis*-stilbene is more stable than *trans*-stilbene, in contrast with experiment. Better agreement with experiment was obtained Fischer-Hjalmars[74] considering the internal rotation in biphenyl and the isomerization of butadiene. Imamura and Hoffmann[75] investigated the conformation of biphenyl in the ground state and in selected excited states. They investigated also the conformation of fulvalene and dicyclobutadiene. A modification of the PPP method which is of particular value for conformational studies was elaborated by Dewar, *et al.*[85,86] The method was used by Dewar and Harget[76] for evaluating the barrier of rotation in butadiene and biphenyl and the isomerization energy of butadiene.

Franchini, Sbrana, and Bossa[87] calculated the isomerization energy of 2,2′-bipyridyl and 5,5′-biisoxazole. These authors criticize strongly PPP based conformational analysis. They claim that the results depend significantly on the degree of approximation of the theory. However, using different modifications of the theory, they did not change the empirical parameters. This seems to be a weak point of their critique.

In many cases PPP based conformational analysis yields rather satisfactory results. There are, however, exceptions, as in the case of the relative stability of isomers of stilbene[73] or in the case of the barrier of internal rotation in butadiene.[74]

A good example of a proper approach to conformational analysis is the work of Van-Catledge and Allinger.[77] It deals with [18]annulene, the conformation of which was a subject of dispute for several years.[56,77,88] On one hand, they minimize the strain energy estimating ΔE_σ with the Hooke model and ΔW with Hill's potential.[7] On the other hand, they compare the calculated and observed spectrum in the uv region. Considering five different conformations they have found that optimal results are obtained for a planar conformation with alternating bond lengths in the ring.

c. Allinger and Sprague's Method

A useful method was worked out by Allinger and Sprague.[81] The principles of their method are as follows. From input data they calculate the molecular geometry and assign all semiempirical parameters which do not depend on bond orders. Then a VE SCF calculation is undertaken, the variable electronegativity version of the PPP method. The resulting bond orders are used to assign stretching parameters. If the molecule is nonplanar, the direction cosines of the $2p_\pi$ orbitals are estimated and a second VE SCF calculation is undertaken in order to obtain bond orders suitable for establishing torsional constants. The steric energy is then minimized with respect to geometry as in the classical scheme. If the geometry has been changed significantly during the minimization, VE SCF calculations are repeated and the new bond orders are used to assign new stretching and torsional parameters.

The minimization VE SCF cycle is repeated until self-consistency is reached.

The method was applied to many simple hydrocarbons like butadiene, benzene, biphenyl, and naphthalene and also to more complicated systems such as o-di-*tert*-butylbenzene, pregeijerene, the annulenes, and bridged annulenes. The agreement with experiment was generally good.

3. MIM Based Analysis

In a few cases the original Pariser, Parr, and Pople theory is replaced by the "molecules in molecules" (MIM) theory, applied to biphenyl first by Longuet-Higgins and Murrell.[89] Gamba, Tantardini, and Simonetta[90] studied the conformation of biphenyl again with this method, applying a CI limited to singly excited configurations and including stretching energy of σ bonds and the nonbonded interaction energy. Both the ground state and some excited states were studied. Agreement with experiment was good.

III. Uniform Methods

In this chapter we are going to review methods which deal with quantum-mechanical calculations for all or at least all-valence electrons.

Most methods are based on the concept of molecular orbitals and the SCF theory.[59] Molecular orbitals $\psi_1, \psi_2, \ldots, \psi_n$ are expanded in terms of a certain set of atomic orbitals $\varphi_1, \varphi_2, \ldots, \varphi_N$

$$\psi_s = \sum_i c_{is}\varphi_i \tag{29}$$

In the case of closed-shell systems, the expansion coefficients c_{is} and the orbital energies of electrons follow from the set of secular equations

$$\sum_j c_{js}(F_{ij} - e_s S_{ij}) = 0, \qquad i = 1, 2, \ldots, N \tag{30}$$

where S_{ij} is the overlap integral

$$S_{ij} = \int \varphi_i^* \varphi_j \, \mathrm{d}V \tag{31}$$

and F_{ij} is an element of the matrix of what is called the Hartree–Fock operator

$$F_{ij} = f_{ij} + \sum_{k,l} p_{kl}(G_{ij,kl} - \frac{1}{2} G_{il,kj}) \tag{32}$$

where

$$f_{ij} = \int \varphi_i^*(\hat{T} + V_{el-n})\varphi_j \, \mathrm{d}V \tag{33}$$

$$p_{kl} = 2\sum_{s=1}^{N/2} c_{ks}^* c_{ls} \tag{34}$$

$$G_{ij,kl} = \int\int \varphi_i^*(r_1)\varphi_j(r_1)\frac{e^2}{r_{12}}\varphi_k^*(r_2)\varphi_p(r_2)\, \mathrm{d}V_1 \mathrm{d}V_2 \tag{35}$$

