Stereoselection Controlled by Electronic Effect of a Carbonyl Group in Oxidation of NAD(P)H Model

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Newly synthesized NAD(P)H model compound (1,4,6,7-tetrahydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin; 11Me-MMPAH) has an axial chirality with respect to carbonyl dipole in the side chain amide group. The orientation of carbonyl dipole is fixed with sticking out of the dihydropyridine ring. In oxidation of this compound with a series of *p*-benzoquinone derivatives, we investigated the relationship between the orientation of carbonyl dipole in nicotinamide and the stereochemistry of the reactions of NAD(P)H

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The pyridine nucleotide coenzymes NADH and NADPH are ubiquitous in all living systems. They are required for the redox reactions of more than 370 different kinds of enzymes. Although pyridinium/dihydropyridine moieties in $NAD(P)^+$ / NAD(P)H coenzymes are achiral, *re*- and *si*-faces of the molecules are recognized by a substrate when they are set in a pocket of an enzyme. Formally, a hydride ion is transferred stereospecifically and reversibly between the 4-position of $NAD(P)^+$ or NAD(P)H and substrate. From the viewpoint of chemical evolution of an enzyme, the difference in stereochemistry as well as the mechanism of the redox reactions involved is an interesting subject.

It is considered that the stereochemistry of the reactions of NAD(P)H is influenced by the orientation of the carbonyl dipole in the side-chain amide group. To clarify this relationship, we designed and synthesized new NAD(P)H model compound (11Me-MMPAH) [1]. In this compound, the methyl substituent at 11-position in an *o*-phenylene group prevents a flipping of the *o*-phenylene moiety, and, therefore, a flipping of the carbonyl group at room temperature. At the same time, in the oxidized form (11Me-$MMPA^+I^-$), the axial chirality with respect to the orientation of the carbonyl dipole in 11Me-MMPAH is sophisticatedly preserved. This model fixing the orientation of carbonyl dipole with sticking out of the dihydropyridine ring, we can readily investigate the relationship between the orientation of carbonyl dipole in nicotinamide and the stereochemistry of the reactions of 11Me-MMPAH.

In order to investigate the selectivity of the faces in which a (net) hydride is transferred, oxidations of 11Me-MMPAH, which are predominantly

BIOORGANIC CHEMISTRY — Bioorganic Reaction Theory —

Scope of research

Biochemical reactions are studied from the viewpoint for physical organic chemistry. Specifically, the reaction mechanism and stereochemistry of NAD-dependent oxidoreductases are explored. Stereospecific redox transformations mediated by certain biocatalysts such as microbes, enzymes, cultured tissues are also studied. The results will be applied to develop new organic reactions.

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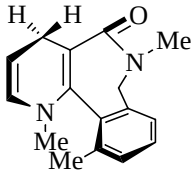
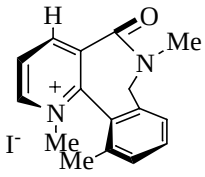
deuterated the *syn*- and *anti*-hydrogen with respect to carbonyl dipole respectively, with a series of *p*-benzoquinone derivatives in the absence and presence of Mg^{2+} were studied [2,3]. Without Mg^{2+}, relative reactivity ratio for *syn*- and *anti*-hydrogens with respect to carbonyl dipole in 11Me-MMPAH indicated uniformly high *anti*-selectivity in oxidation with all quinones; *anti*-hydrogen is 3-32 times more reactive than *syn*-hydrogen. On the other hand, a dramatic change in the *syn*/*anti* selectivity was observed when Mg^{2+} was present in the system.



11Me-MMPAH



11Me-MMPA$^{+}I^{-}$

In addition, as the reduction potential of *p*-benzoquinone derivative decreases, the reactivity of the *syn*-hydrogen becomes larger. This tendency is emphasized in the reaction with a weakly oxidizing agent such as 2,6-dimethyl-*p*-benzoquinone; *syn*-hydrogen is 5 times more reactive than *anti*-hydrogen.

These observed selectivity in the absence and presence of Mg^{2+} can be explained by the contribution of initial electron transfer process prior to the proton transfer. In the *syn*-hydrogen transfer reaction, the carbonyl oxygen points toward the pairing *p*-benzoquinone derivative, whereas the pairing *p*-benzoquinone derivative sits itself in the opposite side of the carbonyl oxygen in the *anti*-hydrogen-transfer reaction. In the absence of Mg^{2+}, the transfer of the *anti*-hydrogen takes place easier than that of the *syn*-hydrogen because the *anti*-face is electronically more favored than the other; electrostatic repulsion of the *syn*-side between the carbonyl dipole of radical cation of 11Me-MMPAH and the radical anion and/or carbonyl dipole of quinone is much larger than that of *anti*-side (Fig. 1(a)). The change in the reactivity of the *syn*/*anti*-hydrogen strongly suggests an important contribution of Mg^{2+} in the pre-association complex for determining the stereochemistry of the reaction. There is no doubt that Mg^{2+} play the role of a Lewis acid catalyst to promote the reaction, because a weakly oxidizing quinone such as 2,6-dimethyl-*p*-benzoquinone can not oxidize 11Me-MMPAH without Mg^{2+}. The reactivity of relative weakly oxidizing agent is not sufficient to abstract an electron from 11Me-MMPAH in the model-quinone binary complex, or the reactant and quinone not to bring them into closer face-to-face contact in the *syn*-face without catalytic assistance of Mg^{2+}. Thus, in the oxidation with relative weakly oxidizing agent, catalytic contribution of Mg^{2+} becomes large to undergo the reaction and, therefore, the *syn*-hydrogen is inevitably involves a model-Mg^{2+}-quinone ternary complex as a pre-association intermediate (Fig. 1(b)).

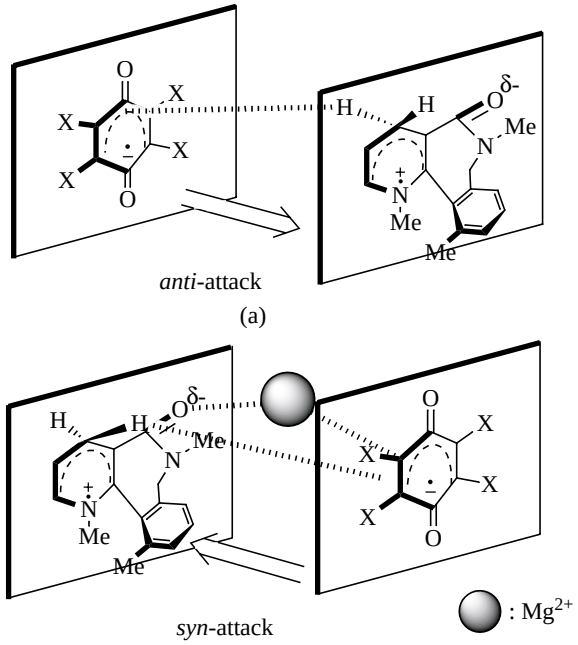


Figure 1. Pre-association complex between NAD(P)H model and quinone without Mg^{2+} (a) and with Mg^{2+} (b) from initial electron transfer.

We showed that the orientation of carbonyl dipole in model compound as well as the presence or absence of Mg^{2+} controls the stereochemistry of oxidation of an NAD(P)H model compound with *p*-benzoquinone derivative. Such a strong control of the stereochemistry by an electronic(nonsteric) effect may be a mimic of stereochemical controls in biological reactions catalyzed by archaic enzymes, where structural sophistication was insufficient to exert a perfect control of the stereochemistry.

References

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