CROATICA CHEMICA ACTA CCACAA 57 (5) 901—910 (1984)

YU ISSN 0011-1643
CCA-1501 UDC 541
Original Scientific Paper

Chemical Fragmentation for Molecular Orbital Calculations on Proteins

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Received January 16, 1984

The conceptual and mathematical basis of a molecular orbital method which enables the calculation of conformational energy changes and other properties of proteins, is presented. The information inherent in the chemical formulae of the polypeptide backbone and side chains is maximally exploited. A basis of strictly localized molecular orbitals is used, thus allowing the partitioning of the molecule into four fragments: central part (C), delocalization (D), inductive (I) and transferable bond (T) regions. Fragment C consists of bonds which undergo the most important chemical changes. For this conventional self-consistent field equations with an effective core Hamiltonian accounting for the influence of fragments D, I and T, are given. Simple perturbation expressions are used for fragment D in order to calculate tails of strictly localized molecular orbitals, which account for charge transfer from and to the central part. Only inductive effects are considered for fragment I by solving a coupled set of 2×2 secular equations in order to optimize coefficients of strictly localized molecular orbitals. Regions C and T lie very far from each other and therefore empirical strictly transferable coefficients are used for the latter. The above procedure allows the treating of proteins at the zero differential overlap level, since with increasing molecular size the amount of computational work becomes proportional to the first power of the number of bonds. Applicability of the present concept is discussed on the basis of numerical results obtained for the electrostatic potential and conformational properties of serine proteinases.

INTRODUCTION

Quantum chemical computation methods are mostly based on the molecular orbital (MO) concept.[1] One-electron functions, required in the independent-particle approximation, are expanded on the basis set of atomic orbitals. This allows an elegant and economic treatment of the accompanying mathematical problem: solution of a secular equation. The appearance of more and more powerful computers as well as exploitation of a number of technical tricks in software resulted in very effective programs for the solution of self-consistent MO problems. Treatment of molecules with less than 40 or 10 heavy ($Z > 2$) atoms have became routine at the semiempirical or *ab initio* levels, respectively.

Despite the spectacular success of the MO concept, at least two important aspects of quantum chemistry seem to resist its power: the theory of the

chemical bond and the treatment of very large molecules such as proteins. We feel that these two problems can be approached from a common starting point: an appropriate counterpart of the bond concept has to (and can) be found in quantum chemistry and such a concept could also help in treating very large molecules quantitatively. We firmly believe that in order to reach this goal the chemist's way of thinking has to be followed. Our studies are restricted to classical molecules which have a well-defined chemical formula. Quantum chemical computational methods should exploit all information inherent in the formula. This philosophy serves as a basis for our considerations, and supports our feeling that, despite its methodological character, the present paper fits well into the topic of this Special Issue: *Conceptual Quantum Chemistry — Models and Applications.*

The bond concept is very old in quantum chemistry. The valence bond model of Pauling and others[2] achieved spectacular success at the qualitative level and its failing reputation is primarily due to technical problems. An alternative way of making use of the chemical formula in numerical calculations is offered by strictly localized MOs or, in other terms, bond orbitals.[3–15] These may serve as building blocks in constructing approximate wave functions thus reducing the computational work considerably. The crucial points in applying bond orbitals in quantum chemical calculations is their transferability and localizability. We have been continuously studying this question in our laboratory and proposed efficient methods for correcting deficiencies arising from the partial violation of the above conditions.[15–20]

In the present paper we are presenting an outline of a method which is capable of treating very large molecules, especially proteins, at the CNDO/2 level of approximation. Its application is restricted to such problems where chemical events are localized to a relatively small region of the molecule; other parts remain fixed and function as an environment. An example is conformational behaviour of protein side chains, which can be studied successfully by the simple CNDO/2 method as well.[19] Bulk properties, such as skeletal vibrations or electric conductivity seem to be beyond the scope of this method.

The chemical model is presented in the next section followed by physical aspects and mathematical formulae. The present paper is closely related to that of Surján[21] in this issue, in which further details can be found. Although we do not have a complete computer program at present which would encompass the calculations outlined in this paper, several results obtained by various bond orbital methods are available. These will be discussed however, and the paper ends with an outlook for further applications.

