NAD(P)$^+$−NAD(P)H Models. 90. Stereoselection Controlled by Electronic Effect of a Carbonyl Group in Oxidation of NAD(P)H Analog

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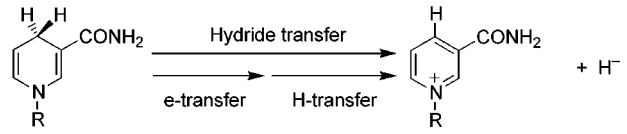
4-Monodeuterated NAD(P)H model compounds (1,4,6,7-tetrahydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin; 11Me-MMPAH) have been oxidized with a series of *p*-benzoquinone and its derivatives in the presence of Mg^{2+}. The models have an axial chirality with respect to the orientation of carbonyl dipole, the dihedral angle of which is larger than 55° out of the plane of dihydropyridine ring. Without Mg^{2+}, the anti (with respect to the carbonyl dipole)-hydrogen is 3 to 32 times more reactive than the corresponding *syn*-hydrogen, whereas, when Mg^{2+} is present in the system, the selectivity is shifted toward the *syn*-preferency. Mg^{2+} plays the role of a Lewis acid catalyst to control the stereochemistry at the same time as it catalyzes the reaction.

Introduction

A net hydride transfers between pyridine nucleotide coenzyme, NAD(P)(H),[1] and a redox substrate, and the reaction is catalyzed by many enzymes. A large number of studies using model compounds of the coenzyme have revealed the reaction mechanism including an electron-transfer (e-transfer).[2−9] The e-transfer occurs prior to the transferring of a hydrogen atom or a proton (H-transfer) in some cases, and they almost occurs simultaneously in other cases, observed as a one-step hydride-transfer, especially in enzymatic systems (Scheme 1).[10]

Stereochemistry of the redox reactions is another interest. Either on the *re*- or *si*-face of NAD(P)(H) occurs the net hydride-transfer depending on the enzyme.

Scheme 1



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

R=Adenine dinucleotide

However, the stereochemistry originates assumably from the reactivity of a redox substrate.[11]

Donkersloot et al. have reported the role of the $CONH_2$ group in nicotinamide in a hydride-transfer based on MINDO/3 and STO-3G calculations.[12] They concluded that the conformation in which the carbonyl dipole in nicotinamide points toward the substrate (the reacting C4-H and C═O bonds in *syn*-configuration) corresponds to the reaction of low enthalpy of activation. Alternatively, the conformation in which the dipole away from the substrate (C4-H and C═O bonds in *anti*-configuration) is associated with high enthalpy of activation on the calculations.

A few reports have discussed the effect of conformation of the amide group on stereoselectivity in the oxidation of NAD(P)H models.[13−16] Bourguignone and co-workers have proposed that the out-of-plane orientation of the

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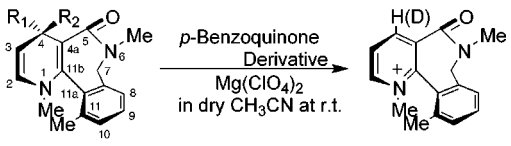
Scheme 2



1 : R_1=H(80%), R_2=D(80%)
2 : R_1=D(80%), R_2=H(80%)

amide carbonyl dipole with respect to the dihydropyridine ring is responsible for high stereoselectivity in the reduction of α-keto esters with NAD(P)H models.[13] We have reported that the stereochemistry of redox reactions of NAD(P)(H) models having interconversion of a central and an axial chirality depends on the reactivity of a redox substrate and on the conformation of the substituted amide group.[14,15] Several redox reactions of the model compounds have been studied extensively, and a lot of significant knowledge have been obtained so far, which, however, are not enough to apply to the redox reactions of NAD(P)(H) catalyzed by enzymes because the model systems have been studied are limited in number.

Recently, we designed and synthesized 6,7-dihydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin-1-ium (11Me-MMPA$^+$) as an NAD(P)$^+$ model.[17] It has a steric hindrance between a methyl substituent in an *o*-phenylene group and a pyridinium ring, which prevents the *o*-phenylene group from flipping and, therefore, makes the conformation of a carbonyl group stable at room temperature. Crystallographic study of 11Me-MMPA$^+$ revealed that the carbonyl group extends from the pyridinium plane at an angle of 55°. That is, the compound has two axial chiralities with respect to the C4a−C5 and C11a−C11b bonds, but has only a pair of enantiomers because one chirality is accompanied by the other. Furthermore, the axial chiralities in 11Me-MMPA$^+$ are sophisticatedly preserved in its reduced form (11Me-MMPAH). Thus, we can investigate the relationship between the orientation of a carbonyl dipole in nicotinamide and the stereochemistry of the reaction by employing 11Me-MMPA(H) as a model of NAD(P)(H).

