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Accounts

Stereoselection without Steric Effect but Controlled by Electronic Effect: Important Contribution of Ground State

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Stereoselectivity controlled by an electronic effect but not by a steric effect is presented. A modern concept of stereochemistry is proposed where stereochemistry is controlled by acceleration of the reaction instead of deceleration, as has been proposed based on classical concept. The mechanism of (net) hydride transfer from a dihydronicotinamide adenine dinucleotide (NADH)/dihydronicotinamide adenine dinucleotide phosphate (NADPH) analogue to certain oxidizing agents is discussed in relation to this modern stereochemistry concept. The reaction involves a preassociation complex where the stereochemistry of the reaction is defined. Only a complex that has appropriate intermolecular arrangement can proceed to the transition state. The difference in free energy between the two stereoisomers of the preassociation complex contributes to almost all of the difference in the free energy of activation for the stereoisomers in the transition state, then to the ratio of stereoisomers in the product. Thus, the transition state does not participate in determining the stereochemistry of the reaction.

Similarities between the present and enzymatic reactions from the viewpoint of the reaction scheme are also suggested.

Classical theory of steric effect predicts that a reaction takes place in an open face; i.e., when a reacting carbon center is substituted by large, medium, and small substituents, a steric barrier prevents the center from the reaction, and the attacking reagent approaches the reaction center in the face occupied by the smallest substituent (Fig. 1a). In other words, stereoselectivity of a reaction is achieved with inevitable deceleration of the reaction, according to the classical concept.

Quite often, the transition state of a reaction is proposed, without reasonable evidence, to form a six-membered ring regardless of the kind of constituent atoms. Generally, the open site of this six-membered ring system is proposed to be the reaction site in order to explain the stereochemical result of a reaction. It should be noted, however, that a six-membered ring in the chair form is most stable only when the system is composed of tetrahedral carbon atoms. A hydrogen-bonding system, for example, is most stable when X–H···Y system is arranged linearly. It is evident that such an explanation of a transition-state structure without evidence has little scientific significance for understanding the reaction. The stereochemical result yielded by the difference in the steric bulk of substituents is obvious; thus, there is no need to further explain the result using this concept.

On the other hand, modern concepts of stereoselection predict that stereoselectivity can be induced by accelerating the reaction; when a polar substituent attracts the attacking reagent, one face of reacting center that involves the substituent acquires a greater possibility of the occurrence of the reaction in spite of larger steric hindrance in this face. If this attracting force is also effective for reducing the free energy of activation, then the stereoselection observed in this system is associated with the acceleration of the reaction (Fig. 1b). An enzyme catalyzes a reaction and, at the same time, exerts perfect stereoselectivity. Here, the reactivity-selectivity principle is violated.

The interaction between the substituent and the attacking reagent is not necessarily attractive. Repulsive interaction will push the attacking reagent away from the substituent, increasing the effective concentration of the attacking reagent in the other face; then a more facile reaction will take place in this open face. The entropically accelerating effect proposed by the modern concepts of stereochemistry contrasts with the entropically decelerated reaction proposed in the classical concept.

An enantioface-differentiating (net) hydride transfer between 1-benzyl-1,4-dihydronicotinamide, abbreviated by us to **BNAH**, and 3-aryl-10-(4-*t*-butylphenyl)pyrimido-[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione (**dFl$_{ox}$**; a 5-deazaflavin model) shown in Scheme 1 provides an example of this stereoselection in the modern concept.[1—4] **dFl$_{ox}$** has atropisomerism with respect to the axis between N(3) and the aryl substituent on it. The face that includes the substituent R is defined as *syn* and the other as *anti*.

The reaction hardly proceeds at all in the absence of a

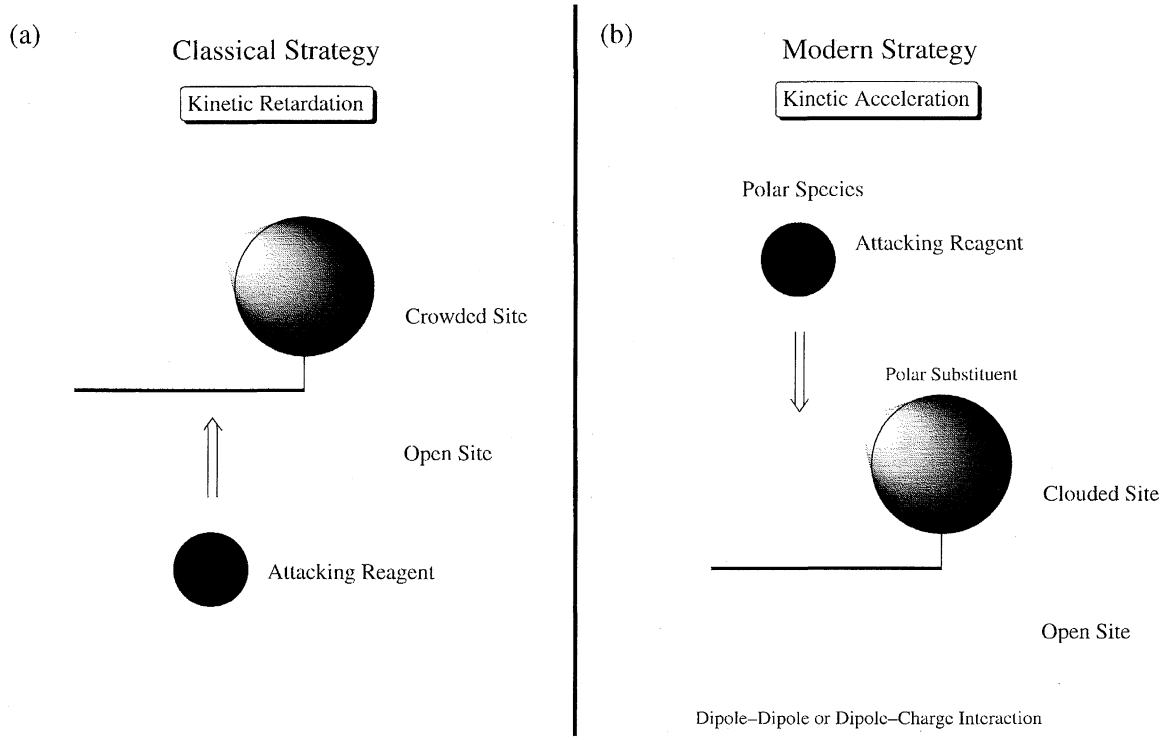
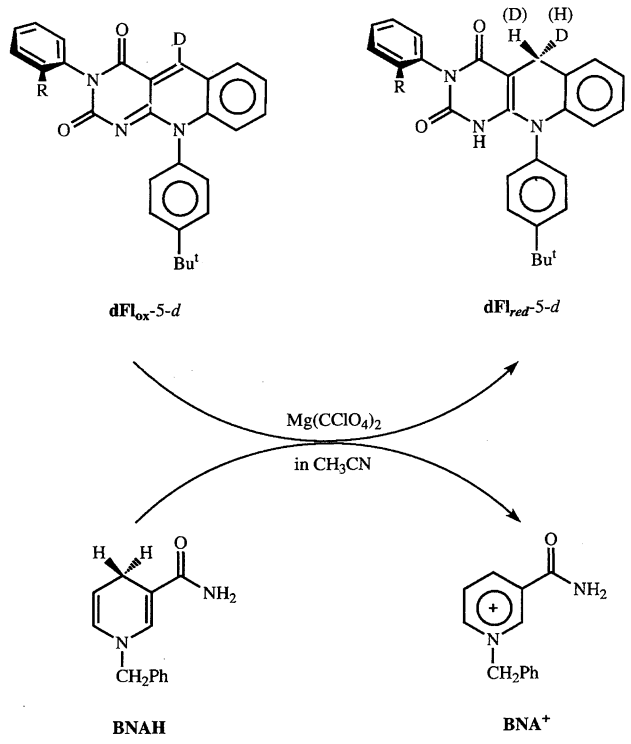