MODEL

We divide a biomacromolecule (*e. g.* protein) into four parts (*cf.* Figure 1). By using chemical intuition let us first define a *central region* (C). The majority of actual changes, like rotation around a bond, geometry distortion, or local electronic excitations, can be localized in this group of atoms. The central region concept is exploited in biomimetic chemistry[22] where appropriate molecular models, containing not more than some dozen atom, are studied instead of the biomacromolecule as a whole. The second region, directly linked to the first one, is the delocalization part (D). Region D is not very much affected by

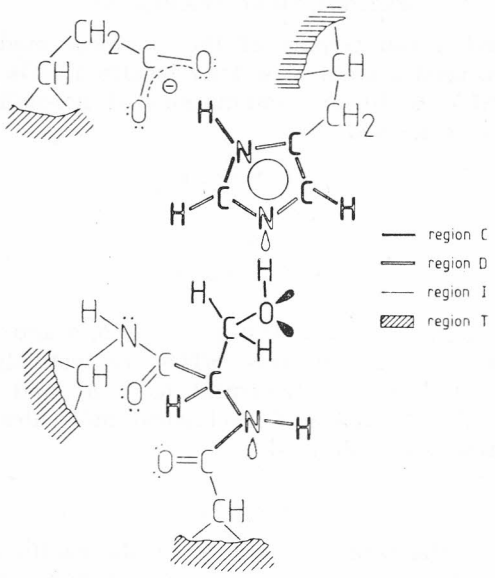

Figure 1. Chemical fragmentation of the active site in α-chymotrypsin.

the events in the central part, but the relatively small alterations in its electronic structure may strongly influence the small energy changes in C. The most important effect is electron delocalization from C to D and *vice versa*. It has been pointed out that this is of primary importance in determining barriers to rotations around single bonds.[18] Besides delocalization, inductive effects are also present, which means that the electrostatic field of C polarizes bonds in D thus producing a different environment for C. In region I delocalization is neglected and only inductive effects are considered. Finally, we define a region, T, which is composed of completely transferable bonds and serves as a rigid, nonpolarizable environment for regions C, D and I.

The advantage of this chemical partition is that for different regions, the degree of sophistication of the applied quantum chemical methods may be different. Thus, an SCF procedure is applied to C accounting for even drastic changes in the electronic structure. This is very time consuming, but it does not have to be applied to regions D, I and T. Delocalization together with electron correlation can be considered by applying perturbation approximations[23] and inductive effects are also calculated very simply.[7,13,15] As a result, the computational work for regions D and I will be proportional to the square of the number of bonds present here. Going a step further, bonds in region T are considered to be strictly transferable, therefore the empirical parameters of the corresponding orbitals can be stored in a computer program and no optimization procedure is necessary. Neglecting nonorthogonality terms, which is allowed if T is far from C, the amount of computational work becomes proportional only to the first power of the number of bonds in the biomacromolecule.[12,16] This allows the treating of real systems of very large size at a low cost.

MATHEMATICAL FRAMEWORK

In order to find a counterpart of the chemical model outlined in the previous section, we used a basis of strictly localized MOs (SLMOs). For each bond, i, a set of SLMOs, linear combinations of normalized atomic hybrid orbitals (HYOs, h_{mi}), is defined

$$\varphi^{\mu}{}_{i} = \sum_{m=1}^{M_i} c^{\mu}_{mi}\, h_{mi} \tag{1}$$

$$h_{mi} = \sum_{p=1}^{5} a^{p}_{mi}\, u^{p} \tag{2}$$

u^p is a Slater-type atomic orbital (STO). $p = 1$, 2, 3, 4 and 5 stands for $1s$ (for a H atom), $2s$, $2p_x$, $2p_y$ and $2p_z$-type STOs, respectively. Notice that the »hybrid« for a H atom is a pure $1s$-orbital, $h_{\mathrm{H}i} = u^{1s}$ and, on the other hand $a^1{}_{mi} = 0$ for heavy ($Z > 2$) atoms. For classical molecules, such as proteins. three types of SLMOs can be defined.

