Thermodynamics and Kinetics of the Hydride-Transfer Cycles for 1-Aryl-1,4-dihydronicotinamide and Its 1,2-Dihydroisomer

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Abstract: Five 1-(*p*-substituted phenyl)-1,4-dihydronicotinamides (GPNAH-1,4-H_2) and five 1-(*p*-substituted phenyl)-1,2-dihydronicotinamides (GPNAH-1,2-H_2) were synthesized, which were used to mimic NAD(P)H coenzyme and its 1,2-dihydroisomer reductions, respectively. When the 1,4-dihydropyridine (GPNAH-1,4-H_2) and the 1,2-dihydroisomer (GPNAH-1,2-H_2) were treated with *p*-trifluoromethylbenzylidenemalononitrile (**S**) as a hydride acceptor, both reactions gave the same products: pyridinium derivative ($GPNA^+$) and carbanion $\mathbf{SH}^-$ by a hydride one-step transfer. Thermodynamic analysis on the two reactions shows that the hydride transfer from the 1,2-dihydropyridine is much more favorable than the hydride transfer from the corresponding 1,4-dihydroisomer, but the kinetic examination displays that the former reaction is remarkably slower than the latter reaction, which is mainly due to much more negative activation entropy for the former reaction. When the formed pyridinium derivative ($GPNA^+$) was treated with $\mathbf{SH}^-$, the major reduced product was the corresponding 1,4-dihydropyridine along with a trace of the 1,2-dihydroisomer. Thermodynamic and kinetic analyses on the hydride transfer from $\mathbf{SH}^-$ to $GPNA^+$ all suggest that the 4-position on the pyridinium ring in $GPNA^+$ is much easier to accept the hydride than the 2-position, which indicates that when the 1,4-dihydropyridine is used the hydride donor to react with **S**, the formed pyridinium derivative $GPNA^+$ may return to the 1,4-dihydropyridine by a hydride transfer cycle; but when the 1,2-dihydropyridine is used as the hydride donor, the formed pyridinium derivative can not return to the 1,2-dihydropyridine by the hydride reverse transfer from $\mathbf{SH}^-$ to $GPNA^+$. These results clearly show that the hydride-transfer cycle is favorable for the 1,4-dihydronicotinamides, but unfavorable for the corresponding 1,2-dihydroisomers.

Keywords: hydride transfer · kinetics · nicotinamide · thermodynamics

Introduction

The reduced form of the nicotinamide-adenine dinucleotide coenzyme [NAD(P)H] with 1,4-dihydropyridine ring plays a vital role in many bio-reductions in living bodies by transfer a hydride ion to the surrounding substrates [Eq. (1)].[1–3] In the past decades studies, the structure and chemical properties of NAD(P)H have been an interesting issue. Before the 1950s, NAD(P)H was generally believed to be a derivative of 1,2-dihydropyridine and at that time some researchers devoted their academic career to the study on the reaction mechanism of NAD(P)H by using small molecule derivatives of 1,2-dihydropyridine as NAD(P)H model compounds.[1, 4] Until the late 1950s, NAD(P)H was unambiguously identified to be a derivative of 1,4-dihydropyridine rather than a derivative of 1,2-dihydropyridine.[1, 4] From then on, various of 1,4-dihydropyridine derivatives such as 1-benzyl-1,4-dihydronicotinamide (BNAH),[5] Hantzsch 1,4-dihydropyridine (HEH),[6] 10-methyl-9,10-dihydroacridine ($AcrH_2$)[7] and many other 1,4-dihydropyridine derivatives[8] have been extensively used to mimic NAD(P)H reduction; this, of course, introduced an interesting question as to why NAD(P)H coenzyme in its biological evolution chooses 1,4-dihydropyridine rather than the 1,2-dihydropyridine structure as its redox active center in its reversible hydride transfer cycle [Eq. (1)]. The answer could result mainly from regiochemistry control of the enzyme. But the difference between NAD(P)H and its 1,2-dihydroisomer in thermodynamics and kinetics caused by the different structures in the hydride transfer cycles still is not clear up till now; this obviously is important and necessary to understand the biological evolution of NAD(P)H coenzyme for the 1,4-dihydropyridine rather than the 1,2-dihydroisomer as the reaction center structure.

In this article, we wish to elucidate the question by using a chemical mimic method. Compounds 1-(*p*-substituted phe-

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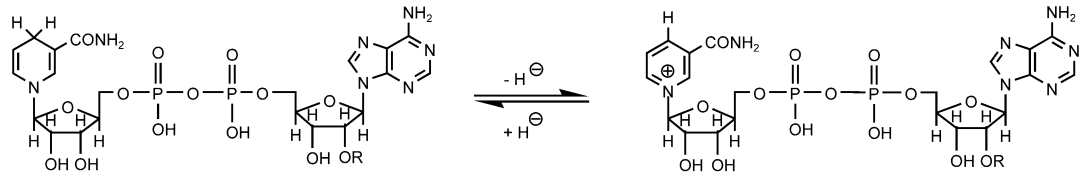
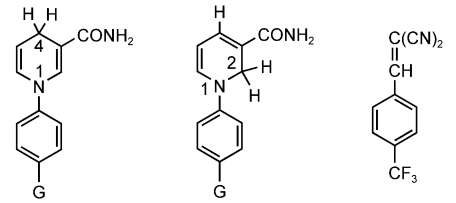


(1)

nyl)-1,4-dihydronicotinamides (GPNAH-1,4-H_2) and their 1,2-dihydroisomers (GPNAH-1,2-H_2) (Scheme 1) were used as NAD(P)H and its 1,2-dihydroisomer models, *p*-trifluoromethylbenzylidenemalononitrile (**S**) was used as a hydride



Scheme 1.

acceptor. From the experimental results, it is interesting to find that i) the 1,4-dihydronicotinamides are more stable by about 1.5 kcal mol^{-1} than the corresponding 1,2-dihydroisomers to release a hydride, but the activation free energy of the hydride transfer from the 1,4-dihydropyridines to **S** is smaller than that from the corresponding 1,2-dihydroisomer by about 2 kcal mol^{-1}; ii) the 4-position on the pyridinium generated from the 1,4- or 1,2-dihydronicotinamides is quite favorable to accept a hydride than the corresponding 2-position in thermodynamics and kinetics. These results show that the active center of NAD(P)H should be also more favorable in thermodynamics and kinetics to choose 1,4-dihydropyridine rather than 1,2-dihydropyridine by the hydride transfer cycle without the steric control of enzyme.

