Tetrahedron Vol. 42, No. 4, pp. 975 to 992, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00
Pergamon Press Ltd.

MECHANISM AND TRANSITION-STATE STRUCTURE OF HYDRIDE-TRANSPER REACTIONS MEDIATED BY NAD(P)H - MODELS

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(*Received in USA* 19 *June* 1985)

SUMMARY
The energy to transfer one electron from NAD(P)H and related 1,4-dihydropyridines to a series of substrates is calculated and compared with the experimental activation energy for transfer of a hydride equivalent between these species. It is concluded that single electron-transfer (SET) cannot occur as a primary step in the overall hydride-transfer process except for substrates with very strong one-electron oxidizing properties. A simple valence-bond configuration mixing (VBCM) model is presented, that rationalizes the general occurrence of concerted hydride transfer as the lowest energy reaction-pathway and furthermore explains why the activation energy of such a concerted pathway is often linearly related to that of a -hypothetical- SET process.
For one intramolecular and two related, intermolecular hydride-transfer reactions the temperature dependence of the primary kinetic isotope effect (TDKIE) was studied. For the intramolecular reaction, where a face to face orientation of the reactants is enforced, the TDKIE parameters suggest the occurrence of a bent hydride-transfer pathway. For both intermolecular reactions, however, a linear transition-state geometry is indicated. MNDO calculations of the reaction profile for hydride transfer from a 1,4-dihydropyridine to either a positively charged substrate (i.e. the pyridinium-ion) or to a neutral substrate (i.e. 1,1-dicyanoethylene) confirm, that a linear transition-state geometry is favoured, unless the system is geometrically restrained to prevent such a geometry. The MNDO calculations furthermore indicate that in a linear transition-state almost unimpeded rotation can occur about the C...H...C axis. This rotation interconverts the relative orientation of the reactants between parallel-exo and tilted-endo, which may have important consequences for the interpretation of the stereochemical outcome of reactions involving (pro)chiral reactants.

INTRODUCTION

Transfer of a hydride equivalent from the reduced pyridine-dinucleotide coenzymes NADH or NADPH to a variety of substrates is catalyzed by enzymes of the dehydrogenase family[1]. Since it was found, that also in the absence of such enzymes NAD(P)H as well as many simple dihydropyridines will transfer a hydride equivalent to sufficiently activated substrates, the latter type of reactions has been studied extensively as a model for the enzymatic process[2-4].

On one hand the study of model reactions has been focused upon efforts to mimic various aspects of the enzymatic process such as catalysis[5] and stereospecificity[6,7]. On the other hand a plethora of publications appeared[8-11], that sought to establish mechanistic details of this seemingly simple reaction. For more than a decade the central mechanistic question under discussion seems to be whether the hydride equivalent is transferred in a single step or via a pathway that involves single electron transfer (SET) as the primary step. This discussion - that for many years appears to have overshadowed other, perhaps equally important, questions - was initiated by the publication of a discrepancy[8] between the kinetic hydrogen isotope-effect and the product isotope-distribution in several NADH-model reductions. A stepwise mechanism seemed the only possibility to explain such a discrepancy.

Although it was recently shown[12-14] that most of these isotope-effect discrepancies are in fact due to the occurrence of side reactions, that had not been recognized initially, much other evidence has been gathered in the meantime that may be interpreted to support the occurrence of SET as a primary step in the overall hydride-abstraction process[15-19].

The present paper seeks to establish a final answer to the question of the feasibility of SET in NADH-model reactions and furthermore to shed some light on the more intimate details of the transition-state of the actual hydride-transfer process.

ON THE QUESTION OF ONE ELECTRON-TRANSFER IN NAD(P)H-MODEL REACTIONS

As early as 1978 we pointed out[20], that the feasibility of SET in NAD(P)H-model reactions can -in principle - be decided from straightforward thermodynamic considerations. This is enabled by the possibility to calculate the change in Gibbs free energy for SET (ΔG_{set}) from electrochemical one-electron redox potentials via eqn. (1):

$$\Delta G_{set} = E_{ox}(PyH_2) - E_{red}(S) - C \qquad (1)$$

In (1) the reversible one-electron oxidation potential of the dihydropyridine and the reversible one-electron reduction potential of the substrate are indicated by $E_{ox}(PyH_2)$ and $E_{red}(S)$, while C stands for the Coulombic stabilization of the radical ion-pair created upon one-electron transfer ($PyH_2^{+\cdot}$ $S^{-\cdot}$) with respect to the separate ions. In a polar solvent the value of the latter term is only small (0.06 eV in acetonitrile)[21] and if S is a positive ion the latter term of course vanishes.

Evidently the Gibbs free energy of activation for any reaction involving primary SET can never be smaller than ΔG_{set} and therefore the maximum rate constant for such[21,22] a reaction (k_{set}^{max}) is given by (2) where $k_{diff.}$ indicates the diffusional rate constant.

$$1/k_{set}^{max} = 1/k_{diff} + 10^{-11}.\exp(\Delta G_{set}/RT) \qquad (2)$$

With a dihydropyridine as the electron donor an additional problem arises in application of (1) because of the irreversible behaviour of the electrochemical oxidation of these molecules, that thwarts the direct determination of $E_{ox}(PyH_2)$. Employing a fluorescence quenching method originally proposed by Weller e.a.[22] we were,however, able to determine for 1-benzyl-1,4-dihydronicotinamide (BNAH) in acetonitrile a value of the one-electron oxidation potential : $E_{ox}(BNAH) = 0.76 \pm 0.02$ V (relative to the saturated calomel electrode at 20°C)[20]. Recently another indirect method was employed by Miller e.a.[18] to determine the one-electron oxidation potential of NADH in aqueous solution. The result $- E_{ox}(NADH) = 0.81$ V (rel. to sce) - not only corroborates our earlier results, but also indicates,that the one-electron donor capacities of NADH and BNAH are very similar,as might be expected from the structural equivalence of the 1-alkyl-1,4-dihydronicotinamide moiety incorporated in these species.

For a number of substrates with known $E_{red}(S)$ Table I now compares the calculated k_{set}^{max} and the reported experimental rate of hydride abstraction by these substrates (k_{hyd}) from BNAH or NADH . In our calculations $E_{ox}(PyH_2) = 0.76$ V (rel. to sce) was adopted and the Coulomb term C was either 0.06 eV for neutral substrates or zero for positive substrates. In all cases the calculated electron transfer rate is far from the diffusional limit whereby eqn.(2) simplifies to: $k_{set}^{max} = 10^{11}.\exp(-\Delta G_{set}/RT)$ $1.mol^{-1}.s^{-1}$.

Table I

Compilation of calculated (according to eqn. (1) and (2) with $E_{ox}(PyH_2)$=0.76 V) data for SET between BNAH or NADH and a series of substrates , as well as literature data for the experimental rate constant of hydride abstraction by these substrates (k_{hyd}).