— Lone pairs

$$\varphi^1{}_{lp} = h_{lp} \tag{3}$$

The orientation and s-character are defined by the coefficients in Eq. (2). The finding of these is not quite simple, however a chemical evidence may help[16] The best choice seems to be the case when chemically reasonable lone-pair HYOs are othogonalized to each other on the same atom.[19]

— Two-centre σ-bond orbitals

$$\varphi^1{}_{\sigma} = c_1 h_1 + c_2 h_2 \tag{4}$$

$$\varphi^2{}_{\sigma} = c_2 h_1 - c_1 h_2 \tag{5}$$

h_1 and h_2 are HYOs on atoms 1 and 2, respectively, oriented in the bond direction. c_1 and c_2 are bond polarities. To ensure normalization within the ZDO assumption $c_1{}^2 + c_2{}^2 = 1$.

— π-bond orbitals delocalized to M_π centres

$$\varphi^{\mu}{}_{\pi} = \sum_{m=1}^{M_\pi} c^{\mu}{}_{m}\, u^{2pz}_{m} \tag{6}$$

Eqs. (1—6) define a minimal basis set if occupied and virtual orbitals in Eq. (6) are also considered. A zeroth order wave function can be constructed from all occupied strictly transferable SLMOs. We use this wave function, appropriate for calculating molecular electrostatic potential maps[16], for region T. Inner regions, I, D and C, have to be described more precisely and therefore bond polarities of Eq. (6) are optimized. We derive the following secular equation for the vector of coefficients of the i-th system

$$\mathbf{F}_i\, \mathbf{c}_{mi} = \varepsilon_{mi}\, \mathbf{c}_{mi} \tag{7}$$

where the Fockian is defined within the frame of the CNDO/2 approximation[24]

$$F_{aa,\,i} = H^{\mathrm{eff}}_{aa,\,i} + \sum_{m=1}^{M_i} P_{mm,\,i}\,(ai;\, ai \mid mi;\, mi) - \\ - \frac{1}{2}\,(P_{aa,\,i} - 1)\,(ai;\, ai \mid ai;\, ai) \tag{8}$$

$$F_{ab,i} = H^{\text{eff}}_{ab,i} - \frac{1}{2} P_{ab,i} (ai; ai \mid bi; bi) \tag{9}$$

Notice that in Eqs. (7)—(9) i represents one index (for σ-bonds) or a set of indices (for π-bonds).

The effective core Hamiltonian is defined as follows

$$H^{\text{eff}}_{aa,i} = H_{aa,i} + \sum_{j=1}^{N} \sum_{m=1}^{M_j} P_{mm,j} (ai; ai \mid mj; mj) + \sum_{k=1}^{N_T} \sum_{m=1}^{M_k} P_{mm,k} (ai; ai \mid mk; mk) \tag{10}$$

$$H^{\text{eff}}_{ab,i} = H_{ab,i} \tag{11}$$

The first and second term in Eq. (10) stand for the interaction between electrons of the i-th bond and those of other bonds within the inner (I, D and C) and outer (T) regions, respectively. The core Hamiltonian is defined as in the CNDO/2 method

$$H_{aa\,i} = -\frac{1}{2} (I_a + A_a) - \sum_{m=1}^{M_i} Z_m (ai; ai \mid mi; mi) \tag{12}$$

$$H_{ab,i} = \beta_{ab} S_{ab,i} \tag{13}$$

I_a, A_a and Z_m are ionization potential, electron affinity and core charge of the corresponding atom in bond i, β_{ab} is the resonance integral in the CNDO/2 approximation. The overlap and Coulomb integrals are defined as usual

$$S_{ab,i} = \int h_{ai} (1)\, h_{bi} (1)\, \mathrm{d}v_1 \tag{14}$$

$$(ai; bi \mid mj; nj) = \int\int h_{ai} (1)\, h_{bi} (1)\, r_{12}^{-1}\, h_{mj} (2)\, h_{nj} (2)\, \mathrm{d}v_1\, \mathrm{d}v_2 \tag{15}$$

$\mathbf{P}$ is the density matrix defined as follows

$$\mathbf{P}_{mn,i} = 2 \sum_{\mu=1}^{N_i} c^{\mu}_{mi}\, c^{\mu}_{ni} \tag{16}$$

Summation in Eq. (16) runs over occupied orbitals belonging to system i (one for σ-bonds and more for π-systems).

