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MO study of Hydride Transfer between NADH and Flavin Nucleotides

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The mechanism has been MO-theoretically described for the reaction of NADH and flavin nucleotides. Their bioactive regions were found to be the part forming transbutadiene type in the molecular by examing the respective HOMO and LUMO electron densities of nicotinamide ring and isoalloxazine ring of flavin. The elecron densities of 1, 2, 3 and 4 positions of the transbutadiene part were found to be considerably larger than those of any other positions in the molecules. A loose molecular complex, which stacks with congruity between C(4) of nicotinamide ring and N(5) of the isoalloxazine ring, was estimated to be formed by calculating the quantities of charge transfer occuring through 1, 2, 3 and 4 positions between them. Accordingly, we propose the mechanism that molecular complex first would be formed and follwed by the hydride transfer.

Introduction

Flavin coenzymes of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are derived coenzymatically from vitamine B_2 riboflavin. They function as tightly bound prosthetic groups of flavoproteins or flavoenzymes. It is well known that the reduction of flavin nucleotides by the reduced nicotinamide adenine dinucleotide (NADH) occurs by the direct hydride transfer.

Hydride (*H⁻) transfers from C(4) of nicotinamide ring to N(5) of isoalloxazine ring of FMN or FAD[1]. Though experimental studies were carried out to explore the above reaction[2], theoritical studies are rarely found[3].

We have shown that the active region of chemical carcinogens is the transbutadiene (TB) part in the molecule[4]. There must exist a corresponding active region for any cellular component to interact with the TB part of chemical carcinogen. Assuming the existence active region of a cellular component, this TB model would be applied to predict the activity of mutagens, toxitants and drugs.

We have confirmed as a matter of fact that active sites of mutagens, toxitants and drugs are all the same 1, 2, 3, and 4 atoms of TB part[8]. An attempt will be made to apply this model to a biochemical reaction of NADH with flavin.

Method and Model

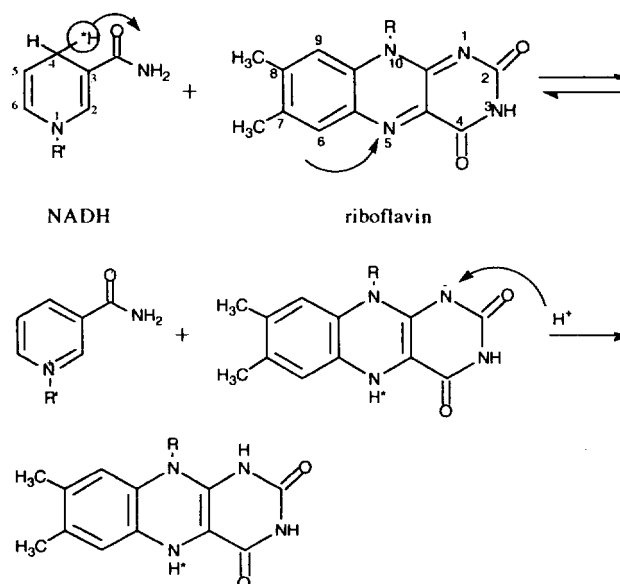MO molecular orbital calculation was carried out at the

Figure 1. Transfer of reducing equivalents from NADH to flavin.

extended Hückel level for the nicotinamide ring and isoalloxazine ring in which CH_3 group were substitude for R. The interatomic distances and bond angles are cited from X-ray data[9].

The respectrive frontier eletron density for r-th atom in

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a molecule in nucleophilic and electrophilic reaction can be expressed as

$$f_r^N = 2(C_r^{LUMO})^2 \text{ and } f_r^E = 2(C_r^{HOMO})^2 \qquad (1)$$

The f_r^N and f_r^E can be regarded as measures of ability of acepting and donating electrons from an eletrophile to a nucleophile, respectively.

Since many cellular components such as DNA and protein are electron rich. It can be considered as nucleophile. Chemical carcinogens are electron deficient compared to the cellular components, hence they acts as the elecrophile when reating cellular components.

