Oxidation Mechanism of NAD Dimer Model Compounds

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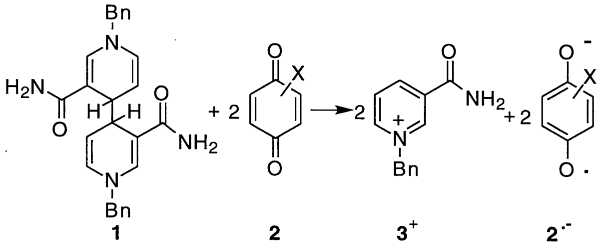
The oxidation of a dimeric *N*-benzyldihydronicotinamide with various oxidants such as quinones, triphenyl carbenium ions and a triplet exited tris(bipyridine) ruthenium(II) complex occurs via initial outer-sphere electron transfer followed by fast C-C bond cleavage and second electron transfer. The kinetic studies allow the determination of the oxidation potential of this compound.

The knowledge of the mechanism of the oxidation of NADH and its model compounds is essential for understanding biological redox reactions with NADH as an electron source. There are indications that the one electron reduction product of NAD^+, a dimeric compound, is also involved in some biological redox-processes.[1,2] However, the fundamental properties of this dimer such as the oxidation potential and the intrinsic barrier for the electron transfer oxidation have been, to our best knowledge, not yet available. We therefore investigated the oxidation properties of the dimeric *N*-benzyldihydronicotinamide **1**, which differs from the NAD dimer only by the substituent at the nitrogen. A unique donor propery of **1** which can act as a pure two-electron donor is reported.

The cyclic voltammogram of **1** (acetonitrile, 298 K) exhibits an oxidation peak but no reduction peak even at high scan rates (v = 10 V s^{-1}), indicating a fast follow-up reaction. In the reaction with quinones two quinone molecules are reduced yielding two pyridinium ions $\mathbf{3}^{+}$ and two semiquinone radical anions $\mathbf{2}^{\bullet -}$ (Scheme 1). The stoichiometry has been confirmed by titrating a solution of **1** with a solution of *p*-chloranil and measuring the concentration of the semiquinone radical anion using UV-Vis spectroscopy.



1 **2** $\mathbf{3}^{+}$ $\mathbf{2}^{\bullet -}$

Scheme 1.

The rates of these reactions have been followed in acetonitrile at 298 K by monitoring the formation of the semiquinone anions (Table 1). The reaction rates obey second-order kinetics, showing the first-order dependence with respect to the concentration of each reactant. As expected, the more electron deficient quinones react faster. Also the rate constant of the electron transfer (ET) reaction of the decamethyl ferrocenium ion $Fe(Me_5C_5)_2^{+}$, an outer-sphere one-electron oxidant, reported by Savéant[3] lies on the same line (Table 1, 5th entry), indicating that in all cases the initial and rate determining step is an outer-sphere ET. This step is probably followed by a fast cleavage of the C-C bond of the dimer and a second electron transfer (Scheme 2). The second electron transfer should be by far faster than the first, as the *N*-benzylnicotinamide radical $\mathbf{3}^{\bullet}$ is a strong reductant (E^{o}_{ox} = -1.08 V vs. SCE).[4]

Table 1. Observed rate constant k_{et} for the ET reactions of **1** with various oxidants and the reduction potential E^{o}_{red} of the oxidant (298 K, acetonitrile)

Oxidant	E^{o}_{red}[a]/ V	k_{et}/ M^{-1} s^{-1} [k]
p-Benzoquinone	-0.50[b]	6.80×10^{-3}
Chloro-*p*-benzoquinone	-0.34[b]	1.01
$(p\text{-}MeOC_6H_4)_3C^+$	-0.21[c]	1.50×10^{1}
2,6-Dichloro-*p*-benzoquinone	-0.18[b]	7.70×10^{1}
$Fe(Me_5C_5)_2^{+}$	-0.10[d]	1.20×10^{2} [e]
$(p\text{-}MeOC_6H_4)_2PhC^+$	-0.07[c]	8.74×10^{2}
p-Fluoranil	-0.04[f]	6.25×10^{3}
p-Bromanil	0.00[b]	1.03×10^{4}
p-Chloranil	0.01[b]	1.50×10^{4}
TCNQ	0.19[g]	6.60×10^{6}
$[Ru(bpy)_3]^{2+*}$	0.77[h]	5.50×10^{9}
Pyrene*	1.23[i]	2.10×10^{10}

[a] 298 K in acetonitrile, vs. SCE. [b] Ref. 4. [c] Measured using CV: S. Fukuzumi and K. Okubo. [d] Ref. 3. [e] Ref. 3, converted to 298 K using the Eyring-equation and an estimated activation entropy of 100 kJ mol^{-1}. [f] Ref. 6. [g] Ref. 11. [h] Ref. 7. [i] Ref. 8. [k] M = mol dm^{-3}.

$$\mathbf{1} + \mathbf{2} \xrightarrow{\text{slow}} \mathbf{1}^{\bullet +} + \mathbf{2}^{\bullet -}$$

(Electron Transfer)

$$\mathbf{1}^{\bullet +} \xrightarrow{\text{fast}} \mathbf{3}^{\bullet} + \mathbf{3}^{+}$$

(C-C Bond Cleavage)

$$\mathbf{3}^{\bullet} + \mathbf{2} \xrightarrow{\text{fast}} \mathbf{3}^{+} + \mathbf{2}^{\bullet -}$$

(Electron Transfer)

Scheme 2.

