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REVIEW

Simulation of NAD(P)$^+$-NAD(P)H Redox System

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Recent development for the model reactions of nicotinamide adenine dinucleotide-dependent dehydrogenases was described.

KEY WORDS: NADH/ 1, 4-Dihydropyridine/ Model reactions/ Mechanism/ Asymmetric reduction/ Role of a metal ion/

INTRODUCTION

Reactions in biological systems are fascinating because of their outstanding features with respect to reactivity and selectivity that can be considered as results of catalysis by enzymes. Namely, biochemical reactions proceed rapidly and selectively under mild conditions without requiring a high temperature and strong acid (or base) as a catalyst. In addition, it should be noted that most enzymatic reactions are stereospecific. These features have encouraged organic chemists to mimic such excellent reactions in artificial systems.

Among many kinds of enzymatic reactions, it is relatively easy to simulate the one in which a coenzyme acts as one of reagents, because the actual reaction site can be readily simplified within a small molecule or molecules by extracting the fateful moiety in the coenzyme combined with a small part of apoenzyme which is important for the catalysis. As a simulation of oxidoreductase, reductions by NAD(P)H analogs have been widely investigated. Since a variety of substrates are reduced rapidly and stereoselectively under the catalysis of dehydrogenases, the simulation has been intended to mimic such reactions without enzymes. Here we will describe the recent development in this field.

NAD(P)H AS A COENZYME

Nicotinamide adenine dinucleotide and its phosphate derivative are widely distributed as coenzymes for biological redox reactions. Structure of the reduced form (NAD(P)H) is depicted in Scheme 1. Within the coenzyme molecule, the nicotinamide moiety, which links with a ribose through a β-glycosidic bond, acts as a

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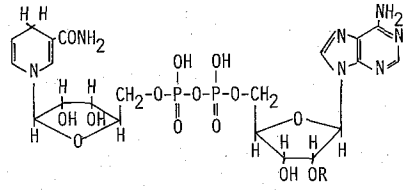
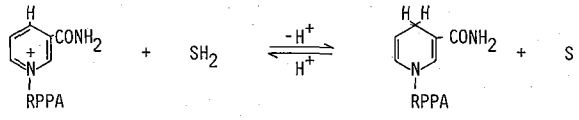


NADH : R = H
NADPH : R = PO_3H_2

Scheme 1

redox reagent by shuttling between 1, 4-dihydropyridine and pyridinium cation structures. It is believed that the remaining part of the coenzyme mainly acts as the binding site toward the apoenzyme.

In the oxidation of a substrate, the pyridinium cation in the oxidized form of the coenzyme accepts two electrons and one proton to be reduced to 1, 4-dihydropyridine which in turn reduces the substrate in the reverse reaction. The redox interconversion of the coenzyme is seen in Scheme 2, where S and SH_2 represent the oxidized and reduced states of the substrate, respectively.



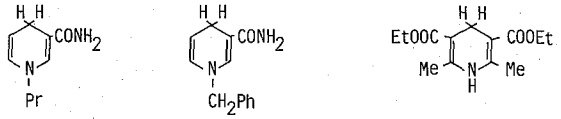
(RPPA represents the dinucleotide moiety of NAD(P)H)

Scheme 2

It has been established, in the reduction by NAD(P)H, that one of the two hydrogens at the 4-position of the 1, 4-dihydronicotinamide ring directly transfers onto the substrate without exchanging with hydrogens in solvent or other parts of the enzyme.[1] Direct transfer of a hydrogen from the substrate has also been ascertained in the reverse reaction, oxidation of the substrate.

MODEL REACTIONS OF NAD(P)H-DEPENDENT DEHYDROGENASES

Within a molecule of NAD(P)H, 1, 4-dihydronicotinamide moiety acts as a reducing reagent. Thus, a 1, 4-dihydropyridine derivative where the ring nitrogen is substituted by a simple substituent, such as 1-propyl-1,4-dihydronicotinamide (PNAH), 1-benzyl-1,4-dihydronicotinamide (BNAH), or Hantzsch ester (HEH), have been utilized as a model compound for NAD(P)H.



