Quantum Chemistry and
Its Application to Life Science

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RESUMEN

Para lograr penetrar a la esencia de las reacciones químicas y de los fenómenos biológicos, uno tiene que apoyarse inevitablemente en la teoría cuántica que describe interacciones entre átomos y moléculas. Sin embargo, es generalmente imposible analizar o diseñar analíticamente las estructuras de moléculas exactamente sobre la base de la mecánica cuántica, a excepción de algunos casos especiales. Así se ha desarrollado una variedad de métodos de aproximación en química cuántica, contribuyendo enormemente al desarrollo de la química y sus campos de aplicación. En este trabajo describimos los conceptos importantes de la química cuántica, tales como el método orbital molecular, la teoría de la frontera del electrón, la interacción intermolecualr, etc. y revisamos sus aplicaciones en los campos de la vida científica. *Palabras clave: teoría cuántica, método orbital molecular, teoría de la frontera del electrón, interacción molecular.*

ABSTRACT

In order to get insight into the essence of chemical reactions and biological phenomena, one inevitably has to rely upon the quantum theory which describes interactions among atoms and molecules. However, it is generally impossible to analyze or design analytically the structures of molecules exactly on the basis of quantum mechanics except some special cases. Therefore a variety of approximate methods have been developed in quantum chemistry, thus greatly contributing to the development of chemistry and its application fields. In this paper we describe the important concepts in quantum chemistry such as the molecular orbital method, the frontier electron theory, the intermolecular interaction, etc. and review their applications to the life science fields. *Keywords. quantum theory, molecular orbital method, frontier electron theory, intermolecular interaction.*

INTRODUCTION

Quantum mechanics was established in 1926 when E. Schrödinger formulated the wave equation, the Schrödinger equation, and independently to him when W. Heisenberg formulated the matrics mechanics. Nowadays it is well recognized that quantum mechanics forms a basis of not only physics but also chemistry.

The question how atoms are combined to form a molecule has been a long-time puzzle. In 1916 G.N. Lewis presented an idea supporting that when forming a molecule out of neutral

atoms, two of these atoms share a pair of electrons to create a combining force. However, the reason why a combining force is generated in such a way was not clear. In 1927, one year after the foundation of quantum mechanics, W. Heitler and F. London clarified the issue of what force acted among two neutral hydrogen atoms to form a hydrogen molecule by solving the Schrödinger equation. The concept of "covalent bond" which is so common nowadays derives from the wave behaviour of electrons. Such concept could not have been understood without quantum mechanics.

The discovery of the periodic table of elements dates back to 1869 when D.I. Mendeleev found that the chemical nature varies periodically when chemical elements are arranged in the order of atomic weight. At the time of discovery of the periodic table, which was created deductively from the chemical nature of elements, it was considered to be a pure empirical rule. However, as the construction of quantum mechanics progressed and the atomic structures were more clearly understood, it became clear that the periodic table originates from the quantum-mechanical concept of "orbital". The present periodic table describes how many electrons are located in each possible atomic orbital. The elements which belong to the same group in the periodic table possess a similar configuration for the "valence electrons" which occupy the outermost orbital. The valence electrons play crucial role in determining chemical nature of atoms. In this way the periodic table can be understood from the standpoint of electron configuration in atoms built according to the quantum-mechanical principles. This fact already indicates clearly that the basic principles in chemistry are based on quantum mechanics.

As pointed out by P.A.M. Dirac (1), all of the issues in chemistry can be clarified by quantum mechanics in principle. However, it is generally impossible to analyze or design analytically the structures of molecules strictly on the basis of quantum mechanics except a few special cases. Therefore a variety of approximate methods have been developed in quantum chemistry (2-5), thus greatly contributing to the development of chemistry and its application fields. The electrons in an atom or molecule can be described by means of atomic orbital functions or molecular orbital functions, respectively. By using the concept of the molecular orbital method one can calculate and understand a variety of properties of molecules as well as the mechanism of their chemical reactions.

Quantum chemistry is also deeply related to the life science fields such as pharmacology and medical science. This is because the mechanism of various reactions in an organism can be understood by quantum chemistry. Quantum chemistry plays also a crucial role in understanding deeper the essence of "life" by clarifying various properties of biopolymers (proteins, nucleic acids, etc.).

In Section 2 we explain the molecular orbital method which forms a basis of quantum chemistry, and in Section 3 and Section 4 we describe the frontier electron theory and the intermolecular interaction together with its applications to life science fields, respectively. Section 5 summarizes the paper.