Results

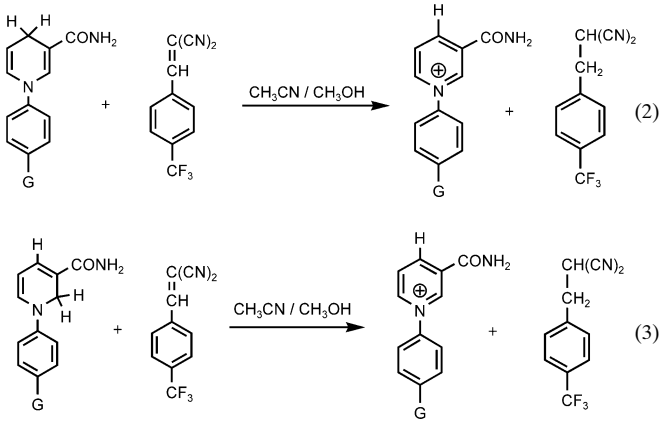
1-(*p*-Substituted phenyl)-1,4-dihydronicotinamides (GPNAH-1,4-H_2)[9] and their corresponding 1,2-dihydroisomers (GPNAH-1,2-H_2)[10] were synthesized according to literature method and were treated with *p*-trifluoromethylbenzylidenemalononitrile (**S**) in acetonitrile/methanol (9:1 *v*/*v*) at room temperature under argon atmosphere, to give the 1-(*p*-substituted phenyl)nicotinamide cations (GPNA$^+$, as NAD(P)$^+$ models) and 2-(*p*-trifluoromethylbenzyl)malononitrile (**SH_2**) [Eqs. (2) and (3)]. 4,4-Dideuterated PNAH-1,4-H_2 (PNAH-4,4-D_2) was used as a substitute for PNAH-1,4-H_2 to react with **S** under the same conditions; one deuterium atom was found to be located at the β-position to the cyano group in the reduced product 2-(*p*-trifluoromethylbenzyl)malononitrile by ^{1}H NMR and MS spectral data. *p*-Dinitrobenzene (*p*-DNB), a stronger electron acceptor,[11] was added into the two reaction mixtures; no remarkable inhibitory effect on the two reaction rates was observed. Redox potentials of the reactants in Equations (2) and (3) were determined by cyclic voltammetry at 100 mV s^{-1} in acetonitrile. The results show that the oxidation potentials of the dihydropyridines cover 0.281 – 0.400 V (vs $Fc^{+/0}$) for GPNAH-1,4-H_2 and 0.199 – 0.302 V (vs $Fc^{+/0}$) for GPNAH-1,2-H_2 and the reduction potential of *p*-trifluoromethylbenzylidene-malononitrile (**S**) is -1.229 V (vs $Fc^{+/0}$). Free energy changes of one electron transfer from the 1,4-dihydropyridines and the 1,2-dihydropyridines to **S** were estimated by using Nernst equation. The detailed results are summarized in Table 1.

Table 1. Oxidation potentials of the 1,4- and 1,2-dihydropyridines (V vs $Fc^{+/0}$) and free energy changes of one electron transfer from the 1,4- and 1,2-dihydropyridines to **S** [kcal mol^{-1}].

NAD(P)H models	E_{ox} (V vs $Fc^{+/0}$)[a]	ΔG_{eT} [kcal mol^{-1}][b]
CH_3OPNAH-1,4-H_2	0.281	34.83
CH_3PNAH-1,4-H_2	0.313	35.55
PNAH-1,4-H_2	0.363	36.72
ClPNAH-1,4-H_2	0.395	37.44
BrPNAH-1,4-H_2	0.400	37.56
CH_3OPNAH-1,2-H_2	0.199	32.92
CH_3PNAH-1,2-H_2	0.222	33.47
PNAH-1,2-H_2	0.251	34.14
ClPNAH-1,2-H_2	0.297	35.19
BrPNAH-1,2-H_2	0.302	35.31

[a] Measured by CV in MeCN at 25 °C and reproducible to 5 mV or better. [b] Free energy changes of one electron transfer from the NAD(P)H models to **S** were obtained from the equation $\Delta G_{eT} \approx -23.06\ [E_{red}(\mathbf{S}) - E_{ox}(\text{GPNAH})]$ [kcal mol^{-1}], taking $E_{red}(\mathbf{S}) = -1.229$ (V vs $Fc^{+/0}$).

Kinetics of the two reactions [Eqs. (2) and (3)] were conveniently monitored with UV/Vis absorption spectra by



(2)

(3)

following the time dependence of the absorbance at $\lambda_{max} =$ 390 nm for the 1,2-dihydropyridines (Figure 1) and at $\lambda_{max} =$

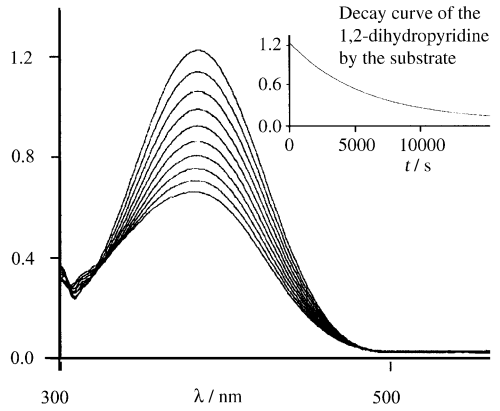


Figure 1. Change in the UV/Vis absorption spectra during the reduction of **S** by PNAH-1,2-H_2. Conditions: 0.127 mM PNAH-1,2-H_2, 10.62 mM **S** in CH_3CN/CH_3OH at 25 °C. Spectra were recorded at 10 min intervals. Inset: Decay curve of PNAH-1,2-H_2 by **S** at $\lambda_{max} = 390$ nm.

360 nm for the 1,4-dihydropyridines under pseudo-first-order reaction conditions with **S** in more than 25-fold excess. The pseudo-first-order rate constants were calculated by Guggenheim's method.[12] The second-order rate constants (k_2) at different temperature between 25 and 45 °C are given in Table 2, which were derived from the slopes of the plots of the pseudo-first-order rate constants versus the concentrations of **S**. Arrhenius activation energy (ΔE_a) and Eyring activation parameters: activation enthalpy ($\Delta H^{\neq}$) and activation entropy ($\Delta S^{\neq}$) for the two reactions [Eqs. (2) and (3)] were summarized in Table 3, which were derived from Arrhenius plots of $\ln k_2$ and Eyring plots of $\ln(k_2/T)$ versus the reciprocal of the absolute temperature ($1/T$), respectively.

Heterolytic dissociation energies of C_4–H bond for the 1,4-dihydropyridines (GPNAH-1,4-H_2) and C_2-H bond for the 1,2-dihydropyridines (GPNAH-1,2-H_2) as well as C_β-H bond for **SH**$^-$ to release a hydride were obtained from their corresponding heat of reaction with *N*-methylacridinium ($AcrH^+$) iodide in dry acetonitrile [Eqs. (4) and (5)]. The heat of reaction of *N*-methylacridinium ($AcrH^+$) iodide with GPNAH-1,4-H_2, GPNAH-1,2-H_2 and **SH**$^-$ can be directly determined by titration calorimetry, respectively (Figure 2). The detailed experimental results are listed in Table 4.