In a previous paper, we demonstrated that the oxidation of 11Me-MMPAH with a series of *p*-benzoquinone derivatives proceeds preferentially in the *anti*-face with respect to the carbonyl dipole (Scheme 2).[18] That the diastereoselectivity of the reactions shifts to *syn*-preference in the presence of Mg^{2+} we wish to report here. Moreover, the reaction mechanism is discussed in accordance with the stereoselectivities, the isotope effects, and the kinetic parameters. A preliminary study has been reported previously.[19]

Table 1. Stereoselectivity in the Oxidation of 11Me-MMPAH with *p*-Benzoquinone Derivatives in CH_3CN in the Presence of Mg^{2+} [a]

		D:H content in 11Me-MMPA$^+$ (*Y*)[b]	
p-benzoquinone derivative	E^o, V[c]	from **1**	from **2**
p-chloranil	0.01	57:43 (1.3)	41:59 (0.69)
p-bromanil	0.00	56:44 (1.3)	37:63 (0.59)
trichloro-*p*-benzoquinone	−0.09	59:41 (1.4)	51:49 (1.0)
2,6-dichloro-*p*-benzoquinone	−0.18	62:38 (1.6)	53:47 (1.1)
2,5-dichloro-*p*-benzoquinone	−0.18	62:38 (1.6)	60:40 (1.5)
chloro-*p*-benzoquinone	−0.34	60:40 (1.5)	59:41 (1.4)
p-benzoquinone	−0.50	56:44 (1.3)	67:33 (2.0)
methyl-*p*-benzoquinone	−0.58	45:55 (0.82)	72:28 (2.6)
α-naphthoquinone	−0.66	47:53 (0.89)	76:24 (3.2)
2,6-dimethyl-*p*-benzoquinone	−0.67	40:60 (0.67)	77:23 (3.3)

[a] $Mg(ClO_4)_2$ was used as the source of Mg^{2+}. [**1**] or [**2**] = 6.3×10^{-3} M, [quinone] = 1.3×10^{-2} M, [$Mg(ClO_4)_2$] = 6.3×10^{-2} M. In the dark under Ar at room temperature. [b] Measured by ^{1}H NMR spectroscopy. Estimated errors are ±3 in D:H content. Y = D content/H content ratio. [c] Reduction potential of quinone (versus SCE); ref 21.

Results

Oxidation of 11Me-MMPAH with *p*-Benzoquinone Derivatives. 11Me-MMPAH-4-*d*, **1**, and **2**, which are deuterated predominantly at the 4-*syn*- and 4-*anti*-positions with respect to the carbonyl dipole, respectively, were prepared according to the procedure reported previously.[18,20] That is, we obtained a mixture, **1**, composed of 80% 11Me-MMPAH-4-*syn*-*d* (4-*syn*-deuterated 11Me-MMPAH) and 20% 11Me-MMPAH-4-*anti*-*d* (4-*anti*-deuterated 11Me-MMPAH) and another mixture, **2**, composed of 80% 11Me-MMPAH-4-*anti*-*d* and 20% 11Me-MMPAH-4-*syn*-*d*. Racemic mixtures of **1** and **2** were used for the redox reactions below.

In the absence[18] and presence[19] of Mg^{2+}, **1** and **2** were oxidized with a series of *p*-benzoquinone derivatives, and the ratio of hydrogen and deuterium at C4-position in the product 11Me-MMPA$^+$ was measured by ^{1}H NMR spectroscopy. It was confirmed that the ratio is independent of reaction time, certifying that under the reaction conditions no isotopic scrambling occurs between the reduced and oxidized forms of the model.[21] An excess of Mg^{2+} did not affect the isotopic ratios in the product even if it is added in more than a 6-fold amount of 11Me-MMPAH or a quinone. The reaction with all quinones employed proceeded to completion. Isotopic ratios in the products, that is, apparent product isotope effect, from the reaction with and without Mg^{2+} are summarized in Tables 1 and 2, respectively.

Very strongly oxidizing agent such as 7,7,8,8-tetracyanoquinodimethane (TCNQ) did not afford the desired product, and unidentified materials were isolated when Mg^{2+} was present and absent. Quinones weaker than chloro-*p*-benzoquinone, e.g., *p*-benzoquinone, could not oxidize 11Me-MMPAH in the absence of Mg^{2+}. On the other hand, the reaction proceeded smoothly with these weakly oxidizing quinones when Mg^{2+} was present in the reaction system; Mg^{2+} catalyzes the oxidation.