Fig. 1. Schematic representations for (a) classical and (b) modern concept of stereoselection.



Scheme 1.

Lewis acid, Mg^{2+}; i.e., the reaction is catalyzed by magnesium ions. When R in the aryl group is a methyl, trifluoromethyl or *t*-butyldimethylsilyloxymethyl (TBDMSOCH$_2$), the (net) hydride from **BNAH** attacks C(5) of **dFl$_{ox}$** in the *anti* face with respect to the R group, because steric hindrance in the classical sense prevents the *syn* face from being a site of the reaction and only the *anti* face is open to the reaction; the results are listed in Table 1.

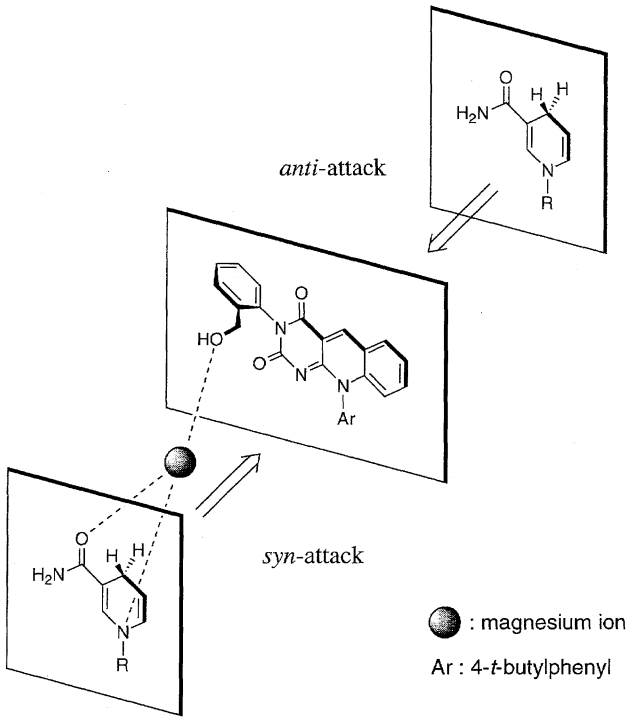
On the other hand, when the reaction of a compound with R = CH_2OH is induced in the presence of magnesium ions, the stereoselectivity changes to *syn* preference, where the (net) hydride attacks C(5) of **dFl$_{ox}$** in the *syn* face. Thus, a hydroxy group coordinates onto the magnesium ion which, in turn, attracts **BNAH** to form a **BNAH**–Mg^{2+}–**dFl$_{ox}$** ternary complex[5] and the chemical reaction takes place in this ternary complex (Scheme 2). It is apparent from the time necessary to complete the reaction (Table 1) that a combination of the hydroxymethyl group and a magnesium ion significantly accelerates the reaction. Consequently, the face that includes the hydroxymethyl group becomes more reactive and selective than the other face.

The stereochemical reversion does not take place for this compound when the reaction is catalyzed by a Brønsted acid, which is not only much less effective catalyst than a Lewis acid but is also unable to attract **BNAH** to form a ternary complex.

Table 1. Enantioface-Differentiating (Net) Hydride Transfer between **dFl$_{ox}$**-5-*d* and **BNAH**

R in **dFl$_{ox}$**-5-*d*	Catalyst (equiv)[a]	Reaction time/min	Ratio of reacting faces, *syn* : *anti*
CH_2OH	$Mg(ClO_4)_2$ (5)	10	78 : 22
	CCl_3CO_2H (10)	60	31 : 69
CH_3	$Mg(ClO_4)_2$ (5)	180	30 : 70
$CH_2OTBDMS$	$Mg(ClO_4)_2$ (5)	180	20 : 80
CF_3	$Mg(ClO_4)_2$ (5)	120	29 : 71

a) Equivalency to **dFl$_{ox}$**-5-*d*.



Scheme 2.

