

A Remarkable Kinetic Isotope Effect in One-Electron Transfer from 1-Benzyl-1,4-dihydronicotinamide

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Kinetic isotope effects can be extremely informative in mechanistic studies of organic and bioorganic reactions, especially for reactions involving hydrogen (including proton and hydride) transfer.¹ It is generally believed that only small secondary kinetic isotope effects are involved in one-electron-transfer reactions. As a matter of fact, to our knowledge, no large kinetic isotope effect has hitherto been reported for one-electron-transfer reactions related to nicotinamide and its derivatives, although some remarkable equilibrium isotope effects in electron-transfer reactions have been reported by Stevenson² and other groups.^{3,4} These large equilibrium isotope effects necessarily mean that the kinetic isotope effects for the forward electron-transfer reactions are at variance with that for the reverse reactions in the electron-transfer equilibrium system. These facts have prompted us to investigate the kinetic isotope effects in electron-transfer reactions. Herein, we wish to report the first observation of remarkable kinetic isotope effect in the one-electron-transfer process from 1-benzyl-1,4-dihydronicotinamide (BNAH) to 9-fluorenylidene malononitrile (**1**).

In the previous paper,⁵ we reported the reduction of **1** by BNAH in dry acetonitrile to give the thermodynamically unfavorable 9-dicyanomethylfluorenyl anion and BNAH⁺, which cannot be rationalized in terms of one-step direct hydride transfer from BNAH to **1**. Subsequent studies reported here showed that the reaction proceeded via a multistep hydride transfer mechanism initiated by one-

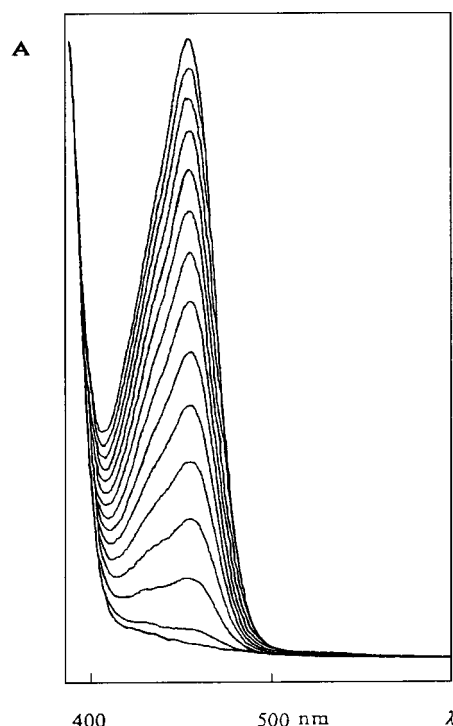


Figure 1. UV-vis spectra obtained from the reaction of BNAH with **1** in dry acetonitrile at 25 °C at 10 min intervals: 0, 10, 20, ... min (going upward).

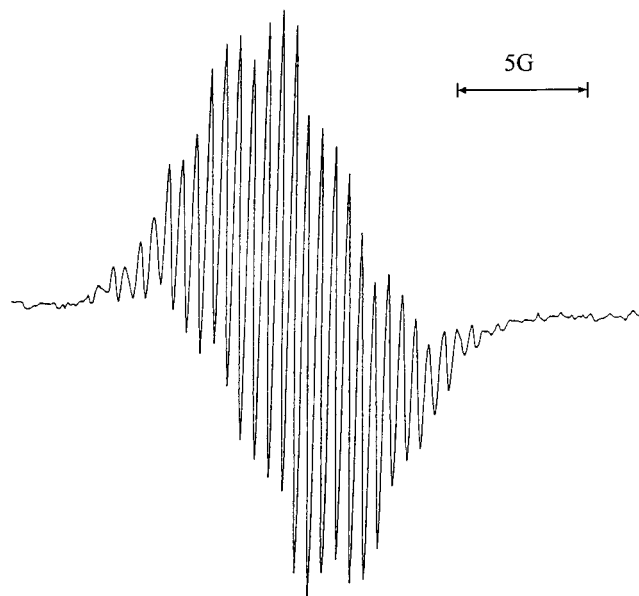


Figure 2. The EPR spectrum obtained from the reaction of a sample containing **1** (0.05M) with BNAH (or BNAH-4,4-d₂) in dry acetonitrile.

electron transfer from BNAH to **1**, and a remarkable kinetic isotope effect was observed in this step.