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Table 2. Stereoselectivity in the Oxidation of 11Me-MMPAH with *p*-Benzoquinone Derivatives in CH_3CN in the Absence of Mg^{2+} [a]

		D:H content in 11Me-MMPA$^+$ (*Y*)[b]	
p-benzoquinone derivatives	E^o, V[c]	from **1**	from **2**
p-chloranil	0.01	81:19 (4.3)	25:75 (0.33)
p-bromanil	0.00	82:18 (4.6)	27:73 (0.37)
trichloro-*p*-benzoquinone	−0.09	86:14 (6.1)	38:62 (0.61)
2,6-dichloro-*p*-benzoquinone	−0.18	86:14 (6.1)	47:53 (0.89)
2,5-dichloro-*p*-benzoquinone	−0.18	86:14 (6.1)	48:52 (0.92)
chloro-*p*-benzoquinone	−0.34	84:16 (5.3)	57:43 (1.3)

[a] [**1**] or [**2**] = 6.3×10^{-3} M, [quinone] = 1.3×10^{-2} M. In the dark under Ar at room temperature. ref 20. [b] Measured by ^{1}H NMR spectroscopy. Estimated errors in the contents of D and H are ±1. Y=D content/H content ratio. [c] Reduction potential of quinone (versus SCE); ref 21.

In the presence of Mg^{2+}, the apparent product isotope effect, *Y* (D/H content ratio at 4-position in product 11Me-MMPA$^+$, Table 1), for oxidation of **1** is considerably smaller than that in the absence of Mg^{2+}. That is, the D in **1** that is 80% content in the 4-*syn*-position is more transferred in the presence of Mg^{2+} than in its absence. Similarly Mg^{2+} makes the 4-*syn*-hydrogen more reactive than 4-*anti*-hydrogen in **2**. This is although the *syn*-face is sterically more crowded, if any, than the other.

Calculation of Intrinsic Product Isotope Effect and *Syn*/*Anti* Selectivity. It is apparent that the reactivities of the *syn*- and *anti*-hydrogens are different in 11Me-MMPAH, and their isotopic purities are not 100%. Therefore, the D/H content in the product, *Y*, does not correspond to the product isotope effect directly.

In the previous paper of the series, we derived an equation (eq 1) to correlate apparent product isotope effect, *Y*, to intrinsic product isotope effect, *F*.[18]

$$Y = F[(1-\beta)(1-\alpha)+\beta\alpha]/[\beta(1-\alpha)+(1-\beta)\alpha] \quad (1)$$

The parameter α, *anti*-selectivity, is the proportion of H or D reacted in the 4-*anti*-position and is assumed to be the same for H and D. β is the fraction of D in the 4-*syn*-position of **1** or **2**, which is equal to the fraction of H in the 4-*anti*-position; $\beta = 0.80$ for **1** and 0.20 for **2**. The terms $[(1-\beta)(1-\alpha)+\beta\alpha]$ and $[\beta(1-\alpha)+(1-\beta)\alpha]$ are the relative amounts of H and D reacted, respectively, described in the previous paper.[18] Because these terms do not include the difference between the reactivities of H and D, *F* is introduced to correct the difference.

F stands for a product isotope effect that might be afforded if 4-*syn*- and 4-*anti*-hydrogens had the same reactivity ($\alpha = 0.5$). Furthermore, it has been pointed out that *F* has another physical meaning; it is an isotope effect associated with the equilibrium process to form an electron-transfer complex that exists prior to the rate-determining transition state (see Discussion).[18,22]

Because *Y* and β for **1** and **2** are experimentally observed with help of ^{1}H NMR, both *F* and α can be calculated by solving quadratic simultaneous equations. The results are summarized in Table 3.

Table 3. Intrinsic Product Isotope Effect *F* and *Anti*-Selectivity α In Oxidation of 11Me-MMPAH with *p*-Benzoquinone Derivatives in CH_3CN at Room Temperature

	without Mg^{2+} [a]		with Mg^{2+} [b]	
p-benzoquinone derivative	*F*	α	*F*	α
p-chloranil	1.2	0.97	1.0	0.63
p-bromanil	1.3	0.97	0.9	0.67
trichloro-*p*-benzoquinone	1.9	0.93	1.2	0.57
2,6-dichloro-*p*-benzoquinone	2.3	0.87	1.4	0.58
2,5-dichloro-*p*-benzoquinone	2.4	0.87	1.5	0.51
chloro-*p*-benzoquinone	2.6	0.78	1.5	0.48
p-benzoquinone	nr	nr	1.6	0.41
methyl-*p*-benzoquinone	nr	nr	1.5	0.27
α-naphthoquinone	nr	nr	1.7	0.24
2,6-dimethyl-*p*-benzoquinone	nr	nr	1.5	0.18

[a] Estimated errors of *F* and α are ±0.1 and ±0.02, respectively. nr = no reaction (Starting material was recovered.); ref 20. [b] Estimated errors of *F* and α are ±0.2 and ±0.04, respectively.

