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ON THE QUESTION OF ONE-ELECTRON TRANSFER IN THE MECHANISM OF REDUCTION BY NADH-MODELS

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Abstract—The fluorescence of 1-benzyl-1,4-dihydronicotinamide (BNAH) is quenched by a variety of electron acceptors. The dependence of the rate constant of the quenching process on the electrochemical reduction potentials of the quenchers corresponds with that expected for quenching by an electron transfer mechanism in which BNAH acts as an electron donor with a one electron oxidation potential of 0.76 ± 0.02 V (in acetonitrile relative to the saturated calomel electrode).

From this oxidation potential, and the reduction potentials of a number of substrates reported to be reduced by BNAH, the rates of thermal one-electron transfer from BNAH to these substrates were estimated via the Rehm–Weller relation for outersphere one-electron transfer. These calculated rates are many orders of magnitude lower than experimental rates reported for the overall reduction processes. This seems to exclude outersphere one-electron transfer as an intermediate step in such reductions.

On the basis of isotopic labelling[1-4] and ESR experiments[5-7] one-electron transfer has been advocated[8-10] as the primary step of the overall hydride transfer from 1,4-dihydropyridines to many substrates. Furthermore several photo-induced hydride transfer reactions of 1,4-dihydropyridines have been reported[6,11,12] without a detailed consideration of the primary photochemical process involved. A closer examination of the electron donor properties of 1,4-dihydropyridines both in their ground and electronically excited state is therefore required to check the "one-electron transfer" hypothesis in the light of current theories[13,14] of electron transfer processes. The present paper describes some results of such an investigation.

RESULTS AND DISCUSSION

Quenching of dihydropyridine fluorescence by electron acceptors. From a systematic study on the fluorescence of 1,4-dihydropyridine derivatives in the presence of molecules of relatively low reduction potential we have found that this fluorescence is efficiently quenched by a number of electron acceptor molecules in a variety of solvents. This phenomenon was quantitatively investigated for 1-benzyl-1,4-dihydronicotinamide (BNAH) in acetonitrile solution, for which some relevant spectral parameters are collected in Table 1.

Quenching of BNAH fluorescence (excited in a wavelength region beyond the quencher absorption) by the electron acceptors 1–11 (see Table 2) obeys the Stern–Volmer relation (1):

$$I_0/I = 1 + k_q\tau[A]. \qquad (1)$$

In (1) I_0/I represents the ratio of the fluorescence intensities measured in the absence ($[A] = 0$) and in the presence of the quencher A; τ the fluorescence lifetime for $[A] = 0$ and k_q the rate constant of the quenching process.

In Table 2 the k_q values obtained for the quenchers 1–11 are presented together with electrochemical data on the reduction potentials ($E(A^-/A)$) of these quenchers.

The free enthalpy change upon one-electron transfer from a singlet excited donor molecule (D^*) to an electron acceptor molecule (A) in a polar solvent can be calculated[14,15] from equation (2):

$$\Delta G_{D^*A} = E(D/D^+) - E(A^-/A) - {}^1\Delta E_{0,0}(D^*) - C. \qquad (2)$$

In (2) ${}^1\Delta E_{0,0}(D^*)$ indicates the 0,0-excitation energy of D which amounts to 71.5 ± 0.5 kcal . mol^{-1} for BNAH (mirror point of absorption and emission), while C indicates the small additional Coulombic stabilization of the D^+A^- ion-pair which amounts to about 0.06 eV[14,15] in acetonitrile.

The one-electron oxidation potential ($E(D/D^+)$) of BNAH cannot be measured precisely[16,17] by electrochemical methods, because of the irreversible nature[18] of this one-electron oxidation on the time scale of electrochemical measurements. From fast-sweep (up to 200 V . s^{-1}) voltammetric measurements[16] in acetonitrile the oxidation potential of the dihydronicotinamide system may however be estimated to lie in the range of 0.6–0.8 V relative to the saturated calomel electrode.