Substrate	$E_{red}(S)$[a] (V vs.sce)	ΔG_{set} (eV)	k_{set}^{max} ($M^{-1}.s^{-1}$)	k_{hyd} ($M^{-1}.s^{-1}$)	conditions	ref.
1. CF_3COPh	- 1.46	2.16	4×10^{-23}	10^{-5}	acetonitrile ,50°C	23
2. BNA^+Cl^-	- 0.97	1.73	2.5×10^{-17}	2×10^{-3}	CH_3CN/H_2O(1/3) ,40°C	24
3. p-benzoquinone	- 0.51	1.21	1.1×10^{-9}	4.77	water ,30°C	25
4. hexachloroacetone	- 0.27	0.97	6.8×10^{-6}	0.25	acetonitrile ,27°C	26
5. N-Me-acridinium	- 0.24	1.00	9×10^{-7}	55	acetonitrile ,20°C	13
6. 2,6-dichloro-p--benzoquinone	- 0.18	0.88	3.1×10^{-4}	805	water ,30°C	25
7. chloranil	+ 0.01	0.71	0.13	1900	acetonitrile ,25°C	27
8. ferrocenium	+ 0.16	0.6	12.8	13.7	1-PrOH/H_2O(1/1) 30°C	18
9. $Fe(CN)_6^{3-}$	+ 0.21	0.49	840	1.36	CH_3CN/H_2O(1/4) ,30°C	19

a) One-electron reduction potentials measured in acetonitrile (see ref. 20 and 28)except for the two last entries,that refer to aqueous solutions.

The occurrence of SET as the primary process in hydride abstraction requires that the ratio k_{hyd}/k_{set}^{max} does not exceed unity. From the data in Table I and from Fig.1 , where this ratio is plotted on a logarithmic scale as a function of ΔG_{set}, it is evident that only the strong one-electron oxidants,that form the two last entries,pass this test for the feasibility of SET. This confirms our earlier report[20] ,that was based on a more limited data base , as well as the recent reports from other investigators[25,29] that showed hydride abstraction by most substrates to occur faster than would be possible if SET were involved. Thus most substrates compiled in Table I must perform hydride abstraction by a mechanism not involving SET,and concerted hydride transfer seems an attractive candidate for such a mechanism as will be discussed below.

Fig. 1 not only shows that most reactions from Table I cannot involve SET (i.e. that in most cases k_{hyd}/k_{set}^{max} exceeds unity) but also suggests,that a certain mechanistic similarity exists leading to a linear relation between ΔG_{set} and the logarithm of this ratio , given by eqn. (3) and indicated by the solid line in Fig. 1.

$$(3) \qquad \log (k_{hyd}/k_{set}^{max}) = -2 + 9.1 \times \Delta G_{set} \ (\text{eV}) \qquad \text{(eV)}$$

Extrapolation of this line suggests, that SET would become feasible at ΔG_{set} values below 0.22 eV . The two one-electron oxidants show that an earlier change-over to a SET mechanism can occur if the substrate has no significant hydride affinity. In these cases the lack of such hydride affinity also shows up in the stoichiometry , that was found to involve a 2 : 1 substrate / PyH_2 ratio , each substrate consuming one electron while the hydrogen nucleus is expelled as such [18,19].

Since ΔG_{set} is directly related to log k_{set}^{max} via eqn.(2) the linear relation expressed by eqn.(3) in fact implies, that log k_{hyd} responds almost linearly to changes in ΔG_{set} over a kinetic range that spans more than 8 orders of magnitude. The existence of such relations has been noted before and it has also been shown, that a more rigorously linear relation occurs if care is taken to compare the reactivities of a series of structurally related compounds[19] instead of the widely different systems compiled in Table I.

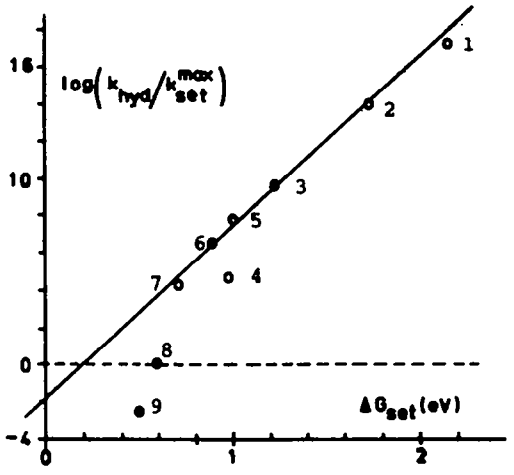


Figure 1 :

Feasibility test for the occurrence of SET in the reactions compiled in Table I.
Systems (8 and 9) at or below the broken line pass the test.
The solid line (eqn.(3)) indicates an approximate linear free-energy relation between the other systems.

It seems of interest to stipulate, that this direct relation between ΔG_{set} and log k_{hyd} is by no means in contradiction with our conclusion that SET is not involved as a separate reaction step. Following the qualitative description of reaction profiles as a result of the mixing between various electronic configurations (i.e. the valence-bond configuration mixing model (VBCM))[30] it can easily be shown , that such a linear free energy relation between ΔG_{set} and log k_{hyd} is in full agreement with the occurrence of concerted hydride-transfer via a transition-state substantially below ΔG_{set} ! Consider the transfer of a hydride-equivalent between two electrophiles P^+ and E^+ i.e.:

$$P\text{-}H + E^+ \rightarrow P^+ + H\text{-}E$$

Using the pictorial representation of singlet electronic configurations put forward by Pross and Shaik[30] the starting materials and products in this reaction are given by ($P^{\cdot}\cdot H$ E^+) and (P^+ $H^{\cdot}\cdot E$). Note that these configurations merely differ by a single electron transfer from P to E !

In Fig. 2 we have drawn solid lines to indicate - according to the rules proposed by Pross and Shaik[30] - the energy of these two electronic configurations as a function of the reaction coordinate, that is created by moving the hydrogen nucleus from P to E. During this process the starting material configuration is progressively destabilized as a two-electron bond is broken and a formal one-electron bond is formed. For the product configuration the reverse holds. At the onset of the reaction the two configurations are separated by an energy-gap that corresponds to ΔG_{set}! During the reaction this energy--gap diminishes leading to increased mixing and an avoided crossing - as indicated by the broken lines in Fig. 2 - that creates a single transition-state with a wavefunction that can be represented by:

(4) $$\Psi_{TS} = 2^{-\frac{1}{2}} \{ (P^{\cdot}\cdot H \quad E^+) + (P^+ \quad H^{\cdot}\cdot E) \}$$

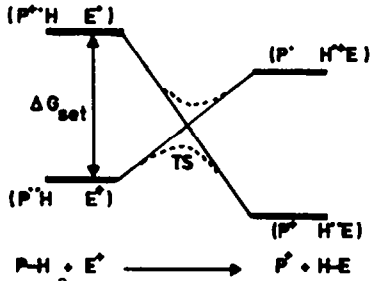


Figure 2 :

Two configuration VBCM model for concerted hydride transfer.