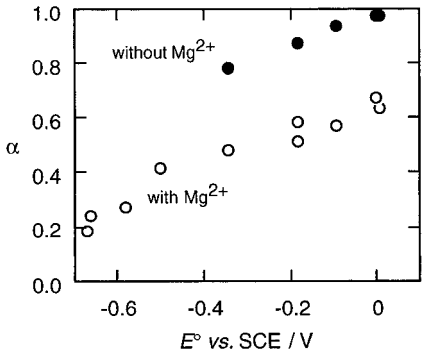


Figure 1. Plots of *anti*-selectivity α in the presence of Mg^{2+} (open circles) and in the absence of Mg^{2+} (filled circles) versus reduction potentials (vs SCE) of *p*-benzoquinone derivatives.

Figure 1 defines the results. In the absence of Mg^{2+}, the less reactive the quinone used is, the larger *F* becomes. This similar tendency is observed in the absence of Mg^{2+}, but it seems that *F* stays at a constant small value except for those from strong oxidants such as *p*-chloranil and trichloro-*p*-benzoquinone. Therefore, the difference between the *F* values in the presence and absence of Mg^{2+} seems to be larger as the oxidant is less reactive. It should be noted that a strong oxidant could react with 11Me-MMPAH without catalytic assistance by Mg^{2+} or, if any, with a little catalytic assistance. Although such complex interactions between Mg^{2+} and reagents make the analysis of the reaction less reliable, it is safe to believe that *F* appears to be a constant, in general, within a reasonable experimental error, under the catalysis of Mg^{2+}.

Anti-selectivity, α, is always smaller in the presence of Mg^{2+} than in its absence, regardless of the reactivity of the quinone. In other words, Mg^{2+} shifts the stereoselectivity of the reaction toward the *syn*-preference from the *anti*-preference in its absence. More interestingly, the more reactive the quinone used is, the larger α becomes both in the absence and presence of Mg^{2+}. Figure 2 exhibits the results clearly. High *anti*-selectivity was observed in the absence of Mg^{2+}; the values of α are 0.78−0.97. The *anti*-hydrogen is from 3 to 32 times more reactive than the *syn*-hydrogen. Mg^{2+} increases the reactivity of the *syn*-hydrogen up to the same level with that of the *anti*-hydrogen in the reaction with strong oxidants such as *p*-chloranil or *p*-bromanil. The smallest value of α is obtained in the reaction with 2,6-dimethyl-

(22) Separated rate- and stereodetermining steps are proposed of an electron-transfer mechanism of the Wittig reaction: Yamataka, H.; Nagareda, K.; Takatsuka, T.; Ando, K.; Hanafusa, T.; Nagase, S. *J. Am. Chem. Soc.* **1993**, *115*, 8570.

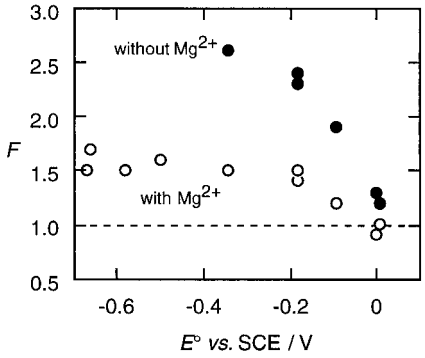


Figure 2. Plots of intrinsic product isotope effect F in the presence of Mg^{2+} (open circles) and in the absence of Mg^{2+} (filled circles) versus reduction potentials (vs SCE) of *p*-benzoquinone derivatives.

Table 4. Kinetic Parameters for the Reactions of a Strongly Oxidizing and a Weakly Oxidizing *p*-Benzoquinones with 11Me-MMPAH without Mg^{2+} at 298 K[a]

second order rate constant[b]	temp, K	*p*-chloranil	2,6-dichloro-*p*-benzoquinone
k_2 ($M^{-1}\cdot s^{-1}$)	278	3,47	70.5
	288	4020	99.2
	298	4460	132
	308	5340	233
	318	6120	298
kinetic parameter[c]			
E_a ($kJ\cdot mol^{-1}$)		10.45	27.17
$\Delta G^{\ddagger}$ ($kJ\cdot mol^{-1}$)		51.41	59.77
$\Delta S^{\ddagger}$ ($J\cdot mol^{-1}\cdot deg^{-1}$)		−148.0	−137.1
$\Delta H^{\ddagger}$ ($kJ\cdot mol^{-1}$)		7.86	19.86
$-T\Delta S^{\ddagger}$ ($kJ\cdot mol^{-1}$)		44.31	40.96
stereoselectivity (α)[d]		0.97	0.87

[a] [11Me-MMPAH] = (4.2−5.3) × 10^{-2} mM, [quinone] = 0.64−2.0 mM in CH_3CN (under pesude-first-order conditions). [b] Estimated errors are ±5%. [c] Estimated errors are ±10%. [d] Estimated errors are ±0.01.

p-benzoquinone, which is the least reactive quinone used. The *syn*-hydrogen is 5 times more reactive than the *anti*-hydrogen.