The most important point is that intermolecular arrangement at the ternary complex is crucial for realizing the observed stereochemistry. The arrangement at the transition state is a consequence of the intermolecular arrangement at the ground state. The ternary complex with the correct arrangement can proceed to the transition state and others dissociate to return to individual molecules. The situation is similar to the formation of a Michaelis (ES) complex in enzymatic reactions. In order to obtain further insight into the driving force in the construction of a particular arrangement of molecules to accelerate the reaction, we studied stereochemistry, thermodynamics, kinetics, spectroscopies, and other characteristics of a series of reactions that exert electronic effects on the stereochemical results.

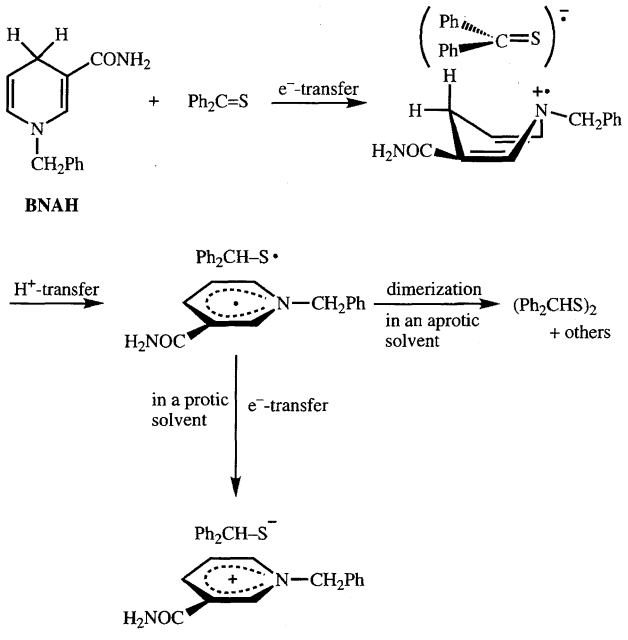
The author would like to emphasize that the electronic effect that will be discussed in this account is entirely different from the well-known stereoelectronic effect.[6—9] The latter effect is intrinsic to a single molecule, whereas the former operates as a relativistic effect of two (or more) reacting molecules.

1. Electron-Transfer in the Reaction of NAD Analogues

Ables et al. reported that **BNAH**, a model of dihydronicotinamide adenine dinucleotide (NADH)/dihydronicotinamide adenine dinucleotide phosphate (NADPH), transfers a hydride to thiobenzophenone, a model of biologically active ketones, via a one-step process.[10] From our studies on the chemistry of thiobenzophenone, we concluded that this compound is a very efficient one-electron acceptor.[11,12] Electronegativities of carbon and hydrogen atoms indicate that a carbon–hydrogen bond stretches in order to allocate a partial positive charge on the hydrogen atom while a partial negative charge remains on the carbon atom. In a hydrogen-transferring system, a carbon–hydrogen bond, for example, is stretched along the reaction coordinate to dissociate the hydrogen. Therefore, we wanted to determine how a "hydride" can leave a carbon. Reinvestigation of the system proposed by Ables et al. using the more sophisticated techniques of ESR and NMR spectroscopies, revealed that the reaction initially affords a radical-ion pair as an intermediate via an electron transfer.[13] This radical-ion pair is converted into a pair of free radicals via a proton transfer within the pair. The final products depend on the property of the solvent; a polar protic solvent stabilizes an ion pair, stimulating another electron transfer to give the corresponding pair of diphenylmethanethiolate and 1-benzyl-3-carbamoylpyridinium ions, whereas a nonpolar solvent is unable to stabilize ionic species and results in the formation of bis(diphenylmethyl) disulfide, a radical-coupling product, and other unidentifiable compounds (Scheme 3).[13]

There is an inevitable disadvantage associated with spectroscopic studies; the species may be abortive and those detected are not necessarily reaction intermediates. Studies on electronic effects such as the substituent effect and solvent effect contribute very little to elucidating the reaction mechanism, because both one-step hydride transfer and multi-step electron–proton–electron (or electron–hydrogen atom) transfer mechanisms predict that a negative charge is transferred at the transition state of the rate-determining step.

Sometimes, a fatal discrepancy between the values of the kinetic isotope effect and the isotopic ratio in the product, which we call the "product isotope effect", is observed.[14—18] This has been attributed to the presence of at least one reaction intermediate along the reaction coordinate. However, this argument again was criticized on the basis of the contribution of some side reactions. Namely, contamination by a trace amount of water in the solvent was pointed out as



Scheme 3.

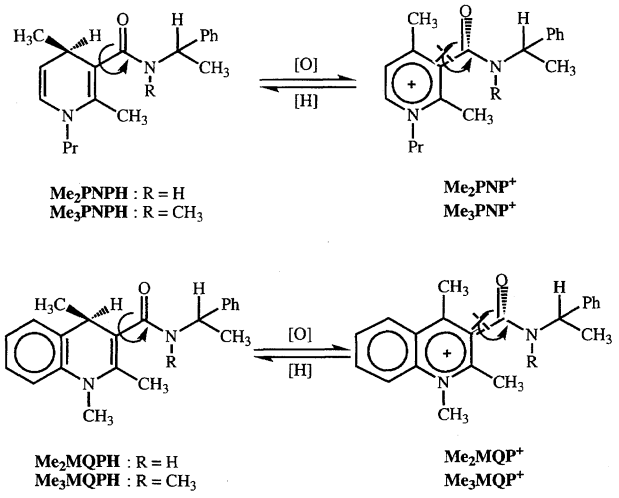
crucial in the discrepancy.[19,20]

Thus, it has been difficult to obtain evidence to understand the driving force of this *net* hydride transfer process by means of the conventional methodology used in physical organic chemistry.