PNAH BNAH HEH

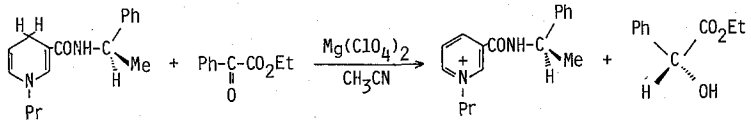
Scheme 3

Simulation on the reactions of dehydrogenases by the use of 1, 4-dihydropyridine derivatives has been widely investigated.[2-4] These compounds reduce C=O, C=C, C=N, and C=S double bonds as well as flavin and metal ions.[4] However, they are not so reactive toward the reduction as compared with NAD(P)H in biological systems, where the corresponding apoenzyme participates as a catalyst, in spite of the redox potential for 1-methyl-1, 4-dihydronicotinamide (−403 mV) and BNAH (−362 mV) being sufficiently lower than that for NADH (−320 mV).[5]

Considering the low reactivity of 1, 4-dihydropyridine moiety extracted from dehydrogenases, it is easily noticed that a specific field constructed by amino acid residues of apoenzyme is quite important for acceleration of the reaction. At the same time, it should be noted that such reaction field at the active site contributes to the stereospecificity of the reaction.

MIMETIC REACTION IN THE PRESENCE OF A METAL ION

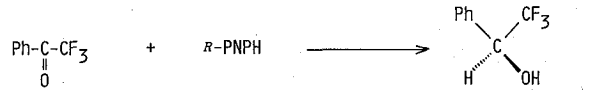
In order to run the mimetic reaction system, it is necessary to add something which has a catalytic power as an enzyme-equivalent. On the basis that alcohol dehydrogenase contains Zn (II) as a cofactor, divalent metal ions such as Mg (II) and Zn (II) have been employed in mimetic reactions.[6] By the addition of a metal ion, rates of reduction of some substrates such as acridinium salt[7] and thioketone[8] were retarded. Most of the substrates, however, were facilitated to be reduced in the presence of a metal ion. Furthermore, it was found that Mg (II) plays an intrinsic role for the asymmetric induction from a chiral 1, 4-dihydropyridine derivative to a substrate. By the use of a 1, 4-dihydronicotinamide derivative which contains chiral *R*-α-methylbenzymamine moiety in the carbamoyl side-chain (*R*–PNPH), ethyl benzoylformate (EBF) was reduced in the presence of magnesium perchlorate into ethyl *R*-mandelate (*R*–EM) in 19% enantiomer excess (e.e.).[9]



R-PNPH EBF *R*-PNP$^+$ *R*-EM

Scheme 4

It should be noted that Mg (II) is indispensable here not only for the reduction but also for the induction of the chirality. Namely, the reduction did not proceed without Mg (II). In the reduction of α, α, α-trifluoroacetopheneone (TFA) asym-



TFA

with Mg(II) 16 % e.e.
without Mg(II) 0 % e.e.

Scheme 5

metric reduction was not achieved in the absence of Mg (II), whereas the e.e. value in the product came up to 16% by the addition of Mg (II).[10]

The observation of the rate acceleration by a divalent metal ion in the model system readily leads to the idea that the metal ion may polarize the carbonyl group of the substrate as a Lewis acid to facilitate the reduction.[11,12] However, this interpretation cannot explain the contribution of the metal ion to the asymmetric induction. More intrinsic function involving an interaction between the metal ion and the 1,4-dihydronicotinamide moiety should be considered. In fact, it has been established, based on the spectroscopic study, that Mg (II) forms a complex with a 1, 4-dihydropyridine derivative. For example, electronic absorption at around 350 nm due to the π-π* transition of the dihydropyridine moiety shifts bathochromically and the extinction coefficient increases as the 1, 4-dihydropyridine forms a complex with a metal ion.[13] On the other hand, in contrast to the case of acylpyridine derivatives, EBF has little ability to coordinate onto a metal ion. No spectroscopic change due to the complexation of EBF with Mg (II) was observed.[13] Therefore, the role of the metal ion in this system can be considered as follows; metal ion binds the 1, 4-dihydropyridine to facilitate the electron transfer to the substrate and the substrate is stabilized *at the transition state* by the coordinated metal ion within the ternary complex where, at the same time, the orientation of the reactants is fixed to exhibit stereoselectivity. In this type of complex, Mg (II) would locate between the dihydropyridine and the substrate as shown in Fig. 1.[13,14] Such fassion of the complexation is also supported by infrared spectroscopy, where no apprecable shift of the absorption corresponding to the stretching vibration of the amide carbonyl was observed.[13] ^{13}C–NMR data showed a different situation; according to a report by Gase *et al.*, it seems that Mg (II) is coordinated by the amide oxgen of BNAH judging from down-field shifts of the signal from C2 and the carbonyl carbon and an up-field shift of the signal from C3.[15] Though not all of the spectroscopic data tend to be forcused into the same result as to the position of the coordination to the metal ion, it is sure that the interaction between Mg (II) and the dihydronicotinamide plays an important role for the reduction. The association constant is relatively large; for example, that of PNAH and magnesium perchlorate is measured to be about 15,300 mol/L in dry acetonitrile at 293 K.[16]

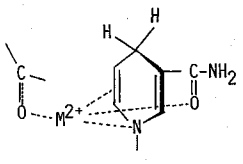


Fig. 1. Schematic representation of the transition state of the reaction in the presence of a divalent metal ion (M^{2+}).

