

- Scaiano, J. C. *J. Am. Chem.* **1992**, 114, 2630.
9. Tanigaki, K.; Ebbesen, T. W. *J. Am. Chem. Soc.* **1987**, 109, 5883.
10. Tanigaki K.; Ebbesen, T. W. *J. Phys. Chem.* **1989**, 93, 4531.
11. (a) Zeller, K. P. *Chem. Ber.* **1975**, 108, 3566; (b) Zeller, K. P. *Chem. Soc. Chem. Commun.* **1975**, 317.
12. Rosenfeld, A.; Mitzner, R.; Baumbach, B.; Bendig, J. *J. Photochem. Photobiol. A Chem.* **1990**, 55, 259.
13. (a) Hayes, R. A.; Hess, T. C.; McMahon, R. J.; Chapman, O. L. *J. Am. Chem. Soc.* **1983**, 105, 7786; (b) McMahon, R. J.; Chapman, O. L.; Hayes, R. A.; Hess, T. C.; Krimmer, H. P. *J. Am. Chem. Soc.* **1985**, 107, 7597.

MO study of Hydride Transfer between NADH and Flavin Nucleotides

Byung-Kak Park, Seong-Tak Doh, Gwan-Su Son, Jong-Mun Kim, and Gab-Yong Lee*

Department of Chemistry, Yeungnam University

*Department of Chemical Education, Hyosung Women's University

Received September 24, 1993

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 examining the respective HOMO and LUMO electron densities of nicotinamide ring and isoalloxazine ring of flavin. The electron 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 occurring through 1, 2, 3 and 4 positions between them. Accordingly, we propose the mechanism that molecular complex first would be formed and followed by the hydride transfer.

Introduction

Flavin coenzymes of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are derived coenzymatically from vitamin B₂ 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 FAD¹. Though experimental studies were carried out to explore the above reaction², theoretical studies are rarely found³.

We have shown that the active region of chemical carcinogens is the transbutadiene (TB) part in the molecule⁴. 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, toxicants and drugs.

We have confirmed as a matter of fact that active sites of mutagens, toxicants and drugs are all the same 1, 2, 3, and 4 atoms of TB part⁸. 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

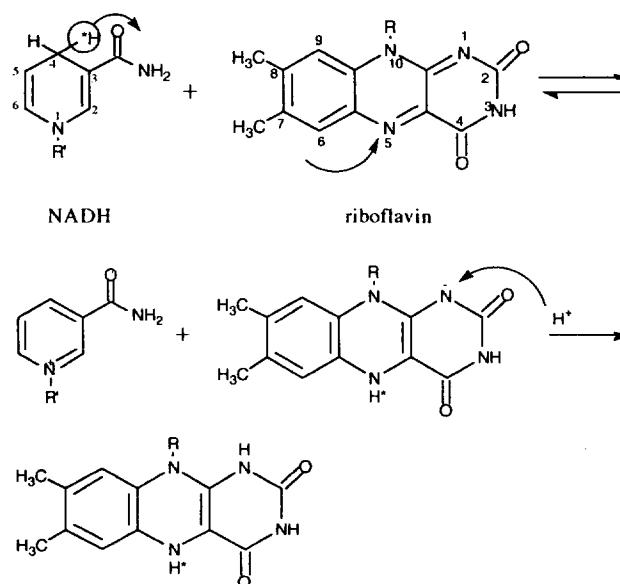


Figure 1. Transfer of reducing equivalents from NADH to flavin.

extended Hückel level for the nicotinamide ring and isoalloxazine ring in which CH_3 group were substitute for R. The interatomic distances and bond angles are cited from X-ray data⁹.

The respective frontier electron density for r-th atom in

a molecule in nucleophilic and electrophilic reaction can be expressed as

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

The f_r^N and f_r^E can be regarded as measures of ability of accepting and donating electrons from an electrophile 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 electrophile when reacting cellular components.

