NAD(P)$^+$-NAD(P)H Models. 88. Stereoselection without Steric Effect but Controlled by Electronic Effect of a Carbonyl Group: Syn/Anti Reactivity Ratio, Kinetic Isotope Effect, and an Electron-Transfer Complex as a Reaction Intermediate

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Abstract: 1,4,6,7-Tetrahydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin (11Me-MMPAH) and its 4-mono- and 4,4-dideuterated analogues have been oxidized with a series of *p*-benzoquinones. The compounds have axial chirality with respect to the orientation of the carbonyl dipole. The hydrogen (deuterium) at the 4-position has different reactivity toward oxidation: the anti (with respect to the carbonyl dipole) hydrogen is from 3 to 32 times more reactive than the corresponding syn hydrogen (deuterium). The syn/anti reactivity ratio depends on the reactivity of the quinone (stereoselection without steric effect). The initial electron-transfer process, which is associated with the weakening of the $C_4-H(D)$ bond, results in the formation of an electron-transfer complex prior to the chemical reaction. The isotope effect affecting this equilibrium constant is the origin of the "product isotope effect", which has long been a subject of controversy. Kinetic primary and secondary isotope effects in the oxidation are also calculated.

Introduction

In previous papers of this series, we reported that a difference exists in reactivity between the molecular faces of certain NAD(P)$^+$/NAD(P)H analogues when they are reduced or oxidized by an achiral reagent.[1−6] Electrochemical oxidation under base catalysis also demonstrates differential reactivity.[7] Interestingly, the preference for a reacting face, or selectivity, depends on the chemical reactivity of the reducing or oxidizing agent: the more reactive, the more antiselecting with respect to the orientation of the dipole due to a side-chain carbonyl or sulfinyl functional group on the NAD(P)$^+$/NAD(P)H analogue. The analogues have no steric discrimination at their reacting faces except for the orientation of the dipole. Thus, we demonstrated a system in which the reacting face is discriminated by a polar effect[8] instead of by the steric bulk of substituents, which is a classic steric effect.[4] It is worthy noting that similar discrimination of reacting face is also observed in enzyme chemistry.[9−11]

Abbreviations for the analogues studied so far are summarized in Chart 1 with their respective structures.

Among these analogues, 11Me-MMPA$^+$/11Me-MMPAH and Me_2MPTSO$^+$/Me_2MPTSOH have stable configurations and are easy to isolate as (*R*) and (*S*) enantiomers (Chart 2). Therefore, the compounds are suitable for studying the syn/anti face selectivity ratio with respect to the orientation of the dipole.

When 11Me-MMPA$^+$ or Me_2MPTSO$^+$ is reduced by a (net) deuteride, the 4-position of the resulting dihydropyridine moiety becomes chiral, and it is now possible to study the selectivity associated with the oxidation reactions using this deuterated compound. Thus, these deuterated analogues can afford quantitative results unambiguously on selectivities for both reduction and oxidation reactions.

Using 11Me-MMPAH and its deuterated analogues, we studied the selectivity of oxidation to confirm the idea of stereochemistry controlled by an electronic effect and, at the same time, to elucidate various kinetic isotope effects associated with the reaction. We also mention a physical interpretation of the so-called product isotope effect.[12,13] Steffens and Chipman found that the hydrogen/deuterium isotopic ratio in the product is much larger than that expected on the basis of the kinetic isotope effect, and they suggested the existence of at least one intermediate in the reaction.[14] Later, we named

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(1) Ohno, A.; Tsutsumi, A.; Kawai, Y.; Yamazaki, N.; Mikata, Y.; Okamura, M. *J. Am. Chem. Soc.* **1994**, *116*, 8133−8137.
(2) Ohno, A.; Yamazaki, N.; Tsutsumi, A.; Mikata, Y.; Okamura, M. *Heteroat. Chem.* **1995**, *6*, 51−56.
(3) Mikata, Y.; Mizukami, K.; Ikehara, K.; Ohno, A. *Tetrahedron Lett.* **1995**, *36*, 6491−6494.
(4) Ohno, A.; Yamazaki, N.; Okamura, M.; Kawai, Y.; Tsutsumi, A.; Mikata, Y.; Fujii, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1093−1098.
(5) Ohno, A.; Tsutsumi, A.; Yamazaki, N.; Okamura, M.; Mikata, Y.; Fujii, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1679−1685.
(6) Bédat, J.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Chem. Lett.* **1996**, 359−360.
(7) Okamura, M.; Kashiwagi, T.; Mikata, Y.; Maruyama, T.; Ohno, A. *Tetrahedron Lett.* **1991**, *32*, 1475−1478.
(8) Compare, for theoretical background: Donkersloot, M. C. A.; Buck, H. M. *J. Am. Chem. Soc.* **1981**, *103*, 6554−6558.
(9) Nambiar, K. P.; Stauffer, D. M.; Lolodziej, P. A.; Benner, S. T. *J. Am. Chem. Soc.* **1983**, *105*, 5886−5890.
(10) Schneider-Bernlöhr, H.; Adolph, H.-W.; Zeppezauer, M. *J. Am. Chem. Soc.* **1990**, *63*, 1735−1737.
(11) Nakamura, K.; Shiraga, T.; Miyai, T.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 294−296.
(12) Ohno, A.; Yamamoto, H.; Oka, S. *J. Am. Chem. Soc.* **1981**, *103*, 2041−2045.
(13) Ohno, A.; Shio, T.; Yamamoto, H.; Oka, S. *J. Am. Chem. Soc.* **1981**, *103*, 2045−2048.