Molecular Orbital Method

The Schrödinger equation which describes the electron behaviour moving around a nucleus is expressed as follows:

$$\hat{H}^e \psi^e = E \psi^e,$$

(Eq. 1)

Where $\hat{H}^e$, the Hamiltonian operator of the electrons, consists of two terms: the kinetic energy of electrons moving around in the field of a nucleus, $\hat{T}^e$ and the Coulomb potential energy between electrons and nucleus, $\hat{V}$. That is,

$$\hat{H}^e = \hat{T}^e + \hat{V}.$$

(Eq. 2)

The symbol ^ in $\hat{H}^e$ for example, expresses that $\hat{H}^e$, is the operator and the subscript e means that it describes electron(s). Using the atomicunit system, $\hat{T}^e$ and $\hat{V}$ are expressed as

$$\hat{T}^e = -\frac{1}{2} \sum_{\mu}^{electrons} \left(\frac{\partial^2}{\partial x_{\mu}^2} + \frac{\partial^2}{\partial y_{\mu}^2} + \frac{\partial^2}{\partial z_{\mu}^2} \right),$$

(Eq. 3)

$$\hat{V} = -\sum_{\mu}^{electrons} \sum_{A}^{nuclei} \frac{Z_A}{\tau_{\mu A}} + \sum_{\mu > \nu}^{electrons} \frac{1}{r_{\mu\nu}},$$

(Eq. 4)

respectively. In the atomic unit system one uses as the fundamental units the mass of electron, m, the Planck constant devided by $2\pi, \hbar(= h / 2\pi)$ and $e^2 / 4\pi\varepsilon_o$ (e: the absolute value of electron charge). In this system the unit of length is measured by $\hbar^2 / me^2$ and the unit of energy is measured by $me^4 / \hbar^2$. ZA is the charge of the nucleus of an atom A. Since the kinetic energy of electrons and the electrostatic potential energy between the $\mu - th$ electron and the nucleus A depend only on the coordinate of the $\mu - th$ electron, they are called one-electron term. On the other hand, the Coulomb repulsion energy between the $\mu - th$ and $\nu - th$ electrons depends on the coordinates of two electrons, hence is called two-electron term. Separating the Hamiltonian of electrons into the one-electron term and the two-electron term, one can write:

$$\hat{H}^e = \sum_{\mu} \hat{H}(\mu) + \sum_{\mu > \nu} \frac{1}{r_{\nu\mu}},$$

(Eq. 5)

where $\hat{H}(\mu)$ is

$$\hat{H}(\mu) = -\frac{1}{2} \left(\frac{\partial^2}{\partial x_{\mu}^2} + \frac{\partial^2}{\partial y_{\mu}^2} + \frac{\partial^2}{\partial z_{\mu}^2} \right) - \sum_{A} \frac{Z_A}{r_{\mu A}}.$$

(Eq. 6)

The wave function of electrons, ψ^e, is

expressed by the so-called Slater matrix which is the combination of molecular orbitals to which each electron belongs. In the case when an electron with spin α and an electron with spin, β are located in one molecular orbital ϕ_i and correspondingly 2n electrons are located in n molecular orbitals, the wave function, ψ^e, can be expressed as

$$\psi^e = \frac{1}{\sqrt{(2n)!}} \begin{vmatrix} \phi_1(1)\alpha(1) & \phi_1(1)\beta(1) & \phi_2(1)\alpha(1) & \cdots & \phi_n(1)\beta(1) \\ \phi_1(2)\alpha(2) & \phi_1(2)\beta(2) & \phi_2(2)\alpha(2) & \cdots & \phi_n(2)\beta(2) \\ \vdots & \vdots & \vdots & & \vdots \\ \phi_1(2n)\alpha(2n) & \phi_1(2n)\beta(2n) & \phi_2(2n)\alpha(2n) & \cdots & \phi_n(2n)\beta(2n) \end{vmatrix}$$

(Eq. 7)

where $\frac{1}{\sqrt{(2n)!}}$ is a normalization constant. Assuming that the molecular orbitals constitute the normalized orthogonal system, one can write

$$\int \overline{\phi}_i(\mu)\phi_j(\mu)d\upsilon_{\mu} = \delta_{ij}.$$

(Eq. 8)

where $\overline{\phi}_i$ is the complex conjugate of ϕ_i and δ_{ij} is Kronecker's symbol taking the value 1 for i = j and 0 for i ≠ j. The total energy of electrons is obtained by multiplying the complex conjugate of ψ^e to each side of (Eq. 1) from the left and integrating it over the whole space. That is.

$$E = \int \overline{\psi}^e \hat{H}^e \psi^e d\upsilon,$$
$$= \sum_i H_i + \sum_{i,j} (2 J_{ij} - K_{ij}).$$

(Eq. 9)

where H_i, J_{ij} and K_{ij} in (9) read

$$H_i = \int \bar{\phi}_i \hat{H}(\mu)\phi_i(\mu)d\upsilon_\mu,$$

(Eq. 10)

$$J_{ij} = J_{ji} = \int \bar{\phi}_i(\mu)\phi_i(\mu)(\tfrac{1}{r_{\mu\nu}})\bar{\phi}_j(\nu)\phi_j(\nu)d\upsilon_\mu d\upsilon_\nu,$$