2. Enantioselectivity Dependent on Chemical Potential

We were the first to report an example of the conversion of a central chirality into an axial chirality (chirality sink) or vice versa in the oxidation or reduction of **Me$_n$PNPH/Me$_n$PNP$^+$** and **Me$_n$MQPH/Me$_n$MQP$^+$** (n = 2 or 3), respectively (Scheme 4).[21—24] The phenomenon was observed during our studies on stereospecific reactions with NADH/NADPH analogues.[25,26]

In these redox processes, stereochemical yields change with a change in the reactivity of the attacking reagent. For example, the enantioselectivity in the reaction of 2,4-dimethyl-3-[*N*-(1-phenylethyl)carbamoyl]-1-propyl-1,4-dihydropyridine (**Me$_2$PNPH**) with a series of *p*-benzoquinones changes linearly with the change in reduction potential of the quinone, as shown in Fig. 2.[21] It is necessary to note here that the quinones that afford the *syn*-product predominantly (*syn* selectivity) require the catalysis by a magnesium ion.



Scheme 4.

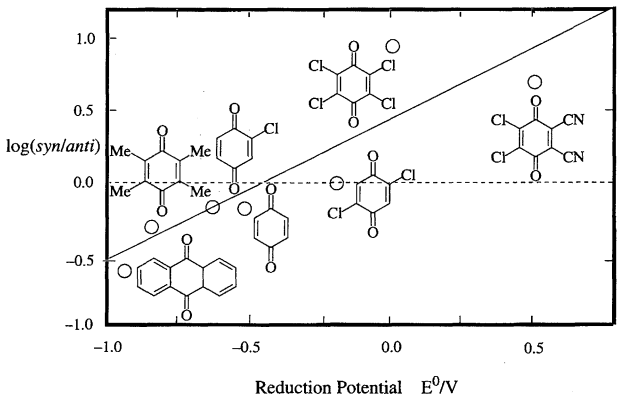


Fig. 2. Linear relationship between stereoselectivity and reduction potential in the oxidation of **Me$_2$PNPH** with a series of quinones.

The role of magnesium ions will be discussed later in detail (vide supra). The linear dependence observed between the efficiency of chirality preservation and the reagent reactivity is not only limited to the reduction potential of the oxidizing agent but also kept between the basicity of amine as a catalyst and the reagent reactivity (Brønsted-type relationship) in anodic oxidation, as illustrated in Fig. 3.[27]

Interestingly, a similar relationship is seen in nature; the reactivity of a substrate influences the stereochemistry of the reaction mediated by NADH/NADPH-dependent dehydrogenases and reductases.[28—31] Similar phenomena in biochemical and organic systems indicate that essentially the same factor is responsible as the driving force of the reactions in both systems. In other words, the search for the driving force for the dissociation of a (net) hydride from a carbon–hydrogen bond has significance not only in physical organic chemistry but also in biochemistry in relation to the chemical evolution of redox enzymes.

Axial chirality is more sophisticatedly preserved in 1,4,6,7-tetrahydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido-[2,3-*e*]azepin (**11Me-MMPAH**), where the rotation of the side-chain amide group is prohibited by a cyclic structure (Scheme 5).[32,33] Kinetics on this (**1**) and its deuteriated analogues (**2**—**4**) afford various important parameters according to Eq. 1 through Eq. 4.

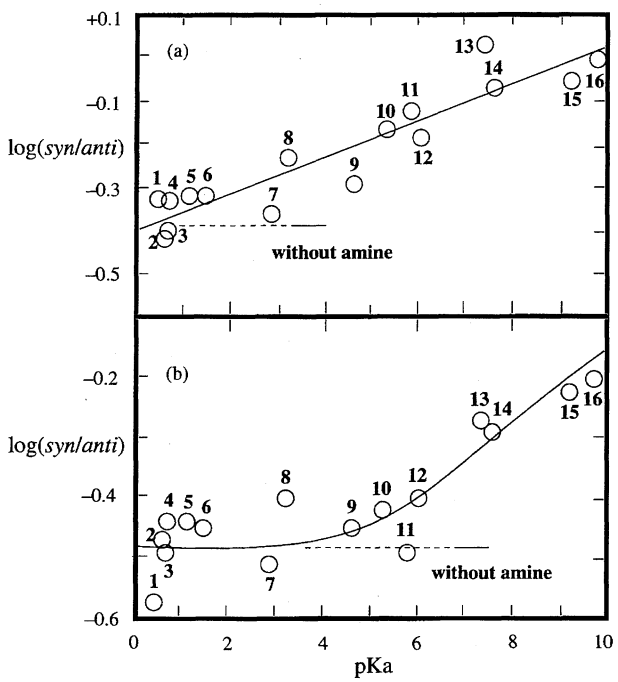
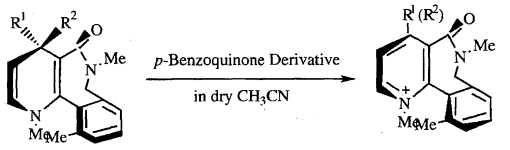


Fig. 3. Linear relationships between stereoselectivities and basicity of amine in the anodic oxidation of (a) **Me$_3$PNPH** and (b) **Me$_3$MQPH** in the presence of a series of amines: **1**, 2-fluoropyridine; **2**, 4-nitro-*N*,*N*-diethylaniline; **3**, 3,5-dichloropyridine; **4**, 2-chloropyridine; **5**, 4-nitroaniline; **6**, 3-cyanopyridine; **7**, 3-chloropyridine; **8**, 3-acetylpyridine; **9**, 3-phenylpyridine; **10**, pyridine; **11**, 3-methylpyridine; **12**, 4-methylpyridine; **13**, 1-methylimidazole; **14**, 2-methylimidazole; **15**, 4-aminopyridine; **16**, 4-(*N*,*N*-dimethylamino)-pyridine.