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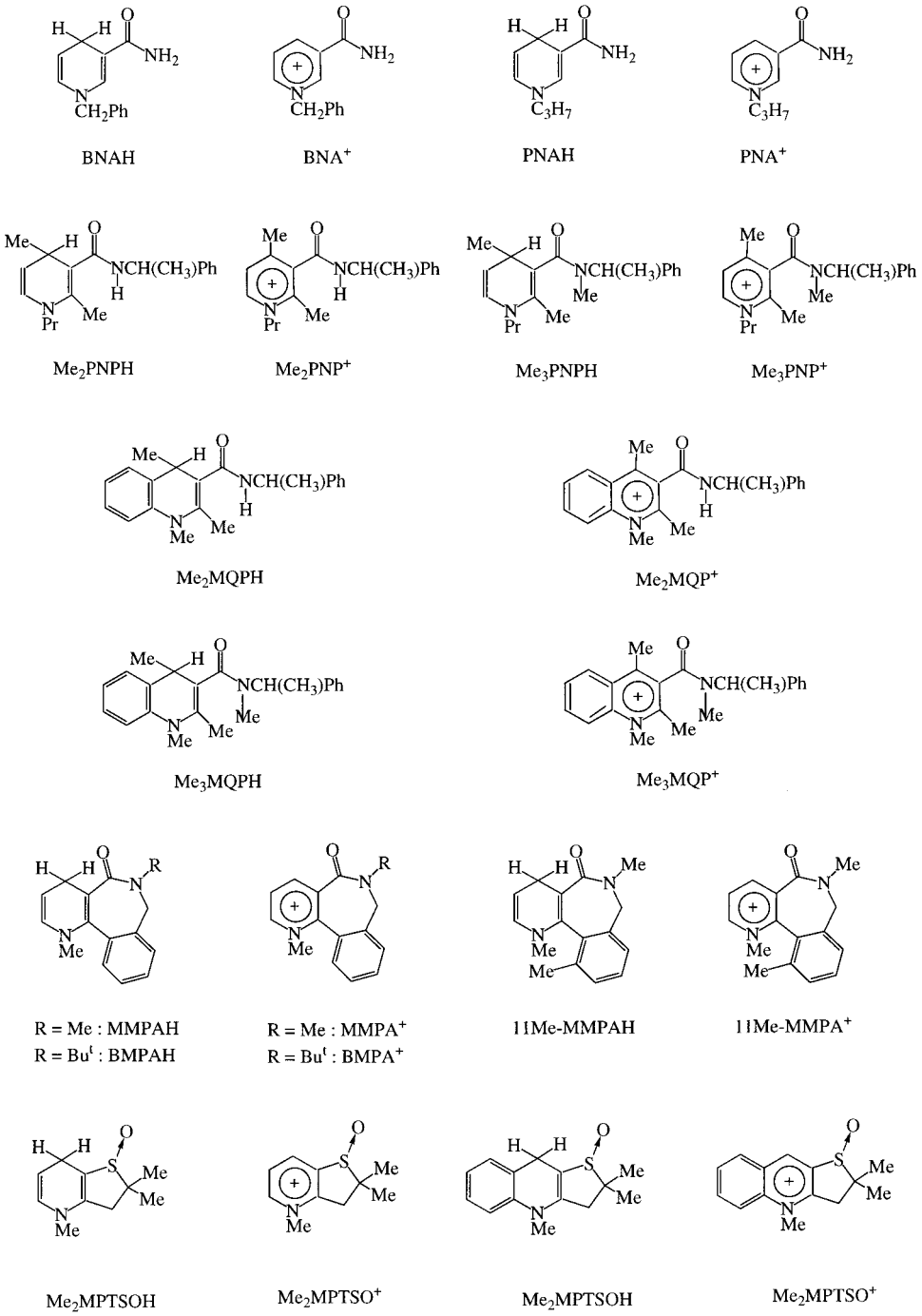
Chart 1



the ratio the "product isotope effect" and employed it as important evidence for the presence of an electron-transfer intermediate prior to the proton-transfer process in a (net) hydride-transfer reaction.[15,16] The discrepancy between kinetic and product isotope effects was subjected to a discussion; namely it was claimed that the discrepancy is not an essential phenomenon but an artificial product resulted by contaminating water in the solvent.[17] The claim was tested and rejected; the contaminating water does not affect the reaction seriously as long as its concentration in the solvent is kept as small as 2% or less.[18] Now there is no doubt on its significance. However, the origin and the physical interpretation of the product isotope effect still remains unclarified. This paper also discusses on its physical significance.

Results

X-ray Crystallographic Structure. Although elucidation of the X-ray crystallographic structure of 11Me-MMPAH has not yet been accomplished, those of 11Me-MMPA$^+$ and its precursor, 6,7-dihydro-6,11-dimethyl-5-oxo-5*H*-benzo[*c*]pyrido-[2,3-*e*]azepin (11Me-MPA), have been obtained with reasonable

(14) Steffens, J. J.; Chipman, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 6694−6696.

