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REVIEW

Model Studies with Nicotinamide Derivatives

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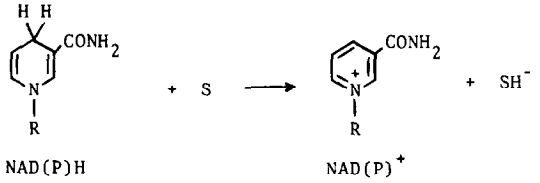
Studies with 1,4-dihydronicotinamide derivatives as a model of NAD(P)H have been done extensively. This review summarizes the results of these model studies with emphasis on the mechanistic aspects, in particular on the controversy with respect to a (net) hydride transfer. Stereospecific reduction, application to organic synthesis, and some other aspects of nicotinamide derivatives are also mentioned.

Nicotinamide adenine dinucleotide (NAD^+) and its 2′-phosphoric acid derivative ($NADP^+$) are coenzymes that are well known because of their ubiquity throughout most organisms. In dehydrogenase-catalyzed redox reactions, the oxidized form, $NAD(P)^+$, acts as an oxidant by accepting a hydride onto the C-4 position of its nicotinamide moiety, and the reduced form, NAD(P)H, acts as a reductant by releasing a hydride from this position:



NAD(P)H NAD(P)$^+$ (1)

Such an apparently clear-cut feature of the $NAD(P)^+$–NAD(P)H redox system as well as the availability of the dihydronicotinamide moiety as an organic compound has prompted organic chemists to study NAD(P)H-mediated reductions from the viewpoint of organic chemistry. In 1955, Westheimer and co-workers studied the reductions of malachite green and methylene blue to the corresponding leuco bases by a simple dihydronicotinamide derivative, 1-benzyl-1,4-dihydronicotinamide (BNAH)[1] (*1*). Despite the fact that these dyes have structures largely different from those of the substrates in biological systems, these reductions were investigated and discussed in comparison to enzyme-promoted reac-

[1] Abbreviations used: BNAH, 1-benzyl-1,4-dihydronicotinamide; HEH, 2,6-dimethyl-3,5-dicarboalkoxy-1,4-dihydropyridine (Hantzsch ester); PNAH, 1-propyl-1,4-dihydronicotinamide; HLADH, horse liver alcohol dehydrogenase; BSA, bovine serum albumin; CT complex; charge-transfer complex; BNA^+, oxidized form of BNAH; TCNQ, tetracyanoquinodimethane; e.e., enantiomer excess.

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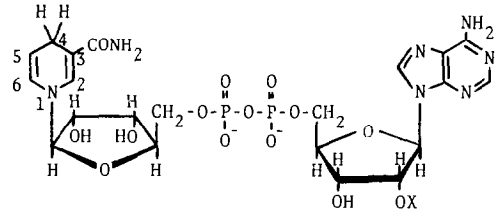
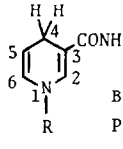


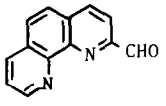
NADH; X = H

NADPH; X = OPO_2H_2



BNAH; R = CH_2Ph

PNAH; R = $CH_2CH_2CH_3$



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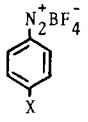
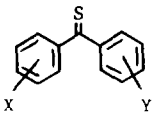


X = H, Me, NO_2

3



2a; X = p-Cl, Y = H

2b; X = Y = H

2c; X = p-OH, Y = H

2d; X = o-OH, Y = H

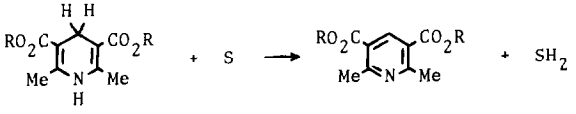
2e; X = p-MeO, Y = H

2f; X = o-MeO, Y = H

2g; X = Y = p-MeO

tions of NAD(P)H. Therefore, one could regard this work as the first "model" study of NAD(P)H. Subsequently, it was found that BNAH and related compounds can hydrogenate a variety of potentially activated functional groups such as the carbonyl group of hexachloroacetone (*2*) or certain thiocarbonyl groups (*3*).

Another class of compound, 2,6-dimethyl-3,5-dicarboalkoxy-1,4-dihydropyridine (Hantzsch ester; HEH), also donates a hydride to a variety of organic compounds (*4, 5*):



HEH (2)

The reduction of pyruvic acid, which is a biological substrate, was nonenzymatically accomplished by HEH under vigorous conditions to afford lactic acid in ca. 5% yield (*6*). Unfortunately, very few examples of oxidation by an $NAD(P)^+$ model have been presented.

Some dehydrogenases such as horse liver alcohol dehydrogenase (HLADH) use zinc ion as a cofactor in redox reactions mediated by an NAD(P)H–NAD(P)$^+$ couple, and the role of metal ion in enzymatic reactions has been studied for a long time (*7*). In 1971, Creighton and Sigman found that zinc ion is an excellent catalyst for the nonenzymatic reduction of 1,10-phenanthroline-2-carboxaldehyde (**1**) by 1-propyl-1,4-dihydronicotinamide (PNAH) (*8*). Following this successful work, the reductions of a large number of substrates by dihydronicotinamides with the aid of a bivalent metal ion have been presented.

One important feature of enzyme-catalyzed reductions is stereospecificity. A large number of dihydronicotinamide derivatives possessing a chiral center have been synthesized to accomplish stereospecific reductions in nonenzymatic systems. It has been reported that the chirality on the reaction center, the C-4 position of the 1,4-dihydronicotinamide moiety, is almost quantitatively transferred into the reduction product (*9*).

Contrary to the successful works in stereochemistry mentioned above, two contradictory mechanisms have been proposed for a (net) hydride transfer from a dihydronicotinamide to a substrate; one is the single-step mechanism with direct hydride transfer, and the other is the multistep mechanism including initial one-electron transfer. Although many experiments have been performed in order to determine a plausible mechanism, no definitive evidence has been obtained. Quite a few organic reactions are believed to involve a "net" hydride transfer process. Since the Pauling's electronegativity scale is much larger for carbon (2.5) than for hydrogen (2.1), it is important to determine whether and/or how a "hydride" can dissociate from a carbon–hydrogen bond. In this relation, the present review mainly concerns the mechanism of "hydride" transfer from NAD(P)H and their analogs.

The chemistry of dihydropyridine derivatives has provided interesting devices in organic syntheses (*10–13*). This review also describes briefly the application of NAD(P)H models to organic syntheses.

Dihydronicotinamide derivative (and related compounds) is hereafter called "an NAD(P)H model" or simply "a model."

MECHANISM OF "HYDRIDE" TRANSFER

Tracers

In their pioneering work in 1951, Westheimer *et al.* briefly proposed the mechanism of NAD$^+$-mediated oxidation of ethyl alcohol into acetaldehyde in the presence of alcohol dehydrogenase (*14*). Based on experiments with deuterium as a tracer, they proved that a hydrogen nucleus is transferred directly from the α-carbon of the alcohol to the NAD$^+$ molecule. They did not, however, specify the charge on the transferring hydrogen nucleus. Hydrogen transfer without exchange with a hydrogen from solvent was also observed in nonenzymatic reductions of malachite green (*1*) and thiobenzophenones (**2**) (*3*) by BNAH. Similarly, a deuterium-labeling technique confirmed that a hydrogen is directly transferred in the

reductions of indolenines by BNAH (*15*). Therefore, the single-step mechanism had been accepted for the hydride transfer in both biological and model systems.