Table 2. Second-order rate constants k_2(GPNAH-1,4-H_2) and k_2(GPNAH-1,2-H_2) [$M^{-1}s^{-1}$] for the reductions of **S** in acetonitrile/methanol at different temperatures between 25 and 45 °C.[a]

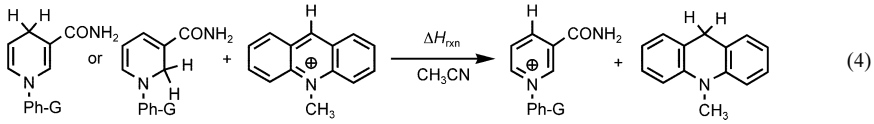
T[°C]	k_2(GPNAH-1,4-H_2) × 10^2				
	p-OMe	*p*-CH_3	*p*-H	*p*-Cl	*p*-Br
25	4.19 ± 0.02	3.52 ± 0.01	2.64 ± 0.02	1.89 ± 0.02	1.95 ± 0.02
30	5.74 ± 0.02	5.19 ± 0.02	4.02 ± 0.02	2.95 ± 0.02	2.86 ± 0.01
35	9.73 ± 0.03	8.43 ± 0.02	6.97 ± 0.02	5.21 ± 0.02	5.19 ± 0.02
40	14.49 ± 0.03	12.02 ± 0.02	10.69 ± 0.03	8.15 ± 0.03	8.07 ± 0.09
45	23.23 ± 0.22	21.18 ± 0.18	17.62 ± 0.15	13.74 ± 0.12	13.68 ± 0.11
T[°C]	k_2(GPNAH-1,2-H_2) × 10^2				
25	1.23 ± 0.01	1.12 ± 0.02	0.96 ± 0.02	0.76 ± 0.02	0.77 ± 0.02
30	1.54 ± 0.01	1.40 ± 0.02	1.22 ± 0.02	1.00 ± 0.02	1.01 ± 0.02
35	2.20 ± 0.02	2.04 ± 0.02	1.77 ± 0.03	1.48 ± 0.03	1.49 ± 0.02
40	2.77 ± 0.04	2.56 ± 0.03	2.27 ± 0.02	1.91 ± 0.03	1.91 ± 0.04
45	3.81 ± 0.04	3.55 ± 0.04	3.14 ± 0.04	2.69 ± 0.04	2.66 ± 0.04

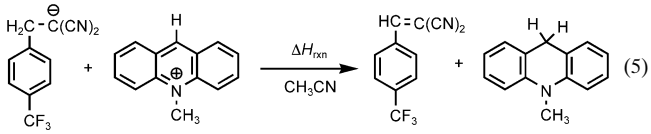
[a] Second-order rate constants k_2 were obtained from the corresponding pseudo-first-order rate constants by the linear correlation against the concentration of **S**.

Table 3. Activation parameters for the reductions of **S** with GPNAH-1,4-H_2 and GPNAH-1,2-H_2 in acetonitrile/methanol.

NA(P)H models	ΔE_a[a]	$\Delta H^{\neq}$[b]	$\Delta S^{\neq}$[c]	$-T\Delta S^{\neq}$[d]
GPNAH-1,4-H_2				
p-OCH_3	15.7 ± 0.9	15.1 ± 0.9	−14.4 ± 2.8	4.3 ± 0.8
p-CH_3	16.0 ± 0.9	15.4 ± 0.9	−13.7 ± 2.9	4.1 ± 0.9
p-H	17.2 ± 0.7	16.6 ± 0.7	−10.0 ± 2.2	3.0 ± 0.6
p-Cl	18.0 ± 0.7	17.4 ± 0.7	−8.1 ± 2.2	2.4 ± 0.6
p-Br	17.8 ± 0.9	17.2 ± 0.9	−8.8 ± 2.9	2.6 ± 0.9
GPNAH-1,2-H_2				
p-OCH_3	10.3 ± 0.6	9.7 ± 0.6	−34.9 ± 1.8	10.4 ± 0.5
p-CH_3	10.5 ± 0.6	9.9 ± 0.6	−34.3 ± 2.1	10.2 ± 0.6
p-H	10.8 ± 0.6	10.2 ± 0.5	−33.6 ± 1.8	10.0 ± 0.5
p-Cl	11.5 ± 0.6	10.9 ± 0.5	−31.9 ± 1.8	9.5 ± 0.5
p-Br	11.2 ± 0.6	10.7 ± 0.5	−32.5 ± 1.8	9.7 ± 0.5

[a] From the Arrhenius plots, the unit is [kcal mol^{-1}]. [b] From the slope of the Eyring plots, the unit is [kcal mol^{-1}]. [c] From the intercept of the Eyring plots, the unit is [cal mol^{-1} K^{-1}]. [d] The unit is [kcal mol^{-1}].





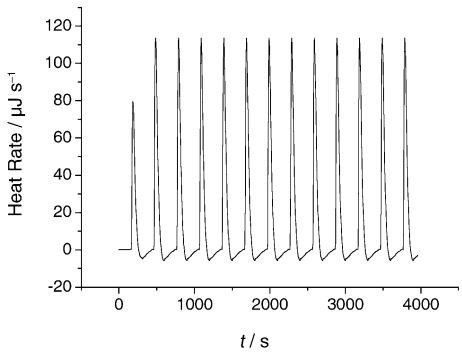


Figure 2. Titrated calibration graph: $AcrH^+$ in acetonitrile was titrated into *p*-trifluoromethylbenzyl- malononitrile-2-yl carbanion (**SH**$^-$) in acetonitrile solution ([**SH**$^-$] ≈ 0.011 M, [$AcrH^+$] = 0.0105 M). ΔH_{rxn} = 18.0 kcal mol^{-1}.

Discussion

Mechanisms of the two reactions [Eqs. (2) and (3)]: According to the product analysis and the isotope deuterium atom tracing experiment mentioned above, it is conceived that the reactions of GPNAH-1,4-H_2 and GPNAH-1,2-H_2 with **S** were

Table 4. Heat of reaction of $AcrH^+$ with the 1,4-dihydropyridines, 1,2-dihydropyridines and $\mathbf{SH}^-$ in dry acetonitrile and the heterolytic C_4-H, C_2-H and C_β-H bond dissociation energies in the 1,4-dihydropyridines, 1,2-dihydropyridines and $\mathbf{SH}^-$ in acetonitrile [kcal mol^{-1}].

