The Mechanism of NAD(P)H Reduction Reactions

Satoshi INAGAKI and Yoshio HIRABAYASHI

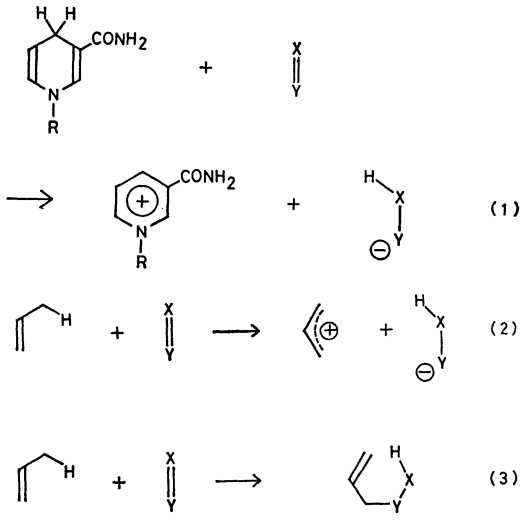
Department of Synthetic Chemistry, Faculty of Engineering, Gifu University, Kakamigahara, Gifu 504

(Received June 25, 1977)

The mechanism of reduction reactions by 1,4-dihydronicotinamides is investigated from the theoretical point of view of the electron configuration and orbital interactions for many systems. The following conclusions are drawn: (1) The reactions are situated near the one-electron-transfer region in the mechanistic spectra dependent on the donor-acceptor property of the reactants; (2) the hydride-equivalent transfers involved, whether concerted or not, proceed more or less in accordance with the nature of the sequential electron-proton-electron shift rather than *via* direct hydride-ion transfer; (3) the paradoxical frontier orbital interaction between the σ-LUMO of C_4–H of 1,4-dihydronicotinamides and the LUMO of substrates is significantly involved in the transfer of the protonic entity. Pseudoexcitation is classified into Type I, where the normal HOMO-LUMO interaction remains important in addition to the LUMO-LUMO and HOMO-HOMO interactions, and Type II, where the HOMO-LUMO interaction contributes little. The NAD(P)H reduction reactions are predicted to belong to Type II.

The roles of nicotinamide-adenine dinucleotide (NAD^+) and its phosphoric acid derivative ($NADP^+$), and their reduced form (NAD(P)H) in enzymic oxidation-reduction reactions have been interesting subjects not only in biochemistry, but also in organic chemistry.[1] These coenzymes catalyze similar reactions. Here they can be considered together. The enzymic reactions involve the transfer of a hydride equivalent between the pyridine nucleus in the coenzymes and substrates, generally formulated as in Eq. 1. The reduction reaction is regarded as a special case of further simplified process in which a hydride equivalent is transferred from an allylic position of one molecule to an unsaturated atom of another molecule (Eq. 2).

Theoretically of interest are the fact that no bonds form between the usually very reactive π bonds of 1,4-dihydronicotinamide groups and unsaturated substrates, and the nature of the hydride-equivalent shift. In this paper we shall present a qualitative molecular orbital argument to disclose underlying factors which differentiate the hydride-equivalent shift from the ene reaction (Eq. 3). The mechanism of NAD(P)H reduction reactions is inferred from the theoretical results.



(1)

(2)

(3)

Theoretical

The reaction we are interested in is a bimolecular reaction between electron-donating unsaturated compounds with a reactive σ bond at the allylic position and electron-accepting unsaturated compounds. The weak interaction between the σ bond (M) and the π bond (D) in the donor allows us to suppose our reaction to be a termolecular interaction of M, D, and the acceptor π bond (A).[2,3]

Let the ground-state wavefunction, Ψ, be a linear combination of the electron configurations, Φ_K's, constructed by using the molecular orbitals of each system, *i.e.*,

$$\Psi = \sum_K C_K \Phi_K. \tag{4}$$

The electron density, $\rho(1)$, is then given by

$$\rho(1) = \sum_K C_K^2 \rho_{K,K}(1) + 2\sum_{K>L} C_K C_L \rho_{K,L}(1), \tag{5}$$

$$\rho_{K,K}(1) = n\int \Phi_K^2 dv_2 \cdots dv_n d\sigma_1 \cdots d\sigma_n,$$

$$\rho_{K,L}(1) = n\int \Phi_K \Phi_L dv_2 \cdots dv_n d\sigma_1 \cdots d\sigma_n.$$