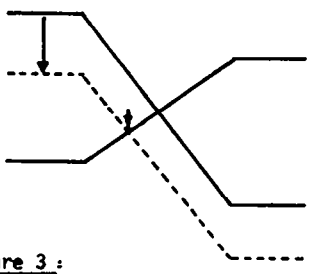


Figure 3 :

Proportional lowering of ΔG_{set} and the activation energy.

This very simple two configuration model of concerted hydride-transfer leads to a number of very illuminating results. Thus substitution of E^+ by a stronger one electron acceptor not only lowers ΔG_{set} but also shifts the crossing and thereby the transition-state to an earlier point on the reaction coordinate (see Fig. 3). As a result the activation energy for transfer is lowered proportionally and furthermore the difference between this activation energy and ΔG_{set} is decreased as experimentally observed (see Fig. 1 and eqn.(3)). Furthermore the transition-state description provided by the two configuration mixing (c.f. eqn.(4)) shows, that although a hydride equivalent is transferred, this not neccessarily implies that a substantial negative charge develops around the hydrogen nucleus in flight. Inclusion of configurations such as (P^+ H^- E^+) and ($P^\cdot$ H^+ $E^\cdot$), that are way up in energy at the initial and product stage, but probably contribute at intermediate stages, will lead to a slight modification of this picture. It is not an easy task, however, to quantify the contribution of such configurations within the qualitative framework of the VBCM method and efforts to do so tend to obscure the insight gained from the primary approach. Therefore a more detailed discussion of the charge distribution in the transition-state is postponed to a later section of this paper where it will be derived from MNDO calculations.

TEMPERATURE DEPENDENCE OF THE PRIMARY KINETIC ISOTOPE EFFECT AS A PROBE FOR TRANSITION-STATE GEOMETRY

As explained in the preceding section it now seems fully established, that for the majority of hydride transfer reactions mediated by NAD(P)H-models the kinetic hydrogen isotope effect must reflect that of C-H bond cleavage in the rate determining transition-state (TS) without masking effects from partially rate limiting preequilibria such as SET. It has been proposed [31] - mainly on a semiempirical basis - that under such conditions a study of the temperature dependence of the primary kinetic isotope effect (TDKIE) can yield valuable information about the TS geometry. For this purpose the experimental rate constants (i.e. k_H and k_D) are fitted to the Arrhenius equation to yield the frequency factors (A_H and A_D) and the activation energies ($E_a(H)$, $E_a(D)$) for hydrogen and deuterium transfer.

Three main cases are distinguished, each thought to characterize a specific mode of hydrogen transfer. Thus hydrogen transfer via a bent TS is assumed to lead to a negligible isotope effect on E_a (i.e. $E_a(D) - E_a(H) = 0$) and therefore to a temperature independent kinetic isotope effect that equals the ratio of the frequency factors ($k_H/k_D = A_H/A_D$) and typically falls in the range $2^{\frac{1}{2}} \rightarrow 6$.

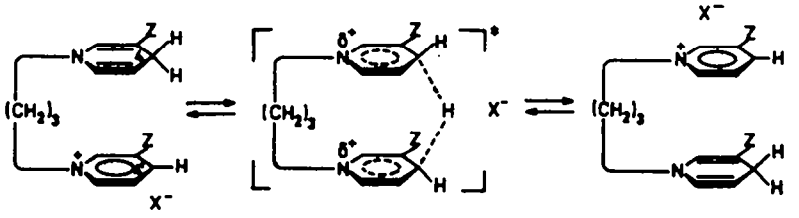
A linear TS should lead to a significant difference between $E_a(H)$ and $E_a(D)$ with the difference between the zero-point vibrational energies of C-H and C-D stretching modes as an upper limit ($\simeq$1.15 kcal/mol), while furthermore the ratio of the frequency factors is typically found in the range $0.7 \rightarrow 2^{\frac{1}{2}}$.

Finally , if the difference between $E_a(D)$ and $E_a(H)$ exceeds the zero-point vibrational energy difference, this is assumed to indicate the occurrence of hydrogen tunnelling.

Although the applicability of these semiempirical criteria as a tool to probe the TS has met severe criticism [32,33], we deemed it worthwhile to study the TDKIE of NADH-model reactions for which the kinetics can be measured with sufficient accuracy. At the onset of this investigation we in fact shared the rather widespread [17,34] prejudice, that in the TS the dihydropyridine and the substrate are orientated in a parallel face to face ('sandwich') configuration that resembles the orientation quite generally found [28] in pi-molecular complexes between electron-rich and electron-poor species.

In fact we have shown earlier [35] that reasonably fast intramolecular hydride exchange occurs (effective molarity approximately 200 mol/l) in a system 1 where such a face to face TS seems to be enforced (cf. Fig. 4). Evidently this made the reaction depicted

in Fig. 4 an attractive test case for the TDKIE method since a sandwich orientation may be expected to lead to a bent TS[34,36]. Kinetic measurements on 1 and its 4,4'-trideuterio analogue were performed by ^{1}H-NMR employing the spin-saturation transfer technique as described earlier[35]. Care was taken to use identical concentrations and identical counter-ions ($X^- = Cl^-$) in both series of measurements. Especially the effect of the counter-ion on the activation parameters was found to be sufficiently large to make TDKIE measurements with different counter-ions for H and D transfer meaningless !



1 [X = Cl ; Z = $CONH_2$]

Figure 4 Intramolecular hydride exchange and proposed transition-state structure in system 1 .

Table II

Rate constants (s^{-1}) for intramolecular hydride (k_H) and deuteride (k_D) exchange in 1 and in 1-($4d_2$,4'd) at various temperatures (solvent DMSO-d_6) as well as the Arrhenius equations (see also Fig. 5) and the activation parameters derived from these data.

