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REVIEW COMMENTARY

NON-STERIC STEREOCHEMISTRY SOLELY CONTROLLED BY ORIENTATION OF DIPOLAR FUNCTION

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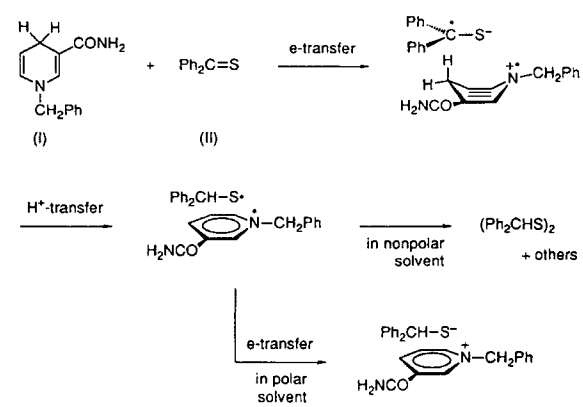
The mechanism of biologically important (net) hydride transfer from NADH or NADPH to a substrate has been discussed from the viewpoint of physical organic chemistry. It is emphasized that the (net) hydride transfer involves an electron-transfer complex as an intermediate of the reaction. The intermediate plays a crucial role in determining the stereochemistry of the reaction. Orientation of a dipolar functional group such as carbonyl or sulphinyl determines the molecular face for complexation, and consequently defines the face of reaction. Steric bulkiness is of secondary importance in defining the face of reaction. The mechanism observed is called non-steric stereochemistry. Molecular interactions observed in organic reactions and discussed herein are found to be closely related to those observed in biological reactions.

INTRODUCTION

In 1957, Abeles *et al.*[1] reported that 1-benzyl-1,4-dihydronicotinamide, which was later abbreviated by us to BNAH, a model of NAD(P)H, transfers a hydride to thiobenzophenone, a model of biologically active ketones, via a one-step process. From our studies on the chemistry of thiobenzophenone, which started in the late 1960s, we concluded that this compound is a very efficient one-electron acceptor.[2,3] In order to confirm the contribution of a one-electron transfer process to the reaction of thiobenzophenone, we reinvestigated Abeles *et al.*'s reaction system using more sophisticated technology: ESR and NMR spectroscopy revealed that the reaction of BNAH with thiobenzophenone involves a radical-ion pair as an intermediate (Figure 1). This radical-ion pair is converted into a pair of free radicals via a proton transfer within the pair. The final products, either dibenzhydril disulphide or diphenylmethanethiol and BNA^+, are afforded from this free-radical pair depending on the reaction conditions (Scheme 1).[4]

According to Professor Westheimer, the multi-step mechanism proposed by us '*may be* true for *this particular* reaction.' Some groups doing independent studies found evidence that agreed with ours, while others criticized the newly proposed mechanism. Since both an electron and a hydride are associated by a negative charge on them, studies on the substituent effect can contribute very little to the elucidation of the mechanism. The major part of the discussion on the mechanism was therefore focused on the discrepancy between kinetic and product isotope effects (the product isotope effect was named by us to indicate the ratio of different distributions of isotopic nuclei in the product).



Scheme 1

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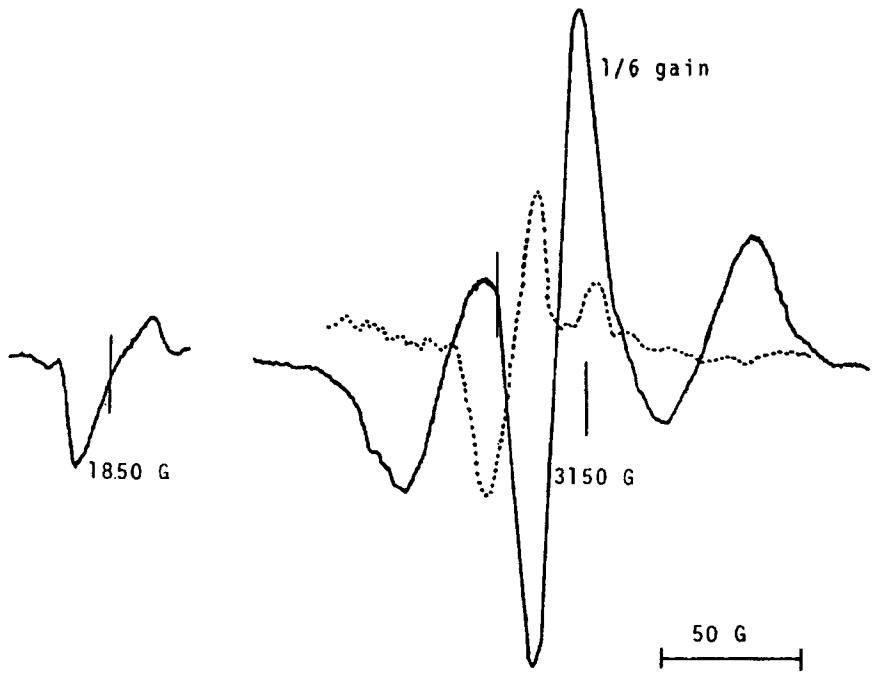