Electron delocalization, responsible for the formation of covalent bonds, comes from the HOMO-LUMO interaction or from the mixing of the electron-transferred configuration, D^+A^-, into the initial configuration, DA.[4] The frontier orbital interaction contributes both to stabilizing the system and to accumulating electrons in the intermolecular region where bonds occur.[5] It may be a good approximation in our qualitative arguments to take into consideration the reorganization of the electronic structure due to electron transfer or promotion from HOMO to LUMO.

A further selection of configurations is possible from the point of view of intermolecular electron density. The density fraction, $\rho_{K,K}$, is approximated as the sum of the squares of the occupied orbitals in Φ_K. This term has little to do with the intermolecular electron density. Some $\rho_{K,L}$'s contain a product of two orbitals which belong to different molecules. These terms contribute significantly to the intermolecular density. Such a pair of configurations, K and L, should be obtained from each other by shifting an electron from one molecule to another. Figure 1 displays the configuration pairs (see Appendix).

Suppose that the donor-acceptor property of D and A is less significant. The ground-state wavefunction can then be approximated as a linear combination of

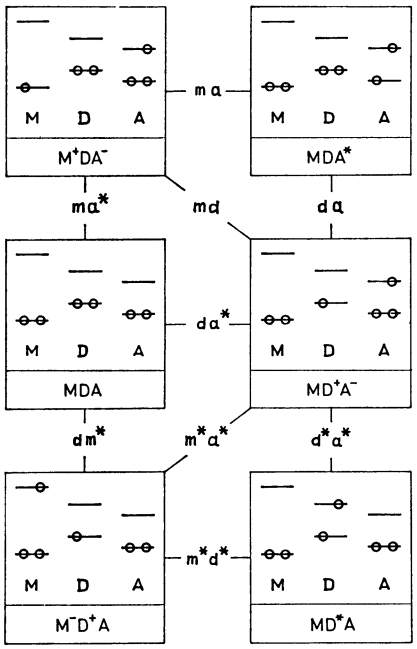
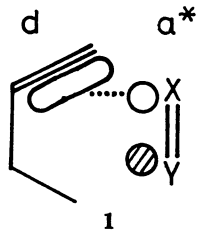


Fig. 1. Electron configuration pairs responsible for intermolecular electron density.

MDA and MD^+A^- (Eq. 6),

$$\Psi \simeq C_{MDA}\Phi_{MDA} + C_{MD^+A^-}\Phi_{MD^+A^-}, (C_{MDA} > C_{MD^+A^-}). \quad (6)$$

The intermolecular density is due to the orbital overlap between d and a*, *i.e.*, the first term in ρ_{MDA,MD^+A^-} (Eq. A7). For this donor-acceptor relation, bond formation neither between M and D nor between M and A is expected, while an attractive interaction gives rise to the association of D and A. The geometrical structure favoring the d-a* interaction was previously shown to be a three-centered interaction such as **1**.[6-8] No reactions of interest are likely to occur.



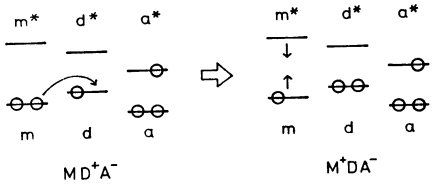
1

Second, let the power of A increase. The energy level of MD^+A^- then lowers and approaches that of MDA so closely that both configurations contribute comparably to the ground-state wavefunction. The comparable contribution of MD^+A^- accompanies an appreciable mixing-in of K's which have a large matrix element with MD^+A^-.[9] The M^+DA^-, M^-D^+A, MD*A, and MDA* configurations are here taken into consideration. The mixing-in of ditransferred configurations, $M^+D^+A^{--}$, $MD^{++}A^{--}$, and $M^-D^{++}A^-$, may be negligible because of the large energetical separation from MDA and MD^+A^-. The ground-state wavefunction is then approximated to be