Temp. (K) :	303	313	318	323	328	333	343
k_H	0.26	0.43	0.51	0.65	0.81	0.99	-
k_D	-	0.15	0.19	0.24	-	0.37	0.53

$A_H/A_D = 2.7 \pm 1.2$

$E_a(D)-E_a(H) = 0.0 \pm 0.2$ kcal/mol

$k_H/k_D = 2.7$

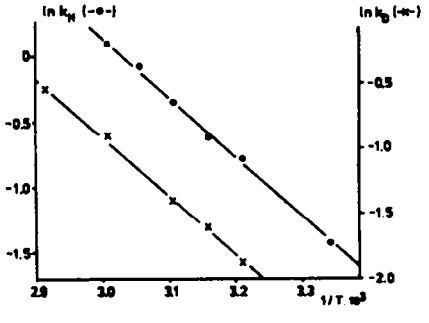
$\ln k_H = (13.4 \pm 0.2) - (8.89 \pm 0.12$ kcal/mol)/RT (r=0.999)

$\ln k_D = (12.4 \pm 0.4) - (8.89 \pm 0.24$ kcal/mol)/RT (r=0.998)

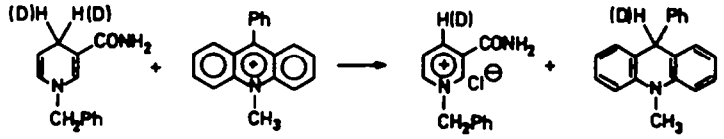
Table II compiles the results obtained while the Arrhenius plots derived from the kinetic data are shown in Fig. 5. The kinetic isotope effect was thus found to be virtually constant over the (limited) temperature range studied. This result thus seems to lend direct experimental support to the hypothesis[31] that a bent TS may be typified by the occurrence of a substantial but temperature independent KIE!

Figure 5

Arrhenius plots for hydride and deuteride transfer in 1 and 1-($4d_2$,4'd) (see Table II).



While the TDKIE data for intramolecular hydride exchange in 1 thus nicely fulfilled our expectations, a surprise turned up as we switched to the study of a related intermolecular reaction. As we already reported earlier [37], the TDKIE parameters for hydride transfer from BNAH to the 10-methyl-9-phenylacridinium ion ($AcPh^+$) (see Fig. 6) lead to a completely different picture. From the kinetic data and the corresponding Arrhenius parameters compiled in Table III it is clear that the KIE of this reaction decreases upon increasing temperature. The difference in activation energy and the ratio of the frequency factors both fall in the range proposed to typify a linear TS.



BNAH AcPh⁺ (BNA⁺) AcPhH(D)

Figure 6

Table III

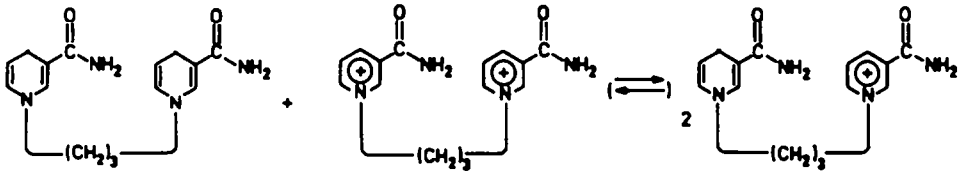
Rate constants ($l.mol^{-1}.s^{-1}$) for hydride and deuteride transfer from BNAH and BNAH-($4d_2$) to $AcPh^+$ at various temperatures (solvent acetonitrile) as well as the Arrhenius equations and activation parameters derived from these data.

Temp. (K) :	293	298	303	308	313	318	323	328
k_H	1.78	2.26	2.77	3.20	3.63	3.88	5.15	-
k_D	0.44	0.54	0.70	0.82	0.98	1.77	1.39	1.65

$\ln k_H = (11.1 \pm 0.6) - (6.11 \pm 0.38$ kcal/mol)/RT (r=0.989)
$\ln k_D = (11.4 \pm 0.2) - (7.14 \pm 0.09$ kcal/mol)/RT (r=0.999)

$A_H/A_D = 0.74 \pm 0.46$
$E_a(D)-E_a(H) = 1.03 \pm 0.38$ kcal/mol
$k_H/k_D = 4.17$ (298 K)

As a second intermolecular reaction the hydride transfer between 2 and 3 (see Fig. 7) was studied. This reaction constitutes the last step in the synthesis of 1 and can be followed spectrophotometrically by monitoring the growth of the typical longwavelength, intramolecular charge-transfer absorption characteristic for 1 (ε = 407 $l.mol^{-1}.cm^{-1}$ at 460 nm (sh)).The reaction leads to an equilibrium that lies sufficiently to the right ($K > 10$)[35] to allow determination of the forward rate constant under pseudo first-order conditions (3 >> 2).



2 Figure 7 3 1

Table IV

Rate constant ($l.mol^{-1}.s^{-1}$) for hydride and deuteride transfer from 2 and 2-(d_4) to 3 at various temperatures (solvent: aqueous borate buffer , pH 8.22) as well as the Arrhenius equations and activation parameters derived from these data.

Temp. (K) :	293	295	298	303	308	313	318	323
k_H ($x10^2$)	-	1.56	-	2.45	3.14	4.04	-	6.65
k_D ($x10^3$)	4.21	-	5.68	7.91	-	13.43	16.91	21.71

$\ln k_H = (12.5 \pm 0.1) - (9.75 \pm 0.07$ kcal/mol)/RT (r=0.999)
$\ln k_D = (12.2 \pm 0.3) - (10.27 \pm 0.14$ kcal/mol)/RT (r=0.993)

$A_H/A_D = 1.4 \pm 0.2$
$E_a(D)-E_a(H) = 0.52 \pm 0.17$ kcal/mol
$k_H/k_D = 3.23$ (298 K)

Once again the TDKIE parameters (see Table IV) fall within the range proposed to typify a linear TS.

As mentioned above, the use of TDKIE as a tool to distinguish between bent and linear TS geometries has been criticized severely.[32,33] In particular a recent theoretical study[33] led to the conclusion, that a bent TS (or a linear TS) can never give rise to a temperature independent KIE with a value significantly larger than unity.

Our present observation of such a situation for the intramolecular reaction in 1 seems to militate against such a generalization and adds some new credibility to the value of the TDKIE method that was so actively advocated by the late Harold Kwart[31] !

On the experimental side , however, the applicability of the TDKIE method in the field of NADH-model reactions seems severely limited by the problems arising in the determination of the kinetics of such reactions with sufficient accuracy over an acceptable temperature range. Furthermore interpretation of the present data is complicated by the possible occurrence of secondary isotope effects (although these are probably small[36,38] and their temperature dependence is therefore expected to be extremely small) and especially by the possible contribution of tunnelling.[39]

Several recent reports indicate a significant tunnelling contribution to hydride transfer mediated by NADH and its models both under enzymatic[40] and under non-enzymatic[34,38] conditions. It should be noted that especially for the reaction depicted in Fig. 6 the upper experimental limit of $E_a(D)-E_a(H)$ enters the range typical for tunnelling. For a closely related reaction Bruice e.a. recently reported an even larger difference in activation energy and attributed this to an important tunnelling contribution[34].

In view of the remaining uncertainty about the exact nature of the TS both regarding its spatial structure and the charge distribution occurring, we decided to approach this problem via a quantummechanical calculation of the complete reaction profile for some hydride-transfer processes closely related to the systems discussed above.

MNDO CALCULATION OF REACTION PATHWAYS[41]

Model systems and calculational method

The reactions (I) and (II) for which calculations have been performed are represented in Fig. 8.