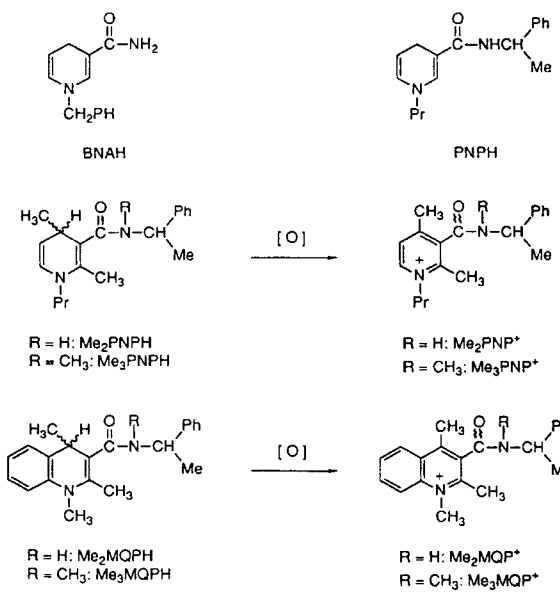
Figure 1. ESR spectra of a mixture of BNAH and thiobenzophenone in 2-methyltetrahydrofuran taken at 77 K (solid line) and at room temperature (dashed line). The signal at 1580 G indicates the presence of a triplet pair of cation and anion radicals in the mixture

It was found that the amount of water contaminating the solvent had a marked effect on the reaction course.[5,6] The contribution of magnesium ion as a catalyst was also discussed.[7] Detailed discussions on the mechanism from the viewpoint of kinetics and thermodynamics appeared in two reviews.[8,9]

STEREOCHEMISTRY

As mentioned above, the kinetics and thermodynamics based on electronic effects remain ambiguous in the discussion of electron transfer vs. hydride transfer, because these processes predict the same change in electronic charge from a ground state to the corresponding transition state.[10,11] A novel methodology for the elucidation is desired.

Meanwhile, we were the first to report on examples of stereospecific reduction of certain α-keto esters and ketones by chiral analogues of NAD(P)H, *N*-(α-methylbenzyl)-1-propyl-1,4-dihydronicotinamide (PNPH) or *N*-(α-methylbenzyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH) (Scheme 2).[12,13] Central chirality in these analogues has been extended to axial chirality. The central chirality reserved in the re-



Scheme 2

duced form of the analogue is changed to the axial chirality in its oxidized form with excellent efficiency, where orientation of the carbonyl group in the side-chain amide group defines the *re*- and *se*-faces of the molecule.[14] Further, it was found that the stereospecificity of the reaction depends on the reactivity of the substrate or oxidizing agent: a linear relationship is observed between the oxidation potentials of a series of quinones and the efficiency of chirality reservation, as shown in Figure 2;[15] stereospecificities in electrode oxidation of chiral *N*-methyl-*N*-(α-methylbenzyl)-1-propyl-1,2,4-trimethyl-1,4-dihydronicotinamide (Me_3PNPH) and 3-[*N*-methyl-*N*-(α-methylbenzyl)]-1,2,4-trimethyl-1,4-dihydroquinoline (Me_3MQMH) are related linearly with the basicity of the amine present in the reaction system as the proton-abstracting agent, as shown in Figure 3.[6] A reactive substrate (or a strong base) prefers the reaction in the *anti* face with respect to the carbonyl group, whereas a weekly reacting reagent prefers the reaction in the *syn* face (Scheme 3).

It is noteworthy that a similar relationship can be seen in nature: *re*- and *si*-face selectivities in the reactions of NAD(P)H mediated by dehydrogenases and reductases depend on the reactivity of the substrate (Table 1).[17] The observation has been discussed in relation to the chemical evolution of enzymes. Comparison of similar phenomena in biological and organic systems may shed light on the complex mechanisms involved in enzyme chemistry.

The dependence of stereospecificity on the reactivity of a substrate cannot be explained by a one-step mechanism. The electrode reaction demonstrates clearly that the process is composed of at least two steps: electron- and proton-transfer processes. In addition, quinones and amines and also the electrode are achiral substances; hence the origin of asymmetric induction observed in these reactions cannot be accounted for

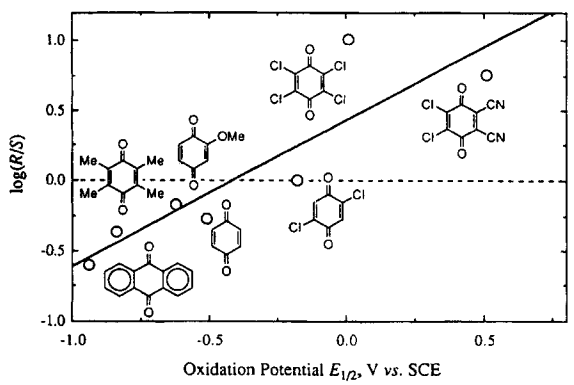


Figure 2. Linear relationship between stereospecificity and oxidation potential in the oxidation of chiral Me_2PNPH with a series of quinones