$\hat{T}$ being the kinetic energy operator of an electron and V_{el-n} the Coulomb interaction energy of the electron at a fixed position with the set of all nuclei. The total energy is then

$$E = \sum_{s=1}^{N/2} e_s + \frac{1}{2} \sum_{k,l} p_{kp} f_{kp} + V_{n-n} \tag{36}$$

where the last term represents the Coulomb repulsion energy of nuclei or the atomic cores (nuclei and inner shells).

The SCF MO theory is based on the independent particles model. It neglects what is called the correlation energy of electrons. The theory can be improved, in principle, by what is called configuration interaction (CI).[59] Suppose that $\psi_1{}^2\psi_2{}^2 \ldots \psi_n{}^2$ is the ground-state configuration according to the SCF MO theory. Assigning to one of the electrons, being described so far by orbital ψ_a, a virtual orbital ψ_x, we obtain a singly excited configuration $\psi_1{}^2\psi_2{}^2 \ldots \psi_a{}^1 \ldots \psi_n{}^2\psi_x{}^1$. There is a wave function related to this configuration, of a given total spin. In a similar way we can construct doubly, triply, and higher excited configurations and relate them to definite wave functions. In the CI method it is assumed that the correct total wave function is a superposition of wave functions of all possible configurations.

CI is highly important for conformational studies of excited states. In the case of the ground-state conformation, the SCF MO theory is believed to be satisfactory except for some unusual cases. In other words, the correlation energy is assumed to be independent of the detailed structure of the molecule. This is definitely a wrong assumption if one of the conformers is a closed-shell system and the other one an open-shell case.

A. Semiempirical Conformational Analysis

Practical application of the SCF MO theory is limited by the capabilities of computers. To reduce the computer time and to extend the range of application, many numerical simplifications are introduced, and integrals are often replaced by semiempirical parameters. Most drastic simplifications are introduced in what is called the extended Hückel theory (EHT).

1. EHT Based Analysis

a. General Principles

Let us consider the secular equations 30. In EHT the overlap integrals S_{ij} are calculated theoretically for Slater-type atomic orbitals. The diagonal element of the Hartree–Fock operator, F_{ii}, is approximated by the negative value of the valence orbital ionization potential (VOIP). Off-diagonal elements are approximated by the Wolfsberg–Helmholz formula

$$F_{ij} = \frac{1}{2}(F_{ii} + F_{jj})KS_{ij} \tag{37}$$

where K is an empirical parameter. According to Hoffmann[91] $K = 1.75$. It is assumed that

$$E \sim 2\sum_{s=1}^{N/2} e_s \tag{38}$$

where the total energy E is supposed to include the repulsion energy of atomic cores.

Hoffmann was the first to apply EHT to conformational studies of organic molecules.[91-99] The theoretical basis of EHT was analyzed by Ehrenson[100,101] and Allen and Russell.[102]

Despite many successes of this theory, it is safe to say that the method can yield disappointing results. A simple example is the water molecule. According to EHT the molecule should be linear.

b. Applications

In older works, Hoffmann investigated the conformations and the rotational barriers for molecules such as ethane, propane, butane, isobutane, pentane, etc. In a subsequent paper he analyzed the isomerization of diazirine and diazomethane in several excited states.[99] Barriers to rotation around a single bond have been analyzed for RCHO molecules, where R = cyclopropyl, vinyl, phenyl, isopropyl and cyclobutyl.[97] The relative stabilities of radicals and anions of allylic systems, and of polyenes in excited states were discussed by Hoffmann and Olofson.[103] They have found that in an excited state, or in the anion, a weak bonding can appear between two fragments of the molecule which are not bonded in the ground state. In other work Hoffmann, *et al.*,[104] carried out a conformational analysis of the ground state and several excited states of derivatives of methylene: methyl-, dimethyl-, phenyl-, diphenyl-, vinyl-, formyl-, nitro-, cyclopropyl-, cyano-, dicyano-, fluoro-, difluoro-, chloro-, dichloro-, bromo-, dibromo-, trifluoromethyl-, and methoxymethylene. Other derivatives of methylene have also been investigated using this method.[105] The energetics of the isomerization R–CN $\rightleftarrows$ CN–R was studied, where R = H, CH_3, and C_6H_5, as well as the conformation of the corresponding isomers in the ground state and in the excited states.[106] In the ground state both conformations are linear, and in the first excited state both are angular. The optimal conformations of phenyl, diphenyl, and triphenylcarbonium ions, radicals, and anions, of phenyl-, diphenyl-, and triphenylcyclopropenium cations, and of phenylcyclopentadienide anion, phenyltropylium ion, and phenylallyl and phenylpentadienyl species were also studied.[107] According to EHT, there exists one only stable conformation of triphenyl carbonium ion: its shape is that of a propeller. Scholz and Köhler looked for a stable conformation of *exo*-methylenecyclopentane and 1-methylcyclopentene.[108] van der Meer determined the stable conformation of propylene, methylallene, and methylketene.[109] General agreement with experiment was good except for two valence angles in methylketene.