(Eq. 11)

$$K_{ij} = K_{ji} = \int \bar{\phi}_i(\mu)\phi_j(\mu)(\tfrac{1}{r_{\mu\nu}})\bar{\phi}_j(\nu)\phi_i(\nu)d\upsilon_\mu d\upsilon_\nu,$$

(Eq. 12)

respectively. H_i, which is called "core integral", is the energy of an electron in a molecular orbital, ϕ_i, moving in the attractive field of electrostatic potential of the nucleus. J_{ij}, which is called "Coulomb integral", is the repulsion energy between an electron in a molecular orbital, ϕ_j, and an electron in a molecular orbital, $\hat{J}_j$, K_{ij}, which is called "exchange integral", is specific to quantum mechanics and is derived from the fact that the wave function is expressed by the Slater matrix, (Eq. 7). Note that differing from H_i and J_{ij}, K_{ij} cannot be interpreted by the classical term. Furthermore defining the Coulomb operator, $\hat{J}_i$, and the exchange operator, $\hat{K}_i$, as

$$\hat{J}_i\phi(\mu) = \left(\int \frac{\bar{\phi}_i(\nu)\phi_i(\nu)}{r_{\mu\nu}}d\upsilon_\nu\right)\phi(\mu),$$

(Eq. 13)

$$\hat{K}_i\phi(\mu) = \left(\int \frac{\bar{\phi}_i(\nu)\phi(\nu)}{r_{\mu\nu}}d\upsilon_\nu\right)\phi_i(\mu),$$

(Eq. 14)

J_{ij} and K_{ij} in (Eq. 11) and (Eq. 12) can be reformulated as

$$J_{ij} = J_{ji} = \int \bar{\phi}_i(\mu)\hat{J}_j\phi_i(\mu)d\upsilon_\mu,$$

(Eq. 15)

$$K_{ij} = K_{ji} = \int \bar{\phi}_i(\mu)\hat{K}_j\phi_i(\mu)d\upsilon_\mu,$$

(Eq. 16)

The molecular orbital δE can be obtained from the condition that the total energy of electrons, E, in (Eq. 9), takes the minimum value for the real molecular orbital. To fulfill such condition, the variation δE has to equal to 0 when ϕ_i gets small changes, $\phi_i \longrightarrow \phi_i + \delta\phi_i$ in (Eq. 9). Thus taking the variation of (9), we obtain

$$\delta E = \sum_i \delta H_i + \sum_{i,j}(2\delta J_{ij} - \delta K_{ij}).$$

(Eq. 17)

where δH_i, δJ_{ij} and δK_{ij} in (17) read

$$\delta H_i = \int \delta\bar{\phi}_i(\mu)\hat{H}(\mu)\phi_i(\mu)d\upsilon_\mu + \int \bar{\phi}_i(\mu)\hat{H}(\mu)\delta\phi_i(\mu)d\upsilon_\mu,$$

(Eq. 18)

$$\delta J_{ij} = \int \delta\bar{\phi}_i(\mu)\hat{J}_j\phi_i(\mu)d\upsilon_\mu + \int \bar{\phi}_i(\mu)\hat{J}_j\delta\phi_i(\mu)d\upsilon_\mu,$$

(Eq. 19)

$$\delta K_{ij} = \int \delta\bar{\phi}_i(\mu)\hat{K}_j\phi_i(\mu)d\upsilon_\mu + \int \bar{\phi}_i(\mu)\hat{K}_j\delta\phi_i(\mu)d\upsilon_\mu.$$

(Eq. 20)

One has to derive the equations under the normalized orthogonal condition for ϕ_i, i.e. (Eq. 8). Thus taking the variation of the normalized orthogonal condition in (Eq. 8) as:

$$\int (\delta \bar{\phi}_i)\phi_j d\upsilon + \int (\delta \phi_i)\bar{\phi}_j d\upsilon = 0.$$

(Eq. 21)

Summing up (Eq. 21) multiplied by an undetermined constant, $-\varepsilon_{ij}$ and the (Eq. 17), we obtain

$$\int \delta \bar{\phi}_i \left\{ \hat{H} + \sum_j (2\hat{J}_j - \hat{K}_j) - \sum_j \varepsilon_{ji} \right\} \phi_i d\upsilon + (complex\ conjugate) = 0$$

(Eq. 22)

In order to hold (Eq. 22) for arbitrary $\delta \phi_i$, the following conditions should be satisfied.

$$\left\{ \hat{H} + \sum_j (2\hat{J}_j - \hat{K}_j) \right\} \phi_i = \sum_j \varepsilon_{ji} \phi_i.$$

(Eq.23)

The elements of Hermitian matrix ε_{ij} can be diagonalized by a unitary transformation. Denoting the diagonalized value of ε_{ij} as ε_i and introducing the notations:

$$\hat{F} = \hat{H} + \sum_j (2\hat{J}_j - \hat{K}_j),$$

(Eq. 24)

(Eq. 23) can be expressed as:

$$\hat{F}\phi_i = \varepsilon_i \phi_i,$$

(Eq. 25)

(Eq. 25) is called Hartree-Fock equation.