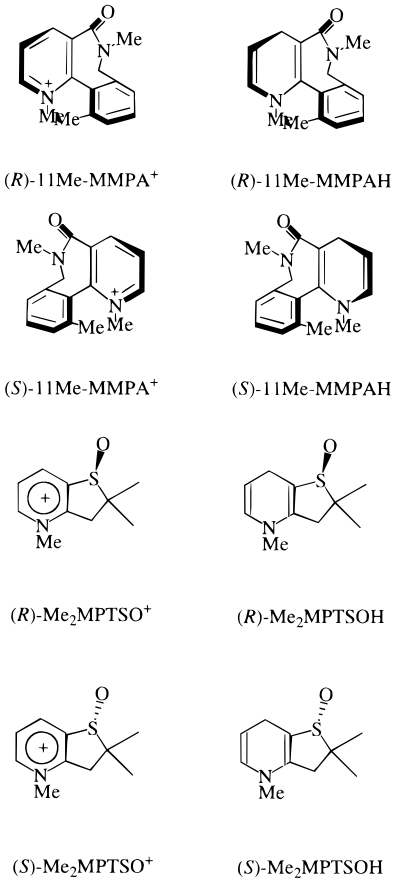
(15) Ohno, A.; Yasui, S.; Yamamoto, H.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 294−296.

(16) Ohno, A.; Yamamoto, H.; Okamoto, T.; Oka, S.; Ohnishi, Y. *Chem. Lett.* **1978**, 65−68.

(17) Powell, M. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 5834−5836.

(18) Ohno, A.; Kobayashi, H.; Nakamura, K.; Oka, S. *Tetrahedron Lett.* **1983**, *24*, 1263−1264.

Chart 2



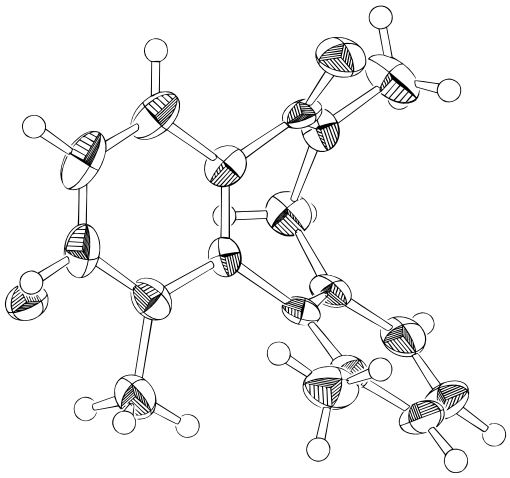


Figure 1. ORTEP drawing of 11Me-MMPA$^+$.

precision. Figures 1 and 2 confirm that the structures of these compounds are not very different from that of MMPA$^+$ reported previously.[1] Thus, the orientation of the amide carbonyl dipole differentiates one face of the molecule from the other, and no meaningful steric effect is expected for the reaction at the 4-position. Table 1 lists crystallographic parameters for these compounds.

Isotopically Substituted Compounds. Reduction of 11Me-MMPA$^+$ to afford 11Me-MMPAH (**1**) was reported previously.[5] The selectivity in the reduction, which is expressed by a syn/anti ratio, is 80/20. Thus, we obtain a mixture (**2**) composed of 80% 11Me-MMPAH-4-*syn-d* and 20% 11Me-MMPAH-4-*anti-d* by reducing 11Me-MMPA$^+$ with $Na_2S_2O_4$ in D_2O. Repeated oxidations (chloranil in CH_3CN) and reductions

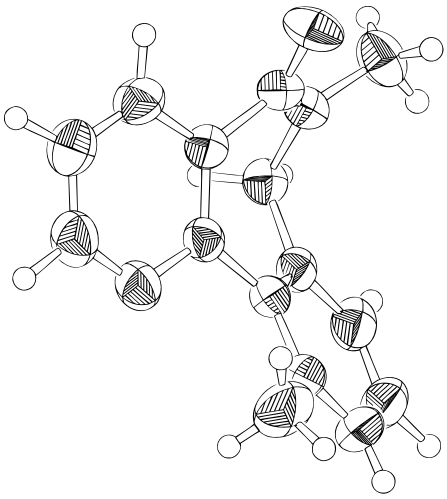


Figure 2. ORTEP drawing of 11Me-MPA.

Table 1. Crystallographic Parameters for 11Me-MMPA$^+$ and 11Me-MPA$^+$

parameter	11Me-MMPA$^+$	11Me-MPA
formula	$C_{16}H_{17}N_2OI_{0.5}BrZn_{0.5}$	$C_{15}H_{14}N_2O$
formula weight	429.37	238.29
crystal dimensions	0.30 × 0.20 × 0.15 mm	0.60 × 0.50 × 0.20 mm
crystal system	monoclinic	monoclinic
lattice parameters	a = 28.480(6) Å	a = 8.397(1) Å
	b = 10.205(5) Å	b = 12.957(1) Å
	c = 26.793(5) Å	c = 11.823(2) Å
	β = 123.07(1)°	β = 104.32(1)°
	V = 6526(3) Å^3	V = 1246.3(3) Å^3
space group	$C2/c$ (no. 15)	$P2_1/c$ (no. 14)
Z value	16	4
R	0.066	0.047
R_w	0.083	0.078
S	1.68	1.75

($Na_2S_2O_4$ in D_2O) of the mixture affords 11Me-MMPAH-4,4-d_2 (**4**). On the other hand, oxidation (chloranil in CH_3CN) and reduction ($Na_2S_2O_4$ in H_2O) of **4** yields a mixture (**3**) composed of 20% 11Me-MMPAH-4-*syn-d* and 80% 11Me-MMPAH-4-*anti-d*.