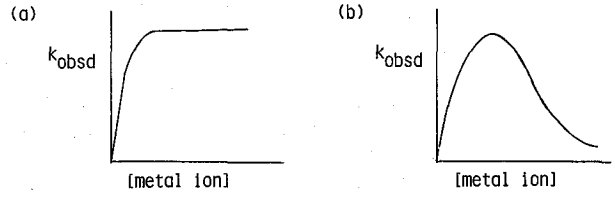


Fig. 2. Rate-metal ion concentration profiles for the reduction of (a) EBF and and (b) 2-acylpyridine derivative.

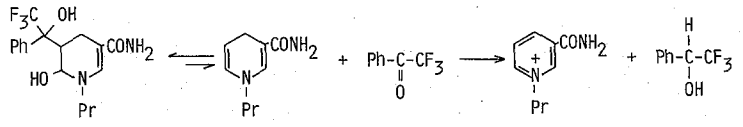
Difference in the kinetic profile of the reduction also supports the idea mentioned above. The observed rate constant (k_{obsd}) for the reduction of a substate, such as

EBF or TFA, which has low ability of complexation with a metal ion, increases as the concentration of the metal ion increases as depicted in Fig. 2(a).[14] On the other hand, with a substrate such as 2-acetylpyridine, which can form a complex with a metal ion, k_{obsd} changes pecuriarly as the concentration of the metal ion increases as shown in Fig. 2(b).[15] The optical yield of the reaction with PNPH depends on the concentration of Mg (II) in absolutely the same manner as the dependency of k_{obsd}.[17] The profile of 2-acetylpyridine was interpreted in terms of the formation of two different types of complexes.[18] In the presence of excess metal ion, both the substrate and the 1, 4-dihydropyridine derivative are complexed by the metal ion, respectively, which supresses the formation of the ternary complex that is indispensable for the reduction. It should be emphasized that the formation of a ternary complex by the chelation with a metal ion is the most important factor for the metal ion-catalyzed model system.

MECHANISM OF THE REDUCTION WITH NAD(P)H MODELS

Discussion in the previous section leads to a question to be solved. How the 1, 4-dihydropyridine moiety releases a negative species, "hydride", after being coordinated by a metal ion which has an electron-withdrawing property?

Based on the fact that the hydrogen at the 4-position of 1, 4-dihydropyridine ring transfers directly to the substrate, one-step hydride transfer mechanism proposed by Westheimer *et al.* in early days[1,19] had been accepted. However, it is very curious to consider the polarization where a partial negative charge localizes on less electronegative hydrogen atom in a C–H bond. In this connection, it has been suggested that apparent hydride transfer involves an initial one-electron transfer to produce an intermediate which corresponds to an ion-radical pair or a charge transfer complex between the substrate and the 1, 4-dihydropyridine derivative. The electron transfer mechanism (ET-mechanism) was first suggested by Steffens and Chipman based on the discrepancy between the kinetic isotope effect of the reduction (k_H/k_D) and the deuterium content in the produced alcohol (product isotope effect; Y_H/Y_D) in the reaction of TFA with PNAH or PNAH-4-*d*.[20] It was proved later that the discrepancy was caused as a result of a side reaction which readily occurs in an aqueous solution.[21,22]



Scheme 6

However, such a discrepancy between the two isotope effects was observed also in dry acetonitrile where the side reaction does not take place.[23] This evidently indicates that a certain step precedes the hydrogen transfer, which can be regarded as an electron transfer step, and that the existence of an intermediate or intermediates should be considered. In addition, from the floating ρ-value in the reaction of sub-

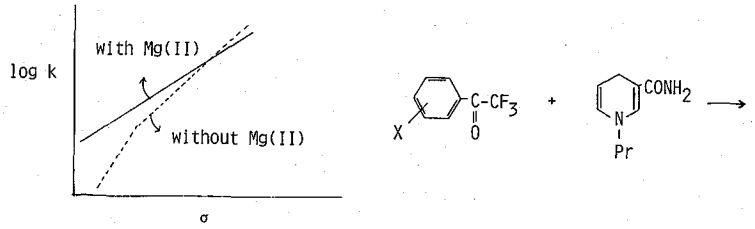


Fig. 3. Hammett plots for the reduction of substituted trifluoroacetophenone derivatives with PNAH in the presence and absence of Mg (II).