In case of an atom, the Hartree-Fock equation becomes one dimensional integro-differential equation with a variable r, a distance from a nucleus to an electron, and thus it can be solved numerically with high accuracy. In case of a molecule, however, solving the Hartree-Fock equa-

tion directly by numerical integration is almost impossible except for simple diatomic molecule cases. Then to proceed further, we assume that the wave function of an electron in a molecule, ϕ_i (molecular orbital), is expressed by the combination of the wave functions χ_r (atomic orbital) of electrons in atoms which constitute the molecule as:

$$\phi_i = \sum_r \chi_r c_{ir}.$$

(Eq. 26)

Since in (Eq. 26) the molecular orbital (MO) is approximated by the linear combination (LC) of atomic orbitals (AO), such approximation is called LCAO-MO method. Substituting (Eq. 26) into (Eq. 25), multiplying it by $\bar{\phi}_i$ from the left and integrating it over the whole space, one can get the following Hartree-Fock-Roothaan equation:

$$\mathbf{F}\mathbf{c}_i = \varepsilon_i \mathbf{S}\mathbf{c}_i,$$

(Eq. 27)

where $\mathbf{c}_i$ and $\mathbf{S}$ are matrices. The Fock operator, $\hat{F}$, is expressed by the sum of one-electron term, $\hat{H}$, and of two-electron term, $\hat{P}$, as

$$\hat{F} = \hat{H} + \hat{P}.$$

(Eq. 28)

Putting the Fock operator $\hat{F}$, between $\bar{\chi}_r(\mu)$ and $\chi_s(\mu)$ and integrating it over the whole space (υ_μ) of the $\mu - th$ electron, one gets

$$H_{rs} = \int \bar{\chi}_r(\mu)\hat{H}\chi_s(\mu)d\upsilon_\mu,$$

(Eq. 29)

$$P_{rs} = \int \bar{\chi}_r(\mu)\hat{P}\chi_s(\mu)dv_\mu = \sum_{t,u} P_{rs,tu} \cdot D_{tu},$$

(Eq. 30)

where

$$D_{tu} = \sum_j 2\bar{c}_{tj}c_{uj},$$

(Eq. 31)

$$P_{rs,tu} = (rs \mid tu) - \frac{1}{2}(rt \mid su),$$

(Eq. 32)

and

$$(rs \mid tu) = \int \bar{\chi}_r(\mu)\bar{\chi}_s(\mu)(1/r_{\mu v})\chi_t(v)\chi_u(v)dv_\mu dv_v.$$

(Eq. 33)

The elements of matrix **S** are expressed as

$$S_{rs} = \int \bar{\chi}_r(\mu)\chi_s(\mu)dv_\mu.$$

(Eq. 34)

Rewriting (Eq. 27) as

$$\sum_r c_{ir}(F_{rs} - \varepsilon_i S_{rs}) = 0.$$

(Eq. 35)

where

$$F_{rs} = \int \bar{\chi}_r(\mu)\hat{F}\chi_s(\mu)dv_\mu,$$

(Eq. 36)

we obtain the secular equations representing a system of linear equations of c_{ir}. Solving the secular equations and obtaining a set of c_{ir}, one can compose the molecular orbital from (Eq. 26). However, one can realize from (Eq. 31) that the system of (35) is not solvable without knowing the LCAO coefficient, c_{ir}. So usually one proceeds as follows: first solve (Eq. 35) and obtain F_{rs} by assuming in some way values of c_{ir}. Next, use thus obtained F_{rs} and solve again the system of (Eq. 35) to get a new set of c_{ir}. If the new set and the old set of c_{ir} do not coincide, the system of (Eq. 35) should be solved by using F_{rs} with the new set of c_{ir}. This procedure is repeated until the two sets of c_{ir} converge to coincide. The converging solutions obtained in this way are said to be self-consistent(SC) and correspondingly the molecular orbitals are said to be in a self-consistent-field (SCF). This method of deriving the molecular orbitals is called LCAO-SCF-MO method. Until now, we have derived the equations assuming the closed shell system. In the case of the open shell system one can proceed similarly.