Compounds	ΔH_{rxn}[a]	ΔH_{het}(C–H)[b]
CH_3OPNAH-1,4-H_2	14.7	68.3
CH_3PNAH-1,4-H_2	13.6	69.4
PNAH-1,4-H_2	12.0	71.0
ClPNAH-1,4-H_2	10.5	72.5
BrPNAH-1,4-H_2	10.8	72.2
CH_3OPNAH-1,2-H_2	16.2	66.8
CH_3PNAH-1,2-H_2	15.1	67.9
PNAH-1,2-H_2	13.5	69.5
ClPNAH-1,2-H_2	11.7	71.3
BrPNAH-1,2-H_2	12.2	70.9
$\mathbf{SH}^-$	18.0	65.0

[a] The reaction heats of $AcrH^+$ with the 1,4-dihydropyridines (GPNAH-1,4-H_2), 1,2-dihydropyridines (GPNAH-1,2-H_2) and $\mathbf{SH}^-$ measured by titration calorimetry in dry CH_3CN at 25 °C. The data obtained were average values of at least two independent runs, each of which was again an average value of 10 consecutive titrations except for the first. The reproducibility is 0.5 ± 0.2 kcal mol^{-1}. [b] Obtained from the equation $\Delta H_{het}(C{-}H) = \Delta H_{het}(AcrH_2) - \Delta H_{rxn}$, taking $\Delta H_{het}(AcrH_2) = 83$ kcal mol^{-1} in acetonitrile from ref. [13]. Standard deviation was estimated to be smaller than 1 kcal mol^{-1}.

carried out first by a formal hydride transfer from the dihydropyridines (GPNAH-1,4-H_2 and GPNAH-1,2-H_2) to the β-position to cyano group in the substrate **S**. No remarkable inhibitory effect of *p*-dinitrobenzene on the two reaction rates[14] and the estimation of large positive free energy changes for one electron transfer from the dihydropyridines to **S** (see Table 1) suggest that the formal hydride transfer from the dihydropyridines to **S** could not be initiated by single electron transfer.[15] A tentative reduction mechanism of **S** by GPNAH may be proposed as shown in Scheme 2: a hydride departs from the dihydropyridines first attached the β-carbon of **S** to form a carbanion intermediate $\mathbf{SH}^-$, which then attracts a proton from methanol to form the final reduction product $\mathbf{SH_2}$.

In order to determine the rate-limiting step in the reaction route (Scheme 2), Hammett-type free energy analyses of the two reactions were made, which provide two excellent straight lines of $\log k_2$ against the σ constant of the substituents G with reaction constant ρ values of -0.672 and -0.413 for the 1,4-dihydropyridines and for the 1,2-dihydropyridines as the hydride donors, respectively (Figure 3). The negative ρ values indicate the developing positive charge on the pyridine ring in the rate-limiting step.[16] The magnitude of the ρ values is a measure of the increase of the effective positive charge at the 1-position nitrogen atom on the pyridine ring in going from the dihydropyridines to their corresponding transition

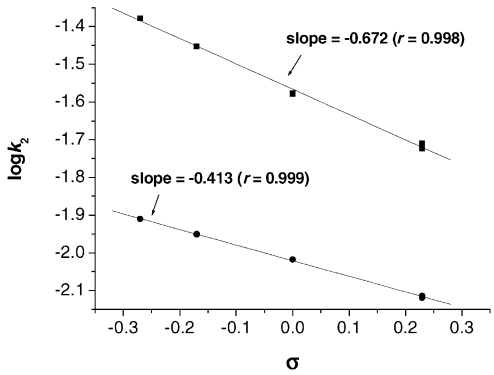


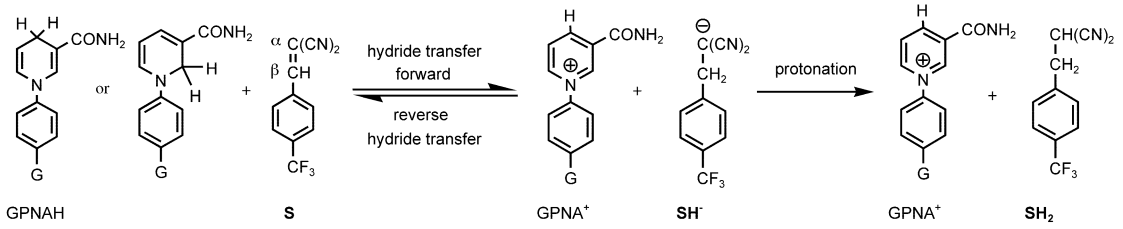
Figure 3. Correlation of $\log k_2$ (at 25 °C) versus σ constants for the reactions of GPNAH-1,4-H_2 (■) and GPNAH-1,2-H_2 (●) with **S**.

states.[17] Due to the significant dependence of the $\log k_2$ on the remote substituent G and the negative ρ values for the two reactions, the rate-limiting step should be the initial hydride transfer rather than the second step protonation of $\mathbf{SH}^-$; this indicates that the reaction rates of **S** with the dihydropyridines obtained by following the disappearance of the dihydropyridines (Table 2) should be controlled by the initial hydride transfer rather than the second step protonation of $\mathbf{SH}^-$.

Thermodynamics and kinetics of the initial hydride transfer and the hydride reverse transfer: In order to elucidate the difference of the redox reactivity between NAD(P)H and its 1,2-dihydroisomer caused by the different center structures in the hydride transfer cycles, thermodynamics and kinetics of the hydride transfer from the two types of dihydropyridines to **S** and the hydride reverse transfer in Scheme 2 were examined. The standard state energy change and the activation free energy for the initial hydride forward transfer were obtained from the heterolytic dissociation energies of the related C–H bonds (Table 4)[18] and from the relationship $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$, respectively. The detailed results are summarized in Table 5.

The standard state energy change and the corresponding activation free energy for the hydride transfer from $\mathbf{SH}^-$ to $GPNA^+$ (the hydride reverse transfer) were obtained according to the principle of *microscopic reversibility*,[19] that is under the same conditions, the mechanism for the hydride forward transfer is the same as that for the hydride reverse transfer (see Figure 4) and the detailed thermodynamic and kinetic data were listed in Table 6.[20]

The most eye-catching feature in the second column of Table 5 is that the standard state energy changes of the initial hydride transfer from the 1,4-dihydropyridines and from the 1,2-dihydropyridines to **S** are all positive values, which



Scheme 2.

Table 5. Standard state energy change and activation free energies of the hydride transfer from the 1,4-dihydripyridines and the 1,2-dihydropyridines to **S** (hydride forward transfer) in acetonitrile solution [kcal mol^{-1}].