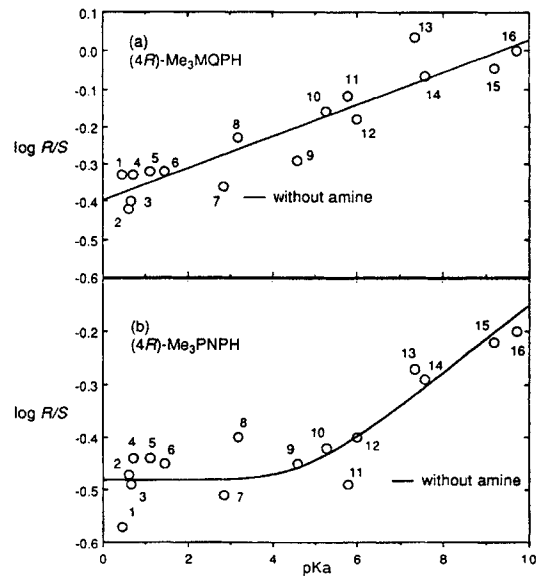
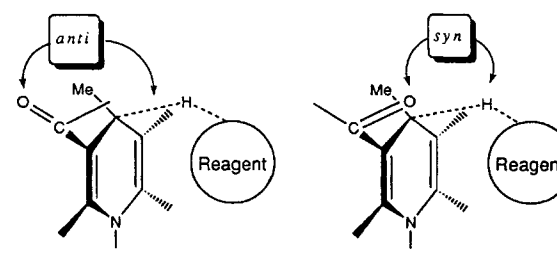


Figure 3. Linear relationships between stereospecificities and basicity in the electrode oxidation of Me_3PNPH and Me_3MQPH in the presence of a series of amines. **1**, 2-Fluoropyridine; **2**, 4-nitro-*N*,*N*-diethylaniline; **3**, 3,5-dichloropyridine; **4**, 2-chloropyridine; **5**, 4-nitroaniline; **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

from the viewpoint of steric effects generally accepted in the chemistry of this field (although the α-methylbenzyl group in Me_2PNPH is a chiral substituent, it has been established that configuration of this functional group does not affect the stereochemistry of the overall reaction[18]). Thus, with two objectives at hand, i.e. to prove the contribution of electron-transfer process to the (net) hydride-transfer reaction and to elucidate the mechanism of non-steric stereochemistry, we proceeded with research on related reactions.



Scheme 3

Table 1. Stereochemistry associated with the reduction mediated by NAD(P)H-dependent dehydrogenases and reductases[17]

Enzyme	$-\text{Log } K_{eq}$ [a]	Stereochemistry [b]
Glyoxylate reductase	17·5	*pro-R*
Glyoxylate reductase ($NADP^+$)	17·5	*pro-R*
Tartronate-semialdehyde reductase	13·3	*pro-R*
Glycerate dehydrogenase	13·3	*pro-R*
Glycerol 1-dehydrogenase	12·8	*pro-R*
Hydrooxypyruvate reductase ($NADP^+$)	12·4	*pro-R*
Malate dehydrogenase	12·1	*pro-R*
Malate dehydrogenase ($NADP^+$)	12·1	*pro-R*
Malic enzyme	12·1	*pro-R*
Malic enzyme ($NADP^+$)	12·1	*pro-R*
L-Lactate dehydrogenase	11·6	*pro-R*
D-Lactate dehydrogenase	11·6	*pro-R*
Ethanol dehydrogenase (yeast)	11·4	*pro-R*
Glycerol 2-dehydrogenase	11·3	*pro-R*
Glycerol-3-phosphate dehydrogenase	11·1	*pro-S*
Homoserine dehydrogenase	10·9	*pro-S*
Carnitine dehydrogenase	10·9	*pro-S*
3-Hydroxyacyl-CoA dehydrogenase	10·5	*pro-S*
3-Hydroxybutyrate dehydrogenase	8·9	*pro-S*
3β-Hydroxysteroid dehydrogenase	8·0	*pro-S*
Oestradiol 17β-dehydrogenase	7·7	*pro-S*
Testosterone dehydrogenase	7·6	*pro-S*
3-Oxoacyl-ACP dehydrogenase	7·6	*pro-S*
β-Hydroxysteroid dehydrogenase	7·6	*pro-S*

[a] K_{eq} = [ketone][NADH]/[alcohol][NAD^+].
[b] Hydrogen at C-4 of NAD(P)H employed for the reaction.