Also as shown above, it is clear that Mg^{2+} catalyzes the redox reaction, especially with a less reactive quinone, which does not oxidize 11Me-MMPAH without Mg^{2+}. When such a quinone is used, the 4-*syn*-hydrogen is forced to undergo the reaction more readily than the 4-*anti*-hydrogen. Therefore, it is considered that Mg^{2+} mediates the interaction between 11Me-MMPAH and the oxidant preferentially at the *syn*-side. The reactions with very weak oxidants such as methyl-*p*-benzoquinone, α-naphthoquinone, and 2,6-dimethyl-*p*-benzoquinone exert the *syn*-selectivity. The similar stereochemistry has been reported for the reactions of other NAD(P)H models with *p*-benzoquinone derivatives.[14,15]

Kinetic parameters for the reactions with strong and medium oxidants represented by *p*-chloranil and 2,6-dichloro-*p*-benzoquinone, respectively, in the absence of Mg^{2+} are listed in Table 4. The results reveal that almost all of the free energy of activation is controlled by entropy term; the enthalpy term contributes only slightly to the free energy of activation.[18] The enthalpy term has a larger contribution to the free energy for the reaction with 2,6-dichloro-*p*-benzoquinone than for that with *p*-chloranil. Two quinones employed here prefer the less-hindered, hence entropically favorable, *anti*-face of 11Me-MMPAH to react, as shown above.

Since kinetic behavior in the presence of Mg^{2+} is complex, we have not yet succeeded in elucidating kinetic isotope effects with convincing accuracy in the presence of Mg^{2+}. However, the following discussion and much evidence reported previously[2−4,6,14] lead us to conclude that the reaction in the presence of Mg^{2+} proceeds via the same multistep mechanism as in the absence of Mg^{2+}.

Discussion

Intrinsic Product Isotope Effects. The evidence for a multistep mechanism often shows a discrepancy between kinetic and product isotope effects.[3,4,7] This discrepancy means that the rate-determining step is apart from the product-determining step and is observed in the quinone oxidations of 11Me-MMPAH in the absence of Mg^{2+}.[18] Values of 3.1−4.2 for the kinetic primary isotope effect are large, so that the transition state of the reaction involves largely a transfer of a hydrogen nucleus. The corresponding product isotope effects, F, are smaller than the kinetic isotope effects (Table 3), and the discrepancy between the two isotope effects has been ascribed to a multistep mechanism in that the product-determining e-transfer precedes the rate-determining H-transfer (Scheme 3). Moreover, the first e-transfer is associated with a weakening of the reacting C4-H bond, and the isotope effect on this movement is the origin of the F factor: the values of F exceed unity. In this sense, the e-transfer is not of the Franck−Condon type but is associated with the movement of a hydrogen nucleus.[18] The F factor, therefore, means an isotope effect on the equilibrium constant, K^H/K^D, for the preequilibrium state ascribable to an e-transfer complex prior to H-transfer (Scheme 4).

The same conclusions have been obtained for quinone oxidations of 1-benzyl-1,4-dihydronicotinamide (BNAH);[4] this is a simple NAD(P)H model compound. The values of F are 2.3−2.6 for the oxidations by the same quinones as studied herein in the absence of Mg^{2+} and 2.2−2.4 for those in the presence of Mg^{2+}. Compared with those values, the smaller values of F are observed for 11Me-MMPAH in quinone oxidations with Mg^{2+} and in oxidations by reactive quinones without Mg^{2+}. Further, Mg^{2+} makes F small, even constant, in the reactions of 11Me-MMPAH. This smaller F is considered that a hydrogen nucleous moves in a shorter distance and the movement is less important for an e-transfer. Thus, Mg^{2+} effectively catalyzes the e-transfer[23] in the reaction of 11Me-MMPAH and therefore facilitates the formation of the e-transfer complex. Such catalysis, however, appears not to affect the F from the reactions of BNAH although increasing the rate constants.[5] Another proposal is that, simultaneously, an e-transfer complex between 11Me-MMPAH and a strong oxidant is formed at its open *anti*-face more tightly, requiring little movement of a hydrogen nucleus as a result of its rigid structure than that between BNAH and the oxidant. Consequently, it is considered that a hydride-transfer occurs in multistep in the quinone oxidation of 11Me-MMPAH in the presence of Mg^{2+} as well as its absence although the kinetics concerning Mg^{2+} are complex and have been not shown yet.