A noncovalent molecular complex between a cellular component and a chemical carcinogen is generally acepted as the first step in chemical carcinogenesis. The larger the ability if a cellular component to donate electrons and the ability of a chemical carinogens to accept electrons, the easier the formation of a molecular complex. Stated in a different way, the larger values of f_r^N and f_r^E indicate the tendency of the higher charge transfer between them. The extent of charge transfer can be expressed as;

$$dQ = 2\left[\sum_j^{OCC} \sum_k^{UNOCC} - \sum_j^{UNOCC} \sum_k^{OCC}\right] \frac{(C_r^j C_s^k \gamma_1 + C_r^j C_u^k \gamma_2 \cdots)^2}{(E_{Aj} - E_{Bk})^2} \qquad (2)$$

Here C_r^j is the eigenvector of r-th atomic orbital in j-th molecular orbital; E_A^j is the eigenvalue of a molecule in j-th molecular orbital; $\sum_j^{OCC}$ and $\sum_j^{UNOCC}$ denotes the summation of all occupied and unoccupied molecular orbital, respectively; γ_1 is the resonance integral between r and s atoms.

On the basis of this idea, we have examined whether any atom in carinogens has particularly large values of f_r^N. We found that 1-4 atoms forming TB frame in a carcinogen have relatively large of LUMO electron densities (f_r^N) compared to the others.

Accordingly, we have postulated that the region of TB structure is the active region of carcinogens in their carcinogenesis, and the sum of LUMO electron densities$(F^{(N)}_{1,2,3,4})$ of the 1-4 atoms can be regarded as a reactive index of precarcinogens[7].

Therefore, the reactive index is

$$f^{(N)}_{1,2,3,4} = f_1^{(N)} + f_2^{(N)} + f_3^{(N)} + f_4^{(N)} \qquad (3)$$

On the basis of the above TB model, we have reported previously that this model can be applied to the interations not only between carcinogens but also between mutagens, toxidants, drugs and all components[8].

The TB model may be applied to general biochemical reactions, such as the redox reaction between NADH and flavins.

Sine there exist many occupied and unoccupied molecular orbitals due to many atoms in biochemical compounds, it will be convenient to obtain an approximate charge transfer.

The approximate charge transfer equation considering only HOMO-LUMO interaction is as follws:

$$dQ = 2\left[\sum_A^{HOMO} \sum_B^{LUMO} - \sum_A^{LUMO} \sum_B^{HOMO}\right] \frac{(C_rC_s + C_T + C_U + \cdots)^2\gamma^2}{(E_A^{HOMO} - E_B^{LUMO})^2} \qquad (4)$$

As approximation, $\gamma_1, \gamma_2, \gamma_3 \cdots$(at eq. 2) can be replaced by γ, since $\gamma_1, \gamma_2, \gamma_3 \cdots$ Would be almost the same between
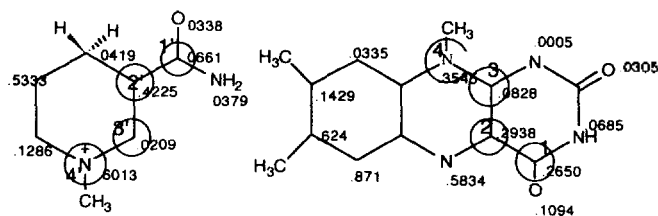
LUMO = -9.17473   LUMO = -10.42826
HOMO = -11.28169   HOMO = -11.93421

Figure 2. Frontier electron densities and energy levels of NADH and flavin.
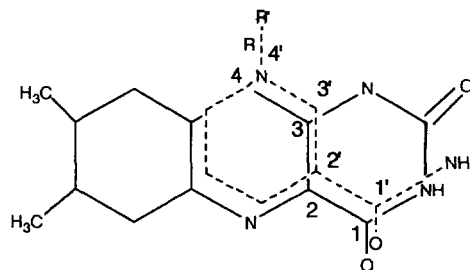

Figure 3. The molecular complex between NADH and flavin.

two atom stacking nuleophile and electrophile because of larger distance than usual chemical bonds.

Results and Discussion

As shown in Introduction, the hydride transfer occurs from NADH to flavin in their reaction. The HOMO and LUMO electron density must be known for the reduced NADH nucleus and the oxidized flavin nucleus, respectively. The data obtained are shown in Figure 2.

The region indicated in Figure 1 forms trans butadiene frame and tentatively numbered 1, 2, 3 and 4 atoms is considerably larger than those of any other atoms in NADH and flavin nucleus.