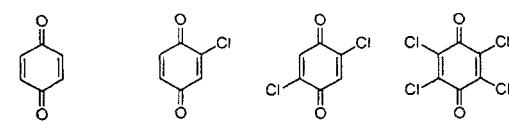
MECHANISM

Based on stereochemical results from the reactions of chiral NAD(P)H analogues, it has been concluded that the *anti*/*syn* preference in the transition state depends on the lateness or earliness of the transition state. In order to understand the mechanism in detail, we studied the kinetics of the reactions of various analogues, Me_2MQPH, Me_2PNPH, BNAH and their deuterated derivatives with chloranil (**Q4**) and 2,6-dichloro-1,4-benzoquinone (**Q2**) (Scheme 4), representatives of strongly and weakly reactive substrates, respectively. Selected results are summarized in Tables 2 and 3.

Tables 2 and 3 reveal that about 50–90% of the free energy of activation is contributed by the entropy term. This is an important finding, because almost all discussions on the mechanism to date have dealt with the energy term. In other words, previous discussions based on energetics should be neglected and a new mechanism based on entropy must be established in the theory of this (net) hydride-transfer reaction.

Detailed inspection of the results led us to assume that an electron-transfer process with low activation energy (early transition state) is followed by a slow proton-transfer process with high activation energy and vice versa.

It is noteworthy that, although the *anti*/*syn* preference of stereochemistry is controlled by the electronic effect from the reagent(s), or a linear free energy–



Scheme 4

Table 2. Kinetic parameters, kinetic isotope effects and stereochemistry of the oxidation of NAD(P)H analogue with chloranil (**Q4**)

Parameter	Me_2MQPH	BNAH	Me_2PNPH
ΔG^* (kcal mol^{-1}) (298 K)	14·6	13·2	11·1
ΔH^* (kcal mol^{-1})	4·98	3·00	0·47
ΔS^* (cal mol^{-1} K^{-1})	−32·7	−34·3	−35·6
$(k_H/k_D)_{obsd}$	4·68	5·14	2·30
anti/*syn* ratio	1·2/1·3/1	—	2·4/1

[a] 1 cal = 4·184 J.

Table 3. Kinetic parameters, kinetic isotope effects and stereochemistry of the oxidation of NAD(P)H analogue with 2,5-dichloro-1,4-benzoquinone (**Q2**)

Parameter	Me_2MQPH	BNAH	Me_2PNPH
ΔG^* (kcal mol^{-1}) (298 K)	15·6	14·8	12·3
ΔH^* (kcal mol^{-1})	6·99	5·23	0·829
ΔS^* (cal mol^{-1} K^{-1})	−28·8	−32·2	−38·4
$(k_H/k_D)_{obsd}$	3·75	6·01	3·03
anti/*syn* ratio	1·2/1·1/1	—	1/2·3–2·4

reactivity–stereochemistry relationship holds, the entropy (or steric) effect instead of the enthalpy effect plays the role of a backbone of the electronic effect observed here. That is, the electronic effect controls the molecular assembly (both stiffness and preferred face) at the electron-transfer intermediate and/or transition state, but, at the same time, the molecular assembly is also controlled by entropy. Consequently, the electronic effect is related to the entropy effect and, therefore, to stereospecificity. In this sense, the electronic effect discussed herein is entirely different from the stereoelectronic (anomeric) effect proposed and developed by Delongchamps and other researchers.[19]

Based on the fact that the *anti* conformation is preferred by the early transition state, it has also been proposed that the *anti* conformation is more favoured than the *syn* conformation by the entropy term, and the validity of the proposal was tested by elucidating the difference in kinetic parameters for the reactions leading to *anti* and *syn* transition states. However, the difference was so small that it was very difficult to obtain conclusive experimental results. Nevertheless, after repeated measurements conducted over 2 years, we succeeded in obtaining reasonably reproducible values, which are listed in Table 4. It is known that magnesium ion shifts the preference to the *syn* conformation, and the results obtained in the presence of magnesium ion are also listed in Table 4.

Not much can be said regarding the reaction of Me_3MQPH in the absence of magnesium ion owing to insufficient data being available. The reactions of Me_3PNPH, however, reflect the stereospecificities: the difference in free energy of activation is negative for **Q4** only, and positive for **Q2** and **Q1**. The reaction with **Q4** is a representative of *anti* specificity and reactions with **Q2** and **Q1** are representative of *syn* specificity. The result that virtually all differences in the entropy of activation are positive supports the assumption that the *anti* conformation is more preferred (less negative) entropically than the *syn* conformation. On the other hand, all differences in the enthalpy of activation are positive, suggesting that the *syn* conformation may be energetically more preferable than the *anti* conformation.