$$\Psi \simeq C_{MDA}\Phi_{MDA} + C_{MD^+A^-}\Phi_{MD^+A^-} + C_{M^+DA^-}\Phi_{M^+DA^-} + C_{M^-D^+A}\Phi_{M^-D^+A} + C_{MD^*A}\Phi_{MD^*A} + C_{MDA^*}\Phi_{MDA^*}, \quad (7)$$
$$(C_{MDA} \simeq C_{MD^+A^-} > C_{M^+DA^-} \simeq C_{M^-D^+A} \simeq C_{MD^*A} \simeq C_{MDA^*}).$$

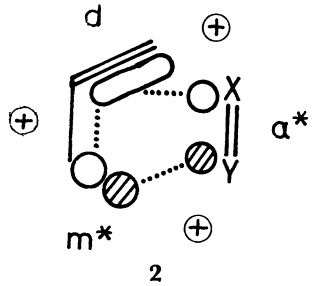
The coefficients, C_{MDA} and $C_{MD^+A^-}$, are larger than any others. Of primary concern are the configurations which contribute to the intermolecular density by means of the interactions with MDA or MD^+A^- (Eqs. A7—A13).

The most important interaction remains the one between MDA and MD^+A^- or between d and a*. A favorable geometry must resemble **1**, although the additional interactions singled out above may modify it. Most interesting is the interaction between MD^+A^- and M^+DA^-, since the weights of both configurations increase to a greater extent as the energy levels lower with an increase in the electron-acceptability of A. This interaction delocalizes the electrons from M to D through the m-d overlap (Eq. A10). The removal of the bonding electrons from m results in a weakening of the σ bond. The concurrent bond-lengthening lowers the m* level, increasing the ability of M to accept electrons



Scheme 1.

(Scheme 1). The M^-D^+A configuration is then allowed to mix effectively. The interaction of M^-D^+A with MD^+A^-, involving the m*-a* overlap (Eq. A11), leads to the structural change from **1** to a transient six-membered-ring state, **2**. As a result, the key orbital interaction occurs among d, a*, and m*. Ene reactions (Eq. 3) take place in this donor-acceptor region.[3]



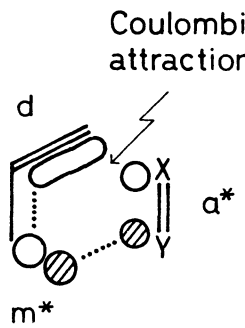
2

Finally, let us discuss the nature of the interaction with the more powerful A. The weights of MD^+A^- and M^+DA^- increase further while the weight of MDA decreases. Consequently, the M^-D^+A configuration contributes to a greater extent. The ground-state wavefunction is then approximated as

$$\Psi \simeq C_{MD^+A^-}\Phi_{MD^+A^-} + C_{M^+DA^-}\Phi_{M^+DA^-} + C_{M^-D^+A}\Phi_{M^-D^+A}, \quad (8)$$
$$(C_{MD^+A^-} > C_{M^+DA^-} \simeq C_{M^-D^+A}).$$

The main configuration is MD^+A^-. The significant interactions are those with MD^+A^-, *i.e.*, the MD^+A^--M^-D^+A and MD^+A^--M^+DA^- interactions. The m*-a* orbital overlap involved in the MD^+A^--

M^-D^+A interaction (Eq. A11) is responsible for the hydride-equivalent transfer, while the d-m orbital overlap involved in the MD^+A^--M^+DA^- interaction (Eq. A10) contributes to π-bond formation between D and M. It should be noted that the ρ_{MDA,MD^+A^-} term predominantly responsible for D-A bonding disappears, since $C_{MDA} \simeq 0$. The extreme stabilization of MD^+A^- disfavors the bond formation between D and A, although D and A are presumably bound through the Coulombic attraction. This difference from the preceding cases characterizes the reactions of powerful A's. The key orbital interaction is illustrated in **3**. The reactions for this donor-acceptor region take place *via* an almost one-electron transfer prior to the transfer of H as a protonic entity, with no σ-bond formation between the π bonds of the reactants.