H:D Ratio in the Product and Kinetics of Oxidation. The monodeuterated compounds **2** and **3** were oxidized with a series of *p*-benzoquinone derivatives and the H:D ratio 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 there occurs no isotopic scrambling between the reduced and oxidized forms of the analogue under the reaction conditions. When the concentration of the analogue becomes sufficiently large, the scrambling becomes serious.[19] The results were employed for elucidation of the stereoselectivity of the reaction. The reactions with all quinones employed proceeded to completion.[20] Kinetics for the same oxidation in acetonitrile at 298 K were also studied for compounds **1**−**4**. Isotopic ratios in the products and kinetic results are summarized in Tables 2 and 3, respectively. Table 2 also includes the redox potentials of the quinones employed as the oxidizing agents.

Selectivity. Because 11Me-MMPAH demonstrates different reactivities for its *syn*- and *anti*-hydrogens (deuteriums) and the hydrogen (or deuterium) contents in the syn and anti positions

(19) Ohno, A.; Kimura, T.; Oka, S.; Ohnishi, Y. *Tetrahedron Lett.* **1978**, 757−760.

(20) Very strong oxidizing agent such as duroquinone and TCNQ did not afford 11Me-MMPA$^+$, and unidintified decomposition products were obtained.

Table 2. Stereoselectivity in the Oxidation of 11Me-MMPAH with *p*-Benzoquinone Derivatives in CH_3CN

p-benzoquinone derivative	$E°$, V	D:H content in 11Me-MMPA$^+$ (Y)[a,b] from **2**	from **3**
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] Measured by ^{1}H NMR spectroscopy. [b] Estimated errors in the contents of D and H are ±1 and ∓1, respectively.

Table 3. Kinetics in the Oxidation of 11Me-MMPAH with *p*-Benzoquinone Derivatives in CH_3CN at 298 K

p-benzoquinone derivative	k,[a] M^{-1} s^{-1} **1**	**2**	**3**	**4**
p-chloranil	4.5×10^3	3.5×10^3	1.5×10^3	9.5×10^2
p-bromanil	4.3×10^3	3.5×10^3	1.4×10^3	9.2×10^2
trichloro-*p*-benzoquinone				
2,6-dichloro-*p*-benzoquinone	1.3×10^2	9.3×10^1	6.6×10^1	3.6×10^1
2,5-dichloro-*p*-benzoquinone	9.2×10^1	6.9×10^1	4.6×10^1	2.8×10^1
chloro-*p*-benzoquinone				

[a] Estimated errors are ±5%.

are not 100%, the ratio of hydrogen to deuterium in the product does not directly correspond to the product isotope effect. To elucidate the product isotope effect and reactivity ratio for the *syn*- and *anti*-hydrogens (deuteriums), the following equations are formulated.

The D/H isotopic ratio in the product, Y, can be expressed by eq 1

$$Y = F[(\text{D content at the anti position of 11Me-MMPAH}) \times (\text{D which originates at the anti position and remains in 11Me-MMPA}^+ \text{ after the oxidation}) + (\text{D content at the syn position of 11Me-MMPAH}) \times (\text{D which originates at the syn position and remains in 11Me-MMPA}^+ \text{ after the oxidation})]/[(\text{H content at the anti position of 11Me-MMPAH}) \times (\text{H which originates at the anti position and remains in 11Me-MMPA}^+ \text{ after the oxidation}) + (\text{H content at the syn position of 11Me-MMPAH}) \times (\text{H which originates at the syn position and remains in 11Me-MMPA}^+ \text{ after the oxidation})] \quad (1)$$

where F stands for the intrinsic product isotope effect.

We define two parameters α and β as follows: α is the proportion of H or D reacted in the anti position (anti reactivity parameter). The value is independent of the kinetic isotope effect and is the same for H and D. β is the fraction of D at the syn position of 11Me-MMPAH, which is equal to the fraction of H present at the anti position of 11Me-MMPAH.

The fraction of H or D reacted in the syn position is then expressed as $1 - \alpha$. The quantity $1 - \beta$ represents either the fraction of D present in the anti position or the fraction of H present in the syn position of 11Me-MMPAH that remains unreacted.

Furthermore,

$$\text{the fraction of L (L = H or D) remaining in 11Me-MMPA}^+ \text{ after the oxidation} = 1 - (\text{fraction of L reacted}) \quad (2)$$

By substituting these parameters into eq 1, we obtain eq 3:

$$Y = F[(1-\beta)(1-\alpha) + \beta\alpha]/[\beta(1-\alpha) + (1-\beta)]\alpha$$
$$= F[(2\beta - 1)\alpha + (1-\beta)]/[\beta - (2\beta - 1)\alpha] \quad (3)$$

Because Y and β in eq 3 are experimentally observable by ^{1}H NMR, both F and α can be calculated by solving these quadratic simultaneous equations based on the results from **2** and **3**. The value of β was 0.8 for **2** and 0.2 for **3**. Experimentally observed Y values for each oxidation are listed in Table 2 in parentheses.

Isotope Effect. Combined results from the kinetics on **1**−**4** can be used to determine the kinetic primary and secondary isotope effects as follows.