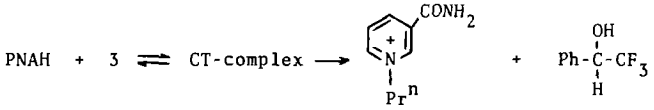
However, there appeared the reductions in which the transferring hydrogen exchanges with a hydrogen from solvent during the reaction. Arenediazonium salts, **3**, undergo dediazoniation with BNAH in the dark (*16*). When this reaction was carried out in methanol-d_4, a part of the product, the corresponding arene, was monodeuterated. The amount of deuterium incorporated into the product depended on the stability of the corresponding aryl free radical; the more stable the free radical, the larger the deuterium content in the product. In addition, the stoichiometry of the reaction and effects of free radical chain inhibitors on the yield of products clearly indicate that this reaction proceeds through a free radical chain mechanism initiated by one-electron transfer from BNAH to **3**. Thus, non-deuterated product obtained was concluded to be formed by a hydrogen atom (or a proton) transfer from the cation radical of BNAH to the generated aryl free radical within a cage of solvent rather than by a direct hydride transfer.

Accordingly, it is evident that the apparent "direct" hydride transfer observed in previous works is merely the result of successive transfers of an electron, a proton, and an electron (or an electron and a hydrogen atom) within a cage of solvent or in a pocket of an enzyme. When the anion radical generated from the substrate as an intermediate is stable enough, it has a chance to escape from the cage of solvent and abstracts a proton from the solvent.

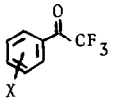
Another example is the reduction of a series of thiobenzophenones, **2a**, **b**, **d**, and **g**, by BNAH and its derivative. Disulfides partially deuterated at the methine position were obtained by the reaction in deuterated solvent (*17*). This result unambiguously demonstrates that the anion radical exists as an intermediate along the reaction coordinate. The amount of deuterium in the product increases as the anion radical from **2** becomes more stable and the solvent becomes more polar.

Isotope Effects

In 1971 Steffens and Chipman claimed that a hydride is not transferred in a single step at least in a model system (*18*). From the observation that the primary kinetic isotope effect (k_H/k_D) is much smaller than the isotopic ratio in the product (Y_H/Y_D) in the reductions of α,α,α-trifluoroacetophenone (**4a**) by 1-propyl-1,4-dihydronicotinamide (PNAH) and its 4-*d* analog (PNAH-4-*d*), they postulated the existence of an intermediate along the reaction course. Indeed, to explain the smaller value for k_H/k_D than for Y_H/Y_D with the single-step mechanism, a secondary α-deuterium isotope effect with a large inverse value should be obligatorily suspected, which is very unlikely. They assumed a charge-transfer (CT) complex between PNAH and the substrate as an intermediate:

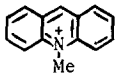


(3)



4a; X = H
4b; X = p-Cl
4c; X = p=Br
4d; X = m-F
4e; X = m-Br
4f; X = m-CF_3
4g; X = m-NO_2
4h; X = m-CF_3, m'-NO_2
4i; X = m,m'-$(NO_2)_2$
4j; X = p-MeO
4k; X = p-Me

5a; R = H
5b; R = Me
5c; R = Ph



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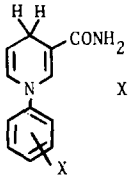
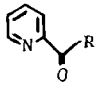


X = p-MeO, p-$PhCH_2O$, p-Me, H, p-Br, m-Br, m-CF_3, p-CN

7



8a; R = H
8b; R = Me
8c; R = Ph
8d; R = 2-Py
8e; R = Et
8f; R = Pr^i
8g; R = Bu^t
8h; R = CH_2F
8i; R = CHF_2
8j; R = CF_3

Prior to transfer of a proton (or a hydrogen atom), one electron is transferred, at least partially, from PNAH to the substrate. Although they retracted this conclusion later, this work has an important historical meaning (vide infra).

A large number of examples that show discrepancies between k_H/k_D and Y_H/Y_D values have since been reported. They include the reductions of **4a–d** (*19*), 1,10-phenanthroline-2-carboxaldehyde (**1**) (*20*), 1-acetylisoquinoline (**5b**) (*21*), and *N*-methylacridinium ion (**6**) (*22–24*) by NAD(P)H models in the presence or absence of a metal ion. Most of these were best interpreted by postulating an initial one-electron transfer from a model to a substrate. Namely, kinetics for the reduction of **6** by a series of 1-aryl-1,4-dihydronicotinamides (*7*) revealed a three-step mechanism with successive transfers of an electron, a proton, and an electron in this order (*25*). Other authors suggested a two-step mechanism with transfers of an electron and a hydrogen atom in the reduction of similar substrates, 6-substituted *N*-methylacridinium ions, by BNAH (*26*).

Moreover, examination of isotope effects in the transhydrogenation between BNAH and its oxidized form (BNA^+) showed that the reaction involves initial one-electron transfer followed by a proton and another electron transfer (*27*). The mechanism was further supported later by more detailed investigation in consideration of the BNA^+-catalyzed hydration of BNAH as well as the exchange of the C-4 hydrogen of BNAH with that from the solvent, water (*28*). Similar discussion appeared in the succeeding paper published by the same authors, which describes the study of reactions of 2-acylpyridines, **8a** and **8d**, with isotopically labeled BNAHs (*29*).

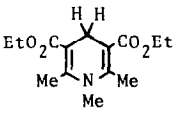
Recently, Chipman *et al.* reinvestigated their own kinetic results reported previously for the reduction of **4a** by PNAH and they concluded that the discrepancy between the values of k_H/k_D and Y_H/Y_D is not the result of the presence of a productive intermediate but is due to the reversible formation of an abortive covalent adduct between PNAH and **4a** (*30*). The formation of an adduct between BNAH and **6** was also reported (*31*). Nevertheless, it should be noted that these experiments were carried out in aqueous solvents. Indeed, the formation of such an adduct in nonaqueous solvent has not yet been observed. Although it was also pointed out that magnesium ion accelerates the reduction rate because it acts as a drying agent for the solvent (*30*), the postulation cannot explain the inhibitory role of this metal ion in the reductions of thiopivalophenone and *m*,*m*′-dinitro-α,α,α-trifluoroacetophenone (**4i**). In addition, the results from the experiments on magnesium ion-catalyzed reduction of **4a** in wet acetonitrile negated this possibility (*32*); contamination by a small amount of water does not affect the catalytic activity of magnesium ion.

Bruice *et al.* claimed that smaller value of k_H/k_D than of Y_H/Y_D previously reported in the reduction of **6** by an NAD(P)H model is the result of rapid isotope scrambling between the product, *N*-methylacridan, and the reactant, **6**, or another product, nicotinamidium salt (*33*). Similar rapid hydrogen exchange between 1,4-dihydropyridine, **9**, and its oxidized form had already been reported (*34*). Thus, it was concluded that the measured deuterium content in the reduction product does not reflect the "true" value of Y_H/Y_D because the exchange of hydrogen is kinetically significant within the time scale employed for the product studies in the previous works. Considering the effect of isotope scrambling and tunneling on k_H/k_D and Y_H/Y_D, they presented the single-step mechanism for the reduction of **6** by an NAD(P)H model (*35*). The authors believe, however, that the isotope scrambling thus observed in the reduction of **6** is an exceptional case and does not operate at least in the reduction of **4a**, though this substrate also shows a discrepancy between kinetic and product isotope effects.