3

It was proposed that the chemical processes significantly involving the HOMO-HOMO (D^+A^--DA*) and/or LUMO-LUMO (D^+A^--D*A) interactions(s) even on the ground-state potential energy surface be termed "pseudoexcitation."[9] Attention was not paid to whether or not the HOMO-LUMO interaction remains important in addition to the HOMO-HOMO and LUMO-LUMO interactions. The pseudoexcitation is here proposed to be classified into Types I and II. Type I involves the HOMO-LUMO interaction significantly, while Type II does not (Fig. 2). The hydride-equivalent shift belongs to Type II (see **3**), while the ene reaction belongs to Type I (see **2**).

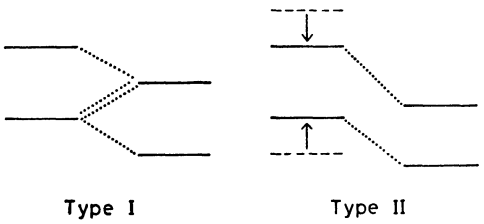
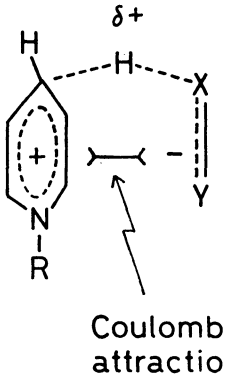


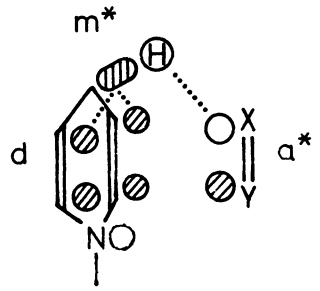
Fig. 2. Pseudoexcitation.

Discussion

From the preceding theoretical arguments on the prototype reaction, it can be suggested that the reduction of unsaturated bonds by 1,4-dihydronicotinamides occurs more or less in accordance with the nature of the sequential electron-proton-electron shift. The hydride-equivalent shift is likely to occur in a concerted manner if the reaction is favored by the donor-acceptor property and other properties. In the transition state, hydrogen migrates as a protonic entity from the cationic dihydronicotinamides to the anionic substrates (**4** and **5**), but not as a hydride anion, as was proposed by Westheimer *et al.*[10]

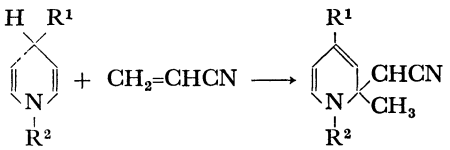


4

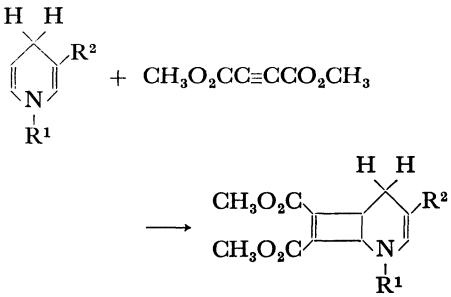


5

When substrates are not such powerful acceptors as to induce the Type II pseudoexcitation, the reactions fall in the Type I pseudoexcitation region. At least one bond forms between the π bonds of dihydronicotinamides and substrates. In fact, acrylonitrile reacts with 1,4-dihydropyridines to give the ene reaction product (Eq. 9),[11] while alkylidene- and arylmethylene-malononitriles are reduced.[12] Another example of the bond formation between the π bonds is the 2+2 cycloaddition reaction with dimethyl acetylenedicarboxylate (Eq. 10).[13]

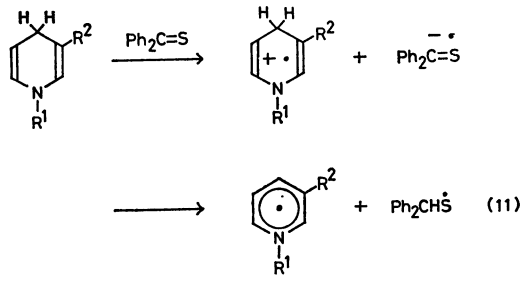


(9)