The results of EHT calculations may depend on the choice of the exponent (effective nuclear charge) in Slater-type atomic orbitals. The effect of such a variation on the isomerization energy of acetaldehyde and propionaldehyde was investigated by Köhler.[110] The effect is not negligible.

Long and Goldstein investigated the internal rotation in nicotinamides and benzamide.[111] Also the following systems of some biological interest have been discussed: 5′-adenosine monophosphate[112] and 5-hydroxytryptamine.[45]

The extended Hückel method was applied to estimate the structure of the activated complex.[113] Molecular complexes such as naphthalene–tetracyanoethylene and anthracene–trinitrobenzene[114] have also been investigated with this method. Systems with hydrogen bonds have been studied: pyridine–water and pyridine–methanol.[115] According to EHT, the first system should be planar and the hydrogen bond linear. Murthy, Davis, and Rao discussed the association of methanol and formic acid.[116]

In most cases EHT based conformational analysis yields valuable results. Another positive example is the calculation of the barrier to internal rotation in substituted ethanes, reported by Pachler and Tollenaere.[117] The point is, however, that the predictions are not always adequate. Herndon and Feuer claim that even qualitative agreement with experimentally evaluated barriers is not always obtainable, especially if the molecular species are relatively large or contain heteroatoms.[118] Extremely poor bond lengths and valence angles were obtained by Schmid and Hallman in the case of methyl fluoride.[119] The EHT (as well as MINDO/2)-type calculations fail to predict correctly the conformational behavior of ethylbenzene.[120] An evident fallacy in the EHT results is the prediction of a wrong conformation of monofluoroacetic acid.[121]

2. Conformational Applications of CNDO, INDO, MINDO, and NDDO Methods

a. General Principles

Let us consider the secular equations 30 again. In more advanced treatments, elements of the Hartree–Fock operator, F_{ij}, are considered explicitly. However, to do so, one requires roughly $N^4/8$ integrals $G_{ij,kl}$. In the case of naphthalene, N = 48 if inner shells are neglected or 68 otherwise. The number of integrals is thus of the order of a million. Therefore, many numerical approximations are usually introduced. First of all, only valence electrons are considered explicitly. The nuclei and the inner shells are considered as unpolarizable cores. The most radical approximation, however, is introduced by the zero differential overlap approximations. The last simplification can be introduced to different extents: (i) in the CNDO method $\varphi_i(r)\varphi_j(r) = 0$ except for $i = j$; (ii) in the NDDO method $\varphi_i(r)\varphi_j(r) = 0$ for $i \neq j$, provided orbitals φ_i and φ_j are atomic orbitals of different atoms; (iii) in the INDO method approximation i is introduced in the case of integrals $G_{ij,kl}$, where orbitals φ_i, φ_j, φ_k, and φ_l refer to the same atom. In the case of all remaining integrals the approximation ii is assumed.

Approximations i–iii are not introduced in the case of core integrals, f_{ij}.

CNDO means complete neglect of differential overlap; NDDO, neglect of diatomic differential overlap; and INDO, intermediate neglect of differential overlap. Many of the remaining integrals are estimated semiempirically, leading to various versions like CNDO/1, CNDO/2, CNDO/BW, MINDO (modified INDO), MINDO/2, etc.

Obviously, the results of a calculation should not depend on the choice of coordinate system or on the assumed starting hybridization. To ensure this invariancy, additional serious approximations are required, like independency of Coulomb interactions on the type of atomic orbital s, p_x, p_y, or p_z. This additional requirement is necessary in the case of CNDO- and INDO-type schemes.

