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NAD (P)$^+$-NAD (P)H Models. 69. Mechanism of Stereospecific (NET) Hydride Transfer Controlled by Electronic Effect

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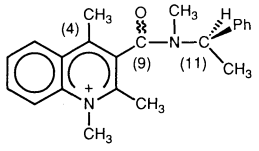
The enantiotopic C_4-hydrogen in Me_3MQPH is abstracted stereospecifically by certain oxidizing reagent such as metal ions and quinones. The stereospecificity depends on the reactivity of the oxidizing reagent. Namely, in the oxidation with Fe(III) or Co(III) ion, a Brønsted-like correlation is observed between the specificity and pK_a of amine added to the reaction system, whereas the stereospecificity of the oxidation with quinones is not affected by amine. The mechanism of this electronically controlled stereospecificity is discussed.

In previous papers of this series from our laboratory,[1] it was reported that 3-(*N*-methyl-*N*-α-methylbenzyl)-carbamoyl-1,2,4-trimethylquinolinium cation (Me_3MQP^+) is reduced by certain reducing reagent into 3-(*N*-methyl-*N*-α-methylbenzyl)carbamoyl-1,2,4-trimethyl-1,4-dihydroquinoline (Me_3MQPH).[1-4] The former compound has an axial chirality with respect to the ring-C_3-carbonyl carbon single bond because the free rotaion of this carbonyl group is prohibited. Although the free rotation of the carbonyl group in the latter compound is allowed, it has a central chirality at the ring-C_4 position. These two different kinds of chiralities are interconverted each other on reduction and oxidation. However, the stereospecificity associated with the redox reactions varies largely from racemic to quantitative and the specificity of the reduction from Me_3MQP^+ to Me_3MQPH varies from 33% e.e. to more than 98% e.e. depending on the reducing reagent employed.[3,4] Using a chiral reducing reagent, it has been demonstrated that the reacting face of Me_3MQP^+ is strictly defined and the orientation of the carbonyl group plays a crucial role in determining the reacting face.[4,5] At the same time, oxidation of Me_3MQPH to Me_3MQP^+ takes place with a variety of stereospecificity and, sometimes, the reversion of the configuration, say, from the *R*- to the *S*-preferency or vice versa, is observed.[6-8] Both in oxidation and reduction, the (net) hydride syn to the carbonyl-oxygen seems to be more reactive than the anti one.

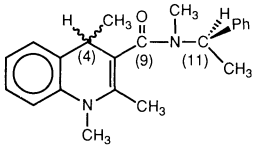
When a series of substituted benzoquinones are employed as the oxidants, a good linear free energy relationship (LFER) can be observed between the half-wave reduction potential of the quinone and logarithm of the stereospecificity; the logarithmic ratio of the yields of (*R*)- and (*S*)-Me_3MQP^+ (log *R*/*S*).[6] On the other hand, when a series of β-diketonato complexes of metal ions are subjected to the oxidation, LFER no more holds. Instead, the reactivity (measured as the yield of Me_3MQP^+ after 24 hours of the reaction) seems to have certain extent of the linear relationship with log *R*/*S*.[7]

Since substituents in both benzoquinones and metal complexes have no appreciable difference in steric bulkiness, steric effect is not a candidate to explain the difference in stereospecificity of the reactions. Thus, we believe that the stereospecificities observed in these redox reactions are controlled solely by an electronic effect. There has been only one example, to the author's best knowledge, in which the variation in stereospecificity can be accounted for by the electronic effect from the substituent.[9]

In order to elucidate the mechanism to control the stereochemistry of the reaction by electronic effect, we have studied the reaction in detail and found that the presence of an amine affects the stereochemistry in the oxidation of Me_3MQPH by certain class of oxidizing reagents, whereas the oxidation by other oxidizing reagents is not affected by amines. This report will describe the mechanism of amine-controlled stereochemistry and, at the same time, the total aspects of the mechanism of (net) hydride transfer from a carbon-hydrogen bond in a dihydropyridine ring.



(11*R*)-Me_3MQP^+



(11*R*)-Me_3MQPH

Results

(4*R*)-Me_3MQPH was reacted with two equivalent amounts of tris(1,10-phenanthroline)Fe(III) ion, Fe(phen)$_3^{3+}$, or with tris(2,2′-bipyridine)Co(III) ion, Co(bpy)$_3^{3+}$, in acetonitrile at room temperature under an argon atmosphere for 7 h (for Fe(phen)$_3^{3+}$) or 12 h (for Co(bpy)$_3^{3+}$) in the dark in the presence or absence of an equivalent amount of amine or of Mg(II) ion.