11Me-MMPAH : $R^1 = R^2 = H$: **1**
11Me-MMPAH-7_{anti}-*d* : R^1 = D (80%), R^2 = H (80%) : **2**
11Me-MMPAH-7_{syn}-*d* : R^1 = H (80%), R^2 = D (80%) : **3**
11Me-MMPAH-7,7-d_2 : $R^1 = R^2 = D$: **4**

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

Scheme 5.

$$Y^H/Y^D = F[(2\beta - 1)\alpha + (1 - \beta)]/[\beta - (2\beta - 1)\alpha], \quad (1)$$

$$k_4S^2 - (k_2 + k_3)S + k_1 = 0, \quad (2)$$

then

$$S = [(k_2 + k_3) - \{(k_2 + k_3)^2 - 4k_1k_4\}^{1/2}]/2k_4, \quad (3)$$

$$P = (k_1/k_4)/S = [(k_2 + k_3) + \{(k_2 + k_3)^2 - 4k_1k_4\}^{1/2}]/2k_4, \quad (4)$$

where Y^H/Y^D, α, and β denote the product isotope effect, *anti* selectivity (the proportion of anti hydrogen to the total hydrogens reacted), and isotopic purity of D at the *syn* position (at the same time, the purity of H at the *anti* position), which is equal to 0.8 for **2** and 0.2 for **3** in the present experiments. F is a factor that is introduced to adjust for the discrepancy between kinetic and product isotope effects. The parameter F to be mentioned later is the intrinsic product isotope effect that will be observed if *syn* and *anti* hydrogens had the same reactivity. P and S are primary and secondary deuterium kinetic isotope effects, respectively, and k_is stand for the rate constants for the oxidation of compound ***i*** (***i*** = **1**, **2**, **3**, or **4**).

The parameters thus calculated are summarized in Table 2. The calculated values of P and S agree well with those previously obtained for the oxidation of **BNAH** with a series of *p*-benzoquinone derivatives[34] and those reported elsewhere.[15,35—37] The large P value indicates that the transition state of oxidation is composed largely of a transferring hydrogen nucleus. Normal and moderate values of S may suggest that the stretching mode of the carbon–hydrogen bond contributes largely to the transition state of the rate-determining step. Enzymatic reactions exert greater secondary isotope effects than those observed in model systems.[38—40] Contributions of a bending mode and a tunneling effect to the reaction coordinate have also been suggested for these enzymatic reactions.[41]

Table 2. Kinetic Primary (P) and Secondary (S) Isotope Effects, Intrinsic Product Isotope Effect (F), and *anti*-Selectivity Parameter (α) in Oxidation of **11Me-MMPAH** and Its Deuterated Analogues with a Series of *p*-Benzoquinone Derivatives[a]

p-Benzoquinone derivative	E^0/V[b,c]	P	S	F	α
p-Chloranil	0.01	4.19	1.12	1.2	0.97
p-Bromanil	0.00	4.19	1.13	1.3	0.97
Trichloro-*p*-benzoquinone	−0.09	—	—	1.9	0.93
2,6-Dichloro-*p*-benzoquinone	−0.18	—	—	2.3	0.87
2,5-Dichloro-*p*-benzoquinone	−0.18	3.09	1.07	2.4	0.87
Chloro-*p*-benzoquinone	−0.34	—	—	2.6	0.78

a) In CH_3CN at 298 K. b) Reduction potential of quinone. c) Ref. 34.

The α value of 0.97 in the reaction with *p*-chloranil indicates that the ratio of reactivities of *syn* and *anti* hydrogens is 3/97, i.e., the *anti* hydrogen is 32 times more reactive than the *syn* hydrogen. The value decreases as the reactivity (reduction potential) of the quinone decreases. On the contrary, the F value increases as the reactivity of the quinone decreases. Since factor F has been introduced as a nonkinetic parameter, the value should reflect isotopic discrimination at the ground state.

The preceding discussion and much of the evidence previously reported lead the author to conclude that the reaction has a preequilibrium state, and the isotope effect on the equilibrium constant for this preequilibrium is factor F (Scheme 6). In Scheme 6, Q and M_{XY} represent a quinone and **11Me-MMPAH** substituted by X and Y at C(7), respectively, and k_Y^X is the rate constant for the reaction of atom Y on C(7) which is substituted by an atom X. Suffixes X and Y stand for atoms H or D.

Since a weak oxidizing agent is associated with a large F value, or requires strong assistance by dissociation of the reacting carbon–hydrogen bond, the force that makes two reagents interact must be an electron-transfer type.[42] In the process of the formation of a preassociation complex, an electron partially migrates from **11Me-MMPAH** to a quinone. However, this electron migration is insufficient to complete the formation of a preassociation complex without assistance by the stretched carbon–hydrogen bond at C(7). *p*-Chloranil is a very strong oxidizing agent and requires little assistance from carbon–hydrogen stretching, resulting in a small F value, whereas chloro-*p*-benzoquinone is the weakest of all the compounds studied and the electron-transfer must be assisted by stretching, affording the largest possible value of F. It is necessary to note that the migrating hydrogen does not interact with the quinone at this stage. The subsequent kinetic process exerts an intermolecular bonding interaction between these two molecules.

In the preassociation complex, the quinone and **11Me-**

$$\xleftarrow{k_D^H} QM_{D,H} + M_{H,H} \xrightleftharpoons{K} QM_{H,H} + M_{D,H} \xrightarrow{k_H^H}$$

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

Scheme 6.

MMPAH moieties bear partial negative and positive charges, respectively, as a result of partial electron-transfer.[43] *This is the driving force* that stimulates the C(7) hydrogen to migrate *as a proton*. The free energy surface of the reaction is illustrated in Fig. 4.

Since only those molecules that have formed an appropriate preassociation complex where the reacting proton readily dissociates from C(7) can proceed to the transition state, stereochemistry of the reaction is defined at the ground-state complex instead of the transition state, or the preequilibrium is the stereo-determining step of the reaction. In this sense, it is safe to note that the parameter α indicates the *anti* preference in the preassociation complex. The rate-determining transition state is merely one of those points along the reaction coordinate through which the reacting species pass.