Details of these methods can be found in books.[122] The CNDO method is due to Pople, Santry, Segal, and others,[123-126] the INDO method to Pople, Beveridge, and Dobosh,[127] the NDDO method to Pople, *et al.*,[123,126] and to Sustmann, Williams, Dewar, Allen, and Schleyer,[128] and the MINDO method to Baird, Dewar, and Sustmann.[129,130] Highly valuable in conformational analysis is also the version CNDO/BW of Boyd and Whitehead.[131]

b. Review of Applications of the CNDO Method

There are a considerable number of references concerned with the CNDO-type conformational analysis. Using the CNDO/2 method, Tinland investigated the twisting of the central bond in biphenyl. Unfortunately the calculated angle (90°) is far from the experimental one (42°).[132] Gordon discussed the conformations and barriers for internal rotations of ethane, methylamine, methyl alcohol, fluoro-substituted propenes, and fluoro-substituted ethanes.[133] In his opinion, the estimate of the barrier is correct if the interaction between strongly electronegative atoms in the molecule plays a secondary role. The angle between the two rings in 2,2′-bipyridyl and 5,5′-biisoxazole was discussed by Bossa, Ramunni, and Franchini.[134] Their results are not very satisfactory, however. According to Olsen and Kang's calculations, the endo conformation of acetanilide is more stable than the exo one by 1.2 kcal/mol.[135] The isomeric *cis*- and *trans*-stilbenes were analyzed by Ljunggren and Wettermark. Their results are hardly satisfactory, however. They predict that the cis form should be more stable than the trans one, in contrast to experiment. The predicted barrier of isomerization is three times too large. The minimum energy corresponds to the form with the phenyl rings twisted by 90°. The phenyl rings are predicted to be essentially free to rotate, however.[136]

According to Grimison, the phenanthrene molecule should be planar.[137] From X-ray data it is known that it is not.

Wagner made some CNDO, INDO, and *ab initio*-type calculations for the barriers of internal rotation in N_2H_4, N_2F_4,[138] P_2H_4, and P_2F_4.[138] The *ab initio* results appeared to be definitely the best. The author expresses doubt as to whether the CNDO method is applicable at all to conformational problems and molecules of this type. Recently, however, successful calculations for $(CH_3)_2SO_2$ and $(CH_3)_2SO$ have been reported.[139,140] Calculated barriers of rotation of methyl groups, 3.65 and 3.5 kcal/mol, compare favorably with the experimental values, 3.4 and 2.8 kcal/mol.

The list of molecules for which conformations have been studied with the CNDO method is quite long. Some further examples follow: ethylene in the ground state, in excited state, and in the ionized state;[141] formaldoxime ($H_2C{=}N{-}OH$),[142] cyclobutane,[143] H_2CO, HCN, and CH_2CO for the singlet excited states;[144] formyl radical and formaldehyde for the ground state and the lowest excited state;[145] preferred conformations of 1,1-dimethylhydrazine and 1,1-dimethylhydrazine–borontrifluoride complex;[146] barrier to internal rotation in bispyridine halogen cations;[147] preferred conformations of $(CH_3)H_2P{\cdot}BH_3$;[148] conformations of croconic acid and its derivatives;[149] geometrics and barriers to internal rotation of glycine and its zwitterion;[150] preferred conformations and rotational barriers of methylcyclopropane, cyclopropylamine, and cyclopropylphosphine;[151] torsional angles in acetylcholine;[152] structure of cyanamide and barrier to inversion;[153] bond angles in the uronium ion;[154] and even a Dewar structure of benzene.[155]

In several cases molecular systems with a hydrogen bond have been studied. Applying the CNDO and the INDO methods, Jakubetz and Schuster[156] analyzed the energetics of the systems HF–benzene and HF–pyridine. Schuster and Funck[157] determined the energies of six conformers of the dimer of the formic acid. Schuster[158] also investigated other systems of this type: formaldehyde–water, formic acid and its dimer,[158] β-hydroxypropionaldehyde, enol form of malonaldehyde,[159] H_2CO–NH_3, H_2CO–HF, pyridine–HF, etc.[160] The pyrrole–H^+ system was discussed by Heidrich and Grimmer[161] for various positions of the proton. Three local minima were found, with the proton being above one of the C–C bonds. Köhler analyzed acetaldehyde[162] and the hydrogen bond in the formic acid dimer.[163] Configurational analysis for hydrogen-bonded systems like methanol, formic acid and hydrogen maleate ion was carried out by Morita and Nagakura.[164]