The correlation between the observed rate constant and the reduction potential of the oxidant can provides the information about the oxidation potential of the dimer **1** and the reorganization energy of its oxidation. In order to get a better basis for this analysis, we investigated also the electron transfer reaction to triphenyl carbenium ions and the fluorescence quenching of the tris(bipyridine) ruthenium(II) complex $[Ru(bpy)_3]^{2+*}$ and pyrene* (*denotes the excited state).

The empirical Eq. 1 developed by Weller and Rehm[5] for outer-sphere electron transfer reactions can be used to derive redox potentials, where $\Delta G^{\neq}$ is the activation Gibbs energy of the electron transfer, ΔG° the reaction Gibbs energy and $\Delta G^{\neq}_{o}$ the intrinsic barrier of the reaction .

$$\Delta G^{\neq} = \Delta G^{\circ}/2 + [(\Delta G^{\circ}/2)^2 + (\Delta G^{\neq}_{o})^2]^{1/2} \quad (1)$$

with $\Delta G^{\circ} = F\,(E^{o}_{ox} - E^{o}_{red})$.

The activation Gibbs energy of the electron transfer ($\Delta G^{\neq}$)

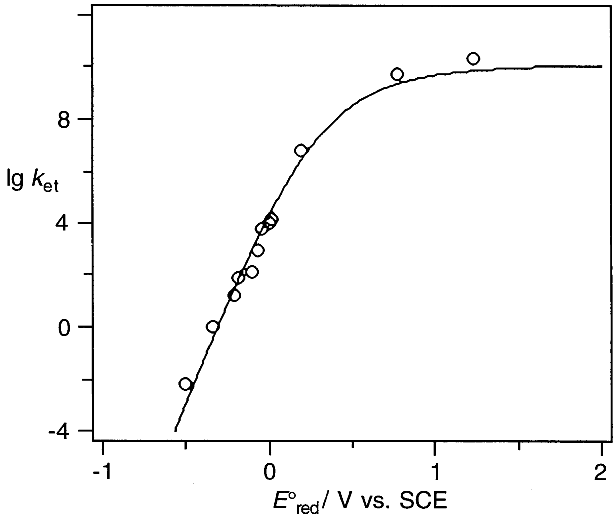
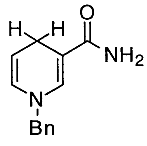


Figure 1. Plot of the logarithm of the observed rate constant lg k_{et} of ET reactions of **1** with various oxidants vs. the reduction potential of the oxidant E°_{red} (298 K, acetonitrile).

can be calculated from observed rate constant of the electron transfer k_{et} using Eq. 2, which includes the effect of the diffusion (Z : collision frequency = 1 x 10^{11} M^{-1} s^{-1}, k_d: diffusion constant = 2 x 10^{10} M^{-1} s^{-1}).

$$\Delta G^{\neq} = RT \ln [Z(k_{et}^{-1} - k_d^{-1})] \qquad (2)$$

Using Eq. 1 the values of E°_{ox} = 0.26 V vs. SCE for the oxidation potential and $\Delta G^{\neq}_0$ = 23 kJ mol^{-1} for the intrinsic barrier for the outer-sphere ET reactions of **1** have been obtained by least-square-fitting (Figure 1). The oxidation potential of **1** is significantly lower than that of the monomeric *N*-benzyldihydronicotinamide (**4**); (E°_{ox} = 0.57 V vs. SCE).[4] This corresponds to an increase in the rates of outer-sphere ET reactions of a factor of more than 100 000. The change in the oxidation potential seems to be due to hyperconjugation of the C(4)-C(4')-bond in the radical cation $1^{\bullet +}$. Semiempirical calculations using the PM3 hamiltonians[9] show that this bond is significantly longer in the radical cation (d = 1.572 Å) than in the neutral compound (d = 1.557 Å).[10] Hence, the electron is partially taken from this C-C bond leading to a stabilization of the radical cation. The elongation of the C-C bond facilitates the bond cleavage. The bond cleavage seems to be always faster than the competing back electron transfer.



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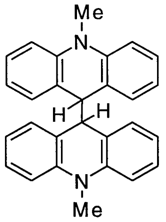

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On the other hand, the steric hindrance of **1** reduces its reactivity for hydride transfer reactions. The monomeric *N*-benzyldihydronicotinamide (**4**) reacts with quinones via formal hydride transfer from **4** to the quinone. The reaction of **4** with chloro-*p*-benzoquinone is even faster (k = 7.6 M^{-1} s^{-1}) than the corresponding reaction of **1**.[4] While the NAD dimer model compound **1** acts as a pure two-electron donor, while the corresponding monomer **4** is a hydride (two electrons and a proton) donor.

A similar behavior has been found for a dimeric dihydroacridane, the 10,10'-dimethyl-9,9',10,10'-tetrahydro-9,9'-biacridine **5**.[11] The difference in the oxidation potential of monomeric and dimeric dihydroacridine is, however, smaller in this case (0.80 V and 0.62 V, respectively). Another comparison between **5** and **1** is also interesting. The intrinsic barrier of the oxidation of **5** is 12.1 kJ mol^{-1}, hence, significantly smaller than in the case of the **1**. Both effects, the difference in the shift of the oxidation potential and the difference in the intrinsic barrier seem to be connected. Semiempirical calculations show that in the radical cation of **5** the elongation of the C-C bond in the radical cation is smaller indicating a smaller hyperconjugation (Δd = 0.010 Å)[10] leading to a smaller change in the oxidation potential. The smaller structural change during the oxidation of **5** causes also the smaller intrinsic barrier.

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References and Notes

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10 Although the error in the absolute value might be within the range of the deviation, the trend should be calculated correctly.
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