(23) Catalysis of electron-transfer by Mg^{2+} is observed in several reactions: (a) Fukuzumi, S.; Okamoto, T.; Otera. J. *J. Am. Chem. Soc.* **1994**, *116*, 5503. (b) Fukuzumi, S.; Okamoto, T. J. *J. Chem. Soc. Chem. Commun.* **1994**, 521. (c) Fukuzumi, S.; Okamoto, T. J. *J. Am. Chem. Soc.* **1993**, *115*, 11600.

Scheme 3

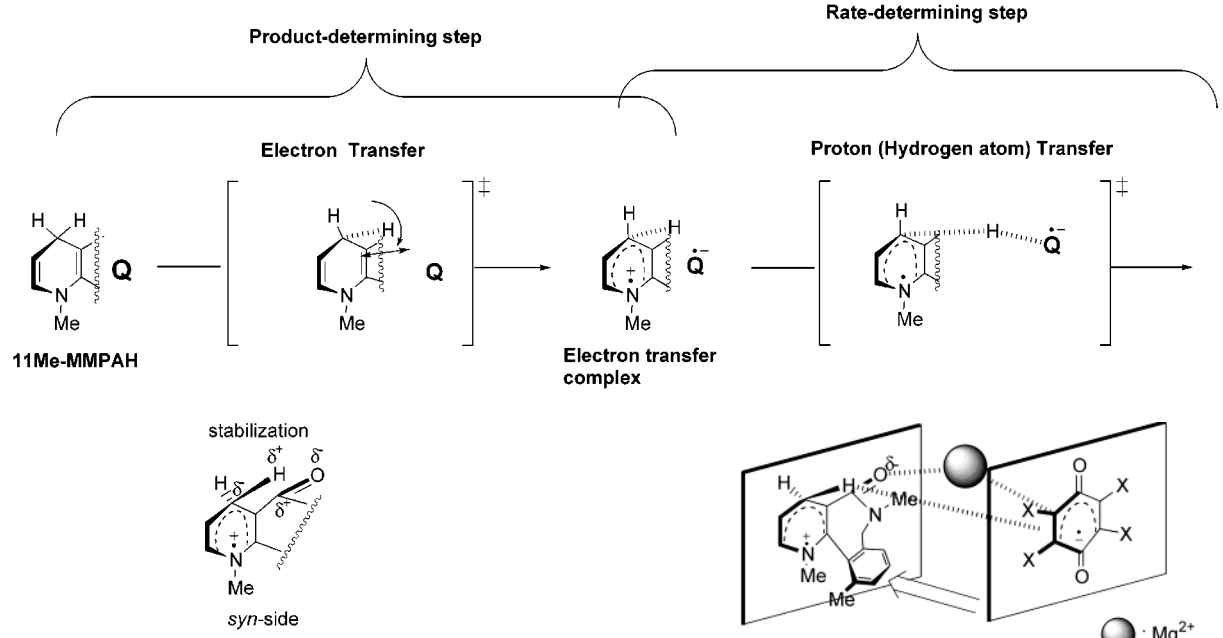
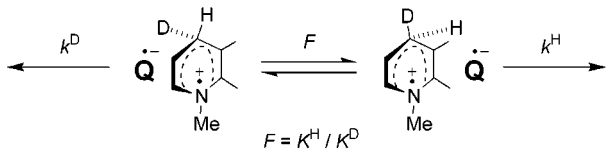


Figure 3. Stabilization of electron-transfer complex by dipole−dipole interaction.

Scheme 4



Stereochemistry. When a weak oxidant is employed for the reaction in the absence of Mg^{2+}, the e-transfer requires more catalytic assistance to move a hydrogen nucleus, and the isotope effect associated with this process, *F*, appears large compared to that from the reaction with a strong oxidant. Simultaneously, the movement of 4-*syn*-hydrogen nucleus becomes more advantageous than that of its counterpart because the partial dissociation of the proton at the *syn*-face results in the formation of a dipole, $C^{\delta-}-H^{\delta+}$; this is thermally stabilized by another dipole in the molecule, $C^{\delta+}=O^{\delta-}$, in the same face (Figure 3). Such stabilization of the system by dipole−dipole interactions, or enthalpic stabilization, has been shown kinetically as above. It should be emphasized that the small part of the free energy of activation is the factor to discriminate *syn*- and *anti*-selectivity of the reaction, supported by studies of the reaction of NAD(P)H models having interconversion of a central and an axial chirality: the stereochemistry depends on the reactivity of an oxidant, and the *syn*- and *anti*-hydrogens of model compounds transfer preferentially to the less and more reactive oxidants, respectively.[14,15]

The reaction with a strong oxidant is not associated with appreciable formation of the $C^{\delta-}-H^{\delta+}$ dipole because the oxidant prefers the *anti*-hydrogen of 11Me-MMPAH. Moreover, the stabilization by dipole−dipole interactions is not so important as that in the reaction with a weak oxidant.