A noncovalent molecular complex between a cellular component and a chemical carcinogen is generally accepted as the first step in chemical carcinogenesis. The larger the ability of a cellular component to donate electrons and the ability of a chemical carcinogens 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;

$$dQ = 2 \left[\sum_j^{OCC} \sum_k^{UNOCC} - \sum_j^{UNOCC} \sum_k^{OCC} \right] \frac{(C_j^i C_k^s \gamma_1 + C_j^i C_k^t \gamma_2 \dots)^2}{(E_{Aj} - E_{Bk})^2} \quad (2)$$

Here C_j^i is the eigenvector of i -th atomic orbital in j -th molecular orbital; E_{Aj} 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 carcinogens 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 ($f_{1,2,3,4}^N$) of the 1-4 atoms can be regarded as a reactive index of precarcinogens⁷.

Therefore, the reactive index is

$$f_{1,2,3,4}^N = f_1^N + f_2^N + f_3^N + f_4^N \quad (3)$$

On the basis of the above TB model, we have reported previously that this model can be applied to the interactions not only between carcinogens but also between mutagens, toxicants, drugs and all components⁸.

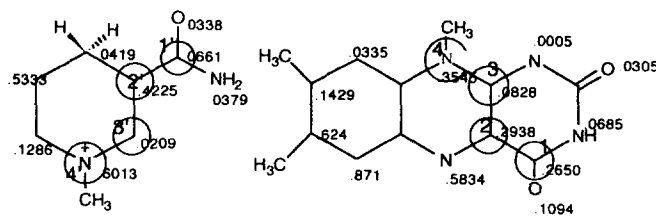
The TB model may be applied to general biochemical reactions, such as the redox reaction between NADH and flavins.

Since 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 follows:

$$dQ = 2 \left[\sum_A^{HOMO} \sum_B^{LUMO} - \sum_A^{LUMO} \sum_B^{HOMO} \right] \frac{(C_A^H C_B^L + C_A^L C_B^H + \dots)^2}{(E_A^{HOMO} - E_B^{LUMO})^2} \quad (4)$$

As approximation, $\gamma_1, \gamma_2, \gamma_3 \dots$ (at eq. 2) can be replaced by γ , since $\gamma_1, \gamma_2, \gamma_3 \dots$ Would be almost the same between



LUMO = -9.17473

HOMO = -11.28169

LUMO = -10.42826

HOMO = -11.93421

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

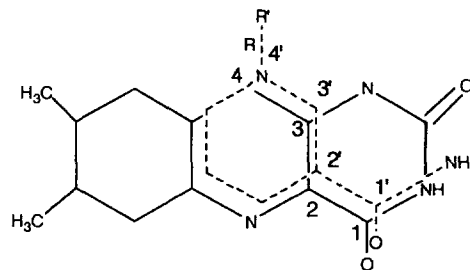


Figure 3. The molecular complex between NADH and flavin.

two atom stacking nucleophile 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:

$$\begin{aligned} f_{1,2,3,4}^E &= f_1^E + f_2^E + f_3^E + f_4^E \\ &= 0.0661 + 0.4225 + 0.0209 + 0.6013 = 1.1108 \end{aligned}$$

$$\begin{aligned} f_{1,2,3,4}^N &= f_1^N + f_2^N + f_3^N + f_4^N \\ &= 0.2650 + 0.2938 + 0.0828 + 0.3545 = 0.9961 \end{aligned}$$

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 (γ/eV)² when the charge transfer is assumed to occur through 1, 2, 3 and 4 positions of flavin and NADH.