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Table 1. Effect of Base on the Stereochemistry of Oxidation of (4*R*)-Me_3MQPH with $Fe(phen)_3^{3+}$

No.	Amine	pK_a	Diastereomer ratio/ (*R*/*S*)[a]	Chemical yield/%
1	Mg^{2+}	—	1/3.3	88
2	None	—	1/2.8	94
3	4-Nitroaniline	1.11	1/1.8	88
4	3-Cyanopyridine	1.45	1/1.8	98
5	3-Nitroaniline	2.47	1/1.3	83
6	3-Acetylpyridine	3.18	1/1.5	68
7	3-Chloroaniline	3.50	1/1.5	79
8	2-Naphthylamine	4.10	1/4.3	76
9	2,2′-Bipyridine	4.12	1.2/1	60
10	2-Methylaniline	4.45	1/3.1	100
11	3-Phenylpyridine	4.58	1/1.1	72
12	Aniline	4.60	1/2.7	84
13	8-Methylquinoline	4.60	1.3/1	79
14	3-Methylaniline	4.72	1/2.2	100
15	4,4′-Bipyridine	4.82	1.2/1	99
16	*N*,*N*-Dimethylaniline	5.06	1/3.3	71
17	4-Methylaniline	5.10	1/2.1	75
18	Pyridine	5.29	1.0/1	70
19	4-Methoxyaniline	5.34	1/2.4	75
20	2-Methylquinoline	5.42	1/1.1	82
21	3-Methylpyridine	5.79	1.2/1	90
22	4-Methylpyridine	5.98	1/1.2	83
23	1-Methylimidazole	7.33	1.3/1	73
24	2-Methylimidazole	7.56	1.4/1	94
25	1,2-Dimethylimidazole	7.85	1.2/1	91
26	4-Aminopyridine	9.17	1.3/1	92
27	4-(Dimethylamino)pyridine	9.71	1.1/1	63
28	1,8-Bis(dimethylamino)-naphthalene (H^+-Sponge)	12.3	1/3.4	72

a) Diastereomeric ratio in Me_3MQP^+.

Table 2. Effect of Base on the Stereochemistry of Oxidation of (4*R*)-Me_3MQPH with $Co(bpy)_3^{3+}$

No.	Amine	pK_a	Diastereomer ratio/ (*R*/*S*)[a]	Chemical yield/%
1	Mg^{2+}	—	1/6.2	76
2	None	—	1/7.7	58
3	4-Nitroaniline	1.11	1/6.2	75
4	3-Cyanopyridine	1.45	1/5.8	67
6	3-Acetylpyridine	3.18	1/4.4	65
12	Aniline	4.60	1/5.6	76
14	3-Methylaniline	4.72	1/8.1	55
21	3-Methylpyridine	5.79	1/5.4	82
24	2-Methylimidazole	7.56	1/3.0	77
25	1,2-Dimethylimidazole	7.85	1/3.0	88
26	4-Aminopyridine	9.17	1/1.7	53
27	4-(Dimethylamino)pyridine	9.71	1/2.9	50

a) Diastereomeric ratio in Me_3MQP^+.

The syn/anti selectivity[10] of the reaction was monitored by measuring relative intensities of the signals from protons in the methyl group of the reaction products, (*S*)- and (*R*)-Me_3MQP^+, by 200 MHz ^1H NMR spectroscopy. Chemical yield was also monitored on a ^1H NMR spectrum with an internal standard of 1,1-diphenylethylene. Results are summarized in Tables 1 and 2.

In the oxidation of Me_3MQPH with a series of quinones, the presence of amine did not affect the stereochemical result of the reaction. The oxidations with β-diketonato complexes of Fe(III), Co(III), and other metal ions did not proceed in the presence of an amine, probably because the amine chelates onto the metal ion resulting in the decrease in its oxidizing power.

Discussion

When logarithm of the *R*/*S* ratio is plotted against the pK_a of amine, it is recognized that a linear free