Being sandwiched by a NAD(P)H model and a substrate,[18,24] Mg^{2+} would coordinate negative poles of both molecules, apparently carbonyl oxygens in the redox

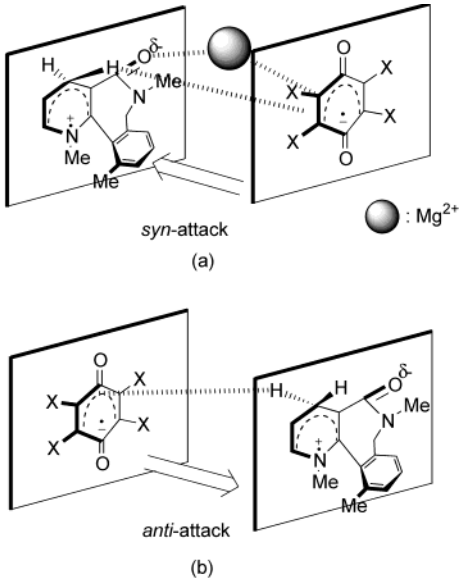


Figure 4. Preassociation complex with Mg^{2+} (a) and without Mg^{2+} (b) from initial electron transfer.

system studied herein. Therefore, a oxidant is forced to attack 11Me-MMPAH in the *syn*-face by Mg^{2+}, even if this is sterically more crowded than the other, resulting in a high *syn*-selectivity of the reaction depicted in Figure 4(a). In the absence of Mg^{2+}, on the other hand, the sterically less crowded *anti*-face is preferred entropically (Figure 4b).

Mechanism. All experimental results we obtained and listed in Table 3 coincide well with the prediction mentioned above, again implying that a hydride-transfer from 11Me-MMPAH to a quinone proceeds through a successive multistep process consisting of tandem e-transfer and H-transfer.

The discussion above is consistent with the reaction diagram shown in Figure 5. When a strong oxidant is employed for the reaction (dashed line), an e-transfer complex as an intermediate is formed easily, or the transition state of this process comes earlier, keeping the equilibrium isotope effect smaller than that of the reaction with a weak oxidant, which would exert a relatively large equilibrium isotope effect (solid line). However, the reaction with a strong oxidant requires higher free energy of activation to approach the transition state in the rate-

(24) Ohno, A.; Kimura, T.; Yamamoto, H.; Kim, S. G.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1535.

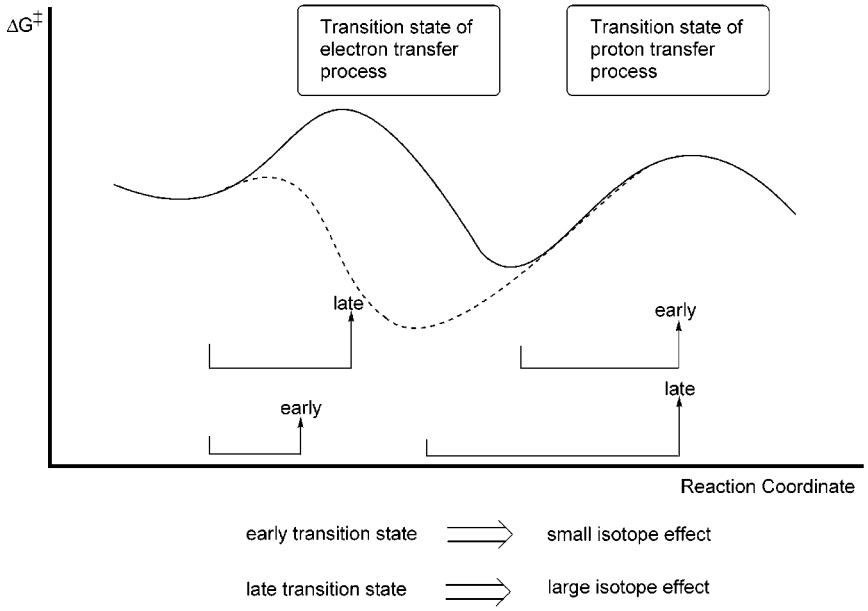


Figure 5. Schematic diagram of the free energy profile in the reaction of 11Me-MMPAH with a strongly oxidizing quinone (dashed line) and a weakly oxidizing quinone (solid line).

determining H-transfer process and shows a larger kinetic isotope effect than that with a weak oxidant. It should be noted that kinetics are measured experimentally starting from the intermediate instead of the initial state where each reagent exists separately.

In the absence of Mg^{2+}, the formation of an e-transfer complex in the *syn*-face requires more energy than that in the *anti*-face, because of electronic repulsion between a negative pole, i.e., carbonyl oxygen, of 11Me-MMPAH and a radical anion of the oxidant produced. On the other hand, in the presence of Mg^{2+}, the *syn*-face becomes more favorable in forming the e-transfer complex because of adhesive role of Mg^{2+}.