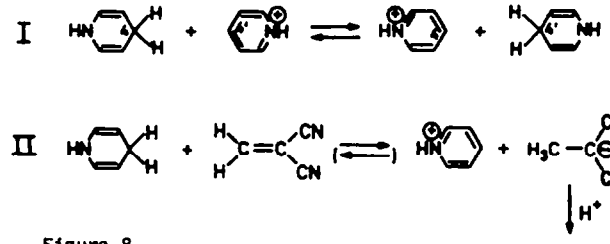


Figure 8.

As a calculational model representing NAD(P)H the bare 1,4-dihydropyridine molecule was chosen, since it is the reactive part of these coenzymes apart from the $-CONH_2$ group. Variation of the latter has been found[42] not to affect the stereochemical course of hydride transfer under enzymatic conditions.

As models for substrates we have chosen two molecules closely related to systems of practical relevance. The pyridinium cation was chosen to represent positively charged substrates (reaction(I)). This offers the calculational advantage of symmetrical transition-states (vide infra). As a model for neutral substrates, like activated carbonyl compounds and electronegatively substituted olefines, the molecule 1,1-dicyanoethene was chosen (reaction (II)). As indicated in Fig. 8 the reactions represented by (II) are usually accompanied by irreversible protonation of the incipient anion produced upon hydride transfer to a neutral substrate. The role of this protonation step will be discussed in more detail below.

The dimensions of the systems under consideration practically excluding ab-initio methods, we decided to use the MNDO method. This has not only been found to allow a good prediction of molecular properties[43] but also to reproduce the qualitative features of ab-initio potential surfaces and transition structures[44]. A local version of the MNDO program[45,46] was used. This version offers the possibilities of symmetry and dependence relations in the definition of molecular geometries.

The system dihydropyridine/pyridinium-ion (I)

During a first search of the reaction coordinate for reaction-(I) both ring systems were assumed to retain planarity and standard bondlengths and angles were used except for the C(4)-H bonds. Two relative orientations of the reactants were initially considered, a parallel-endo orientation and a parallel-exo orientation (see Fig. 9). It has often been suggested[34], that a parallel-endo ("sandwich") orientation evolves from a primary charge-transfer type complex between the electron-rich 1,4-dihydropyridines and the electron-poor substrates and that such an orientation leads to non-linear hydride transfer. In our initial calculations on this reaction geometry

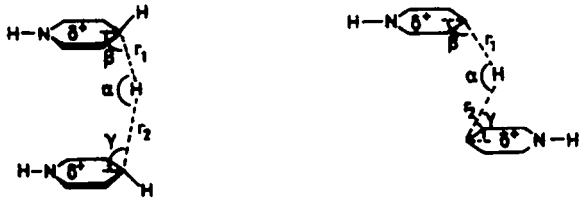


Figure 9 : parallel-endo ('sandwich') and parallel-exo reactant orientations initially considered for reaction I.

the positions of the rings were defined with respect to the hydride. The rings were kept parallel by imposing the following dependence relation: $\gamma = 2\pi-\alpha-\beta$ (in which the angles α and β were varied). In this way the rings still had the possiblity of moving parallel to each other. Concerning the latter it should be noted that, even in quite asymmetrical positions of the hydride, the rings hardly did move relative to each other, i.e. the angles β and γ assumed (almost) equal values. Calculations were carried out for points (r_1, r_2) with intervals of 0.1 Å, in the range of 1.1 to 1.9 Å. An advantage of the symmetry of the system was, that only half of the points had to be calculated. The resulting enthalpy-contour diagram, as drawn by interpolation of the calculated enthalpy values, is shown in Fig. 10.
From this contour diagram follows a transition state with C_{2v} symmetry, with $r_1 = r_2 = 1.62$ Å and $\Delta H_f^0 = 289.6$ kcal/mol. In the TS the angle α was found to be 158.2^0 (so $\beta = \gamma = 100.9^0$) thus confirming the expectation[34,36] that a parallel-endo ("sandwich") orientation of the reactants induces a non-linear hydride transfer.

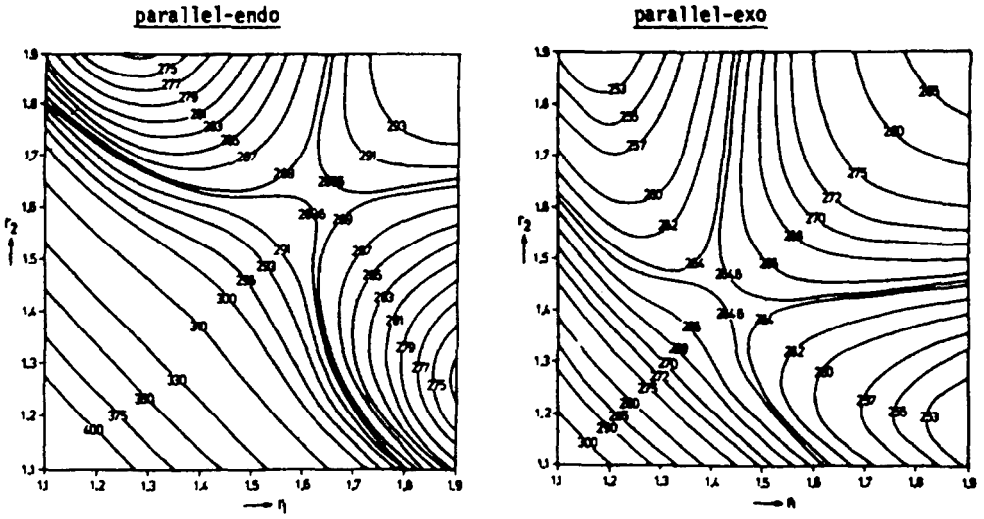


Figure 10 : Enthalpy-contour diagrams for reaction I in a parallel-endo (left) and a parallel-exo (right) orientation. Enthalpy values in kcal/mol.

From our study on the temperature dependence of the primary kinetic isotope effect for a type I reaction we concluded that a linear TS is in fact more likely than a bent TS. Although this conclusion was challenged by others[32,34], calculations by Buck c.s.[47] on the dihydropyridine/cyclopropeniumion system also indicated a preference for a linear TS resulting from hydride transfer with the reactants in a parallel-exo arrangement. However Buck c.s. did not study this pathway for the dihydropyridine/pyridinium-ion system nor were they able to make a quantitative comparison with the parallel-endo arrangement.

We now calculated an enthalpy-contour diagram for reaction-I in a parallel-exo arrangement by implementing the dependence relation $\gamma = \alpha + \beta - \pi$ with α and β left free to be optimized at each set of r_1/r_2 values. In this way the rings are kept anti-parallel, but the program is "free to choose" a linear ($\alpha = \pi$) or a non-linear ($\alpha \neq \pi$) TS. The resulting contour map is shown in Fig. 10. The TS was found to be linear indeed ($\alpha = 180^{\circ}$) and to have C_{2h} symmetry with $r_1 = r_2 = 1.43$ Å and $\Delta H_f^{\circ} = 264.6$ kcal/mol.