In the presence of magnesium ion, all reactions afford the product from the transition state of *syn*

Table 4. Difference in kinetic parameters between *anti* and *syn* conformations at the transition state in the reactions of Me_3MQPH and Me_3PNPH with a series of quinones[a]

Reducing agent	Quinone	Mg^{2+}	E^0 (V vs SCE)[20]	$\delta\Delta G^*$ (kcal mol^{-1})	$\delta\Delta H^*$ (kcal mol^{-1})	$\delta\Delta S^*$ (cal mol^{-1} K^{-1})
Me_3MQPH	**Q4**	−	+0·01	−0·19	+0·20	+1·30
	Q2	−	−0·18	−0·22	+0·44	+0·86
	Q1	−	−0·34		Low yield[b]	
	Q0	−	−0·50		No reaction	
Me_3MQPH	**Q4**	+	+0·01	−0·19	+0·33	+1·76
	Q2	+	−0·18	+0·02	−0·05	−0·24
	Q1	+	−0·34	+0·38	+0·65	+0·89
	Q0	+	−0·50	+1·13	+1·15	+0·04
Me_3PNPH	**Q4**	−	+0·01	−0·46	+1·09	+5·32
	Q2	−	−0·18	+0·37	+1·18	+2·72
	Q1	−	−0·34	+0·67	+0·92	+0·84
	Q0	−	−0·50		No reaction	

[a] $\delta\Delta X^* = \Delta X^{***}_{anti} - \Delta X^{***}_{syn}$.
[b] Yields were too low to allow reliable evaluation.

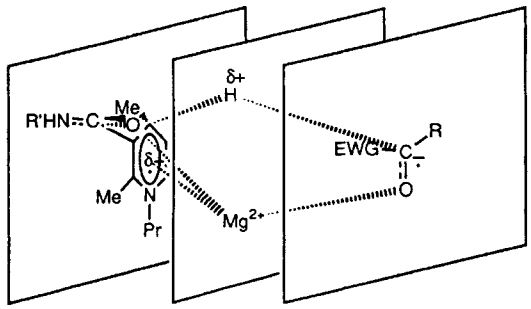


Figure 4. Schematic illustration of the transition state for the initial electron-transfer process

conformation. This observation is again supported by differences in kinetic parameters. The structure of the encounter complex involved in the reaction in the presence of magnesium ion may be that shown in Figure 4.

The term 'entropy' can be substituted by the 'probability of the reaction to occur.' The present results, therefore, suggest that the effective encounter between the reducing and oxidizing agents hardly occurs without magnesium ion in the reaction with less reactive quinones. The effective encounter complex which stimulates an electron to transfer from the reducing agent to the oxidizing one also undergoes further reaction to migrate a proton. The encounter complex which could not undergo electron transfer returns to the initial state. This electron-transfer process to form an encounter complex, not the proton-migration process, determines the stereochemistry of the reaction. Once the electron transfer is initiated in the encounter complex, the reaction system enters an irreversible process to climb up the hill of potential surface along the reaction coordinate to its transition state. The possibility for the reaction to occur (i.e. entropy) governs the stereochemistry of the reaction.

The phenomenon observed here is exactly the same as that observed in enzymatic reactions, where a substrate trapped in a pocket of enzyme in a sterically correct manner only can be converted into the product, whereas that showing steric mismatch does not undergo the reaction.

ELECTRON-TRANSFER COMPLEX

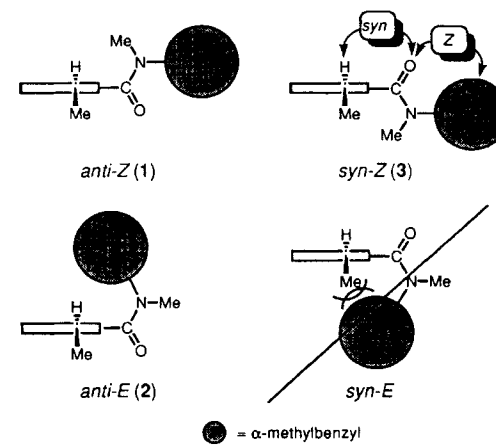
We have discussed the conformation of the transition state, and emphasized the importance of an electron-transfer intermediate (or transition state). We now focus our attention on the ground state of the reaction to obtain greater insight into the variation in the potential surface along the reaction coordinate.

^{1}H NMR spectroscopy permitted the detection of signals from three out of four possible conformers of Me_3MQPH (Scheme 5).[21] The existence of the remaining conformer seems impossible because of large steric repulsion within the molecule.

It is possible to elucidate the relative amounts of the three conformers by ^{1}H NMR spectroscopy in the presence or absence of magnesium ion. The results are shown in Table 5 together with the *anti*/*syn* ratios in the transition states of the reactions with **Q4** and **Q0**.[21]

Conformer **2**(*anti-E*) seems unresponsive to the reaction, because the hydrogen for reaction is blocked by a large α-methylbenzyl group. Therefore, it is conceivable that the reaction proceeds via conformers **1**(*anti-Z*) and **3**(*syn-Z*). The ratios of the amounts of **1** to **3** in the presence and absence of magnesium ion are also listed in Table 5.