NAD(P)H models	$\Delta H(H^-_T)$ (forward)[a]	ΔG^+ (forward)[b]
GPNAH-1,4-H_2		
CH_3O	3.3	19.4
CH_3	4.4	19.5
H	6.0	19.6
Cl	7.5	19.8
Br	7.2	19.8
GPNAH-1,2-H_2		
CH_3O	1.8	20.1
CH_3	2.9	20.1
H	4.5	20.2
Cl	6.3	20.4
Br	5.9	20.4

[a] $\Delta H(H^-_T) = \Delta H_{het}(GPNAH) - \Delta H_{het}(\mathbf{SH}^-)$. [b] Obtained from the equation of $\Delta G^+(forward) = \Delta H^+(forward) - T\Delta S^+(forward)$. The values of ΔH^+ and ΔS^+ can be obtained from Table 3.

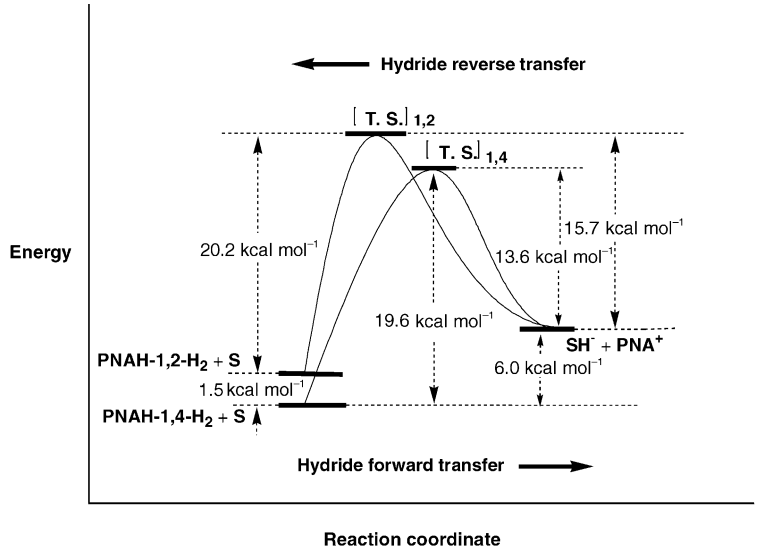


Figure 4. Reaction coordinate diagram for the hydride transfer from 1-phenyl-1,2-dihydronicotinamide (PNAH-1,2-H_2) and from 1-phenyl-1,4-dihydronicotinamide (PNAH-1,4-H_2) to **S** and for the hydride reverse transfers.

Table 6. Standard state energy change and activation free energies of the hydride transfer to the 4-position and to the 2-position in GPNA$^+$ from $\mathbf{SH}^-$ (hydride reverse transfer) in acetonitrile solution [kcal mol^{-1}].

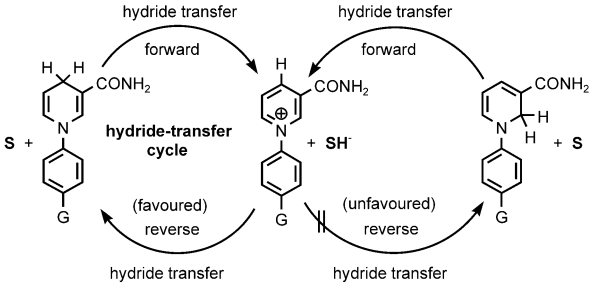
NAD(P)$^+$ models	$\Delta H(H^-_T)$ (reverse)[a]	ΔG^+ (reverse)[b]
attack to the 4-position		
CH_3OPNA^+	– 3.3	16.1
CH_3PNA^+	– 4.4	15.1
PNA^+	– 6.0	13.6
$ClPNA^+$	– 7.5	12.3
$BrPNA^+$	– 7.2	12.6
attack to the 2-position		
CH_3OPNA^+	– 1.8	18.3
CH_3PNA^+	– 2.9	17.2
PNA^+	– 4.5	15.7
$ClPNA^+$	– 6.3	14.1
$BrPNA^+$	– 5.9	14.5

[a] Obtained from the equation of $\Delta H(H^-T)(reverse) = -\Delta H(H^-T)(forward)$, the unit is kcal mol^{-1}. The related data were listed in Table 4. [b] Calculated according to the equation of $\Delta G^+(reverse) = \Delta G^+(forward) - \Delta H(H^-T)(forward)$, the unit is kcal mol^{-1}. The related data were listed in Table 3.

indicates that the initial hydride transfer from the 1,4- or 1,2-dihydropyridines are not spontaneous in thermodynamics.[21] Evidently, the initial hydride transfer requires some energies which can easily be compensated from the follow-up protonation of $\mathbf{SH}^-$. The experimental results that no reactions of the dihydropyridines with **S** were observed in dry acetonitrile without methanol may be used to support this. From the comparison of the changes in energy of the hydride forward transfer from the 1,4-dihydropyridines and from the 1,2-dihydropyridines to **S**, it is clear that the energy required for the hydride transfer from the 1,4-dihydropyridines to **S** is larger than the energy required for the hydride transfer from the corresponding 1,2-dihydropyridines to **S**; the reason is that the heterolytic dissociation energy of the C_4-H bond in the 1,4-dihydropyridines is larger than that of the C_2–H bond in the corresponding 1,2-dihydropyridines, which appears to indicate that the hydride transfer from the 1,2-hydropyridines to **S** should be faster than the hydride transfer from the 1,4-hydropyridines to **S**, but the experimental results show that the cases are just reverse (see Table 2),[18] the reason is that the activation free energies of the hydride transfer from the 1,2-dihydropyridnes (20.1 – 20.4 kcal mol^{-1}) are generally larger than that of the hydride transfer from the corresponding 1,4-dihydropyridnes (19.4 – 19.8 kcal mol^{-1}). Detailed comparison of the values of ΔH^+ and the values of $-T\Delta S^+$ in Table 3 for the two reactions shows that for the hydride transfer from the 1,4-dihydropyridines to **S**, the ΔH^+ is larger (in an absolute sense) than the corresponding $-T\Delta S^+$ by 10.7 – 14.6 kcal mol^{-1}; this indicates that the hydride transfer from the 1,4-dihydropyridines to **S** is mainly controlled by activation enthalpy, but for the reaction with the 1,2-dihydropyridines, the ΔH^+ is not larger than the corresponding $-T\Delta S^+$, which indicates that the hydride transfer from the 1,2-dihydropyridines to **S** is not only controlled by activation enthalpy but also quite more controlled by activation entropy. Obviously the latter is a main factor which makes the activation free energy of the hydride transfer from the 1,2-dihydropyridines to **S** larger than that of the hydride transfer from the 1,4-dihydropyridines to **S**. According to the structures of the 1,4-dihydropyridines and 1,2-dihydropyridines, it is clear that in the 1,4-dihydropyridines only one substituent resides proximate to the reaction center to repulse the substrate in the transition state, whereas in the 1,2-dihydropyridines there are two substituents located at the *ortho*-positions to repulse the approach of the substrate in the transition state (see Scheme 4); this can be used to explain why the activation entropy (ΔS^+) for the hydride transfer from the 1,2-dihydropyridines to **S** (– 31.9– – 34.9 cal mol^{-1}K^{-1}) is much more negative than that for the hydride transfer from the

corresponding 1,4-dihydropyridines to **S** (−8.8– −14.4 cal mol^{-1} K^{-1}).