(10)

The hydride-equivalent shift may be intercepted or retarded by a radical ion-pair intermediate when more powerful acceptors are employed, or when reaction conditions—for example, the temperature and solvent, favor the formation and existence of the intermediate. Ohno and Kito[14] employed the ESR spectroscopic technique to demonstrate the nature of the sequential electron-proton-electron shift in the reduction of thiobenzophenone by 1,4-dihydronicotinamide. The ESR signal of the thiobenzophenone anion radical was detected at a low temperature (77K); the signal faded on warming to room temperature, giving rise to a new signal ascribable to the thiyl radical (Eq. 11). The competition between the reduction and the radical

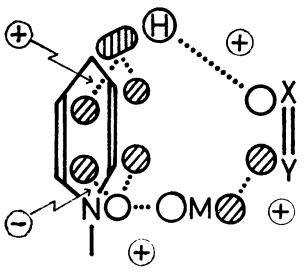


reaction observed by Dittmer and Fouty[15] is understood in terms of two mechanisms near the one-electron transfer region. At least one kinetically important intermediate suggested recently[16,17] is likely to be an ion-radical-pair complex.

Catalysts may affect the reaction course and the efficiency through changing the donor-acceptor property. For example, Lewis acids enhance the electron acceptability of carbonyl compounds by coordination to the carbonyl oxygen. Metal cations were found to assist the reduction of carbonyl compounds.[18-20] This may be explained in terms of the π^* orbital of the carbonyl function being energetically lowered by the positive charge of metal cations.[21] A similar positive-charge effect may also be responsible for the enhanced reactivity of carbonyl groups with an intramolecular hydrogen bond.[10,20,22] The phenolic proton involved provides the carbonyl oxygen with the electrostatic field. In contrast, 1-benzyl-1,4-dihydropyridines were found to be activated by an anionic group in the ortho position of the 1-benzyl substituent.[23] The negative charge may elevate the π-HOMO of the dihydropyridines.

Metal cations can catalyze the reduction reaction in another way, in which the cations are involved in cyclic interaction with dihydronicotinamides and substrates (**6**). In the cyclic interaction the lone-pair orbital on the nitrogen and the C=C bond of dihydronicotinamides are electron-donors, while the C_4–H bond, the unsaturated bond of substrates, and metal cations are acceptors. The orbital-phase requirements for stabilization[2,3] are satisfied if the metal cation provides the cyclic interaction with a low-lying vacant p- or d-orbital. The catalytic reduction should be carefully investigated with this possibility in mind.[24]

Other possible effects of catalysts should also be noted. Some reactions, favored by the donor-acceptor property under uncatalyzed conditions, may be retarded or inhibited if the optimum D-A relation is destroyed by added metal cations which coordinate onto 1,4-dihydronicotinamides or substrates.[25]



6

The theoretical results suggest that the mechanistic features of the reactions of dihydronicotinamides with unsaturated molecules change from one to another. The reduction mechanism can be predicted to be situated near the one-electron transfer region (Type II pseudo-excitation). Consequently, photochemical and catalytic reactions are expected to be of synthetic utility. A useful acceptor of hydride equivalents, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[26] is now available to us. The reagents which are more electron-donating than 1,4-dihydronicotinamides and which are similar in structure are promissing candidates as effective donors of hydride equivalents.

The authors wish to express their thanks to Professor Kenichi Fukui of Kyoto University for his helpful discussion, and to Professor Atsuyoshi Ohno of Kyoto University for his stimulating discussion and for the personal communication of his results prior to publication. The present work was partially supported by a Grant-in-Aid from the Ministry of Education (No. 139012).

