J. Org. Chem. **2000,** *65,* 7213−7214

Is There a Deuterium Kinetic Isotope Effect in the One-Electron Transfer from 1-Benzyl-1,4-dihydronicotinamide to 9-Fluorenylidenemalononitrile?

Agnès Anne,* Jacques Moiroux, and
Jean-Michel Savéant

Laboratoire d'Electrochimie Moléculaire, Unité Mixte de
Recherche Université-CNRS No 7591,
Université de Paris 7 - Denis Diderot, 2 place Jussieu,
75251 Paris Cedex 05, France

anne@paris7.jussieu.fr

Received April 27, 2000

A remarkable deuterium isotope kinetic effect, ranging from 2.70 to 2.55 between 15 and 35 °C, has been recently ascribed to the one-electron transfer from 1-benzyl-1,4-dihydronicotinamide ($BNAH_2$, $BNAD_2$) to 9-fluorenylidenemalononitrile, **1** (Scheme 1).[1]

Unlike in previous reports[2] of such deuterium isotope kinetic effects in similar reactions involving synthetic analogues of NADH, the effect was ascribed to a one-electron transfer between the tittle compounds, deemed to be the first, and rate-determining, step of the stepwise overall transfer of a hydride ion (viz. D^-) from BNAH-$(D)_2$ to **1** (Scheme 2).[3] This assignment was based on the assumption that the cation radical is a strong acid and that the $BNAH(D)^\cdot$ radical is unstable, thus rendering steps 2 and 3 irreversible, and, on the appearance of the red-colored anion radical, characterized by its UV and ESR spectra, during the course of the reaction.

These results are puzzling in view of the estimations that may be made of the thermodynamics of reaction 1. The equilibrium constant, K_1, is related to the standard potentials of the two redox couples according to eq 1.

$$K_1 = \exp\left[\frac{F}{RT}\left(E^0_{1/1^{\cdot-}} - E^0_{\mathrm{BNAH_2^{\cdot+}/BNAH_2}}\right)\right] \qquad (1)$$

where $E^0_{\mathrm{BNAH_2^{\cdot+}/BNAH_2}} = 0.78$,[4] and $E^0_{1/1^{\cdot-}} = -0.660$ V vs SCE.[5]

It follows that $K_1 = 3.5 \times 10^{-25}$. The rate constant of the reverse step is at most equal to the bimolecular diffusion limit, i.e., $k_{-1} \leq 10^{9.9}\ \mathrm{M^{-1}\ s^{-1}}$, [4] and thus, $k_1 \leq 4 \times 10^{-15}\ \mathrm{M^{-1}\ s^{-1}}$, thus making it clear that the observed deuterium isotope kinetic effect does not concern the electron transfer from $BNAH(D)_2$ to **1** (at the highest $BNAH(D)_2$ concentration used in ref 1, the half-reaction time would be of the order of one million centuries). A one-step hydride transfer (reaction 4 in Scheme 3) is a much more likely alternative endowed with a reasonable value of the standard free energy of reaction as will be seen later on. It remains to understand the reason of the appearance of red anion radical of **1** in the course of the reaction.

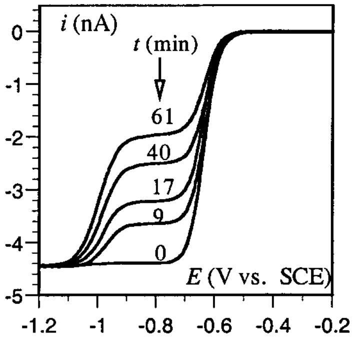
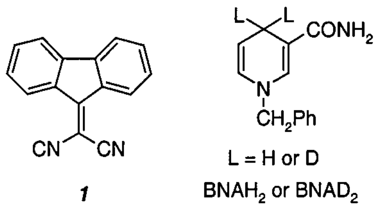


Figure 1. Reaction of **1** (1 mM) with $BNAH_2$ (19 mM) in acetonitrile + 0.1 M $TBAPF_6$, under an argon atmosphere, monitored by means of 10 μm-diameter carbon fiber microdisk electrode. $T = 20$ °C.

Scheme 1



Scheme 2

$$\mathrm{BNAL_2} + \mathbf{1} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{1}^{\cdot-} + \mathrm{BNAL_2^{\cdot+}} \qquad (1)$$

$$\mathrm{BNAL_2^{\cdot+}} + \mathrm{BNAL_2} \xrightarrow{k_2} \mathrm{BNAL^\cdot} + {}^{+}\mathrm{L(BNAL_2)} \qquad (2)$$

$$\mathbf{1} + \mathrm{BNAL^\cdot} \xrightarrow{k_3} \mathbf{1}^{\cdot-} + \mathrm{BNAL^+} \qquad (3)$$

L = H or D

Scheme 3

$$\mathrm{BNAL_2} + \mathbf{1} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \mathbf{1L}^{-} + \mathrm{BNAL^+} \qquad (4)$$