The respective values of frontier electron densities of NADH and flavin determined by eq. (4) are as follows:

$$f^{(E)}_{1,2,3,4} = f_1^{(E)} + f_2^{(E)} + f_3^{(E)} + f_4^{(E)}$$
$$= 0.0661 + 0.4225 + 0.0209 + 0.6013 = 1.1108$$

$$f^{(N)}_{1,2,3,4} = f_1^{(N)} + f_2^{(N)} + f_3^{(N)} + f_4^{(N)}$$
$$= 0.2650 + 0.2938 + 0.0828 + 0.3545 = 0.9961$$

The abilities of donating and accepting electrons can be seen to be considerably large in the above frontier electron density calculation.

Therefore, it may be postulated that the HOMO-LUMO interaction occurs between NADH and flavin to form a molecular complex as shown in Figure 2.

It is clearly seen in Figure 2 that the 1, 2. 3 and 4 positions of NADH correspond exactly to 1, 2, 3 and 4 of flavin.

According to eq. (4), the quantity of charge transfer, dQ_{app}, is 0.9265 $(\gamma/eV)^2$ when the charge transfer is assumed to occur through 1, 2, 3 and 4 positions of flavin and NADH.
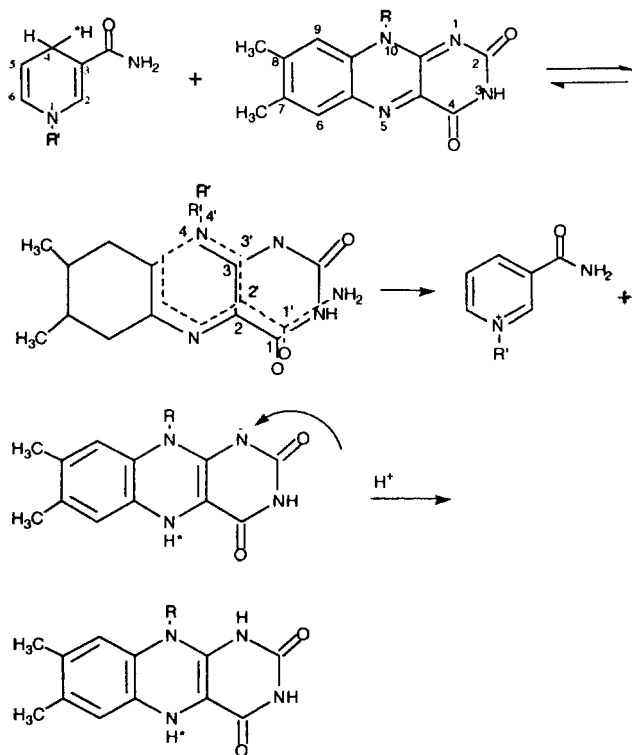
Figure 4. The mechanism of hydride transfer form NADH to flavin.

The charge transfers between other atoms are found to be negligible compared to those between the 1, 2, 3 and

4 positions.

Accordingly, it is proposed that a loose NADH-flavin molecular complex is formed before hydride transfer in the first step, and followed by hydride transfer:

This model nicely explains the fact that hydride at C(4) of NADH transfers to N(5) of flavin.

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The Kinetics of Formation and Dissociation of the 1,4,7,10,13,16-Hexaazacyclooctadecane-1,4,7,10,13,16-hexaacetate Complex of Cerium(III)

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The formation and dissociation rates of the 1,4,7,10,13,16-hexaazacyclooctadecane-1,4,7,10,13,16-hexaacetic acid (H_6heha) complex of Ce(III) ion have been measured by stopped-flow and conventional spectrophotometry. Observations were made at 25.0±0.1℃ and at an ionic strength of 0.1 M $NaClO_4$. The formation reaction takes place by rapid formation of an intermediate complex in which the metal ion is incompletely coordinated. In the pH range 4.1-5.2, the H_3heha^{3-} species is the kinetically active one despite of its low concentration. The exchange reaction occurring between the [Ce(heha)]$^{3-}$ complex and Cu^{2+} ion proceeds via both an acid-independent and an acid-catalyzed pathway. The buffer concentration dependence of the dissociation rate has also been investigated. The dissociation rate of the [Ce(heha)]$^{3-}$ complex is much faster than that of [Ce(nota)] and [Ce(dota)]$^-$. The chelate ring size effect is discussed by comparing the rate constants to those of analogous nota and dota systems.

Introduction

The lanthanide complexes with the macrocyclic dtpa bis (amide)s and polyazapolycarboxylates, 1,4,7-tris(carboxyme-thyl)-9,14-dioxo-1,4,7,10,13-pentaazacyclopentadecane (H_3dtpa-eam), 1,4,7-triazacyclononane-1,4,7-triacetic acid (H_3nota), 1,4,