stituted α, α, α-trifluoroacetophenones with BNAH (Fig. 3), it was proved that the rate-determining step changes from the electron transfer step to the hydrogen nucleus transfer step as the ability of a substrate for electron acception increases. On the other hand, in the Mg (II)-catalized reaction, the migration of the rate-determining step was not observed, which was interpreted in terms of a facile transfer of an electron to the substrate under the catalysis of a metal ion (Fig. 3).[23]

When a 1, 4-dihydronicotinamide derivative with a relatively low reducing power is utilized, a bent line was obtained in the Hammett plot of the reaction with Mg (II) as shown in Fig. 4.[24,25] This indicates that, even in the Mg (II)-catalyzed reaction, the electron-transfer process remains as the rate-determining step when the potential of the reductant to release an electron is low.

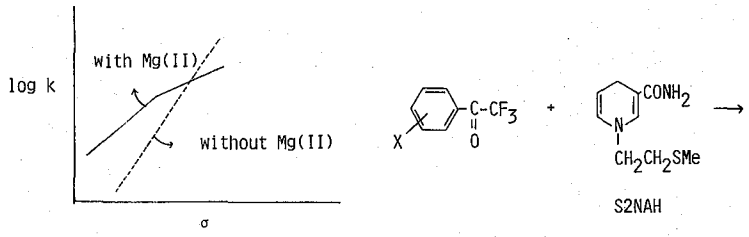


Fig. 4. Hammett plots in the reduction of substituted trifluoroacetophenone derivatives with S2NAH in the presence and absence of Mg (II).

Similar discussion based on the discrepancy between the two isotope effects was presented for the reduction of an acridinium cation as a substarte.[26–29] However, in the system uncertainty due to side reactions, scrambling of the isotope, cannot be excluded.[30,31]

More direct proof for the ET-mechanism is the detection of the intermediate. The anion radicals that were derived from the substrate such as thiobenzophenone[32] or benzil[33] by one-electron transfer in the course of the reduction were detected ESR spectroscopically. Formation of charge transfer complexes between the substrate and 1, 4-dihydropyridine derivatives were also reported.[34,35] Hydrogen abstraction by the anion radical of the substrate from the solvent was observed in a well-designed system. The phenomenon had not been observed in ordinal reduction systems probably because the initial electron transfer and the following reactions take place within a cage of the solvent.[36–38] At the same time. Shinkai *et al.* observed that the charge separation prompts to initiate some kinds of polymerization.[38,39] It was

reported that the reduction of diazonium salts[40,41] and halides[42,43] proceed through a radical-chain mechanism involving a one-electron transfer. In particular, Fukuzumi *et al.* discussed details of the mechanism for the reduction of halides,[42,43] TCNE[44] and *p*-benzoquinone[45] by BNAH.

On the other hand, it has also been suggested that the reduction by a 1, 4-dihydropyridine derivative proceeds through a one-step hydride transfer mechanism (HT-mechanism), which seems to be contrary to the ET-mechanism described above. This assertion is mainly based on the results from the reduction of cationic substrates such as quinolinium and acridinium salts. For example, Ostović *et al.* reported that the value of kinetic isotope effect does not change significantly in the reactions with a series of substrates in a wide range of redox equilibrium constants.[46] Roberts *et al.* concluded that the multi-step mechanism involving an electron transfer process can be excluded considering from the α-value of Brønsted plot ($\alpha=0.5$) observed over a wide variety of cationic substrates, which agrees with the Marcus theory of atom transfer.[47] Bunting *et al.* insisted on that the transferring hydrogen carries a partial negative charge, based on the quantitative calculation from the Hammett ρ-values in the reduction of isoquinolinium salts.[48-51] The Hammett ρ-value is, however, not at all quantitative character to be able to elucidate a physical property such as a charge density and the calculation seems to have no meaning.

Since a cationic substrate easily accepts an electron, it is difficult to observe the fast initial electron transfer step even if it is surely present. Namely, kinetically observable process is only the rate-determining hydrogen transfer step. It should be noted that the evidence provided for the proof for the one-step mechanism is not necessarily the proof for the HT-mechanism. Hydrogen may transfer as a proton or a hydrogen atom after donation of one electron to the substrate. Thus, there is no contradiction to conclude that the reaction is composed of three steps, electron-proton-electron transfer, and the relative importance of each step changes depending on the nature of the substrate. The rate-determining electron transfer and rate-determining hydrogen transfer are two different extreme situations in a spectrum of the same phenomenon, a "hydride" transfer. Most discussions so far argued whether the reduction involves an initial electron transfer or not, should be replaced by the discussion whether the rate-determining step is the electron transfer process or the process for the transfer of a hydrogen nucleus. Namely, the discussion should be focused on the question whether the activation energy for electron transfer step is large enough to be observed or too small to be neglected. Figure 5 shows examples of energy diagrams