An interesting conclusion that can be drawn based on the above discussion is that the reaction with **Q4** proceeds independently even in the presence of the magnesium ion. In other words, an uncomplexed molecule is responsible for the reaction, and the *anti*/*syn* ratio at the transition state is the same as the *anti*/*syn* conformer ratio in the reactant. In contrast, the stereochemistry of the reaction with **Q0** depends on the amount of magnesium ion, an indication that the reaction proceeds via the complex. In the latter reaction, the *S*/*R* ratios of the product, which are related directly to the *anti*/*syn* ratio at the transition state, are the same as those in the intermediate complex. That is, the stereochemistry at the transition state of the reaction is already defined at its ground state. There is no doubt that the proton-transfer process requires a higher energy of activation than the electron-transfer process that precedes it, because the overall reaction exerts a certain amount of kinetic isotope effect. Nevertheless, once the reacting molecules are assembled into an intermediate complex via the electron-transfer interaction, the subsequent proton transfer takes place spontaneously. Free energies of activation of the reactions starting



Scheme 5

Table 5. Equilibrium composition of rotational isomers of Me_3MQPH and *anti*/*syn* ratios in product from the reactions with chloranil (**Q4**) and 1,4-benzoquinone (**Q0**) as a function of $[Mg^{2+}]/[Me_3MQPH]$[a]

$[Mg^{2+}]/[Me_3MQPH]$	0	0·5	1·0	10	100
Complex (%)	0	50	92	100	100
1(*anti*-*Z*)[b] (%)	34	16	14	13	—
2(*anti*-*E*)[b] (%)	41	19	16	19	—
3(*syn*-*Z*)[b] (%)	26	65	70	68	—
1/**3** ratio	1:1·31	1:4·06	1:5·00	1:5·23	—
anti/*syn* (**Q4**)[c]	1·28	1·16	1·33	—	1·80
anti/*syn* (**Q0**)[c]	—[d]	—	1/7·61	—	1/10·8

[a] At 293 K.
[b] Total of complexed and uncomplexed species.
[c] Results obtained by using (4*R*)-Me_3MQPH. The values are directly related with the *anti*/*syn* ratios at the transition states.

from appropriate, or reacting, conformers are not appreciably different from each other. The transition state of the overall reaction is not a special state but is one of the states that must be passed through by the reacting molecules during the reaction. This conclusion, which emphasizes the importance of an electron-transfer intermediate along the reaction coordinate, is consistent with that mentioned in the previous section.

Quantitative free-energy diagrams for the oxidations of *anti*- and *syn*-(4*R*)-Me_3MQPH with **Q4** and **Q0** are shown in Figure 5.

NON-STERIC STEREOCHEMISTRY

It has been elucidated that an electron-transfer complex is formed as an intermediate before the transition state of the proton-transfer process. The molecular assembly affords the electron-transfer complex preferably when

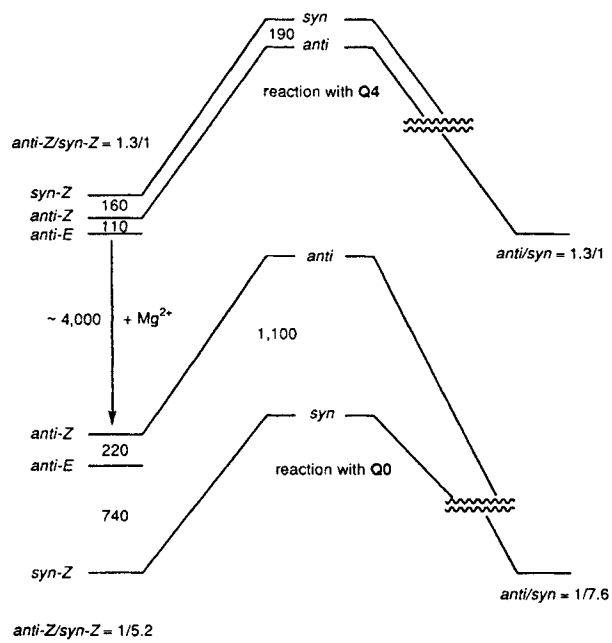
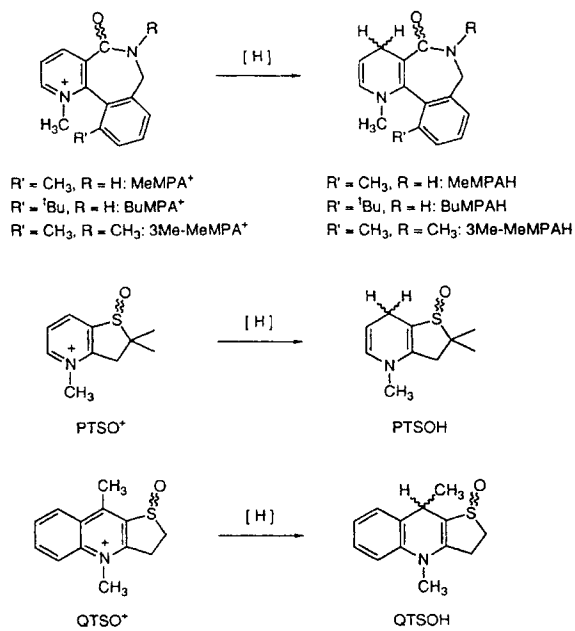