It is generally accepted[19] that the free enthalpy of activation for electron transfer ($\Delta G^{\neq}$) can be calculated

Table 1. Spectral parameters (electronic absorption and emission) for 1-benzyl-1,4-dihydronicotinamide (BNAH) in acetonitrile solution at 20°

	λ_{max}(nm)	$\tilde{\nu}_{max}$(cm^{-1}x10^3)	ϵ(l.mol^{-1}.cm^{-1})	τ(nsec)
Absorption	348±0.5	28.7	6000±50	-
Emission	443±2	22.6	-	0.76±0.03

Table 2. Rate constants (k_q) for quenching of BNAH-fluorescence by various electron acceptors and reduction potentials $E(A^-/A)$ of these acceptors both in acetonitrile at 20°

	Acceptor	$-E(A^-/A)^{\underline{a}}$ (Volts)	$k_q\tau^{\underline{b}}$ ($l.mol^{-1}$)	$k_q^{\underline{c}} \times 10^{-9}$ ($l.mol^{-1}.s^{-1}$)
1	α,α,α-trifluoroacetophenone	1.46	13.4±0.7	17.6±1.7
2	diethylfumarate	1.50	11.8±0.6	15.5±1.5
3	dimethylterephthalate	1.78	13.1±0.7	17.2±1.7
4	benzophenone	1.86	12.9±0.7	16.9±1.7
5	1-cyanonaphthalene	1.96	11.9±0.6	15.6±1.5
6	acetophenone	2.10	7.1±0.4	9.4±1.[illegible]
7	E-stilbene	$2.20^{\underline{d}}$	5.8±0.3	7.6±1.0
8	cyanobenzene	$2.35^{\underline{d}}$	3.7±0.3	4.9±0.9
9	methylbenzoate	2.37	2.3±0.2	3.0±0.7
10	styrene	$2.45^{\underline{e}}$	0.1±0.05	0.13±0.06
11	1-methylnaphthalene	$2.59^{\underline{d}}$	<0.02	<0.03

a In acetonitrile relative to the saturated calomel electrode.

b Slope of the Stern-Volmer plot (cf. text).

c Calculated for τ = 0.76 ± 0.03 nsec.

d From ref. 31.

e Value measured in dimethylformamide cf. ref. 32.

from the rate of electron transfer (k_q) via eqn (3).

$$1/k_q = 1/k_{diff.} + 10^{-11}\exp(\Delta G^{\neq}/RT). \qquad (3)$$

In (3) $k_{diff.}$ is the rate constant for a diffusion controlled process. In a rigorous treatment[14], calculation of $k_{diff.}$ requires determination of the individual diffusion coefficients of the molecules studied. More commonly an average $k_{diff.}$ value is assumed to be given by the Debye relation $k_q = 8RT/p\eta$ where η represents the macroscopic solvent viscosity and p is a constant with a value[20] between 2000 and 3000 for organic molecules of intermediate size. We have set p at 2500 which gives $k_{diff.} = 2.3 \times 10^{10}\ l.mol^{-1}.s^{-1}$ in acetonitrile at 20°C.

The empirical relation (4) between ΔG—as calculated from eqn (2)—and $\Delta G^{\neq}$ has been shown[14] to be valid for a wide range of positive and negative ΔG values for outersphere electron transfer.

$$\Delta G^{\neq} = \frac{\Delta G}{2} + \sqrt{\left[\left(\frac{\Delta G}{2}\right)^2 + (\Delta G^{\neq}(0))^2\right]}. \qquad (4)$$

In (4) $\Delta G^{\neq}(0)$ represents the free enthalpy of activation for outersphere electron transfer when $\Delta G = 0$ (e.g. for electron exchange). This value is known[19] to depend only slightly on the solvent and the type of molecule involved. A value of $\Delta G^{\neq}(0) = 2.4\ kcal.mol^{-1}$ has been adopted[14] in acetonitrile solution at 20°C.