Now multiplying $\bar{\phi}_i$ to both sides of (Eq. 25) from the left and integrating over the whole space of the $\mu - th$ electron, one gets

$$\varepsilon_i = \int \bar{\phi}_i(\mu)\hat{F}\phi_i(\mu)dv_\mu.$$

$$= H_i + \sum_j (2J_{ij} - K_{ij}).$$

(Eq. 37)

The first term in the right hand of (Eq. 37) represents the sum of the kinetic energy and the Coulomb energy (in the field of the nucleus) of the electron in the molecular orbital, ϕ_i, and the second term represents the repulsion energy among the electrons. The energy which includes all the types of electron energy in the molecular orbital, ϕ_i, is called orbital energy.

The orbital energy ε_i is related to the ionization energy and/or electron affinity.

In the case when $2n$ electrons enter into n molecular orbitals, $\phi_i(i = 1 \sim n)$, one can transform the equations by assigning these $2n$ electrons to each atom or each pair of atoms as follows:

$$2n = \sum_i \int 2\bar{\phi}_i(\mu)\phi_i(\mu)dv_\mu,$$

$$= \sum_i (\sum_r 2\bar{c}_{ir}c_{ir} + \sum_{r \neq s}\sum 2\bar{c}_{ir}c_{is}S_{rs}),$$

$$= \sum_i \int 2 \sum_r \bar{\chi}_r(\mu)\bar{c}_{ir} \sum_s \chi_s(\mu)c_{is}dv_\mu,$$

$$= \sum_i \left[\sum_A \left\{ \sum_{r(\in A)} (2\bar{c}_{ir}c_{ir} + \sum_{B(\neq A)}\sum_{s(\in B)} (2\bar{c}_{ir}c_{is}S_{rs}) \right\} \right],$$

$$= \sum_A \left\{ \sum_{r(\in A)} (D_{rr} + \sum_{B(\neq A)}\sum_{s(\in B)} D_{rs} \cdot S_{rs}) \right\},$$

$$= \sum_A N_A.$$

(Eq. 38)

In rewriting the formulas we used the normalization condition for each AO. $\sum_{r(\in A)}$ means the summation over the atomic orbitals r belonging to an atom A. The density matrix D_{rs} is defined by (Eq. 31) and the overlap integral S_{rs} is defined by (Eq. 34). NA is a number of electrons belonging to the atom A.

The molecular orbital (hereafter abbreviated as MO) method (2) can be classified into three types. In the order of accuracy of approximation from the lower level to the higher level they are: the empirical MO method, the semiempirical MO method and the ab initio MO method

- Empirical MO method
  Simple Hückel method, Extended Hückel method.

- Semiempirical MO method
  PPP(Pariser-Parr-Pople) method, CNDO (Complete Neglect of Differential Overlap) method, INDO(Intermediate Neglect of Differential Overlap) method, MINDO(Modified INDO) method, MNDO(Modified Neglect of Diatomic Overlap) method, AM1(Austin Model 1) method, MNDO-PM3(Parametric Method 3) method, etc.
- Ab initio MO method

The Huckel method employs the appoximation where there is no interactioN among electrons, so that the entire Hamiltonian is represented by a sum of only one-electron Hamiltonians. In the case of the simple Hückel method which takes into account only the contributions of p electrons the secular equation takes a rather simple form. In the early stage of development of the MO method, this method was applied mainly to larger molecules such as aromatic hydrocarbons to predict the behaviour of carbon atoms which are sensitive to electrophilic substitution reactions and/or nucleophilic displacement reactions. The method was also applied to saturated hydrocarbons treating s electrons. The extended Huckel method does not distinguish the s electrons from the p electrons and in addition it takes into account the contributions of all valence electrons. Even now, this method is sometimes applied to the calculations for a large system including transition metals. In the empirical MO methods one seldom calculates the integrals which appear on deriving the secular equation Instead of calculating the integral values, one rather treats them as parameters whereby drastically simplifying the secular equation and shortening the calculation time. However, the results obtained remain solely at qualitative level

In the semiempirical MO methods one uses some sort of approximations to simplify calculation of the Fock operators. There are a variety of approximations which allow more quantitative considerations than in the case of the empirical methods. It may safely be accepted that the calculated heats of formation using the MNDO-PM3 method reproduce well the experimental values However, when using the semiempirical MO methods, one has to be careful what approximations were used and which experimental values were used for the integrals.

The ab initio MO method does not rely upon any approximations in calculating the Fock operators. However, the method is not almighty The accuracy of the ab initio MO method depends on the quality of the basis functions and the type of wave functions applied. There are a variety of basis functions which can be selected depending on the purpose of the calculations. Correspondingly one has to decide what level of basis functions or wave functions should be used depending on what physical quantities are to be calculated. Thanks to the recent rapid advance in computer technology the ab initio MO method is now finding wide applications.