Figure 5. Energy diagram for reactions of (4*R*)-Me_3MQPH with chloranil (**Q4**) and 1,4-benzoquinone (**Q0**) in the presence and absence of magnesium ion. Energies are shown in cal mol^{-1}

an oxidizing agent occupies the same face as that occupied by the carbonyl dipole on the side-chain of the NAD(P)H analogue. This means that the stereochemistry of the reaction is controlled by the orientation of the carbonyl group. This is a novel concept in the stereochemistry of organic reactions. Before this concept can be applied to a wide variety of reactions in general, it should be tested on as many examples as possible. Since the NAD(P)H analogues so far employed in our studies are those that have two central chiralities in their molecules, i.e. they are diastereomeric, and even though it has been confirmed that the chirality at the non-reacting centre on the side-chain of the analogue plays no crucial role in determining the stereochemistry of the reaction, we extended our research using enantiomeric analogues in order to avoid any unnecessary ambiguity.[18]

The new models designed by us are those that have axial chirality only with respect to the orientation of a dipolar functional group in the molecule (Scheme 6).[22,23]

The absolute configuration of 6,7-dihydro-6-methyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepinium ion ($MeMPA^+$) was elucidated by x-ray crystallography of its (+)-D-camphorsulphonate salt. Although the structure of 6,7-dihydro-6-methyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-(3-methylbenz)azepinium ion ($3Me\text{-}MeMPA^+$) has not yet been confirmed by x-ray crystallography, since the structures of $MeMPA^+$ elucidated experimentally by x-ray crystallography and theoretically by MO calculations coincided with each other, the conformation and configuration of $3Me\text{-}MeMPA^+$ predicted by MO calculations, which are essentially the same as those of $MeMPA^+$, are highly plausible. The absolute configuration of 2,3-dihydro-2,2,4-trimethylthieno[3,2-*b*]pyridinium 1-oxide iodide ($PTSO^+I^-$) was determined by x-ray crystallography using the abnormal dispersion technique.



Scheme 6

It has been found that not only a carbonyl group but also a sulphinyl group can behave as a dipole to control the reacting face of the molecule. Moreover, the inspection of the reactions of an enantiomeric pair of a new chiral analogue with a chiral $Me_nPNPH\text{-}4\text{-}d$, where the molecular assembly affords a diastereomeric complex, might reveal more details of the molecular arrangement in the complex. The result is discussed below for the reaction of (*S*)-(+)- and (*R*)-(−)-$PTSO^+I^-$ with (4*S*)-$Me_nPNPH\text{-}4\text{-}d$ ($n = 2$ and 3).[24] The reaction of $3Me\text{-}MPA^+$ proceeds similarly.[25] Stereospecificities of the reactions with various combinations of the reagents are summarized in Table 6.

In the reaction of (*S*)- and (*R*)-$PTSO^+$ with (4*S*)-$Me_nPNPH\text{-}4\text{-}d$($n = 2$ and 3), for example, there are four possible molecular arrangements in the electron-transfer complex along the reaction coordinate, as shown in Scheme 7 (it is assumed that the molecules orient in a manner which gives maximum overlap of their faces; this assumption has been partly proved[26,27]).

Differences in the *anti*/*syn* ratio for different pairs of reagents, as shown in Table 7, allow the estimation of the relative abundance (stability) of each pair, which is also shown in Scheme 7. Based on these results, we obtain the following rules:

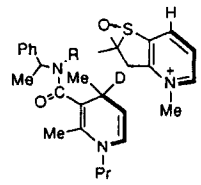
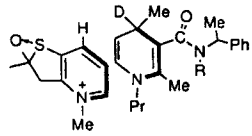
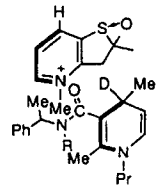
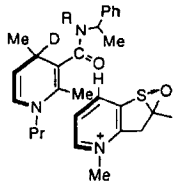
(1) in the complex, polar parts of the molecules (pyridinium moiety in $PTSO^+$ and carbamoyl side-chain in $Me_nPNPH\text{-}4\text{-}d$) tend to face each other;

(2) the reaction takes place in the same face as that occupied by the polar substituent which defines the axial chirality (sulphinyl group).

In the present reaction, the sulphinyl oxygen in (*S*)-(+)-$PTSO^+$ orients itself towards the *re*-face of the ion. Therefore, the reacting $Me_nPNPH\text{-}4\text{-}d$ mainly attacks (*S*)-(+)-$PTSO^+$ from its *re*-face. Needless to say, the complex formed by using the *si*-face of (4*S*)-

Table 6. Diastereoface differentiating (net) hydride transfer reactions between $PTSO^+$ and (4*S*)-$Me_nPNPH\text{-}4\text{-}d$ ($n = 2$ and 3)

	(*S*)-(+)-$PTSO^+$		(*R*)-(−)-$PTSO^+$	
n	*syn*	*anti*	*syn*	*anti*
2	86	14	38	62
3	87	13	35	65

Type	Structure	Rel. Stability
(*R*)-(−)-syn		11
(*R*)-(−)-anti		19
(*S*)-(+)-syn		61
(*S*)-(+)-anti		9

Scheme 7

Me_nPNPH-4-*d* is abortive and does not participate in the reaction, because the face has no hydrogen to participate in the reaction. Thus, the combinations of (*S*)-(+)-*syn*- and (*S*)-(+)-*anti*-type complexes are the most and the least favourable, respectively. In contrast, the (*R*)-(−)-*anti*-type complex is favoured over the (*R*)-(−)-*syn*-type complex, which indicates that rule 1 overrules rule 2.