The observed rate constants for **1**−**4** are expressed by eqs 4−7:

$$k_{\mathbf{1}} = {}_{\mathrm{s}}k^{\mathrm{H}}_{\mathrm{HH}} + {}_{\mathrm{a}}k^{\mathrm{H}}_{\mathrm{HH}} \quad (4)$$

$$k_{\mathbf{2}} = (1-\beta){}_{\mathrm{s}}k^{\mathrm{H}}_{\mathrm{HD}} + \beta{}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{HD}} + \beta{}_{\mathrm{a}}k^{\mathrm{H}}_{\mathrm{HD}} + (1-\beta){}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{HD}} \quad (5)$$

$$k_{\mathbf{3}} = \beta{}_{\mathrm{s}}k^{\mathrm{H}}_{\mathrm{HD}} + (1-\beta){}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{HD}} + (1-\beta){}_{\mathrm{a}}k^{\mathrm{H}}_{\mathrm{HD}} + \beta{}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{HD}} \quad (6)$$

$$k_{\mathbf{4}} = {}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{DD}} + {}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{DD}} \quad (7)$$

where ${}_i k^{\mathrm{N}}_{\mathrm{LM}}$ stands for a rate constant for the transfer of a nucleus N (N = L or M) from the i side (i = syn or anti) in a compound that is substituted by nuclei L and M (L, M = H or D).

If we assume that the kinetic primary (P) and secondary (S) isotope effects from the syn and anti positions are equal, then

$$S = {}_{\mathrm{s}}k^{\mathrm{H}}_{\mathrm{HH}}/{}_{\mathrm{s}}k^{\mathrm{H}}_{\mathrm{HD}} = {}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{HD}}/{}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{DD}} = {}_{\mathrm{a}}k^{\mathrm{H}}_{\mathrm{HH}}/{}_{\mathrm{a}}k^{\mathrm{H}}_{\mathrm{HD}} = {}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{HD}}/{}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{DD}} \quad (8)$$

and we obtain eqs 9 and 10 by modifying eqs 5 and 6 by using eq 8:

$$k_{\mathbf{2}} = (1-\beta)({}_{\mathrm{s}}k^{\mathrm{H}}_{\mathrm{HH}} + {}_{\mathrm{a}}k^{\mathrm{H}}_{\mathrm{HH}})/S + (1-\beta)({}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{DD}} + {}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{DD}})S + (2\beta - 1)[({}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{HH}}/S) + {}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{DD}}] \quad (9)$$

$$k_{\mathbf{3}} = \beta({}_{\mathrm{s}}k^{\mathrm{H}}_{\mathrm{HH}} + {}_{\mathrm{a}}k^{\mathrm{H}}_{\mathrm{HH}})/S + \beta({}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{DD}} + {}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{DD}})S - (2\beta - 1)[({}_{\mathrm{s}}k^{\mathrm{D}}_{\mathrm{HH}}/S) + {}_{\mathrm{a}}k^{\mathrm{D}}_{\mathrm{DD}}] \quad (10)$$

The addition of eq 9 to eq 10 yields

$$k_{\mathbf{4}}S^2 - (k_{\mathbf{2}} + k_{\mathbf{3}})S + k_{\mathbf{1}} = 0 \quad (11)$$

Then, we finally obtain

$$S = [(k_{\mathbf{2}} + k_{\mathbf{3}}) - \{(k_{\mathbf{2}} + k_{\mathbf{3}})^2 - 4k_{\mathbf{1}}k_{\mathbf{4}}\}^{1/2}]/2k_{\mathbf{4}} \quad (12)$$

and

$$P = (k_{\mathbf{1}}/k_{\mathbf{4}})/S = [(k_{\mathbf{2}} + k_{\mathbf{3}}) + \{(k_{\mathbf{2}} + k_{\mathbf{3}})^2 - 4k_{\mathbf{1}}k_{\mathbf{4}}\}^{1/2}]/2k_{\mathbf{4}} \quad (13)$$

P, S, F, and α thus calculated are summarized in Table 4.

Discussion

Selectivity Parameter, α. Table 4 indicates that the syn:anti reactivity ratio in the reaction with *p*-chloranil is 3:97, or the *anti*-hydrogen in 11Me-MMPAH is 32 times more reactive than the corresponding *syn*-hydrogen. The anti selectivity observed for the oxidation is in sharp contrast to the syn selectivity for the reduction reported previously.[5] Because the

Table 4. Kinetic Primary (*P*) and Secondary (*S*) Isotope Effects, Intrinsic Product Isotope Effect (*F*), and Anti Selectivity Parameter (α) in Oxidation of 11Me-MMPAH with *p*-Benzoquinone Derivatives in CH_3CN at 298 K

p-benzoquinone derivative	*P*	*S*	*F*	α
p-chloranil	4.19	1.12	1.2	0.97
p-bromanil	4.19	1.13	1.3	0.97
trichloro-*p*-benzoquinone			1.9	0.93
2,6-dichloro-*p*-benzoquinone	3.32	1.11	2.3	0.87
2,5-dichloro-*p*-benzoquinone	3.09	1.07	2.4	0.87
chloro-*p*-benzoquinone			2.6	0.78

conformation of 11Me-MMPAH is stable, the difference in reactivity between syn and anti positions appears maximum and the largest syn:anti ratio among those reported so far is observed.[21]

The anti selectivity decreases with a decrease in the redox potential of the quinone, and the ratio is only 1:3 in the reaction with chloro-*p*-benzoquinone. Thus, here again it appears that the stereochemical result depends on the reactivity of the oxidizing agent: the more reactive, the more anti preference.

