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NAD(P)$^+$-NAD(P)H Models. 89. Effect of Magnesium Ion on the Stereochemistry in Oxidation of NAD(P)H Analog

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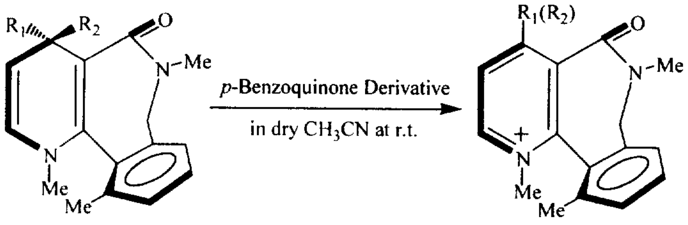
Abstract: In oxidation of NAD(P)H analog with *p*-benzoquinone derivatives in the presence of Mg^{2+}, it has been found that the reactivity of *syn*-hydrogen becomes larger as the reduction potential of *p*-benzoquinone derivative decreases. The selectivity shifts toward the *syn*-preferency in the presence of Mg^{2+} from the *anti*-preferency in the absence of Mg^{2+}. © 1999 Elsevier Science Ltd. All rights reserved.

In previous papers of this series, we reported stereoselectivity of the oxidation of 1,4,6,7-tetrahydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin (11Me-MMPAH; **1**) and its deuteriated analogs with *p*-benzoquinone derivatives (Scheme 1).[1-3] Axial chirality with respect to the orientation of carbonyl dipole in this reduced form is sophisticatedly preserved in its oxidized form, where the rotation of the side-chain amide group is prohibited by a cyclic structure in the compound.

Without Mg^{2+}, the *anti*-hydrogen with respect to the carbonyl dipole is 3 - 32 times more reactive than the corresponding *syn*-hydrogen. The anti selectivity of the reaction has been explained by the contribution of initial electron-transfer process prior to the proton transfer.[1] In the *syn*-hydrogen-transfer reaction, the carbonyl oxygen points toward the pairing *p*-benzoquinone, whereas the pairing *p*-benzoquinone sits itself in the opposite side of carbonyl

Scheme 1



11Me-MMPAH : R_1=R_2=H : **1**
11Me-MMPAH-7$_{syn}$-*d* : R_1=H (80%), R_2=D (80%) : **2**

11Me-MMPA$^+$
11Me-MMPA$^+$-7-*d*

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oxygen in the *anti*-hydrogen-transfer reaction. Thus, 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 in the absence of Mg^{2+}.

In this paper, we wish to report preliminary results from the oxidation of 11Me-MMPAH with a series of *p*-benzoquinone derivatives in the presence of Mg^{2+} revealing that Mg^{2+} shifts the selectivity of reaction to the *syn*-preference. All the reactions using 11Me-MMPAH-7_{syn}-*d* (**2**) which has 80%/20% deuterium content in the syn and anti positions, respectively, were carried out in dry acetonitrile at room temperature. The amount of Mg^{2+} present in the reaction system is 10 equivs. to **2**. It was confirmed that further increase in the amount of Mg^{2+} does not alter isotopic ratios in the products. The H/D ratio in the product 11Me-MMPA$^+$ was measured by ^{1}H NMR spectroscopy according to a similar manner as described previously.[1] The results are summarized in Table 1.

Apparently, H-content in 11Me-MMPA$^+$ increases when Mg^{2+} is present in the system, which indicates that the *syn*-hydrogen is more reactive in the presence of Mg^{2+} than that in the absence of Mg^{2+}, despite the fact that the *syn*-face is sterically more clowded than the *anti*-face.

To elucidate the reactivities of *syn*- and *anti*-hydrogens in detail, we introduced the following equation: the D/H isotopic ratio in the product, Y, can be expressed by eq. 1, which is detailed in a previous paper,

$$Y = F \times [\,0.2 \times (1 - \alpha) + 0.8 \times \alpha\,] \,/\, [\,0.8 \times (1 - \alpha) + 0.2 \times \alpha\,] \qquad (1)$$

where F stands for the intrinsic product isotope effect and α stands for the proportion of H or D reacted in the anti position (i.e. anti reactivity).[1] It was pointed out in a previous paper that these parameters are nonkinetic.[1] For calculating the parameter α for the present reactions in the presence of Mg^{2+}, we tentatively employed the values of F factor in the absence of Mg^{2+}, since the value of F factor obtained from the reaction is not affected largely by the presence or absence of Mg^{2+} when *p*-benzoquinone derivatives are employed as oxidizing agents.[4] The results are summarized in Table 2.