Bruice and co-workers also critically reexamined several model reactions that had been reported to exert different k_H/k_D and Y_H/Y_D values and found no such discrepancies (*35*). On the other hand, they recognized that the stepwise mechanism cannot be unequivocally ruled out in certain cases, although an investigation on the Brønsted correlation in the reduction of **6** seemed to support the single-step mechanism for this reaction. Namely, the one-electron transfer from a model to an oxidant is significant when the oxidant has a high redox potential (*35*).

Charge-Transfer Complexes

Charge-transfer (CT) complexes have been detected by physical methods or assumed kinetically in the reactions with NAD(P)H models. Kosowar has proposed the formation of CT complexes in the addition reaction of various electron donors to 1-methylpyridinium ion (*36*). In addition, Bruice *et al.* have emphasized that the formation of a productive noncovalent CT complex is kinetically important in the reduction of flavins by NADH or its analog, PNAH (*37*). The positive ρ



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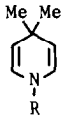
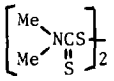


$R = CH_2CH_2CH_3$, CH_2Ph

10



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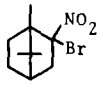

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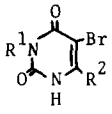
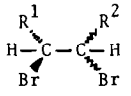


R^1 = H, Me
R^2 = H, NMePh(p-Br), OPh, SPh

14

15



R^1, R^2 = CO_2Et, Ph

16

value observed in the reduction of 4-substituted 2,6-dinitrobenzenesulfonate by BNAH was supposed to indicate the formation of a CT complex as an activated intermediate (*38*). Moreover, transient uv absorbances observed during the reaction of perchloroacetone with BNAH were well accommodated with the concept of CT complex formation along the reaction path even though the value of k_H/k_D was identical to that of Y_H/Y_D in this reaction (*39*). Transient CT bands were also detected in the reduction of *N*-methylacridinium ion (**6**) (*40*), chloranil (*41a*), and bromanil (*41b*) by BNAH as well as the magnesium ion-catalyzed reduction of 2,6-dichloro-*p*-benzoquinone (*42*) by BNAH.

More convincingly, during the reductions of thiobenzophenone (**2b**) (*43*), benzil (*44*), and *p,p'*-dichlorobenzil (*44*) by BNAH, ESR signals ascribable to the corresponding anion radicals from these substrates were observed. It is important that the anion radical generated from **2b** was observed to pair with a cation radical, probably that from BNAH. Similarly, in the presence of 1-substituted 4,4-dimethyl-1,4-dihydropyridine (**10**) which has no hydrogen to be transferred, an ESR signal ascribable to an anion radical stemming from *m*-trifluoromethyl-*m'*-nitro-α,α,α-trifluoroacetophenone (**4h**) was observed (*45*). Dihydropyridine derivatives of this type display CT bands with 1,3,5-trinitrobenzene, tetracyanoquinodimethane (TCNQ), **6**, or **4e–h** (*45, 46*).

These findings can be regarded as support for the multistep mechanism including initial one-electron transfer. Nevertheless, there remains a possibility that the radical species demonstrated by spectroscopy during the reactions do not lie on the reaction coordinate as pointed out by Hood *et al.* (*47*).

NAD(P)H Model as a One-Electron Donor

In order to confirm the multistep mechanism, it is important to show the intrinsic ability of an NAD(P)H model as a one-electron donor against a certain substrate. In fact, an NAD(P)H model seems to be a good one-electron donor and the existence of a cation radical from a model along the reaction path has been supposed in numerous thermal reactions, e.g., reduction of *N*,*N*,*N*′,*N*′-tetramethylthiuram disulfide (**11**) by BNAH (*48*), reductive debromination of *geminal* bromo–nitro compounds, **12** and **13**, by BNAH (*49*), reductions of transition-metal salts by PNAH (*50, 51*), radical polymerization of acrylamide initiated by 1-hexadecyl-1,4-dihydronicotinamide in the presence of sodium dodecyl sulfate and potassium persulfate (*52*), thermal and photosensitized reductions of diaryl disulfides to the corresponding thiol by BNAH (*53*), reductive desulfonation of 2,4,6-trinitrobenzenesulfonate by N^3-dodecyl-1-benzyl-1,4-dihydronicotinamide bound to sodium dodecyl sulfate micelle (*54*), reductive debromination of 5-bromouracils (**14**) by BNAH (*55*), reduction of sulfur dioxide by BNAH probably to HSO_2^- (*56*), reductions of iron(III) complexes and tetracyanoethylene by BNAH (*57*), and reductions of sulfoxides and sulfilimines by BNAH catalyzed by metalloporphins (*58*). Moreover, NADH itself nonenzymatically reduces ferrocenium salts into the corresponding ferrocenes, where the one-electron transfer step forming the cation radical of NADH is recognized to be rate limiting (*59*).

Photochemical generation of a cation radical from an NAD(P)H model was postulated in reduction of bromotrichloromethane to chloroform by HEH through a free radical chain mechanism (this reaction also proceeds thermally) (*60*), reductions of alkylthallium(III) compounds and alkylmercury(II) acetates by BNAH (*61*), reductive denitration of aliphatic nitro compounds by BNAH (vide infra) (*62*), $Ru(bpy)_3^{2+}$-mediated reduction of olefins and carbonyl compounds by BNAH (*63*), reductive desulfonation of α-nitrosulfones, **15**, by BNA (*64*), reduction of benzyl bromide and methyl iodide by BNAH (*65*), and reduction of thioindigo to its leuco form by BNAH (*66*).

Interestingly enough, BNAH was found to accomplish reductive debromination of *vic*-dibromides, **16**, in the dark through the one-electron transfer process, even though this reaction is susceptible for both one-electron and two-electron reductants (*67*).

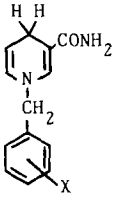
Negative Charge on an "In-Flight Hydrogen"

Several workers have argued against the multistep mechanism based on several findings which are apparently explainable in terms of the single-step mechanism with direct hydride transfer. As an early work, the ρ^* value of -1.91 obtained in the reductions of flavins by a series of 1-substituted 1,4-dihydronicotinamides was readily concluded to be consistent with the direct hydride transfer mechanism

(*68*). However, this conclusion was deduced without taking into consideration the multistep mechanism.

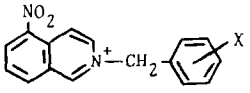
The direct hydride transfer mechanism was also proposed in the (net) hydride transfer reactions from 1-(substituted benzyl)-1,4-dihydronicotinamides (**17**) to 2-(substituted benzyl)-5-nitroisoquinolinium cations (**18**) and to 2-(substituted benzyl)-3,4-dihydroisoquinolinium cations (**19**). This proposal was based on the ρ-values of reactions, and negative charges of -0.44 and -0.33 were estimated on the traveling hydrogen nuclei at the transition states of the former and the latter reactions, respectively (*69a,b*). Along the studies of this series, it was also observed that the relatively strong 1 : 1 complexes between the oxidant, **18**, and the reductant, 1,4-dihydronicotinamides, are nonproductive (*69c*). This observation may provide evidence (although not decisive) against the multistep mechanism.