The last sum in the effective core Hamiltonian of Eq. (10) comes from region T (containing N_T bonds) and is an additive constant. On the other hand, the first sum represents the electronic interaction between bonds in regions C + D + I (containing N bonds) and changes continuously in the iteration process. Consequently, solution of the secular equation in Eq. (7) corresponds to an ordinary, $M_i \times M_i$ eigenvalue problem which depends on N through Eq. (10) quadratically. As a result, the dimensionality of Eq. (7) is quasi-independent of the number of bonds (electrons) in regions C + D + I. For proteins, the largest π-system is that of tryptophan ($M_i = 9$), which means that numerical problems at this level of approximation are negligible.

Once we have optimized parameters in the SLMO basis set, the molecular orbitals for region C can be written as

$$\psi^{c}_{m} = \sum_{k=1}^{M_c} a_{mk}\, \varphi_k \tag{17}$$

where φ_k is an SLMO formally defined by Eqs. (1)—(6). Notice that coefficients in Eqs. (5)—(6) are optimized by solving Eq. (7). Summation in Eq. (17) runs over occupied and virtual orbitals *i. e.*

$$M_c = 2N_\sigma + 2N_\pi + N_{lp} \tag{18}$$

where N_σ, N_π and N_{lp} are the number of two-centre σ-bonds, occupied π-orbitals and lone pairs, respectively.

To find the best wave function for the central region, the a_{mk} coefficients should be optimized. This is done by solving the following secular equation

$$\mathbf{F}^c \mathbf{a}_m = \varepsilon^c{}_m \mathbf{a}_m \tag{19}$$

$$F_{ij} = H_{ij}^{\text{eff}} + \sum_{k,l \in C}^{M_c} P_{kl} [(ij \mid kl) - \frac{1}{2} (ik \mid jl)] \tag{20}$$

$$H_{ij}^{\text{eff}} = H_{ij} + 2 \sum_{k \in D_e, I, T} (ij \mid kk) \tag{21}$$

Eqs. (19)—(21) were derived by applying the variation principle to the total energy of the central part and making use of the special form of the density matrix **P** (*cf.* Figure 2).[20] Electron repulsion integrals $(ij \mid kl)$ are obtained

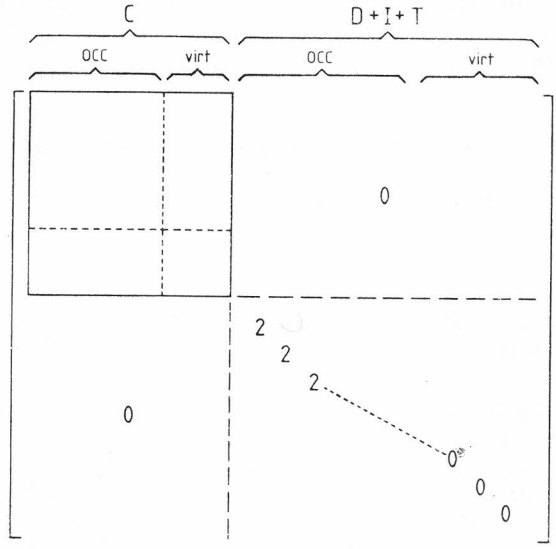

Figure 2. Schematic representation of the density matrix in Eq. (20)

formally from Eq. (15) by replacing h_{ai}, h_{bi}, h_{mj} and h_{nj} by φ_i, φ_j, φ_k and φ_l, respectively. A similar relation exists between core Hamiltonians of Eq. (21) and Eqs. (10—16). Notice that even by applying the ZDO assumption, the $\varphi_i \varphi_j$ differential overlap does not vanish necessarily (*e. g.* in case of occupied-virtual combinations of σ-bonds). M_c is the dimensionality of the secular equation in Eq. (19). The principal feature of our method is that it *is independent of the*

size of the whole molecule. Its value depends only on the number of bonds which participate directly in the chemical event.