The structures of molecules obtained by the ab initio MO method have been compared so far with the ones obtained by experiments in various cases and the level of reliability of the structures by this method (depending on the basis functions used) is now well established. Now the structures obtained by the ab initio MO method are seldom questioned if only one is careful in choosing the basis function system. Moreover, not only the most stable structure for a molecule, but also other structures and their relative stabilities can be analyzed by calculation. Although the most stable structure can be achieved by experiments as well, it is difficult to realize unstable structures experimentally. Therefore, the ab initio MO method can provide with the precious informations on the molecular structures of various isomers and the irrelative stabilities and/or the molecular structures in the excited states.

Frontier Electron Theory

K. Fukui of Kyoto University was awarded a Nobel prize for chemistry in 1981 by his achievement in the "frontier electron theory"(6). According to the theory, it is possible to predict in which part of a molecule and with what probability a certain chemical reaction can take place by examining the orbital energy of the specific orbital called "frontier orbital", signs as well as size of the LCAO coefficients. The MO method allows to know the location in the molecules where and with what probability a reaction takes place. When 2n electrons are located on n molecular orbitals, these n orbitals are called occupied orbitals. On the other hand the orbitals in higher energy where no electrons are located are called unoccupied orbitals Among the occupied orbitals the highest occupied molecular orbital HOMO is most related to the reactions. Among the unoccupied orbitals the lowest unoccupied orbital LUMO is most involved in the reactions. The HOMO and the LUMO are both called frontier orbitals, and the electrons which occupy those orbitals are called frontier electrons (Fig. 1).

The frontier electron theory predicts the locations in a molecule where reactions take place with the highest probability as follows:

• An electrophilic reaction takes place at the location where the (probability) density of electrons belonging to the HOMO is the highest, that is, the place where $2 (c_{HOMO,r})^2$ takes the largest value.
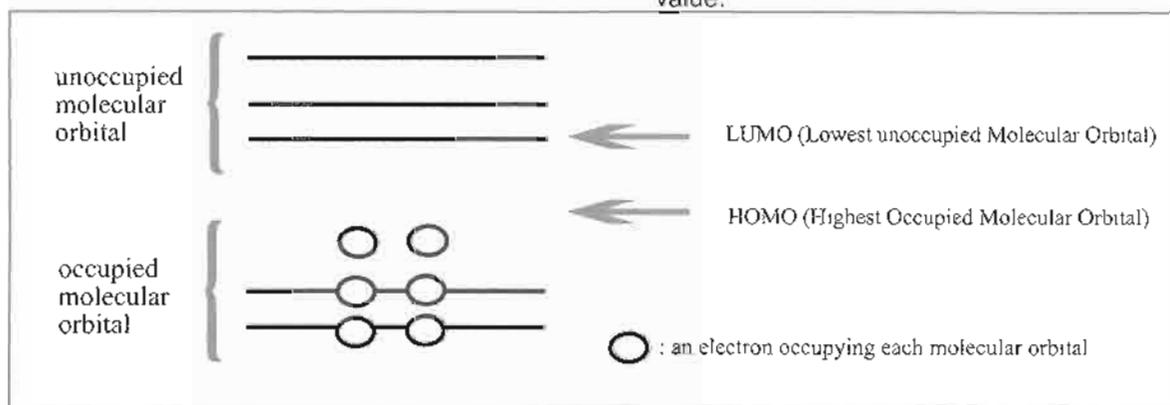

Figure 1:
• A nucleophilic reaction takes place at the location where two electrons are located on the LUMO, that is, the place where the density of these two electrons, $2(c_{LUMO,r})^2$, takes the largest value.
• A radical reaction takes place at the location where the sum of density of two electrons, one on the HOMO and the other on the LUMO takes the largest value.

Before the invention of the frontier electron theory (1952), the necessity had been believed to examine in detail all the orbitals where electrons are located in order to find the location where reactions go with high probability. Fukui could simplify the situation by showing that it is enough to examine only the HOMO in the case of electrophilic reactions while the LUMO in the case of nucleophilic reactions among those orbitals.

This method was established in 1952 by applying the Hückel method to aromatic hydrocarbons (conjugated compound) and comparing the results with a number of experimental facts. It has been demonstrated that the maximum factor deciding reactions is the stabilization due to the localization of electrons in the transition state. That is, it is the frontier electrons that contribute at most. Thanks to such progress of the theory and computer (7), nowadays, it has become possible to realize in computer graphics simulation film on the basis of the accurate calculation by the ab initio MO method, for example, how, when a reagent attacks a molecule, both molecules produce products.