In almost all cases cited the authors used the CNDO/2 version of the method. A weak point of this version is that it was not optimized for the purpose of conformational analysis. A better reproduction of experimental valence angles and bond lengths is obtainable in the case of hydrocarbons with the CNDO/FK version of Fischer and Kollmar.[165] A definitely better agreement with experiment with respect to valence angles and bond lengths in small molecules is obtainable also with the CNDO/BW version of the method published by Boyd and Whitehead.[131]

c. Applications of the INDO and MINDO Methods

INDO-type conformational studies are not extensive. Many authors do not see any superiority of this method in a conformational study in comparison to CNDO. In a work which has become almost classical, Gordon and Pople[166] applied the method with success to the structural analysis of AH_2, AHF, AF_2, AH_3, AHF_2, AF_3, CH_nF_{4-n}, XAB, X_2AB, XAAX, X_2ABY, X_2AAX_2, X_3ABY, X_3ABY_2, and X_3ABY_3, where A, B = C, N, or O and X, Y = H or F. A good contrast regarding the complexity of molecules which may be treated by this method is the conformational study of hydroxytryptamine.[167] This is an example of a molecule, the conformation of which can be hardly determined with methods of the classical stereochemistry. The question of ring opening was discussed by Olsen, *et al.*, for cyclopropanone[168] and methylenecyclopropane.[169] In contrast to EHT-type calculations, the authors obtained good agreement with the experimental results.

Extended INDO-type studies were carried out by Pelissier, *et al.*, for cyclopropylcarboxaldehyde,cyclopropyl methyl ketone, and 2-methylcyclopropyl methyl ketones,[170] for methylcyclopropane, cyclopropylamine, and cyclopropylphosphine,[171] and for bicyclopropyl.[172] Similar calculations were performed by Danen[173] for the preferred conformations of isobutyl, cyclopropylcarbinyl, and oxirylcarbinyl cations, radicals, and anions.

Conformational studies of acetylcholine were performed by Froimowitz and Gans.[174] The authors observe a difficulty in the INDO method in that it allows nonbonded atoms to approach to almost within bonding distances.

In the MINDO method, the semiempirical parameters have been chosen such as to optimize the ground-state properties. No wonder, therefore, that results obtained by the MINDO method are often better than in the case of the CNDO and INDO methods. The method was applied with success for the evaluation of strain energies of several molecules such as cyclopropane, cyclobutane, cyclopentane, bicyclobutane, spirohexane, etc.[175] In another paper the author estimated the stabilization energy due to hyperconjugation in propene, 1-butene, isobutylene, 1,3-pentadiene, acetaldehyde, ethyl cation, and isopropyl cation.[176] It appeared that this energy is about 4% of the C–C bonding energy. Shanshal also obtained better agreement with experiment than in the case of other methods for the rotational barrier in the cyclopropylcarbinyl cation.[177] In contrast to EHT, this method predicts properly the stable conformation of cyclopropanone.[178] The CNDO/2-type calculations of bond lengths of croconic acid have been rather satisfactory,[149] yet the results obtained with the MINDO/2 method[184] are still better.

d. On the NDDO Method

In principle the NDDO method should yield better results than methods of the CNDO or INDO type because the approximations are less drastic. In practice this is not necessarily so. Davidson, Jorgensen, and Allen[179] carried out a detailed analysis for methane, ethane, ethylene, acetylene, propane, cyclopropane, propene, benzene, butane, cyclohexane, butadiene, and 2-butene, using both the CNDO and the NDDO methods. The NDDO method yielded slightly better results for the geometrical parameters, but rather poorer results for isomerization energies, barriers to rotation, dipole moments, and force constants. However, this may be a matter of parametrization. Another conclusion was drawn by Köhler and Birnstock in their study of the formic acid.[180] For the trans to cis barrier, they obtained 5.32 kcal/mol from the CNDO method, 7.35 from INDO, and 13.42 from NDDO. The last value is closest to the experimental value, 10.9 kcal/mol. The estimate of the isomerization energy also improves in the same order: CNDO, 1.27 kcal/mol; INDO, 1.76 kcal/mol; NDDO, 2.65 kcal/mol.

e. Reliability of EHT, CNDO, INDO, and MINDO Methods

The reliability of a quantum-mechanical conformational analysis should obviously increase in the following order: EHT, CNDO, INDO, MINDO, NDDO. In general, indeed, the EHT method seems to be the least reliable one. Several examples have been given in preceding sections. Let us add some more. Tetrahedrane is predicted to be much more stable than cyclobutadiene,[181] in contrast to extended *ab initio* calculations.[182] In contrast to CNDO/2-type calculations, the EHT predicts a wrong stable conformation for cinnamic acid.[183] On the other hand, the intra-ring angle in biphenyl is somewhat better in the case of the EHT method (60°)[75] than in the case of the CNDO/2 one (90°).[132] The experimental value is 42°.