The total energy of the system is written as follows

$$E = E_{nucl}^{C+D+I} + \frac{1}{2} \sum_{i,j \in C} P_{ij} (F_{ij} + H_{ij}^{eff}) +$$

$$+ \sum_{i \in D,I} \sum_{ab}^{M_i} P_{ab} (F_{ab,i} + H_{ab,i}^{eff}) + E^D + E^T \tag{22}$$

The first term stands for repulsion between nuclei of regions C, D and I, the second and third sums are electronic energies of the central part and delocalization plus inductive regions, respectively. E^D comes from electron delocalization from and to the central region. It is associated with tails, η_{ij^*} and η_{ji^*}, of SLMOs in the following form

$$E^D = 2 \sum_{\substack{i \in C \\ j^* \in D}} \eta_{ij^*} H_{ij^*} + 2 \Sigma \eta_{ji^*} H_{ji^*} \tag{23}$$

In other words, η_{ji^*} is a coefficient for mixing virtual SLMOs to the occupied one in order to account for delozalization

$$\varphi_i = N_i (\varphi_i + \sum_{j^* \in D}^{virt} \eta_{ij^*} \varphi_{j^*}) \tag{24}$$

where N_i is a normalization factor. Although for classical molecules, η_{ij^*} is relatively small,[19] it may be extremely important *e. g.* if a hydrogen bond is formed between regions C and D. This is indicated by the fact that the calculated rotational energy curve of region C in Figure 1 strongly depends on the choice of C if the correction in Eq. (23) is not considered.[20]

Tails of SLMOs can be easily calculated in the framework of the linearized SCF model of Surján and Mayer.[17] Thus

$$\eta_{ij^*} = \frac{\Delta E_{ji^*} H_{ij^*} + (ii^* \mid jj^*) H_{ji^*}}{(ii^* \mid jj^*)^2 - \Delta E_{ij^*} \Delta E_{ji^*}} \tag{25}$$

with

$$\Delta E_{ij^*} = F_{j^*j^*} - F_{ii} - (ii \mid j^*j^*) \tag{26}$$

Eq. (26) defines the energy of the $i \rightarrow j^*$ excitation. Other terms in Eq. (25) are defined as in Eqs. (20)—(21).

Finally, E^T of Eq. (22) is the energy of the strictly transferable region including the nuclear repulsion with regions C, D and I. Owing to the large distance from the central region, E^T is considered as constant and therefore is dropped if calculating energy differences coming from chemical changes in C. It has to be noticed that E of Eq. (22) is not a strict upper bound for the total energy. This is a feature similar to the PCILO method.[23]

DISCUSSION AND OUTLOOK

In the previous section the mathematical background of our method has been presented. On this basis a computer program for the quantum chemical treatment of very large molecules, especially proteins, can be set up. Although

such a program is not yet available, we have several reasons to suppose that it would work for cases where chemical events can be localized to a small group of atoms in the macromolecule. Now we discuss these reasons in detail.

Transferable SLMOs are appropriate building blocks of a zeroth order (»rigid«) wave function for very large molecules.[16,25] This wave function may be used to calculate molecular electrostatic potentials for protein molecules with up to 5000 atoms.[26,27] Since, due to the large distance, the effect of region T on the central part C, is purely electrostatic, it is reasonable to suppose that it is appropriately treated by the effective core Hamiltonians of Eqs. (10), (11) and (21). This feature is of primary importance since it means that the computational work necessary for obtaining the corresponding matrix elements is proportional only to the first power of the number of bonds in region T. As a result, protein molecules can be treated in full at reasonable cost and storage capacity. Obtaining charge distributions with a correct consideration of inductive effects, *i. e.* solving a simplified form of Eq. (7), was first proposed by Del Re in his σ-orbital method.[7] It was later extended and applied to more complicated systems,[13,15,28] and found to work well at low cost. In our case the computational work increases quadratically with the number of bonds in regions C, D, and T, but the proportionality constant is small and therefore systems with 80—100 atoms can be handled successfully.