The large negative ρ (or ρ^*) value associated with the above reactions, however, would also be expected if a cation radical is generated according to the multistep mechanism. Moreover, since a ρ value is a parameter responsible for solvation and all other environmental effects, the authors believe that a ρ value



X = p-Me, H, p-F, p-Br, m-F, m-CN, p-CN

17



X = p-Me, H, p-F, p-Br m-F, p-CF_3, m-CN, p-CN

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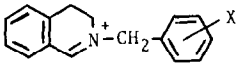

X = p-Me, H, p-Br m-F, m-CN, p-CN

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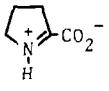

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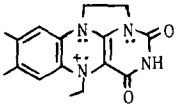

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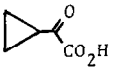

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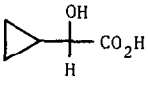

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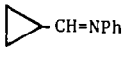

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should not be used for the quantitative calculation of charge density on a particular atom. It is simply a measure of (net) susceptibility to substituent effect, σ as originally defined.

Other workers have presented kinetic results standing on the critical point against the multisep mechanism. Reaction rates and equilibrium constants obtained in hydride transfer reactions between certain NAD^+ analogs were analyzed by the aid of Marcus theory. The magnitude of negative charge on an in-flight hydrogen was calculated to be -0.23, and the value was claimed to be reasonable as a hydridic character (*70*).

Recently, Bruice *et al.* reinvestigated the reduction of ferricyanide ion, $Fe(CN)_6^{3-}$, to ferrocyanide ion, $Fe(CN)_6^{4-}$, by 1-substituted 1,4-dihydronicotinamides and their analogs and argued this reaction in terms of "hydride-like hydrogen transfer" [a slow electron transfer onto $Fe(CN)_6^{3-}$ with a rapid proton transfer onto a base] (*71*). This concept agrees with that of the multistep mechanism.

On the other hand, it has been predicted, by comparing the reduction of flavins with that of a Schiff base, Δ^1-pyrroline-2-carboxylic acid (**20**), that the former compounds are reduced by NAD(P)H and its analogs with the direct hydride transfer mechanism (*72*). In contrast to such indirect evidence, the deficiency of 1,10-ethano-5-ethyllumiflavinyl cation (**21**) to accept an electron from a model was observed. Then, it was deduced that the reductions of the corresponding neutral or cationic species occur through the single-step mechanism (*73*). However, it should be pointed out that **21** cannot accept any hydrogenic species after the acceptance of one electron, which necessarily means that no net chemical reaction can be observed with this system.

Attempts to Detect Radical Intermediates by Chemical Method

Enzymatic or nonenzymatic reduction of cyclopropaneglyoxylic acid (**22**) into cyclopropaneglycolic acid (**23**) by NADH or BNAH, respectively (*74*), as well as reduction of a Schiff base containing a cyclopropane ring, **24**, by HEH (*75*) was studied. These reductions occurred without cleavage of the three-membered rings. The enzymatic reductions of nortricyclanone (**25**), 2,2-dimethyl-5-hexenal (**26**), and *cis*-3-phenylpropenal (**27**) by NADH were shown to proceed without ring-opening, ring-forming, and *cis–trans* interconversion, respectively (*76*). In addition, oxidations of α-hydroxyalkylcyclopropanes by NAD^+ catalyzed by HLADH, the reaction of opposite direction, also took place without ring-opening (*77*).

These findings are readily explainable in terms of the direct hydride transfer mechanism because free radical intermediates, if formed, are expected to undergo further reactions such as ring-opening, ring-forming, and *cis–trans* interconversion. Yet, one can also suppose another possibility: that the anion radical species generated via the initial one-electron transfer from the reductant to a substrate may be trapped so rapidly by a proton (or a hydrogen atom) from the cation radical of the reductant within a cage of solvent or in a pocket of an enzyme that no such rearrangements take place. These findings, therefore, cannot be exclusive

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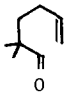

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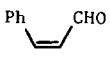

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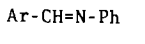
28a; R = Me
28b; R = Et



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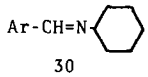

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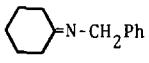

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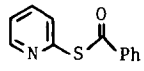

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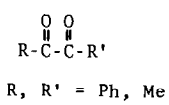
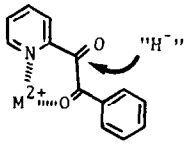


R, R' = Ph, Me

33



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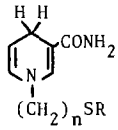
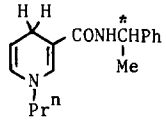


R = Me, Ph
n = 2, 4

35



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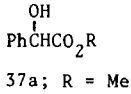
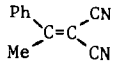


37a; R = Me
37b; R = Et



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evidence for direct hydride transfer. Of course, this evidence cannot be denied as strong support for the single-step mechanism.

Concluding Remarks

Many experimental results have been presented as evidence for both the single-step and the multistep mechanisms. Hence, our next aim must be to develop a novel concept that unifies two "contradictory" mechanisms. One such concept would be the following:

When an electron-transfer step is well separated from a proton (or hydrogen atom)-transfer step, as shown in Fig. 1a, both steps will be recognized easily as independent steps even if the latter step has a higher activation energy than the former step (i.e., rate-determining chemical step). Physical processes such as photochemical electron transfer and redox reaction on an electrode belong in this category.

As shown in Fig. 1b, when a proton (or hydrogen atom)-transfer step has little overlap with an electron-transfer step, the charge-transfer complex is no more a

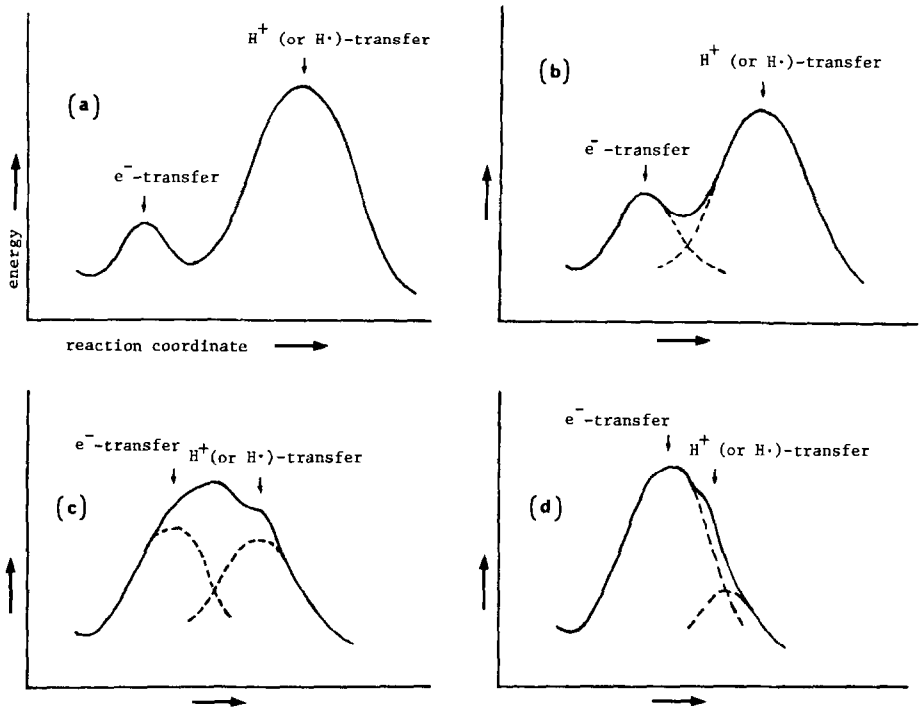


FIG. 1. Energy diagrams for the reductions by an NAD(P)H model. Change from a to d corresponds to the increase in the degree of overlap between an electron-transfer step and a proton (or hydrogen atom)-transfer step; see text for details.

stable intermediate, and the complex will be detected in some cases but not in others. Importantly, all information available from a kinetic approach for the reaction in this category may be accommodated with the idea of the single-step hydride transfer because a negative charge more or less develops on the substrate (in turn, a positive charge develops on the model) at the rate-determining transition state. Reductions of *N*-methylacridinium ion (**6**), metal ions, and many other strongly electron-deficient substrates belong in this category.