In the reaction of $BNAH_2$ with **1**, the consumption of **1**, the production of $BNAH^+$, and possibly, the production of the radical anion of **1** may be readily monitored by means of ultramicroelectrode voltammetry used in a steady-state regime.[6] These three species are indeed expected to give rise to the following responses: an anodic plateau current proportional to the concentration of radical anion of **1** at potentials above −0.5 V vs SCE; a cathodic plateau current proportional to the concentration of **1** at potentials below −0.8 V vs SCE and a cathodic plateau current proportional to the sum of **1** and BNAH-$(D)^+$ concentrations below −1.1 V vs SCE. As shown in Figure 1, **1** does react with $BNAH_2$, one molecule of $BNAH^+$ being produced per each molecule of **1** consumed. We, however, never detected any anodic current, indicating the formation of the radical anion of **1**, nor did we observe its characteristic red color. However, it is impor-

---

[1] Zhu, X. Q.; Liu, Y. C.; Wang, H. Y.; Wang, W. *J. Org. Chem.* **1999**, *64*, 8982−8983.

[2] (a) Sinha, A.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 7291−7292. (b) Fukuzumi, S.; Kondo, Y.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 673−679. (c) Yasui, S.; Ohno, A. *Bioorg. Chem.* **1986**, *14*, 70−96 and references therein. (d) He, G. X.; Blasko, A.; Bruice, T. C. *Bioorg. Chem.* **1993**, *21*, 423−430. (e) Fukuzumi, S.; Tokuda, Y.; Kitano, T.; Okamoto, T.; Otera, J. *J. Am. Chem. Soc.* **1993**, *115*, 8960−8968. (f) Anne, A.; Fraoua, S.; Hapiot, P.; Moiroux, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1995**, *117*, 7412−7421.

[3] Zhu, X. Q.; Liu, Y. C. *J. Org. Chem.* **1998**, *63*, 2786−2787.

[4] Anne, A.; Hapiot, P.; Moiroux, J.; Neta, P.; Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 4694−4701.

[5] Sertel, M.; Yildiz, A.; Baumgärtel, H. *Electrochem. Acta* **1986**, *31*, 1625−1632.

[6] Amatore, C.; Bento, F. M.; Montenegro, M. I. *Anal. Chem.* **1995**, *67*, 2800−2811.

10.1021/jo000651d CCC: $19.00 © 2000 American Chemical Society
Published on Web 09/15/2000

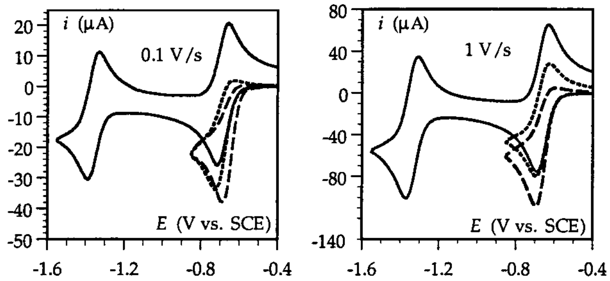
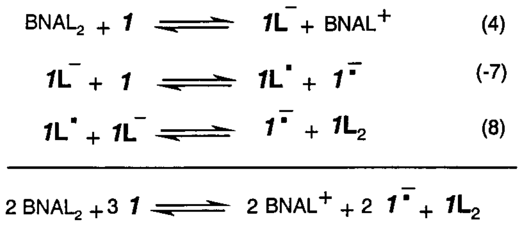


Figure 2. Cyclic voltammetry of **1** (1 mM) in acetonitrile + 0.1 M $TBAPF_6$ at a 3 mm-diameter glassy carbon disk electrode. Full lines: no buffer added. Dotted lines: in the presence of 3-MePy (45 mM)/3-$MePyH^+$ (5 mM) buffer. Dashed lines: in the presence of 3-MePy (5 mM)/3$MePyH^+$ (45 mM) buffer. $T = 20$ °C.

Scheme 4



tant to note that the red color did appear when a small amount of air was admitted in the reaction vessel, which is normally deaerated with argon before the experiment, and maintained under argon during the whole experiment. The appearance of the radical anion results from the oxidation of the hydride $\mathbf{1H}^-$ (electron-transfer coupled with deprotonation). Admission of more oxygen results in the regeneration of the pale yellow **1**.

Another possible source of the radical anion of **1** should be examined, namely the coproportionation of $\mathbf{1H}^-$ and **1** (Scheme 4).

As shown later on, the equilibrium constant for reaction (−7) is smaller than 3×10^{-10}. Reaction 8 should therefore be very downhill if any appreciable amount of the radical anion of **1** is to be formed by this mechanism. This is in fact not the case since $\mathbf{1L}^-$ is a weak base. There is an additional manner to rule out the formation of the radical anion of **1** by this mechanism, namely, the fact one molecule of $BNAL_2$ is consumed each time one molecule of **1** is consumed, instead of the 2-to-3 stoichiometry predicted with the coproportionation mechanism (Scheme 4).