The free energy surface of the reaction depicted in Fig. 4 is similar to those observed in enzymatic reaction: An enzyme and a substrate form an ES complex which is energetically more stable than the reactant state. Nevertheless, the enzyme catalyzes the reaction, because local free energy at the reaction center in the ES complex is higher than the free energy of the reactant state despite the total stability of the system. In addition, stereochemistry of an enzymatic reaction is absolutely defined at its ES complex. Those molecules that form appropriate intermolecular arrangement at the ES complex can proceed to their transition states. Thus, the stereo-

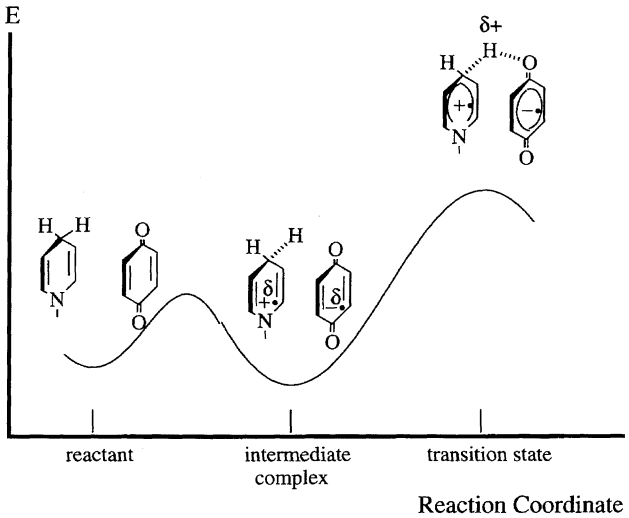


Fig. 4. Schematic diagram of the free energy profile in the reaction of NADH/NADPH analogue with a quinone; the driving force of the reaction stems from initial electron transfer at the stage of the formation of preassociation complex.

determining step is independent of the subsequent chemical reactions in enzymatic reactions, and the present redox reactions mimic biochemical reactions quite well. Both reaction systems set an entropy-losing (and stereo-controlling) process prior to the rate-determining step in order to accelerate the reaction. The author wishes to emphasize that biochemical reactions that are catalyzed by the corresponding enzymes exhibit no special trick that cannot be explored by organic chemistry.

3. Factors That Control Stereoselectivity

Next, interest has been focused on the mechanism that controls the stereoselectivity in the formation of a preassociation complex, and activation parameters of the reaction have been elucidated. The results of the reactions with *p*-chloranil and 2,6-dichloro-*p*-benzoquinone as representatives of strong and weak oxidizing agents, respectively, are listed in Table 3. Table 3 reveals two important pieces of evidence:
(1) the reaction is essentially entropy-controlled and
(2) the less selective reaction is associated with higher enthalpy of activation than the more selective reaction.

It is apparent that the analysis of the reaction from the viewpoint of potentials contributes little in attempts to determine the reaction course. Entropic factor(s) must be taken into consideration as the most important parameter for the promotion of reaction. Similar results on kinetic parameters have been obtained from the reactions of other NADH/NADPH analogues with quinones.[44] This is an important finding, because almost all discussions to date on the mechanism have dealt with the enthalpy term. It is not necessary to state that calculations on molecular orbital energies reveal nothing of the reaction mechanism.

The importance of parameters corresponds quite well with the discussion mentioned above. The formation of a preassociation complex associated with partial transfer of an electron freezes the movement of reagent and solvating molecules, bringing a large negative entropy change in the system. This nonkinetic process constitutes a major part of the reaction. Once the preassociation complex is formed, the following chemical reaction (intracomplex transfer of a proton) proceeds without requiring appreciable free energy to promote the reaction.

Then, a minor contribution of enthalpic factors controls the stereoselectivity. The partial electron transfer from the NADH/NADPH analogue to an oxidizing agent generates a partial negative charge on the latter. Since there is no doubt that the carbonyl oxygen in an NADH/NADPH analogue bears a partial negative charge, repulsive force arises be-

Table 3. Activation Parameters in the Reaction of **11Me-MMPAH** with *p*-Chloranil or 2,6-Dichloro-*p*-benzoquinone as Typical Strong and Weak Oxidizing Agents, Respectively

Quinone	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	α
	kcal mol^{-1}	kcal mol^{-1}	cal mol^{-1} K^{-1}	
p-Chloranil	12.3	1.88	−35.4	0.97
2,6-Dichloro-*p*-benzoquinone	14.3	4.75	−32.8	0.87

tween the carbonyl oxygen and the oxidizing agent within the complex when the agent approaches the analogue in the face where the carbonyl oxygen projects. Thus, electronic repulsion causes the attacking reagent to come from the *anti* side with respect to the carbonyl group (Fig. 5a), i.e., the stereoselectivity is controlled by an enthalpic effect. Note that the electronic repulsion is not a retarding force, but the *anti* face is enhanced in reactivity by an entropic (concentration) factor.

Anodic oxidations of **Me$_3$PNPH** or **Me$_3$MQPH** take place preferentially in the *syn* face as mentioned above.[27] Because an electron is withdrawn from the analogue, resulting in the formation of the corresponding radical cation under the reaction conditions, and the base accepts the proton that departs from this cation radical, the dipole–dipole interaction between the amide–carbonyl and the reacting carbon–hydrogen bond stabilizes the system in the *syn* face (Fig. 5b).

In contrast, reduction of the analogue as studied thus far proceeds in the *syn* face only, although examples of the reduction are not yet systematic and insufficient in number for a discussion on the general mechanism. The proposed idea can be used to explain the observation. When the reducing agent is a neutral species such as an NADH/NADPH analogue, an electron transfer from the reducing agent to an analogue in the oxidized form preserves a partial positive charge on the reducing agent, which may undergo electrostatic stabilization in the *syn* face of the carbonyl group (Fig. 5c). The analogue can also be reduced by anions such as $S_2O_4^{2-}$ or BH_4^-. In this case, the situation becomes complicated. The participation of counter cation of the salt which interacts with the carbonyl–oxygen cannot be ignored, and the situation is similar to that observed in the reaction in the presence of magnesium ions (vide infra). In the case of reaction with $S_2O_4^{2-}$, however, there is another possibility that the salt dissociates even in acetonitrile. If this is the case, electrostatic repulsion, which is a hard interaction, between the attacking anion and negatively charged carbonyl–oxygen makes the *anti* face preferable for the approach (Fig. 5d) and form a carbon–sulfur covalent bond in this face. Consequently, a proton from water comes from the *syn* face.