The total scheme of the reaction predicts that only the e-transfer complex of appropriate arrangement can undergo further reaction while the inappropriate complex reverts to the reactants without undergoing net hydride-transfer. This is the reason that the initial e-transfer process constitutes the stereodetermining step separately from the rate-determining H-transfer step.

It is interesting to note that Mg^{2+} plays dual catalytic roles: it promotes the reactions with weak oxidants and, at the same time, controls stereoselectivity of the reaction. This contradicts the "reactivity−selectivity relationship" as normally recognized in organic reactions, but resembles the role of enzymes in biochemical reactions, where both stereoselectivity and reactivity are increased. It is also interesting to note that the separation of stereo- and rate-determining steps again resembles phenomena seen in enzymatic reactions.

Stereochemistry controlled by the orientation of a dipole in a molecule is also reported in the reduction of a deazaflavin analogue by one of NAD(P)H models.[25]

Experimental Section

Instruments. Kinetic measurements were preformed with a Union Giken RA-401 Rapid Reaction Analyzer equipped with a Union Giken K2R temperature controller.

Materials. 11Me-MMPA$^+$I$^-$ and 11Me-MMPAH were prepared as described previously.[18] A mixture, **1**, composed of 80% 4-*syn*-deuterated 11Me-MMPAH (11Me-MMPAH-4-*syn*-*d*) and 20% 4-*anti*-deuterated 11Me-MMPAH (11Me-MMPAH-4-*anti*-*d*), was obtained by reducing 11Me-MMPA$^+$ with $Na_2S_2O_4$ in D_2O. Another mixture, **2**, composed of 80% 4-*anti*-deuterated 11Me-MMPAH (11Me-MMPAH-4-*anti*-*d*) and 20% 4-*syn*-deuterated 11Me-MMPAH (11Me-MMPAH-4-*syn*-*d*), was synthesized by repeated oxidation of **1** with *p*-chloranil in CH_3CN and reduction of the resulted 11Me-MMPA$^+$-4-*d* with $Na_2S_2O_4$ in D_2O to obtain 11Me-MMPAH-4,4-d_2. Then, the resulting 11Me-MMPAH-4,4-d_2 was finally oxidized with *p*-chloranil in CH_3CN to obtain 11Me-MMPA$^+$-4-*d*, which was reduced with $Na_2S_2O_4$ in H_2O. *p*-Benzoquinone and its derivatives were purchased from commercial sources except for chloro-[26] and trichloro-*p*-benzoquinones,[27] which were synthesized according to literature procedures, respectively. Column chromatography was performed with alumina 90 active neutral (Merck, 70−230 mesh). Magnesium perchlorate was dried at 100 °C in vacuo for 12 h and used immediately. Acetonitrile was distilled freshly from calcium hydride prior to the use. A buffer solution was prepared with KH_2PO_4 and NaOH, adjusted at pH 7.5, and degassed prior to the use.

Oxidation of 1 and 2 with *p*-Benzoquinone Derivatives in the Presence of Mg^{2+}. *p*-Benzoquinone derivative (2 equiv) was placed in a 30 mL round-bottomed flask. The flask was degassed and filled with argon. The procedure was repeated several times. Dry CH_3CN (10 mL) was added, and an argon-purged solution of **1** (or **2**) (27 mg, 0.10 mmol) and $Mg(ClO_4)_2$ (223 mg, 1.0 mmol) in dry CH_3CN were added successively to the contents of the flask through a syringe. The reaction mixture was stirred for 1 h at room temperature under an argon atmosphere in the dark. The solution turned red. After the solvent was evaporated from the mixture under reduced pressure, the residue was washed with water and extracted with dichloromethane. The dichloromethane solution was dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was subjected to column chromatography on an anion-exchange resin (chloride form of IRA-400) to afford 20 mg of 11Me-MMPA$^+$Cl$^-$ as white crystals in 66% yield. D/H content ratio at C4-position in the product 11Me-MMPA$^+$ was determined by ^{1}H NMR spectroscopy in the same manner as previously reported.[18]

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(27) Biltz, H.; Giesse, W. *Chem. Ber.* **1904**, *37*, 4010.

Kinetic measurements were carried out by using a stopped-flow apparatus for the reactions of **1** and **2** with *p*-chloranil and 2,6-dichloro-*p*-benzoquinone in CH_3CN at 278, 288, 298, and 318 K. Reaction rates were followed by observing the increase in intensity at the absorption maxima of the respective radical anions (λ_{max} = 449 nm for *p*-chloranil; 448 nm for 2,6-dichloro-*p*-benzoquinone) under pseudo-first-order conditions of more than 10-fold excess quinone. Pseudo-first-order rate constants were obtained by the Guggenheim method.[28] Kinetic activation parameters were calculated according to the Arrhenius and Eyring methods.

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