Several examples already have been cited to show that the agreement with experiment improves indeed when passing to more advanced treatments.

All things considered, the safest approach is to study a conformational problem simultaneously with two or even more methods. An example is the work of Yan, *et al.*,[185] who studied the rotational barriers in formamide, *N*-methylformamide, *N,N*-dimethylformamide, acetamide, *N*-methylacetamide, *N,N*-dimethylacetamide, and acetyl-1-prolinamide. A second example is the work of Bossa, *et al.*,[186] who studied the conformation of the three amino terminal peptides: $NH_3^+CH_2CONHCH_3$, $NH_3^+CH(CH_3)CONHCH_3$, and $NH_3^+CH_2CON(CH_2)_4$. The agreement with X-ray results was good in the last case. A third example is given by Hoffmann and Swenson,[187] who studied the conformation of benzophenone and benzaldehyde in the ground state and in the first excited state (n,π^*), and compared the results of EHT-type calculations with those of CNDO.

3. *Applications of the PCILO Method*

The methods described so far have been based on the SCF-LCAO MO scheme. In rare cases a CI calculation was added, usually when studying an excited state. Thus the methods just described do not consider the role of the correlation energy. An alternative treatment is possible within the PCILO scheme, the perturbative configuration interaction using localized orbitals.[188-191] In this method one starts with a set of localized bonding and antibonding molecular orbitals. In the next step, one makes a perturbational treatment of configuration interaction to a rather high order, disregarding, however, the condition that a wave function should be an eigenfunction of a square of the total spin, $\hat{S}^2$.

The method can be used with approximations carried out in many different ways. Usually it was used in combination with the CNDO/2 scheme. In such an approximation it was applied to conformational studies of large molecules, such as acetanilide,[192] acetamide, *N*-methylformamide, *N*-methylacetamide, dipeptides,[193] glycyl and alanyl residues,[194] seryl and threonyl residues,[195] maltose, cellobiose and sucrose,[196] retinal and β-ionylidenecrotonic acid,[197] molecules related to vitamin A,[198] and others.[199-201] The agreement with experiment is in general satisfactory.

B. Nonempirical Analysis

In any semiempirical analysis it is necessary to assume some properties of the molecules in order to predict other properties. No such defects are present in nonempirical quantum-mechanical treatments. This does not mean their predictions are necessarily correct. SCF MO calculations neglect the correlation energy. Configuration interaction, even if included, must be limited to a few electronic excitations. The calculations are very time consuming and expensive. Nevertheless, the number of nonempirical *ab initio* conformational studies which have been reported is increasing very rapidly. Good progress has been made owing to the development of modern computers and an improvement in numerical techniques. Here is an example taken from an article by Clementi.[202]

In order to carry out SCF MO calculations for N_2 in 1955, Scherr needed 5.25×10^5 min. Analogous calculations on a first-generation computer Univac-1103 required 3×10^3 min. Using a second-generation computer IBM-7094, it was possible to obtain the results in 2×10^{-2} min. Thus within 10 years the time of computation was shortened by a factor of greater than 20 million. On a third-generation computer, like the IBM 360/195, the gain in time would be still more impressive. Also, owing to a better organization of the computational scheme, it was possible[202] to reduce the computer time by a factor of 10.

Thus nonempirical conformational analysis although much more limited than semi-empirical quantum-mechanical or classical methods of analysis, has become an important tool in organic stereochemistry.

Several different expansions of molecular orbitals are used in *ab initio* calculations:

(a) Expansions into Slater-type atomic orbitals of the atoms in question.

(b) Expansions into 3–5 times larger set of Cartesian Gaussian orbitals divided in what are called *contracted sets.*

(c) Expansions into 1s-type Gaussian functions in what is called the Gaussian lobe function approximation (in this approximation each branch of a p-type atomic orbital is expanded into 1s-type Gaussian functions independently, the expansion coefficients being related, however, through the antisymmetry property).