Although not only the carbonyl oxygen but also the phenyl ring sticks out of the molecular plane in the syn face, it is evident that the anti selectivity observed herein does not originate in steric interference by these groups, because the reduction proceeds with the syn preference in the ratio of syn:anti = 80−70:20−30[5] and, moreover, the selectivity changes depending on the redox potential of the oxidizing agent. Instead, some electronic effect which can be correlated to redox potential might be responsible for the selectivity. The significance of α value together with that of *F* factor will be discussed in a latter section again in relation with the reaction mechanism.

Intrinsic Product Isotope Effect, *F*. The amide carbonyl in BNAH can rotate freely, and there is no discrepancy between the reactivity of two hydrogens at the 4-position. In other words, the syn:anti reactivity ratio of BNAH is 1:1. Therefore, when one of two hydrogens is substituted by a deuterium, isotopic distribution in the product, BNA^+, (the product isotope effect) must coincide with the kinetic isotope effect associated with its oxidation. However, in many cases including the oxidation of BNAH, a large discrepancy is observed between these two isotope effects. To adjust the two isotope effects, a factor *F* is introduced into eq 1. The introduction of the *F* factor into eq 1 inevitably means that it is insufficient to elucidate the isotopic distribution in the product, *Y*, for the oxidation of 11Me-MMPAH based on the reactivity terms corrected by isotopic distribution only. The *F* factors, for example, for the oxidations of the simplest NAD(P)H analogue, BNAH, by several benzoquinones were reported to be 2.2−2.3.[22] The values are in good agreement with those calculated for the oxidations herein. Thus, the reliability of the procedure employed in the present research for elucidating α and *F* has been confirmed.

By definition, the *F* factor should be a nonkinetic parameter. In a previous paper in this series, we emphasized the importance of the configuration of the molecule in its ground state for determining the stereochemical course of the reaction.[23] This result indicates that there is an isotopic discrimination at the ground state prior to the chemical process. Because the value of the *F* factor decreases with an increase in the reactivity (redox potential) of the benzoquinone, it is expected that the factor is a quantity associated with a nonkinetic interaction between 11Me-MMPAH and a quinone in the ground state. The interaction is the one which follows the reactivity−selectivity principle. Physical meaning of the *F* factor will be discussed again latter section.

Kinetic Primary and Secondary Isotope Effects, *P* and *S*. The values of *P* and *S* calculated herein agree quite well with those previously obtained for the oxidation of BNAH with benzoquinones[22] and those reported elsewhere.[24−27] A large *P* value predicts that the transition state of the reaction is composed largely of a transferring hydrogen nucleus.

The values of *S* so far reported range from 0.8 to 1.2; an inverse isotope effect has also been reported in one case.[28] Because an inverse secondary isotope effect reflects a larger force constant in the reacting bond in the transition state of the reaction than that in the ground state, the formation of an electron-transfer complex prior to the reaction is a plausible step in the mechanism when one observes an inverse isotope effect: a radical cation deduced from the NAD(P)H analogue as an intermediate is stabilized more by an electron-donating deuterium than by a protium.[29−32] However, a majority of the results from the oxidation of NAD(P)H analogues, including those herein, yield normal secondary isotope effects as indicated in references and notes. The secondary isotope effects observed for a series of oxidations of NAD(P)H analogues are the ones that stem from a chemical reaction instead of a preequilibrium process.

On the other hand, relatively large secondary isotope effects have been reported for enzymatic reactions.[33−35] Contributions of a bending mode and a tunneling effect to the reaction coordinate have been suggested for these reactions.[36] Values of 1.14 and 1.17 calculated for the oxidations in this study are moderate in magnitude among those reported so far and suggest that the transition state of the reaction is composed largely of the stretching mode with a small contribution from a bending mode of the reacting C−L (L = H or D) bond.

Presence of Preequilibrium State and Isotope Effect on Equilibrium Constant. The preceding discussion and much evidence reported previously[37] lead us to conclude that the reaction system has a preequilibrium state ascribable to an

(21) Okamura, M.; Mikata, Y.; Yamazaki, N.; Tsutsumi, A.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1191−1196.

(22) Goto, M.; Mikata, Y.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2682−2686. *P* = 2.0−6.3; *S* = 1.0 (assumed).

(23) Okamura, M.; Mikata, Y.; Yamazaki, N.; Tsutsumi, A.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1197−1203.

(24) Colter, A. K.; Sato, G.; Sharom, F. J.; Long, A. P. *J. Am. Chem. Soc.* **1976**, *98*, 7833−7835. *P* = 5−13; *S* = 1.1 with quinones.

(25) Kurz, L.; Frieden, C. *Biochemistry* **1977**, *16*, 5207−5216. *P* = 4.7−4.9; *S* = 1.2 for nonenzymatic reactions; *P* = 4.3−5.7 for enzymatic reactions with substituted benzenesulfonates.

(26) Kurz, L.; Frieden, C. *J. Am. Chem. Soc.* **1980**, *102*, 4198−4203. *P* = 5.3−5.5; *S* = 1.1 with 4-cyano-2,5-dinitrobenzenesulfonate. Equation 12 is also proposed in this paper.

(27) Chipman, D. M.; Yaniv, R.; van Eikeren, P. *J. Am. Chem. Soc.* **1980**, *102*, 3244−3246. *P* = 5.3; *S* = 1.0 (assumed) with α,α,α-trifluoromethylbenzophenone.