When equimolar amounts of BNAH and **1** were dissolved in dry CH₃CN and the yellow-colored solution was rigorously deaerated and allowed to stand at 25 °C, a red color gradually developed. UV-vis spectroscopy showed the appearance of a new absorption peak at $\lambda_{\text{max}} = 452 \text{ nm}$, and the absorbance increased with the reaction time (Figure 1). Meanwhile, the mixture gave an EPR signal with $g = 2.0048$

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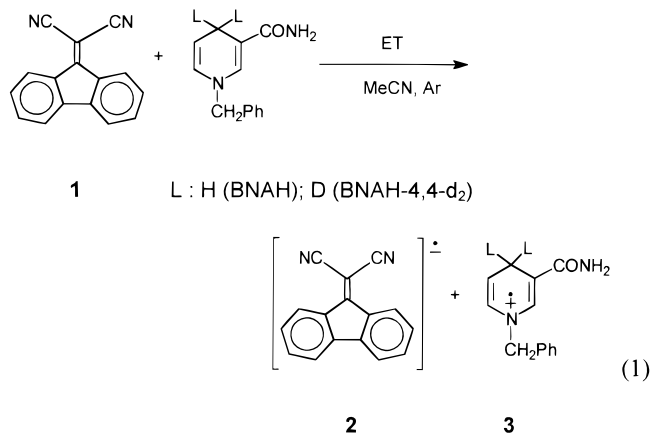
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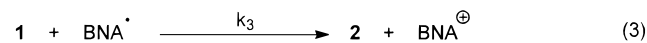
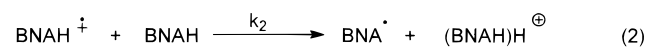
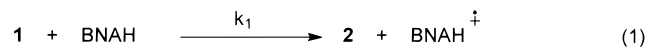
(Figure 2), and the intensity of the signal increased with time in concordance with that of the absorption at $\lambda_{\max} = 452$ nm. When the ESR signal diminished, the UV-vis absorption at $\lambda_{\max} = 452$ nm disappeared. These facts clearly indicate that the EPR signal and the UV-vis absorption at $\lambda_{\max} = 452$ nm originated from the same reactive radical intermediate. To identify the radical species, BNAH-4,4- d_2 was used as the reducing agent for the reduction of **1** under the same conditions, and the same EPR signal and UV-vis absorption spectrum were obtained, demonstrating that the two reactions gave the same radical intermediate. It is conceivable that the radical species must be 9-fluorenylidene malononitrile anion radical (**2**) derived from **1** upon one-electron transfer from BNAH (or BNAH-4,4- d_2) (eq 1).⁶



To further confirm the anion radical **2**, we used Stevenson's method⁷ to generate **2** by reducing **1** with sodium in hexamethylphosphoramide (HMPA) and obtained the same EPR spectrum as that from the reduction of **1** by BNAH or BNAH-4,4- d_2 as described above, indicating that the EPR signal was indeed originated from anion radical **2**.

The kinetic studies of the one-electron-transfer reaction from BNAH to **1**, as well as from BNAH-4,4- d_2 to **1**, were carried out under pseudo-first-order reaction conditions with BNAH or BNAH-4,4- d_2 in more than 20-fold excess by measuring the absorption of the reaction mixture at $\lambda_{\max} = 452$ nm. The pseudo-first-order rate constants obtained for a series of experiments at different temperatures between 15 and 35 °C and at various concentrations of reactants are shown in Table 1 (Supporting Information) for the normal and deuterated BNAH reacting with **1**. The measured values of the pseudo-first-order rate constants (k_{obs}) at each concentration were plotted for each temperature against the concentration of BNAH or BNAH-4,4- d_2 , the second-order rate constants (k) for the electron-transfer reaction were obtained from the slopes of the graphs, which were calcu-