Thus, electronic interactions in the preassociation complex play a crucial role in determining the stereochemical result of the reaction.

The sulfinyl group, another dipolar functional group, behaves similarly to the carbonyl group,[45,46] which reveals that the dipole–dipole or dipole–charge interaction as a factor

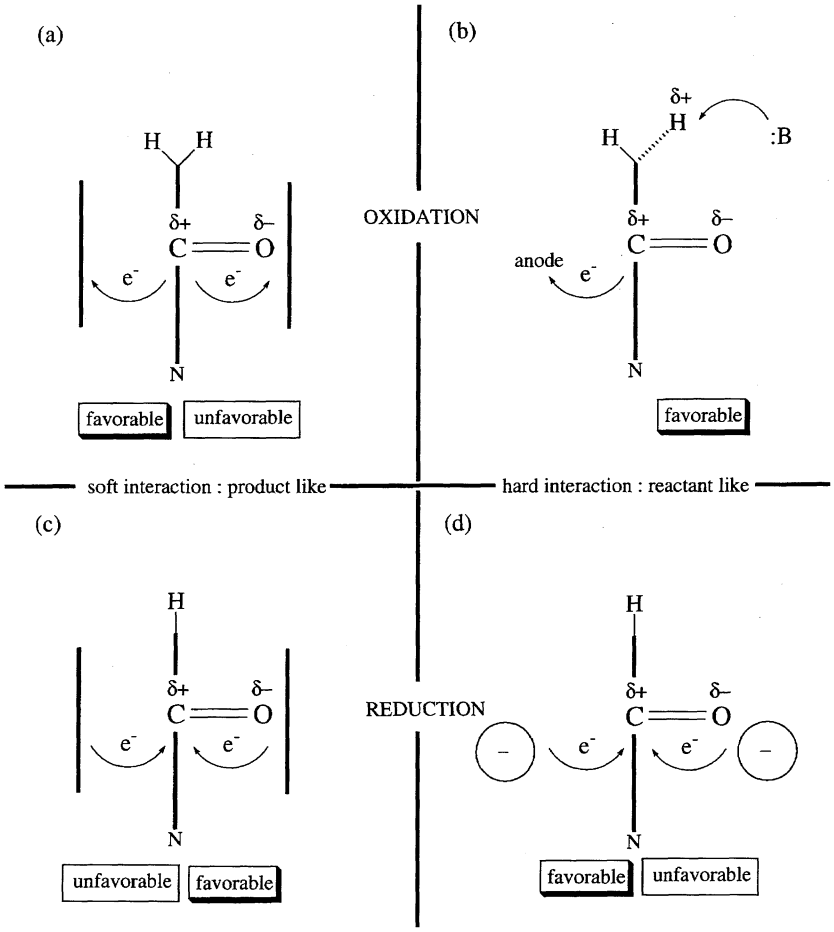


Fig. 5. Schematic illustration of stereoselective interactions: (a) oxidation under soft interaction with a neutral oxidizing agent that affords a negatively charged product; (b) anodic oxidation; (c) reduction under soft interaction with a neutral reducing agent that affords a positively charged product; and (d) reduction under hard interaction with a negatively charged reducing ion.

that controls the stereochemistry of a reaction observed in the chemistry of the carbonyl group, is not limited to the chemistry of the carbonyl group but can also be extended to the chemistry of all other polar functional groups.

4. The Role of Magnesium Ion

Readers might wonder why the author has not mentioned reactions in the presence of magnesium ions. Before addressing this, the author would like to point out that almost all oxidations without magnesium ions exert *anti* preference and the stereoselectivity varies within the limit of *anti* preference. On the other hand, the *syn* preference is seen in the reaction under magnesium-ion catalysis.

There is no doubt that magnesium ions play the role of a Lewis acid catalyst to promote the reaction, because, for example, oxidation with anthraquinone or tetramethyl-*p*-benzoquinone does not proceed without this ion.[21] In this sense, the ion that has the highest positive surface–charge density may be the most effective as a catalyst. Indeed, the scandium(III) ion has been found to be more effective than magnesium ion.[47] However, from the viewpoints of solubility and availability of dry material, the author believes that magnesium perchlorate (in acetonitrile) is the most convenient for practical use. Biological systems quite often use zinc ions for the same purpose.

It is known that magnesium ions ligate NADH/NADPH or its analogues.[5] We have found that a magnesium ion freezes the conformation of the analogue in a particular form:[48] ^{1}H NMR spectroscopy of 1,2,4-trimethyl-3-[*N*-methyl-*N*-(1-phenylethyl)carbamoyl]-1,4-dihydroquinoline (**Me$_3$MQPH**) indicates that this analogue exists in acetonitrile, assuming three different conformers out of a possible four (Fig. 6).

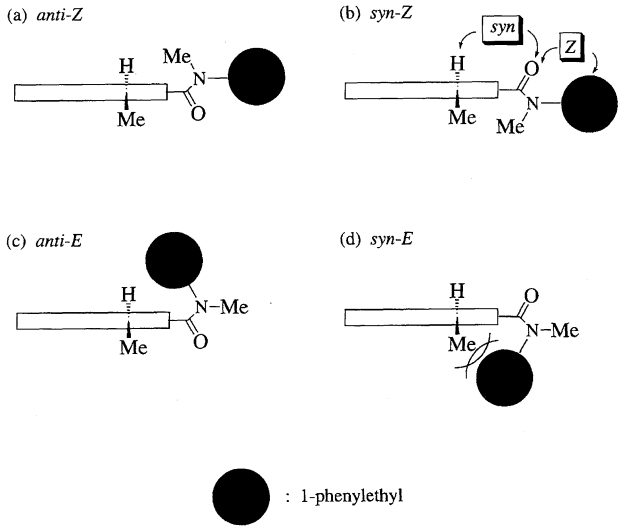


Fig. 6. Four possible conformers of **Me$_3$MQPH** in acetonitrile.