INTERMOLECULAR INTERACTIONS

In molecular assemblies, there arise interactions among molecules. As in the case with covalent bonds which combine two atoms to form a molecule, the origin of the intermolecular interaction between two molecules is also a quantum-mechanical force. When the molecular interaction becomes stronger, chemical reactions take place by accompanying disconnection or formation of covalent bonds. There are always interactions albeit not so strong between molecules.

Intermolecular Interactions in a Living Body

In a living body we encounter a situation in which molecules are distributed not at random, but rather specific intermolecular interactions are functioning so that specific molecules are combined with certain inevitability or regularity. In addition, as in the case with antigen-antibody reaction, molecules specifically recognize another molecules, whereby identifying and eliminating objects which might be danger to the normal existence of a living body, or, on the contrary, collecting or accepting objects which are necessary for the living body.

When certain molecules maintain physiological activity in a living body, there exist the interactions between these molecules and the biopolymers that accept them. If the molecules from another site manage to specifically couple with biopolymers such as protein, we say that the molecules have been "recognized". These molecules are called a ligand (substrate) and a receptor, respectively. Discovering a ligand with higher binding activity can lead to development of effective medicaments.

In order to identify a ligand with higher binding activity, one has to identify a molecule which possesses stronger interaction. In general in order to synthesize various molecules by repeating experiments in laboratory one needs enormous time and money. On the other hand the quantum chemical technique allows one to calculate the molecular interaction energy and charge distribution, and so on, with reliable precision. The electrostatic force which is a far-reaching force plays an important role when a biopolymer such as protein and nucleic acid interacts with a substrate. Thus, the knowledge of the charge distribution on the molecular surface provides the information about a global nature of the molecular interactions.

The situation where a molecule A "recognizes" a molecule B, but it does not "recognize" a molecule C is controlled as follows: When the A "recognizes" the B, there exists specific intermolecular interaction between these molecules. In other words the "recognition" between molecules occurs only when such specific interaction exists and if there is no such molecular interaction between the molecules A and C, the molecule A does not "recognize" the molecule C.

Hydrogen Bond

It is a hydrogen bond that plays the most crucial role in the recognition between molecules. The hydrogen bond is generally represented as -X-H°Y-, where X is an atom with large electronegativity such as N (nitrogen atom) and O (oxygen atom), so that a X-H bond has strong polarity: electrons are attracted to X and H (hydrogen atom) is slightly positively charged (δ^+). An atom Y possesses large electronegativity and is

slightly negatively charge (δ^-). Thus the hydrogen bond is generated by the interaction between X-H with strong polarity and Y with large electronegativity. The main feature of the hydrogen bond consists in its directionality. When X-H lines up with Y, the interaction energy becomes most stable A concrete image of the interaction between the peptide main chains comprising protein is as shown in Fig. 2. Thus when N-H lines up with O=C, the interaction between peptides becomes most stable. On the other hand if the angle between N-H and O=C is deviated far from 180°, no stable hydrogen bonds can be formed between peptides.

In this way the stable hydrogen bonds are formed only when certain specific atoms exist in a specific configuration. They play the leading role a specific molecular interaction. An antigen-antibody reaction is often compared to a relationship between a key and keyhole.

In the antigen-antibody reaction it is the hydrogen bonds that play the leading role of specific recognition reaction

There are 8 types of hydrophobic amino acid, 4 types of charged amino acid and 8 types of polar amino acid among the amino acids that form normal protein.[8] It is the charged amino acid and the polar amino acid that are mainly involved in the formation of hydrogen bonds. The interaction between the charged groups is sometimes called an ionic bond. However, actually, the interaction between the charged groups includes largely characteristics of hydrogen bonds. For example, the interaction between a negatively charged carboxyl group ($-COO^-$) and a positively charged amino group ($-NH_3^+$) is due to a hydrogen bond whose stabilization energy shows strong directionality.

The hydrogen bond energy is about a few kcal/mol and such hydrogen bond is not stably formed unless both molecules are close enough. The distance-dependency and angle-dependency of