In Fig. 1 the relation between k_q and ΔG as predicted by eqn (3) and (4) is shown graphically. Furthermore the experimental data for quenching of BNAH fluorescence by compounds 1–11 have been plotted with ΔG values calculated from (2) for an BNAH oxidation potential set at $E(D/D^+) = 0.76 \pm 0.02$ V. The deviation of the measured k_q values from the theoretical curve is in the same order of magnitude as their experimental uncertainty (see Fig. 1 and Table 2).

It is thus concluded that quenching of BNAH fluorescence by 1–11 involves outersphere electron transfer in which BNAH acts as an electron donor with an oxidation potential of 0.76 ± 0.02 V.

Implications for the mechanism of reductions mediated by 1,4-dihydropyridines. Photo-induced reduction of 2 by BNAH has been reported[11] to occur with low quantum yield. From the present data a photo-induced one-electron transfer seems very likely as the primary process in such photochemical reactions.

Of more interest however are the thermally activated reductions mediated by 1,4-dihydropyridines like BNAH, which are commonly denoted[9] as model systems for the NADH coenzyme. The free enthalpy change for thermal electron transfer from D to A in a polar solvent can be evaluated in analogy with (2) from eqn (5):

$$\Delta G_{D,A} = E(D/D^+) - E(A^-/A) - C. \qquad (5)$$

Since we have shown that a value $E(D/D^+) = 0.76$ V applies to BNAH, $\Delta G_{D,A}$ can now be calculated for any combination of BNAH with a compound (substrate) of known reduction potential ($E(A^-/A)$). Then the rate of outersphere one-electron transfer (k_q) from BNAH to this substrate can be calculated via (3) and (4).

If outersphere electron transfer is involved in the mechanism of reduction of a substrate by BNAH the k_q value thus calculated should equal or exceed the overall rate constant (k_{red}) of the reduction process. Rate constants (k_{red}) for 1,4-dihydropyridine mediated reductions are scarcely available in the literature. Table 3 summarizes a number of these kinetic data together with electrochemical data on the substrates and the rate con-

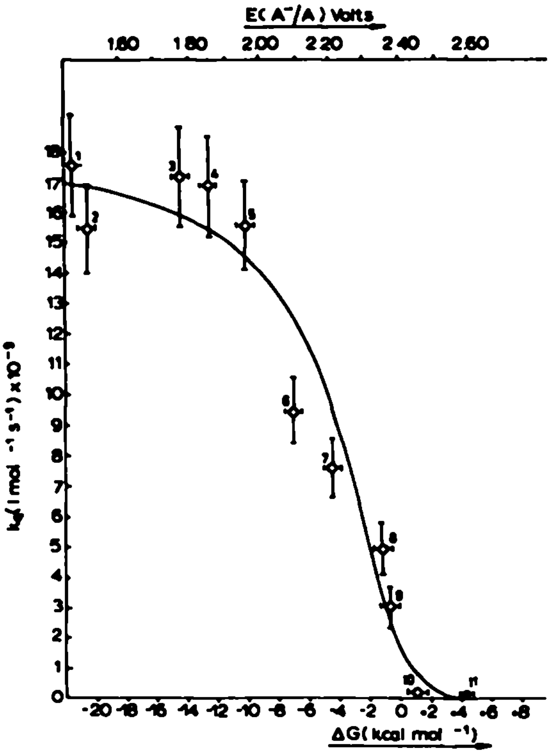

Fig. 1. Relation between k_q and ΔG according to Ref. 14 (drawn curve) and experimental data for quenching of BNAH fluorescence by 1-11 with an oxidation potential of 0.76 ± 0.02 V assumed for BNAH.

stants (k_q) calculated for outersphere electron transfer.

It is found that the experimental k_{red} values exceed the calculated k_q values by many orders of magnitude ($k_{red}/k_q = 10^4 - 10^{18}$ corresponding to $\Delta G^{\neq}$ differences between 5 and 24 kcal . mol⁻¹. It should be stressed that since relation (4) leads to $\Delta G = \Delta G^{\neq}$ for strongly endothermic electron transfer processes, the calculated k_q values in Table 3 represent an upper theoretical limit. Application of another commonly used relation between ΔG and $\Delta G^{\neq}$ such as that proposed by Marcus[13] leads to even larger discrepancies.