As the electron deficiency of the substrate becomes smaller, the time lag between the electron-transfer and proton (or hydrogen atom)-transfer steps becomes shorter and the overall process appears as a "single-step" reaction (Fig. 1c). Thus, one cannot have any device that divides the process into two steps. However, the authors emphasize that initial distortion of the electron cloud is the major driving force for the dissociation of the hydrogen nucleus from the carbon–hydrogen bond.

Figure 1d shows that when an electron-transfer step is completely included in a proton (or hydrogen atom)-transfer step, the reaction is recognized to proceed via a single-step "hydride" transfer. In the strict meaning, however, the transition states for both electron- and hydrogen atom-transfer steps should exist at exactly the same position in the reaction coordinate if the "hydride" is the real in-flight species at the rate-determining step of the reaction.

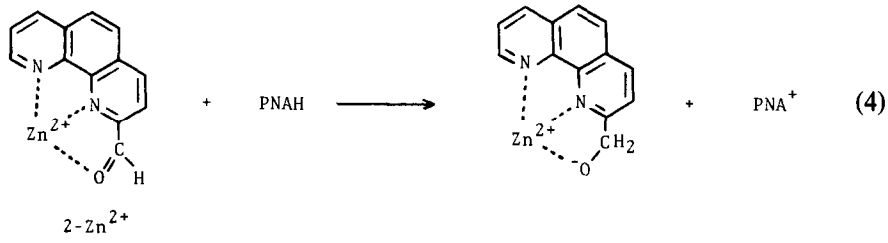
Thus, the authors believe that the single-step and multistep mechanisms are not different from each other. Instead, depending on the substrates employed, either mechanisms might be elucidated as one particular point of a spectrum of "net hydride-transfer" phenomena.

ROLE OF A METAL ION

Bivalent Metal Ion-Catalyzed Reduction

The first model study which referred to the role of metal ion in biological systems is that presented by Westheimer *et al.* concerning the reduction of thiobenzophenones (**2a–f**) (*3*). The *ortho*-hydroxyl-substituted derivative, **2d**, was reduced more rapidly than anticipated from the reactivity–electronic character relationship found for **2a–c**, **e**, and **f**. This anomaly was interpreted by considering that the hydrogen bonding between the proton on the *ortho*-hydroxyl group and the thiocarbonyl sulfur would facilitate the reaction by stabilizing the transition state. Hence, it was speculated that zinc ion involved in HLADH, for example, may similarly interact with the oxygen of the carbonyl group in a substrate to be reduced. The contribution of hydrogen bonding to the reduction rate in the reduction of *o*-hydroxybenzaldehyde by HEH was also argued (*78*).

Catalysis of a metal ion in a model system was examined by Creighton and Sigman for the first time. They found that zinc ion dramatically catalyzes the reduction of 1,10-phenanthroline-2-carboxaldehyde (**1**) into the corresponding carbinol by PNAH (*8*). This substrate is hardly reduced in the absence of the metal ion. A coordination or proximity effect of the metal ion on the aldehyde was proposed for activation of the carbonyl group as shown in



2-Zn^{2+}

On the other hand, it was found that metal ion catalysis also operates in the BNAH-mediated reduction of methyl benzoylformate (**28a**) even though **28a** has very little affinity toward metal ion (*79*). Thus, the above explanation is not applicable to the metal ion catalysis in this reaction. Instead, an NAD(P)H model is able to effectively coordinate to a bivalent metal ion. Based on a spectroscopic investigation, as well as molecular orbital considerations, the formation of a model–metal ion–**28a** ternary complex at the transition state, analogous to a coenzyme–enzyme–substrate ternary complex in biological systems, was predicted.

Along with the above-mentioned examples, many workers have presented a variety of bivalent metal ion-catalyzed reductions by NAD(P)H models. Carbonyl

groups in 2-acylpyridine derivatives (**8a–c**) (*21, 80–83*) and 1-acylisoquinoline derivatives (**5**) (*21*) as well as the carbon–carbon double bond in 2-cinnamoylpyridine (*84*) and carbon–nitrogen double bonds in some imine compounds such as **29–31** (*85, 86*) were smoothly hydrogenated by a model in the presence of metal ion. The zinc ion-catalyzed reduction of *S*-(2-pyridyl) thiobenzoate (**32**) by BNAH, which produces benzaldehyde in 37% yield, was also reported (*87*). Further, 1-methyl-1,4-dihydropyridines, highly reactive models, reduced even cyclohexanone, a less highly activated carbonyl compound, into cyclohexanol in moderate yields with the aid of magnesium ion (*88*). Some of these reactions were interpreted by taking into account the substrate–metal ion complexation, while others were rationalized by considering the model–metal ion counterpart.

The order of catalytic efficiency of bivalent metal ions has been explored. Studies on the reduction of pyridoxal phosphate and its analogs by HEH in the presence of a bivalent metal ion demonstrated the order of effectiveness of metal ion catalysis to be $Ni^{2+} > Co^{2+} > Zn^{2+} > Mn^{2+} > Mg^{2+}$ (*89*). In addition, the reduction of **8a** by BNAH followed the order $Cu^{2+} > Zn^{2+} > Pb^{2+} > Cd^{2+}$ (*90*). However, one must be careful in the assessment of these results because the efficiency is sensitive to the procedures of purifying a catalyst, a substrate, a model, solvent, etc. Moreover, the kinetic result for the Cu^{2+}-catalyzed reduction of **8a** by BNAH in the latter study may be erroneous since BNAH reduces Cu^{2+} into Cu metal much faster than it reduces **8a** (*91*). Lithium ion exerts no effect on the reduction although its radius is almost the same as that of magnesium ion, indicating that the catalytic efficiency of a metal ion depends largely on the charge density rather than on the ionic radius (*79*).

Kinetic Investigation for Metal Ion Catalysis

Along with attempts to obtain general insight into the role of bivalent metal ion in reduction by NAD(P)H models, it has become apparent that the catalytic behavior of metal ion depends on the type of substrate. These are divided into three categories:

(i) Effective catalysis by a metal ion in which kinetic saturation is observed: Substrates that cannot form any complexes with a metal ion effectively are in this category, e.g., methyl benzoylformate (**28a**) (*92*), α,α,α-trifluoroacetophenone (**4a**) (*93*), and certain α-diketones (**33**) (*94*).

(ii) Retardation of the rate by metal ion: An active substrate which is reduced by a model without a metal ion belongs in this category, e.g., thiopivalophenone (*95*).

(iii) Regulation of the rate by a metal ion in such a way that the rate increases, comes to a maximum, then decreases as the concentration of the metal ion increases: Such effects are observed in the reduction of substrates that have comparable affinity to a metal ion as those of NAD(P)H models, e.g., 1-acylisoquinolines (**5**) and 2-acylpyridines (**8a–c**) (*21, 80–82*).