(d) Expansions into 1s-type Gaussian functions put somewhere in space (instead of centered on the atoms) in order to minimize the total energy, in what is called the floating spherical Gaussian orbital model; σ bonds, for example, are approximated by 1s-type Gaussian functions localized between the two bonded atoms.

(e) Other expansions. The most rapidly convergent is the expansion into Slater-type atomic orbitals. However, there are significant difficulties in a rapid calculation of appropriate integrals. No such problems appear in the case of the Gaussian-type basis. Unfortunately, however, much larger expansions have to be used in this case. Gaussian functions can be used with a hydrogen-like angular part of an atomic orbital (Cartesian Gaussians) or in the Gaussian lobe function approximation. The programming in the last case is much simpler. Concerning the computer time, it is hard to say which method is to be preferred. Concerning the results, both methods seem to be equivalent.

(i) Slater-type basis. Except for diatomics, very few structural studies have been performed in this basis. Notable exceptions are the study of the rotational barrier in ethylene[203] and the optimization of the structure of ethane.[204] In the last case it was found that optimization of the structure during the twisting of the central bond has almost no influence on the calculated barrier of rotation. The calculated barrier was in a good agreement with experiment.

(ii) Cartesian Gaussian-type basis. Calculations with this basis have been mostly performed using one of the versions of the IBMOL program,[205-214] POLYATOM,[215,216] or MOLE.[217] Investigated were some conformational problems of methylenimine ($H_2C{=}NH$),[206,209] $HN{=}NH$,[206] $HN{=}C{=}NH$,[206] aziridine,[207] oxaziridine,[207] vinyl anion,[209] ethane,[211,219] 1,3-butadiene,[212] cyclopropylamine,[213] glyoxal,[214] propylene,[215] allene,[216] formic acid,[217] propene and fluoropropene,[218] and acetaldehyde.[219] The list is thus quite long already. Agreement with experiment is usually good.

(iii) GLF-type basis. The pioneers of Gaussian lobe functions calculations are Buenker and Peyerimhoff.[220-222] Investigating CO_2 and some other simple molecules, they searched for a dependence between the orbital energies of electrons and the structural parameters of the molecule. They succeeded in finding such a dependence in the case of valence angles but not in the case of bond lengths.

Certain conformational problems like barriers, isomerization energies, bond angles, and relative stability were studied with this method, usually for the ground state, in some cases for excited states. In few cases an extended CI calculation was performed. The analysis was concerned with the following systems: ethylene,[223] allene,[223,224] *cis*- and *trans*-butadiene,[225,226] reaction path between cyclobutene and *cis*-butadiene,[227] cyclopropene and methylacetylene,[224] allyl cation, radical and anion,[228] cyclopropane,[229] cyclobutadiene,[182,230] tetrahedrane,[182] two conformations of $C_2H_6^{2+}$,[231] formaldehyde,[232] formic acid[233] and its anion,[233,234] ozone,[234,235] glyoxal,[236] and cyclopropenyl cat-

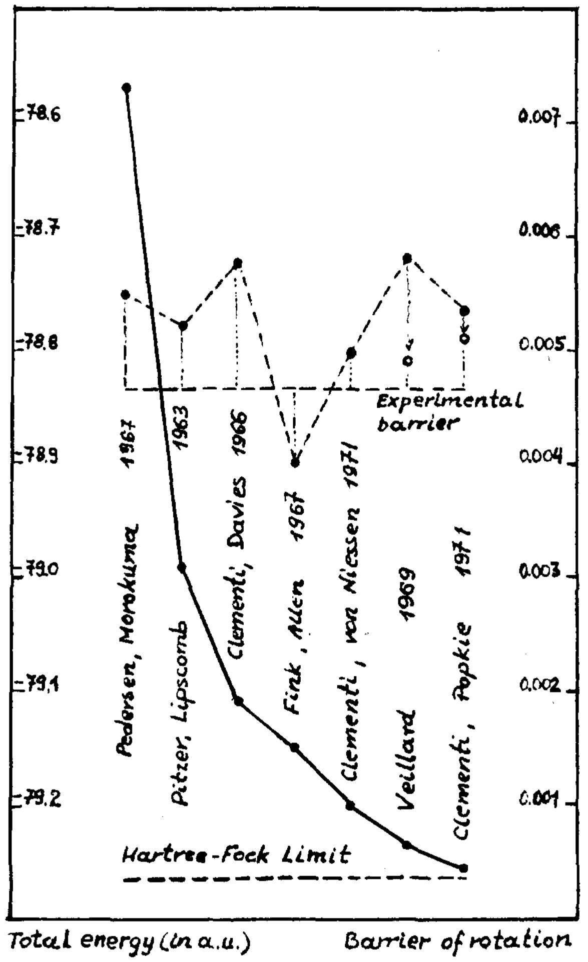

Figure 2. Computed total energy and barrier of rotation for ethane.

ion, anion, and radical.[237] Owing to the limited space of this review we are unable to discuss these applications in detail. We wish to pay attention to one somewhat peculiar result, however. According to these calculations, carbon atoms in cyclopropane do not form an equilateral triangle but rather an isosceles one with one angle about 65°.