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C_a denotes the C_a atom in each amino acid, while R indicates the side chain peculiar to each amino acid.
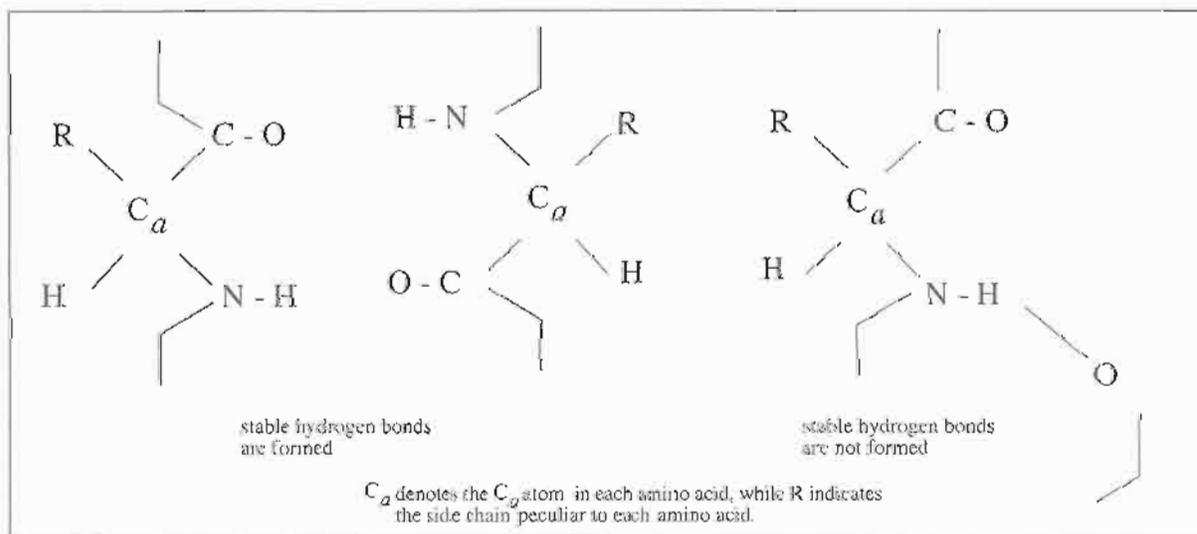
Figure 2:
The hydrogen bond energy can also be calculated in the framework of quantum-chemical methods. Thus questions such as to what level of stability molecules can be coupled etc. can be solved by quantum-chemical calculations.

DRUG DESIGN

Recently, a variety of molecular-design techniques called drug design are applied to the development of new medicaments. Rather than synthesizing a series of compounds and measuring all their activity, quantum-chemical calculations allow to obtain more effectively information about the structures and their reactions. Of course, it is impossible to produce new medicaments by basing only on the quantum-chemical calculations, but such calculations unquestionably would facilitate and assure the process of their development.

DNA and Genetic Informations

The DNAs normally exist as a double helix and contain genetic informations (9) In order for the genetic informations contained in the DNAs to be preserved forever and transmitted from generation to generation without errors, four DNA bases, adenine (A) and thymine (T), and guanine (G) and cytosine (C) play a crucial role. The fact that these bases form hydrogen-bond pairs stably provides the basis of existence of our living bodies. By clarifying the distance-dependency and angle-dependency of the hydrogen-bond energy between A and T, and between G and C by means of quantum-chemical calculations, it has been found that the relative configuration of bases in the DNA double helix corresponds to such a configuration that allows A and T, and G and C to form the hydrogen bonds. Namely, the remaining part of a DNA (sugar and phosphate group) prepares an environment in which A and T, and G and C can form the hydrogen bonds stably.

It is known that the DNAs take structures which are roughly classified into 3 types, type A, type B and type Z. The DNAs of type A and type B have a double right-handed helix structure. On the other hand the DNAs of type Z consist of an anti-clockwise helix with a zigzagged framework of sugar and phosphate groups. However, if we focus only on the hydrogen bonds between bases, the structure of hydrogen bond pairs are common to all these types. Although the sugar and phosphate groups can move freely and change the structure, the relative configuration among the bases remain unchanged. The DNA's global structure varies subtly according to the base sequence. While protein recognizes a DNA according to the recognition of the functional groups specific to four types of bases, it is also possible that any deformation in the DNA's global structure could be a signal for the DNA recognition.

If these bases are modified or replaced by other substances, the genetic informations might be changed and the function of the resulting protein might be affected, or in some cases even the required protein might not be produced at all, or no control might be effective. Such a process might be a cause of cancer. Quantum chemistry offers a powerful tool to identify the specificity of the interactions between nucleic acid bases as well as the interactions between nucleic acid bases and amino acids. What part of the nucleic acid does protein (which controls the appearance of genetic informations of the nucleic acid) recognize and combine specifically to perform the function? -this is one of the most important themes which the modern molecular biology is actively studying. The quantum-chemical techniques in parallel with experiments are indispensable to clarify the issues.

DISCUSSION

The progress in chemistry and its application fields would not be possible without understanding the essence of chemical phenomena and reactions. Such understanding can be achieved only through quantum chemistry. By the progress in understanding a variety of chemical phenomena it becomes possible to expect synthesization of a variety of industrial products with high quality, to develop an efficient synthesis method, to compose new medicaments effectively, to clarify the causes of cancers, etc. More importantly the achievement of quantum chemistry gives stimulus to the developments of the life science fields, such as the molecular biology, and is making possible the deeper understanding of the essence of "life". As is well known life sciences find also a variety of applications in medicine, such as genetic therapy. As is explained in this paper quantum chemistry plays a fundamental role in under-standing things closely related to our life.

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