Results of the reduction of $PTSO^+$ by various reducing agents in different solvents are listed in Table 7.[24] It is seen that stereospecificity changes depending on the reactivity of the reducing reagent: the strongly reactive agent prefers the reaction in the *anti* face, whereas the weakly reactive agent reacts in the *syn* face. The reactivity–stereochemistry relationship observed here is similar to that observed in the oxidation of the reduced form of the analogue by a series of quinones.

Preference for the *anti* face is marked in weakly solvating solvents, which is again accounted for by the reactivity–stereochemistry relationship. That is, the strongly solvating solvent reduces the activity of the reagent, leading to an overall tendency of the reaction to shift towards the *syn* preference.

Table 7. Diastereoface differentiating (net) hydride transfer from various reducing agents to racemic $PTSO^+$ in different solvents

Reducing agent	Solvent	Ratio of reacting faces	
		syn	*anti*
$Na_2S_2O_4$	H_2O	18	82
$NaBH_4$	CH_3CN	18	82
	CH_3OH	21	79
	H_2O	46	54
rac-Me_2PNPH	CH_3CN	72	28
BNAH	CH_3CN	77	23

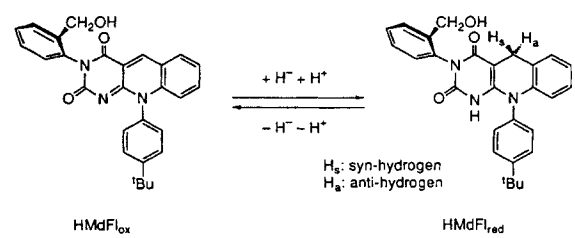
STEREOCHEMISTRY IN A 5-DEAZAFLAVIN MODEL

The two rules described above have been proved to be applicable to the reduction of an oxidized form of a 5-deazaflavin analogue ($HMdFl_{ox}$) (Scheme 8), which, again, has an axial chirality with respect to the orientation of the 2-hydroxymethylphenyl group on the ring nitrogen. Although the absolute configuration of this compound has not yet been elucidated, comparison with other analogues allows the estimation of its configuration with high probability.[28] We use this estimated configuration in the present discussion.

Although the reduction proceeds very slowly in the absence of magnesium ion, its presence accelerates the reaction appreciably. Stereochemical results from the reductions of (+)-$HMdFl_{ox}$ with (4*R*)- and (4*S*)-Me_3PNPH are summarized in Table 8.

Analysis of the results in Table 8 leads to the same conclusion as mentioned above. In addition, since magnesium ion participates in these reactions, other factors that control stereochemistry can be determined.[29]

(1) Magnesium ion assists the 'maximum overlap' of polar groups in the reacting molecules. That is,



Scheme 8

Table 8. Diastereoface differentiating (net) hydride transfer reactions between racemic $HMdFl_{ox}$ and chiral Me_2PNPH

Configuration of Me_2PNPH	$Mg(ClO_4)_2$[a]	Reactivity ratio		Ratio *anti*/*syn*[b]
		(+)-$HMdFl_{ox}$	(−)-$HMdFl_{ox}$	
4S	0	47	53	1·1:1·0
4*S*	10	62	38	1·0:1·6
4*S*	50	74	26	1·0:2·8
4*R*	0	52	48	1·0:1·1
4*R*	10	36	64	1·0:1·8
4*R*	50	28	72	2·6:1·0

[a] Equivalency to $HMdFl_{ox}$.
[b] The ratio is constant for all the reactions within experimental error.

magnesium ion is not only a catalyst to accelerate the reaction but also a catalyst to improve stereospecificity. Our observations reveal that an intermediate is afforded along the reaction coordinate before the chemical reaction takes place. In this and other model reactions discussed here, magnesium ion mimics the role of enzymes in biological reactions in the sense that it accelerates reaction rate and improves stereospecificity/selectivity.

(2) In the reaction of $HMdFl_{ox}$, the hydroxymethyl group does not behave as a dipolar substituent. Therefore, this group exerts steric inhibition in the absence of magnesium ion. However, the hydroxymethyl group can behave as a dipolar group in the presence of magnesium ion, probably because the ion coordinates with the hydroxyl group, making this moiety polar. Consequently, stereospecificity of the reaction in the presence of magnesium ion is reversed in the absence of this metal ion.

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