It is thus concluded that outersphere one-electron transfer cannot be involved to any significant extent in the reductions compiled in Table 3.

It is known[21,22] that interaction of electron acceptors (most significantly of carbonyl compounds) with Lewis acids may considerably enhance their electron affinity. The activation energy for electron transfer can substantially be lowered by concerted Lewis acid complexation[23] of the developing substrate radical anion, a pathway which avoids the high energy intermediates involved in either outersphere electron transfer to or Lewis acid complexation of the substrate. Thus one-electron transfer may become important in 1,4-dihydropyridine mediated reductions under the influence of electrophilic catalysts.[24,25] The possible occurrence of such a mechanism will be the subject of further investigation.

EXPERIMENTAL

1-Benzyl-1,4-dihydronicotinamide (BNAH) was prepared according to the literature;[26] m.p. 120–122° (dec.). Compounds 1–11 were obtained commercially and purified by standard procedures whenever necessary. Acetonitrile of Merck (fluorescence spectroscopy grade) was used without further purification. UV-absorption spectra were measured on a Cary 17-D recording spectrophotometer. Fluorescence spectra were recorded with a modified Zeiss spectrofluorimeter described elsewhere.[27]

In the quenching experiments an excitation wavelength beyond the quencher absorption (normally 360 nm but 400 nm in the case of 4, 6 and 7) was selected. The fluorescence intensity was monitored at 440 nm (500 nm in the case of 4, 6 and 7). The BNAH concentration was kept at about 10^{-4} mol . l⁻¹ while the quencher concentration was increased in eight steps up to about 0.1 mol . l⁻¹ for the more efficient quenchers and up to 0.5 mol . l⁻¹ for the least efficient quencher (11). The data were then evaluated graphically via the common Stern–Volmer plotting procedure. The Stern–Volmer plots were linear without indications for ground-state complexation even at the highest quencher concentrations. Degassing of the solutions was found to have no detectable influence on the fluorescence intensity, in accordance with the short lifetime of BNAH fluorescence.

Fluorescence lifetime of BNAH was measured by monitoring the fluorescence decay at 440 nm of a 1.5×10^{-4} mol . l⁻¹ solution in acetonitrile via the single photon counting technique[28] upon excitation at 290 nm with picosecond pulses resulting from frequency doubling of the pulses obtained by mode-locked synchronous pumping of a dye laser (Cr 490 with Rhodamine 6G as the laser dye) with an argon-ion laser (Cr-5) as described elsewhere.[29] The fluorescence followed a single exponential decay with $\tau = 0.76 \pm 0.03$ nsec.

Electrochemical reduction potentials were recorded at 20°C on a Metrohm E-261 instrument by DC-polarography at the dropping mercury electrode (Metrohm E-354) relative to an Ag/AgCl, KCl (s) electrode (−0.042 V relative to the saturated calomel electrode[30]) in acetonitrile containing tetraethylammonium perchlorate (0.1 mol . l⁻¹) as a supporting electrolyte.

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Table 3. Comparison of literature data on the rate constants (k_{red}) for thermal reduction of several substrates by BNAH in acetonitrile solution and the rate constants (k_q) calculated for outersphere one-electron transfer from BNAH to these substrates

	Substrate (A)	$-E(A^-/A)^a$ (Volts)	k_q $l.mol^{-1}.s^{-1}$	k_{red}: $l.mol^{-1}.s^{-1}$	reaction conditions	ref.
1	α,α,α-trifluoroacetophenone	1.46	10^{-23}	10^{-5}	CH_3CN,50°C	34
12	N-methylacridiniumchloride	0.24	10^{-6}	65	CH_3CN,25°C	3
13	chloranil	-0.01^b	10^{-1}	1.9×10^3	CH_3CN,25°C	3
14	hexachloroacetone	0.27	10^{-6}	0.25	CH_3CN,26.6°C	35

a Substrate reduction potential in acetonitrile at 20°C relative to the saturated calomel electrode.

b From ref. 33.

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