Appendix

The configuration functions in Fig. 1 and the electron-density fractions are as follows. The letters, m, d, and a, are used to denote the HOMO's of M, D, and A. The asterisk stand for the LUMO of each system.

$$\Phi_{MDA} = \frac{1}{\sqrt{6!}}|m(1)\bar{m}(2)d(3)d(4)a(5)\bar{a}(6)| \quad (A1)$$

$$\Phi_{MD^+A^-} = \frac{1}{\sqrt{2}\sqrt{6!}}\{|m(1)\bar{m}(2)a^*(3)d(4)a(5)\bar{a}(6)| + |m(1)\bar{m}(2)d(3)\bar{a}^*(4)a(5)\bar{a}(6)|\} \quad (A2)$$

$$\Phi_{M^+DA^-} = \frac{1}{\sqrt{2}\sqrt{6!}}\{|a^*(1)\bar{m}(2)d(3)d(4)a(5)\bar{a}(6)| + |m(1)\bar{a}^*(2)d(3)\bar{d}(4)a(5)\bar{a}(6)|\} \quad (A3)$$

$$\Phi_{M^-D^+A} = \frac{1}{\sqrt{2}\sqrt{6!}}\{|m(1)\bar{m}(2)m^*(3)d(4)a(5)\bar{a}(6)| + |m(1)\bar{m}(2)d(3)\bar{m}^*(4)a(5)\bar{a}(6)|\} \quad (A4)$$

$$\Phi_{MD^*A} = \frac{1}{\sqrt{2}\sqrt{6!}}\{|m(1)\bar{m}(2)d^*(3)d(4)a(5)\bar{a}(6)| + |m(1)\bar{m}(2)d(3)d^*(4)a(5)\bar{a}(6)|\} \quad (A5)$$

$$\Phi_{MDA^*} = \frac{1}{\sqrt{2}\sqrt{6!}}\{|m(1)\bar{m}(2)d(3)d(4)a^*(5)\bar{a}(6)| + |m(1)\bar{m}(2)d(3)d(4)a(5)\bar{a}^*(6)|\} \quad (A6)$$

$$\rho_{MDA,MD^+A^-} = \sqrt{2}\,[da^* + (2m^2+d^2+2a^2)s_{da^*} - ma^*s_{md} - mds_{ma^*} - aa^*s_{da}] + \quad (A7)$$

$$\rho_{MDA,M^+DA^-} = \sqrt{2}\,[ma^* + (m^2+2d^2+2a^2)s_{ma^*} - da^*s_{md} - mds_{da^*} - aa^*s_{ma}] + \quad (A8)$$

$$\rho_{MDA,M^-D^+A} = \sqrt{2}\,[m^*d + (2m^2+d^2+2a^2)s_{m^*d} - m^*as_{da} - das_{m^*a} - mm^*s_{md}] + \quad (A9)$$

$$\rho_{MD^+A^-,M^+DA^-} = -[md + (m^2+d^2+2a^2+a^{*2})s_{md} - 2ma^*s_{da^*} - 2da^*s_{ma^*} - mas_{da} - das_{ma}] + \quad (A10)$$

$$\rho_{MD^+A^-,M^-D^+A} = m^*a^* + (2m^2+d^2+2a^2)s_{m^*a^*} - mm^*s_{ma^*} - aa^*s_{m^*a} + m^*ds_{da^*} + da^*s_{m^*d} \quad (A11)$$

$$\rho_{MD^+A^-,MD^*A} = d^*a^* + (2m^2 + d^2 + 2a^2)s_{d^*a^*} - md^*s_{ma^*} - ma^*s_{md^*} + dd^*s_{da^*} - aa^*s_{d^*a} \quad \text{(A12)}$$

$$\rho_{MD^+A^-,MDA^*} = -[da + (2m^2 + d^2 + a^2 + a^{*2})s_{da} - mds_{ma} - mas_{md} - 2aa^*s_{da^*}] \quad \text{(A13)}$$

References

1) For example see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanism," Benjamin, Vol. 2, New York, N. Y. (1966), Chap. 9.

2) K. Fukui and S. Inagaki, *J. Am. Chem. Soc.*, **97**, 4445 (1975).

3) S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, **98**, 4693 (1976).

4) K. Fukui, *Fortschr. Chem. Forsch.*, **15**, 1 (1970).