Generation of tails in the delocalization and central regions by the formulae in Eqs. (25)—(26) is an economic procedure and its efficiency has been tested on several model molecules.[19] It has been found that beyond a distance of 4—500 pm, tails are negligible and, therefore, this is a reasonable radius for defining the extension of region D (*cf.* Figure 1). Lone-pair tails are longer and this has to be borne in mind if defining the cut-off radius.

The quantum chemical partitioning of a large molecule into a central region and environment has been proposed by several authors.[29–32] The intrinsic problem of all propositions is the definition of the central part which is often impractical and arbitrary. By using SLMOs a natural partitioning becomes possible as has already been indicated in a previous paper[20] where regions D, I and T were handled together. In defining the central part as sufficiently large, an almost quantitative agreement with full SCF results was achieved at the CNDO/2 level. The reason for defining a delocalization region around the central parts, is that the size of C, for which a full SCF calculation has to be done, can be reduced to a minimum.

A drawback of our method is that, in its present stage, it is semi-empirical. The general use of powerful computers allows the performing of *ab initio* calculations for medium-size molecules and therefore the popularity of semi-empirical methods continuously declines. For example, it is impossible to provide a correct energy curve for the O—H . . . O proton transfer in the water dimer (and in other systems *e. g.* proteins) by CNDO/2 calculations. However, reasonable proton transfer energy curves can be obtained if a combined *ab initio*/semi-empirical calculation is performed (*cf.* Figure 3). A small, but adequate model, *e. g.* the $(H_2O)_2$ system, can be studied at the *ab initio* level by using a large basis set. The same system at the same geometries can be treated by the CNDO/2 method, and by comparing the calculated values with the *ab initio* ones a correction is obtained. Adding this correction to the results, obtained by the present method for the real protein (Figure 3c), a reasonable proton-transfer curve is achieved which accounts for short-range and environ-

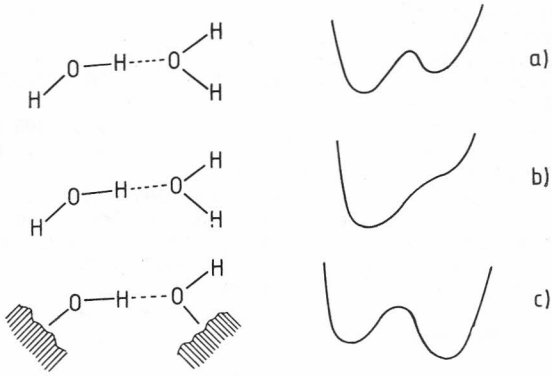

Figure 3. Schematic proton transfer energy curves in a hypothetical protein and in model systems. a) *ab initio* calculation with a large basis set, b) CNDO/2 calculation, c) corrected CNDO/2 curve including environmental effects.

mental effects, as well. A calculation based on the above principle, was done to estimate proton-transfer energies for the Asp ... His catalytic diad in subtilisin.[33] Clearly, environmental effects which cannot be accounted for by a CNDO/2-type approximation (*e. g.* dispersion forces) will be neglected in this combined approach, too.

Acknowledgement. — The author is indebted to Dr. P. R. Surján for fruitful discussions.

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SAŽETAK

Molekulsko-orbitalni računi na proteinima primjenom postupka kemijske fragmentacije

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Dana je teorijska osnova za računanje promjena konformacijskih energija proteina u okviru MO metode. Pri tome se maksimalno koriste informacije o polipeptidnoj kralježnici i perifernim lancima, koje su pohranjene u kemijskim formulama. Pristup se temelji na potpuno lokaliziranim orbitalama. Čitava se molekula može tada podijeliti u četiri regije: centralni dio (C), delokalizacijski dio (D), induktivni dio (I) te regiju transferabilnih veza (T). Najvažnije kemijske promjene zbivaju se u fragmentu C. Za taj su dio formulirane jednadžbe samousklađenog polja pri čemu se rabi hamiltonijan efektivne koštice, a zatim se uzima u obzir utjecaj fragmenata D, I i T. Ovaj pristup omogućuje tretman proteina primjenom aproksimacije nultog diferencijalnog prekrivanja. Metoda je ilustrirana numeričkim rezultatima za elektrostatski potencijal i konformacijska svojstva serin-proteinaze.