These profiles are schematically shown in Fig. 2. Interestingly, the stereospecificity of the reduction parallels the reaction rate in categories i and iii, whereas it is independent of the concentration of metal ion in the reduction of substrates that belong in category ii.

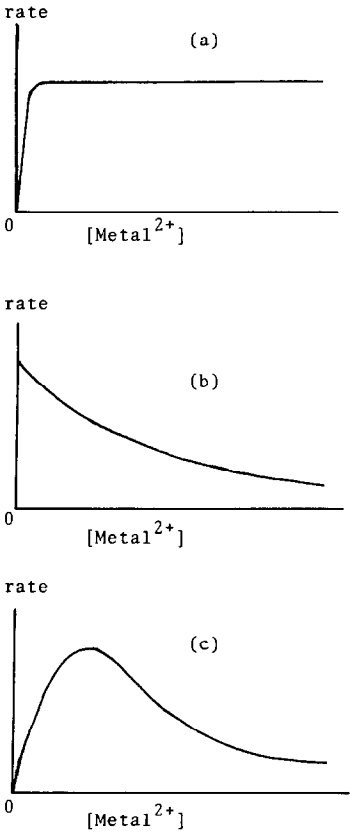


FIG. 2. Rate–metal ion concentration profiles. a, b, and c represent categories i, ii, and iii, respectively; see text for details.

Two contradictory explanations were presented for the existence of the maximum point on the rate–metal ion concentration profile for the reductions of **8a–c** (i.e., for the reductions in category iii); one consists of competitive activation and deactivation of the model and the substrate by complexation with a metal ion, respectively (*21*), and the other postulates the reverse situation (*80, 84b*). The former idea, activation of a model by a metal ion, is supported by the following observations: the order of reactivities in the reductions of **5** and **8a–c** by a model is not always in accordance with that of association constants with a metal ion (*21*); in the reduction of 1-phenyl-2-(2-pyridyl)-1,2-ethanedione, the carbonyl group to be reduced is different from that subjected to coordination to a metal ion (cf. structure **34**) (*96*). Thus, an effective ligand to a metal ion is not necessarily a facile substrate for the reduction. Strong coordination of a metal ion to the reaction site of a substrate facilitates formation of the substrate–metal ion complex but often inhibits reduction by stabilizing the intermediate. It should be noted that the transition state has to be stabilized in order to accelerate the reaction. Stabilization of the ground state causes only retardation (*97*). Complexation between a

model and a metal ion (i.e., activation of a model by a metal ion) is, in turn, significantly responsible for the reactivity of the reduction. In fact, the reductions of 2-acylpyridine derivatives, **5** and **8a–c**, were concluded to proceed via the formation of a model–metal ion–substrate ternary complex based on detailed kinetic analyses (*21*). The reaction sequence thus postulated for these reactions is very similar to that of a random order mechanism which has been suggested for glutamate dehydrogenase-catalyzed reduction of trinitrobenzenesulfonate by NADPH (*98*). It is evident that a metal ion in a nonenzymatic reaction plays an "enzyme-like" role.

One report from the literature which presents highly refined kinetics, with kinetic (k_H/k_D) and product (Y_H/Y_D) isotope effects, emphasizes that the difference in the catalytic behavior of a metal ion is nothing but its appearance (*19*). A series of substrates with continuous variation in electronic character, unsubstituted and 8-substituted α,α,α-trifluoroacetophenones (**4a–i**) (substituent constants of which range from $\sigma = 0$ to $\sigma = 1.42$), were subjected to reduction by PNAH, PNAH-4-*d*, or PNAH-4,4-d_2 in the presence and absence of magnesium ion. The rates of reduction of **4a–h** were accelerated by magnesium ion whereas that of **4i**, the substrate with a strongly electron-deficient carbonyl group, was retarded by magnesium ion. These results unambiguously manifest that the above-mentioned categories i and ii are merely different outcomes of one phenomenon. The results obtained are compatible only with the multistep mechanism initiated by one-electron transfer and are well interpreted on the basis of the consideration that magnesium ion lowers the free energy of activation for the initial one-electron transfer step as well as that of the intermediate (the radical ion pair of the anion radical from the substrate and the cation radical from the model). The succeeding proton (or hydrogen atom)-transfer step is little affected, if any, by the metal ion. As the carbonyl group to be reduced becomes more electron deficient, the stabilization by the metal ion in the one-electron transfer step becomes less important or results in inhibition. Energy diagrams for the reactions are represented in Fig. 3.

Kinetics for the reduction of these substrates by sulfur-containing dihydropyridines, **35**, confirmed the concept mentioned above (*99, 100*). Since category iii may be recognized as a combination of categories i and ii, the concept established on the basis of the multistep mechanism can explain all "peculiar" effects of the metal ion. Interestingly, the reduction of *N*-methylacridinium ion (**6**) by BNAH shows a discrepancy between the k_H/k_D and Y_H/Y_D values in the absence of metal ion, whereas the magnesium ion-catalyzed reduction of **6** gives identical values for these two isotope effects (*101*).

MIMETIC SYSTEMS

Stereospecific Reduction

Biological reactions are highly stereospecific. To mimic this feature is one object to be attained by organic chemists. Stereospecific reduction by a chiral NAD(P)H model was attempted in 1975 for the first time. This work showed that

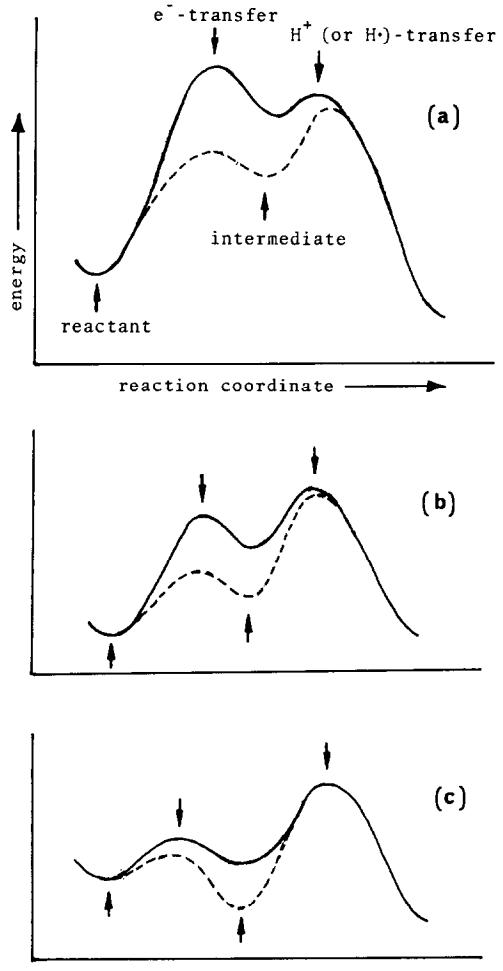
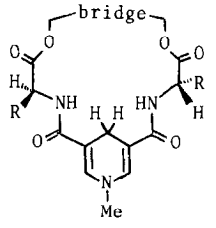


FIG. 3. Energy diagrams for various reductions by PNAH. —, In the absence of Mg^{2+}. ---, In the presence of Mg^{2+}. (a) For substrates with a weakly electron-withdrawing substituent. (b) For substrates intermediate to a and c in electronic property. (c) For substrates with a strongly electron-deficient substituent(s). Note that the intermediate in this category becomes more stable than the reactant when Mg^{2+} is added to the reaction system.

optically active model, (*R*)- or (*S*)-*N*-(α-methylbenzyl)-1-propyl-1,4-dihydronicotinamide (**36**), quantitatively reduces ethyl benzoylformate (**28b**) into ethyl mandelate (**37b**) in the presence of magnesium ion with 19% e.e. (*102*). It was also found that magnesium ion-catalyzed reduction of α,α,α-tri-fluoroacetophenone (**4a**) by **36** affords the corresponding carbinol in 58% yield with 16% e.e. (*103*). An electron-deficient carbon–carbon double bond in an olefin, **38** (*104a*), and a carbon–oxygen double bond in 2-acetylpyridine (**8b**) (*104b*) were also hydrogenated by **36** with 8 and 20% e.e., respectively, in the presence of magnesium ion.