Because of *syn-E* conformation shown in Fig. 6d has large steric hindrance, this conformer does not exist in the solution. In addition, the *anti-E* conformer (Fig. 6c) is considered to be unreactive, because the hydrogen that should be involved in the reaction is blocked by a bulky 1-phenylethyl group.

The ratio of conformations, *anti-Z*/*syn-Z*, of **Me$_3$MQPH** appears to be 34/26 = 1.31 in acetonitrile at 293 K in the absence of magnesium ions. When ten times excess magnesium perchlorate is added to this system, however, the ratio is reversed to 13/68 = 0.19, which proves that the magnesium ion freezes the conformation of **Me$_3$MQPH** to the *syn* form preferentially.

Interestingly, the *anti*/*syn* ratios observed in the product

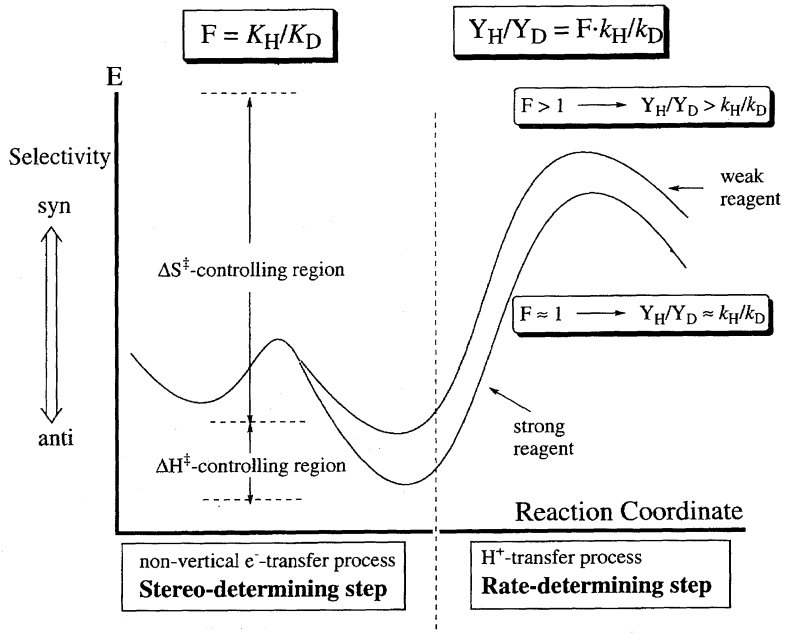


Fig. 7. Schematic free energy surface along the reaction coordinate with weak or strong oxidizing agent, illustrating the contribution of enthalpy term at the ground state to the stereoselectivity of reaction. Difference in free energy between the stereoisomers of complex is kept almost unchanged in their transition states. Magnesium ions reduce the free energy of intermediate complex, but afford the *syn* product, because the intermediate complex is ternary and of sandwich type.

Me_3MQP^+ are 1.1—1.3 in the oxidation with *p*-chloranil and 0.09—0.13 in the oxidation with *p*-benzoquinone.[49] Since the former quinone is reactive and does not require the catalysis, or rather is interfered with by magnesium ions, whereas the latter does not undergo the reaction without the catalysis (vide infra), the experimentally observed ratios indicate that the difference in free energy of the conformers at the ground state of **Me_3MQPH** is directly reflected to the conformational ratio in the product.

The observation is understandable when one considers the fact that the transition state of the reaction is possible only from the appropriately arranged complex. That is, the transition state for the proton transfer must be similar in structure to the *syn*- and *anti*-selective preassociation complex. Thus, the magnesium ion plays dual roles in catalysis: One of accelerating the reaction and the other of controlling the stereochemistry of the reaction, similar to the reaction of **dFl_{ox}** (vide infra). This is another example of a modern stereochemical control concept.

Consequently, we can draw free energy diagrams for the reactions of NADH/NADPH analogues with strong and weak oxidizing agents, as illustrated in Fig. 7

A Lewis acid defines the reacting face regardless of the reactivity of the attacking reagent. However, it should be noted that a strong oxidizing agent is an electron-deficient species and an approach of a reagent of this kind is interfered with electrostatic repulsion due to the positive charge on the magnesium ion that coordinates on an electronegative functional group(s) of the analogue. The repulsion results in the preferential use of the other face; i.e., positive selection of the *anti* face.

The author wishes to thank all collaborators who have been involved in this research project. Some names appear in the references cited, while some others are missed. The author hopes that this account may be accepted as a record of their excellent contributions. The author also appreciates financial support of the project from many sources, including Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture.

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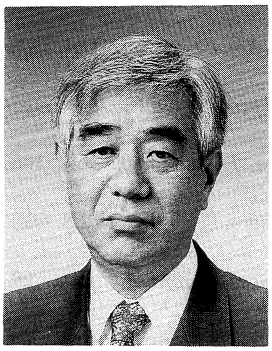
49) If one wishes to have a precise expression, the phrase "*anti/syn* ratio in the product" should be changed to "*anti/syn* ratio at the transition state". However, for simplicity, the author uses the former. The stereochemistry in the product directly reflects the *anti/syn* ratio at the transition state.



Dr. Atsuyoshi Ohno was born in Hiroshima in 1936. He was graduated from Kyoto University in 1958 with B. Sc. in organic chemistry. He also received his M. Sc. in organic chemistry in 1960 from the same university. Then, he joined the Radiation Center of Osaka Prefecture, where he did his research under the supervision of Dr. Shigeru Oae and received his Ph. D. in Science from Osaka City University in 1963. In the same year, he moved to MIT as a research associate for Prof. C. Gardner Swain, then in 1965, to Purdue University to work for Prof. Robert E. Davis. He came back to Japan at Sagami Chemical Research Center in 1966, and moved in 1974 to the Institute for Chemical Research, Kyoto University as an associate professor, where he has been a professor since 1990. His current research interest is in the area of physical organic chemistry and bioorganic chemistry. Namely, his recent research is focused on the mechanism of stereoselection in biochemical and organic reactions, and biochemical syntheses of chiral auxiliaries. He is the author of several books in physical organic chemistry and bioorganic chemistry as well as in chemistry of organic sulfur compounds.