For the hydride transfer from **SH**$^-$ to GPNA$^+$ (the hydride reverse transfer), the standard state energy changes and the activation free energies are not only dependent on the nature of the two reactants but also on the sites of the reaction center on the pyridinium ring where the hydride from **SH**$^-$ attacks. From Table 6, it is clear that when the hydride from **SH**$^-$ attacks the 4-position on the pyridinium ring, not only the thermodynamic driving force (−3.3– −7.5 kcal mol^{-1}) is larger than that when the hydride attacks to the 2-position (−1.8– −6.3 kcal mol^{-1}), but the activation free energy (16.1–12.6 kcal mol^{-1}) is also smaller than that when the hydride attacks the 2-position (18.3–14.5 kcal mol^{-1}); this indicates that when GPNA$^+$ reacts with **SH**$^-$, it is much easier for t 4-position in GPNA$^+$ to accept the hydride ion than for the 2-position to accept the hydride ion. This result means that the pyridinium derivatives formed from the 1,2-dihydropyridines cannot return to the original reduced form, 1,2-dihydropyridines by accepting a hydride from **SH**$^-$. The oxidation–reduction cycles of the 1,4-dihydropyridines and the 1,2-dihydroisomers in the reactions with **S** are shown in Scheme 3.



Scheme 3. Hydride-transfer cycles of the 1,4-dihydropyridines and the 1,2-dihydroisomers in the reactions with **S**.

In the hydride transfer cycle of the 1,4-dihydropyridines in the reaction with **S**, a hydride from the 1,4-dihydropyridines transfers to the substrate **S** to produce GPNA$^+$ and **SH**$^-$ (hydride forward transfer). In reverse order, the pyridinium GPNA$^+$ formed may return to the initial reduced form, 1,4-dihydropyridines, by the hydride reverse transfer from **SH**$^-$ to the 4-position on the pyridinium ring. Whereas in the oxidation–reduction cycle of the 1,2-dihydropyridines in the reaction with **S**, the hydride transfers from the 1,2-dihydropyridines to the substrate **S** to produce GPNA$^+$ and **SH**$^-$ (hydride forward transfer). In the reverse order, however, the GPNA$^+$ formed can not return to the initial reduced form, 1,2-dihydropyridines, by the hydride reverse transfer from **SH**$^-$ to the 2-position on the pyridinium ring, because it is much more favorable for the hydride to attack the 4-position than to attack the 2-position in both thermodynamic and kinetic terms, which makes the oxidation–reduction cycle of the 1,2-dihydropyridines in the reactions with **S** break in the reverse process.

In order to support the above proposal, the reaction of GPNA$^+$ with **SH**$^-$ was examined. When GPNA$^+$ (G = H) was treated with **SH**$^-$ in dry acetonitrile under argon atmosphere, the 1,4-dihydropyridine was obtained as the major reduced product (the yield of more than 90%)[22] with a trace of the 1,2-dihydroisomer,[23] which is well consistent with the assumptions made according to the thermodynamic and kinetic analyses above mentioned.

Nature of the transition state in the hydride forward transfer and the hydride reverse transfer: In order to further support the proposal that the 1,4-dihydropyridine is much more easy to form than the corresponding 1,2-dihydropyridine from GPNA$^+$ by hydride transfer from **SH**$^-$, the nature of the transition states in the hydride transfer from the 1,4- and 1,2-dihydropyridines to **S** was examined. When the standard state enthalpy changes [ΔH(H$^-$T)] and the activation enthalpies ($\Delta H^{\neq}$) for the two reactions [Eqs. (2) and (3)] were plotted against the Hammett substituent constant σ, four excellent straight lines were observed (see Figure 5) with slope values

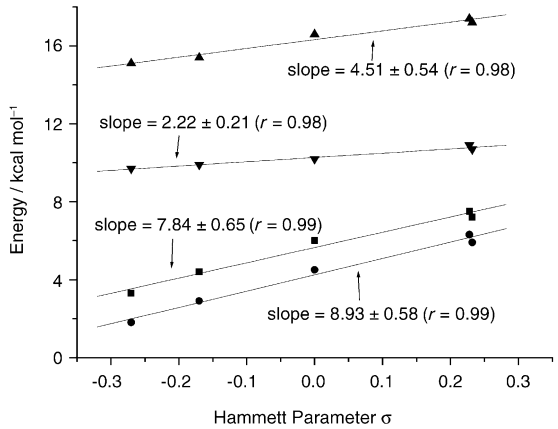


Figure 5. Hammett plots of $\Delta H^{\neq}$(1,4-) (▲) and $\Delta H^{\neq}$(1,2-) (▼), $\Delta H_{1,4}$(H^-_T) (■), $\Delta H_{1,2}$(H^-_T) (●) vs σ. The values of $\Delta H^{\neq}$(1,4-), $\Delta H^{\neq}$(1,2-), $\Delta H_{1,4}$(H^-_T), and $\Delta H_{1,2}$(H^-_T) are listed in Tables 3 and 5, respectively.

of 4.51 ± 0.46 (equivalent to Hammett reaction constant ρ of −0.79)[24] for the activation enthalpy of the reaction with the 1,4-dihydropyridines [$\Delta H^{\neq}$(1,4-)], 2.22 ± 0.21 (equivalent to ρ of −0.39) for the activation enthalpy of the reaction with the 1,2-dihydropyridines [$\Delta H^{\neq}$(1,2-)], 8.93 ± 0.58 (equivalent to ρ of −1.57) for the standard state enthalpy changes of the reaction with the 1,2-dihydropyridines [$\Delta H_{1,2}$(H$^-$T)] and 7.84 ± 0.65 (equivalent to ρ of −1.38) for the standard state enthalpy changes of the reaction with the 1,4-dihydropyridines [$\Delta H_{1,4}$(H$^-$T)]. The positive slope values reflect that positive charge increases on the nitrogen atom at the 1-position in going from the GPNAH to the transition state or to GPNA$^+$ and the magnitude of the slope values is a indicator for the relative change of the effective charge at the 1-position nitrogen atom.[25] In order to quantitatively evaluate the effective charge on the 1-position nitrogen atom in the 1,4-dihydropyridines and the 1,2-dihydropyridines in the transition states, we defined the effective charge on the 1-position nitrogen atom in GPNAH-1,4-H_2 and GPNAH-1,2-H_2 as zero, and the effective charge on the 1-position nitrogen atom in GPNA$^+$ as the positive, one unit from our basic knowledge of the electronic structures of the neutral