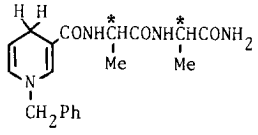
Similarly, several asymmetric reductions were performed with dihydronicotinamide derivatives modified by a chiral moiety on the nitrogen of the carbam-



bridge = $-(CH_2)_2O(CH_2)-$,
$-(CH_2)O(CH_2)O(CH_2)-$,
$-(CH_2)_{4\sim12}-$,


R = Me_2CH, $PhCH_2$

39



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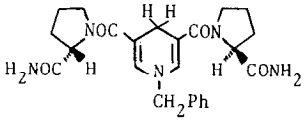

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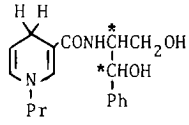

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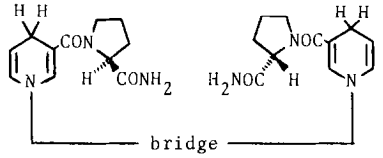


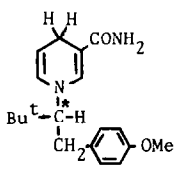
43a; bridge = $-CH_2-C_6H_4-CH_2-$
43b; bridge = $-(CH_2)_6-$

oyl group (*105*) as well as HEH with chiral groups on the two alkoxycarbonyl groups (*106*); a dihydropyridine containing a chiral macrocycle, **39**, reduced **28b** into **37b** with 86% e.e. (*107*). This substrate was also reduced by chiral models **40** (*108*), **41** (*109*), and **42** (*110*) with 45, 47, and 52% e.e., respectively. Chiral bis(NAD(P)H) models, **43a** (*111*) and **43b** (*112*), afforded **37b** from **28b** with 98 and 96% e.e., respectively.

It is noteworthy that in these reductions the chirality at the position remote from the reaction center by five atoms is effectively transferred into the reduction product. In this connection, there is an attractive report which indicates that the stereospecificity of the reduction depends on the efficiency of conjugation between the dihydropyridine ring and the chiral center (*113*). It is also interesting that the $NAD(P)^+$ analog formed as the reaction proceeds affects optical purity in the product (*114, 115*).

Some NAD(P)H models substituted by a chiral moiety on the ring nitrogen were also subjected to asymmetric reduction; a model, **44**, gave **37a** from **28a** with 27% e.e. (*116*); model **45** reduced 3,3,5-trimethyl-2-cyclohexylidene iminium salts with 3–31% e.e. (*117*).

An example in which the chirality of the reaction field gives rise to asymmetric



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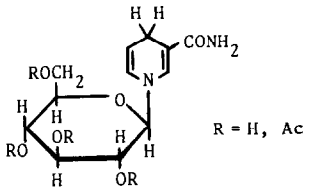

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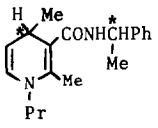

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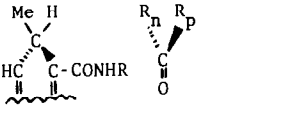
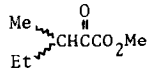


R_p = polar substituent

R_n = nonpolar substituent

48



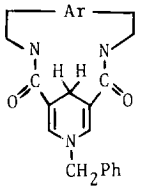
49

reduction is seen in the reduction of **4a** by PNAH in the presence of a protein, bovine serum albumin (BSA) (*118*). In this reaction, the reduction product had 47% e.e. In contrast, reduction of the same substrate, **4a**, by a model covalently bound to BSA, **46**, resulted in only 11% e.e. (*119*). Thus, interestingly a covalent bond between the dihydronicotinamide moiety and the protein decreases the enantioselectivity.

The chirality at the reaction center, the C-4 position of a dihyronicotinamide moiety, is expected to exert high stereospecificity. An NAD(P)H model, **47**, in which one of two prochiral hydrogens is substituted by a methyl group, reduced a variety of carbonyl compounds in the presence of magnesium ion with 62–100% e.e. (*9*). The stereochemical course was proved to be governed by both the configuration at the C-4 position of **47** and the electronic character of the substrate as shown in **48**. Thus, one diastereomer of **47** with *R*-configuration at the C-4 position, for example, from which *pro-S* hydrogen is transferred, gives enantiomerically almost pure methyl (*R*)-trimethyllactate from methyl trimethylpyruvate. Further studies were carried out on the effects responsible for the stereospecificity of reductions by **47**, i.e., steric and electronic effects of a substrate as well as the effect of magnesium ion in the reductions of 2-acylpyridines (**8b** and **e–j**) (*120*) and substituent effect in the reductions of α,α,α-trifluoroacetophenones (**4a–c**, **f**, **j**, and **k**) (*121*). The results obtained in these studies were well interpreted in terms

of the three-step mechanism including initial one-electron transfer. In addition, these studies as well as product analyses in the reduction of camphorquinone by four diastereomers of **47** confirmed the concept that the more electronegative substituent in the substrate prefers to face the carbamoyl group of the model at the transition state (cf. the structure **48**), which is the most important factor in determination of the stereochemical course of the reduction (*122*). The importance of hydrophobic or polar effects rather than steric effects for stereoselectivity and/or stereospecificity was also suggested in the reduction of racemic and optically active methyl 2-oxo-3-methylpentanoate (**49**) by **47** (*123*).

In its reduction course in a biological system, NAD(P)H specifically utilizes one of two prochiral hydrogens at the C-4 position of the dihydropyridine ring. Studies in both biological and model systems are currently performed in order to find the factor to choose the transferring hydrogen (*124–127*). Molecular orbital calculations on some NAD(P)H models have predicted that stereospecificity can be correlated with an out-of-plane orientation of the carbamoyl oxygen in a dihydronicotinamide moiety at the transition state of the reaction (*128*). This concept was verified by several experimental results with a model, **47** (*129*). On the other hand, on the basis of results from the hydride-transfer reaction with models possessing a bridged structure, **50**, it was concluded that distortion of the dihydronicotinamide moiety of enzyme-bound NAD(P)H is of minor importance for stereospecificity, while the models, **50**, exert favorable dissociation of the axial hydrogen in a distorted dihydropyridine ring (*130*).