(iv) STO-3G scheme. In some recent nonempirical conformational studies the Slater-type orbital (STO) basis is used. However, to simplify the calculation of most molecular integrals, a short expansion of Slater-type orbitals into three Gaussian-type functions is used. In this way the geometry and the energetics were investigated for molecules such as propane, allene, cyclopropene, propene, cyclopropane,[238] CH_4, C_2H_6, C_2H_4, C_2H_2, CNH_5, CNH_3, CNH, COH_4, COH_2, CFH_3, etc.,[239] HCN dimer and trimer,[240] 1,2-disubstituted ethanes ($-CH_3$, $-NH_2$, $-OH$, $-F$),[241] and trisubstituted methanes.[242] It is perhaps worthwhile to note that unlike CNDO/2, this small *ab initio* basis predicts the correct geometry for the HCN dimer.[240]

Somewhat similar to the STO-3G idea is the Gaussian function mixed basis scheme. In this scheme large expansions are used for integrals of expected large absolute value, and small expansions in the case of remaining integrals.[243] This method was, however, criticized recently.[244]

(v) The FSGO model. Most calculations with this model dealt with hydrides of the second row.[245-248] Also the following organic molecules were studied with this simple method: methane, ethane, ethylene, acetylene, cyclopropane,[249] and 1,4-dioxadiene.[250] In the case of hydrocarbons, bond lengths and bond angles were obtained with average absolute deviations of 1.7 and 1.0%, respectively, from observed values.

The method seems to be oversimplified. Nevertheless, in the case of BH_3-NH_3 and B_2H_6, the authors of this method obtained a slightly better estimate of bond lengths than Peyerimhoff and Buenker in a more extended calculation.[231,251]

(vi) The molecular fragment method. Newton, Boer, and Lipscomb[252-255] suggested a simplified version of the SCF LCAO MO method. They suggest that elements of the Hartree-Fock operator F_{ij} for a large molecule be estimated by analogous quantities for small molecules (fragments). This method was applied by Bushweller, Stevenson, Golini, and O'Neil to calculate the optimal conformation and the barrier to rotation around the CN bond of urea, formamide, thioformamide, selenoformamide, and carbamic acid.[256] Agreement with experiment was qualitative.

A different realization of the molecular fragment method was suggested by Christoffersen.[257] He starts with Frost's FSGO model and passes to delocalized molecular orbitals through a linear combination of FSGO's. The method was applied to the conformational study of acetylcholine.[258]

IV. Final Comments

As follows from the review, considerable progress has been made in the theoretical conformational analysis of organic molecules. Unfortunately, however, results obtained in semiempirical treatments are not always adequate. Although much has been done already, the methods still have to be improved.

The *ab initio* treatments seem to be promising. However, they must be limited to relatively small molecular systems. Even then it is not so easy to obtain exact results concerning the barriers or relative stabilities. The reason is that the quantity we are looking for is a small difference between two large energies. A good example is the case of ethane in the SCF MO approximation. It is illustrated in Figure 2. With a continuous line are connected points which refer to the total energy of the eclipsed configuration, according to various authors. The broken line shows a corresponding estimate of the barrier to internal rotation. In the case of open circles the conformation of the twisted molecule was optimized and in the case of full ones—not. Apart from some minor changes, the figure was taken from an interesting article published by Clementi.[202] It seems to follow from the figure that the error of the estimated barrier is somewhat independent of the accuracy of SCF MO type calculations. The error is smaller, however, if the remaining structural parameters are optimized also for the twisted case.

We hope to have given a satisfactory illustration of the present day state of the theoretical conformational analyses of organic molecules. These methods are important not only in that they estimate ground-state and excited-states conformations, barriers, and isomerization energies, but they also give a physical insight and help to understand the genesis of barriers and intermolecular strains. Such an analysis is outside the scope of this review, however.

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