GPNAH-1,4-H_2 and GPNAH-1,2-H_2 as well as their corresponding production quaternary ammonium salts;[26] this indicates that the slope value of 7.84 for the hydride transfer from the 1,4-dihydropyridines to **S** [$\Delta H_{1,4}(H^-T)$] is equivalent to a positive charge increase of *one* unit on the 1-position nitrogen in going from GPNAH-1,4-H_2 to $GPNA^+$, and from which it is easily available that the slope value of 4.51 for [$\Delta H^{\neq}(1,4\text{-})$] is equivalent to positive charge increase of 0.58 on the 1-position nitrogen atom in going from GPNAH-1,4-H_2 to the transition state. Since the effective charge on the 1-position nitrogen in GPNAH-1,4-H_2 has been defined as zero, the effective charge on the 1-position nitrogen in the transition state of the 1.4-dihydropyridines should be +0.58 (Scheme 4). Similarly, according to the slope value of 8.93 for the hydride transfer from the 1,2-dihydropyridines to **S** [$\Delta H_{1,2}(H^-T)$] equivalent to positive charge increase of *one* unit on the 1-position nitrogen in going from GPNAH-1,2-H_2 to $GPNA^+$, it is clear that the effective charge on the 1-position nitrogen in the transition state of the 1.2-dihydropyridine is +0.25 (Scheme 4).[27] Comparing the effective charges on the 1-position nitrogen atom in the two transition states shows that the effective charge on the 1-position nitrogen atom in the transition state of 1,2-hydropyridines (+0.25) is quite smaller than the effective charge in the corresponding in the transition state of 1,4-hydropyridines (+0.58); this indicates that the location of the transition state of 1,2-dihydropyridines is close to the side of reactants GPNAH-1,2-H_2 (early reagent-like), but the transition state of 1,4-dihydropyridines is in the middle or slight close to the side of products $GPNA^+$ (see Scheme 4 and Figure 4).

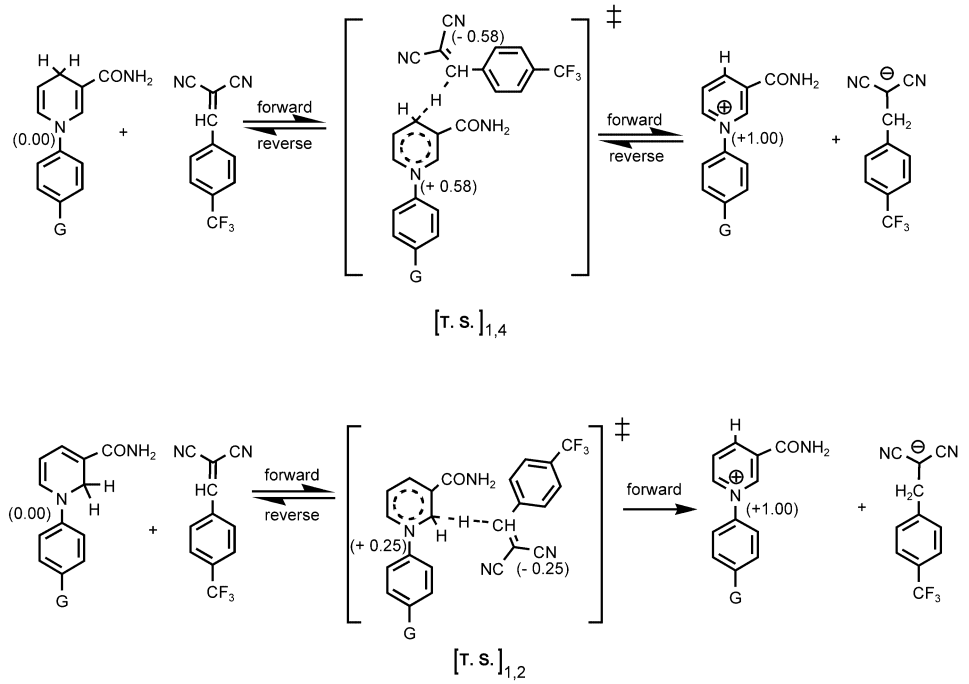
As shown from the hydride reverse transfer from $\mathbf{SH}^-$ to $GPNA^+$ in Figure 4 and Scheme 4, it is clear that the position of the transition state in the reaction coordination for the hydride transfer from $\mathbf{SH}^-$ to the 4-position of $GPNA^+$ is much more close to the side of the initial reactants ($\mathbf{SH}^-$ + $GPNA^+$) than that of the hydride transfer to the 2-position; this indicates that the transition state of the hydride transfer from $\mathbf{SH}^-$ to the 4-position is formed easier and earlier than the other transition state, since the two reactions were initiated from the same reactants ($\mathbf{SH}^-$ + $GPNA^+$).[28] This result again supports that the 1,4-dihydropyridines have precedence over the corresponding 1,2-dihydropyridines to form from the reduction of the corresponding pyridinium cation $GPNA^+$ by hydride donor $\mathbf{SH}^-$.

According to the thermodynamic and kinetic examination for the hydride reverse transfer from $\mathbf{SH}^-$ to $GPNA^+$ above mentioned, we know that there are two main factors which make the activation energy potential of the transition state to yield the 1,4-dihydropyridines much lower than that of the transition state to yield the 1,2-dihydropyridines: one is that the heterolytic dissociation energy of C_4–H bond in the 1,4-dihydropyridines is larger than that of C_2–H bond in the corresponding 1,2-dihydropyridines; the other is that hindrance at the 2-position on the pyridinium ring in $GPNA^+$ is larger than that at the 4-position.

Conclusion

According to the thermodynamic and kinetic examination of the two reactions of five 1-(*p*-substituted phenyl)-1,4-dihydronicotinamides (GPNAH-1,4-H_2) and five 1-(*p*-substituted phenyl)-1,2-dihydro- nicotinamides (GPNAH-1,2-H_2) with *p*-trifluoromethylbenzylidenemalononitrile (**S**), following conclusions can be drawn:

1) The oxidation potential of the 1,4-dihydropyridines is generally larger than that of the corresponding 1,2-dihydroisomers by 0.082–0.112 V and the heterolytic dissociation energy of C_4–H bond in the 1,4-dihydropyridines is also larger than that of C_2–H bond in the corresponding 1,2-dihydroisomers by 1.2–1.5 kcal mol^{-1}, which indicates that to the same substrate, the thermodynamic driving force of the 1,4-dihydropyridines offers an electron or a hydride is smaller than that of the corresponding 1,2-dihydroisomers.
2) When the two types of the dihydropyridines were treated with the same substrate (**S**), though the thermodynamic driving force of the hydride transfer from the 1,4-dihydropyridines is quite smaller than that of the corresponding 1,2-dihydroisomers, the activation free energy of the latter reactions is larger than that of the former



Scheme 4. Effective charge maps on the rate-determining transition states in the reactions of **S** with 1,4-dihydronicotinamide and with 1,2-dihydronicotinamide.

reactions, which is due to the more negative activation entropy for the latter reactions.