A dramatic change in the syn/anti selectivity is observed when Mg^{2+} is present in the system. In addition, as the reduction potential of *p*-benzoquinone derivative decreases, the reactivity of the *syn*-hydrogen becomes larger. Even in the reaction with a strongly oxidizing agents such as *p*-chloranil or *p*-bromanil, the reactivity of the *syn*-hydrogen increases up to the same level with that of the *anti*-hydrogen. The tendency is emphasized in the reactions with a weakly oxidizing agents such as chloro-*p*-benzoquinone; the *syn*-hydrogen becomes 2.6 times more reactive than the *anti*-hydrogen.

The change in reactivity of the hydrogens strongly suggests an important contribution of Mg^{2+} in the pre-association complex for determining the stereochemistry of the reaction. That is, a weakly oxidizing quinone requires catalytic contribution of Mg^{2+} to undergo the reaction, because the reactivity of the quinone of this kind is not sufficient to abstract an electron from **1**

Table 1. Stereoselectivity in the Oxidation of **2** with *p*-Benzoquinone Derivatives in CH_3CN at Room Temperature

		D : H content in 11Me-MMPA$^+$ (Y) [a]	
p-Benzoquinone derivative	E^0/V [b]	without Mg^{2+} [c]	with Mg^{2+} [d]
p-Chloranil	0.01	81 : 19 (4.3)	57 : 43 (1.3)
p-Bromanil	0.00	82 : 18 (4.6)	56 : 44 (1.3)
Trichloro-*p*-benzoquinone	-0.09	86 : 14 (6.1)	59 : 41 (1.4)
2,6-Dichloro-*p*-benzoquinone	-0.18	86 : 14 (6.1)	62 : 38 (1.6)
2,5-Dichloro-*p*-benzoquinone	-0.18	86 : 14 (6.1)	62 : 38 (1.6)
Chloro-*p*-benzoquinone	-0.34	84 : 16 (5.3)	60 : 40 (1.5)

a) Measured by ^1H NMR spectroscopy. Y = D content / H content.
b) Reduction potential of quinone. Ref. 5. c) Estimated errors are ±1 in D : H content. Ref. 1.
d) Estimated errors are ±3 in D : H content.

Table 2. Intrinsic Product Isotope Effect (F), and Anti Selectivity Parameter (α) in the Oxidation of **2** with *p*-Benzoquinone Derivatives in CH_3CN at Room Temperature

		α	
p-Benzoquinone derivative	F [a,b]	without Mg^{2+} [a,c]	with Mg^{2+} [d]
p-Chloranil	1.2	0.97	0.54
p-Bromanil	1.3	0.97	0.49
Trichloro-*p*-benzoquinone	1.9	0.93	0.39
2,6-Dichloro-*p*-benzoquinone	2.3	0.87	0.36
2,5-Dichloro-*p*-benzoquinone	2.4	0.87	0.34
Chloro-*p*-benzoquinne	2.6	0.78	0.28

a) Ref. 1. b) Estimated errors are ±0.1. c) Estimated errors are ±0.02.
b) Estimated errors are ±0.08.

(or **2**) in the analog-quinone binary complex, or the reaction and a quinone to bring them into closer face-to-face contact in the *syn*-face and, therefore, the *syn*-hydrogen is on inevitably involves an analog-Mg^{2+}-quinone ternary complex as a pre-association intermediate. In this ternary complex, the Mg^{2+} is sandwiched by the analog transferred preferentially giving the α value of 0.28.

On the other hand, because a repulsion between positive charges on Mg^{2+} and partial positive charge on the skeleton of quinone molecule becomes serious in the reaction with a strongly oxidizing quinone, the ternary complex is hardly constructed and the major part of the reaction proceeds through the analog-quinone binary complex, or less contribution of Mg^{2+} is expected in the reaction, giving the α value of about 0.5. Indeed, quinones of this kind do not require catalytic assistance by Mg^{2+}. In the binary complex, a quinone sits itself in less clowded face, or the *anti*-position with respect to the orientation of carbonyl oxygen of an analog. Thus, the *anti*-hydrogen is selected preferentially for the reaction.

The *syn*-preferency of the reaction has been reported in the reactions of other NAD(P)H analogs with *p*-benzoquinone, one of the least reactive quinones so far studied, under catalytic assistance of Mg^{2+}.6-8)

The same role of Mg^{2+} has also been reported for the reaction of deazaflavin analog,9) where the stereochemistry of the oxidation of deazaflavin analog with an NAD(P)H analog is controlled by the orientation of a polar substituent as well as the presence or absence of Mg^{2+}. The observation affords an insight into the stereochemical driving force of enzymatic reactions.

Further studies on this series including kinetic measurements are in progress and will be reported in due course.

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