5) a) H. Fujimoto, S. Yamabe, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **44**, 2936 (1971); b) K. Fukui, 23rd Intern. Congress of Pure and Applied Chemistry, Butterworths, Vol. 1, London (1971), pp. 65—89.

6) a) S. Inagaki, S. Yamabe, H. Fujimoto, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **45**, 3510 (1972); b) S. Inagaki and K. Fukui, *J. Am. Chem. Soc.*, **97**, 7480 (1975).

7) D. M. Hayes and R. Hoffmann, *J. Phys. Chem.*, **76**, 656 (1972); S. Inagaki and K. Fukui, *Bull. Chem. Soc. Jpn.*, **46**, 2240 (1973).

8) R. Sustman, A. Ansmann, and F. Vahrenholt, *J. Am. Chem. Soc.*, **94**, 8099 (1972).

9) S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, **97**, 6108 (1975).

10) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **79**, 712 (1957).

11) R. A. Sulzbach and A. F. M. Iqbal, *Angew. Chem.*, **83**, 758 (1971).

12) K. Wallenfels, W. Ertel, and K. Friedrich, *Justus Liebigs Ann. Chem.*, **1973**, 1663.

13) R. M. Acheson, N. D. Wright, and P. A. Tasker, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2918.

14) A. Ohno and N. Kito, *Chem. Lett.*, **1972**, 369.

15) D. C. Dittmer and R. A. Fouty, *J. Am. Chem. Soc.*, **86**, 91(1964).

16) J. J. Steffens and D. M. Chipman, *J. Am. Chem. Soc.*, **93**, 6694 (1971).

17) a) D. J. Creighton, J. Hajdu, G. Mooser, and D. S. Sigman, *J. Am. Chem. Soc.*, **95**, 6855 (1973); b) J. Hajdu and D. S. Sigman, *ibid.*, **98**, 6060 (1976).

18) a) D. J. Creighton and D. S. Sigman, *J. Am. Chem. Soc.*, **93**, 6314 (1971); b) D. J. Creighton, J. Hajdu, and D. S. Sigman, *ibid.*, **98**, 4619 (1976).

19) Y. Ohnishi, M. Kagami, and A. Ohno, *J. Am. Chem. Soc.*, **97**, 4766 (1975); *Tetrahedron Lett.*, **1975**, 2437.

20) S. Shinkai and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 8258 (1972); *Biochemistry*, **12**, 1750 (1973).

21) For example, the π-LUMO of acrolein was shown by a SCFMO calculation to be appreciably lowered through the protonation on a lone pair of the carbonyl oxygen [K. Fukui and H. Fujimoto, *Nippon Kagakuseni Koen-shu*, **29**, 27 (1972)]. See also the following papers about the electrostatic-field effects on the electronic structures of molecules: (a) H. Fujimoto and R. Hoffmann, *J. Phys. Chem.*, **78**, 1874 (1974); (b) A. Imamura and T. Hirano, *J. Am. Chem. Soc.*, **97**, 4192 (1975).

22) U. K. Pandit and F. R. Mas Cabre, *Chem. Commun.*, **1971**, 552.

23) J. Hajdu and D. S. Sigman, *J. Am. Chem. Soc.*, **97**, 3524 (1975).

24) A. Ohno, T. Kimura, H. Yamamoto, S. G. Kim, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Jpn.*, **50**, 1535 (1977). Magnesium percholate, which accelerates the dihydronicotinamide reduction of methyl benzoylformate, appreciably affects the UV absorption spectra of dihydronicotinamides, but not those of the substrate. This result suggests the possibility that the metal cation does not always activate carbonyl compounds.

25) a) D. C. Dittmer, A. Lombardo, F. H. Batzold, and C. S. Greene, *J. Org. Chem.*, **41**, 2976 (1976); b) A. Ohno, private communication: magnesium percholate retards the reduction of phenyl *t*-butyl thioketone in contrast to that of methyl benzoylformate.[24]

26) H. O. House, "Modern Synthetic Reactions," 2nd ed, Benjamin, Menlo Park, California (1972), pp. 37—44.