(6) ¹H NMR experiment showed that the counterion of **2** is BNA⁺ in the reaction system, implying that radical anion **2** could be formed from two different reaction steps (1) and (3):



Since the pK_a of BNAH⁺ in CH₃CN is -5.9 determined in our group (unpublished) and radical BNA[•] is also a very active reaction intermediate, reaction 1 would be the rate-determining step. Using the steady-state approximation of the intermediates BNAH^{•+} and BNA[•], we can derive the equation $d[2]/dt = 2k_1[1][\text{BNAH}]$, which indicates that the rate of **2** formation is dependent only on the one-electron transfer in the reaction 1.

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Table 2. Second-Order Rate Constants for the Electron-Transfer Reactions, $k(\text{BNAH})$ and $k(\text{BNAH-4,4-}d_2)$ in $\text{M}^{-1} \text{s}^{-1}$, with Standard Deviations

T (°C)	$k(\text{BNAH})$ (10^2)	$k(\text{BNAH-4,4-}d_2)$ (10^2)	$k_{\text{H}}/k_{\text{D}}$
15	2.10 ± 0.08	0.752 ± 0.035	2.79
20	3.92 ± 0.1	1.436 ± 0.031	2.73
25	6.40 ± 0.18	2.41 ± 0.08	2.66
30	10.98 ± 0.37	4.22 ± 0.11	2.60
35	18.72 ± 0.53	7.35 ± 0.17	2.55

Table 3. Activation Parameters for the Electron Transfer Reactions (E_a and ΔH^\ddagger in kJ Mol^{-1} , ΔS^\ddagger in J K^{-1}) All with Standard Deviations

param	1 + BNAH	1 + BNAH-4,4- d_2	Δ param
E_a	79.8 ± 0.2	83.2 ± 0.2	3.4 (kJ mol^{-1})
ΔH^\ddagger	77.3 ± 0.4	80.8 ± 0.5	3.5 (kJ mol^{-1})
ΔS^\ddagger	-8.2 ± 0.6	-4.7 ± 0.7	3.5 (J/K)

lated by the method of least squares. Table 2 shows these constants, and also the isotopic rate ratios for the BNAH and BNAH-4,4- d_2 reactions.

The values of $\ln k$ were plotted against the reciprocal of the absolute temperature, and the activation parameters as given in Table 3 were calculated by the least-squares method.

From Table 2, it is interesting and also surprising to note that the rate constant for the one-electron transfer from BNAH to **1** to give anion radical **2** is larger than that from BNAH-4,4- d_2 to **1** by a factor of 2.73 (20 °C), demonstrating a significant secondary kinetic isotope effect $k_{2\text{H}}/k_{2\text{D}}$. This secondary kinetic isotope effect is close to some reported primary kinetic isotope effects.⁸ This result suggests that in mechanistic studies of electron-transfer reactions one has to be careful in making a conclusion that the formation and/or cleavage of bond containing the isotopically labeled atom must be involved in or in front of the rate-determining step, based on a large kinetic isotope effect of the reaction only. It is seen from Table 3 that the activation enthalpy of the one-electron transfer from BNAH to **1** is smaller (77.3 kJ mol^{-1}) than that (80.8 kJ mol^{-1}) of the one-electron transfer from BNAH-4,4- d_2 to **1**, the difference is 3.5 kJ mol^{-1} ; the activation entropy of the former is -8.2 J K^{-1} , smaller than that (-4.7 J K^{-1}) of the latter; the difference is about 1.04 kJ mol^{-1} much smaller than the difference of the activation enthalpies. These results imply that the enthalpy term is mainly responsible for the remarkable kinetic isotope effect.

The origin of the large secondary kinetic isotope effect may be related to the differential stability of the radical cations of BNAH and BNAH-4,4- d_2 , the details of which are now under investigation.

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Supporting Information Available: Observed first-order rate constants for the electron transfer from BNAH (or BNAH-4,4- d_2) to **1** (Table 1). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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