Although it should be noted, that the contour diagrams in Fig. 10 were calculated with partial geometry optimization (all bond-lengths and bond-angles fixed at standard values except for the C(4)-H bonds) the 25 kcal/mol ΔH_f° difference between the parallel-endo and parallel-exo TS suggests that the latter constitutes the preferred pathway for type-I reactions. This also seems quite in line with our earlier conclusion that in type-I reactions hydride transfer occurs via a linear TS as indicated by the temperature dependence of the primary kinetic isotope effect. Upon closer inspection, however, the situation turned out to be more complex. This became evident upon investigation of the effect of rotation about the C(4)-hydride-C(4') axis in the parallel-exo TS. It was found that such rotation is virtually unimpeded thus changing the parallel-exo TS into a tilted-endo TS via a continuum of equi-energetic intermediate structures (see Fig. 11)!

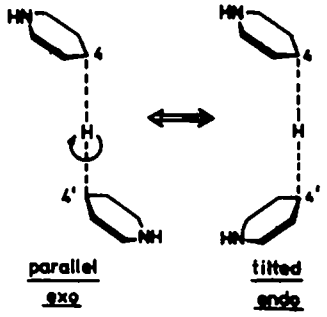


Figure 11 :
Interconversion of parallel-exo and tilted-endo arrangements by rotation about the C(4)-Hyd-C(4') axis.

Thus the experimental [37] finding of a linear TS can no longer be taken as evidence for an exo arrangement of the reactants. In order to confirm these conclusions it was decided to recalculate the three TS structures (i.e. parallel-endo, parallel-exo and tilted-endo) under full geometry optimization. The TS structural parameters thus obtained are given in Table V, where the angles β and γ now should be interpreted as the angles N(1), C(4), Hyd and N(1'),C(4'), Hyd respectively. Table V also gives the activation enthalpies calculated relative to the optimized reactants.
A first striking result of the full geometry optimization is that in the parallel-endo TS the rings no longer are planar. Due to repulsive (electrostatic and/or steric) interaction the carbon atoms in the rings bend away from each other around the lines

Table V : Parameters for the three fully optimized transition-state arrangements shown in Fig. 12.

	parallel-endo	parallel-exo	tilted-endo
$r_1=r_2$ (Å)	1.467	1.383	1.382
α	168.2°	180°	180°
$\beta=\gamma$	95.9°	113°	114.6°
r[C(4)-C(4')] (Å)	2.919	2.766	2.765
ΔH_f^o (kcal/mol)	255.84	239.55	240.82
ΔH_f^* (kcal/mol)	42.56	26.26	27.54

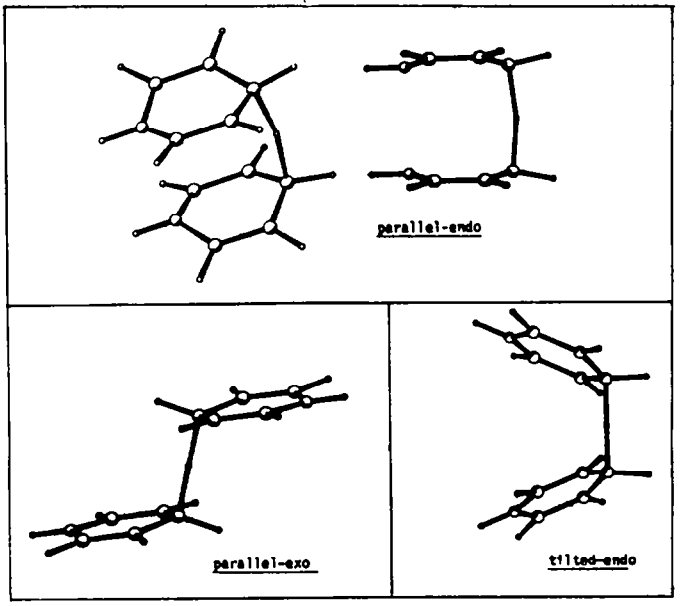


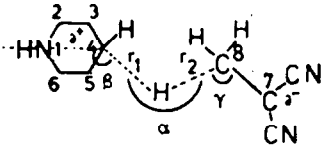
Figure 12 : PLUTO drawings of the fully optimized transition-state arrangements for reaction I.

N(1)-C(4) (it should be noted, that these lines had been kept parallel artificially in this geometry). In the two other TS orientations the rings retain planarity. These results can be illustrated by the PLUTO drawings shown in Fig. 12.
From Table V it is clear that also after full optimization a TS involving linear hydride transfer remains strongly favoured over the bent mode. This is reflected in the distances of the hydride to the C(4) atoms; in the linear transition states these are considerably shorter than in the parallel-endo TS.
Apparently the repulsive steric and electrostatic ring-ring interaction in the parallel-endo geometry prevents an approach of the rings, close enough for a favourable hydride-transfer.
These considerations make clear that the parallel-endo pathway and the non-linear hydride transfer evoked by it are computational artefacts and will not occur in real reactions of type-I unless enforced by strong stereochemical constraints .
In the course of the reaction by either of the pathways considered, only a slight amount of negative charge is calculated to build up on the "hydride". This seems to confirm the qualitative correctness of the VBCM model discussed earlier (see Fig. 2 and 3). Charges were found of -0.13 for the parallel-endo, -0.12 for the parallel-exo, and -0.11 for the tilted-endo transition states. In all three transition states the population on the C(4)-Hyd bonds is 0.44 thus demonstrating that the C(4')-Hyd bond-formation occurs in concert with the C(4)-Hyd bond-breaking.
It can now be stated that our earlier conclusions (vide supra) that in type-I reactions hydride transfer occurs by a one-step mechanism involving a linear TS are fully confirmed by the calculational results. However, the system seems completely free to choose between either an endo or an exo geometry! The small differences (as seen in Table V) between the (gas-phase!) values obtained for the two linear geometries will probably vanish in solvents of high dielectric constant; secondary factors will then be decisive in determining the ultimate reaction geometry both under non-enzymatic and under enzymatic conditions.

The system 1,4-dihydropyridine/1,1-dicyanoethene (II)

For the system 1,4-dihydropyridine/1,1-dicyanoethene (DCE) three reaction geometries analogous to the parallel-endo, parallel-exo and tilted-endo arrangements mentioned above were considered. First, orientating calculations with partial geometry optimization were carried out. The relative positions of the molecules were defined analogously to the system described above, the meaning of the various parameters being indicated in Fig. 13.
As a consequence of the lower symmetry of system II (C_s for all reaction geometries) the angles β and γ are not automatically equal. However, the calculations with partial geometry optimization at a series of r_1/r_2 values showed that β and γ attain nearly equal values at the TS despite the fact that r_1 and r_2 are strongly different (vide infra).