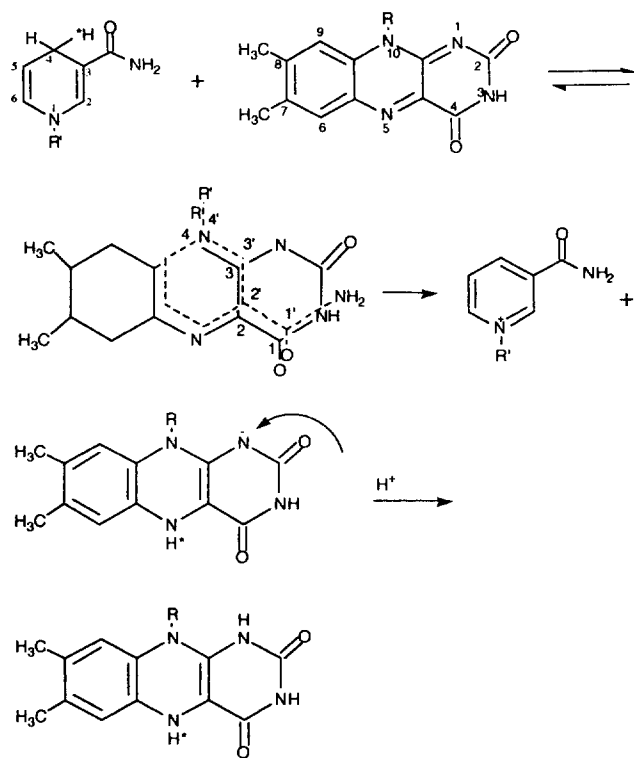


Figure 4. The mechanism of hydride transfer from NADH to flavin.

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.

References

- (a) Haper, J. David Rawn; Publishers, Row *Biochemistry* **1983**, 412; (b) Christopher Walsh, Freeman, W. H.; Company, *Enzymatic Reaction Mechanism* **1979**, 362.
- (a) Umeyama, H.; Imamura, A.; Nagata, C. *J. Theoret. Biol.* **1974**, 46, 1; (b) Eys, J. V.; Stolzenbach, F. E.; Sherwood, L.; Kosower, N. O. *Biochem. Biophys. Acta*, **1958**, 27, 63; (c) Kosower, E. M. *Biochem. Biophys. Acta*, **1962**, 56, 474.
- (a) Nishimoto, K. *Bull. Chem. Soc. Japan* **1967**, 40, 2493; (b) Song, P. S. *Ann. New York Acad. Sci.* **1969**, 158, 410.
- Park, B.-K. *J. Kor. Chem. Soc.* **1980**, 24, 3.
- Hoffman, R. J. *Chem. Phys.* **1963**, 39, 1390.
- (a) Streitweiser, A. *Molecular Orbital Theory for Organic Chemists*; John Wiley and Sons Inc.: New York, 1961; (b) Fukui *et al.*, *J. Chem. Phys.* **1952**, 20, 722.
- (a) Park, B.-K.; Lee, M.-H.; Doh, S.-T. *Bull. Kor. Chem. Soc.* **1985**, 6, 103; (b) Park, B.-K.; Suh, M.-C. *ibid.* **1986**, 7, 183.
- Park, B.-K. 33th seminar in Korean Physical Organic Chemistry 1992.
- Sutton, L. E.; Phil, M. A. D. *Table of Interatomic Distances and Configuration in Molecules and Ions*; Chemical Society Burlington House: London, 1965.

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)

Ki-Young Choi* and Choon Pyo Hong†

*Department of Chemistry, Mokwon University, Taejeon 301-729

†Department of Chemical Education, Kongju National University, Kongju 314-701

Received November 22, 1993

The formation and dissociation rates of the 1,4,7,10,13,16-hexaazacyclooctadecane-1,4,7,10,13,16-hexaacetic acid ($H_6\text{heha}$) complex of Ce(III) ion have been measured by stopped-flow and conventional spectrophotometry. Observations were made at $25.0 \pm 0.1^\circ\text{C}$ and at an ionic strength of 0.1 M NaClO₄. 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 $H_6\text{heha}^{3-}$ species is the kinetically active one despite of its low concentration. The exchange reaction occurring between the $[\text{Ce}(\text{heha})]^{3-}$ 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 $[\text{Ce}(\text{heha})]^{3-}$ complex is much faster than that of $[\text{Ce}(\text{nota})]$ and $[\text{Ce}(\text{dota})]^-$. 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(carboxymethyl)-9,14-dioxo-1,4,7,10,13-pentaazacyclopentadecane ($H_3\text{dtpa}$ -eam), 1,4,7-triazacyclononane-1,4,7-triacetic acid ($H_3\text{nota}$), 1,4,