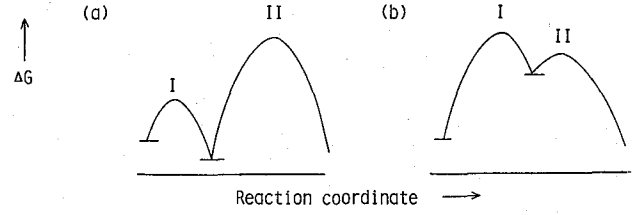


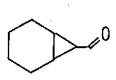
Fig. 5. Schematic illustration of energy diagrams for two types of the reduction; (a) rate-determining hydrogen atom transfer and (b) rate-determining initial electron transfer.

for the three-step mechanism; a) reduction where the hydrogen atom transfer is rate-determining and b) reduction where the initial electron transfer step is rate-determining.

It is the role of a metal ion that should be noted again. Acceleration by the addition of a metal ion is resulted from the facilitation of the electron transer step which otherwise has a higher barrier than the succeeding hydrogen atom (or proton) transfer process. On the other hand, for the substrate whose reduction is retarded by the addition of a metal ion, the reduction proceeds *via* an energy diagram shown in Fig. 5(a) where the electron transfer step is associated by a lower energy of activation than the other step and the metal ion stabilizes the intermediate unnecessarily to result in a larger difference in energy between the intermediate and the rate-determining transition state of the reaction than that in the reaction without the metal ion. One should notice that the stabilization of reactant at the ground state results in the *retardation* of reaction and waste catalytic power. The stabilization of transition state is the entire and sole factor to accelerate the reaction.

It seems necessary to emphasize that the electron transfer process we are interested in here is not the physical process such as those observed in spectrophotometry or voltanmetry, but is the chemical process associated by a certain amount of kinetic isotope effect, or the movement of atomic nuclei is involved in the process.

It is of interest to clarify whether the reduction in a biological system involves an initial electron transfer process. Recently, one-step hydride transfer mechanism was suggested for the reduction with an alcohol dehydrogenase on the basis of the reduction of cyclopropyl derivatives such as **1**[52] and **2**.[53] If the reduction proceeds through a radical intermediate, open chain products would be obtained. In fact the produced alcohol remained the cyclopropyl structure. The same result was reported in the non-enzymatic reduction with a 1, 4-dihydropyridine derivative.[54]



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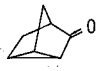

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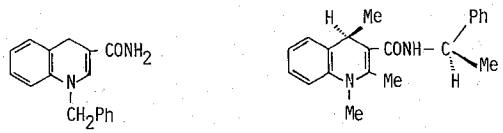
Scheme 7

APPLICATION TO ORGANIC SYNTHESIS

1, 4-Dihydropyridine acts as an effective reducing agent in biological systems, whereas the activity in the non-enzymatic system is very low. This feature is a disadvantage to use the 1, 4-dihydropyridine derivatives as reducing agents in organic syntheses. Considering that the catalytic zinc ion in an alcohol dehydrogenase acts as a Lewis[55,56] or a general acid[57–59] catalyst, the activated reduction is expected by means of the acid catalysis. As an analogy to the catalytic zinc ion, divalent metal ions that can be regarded as weak Lewis acids were employed and found to be effective to facilitate the mimetic reduction. However, stronger acids cannot be utilized because the 1, 4-dihydropyridine moiety is labile toward acids due to hydration to enamine double bond. Shinkai *et al.* synthesized 1-benzyl-3-carbamoyl-1, 4-dihydro-



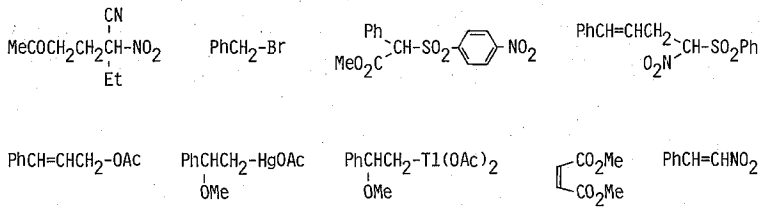
BNQH Me_2MQPH

Scheme 8

quinoline (BNQH) as an acid-stable model[60] and subjected it to the reduction of a variety of substrates[61-64] including non-activated carbonyl compounds[65] under the condition of general acid catalysis.