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Scheme 1

$$\xleftarrow{k_D^H} QM_D + M_H \rightleftharpoons[K] QM_H + M_D \xrightarrow{k_H^H}$$

Q , quinone: M_L, NAD(P)H analogsubstituted by L (L = H or D)

electron-transfer complex prior to the transfer of hydrogen nucleus either as a proton or a hydrogen atom (Scheme 1).

This electron-transfer process, however, is associated with a weakening of the reacting C−L (L = H or D) bond, and the isotope effect on this movement is the origin of the *F* factor. The physical meaning of the "product isotope effect" is an isotope effect on the equilibrium constant for the preequilibrium, K_H/K_D. In this sense, the electron-transfer in this system is not a pure Franck−Condon-type process. Instead, to transfer an electron from the analogue to an oxidizing agent, hyperconjugative assistance by the reacting proton (or deuteron) is required to supply negative charge to the carbon at the 4-position, and the C_4−H bond is elongated in some extent.[38] The requirement for hyperconjugative participation differs from system to system, depending on the reactivity, or redox potential, of the oxidizing agent. Thus, the *F* factor becomes larger as the reactivity, as measured by the redox potential, becomes smaller (reactivity−selectivity principle).

Stereoselectivity in the Electron-Transfer Complex. To compose an electron-transfer complex as a preequilibrium intermediate, there are two possible approaches to the oxidizing agent: approach at the syn face or in the anti face of the analogue. An α value of 0.78−0.97 certifies that the latter approach is preferable to the former.

Stereochemical results obtained herein from the reaction of 11Me-MMPAH, a conformationally stable compound, strongly suggest that the oxidation with a series of benzoquinones proceeds essentially at the anti face, and it is highly plausible that the syn preference observed in the reaction of 1,4-benzoquinone, one of the least reactive quinones so far studied and which requires the catalytic assistance of magnesium ion, results from the formation of an analog−Mg^{2+}−quinone ternary complex:[21,39] the magnesium ion is sandwiched by the analogue and a quinone resulting in a syn-oriented molecular arrangement. The same role for magnesium ion has been reported for the reaction of the deazaflavin analogue.[40] Nevertheless, it still should be kept in mind that the anti preference of the reaction is a function of the reactivity (redox potential) of the quinone, which is a variable. It is noteworthy that the reduction of 11Me-$MMPA^+$, which exhibits a syn preference, is a reaction that takes place through a charge−dipole or charge−charge interaction, whereas the reaction herein proceeds through a dipole−dipole interaction; the syn preference is seen in the reaction that involves a charged species. This observation may afford a hint at elucidating the mechanism of unusual stereochemistry controlled by an electronic effect(s) reported herein. As a candidate for the stereoselectivity, we propose that entropic loss in the syn-type complex is larger than that in the anti-type complex,[21] because dipole−dipole interaction requires a closer proximity between the two components of the complex than charge−charge or charge−dipole interaction. Electrostatic attractive forces may be smaller in the former system than in the latter, and the intermolecular distance between the two components of the complex of the former type must be shorter than that in the latter. As an alternative explanation, electrostatic repulsive force may be pointed out: electron transfer in the complex results in partial negative charge on the molecule of *p*-benzoquinone in the electron-transfer complex, which may cause more unfavorable interaction with the carbonyl dipole ($^{\delta+}C{=}O^{\delta-}$) of 11Me-MMPAH in its syn face than in the other.

Since these two postulations dealt with two different (early and late) stages of the complexation, it is highly possible that both effects are responsible to the discrimination cooperatively.

Although the reason for a high anti preference in the oxidation of the analogue, whereas highly syn preferency is observed in its reduction, remains unclear at present, a large α value and appreciable value for the *F* factor emphasize again the importance of the molecular arrangement in the ground state for the particular stereochemical result in the overall reaction.[23]

Reaction Scheme. Finally, we can write the reaction as shown in Scheme 2, where k_L^N is a rate constant for the transfer of a nucleus N (N = H or D) from an analogue that is substituted by H and another nucleus L (L = H or D) at its 4-position. M_L is the analogue which is substituted by H and a nucleus L (L = H or D) at its 4-position, and QM_L^{syn} and QM_L^{anti} are complexes between a quinone and the analogue in which the quinone sits in the syn or anti positions of the analogue, respectively. The analogue is substituted by H and another nucleus L (L = H or D) at its 4-position.

Experimental Section

Instruments. ^{1}H NMR spectra were recorded at 200 MHz on a Varian VXR 200 FT-NMR spectrometer. Kinetic measurements were performed with a Union Giken RA-401 Rapid Reaction Analyzer equipped by a Union Giken K2R temperature controller.

X-ray crystallographic studies were made on a Rigaku AFC7R diffractometer with filtered Cu Kα radiation and a rotating anode generator.

Materials. 11Me-$MMPA^+I^-$ and 11Me-MMPAH were prepared as described previously.[5] *p*-Benzoquinones were purchased from commercial sources except for chloro-[41] and trichloro-*p*-benzoquinone,[42] which were synthesized according to the literature procedures, respectively. Column chromatography was performed with alumina 90 active neutral (Merck, 70−230 mesh). 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.