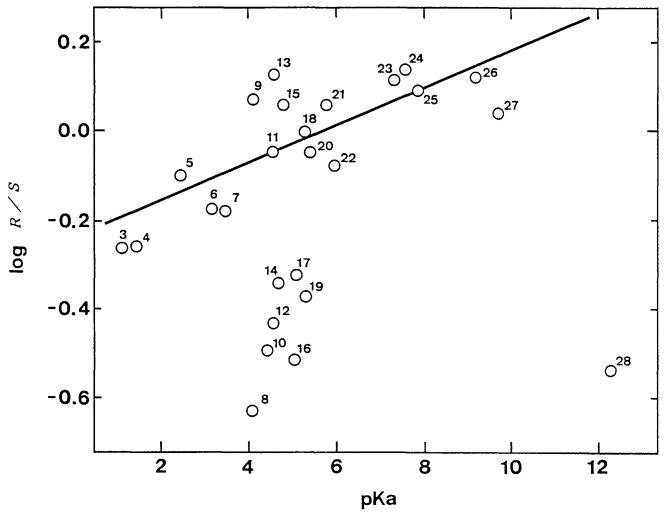


Fig. 1. The linear free energy relationship observed for the stereoselectivity and the pK_a of conjugated acid of amine in the oxidation of (4*R*)-Me$_3$MQPH with Fe(phen)$_3^{3+}$. The numbers correspond to those listed in Table 1.

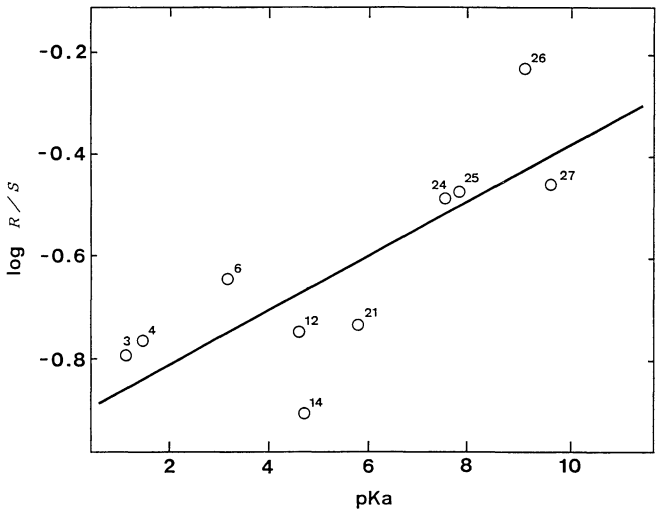


Fig. 2. The linear free energy relationship observed for the stereoselectivity and the pK_a of conjugated acid of amine in the oxidation of (4*R*)-Me$_3$MQPH with Co(bpy)$_3^{3+}$. The numbers correspond to those listed in Table 2.

energy relationship, the Brønsted-type correlation, exists except for a particular group of amines of pK_a 4—6 as depicted in Figs. 1 and 2. That is, stereochemistry of the oxidation of Me$_3$MQPH by Fe(phen)$_3^{3+}$ or Co(bpy)$_3^{3+}$ ion is affected by the basicity of the amines. This is not true in the oxidation with a series of non-DDQ quinones.[11] It should be noted that the metal cations have much higher oxidizing power than the quinones. The influence of amines on the present oxidation reaction indicates that the stereo-determining step in the reaction with a metal ion,

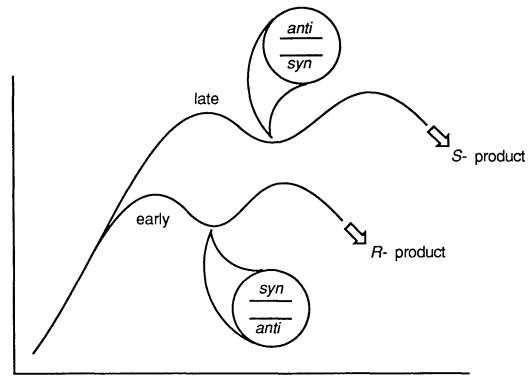


Fig. 3. Schematic energy diagram for the oxidation of (4*R*)-Me$_3$MQPH with quinones, where the first process contributes mainly to the rate-determining step.

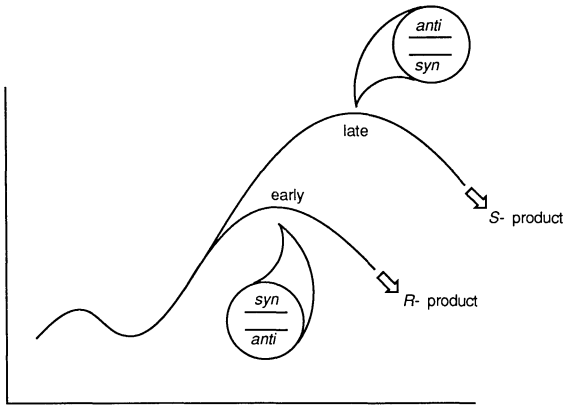


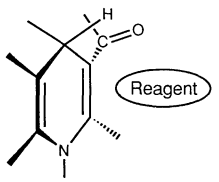
Fig. 4. Schematic energy diagram for the oxidation of (4*R*)-Me$_3$MQPH with metal ions, where the second process contributes mainly to the rate-determining step.

which has a high oxidation potential, involves a process of proton-transfer (or, more precisely, a process which can be a subject of base-catalysis) as the rate-determining step, whereas the stereoselectivity of the reaction with a substrate of low oxidizing power such as quinones is determined in a step which is not affected by the presence of a base, or non-proton-migrating process. The Hammett-type correlation observed in the reaction of quinones suggests that this initial process is equivalent to the electron-transfer.