Reductions of carbonyl groups in α, β-unsaturated aldehydes under the catalysis of Lewis acids have been succeeded by the use of the same kind of compound, Me_2MQPH, which has more electron-rich dihydroquinoline ring than BNQH.[66]

Photo-activation and/or catalysis by transition metals have been revealed to be effective for a variety of reductions such as reductive conversion of R–NO_2,[67,68] R–X(X: halogen),[42,43] R–OSO_2Ar,[69] R–SO_2Ph,[70] R–OAc,[71] R–HgOAc,[72] and R–Tl[73] into R–H. These systems utilize the one-electron-donating ability of 1, 4-dihydropyridine as the driving force of the reduction. The reduction seems to proceed through a radical-chain mechanism. It has also been reported that olefinic double bonds which are conjugated with an electron-withdrawing group such as C=O or NO_2 are selectrively reduced without affecting the other functions.[74-76] Typical substrates subjected to the reduction in this category are depicated in Scheme 9.



Scheme 9

ASYMMETRIC REDUCTION

It is very fascinating that the reduction by NAD(P)H on dehydrogenases proceeds with stereochemical completeness. For example, lactate dehydrogenase (EC 1.1.1.27.) catalyzes the reduction of pyruvate by NADH to produce L-lactate. In addition, an enzyme can also differentiate enantiotopic groups or faces that are non-enzymatically (chemically) equivalent. In the reaction catalyzed by alcohol dehydrogenase (ADH, EC 1.1.1.1.), diastereotopic hydrogens at the 4-position of the 1, 4-dihydronicotinamide ring in NADH and enantiotopic hydrogens in ethanol are clearly discriminated in the course of redox interconversion,[77,78] the *pro-R* hydrogen[79] on NADH transfers from the *re*-face of acetaldehyde to become the *pro-R* hydrogen in[80] the 1-position of ethanol and the same hydrogen returns onto NAD^+ in the reverse reaction.

Dehydrogenases that utilize the *pro-S* hydrogen at the 4-position have also been

known. Thus, NAD(P)H-dependent dehydrogenases are divided into two classes. Dehydrogenases that exhibit the same specificity as ADH does belong to A-type and use H_A (*pro-R* hydrogen) whereas those that exhibit the opposite specificity are called B-type and use H_B (*pro-S* hydrogen). Such kind of specificity with respect to the face of 1, 4-dihydropyridine ring seems to play an important role not only for the enzymatic reduction but also for the model system as will be mentioned below.

As a simulation of such stereoselective reductions in biological systems, a variety of 1, 4-dihydropyridine derivatives carrying chiralities within the molecule have been employed to achieve asymmetric reduction,[81] after the first report on this subject.[9]

In this type of reduction a divalent metal ion is indispensable for the asymmetric induction. As mentioned above, it is reasonable that the reduction by a 1, 4-dihydropyridine derivative catalyzed by a metal ion proceeds *via* a ternary complex as shown in Fig. 1. In the reduction by PNPH, the factor that determines the stereochemistry of the product is the mode of the approach of the substrate to PNPH. Namely, the relative orientation between the 1, 4-dihydropyridine ring and the substrate in the ternary complex is important. There are, however, many possibilities in the molecular arrangement in the ternary complex as well as the fassion of the coordination of PNPH toward Mg (II), which makes it difficult to consider the cause of asymmetric induction and to achieve a reduction with a high e.e. value. Therefore, it is expected that if one of the hydrogens at the 4-position of 1, 4-dihydropyridine derivative is specifically freezed toward the reduction, as observed in enzymatic systems, a high degree of stereoselective reduction would be achieved.

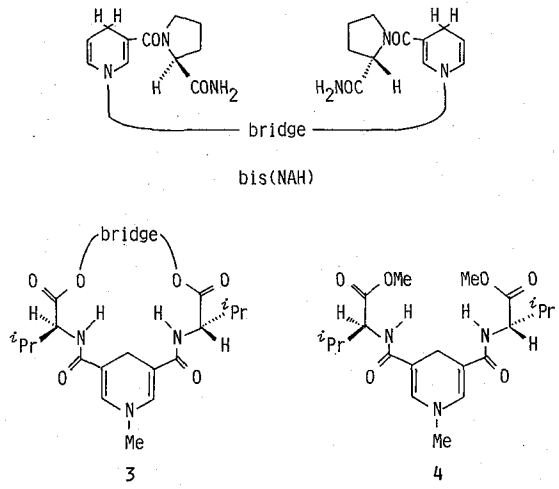
The idea was realized by the substitution of one of the two hydrogens at the 4-position for a methyl group. This means the introduction of chirality at the reaction center. Ohno *et al.* synthesized *N*-α-methylbenzyl-1-propyl-2, 4-dimethyl-1, 4-dihydronicotinamide (Me_2PNPH) which contains two chiral centers within a molecule. By the reduction of EBF with *RR*–Me_2PNPH,[82] one of the diastereomers of Me_2PNPH, *R–EM* was produced in 97.6% e.e.[83,84]