Reduction of 11Me-$MMPA^+$ in D_2O. The buffer solution employed for the reaction was prepared with D_2O instead of H_2O. CH_2Cl_2 (8 mL) and $Na_2S_2O_4$ (50 mg, 0.29 mmol) dissolved in a buffer (5 mL) were added successively to 11Me-$MMPA^+I^-$ (50 mg, 0.13 mmol) dissolved in a buffer solution (5 mL), and the mixture was stirred for 5 h. The organic layer was separated and was washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. Immediately, the residue was subjected to column chromatography on alumina with CH_2Cl_2 as an eluent to afford 27 mg of 11Me-MMPAH-4-*d* (syn:anti = 80:20) as yellow paste in 80% yield. ^{1}H NMR δ($CDCl_3$): 2.31 (s, 3H, C11−CH_3), 2.56 (s, 3H, N1−CH_3), 2.92 (s, 3H, N6−CH_3), 3.14 (ddd, 0.80H, C4−H*e*), 3.68 (dd, 0.20H, C4−H*a*), 3.72 (d, J = 14 Hz, 1H, CH_2), 4.68 (d, J = 14 Hz, 1H, CH_2), 4.76 (ddd, $J_{2,3}$ = 7.7, $J_{3,4a}$ = 4.0, $J_{3,4e}$ = 2.9 Hz, 1H, C3−H), 5.79 (dd, $J_{2,3}$ = 7.7, $J_{2,4e}$ = 2.0 Hz, 1H, C2−H), 7.02−7.25 (m, 3H, arom.).

Oxidation of 11Me-MMPAH-4-*d* (syn:anti = 80:20). *p*-Benzoquinone (2 equiv) was placed in a 30 mL round-bottomed flask. The

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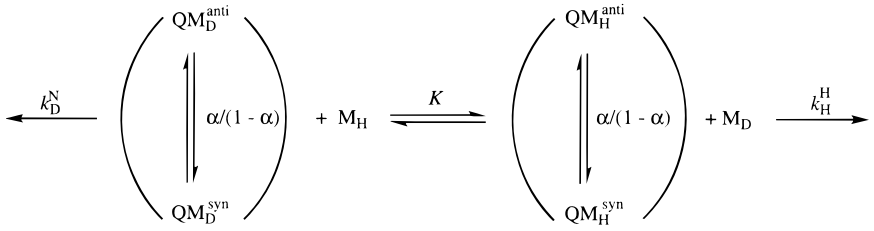
Scheme 2



$$F = K_H/K_D;\ P = k_H^H/k_D^H = k_H^D/k_D^D;\ S = k_H^H/k_H^D = k_D^H/k_D^D$$

flask was degassed and filled with argon several times. Dry CH_3CN (10 mL) and argon-purged solution of 11Me-MMPAH-4-*d* (27 mg, 0.10 mmol) in dry CH_3CN (6 mL) were added to the content in the flask through a syringe. The reaction mixture was stirred for 1.5−4 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 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. ^{1}H NMR δ($CDCl_3$): 2.22 (s, 3H, C11−CH_3), 3.10 (s, 3H, N6−CH_3), 3.91 (d, 1H, CH_2), 4.49 (s, 3H, N1−CH_3), 5.19 (d, 1H, CH_2), 7.27−7.58 (m, 3H, arom.), 8.18 (dd, 1H, C3−H), 8.78 (dd, xH, C4−H), 10.10 (dd, 1H, C2−H), where x = [11Me-MMPA$^+$]/([11Me-MMPA$^+$-4-*d*] + [11Me-MMPA$^+$]).

It was confirmed by ^{1}H NMR spectroscopy that the D:H ratio in the product stays constant throughout the reaction, which certifies that no scrambling takes place appreciably between the reduced and oxidized forms of the analogue.

Preparation of 11Me-MMPAH-4,4-*d*$_2$. The whole procedures for the reduction of 11Me-MMPA$^+$ in D_2O and oxidation of 11Me-MMPAH-4-*d* were repeated three times. Thus obtained 11Me-MMPA$^+$Cl$^-$ was reacted with $Na_2S_2O_4$ in D_2O again. The reaction conditions and workup procedures were the same as described for the reduction of 11Me-MMPA$^+$ in D_2O. The deuterium content at the 4-position was determined by ^{1}H NMR to be 100% within the limitation of measurement.

Crystallographic Study. The structure of 11-Me-MMPA$^+$I$^-$ or 11Me-MPA was solved by direct methods (SIR92 for 11-Me-MMPA$^+$I$^-$, SHELXS86 for 11-Me-MPA) and expanded using the Fourier technique (DIRDEF94). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. An ORTEP drawings are presented in Figures 1 and 2, and the crystallographic parameters are listed in Table 1.

Kinetic Measurement. Kinetic measurements were carried out by using a stopped-flow apparatus for the reactions of 11Me-MMPAH, 11Me-MMPAH-4-*d*, and 11Me-MMPAH-4,4-d_2 with a series of *p*-benzoquinone derivatives in CH_3CN at 298 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; 452 nm for *p*-bromanil; 448 nm for 2,5- and 2,6-dichloro-*p*-benzoquinone) under first-order conditions of more than 10-fold excess quinone. First-order rate constants were obtained by the Guggenheim method.[43]

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Supporting Information Available: Tables S1 and S2 giving complete crystallographic details, atomic coordinates, anisotropic temperature factors, and complete listings of bond distances and angles for 11Me-MMPA$^+$ and 11Me-MPA (32 pages). See any current masthead page for ordering information and Web access instructions.

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