Figure 13:
Numbering scheme and various geometry parameters used in the description of reaction II.



Furthermore these calculations showed that for the parallel-exo and tilted-endo arrangements α acquires a value of 180^0 in the TS. Again transformation between these linear TS geometries occurs completely unimpeded by rotation around the C(4)-C(8) axis. Because of the lack of intrinsic symmetry it was impossible to pinpoint and calculate the TS geometries directly by imposing the symmetry relations $r_1 = r_2$ and $\beta = \gamma$, as was done for system I. However, the calculations with partial geometry optimization at a series of r_1/r_2 values had yielded enthalpy-contour diagrams from which the approximate TS values for r_1 and r_2 and, consequently, their ratio had been obtained. A more accurate estimate of this ratio was obtained by a procedure in which r_2 was assigned a value via the dependence relation $r_2 = k.r_1$, in which r_1 was left variable and the constant k was given values within a certain range. For each value a calculation -with partial geometry optimization- was carried out. The enthalpies thus obtained were plotted against k, and by interpolation the extremum was determined. For the k values thus obtained final calculations of the three transition states were carried out, together with full optimization.
Fig. 14 shows PLUTO drawings of the three optimized TS structures thus obtained, while Table VI lists some relevant numerical values (the $\Delta H_f^{\ddagger}$ values have been determined relative to the fully optimized reactants).

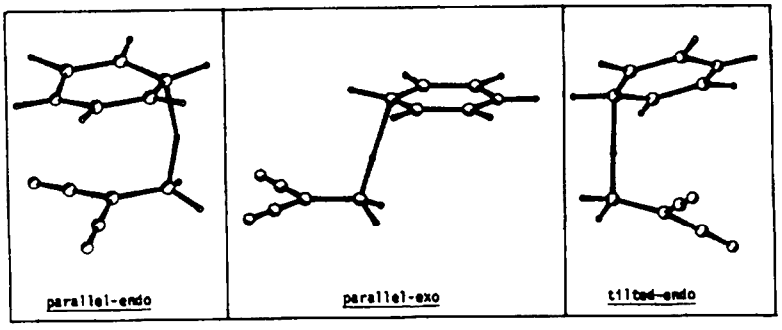


Figure 14 : PLUTO drawings of the fully optimized transition-state arrangements for reaction II.

Table VI : Parameters for the three optimized transition-state arrangements of reaction II shown in Fig. 14.

	parallel-endo	parallel-exo	tilted-endo
r_1 (Å)	1.580	1.749	1.608
r_2 (Å)	1.356	1.198	1.236
α	160.2°	180.0°	180.0°
β	96.8°	108.0°	103.7°
γ	103.0°	108.0°	107.6°
r[C(4)-C(8)] (Å)	2.893	2.947	2.844
ΔH_f° (kcal/mol)	157.9	154.1	150.0
$\Delta H_f^{\ddagger}$ (kcal/mol)	55.9	52.1	47.9

It is striking that the linear transition states quite closely resemble the reaction products. Only a small negative charge ($\approx$ -0.1) is found on the migrating "hydride" in these late transitions states. This once again supports the correctness of the VBCM model, that predicts minor charge development irrespective of the location of the TS. From Table VI it is seen that here, as for the positive substrate, the linear transition states are favoured over the bent TS, although the difference is much

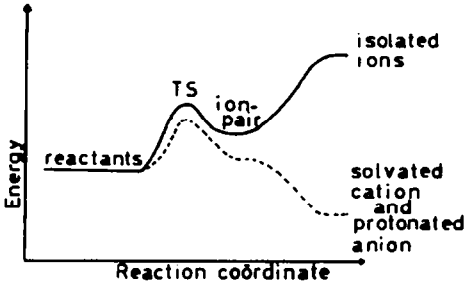
less pronounced. This is clearly a consequence of the fact that now opposite charges are induced in the reacting systems thus leading to electrostatic stabilization of the parallel-endo and, to a lesser degree, of the tilted-endo TS over the parallel--exo TS. For the parallel-endo TS this electrostatic advantage is not sufficient, however, to make it the most stable TS even in the gasphase.
Therefore this TS is once again considered to be rather inaccessible especially in solvents of high dielectric constant. In the gasphase the electrostatic advantage of the tilted-endo TS stabilizes it slightly over the parallel-exo TS. In solution this difference is bound to disappear and therefore also type II reactions may be concluded to occur preferentially through a linear TS, the relative orientation (endo or exo) being determined by secondary factors.

Solvent and acid catalysis of type-II reactions

While reactions I and II are found to resemble each other closely from a stereochemical point of view, their thermodynamical features are dramatically different. Reaction I represents a degenerate "charge-exchange" process for which reactants and products have an equal ΔH_f^o irrespective of the reaction medium. In reaction II, however, charge separation occurs producing an ion-pair from neutral reactants. As indicated above, the calculated TS structure (in the gasphase!) already resembles such an ion-pair. Following the reaction coordinate across this TS first leads to a small decrease of the total enthalpy, indicating that the ion-pair attains its equilibrium geometry, but pulling the ions apart requires an enormous amount of energy in the gasphase. Thus while the total enthalpy of the reactants is 102.1 kcal/mol that of the separate product ions amounts to 204.3 kcal/mol! In other words reaction II is completely impossible in the gasphase, as shown qualitatively in Fig. 15.
A polar solvent will lower the enthalpies of the TS, the ion-pair and especially of the separated ions. However, in many cases that may not be enough to render the reaction thermodynamically feasible.

Figure 15 :

Qualitative representation of the reaction coordinate for hydride transfer from a 1,4-dihydropyridine to a neutral substrate (reaction II) in the gasphase (solid line) and in solution in the presence of a proton donor (broken line).



This makes clear why the reactions of 1,4-dihydropyridines with neutral substrates often require the presence of (Lewis) acids[5,11]. Clearly protonation (or Lewis acid coordination) of the product anion (see Fig.15) is a very effective method to stabilize the product side. The product-like character of the TS allows such stabilization to be felt early on the reaction coordinate, thus not only shifting the reaction equilibrium to the right but also enhancing the rate of the forward process, making (Lewis) acids effective catalysts for type-II reactions.