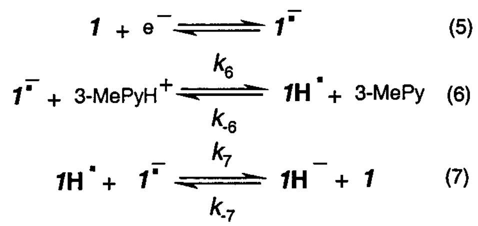
The rate constant $k_4 = 2 \times 10^{-2}\ M^{-1}\ s^{-1}$, derived from our experiments, is not significantly different from the value reported in ref 1. We may now check that the thermodynamics of reaction 4 makes its, unlike reaction 1, a likely event. The equilibrium constant may be estimated according to the following procedure.

Cyclic voltammetry of **1** shows two reversible one-electron waves (Figure 2) corresponding to the two standard potentials:[5]

$$E^0_{1/1^{\bullet-}} = -0.660,\ E^0_{1^{\bullet-}/1^{2-}} = -1.340 \text{ V vs SCE}$$

Upon addition of an acid, the first wave tends to become irreversible and to double in height. In the experiments in Figure 2, the acid was introduced into the solution as two different buffers containing 3-methylpyridine (3-MePy). These observations point to the occurrence of a classical disproportionation[7] mechanism triggered by the protonation of the anion radical which gives rise to a neutral radical that is easier to reduce than the starting molecule (Scheme 5). Simulation of the voltammograms according to this mechanism, using the Digisim© package (Bioanalytical Systems Inc.), [8] led to $K_6 = 2 \times 10^{-6}$ and $k_6 = 4 \times 10^3\ M^{-1}\ s^{-1}$ and showed that $K_7 \geq 3 \times 10^9$. The pK_a of potential of the $\mathbf{1H}^-/\mathbf{1} + H^+ + 2e^-$ redox reaction is given by the following equation:

Scheme 5



$$E^0_{1H^-/1,H^+} = E^0_{1/1^{\cdot-}} + \frac{RT}{2F}\ln\left(\frac{K_7}{K_a,1H^{\cdot}}\right)$$

It follows that $E^0_{1H^-/1,H^+} \geq -0.17$ V vs SCE. The standard potential of the $BNAH_2/BNAH^+ + H^+ + 2e$ redox reaction is 0.022 V vs SCE.[4] The equilibrium constant of reaction 4 may thus be expressed as $K_4 = 10^{-15.2}$, $K_7 \geq 2 \times 10^{-6}$, using the values of K_a, 1H$^{\cdot}$, $E^0_{1/1^{\cdot-}}$ and the lower limit of K_7 that have been determined earlier. It follows that $k_{-4} = k_4/K_4 \leq 10^4\ M^{-1}\ s^{-1}$. The values found for the rate constants k_{-4}, k_4 and a kinetic isotope effect of 2.7,[1] are consistent with those found for various examples of one-step hydride transfers from NADH analogues to other NADH analogues,[2d] quinones,[9,10] carbonyl compounds and carbon−carbon double bonds.[2c]

In conclusion, the deuterium isotope kinetic effect previously assigned to the one-electron transfer from $BNAH_2$ ($BNAD_2$) to 9-fluorenylidenemalononitrile, actually occurs during one-step hydride transfer between the two reactants.[11] The electron transfer step is predicted, based on its thermodynamics to be exceedingly slow and the appearance of the anion radical of the electron donor was due to incomplete deoxygenation of the reaction mixture.

JO000651D

---

(7) Andrieux, C. P.; Savéant, J.-M. Electrochemical Reactions. In *Investigations of Rates and Mechanisms of Reactions, Techniques in Chemistry*; Bernasconi, C., Ed.; Wiley: NewYork, 1986; Vol. 6, 4/E, Part 2, pp 305−390.

(8) Rudolph, M.; Reddy, D. P.; Feldberg, S. W. *Anal. Chem.* **1994**, *66*, 589A−600A.

(9) (a) Fukuzumi, S.; Nishizawa, N.; Tanaka, T. *J. Org. Chem.* **1984**, *49*, 3571−3578. (b) Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1987**, *109*, 305−316.

(10) Anne, A.; Moiroux, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1993**, *115*, 10224−10230.

(11) One of the reviewers suggested that the electron-transfer mechanism depicted in Scheme 2 could be an alternative to the hydride transfer mechanism if an attractive interaction within the ion pair, ($\mathbf{1}^{\cdot-}$, $BNAL_2^{\cdot+}$) were taken into account. If it is furthermore assumed that this electron-transfer step acts as a preequilibrium in front of rate-determining proton exchange step, the observed deuterium kinetic isotope effect might thus be consistent with an electron-transfer mechanism even though the deuterium kinetic isotope effect would concern a proton-transfer reaction and not an electron-transfer reaction. The possibility of such a mechanism was indeed discussed in the favorable case were the electron donor was chloranil, implying a stabilizing interaction of 0.2 eV in the caged ion-pair.[10] In the present case, adherence to the experimental data would imply an interaction of at least 0.8 eV, which is far too large for ion pairing between two large ions in a polar solvent (the energy of interaction between two charges immerged in a solvent like acetonitrile or DMF and separated by a distance as short as 3 Å is only 0.133 eV). Such an electron transfer mechanism is thus ruled out leaving us with the conclusion that the reaction actually involves a one-step hydride transfer pathway.