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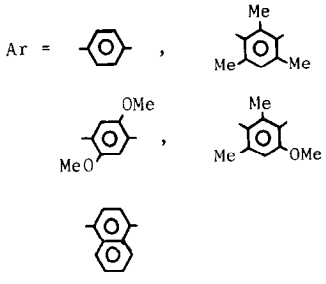

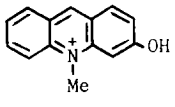

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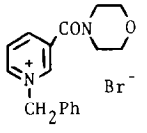
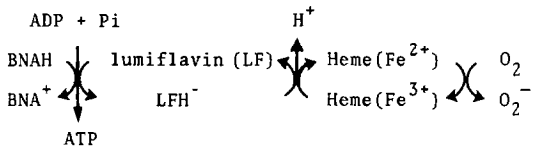


52

Mimetic Systems for NAD(P)H in Biological Actions

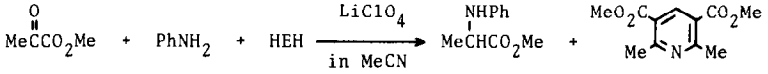
Various reactions to mimic the action of NAD(P)H in biological systems have been presented. An artificial electron bridge starting from BNAH was constructed in analogy with a respiratory chain in a mitochondrion where NADH acts as an electron carrier (*131*):



(5)

An electron bridge including a flavin mononucleotide and an NAD^+ analog, 3-hydroxy-*N*-methylacridinium ion (**51**), was also presented as an efficient model for biological electron-transport system from flavin to NAD^+ (*132*).

Conversion of methyl pyruvate to the methyl ester of *N*-phenylalanine (52% yield) by HEH in the presence of aniline



(6)

is interesting as a model reaction for glutamate dehydrogenase-catalyzed reduction of α-ketoglutarate to L-glutamate by NADH (*133*).

Application of a phase-transfer system to the reduction of thiopivalophenone by BNAH made it possible for the model to act catalytically, although the recycle number is small (*134*).

Oxidation by an NAD(P)$^+$ Model

Very few reactions are available to elucidate the mechanism of $NAD(P)^+$-mediated oxidation. Probably because of their redox potentials, $NAD(P)^+$ analogs scarcely give rise to oxidation of alcohols into ketones or aldehydes, whereas reactions in both directions, reduction by NAD(P)H and oxidation by $NAD(P)^+$, take place reversibly under biological regulations.

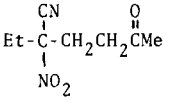
Reduction of BNA^+ with *N*,*N*′-diethylethylenediamine in acetonitrile was found to give BNAH in 18% yield with small contamination of its 1,6-dihydro isomer (*135*). Reduction of BNA^+ by potassium formate also took place in acetonitrile in the presence of 18-crown-6 ether, giving BNAH and its 1,6-dihydro isomer in 80 and 20% yields, respectively (*136*). Shinkai *et al.* recognized that **51** easily oxidizes benzyl alcohol and cyclohexanol to benzaldehyde and cyclohexanone, respectively, in the presence of potassium *tert.*-butoxide (*137*). Recently, they reported that alkoxymagnesium bromides are capable of reducing an $NAD(P)^+$ analog, 1-benzyl-3-morpholinocarbonylpyridinium bromide (**52**), into the corresponding 1,4-dihydronicotinamide derivative in satisfactory yields (*138*).

Reactions of BNA^+ and PNA^+ with glyceraldehyde or related compounds gave BNAH and PNAH, respectively, in poor yields (*139*). Studies on these reactions with deuterium-labeled compounds revealed that the reactions proceed, unfortunately, through a mechanism different from that for glyceraldehyde-3-phosphate dehydrogenase-catalyzed oxidation by NAD^+ (*140*).

In cathodic two-electron reductions of certain $NAD(P)^+$ analogs, 1-phenyl-3-aminocarbonylpyridinium salts gave 1,4-dihydronicotinamides quantitatively, whereas 1-benzyl and 1-methyl derivatives gave 1,6-dihydro isomers only (*141*).

APPLICATION TO ORGANIC SYNTHESIS

The ability of the NAD(P)H model as a one-electron donor is a remarkable property applicable to organic synthesis. Light-induced reduction is one successful example. Under infrared radiation from a tungsten lamp, BNAH selectively gives rise to reductive denitration from aliphatic nitro compounds possessing a cyano, alkoxycarbonyl, or carbonyl group at the α-position of nitro group; 3-cyano-3-nitroheptan-6-one (**53**) esters of 4-nitropentanenitrile-4-carboxylic acid (**54**) and unsubstituted and *p*-substituted α-nitroisobutyrophenones (**55**) are successfully denitrated in satisfactory yields (*62*). Moreover, carbon–oxygen bonds in sulfonate esters, **56**, are converted into carbon–hydrogen bonds by BNAH under irradiation of visible light (*142*). These reactions are initiated by one-electron transfer from BNAH to the substrates.



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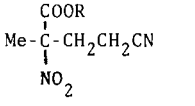

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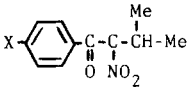
R = Me, Et, Pr^i



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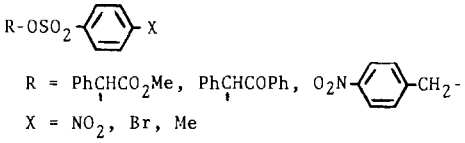
X = H, Cl, Me, MeO, NO_2



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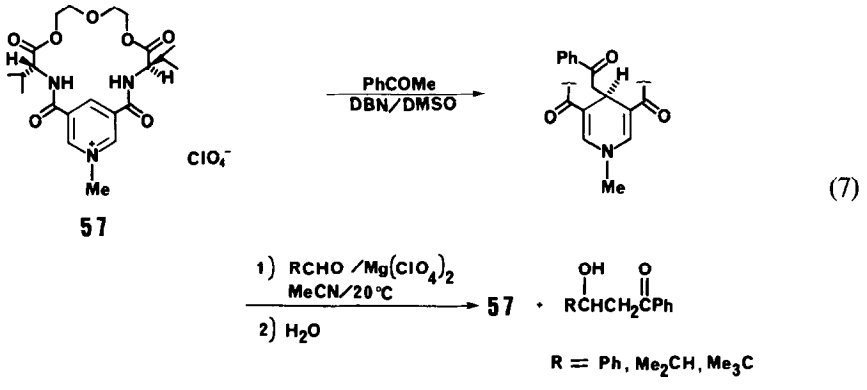
Rhodium(I) complex catalyzes the selective reductions of carbon–halogen bonds in aryl, benzyl, phenacyl, and vinyl halides (*10*) as well as carbon–heteroatom bonds in allylic derivatives (*11*) into carbon–hydrogen bonds by BNAH or PNAH in the dark. Functional groups such as nitro, amino, alkenyl, and ester groups remain unaffected under the conditions. In the presence of this catalyst, carbon–carbon double bonds in α,β-unsaturated carbonyl compounds are also selectively reduced by PNAH (*12*). Similarly, chemoselective reductions of carbon–carbon double bonds in α,β-unsaturated carbonyl compounds and α-nitroolefins is accomplished by HEH on silica gel in benzene (*13*). Thus, excellent chemoselective reductions are successful with NAD(P)H models with the aid of an appropriate catalyst.

Another interesting example was presented by Kellogg and co-workers. They attempted to use an $NAD(P)^+$ analog as an enolate transferring agent (*143*). Acetophenone, for example, adds to the C-4 position of $NAD(P)^+$ analog, **57**, in the

presence of a base. The adduct thus formed undergoes smoothly, at room temperature, aldol condensation with aldehydes in the presence of magnesium ion, giving an aldol product. The analog, **57**, is regenerated after the procedure as shown in



(7)

The successful methods thus established suggest that the scope and limitation of the reduction by an NAD(P)H model in organic syntheses are quite promising.

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