Based on the observation described above, we can propose energy diagrams for the reactions as depicted in Figs. 3 and 4, provided the following two important assumptions are acceptable.

1. The reaction involves at least one diastereomeric charge-transfer intermediate.

2. The syn-type structure (**1**) is more preferred than the anti-type structure (**2**) when the proton-acceptor comes closer to the intermediate at the transition-state of the proton-transfer process or vice versa.



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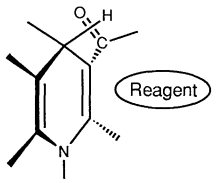

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In Fig. 3, which represents the reactions with quinones, the formation of the intermediate is reversible and rate-determining. The transition-state for the initial electron-transfer step comes earlier in the reaction with a substrate of high oxidation potential than that with a substrate of low oxidation potential, and the charge-transfer complex intermediate formed from a substrate of the former type has looser interaction between the electron-donor and -acceptor than the complex from a substrate of the latter type. Since the charge-transfer electron-acceptor is at the same time the proton-accepter in this reaction, and since the proton-transfer is a fast process, the transition-state for the proton-transfer process has tighter structure in the reaction with a substrate of low oxidation potential than in the reaction with a substrate of high oxidation potential. Therefore, the assumption 2 predicts that the reaction with a substrate of high oxidation potential tends to produce the *R*-product, whereas a substrate of low oxidation potential prefers to produce the *S*-product. Thus, the proton-transfer step is fast in the reaction with quinones, the base-catalysis is not observed. When the reactivity, or the oxidizing power, of a substrate becomes stronger, the energy level of the intermediate is lowered remarkably and the electron-transfer process is no more the rate-determining as shown in Fig. 4. In other words, there is no meaningful difference in stability of the syn- and anti-type intermediates in this reaction. Rather, the interaction between the electron-donor and -acceptor in the charge-transfer complex is very weak in this reaction. On the other hand, since the proton-abstraction process is now the rate-determining, a stronger base catalyzes the reaction more efficiently than a weak base and the transition-state for the former reaction comes earlier than that in the latter reaction. Again, the assumption 2 predicts that the former reaction produces the *R*-product, whereas the latter reaction produces the *S*-product, predominantly. Without added amine, acetonitrile, the solvent, plays a role of a base and this very weak base requires very tight interaction at the transition-state of proton-abstraction to afford the *S*-product predominantly.

The above explanation explains why the reaction with metal ions exerts a Brønsted-type correlation with the pK_a of the catalyzing amines instead of a Hammett-type correlation with the oxidation potentials of the metal ions.[13]

The energy diagrams drawn in Figs. 3 and 4 are the same with that proposed previously based on kinetics and thermodynamics,[14–16] where the proposal offered an initial electron-transfer to form a charge-transfer intermediate and the proton-transfer from the intermediate as the second step. However, it was impossible to prove the presence of an intermediate of relatively high energy-level unequivocally from the viewpoint of kinetics and thermodynamics, and successive electron and proton transfers cannot be distinguished from a one-step hydrogen-transfer process.[12,17–20] However, stereochemical viewpoint, which has a background entirely different from kinetics and thermodynamics, has succeeded to prove the existence of an intermediate of high energy-level along the reaction coordinate of (net) hydride-transfer. The energy diagram proposed herein does not contradict to the observation and proposal by Miller and his co-workers that DDQ exerts an exceptional behavior among other quinones in the oxidation of *N*-benzyl-1,4-dihydronicotinamide (BNAH):[12] this strongly electron-deficient quinone produces as stable intermediate complex as those from metal ions and the stereochemical course from this intermediate turns out to be the *S*-preference.

The energy diagram explains why the reaction of Fe(III) complex ($E°$=1.07 V)[21] is so largely affected by amines as to invert its stereospecificity, whereas the Co(III) complex ($E°$=0.30 V)[21] is not affected so seriously: the Marcus theory[22] predicts that the less reactive $Co(bpy)_3^{3+}$ requires higher activation energy for the initial electron-transfer process than the $Fe(phen)_3^{3+}$. Therefore, the stereo-determining proton-transfer process becomes more important in the reaction with $Fe(phen)_3^{3+}$ than that in the reaction with $Co(bpy)_3^{3+}$.