RR-Me_2PNPH　　*SR*-Me_2PNPH

Scheme 10

High values in e.e. in this system were explained in terms of a specific coordination of Me_2PNPH and EBF to Mg (II) at the transition state where the polar group in Me_2PNPH and the polar group in EBF face each other by the aid of Mg (II).[84] This explanation is supported by the study using a series of polyfluoroacetylpyridines[85] and camphoroquinone.[86]

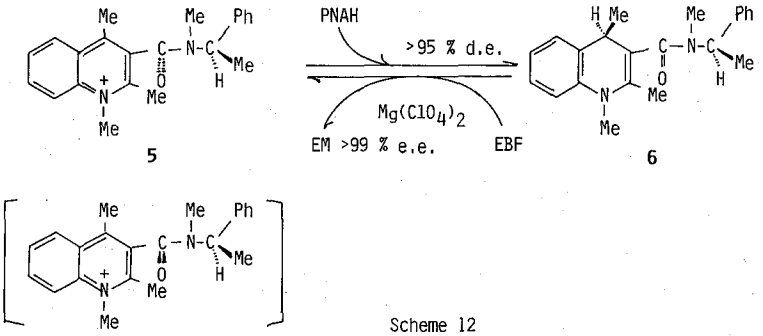
An asymmetric induction due to specific freezing of one of the two faces of 1, 4-dihydropyridine is attained in the system using bis-nicotinamide derivatives, bis(NAH),



Scheme 11

that contain two 1, 4-dihydropyridine moieties within each molecule.[87,88] The idea was based on the expectation that a specific chiral field due to C_2 symmetry in bis(NAH) would be formed by an interaction between the two 1, 4-dihydronicotinamide moieties by the aid of Mg (II). Xylene moieties or polymethylene chains were employed as bridges and L-proline attached to the 3-position of the 1, 4-dihydropyridine were uitlized as a chiral source. The optical yield of the reduction depended on the difference in the structure or the length of the bridge, which indicates the importance of an interaction between the two 1, 4-dihydronicotinamide moieties. In the reduction by bis(NAH) with *p*-xylene and $-(CH_2)_6-$ as bridges, EBF was reduced in 98.1% e.e.[87] and 95.6% e.e.,[88] respectively.

Another successful results in the field of asymmetric reduction were acomplished by the use of 1, 4-dihydropyridine derivatives containing chiral macrocyclic moieties such as **3**.[89,90] By the reduction with these 1, 4-dihydropyridines, good to excellent optical yields were obtained. EBF was reduced in 90% e.e. by **3** in the presence of Mg (II). The optical yields obtained from the reductions with non-cyclic derivatives (**4**) were low.[90] These results suggest that the cyclic structure which affords a chiral



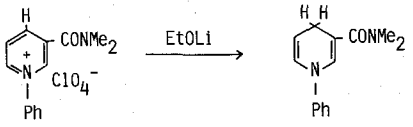
Scheme 12

environment by an interaction with Mg (II) is important for the excellent stereoselectivity.

Recent result from our laboratory revealed that a stereospecific shuttle between **5** and **6** is possible.[91] This interconversion involves self-immolative transfer of the axial chirality at the carbonyl group of the oxidized form into the central chirality at the 4-position of the corresponding reduced form and *vice versa*. The asymmetric induction with the help of a "chirality sink" is a brand-new type system.

REDUCTION OF PYRIDINIUM SALT

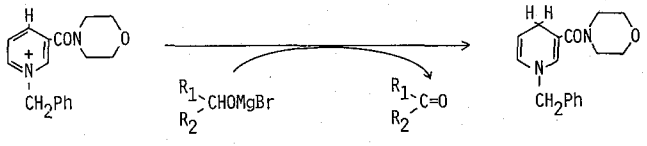
As a simulation of NAD(P)$^+$–NAD(P)H biological redox systems, many investigations have been concentrated on the reduction by 1, 4-dihydropyridine derivatives. On the other hand, the reverse reaction, reduction of a pyridinium salt to a 1, 4-dihydropyridine, has not been investigated so extensively.[92,93] Sodium dithionite is frequently utilized as a reductant which affords the 1, 4-dihydro-form quantitatively. By the use of other reductant such as sodium borohydride[94] as well as electrochemical reduction[95–101] produce not only the 1, 4-dihydro-derivative which is effective as a coenzyme model but also the 1, 6-dihydro-isomer and other reduced products. Since in biological reduction of NAD(P)$^+$, organic substrates such as alcohol and amine act as reducing agents to afford NAD(P)H, the corresponding biomimetic reactions are also desired to be studied.