3) When the hydride reverse transfers from $\mathbf{SH}^-$ to the pyridinium $GPNA^+$, the hydride transfer to the 4-position on the pyridinium ring to form the 1,4-dihydropyridines is much more favorable than the hydride transfer to the 2-position on the pyridinium ring to form the 1,2-dihydropyridines in both of thermodynamics and kinetics, which indicates that the pyridinium derivatives $GPNA^+$ [as $NAD(P)^+$ models] can return to the 1,4-dihydropyridines rather than the 1,2-dihydropyridines by abstracting a hydride.

These results indicate that the active center of NAD(P)H is also more favorable to choose the 1,4-dihydropyridine rather than 1,2-dihydropyridine in the hydride transfer cycle without the steric control of enzyme.

Experimental Section

Materials: 1-(*p*-Substituted phenyl)-1,4-dihydronicotinamides (GPNAH-1,4-H_2) were prepared according to the following general methods: the appropriate aniline (1 mmol) dissolved in dry methanol (10 mL) was added into a solution of 1-(2,4-dinitrophenyl)nicotinomide chloride (1 mmol),[29, 30] a so-called Zincke salt, in dry methanol (100 mL). The resulting red solution was then heated gently overnight or until the red color fated to yellow, indicating the formation of 2,4-dinitroaniline. The solution was cooled, and the precipitated side product was removed by filtration. The filtrate was then evaporated in vacuum, and the residue was dissolved in H_2O (100 mL). The aqueous phase was then exhaustively washed with diethyl ether. The water layer was then evaporated under reduced pressure to give a crude product, which was recrystallized from methanol/Et_2O. Reduction of the pyridinium salt was performed in aqueous basic sodium dithionite to give the corresponding 1,4-dihydropyridine derivatives. 4,4-Dideuterated PNAH-1,4-H_2 was synthesized according to the literature,[9] the deuterium content was larger than 95% (^{1}H NMR method). 1-(*p*-Substituted phenyl)-1,2-dihydronicotinamides (GPNAH-1,2-H_2) were obtained from reductions of the corresponding pyridinium salt by $NaBH_4$ according to the literature method.[10] *p*-Trifluoromethylbenzylidenemalononitrile was prepared by Knoevenagel condensation of *p*-trifluoromethylbenzaldehyde with malononitrile in the presence of a base.[31] $\mathbf{SH}^-$ was obtained from the reaction of *p*-trifluoromethylbenzylmalononitrile with KH in dry acetonitrile. *p*-Trifluoromethylbenzylmalononitrile was available from the reduction of *p*-trifluoromethyl-benzylidenemalonotrile by 1-phenyl-1,4-dihydronicotinamide in acetonitrile/methanol. 10-Methylacridinium iodide ($AcrH^+I^-$) was obtained from the treatment of acridine by methyl iodide following the literature.[32] Reagent grade acetonitrile was distilled from P_2O_5 being passed through a column of active neutral alumina to remove water and protic impurities.

Kinetic measurements: Kinetic measurements were carried out in acetonitrile/methanol (9:1 *v*/*v*) using a Hitachi U-3000 spectrophotometer connected to a super-thermostat circulating bath to regulate the temperature of cell compartments. The oxidation rate of the 1,4-dihydropyridines and the 1,2-dihydropyridines by **S** were measured at 25–45 °C by monitoring the changes of absorption of GPNAH ([GPNAH] = 0.127 mM) at $\lambda_{max} = 360$ nm for GPNAH-1,4-H_2 and at $\lambda_{max} = 390$ nm for GPNAH-1,2-H_2 under pseudo-first-order conditions (**S** in over 25-fold excess). The pseudo-first-order rate constants were then converted to k_2 by linear correlation of pseudo-first-order rate constants against the concentrations of **S**. The activation parameters were derived from Arrhenius plots and from Eyring plots.

Titrated calibration experiments: The titration experiments were performed on a CSC4200 isothermal titration calorimeter in acetonitrile at 25 °C. Prior to use, the instrument was calibrated against an internal heat pulse, and the functional response was verified by determination of the heat of dilution of a concentrated sucrose solution.[33] Data points were collected every 2 s. The heat of reaction was determined following 10 automatic injections from a 250 μL injection syringe (containing 0.0105 M 10-methylacridinium iodide) into the reaction cell (1.00 mL) containing 0.011 M NAD(P)H models or $\mathbf{SH}^-K^+$. Injection volumes (10 μL) were delivered 0.5 s time interval with 500 s between every two injections. The reaction heat was obtained by area integration of each peak except for the first.

Electrochemical experiments: All electrochemical experiments were carried out by CV (sweep rate, 100 mV s^{-1}) using a BAS-100B electrochemical apparatus in acetonitrile under an argon atmosphere as described previously.[34] Bu_4NPF_6 (0.1 M) was employed as the supporting electrolyte. A standard three-electrode assembly consisted of a glassy carbon disk as the working electronic, a platinum wire as counter electrode, and 0.1 M $AgNO_3$/Ag as reference. All sample solution was 1.0 mM. The ferrocenium/ferrocene redox couple ($Fc^{+/0}$) was taken as an internal standard. Reproducibility is generally smaller than 5 mV.

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[15] If the hydride transfer were initiated by single electron transfer, the free energy change for this process could be estimated to be 34.83–37.56 kcal mol^{-1} for the 1,4-dihydropyridines as the electron donor and 32.92–35.31 kcal mol^{-1} for the 1,2-dihydropyridines as the electron donor according to Nernst equation (see Table 1), which, obviously, is quite larger than the corresponding activation free energy change of the two reactions ($\Delta G^{\neq}$: 19.4–19.8 kcal mol^{-1} for the reactions with the 1,4-dihydropyridines and 20.1–20.4 kcal mol^{-1} for the reactions with the 1,2-dihydropyridines see Table 5). Thus it is impossible that the hydride transfer from the dihydropyridines to **S** was initiated by single electron transfer.
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[21] Here we used reaction enthalpy to take place of Gibbs free energy to predict the spontaneity of the reactions, since standard ground entropy change for the hydride transfer is generally quite small.
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