Fukuzumi and his co-workers have studied the kinetics of the amine-catalyzed reaction of $Fe(phen)_3^{3+}$ with BNAH extensively.[23] They proposed that an electron is transferred from BNAH to $Fe(phen)_3^{3+}$ at the initial step. In the second step, a proton in the resulted cation-radical, $BNAH^{+\cdot}$, is abstracted by an amine to afford a free radical, BNA·, which is followed by another electron-transfer process to yield the final products. Thus, the mechanism proposed by the present authors on the bases of stereochemistry again coincides with that proposed on the bases of kinetics.

Substituted anilines of pK_a 4—6 behaved differently from other amines (Fig. 1). Although, at present, the authors have no conclusive explanation for this special effect, the deviation from the linear relationship can be understood in terms of tight interaction to predominate the syn-route. All the amines in this class except for *N*,*N*-dimethylaniline have a proton or protons to hydrogen bond onto the carbonyl oxygen in Me_3MQPH. Further studies are required to obtain a

conclusion on this phenomenon.

The stereochemistry controlled by electronic effect can be seen in the reactions catalyzed by dehydrogenases.[24] Hence, the present observation seems to provide, from the viewpoint of organic chemistry, an important evidence on the mechanism of chemical evolution of isozymes. In order to make the stereochemical proof unequivocal, relative stability of the syn- and anti-type structures, which was assumed at the beginning of the present discussion without any scientific reason, should be elucidated. The order in stability proposed for the syn- and anti-type structures should also be witnessed in the future.

Experimental

Instruments. ^{1}H NMR spectra were recorded at 100 and 200 MHz on a JEOL JNM-FX100 FT and Varian VXR 200 FT NMR spectrometers, respectively. IR spectra were recorded on a Hitachi EPI-S2 infrared spectrometer. UV-visible spectra were recorded on a Union Giken SM-401 spectrophotometer. Elemental analyses were perfomed with a Yanaco MT-3 elemental analyzer.

Materials. Me_3MQP^+,[3] Me_3MQPH,[3] $Fe(phen)_3(ClO_4)_3 \cdot H_2O$,[21] and $Co(bpy)_3(ClO_4)_3 \cdot 3H_2O$[25,26] were synthesized according to the literature procedures, respectively. The stability of axial and central chiralities in Me_3MQP^+ and Me_3MQPH, respectively, under the reaction conditions was confirmed previously.[3] Tetrahydrofuran was distilled in the presence of sodium ketyl of benzophenone. Acetonitrile was distilled over diphosphorus pentaoxide. Magnesium perchlorate was powdered, dried at 100 °C under reduced pressure in the presense of diphosphorus pentaoxide, and kept in a vacuum-sealed tube. Other reagents were purchased from commercial sources. Metal complexes were purified by recrystallization.

Oxidation of Me_3MQPH. In a 50 mL round-bottomed flask equipped with a magnetic stirrer and sealed with a serum cap, 0.06 mmol of a metal complex was placed. The atmosphere inside the flask was replaced with argon and 8 mL of acetonitrile was injected through a syringe. To the solution, 10 mg (0.03 mmol) of (4*R*,11*R*)-Me_3MQPH (and 0.03 mmol of a base, if necessary) in 7 mL of acetonitrile was injected through a syringe. The mixture was stirred for 7 h (for oxidation with $Fe(phen)_3^{3+}$) or 12 h (for oxidation with $Co(bpy)_3^{3+}$) at room temperature in the dark. After the evaporation of the solvent below 40 °C, Me_3MQP^+ was extracted with THF from the residue. After the evaporation of THF, crude Me_3MQP^+ was dissolved in CD_3CN and subjected to ^{1}H NMR spectroscopy to elucidate the diastereomer ratio and the yield of the product. The procedure for the quantitative analyses was described in the previous paper.[3] Results are listed in Tables 1 and 2.

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1) α-Methylbenzyl group used in the present work always has the *R*-configuration. In order to make the discussion clear, Me_3MQP^+ and Me_3MQPH will be regarded as enantiotopic molecules ignoring the chirality at the benzylic position. It has been confirmed that the chirality at the benzylic position exerts little effect, if any, one the stereochemistry of the reaction.[2]

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13) Entirely different explanation may be possible based on different assumptions. However, unpublished results from our laboratory on kinetic deuterium isotope effect, deuterium isotope effect on stereochemistry, the effect of reactivity of the NAD(P)H models on stereochemistry, and the effect of added magnesium ion on the stereochemistry in the reaction with quinones, which will be published elsewhere in near future, also support the proposal.

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