The Prelog orientation model revisited

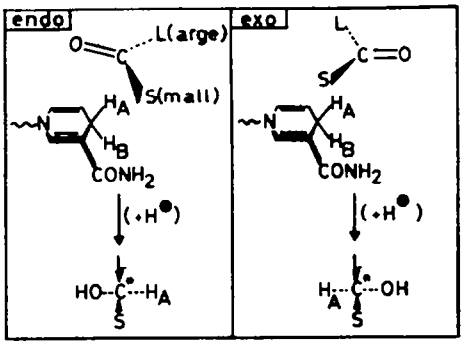
The reduction of prochiral substrates by NAD(P)H under enzymatic conditions or by simple chiral NAD(P)H-models generally leads to chiral products. A widely accepted model[48] to predict the preferred product chirality has been proposed by Prelog. In this model the substrate is assumed to approach specifically one of the faces of the

dihydronicotinamide ring and to adopt a specific orientation with respect to that face. While the factors determining the differential accessibility of the two ring faces have remained a topic of debate[49] the relative orientation of the substrate has generally been assumed[7,48] as represented in Fig. 16. It is now obvious that such an orientation is equivalent to the endo-orientations (either parallel or tilted) discussed in the previous sections with the L(arge) substituent positioned to avoid contact with the $-CONH_2$ group.

As shown above, however, an exo orientation of the substrate is probably at least as easily attained. If in such an exo-orientation the L(arge) substituent is once again positioned to avoid contact with the $-CONH_2$ group the opposite product chirality results (see Fig. 16). It thus seems clear that the Prelog model alone is not enough to

Figure 16 :

Comparison of the stereochemical consequences of endo ('Prelog') and exo orientation of the same prochiral substrate with respect to the A (pro R) face of NAD(P)H.



explain the complete chiral induction of hydride transfer under enzymatic conditions. The enzyme not only functions to make a single face of the coenzyme accessible to the substrate but also plays an active role in orientating the substrate at that face.

CONCLUDING REMARKS

The MNDO calculations presented above confirm beyond any reasonable doubt that hydride transfer mediated by NAD(P)H-'models' under thermal conditions occurs most readily via a concerted pathway. This corroborates both the thermodynamic considerations- that show SET to be inaccessible except for strongly oxidizing substrates with low hydride affinity - and the predictions from a simple VBCM model that suggests the general availability of a low-energy concerted pathway. This VBCM model also provides an illuminating rationalization for the minor charge development on the migrating 'hydride' - as calculated by MNDO - and for the occurrence of a free energy relation between the activation energy of concerted hydride transfer and the - calculated - energy required for SET between the reactants. Furhermore the MNDO calculations add a new and very important dimension to the mechanistic picture by predicting the relative orientation of the reactants in the transition-state. Thus an endo-orientation (i.e. a 'Prelog orientation') was calculated to be no more (for neutral substrates) or even less (for positive substrates) likely than an exo-orientation. Evidently this prediction, that seems accessible to experimental verification by studying model systems geometrically restrained to react either exo or endo ,should influence the interpretation of the stereochemical outcome of reactions involving (pro)chiral reactants and furthermore it may shed light on the role of complexing catalysts (e.g. Mg^{2+}) in determining such stereochemistry.

The results of the limited number of TDKIE measurements performed suggest, that these may provide a method to discriminate transition-state geometries in NAD(P)H-model reactions. More experimental data however and especially a more elaborate evaluation of the factors governing TDKIE are required.

EXPERIMENTAL

Materials

Propane-1,3-bis-nicotinamidium dichloride (3), was prepared from 1,3-dichloropropane and nicotinamide according to the method given in ref. 50 and recrystallized from ethylacetate-ethanol-water (1:1:1). Yield: 82% , mp.: 261-263°C.

Propane-1,3-bis-(1,4-dihydro)nicotinamide (2). An aqueous solution (15 ml) of 7 g sodiumdithionite and 4 g sodiumcarbonate was added dropwise (30 min.) to a stirred solution of 5 mmol 3 in 10 ml water kept in an ice bath and under a nitrogen atmosphere. The mixture turned yellow and became turbid as 2 precipitated. After the addition stirring was continued for another 30 min. at room temperature. The precipitate was filtered and recrystallized from ethanol-water. MS and ^{1}H-NMR (see ref 35) confirmed that reduction of both nicotinamidium moieties had occurred. Yield : 62 %.

Propane-1-(1,4-dihydro)nicotinamide-3-nicotinamidium chloride (1). This system was prepared in-situ by equilibration between 2 and 3 (see Fig. 7) as described before[35].

1-Benzyl-1,4-dihydronicotinamide (BNAH) and 10-methyl-9-phenyl-acridinium chloride (AcPh$^+$), were available in our laboratory from previous studies[13].

Deuterated compounds BNAH-(4d$_2$) , 1-(4d$_2$,4'd) , 2-(4d$_2$,4'd$_2$) and 3-(4d,4'd), were prepared by repeated oxidation (with benzylidenemalonitrile as an oxidant[51]) and reduction (with dithionite in D_2O) cycles using standard routines[51], except for 1-(4d$_2$,4'd) that was prepared by equilibration between fully C-4,4' deuterated 2 and 3 . The degree of deuteration was > 95% as checked by ^{1}H-NMR.

Kinetic measurements

Intramolecular hydride and deuteride exchange in 1 , was followed by ^{1}H-NMR at 250 MHz via the spin-saturation transfer technique as descibed earlier[35]. The solutions were prepared by mixing equimolar amounts of 2 and 3 in DMSO-d$_6$ (total concentration 0.5×10^{-2} mol.l^{-1}) and allowing this to equilibrate overnight in a sealed NMR tube.

Hydride and deuteride transfer from BNAH to AcPh$^+$,was followed spectrophotometrically in acetonitrile by monitoring the disappearance of the characteristic long-wavelength absorption of AcPh$^+$ ion (ε = 5300 at 430 nm) employing pseudo first-order conditions (initial concentrations ~ 10^{-3} mol.l^{-1} for BNAH and ~ 10^{-4} mol.l^{-1} for AcPh$^+$) as described extensively before[13].

Hydride and deuteride exchange between 2 and 3 ,was followed spectrophotometrically under pseudo first-order conditions by monitoring the growth of the typical long-wavelength,intramolecular charge-transfer absorption[52] of 1 (ε = 407 at 460 nm(sh)) that occurs in a region where both 2 and 3 show no significant absorption. Because of the small rate constant and the relatively weak absorption of 1 at the monitoring wavelength, rather high concentrations had to be used especially of the compound (3) employed in excess. This required the use of an aqueous solvent. A borate buffer (pH = 8.22) was found to be suitable since in this buffer the hydratation of 2 is extremely slow in contrast to the situation observed in e.g. a phosphate buffer of the same pH[16] : The reaction mixtures were prepared by mixing in a thermostated spectrophotometric cell, 100 microliters of a ~ 2.5×10^{-3} mol.l^{-1} stock solution of 2 in DMSO and 2 ml of a ~ 7.5×10^{-2} mol.l^{-1} stock solution of 3 in the borate buffer. The last solution was also put into the reference cell. Kinetic runs were performed in triplicate at each temperature.

Quantum-mechanical calculations. A local version[46] of the MNDO program[45] was used. All calculations were performed at the Amsterdam academic computing centre (SARA).

ACKNOWLEDGEMENTS

We thank prof. U.K. Pandit for his continuing interest and for stimulating discussions.

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