7 **8**

Scheme 13

Shirra *et al.* reported the reduction of pyridinium salts by substituted benzyloxides.[102,103] They detected the production of benzaldehyde derivatives but no attention was paid for the formation of the 1, 4-dihydropyridine. The reported kinetic isotope effects obviously indicate that the reaction does not involve the "direct hydride transfer".



9 **10**

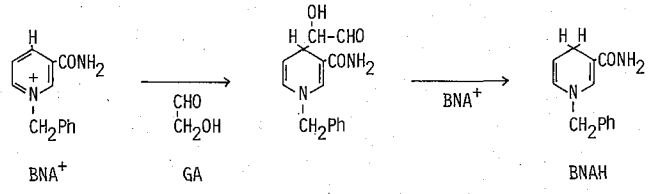
Scheme 14

In the reduction of **7**, Ohnishi *et al.* found that the corresponding 1, 4-dihydropyridine (**8**) was produced.[104]

Shinkai *et al.* reported the reduction of **9** to **10** by alkoxymagnesium bromide derived from the alcohol and Grignard reagent.[105] Although diphenylmethanol and 1-phenylethanol were oxidized to the corresponding carbonyl compounds in good yields, benzyl alcohol, 1-octanol, and cyclohexanol afforded the corresponding oxidized products only in poor yields.

In the biological reduction of NAD^+, it is well known that the hydrogen on the 1-position of alcohol directly transfers onto the 4-position of NAD^+. It should be clarified whether the mimetic reductions proceed in the same manner as the enzymatic reactions. Ohnishi *et al.* found in their system by the use of deuterium-labelled alkoxides that the deuterium was not incorporated into the 4-position of the 1, 4-dihydropyridine produced.[104] This indicates that the route in the model system is different from that in the biological system.

Another interesting enzyme concerning the reduction of NAD^+ is glyceraldehyde 3-phosphate dehydrogenase (GAPDH, EC 1.2.1.12), which catalyzes the reduction of NAD^+ to NADH coupled with the oxidation of glyceraldehyde 3-phosphate to 1, 3-diphosphoglycerate.[106] It was found that a similar reaction, reduction of pyridinium cation, took place in a mimetic system.[107,108] In the reaction with 1-benzyl-3-carbamoylpyridinium cation (BNA^+) and α-hydroxycarbonyl compounds such as glyceraldehyde and glycolaldehyde (GA) the production of BNAH was observed. However, it was concluded that the mechanism of the mimetic reaction is different from that suggested for the GAPDH system, in which the formyl hydrogen of the substrate directly transfers onto the 4-position of NAD^+ *via* a hemithioacetal intermediate.[106] In the mimetic system, the hydrogen at the 4-position of the adduct between BNA^+ and GA, which has a 1, 4-dihydropyridine structure, transfers onto the 4-position of another molecule of BNA^+ to afford BNAH.[109]



Scheme 15

It is known that an amine acts as a reductant in the biological reduction of NAD^+. For example, NAD^+ is reduced to NADH by glutamate on glutamate dehydrogenases (EC 1.4.1.2–4) with simultaneous production of 2-iminoglutarate.[110] Ohnishi reported that a similar reaction proceeds in a model system.[111] However, the mechanism was again found to be different from that operating in the enzymatic system.[112]

Formate is effective for the non-enzymatic reduction of a pyridinium salt[94] as observed in the biological system with a formate dehydrogenase (EC 1.2.1.2.). It was ascertained that the hydrogen in the formate "directly" transfers to the 4-position of the pyridinium salt.[112,113] This is the only one mimetic system which has been proved to involve a direct hydrogen transfer process.

CONCLUDING REMARKS

Mimesis for biological NAD(P)$^+$–NAD(P)H redox systems have been extensively investigated in last three decades and many successful results have been obtained. Simulation of some of the excellent features in enzymatic systems has also been achieved in model systems as mentioned in this review. However, in both reactivity and specificity, the mimetic reactions are still much inferior to the biological reactions where the dehydrogenase makes a great contribution. Within a molecule of the enzyme, the catalytic groups locate appropriately at the active site where the substrate is bound with a large affinity. These properties in an enzyme are desirable to be introduced into a model system for the construction of an artificial enzyme. When the catalytic groups are arranged properly toward the substrate by a proper molecular design, such an excellent reactions as observed in the enzymatic system might be realized without the use of a macromolecule. In this connection, further development is expected.

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